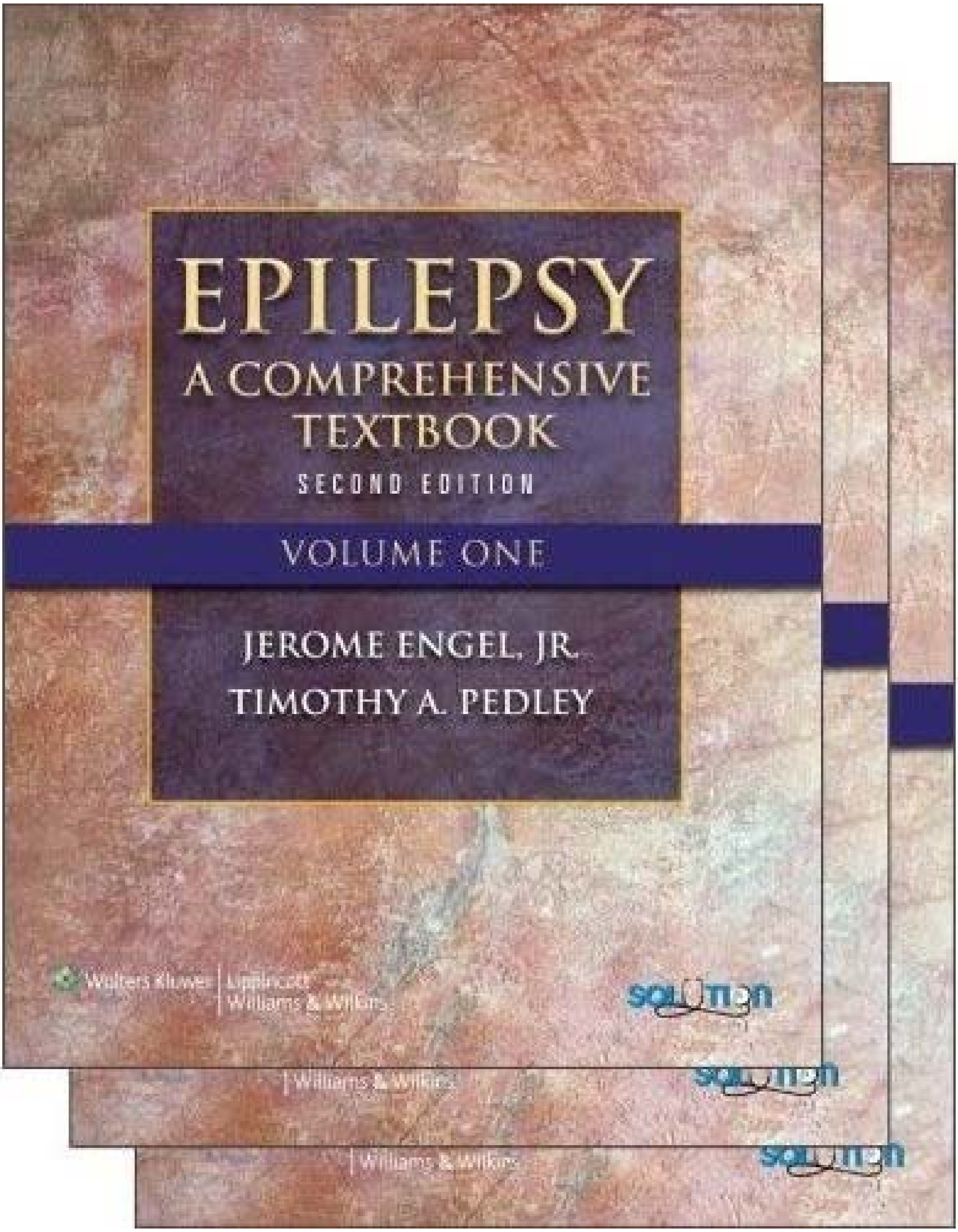

EPILEPSY

A COMPREHENSIVE TEXTBOOK

SECOND EDITION

VOLUME ONE

JEROME ENGEL, JR.
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Editors: **Engel, Jerome; Pedley, Timothy A.**
Title: *Epilepsy: A Comprehensive Textbook, 2nd Edition*

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> Front of Book > Acknowledgments

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Jerome Engel Jr. MD, PhD

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Editors: **Engel, Jerome; Pedley, Timothy A.**
Title: *Epilepsy: A Comprehensive Textbook, 2nd Edition*

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> Front of Book > Dedication

Dedication

We dedicate this edition to our wives, Catherine and Barbara, and the others in our families who all too often lost us to these volumes. Above all, this book is for persons with epilepsy and their families, who daily give meaning to our work.

Editors: **Engel, Jerome; Pedley, Timothy A.**
Title: *Epilepsy: A Comprehensive Textbook, 2nd Edition*

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> Front of Book > Preface to the Second Edition

Preface to the Second Edition

A decade has intervened between the first and second editions of *Epilepsy: A Comprehensive Textbook*. The process of revision afforded a unique opportunity to observe the extraordinary advances in research and the great improvements in clinical care that have occurred during this time. New insights into the basic mechanisms of seizures and epilepsy can be attributed largely to the increased application of cellular and molecular biology to the study of epileptic phenomena. In addition, there have been more direct investigations of patients using the tools of genetics and various brain imaging techniques. All aspects of treatment have improved, and both seizure control and quality of life for people with epilepsy are better today than ever before.

This progress is symbolized by noting that the second edition contains 20 more chapters than the first, of which 42 are completely new and 251 have been extensively rewritten. There were 351 contributors in the first edition; there are 444 in the second, of whom 225 are returning authors and 219 are new. As a result, although the book's outline follows that of the first edition, this is essentially an entirely new textbook.

As with the first edition, our objective with the second is to create a comprehensive textbook that addresses all aspects of epilepsy, from basic pathophysiology at cellular, molecular and organ levels to clinical phenomenology, diagnostic evaluation, treatment options, comorbidities, psychosocial rehabilitation and health care delivery. All chapters are written by distinguished experts in each field, and most have two or more authors representing different points of view to provide an authoritative consensus on each topic. Selection of editors and authors was designed to assure a perspective that is truly international. Therapeutic recommendations are evidence-based to the extent that is currently possible.

With completion of the second edition, we are acutely aware how much we owe to the section editors and, especially, our associate editors, all of whom are themselves internationally recognized experts in epilepsy. Without their help, chapters would not have been as consistently rigorous, balanced or current.

We also note with sadness the passing of colleagues who participated in the first edition, many of whom also contributed, or were scheduled to contribute, to the second. They include John Fred Annegers, Frank Benson, Fritz E. Dreifuss, John R. Gates, Richard W. Homan, Peter Kellaway, Pierre Loiseau, Eric Lothman, K. S. Mani, Frank Morrell, Claudio Munari, J. Kiffen Penry, Luis Felipe Quesney, A. James Rowan, Masakazu Seino, Arthur Sonnen and Sheila J. Wallace. We miss them, but they live on through their work and accomplishments, and the fond memories we have of them.

The first edition of *Epilepsy: A Comprehensive Textbook* was intended to be a work in progress, a basis for developing a comprehensive reference resource in a format that had the potential to be updated regularly. A CD-ROM was subsequently prepared that included additional materials and revisions of some chapters. The second edition will have a digital version that is Internet based for inclusion of additional figures and images, more color illustrations, and other enhancements, as well as advanced search capabilities. The Internet version of the textbook affords an opportunity for all authors to update their chapters on an ongoing basis, to ensure that the electronic version remains current with the very latest information.

As always, we welcome suggestions and constructive criticism from readers. This input will not only assist in improving future hard copy editions but also help us to provide an Internet-based digital version that is as useful as possible.

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Chapter 1

Introduction: What Is Epilepsy?

Jerome Engel Jr.

Timothy A. Pedley

Introduction

Epilepsy is one of the most common disorders of the brain.[28] One of every ten people will have at least one epileptic seizure during a normal lifespan, and a third of these will develop epilepsy. Worldwide, epilepsy affects 50 million people. According to a World Health Organization (WHO) survey, epilepsy accounts for 1% of the global burden of disease, a figure equivalent to breast cancer in women and lung cancer in men.[15]

Epilepsy has been known since antiquity. An Assyrian-Babylonian textbook written over three millennia ago provides an accurate clinical description of the condition,[12] and Indian and Chinese physicians of that time were also familiar with it. The word *epilepsy* is derived from the Greek verb ÎµÎ»Î±ÂµÎ²Î±Î½ÎµÎ¹Î½ (*epilamvanein*) (â€œto be seized,â€ â€œto be taken hold of,â€ or â€œto be attackedâ€). In ancient Greece, as now, people spoke of â€œhaving seizedâ€ and of having had an â€œattack.â€ This terminology derived from the very ancient notion that all diseases represented attacks by the gods or evil spirits, usually as punishment. Because seizures were the most vivid example of demonic possession, epilepsy was considered to be â€œthe sacred disease,â€ and by the fifth century BC, the word had gradually acquired the specific and particular meaning associated with it today.[25] Indeed, the battle between prejudice and acceptance, ignorance and knowledge, myth and science, and charlatanism and rational therapy has been long and difficult, and even today it has not yet been fully won. Even in comparison with all the advances made during the last centuryâ€”more than at any other time in historyâ€”consider how enormous and fundamental was that first step attributed to Hippocrates in about 400 BC, that epilepsy is a disease of the brain that must be treated by diet and drugs, not religious incantations.[9]

Epilepsy is, of course, not a specific disease, or even a single syndrome, but rather a broad category of symptom complexes arising from any number of disordered brain functions that themselves may be secondary to a variety of pathologic processes. The terms *convulsive disorder*, *seizure disorder*, and *cerebral seizures* are used synonymously with epilepsy: They all refer to recurrent paroxysmal episodes of brain dysfunction manifested by stereotyped alterations in behavior. Modern concepts of epilepsy originate in the work of midâ€“19th-century physicians and scientists, the most important among them being John Hughlings Jackson.[10] At a time when epilepsy denoted disorders manifested by generalized convulsions, which were believed to arise from disturbances in the medulla oblongata, Hughlings Jackson established the important concept that there were different categories of seizures, each with its own physiology and semiology. His explanation of â€œdreamy statesâ€ and â€œuncinate group of fitsâ€ as focal seizures originating from discrete areas within the cerebral cortex comes close to present-day views of limbic seizures. Similarly, his recognition of focal motor seizures (â€œjacksonian seizuresâ€) not only identified the responsible locus within the brain, but also allowed him to draw inferences that have forever changed our concepts of cortical motor representation and cerebral control of voluntary movement. Hughlings Jackson, more than anyone, established a scientific approach to the study of epileptic phenomena.

Today, a large number of clinical phenomena are recognized as epileptic *seizures*, some of which (e.g., myoclonic and atonic seizures) are currently poorly understood and might, in fact, reflect neuronal mechanisms that are somewhat different from the pathophysiologic processes traditionally considered to be â€œepileptic.â€ A variety of conditions or *epilepsies* have been categorized and defined not only by the types of seizures they manifest, but also by other, associated clinical features. Specific *epileptic syndromes* have been identified by their characteristic seizure types, pattern of seizure recurrence, age of onset, associated neurologic and other clinical signs, electroencephalographic (EEG) findings, presence or absence of familial occurrence, and prognosis. Epilepsies and epileptic syndromes are broadly divided into *idiopathic* and *symptomatic* disorders. *Idiopathic* epilepsies are generally benign in the sense that they are not associated with brain lesions, neurologic abnormalities other than seizures, or mental impairment, and that they tend to be self-limited or respond readily to antiepileptic drugs. Genetic factors are important, and manifestations are typically age related. This is epilepsy *sui generis* (â€œby itselfâ€), which conforms to the original Greek meaning of â€œidiopathic,â€ in contrast to the commonly used but incorrect meaning of â€œcause unknown.â€ *Symptomatic* epilepsies are those in which seizures are the consequence of an identifiable lesion or other demonstrable physical or metabolic etiology. When epilepsies are presumably symptomatic but currently of unknown specific etiology, they have been termed *cryptogenic*,[2] a term also used in epidemiologic studies to mean unknown as to whether idiopathic or symptomatic.[4] Because of its ambiguity, â€œcryptogenicâ€ is a term that should be replaced by the more accurate â€œprobably symptomatic.â€[5]

The Role of Research

Advances in the understanding and treatment of epilepsy have occurred because of active and continuing research efforts. Indeed, it is not an exaggeration to say that many of the exciting developments in basic neuroscience in the middle and latter parts of the last century were related to epilepsy, either directly (e.g., in cellular studies of disease mechanisms) or indirectly (e.g., in investigations of cortical excitability and its control). Clinical investigation is an essential part of practice, and clinicians have played important roles in developing hypotheses that can be subjected to experimental investigation.

An important change that has occurred and accelerated in the last two decades has been the growing ability to carry out basic studies in humans. For example, intracranial monitoring techniques used to evaluate patients with intractable seizures for surgery, and the removal of brain tissue during surgical procedures now offer investigators opportunities to investigate basic physiologic, biochemical, and molecular phenomena in patients that could previously be studied only in experimental animal models of epilepsy. Similarly, modern brain imaging methods, such as functional magnetic resonance imaging (fMRI), magnetic resonance spectroscopy (MRS), positron emission tomography (PET), and single-photon emission computed tomography (SPECT), allow noninvasive study of basic biologic questions in the living, intact brain. New insights derived from these studies make it possible to determine which abnormalities found in animal models of epilepsy have counterparts in humans, which experimental observations are valid for the human condition and which are not, and which experimental data fit within reasonable conceptual frameworks for developing further hypotheses that can be tested either in humans directly or in relevant animal models.

Epilepsy Is More Than Seizures

There have been many attempts to obtain a consensus on definitions of *epileptic seizure* and *epilepsy*. Recently, the International League against Epilepsy (ILAE) has proposed new definitions for both.[7] In this proposal, an epileptic seizure is defined as â€œa transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain.â€ This definition acknowledges that previous concepts of decreased inhibition and increased excitation were oversimplifications, because inhibition is actually increased in some forms of epilepsy where phasic inhibition is a central element in the primary epileptogenic abnormality. An epileptic seizure can also be a natural response of the normal brain to transient disturbance in function and, therefore, not necessarily an indication of an epileptic disorder. Such seizures are often referred to as *provoked*, *acute symptomatic*, or *reactive*. This accounts for a greater incidence of seizures (about 7% by age 80) than epilepsy (nearly 3%).

Epilepsy is a group of neurologic conditions, the fundamental characteristics of which are recurrent, usually unprovoked, epileptic seizures. A common operational definition of epilepsy is two or more unprovoked seizures occurring more than 24 hours apart.[4] However, the new ILAE proposal[7] offers a more fundamental definition of epilepsy: â€œA chronic condition of the brain characterized by an enduring propensity to generate epileptic seizures, and by the neurobiological, cognitive, psychological, and social consequences of this condition.â€ This definition emphasizes the existence of a persistent intrinsic epileptogenic abnormality that is a property of the brain itself and thus present even when seizures are not occurring. This contrasts with seizures that are dependent upon acute insults or other conditions that transiently affect an otherwise normal brain. An intrinsic epileptogenic abnormality of the brain necessary for a diagnosis of epilepsy, however, can resolve spontaneously, as in some age-related idiopathic epilepsies that typically remit.

The new ILAE definition also acknowledges importantly the psychological and social consequences of epilepsy. This change recognizes that to the affected patient, epilepsy is more than seizures, and that the condition in its entirety comprises many facets, different for each individual, that contribute to disability and impaired quality of life (Fig. 1). Treatment that focuses solely on seizures often does little to lessen disability. This is most dramatically illustrated by the patient who, having undergone successful surgical resection of epileptogenic brain tissue, becomes seizure free but remains socially isolated and unemployed, with little evidence of an improved life. Therapeutic intervention can be optimal only when the multiple medical, psychological, and environmental factors that constitute epilepsy are addressed. Thus, the physician's role is properly defined, and sometimes circumscribed, by asking a series of questions: â€œWhat are the problems that are contributing to the patient's predicament?â€ â€œWhich of these can or need to be treated?â€ â€œWhat will be the consequences of treatment?â€ and â€œWhat outcome measures will appropriately gauge the treatment's success?â€

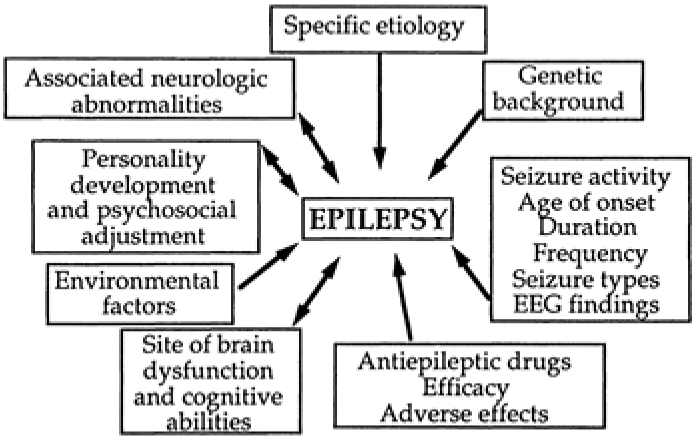

FIGURE 1. The multiple, interacting factors that contribute to the totality of epilepsy for an individual patient.

The existing ILAE Classification of Epilepsies and Epileptic Syndromes[2] and Classification of Epileptic Seizures[3] are presently under review. An ILAE Task Force on Classification and Terminology has proposed a diagnostic scheme for use when describing individual patients[5] (Table 1). Axis 1 consists of a detailed phenomenologic description of the ictal events, which is useful in certain situations, such as a presurgical evaluation, but otherwise can be abbreviated or omitted. Axis 2 is a new concept, recognizing seizure types as diagnostic entities based on distinct pathophysiologic and anatomic features that provide information useful for determining etiology, therapy, and prognosis. Diagnosis of a specific seizure type is especially important when diagnosis of an epilepsy syndrome is not possible. Axis 3 consists of accepted epilepsy syndromes and recognizes that a syndromic diagnosis is not always possible. An epilepsy syndrome as used here refers to â€œa complex of signs and symptoms that define a unique epileptic condition. This must involve more than just a seizure type: Thus, frontal lobe seizures per se, for instance, do not constitute a syndrome.â€ In contrast, an epileptic disease is defined as â€œa pathologic condition with a single, specific, well-defined etiology. Thus, progressive myoclonus epilepsy is a syndrome, but Unverricht-Lundberg myoclonic epilepsy is a disease.â€ Axis 4 is etiology, which includes a wide variety of genetic and nongenetic diseases associated with epilepsy, specific epilepsy genes, and acquired cerebral injuries such as trauma and infection. Axis 5, which assesses the degree of disability caused by the epilepsy, is taken from a WHO classification of impairment for neurologic disorders and is optional.

Physiologic Considerations

It is readily apparent from observing the diverse ictal phenomenology of patients with epilepsy that most seizures consist of evolving processes that depend on multiple pathophysiologic mechanisms and anatomic substrates. Two essential epileptogenic factors represent the net effect of many complex interrelated events. The first is an abnormality of cellular excitability that arises from mechanisms that affect membrane

depolarization and repolarization. The second is a â€œnetwork defectâ€ that derives from mechanisms underlying the development of aberrant neuronal integration, resulting in abnormal synchronization of neuronal populations and propagation of the epileptic discharge within neural pathways. Both sets of disturbances must be present before a seizure can occur.

Table 1 Proposed Diagnostic Scheme for People with Epileptic Seizures, and with Epilepsy

Epileptic seizures and epilepsy syndromes are to be described and categorized according to a system that utilizes standardized terminology and that is sufficiently flexible to take into account the following practical and dynamic aspects of epilepsy diagnosis:

1. Some patients cannot be given a recognized syndromic diagnosis.
2. Seizure types and syndromes change as new information is obtained.
3. Complete and detailed descriptions of ictal phenomenology are not always necessary.
4. Multiple classification schemes can, and should, be designed for specific purposes (e.g., communication and teaching; therapeutic trials; epidemiologic investigations; selection of surgical candidates; basic research; genetic characterizations).

This diagnostic scheme is divided into five parts, or Axes, organized to facilitate a logical clinical approach to the development of hypotheses necessary to determine the diagnostic studies and therapeutic strategies to be undertaken in individual patients:

- Axis 1: Ictal phenomenologyâ€"from the Glossary of Descriptive Ictal Terminology; can be used to describe ictal events with any degree of detail needed.
- Axis 2: Seizure typeâ€"from the List of Epileptic Seizures. Localization within the brain and precipitating stimuli for reflex seizures should be specified when appropriate.
- Axis 3: Syndromeâ€"from the List of Epilepsy Syndromes, with the understanding that a syndromic diagnosis may not always be possible.
- Axis 4: Etiologyâ€"from a Classification of Diseases Frequently Associated with Epileptic Seizures or Epilepsy Syndromes when possible, genetic defects, or specific pathologic substrates for symptomatic focal epilepsies.
- Axis 5: Impairmentâ€"this optional, but often useful, additional diagnostic parameter can be derived from an impairment classification adapted from the World Health Organization International Classification of Functioning, Disability, and Health 2.

From Engel J Jr. A proposed diagnostic scheme for people with epileptic seizures and with epilepsy: report of the ILAE Task Force on Classification and Terminology. *Epilepsia.* 2001;42:796â€"803, with permission.

Part of the diversity that characterizes the clinical expression of seizures is due to the fact that different brain areas are responsible for different aspects of epileptic phenomenology[14] (Table 2). Generally, these different regions are spatially proximate, although they are rarely congruent. Sometimes, however, quite distant areas give rise to some of the clinical or EEG features of a particular patient's seizures.

The *irritative zone* is the area of cortex that generates interictal EEG spikes. This is clearly related but frequently not identical to the *ictal onset zone*, which is the area of cortex that initiates seizures. Indeed, although the interictal EEG spike has provided an enormous impetus to basic laboratory research and has led to a definition of the cellular mechanisms underlying interictal discharges, it is still not known whether any given interictal spike reflects mechanisms important in triggering seizures, is a marker of inhibitory mechanisms involved in maintaining the interictal state, or is merely an interesting epiphenomenon unrelated in any direct way to seizure occurrence. In any event, in some instances the irritative zone can include multiple spike sites, some of which are located at a distance from the ictal onset zone, even in the opposite hemisphere. This became clear early in the experience with long-term, especially intracranial, EEG monitoring, in which recordings showed that interictal epileptiform discharges are commonly more widespread than had been suggested by routine EEG or than would be expected solely on the basis of the area of ictal onset. For example, in scalp recordings from patients with unilateral mesial temporal lobe epilepsy, contralateral temporal spikes are frequently encountered, although they are usually concentrated on the side of seizure onset, at least in the majority of patients who have successful surgical outcomes. Intracranial recordings frequently demonstrate widespread ipsilateral spikes, and postsurgical electrocorticograms show that many of these may remain after resection, apparently without major adverse consequences for seizure outcome. The classic scalp EEG â€œspike focus,â€ therefore, is a very limited reflection of complex underlying physiologic events. Interictal PET scans, too, consistently demonstrate that cerebral metabolic dysfunction is more extensive than clinical evidence, scalp EEG, and structural brain imaging would suggest.

In symptomatic epilepsies, the *epileptogenic lesion* is the pathologic substrate for the epilepsy; it can usually be identified on MRI, although EEG remains necessary to demonstrate epileptogenicity of a lesion. Seizures can arise within, adjacent to, or even sometimes distant from an epileptogenic lesion. The *symptomatogenic zone* is that portion of the brain responsible for producing the first clinical ictal symptoms or signs, whereas the *functional deficit zone* is the cortical area or areas exhibiting focal nonepileptic dysfunction. Finally, the *epileptogenic zone* is the total area of brain that is necessary and sufficient to generate seizures and that must be removed to abolish seizures. The fact that the epileptogenic zone cannot be defined with precision accounts for the lack of a uniformly successful outcome following resective surgery for focal seizures. The problem is greater in extratemporal than in temporal lobe epilepsy.

Table 2 Abnormal Brain Areas in Partial Epilepsy

Brain area	Definition	Measure
Irritative zone	Area of cortex that generates interictal spikes	EEG
Ictal onset zone	Area of cortex that initiates or generates seizures	EEG
Epileptogenic lesion	Structural pathology of the brain that is the direct cause of seizures	CT, MRI, tissue pathology

Symptomatogenic zone	Portion of the brain that produces the first clinical symptoms	EEG, behavioral observation
Functional deficit zone	Cortical area producing nonepileptic dysfunction	Neurologic exam, neuropsychology, PET, SPECT
Epileptogenic zone	Total area of brain that is necessary to generate seizures and that must be removed to abolish seizures	Unknown

CT, computed tomography; EEG, electroencephalography; MRI, magnetic resonance imaging; PET, positron emission tomography; SPECT, single-photon emission computed tomography.
Adapted from LÃ¼ders HO, Engel J Jr, Munari C. General principles. In: Engel J Jr, ed. *Surgical Treatment of the Epilepsies*. New York: Raven Press; 1993:137â€“153, with permission.

The Interictal State

There can be little question that at least some types of seizures, especially if prolonged or repeated frequently, can damage the brain.[24] Indeed, the association between chronic epilepsy and pathologic changes in the brain, especially hippocampal sclerosis, is one of the oldest and best-documented clinicopathologic correlations. The concept of an *epileptic encephalopathy* as a condition in which the epileptic processes themselves are believed to contribute to progressive disturbances in cerebral function is now accepted.[5] The question of the relationship between seizures and interictal neurologic or psychiatric findings still generates controversy, however, because it is often not possible to distinguish among the effects of epilepsy per se, cerebral disease, psychological and social factors, and toxicity from chronic use of antiepileptic drugs. Whether distinct behavioral traits or profiles are associated with temporal lobe or other forms of epilepsy remains a matter of debate. Although it seems to have been impossible to devise a definitive clinical study of this issue, it would be surprising if the profound and widespread disturbance of neuronal activity caused by some epileptiform events, and the neuropathologic

findings observed in surgical and autopsy specimens of epileptogenic brain areas, never produced enduring interictal consequences, even subtle, for behavior, personality, and social functioning.

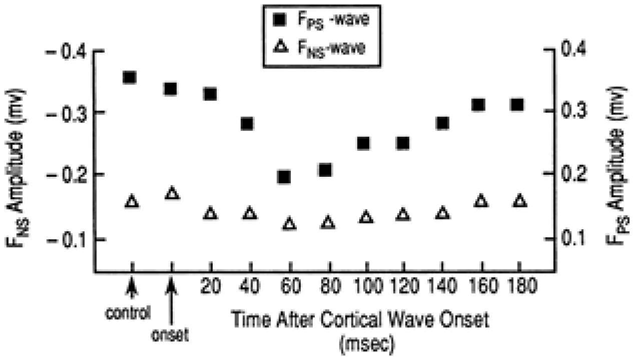

FIGURE 2. Graph showing the effect of the corticofugal volley from a cortical epileptiform discharge, evoked by stimulating a forepaw nerve, on the negative (*triangles*) and positive (*squares*) components of the cuneate nucleus field potential. Maximal inhibition of the cuneate sensory response occurred about 60 msec after the cortical spike. The amplitude of the positive component (F^{PS}) of the cuneate potential was affected much more than the negative component (F^{NS}). (From Schwartzkroin PA, van Duijn H, Prince DA. Effects of projected cortical epileptiform discharges on field potentials in the cat cuneate nucleus. *Exp Neurol.* 1974;43:88â€"105, with permission.)

It is even likely that interictal electrical abnormalities, although traditionally considered subclinical and â€œsilent,â€ also have important functional effects, because of the disruption they cause in normal information processing. Such disruption may be as much the result of excessive or abnormal inhibition as of â€œhyperexcitability.â€ Over 30 years ago, Schwartzkroin et al.[21] asked the question, â€œWhat is the downstream effect of focal cortical epileptiform activity, and can it influence incoming sensory inputs?â€ To study this, they recorded field potentials and unit activity in the cuneate nucleus of cats contralateral to an experimental cortical epileptogenic focus. They discovered that when an afferent sensory volley, triggered by stimulation of a forepaw nerve, occurred in close relation to a cortical spike discharge, the amplitude of the evoked cuneate field potential was substantially and predictably decreased (Fig. 2). In other words, isolated cortical epileptiform discharges had a powerful inhibitory effect on sensory signal transmission by cuneate relay neurons. Subsequently, Shewmon and Erwin[22,23] provided suggestive evidence in humans that interictal spikes, or more likely the after-going slow waves, can similarly result in transient dysfunction as measured by longer reaction times to particular stimuli and increased nonperception of visual stimuli, especially those in the visual field contralateral to the spike discharge. Thus, epileptiform activity occurring at critical times may substantially modify or â€œcolorâ€ the processing of sensory information.

Finally, there is now a substantial body of experimental evidence that activity-dependent behaviors of individual neurons, including those associated with seizures, rapidly initiate a cascade of changes in gene expression. These in turn may lead to further alterations in neuronal excitability within local areas or circuits, some of which are long lasting and associated with (although not yet proved to be causative of) structural remodeling. Some induced genes may relate to future seizure susceptibility, others to intrinsic protective or trophic mechanisms, and still others to plastic structural and functional changes that accompany recurrent seizures and that could, conceivably, produce changes in interictal neuropsychiatric behavior.

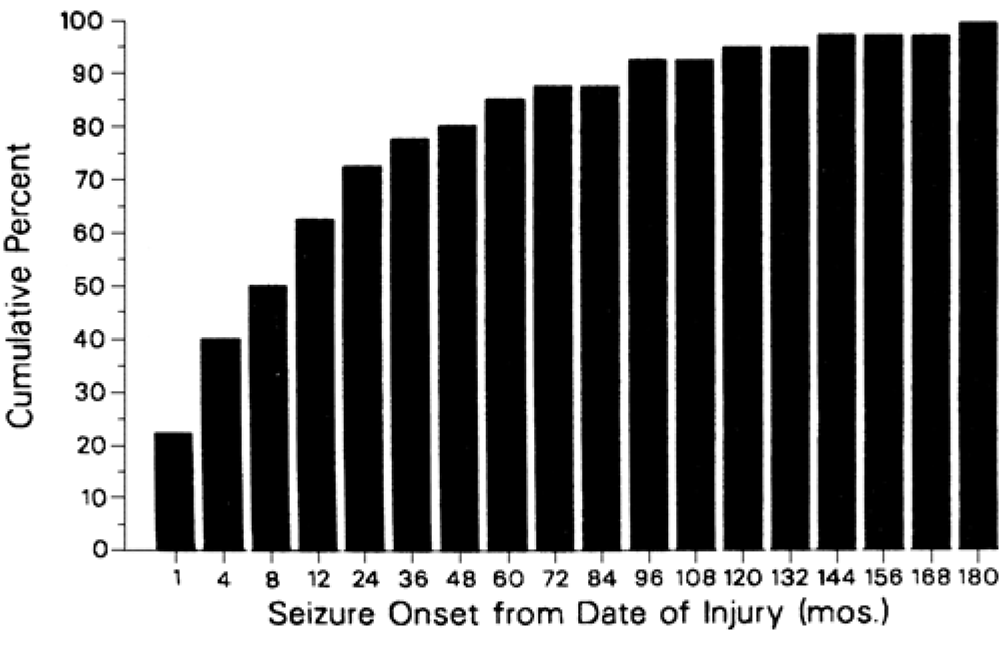

FIGURE 3. Latency of seizure onset in the Vietnam Head Injury Study. The *y axis* shows the cumulative percentage of patients (n = 197) with seizures by time after injury (*x axis*). Note that the time scale is expanded for the first year. (From Salazar AM, Jabbari B, Vance SC, et al. Epilepsy after penetrating head injury. I. Clinical correlates: report of the Vietnam Head Injury Study. *Neurology.* 1985;35:1406â€"1414, with permission.)

Epilepsy as a Discontinuous Process

Depending on the patient, seizures can occur frequently or infrequently, only at night or after awakening, in a cyclic pattern suggesting hormonal influences, only with highly specific triggers, in many other permutations, and, most commonly, without any apparent predictability. However, even patients with refractory seizures have attacks relatively infrequently compared with the total time available in their lives. The factors that precipitate seizure occurrence are still poorly understood, but clinical observations indicate that specific mechanisms must govern whether a patient is in an interictal or ictal state, and how the transition from the interictal to the ictal condition is made. Many environmental and physiologic factors modulate the probability of seizure occurrence: Fever, sleep deprivation, alcohol withdrawal, highly specific triggers in reflex epilepsy, hormonal fluctuations, and even nonspecific stress in some susceptible individuals. It is unknown, however, how these perturbations translate into increased epileptic susceptibility at the cellular or molecular level. In most patients, it is not possible to identify external or internal factors that explain why a

seizure happened at a particular time, rather than a week before or a few minutes later. Changes that alter neuronal excitability or the potential for synchronous interactions among neurons are undoubtedly important but remain to be specified in detail. As but one example, consider the disturbances that can occur in the extracellular microenvironment in epileptic brain regions and, in particular, the possibility that increased potassium concentration within extracellular spaces, which have perhaps been abnormally reduced because of gliosis, cell swelling, or other pathologic factors, may serve as a mechanism for increasing the excitability level of a population of neurons to a critical threshold for seizure generation. Equally mysterious is the fundamental nature of the inherent homeostatic forces in the brain that limit ictal spread after seizures have begun and that terminate them within seconds of their onset. Undoubtedly, the basic neuronal mechanisms underlying these processes are as diverse as those leading to seizure onset. As demonstrated by the condition of *epilepsia partialis continua*, the mechanisms mustered by the brain to limit ictal spread are different from those utilized to terminate the seizure discharge.

The Latent Interval

More than 125 years ago, Gowers[8] first recognized that there is almost always a seizure-free interval between a causative cerebral injury and onset of symptomatic epilepsy. The latency of occurrence of posttraumatic seizures is the clearest example of this point. Figure 3, taken from the Vietnam Head Injury Study,[19] shows the cumulative percentage of patients with posttraumatic seizures as a function of time after injury. Whereas seizures developed most often within the first 2 years of injury, more than 15% of veterans did not have their first seizure until 5 or more years later.

This latent period, which characterizes many (and perhaps all) cases of symptomatic epilepsy, raises important issues about the process of *epileptogenesis*. The clinical data suggest that this process is a dynamic and evolving one that progressively alters neuronal excitability, establishes critical interconnections, and perhaps requires critical structural changes before the first clinical seizure appears. A sequence that seems to be essential for at least one common form of epilepsy, mesial temporal lobe epilepsy with hippocampal sclerosis, involves an insult early in life that causes selective neuronal death, synaptic reorganization, and altered firing patterns within a defined neuronal population. Enhanced excitation and inhibition result in a propensity for hypersynchronization.[6] Recurrent hypersynchronous discharges recruit efferent structures into this epileptogenic process until a sufficient area of brain tissue is involved to manifest as clinical epileptic seizures. A genetic predisposition may influence the pattern of cell loss and synaptic reorganization, or the effect of these anatomic changes on local excitability, or the influence of these local excitability changes on projection areas and eventual manifestation of ictal events. Although this sequence of events has been developed from research on experimental animal models of mesial temporal lobe epilepsy, what is lacking in humans, of course, is evidence of a *subclinical* epileptogenic abnormality preceding the appearance of clinical seizures. Thus, if it were possible to have depth electrodes placed in the hippocampus from the time of the epileptogenic injury, it is likely that epileptiform changes would be detected long before any clinical hint of epilepsy. That a similar epileptogenic evolution in fact occurs in humans is suggested by the occasional observation of focal EEG spikes in patients with a brain tumor or vascular malformation, even in the absence of clinical seizures.

Because of the great variability in latent periods seen among patients, there must be both intrinsic and acquired modifying factors unique to each individual. One of these is undoubtedly genetic background, which is an inherent determinant of a person's susceptibility to seizures (â€œseizure thresholdâ€). Another factor is the location and spatial dimension of the injury, and a third is the severity of the injury, which may be expressed in terms of the effect a specific lesion has on adjacent or displaced brain tissue.

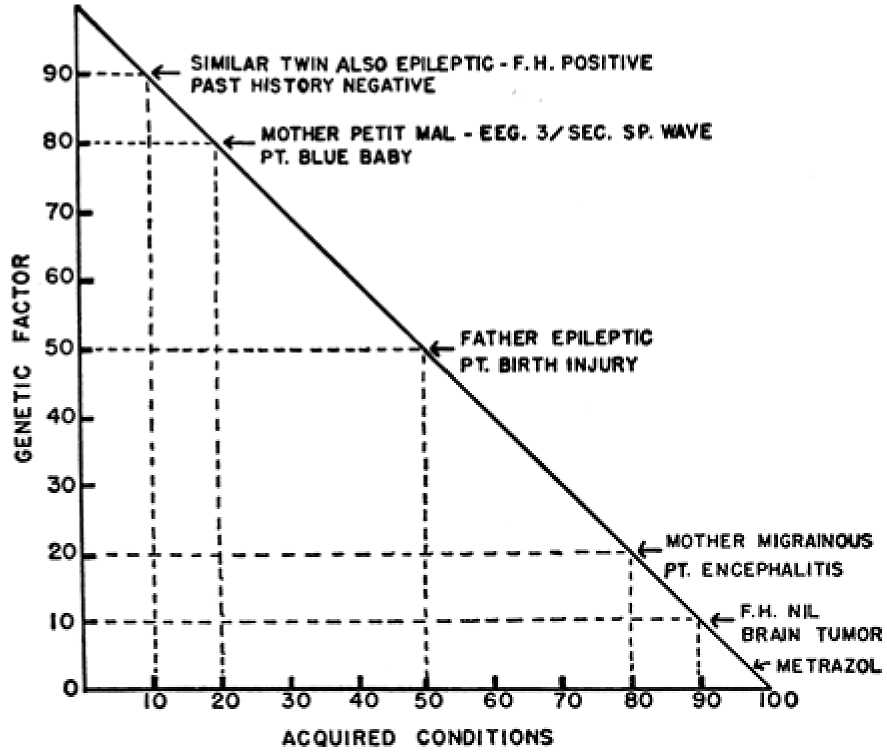

FIGURE 4. The interrelation of genetic and acquired factors in the development of seizures, as proposed by Lennox. (From Lennox WG. *Epilepsy and Related Disorders*. Boston: Little, Brown; 1960:532â€“574, with permission.)

The Era of Molecular Biology

This is the era of molecular genetics applied to human disease. Among the many individual epileptic syndromes described in humans, there are a number of idiopathic epilepsies that are considered to be familial and in which genetic determinants appear to be prominently involved. Twin studies[1,26] implicate strong genetic determinants in many types of seizures and seizure disorders, especially such ones as childhood absence epilepsy, juvenile myoclonic epilepsy, and idiopathic grand mal seizures. However, the role of genetic factors is not straightforward; to the contrary, it is quite complex. For example, seizures develop at increased rates in children of parents with

either idiopathic or symptomatic epilepsy, although the difference is greatest for children of parents with idiopathic generalized forms of epilepsy.[17] Thus, there may be some degree of shared genetic susceptibility present in both the idiopathic and symptomatic epilepsies. However, there are undoubtedly specific genetic determinants of the susceptibility of the brain to seizures and epilepsy following a particular injury, as well as other genetic factors that determine the occurrence of individual familial idiopathic epilepsy syndromes. Furthermore, some inherited disorders, such as tuberous sclerosis and neurofibromatosis, are associated with brain lesions that in turn give rise to symptomatic epilepsies. Whereas mutations in single genes account for some rare epilepsy syndromes and familial diseases that cause epileptic seizures, multiple genes must determine the various neuronal functions that alter seizure threshold and predispose to development of symptomatic epilepsy. For most epileptic disorders, it remains to be determined to what degree abnormalities of single genes, or concordance of key overlapping genes, determine the phenotypic expression of any given epileptic condition.

It is also important to underscore the importance of interactions between genetic predisposition and environmental factors in the manifestation of seizures and the particular expression of a given disorder. Lennox[13] was among the first to postulate a continuum between idiopathic and symptomatic epilepsies. He suggested that the occurrence of epileptic seizures derives from the complex interrelation of genetic factors and brain disease (Fig. 4). In any given patient, the *relative* contribution of genetic or acquired pathologic factors determines whether the epilepsy takes the form of an idiopathic disorder or a symptomatic one. Thus, although there is unequivocal evidence of hereditary factors in epilepsy, family studies do not clearly define a *pattern* of inheritance for the common forms of epilepsy. Furthermore, the data suggest a complex hereditary component in *all* forms of epilepsy, localization related and generalized, idiopathic and symptomatic.[17]

Animal models have allowed definition of a growing number of â€œepilepsy genesâ€ and their encoded proteins. Information obtained from animals with single gene mutations producing some aspect of an epileptic phenotype is permitting identification of protein products responsible for the molecular aberrations underlying the abnormal excitability and synchrony responsible for recurrent epileptic seizures. The genes and functional consequences identified in fortuitous mouse models are providing important tools for defining key sites of vulnerability in the brain's carefully regulated control of excitability.[16] Creation of transgenic animal models that overexpress particular genes on the one hand, or â€œknockoutâ€ selected genes on the other, has become a vitally important step in studying candidate genes and understanding the molecular basis of defects that result in epileptic excitability. At the same time, a growing number of specific genes and gene mutations are being isolated and cloned from cases of human epilepsy. A major problem facing investigators is that the population of genes that encode molecules contributing to regulation of cortical excitability through membrane and synaptic functions (and are therefore possible candidate genes in epilepsy) is very large. The complexity issue is further magnified if genes for various second messenger cascades, which indirectly regulate membrane proteins involved in signal transduction, are considered. Another daunting consideration is that genetic studies have identified both animal and human seizure phenotypes in which the genetic mutation and protein product have no previously known association with epileptogenesis (e.g., the LGI1 mutation in autosomal dominant temporal lobe epilepsy with auditory features[11] or cystatin B in Unverricht-Lundborg disease[18]). Finally, epilepsy may result from structural and functional changes occurring as a reaction to a transient genetic defect or a time-limited aberration that is present early in development but may have vanished by the time clinical seizures appear.

So what is the present status of the genetic basis of epilepsy? There can be no doubt about the importance of hereditary factors in epilepsy, in some syndromes more than others. But although specific gene mutations have been identified in a number of rare monogenic forms of idiopathic epilepsy and there is no lack of possible candidate genes for others, a *single* causative genetic mutation will not be found for most cases of epilepsy. Rather, there is considerable evidence that in the majority of cases, the genetic influence on risk of developing epilepsy is conferred by complex â€œsusceptibilityâ€ genes that

interact with other acquired or genetic disturbances, rather than cause epilepsy by themselves.[17] Generalized epilepsy with febrile seizures plus (GEFS+) may reflect this phenomenon.[20,27] For most patients, epilepsy is the consequence of diverse alterations in the complex interactions that occur within neuronal populations and circuits and in the multiple factors that modulate excitability within these circuits, all of which are ultimately under genetic control. And one must not forget that at the clinical level, epilepsy also comprises the neurologic, behavioral, psychological, and social consequences of the molecular, cellular, and network alterations that underlie seizures.

Summary and Conclusions

The answer to the question â€œWhat is epilepsy?â€ is not simple; it is many things at different times, and the patient's reply may be different from that of the physician. Answers are beginning to emerge, however, to both biologic and psychosocial aspects of the question. The diversity with which human epilepsy expresses itself indicates that it is not a unitary problem and that a single solution to any of its many facets is therefore unlikely. Nonetheless, the potential of new investigative tools, especially those of neuroimaging and molecular neurobiology, are providing unparalleled and heretofore unimagined insights into the mechanisms of epilepsy and epilepsy-related brain dysfunction, and are offering greater hope than ever before for prevention, effective treatment, and even cure.

This book was created in the belief that physicians today can be most effective when their practice has a sound scientific basis, and that the results of ongoing basic and clinical research increasingly affect patient management directly. That so much has been achieved is a tribute to past and present investigators; that there is still so much to do is a challenge to future ones. The conquest of epilepsy, as of any human disease, requires a sustained creative effort, with past, present, and future research representing an unbroken continuum of endeavor and achievement.

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Chapter 2

Overview: Epidemiology, Pathology, and Genetics

W. Allen Hauser

Introduction

This is an exciting era for clinicians and investigators interested in the mechanisms of epileptogenesis. Advances in technology during the last three decades have made possible the detailed assessment of intracellular electrophysiologic changes, the determination of membrane responses to neurotransmitters, and even the identification and cloning of specific receptors and channels, some of which are mutated in inherited forms of epilepsy. Through these procedures, knowledge of the fundamental biology underlying cellular excitability and membrane stability has been acquired, sites of action and methods of modifying the function of various neurotransmitters have been determined, and our understanding of the manner in which neural networks enhance or impede seizure occurrence has greatly increased. These exciting developments in the laboratory sometimes result in a tendency to overlook important developments that have occurred within the same time period in the more clinically relevant areas of epidemiology, pathology, and genetics. As one peruses the chapters in this section, it becomes clear that these areas have been equally dynamic in terms of the development of new concepts and ideas. The substantial body of knowledge acquired in epidemiology, pathology, and genetics represents more than an addition to the assumptions that have been considered fact for the last three decades. Indeed, current concepts provided by recent studies in epidemiology and genetics contradict various ideas that were considered well established in the 1970s. The present state of our knowledge suggests various directions for future exploration, not only to students of these observational sciences, but also to those addressing basic neurophysiology.

Epidemiology

Through application of the techniques of descriptive and experimental epidemiology, our understanding of seizures and the epilepsies as these conditions affect humans has been expanded substantially, and this expansion parallels the explosion of discoveries in basic neurobiology. The discipline of epidemiology provides the rigor and broad scope of view that is lacking in clinical series and case reports, which are often viewed with relative skepticism by basic scientists. It is true that the study of real people is complex, but the study of mechanisms at the level of the single cell is equally difficult to integrate into broader concepts.

The development of sophisticated study designs and analytic methods for human investigations is not the only reason for recent advances in knowledge. An emerging classification for seizures and the epilepsies not only provides definitions of seizure type[1] and aggregation of symptoms,[2] but also deals with specifics of etiologic classification and case assignment,[3] thereby enabling the application of uniform definitions across studies. Although complex and in general relatively expensive, the studies of incidence performed during the last three decades have provided knowledge of the true frequency with which seizures and epilepsy occur in the general population and have also informed our understanding of the interpretive complexities involved in the much more readily available studies of prevalence. Although important in determining service needs, studies of prevalence provide no insight regarding the important areas of etiology, prognosis, and prevention. These discrepancies are elucidated in Chapter 5. The consistency of recent epidemiologic studies of incidence in terms of age of individuals affected and distribution of etiology and seizure type is impressive, and the now-well-accepted concept of epilepsy as a condition that affects the elderly as well as the very young, at least in Western countries, is clear.

The patterns of epilepsy in developing countries are explored thoroughly in Chapter 11. These studies are often difficult because of the lack of organized medical systems in many areas, and interpretations are blurred because of the lack of information derived from clinical and laboratory evaluations generally available in Western countries. Fortunately, incidence data from these areas allow a more accurate assessment of frequency and individuals at risk. It is clear that data from more economically developed countries cannot be directly applied to developing areas, but from many standpoints, epidemiologic patterns are similar. Additional clues are usually present that may allow hypotheses to account for any differences to be generated. For example, there is evidence for urbanâ€“rural differences in incidence. In rural areas of underdeveloped countries, many people with epilepsy have never been treated with antiepileptic drugs. Thus, a natural experiment can be undertaken to evaluate the effect of drugs on prognosis. Chapter 4 explores the sociocultural perceptions of epilepsy in such communities and further clarifies the reasons for the social consequences discussed in Chapter 11.

The exploitation of incidence and inception cohorts from industrialized countries (including but not limited to the United States, the United Kingdom, France, Iceland, Sweden, the Netherlands, and Japan) to identify antecedents has been a natural consequence of the identification of incidence cohorts. The results of the systematic evaluation of classic as well as novel risk factors are addressed in Chapter 6. The study of large birth cohorts[8,9] and cohorts with putative risk factors, such as stroke, head injury, infection, and degenerative disease of the nervous system, enable determination of the absolute risk for epilepsy and seizures, provide information regarding the impact of these putative risk factors that is more readily understandable and relevant to clinicians, and may lead to interventions. The role of factors such as adverse prenatal and perinatal events and febrile convulsions is being clarified, and questions regarding the influence of conditions not invariably associated with structural pathology of the brain, such as hypertension, cardiovascular disease, migraine, and such psychiatric disorders as depression and attention-deficit disorder, not only provide new insights into factors that have traditionally been considered

either consequences of epilepsy or only marginally related to epilepsy, but also supply the basis for possible new treatment strategies.[4,5,7]

Another consequence of the identification of incidence cohorts is the ability to determine more precisely the natural history of epilepsy through systematic follow-up of patients. Chapter 7 provides data regarding the prognostic measure closest to the hearts of clinicians, namely seizure control. This review of natural history and prognosis also provides information about other outcomes, including social integration, intellectual function, and comorbid conditions. Contrary to opinions held even into the last decade, epilepsy must now be considered a condition that, in the majority of cases, is relatively benign. Most patients with newly diagnosed epilepsy achieve complete freedom from seizures, and the majority of those who become seizure free can be expected to discontinue antiepileptic drugs without experiencing further seizures. The challenge to clinical investigators now is to clarify those factors associated with good and bad prognoses.

Most studies of cohorts with epilepsy have suggested that individuals with epilepsy are at increased risk for death. The reasons for this apparent increase in mortality, particularly among those with epilepsy of unknown cause, are obscure. In Chapter 10, the proportionate increases in overall mortality and cause-specific mortality are reviewed and compared with data from the general population. The minimally increased mortality in individuals with idiopathic or cryptogenic epilepsy is encouraging, but exploration of the factors that differ between these individuals and the general population is important. Certain conditions affect unique subgroups of people with epilepsy. Sudden death in people with intractable epilepsy is an example of a problem that is not well understood and needs to be addressed further. This specific topic is dealt with in a later section (Chapter 189).

Inducers and precipitants of seizures are discussed in Chapter 9. The distinctions among precipitants (e.g., sleep deprivation), triggers (stimulus-sensitive epilepsies), and modulators (stress, hormonal variation) are reviewed. The need for identification of these factors in developing an individualized approach to people with epilepsy seems clear. Patients with acute symptomatic seizures, reviewed in Chapter 8, represent a unique subset of individuals for whom, unlike people with epilepsy, there is little question regarding cause and effect. These individuals in general would not be expected to have seizures in the absence of a concurrent medical condition or particular set of circumstances. In general, the mortality of people with acute symptomatic seizures is high, and survivors have an increased risk for subsequent epilepsy. The identification of acute symptomatic seizures is important for presenting an accurate and comprehensive picture of seizures and epilepsy in industrially advanced countries and meaningfully assessing prognosis. It also makes possible a comparison with data from developing countries, where survivors of this class of seizures can seldom be distinguished accurately from those with epilepsy.

Pathology

Chapter 12 discusses the failure to identify structural or neurochemical features that might be causes of epilepsy and the difficulty of identifying specific pathology outside the hippocampus that may be associated with clinical seizures. This chapter also reviews the important issue of distinguishing pathologic changes that are the consequences of epileptic seizures from those that may be reasonably considered to be causative of them. Finally, the chapter discusses those brain lesions that are commonly associated with epilepsy, including neoplasms, inflammatory disorders, and brain injuries.

Changes in brain structure that may be attributable to epilepsy are also discussed. Chapter 13 reviews the unique pathology, electrophysiology, and molecular biology of hippocampal sclerosis. Hippocampal sclerosis is a consequence of an initial precipitating injury, which is not age specific and participates in the genesis of temporal lobe epilepsy. Recurrent seizures or status epilepticus modifies the pathology, but whether these are directly causal is controversial.

Our understanding of the neuropathology of epilepsy and epileptogenesis has been greatly modified in recent years. Chapter 14 discusses the role of cortical developmental malformations, which can now be readily identified in clinical practice by magnetic resonance imaging (MRI) brain scans and evaluated pathologically from surgical specimens. Such lesions are responsible for most of the identified structural pathology associated with epilepsy in children, and careful evaluation may provide clues to the timing and mechanisms of epileptogenesis. The single-gene disorders associated with developmental malformations also provide clues to underlying biologic behavior.

Genetics

The identification of a chromosomal locus for some epilepsy syndromes and the elucidation in a growing number of cases of the responsible genes have been important developments and the focus of considerable recent attention. The necessary groundwork for many of these genetic advances is provided by population genetic studies, and Chapter 15 discusses the importance of family studies. This chapter considers the complexities involved in interpreting such studies and stresses such factors as genetic heterogeneity, pleiotropy, and the role of geneâ€“environment interactions. The development of sophisticated mathematical models of inheritance patterns has been made possible by computer techniques.

Additional complexities entailed in family studies of epilepsy are addressed in the review of electroencephalographic (EEG) traits in Chapter 16. Many EEG patterns are clearly inherited, often as a single-gene trait. The relationship of these patterns to clinical epilepsy, however, is elusive. The failure to distinguish between familial aggregations of EEG patterns and familial aggregations of seizures or epilepsy continues to cause confusion and would appear to be an important area for further study.

Chapter 19 discusses the use of family data for patient counseling and the empirical risks for seizure and epilepsy within families. The important concept of presymptomatic detection of those at riskâ€”now possible for only a few of the convulsive disordersâ€”and its implications are also discussed. Although it is unlikely that such detection will play an important role in regard to the most frequently occurring types of epilepsy in the near future, investigators need to address the ethical considerations and approaches to such evaluation.

In a number of single-gene diseases, seizures are included in the constellation of symptomatology. Some of these are reviewed in Chapter 17. The review of the biochemical and structural bases of these syndromes can provide additional understanding of epileptogenic mechanisms. The question of why epilepsy develops in some individuals with a given genotype and not in others is the subject of active investigation.

Chapter 18 discusses genes specific for epilepsy. Those that have been identified most often involve channelopathies as the underlying primary mechanism.[10] In many situations, however, the genetic mechanisms remain obscure in both mice and humans.[6] An integrated effort by epidemiologists, molecular and population geneticists, and clinical and basic

neuroscientists is clearly needed to acquire a full understanding of specific genetic actions.

Summary and Conclusions

The rapidly growing pool of information regarding basic mechanisms of epileptogenesis emanating from modern laboratories has been paralleled by an increase in clinically relevant information. Both the laboratory and clinical approaches are important, and the results provided by each should be integrated to determine future research directions.

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Chapter 3

Epilepsy: Historical Perspectives

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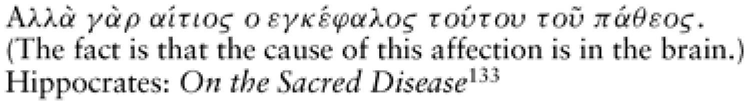
Αλλὰ γὰρ αίτιος ο εγκέφαλος τούτου τοῦ πάθεος.
(The fact is that the cause of this affection is in the brain.)
Hippocrates: *On the Sacred Disease*[133]

(The fact is that the cause of this affection is in the brain.)

Hippocrates: *On the Sacred Disease*[133]

Introduction

Among the diseases that have plagued humans over the centuries, few exhibit the brief, frightening manifestations of an epileptic attack and the relatively quick, seemingly miraculous recovery. Accounts of what may have been epileptic seizures can be found in several ancient scriptural accounts such as reference to the prophet Balaam falling down with the eyes open (Numbers, XXIV, 1) and to King Saul's fits of rage (Samuel I, 18, 10 and 19,9). While *naphal* and *nÃ´phÃªl* were Old Testament and Talmudic terms for epilepsy, Israelites also used *nikpheh* to refer to the disease.[201,204] Similarly, the prohibition against entering the temple by those *possessed by a malevolent power* in the ancient Egyptian text of Esra has also been thought to be a reference to epilepsy.[218] In contrast, the papyrus of Ebers, the oldest Egyptian medical book, has no mention of the condition. Initially, these ancient accounts of falling attacks attributed such â€œseizuresâ€ to an evil entity or punishment inflicted by a god or, later, to some natural cause. Not until Hippocrates was the origin of epilepsy placed in the brain. Temkin, in his book *The Falling Sickness,* describes a battle between rational, scientific thinking and magical beliefs that started with Hippocrates' connection of epilepsy to the brain and continued at least until Jackson's time.[232]

Sakkiku

The oldest medical reference to epilepsy consists of two clay tablets written in Assyrian-Babylonian, which are copies of portions of a comprehensive medical textbook known as *Sakkiku* that dates to the reign of King Adad-apla-iddina (1067â€“1046 BCE). The tablets were discovered during separate archaeologic expeditions in Turkey and Iraq (Fig. 1A, B); they were subsequently translated by Wilson and Reynolds.[248] Although written over 3,000 years ago, they provide remarkably accurate accounts of some characteristic clinical manifestations of the disease.

â€œIt is he again!â€ probably implies an aura. Descriptions of seizure phenomena include generalized convulsions; repetitive occurrence as in status epilepticus; partial motor seizures (â€œhis eyes roll to the side, a lip puckers, and his left hand, leg and trunk jerkâ€); adversive attacks and sensory symptoms, such as auditory hallucinations; and epigastric aura. Gelastic epilepsy was reported for the first time: â€œ[If at the] time of his epilepsy he laughs loudly for a long time, his legs (his hands and legs) being continuously flexed and extended.â€ The impressive astuteness of the clinical observations is matched by a detailed description of various demons that were considered responsible for each symptom. Interestingly, there is no discussion of treatment.

China

Epilepsy was apparently known in ancient China, but no chapter devoted to epilepsy is known to exist in the ancient Chinese medical literature. Lai and Lai[161] presented the information offered on epilepsy in *Huang Di Nei Jing* (The Yellow Emperor's Classic of Internal Medicine), a collective work of Chinese physicians that was compiled between 770 and 221 BC. In the *Ling Shu* volume the term *dian-kuang* was applied to a generalized attack preceded by behavioral alterations. At first, this term was used interchangeably for epilepsy and psychosis, but the two entities were differentiated around 200 BCE in the medical text *Nan Jing.*[161] Epilepsy was generally considered congenital, but other causes including phlegm and insufficiency of blood or kidney were mentioned. Treatment was focused on restoring the balance between the energies, the *yang* from the sun and the *yin* from the moon, or among the five elements *metal, wood, water, fire,* and *earth* that were considered disturbed during disease states.

India

The three ancient Indian medical systems of *Siddha, Ayurveda,* and *Unani* all recognized epilepsy.[226] The most elaborate descriptions are found in the *Ayurveda* (science of life), the oldest known medical system that evolved continuously from 4500 to 1500 BCE. The views on epilepsy are attributed to the physician Atreya (about 900 BCE). The compendium of Ayurvedic medicine known as *Charaka Samhita* (6th century BCE) used the term *apasmara* (*apa*, loss of; *smara*, consciousness or memory) for epilepsy.[19] Visual hallucinations; twitching of the tongue, eyes, and eyebrows; and jerking of the hands and feet accompanied by excessive salivation were some of the symptoms noted, as well as the observation of a patient awakening after the attack as if from sleep.[176] The term *Apasmara poorva roopa* was used for auras that included visual, auditory, and somatic symptoms, as well as behavioral disturbances.

The Ayurvedic system attempted to classify seizures into four types based on the defects in one the three *doshas* (humors). It also recognized external trigger factors such as high fever, internal bleeding, extreme mental agitation, and even excessive sexual intercourse. In addition to the traditional Ayurvedic approach to treat the whole body (physical, mental, and spiritual), cleansing through enemas, purgation, or emesis as well as medicinal preparations based on herbs were employed.

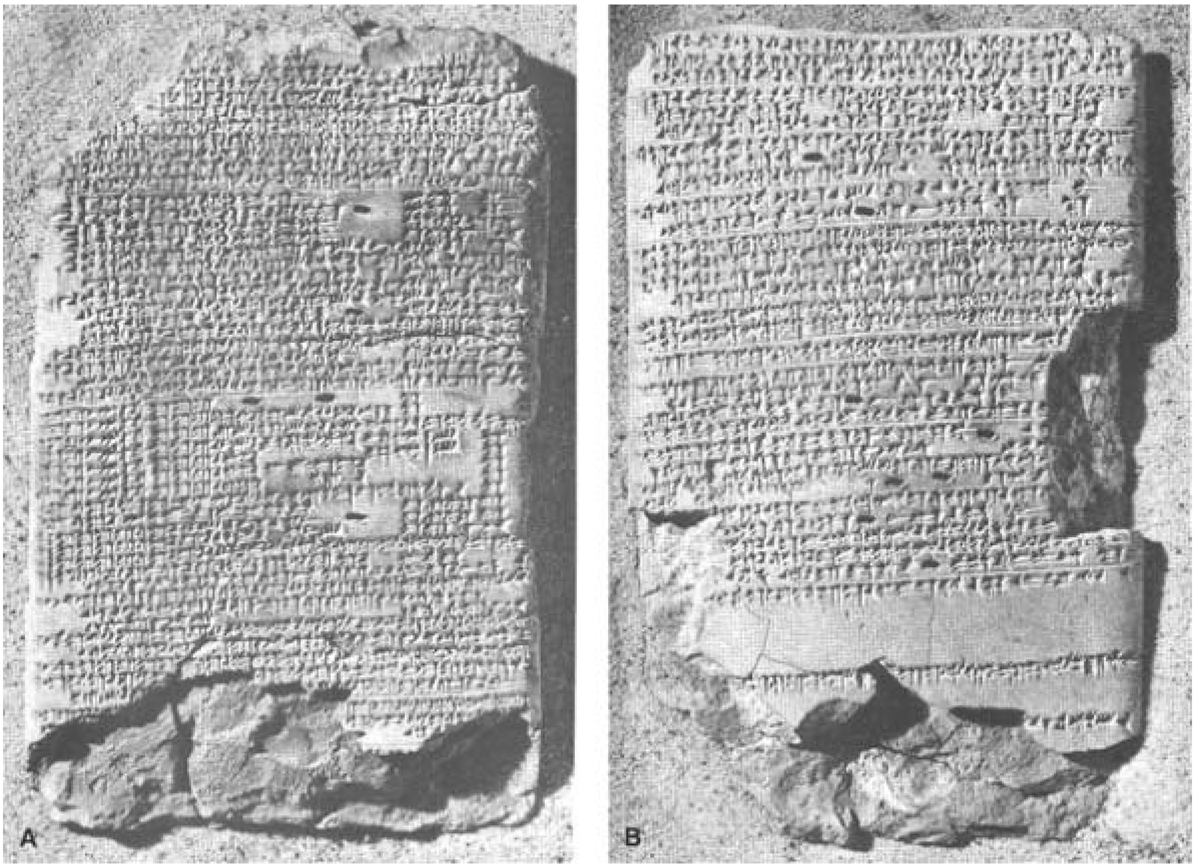

FIGURE 1. Tablet BM 47753, obverse **(A)** and reverse **(B).** (London, The British Museum, reproduced courtesy of the Trustees. Copyright British Museum.)

Hippocrates

The Hippocratic treatise *On the Sacred Disease*[133] is not a medical text; it was apparently written for the layperson. It begins with an attack against common popular superstitions

and all those who labeled epilepsy as â€œsacredâ€ to conceal their ignorance about its cause and justify their fraudulent practices. Contrary to the Babylonian text, the Hippocratic writings challenged the widespread beliefs of the time that epileptic seizures were caused by actions of demons or gods. The Babylonian text described in detail various epileptic symptoms, as caused by a particular demon, while Hippocrates (Fig. 2) attempted to disconnect the physical phenomena from supernatural forces. After a brief description of the generalized epileptic attack, the author recognized the hereditary nature of the disease and the greater frequency with which children were affected.

The fundamental difference, however, between Hippocrates' and other contemporary or older medical explanations (Assyrian, Indian, and Chinese) lies in the unequivocal statement about the origin of the disease: â€œthe factâ€¦that the cause of this affection (epilepsy)â€¦ is in the brain.â€ Hippocrates further recognized that all cognitive functions or emotional manifestations are related to the brain, emphasizing that â€œmen ought to know that from the brain, and from the brain only, arise our pleasures, joys, laughter and jests, as well as our sorrows, pains, grieves and tears. Through it, in particular we think, see, hear and distinguish the ugly from the beautiful, the bad from the good, the pleasant from the unpleasantâ€¦â€ Thus, Hippocrates importantly dissociated epilepsy from religion and magic, arguing forcibly and eloquently that epilepsy was properly a subject not for incantation but for medical investigation and study.

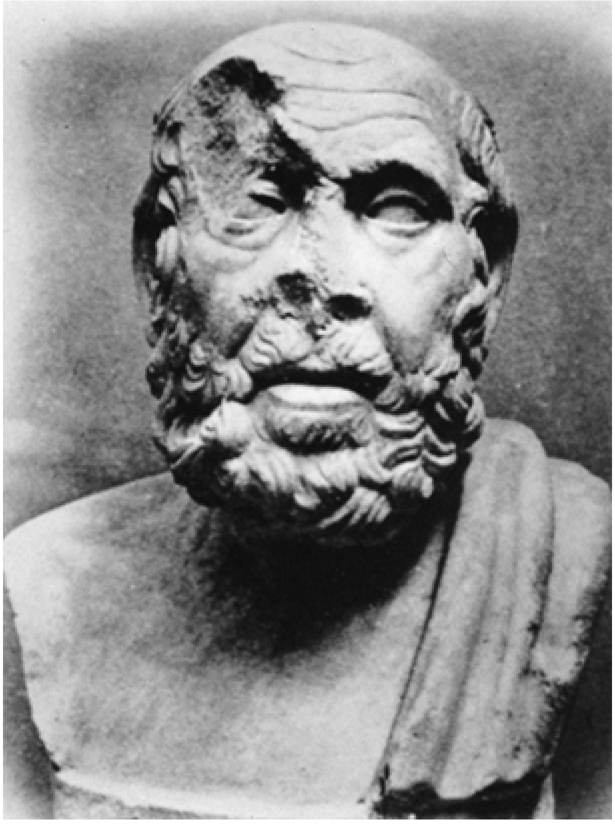

FIGURE 2. Hippocrates (c. 460â€“377 BCE), presumed author of the essay *On The Sacred Disease.* (Museo della Via Ostiense, Rome.)

His explanation that phlegm rushes into the cerebral vessels, preventing air from flowing into the brain, was the first attempt to explain the cause of epilepsy based on a physiologic process that affected the brain. Another important Hippocratic contribution to medicine was the introduction of prognosis. In the essay *On the Sacred Disease*, he commented on

the grave outcome of status epilepticus and the spontaneous remission of epilepsy in children as they mature. In *Wounds of the Head,* Hippocrates for the first time recognized laterality in brain function,[134] when he described trauma to the temple as producing spasm of the contralateral limbs. In his attempt to prove that there was nothing â€œsacredâ€ about epilepsy, Hippocrates stated that there was treatment for the disease, but no specific suggestions occur in his writings.

Post-Hippocratic Hellenistic and Roman Medicine

Attempts to define epilepsy started during Hellenistic times and continued during the time of the Roman Empire. The description of questionable authenticity,[232] attributed to the Alexandrian physician Erasistratus (3rd century BCE), â€œthat epilepsy is a convulsion of the body together with an impairment of the leading functionsâ€ emphasized two cardinal symptoms, convulsions and loss of consciousness. An interesting observation of that time was that sensory stimuli such as bad smell[133] or the sight of whirling wheels[5] were potentially epileptogenic. Greeks and Romans used this knowledge to evaluate the fitness of slaves being sold by having them face the sun while looking through a turning potter's wheel. Intermittent photic stimuli produced by his marching soldiers were reported to have triggered some of Julius Caesar's attacks.

Among those in the 1st and 2nd century CE whose writings have survived are Soranus of Ephesus and Celsus in Rome. Our knowledge of medical attitudes during the post-Hippocratic, pre-Christian era, from the 4th century BCE on, is limited to the information available from Soranus through Caelius Aurelianus.[47] None of Soranus' works in Greek have survived. It is believed, however, that the 5th-century CE physician, Caelius Aurelianus, preserved them in Latin translation. These writings contain an extensive list of symptoms that could precede epileptic attacks, including excessive sexual excitement accompanied by sexual acts (possibly seizures of frontal lobe origin), and they also discuss psychic causes, such as fright and anger, as precipitating factors. The seriousness of repetitive attacks was noted, and physicians were advised to warn relatives about their severity and lack of treatment to avoid possible repercussions after a patient's death. Consumption of wine was associated with seizures, and even drunkenness of the wet nurse was implicated as a cause of epileptic seizures in children. Soranus criticized Hippocrates' statement about the existence of treatment, when none was mentioned in the *Sacred Disease*. Soranus also attacked contemporary practices like Diocles' use of various substances in enemas, or the administration of animal or human excrements by Praxagoras, Asclepiades, and Serapion. Patients whose attacks had a predictable pattern of recurrence were bled in anticipation and purged with emetics (white hellebore) or cathartics (scammony or black hellebore). This type of â€œcatharsisâ€ was popular by Greek and Roman physicians from 300 BCE to 100 CE.[47]

Celsus in the *Comitialis, Book III, 23*[54] described both generalized convulsions and what were probably atonic and myoclonic attacks. He noted that epilepsy was more common among men and children but added that onset in childhood was associated with a better prognosis. He never discussed possible causes but advised dietary measures and avoidance of cold, heat, and wine, and opposed the practice of administering blood of dead gladiators.

In the 2nd century CE, the two main contributors to epileptology were Galen of Pergamon and Aretaeus of Cappadocia. Unlike Hippocrates, whose description of seizures in the essay *On the Sacred Disease* emphasized only major symptoms, Aretaeus provided a detailed narrative of generalized convulsions[6]:

â€œThe man lies unresponsive with the arms in spasm and the legs stiffened and then shaking; the head is twisted, either bent to the sternum or backwards as if pulled violently by the hair; the mouth is open with the tongue protruding at risk of being injured or cut; the eyes are turned upwards, while the lids blink; if they are not closed, the white of the eye shows; the face is distorted and changed, because the eyebrows frown or are pulled to the temples; the lips either protrude or are pulled to the side and shake; the initial redness of the face is replaced by paleness; the blood vessels of the neck dilate; the pulses are initially fast and then slow; towards the end there is loss of urine and feces or in some men ejaculation, while froth comes from the mouth.â€

Further recognizing the variety with which epilepsy could express itself, he stated: â€œEpilepsy is an illness of various shapes and horrible.â€ Without using the term, he described a visual auraâ€"â€œred or black lights or both together appear in arcs before the eyes, similar to the rainbowâ€â€"and gave a detailed list of auditory (ringing in the ears), olfactory (foul smell), and other sensory symptoms. Like Hippocrates, Aretaeus observed the greater frequency with which seizures occurred in children as compared to adults, as well as the spontaneous remission in old age: â€œIf it passes the peak of life, it co-ages and dies out.â€ Todd paralysis, first observed by Hippocrates, was termed â€œparetic handâ€ by Aretaeus.

Galen's descriptions of epileptic seizures[43,99,224,231] are scattered throughout his works and include â€œloss of consciousness and the leading functions,â€¦sudden fall,â€¦the presence of spasms, or sometimes (loss of consciousness) in the absence of them,â€¦secretion of froth from the mouth,â€¦loss of urine,â€¦ejaculation,â€¦changes in pulse rate.â€ He apparently did not restrict the diagnosis of epilepsy to generalized convulsions as he wrote â€œif there is not only convulsion, but also interruption of the leading functions, then this is called epilepsy.â€ Galen differentiated types of seizures based on their clinical features and the anatomic part involved in the aura. His classification of seizures as primary (originating in the brain) or sympathetic (arising either from the stomach or from other parts of the body) was the first and influenced the approach to epilepsy for centuries. Galen also noted the more frequent occurrence in childhood, a relation between seizures and the menstrual cycle, and the precipitation of seizures by prolonged starvation. Galen is credited with introducing the term *aura* (in Greek, sea breeze), which he described in a young man who reported the feeling of a â€œcool auraâ€ that started in his foot, marched upward, and heralded the onset of the attack.[100]

Treatment in the Hellenistic and Roman times was guided by the theories of three schools: The dogmaticâ€”Galen and Aretaeus (based on the pathology of the disease), the empiricâ€”Serapion, and the methodistâ€”Soranus, Themison, and Celsus. What was common to all three schools was the importance of dietary regimens, exercise, sleep, and â€œcatharsisâ€ through emetics, enemas, or bleeding. Various techniques of bleeding and cauterization of the arteries of the scalp, as well as trephination, were used. Both methodists, such as Theodorus Priscianus, and dogmatists, such as Aretaeus, recommended these methods. Soranus, however, and later the Galenist Alexander of Tralles, warned against them, â€œwhich to many become a punishment rather than a cure.â€[231] The use of drugs for epilepsy probably preceded the dietetic treatments that required time and money, and thus were affordable only by the rich. It is, therefore, not surprising that a large number of drugs were developed. Dioscurides (2nd century CE) in his *Materia Medica*[76] lists 45 antiepileptic substances. Temkin[231] divided them into three categories: 18 had no connection to magic and corresponded to contemporary pathologic theories; at least 13 were definitely based on superstition; and 14 had no apparent magical connotation, but the reason for their use was questionable.

Byzantine Medicine

The transfer of the capital of the Empire from Rome to Constantinople in 330 CE marked the transition from the Roman to the Byzantine Empire. The corresponding religious transformation led to significant changes in medical attitudes. While hospitals were built particularly for the care of the poor, religious views changed society's attitude toward medicine. In the case of epilepsy, the description of the miraculous cure of the â€œlunaticâ€ boy by Jesus in Matthew's Gospel (17:14â€“18) heralded a return to pre-Hippocratic beliefs of demonic possession. Origen, one of the early Fathers of the Church, stated, â€œPhysicians physiologize, as they do not consider it [epilepsy] to be a dirty spirit, but a somatic symptomâ€¦ This disease should be considered to be the influence of a dirty, speechless and evil spirit.â€[190] Supporters of this view included St. Athanasius, John Chrysostom, and Hieronymus in the West.[174] The â€œlunar influenceâ€ on epileptics, which was considered by ancient physicians to be the result of humoral changes of the brain, was explained as the devil's attempt to defame God by defaming his creation. In the Eastern Church it was not until several centuries later that the Alexandrine Stefanus of Athens and the 11th century Patriarch Photios in his *Amphilochia* settled this argument in favor of a naturalistic explanation.[173] Among physicians, however, a â€œbiologicâ€ approach to epilepsy based on the Hippocratic and Galenic tradition was retained throughout the thousand years of the Byzantine Empire. The Encyclopedists Oribasius, Aetius Amidenus, Alexander of Tralles, and Paul of Aegina preserved and organized the works of earlier Greek and Roman physicians.[83] Support for epilepsy as a natural disease is indicated by the comments of Leo (9th century CE) that â€œepilepsy occurs from obstruction of the ventricles of the brainâ€; Psellos (11th century CE) that â€œepilepsy is a spasm obstructing the exits for the psychic spirit. It may start at another part, like the hand or the foot as an aura that rises to the brainâ€; and Actuarius (14th century CE) that it is â€œa diseaseâ€¦due to a fine dyscrasia of the brain or the presence of bilious humor in its ventricles.â€[83,174]

Oribasius, physician to the last pagan emperor Julian the Apostate, attempted to challenge religious views on the influence of the moon on epilepsy by arguing â€œas the sunâ€¦warms the bodies, so the moon rather moistens themâ€¦ It makes the brains wetterâ€¦and triggers epilepsy.â€[83,189] Aetius Amidenus (6th century CE), chief physician to emperor Justinian, interpreted the fear that preceded the attacks: â€œthe so called terror is not a demon but intention and preface to epilepsy.â€[3,83] Influenced by Galen, Alexander of Tralles (6th century CE) classified epilepsy into â€œprimary, originating in the brain, one originating from the stomach and a third from other parts of the body, which subsequently reaches the brain.â€ He considered loss of consciousness as the main symptom of the attack but included complex partial seizures as â€œthey get wearied on the head, confused, hard of hearing and sense slowly before the attack.â€ He should be credited with the first description of reading epilepsy: â€œI observed a man falling while reading who sensed the attack from a cold aura starting in the tarsus and rising up to the brain.â€[4] Paulus Aegineta (7th century CE) defined epilepsy as â€œa spasm of the whole body with damage of all princely functions.â€ He explained the prodromal symptoms as â€œan unintentional tension of the soul [that] precedes the epileptic [attack], and dysthymia and oblivion of the future and tumultuous dream visions and headache and continuous head fullness, and irritability with paleness of the face and disorderly movements of the tongue.â€ Paulus noted the possible lethality of the attacks in childhood but also the occasional spontaneous remission after puberty. He recommended abstinence from alcohol â€œâ€¦particularly the old and heavy winesâ€ and sexual intercourse, because orgasm and epilepsy were considered equivalent.[194] Treatment of epilepsy included the use of various drugs and again â€œcatharsisâ€ through emetics, enemas, and venesection.[83]

Contributions from Islamic Medicine

The influence of earlier Persian, Indian, and particularly Greek (notably Hippocrates and Galen) practices set the foundations for Islamic medicine. A reference of a god telling Zoroaster to prohibit epileptics from offering sacrifices in his honor is probably the only mention of epilepsy from the ancient Persian religion. The translation of Greek words resulted in new Persian-Arabic medical terms such as *abilibsyÃ¢* (usually referring to the psychic symptoms) or *Sar* (connoting falling sickness).[240] Islamic medicine, like Byzantine, was strongly influenced by Galenic beliefs. The two main Islamic physicians who mostly influenced the West were Rhazes (865â€“925 CE) and Avicenna (980â€“1037 CE). Their opinions were based on personal observations of epileptic phenomena. Avicenna in his *Canon* deviated from Galenic opinions by not considering convulsions as essential. He defined epilepsy as a sickness that prevented animation of the members, the operation of the senses, movement, and standing erect.[243] Although he invoked the Galenic concept of ventricular obstruction, he differed in concluding that the lower (fourth) ventricle, and not the anterior ventricles, was the area of obstruction by an unhealthy humor, usually phlegm. He considered two possible mechanisms, one originating in the brain and the other in the nerves, proposing that a putrid vapor from the distal part rose to affect the brain. Rhazes used bleeding, emetics, and purgatives, while Avicenna used several traditional herbal and other pharmacologic agents.

Medieval Europe

The Middle Ages started earlier in the Western Roman world than in the East. Fragments of the works of Soranus and Caelius Aurelianus provided concise descriptions of epilepsy. Cassius Felix (5th century CE) recapitulated the old opinions that epilepsy was divided in two types: One accompanied by convulsions, the other by sleep. Like Galen, Cassius Felix believed that seizures originated in the brain due to influence of a melancholic humor or phlegm, the stomach, or any lower part of the body.[50] He used â€œepilepsyâ€ to refer to the idiopathic type originating in the brain, whereas â€œanalepsyâ€ was the type â€œascendingâ€ from the stomach, and â€œcataplexyâ€ the type arising from other parts. Cataplexy, however, was used differently in ancient writings to describe a condition with fever and mental obtundation.[11]

The translation of classical Greek and Arabic texts into Latin and the establishment of medical studies influenced the beliefs of medieval scholastic medicine. Based on older traditions and their own observations, physicians were quite familiar with convulsive epilepsy as well as some of the other forms. Bernard of Goddon (14th century CE)[165] described brief episodes of loss of consciousness and staring spells. The classification of epileptic symptoms was a matter of considerable discussion and description, with the main question centered on how to find the original lesion. Platearius (12th century CE) distinguished between â€œmajor and minor epilepsyâ€ in a way reminiscent of the later distinction between â€œgrand mal and petit malâ€ epilepsy.[231] Another division involved â€œtrueâ€ (Galen's â€œidiopathicâ€) versus â€œspuriousâ€ (originating from other parts) types of epilepsy. Arnold of Villanova (14th century CE) blamed phlegm for the â€œtrueâ€ and black bile mixed with phlegm for â€œspuriousâ€ epilepsy.[243] Gilbertus Anglicus[231] agreed on phlegm as the cause of â€œtrueâ€ epilepsy, but he suggested other humors as the cause of the â€œspuriousâ€ form. John of Gaddesden[164] wrote of three forms: Minor or true (due to obstruction of the arteries to the brain), medium or truer (due to obstruction of the nerves), and major or truest epilepsy (due to obstruction of the ventricles). Significant disagreements existed among medieval authors about the type of humors involved in different forms of epilepsy based on arbitrary or even imaginary signs such as the viscosity of the saliva or the color of the urine. Medieval physicians recognized trauma as a cause of epilepsy probably based on the Hippocratic observation in the *Wounds of the Head.* AlÄ« ibn AbbÄs and Constantinus Africanus associated seizures with fractures of the skull and compression of the brain. Both early Arab and European physicians emphasized the hereditary nature of epilepsy as noted in the essay *On the Sacred Disease*.

During medieval times, Western European, Byzantine Greek, and Arab physicians did not significantly extend the boundaries of our understanding of epilepsy. At a time, however, of prevailing beliefs in falling evil and demonic possession, they deserve recognition for maintaining the tradition of understanding disease in terms of natural causes.[231]

Medieval China

Classification of seizures was published in Chinese medical books in the 7th century CE based on the Chinese philosophy of medicine and the belief of â€œyang and yinâ€ energy and disturbances of their balance. Nowhere was the brain mentioned as being involved in epilepsy. The goal of the treatment was to expel the wind and the phlegm, bring down the fever, activate blood circulation, and energize the kidneys and spleen. The therapy included herbs, acupuncture, *mai yao* (injection of herbs into acupuncture points), *mai xien* (inserting a piece of goat intestine into the acupuncture point), and massage.[161]

Pre-Colombian America

Although three major cultures, Inca, Aztec, and Mayan, flourished across the Atlantic, little documentation survived the colonization. The Inca term for epilepsy in the Quechua language (*sonko-nanay*) was rather erroneously translated by the Spanish chroniclers as â€œmal de corazon.â€ The term *sonko* means the center of the human body and mind located in the chest and upper abdomen and not heart (corazon), and *nanay* means disease. Variations of this term were used to describe different symptoms: *songo-piti* (pulling the heart) and *songo-chiriray* (getting frozen) for grand mal seizures, *nahuin-ampin* (darkening of vision) and *upayacurin* (behavioral arrest) for partial simple seizures, and *upakundiya* (*upa*, fool; *kontiyak*, volcanic) for complex seizures.[46] While the Incas considered epilepsy to be divine punishment, epileptics were considered closer to the supernatural forces. On the other hand, the Aztecs believed epilepsy was related to the influence of evil goddess Cihuapipiltin; children were not allowed to go out on the days of her descent to earth. As in the Greco-Roman world, slaves with epilepsy could not be sold.[84]

The American cultures used religious-magical means as well as the administration of products from plants, animals, or minerals to treat epilepsy. Both Aztecs and Incas employed removal of sin by washing and confession. The ritual of Bacabs (evil deities) was practiced by the Mayans, who invoked the help of good deities against them.[180] Constituents of magical means, such as hair from a corpse, a stag's horn, a dog's bile, or the brain of an ox or weasel, were part of the Aztec remedies. A large number of plants were used for epilepsy on an empirical basis but, unfortunately, none of them was included in a study that evaluated medicinal plants from Central and South America.[191]

The Renaissance

During the Renaissance the beliefs in supernatural or physical causes continued in their separate ways. Physicians believed that bilateral tonicâ€“clonic seizures, often associated with falling to the ground, were the sole manifestation of epilepsy. Nonetheless, there were occasional suggestions that epilepsy might include less dramatic events. Antonio Benivieni[15] described an obvious complex partial seizure without either falling or secondary convulsing and made it clear that he considered this a form of epilepsy that was probably unfamiliar to his contemporaries. In 1470, the Chinese author Fang Xian[161] wrote of olfactory auras and visual hallucinations preceding loss of consciousness without specifying that either falling or bilateral convulsing necessarily followed.

Paracelsus (1493â€“1541) discussed the falling sickness in his posthumously published *Diseases That Deprive Man of His Reason* that was written between 1520 and 1525.[242] He defined five varieties of epilepsy, beginning in the brain, liver, heart, intestine, and limbs, thus extending Galen's three. He tended to think in terms of alchemical processes and perceived resemblances between seizures and earthquakes. In the falling sickness the â€œvital spiritsâ€ of the body, like an earthquake, suddenly boiled up at the site of the apparent origin of the attack and then spread to other parts. Once they reached the brain, consciousness was lost. Such a concept, mounting to sudden spontaneous overactivity in some organs body, though highly fanciful, accurately conveyed the potential violence of the epileptic process. It reflected his belief that epilepsy had a natural rather than a supernatural origin. His disciple, van Helmont (1570â€“1644), further proposed that nearly all seizures originated in the stomach, where the local *Archeus* (the soul, or ruler of that organ) had become injured and angry.[192] This idea was subsequently abandoned, but Paracelsus' concept that seizures arose from abrupt overactivity in some parts of the body was adopted, refined, andâ€”a century laterâ€”restricted to the brain by Willis.

Paracelsus proposed new chemical remedies for epilepsy, many of them of mineral origin, including his allegedly efficacious green vitriolic oil. The chemical nature of these treatments remains obscure largely because the source material cannot be determined and, therefore, they cannot be reproduced. Both their claimed mechanisms of action and alleged efficacy appear highly speculative.

The Scientific Revolution

During the scientific revolution of the 16th and 17th centuries, some present-day authors have identified, though not fully convincingly, what could be regarded as the first descriptions of certain epileptic syndromes, such as benign Rolandic epilepsy by Martinus Rolandus in 1597,[238] focal motor (jacksonian) seizures by the philosopher John Locke in 1676,[194] and juvenile myoclonic epilepsy by Thomas Willis in 1667.[79]

Thomas Willis (1621â€“1675) was the main contributor to epileptology during this period. The evolution of his thinking about the subject can be traced in two separate publications: *Thomas Willis' Oxford Lectures*[75] preserved by Lower and Locke, who kept notes of his lectures between 1661 and 1664 that were published three centuries later, and *Pathologie Cerebri.*[247] Willis' account of hysteria contained descriptions of what would appear to be epileptic manifestations, including the paroxysmal events that befell his â€œvery noble lady of a most curious shape,â€ who may have suffered from juvenile myoclonic epilepsy. It is likely that generations of authors, perhaps going back to Plato himself, mistakenly attributed instances of a rising abdominal discomfort to hysteria, when in reality these

were the epigastric auras of temporal lobe epilepsy. Willis at least realized that hysteria could occur in men and concluded that it arose in the brain and not in the uterus. At autopsy his â€œvery noble ladyâ€ whose seizures were â€œhystericalâ€ had a macroscopically normal uterus, but Willis believed there were abnormalities in her brain.

Willis tended to diagnose epilepsy only when the sufferer was afflicted with â€œinsensibility, and horrid convulsions, and also with foam at the mouth.â€ He regarded preliminary symptoms, such as fits of â€œvertigo or giddinessâ€ associated with confusion, as precursors to, rather than as manifestations of, the seizure. His theories explain epilepsy as movement of the â€œanimal spirits,â€ an intangible entity whose existence had been invoked in the time of Galen as the psychic pneuma,[207] and which had been employed ever since to explain nervous system activity. In the period between 1661 and 1664, Willis suggested that epileptic seizures arose from contraction of meninges that squeezed the â€œanimal spiritsâ€ from the brain into the peripheral nerves, producing widespread muscle contractions. Later in his Oxford lectures, he spoke of a chemically induced boiling of these â€œanimal spiritsâ€ causing the postulated meningeal contraction. At that time he also suggested that the sensory aura produced the actual seizure through the centripetal movement of these spirits that started the aura and also activated a central epileptic explosive mechanism in the brain. By 1667, Willis abandoned the notion of meningeal contractions because he recognized that this was an anatomic improbability due to the dura's firm attachment to the skull. In his final explanation of seizure causation, he concluded that the decisive event was an explosion of animal spirits in the center of the brain. This explosion in the brain caused loss of consciousness, and its force set up a sequential series of chemically initiated explosions in the â€œanimal spiritsâ€ radiating centrifugally. When the explosions reached the origin of the peripheral nerves, it produced a tugging on the nerves that resulted in abrupt muscle contractions. Willis continued to believe that centripetal movement of â€œanimal spiritsâ€ associated with the experience of an epileptic aura could trigger an explosion in the center of the brain, producing a convulsive seizure. Alternatively, he also thought that local explosions near the origin of a peripheral nerve could be the cause of the aura itself, suggesting that a sensory aura might be of central and not peripheral origin.

Willis produced a â€œcomprehensiveâ€ hypothesis of the origin of epileptic seizures based on speculations of an intangible entity, â€œthe animal spirits,â€ whose physical existence had already been questioned by his contemporaries, Harvey,[127] Stensen,[228] and Glisson.[116] Ingenious though it was, Willis' line of thought was not developed further by his successors, though it contained the seeds of ideas that reappeared in the latter half of the 19th century. Through his theories of epilepsy causation, Willis reasoned his way to a rational approach to treating and preventing seizures. In practice, however, this approach justified the use of the multiple conventional antiepileptic remedies of his day, whose application in practice he described in detail in the *Pathologie Cerebri.*

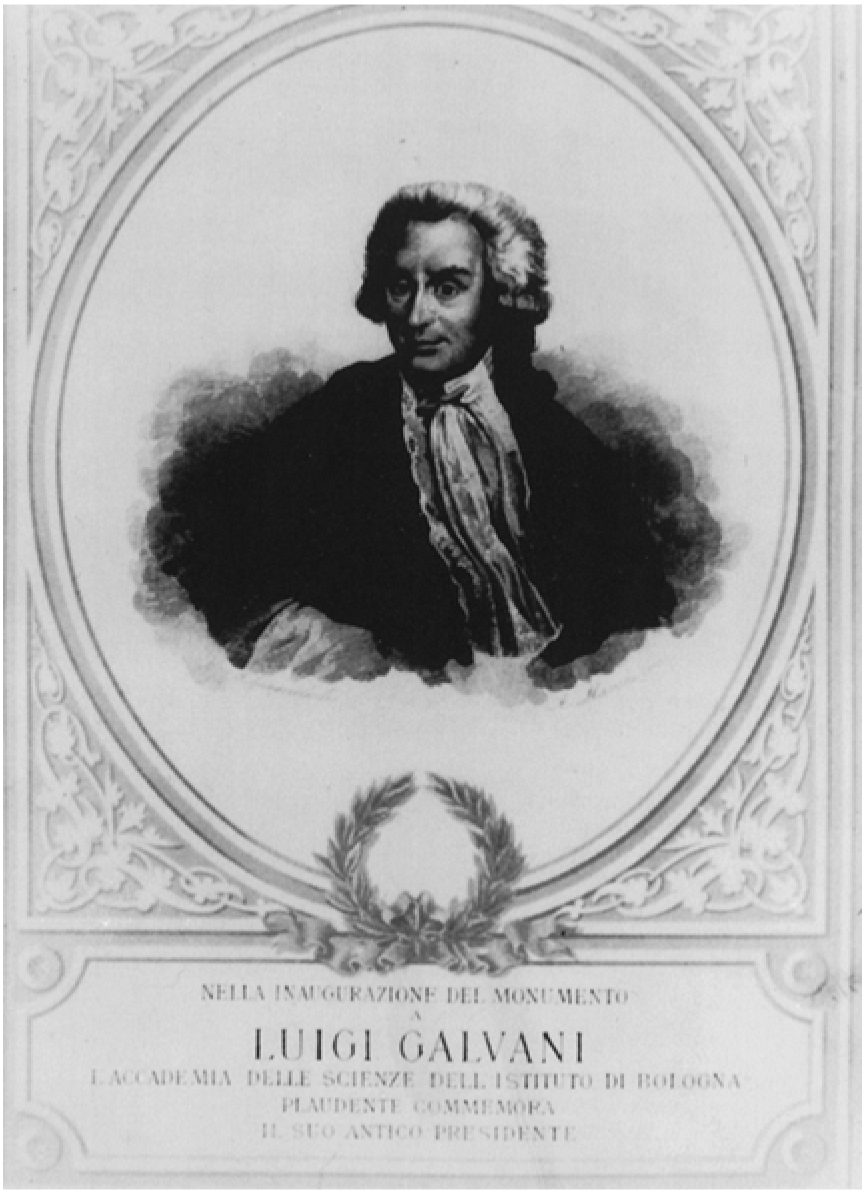
NELLA INAUGURAZIONE DEL MONUMENTO
A
LUIGI GALVANI
L'ACCADEMIA DELLE SCIENZE DELL'ISTITUTO DI BOLOGNA
PLAUDENTE COMMEMORA
IL SUO ANTICO PRESIDENTE

FIGURE 3. Luigi Galvani (1737â€"1798), the discoverer of intrinsic animal electricity. This is an engraving made for the celebration of the 200th anniversary of his birth in 1937. (Courtesy of the National Library of Medicine, Bethesda, MD.)

The 18th Century

The period of the Enlightenment saw a gradual replacement of the notion of the â€œanimal spiritsâ€ as the explanation for neural activity, although it was still employed as late as 1770 by Tissot and 1779 by Morgagni. Concepts such as Cullen's brain â€œenergyâ€[70] or Haller's â€œirritabilityâ€[125] began to be used as the mechanism of neural function. A year after Galvani's discovery of electricity in 1780, Fontana began to write of the â€œelectrical fluidâ€ in nervous tissue.[36] However, the concept of an electrical component was not to be applied to ideas about epilepsy for some time.

During the 18th century, diagnosis of epilepsy generally required the presence of both loss of consciousness and bilateral convulsive activity. Cheyne,[56] however, seemed to imply that falling (presumably from loss of consciousness) might suffice for the diagnosis. Tissot[232] provided a reasonably convincing description of what Calmeil[48] later called absence seizures: â€œthese â€˜petitsâ€™ being accompanied at times by grande accÃ©s,â€ while Cullen in 1789[70] recognized the existence of partial convulsions involving only a localized part of the body with preservation of consciousness that distinguished them from epilepsy: â€œI might treat of particular convulsions, which are to be distinguished from epilepsy by their being more partial: That is, affecting certain parts of the body only; and by their not being attended with a loss of sense, nor ending in such a comatose state as epilepsy always does.â€ Heberden in his *Commentaries,*[129] perhaps following Tissot, wrote of brief minor depressions of consciousness in relation to epilepsy, as well as the familiar bilateral tonicâ€“clonic seizures. By then the clinical spectrum of epilepsy was beginning to widen. It was generally accepted that the origin of epilepsy was located in the brain, but there was little consideration of more precise localization. Boerhaave[27] wrote of â€œtoo great an action of the brainâ€ as the basis of the epileptic seizure, while Cullen[70] attributed it to an excess of brain energy, confessing that he was unable to be more specific. Curiously, Tissot,[232] in his thorough review of the earlier literature on epilepsy, reverted to Willis' notion that brain contraction expelled the â€œanimal spiritsâ€ and caused seizures.

The 18th century saw the development of interest in the pathologic basis of epilepsy. Morgagni,[183] using his experience in neuropathology, suggested that epileptic seizures arose from structural abnormalities of the brain such as hardening (gliosis) or abscess, which diverted the â€œanimal spiritsâ€ from their normal pathways through the brain substance or released an irritant that acted on these spirits to produce seizures. The growing interest in the neuropathologic basis of epilepsy was also reflected in attempts to classify the epilepsies according to the pathology.[27,70] Various structural pathologies as well as inheritance, strong emotions, and speculative chemical abnormalities were included in the causes. The details of these classifications are less important than the fact that etiology and structural pathology had become crucial in the attempt to understand the pathogenesis of epilepsy. Outside of the medical circles, however, beliefs of supernatural influences still persisted.

Gradually some of the more extreme, if not outrageous, remedies of the past began to disappear during the 18th century. Measures such as venesection continued to be used, and the antiepileptic pharmacopoeia became increasingly botanical in nature. Tissot reviewed these treatments[232] and commended valerian more highly than any of its numerous alternatives. Indeed, in appropriate types of seizures and at sufficient dosage, valerian may have had some chemical basis for genuine antiepileptic efficacy.[80]

Biologic Electricity

Luigi Galvani (Fig. 3) created the foundation for the field of electrophysiology and, ultimately, electroencephalography through his monumental discovery of animal electricity in 1791.[101] These fruits of his work would revolutionize the study of epilepsy in the 20th century. Galvani demonstrated that electrical charges produced by friction and stored in Leyden glass jars caused muscle contractions, whether the charge was applied to the muscle or the nerve (Fig. 4). For many years, Galvani's seminal observations had little scientific impact, in spite of confirmation of the phenomenon by Alessandro Volta (Fig. 5) and others. In fact, it was Volta, inventor of the first storage battery, who was largely responsible for the 50-year delay in the general acceptance of animal electricity because of his misinterpretation of Galvani's experimental findings. Volta incorrectly and tenaciously ascribed all of Galvani's evidence of intrinsic nerve transmission to direct muscle stimulation from a battery effect due to the inadvertent use of two dissimilar metals.[241] Galvani, who opposed Napoleon, lost his position at the University of Bologna and the Institute of Sciences, while Volta, a supporter of Napoleon, received many honors, and by outliving Galvani by three decades, used his prestige to continue to deny the validity of his countryman's work. It was not until 1937, 200 years after Galvani's birth, that Bologna's Institute of Sciences celebrated his life and republished his treatise.

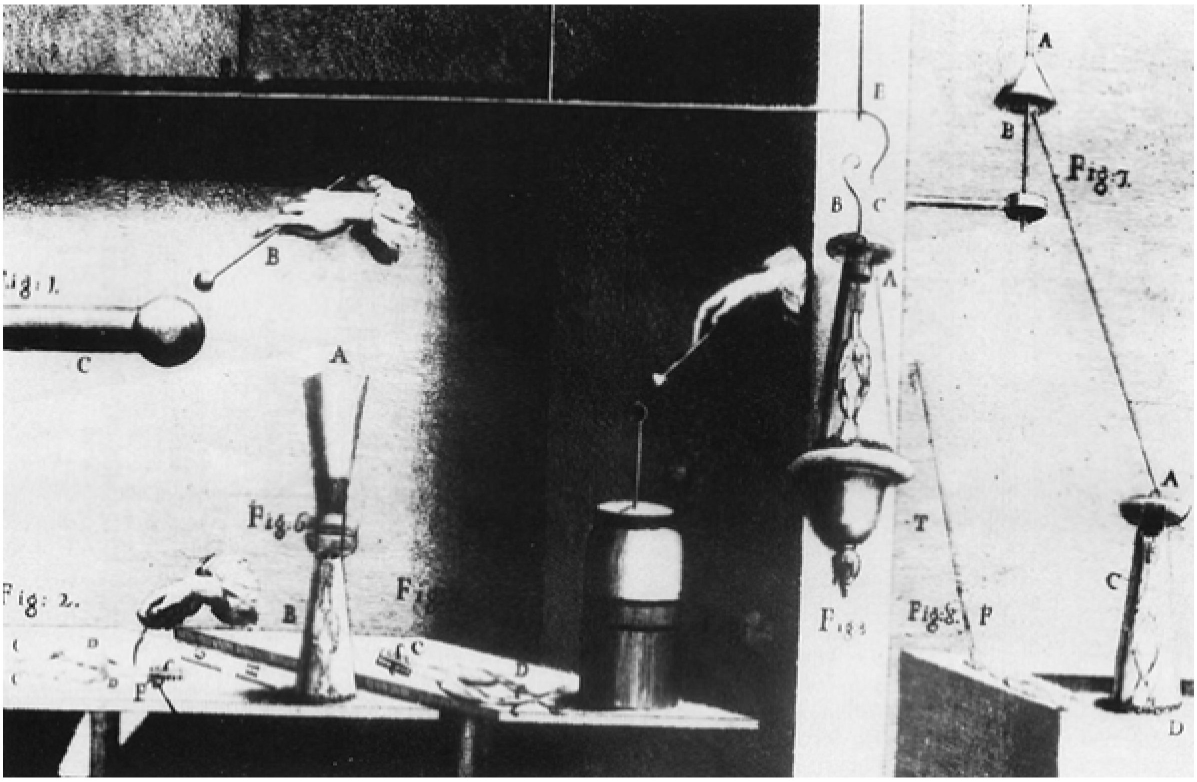
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FIGURE 4. Galvani's laboratory in 1792. Sketch of three frog nerve-muscle preparations in insulated flasks, a Leyden jar, two hand-held metal wands to transfer charges, and metal wire suspended from the ceiling to collect and carry charge to the frog. (Courtesy of the National Library of Medicine, Bethesda, MD.)

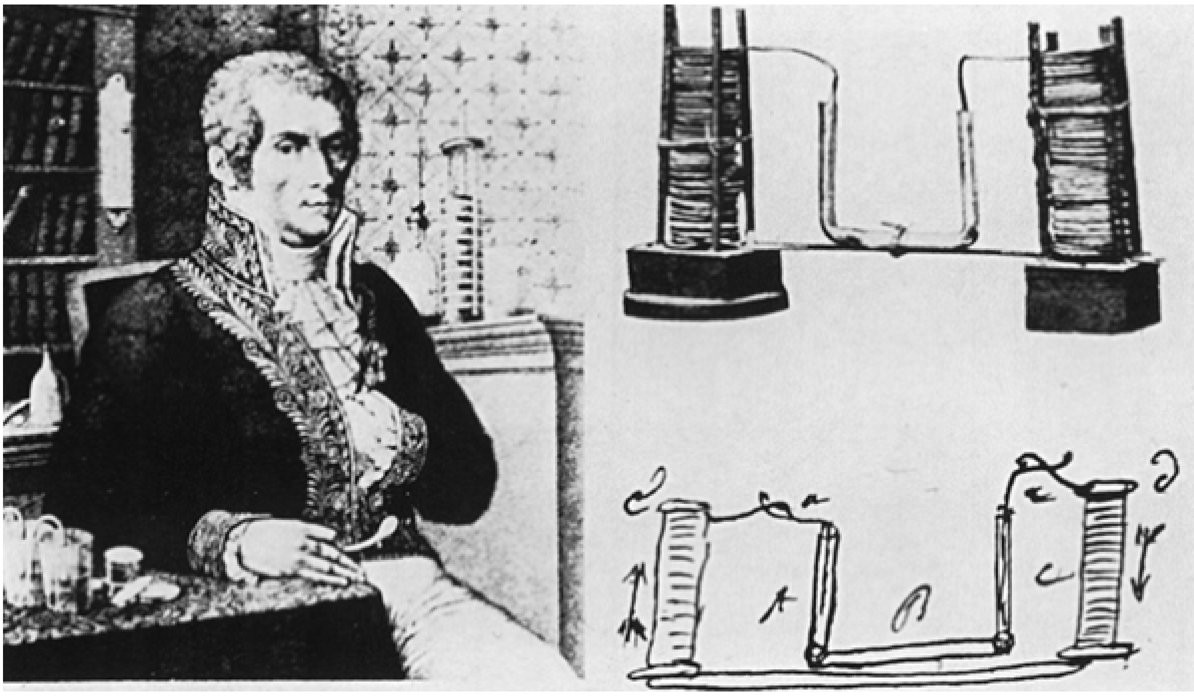


FIGURE 5. Alessandro Volta (1745â€“1827) was an admirer of, and honored by, Napoleon, whose gesture he seems to have caught. **Right:** Original piles (batteries) invented by Volta (*above*) and his own sketch (*below*) of the experiment showing the pile making water alkaline in one arm and acid in the other. (From Brazier MAB. *A History of Neurophysiology in the 17th and 18th Centuries.* New York: Raven Press; 1984, with permission.)

The 19th Century

During the 19th century the acceptance of various clinical manifestations of epilepsy broadened considerably. New theories of the mechanisms underlying the origin of epileptic seizures emerged and provided the basis for today's evolving concepts of epileptogenesis. Supernatural ideas about the origin of epilepsy finally began to fade. Sieveking,[225] however, still cited and interpreted Moreau's statistical study in 1854, on perhaps not entirely justifiable grounds, as finally debunking the ancient belief in a lunar influence on epileptic seizures. And importantly, the first effective antiepileptic drug treatment appeared, almost incidentally, if not frankly, accidentally.

Epileptic Phenomena

In his 1823 review of previous knowledge concerning epilepsy, Cooke[67] continued to insist that loss of consciousness and bilateral tonicâ€“clonic seizures were required for diagnosis. From that time on, however, most authors, while still requiring transient loss of consciousness, have not emphasized bilateral convulsive behavior as a prerequisite for the diagnosis of epilepsy.[39,87,124,205,216,234] Thus, at the end of the 19th century, Beevor[14] could write that â€œepilepsy is the name given to sudden loss of consciousness with or without convulsions.â€

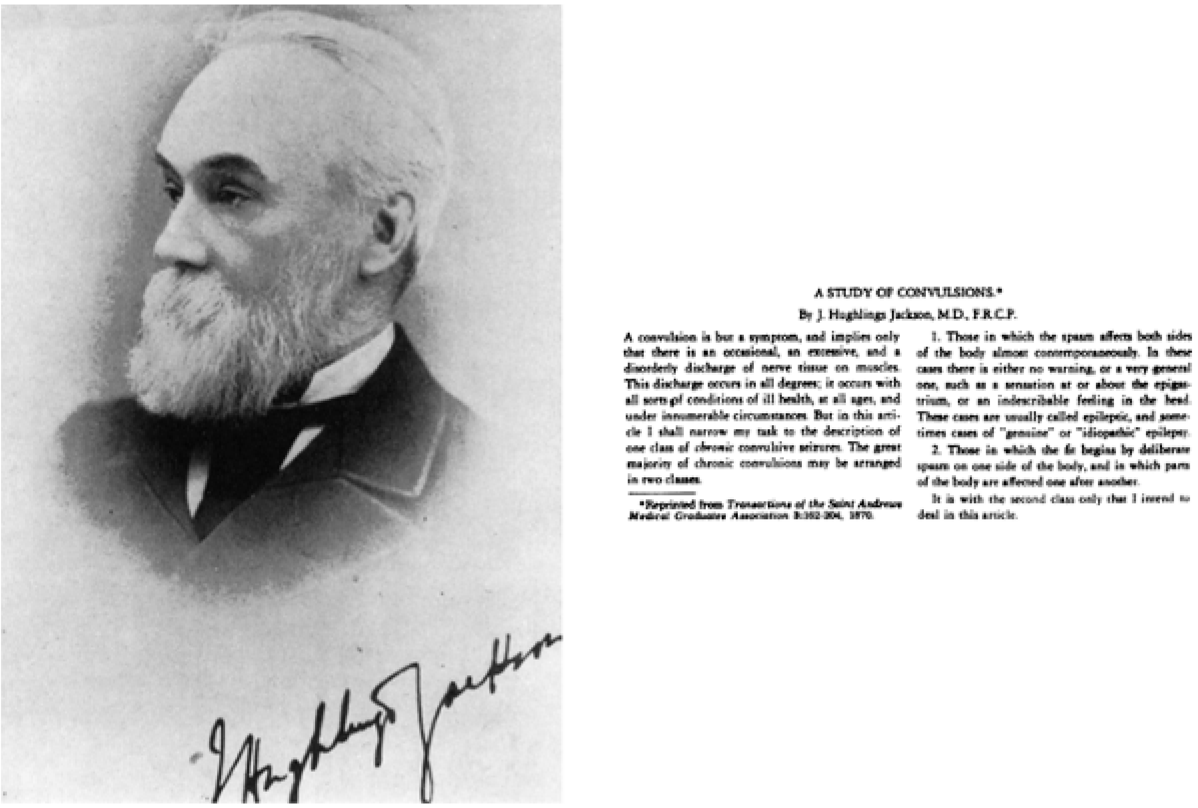
This change in diagnostic requirements triggered an increased interest in the minor manifestations of epilepsy such as the brief losses of consciousness that Tissot[232] had described, termed by Calmeil[48] as â€œabsencesâ€ and by Esquirol[87] as â€œpetit mal.â€ Prichard[205] had included these, along with superficially similar episodes characterized by a prodrome of which the patient was aware (i.e., simple partial seizures evolving into complex partial ones) in his subtype of â€œleiothymia,â€ a term that soon disappeared from use. He also described a tetanic type of epilepsy, probably the same or similar to present-day tonic seizures, and wrote of â€œpartial epilepsyâ€ largely in Cullen's[70] sense of epileptic manifestations appearing only in a part of the body without alteration of consciousness. New epileptic syndromes were described: First Bravais[35] and later Bright[39] and Todd[234] reported focal motor seizures, before Jackson made them the subject of his special interest, and which Charcot later[55] associated with Jackson's name. Todd, and before him Bright, noted the temporary â€œepileptic hemiplegiaâ€ after such focal seizures and which later became known as *Todd paralysis*. West[245] described infantile spasms, sadly, in his own infant son, while Herpin[132] provided a detailed account of juvenile myoclonic epilepsy but did not regard it as a separate entity within the â€œcommotionsâ€ (i.e., myoclonic seizures). An increasing wealth of detail about the prodromes or auras became available in the literature, and Esquirol[87] recognized their occasional occurrence as isolated events without other manifestations of epilepsy. Herpin[132] considered the aura to be not a warning but rather the actual start of the seizure: â€œla premiÃ¨re manifestation de l'attaque.â€

At the same time that a diverse and expanded repertoire of epileptic seizures was being recognized, there was a growing effort to define and limit those phenomena that could legitimately be included under the rubric of epilepsy. This latter development arose from an increasing attempt to classify diseases on an etiologic basis. At the onset of the 19th century, Maisonneuve[174] and later Prichard[205] divided epilepsy into idiopathic and sympathetic types, with the latter further subdivided into gastric, intestinal, hysterical, and hypochondriacal subtypes, based on the part of the body where the first seizure manifestation was experienced. Esquirol[87] added a third type, a symptomatic form of epilepsy due to disease outside the central nervous system.

Delasiauve[73] utilized the same three main categories, but his idiopathic epilepsy was restricted to cases of cerebral origin without brain pathology, while his symptomatic type was characterized by detectable cerebral pathology. Shortly thereafter, Reynolds,[213] in his 1861 monograph on *Epilepsy: Its Symptoms, Treatment, and Relation to Other Chronic Convulsive Diseases*, defined an entity of â€œepilepsy proper,â€ which meant cases without obvious brain pathology. Seizures due to detectable cerebral, or extracerebral, pathology were termed *epileptiform* and not *epileptic*. Unfortunately, defining epilepsy as a disease whose cause was the absence of a detectable cause was virtually guaranteed not to have enduring validity as knowledge advanced. Two decades later, Gowers[121] extended this concept of epilepsy, almost surreptitiously, when he used the term *epilepsy* to refer to all seizures of cerebral origin without â€œactiveâ€ pathology. Contemporaneously, new hypotheses of epileptic mechanisms emerged. In the first third of the century, seizures were commonly ascribed to brain hyperemia or venous congestion.[67,87,205] while Mansford[175] postulated that cerebral plethora caused charged electrical fluid to accumulate in the brain until it could no longer be contained, thus triggering a brain discharge and an epileptic seizure. Romberg[216] accepted both brain plethora and brain anemia as being capable of producing seizures. As an outcome of his study of the neural mechanisms underlying the reflex arc, Hall[123] postulated that excessive activity in the afferent limb of the reflex arc (eccentric epilepsy) or in the central element (centric epilepsy) produced the excessive motor response comprising the convulsion. He proposed that the initial convulsive tightening of the muscles of the neck and larynx obstructed the cerebral venous return, causing brain congestion that led to loss of consciousness. Hall's interpretation did not account for epileptic auras and meant that bilateral convulsive movements began before consciousness was altered, contrary to the usual sequence of events in a seizure. Brown-SÃ©quard[45] overcame these difficulties by postulating that excessive afferent activity, which was sometimes also responsible for the aura, in the central nervous system ascended to structures as high as the medulla oblongata. Upon reaching the medulla it produced a discharge at the medullary vasomotor center, which caused immediate cerebral arterial spasm leading to loss of consciousness. Reynolds[213] combined elements of both Hall's and Brown-SÃ©quard's ideas, proposing that Brown-SÃ©quard's mechanisms initiated the seizure, while Hall's mechanism of venous obstruction mechanism perpetuated the unconscious state with the resultant hypercapnia from cessation of breathing converting the initial tonic convulsion into clonic jerking.

Gradually these postulated mechanisms had become acceptable in explaining convulsive seizures and placed the central events in the medulla oblongata. Van Sweiten' data[239] also settled on the medulla as the critical brain region involved in epileptogenesis, while Sauvages[219] and Nothnagel[187] had claimed the production of convulsions in animals by stimulating the medulla. Kussmaul and Tenner[160] reported convulsions in experimental animals after rapidly exsanguinating them and through sections at different levels of the central nervous system showed that an intact brainstem in continuity with the spinal cord was essential for such anoxic convulsions to occur.

In his animal experiments, Todd (1809â€“1860)[234] found that electrical stimulation of the spinal cord or the medulla produced tonic spasm of muscles and stimulation of the mesencephalon produced clonic convulsions, but stimulation of the cerebral hemispheres led only to slight facial twitching. On this basis he postulated that epileptic seizures arose in the cerebral hemispheres much like a discharge of static electricity from a condenser. If the discharge was restricted to the hemispheres, consciousness was lost but no motor symptoms occurred. If, however, the discharge reached the midbrain, clonic convulsive movements occurred in addition to loss of consciousness, but if it extended into the medulla and spinal cord, tonic components followed. Thus, Todd accounted for all of the elements of the convulsive epileptic seizure, except for the aura. He did not address epileptic unconsciousness without motor accompaniment. His ideas, however, did not attract a following among his contemporaries.



A STUDY OF CONVULSIONS.*

By J. Hughlings Jackson, M.D., F.R.C.P.

A convulsion is but a symptom, and implies only that there is an occasional, an excessive, and a disorderly discharge of nerve tissue on muscles. This discharge occurs in all degrees; it occurs with all sorts of conditions of ill health, at all ages, and under innumerable circumstances. But in this article I shall narrow my task to the description of one class of *chronic* convulsive seizures. The great majority of chronic convulsions may be arranged in two classes.

1. Those in which the spasm affects both sides of the body almost contemporaneously. In these cases there is either no warning, or a very general one, such as a sensation at or about the epigastrium, or an indescribable feeling in the head. These cases are usually called epileptic, and sometimes cases of "genuine" or "idiopathic" epilepsy.

2. Those in which the fit begins by deliberate spasm on one side of the body, and in which parts of the body are affected one after another.

It is with the second class only that I intend to deal in this article.

*Reprinted from *Transactions of the Saint Andrews Medical Graduates Association* 3:162-204, 1870.

FIGURE 6. Left: John Hughlings Jackson (1835â€“1911), the neurologist who was physician to the London Hospital and the National Hospital, Queen Square. (Courtesy of the Archivist of the Royal London Hospital Trust.) **Right:** Jackson's publication in 1870, giving an accurate clinical-physiologic definition of epilepsy in the first paragraph and, in the next, a basic classification of seizures into generalized and focal (partial) that continues in use today. (From *Trans Saint Andrews Grad Assoc* 1870;3:162â€“204.)

In contrast to all of these concepts that were based on brain overactivity, Radcliffe[208] attempted to explain epileptic seizures as a manifestation of reduced neural activity. His ideas received a courteous reception, but were otherwise ignored and never developed further. Thus, by 1860, plausible explanations were available for the mechanisms underlying most aspects of epileptic phenomena, and a consensus had developed that the medulla oblongata was the critical brain region in the production of epileptic seizures. That state of knowledge formed the background against which John Hughlings Jackson's work over the next 40 years was carried out.

John Hughlings Jackson (1835â€“1911)

In the 1860s, Jackson[68] (Fig. 6) set out to analyze and then interpret the mechanisms underlying epileptic seizures. His numerous writings were compiled by Taylor.[230] Jackson, who initially attempted to study bilateral tonicâ€“clonic seizures, soon realized that these were too widespread, developed too rapidly to be followed reliably by the observer, and the patient, being unconscious, could contribute little information. He therefore decided to first try to study focal motor seizures, as events were more localized and easier to follow, and the patient could often describe the experience. Such seizures were sometimes followed by temporary hemiplegia similar to that due to lesions in the internal capsule rather than the brainstem. Spenser's psychology had prepared Jackson for the idea of localization of function within the cerebral hemisphere, although it had not yet been demonstrated. By the mid-1860s, Jackson had named focal motor seizures â€œcorpus striatum epilepsy,â€ as he had perceived that they probably began in neuronal cell bodies in the neighboring striatal gray matter, which had become functionally overactive.

By 1870, after considering Broca's[40,41,42] reports of aphasia from lesions in the posterior-inferior left frontal convolution, Jackson observed that temporary dysphasia occasionally coexisted with Todd paralysis after focal motor seizures involving the right face, and the association of focal motor seizures sometimes with syphilitic nodules in the meninges over the contralateral middle cerebral artery. Jackson[142] concluded that focal motor seizures involving the face or hand probably originated in the lower part of the perirolandic cortex of the opposite cerebral hemisphere. This radical departure from the conventional interpretation of the site of epileptogenesis received independent support within a comparatively short period from Fritsch and Hitzig's experimental studies of cortical stimulation and ablation in animals.[98] This work provided convincing evidence of localized representation of motor function within the cerebral cortex. During the next few years Jackson's concept of epilepsy became increasingly wide ranging:

â€œEpilepsy is not one particular grouping of symptoms occurring occasionally; it is a name for any sort of nervous symptom or group of symptoms occurring occasionally from local dischargeâ€¦ A paroxysm of â€˜subjectiveâ€™ sensation of smell is an epilepsy as much as is a paroxysm of convulsion; each is a result of sudden local discharge of grey matter.â€

Jackson's idea that all convulsions and epileptic manifestations were symptoms was at first criticized on the grounds that he had not studied â€œepilepsy proper,â€ but merely one variety of epileptiform seizure. His reaction to this criticism consisted of convoluted and rather repetitive writing, in which he continued to draw a distinction between focal motor seizures and â€œepilepsy properâ€ to make his ideas more acceptable to his peers, in spite of his private belief that they were manifestations of epilepsy and even occasionally saying so.

In the 1870s experimental physiologists, such as Ferrier,[90,91,92] began to map out aspects of localization of function in the animal cerebral cortex. At the same time Jackson started to pay attention to the minor, often paroxysmal, expressions of human epilepsy. He used the knowledge of the site of pathology in conjunction with the experimental animal findings to locate sites for the representation of various functions within the human cerebral cortex. He accumulated data suggesting that the foot was represented in the upper part of the perirolandic cortex,[145] and that the site responsible for auditory hallucinations and the so-called dreamy state or â€œintellectual auraâ€ was in the anterior part of the temporal lobe.[146,147] Jackson related visual hallucinations to the posterior half of the cerebral hemisphere without being able to more precisely localize the site of their origin. He deduced that consciousness depended on intact function of an extensive part of the prefrontal cortex of at least one hemisphere.[143] He attempted to explain the cortical origin of epileptic auras using these localizations and the belief that an epileptic discharge arose from a sudden release (at times he used the word â€œexplosionâ€) of local brain energy. If the localized discharge achieved sufficient intensity and extent of spread, the aura would progress to unconsciousness and even convulsing. Extensive involvement of the prefrontal cortex by the discharge caused loss of consciousness, while involvement

of the cortical motor areas produced contralateral convulsing. Jackson had originally thought[144] that unilateral motor cortex discharges might finally activate the uncrossed pyramidal pathway, and thus convert contralateral convulsing into bilateral convulsing. Later, following Horsley's experiments,[140] Jackson accepted the idea that the discharge must cross the corpus callosum and other brain commissures for bilateral convulsive movements to occur.

Thus, Jackson finally conceived, for the first time in the history of medicine, a single mechanism capable of explaining the full spectrum of epileptic phenomena: The aura, isolated or subsequent unconsciousness, contralateral and bilateral convulsive behavior. His concept is the basis of the modern understanding of epileptogenesis. Jackson's complete view was in place by 1890, after some 30 years of sustained intellectual endeavor. His ideas did not include primary generalized epilepsy, but in his time, before electroencephalography (EEG) became available, there was no way of knowing that such an entity existed.

Jackson's writing is often difficult to follow. He is often repetitive, using different wordings in different places for the same idea, leaving the reader uncertain if some subtle new insight was intended. It is sometimes further complicated by consequences of Jackson's stated intention to abandon his comprehensive early vision of epilepsy and restrict the word to its then contemporary conventional meaning. Thus, there is some justification for the view that Jackson's thought is more easily followed by reading his younger colleague

William Gowers.

William Gowers (1845â€"1915)

Gowers was probably the most important of Jackson's colleagues. In his monograph *Epilepsy and Other Chronic Convulsive Disorders,*[121] he discussed epileptogenesis. He used a reductionist approach weighing carefully clinicopathologic and experimental data to conclude the following:

â€œThe conclusion, then, is that all the phenomena of the fits of idiopathic epilepsy may be explained by a discharge of gray matter; that the hypothesis of vascular spasm is as unneeded as it is unproved; that there are no facts to warrant seeking the seat of the disease elsewhere than in the gray matter in which the discharge commences; that this is in most cases within the cerebral hemispheres, probably often in the cerebral cortex, although in some instances lower down even in the medulla oblongata; that epilepsy is thus a disease of the gray matter, and has not any uniform seat.â€

Unlike Jackson, who concentrated in one type, Gowers approached epilepsy as a whole. His interest actually included other disorders including hysterical attacks, which he tried to distinguish from real epileptic fits. In epilepsy the attacks tended to occur randomly and the limb movements did not resemble the pattern of voluntary movements, unlike the â€œquasi-purposive aspect and coordinated characterâ€ of the hysterical attacks. He preferred the terms â€œhysteroidâ€ and â€œco-ordinated convulsionsâ€ to avoid Charcot's confusing term â€œhystero-epilepsy.â€ In addressing the nature of Jackson's discharging lesion, Gowers used the term â€œsudden explosive discharge,â€ essentially the same words that caused Wills to be ridiculed two centuries before. He postulated the storage of latent energy in each neuron and a resistance to prevent its appropriate release. He also conceived that the frequent breaking of this resistance could produce repeated seizures as well as increase the nutritive capacity of nerve cells, leading to a facilitation of seizures.

Gower's espousal of Jackson's ideas, his critical consideration of alternative theories, and his concise statement in direct English made Jackson's ideas increasingly acceptable. Gowers almost inevitably tended to soften and harmonize Jackson's more extreme views when writing of them. To perceive, however, Gowers' book largely as a â€œtranslationâ€ of Jackson's thought is to ignore the significance of Gowers' original insights into matters such as the effect of â€œresistance,â€ a notion similar to that of present-day inhibition, in explaining epileptic phenomena.

Therapeutics

In addition to the more adequate interpretation of epileptic seizure mechanisms, in the first half of the 19th century an increasing disillusionment with the inadequacy of the available antiepileptic therapies had developed. Those who believed seizures arose from cerebral congestion continued to employ venesection and other measures to divert blood from the brain. Hall,[122] quite independent of his studies on epilepsy, had already indicated the potential hazards of diminishing the blood volume too quickly. The ancient method of applying a ligature proximal to the site of the appearance of an aura in a limb, itself a comparatively uncommon event, continued to have some demonstrable efficacy. Hall,[124] believing that laryngeal spasm contributed to the loss of consciousness during seizures, advocated and employed tracheostomy, but this approach never achieved any widespread use. Recommendations for certain remedies continued (e.g., oil of turpentine[205] and zinc oxide[131]). Esquirol[87] and Sieveking[225] made scathing comments about the vast array of ineffective antiepileptic drugs that had accumulated over the years: â€œIn fact, there is not a substance in the materia medica, there is scarcely a substance in the world, capable of passing through the gullet of man, that has not at one time or other enjoyed a reputation of being an anti-epileptic.â€[225]

FIGURE 7. Richard Caton (1842â€"1926), the discoverer of spontaneous electrical activity of the brain (EEG) and evoked potentials. (From Brazier MAB. *A History of Neurophysiology in the 17th and 18th Centuries.* New York: Raven Press; 1984, with permission.)

Into this scene of therapeutic destitute, one evening in 1857, came a totally unheralded event. At a meeting of the London Medico-Chirurgical Society following Sieveking's presentation of 52 patients with epilepsy, Sir Charles Locock, the president of the Society, remarked that he had treated 15 women with hysterical (i.e., menstrual) epilepsy with potassium bromide, and had stopped the seizures in all but one. Since potassium bromide could cause temporary impotence in males, he thought it might have useful effects in menstruating women. His observation was never published, but it was recorded in the reports of the meeting published in the *Lancet* and the *Medical Times and Gazette*. Radcliffe's[208] experience with it, however, in â€œhystericalâ€ epilepsy was even more encouraging, and he began to use it in all cases of epilepsy with generally good results. Gradually the use of potassium bromide became widespread, particularly after Wilks[246] rediscovered it. He had sought an alternative to potassium iodide in treating syphilis and, in ignorance of Locock's report, tried potassium bromide. He soon realized that its efficacy in controlling seizures due to cerebral syphilis was due to specific antiepileptic properties. Thus, the first reasonably effective antiepileptic agent came into use. By 1881 Gowers, after listing the numerous recommend antiepileptic therapies, wrote of potassium bromide:

â€œAnd the present generation has witnessed an advance in the treatment of these diseases equaled in perhaps no other branch of therapeutics. Thanks to the influence of one drug and its combinations, hundreds of epileptics have been cured, and thousands are leading useful lives who would otherwise have been incapacitated by the disease.â€[121]

In 1886 Horsley, a pioneering English neurosurgeon, performed the first operations intended to relieve focal motor epilepsy by removing the probable focus of seizure in the human cerebral cortex after locating its expected site by electrical stimulation. He continued this approach for some years,[137,138,139] as it seemed to provide at least short-term benefit in seizure control.

Spontaneous Electricity from the Animal Brain

In the mid-19th century, a renewed interest in the intrinsic electrical activity of muscle and nerve was sparked by Du Bois-Raymond's book *Untersuchungen Ã¼ber Thierische Elektricitat* (Investigations on Animal Electricity).[77] In the second volume, an illustrated description of recording muscle potentials from the surface of the skin of a man established the basis for clinical electromyography.

Inspired by this book, Caton (Fig. 7) at the Royal Infirmary School of Medicine in Liverpool used similar nonpolarizable electrodes and a mirror galvanometer to extend the work on animal nerve and muscle.[51] Based on Fritsch and Hitzig's demonstration of motor responses following electrical stimulation of various cortical areas in the dog,[98] Caton hypothesized that reversely peripheral stimulation might evoke local electrical responses in the brain. In his historic paper,[52] Caton was the first to demonstrate evoked cortical sensory responses in animals. Of much greater importance was that Caton is the first person to observe the continuous spontaneous electrical activity of the brain. He described â€œthe existence of electrical currentsâ€¦of the grey matterâ€ and noted that â€œfeeble currents of varying direction pass through the multiplier [amplifier] when the electrodes are placed on two points of the external surface, or one electrode on the grey matter, and one the surface of the skull.â€[53]

Caton's achievements are better appreciated considering the experimental conditions under which he worked, without electric lights, vacuum tubes, or electronic amplifiers, more than 25 years before the invention of the string galvanometer by Einthoven. The Thomson mirror galvanometer that Caton used had a high-frequency response of only 6 Hz. A stationary â€œoxyhydrogen lampâ€ shone on the galvanometer mirror whose tiny movements reflected the light upon â€œa distant wall with a graduated scale some eight or nine feet in length.â€ The distance between the mirror and its image on the wall was his amplifier (multiplier). There was no photographic method to capture and hold the fleeting data once it had disappeared from the wall. A candle flame was used for photic stimulation. More than 50 years, however, would elapse before the first report of spontaneous electrical activity from the human brain was recorded.

The 20th Century

By the end of the 19th century, there had been a marked quickening of the social conscience regarding care for the chronically ill and disabled. Indeed, for almost four decades, institutional care for people with refractory epilepsy had been gradually recognized as the duty of society. This in turn had generated organizations dedicated to establishing and running institutions thought appropriate for the care of disabled individuals. There was also increased interest in these institutions and in the latter half of the 19th century the Hospital for the Epileptic and Paralysed, Queen Square, London, and the Colony-Farm, Bethel, near Bielefeld in Germany, were founded.

Yet, it was early recognized that the clinical study of epilepsy in some hospitals and institutions had built-in logistical problems: Even in the National Hospital, Queen Square, an early hospital bylaw explicitly forbade bed occupation by long-term chronic patients, thus litigating against the study of epilepsy.[136] Indeed, Muskens,[186] who had studied there, complained that the Hospital for the Epileptic and Paralysed had â€œâ€¦ a tendency to pay too much attention to paralytic conditions.â€ The large number of colonies or colony farms for patients with refractory epilepsy provided ample opportunity for clinical studies.

With regard to the pathophysiologic understanding of the epilepsies, Jackson had elevated the cerebral cortex to play a prime role in the physiology of epilepsy, using the work of Fritsch and Hitzig[98] and Ferrier's ground-breaking findings summarized in *The Functions of the Brain.*[92] While Jackson's hypothesis that â€œcoarse pathologyâ€ such as tumors or infarcts was the cause of focal epilepsies, no such pathology could be seen in postmortem studies of many patients with epilepsy. Lacking such evidence of focal pathology, other lines of investigation focused on systemic-metabolic factors thought to excite the brain were pursued. Rapid advances in laboratory medicine were employed to analyze various relationships between chemical and metabolic parameters in the blood, cerebrospinal fluid, and urine. By the turn of the century, an air of cautious optimism pervaded medical thinking on epilepsy as expressed by Robertson[215]:

â€œThe subject of the pathology of epilepsy occupies at the moment a position of extreme interestâ€¦ For long it has almost completely baffled every sort of scientific investigation to discover its essential nature. But during the past five or six years investigations have been carried out whichâ€¦have so far advanced our knowledge of the subject that today we stand within measurable distance of one of the greatest triumphs of medical science. Already there is good reason to believe that this triumph will not be long delayed.â€

The modern reader would think that Robertson was referring to Hughlings Jackson's work. In fact, his opinion was based on laboratory data that were collected in an attempt to discover putative systemic metabolic causes of seizures. Indeed, enlightenment as to the true cortical pathology of seizure generation lay at least half a century and two world wars away, awaiting the development of undreamt of novel technologies.

The Organization of the Epilepsy Movement

Various organizations, both lay and professional, played an important role in improving the management of epileptics. Not only were the needs of the sufferers and their families recognized at last, but also professional attention was concentrated on their problems. The social burden that had been borne in silence by families either at home or in mental asylums was going to be hopefully relieved by the introduction of â€œcoloniesâ€ or â€œcolony farmsâ€ that offered a more caring and peaceful alternative. In Britain, the Charity Organisations Committee Report *The Epileptic and Crippled Child and Adult* in 1893, a historical landmark in social awareness, provided a clear picture of the needs of epileptics and the grave lack of available resources at that time to meet these needs. Early surveys of similar facilities in other countries were published in the early issues of *Epilepsia*.

The establishment of the International League Against Epilepsy (ILAE) in 1909 marked a major initiative worldwide to organize professional interest in epilepsy but also address scientific and social aspects. During the inaugural meeting in 1909, in Budapest, under the newly elected president, Prof A. Tamburini, ILAE adopted *Epilepsia* as the League's official periodical and outlined the aims of the organization. It continued as a quarterly periodical until 1915, when World War I forced its closure. The first volumes are a rich historical source of the status of epileptology and the international activity of the professional epilepsy movement in the first decade of the 20th century. The political chaos after World War I, combined with the Great Depression of 1929, delayed any resumption of the ILAE activity until the mid-1930s. Coinciding with the second International Neurology Congress in London in 1935, a number of interested physicians met at Lingfield Colony, Surrey, to reactivate the League.

The ILAE once again undertook an international survey of the services and facilities available in various countries. In volume 1 of the second series of *Epilepsia*, considerable data had been assembled before World War II prevented members from corresponding with its editor. Since 1941 the journal has been published in the United States to preserve continuity throughout the war years without interruption. The ILAE was also preserved and resumed its active role after the war, constituting the central spindle of the professional world epilepsy movement ever since. In 1961, the International Bureau for Epilepsy was established.

Two Damaging Diversions for Early 20th-century Epileptology

Over the centuries, the clinical problems of epilepsy have always attracted wayward theories about its cause and treatment. The early years of the 20th century saw the flowering of two such theories, both of which caused considerable difficulties for sufferers and retarded development of the management and the perception of epilepsy both in medical circles and the community.

The Autointoxication Theory of Epilepsy

The lack of neuropathologic evidence to underpin Jackson's concept of the role of the cortex in epilepsy had led even him to consider other causative factors such as a vascular mechanism.[142] For years, the concept of seizure generation by blood-borne chemical agents had been entertained in various forms,[79] and the knowledge of the epileptogenic proclivity of disorders like uremia and poisons such as lead helped bolster this concept.[233,234] The last decades of the 19th century and the first three decades of the 20th century saw the expenditure of an enormous amount of time and money in the quest for this unknown trigger in patients without obvious â€œcoarse pathology.â€ Bolten[28] and Turner[236] give a comprehensive summary of all the avenues hitherto explored. Indeed, the amassing of these data inspired the already mentioned Robertson's[215] sanguine statement at the century's turn.

Epilepsy was conceived by some as a metabolic disease, as presented by Munson at the National Association Meeting in 1906. Further, some senior neurologists in England held the concept of a â€œmetabolic dyscrasiaâ€ underpinning seizure causation until late into the second decade of the 20th century.[64] By the third decade of the 20th century, however, informed opinion was beginning to endow the brain and the brain alone with seizure generation and discharge.[135]

A byproduct of the autointoxication theory was the idea that the gastrointestinal tract was involved in seizures. From the time of Galen, involvement of the stomach in â€œanaleptic seizuresâ€ had held a prominent place in concepts of epilepsy. Based on Bouchard's writings,[30] autointoxication was also reckoned as the basis for epilepsy. This concept focused attention on the gut, this time as a site of stasis and bacterial growth or fermentation resulting in toxin production. The resultant absorption of bacteria or toxins, or both, was thought to give rise to the chemical triggers for seizure production, and accordingly strategies aimed at prevention of this cycle of events could possibly have a significant role in epilepsy management. Bra's work[32,33] in identifying bacteria in the blood of epileptic patients was supported by Reed's[209,210,211] series; despite evidence to the contrary, surgical maneuvers to eliminate putative causes of intestinal stasis and blockage were undertaken on individual patients.[159]

The Epileptic Constitution and Psychoanalytic Concepts of Epilepsy

Refractory epilepsy had long been managed in mental asylums, and physicians working in them such as Esquirol[87] had made substantial contributions to epileptology. Berrios[18] has canvassed the association of epilepsy with insanity and pointed out that this only ceased early in the 20th century. Still the long-standing prejudicial opinion of â€œthe epileptic personality,â€ common in asylum medicine, was prevalent in almost every mental health system of the time.

Clinical opinion, however, derived from an entirely different avenue served to strengthen the impression of a link between epilepsy and psychiatry. Arising from the psychological trauma of World War I, the bizarre episodic events subsumed under the rubric â€œshell shockâ€ were thought of as closely resembling epilepsy or being frankly epileptic. Since the management of shell shock had been undertaken along psychoanalytic lines,[215] it was thought appropriate to extend this to epilepsy. Rows and Bond in their book *Epilepsy, A Functional Illness: It's Treatment*[217] established significant acceptance of this concept. Clark's earlier work at the Craig Colony (1914) had cemented the link of epilepsy with psychiatry. His controversial paper â€œA Personality Study of Epileptic Constitutionâ€ referred to psychoanalytic statements by Pilcz and Ferenczi, who â€œâ€¦made the clever suggestion that a fit represented a regression to the infantile period of wish fulfillment.â€[61] Clark's subsequent publication of a whole series of papers on this subject culminated in his article â€œA Psychological Interpretation of Essential Epilepsy.â€[62] This alternative psychoanalytic explanation held the potential for grave damage.[22] The addition of this psychoanalytic theory of the â€œepileptic constitutionâ€ to the already entrenched perception of the â€œepileptic personalityâ€ in fact constituted a disastrously negative perception of epilepsy by both the medical profession and the public.

Eventually, mainstream neurology overtook this misguided concept and Clark was subjected to public rejection at the October meeting of the New York Neurologic Society. Speaker after speaker commented upon the complete absence of any scientific data to underpin his concept.[62] Rejection was forthcoming from the other side of the Atlantic, too. Kinnier Wilson, in his chapter â€œThe Epilepsiesâ€ in Bumke and Foerster's

Handbuch,[254] summed it up concisely:

â€œDismissing the evidence for visceral, metabolic, humoral and other physical causation, some allege that relief from intolerable pressure of unconscious conflicts is sought in, and accomplished by the epileptic â€œflightâ€ into a fit; without stopping the enquire whether a â€˜flightâ€™ that lands the luckless sufferer in a fireplace or breaks his head open, is as convincing a proof of the validity of the theory as might have been wished.â€[254]

In addition, Wilson deprecated the term â€œessential epilepticâ€: â€œâ€¦the argument of the psychoanalytical school assigning him to an oral and erotic character, and egocentric and narcissistic personality can hardly apply, aside from the fact the conceptions are much too general to be of specific value in a matter of paroxysmal aetiology.â€ In retrospect, the modern reader is left with the question as to how all this could ever occur for, as Wilson implied, it simply defied common sense. By the middle of the 20th century the psychoanalytic theory of epilepsy had all but gone from mainstream neurology. Unfortunately, like the demonic possessions of the past, it took generations before it disappeared from community perception, and its echoes could be heard in psychiatry until quite late into the 1960s.

Important Figures in the Post-Jackson Era

W. Aldren Turner (1864â€“1945) contributed to the conceptual epileptology in the first three decades of the early 20th century[81] and also played an important role in establishing the ILAE as a researcher and contributor to *Epilepsia*. In keeping with the spirit of the times he espoused the cause of the social improvement of the sufferer. His first paper[235] actually discussed the advantages of epilepsy management in colonies, instancing the Chalfont Colony for Epileptics. He correctly judged the severity of both medical and community problems occasioned by epilepsy, and the dire need for radical reform of management policies.

Subsequent papers examined prognosis, nature, treatment, and associated mental conditions. All this culminated in his book *Epilepsy â€“ A Study of the Idiopathic Disease*[236] that was later summarized in his Morison Lectures.[237] They both provide an informed current status report of epileptology of the period. Turner's approach was descriptive and statistical, with large patient numbers derived from three admittedly disparate groups: Private practice, hospital consultancy, and the Chalfont Colony. While fully aware of selection bias by including the patients from Chalfont, he demonstrated that mental decline depended on seizure severity, duration of epilepsy, and age of onset. Although he mentioned â€œfacies epileptica,â€ he did not link it to the use of bromides.

His book[236] summarized his work and clearly depicted the innate problems of the concept of â€œidiopathic epilepsy.â€ Historically it provides a detailed summary of the pathologic processes currently thought significant in the genesis of epilepsy. He noted Ammon horn sclerosis but did not recognize its significance. The book contains the work on systemic body metabolism including examination of blood, sweat, urine, cerebrospinal fluid, and endocrine function during the ictus and interictally in an unsuccessful attempt to identify triggers for seizures. In spite of this failure, the concept of the â€œsystemic triggerâ€ for seizures remained popular as expressed in Collier's â€œmetabolic dyscrasiaâ€[64] and Brain's emphasis on metabolic factors in epilepsy.[34]

William Spratling (1862â€“1915) documented his vast experience as foundation director of the Craig Colony for Epileptics in New York in a textbook *Epilepsy and Its Treatment*.[227] Particularly, Clark and Prout's chapters on the neuropathology of epilepsy and status epilepticus, common conditions in epileptic colonies, was groundbreaking work.[23,59,60,223] Spratling's conclusions are also flawed by selection bias. His basic concepts of the nature and causes of epilepsy offer an informative view of that period: They feature toxic-metabolic causes combined with an â€œinherited seizure proclivityâ€ to explain the intermittent crises of refractory epilepsy. He hardly mentions jacksonian concepts, although it is clear from the text that he had personally discussed epilepsy with Jackson. Clark and Prout, on the other hand, emphasized the centrality of the cortex in seizure generation and in fact maintained that implication of its second layer (â€œa diseased state of the sensory elementsâ€) due to â€œactive nuclear poisonsâ€ underlaid seizure generation. Pathologic changes in Ammon horn were detailed, but their significance still remained uncertain. This well-documented text displayed the reigning conceptual confusion in epileptology at the turn of the century.

Hermann Oppenheimer (1858â€“1919), a prestigious German neurologist with numerous eponymous conditions named for him, offered a textbook that was the â€œgold standardâ€ of neurology. The section on epilepsy[188] demonstrates again the universal confusion in the epileptology of that era. Although he was fully accepting the jacksonian concepts on the role of the cortex, he also entertained possible implications of other brain sites and also felt that â€œtoxicopathicâ€ processes were involved

in seizure generation as suggested by the monumental amount of laboratory data.

L. J. J. Muskens (1872â€“1937), representing the younger generation of epileptologists at the turn of the century, came to be personally identified with the newly established journal *Epilepsia*, of which he became secretary to the editorial board, and then the newly founded ILAE, where he assumed the role of secretary general. Even more importantly, he was central to the revival of the League in 1935 and republication of *Epilepsia* again in 1937. The 1928 English edition of his book *Epilepsyâ€”Comparative Pathogenesis, Symptoms, Treatment*[186] (preceded by Dutch and German editions) offers a documentation of his experimental work on epilepsy and clinical and sociologic aspects of the disease.

In his experiments on myoclonic seizures in animals, he used a toxicologic approach. He thought that myoclonic activity was in fact reflex afterdischarge phenomena, and convulsive activity comprised an adaptive process designed to rid the body of toxic substances causing the seizures. He sited the seizure activity in brainstem structures, but accepted an additional cortical influence on these â€œmedullary convulsive centres.â€ His conceptualization of the type of experimental epilepsy he studied bears similarities to that of Prichard[205] emphasizing the role of reflexes in seizure generation. It is the final chapter of this book, where he discusses the global problem posed by epilepsy and describes his experience in the early days of the ILAE, that contains his main message to his colleagues working in this discipline. This message of advocacy for international cooperation for advancing both clinical enterprise and research in epileptology by a cooperative global effort has accorded him, though only recently, with his proper place in the history of epilepsy.[85]

Samuel Alexander Kinnier Wilson (1878â€“1937) can be considered Hughlings Jackson's direct heir. His early discovery, however, of hepatolenticular degeneration in 1912 delayed his entry into epileptology. His first communication on epilepsy was on â€œTemporo-sphenoidal forms of Idiopathic Epilepsy.â€[249] Jackson et al. had well documented that â€œcoarse pathologyâ€ (tumors, infarcts) occupying the temporal lobe could present with seizures, although seizures could also arise without any evident pathology. The dÃ©jÃ vu phenomenon, which seemed peculiar to temporal lobe epilepsy, could also occur totally unassociated with seizures. Wilson searched for an alternative etiology for these nonepileptic dÃ©jÃ vu episodes and pointed out that except for a few cases due to anoxic damage, most of them were simply inexplicable. Wilson also confronted Jackson's use of the concept of â€œdis-inhibitionâ€ to explain the evocation of the psychic symptoms in temporal lobe seizures. Eventually he reluctantly had to reject this altogether.[25,253]

His Harveian Lecture[250] emphasized the concept of the epilepsies, the absolute failure of the psychoanalytic approach, and the unity of pathophysiology of the many â€œepilepsiesâ€: An explosive hyperactivity of the brain and the primacy of the brain in seizure generation and all clinical manifestations. He took the jacksonian concept of â€œmany epilepsiesâ€ to embrace the potential for seizures to emanate from many areas of the brain, not just the cortex. By the same token, he felt that all epilepsy was manifestly not the same, and that the gloomy view of the condition that persisted in both lay and professional ranks should be abolished, for it handicapped the sufferer in many aspects of life, both medical and social.[252]

During the historical Royal Society's 1927 discussion on epilepsy, he studiously avoided any detailed consideration of metabolic factors in epilepsy, unlike most other speakers. He simply reiterated his concept of the â€œepilepsiesâ€ and then underlined the primacy of the brain alone in seizure generation: â€œâ€¦a fit was the discharge, the setting free, of accumulated nervous energy in healthy neuro-mechanisms.â€[251] In his *Modern Problems in Neurology,*[253] Wilson devoted the first four chapters to problems in epileptology, in which he revised concepts of temporal lobe epilepsy mechanisms, discussed the role of inhibition in epilepsy, emphasized the concept of the â€œepilepsies,â€ and finally offered his usually optimistic prognosis. The psychic symptoms of temporal lobe epilepsy, he decided, were simply a product of local epileptic irritation of that region of the brain, and he formally abandoned the jacksonian concept of disinhibition. He then widened his conceptual views of the overall condition of â€œepilepsyâ€ to embrace a broader range of clinical phenomena. The single most important tenet he emphasized above all was that epilepsy is always symptomatic and never a disease per se. He called for great patience in the study of epilepsy: â€œResearch will eventually disclose the cause of those conditions whose etiology currently eludes us.â€

In the last years of his life, Wilson was able to finish his two most important and almost identical chapters â€œThe Epilepsiesâ€ in Bumke and Foerster's *Handbuch der Neurologie*[254] and his own personal *Textbook of Neurology,* finally published posthumously in 1940,[255] edited by his brother-in-law Ninian Bruce. His immensely detailed grasp of the literature and documentation of the clinical aspects of epilepsy make it a very important resource in the history of the disease.[25] His overall concepts constituted a departure point for the new epileptology that would be ushered in by Lennox to the 1935 London Congress on the use of EEG in the study of epilepsy, an innovation that would change the concept of the condition forever.

W. A. Adie (1886â€“1935) introduced pyknolepsy to an English audience in his address to the Royal Society of Medicine.[1] Although this form of epilepsy had been reported by Friedmann[97] and Heilbronner,[130] Adie emphasized its uniqueness with its many, frequent short-duration attacks; occurrence in the early years of life; explosive onset; and excellent prognosis, and maintained that these features distinguished it from all other forms of epilepsy. In the discussion that followed it was reported that â€œhe was inclined to agree that the disease is only a variety of epilepsy, but its clinical characters are so distinct that it seems worthy of a separate name.â€ Adie introduced the concept of syndromology, with which epileptology continues now to be engaged in reformulating and revising. His work could only be matched by Herpin[132] and Janz and Mathes's early papers[148] that delineated juvenile myoclonic epilepsy.

By the 1930s, a variety of medical, social, and legal issues relating to the care of persons with epilepsy had led to the foundation of the ILAE; the foundation of a dedicated journal, *Epilepsia*; the formation of a number of charities, institutions, and colonies for persons with epilepsy; and an increasing interest in medical research by philanthropic individuals and organizations. Hughlings Jackson's concept of the discharging lesion certainly brought the cerebral cortex into focus as the structure most intimately involved with the production of â€œfits,â€ but the wide variation in the epilepsies, in their age of onset, semeiology, hereditary nature, and course, seemed to defy an explanation based largely on gross lesions of the cerebral hemispheres. These developments certainly produced a medical culture that fostered the study of the epilepsies that influenced epileptology during the 1930s and 1940s, particularly due to the rise of electroencephalography.

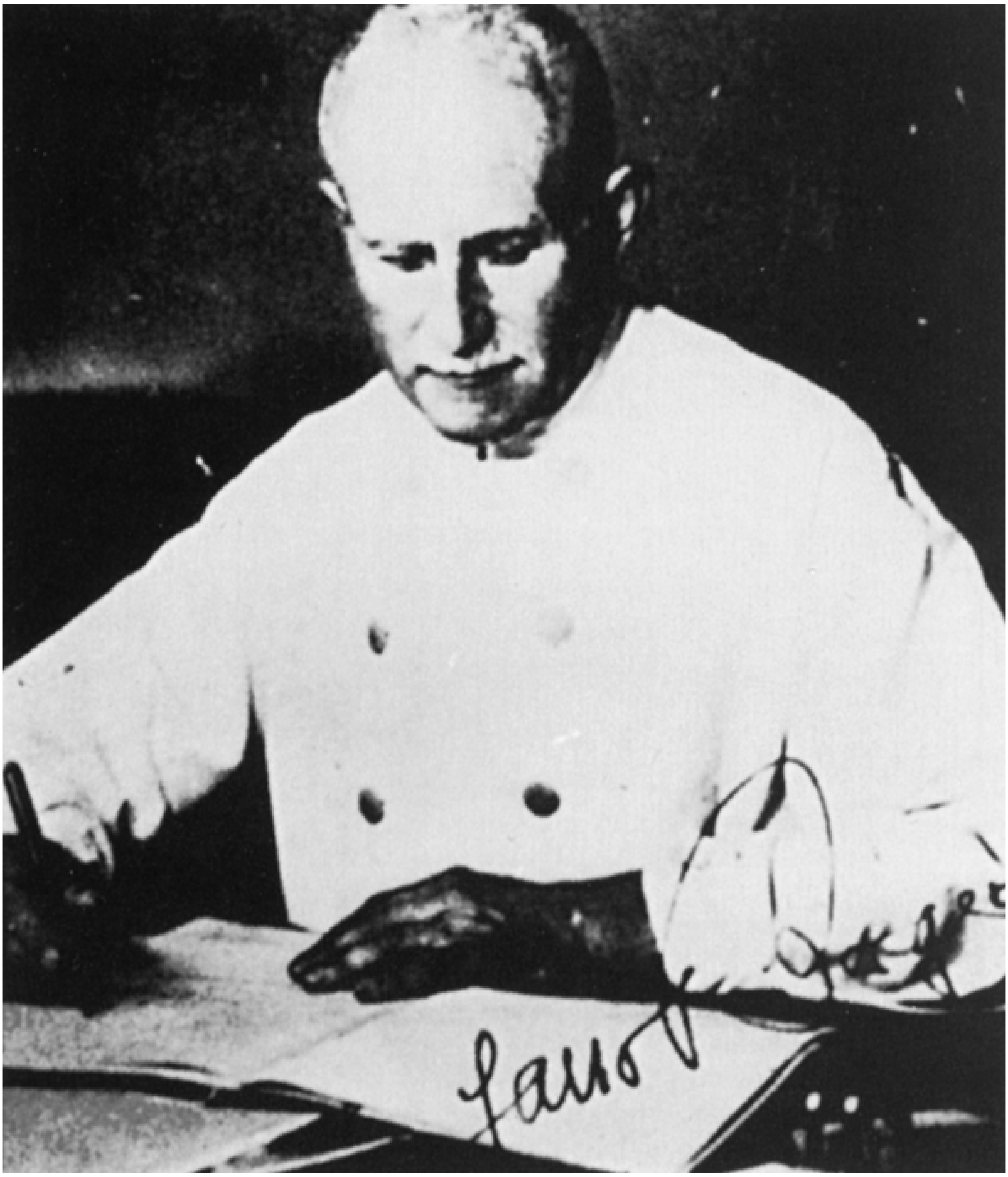


FIGURE 8. Hans Berger (1873â€“1941) photographed in 1925, 4 years before he published his discovery of the electroencephalogram. (From Gloor P. *Hans Berger on the Electroencephalogram of Man*. New York, Amsterdam: Elsevier; 1969, with permission.)

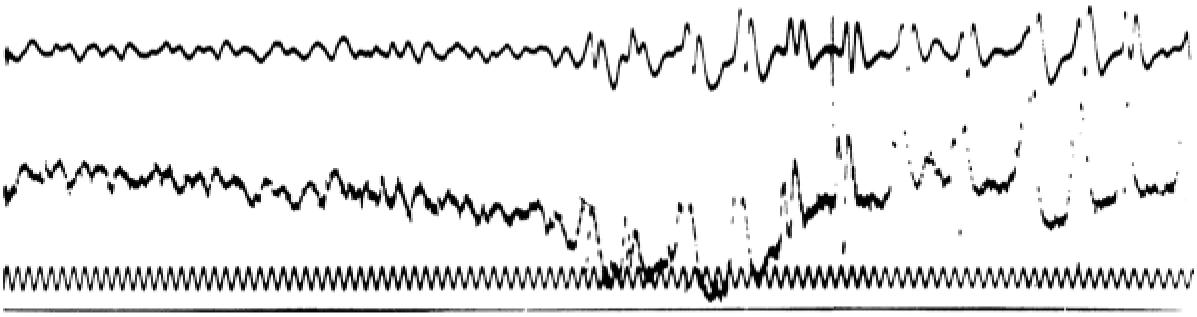


FIGURE 9. A 1931 recording by Berger showing spike-and-wave activity. From O'Leary JL, Goldring S. *Science and Epilepsy*. New York: Raven Press; 1976: 129, with permission.)

Electroencephalography and the Origins of Modern Epileptology

Experimental Electroencephalographic Recordings during Animal Seizures

Experimentally induced seizures were first recorded electroencephalographically by Kaufmann in 1912 in Russia.[158] After reading about spontaneous and evoked electrical activity in the brain, he hypothesized that abnormal brain waves would be present during seizures. By curarizing his dogs and performing meticulous craniotomies, he was able to ascertain that abnormal waves seen during tonicâ€“clonic seizures originated in the cortex and were not injury potentials, movement artifacts, or evoked potentials. Like his predecessors, Kaufmann had no facilities to photograph his data. That same year, also in Russia, the first actual records of EEGs and evoked potentials in animals were preserved photographically and published by Pravdich-Neminski.[202] Two years later, Cybulski and Jelenska-Macieszyna[72] published the first photographs of paroxysms of abnormal cortical EEG activity during experimental seizures. The paroxysms were of very much higher voltage than with spontaneous activity, but their galvanometers were too sluggish to record EEG spikes.

The Human Electroencephalogram

The modern era of epilepsy might be dated to 1929, when Hans Berger (Fig. 8) in Jena, Germany, published his discovery that the brain's electrical activity could be recorded from humans using electrodes placed on the scalp.[16] Berger's eccentric research career, beginning with his studies of cerebral blood flow and culminating in his studies of the human EEG, has been detailed elsewhere.[37,118,183] Berger viewed the dynamic, psychophysical interaction between mind and brain in terms of thermodynamics, and he systematically attempted to measure the energy delivered to the brain and transformed into heat and electricity within the cerebral cortex. In this way, Berger hoped to arrive at a physical measurement of â€œpsychic energy,â€ the component of cerebral energy that was transformed into emotions, sensation, feeling, and rational thought. By 1931, he reported interictal EEG changes in epilepsy, and later that year he recorded human spike-and-wave activity. With funding from the Carl Weiss Foundation to construct a high-impedance vacuum tube amplifier with a high-frequency response of 125 Hz, he was able to produce a more faithful EEG recording. Berger's report in 1932[118] contains a series of four photographic segments showing progressive EEG changes following a generalized tonicâ€“clonic seizure as brain activity returned toward normal during an 11-minute period on a 53-year-old patient. A report in 1933[17] shows a segment of recording from an 18-year-old girl during a brief period of simple automatic activity â€œwith no other movement.â€ It appears to be very-high-voltage spike-and-wave complexes at about 3 Hz (Fig. 9). Berger cited the classic animal experiments of Caton in 1875,[51,52] as well

as later reports by Beck in 1890[12] and Beck and Cybulski in 1892[13] on desynchronization of spontaneous cortical activity in dogs and rabbits produced by light and other sensory stimuli.

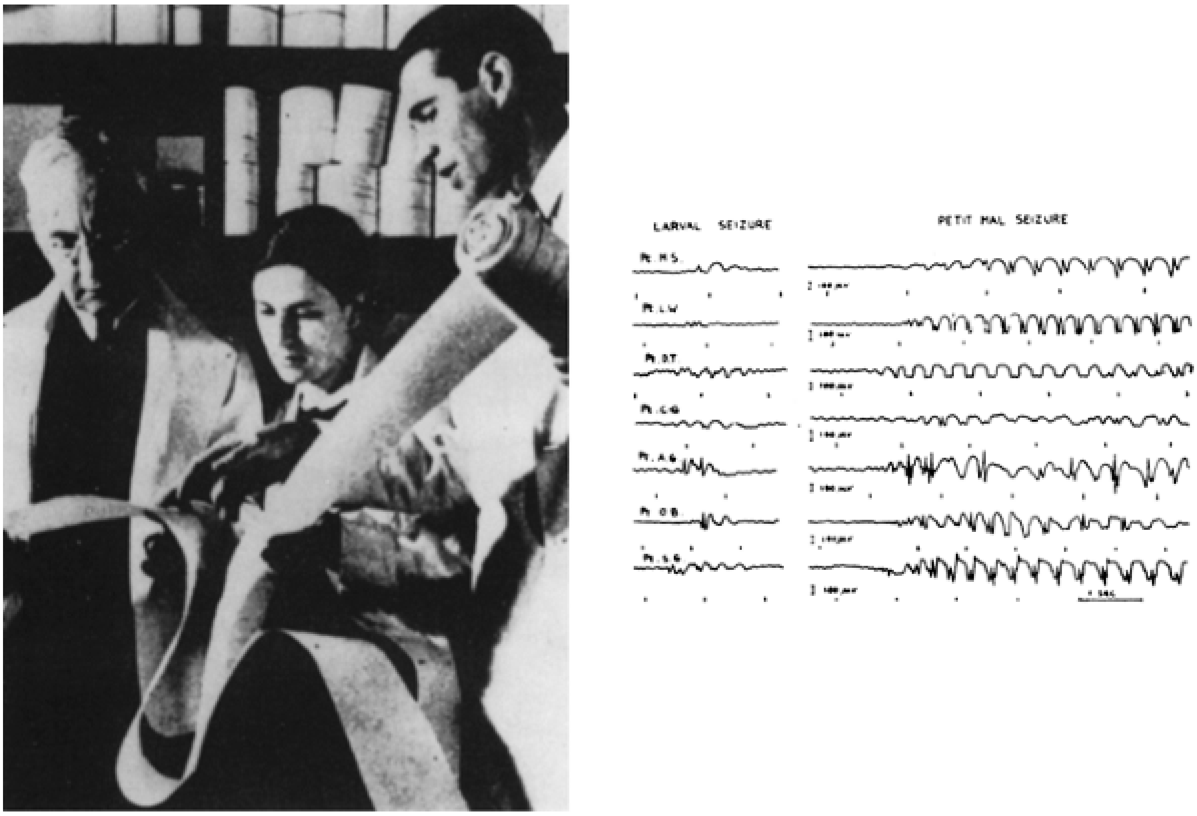


FIGURE 10. Left: William G. Lennox, Erna Gibbs, and Frederick Gibbs (left to right, about 1936) examining an electroencephalogram (EEG) in the Boston City Hospital laboratory. (Courtesy of Ellen Grass, personal collection.) **Right:** The first published recording of the EEG during epileptic attacks from nine of Lennox's petit mal patients by Gibbs, Davis, and Lennox in 1935. The continuous 3-Hz spike-and-wave complexes were associated with impaired consciousness. (From Gibbs FA, Davis H, Lennox WG. The electro-encephalogram in epilepsy and in conditions of impaired consciousness. *Arch Neurol Psychiatry.* 1935;34:1133â€“1148, with permission.)

Although Berger's early papers described his experiments in detail and were supported by numerous photographs of the electroencephalograms, the immediate reception to Berger's work at home was one of open hostility, while the unanimous reaction outside of Germany was one of disbelief. Indeed, most physiologists assumed that Berger had simply recorded some biologic or environmental artifact.[29,182] Berger's approach to understanding brain function was at odds with the main thrust of 1930s German neurophysiology, which had become intensely focused on the problems of cortical localization. Indeed, the leaders of German neurophysiology working at the Kaiser Wilhelm Institute for Brain Research in Berlin considered Berger a naÃ¯ve amateur who rejected the prevailing logic of cortical localization and ignored recent developments in electronic amplification.[156] As his opponents attempted to identify hundreds of different cortical areas in terms of their electrophysiologic profiles, they frequently defined their project in contradistinction to Berger's â€œholisticâ€ interpretation of the EEG, and resisted use of the term â€œelectroencephalogramâ€ due to its holistic connotation.[29,182]

Validation for Berger's work on the human EEG came in 1934, when the distinguished Cambridge physiologist

E.A. (later Lord) Adrian demonstrated *a* blocking in a recording made by Bryan Matthews and presented before the Physiological Society.[2] By this time, a number of research groups in North America had also turned their attention to the human EEG. The first recording of an EEG in North America was obtained in the winter of 1933â€“1934 in Hallowell Davis's physiology laboratory at Harvard University. Subsequent demonstrations in Davis's laboratory kindled the interest of three young researchers, William Lennox, Erna Gibbs (nee Leonhard), and Frederic Gibbs, who had been primarily focused on measuring blood gases in experimental animals and patients in order to test the prevailing vasomotor theory of ictogenesis.

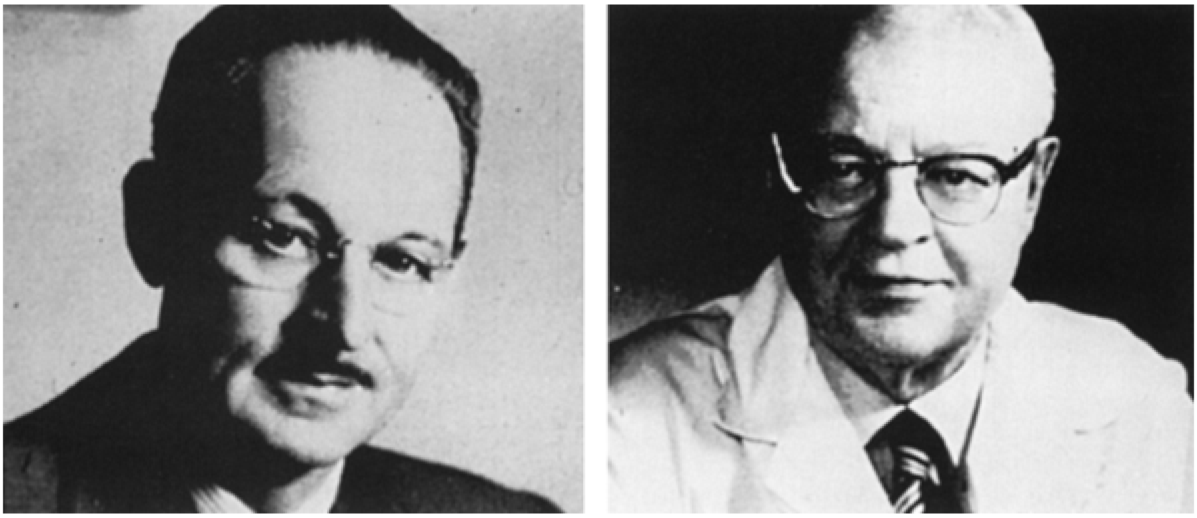


FIGURE 11. Tracy Putnam (1894â€“1975) **(left)** and H. Houston Merritt (1902â€“1978) **(right).** Their studies marked the end of using pure empiricism in finding new anticonvulsant drugs. Their imaginative approach and disciplined method identified phenytoin and instituted a method for evaluating potential anticonvulsants that remained in use for many years.

The Electroencephalographic Contributions to Epilepsy

A growing number investigators quickly transformed EEG from a scientific curiosity into a promising clinical tool. The first recording of the â€œegg and dartâ€ or â€œspike and domeâ€ pattern of petit mal seizures occurred in Davis's laboratory in December of 1934. This discovery ignited an explosion of EEG research in the Boston area. Using a single-channel vacuum tube amplifier and ink writer, Gibbs et al.[109] demonstrated that convulsive and absence seizures were accompanied by different EEG patterns and that â€œlarval seizuresâ€ (i.e., interictal discharges) frequently demonstrated the same morphology as the corresponding ictal rhythm. Over the following year, Gibbs et al. (Fig. 10) described EEG patterns that accompanied â€œpsychomotorâ€ seizures, the use of hyperventilation in provoking seizures, and the effects of phenobarbital and sodium bromide on the interictal EEG, and they performed the first invasive EEG recordings in a patient with intractable epilepsy.[110,163,167]

In 1936, Jasper[150] independently demonstrated focal spikes in localization-related epilepsy. At about the same time, Putnam and Merritt (Fig. 11) embarked on their systematic survey of potential anticonvulsant compounds in the neurologic research laboratory at Boston City Hospital. Putnam later recalled that it was Gibbs's belief that â€œevery true seizure is attended by an electrical â€˜stormâ€™ in the brainâ€ that led to the adoption of an electroconvulsive threshold model (in contrast, for example, to strychnine, camphor, or pentylenetetrazol models) for screening potential antiepileptic drugs.

By 1937, the Gibbses and their colleagues had redefined epilepsy in modern terms: â€œEpilepsy: A Paroxysmal Cerebral Dysrhythmiaâ€ clearly distinguished ictal EEG patterns for petit mal, grand mal, and â€œpsychomotorâ€ seizures; demonstrated the presence of subclinical seizures; and suggested a role for EEG analysis in seizure prediction.[111] That year, the first clinical department to formally perform and charge for EEG services in the United States was opened at Massachusetts General Hospital by Robert Schwab. Other hospital laboratories quickly followed. In an effort to establish valid EEG-clinical correlations, the Gibbs and Gibbs championed a â€œrough and readyâ€ approach, relying on Grass's early portable amplifier-ink writer systems that used a two- or three-channel referential montages to screen large numbers of patients. For most clinical EEG work, they advocated using a referential recording technique that seemed like epileptiform discharges, especially the 3-Hz spike-and-wave pattern of petit mal seizures. They also emphasized the visual art of pattern recognition in electroencephalography.[113] Tirelessly pursuing this streamlined approach to clinical EEG, Lennox and the Gibbses classified the epilepsies based on â€œpathognomonicâ€ or archetypal EEG patterns, proposed that one could render a diagnosis of epilepsy based on a clinical history of spells and â€œlarval seizuresâ€ captured in an interictal EEG, demonstrated the increased sensitivity of nonâ€“rapid eye movement (NREM) sleep for detection of epileptiform discharges, and enthusiasticallyâ€”if prematurelyâ€”advocated for the surgical treatment of epilepsy.

Like Frederic Gibbs, Herbert Jasper also became aware of Berger's publications on the human EEG in the early 1930s. Jasper's skepticism of Berger's work faded after he learned of Lord Adrian's EEG demonstration at the June 1934 meeting of the American Neurological Association (ANA). Jasper had recently become director of the psychology research laboratory at the Emma Pendleton Bradley Home near Brown University and, realizing the value of EEG work in understanding cerebral function, he asked Howard Andrews, an electronics engineer from the physics department, to design a suitable amplification and recording system. Jasper had worked mostly in peripheral neurophysiology, and did not want to rely on an ink writer system, because the friction of this apparatus might dampen high-frequency EEG activity. He also recognized the need to record the electrical activity of the brain and combined the high-frequency response of a fast Westinghouse mirror oscillograph with photographic equipment to record the mirror fluctuations. Jasper and Carmichael recorded their first EEG on July 9, 1934. Unaware of the work already under way in Boston, they briefly reported the results of their study of six normal subjects and two pathologic cases to *Science*, the first report on the human EEG from a North American laboratory.[149] Jasper emphasized the critical importance of instrumentation and recording technique in EEG above all else. His early emphasis on bipolar recordings, his insistence on carefully constructed electrodes and oscilloscope-camera or ink-writing systems to avoid artifact and accurately localize EEG abnormalities, and his opposition to using EEG for the classification of seizures and epilepsies resulted in continuing controversy with the Gibbses.

Jasper's early work focused on the physiologic basis of the human EEG, but he soon turned to clinical applications. Initially, he studied two overlapping populations: Patients with epilepsy referred by local physicians[151] and â€œbehavior problem childrenâ€ admitted to the Bradley Home.[71,152] While Jasper's study of children with attention disorders and behavioral problems established the value of routine EEG testing in this setting, it was his study of 55 epilepsy patients that led to the first set of criteria for identifying epileptogenic foci based on ictal and interictal discharges.[151] In 1937, Wilder Penfield visited Jasper's EEG laboratory, which consisted of a maze of chicken wire, and later recalled that inside â€œwas a young man, moving about like a bird in an aviaryâ€¦a rara avis, Herbert Jasper, a young man driven by one creative idea after another. He could, he said, localize the focus of an epileptic seizure by the disturbance of brain rhythms outside the skull. I doubted that but hoped it might be true.â€[199] Penfield finally was persuaded to operate on two of Jasper's subjects whose EEGs had demonstrated a focal abnormality. With Jasper looking on from the observation room, the predicted lesion was found at surgery, and he invited Jasper to come to Montreal to continue his EEG studies on epilepsy patients.

After 6 months of weekly trips from Providence to Montreal, Jasper and Penfield organized a 4-year research program on the EEG in the epilepsies. Jasper's busy clinical neurophysiology laboratory opened in February 1939. While the Gibbses cast a wide net in their clinical EEG work, exploring EEG patterns in a variety of neurologic and medical conditions and functioning as consultant specialists in the emerging field of electroencephalography, Jasper had the demanding task of routinely predicting the location of a putative lesion during presurgical evaluation on the basis of the EEG findings. Within 2 years, Jasper had evaluated about 1,000 patients in the outpatient EEG department and performed dozens of intraoperative studies, recording the electrical activity of the cerebral cortex surface, subcortical structures, and epileptogenic lesions (in 1960). Penfield and Jasper provided the first descriptions of the focal and generalized seizures, distinguished the EEG correlates of tonic and clonic seizure activity, described the interictalâ€"ictal transition and the propagation of ictal rhythms across the cerebral cortex based on a series of electrocorticography studies, and concluded that persistent epileptiform discharges on electrocorticography after surgical resection had little prognostic value. Perhaps most importantly, Jasper and Penfield reported that using Jasper's bipolar EEG technique, scalp EEG recordings from patients being evaluated for surgery accurately predicted a surgical lesion within 2 to 3 cm in 85% of cases. These electrocorticography studies led Penfield and Jasper to distinguish the â€œseizure onset zoneâ€ from the â€œepileptogenic lesion,â€ which, at the time, was typically visualized on a pneumoencephalogram. It is difficult to clearly establish the impact of EEG on the success of epilepsy surgery during these early years of EEG, but one account describes a dramatic increase in surgical cases[168] and others suggest a precipitous decline in negative surgical explorations, from approximately 50% prior to introduction of routine presurgical EEG to <10% by 1940.[168,203]

As a result of these stunning breakthroughs in epileptology, dozens of investigators in North America, England, and Europe began using EEG in the late 1930s and 1940s. They used the EEG to explore a range of issues in epilepsy, including heritability, pathophysiology, localization, surgical treatment, and classification.

The Electroencephalogram and Seizure Classification

From the standpoint of classification, the EEG findings introduced a critical, physiologic axis for the taxonomy of seizures and epilepsy syndromes. Although phenomenologic distinctions between minor and major types of seizures had existed for centuries, etiologic or physiologic classification had been elusive. Indeed, Craig Colony president F. Peterson lamented in 1897 that such taxonomy â€œis not possibleâ€¦in light of the present knowledgeâ€¦[but] would be more scientific and valuableâ€ than existing systems. The physiologic basis of the EEG, along with the initial appearance of a clear relationship between â€œpathognomonicâ€ electrographic abnormality and seizure type, fostered early enthusiasm for a thoroughgoing revision of existing classification systems. Lennox's and the Gibbses' confidence in the paramount value of the EEG in all aspects of neurologic and psychiatric diseaseâ€"even supervening on clinical signs and symptomsâ€"was clearly evident by 1938:

â€œWe believe physicians should consider dysrhythmias of the electrical waves of the brain as primary and various clinical manifestations of dysfunction of the brain or of the mind as secondary. Abnormal cortical waves may not be demonstrable with the technique available but when they are present they should take precedent in classification, in nomenclature and possibly in treatment.â€[112]

Thus, after their initial descriptions in the mid-1930s of characteristic EEG patterns associated with petit mal, grand mal, and psychomotor seizures, Lennox and the Gibbses later described these EEG patterns in terms of their clinical semeiology. These enthusiastic generalizations were soon challenged by other investigators,[93,153] who failed to find a correlation between clinical seizure types and EEG patterns in larger populations of epilepsy patients. Jasper[153] was particularly critical of such correlations, pointing out that many clinical diagnoses were based on interictal EEGs and that particular EEG patterns were not predictive of clinical semeiology. Complaining that â€œonly confusion arises from the attempt to use clinical terms, grand mal, petit mal and psychomotor to describe types of electroencephalogram,â€ Jasper focused instead on organizing epileptiform EEG abnormalities based on localization (localized, diffuse, or bilateral) and frequency. Despite such early precautions, however, the EEG quickly became a critical tool in the classification of seizures, providing physiologic evidence for the distinction between â€œfocalâ€ and â€œcentrencephalicâ€ seizures by Penfield and Jasper,[197,198] and for the characterization of temporal lobe epilepsy by Gastaut.[102]

Simultaneous Video-electroencephalographic Recordings

The first investigator to design a laboratory for the simultaneous recording of EEG and motion pictures actually had nothing to do with the study of seizures or epilepsy! In 1935, Alfred Loomis, a Wall Street investment banker turned private scientist, had independently discovered the alpha rhythm in his efforts to improve electrocardiography recordings with additional electrodes. Loomis had been fascinated by hypnotism since childhood and the discovery of â€œbrain rhythmsâ€ led him to the study of the EEG changes during hypnosis and sleep. Without any apparent limitations on time, money, or space, Loomis's EEG lab at his Tuxedo Park home contained a bedroom for subjects to sleep and for the first amplification stage; an amplifier room containing two additional stages as well as electrocardiographic and respiration monitors; and a control room located 66 feet away to house the system of three independent sets of high-speed ink writers *and* cathode ray oscilloscopes with cameras for photographic recording of the EEG oscillograph trace.[170,171] As subjects were expected to achieve normal sleep during the experiments, the sleeping room was dressed with heavy drapes. Loomis also equipped the rooms with motion cameras with the fastest lenses available. Infrared film had been specially manufactured by the Eastman-Kodak company and was flown in daily from Rochester on dry ice, and the film was developed in two professional-quality darkrooms in the laboratory.[65]

Around this time, Robert Schwab designed a system using two 16-mm cameras to record clinical seizures and corresponding EEG. Both films had special synchronizing marks that were matched and processed into a composite duplicate, which was shown in 1938 at the 96th meeting of the American Psychiatric Association. Hunter and Jasper later reported a method of simultaneously recording the EEG and clinical seizures with a single camera.[141] The camera was directed at a full-length mirror hanging above the patient and received the image of the patient and the reflected image from the EEG tracing simultaneously through a system of mirrors mounted at angles above the moving EEG paper.

The use of television in the 1950s made the process less cumbersome. The first use of closed-circuit television (CCTV) for simultaneous recording of the EEG and seizures was reported

in 1966 by Goldensohn.[119] At first, the combined split-screen TV images and sound were transferred from the TV to movie film (kinescopes) and later directly to video cassettes.[74,119] Vacuum tube amplifiers in EEG machines were replaced in the 1960s by transistors invented in 1947 by Bardeen, Bratain, and Shockley. The advent of the transistor improved the quality of the routine ink-written EEG record, but it was of much greater importance for the ongoing revolution in computerized handling of all aspects of EEG information related to epilepsy.

The Epileptogenic Electroencephalographic Spike

Much research in neurophysiology has focused on understanding the cellular electrical activities that generate seizures. Although vacuum tube amplifier technology that could reproduce electrical signals from single neurons had been available since 1906, most laboratories generally took a long time to abandon galvanometers. The Boston physiologist Alexander Forbes was the main contributor to the early development and application of vacuum tube amplification to neurophysiologic research,[94] as described in an appreciation by Eccles.[82]

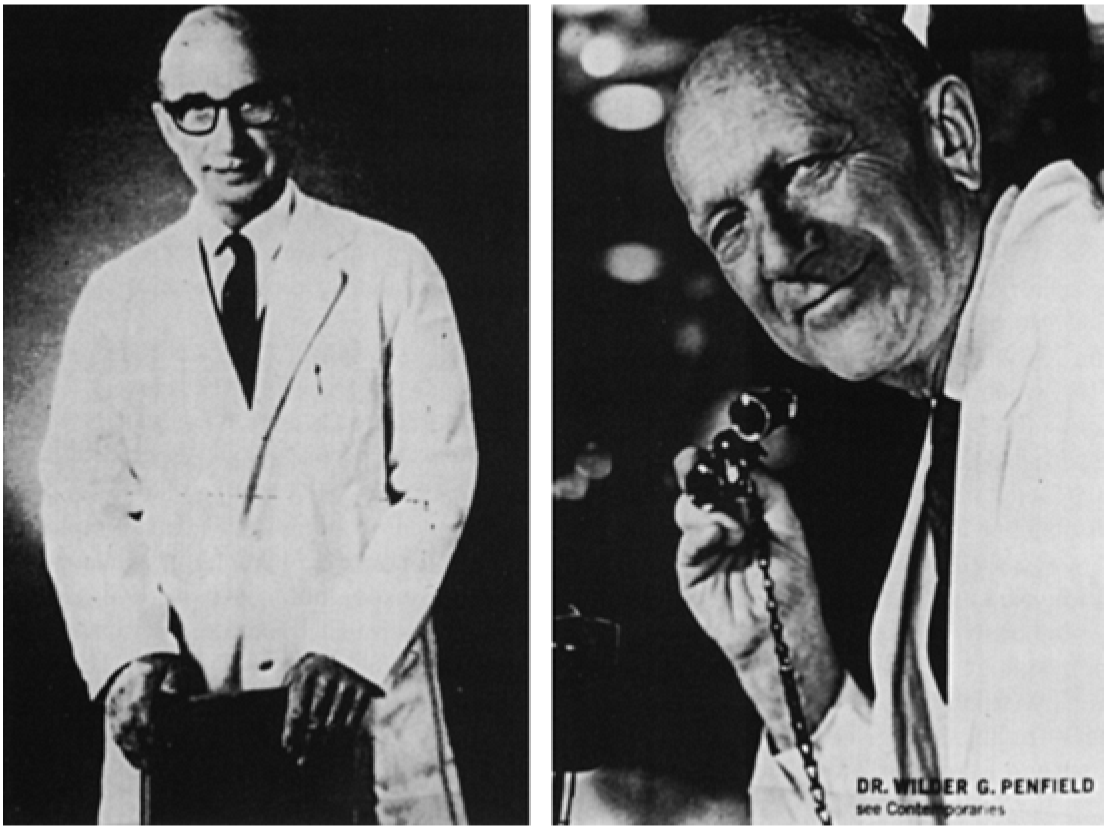


FIGURE 12. Neurophysiologist Herbert Jasper (b. 1906), **(left)** and neurosurgeon Wilder Penfield (1891â€“1976) **(right).** Together, for more than a quarter of a century, they were consistently leaders in applying multidisciplinary scientific and applied advances to the surgical treatment of epilepsy. (Courtesy of the National Library of Medicine, Bethesda, MD.)

At first, most investigators believed that action potentials of axons and cell bodies summated to form EEG waves. Later, the idea emerged that the relatively slow EEG wave might not consist of â€œall or noneâ€ 0.5- to 1.0-msec action potentials, but rather of graded, slower potentials originating at the synapse. Renshaw et al.[212] used extracellular microelectrodes that touched single-cell membranes to show probable relationships between slow potentials of single cells that resembled EEG waves. Li and Jasper,[169] also using extracellular microelectrodes, were able to prevent single-cell action potentials from occurring while slower synaptic potentials temporally related to EEG waves persisted, demonstrating that synaptic potentials, but not action potentials, contributed to the generation of EEG waves. Bishop and Clare[20,57] ascribed surface electrical activity to nonpropagated dendritic potentials, and the concept that brain waves were mainly postsynaptic potentials gathered further impetus. Using high-impedance intracellular electrodes for recording in hippocampal neurons, Kandel and Spencer[157] demonstrated temporal relationships between EEG afterdischarges and transmembrane potentials. With the use of intracellular microelectrodes, Goldensohn and Purpura in 1963 were the first to demonstrate the synaptic origin of interictal EEG spikes in the neocortex.[120] The EEG spikes at the brain surface were found to be summations of depolarizing (excitatory) and hyperpolarizing (inhibitory) postsynaptic potentials (EPSPs and IPSPs) with extreme depolarizations sufficient to prevent firing of the cell. Matsumoto and Ajmone-Marsan in 1964[177,178] described intracellular activity during both ictal and interictal periods and showed that the extreme depolarizationsâ€"paroxysmal depolarization shifts (PDSs)â€"are an essential feature of the spike focus.

Postwar Epileptology: Conceptual Advances

Lennox, in summing up the year's literature for 1944 in *Epilepsia*, remarked: â€œWar the consumer, has drawn the attention of men from the medical problems of epilepsy in the civilian population, and epilepsy as an aftermath of war has not yet had time to assert itselfâ€¦â€

Indeed, this hugely expensive and exhausting war had slowed advances in many areas of medicine to a crawl. Nevertheless, in some areas there had been progress and some special centers had made significant advances.

Wilder Penfield (1891â€“1976) and the Montreal Neurological Institute

For more than a decade and a half, Penfield and his team had been working on the surgical treatment of epilepsy as part of a wider program based on investigating the role of the cerebral cortex of man.[168,200] Penfield and Jasper (Fig. 12) had become experts in applying EEG methods to epilepsy research and practice. Their concept of the centrencephalic system and its role in the mechanisms of what today would be called primary generalized epilepsy[197,198] played a major role in subsequent attempts at seizure classification. In fact, Penfield and Erickson[196] had already made one of the earlier attempts at establishing a framework for classification of specific phenomena[196] based on data obtained from documenting the localized function of various cortical areas. In spite of its obvious limitations, this served to promote further attempts to organize epileptic phenomena with the intention of advancing research.[179]

Penfield's pioneering work attempted to examine the cerebral cortex under direct observation and following stimulation in the operating room. It stands as the first really significant effort to understand the problems posed by abnormal cortical areas involved in epileptic seizures. In a field that has blossomed with the development of modern neuroimaging techniques, the pioneering work in the electrophysiology of the cerebral cortex and the mechanisms of epilepsy of Jasper and Gloor provided an important window into a largely unexplored area.[117,198] The Montreal program, founded by Penfield et al., carried out by a team of exceptional clinicians and scientists, represents a major milestone in mid-20th century epileptology.[115]

Henri Gastaut (1915â€“1995) and the Marseille School

Postwar European epileptology was notable for the early contributions of the Marseille school led by Henri Gastaut (Fig. 13). His program produced a steady stream of publications on many aspects of epilepsy. Through his skills in organizing and financing important meetings that focused on selected aspects of epilepsy, Gastaut initiated a new wave of international interest and cooperation.

Gastaut et al. organized the important third and fourth meetings of the now legendary Colloques de Marseille series, which introduced temporal lobe epilepsy to an international audience. Gastaut's paper on the â€œSo-called â€˜Psychomotorâ€™ and â€˜Temporalâ€™ Epilepsy: A Critical Studyâ€ was presented as a preliminary report to the Scientific Session of the ILAE meeting in Lisbon in 1953. In this he produced a well-documented, wide-ranging study of this topic and included an extended discussion of the subject by a number of international experts who had attended. The fourth Colloque de Marseille in 1954 discussed the pathologic anatomy of temporal lobe epilepsy and it was followed 3 years later by a meeting in Bethesda, Maryland, in which a large number of international experts covered many aspects of the topic. By now a substantial number of centers in several countries had begun resective surgery programs for this type of epilepsy. Gastaut and the Marseille school had played a significant role in arousing international interest in temporal lobe epilepsy.[9,44,102,104]

His 1954 book *Epilepsy: Electro-Clinical Correlations*[103] attempted to present a current account of the mechanisms of epileptic seizure generation in the different forms of epilepsy. Synthesizing the rapidly increasing information on neurophysiologic data from his extensive clinical investigation of patients with various forms of epilepsy, Gastaut introduced new and provocative concepts to explain both partial and generalized seizure forms. His ideas pertaining to the generalized epilepsies

were particularly novel. Eight years later, Gastaut collaborated with Roger Broughton[108] to revise the work in light of more recent data. He then initiated the task of encouraging international neurology to attempt to classify seizures, a work that has continued to progress since that time.

Gastaut's work with Fischer-Williams established the essential electrical and clinical differences between syncope and epilepsy, a problem that had dogged clinical studies in this area for centuries.[105] This contribution was followed by his description of what eventually became known as the Lennox-Gastaut syndrome.[106] Finally, his 1969 classification of epileptic seizures on clinical and EEG criteria (with his dismissal of the concept of â€œidiopathic epilepsyâ€) stands as one of the early attempts to marry the clinical and technologic data to form an organized system of epileptology.[107] Gastaut's unit constituted a powerhouse of European epileptology in the immediate postwar period. His introduction of novel concepts and his research into many facets of this discipline formed the basis for important advances.

Bancaud and Talairach and L'HÃ´pital St. Anne in Paris

Bancaud (1921â€“1994) and his neurosurgical colleague, Talairach, at the L' HÃ´pital St. Anne used specially designed stereotactically implanted electrode arrays to record and plot the paths of various seizure patterns, thus introducing stereoelectroencephalography. With this technique, they demonstrated that seemingly focal seizures could in fact originate from a focus distant from the area of final expression. Bancaud's concepts regarding the spread of the process of focal epilepsy allowed extensive broadening of current thinking about the origin and spread of focal epileptic seizures.[10]

FIGURE 13. Henri Gastaut (1915â€“1995; front row center, with tie but no coat) with participants at the 1964 Marseille Colloquium. (From Dravet C, Roger J. *Epilepsia.* 1996;37:410â€“415, with permission.)

Medical Treatment of Epilepsy: 20th-century Developments

Though some of the older antiepileptic remedies of dubious efficacy had not been completely abandoned, by the beginning of the 20th century, the various bromide salts, particularly potassium bromide, had become the mainstay of the drug therapy of epilepsy. The next effective antiepileptic agent to be recognized was phenobarbital (phenobarbitone). In 1912, Hauptmann,[128] while using it to tranquilize patients, realized it had suppressed the seizures of those who also happened to suffer from epilepsy. Subsequently, two of its congeners, mephobarbital (*N*-methylphenobarbitone)[26] and primidone (desoxy-phenobarbitone),[126] were found effective in treating epilepsy.

Up to this point in time, effective antiepileptic drugs had been discovered by chance during their administration to humans for other purposes, or had been tried in the treatment of epilepsy because of chemical structural analogy with antiepileptic molecules. In the late 1930s, however, Putnam and Merritt began to systematically study in experimental animals molecules with structural resemblances to phenobarbital to find new antiepileptic agents. They tested several hydantoin derivatives (in which the central heterocyclic ring of the molecule lacked one of the carbon atoms of the barbiturate ring) and found that phenytoin (diphenylhydantoin) had an apparently promising balance between sedative and antiepileptic properties. It proved to be effective when tried in human epilepsy[181] and thereafter came into increasingly widespread use. Friedlander[95] has recorded in detail the story of its discovery. Other hydantoin derivatives, such as mephenytoin, were later developed and used in humans, but all proved unsatisfactory for reasons of lesser efficacy or toxicity.

The success of the Putnam-Merritt approach led to further experimental animal studies attempting to find other small heterocyclic molecules with potential antiepileptic properties. Beginning with troxidone (trimethadione),[166] various oxazolidinedione derivatives were shown effective in controlling absence seizures in which barbiturate and hydantoin derivatives were ineffective. Subsequently, succinimide derivatives, in which an oxygen atom replaced one carbon atom in the oxazolidinedione ring, were tested and proved more satisfactory than the oxazolidinediones.[256] Carbamazepine, a dibenzazepine derivative and a congener of the antidepressant imipramine, was tested for antiepileptic activity by the pharmaceutical firm Geigy Ltd. in the 1950s and came into increasing use in humans during the following decade.[221] The next antiepileptic agent, valproate (used as free acid or sodium or hemisodium salt), was discovered by chance. Initially used in 1961 as a solvent for possible antiepileptic agents in experimental animal studies, it became clear that the solvent, and not the putative agents, was the effective antiepileptic substance.[222] Other agents with some effectiveness against seizures (e.g., sulthiame, clonazepam, and other benzodiazepine derivatives) were discovered and came into some use during the 1960s and 1970s. Additional antiepileptic drugs have since been discovered as the outcome of strategies based on several approaches,[220] random screening of numerous molecules with a wide range of chemical structures (e.g., felbamate), testing structural analogs of known antiepileptic agents (e.g., oxcarbazepine, levetiracetam), and rational attempts to modify known factors believed to facilitate epileptic activity (e.g., vigabatrin, lamotrigine, tiagabine, gabapentin). Reminiscent of ancient dietary recommendations, the ketogenic diet has been used since 1922 with some success in controlling seizures, mainly in children with drug-resistant epilepsy.[66]

Seizure Surgery in the 20th Century: Early Days

Surgery for epilepsy has a history dating back to antiquity, although not always confined to the skull and brain. Trepanation (opening the skull) for seizure relief dates back to antiquity and pre-Columbian times.[69] In addition, Cooke[67] had documented surgery for the removal of peripheral lesions thought to cause local irritation, in turn triggering seizures in the area of focal fits. Since seizures were considered equivalent to the orgasm, and onanism or genital irritation were linked by Tissot to seizures, surgery on both male and female genitalia was practiced at various times, particularly after the 18th century.[21,78] Bacon[7] recommended castration as an extreme method of seizure prevention. Gowers,[121] however, condemned it with authoritative brevity: â€œCastration has been proposed as a remedial measure, and this has been performed without effect.â€

Jackson's famous footnote[146] to his article on â€œA Particular Variety of Epilepsyâ€â€”â€œI have suggested that the radical cure of fits in such cases is for the surgeon to cut out that discharging lesion, as well as the tumor, if there be one, producing itâ€â€”was the first suggestion of a potential surgical cure.

Surgery for intracranial lesions, guided solely by clinical localization alone, had been practiced early in the final quarter of the 19th century,[42] and by the time of Jackson's writing Macewen in Glasgow and Horsley in London had been performing resections of symptomatic lesions.[137,138,139,156,172,229] Macewen had targeted tumors presenting with seizures, while Horsley was assisted by Hughlings Jackson in the selection of the operative site to remove posttraumatic lesions producing

focal fits. Most importantly, Jackson's footnote showed his realization of two important principles: The allocation of this special type of seizure to the temporal lobe and the need to remove not only the tumor, but also the epileptogenic cortex.

Early in the 20th century a small number of specialized, mainly European, neurosurgeons were engaged in seizure surgery,[86] such as Krause in Berlin. Epilepsy surgery, however, began to flourish during the interwar era, the second and third decades. Foerster of Breslau is known as an early pioneer, because of his mentoring relationship with Penfield during the Penfield's study visit in 1928. Surgery was directed to remove lesions discovered at operative exploration and actual extirpation was achieved by encompassing all visibly abnormal tissue. In 1934, Penfield at the Montreal Neurological Institute introduced the development of a special team to investigate all aspects of preoperative diagnosis, identification and localization of the epileptic focus. In the postwar years, the introduction of comprehensive management programs to care for the patient with epilepsy in all aspects, both medical and social, constituted a major advance in the overall treatment of epilepsy.[87,88]

The Electroencephalogram, Refractory Epilepsy, and Seizure Surgery

The tremendous impact of EEG on epileptology has been described above, and the impact of this new technique on epilepsy surgery cannot be underestimated. Particularly in North America, which was spared from the destructive effects of World War II, electronics technology saw tremendous advances during the 1940s. These developments allowed the United States and Canada to gain an advantage in applying this novel and productive technology for the investigation of patients with epilepsy surgery by the end of the war.

Evidence for a common pathologic-anatomic substrate for medication-refractory epilepsy, namely, sclerosis of the mesial temporal structures, had been known from postmortem studies since the early 19th century. Yet, the significance of what is now known as â€œhippocampal sclerosisâ€ and its association with epilepsy was much debated.[31,185,255] Consequently, mesial temporal sclerosis had not been of much neurosurgical interest until the advent of the EEG revealed the central role of this condition in temporal lobe epilepsy and introduced newer concepts in its surgical treatment.[89] The first major development in the treatment of refractory epilepsy was the discovery by Gibbs et al.[114] that EEG recordings of patients with so-called â€œpsychomotor epilepsyâ€ revealed a spike focus over the anterior temporal lobe. This discovery was soon followed by the publication of a series of temporal lobectomies for intractable epilepsy based on EEG findings.[8] A small series consisting of five patients subjected to anterior temporal lobectomy without the use of EEG was published by Morris,[184] who correctly emphasized the necessity to remove all the medial temporal structures for effective surgery.[24,89] A larger series of temporal lobectomies for intractable epilepsy was published by Penfield and Flanagan[196] that same year. This nearly simultaneous publication of several surgical series, some of which were guided by EEG data, has led to subsequent controversy about the historical priority. It is also unclear whether Jasper believed that the EEG findings were not specific for a localized epileptogenic zone within the temporal lobe as Gastaut[102] has suggested, or whether Penfield, despite Jasper's opinion, was not convinced of the specificity of the EEG activity to a temporal origin.[153] In any case, it is clear that the first significant series of temporal resections for intractable temporal lobe epilepsy, guided by EEG both preoperatively and intraoperatively, was produced by Bailey and Gibbs,[8] who deserve recognition for this important contribution.[86]

Thus, less than a century after Hughlings Jackson had floated the concept of radical neurosurgery â€œto cut out the discharging lesion,â€ surgery was proven feasible and was set to take its place in routine epilepsy management. Temporal lobectomy for refractory epilepsy was performed in many centers and interest in this very common form of epilepsy and its surgical treatment intensified. The Marseille Colloquia in 1952 and 1953 generated a great deal of international enthusiasm for temporal lobe epilepsy[104] by delineating this syndrome. In the Bethesda, Maryland, meeting in 1957, a large number of contributors from all over the world presented their data.[9] As Bailey remarked, Lennox had â€œâ€¦called the psychomotor epilepsies a crossroads, a meeting ground for various disciplines and research-minded men.â€ It has produced a stream of significant data on the operative treatment of temporal lobe epilepsy, but also on the pathologic etiology and innovative approaches to pre- and postoperative effects of the epilepsy and the surgery.[24] Falconer's concepts of temporal lobe epilepsy and mesial temporal sclerosis[89] and Taylor's introduction of the concepts of cortical dysplasias[229] had constituted significant milestones.

Since then, several epilepsy programs have been established in many countries.[86] The introduction of informative neuroimaging modalities and the use of modern technologies to monitor and record seizures would not only effect radical change in the diagnosis and surgery of epilepsy of focal origin, but along with the radical advances in the genetics of epilepsy, also effect changes in conceptual epileptology at the beginning of the 21st century, seemingly unbelievable to Ford Robertson and his optimistic opinion in the year 1900.

Summary and Conclusions

Over the centuries attempts to understand and explain epilepsy have been plagued by religious, social, and even â€œscientificâ€ explanations. Demonic possessions, the â€œvital spirits,â€ â€œmetabolicâ€ causes, psychoanalytic explanations, or even personal dislikes as well as political oppression were among the factors that had to be fought against to allow progress.

Nevertheless, any advice in our understanding of epilepsy has followed a philosophic or scientific progress or major technologic discovery. By explaining natural phenomena as physical forces and not divine acts, the philosophers of Ionia probably paved the way for Hippocrates' disconnection of epilepsy from the supernatural and connection to the brain. Similarly, the progress in anatomy and physiology, and in particular the observations and experiments in cortical localization of specific functions, influenced Jackson's innovative concepts. The discovery by Galvani and others of nerve and muscle electricity led eventually to Berger's invention of EEG, which revolutionized modern epilepsy. The subsequent development of imaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI) as well as functional imaging such as single photon emission computed tomography (SPECT), positron emission tomography (PET), and functional MRI gave new insights into our understanding of epilepsy.

The current explosion in molecular biology and genetics has been opening new horizons in the study of specific epileptic syndromes and will hopefully lead to the discovery of new specific antiepileptic drugs to control or even prevent the occurrence of seizures.

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Chapter 4

Sociocultural Perspectives

Leon Eisenberg

Introduction

The clinical course of epilepsy is the result of two vectors: The pathophysiology of the disease process and the social context in which the patient lives. The objective of this chapter is to outline the sociocultural factors. A century ago, when there were no effective treatments, clinical course was primarily a function of the underlying biology of the disease. Today, the very successes of medicine and surgery in seizure control[2,9,28] have made the sociocultural factors that govern access to care major determinants of illness trajectory.

In respect to health and illness, the term *sociocultural* focuses on three aspects of social life: First, the set of beliefs by which the members of a community understand the workings of the world they inhabit (and, in particular, the theories they hold about the cause and cure of disease); second, the methods, the techniques, and the organizational means by which care is provided to those who are judged to be sick; and third, the class structure of the community, which governs the likelihood of becoming ill, as well as the probability of receiving care. The world over, those with the fewest resources (in both industrialized and developing countries) are at the greatest risk of becoming ill and are the least likely to receive health care, a phenomenon that the British physician Julian Tudor Hart[14] has termed â€œthe Inverse Care Law.â€

When Western physicians think of culture, they are likely to associate it with the exotic: The beliefs held and the practices observed among peoples remote in space or time from modern Western â€œcivilization,â€ which is assumed to be â€œrationalâ€ and â€œscientific.â€ This cultural chauvinism is a major handicap in analyzing health problems in developing countries. It overlooks the problematic nature of the â€œculturalâ€ beliefs of our own Western medical community; some of what we take to be true is firmly evidence based; much of it is based on no more than the oral tradition physicians call â€œclinical experience.â€ Attributing â€œbeliefâ€ to the â€œnativesâ€ and â€œrationalityâ€ to the â€œdoctorsâ€ is a source of grievous error. Misused, the concept of â€œcultureâ€ can obscure our recognition of the financial and organizational barriers to care and can tend to blame the victims for their own misfortune.

A particularly tragic instance has been described in eloquent language by Anne Fadiman.[10] The book's title, *The Spirit Catches You and You Fall Down*, is an approximate translation of the term for epilepsy among the Hmong peoples, who attribute the disorder to spirit possession and believe it should be treated with animal sacrifices. The Hmong parents, recent refugees from Laos, had no understanding of Western medicine; the doctors in California had no knowledge of Hmong culture. Misunderstanding between physicians and the parents and conflicts between the physicians and the Hmong shaman the parents consulted resulted in brain death even though all of those involved acted from humane intentions.

Medical understanding is always incomplete; it changes as new paradigms arise. Not so long ago, doctors shared the prevailing pessimism about epilepsy and employed desperate, though unavailing, remedies. As recently as 1968, Rodin wrote that four-fifths of all patients with epilepsy are likely to go on to a chronic seizure disorder, as cited by Reynolds.[20] He was echoing Gowers's[13] view that â€œthe spontaneous cessation of the disease was an event too rare to be reasonably expected.â€ Recent studies reveal completely reversed odds. Population-based data reveal that no more than 20% to 30%, rather than 80%, of newly diagnosed patients develop chronic epilepsy. The National General Practice Study of Epilepsy[4] reported that 3-year remission rates were 87% and 5-year rates 71% for idiopathic epilepsy.

Doctors have done far worse than cast a gloomy prognosis. Nineteenth-century physicians dosed patients with bromides, opium, and snake venom extract; they drilled holes in the skull and removed ovaries. As these radical ministrations failed, physicians invoked hereditary explanations that focused on degeneracy and made epileptics into moral lepers.[8] Epilepsy was equated with madness and criminality. Those medical opinions lent credence to early 20th-century immigration laws that restricted the entrance of epileptics into the United Statesâ€"laws not changed until 1965. By the late 19th century, discouraged and frustrated by the failure of even desperate treatment measures, the medical community concluded that epileptics would be â€œbest offâ€ in isolated, out-of-sight communities where, in the euphemistic language of the day, they would receive â€œthe best possible care and treatment.â€ One of the first such institutions, Craig Colony for Epileptics, opened in southwestern New York state in 1896; it did not change its name until 1967.[8] This history is not cited to judge our predecessors with the wisdom of hindsight but to remind us of how widespread ignorance and superstition were in our Western medical culture until phenobarbital and phenytoin revolutionized care in the second third of this century.

Historical Belief about Epilepsy

Epilepsy is an ancient disease that has been â€œexplainedâ€ for as long as it has been perceived. Its manifestations invite arcane theories of its causes and its meanings. Seizures are dramatic, public, and frightening. They occur with unpredictable frequency in unexpected places. The forced cry, the loss of consciousness, the fall, the twitching, and the foaming at the mouth suggest possession by a spirit. The antiquity of the recognition of the disease is attested to by an Akkadian text from the second millennium BC. It describes someone whose neck turns left, whose hands and feet become tense, whose eyes stare wide open, whose mouth froths, and who loses consciousness.[25]

A Babylonian text dated from the middle of the first millennium BC deals with epilepsy, â€œthe falling disease.â€ Its manifestations were attributed to the work of demons and ghosts that â€œpossessedâ€ the victim during the seizure.[31]

Epilepsy was the subject of the first monograph on a single disease.[25] The Hippocratic text *On the Sacred Disease* was written about 400 BC. It records the struggle between â€œscientificâ€ and â€œmagicâ€ interpretations of epilepsy. Epilepsy, the author asserts, is no more divine than are other diseases. The book attacks magicians, wizards, and charlatans, who called the disease â€œsacred.â€ The alleged divine character, the author insists, is nothing more than a blindfold to conceal ignorant and fraudulent practices.

Although belief that the patient is possessed by an evil demon has been the common response, seizures can also be interpreted as divine possession, particularly if they are heralded by auras of ecstasy, such as those that enrapture Myshkin in *The Idiot*[7]:

> â€œSuddenly in the midst of sadness, spiritual darkness and oppression, there seemed at moments a flash of light in his brain, and with extraordinary impetus all his vital fores suddenly began working at their highest tension. The sense of life, the consciousness of self, were multiplied 10 times at these moments which passed like a flash of lightning. His mind and his heart were flooded with extraordinary light; all his uneasiness, all his doubts, all his anxieties were relieved at once; they were all merged in a lofty calm, full of serene, harmonious joy and hope. But these moments, these flashes, were only the prelude of that final second â€¦ with which the fit began. That second was, of course, unendurableâ€¦. â€œWhat if it is a disease?â€ he decided at last. â€œWhat does it matter that it is an abnormal intensity, if the result, if the minute of sensation, remembered and analyzed afterward in health, turns out to be the acme of harmony and beauty, and gives a feeling, unknown and not divined until then, of completeness, of proportion, of reconciliation, and of ecstatic devotional merging in the â€œhighest synthesis of life?â€â€¦ That it really was â€œbeauty and worship,â€ that it really was the â€œhighest synthesis of lifeâ€ he could not doubtâ€¦. At the very last conscious moment, he had time to say to himself clearly and consciously, â€œYes, for this

moment, one might give one's whole life!â€

Beliefs about Epilepsy in Traditional Societies

Belief in supernatural causes is widespread in traditional societies today: The revenge of aggrieved ancestors; visitation by the devil; ghosts; or the evil eye, witchcraft, and bewitchment. Sorcery is a way of trying to explain the relationship between experienced misfortune and the envy, conflict, hatred, and malice in the community.[27] In Ethiopia, patients may be treated as lepers and banished.[12] Among the Navaho, epileptics were suspected of having committed incest.[19] Informants in Kenya and Ecuador reported that they would not let their children play with known epileptics, nor would they let their children marry into such families.[24] Because of the frequency with which burns follow seizures in cooking areas, epilepsy is known as â€œthe burn diseaseâ€ in some societies.[29]

Where epilepsy is considered to be infectious, patients are shunned. Ideas of pollution and contamination create enormous difficulties for patients and families. What is the origin of the belief in the infectious and toxic nature of the epileptic's saliva? Jilek[15] suggests that it stems from a conflation of epilepsy with rabies, given that rabies manifests itself by agitation, spasms, and terminal generalized convulsions with frothing and foaming. The saliva of rabid patients is indeed infectious. The hypothesis that the confusion between epilepsy and rabies accounts for the belief in contagion is supported by the correlation in Africa between the regions where rabies is endemic and those where belief in the infectiousness of epilepsy is prominent.

There have been two recent studies of public attitudes toward epilepsy in developing societies, one in Tanzania and one in China. Whyte[30] examined beliefs about epilepsy in three rural villages and in one urban community in each of two regions of Tanzania. The most common attribution for the cause of the disorder was supernatural powers: Sorcery by others who were jealous or envious of the victim or his or her parents, spirits, ghosts of departed ancestors, or curses put on children by their parents. Accusations of possession and witchcraft as well as actual social deprivation and ostracism were frequent, as were negative attitudes about marriage, sharing accommodations, schooling, and even physical contact. The label *epileptic* carries so strong a stigma that some families employed elaborate rationalizations to pretend to themselves that their children did not have epilepsy. Four out of five of the patients were not in school, either because the school insisted the child stay at home or because the parents were worried about the possibility of self-injury at school.

Lai et al.[18] studied popular attitudes in Henan province, China. More than 90% of the respondents had heard of epilepsy, and three quarters knew at least one patient with the disorder. Nonetheless, more than half the sample stated that they would object to having their children associate in school with epileptics or play with them. More than half believed epileptics should not be employed in jobs alongside ordinary workers. Almost 90%, whether they were poorly educated or well educated, objected to the idea of having their children marry an epileptic.

Beliefs in witchcraft may flourish where medical care is unavailable, but patients remain concerned about confidentiality, even in industrialized countries where legislation formally protects their rights. In a UK study of patients with a recent diagnosis of epilepsy,[3] 70% of the patients feared that knowledge of their illness might jeopardize their employability. Stigma is still alive and well in the West.

Epilepsy and the Family

Kleinman et al.[17] undertook an ethnographic study of families with epileptic members in two poor and fairly remote regions of interior Chinaâ€"not the China of Beijing and Shanghai. They uncovered extensive emotional, financial, and marital burdens. Stigma, loss of face, and diminished self-esteem were widespread. Ideas that attribute the cause of epilepsy to bad fate, heredity, negative geomantic forces, and the malign influences of gods, ghosts, or ancestors are all accusations about moral status. Moral blame is not applied to the patient alone but extends to the entire family. Patients with seizures routinely experience discrimination in school, the workplace, and the community. The emphasis on social control rather than patient rights in China means that pupils with epilepsy may be excluded from the classroom, workers may not be permitted to carry on with their jobs, and work units may discriminate against patients and families who request more resources for treatment.

Families feel a powerful need to protect the child with epilepsy. They are afraid the child will get no help if a seizure does occur in public because of the general fear of contamination. This results in isolating the patient at home. Overprotection of sufferersâ€"a form of intrafamilial social control aimed at preventing epileptic family members from being shamed and from harming themselves if they have a seizure in a public placeâ€"unfortunately often becomes the chief constraint on the patient's life chances.

The financial consequences of epilepsy can be ruinous. The economic constraints often mean the difference between receiving treatment and not, between remission and relapse. For Chinese parents, a child disabled by sickness means that they are both legally and morally responsible for care until

they or the child die or until the child marries. With marriage, the responsibility for care is shifted to the spouse; thus, there is great pressure to conceal the epilepsy and to arrange a marriage. The illness transforms the economic conditions of everyday life, using up limited resources, deepening debt, and forcing families into humiliating negotiations with creditors.

Help-seeking Behavior

Help seeking, in both rural and urban areas of China, relies on consulting traditional Chinese doctors and various folk healers, herbalists, and religious healers.[17,18] Traditional healers are sought after to counteract witchcraft and sorcery by others. Alert and entrepreneurial healers take full advantage of popular suspicions. The most costly treatments were those administered by healers who were frequently consulted even where free government medical services were nominally available. Patients and families do not actually avoid biomedical treatment; too often they are unaware of it. When they do attend Western-style dispensaries, they complain that they are not given a diagnosis. This is rare among those who consult healers. Healers â€œexplainâ€ the disorder in terms that fit with the culture, explanations that â€œmake senseâ€ of the problem, even if the remedies fail to work.

Adherence to Treatment

Although controlled trials leave physicians in no doubt that anticonvulsants control seizures, their effectiveness is much less clear to individual patients and families. Families come seeking cure rather than suppression of seizures; the notion that continuous treatment is needed to prevent recurrence or that partial suppression is worthwhile when total control is not possible is alien. Patients with epilepsy know from their own experience that seizures may continue in spite of treatment and there may be no seizures during periods of no treatment. In the Kleinman[17] study, more than one in four of the respondents had stopped their treatment altogether because of its perceived ineffectiveness, troublesome side effects, or costs. However, that phenomenon is not limited to â€œtraditionalâ€ cultures.

In U.S. studies, noncompliance with drug treatment averages 30% to 40%, with a range from 20% to 70%.[5] Many patients attempt to regulate their own medication. In their lexicon, they are not â€œnoncompliantâ€; they are â€œmanagingâ€ the control of their own illness on the basis of experience. They take extra medication when they anticipate â€œstressful circumstancesâ€ or sense that a seizure is coming on; they reduce dosage when they are feeling â€œflattened outâ€ and anticipate a special need for alertness. Others suspend medication periodically to see if they still â€œneedâ€ it. If seizures return, they go back on drugs. They resent their dependence on medication and want to see if they can get on without them. Regulating medication is an attempt to assert control over a chronic disorder for which there is no cure.[26]

Does â€œCultureâ€ Bar Modern Treatment?

In traditional communities, resort to more than one type of care is common. The available range of explanations includes somatic, psychosocial, hereditary, and supernatural causes. As Whyte[30] points out: â€œ[This] means that elements of neurologic and psychiatric medicine can be accepted without â€¦ excluding other possible explanations.â€ Western and traditional medicine can coexist peacefully, so long as neither asserts a claim to exclusivity. If the patient takes the medication regularly, it will control the fits. If patient and family choose also to participate in healing rituals, the ceremonies may offer psychologic comfort and repair social rifts without impairing drug action.

Reports from Kenya and Malawi document the success of treatment programs employing a limited pharmacopeia but enjoying strong community support because of the provision of responsive services. At both sites, seizures were fully controlled in about half the patients and reduced in another quarter. The Kenya protocol[11] was carried out by primary health workers backed up by a physician. Outcome was similar to that in industrialized countries where about 70% of patients with newly diagnosed epilepsy can be controlled with a modest dose of a single antiepileptic drug.[2] The Malawi study[29] recruited a remarkably large clientele: More than 3,000 patients attending 45 clinical units distributed throughout the country. The medical officer enlisted the enthusiastic support of area chiefs and village representatives. Patients and families were given an explanation of disease pathogenesis (â€œa scar on the brainâ€) that justified the need for continuous treatment (â€œit takes a long time for the scar to healâ€). Program success was based on communication channels appropriate for the culture, educating health care staff as well as patients, a simple treatment regimen, mobile clinics to make care more accessible, ensuring an adequate supply of drugs, treating without charge, and holding monthly clinics, with the patient seen by the same staff member each time.

Patient education for families in rural areas should stress safety in such simple daily tasks as drawing water from a well, cooking on an open fire, fishing, and other mundane activities. Education for the general public must address stigma and institutional discrimination. To succeed, it must enlist local opinion leaders in a continuing campaign to overcome prejudice and reintegrate patients into school, work, and community life.

Gretchen Birbeck and Roy Baskind[1] held focus group discussions to develop working relationships with ten traditional healers in Zambia. The healers (N'Ganga) recognize epilepsy by means of much of the same symptoms neurologists employ, but they believe witchcraft plays a central role in provoking seizures. Treatment incorporates plant and animal products; if it fails, the healer may refer to other â€œmore powerfulâ€ N'Ganga. If there is evidence of associated systemic illness (brain injury, malaria, high fever), they will refer patients to the hospital for Western treatment. The discussion led to an informal agreement for hospital staff to make periodic visits to the villages to see patients referred by traditional healers and for the healers to be welcome observers on the ward.

Magnitude of the Problem

Is epilepsy an important public health problem? The World Health Organization (WHO)[33] estimates that there are some 50 million people with epilepsy worldwide, more than half not treated properly or not treated at all. Each year, there are some 2 million new cases, half preventable. According to World Bank estimates, epilepsy causes about 9% of the total burden resulting from mental and neurologic disease; among children from 5 to 14 years of age, it is the eighth leading cause of morbidity.[32] The incidence and prevalence of epilepsy are probably several times higher in developing than in industrialized countries, particularly in regions where parasitic infections, notably neurocysticercosis, abound.[23] The treatment gapâ€”the percentage of patients with active epilepsy who are not in treatmentâ€”estimated by the WHO to be 50% the world over, is more than 90% in Paki-stan and the Philippines, and more than 80% in Ecuador.[24] Applying today's methods for prevention and treatment

could reduce the worldwide illness burden from epilepsy by 75%.

The Outcome of Untreated Epilepsy

There is a striking discrepancy between incidence and prevalence rates in low-income countries. As noted, prevalence is higher than in industrialized societies, but it is clearly not as high as incidence rates would predict, given that untreated epilepsy is a chronic disease. The reason for the failure of prevalence to rise to expected levels in view of the treatment gap could lie either in unexpectedly high remission rates, which seems unlikely,[21] or in differential mortality, that is, death rates for epileptics considerably greater than those in the general population.[22] Is there any evidence for high mortality?

When Dr. Louise Jilek-Aall[16] returned to the Ulanga district of Tanzania, where she had established a successful treatment program from 1963 to 1971, she discovered that her former patients had been without medication for the two decades since her departure. She was able to obtain information on 164 of the more than 200 patients she had treated 30 years earlier. Two thirds were dead! Where the causes of death could be ascertained, half were due to the epilepsy itself: Status epilepticus, death during a seizure, drowning, or burns. The mortality rate among the former patients was far greater than that for the rural population of the area. In contrast, in industrialized countries, where care is widely available, the mortality rate among epileptic patients is only slightly higher than that of the general population. In the light of the â€œtreatment gap,â€ these outcome data reveal a public health problem of serious magnitude.

Summary and Conclusions

Belief that epilepsy has supernatural causes is widespread among the world's peoples. The disorder may be interpreted as the revenge of aggrieved ancestors, as punishment for sinful past behavior by the patient or the family, or as witchcraft cast upon the family by its enemies. Patients may be banished from the classroom, the playground, and the workplace, lest the disease infect others; they will be rejected as future marital partners, lest epilepsy be passed on within the family. Families may so fear public rejection that they keep their child out of view by isolating him or her at home. The financial consequences of epilepsy can be ruinous; treatments from traditional healers are often very costly.

What allows stigma to persist is the treatment gap: The 80% to 90% of patients in low-income populations who are not in care. When treatment is made accessible, and when it respects patient and family needs, is affordable in cost, and is consistent in its application, seizures can be fully controlled in half the patients and reduced in another quarter of patients in low-income societies. The integrated application of modern methods of prevention and treatment can reduce the illness burden from epilepsy worldwide by three quarters.

The *World Mental Health* report[6] proposes a new structure for a UN World Mental Health Program. The report is designed to persuade the Consultative Committee for Management (the interagency coordinating committee) to undertake epilepsy control as a major project. It is up to health professionals to make certain that epilepsy gets a high priority on the international public health agenda.

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Chapter 5

Incidence and Prevalence

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W. Allen Hauser

Introduction

To develop optimal approaches to the treatment of epilepsy, to evaluate the effectiveness of treatment strategies, and more importantly, to identify interventions that may prevent the development of epilepsy, valid information regarding the frequency, cause, and natural history of the condition is necessary. Such information is provided by descriptive and hypothesis-testing epidemiologic studies. Early reports of the prevalence of epilepsy, which used information from selective service records, provided data similar to those of contemporary studies undertaken in industrialized countries, such as the United States, for the same age groups.[27] Approaches to the study of the epidemiology of epilepsy have become increasingly sophisticated; current epidemiologic studies provide a much more comprehensive picture of the characteristics of persons with epilepsy, which has led to considerable improvement in understanding epidemiologic features of the seizure disorders in general and epilepsy in particular. These improved methods include the development of clear definitions of the condition being studied; use of data provided by incidence studies of the convulsive disorders; and use of these incidence cases and other inception cohorts to determine natural history and identify risk factors. Unfortunately, incidence studies are expensive and difficult to do. Therefore, there are relatively few reports dealing with total populations. Relying on less expensive and relatively less complex studies of prevalence to gain epidemiologic insights can be compared to an epileptologist performing epilepsy surgery based on clinical history alone. One may have some of the pieces, and a correct decision may be made, but in many cases, an inappropriate procedure will be undertaken.

The following discussion reviews data regarding the incidence of seizure disorders and epilepsy, and the risk factors for epilepsy as suggested by these studies. In addition, potential insights provided by prevalence studies are highlighted. Definitions are important in epidemiologic studies. In the present discussion, the term *epilepsy* represents a condition characterized by two or more unprovoked seizures. For other definitions, the reader is referred to the report of the Commission on Epidemiology and Prognosis of the International League Against Epilepsy (ILAE).[46]

Incidence of Epilepsy

Total Population Studies

There are relatively few studies of incidence of epilepsy in total populations. In developed countries, the age-adjusted incidence of epilepsy (recurrent unprovoked seizures) ranges from 24 to 53 per 100,000 person-years.[6,30,44,50,57,58,59,60,72,95,100] Total population studies reporting the incidence of a first diagnosis of unprovoked seizures (differing from incidence of epilepsy by the inclusion of persons with a single unprovoked seizure as well as those with recurrent unprovoked seizures) provides estimates of incidence ranging from 26 to 70 per 100,000 person-years[37,51,57,60,72,90,112] (see Table 1). Given methodologic differences, the incidence in studies of predominantly Western, industrialized countries seems remarkably consistent across geographic areas. This seems particularly true of reports for the last two decades (1986 to 2005).

Several recent studies provide incidence from developing countries. An incidence of epilepsy that is considerably higher than that reported in industrialized countries (114 per 100,000 person-years) has been reported from a rural area of Chile.[66] A study in Tanzania[106] reported the incidence of epilepsy to be 77 per 100,000. These are two to three times the incidence reported in industrialized countries in which similar definitions have been used. A study in Ethiopia reported an incidence of 64, but this fell to 46 after age adjustment, underscoring the importance of age adjustment if comparisons are to be made. A large population-based survey in Ecuador[97] identified all individuals with a history of seizures. Included were all persons with newly occurring nonfebrile seizures (including acute symptomatic seizures) and some children with multiple febrile seizures. Based on the number of people seen with seizures in the year preceding the survey, incidence was higher than that of most other reports (190 per 100,000), although incidence for neurologically confirmed cases was about 30% lower. In studies in France[72] and Rochester, Minnesota,[50] about half of newly occurring afebrile seizures do not fulfill criteria for epilepsy.

Because of the broader case-inclusion criteria in the study from Ecuador and uncertainty regarding age-specific distribution and cause of acute symptomatic seizures, there is no way to compare these incidence studies. Nonetheless, the incidence of epilepsy may likely be higher in developing countries than in industrialized countries.

Table 1 Incidence of Epilepsy in Select Population-based Studies of All Age Groups

					Incidence	
Reference	Publication date	Region	Population/person-years	Number of cases	Crude	Age-adjusted (U.S. 2000 census)
Brewis[21]	1966	England	497,707	141	29	28
De Graaf[30]	1974	Norway	213,116	70	33	26
Granieri et al.[44]	1983	Italy	697,100	230	33	33
Joensen[59]	1986	Faroe Islands	452,584	194	43	37
Rwiza et al.[106]	1992	Tanzania	165,684	122	74	51
Lavados et al.[66]	1992	Chile	90,596	102	113	92
Hauser[50]	1993	Rochester, MN 1975â€œ1984	573,152	275	48	51
Sidenvall et al. and Forsgren et al.[37,112]	1993 & 1996	Sweden	152,275	226	â€”	58[a]
Olafsson et al.[89]	1996	Iceland	90,237	42	47	43
Tekle-Haimanot[116]	1997	Ethiopia	215,901	139	64	43
Jallon et al.[58]	1997	Switzerland	384,657	176	46	â€”
Jallon et al.[57]	1999	Martinique	383,596	246	64	â€”
Annegers et al.[6]	1999	Texas	601,448	197	33	28
MacDonald et al.[77]	2000	England	100,230	69	46	79

Olafsson et al.[90]	2005	Iceland	882,151	501	57[a]	52[a]

[a] All unprovoked seizures.

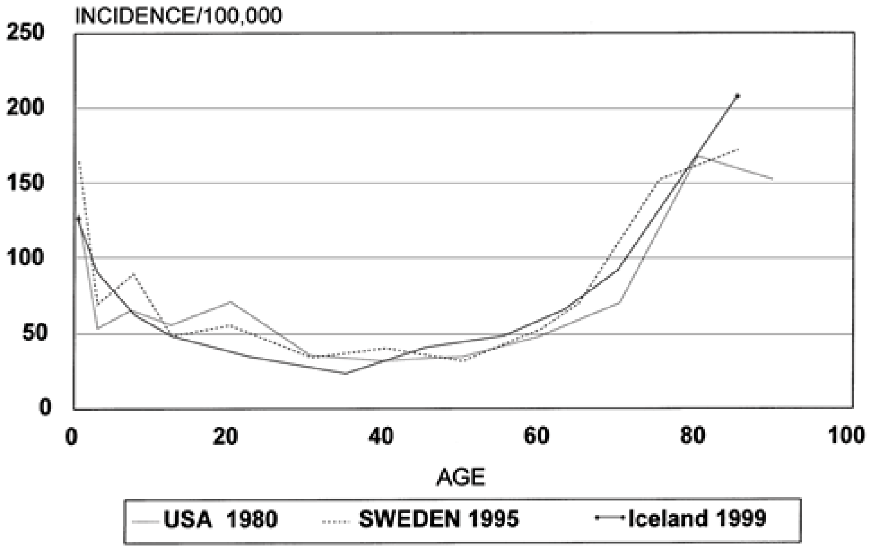


FIGURE 1. Age-specific incidence of epilepsy in industrialized countries.

Studies in Selected Age Groups

A number of studies report the incidence of epilepsy in specific age groups. These include studies of child-ren,[14,15,20,22,24,33,36,38,84,102,111,112,117] adults,[37,50,64,90,95] and the elderly.[71,76,105,115] Evaluation of these studies again requires consideration of definitions used, but in general, information is complementary to and consistent with incidence in total-population studies when age-specific rates are evaluated. For example, the more comprehensive studies limited to children[111,117] include children with neonatal seizures and children with a single unprovoked seizure as incidence cases of epilepsy. Taking this into account, incidence in the youngest

age group in studies limited to children are, in general, similar to those reported in total population studies.

Age-specific Incidence

Contrary to popular belief, epilepsy is a disease with onset at the extremes of life (Fig. 1), at least in industrialized countries. Where provided, age-specific incidence is consistently high in the youngest age groups, with highest incidence occurring during the first few months of life. Incidence falls dramatically after the first year of life, seems relatively stable through the first decade of life, and falls again during adolescence.[22,51,90]

In virtually all studies conducted in industrialized countries, age-specific incidence is lowest during the adult years. Contemporary incidence studies, most of which are in Western countries, show an increasing incidenceâ€”at times dramaticâ€”in the elderly.[37,50,71,88] In Western countries, the incidence of epilepsy is higher after the age of 70 years than during the first 10 years of life. Only about 50% of cases of epilepsy start in childhood or adolescence.[50,90] A British general practice survey reported that almost 25% of all newly identified seizures (not epilepsy) occurred in persons aged 60 years and older.[108]

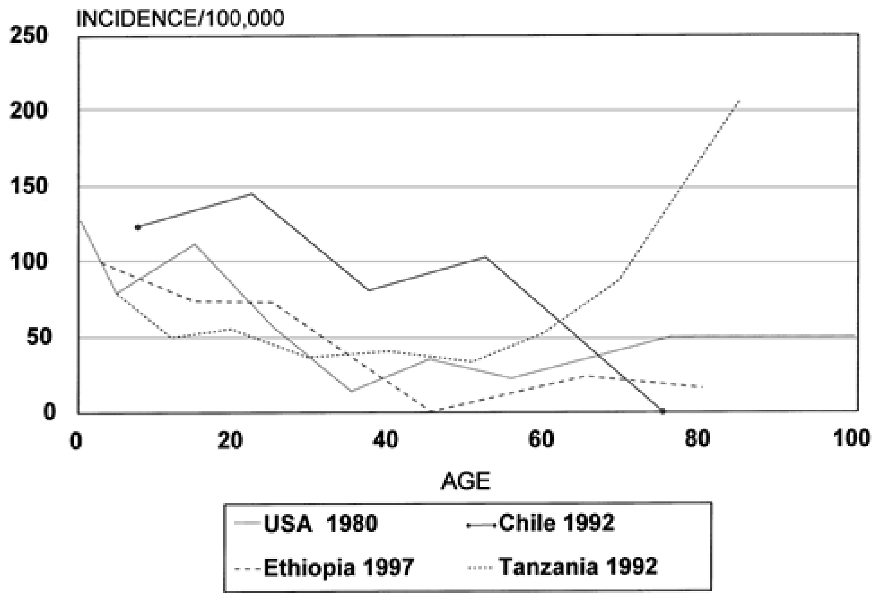


FIGURE 2. Age-specific incidence of epilepsy in developing countries.

Table 2 Classification of Seizure Type in Select Incidence Studies

Reference	Publication date	Region	Partial (%)	Generalized (%)	Unclassifiable (%)
Brewis[21]	1966	England	â€”	â€”	â€”
De Graaf[30]	1974	Norway	â€”	â€”	â€”
Granieri et al.[44]	1983	Italy	32	59	9
Joensen[59]	1986	Faroe Islands	51	39	10
Rwiza et al.[106]	1992	Tanzania	32	58	10
Lavados et al.[66]	1992	Chile	54	38	8
Hauser[50]	1993	Minnesota	57	40	3
Sidenvall et al. and Forsgren et al.[37,112]	1993 1996	Sweden	60	27	13
Olafsson et al.[89]	1996	Iceland	31	69	â€”
Tekle-Haimanot et al.[116]	1997	Ethiopia	20	69	11
Jallon et al.[58]	1997	Switzerland	â€”	â€”	â€”
Jallon et al.[57]	1999	Martinique	â€”	â€”	â€”
Annegers et al.[6]	1999	Texas	â€”	â€”	â€”
MacDonald et al.[77]	2000	England	â€”	â€”	â€”
Olafsson et al.[90]	2005	Iceland	40	58	2

The reported patterns of age-specific incidence are quite different in developing countries. In studies from Africa and South America, the peak incidence of epilepsy occurs in young adults, and the dramatic increase in incidence in the elderly has not been identified (Fig. 2).[66,106,116] It is likely that patterns of incidence, and therefore risks for epilepsy, are different in these populations.

Sex

In most total population studies, incidence of epilepsy or of unprovoked seizures is higher in males than in females. This seems true even after the higher incidence in males of definitive risk factors for epilepsy (i.e., head injury, stroke, central nervous system infection) is taken into account. One exception is the study from Ecuador,[97] in which the male-to-female ratio is 0.8, although this study cannot be used for comparison as it included persons with acute symptomatic as well as unprovoked seizures. The other exception is the study of incidence in children in Sweden (male-to-female ratio of 0.7).[112] For most but not all incidence studies, sex-specific differences in incidence are not statistically significant. The consistency of the male-to-female difference across studies suggests that males are at higher risk than females for unprovoked seizures and epilepsy.

Seizure Type

Seizure-specific incidence or proportions of cases with a specific seizure type based on the International Classification of Epileptic Seizures[100] are provided in several contemporary incidence studies (Table 2). A detailed distribution from the Iceland study[90] is provided in Figure 3. In studies in Rochester, Minnesota,[50] the Faeroe Islands,[59] and Chile,[66] slightly more than 50% of incidence cases were classified as partial seizures. Partial seizures are also the predominant seizure type in Sweden in adults after information from the separate studies of adults and children is combined.[37,112]

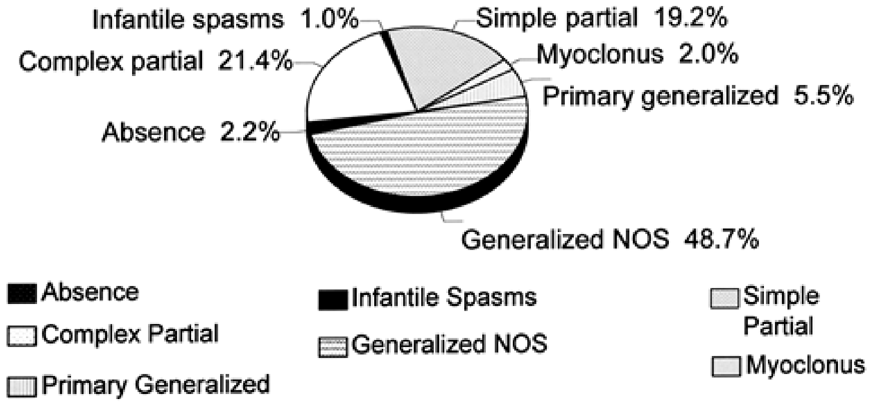


FIGURE 3. Distribution of seizure type in Iceland incidence cases, 1995â€“1999. NOS, not otherwise specified.

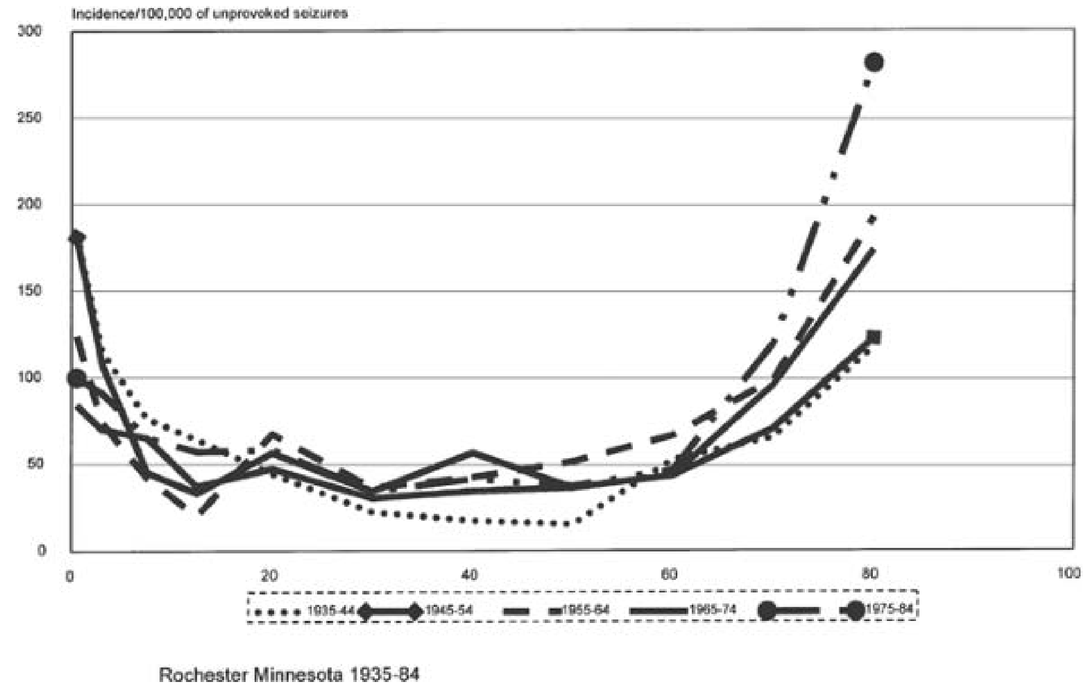


FIGURE 4. Time trends in Rochester, Minnesota, 1935â€“1984.

Race

Most total population incidence studies have been performed in white populations of European extraction. Even in studies of incidence in Asian or African populations, study groups have been homogeneous. Racial differences have been examined only in incidence or cohort studies in children. In the National Collaborative Perinatal Project,[83] incidence of afebrile seizures did not differ across racial groups through the age of 7 years. In studies of Japanese children in Tokyo[117] and Caucasian children in Rochester, Minnesota,[50] age-specific incidence and incidence by seizure type through the age of 14 years were virtually identical. Definitions of epilepsy were similar in these two studies, although methodology was different. A study of children in New Haven, Connecticut,[111] reported incidence of epilepsy through age 15 years to be 1.7 times greater in blacks than in whites, although the definition of epilepsy was quite different from those used in many of the studies mentioned above. This study also made an ecologic comparison based on mean neighborhood socioeconomic level. After controlling for race, incidence of epilepsy was significantly higher in lower socioeconomic classes.

P.48

Time Trends

Information on time trends of incidence is provided in the studies from Copparo, Italy,[44] and Rochester, Minnesota.[50] In the Italian study, the incidence of epilepsy decreased over three time intervals from 1964 to 1978, although this may be related to methodologic issues (Fig. 4). The Minnesota study reports a more than 50% decrease in the incidence of epilepsy in those under the age of 10 years from 1935 to 1984. During these same years, there was an increase in incidence in those over age 60 years, causing the age-adjusted incidence in this community over the entire 50-year interval to show little change.

P.49

The fall in the middle decades of this century is largely unexplained, but the increase after 1975 may be related to increased survivorship of very-low-birth-weight infants. The findings of this study underscore the potential pitfalls in relying on total incidence of epilepsy in children.

In the studies of a British general practice that included all afebrile seizures, incidence under age 20 was 172 per 100,000 between 1964 and 1973, 152 per 100,000 between 1974 and 1983, and significantly lower (61 per 100,000) from 1984 to 1993.[26] This difference may be explained partially by inclusion in the earlier period of nonepileptic episodes, but even cautious interpretation of these data suggest dramatic reductions in the incidence of childhood-onset epilepsy in industrialized countries. The reduction in incidence over time in children is not readily explained by current epidemiologic or clinical data and deserves further investigation.

It appears that the incidence of epilepsy in the elderly is increasingâ€”at least in the United States. This may be related, at least in part, to an increase in the proportion of the population with a history of stroke.[4] Although the incidence of stroke is decreasing, the prevalence is increasing as more people are surviving strokes.

Epileptic Syndromes

There are few total population incidence studies that present the distribution of epilepsy syndromes such as the study conducted in Bordeaux,[72] studies from Rochester,[50] and studies from Iceland.[90] Some studies provide the distribution of epilepsy syndromes among newly diagnosed cases of epilepsy.[63,72,78,112,121]

In Bordeaux, the incidence of idiopathic localization-related epilepsy was 1.7 per 100,000 (7% of all cases). An additional 13.6 per 100,000 (56%) had symptomatic localization-related epilepsy. Thus, if the same criteria are used as in most other contemporary incidence studies, about 60% of cases can be classified as partial seizures. Each of the following syndromes accounted for about 1% of new cases: Juvenile myoclonic epilepsy, awakening grand mal, and West syndrome. About 2% had pyknolepsy. These proportions are similar to those provided by the Rochester, Minnesota, studies.[9] Crude incidence for all epilepsy (about 24.5 per 100,000) was about half that reported in studies in industrialized countries.[37,44,59,89,90] A few reports of incidence of specific epileptic syndromes in other total population studies provide data consistent with the above figures.[37,59,90]

The incidence of nonfebrile situation-related epilepsy in the French study was about 30 per 100,000.[72] Incidence for this class of seizure in Rochester, Minnesota, was about 40 per 100,000.[85] Isolated unprovoked seizures occurred in 18 per 100,000 population in the French study, which is similar to that in Rochester[50] and considerably less than that reported from Iceland.[90]

There are some reports of the incidence of specific syndromes. West syndrome has been studied in different geographic areas,[48,75,90] with an incidence ranging from 2 to 7 per 10,000 live births. Benign rolandic epilepsy is thought to be among the more frequently occurring childhood epileptic syndromes; one Italian study[24] reported this to account for 24% of incidence cases in children with epilepsy between the ages of 4 and 15 years. In Sweden, the incidence of benign rolandic epilepsy in children under 15 years of age was 10.7, accounting for about 14% of childhood epilepsies.[112] In Iceland, benign rolandic epilepsy accounted for 5% all newly diagnosed cases.[90] The incidence of juvenile myoclonic epilepsy in the Faeroe Islands was 1.1 per 100,000 per year, or about 2.5% of cases.[59] In Sweden, five children under the age of 15 years had a diagnosis of juvenile myoclonic epilepsy, making the incidence 6 per 100,000,[112] and in Iceland, juvenile myoclonic epilepsy occurred in 1% of patients,[90] providing an incidence of 0.7 per 100,000 person-years. Data from the Rochester cohort studies suggest that the incidence of juvenile myoclonic epilepsy is about 1 per 100,000 per year.[50] These data seem to be reasonably consistent and suggest a lower frequency of juvenile myoclonic epilepsy than has been suggested in recent clinical studies. Lastly, childhood absence epilepsy occurred in seven patients in Iceland (1%; incidence of 0.8 per 100,000 person-years).[90]

Etiology of Epilepsy in Incidence Cohorts

Most of the population-based incidence studies provide information regarding presumed etiology (Table 3). Rarely have definitions for inclusion been provided, but the proportion of cases with an identified antecedent (remote symptomatic epilepsy) is relatively consistent, ranging from 23% to 39%[50](Fig. 5). In children, epilepsy associated with neurologic deficits from birth seems to be the most important single etiologic relationship, whereas cerebrovascular disease is the most commonly identified cause among adults.

Classic Risk Factors

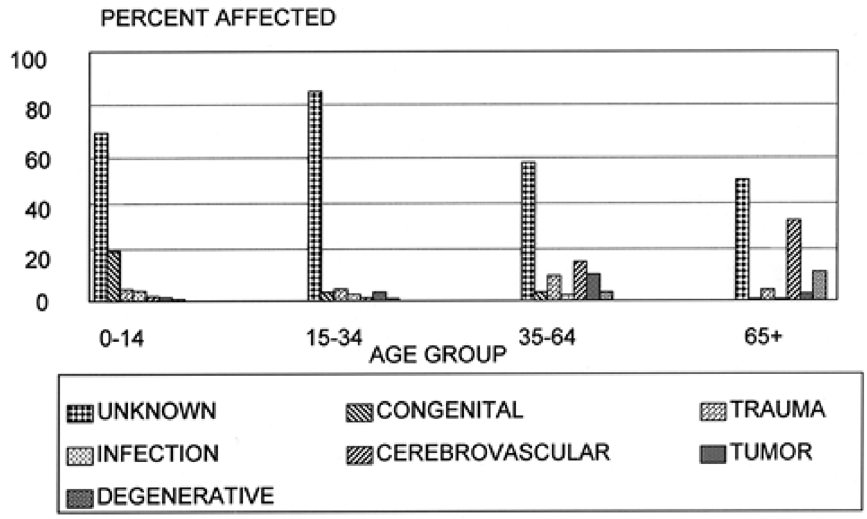
Most physicians have preconceived notions about postnatal antecedents of epilepsy. Head (brain) trauma, stroke, central nervous system infection, and degenerative brain disease are frequently identified.[5,7,9,107] Specific causes of epilepsy may differ across geographic areas, but whether incidence studies are undertaken in developing countries or in developed countries, a definitive etiology has been identified in only about one third of all newly diagnosed cases. In industrialized countries, cerebrovascular disease is the most frequently identified â€œcauseâ€ of epilepsy, accounting for about 12% of all new cases and about one third of cases with an identified cause (Fig. 6).[50,90] In South America, the most frequently identified cause is infection of the central nervous system. In developing and developed countries, cerebral palsy is associated with a large proportion of cases, particularly in children. In incidence studies in endemic areas, neurocysticercosis accounts for about 10% of newly diagnosed cases of epilepsy, confirming the importance of this factor.[23]

Risk Factors Identified in Epidemiologic Studies

Epidemiologic studies have not only confirmed the importance of postnatal insults, but also qualified the risk. As shown in Figure 7, a risk ratio of 1 implies no increase in risk, a risk ratio of â‰¤1 suggests a protective effect, and a risk ratio of >1 suggests an increase in risk. The risk for epilepsy among persons with penetrating head injuries acquired during military service is more than 500 times that expected in the general population.[107] In contrast, individuals who have had brain injury associated with loss of consciousness or amnesia of â‰¤30 minutes' duration have no increase in risk.[5] Studies have also identified other factors (drug and alcohol abuse, depressive illness, suicidality, migraine with aura, hypertension, and risk factors for stroke) that increase the risk for epilepsyâ€”at times as much as or more than the classic risk factors.[2,52,54,55,70,74,85,86,109]

Table 3 Etiology in incident cases of epilepsy or all unprovoked seizures

			Symptomatic (%)				
Reference	Publication date	Region	Progressive	Remote	Idiopathic (%)	Cryptogenic (%)	Unclassified (%)
Brewis[21]	1966	England	â€”	â€”	â€”	â€”	â€”
De Graaf et al.[30]	1974	Norway	â€”	â€”	â€”	â€”	â€”
Granieri et al.[44]	1983	Italy	39	61	â€”	â€”	â€”
Joensen[59]	1986	Faroe Islands					
Rwiza et al.[106]	1992	Tanzania	25	75	â€”	â€”	â€”
Lavados et al.[66]	1992	Chile					
Hauser[50]	1993	Minnesota	8	25	66	â€”	â€”
Sidenvall et al. and	1993	Sweden	15	28	56	â€”	â€”
Forsgren et al.[37,112]	1996						
Olafsson et al.[89]	1996	Iceland	10	21	69	â€”	â€”
Tekle-Haimonot et al.[116]	1997	Ethiopia	14	â€”	86	â€”	â€”
Jallon et al.[58]	1997	Switzerland	15	39	10	35	â€”
Jallon et al.[57]	1999	Martinique	7	30	10	53	â€”
Annegers et al.[6]	1999	Texas	25	â€”	75	â€”	â€”
MacDonald et	2000	England					



Rochester, Minnesota. 1935–1984

FIGURE 5. Age of onset attributable to various antecedents.

There is a continued belief that adverse prenatal and perinatal events are associated with an increased risk for epilepsy (Fig. 8). Although at times these may be risk factors for cerebral palsy, they have not yet been demonstrated, at least in developed countries, to be risk factors for epilepsy in the absence of overt neurologic handicap. Separate or together, pre- or perinatal factors pose little increase in risk, and for most of these factors the differences are not significant. Epidemiologic evidence does not support a causal association between febrile convulsions and epilepsy.

Family History as Risk Factors

A small proportion of cases of epilepsy may be attributable to single-gene disorders. In two syndromes with mendelian inheritance patterns, a chromosomal localization has been achieved. Benign familial neonatal convulsions with a dominant inheritance pattern was initially localized to chromosome 20,[67] but genetic heterogeneity has been demonstrated by a more recent localization to chromosome 8.[68] A gene for progressive myoclonic epilepsy has been localized to chromosome 21.[35] A gene for partial epilepsy with auditory features has been localized to chromosome 10, and several sodium and potassium channelopathies have been identified in association with Dravet syndrome and generalized epileptic seizures plus (GES+) syndromes.[17,119] Although the mode of inheritance is obscure, a localization for juvenile myoclonic epilepsy and other juvenile-onset disorders has been proposed.[35,45] Others question this finding.[120] Localizations for several other epilepsy syndromes have been identified.

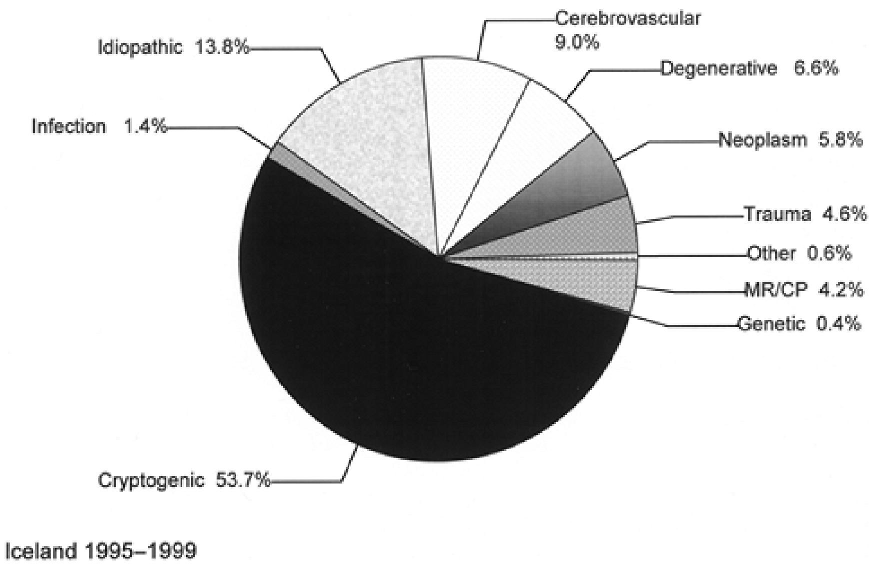
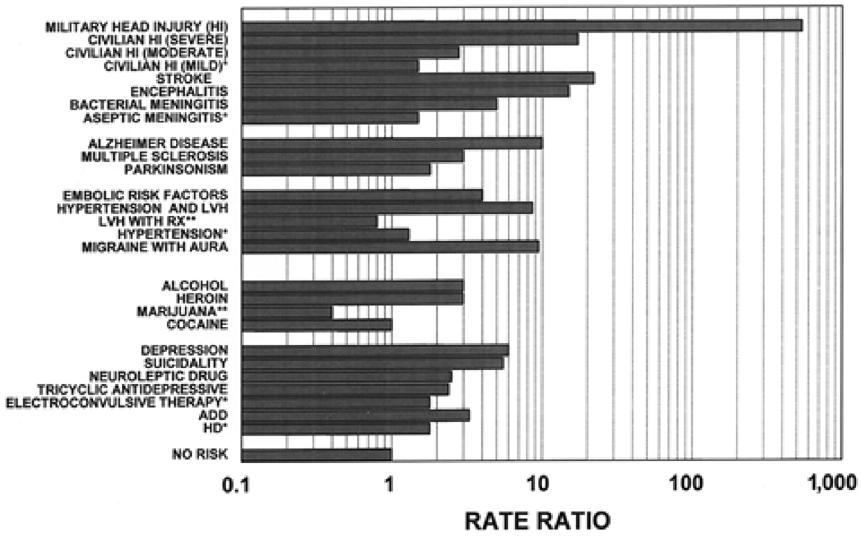


FIGURE 6. Classic risk factors.



*Not significant. **Protective.

FIGURE 7. Change in risk for epilepsy in association with specific antecedents. ADD, attention deficit disorder; HD, hyperactivity disorder; LVH, left ventricular hypertrophy.

Even though a small proportion of cases follow mendelian inheritance patterns, in epidemiologic terms family history may be considered an important risk factor for epilepsy. In the absence of other information, epilepsy in a first-degree relative increases the risk threefold.[8] The absolute increase is modified by which first-degree relative is affected (sibling, mother, father), the seizure type and etiology of epilepsy in the affected relative, and the electroencephalographic pattern in the relative or individual in question.

Cumulative Incidence

Cumulative incidence is the summation of age incidence. Given the modest alteration mortality among people with epilepsy, cumulative incidence provides an estimate of the proportion of the total population that has been affected with epilepsy by a specific age. Estimates of cumulative incidence of epilepsy have been provided in four total population studies.[50,60,89,90] In Denmark, the risk for having epilepsy by the age of 80 years was 1.3%,[60] a substantially lower number than the cumulative incidence of epilepsy for the same age in Rochester, Minnesota (4% for epilepsy and more than 5% for all unprovoked seizures)[50] or the rate of 5.4% for all unprovoked seizures to age 85 from the Iceland study.[90] This difference can be explained by the considerably higher incidence in the elderly in the Minnesota study. As would be expected from age-specific incidence rates, cumulative incidences of epilepsy through childhood are almost identical in Japan and Rochester.[50,117] In Rochester, the cumulative incidence for epilepsy and unprovoked seizures is significantly greater for males than females.

Incidence of All Afebrile Seizures

There are a few studies that include all afebrile seizures in their definitions of epilepsy, and this definition is consistent with some recent recommendations of the ILAE.[57,58,97] Table 4 includes studies from which incidence using this definition have been provided. The incidence is substantially increased in Ecuador,[97] although it is not clear if this is due to a methodologic approach or reflects differences in the burden of epilepsy between developed and developing countries.

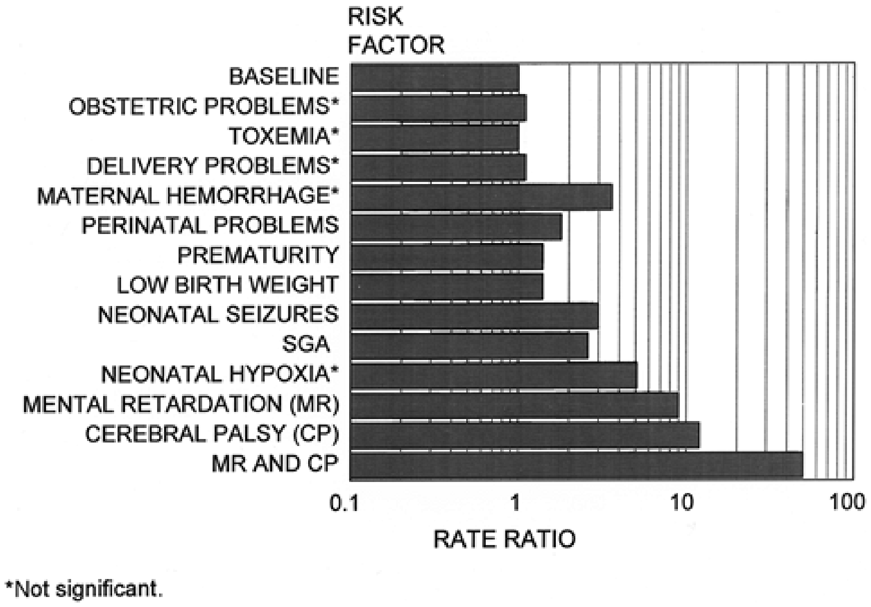


FIGURE 8. Adverse prenatal and perinatal events and risk for epilepsy. SGA, small for gestational age.

Table 4 Incidence of All Afebrile Seizures in Population-based Studies of All Ages

					Incidence	
Reference	Publication date	Region	Population	Number of cases	Crude	Age-adjusted
Placencia et al.[97]	1992	Ecuador	72,121	137	190	174
Hauser[50]	1993	Minnesota 1975â€"1984	573,152	639	111	110

Jallon et al.[58]	1997	Switzerland	384,657	273	71	70
Jallon et al.[57]	1999	Martinique	383,596	309	81	83

Prevalence of Epilepsy

Because it is easier to obtain information about prevalence than about incidence, many prevalence studies of epilepsy from diverse populations have been reported.[1,10,11,13,16,18,19,25,31,32,34,39,40,41,42,43,47,53,61,62,69,73,79,80,81,87,92,94,96,101,103,104,110,113,114] Prevalence is a measure of the interaction of obvious factors such as incidence, death, and remission of illness, and except for geographic isolates such as Iceland, prevalence is also affected by factors such as migration or access to multiple sources of medical care. Prevalence is more a reflection of survival and severity or chronicity of illness than of frequency of illness. Little reliable information regarding etiology or prognosis can be derived from prevalence studies, although they can provide intriguing clues to guide hypotheses that can be tested in properly designed studies. Prevalence data are primarily of value in planning for health care.

There are some well-known difficulties in interpreting prevalence data, related to difficulties in interpreting mortality and remission. Other difficulties stem from inconsistencies in definitions or in the fact that only crude prevalence is reported. Age-specific prevalence in developed and developing countries is difficult to compare, given the dramatic differences in age structure of the populations and the wide variation in age-specific prevalence. Age standardization should be used if any comparisons are to be made, as wide variations in apparent prevalence are demonstrated even in studies of contiguous populations.

Age-Adjusted Prevalence

Age-adjusted prevalence per 1,000 population varies widelyâ€”from 2.7 to more than 40, although most studies show a range from four to eight.[49] Even when the same investigators have used similar protocols, definitions of epilepsy, and methodologies, the prevalence of â€œactiveâ€ epilepsy ranges from 3.6 to 41.3.[18,93] Somewhat higher prevalence (ranging from 14 to 57 per 1,000) has been reported in pilot studies using a standardized World Health Organization (WHO) protocol in Panama,[43] Ecuador,[97] and Colombia.[99] However, the same protocol used in large-scale population surveys yielded low prevalence in India[18,65] and China.[69]

The high prevalence of epilepsy reported in Central and South America by those using the WHO protocol may be a reflection of methodology. One study[97] using the International Community Based Epilepsy Research Group (ICBERG) protocol in rural Ecuador found the prevalence to be considerably lower (8 per 1,000) than that reported in a pilot study[29] by investigators using the WHO protocol in the same region (18.5 per 1,000). The difference may be related to more stringent case verification in the ICBERG study, but this cannot account for all the differences. A recent population survey in a village in rural Mexico, which was age adjusted to the 1980 U.S. population, revealed a prevalence of active epilepsy of 5.9 per 1,000.[53,94] The prevalence in Pakistan is about 10 per 1,000,[12] and in rural Ethiopia about 5 per 1,000.[116]

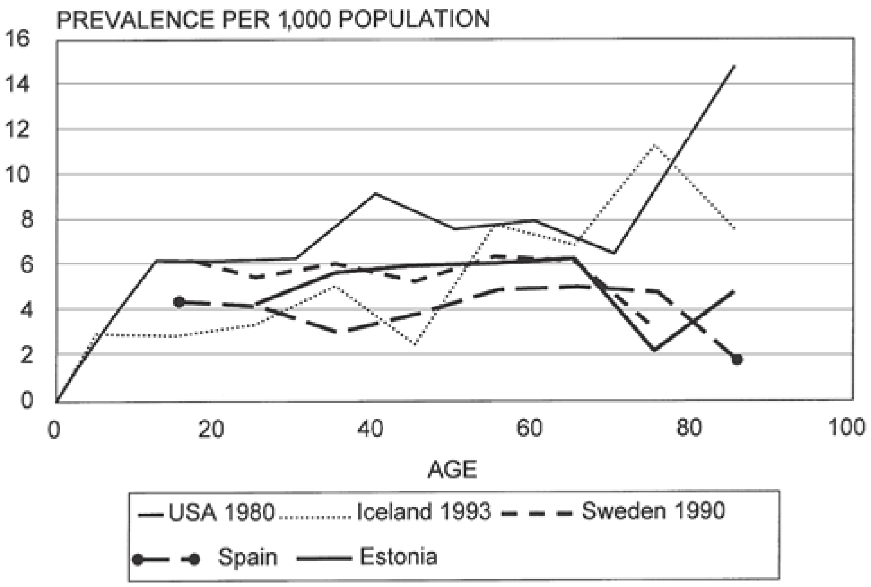


FIGURE 9. Prevalence of epilepsy in industrialized countries.

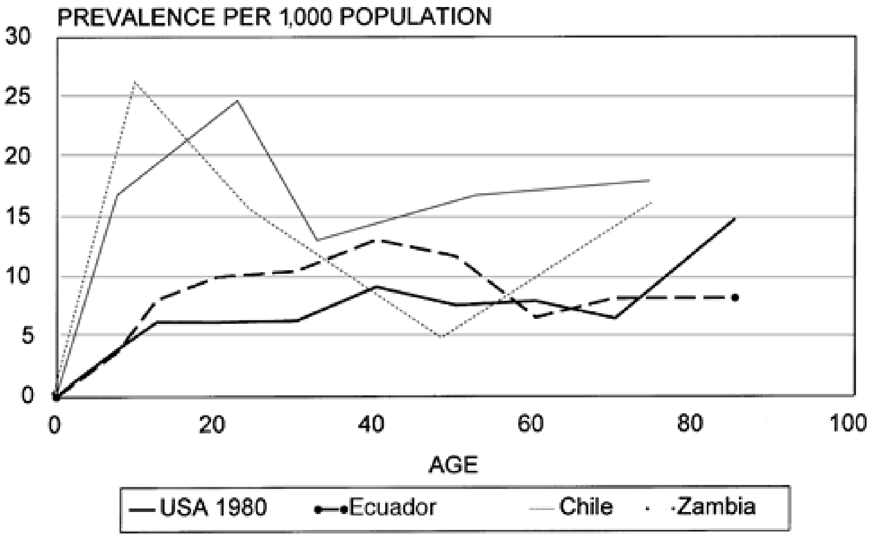


FIGURE 10. Prevalence of epilepsy in developing countries.

Age-Specific Prevalence

Although epilepsy is a disease acquired throughout life, the reported patterns of age-specific prevalence seldom reflect

this. This is particularly striking, as many of the prevalence studies provide data for lifetime prevalence (which should approximate cumulative incidence) rather than for active prevalence (which measures current seizures or current use of antiepileptic drugs). In the studies of prevalence from Rochester, Minnesota,[49] and from Iceland,[91] there is a pattern of active prevalence increasing in each subsequent age group, with the highest prevalence occurring in the elderly (Fig. 9). Studies from other European countries[64,118] and the Faroe Islands[59] report a relatively constant prevalence in adults. In many cases, age-specific estimates are unstable because of small numbers within age groups. Most studies, particularly those from developing countries, report the highest prevalence in the second and third decades of life, with lower prevalence in the elderly[29,53] (Fig. 10).

Gender

As is the case with incidence studies, most studies of prevalence report a higher prevalence in males than in females.

Etiology

For all total population studies providing information, the majority of cases, typically between 55% and 89% (Fig. 11), even in developing countries, have no identified cause.[1,10,11,13,16,18,19,25,31,32,34,39,40,41,42,43,49,53,61,62,65,73,81,87,92,93,94,99,101,103,104,113]

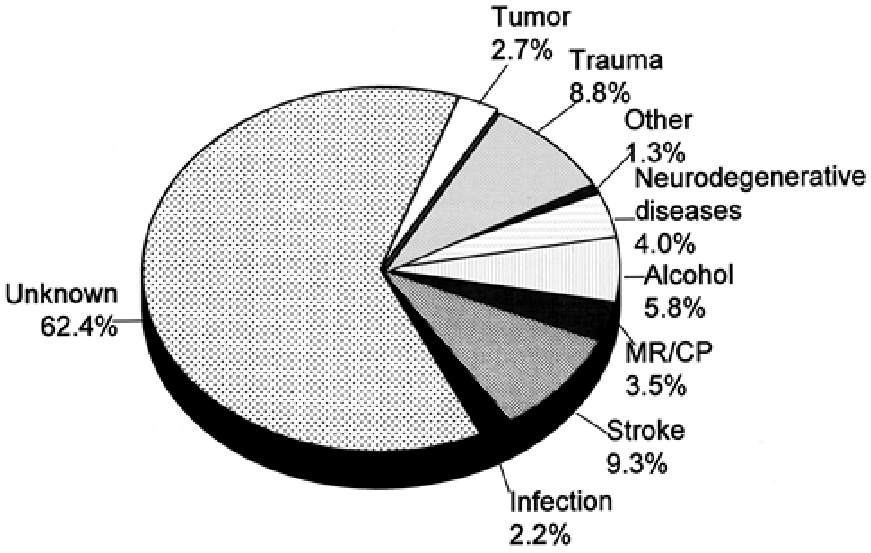


FIGURE 11. Distribution of etiology of epilepsy cases. CP, cerebral palsy; MR, mental retardation.

Race

Race seems more of an issue in the United States than in most other countries, and most studies addressing race or ethnic issues are from this geographic area. There are few studies that provide data on the prevalence of epilepsy in underrepresented populations in the United States.[49] Most studies provide data on prevalence in African-Americans. When comparable data were available, all report a higher prevalence than in the white population, although as usual, definitions cause difficulties in comparison. In Copiah County, Mississippi, the entire population was screened and follow-up evaluations were scheduled with symptoms of seizures or epilepsy to determine the

prevalence of epilepsy.[3,47] Definitions used in this study would include some people now categorized as acute symptomatic epilepsy in other studies such as those in Rochester, Minnesota. The age-adjusted active prevalence in blacks defined as recent seizures or current medication use was 8 per 1,000. This was about 60% greater than the age-adjusted prevalence in the white population in the same county.

A study in a rural Alabama county reported a lifetime prevalence of epilepsy of about 12 per 1,000 in the 2,200 black residents based upon clinic record review. This was almost double the prevalence in whites determined in a similar fashion.[56]

There are reports of prevalence of epilepsy limited to children that include information regarding the prevalence in minorities. The prevalence of epilepsy was determined in three counties in Oklahoma using multiple sources for case identification.[28] The active prevalence in black children of 5.7 per 1,000 compared to 4.2 per 1,000 in white children. The overall prevalence in â€œothers,â€ including Native American and Hispanic children, was 4.5 per 1,000. Prevalence was higher in males than in females for all ethnic groups. The excess in black children seemed attributable to a higher prevalence of generalized seizures and was present for all age groups. No further information is provided for the â€œotherâ€ group.

In Atlanta, multiple sources were used to identify potential cases that were screened to identify children with epilepsy. The lifetime prevalence of epilepsy in black children at age 10 was 6.4 per 1,000, not significantly higher than the prevalence in white children (5.7 per 1,000).[82] The prevalence of generalized seizures was significantly greater in black children than in white children.

Studies of prevalence in minority populations are inexorably confounded by socioeconomic status. Few studies attempt to address the relationship of socioeconomic status and the prevalence of epilepsy. In Ecuador, prevalence was inversely correlated with community ranking by socioeconomic class.[97,98] The prevalence of epilepsy in Pakistan has been reported to be greater in rural than in urban areas.

Summary and Conclusions

As more insight is gained into the epidemiologic characteristics of the epilepsies, apparent discrepancies between epidemiologic and clinical studies will be resolved. In addition, more pointed questions will be asked, and the prime epidemiologic goal of preventing epilepsy and its consequences will be addressed.

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Chapter 6

Risk Factors

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Introduction

Well-established risk factors for unprovoked seizures include head trauma, central nervous system (CNS) infection, Alzheimer disease, clinically detected stroke, febrile seizures, cerebral palsy, and mental retardation. Each of these increases the risk for unprovoked seizures at least 10-fold. Several other risk factors for unprovoked seizures are less well described; these include consumption of alcohol, use of heroin or marijuana, low socioeconomic status, attention deficit hyperactivity disorder, major depression, multiple sclerosis, dementia other than Alzheimer disease, and risk factors for stroke in the absence of clinically detected stroke. Additionally, current diuretic use has been shown to protect against the development of a first unprovoked seizure.

Epidemiologic Study Designs

Epidemiologic studies of risk factors for epilepsy or unprovoked seizures employ one of three study designs: Case control, retrospective cohort, or prospective cohort. These study designs are reviewed briefly before the discussion of risk factors for epilepsy in children and adults.

In case-control studies, potential predisposing factors are compared between patients with epilepsy and control patients without epilepsy. The odds ratio (OR) derived from these studies indicates the extent to which a given factor increases or decreases the risk for epilepsy. Case-control studies are best done with new-onset cases of epilepsy; identification of factors preceding the occurrence of seizures that might increase the risk for developing seizures supersedes investigation of factors that are a consequence of seizures. Population-based case-control studies have advantages over hospital-based studies because they include all cases of epilepsy in a population rather than the select group of patients who seek care at a particular hospital.

Both retrospective and prospective cohort studies begin with people who do not have epilepsy. These people are categorized according to whether or not they were exposed to a factor thought to predispose to epilepsy. Exposed and unexposed people are then followed chronologically to determine risk for epilepsy among people exposed to the predisposing factor relative to the risk among unexposed people. The measure that quantifies this risk is called the relative risk (the risk for disease in exposed subjects compared with the risk for disease in unexposed subjects).

The stronger the association is between a risk factor and a disease, the less likely the association can be explained by another, potentially confounding, factor. For example, it is harder to explain away a relative risk or of 10 than of 2. Associations of 10 or greater are strong enough to be considered clinically detectable by most physicians who see patients with epilepsy. Examples of these include, but are not limited to, head injury and clinically detected stroke.

Risk Factors for Childhood Epilepsy

The risk factors for childhood epilepsy are different from those for epilepsy later in life.[1] Inherited epilepsy is discussed elsewhere (see Chapters 15,16,17,18,19); consequently, this discussion is limited to nongenetic factors. The risk for epilepsy beginning in childhood is increased by febrile seizures, head trauma, CNS infection, mental retardation, cerebral palsy, and attention deficit hyperactivity disorder. Age itself seems to be a risk factor independent of other factors.[23] Adverse events during the prenatal and perinatal period do not influence seizure risk when children with mental retardation and cerebral palsy are excluded. Pertussis vaccination does not appear to alter the risk for unprovoked seizures; nor does low socioeconomic status.

Febrile Seizures

Febrile seizures can be regarded as distinct from childhood epilepsy (Chapter 57). Berg[9] summarizes the epidemiologic evidence for this assertion as follows: The risk of recurrent febrile seizures is far greater than the risk of unprovoked seizures after a febrile seizure; and risk factors for recurrent febrile seizures differ from risk factors for subsequent unprovoked seizures. Large cohort studies demonstrate that following a first febrile seizure, 2% to 4% of children experience a subsequent unprovoked seizure,[6,52,76] a risk four times the risk for unprovoked seizure in the general population. The increased risk for unprovoked seizures after febrile seizure is substantially greater among children with neurologic abnormalities present from birth than among children without such abnormalities. For most children with febrile seizures (i.e., those with simple febrile seizures), the risk of unprovoked seizure is only increased slightly.

Risk factors for unprovoked seizures following a first febrile seizure include a family history of epilepsy, complex features of the febrile seizure (i.e., multiple or focal and lasting longer than 15 minutes), and the presence of neurodevelopmental abnormalities present from birth.[6,10,52,76] Increasing duration of fever prior to the first febrile seizure and high temperature are associated with a reduced risk of developing subsequent unprovoked seizures,[10] suggesting that some children may have a low overall seizure threshold.

The type of febrile seizure influences the type of unprovoked seizure that may develop.[6,47] Repeated simple febrile seizures increase the risk for generalized-onset unprovoked seizures. Additionally, there is an association between complex febrile seizures and partial-onset unprovoked seizures. The suggestion of an underlying brain pathology common to both complex febrile seizure and partial-onset unprovoked seizure has led to the question of whether some febrile seizures lead to the development of mesial temporal sclerosis and subsequent intractable temporal lobe epilepsy. One study of 107 patients with drug-resistant epilepsy[46] showed that 45 (42%) had

focal or diffuse hippocampal volume loss on high-resolution volumetric magnetic resonance imaging (MRI) and most of these had a history of febrile seizures during childhood. If febrile seizures do predispose to some cases of hippocampal sclerosis, this cannot be the only mechanism involved, as 64% of the patients[46] with hippocampal volume loss had no history of febrile seizures. Further insight into this potential association comes from a prospective study[75] in which MRI examinations were performed within days of a prolonged febrile seizure. Among 15 children with focal prolonged febrile seizures, two had chronic hippocampal abnormalities and four had increased T2-weighted signal intensity and increased hippocampal volume associated with a mean seizure duration of 41 minutes: Two of the four with acute injury developed hippocampal atrophy on the follow-up MRI. In contrast, none of the 12 children with generalized prolonged febrile seizures had a definite abnormality on MRI. These data suggest that extremely prolonged focal febrile seizures can cause acute hippocampal injury, leading to later atrophy. Still unanswered is whether or not this atrophy is associated with the development of temporal lobe epilepsy.

Prenatal and Perinatal Risk Factors

Prenatal and perinatal adverse events do not appear to be associated with the occurrence of childhood epilepsy when children with cerebral palsy and mental retardation are excluded. In an early case-control study,[15] 100 children with epilepsy born in four hospitals in a large town in Germany were compared with 100 healthy children of the same age who had been born â€œat virtually the same time.â€ The study indicates that higher age of the mother at birth, toxemia of pregnancy, premature birth, and heavy birth weight were associated with later epilepsy; many other factors were not. This study had methodologic weaknesses: Medical records were reviewed retrospectively, a select group of patients was studied, and children with cerebral palsy and mental retardation were included. It is therefore interesting to compare the results with other, better designed studies.

In a review of large studies of defined populations, including the National Collaborative Perinatal Project (NCPP) cohort, Nelson and Ellenberg[53] concluded that among the hundreds of prenatal and perinatal factors studied, the main predictors of childhood seizure disorders were congenital malformations of the fetus (cerebral and noncerebral), family history of certain neurologic disorders, and neonatal seizures. In agreement with the British National Child Development Study,[67] labor and delivery factors in the NCPP did not appear to contribute to childhood seizure disorders. It seems that maldevelopment, rather than damage at birth to an intact nervous system, is the more common mechanism. In a prospective 1-year birth cohort study performed in northern Finland[61] that included 12,058 children, 208 had epilepsy. Of these children, 8.7% had a prenatal risk factor, 18.2% a perinatal risk factor, 15.9% a postnatal risk factor, and 57.2% no identifiable risk factor. This study included seizures in the neonatal period; some cohort studies, such as the British Child Health and Education Study (CHES),[77] have not included neonatal seizures.

Postnatal Causes

The British CHES cohort[77] has demonstrated that the causes of epilepsy in children, when known or suspected, are heterogeneous. No single cause predominates.

Traumatic Brain Injury

Jennett[42] found that the incidence of posttraumatic epilepsy in children was not markedly different from that in adults (Chapter 253). The risk for later epilepsy after depressed fractures ranged from <30% to 70%. Jennett also drew attention to â€œearlyâ€ epilepsy after head injury; in about 5% of all patients admitted to the hospital, seizures occurred within a week of the head injury. The incidence in children <5 years of age was almost double this. First-week seizures were quite distinct, occurring 30 times more frequently in the first week than the average of any of the 7 succeeding weeks. Fewer than a third of the patients with one or more seizures in the first week had any further epilepsy in the next 4 years.

Vaccination

It is unlikely that a relationship exists between vaccination, in particular pertussis immunization, and serious acute neurologic illness in children[2]; however, diphtheria-tetanus-pertussis (DPT) vaccination appears to increase the risk for fever, resulting in an earlier onset of febrile seizures among children predisposed to such seizures.[37,70] The possibility of an association between DPT vaccination and afebrile seizures was addressed in Great Britain by the National Childhood Encephalopathy Study.[50] In a review of the relationship between pertussis immunization and seizures,[8] Bellman suggested that pertussis vaccination was not associated with a convulsive disorder and instead might act as a nonspecific trigger for the onset of symptoms in children who were already predisposed to the development of infantile spasms. The one study to address this question[20] found no statistically significant increased risk in young children for any type of afebrile seizure in the 7 days after DPT vaccine exposure. Thus, it appears that the only adverse neurologic consequence significantly associated with DPT vaccination is febrile seizure in children who are already predisposed to such seizures.

Attention Deficit Hyperactivity Disorder

Clinically, there is a perception that attention deficit hyperactivity disorder (ADHD) is more common among children with epilepsy, due to the seizure disorder or its treatment.[7,16] When time order is examined, ADHD is associated with increased risk for developing epilepsy. This has been shown in case-control studies of children with epilepsy[7,16,34] and in cohort studies of select populations of children with ADHD.[28,40,41,79] In two prior case-control studies of children with incident unprovoked seizure,[7,16] behavioral disturbances before the onset of first seizure were more frequent than among controls. In one study of 148 children with first unprovoked seizure and 89 seizure-free sibling controls, attention problems as assessed by the Child Behavior Checklist were 2.4-fold more common prior to identification of the first seizure (8.1%) than in controls (3.4%).[7] In a population-based case-control study conducted among Icelandic children,[34] children with incident unprovoked seizure were 2.5-fold more likely than age- and gender-matched controls to have a history of ADHD (95% confidence interval [CI] = 1.1 to 5.5), meeting *Diagnostic and Statistical Manual of Mental Disorders* (DSM)-IV criteria prior to seizure onset. The association was restricted to ADHD-predominantly inattentive type (OR =

3.7; 95% CI = 1.1 to 13). When the occurrence of new-onset seizures is examined in selected samples with ADHD,[28,40,41,79] the percentage of children who develop unprovoked seizures (0.2% to 2%) is greater than the expected rate, because the average annual incidence of seizures is approximately 0.0470 per year in children aged 5 to 16 years.[24] Thus, there is an increased risk for developing seizures in children with ADHD, and the reported increased risk is smaller in case-control studies than in cohort studies, which were limited by small numbers of ensuing unprovoked seizures during short follow-up periods in selected populations. This is consistent

with the 23.1% prevalence of learning disorders reported in an unselected sample of children in Finland.[72]

Other Neurologic Problems

Mental retardation and cerebral palsy both predispose to the development of epilepsy (see Chapter 263). In a cohort of 221 children identified with mental retardation and born between 1951 and 1955 in Aberdeen, Scotland,[21] the cumulative risk for epilepsy was 15% by 22 years of age. In children with mental retardation and no associated disabilities, the cumulative risk at 22 years of age was 5%; in those with mental retardation and cerebral palsy, it was 38%; and in those with a postnatal injury associated with mental retardation, cumulative risk 15 years after the injury was 66%. Interestingly, epilepsy often remitted in mentally retarded individuals. In Rochester, Minnesota, neurologic deficits from birth, mental retardation, and/or cerebral palsy were important antecedents of epilepsy.[24] Thus, in the absence of associated disability or postnatal injury, the incidence of epilepsy in those with mental retardation alone was more than three times that of the general population of Rochester, Minnesota. Additionally, there appears to be an interaction between mental retardation and cerebral palsy on the risk for epilepsy.

Association of Different Risk Factors with Different Types of Epilepsy

Most published works examine risk factors for epilepsy as if epilepsy were a single condition rather than a heterogeneous group of seizure types and syndromes. Rocca et al.[63,64,65] addressed this issue in several articles, using the Rochester data to identify risk factors for different types of epilepsy. The risk for absence seizures was significantly increased by a history of febrile convulsions.[63] For generalized tonicâ€“clonic seizures, the following were significantly more common in cases than controls: A history of epilepsy or febrile seizures in the mother, febrile convulsions, and a history of head trauma.[64] For complex partial seizures, the following were significantly more common in cases than controls: A history of epilepsy or febrile convulsions in the mother, febrile convulsions, neonatal convulsions, cerebral palsy, head trauma, and viral encephalitis.[65] This work emphasizes the importance of accurately identifying seizure types and epilepsy syndromes when considering etiology.

Risk Factors for Epilepsy in Adults

There are several established risk factors for epilepsy in adults: Head trauma, CNS infections, CNS malignancies, occlusive cerebrovascular disease, and Alzheimer disease (Fig. 1). Several other factors have been associated with epilepsy but await confirmation in future studies. These potential risk factors include multiple sclerosis, hypertension, left ventricular hypertrophy, risk factors for embolic stroke, dementia other than Alzheimer disease, major depression, alcohol abuse, use of illicit drugs, and low socioeconomic status (Fig. 1). Acute symptomatic seizures also appear to increase the risk for subsequent epilepsy. There is evidence that diuretic therapy may be protective for the development of epilepsy.

Head Injury

Head injury increases the risk for later unprovoked seizure, with the greatest risk occurring among survivors of severe injury (Chapter 253). Analogous to seizures after penetrating head injuries, unprovoked seizures may be a consequence of neurosurgical procedures to the head.

In a study of Vietnam veterans who survived penetrating head wounds caused by missile injury, risk for remote symptomatic seizures increased 580-fold during the first 12 months after the injury and 25-fold after 10 to 15 years.[11,68] Among those veterans with epilepsy, persistence of epilepsy was associated with features related to the wound and not to functional consequences of the injury.

Penetrating head injuries sustained during war are more severe than all but 17% of cases of head trauma accompanied by loss of consciousness or posttraumatic amnesia in nonmilitary populations.[3] In civilian populations, case-control studies[64,65] and retrospective cohort studies[3] report an increased risk for unprovoked seizure after head trauma. In a retrospective cohort study from Rochester, Minnesota, that excluded people with seizures before head injury, the increased risk for subsequent unprovoked seizure was related to the severity of the injury.[3] Among residents of Rochester with mild injury, defined as unconsciousness or posttraumatic amnesia of less than 30 minutes' duration, risk for unprovoked seizure was increased 1.5-fold, which was not statistically significant. The risk for unprovoked seizure was increased fourfold for residents with moderate injury, defined as skull fracture or 30 minutes to 24 hours of unconsciousness or posttraumatic amnesia. Similar to the risk for seizures among Vietnam veterans 10 to 15 years after head injury, the risk for unprovoked seizure was increased 29-fold after severe injury, defined as more than 24 hours of unconsciousness or posttraumatic amnesia, brain contusion, or intracerebral hematoma. Severity of head injury may be a proxy for the amount of permanent epileptogenic damage inflicted by the injury.

Studies of unprovoked seizures after neurosurgery are complicated by the nature of the underlying disease, the presence of seizures before surgery, and the select nature of the populations studied. In one study, the risk for unprovoked seizures after surgery increased with increasing severity of preoperative neurologic deficit,[43] providing evidence that preoperative neurologic function alters postoperative seizure risk. Data also suggest an increased risk for seizure from the neurosurgical procedure itself. Using life table methodology[18] to study 877 consecutive neurosurgical patients, unprovoked seizures developed in 17% within 5 years of surgery. This cumulative incidence far exceeds the risk for seizures in the general population.[24] Further large and carefully designed studies are needed to untangle the effects of preoperative conditions and neurosurgical procedures in increasing the risk for seizures.

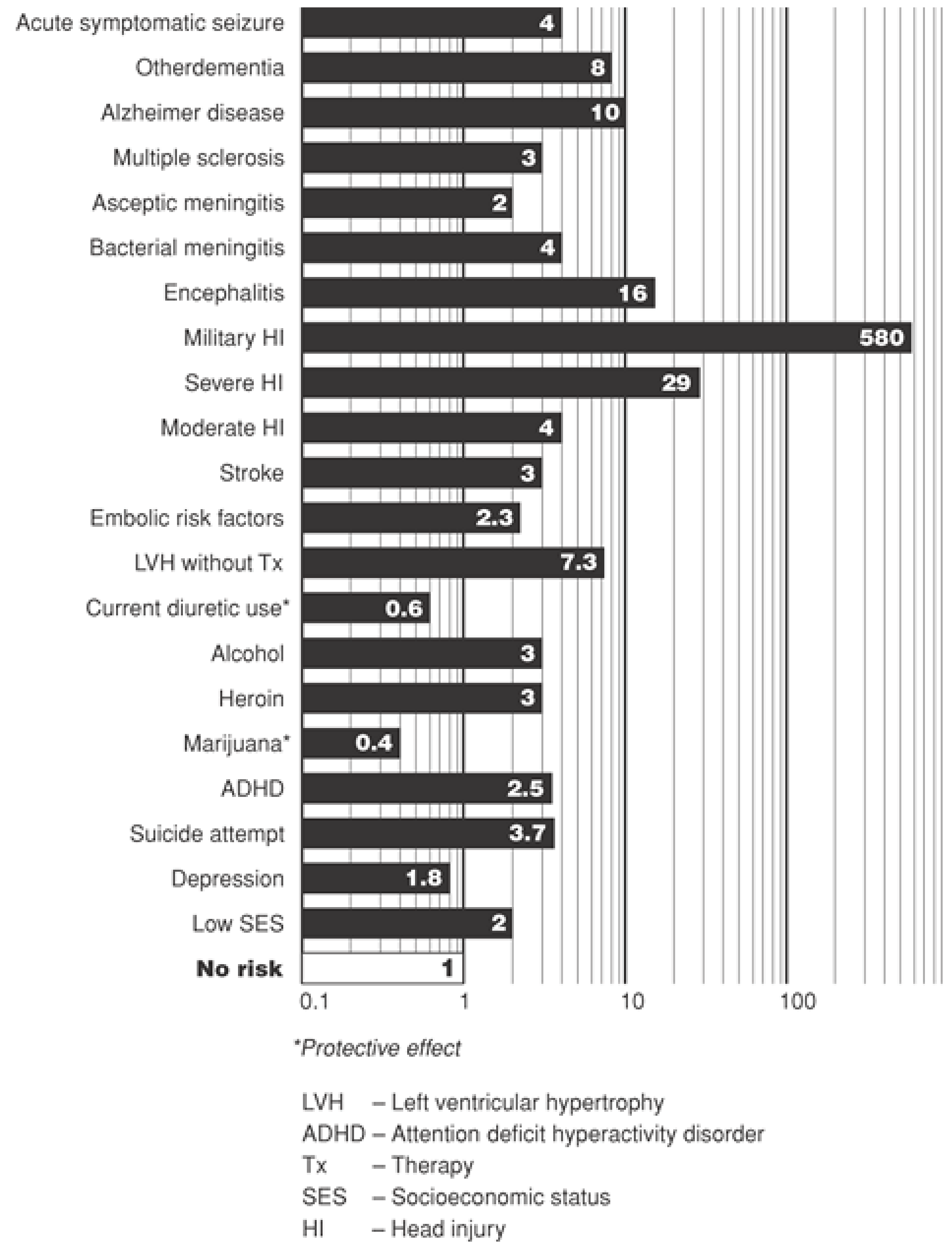

FIGURE 1. Risk factors for seizures in adults.

Central Nervous System Infection

Infections of the CNSâ€”encephalitis and meningitisâ€”are associated with an increased risk for subsequent unprovoked seizures. Among children with complex partial seizures, there is a 31-fold increased risk associated with viral encephalitis.[65] In a retrospective cohort study from Rochester, Minnesota, that followed people of all ages for the development of unprovoked seizure, CNS infections increased seizure risk 11-fold.[4] The risk for seizures varied by type of CNS infection. A 16-fold increased risk was associated with encephalitis, a fourfold increased risk with bacterial meningitis, and a twofold increased risk with aseptic meningitis. Almost all unprovoked seizures occurred during the first 5 years after infection (see Chapter 265 for further discussion).

Central Nervous System Malignancies

Case series have been used to evaluate the risk for epilepsy among patients with brain tumors or the prevalence of brain

tumors in newly diagnosed cases of epilepsy. Series of the former type report that 28% of patients undergoing surgery for brain tumors have seizures,[18,19] a risk far exceeding the incidence in Rochester, Minnesota.[24] Series of the latter type reveal that 12% to 16.3% of adults with newly diagnosed epilepsy have brain tumors[13,49,62]; indeed, seizures are often the first sign of brain tumors (see Chapter 264 for further discussion).

Occlusive Cerebrovascular Disease

A chronic epileptogenic lesion at the stroke site may account for unprovoked seizures that occur more than 1 to 2 weeks after a clinical stroke.[14] Such unprovoked seizures occur after a clinically detected stroke in 2.7% to 35% of patients.[26,38,45,51,59,78] This variability can be attributed to several factors in study design: Variation in length of follow-up, inclusion of only patients with computed tomographic confirmation of stroke, or inclusion of patients with subarachnoid hemorrhage only if they survived long enough to have surgery. Regardless of the selection factors or length of follow-up, the risk for unprovoked seizure after stroke is at least three times that expected based on the incidence among adults in Rochester, Minnesota.[24]

Because stroke produces a focal brain injury that serves as a substrate focus for seizure development, it has been hypothesized that only unprovoked partial seizures should occur after stroke. Generalized seizures are, however, not uncommon after stroke, although some investigators include secondary generalized seizures in this category.[22] Researchers who distinguish primary from secondary generalized seizures find that primary generalized seizures account for 4% to 69% of all unprovoked seizures after stroke.[38,39,45,48,59,74] Undetected onset of partial seizures may account for this variability. Nonetheless, true primary generalized seizures do occur after stroke, perhaps as a result of persistent global alterations in neurotransmitter function after stroke or of factors that alter cerebral autoregulation in people with risk factors for stroke.

Seizure prevalence is greater than expected *before* the occurrence of a first clinical stroke. In a case-control study of acute cerebrovascular accidents,[71] the prevalence of epilepsy preceding stroke was 4.55%, compared with 0.6% among controls selected from patients hospitalized for routine surgery and matched to cases by age, race, and sex. Potential controls were

excluded if they had a history of undefined cerebrovascular disease or if their surgery was related to disseminated carcinoma or alcohol excess, not formally defined abuse. These results have recently been replicated using the UK General Practice Research Database.[12] The cumulative risk for stroke was 10.0% in people with seizures compared with 4.4% in those without seizures ($p < 0.0001$).

This increased prevalence of epilepsy before a first clinically detected stroke has led to the study of risk factors for stroke in the absence of stroke as risk factors for unprovoked seizures. Data from three studies suggest that if hypertension, measured by a physician's diagnosis or blood pressure reading, increases seizure risk, the magnitude of the increased risk is small (OR ranging from 1.0 to 1.7).[29,56,69] Additionally, left ventricular hypertrophy untreated with diuretics is associated with a sevenfold increased risk for developing unprovoked seizures[29] with a 20-fold increased risk for generalized-onset seizures and a threefold increased risk for partial-onset seizures. Thus, risk factors for stroke may increase the risk for unprovoked seizures.

Dementia

The underlying pathology of Alzheimer disease may be associated with an increased susceptibility for seizures. In patients in whom Alzheimer disease was later confirmed by autopsy,[25] there was a 10-fold increased risk for unprovoked seizures compared with the expected risk derived from data from Rochester, Minnesota. In a comparison of the risk for unprovoked seizures in patients with mild probable Alzheimer disease to the risk in cognitively normal controls over a 7.5-year follow-up period,[66] new-onset seizures developed in 16% of patients with probable Alzheimer disease after they became severely demented; no control developed seizures. All seizures in this study were generalized tonicâ€"clonic seizures. In a population-based case-control study[30] there was a sixfold increased risk for unprovoked seizure associated with Alzheimer disease. In contrast with an earlier study,[66] which may have missed partial-onset seizures, this population-based study found an increased risk for both generalized- and partial-onset seizures.

Hesdorffer et al.[30] also evaluated the risk for seizures associated with dementia other than Alzheimer disease determined by ad hoc criteria based on DSM-III. They found that dementia increased the risk for unprovoked seizure eightfold overall; risk was increased for both generalized- and partial-onset seizure. This result suggests that any disease sufficiently severe to result in a dementing process may increase seizure risk.

Multiple Sclerosis

Several studies now suggest that multiple sclerosis is associated with an increased risk for epilepsy,[44,57,60,73] suggesting an epileptogenic role for white matter lesions. In these retrospective cohort studies of people with multiple sclerosis, 1.8% to 4.8% had seizures at the time of diagnosis or developed seizures after diagnosis. Across studies, this risk is more than three times the risk for unprovoked seizures over a similar time period.

Depression and Treatment for Depression

Depression diagnosed according to DSM-III-R criteria, treatment with tricyclic antidepressants, and use of phenothiazine and electroconvulsive shock therapy were studied as risk factors for unprovoked seizures in a population-based case-control study.[31] Only depression increased the risk for seizures after controlling for the other risk factors (OR = 3.7). Additionally, attempted suicide has been shown to increase the risk for first unprovoked seizure,[32] adjusting for depression, alcohol consumption, age, and gender. These associations may be caused by disturbances in neurotransmitter function common to depression, suicide attempt, and seizures (see Chapter 205 for further discussion).

Alcohol

Alcohol intake appears to be associated with seizure occurrence (Chapter 268). A case-control study in Harlem in New York City compared individuals admitted for a first seizure with controls admitted for the first time for an acute surgical procedure.[54] Controls were excluded if they had a condition related to alcohol abuse or had experienced a seizure. Controlling for age, sex, history of hypertension, history of head injury, history of stroke, and heroin use for more than 6 months, there was a dose response between alcohol consumption and the risk for seizure, particularly among male patients (OR = 1.3 to 19.5, depending on the amount of alcohol consumed). Seizure occurrence was not associated with time since last drink. A case-control study from Nigeria also associated alcohol consumption with seizures; however, these authors did not define alcohol use.[58]

Illicit Drugs

The association between heroin and marijuana use and seizures was investigated in the Harlem case-control study.[55] Controlling for age, history of head trauma, history of stroke, and alcohol use, these investigators found that heroin increased the risk for unprovoked seizures threefold and the risk for provoked seizures fourfold. Marijuana use conferred 82% protection against provoked seizures and 64% protection against unprovoked seizures. These interesting results require confirmation in other studies (see Chapter 268 for further discussion).

Acute Symptomatic Seizures

Acute symptomatic seizures typically occur within the first week of an insult known to predispose to seizures (e.g., head trauma) and are not regarded as epilepsy (Chapter 8). In Rochester, Minnesota, the cumulative incidence of acute symptomatic seizures in patients up to 80 years of age is 3.7%.[5] Across many causes of acute symptomatic seizures, studies suggest that such seizures increase the risk for later epilepsy at least threefold, perhaps because their occurrence is a marker for severity of brain injury.[36]

Among Rochester adults with moderate or severe head trauma, early seizures increased the risk for later unprovoked seizures ninefold[3]; children with early seizures were not at increased risk for unprovoked seizures. In military populations with penetrating missile wounds to the head, 50% of men with early seizures experienced later unprovoked seizures.[11] Early postoperative seizures are associated with unprovoked seizures.[18] The magnitude of this increased risk appears related to the underlying disease requiring surgery; patients with vascular or ventricular disease before surgery have the greatest risk (increased fourfold) for unprovoked seizure. Among stroke patients without early seizures, the risk for unprovoked seizure is 19%; for those with early seizures, the risk is even greater.[26] If early seizures occur, the risk for unprovoked seizures after encephalitis is increased threefold, and after bacterial meningitis fourfold.[4]

The Protective Effect of Diuretics

Current diuretic use has been shown to be protective for the development of idiopathic/cryptogenic unprovoked seizures in a population-based case-control study in the elderly.[33] The protective effect was 46% for thiazide use and 39% for furosemide; Aldactazide was not associated with a protective effect for seizure development.

Socioeconomic Status

Indices of low socioeconomic status (SES) are associated with many established risk factors for epilepsy, including cerebrovascular disease, head trauma, congenital malformations, central nervous system infection (meningitis, encephalitis), alcohol intake or abuse, brain neoplasms, and Alzheimer disease. This complicates studies designed to examine the association between low socioeconomic status and the development of epilepsy.

Two studies now show that low socioeconomic status is associated with an increased risk for developing epilepsy,[27,35] and one study fails to find an association.[17] These studies are either community based or population based. A prospective study in England,[27] using a composite measure of SES, concluded that low SES is a risk factor for the development of epilepsy. A case-control study in Iceland[35] found that low education increased the risk for unprovoked seizure twofold, whereas home ownership was protective. When analyses were repeated by seizure etiology, the association persisted only in the idiopathic/cryptogenic group even after adjusting for cumulative alcohol intake. Interestingly, there was no effect of low SES in children, suggesting that there is a cumulative effect of social deprivation associated with the development of epilepsy.

Future Research

Much is known about factors that appear to increase the risk for unprovoked seizures, particularly for risk factors that produce clear structural brain damage. Recently, studies have suggested associations between factors that are not known to lead to such brain damage (e.g., major depression) and unprovoked seizures. Thus, the challenge for future studies of unprovoked seizures is to elucidate risk factors that increase risk in people whose seizures have no established cause. Such studies have the potential to identify novel mechanisms for seizure occurrence or to identify shared genetic susceptibility between a risk factor and unprovoked seizures.

Few studies exist concerning risk factors for seizures in older adults, in whom the incidence of seizures is increased. New studies elucidating novel factors associated with seizures in this population and confirming those already suggested are needed.

Summary and Conclusions

Studies suggest that febrile seizures, mental retardation, and cerebral palsy are risk factors for epilepsy unique to children. Prenatal and perinatal adverse events are not associated with the occurrence of epilepsy when investigators exclude children with mental retardation and cerebral palsy. Among children and adults, established risk factors for epilepsy include CNS infection, head injury, and CNS malignancies. Attention deficit hyperactivity disorder also increases seizure risk in children. In adult populations, cerebrovascular disease and Alzheimer disease are established risk factors for epilepsy. Multiple sclerosis, risk factors for stroke, major depression, alcohol intake, illicit drug use, and low socioeconomic status appear to increase the risk for epilepsy, but further studies are needed to confirm these findings.

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Chapter 7

The Natural History and Prognosis of Epilepsy

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Introduction

For the majority of people with epilepsy, the condition is treatable and the term *prognosis* generally refers to the probability of attaining seizure freedom after treatment has been started, during treatment, and after drug withdrawal. Little is known about the natural history of the untreated condition as most patients, particularly in industrialized countries, are treated. There are only a few reports, mostly from resource-poor countries, on the prognosis of untreated epilepsy.

Methodologic Issues

As with most other chronic conditions, the prognosis of epilepsy depends on the characteristics of the population concerned, the case definition, the spectrum of severity of the condition, the duration of follow-up, and the choice of prognostic predictors, including treatment. More specifically, the design of an ideal study on the prognosis of epilepsy should include the following:

1. Well-defined criteria for the inclusion of patients.
2. Standard (homogeneous) definitions of the prognostic predictors and outcome measures.
3. Adequate duration of follow-up and proper statistical methods to adjust for those lost to follow-up and limited periods of observation.

Ideally, patients should be enrolled at a similar point in the course of the disease (e.g., the time of diagnosis or the time of the index event) and should be representative of the general population of people with epilepsy. Many patients do not seek medical advice until seizures have recurred; using these people as the population under study will exclude those who have had only one seizure and may well influence the prognosis. Additionally, most studies of the prognosis of epilepsy have been carried out in specialized services, generally including predominantly people with complex, difficult to control epilepsy; thus, selection bias may well affect the prognosis of epilepsy.

Homogeneous (preferably standard) definitions for the most common prognostic indicators should be encouraged. For example, there are inconsistent reports that a family history of epilepsy increases the risk of seizure recurrence; this may be explained by the fact that family history is difficult to ascertain and may be unreliable. Details should also be given of *all* the putative prognostic predictors considered, to provide a comprehensive overview of the prognosis of the disease and to give the best explanation of the results after controlling for the known prognostic indicators. Prolonged follow-up is required and attempts should be made to obtain information on the outcome in *all* patients. Outcome measures should be clearly defined and, where possible, reliable indicators should be used. Proper statistical methods (including multivariate analysis models) should be employed to assess the independent role of each prognostic predictor. Most of the differences among studies on the prognosis of epilepsy can be explained by the different methodology, with particular reference to the study design (retrospective or prospective; community based or specialized clinic based), the target population (children and/or adults), the timing of enrollment (interval between first seizure and enrollment), the type of seizure (generalized tonic and/or clonic, partial, and other), the length of follow-up, and the use of antiepileptic drugs.

Overall Prognosis of Epilepsy

The overall prognosis of epilepsy is favorable in the majority of patients. There are several pieces of evidence that support this conclusion. First, reports from several resource-poor countries (where people with epilepsy are largely untreated) give prevalence rates that tend to be broadly similar to those of industrialized countries.[3,7,8,21,22,28,31,48,50,52,59,64,65,69,71] Prevalence rates for active epilepsy are usually between 4 and 10 per 1,000 in both settings. In most resource-poor countries the incidence of epilepsy is higher than that in industrialized countries.[27,30,36,42,43,48,50] Incidence rates in developed countries tend to fall within the range of 30 to 60 cases per 100,000, while most reports from resource-poor countries give figures in excess of 70 per 100,000. The increased mortality of epilepsy in resource-poor countries explains only part of the difference between incidence and prevalence. The most likely explanation for the similarity of the prevalence rates, therefore, is spontaneous remission in some people. Additionally, contrary to old reports,[49] studies done in newly diagnosed patients have consistently shown that 55% to 68% of cases achieve prolonged seizure remission (Table 1).[35]

Table 1 Population-based Studies on the Prognosis of Epilepsy

Country	Population	% (Duration) remission	Source	Follow-up (yr)	Notes
United States	All ages	55% (10-y) at 20 y	Records linkage	33	Included isolated seizures
United Kingdom	All ages	69% (5-y) at 9 y	General practitioners	9	Included isolated seizures
Sweden	Adults	58% (5-y) at 11 y	Multiple	10	Included isolated seizures
France	All ages	62% (complete) at 5 y	Neurologists	5	Included isolated seizures
Switzerland	All ages	68% (complete) at 10 y	Neurologists	10	Included isolated seizures
Ecuador	All ages	21% (complete) at 4 y	Hospitals	4	Only two or more seizures

Holland	Children	62% (2-y) at 5 y	Hospitals	5	Included isolated seizures
Canada	Children	55% (complete) at 7 y (average)	Child neurologists	>20	Included isolated seizures
Finland	Children	68% (5-y) at 30 y	Multiple	>30	Only two or more seizures

Source: Jallon P. In: Jallon P, Berg AT, Dulac O, et al., eds. *Prognosis of Epilepsies.* Montrouge: John Libbey; 2003.

Early Prognosis of Unprovoked Seizures and Epilepsy

Prognosis after the First Unprovoked Seizure

The risk of relapse after a first unprovoked seizure has been reported to range from 23% to 71%[5] and from 14% to 68% when actuarial methods are used. The rates at 2 and 5 years are 21% to 69% and 34% to â‰¥71%, respectively. Population-based studies[2,29] provide more homogeneous relapse rates at 1 (36% to 37%) and 2 years (43% to 45%). In a systematic review of 16 reports,[11] the average overall recurrence risk was 51% (95% confidence interval [CI], 49% to 53%). By 2 years, the recurrence risk was 36% and 47% in prospective and retrospective studies, respectively. After a first unprovoked seizure, the probability of a relapse decreases with time; about 50% of recurrences occur within 6 months of the initial seizure and 76% to 96% within 2 years.[11]

Risk Factors for Relapse of a First Unprovoked Seizure

The two most consistent predictors of recurrence are a documented etiology of the seizure (as opposed to idiopathic or cryptogenic seizures) and an abnormal (epileptiform and/or slow) electroencephalogram (EEG) pattern.[11] The pooled recurrence risk in patients with an idiopathic or cryptogenic first seizure is 32% (95% CI, 28% to 35%), compared with 57% (95% CI, 51% to 63%) for a remote symptomatic seizure (i.e., a seizure with an underlying, nonacute brain problem). The recurrence risk ranges from 27% (95% CI, 21% to 33%) with a normal EEG tracing to 58% (95% CI, 49% to 66%) with an EEG showing epileptiform abnormalities. Epileptiform abnormalities tend to be associated with a higher risk of seizure recurrence than do nonepileptiform abnormalities. The pooled 2-year recurrence risk is lowest for an idiopathic or a cryptogenic first seizure with a normal EEG (24%; 95% CI, 19% to 29%), intermediate for a remote symptomatic seizure (48%; 95% CI, 34% to 62%) with normal EEG *or* an idiopathic/cryptogenic seizure with an abnormal EEG (48%; 95% CI, 40% to 55%), and highest with a remote symptomatic seizure with an abnormal EEG (65%; 95% CI, 55% to 76%). Seizures occurring during sleep tend to be associated with a higher risk of recurrence in both children and adults.[34,57,68] Partial seizures, which are usually associated with a documented brain injury, are also correlated with a higher risk of recurrent seizures, even after controlling for etiology and EEG abnormalities.[2,15] A positive correlation between seizure relapse and family history of seizures has only been confirmed in patients with idiopathic or cryptogenic first seizures in one study.[33] A history of prior acute symptomatic seizures has occasionally been found to increase the risk of relapse, while evidence is inconclusive or lacking for sex, age, and presentation with status epilepticus.[11]

Treatment, Risk of Recurrence, and Long-term Prognosis of a First Seizure

There are at least five published randomized studies assessing the effects of treatment of the first unprovoked seizure.[16,20,23,25,44,46] The results of these studies consistently show that treatment of the first seizure seems to reduce the risk of short-term relapse but is apparently ineffective on the chance of long-term seizure remission. A large multicenter Italian trial[23] (the FIRST study) of 397 children and adults was conducted to assess the effectiveness of treatment of the first seizure on the risk of relapse and the long-term prognosis of epilepsy. Patients seen within 7 days after a first witnessed unprovoked tonicâ€“clonic seizure with or without partial onset were randomized to be treated or to be left untreated until the time of a second seizure. The mean period of observation was 274 days in patients given immediate treatment and 309 days in patients who did not receive treatment. Overall, 36 of 204 treated patients and 75 of 193 untreated patients were referred for seizure relapse. In this trial, the cumulative time-dependent risk of recurrence in treated patients was 17% at 12 months and 25% at 24 months, and in untreated patients was 41% and 51%, respectively. The differences tended to disappear, however, when the end-point was the chance of initiating a 2-year remission. The cumulative probability of long-term remission in the two treatment groups tended to be similar from the second year of follow-up until 15 years after randomization.[41a] The results of this study were confirmed by an even larger pragmatic randomized European trial (the MESS study) comparing immediate and deferred treatment for early epilepsy and single seizures.[44] Patients aged at least 1 month were randomized if both the clinician and the patient were uncertain whether to proceed with treatment. In this trial, 722 patients were randomized to immediate treatment and 721 to deferred treatment. Of these, 404 and 408, respectively, had a single seizure at randomization. Immediate treatment prolonged the time to the first relapse (risk ratio [RR] 1.5; 95% CI, 1.2 to 1.8) and increased the proportion of patients achieving immediate 2-year remission (64% vs. 52%) ($p = 0.023$). However, at the 2-year follow-up, 32% of those with immediate treatment had had a recurrence compared with 39% of those with deferred treatment. In addition, 92% versus 92% patients achieved 2-year remission at 5 years and 95% versus 96% at 8 years, respectively. The results of these trials tend to confirm several observational reports that the long-term prognosis of the first seizure is substantially unaffected by immediate treatment. However, the comparative effects of the treatment of the first seizure and treatment only on relapse on the chance of long-term remission (without drugs) have not yet been assessed.

Prognosis of Untreated Epilepsy

With one exception,[37] the prognosis of untreated epilepsy has been assessed only in resource-poor countries where epilepsy is

largely untreated (treatment gap ranging from 70% to 94%). In a population-based study conducted in Ecuador,[48] the cumulative annual incidence rate was 190 per 100,000 and the prevalence rate of active epilepsy was 7 per 1,000, which implies a remission rate of at least 50%. Similar prevalence rates of active epilepsy (5 per 1,000) were found in Nigeria,[47] where only 4% of patients were treated at the time of the survey, and in Ethiopia.[65] In a smaller study conducted in Malawi,[70] duration of active epilepsy was similar to that of industrialized countries. All these findings lend support to the hypothesis that spontaneous remission of untreated epilepsy is a common event. In a field study conducted in Warsaw in the 1970s, almost one third of those who had never been treated, including some who had previously had frequent generalized seizures, had been free of seizures for more than 5 years.[72] A small study in Finland, conducted in those with untreated epilepsy, found the probability of remission to be 42% by 10 years after the onset of epilepsy.[37]

Prognosis of Newly Diagnosed Epilepsy

In industrialized countries treatment of epilepsy is generally started at the time of diagnosis, which is not usually made until at least two unprovoked seizures have occurred. In fact, after a second unprovoked seizure the risk of a third seizure has been estimated as 73%, and after a third seizure the risk of a fourth seizure has been estimated as 76%.[32] Population-based studies on the long-term prognosis of treated epilepsy report a 58%

to 65% cumulative 5-year remission rate at 10 years.[1,18] This number rises to about 70% by 20 years following seizure onset.[1] The 5-year remission rate at 10 years is 61% in adults[41] and the 3- to 5-year remission rate at 12 to 30 years in children is 74% to 78%.[24] In a Finnish cohort of patients with childhood-onset epilepsy, after over 30 years of follow-up 64% of cases were in 5-year terminal remission, of whom 74% were off medications.[60]

Principal Prognostic Predictors

The etiology of the epilepsy is by far the strongest prognostic predictor for seizure recurrence. In general, idiopathic epilepsy has a better chance of seizure remission than symptomatic or cryptogenic epilepsy. In the population-based study from Rochester, Minnesota, people with symptomatic epilepsies were found to have a significantly lower chance of 5-year remission than those with idiopathic epilepsies (30% vs. 42% at 15 years).[1] Within the group of those with symptomatic epilepsies, patients with neurologic dysfunction present at birth had the lower chance of remission (46% and 30% off drugs at 20 years). Lower, albeit less significant, remission rates in patients with symptomatic epilepsies were also found in the United Kingdom, Sweden (adults), and Finland (children).[35] A documented etiology of epilepsy has also been found to be a significant predictor of seizure intractability in childhood-onset epilepsy.[62] In the Connecticut study of childhood-onset epilepsy, early predictors of intractability included known etiology, high initial seizure frequency, and focal EEG slowing.[9] Other prognostic indicators of 5-year remission in the Rochester, Minnesota, population included absence of EEG epileptiform abnormalities (odds ratio [OR] 1.6) and absence of generalized tonicâ€"clonic seizures.[55] In the UK National General Practice Study of Epilepsy (NGPSE), the only independent predictor of 1-year and 2-year remission was the number of seizures experienced by the patient in the 6 months after the first seizure.[18,43] When other prognostic predictors are taken into consideration, there is no evidence that age at onset of seizures affects seizure outcome. With the exception of epilepsies associated with rare inherited sex-linked disorders, sex has not been indicated as a significant prognostic predictor.

Prognosis of Epilepsy Syndromes

An epileptic syndrome is a symptom complex that is characterized by a fairly uniform clinical and electrographic picture. In addition to seizure type, defining features of epileptic syndromes also include family history, age at onset, presumed etiology, and EEG and neuroimaging findings.[19] To some extent, particularly in children, different epileptic syndromes have various and sometimes distinct outcomes and responses to treatment. It has been suggested[52] that epilepsy syndromes can be classified into four prognostic groups:

1. Excellent prognosis (about 20% to 30% of the total) with high probability of spontaneous remission: These include neonatal seizures, benign partial epilepsies, benign myoclonic epilepsy in infancy, and epilepsies provoked by specific modes of activation.

2. Good prognosis (about 30% to 40%) with easy pharmacologic control and possibility of spontaneous remission: These include infantile absence epilepsy, epilepsies with generalized tonicâ€"clonic seizures secondary to specific conditions, and some partial epilepsies.

3. Antiepileptic drugâ€"dependent prognosis (about 10% to 20%), which may respond to drugs, but tend to relapse after treatment withdrawal: These include juvenile myoclonic epilepsy and most partial epilepsies (symptomatic or cryptogenic).

4. Guarded prognosis (about 20%) in which seizures tend to recur despite intensive treatment: These include epilepsies associated with congenital neurologic defects, progressive neurologic disorders, and some symptomatic or cryptogenic partial epilepsies.

The prognosis of specific epilepsy syndromes may be significantly different and reflects, at least in children, the inherent severity of epilepsy more than the quality of the therapeutic approach.[58]

Antiepileptic Drugs and Seizure Outcome

Antiepileptic drugs (AEDs) are often successful in suppressing seizures, but they do not seem to alter the long-term prognosis of epilepsy. In addition, in the FIRST and MESS studies[44,46] there was evidence of less than optimal outcome of seizures in about 20% of patients with newly diagnosed epilepsy.

There are virtually no reports on the comparative efficacy of old and new AEDs on the long-term outcome of epilepsy, and there is no evidence to suggest that the newer medications are more efficacious.[4,40] Although individuals seem to present differing responses to the available drugs, all first-line AEDs seem to be equally effective at a community level. In a single-center hospital-based study of 470 patients diagnosed, treated, and followed for a mean period of 5.6 years, 47% of cases became seizure free with the first prescribed drug.[39] There was no significant difference in the proportion of cases with inadequate seizure control among those treated with carbamazepine, valproate, or lamotrigine. The majority of seizure-free patients required only a moderate daily dose of AED.

Prognosis of Epilepsy after Treatment Withdrawal

A long-term population-based study has shown that 5-year terminal remission of epilepsy (without drugs) is 61%.[1]

Discontinuation of drug treatment is thus a valuable option in patients with epilepsy who are seizure free for 2 years or longer. In a critical review of 28 studies accounting for 4,615 cases, most of whom had at least 2 years of seizure remission, the proportion of patients with relapses during or after treatment withdrawal ranged from 12% to 66%.[63] Using life-table analysis, the cumulative probability of remaining seizure free in children was 66% to 96% at 1 year and 61% to 91% at 2 years. The corresponding values in adults were 39% to 74% and 35% to 57%, respectively. The relapse rate was highest in the first 12 months (especially in the first 6 months) and tended to decrease thereafter. In a meta-analysis of 25 studies, the pooled relapse risk was 25% (95% CI, 21% to 30%) at 1 year and 29% (95% CI, 24% to 34%) at 2 years.[10]

In the only randomized trial on the effects of AED withdrawal on seizure relapse, 22% of patients randomized to continued treatment had relapsed by 2 years, while 41% of patients randomized to slow drug withdrawal had relapsed.[45] This differential risk of relapse was maximal between 1 and 2 years and declined thereafter. After 2 years, the risk of subsequent relapse was the same for both treatment groups. The risk of recurrence was also similar in patients who relapsed after withdrawal of AEDs and in those who relapsed while remaining on treatment.[17]

Factors Predicting Seizure Relapse after Treatment Withdrawal

A number of factors have been associated with favorable or unfavorable seizure outcome after treatment discontinuation. Factors consistently indicating a higher-than-average risk of seizure relapse include adolescent-onset epilepsy, partial seizures, presence of an underlying neurologic condition, and abnormal EEG findings (in children). Factors associated with a lower-than-average risk were childhood-onset epilepsy, idiopathic generalized epilepsy, and (in children) normal EEG. Selected epilepsy syndromes (e.g., benign epilepsy with centrotemporal spikes and juvenile myoclonic epilepsy) may be associated with significantly different outcomes after treatment withdrawal.[63] In the Medical Research Council AED withdrawal study, independent predictors of relapse included history of partial seizures, primarily or secondarily generalized tonicâ€“clonic seizures, or myoclonic seizures; use of more than one AED; seizures after treatment start; and a shorter seizure-free period at randomization.[45] In a meta-analysis of 25 studies, those with adolescent age at onset of seizures had a 1.34-fold increased risk of relapse (95% CI, 1.00 to 1.81) compared with those with adult age at onset.[10] Patients with remote symptomatic seizures had a 1.55-fold increased risk of relapse (95% CI, 1.21 to 1.98). An abnormal EEG prior to drug discontinuation was associated with a 1.45-fold increased risk of relapse (95% CI, 1.18 to 1.79). In the same review, prognosis following drug withdrawal was similar whether a 2-year or a 4-year seizure-free interval was considered. Additionally, a randomized trial comparing a 6-week taper with a 9-month taper after 2-year seizure remission in children with epilepsy showed no difference in recurrence risk at 2 years.[66]

Psychosocial Outcome

People with epilepsy are more likely to be unemployed than people in the general population, with unemployment rates ranging from 24% to 36%.[51] In a population-based study of adults who had childhood-onset epilepsy, independent predictors of low socioeconomic status included poor fine-motor performance (OR 14.8), poor short-term outcome after treatment (OR 9.8), and presence of psychoneurotic symptoms (OR 3.2).[61] In that study, 15% required little assistance in daily living activities and about 50% were socially disabled, of whom 60% had moderate to severe handicap. School achievement in children and adolescents with epilepsy is lower than that in the general population. Low achievement may occur even when epilepsy is not associated with other neurologic sources of impairment.[41] A lower intellectual level is the most likely explanation for underachieving at school. Learning disabilities and cognitive dysfunction are commonly reported in children with epilepsy.[13] Factors associated with underachieving at school include epilepsy, use of AEDs, and psychosocial factors. The strongest independent predictors of underachieving at school include early onset of seizures and cumulative number of seizures.[54] Alteration of cognition might reflect a chronic adverse effect of AEDs, but the negative effects of the drugs are only one of several factors that may influence cognition. In addition, subjective complaints of cognitive deficits (e.g., memory problems or attention) may also reflect aspects of adverse effects other than those concerning specific cognitive functions (e.g., mood and anxiety).[14] Although intuitive, the correlation between underachieving at school and psychosocial factors is not supported by studies with robust methodology.

Lower rates of marriage and fertility (even after adjustment for marriage) have also been reported in people with epilepsy when compared with the general population.[53] Several sociocultural limitations may explain the lower likelihood of marriage in the presence of epilepsy. Although adverse treatment effects may be implicated, the cause of decreased fertility remains unclear.

In the absence of seizures (with or without treatment), the risk of accidents and injuries is clearly decreased compared with those with ongoing seizures, and tends to be close to that of the general population.[38,67] In a multicenter cohort study conducted in six western European countries (Italy, Germany, England, Holland, Spain, and Portugal) and three eastern European countries (Russia, Estonia, and Slovenia), 951 children and adults with early idiopathic, cryptogenic, or remote symptomatic epilepsy and 909 matched controls were followed prospectively for 17,484 and 17,206 person-months, respectively.[6,67] Two hundred and seventy accidents were reported by 199 people with epilepsy (21%) compared with 149 accidents reported by 124 controls (13%). About one quarter of accidents in people with epilepsy were seizure related. The most common accidents in people with epilepsy were, in decreasing order of frequency, contusions, wounds, fractures, abrasions, and brain concussions. Contusions followed by wounds and sprains or strains predominated in the controls. In people with epilepsy, about one third of brain concussions, contusions, and fractures were seizure related compared with one fifth of burns and less than one sixth of wounds. Most accidents occurred at home, followed by traffic, sports and other leisure activities, work, and school. About one half of domestic accidents were seizure related. About one third of school accidents and one quarter of traffic accidents were seizure related. Apart from brain concussions, accidents occurring both in patients with epilepsy and in nonepileptic controls were mostly trivial. The proportion of road accidents attributable to seizures in people with active epilepsy is extremely low, ranging from 0.02% to 0.2%.[12,56]

Summary and Conclusions

In the past, studies from tertiary referral centers offered a picture of epilepsy as a chronic, progressive, unremitting disorder.[26,49] Epidemiologic evidence indicates that the poor prognosis observed in earlier studies was largely the result of selection bias. More recently, the results of epidemiologic studies and randomized clinical trials have greatly changed our

understanding of the nature and natural history of seizures and of epilepsy. On this basis, one can assume that epilepsy is a fairly benign condition in the majority of cases, with a good prognosis for seizure control and, ultimately, discontinuation of AEDs. However, epilepsy is a heterogeneous clinical condition and many different syndromes have been recognized. The outcome is determined to some extent by the type of epilepsy. Factors influencing the prognosis of epilepsy include etiology, EEG abnormalities, presence of generalized tonicâ€“clonic seizures, the number of seizures experienced after the onset of treatment, and the syndromic pattern. Antiepileptic drugs are successful in suppressing seizures, but do not alter the long-term prognosis of epilepsy. The available compounds seem to be equally effective, about 50% of patients being satisfactorily controlled by the first drug, given as monotherapy. In contrast to the medical prognosis, the psychosocial prognosis of epilepsy is at best fair, reflecting the negative aspects of the disease on the daily living activities and the quality of the patient's life. The heterogeneous spectrum of the disease, the adverse treatment effects, and stigma may all concur in affecting the psychosocial outcome of epilepsy.

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Chapter 8

Epidemiology of Acute Symptomatic Seizures

W. Allen Hauser

Introduction

What condition looks like epilepsy, is frequently called â€œepilepsy,â€ is frequently counted as epilepsy in epidemiologic studies, but in general has a different basis from that of epilepsy and is seldom treated as epilepsy? The answer is *acute symptomatic seizures,* also referred to as *reactive seizures, provoked seizures,* or *situation-related seizures.* Acute symptomatic seizures are seizures that occur at the time of a systemic insult or in close temporal association with a documented brain insult.[7,8,16] This class of seizure falls into the category of situation-related seizures in the Revised Classification of Epilepsies and Epileptic syndromes suggested by the International League Against Epilepsy.[7]

Acute symptomatic seizures differ from epilepsy in several important aspects: First, unlike epilepsy, these seizures have a clearly identifiable proximate cause, to the extent that one can never be certain of a causal association. When one considers the temporal sequence of acute symptomatic seizures (e.g., uremia, head injury, or stroke immediately preceding a seizure), the biologic plausibility (acute disruption of brain integrity or metabolic homeostasis) and in many cases the dose effect (severity of injury correlated with the risk for seizures) all quite compellingly indicate causation. Although a risk ratio for the immediate association between cause and effect has not been calculated, it must be enormous. Second, unlike epilepsy, acute symptomatic seizures are not characterized by a tendency to recur. The risk for subsequent epilepsy may be increased in individuals experiencing such insults; in general, one does not expect seizures to recur unless the underlying condition recurs. As a corollary, such individuals usually do not need to be treated with antiseizure medication on a long-term basis, although such treatment may be warranted on a short-term basis until the acute condition is resolved.[34]

Few epidemiologic studies report the frequency of acute symptomatic seizures. This may be caused in part by the difficulties involved in identification. Such seizures are seldom indexed as acute symptomatic seizures; rather, the underlying condition is likely to be diagnosed and coded. This makes a study design relying on medical record review inefficient and probably leads to gross underenumeration. Individuals with acute symptomatic seizures are seldom referred to neurologists for long-term follow-up, and given the acute nature of the condition, an electroencephalographic evaluation may not be warranted or appropriate. These important sources of patient identification are thus eliminated. In studies relying on field surveys, a moderate amount of sophistication is necessary to distinguish acute symptomatic seizures from unprovoked seizures. Thus, even though causation and prognosis of acute symptomatic seizures are quite different from those of epilepsy, some recent epidemiologic studies have categorized individuals with such seizures as having â€œepilepsy,â€[31] have failed to distinguish between unprovoked and acute symptomatic seizures,[28] or have not provided detailed information on cause, age, or gender.[13,20,21] To study acute symptomatic seizures properly, it is more efficient to study the associated conditions, such as head injury or stroke. This procedure is not usually undertaken by most epileptologists, and seizures are not a major interest to specialists treating underlying conditions such as stroke or hyponatremia. Nonetheless, in aggregate, acute symptomatic seizures account for more than half, and in some geographic areas as much as 80%, of all newly occurring seizures. Failure to consider these conditions separately will greatly modify the apparent epidemiologic characteristics of what is called â€œepilepsy.â€ In addition to greatly increasing the apparent incidence of â€œepilepsyâ€

mortality, age and gender structure of those affected is quite different if such cases were included as epilepsy, as has been suggested by some.[14,18,27] At present, acute symptomatic seizures continue to be a useful concept for classification and prognosis, and the suggestions by some that the term (and presumably the concept) be abolished seems inappropriate.

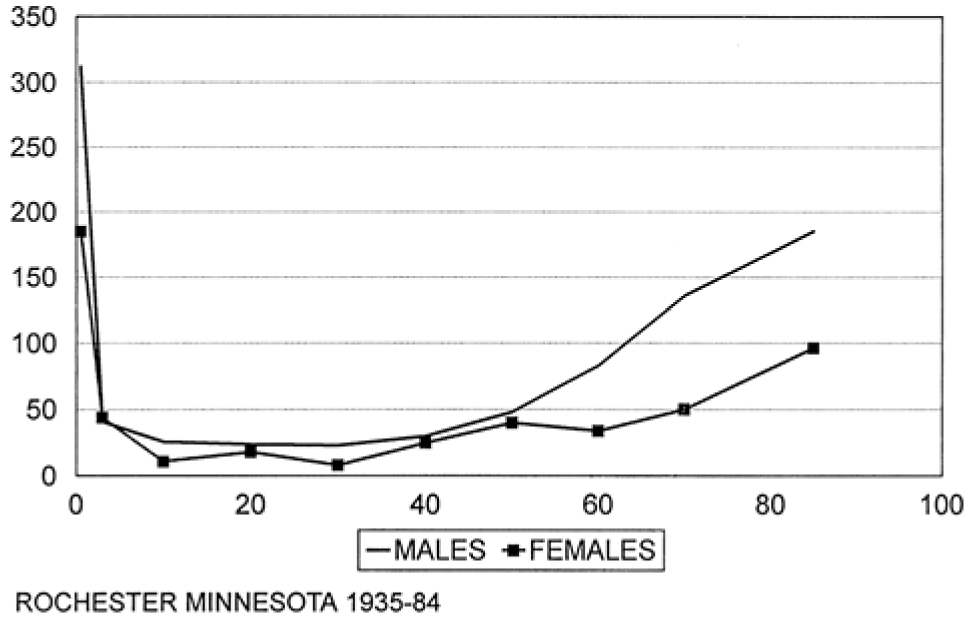

FIGURE 1. Age-specific incidence of acute symptomatic seizures (excludes childhood febrile seizures). CVD, cerebrovascular disease.

A major difficulty with acute symptomatic seizures remains their definition. For conditions such as stroke or brain trauma, seizures occurring in the first week of an insult have generally been classified as acute symptomatic. This is clearly an artificial cut-point of convenience and would better include all seizures occurring until the point of clinical stabilization. For metabolic conditions, it is frequently unclear for systemic metabolic derangements how severe a derangement must be or for what duration it must persist. For some conditions (e.g., neurocysticercosis), the acute insult may persist for weeks or months, defying a strict temporal definition.[11] This chapter reviews the incidence of acute symptomatic seizures and the incidence of seizures in conditions associated with acute symptomatic seizures. Although febrile seizures in childhood are by definition acute symptomatic seizures, they differ from other acute symptomatic seizures in their unique age specificity, high frequency in the population (up to 9%), and universality of exposure. It therefore seems appropriate that they be discussed separately.

Incidence of Acute Symptomatic Seizures

Overall Incidence

Only two studies provide detailed information regarding the incidence of acute symptomatic seizures.[5,24,26] The incidence of seizures occurring at the time of systemic metabolic insults or temporally associated with an insult to the central nervous system (CNS) was determined for the residents of Rochester, Minnesota. The age-adjusted incidence rates for 1955 to 1984, the period of most complete case ascertainment, was 39 per

100,000 person-years (U.S. 1970 population). This represents about 40% of all cases of afebrile seizures identified in the community during the study period and underscores the overall importance of this class of seizure disorder in population-based incidence surveys.

This rate is somewhat higher than that reported in Gironde, Bordeaux, France, which was 29 per 100,000 person-years. In this community-based study, acute symptomatic seizures also accounted for about 40% of all newly identified cases of afebrile seizures. The difference in absolute incidence of acute symptomatic seizures in these two communities may reflect a difference in the completeness of case ascertainment or a difference in the frequency of underlying conditions rather than any true difference in the epidemiologic characteristics. In any case, the similarities in the patterns and causes reported in the two studies are considerable.

Other studies provide some concept of frequency, but do not provide additional detail about age, etiology, or gender. In Switzerland, incidence was 25.2 per 100,000, accounting for 35% of all new cases of unprovoked seizures (Jallon). In Martinique, the incidence was 17 per 100,000, accounting for about 20% of all incident cases; in a study in children in Tunis, about 10% of all new cases were acute symptomatic. Although not specifically population based, a study from a British general practice survey[33] reported 21% of newly occurring seizures to fall into the category of acute symptomatic seizures.

Gender

From what we know about the conditions associated with acute symptomatic seizures, men seem to be at higher risk than women. In both the French study and the U.S. study, the age-adjusted incidence in men was considerably higher than that in women. Sex-specific incidence in the French study, adjusted to the U.S. 1970 population, was 33 for men and 17 for women. In contrast, the adjusted incidence in the United States during a similar time interval was 56 for men and 33 for women. These differences would seem to reflect gender-related differences in incidence of underlying conditions associated with acute asymptomatic seizures rather than any specific biologic phenomena.

Age

The age-specific incidence of acute asymptomatic seizures in the U.S. study was by far the highest during the first year of life (Fig. 1). This is attributable to the high incidence of acute symptomatic seizures associated with metabolic, infectious, and encephalopathic causes during the neonatal period. Incidence declined in childhood and the early adult years and reached a nadir of 15 per 100,000 person-years among those 25 to 34 years of age. After 35 years of age, the incidence increased progressively, and reached 123 per 100,000 among those older than 75 years of age. Cerebrovascular disease accounted for about half of all acute symptomatic seizures in persons older than 65 years of age.

As mentioned previously, age-adjusted incidence is considerably higher in men than women. The sex difference was greatest at the extremes of age. Between the ages of 15 and 44, there were few differences among all causes of acute symptomatic seizures. Seizures associated with eclampsia in women of childbearing age offset a lower incidence of seizures among women associated with other causes.

The age-specific incidence rates of acute symptomatic seizures in the French and U.S. studies were similar in middle-aged men, but the U.S. rates were higher in children younger than 15 years of age and in the elderly. Because incidence rates by etiologic groups were not provided in the French study, it is not possible to contrast the rates by etiology or to judge whether the differences in overall incidence might be attributable to differing distributions of the underlying insults associated with acute asymptomatic seizures.

Causes of Acute Symptomatic Seizures

The major causes of acute symptomatic seizures in both the French and U.S. studies were traumatic brain injury, cerebrovascular disease, drug withdrawal, and CNS infection. The underlying causes of the seizures are reflected in patterns of age, sex, and time period. Although the overall proportional distribution by cause was similar in the United States and France, no age- or etiology-specific data are available for the latter study. Cause-specific data from the U.S. study are presented in FIGURE 2.

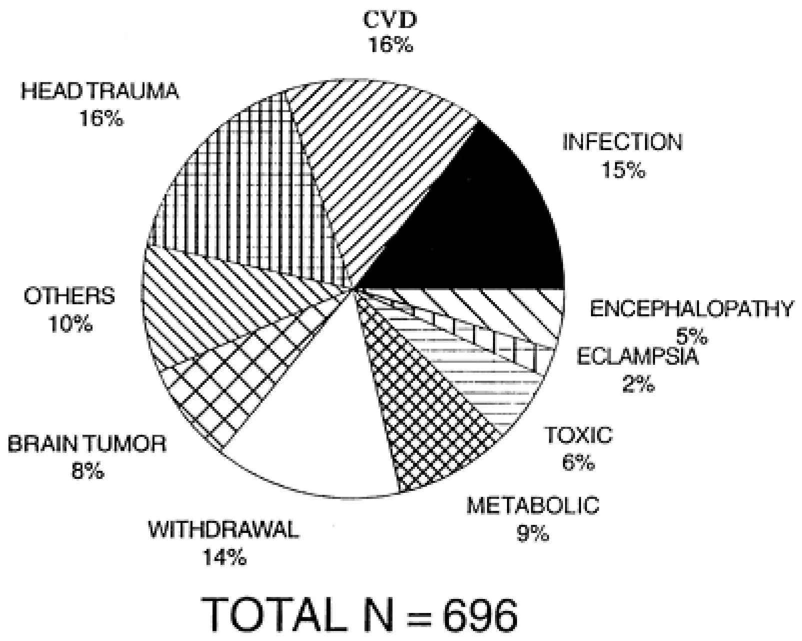

FIGURE 2. Acute symptomatic seizure precipitating causes.

Acute Symptomatic Seizures Associated with Primary Brain Insults

Central Nervous System Infection

Acute symptomatic seizures in infections of the central nervous system are those occurring during the acute phase of infection. About 5% of people with CNS infection can be expected to experience an acute symptomatic seizure.[4] Infections of the CNS accounted for about 15% of all acute symptomatic seizures in both Bordeaux, France, and Rochester, Minnesota. In the latter study, the age-specific trends of acute symptomatic seizures associated with CNS infection followed the pattern of incidence of CNS infection.[29] The highest incidence was during the first year of life and in children younger than 15 years of age; the incidence was lower in adults. The age-adjusted incidence of 5.2 per 100,000 person-years has been relatively constant over time. Overall, the age-adjusted incidence in men is twice that in women.

Neurocysticercosis (NC) represents a special category of CNS infection and also a special category of acute symptomatic seizures. Seizures are second only to headache as a presenting symptom of NC. It is assumed that most of these seizures are acute symptomatic and are associated with the response to the acute inflammatory response associated with transitional cyst degeneration.[10] Unlike most time-delimited insults associated with acute symptomatic seizures, the inflammatory response may last from weeks to months, thus requiring a modification of some of the usual concepts of acute symptomatic seizures.[11]

Brain Trauma

Seizures occurring within the first week of a traumatic brain injury are generally assumed to be acute symptomatic. Seizures occurring after that time are generally considered late or unprovoked, although it would certainly be more appropriate to include the concept of stabilization in such definitions. In civilian studies of traumatic brain injuries, about 6% of all cases are associated with acute symptomatic seizures.[2,32] The frequency of early seizures increases with severity of injury and probably represents a surrogate for severity. Acute symptomatic seizures associated with head trauma accounted for about 15% of all acute symptomatic seizures occurring in Rochester and only about 5% of all cases in Bordeaux. The higher frequency in Rochester reflects the fact that all cases of head injury in the community were reviewed, whereas the

French study depended on identification of only those people with seizures. Traumatic acute symptomatic seizures in Rochester were more common in men (age-adjusted rate, 8.6) than in women (age-adjusted rate, 4.8) at all ages. The age-specific incidence of head trauma is trimodal.[3,9] Given similar levels of severity of injury, children are at higher risk for acute symptomatic seizures than adults.[2]

Cerebrovascular Disease

Following the example of brain injury, acute symptomatic seizures associated with cerebrovascular disease are generally limited to seizures occurring within 1 week of the acute ictus. Between 5% and 10% of individuals with a cerebrovascular insult experience a seizure at the time of stroke.[22,30,35] The frequency varies with the nature of the insult and is probably highest in those with intracerebral hemorrhage. In Bordeaux, cerebrovascular disease accounted for about one third of all cases of acute symptomatic seizures, compared with only 15% of all cases in Rochester.

Paralleling the incidence of cerebrovascular disease,[6] acute symptomatic seizures associated with stroke are rare in persons younger than 55 years of age; the incidence rises rapidly with increasing age, reaching 54.6 per 100,000 among persons older than 75 years of age. The age-adjusted incidence of acute symptomatic seizures is higher in men than in women (9.4 vs. 4.7 per 100,000 cases).[6] The sex-specific difference is particularly dramatic in those 65 to 74 years of age: 55.1 per 100,000 in men versus 15.5 per 100,000 in women.

In Rochester, the age-specific incidence of acute symptomatic seizures associated with cerebrovascular disease was stable from 1945 through 1974 but fell in the final decade along with the incidence of stroke.[6] The age-adjusted incidence fell through the years from 8.6 in the decade 1955 to 1964 to 6.5 in the decade 1964 to 1974 to 5.1 in the decade 1975 to 1984.

Brain Tumor

There is debate about how to classify seizures associated with brain tumors. A high proportion of individuals with brain tumors may experience acute symptomatic seizures.[15] In Rochester, acute symptomatic seizures associated with primary or secondary brain tumors occurred at all ages but were rare in persons younger than 45 years of age. The age-specific incidence rates in persons older than 45 years of age were constant at 6 to 8 per 100,000 person-years. Unlike most other acute symptomatic seizures, seizures associated with neoplasm were equally common in men and women.

Acute Symptomatic Seizures Associated with Systemic Disturbances

Seizures occurring in association with systemic insults are easy to identify, although strict operational definitions are elusive. The severity of a systemic insult or the timing of the seizures from the start of the insult is seldom specified.[12] Nonetheless, this category accounts for a substantial proportion of all acute symptomatic seizures.

Eclampsia

In the Rochester studies, 15 women had seizures attributed to eclampsia during a 50-year period; this accounted for about 3% of acute symptomatic seizures in women, an incidence of 2.8 per 100,000 women ages 15 to 44 years. The incidence of eclampsia may more appropriately be expressed as a proportion of deliveries. The risk per 1,000 deliveries was 1.1 in the decade 1934 to 1944, 0.6 during 1945 to 1954, 0.4 during 1955 to 1964, 0.2 during 1965 to 1974, and 0.1 during 1975

to 1984. Because a higher proportion of deliveries occurred at home during the 1930s and 1940s, cases of eclampsia have been missed during this period, leading to an underestimation in the true decline in incidence in this community. The progressive decline of the incidence of eclampsia since 1935 probably reflects better management of toxemia in pregnancy.

Socioeconomic factors probably play a role in incidence rates of eclampsia. In Houston, Texas, the incidence of eclampsia in two inner-city hospitals from 1982 to 1992 was 0.7 per 1,000 deliveries,[1] a frequency similar to that in Rochester, Minnesota, in the 1940s. Seizures associated with eclampsia were not separately reported in the Bordeaux study.

Toxic Insults

Seizures may occur in association with a variety of toxic insults (e.g., carbon monoxide poisoning or acetylsalicylic acid overdose). Toxic insults accounted for about 5% of all acute symptomatic seizures in Rochester, but only a small proportion of cases in Bordeaux. This may be a consequence of differences between these two studies in inclusion criteria for this category. In Rochester, the overall incidence of acute symptomatic seizures associated with toxic insults was 2.2 per 100,000 cases, with the highest incidence in the elderly (older than 75 years of age).

Drug Withdrawal

Most drug withdrawal seizures are associated with abuse of ethanol and, less frequently, barbiturates or other substances. This category of acute symptomatic seizures accounted for about 15% of cases in Rochester and about one third of cases in Bordeaux. Incidence for this group of acute symptomatic seizures peaked in the 35- to 54-year-old age group, and the age-adjusted incidence was considerably higher in men than women (10.5 per 100,000 person-years vs. 3.4 per 100,000 person-years). Withdrawal seizures were the primary cause of acute symptomatic seizures for those 25 to 55 years of age. The incidence of seizures attributed to this cause progressively increased during the study period. Seizures associated with alcohol or drug abuse or withdrawal may be less completely ascertained than seizures associated with other causes because, unlike evaluations of stroke, head trauma, CNS infection, and brain tumors, each alcohol-related patient evaluation is not systematically reviewed for seizures.

Metabolic Insults

Systemic metabolic illness accounted for about 10% of all acute symptomatic seizures in Rochester and about 15% of cases in Bordeaux. In Rochester, the incidence of acute symptomatic seizures attributed to metabolic insults was highest during the first year of life. This was largely caused by hypocalcemia or hypoglycemia in newborns. These cases were identified primarily before 1960; they are virtually nonexistent at the present time in this community, although it is conceivable that they continue to account for a substantial proportion of newborn cases in less medically sophisticated areas. Seizures associated with metabolic disturbances were rare between the second week of life and 55 years of age. There was a slight rise in incidence after this age. The incidence of seizures attributed to metabolic causes among newborns fell from 105 per 100,000 cases during the decade 1945 to 1954 to 50 per 100,000 in the decade 1975 to 1984.

Cumulative Incidence of Acute Symptomatic Seizures

In Rochester, the risk for experiencing an acute symptomatic seizure during an 80-year life span is 3.6%; this approaches the risk for epilepsy. The risk for any type of acute symptomatic seizure from birth through 80 years of age is almost 5% in men and a little more than 2.5% in women. The prevalence of history of acute symptomatic seizures is somewhat lower than the cumulative incidence because of the high mortality rate associated with many of the causes of acute symptomatic seizures.

Prognosis of Acute Symptomatic Seizures

In general, acute symptomatic seizures are a reflection of disease severity and, as such, are associated with a relatively high mortality rate.[18,23,27] However, prognosis obviously varies with the underlying condition. No studies address the influence of acute symptomatic seizures on risk for mortality within given conditions, so it is impossible to assess the contribution of seizures per se on mortality. In survivors of neurologic insults, those with acute symptomatic seizures seem to be consistently at increased risk for subsequent epilepsy compared with those without acute symptomatic seizures.[2,4,19] This is probably not related to a kindling phenomenon but rather to the increased severity of initial insult in those with acute symptomatic seizures. Acute symptomatic seizures associated with metabolic insults are not associated with a similar increase in risk for subsequent epilepsy. None of the cases of eclampsia in the Rochester cohort had subsequent seizures. There has been no systemic study of the risk for epilepsy in people with other metabolic conditions.

Summary and Conclusions

Acute symptomatic seizures account for a substantial proportion of all newly occurring seizures, even when febrile seizures are excluded. Acute symptomatic seizures continue to be a useful concept for classification and prognosis, and the suggestions by some that the term (and presumably the concept) be abolished seems inappropriate. The causes and prognosis of acute symptomatic seizures require further systematic study and greater consideration when the total picture of the epilepsies is considered.

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Chapter 9

Seizure Precipitants

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Introduction

Seizures occur in patients with and without epilepsy. In patients *without* epilepsy, provoked seizures may arise from an underlying systemic disorder or be caused by direct cerebral insult. These provoked seizures, called *acute symptomatic seizures* (Commission) or *situation-related seizures*, are considered extensively in Chapter 8. Although epilepsy is defined as a condition characterized by recurrent, unprovoked seizures, it has long been recognized that even if most seizures appear to occur spontaneously, they may be provoked or the occurrence modulated by a variety of endogenous and environmental phenomena. Seizure precipitants are â€œthose circumstances that precede the onset of an epileptic attack and are considered by both patient and neurologist to be a possible explanation for why the seizure happened when it did, and not earlier or later.â€[4] These precipitants include both seizure-inducing and seizure-triggering factors. Seizure-inducing factors are of environmental or endogenous origin and produce transient lowering of the seizure threshold.[1] More than 40 precipitating factors have been reported in the literature.[1] Seizures may be triggered by *specific* stimuli. The terms *reflex seizures* and *reflex epilepsies* have been proposed and this nosographic group will be developed in Chapter 257.

Knowledge of seizure precipitants has practical implications in patient treatment and counseling. Some 53% to 92% of patients reported one or more seizure precipitants.[6,19,24,26] Precipitants are much more frequent in patients with active and/or intractable epilepsy and in some epileptic syndromes such as idiopathic generalized epilepsies with myoclonic seizures.[3,6,10] Patients often mention several factors. It is often difficult for a patient and/or the doctor to determine exactly which specific precipitant may have facilitated or triggered a seizure or to discern the relative importance of the individual factors.

Common Reported Seizure Precipitants

Emotional Stress

Although difficult to quantify, emotional stress is the most common factor (30% to 66%) identified by patients, mostly by women.[6,19,24,27] Since the time of Hughlings Jackson and Gowers, attention has been paid to the role of the emotions in the precipitation of epileptic seizures. Many reports provide evidence of an association between stressful life events or tension states and seizures.[7,10,18,19,26] In one study,[18] 58% of patients reported emotional stress, such as worry, anxiety, frustration, and anger, as the second most frequent precipitating or modulating factor for seizures. Another study[7] examined the psychologic factors confronting psychiatric patients with epilepsy before the onset of epilepsy. No fewer than 20 of 51 patients had experienced a severe emotional disturbance shortly before the first attack, caused, for example, by a mother-in-law's serious illness, the death of a mother, arrest by the Gestapo, a husband's heart attack, retirement after 45 years with the same firm, severe financial difficulties, and frequent unemployment. In patients subjected to a stress interview with electroencephalogram (EEG) recordings, neuronal instability increases during procedures, as evidenced by a seizure or emergence or increase in epileptiform activity. The mechanisms whereby emotional factors may elicit seizures have yet to be determined. An activation of specific networks has been involved.

Patients with generalized seizures and those with partial seizures seemed to be equally sensitive to emotional stress.[19] However, patients with temporal lobe epilepsy would be expected to be more vulnerable to emotional activation of seizures than patients with complex partial seizures because the anatomic structures involved during complex partial seizures are those that handle normal emotional responses. In one study,[10] stress represented 30% of seizure precipitants. Patients with temporal lobe epilepsy were the most likely to identify stress (46%) and patients with cryptogenic epilepsies were the least (15%). However, multiple factors may converge. Emotional disturbance may lead to sleep deprivation, noncompliance, excessive drinking, and even hyperventilation. Stress may be present during a period of time ranging from minutes to days, weeks, or years. Relaxation was the most commonly used technique for aborting seizures by 53.7% of the patients, which is consistent with the fact that 53% of the patients who could identify seizure precipitants reported that stress or tension could trigger their seizures.[25]

Sleep and Sleep Deprivation

Many patients have seizures only at night. In the 1950s, some neurologists erroneously considered sleep (â€œmorpheicâ€) epilepsy as an entity. In several epileptic syndromes, such as idiopathic epilepsies, benign partial epilepsy of childhood with centrotemporal sharp waves, and symptomatic or cryptogenic frontal and temporal lobe epilepsies, seizures appear preferentially during sleep. Sleep deprivation is the second most often reported seizure precipitant in four studies.[3,6,10,19,22,26] As sleep deprivation usually occurs during periods of overactivity or tension often associated with the use of stimulants and overhydration, its role is not always clinically clear.[1] Patients with idiopathic epilepsies frequently reported sleep deprivation as a significant precipitant.[10] There is no gender distribution. Sleep deprivation is a common precipitant of seizures in juvenile myoclonic epilepsy (JME).[6] In the adolescent and young adult population affected by JME, late nights of studying or socializing frequently result in myoclonic jerks and generalized tonicâ€"clonic seizures (GTCSs). Sleep deprivation as an activator of EEG epileptiform discharges is commonly used as a diagnostic aid in epilepsy[9] but has been recently reported as not affecting seizure frequency during video EEG monitoring[17] (see Chapter 188). Sudden awakening is a major precipitant of JME. Provoked awakenings are more dangerous than spontaneous ones.

The effect is more noticeable when sleep is interrupted during unstable phases, such as rapid eye movement (REM) sleep during the early part of the night and phase 2 sleep at the end of the night.

Fatigue and Exercise

Reports on the effects of fatigue and exercise on seizure frequency have been controversial. In Nakken's study, which compared seizure precipitants in three twin registries (Norway, Denmark, and United States), tiredness is the third most frequently reported seizure precipitant.[19] Physical activity was given as a precipitant factor by 6% of the Norwegian sample but accounted for only 0.3% and 0.7% of the reported precipitants by Danish and American populations, respectively. Some studies[7] have suggested that aerobic exercise raises seizure thresholds, thereby conferring a protective effect. Hyperventilation in the resting patient is very different from that in response to exercise and rarely provokes seizures. This is a consequence of metabolic acidosis that occurs during exercise. Seizures induced by exercise are actually seizures occurring shortly after exercise. The risk is greater after continuous exercise than after intermittent exercise. The lower the pH and base excess values are after exercise and during the recovery phase, the greater the number is of EEG epileptiform abnormalities. Sustained hypoxia or hypoglycemia after vigorous physical exercise is probably also involved. Physical activity such as running or jumping is reported by 7% of the patients as a technique for aborting seizures.[24]

Alcohol

The interactions between alcohol and epilepsy are complex. Chronic and acute effects of alcohol on the central nervous system are quite different and, sometimes, even opposite to one another.[2] These interactions are discussed more thoroughly in Chapter 268. It is commonly perceived that alcoholic beverages are a frequent cause of seizures in adult patients with epilepsy. Alcohol consumption was the fourth most frequent precipitant (5.7%) reported in one study.[19] Given the usual reluctance to admit alcohol use, this proportion is clearly underestimated. Alcohol abuse is often associated with poor compliance and sleep deprivation. However, there is little experimental evidence that moderate ingestion of alcohol influences seizure occurrence.[13] In fact, one study[18] found that moderate alcohol intake does not trigger seizures and can even decrease EEG epileptiform abnormalities! Alcohol abuse may be accompanied by seizures in two situations.[2] On the one hand, chronically alcoholic patients with or without epilepsy experience attacks during bouts of heavy drinking but more frequently on withdrawal. On the other hand, seizures may be precipitated in nonalcoholic patients with epilepsy after excessive drinking. Seizures occur during the period of rapidly falling alcohol blood levels, especially when excessive alcohol intake is associated with insufficient sleep.[18]

Missed Antiepileptic Medication

Penetrating insights on compliance with antiepileptic drugs (AEDs) have been published.[23] It is generally accepted that about one third to one half of people receiving long-term therapy take their medication in ways that differ from the clinical prescription. In a small series involving 40 patients admitted with seizures, noncompliance was the most common potentially preventable precipitating factor (45%),[26] and patients with subtherapeutic AED levels despite good compliance was the second most common precipitating factor. Noncompliance is probably underestimated and the degree of compliance varies considerably, as does the motivation for the consequences of poor compliance. Despite some patients' beliefs, occasional omission of one or two doses can be harmless. Because of a longer drug-free period, however, a greater risk exists when patients decide for themselves that they are cured and stop taking their medication. Two mechanisms explain the occurrence of seizures in such situations. First, a seizure can reflect the natural course of pharmaco-dependent disease. Seizures occur with different lag times, which vary according to the severity of epilepsy and with the drug (lag times are short with most AEDs but longer with valproate, probably because of a carry-over effect). Usually, a single seizure is observed, at least in moderate epilepsies, when AEDs are withdrawn, but status epilepticus is possible in severe epilepsies. Second, withdrawal seizures may also occur when barbiturates or benzodiazepines are stopped, as is observed in persons without epilepsy. These are generalized seizures, and they occur shortly after drug withdrawal.

Drugs Lowering Seizure Threshold

Many classes of pharmacologic agents prescribed at therapeutic dosages have been implicated in lowering the seizure threshold: Antidepressants, antipsychotics, central nervous system (CNS) stimulants, hypoglycemic agents, antimicrobial agents, aminophylline, antihistaminics, ephedrine, steroids, and a wide variety of other drugs.[11,15,16,29]

Metabolic Factors

Significant metabolic derangements can result from diarrhea, constipation, acute infections, liver and renal failure, and diuretic intake, especially in the very young and very old. Hypernatremia or hyponatremia, hypocalcemia, and hypoglycemia can provoke seizures in patients with or without epilepsy. In patients with diabetes, seizures frequently occur with overdose of insulin or sulfonamides, and perhaps during hypoglycemia following a large meal.[1]

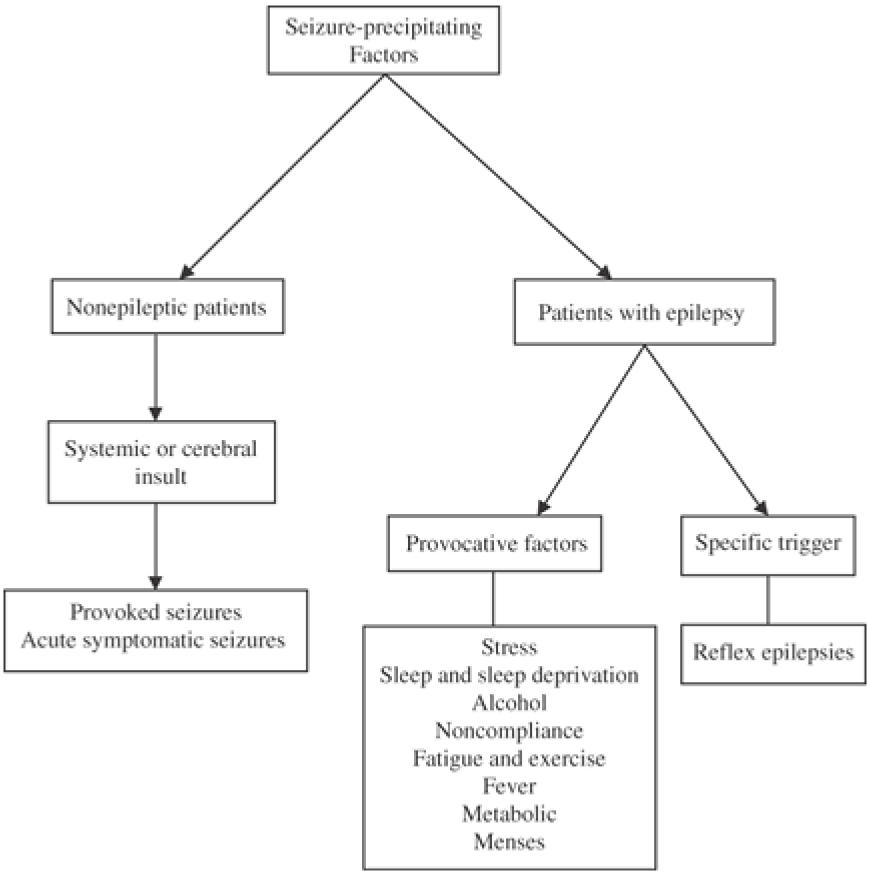
Seizure-precipitating Factors
Nonepileptic patients
Patients with epilepsy
Systemic or cerebral insult
Provocative factors
Specific trigger
Provoked seizures
Acute symptomatic seizures
Stress
Sleep and sleep deprivation
Alcohol
Noncompliance
Fatigue and exercise
Fever
Metabolic
Menses
Reflex epilepsies

FIGURE 1. Seizure-precipitating factors.

Hyperventilation

Hyperventilation produces a respiratory alkalosis that causes central vasoconstriction and, if sufficiently marked, can modify the level of cerebral oxygen and glucose. Excessive breathing incommensurate with or without physical effort may eventually induce seizures in some patients.[5] Hyperventilation easily elicits absence seizures in children and, less commonly, other types of seizures.[12] Involuntary hyperventilation may occur in the course of a patient's daily activities due to anxiety, sobbing, or sexual activity.

Fever

Febrile convulsions are a special syndrome, characterized by seizures caused by a sudden rise in body temperature (see Chapter 57). They are seen only in children <5 years of age, usually <3 years of age. At any age, but mainly in the elderly, an acute febrile infection may provoke a seizure in the susceptible patient. Nevertheless, fever is often reported by patients as a precipitant factor of their seizures.[10,19]

Hormones

Catamenial epilepsy is defined as the occurrence of at least 75% of seizures per month within a period including the 3 days

preceding and the 4 days following menstruation.[20] While this is an uncommon condition, seizure frequency is reported to be affected by the menstrual cycle in 10% to 70% of women with epilepsy.[21] Many women report an increase in seizure frequency around the time of their menses. Herzog described three distinct patterns of catamenial epilepsy: Perimenstrual, periovulatory, and inadequate luteal-phase catamenial seizures.[14] Cyclic changes of ovarian hormonesâ€"estrogens (proconvulsivant) and progesterone (anticonvulsivant)â€"seem to play an essential role in the occurrence of catamenial seizures, as do possible variations in AED levels during the menstrual cycle. Natural progesterone therapy has proven to be effective and the use of neurosteroids in the future has to be explored.

Pregnancy has relatively little influence on seizure frequency. Altered disposition of AEDs and noncompliance seem to be the major reasons for increased seizure frequency (see Chapter 198).

Diagnosis

Clinicians must be aware of possible seizure precipitants (Fig. 1) and look for them. Skilled questioning and history taking based on knowledge of seizure-inducing mechanisms are essential.[1] The results of studies about seizure precipitants are quite different when the patients report the different factors spontaneously versus when a list of the factors is proposed.[24] In some cases it may be difficult or impossible to discern the relative importance of one or several factors. Too often, patients and family members give what appears to them a logical explanation for their seizures. Patients can use these factors to simplify the explanation for their seizures or to hide noncompliance. Some skepticism is necessary. Although a seizure precipitant is identified in association with a seizure, this does not necessarily prove a causal relationship between the two. However, the body evidence supporting an association is a major argument for addressing patients and their families in education. Tan et al.[26] reported that, in their small cohort, despite the frequent occurrence of noncompliance as a precipitating factor only 5% of patients were aware that neglecting their medication was the precipitant for their seizures.

There are few studies about the distribution of seizure precipitants among epilepsy syndromes. Generalized epilepsiesâ€"and particularly idiopathic generalized epilepsiesâ€"are more sensitive to stress, sleep deprivation, and menstruation.[3,6]

In the subjects who have recognized their seizure precipitants, 60% reported that they use this information to control their epilepsy by avoiding high-risk situations; however, 6% reported deliberately seeking this high-risk situation to have seizure.[24,25]

Summary and Conclusions

Common treatment measures are indicated for common seizure precipitants. These include educational interventions, wherein patients are counseled regarding situations that must be avoided or countermeasures that must be employed (e.g., detailed and repeated explanations on the necessity of sufficient sleep, proper dietary intake, and adherence to prescribed regimens of drugs).

Identification of modulators of seizure occurrence offers the possibility of improved control in some patients through alternative interventions. Emotional and tense states are among the most difficult of the inducing factors to manage. Nonpharmacologic (i.e., psychologic) methods of seizure control may be helpful as an adjunct to AED therapy. Numerous articles and several excellent reviews concerning behavioral methods of seizure control are available in print.[28] The issues and results of these are discussed in more detail in Chapter 132. Treatment with psychotropic drugs such as neuroleptics, lithium, or tricyclic antidepressants and other antidepressants is sometimes necessary. Seizure frequency in most patients is not increased when psychotropic medications are used in low to moderate

doses and introduced progressively. However, it is safer to preferentially employ medications that minimally affects seizure threshold.[16]

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Chapter 10

Mortality

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Introduction

The majority of patients with epilepsy have a good prognosis that allows them long periods of seizure freedom.[9,10,43] Despite this, it is known that the mortality rate in epilepsy is raised to two to three times that of the general population[8,19,28,29,32,39,53] and life expectancy in some of these patients is reduced.[17] Studies in the last two decades have thrown considerable light on the various factors that influence mortality and also on the various causes of mortality in epilepsy in the developed world.[8,19,28,29,32,39,53] However, there are no large-scale studies of mortality in epilepsy from resource-poor countries.[7]

There are many problems inherent to the study of mortality in epilepsy, including the problems of case ascertainment. Death certificates have been found to be an unreliable source of case ascertainment,[3] and prospective studies of cohorts of people with epilepsy are more likely to provide accurate data on mortality.

Several aspects of epilepsy may affect mortality:

1. Seizures themselves can be a cause of death, either directly as in prolonged status epilepticus or indirectly because of increased risk of accidental death, especially drowning.
2. Some of the risk factors for epilepsy (e.g., brain tumors, cerebrovascular disease, traumatic brain injury) are associated with increased mortality whether or not epilepsy is present.
3. There is an increased risk for sudden unexpected death in epilepsy (SUDEP).
4. The long-term use of antiepileptic drugs (AEDs) has been thought to increase the incidence of malignant neoplasia and osteoporosis, thereby potentially affecting long-term mortality rates in persons with epilepsy, especially in younger adults (ages 15 to 49 years). Although rare, other adverse effects of idiosyncratic type can also occasionally be fatal.

The objectives of this chapter are to review the evidence for, and patterns of, mortality in persons with epilepsy and to evaluate the current understanding of these factors.

Overall Mortality

The most often used and preferred statistical measure of epilepsy mortality is the standardized mortality ratio (SMR). This is the ratio of the number of observed deaths in a study population to the expected number of deaths in the age- and sex-matched general population in that time period. Older studies utilize the proportional mortality ratio (PMR), which expresses mortality as a ratio of the number of observed deaths due to a particular cause in a study population to the total number of deaths in that study population. This method is subject to more bias, depending on the kind of cohort studied, where deaths due to any one cause may be overrepresented, and is not a measure of the mortality rate in epilepsy versus the general population. SMRs among people with epilepsy have been evaluated in several population-based studies (Table 1) and vary from

1.6 to 8.8. Although these studies span several decades and countries, follow incidence or prevalence cases, and vary in terms of the age composition and characteristics of the patients studied, most are consistent in reporting a twofold to threefold increased mortality rate for people with epilepsy. Similarities between the population-based epidemiologic studies and the more selective hospital-based studies are not truly consistent with each other but probably the result of compensating biases. It should also be noted that the overall relative increased premature mortality of twofold to threefold should not be applied to all people with epilepsy; this is a summary measure that masks very important differences among those with epilepsy. The most important of these are the etiology of epilepsy, age, duration, and type of epilepsy.

Etiology of Epilepsy

The increased mortality rates of epilepsy reflect both the effects of epilepsy and also the effects of central nervous system (CNS) insults, such as brain tumors, cerebrovascular disease, and head trauma, which are the presumed cause of approximately one third of all epilepsy cases.[33] In epidemiologic studies, seizure disorders have often been classified into four broad groups according to presumed etiology:

1. Idiopathic (or cryptogenic) epilepsy.
2. Remote symptomatic epilepsy, related to CNS lesions acquired postnatally from trauma, brain tumors, cerebrovascular disease, infection, or chronic degeneration.
3. Acute symptomatic seizures, related to CNS insults where seizures manifest within a week of the acute insult (e.g., head injury, cerebral hemorrhage, or infarction).
4. Major neurologic dysfunction of uncertain cause but presumed to have been present at birth and manifested by gross neurologic deficit (spasticity, hemiparesis), or mental retardation (IQ <70).

Table 1 Overall Mortality in Epilepsyâ€"Standardized Mortality Ratios (SMR)

Author	Country	Study design	Age	Follow-up years	SMR (95% CI)
		Population-based studies			
Zielinski 1974[53]	Poland	Prevalence	All		1.8 (1.6â€"2.1)
Hauser 1980[19]	United States	Retrospective	All	33	2.3 (1.9â€"2.6)
Cockerell 1994[8]	United Kingdom	Prospective	All	9	2.5 (2.1â€"2.9)
Olafsson 1998[39]	Iceland	Retrospective	All	30	1.6 (1.2â€"2.2)

Lindsten 2000[29]	Sweden	Prospective	Adult	11	2.5 (1.2â€“3.2)
Lhatoo 2001[28]	United Kingdom	Prospective	All	14	2.1 (1.8â€“2.4)
Camfield 2002[6]	Canada	Retrospective	Children	20	5.3 (2.29â€“8.32) First 10 years 8.8 (4.10â€“13.4) Second 10 years
Berg 2004[4]	United States	Prospective	Children	8	7.54 (4.38â€“12.99)
Hospital-based studies					
Klenerman 1993[22]	United Kingdom	Retrospective	Adults		1.9 (1.6â€“2.3)
Nilsson 1997[38]	Sweden	Retrospective	Adults	>16	3.6 (3.5â€“3.7)
Shackleton 1999[44]	Netherlands	Retrospective	All	30	3.2 (2.9â€“3.5)
Callenbach 2001[5]	Netherlands	Clinical series	Children	5	6.6 (2.2â€“15.5) Males
					7.4 (2.0â€“19.0) Females

CI, confidence interval; SMR, standardized mortality ratio.
SMR = Observed deaths/expected deaths.

Table 2 Standardized Mortality Ratios (with 95% Confidence

Intervals) According to Etiology

Country	Idiopathic	Remote symptomatic	Acute symptomatic	Neurodeficit
United States 1980[19]	1.8 (1.4â€“2.3)	2.2 (1.8â€“2.7)		11.0 (6.9â€“16.4)
United Kingdom 1994[8]	1.6 (1.0â€“2.4)	4.3 (3.3â€“5.5)		50.0 (10â€“146)
France 1999[32]	1.5 (0.4â€“3.9)	6.5 (3.8â€“10.5)		
Sweden 2000[29]	1.1 (0.5â€“2.4)	3.3 (2.4â€“4.5)		
United Kingdom 2001[28]	1.3 (0.9â€“1.9)	3.7 (2.9â€“4.6)	3.0 (2.0â€“4.3)	25 (5.1â€“73.1)
United States 2004[4]	1.43 (0.36â€“5.73)	33.46 (18.53â€“60.43)		

NBâ€”idiopathic, idiopathic or cryptogenic or nonsymptomatic.

The level of increased premature mortality appears greatest in patients with epilepsy in association with a neurologic deficit present from birth. Such patients had a considerably high SMR of 7.0 (95% confidence interval [CI], 4.6 to 10.2) in the Rochester, Minnesota, study[19] and of 25 (95% CI, 5.1 to 73.1) in the UK General Practice Study (although this latter SMR was based on only a few deaths).[28] The extremely high SMR in the neurologic deficit group reflects the large number of observed deaths at relatively young ages, when few deaths are expected. Mortality is also high in individuals with symptomatic epilepsy compared to those in other groups. In the Rochester study,[19] persons with epilepsy as a result of postnatal CNS insults had an SMR of 2.76 (95% CI, 2.3 to 3.4). In the UK study, the SMR for postnatally acquired epilepsy was 3.7 (95% CI, 2.9 to 4.6).[28] The higher relative mortality in the British study may

be a consequence of the comparatively shorter mean follow-up period, as SMRs decline with duration.

Studies that present SMRs for all patients and separate SMRs for persons with idiopathic (or cryptogenic) epilepsy (epilepsy without a presumed cause) show considerably lower SMRs for patients with idiopathic epilepsy than for all patients with epilepsy. The mortality rates among those with idiopathic epilepsy from Rochester,[19] Sweden,[29] and the UK General Practice Study[28] are still raised above those of the general population, but only by 50% to 60% and not significantly so in the latter two studies (Table 2). The UK General Practice Study also studied patients with acute symptomatic seizures as a separate category as defined above and found an SMR of 3.0 (95% CI, 2.0 to 4.3) in this group.[28]

Age

The population-based studies that present age-specific SMRs are shown in Table 3. Mortality rates are increased at all ages among persons with epilepsy, but the increase is not uniform across age groups. There is a sharp decline in SMRs with age in these study populations. The higher SMRs in persons under 50 years of age are caused in part by the extremely high relative death rates for patients with epilepsy in association with neurologic deficits and the low expected mortality in these age groups. However, in the UK General Practice Study, the 50- to 59-year age group had higher mortality rates than all other age groups, and this may be explained by the high incidence of brain tumors in this population.[28] Head trauma in younger patients may be another contributory factor. Another factor is the increased risk for sudden death in younger adults with epilepsy; it is uncertain whether this increased risk persists among elderly patients with epilepsy. Although the SMRs decrease with age, the death rates among the elderly (>65 years of age) with epilepsy are still 50% to 60% above the rates in the general population and remain significantly elevated even in patients over the age of 80 years.[19]

Table 3 Standardized Mortality Ratios (SMRs) According to Age

	SMRs (95% CI)			
Age (y)	**Poland**	**United States[19]**	**United Kingdom[28]**	**Sweden[29]**
0â€“24		8.5 (5.4â€“12.9)		
0â€“29	3.5			
0â€“49			7.6 (4.2â€“12.5)	
15â€“39				9.5 (3.1â€“29.4)
25â€“44		7.7 (5.1â€“11.0)		
30â€“49	3.4			
45â€“54		3.5 (2.0â€“5.7)		
40â€“59				10.7 (6.5â€“17.6)
50â€“59	2.5		8.6 (4.7â€“14.1)	
55â€“64		3.0 (2.0â€“4.5)		

60â€“69	1.8			
60â€“79				2.4 (1.6â€“3.8)
65â€“74		1.5 (1.0â€“2.2)		
70â€“79			1.9 (1.2â€“2.8)	
â‰¥70	1.5			
â‰¥75		1.4 (1.1â€“1.9)		
â‰¥80			2.6 (1.8â€“3.6)	1.3 (0.7â€“2.4)

CI, confidence interval.

Table 4 Standardized Mortality Ratios (SMRs) for Each Year of Follow-up after Index Seizure in Patients with Newly Diagnosed Epilepsy and Patients with Newly Diagnosed Idiopathic Epilepsy in the UK National General Practice Study of Epilepsy

Years after index seizure	No. of deaths				
	Observed	Expected	No. at risk	SMR	95% CI
		Definite epilepsy (n = 564)			
0â€“1	564	49	7.4	6.6	4.8, 8.7
1â€“2	515	16	6.1	2.6	1.5, 4.2
2â€“3	499	13	5.7	2.3	1.2, 3.9
3â€“4	486	16	5.1	3.1	1.8, 5.1
4â€“9	470	33	21.6	1.5	1.0, 2.1

9â€“14	437	22	12.3	1.8	1.1, 2.7
Idiopathic epilepsy (n = 346)					
0â€“1	346	6	2.8	2.2	0.8, 4.7
1â€“2	340	3	2.5	1.2	0.2, 3.5
2â€“3	337	5	2.3	2.2	0.7, 5.2
3â€“4	332	5	1.9	2.7	0.8, 6.3
4â€“9	327	11	9.4	1.2	0.6, 2.1
9â€“14	316	4	7.0	0.6	0.1, 1.5

CI, confidence interval; NBâ€”idiopathic, idiopathic or cryptogenic.
From Lhatoo SD, Johnson AL, Goodridge DM, et al. Mortality in epilepsy in the first 11 to 14 years after diagnosis: multivariate analysis of a long-term, prospective, population-based cohort. *Ann Neurol.* 2001;49(3):336â€“344.

Table 5 Causes and Categories of Death in Epilepsy

Epilepsy-related deaths

Directly related
  SUDEP
  Status epilepticus
Indirectly related
  Accidents as a consequence of seizures
  Aspiration pneumonia after seizures
  Iatrogenic; drug toxicity and idiosyncratic reactions
  Suicides

Underlying disease related deaths

Primary and secondary CNS neoplasia
Cerebrovascular disease

CNS infections
Inherited neurodegenerative disorders

Unrelated deaths

Non-CNS neoplasia
Ischemic heart disease
Pneumonia
Accidents unrelated to seizures

CNS, central nervous system; SUDEP, sudden unexpected death in epilepsy.

Duration of Epilepsy

Due to a high proportion of so-called â€œagonalâ€ seizures in patients with newly diagnosed epilepsy who have serious underlying brain pathologies such as brain tumors and cerebrovascular disease, mortality is highest in the first few years

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following diagnosis. This is well illustrated by the UK General Practice Study where the highest SMR of 6.6 (95% CI, 4.8 to 8.7) was reported in the first year compared to an SMR of 1.5 (95% CI, 1.0 to 2.1) at 4 to 9 years (Table 4).[28] The Swedish study reported a similar trend with an SMR of 7.3 (95% CI, 4.4 to 12.1) in the first year and no elevation of SMR at 6 years after diagnosis.[29] In the Rochester study,[19] persons with idiopathic epilepsy had significantly increased mortality rates (SMR 1.9) during the first 10 years after the diagnosis of epilepsy but only slightly increased rates thereafter. Persons with epilepsy caused by a postnatal neurologic insult had a threefold increased death rate during the first decade after diagnosis and a twofold increased rate after 10 years. Those with epilepsy in association with a neurologic deficit

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had high mortality rates throughout follow-up. A late increase in mortality, thought to be directly caused by epilepsy, occurred in the third decade.[19] It is an interesting observation, since the influence of underlying pathologies on mortality could be expected to be much less than at diagnosis, and mortality due to status epilepticus and SUDEP in those with refractory seizures may conceivably become more prominent. This remains speculative at the current time. A small but similar late rise in mortality occurred after 9 years in the UK study, but with only three direct epilepsy-related deaths in this cohort during this time, this rise is not easily explained.[28] The Swedish study also reported a late increase in mortality after 9 to 11 years.[29]

Table 6 Cause-specific Mortality in Epilepsy (SMRs with 95% Confidence Intervals)

	Study		
Cause	**United States[19]**	**United Kingdom[28]**	**Sweden[29]**
Cerebrovascular	2.6 (1.8â€“3.6)	3.7 (2.3â€“5.5)	5.3 (4.9â€“5.8)

Heart disease	1.1 (0.8â€“1.5)[a]		
Ischemic heart disease		1.1 (0.6â€“1.7)	2.5 (2.3â€“2.7)
Myocardial insufficiency			
Other circulatory	7.1 (3.4-13)		
Neoplasms	2.9 (2.1â€“3.9)	3.5 (2.6â€“4.6)	2.6 (2.4â€“2.8)
Neoplasms excluding brain tumors	1.8 (1.1â€“2.6)	2.4 (1.7â€“3.4)	2.0 (1.9â€“2.2)
Pneumonia	3.5 (1.6â€“6.6)	7.3 (4.8â€“10.6)	4.2 (3.6â€“4.8)
Accidents	2.4 (1.3â€“3.7)		4.7

SMR, standardized mortality ratio; CI, confidence interval.

[a] Significant increases in ages 25â€“44 years (SMR 5.7 [95% CI 1.8â€“13.3]) and 45â€“64 years (SMR 2.5 [95% CI 1.4â€“4.1]).

Cause-specific Mortality in Patients with Epilepsy

Causes of death (Table 5) vary in both epilepsy-related and -unrelated mortality according to the populations studied. The commonest causes of death in community-based analyses are usually pneumonia, cerebrovascular disease, and CNS-related, as well as nonâ€“CNS-related, neoplasia, whereas the hospital-based analyses have larger representations of sudden unexpected deaths and epilepsy-related mortality. Table 6 shows the SMRs of cause-specific mortality in these studies.

Sudden Unexpected Death in Epilepsy

SUDEP is defined as a sudden, unexpected, witnessed or unwitnessed, nontraumatic, and nondrowning death in patients with epilepsy, with or without evidence of a seizure having occurred, excluding documented status epilepticus, in which postmortem analysis does not reveal an anatomic or toxicologic cause of death.[33] Studies in the United Kingdom suggest that there are approximately 500 deaths per year attributable to SUDEP.[18] Several studies have attempted to examine the incidence of SUDEP and these are represented in Table 7. Their results reflect the varying case ascertainment methods and study populations used.

Population-based studies, with less selection bias, provide lower figures for SUDEP incidence (0.09 to 2.7 per 1,000) than do selected cohorts that constitute large numbers of patients with refractory epilepsy (0.2 to 9.3 per 1,000). In one comprehensive and often quoted population-based study, the estimated incidence of SUDEP was 0.35 per 1,000 person-years, occurring in 8.6% of recorded deaths in people aged 15 to 44 years.[16] The SMR for sudden death in the 20- to 40-year age group was 23.7, suggesting a large increased risk for sudden death in patients with epilepsy compared to that of sudden death in the general population. Although fairly uncommon in population-based incidence cohorts, SUDEP may be the leading cause of death in patients with refractory epilepsy.[51]

The mechanisms that underlie SUDEP are unknown, but there is mounting evidence that it is a seizure-related

phenomenon. Risk factors for SUDEP have been analyzed in case-control studies.[51] These and the hypothetic mechanisms behind SUDEP are discussed in more detail in a separate chapter (Chapter 189).

Table 7 Rates of SUDEP (per 1,000 Person-years) in Community-based Studies of Epilepsy and in Studies of Selected Epilepsy Cohorts

	SUDEP		
Reference	**Population**	**Case Ascertainment**	**Incidence**
	Community-based studies		
Terrence et al., 1975[49]	Community[a]	Retrospective review of autopsy records	0.9
Leestma et al., 1984[26]	Community[a]	Retrospective review, medical examiner	0.5â€“0.9
Leestma et al., 1989[27]	Community[a]	Prospective, medical examiner	0.9â€“2.7
Jick et al., 1992[20]	â€œPrimary epilepsy,â€ age 15â€“49 years, based on AED prescriptions	Retrospective review of death certificates and autopsy reports	1.3
Tennis et al., 1995[48]	â€œPrimary epilepsy,â€ age 15â€“49 years, based on AED prescriptions	Retrospective review of death certificates and autopsy reports	0.5â€“1.4
Ficker et al., 1998[16]	Community	Retrospective review of all deaths in Rochester	0.35
Langan et al., 1998[24]	Community	Retrospective review of autopsy reports	1.5
Lhatoo et al., 2001[28]	Community	Prospective, general practice based	0.09

Camfield et al., 2002[6]	Community	Retrospective	0.11
	Selected epilepsy cohorts		
Dasheiff, 1991[12]	Referrals for epilepsy surgery	Prospective	9.3
Lip and Brodie, 1992[30]	Epilepsy clinic	Retrospective	4.9
Timmings, 1993[50]	Epilepsy clinic	Retrospective review of medical records and death certificates	2.0
Nashef et al., 1995[34]	Epilepsy and learning disabilities	Retrospective	3.4
Nashef et al., 1995[35]	Tertiary referral center	Retrospective	5.9
Derby et al., 1996[14]	>2 AEDs per patient (refractory epilepsy, age <50 years)	Retrospective	2.2
Leestma et al., 1997[25]	Lamotrigine trials (refractory)	Retrospective	3.5
Nilsson et al., 1999[38]	Case series based on hospital admissions	Retrospective	1.5
Annegers et al., 1998[1]	Vagus nerve stimulation (refractory patients)	Retrospective	4.5
Donner et al., 2001[15]	Coroners, children	Retrospective	0.2
Racoosin et al., 2001[41]	Drug development programs In epilepsy centers	Retrospective	3.8

Nilsson et al., 2003[37]	Epilepsy surgery register	Retrospective	2.4

AED, antiepileptic drug; SUDEP, sudden unexpected death in epilepsy.
[a] Estimates based on assumed epilepsy prevalence data.

Status Epilepticus

The incidence of status epilepticus (SE) in population-based studies varies from 9.9 in Switzerland[11] to 57 per 100,000 in a nonwhite population in Richmond, Virginia.[13] Case fatality rates similarly vary from 7.6% in the same Swiss study to 31% in a study from Bologna in Italy.[52] The etiology of SE is the most important determinant of mortality, and most deaths in the first 30 days are due to acute symptomatic causes such as anoxic brain damage, CNS infections, brain trauma, and cerebrovascular events. In one large study, no deaths were found in those cases with SE due to idiopathic causes, whereas almost 90% belonged to the acute symptomatic group.[31]

Accident-related Deaths

The risk of death due to injury in patients with epilepsy is estimated at 2.68 per 100,000 persons per year.[21] Other studies quote up to 16% of deaths in epilepsy patients arising as a consequence of accidents, and SMRs for accidents are thus significantly increased at 2.4 to 10.4.[19,38,44] These most often occur in water or as a result of burns or trauma. In one Canadian study, 5% of all drownings were attributable to seizures, 60% of which occurred in bathtubs.[42] Fatalities in motor vehicle accidents due to seizures were found to be uncommon in an American study where only 0.2% of over 44,000 deaths were attributable to seizures.[45] In the UK General Practice Study, there were three accidental deaths (a bathtub drowning, a fall resulting in a cervical fracture, and severe burns) in over 11,400 person-years of follow-up, suggesting that accidental deaths in community-based populations may be rare.[28]

Suicides

The risk of suicide is said to be higher in patients with epilepsy, and most studies that have attempted to address this issue have been of selected cohorts, reporting up to a fivefold elevation in suicide rates compared to that of the general population. However, community-based studies such as the Rochester study and the UK General Practice Study have found no increased risk. The attendant psychiatric comorbidity in many patients with refractory epilepsy may be an important factor that explains this disparity. Depression may occur in up to 62% of patients with epilepsy. A recent case-control study from Sweden identified 49 epilepsy patients who had committed suicide (26 definite and 23 possible) and found that there was a ninefold increase in suicide risk with concurrent mental illness and a 10-fold increase with the use of antipsychotic drugs. A softer association of increased risk was found with high seizure frequency and antiepileptic drug polytherapy.[36]

Neoplasia

Increased mortality due to primary and secondary brain tumors in patients with epilepsy is to be expected and so is consistently reported by many studies. High SMRs due to non-CNS neoplasia, particularly lung cancer, in patients with epilepsy have been noted in several studies, although the design and interpretation of many of these studies are easy to criticize. A carcinogenic effect of antiepileptic drugs has been postulated, although this has not really been substantiated and indeed, most neoplasia related deaths occur soon after diagnosis, rendering this association unlikely.[8,28,46] Some studies show a trend toward an increased incidence of lymphatic malignancies,[22,40,46] although this is not significant and has not been confirmed in larger studies. In animal studies, phenobarbital has been shown to be associated with liver and thyroid malignancies, phenytoin with liver and lymphoid malignancies, valproate with uterine adenocarcinoma, carbamazepine with hepatic and testicular tumors, and gabapentin with pancreatic tumors. In humans, only phenobarbital and phenytoin are considered possibly carcinogenic by the International Agency for Research on Cancer.[47]

Pneumonia

Pneumonia is a frequent cause of death in epilepsy (SMR 3.5 to 7.2) in community-based studies[8,19,43] as well as in hospital-based studies.[22,23,38,53] This is a common terminal event in the elderly, and the mean age of patients who died of pneumonia in the UK General Practice Study was 81.3 years.[8,28] The consistently raised SMRs that reflect this may represent an increased tendency in elderly patients with epilepsy to hospitalization in comparison to those of a similar age without epilepsy in the general population.

Vascular Disease

As with CNS neoplasia, the significantly increased mortality due to cerebrovascular disease in epilepsy in community-based studies (SMR 2.5 to 3.7[8,19,28]) as well as in hospital-based studies (2.5 to 5.3[38,44]) reflects mainly on the increased mortality associated with the underlying pathology. Ischemic heart disease, however, does not appear to be a significant cause of mortality in epilepsy, and in both the Rochester study[19] and the UK General Practice Study,[8,28] SMRs did not reach significance. This was similarly true of hospital-based studies.[44] Other studies have found elevated SMRs, especially in patients under the age of 65 years, although these may reflect methodology rather than a true increase in mortality.[2,38]

Summary and Conclusions

Individuals with epilepsy have mortality rates in the order of two to three times that of the general population. However, much of this increase is due to the causes of acquired epilepsy-brain tumors, cerebrovascular disease, traumatic brain injuryrather than epilepsy itself. Increased mortality is not consistently associated with idiopathic epilepsy. The relative mortality of individuals with epilepsy is influenced by age, as the younger ages have higher relative mortality rates than older individuals with epilepsy. In addition to the excess mortality associated with the causes of acquired epilepsy, the major contributors to increased mortality among individuals with epilepsy are deaths associated with accidents and those attributed to SUDEP.

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Chapter 11

Epidemiology in Developing Countries

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Introduction

The term *developing* is taken usually to mean economically developing from poverty toward affluence. Geographically, most such countries are found in Asia, Africa, and Central and South America. However, several countries or parts of countries in these areas are considered quite affluent and correspondingly, some parts of developed countries are economically developing, namely, Eastern Europe.

Although there are no inherent differences between developing and developed countries regarding the biologic and clinical aspects of epilepsy, differences are found in incidence, etiology, social and cultural factors, and systems of health care delivery and treatment.

Developing countries often do not have an organized health care system. Record keeping is generally poor and research minimal. Neuroimaging and drug monitoring facilities may be available, but patients are often too poor to afford what can be obtained. Antiepileptic drugs (AEDs) also may not be available and for various reasons may not be taken. As a result, a large proportion of people with epilepsy do not get treatment. In addition, little accurate scientific data have come from developing countries. In view of this paucity of information, it is easy to assume that the experience of developed countries in treating epilepsy can be applied without modification to developing countries. The purpose of this chapter is to highlight differences in the epidemiology of epilepsy between developed and developing countries, so that such experience can be meaningfully and profitably applied for the benefit of patients.

Incidence and Prevalence

The evaluation of published vital statistics in epilepsy is often complicated by methodologic problems that have not been fully addressed.[91,93] Problems that bedevil studies of incidence and prevalence in developing countries include diagnosis, case ascertainment, and definitions of seizures and epilepsy. The early pioneer studies particularly exhibited these weaknesses, although they did provide approximate statistics upon which later investigations could build.

Methodology

Diagnosis

Accurate diagnosis is essential, both at presentation and during treatment. It is mainly clinical, depending on history and examination. Electroencephalography (EEG) contributes to, but does not always confirm, the diagnosis. Accuracy of diagnosis is vitiated by lack of an eyewitness account. A therapeutic trial of antiepileptic drugs is never warranted. Even in developed countries in patients referred with a diagnosis of refractory epilepsy, the rate of misdiagnosis may be as high as 26.1%.[103] The most common misdiagnoses are psychogenic, nonepileptic seizures and syncope. In two Indian population-based studies, syncope was frequent in one and psychogenic seizures in another.[9,52] Such information is invaluable to a clinician working in India.

Case Ascertainment

In developing countries, concealment of epilepsy for social reasons is common. People also may be genuinely unaware of seizures that present differently from tonicâ€“clonic seizures. Accurate case ascertainment requires a community-based door-to-door survey using a locally validated questionnaire in order to screen the population, with the informed consent of the individuals concerned, the family, and community leaders. If key informants and local medical workers are used, including traditional healers, then case ascertainment will be much better. The capture-recapture method also uses information from different sources to obtain a prevalence ratio that is higher than that obtained from using a door-to-door survey alone.[27] Another way of enhancing the yield of a door-to-door survey is to examine a random sample of those people who in the door-to-door survey had been found not to have epilepsy. This enables calculation of the rate of false negatives.[86]

Definition of Seizures and Epilepsy

In 1993, the International Commission of Epidemiology and Prognosis of the International League against Epilepsy (ILAE) published guidelines for epidemiologic studies.[45] These guidelines give definitions of seizures and epilepsy, a classification, risk factors, and recommended measurement indices. These are particularly useful for field studies in developing countries, where facilities for investigation are unavailable. Unfortunately, these guidelines are not always followed.

It should be remembered that acute symptomatic seizures, although not considered epilepsy, are common. Such patients do not need long-term treatment for seizures, but they do need treatment for the acute seizure and for the underlying condition, which, in developing countries, most commonly is neurocysticercosis.[75] In addition, the terms *idiopathic* and *cryptogenic epilepsy* should not be confused. In a developing country without investigations, making the distinction is not always possible in a field study. Studies should mention the amount of active epilepsy (i.e., those who have had at least one seizure within the past 5 years). These people are important from the point of view of public health.

Table 1 Incidence Studies of Epilepsy in Developing Countries

	Year of publication	Authors	Incidence per 100,000 person-years
China[58]	1985	Li et al.	35
Ecuador[86]	1992	Placencia et al.	122â€“190
Chile[56]	1992	Lavados et al.	113
Tanzania[89]	1992	Rwiza et al.	73
Ethiopia[105]	1997	Tekle-Haimanot et al.	64
India[65]	1998	Mani et al.	49

Table 2 Incidence of Epilepsy in the Americas

Author (y)	Country	Population	Case ascertainment	Incidence[a]
Lavados et al. (1992)	Chile[56]	17.694	Record review	95
Placencia et al. (1992)[b]	Ecuador[86]	72.121	Door-to-door survey	172
Hauser et al. (1993)	United States[38]	516.903	Record review	44
Camfield et al. (1996)	Canada[13]	850.000	EEG	44

EEG, electroencephalogram.

[a] Rate per 100,000, adjusted to the 1990 U.S. population.

[b] Incidence of a first afebrile seizure.

Source: Carpio A. Perfil de la epilepsia en el Ecuador. *Revista Ecuatoriana de Neurologia.* 2001;10:20â€“26.

Incidence is defined as the rate of occurrence of new cases in a specified population per unit time, usually 1 year. The numerator is the number of new cases. The denominator is the number of persons at risk, although usually the total population is used. Prevalence is defined as the proportion of a specified population with the disease at a specified time. Point prevalence is this proportion on a particular day.

Both incidence and prevalence studies are useful for health service providers, especially in developing countries with few neurologists and 80% of the burden of epilepsy. Incidence studies give clues to risk factors and information about prognosis, but there are few studies from developing countries because they are difficult to carry out.

Incidence

In developed countries, the age-adjusted incidence of epilepsy, defined as recurrent unprovoked seizures, ranges from 28.9 to 53.1 per 100,000 person-years, with most studies falling toward the higher end of this range.[42] If single unprovoked seizures are included, higher figures, up to 70 per 100,000 person-years, are obtained. The few available studies in developing countries, none of which is prospective (Table 1), give a range from 35 to 190 per 100,000 person-years. The Ecuadorian study, in which the incidence range was 122 to 190 per 100,000 person-years, includes single seizures and acute symptomatic seizures.[86] The incidence of epilepsy in five sub-Saharan African studies ranges from 63 to 158 per 100,000 person-years.[87] Comparisons of rates are valid only when age-adjusted to the same population. This has been done for the Americas[22] and is given in Table 2. The higher incidence in developing countries may be a consequence of the fact that populations in the developing world are younger and have poorer medical facilities, poorer general health, and a lower standard of living. Specifically, there are more infections of the central nervous system (CNS), especially with cysticercosis, tuberculosis (TB), and human immunodeficiency virus (HIV). Perinatal morbidity, head injuries, and consanguinity are also more common. The relative importance of these factors is unknown.

The graph of age-specific incidence of epilepsy in developed countries is a U-shaped curve, with the highest incidences in those <1 year old and >60 years old. It rises sharply after age 60. In developing countries, the peak incidence occurs in young and middle-aged adults[10,56] (Fig. 1). The different age-specific incidence rates in developed and developing countries have two implications. One is that the risk factors may differ. In developing countries infections and parasitic diseases are endemic. The second is the difficulty of comparing studies from countries with differing stages of development and age distribution of the population without age adjustment to a common population as the denominator.

The age-specific incidence of epilepsy in developed countries has been changing over time. There has been a decrease in childhood epilepsy due to better perinatal care, as well as an increase in epilepsy among the elderly because of rising cerebrovascular disease. Such data are not available for developing countries, but that from developed countries suggests the possibility of reducing the present burden by improving obstetric and perinatal care and diminishing future burden by early attention to prevention of cardiovascular disease.

Incidence throughout the world is slightly higher in males than females. The Ecuadorian study found a preponderance of females. Many studies have found no difference. When found a difference, it was slight.

Seizure Type

In general, partial seizures are more common in developed countries than other seizure types, accounting for just over 50%. In developing countries, where symptomatic epilepsy is more common, one would expect partial seizures to predominate. However, in differing circumstances, generalized tonicâ€“clonic seizures tend to be more commonly noted for the following reasons, none of which seems to apply to all situations:

1. The partial onset of a seizure that rapidly generalizes will be missed by the patient or the field worker.
2. Untreated partial seizures may become generalized more rapidly.
3. A questionnaire may not be designed to pick up anything apart from generalized tonicâ€“clonic seizures.
4. There is a lack of the EEG to pick up a focal onset.

There are no population-based incidence studies of epilepsy syndromes from developing countries.

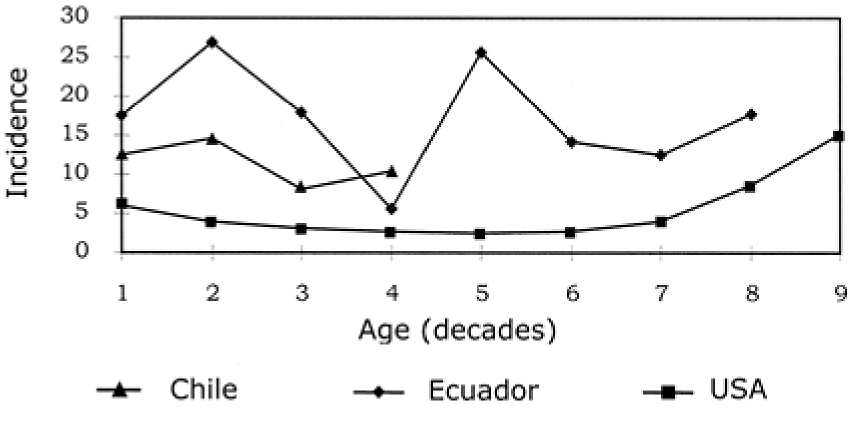

FIGURE 1. Age-specific incidence of epilepsy in the Americas. (From Carpio A. Perfil de la epilepsia en el Ecuador. *Revista Ecuatoriana de Neurologia.* 2001;10:20â€“26.)

Table 3 Prevalence of Active Epilepsy in the Americas

Author (y)	Country	Population	Crude prevalence	Adjusted prevalence[a]
Hauser et al. (1991)	United States[37]	56.447	6.8	6.8
Lavados et al. (1992)	Chile[56]	17.694	17.7	18
Placencia et al. (1992)	Ecuador[86]	72.121	8	9
Mendizabal and Salguero (1996)	Guatemala[70]	1.882	8.5	5.6
Nicoletti et al. (1999)	Bolivia[78]	10.124	11.1	12

[a] Rate per 1,000, adjusted to the 1990 U.S. population.

Source: Carpio A. Perfil de la epilepsia en el Ecuador. *Revista Ecuatoriana de Neurologia.* 2001;10:20â€“26.

Prevalence

There have been many more studies of the prevalence of epilepsy than of incidence because they are much more easily carried out. Although methodologic differences among these

studies make comparisons difficult, it seems clear that, unlike incidence, the prevalence of active epilepsy remains within the range of 4 to 10 per 1,000 population throughout the world.[46] Higher prevalences have been reported from sub-Saharan African countries (e.g., 35.1 per 1,000 in Benin using the capture-recapture method[27] and the prevalence of 49 per 1,000 in Grand Bassa county in Liberia[36]). A rate of 20 per 1,000 was found among the Wapogoro in Tanzania.[50] In South and Central America, a rate of 57 per 1,000 has been found among the Guaymi Indians of Panama.[34] In areas with a high prevalence, there is often a strong family history of both epilepsy and consanguinity, possibly as a result of social stigma forcing intermarriage. A large number of studies in India and China suggest a prevalence of active epilepsy of between 4 and 6 per 1,000, similar to that in developed countries.[9,54,104,111]

As with incidence, rates that are age-adjusted to a common denominator for the Americas allow more meaningful comparisons (Table 3).[22]

Age-specific Prevalence

Age-specific prevalence rates for epilepsy vary in different studies and are difficult to interpret, possibly because of small numbers and methodologic differences. FIGURE 2 shows age-specific prevalence of epilepsy in the Americas. This is more fully discussed by Hauser in Chapter 5.

Sex

As with incidence, there is a predominance of males, with some exceptions in Africa,[89] South America,[79] and one study in Pakistan.[5]

Seizure Type

As is the case with incidence studies and for the same reasons, generalized seizures are more common than partial seizures in developing countries. There are exceptions. In the Ecuadorian study, 49% had partial seizures, which may reflect the input of the specialist medical team. The Parsis had 54.5% partial seizures, a figure possibly resulting from the medical input and the community's higher level of education. When EEG is used in addition, the proportion of partial seizures increases. In a Ugandan study it rose from 24% to 42%[51] and in a Bolivian study from 34% to 53%.[78]

Socioeconomic Factors

Studies in developed countries have suggested that socioeconomic deprivation increases the risk of epilepsy.[33,44,60,73] Studies in Ecuador, Pakistan, and Turkey showed the prevalence of epilepsy to be higher in rural areas, but the reverse was shown in the meta-analysis of the Indian studies.[4,5,86,104] In India, poverty is greater in rural areas where it is more difficult to conceal epilepsy. The whole relationship of socioeconomic factors to epilepsy needs further exploration.

Incidence-prevalence â€œGapâ€

The term *incidence-prevalence gap* refers to the higher incidence of epilepsy in developing countries than in developed countries, whereas prevalence values are similar throughout the world.[11,16,57,70,78,86,89] Possible explanations are differences in methodology, namely, inclusion of acute symptomatic seizures as incidence cases in developing countries; the higher mortality rate in developing countries[10,15]; and higher rates of remission, which would imply a more benign prognosis. There are no answers yet to these speculations, nor will there be until there are well-conducted incidence studies and population-based outcome studies from developing countries. Certainly, there need be no further prevalence studies, unless they are designed to look at specific epilepsy syndromes or health status.

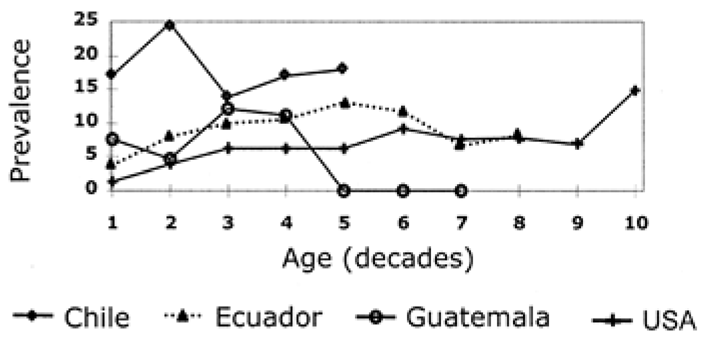

FIGURE 2. Age-specific prevalence of epilepsy in the Americas. (From Carpio A. Perfil de la epilepsia en el Ecuador. *Revista Ecuatoriana de Neurologia.* 2001;10:20â€“26.)

Prognosis

The prognosis of epilepsy is defined by Hauser and Hesdorffer[39] as the risk of recurrence following a first seizure or more seizures; the probability of remission, both spontaneous and with treatment; the risk of relapse following drug withdrawal; and the mortality of epilepsy. It has been suggested that in these countries, the prognosis of epilepsy is different, but few studies of natural history allow comparisons.[1,12,16] Methodologic shortcomings have contributed to the uncertainties.[39,90]

Recurrence after a First Unprovoked Seizure

In developed countries, prognosis for full seizure control is very good. More than 70% of patients achieve long-term remission, most within 5 years of diagnosis.[40,61,101] In developing countries, after a first unprovoked seizure, the risk of recurrence is 33% to 37%, similar to that from developed countries.[18,26,53,94] Studies from developing countries show that patients with epilepsy secondary to underlying structural causes and with an abnormal EEG have the worst prognosis.[18,53,94] The type of seizure and drug treatment used seem not to affect prognosis. Developing countries have produced no published studies of the prognosis of epileptic syndromes.

Recurrence in Newly Diagnosed Epilepsy (or Probability of Remission)

In developed countries, most studies of seizure prognosis or epilepsy prognosis in adults[23,40,61,62,96] and children[3,99,101] have examined the risk of recurrence following a first unprovoked seizure, but according to ILAE definitions, a single unprovoked seizure does not constitute epilepsy. Very few studies have reported the risk of recurrence after a second seizure.[41,100] Hauser et al.,[41] in the United States, reported that the risk of a third unprovoked seizure was 73% after 4 years of follow-up. The study by Shinnar and Pellock,[100] in the United States, showed that the cumulative risk of a third seizure was 71% at 5 years. Carpio et al.,[18] in Ecuador, found that in 340 newly diagnosed epilepsy patients with one recurrent unprovoked seizure, the risk of a third unprovoked seizure was 79% after 4 years of follow-up. Etiology was an independent predictor of recurrence. Patients with idiopathic cryptogenic epilepsy had less risk of recurrence than patients with symptomatic epilepsy (38% vs. 52%, *p* <0.05). FIGURE 3 shows the probability of seizure recurrence. Multivariate analysis showed no significant differences in recurrence risk due to sex, age, family history of epilepsy, EEG results, or the type of seizure.

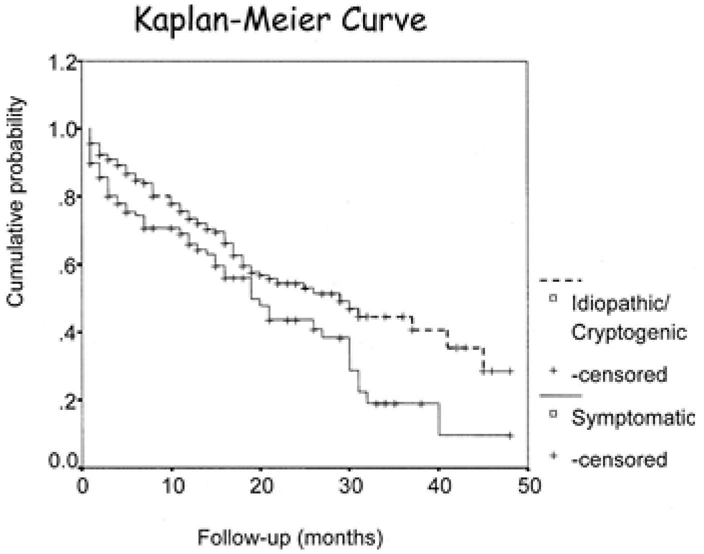

FIGURE 3. Probability of seizure recurrence in 289 patients with epilepsy as a function of etiology. (From Carpio A, Hauser WA, Lisanti N, et al. Prognosis of epilepsy in Ecuador: a preliminary report.

Epilepsia. 1999;40[Suppl 2]:110.)

Prognosis for Seizure Recurrence in Patients with Neurocysticercosis

Very few studies estimate the prognosis of acute symptomatic seizures. Seizures due to neurocysticercosis (NC) demonstrate prognosis well. In a prospective, cohort study in Ecuador, Carpio and Hauser[19] found that 40% of patients had a recurrence. Multivariate analysis showed that the only predictor of recurrence was a change in appearance on the computed tomography (CT) scan. Twenty-two percent of patients in whom cysts disappeared had no further seizures, but 56% of those with persistent cysts had a recurrence (p <0.05). The authors' conclusion that seizure recurrence is high following a first acute symptomatic seizure due to NC, therefore, seems related to persistence of active brain lesions. However, when the NC lesion clears up, the recurrence risk is low and in keeping with the risk following other brain insults leading to a static encephalopathy. There was no correlation between treatment with antihelminthic agents and seizure recurrence.

Spontaneous Remission and Effect of Treatment on Prognosis

Some patients spontaneously enter remission.[57] In a retrospective survey of 460 previously untreated patients attending newly established epilepsy clinics in Malawi, Watts[112] indirectly demonstrated spontaneous remission. The study found that as the duration of epilepsy increased, the number of patients with active epilepsy decreased. Thus, remission without therapy is common. This finding is substantiated by an Ecuadoran survey in which 28% of all identified cases entered remission without treatment[84] and by Mani et al.[66] in a rural community in south India, from which he reported a remission rate of 50% of untreated patients.

Antiepileptic drug trials[30,31,85] reported from Nakuru, Kenya, and Ecuador show a generally excellent response to standard therapy. These studies also show that in patients who had not previously received antiepileptic drug (AED)

treatment, neither the duration of the disease nor the number of seizures before treatment are predictors of outcome. This was corroborated by a more recent study from Yelandur, India.[64] Therefore, failing to treat seizures at the earliest possible opportunity does not increase the likelihood of chronicity and agrees with findings from developed countries that for most patients, the chance of remission is not improved by early treatment.[68,76] Treatment reduces the rate of recurrence of seizures but does not affect the natural history of epilepsy. There is some conflicting evidence from a hospital-based study in Glasgow, which showed that those who had had 20 or more seizures before starting treatment were more likely to have refractory epilepsy.[55] The authors concluded that there was some underlying abnormality of the brain, which rendered the epilepsy refractory from its inception (i.e., frequent seizures could be an indicator of refractoriness rather than cause). The study from Yelandur in India also suggested that those with a lifetime total of more than 30 seizures had less chance of entering remission. More outcome studies are needed from developing countries with populations whose epilepsy is still largely untreated.

Risk of Relapse following Drug Withdrawal

There have been no studies from developing countries.

Epilepsy Mortality

In developed countries, the overall mortality associated with epilepsy is two to three times that of the general population from other causes.[7,14,32,49,59,88] In developing countries, it is almost impossible to ascertain the number of deaths due to epilepsy because incidence studies are difficult, death certificates are unreliable, autopsies are not easy to obtain, and the cause of death is not usually known with certainty.[10,15] The overall autopsy rate is probably <5% in public hospitals and almost zero in private hospitals. There are few reliable coroners' reports, and if available, they are incomplete. Migration makes large, prospective, population-based mortality studies of epilepsy very difficult to carry out.

Two Indian population studies of mortality among the Parsis in Bombay and a semiurban community in Vasai[10,15] appear to suggest that epilepsy may confer a protective effect against mortality in Parsis, who form a small, urbanized, literate community of higher socioeconomic status than the general Indian population. Comparing these two results is misleading because Parsis with epilepsy probably take better care of their health than those without it, and cases studied were mainly prevalent, so the result was biased in favor of survivors whose epilepsy was less active than that of the patients in Vasai. The methodologic advantages of the Parsi study are that it is a population study in which the diagnosis of epilepsy was made by a neurologist and follow-up is virtually complete. Comparison of the Vasai and Parsi studies suggests that the poorer, rural population with epilepsy has a much higher mortality rate than the urban one. Factors possibly responsible for this are being explored elsewhere.

In Ecuador, a prospective cohort study of 412 patients with newly diagnosed epilepsy gave a crude standardized mortality ratio (SMR) from all causes of 6.3.[15] The age-specific SMR at entry is summarized in Table 4. The overall mortality of epilepsy in Ecuador is higher than reported in the general population of a developed country. Present cohort studies of sudden unexpected or unexplained deaths in epilepsy (SUDEP) have produced rates varying from 1.5 to 9 per 1,000 patient-years.[32,49,59,88] Rates depend on the methods used and the population studied. The Ecuadorian SUDEP rate of 2.6 per 1,000 patient-years was nearly ten times that of 0.3 per 1,000 patient-years in an incidence study from Rochester, Minnesota,[43] and as high as those reported in patients with severe epilepsy. Mortality rates may be high because only the severe cases were picked up.

Table 4 All-cause Mortality in Patients with Epilepsy In Ecuador

Age	Patients with epilepsy	Expected deaths[a]	Observed deaths	SMR[b]
0â€“19	268	0.56	4	7.7
20â€“59	102	0.31	2	7.1
>60	9	0.41	1	3.2
Total	379	1.28	7	6.3

SMR, standardized mortality ratio.
[a] Calculated by multiplying the number of person-years with epilepsy with the corresponding mortality rate of the Ecuadorian general population divided by 100.
[b] Observed number of deaths divided by expected number of deaths.
Source: Carpio A, Bharucha NE, Jallon P, et al. Mortality of epilepsy in developing countries. *Epilepsia.* 2005;46(Suppl 11):28â€“32.

It is also possible that the risk of death was overestimated because the less severe, new-onset cases of epilepsy were not ascertained at hospitals. This affects the distribution of cause of deathâ€”those patients lost to follow-up may have had different causes of death from those who were followed. Also, small numbers prevent comparison of SUDEP rates by seizure type, etiology, age, or sex. As expected, only one patient had an autopsy. On the other hand, in cohort studies the diagnosis of epilepsy is well documented and definitions and analytic procedures are current.

In Martinique in the Caribbean, death certificates were used to follow a cohort for 1 year.[15,49] The mortality rate was 5.73 per 100,000 population and the SMR was 4.25. There were no data concerning cause of death or the exact relationship of epilepsy with the death.

In summary, it seems that mortality of epilepsy in developing countries is generally higher than the mortality reported in developed countries. The SMR ranges broadly from 0.76 in a population study of a select community in India to 6.3 in a prospective cohort study in Ecuador. It is incorrect to generalize from such selected populations.

Table 5 Distribution of Epilepsies and Epilepsy Syndromes in Patients with Newly Diagnosed Unprovoked Seizures (All Age Groups)

	Carpio et al., 2001 (Ecuador[17])[a]		**Manford et al., 1992 (England[63])[b,c]**		**Jallon et al., [48])[d]**	
	310	(%)	594	(%)	1,016	(%)
1. Localization related	**179**	**(58)**	**252**	**(42)**	**482**	**(47)**
1.1 Idiopathic	10	(3)	7	(1)	48	(5)
1.2 Symptomatic	84	(27)	96	(16)	137	(13.5)
1.3 Cryptogenic	85	(27.5)	146	(24.5)	297	(29)
2. Generalized	**93**	**(30)**	**66**	**(11)**	**343**	**(34)**
2.1 Idiopathic	75	(24)	55	(9)	278	(27)
2.2 Cryptogenic or symptomatic	7	(2.3)	0	(0)	39	(4)
2.3 Symptomatic	11	(3.5)	11	(2)	26	(3)
3. Undetermined whether focal or generalized	**38**	**(12)**	**190**	**(32)**	**177**	**(17)**

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[a] Carpio A, et al. Etiology of epilepsy in Ecuador. *Epilepsia.* 2001;42(Suppl 2):122.

[b] Manford M, et al. The National General Practice Study of Epilepsy: the syndromic classification of the ILAE applied to epilepsy in the general population. *Arch Neurol.* 1992;49:801â€"808.

[c] Excluding patients with special syndromes.

[d] Jallon P, et al. Newly diagnosed unprovoked epileptic seizures: presentation at diagnosis in CAROLE study. *Epilepsia.* 2001;42:464â€"475.

Table 6 Distribution of Epilepsies and Epilepsy Syndromes in Prevalent Unprovoked Seizures (All Age Groups)

	Senanayake, 1995 (Sri Lanka[97])[a]		**Murthy et al., 1998 (India[74])[b],)[c]**		**ILAE, 1995 (Italy[47]))[d]**	
	1,250	(%)	2,531	(%)	6,889	(%)
1. Localization-related	**917**	**(73)**	**1,591**	**(63)**	**4,323**	**(63)**
1.1 Idiopathic	24	(2)	18	(1)	375	(5.4)
1.2 Symptomatic	133	(11)	997	(39)	1,991	(29)
1.3 Cryptogenic	760	(61)	456	(23)	1,957	(28.4)
2. Generalized	**228**	**(18)**	**299**	**(12)**	**1,750**	**(25)**
2.1 Idiopathic	214	(17)	162	(6.5)	1,272	(18.5)
2.2 Cryptogenic or symptomatic	0	(0)	64	(2.5)	287	(4)
2.3 Symptomatic	14	(1)	73	(3)	152	(2)
3. Undetermined whether focal or generalized	**104**	**(8)**	**503**	**(20)**	**227**	**(3)**

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[a] Senanayake N. Classification of epilepsies and epileptic syndromes using the 1989 ILAE classification: a hospital-based study of 1,250 patients in a developing country. *Epilepsia.*

1995;8:33â€“40.

[b] Excluding special or unclassified syndromes.

[c] Murthy JM, et al. The syndromic classification of the ILAE: a hospital-based study from South India. *Epilepsia*. 1998;39:48â€“54.

[d] Italian League Against Epilepsy. First Italian Observational Data Bank on Epilepsies. General Results after One Year of Data Collection.

21st International Epilepsy Congress, Sydney, Australia, September 1995.

Etiology and Risk Factors

In developing countries, analytic epidemiology designed to establish associations and determinants of epilepsy has been scarce. Comparing results of studies of etiology is difficult because of differences in definitions and lack of diagnostic criteria.[16] Most studies lack information on the latency between the first acute symptomatic seizure and the first unprovoked seizure, and the age at onset of seizures and age at diagnosis.

In studying etiology, it is necessary to use incident cases and not prevalent cases, because one cannot assess the importance of potential etiologic factors that preceded the onset of epilepsy from those which occurred after the disease developed. Cause and effect become confused.[20]

In children, the proportion of patients with generalized idiopathic epilepsy is fairly similar in studies from Ecuador (29%), the United States (21%), and Finland (22%).[6,17,102] However, symptomatic localization-related epilepsies are a group of more diverse syndromes, probably due to different risk factors for epilepsy in developed and developing countries.

Tables 5 and 6 show the reported frequencies in all age groups of localization-related epilepsies in the series from

developing countries: 58% in Ecuador, 63% in India, and 73% in Sri Lanka.[22,74,97] Differences are probably due to methodologic differences. The Ecuadorian study included only newly diagnosed patients, whereas the Indian and Sri Lankan studies used prevalent cases. The frequency of localization-related epilepsies in newly diagnosed epilepsy in developed countries is lower: 42% in England and 47% in Switzerland.[48,63] In childhood, localization-related epilepsies account for 55% in India in newly diagnosed unprovoked seizures, similar to the reported frequencies in the United States of 58% and Finland of 61%.[6,98,102]

Symptomatic localization-related epilepsy in all age groups was 39% in India, much higher than the reported frequency of 13.5% from Switzerland and 29% from Italy.[47,48,74] However, the frequency of 27% in the Ecuadorian study and 27% in another Indian study[17,98] are similar to those from developed countries.

Generalized epilepsies and epilepsy syndromes accounted for 12% of epilepsy in India and 30% in Ecuador, probably related to the patient populations studied. However, in Indian children, generalized epilepsies and epilepsy syndromes accounted for 35% of all epilepsy.[74] Idiopathic epilepsy accounted for 24% of epilepsy in Ecuador, similar to the 27% in Switzerland and 18.5% in Italy.[17,47,48]

The diagnostic categories for age-related partial and generalized idiopathic epilepsies apply to all countries. The overall frequency of symptomatic and cryptogenic, localization-related epilepsies is similar, but there are differences within the symptomatic group because of differing risk factors.

Despite etiologic differences in developed and developing countries, the ratio of idiopathic/cryptogenic to symptomatic epilepsy remains fairly constant throughout the world. In Rochester, 65.5% of newly diagnosed cases of epilepsy were idiopathic.[38] Developing countries show a similar proportion

of idiopathic cryptogenic (60% to 70%) and symptomatic epilepsy (30% to 40%),[20] but the causes of the symptomatic group are different. In developed countries, cerebrovascular diseases account for a significant proportion of symptomatic epilepsy,[38] whereas perinatal brain damage, neurocysticercosis, CNS infections, and traumatic brain damage are the most frequent risk factors in developing countries.[1,12,16]

Etiology and risk factors for epilepsy vary with age and geographic location. Congenital, developmental, and genetic conditions are mostly associated with epilepsy in childhood, adolescence, and early adulthood. Head trauma, CNS infections, and tumors may occur at any age and may lead to epilepsy, although tumors are more likely over age 40. Cerebrovascular disease (CVD) is the most common risk factor for epilepsy in people over 60 years of age. In some parts of developing countries, endemic infections, such as malaria, neurocysticercosis, paragonimiasis, and toxocariasis, are associated with epilepsy.[8,71,81,87,89]

Few case-control designs have been applied in developing countries. These studies found febrile seizures to be a significant risk factor. Some studies from India also suggested that head injury, development delay, and family history of epilepsy were significant risk factors.[9,83,92]

Prenatal and Perinatal Pathology

Poor prenatal or perinatal care resulting in brain damage is often claimed to be a reason for the high prevalence of epilepsy in the tropics,[1,81,97] but few tropical studies define inclusion criteria for this category. In developed countries, the presence of prenatal and perinatal events does not appear to be associated with the occurrence of childhood epilepsy when children with cerebral palsy and mental retardation are excluded.[39]

The American Collaborative Perinatal Project,[77] which prospectively followed a large population, found that 14% of children who had nonfebrile seizures also had cerebral palsy to some degree. Conversely, 21% of children with cerebral palsy had had at least one nonfebrile seizure by the age of 7 years. However, seizure disorders in children of low birth weight without cerebral palsy were not found to be significantly more frequent. Of the late pregnancy and birth conditions evaluated, including conditions considered to be associated with anoxia and markers of fetal distress, none was found to be an important antecedent of seizure disorders in children without motor handicap. Among factors observable in the neonatal period, delay of the first cry by 3 minutes or longer, abnormality of tone, and neonatal seizures or meningitis were leading predictors of later seizures.

We cannot extrapolate these findings to the situation in developing countries, where health care systems are quite different. In developing countries, most deliveries in rural areas are conducted by traditional birth attendants, families are large, and the frequency of preterm deliveries is at least twice as high as in developed countries.[1,12] Many mothers are malnourished and exposed to a variety of infections that may affect the baby in utero or at the time of delivery. These factors need further study to evaluate their contribution to perinatal brain damage. In developing countries perinatal brain damage accounts for 13% to 14% of later epilepsy in children.[24] In a hospital-based study from south India, static encephalopathy related to perinatal brain damage accounted for 9% of all later epilepsy and 13.5% of remote symptomatic epilepsies.[74]

Infections of the Central Nervous System

Infectious and parasitic diseases are the most common causes cited for the higher incidence of seizures in developing countries. Acute infections of the CNS are significant risk factors for both acute symptomatic seizures and epilepsy. In a retrospective cohort study from Rochester, Minnesota, CNS infections increased the risk for the development of unprovoked seizures by 11-fold.[38] In Ecuador, infectious diseases, mostly TB plus bacterial meningitis, preceded development of epilepsy in 4.5% of cases.[17] Epilepsy followed tuberculous meningitis in 8%.[16,20] Seizures are also common manifestations of intracranial tuberculomas. There are no reliable data available on long-term sequelae of bacterial meningitis, endemic or epidemic.

CNS toxoplasmosis is common in patients with acquired immunodeficiency syndrome (AIDS).[12] As AIDS incidence increases in tropical countries, toxoplasmosis may become a more important cause of epilepsy. Epilepsy is a well-recognized consequence of toxoplasmosis in about 25% of affected people.[1,12] Mental retardation and seizures follow brain damage associated with congenital toxoplasmosis. In an institution for mentally handicapped children, 6.8% of patients with epilepsy had congenital toxoplasmosis.[20]

Neurocysticercosis

Studies of selected hospital patients with seizures or epilepsy in some developing countries report NC as its cause in 30% to 50% of patients.[1,12] A prospective multicenter study in Ecuador[17] found that NC was a risk factor in 8.3% of newly diagnosed patients with epilepsy. Other studies, where acute symptomatic seizures were excluded, found only 5.3% to 11% of patients with epilepsy had NC.[2,67] Most have acute symptomatic seizures that do not develop into epilepsy. This high incidence probably occurred because of failure to differentiate between epilepsy and seizures.[19] Although it is one of the most frequent antecedents among the symptomatic group, NC is not the main cause of epilepsy.

Surprisingly, the proportion of epilepsy associated with cysticercosis discovered using immunologic tests is considerably lower than that found using CT. Only 12% of patients with epilepsy attending an outpatient clinic in Peru had serologic evidence of *Taenia solium* by enzyme-linked immunotransfer blot (EITB) test.[21] There are also clinical inconsistencies in the link between epilepsy and NC. Parasite location may be remote from the apparent epileptogenic region.[67] There is no correlation between the burden of cysticercal lesions and the severity of epilepsy. Patients with severe refractory seizures may have only one calcified lesion, whereas other patients may have multiple cysts or calcifications but no epilepsy. Since NC and epilepsy are common diseases in most developing countries, a causal as well as fortuitous relationship between the two conditions might exist independently.[21,67,81,106]

Recent new studies have not modified this position. A report from Brazil[94] concluded that the presence of calcifications on CT does not increase the risk of seizure recurrence. A Brazilian study[106] confirms the good prognosis of parenchymal NC. The authors point out that, if it is assumed that NC can be an incidental finding in a considerable number of patients with epilepsy in endemic regions, inflammatory processes related to parasitic infection, death, degeneration, and calcifications in the brain of the host do not significantly aggravate the cognitive deficits observed in medically refractory mesial temporal lobe epilepsy. A study in rural Ecuador[28] affirms that NC is associated with one in three cases of epilepsy and is possibly the cause of the excessive proportion of epilepsy in that population. However, results were not statistically significant and only 3 (8%) of 24 patients with epilepsy had â€œdefinitiveâ€ NC. A community survey[72] concluded that brain CT abnormalities compatible with NC were more frequent in individuals with seizures and in those with positive immunoserologic assay (EITB) for cysticercosis. Most of the patients who were diagnosed with NC in this study had only calcifications (half of them had just one calcification); however, it is well known

that brain calcifications do not necessarily mean that a patient has NC.

The small numbers of the above studies do not allow generalizations. So far, there are no case-control or prospective studies in which CT scan has been used for providing information on the proportion of NC patients or seropositive individuals that will develop seizures. In addition, some authors have reported an association between seizures and NC, based on positive serum antibodies to *T. solium*/cysticercosis; unfortunately, the presence of antibodies may indicate only previous exposure to or infection with the parasite, but not necessarily brain infection.[35]

Cerebrovascular Diseases

Cerebrovascular disease in developed countries is the most commonly identified cause of epilepsy, accounting for about 11% of all new cases and about one third of cases with any identifiable cause.[39] However, in Ecuador, cerebrovascular diseases accounted for only 4.4% of new cases.[17] In developing countries, cerebrovascular diseases are thought to account for only a small proportion of epilepsy.[12]

Other Tropical Diseases

Malaria is endemic in tropical America, Africa, and some Asian countries. Acute cerebral malaria encephalopathy,[71] despite appropriate treatment, still carries a mortality of 22%.[108] Epilepsy has long been recognized as a late sequela of cerebral malaria.[97] Pathologic examination of the brain in fatal cases has shown severe vasculopathy with hemorrhages, and granuloma of DÃ¼rck formed by astroglial reaction.[108] The lesions may act as epileptogenic foci in those who survive, giving rise to chronic epileptic seizures. A special relationship has been described between cerebral malaria and febrile convulsions. Together they are responsible for 5% of pediatric emergency consultations in endemic areas in central Africa and the Amazon forest.[12,20] However, it is difficult to ascertain whether these convulsions are in fact febrile seizures or secondary to cerebral malaria.

In *schistosomiasis*, seizures occur frequently during the acute meningoencephalitic phase, but only 2.4% to 3.8% of patients with confirmed cerebral deposition of ova have seizures during the chronic phase.[12] In *paragonimiasis*, another trematode infection prevalent in South America, the lung is the primary site of infection, but the brain is often involved. Seizures, usually focal motor, are the most common manifestation of cerebral paragonimiasis.[12,16]

American trypanosomiasis or *Chagas disease* is a public health problem in rural areas of Central and South America.[79] CNS involvement is secondary to cerebral embolization from cardiac blood clots. Immunologic reactions probably underlie the pathology of the disease, including diffuse meningoencephalitis with edema and arachnoiditis. These may cause late-onset epilepsy, with a high frequency of partial seizures.[12,16]

Approximately one in three patients with cerebral *hydatid cysts* develops epilepsy.[98] Signs of focal cerebral involvement or of raised intracranial pressure are found at the onset of epilepsy in all patients. Seizures secondary to cerebral *amoebiasis* and cerebral *toxocariasis* have also been described,[20] but their contributions to the etiology of epilepsy require further study.

Principles of Evaluation

Principles of evaluation and treatment of a patient with epilepsy are the same the world over. In developing countries, however, where investigatory facilities are minimal, a diagnosis of epilepsy is essentially clinical. A first-hand, eyewitness account from the time of onset of symptoms is necessary. Often, description alone may be inadequate and it may be more helpful if the witness is able to act out the movements and sounds of the seizure. (It should be carefully considered whether the patient is to be present during this act, as it may be embarrassing.) Pseudoseizures, hyperventilation, and other nonepileptiform disorders should be excluded. Careful enquiry both from the patient and observer about symptoms and signs at the onset will help to identify more partial seizures than are usually diagnosed in developing countries. If available, EEG should be used judiciously when the onset of the seizure occurs during sleep, when the seizure appears to be primarily generalized, and to differentiate petit mal or absence seizures from complex partial seizures in children.

The indications for neuroimaging are generally the same throughout the world. Neuroimaging is done primarily when a focal lesion is suspected. If the suspected lesion is nonprogressive or not amenable to definitive treatment, as with cerebral palsy and mental retardation, neuroimaging should be withheld. It will not alter management. In developing countries, there are exceptions to this policy because parasitoses can appear at any age, often with a primarily generalized seizure, so neuroimaging should be done more often to identify these infections. Other investigations for parasitoses include examination of urine, stool, and blood; tissue biopsy to look for the parasite by microscopy; skin tests; serologic methods; demonstration of antigen by chemical methods; and DNA or RNA probes. The main problems with serologic tests are that their accuracy or validity may not be known in a given location and they may not distinguish between past and present infection. Because parasites are often confined to the CNS, examination of cerebrospinal fluid may also be necessary.

Treatment

The major issues relevant to treatment and prevention in developing countries are discussed in the section on Providing Health Care later in this chapter (see Section XII).

Pharmacologic Methods

To ensure compliance from their patients, allopathic doctors must be aware of traditional cultural beliefs and practices in their areas and give simple accounts of the illness and what patients may reasonably expect from drug treatment. The choice of drug depends on availability and cost. Phenobarbital and phenytoin are commonly available and inexpensive and are the drugs used most often in developing countries. A community-based trial of phenytoin versus phenobarbitone in children in rural India found both drugs to be equally acceptable.[82] Both have associated problems, however. Phenobarbital is sedative in adults and induces hyperactivity in children. If stopped suddenly for any reason, it produces more withdrawal seizures than other AEDs. In many places, it is unavailable without prescription and only a few stores stock it. In developing countries, the main problem with phenytoin is that it is usually available only in 100-mg tablets, so adjusting the dose for children is neither easy nor accurate. Drug-level assays are needed for all AEDs but are most necessary for phenytoin, because of the pharmacokinetics of its metabolism. Chronic phenytoin intoxication may lead to cerebellar atrophy, encephalopathy, or both. Gingival hyperplasia is a problem in people who already have poor oral hygiene.

Widely available but more expensive choices than phenobarbital and phenytoin are carbamazepine and sodium valproate.

If used, they too entail problems. Use of sodium valproate requires liver function tests and serum ammonia estimation, particularly in children who are mentally retarded. Rarely, carbamazepine therapy can depress one or all of the three blood elements and cause hepatic dysfunction. If suggestive symptoms should arise, patients are asked to seek immediate medical attention and have a blood cell count. Anemia and hepatitis are already common problems in developing countries. Especially in rural areas where laboratory facilities are unavailable, it may be impossible to differentiate problems of AEDs from concurrent illnesses.

Dosages of AEDs in developing countries follow the milligram per kilogram of body weight scale used in developed countries. In general, however, because high doses often are not tolerated, the initial dose is lower and increased gradually if necessary. Malabsorption syndromes, malnutrition with hypoproteinemia, and hepatic dysfunction may interfere with the pharmacokinetics of AEDs. Calcium and vitamin D supplementation are desirable for all patients taking phenytoin and other drugs capable of inducing hepatic enzymes.[80] In those susceptible to rickets or osteomalacia, they are essential. Folic acid supplementation is particularly important for young women likely to become pregnant. Ideally, this should be given with vitamin B_{12} to prevent precipitating subacute combined degeneration in a B_{12}-deficient vegetarian community, such as in India. Patients are often unwilling to take so many tablets for a long period of time.

The newer AEDs clobazam, oxcarbazepine, lamotrigine, gabapentin, topiramate, levetiracetam, and pregabalin are available, and indeed locally manufactured, and sold in countries with a developed pharmaceutical industry, as in India. Many are still unaffordable to most of the population, so cost should always be considered before prescribing them, particularly since expenses will have to be borne out of pocket and parents will always make sacrifices for their children.

Nonpharmacologic Methods

Epilepsy surgery, vagus nerve stimulation, and a ketogenic diet are alternatives to pharmacologic treatment. Vagus nerve stimulation is no more effective than medical treatment and is very expensive, and the device requires maintenance. A ketogenic diet is difficult to sustain. Epilepsy surgery, in appropriately selected patients, renders the patient seizure free in 70% to 80% of cases. It should be considered early to decrease medical and psychosocial consequences of repeated seizures and ultimately to diminish the cost of continued expensive medication.[107]

Pregnancy Register

Pregnant women with epilepsy, whether on or off treatment, should be entered in a national pregnancy register, which should conform to the methodology of established registries in developed countries. The aim of this is to assess the risk of major congenital malformations, and it will allow optimal treatment of pregnant women with epilepsy under differing local circumstances, with due consideration to both mother and baby.

Compliance

Ensuring compliance is a difficult matter in any country. Pregnant women, and sometimes their doctors, may fear that AED treatment will harm the fetus. Parents may fear that AEDs will retard their child's development.

Students may be made sleepy from the AEDs, preventing them from studying at night. Newly married women may have concealed their epilepsy from their husbands and fear being caught taking medication. In developing countries people believe that allopathic medicine produces unacceptable side effects and they fear that they will become dependent on their drugs. If the drugs do not fulfill expectations, the patient may change doctors and treatment, or turn to traditional healers. If the patient wishes to go to a traditional healer while receiving allopathic medicine, this should not be discouraged, unless traditional methods require taking oral medicines that may contain unknown quantities of anticonvulsant. In addition, some traditional medicines have their own side effects, which the patient may attribute to allopathic medicines. Conversely, if benefits occur with allopathic therapy, the patient may attribute any improvement to the traditional methods of treatment and stop taking the allopathic drugs alto-gether.

As in developed countries, compliance can be assessed by interviewing the patient and by taking pill counts. Techniques to monitor AED blood levels are not always available and not always standardized.

Prevention, Safety, and First Aid

In addition to compliance, other general measures that will help patients live with epilepsy should be explained and emphasized. These include getting adequate rest and avoiding alcohol, fasting, and stress. In developing countries, religious fasts are common and often prolonged. Lack of food alone may provoke seizures during these times and the patient may also omit taking medication. Activities that may endanger the patient or others, such as cooking beside an open fire, standing in the doorway of a train, or driving, should be avoided as much as possible. Alternatives should be worked out with the patient.

The family of the patient needs to be made aware of first-aid measures. During a seizure, the patient should be turned on the side in a semiprone position, head down if possible, to allow drainage of secretions and vomitus. Nothing should be put in the mouth, as this obstructs the airway and might result in injury to the patient's teeth or tongue. If there is status epilepticus, the patient should be hospitalized as soon as possible. Rectal diazepam or buccal midazolam may be used at home.[95]

Treating the Cause of Epilepsy

Finally, the cause of the epilepsy needs to be treated. In developing countries, this mainly involves treating the chronic parasitoses and tuberculomas. The management of neurocysticercosis in particular remains difficult. Treatment depends on the number and location of the cysts and whether they are vesicular, degenerating, or calcified.

Diagnosis of the cause is mainly by neuroimaging with some help from serology. The treatment armamentarium consists of antiepileptic drugs, cysticidal agents, steroids, and surgery. The choice of treatment is a delicate and controversial matter.[35]

Prevention

Epidemiology has contributed less to our knowledge of etiology and prevention of epilepsy than it has to that of lung cancer and stroke. In over half the cases of epilepsy in developing and developed countries, no cause can be found. If all cases of known cause were prevented, more than half the total number of cases would still occur. When the etiology is known, seizures can be prevented by combining treatment of known risk factors in the community with prophylactic AED therapy.

Providing Health Care

Health Care Delivery

Epilepsy is treatable with relatively cheap medication, but the treatment gap in developing countries is still very high, up to 80% to 90%. Epilepsy has not only medical, but also psychologic, sociologic, economic, and cultural dimensions. Of particular importance in developing countries is symptomatic epilepsy related to endemic parasitic and infectious diseases, head trauma, and poor perinatal care. Levels of education, ability of health care workers and patients to communicate, and lack of availability of resources for the health care system influence the management of epilepsy and related problems. Few developing countries have established programs and institutions to deal with these problems.

Costs

The cost of providing care in developing countries is a major issue. Phenobarbital and phenytoin are the cheapest drugs, although the latter is available only in some countries. One of these two drugs is prescribed in 65% to 85% of treated patients with epilepsy,[29] and the drugs are available at most health centers and/or community pharmacies. The annual cost of phenobarbital, at 100 mg/day, ranges from $4 to $16, compared with $3 to $30 for phenytoin. Other less widely prescribed drugs including carbamazepine (CBZ), valproate (VPA), and injectable diazepam (DZP) are 6- to 12-fold more costly.[113]

Sub-Saharan Africa is the home of 11% of the world population, but it benefits from only 1.3% of world income. In 2001, the mean Gross Domestic Product per capita in the sub-Saharan countries was $1,690, ranging from $12,508 (Seychelles) to $490 (Sierra Leone), versus $24,973 in the developed world. Among the 40 least wealthy countries in the world, 32, or 80%, are in Africa.[110]

The provision of AEDs through government-funded schemes is therefore impossible in some cases. Not only do governments lack resources, but also people are unable to pay for AEDs from their own incomes. Between 61% and 72.8% of the population in the poorest countries of the world live on less than $1 per day.[110]

Phenobarbital will remain the only treatment until drug companies bring down their prices and make their products affordable to small health centers in the developing world.

Treatment Gap

Treatment gap has been defined by the International League Against Epilepsy as â€œthe difference between the number of people with active epilepsy and the number whose seizures are being appropriately treated in a given population at a given point in time, expressed as a percentage.â€ This is estimated at between 80% and 90% in developing countries. While cost is a major issue, other factors such as inadequate planning at government level, poor infrastructure, insufficient availability of drugs, and scarcity of trained medical personnel, particularly in rural areas, are also significant. Cultural factors also play a major part.

Cultural Influences and Traditional Medicine

In many developing countries, epilepsy is perceived as a manifestation of supernatural forces, caused by ancestral spirits or attributed to possession by evil spirits. People with epilepsy are often stigmatized. Stigma generates a hidden burden, which discourages patients from seeking another diagnosis and the care they need and deserve. Furthermore, discrimination against people who have seizures excludes them from adequate employment. In some societies, fear of â€œcontaminationâ€ by the breath, blood, sperm, and genital secretion of people with epilepsy produces unacceptable responses such as ignoring or avoiding a person having a seizure, which may lead to death, drowning, burns, and other injuries. Children with untreated epilepsy often face discrimination and isolation at school, resulting in low self-esteem and underachieve-ment.

Sociocultural factors, and in particular what the person believes is the cause of his or her epilepsy,[69] can explain why patients often first seek advice from the many traditional therapists and healers.[25] In developing countries, traditional healing is usually the first treatment sought. Sometimes between 6.5 and 13.4 years elapse before the patient receives allopathic treatment.[25,29,109,112] Traditional healing should not be completely discredited, since often patients obtain secondary benefits such as reassurance and emotional support. It should be integrated with Western methods to provide full support and care for the patient and his or her family.[31] Sharing information with and offering training to traditional healers has shown that working in close connection with traditional healers and community and religious leaders promotes acceptance of the primary health care worker by the community and enables him or her to modify certain harmful practices. The challenge is how to marry the differing convictions that determine traditional and scientific treatment concepts.

Role of Physician and Paraprofessionals

In those developing countries that have specialists in the neurosciences, there is a very low doctor-to-population ratio. In Europe there is one neurologist for 100,000 people, but in developing countries the ratio is one neurologist for up to 6 million people. The World Health Organization (WHO) recommends one neurologist for 50,000 people. In developing countries, everyone qualified should be actively involved in health care delivery. In addition, diagnostic centers are very few and mostly located in capital cities. Such a shortage of professionals makes the role of paramedical staff essential, prevention of epilepsy paramount, and coordination of government programs imperative.

Since complications in the peripartum period are the leading cause of future epilepsy in developing countries, the epilepsy program should be included in plans for primary health care at both government and community levels. It should also be coordinated with other public health programs, such as antenatal and postnatal care and pediatric health in the first 10 years of life, including immunization programs. Prevention of head trauma and alcohol and drug abuse should also be priorities.

Early detection and appropriate treatment will reduce disabilities caused by epilepsy. Publicizing, preventing, and managing those infectious diseases that affect the brain and prevention of consanguineous marriages should also be considered priorities for public health. Eradication of neurocysticercosis should receive special attention.

The following goals are essential:

- To ensure availability of phenobarbitone to patients.
- To promote the use of generic drugs and carry out quality control checks from time to time.
- To continue to permit use of traditional medicine that is not dangerous, but ensure that the patient keeps on taking AEDs.

- To establish drug banks: An agreement between ILAE/International Bureau for Epilepsy (IBE) national chapters and drug suppliers could ensure availability and supply of cheap AEDs; such a system could employ its own funding mechanism and become sustainable and relatively autonomous.
- To establish specialized investigatory facilities with an EEG machine, a CT scanner, and a drug monitoring laboratory.

Public and Private Agencies

To deal with the gradual decline in the provision of health care services as a result of poverty in African states, the WHO resolved to revitalize district health systems by establishing community-based management centers and employing only essential drugs to combat major public health problems. This was called the Bamako Initiative. Phenobarbital for epilepsy is on the list of essential drugs. As it is cheap and taken only once a day, its use should be explained and it should be prescribed to most patients with epilepsy. Fifteen years down the line, much progress has been made, but much is yet to be done. There are operational problems caused by poverty, lack of human resources, demographic pressure, sociocultural differences, and recurring emergency situations. The next step will be to include a larger number of drugs, particularly those that are in generic form, with effective, sustainable quality control. Public and private sectors need to cooperate to expand drug coverage.

Community-based Epilepsy Programs

The treatment of epilepsy in developing countries is not only a medical, but also a political issue. Widespread poverty, stigma, and discrimination in employment and education against people with epilepsy obstruct the effective delivery of services and treatment of patients. These wider issues need to be addressed at both the individual and the societal level.

Summary and Conclusions

The essential components of an effective strategy for addressing epilepsy in developing countries are as follows:

1. Adequate financing.
2. Changing laws and community attitudes.
3. Making people with epilepsy and their families aware of their rights and what treatment should be available to them.
4. Actively providing psychosocial rehabilitation, educational opportunities, and income generating projects, including incorporation of traditional with allopathic approaches to treatment.
5. A public education program to ensure that awareness of and sensitivity to the needs of people with epilepsy permeate education, employment, health, and the legal system.
6. Adopting a multidisciplinary approach involving patients and their families interacting with health and social workers; this would be promoted by government and delivered through a range of agencies to include community leaders, pharmaceutical companies, nongovernmental organizations (NGOs), and international groups.

However, these issues also need to be tackled at the global level. The Global Campaign Against Epilepsyâ€"Epilepsy out of the Shadows is an international and collaborative initiative set up by the IBE, ILAE, and WHO. With the support of governments, interested UN agencies, international institutions, NGOs, and the pharmaceutical industry, the ultimate aim of the Global Campaign is to free every person in the world who has epilepsy from the burden of any preventable or manageable epileptic disorder. This two-part strategy consists of the provision of a platform for international awareness and assisting health departments to develop national epilepsy programs.

By comparison with developed countries, epilepsy in developing countries presents unique problems due to differences in incidence, etiology, cultural, and socioeconomic factors. In addition, the health care delivery systems in these countries are often inadequate, poorly organized, excessively bureaucratic, and underfinanced. Although there are no significant differences in most parameters of epilepsy prognosis, mortality seems to be higher than in developed countries. Developing countries need more incidence studies, prospective studies on large cohorts with recent-onset epilepsy to determine mortality, and analytic case-control studies on incidence cohorts. Prevention of cerebral infections by immunization and control of parasitic diseases through improved sanitation, hygiene, and elimination of the responsible vectors together with prevention of head injuries will reduce the incidence of new symptomatic cases, as will good maternal and child care. A major impediment to raising the standard of medical care is the unavailability of physicians or other trained personnel and the lack of modern diagnostic and treatment facilities, especially in rural areas. A multidisciplinary approach involving public and private agencies, professionals, paraprofessionals, and even traditional healers is required in many developing countries. Community-based epilepsy programs should be incorporated in national health care programs. Finally, a continuing challenge is the treatment gap, which is estimated to be 80% to 90% at any one time in some countries. It needs to be addressed by measures such as the Global Campaign, which increase awareness of epilepsy and strengthen national epilepsy programs.

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Chapter 12

General Neuropathology of Epilepsy

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Introduction

The history of the study of structural brain changes in patients with intractable epilepsy is characterized by continuing debate concerning the primacy of neuropathologic abnormalities in seizure genesis in temporal lobe epilepsy (TLE) (see Chapter 13), and intractable seizure disorders in infants and children,[4,156,157] and subtle cortical cytoarchitectural alterations in primary generalized epilepsy.[113,119] This chapter will focus on neocortical pathologic abnormalities and will rely for the most part on studies using human tissue. Specific structural alterations in brain tissue, which may serve as a final common pathway for the development of many diverse epilepsy-associated conditions, are discussed. Neuropathologic changes that may be attributed to epilepsy, including the neuropathologic consequences of status epilepticus (SE), are also discussed. Characteristic neuropathologic conditions that result in epilepsy syndromes (excluding developmental malformations but including epilepsy-associated neoplasms) are described.

Are There Unique Morphologic Substrates That Subserve Intrinsic Epileptogenicity in Human Neocortex?

Advances in epilepsy neuroimaging[53,54,144,158] have created new challenges for the diagnostic neuropathologist, but also provide a unique opportunity to better characterize the nature of the epileptogenic lesion. A key issue in the investigation of patients with lesional epilepsy is to determine the relative contribution of the lesion and of the surrounding perilesional brain tissue to seizure genesis. Virtually all epilepsy-associated lesions may also occur in the absence of epilepsy. What, then, distinguishes the lesion that has caused epilepsy from the one that has not? Is there an underlying genetic basis for epilepsy susceptibility in such patients, and/or are there unique structural changes present in the perilesional brain tissue that provide the pathologic substrate for seizure generation? There is good evidence that some lesions are of themselves intrinsically epileptogenic; in this regard dysplastic cortical tissue is hyperexcitable.[34,110] However, hyperexcitability alone is insufficient for seizure genesis. None of the epilepsy lesions has ever been shown to demonstrate spontaneous depolarization using current patch clamp techniques in an in vitro environment. Furthermore, it is clear that some lesions such as cavernous angiomas cannot be intrinsically epileptogenic, and in such cases alterations in the surrounding cortex will almost certainly provide the key to understanding seizure genesis.[178]

It is useful to consider a number of definitions that relate to the epileptogenic lesion and surrounding brain tissue. The lesion itself may or may not contain functionally active neural tissue. The epileptogenic zone is the area located immediately adjacent to the lesion, which is essential for seizure genesis and whose removal is generally considered to be essential for improved seizure control.[17] Usually, but not always, the epileptogenic zone includes the seizure onset zone. Ideally, the functional deficit zone, which by modern neuroimaging techniques is shown to have functional abnormalities during seizure development, overlaps with the epileptogenic zone, though again this may not always be the case. Ictal symptoms result when an area of cortex is activated during epileptiform discharge and is referred to as the symptomatogenic zone. Interictal spikes utilized in the past for localization purposes reflect activity in an irritative zone, which may or may not be included within the epileptogenic zone. Finally, there is a defined area from which the seizure typically begins, referred to as the seizure onset zone. Ideally, the area in the immediate vicinity of the epileptogenic lesion would include all of the above zones, though seldom does this occur in practice. Spectacular advances in neuroimaging have led to a situation whereby the pathologist in receipt of tissue originating from epilepsy surgery can now be more certain that the resected material includes the epileptogenic zone. Additional techniques such as magnetoencephalography (MEG) have been used to map the extent of the epileptogenic zone surrounding relatively inert epilepsy-inducing lesions such as cavernomas.[92,124]

In attempting to determine if there is a specific pathologic change in the epileptogenic zone, immediate difficulties are encountered in terms of procuring adequate control tissue. Comparison of perilesional tissue from patients without epilepsy with the perilesional epileptogenic zone from patients with epilepsy, both having similar underlying lesions, would go a long way toward resolving the nature of any epilepsy-induced brain changes. Rarely has this been achieved. Nevertheless, new developments in molecular and pathologic techniques have provided a unique opportunity to answer questions regarding specific structural changes in the epileptogenic zone.[40,41,118,121,182] Standard immunocytochemical techniques have now been supplemented with a bewildering array of sophisticated analytic techniques capable of probing the genetic and neurochemical profile of individual neurons within an epileptogenic zone. Laser capture microscopy facilitates analysis of individual neurons both in terms of neurochemical profile and surface receptor expression. Coupled with microarray studies of gene expression, it is now possible to build a very accurate genetic profile of individual neurons arising within the epileptogenic zone.[27] Additionally, in vitro slice current-clamp recordings have been obtained from neurons in dysplastic brain tissue.[139]

Any morphologic approach to the study of the epileptogenic zone must go some way to explaining the key neurophysiologic

events in seizure genesis, namely, the recruitment and repetitive and sustained synchronous discharge of groups of neurons. Since the first Golgi studies, there has been awareness that epileptogenesis is associated with altered synaptic morphology in groups of neurons. More recently, the concept of an intrinsic deficit in neuronal function has been confirmed by the demonstration of genetically determined alterations in structural and functional properties of neuronal ion channels.[64,170]

Decreased Inhibitionâ€“Increased Excitation

Morphologic studies to date have focused on the demonstration of decreased inhibition or increased excitation in the epileptogenic zone. At the very least the concept of decreased inhibition (Î³-aminobutyric acid [GABA]-ergic) is simplistic and does little to elucidate the sequential change that undoubtedly take place in the epileptogenic zone as seizures become more chronic, more prolonged, and generally more severe. Attempts to determine the severity of loss of inhibitory interneurones[108,120] coupled with the extent of increased excitation, resulting perhaps from axonal sprouting leading to new facilitated excitatory pathways,[135] is perhaps beyond the resolution of even the sophisticated neuropathology techniques outlined above. Probing more deeply, it is difficult to see how alterations in receptor density expression on individual neurons might be used to define the origin of an epileptic focus, especially as evidence for the existence of intrinsically epileptic neurons is still not completely convincing.[76,93,111,126,149] In an individual epileptogenic zone it may well be that very subtle alterations in inhibition combined with reorganization of excitatory circuits (glutamatergic) will be sufficient to result in epileptogenesis. The complexity of the decreased inhibitionâ€“increased excitation concept is illustrated by studies on chandelier cells and other cortical inhibitory interneurons in epileptogenic brain tissue, in which there is considerable variation of results within and between individual cases.[6,48,49,71,88]

The Neocortex in Temporal Lobe Epilepsy

Human neocortical neurons can, in response to stimulation, generate bursts of action potentials, which are caused by activation of *N*-methyl-D-aspartate (NMDA) receptors.[13,14,65] Neurons adjacent to cavernous angiomas show spontaneous excitatory and inhibitory synaptic events and, following stimulation, demonstrate multiple action potentials.[178] Spontaneous inhibitory potentials related to GABA receptor activation may also be demonstrated in human brain slices.[12,15,165] Pharmacologic manipulation of receptors can lead to generation of epileptiform activity in resected neocortex, but receptor blockade or stimulation in isolation is often insufficientâ€”the addition of an electrical stimulus being required to generate epileptiform discharges.[52] Nevertheless, there is increasing evidence that synchronization, a key element in the generation of epileptiform discharges, is in part mediated by GABA receptorâ€“mediated potentials in epileptogenic neocortex.[43]

Cortical Dysplasia (CD)

The spectrum of cortical dysplasia (CD)[128] almost certainly extends beyond the classic description of Taylor et al., in which a combination of balloon cells and large malorientated neurons with coarse Nissl substance were the defining pathologic features.[166] Detailed morphometric studies of human temporal neocortex obtained from patients undergoing resective surgery for TLE has shown a significant increase in mean neuronal somal volume in neocortical and ectopic white matter neurons.[26] This subtle form of CD is not recognizable without recourse to morphometry. It is reasonable to assume that the neurophysiologic properties of classic â€œTaylor typeâ€ CD might also be present in subtle CD.[126] For many years it has been recognized that CD tissue shows a general decrease in density of inhibitory neurons and an increase in excitatory neurons. However, detailed quantitative analysis of CD demonstrates considerable variation in the distribution and severity of GABAergic system alterations both within and between cases.[3,30,64,159,167] Additionally, these studies have demonstrated considerable variation in the number of synapses per neuron both between different cases and within individual cases. The difficulty with all of these studies is a determination of the contribution of the epileptic activity itself to alterations in synaptic density, especially in terms of functional reorganization that might contribute to new synapse formation.

Intracellular recordings from the giant neurons of CD (but not from the balloon cells) show evidence of hyperexcitability when depolarized, in contrast to the balloon cells, which are essentially inert.[34] Additionally, these large neurons have larger voltage-gated currents than normal-appearing neurons. Furthermore, the large neurons have increased immunoreactivity for glutamergic receptor subunits such as NMDA and also show alterations in the composition of NMDA subunits when compared with normal-appearing neurons from nonepileptic tissue.[33] Intriguingly, some but not all â€œnormalâ€ neurons from CD tissue show similar consistent variations in NMDA subunit expression. However, in spite of all the excellent work that utilizes human epileptic tissue in vitro, it has not been possible, to date, to demonstrate intrinsic spontaneous epileptiform activity.

A Role for Glial Cells in Epileptogenesis

More recently, the contribution of the astrocytic component in any epileptogenic zone has received attention.[42,68] Astrocytes are functionally active and express ion channels and neurotransmitter receptors similar to neurons. Astrocytes play a key role in modulating the neuronal extracellular environment. Long believed to be a relatively inert cell type, it is now widely recognized that astrocytes, through their ability to buffer potassium, may contribute to neuronal hyperexcitability.[160] In virtually all structural lesions associated with epilepsy there are increased numbers of astrocytes either within or surrounding the lesion. Astrocytes possess voltage-activated potassium [K^+] channels through an inwardly rectifying K^+ channel (K_{IR}), which have a critical role in buffering potassium levels.[10,78,82,151] Fluctuations in extracellular calcium and potassium levels might well be the ionic basis for conversion of regular firing neurons into burst firing neurons capable of functioning as pacemaker neurons having the ability to recruit other neurons. There is recent evidence that genetic alterations in K_{IR} channel subunits may contribute to the development of epilepsy susceptibility.[68,163] Such alterations in potassium channel function might also be due to environmental factors. Impaired clearance of extracellular potassium could result in neuronal hyperexcitability. What is required now is a comparative study of glial cell functional properties in epileptic and nonepileptic brain tissue.

In summary, although there have been spectacular advances in neuroimaging and in the array of molecular techniques available to study the epileptogenic zone, the evidence, to date, for common underlying epilepsy-specific pathologic abnormalities that distinguish the epileptogenic zone surrounding an inert epileptic lesion from nonepileptogenic tissue surrounding a similar lesion is difficult to delineate.

Common Neuropathologic Changes That Result From Epilepsy

The effects of recurrent and prolonged seizures on the developing brain and also on the fully formed adult brain require careful consideration. Before discussing whether or not specific neuropathologic changes develop as a consequence of recurrent and prolonged seizures, it is necessary to examine whether or not there are recognizable clinical deficits that occur as a consequence of seizure activity. Intuitively, all clinicians involved in the care of patients with epilepsy suspect that frequent and/or prolonged seizures amounting to status epilepticus (SE) are harmful to the developing and mature brain. Gradual decline in school performance and behavior is frequently attributed to the effects of recurrent seizure activity in children. However, a careful examination of the literature reveals a paucity of detailed long-term prospective studies that attempt to correlate seizure frequency over many years with objective measures of cognitive function. Nevertheless, in a critical review of the studies to date (however imperfect), a statistically significant relationship was confirmed between the number of seizures or the presence of SE and decreased scores on cognitive performance.[50] The effect on cognitive performance was greater for patients having uncontrolled seizures of the generalized tonicâ€"clonic type. A similar effect was not seen with partial epilepsy. When neuroimaging findings are included, it has been shown that brain atrophy in temporal lobe epilepsy as measured by quantitative magnetic resonance imaging (MRI) is the primary mediator of the effect of epilepsy duration on neuropsychological morbidity.[127]

In relation to the specific issue of intellectual decline following SE in adult patients, the problem is more difficult to resolve. Significant memory impairment may occur as a result of SE, though in the majority of instances this is not permanent. Frequently SE is a reflection of underlying cerebrovascular or other serious systemic disease, the presence of which more likely determines the patient's subsequent intellectual and cognitive performance. In a series of 1,685 patients with epilepsy who underwent comprehensive neuropsychological testing, comparison of IQs and Wechsler Adult Intelligence Scale (WAIS) scores between those who experience SE and a control group who did not, failed to demonstrate any significant intellectual decline following SE.[1] Although the study may be criticized on the suitability of the WAIS-R test for measuring all cognitive functions, particularly amnesia and memory, it was not possible to demonstrate any long-lasting intellectual dysfunction.

Neuroimaging Studies

Before attempting to determine if epilepsy causes seizure-induced (recurrent unprovoked or SE) permanent neuronal injury, several confounding factors must be considered, including the neurotoxicity of antiepileptic drugs, the neuropathologic consequences of any systemic illness associated with epilepsy, any brain injury sustained during seizure episodes, and the initial precipitating event such as a prolonged febrile seizure, together with the nature of the underlying process that may have caused the epilepsy to develop in the first place. It is immediately obvious that human pathologic studies are unlikely to be able to tease out these interdependent variables. Longitudinal prospective imaging studies can readily detect alterations in the volumes of specific regions such as the hippocampus and the neocortical ribbon. Surprisingly, and although in their infancy, such studies have shown that progressive brain atrophy is not an inevitable accompaniment of epilepsy and that when volume loss does occur, it does so independently of seizure frequency and antiepileptic drug usage.[101] In fact, it is felt that any developing atrophy is more likely to be due to a combination effect of normal aging and the underlying disease process that caused the epilepsy to occur in the first place. It must be stressed that such studies are difficult to execute and will require large numbers and several years of follow-up.

Patients with temporal lobe epilepsy demonstrate mean reductions of from 4% to 6.6% in cerebellar volume when compared with nonepileptic control patients; in general, a longer duration of TLE with an increased lifetime number of generalized tonicâ€"clonic seizures were present in those with cerebellar atrophy. Furthermore, the cerebellar atrophy appeared to occur independently of cerebral cortical atrophy.[75]

Recent neuroimaging studies, especially those which measure water diffusion through the brain, have demonstrated alterations in diffusivity after both prolonged seizure activity and single seizures. Single seizures may be followed by focal changes in diffusion-weighted imaging (DWI), which invariably return to interictal levels within a few hours.[147] The pathologic correlate of the altered DWI is as yet unknown, though it is likely that transient edema may occur. Alterations in DWI that have developed following prolonged seizure or SE[79] have gradually returned to interictal levels, though in a few instances the changes in DWI have been followed by brain atrophy.[96] SE with minor or no motor disturbance (i.e., nonconvulsive SE), either generalized or focal, may be associated with MRI changes.[37] Thus, although the neuroimaging evidence for seizure-induced neuronal injury is beginning to accumulate, currently it is difficult to be certain of the long-term significance of these changes in terms of clinically apparent brain injury.

Human Pathologic Studies

In a few well-documented human pathologic studies, it has been possible to demonstrate neuronal injury that has clearly occurred as a direct result of seizure activity. In a detailed imaging and autopsy study, a 28-year-old man was shownâ€"during 5 months of idiopathic convulsive SEâ€"to develop evolution of generalized cerebral cortical atrophy with severe neuronal loss and gliosis. The patient had not become hypoxic or hypotensive in the course of the illness.[132] In another report, a 9-year-old girl with refractory focal SE developed progressive generalized brain atrophy over a 3-year period during which the MRI showed progression from normal through increased focal T2 signal to generalized atrophy. Brain biopsy demonstrated neuronal loss and gliosis.[51] Again, there was no evidence of any confounding variable such as hypotension or hypoxia. Crossed cerebellar atrophy has been demonstrated by MRI,[94,116] positron emission tomography (PET),[85] and pathologically[97,164] in the cerebellar hemisphere contralateral to the cerebral hemisphere from which unilateral persistent seizure activity arose, thereby providing good evidence for enhanced neuronal activity, transmitted via corticocerebellar pathways, as the likely explanation for neuronal injury.

Although the neuropathologic consequences of SE in humans have not been extensively studied in recent years,[154,175] there is good evidence from autopsy examinations that widespread neuronal necrosis with varying degrees of gliomes-odermal proliferation may occur,[103] though not invariably so, after SE.[38] There is general agreement that the severity of such neuronal injury is less in children than in adults.[70] The hippocampus shows the most striking changes, with widespread neuronal necrosis. Similar changes may be present in the thal-amus and in a patchy distribution throughout the neocortex. The extent of any associated astrogliosis or microglial cell proliferation depends, to a large extent, on the duration of a given patient's survival following SE. Repeated episodes of SE could result in sufficiently severe degrees of neuronal loss to eventually lead to cortical atrophy.

Controversy has arisen in relation to watershed/borderzone ischemic lesions occurring in SE. In a review of the neuropathologic consequences of SE,[28] which cited the classic work of Corsellis and Bruton, it was suggested that watershed distribution necrosis is feature of SE. In subsequent correspondence, Bruton[29] explicitly stated that such lesions were not described in his original publication. In reply, the editors cited incorrect referencing, declaring that the description of watershed lesions in SE should have been credited to the classic work of Norman,[123] originally published in 1966 and reprinted in 1987. Unfortunately, however, a very careful scrutiny of the original 1966 work and of the subsequent 1987 reprint has failed to locate any reference whatsoever to watershed lesions in the brains of patients dying of SE. It is our belief that neuronal necrosis having a watershed distribution cannot be attributed to SE alone and that some other contributory factor, such as profound hypotension, should be sought, either as the cause of or a complication of SE.

Common Brain Lesions Associated with Epilepsy

In this section, selected features of several characteristic neuropathologic entities associated with seizure disorders are described. Structural features of these lesions (and their relationship to epilepsy) will be emphasized and selectively illustrated. Especially in patients with temporal lobe epilepsy, â€œdual pathologyâ€ (e.g., mesial temporal/hippocampal sclerosis *together with* cortical dysplasia or a cortical neoplasm) is not infrequently encountered.[146]

Neoplasms

Both primary and secondary (metastatic) neoplasms of the central nervous system (CNS) are characterized by their distinctive histologic appearance, location(s), and immunohistochemical phenotype. Preoperative neuroimaging studies, including magnetic resonance spectroscopy (to look for levels of *N*-acetylaspartate, choline, and creatine, as well as choline:creatine ratios) may be helpful in predicting how aggressive a neoplasm is likely to be.[57] The predicted biologic behavior of *primary* brain tumors is reflected in how they are categorized according to the World Health Organization (WHO) classification system.[90,91] When astrocytic tumors are considered as a major subset of all infiltrating glial neoplasms (*gliomas*), their degree of malignancy is readily ascertained by examining distinctive histologic features present in the tumorâ€"characteristics that can quite accurately be evaluated in a simple hematoxylin-eosinâ€"stained tissue section.[46] Unfortunately, these grading parameters appear to be less useful in evaluating CNS tumors in the pediatric age group.[66] However, the neuropathologic diagnosis and study of brain neoplasms is now being rapidly refined using tools of immunohistochemistry and molecular genetics.[112] These methodologies will almost certainly supersede evaluation of the subjective or semi-objective histologic criteria upon which tumor diagnosis is now based, in terms of their predictive value. Immunohistochemical techniques can detect evidence of tumor differentiation along astrocytic and/or neuronal lines, or (in the case of a metastasis) suggest a site of origin of the neoplasm, even when this is not apparent on initial workup of a given patient. Assessment of the â€œproliferative potentialâ€ of tumor cells can now be undertaken by using one or more several straightforward immunohistochemical markers (e.g., anti-Ki-67), many of them effectively used in paraffin sections,[133,134] thereby allowing for meaningful studies on archival material. Without question, modifications of the histopathologic approach to classify CNS neoplasms have also resulted from recent molecular-genetic studies. Further advances in the â€œmolecular pathologyâ€ of CNS neoplasia are likely to revolutionize how we categorize and treat gliomas, which remain highly refractory to even the â€œbestâ€ medical therapy. Association between allelic losses and sensitivity to polychemotherapy in oligodendrogliomas[58,63,81,171] or epigenetic regulation of D-6-methylguanine-DNA methyltransferase (MGMT) with better responsiveness to temozolomide are hallmarks of this progress.[74] Even tumors that we have in the past â€œlumped togetherâ€ (e.g., using the term *glioblastoma*) are now known to have distinctive molecular signatures (defined by patterns of expression of epidermal growth factor receptor [EGFR] components and PTEN) that predict how these neoplasms are likely to respond to EGFR kinase inhibitors.[114] Highly individualized therapy for primary brain tumors is likely to result from such advances. Further analysis of the complex molecular genetic interface between familial brain tumor syndromes (e.g., neurofibromatosis) and neurocutaneous disorders/phakomatoses is rapidly evolving.[95,102,103,112]

The study of neoplasms associated with epilepsy, which in general tend to behave in an anomalous (and usually fairly benign) fashion, by means of these new cellular and molecular tools will be of particular interest. However, it is important to remember that *any* intra-axial neoplasm, in particular one with a cortical (especially hippocampal) component (Fig. 1), can cause seizures, as can any extra-axial tumor that significantly compresses, displaces, or invades the cerebral hemispheres. In one large series of almost 500 patients with brain metastases, seizures were noted at the time of presentation or at some point during the course of the illness in over 25% of individuals. Seizure likelihood was highest with melanoma (occurring in two thirds of affected individuals), while tumors that had spread to the CNS from lung, breast, or an unknown primary were also a common cause of seizures.[55] Seizures have been estimated to occur in 80% of low-grade (2 out of 4) glioma patients, in almost one third of those with high-grade glioma, 20% of those who harbor a meningioma, and one tenth of patients with primary CNS lymphoma.[77] The pathophysiology of tumor-related seizures is multifactorial and extremely complex (for an excellent topical review, see reference 148). Important factors that contribute to tumor-related seizures may include a relative loss of inhibitory synapses or inhibitory interneurons in tumor-adjacent tissue, subtle pH alterations (peritumoral pH is slightly alkaline), ion level changes (e.g., decreased extracellular Mg^{2+}), amino acid fluctuations (e.g., affecting alanine, phosphoethanolamine, and glutamine), enzymatic derangements and increased excitatory activity in peritumoral tissue secondary to abnormal glutamatergic transmission associated with altered receptor subunit expression, and abnormal intercellular communication resulting from derangements in gap junction proteins (e.g., connexins CX43 on astrocytes, CX32 on oligodendroglia, and CX26 and CX32 on neurons).

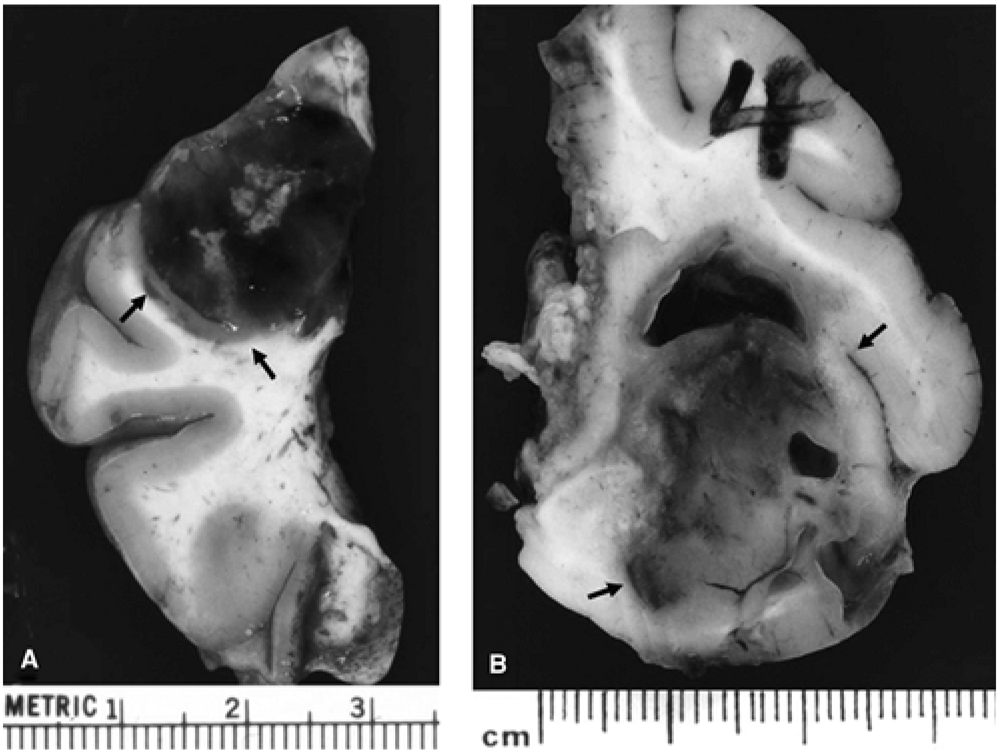

FIGURE 1. Tumors associated with intractable epilepsy, resected from two different patients. Note clear demarcation of the tumors from surrounding brain (indicated by *arrows*). Tumor shown in panel **A** is significantly hemorrhagic, whereas neoplasm in panel **B** is relatively homogeneous with focal cavitation. Both tumors clearly involve the cortex. (See the color insert.)

Table 1 Brain Tumors Associated with Epilepsy

Consecutive series of 722 tumor specimens obtained from the German neuropathologic data bank for epilepsy surgery

Tumor Entity	WHO grade	Number (%)	Age (yr)	Duration (yr)
Ganglioglioma	I	423 (58)	25	13.6
DNET	I	129 (17)	26.9	12.9
Astrocytoma, pilocytic	I	37 (5)	27.2	17.2

Astrocytoma, isomorphic variant*	I	13 (2)	29.4	17.8
Astrocytoma, pleomorphic and xanthochromic	II	22 (3)	30.7	17.0
Astrocytoma, fibrillary	II	40 (6)	33.5	8.6
Oligodendroglioma	II	36 (5)	36.6	11.1
Astrocytoma, anaplastic	III	22 (3)	40.1	3.2

DNET, dysembryoplastic neuroepithelial tumor; WHO, World Health Organization.
Consecutive series of 722 tumor specimens obtained from the German neuropathologic data bank for epilepsy surgery (www.epilepsie-register.de).
* A new epilepsy-associated isomorphic variant of diffuse astrocytomas was recently described.[101]
Number of patients encountered in our series (% of total, n = 722). Age at operation, duration of epilepsy. Note that 82% of all patients were under age 30 and had a seizure history of more than 13 years at the time of operation.

The proportion of tumors seen among resected specimens from epileptic patients varies tremendously among epilepsy surgery centers, depending obviously on the interests and expertise of local clinicians as well as referral patterns to a given institution. In large series describing the neuropathologic features of temporal lobe resections carried out for pharmacoresistent seizures, neoplasms account for 25% to more than 50% of the resultant specimens.[104,105,131,179,180,181] Some tumors (see below) may coexist with foci of cortical disorganization or dysplasia. In patients with pharmacoresistent TLE, dual and even multiple lesions may be encountered (e.g., hippocampal sclerosis together with malformations of cortical development and/or low-grade neoplasms).[56] The range of tumors encountered in patients with TLE is variable and includes the full spectrum of primary brain tumors, although gangliogliomas, pilocytic astrocytomas, and dysembryoplastic neuroepithelial tumors (WHO grade I tumors) are unusually common.[179,180,181] Extratemporal resections for intractable epilepsy also often yield neoplasms, usually of low histologic grade and having histopathologic features comparable to those encountered in

the temporal lobes. All studiesâ€"in both adults and childrenâ€"emphasize the remarkably high likelihood of patients being seizure free (i.e., an Engel class I outcome) after tumor resection, even when only a â€œlesionectomyâ€ is performed.[31,67] The Bonn group, with one of the world's largest experiences of epilepsy-associated neoplasia, has emphasized that biologically aggressive infiltrating glial tumors or tumors with a ganglion cell component (astrocytoma or ganglioglioma WHO grade III) are distinctly unusual among tumor resections performed for intractable seizure disorders.[104] The biologic behavior and appearance of some of the specific tumor types commonly encountered are worth reviewing in greater detail (see Table 1).

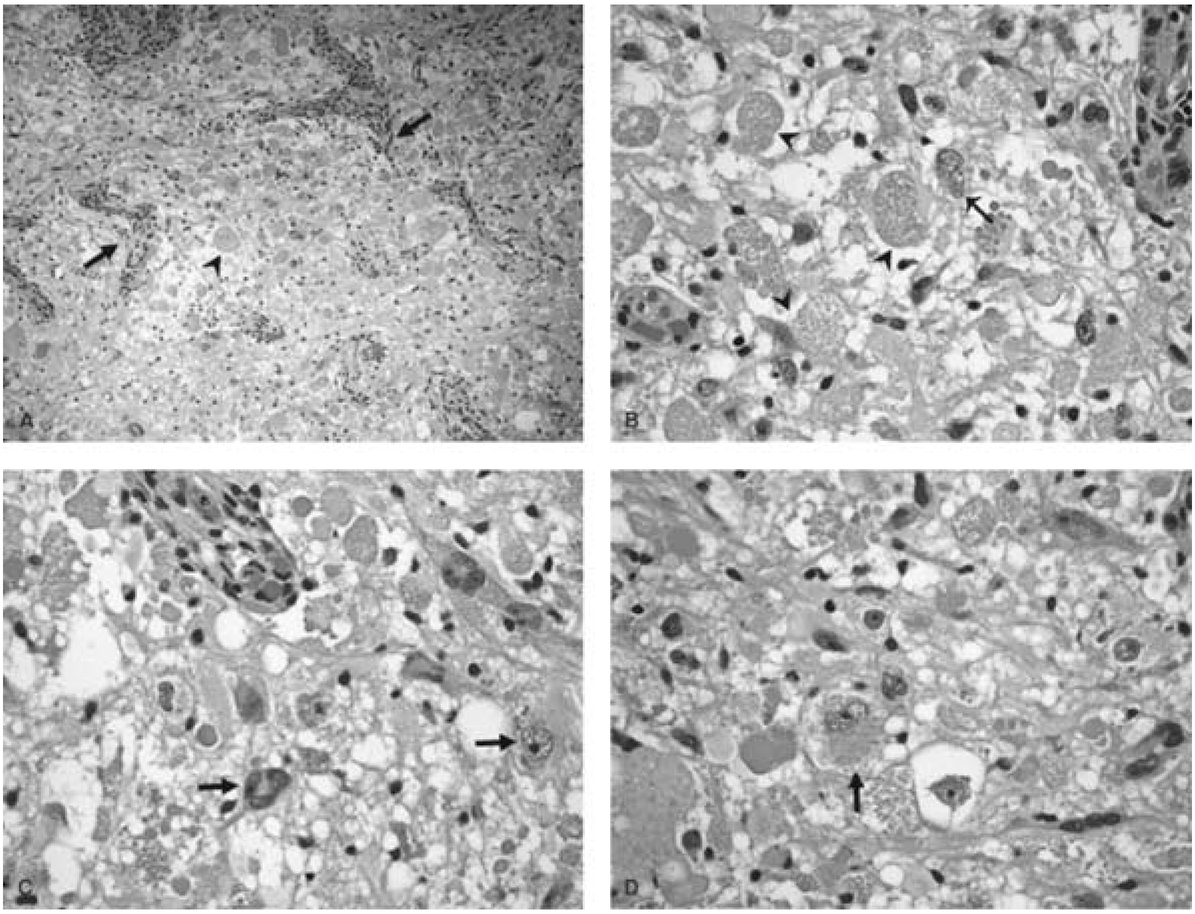

FIGURE 2. Ganglioglioma. **A.** Prominent vascularity in the tumor, with scattered perivascular lymphocytes (*arrows*). *Arrowhead* indicates a granular eosinophilic (cytoid) body; several of these are shown at higher magnification in panel **B.** *Arrow* in panel B shows a lobulated, dysmorphic nucleus. **C.** Several lobulated and bizarre nuclei are seen, though at least one cell (at right) retains neuronal features, including nucleolated nucleus and basophilic cytoplasm. **D.** Several dysmorphic neurons (e.g., highlighted by *arrow*). (All sections stained with hematoxylin & eosin.) (See the color insert.)

Ganglioglioma

This tumor has been recognized as a distinct entity at least since the 1930s.[112] Several excellent clinicopathologic reviews of experience with this entity have been published in recent years, including detailed immunohistochemical and mutational analyses that link them to malformative lesions (cortical

dysplasia, tubers of tuberous sclerosis).[22,25,106,136,152,155,183] Most commonly, epileptic seizures are the initial clinical manifestation of gangliogliomas (GGs), with focal neurologic deficits the presenting feature in fewer than 10% of cases. Patients may be symptomatic for long time periods (sometimes 10 to 20 years or more) before they come to surgical attention. Most often found in a supratentorial location, GGs are frequently encountered in the temporal lobes, and sometimes even in unusual loci such as the optic chiasm.[100] Their histopathologic features and clinical behavior both suggest that these neoplasms are very slow growing (the vast majority are WHO grade I), and they seem to be most effectively treated by complete or radical surgical excision. When these tumors are resected in patients with intractable epilepsy, there is almost always a marked improvement in the seizure disorder, or at least a diminution in seizure frequency and severity; often, the surgery is curative.[22,136,152,155,183] The UCLA group has estimated that progression-free survivals after gross total resection of both low- and high-grade GGs was almost identical, 78% and 75%, respectively, while these rates were 63% and 25% after *subtotal* resection.[152]

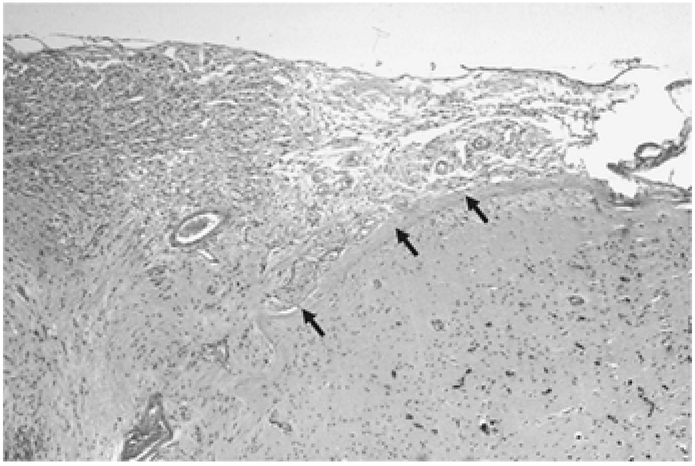

FIGURE 3. Gangliogliomas often extend into the subarachnoid space, even when they otherwise lack malignant (high-grade) features. *Arrows* indicate pial margin; large excrescence of tumor is seen at upper left. (Hematoxylin & eosin stain.) (See the color insert.)

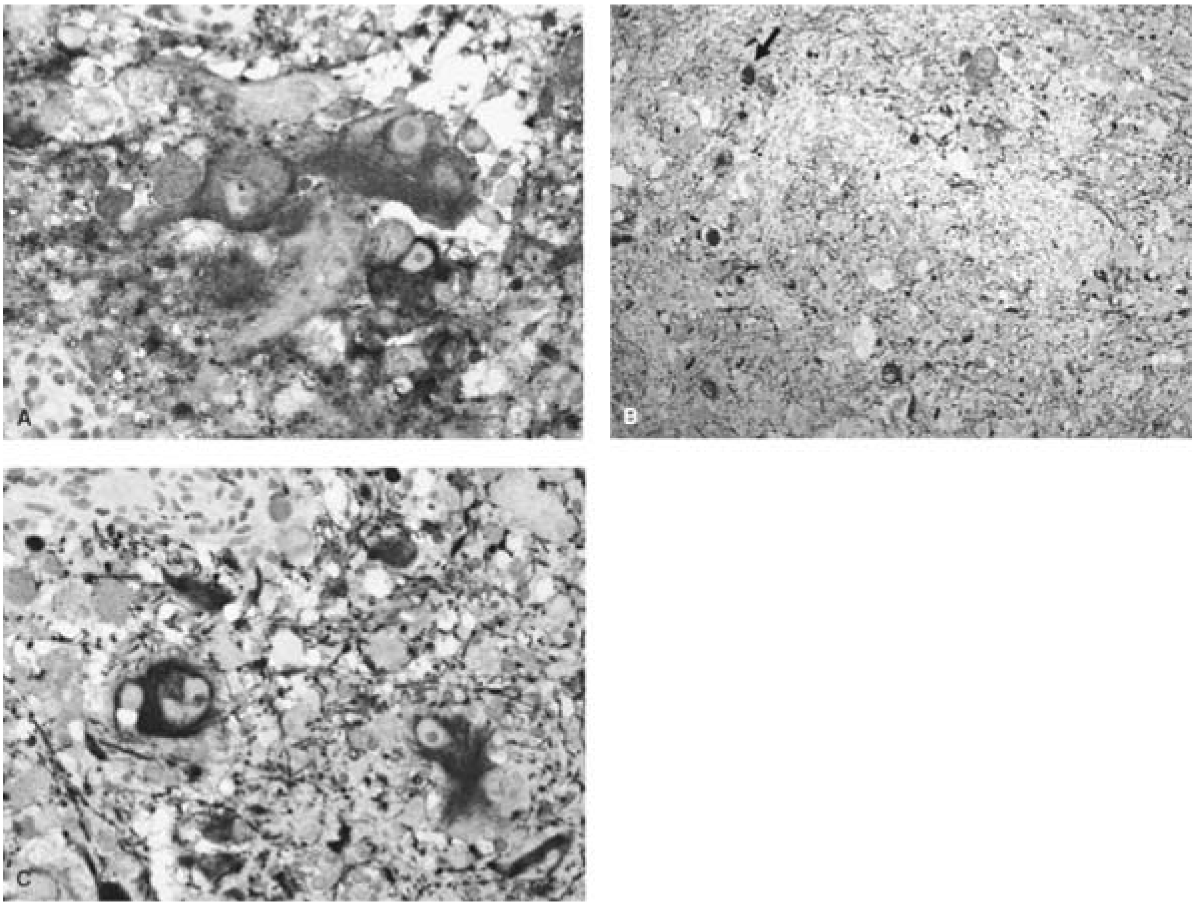

FIGURE 4. Immunohistochemical features of ganglioglioma. Panel **A** shows a section immunostained with antisynaptophysin, whereas panels **B** and **C** show sections immunostained with primary antibodies to neurofilament. All antibodies â€œdecorateâ€ atypical and dysmorphic neurons; antineurofilament also highlights neuronal processes throughout the field. (See the color insert.)

GGs are characterized by an admixture of neoplastic glial elements and atypical and disorganized neuronal (ganglion) cells (Figs. 2 and 3), sometimes including binucleate or multinucleate forms and ganglion cells with dysmorphic nuclei. (A rare variant of this tumor is composed exclusively of atypical neurons, and thus more appropriately described as a gangliocytoma.) Gliosis and calcification are common in and around the neoplasm, as are cytoid bodies.[112] The greatest challenge to the surgical neuropathologist is to distinguish ganglioglioma from an infiltrating glial neoplasm that extends into normal cortex; in the latter situation, neurons retain their distinctly characteristic cytologic and nuclear features. (This differential diagnosis may be extremely problematic, even impossible, at the time of frozen section/intraoperative consultation.) Most GGs are WHO grade I or II, the difference between these two grades being highly subjective, though such tumors are characterized by a relatively uniform glial component and the absence of mitoses. The glial element within the tumor may include elongated bipolar cells, typical gemistocytes, and sometimes even foci resembling oligodendroglioma. With increasing cytologic atypia and mitotic activity (usually in the glial component), the tumor grade increases to III; rarely, an otherwise typical glioblastoma (WHO grade IV) has a significant neuronal component and is thus presumed to have originated from a GG. Regions of cortex adjacent to a GG may show clear evidence

of cortical dysplasia,[40,117] and these tumors frequently extend into the subarachnoid space (Fig. 3).

Immunohistochemistry with antibodies to CD34 and MAP2 may further help to distinguish between dysplastic/neoplastic ganglion cells and entrapped normal neurons.[21,22,24,112,136] As expected, the glial element within a GG is usually glial fibrillary acidic protein (GFAP) immunoreactive (though only rarely is this immunoreactivity uniform throughout the neoplasm), while the ganglionic/neuronal component is immunoreactive with antibodies to neurofilament and synaptic proteins, especially synaptophysin (Fig. 4).[112] Synaptophysin immuno-stains often show a pattern of punctate immunoreactivity along ganglion cell membranes. Given the appearances of GGs, it is tempting to speculate that atypical neuronal cells within the tumors are â€œgeneratingâ€ epileptic seizure activity; however, the authors are aware of no good electrophysiologic evidence for this. There is a relative paucity of molecular genetic data on these tumors, though they frequently show polymorphisms (but not mutations) of the genes associated with tuberous sclerosis complex (*TSC1* and *TSC2*). Ultrastructural examination of GGs, which is seldom necessary to confirm the diagnosis, shows cytoplasmic dense core vesicles (usually 125 to 180 nm in diameter) and occasional synapselike contacts between cells, the latter probably an explanation for the distinctive membranous punctate synaptophysin immunoreactivity that is a â€œsignatureâ€ of GG, though also seen in other CNS lesions, including cortical dysplasia and the cortical tubers of tuberous sclerosis. Recent immunocytochemical and immunoblot investigations have found prominent neuronal expression of multidrug transporter proteins, including multidrug resistanceâ€“associated protein 1 (MRP1) and P-glycoprotein, in both gangliogliomas and cortical dysplasia. Major vault protein (MVP), which may also play a role in multidrug resistance, was found to be prominently expressed in GG.[7,9] One obvious implication of such studies is that overexpression of molecules related to multidrug resistance may contribute to

the intractability of tumor-related seizures. GGs and dysembryoplastic neuroepithelial tumors (see below) also contain a significant complement of microgliaâ€”their density correlating with duration of a given epilepsy as well as with seizure frequency prior to tumor resectionâ€”suggesting a functional relationship to the seizure-causing lesion, though of unclear causal significance.[8] Expression of survivin, an antiapoptotic protein, has been detected in the astrocytic component of GGsâ€”expression in more than 5% of cells being associated with more aggressive tumor behavior.[143] Reelin pathway components *disabled-1* and *p35* have been examined using molecular techniques in GGs and were found to contain no mutations, although the relevant gene transcripts were seen in lower levels in GGs than controls.[83] Immunolaser microdissection together with in situ reverse transcription and real-time polymerase chain reaction (RT-PCR) methodology has been used to study neuronal elements within GGs. The rather straightforward conclusion reached (that GGs contain neuronal elements with compromised or atypical differentiation) is perhaps less important than the compelling evidence that such technology can be used to study epilepsy-associated tumors and malformative lesions in exquisite molecular detail.[62]

GGs are relatively uncommon tumors in children, in whom they are also most frequently encountered in a supratentorial location, usually in the temporal lobes.[67] A variant of GG with associated dense desmoplasia, appropriately termed *desmoplastic ganglioglioma (DIG)*, has been described in infants and children.[35,125] Rarely, as with almost any other neoplasm that usually behaves in an indolent fashion, an otherwise typical example of GG shows malignant â€œdegeneration,â€ with the neoplastic transformation affecting both the glial and neuronal components or the glial component alone.[2,22,112] On rare occasions, GG may evolve into glioblastoma.[89] However, the vast majority of GGs are benign, with only a 3% recurrence rate, 2% malignant progression, and 1% death according to one series of 184 patients with a median follow-up period of 8 years.[105]

Dysembryoplastic Neuroepithelial Tumors

This category of neoplasm, identified and defined <20 years ago,[44,45,112] shows extremely indolent behavior and a very strong association with epilepsy. Dysembryoplastic neuroepithelial tumors (DNETs) almost always occur in association with partial seizures that start before the age of 20 years, often with no associated neurologic deficit or evidence for a neurocutaneous disorder/phakomatosis. Neoplasms that would now probably be classified as DNETs were described by other names in earlier reports.[112] Even though represented disproportionately in epilepsy surgery centers, they constitute just over 1% of CNS neuroepithelial tumors in those under 20 years of age, and only about 0.2% of such lesions in older patients. Large series show a slightly higher incidence of DNETs in men than in women. On gross inspection, DNETs give the appearance of â€œmucoid nodules situated within an expanded cortical ribbon.â€[112] Histologically, the tumors are characterized by (a) cortical location (most often in the temporal lobes, though DNETs have been reported in virtually all regions of the central neuraxis); (b) multinodular architecture, the nodules showing astrocytic, oligoastrocytic, or pure oligodendroglial differentiation with admixed normal-appearing neurons and astrocytes (Fig. 5); (c) foci of (nearby) cortical disorganization/dysplasia; (d) a glioneuronal element showing a columnar or alveolar structure perpendicular to the cortical surface; and (e) a characteristic appearance of neurons that appear to be floating or suspended within the myxoid matrix of the tumor.

â€œSimpleâ€ and â€œcomplexâ€ forms of the tumor have been defined, the latter characterized by zones almost identical to pilocytic or fibrillary astrocytoma or oligoastrocytoma. DNETs may show nuclear atypia (among the glial element) and infrequent mitoses, although of interest is the finding in some laboratories that markers of cell proliferation can label a high proportion of cells in some regions of the tumor, a surprising observation in view of the widely held view that these mass lesions may be more akin to malformations/hamartomas than true neoplasms. They are almost always considered to be WHO grade I tumors. DNETs have slow growth, as reflected in low labeling indices for the proliferating cell marker MIB-1 (Ki-67). Neuronal cells within DNETs have been shown to be immunolabeled with antibodies to a developmentally regulated embryonal form of the neural cell adhesion molecule (E-NCAM).[179] Not surprisingly, DNETs can also be immunolabeled with GFAP and a variety of neuronal markers, including *Î²*-tubulin, microtubule-associated protein-2 (MAP-2), phosphorylated and nonphosphorylated neurofilament, NeuN neuronal nuclear protein, synaptophysin, and myelin oligodendrocyte glycoprotein, among others.[72,112] There is an excellent chance of complete freedom from seizures with total removal of a DNET.[36,44,45,112,122] Just as with GGs (see above), the â€œepileptogenicityâ€ of DNETs may result from foci of cortical dysplasia *adjacent to* the neoplasm, rather than the tumor itselfâ€"which has obvious implications for its definitive surgical treatment, ascertainment of â€œtumor-freeâ€ resection margins, etc.[145,161]

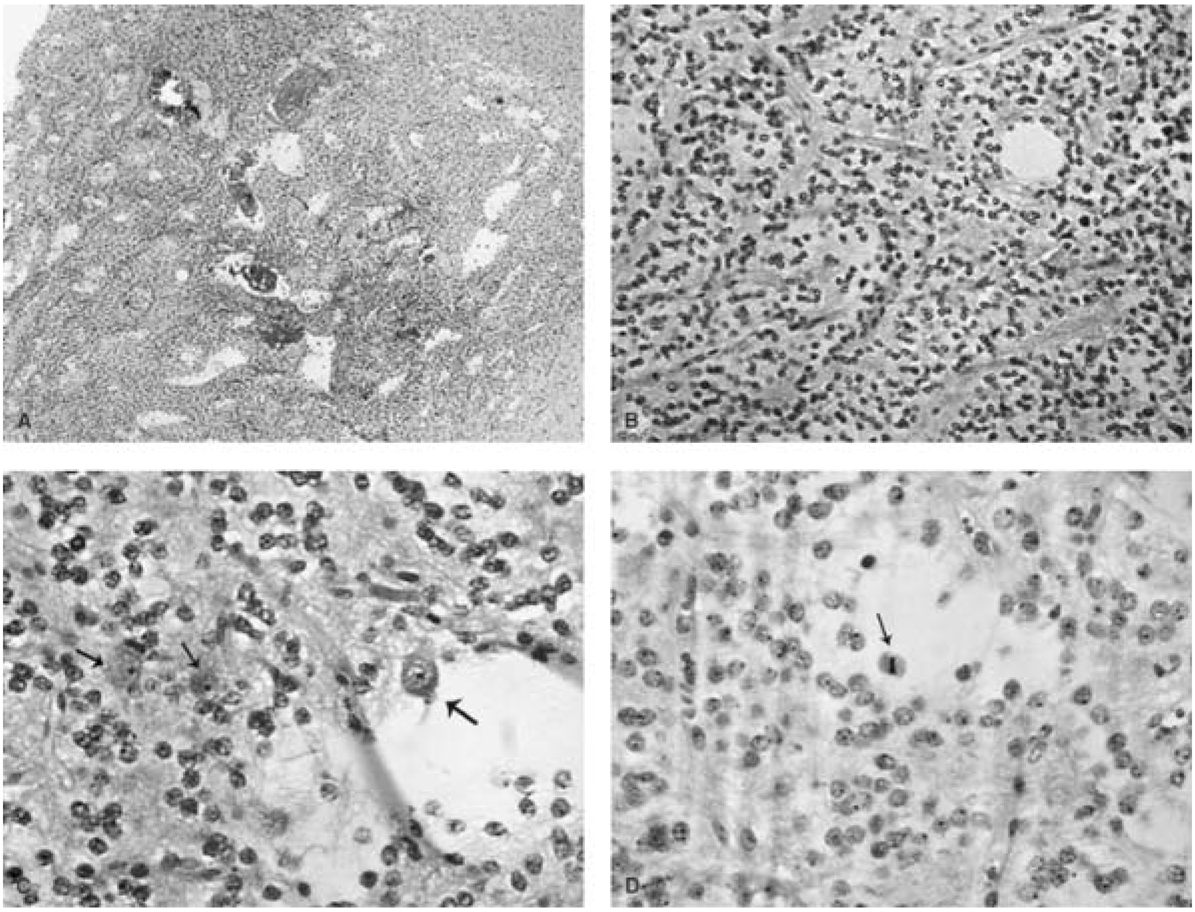

FIGURE 5. Dysembryoplastic neuroepithelial tumor. **A,B.** Representative fields in the tumor show sheets of relatively uniform round, oligodendroglia-like cells with compact nuclei and microcystic spaces. Panel **C** shows cells with distinctly neuronal phenotype (*arrows*). Neuron at right of this panel appears to be â€œsuspendedâ€ in a vaguely mucoid matrix. Panel **D** shows a mitotic figure (*arrow*), an unusual feature in this neoplasm. (All sections stained with hematoxylin & eosin.) (See the color insert.)

Pleomorphic Xanthoastrocytoma

Pleomorphic xanthoastrocytoma (PXA), initially defined and characterized by Kepes in the early 1970s,[86,87] usually appears as a superficially growing lesion with a meningeal component in young people (*meningocortical* PXA); presentation is usually before the age of 30 years, although as with most tumors, â€œoutlierâ€ examples have been encountered in older patients. PXA occurs with equal frequency in male and female patients.[47,112] Ten of 47 patients documented in a review of the literature[119] died at a mean of 7.5 years after diagnosis. A longstanding (mean, 4 years; range, 3 months to 16 years) history of seizures is found in almost 80% of affected patients.[80] Almost one third of tumors recur following initial resection, but a 70% 10-year survival rate compares favorably with that of glioblastoma. The tumor may arise from subpial astrocytes and shows novel histopathologic features (Fig. 6): A prominent xanthomatous or foam cell component, bizarre nuclear atypia and pleomorphism with a relative paucity of mitotic figures and regions of necrosis, and frequent mononuclear inflammatory infiltrates. Some who describe this neoplasm comment on its biphasic appearance, one â€œphaseâ€ including compact spindle-shaped cells in a fascicular pattern, the other composed of large eosinophilic astrocyte-like cells (sometimes multinucleated) containing foamy cytoplasm.[112]

Special stains and immunohistochemistry demonstrate that many of the cells in a PXA are immunoreactive with anti-GFAP (Fig. 7) antibodies and have a rich reticulin network among nests of tumor cells or surrounding individual tumor cells. In addition, almost 75% of tumor specimens can be labeled with antibodies against the CD34 epitope.[140] A difficult differential diagnosis may be between gigantocellular glioblastoma and PXA; immunohistochemical approaches to making this distinction have been suggested (e.g., using antibodies to different neuronal antigens).[109] A rare â€œpigmentedâ€ variant of PXA has been described.[153] Although PXA is graded as WHO II, it is recognized that anaplastic transformation may occur if there are more than five mitoses per ten high-power fields found on microscopic examinationâ€”these tumors are sometimes described as â€œ*pleomorphic* xanthoastrocytoma with *anaplastic* featuresâ€ (which seems oddly redundant) and designated WHO grade III[112]

Novel, Rare and â€œEmergingâ€ Tumor Entities

An isomorphic variant of diffuse astrocytomas has been identified from a series of 207 long-term epilepsy-associated tumors (LEATs).[23,150] These tumors can occur in different lobes, including a temporal location; diffusely infiltrate the neocortex; and express GFAP. In contrast to ordinary astrocytomas, neither MAP2 nor p53 are expressed within them and the proliferative activity is very low (Ki-67 labeling index usually <1%). By use of Kaplan-Meier curves, this isomorphic subtype had 50% fewer recurrences at 7.5 years and an estimated long-term survival of 80%. Temporal location did not influence the outcome, and the presence of epilepsy per se in affected patients was also not a prognostic factor.

A novel epilepsy-related clinicopathologic entity was recently designated as angiocentric neuroepithelial tumor (ANET).[98,174] Neuropathologic hallmarks of ANETs include an angiocentric polarity with GFAP-positive fusiform and bipolar astrocytic cells arranged around blood vessels. There is also a neuronal component, which may be best visualized using immunohistochemical markers for synaptophysin, chromogranin, or neurofilament protein. An ependymal component may also be present (expressing epithelial membrane antigen [EMA] immunoreactivity) and most tumors show stalk-like extensions to the ventricle on MRI.

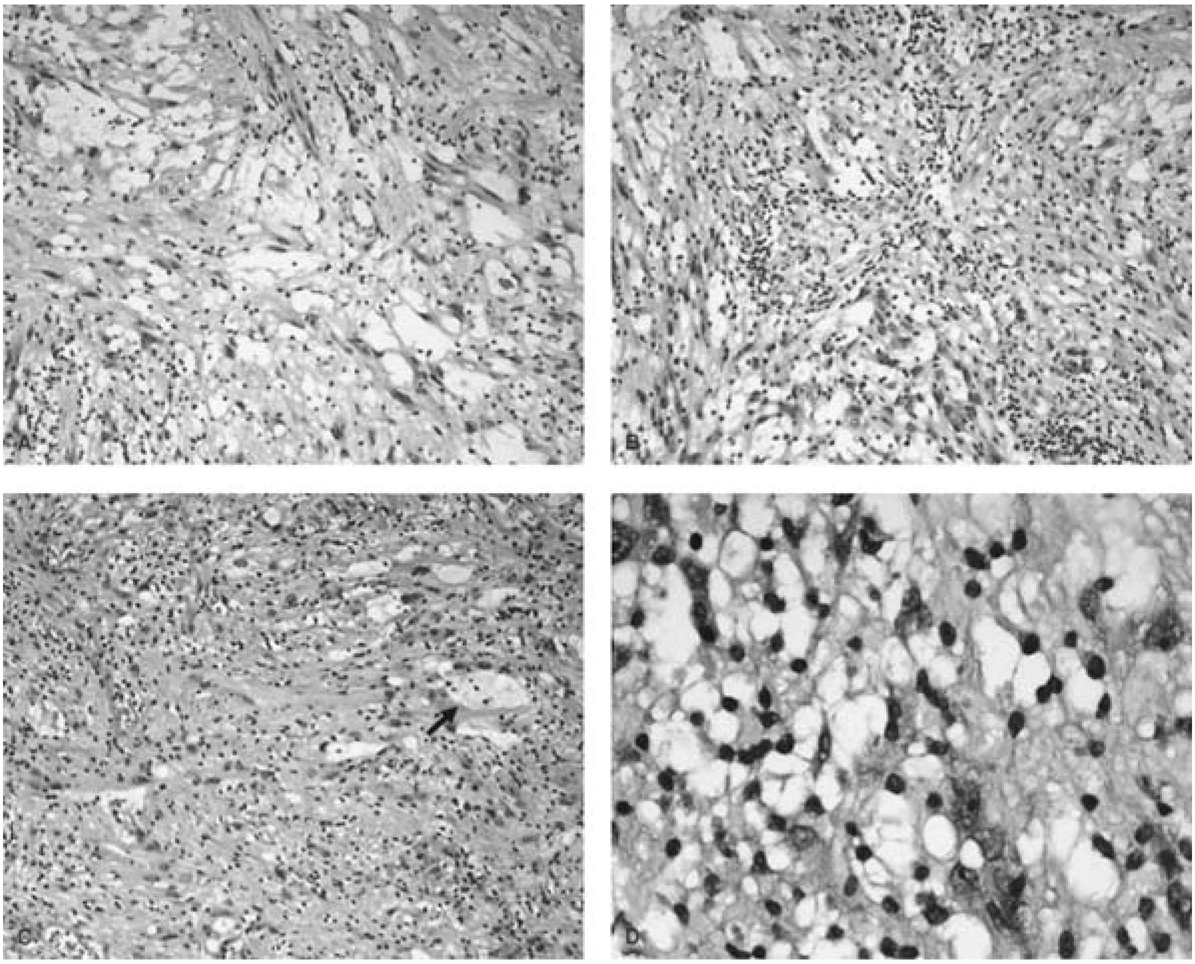

FIGURE 6. Pleomorphic xanthoastrocytoma. All panels (from hematoxylin & eosinâ€“stained sections) show a pleomorphic neoplasm composed of spindled or compact cytoplasmic elements. Panel **B** shows a sparse lymphoid infiltrate, a common finding in this tumor. Xanthomatous or foamy cells sometimes aggregate into small groups (*arrow* in panel **C**). Cells with foamy, clear, and multiloculated cytoplasm and pleomorphic nuclei are highlighted in panel **D**. Despite this, mitoses are relatively rare in this tumor. (See the color insert.)

In considering LEAT, ANET, and other â€œnewâ€ tumors, there has been an unfortunate and disorienting tendency to â€œre-reviewâ€ clinicopathologic material and to redefine tumor entities, including those associated with epilepsy.[32] For example, DNETs would in most instances have simply been described as astrocytomas, oligoastrocytomas (mixed gliomas), or gliomas before the â€œbirthâ€ of this new entityâ€”the nosology of which, however, is now widely accepted. This means that earlier series describing tumor-associated epilepsy or epilepsy-associated tumors need to be re-evaluated in light of the newly evolving tumor nomenclature, which perhaps has created some confusion and an implicit tendency to discount older studies of epilepsy-associated CNS neoplasms, but has led to a more realistic appreciation of the neurobiology of tumors that cause (or are often associated with) seizures.

Meningioangiomatosis (MA), a rare entity, deserves mention because of its strong association with intractable epilepsy and its unique nosologyâ€”understanding MA involves the combined study of neurogenetics and vascular, malformative, and neoplastic diseases of the CNS.[69] This lesion often occurs with

neurofibromatosis type 2 (NF2) and usually presents before the age of 20 years with headache and intractable seizures. Grossly, the lesions appear as plaque-like structures overlying the cortex, single in sporadic examples but often multiple when present in the context of NF2. Neuropathologic features in a resection specimen include disorganized and gliotic islands of neuroglial tissue surrounding thickened, sclerotic, and focally calcified blood vessels, which may in turn contain meningothelial elements in their wallsâ€"psammoma body-like structures may be present in the adjacent brain, which may also harbor an overlying meningioma (Fig. 8).

Brain Inflammation and Epilepsy

One of the most common â€œinflammatoryâ€ lesions encountered in corticectomies (including temporal lobectomies) for epilepsy is the chronic inflammatory reaction (often with a pronounced granulomatous component) that is left by depth electrodes implanted for preoperative monitoring purposes within the brain parenchyma. Leaving aside the obvious fact that any inflammatory disorder of the brain (especially viral encephalitides, e.g., caused by herpes simplex or West Nile virus infection) may be accompanied by seizure activity, evidence is emerging of an increasingly important role for brain inflammation in epilepsy (see Chapter 25). Steroids and adrenocorticotropic hormone (ACTH) have powerful anticonvulsant effects, especially in children with infantile spasms or West syndrome. Seizure activity is regularly associated with a cerebrospinal fluid (CSF) pleocytosis and elevated CSF proinflammatory cytokines. Though controversial, evidence is emerging that patients who develop temporal lobe epilepsy with hippocampal sclerosis (TLE-HS) following febrile convulsions may have been at risk for developing TLE-HS because of polymorphisms in the interleukin (IL)-1Î²-511T allele.[84] Studies of temporal lobes resected from patients with temporal lobe epilepsy have demonstrated overexpression of NFÎºB, a transcription factor involved in acute inflammation.[39] There is indirect evidence that new-onset refractory status epilepticus (NORSE) may have an inflammatory basis in that many patients have an antecedent

inflammatory/infectious illness and CSF usually shows a pleocytosis.[177] A subgroup of patients with encephalitis may go on to develop postencephalitic catastrophic epilepsy with progressive brain atrophy due to persistence of the inflammatory process.[11,169]

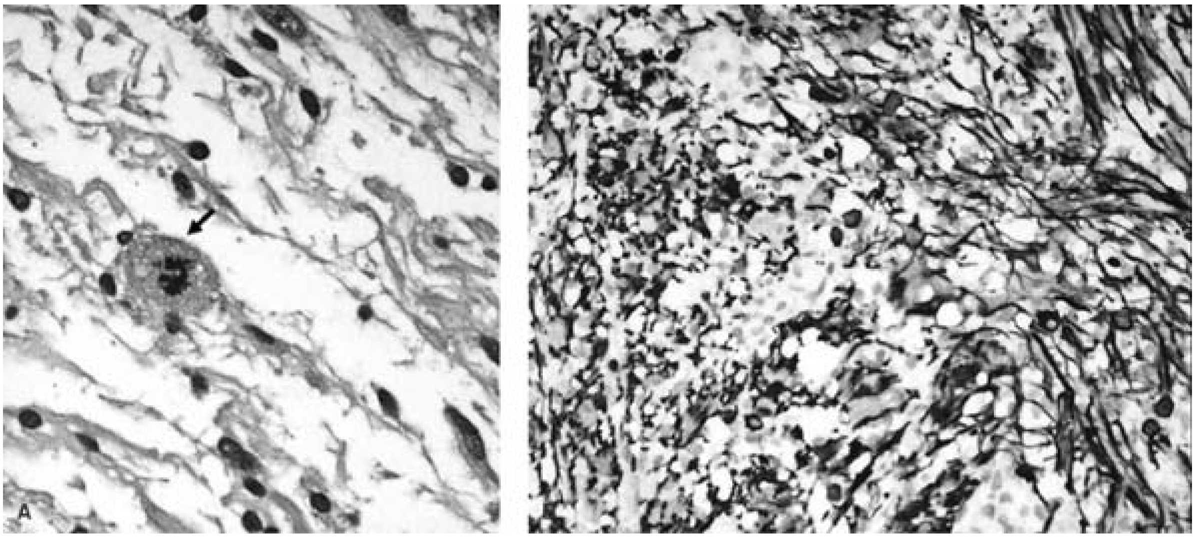

FIGURE 7. Pleomorphic xanthoastrocytoma (PXA). **A.** Atypical mitosis, a relatively rare finding in most PXAs (Hematoxylin & eosinâ€"stained section.) **B.** Glial fibrillary acidic proteinâ€"immunostained section shows prominent cytoplasmic immunoreactivity. (See the color insert.)

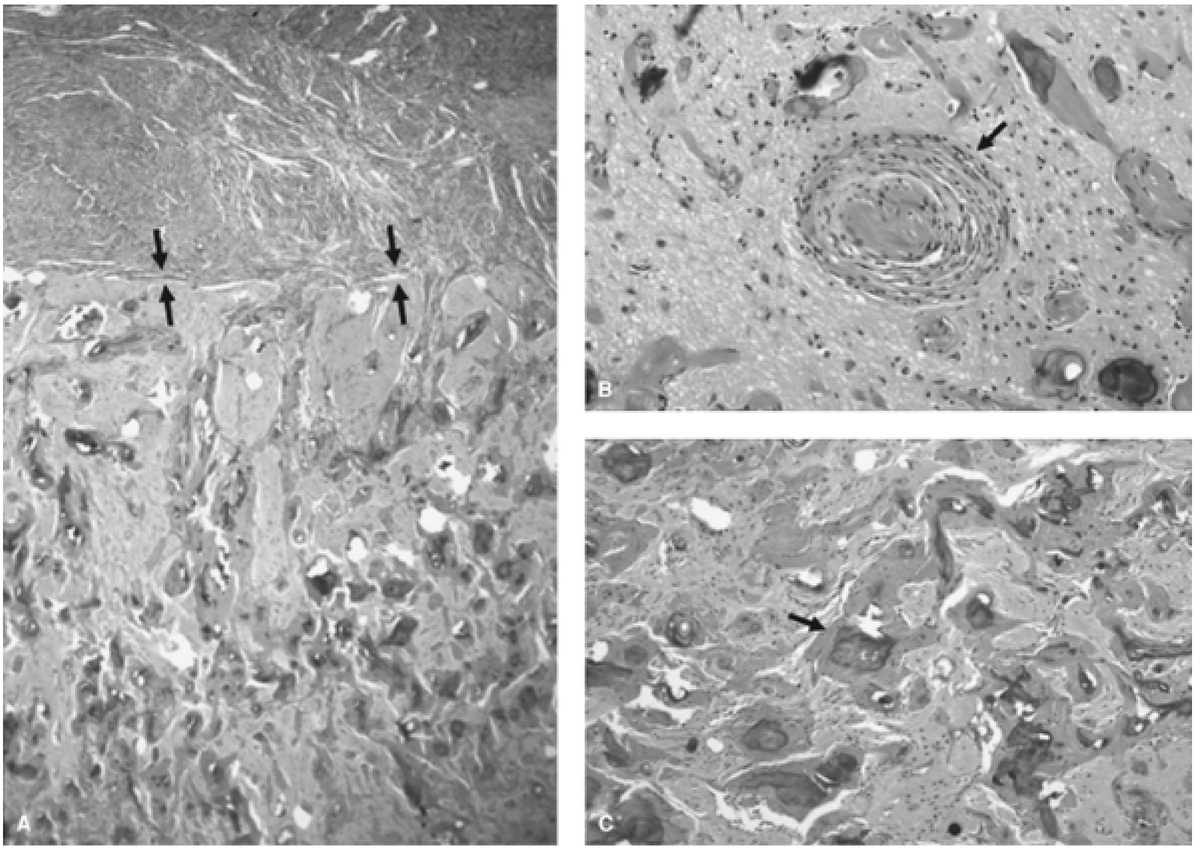

FIGURE 8. Meningioangiomatosis, with overlying meningioma. **A.** *Arrows* indicate the interface between brain parenchyma (lower portion of the image) and meningioma (above). The brain parenchyma shows thickened, focally calcified blood vessels surrounding islands of disorganized neuroglial tissue. Details of the parenchymal abnormality are seen in panel **C**; *arrow* (in C) highlights a region of dystrophic calcification. Panel **B** shows a thrombosed thickened artery (*arrow*) with prominent smooth muscle cell hyperplasia in its wall. (All sections stained with hematoxylin & eosin.) (See the color insert.)

Table 2 Rasmussen Syndrome: Diagnostic Criteria

Rasmussen encephalitis (RE) can be diagnosed if either all three criteria of Part A or two out of three criteria of Part B are present. Check first for the features of Part A, then, if these are not fulfilled, of Part B.

PART A:

1. Clinical focal seizures (with or without epilepsia partialis continua) and unilateral cortical deficit(s)
2. Electroencephalographic (EEG) unihemispheric slowing with or without epileptiform activity and unilateral seizure onset
3. Magnetic resonance imaging (MRI) unihemispheric focal cortical atrophy and at least one of the following:

   a. Gray or white matter T2/fluid-attenuated inversion recovery (FLAIR) hyperintense signal
   b. Hyperintense signal or atrophy of the ipsilateral caudate head

PART B:

1. Clinical epilepsia partialis continua or progressive* unilateral cortical deficit(s)
2. MRI progressive* unihemispheric focal cortical atrophy
3. Histopathology T-cell-dominated encephalitis with activated microglial cells (typically but not necessarily forming nodules) and reactive astrogliosis

Numerous parenchymal macrophages, B cells, or plasma cells or viral inclusion bodies exclude the diagnosis of RE.

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* â€œProgressiveâ€ means that at least two sequential clinical examinations or MRI studies are required to meet the respective criteria. To indicate clinical progression, each of these examinations must document a neurologic deficit, and this must increase over time. To indicate progressive hemiatrophy, each MRI must show hemiatrophy, and this must increase over time (Reproduced with permission from Bien CG, Granata T, Antozzi C, et al. Pathogenesis, diagnosis and treatment of Rasmussen encephalitis: a European consensus statement. *Brain.* 2005;128:454-471.)

Rasmussen Syndrome

Rasmussen syndrome (RS; Rasmussen encephalitis [RE]), the classic form of epilepsy-associated chronic inflammatory disorder, is characterized by intractable focal seizures (usually epilepsia partialis continua [EPC]) with progressive hemiparesis, both attributed to chronic pathogen-free inflammation of gray and white matter, with progression to unihemispheric atrophy.[137,138,141] A recent European consensus meeting on RS has formulated diagnostic criteria, which incorporate clinical, electroencephalographic (EEG), MR, and pathologic findings[19] (see Table 2). The cause of RS remains a mystery. Although the pathologic appearances of affected brain tissue suggest a chronic viral infection, no such virus has ever been consistently isolated from RS brain tissue or discovered within it using modern molecular techniques (e.g., PCR).[59,173] Circulating anti-glu-R3 antibodies were reported to be of etiologic importance in some patients with RS,[5,142] but subsequently these antibodies were found to also occur in other seizure disorders.[107,176] Furthermore, it has never been possible to passively transfer RS to animals using glu-R3 antibodies. Very recently, autoantibodies against the NMDA glutamate receptor (NMDA-type GluR) Îµ2 subunit and its epitopes were reported in RS patients.[162] However, although the initial report is highly promising, the diagnostic specificity of GluRÎµ2 for RS remains to be confirmed. Any explanation for RS will ultimately have to account for the unihemispheric nature of the disorder. Rarely have pathologic studies demonstrated bihemispheric involvement.[168]

Neuropathologic Findings

The neuropathology of RS is said to comprise four merging stages,[19,20,129] the earliest of which is characterized by inflammation, especially perivascular lymphocytes, and microglial nodule formation within brain parenchyma, but little morphologic evidence of neuronal injury. In stage 2, lymphocytic infiltration increases in density and both astrocytes and microglial cells become more extensive in distribution, tending to involve all cortical layersâ€”a so-called â€œpanlaminarâ€ pattern of cortical inflammation and gliosis. Patchy neuronal loss may be present. In stage 3 the neuronal population is depleted either patchily or in a panlaminar pattern, with severe cortical degeneration and gliosis. In stage 4 there is profound cortical atrophy with gliosis and vacuolation of the neuropil, rising to the level of cavitation in many cases (Figs. 9 and 10). Frequently, areas of relative cortical normality surround zones of atrophic cortex. This geographically defined severe pathologic change, often seen a few micrometers away from relatively (or entirely!) normal brain parenchyma, means that a negative brain biopsy taken with the intent of establishing the diagnosis of RE never truly *excludes* the diagnosis, because of the risk of sampling an unaffected region in a cerebral hemisphere that actually harbors RS. Occasionally, dual pathology including malformative elements of cortical dysplasia or vascular malformations *and* chronic inflammation are seen in a corticectomy originating from an epilepsy patient, suggesting that the two lesions may be etiologically connected, though the precise *mechanism* of this linkage remains speculative.[73]

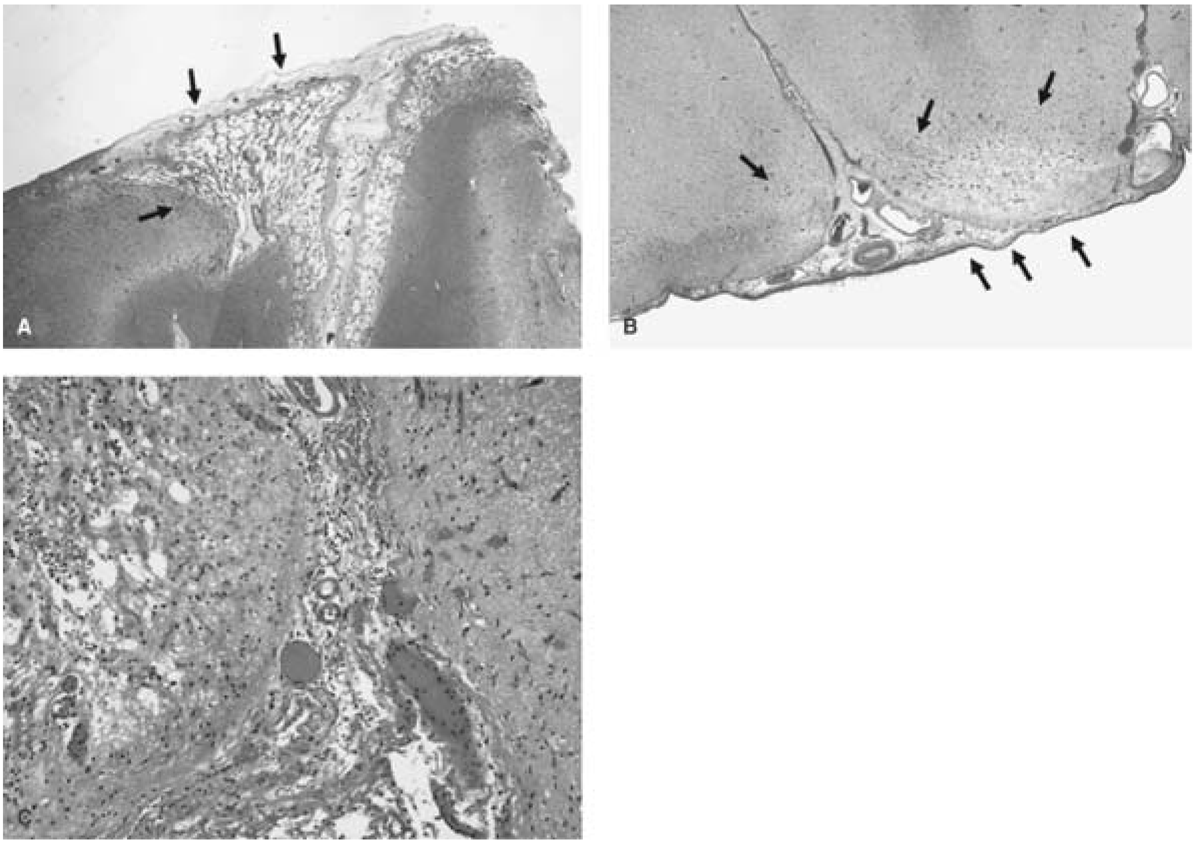

FIGURE 9. Rasmussen encephalitis (RE). Panel **A** shows extensive cortical cavitation, in one region affecting an entire gyrus (*arrows*). Panel **B** shows a more circumscribed region of cortical injury showing faint cystic cavitation, delineated by the *arrows*. Panel **C** shows detail of the region of microvacuolization, with intense astrocytic gliosis. (All panels are from sections stained with hematoxylin & eosin.) (See the color insert.)

There is little interlobar variation in severity of the disease, though usually the occipital cortex is less severely involved than

the others. Subcortical white matter may show evidence of axonal injury in the form of neuroaxonal spheroids, though whether this is secondary to Wallerian degeneration or represents a separate cytotoxic attack on axons is uncertain. Deep central gray matter may also be involved. Areas completely devoid of inflammation or neuronal loss may be located in close proximity to areas showing intense inflammation and cell loss. Furthermore, the inflammation/neuronal destruction varies in its *timing and progression* from area to area. Early changes consisting of inflammation only may be located adjacent to areas showing intense neuronal loss and gliosis. In this respect the regional variability in timing and intensity of inflammation is similar to other immune-mediated neurologic disorders of unknown etiology such as multiple sclerosis. However, the almost unique unilateral nature of RS separates it from all other immune-mediated disorders of the nervous system. Ultrastructural studies of RE/RS have failed to demonstrate viral particles consistently in brain biopsies/resections from affected patients, though rarely measles virus-like particles have been noted; rare cerebral endothelial cells in one case contained tubuloreticular inclusions of the type usually seen in skeletal muscle endothelium of patients with dermatomyositis.[130] Gene expression profiling of a brain specimen from an RE patient has shown a dramatic *increase* in expression of several genes related to inflammation, and a pronounced *down-regulation* of several GluRs, especially GluR4.[16]

Immunopathology/Immunopathogenesis

The lymphocytic infiltrate in RS brain consists predominantly of CD8-positive T cells.[18,61] The lymphocytes lie adjacent to major histocompatibility complex (MHC) class I(+)â€“expressing neurons and contain granzyme B, which has been suggested as the local mediator of T-cellâ€“mediated cytotoxic neuronal death in RS.[18] There is little evidence to support a humoral process in that B cells, immunoglobulin, and complement are rarely found in RS brain tissue. The T-cell infiltrate is of relatively restricted clonality,[99] but as with oligoclonal bands in MS, this does not provide much enlightenment on possible or likely immunogenic stimuli that evoked the response in the first place.

As indicated above, the patchy nature of the inflammatory infiltrate in RS raises the possibility that brain biopsy, even in patients with relatively well-established disease, might yield a spuriously negative result. Therefore, the recently formulated diagnostic criteria for RE,[19] which include clinical and neuroimaging considerations, are a welcome addition; adherence to these criteria may obviate the need for brain biopsy in future. However, the validity of the criteria awaits testing in prospective studies.

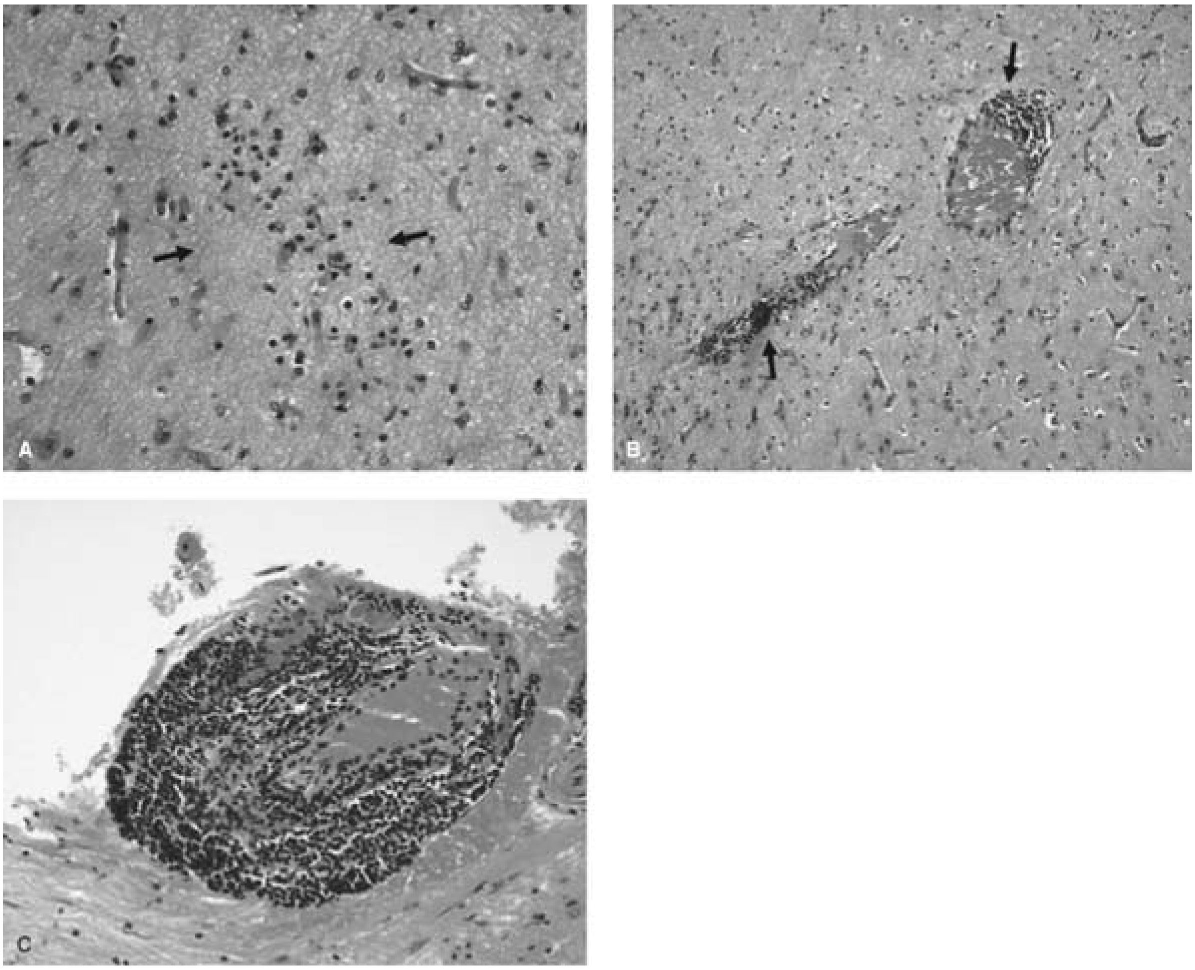

FIGURE 10. Rasmussen encephalitis/Rasmussen syndrome. **A.** *Arrows* indicate a poorly defined

inflammatory/microglial nodule. **B.** Prominent angiocentric chronic inflammation in a region of brain with slight rarefaction and gliosis. Notice patchy nature of the inflammatory infiltrate. **C.** A meningeal vein showing dense transmural lymphocytic infiltrate *without* evidence of injury of the vessel wall or thrombus. (All panels are from sections stained with hematoxylin & eosin.) (See the color insert.)

Treatment

Hemispherectomy remains the mainstay of RS treatment. Decisions to offer hemispherectomy are based on the patient's age; involvement of dominant hemisphere; severity of motor and speech deficits at the time of presentation; and the severity of seizures. The primary goal is to minimize seizure frequency and severity and, where possible, to preserve motor and language functions. In many cases this goal is not obtainable. Paradoxically, seizure activity may subside spontaneously in the later stages of the illness. A therapeutic algorithm is included in the

consensus report on RE/RS.[19] To date, trials of treatment have not taken place and most outcome reports are anecdotal. Individualized treatments carefully chosen on the basis of patient's age, neurologic deficit, seizure frequency, and phase of the illness will remain the basis for management in the immediate future. Carefully designed multicenter trials will almost certainly be essential to establish optimal therapeutic guidelines for this rare disorder.

It has been suggested that the unilaterality of RE may in part be due to a synergy between seizures and the underlying inflammatory process.[19] However, other brain lesions that give rise to intractable partial epilepsy generally do not show inflammatory changes similar to those seen in RE, so it is difficult to argue that the inflammatory changes are a secondary phenomenon, although we have seen rare cases in which cortical dysplasia is accompanied by focally prominent chronic inflammation, prompting consideration of â€œdual pathologyâ€ (malformative and inflammatory) in these individuals. Also, in our experience, some patients with fatal classic RS may be found at autopsy to have little or no evidence of an underlying inflammatory process, showing instead intense gliosis Â± atrophy, restricted to one cerebral hemisphere. These cases are particularly difficult to understand. While the inflammatory process may have burned itself out by the time of death, the possibility remains that these unusual cases represent another disease process.

Recent insights into possible mechanisms of virally triggered immune-mediated encephalitis may go some way toward explaining RE/RS. Neonatal mice eliminate lymphocytic choriomeningitis virus (LCMV) from all tissues except the brain, where the virus persists for several years. These viral-rich neurones remain in perfect harmony with virus-specific cytotoxic T cells. Later, following exposure in adulthood to wild-type LCMV (the precipitating virus), cytotoxic T cells are triggered to attack mouse brain, causing an encephalitis similar in many respects to that seen in adult humans with RE. Infiltrating T cells exhibit biased receptor usage highly suggestive of an antigen-specific process.[115]

Destructive Lesions

Destructive lesions, with the appearance of regions of cystic encephalomalacia, are commonly encountered in corticectomies for epilepsy, especially in infants and children.[60,172] They are presumed to represent sequelae of intrauterine, perinatal, or (rarely) postnatal brain infarcts and/or hemorrhages, the etiology of which is multifactorial, extremely complex, and beyond the scope of this chapter. For an excellent recent monograph on pathophysiologic mechanisms important in the evolution of destructive brain lesions that may cause seizures, see reference 69.

Summary and Conclusions

Neuropathology has made vital contributions to understanding morphologic substrates of seizure disorders. This has rarely, however, been done in isolationâ€"simple morphologic characterization of *epileptogenic* lesions has finite value. Rather, important advances have resulted from synergistic interactions between neuropathologists and their clinical colleagues, electrophysiologists, and (especially in recent years) neuroradiologists. The combined multidisciplinary approach to analysis of complex lesions is illuminating. Indeed, one of the great challenges going forward will be to closely compare neurohistologic findings in *epileptogenic tissue* with its appearances assessed using (preoperative) high-resolution and metabolic neuroimaging studies. Neurophysiologists will continue to provide important information on whether *structurally abnormal* tissue is also functioning in such a way as to produce abnormal discharges that may manifest as seizuresâ€"the *disconnect* between morphologic and functional abnormalities can often be striking and, paradoxically, informative. These correlations will be facilitated by new approaches to examining gene expression patterns in tissue, something that is now done almost routinely. High-throughput methodologies such as tissue microarray[118] will be useful for comparing signaling pathway regulation in vast numbers of (surgically resected) brain specimens. The novel properties of neoplasms that cause seizures (especially GGs and DNETs; see above) will be better understood through the same molecular genetic approaches that have yielded crucial dataâ€"ones that now greatly impact treatment strategiesâ€"on high-grade gliomas. Unlike the situation with high-grade gliomas, however, most tumors that cause seizures are cured by an operation. Rasmussen encephalitis remains, unfortunately, nearly as enigmatic as it was when first described almost 50 years ago. There is much work to be done!

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Chapter 13

Hippocampal Sclerosis

Gary W. Mathern

Charles L. Wilson

Heinz Beck

Introduction

Hippocampal sclerosis is the most frequent pathologic finding in patients with temporal lobe epilepsy undergoing resective neurosurgery, and its association with epilepsy has been recognized since the early 1800s. This chapter will focus on the following: The first section reviews the important historical literature to introduce the pathology and highlight some of the clinical controversies that often first arose years ago that are still argued about today.[189] The middle section describes in vivo electrophysiologic findings associated with hippocampal sclerosis, with special emphasis on newly identified fast ripples that may be a surrogate marker of epileptogenesis. The final section highlights recent molecular studies that are beginning to identify possible epileptogenic mechanisms in hippocampal sclerosis related to changes in synaptic circuits, postsynaptic receptors, and intrinsic membrane properties. Because of the extensive literature, this chapter emphasizes findings mainly from human studies. Relevant studies related to animal models of temporal lobe epilepsy can be found in Chapters 36 and 40 and in other texts.[163]

Early History and Histopathologic Description of Hippocampal Sclerosis

The literature describing the clinicopathologic relationship between seizures and hippocampal pathology spans more than 150 years. Early studies were limited to autopsy material and concentrated on determining if individuals with seizures of any type showed cerebral and hippocampal pathology. It was not until autopsy studies in the 1930s and correlative surgical-pathology studies in the 1960s that the mesial temporal lobe epilepsy syndrome was linked to severe neuronal loss in a characteristic pattern, referred to in this chapter as *hippocampal sclerosis*. This clinicopathologic association has been complicated by a literature that uses numerous names for the hippocampal pathology found in individuals with epilepsy. Understanding the historical use of these terms in the context of the different clinicopathologic studies is perhaps the best way to comprehend what constitutes hippocampal sclerosis and the relationship of this pathologic substrate with temporal lobe epilepsy.

Early autopsy studies frequently observed hippocampal damage in patients with different types of epilepsy. At first, the term *sclerosis* referred to the gross macroscopic features of a hard shrunken hippocampus, first described by Bouchet and Cazauvielh in 1825,[31] and in other autopsy studies of that era of individuals with chronic epilepsy.[141,160] Probably the first microscopic description of hippocampal sclerosis was by Sommer in 1880,[178] and his case study illustrates several important clinicopathologic features of temporal lobe epilepsy that are still relevant today. The patient was a 25-year-old man with what were described as two to six â€œpetit malâ€ attacks each day, and several â€œcompleteâ€ seizures each week. As part of his epileptic syndrome, he had vivid hallucinations in which God told him he could fly, and once, as proof of his belief, he jumped from a roof. He survived the fall only to die some years later of a systemic infection. Sommer observed that the only cerebral pathology found at autopsy involved the hippocampus, and using a microscope he noted a unique pattern of neuron loss. Specifically, the pyramidal neurons of the Ammon horn were largely destroyed, especially in the portion of the hippocampus that Lorente de NÃ³[106] would later label as CA1 and prosubiculum. Neuron loss in CA1 is such a consistent finding in hippocampal sclerosis that this region is often referred to as the *Sommer sector* (see *SS* in Fig. 1B). Furthermore, Sommer described other hippocampal damage involving the granule cells and hilar neurons of the fascia dentate.

Sommer's other historical contribution, in addition to the earliest microscopic description, was his interpretation that there must be a pathologic relationship between hippocampal damage and clinical seizure symptoms. He reasoned that the hippocampus was probably the initial site for seizure generation involving a prodrome of abnormal sensory phenomena or illusions. This is probably the first time that hippocampal pathology was associated with clinical features of what would probably be recognized today as mesial temporal lobe epilepsy.

The other important historical figure of the 1800s was Bratz.[36] His contribution was a detailed histologic description of hippocampal sclerosis and the observation that not all seizure types were associated with hippocampal pathology. He reported pathologic findings in the brain from 50 autopsy specimens of patients with antemortem chronic seizures associated with various etiologies common in his day, such as syphilis and cysticercosis. Bratz found hippocampal sclerosis in 25 (50%) specimens. His 1899 microscopic observations were remarkably accurate, and neuropathologists today would use the same histopathologic criteria to define hippocampal sclerosis (Fig. 1). Bratz noted that there was severe pyramidal neuron loss and gliosis throughout the hippocampus, especially in the Sommer sector of the Ammon horn. In addition, he noted that subicular neurons were not as depleted and that a fairly sharp boundary separated the profound prosubiculum neuron loss from the relatively preserved subiculum (Fig. 1B, *dashed line*). Within the remainder of the hippocampus, there was a second area of severe damage involving neurons between the granule cell blades. This area, later termed the *end folium* by Margerison and Corsellis,[111] included the CA4 pyramids and hilar neurons as described by Lorente de NÃ³.[106] By comparison, fascia dentate granule cells were only partially destroyed. In contrast to the severe neuron loss in the Sommer sector and the end folium, pyramidal neurons in CA3 and, especially, CA2 seemed to be more â€œresistantâ€ to injury (therefore termed the *resistant sector*).

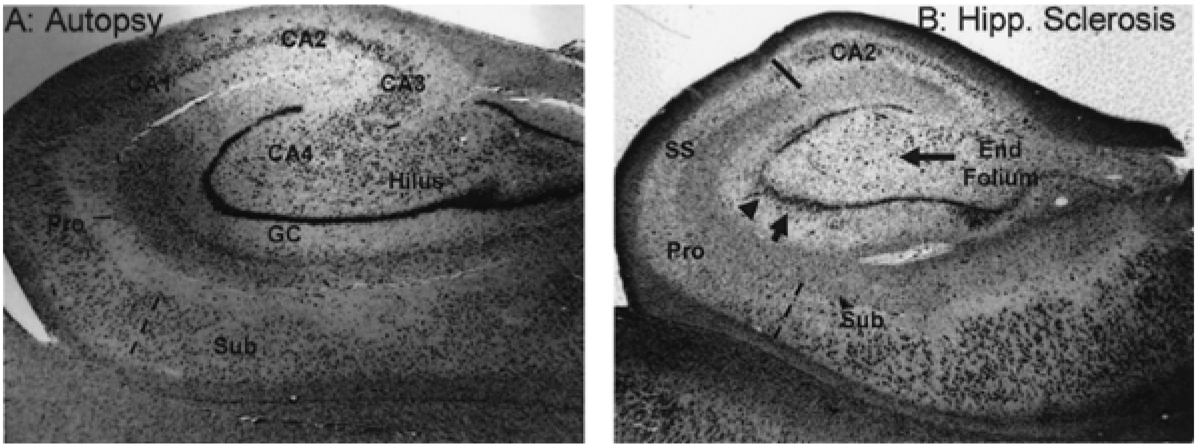


FIGURE 1. Examples of human hippocampus with Nissl staining, demonstrating normal appearance and hippocampal sclerosis. **A:** Normal autopsy. The hippocampal subfields are labeled using the nomenclature of Lorente de NÃ³ (1934) for fascia dentate granule cells (*GC*) and hilar neurons (*Hilus*). The four cornu ammonis subfields are labeled *CA1* to *CA4*, along with the prosubiculum (*Pro*) and subicular (*Sub*) neurons. The border between the prosubiculum and subiculum is identified by the *dashed line*. **B:** Hippocampal sclerosis. There is severe damage in the Sommer sector (*SS*; CA1 and prosubiculum; area between *solid* and *dashed lines*) and end folium (CA4 and hilus; *arrow*). The subiculum is spared and there is a relatively â€œresistantâ€ sector in CA2. Granule cells also show damage and dispersion (*arrowheads*).

Bratz's histopathologic description of hippocampal sclerosis is different from the hippocampal neuronal injury associated with other cerebral diseases. For example, neuron loss related to chronic liver disease or hypoxia-ischemia involves the entire hippocampus, including CA2, along with the subiculum and parahippocampal gyrus. Hence, neuron loss and gliosis by themselves are insufficient histopathologic criteria for the diagnosis of hippocampal sclerosis. This explains the confusion that has arisen from claims by some authors that hippocampal sclerosis can be found in conditions without seizures, such as Alzheimer disease.[1,84] Thus, the histopathologic diagnosis of *hippocampal sclerosis* should be restricted to specimens that display the microscopic pattern of selective neuron loss as originally described by Bratz.

Bratz also noted that the neuronal loss in hippocampal sclerosis appeared old and chronic. Because hippocampal sclerosis was found in only half of the autopsy specimens of patients with epilepsy, he reasoned that this pattern of damage was not the result of repeated seizures. Instead, he suggested that hippocampal sclerosis probably generated certain types of seizures, similar to the conclusion of Sommer.[178] Bratz's final contribution was his observation that many of the patients with hippocampal sclerosis had clinical histories involving early childhood convulsions. This finding would resurface about 60 years later in clinicopathologic studies of surgical patients with mesial temporal lobe epilepsy, and the nearly continuous debate since then about the pathogenesis of hippocampal sclerosis.

Clinicopathologic Studies of Patients with Temporal Lobe Epilepsy

The studies of the 1800s confirmed an association between seizures and hippocampal pathology, but the link between hippocampal sclerosis with psychomotor and complex partial temporal lobe seizures took several more decades to confirm. The clinical autopsy study of Stauder[187] was probably the first. He studied 53 patients with chronic epilepsy to determine whether hippocampal sclerosis was associated with those ictal symptoms and signs that he was convinced could only be attributed to temporal lobe seizures, such as olfactory and gustatory auras. Autopsy cases were separated into three clinical groups with definite, probable, or no ictal temporal lobe symptoms by clinical description. Of the 36 hippocampal sclerosis cases at autopsy, 33 (92%) had a history of definite or probable temporal lobe seizures. By contrast, of the 17 cases without sclerosis, only two (12%) showed only probable (not definite) temporal lobe seizure symptoms and 15 (88%) had none of his defined clinical signs. These results linked antemortem temporal lobe seizure symptoms with hippocampal sclerosis at autopsy.

In another famous autopsy study from the 1960s, Margerison and Corsellis[111] examined pathology results in 55 patients with epilepsy and found a clinicopathologic association between antemortem temporal lobe seizures using clinical and electroencephalogram (EEG) criteria and postmortem hippocampal sclerosis. This study is often cited in the literature, and the reader should be aware of this study's design, findings, and limitations. For example, their patient population is somewhat different than contemporary surgical case series of temporal lobe epilepsy patients. The patients resided in two long-term care hospitals in London because of severe mental and physical handicaps. Fifteen (27%) patients had chronic motor paralysis; in 17 (31%) the first habitual seizure was before the age of 1 year, and in 20 (36%) there were other cerebral cortical abnormalities such as congenital brain malformations, evidence of cerebral trauma, or old infections. Surgical patients with temporal lobe epilepsy typically have a lower incidence of paralysis and cerebral malformations, and the first habitual seizure usually begins around the age of 10 years.[114] Margerison and Corsellis found that most of their patients regularly experienced generalized convulsions and only a proportion of the time had temporal lobe seizures. Margerison used clinical characteristics (n = 26; 47%) or interictal scalp EEG (n = 33; 60%) to identify those cases that in addition to generalized seizures, also probably had temporal lobe convul-sions.

Table 1 Autopsy-based Comparison of Qualitative Hippocampal Pathology in Patients with Intractable Seizures, Including Temporal Lobe Epilepsy

Criteria	Typical hippocampal	End-folium sclerosis	No hippocampal

	sclerosis		pathology
Clinical			
TLE+ (n = 26)	15 (58%)	7 (27%)	4 (15%)
TLE- (n = 29)	7 (24%)	7 (24%)	15 (52%)
Interictal EEG			
TLF+ (n = 33)	19 (58%)	10 (30%)	4 (12%)
TLE- (n = 22)	3 (14%)	4 (18%)	15 (68%)

Clinical TLE+, patients with temporal lobe epilepsy based on clinical criteria; clinical TLE-, patients with typical seizures that, by the authorsâ€™ criteria, were not temporal lobe epilepsy TLE, were questionable, or were not known; TLF+, temporal lobe focus based on interictal electroencephalogram (EEG) criteria; TLE-, without temporal lobe focus based on interictal EEG criteria.

Modified from Margerison JH, Corsellis JA. Epilepsy and the temporal lobes. A clinical, electroencephalographic and neuropathological study of the brain in epilepsy, with particular reference to the temporal lobes. *Brain.*1966;89:499â€“530 (Fig. 12).

At autopsy, Corsellis defined two types of hippocampal damage. The first consisted of classic â€œAmmon horn sclerosisâ€ and the second was a new entity characterized by neuron loss limited only to the end folium. Corsellis introduced the term *hippocampal sclerosis* and defined it as an inclusive term that included both Ammon horn sclerosis and end folium sclerosis. (As a reminder, this chapter uses the term *hippocampal sclerosis* only to refer to what Corsellis considered classic *Ammon horn sclerosis*.) As shown in Table 1, hippocampal sclerosis (Ammon horn sclerosis) was found in 58% of autopsy specimens of patients with clinical or EEG criteria for temporal lobe seizures. By contrast, 60% of patients without clinical or EEG criteria for temporal lobe epilepsy had no hippocampal pathology (Chi-square; p <0.005). The incidence of end folium sclerosis averaged 25% for all patients with epilepsy, and was not associated with temporal lobe seizures (p <0.25). Hence, as in Stauder's 1936 study,[187] hippocampal sclerosis at autopsy was linked specifically to clinical and EEG characteristics of temporal lobe epilepsy. End folium sclerosis, however, was associated with repeated generalized seizures and was not a marker of temporal lobe epilepsy, as has been suggested by some authors.[177]

In addition to hippocampal neuron injury, Margerison and Corsellis found that there could be damage to other cerebral brain areas. For example, in their 22 cases of hippocampal sclerosis, additional damage was noted in the amygdala (64%), thalamus (50%), and neocortex (27%). Such findings are not limited to autopsy studies of patients with temporal lobe epilepsy. Falconer et al.[67] found pathologic evidence for injury to the amygdala and white matter in an unspecified number of en bloc temporal lobe surgical specimens from patients with temporal lobe epilepsy and hippocampal sclerosis. These authors proposed the term *mesial temporal sclerosis* to indicate damage to the hippocampus and other mesial temporal sites. Recent magnetic resonance imaging (MRI) studies confirm the original autopsy pathology studies by finding evidence for extrahippocampal signal changes in a proportion of patients with temporal lobe epilepsy.[19,48,145,208] Thus, while the traditional focus has been on hippocampal sclerosis as the probable site that generates chronic seizures, many patients will also demonstrate extrahippocampal injury. Such findings are germane to understand the pathogenesis of hippocampal sclerosis and how this pathology contributes to the development of seizures, and in deciding the extent of surgical resection in order to best achieve seizure control.

The Asymmetric Nature of Hippocampal Injury in Temporal Lobe Epilepsy

Autopsy and surgical studies support the idea that patients with intractable temporal lobe epilepsy frequently have bilateral hippocampal damage. However, the amount of damage is usually asymmetric, with one side showing hippocampal sclerosis and the other side milder forms of neuron loss. The best evidence comes from the study of Margerison and Corsellis,[111] where of the 22 patients with EEG criteria for temporal lobe epilepsy and hippocampal sclerosis, the sclerosis was unilateral in 90% and bilateral in 10%. Similar results were reported by Sano and Malamud[168] in another autopsy study of 29 patients with antemortem ictal â€œpsychic phenomena.â€ Bilateral hippocampal damage was noted in 11 cases (39%). Meencke and Veith[138] reported on results from 650 autopsy cases of patients with chronic epilepsy. They found hippocampal sclerosis in 198 (30.5%) and in 56% of these, the findings were bilateral but asymmetric. Similar results have been reported in the limited number of surgically treated temporal lobe epilepsy patients who later died and in whom the other hippocampus became available for study.[6,126] In agreement with the pathology studies, brain MRI findings have shown that many patients with temporal lobe epilepsy have abnormal signal changes contralateral to the atrophic epileptogenic hippocampus.[174,198] Thus, the available data support the concept that while hippocampal damage is often bilateral in patients with temporal lobe epilepsy, most of the time hippocampal sclerosis is unilateral and coincides with the epileptogenic focus.

Pathogenesis of Hippocampal Sclerosis

The pathologic origins of hippocampal sclerosis have been debated, often contentiously, for over 60 years, and center on whether neuron loss is the â€œcauseâ€ or â€œconsequenceâ€ of repeated temporal lobe seizures. Despite the remarkable astute clinicopathologic observations of Sommer[178] and Bratz[36] supporting the hypothesis that hippocampal sclerosis represented an area of chronic damage and gliosis that probably generated seizures, Spielmeyer,[183] Scholz,[172] Peiffer,[159] and more recently Sutula and Pitkanen[189] have argued that hippocampal injury is the consequence of repeated seizures. As will be detailed below, the correct answer probably lies somewhere in between.

Earnest debate of the pathogenesis of hippocampal sclerosis began in the 1950s when surgical specimens became available from patients with temporal lobe epilepsy. Probably the first â€œmodernâ€ concept regarding pathogenesis was that of Earle et al.[60] They examined 157 of Penfield's temporal lobe resections and found macroscopic pathologic abnormalities in 100, ranging from focal gyral toughness to atrophy of the entire lobe. It should be noted that for many years Penfield did not routinely remove the hippocampus en bloc for histopathologic examination. Earl et al.[60] suggested that the most likely explanation as to the â€œcauseâ€ of hippocampal sclerosis was transtentorial herniation of the mesial temporal lobe during a difficult delivery or as a result of birth anoxia with secondary brain swelling. They proposed that in herniating across the tentorium, the mesial temporal lobe compressed the adjacent posterior cerebral and anterior choroidal arteries to generate an ischemic lesion they termed *incisural sclerosis*. With time, this brain lesion â€œripenedâ€ into an epileptic focus. Of interest, however, is that only 10% of their patients had a difficult birth history.

For the next 10 years, birth injury was considered to be the pathogenic etiology for hippocampal sclerosis, and this concept was initially supported by Falconer et al. in the United Kingdom.[43,140] However, after reviewing their first 100 surgical cases in the early 1960s, Falconer began to realize that there was more than one possible clinical factor associated with hippocampal sclerosis. Of 47 cases of hippocampal sclerosis, a history of difficult birth, early childhood convulsions, or head injury was noted in 42 (89%). Of these, childhood seizures were the most common predisposing factor. Falconer et al. concluded that there was a strong association between a clinical history of childhood seizures, especially febrile seizures, and the finding of hippocampal sclerosis at surgery,[39,67,68] and hypothesized that early seizures are a cause of hippocampal sclerosis. This idea has subsequently been referred to as Meyer's hypothesis.[139]

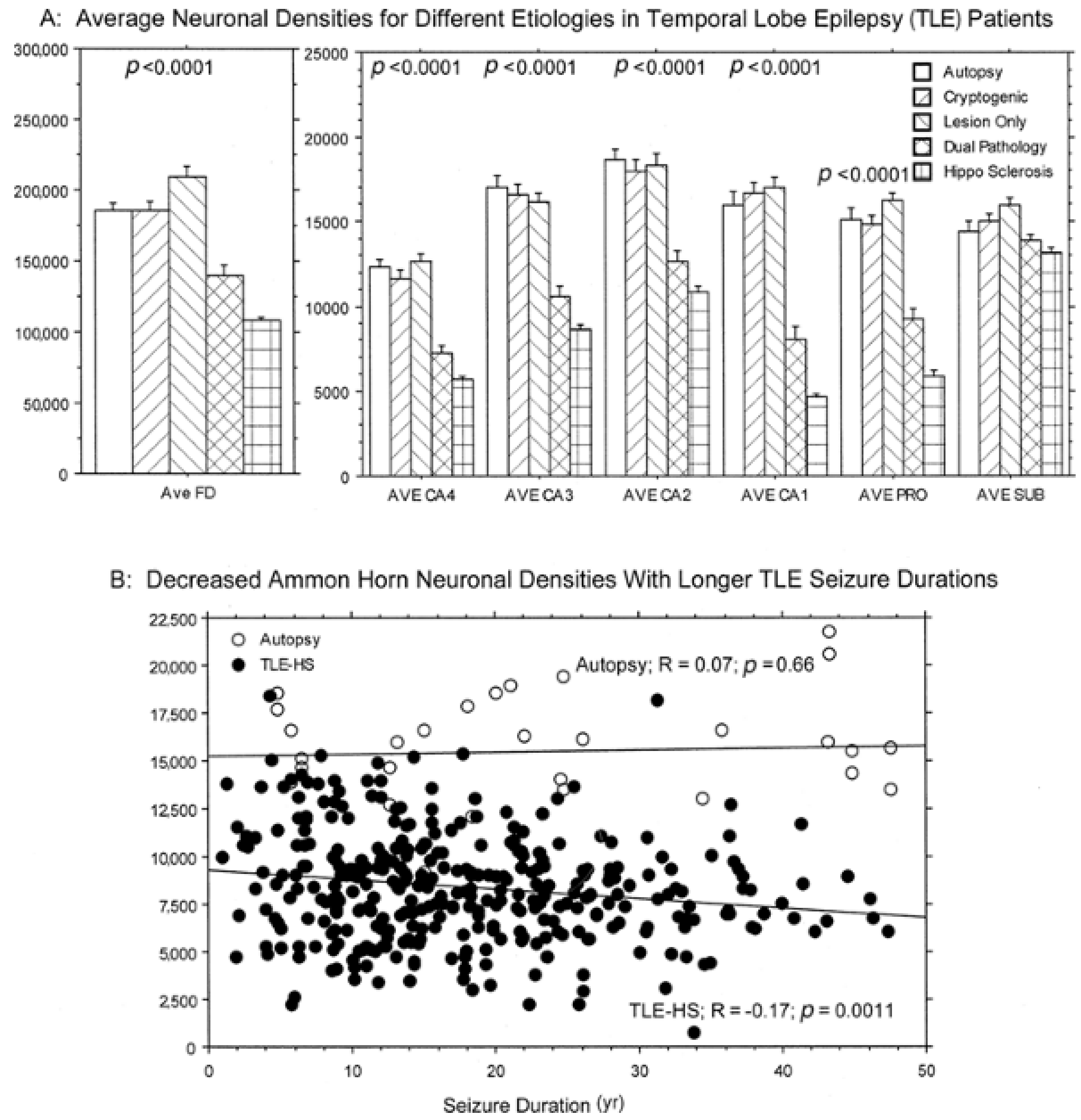
This concept, however, has been challenged by epidemiologic studies showing that the risk of temporal lobe epilepsy after febrile convulsions is very low.[3,42,149] Beginning in the mid-1990s, the UCLA group readdressed Falconer's hypothesis in clinicopathologic studies of a large series of surgical patients with temporal lobe epilepsy.[118,121,125] By expanding the concept of potential brain insults to include any significant medical event likely to injure the brain that occurred before the onset of epilepsy, the authors found that initial precipitating injuries were strongly linked to hippocampal sclerosis in surgical cases (Fig. 2A). However, initial precipitating injuries, while most likely to occur under age 5 years, were not restricted to a young age or to febrile convulsions. In fact, studies of hippocampi removed from pediatric patients with frequent nontemporal lobe seizures generally find only limited hippocampal neuron loss, an observation that supports the notion that childhood seizures, by themselves, do not lead to hippocampal sclerosis.[121,123] Thus, the UCLA data supported previous arguments that hippocampal sclerosis predates the onset of epilepsy, is associated with some significant brain injury not necessarily linked with seizures or an early age, and is probably a cause of temporal lobe epilepsy. However, the UCLA group also found that seizure durations of 15 years or more were associated with progressive hippocampal neuron loss in all subfields of the hippocampus, and this occurred in temporal lobe epilepsy patients with or without hippocampal sclerosis (Fig. 2B). In other words, repeated seizures over time are associated with hippocampal neuron loss, but the damage is throughout the hippocampus and not in the selective pattern consistent with sclerosis. Recent neuroimaging and other studies have supported this conclusion.[189] Thus, the pathogenesis of most cases of hippocampal sclerosis appears to be from some antecedent brain injury (thus acquired), but there is also progressive neuron loss with longer seizure durations. The latter finding may impact the decision as to when to refer patients with temporal lobe epilepsy for surgery.

Dual Pathology

Surgical patients with temporal lobe epilepsy sometimes have more than one lesion or area of injury within the temporal lobe. This is termed *dual pathology*, and it appears to be more common in younger patients with temporal lobe epilepsy.[144] It has been difficult to interpret these studies because the definition of what constitutes a â€œsecondâ€ pathology is sometimes vague, and it may also be unclear if both abnormalities are epileptogenic. For example, Babb and Brown[7] found a 13% incidence of dual pathology when the other pathology was defined as a macroscopic mass lesion. Levesque et al.,[96] using the same UCLA database, included microscopic lesions, such as heterotopias, and found dual pathology in 30% of temporal lobe resections. Other authors have reported rates of dual pathology ranging from 3% to 95% depending on the definition of a second pathology.[5,88,190] Thus, a variable percentage of temporal lobe epilepsy patients will have hippocampal sclerosis plus some other histopathologic finding in the surgical specimen, such as an increase in heterotopic neurons in the subcortical white matter, but whether that second pathology contributes to seizure generation remains unclear despite recent attempts using intracranial EEG recordings.[69,86]

In Vivo Electrophysiologic Studies of Hippocampal Sclerosis

Intraoperative electrophysiologic recordings in the form of electrocorticography (ECoG) were the original source of functional data used to localize interictal spikes (see also Chapter 172). Histologic changes such as gliosis and neuronal loss in the resected tissue often correlate with interictal spikes and other abnormalities in the ECoG. A limitation of ECoG is that the activity comes from the cortical surface, not from deep structures like the hippocampus. Early attempts to examine the properties of the â€œepileptic neuronâ€ were based on single unit recordings from the lateral temporal or frontal cortex carried out in the late 1960s and early 1970s.[41,165] In a slightly later study, Wyler et al.[207] sought to evaluate cellular discharges during intracranial recordings by identifying single unit burst discharge patterns that accompanied interictal spikes, and described synchronization of single unit discharges with one another and with local and surface field potentials during occasional intraoperative ictal events.


A: Average Neuronal Densities for Different Etiologies in Temporal Lobe Epilepsy (TLE) Patients

B: Decreased Ammon Horn Neuronal Densities With Longer TLE Seizure Durations

FIGURE 2. A: Bar graphs showing the mean (Â± SEM) neuron densities for the hippocampal subfields as labeled in FIGURE 1A for different etiology subgroups of temporal lobe epilepsy patients. Cryptogenic cases are those without magnetic resonance imaging (MRI) or histopathology-identified epileptogenic lesions. Lesion-only cases had an MRI-identified mass, such as a tumor or area of cortical dysplasia without hippocampal sclerosis. Dual pathology represents cases with hippocampal sclerosis and a mass lesion outside the hippocampus. An initial precipitating injury (IPI) was noted in 87% of patients with hippocampal sclerosis alone compared with 54% for those with dual pathology and 23% for those with cryptogenic temporal lobe epilepsy. ANOVA *p* values are illustrated above each subfield. Notice that neuronal densities for cryptogenic and lesion-only patients were similar to nonseizure autopsy cases, while dual pathology and hippocampal sclerosis patients with the higher incidence of IPIs had neuron loss in the profile expected with more damage in CA4, CA1, and prosubiculum. By comparison, damage in the subiculum for all cases was much less. **B:** Scatter plot illustrating progressive neuronal loss for the entire Ammon horn with longer duration of seizures in hippocampal sclerosis patients compared with autopsy cases. Notice that the progressive neuron loss in sclerosis patients required over 20 years of seizures and a large number of patients in the study group.

Although McKhann et al.[135] described use of ECoG re-corded directly from the hippocampus for determining the extent of hippocampal resection, intraoperative single neuron recordings from hippocampus are technically challenging and difficult to perform, particularly in terms of correlating such activity with hippocampal sclerosis. Perhaps the most direct intraoperative electrophysiologic correlates of hippocampal sclerosis were published by Rutecki et al.[166] Prior to resection of hippocampal tissue, they stimulated the entorhinal cortex or alveus and recorded either from the surface of or from within the hippocampus. They compared evoked potentials recorded

in 16 patients with hippocampal sclerosis and eight without sclerosis. They found that the patients with hippocampal sclerosis showed simple monophasic or biphasic responses with long-onset latencies (mean, 21.9 msec), whereas those without sclerosis responded with complex, multiphasic potentials that had much shorter-onset latencies (11.8 msec). This is consistent with expectations for hippocampi with severe neuronal damage and gliosis characteristic of hippocampal sclerosis. However, such findings do not explain the epileptogenicity of hippocampal sclerosis, nor do they provide histologic identification of the position of the recording electrode in relation to hippocampal laminae. Of more promise are recent investigations using multiple contact microelectrodes with vertical spacing small enough to study the voltage depth profile of tissue in hippocampal sclerosis.[192]

Electrical Stimulation and Hippocampal Sclerosis

Intra- and extraoperative electrical stimulation has been used since the time of Penfield in the evaluation of epilepsy patients. Studies carried out in patients with depth electrodes have focused on the mental phenomena or memories evoked in awake subjects during trains of high-frequency hippocampal stimulation.[17,73,75] However, electrical stimulation of mesial temporal structures, including hippocampus, has also provided localizing data based on evocation of the stereotyped auras or behavioral changes associated with a patient's characteristic spontaneous seizures.[23] Although the relationship between behavioral responses to stimulation and hippocampal sclerosis is unclear, hippocampal stimulation has provided evidence for both increased evoked potential thresholds and increased afterdischarge thresholds in sclerotic hippocampi compared with nonsclerotic tissue.[45] In 74 patients with depth electrodes, single pulse stimulation was used to measure the functional intrinsic connectivity and the efferent and afferent connections of hippocampus with other mesial temporal and limbic structures.[202] Latencies and conduction velocities of field potentials evoked by single pulses of electrical stimulation varied among the seven limbic sites studied, but the two mesial temporal structures that showed greatest connectivity with all other areas were the entorhinal cortex and the presubiculum. This finding is expected based on the known afferent and efferent pathways of the hippocampus. In a subsequent study, functional connections on the side of seizure onset were found to be significantly decreased within the entorhinal cortex, between the anterior and more posterior hippocampus, and between the hippocampus and amygdala.[200] If one assumes that the preponderance of unilateral mesial temporal onsets in these patients were associated with the presence of sclerotic hippocampi, these results provide further support for reductions in neuronal network connectivity in hippocampal sclerosis.

Paired pulse stimulation has also been employed in evaluating excitability in the hippocampus.[203] In 15 patients, paired pulse suppression in the perforant pathway was significantly greater in the epileptogenic hippocampus compared to the contralateral side. These results demonstrate that inhibition is maintained or even increased in the synaptically reorganized hippocampus in spite of the cell loss and gliosis characteristic of hippocampal sclerosis.

Microdialysis Studies in Hippocampal Sclerosis

In some surgical centers, electrophysiologic recording from depth electrodes has been accompanied by in vivo micro-dialysis.[59,204] This has provided an opportunity to evaluate the release of glutamate and other neurotransmitters associated with hippocampal seizure activity. During and Spencer[59] showed that glutamate release occurred not only during seizures, but also preceding seizure onset. Furthermore, the glutamate release was much greater on the side of seizure onset in patients with hippocampal sclerosis. They suggested that the high levels of glutamate occurring during seizures could reach neurotoxic levels and play a role in the progressive neuronal loss associated with hippocampal sclerosis (Fig. 2B). They also speculated that reuptake transporters were not functioning properly. This study also showed prominent Î³-aminobutyric acid (GABA) release during seizures in the nonsclerotic hippocampus and less release on the side of hippocampal sclerosis. In another paper, During et al.[58] showed that GABA release during K^+depolarization was increased in the hippocampus of the epileptogenic temporal lobe, but there was no difference from baseline when the microdialysis perfusate was Ca^{+2} free. During et al. provided additional evidence suggesting that this GABA release was mediated by reverse transport, not synaptic release. Such findings are consistent with anatomic data showing changes in glutamate and GABA transporters.[124] A more recent study by Cavus et al.,[44] using zero flow measures of baseline amino acids, supports the conclusion that hippocampal sclerosis is associated with high lactate levels, a general reduction in the glutamate-glutamine cycle and glutamate uptake, which leads to increased glutamate levels and neurotoxicity (see Chapter 87).

Ictal and Interictal EEG Correlates of Hippocampal Sclerosis

The well-established association between histologic damage and seizure propensity has been clarified over the years by correlating the electrographic changes recorded using depth electrodes with various measures of neuronal loss. These include the presence of hippocampal sclerosis with focal ictal onsets or interictal spikes,[64,102,197] the pattern of hippocampal pyramidal and granule cell loss correlated with the area of hippocampal ictal onset,[8,12,180,181] cell density in sclerotic or atrophic hippocampus correlated with interhemispheric propagation time,[99,101,179,182] or hippocampal thiopental EEG activation.[100] The correlation of interictal spikes with hippocampal sclerosis is clearly state dependent, because interictal spikes are widespread during slow-wave sleep but may be focal during rapid eye movement (REM) sleep.[103,109,110,167] Sensory-evoked or event-related potentials also have been considered a means of assessing hippocampal or mesial temporal damage associated with temporal lobe epilepsy.[46,75,133,134,136,137]

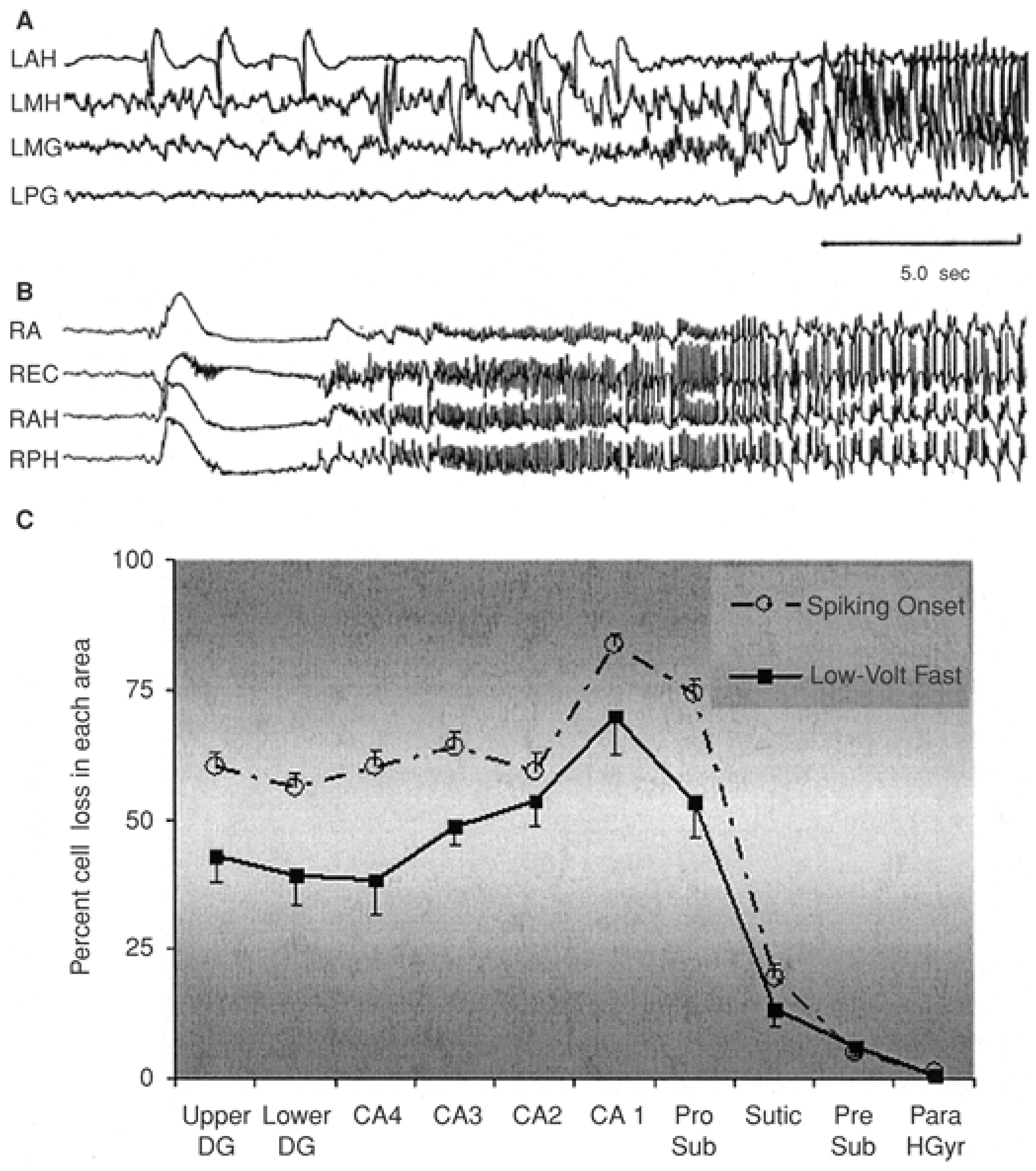


FIGURE 3. Unilateral recordings from hippocampus and adjacent structures in two different patients. **A:** A hypersynchronous spiking on-set. LAH, left anterior hippocampus; LMH, left middle hippocampus; LMG, left middle parahippocampal gyrus; LPG, left posterior parahippocampal gyrus. **B:** A low-voltage fast (LVF) onset. RA, right amygdala; REC, right entorhinal cortex; RAH, right anterior hippocampus; RPH, right posterior hippocampus. **C:** Mean percentage cell loss (Â± SEM), with LVF (14 patients) versus hypersynchronous (29 patients) on-sets. Notice that both groups have a neuronal loss profile consistent with hippocampal sclerosis with slightly less damage in those with the hypersynchronous spiking onset. Upper DG, upper blade of dentate gyrus; Lower DG, lower blade of dentate gyrus; CA1â€“4, hippocampal fields 1â€“4; Pro Sub, prosubiculum; Subic, subiculum; Pre Sub, presubiculum; Para HGyr, parahippocampal gyrus. All sites were significantly different at *p* <0.05 or better with the ex-ception of CA2, Subic, Pre Sub, and Para HGyr.

One of the most studied depth electrode EEG correlates of hippocampal sclerosis has been the morphology of ictal onsets.[63,108,157,171,180,181,194] In these studies, a clear marker of hippocampal sclerosis has been seizure onsets characterized by repetitive high-amplitude sharp waves just before or at ictal onset. This has been variously called â€œhypersynchronous spiking,â€ â€œperiodic spiking,â€ â€œrepetitive spike pattern,â€ or â€œrhythmic sharp wavesâ€ (Fig. 3A), although some difference of opinion still exists over whether the spiking precedes or is part of the onset.[198] A second pattern that is commonly seen in depth EEG recordings is a low-voltage fast discharge (Fig. 3B), which occurs more commonly in nonsclerotic mesial temporal lobe, in sclerotic hippocampus after periodic or repetitive spiking, or in sclerotic hippocampus at the point of propagation to the contralateral hemisphere. Quantification of hippocampal cell loss is different between these two ictal patterns in all hippocampal fields except CA2, with cell loss greater in patients with the hypersynchronous spiking type of onset (Fig. 3C).

Microelectrode Recordings in Hippocampal Sclerosis

As was the case with some of the first studies using chronic depth electrodes, early microelectrode studies obtained chronically from patients outside the operating room often assumed the presence of hippocampal sclerosis without providing quantitative evidence based on cell counts. Thus, studies by Babb et al.[9] and Babb and Crandall[10] focused on descriptions of the bursting patterns of action potential discharge in the hippocampus of patients with mesial temporal lobe epilepsy or changes in firing rates that occurred at seizure onset.[16] Later studies compared hippocampal unit activity recorded from the epileptogenic temporal lobe with that of the contralateral nonepileptic side and quantified differences in a number of measures of neuronal discharge.[201] For example, the duration of firing suppression following single pulse electrical stimulation was significantly greater on the side of seizure onset, and cells showing this suppression were those that fired synchronously with adjacent neurons.[83] Early quantification of firing rate, burst discharge, and degree of synchronous discharge was difficult to interpret until later studies showed that these variables were highly state dependent.[186] Although there were no significant differences during the waking state, recordings during polysomnographically staged non-REM sleep and REM sleep showed that neurons on the side of seizure onset had significantly greater firing rates, burst propensity, and synchronous firing as might be expected for epileptogenic tissue.

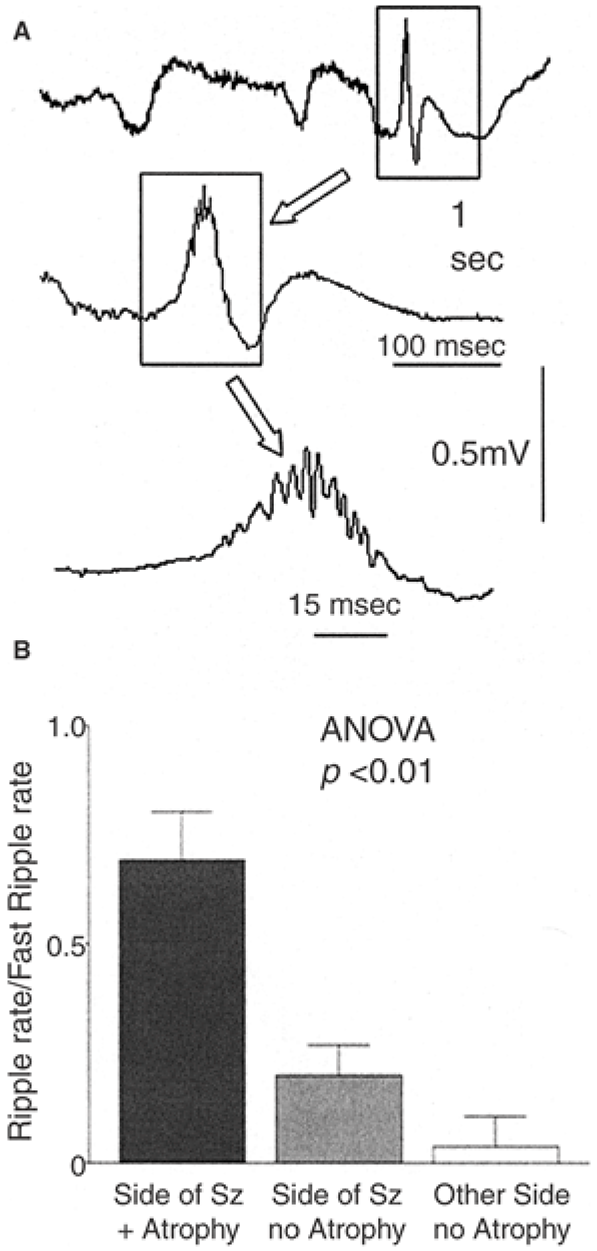


FIGURE 4. A: Interictal spike in wide band electroencephalogram with slow time base appears similar to those commonly seen in conventional recordings. When time base is increased to 100 msec, high-frequency oscillation becomes evident, and with a 15 msec time base, the interictal spike is revealed as a 300 Hz fast ripple oscillation. **B:** When ripple oscillation rate is divided by the fast ripple rate of discharge recorded from the mesial temporal lobes of a group of 25 patients with temporal lobe epilepsy, the resulting ratio is clearly greater on the side of seizure onset in the presence of hippocampal atrophy (and presumed sclerosis) compared with either the side of seizure onset without atrophy or the contralateral side.

High frequency oscillations (HFOs) in the range of 80 to 500 Hz were discovered by Bragin et al.[33,34] during wide band field recordings from depth microelectrodes in the human hippocampus. Oscillations in the range of 100 to 200 Hz had previously been described in the normal rat hippocampus as â€œrippleâ€ oscillations,[209] but in the unilateral intrahippocampal kainic acidâ€"injected rat, oscillatory activity up to 500 or even 600 Hz can be recorded.[35] Therefore, high-frequency oscillations in both epileptic rat and epileptic human hippocampus are called â€œfast rippleâ€ oscillations to distinguish them from endogenous ripples. In patients with temporal lobe epilepsy, these oscillations are often associated with interictal spikes in which the use of wide band microelectrode recordings reveals high-frequency oscillations (Fig. 4). Quantitative studies by Staba et al.[185] showed that the distribution of high-frequency activity recorded in patients was bimodal, with ripples falling in the range of 80 to 150 Hz and fast ripples from 150 to 500 Hz. When oscillations were separated on the basis of the temporal lobe of seizure onset versus the contralateral temporal lobe,

fast ripple activity was found most frequently in the former and ripple activity in the latter (Fig. 4B). Of patients with unilateral seizure onsets, those with hippocampal atrophy have a higher rate of fast ripple oscillations and a lower rate of endogenous ripple oscillations.

Subsequent analysis has shown that the degree of atrophy and percent of cell loss correlates with the ratio of ripple to fast ripple discharges, indicating that hippocampal sclerosis is associated with a decrease in the rate of normal endogenous ripples and an increase in the rate of pathologic fast ripple oscillations.[184] In addition, the presence of high-frequency discharges during seizure onset has been demonstrated in patients with temporal lobe epilepsy during hypersynchronous spiking seizure onsets in the epileptic rat[32] and during spiking and low-voltage fast seizure onsets in human hippocampus.[85] Because of the association between fast ripple oscillations and hippocampal epileptogenesis, the presence of these oscillations has been suggested as a surrogate marker for localization sites for surgical treatment of mesial temporal lobe epilepsy.[65] In FIGURE 5, an example of both ripple and fast ripple oscillations during the onset of a low-voltage fast seizure onset is shown during a wide band recording (C. Wilson, unpublished data). In FIGURE 5A, with a time base of 200 msec in this wide band recording, fast oscillations and details of the unit activity in entorhinal cortex are visible, and with a time base of 25 msec, oscillations of 400 Hz are present on a hippocampal microelectrode (Fig. 5B). In the study by Jirsch et al.,[85] similar high-frequency oscillations were recorded using wide band amplifiers, but without microelectrodes, indicating that this marker of potential pathologic tissue may be visible in wide band recordings from depth electrodes without microelectrodes.

Hippocampal Sclerosis and Epileptogenesis

Multiple cellular and molecular changes have now been described in human hippocampal sclerosis. One of the challenges for epilepsy researchers is to determine which of these are related to the neuron loss associated with hippocampal sclerosis and which are from repeated seizures. To sort this out, most studies compare findings from temporal lobe epilepsy patients with hippocampal sclerosis with findings from patients whose seizures arise from macroscopic mass lesions where the hippocampus is less damaged.[116,117] The advantage of this experimental design is that tissue from both groups can be identically processed after surgical removal, which is especially suitable for experiments that require living tissue (i.e., molecular biology, electrophysiology). While hippocampi from patients with lesions are less severely affected than those with hippocampal sclerosis, they still must be considered abnormal because of frequent seizures. Thus, parallel studies in animal models of temporal lobe epilepsy have proved to be a fruitful approach to delineate mechanisms underlying the development of neuropathologic and functional changes. Conversely, experiments on human tissue have been important to evaluate which aspects of human temporal lobe epilepsy are best replicated by animal models.

From experiments using tissue from humans with hippocampal sclerosis and experimental models of temporal lobe epilepsy, several molecular and cellular changes have emerged that likely play an important role in the propensity of the human hippocampus to generate seizures. Possible mechanisms of epileptogenesis can be broadly categorized into three groups: Changes in synaptic properties, neuronal connectivity, and alterations in the intrinsic properties of neurons. In additional to changes in neurons, glial cells have emerged as important players in mediating hyperexcitability in hippocampal sclerosis.

Synaptic Changes in Hippocampal Sclerosis

In association with neuronal loss, aberrant axon and synaptic reorganization is a characteristic feature of human hippocampal sclerosis.[11,188] The best characterized type of aberrant axon sprouting, both in human and experimental epilepsy, is the synaptic reorganization of the mossy fiber system (the axons of dentate granule neurons) because mossy fibers can be easily identified using the Timm staining procedure (Fig. 6). Mossy fiber sprouting is characterized by the formation of novel, aberrant synaptic contacts of mossy fibers onto the proximal dendrites of hippocampal dentate granule neurons.[40,79,82] The trigger that initiates synaptic reorganization probably involves multiple mechanisms. The traditional concept is that loss of axon afferents onto the proximal dendrites of granule cells from death of hilar neurons initiates this process.[49] This idea is in line with neuropathologic studies demonstrating that the amount of hippocampal pyramidal cell loss in the CA3 region correlates with the extent of mossy fiber sprouting.[62] Another hypothesis has suggested that granule cell neurogenesis, which is increased following status epilepticus in rats, may lead to outgrowth of new mossy fiber axons, which are then misrouted. Evidence from animal models argues against a profound impact of neurogenesis in synaptic reorganization, because disrupting status epilepticusâ€"induced granule cell neurogenesis by irradiation does not inhibit mossy fiber sprouting.[155] Given the prominence of axon reorganization in human hippocampal sclerosis (Fig. 6), studies have focused on determining the distribution of proteins that are known to influence axonal outgrowth and targeting. In hippocampal sclerosis, changes in some of these proteins have been reported, such as the extracellular matrix component tenascin and the reticulin protein Nogo-A.[18,170]

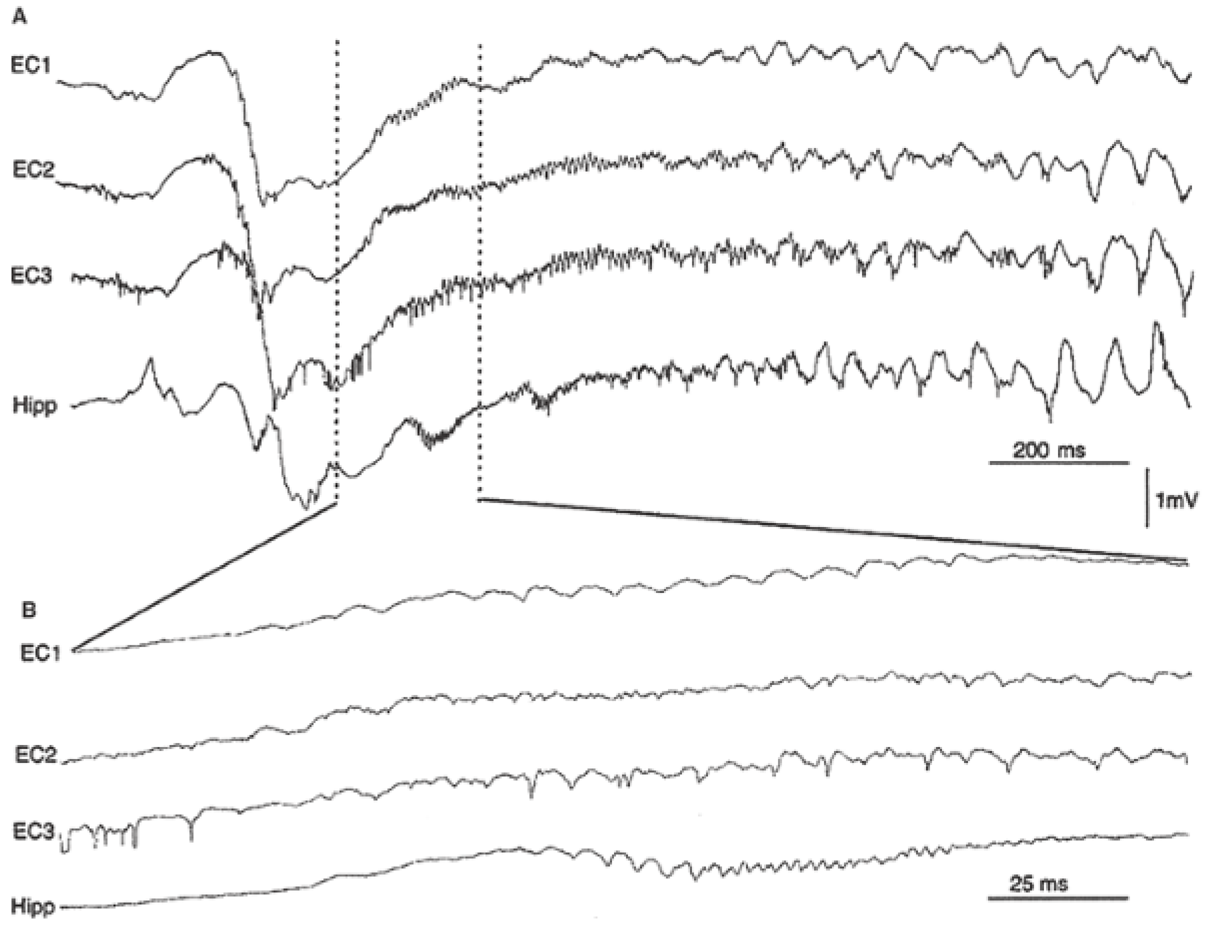


FIGURE 5. Wide band microelectrode recording of the initial 1.5 seconds of the seizure onset shown in FIGURE 2B (low-voltage fast onset) at two time resolutions, illustrating high-frequency oscillations (HFOs) in three microelectrodes from the left entorhinal cortex (EC1,2,3) and the right anterior hippocampus (Hipp). Single-unit activity is visible in EC3. The activity in hippocampus indicated by the arrow has a frequency of approximately 400 Hz.

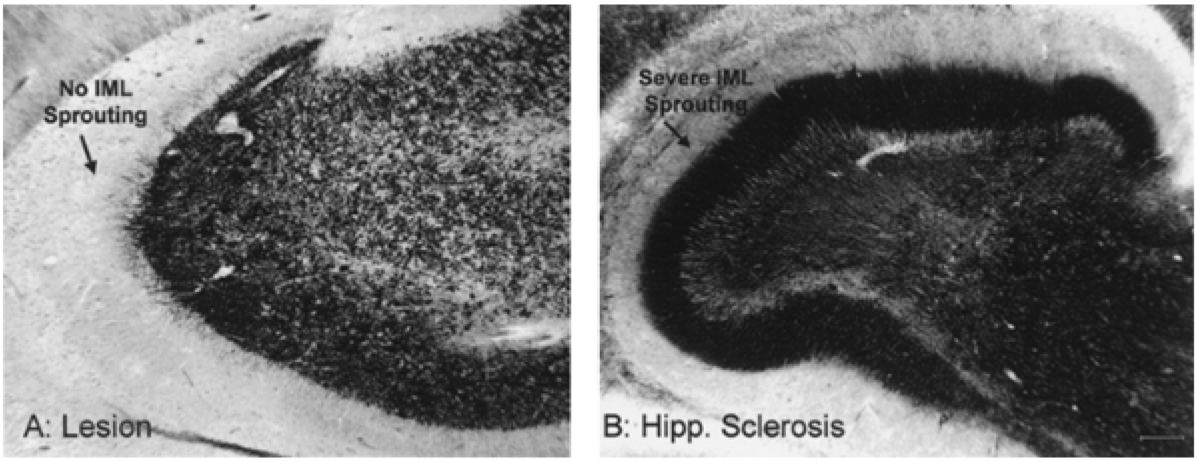


FIGURE 6. Examples of neo-Timm staining illustrating aberrant inner molecular layer (IML) mossy fiber sprouting in human temporal lobe epilepsy patients. **A:** This patient has a tumor generating seizures from the anterior temporal pole. Neo-Timm staining shows only a few black stained strands in the IML. **B:** By comparison, this patient with hippocampal sclerosis demonstrates robust neo-Timm staining in the IML consistent with aberrant mossy fiber sprouting.

The formation of recurrent collaterals of granule cell axons onto other granule cells has been proposed as a major epileptogenic mechanism that may compromise the normally inhibitory function of the dentate gyrus promoting spontaneous seizures.[11,188] The properties and functional importance of this aberrant circuitry has been partially demonstrated in human hippocampal sclerosis patients.[70,79,80] However, in animal models of hippocampal sclerosis, recordings from such aberrant synaptic connections support the existence of monosyn-aptic excitatory recurrent synapses consistent with mossy fibers.[70,80,81,82] It should be noted that under normal circumstances, an excitatory disynaptic feedback circuit via mossy fiber activation of mossy cells, which project back to the dentate gyrus, also exists. Due to the loss of mossy cells and the presence of recurrent mossy fiber sprouting in hippocampal sclerosis, this normal disynaptic circuit is replaced by an abnormal more local monosynaptic one.[40] Apart from creating a monosynaptic recurrent excitatory loop, a mechanism that may further compromise inhibition is the synaptic-mediated release of zinc by mossy fibers onto the proximal dendrites of granule neurons. Because granule cells in chronic human and experimental epilepsy express GABA receptors with increased zinc sensitivity, this has been thought to cause a collapse of GABAergic inhibition, especially at the start of seizure activity.[37,38]

Synaptic reorganization in hippocampal sclerosis is not restricted to the fascia dentata and excitatory mossy fiber system. Aberrant axon collaterals of CA1 pyramidal cells are increased in human and experimental temporal lobe epilepsy, and project to the stratum pyramidale and the stratum radiatum of area CA1.[95] In addition, it is likely that the projections of GABAergic interneurons also undergo significant axon reorganization[15,115] as noted for Chandelier cells.[4] It is likely that newly formed synapses have properties that distinguish them from pre-existing synapses, and it will be important to extend our understanding of the elementary properties of these synapses in determining mechanisms of epileptogenesis in hippocampal sclerosis.[169]

Glutamate and GABA Receptor Alterations in Hippocampal Sclerosis

Considerable effort has been expended on characterizing inhibitory and excitatory neurotransmission in the epileptic human hippocampus.[13,14,25,26,30,51,52,53,54,55,112,113,119,122,127,128,129,130,131,132] Excitatory glutamatergic synaptic transmission is altered in hippocampal sclerosis.[81] *N*-methyl-D-aspartate (NMDA) receptors, one type of inotropic glutamate receptor, are assembled from different subunits termed NR1 and NR2 Aâ€"D.[146] The subunit composition of NMDA receptors and their alternative splicing determine the functional properties of the receptor channel. Hyperexcitability in human epilepsy has been attributed in part to modified NMDA receptor function, presumably due to prolongation of channel opening, increase in agonist sensitivity, and/or decrease in Mg^{2+} sensitivity.[90,104] Changes in the expression of NMDA receptor subunits have been described on the protein and mRNA levels, as well as in ligand binding studies in human hippocampal sclerosis.[51,53,80,81,128,132] In addition to changes in the expression of NMDA receptor subunits, their posttranscriptional regulation appears to play an important role in chronic epilepsy. The increased open times observed in human epileptic tissues are likely due to a persistent decrease in calcineurin activity, an intracellular phosphatase that normally curtails NMDA receptor openings.[191]

Î±-Amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptors, another class of inotropic glutamate receptor, are composed of the GluR1-4 subunits, each of which exists in two alternatively spliced forms. The functional properties of AMPA receptors are critically dependent on their subunit composition and the process of alternative RNA splicing.[148,195] Studies in human surgical tissue have demonstrated region-specific changes in AMPA receptor expression on the mRNA and protein level.[13,26] Similar findings have been reported for kainate receptor subunits, another type of inotropic glutamate receptor subtype.[127]

Metabotropic glutamate receptors (mGluRs) are also altered in human epilepsy with hippocampal sclerosis,[28,97,151] and these may profoundly modulate the generation and propagation of epileptiform activity.[205] The mGluR family consists of at least eight different subtypes.[150] Activation of class I mGluRs (i.e., mGluR1 and mGluR5) leads to an excitatory membrane depolarization followed by release of Ca^{2+} from intracellular stores, which appears to be mediated by inositol phosphate hydrolysis. Class II (mGluR2 and mGluR3) and class III (mGluR4 and mGluR6-8) mGluRs operate mainly via a G-proteinâ€"mediated inhibition of adenylate cyclase. mGLuR receptors are predominantly presynaptic, and they reduce transmitter release in rodent and human hippocampus,[56] probably via inhibition of voltage-gated Ca^{2+} channels.[173]

GABA is the predominant inhibitory neurotransmitter in the adult brain and plays a critical role in the regulation of excitability of neuronal networks.[142] GABA binding to inotropic $GABA_A$ receptors opens the receptor ionophore, which is permeable to Cl^- and, to a lesser extent, to HCO_3. In the presence of a normal adult transmembranous Cl^- gradient, this results in expression of an inhibitory postsynaptic current that hyperpolarizes the postsynaptic neuronal membrane. $GABA_A$ receptorâ€"mediated synaptic currents have been studied in human hippocampal neurons from epilepsy patients.[37,176] These studies have revealed a significantly higher sensitivity of human $GABA_A$ receptors to zinc, a finding also observed in chronic epilepsy animal models. Increased zinc sensitivity of $GABA_A$ receptors is thought to render them susceptible to blockade by zinc released from recurrent mossy fibers during seizures, potentially causing a breakdown of dentate inhibition.[142] Studies of mRNA expression for different $GABA_A$ receptor subunits and correlation with physiologic and pharmacologic properties suggest that $GABA_A$ receptors are regulated in a coordinate fashion in human hippocampal neurons.[38] The epilepsy-associated regulation of $GABA_A$ receptor subunits has been addressed using immunohistochemistry and in situ hybridization in hippocampal sclerosis.[107,161]

Apart from changes in GABA receptors, GABAergic neurotransmission is also influenced by changes in the transmembrane chloride gradient. Indeed, $GABA_A$ receptor activation becomes depolarizing because of altered chloride homeostasis in a subset of subicular neurons in human epilepsy.[47,206] GABAergic inhibitory postsynaptic potentials are governed by the time course with which GABA is removed from the synaptic cleft. This task is subserved by GABA transporters, which may be impaired in the human dentate gyrus.[158] The molecular substrate for this phenomenon may be down-regulation of the underlying transporter proteins.[93,124] Impaired uptake of GABA may underlie prolonged $GABA_A$-mediated responses in hippocampal sclerosis.[199] Metabotropic $GABA_B$ receptors inhibit neurotransmitter release from presynaptic terminals and mediate the late inhibitory postsynaptic potential. The expression of $GABA_B$ receptors has been examined in human temporal lobe epilepsy using various approaches, including in situ hybridization, immunohistochemistry, and ligand labeling.[164] Given the significant changes in synaptic properties as well as the profound changes in Ca^{2+} dynamics and handling, it is not surprising that synaptic plasticity is greatly impaired in hippocampal sclerosis.[20]

Intrinsic Neuronal Properties in Hippocampal Sclerosis

In addition to synaptic properties, the inputâ€"output relation of neurons also depends on intrinsic membrane properties of dendrites that influence the propagation of synaptic potentials toward the cell body. At the cell soma and axon initial segment, intrinsic neuronal properties shape the neuronal firing pattern following synaptic activation. Thus, activity-dependent changes in the inputâ€"output relations of neurons that increased excitability may involve alterations either in synaptic strength and/or in intrinsic membrane properties. In human hippocampal sclerosis, our knowledge about changes in intrinsic properties of neurons is limited compared to the extensive literature from animal models. Nevertheless, changes in the expression or regulation of different classes of voltage-gated ion channels have been described. Changes on a transcriptional level have been found for Na^+ channel subunit expression in human epilepsy.[105,196]

Both pore-forming and auxiliary voltage-gated Ca^{2+} channel subunits have also been shown to be differentially expressed in human hippocampal sclerosis using immuno-histochemistry.[57,98] Notably, astrocytes, which usually do not express calcium channel subunits, were strongly immunoreactive for a Ca^{2+} channel subunit mediating L-type Ca^{2+} currents in hippocampal sclerosis, suggesting that Ca^{2+} channel subunits may be ectopically expressed. It should be noted that voltage-gated calcium channels are powerfully regulated by second messenger systems, as well as by the intracellular calcium concentration. It appears that regulation of human hippocampal calcium channels by intracellular calcium may be altered in hippocampal sclerosis, due to loss of the intracellular calcium-binding protein calbindin D-28k. The loss of this protein from hippocampal neurons markedly increased the Ca^{2+}-dependent inactivation of voltage-dependent Ca^{2+} currents, thereby diminishing Ca^{2+} influx during repetitive neuronal firing.[147] In addition, other voltage-gated channels such as the H-current, a mixed cationic current activated by hyperpolarization, are also regulated in hippocampal sclerosis in a cell-typeâ€"specific manner.[21]

In summary, seizure activity and neuron loss associated with hippocampal sclerosis may evoke multiple transcriptional modifications of ion channels. In addition, there are examples of posttranslational modifications of ion channel proteins.[22] There is also evidence for altered regulation of ion channels by accessory subunits, the lipid environment, or intracellular Ca^{2+}.[147] Thus, the picture of changes regarding voltage-gated ion channels in human epilepsy is far from complete, and in parts is at odds with experimental models of epilepsy. A concerted effort will be required to determine which of the many potential intrinsic changes are relevant for human epilepsy with hippocampal sclerosis.

Metabolic Dysfunction and Energy Failure in Hippocampal Sclerosis

Metabolic dysfunction has been implicated in the pathogenesis of temporal lobe epilepsy, and the cellular basis for this effect is beginning to emerge. In hippocampal sclerosis, as well as lesion-associated epilepsy, fluorescent recording of NADP(H) levels has revealed changes indicative of impaired energy supply in the dentate gyrus, CA3, CA1, and subiculum regions.[87] It is likely that altered mitochondrial function contributes to this effect. Mitochondria are cellular organelles crucial for energy supply and calcium homeostasis in neurons, and their dysfunction causes seizure activity in some rare human epilepsies. Indeed, temporal lobe epilepsy patients with hippocampal sclerosis show specific deficiency of complex I of the mitochondrial respiratory chain in hippocampal tissue. In contrast, temporal lobe epilepsy patients with a parahippocampal epileptic focus showed reduced complex I activity only in parahippocampal tissue.[92] Functional experiments revealed that the observed reduction in complex I activity is sufficient to affect the adenosine triphosphate production rate.

Glial Dysfunction in Hippocampal Sclerosis

Glial cells have classically been thought to mediate homeostasis of the extracellular space. This includes controlling activity-dependent rises in extracellular K^+, uptake of neurotransmitters, and metabolic support of neurons. While glial cells have recently been shown to be capable of subserving functions initially thought to be exclusively neuronal, astrocytes do mediate extracellular space homeostasis in the normal central nervous system (CNS). There are several lines of evidence suggesting that these functions are disrupted in human hippocampal sclerosis.[175,193] First, uptake of K^+ into astrocytes seems to be impaired in hippocampal sclerosis.

This is suggested by experiments in which the K^+ channels primarily mediating astrocytic K^+ uptake were blocked with low concentration of Ba^{2+}. Following application of Ba^{2+}, stimulation-induced rises in the extracellular K^+ concentration measured with ion-selective microelectrodes were strongly increased in nonsclerosis human hippocampal specimens. In marked contrast, Ba^{2+} effects were lost in hippocampal sclerosis specimens, which is consistent with a loss of glial Ba^{2+}-sensitive K^+ uptake pathways.[71,72,89] Indeed, a careful examination of K^+ channels expressed in astrocytes has revealed that inwardly rectifying K^+ current densities are significantly smaller in astrocytes from the hippocampal sclerosis group compared with lesion-associated temporal lobe epilepsy patients.[77]

Experimental studies have shown that clearance of extracellular K^+ is compromised by removal of the perivascular pool of the water channel aquaporin 4 (AQP4)[2] or knockout of this protein,[24] suggesting that an efficient clearance of K^+ depends on a concomitant water flux through astrocyte membranes. AQP4, the predominant water channel in the brain, displays pronounced changes in human hippocampal sclerosis. Overall, a significant increase in AQP4 was observed in sclerotic, but not in nonsclerotic, hippocampi.[94] A more detailed analysis,

however, revealed that the density of AQP4 along the perivascular membrane of astrocytes was in fact strongly reduced in sclerotic versus nonsclerotic hippocampus.[61] These findings are also interesting because the increase in the T2-weighted signal in magnetic resonance imaging and the higher diffusion coefficient in diffusion-weighted imaging indicate higher water content in hippocampal sclerosis in vivo.

Taken together, these studies suggest impaired K^+ handling in hippocampal sclerosis. This would be expected to result in a more pronounced and prolonged depolarization of glial cells and neurons in response to activity-dependent K^+ release. Indeed, induction of epileptiform activity in human hippocampal slices by elevation of extracellular K^+ requires smaller increases in K^+ in slices displaying hippocampal sclerosis compared to nonsclerosis slices.[72]

Neurogenesis and Granule Cell Dispersion

It was long held as an axiom of neurobiology that new neurons are not produced in the adult brain. It has now become clear that niches in the adult brain of rodents contain neuronal precursors that continue to produce new neurons throughout life. Whether this occurs in the normal adult human brain with hippocampal sclerosis is still unclear. One such area is the subgranular zone in the hippocampus, in which the generation of new dentate granule cells persists throughout life in rodents.[91] In humans, it has been possible to demonstrate generation of new granule cells in terminally ill cancer patients receiving bromodeoxyuridine (BrDU), which can be used to label dividing cells in vivo.[66] It has also been possible to isolate multipotent precursor cells from human dentate gyrus that can give rise to functional neurons in culture.[143] It is well established that neurogenesis in the dentate gyrus is increased in animal models of mesial temporal lobe epilepsy.[154,155,156] In human epilepsy, demonstrating increased neurogenesis unequivocally has been more difficult, primarily because labeling dividing cells in vivo is not possible. Nevertheless, a few studies have shown increased expression of division markers, as well as increased expression of markers labeling neural progenitors and immature neurons in patients with temporal lobe epilepsy. These include, among others, Musashi-1, a marker of neural progenitors, nestin, doublecortin, and the polysialated neural cell adhesion molecule PSA-NCAM.[29,50] These findings suggest the possibility that neural progenitors proliferate in hippocampal sclerosis. However, hippocampal sclerosis patients do not demonstrate increased granule cell neuronal densities arguing against neurogenesis, and children with severe epilepsy demonstrate evidence for decreased granule cell neurogenesis.[115,121]

The generation of new neurons in the epileptic dentate gyrus raises the question of where and how these neurons integrate into the pre-existing neuronal network. A systematic analysis of where newly generated neurons incorporate has revealed that progenitors migrate aberrantly to the hilus and molecular layer after prolonged seizures and differentiate into ectopic dentate granule cells (DGCs) in rats.[153] In human hippocampal sclerosis, ectopic putative DGCs were also found in the hilus and molecular layer of epileptic human dentate gyrus. Furthermore, hippocampal sclerosis is frequently accompanied by granulecell dispersion, a broadening of the granule cell layer suggestive of aberrant migration.[78]

It has been speculated that granule cell dispersion results from abnormal positioning of newly generated granule cells. The positioning of granule neurons in the dentate gyrus is controlled by the reelin protein, which acts as a stop signal for migrating neurons. In human hippocampal sclerosis, numbers of calretinin-containing putative Cajal-Retzius cells were increased.[27] Interestingly, expression of reelin mRNA by hippocampal Cajal-Retzius cells is decreased, and correlates with the extent of granule cell dispersion, raising the possibility that decreased reelin production may contribute to granule cell dispersion in human temporal lobe epilepsy.[74] It is also possible that other proteins such as, for instance, cystatin C, a protease inhibitor linked to both neurodegeneration and neurogenesis, may play a role in granule cell dispersion.[162] However, it should be noted that granule cell dispersion is observed in only 50% of patients with hippocampal sclerosis (not all cases), has not been observed in children with early-onset epilepsy, and has been found in circumstances of hippocampal damage without seizures.[76,120,123] Thus, the etiology of granule cell dispersion, its relationship with neurogenesis, and the role these cells might play in epileptogenesis remains unclear.

Summary and Conclusions

Since its discovery in the 19th century, much has been learned about hippocampal sclerosis and its relation to temporal lobe epilepsy. The pace of discovery has accelerated, particularly with the increased availability of human tissue following temporal lobe resections and the application of the tools of cellular and molecular neurobiology. There are still many unanswered questions, however, and we still do not know how to treat mesial temporal lobe epilepsy without surgery. There are also a number of clinically important questions that remain to be answered. For example, it is not clear why only a minority of patients exposed to initial precipitating brain injuries, like childhood febrile convulsions, develop hippocampal sclerosis and temporal lobe epilepsy. What are the genetic or clinical factors that predispose an individual to developing sclerosis after being exposed to injuries that otherwise do not harm others? Are there surrogate markers that can be used to identify individuals at risk for developing hippocampal sclerosis after an initial precipitating injury? Can the processes, like synaptic reorganization, that convert a damaged hippocampus into one capable of producing seizures be identified and, more critically, be augmented or prevented? What are the molecular markers and processes that produce seizures in hippocampal sclerosis?[152] Can we begin to take what appear to be diverse findings from molecular and electrophysiologic studies and convert them into a unified global hypothesis of epileptogenesis in hippocampal sclerosis? Can these ideas lead to treatments without surgery, or at least prevent late recurrent seizures after surgical treatment? These and other questions pose future challenges to the study and treatment of temporal lobe epilepsy patients with hippocampal sclerosis.

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Chapter 14

Neuropathology of Developmental Disorders Associated with Epilepsy

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Introduction

Structural lesions associated with epilepsy can be categorized into the following groups: (a) malformative, (b) neoplastic, (c) familial/metabolic, (d) vascular/traumatic, (e) infectious/inflammatory, and (f) associated with Ammon's horn (hippocampal, mesial temporal) sclerosis.[44,184] Several authors have suggested that some of these pathologic processes may overlap in epilepsy patients,[12,16] and *dual pathology* (e.g., a corticectomy showing features of both a malformative and destructive lesion) may occasionally be encountered.[116] Some of the causal lesions are amenable to definitive surgical treatment (e.g., low-grade neoplasms), whereas others (e.g., metabolic diseases) frequently undergo diagnostic brain biopsy, sometimes unintentionally. This chapter focuses on developmental malformations of the neocortex that account for the majority of structural lesions seen in infants and children with intractable epilepsy, especially those with infantile spasms (IS). (The other categories of *epileptogenic* structural lesions are discussed elsewhere.) More subtle malformations are also recognized with increasing frequency in adults with epilepsy.

Neocortical malformations have usually been considered to represent developmental disorders of neuronal migration (or vascular formation), and have variously been classified with regard to morphology or putative etiology.[8,135,138] The categorization of these heterogeneous lesions is increasingly being modified by (a) the availability of high-resolution multimodality neuroimaging techniques that can be used to predict pathologic abnormalities in a given patient[24,26,158] and (b) molecular genetic clues to pathogenesis based on techniques such as gene expression profiling following laser capture microdissection of surgical specimens.[32] The genetic basis of some types of lissencephaly (e.g., Miller-Dieker syndrome) is now quite well understood.[32,147] They can be roughly categorized as follows: (a) cortical dysplasia (CD), which accounts for the majority of malformations associated with pediatric epilepsy and encompasses the full spectrum of neuronal migration disorders (NMDs), sometimes also described as malformations of cortical development (MCDs), ranging from the most subtle to the most severe; (b) structural lesions associated with tuberous sclerosis complex (TSC); (c) Sturge-Weber-Dimitri syndrome (SWDS), also known as encephalotrigeminal angiomatosis; (d) neurofibromatosis type 2, which may be associated with meningio-angiomatosis; and (e) vascular malformations.

This chapter discusses clinicopathologic associations between the recognized pediatric epilepsy syndromes and their neuroradiologic and neuropathologic substrates. We review the terminology used to characterize these complex malformative lesions in the light of modern neuroimaging data. We give a brief overview of development of the cerebral cortex and identify the points of susceptibility at which the error or errors (genetic or environmental) resulting in cortical malformations may occur.

Clinicopathologic Features

Epilepsy has traditionally been classified into syndromes based on clinical presentation and electroencephalographic (EEG) findings. However, there is often a marked discrepancy between the clinical phenomenology of a seizure disorder and its neuropathologic substrate(s). Infantile spasms (IS, West syndrome) and Lennox-Gastaut syndrome can be seen with a wide range of cerebral lesions,[69,106,153] indicating the nonspecific nature of these seizure disorders. The clinical form of epilepsy seen in a given patient appears to depend more on *when* during cerebral development the lesion occurred than on the specific *type* or topographic distribution of lesions.[69,108] It has been suggested that the central nervous system (CNS) lesions associated with IS can be functionally categorized into three groups: (a) diffuse, (b) focal or multifocal cerebral lesions, and (c) cases with minimal neuropathologic change.[153] Diffuse hemispheric lesions include hemimegalencephaly (HME), agyria/pachygyria-lissencephaly, and Aicardi syndrome.[1] Focal and multifocal lesions include CD and destructive lesions (vascular and infectious), as well as cortical tubers seen in patients with TSC.

Developmental malformations of the neocortex (malformations of cortical development, MCDs) can be considered a spectrum of CD resulting from derangement of the normal process of cortical development.[117,120,130,131,142] This spectrum consists of a range of morphologic features associated with multiple putative etiologic factors, including genetic and environmental (e.g., destructive) influences. CD encompasses the full spectrum of neocortical malformations, ranging from the most subtle (*microdysgenesis*) to the most severe (HME), and includes such conditions as agyria/pachygyria-lissencephaly, polymicrogyria (PMG), and focal CD. CD, therefore, comprises a spectrum of derangements in neocortical development that are associated with a range of morphologic features and with multiple putative etiologic factors, including genetic and environmental influences. The resultant neuropathologic features may reflect abnormalities that probably occur within discrete time windows during brain development. Clinically there is an inverse correlation between the size and severity of CD and the age at clinical presentation,[26,117] supporting the notion that there is a predominance of pathologically severe CD in neonates and infants with seizures, including those with IS.[73] Although CD accounts for the majority of malformations associated with pediatric epilepsy, other malformative lesions are also capable of producing these epilepsy syndromes, and they frequently show neuropathologic changes that overlap significantly with those seen in patients with CD.

Jellinger[69] noted that the clinical severity of a given seizure disorder appears to be more closely related to the *timing* of the insult (whether genetic or environmental) and its effect on the processes of development than to the nature of the lesion itself. This may explain some of the heterogeneity of neuropathologic lesions seen in children with epilepsy because the clinical phenotype results not only from the lesion or putative insult to the developing CNS, but also from the developmental processes it affects.

A puzzling feature noted in pediatric epilepsy is the finding in cases of IS of diffuse and transient suppression of cortical activity in the presence of focal or multifocal lesions.[153] This diffuse cortical suppression has not been linked to particular distributions or types of neuropathologic change. Rather, Robain and Vinters suggested that this feature of IS is associated with neocortical immaturity.[153] The pattern of evolution of IS from transient and diffuse suppression of cortical discharge to ultimately focal or generalized seizures may represent a maturation of the malformed cortex.[153]

Nosology

The nosology and understanding of the full spectrum of CD are evolving and reflect a progressive elucidation of the basis of these extremely complex lesions. Initially, cortical malformations were referred to largely by their gross characteristics (i.e., agyria/pachygyria-lissencephaly, HME, microgyria). As investigators discovered the range of microscopic cortical malformations that produce epilepsy but show no (or relatively mild) gross abnormalities, additional terms such as *microdysgenesis*,[57,107,108] *dysplastic cortical architecture* (not otherwise specified),[157] *focal cortical dysplasia*,[119,174] and *generalized or diffuse cortical dysplasia*[78,83,96] were added to the literature. The nomenclature of CD has evolved through several schema of classification, each intended to provide correlations with morphology of seizures and reflect etiologic mechanisms.[8,9,117] *Focal cortical dysplasia* was initially used to specify lesions in which cytomegalic neurons were present,[174] although its frequent use to refer to a localized *region* of CD renders the term somewhat ambiguous. Some investigators prefer to use a traditional classification of migrational disorders into four main groups: (a) agyria/pachygyria-lissencephaly, (b) microgyria-polymicrogyria, (c) dysplastic cortical architecture, and (d) heterotopias.[157] Others, to denote the belief that these lesions are related and reflect developmental abnormalities along a continuous spectrum, have chosen to refer to this group of lesions as neuronal migration disorders or *NMDs*,[8,130,131] *cerebral dysgenesis*,[159] or *synaptic dysgenesis*.[13] The nosology of developmental neocortical malformations will continue to evolve, especially in the era of high-resolution magnetic resonance imaging (MRI), and reflect a progressive understanding of the underlying biology of these complex lesions (see Chapter 259). A recent consensus conference resulted in a proposal to subclassify CD or grade its severity (in surgical resection specimens) using simple morphologic criteria identifiable by any experienced neuropathologist, for example, presence or absence of cortical disorganization, enlarged or dysmorphic neuronal cell bodies, and â€œballoon cellsâ€ (see later discussion).[132] This classification scheme has been adopted widely enough that surgical pathology reports on corticectomy specimens now frequently contain the terminology â€œ*Cortical dysplasia, Palmini type*â€¦.â€

Development of the Neocortex

Overview of Neocortical Development

The neuropathologic changes seen in children with epilepsy frequently represent the end results of insults to a rapidly developing brain. This section briefly summarizes the normal process of neocortical development and identifies the points of susceptibility at which the error or errors (genetic, environmental, or both) result in cases of pediatric epilepsyâ€”usually due to CD. We also briefly introduce some recent advances in the genetic and molecular mechanisms that regulate cortical development. Many excellent reviews have summarized the historical evolution in our understanding of the complex neurobiologic, cellular, and molecular processes that work in concert to create a normally functioning cerebral cortex.[30,52,67,141,160] Neocortical development after neural tube formation can roughly be considered to be the result of a series of overlapping processes: (a) cell proliferation in the ventricular zone and subventricular zone (VZ/SVZ), (b) early differentiation of neuroblasts and glioblasts, (c) programmed cell death of neuronal precursors and neurons, (d) migration of neuroblasts to form the cortical plate, (e) late neuronal migration, (f) organization and maturation of the cortex, and (g) synaptogenesis.[1,8,157,175] Abnormalities of these processes result in abnormalities of cortical architecture and, by inference, its electrophysiologic properties. Most developmental disorders of the brain commonly associated with epilepsy are believed to originate from the perturbation of developmental events *after* the embryonic period, i.e., after 6 weeks' gestation, when cell proliferation starts along the wall of the neural tube. This generates a collection of matrix cells,[45] or precursor cells for all neuroblasts and glioblasts, forming ventricular and subventricular zones (VZ/SVZ) in the pallium, as well as the ganglionic eminence in the subpallium (Table 1).

Table 1 Major stages of human central nervous system development and associated epileptic disorders

Stages	Time of occurrence (wk)	Morphologic changes and events	Corresponding disorders commonly associated with intractable epilepsy
Embryonic period			

Formation and separation of germ layers	2	Neural plate	Enterogenous cysts and fistulas Split notochord syndrome
Dorsal induction: primary neurulation	3â€“4	Neural tube, neural crest and derivatives	Anencephaly, encephalocele
		Closure of rostral and caudal neuropores	Chiari malformation
Ventral induction: telencephalization	4â€“6	Development of forebrain and face	Holoprosencephaly
		Formation of cerebral vesicles Optic and olfactory placodes	Dandy-Walker malformation
Fetal period			
Neuronal and glial proliferation	6â€“16	Cell proliferation in ventricular and subventricular zones	Microcephaly Hemimegalencephaly
		Early differentiation of neuroblasts and glioblasts	Cortical tuber of tuberous sclerosis Cortical dysplasia with balloon cells
		Programmmed cell death	Dysembryoplastic neuroepithelial tumor ganglioglioma, gangliocytoma
Migration	12â€“24	Migration of cortical neurons	Type I lissencephaly
		Formation of corpus callosum	Type II lissencephaly (cobblestone) Heterotopia

Perinatal period			
Organization	24 to postnatal	Late neuronal migration	Polymicrogyria, schizencephaly
		Organization and maturation of cerebral cortex Synaptogenesis	Cortical dysplasia without balloon cells Mild cortical dysplasia â€œMicrodysgenesisâ€
Myelination	24 to 2 yr postnatally		Destructive lesions Myelination disorders

Modified from Aicardi (1992), Barkovich et al. (2005), and ten Donkelaar et al. (2006).

Programmed cell death (PCD) is an essential mechanism for normal brain development, determining the size and shape of the nervous system. In normal brain development, there is a 25% to 50% overproduction of neuroblasts; these undergo physiologic PCD.[159] Neuroblasts and glia undergo this process as well. PCD appears to be under tight genetic control, as demonstrated in the *Caenorhabditis elegans* model.[39] It is an active process that can be blocked by inhibitors of protein synthesis and RNA transcription.[70] Failure of PCD may lead to mechanical barriers to migration and abnormal numbers of neurons. Supplemental to PCD, there is a conspicuous elimination of synapses occurring during development that is essential to remodeling of the cortex.[140] This may be accomplished by different mechanisms, and competition for trophic substances has been suggested as one. Synapse elimination is highly intertwined with the remodeling of cortical connections and is a highly dynamic process[140] demonstrated both in vivo and in vitro.[180]

Terminal differentiation of a neuroblast appears to be a multistep process.[22,102,128] Cell surface properties and extracellular matrix molecules play a crucial role in influencing migration and terminal differentiation of neuroblasts. Neural adhesion and migration are governed by a series of morphoregulatory molecules, cell-adhesion molecules (CAMs), and substrate-adhesion molecules (SAMs). CAMs

are transmembrane molecules bearing extracellular domains that are homologous to domains of the immunoglobulin superfamily[38] and are engaged in homotypic binding. The binding functions interact with the cytoskeleton because CAMs are transmembrane molecules. These molecules are involved in cell adhesion, axon binding, growth cone interactions, and other migrational mechanisms. SAMs, extracellular matrix molecules, are involved in the regulation of cell shape, motion, and process extension.[36] These molecules are expressed in a spatial-temporal fashion and are under the control of homeobox-containing genes that are known to govern place-dependent morphology.[74,75] The time-dependent levels of expression of the molecules are characteristic of a given anatomic area but are dynamically regulated and subject to local influences. The activities of these molecules are further modulated by neural activity itself.[37] These morphoregulatory molecules can mediate neuronâ€“neuron interactions (NCAMs), neuronâ€“glia interactions (Ng-CAMs), or neuronâ€“extracellular matrix interactions.[30,60,61] Extracellular matrix molecules also appear to be important in cell motion, attraction, repulsion, and growth cone migration; soluble trophic factors have an important role in these processes.[34]

Radial Migration of Neuroblasts from the Subventricular Zone

Radial migration refers to the process by which neuroblasts from the VZ/SVZ migrate along the processes of radial glia to reach the (neo)cortex. Radial glia initially have cell bodies in the ventricular zone and end-feet on the pial surface; with time, they detach themselves from the ventricular lining and migrate toward the cortex.[32a,41] They function as a permissive scaffold on which neuroblasts may migrate from the ventricular zone to the cortical plate.[60] At approximately 4 weeks' gestation, the neural tube forms with a simple pseudostratified neuroepithelium, component cells of which then proliferate around the developing ventricular system, eventually becoming the ventricular zone. The ventricular zone can be described as a mosaic of precursors that will give rise to neurons, astrocytes, and oligodendroglia, as demonstrated using retroviral markers.[139] The first postmitotic cells form the preplate or primordial plexiform layer[98,110,112,168,194] above the ventricular zone and beneath the pia. Toward the end of the embryonic period, cells from the ventricular zone migrate to form the cortical plate within the preplate; that is, the cortical plate is formed dividing

the preplate (preplate splitting) into (a) a thin superficial component, the marginal zone, and (b) a thick, deeper component, the subplate. The intermediate zone or future subcortical white matter also appears by this stage,[157] and this cortical plate formation continues until 16 weeks' gestation.[9] The neocortex is formed in an â€œinside-outâ€ fashion: Neuroblasts born first, destined for the deepest cortical layers, migrate first, whereas neuroblasts born later, destined for the more superficial cortical layers, migrate past the already present cortical neuroblasts,[6] eventually forming a six-layered structure.[163] Even after this point, however, neuroblasts continue to migrate through the intermediate zone (future white matter) to the cortex, a process that can continue up to a few months after birth.[163] Abnormalities of radial glia may occur through various molecular mechanisms either focally or diffusely in malformations of cortical development (MCDs), including Fukuyama congenital muscular dystrophy (FCMD)[169] and tuberous sclerosis complex (TSC).[133] Alterations of signaling pathways that regulate microtubule dynamics either directly or indirectly may also result in a derangement of radial glial fibers, as has been demonstrated in *reeler* mice[64] and *Lis1* mutant mice.[19] Radial glia have long been known to serve as guides for migrating neuroblasts and finally give rise to cortical astrocytes. However, recent evidence in mice indicates that radial glial cells also generate neurons in the developing cerebral cortex. Three distinct subsets are thus identified, including subpopulations important in gliogenesis, neurogenesis, and both.[7,58]

Tangential Migration of GABAergic Interneurons From Ganglionic Eminence

Tangential migration refers to the process by which neuroblasts from the ganglionic eminence migrate in a nonradial, â€œneurophilicâ€ fashion, possibly along neuronal processes rather than radial glial fibers, moving tangential to the pial surface to form complex three-dimensional neural structures.[143] Ganglionic eminence, primarily considered to be a source of basal ganglia neurons, consists of three parts. The medial ganglionic eminence, derived from the diencephalon, gives rise to globus pallidus. The lateral ganglionic eminence, derived from the telencephalon, gives rise to the caudate nucleus and putamen. The caudal ganglionic eminence primarily gives rise to amygdala. Both lateral and median ganglionic eminences, however, are also involved in the formation of cerebral cortex. In fact, mechanically separating the ganglionic eminence from the cortex results in a loss of calbindin and Î³-aminobutyric acid (GABA)â€“positive neurons in the cortex,[2] and 35% of cortical GABAergic interneurons arise form both ganglionic eminences by way of tangential migration.[3,87] This contrasts with the origin of pyramidal neurons of the cerebral cortex, which arise from the ventricular zone of the pallium by way of radial migration. Although 65% of cortical GABAergic interneurons arise from the ventricular zone of the pallium, they are considered to migrate in nonradial, neurophilic fashion at least within the VZ/SVZ.[87] Migration of GABAergic interneurons seems to be much more complex, because â€œventricle-directed migrationâ€ has also been demonstrated in mice.[122] GABAergic interneurons are immunoreactive for calcium-binding proteins such as calbindin. Studies of macaque monkey brain have suggested that calcium-binding-proteinâ€“containing interneurons make up 90% of all GABAergic neurons in the cerebral cortex.[91] The number and distribution of calcium-binding-proteinâ€“containing neurons in the neocortex can be reorganized in early postnatal life[149]; by 28 weeks after birth, the laminar distribution of calbindin-immunoreactive cells shifts from layer IV to layer II. It has been suggested that doublecortin (DCX) is important for nonradial migration because it is rather selectively expressed in tangentially oriented postmitotic neurons in the subventricular and intermediate zones.[113]

Origin of Cajal-Retzius Cells and Their Biologic Significance

The marginal zone, future molecular layer or cortical layer I, is composed largely of Cajal-Retzius cells. They secrete the extracellular glycoprotein reelin that is required for the normal inside-out positioning of neurons as they migrate from the ventricular zone along radial glia. Human Cajal-Retzius cells, characterized by the combined expression of reelin and p73, are transient cells, are present from the preplate stage at 8 weeks' gestation, and gradually increase in number (by tangential migration) until they disappear by the end of gestation.[110,113] One possible origin of Cajal-Retzius cells is considered to be the boundary between prospective hippocampus and choroid plexus epithelium or â€œcortical hemâ€ in the dorsal telencephalon.[113] In mice carrying mutations in *RELN* (*reeler* mice) and in *disabled-1* (*Dab1*) as well as in mice carrying double mutations of both very low density lipoprotein receptor (*VLDLR*) and apolipoprotein E receptor 2 (*ApoER2*), normal neuroblast migration with an inside-out fashion is inverted.[178] This suggests a role for these genes in the control of cell positioning in the developing central nervous system and even predicts a pattern of cytoarchitectural alteration in patients carrying alterations in the reelin/lipoprotein receptor/Dab1 pathway, as well as *RELN* mutations causing lissencephaly.[63] LIS1 also appears to have important effects on neuronal migration, and significant interactions with Cajal-Retzius cells: LIS1 deficiency negatively affects the migration and differentiation of both doublecortin- and reelin-positive neurons in the developing human brain.[114]

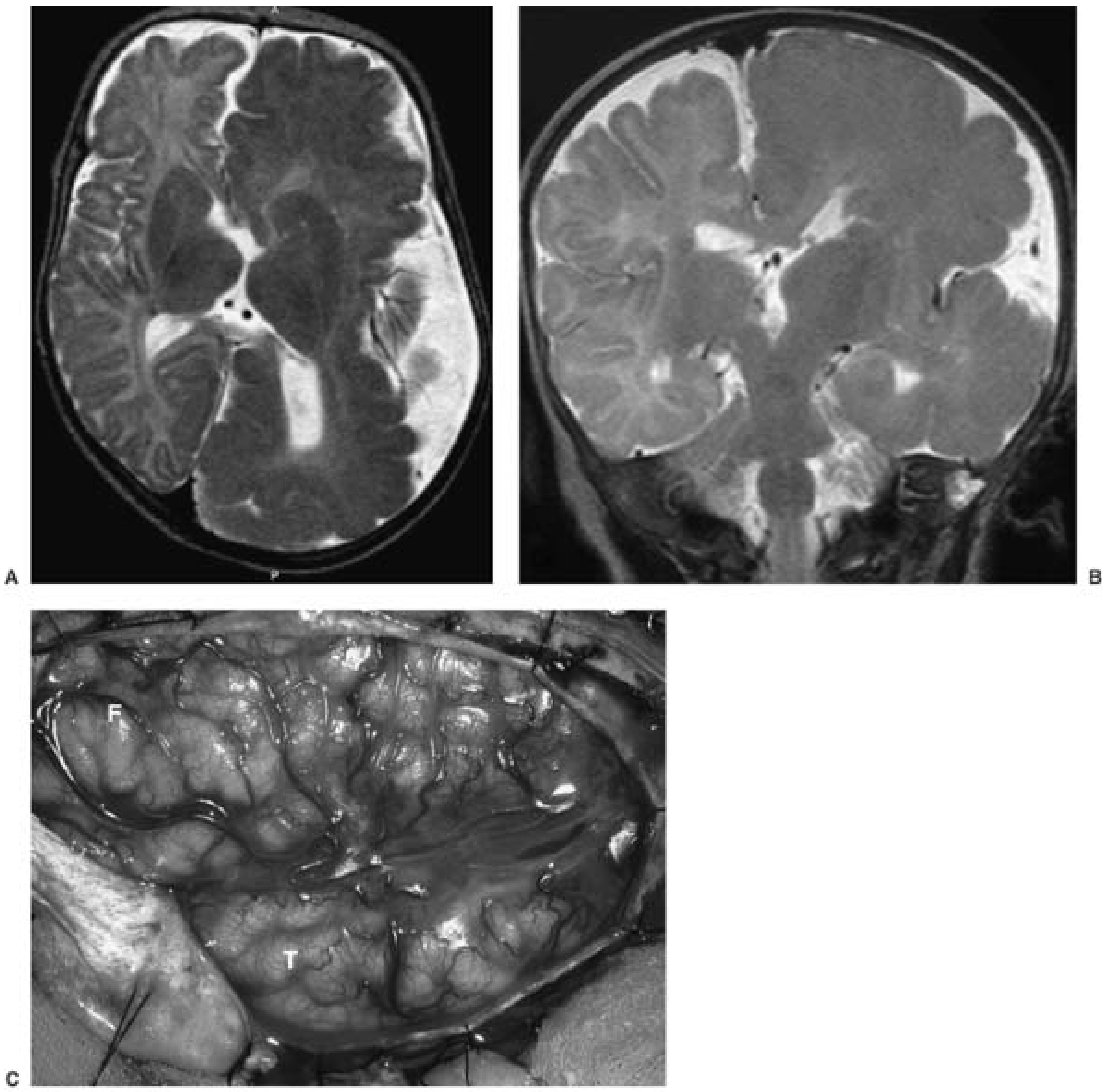

FIGURE 1. Hemimegalencephaly (HME) in a 6-month-old child. Axial **(A)** and coronal **(B)** T2-weighted magnetic resonance imaging (MRI) images show markedly enlarged left cerebral hemisphere with thickened gyri and smooth surface, consistent with HME. The left lateral ventricle and caudate head are deformed. White matter is diffusely hypointense compared with the unaffected right cerebral hemisphere, suggesting accentuated myelination. **C:** Intraoperative photograph of the region of HME oriented with the frontal lobe (F) in the top left and the temporal lobe (T) in the lower middle portions of the image. Notice the diffuse cortical disorganization of all gyri. This child had a monozygotic twin who was normal. (Panel B is from Salamon N, Andres M, Chute DJ, et al. Contralateral hemimicrencephaly and clinical-pathological correlations in children with hemimegalencephaly. *Brain*. 2006;129:352â€“365; with permission of the editor of *Brain* and Oxford University Press.)

Origin of Superficial Granular Layer and Its Biologic Significance

The superficial or subpial granular layer (SGL) is a transient cell layer and appears beneath the pial surface between 13 and 24 weeks' gestation.[18,44] Cells in the SGL originate from the basal periolfactory subventricular zone[18,46,111] and migrate tangentially beneath the pia to cover the neocortical marginal zone. Cells in this layer express interneuron markers such as calretinin, calbindin, and GABA,[145] suggesting that they are equivalent to GABAergic interneurons. The biologic significance of the SGL, however, remains to be elucidated. Programmed cell death may, at least in part, contribute to elimination of the SGL.[166] There is controversy in this research area because the SGL is also suggested to be an additional source of cortical interneurons; it disappears probably as the result of inward or ventricle-directed migration of its component cells.[122,144,145]

Subplate Neurons as Pioneer Cells to Form Early Thalamocortical Projections

The human subplate contains large multipolar neurons. Subplate neurons in the developing cerebrum, although they are transient and most disappear in early postnatal life, are believed to be important in organizing cortical connections in the developing cerebrum. They are believed to act as pioneer corticofugal axons.[29,49,50,101]

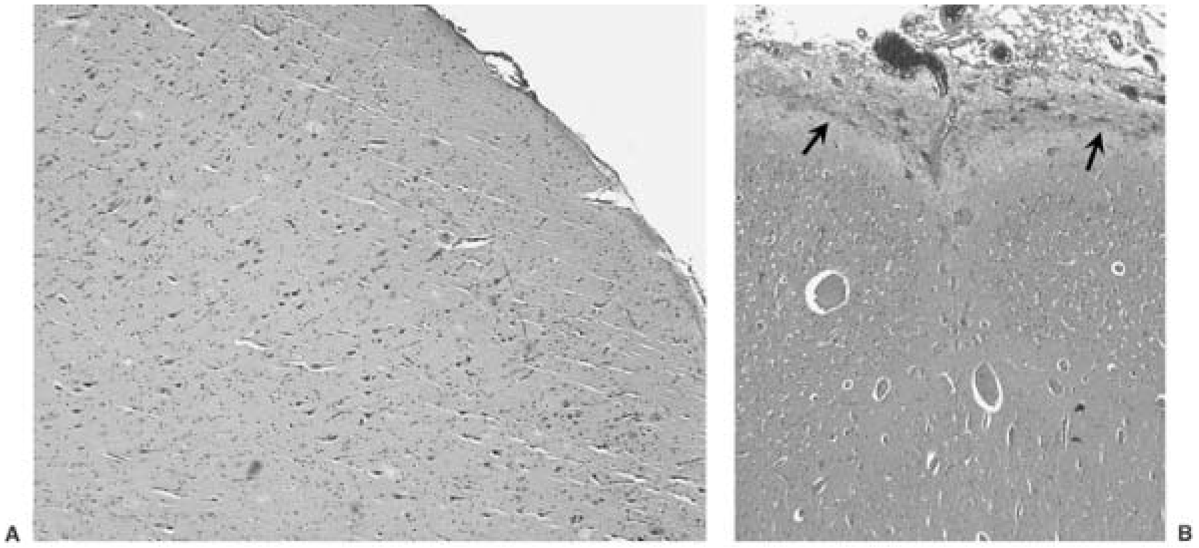

FIGURE 2. Representative micrographs of the resection specimen obtained from the child with magnetic resonance imaging (MRI) and intraoperative appearances illustrated in Fig. 1. **A:** Low-magnification view of a representative region of cortex shows a modest degree of neuronal disorganization. **B:** A focus of polymicrogyria, one of many seen in the resection specimen. Also note a â€œrindâ€ of disorganized glial tissue covering the pia, with apparent extension into the subarachnoid space (*arrows*). (Hematoxylin and eosin stain.) (See the color insert.)

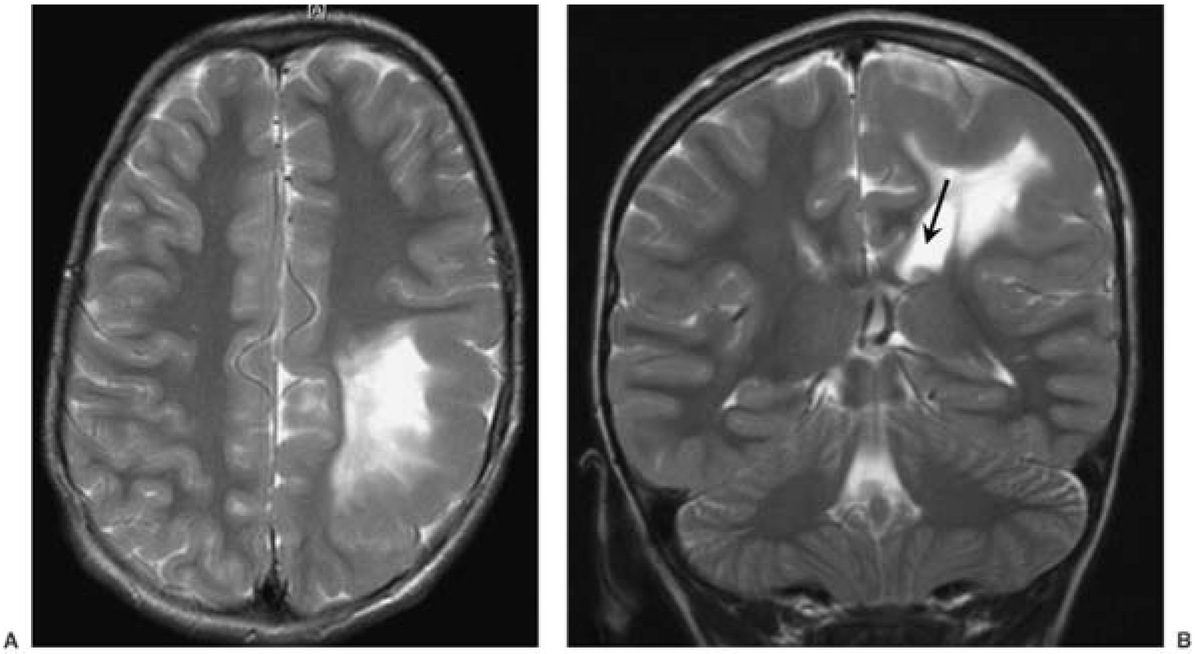

FIGURE 3. Focal cortical dysplasia extensively involving the left parietal lobe. T2-weighted axial **(A)** and coronal **(B)** images show thickened gyri and hyperintense signal in the white matter of the left parietal lobe. The left lateral ventricle is enlarged (*arrow*).

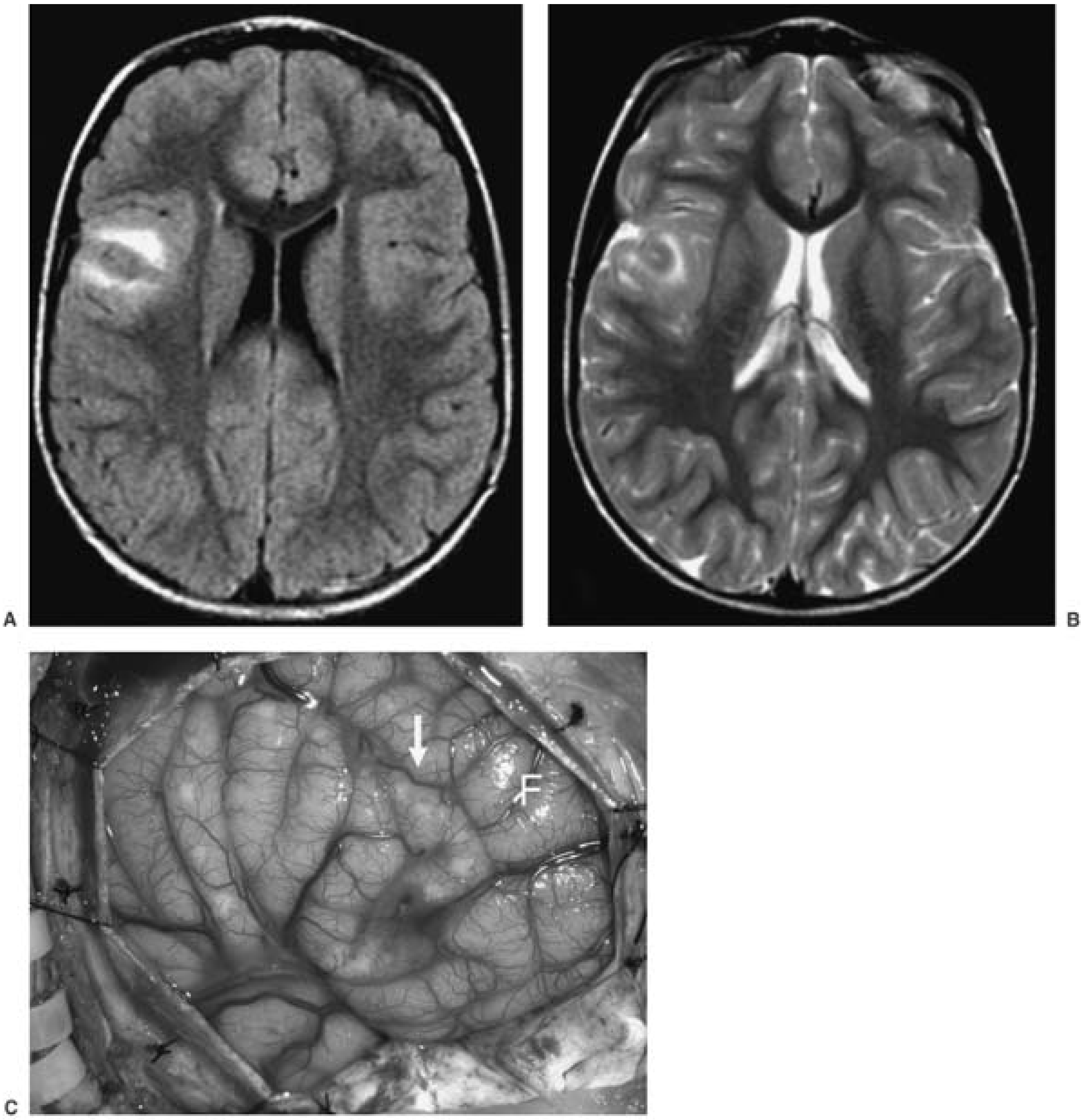

FIGURE 4. Axial FLAIR (fluid attenuated inversion recovery) **(A)** and T2-weighted axial **(B)** images demonstrate hyperintense signal area in the subcortical white matter of the right frontal operculum in a 4-year-old girl. The gray matter in this region is thickened, but there is no mass effect. The findings are suggestive of cortical dysplasia. **C:** View of the lesion intraoperatively (*arrow*). Histopathology of this lesion showed classic features of Palmini grade IIB cortical dysplasia. F, frontal lobe.

Neuropathology and Pathophysiologic Significance of Cortical Dysplasia

The Pediatric Epilepsy Surgery program at UCLA Center For the Health Sciences, active since 1986, has enabled us to examine over 500 surgically resected specimens from infants and children with intractable seizures, ranging from partial lobectomies to complete and partial (functional) hemispherectomies. The most common morphologic substrate for this was CD, this being of etiologic importance as a cause of intractable pediatric seizures in >80% of children <3 years of age. The extent of CD neuropathology can be predicted by high-resolution neuroimaging studies. Such neuroimaging allows for stratification of CD cases into those that show hemimegalencephaly (HME), with diffuse enlargement of the gray and white matter, including thickening of the cortical ribbon, within an entire cerebral hemisphere (Figs. 1 and 2); hemispheric CD, with multifocal CD affecting one cerebral hemisphere (although *not* causing enlargement of that hemisphere); and multilobar, lobar, or focal CD (Figs. 3 and 4), the latter affecting as few as one or two adjacent gyri. HME is easily recognized by neuroimaging. The MRI findings include an enlarged cerebral hemisphere and markedly thickened gyri, with loss of sulcation. There is deformity and enlargement of the ipsilateral ventricle. Palmini type IIB CD is also easily identified by MRI, with focal thickness of the gyrus (gyri) and associated hyperintense T2-weighted signal changes in the adjacent white matter. It is difficult to visualize Palmini type I CD by MRI; however, on combining this with other modalities, such as positron emission tomography (PET) and magnetic source imaging (MSI), the detectability of this

lesion increases and foci of subtle grayâ€“white matter blurring may be visualized intraoperatively.

Macroscopic heterotopia and polymicrogyria (PMG) are occasionally seen in resection specimens from such patients. Loss of the normal cortexâ€“white matter junction, best appreciated with a KlÃ¼ver-Barrera or other myelin stain, is a frequent accompaniment and excellent predictor of severe microscopic CD. Many specimens, however, exhibit no striking gross cortical abnormalities. CD can be further characterized with regard to specific and easily identifiable microscopic abnormalities,

which include cortical laminar disorganization (Fig. 5), single heterotopic white matter neurons, excess neurons in the neocortical molecular layer, marginal glioneuronal heterotopia, white matter neuronal heterotopia, neuronal cytomegaly with or without associated dysmorphic features of the cytoplasm (the latter almost invariably accompanied by cytoskeletal abnormalities) (Fig. 6), and balloon cell change (Fig. 7).[117] These microscopic features can be used as the basis for a grading system for CD; one widely used schema is that presented recently by Palmini et al.[132]

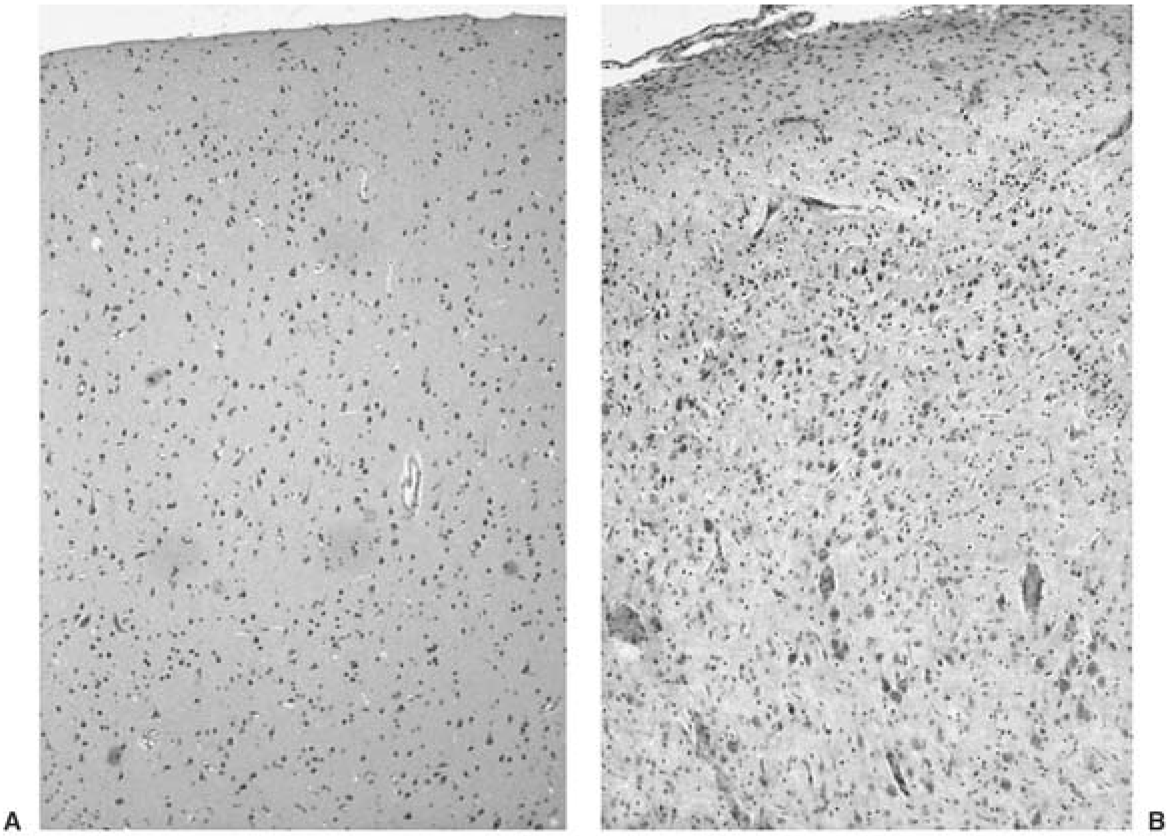

FIGURE 5. A: Relatively normally organized cerebral cortex from a surgical resection specimen. **B:** Region with severe cortical dysplasia shows pronounced cortical disorganization, with abnormal crowding of

neurons and abnormal orientation of many cells. Both panels are from micrographs photographed at the same magnification from sections stained with routine hematoxylin and eosin stains. (See the color insert.)

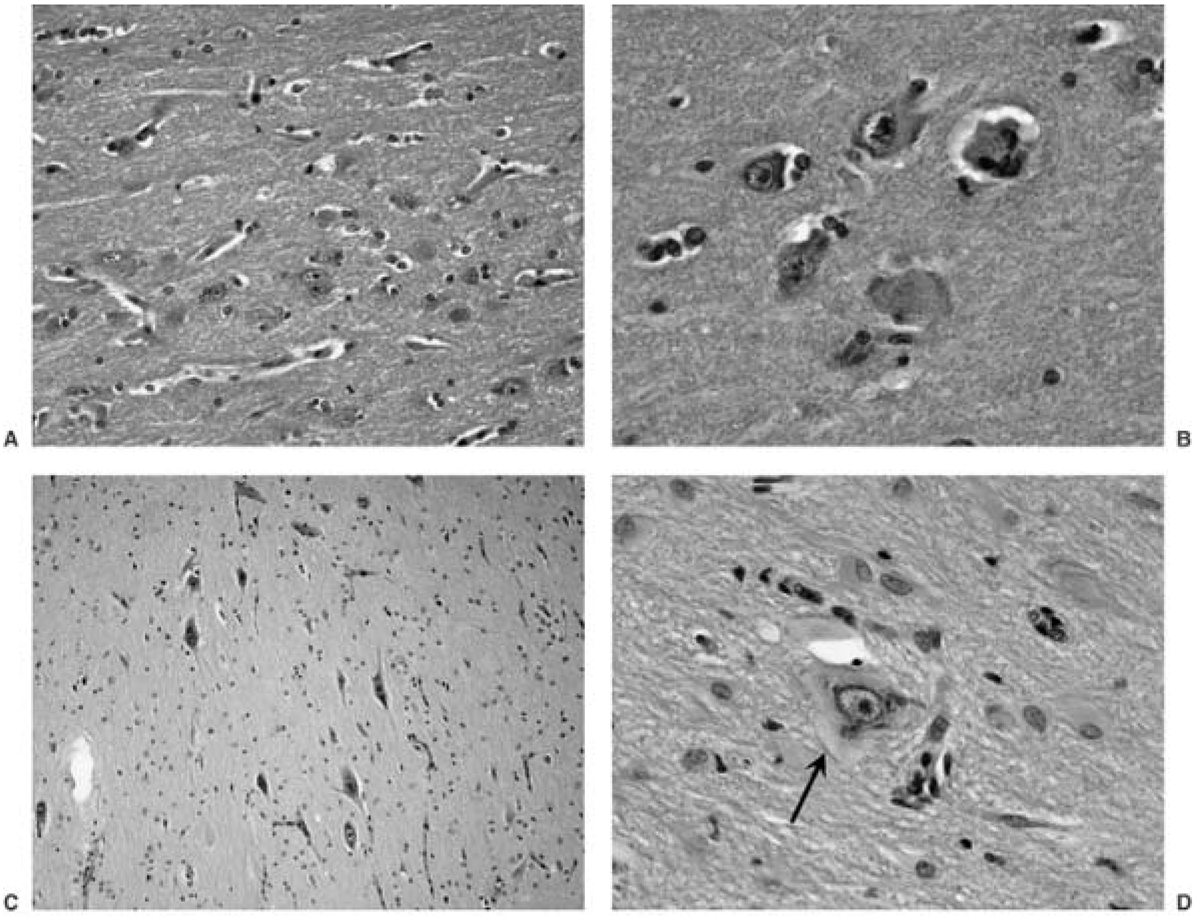

FIGURE 6. Neuronal disorganization and dysmorphism in cortical dysplasia/malformations of cortical development. **A:** Intermediate-magnification micrograph shows crowded and abnormally oriented neuronal cell bodies. **B:** Same features shown at a higher magnification. **C:** Variably enlarged and abnormally distributed neurons near the cortexâ€"white matter junction. **D:** Magnified view of a dysmorphic neuron (*arrow*) with clumping of Nissl substance around the nucleus and clearing of the peripheral cytoplasm. Gemistocytic astrocytes are seen distributed around this neuron. (All panels are from hematoxylin and eosinâ€"stained sections.) (See the color insert.)

Cortical laminar disorganization is the most ubiquitous microscopic finding, obviously because it represents a defining histopathologic feature of CD. Because neocortical architecture is the end result of the developmental processes of proliferation of neuronal precursors, migration, terminal differentiation, PCD, and cortical remodeling (see earlier discussion), abnormalities in any of these processes may result in abnormal cortical architecture. Cortical disorganization (as well as cytologic abnormalities in individual neurons, especially when fairly subtle) can be highlighted using immunohistochemistry that incorporates primary antibodies to neurofilament epitopes (Fig. 8). Although many neurons still reside in the intermediate zone/white matter in the last trimester of pregnancy and even into postnatal life,[80,163] the phenomenon of single heterotopic neurons in the white matter is accentuated in CD.[108] It is present in the majority of our patients with CD, and has been demonstrated in other series using morphometric techniques.[105] It has been suggested that injury to the radial glial fibers leads to a stranding of the migrating neuroblasts within the white matter, where they further differentiate into

mature neurons.[159] Alternatively, overproduction of neurons late in neurogenesis may lead to crowding of migrating neurons toward the cortical surface.[5] Morphometric analysis has also demonstrated a statistically significant increase in the number of neurons within the molecular layer of the cortex in epileptic patients versus controls,[107] and this is considered to be evidence of a slight maldevelopment of the neocortex, sometimes described as *microdysgenesis*, although this term is now felt to be imprecise and best avoided.[132] Persistence of the superficial granular layer (SGL) has been seen in association with many cortical malformations.[117] Marginal glioneuronal heterotopia consists of excrescences of disorganized neuroglial tissue extending from the pial surface into the subarachnoid space. They are often found in association with persistent SGL and tend to occur in the same brain region as the other malformations. These lesions may be associated with a failure of the glia limitans.[117] White matter neuronal heterotopia consists of disorganized masses of neurons in the white matter that usually occur in a periventricular position with a nodular morphology, although rare instances of laminar subcortical bands of heterotopic gray matter have been known to produce the appearance of a double cortex. It has been suggested that these are associated with injury to a group of radial glia, leading to failure of a group of neuroblasts to migrate.[159] Alternatively, a defect in genes controlling neuroglial interactions, neuroblast proliferation, and PCD has been suggested as being causal.[157]

PMG denotes small meandering gyri, often with bridging of the sulci by fusion of the molecular layers. It consists of two histologic types: Four-layered PMG is most frequently considered to result from a destructive lesion occurring approximately at 20 to 24 weeks' gestation, whereas an unlayered form is believed to result from an insult earlier in development (at approximately 13â€"16 weeks).[5] Whether PMG represents a destructive lesion with secondary malformation or a primary malformative lesion continues to be debated.[124,126,158]

Neuronal cytomegaly denotes enlarged neurons, some of which may also be dysmorphic (Fig. 9); these were first described by Taylor et al.[174] in association with seizure-producing focal cortical malformations or regions of dysplasia. Nerve cell hypertrophy was convincingly shown by Bignami et al.[15] using quantitative histochemistry in a case of HME. The differentiation of *cytomegalic* versus *dysmorphic* neurons is of importance in assigning a Palmini grade to a given lesion. Neurons that show enlargement of their cell bodies only are, in association with cortical architectural disorganization, typical of Palmini type IB lesions, whereas corticectomies that also contain dysmorphic neurons (defined as showing abnormalities of shape with abnormal orientation, cytoskeletal structure, and atypical dendritic arborizations) are characteristic of Palmini type II CD; when balloon cells are absent, the lesion is described as Palmini type IIA, and when they are present, it becomes Palmini type IIB. (Palmini IIB CD corresponds to what has been described as *Taylor-type focal cortical dysplasia* [T-FCD].) Dysmorphic neurons bear an extremely complex dendritic arborization as well as an abundance of perisomatic synapses and a paucity of axosomatic synapses.[28,154] Increased neuronal size has been associated with an increased DNA and RNA content, as well as increased nuclear and nucleolar volume suggestive of heteroploidy.[13,95] Many cytomegalic and dysmorphic neurons contain cytoskeletal abnormalities. Argyrophilic, neurofibrillary-like tangles, and cytoplasmic vacuoles have been demonstrated within many such neurons,[186] as has the existence of paracrystalline intracytoplasmic structures

visible on ultrastructural examination.[33] These neurofibrillary-like cytoplasmic inclusions are, like the neurofibrillary tangles seen in Alzheimer disease, strongly immunoreactive with antibodies to high- and medium-molecular-weight neurofilament (including phosphorylated and nonphosphorylated proteins), ubiquitin, and tau. However, they differ from the neurofibrillary tangles of Alzheimer disease in that they do not harbor paired helical filaments.[35] It is of interest that many cells within a focus of CD can coexpress neuronal and astrocytic epitopes, a phenomenon that can be easily demonstrated using confocal laser microscopy or immunohistochemistry on serial sections (Fig. 10).[32]

Balloon cells, showing considerable similarity to gemistocytic astrocytes, have eccentric nuclei and ballooned, opalescent eosinophilic cytoplasm (Fig. 7). They often demonstrate binucleation or dysmorphic nuclei, sometimes showing bridges of nucleoplasm between two separate islands of nuclear material within a cell.

They are noted to cluster at the cortexâ€“white matter junction or may be abundant within subcortical white matter.[32,184] Frequently, they are admixed with dysmorphic and enlarged neuronal cell bodies. Ultrastructurally, they are packed with filaments ranging in size from 400 to 600 nm in length and 30 nm in thickness, interspersed with nonâ€“membrane-bound, electron-dense, helical structures.[42] Vinters et al.[186] and others have demonstrated dual staining of many cells in dysplastic cortex (including some balloon cells) with antibodies to both neuronal and glial markers (synaptophysin and glial fibrillary acidic protein), implying either a failure of the cells to commit to a specific phenotype or a dedifferentiation. The resemblance of balloon cells to cells found within the cortical tubers of TSC has suggested the possibility that cases of CD harboring balloon cell change may represent a *forme fruste* of TSC,[32,42,130,131,155] as is discussed later. At least one group[179] has suggested that T-FCD (Palmini type IIB cortical dysplasia), when resected, has good postsurgical outcome.

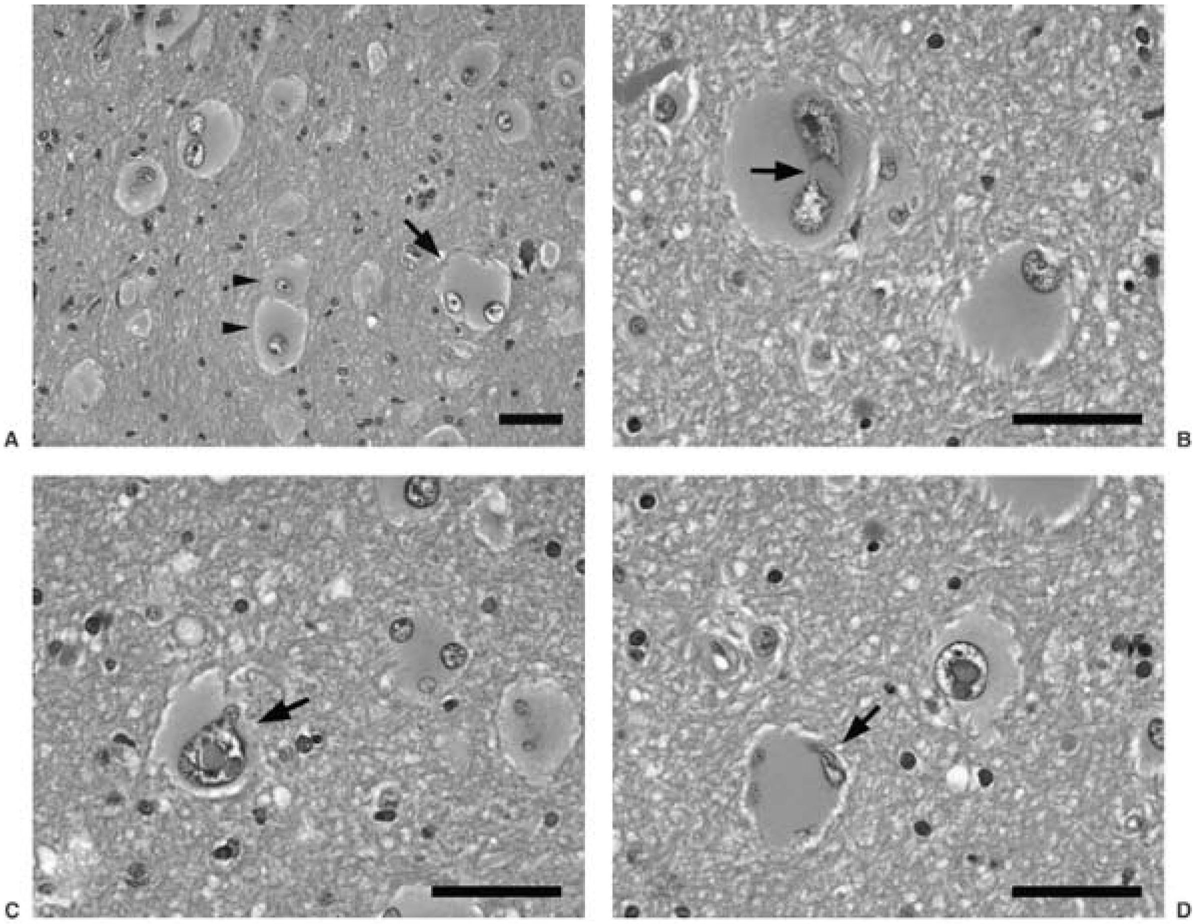

FIGURE 7. Typical balloon cells, with variably pronounced nuclear atypia. Hematoxylin and eosin stains. **A:** Balloon cells often show binucleation (*arrow*). Paired balloon cells are also seen (*arrowheads*). **B:** A balloon cell with a nuclear bridge connecting two nuclei (*arrow*). **C:** Balloon cell with marked nuclear atypia and/or nuclear invagination with nuclear budding (*arrow*). Also note the Marinesco body-like intranuclear inclusion. **D:** Balloon cell with multinucleation and/or micronucleation (*arrow*). Bars = 50 Âµm. (From Crino PB, Miyata H, Vinters HV. Neurodevelopmental disorders as a cause of seizures: neuropathologic, genetic, and mechanistic considerations. *Brain Pathol*. 2002;12:212â€“233; with permission.) (See the color insert.)

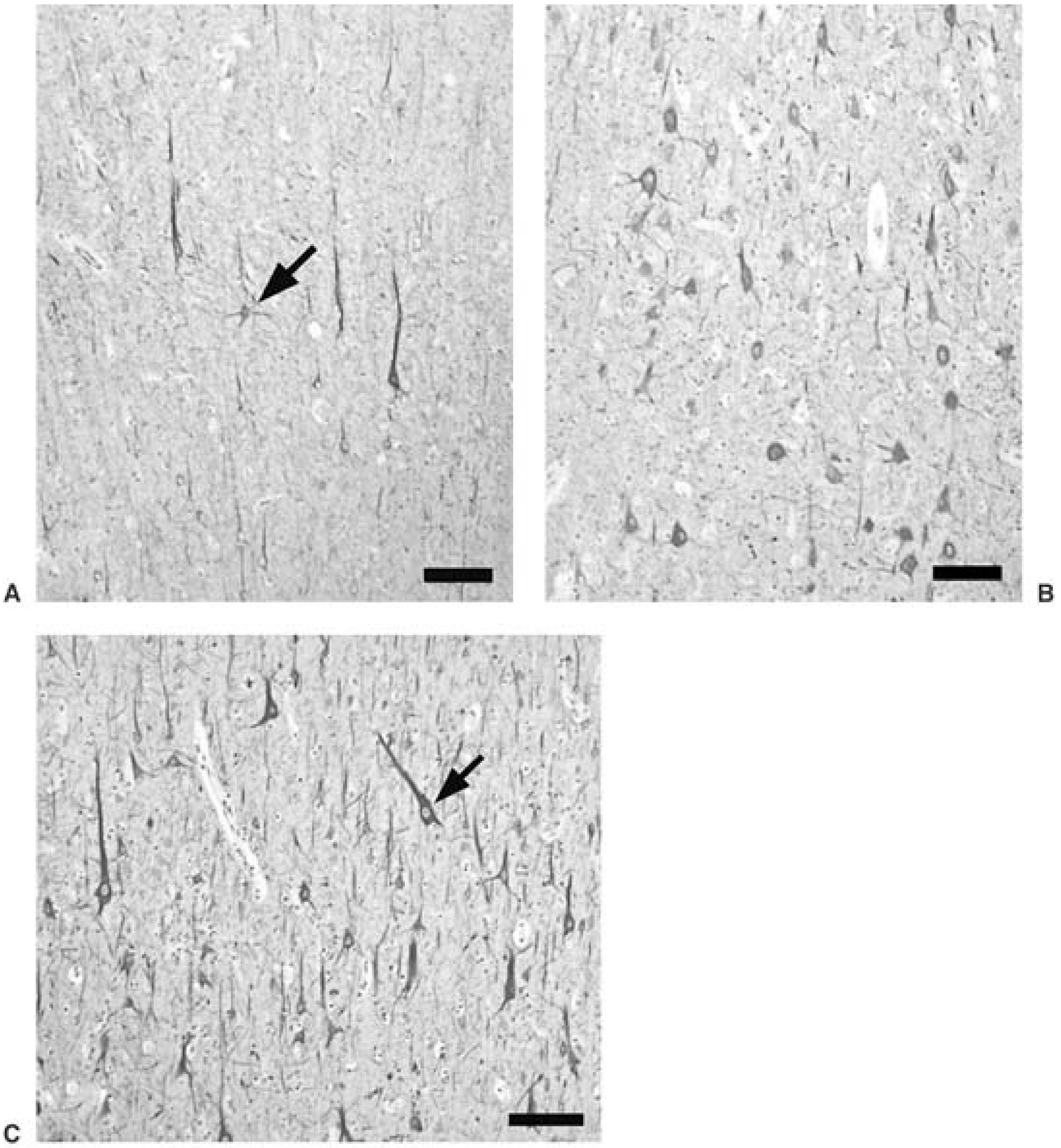

FIGURE 8. Neurofilament (N52, high-molecular-weight neurofilament antibody) immunohistochemistry of surgically resected corticectomies. **A:** Relatively normal cortex from a patient with temporal lobe epilepsy. Some, although not all, of the pyramidal neurons in layers III and V as well as multipolar interneurons (*arrow*) are positive for N52. **B:** Focal cortical dysplasia. Neuronal dyslamination and dysmorphic, multipolar, cytomegalic neurons are evident. **C:** Relatively normal cortex adjacent to a region of cortical dysplasia. More pyramidal neurons (in layers III and V) are more strongly immunoreactive for N52 than in control cortex (A), and an abnormally oriented pyramidal neuron (*arrow*) is also easily identified. The pial surface is at the top in each panel. Bars = 100 Âµm. (From Crino PB, Miyata H, Vinters HV. Neurodevelopmental disorders as a cause of seizures: neuropathologic, genetic, and mechanistic considerations. *Brain Pathol*. 2002;12:212â€"233; with permission.) (See the color insert.)

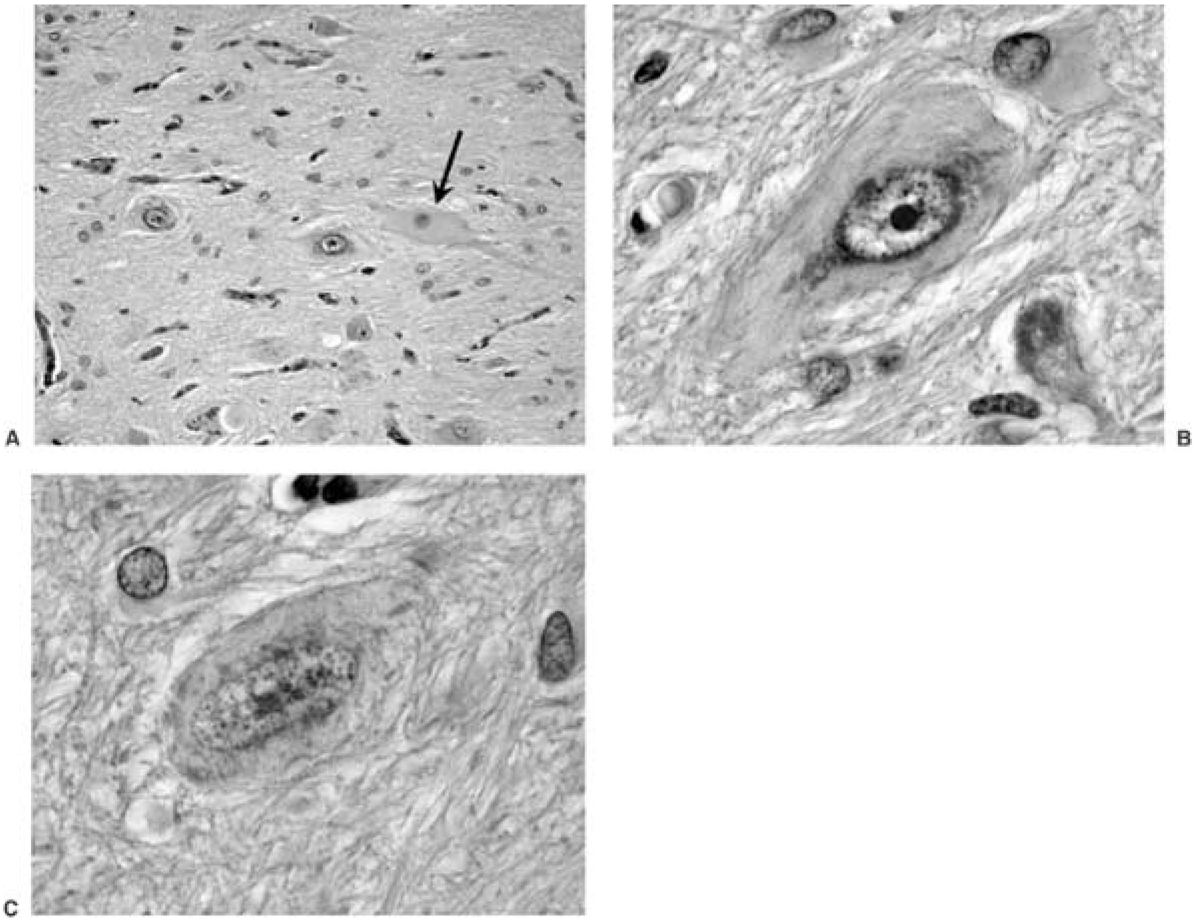

FIGURE 9. Histologic features of severe cortical dysplasia. **A:** Dysmorphic and enlarged neuronal cell bodies. Arrow indicates a cell that shows a â€œneuronalâ€ nucleus but pale, glassy amphophilic cytoplasm (lacking Nissl substance) of the type more commonly seen in gemistocytic astrocytes. **B, C:** Dysmorphic, enlarged neurons with coarseness of the cytoplasm, suggestive of neurofibrillary change. (All panels are micrographs from hematoxylin and eosinâ€“stained sections.). (See the color insert.)

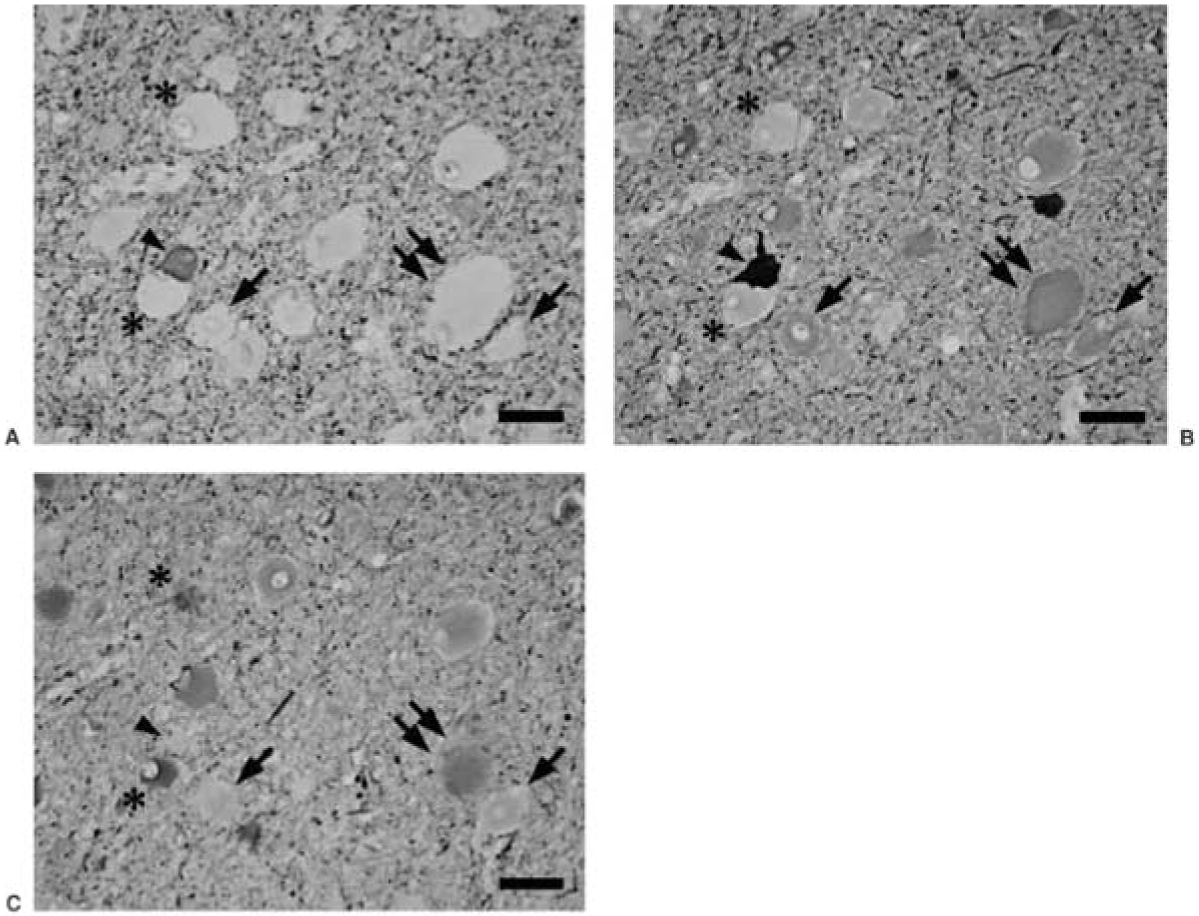

FIGURE 10. Balloon cells show various patterns of neuroectodermal differentiation. Some show only glial (glial fibrillary acidic protein [GFAP]) or neuronal (neurofilament) differentiation, whereas others show both GFAP and neurofilament immunoreactivity. Only rare balloon cells are immunoreactive for phosphorylated neurofilament (*arrowhead*, panel A). However, most are immunoreactive with nonphosphorylated neurofilament (panel B) with varying intensities. Some are immunoreactive for both GFAP and nonphosphorylated neurofilament (*double arrows*, panels B and C). Symbols and arrows in all panels indicate the same cell identified in serial sections. Arrowhead indicates a balloon cell that is phosphorylated neurofilament (p-NF)-positive, NF-positive, and GFAP-negative. Arrows indicate balloon cells that are p-NF-negative, NF-positive, and GFAP-negative. Asterisks indicate balloon cells that are p-NF and NF-negative but GFAP-positive. Double arrow indicates a balloon cell that is p-NF-negative, NF-positive, and GFAP-positive. Bars = 50 Âµm. (Panel A, section stained with primary antibody to phospho-NF, panel B with primary antibody to NF, panel C with primary antibody to GFAP). (From Crino PB, Miyata H, Vinters HV. Neurodevelopmental disorders as a cause of seizures: neuropathologic, genetic, and mechanistic considerations. *Brain Pathol*. 2002;12:212â€“233; with permission.) (See the color insert.)

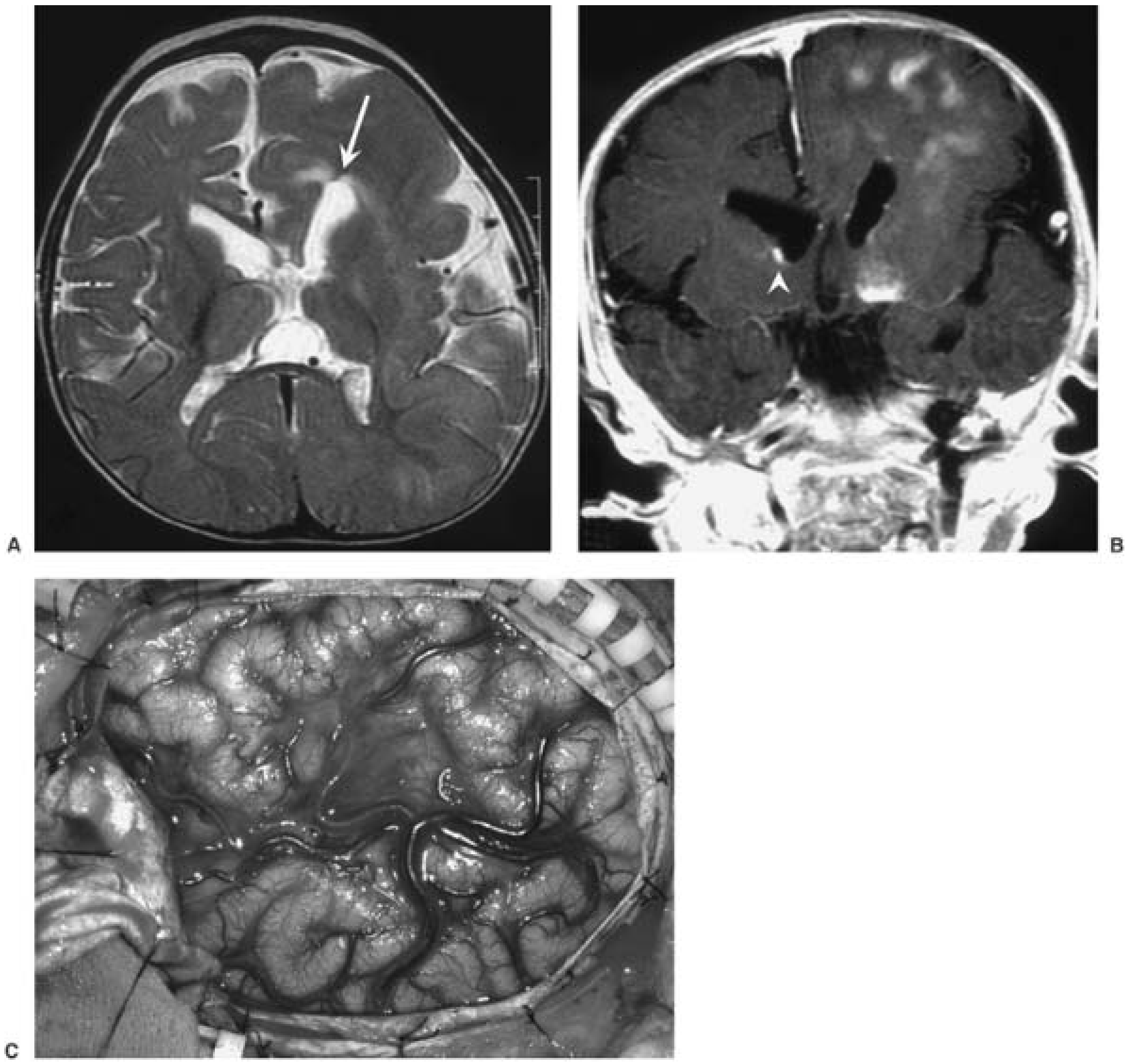

FIGURE 11. Hemimegalencephaly (HME) in a 13-month-old child with tuberous sclerosis complex (TSC). **A:** Axial T2-weighted image shows thickened gyri of the left frontal lobe, with an enlarged left cerebral hemisphere, suggesting HME. Most of the white matter in the left cerebral hemisphere is poorly myelinated. A well-defined subcortical hyperintense T2-weighted signal is noted in the left anterior cingulate gyrus, consistent with a tuber (*white arrow*). **B:** Postcontrast T1-weighted coronal image shows patchy foci of enhancement in the left cerebral hemispheric white matter, suggesting locations of tubers. A small, round focus of enhancement in the inferior aspect of the right frontal horn of the lateral ventricle (*white arrowhead*) represents a subependymal nodule, also characteristic of TSC. **C:** Intraoperative view of the left cerebral hemisphere showing multiple areas of abnormal cortical organization. The frontal lobe is in the upper left and the parietal lobe is in the upper right of the image.

Pathogenesis of Cortical Dysplasia

Although it is accepted that cortical dysplasia involves abnormal cerebral cortical development, it is unclear when it occurs and how it produces seizures. Most classification systems of MCDs are based on speculating when the first development steps involving cell proliferation, neuronal migration, and cortical organization abnormality occurs to produce the malformed cortex. Previously, the presumed mechanisms of surgically treated CD pathogenesis have been believed to be defects in neuronal migration to explain subcortical heterotopic neurons, and altered periventricular neuroglial differentiation to account for the abnormal cytomegalic and dysmorphic neurons and balloon cells.[146,161,179] Although such mechanisms appear to be operant in genetic forms of malformations of cortical development, clinicopathologic investigations have challenged this singular interpretation in surgically treated cortical dysplasia.[8,23,24,25,26]

In recent studies, the UCLA group has found evidence that surgically treated cortical dysplasia seems to involve retention of cells of the human pre- and subplate along with overproliferation of cortical neurons. Prenatal human subplate cells have morphologic features similar to those of dysmorphic neurons found in postnatal CD tissue.[23] The normal human subplate contains large multipolar neurons similar to cytomegalic neurons, and polymorphous and fusiform neurons with thick primary dendrites along with inverted pyramidal-shaped neurons, a feature seen in dysmorphic CD neurons.[80] Most human subplate cells degenerate in the 4 to 6 weeks prior to birth,[29,43] which coincides with increasing definition of the grayâ€"white matter junction and secondary gyral folding.[27] Furthermore, toward the end of normal neurogenesis, periventricular radial glial cells attach themselves to the tailing processes of the last-produced cortical pyramidal neurons and migrate toward the cortex, where they detach and eventually transform into protoplasmic astrocytes.[82,121,123] This may explain why balloon cells in CD tissue have morphologic and other characteristics similar to those of radial glia.[40,176,193]

The UCLA group has proposed that CD pathogenesis probably involves partial failure of later phases of corticogenesis. As a consequence, subplate and radial glial degeneration and transformation would be reduced or prevented, giving the appearance of abnormal dysmorphic cells in postnatal CD tissue. In addition, failure of late cortical maturation could explain the

presence of abnormally thickened gyri with indistinct cortical grayâ€"white matter junctions in MRI scans of CD patients.[24] The timing of these events during cortical development would explain the different forms of CD identified by MRI and severity of CD by histopathology. Developmental alterations during the late second or early third trimester would account for severe CD, like hemimegalencephaly, whereas events occurring closer to birth (after the subplate has nearly degenerated) would explain milder forms of CD. In addition, it appears that there is an overproduction of neurons in later phases of cortical development. MRI cerebral hemisphere volumes were normal or increased in the case of hemimegalencephaly, and cortical thickness was the same or slightly increased.[5,158] Furthermore, neuronal densities were increased in the upper gray matter, molecular layer, and subcortical white matter. The location of excess neurons would be consistent with the idea that this process occurred in later periventricular cell cycles (i.e., the ones toward the end of neurogenesis). Thus, heterotopic subcortical white matter neurons are likely the result of excessive late generated pyramidal neurons trying to migrate toward the already overly crowded cortical ribbon, in combination with residual prenatal subplate neurons that failed to degenerate prior to birth.

Cortical Tubers of Tuberous Sclerosis Complex (TSC)

Tuberous sclerosis complex (TSC, or Bourneville disease) is an autosomal-dominant, multisystem disorder in which the CNS, eyes, kidneys, skin, and heart are most commonly

affected by malformative, hamartomatous, or neoplastic lesions.[31,51,84,162,187] It has an incidence of 1 in 9,400 to 10,000 births[31,51]; however, accurate estimates are difficult to ascertain because of the markedly variable penetrance of the disorder; it may go unrecognized for many years, and a high rate of spontaneous TSC gene mutations has been described.[31,188] The clinical presentation of an individual with TSC may be with infantile spasms, autism, or mental retardation. Approximately 85% of TSC patients who come to medical attention have experienced an epileptic seizure at some time. Because genetic analysis to confirm the diagnosis of TSC remains unavailable to most physicians, *diagnostic criteria* for TSC have been enunciated.[151,152] In the 1992 iteration, these included *primary* features of the disease (facial angiofibromas, multiple subungual fibromas, a [histologically confirmed] cortical tuber, [histologically confirmed] subependymal nodule (SEN) or subependymal giant cell astrocytoma (SEGA), [radiographically confirmed] multiple calcified SENs protruding into the ventricular cavity, and multiple retinal astrocytomas); *secondary* features (an affected first-degree relative, cardiac rhabdomyoma [confirmed by histopathology or radiographically], retinal hamartoma or achromic patch, cerebral tubers [radiographically confirmed], a Shagreen patch, forehead plaque, [histopathologically confirmed] pulmonary lymphangiomyomatosis or renal cysts); and *tertiary* features (hypomelanotic macules, [radiographically confirmed] renal cysts, etc.). In the 1998 revised criteria, some clinical features previously thought to be pathognomonic for TSC were considered less specific, whereas clinical/radiographic features of the disease were subdivided into major and minor categories based on their apparent degree of specificity for TSC. Based on these newer revised criteria, a definitive diagnosis of TSC is made by the confirmation of two or more distinct types of lesion in a patient, rather than multiple lesions of the same type (e.g., tubers) in the same organ system. In other words, no single lesion is one that *defines* the disease.

Neuropathology of Cortical Tubers as a Cause of Seizures

Individuals with TSC may rarely present with HME (Fig. 11). However, the characteristic brain abnormalities of TSC include neocortical tubers (Figs. 12 and 13), SENs, and SEGAs. Cortical tubers are very often associated with infantile spasms and intractable epilepsy in children. The lesions manifest as enlarged gyri in which the cortex/white matter junction has become blurred, resembling sporadic, severe cortical dysplasia.[32,117] Histologically, these lesions show disorganized neocortex, with a variety of dysmorphic, markedly enlarged neurons and bizarre gemistocytic astrocyte-like â€œballoon cellsâ€ having eccentric nuclei containing relatively coarse chromatin and glassy eosinophilic cytoplasm (Fig. 13). Balloon cells seen in TSC strongly resemble those seen in severe cortical dysplasia or focal cortical dysplasia of Taylor type. This observation has frequently raised the possibility that cases of CD with

balloon cell change represent a *forme fruste* of TSC.[42,130,131,155] Balloon cells, like those seen in FCD, show morphologic and immunohistochemical features of both neurons and astrocytes, suggesting a failure of commitment in neuroglial differentiation (Fig. 14), that is, they are variably immunoreactive, even among cells within a tuber, for glial fibrillary acidic protein (GFAP) and neuronal markers. Balloon cells may cluster together, particularly in the subpial region or subcortical white matter, or be scattered among dysmorphic neurons. Tubers may show prominent punctate calcification. Whereas cortical tubers demonstrate reduced immunoreactivity for the synaptic protein synapsin 1,[88] giant cells within TSC tubers show dramatic halos of synaptophysin immunoreactivity resembling those noted in gangliogliomas, as well as strong immunostaining with antibodies to the microtubule-associated protein 2 (MAP-2).[192] Alpha B-crystallin, a member of the heat-shock-protein family of peptides, is found in abundance within dysgenetic cells of tubers and within both SEGAs and SENs.[66] Dysmorphic cytomegalic neurons express high levels of tuberin, as do individual cells within SEGAs and SENs. In a developmental time frame, tuberin appears to be present in most neuronal populations of the CNS from at least 20 weeks of gestation, with an apparent upregulation of its expression after 40 weeks of gestation.[187] Hamartin was found, albeit with a weaker signal, in the same cell types during CNS development.

Whereas architectural disarray is a defining feature of a tuber, cellularity of a lesion may be extremely variable, although when high cell density is noted, a tuber may resemble a ganglioglioma.[150,187] Although the proliferative potential of these lesions appears to be low, as judged by immunohistochemistry for Ki-67, other markers of cellular proliferation (e.g., collapsin response mediator protein 4 [CRMP4], doublecortin) are expressed within giant cells of cortical tubers and SEGAs (human-derived material) and SENs of Eker rats, suggesting that they may represent newly generated cells that have migrated into tubers from the subventricular zone.[86]

Genetic and Molecular Biologic Aspects of Tuberous Sclerosis Complex Pathogenesis

Our understanding of the molecular pathogenesis of TSC represents a triumph of multidisciplinary, multicenter (often multicontinent) collaborations through the early 1990s focused on characterizing the complex gene defects that cause this disorder.[41,68,137,181] TSC is caused by mutations in one of two nonhomologous tumor suppressor genes: *TSC1*[181] on chromosome 9 (9q34) encoding a 130-kDa protein, hamartin, and *TSC2*[41] on chromosome 16 (16p13.3) encoding a 200-kDa protein, tuberin. About half of TSC families show linkage to each of the two identified genes. *TSC1* mutations, accounting for a minority of mutations identified, are slightly less common in sporadic TSC patients and are more common in familial cases (13%â€"50%).[94] The putative functions of both *TSC1* and *TSC2* gene products have been intensively studied using

mostly *Drosophila* and rodent models of TSC, but also using human tissues and loss-of-heterozygosity analyses of TSC hamartomas. These initially suggested that both *TSC1* and *TSC2* gene products, even before the details of their encoded proteins were known, had growth suppressor properties.[20,53,54] Significant interactions of TSC genes with intracellular signaling pathways have been implicated, as shown in FIGURE 15. Hamartin possesses a coiled-coil domain in its carboxy region, suggesting the possibility of a functional proteinâ€"protein interaction with tuberin[181] to regulate cell proliferation and cell cycle progression.[21,62]

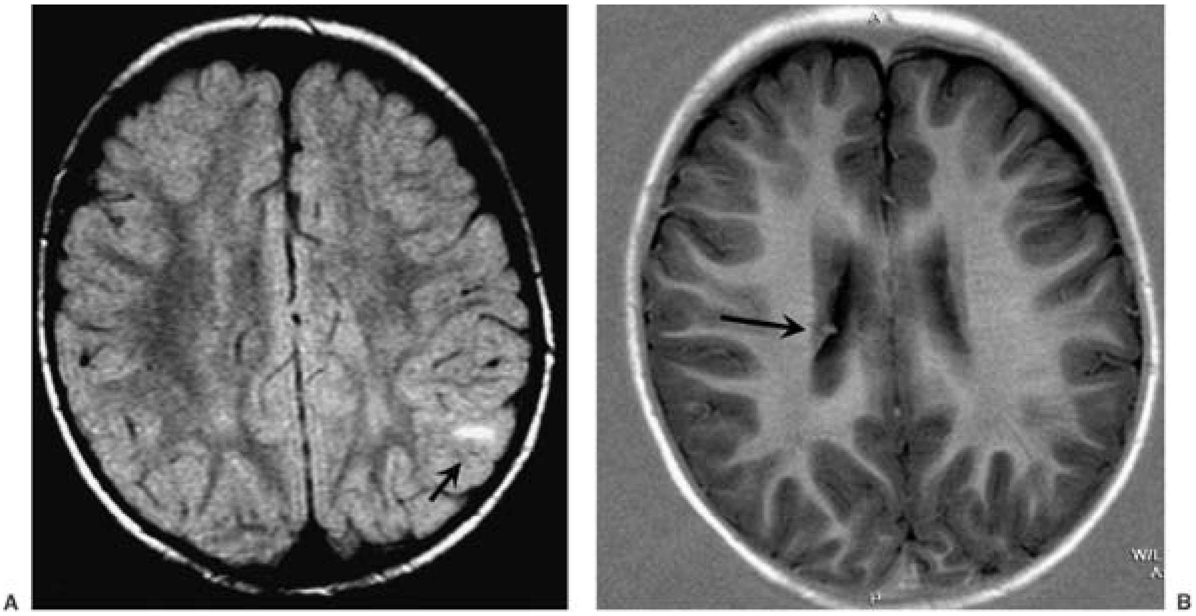

FIGURE 12. Tuber of tuberous sclerosis complex. **A:** Axial FLAIR (fluid attenuated inversion recovery) image shows a focus of hyperintensity in the left parietal lobe subcortical white matter (*arrow*). This patient also has multiple similar foci in the cerebrum. **B:** Axial T1-weighted inversion recovery image shows foci of subependymal nodules (*arrow*) along the ventricular wall.

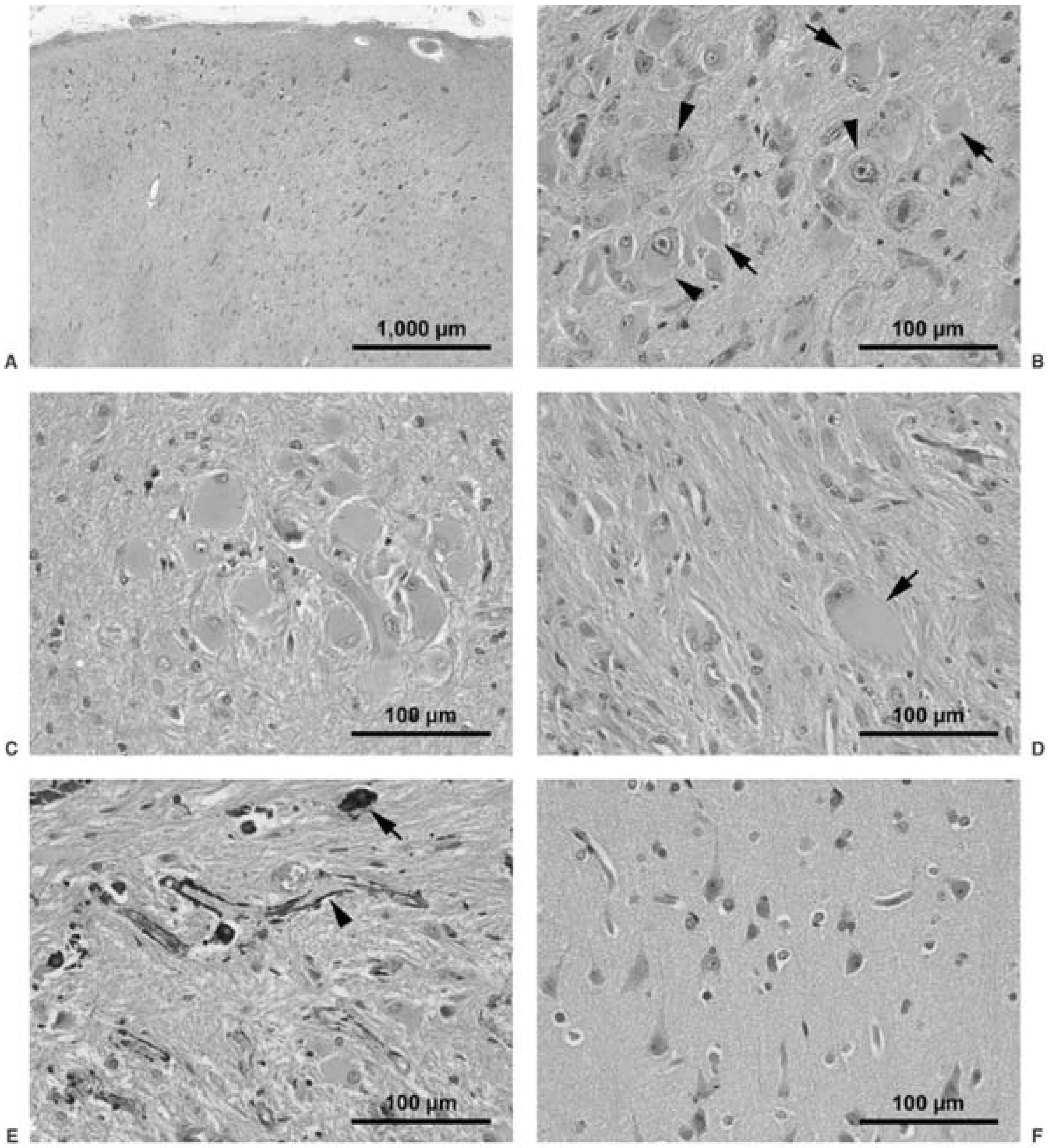

FIGURE 13. Cortical tuber in a child with tuberous sclerosis complex (TSC). **A:** Low-magnification view shows a disorganized collection of neuroglial cells, some enlarged. **B:** Magnified view of the lesion showing â€œballoon cellsâ€ with eccentric nuclei and glassy eosinophilic cytoplasm (*arrows*), admixed with dysmorphic, markedly enlarged neurons containing Nissl substance in their cytoplasm (*arrowheads*). **C:** A cluster of balloon cells within the tuber. **D:** An abnormal neuroglial cell showing morphologic features of both dysplastic neuron and balloon cell (*arrow*). Note the eccentric nucleolated nucleus and the enlarged pale but slightly basophilic cytoplasm, raising the possibility that the cell represents a transitional form of neuroglial cell. **E:** Various degrees of punctate calcification (*arrows*) and calcifications along vessel walls (*arrowheads*) are often seen in TSC tubers. **F:** Morphologically normal cerebral cortex (for comparison with features of the tuber). (All panels are micrographs from sections stained with hematoxylin and eosin.) (See the color insert.)

Hamartin may also interact with other proteins, including the ERM (ezrin, radixin, and moesin) family of actin-binding proteins, to activate small GTPases of the Rho subfamily (Rho GTPases).[85] Rho GTPases are important regulators of the actin cytoskeleton and are thought to be involved in neuronal developmental processes including neuronal migration, establishment of polarity, axon growth and guidance, dendrite elaboration and plasticity, and synapse formation.[92] ERM proteins belong to the band-4.1 superfamily of membrane-cytoskeleton linking proteins.[173] These proteins are believed to function in multiple different fashions according to their interaction with various membrane proteins, Ras superfamily GTPases, and the actin cytoskeleton, and appear to be involved in the formation of microvilli, cellâ€"cell adhesion, maintenance of cell shape, cell motility, and membrane trafficking.[90] The fact that hamartin binds to ezrin in vivo and can modulate the activity of RhoA (Ras homologous member A)[85] suggests that tuberin and hamartin may be attached to the membrane-cytoskeletal cortex through activated ERM proteins.[72] Evidence from several reports suggests that ERM proteins function at a position upstream and downstream of Rho GTPases to regulate cellular adhesion and motility.[103,170,171] ERM proteins (ezrin and moesin) are expressed in germinal matrix cells, migrating cells, and radial glial fibers in the developing human brain,[72] correlating with RhoA expression in proliferating and migrating cells in the developing rat brain.[129] Dysfunction of tuberin and hamartin may perturb communication between ERM proteins and Rho GTPase to cause abnormal neuronal migration, polarity, and morphology, resulting in the formation of dysplastic

cortex. Hamartin and tuberin are coexpressed within a population of abnormal neuroglial cells,[71] and both TSC gene products and ERM proteins are also coexpressed within a subpopulation of abnormal neuroglial cells in TSC tubers,[72] suggesting the upregulation of ERM proteins within these cells in response to a TSC gene mutation. Abnormalities of radial glia have also been implicated in the pathogenesis of brain lesions of TSC.[133]

Tuberin contains a conserved 163-amino acid carboxy-terminal region that exhibits sequence homology to the catalytic domain of a GTPase-activating protein (GAP) for the low-molecular-weight GTPase Rap1[189] and for Rab5.[191] Based on in situ hybridization with a digoxigenin-labeled cDNA probe, TSC2 mRNA was found to be widely expressed in various cell types throughout the body, including epithelia, lymphocytes, and endocrine organs; within the CNS, it was prominently and selectively expressed within neurons, especially motor neurons, including cortical, brainstem, and spinal cord neurons.[109] Widespread expression of the *TSC2* gene within developing and adult nervous system was noted in another study using reverse transcription-polymerase chain reaction (RT-PCR), Northern blot, and in situ hybridization analysis.[48] The results of a study in mice showed that tuberin localized to the perinuclear region of cerebellar Purkinje cells, whereas hamartin was noted to distribute along neuronal or astrocytic processes.[56] Bases on human autopsy and biopsy material, *TSC2* mRNA and tuberin were found in abundance in many CNS cell types, including neurons and ependymal cells.[79] *TSC2*-negative fibroblasts show inactivation of the cyclin-dependent kinase inhibitor p27.[165] Mutations in *TSC2* may result in constitutive activation of Rap1, leading to enhanced proliferation or incomplete cellular differentiation.[164]

TSC1 and *TSC2* gene products colocalize within tubers (and sometimes within individual dysmorphic cells) of patients with TSC.[71] Tissue culture experiments in various cell types, using both confocal laser microscopy and coimmunoprecipitation, show that both hamartin and tuberin interact with the G2/M cyclin-dependent kinase CDK1.[21] It has further been suggested that hamartin and tuberin have separable functions in mammalian cell cycle regulation,[115] that is, that hamartin itself has the ability to modulate cell proliferation independent of the presence of functional tuberin, and binding to hamartin is not always essential for tuberin to affect cell proliferation. *Tsc1* and *Tsc2*, *Drosophila* homologs of *TSC1* and *TSC2*, function together in vivo to negatively regulate cell size, cell proliferation, and organ size in the insulin signaling pathway (PI3Kinase-Akt/PKB-mTOR-S6K-S6) at a position downstream of *dAkt* (*Drosophila Akt*) and upstream of *dS6k* (*Drosophila S6 kinase*).[136] This has been clearly confirmed in surgically resected TSC tubers by means of quantitative immunohistochemical evaluation using tissue microarray methodology,[118] and constitutive activation of S6K has been observed in TSC tubers but not in focal cortical dysplasia of Taylor type (T-FCD or CD Palmini type IIB), suggesting one difference between these MCDs (Fig. 16).[11,118] Recent studies have also revealed Rheb (Ras homolog enriched in brain) GAP activity of tuberin playing a role in regulation of S6K and 4E-BP1,[65,167,195] indicating indirect regulation of the insulin signaling pathway by TSC genes through the inhibition of Rheb activity.

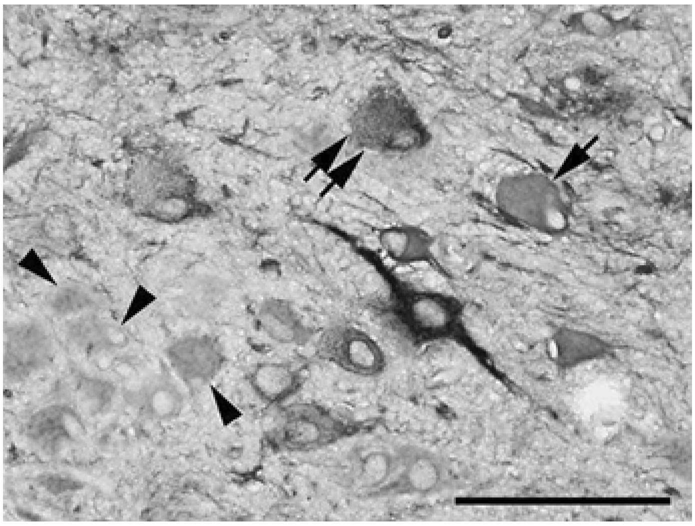

FIGURE 14. Immunohistochemical findings in a tuberous sclerosis complex (TSC) tuber. Double-label immunohistochemistry confirms colocalization of glial fibrillary acidic protein (GFAP) (*brown color*) and nonphosphorylated neurofilament (*purplish-blue*) in a subpopulation of balloon cells (*arrowheads*) in a TSC tuber, suggesting a failure of commitment in neuroglial differentiation. Note that some abnormal neuroglial cells are immunoreactive for GFAP (*arrow*) or nonphosphorylated neurofilament (*double arrows*). Scale bar = 100 Âµm. (See the color insert.)

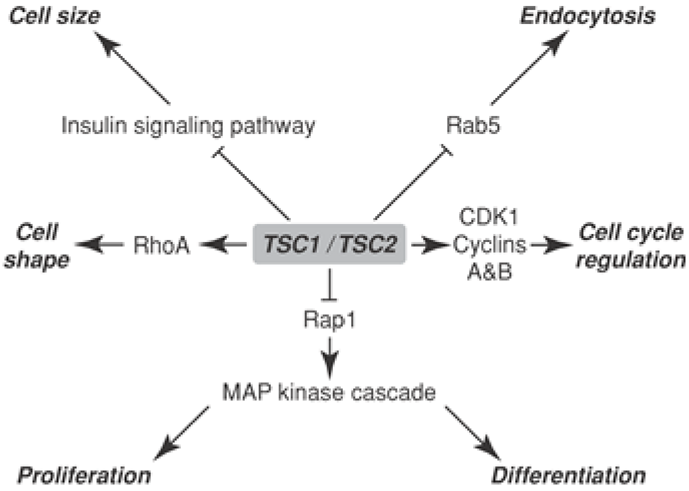
Cell size
Endocytosis
Insulin signaling pathway
Rab5
Cell shape
RhoA
TSC1 / TSC2
CDK1 Cyclins A&B
Cell cycle regulation
Rap1
MAP kinase cascade
Proliferation
Differentiation

FIGURE 15. Schematic summary of the functions of tuberous sclerosis complex (TSC) genes. The functions of both *TSC1* and *TSC2* gene products have been intensively studied using mostly *Drosophila*, tissue culture, and rodent models. This diagram briefly summarizes significant interactions of TSC genes with intracellular signaling pathways. CDK, cyclin-dependent kinase; MAP, microtubule-associated protein.

Sturge-Weber-Dimitri Syndrome/Encephalo-Trigeminal Angiomatosis

This is a rare, nonfamilial, neurocutaneous syndrome of unknown etiology[124,126,182] encountered in surgical specimens from infants and children with intractable epilepsy, although much less commonly than destructive and malformative/hamartomatous lesions. The frequency of Sturge-Weber-Dimitri (SWD) syndrome is estimated to be 1 per 50,000 live births,[59] and 75% to 90% of children with SWD syndrome

develop partial seizures by 3 years of age.[97] Clinicopathologic reports describe the association of the cerebral lesion, usually localized to the occipital cortex, with facial capillary hemangioma (â€œport-wine stainâ€) in the distribution of the ophthalmic division of the trigeminal nerve, and provide excellent accounts of the natural history of the disorder.[127,182,190] Visceral angiomas may be encountered in some patients.[14] Neuroimaging features are highly characteristic (Fig. 17).

Neuropathologic abnormalities in cortical resection specimens (Fig. 18) are easily appreciated at low magnification, and soft tissue radiographs of the sliced specimen may show the characteristic â€œtram-trackâ€ pattern of neocortical calcification. The leptomeningeal angiomatosis is a key diagnostic feature of SWD syndrome,[177] characterized by some authors as a venous angioma,[190] consisting of dilated and tortuous thin-walled blood vessels within the subarachnoid space and pia, which may extend into the underlying cerebral cortex and even subcortical white matter. The cortex itself shows calcifications centered on microvessels, with associated neuronal loss, astrocytic gliosis, and extensive cortical atrophy[124,126] that is assumed to result from ischemic phenomena secondary, at least in part, to the meningeal angiomatosis. Associated malformations such as polymicrogyria, agyria/pachygyria, heterotopias, and cortical disorganization can also be seen.[182] Ultrastructural studies of the parenchymal calcifications in Sturge-Weber brain have suggested that the earliest calcium deposits occur within perithelial cells of small blood vessels, and that the underlying cause of the calcification may be anoxic injury to endothelial, perithelial, and glial mitochondria due to stasis and abnormally increased vascular permeability of vessels in the hemangioma.[55,125]

Neurofibromatosis, Meningio-angiomatosis, and Other Neurocutaneous Syndromes

Central neurofibromatosis (NF-2) is a genetic disorder characterized by neoplastic and dysplastic lesions of Schwann cells, meningeal cells, and glia.[89,104] It is associated with (a) Schwannomas, both central and peripheral, including bilateral acoustic Schwannomas; (b) meningiomas; (c) gliomas; and (d) glial hamartomas. It is inherited in an autosomal-dominant fashion, with a high rate of sporadic mutations (up to 50%).[89,104] The *NF-2* gene, postulated to be a tumor-suppressor gene, has been localized to chromosome 22q12 and encodes a widely expressed protein, merlin (moesin, ezrin, radixinâ€“like protein) or schwannomin, which is a new member of the protein 4.1 family of cytoskeleton-associated proteins.[89,93] Although seizures can develop in patients with NF-2, these are usually caused by a primary neoplasm rather than a primary malformative lesion. The most frequent malformations seen in association with NF-2 are meningio-angiomatosis and glial hamartomas. Meningio-angiomatosis[77,134] is a rare malformation of the cerebral cortex of unknown etiology, described in more detail in Chapter 12, where it is placed in the context of other neoplasms that are associated with seizures. Rare neurocutaneous syndromes, such as epidermal nevus syndrome and hypomelanosis of Ito,[81] have also been associated with pediatric epilepsy, serving to emphasize the interrelated development of the CNS and overlying mesenchyme. The pathologic changes seen within the cerebral cortex of these patients are virtually identical to those seen in patients with CD.

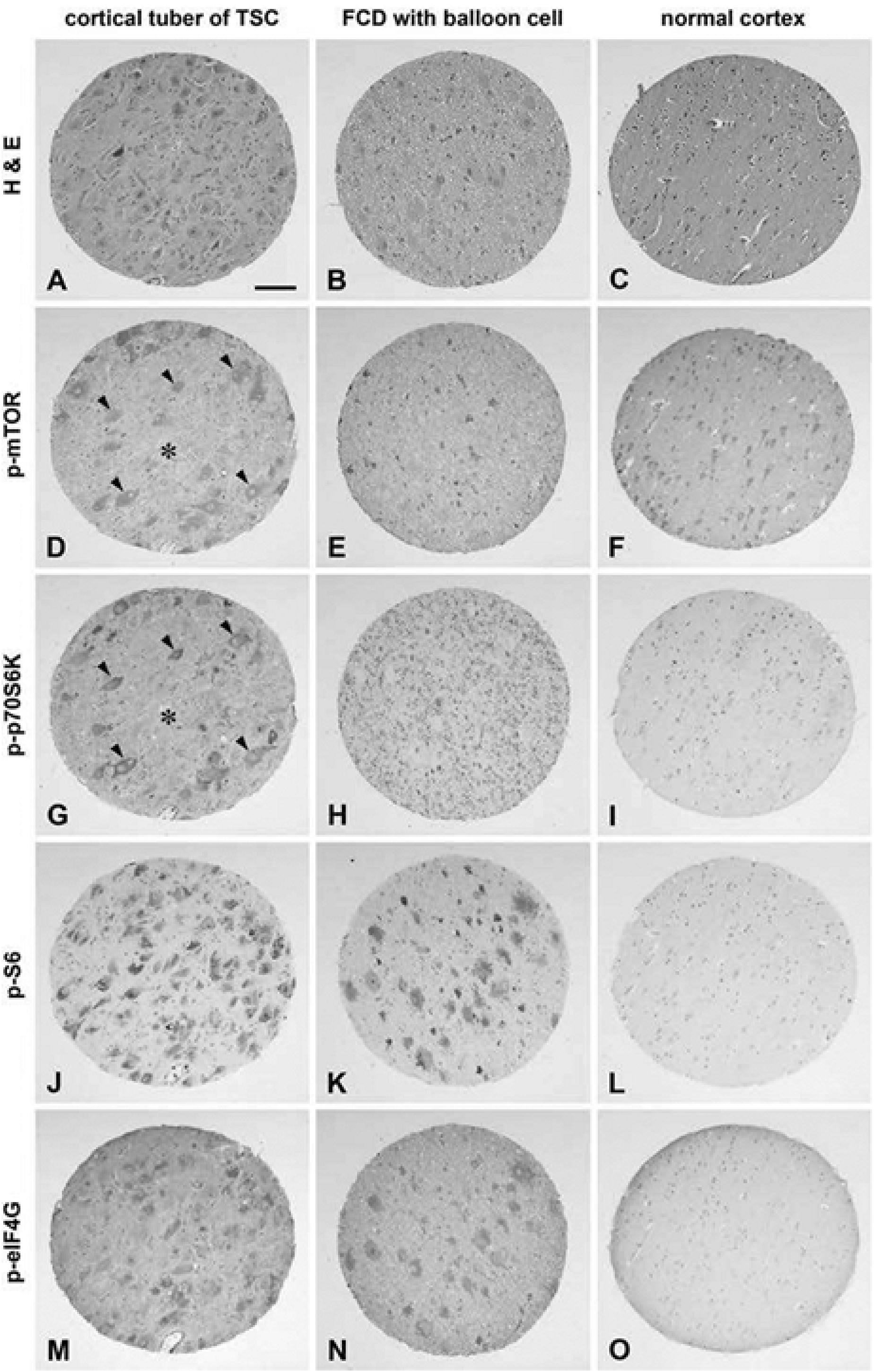

FIGURE 16. Tissue microarray (TMA) analysis of insulin signaling pathways in tuberous sclerosis complex (TSC) tubers, focal cortical dysplasia, and control tissues. The left column represents sample cores from a TSC tuber **(A, D, G, J, M)**; the middle column represents focal cortical dysplasia (FCD) with balloon cells (Palmini type IIB) **(B, E, H, K, N)**; and the right column represents histologically normal cerebral cortex **(C, F, I, L, O)**. Stained with hematoxylin and eosin (H&E) (Aâ€"C), p-mTOR (Dâ€"F), p-p70S6K (Gâ€"I), p-S6 (Jâ€"L), and p-eIF4G (Mâ€"O). Immunostains were performed on consecutive serial sections, and the same cells can be easily identified in different stains (e.g., *arrowheads* in D and G). Expression of p-p70S6K appears to be specific to the TSC tuber (panel G). Note the population of abnormal neuroglial cells in the TSC tuber expressing p-S6 and/or p-eIF4G (e.g., central area of each

core shown in panels J and M), despite negative expression of p-mTOR and p-p70S6K (the same areas indicated by asterisks in panels D and G). Each core has a 0.6-mm diameter. Bar = 100 Âµm. eIF4G, eukaryotic translation initiation factor 4G; mTOR, mammalian target of rapamycin; p-, phospho-; p70S6K, 70-kDa ribosomal protein S6 kinase; S6, 40S ribosomal protein S6. For details of methodology, see Miyata et al. (2004). (From Miyata H, Chiang ACY, Vinters HV. Insulin signaling pathways in cortical dysplasia and TSC-tubers: tissue microarray analysis. *Ann Neurol*. 2004;56:510â€“519; with permission.) (See the color insert.)

Vascular Malformations

Cerebral vascular malformations are a group of â€œcongenitalâ€ developmental abnormalities of the cerebral blood vessels, which can be divided, based on pathologic features, into five main groups: (a) arteriovenous malformations, (b) cavernous hemangiomas, (c) venous angiomas, (d) capillary telangiectases, and (e) varix or aneurysm of the great vein of Galen (which is actually an arteriovenous malformation or fistula).[76,100,183] The term â€œcongenitalâ€ is placed in quotation marks because neuropathologists almost never encounter these lesions (with the exception of vein of Galen aneurysms) in infants or young children. Despite this, there is a widespread belief that the nidus of a future vascular malformation is present early in brain development. Arteriovenous malformations

(AVMs) consist of a tangle of tightly interwoven blood vessels in the leptomeninges and underlying cerebral cortex and white matter. Brain tissue fragments among and adjacent to the abnormal vascular channels of a hemangioma (AVM) often show disorganization and reactive gliotic change, some of which may suggest the propensity of the tissue to generate seizures. These vascular lesions contain arteries, veins, and â€œarterialized veins,â€ muscularized vessels intermediate between an arterial and venous channel (Fig. 19). Cavernous hemangiomas are composed of a cluster of dilated, ectatic, and hyalinized vessels with no normal intervening brain parenchyma, and there is almost always abundant surrounding evidence of old hemorrhage. Venous angiomas contain dilated ectatic and venous channels with normal intervening brain parenchyma. Capillary telangiectases consist of dilated capillaries separated by normal brain parenchyma. The varix of vein of Galen (vein of Galen aneurysm) is a large, dilated, ectatic vein of Galen, which is usually in direct connection to a branch of one of the major arterial blood vessels at the base of the brain; varix of vein of Galen can therefore be considered a variant of AVM.[47,76,100]

Clinically, AVMs are the vascular malformations most likely to cause symptoms, although cavernous hemangiomas and occasionally venous angiomas can be symptomatic.[99] Mechanisms of seizure genesis by these lesions include subclinical hemorrhage, compression and scarring of brain tissue around the vascular malformation, and a â€œstealâ€ of blood from normal brain, rendering it at risk for seizure activity. Capillary telangiectases usually represent an incidental finding at autopsy and are almost never found within cortex or subcortical white matter.[47,76] Although hemorrhage is the most common and severe manifestation of AVMs, seizures occur at some time in up to 70% of affected patients.[99,100] Seizures are also frequently

seen (in addition to congestive heart failure) in infants and neonates with varix of the vein of Galen.[76,99,100,172]

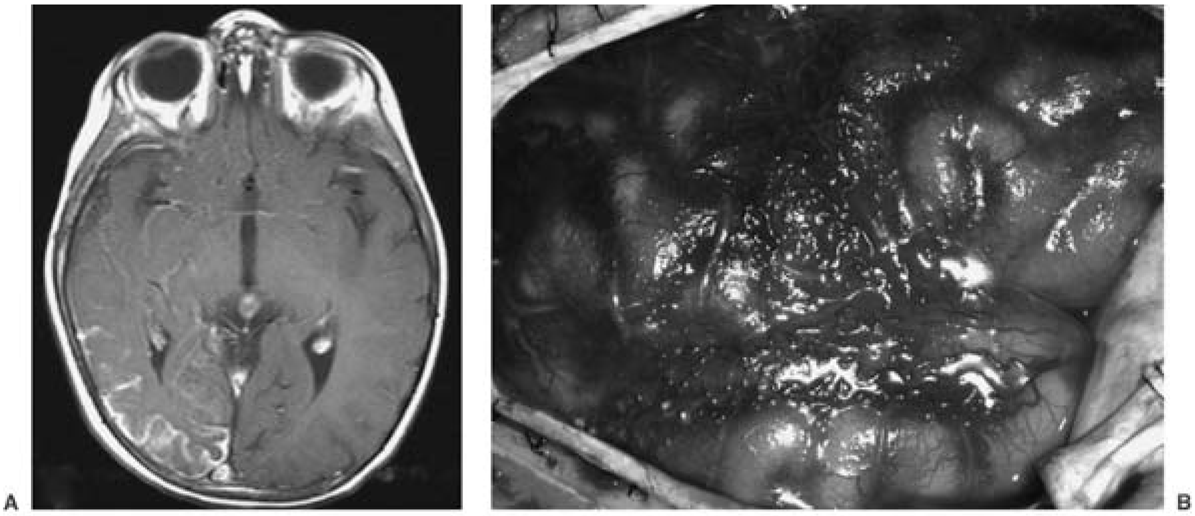

FIGURE 17. Sturge-Weber-Dimitri syndrome (SWDS). **A:** Postcontrast T1-weighted axial image shows global right cerebral hemispheric atrophy with smooth leptomeningeal enhancement along the right parieto-occipital region. There is faint meningeal enhancement in the right frontal operculum. Enlarged deep white matter veins are also seen in the right frontal region. The right frontal calvarium is thicker than the left. These features are consistent with SWDS. **B:** Intraoperative photograph illustrating marked angiomatosis of the arachnoidal surface in the frontal region over the sensorimotor cortex.

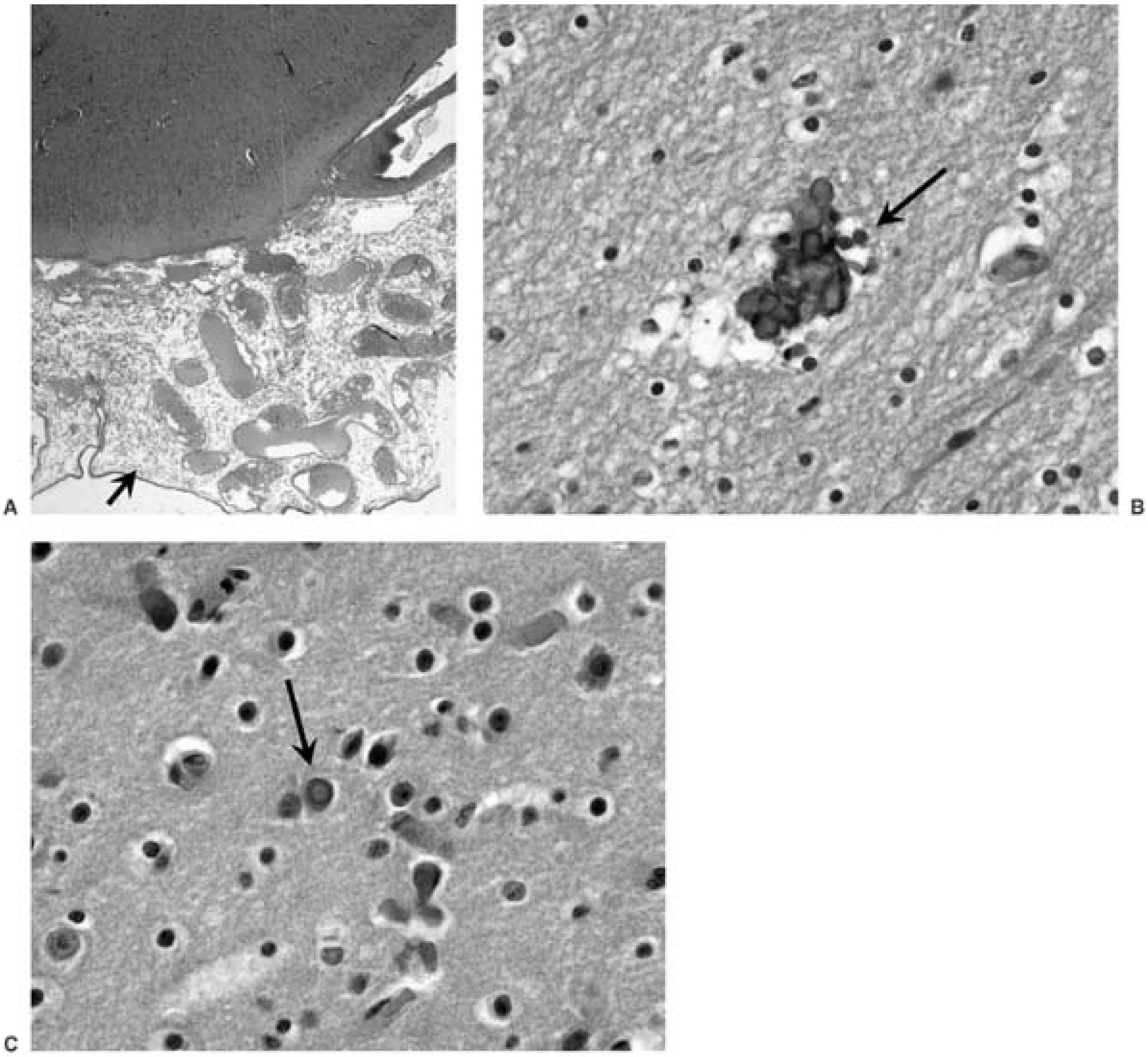

FIGURE 18. Sturge-Weber-Dimitri syndrome, microsco-pic features. **A:** Dense angiomatosis of meningeal vessels in the occipital region (*arrow*). **B, C:** Punctate calcifications (*arrows*) in the underlying brain parenchyma. (See the color insert.)

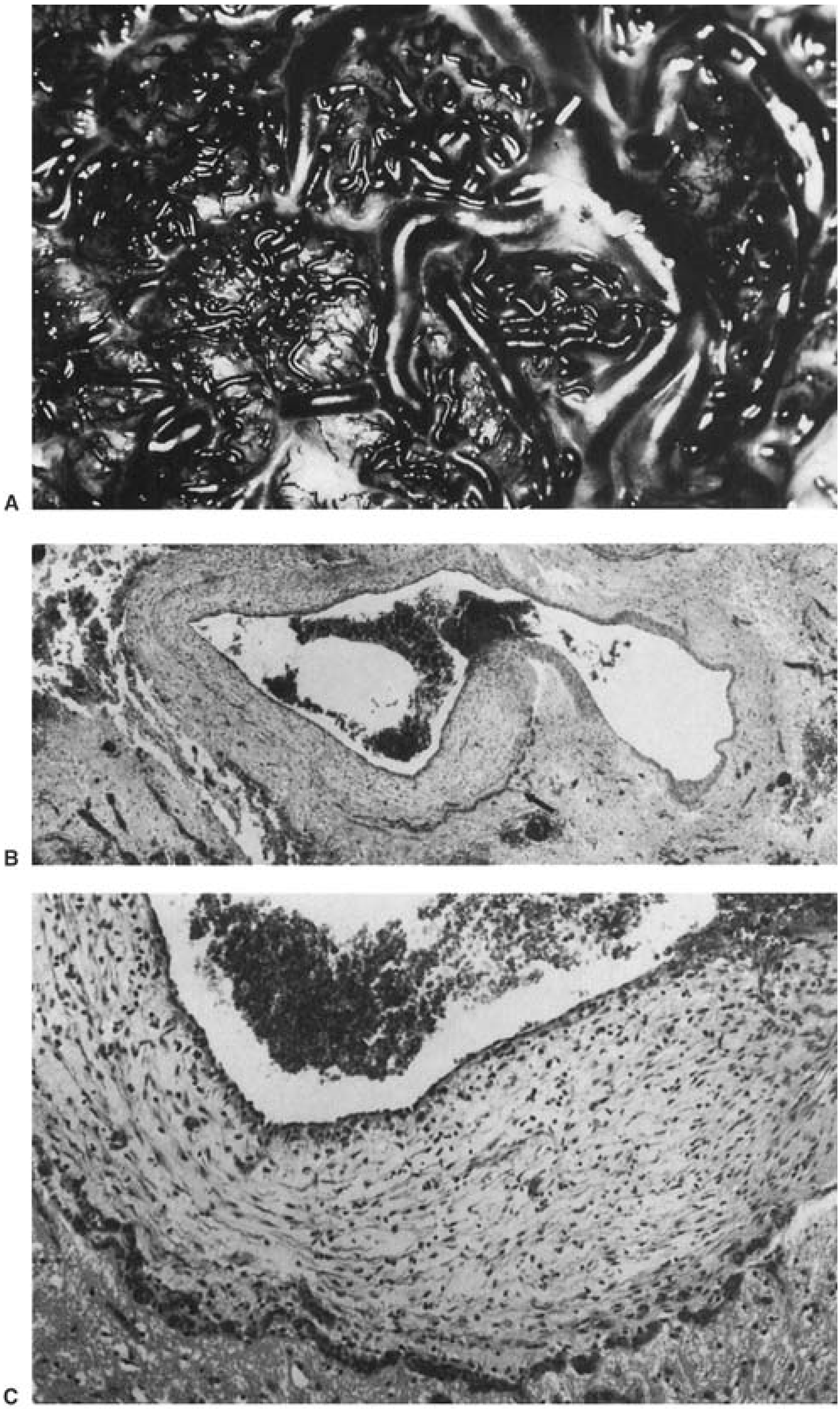

FIGURE 19. Massive hemispheric vascular malformation, best categorized as an arteriovenous malformation, from a 9-year-old boy who underwent hemispherectomy. **A:** Operative photograph of the vascular malformation in situ. **B:** Representative histologic section showing two complete (and one

partial) vascular channels with ectasia and striking variability in wall thickness. **C**: Higher magnification of the region shown by the arrow in panel B, highlighting the degree of fibromuscular thickening of this segment of the vessel (many of the cells immunostained with antibodies to smooth muscle actin, not shown). Brain parenchyma adjacent to the vascular channels showed dystrophic changes, with focally pronounced calcification. Hematoxylin and eosin (panels B and C), Ã—45 (panel B), Ã—175 (panel C). (Panel A courtesy of Dr. Warwick Peacock and Mr. Eric Behnke.)

Summary and Conclusions

The neuropathologist plays a crucial role in the evaluation of the complex lesions described in this chapter, which produce seizures as a major clinical manifestation. She or he has a major role in giving a definitive diagnosis for the structural abnormality/abnormalities present within a corticectomy specimen and at least suggesting how it may have contributed to intractable seizures (the latter assignment often more challenging than the former). Gross and microscopic examinations remain the gold standard for the diagnosis of CD as well as for other nonmalformative structural lesions of the neocortex.

Correlation between pathologic features and clinical presentation is essential for understanding biologic behavior.[185] Furthermore, neuropathologic examination of resected tissue can yield important clues regarding the timing of a putative developmental aberration that led to the development of a lesion, which can aid in understanding the causes and course of CD and related developmental abnormalities. Because the resected specimens represent a valuable resource for furthering our understanding of cortical development and maldevelopment, the neuropathologist plays a role as a conduit for the resected tissue, ensuring maximal effective use for diagnosis and research that utilizes the specimen. Research questions can only be addressed (in human brain tissue specimens) using optimally preserved resection specimens that are preserved for electrophysiologic, neurochemical, and molecular investigations.[4,17] However, when such tissue is available, it is as valuable asâ€"and arguably more valuable thanâ€"tissues obtained from experimental animals. For example, laser capture microscopy coupled with molecular analytic techniques has facilitated the study of neurotransmitter receptor subunit analysis in HME.[10]

Malformative lesions of the neocortex are responsible for the majority of structural pathologic features seen in infants and children with seizure disorders, especially in those with IS. CD, which represents a spectrum of neuropathologic changes associated with disruption of development of the normal neocortex, accounts for most of these malformations, although structural lesions associated with TSC, SWDS, NF-2, and meningio-angiomatosis and vascular malformations are also seen. Multiple etiologic factors have been associated with these developmental disorders, including genetic mutations, prenatal vascular insults,[148] and toxic and environmental exposures.

Although advances have been made in understanding these complex developmental lesions, especially from neuroimaging and molecular perspectives, much remains to be learned. Promising animal models have been developed[156] in which cortical malformations have been induced in rats. These experimental lesions, which conferred an increased propensity for seizures, demonstrated some changes identical to those seen in patients with CD, including cortical laminar disorganization, neurons in the cortical molecular layer, and periventricular and laminar heterotopia.[156] Experimental models such as this one provide an excellent opportunity for examining the basic biologic derangements that occur in the evolution of epileptogenic cortical malformations. Continued morphologic, immunohistochemical, clinicopathologic, and molecular research is necessary to characterize better the time course and associations of these lesions. Investigations seeking to understand the molecular events involved in the basic processes of cell proliferation, migration, terminal differentiation, PCD, and cortical remodeling will help to elucidate the fundamental mechanisms of brain development and significantly aid in the understanding of cortical malformations responsible for seizure disorders.

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Chapter 15

Genetic Epidemiology

Ruth Ottman

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Introduction

A genetic contribution to the epilepsies has been suspected for centuries, but until recently, progress in elucidating the specific genetic influences was relatively slow. This slow progress was attributed in part to methodologic problems in research design and analysis, and in part to inherent complexity in the role that genetic factors play in increasing the risk for epilepsy. With the rapid development of research tools in molecular genetics, however, significant advances have been made over the last 10 years, and a number of genes that influence risk for either idiopathic or symptomatic epilepsy syndromes have been identified. Despite these very important advances, most epilepsy is not explained by mutations in these genes, and efforts to identify other genetic influences are continuing.

Identification of genes that influence risk for epilepsy has great implications for public health. It is a first step in investigating the physiologic effects of the susceptibility genes, which can lead to a better understanding of pathogenesis of epilepsy and to new strategies for treatment and prevention. It also facilitates early identification and treatment of susceptible individuals, and perhaps someday, even prevention of epilepsy in some people. See Chapters 17 and 18 for further discussion of these and other related issues.

Gene discoveries also raise important ethical and social issues. For example, when is it appropriate to offer genetic testing, who should offer it, and how should the results be presented to patients (e.g., by the treating physician or a genetic counselor)? These issues have only begun to be considered as the pace of discoveries in genetic research on the epilepsies increases. Some of these issues are discussed in Chapter 19.

Genetic Influences on the Epilepsies: Current Knowledge

So far, almost all of the progress in epilepsy gene identification has come from analysis of rare families with mendelian modes of inheritance (autosomal dominant, autosomal recessive, or X-linked). As of December 2005, 12 genes had been identified in autosomal dominant forms of eight idiopathic epilepsy syndromes (Table 1). All but two of these genes encode voltage-gated or ligand-gated ion channels. In families with benign familial neonatal seizures, mutations have been found in the potassium channel genes KCNQ2 and KCNQ3.[18,106] Mutations in the genes encoding three sodium channel subunits, SCN1A, SCN1B, and SCN2A, have been found in different families with generalized epilepsy with febrile seizures plus (GEFS+),[30,107,111,112,126] and mutations in SCN2A have also been found in families with a different phenotype, benign familial neonatal-infantile seizures.[12,43] Mutations in GABRG2, the gene encoding the Î³-2 subunit of the Î³-aminobutyric acid subtype A (GABA$_A$) receptor, have been found in families with GEFS+[10,38] and in families with childhood absence epilepsy with febrile seizures.[50,125] In a large French Canadian family with an autosomal dominant form of juvenile myoclonic epilepsy (JME), a mutation was identified in GABRA1, encoding the Î±-1 subunit of the GABA$_A$ receptor.[21] Mutations in EFHC1, encoding a protein with an EF-hand motif that appears to influence calcium currents, were identified in another set of families with JME.[114] In three families with an autosomal dominant form of idiopathic generalized epilepsy (IGE) with a range of different syndromes, mutations were identified in the chloride channel gene CLCN2.[40] Mutations have been found in the genes encoding two subunits of the neuronal nicotinic acetylcholine receptor (CHRNA4 and CHRNB2) in families with autosomal dominant nocturnal frontal lobe epilepsy.[22,108] In families with autosomal dominant partial epilepsy with auditory features (ADPEAF), mutations have been found in the leucine-rich glioma inactivated 1 gene (LGI1), which encodes a leucine-rich repeat protein.[49,62,88] The mechanism by which LGI1 influences epilepsy risk is still not well understood, but based on protein homology, it appears likely to be involved in development of the central nervous system.[49]

Genes have also been identified in a number of mendelian symptomatic epilepsy syndromes. These include progressive myoclonic epilepsies (e.g., Unverricht Lundborg disease, Lafora disease, and the neuronal ceroid lipofuscinoses[104]), X-linked myoclonic epilepsy with mental retardation,[109] and cortical malformation syndromes such as polymicrogyria, pac-hygyria, and periventricular nodular heterotopia.[35,61] In addition, mutations in SCN1A have been identified in many patients with severe myoclonic epilepsy of infancy (SMEI).[19,69,110,124]

Despite the clear importance of these gene discoveries, they apply to only a small proportion of people with epilepsy. Most people with epilepsy have no affected relatives, and only a tiny fraction come from families with mendelian modes of inheritance. In the Epilepsy Family Study of Columbia University (EFSCU),[79,83,86,87] we collected family history information on 1,957 people with epilepsy, ascertained from voluntary organizations for epilepsy without regard to their family histories. The proportion of subjects with a positive family history (with one or more first-degree relatives with epilepsy) was 15% in those with IGE and 12% in those with cryptogenic localization-related epilepsy (LRE). Moreover, most of those with a family history had just one affected relative (probands with IGE 77%, cryptogenic LRE 79%), and very few families appeared consistent with a mendelian mode of inheritance.[81]

Table 1 Mendelian Idiopathic Epilepsy Syndromes with Genes Identified by Positional Cloning (as of December, 2005)

Epilepsy syndrome	Gene	Chromosomal location	References
Benign familial neonatal seizures	KCNQ2	20q13	106
	KCNQ3	8q24	18
Generalized epilepsy with febrile seizures plus	SCN1B	19q13	126
	SCN1A[b]	2q24	30,111
	SCN2A[a]	2q24	112
	GABRG2[a]	5q31	10,38
Benign familial neonatal-infantile seizures	SCN2A[a]	2q24	12,43

Childhood absence epilepsy with febrile seizures	GABRG2[a]	5q31	50,125
Autosomal dominant juvenile myoclonic epilepsy	GABRA1	5q34	21
	EFHC1	6p12	114
Autosomal dominant idiopathic generalized epilepsy	CLCN2	3q26	40
Autosomal dominant nocturnal frontal lobe epilepsy	CHRNA4	20q13	108
	CHRNB2	1q21	22
Autosomal dominant partial epilepsy with auditory features	LGI1	10q24	49,62

[a] Mutations identified in more than one epilepsy syndrome.

[b] Mutations (many of which are *de novo*) also identified in severe myoclonic epilepsy of infancy.

In the large group of people with nonmendelian forms of epilepsy, the genetic influences on risk probably consist mainly of â€œcomplexâ€ disease genesâ€"that is, genes with only a small effect, which act additively to raise risk, possibly in combination with environmental factors.[70] Research is under way to identify these complex epilepsy genes, but progress has been slow and few findings have been confirmed.[116] Given that most of the genes identified in families with mendelian inheritance so far have encoded voltage-gated or ligand-gated ion channels, variants in ion channel genes may well contribute to risk for genetically complex epilepsies also.

Other types of genetic effects may also play a role in some cases. First, some â€œsporadicâ€ epilepsies (i.e., those occurring in the absence of a family history) may be caused by *de novo* mutations. This mechanism is important in SMEI, where many of the mutations identified in SCN1A have been *de novo*.[19,69,110,124] Second, some epilepsies may be caused by somatic mutations occurring in critical brain regions. Third, mitochondrial genetic defects have been demonstrated to underlie disorders in which epilepsy is a significant part of the phenotype (myoclonus epilepsy with ragged red fibers [MERRF] and mitochondrial encephalomyopathy with lactic acidosis and strokelike episodes [MELAS]),[24] and could be involved in other forms of epilepsy as well.[82] Finally, some of the genetic influences on epilepsy may involve either genomic imprinting, in which expression of a genotype is influenced by the sex of the parent from whom it is inherited,[36] or trinucleotide repeat expansion, involving an amplification of the number of tandem repeats in a DNA sequence rather than a change in the nucleic acid sequence *per se*.[115]

Complexities in the Genetics of the Epilepsies

The search for genetic contributions to epilepsy is complicated by a number of factors. The relations between genotype (i.e., the genes that influence risk) and phenotype (i.e., the detectable clinical signs and symptoms) in the epilepsies are not at all straightforward. Even in the genes identified in families with mendelian forms of epilepsy, most of the identified mutations have *reduced penetrance*: Some of those who inherit the mutation are unaffected. This implies that some other factorâ€"an environmental exposure or genotype at a different locusâ€"is required for phenotypic expression of the mutation. Consequently, in families with multiple affected individuals, one cannot assume that unaffected individuals do not carry a susceptibility gene. A special case of this is age-related penetrance: Because risk for epilepsy increases with age, gene carriers may be unaffected if studied at young ages.

Another complication is *etiologic* and *genetic heterogeneity*. The epilepsies are extremely clinically heterogeneous, varying by seizure types, ages at onset, brain localization, electrophysiologic and neuroanatomic abnormalities, response to treatment, and many other factors. These differences are so striking that most epileptologists view the epilepsies as a collection of different disorders, or syndromes, with different etiologies. But to what extent do the different clinical entities also differ with respect to their genetic contributions? Which features can best be used to separate the epilepsies into subgroups likely to share susceptibility genes? The answers to these questions are still unknown. Discovery of clinical features that distinguish between epilepsies with larger and smaller genetic contributions and investigation of shared and distinct genetic contributions to different types of epilepsy are important research goals. Such distinctions could aid in the design of studies aimed at gene identification and greatly refine classification of syndromes.

With *locus heterogeneity*, different genes influence the risk for the same epilepsy syndrome; hence, different families with the same syndrome carry mutations in different susceptibility genes. This phenomenon is well documented in the epilepsies. Multiple autosomal dominant susceptibility genes have been identified in four syndromes: Benign familial neonatal seizures (KCNQ2 and KCNQ3), autosomal dominant nocturnal frontal lobe epilepsy (CHRNA4 and CHRNB2), GEFS+ (SCN1A, SCN1B, SCN2A, and GABRG2), and autosomal dominant JME (GABRA1 and EFHC1). Moreover, different genetic mechanismsâ€"single gene versus complexâ€"can produce the same syndrome in different families, making it impossible to classify syndromes according to genetic mechanisms. For example, the IGEs are genetically complex in most cases, but some families have autosomal dominant inheritance.[21,40,114] Although mutations in LGI1 have been found in 50% of families containing two or more subjects with temporal lobe epilepsy with ictal auditory symptoms,[88] most patients with these symptoms are sporadic and do not have LGI1 mutations.[15,32]

Another complication is *variable expressivity*, in which a mutation in a single gene produces different epilepsy phenotypes in different individuals. For example, in GEFS+, the seizure disorders in family members who have inherited the same SCN1A mutation can vary from simple febrile seizures, febrile seizures plus (in which febrile seizures persist beyond age 6 or are accompanied by afebrile generalized tonicâ€"clonic seizures), idiopathic generalized epilepsy, temporal lobe epilepsy, or myoclonic-astatic epilepsy.[107] This variable expressivity within families suggests that other genes or environmental factors are involved in the causal pathway leading to a particular epilepsy phenotype. Further, in three of the four genes found to be mutated in GEFS+ families, mutations have been identified in other syndromes also: SCN1A mutations (many of which are de novo) in patients with SMEI,[19,69,110,124] SCN2A mutations in families with benign familial neonatal infantile seizures,[43] and GABRG2 mutations in families with childhood absence epilepsy with febrile seizures.[50,125] Again, this variable expression across families probably reflects the involvement of other genes or environmental factors in the phenotypes under study, although variation in the types of mutations in the gene involved may also play a role.

Finally, the effects of some genotypes on epilepsy may involve *geneâ€"environment interaction*, that is, the joint influence of genetic and environmental factors in a causal pathway leading to disease.[71,72,95] Geneâ€"environment interaction might explain some of the reduced penetrance observed in the epilepsy genes discovered so far. For example, some genotypes might not affect risk directly, but instead might increase susceptibility to the effects of environmental factors. In this case, individuals who inherit the risk-raising genotype would not develop epilepsy unless they were also exposed to the environmental factor; hence, some susceptibility genes might contribute to remote symptomatic epilepsy and even to acute symptomatic seizures as well. In a study by Schaumann et al.,[98] seizure risk was increased in the relatives of people who had seizures associated with heavy alcohol consumption (either unprovoked seizures associated with chronic alcohol abuse or acute symptomatic seizures associated with alcohol intoxication), suggesting that some genotypes may interact with alcohol exposure to raise risk. In the same study, however, risk was not increased in the relatives of people with posttraumatic epilepsy.

Research Approaches in Genetic Epidemiology

In the study of a complex disorder such as epilepsy, genetic epidemiologists use a series of study designs to elucidate the genetic contributions on the population, family, and molecular levels. These studies begin with the assessment of *familial aggregation*: To what extent is the risk of epilepsy (or other disorders) increased in the relatives of people with epilepsy? Evidence of familial aggregation has only limited utility in evaluating genetic hypotheses; significant familial clustering can arise from shared environmental exposures (e.g., air pollutants) or high-risk behavior practices (such as diet) in members of the same family, in addition to genetic factors. Thus, the next step is to use special designs such as *twin studies* or *adoption studies* to ask: To what extent is the familial aggregation due to shared genes as opposed to shared environment? If a significant genetic effect is observed, additional studies must be carried out to determine what types of genetic effects underlie susceptibility. At one extreme, the genetic effects could involve single genes with a major effect on susceptibility, whether autosomal or X-linked, dominant or recessive. At the opposite extreme, some genetic influences could be polygenic; that is, they could be a consequence of the effects of a large number of genes at different loci, each of which individually contributes only slightly to the risk. Between these two extremes, some influences might involve pairs or small groups of genes, possibly with interactive (epistatic) effects. One method that can be used to distinguish among these possibilities, *segregation analysis*, involves examining the distribution of disease occurrence in families and testing its consistency with various mendelian models (autosomal dominant, autosomal recessive, X-linked dominant, X-linked recessive, X-linked dominant). This method has been used in only a few studies of human epilepsies.[34,47,68,81,92] Finally, studies must be designed to investigate the molecular mechanisms by which the genes influence risk. At this stage, the specific genes involved need to be identified, and their basic pathophysiologic effects studied. So far, most studies aimed at gene identification have employed *linkage analysis* and subsequent positional cloning; many newer studies are using *allelic association* designs. Below we review these approaches and what has been learned from each in genetic studies of the epilepsies.

Collection of Family History Data

Accurate information about seizure occurrence in family members is essential for almost all designs used to test genetic hypotheses about epilepsy and other seizure disorders. In most genetic studies of epilepsy, data are obtained indirectly, in â€œfamily historyâ€ interviews in which the proband with epilepsy (or a parent or other caregiver, if the proband is a child) is interviewed about seizures in other family members. For many disorders, family history data obtained in this way have low sensitivityâ€”many truly affected relatives are misclassified as unaffected. This problem can usually be remedied by using a â€œfamily studyâ€ design, in which each relative is examined or given a diagnostic interview directly. Study of the genetic epidemiology of epilepsy presents a unique problem, however, because the diagnosis in both probands and relatives cannot usually be made on the basis of physical examination or laboratory testing. It is essentially historical, based on a description of seizure events that occurred prior to visiting the physician.

Ottman et al. evaluated the validity of family history data on parents and siblings, collected in semistructured family history interviews with adults with epilepsy.[83] In this study, many of the parents and siblings of these subjects were also interviewed about their own seizure histories and those of their other family members. The relatives' self-reports or their mother's reports were used as the â€œgold standardâ€ in deciding whether or not they had seizure disorders. The results suggested that adults with epilepsy can report reasonably accurately about epilepsy in their parents and siblings, but isolated unprovoked seizures and acute symptomatic seizures are underreported. Sensitivity for epilepsy (i.e., the proportion of relatives with epilepsy who were correctly reported to have had seizures in the family history interview) was 87% assuming the mother's report was correct, and 93% assuming the self-report was correct. For other seizure disorders in relatives, sensitivity was only 32% assuming the mother's report was correct, and 18% assuming the self-report was correct.

Evidence also suggests that family history information on epilepsy is less accurate for older relatives than for younger relatives. One study based on family history reports found an apparent â€œcohort effectâ€ in the familial risks for epilepsy, with a 50% increase in the proportion of relatives reported to be affected, for each 20-year increase in birth year of the relatives.[85] This effect could not be attributed to a real change in risk over time, because the age-specific incidence rates of epilepsy among persons younger than 40 years did not increase during the time periods investigated.[42] Instead, the apparent cohort effect was probably an artifact of better recall of recent events than of past events. In the older relatives, a diagnosis of childhood onset epilepsy would have occurred many years before the family history interviews were done, whereas in the younger relatives such a diagnosis would have occurred more recently. Thus, the subjects who were interviewed about their family histories were probably less likely to remember (or even to know

about) epilepsy in their older relatives than in their younger relatives.

Familial Aggregation Studies

Most early studies of the genetics of epilepsy were devoted to assessing familial aggregation, that is, an increased risk for epilepsy in the relatives of affected persons compared with risks in the general population (or relatives of unaffected persons). In familial aggregation studies a sample of people with epilepsy (probands) is ascertained, and then the risk of epilepsy is examined in the relatives of the probands and compared with the risk in the population or in the relatives of controls without epilepsy. The probands may also be divided into subsets based on syndromes or other clinical features (etiology, age at onset, seizure type, etc.), and the risks in the relatives of the different subsets compared. Also, the risks of specific clinically defined subsets of epilepsy (or other disorders) may be examined in the relatives and compared with the risks of the same outcomes in the relatives of controls (or the general population).

Several problems of epidemiologic design and analysis have impeded progress in these studies. Many studies used highly selected populations, possibly introducing bias in the estimates of the magnitude of increased risk. Few studies used comparison groups, rigorous methods for obtaining information about family history, or standardized interview methods. Many studies failed to specify which classes of relatives were included. In the analysis of risks in relatives, age adjustments were seldom made. Definitions of epilepsy were often ambiguous. The outcome of interest in the relatives was seldom clearly defined. Some studies defined only those with epilepsy as affected, whereas others included those with any type of seizure disorder or those with only electroencephalogram (EEG) abnormalities.

The best estimates of familial aggregation are derived from the work of Annegers et al., using population-based data from the Rochester Epidemiology Project.[3,5,6,7,76,77,78] The Rochester Epidemiology Project is a unique exception to the usual methods used in familial aggregation studies of the epilepsies and other disorders. It takes advantage of the records linkage system of the Mayo Clinic, which includes essentially all medical, surgical, and pathologic diagnoses of residents of Olmsted County from 1922 to the present, and therefore provides an excellent resource for epidemiologic studies of epilepsy and other disorders.[8,59] This system was adapted for collection of genetic information using a three-step procedure that avoids the use of interviews completely. First, probands with epilepsy were identified by searching the records of the Mayo Clinic to identify all children aged younger than 16 years with diagnoses of idiopathic or cryptogenic epilepsy or isolated unprovoked seizures while residing in Rochester after 1935. Second, the records were used to identify the parents of these probands, and all of the other descendants of the parents (i.e., the probands' siblings, children, nieces and nephews, and grandnieces and grandnephews). Third, the medical records of these relatives at the Mayo Clinic and all other medical facilities serving southeastern Minnesota were reviewed for evidence of seizure dis-orders.

This study design offers several unique advantages for genetic studies. The problem of selection bias is avoided because all incident cases of epilepsy during a specified time period were included; the data on seizure disorders in relatives have high validity, because they are obtained by careful, page-by-page review of the relatives' medical records rather than by proband interviews; and the clinical detail on both probands and relatives is extensive. This approach would be impossible in most studies, because family members often live in different areas and access to their medical records is very difficult to obtain.[80] The only major disadvantages are the limitation in sample size imposed by the relatively small population of Rochester and the restriction to probands with childhood onset, idiopathic or cryptogenic epilepsies, which limited some of the comparisons that could be done in the analysis.

In the Annegers et al. study, the cumulative incidence of epilepsy to age 20 years was 3.6% in siblings and 10.6% in offspring of probands with idiopathic or cryptogenic epilepsy beginning before age 16, compared with 1.7% in the Rochester population.[4] The standardized incidence ratios (SIRs) for epilepsy in the relatives of individuals with idiopathic or cryptogenic, childhood-onset epilepsy were 2.5 (95% confidence interval [CI], 1.3 to 4.4) in siblings and 6.7 (95% CI, 1.8 to 17.1) in offspring.[5] Risk for unprovoked seizures was not increased in more distant relatives (e.g., nieces and nephews or grandchildren). In a later study of the same population with additional live births and follow-up, Ottman et al.[76] found that the SIR for offspring was lower than in the Annegers et al. study: 3.4 (95% CI, 2.1 to 5.1). The lower risks in the more recent study were partly due to a larger number of offspring, leading to greater precision in the risk estimates than in the earlier study. Another possible explanation relates to a difference in study design: The probands in the Annegers et al. study were restricted to incident idiopathic or cryptogenic epilepsy cases with onset prior to age 16, whereas those in the Ottman et al. study were all prevalent epilepsy cases during a specified time period (regardless of etiology or age at onset).

Table 2 Risk of Epilepsy in Siblings, by Etiology of Epilepsy in the Proband[a]

	Classification of epilepsy in probands	
	Idiopathic or cryptogenic	**Symptomatic**
Harvald[39]	4.2	1.2
Eisner et al.[28,b]	5.5	
Annegers et al.[4,b]	2.7	
Ottman et al.[79]	2.4	0.8

[a] Cumulative incidence to age 20 reported in all studies except Harvald.

[b] Restricted to siblings of probands with onset prior to age 16.

Familial aggregation studies can provide important information about etiologic and genetic heterogeneity. Comparisons of probands with different epilepsy syndromes or other clinical characteristics, in terms of the risks for seizure disorders in close relatives, have indicated which subgroups are most strongly influenced by a genetic susceptibility. One of the most consistent findings has been that relatives of patients with idiopathic or cryptogenic epilepsy have a higher risk than relatives of those with remote symptomatic epilepsy.[2,39,56,79,86,120] Table 2 shows the results of four studies that reported sibling risks of epilepsy, stratified by the etiology of epilepsy in the probands. Risks to age 20 years ranged from 2% to 5% in the siblings of probands with idiopathic or cryptogenic epilepsy. However, two studies that examined risks in siblings of probands with symptomatic epilepsy found risks of approximately 1%, which is not higher than in the general population. This lack of increased risk in the relatives of probands with symptomatic epilepsies suggests that genetic influences are relatively minor in most symptomatic epilepsies (caused by traumatic brain injury, stroke, brain infection, etc.). On the other hand, genes that raise susceptibility to the effects of specific types of brain insults may play a role in some symptomatic cases. If this is true, then in the families of these symptomatic probands, an increased risk would be

expected only in the relatives who were exposed to the same types of brain insults as the probands. Since these exposures are likely to be uncommon, the risk in their relatives overall (without taking into account which are exposed) is unlikely to be increased.

Risk of epilepsy has also been found to be higher in the relatives of probands with earlier age at onset of epilepsy than in the relatives of those with later onset.[2,28,56,79,86] Lennox[56] reported a gradient of risk in first-degree relatives with proband age at onset. Risks were highest in relatives of probands with onset before 5 years of age, intermediate in relatives of probands with onset between 5 and 19 years of age, and lowest in relatives of probands with older ages at onset. In the Minnesota Clinical Epilepsy Research Program,[2] sibling risks were higher for probands with age of onset at 25 years or less than for those with later ages of onset. Eisner et al.[28] found the highest risks in first-degree relatives of probands with onset before 4 years of age. Ottman et al. also found a higher risk in the relatives of probands with earlier age at onset.[79,86] Moreover, they found that the degree of increased risk diminished with increasing age of the relatives; among relatives who reached age 35 without developing epilepsy, risk was not increased.[79]

Another important finding is that risks are higher in the remaining relatives of probands with a family history than in the relatives of those without a family history.[51,60,81] In one study, the siblings of probands with IGE had a 4% risk of idiopathic or cryptogenic epilepsy overall, but a much higher risk if they also had an affected parent (15%) or another affected sibling (22%) in addition to the proband.[81] In the same study, the siblings of probands with cryptogenic localization-related epilepsy had a 2% risk of idiopathic or cryptogenic epilepsy overall, but a 3% risk if a parent was affected and a 10% risk if another sibling was affected.[81]

It is widely assumed that risk is higher in the relatives of patients with generalized epilepsy than in relatives of those with localization-related epilepsy, but in most studies the difference between these two groups is small.[73,74] In analyses of offspring of epilepsy patients in Rochester, Minnesota,[77] the higher risk in offspring of parents with generalized seizures was entirely attributable to very high risks in offspring of the subset with absence seizures. Thus, for the majority of patients with generalized seizures, risk in offspring was no higher than in the offspring of patients with partial seizures.

In understanding the relations between genotype and phenotype in the epilepsies, two alternative models can be envisioned.[128,130] The first model postulates that different sets of genes influence risk for different epilepsy syndromes (â€œdistinct genetic influencesâ€), and the second, that the same genes influence risk for different epilepsy syndromes (â€œshared genetic influencesâ€). Familial aggregation studies can be used to distinguish between these possibilities by investigating whether, in the families of probands with specific types of epilepsy, risk is increased only for the same types as in the probands or for all types of epilepsy. If the genetic influences on different types of epilepsy are distinct, then among the relatives of probands with a given type, risk will be increased only for the same type as in the proband. On the other hand, if the genetic influences on different types of epilepsy are shared, risk in the relatives will be increased for all types, including those different from that in the proband. In two studies that used this approach, evidence was obtained for shared genetic influences on generalized and localization-related epilepsy. In the relatives of probands with generalized epilepsy, risk for localization-related epilepsy was significantly increased (fourfold), both in population-based data from Rochester, Minnesota,[77] and data from the Epilepsy Family Study of Columbia University.[84]

However, other studies suggest that clinical characteristics of epilepsy tend to cluster in families. Both Tsuboi[119] and Beck-Mannagetta et al.[11] found that the distribution of seizure types in affected relatives was skewed toward the same types of seizures as in the probands, although different seizure types were also seen. In a study of 72 families of probands with idiopathic generalized epilepsies, each of which contained more than three affected individuals, multiple idiopathic generalized epilepsies were seen in 75% of families, but there were very few cases of localization-related epilepsy.[1] These findings are difficult to interpret because they do not take into account what distribution of syndromes would be expected in the families by chance alone.

Winawer et al. developed a method based on permutation testing to test hypotheses about shared and distinct genetic influences on different clinically defined subsets of epilepsy.[128,129,130,131] The method, *family concordance analysis*, assesses the concordance of epilepsy types (syndromes, seizure types, or subsets defined by other clinical features) in families containing multiple affected individuals. The rationale for the analysis is that if some of the genetic influences on different epilepsy types are distinct, families will tend to be concordantâ€"that is, the proportion of families in which all affected individuals have the same type of epilepsy will exceed that expected by chance. The results of studies using this approach have provided evidence for distinct genetic influences on generalized and localization-related epilepsy.[130] Within the IGEs, these studies found evidence for distinct genetic influences on different *seizure types*: Myoclonic, absence, and generalized tonicâ€"clonic.[129,131] With respect to different *syndromes* within the IGEs, they found evidence for distinct genetic influences on JME versus the two absence epilepsy syndromes (childhood absence epilepsy [CAE] and juvenile absence epilepsy [JAE] combined), but not for distinct influences on CAE versus JAE.[129,131]

There is a strong basis for assuming a common genetic basis for epilepsy and febrile seizures. Hauser et al.[41] found that risk for epilepsy is increased to the same extent in relatives of probands with febrile seizures as in relatives of probands with epilepsy. However, when the proband had both epilepsy and febrile seizures, risk for epilepsy was increased to a greater extent, suggesting that a higher genetic liability is required to manifest both disorders. These results parallel those from recent studies of GEFS+, in which the identified genes raise risk for both epilepsy and febrile seizures.[9]

The findings of three previous studies suggest the possibility of a shared genetic susceptibility to epilepsy and cerebral palsy. In the National Collaborative Perinatal Project, incidence of cerebral palsy in offspring was associated with the mother's history of epilepsy[67]; and incidence of nonfebrile seizure disorders in offspring without cerebral palsy was associated with a history of motor deficits in siblings.[66] Similarly, Rimoin and Metrakos[93] reported an increased prevalence of convulsions and epileptiform EEG abnormalities in relatives of children with hemiplegia, a specific form of cerebral palsy. Finally, Ottman et al. found an increased risk of idiopathic or cryptogenic epilepsy in the first-degree relatives of probands with epilepsy associated with neurologic deficits presumed present at birth (many of whom had cerebral palsy), although the numbers were too small to reach statistical significance.[79]

Table 3 Percent of Offspring with Epilepsy, by Sex of Affected Parent

	% of offspring with epilepsy, among	
Authors	**Offspring of mothers with epilepsy**	**Offspring of fathers with epilepsy**
Tsuboi and Endo[120]	2.9	1.7
Janz and Beck-Mannagetta[46]	4.0	2.7
Ottman et al.[76]	8.7[a]	2.4[a]

[a] Cumulative incidence of epilepsy to age 25 in offspring.

An intriguing aspect of the familial distribution of epilepsy pertains to the risks in offspring: Risks of epilepsy and febrile seizures are higher in the offspring of affected women than in the offspring of affected men (Table 3).[7,46,76,82,120] This *maternal effect* has been observed consistently in previous studies, and is not compatible with any conventional genetic model.[75,82] In population-based data from Rochester, the risk of epilepsy by age 25 years was 8.7% in offspring of affected women and 2.4% in offspring of affected men, compared with 1.6% in the Rochester population.[76] Additional analyses indicated that this difference could not be explained by intrauterine exposure to seizures or anticonvulsants in offspring of women with epilepsy, or patterns of selective fertility that might lead to a

higher proportion of affected mothers than affected fathers with familial forms of epilepsy.[76,101,102,103] An increased frequency of some complications of pregnancy and delivery has been reported in women with epilepsy, but these complications are not associated with increased risk for seizures in their offspring[113] and thus could not explain the higher seizure risk in offspring of women than of men with epilepsy. The possible roles of mitochondrial genes, imprinted nuclear genes, or expanded repeat mutations remain to be investigated.

Twin Studies

Studies of twins are ideal for disentangling genetic from nongenetic causes of familial aggregation. For this purpose, the within-pair similarities (or concordance rates) of monozygotic (MZ) and dizygotic (DZ) twins are compared, on the assumption that genetic effects would produce greater similarity in the two co-twins of a monozygotic pair (who share 100% of their genes) than in the two co-twins of a dizygotic pair (who share 50% of their genes on average).

Concordance rates for epilepsy are consistently higher in monozygotic twins than in dizygotic twins[13,20,45,52,53,55,57,105,121] (Table 4), although the concordance rates vary across studies because of differences in methodology such as twin ascertainment methods, numbers of pairs included, approaches for diagnosis and classification, and methods used to calculate concordance. In the classic twin study by Lennox,[55] concordance rates were higher in MZ than DZ pairs only for twins with â€œintact brains,â€ illustrating the greater importance of genetic factors in idiopathic or cryptogenic epilepsies than in symptomatic epilepsies.

Table 4 Concordance Rates of Epilepsy in Monozygotic and Dizygotic Twins

	Concordance rate (%)	
Authors (reference)	**Monozygotic twins**	**Dizygotic twins**
Lennox[55]		
Brain injured	11	7
Intact	70	6
Inouye[45]	54	7

Corey et al.[20]	19	7
Silanpaa et al.[105]	10	5
Berkovic et al.[13]		
Generalized epilepsy	82	26
Localization-related epilepsy	36	5
Kjeldsen et al.[52]		
Generalized epilepsy	65	12
Localization-related epilepsy	30	10
Vadlamudi et al.[52,a]		
Generalized epilepsy	80	27
Localization-related epilepsy	9	6

[a] Reanalysis of data from Lennox.[56]

More recently, twin studies have been used to investigate the shared and distinct genetic influences on different types of epilepsy and to provide evidence for distinct genetic effects on generalized and localization-related epilepsies. In a study of 253 Australian twin pairs, Berkovic et al.[13] found evidence not only for the genetic influences on epilepsy as a whole, but also for specific epilepsy subtypes. For example, MZ concordance rates were higher than DZ concordance rates in analyses restricted to either generalized epilepsy or localization-related epilepsy (Table 4). Among MZ twin pairs concordant for epilepsy, 94% had the same International League against Epilepsy (ILAE) major epilepsy syndrome compared with 71% of DZ twin pairs with epilepsy. Re-examination of Lennox's twin data with classification of seizure types and syndromes by modern ILAE criteria confirmed these findings: 86% of MZ pairs and 60% of DZ pairs were concordant for ILAE syndrome.[121] The results were very similar in another recent population-based twin study.[52] Concordance rates were higher in MZ than in DZ pairs not only for epilepsy overall, but also for generalized epilepsy and localization-related epilepsy specifically (Table 4); and among pairs concordant for epilepsy, 83% of MZ pairs and 65% of DZ pairs were concordant for syndrome. These findings are consistent with those from the family concordance study of Winawer et al.[130] but differ from those in the familial aggregation studies, in which the risks for localization-related epilepsy were elevated in the families of probands with generalized epilepsy.[77,84] One possible explanation is that some genetic influences on generalized and localization-related epilepsies are distinct and others shared, and the different study designs vary in their ability to detect these different influences.

Linkage Analysis

Linkage analysis is a powerful tool used to localize, or map, a gene to a small chromosomal region. This is a first step in *positional cloning*, in which a disease-related gene is identified from among the 20,000 to 30,000 genes in the human genome by first narrowing the search to a small number of genes in a specific chromosomal region, and then examining the nucleotide sequence of the genes in that region to identify a mutation that is likely to affect disease risk. The basic approach to linkage analysis is an investigation of the co-inheritance of genes or disease with genetic marker alleles within families. The closer two genes are on a chromosome, the less likely they are to be separated by recombination; hence, the alleles of genes located close together are inherited together more often than expected by chance. The direct linear relationship between number of recombination events and the distance between genes is at the root of genetic linkage analysis. The statistic used to assess the evidence for linkage is the lod score, defined as the $\log_{10}$ of the ratio of two probabilities: The probability that the family

data would be observed under the hypothesis of linkage at a specific recombination fraction (numerator) and the probability that the data would be observed under the hypothesis of no linkage (denominator). In a genome-wide analysis, a lod score of 3.0 is generally accepted as significant evidence for linkage at $p < 0.05$.

Many linkage findings have been reported in various epilepsy syndromes or subsets. Some, but not all, of these have led to the identification of mutations in risk-raising genes, and some of the published findings will probably turn out to be false positives. The linkage findings are too numerous to list all of them here, but some of the most important and consistent results are summarized below.

An intense effort has been made to identify linkage in the IGE syndromes, which show strong familial aggregation and usually nonmendelian inheritance (although mendelian forms of IGE have also been described, and three genes listed in Table 1, CLCN2,[40] GABRA1,[21] and EFHC1,[114] were identified in these forms). In the genetically complex IGEs, evidence has been reported for linkage to a wide array of chromosomal regions, including 2q36,[97] 3q26,[97] 5p,[25] 6p21,[21,26,34,89,96,117,127] 6p12,[21,114] 8p12,[25,27] 13q31,[117] 14q23,[97] 15q14,[29] and 18q12.[25] The most consistent result is linkage to the HLA region (chromosome 6p21); many of the other linkage findings have been inconsistent across groups.

One particularly promising linkage finding at present is in familial partial epilepsy with variable foci, a syndrome first described in a family with complex partial and secondarily generalized, primarily nocturnal seizures.[99] Interictal EEGs in affected family members revealed frontal, temporal, and occasionally occipital epileptic foci.[99,132] Linkage to chromosome 22q11 has been reported in three large families with this syndrome.[14,16,132] The gene has not yet been identified, but the minimal genetic region has been narrowed to a 5.2 megabase region on chromosome 22. Identification of a gene that raises risk for this syndrome could provide interesting information about the heritable mechanisms underlying multifocal pathology.

A number of studies have used linkage analysis to localize genes for febrile seizures, but these findings have not led to gene discoveries so far. In studies of large families with apparently autosomal dominant inheritance, evidence was found for linkage to four chromosomal regions: FEB1 on chromosome 8q13-21,[123] FEB2 on chromosome 19p13,[48,54] FEB3 on chromosome 2q23-24,[90] and FEB5 on chromosome 6q22-24.[64] In a series of 47 small families, another study found evidence for linkage to another region, FEB4 on chromosome 5q14-15.[65] One of the challenges in these studies is distinguishing the different phenotypes of febrile seizures. In many of the reported families, it is unclear whether the phenotype should be called isolated febrile seizures or GEFS+ (involving febrile seizures persisting to late ages or accompanied by afebrile generalized tonicâ€"clonic seizures), and no standardized criteria for GEFS+ are available to help resolve this problem. For example, some investigators suggested that the family in which the FEB3 locus was reported on chromosome 2q23-24 actually had GEFS+, so the locus should not have been named FEB3.[63,100]

Allelic Association Studies

In epilepsy as in other disorders, allelic association studies are now being used as an alternative to positional cloning for the detection of disease genes.[116] These studies are aimed at detecting genetic variants that are more common in people with epilepsy than in unaffected persons from the same population. A significantly increased frequency of a variant in people with epilepsy would suggest either that it directly affects risk for epilepsy, or that it is located very close to a functional variant on the same chromosome, and very often inherited with the functional variant (linkage disequilibrium). The genetic variants examined are usually single nucleotide polymorphisms (SNPs), common DNA sequence variations where one of the four nucleotides is substituted for another, found every 1,000 to 2,000 nucleotides in the human genome and accounting for about 90% of all DNA polymorphisms. Most allelic association studies have focused on variants in candidate genes with a hypothesized effect on disease risk (such as genes encoding ion channels). Recently, however, investigators have begun to undertake genome-wide association studies, and this approach will be used in the epilepsies soon.[17,44]

Allelic association studies have important advantages for the study of complex diseases. Unlike linkage studies, they do not require families with multiple affected individuals, which are so rare in the epilepsies. Also, they have greater statistical power than linkage studies for the detection of genes with a small effect on disease risk.[94]

Allelic association studies also have potential limitations. The validity of their basic underlying assumptionâ€"that nonmendelian epilepsies result from DNA variations common to a relatively large proportion of cases (the so-called â€œcommon disease-common variant hypothesisâ€)[37]â€"is still unknown. If many different combinations of risk-raising variants in multiple genes produce similar epilepsy phenotypes, none of the variants may be common enough to be detected through allelic association. Also, the contributions of somatic mutations and *de novo* mutations to complex epilepsies are unknown.

The potential for population stratification, a special type of confounding, must be considered in the design and interpretation of allelic association studies. It arises when the cases and controls in a study have different genetic ancestries and the ancestral groups differ in their allelic distributions. As a result, the cases and controls could differ in the frequency of an SNP of interest for reasons unrelated to the disease. The magnitude of the effect of stratification on current allelic association studies is controversial.[118,122] but fortunately, a number of methods have been developed to control for its effects, including family-based association tests,[133] genomic control,[23] and structured association tests.[91]

In the epilepsies, a large number of candidate gene-based allelic association studies have been published, and the pace of publication has increased dramatically in recent years (reviewed in reference 116). Many of the published studies have been plagued by methodologic limitations such as small sample size, lack of control for population stratification, and failure to adjust for multiple statistical tests. Few genetic variants have been examined in more than a single study, and among those that have, few of the reported associations have been replicated.[88,116] Thus, although clearly this approach holds great potential, we are still in the earliest stages of its application in the epilepsies.

Another approach, combining linkage and association analysis, has been used in the IGEs with promising results. A genome scan of 91 families with genetically complex adolescent-onset IGEs provided evidence for a locus common to most IGEs on chromosome 18q21, a locus on chromosome 6p21 for JME, and other loci (on chromosomes 8 and 5) influencing risk for other forms of IGEs.[25] The authors suggested that interactions of different combinations of these genes produce the varied phenotypes found in IGE families. In subsequent association studies in the same set of families, they found an association of JME with two SNPs in the promoter region of the BRD2 (RING3) gene on chromosome 6, suggesting that this might be the chromosome 6p21-linked JME gene, although no causative mutations were identified.[89] They also found evidence for association of IGEs with a haplotype of SNPs within the malic enzyme 2 gene on chromosome 18, suggesting that this might be the chromosome 18-linked gene predisposing to

IGE[33]; however, a subsequent study by other authors failed to confirm this finding.[58]

Studies in *pharmacogenomics* use allelic association designs to attempt to identify genetic variations related to antiepileptic drug response or toxicity. This is a rapidly expanding research area that may transform the use of anticonvulsants as well as other medications.[31] The polymorphisms examined are usually in genes coding for drug-metabolizing enzymes, receptors, and transporters. Understanding the genetic influences on individual variability in drug response may someday help health care practitioners identify patients at risk of toxicity from certain medications, adjust doses based on genetically determined rates of drug metabolism, and select appropriate medications for patients based on their metabolic profile.

Summary and Conclusions

Research in the genetic epidemiology of the epilepsies is advancing very rapidly; a number of genes that influence risk for mendelian forms of epilepsy have already been identified, and efforts to identify others are continuing. Despite the importance of these gene discoveries, however, they apply to only a small minority of patients. Research to elucidate the genetic influences in the remaining patientsâ€"most of whom have no affected relativesâ€"is one of the most challenging and exciting prospects for the near future. Current evidence indicates that the genetic mechanisms that contribute to risk vary across some clinically defined subgroups of epilepsy. Genetic mechanisms also vary across families, even within narrowly defined clinical subsets or syndromes. Environmental factors may also contribute to susceptibility, even in the presence of genetic influences. Further research on the mechanisms by which genes influence risk is extremely important. It could transform clinical management of the epilepsies, leading the way to the development of new therapies and perhaps even ways to prevent epileptogenesis in the future.

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Chapter 16

EEG Traits

Timothy A. Pedley

Introduction

At the most fundamental level, cortical excitability and electrical organization are genetically specified, and it is probable that each identifiable electroencephalographic (EEG) pattern is a heritable trait or made up of a combination of heritable traits. As yet, no specific genetic locus has been identified in humans as controlling any spontaneous brain rhythm, whether normal or abnormal, although this will likely one day be possible. A spontaneous, synchronized EEG pattern has been discovered in the *mocha* mice mutant that is regulated by a single recessive locus.[89] In addition, a defect in a single genetic locus can result in generalized spike-and-wave activity in mutant mice, and a number of independent loci have been identified that give rise to phenotypically similar spike-and-wave patterns, but each of these is associated with different abnormalities of cellular excitability[13,88] (see also Chapter 37). In terms of epilepsy, it is now clear that rare epileptic syndromes that aggregate in families result from definable monogenic abnormalities (see Chapters 15 and 18). It is also evident, however, that seizure *susceptibility* reflects complex alterations in multiple factors governing neuronal excitability. At the present time, recording the EEG is the only readily available method for detecting an abnormal seizure tendency in asymptomatic individuals, or for classifying the physiologic basis of persons with seizures or epilepsy. Electroencephalography has accordingly assumed major importance in the genetic analysis of epilepsy.

Genetic Studies of Electroencephalographic Patterns

Normal Electroencephalographic Activity

The role of genetic factors has interested investigators from the beginning of scientific study of EEG phenomena. A variety of evidence supports substantial genetic influence on patterns of cerebral electrical activity, although results of many studies cannot be accepted uncritically. Davis and Davis[20] first pointed out similarities in the EEGs of eight pairs of identical twins, and their observations were corroborated by Loomis et al.[75] and by Raney.[93] Lennox et al.[70,71] studied nonepileptic identical and fraternal twins. Electroencephalograms from monozygotic twins were judged to be identical in 85% of twin pairs, whereas EEGs from nonidentical twins were viewed as different 95% of the time. Later quantitative studies of alpha frequency, voltage and phase relations, and sleep patterns have consistently identified EEGs as concordant from identical but not from nonidentical twins.[59,113] Differences between EEG recordings from a pair of monozygotic twins are no greater than the variations that occur spontaneously in sequential recordings from the same individual. Rates of EEG maturation, the appearance and disappearance of age-specific patterns, and, in older subjects, age-related slow activity are all virtually identical in monozygotic twins.[101,114,115] Lykken et al.[76] studied frequency spectra in twins and found them to be the same in 96% of monozygotic pairs. Butler et al.[12] related asymmetries in alpha rhythm to hereditary factors. Vogel et al. have also reported that other patterns aggregate in families, suggesting a genetic basis. These include low-voltage EEG background activity in children,[115] variants of the alpha rhythm,[116] and some types of beta activity.[112,117] The evidence in support of these last examples is not entirely convincing because of the lack of adequate controls for state of alertness, details about drug effects, and the possible influence of anxiety or stress related to the recording methods and circumstances. However, Kubicki[67] has also reported that the presence of rhythmic posterior beta activity is under genetic control, and Koshino and Isaki[66] demonstrated familial occurrence of the *mu* rhythm. Although different modes of inheritance have been proposed for some of these patterns, none can yet be accepted as proved. A low-voltage alpha EEG pattern is a genetic trait that has been associated with psychiatric disorders, most notably anxiety disorders and alcohol use.[40,41] There is some evidence that this trait is linked to the same region of chromosome 20q as panic disorder. Alpha rhythm traits have not been associated with epilepsy. Ellingson et al.[39] studied the occurrence of 14/s and 6/s positive spike bursts in the EEGs of twins and triplets and concluded that this was genetically determined. However, similar rates for 14/s and 6/s positive spike bursts have been reported in the EEGs of unselected and unrelated children.[74]

Nonspecific Abnormal Electroencephalographic Patterns

Kuhlo et al.[68] more fully characterized a rare pattern of 4- to 5-Hz rhythmic activity over the posterior head regions of young adults; this had been described earlier by Vogel et al.[116] Once present, this finding persisted in serial EEGs. Kuhlo et al.[68] concluded that the pattern was genetically determined, because it occurred identically in two monozygotic twin pairs and in 10% of siblings of affected probands.

Doose et al.[27,29] have described â€œabnormal theta rhythmsâ€ in young children, which they correlated with increased susceptibility to febrile seizures and generalized idiopathic epilepsy. The pattern is mainly one of 4- to 6-Hz rhythmic activity, maximal over the parietal areas, and is more common in boys than girls. The finding was strongly age dependent and occurred in about 30% of siblings at ages 3 to 4 years. More recently, Baier and Doose[4] have demonstrated an increased risk for generalized epileptiform activity in the EEGs of siblings if probands show abnormal theta rhythms. In the authors' laboratory, it has sometimes been difficult to distinguish this pattern unequivocally from rhythmic slow activity occurring normally during drowsiness or as part of nonspecifically abnormal generalized slowing of background activity. Another age-dependent finding is 2- to 4-Hz rhythmic activity over the occipital and posterior head regions.[46] The genetic features of this, however, are even

less clear. First, rhythmic occipital delta waves occurred as often in siblings of controls as in siblings of delta-positive probands. Second, in younger children (ages 3 to 4 years), occipital delta rhythms were more common in the siblings of controls than in siblings of probands, but the reverse was true in older children (ages 5 to 10 years). Third, delta rhythms did not correlate with epileptiform activity, but their occurrence with generalized epileptiform activity reduced the frequency with which generalized spike-and-wave activity or photoparoxysmal responses were identified in siblings.

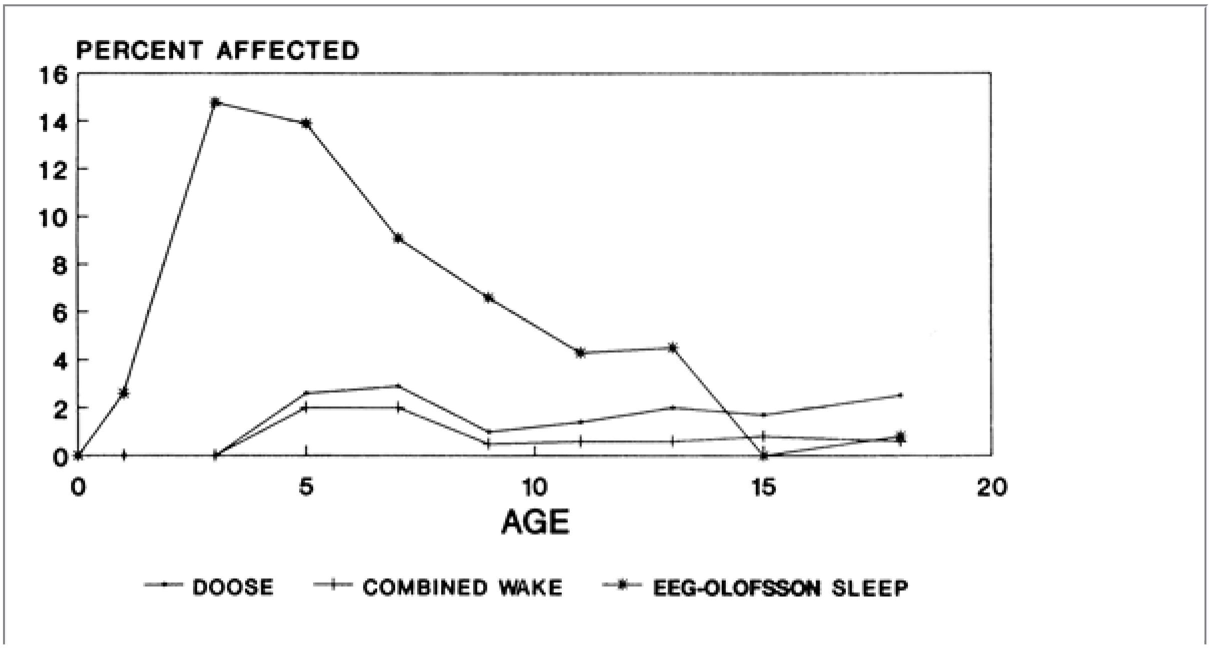


FIGURE 1. Prevalence of generalized spike-and-wave activity in normal children. (Data from Gerken H, Doose H. On the genetics of EEG anomalies in childhood. III. Spikes and waves. *NeuropÃ¤diatrie.* 1973;4:88â€"97 [Table III]; and Eeg-Olofsson O. The development of the electroencephalogram in normal children and adolescents from the age of 16 through 21 years. *NeuropÃ¤diatrie.* 1971;3:11â€"45. [Fig. 10]; graphs kindly prepared by Dr. W. A. Hauser.)

Epileptiform Activity

Generalized Spike-and-Wave Activity

Generalized spike-and-wave (GSW) activity is a genetically determined epileptiform pattern that aggregates in families. Lennox[70] first proposed that GSW discharges were the manifestation of a genetic trait, and the now classic studies of the Metrakoses et al.[81,82,83,84] unambiguously established the familial occurrence of GSW activity. About 35% of siblings and about 10% of parents of probands with GSW discharges show a similar (but not necessarily identical) epileptiform abnormality in their EEGs.[83] Metrakos and Metrakos[83] concluded that GSW activity was caused by an autosomal dominant gene with age-dependent penetrance. In the general population, GSW discharges have been reported in the waking EEGs of 0.3% to 1.8% of all children,[14,37,38,47] but the finding is age dependent and peak prevalence is 2.8% in children 7 to 8 years old (Fig. 1). If EEGs include sleep, GSW activity can be demonstrated in 15% of normal 3- to 4-year-old Swedish children (7.9% of Swedish children of all ages)[38] and in 16.8% of normal 3-year-old Japanese children.[106,107] Studies of GSW activity in siblings and offspring are complicated by the presence of epilepsy in most probands. That the two may not be invariably linked is clear from the studies of Metrakos and Metrakos,[82,84] who showed that the EEG spike-and-wave trait can be dissociated from clinical seizures. Thus, it is possible that the rates of GSW activity reported in relatives are confounded by the presence of epilepsy, and presumably the type of epilepsy, in the proband. Nonetheless, it is unarguable that a substantial percentage of siblings of children with epilepsy and GSW activity will also exhibit the spike-and-wave trait. Figures range from 7% to 17%,[24,47] but as in population studies, rates are age dependent and, perhaps additionally, related to the subtype of idiopathic epilepsy. Thus, 13% of siblings of all probands have GSW activity between the ages of 3 and 6 years.[47] In probands with â€œgeneralized minor seizures,â€ the figure increases to 34% in siblings between the ages of 2 and 3 years.[25] In children of parents with idiopathic generalized epilepsy, 19% manifest GSW activity in their EEGs,[6] and multiple spike-and-wave (â€œpolyspikeâ€) activity occurs in 15% of family members with myoclonic seizures.[109] Degen and Degen[21] have reported that 72% of siblings of patients with absence epilepsy and nearly 50% of siblings of probands with febrile seizures have EEGs showing generalized 2.5- to 4-Hz spike-and-wave activity, but these data cannot be accepted without further confirmation. The exact mode of inheritance of the GSW EEG trait remains uncertain, and both autosomal dominant and polygenic modes of inheritance have been proposed.

A susceptibility gene at the EJM1 locus on chromosome 6 is involved in the juvenile myoclonic epilepsy phenotype in some families.[51] The same gene also seems to influence expression of the EEG abnormality in juvenile myoclonic epilepsy.[36,50]

GSW discharges most likely involve epileptogenic alterations in thalamocortical circuitry that have been implicated in absence seizures based on studies of spontaneously occurring homozygous mouse mutants[11] (Chapter 37), the WAG/Rij rat model of absence epilepsy,[80] and supporting clinical data. The three key elements in the circuit are believed to be thalamic relay neurons, thalamic reticular neurons, and cortical pyramidal neurons.[15] Abnormalities in this thalamocortical system predispose to absence seizures and characteristic EEG discharges,[100] although details remain incomplete. A contributing abnormality appears to be mutations in one of the genes (CACNA1H) that encode the T-type calcium channels that control phasic activation of cortical pyramidal neurons.[16,65] Physiologic studies of several of the mutations have demonstrated functional changes in channel behavior that would favor epileptogenic firing patterns.[65] Point mutations in the CACNA1A gene, which encodes a $Ca_v2.1$ P/Q-type calcium channel, have been implicated in a family in which absence epilepsy is inherited through several generations in an autosomal dominant pattern.[57] Several affected family members also have cerebellar ataxia. In all individuals with both ataxia and absence seizures, there was a point mutation in the CACNA1A gene, which encodes the main subunit of Ca_V2.1 channels. In one asymptomatic family member with typical 3-Hz spike-and-wave discharges, however, the mutation was absent. Î³-Aminobutyric acid $(GABA)_B$ mechanisms have also been implicated in absence seizures and generalized spike-and-wave discharges.[12] Thus, while

thalamocortical circuits, calcium channel mutations, and GABAergic inhibition all seem to be involved in the absence epilepsy phenotypeâ€”and probably other idiopathic generalized epilepsy phenotypes as wellâ€”details of how individual components of these phenotypes, including differences in the pattern of generalized spike-and-wave activity, remain unclear. Recent studies of genetic absence rats from Strasbourg (GAERS) using genomewide scans indicate polygenic control of specific spike-and-wave discharge variables.[96]

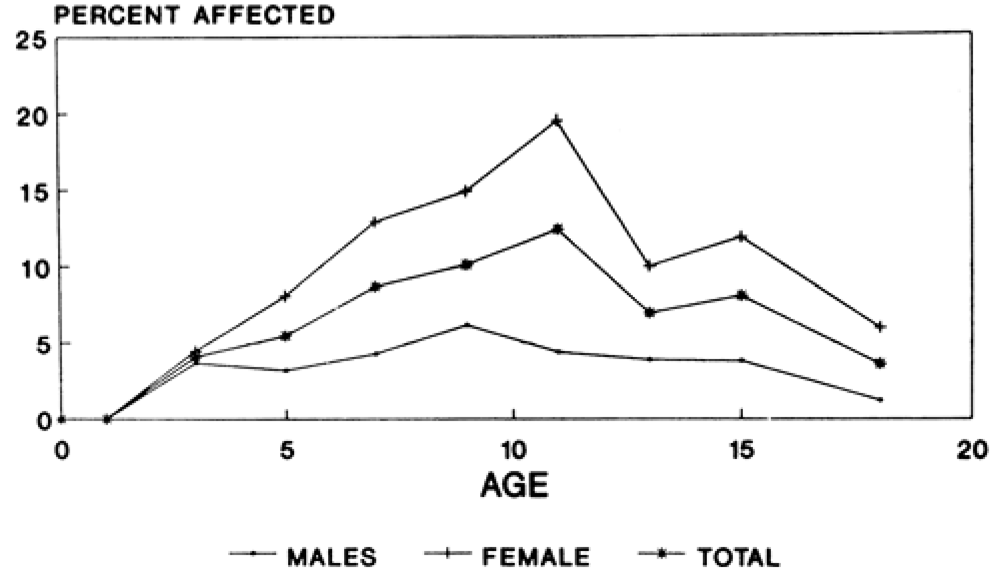


FIGURE 2. Prevalence of photoparoxysmal responses in normal children. (Graphs kindly prepared by Dr. W. A. Hauser and derived from combined data of Doose H, Gerken H. On the genetics of EEG anomalies in childhood IV. Photoconvulsive reaction. *NeuropÃ¤diatrie.* 1973;4:162â€“171; and Eeg-Olofsson O. The development of the electroencephalogram in normal children and adolescents from the age of 16 through 21 years. *NeuropÃ¤diatrie.* 1971;3:11â€“45. [Figs. 7 and 8].)

Photoparoxysmal Responses

Photosensitivityâ€”that is, the development of generalized bursts of irregular spike, multiple spike, and spike-and-wave activity in response to intermittent unpatterned light stimulationâ€”is a familial trait, as first pointed out by Nekhorocheff[86] and then studied more completely by Daly and Bickford,[17] Davidson and Watson,[19] Watson and Davidson,[120] Daly et al.,[18] Schaper,[99] and Watson and Marcus.[121] Despite differences in definitions of photosensitivity, criteria for terming a response photoparoxysmal, and recording methods, these early studies found that photoparoxysmal responses occurred in about 20% to 60% of near relatives of probands. Later studies have found somewhat lower rates. Doose and Gerken[26] and Doose et al.[31,33] compared EEG findings in siblings of children who had photoparoxysmal responses with those of nonepileptic controls. Overall, a photoparoxysmal response could be recorded in about 16% of siblings, but rates were strongly age dependent (Fig. 2). Thus, photoparoxysmal responses to rhythmic light flashes were rare below age 4 but were seen in 32% of siblings ages 11 to 12 years, and abnormal photic responses were more common in girls than in boys. Photoparoxysmal responses occurred in about 5% of control children. Electroencephalographic photosensitivity could be demonstrated in 10% to 20% of siblings of children with epilepsy but without photoparoxysmal responses. The presence of GSW activity in the EEGs of probands did not increase the chance of photoparoxysmal responses occurring in siblings, and photoparoxysmal responses without other EEG abnormalities did not increase seizure risk in siblings. Thus, GSW activity and photoparoxysmal responses appear to be genetically independent phenomena. More recently, Waltz and Stephani[118] also studied photoparoxysmal responses in the siblings of patients with epilepsy. The occurrence of photoparoxysmal responses was age dependent with maximum rates seen between 5 and 15 years of age. If one parent was photosensitive, about 39% of all siblings were also photosensitive. However, in siblings between 5 and 15 years of age, the rate was 50%. When a proband was photosensitive but neither parent was, 14% of siblings demonstrated photosensitivity. Sisters were somewhat more likely to be photosensitive than their brothers.

Photoparoxysmal responses are a feature of the idiopathic generalized epilepsies. They are found in 13% to 18% of patients with absence epilepsy and in 30% to 35% of patients with juvenile myoclonic epilepsy.[52] Tauer et al.[102] performed genomewide linkage scans to identify susceptibility loci for photosensitivity and to determine the genetic relationship with idiopathic generalized epilepsy. Families were studied in which at least two siblings had photoparoxysmal responses. For the analysis, the families were divided into two groups. In one, affected family members had predominantly photoparoxysmal responses or photic-induced seizures (PPR families). The other group included families with photoparoxysmal responses and either unprovoked spontaneous GSW discharges or unprovoked idiopathic generalized seizures (PPR/IGE families). In the PPR families, there was a significant association with chromosomal region 6p21.2. In the PPR/IGE families, there was linkage to chromosomal region on 13q31.3. Based on additional analyses, the authors concluded that the locus on 13q31.3 contributes to an epileptogenic mechanism that is shared by both the photoparoxysmal responses and idiopathic generalized epilepsy. The locus on 6p21.2 appears to predispose to photosensitivity itself. That photoparoxysmal responses are genetically heterogeneous is supported by an earlier report of 16 families with juvenile myoclonic epilepsy.[91] In this study, genomewide scans showed significant linkage to chromosomes 7q32 and 16p13. These findings suggest that different genetic loci for photosensitivity contribute to the different idiopathic generalized epilepsy phenotypes.

Focal Epileptiform Activity

The central-midtemporal sharp wave discharge is associated with idiopathic localization-related epilepsy in children (benign focal epilepsy of childhood with central-midtemporal sharp waves; â€œbenign rolandic epilepsyâ€) but often occurs as an asymptomatic expression of a genetic trait. Central-midtemporal sharp waves occur in about 35% of siblings and in about 3% to 20% of parents of probands with this EEG finding.[9,22,55] The discharges have generally been considered to be highly concordant in twins, but recent data suggest that the genetic influence on benign rolandic epilepsy is much less than previously thought.[108a] In some reports, up to 66% of probands[28] and nearly 15% of siblings and parent[10,95] have

had bilateral EEG abnormalities that included GSW activity and bursts of intermittent rhythmic delta waves. In other studies, however, transmission of central-midtemporal spikes has not correlated with other genetic EEG patterns.[35,47] Focal spikes, mainly of the central-midtemporal variety, can be detected in about 1% to 3% of normal children in population studies.[14,35,38] Both autosomal dominan[9,55] and polygenic[21] modes of inheritance have been postulated to account for the familial occurrence of the central-midtemporal spike trait, but there has been considerable variability in study design and often failure to separate asymptomatic individuals with EEG abnormalities only from those with the characteristic EEG discharge and benign rolandic epilepsy.

Doose et al.[28] found that only 22% of 147 children with central-midtemporal sharp waves had benign rolandic epilepsy. Other children with central-midtemporal sharp waves had neonatal seizures, febrile seizures, generalized tonicâ€“clonic seizures, or other focal seizures that were not typical of rolandic epilepsy. In an analysis of 18 twin pairs, with at least one twin having typical benign rolandic epilepsy, Vadlamudi et al.[110] were unable to demonstrate concordance for classic rolandic epilepsy, although all twins had seizures. They concluded that the mode of inheritance of benign rolandic epilepsy (*not* just central-midtemporal sharp waves) is much more complex than has been thought, and that noninherited factors are likely to be of importance.

Degen et al.[23] recorded waking and sleep EEGs in patients with complex partial seizures. The study included 19 patients and 29 siblings. Seven asymptomatic siblings (24%) showed epileptiform activity, and seven of the patients (37%) had at least one sibling with an epileptiform EEG.

Gibbs et al.[48,49] were the first to observe occipital sharp waves that disappeared with age in children without seizures. Gastaut[44] drew attention to â€œbenign partial epilepsy with occipital spike waves,â€ although Camfield et al.[13] had earlier described four similar cases as a form of migraine. Today, two forms of benign childhood occipital epilepsy are recognized: An early-onset form (Panayiotopoulos type; see Chapter 237) and a late-onset form (Gastaut type; see Chapter 238). The interictal features of the two syndromes are identical. Occipital sharp waves are found in about 0.6% of normal children between 1 and 16 years of age.[14,38] The highest peak is in younger children: 0.9% of children ages 2 to 4 years will have occipital sharp waves.[14] As with central-midtemporal sharp waves, the prevalence of occipital sharp waves in normal children decreases with age: Only about 0.1% after the age of 6 years.[14,90] In one large EEG laboratory, occipital sharp waves occurred in 10.7% of children referred for a variety of reasons.[60] Genetic aspects of occipital sharp waves and benign occipital epilepsy have been less well studied than central-midtemporal sharp waves and benign rolandic epilepsy. While Gastaut and Zifkin reported that 36% of affected children had a family history of epilepsy,[45] children with benign occipital seizures do not usually have a family history of similar seizures. Ferrie et al.[42] analyzed 113 patients with early-onset benign occipital epilepsy. Febrile seizures occurred in 15%, and there was a history of epilepsy in 7% of first-degree relatives. Other EEG abnormalities occurred in 25% of the patients and included central-midtemporal sharp waves, frontal sharp waves, and generalized discharges. A few families with several affected children have been reported in somewhat more detail. Kuzniecky and Rosenblatt[69] described a family in which three of four children had symptoms consistent with late-onset benign occipital epilepsy. The fourth asymptomatic child had occipital sharp waves on EEG. Occipital sharp waves were also found in 26% of other asymptomatic younger family members. In the family described by Nagendran et al.,[85] two children had occipital sharp waves. One of these had visual hallucinations followed by drowsiness; the other had visual hallucinations and two generalized convulsions. Two children were asymptomatic, but the EEG in one showed central-midtemporal sharp waves and occipital slowing in the other. Doose et al.[32] studied 19 patients with occipital sharp waves. Seizures consistent with early-onset benign occipital epilepsy occurred in 7 (37%); only five of these had occipital sharp wave foci. Occipital foci were found in 43% of 21 relatives. Only 1 of 11 relatives of probands with benign occipital epilepsy also had occipital seizures. Children with occipital seizures also had febrile seizures (one relative), benign rolandic seizures (one relative), and generalized tonicâ€“clonic seizures (six relatives).

Limitations in Using the EEG for Genetic Studies

Although EEG has been, and continues to be, a major tool in genetic studies of epilepsy, several factors limit its utility or at least require careful consideration in study design and data analysis. These include maturational, biologic, and interpretive issues.

Maturational Issues

Virtually all studies of genetic EEG patterns show age dependence. Thus, prevalence figures derived without taking age into account will be inaccurate or even misleading.

All EEG activity in the first decade of life and during much of the second reflects maturational processes taking place within the central nervous system, and some of these are gender related.[7] Although these maturational processes cannot yet be specified in detail for any EEG phenomenon, they presumably are determined by genetically controlled changes in neuronal cell types, numbers, and connectivity; neurotransmitters and receptors; synaptic interactions; myelination; and circuitry. In general, the younger the child, the more pronounced are EEG differences between any two points in time. In premature infants, for example, substantial changes in EEG activity may normally occur at intervals of 1 to 2 weeks. On the other hand, the EEG in a normal 6-year-old child is not very different from that of an 8-year-old, but both can be distinguished from the EEG of a healthy young adult. Acquired brain insults and abnormal genetic influences are superimposed on this normal developmental substrate. Thus, clinical and EEG findings are always the result of complex interactions between normal maturational events and the modifying effects of acquired or adverse genetic factors. It may well be that the expression and character of certain EEG patterns depends on critical interactions occurring within a fairly narrow time window. It is therefore not surprising that age histograms differ for various epileptiform patterns[60,61] (Fig. 3). Furthermore, it is not known how or in what ways genetic control of cerebral excitability and electrical organization is altered in the presence of an abnormal substrate, for example, one injured by hypoxia or intracerebral hemorrhage.

Biologic Issues

Variability of Electroencephalographic Findings

Electroencephalographic activity in the healthy adult is normally very stable over considerably long periods of time.[8,79,105,109,111] Almost nothing, however, is known of the stability of epileptiform patterns, especially in terms of the morphologic and other distinguishing features that form the basis for most interpretations and classifications.

It is well accepted that sleep affects the morphology of generalized epileptiform discharges. This is most readily seen

with classic 3-Hz spike-and-wave activity, in which the well-formed spike-and-wave paroxysms seen with the patient awake give way during sleep to discharges of shorter duration, composed of spikes and multiple spikes that recur in a fragmentary way, either with or without a consistent slow-wave component.[87,98,99] It is possible to demonstrate similar although often less dramatic effects of sleep on other types of generalized epileptiform activity as well. To the extent that morphology is used to classify patients with similar seizures or syndromes, awareness of the effect of state is important.

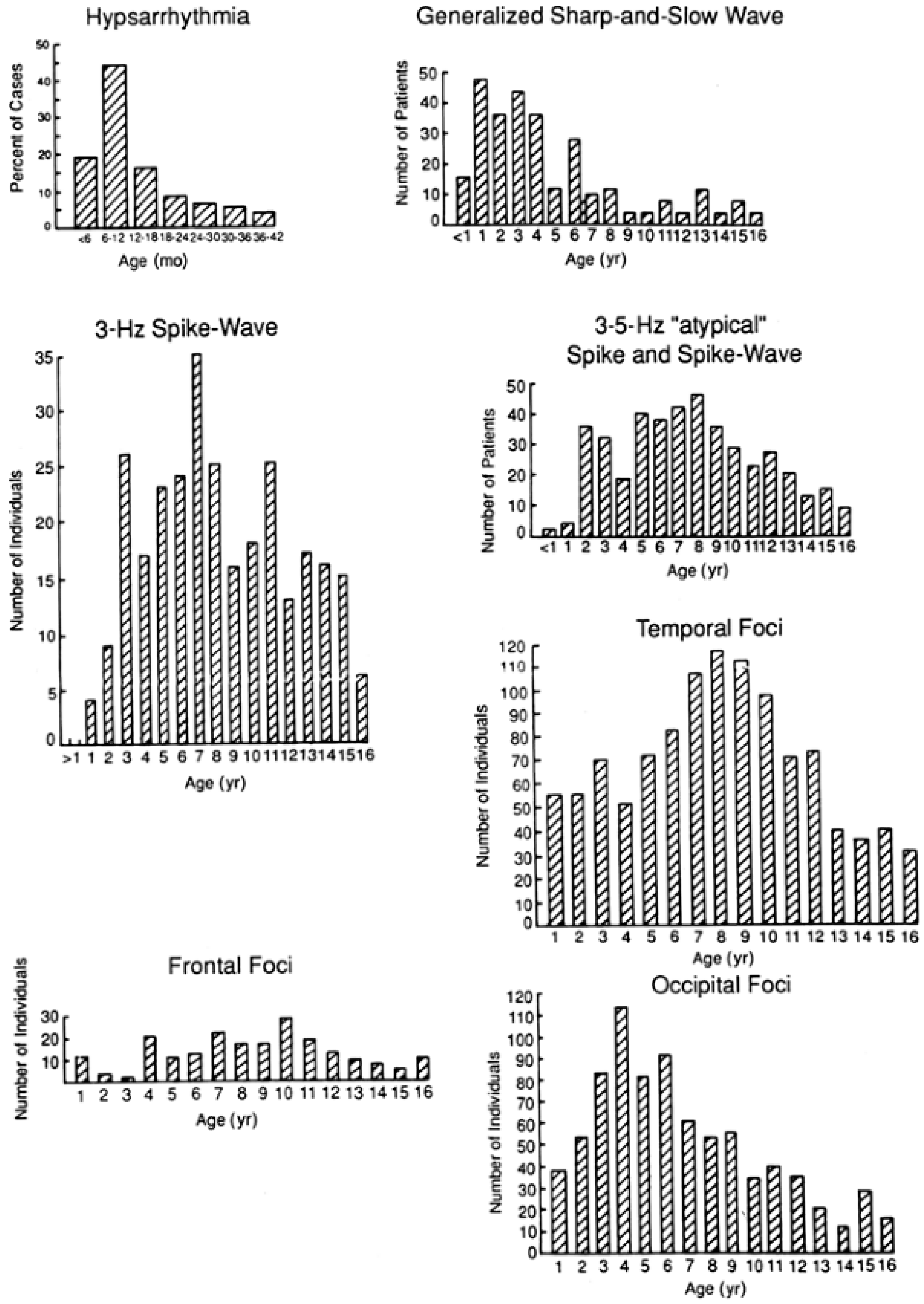
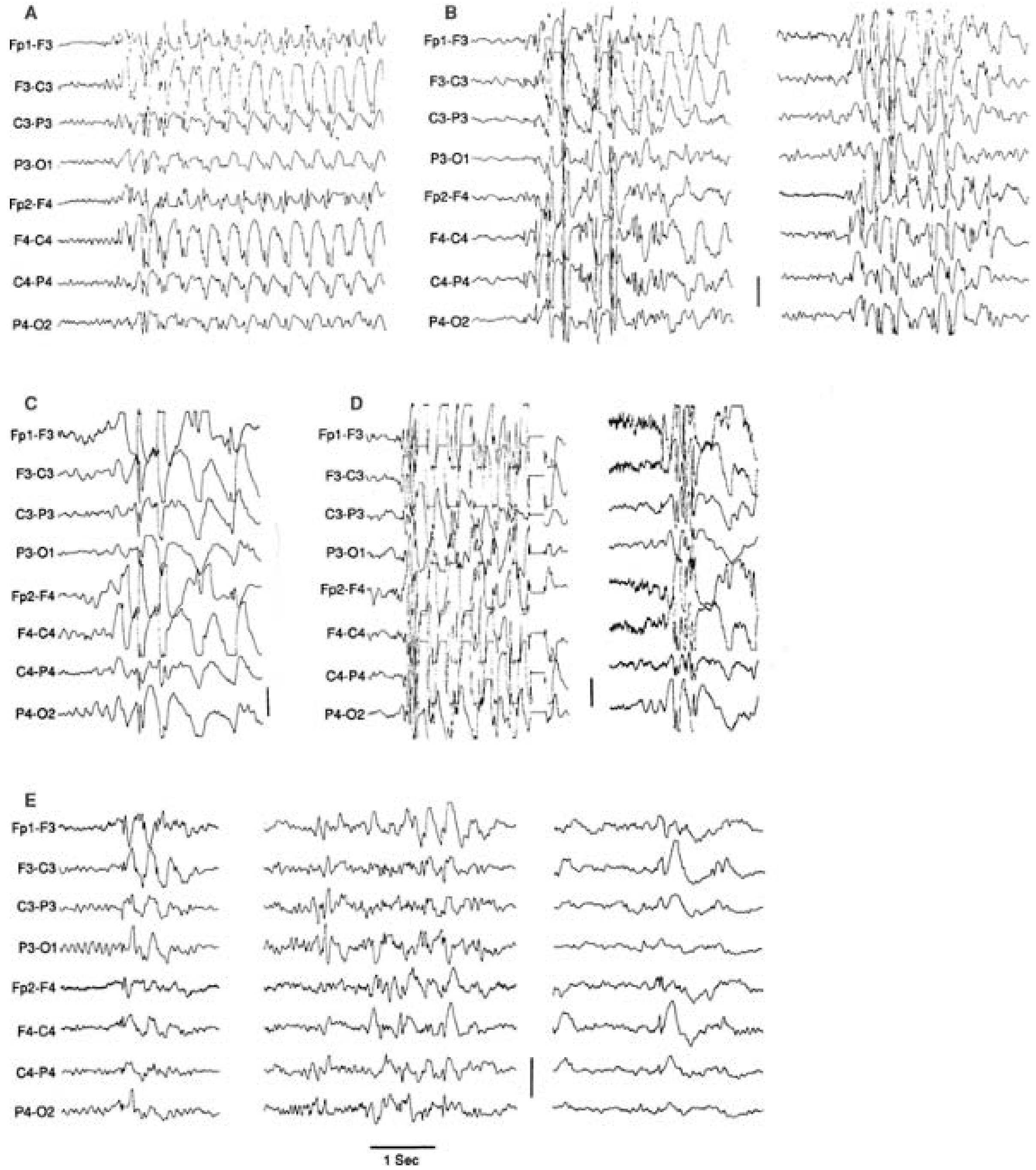


FIGURE 3. Age histograms of various epileptiform patterns in children. (Reproduced from Kellaway P. Maturational and biorhythmic changes in the electroencephalogram. In: Anderson VE, Hauser WA, Penry JK,

et al., eds. *Genetic Basis of the Epilepsies*. New York: Raven Press; 1982:21â€“33.)


A
Fp1-F3
F3-C3
C3-P3
P3-O1
Fp2-F4
F4-C4
C4-P4
P4-O2
B
Fp1-F3
F3-C3
C3-P3
P3-O1
Fp2-F4
F4-C4
C4-P4
P4-O2
C
Fp1-F3
F3-C3
C3-P3
P3-O1
Fp2-F4
F4-C4
C4-P4
P4-O2
D
Fp1-F3
F3-C3
C3-P3
P3-O1
Fp2-F4
F4-C4
C4-P4
P4-O2
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Fp1-F3
F3-C3
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FIGURE 4. Different patterns of generalized spike-and-wave activity.

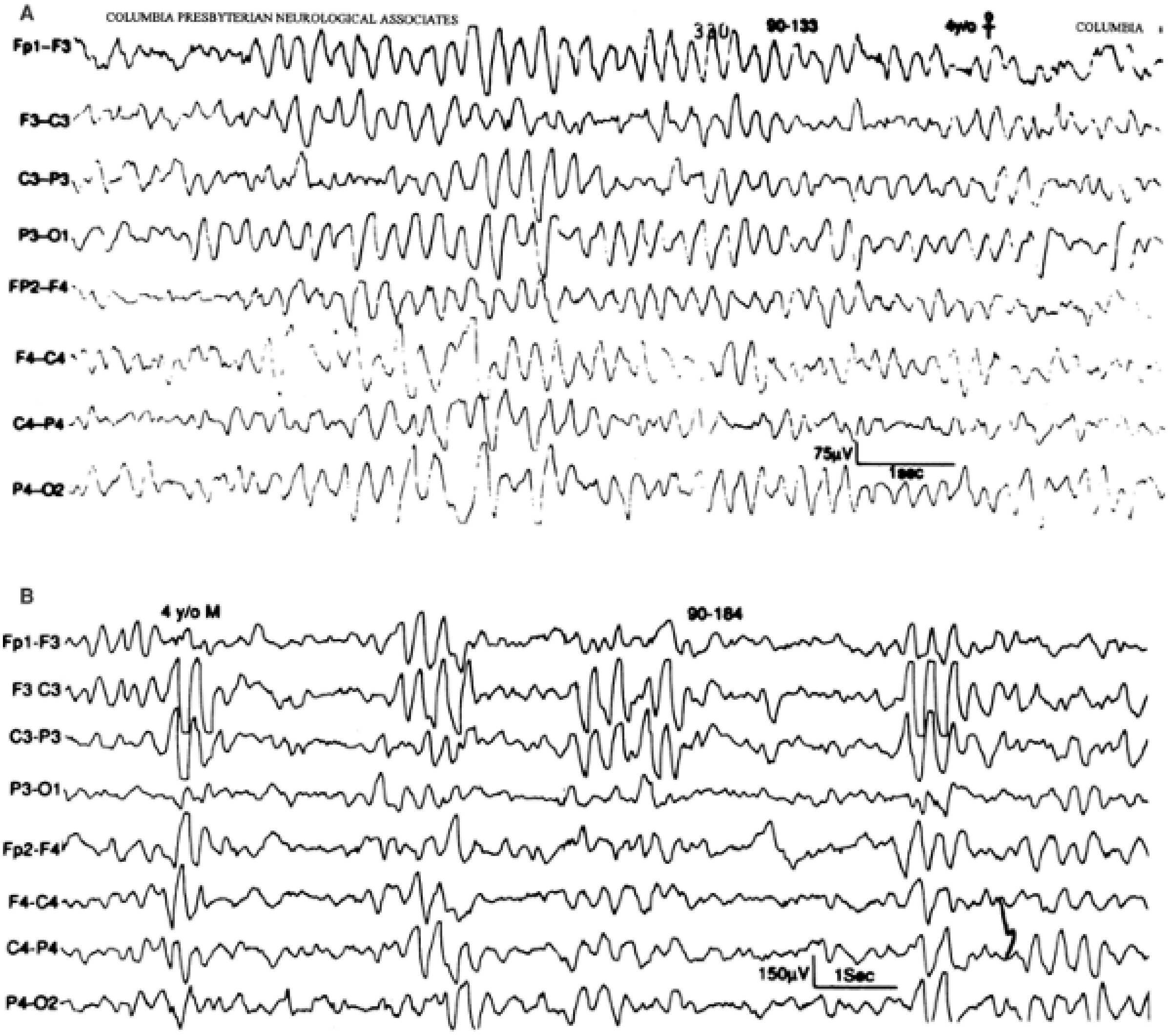

FIGURE 5. Examples of normal drowsy patterns in children. **A:** Continuous generalized rhythmic theta activity. **B:** Paroxysmal bursts of bisynchronous rhythmic delta activity.

In generalized-onset seizures, interictal EEGs show bilateral, symmetric, synchronous spikes with spike-and-wave and multiple spike-and-wave discharges. Beyond this generic description, however, considerable variability exists in details of how the epileptiform activity is expressed (Fig. 4). Patients with mainly generalized tonicâ€“clonic seizures, for example,

most commonly demonstrate â€œatypicalâ€ spike-and-wave activity, consisting of bursts of spikes and irregularly repeating 4- to 6-Hz spike-and-wave complexes. Sometimes, however, such patients also show 3-Hz spike-and-wave paroxysms or bursts of multiple spike-and-wave activity. In childhood absence seizures, the EEG most commonly reveals classic 3-Hz spike-and-wave activity, but close inspection reveals that the initial frequency is often 4 Hz and that the terminal frequency, especially in paroxysms lasting 10 seconds or longer, is usually 2 to 2.5 Hz. Some children with clinically typical childhood absence seizures show quite irregular spike-and-wave discharges,[72] and this does not appear to affect the character or prognosis of the disorder.[73] In relatives of children with absence seizures, even greater variability is seen in the expression of the spike-and-wave trait. In juvenile myoclonic epilepsy, multiple spike-and-wave activity is considered to be the characteristicâ€”even pathognomonicâ€”interictal EEG finding. Although this pattern may be the most specific, it occurs in fewer than half the patients clinically classified as having the disorder.[58,108] Other common epileptiform abnormalities in single EEGs of patients with juvenile myoclonic epilepsy include 3-Hz spike-and-wave activity and â€œatypicalâ€ 4- to 6-Hz spikes and spike-and-wave activity. No systematic study of the variability in patterns of epileptiform activity over time in individual patients has been performed. In all syndromes of idiopathic generalized epilepsy, almost all variations of GSW activity can be seen, although one or another pattern may statistically predominate in some seizure types.[119] Thus, it is probably not biologically meaningful or even accurate to use frequency or morphologic details of GSW activity as major criteria for narrowly defined epileptic phenotypes. It may, however, be reasonable to attempt to study the genetics of different EEG patterns alone. This issue is of considerable importance as molecular biologists are transforming our understanding of epilepsy by identifying chromosomal loci and specific genes associated with different types of epilepsy. The clinician plays a pivotal role in linkage studies by providing precise and useful definitions of the condition under study. What role EEG and other features should play in defining epileptic syndromes and how elastic or inflexible these definitions should be are important issues for the genetic study of epilepsy (as well as for classification schemes). Some critical discriminating factors are already evident, as in the need to separate photoparoxysmal responses from spontaneous or hyperventilation-induced GSW activity. Another important issue is the dissociation that can occur between EEG findings and clinical manifestations. Genetic EEG traits can be expressed in asymptomatic individuals in the population at large as well as in families with both clinically affected and unaffected members. More than one heritable EEG pattern may be seen in individuals with a â€œclassicalâ€ clinical phenotype (e.g., central-midtemporal spikes or generalized spike-and-wave discharges in patients with benign occipital epilepsy). Genetic studies that use EEG need to recognize this variability in their design. At present, no single electrical event is unique to a particular form of epilepsy or epileptic syndrome.

Timing of Electroencephalographic Recordings

Kellaway et al.[64] have demonstrated that the occurrence in the EEG of GSW activity shows consistent time distributions that reflect modulation by interactive but independent circadian and ultradian processes. Similar biorhythmic modulation may affect the ability to record focal spikes as well.[63] From a practical standpoint, sleep and sleep deprivation will increase the yield of â€œpositiveâ€ EEGs. Timing of EEG samples, therefore, may be a critical factor in genetic studies. A related problem is that of sampling. Longer EEGs and EEGs recorded on more than one occasion increase the chance of demonstrating a specific epileptiform abnormality. In patients with probable epilepsy, about 29% to 50% will have epileptiform abnormalities on the first EEG, but if multiple EEGs are obtained, the yield increases to 59% to 92%.[77,97]

The Issue of Epileptogenicity

Epileptiform patterns are a reliable signature of an individual's susceptibility to seizures, but they do not quantify the magnitude of this risk. In other words, there is a strong but by no means absolute correlation between seizures and interictal epileptiform discharges. This consideration has implications for using EEG data to estimate seizure risk (see further on). Behavioral and EEG expressions of epilepsy appear to be under at least partially separate genetic control, and development of recurrent seizures best fits a multifactorial model involving both genetic and environmental factors.[1] Thus, prevalence studies in relatives of probands with epilepsy always show higher rates for EEG abnormalities than for seizures.[1] It is clear that the various epileptiform patterns differ in their degree of epileptogenicity. For example, among children referred to an EEG laboratory for various reasons, including known or possible epilepsy, only about 40% of those with central-midtemporal spikes had seizures.[60,61] In the same cohort, on the other hand, seizures occurred in about 90% of children with other temporal spike foci and in about 75% of those with frontal or multifocal spikes. Of children with generalized epileptiform discharges, about 70% with â€œatypicalâ€ 4- to 6-Hz spike-and-wave activity and nearly 100% with 3-Hz spike-and-wave activity had seizures. With rare exceptions, however, there is at present no reliable way to relate quantitatively any interictal measure of epileptiform activity to clinical seizures.[103] Frost et al.[43] provided preliminary evidence of computer-derived parameters of interictal spike waveforms that showed promise in assessing seizure risk.

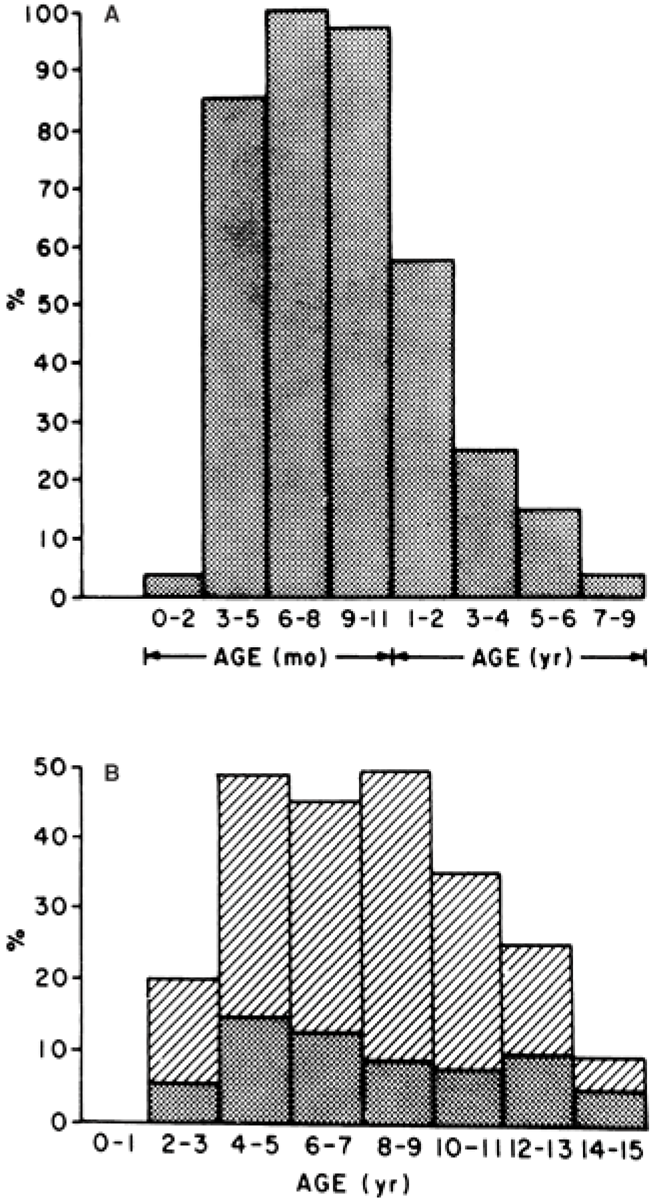

FIGURE 6. Age histograms of continuous **(A)** and paroxysmal **(B)** drowsy patterns in children. Paroxysmal bursts of rhythmic delta activity often normally contain sharply contoured or spikelike components (*lower dotted sections* in B). (Reproduced from Kellaway P. An orderly approach to visual analysis: characteristics of the normal EEG of adults and children. In: Daly DD, Pedley TA, eds. *Current Practice of Clinical Electroencephalography*. 2nd ed. New York: Raven Press; 1990:139â€“199, with permission.)

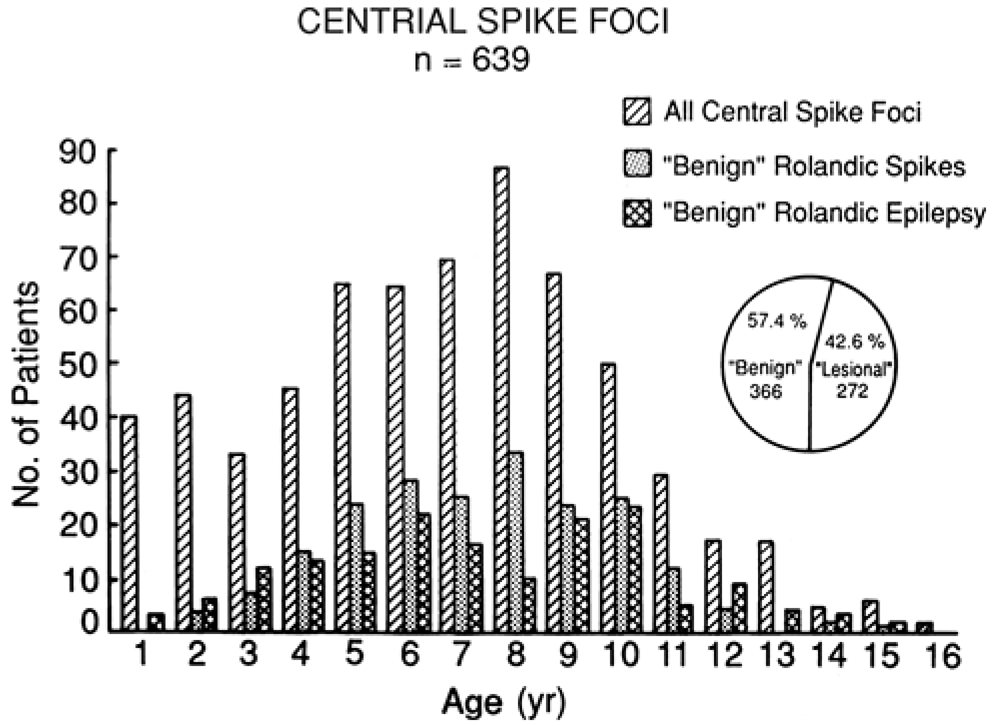

FIGURE 7. Age histograms of â€œlesionalâ€ and â€œbenignâ€ central spike foci in children. (Reproduced from Kellaway P. Maturational and biorhythmic changes in the electroencephalogram. In: Anderson VE, Hauser WA, Penry JK, et al., eds. *Genetic Basis of the Epilepsies*. New York: Raven Press; 1982:21â€“33, with permission.)

Interpretive Issues

Interpretation of the biologic significance of EEG findings by the electroencephalographer can play an important role in genetic studies. At the simplest level is the electroencephalographer's concept of â€œnormalâ€ or â€œabnormalâ€ and view of deviations from normative data (to the extent these exist). What are the limits of normal biologic variability, and when do deviations reflect abnormal brain function? A related issue is the identification of patterns considered epileptogenic. The electroencephalographic literature is an embarrassing repository of confused, ill-considered, and unsupported opinions regarding the epileptic significance of various EEG patterns. Although most electroencephalographers no longer consider 14/s and 6/s positive spike bursts, wicket spikes, rhythmic temporal theta bursts of drowsiness (psychomotor variant), or small sharp spikes as anything other than benign variants having no association with seizures, other problems remain. Not all sharply contoured transients or paroxysmal discharges are epileptiform, and not all epileptiform patterns are epileptogenic. Some discrepancies in prevalence figures undoubtedly relate to more or less liberal criteria for considering a discharge epileptiform. Thus, Metrakos and Metrakos[81] reported that GSW activity occurred in 10% of their control subjects, whereas Doose et al.[30,34] and Andermann and Straszak[2] found GSW discharges in fewer than 2% of controls. Paroxysmal delta activity occurring normally during drowsiness in children is an especially vexing problem, because these hypnagogic bursts often contain sharp or spikelike components[62] (Fig. 5). To the eye of this author, for instance, FIGURE 1 of Doose and Gundel[27] does not show â€œabortive bilateral synchronous spikes and wavesâ€ but rather illustrates a nonspecific burst of rhythmic delta waves during drowsiness, probably a normal phenomenon. Furthermore, drowsy patterns in children may be either continuous or paroxysmal, and this characteristic is age elated[62] (Fig. 6). Another seemingly unsolvable problem is that of the 6-Hz spike-and-wave discharge. When this takes the â€œphantomâ€ form described by Marshall,[78] most electroencephalographers consider it of no consequence. When the discharge is of higher voltage and maximal frontally, however, considerable controversy exists regarding its clinical significance. Some investigators deny that it has any relation to epilepsy,[104] whereas others consider it a variation of GSW activity.[56] It is even sometimes difficult to tell from a single EEG if the epileptiform activity is focal or generalized. In many patients with GSW activity, for example, the paroxysmal discharge occasionally appears in a limited or incomplete form. Such fragments of an otherwise typical generalized abnormality then appear as â€œfocalâ€ spikes, especially over the frontal or frontal-central regions. Conversely, some epileptogenic foci, most often those involving mesial parasagittal areas, give rise in scalp EEG recordings to bilateral discharges (â€œsecondary bilateral synchronyâ€), which can be misinterpreted as generalized spike-and-wave activity. Especially if epileptiform activity is not abundant, a single EEG sample may not be sufficient to characterize the discharge unequivocally as focal or generalized. Accurate discrimination among different types of unambiguous spike discharge is also necessary. Thus, not all spikes occurring in the central and midtemporal areas are â€œbenignâ€ (Fig. 7). Finally, there is considerable variability in EEG interpretation, including recognition of artifact, among different observers,[92] and this variability is influenced in part by specific reader characteristics.[122]

Role of Electroencephalogram in Estimating Risk for Seizures in Siblings and Offspring

Despite the limitations already described, knowledge of the proband's EEG is of some help in estimating the risk for epilepsy in siblings. Although data from siblings are frequently used to estimate risk for offspring, the two groups are not, of course, genetically comparable. Epidemiologic studies suggest that risk for epilepsy in offspring is similar to that reported for siblings.[53] However, it is not possible to determine in what way EEG findings modify this risk. This is because data are either unavailable or derived from sample sizes too small to provide reliable risk estimates.

In siblings of probands with epilepsy and GSW activity, risk for seizures or epilepsy does not appear to be increased above that conveyed by the proband's epilepsy alone.[3,53] Similarly, if the proband has epilepsy and a photoparoxysmal response that is not accompanied by spontaneous or hyperventilation-activated GSW activity, sibling risk for seizures is not increased above that related to the proband's epilepsy alone.[3,31,54] However, if the proband's EEG contains both GSW discharges and a photoparoxysmal response, risk for epilepsy in siblings more than doubles.[54] Thus, the genetic effects of GSW activity and photoparoxysmal responses seem to be additive.

Summary and Conclusions

The EEG is an important tool for identifying individuals with increased susceptibility to seizures, including carriers of genetic traits. Evidence is growing that specific EEG patterns are under

complex and heterogeneous genetic control, and animal studies indicate that similar EEG patterns may arise from different and independent genetic mechanisms. Although the EEG has been and will continue to be an important phenotypic determinant in genetic studies of epilepsy, its use is limited by maturational, biologic, and interpretive considerations. Used with caution, the EEG can be helpful in estimating the risk for seizures in siblings and offspring of probands with epilepsy.

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Chapter 17

Genetic Diseases Associated with Epilepsy

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V. Elving Anderson

Introduction

Genetics has become increasingly important for understanding epilepsy. Since the advent of molecular genetic technology in the 1980s, it has been possible to categorize and diagnose many neurologic diseases that were previously poorly defined. A number of specific â€œepilepsy genesâ€ have been identified and are discussed in Chapter 18. However, there are also many genetic disorders that feature epilepsy as a common or prominent symptom. In this chapter we review genetic disorders associated with an increased risk for epilepsy.

Patients having genetic or chromosomal syndromes associated with epilepsy account for 2% to 3% of all cases of epilepsy; in fact, these patients are more likely to be seen first by a pediatrician, family practitioner, or geneticist for diagnosis and treatment of the genetic syndrome. What, then, is the benefit of approaching the epilepsies using a framework of genetic classification of disease?

First, for the clinician, knowing which genetic disorders have a high risk for epilepsy can aid in differential diagnosis. The background population rate of epilepsy is 2% to 4%, whereas in some disorders, epilepsy can be present in almost 100% of patients, and the type of epilepsy can be characteristic of the disorder.

Second, investigation of the disorders that are associated with epilepsy is providing insight into the causes of epilepsy. Understanding that epilepsy is not a general consequence of all chromosomal aberrations but is present in specific chromosomal disorders, for example, has led to a search for epilepsy-related genes at specific chromosomal sites.

Third, by studying the effects of specific gene mutations on intracellular and cell membrane function, by creating animal models of human epilepsy disorders, and by studying in detail the cellular effects of human mutations, the mechanisms of epileptogenesis will be better understood. For most of the conditions described below, the actual mechanism of epileptogenesis is at present poorly understood.

Finally, for the patients and their families, diagnosis of their disorder provides the opportunity for treatment, for genetic counseling, and for tailored treatment of their seizures as well as for health maintenance issues that may arise later in the course of their disease.

Basic Genetic Concepts

Most of the conditions in this chapter involve mendelian (single gene locus) inheritance.[71] Because of the rapidly changing knowledge about these disorders, we commonly use two searchable Web-based sites to help with our diagnosis and testing: *GeneTests* (www.genetests.org) and *OMIM* (Online Mendelian Inheritance in Man: www.ncbi.nlm.nih.gov/entrez/query.fcgi?db = OMIM). These sites are funded by the National Institutes of Health (NIH), and include clinical and molecular information about genetic disorders, references, and clinical laboratories that test for the different disorders.

Testing (and thus the diagnosis) of genetic disorders associated with epilepsy continues to provide challenges to the clinician. Further, the technology and means of testing is in constant flux. Again, *GeneTests* is an invaluable resource for finding laboratories that provide clinical testing. Unfortunately, in many instances our knowledge of the diseases has outstripped the ability of laboratories to provide clinical testing. In many diseases any one test is not 100% sensitive, so if the clinical suspicion is high enough, further testing may be warranted.

All testing should be preceded by adequate counseling about the purpose and possible outcomes of the testing and potential choices that might arise (see Chapter 19). The clinical complexity and overlap in phenotypes of these disorders, the implications for genetic testing of other family members, and ramifications on insurance coverage mandate responsible clinical judgment.

A basic grasp of genetic concepts is important for understanding the disorders in this chapter. We have grouped these topics into four areas: Genetic transmission, gene expression, genomic integrity, and genetic heterogeneity.

Genetic Transmission

Four major modes of inheritance have been characterized in detail: Autosomal dominant, autosomal recessive, X-linked recessive, and mitochondrial.

Autosomal dominant traits can be expressed when only one of the paired alleles (genes) at a given locus is of a mutant form. However, apparent â€œskipsâ€ in a pedigree may occur as the result of incomplete *penetrance*. Incomplete penetrance is the presence in an individual of a dominant disease gene without full expression of the mutant phenotype. Sometimes, however, careful examination of individuals carrying a dominant disease gene reveals minimal signs of the condition, indicating variable expression of disease symptoms.

For an *autosomal recessive* trait to be expressed, both alleles must be of a mutant form (although not necessarily with the same mutation). Both parents of an affected individual are heterozygous disease gene carriers, and careful examination or laboratory evaluation may sometimes reveal heterozygous effects. Ordinarily, however, carriers of a single recessive disease gene are clinically asymptomatic. Because autosomal recessive alleles are generally rare, a detailed family history should be taken to search for any consanguinity.

The hallmark of *X-linked diseases* is the absence of male-to-male transmission of the genetic trait, since males pass on a Y chromosome, not an X chromosome, to their sons. Thus, the condition usually is found only in male subjects who are in turn related through female carriers. Some X-linked disorders (such as incontinentia pigmenti) are lethal in affected males, so that only female carriers of the abnormal gene survive fetal life.

Mitochondrial mutations follow a maternal inheritance pattern. In this situation, the frequency of a trait is the same in male and female subjects, but the condition is always transmitted from an affected mother to most of her children, never from an affected father. A human egg contains several hundred thousand copies of mitochondrial DNA (mtDNA), compared with only a few in sperm. Theoretically, all children of an affected mother should be affected. The expression of a mitochondrial mutation, however, depends on the relative proportion of mutant and wild-type mtDNAs in a given cell (termed *heteroplasmy*), and this proportion can shift during cell division. Because of a â€œthreshold effect,â€ tissues with a low proportion of mutant mtDNAs may not show an effect, whereas tissues that have reached the threshold begin to show effects of mitochondrial dysfunction. Organs that have a high rate of energy consumption, such as brain, heart, and muscle, are most often affected by mitochondrial disorders. It must also be noted that some mitochondrial disorders result from mutations in nuclear genes; these defects are inherited in a regular mendelian pattern.

Anticipation is the tendency for affected individuals in successive generations to present with earlier and/or more severe symptoms. This occurs in some genetic disorders, especially those associated with trinucleotide repeat expansions. Certain disorders have a predilection for repeat instability when passed on via either the paternal or maternal germ-line.

Mosaicism, or the presence of more than one genotype in the body, must also be considered in situations when multiple siblings have a disorder despite the absence of any family history of the disorder. In this situation, the parent is phenotypically normal because most of the somatic cells of the body carry the wild-type allele, but the germ cells carry the mutant allele, which is thus passed on to all the offspring.

Polygenic disorders remain a major frontier in our understanding of genetic mechanisms of disease. These disorders are common (e.g., idiopathic epilepsy) and show complex inheritance, involving multiple (possibly interacting) genes, with or without additional environmental influences. Identifying the causative genes is challenging.[51]

Gene Expression

The pathways from genes (the genotype) to physical or clinical traits (the phenotype) are extraordinarily complex. The molecular and developmental events that control phenotypic expression are numerous. They include DNA regulatory elements that control location, levels, rate, and timing of gene expression[73]; alternative splicing of the primary mRNA transcript to produce different mRNAs; *imprinting*, or the differential expression of a gene depending on which parent contributed the gene; regulation of mRNA expression by small RNA molecules[107]; and combinatorial protein and enzymatic complexes.

Genomic Integrity

Deletion or duplication of DNA segments on a chromosome can produce significant clinical effects. Larger deletions, duplications, or translocations can disrupt many genes and produce severe symptoms, including mental retardation and growth failure. Microdeletions, which may not be detectable by standard cytogenetic analysis, can produce *contiguous gene syndromes* that involve the loss of several neighboring genes and can lead to unique phenotypes depending upon the specific genes deleted.

Recently, a series of inherited disorders has been shown to involve the expansion of DNA trinucleotide repeat sequences. These include myotonic dystrophy, fragile X syndrome, Huntington disease, and some of the spinocerebellar ataxias. Normal individuals show variation in the number of repeats, but above a certain threshold the repeat length becomes unstable, with a tendency for further increase in number of repeats in later generations. Higher repeat numbers are associated with an earlier onset of the condition, greater severity of symptoms, or bothâ€”a phenomenon known as *anticipation.* The mechanisms by which trinucleotide repeat expansions cause disease remain unknown.

Genetic Heterogeneity

Genetic heterogeneity (or locus heterogeneity) is the phenomenon whereby a single clinical phenotype can result from mutations in different genes. This possibility must be considered in the genetic study of any disorder, as it may affect both diagnosis and treatment and also causes problems in gene mapping studies. Thus, the epilepsies are a limited group of phenotypes that may be caused by a number of different genes. For example, seizures can occur from changes in neuronal excitability, neuronal inhibition, or control of the spread of a seizure state, each of which is regulated by many different genes.

From a diagnostic perspective, it is not sufficient to classify epilepsy simply on the basis of the clinical or electrographic appearance of the seizures; some consideration of the underlying cause must be included. To say that a patient has mental retardation and epilepsy could miss the point that both conditions are manifestations of an underlying cause, for example, Angelman syndrome. On the other hand, a purely genetic classification is not satisfactory either, and lacks the clinical and treatment paradigms. Godfrey[28] emphasized the continuing interdependence between clinicians and molecular scientists in resolving this problem:

> â€œDo we begin to classify disorders on the basis of molecular lesions or on the basis of clinical criteria? Neither alone seems satisfactory any more. Therefore, we will use both, singly and in combination, but heterogeneity will continue to pose dilemmas in our practices and laboratories.â€

Table 1 Risk for Epilepsy, and Other Seizure Associations, in Genetic Disorders

Risk for epilepsy

>75%
Angelman syndrome
Fukuyama congenital muscular dystrophy
Hemimegalencephaly
Lissencephaly
MELAS syndrome
Periventricular nodular heterotopia
Sturge-Weber syndrome
Tuberous sclerosis
Zellweger spectrum disorders

50%â€“75%
Biotinidase deficiency
Christian syndrome
Landau-Kleffner syndrome
Linear nevus sebaceous syndrome
Rett syndrome
Wolf-Hirschhorn syndrome

30%â€“50%
Congenital disorders of glycosylation
Glycogen storage disease I and III
Hypomelanosis of Ito
McLeod neuroacanthocytosis syndrome
Metachromatic leukodystrophy
Niemann-Pick disease, type C
Saethre-Chotzen syndrome
Schizencephaly

<30%
Acute intermittent porphyria
Adrenoleukodystrophy Alzheimer disease
Autism
BÃ¶rjeson-Forssman-Lehmann syndrome
Brachmann-de Lange syndrome
Cardiofaciocutaneous syndrome
Cohen syndrome
Crouzon syndrome
Fragile X syndrome
Huntington disease
Homocystinuria
Leigh syndrome
Neurofibromatosis types 1 and 2
Parry-Romberg syndrome
Prader-Willi syndrome
Trisomy 13
Trisomy 21
Velocardiofacial syndrome
Wilson disease

No increased risk
Cri-du-chat syndrome
Sex chromosome aneuploidies
Subtelomeric deletions
Williams syndrome
Smith-Magenis syndrome
Lesch-Nyhan syndrome
Mucopolysaccharidoses

Seizure associations

Burst-suppression
Nonketotic hyperglycinemia

Hypsarrhythmia
Menkes disease Nonketotic hyperglycinemia

Infantile spasms
Hypomelanosis of Ito
Lissencephaly
Tuberous sclerosis
Wolf-Hirschhorn syndrome

Other nonepileptic events
Alzheimer disease (myoclonus)
Angelman syndrome (myoclonus)
Coffin-Lowry syndrome (stimulus-induced drop attacks)
Niemann-Pick disease, type C (gelastic cataplexy)
Trisomy 13 (apneic spells)

MELAS, mitochondrial encephalomyopathy with lactic acidosis and strokelike episodes; WAGR, Wilms tumor, aniridia, genitourinary anomalies, and mental retardation.

Genetic Disorders Associated with Epilepsy

Table 1 summarizes the genetic disorders discussed in this chapter. It lists the disease name, its associated gene (if known), and seizure frequency. We have organized the genetic disorders in the following broad categories:

- Chromosome disorders
- Contiguous gene disorders
- Metabolic disorders
- Genetic syndromes; which are further subdivided as follows:
  - Short stature
  - Early overgrowth
  - Skeletal dysplasias
  - Facial defects
  - Connective tissue
  - Neurocutaneous
  - Ectodermal and mesodermal dysplasias
- Disorders of brain development
- Neurodegenerative disorders

Chromosome Disorders

The chromosome disorders represent a wide array of possible disorders caused by additions, deletions, or rearrangements of chromosomal material (see Chapter 261). Classical cytogenetic methods are now complemented by more sensitive methods such as high-resolution chromosome banding, fluorescent in situ hybridization (FISH), and the polymerase chain reaction (PCR). Small deletions or duplications are now detectable, and the contribution of an individual gene to the overall phenotype of a chromosome disorder can often be determined.

Six percent of patients with epilepsy and intellectual impairment have chromosomal abnormalities, while 50% of patients with epilepsy and multiple congenital abnormalities have chromosomal abnormalities, as noted by Singh et al.[105] in their review of the frequency and types of epilepsies resulting from disorders of each of the chromosomes (see also the review by Battaglia and Guerrini[4]).

Epilepsy occurs in 1% to 10% of patients with *trisomy 21 syndrome* (*Down syndrome*), and electroencephalographic (EEG) abnormalities are present in more than 20%.[21,104,118] EEG abnormalities ranged from slowing, asymmetry, and asynchrony to diffuse or focal epileptiform activity.[21] Seizures most often begin early in childhood, and can be of different types; infantile spasms occur occasionally (0.5% to 2% of patients), while myoclonic seizures are distinctly uncommon.[89,104,123]

Trisomy 13 syndrome is commonly accompanied by severe developmental retardation, microcephaly, and severe craniofacial dysgenesis, including holoprosencephaly. Seizures occur in 25% of patients and apneic spells in 58%.[33]

Trisomy 18 syndrome, the third common autosomal trisomy, is characterized by poor somatic growth and hypoplasia and dysplasia of many internal organs, including the brain. Gross malformations of the brain range from heterotopias to holoprosencephaly, which may be associated with apneic episodes and seizures.[33] Others report a much lower incidence of seizures in trisomy 18 patients than in trisomy 13.[125]

More than 50% of patients with *Wolf-Hirschhorn syndrome* (del4p16) have seizures, which can be difficult to control. Characteristic EEG and seizure patterns (including infantile spasms) are associated with this syndrome.[3] The incidence of seizures may depend on the exact site of the deletion, as the â€œcritical regionâ€ is still being delineated. In contrast, patients with cri-du-chat syndrome (del[5p]) are microcephalic but generally do not have severe seizures.

The *fragile X syndrome* is included here as a chromosome disorder for historical reasons. The first diagnostic test for this disorder was cytogenetic, based on the presence of a visible disruption in the X chromosome (the â€œfragile Xâ€) when cells of affected individuals were grown in a culture medium low in folate. Fragile X syndrome is now known to be a trinucleotide repeat disease caused by the expansion within the *FMR-1* gene of a trinucleotide that is repeated in tandem only a few times in normal individuals. Fragile X syndrome is responsible for about 2% to 5% of all cases of mental retardation in male individuals, and also has been associated with mental retardation in females, although usually less severe than in their

male relatives. In large series, about 20% of males and 5% of females with fragile X syndrome have clinically apparent seizures, and about 50% have abnormal EEGs.[6,121] No patient had infantile spasms. EEG abnormalities included nonspecific slowing as well as epileptiform or paroxysmal discharges; other authors have reported a high incidence of centrotemporal (rolandic) spike discharges in *FMR-1* mutation carriers in the second half of the first decade of life, both with and without clinical seizures. Seizures and EEG abnormalities in individuals with fragile X syndrome tend to improve with age.

Other less common chromosome deletion and translocation syndromes are associated with the presence of epilepsy. Seizures were present in a series of over 400 different chromosome imbalances[105]; eight disorders were highly associated with epilepsy: *Wolf-Hirschhorn (4p-) syndrome*, *Miller-Dieker syndrome* (del 17p13.3), *Angelman syndrome* (del 15q11-q13), the inversion duplication 15 syndrome, terminal deletions of chromosome 1q and 1p, and ring chromosomes 14 and 20. Notably, epilepsy is not a prominent feature of the sex chromosome aneuploidies, such as Turner syndrome or Klinefelter syndrome. Subtelomeric deletions at the ends of chromosomes have been reported to be a significant cause of mental retardation,[61] but seizures appear to only be an occasional association.

Contiguous Gene Disorders

Three contiguous gene disorders associated with seizures are discussed below: *Angelman syndrome*, *Prader-Willi syndrome*, and *Velocardiofacial syndrome* (*Miller-Dieker syndrome* is discussed later in this chapter). Other contiguous gene disorders not associated with an increased risk of seizures include Williams syndrome, WAGR (Wilms tumor, aniridia, genitourinary anomalies, and mental retardation) syndrome, Potocki-Shaffer syndrome, and Smith-Magenis syndrome.

Angelman syndrome was first identified cytogenetically as involving loss of the maternal chromosome region 15q11-13. Affected patients have severe mental retardation, epilepsy, ataxic jerky movements, inappropriate laughter, and absence of speech. *UBE3A*, a ubiquitin-protein ligase, is the minimal gene mutation responsible for the core phenotype, but the phenotypic presentation depends on the type of mutation and which associated genes are involved.[60,70]

Seizures with onset at <3 years of age and EEG abnormalities are findings in more than 80% of patients, and are part of the diagnostic criteria for Angelman syndrome.[120] Abnormal EEGs are commonly present in infancy and may be the first diagnostic sign.[8,24] EEG abnormalities in infants often include irregular, generalized, high-voltage sharp-wave and spike-wave activity. Although only 30% of patients have seizures in the first 2 years of life, by 3 years of age 85% will have developed seizures, most often of the absence, myoclonic, or generalized tonicâ€“clonic types. However, some of the abnormal movements in Angelman syndrome are cortically based myoclonus, responsive to GABAergic (Î³-aminobutyric acid) drugs.

Prader-Willi syndrome also involves chromosome region 15q11-13, but in contrast to Angelman syndrome, results from loss of the paternally derived chromosome. Patients with Prader-Willi syndrome have infantile hypotonia, short stature, small hands and feet, hypogonadism, and mental retardation, and as children develop hyperphagia and obesity.[37] Seizures are present in 15% to 20% of patients, but in contrast to Angelman syndrome, the seizures are not severe, chronic, or therapeutically challenging.[9] Molecular diagnosis is based on abnormal methylation studies, which detect 99% of cases.[13]

Velocardiofacial syndrome, a contiguous gene deletion involving chromosome region 22q11.2, is characterized by congenital heart disease, palatal abnormalities, characteristic facial features, learning difficulties, and immune deficiency. Former names for velocardiofacial syndrome are DiGeorge syndrome and Shprintzen syndrome. Seven percent of patients with velocardiofacial syndrome develop seizures.[57] In addition, infants with velocardiofacial syndrome sometimes present with seizures secondary to hypocalcemia because of parathyroid deficiency.

Metabolic Disorders

There are several general mechanisms by which metabolic disorders can result in seizures (see also Chapters 261 and 262). First, any disorder that alters the cellular metabolic environment (such as hyperammonemia) can provoke seizures. Second, some metabolic disorders can lead to secondary structural abnormalities in the brain. For instance, cortical infarctions can develop in patients with MELAS (mitochondrial encephalomyopathy with lactic acidosis and strokelike episodes) that can act as epileptogenic foci even in the absence of acute systemic metabolic disturbance. Finally, a tendency to epilepsy may be intrinsic to the metabolic disturbance or disease itself, if the metabolic pathway is necessary for the function of neurons and/or glia. The treatment of seizures in patients with metabolic disorders must include treatment of the metabolic derangement; seizures are likely to persist despite anticonvulsant therapy if an untreated metabolic abnormality is present, and anticonvulsant therapy may not be necessary if the metabolic derangement is brought under control.

Wolf et al.[124] reviewed the main characteristics of the epilepsies that are found in the inborn errors of metabolism and outlined a general approach to diagnosis and treatment. For more detailed information see also *The Molecular and Metabolic Basis of Inherited Disease*,[103] *Diagnostic Recognition of Genetic Disease*,[81] and *Atlas of Metabolic Diseases*.[80]

In patients with disorders of carbohydrate metabolism and glycogen storage diseases, seizures occur in association with hypoglycemia or during times of metabolic stress. Accordingly, seizures occur in 25% to 40% of patients with *glycogen storage disease types I* and *III* and rarely in other types, in which systemic hypoglycemia is uncommon. Patients with *d-glyceric acidemia* and *galactosemia* have myoclonic seizures, and abnormal waking EEGs are seen in more than 50% of children with galactosemia.

Niemann-Pick disease, type C (NPC) is a lipid storage disease with a variable age of onset, typically presenting with ataxia, vertical supranuclear gaze palsy, dementia, and, in infants, hypotonia and organomegaly.[85] Inheritance is autosomal recessive; most cases are caused by mutations in *NPC1*, and diagnosis is based on impaired cholesterol esterification in cultured fibroblasts that show positive filipin staining. About one third of patients with NPC have seizures, which are often resistant to treatment. Ironically, seizures tend to decrease with prolonged survival, possibly due to continued neuron loss. Gelastic cataplexy, the sudden loss of muscle tone from humorous stimuli, is present in about 20% of children with NPC.[56,88]

A number of the disorders of amino acid metabolism (including the urea cycle disorders) feature seizures or epilepsy. The urea cycle defects are especially marked by significantly elevated levels of ammonia; about 50% of neonates with elevated ammonia will have seizures, along with cerebral edema.[110] The use of valproic acid is contraindicated in these disorders because it can raise ammonia levels. Seizures are also prominent in *HHH* (*hyperammonemia, hyperornithinemia, hypercitrullinemia*) *syndrome*, *nonketotic hyperglycinemia*, and *homocystinuria*.

HHH syndrome, like other disorders of the urea cycle, may present at any time from infancy to adulthood with lethargy, episodes of vomiting or neurologic dysfunction, seizures, and coma. It is somewhat more likely to appear later in life than other disorders of the urea cycle, which usually develop in infancy or childhood.

Nonketotic hyperglycinemia (NKH) presents in infancy with intractable generalized or myoclonic seizures, hypotonia, apnea, and high levels of glycine in the blood and cerebrospinal fluid (CSF). NKH has autosomal recessive inheritance, and is caused by mutations in the glycine cleavage system. The EEG most commonly shows a burst-suppression pattern, but hypsarrhythmia can also be seen. NKH should be considered in the differential diagnosis of a patient with infantile spasms. Most patients die before 1 year of age, although affected males have a longer survival rate and better neurologic function.[48] Diagnosis can be made by detecting elevated levels of glycine in the serum, but in some cases CSF amino acid analysis is necessary, as glycine levels may only be elevated in the CSF and not in the serum. Brain magnetic resonance imaging (MRI) can be useful for diagnosis as well, as reported abnormalities include ventriculomegaly, absent corpus callosum, posterior fossa cysts, delayed myelination, areas of diffusion-restriction, and an elevated glycine peak on magnetic resonance spectroscopy (MRS).[59] Treatment with standard anticonvulsants may not be successful, and treatments directed toward lowering glycine levels have met with only mild success.

Homocystinuria is a relatively common metabolic disorder. The frequency of epilepsy in homocystinuria has been estimated at 21%, with the most common seizure type being generalized tonicâ€"clonic seizures.[74] These seizures are not associated with any identifiable metabolic â€œcrisis,â€ and epileptiform EEG findings are common both in patients with seizures and in patients who are clinically asymptomatic.[17]

Pyridoxine-dependent seizures (PDS) occur within the first hours or days of life and respond dramatically to treatment with vitamin B_6. PDS has autosomal recessive inheritance, and several different gene loci have been implicated.[5] Any infant presenting with idiopathic seizures in the first week of life warrants a trial of pyridoxine, as appropriate treatment can lead to a seizure-free, neurologically normal outcome.[115]

Seizures commonly accompany the metabolic crises of not only the urea cycle disorders, but also of the organic acidurias, such as *propionic acidemia*, *isovaleric acidemia*, *biotinidase deficiency*, and *glutaric aciduria, type I*. The most common seizure types are generalized myoclonic or infantile spasms. In general, seizures are more likely to be a presenting feature in infants or young children with these disorders than in children with variants of later onset. Biotinidase deficiency can present with ataxia, developmental delay, seizures, and an eczematous rash. Seizures were the presenting feature in 38% of patients, and 55% of patients had seizures.[100] Glutaric aciduria, type I, is an autosomal recessive disorder presenting with macrocephaly, a progressive movement disorder that can be misdiagnosed as cerebral palsy, and progressive neurologic symptoms that may acutely worsen during periods of illness.[47] MRI may show frontotemporal atrophy and enlarged CSF spaces in the sylvian fissures (â€œbat-wingâ€ appearance)[80] (see also Chapter 262). Seizures more commonly accompany the acute decompensatory episodes.

Mitochondrial disorders typically can be diagnosed by elevated blood and/or CSF lactate levels (see also Chapter 263). *Leigh syndrome* (subacute necrotizing encephalomyelopathy) is a group of disorders that manifests in infancy with lethargy, failed neurologic development, seizures, and progressive respiratory dysfunction. Leigh syndrome can be caused by mutations in mitochondrial or nuclear DNA. Seizures are present in roughly 30% of patients.[90] Older children or adolescents may have symptoms of the mitochondrial deletion disorders *MERRF* (*mitochondrial encephalomyopathy with ragged red fibers*) and *MELAS* (*mitochondrial encephalomyopathy with lactic acidosis and strokelike episodes*). (MERRF is discussed in Chapter 262 as one of the primary genetic epilepsy syndromes.) Seizures in MELAS occur initially at times of metabolic disarray and lactic acidosis, but they may become self-perpetuating as structural lesions accumulate in the brain. During the strokelike episodes, the EEG can show characteristic focal high-voltage delta waves with polyspikes.[25] Seizures are a presenting sign in 28% of patients with MELAS and are present at some point in 96% of patients.[45]

The peroxisome biogenesis disorders (the Zellweger spectrum disorders, including *Zellweger syndrome*, *neonatal adrenoleukodystrophy*, and *infantile Refsum disease*) have autosomal recessive inheritance. Seizures are very common, and are a significant management problem in neonatal adrenoleukodystrophy.[111] The EEG shows diffuse or multifocally abnormal patterns or hypsarrhythmia. In severely affected patients, aberrant cortical structure can sometimes be seen with central nervous system (CNS) imaging. Most severely affected patients die within the first 1 to 2 years of life.

Among the lysosomal storage disorders, epilepsy is a prominent or early feature of *Krabbe disease* and some forms of *Gaucher disease*. Generalized or myoclonic seizures become prominent during the course of *Tay-Sachs disease* and *Sandhoff disease*, and they can also be seen in patients with *sialidosis* and *Farber disease*. Seizures occur as a later phenomenon in about 20% of patients with *adrenoleukodystrophy* and in up to 46% in patients with *metachromatic leukodystrophy*.[1] The EEG features of these diseases have been reviewed.[76]

Acute intermittent porphyria, caused by deficiency of the enzyme porphobilinogen deaminase, leads to recurrent seizures in about 10% to 20% of affected patients. The treatment of seizures is difficult because many of the standard anticonvulsants (phenytoin, valproic acid, and in particular the barbiturates) can trigger metabolic crises in individuals with porphyria and are therefore considered unsafe to use. Reynolds and Miska[94] have recommended diazepam, paraldehyde, or bromides for treatment of seizures during acute metabolic crises. A recent report documents the successful treatment of seizures with gabapentin.[112] Gabapentin and other nonhepatically metabolized drugs such as levetiracetam are appealing drugs to consider in patients with porphyria.

Menkes disease is an X-linked disorder of copper metabolism caused by mutations in the adenosine triphosphatase (ATPase) copper-transporting gene *ATP7A*. Symptoms, which appear within the first 3 months of life, include failure to thrive, developmental regression, hypotonia, coarse short hair, and seizures. EEGs obtained early in the course show multifocal spikes, but hypsarrhythmia develops as the neurologic disorder progresses. Seizures may be generalized or partial, and they are variable in severity. Copper therapy does not affect the EEG, but seizures may respond to standard anticonvulsant therapy.[23]

In general, seizures are not a primary feature of disorders of purine metabolism (e.g., Lesch-Nyhan syndrome), endocrine and exocrine disorders, and the immune deficiency disorders. In addition, the mucopolysaccharidoses, some of which produce profound declines in mental function, are not associated with seizures or epilepsy.

An exciting advance in the past decade has been the recognition of two novel types of metabolic disorders: congenital disorders of glycosylation and CSF neurotransmitter disorders.

Congenital disorders of glycosylation, also known as carbohydrate-deficient glycoprotein syndromes, are a heterogeneous group of disorders with multiorgan effects caused by defects in glycoprotein biosynthesis.[53] Patients may have developmental delay, ataxia, neuropathy, and characteristic physical findings including inverted nipples and facial dysmorphism. Diagnosis is made by serum transferrin isoelectric focusing. Seizures have been reported in up to 50% of patients.[86]

CSF neurotransmitter disorders are a group of metabolic diseases that affect the production of neurotransmitters; diagnosis relies upon CSF fluid collection and measurements of neurotransmitters, their metabolites, and their intermediates. Symptoms include seizures, dystonia and other extrapyramidal disorders, ocular movement abnormalities, autonomic instability, and ataxia.[46,49] Timely diagnosis is difficult but important because of the effective treatments available for many of these disorders. Because of limited data regarding the prevalence and symptoms, seizure frequencies are not known for the different CSF neurotransmitter disorders.

Genetic Syndromes

Many disorders seen by the neurologist or geneticist are not easily classifiable; often, they have been grouped according to a prominent physical finding or abnormality. It is important to realize, however, that disorders lumped into a certain category may share nothing except the presence of a single cardinal feature and yet differ widely in regard to their tendency to cause epilepsy.

In genetics, use of the term *syndrome* implies that a common etiology underlies all symptoms and signs included as part of the syndrome, whereas in the epilepsy literature, *syndrome* is used to describe a collection of signs or symptoms that commonly occur together; a specific or constant etiology is not implied. (For instance, the Lennox-Gastaut epilepsy syndrome may be present in patients with a number of different genetic disorders or syndromes!) In the discussion below, the terms *disease*, *disorder*, and *syndrome* are used interchangeably to refer to genetically defined entities.

The outline of this section follows the format of Smith's Recognizable Patterns of Human Malformation.[54]

Disorders with Short Stature

Seizures are noted particularly in some of the syndromes associated with short stature, including *Brachmann-de Lange syndrome* (14% to 20%),[2,43] Marinesco-SjÃ¶gren syndrome, *Smith-Magenis syndrome*, and the *DeSanctis-Cacchione* variant of *xeroderma pigmentosa* (but not in other variants of xeroderma pigmentosa or in other â€œpremature agingâ€ disorders, such as progeria, Seckel syndrome, or Cockayne syndrome).

Disorders of Early Overgrowth

Seizures have been described in up to 25% of patients with *BÃ¶rjeson-Forssman-Lehmann syndrome*, caused by mutations in the X-linked *PHF6* gene.[68] Further, EEG abnormalities, consisting mostly of low-voltage fast activity or nonspecific slowing, were present in at least 50% of patients, as well as in otherwise asymptomatic female carriers.[96] Neonates with *Beckwith-Wiedemann syndrome* may present with seizures secondary to hypoglycemia, and occasional patients have an ongoing seizure disorder. Finally, seizures with or without severe brain malformation may be seen in patients with hemihypertrophy (which is in itself not a diagnosis, but rather a physical sign of diverse etiologies); patients with significant somatic asymmetry should always be evaluated for CNS structural abnormalities.

The incidence of epilepsy has not been reported to be significantly elevated in the syndromes of Bannayan-Riley-Ruvalcaba, Cohen (6% incidence of seizures), Marshall-Smith, Simpson-Golabi-Behmel, Sotos, and Weaver.

Skeletal Dysplasias

Many of the skeletal dysplasias cause abnormal skull or facial shape. However, deformation of the cranial contents alone does not necessarily result in seizures. Thus, patients with achondroplasia, metaphyseal dysplasias, or the osteopetrosis syndromes do not have a high risk for epilepsy or seizures. However, seizures do occur in patients with bony diseases related to systemic hypocalcemia, such as *Albright osteodystrophy* and *hypophosphatasia* (2% to 24%, greater frequency with earlier age of onset); the seizures are presumably related to the metabolic disruption and are not a primary feature of the bony disease. Patients with *osteogenesis imperfecta* do not have increased seizure risk, although a single study demonstrated EEG abnormalities in half of 56 patients.[93] Finally, cortical dysplasias (and thus an increased risk for seizures) have been reported in thanatophoric dysplasia.

Craniosynostosis can arise from diverse syndromic, chromosomal, metabolic, hematologic, and environmental causes. Thus, the presence of seizures in a patient with craniosynostosis should prompt an evaluation of the etiology of the craniosynostosis, as well as CNS imaging. Seizures occur frequently (percentage in parentheses) in patients with *Christian syndrome* (60%),[33] *Crouzon syndrome* (12%),[64] and *Saethre-Chotzen syndrome* (36%),[20] but not in Apert syndrome.

Disorders with Facial Defects

A large number of genetic syndromes affect facial morphogenesis, or cranial nerve formation, but the majority do not have associated seizures (see Gorlin et al.).[33] Teratogens such as anticonvulsants can also result in facial defects, but these are not discussed here. A significant risk for seizures in patients with oral-facial syndromes is the presence of CNS structural abnormalities. For example, *FG syndrome* is characterized by hypotonia, characteristic facial appearance, and agenesis of the corpus callosum.[34] EEG abnormalities have been described in FG syndrome patients,[82] and seizures have been reported in 0% to 60% of patients.[98]

Cardiofaciocutaneous syndrome (CFC syndrome), characterized by distinctive facial appearance; unusually sparse, brittle, curly hair; skin abnormalities; heart malformations; growth delays; and/or varying degrees of mental retardation, has been reported to have fairly common seizures (5 of 22 cases).[26] Recent molecular evidence shows that CFC syndrome and Noonan syndrome (which also has unusual facies and congenital heart defects) are distinct entities.[52]

Patients with Coffin-Lowry syndrome may have paroxysmal drop attacks (stimulus-induced drop episodes [SIDES]) that in the past were believed to be seizures. However, detailed characterization of these events has revealed that they are nonepileptic events with features of both cataplexy and hyperekplexia.[77]

Eleven percent of patients with *Parry-Romberg syndrome* develop seizures.[108] Affected patients have progressive hemifacial atrophy, often with trigeminal neuralgia and ophthalmologic abnormalities; the etiology is unclear, and there is some discussion as to whether the disease is a form of autoimmune scleroderma.

Facial disorders not associated with an increased risk of seizures include branchial arch syndromes, facial clefting syndromes, Langer-Giedion syndrome, Moebius syndrome, Treacher Collins syndrome, and Smith-Lemli-Opitz syndrome.[58]

Connective Tissue Disorders

Seizures do not occur with increased frequency in any of the connective tissue disorders (Marfan syndrome, Ehlers-Danlos syndromes, osteogenesis imperfecta), with the exception of homocystinuria (discussed above).

Neurocutaneous Disorders

The diagnosis of a neurocutaneous disorder should prompt surveillance for seizures, as epilepsy is a common feature in these disorders.[63]

Neurofibromatosis type 1 (NF1) is the most common of the neurocutaneous disorders. The incidence of epilepsy in NF1 is reported to be 5% to 11%.[119] NF1, also known as von Recklinghausen disease, is characterized by multiple cafÃ© au lait spots, axillary and inguinal freckling, multiple discrete dermal neurofibromas, and iris Lisch nodules. NF1 has autosomal dominant inheritance and its associated gene (neurofibromin) has been identified, but because of the large size of the gene, diagnosis is based on clinical criteria.[38] New-onset seizures in a patient with a personal or family history of NF1 should prompt a search for intracranial neoplasm, as patients have a lifelong increased risk for a variety of CNS tumors, especially optic nerve and brainstem gliomas.

Neurofibromatosis type 2 (NF2), an autosomal dominant mutation in neurofibromin-2 (merlin), is genetically and clinically distinct from NF1. NF2 is associated with bilateral vestibular schwannomas, multiple meningiomas, and other CNS tumors. NF2 has an approximately 8% seizure risk.[22]

Tuberous sclerosis complex (TSC) is characterized by hypomelanotic macules, facial angiofibromas, shagreen patches, ungula fibromas, brain tubers and/or subependymal nodules, seizures, mental retardation, kidney angiomyolipomas, and cardiac rhabdomyomas. Inheritance is autosomal dominant, caused by mutations in either *TSC1* (hamartin) or *TSC2* (tuberin).

Seizures affect up to 80% of TSC patients,[31,64] and infantile spasms occur in up to one third of patients.[113] The most common cause of infantile spasms is TSC; 25% of patients with infantile spasms have TSC. Because of this association, an infant presenting with infantile spasms should have a careful skin examination, and if indicated, an examination with a Wood lamp to look for hypomelanotic macules. Further, significant evidence suggests that first-line treatment for infantile spasms in TSC patients is vigabatrin (not adrenocorticotropic hormone [ACTH], which is used for non-TSC infants with infantile spasms).[40]

Overall, 60% of TSC patients are mentally retarded, and of these 98% have seizures; only 59% of those TSC patients without retardation had seizures.[101] Sixty-four percent of patients with TSC who have infantile spasms will develop mental retardation.[30]

Subependymal glial nodules occur in 90% of individuals with TSC, and cortical or subcortical tubers in 70%.[19] Patients with more than four cortical lesions visible on MRI were more likely to have intractable seizures.[95] Progressive intracranial calcification (of uncertain relevance to the seizure disorder) develops in children with this disease, and they are at risk for brain tumors, in particular giant-cell astrocytomas.

Infantile-onset seizures, often severe, are a presenting feature of *encephalocraniocutaneous lipomatosis*. This disorder involves skin, eye, adipose tissue, and brain. Neurologic manifestations include seizures, ventricular enlargement, calcifications, mental retardation, and cerebellopontine angle tumors.[67]

Proteus syndrome is a complex disorder with uncertain etiology; clinical features include disproportionate, asymmetric overgrowth of body parts; connective tissue nevi; epidermal nevi; vascular malformations of the capillary, venous, and lymphatic types; and dysregulated adipose tissue.[15] Seizures have been reported in association with Proteus syndrome, although the incidence is not known. *Hemimegalencephaly* refers to hamartomatous malformation of the brain with diffuse migrational abnormalities of an entire cerebral hemisphere; there are both â€œisolatedâ€ and syndromic (including some of the neurocutaneous syndromes such as Proteus syndrome) causes. Seizures tend to have onset in infancy and may be difficult to control medically. A recent study listed seizures in 100% of patients, with 26% requiring hemispherectomy to achieve seizure control.[102]

Epidermal nevus syndrome is characterized by nevi following the lines of Blaschko, along with noncutaneous involvement of the brain, eye, and skeletal systems; but it is most likely a collection of several separate entities with similar clinical features (including linear nevus sebaceous syndrome). *Linear nevus sebaceous syndrome* is characterized by midline nevus sebaceous, seizures (in 67% of patients), mental retardation, and associated CNS abnormalities including hemiatrophy and ventricular dilatation.[116]

Sturge-Weber syndrome is a sporadically occurring disorder of the vasculature of the face and head. Intracranially, unilateral leptomeningeal angiomas and calcifications develop, which commonly follow the course of the angiomatous vessels.[87] Seizures occur in 80% of patients with Sturge-Weber syndrome.[109] Unilateral or bilateral epileptiform discharges can be present, with or without unilateral or bilateral background slowing.[10,97]

Incontinentia pigmenti is an X-linked disorder of the skin, hair, nails, teeth, eyes, and CNS, caused by mutations in the NEMO gene (NF-kappaB essential modulator).[106] CNS malformations and seizures have been reported in this disorder, although the prevalence is uncertain. Patients with *hypomelanosis of Ito* have skin depigmentation along the lines of Blaschko and neurologic symptoms including language disabilities, seizures, hypotonia, mental retardation, and autistic behavior, with underlying abnormalities in the CNS white matter.[99] The disorder is probably an etiologically diverse group of conditions with genetic mosaicism as a common feature.[65] Seizures are reported in up to 49% of patients, and infantile spasms in 8% of patients.[84]

Hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu disease), characterized by the presence of multiple arteriovenous malformations (AVMs), does not have an increased risk of seizures. However, brain MRI with vascular imaging is indicated early in life to look for cerebral AVMs, and antibiotic prophylaxis is indicated for patients with a pulmonary AVM, as they can develop a cerebral abscess and seizures. Lipoid proteinosis (Urbach-Wiethe syndrome), nevus basal cell carcinoma syndrome (Gorlin-Goltz syndrome), pseudoxanthoma elasticum, and SjÃ¶gren-Larsson syndrome are not associated with seizures.

Ectodermal and Mesodermal Dysplasias

Seizures are not a feature of the ectodermal dysplasias. Diseases that disrupt the development of primarily mesodermal structures, such as the multiple intestinal polyposis syndromes and the multiple endocrine neoplasias, also are not associated with epilepsy.

Genetic Disorders of Brain Development

The past 10 years have seen an explosion in information about the genetics of CNS developmental abnormalities. In part, this has been facilitated by the advances in CNS imaging made possible by high-resolution MRIs, which have revealed underlying brain abnormalities in many patients with seizures (see Chapters 14, 79, and 260). Guerrini and Filippi[36] reviewed the frequency of seizures and EEG findings in each disorder and also outlined procedures for genetic testing and genetic counseling (see also the review by Mochida[72]).

Holoprosencephaly is characterized by failure of the forebrain to divide into separate hemispheres and ventricles; there is a continuum of clinical features and severity, often with other malformations of the CNS and neuronal migrational abnormalities. Causes include teratogens, gross chromosome abnormalities in structure or number (25% to 50% of cases), syndromes, and single gene mutations in 18% to 25% of cases.[75] If genetic testing is indicated, high-resolution chromosome karyotypes should be obtained, and if necessary, FISH analysis of the known genes. About 80% of patients with holoprosencephaly also will have a craniofacial abnormality.[14] Seizures are common, but incidence depends on the etiology of the holoprosencephaly and the extent of malformations. In addition, hypersynchronous activity on EEG was seen in patients with holoprosencephaly without seizures.[39]

Schizencephaly is a structural brain abnormality, in which a CSF-filled cleft, lined by gray matter, extends from the pial surface of the brain to the ventricle. A variety of etiologies are hypothesized, and there are syndromic and familial cases, although no causative genes have yet been identified. Seizures are present in about 50% of patients.[35]

Septo-optic dysplasia (de Morsier syndrome) is a midline CNS disorder characterized by hypoplastic or absent optic discs and nerves, absent septum pellucidum, and pituitary deficiencies; seizures occasionally accompany this disorder. Mutations in the homeobox gene *HESX1* have been found in some patients with septo-optic dysplasia.[16]

Seizures are not a typical feature of the developmental disorders of the posterior fossa, such as Arnold-Chiari malformation, Dandy-Walker malformation, or Joubert syndrome. Seizures have been reported in patients with Arnold-Chiari I malformation (in which the cerebellar tonsils are displaced downward through the foramen magnum), although it is not clear if the incidence is increased.[11] The unusual respiratory pattern and eye movements in infants with Joubert syndrome, however, can mimic seizures.

Lissencephaly, or smooth brain, is a pathologic or MRI finding of abnormal neuronal migration, resulting in absent (agyria) or reduced number (pachygyria) of gyri. Ninety percent of patients with lissencephaly have seizures, with onset before age 6 months in 75%. Almost 80% have infantile spasms. Different types of lissencephaly have been described including *LIS-1*â€“associated lissencephaly (Miller-Dieker syndrome), X-linked lissencephaly with corpus callosum agenesis and ambiguous genitalia (caused by mutations in *ARX*), and *DCX*-associated lissencephaly. Miller-Dieker syndrome is a microdeletion (contiguous gene deletion) of chromosome region 17p13.3, characterized by lissencephaly (with four rather than six nerve cell layers in the cortex) and a specific facial phenotype. The lissencephaly is caused by mutations in *LIS-1*,[92] while the facial features are due to the contiguous genes deleted in the syndrome.

Polymicrogyria is characterized by multiple small gyri with abnormal cortical lamination, frequently accompanied by seizures. Types include bilateral frontoparietal polymicrogyria, bilateral frontal polymicrogyria, and bilateral perisylvian polymicrogyria. *Heterotopias* are abnormal collections of gray matter, typically either in the deep white matter of the cerebral hemispheres or in the periventricular regions. X-linked periventricular nodular heterotopia has been associated with mutations in the *FLN1* and *ARGEF2* genes. Approximately 90% of patients with periventricular nodular heterotopia have epilepsy.

Three disorders have been described with the combination of brain abnormalities and congenital muscular dystrophy: *Muscle-eye-brain disease* (MEB), *Walker-Warburg syndrome* (WWS), and *Fukuyama congenital muscular dystrophy* (FCMD).[32] All three are characterized by infantile hypotonia and a â€œcobblestoneâ€ appearance of lissencephaly in their brain MRIs. There is significant clinical overlap in their symptoms; MEB and WWS also may have eye abnormalities, hydrocephalus, and leukoencephalopathy.[117] MEB and WWS are caused by mutations in genes (*POMGnT1* and *POMT1*, respectively, although there are several other gene loci also identified) involved in the glycosylation of *a*-dystroglycan, a structural protein.[117] FCMD is caused by mutations in the fukutin protein; seizures are present in 80% of patients with an average onset age of 3 years.[126] In MEB and WWS, seizures have been reported, although the incidence has not been established.

Neurodegenerative Disorders

Rett syndrome is an X-linked progressive neurologic disease characterized by initial normal development, followed by a plateau and then regression of cognitive and motor skills, deceleration of head growth, and the development of autistic-like features.[127] The classic phenotype is only present in girls; however, some few cases of affected males (with much worse clinical characteristics) have also been reported. Rett syndrome is caused by mutations in the *MECP2* gene.

EEG abnormalities are an invariable feature of Rett syndrome, and seizures are present in 50% of patients.[78,83] The waking EEG usually shows a poorly organized, slow background, which is interrupted by multifocal or bilaterally synchronous spikes or sharp waves that may become constant during sleep. Later in the course, the EEG may show only nonspecific low-voltage activity. The percentage of rapid eye movement (REM) sleep is diminished throughout the course of the disease. It has also been noted that not all â€œspellsâ€ in patients with Rett syndrome are epileptic.[27] Nearly 25% of 62 patients had episodes of breath holding, staring, laughing, or jerking that were without EEG correlation.

Autism, autistic-spectrum disorders, Asperger disorder, *Landau-Kleffner syndrome* (LKS), and pervasive developmental delay represent a spectrum of disorders with diverse etiologies. Thirteen percent of children with autism have epilepsy; another 22% have EEG abnormalities but no seizures.[12] Exact diagnostic criteria for LKS (or acquired epileptic aphasia) remain contentious, but patients present with a progressive childhood-onset aphasia associated with EEG abnormalities, most commonly continuous spike-and-wave discharges during sleep (electrical status epilepticus of sleep). Up to 70% of patients have clinical seizures.[114]

Seizures occur at an increased frequency in *Alzheimer disease* (10% of autopsy-proven cases,[42] 16.8% of institutionalized patients[7]), but they may not recur or require treatment. Myoclonus occurs in up to 10% of patients, and nonspecific EEG slowing is common, particularly as the disease progresses.

Seizures are a prominent feature of the *neuronal ceroid lipofuscinoses (NCLs)*. Patients present with a combination of visual loss, seizures, and progressive cognitive impairment or dementia. The NCLs are autosomal recessive lysosomal storage disorders, characterized pathologically by electron microscopy revealing fingerprint or curvilinear profiles, or granular osmiophilic deposits.[29] At least six different genes have been identified; diagnosis relies upon a combination of enzymatic testing for the protein defect and/or electron microscopy studies. The seizure disorder may appear as a progressive myoclonic epilepsy.[62] Raininko et al.[91] reported abnormal EEGs in 25 of 33 patients with juvenile NCL; 23 of these 25 EEGs showed paroxysmal activity, either focal or generalized. The EEG typically shows posteriorly prominent, light-induced spikes, and as the disease progresses, low-voltage activity with marked slowing predominates. Treatment of the seizures can be difficult; valproic acid tends to be poorly tolerated because of side effects, while lamotrigine appears to be more effective.[122]

Seizures are reported to occur frequently (30%) in patients with *Huntington disease* whose symptoms first appear in

childhood or adolescence, but much less often (2%) in the more typical adult-onset disease.[41] Huntington disease is caused by an autosomal dominant trinucleotide repeat expansion in the *HD* gene. Generalized, akinetic, or myoclonic seizures, rather than partial seizures, are seen. EEG abnormalities are seen in 74% of juvenile-onset Huntington disease patients.[66]

Epilepsy is not a feature of Parkinson disease and its variants, except that Nygaard et al.[79] reported complex partial seizures in 7 of 55 patients with progressive supranuclear palsy.

The *spinocerebellar ataxias* (SCAs) are a large and heterogeneous group of genetic disorders, characterized chiefly by progressive cerebellar ataxia. Epilepsy is reported in *SCA10*, *SCA17*, and *dentatorubropallidoluysian atrophy* (Haw river syndrome) (DRPLA),[69] which are caused by dominantly inherited triplet repeat expansions. Epilepsy is reported in 20% to 100% of SCA10 patients. Myoclonus and epilepsy are a defining feature of the â€œmyoclonus epilepsyâ€ form of DRPLA, but are infrequent or absent in the ataxic or choreic forms of the disease. Epilepsy occurs in all DRPLA patients with onset before age 20.[50] This disease appears to be less common in the United States than in Japan, where it may be responsible for 10% to 20% of adolescent- or adult-onset progressive myoclonus epilepsy.

In *Wilson disease*, an autosomal recessive disorder of copper metabolism that can present with hepatic, neurologic, or psychiatric disturbances, 6% of patients develop epilepsy with a greater incidence in patients with juvenile onset of symptoms.[18] *McLeod neuroacanthocytosis syndrome* is an X-linked disorder with red blood cell acanthocytosis and basal ganglia degeneration; up to 40% of patients develop seizures.[55] Pantothenate kinaseâ€“associated neurodegeneration (PKAN) (Hallervorden-Spatz syndrome) is characterized by progressive dystonia, dysarthria, rigidity, and pigmentary retinopathy. No seizures were reported in any patient with classic PKAN.[44]

Summary and Conclusions

More than half of the references cited here are new since the first edition of *Epilepsy*. This reflects the impressive strides in diagnosis made possible by advances in molecular and radiologic diagnostics, and the corresponding attention given to the topic both by epileptologists and by geneticists. The material includes comprehensive reviews of the epilepsies in broad genetic categories (such as chromosome abnormalities, inborn errors of metabolism, and neuronal migration disorders) as well as in specific disorders (such as the tuberous sclerosis complex).

In some of the disorders discussed in this chapter, the underlying genetic involvement is obvious, for example, the patient with trisomy 13 and dysmorphic characteristics on examination. In other situations the clinician must associate the findings of history and examination with characteristics of the epilepsy to make a diagnosis, as in patients with Angelman syndrome. A key point is that in many instances, the genetic syndromes with epilepsy now have specific genetic diagnoses.

This discussion of genetic syndromes and epilepsy is not exhaustive, but it provides a summary of the more common disorders a neurologist or geneticist might encounter. Appropriate treatment is dependent upon diagnosis, and diagnosis can be aided by recognizing those genetic syndromes accompanied by epilepsy. Thus, identification of the genetic and molecular bases for these disorders may provide an opportunity for directed pharmacotherapy. It may be noted that this approach complements the study of comorbidities that are observed in patients with primary epilepsies in which seizures are the primary manifestation. With these points in mind, this chapter should be of interest to epileptologists and other neurologists as well as to geneticists.

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Chapter 18

Genetics of Epilepsy Syndromes

Ortrud K. Steinlein

Introduction

The term *epilepsy* describes a heterogeneous group of disorders, with a lifetime cumulative incidence of 3%. There are disorders in which seizures are the main or only symptom, and those in which seizures are just one symptom among others. The reasons why individuals develop epilepsy are numerous. Examples for mostly nongenetic causes of epilepsy are trauma, tumor, and infections. On the other end of the spectrum are epilepsies that have no obvious etiology but are suspected to be mainly genetic in origin. The latter group of epilepsies has been termed idiopathic, in the meaning that they are â€œnot preceded or occasioned by another disorderâ€[32] and that â€œthere is no underlying cause other than a possible inherited predispositionâ€ and â€œa symptomatic origin is neither detected nor suspected.â€[33] By now the distinction between symptomatic and idiopathic epilepsies has become blurred because of our growing knowledge about the complex and diverse etiology of epilepsies. Genes for several idiopathic epilepsies have already been discovered, and most of these genes are able to (at least temporarily) change the functional state of the brain. Some of them are expressed during embryogenesis, rendering it possible that some of them might even interfere with normal brain development and cause subtle changes of the brain's microanatomy. On the other hand, there is a large group of epilepsies and disorders with epilepsy that have been termed â€œsymptomaticâ€ because they are due to known metabolic, neurodegenerative, or structural brain damage. Many of these disorders have by now shown to be caused by clearly defined genetic factors. It is likely that in the future the terms *nongenetic epilepsies*, *genetic epilepsies*, and *genetic disorders with epilepsy* will more and more replace terms like *idiopathic* and *symptomatic*. For this chapter exemplary members of both groups have been chosen to illustrate principal etiologic categories of the disorder â€œepilepsyâ€ and trace the various genetic pathways to epileptogenesis.

Inheritance and Genes in Common Idiopathic Epilepsies

About 30% to 40% of all epilepsies, especially during childhood and adolescence, are summarized under the term *idiopathic epilepsies*. They can be roughly divided into the group of common, mostly generalized idiopathic epilepsies (IGEs) and the various rare monogenic forms of partial or generalized idiopathic epilepsy. The first group, IGE, includes age-related subtypes like juvenile myoclonic epilepsy, childhood absence epilepsy, juvenile absence epilepsy, and grand mal epilepsy on awakening. The high concordance rates found in twin studies support the hypothesis of an almost complete genetic etiology of IGE.[10] Nevertheless, recurrence risks in first-degree relatives of patients with IGE are considerably lower than in monogenic disorders, arguing for an oligogenic or polygenic model of inheritance. It can be assumed that several susceptibility genes are involved in each patient, and that the interaction between these gene loci is multiplicative rather than additive. Some IGE genes might determine the seizure threshold by influencing neuronal excitability, while other susceptibility genes might be responsible for the age of onset and therefore the seizure subtype.[146]

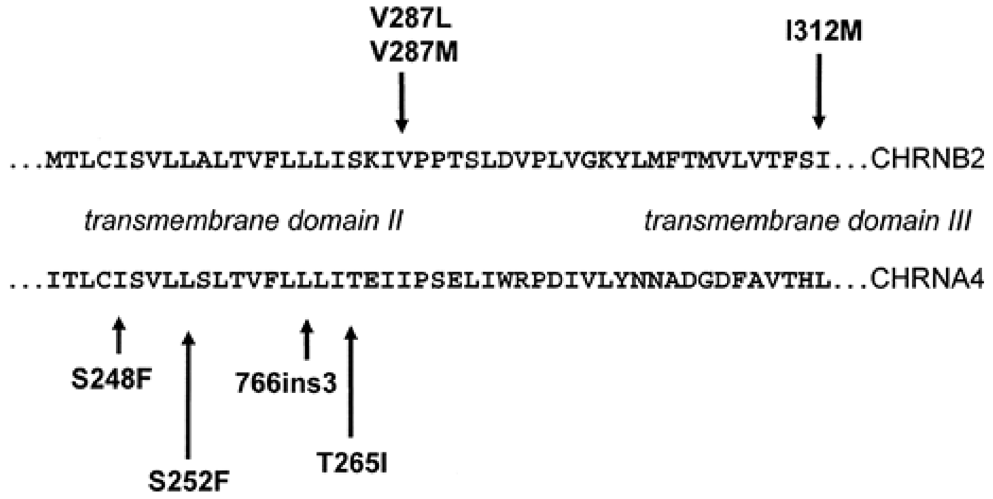

V287L
V287M
I312M
...MTLCISVLLALTVFLLLISKIVPPTSLDVPLVGKYLMFTMVLVTFSI...CHRNB2
transmembrane domain II
transmembrane domain III
...ITLCISVLLSLTVFLLLITEIIPSELIWRPDIVLYNNADGDFAVTHL...CHRNA4
S248F
766ins3
S252F
T265I

FIGURE 1. Mutational spectrum in autosomal dominant nocturnal frontal lobe epilepsy. The parts of nicotinic acetylcholine receptor subunit genes *CHRNA4* and *CHRNB2* containing transmembrane domains II and III are shown.

Two different models have been proposed to explain the complexity of genetic factors and geneâ€“gene interactions in common IGE. In the *ancestral common variant complex epilepsy* model (ACVCE), the existence of common IGE-associated alleles is assumed. In homogeneous patient samples, such alleles should be detectable by association studies. The second model, named *multiple rare variant complex epilepsy* model (MRVCE), describes the existence of many different rare, slightly deleterious mutations that cannot be detected by association studies. Both models would be able to explain the complex inheritance patterns seen in IGE, and both common and rare gene variants have already been identified.[86] For example, both the ACVCE and the MRVCE models of complex inheritance apply to sequence variants in the T-type calcium channel gene *CACNA1H* on chromosome 16p13.3. Several rare *CACNA1H* variants that markedly alter channel properties have been found in patients with childhood absence epilepsy (F161L, E282K, V831M) or other IGE subtypes (P618L, G755D). Interestingly, a common *CACNA1H* sequence variant exists that, in combination with one of the above-mentioned rare variants, is able to alter the calcium channels' biopharmacologic properties in a way that neither the rare nor the common variant separately do.[67] Additional examples consistent with both the ACVCE and the MRVCE models are found in the *GABRD* gene that codes for the Î´-subunit of the Î³-aminobutyric acid (GABA)$_A$ receptor. The *GABRD* sequence variant E177A was described in one family and, compared to wild-type receptors, was shown to significantly reduce the GABA$_A$ receptor's maximal current. A more common *GABRD* variant, R220H, was detected in both epilepsy patients and controls. Receptors heterozygous for R220H had a significantly decreased peak current in comparison with the wild type; thus, R220H may act additively as a susceptibility factor in combination with other, yet to be identified sequence variants.[38] Nevertheless, *CACNA1H, GABRD*, and other genes that are presently discussed as susceptibility factors probably still account only for a very small fraction of the genetic contribution to common IGE syndromes. Many more genes remain to be discovered, a process that has so far been most successful in the monogenic forms of idiopathic epilepsy described in the next paragraphs.

Idiopathic Epilepsies Are Often Channelopathies

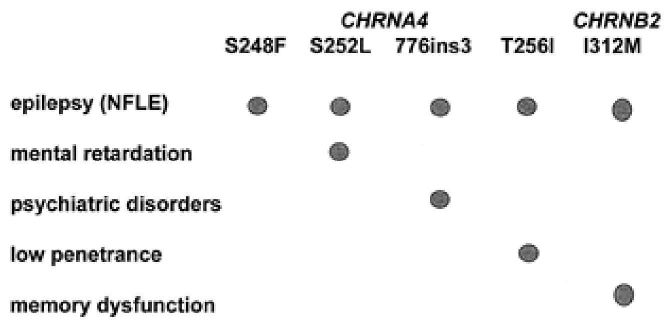
The progress in identification of genes in monogenic forms of epilepsy illustrates the important role of ion channels in epileptogenesis. A great variety of different ion channels regulate brain excitability and prevent hypersynchronization of neuronal networks. Mutations in any of those ion channels might change the delicate balance between excitatory and inhibitory input, resulting in recurrent firing, hyperexcitability, and, finally, seizures.

Familial Nocturnal Frontal Lobe Epilepsy

In 1994, autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) was first described as an inherited form of partial epilepsy. ADNFLE is characterized by clusters of brief motor seizures, which occur mostly during nonâ€“rapid eye movement (REM) sleep.[106] Nonspecific aura phenomena including epigastric, sensory, or psychic symptoms sometimes precede the seizures. The seizures start with gasps, grunts, or some vocalizations followed by thrashing hyperkinetic activity or tonic stiffening of the limbs, often with superimposed clonic jerking. The consciousness is only infrequently impaired. Seizure frequency can be highly variable even within the same family. In some of the patients seizures are frequent and tend to cluster, while in others seizure occurrence is more sporadic and long periods of spontaneous remission are reported. In general, seizure frequency tends to decrease in later adulthood. Physical examinations and brain imaging results are usually normal. Interictal electroencephalographic (EEG) abnormalities are rarely seen, and only some patients show ictal epileptiform activity. The onset of ADNFLE is usually during childhood or early adolescence, with a penetrance of 70% to 80%. Seizures are often, but not in all patients readily controlled by antiepileptic drugs, especially carbamazepine.

Mutations in two genes have so far been identified in different ADNFLE families.[46,121] *CHRNA4* and *CHRNB2* encode the Î±4- and Î²2-subunits of the neuronal nicotinic acetylcholine receptor (nAChR), respectively. The first *CHRNA4* mutation, a S248F amino acid exchange within the second transmembrane domain, was identified in 1995.[121] Descriptions of other nAChR mutations, either in *CHRNA4* or in *CHRNB2*, followed.[62,73,98,122] With the exception of one mutation (*CHRNB2*-I312M in transmembrane domain III), all known ADNFLE mutations are located within the second transmembrane domain. Both the second and the third transmembrane domain contribute to the walls of the ion channel; thus, it seems that only mutations that have a direct effect on the ion pore are able to cause ADNFLE. In total, four *CHRNA4* and three *CHRNB2* mutations have been described. These include six amino acid exchanges and one small *in frame* insertion. Some of those mutations have been found again in unrelated families. They offer the opportunity to study the effects differences in genetic and ethical backgrounds might have on the penetrance of the disorder and the clinical features associated with these mutations (Fig. 1).

The nAChRs, like the glycine, GABA$_A$, and serotonin receptors, are members of the large family of ligand-gated ion channels. They are constituted by the assembly of five subunits arranged pseudosymmetrically around the central axis, forming a cation-selective ion pore. Pharmacologic and ligand-binding studies have shown that, depending on their subunit composition, the different subtypes of homo- or heteropentameric nAChRs not only vary with respect to their expression patterns in the brain, but also display different biopharmacologic channel properties.[11] Both Î±4- and Î²2-subunits are found in almost all brain regions, and the heteropentameric *Î±4*/*Î²*2 receptor is thought to be the major high-affinity nicotine nAChR subtype in mammalian brain. The surprising and so far not very well understood part is that an nAChR subtype ubiquitously present in brain is able to cause a partial type of epilepsy rather than a generalized one. In support of the recognized importance of the cholinergic system in brain functions, recent work has shown that nAChR mutations not only cause epilepsy, but can also be associated with additional neurologic and psychiatric features or cognitive deficits.[29,62,80] Examples are the *CHRNA4*-776ins3 mutation and the *CHRNA4*-S252L mutation. The 776ins3 mutation was found in 11 members of a large Norwegian ADNFLE family. Six of the 11 mutation carriers not only had epilepsy, but also had serious psychiatric problems, mostly schizophrenia, negative symptoms of schizophrenia, or recurrent unclassified psychosis. These observations suggest that the 776ins3 mutation may be a risk factor for psychiatric disorders.[80] The S252L mutation has been described in two unrelated families of Korean and Japanese origin. In both families the seizures not only tended to be resistant to carbamazepine treatment, but were also associated with a high rate of mental retardation and/or behavioral problems.[29,62] The similarities of the clinical phenotype in two families with different genetic background but the same S252L-ADNFLE mutation strongly suggest that the associated neurologic features are mutation specific rather than caused by modifying genes or environmental factors (Fig. 2).



	CHRNA4				*CHRNB2*
	S248F	S252L	776ins3	T256I	I312M
epilepsy (NFLE)	●	●	●	●	●
mental retardation		●			
psychiatric disorders			●		
low penetrance				●	
memory dysfunction					●

FIGURE 2. Clinical features frequently associated with different nicotinic acetylcholine receptor mutations in autosomal dominant nocturnal frontal lobe epilepsy families. NFLE, nocturnal frontal lobe epilepsy.

Functional analysis carried out with recombinant nAChR receptors in *Xenopus* oocytes or HEK cells, including patch clamp characterization of several known ADNFLE mutations, revealed different biopharmacologic profiles.[11] Co-expression of the S248F mutation and the wild-type *CHRNA4* allele yielded acetylcholine-evoked currents of amplitudes comparable to wild-type receptors but with a higher sensitivity for the natural agonist. Receptors carrying either the 776ins3, S252L, or V287M mutation displayed increased acetylcholine sensitivity but to different degrees compared with the S248F mutation. A reduction of calcium permeability was observed for the mutants S248F and 776ins3 but not for the S252L mutation.[11] Increased acetylcholine sensitivity and therefore a gain-of-function effect is the only functional feature common to all known ADNFLE mutations. It is tempting to speculate that the particular functional signatures of each mutant contribute to the above-described observations of associated neurologic features in ADNFLE, while the gain-of-function effect might be responsible for the epilepsy phenotype. The latter part of this hypothesis is supported by the observation that, compared to wild-type litter mates, mice carrying gain-of-function mutations in the *CHRNA4* gene are dramatically more sensitive to nicotine-induced seizures. Furthermore, nicotine application in these mice resulted in enhanced hippocampal theta rhythms, as demonstrated by in vivo electrophysiologic recordings. This observation would be consistent with a model in which gain-of-function effects in presynaptically located nAChRs activate inhibitory GABAergic interneurons in the neocortex and hippocampus. The enhanced GABA release could then increase network excitability by inhibiting inhibitory pathways. Alternative models for the epileptogenic effect of nAChR mutations could include a disturbance of hippocampal â€œpeacemakerâ€ theta activity due to increased input from septal cholinergic neurons.

Benign Familial Neonatal Convulsions

Benign familial neonatal convulsions (BFNC) is a rare autosomal dominant seizure disorder of the newborn (see also Chapter 223). The disorder is characterized by an age of onset between the first day and, latest, the fourth month of life. The seizures are mostly unprovoked, generalized, or multifocal and of the tonic and/or clonic type. The course of the disorder is often benign and self-limiting, and, with or without pharmacotherapy, in most patients the seizures remit spontaneously within a few days or weeks.[103,137] Later in life seizures can reoccur in up to 15% of the patients, starting mostly at school age or in young adulthood. These so-called late-onset seizures tend to be infrequent and are often provoked, for example, by lack of sleep. Several untypical BFNC patients with a more severe course of the disorder have been described. These patients often show a higher frequency of seizures and seizures still occur after the age of 4 months. Follow-up studies often revealed moderate delays of psychomotor development, and in some patients have a family history positive for epilepsy and mental retardation. Two BFNC families have come to attention in which a mutation carrier developed drug-resistant seizures and/or epileptic encephalopathy shortly after birth, resulting in severe psychomotor retardation. In one of the two severely affected index patients a de novo mutation was found, while the second index patient inherited his mutation from a parent with typical â€œbenignâ€ BFNC.[36,109] It remains unclear if these two patients had a second yet unrecognized condition or if certain risk factors (e.g., perinatal hypoxia) in combination with a BFNC mutation increase the risk for such an unfavorable outcome.

The molecular basis of BFNC is a mutation in the voltage-gated potassium channel genes *KCNQ2* or *KCNQ3* (chromosome 20q13.3 and 8q24, respectively).[13,27,115] Both the *KCNQ2* and *KCNQ3* genes encode ion channel subunits that are composed of six transmembrane domains. The subunits have identical structures including a voltage sensor in transmembrane domain 4, a loop between transmembrane domains 5 and 6 that builds the ion channel pore, and a long C-terminal region of unknown function. The BFNC mutations found so far in *KCNQ2* are either missense mutations located in one of the transmembrane domains or truncating mutations (including nonsense, insertion/deletions, and splice site mutations) located mostly in the C-terminal region. Most mutations are private, meaning that they have not been found in other BFNC families. So far, only three mutations have been found in *KCNQ3*. All known *KCNQ3* mutations are missense mutations located within the vicinity of the pore region.

KCNQ2 and *KCNQ3* encode subunits of the M-channel, a very slowly opening and closing potassium channel that is ubiquitously found in brain.[141] The M-current, first discovered some 20 years ago,[21] is a powerful controller of neuronal repetitive firing. M-currents regulate the number of action potentials of individual neurons by opposing sustained membrane depolarization. M-channels activate at membrane potentials that are more negative than the action potential threshold and at which few other ion channels are active. Therefore, they can be assumed to have a pivotal role in the stabilization of membrane potentials and are likely to control excess neuronal excitability and prevent seizures. Expression studies in *Xenopus* oocytes and HEK cells have shown that BFNC mutations cause only modest reductions (20% to 30%) of potassium currents in reconstitution experiments. It seems, therefore, that even slight alterations of M-channel activity are sufficient to cause seizures.[13]

Exceptions to this haploinsufficiency concept are some rare *KCNQ2* mutations that appear to have a dominant negative effect on channel function, as demonstrated by a >50% reduction in current magnitude. One of these mutations is *KCNQ2*/R207W, which causes the BFNC/myokymia syndrome. The mutation abolishes the third of six positive charges in transmembrane domain 4 that is thought to represent the voltage sensor in the cation channel superfamily. The R207W amino acid exchange was the first *KCNQ2* mutation described that causes a disorder with symptoms outside the central nervous system; it is associated not only with episodic symptoms, but also with continuous symptoms. On the clinical level, heterozygosity for the R207W mutation causes both BFNC and myokymia, a spontaneous and repetitive involuntary contraction of muscle fiber groups.[37] In the BFNC/myokymia syndrome, multifocal or generalized tonicâ€"clonic convulsions typically start around day 3 after birth and disappear spontaneously after a few weeks or months. Electromyographic (EMG) recordings in the patients are initially normal but,

starting in infancy, reveal spontaneous repetitively discharged normal motor unit potentials of 20 to 60 msec in duration. Generalized myokymia with spontaneous finger twitching occurs some years later. The association with both central and peripheral neurologic symptoms might be explained by the unusual electrophysiologic profile of the underlying mutation. R207W causes a loss of K^+ current, whose magnitude depends strongly on the pattern and time course of depolarization. With short periods of depolarization the loss of current is more severe than with other known BFNC mutations. The dominant negative effect is not observed with longer periods of activation. Thus, at long (>1 second) trains of action potentials or during seizure activity, R207W mutant channels may be activated significantly and may even reach wild-type levels. It is possible that the time-dependent dominant negative effect of R207W establishes itself only in the peripheral nervous system and that this might be the reason for peripheral neurologic symptoms like myokymia. This hypothesis rests on the assumption that the neuronal activity of motoneurons is interrupted by longer quiescent periods than is the activity of central neurons whose hyperexcitability triggers seizures. Under such conditions, the dominant negative effect of the R207W mutation would have consequences for motoneurons but not for central neurons.[37]

In mice, *KCNQ2* knockout experiments resulted in early postnatal lethality in homozygous animals, while hemizygous knockout mice developed and behaved normal but showed an increased sensitivity to pentylenetetrazole, an epileptic inducer.[142] Transgenic mice that conditionally express a dominant negative *KCNQ2* pore mutation in the brain only during defined developmental periods demonstrated the critical role of M-channel activity in early postnatal brain development. Suppression of the M-current during the first postnatal weeks was associated with spontaneous seizures, behavioral hyperactivity, and morphologic changes in the hippocampus.[96] These results support the notion that M-currents are critical determinants of cellular and neuronal network excitability. The changes in brain morphology found in transgenic mice also raise the interesting question of whether BFNC caused by *KCNQ2* mutations in humans might be (at least in part) due to submicroscopic structural brain changes (morphologic etiology) rather than exclusively to a reduction of M-currents (functional etiology).

Benign Familial Infantile Convulsions

Benign familial infantile convulsions (BFIC) can be distinguished from BFNCs by a later age at onset[135] (Fig. 3). The autosomal dominant disorder is characterized by the onset of seizures around 6 months of age (range 3 to 9 months). Seizures occur in clusters and respond well to antiepileptic drug treatment. The seizures are partial with secondary generalization and in most patients spontaneous remission has occurred by the age of 12 months. Usually no subsequent neurologic abnormalities develop. Two putative loci were reported, BFIC1 (19q) and BFIC2 (16p12-q12), but no genes have been identified yet.[23,54] Interestingly, three other disorders with overlapping neurologic features map to the same region as BFIC2: The infantile convulsions and choreoathetosis syndrome (ICCA; OMIM 602066),[124] paroxysmal kinesigenic choreoathetosis (PKC; OMIM 128200),[129] and a syndrome comprising rolandic epilepsy, paroxysmal exercise-induced dystonia, and writer's cramp (EPRPDC; OMIM 608105).[53] Therefore, the possibility exists that the four disorders are allelic.

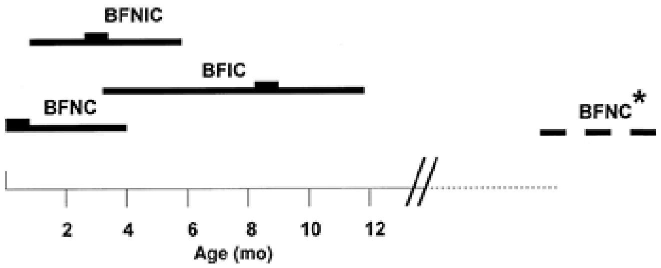


FIGURE 3. Age of onset and remission in benign familial neonatal convulsions (BFNC), benign familial neonatal/infantile convulsions (BFNIC), and benign familial infantile convulsions (BFIC).

A rare seizure disorder with an age of onset intermediate between BFNC and BFIC is benign familial neonatal/infantile convulsions (BFNIC). BFNIC has been shown to be caused by mutations in the voltage-gated sodium channel subunit gene *SCN2A*[9,61] (Fig. 3).

Febrile Seizures

Febrile seizures (FSs) affect 5% to 10% of children under the age of 6 years. Twin and family studies demonstrated the involvement of genetic factors in the etiology of febrile seizures. In most patients an oligo- or polygenic background rather than a monogenic one can be assumed, and a substantial degree of heterogeneity is likely. However, rare families with an apparent autosomal dominant mode of inheritance have been described, and linkage studies identified several putative gene loci, including *FEB1* on chromosome 8q13-q21, *FEB2* on 19p, *FEB3* on 2q23-q24, *FEB4* on 5q14-q15, *FEB5* on 6q22-q24, and *FEB6* on 18p11.2.[64,81,88,90,92,138] In one family with febrile and afebrile seizures, a nonsense mutation (S2652X) was identified in the *MASS1* gene. *MASS1* is part of the large G-protein coupled receptor gene *VLGR1*.[90] The mutation causes a deletion of the C-terminal 126 amino acid residues in the predicted MASS1 protein. If confirmed in independent families, *MASS1* can be regarded as a rare cause for familial febrile convulsions. In another family a missense mutation in the *SCN1A* gene chromosome 2q23-24 has been found to cosegregate febrile seizures, indicating that familial febrile seizures should also be considered a channelopathy.[81]

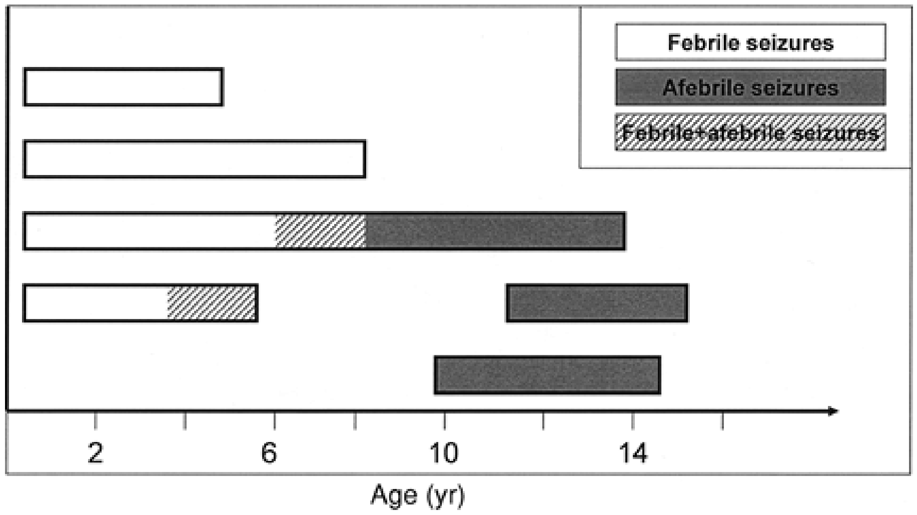


FIGURE 4. Clinical phenotypes in generalized epilepsy with febrile seizures plus (GEFS+). Range of phenotypes found in GEFS+ families is shown. Febrile seizure plus phenotypes include febrile seizures that persist beyond the age of 6 years and/or febrile seizures overlapped or followed by different types of (mostly generalized) afebrile seizures. (Adapted from Baulac S, Gourfinkel-An I, Nabbout R, et al. Fever, genes, and epilepsy. *Lancet Neurol.* 2004;3:421â€"430.)

Generalized Epilepsy with Febrile Seizures Plus and Dravet Syndrome

Febrile seizures are the most common seizure type in families with the recently described syndrome of generalized epilepsy with febrile seizures plus (GEFS+) (see also Chapter 256), followed by febrile seizures plus (FS+; seizures with fever may persist beyond the age of 6 years and/or may be associated with variable afebrile seizures). Afebrile seizure types in affected GEFS+ individuals include generalized tonicâ€"clonic, myoclonic, absence, and atonic seizures or, at least in some families, partial seizures[105] (Fig. 4). Given the highly variable clinical phenotype, it is not surprising that the mode of inheritance underlying GEFS+ is still a matter of debate. Although in some families the trait is likely to be autosomal dominant, in others it is probably better described as oligogenic or as a major gene effect. A genetic concept involving more than one gene would also better fit the clinical variability observed within and between GEFS+ families. The first GEFS+ mutation (C121W) was identified in the *SCN1B* gene on chromosome 19q13.1.

SCN1B encodes a small accessory subunit of the voltage-gated sodium channel. The mutation C121W can be predicted to disrupt a disulphide bridge and to interfere with the ability of the Î²-subunit protein to modulate the function of the much larger, pore-forming Î±-subunits.[140] Subsequent studies showed that most GEFS+ mutations are located in the gene coding for the Î±1-subunit of the voltage-gated sodium channel, *SCN1A*, on chromosome 2q24.[41] *SCN1A* codes for a large ion channel protein composed of four domains, each containing six transmembrane segments (S1 to S6). Minor GEFS+ genes are *SCN2A*, coding for the Î³2-subunit gene of the voltage-gated sodium channel, or the Î³2-subunit gene of the $GABA_A$ receptor (*GABRG2*).[8,56,66,82,123,139]

Mutations in the *SCN1A* gene have also been identified in the majority of patients with the syndrome of severe myoclonic epilepsy of infancy (SMEI = Dravet syndrome; also Chapter 230) and in some cases of phenotypically overlapping syndromes like borderline SMEI (SMEB) or intractable childhood epilepsy with generalized tonicâ€"clonic seizures (ICEGTC).[31,45] The clinical phenotype of SMEI is characterized by an initially normal psychomotor development, onset of febrile seizures within the first year of life, and subsequent manifestation of various afebrile seizure types including absence, myoclonic, and partial seizures. During the second year of life psychomotor delay becomes evident.

Although caused by the same gene, *SCN1A*, differences in the mutation detection rates and the mutational spectrum present in GEFS+ and SMEI patients are obvious.[87] *SCN1A* mutations are only found in 5% to 10% of GEFS+ patients but are present in 33% to 100% of SMEI patients (the variation is likely to be due to different mutation detection methods and/or patient inclusion criteria). All known GEFS+ mutations are missense mutations that cause amino acid exchanges in the encoded protein, while SMEI mutations are composed of truncating (nonsense or frame shift) mutations (47%), missense mutations (43%), splice site mutations (7%), and deletions (3%). Nearly all reported SMEI mutations (76 of 80) are de novo; only a few of them (4 of 80) were inherited from a parent with a less severe type of epilepsy. Mutations in SMEI tend to be either truncating and/or located in functionally critical parts of the gene. GEFS+ mutations are mostly found in less highly conserved parts of *SCN1A* such as the distal parts of S1 to S4 segments or in the short loops connecting those segments (Fig. 5). It is therefore likely that SMEI and GEFS+ mutations differ with respect to their predicted impact on ion channel function. SMEI mutations can be expected to cause a more severe disturbance of protein function, consistent with the more severe phenotype.

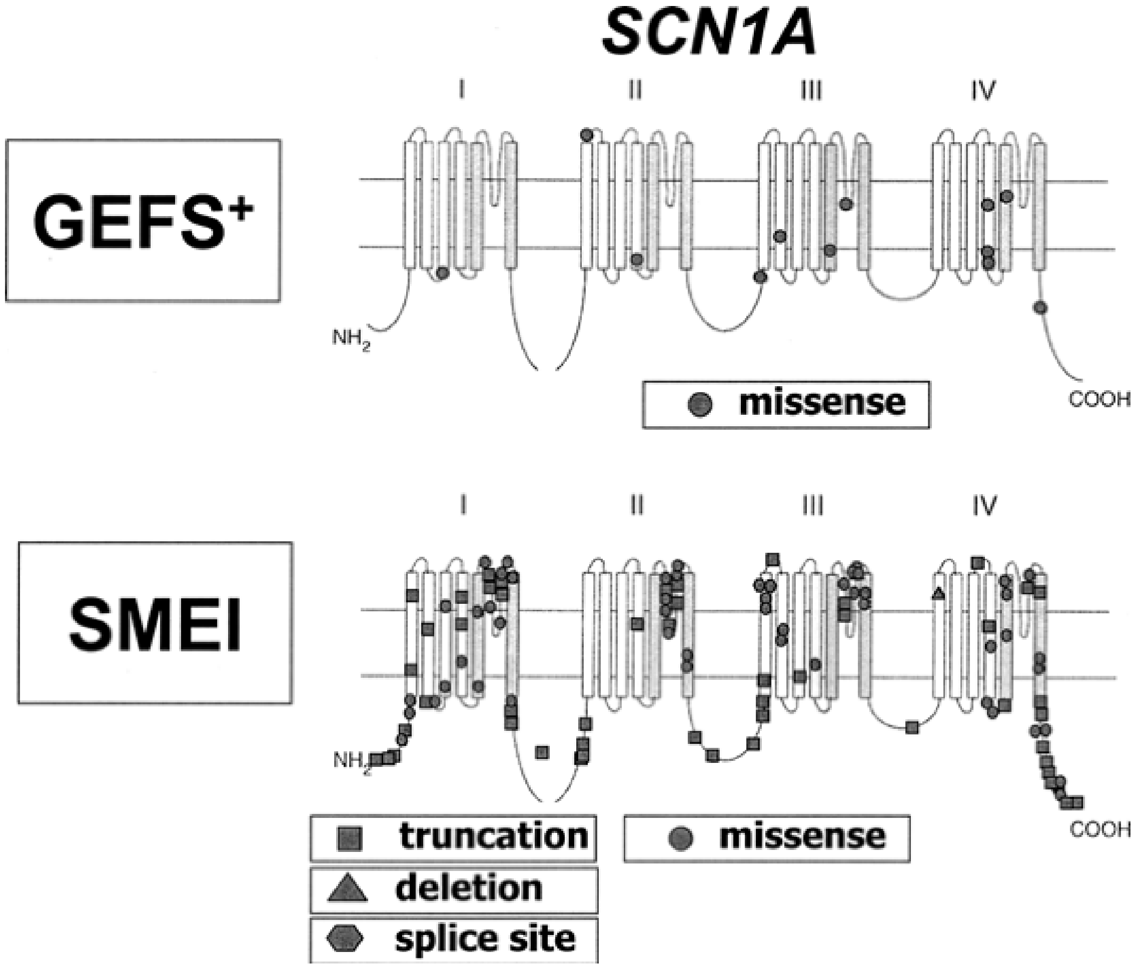


FIGURE 5. Schematic representation of *SCN1A* mutational spectrum in generalized epilepsy with febrile seizures plus (GEFS+) and severe myoclonic epilepsy of infancy (SMEI). All reported GEFS+ mutations are missense mutations. In SMEI different types of mutations are found, and most of these mutations are either truncating mutations or missense mutations affecting functionally important structures like the channel's ion pore. (Adapted from Baulac S, Gourfinkel-An I, Nabbout R, et al. Fever, genes, and epilepsy. *Lancet Neurol.* 2004;3:421â€"430.)

The exact functional effects of SMEI and GEFS+ mutations and their correlations to clinical phenotypes are still unclear. Expression studies of *SCN1A* channels with different SMEI and GEFS+ mutations in *Xenopus* oocytes or HEK293 cells showed a variety of biophysical aberrations including complete loss of function, altered gating properties, and even gain-of-function effects.[77,78,101] These conflicting results can probably partially be explained by different experimental setups, since the biophysical properties of voltage-gated sodium channels strongly depend on the expression system used in the experimental setup. SCN1A channels expressed in HEK293 cells are known to differ from those expressed in *Xenopus* oocytes with respect to their kinetic properties and their sensitivity to Î²-accessory subunits. Furthermore, to be able to compare the different functional studies, the question needs to be addressed whether SMEI and/or GEFS+ mutations alter channel surface expression by affecting gene transcription, mRNA stability, protein folding, or trafficking.

Another syndrome of early childhood epileptic encepha- lopathy that is phenotypically and etiologically related to both SMEI and GEFS+ is ICEGTC. Both GEFS+ and ICEGTC are severe types of early childhood epilepsy that are characterized by fever sensitivity, intractable seizures, and developmental decline after seizure onset. Contrary to GEFS+, myoclonic or absence seizures usually do not occur in ICEGTC patients. *SCN1A* mutations were found in 7 of 10 ICEGTC patients. All mutations were missense mutations that were, similar to SMEI mutations, either located in highly conserved (S4 to S6, pore loop) or, as in GEFS+, less conserved parts of the gene (S1 to S4). Two of the seven published ICEGTC patients inherited their *SCN1A* mutations from a parent with GEFS+-like epilepsy, raising the possibility that additional genetic and/or environmental factors contribute to the more severe phenotype in ICEGTC.[45]

Novel Gene Families in Idiopathic Epilepsy

Most of the genes mentioned above either code for ligand-gated or voltage-gated ion channels (i.e., *CHRNA4/B2*, *GABRG2*, *KCNQ2/3*, *SCN1A/2A*) or for proteins that modulate ion channel function (i.e., accessory channel subunits). Recently, genes of so far unknown function belonging to newly identified gene families were found in some rare idiopathic epilepsies. The first of those was the *LGI1* gene discussed below. These findings demonstrate that â€œchannelopathiesâ€ are not the only etiologic concept in idiopathic epilepsies, but that other mechanisms might exist.

Autosomal Dominant Lateral Temporal Lobe Epilepsy

The syndrome of autosomal dominant lateral temporal lobe epilepsy (ADLTE, also named autosomal dominant partial epilepsy with auditory features [ADPEAF]) is characterized by simple partial seizures with mainly acoustic and sometimes even visual hallucinations.[144] The age of onset is usually in the second or third decade of life. In some families the seizures tend to start with a brief sensory aphasia without reduced consciousness.[51] In 2002, positional cloning efforts let to the identification of the *LGI1* gene (*leucine-rich glioma inactivated gene 1*) on chromosome 10q24 as the gene responsible for ADLTE/ADPEAF.[44,51,65,85,100] The mutational spectrum includes both missense mutations and truncating mutations, and no mutation hotspot has emerged yet. There are no obvious clinical differences between patients with truncating mutations and those with amino acid exchanges in the *LGI1* gene.

Table 1 Neuronal Ceroid Lipofuscinoses (NCL)

Disorder	Alias	Gene	Locus	Protein	Inheritance
Infantile NCL	CLN1 Santavuori-Haltia disease	*PPT*	1p32	Palmitoyl-protein thioesterase-1	AR
Late infantile NCL	CLN2 Jansky-Bielschowsky disease	*CLN2*	11p15.5	Pepstatin-insensitive lysosomal peptidase	AR
	CLN5 Finnish variant	*CLN5*	13q21.1-q32	nn	AR
	CLN6	*CLN6*	15q21-q23	Linclin	AR

Juvenile NCL	CLN3 Vogt-Spielmeyer disease Batten disease	*CLN3*	16p12.1	nn	AR
Adult NCL	CLN4 Kufs disease, autosomal recessive type	*PPT*	1p32	Palmitoyl-protein thioesterase-1	AR
	CLN4 Kufs disease, autosomal dominant type Parry disease	nn	â€”	â€”	AD

AD, autosomal dominant; AR, autosomal recessive; nn, not known.

So far the function of the *LGI1* gene, which shows a strong expression in neurons within the temporal lobe, is mostly unknown. The LGI1 protein has a distinctive leucine-rich repeat (LRR) motif in its N-terminal end. This motif might be indicative of either receptor function or an interaction with the extracellular matrix. The LRR motif consists of repeated Î²-strands and Î±-helices connected by loops, building a domain that usually serves as a framework for the formation of proteinâ€“protein interactions and is present in a large number of proteins with diverse functions. The C-terminal half of the LGI1 protein contains seven epilepsy-associated repeats (EARs). EARs are characterized by tandem repeats with a core of about 50 residues that probably folds into a Î²-propeller structure.[120] The EARs were also identified in another epilepsy-relevant protein, MASS1/VLGR1, which is mutated in audiogenic epilepsy in mice and in one family with febrile seizures (see above).[91,116] Within the MASS1/VLGR1 protein, the epitempin repeat is part of the ligand-binding ectodomain, suggesting that this repeat, like the LRR domain, might be involved in proteinâ€“protein interactions.

LGI1 was first found to be interrupted by a translocation breakpoint in a glioblastoma cell line and was therefore labeled as a candidate tumor suppressor gene for gliomas.[28] This theory seemed to be supported by the observation that *LGI1* expression is low or absent in high-grade gliomas.[12]

However, it has been demonstrated that *LGI1* is mainly expressed in neurons rather than in glia cells.[52] Therefore, a gradual loss or displacement of neurons during progression toward higher malignancy would be a plausible explanation for the low or absent *LGI1* expression in high-grade gliomas. The absence of *LGI1* expression would then represent a secondary effect rather than a causative event. This interpretation is supported by studies that found fewer *LGI1*-expressing cells in high-grade gliomas compared with low-grade tumors.[12] Furthermore, no evidence was found that the *LGI1* mutations present in ADLTE families increase the rate of brain tumors or other malignancies. It is therefore unlikely that *LGI1* acts as a first step or high penetrance tumor suppressor gene.[20] Nevertheless, experimental evidence exists that *LGI1* plays a role in the suppression of cell migration. For example, experimentally forced expression of *LGI1* significantly reduced the proliferation and migration ability of glioma cells. Invasion assays showed that glioma cells transfected with *LGI1* lost their ability to migrate freely. These results suggest that *LGI1* is involved in cellular control mechanisms concerning migration and invasiveness. Thus, the possibility remains that, although not a bona fide tumor suppressor gene, *LGI1* plays a role in determining the malignancy grade of an already existing tumor.[70] It will be interesting to know if *LGI1* also plays a role in the migration of neuronal cells during embryogenesis. ADLTE/ADPEAF mutations that interfere with such a function could theoretically cause subtle changes in the brain's cytoarchitecture that might cause seizures through abnormal neuronal networks.

Genetic Disorders with Seizures as a Primary Feature

Seizures are an unspecific symptom commonly associated with structural or functional brain damage. It is therefore not surprising that seizures are a predominant feature in a variety of neurogenetic disorders of diverse etiology. Examples are neurodegenerative metabolic disorders, mitochondrial disorders affecting cellular energy metabolism, structural chromosomal aberrations, and neuronal migration disorders. The seizures might be the leading symptom or just one symptom among others. Unlike in the above-discussed idiopathic epilepsies, the seizures are often difficult to control. In some of these disorders the underlying mutations affect the mitochondrial DNA (mtDNA), but most mutations are found in nuclear genes or chromosomes. The modes of inheritance and the recurrence risks depend on the type of mutation, its localization in the genome, and the effect this mutation has on the phenotype.

Neurodegenerative and Metabolic Disorders with Epilepsy

Seizures and myoclonus are common to many neurodegenerative and metabolic disorders (see also Chapter 261). In the following paragraphs some of the disorders in which epilepsy and/or myoclonus constitute a major feature are exemplarily described.

Neuronal Ceroid Lipofuscinoses

There are at least eight human disorders belonging to the group of neuronal ceroid lipofuscinoses (CLN1 to CLN8).[49] The neuronal ceroid lipofuscinoses (NCL) subtypes, which mainly differ with respect to their age of onset, are characterized by progressive visual failure, epilepsy, and myoclonus. Accumulations of an autofluorescent lipopigment in lysosomes of neurons and other cell types are a characteristic feature of NCL. The NCLs are lysosomal proteinoses, and most of them are autosomal recessively inherited. Depending on the subtype and the mutated gene underlying this subtype, the composition of the lysosomal storage material can differ. In the infantile form, mainly sphingolipid activator proteins (saposins A and D) are stored, while in the late infantile and juvenile NCL subtypes mitochondrial adenosine triphosphate (ATP) synthase subunit C is the main storage material. The genes for several NCL subtypes have been identified, but the function of most of them is still unknown[73] (Table 1).

The infantile subtype of NCL, Santavuori-Haltia-Hagberg disease (CLN1), occurs primarily in the Finnish population and is caused by mutations in the gene for palmitoyl-protein thioesterase on chromosome 1p32. The age of onset is within the first or second year of life, and the course is characterized by profound mental and motor deterioration, hypotonia, ataxia, myoclonus, epilepsy, and blindness. Death usually occurs at age 8 to 11 years. The mutations in the palmitoyl-protein thioesterase gene render enzyme activity in the brain of patients undetectable, causing intracellular accumulation of polypeptides.[134]

The classical late infantile form of NCL, Jansky-Bielschowsky disease (CLN2), starts at age 2 to 4 years with myoclonus and seizures. Additional clinical features are dementia and blindness with macular degeneration and retinitis pigmentosa. Death occurs by the age of 15 years. CLN2 is caused by mutations in a gene named tripeptidyl peptidase-1 that is likely to code for a lysosomal pepstatin-insensitive carboxypeptidase.[117]

Juvenile-onset NCL (Batten disease, Vogt-Spielmeyer disease) is the most common neurodegenerative disorder of childhood with an incidence of 1 in 25,000 births. Onset begins with visual failure at age 5 to 10 years, followed by epilepsy and mental deterioration. The exact function of the *CLN3* gene, which is mutated in juvenile NCL, is still unknown. Functional studies suggest that the *CLN3* gene product is an integral membrane protein that localizes primarily to the Golgi apparatus and is thought to have a role in neuronal transport pathways.[79,127]

Kufs disease or adult NCL (NCL4) is distinguished clinically from the infantile and juvenile subtypes by onset of progressive myoclonus epilepsy in adulthood and by absence of ocular involvement. The autosomal recessive form of Kufs disease is, in at least one family, caused by mutations in the above-mentioned palmitoyl-protein thioesterase-1 gene. There is also an autosomal dominant variant of Kufs disease for which no gene has been identified yet.[132]

There are at least three disorders that belong to the subgroup of late infantile NCL. These include the Finnish variant (CLN5), a variant of late infantile NCL (CLN6), and the Turkish variant of NCL (CLN8). All three variants are caused by genes of unknown function that probably encode lysosomal proteins or proteins located in or outside the endoplasmic reticulum (ER).[47,104] The *CLN8* gene also causes Northern epilepsy or progressive epilepsy with mental retardation. Northern epilepsy is a recently described novel autosomal recessive epilepsy of childhood onset that is only found in parts of northern Finland. Age of onset is between 5 and 10 years, followed by progressive mental deterioration. Ocular affection has not been reported in those patients, and life expectancy is considerable longer than in other NCL subtypes. The *CLN8* gene encodes a novel transmembrane protein of unknown function. CLN8 protein is probably located outside the ER and might be involved in vesicular neuronal transport mechanism[76] (Table 1).

Juvenile Sialidosis

The cherry redâ€“spot myoclonus syndrome or juvenile sialidosis (sialidosis type 1, mucolipidosis) is an autosomal recessive storage disorder.[39,119] The patients show a slowly progressive reduction of vision and a crippling myoclonus epilepsy. Onset is usually in the second to third decade. A characteristic feature are cherry-red spots in the macula; however, the age of appearance of the spots is extremely variable, and they are therefore not always helpful to establish the diagnosis. Seizures and myoclonus start in the second decade of life. Two different types of myoclonus might appear in patients: A stimulus-insensitive facial myoclonus without a corresponding EEG correlate or a stimulus-sensitive generalized myoclonus with massive jerks associated with EEG spikes. Juvenile sialidosis is caused by mutations in the *NEU1* gene located on chromosome 6p21.3. *NEU1* encodes a neuraminidase and mutations in this gene are suspected to interfere with substrate binding or impaired folding of the enzyme.[110] This consequently leads to progressive lysosomal storage of sialylated glycopeptides and oligosaccharides.[15,94] The excretion of sialic acid covalently linked to a variety of oligosaccharides and/or glycoproteins is a typical feature, but oligosacchariduria is often no longer detectable if diagnosis is delayed into adulthood.

Dentatorubral-Pallidoluysian Atrophy

The autosomal dominant syndrome of dentatorubral-pallidoluysian atrophy (DRPLA) is mostly found in Japan, but reports of several families of non-Japanese ancestry have been published. DRPLA presents with variable combinations of epilepsy, myoclonus, cerebellar ataxia, choreoathetosis, and dementia.[89,118] Three clinical phenotypes are evident in DRPLA; one is dominated by initial ataxia and subsequent choreoathetosis, one is Huntingtonlike with choreatic movements and dementia, and the third is characterized by progressive myoclonus epilepsy. The age of onset is extremely variable and ranges from 6 to 70 years. Anticipation has been reported in several families.[136] These observations can be explained by the fact that DRLPA belongs to the group of trinucleotide repeat disorders and is caused by an expanded CAG repeat in the DRPLA gene on chromosome 12p13.[69] Normal alleles usually have up to 35 repeats, whereas pathologic alleles (full mutation alleles) have 40 to 100 CAG repeats. The full mutation alleles show somatic mosaicism and intergenerational instability. Large increases in repeat length are usually associated with paternal transmission. The repeat size correlates closely with the age of onset and the severity of the disorder. Translated into protein, such expanded polyglutamine stretches have been shown to form aggregates that have a toxic effect on cells. Intracellular accumulation of DRPLA protein and subsequent neurodegeneration are widespread in the central nervous system. The aggregate formation potential of mutated DRPLA protein increases in a CAG-repeat length-dependent manner, explaining the earlier age of onset in patients with larger repeat sizes.[93,113]

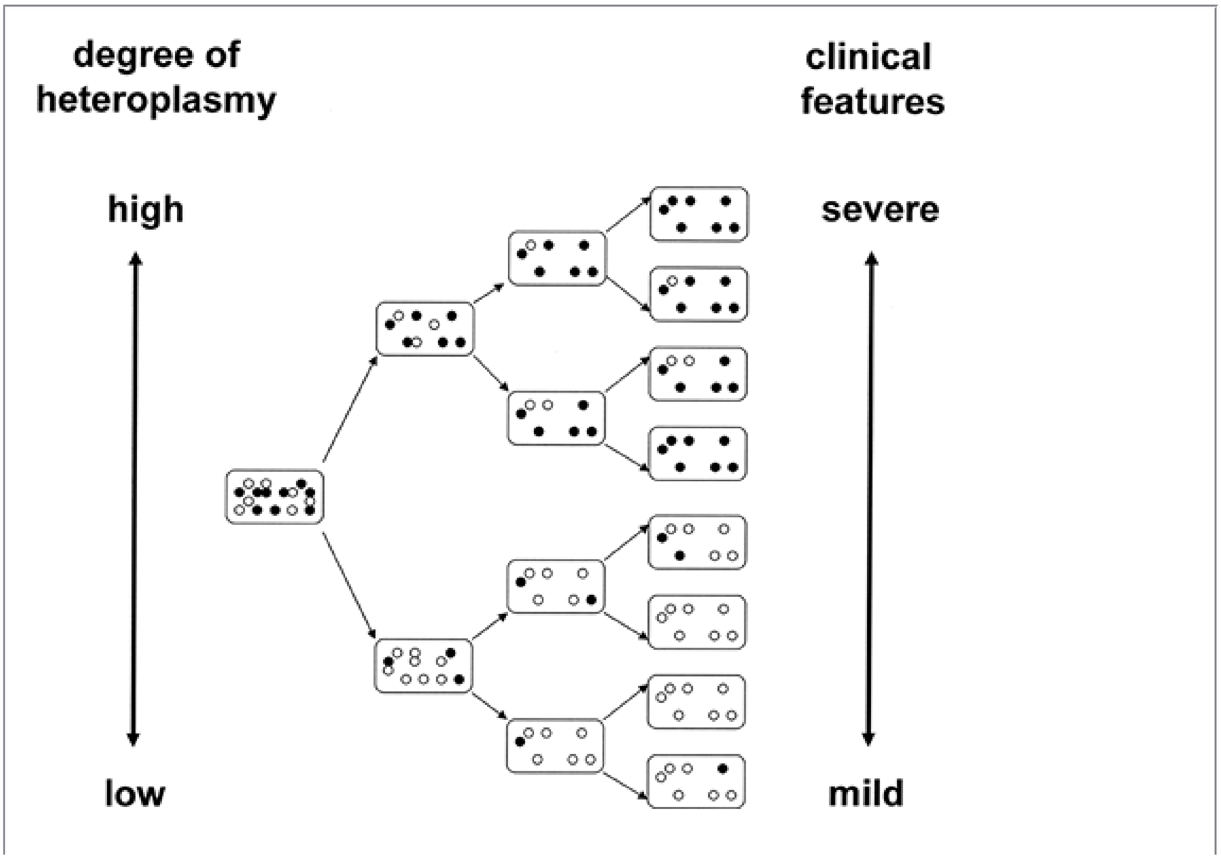


FIGURE 6. Heteroplasmy in mitochondrial inheritance. Cells contain hundreds of mitochondria that behave as semiautonomous organisms and multiply by replication rather than by de novo synthesis. When a cell divides it is a matter of chance which mitochondria will be partitioned in which daughter cell. The resulting mixed population of mutated and wild-type mitochondria is known as heteroplasmy. In heteroplasmy the percentage of mutated mitochondria varies not only from one offspring to the next, but also from tissue to tissue within the same individual. *Filled black circles* indicate mitochondria containing mutated mitochondrial DNA.

Unverricht-Lundborg Disease

Unverricht-Lundborg disease (ULD; also known as Baltic or Mediterranean myoclonus epilepsy) is the most common form of progressive myoclonus epilepsy worldwide. ULD is an autosomal recessive neurodegenerative disorder characterized by progressive stimuli-sensitive myoclonic jerks and generalized tonicâ€“clonic seizures. The age of onset is between 6 and 18 years of age, and the course of the disorder is usually about 10 to 20 years in duration. Mental deterioration, intention tremor, dysarthria, and mild ataxia may develop in later stages of the disorder. Pathologic findings demonstrate a marked loss of Purkinje cells in the cerebellum, neuronal loss in the spinal cord and the medial thalamus, and a proliferation of Bergman glia.[55] Mutations in the *CSTB* gene (cystatin B, also stefin B) on chromosome 21q22.3 have been found in ULD patients. In most patients the disorder is caused by an unstable expansion of a dodecamer repeat located upstream of the initiation codon of *CSTB*.[72] Northern blot analysis demonstrated that tissues from patients carrying the expanded repeat have no detectable *CSTB* mRNA levels. It can therefore be assumed that in these patients ULD is caused by loss of function mutations in the *CSTB* gene. In addition to the repeat mutation, seven other mutations have been identified that can be predicted either to alter the structure of CSTB or to cause alternative splicing. CSTB encodes the cystatin B protein, a widely expressed cysteine protease inhibitor that is thought to have a lysosome-associated physiologic function.[74,95] A major pathophysiologic

mechanism in ULB is probably the loss of CSTB-mediated protection from protein degrading in neurons.[1] It has also been hypothesized that, at least in a subset of ULD patients, mutated cystatin B protein itself may aggregate and have a toxic effect on the cell.

Lafora Disease

Lafora disease (LD) is an autosomal recessive disorder of adolescent onset that belongs to the group of progressive myo- clonus epilepsies. LD is characterized by severe myoclonus, epilepsy, and rapidly progressive dementia. Death usually occurs within 10 years of onset. Rare forms exist that show a somewhat more benign course of the disorder. The diagnosis can be established by the presence of characteristic periodic acid-Schiff (PAS)â€“positive inclusions, the Lafora bodies, in skin biopsy. Lafora bodies are dense aggregates of abnormally branched glycogen molecules (polyglucosans) that are found in both eccrine duct cells and apocrine myoepithelial cells from LD patients. The Lafora bodies also form in various other tissues and organs like the central nervous system, retina, axis cylinders of spinal nerves, heart muscle, liver cells, and striated muscle fibers.[2,25,57] Recent studies have shown that LD can be caused by mutations in either the *EPM2A* gene (laforin) on chromosome 6q24 or the *NHLRC1* gene (malin) on chromosome 6p22.3.[26,84] A clinical analysis found that LD patients with *NHLRC1* mutations had a slightly longer disease course and later age at death compared to patients with *EPM2A* mutations.[50]

Laforin is a protein tyrosine phosphatase with a carbo- hydrate-binding domain in the N-terminus, while malin is an E3 ubiquitin ligase containing a zinc finger of the RING type in the N-terminal half and 6 NHL-repeat domains in the C-terminal half. It has been demonstrated that laforin is a physiologic substrate of malin. Normally, malin interacts with and polyubiquitinates laforin, leading to its degradation. Mutations in malin found in LD patients diminish this interaction. It has been suggested that laforin's role is to detect polyglucosan appearances during glycogen synthesis and prevent the accumulation of insoluble glycogen molecules resulting from glycogen synthetase overreactivity.[43,75] Thus, one of several possible scenarios would be that the neurodegenerative changes underlying LD occur because loss-of-function mutations in malin cause the accumulation of laforin and lead to suppression of glycogen metabolism. Patients with mutations in laforin would develop LD because laforin would be unable to dephosphorylate a necessary substrate in glycogen metabolism.[48]

Epilepsies with Mitochondrial Inheritance

The chromosomes located in the nucleus are not the only source of coding DNA in our cells. Mitochondria, the reminders of an ancient endosymbiosis between early eucaryotic cells and a proteobacteriumlike ancestor over 1.5 billion years ago, possess their own circular DNA molecule (mtDNA). The original bacterial genome lost most of its genes during evolution, and the few genes that survived on the mtDNA until today can be separated into two groups. Mitochondrial genes either code for proteins that take part in the process of aerobic respiration or code for the mitochondria's transcription/translation system. Mitochondrial inheritance differs from mendelian inheritance in several aspects. The inheritance is strictly maternal, since the sperm mitochondria are selectively eliminated at fertilization. Mutations in mtDNA that seriously harm or abolish the ability of mitochondria to perform their various cellular processes are always heteroplasmic. Heteroplasmic disorders are characterized by a mixed intracellular population of normal and mutated mitochondria. With each cell division it is a matter of chance how many mutated and how many wild-type mitochondria each daughter cells inherits. Hence, heteroplasmy is one of the reasons for the great clinical variability typical for most mitochondrial disorders (Fig. 6).

Myoclonic Epilepsy and Ragged-Red Fiber Disease

Myoclonic epilepsy and ragged-red fiber disease (MERRF) is characterized by progressive myoclonus epilepsy, myopathy, and slowly progressive dementia. Hearing loss and ataxia are common, and patients often develop multiple lipomas or cervical lipomatosis. In most patients ragged-red fibers and abnormal mitochondria with concentric cristae are found in muscle biopsy. Onset ranges from childhood to late adulthood, and, consistent with a heteroplasmic population of mtDNAs, the severity of the disorder can vary considerably, even within one and the same family. In approximately 80% to 90% of patients, MERRF is caused by the T8344C point mutation that affects the $\text{tRNA}^{\text{Lysine}}$ gene within the mtDNA.[114] Rare MERRF point mutations are T8356C and G8344A, but the syndrome can also be caused by other types of mtDNA mutations including single or multiple deletions. Furthermore, there are several mutations that can cause more than one mitochondrial disorder. An example is the MELAS mutation G8344G that is sometimes found in MERRF patients. The proportion of mutated mitochondria varies between different tissues in MERRF patients. Skeletal muscle frequently has the highest percentage of mutated mtDNAs and correlates best with the clinical severity of the disorder. Muscle biopsy is therefore the first choice for diagnostic mutation analysis.[17]

The G8344A mutation in the $\text{tRNA}^{\text{Lysine}}$ gene has been shown to inhibit mitochondrial protein synthesis. The translation efficiency and the cytochrome C oxidase activity decline sharply in mutation-carrying mitochondria. Cells with an intracellular percentage of mutated mtDNA that exceeds 85% are extremely sensitive to further damage.[17] It has been speculated that these cells need to accumulate only a few more age-related somatic mtDNA mutations in order to decompensate and cause clinical symptoms. The need for an accumulation of somatic mtDNA mutations in addition to the inherited mtDNA defect would explain the delayed onset and progressive course of the disorder.[34,58,131] Further discussion is available in Chapter 262.

Chromosomal Rearrangements

Cytogenetically visible chromosomal rearrangements often cause the loss or gain of several or many genes. Since approximately 50% of our genes are, at least temporarily, expressed in brain, the resulting cross-genetic imbalance can be expected to cause major structural or functional disturbances in the central nervous system. It is therefore not surprising that seizures are a common finding in these patients.[107] Most chromosomal rearrangements occur de novo in one of the parental germ cells. Thus, even taken into account the rare possibility of a parental germ cell mosaicism, the recurrence risk for siblings is small in these families. Nevertheless, parents need to be karyotyped to exclude the possibility of familial chromosomal rearrangements. Such familial chromosomal rearrangements are mostly balanced translocations where two or more chromosomes exchanged fragments or whole chromosomes are fused together. The carrier of such a balanced translocation is phenotypically normal since he or she has the correct gene copy number, but can have germ cells with an unbalanced chromosomal status. This increases the risk for spontaneous abortions and/or the birth of a severely affected child. Given the number of chromosomes in our cells and size of our genome, the possibilities for individual chromosomal rearrangements are countless. Most of them have been described only in a single or few patients and no typical patterns of clinical features are known. Exceptions are structural rearrangements of certain chromosomal regions that, often due to the presence of repeated DNA elements, have an above-average chance to occur. The underlying mechanism is often a mispairing and incorrect exchange between homologous chromosomes in meiosis. An example that is frequently associated with epilepsy is the inv dup(15) marker chromosome.[30] Additional examples for clinically well-defined syndromes caused by structural chromosomal aberrations are the ring chromosome 20 syndrome, Miller-Dieker syndrome (see also Neuronal Migration Disorders), most cases of Angelman syndrome, Wolf-Hirschhorn syndrome, and the 1p36 deletion syndrome.

Inv Dup(15) Syndrome

The karyotype in individuals with inv dup(15) or idic(15) syndrome is characterized by an extra structurally abnormal chromosome.[35] The supernumerary marker chromosome is formed by the inverted duplication of proximal chromosome 15. Two types of inv dup(15) marker chromosomes with different phenotypic consequences are known. One is a metacentric or submetacentric chromosome that contains mainly heterochromatin and is usually associated with a normal phenotype (karyotype dic[15][q11]). The second type of inv dup(15) (karyotype dic[15][q12 or q13]) is the one that causes the inv dup(15) syndrome. This marker chromosome is considerably larger and contains, among other genes, the Prader Willi/Angelman syndrome critical region.

Functionally, the inv dup(15) syndrome results from gene dosis imbalances due to tetrasomy 15p and partial tetrasomy 15q. The inv dup(15) is the most common of the heterogeneous group of the extra structurally abnormal chromosomes. The estimated incidence at birth is 1 to 30,000. Patients with inv dup(15) syndrome show moderate to profound developmental delay/mental retardation. Physically, muscle hypotonia is the most common clinical feature, whereas other physical findings are rather unspecific. The patients often display an autistic or autisticlike behavior, with gaze and body contact avoidance and no interest toward their peers.[6,16,102] Expressive language may be absent or may remain very poor, and echolalias are common. Stereotypies are frequently seen, including hand flapping, hand wringing, and head turning.

A wide variety of seizures might occur in patients with inv dup(15)-syndrome, with age of onset ranging from 6 months to 9 years. Infantile spasms associated with a hypsarrhythmic EEG have been reported in several cases, while others were diagnosed as having Lennox-Gastaut syndrome or Lennox-Gastaut-like syndrome.[5,143] These patients had tonic/atonic seizures (as head drops or drop attacks), tonicâ€“clonic seizures, and atypical absences with onset between 4 and 8 years of age. Seizures are mostly difficult to control, despite adequate antiepileptic treatment.

Ring Chromosome 20 Syndrome

Ring chromosome 20 (r[20]) syndrome is a rare chromosomal disorder characterized by an indistinct phenotype, epilepsy, mild to moderate mental impairment, and (infrequently) malformation. Most patients are mosaics for the ring chromosome 20; however, the percentage of mosaicism in lymphocytes is not predictive for the severity of the epilepsy or the cognitive problems. All patients have a degree of learning difficulties varying from mild, specific difficulties to severe global learning disability with autistic features. The seizures start between 4 and 6 years of age, and thereafter a slowdown of motor and mental development becomes obvious. Sometimes even deterioration can be observed. Behavioral and adaptation difficulties are frequent, as are emotional immaturity and disturbed fine motor coordination.[19,97] The ictal EEG in ring chromosome 20 patients shows slow theta waves and sharp spikes.[24,68] Long runs of epileptiform activity in the EEG that are not accompanied by confusion or diminished consciousness are characteristic for ring chromosome 20 syndrome. Among other possible mechanisms, ring chromosomes can be formed after breakage in both chromosome arms, loss of the distal fragments, and subsequent fusion of the points of fracture. The loss of distal chromosomal material often explains the abnormal phenotype. Interestingly, the subtelomeric end of the long arm of chromosome 20 contains the two known epilepsy genes *KCNQ2* and *CHRNA4*. It is possible that one or two of these genes are deleted in ring chromosome 20 syndrome, contributing to the cause of epilepsy in these patients.

Angelman Syndrome

Angelman syndrome is characterized by severe motor and intellectual retardation, ataxic gait, hypotonia, EEG abnormalities, epilepsy, absence of speech, microcephaly, and facial characteristics including a low forehead, macrostomia, and prominent mandible. The syndrome was first described by Harry Angelman, London, as â€œhappy puppet syndrome,â€[3] a term referring to the often excessive, inappropriate laughter characteristic for patients with Angelman syndrome. The distinctive EEG discharges often start before the onset of seizures. The EEG pattern consists of high-amplitude bilateral spike-and-wave activity that is symmetric, synchronous, and most often monorhythmic with a slow-wave component at 2/s. In about 80% of the patients epilepsy sets in between 6 and 18 postnatal months. Seizure types include absence and myoclonic seizures. Insidious episodes of nonconvulsive or subtle myoclonic status can occur that are easily overlooked as children appear apathetic or in a state of neurologic regression. Seizures are difficult to control by antiepileptic treatment, but seizure frequency tends to decrease in later childhood.[18,71,83]

The genetic etiology of Angelman syndrome is complex, and the majority of cases are due to de novo mutations and are therefore sporadic. In approximately 60% of patients, a cytogenetically detectable deletion of chromosome region 15q11-q13 is found; in another 10% to 15% a submicroscopic deletion of the *UBE3A* gene (ubiquitin protein ligase

E3A)â€“containing critical region for Angelman syndrome can be detected. The chromosome 15 carrying the deletion is always of maternal origin. The paternally inherited Angelman region on chromosome 15 is always inactivated (imprinted); thus, with the loss of the maternally inherited region no active genes remain. A further 3% to 5% of patients have paternal uniparental disomy of chromosome 15 (UPD15). In UPD15, chromosome 15 (or at least the parts of the chromosome containing the region 15q11-q13) is inherited from the father and the patient is missing a maternal copy. A possible mechanism for UPD15 could be a monosomy 15 conception, followed by a postzygotic duplication of the paternal chromosome 15. Familial occurrence of Angelman syndrome is only observed in some of the cases where the disorder is caused by a mutation either in the *UBE3A* gene or in the Angelman region-imprinting center. All types of mutations have the effect that *UBE3A* and other genes expressed exclusively from the maternal chromosome 15 are deleted or functionally silenced. *UBE3A*, although expressed from both alleles in most tissues, is transcribed predominantly from the maternal allele in brain. Another gene that is frequently deleted in Angelman patients is *GABRB3*, the gene coding for the Î²3 subunit of the GABA$_A$ receptor. The exact role of *UBE3A* and *GABRB3* in the etiology of Angelman syndrome is still unknown. A possible mechanism might involve dysregulation of synaptic neurotransmission through the *UBE3A*-related modulation of functional GABA$_A$ receptor complexes.

Wolf-Hirschhorn Syndrome (4p- Syndrome)

Wolf-Hirschhorn syndrome (also known as deletion 4p syndrome or 4p- syndrome) is a contiguous gene syndrome located on the short arm of chromosome 4 in band p16.3. Approximately 87% of the patients carry a de novo deletion, while in the remainder one of the parents is the carrier of a balanced translocation. The characteristic facial features in Wolf-Hirschhorn syndrome include hypertelorism, prominent glabella, epicanthal folds, and cleft lip or palate. Additional features are microcephaly, cardiac defects, growth and mental retardation, and seizures. Epilepsy in Wolf-Hirschhorn syndrome usually starts within the first year of life, and seizures are initially difficult to control but tend to disappear with age. Characteristic are generalized or unilateral myoclonic seizures followed by brief atypical absences. The EEG typically shows centroparietal or parieto-occipital sharp waves, high-voltage waves with superimposed spikes, and bursts of diffuse spikes and waves during drowsiness and sleep, often associated with myoclonic jerks.[111,145]

The theretofore accepted critical region (WHSCR1) is a 165-kb interval on 4p16.3 defined by the loci D4S166 and D4S3327. Recently, Zollino et al.[147] proposed a new critical region for Wolf-Hirschhorn syndrome, and referred to this region as WHSCR2. On the basis of genotype-phenotype correlation analysis, they recommended dividing the Wolf-Hirschhorn syndrome phenotype into two distinct clinical entities, a â€œclassicalâ€ and a â€œmildâ€ form. The exact genotype-phenotype correlations are not fully understood, but it is obvious that the severity of the phenotype strongly correlates with the 4p deletion size. WHSCR2 contains the gene *LETM1* that can be considered as a candidate gene for the seizures observed in most Wolf-Hirschhorn patients. The *LETM1* gene encodes a putative 83.5-kDa protein with a single transmembrane domain, two calcium-binding EF-hand motifs, a leucine zipper, and several Î±-helical structures with high probabilities for forming coiled coils. *LETM1* shows significant amino acid sequence identity to mitochondrial proteins from different species and has been shown to be associated with mitochondrial morphology. The data suggest that the seizures and other neurologic features of Wolf-Hirschhorn syndrome may, at least in part, represent a disorder of mitochondrial dysfunction caused by haploinsufficiency of the *LETM1* gene.[40,108]

Table 2 Genetic Disorders with Generalized Patterns of Abnormal Neuronal M

Type of malformation	Disorder	Gene	Locus	Protein
Lissencephaly type 1	Isolated lissencephaly	*LIS1*(*PAFAH1B1*)	17p13.3	Platelet-activating factor acetylhydrolase, isoform 1b, Î±-subunit
	Miller-Dieker syndrome	Microdeletion including *LIS1, 14-3-3-epsilon*	17p13.3	

	X-linked lissencephaly/double cortex syndrome	*DCX*(*DBCN*)	Xq22.3-q23	Doublecortin
	Norman-Roberts syndrome	*RELN*	7q22	Reelin
Cobblestone dysplasia	Walker-Warburg syndrome	*POMT1* *FCMD* (*FKTN*)	9q34.1 9q31	Protein O-mannosyltransferase Fukut
	Fukuyama congenital muscle dystrophy	*FCMD* (*FKTN*)	9q31	Fukutin
	Muscle-brain-eye disease	*POMGNT1*	1p34-p33	O-mannose *Î²*-1,2-*N*-acetylglucosaminyltransferas
Heterotopia	X-linked bilateral periventricular heterotopia	*FLNA* (*FLN1*)	Xq28	Filamin-A
	Periventricular nodular heterotopia with microcephaly (periventricular nodular heterotopia type 2)	*ARFGEF2*	20q13.13	Brefeldin A-inhibited guanine nucleotide exchange protein
	Periventricular nodular heterotopia type 3	nn	5p	nn

AD, autosomal dominant; AR, autosomal recessive; nn, not known; XD, X-linked dominant.

1p36 Deletion Syndrome

Terminal deletions of 1p36 occur in approximately 1 in 5,000 live births, making the 1p36 deletion syndrome (also named monosomy 1p36) one of the most common mental retardation syndromes in humans. The clinical features include craniofacial anomalies like tower skull with microcephaly, a prominent forehead, deep-set eyes, and a flat nasal bridge. Additional features are hearing loss, growth retardation, cardiomyopathy, and orofacial clefting. Some patients develop a Prader-Williâ€“like phenotype with obesity and hyperphagia in early childhood. Several patients have been documented to have cerebral atrophy, ventricular asymmetry, hydrocephalus, delayed myelination, or focal cortical dysplasia.[14,112] Seizures occur in about 50% of patients and are of different types, including infantile spasm, simple/complex partial, generalized tonicâ€“clonic, myoclonic, and absence spells. Seizures mostly start during infancy or childhood, and are in most patients well controlled by antiepileptic drugs. EEG abnormalities vary greatly and include focal and multifocal spikes, hypsarrhythmia, and slow-wave activity. Hemizygosity for the 1p36-deleted voltage-gated potassium channel gene *KCNAB2* is associated with a severe seizure phenotype in 1p36 located syndrome.[59,60]

Neuronal Migration Disorders

In the human cortex, neuronal migration starts at approximately 7 weeks of gestation. Neurons originating from the proliferative ventricular zone migrate radially along

specialized glial processes to their final locations. The correct migration depends on several factors, one of the most important being the contact between the migrating neuron and the radial glial fiber. This requires the interaction of adhesion molecules, trophic factors, and guidance molecules, all of them possible candidates for the various disorders of neuronal migration. A second mode of migration has been recently described, in which cells born in the ventricular zone migrate perpendicular to radial glial processes. This nonradial pathway is used by most future inhibitory interneurons. Disturbances of this complicated pattern of cortical development and migration can cause severe neurologic disorders that are often accompanied or characterized by seizures (Tables 2 and 3). Neuronal migration disorders can be noninherited or genetic with distinct inheritance patterns. The malformations found in nongenetic forms are often (but not always) focal, while in the genetic ones the pattern of abnormal neuronal migration is usually generalized. The group of genetic neuronal migration disorders includes different lissencephaly syndromes, disorders with neuronal dysplasia, abnormal neuronal proliferation, and several conditions with heterotopia. Two of the five genes underlying major syndromes with lissencephaly as well as the tuberous sclerosis complex will be exemplarily described here. (See Chapter 259 for further discussion).

Isolated Lissencephaly and Miller-Dieker Syndrome

Classical or type I lissencephaly is histopathologically characterized by four abnormally positioned layers instead of the normal six cortical layers. In magnetic resonance imaging (MRI) the main findings are a smooth brain with a severely thickened cortex and absent (agyria) or simplified (pachygyria) gyri or convolutions. Typical clinical features are global developmental delay, muscle hypotonia, and different seizure types including febrile seizures, absence seizures, and myoclonic jerks. Classical lissencephaly is most commonly caused by mutations in the *LIS1* gene (also named *PAFAH1B1*, platelet-activating factor [PAF] acetylhydrolase, isoform 1B, Î±-subunit) on chromosome 17p13. *LIS1* codes for the noncatalytic *Î²*-subunit of PAF acetylhydrolase, an inactivating enzyme for PAF. PAFs are lipid mediators involved in a variety of biologic and pathologic processes, and *LIS1* is suspected to be involved in different regulatory pathways.[126] Several molecules have already been identified that interact with LIS1 protein. One of them is dynein, a molecular motor responsible for cargo transport in cells that modulate neuronal migration via microtubule organization.[4,125,128] LIS1 has also been implicated in functions like cell adhesion and cytokinesis. Heterozygous *Lis1* mutant mice have been found to display defects in neuronal migration and layering comparable to those found in humans.[22]

Table 3 Genetic Disorders with Focal/Multifocal Patterns of Abnormal Neuronal Migration

Type of malformation	Disorder	Gene	Locus	Protein	Inheritance
Focal subependymal nodular heterotopia	Aicardi syndrome (Aicardi-Goutieres syndrome)	nn	3p21 13q14-21	nn	AR
	Zellweger syndrome		7q21 8q 6q 12 6p 1p36.2 22q11.21	Peroxin-1 Peroxin-2 Peroxin-3 Peroxin-5 Peroxin-6 Peroxin-14 Peroxin-26	AR

Adrenoleukodystrophy (Bronze-Schilder disease, Siemerling-Creutzfeldt disease)	*ABCD1* (*ALDP*)	Xq28	ATP-binding cassette transporter adrenoleukodystrophy protein	XR
Multiple acyl-CoA dehydrogenase deficiency (glutaric aciduria II)	*ETFA* *ETFB* *ETFDH*	15q23-q25 19q13.3 4q32-qter	Electron transfer flavoprotein, Î±-polypeptide Electron transfer flavoprotein, Î²-polypeptide Electron transfer flavoprotein dehydrogenase	AR

AD, autosomal dominant; AR, autosomal recessive; ATP, adenosine triphosphate; nn, not known; XR, X-linked recessive.

Microdeletions including not only *LIS1*, but also genes distal to *LIS1*, are the cause of Miller-Dieker syndrome (MDS). Patients with MDS are characterized by severe psychomotor retardation, failure to thrive, and intractable epilepsy. Typical craniofacial features are microcephaly, bitemporal narrowing, high forehead, small nose, protuberant upper lip, and micrognathia. Death usually occurs before 2 years of age. In most patients the microdeletion is de novo; however, families with balanced translocations and high recurrence risk are known. There is evidence that the greater severity of MDS compared to isolated lissencephaly may be due to deletion of the gene encoding 14-3-3-epsilon protein, which is also involved in cytoplasmic dynein function.[130]

X-linked Lissencephaly/Double Cortex Syndrome

X-linked lissencephaly (XLIS) and double cortex syndrome (DCX; subcortical band heterotopia) are allelic disorders caused by mutations in the *DCX/XLIS* gene on Xq22.3-q23. XLIS, the male sex-determined manifestation of the two disorders, is characterized by classical lissencephaly, severe epilepsy, and mental retardation. Lethality is high, and family history often reveals multiple miscarriages of male fetus. In females mutations in the *DCX/XLIS* gene usually manifest as a milder phenotype known as double cortex syndrome, named after the typical broad heterotopic zone of neurons visible on MRI scans. *LIS1* and *DCX* mutations differ with respect to their associated pattern of cortical manifestations. Whereas with *LIS1* mutations the clinical manifestation is more severe over the parietal and occipital regions, the *DCX/XLIS* neuronal phenotype is more pronounced over the frontal cortex. The distinct patterns suggest that *LIS1* and *DCX/XLIS* may be part of overlapping, but distinct, signaling pathways that are involved in neuronal migration. It is therefore not surprising that the *DCX/XLIS* protein has been found to be microtubule associated where it is assumed to have a stabilizing function.[99]

Tuberous Sclerosis

Tuberous sclerosis (TS) is an autosomal dominant multiorgan disorder characterized by a great inter- and intrafamilial variation in clinical severity. The phenotypic spectrum of TS includes seizures, mental retardation, renal dysfunction, and dermatologic features such as hypomelanotic macules, facial angiofibromas (adenoma sebaceum), and shagreen patches. Hamartomatous brain lesions, such as cortical tubers, sub- ependymal nodules (SENs), or subependymal giant cell astrocytomas (SEGAs), are typical focal cortical dysplasias found in TS patients. TS results from mutations in either of two genes, *TSC1* on 9q34[133] or *TSC2* on 16p13.[42] The proteins encoded by both genes, hamartin and tuberin, are thought to play important roles in several cell-signaling pathways. Both hamartin and tuberin interact with each other to build the intracellular tuberous sclerosis complex that functions as a guanosine triphosphatase (GTPase)-activating protein (GAP). Important functions of the complex are the enhancement of the intrinsic GTPase activity of Rheb and the inhibition of mTOR signaling.[63] mTOR is a checkpoint kinase (target of rapamycin) that has been linked to numerous human cancers. *TSC1* and *TSC2* regulate the mTOR pathway to control translation and cell growth in response to nutrient and growth factor stimuli. Mutations in either *TSC1* or *TSC2* are likely to cause the cortical dysplasias underlying epilepsy in TS patients at least in part through dysregulation of the mTOR pathway.[36]

Summary and Conclusions

The examples presented in this chapter demonstrate that the different genes underlying epilepsies and syndromes with epilepsy are involved in a broad spectrum of diverse functions and functional pathways. There are gene mutations that cause progressive neurodegeneration as seen in the various subtypes of progressive myoclonus epilepsy including the neuronal ceroid lipofuscinoses, sialidoses, Lafora disease, and Unverricht-Lundborg disease. Mutations in another heterogeneous group of genes interfere with normal brain development and disturb the precisely orchestrated proliferative, migratory, and maturational events needed to form the mature six-layered cortex. Structural chromosomal aberrations that usually affect more than one gene represent a third example for the diversity of genetic mechanisms underlying epileptogenesis. Some of the chromosomal aberrations in which epilepsy is a constant finding have been discussed in this chapter, exemplary for syndromes in which epilepsy is not caused by the action of a single gene but by the combined action or failure of a number of genes within the aneuploid segment. As shown, one of the most important pathogenetic mechanisms in human epilepsy is based on mutations in various ion channel genes. With a few exceptions, all idiopathic epilepsies with known genes belong to the heterogeneous group of â€œchannelopathies.â€ There are many mechanisms by which mutated ion channels can cause neuronal hyperexcitability, and the ongoing studies of various channelopathies have already contributed much to our understanding of the complexity of pathways that can lead from a single gene mutation to episodic symptoms.

The identification of additional genes and the functional characterization of their gene products will further increase our knowledge about pathogenic mechanisms in epileptogenesis. The growing knowledge will help future generations of neurologists to more precisely classify the epilepsies affecting their patients. It can also be expected to facilitate the development of new antiepileptic drugs for the effective treatment, and perhaps even prevention, of epilepsies.

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Chapter 19

Genetic Counseling

Frances Elmslie

Introduction

Genetic counseling has become an integral component of care of many conditions that display mendelian inheritance, and increasingly those that show complex inheritance, such as autism. However, individuals with epilepsy have not been offered genetic counseling in the past, as the genetic contribution to their seizures may not have been recognized or it was felt that little could be offered. As mendelian forms of epilepsy have been described and mutations in the causative genes identified, this situation is beginning to change, and increasing numbers of people with epilepsy are being referred to the genetics clinic. This chapter will summarize the geneticist's approach to the individual with epilepsy and discuss the issues raised by the availability of genetic counseling and genetic testing.

The Process of Genetic Counseling

Genetic counseling may be defined as â€œa communication process that deals with human problems associated with the occurrence, or the risk of occurrence, of a genetic disorder in a family.â€

This process is undertaken in an attempt to help individuals and families:

- Comprehend the medical facts including the diagnosis, probable course of the disorder, and available management.
- Appreciate the way heredity contributes to the disorder and the risk of recurrence in specified relatives.
- Understand the alternatives for dealing with the risk of recurrence.
- Choose a course of action that seems to them appropriate in view of their risk, their family goals, and their ethical and religious standards and act in accordance with that decision.
- Make the best adjustment to the disorder in an affected family member and/or to the risk of recurrence of that disorder.[9]

Until recently, geneticists have not often been involved in the care of women with epilepsy, but as more genes are identified that are implicated in the etiology of epilepsy, the involvement of a geneticist will become more important. It is recommended that any individual who is undergoing genetic testing, particularly when the testing has implications for the family, be seen by the clinical genetics team or an individual who has received training in genetics.

Two main groups of individuals undertake genetic counseling: Clinical geneticists, who are medically trained, and genetic counselors, who come from a variety of different backgrounds, including nursing and scientific. The roles of these two groups are complementary, but different. The primary role of the clinical geneticist is to try to establish a diagnosis, which may or may not be genetic, in order to counsel accurately about offspring risks or risks to other family members. Genetic counselors counsel families in which the diagnosis is established and usually where the condition displays mendelian inheritance. They provide follow-up and support for families in which a genetic diagnosis has been made. In order to be able to counsel an individual accurately, one needs to establish an accurate diagnosis, and in the context of epilepsy, it would be essential to identify predisposing conditions in which epilepsy forms part of the phenotype. Therefore, the clinical geneticist undertakes the genetic management of patients with epilepsy, although a genetic counselor may provide long-term support.

Blandfort et al.[6] established three main reasons why a person with epilepsy may seek genetic counseling:

- An individual with epilepsy may be concerned about the risk of his or her offspring developing epilepsy.
- The parent of a child with epilepsy may be concerned about the risk of future siblings, or an apparently unaffected sibling, developing epilepsy.
- A woman with treated epilepsy may be concerned about the risk of malformation and developmental delay in a child exposed to anticonvulsants in utero.

Until recently, most epilepsy patients seen in the genetics department fell into the second category. The parents of a child with severe epilepsy, often in the context of developmental delay or another neurologic deficit, seek advice about the risk of having another similarly affected child. In addition, the clinical geneticist has a role in confirming or refuting a diagnosis of a fetal anticonvulsant syndrome and in advising about future pregnancies. However, it has only been recently that individuals with a significant family history of epilepsy have been referred to the genetics department, and this comes with the increasing recognition of mendelian forms of epilepsy.

A Framework for Genetic Counseling

One of the primary goals of genetic counseling is to provide information to enable a couple or an individual to make an informed reproductive choice. This is achieved by nondirective counseling, which helps to ensure that decisions are made in the context of the individual's beliefs, values, and background. This differs from some other areas of medicine, in which, for example, a physician may make a specific recommendation about one form of treatment over another. An important component of an individual's ability to make an informed choice is the risk that his or her future children will be affected. It is therefore imperative that the risk given by the geneticist be as accurate as possible and based on knowledge of the family, the specific epilepsy syndrome, electroencephalographic (EEG) and cranial imaging findings, and the presence or absence of a predisposing condition.

Reproductive decisions are based on the couple's perception of the risk figure given and the burden on the parents if a child is affected. Perception of risk varies enormously from one couple to another. For example, one couple may consider a risk of 2% to be high and another may view it as low, although this will be influenced by the severity of the condition for which the risk is being given.

The Geneticist's Approach to Epilepsy

The Family History

The first component of a genetics consultation is the compilation of the family tree. This should be as detailed as possible, and as a minimum should go back and forward two generations from the consultand. Information on first and second cousins should be included if possible. The amount of information that families share differs from family to family. The accuracy of the family information is a particular problem in epilepsy, in which the phenotype is often age dependent, and may be forgotten, or even hidden. In many families, one or more family member will have or have had epilepsy because of the high prevalence in the general population. Occasionally, the family tree will show clear evidence of mendelian inheritance, most commonly autosomal dominant inheritance. It is possible that some people in such a family do not have seizures, but their siblings and children do. These people are described a nonpenetrant; that is, they carry a mutation in a specific gene but never manifest the disease. All autosomal dominant idiopathic epilepsy genes described to date show incomplete penetrance.

If consanguinity is present, autosomal recessive inheritance should be considered but not presumed. The family history may suggest X-linked inheritance if there is no male-to-male transmission, or if males are more severely affected. Similarly exclusive female transmission may indicate a mitochondrial disorder.

Wherever possible, the diagnoses volunteered by the consultand should be confirmed directly with the treating physician, because accurate information is needed to give accurate risk figures.

Identifying Predisposing Conditions

Conditions that may present with epilepsy have been covered elsewhere. The most important conditions to identify for the purposes of genetic counseling are those that would significantly alter the recurrence risk. A thorough evaluation of the proband would include a full clinical evaluation, including the following:

- Clinical examination including Wood light examination
- Developmental assessment in a child
- EEG data
- Cranial imaging
- Other investigations informed by the clinical presentation (e.g., tests for a suspected metabolic disorder; echocardiography and renal imaging for suspected tuberous sclerosis)

These investigations are most effectively done in partnership with the pediatrician or neurologist who cares for the patient.

An example of an important predisposing condition is that of tuberous sclerosis (TS). Individuals with TS may present with epilepsy at any time from infancy to early adulthood, but approximately 25% of children presenting with infantile spasms will have TS, and therefore all such children should be fully screened for TS. Once a diagnosis of TS is established in a child, the parents should be screened clinically, and if a mutation is identified in the child, by genetic testing. If TS has arisen de novo in the child, the recurrence risk is approximately 2% because of the possibility that one parent carries the mutation in their gonads (gonadal mosaicism), but if a parent has clinical evidence of TS or carries the familial mutation, the recurrence risk is 50%.

Chromosomal analysis would be indicated if the epilepsy occurs in the context of learning difficulties or a physical abnormality. In addition, epilepsy that is difficult to manage (such as that seen in ring chromosome 20 mosaicism) would be an indication for chromosomal analysis. Once a child has been found to have a chromosomal abnormality, it is important to exclude a familial rearrangement in an asymptomatic parent, because this may have implications for future children.

A full metabolic workup is indicated in an infant with early-onset seizures or if there is evidence of regression or precipitating factors such as intercurrent illness.

If cranial imaging reveals a neuronal migration abnormality, further investigations should be performed in an attempt to distinguish between genetic and nongenetic forms.

Identifying the Specific Epilepsy Syndrome

A specific epilepsy diagnosis is important, because family studies have demonstrated that certain epilepsy syndromes show a greater genetic predisposition than others, and this will affect the offspring or sibling risks. Some patients do not know their precise epilepsy diagnosis, and in some instances no attempt has been made to classify their epilepsy, particularly if the diagnosis was made many years ago. Therefore, unless the geneticist has specialist knowledge of epilepsy, the patient will need assessment by a neurologist as well. Factors that are particularly important to consider are the following:

- Age of onset
- Seizure types
- EEG features

- Acute precipitating factors
- Previous history
- Presence of neurologic dysfunction other than seizures

Genetic Risks

Individuals seeking genetic advice fall into two main groups: Those who have epilepsy themselves and want to understand the risk to their offspring, and parents of a child with epilepsy who are concerned about the risk to their future offspring.

Mendelian Epilepsies

When a diagnosis of a mendelian condition has been established, the risk to offspring or siblings is straightforward. In autosomal dominant conditions in which a parent is affected, the risk of a child inheriting the gene mutation is 50%. However, the risk of developing epilepsy will be lower because of nonpenetrance. Genetic studies have shown that penetrance in most autosomal dominant mendelian epilepsy syndromes is of the order of 70%, and therefore the offspring risk of epilepsy can be modified to 35% (0.5 Ã— 70%). If the parents are unaffected and are concerned about a sibling risk, the family history and the results of genetic testing must be taken into account (discussed in more detail below).

Table 1 Recurrence Risks According to Type of Epilepsy and Whether Parent or Sibling Affected

Type of epilepsy	Parent affected	Sibling affected	Reference
Idiopathic generalized epilepsy	2.5%â€“5%	2%â€“5%	3
Childhood absence epilepsy	8%â€“10%	4%â€“6%	3
Juvenile myoclonic epilepsy	6%â€“10%	6%â€“7%	12
Photosensitive epilepsy	6%â€“10%	6%â€“10%	6
Infantile spasms	Unknown	1%â€“2% for infantile spasms (X linkage and tuberous sclerosis excluded)	6
Partial epilepsy	2%â€“3%	2%â€“3%	3
Benign childhood epilepsy with centrotemporal spikes	12%â€“15% (estimate)	12%â€“15%	6

Febrile convulsions	10%	10%â€“20%	6

Modified from Blandfort M, Tsuboi T, Vogel F. Genetic counselling in the epilepsies. *Human Genet.* 1987;76:303â€“331.

Counseling families in which the proband has an established diagnosis of a progressive myoclonic epilepsy including Unverricht-Lundborg disease, Lafora disease, and the neuronal ceroid lipofuscinoses is straightforward as they are all inherited in an autosomal recessive manner. Therefore, the recurrence risk for a couple that has had one affected child is 25% in each pregnancy. The risk of a person with a progressive myoclonic epilepsy having an affected child depends on the partner's carrier status. If the partner is also a carrier, the risk to the offspring increases to 50%. If he or she is not, then all the offspring will be carriers but will not be affected.

Similarly, in X-linked recessive conditions the sibling risk for an affected male is 25%. X-linked dominant conditions such as that caused by mutations in *DCX* or *XLIS* confer an overall 50% offspring risk, as both males and females can be affected to different degrees. However, some genetic conditions in this group result in male lethality, with the result that the significant offspring risk is for a live-born affected female and is 25%.

However, mendelian epilepsies account for only a small fraction of epilepsy in the general population. Most epilepsy syndromes display â€œcomplexâ€ inheritance, meaning that many genes may be involved or that factors other than genetics play a role in the etiology.

Complex Epilepsies

Numerous family studies have demonstrated that the risk of seizures in the siblings and offspring of a person with epilepsy or febrile convulsions is greater than that of the general population. A number of factors increase the risk of epilepsy in relatives of individuals with epilepsy (summarized in Winawer and Shinnar[24]):

- Gender of the affected parent
- Age of onset
- Idiopathic versus symptomatic epilepsy
- Epilepsy phenotype in the proband
- Presence of EEG abnormalities
- Number of affected relatives

It is well established that there is an increased risk of epilepsy in the offspring of an epileptic woman (approximately 2.9% to 8.7% to age 25) compared with an epileptic man (1% to 3.6%).[3,22] In addition, there is an increased incidence in the daughters of an affected individual compared with sons, and there is a greater incidence among the relatives of an affected woman. The basis of this increased risk is unknown.[16]

Early parental age of onset also influences the risk of epilepsy. Onset of epilepsy before the age of 20 confers a 2.3% to 6% risk to offspring (compared with a background risk of 1% to age 20), whereas onset after 20 gives a 1% to 3.6% risk.[22] Similarly, the sibling risk is greatest when the age of onset is between 0 and 9 years, being 9.5%; the risk is 5.8% for onset between 10 and 24 years and 2.6% for onset between 25 and 39 years.[2] There is no increased risk where the onset of epilepsy has occurred after the age of 35[18]. Idiopathic epilepsies are associated with a greater offspring risk than symptomatic epilepsies (Ottman et al., 1996). However, partial and generalized epilepsies are associated with similar offspring risks, indicating that genetic factors are equally important in the etiology of both groups of epilepsy[16,17]. There is good evidence that childhood absence epilepsy is associated with the greatest offspring and sibling risk of the generalized epilepsies.[17]

The family tree must be taken into account when discussing offspring or sibling risks. The risk of epilepsy in the offspring or siblings of an affected individual increases with increasing numbers of affected relatives.[3] Some families will have a phenotype and family history that fits well with one of the known mendelian epilepsy syndromes such as generalized epilepsy with febrile seizures plus (GEFS+). In others, there may be evidence of mendelian inheritance even though they do not fit any of the well-described mendelian epilepsy phenotypes. Such families may represent â€œnewâ€ epilepsy syndromes. However, it is important to remain conscious of the fact that epilepsy is a common condition with multiple etiologies, and that familial clustering could still have occurred by chance.

If the incidence of epilepsy in the family is higher than that expected for a particular epilepsy syndrome, it would be important to review the diagnosis, or consider whether the family displays mendelian inheritance. In such families it would not be appropriate to counsel a â€œstandardâ€ risk; the risk should be tailored to the family history. Genetic testing may help to clarify the risk in a few families.

A number of twin studies have demonstrated concordance for epilepsy and for the specific epilepsy syndrome, although this relationship is not absolute.[1,5,14] The risk that the affected offspring or sibling of an affected person may not have an identical phenotype needs to be discussed. Estimates of the offspring

and sibling risk figures for complex epilepsy syndromes derived from such family studies are given in Table 1. However, when counseling families, all the factors previously discussed need to be taken into account.

Febrile Convulsions

Febrile convulsions should be considered separately as the general rules for offspring risk do not apply. Febrile seizures affect about 3% of children before the age of 5 years, but higher cumulative incidences have been reported of up to 9% in Japan and 15% in Guam. One third of children with an initial febrile seizure will have a second one, and of these 50% will have a third. However, only a small minority will go on to have afebrile seizures.

It has long been recognized that febrile convulsions run in families. Estimates of the proportion of probands with an affected first-degree relative vary from study to study with figures of between 8%[19] and 49%[22] in siblings and parents being obtained. A number of modes of inheritance have been suggested, but the best evidence indicates that the polygenic model is the most feasible.[19]

Although febrile seizures therefore usually display a complex pattern of inheritance, large pedigrees or groups of families with febrile seizures consistent with autosomal dominant inheritance have been identified. Johnson et al.[13] for example, studied 52 probands and found that the mode of inheritance in multiplex families best fitted the hypothesis of autosomal dominant inheritance with reduced penetrance. A number of gene loci have been mapped in families displaying autosomal dominant inheritance.

Therefore, the family history is of prime importance, as is the nature of the seizures. Some families with atypical febrile seizures may have a diagnosis of GEFS+, particularly if afebrile seizures are also present in the family.

Ethical Considerations in Genetic Testing for Epilepsy

Genetic testing for a number of the mendelian epilepsies is now possible. The value of genetic testing when it helps to establish a diagnosis, to clarify risk, or to enable a prenatal test to be offered in future pregnancies is well established. The progressive myoclonic epilepsies provide a good example of this approach. Genetic testing now forms part of the diagnostic workup of a person with a suspected progressive myoclonic epilepsy. These conditions display full penetrance; that is, individuals who carry two mutations in the causative gene will develop the condition, which ultimately leads to progressive neurologic deterioration and early death. If both mutations are identified in the proband, the diagnosis is established and prenatal diagnosis would be justified in future pregnancies if the parents wish to have it.

However, genetic testing in the idiopathic epilepsies represents more of problem. Genes for the mendelian epilepsies have been identified through the collection of DNA samples from large families after obtaining explicit informed consent. It would be standard practice for the families not to receive results from the research study, although in some cases results will be verified in a diagnostic laboratory and fed back to the family. Those same laboratories may continue to offer testing for a number of months or years in order to build up their knowledge of the genetic mechanisms and functional effects of particular mutations. However, in time, a genetic test may become a diagnostic tool, and it is therefore appropriate for the testing to be done in a diagnostic laboratory.

The ethical implications of testing then need to be considered more carefully. These have been well addressed by Godard and Cardinal.[10] Whether genetic testing is done in a research setting or a diagnostic setting, the results frequently raise issues for the wider family, and these need to be discussed before proceeding with testing. The ethical principles that underlie the practice of medicine that are particularly relevant to genetic testing are as follows:

- Autonomyâ€"respect for the self-determination of individuals and the protection of those with diminished autonomy (i.e., children, or individuals with learning difficulties)
- Beneficenceâ€"maximizing the benefit to health
- Nonmaleficenceâ€"avoiding, preventing, or reducing harm
- Justiceâ€"equity of access

One major way in which genetic testing differs from other forms of diagnostic testing is that the results may have implications for other family members, and therefore these ethical principles need to be considered not only in relation to an individual, but also to the wider family. Testing must take into consideration the cost and efficacy of the test, the duty to warn versus the right not to know, and the possible detrimental effects on other family members.

The Benefits of Testing?

As the genetic basis of more idiopathic epilepsy syndromes is understood, genetic testing is becoming an additional tool to aid diagnosis. This may, in turn, reduce the need for other, more invasive investigations and possibly even affect the choice of treatment. As ongoing studies of drug responsiveness and genotype come to fruition, a genetic test may be used to both determine the most effective drug and anticipate possible adverse drug reactions.

Currently, genetic testing is of greatest benefit when the epilepsy syndrome is severe and life threatening. A good example is severe myoclonic epilepsy of infancy, which is associated with mutations in the gene encoding a sodium channel alpha subunit (SCN1A). Genetic studies have demonstrated that this is virtually always sporadic, and mutations have arisen de novo in most affected individuals.[7] If a mutation has been identified in an affected child that is not present in either parent, it is possible to be very reassuring about the risk to future children. There is a small risk of gonadal mosaicism, and prenatal diagnosis could be offered. More rarely, one parent is shown to carry the mutation, and there is usually a family history of epilepsy. In this case the risk to offspring will be 50%, and the phenotype is likely to be more variable. However, if the parents have had one severely affected child, prenatal diagnosis and termination of pregnancy would be justified.

There is also a potential benefit in familial epilepsy syndromes in which seizures may be misinterpreted, and the diagnosis missed. A good example is that of autosomal dominant frontal lobe epilepsy, in which episodes are frequently misdiagnosed as psychiatric disease, night terrors, etc. If a person at risk had had a genetic test, investigation and treatment of such episodes would be accelerated.

The Risks of Genetic Testing

Many mendelian epilepsy syndromes are benign, self-limiting, or easily treated. In addition, all mendelian epilepsy syndromes

described to date show incomplete penetrance. Genetic testing in this situation raises particular issues. For example, an individual with autosomal dominant nocturnal frontal lobe epilepsy is found to have a mutation in CHRNA4. She has two children, and asks for them to be tested. At this stage there should be a full discussion about the value of testing with reference to the interpretation of the result. What would a positive result mean for the children? What is their risk of epilepsy? How can this risk be modified? What is the risk to their children? What would a negative result mean? Has the right of the children not to know been taken into account? Have the children understood and given assent? Are there implications for other family members? How will the results be communicated to the individuals being tested and also to the wider family?

After a full discussion, testing goes ahead. One child is found to have the mutation. It is possible that the child will never develop epilepsy, and if he does it is impossible to predict at what age the epilepsy will occur. There is no recognized screening program that can be offered, and the mother may interpret any unusual symptoms as the onset of epilepsy. In addition, the presence of the mutation may jeopardize the child's future insurance prospects, perhaps preventing him from obtaining a driving license or restricting his future choice of occupation. There may also be implications for the child who tested negative. He is still at risk for epilepsy because of the background population risk and may believe himself to no longer be at risk. In addition, he may feel guilty that he escaped the genetic burden of the family, so-called survivor guilt. The particular implications of genetic testing in childhood have been well discussed,[8] and international guidelines for genetic testing proposed.[23]

In the future, genes that cause the complex epilepsies may be identified. It is likely that such genes will cause an increased susceptibility to seizures in a similar way to the increased risk of Alzheimer disease in individuals who carry Apo-E4.[11] The ethics of such testing has not been fully explored, but the principles of beneficence and nonmaleficence will be of particular importance in the future genetic counseling of families with epilepsy.

Summary and Conclusions

Genetic counseling in the epilepsies presents particular challenges, both because of the broad spectrum of potential diagnoses and because of the ethical considerations of genetic testing. This is a rapidly changing field, and these guiding ethical principles must not be forgotten in the enthusiasm to identify new genes.

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Chapter 20

Overview: The Neurobiology of Epilepsy

Marc A. Dichter

Introduction

The epilepsies are a complex group of disorders whose common feature is a tendency for hyperexcitability to develop in one or another region of the central nervous system (CNS). Epileptic syndromes and seizure types can be quite variable and may have many causes. Similarly, multiple underlying cellular and molecular mechanisms are likely to be responsible for various epileptiform phenomena. Much research has been, and continues to be, directed at unraveling the mechanisms underlying epileptic events, based on the premise that increased understanding will make it possible to devise either better treatment strategies or better methods to prevent epilepsy.

Neuronal Excitability

The hyperexcitable states that underlie the various forms of epilepsy represent complex functional changes in normal brain anatomy, physiology, and pharmacology. To begin to understand such changes, it is necessary to understand the normal brain substrate on which these alterations are occurring and the developmental patterns that result in the normal functioning. The next 15 chapters in this book are devoted to a systematic discussion of the physiology of normal brain function, organized according to the component parts that may be altered when epilepsy develops. Each chapter focuses on one broad area of neuronal activity, starting with an analysis of normal function at the system, cellular, and molecular levels, and then proceeding to a consideration of where this aspect of physiology might be perturbed to produce epilepsy and how naturally occurring forms of epilepsy might involve this system. Initial focus is on the excitability of individual neurons; detailed considerations of synaptic transmission, both excitatory and inhibitory, and synaptic modulation are then presented, followed by discussions of neuronal circuitry in the neocortex and limbic cortex, and the role of various subcortical structures on CNS excitability. Consideration is also given to the regulation of gene expression by both normal and pathologic activity in CNS pathways and the developmental aspects of CNS function. All this material serves as a basic scientific underpinning for the discussions of experimental seizure models and the human epilepsy syndromes, and also provides potential targets for the actions of antiepileptic drugs.

Experimental Models

To study epileptic phenomena at a network, cellular, or molecular level, model systems are needed. The second half of this section provides detailed analyses of various experimental models used for studying seizures and epilepsy. Such models can be designed to mimic some forms of human epilepsy closely (see Chapters 36,37,38,39) but, as discussed in Chapter 41, no animal model can mimic all the features of any human epilepsy at this time. Alternatively, much simpler models can be developed that allow the isolation of specific individual epileptiform activity in ways that can be analyzed using a reductionist system. In fact, most of what is known about the cellular mechanisms of specific epileptiform events has been derived from studies of simplified systems and acutely provoked seizure activity. These studies were initially performed using in vivo animal models and, as techniques evolved for analyzing CNS tissue in vitro, they were extended to CNS models in acute slice preparations and cell culture. One of the challenges of modern epilepsy research is to extrapolate such findings to the more complex CNS of humans and the more complex problem of chronic epilepsy. The last chapter in this section discusses attempts at conducting such studies in humans, or at least in human tissue.

Epileptogenesis

Most, if not all, forms of epilepsy develop over a defined time period. That is, at some point in time, the brain functions normally (and may be normal), but either after a specific developmental sequence or in response to some form of injury, a new state develops in which the neuronal circuits become hyperexcitable, leading to spontaneous recurrent seizures. This process, referred to as *epileptogenesis*, has been too little studied. Much less is currently understood about the process of epileptogenesis than about the phenomenology of seizures. At a clinical level, not much can yet be done to protect individuals who are known to be at high risk for the development of epilepsy, in comparison with what can be done to suppress seizures once they develop.

Fundamental Mechanisms

What can be said at present about the fundamental mechanisms of different forms of epilepsy? In partial epilepsy, it appears that areas of hyperexcitability are associated with some form of synaptic reorganization that occurs after brain injury. Some areas of brain seem much more susceptible than others, and the limbic structures in the mesial temporal lobeâ€"notably the hippocampus, parahippocampal regions, subiculum, entorhinal cortex, and amygdalaâ€"seem particularly vulnerable. Neurons within epileptic areas in these structures undergo synchronous and paroxysmal depolarizations, and fire bursts of action potentials. These bursts are followed by periods of inhibition. Most often, such events occur singly, and relatively little perturbation of function can be detected. These represent â€œspikesâ€ on the electroencephalogram (EEG). At times, such discharges do not remain confined in either anatomic space or time, and seizures result. More and more neurons are recruited into the hypersynchronous activity, both in local areas and, via synaptic pathways, distant areas subcortically and contralaterally. Why such events occur at all, and why they occur at any

specific point in time remains unknown. After all, even in the most severely affected individuals with epilepsy, seizures occur only intermittently.

It is known that seizure activity involves alterations in the fundamental excitability of neurons and in the synaptic connections between neurons. It is also known that seizures can be produced artificially by altering any of multiple cellular processesâ€"for example, enhancing synaptic excitation or reducing synaptic inhibition. Thus, seizures develop by utilizing slight perturbations in normal cellular excitability or normal synaptic transmission and by utilizing normal anatomic pathways for both control and spread. The recognition of these principles has stimulated epilepsy researchers to lead inquiries into the physiology of normal cortical microanatomy, physiology, and pharmacology, and, most recently, molecular biology.

Primary generalized seizures present a different set of challenges to epilepsy researchers. Unlike the seizures of partial epilepsy, these events appear to start in diffuse bilateral brain areas all at once, and therefore do not provide a focal target for detailed examination by physiologists. In addition, many of the epileptic syndromes involving generalized seizures are the result of genetic alterations in CNS function, several of which are currently being unraveled. For example, studies of thalamic nuclei and thalamocortical circuits have provided dramatic new insights into the fundamental cellular mechanisms underlying some forms of primary generalized seizures. These are discussed in Chapter 31. Moreover, in both mouse and man, single gene mutations that can result in primary generalized epilepsy have been identified. As in the partial epilepsies, small perturbations in the basic cellular mechanisms of excitability and synaptic function are responsible for the underlying abnormal activity.

Most recently, studies of the fundamental mechanisms underlying epilepsy have progressed to the molecular level. Increased understanding of voltage-gated ion channels in excitable membranes, neurotransmitter receptors, neurotransmitter transport molecules, trophic substances, and other neuronal proteins has made it possible for some of the molecular changes associated with the epileptic state to be described. In addition, it is clear that the kind of excess excitability seen during epileptiform events is capable of inducing a number of specific genetic activation patterns in different circuits within the CNS. These are discussed in Chapters 21,22,23,24, 28, 31, 36, 37, and 41. Whether and how these molecular changes contribute to the stabilization of the epileptic state, or whether they are designed to counteract some of the hyperexcitability and suppress seizures remains to be determined. As new techniques in molecular neuroscience are applied to problems in epilepsy, it is likely that at least some of these questions will be answered.

Genetic Studies

Implicit in our understanding of the myriad possible perturbations of normal cellular anatomy, physiology, and pharmacology that can produce seizures in animals is the realization that genetic alterations in any of these processes may produce epilepsy. In fact, many examples of genetically determined epilepsy have been described in a variety of animal species, several of which closely mimic one or another form of epilepsy in humans. Much of this is reviewed in Chapter 37; the human genetic epilepsies are discussed in Chapter 18. Several major principles are emerging from these and other genetic studies, especially those related to the creation of transgenic animals with specific knockouts or abnormalities of single genes. It is clear that full-blown epileptic syndromes can occur in the context of single-gene mutations, but in some cases, other components of the genetic background can influence the phenotypic expression of hyperexcitability. In addition, different components of the epileptic phenotype can be specifically influenced by single genes, for example, EEG patterns. Among the more surprising recent results, however, is the realization that alterations in genes that had not been thought to be specific for brain functionâ€"such as those for enzymes in energy-producing pathwaysâ€"can produce epileptic phenotypes. In fact, seizures are a common and surprising occurrence in many transgenic mice that were developed to study genes whose function was not thought to be related to neurologic diseases. These studies are likely to broaden our understanding of epileptic processes in the CNS and open the analysis of the epileptic state to new approaches, perhaps beyond the usual realm of traditional neuroscience. In turn, these new approaches may lead to new treatment strategies.

Clinical Applications

As mentioned at the beginning of this chapter, a fundamental premise for all this work is that an increased understanding of epileptic processes will result in new treatment strategies or new approaches to prevention. By contrast, until now, essentially all currently available drugs or other treatments for seizures have been discovered by accident or by general screening against seizure models. This is true despite dramatic advances in our understanding of normal brain function and the mechanisms underlying epileptic phenomena over the past 50 years. It appeared that this trend would be reversed when neuroscientists discovered the importance of the inhibitory neurotransmitter Î³-aminobutyric acid (GABA) in epileptiform activity. Drugs could now be targeted for a specific mechanism. This led to the development of two drugs that were specifically designed to enhance the activity of GABA: Vigabatrin, which blocks GABA metabolism, and tiagabine, which blocks the reuptake of GABA after synaptic release. Although each has been demonstrated to be effective in both animal models of epilepsy and in patients with intractable partial seizures, neither drug has proved to be as valuable as first predicted, either because of unexpected toxicity or because of complex relations between different forms of GABA-mediated inhibition in different brain regions in different epilepsy syndromes. Other drugs targeted for the GABA system proved useful, but were then found to *not* act on the GABA system. Similarly, drugs developed specifically to dampen excitatory synaptic function have also been unsuccessful so far. Despite these caveats, however, most epilepsy researchers remain optimistic that, as our understanding of basic mechanisms of epilepsy and epileptogenesis increases, these findings will be directly applied to the clinical problem. Hopefully, within the next 5 to 10 years, new clinical approaches to seizure control and epilepsy prevention will be forthcoming.

Summary and Conclusions

Epilepsy is a complicated disorder involving disturbances of brain function at multiple levels. A variety of experimental models are currently being studied to gain an understanding of the fundamental system-level, cellular, and molecular mechanisms underlying different forms of epilepsy. In addition, human patients with epilepsy can be studied in ways that were not possible only several years ago, utilizing advanced imaging and new electrophysiological tools. Brain tissue from human patients, removed at surgery, can also be used to analyze underlying abnormalities. It is hoped that the increased understanding developed by these approaches will lead to new strategies for the treatment or prevention of epilepsy.

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Chapter 21

Control of Neuronal Excitability

Uwe Heinemann

Istvan Mody

Yoel Yaari

Introduction

The behavior of nerve cells is determined by ionic channels. These are transmembrane proteins with a pore that permits ions to pass across the lipophilic membrane. Ion channels may be permanently open or regulated by stretch, voltage, or chemical compounds. Currents flow through these channels in an inward or outward direction dependent on the driving force, which is set by the difference between the actual membrane potential and the equilibrium potential for the given ion(s). An inward current depolarizes the membrane and is carried either by movement of positive charges (Na^{+}, Ca^{2+}) into the cell or of negative charges (Cl^{-}) out of the cell. Conversely, outward currents drive the membrane potential in a hyperpolarizing direction and are carried either by cation (K^{+}) currents out of or anion (Cl^{-}) currents into the cell. At resting membrane potential, which is negative in all cells, inward and outward currents balance each other. The proteins that encode the water-filled, voltage-dependent ion channels are called Î± subunits. They are often associated with Î², Î³, and other auxiliary subunits. These may modulate properties of the channels, but they also regulate membrane anchoring and trafficking of ion channels. The receptor-gated ion channels usually consist of different Î±, Î², and so on subunits, which all are required to form the ion channel. The nomenclature for ion channels is rather diverse. Physiologists and biophysicists originally named most ion channels according to their ion selectivity and dependence on voltage, ligand binding, or role in cellular function such as stretch, generation of receptor potentials, and so on. A second nomenclature often derives from studies of mutations in the fruit fly *Drosophila*. Scientists who originally cloned ion channels developed yet another nomenclature, and, finally, human geneticists use yet another. This makes reading the original literature difficult and sometimes time-consuming. I find the International Union of Basic and Clinical Pharmacology (IUPHAR) compendia on ion channels rather useful in this respect because it gives all the names used in the literature for all voltage-gated ion channels. I will follow the 2005 nomenclature of ion channels proposed by the International Union of Pharmacological Sciences. The most comprehensive survey of properties of ionic currents and their physiologic meaning is given by Hille.[65]

Receptor-gated ionic channels mediate the information traffic between cells and set the membrane potential as a function of changes in the intracellular milieu such as those of adenosine triphosphate (ATP), pH, or calcium. Voltage-gated ionic channels determine how a neuron integrates synaptic information and propagates it to another neuron or to effector organs. Voltage-gated channels regulate the membrane potential, influence the integrating properties of the dendrites and the discharge mode of a cell, and are responsible for the generation and propagation of action potentials. At the presynaptic terminals, they influence Ca^{2+} loading of the terminals, which is a prerequisite for transmitter release. It is important to note that the distribution of ion channels over the surface of a neuron is not homogeneous. Neurons are polarized cells, which often express in their dendrites other channels than in the soma, the axon, and the presynaptic terminals. Regulation of sorting and direction into axonal and dendritic transport in neurons is much less understood than in epithelial and endothelial cells, which are also polarized. The anchoring of ion channels at distinct sites within and outside the synapse is another important issue because it determines the strength of synaptic coupling and the integration properties of neurons. This has become clear because mutations in stargazing and other anchoring proteins can contribute to epileptogenesis.[102] Similarly, proteins involved in vesicle cycling and other presynaptic functions can contribute to epileptogenesis.[5]

For ionic currents to flow, an electrochemical gradient must be provided, which depends on transport processes across the neuronal membrane. Changes in membrane potentials can be brought about by electrogenic active or secondarily active transport, and such processes frequently influence the responsiveness of neurons. Therefore, in this chapter, I first consider the operation of such ion transport mechanisms. Subsequently, I treat the properties of channels that control the resting membrane potential. I then describe voltage-operated ionic channels that account for neuronal excitability and different discharge modes of neurons. The excitability of neurons is also controlled by low-affinity subsynaptic Î³-aminobutyric acid (GABA), glycine, acetylcholine, and glutamate ionotropic receptors and by high-affinity ionotropic or metabotropic receptors, which are often located at extrasynaptic sites.

Properties of Ion Transporters and Generation of Membrane Potentials

A simple way for ions to cross the plasma membrane is by means of energy-driven pumps, which use the energy from ATP to overcome the barrier imposed by the plasma membrane. Ion pumps are proteins responsible for generating and maintaining the concentration gradients of Na^+, K^+, Ca^{2+}, H^+, and Cl^- ions across the plasma membrane; of H^+ across vesicular membranes; and of Ca^{2+} across the mitochondrial membrane and the endoplasmic reticulum. They bind ions on one side of the membrane, physically transport it across the bilayer, and release it on the other side. Because energy is expended in this process (ATP hydrolysis), it is possible for such active transporters to move ions against a concentration gradient. The energy for this transport comes directly from ATP. It is therefore important that the respiratory chain is intact. The Na,K-ATPase is formed

by Î± and Î² subunits. Four Î± subunits and four Î² subunits have been identified, and two Î± and Î² subunits are necessary for the transport process.[55,145] The ATP-dependent ion transporters affect the electrical behavior of a cell in two ways: They set up the electrochemical ionic gradients that underlie current flow when voltage- or ligand-gated channels are activated. They also affect membrane potential because the transporters are often electrogenic. As an example, Na,K-ATPase transports three Na^+ ions out of a cell in exchange for only two K^+ ions. Hence, the Na,K-ATPase imposes a hyperpolarizing drive on the membrane potential and thereby drives the membrane potential in a negative direction. In fact, the reversal potential for this transporter is quite negative. The membrane potential of neurons and glia would sit very much negative to -100 mV; if not, conductances for Na^+, K^+, and Cl^- would clamp the membrane potential to more depolarized potentials. In fact, it is the Na-K pump that causes K^+ to accumulate within cells and sets up the gradient for Na^+ to enter cells once Na^+-permeable channels are open.[133] Because under resting conditions mostly K^+ channels are open, K^+ ions tend to leave the cells along their chemical gradient. This is prevented by the retaining force set up by negatively charged proteins. Thus, an equilibrium between influx and outflux of K^+ is generated. This equilibrium is described by the Nernst equation. A membrane potential dominated by the K^+ concentration gradient over the membrane would be close to -90 mV. This situation is approached in many astrocytes,[116] which therefore respond to a change in extracellular K^+ concentration more effectively than do neurons.

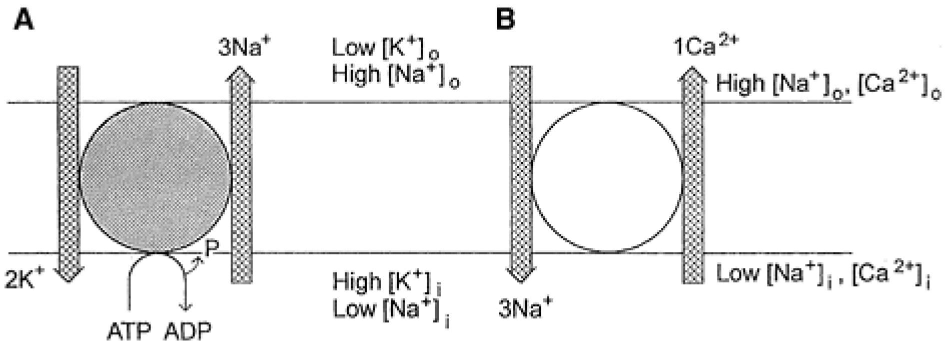

FIGURE 1. A: Active transporter. Principles of action of the electrogenic Na^+,K^+-ATPase. One adenosine triphosphate (ATP) molecule is used to transport three Na^+ ions against the concentration gradient out of the cell, and two K^+ ions are transported against the concentration gradient into the cell. **B:** Secondarily active transporter. In the example of this antiporter, three Na^+ ions are moved along the electrochemical gradient into the cell, and one Ca^{2+} ion is moved against the electrochemical gradient out of the cells. Note that all transporters have a reversal potential. ADP, adenosine diphosphate.

Most neurons and muscle cells have membrane potentials more positive than -90 mV. This is because channels permeable to Na^+ and Cl^- are open under resting conditions. These conductances are much smaller than those for K^+. Nevertheless, the existence of Na^+ leak channels implies that for each K^+ ion that leaves a nerve cell, one Na^+ ion can enter. The cells would slowly depolarize to zero if the Na-K pump did not become activated on intracellular accumulation of Na^+ and thus restore the concentration gradients. Thus, the Na-K pump ultimately is responsible for the generation of the Na^+ and K^+ concentration gradients and the membrane potential. The Na-K pump can be activated by accumulation of both extracellular K^+ and intracellular Na^+.[58] During a seizure resulting from activation of Na^+ and K^+ channels, Na^+ accumulates within the neurons and K^+ in the extracellular space. This leads to activation of the electrogenic Na^+ pump and then to a hyperpolarizing drive. This hyperpolarizing drive contributes to the termination of seizures and is responsible for the long-lasting afterhyperpolarization that follows a single seizure.[61] When Na^+ pumps lose their efficacy, afterhyperpolarizations become smaller, and such loss of efficacy may well underlie episodes of status epilepticus. Indeed, it has been shown that accumulation of intracellular Ca^{2+} can impair the function of the pump.[50] This may be caused by depolarization of mitochondrial membranes, which interferes with the generation of ATP,[89] by consumption of ATP in pumping Ca^{2+} out of cells and into intracellular stores, or by a direct modulation of Na,K-ATPase.

The electrochemical gradient set up by such pumps can be exploited by secondarily active transporters. These use the electrochemical force for inward or outward movement set up by active pumps to transport a second molecule against the concentration gradient. Such transporters import glucose, amino acids, and other agents into the cells as well as export metabolites, calcium, and protons. Often these transporters are not electrically neutral, and thus they can influence the membrane potential (FIGURE 1).

Secondarily active pumps are also involved in regulating the intracellular and extracellular ionic environment. They can use the electrochemical gradient for one ion species to move another ion in the same direction (cotransport) or in the opposite direction over the membrane (antiport). Such transporters do not affect the membrane potential if they are electrically neutral. However, in many cases the transporter is not electrically neutral. For example, the Na^+-Ca^{2+} exchanger in most cases transports three Na^+ ions into the cell against one Ca^{2+} ion out of the cell, thus providing a depolarizing drive to the cell.[13,14]

Secondarily active transporters have a reversal potential. Thus, when the membrane potential moves beyond the reversal potential, the transport direction is also reversed. For example, the reversal potential for the Na$^+$-Ca^{2+} exchanger is somewhere around -30 mV. This implies that depolarizations beyond this potential would drive Ca^{2+} into the cell, and there is indirect evidence that this occurs during spreading depression and anoxic depolarization.[84] Because the transmembrane ionic gradients strongly change during such conditions, however, the reversal potential also shifts. It is therefore necessary to consider in any of these conditions the actual reversal potential for a given transporter. This also applies to situations in which GABA or glutamate is released by reversed transport from nonvesicular compartments.[2,3]

The intracellular Cl concentration is also affected by secondarily active transporters and in addition by Cl channels. Early during neuronal development, the NKCC1 transporter sets the Cl equilibrium potential above the resting membrane potential of neurons.[119] As a result, inhibitory transmitters such as GABA and glycine produce depolarizations that early during development are sufficient to excite neurons.[28] These GABA-driven giant depolarizing potentials are part of early spontaneous depolarization waves in most neuronal structures.[1] Later in life (in humans, likely during the last trimester of embryonic development[83]), the NKCC1 transporter is replaced by the KCC2 transporter, which extrudes Cl from cells and sets the reversal potential of Cl to values below the resting membrane potential, probably dependent on certain trophic factors.[82] Even then, however, the direction of transport is regulated by the extracellular potassium concentration, and it may reverse

transport direction at about 5.5 mM, resulting in a depolarizing Cl equilibrium potential.[76]

Ion Channels Determining Resting Membrane Potentials

The K channels that most strongly contribute to generation of resting membrane potentials are likely two-pore domain potassium channels consisting of four transmembrane loops with two pores.[57] The K$_{2P}$ channels are encoded by *KCNK* genes, with 11 members so far of the family expressed in the brain. These channels can be influenced by stretch, protons, oxygen tension, and lipids (e.g., arachidonic acid, anadamides), but also by volatile anesthetics and drugs such as riluzole, quinine, quinidine, and bupivacaine, as well as barium at concentrations of 1 to 2 mM.[92] K$_{2P}$ channels are outwardly rectifying and are likely a major route by which potassium is released from cells when they depolarize.

The resting membrane potential is also influenced by potassium inward rectifying (Kir) channels. Seven families of these channels are encoded by *KCNJ* genes.[90] These consist usually of four subunits with two transmembrane segments. These channels rectify because Mg and polyamines block the outflow of potassium through them. Kir channels frequently increase conductance when K accumulates outside the cells. Strongly rectifying Kir 3 family members are activated by G proteins through Î²Î³ subunits and weakly rectifying Kir 6 channels by the ratio of ATP to adenosine diphosphate (ADP). Kir 2 channels are expressed apart from neurons on muscle cells and are involved in vasodilation when K accumulates outside smooth muscle cells.[29] Kir 4.1 channels (perhaps together with Kir 5.1) form the astrocytic K channels involved in spatial K buffering.[74] These channels are very sensitive to Ba in low concentrations. This is in contrast to Kir 7 family members, which are only blocked by Ba at high concentration of about 100 ÂµM. Studies on weaver mice suffering from epilepsy[75] have clarified that mutations in the selectivity filter in the pore-forming loop lead to permeability also for sodium ions and resulting depolarization when Kir 3.3 channels are activated by G proteins.

The ion channels that confer Na and Ca permeability to the membrane at resting membrane potential are not well understood. Some transient receptor potential (TRP) channels may be involved.[30,115] These are rather unselective cation channels with little rectification, which are thought to be involved in receptor potential generation. However, some of them are widely distributed throughout the brain. Thus, all TRPC member channels are expressed in the brain. They are usually activated by the Gq type of G proteins, diacylglycerol (DAG), and also neurotrophic factors. TRPV1â€“4 channels are expressed not only in peripheral, but also in many central neurons. TRPM2â€“4 channels are also expressed in brain and are modulated by arachidonic acid, redox state, and cytokines.

Ion channels that likely also influence membrane resting potential are the cyclic nucleotideâ€“regulated ion channels.[69] They are rather unselective cation channels permeable for both sodium and potassium. They play an important role in phototransduction, but many of them are also expressed in central neurons. They are regulated by intracellular nucleotides such as guanosine 3â€²,5â€²-cyclic monophosphate (cGMP) or cyclic adenosine 3â€²,5â€²-monophosphate (cAMP) and show little voltage dependence. This is in contrast to the hyperpolarization-activated, cyclic nucleotide-gated (HCN) channels, which are also relatively unselective cation channels. These ion channels are activated by hyperpolarization and shift the membrane potential back toward resting membrane potential. The activation curves for these ion channels are regulated by cAMP and cGMP. There are four subunits of these ion channels, all of which are expressed in the brain. They are frequently involved in membrane potential oscillations and are also important for rhythmogenesis in thalamic neurons and other neurons displaying membrane potential oscillations. Cells that express these channels often show resonance properties: This implies that neurons become especially sensitive to specific frequencies of synaptic input usually in the Î¸ and Î± frequency ranges. Upregulation of such channels may be involved in homeostatic plasticity but also following hyperthermia-induced convulsions.[26]

Which chloride channels are contributing to resting membrane potential is unclear. Two calcium-dependent chloride channels have been cloned from rat brain, but their functional role is unclear. Whether-volume activated chloride channels are expressed in neurons is unclear, but such channels could be involved in osmoregulation of astrocytes.

Voltage-Gated Ionic Channels

These channels determine the excitability of neurons, the different firing modes, the integrating properties of dendrites, and the mechanisms that lead to transmitter release from presynaptic terminals. Except for voltage-dependent chloride channels, most voltage-gated ion channels belong to one superfamily.[160] They all build on a pore-forming unit contained in the Î± subunits. Voltage-regulated Na and Ca channels consist of four homologous motifs with six transmembrane Î± helices termed S1 to S6 with a membrane reentrant loop between S5 and S6. The voltage-gated potassium channels consist of four Î± subunits, which combine to form a voltage-regulated potassium channel. As in voltage-gated Na and Ca channels, the ion-conducting pore and selectivity filter are formed by the S5 and S6 segments and the reentrant pore loop between them. Four subunits are also used to form cyclic nucleotideâ€“gated (CNG), HCN, and TRP channels. Heteromeric assembly of different subunits, combinations with different auxiliary subunits, RNA editing, and splicing confer very different properties to these channels.

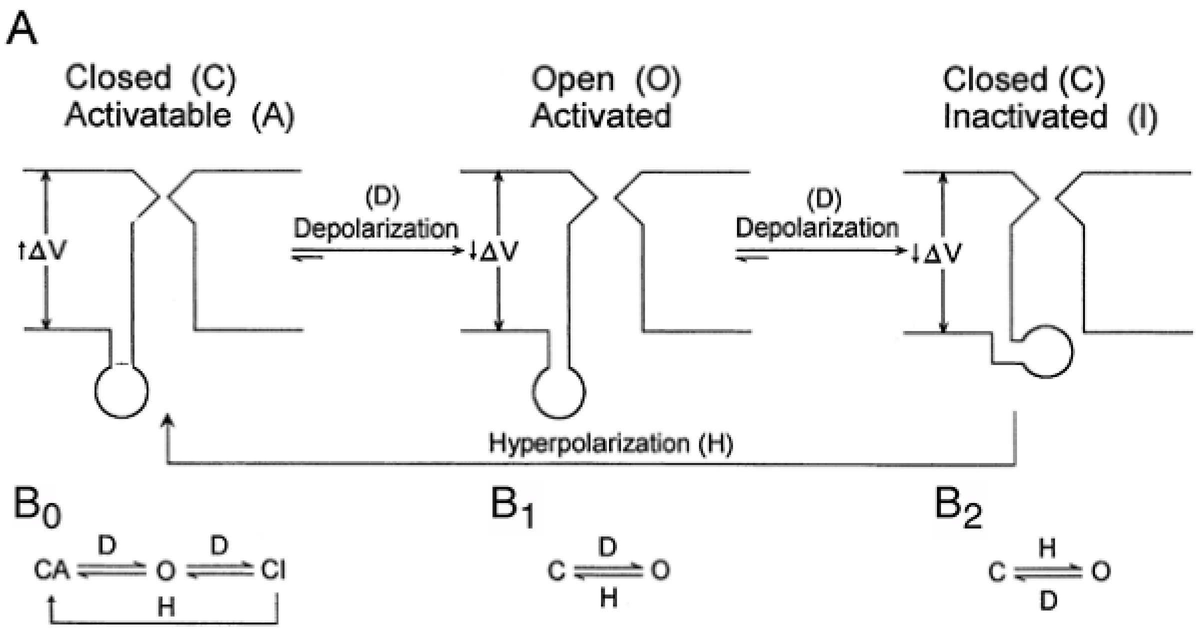

FIGURE 2. Reaction schemes of voltage-gated channels. **A:** Principle of action of transient Na^+ or K^+ channels.

At rest, the channel is closed by the position of a gate in the outer mouth of the channel (closed, activatable). On depolarization, the channel proteins change their conformation, permitting passage of ions. The conformation change is controlled by a voltage sensor that measures the potential difference across the neuronal membrane. On further depolarization, an inner, ball-like structure moves into the inner mouth of the channel, obstructing the passage of ions (closed, inactivated). Hyperpolarization is required to change the conformation from the inactivated state to the activatable state. **B0, B1, B2:** Summary of typical reaction schemes of voltage-operated channels. C, closed; CA, closed activatable; CI, closed inactivatable; D, depolarization; H, hyperpolarization; O, open.

Voltage-gated ionic channels are thus membrane-spanning proteins that form a pore; the opening and often also the closing of the pore are regulated by the transmembrane voltage gradient. The voltage sensor is contained in the S1-to-S4 segment of the Î± subunits, forming the channel, which is absent in Kir and K_{2P} channels. Voltage-gated ionic channels usually have auxiliary subunits.[160] The voltage-gated sodium channels possess only four Î² subunits, which modulate channel activation and regulate membrane surface expression. Therefore not only mutations in Î± subunits but also those in Î² subunits can lead to epilepsy. Voltage-gated Ca channels are regulated by Î², Î³, and Î±2Î´ subunits. The four Î² subunits are all intracellular proteins that regulate channel gating and surface expression. Mutations in Î² subunits can thus also lead to channelopathies, including epilepsy. There are eight Î³ subunits including stargazing,[102] which link the Ca channels to other transmembrane proteins, including Î±-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA)-type glutamate receptors. The Î±2Î´ subunits are binding sites for anticonvulsants such as pregabalin and gabapentin.[39]

Voltage-regulated K channels have different types of auxiliary subunits.[93] K_V1 channels are associated with Î²1â€“3 subunits; K_V4 channels with Kchip 1â€“4; and K_V3, 4, 7, 10, and 11 channels with the five members of mink-like subunits.[160] The Î² subunits in the K_V1 channel family influence channel closing. Kchips belong to the superfamily of Ca sensor proteins and regulate channel kinetics and channel membrane surface expression. The mink-like subunits are also important regulators

of channel dynamics. Finally, the K_V2 family is modulated by K_V5, 6, 8, and 9 modifier/silencer subunits.

The gating of these ionic channels occurs preferentially at a defined membrane potential at which the probability of channel opening increases strongly. However, because the sensor for the gating is located within the membrane, it recognizes the voltage difference between the inside and outside leaflets of the membrane. On both sides of the membrane, there are negative surface charges that attract preferentially Ca, Mg, and H ions. Consequently, changes in H^+, Ca^{2+}, and Mg^{2+} and proton concentration can influence the gating properties.[66] Occasionally, these ions can also modify permeability properties. Well-known examples are cation channels, which can become activated during rapid decreases in Ca^{2+} concentration.[63,156]

In addition, ionic channels can be influenced by intracellular metabolism. For example, certain K channels are rather sensitive to the ATP content of a cell. At physiologic ATP levels, these channels are closed, whereas depletion of ATP leads to opening of K channels and consequently to hyperpolarization. Block of such channels can induce seizures.[7] Some ionic channels possess redox sites such as voltage-gated K channels and K_{2P} channels, which react to the formation of free oxygen radicals or are sensitive to arachidonic acid and its derivatives.[103] Most ionic channels change their properties on phosphorylation, and many protein kinases and some phosphatases can therefore affect the opening and closing of voltage-gated channels. In some cases, such modulations give the cells distinctly different discharge modes, whereas in others, there is a continuum of modifications in the reactivity of a given neuron. In addition, the intracellular level of Ca^{2+} can cause activation and occasionally inactivation of ionic channels.

Based on permeability of the pore, the resulting transmembrane currents are differentiated as Na^+, K^+, Ca^{2+}, and Cl^- currents. Proton currents have also been described and are a prerequisite for formation of radical oxygen species released from activated microglial cells.[43] Within these different species of ionic currents, a distinction is made between persistent and transient currents. Most of the persistent channels open on depolarization and some on hyperpolarization of the membrane potential with respect to the resting membrane potential. Such channels behave according to the reaction schemes illustrated in FIGURE 2B. When persistent ionic currents are activated, the channels open and close, with an increased probability of being open for the whole period of time that the membrane potential is above the threshold for channel opening.

Transient currents show a time-dependent variation of probability of being open when the membrane potential is above that required for channel gating. Their reaction scheme can be formally described as in FIGURE 2A. In these channels, the open probability strongly decreases with time. This time-dependent inactivation is often mediated by a ball formed by the intracellular end of transmembrane proteins. These balls move into the inner mouth of the channels, thereby preventing further passage of ions. This type of inactivation is designated chain-and-ball inactivation and resides at the N terminal of the channel protein.[66] By contrast, there is also a C-type inactivation, which depends on conformational changes in the channel itself. Inactivation of either type makes the channel temporarily refractory and induces a time-dependent short-term memory into channel properties. The conditions and time it takes to remove inactivation are usually studied in paired pulse experiments. Removal of inactivation in sodium channels is typically delayed when anticonvulsants such as carbamazepine or phenytoin are applied.[118] Besides the kinetics of an ion channel, the steady-state behavior also is used to describe the channel properties.[68] Steady-state inactivation curves are determined by current measurements with pulses evoked from different membrane potentials to a potential at which the current is maximal. Conductances are then derived from Ohm's law by taking into account the driving force for the ion species and the measured current amplitude. Normalized conductance curves are then plotted and give the percentage of ion channels that can be maximally opened as a function of resting membrane potential. The steady-state activation curve describes the relative conductance as a function of the membrane potential achieved during a voltage step. A leftward shift of the steady-state

inactivation curve then indicates that at a given membrane potential a fewer channels are available for current generation. Such leftward shifts of steady-state inactivation curves contribute to effects of anesthetics and anticonvulsants. A leftward shift of the steady-state activation curve indicates that more channels can contribute to an ionic current and for the sodium channel would indicate a lower threshold for the generation of action potentials.

Thus, voltage-gated ionic channels can frequently be modulated by drugs. These often affect membrane fluidity, changing the energy barriers that a channel protein must overcome to change its conformation from a closed to an open state. Moreover, drugs can bind to channel proteins, stabilizing a given conformation and changing its threshold for activation. Especially interesting are drugs that are use dependent, that is, they bind to a channel protein only when it is activated. Such drugs often enter the open mouth of an ionic channel and then move very slowly through the channel, preventing further current flow. In some cases, they affect the transition from an inactivated to an activatable state and thereby also produce a use-dependent effect. On the other hand, some drugs and toxins impede the inactivation process, changing a transient into a persistent current.

Voltage-Gated Sodium Currents

The fast transient Na^+ currents are mainly involved in the generation of action potentials, first described by Hodgkin and Huxley.[67] The rapid upstroke of the action potential is the result of a voltage-dependent increase in membrane Na^+ conductance. The threshold for action potential generation is defined as the membrane potential at which Na (and Ca) conductances equal those of K (and Cl) conductances. This implies that Na channels must also be active in the subthreshold range. In most central neurons, the threshold of activation for the fast Na^+ current is about -60 mV.[23] The currentâ€“voltage relationship of this current is characteristically a U-shaped curve, for which the maximum of current amplitude is usually reached at about -20 mV. The fast transient Na^+ currents inactivate rapidly. The inactivation behavior of the current has been described with time constants of 2 to 4 msec in most neurons studied. The Na channel can only reactivate when inactivation is removed. This is a voltage-dependent and time-dependent process often involving two time constants.[118] Rapid removal of inactivation is typical for interneurons, which therefore can fire in higher frequencies than most glutamatergic neurons. By means of electrophysiologic and biochemical techniques, several toxins have been identified as blocking Na^+ channels. After it was found that tetrodotoxin (TTX) acts in nanomolar concentrations as a selective blocker of most neuronal Na^+ channels, it became a useful chemical tool for studying properties of these channels in more detail.[80] In addition to TTX-sensitive channels, TTX-resistant Na^+ channels have been detected.[159] Acutely isolated neurons from the medial entorhinal cortex of the rat exhibit a TTX-resistant Na^+ current in addition to the TTX-sensitive Na^+ current.[154] Like TTX, saxitoxin and Âµ-conotoxin are able to block Na^+ conductance by either occluding the channels or causing conformational changes.[31] Moreover, a number of lipid-soluble alkaloid toxins, including batrachotoxin, veratridine, aconitine, and grayanotoxin, can shift the voltage dependence of activation in a hyperpolarizing direction and prevent current inactivation, resulting in persistent channel activation at normal membrane potentials.[24] The voltage dependence of Na^+ currents is also changed by the application of Î²-scorpion toxins, which cause enhanced activation. Brevetoxins and ciguatoxins can cause repetitive firing of nerve cells by shifting the activation curve of Na^+ currents to more negative potentials.[24] Toxins such as veratridine and brachatoxin can therefore readily induce convulsant activity.[107]

Sodium currents are encoded by nine different Î± subunits, which combine with four different Î² subunits. Na_V1.1â€“1.3, 1.5, and 1.6 are expressed in central neurons. Na_V1.1 (*SCN1A*) channels associate with Î²1 to Î²4 subunits.[24] Na_V1.1 channels are highly expressed in hippocampal interneurons, and deletion of this channel leads to reduced firing of interneurons in the hippocampus, which explains some of the hereditary epilepsies associated with mutations in these channels such as generalized epilepsy with febrile seizures plus (GEFS+) and myoclonic epilepsy. The Î²4 subunit in this and other channels accelerates removal of inactivation, permitting high-frequency generation of action potentials, as is typical for many interneurons. Na_V1.2 (*SCN2A*) can also interact with all Î² subunits. It is highly expressed in axons of central neurons. Mutations in these channels have also been linked to epilepsy.[143] Na_V1.3 channels are highly expressed during development but are also expressed on somata in adult brain cells. These channels are upregulated after nerve injury and, due to rapid removal of inactivation, can be involved in high-frequency axonal discharges. This implies that the action potential frequency in somatic recordings may not necessarily be the same in axon terminals. They interact with Î²1 and Î²3 subunits. Na_V1.5 channels (*SCN5A*) are insensitive to TTX and, besides heart muscle cells, are also expressed on subgroups of central neurons. They can interact with all four Î² subunits. Finally, Na_V1.6 (*SCN8A*) channels are expressed in central neurons and mostly on the somatodendritic region of output cells in the cerebral cortex, hippocampus, and cerebellum. It is thought that these ion channels contribute at least partially to persistent sodium channels.

The Î² subunit 1 occurs with different mutations, leading to GEFS+ and also to temporal lobe epilepsy (TLE).[73] Persistent noninactivating Na^+ current has been found in a number of neurons.[4,6,48] Its activation threshold was determined at potentials more negative than that of the fast transient Na^+ current, at about -70 mV. Because of activation near the resting membrane potential of neurons and the loss of inactivation, this current can contribute to subthreshold membrane potential oscillations and resonance, playing an important role in the genesis of the Î¸ rhythm in these cells.[4] It is likely that also some metabolites can remove inactivation and thereby permit generation of persistent sodium currents. Another possibility is that persistent sodium channels are due to window currents. When the steady-state activation and inactivation curves are considered, they often overlap and generate a voltage range in which a portion of these channels is frequently open.

Voltage-Gated Calcium Currents

Calcium currents play a major role in neuronal excitability, directly by their contribution to membrane depolarization and indirectly through the elevation of the intracellular concentration of free Ca^{2+}. Voltage-dependent Ca^{2+} conductances in neurons contribute to the generation of dendritic spikes, slow somatic depolarizations, and related burst discharges.[22] Influx of Ca^{2+} through voltage-gated Ca^{2+} channels can activate Ca^{2+}-dependent K^+ channels and regulate many intracellular Ca^{2+}-dependent processes. Calcium channels are also responsible for rapid delivery of Ca^{2+} to trigger transmitter release.[46,150]

Voltage-gated Ca^{2+} channels consist of Î±1 subunits with which Î² subunits, Î±2Î´, and Î³ subunits can be associated.[25] In the classic studies of sensory neurons by Carbone and Lux,[19] they showed that voltage-gated Ca^{2+} channels could be differentiated into two major categories: (a) low-voltage-activated (LVA) and (b) high-voltage-activated (HVA)

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channel types. The Î±1 subunits of Ca channels can be differentiated into three families: (a) Ca$_V$1, (b) Ca$_V$2, and (c) Ca$_V$3 members.[25] The Ca$_V$1 family shares high threshold of activation, no voltage-dependent inactivation, and sensitivity to dihydropyridines, and these are often referred to as L-type Ca channels. In the central nervous system (CNS), only Ca V 1.3 (Î±1c, *CACNA1C*) channels are expressed on somata and dendrites of neurons, with little effect on regulation of transmitter release. The Ca$_V$2 subfamily (Ca$_V$2.1â€“2.3) has three members, which are all insensitive to dihydropyridines. Ca$_V$2.1 (Î±1A, *CACNA1A*, or P/Q-type) channels are involved in transmitter release but are also found in many neurons expressed on dendrites. They are sensitive to Ï‰-agatoxin IVa. The Ca$_V$2.2 (Î±1B, *CACNA1B*, or N type) channels are also expressed presynaptically and on dendrites. These channels show time-dependent inactivation and are blocked by Ï‰-conotoxin GVIA. Like Ca$_V$1 channel members, these two channels require high levels of depolarization to become activated. Ca$_V$ 2.3 channels (Î±1E, *CACNA1E*, or R-type channels) require less strong depolarization for activation, are expressed on somata and dendrites, and are sensitive to the peptide SNX-482. They can be involved in epilepsy.[144] Low-voltage-activated channels contain Ca$_V$3.1 to 3.3 members (Î±1G, H, I; *CACNA1G*, H, I), are rather sensitive to low concentrations of Ni, and form the T-type Ca channels. In most neurons, these channels activate at potentials positive to -70 mV. Inactivation of the T-type Ca^{2+} channels develops monoexponentially within tens of milliseconds and shows a strict dependence on voltage. Unlike in L-type Ca channels, the inactivation kinetics is independent of Ca^{2+} influx through the channel.[20,21] No specific high-affinity antagonist has so far been identified for the T-type Ca^{2+} current, although antiepileptic drugs used to treat petit mal, such as ethosuximide and dimethadione, reduce T-type Ca^{2+} currents in thalamic neurons and dorsal root ganglion cells.[35]

The behavior of voltage-gated Ca currents is influenced by different subunits. The intracellular Î² subunit consists of four known isoforms Î²1 to Î²4 (*CACNB1*â€“*CACNB4*). Mutation in Î²4 subunits also are involved in ataxia and epilepsy in mice and humans.[18] The Î² subunits regulate current density by controlling the amount of Î±1 subunit expressed at the cell membrane. In addition to this trafficking role, the Î² subunits regulate the activation and inactivation kinetics and shift the voltage dependence for activation of the Î±1 subunit pore in the hyperpolarizing direction.

The Î±2Î´ subunits are formed from a distinct gene. The Î±2 subunit is the extracellular glycosylated subunit that interacts the most with the Î±1 subunit. The Î´ subunit has a single transmembrane region with a short intracellular portion, which serves to anchor the protein in the plasma membrane. There are four Î±2Î´ genes: *CACNA2D1* to *CACNA2D4*. Coexpression of the Î±2Î´ enhances the level of expression of the Î±1 subunit and causes an increase in current amplitude, faster activation and inactivation kinetics, and a hyperpolarizing shift in the voltage dependence of inactivation.[146] Some of these effects are observed in the absence of the Î² subunit, whereas in other cases the coexpression of Î² is required. The Î±2Î´-1 and Î±2Î´-2 subunits are the binding sites for at least two anticonvulsant drugs, gabapentin and pregabalin, which also find use in treating chronic neuropathic pain.[39]

The Î³ subunits are associated with only some of the Î±1/Î² complexes. The Î³ subunits do not affect trafficking and for the most part are not required to regulate the channel complex. There are eight genes for the Î³ subunit: *CACNG1* to *CACNG8.* The Î³1 subunits are expressed in skeletal muscle, and the Î³2 and Î³3 subunits may be associated with the P/Q- and N-type channels. Some Î³ subunits (Î³3, Î³4, and Î³8) and particularly stargazing (Î³2) associate Ca channels with AMPA-type glutamate receptors.[148,149]

Voltage-Gated Potassium Currents

Whereas voltage-gated sodium and calcium channels are formed by a distinct subgroup of proteins forming the Î± subunit, most voltage-dependent potassium channels are formed by four subunits.[60,160] The first cloned potassium channels were detected in *Drosophila* and named shaker (K$_V$1.1â€“1.8; *KCNA1â€“7*, *KCNA10*), followed by shab (K$_V$2.1 and 2.2; *KCNB1.2*), shaw (K$_V$3.1â€“3.4; *KCNC1â€“4*), and shal (K$_V$4.1â€“4.3; *KCND1â€“*3) related subunits. The M-type potassium channels modulated by muscarine were originally detected in sympathetic ganglia and form the K$_V$7 family with five members (*KCNQ1â€“5*). The identification of the voltage-dependent potassium channels forming the K$_V$10 to 12 families (eag, erg, and elk; *KCNH1â€“8*) was based on the identification of the ether-a-go-go channel in *Drosophila*. In the different families, the same subunits can form homomeric potassium channels, or different subunits can combine to form heteromeric channels. Heteromeric channel formation is well documented for K_V1, K_V7, and K_V10 families but likely also occurs in other families of voltage-gated potassium channels. The combination of subunits in heteromeric channels frequently confers different properties to the ion channels than those expected from the characteristics of homomeric potassium channels in a given family. The diversity of potassium channels is further increased by silencer and modifier subunits belonging to the K_V5, 6, 8, and 9 families. These subunits do not form conducting channels but can combine with members of the K_V2 family to form functional channels with different properties than those observed in homomeric K channels from this family. As with Na and Ca channels, Î² subunits have been identified that can combine with members of the K_V1 and K_V2 families to provide for altered channel properties but also likely are involved in channel trafficking and surface expression. Kchip1 can associate with K_V4 family members and modify their properties. Calmodulin interacts with K_V10 members and minK proteins with Kv11 family members. In addition, alternative splicing confers different properties to K channels.

Thus a wide variety of K^+ currents exists in excitable cells, and potassium channels represent the most diverse type of voltage-gated ion channels known, comparable only to $GABA_A$ receptors. Apart from their genetic identity, potassium currents can be distinguished by their voltage sensitivity, kinetics of activation and inactivation, single-channel behavior, and pharmacologic modulation. With respect to these properties, macroscopic voltage-gated K^+ currents found in neurons can be subdivided into two types: (a) outward delayed rectifying K^+ currents and (b) (fast) transient K^+ currents.

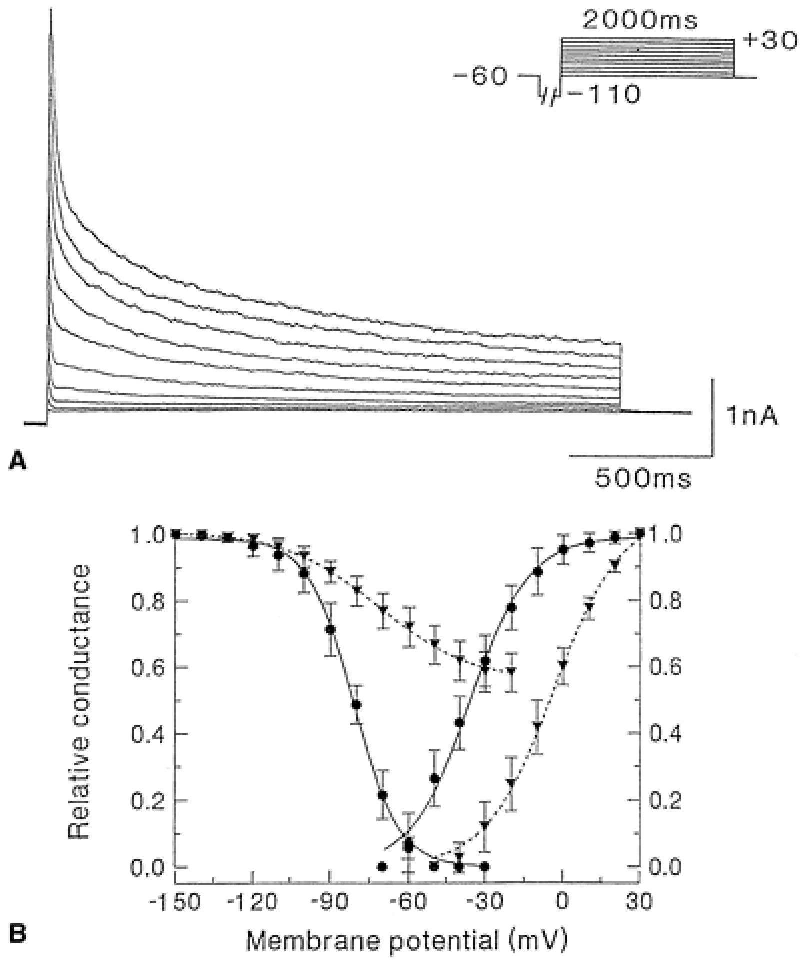

FIGURE 3. Outward K^+ currents activated by depolarizing voltage changes preceded by a hyperpolarizing prepulse. Currents were recorded in an acutely isolated entorhinal cortex cell. **A:** Currents were evoked by application of depolarizing voltage commands from the holding potential of -60 mV to potentials

between -60 and -30 mV for 200 msec following a hyperpolarizing prepulse to -110 mV for 1,000 msec. **B:** Steady-state activation and inactivation curves for isolated fast transient A-type currents (*closed lines*) and delayed rectifying currents (*dotted lines*). Overlap of steady-state inactivation and activation curves indicates the voltage range in which channels open and close permanently. Note that around resting membrane potentials A-type currents can contribute to the stabilization of membrane potential.

Most of the delayed rectifying K^+ currents (I_K) have a relatively high activation threshold. The currents activate at potentials more positive than -40 mV.[47,68,132] Therefore, I_K seems to activate only during action potentials, not in the subthreshold voltage range. Hence, I_K contributes to spike repolarization.[139] In addition, I_K may be partly responsible for spike broadening during repetitive firing, due to slow accumulating current inactivation. In many neuronal preparations, time constants of 2 to 5 seconds have been determined to describe the inactivation behavior of this current (FIGURE 3).[8,105] Pharmacologically, these currents are sensitive to tetraethylammonium (TEA). Delayed rectifier currents can be encoded by most members of the K_V1 family, which are all expressed in the central nervous system except for $K_V1.7$. Except for $K_V1.4$, they all encode for delayed rectifier-like ion channels. Members of the $K_V1.1$ and 1.2 families share a relatively high sensitivity to kaliotoxin and to dendrotoxin. In addition, $K_V1.6$ is sensitive to dendrodotoxin. Delayed rectifier channels can also be encoded by K_V2 family members, which are modulated by a number of accessory subunits. Their pharmacology is relatively sparse. They are sensitive to TEA and show only low sensitivity to 4-aminopyridine (4-AP). It is interesting that $K_V2.2$ is sensitive to phencyclidines, which are generally known to cause open channel block in *N*-methyl-D-aspartic acid (NMDA) receptors, and otherwise are used for studies on NMDA receptors.[49] Finally, members of the K_V3 and K_V4 families can encode delayed rectifier currents. K_V3 family members encoding delayed rectifier currents are rather sensitive for 4-AP, whereas K_V4 family members show low sensitivity. The K_V3 family members are all expressed in central neurons except for $K_V3.3$. It is interesting that $K_V3.1$ and 3.2 encode for delayed rectifier currents in many interneurons. They are sensitive to relatively low levels of TEA and 4-AP. On one hand, these drugs prolong action potentials in interneurons, but on the other hand, they strongly reduce firing frequency and thereby GABA release. It is believed that these effects contribute to the convulsivogenic effects of TEA and 4-AP in low concentrations.

Fast transient A-type currents (I_A) markedly differ from I_K in their kinetics; they show a fast activation following depolarization and inactivate rapidly, within tens of milliseconds.[47,86,104] Their threshold of activation is at about -45 to -60 mV, that is, at a more hyperpolarized level of membrane potential than that of I_K[71] and below the threshold for action potential generation. Moreover, at membrane potentials more positive than -50 to -30 mV, A-type currents cannot be activated because they show a strong steady-state inactivation behavior. In most neurons, half-maximal inactivation for A currents was determined at potentials between -85 and -70 mV.[106] The pharmacologic sensitivity of I_A is also different from that of I_K. The A-type current is selectively blocked by 4-AP in the micromolar (K_V1 and K_V3 family members) to millimolar concentration range (K_V4 family members), but it is relatively insensitive to TEA. In hippocampal neurons, the I_A can also be blocked by low concentrations of the snake toxin dendrotoxin.[100]

It has been shown that I_A plays an important role in determining the onset of discharge in response to a depolarizing stimulus and in the regulation of repetitive firing.[32,104] In addition, I_A seems to be involved in repolarization of the action potential because the spike is broadened when I_A is blocked by 4-AP.[141]

In a few reports, a K^+ conductance (I_D) has been characterized that activates rapidly within milliseconds, like I_A, but inactivates slowly over several seconds.[59,140] In contrast I_K, this current is insensitive to TEA, but it is very sensitive to 4-AP and dendrotoxin. These potassium conductances seem to be responsible for a longer delay in the onset of firing in response to long-lasting depolarizing stimuli. Because I_D activates rapidly on depolarization, it tends to keep the cell from depolarizing further. Only as I_D slowly inactivates does the cell reach threshold and fire after delay, which can have a duration of up to about 15 seconds.[141] The rapid activation of I_D suggests that it may also participate in spike repolarization.

In the K_V1 family (*KCNA1â€"7*, *KCNA10*) only $K_V1.4$ (*KCNA4*) encodes for an A-type current. $K_V1.4$ is highly expressed on mossy fibers and axons, and it is believed that K_V1.4 alone or in combination with K_V1.2 controls presynaptic transmitter release in many central neurons. Indeed, 4-AP in relatively low concentrations increases presynaptic Ca uptake in Schaffer collaterals and mossy fiber terminals. For pharmacologic studies of effects of Ca channel blockers, it is noteworthy that many members of the K_V1 family are also moderately sensitive to L-type Ca channel blockers. One family member (K_V1.2) is also sensitive to picrotoxin. The A currents can also be encoded by K_V3 and K_V4 family members.

Whereas K_V3.1 and 3.2 genes (*KCNC1*, *KCNC2*) encode for delayed rectifier currents, that for 3.4 encodes for transient potassium currents with a relatively high sensitivity to TEA and for A-type potassium currents in hippocampal granule cells. The genes for the K_V4 channel family members (*KCND1â€“3*) all encode for A-type potassium currents with low sensitivity to 4-AP. They seem to be expressed in the somatodendritic region of pyramidal cells and regulate backpropagation of action potentials and modulate excitatory input to dendrites.[77] The expression of these channels is modulated by Kchip subunits, which also influence their kinetics.

The M-type current (I_M) is encoded by *KCNQ* genes and belongs to the K_V7 family. I_M is a small, subthreshold, voltage-dependent outward K^+ current that is activated at more hyperpolarized potentials (positive to -60 mV) than the delayed rectifying current. The current activates and deactivates slowly and does not inactivate.[15] Thus, as the only K^+ current that both activates below the spike threshold and does not inactivate, I_M can play a unique role in the control of cell excitability. In addition, I_M contributes to the resting membrane potential in many neurons.[34,38,96] It also seems to contribute to the early spike-frequency adaptation and is involved in generation of the medium afterhyperpolarization, an up-to-100-msec undershoot that follows an action potential or a spike train.[141] The M current can be completely suppressed by muscarinic agonists and by specific blockers such as XE-991 or linopiridine. It is encoded by family members of the K_V7 family, also named KCNQ channels. It is of interest that heteromultimers of K_V7.2 and 7.3 are usually expressed in central neurons and their axons. In addition, K_V7.5 also is expressed in central neurons. The expression of these channels is particularly high during development, when the expression of K_V1, 2, and 3 members is still low. This implies that K_V7 deletions or mutations in mice are often lethal. Recently a transgenic mouse has been made in which the expression of KCNQ channels can be downregulated at desired time points. These animals all develop epilepsy.[112] This channel family has been gaining in interest because relatively specific agonists such as retigabine are available that are powerful anticonvulsant drugs.[40,122] K_V7 channels are strongly involved in rhythmogenesis and in resonance phenomena.[112]

Based on the *Drosophila* ether-a-go-go channels, three families of voltage-gated potassium channel families have been detected, most of which are also expressed in the brain.[16,60] These belong to the K_V10 (*KCNH1* and *KCNH5*; *EAG1* and *EAG2*), K_V11 (*KCNH2*, *KCNH5*, and *KCNH*7; *erg1* to *erg3*), and K_V12 (*KCNH8*, *KCNH3*, and *KCNH4*; *elk3*, *elk2*, and *elk1*) families. Most of the family members are expressed in brain except for perhaps K_V12.3. Some of the family members are activated at very low membrane potentials and therefore can contribute to resting membrane potential. Their activation can be very slow. K_V10.1 is a potassium channel that is also permeable for calcium ions and is blocked by calcium/calmodulin.[17] K_V10.2 is also blocked by intracellular calcium. It activates at â€“100 mV. The K_V10 family members are blocked by imipramine and by astemizole.[52] The K_V11 members can form heteromeric channels. Because of the involvement of one of their members in the long-QT syndrome in heart disease, there is a wealth of pharmacologic agents available with which it should be possible to learn more about their functional role in central neurons. K_V12 channels activate at hyperpolarized membrane potentials with rather slow kinetics and are insensitive to 4-AP and TEA but sensitive to barium.

Calcium- and Sodium-Activated Potassium Channels

With respect to their kinetic properties and their sensitivity to various pharmacologic agents, at least three different types of Ca^{2+}-activated K^+ currents have been distinguished in neurons of the central nervous system. A Ca^{2+}-activated K^+ current of large single-channel conductance (150 to 300 pS) has been detected in most neurons studied.[91] This current is also voltage dependent and contributes to spike repolarization and fast afterhyperpolarization. The channel is constituted by a K_{Ca}1.1 Î± subunit encoded by the *KCNMA1* gene. These channels associate in the brain with one of three Î² subunits, Î²2 to Î²4. The Î²2- and Î²3-containing $K_{Ca}1.1$ channels are sensitive to charybotoxin and iberotoxin, and the Î²4-containing channels are not but are potentiated by 17Î²-estradiol. Î²2 and Î²3 subunits confer inactivation to these channels. It is of interest that a number of other activators exist for these channels that may have potentially anticonvulsant effects. These include drugs such as NS 1608, NS 1619, and BMS 204352.[153] Mutations in the Î²3 subunit have recently been associated with susceptibility to idiopathic epilepsies.

The second class of Ca-activated K currents belong to the $K_{Ca}2$ family (*KCNN1*â€“*KCNN3*), which has three members.[153] These SK channels are exclusively regulated by intracellular Ca and are not voltage dependent. Voltage-clamp studies have suggested that they encode medium-duration Ca^{2+}-activated K^+ currents with a single-channel conductance of 20 to 60 pS, which can contribute to the medium afterhyperpolarizations during spike trains and to afterhyperpolarizations that last for about 200 msec.[111,138] These channels are blocked by bicucullin methiodide and may contribute to the epileptogenic action of bicuculline. It is interesting that the SK-type channels can be activated by drugs such as EBIO, NS 309, and riluzole.[110] The $K_{Ca}3.1$ channel (*KCNN4*) is not expressed on neurons but is expressed strongly on microglial cells and may contribute to neuronal damage during status epilepticus.[125] Blocking these channels prevents activation of inducible nitric oxide synthase (iNOS)- and nitric oxide (NO)-dependent neuronal damage.[81] These channels are also activated by methylxanthines such as caffeine and theophylline.

A prominent Ca-dependent K current (I_{AHP}) accounts for the late afterhyperpolarizations that contribute to afterhyperpolarization following seizures. These currents are blocked by cAMP and consequently by norepinephrine through Î² receptors, dopamine through D1-like receptors, and through other agents that upregulate cAMP.[62] These currents are resistant to TEA and also to other K_{Ca} channel-blocking toxins. Their molecular nature has not been identified.

Closely related to Ca-activated potassium channels are Na-dependent K channels named K_{Ca} 4.1 (*SLACK*, *SLOW2.2*, *KCNT1*) and K_{Ca} 4.2 (*SLICK*, *SLOW2.1*, *KCNT2*). These channels are already active at physiologic intracellular sodium concentration and Cl concentrations and can form heteromultimers in which the $K_{Ca}4.2$ subunit is dominant. These ion channels are regulated by $G_{Î±q}$-type receptors, which activate protein kinase C. This is of interest because mGluR1 and muscarinic M1 receptors use this pathway. The two subunits are differently regulated. Whereas $K_{Ca}4.2$ is suppressed by muscarinic agonists, $K_{Ca}4.1$-mediated currents are increased. Therefore these ion channels may contribute to the differential effects of muscarinic and mGluR receptorâ€“mediated effects in different neurons. The sodium-dependent K conductances are only blocked by very high concentration of Ba and quinidine.[153]

A further, not yet genetically identified ionic channel underlies cation currents activated by elevation in intracellular Ca concentration.[109] These so-called CAN channels are sensitive to flufenamic acid, which in hippocampal neurons was shown to affect depolarizing afterpotentials and paroxysmal depolarizations during seizure-like events.[124] The molecular identity of these ionic channels is not known, but it is likely that TRP channels are involved in these currents.

Finally, a cation current can be activated by lowering the extracellular Ca concentration, which may contribute to epileptogenesis because sometimes the extracellular Ca concentration drops to very low levels during seizure-like events.[63,64,157]

Bursting Behavior

Spontaneous generation of seizures seems frequently to depend on the presence of burster cells. These are neurons that, when excited, produce an all-or-none response, consisting of a depolarizing envelope that triggers a burst of action potentials. Such burster neurons have been described in the neocortex,[33] hippocampal areas CA3 and CA1,[155] and the subiculum.[11] The area most abundantly equipped with burster neurons is the subiculum, where about 50% of pyramidal cells have bursting properties. In the neocortex, the hippocampus, and the subiculum, the bursting behavior is caused by a persisting Na^+ current, whereas in CA1 pyramidal cells of epileptic animals, the bursting behavior seems to depend on T-type inward Ca^{2+} currents.[158] The notion that persistent Ca^{2+} currents are involved in ictogenesis is supported by the observation that Ca^{2+}-channel blockers possess anticonvulsant properties. In the concentration ranges in which these agents have anticonvulsant effects, however, they may no longer be specific for Ca^{2+} channels.[135] On the other hand, many anticonvulsant drugs

not only affect the kinetics of fast Na channels, but also block persistent Na channels and some Ca channels.[120]

Membrane Potential Oscillations and Resonance Behavior

Voltage-gated currents are also involved in the synchronization of neurons, which is necessary for the generation of epilepsy. The finding that drugs that suppress primarily generalized nonconvulsive seizures, such as absences, block T-type Ca^{2+} currents has made this very clear.[34] This phenomenon is discussed in Chapter 31.

A second current apparently involved in synchronization is I_Q (I_H, I_F), which is encoded by *HCN* genes. This current is activated on hyperpolarization and deactivates very slowly. Therefore, a depolarizing sag develops during hyperpolarization that depolarizes a cell toward resting potential and causes an afterdepolarization following a hyperpolarizing event.[108] Under appropriate conditions, such currents cause bursting in subicular neurons and also in CA1 and CA3 neurons. These currents, together with M -type potassium currents and persistent sodium currents, are frequently involved in membrane potential oscillations, which occur already at rest or close to action potential threshold.[70,72,112] These membrane potential oscillations have been observed in neocortical neurons and are readily induced in perirhinal and entorhinal cortex cells.[128] They also occur in certain interneurons.[113] These types of ionic currents also induce resonance behavior.[45,129] In cells that express these currents, the input resistance changes as a function of frequency of current input to the neurons. Resonant cells frequently have the largest impedance at frequencies between 4 and 15 Hz. This implies that these cells integrate synaptic input more effectively when it occurs at resonance frequencies. Such mechanisms are important in determining oscillatory activity preceding seizures, contribute to Î¸ and Î³ activity, and are also involved in Î± rhythm activity. It is expected that such mechanisms are altered in epilepsy.

Voltage-Gated Currents and Epilepsy

There is considerable evidence that voltage-gated currents contribute to the generation of seizure. This evidence stems from various observations. It has been shown that toxins that prolong Na^+ channel opening cause seizures.[51] Similarly, drugs that prevent activation of K^+ currents also induce seizures. These include muscarinic receptor agonists, which reduce M-type currents, certain Na-dependent K conductances and EAG channel activity, and 4-AP, which can block K^+ currents. Surprisingly, TEA, which affects many K^+ currents, is a much less potent convulsant agent than 4-AP. Because A-type currents are rapidly inactivated during depolarization, it is unlikely that they contribute much to epileptogenesis. When TEA is applied in a concentration of 2 mM, which reduces I_K in a similar way as 4-AP at a concentration of 50 to 100 ÂµM, short recurrent discharges with a frequency of 0.1 Hz are induced in entorhinal cortex and hippocampal slices, whereas 4-AP induces convulsion-like events. Because 4-AP augments presynaptic uptake of Ca^{2+} much more than TEA, it is likely that augmented transmitter release causes the seizures.[54,78] The second line of evidence comes from experiments with transgenic mice. Many of the potassium-channel-knockout animals develop epilepsy. Mutations in ion channels have also been found in inherited epilepsies in mice and rats. These studies are often also supported by studies of human inherited epilepsies in which Na channel mutations, Ca channel mutations, and K channel mutations have all been identified as causes of epilepsy.

It is of interest that epilepsies can also be accompanied by acquired channelopathies. Thus, it was shown in a number of convincing studies that bursting behavior of neurons is upregulated in different acquired epilepsies.[142] The best-studied channels in this respect are HCN channels, which are upregulated following hyperthermia-induced seizures.[27,130] Upregulation of these channels has also been seen after repetitive stimulation of a kind that induces neither long-term potentiation nor long-term depression, and it was suggested that they are involved in homeostatic plasticity.[151] Changes in expression of K currents have been described in a model of temporal lobe epilepsy in which downregulation of the A-type-encoding $K_V4.2$ channel has been described.[12] This channel is involved in limiting backpropagation of action potentials and in reducing the transfer of excitatory postsynaptic potential (EPSPs) from apical dendrites into the soma. It is interesting that in the same model upregulation of T-type Ca channels also has been described, resulting in increased bursting behavior of hippocampal neurons.[142] For acutely isolated hippocampal neurons of the CA1 region, it was shown that the amplitude of voltage-gated Ca^{2+} currents of the HVA type is increased after kindling.[88] Enhancement of Ca^{2+} currents persisted for at least 6 weeks without further tetanic stimulation. Whole-cell patch-clamp recordings of acutely dissociated granule cells from the dentate gyrus of kindled adult rats demonstrated a markedly enhanced Ca^{2+}-dependent inactivation of Ca^{2+} currents, which was correlated with lack of the cytoplasmic Ca^{2+}-binding protein calbindin-D$_{28K}$ during kindling-induced epilepsy.[87,88]

Many of the voltage-gated currents are targets for antiepileptic drugs. The effects on Na$^+$ currents of some of the antiepileptic drugs, such as phenytoin and carbamazepine, are well known.[95,120] Agents that act on presynaptic uptake of Ca^{2+},[39] or that activate K$^+$ currents, are of considerable interest. Thus, it has been shown that drugs that activate ATP-dependent K$^+$ currents, M currents, and Ca-activated K currents can have antiepileptic effects.[7,9,10,53] More recently, some interest has developed in the properties of Na$^+$ currents in epileptic tissue of patients with drug-resistant epilepsy. It may well be that transient Na$^+$ currents in the tissue of such patients have a reduced sensitivity to phenytoin and carbamazepine.[117]

Ligand-Gated Ionic Channels

Ligand-gated ionic channels open when a neurotransmitter binds to a receptor. These channels also comprise various subunits. Ligand-gated channels open fast, in the range of milliseconds, and are therefore used in fast synaptic transmission. The most important inhibitory ligands are GABA and glycine; they open a Cl$^-$- (and HCO$_3^-$-) permeable channel.[79] Depending on membrane potential and the reversal potential for Cl$^-$, this results in either depolarization or hyperpolarization. The Cl$^-$ reversal potential depends on the activity of a Cl$^-$ pump.[94] If this is inwardly directed, mediated by the NKCC1 transporter, the Cl$^-$ equilibrium potential is above the resting membrane potential, and consequently a depolarizing GABA or glycine potential results. When the Cl$^-$ transporter is outward mediated by the KCC2 transporter, the Cl$^-$ potential is hyperpolarizing with respect to the resting membrane potential, and hyperpolarizing inhibitory postsynaptic potentials are generated on binding of the agonist to the receptor. In addition to NKCC1 and KCC2, the carbanhydrase activity also plays a role, which determines the bicarbonate reversal potential.[119,152]

Depending on subunit composition, the GABA-operated ion channel is also permeable to bicarbonate. Because the bicarbonate equilibrium potential is depolarizing with respect to resting membrane potential, bicarbonate-permeable ion channels exert a depolarizing drive, and the resulting GABA-mediated potentials are depolarizing. In fact, after an initial hyperpolarization, prolonged activation of GABA channels lead to a depolarization that is sensitive to carbanhydrase inhibitors. The subunit composition also determines whether GABA-gated channels respond to furosemide, zinc, benzodiazepines, and Î²-carbolines. In general, barbiturates seem to prolong the mean open time of GABA-gated Cl$^-$ channels (see Chapter 23). A subgroup of GABA receptors does not fit the pharmacologic sensitivity of GABA receptors. These receptors contain Ï subunits. Their role in synaptic mechanisms is not fully understood.

GABA receptors containing Î´ subunits[137] have a high affinity for GABA and therefore sense ambient GABA levels. These receptors mediate tonic inhibition.[134] Recent evidence suggests that tonic inhibition is very sensitive to neurosteroids.[97] It is likely that tonic inhibition is affected in epilepsy.[56,85,131]

A potentially important second mechanism providing for tonic inhibition relies on activity-dependent editing of glycine receptors with a subsequent manifold increase of glycine receptors to glycine, making them sensitive to ambient levels of glycine and taurine.[99] Preliminary evidence suggests that this occurs also in human temporal lobe epilepsy.

Acetylcholine, when bound to nicotinergic receptors, and glutamate, when bound to AMPA, kainate, or NMDA receptors, are ionic channels permeable to small cations such as Na$^+$ and K$^+$ and to a variable degree also to Ca^{2+} ions (see Chapter 22). These ionic channels mediate fast excitatory synaptic transmission. In addition, serotonin can bind to receptors that gate an ion channel directly. The 5HT3 receptors are predominantly expressed on interneurons. Nicotinergic receptors are also important, however, as shown by the recent discovery that a mutation in an Î± subunit of the nicotinergic receptor accounts for a genetically determined type of epilepsy in humans.[85,136]

For excitatory synaptic transmission in the central nervous system, the glutamate receptors are most important. The duration of excitatory postsynaptic potentials in the central nervous system is largely regulated by a fast desensitization,[42,114] whereas the duration of inhibitory postsynaptic potentials is regulated by GABA uptake into presynaptic terminals and glia.[41,44]

Metabotropic Receptors

Receptors are said to be *metabotropic* when the binding of a ligand does not directly lead to a conformational change of an ion channel. Instead, the receptors interact with G proteins. These can directly influence membrane channels, particularly Ca^{2+} channels,[121] or the activation of enzymes can lead to the production of second messengers such as inositol-1,4,5-triphosphate (IP3), cyclic adenosine monophosphate (cAMP), and diacylglycerol, which activate protein kinases (see Chapter 27). These affect voltage- and ligand-gated channels in the membrane. The effects are rather slow and therefore account for slow depolarizations or hyperpolarizations. Activation of metabotropic receptors often produces long-lasting effects, in that phosphorylation of an ion channel persists until the channel is used; the information conveyed by an appropriate stimulus also affects later synaptic potentials and the integration properties of neurons for subsequent signals. Finally, second messengers can activate gene-regulating peptides and thereby affect the production of proteins, a process involved in the formation of long-lasting memory traces.

Three classes of ionotropic transmitters (GABA, glutamate, and acetylcholine) interact with metabotropic receptors. Whereas changes in metabotropic $GABA_B$ receptors and mGluR receptors have been well studied in different epilepsy models, less is known on the alterations in muscarinergic receptors and the cholinergic signaling pathway. Neuromodulators such as serotonin, norepinephrine, dopamine, and histamine also interact with metabotropic receptors. Finally, most neuroactive peptides act via G proteins.

The activation of metabotropic receptors leads to different cellular effects that can be either excitatory or inhibitory. This depends on the type of G protein activated, the intracellular second messenger, and the target in a given cell as well as in a given neuronal network. Thus, glutamate can probably activate three different classes of metabotropic receptors.[37,98] Potassium channels are activated by GABA via $GABA_B$ receptors, but GABA also inhibits Ca^{2+} currents. Acetylcholine and glutamate often block K^+ channels via metabotropic receptors. The same applies to serotonin (5-HT) and norepinephrine. These agents, however, can also activate K^+ currents. In general, metabotropic receptors are likely future targets for anticonvulsant drugs.[101]

Presynaptic Receptors

As initially demonstrated in the spinal cord, it is now well established that presynaptic terminals express both ionotropic and metabotropic receptors. These can be autoreceptors, in which the released transmitter binds to the presynaptic membrane and then interferes with further transmitter release. They can also be heteroreceptors, in which the released transmitter diffuses to terminals in the surrounding area. In the spinal cord and brainstem, presynaptic terminals are themselves innervated by afferent fibers. There, ionotropic GABA receptors can impose a depolarization on the axon terminal, which blocks Na^+ currents through depolarization, thereby interfering with synaptic transmission.[126] In cortical structures, inhibitory effects of $GABA_B$ receptors on presynaptic GABA release have been frequently demonstrated.[36,147] Glutamatergic nerve endings also possess presynaptic autoreceptors, however, which often differ from postsynaptic receptors in their binding properties, including those for kainate[127] and mGluR receptors.[123] Presynaptic receptors modulating transmitter release have been described for adenosine and many neuromodulators and neuropeptides as well. Their physiologic and pathophysiologic function is little understood. However, such presynaptic receptors may be suitable targets for new classes of antiepileptic drugs (FIGURE 4).

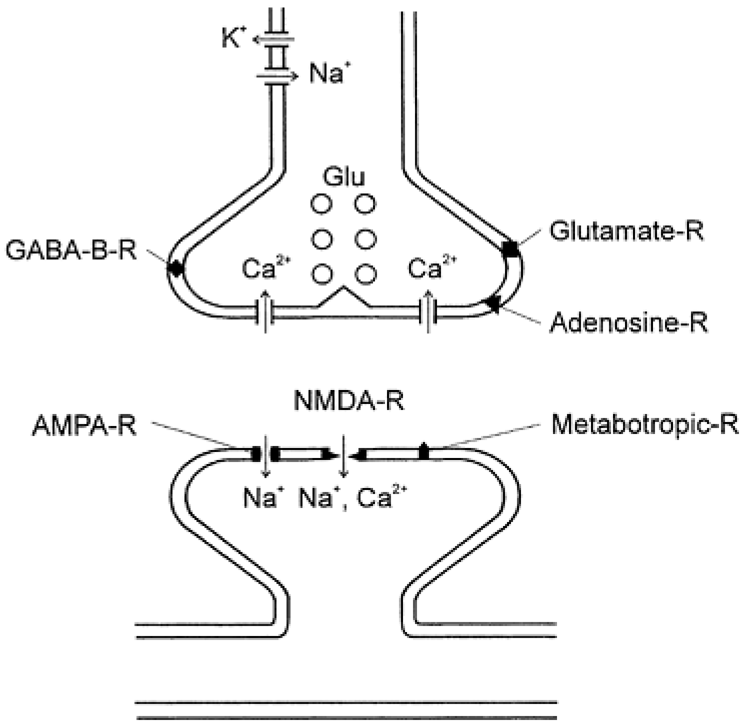

FIGURE 4. Location of different presynaptic and postsynaptic transmitter receptors. Receptors for Î³-aminobutyric acid B ($GABA_B$), adenosine, and glutamate can regulate transmitter release. AMPA, Î±-amino-3-hydroxy-5-methyl-4-isoxazolepropionate; NMDA, *N*-methyl-D-aspartic acid; R, receptor.

Summary and Conclusions

The trafficking of information in the central nervous system depends critically on voltage- and transmitter-gated ionic channels. Storage of information and adaptation to metabolic needs probably depend on metabotropic receptors, which process short-term information into longer-lasting modifications of neuronal transfer of information and may even alter the preferred state of neuronal firing. Through activation of gene-regulatory peptides, they appear to be involved in long-term storage of information of physiologic or pathologic significance.

Any transfer of information leads to a perturbation of ionic gradients, which requires the functioning of ion transporters. Thus, ion pumps are involved not only in regulating membrane potential and loading the â€œbatteryâ€ for activation of voltage- and transmitter-gated currents, but also in setting up ionic gradients for the uptake of nutrients and the outward transport of metabolites. Ion transporters are usually not electrically neutral and so contribute to the electrical behavior of neurons and glia.

Through modern techniques of molecular biology, information about the binding properties of voltage- and transmitter-gated channels is expanding, and new approaches to the development of region-specific toxins and drugs are being undertaken. These will soon offer more-specific tools for manipulating neuronal activity. Increased knowledge of the presynaptic terminal, with its autoreceptors and heteroreceptors and various amino acid transporters, offers new possibilities for the development of antiepileptic drugs. Better understanding of the role of metabotropic receptors and their individual functions may even make it possible for drugs to be designed that interfere with the epileptogenic process itself.

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Chapter 22

Excitatory Synaptic Transmission

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Introduction

Information processing throughout the central nervous system (CNS) occurs through synaptic transmission between neurons coupled via chemical synapses. Excitability at chemical synapses is controlled by both the amount of excitatory neurotransmitter released and by the way in which the postsynaptic neuron responds to the released transmitter. Multiple regulatory mechanisms exist within the CNS to maintain a controlled and focused level of excitability and to prevent excess excitation. These include mechanisms intrinsic to excitatory systems and mechanisms extrinsic to these systems; regarding the latter, direct inhibition and indirect modulation are noteworthy. Excess activation of excitatory pathways in specific circuits can lead to epileptic activity, neuronal damage, and even cell death. This chapter discusses what is known concerning the inotropic and metabotropic glutamate receptors that underlie excitatory synaptic transmission and the role(s) that they play in epilepsy.

Excitatory Neurotransmitters

A variety of endogenous compounds have been identified as agonists at excitatory amino acid (EAA) receptors. However, the two EAAs that are thought to be the most likely neurotransmitter candidates are L-glutamate and L-aspartate. Both compounds act as agonists at all subtypes of inotropic glutamate receptors. Other endogenous compounds present in the CNS that act as agonists at EAA receptors and can depolarize neurons include *N*-acetylaspartylglutamate (NAAG), quinolinic acid, and the sulfur-containing amino acid analogs of glutamate: Cysteic acid, homocysteic acid, cysteine sulfinic acid, homocysteine sulfinic acid, and S-sulfocystein.[28] Whether any or all of these act as neurotransmitters at specific synaptic sites remains to be determined.

Glutamate Synthesis and Uptake Mechanisms

Glutamine and Î±-ketoglutarate are thought to be the major precursors for glutamate, which is subsequently packaged into vesicles for future release into the synaptic cleft. Glutamine is taken up into the presynaptic terminal via an active, sodium (Na)-dependent uptake protein. It is then transported to mitochondria, where it is converted via phosphate-activated glutaminase to glutamate and ammonia. Î±-Ketoglutarate is also actively taken up into the presynaptic terminal, where it is transaminated into glutamate. The glutamate anion in the terminal is then actively taken up into vesicles for future release. Upon release into the cleft, the glutamate either is actively taken back up via a neuronal glutamate transporter and repackaged, or it diffuses away from the cleft and glial glutamate transporters, most often excitatory amino acid transporter (EAAT)-2, internalize the extracellular glutamate.[17]

Once in astrocytes, the glutamate can either be (a) released again into the synaptic cleft via a calcium-dependent vesicular release,[13] (b) metabolized via glutamine synthetase into glutamine, or (c) metabolized into Î±-ketoglutarate by either glutamate oxaloacetate transaminase or glutamate dehydrogenase.

This glutamine and Î±-ketoglutarate is then actively transported out of the glial cells and back into the presynaptic terminals for subsequent resynthesis of glutamate (Fig. 1).[51] Recent work by a number of groups suggests that patients with temporal lobe epilepsy (TLE) may have a deficiency in glutamine synthetase in the astrocytes of sclerotic tissue. This reduced glutamine synthetase may underlie the elevation in extracellular glutamate often associated with TLE[47,155] by reducing the rate of glutamineâ€“glutamate cycling.[119]

Clearly, glutamate uptake molecules perform a vital function in maintaining large precursor levels for glutamate synthesis and low extracellular concentrations of glutamate. To date, five high-affinity glutamate transporter proteins have been cloned.[17,66,67,120,145] All five transporter proteins have been shown to be sodium-dependent, and they are preferentially located in neurons, astrocytes, or other types of glial cells. The recent development of highly specific antagonists of these glutamate transporters will prove quite valuable in ascertaining the contribution these transporters make to neurotransmission at excitatory synapses.

Ionotropic Excitatory Amino Acid Receptors

Three pharmacologically distinct classes of inotropic glutamate receptors (iGluRs) have been identified. The names of these iGluR subfamilies are based on the synthetic agonists that bind to the specific receptor subtypes and selectively open the associated ion channels: The Î±-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor, the kainic acid (KA) receptor, and the *N*-methyl-D-aspartate (NMDA) receptor. This initial pharmacologic classification was supported by the subsequent identification of separate gene families whose sequence similarities were correlated with their affinity for the agonists previously described: GluR1 through GluR4 (which encode AMPA receptor subunits); GluR5 through GluR7; KA1 and KA2 (which encode low- and high-affinity KA receptor subunits, respectively); and NR1, NR2A through NR2D, and NR3A and NR3B (which encode NMDA receptor subunits). Two orphan receptor subunits, GluRÎ´1 and GluRÎ´2, have also been identified.[69]

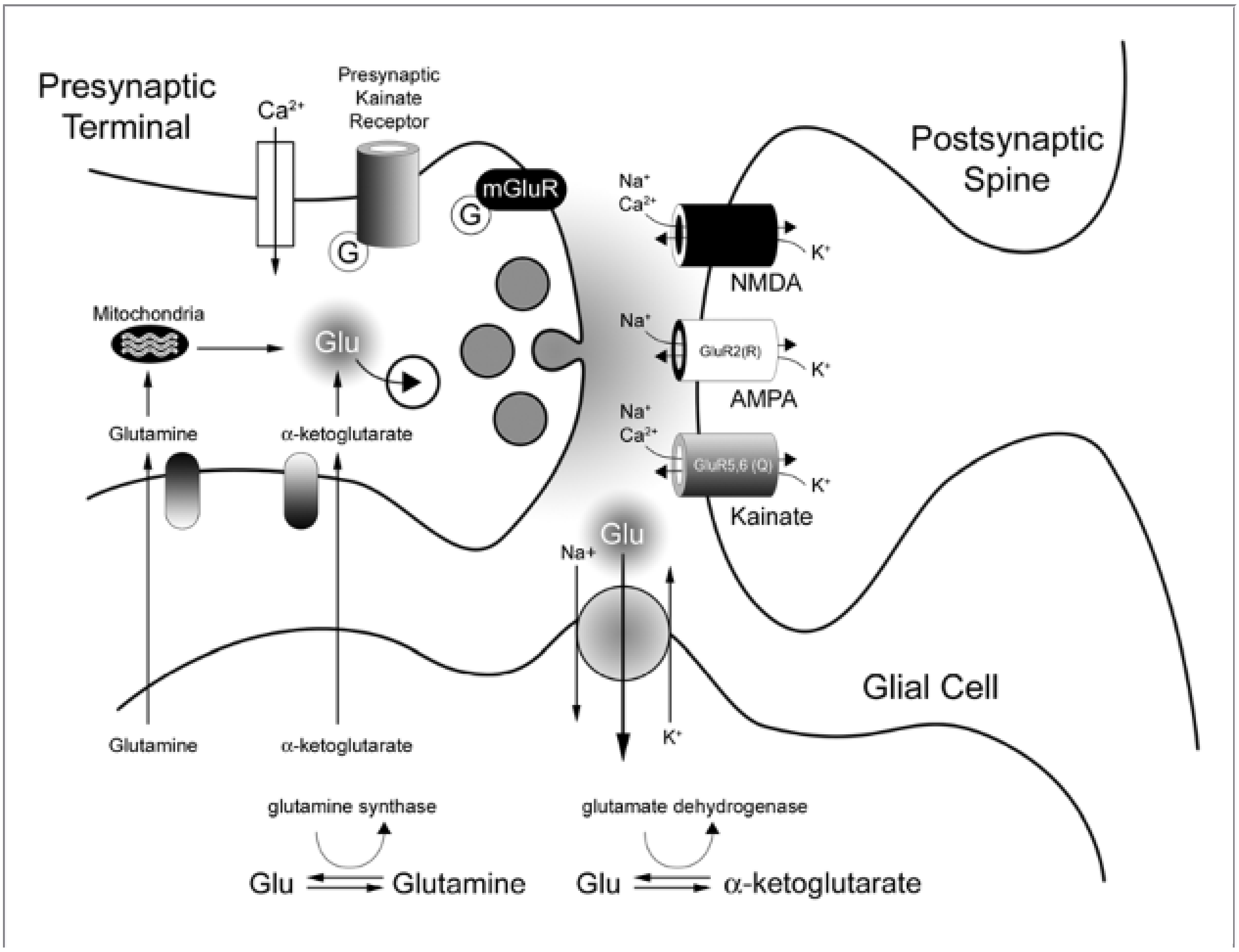

Presynaptic Terminal
Ca2+
Presynaptic Kainate Receptor
G
G
mGluR
Postsynaptic Spine
Na+
Ca2+
K+
NMDA
Mitochondria
Glu
Na+
GluR2(R)
K+
AMPA
Glutamine
α-ketoglutarate
Na+
Ca2+
GluR5,6 (Q)
K+
Kainate
Na+
Glu
Glial Cell
Glutamine
α-ketoglutarate
K+
glutamine synthase
glutamate dehydrogenase
Glu ⇌ Glutamine
Glu ⇌ α-ketoglutarate

FIGURE 1. Schematic diagram of a model excitatory synapse.

All iGluR subunits have an extracellular N-terminus, an intracellular C-terminus, three transmembrane domains (M1, M3, M4), and a membrane re-entrant loop (M2) that forms the pore (Fig. 2). The ligand binding domain of iGluRs is formed by

stretches of amino acids in the N-terminal domain (S1) as well as the linker between M3 and M4 (S2). This ligand binding domain has been crystallized in various functional conformations, and has provided insight into key features of glutamate receptor agonist affinities, activation, desensitization, subunit association, and receptor assembly. Several articles offer excellent in-depth review of this topic.[86,92,93] Functional receptor-gated ion channels are formed when subunits within, but not between, families come together to form homo- or hetero-oligomers. Although the precise subunit stoichiometry of iGluRs was debated for some time, recent studies now suggest that these receptors are composed of four subunits.[91] The reader is directed to several excellent reviews on this topic.[42,69,139]

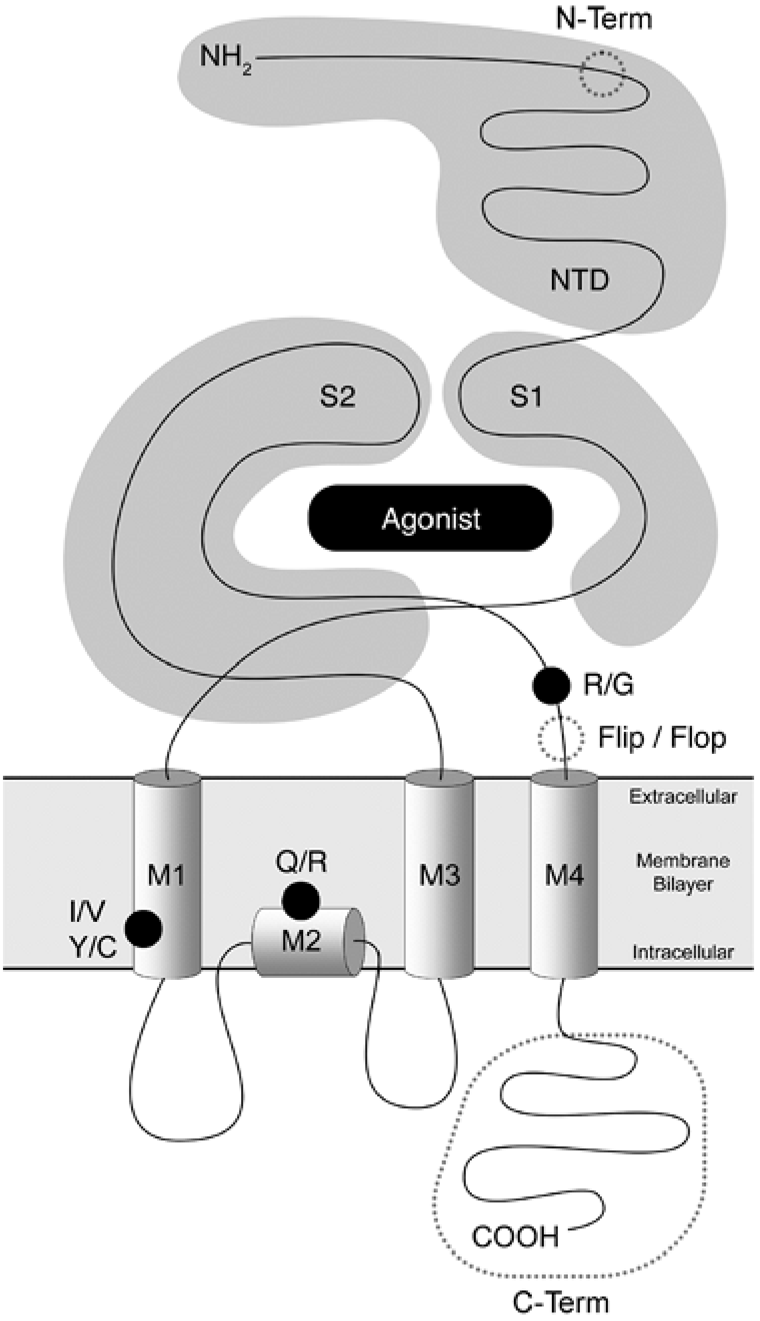
AMPA Receptors

Molecular Biology

Post-transcriptional Modification.

The AMPA receptor subunits GluR1 through GluR4 are each comprised of approximately 900 amino acids and share approximately 70% sequence homology. Additional diversity among the subunits can be generated by post-transcriptional modifications (alternative splicing and RNA editing). All four AMPA receptors undergo alternative splicing of a 38-amino acid sequence in the extracellular domain between M3 and M4. This gives rise to two splice variants, â€œflipâ€ and â€œflop.â€[141] These receptors exhibit differing biophysical and pharmacologic characteristics; the flip variant tends to desensitize more slowly and to a lesser extent than do flop variants, which can influence the amplitude of the AMPA receptor responses.[104] Flip variants also have a greater sensitivity to the allosteric modulator cyclothiazide than do the flop variants. Expression levels of these variants are regulated developmentally, regionally, and in a cell-typeâ€“specific manner, and are also modified by disease states such as epilepsy.

In addition to the flip and flop splice variants, the GluR1, GluR2, and GluR4 AMPA receptors can undergo alternative splicing of their C-termini. This splicing results in isoforms with â€œlongâ€ and â€œshortâ€ cytoplasmic C-terminal domains, and these variants are named as such. Variation in the length of these receptors' C-terminal domains can influence their interactions with cytoplasmic proteins through the presence (â€œshortâ€ C-termini) or absence (â€œlongâ€ C-termini) of a PSD-95/Disc-large/ZO-1 (PDZ) binding domain.[39]


N-Term
NH$_2$
NTD
S2
S1
Agonist
R/G
Flip / Flop
Extracellular
Membrane Bilayer
Intracellular
M1
Q/R
M2
M3
M4
I/V
Y/C
COOH
C-Term

◌ **Alternative Splicing**

	N-term	**C-term**	**Flip / Flop**
AMPA		GluR2, GluR4	GluR1-4
Kainate	GluR5	GluR5-7	
NMDA	NR1	NR1	

● **RNA editing**

	Q / R	**R / G**	**I / V & Y / C**
AMPA	GluR2	GluR2-4	
Kainate	GluR5, GluR6		GluR5, GluR6
NMDA			

FIGURE 2. Schematic diagram of iGluR structure within membrane.

It has been observed that homomeric or heteromeric AMPA receptors that lack the GluR2 subunit are permeable to calcium and exhibit a voltage-dependent block by intracellular polyamines that results in an inwardly rectifying current-voltage (IV) relationship. The ability of the GluR2 subunit to influence these AMPA receptor properties resides in a single amino acid substitution (the genomically encoded glutamine is converted to arginine) in the pore forming M2 segment. This Q/R substitution is the consequence of post-transcriptional editing of premessenger RNA.[142] AMPA receptors that contain edited GluR2(R) are impermeable to

calcium, have a low single-channel conductance, and have linear IV relationships.[147] Most neurons in the adult CNS have been shown to possess AMPA receptors with these qualities, and this suggests that the GluR2(R) subunit is a constituent of most native AMPA receptors. One notable exception to this rule is receptors expressed in various interneurons that appear to be calcium permeable, inward-rectifying, and are therefore believed to lack the GluR2 subunit.[73]

A second known post-transcriptional modification to AMPA receptors via RNA editing is the substitution of the genomically encoded arginine (R) for glycine (G) in GluR2, GluR3, and GluR4. This R/G site is located just before the flip/flop cassette in the extracellular domain between M3 and M4. Generally speaking, homomeric and heteromeric assemblies of edited (G) receptors have faster kinetics for recovery from desensitization (resensitization) than do their unedited (R) counterparts. Variations also occur in the kinetics of desensitization in edited (G) versus unedited (R) receptors, with a tendency toward slower desensitization rates. Akin to the other post-transcriptional splice variants and RNA-edited forms of AMPA receptors, the R/G edit progresses with brain development in a subunit and splice variant-dependent manner.[42]

Post-translational Modifications.

As another way to generate additional diversity, AMPA receptors also undergo post-translational modifications in the forms of glycosylation and phosphorylation. All AMPA receptors contain extracellular glycosylation sites but different subunit combinations appear to be affected differently by the presence or absence of bound oligosaccharides. For example, with the exception of GluR2, the lectin concanavalin-A potentiates AMPA receptorâ€“mediated currents by binding to these carbohydrates and inhibiting desensitization.[50] Although it is not entirely clear what the function of glycosylation is in these receptors, it is thought that this modification is involved in the maturation and transport of receptors and possibly the protection of AMPA receptors from degradation.[116]

Additionally, AMPA receptors have been shown to be phosphorylated basally or in response to varying types of synaptic activity. Although commonalities exist, the particular phosphorylated amino acid residues and kinases responsible for these modifications vary on a subunit basis. Phosphorylation of these residues leads to alterations in the receptor-gated channel properties. One of the most extensively studied instances of this phenomena is the phosphorylation of specific residues in the C-terminal domain of GluR1. GluR1 subunit phosphorylation potentiates receptor activation and leads to an increase in channel conductance and open probability,[7,38,124] and these modifications have been shown to be involved in forms of plasticity such as long-term potentiation (LTP) and long-term depression (LTD).[76] A complete description of this work is beyond the scope of this review, and the reader is directed to an excellent review.[116]

Structure and Function of AMPA Receptors.

The structure of the ligand-binding core of AMPA receptors, as well as other iGluRs, has been determined through the application of X-ray diffraction, and this has led to considerable insight into the molecular mechanisms of receptor activation and desensitization.[56] By using a water-soluble construct of the li- gand binding domain (S1 and S2), the structure was determined to have a hinged clamshell shape, in which the agonist binds in the cleft between each shell. In the absence of agonist, the clamshell is mostly open, whereas in the presence of agonist, the clamshell closes to varying degrees depending on the particular agonist. The degree of closure was shown to correlate with the degree of receptor activation (in which kainate, a partial agonist for AMPA receptors, caused an intermediate degree of closure relative to the full agonists AMPA and glutamate). Furthermore, competitive antagonists like 6,7-dinitro-quinoxaline-2,3(1H,4H)-dione (DNQX) were shown to stabilize the open conformation of the ligand-binding clamshell. Finally, the observation that these receptor fragments tended to favor crystallizing as dimers led to hypotheses and subsequent studies examining the tetrameric stoichiometry of these receptors (a dimer of dimers), as well as the conformational changes that are necessary for the closing of the clamshell

binding pocket to translate to opening of the channel and desensitization of the receptor complex.

Electrophysiology

As noted earlier, the ligand-binding pocket of iGluRs consists of a bilobed â€œhinged clamshellâ€ structure that adopts differing conformations in the absence or presence of agonist. Upon binding of the full agonists glutamate or AMPA, the cleft between the two lobes (S1 and S2) closes by approximately 20 degrees relative to each other, whereas binding of the partial agonist kainate induces a cleft closure of approximately 12 degrees.[56,86] In either event, this cleft closure is coupled to receptor activation and ion channel opening. In most natively expressed receptors, the ion channel is equally permeable to Na^+ and potassium (K^+), and the resulting current has a depolarizing effect on the neuron by driving the membrane potential toward an equilibrium potential of approximately 0 mV. However, in AMPA receptors that either lack the GluR2 subunit, or in which the GluR2 subunit is unedited, there is also a significant permeability to calcium (Ca^{2+}).

Electrophysiologic studies using single-channel recordings of recombinant AMPA receptors have shown that homo- and heteromeric channel assemblies display multiple conductance levels whose amplitudes vary in a subunit-dependent manner, as well as in response to post-transcriptional and post-translational modifications.[38,129,147] For example, homomeric receptors composed of the unedited GluR4(Q), as well as heteromeric receptors composed of unedited GluR4(Q) and GluR2(Q), have single-channel conductance between 20 and 30 picosiemens (pS). On the other hand, inclusion of edited GluR2(R) into these heteromeric assemblies reduces the conductance to approximately 10 pS, and homomeric assemblies of GluR2(R) have conductances in the femtosiemens (fS) range.[147] Native AMPA receptors in a variety of neurons have single-channel conductance similar to those reported for recombinant receptors. For example, cultured cerebellar granule cells have AMPA receptors that fall into three categories based on their single-channel conductance: Highâ€“conductance (10â€“30 pS), low-conductance (5â€“10 pS), and femtosiemens channels (<1 pS).[35,162]

One of the most dramatic features of this receptor, relative to the NMDA receptor, is the rapid desensitization observed when the receptor is exposed to the full agonists AMPA or glutamate.[151,154] After rapid application of an agonist, the channel opens. However, in the continued presence of the agonist, the amount of current flow is rapidly reduced, with a time constant of decay of <10 msec. If the agonist application is terminated and then reapplied, the current is again quite large, so that desensitization does not last long in the absence of agonist. Electrophysiologic studies have led to the conclusion that desensitization probably contributes, at least in part, to the rapid decay of excitatory postsynaptic currents (EPSCs) observed during neurotransmission at excitatory synapses.[151,152]

Pharmacology

AMPA receptors are responsible for most of the rapid excitatory neurotransmission within the vertebrate CNS. When compared to NMDA receptors, AMPA receptors have a relatively low affinity for glutamate, the endogenous amino acid that represents the most likely candidate in mediating neurotransmission at both these receptors.[117] In addition to AMPA and glutamate, AMPA receptors can be activated following the binding of quisqualic acid, derivatives of willardiine, and natural toxins such as domoic acid. However, as mentioned earlier, the most potent selective agonist for this class of EAA receptor is AMPA[67a]. As noted earlier, binding of agonists to AMPA receptors often results in various degrees of desensitization, and the desensitization observed appears to be agonist-specific. Little to no desensitization occurs when a partial agonist, such as kainate, is used to induce a current. However, AMPA, quisqualic acid, glutamate, and many other full agonists result in a desensitizing current at this receptor.

Both competitive and noncompetitive antagonists of AMPA receptors have been described. Competitive antagonists of this receptor include 5-cyano-7-nitroquinoxaline-2,3-dione (CNQX) and other analogs of the quinoxalinedione family such as 1,2,3,4-tetrahydro-6-nitro-2,3-dioxo- benzo[f]quinoxaline-7-sulfona- mide (NBQX), DNQX, and 1,4,7,8,9,10-hexahydro-9-methyl-6-nitropyride[3,4-f]quinoxaline-2,3-dione (PNQX).[60] This family of antagonists has limited utility in discriminating between AMPA and kainate receptors. Fortunately, noncompetitive antagonists that have a sufficiently higher affinity for AMPA than kainate receptors have been developed; 2,3-benzodiazapines, such as GYKI 52466 and 53655, are relatively selective for AMPA receptors and have allowed for the functional examination of kainate receptors (see below).[69]

Regulation of AMPA Receptor Subunit Expression and Function

Anatomic Distribution.

The anatomic distribution of AMPA receptors in the CNS has been determined by in situ hybridization, receptor autoradiography, and immunocyto-chemistry.[69] These receptors are widely present in projection neurons and interneurons throughout the brain, although regional differences exist in the relative amounts of each of the receptor subunits. For example, whereas GluR1, GluR2, and GluR3 are rather ubiquitously expressed throughout the CNS, GluR4 expression is limited to select regions of the thalamus and cerebellum. In addition, whereas principal neurons utilize AMPA receptors including the GluR2 subunit, interneurons are more likely to express AMPA receptors lacking GluR2 and are thus permeable to Ca^{2+}. AMPA receptors are thought to be located primarily postsynaptically, although some evidence suggests that presynaptic AMPA receptors are present in some neurons and can influence neurotransmitter release.

In addition to neurons, AMPA receptors are also found in glia, where they are thought to be able to sense nearby neuronal activity.[156] With regards to epilepsy, the functional properties of these receptors may be modified by changes in the expression levels of individual subunits and/or their pre- and post-translational modifications. For example, it has been demonstrated that GluR1 receptors expressed in hippocampal astrocytes have an elevated flip-to-flop ratio in tissue from humans with pharmacoresistent TLE.[135,136] This increase in the flip isoform could result in receptors with slower desensitization and enhanced depolarizations in astrocytes.

Developmental Regulation.

GluR1, GluR2, and GluR3 are all present and expressed at birth in the rat, whereas the GluR4 subunit is not expressed until approximately postnatal day 14. There is considerable developmental regulation of the splice variant forms of the AMPA receptor, and these changes over time can dramatically impact the function of the receptor and ultimately the excitability of the neuron.[102] In general, in the adult animal, most AMPA receptors contain the flop form of the receptor subunits. This results in receptors that are generally impermeant to calcium and desensitize rapidly. However, in the young brain, a greater flip-to-flop ratio is present, which results in receptors that are more permeant to calcium and open for longer durations. This contributes greatly to the hyperexcitability observed in the young brain.

Trafficking and Associated Proteins.

Interestingly, it is thought that AMPA receptors are not initially present at excitatory synapses, although NMDA receptors are present at postsynaptic sites at birth. Furthermore, transcription as well

as insertion of AMPA receptors into postsynaptic sites is tightly regulated and, for some forms of the receptor, is activity dependent. Recent work has dramatically increased the understanding of AMPA receptor trafficking at synapses, and the reader is encouraged to see some excellent recent reviews on this extensive topic.[111,116]

Briefly, AMPA receptors are assembled in the endoplasmic reticulum, transported through the Golgi, and targeted to the dendrites. The exact mechanisms whereby the receptors are targeted to dendrites and delivered there are currently under investigation. However, because AMPA receptors lack motor components, it is believed that associated proteins are involved in propelling the receptors along cytoskeletal tracks to the dendrites. For GluR2 and GluR3 receptor subunits, interactions with the C-terminus with glutamate receptor interacting protein/AMPA binding protein (GRIP1/ABP) is thought to be necessary for proper dendritic delivery, whereas the interaction of the C-termini of the GluR1 and GluR4 receptors with protein 4.1N seems to be essential for proper delivery of these subunits.[16,49,111,138] Although cytoplasmic vesicles are responsible for initial delivery of AMPA receptors, it is unclear whether they deliver them to the postsynaptic or extrasynaptic sites. Indeed, a number of studies indicate that extrasynaptic receptors are free to diffuse to synaptic sites, where they are then anchored in place by a number of scaffolding proteins.

Once at the dendrite, GluR2- and GluR3-containing receptors are free to rapidly cycle between the postsynaptic sites and intracellular compartments constitutively in an activity-independent fashion. Thus, it is thought that these receptors help to maintain a constant level of receptors at the synapse. In contrast, AMPA receptors containing GluR1 and GluR4 subunits are tightly regulated at the synapse in an NMDA- and activity-dependent fashion. It is believed that this activity-dependent regulation of receptor number at the synapse results in both LTP and LTD (see Chapter 35).

Critical to the ability of AMPA receptors to be inserted into the postsynaptic membrane is the presence of the transmembrane AMPA receptor regulatory proteins, or TARPs. These auxiliary proteins have been found to be important for the selective delivery of AMPA receptors to extrasynaptic regions. In addition, TARPs have now been shown to regulate the activity of AMPA receptors. For example, the first TARP to be examined, stargazin, has been shown to increase the affinity for glutamate at the AMPA receptor and also decrease desensitization and deactivation rates.[121,134,153] An interesting aside to this story is that the stargazin gene has been implicated in absence seizures observed in the stargazer mouse, although the seizures appear to be linked to the proteins' interaction with voltage-gated calcium channels in the thalamus.[82,83]

Different AMPA receptor subunits combine with different combinations of auxiliary proteins that can oversee a myriad of functions of AMPA receptors. In general, the associated proteins fall into one of two categories: PDZ domainâ€“containing proteins and non-PDZ domainâ€“containing proteins. A thorough description of all associated proteins is well beyond the scope of this chapter, and the reader is referred to several recent reviews.[116] However, as we learn more about the assembly, targeting, and regulation of function of AMPA receptors, a number of potential therapeutic targets for the treatment of a variety of seizure disorders will no doubt emerge.

AMPA Receptors and Seizures

Clearly, excitatory synaptic transmission is involved in many aspects of synchronization and seizure generation, and there is no doubt that AMPA receptor number and function are critically involved in these mechanisms. Not only are there alterations in excitatory circuits in some forms of epilepsy (most notably mossy fiber sprouting in TLE), but a number of studies have demonstrated that following seizures, changes occur in a number of cell types with regards to the type of AMPA receptor subunits that are expressed. Changes in subunit expression have been observed in both animal models of epilepsy as well as in human epilepsy.[37,43,57,61,90,122,131,143] Clearly, these alterations in subunit expression have important ramifications with respect to the function and regulation of excitatory synaptic transmission, and these alterations are just beginning to be understood at the circuit level. Many of these changes in excitatory synaptic transmission are addressed in a number of other chapters in this book and will not be elaborated upon here.

Kainate Receptors

Molecular Biology

Cloning studies have revealed the existence of five kainate receptor (KAR) subunits: The low-affinity subunits GluR5, -6, and -7, and the high-affinity subunits KA1 and KA2. (This topic has been reviewed.)[42,80] Multiple alternative splice variants have been identified for GluR5 through GluR7. Additionally, post-transcriptional editing occurs in GluR5 and GluR6 at the glutamine/arginine (Q/R) site, but this does not occur in the GluR7, KA1, or KA2 subunits. GluR5 through GluR7 can form functional homomeric KARs in expression systems, whereas the KA1 andKA2 subunits cannot. However, KA1 and KA2 subunits can assemble with GluR5, -6, and -7 to form functional heteromeric receptors. Clearly, this inherent molecular diversity can lead to the assembly of a sizeable number of different KARs with distinct stoichiometries. As was the case for AMPA receptors, subunit assembly can dictate the functional properties of the resulting receptor-gated ion channels, including permeability, conductance, and pharmacology. For example, homomeric assemblies of GluR5 or GluR6 that possess an arginine at the Q/R site are functionally different from receptors composed of subunits possessing a glutamine.[10] These edited, arginine-containing receptors have a reduced calcium permeability, a linear or slightly outward rectifying current-voltage relationship instead of an inward or double rectifying relationship, a single low conductance state as compared with multiple conductance states, and an increased chloride permeability.

Electrophysiology

Postsynaptic Kainate Receptors.

Functional postsynaptic KARs are present in a variety of cell types. Examples include cerebellar granule cells and Golgi cells[18,140]; retinal bipolar cells[40]; neurons of the superficial dorsal horn,[84] lateral superior olive,[158] and motor and somatosensory cortex[2,45,71]; and a variety of neurons in the hippocampus and amygdala.[22,31,32,52,53,54,58,127,157,160] As originally described in CA3 neurons of the hippocampus, KAR-mediated EPSCs are defined as being resistant to inhibition by the AMPA receptor-selective 2,3-benzodiazepine GYKI 53655 (or GYKI 52466), but sensitive to inhibition by CNQX.[22] Furthermore, KAR-mediated EPSCs are smaller than their AMPA receptor-mediated counterparts, have significantly slower rise and decay kinetics, and are not potentiated by cyclothiazide.[22,157] Even though the KAR contribution to combined AMPA/kainate-mediated EPSCs is relatively small, postsynaptic KARs participate in synaptic transmission and may even be segregated to their own synapses.[31] Data using glutamate uptake blockers suggests that the KARs' slow kinetics are due to intrinsic characteristics[18,71] and may impose unique integrative properties to neurons.[53]

Presynaptic Kainate Receptors.

Presynaptic KARs have been found to modulate the release of glutamate at a variety of synapses in the CNS and peripheral nervous system (PNS).[24,29,55,65,68,70,128,132,133] One of the best studied examples of this is the mossy fiberâ€“CA3 synapse in the hippocampus. At this synapse, presynaptic KARs modulate glutamate release in a bidirectional manner; low KAR agonist concentrations in the nM range increase glutamate release, whereas larger concentrations in the ÂµM range depress the synaptic response. Furthermore, these kainate autoreceptors may sense synaptically released glutamate and play a role in frequency-dependent facilitation.[29,75,133] The hippocampal CA3-CA1 is another excitatory synapse modulated by presynaptic KARs. KAR agonist application reduces glutamate release at this synapse by metabotropically inhibiting calcium influx at the terminal.[24,29,55] Depolarization of the presynaptic terminals is not necessary for the reduction in glutamate release. This appears to be in contrast to the actions of presynaptic KARs at the mossy fiberâ€“CA3 synapse. This has led some to suggest that modulation of transmitter release by KARs could obey different mechanisms and rules at different synapses.[78]

Presynaptic KARs have also been found to modulate the release of Î³-aminobutyric acid (GABA).[3,9,14,30,62,85,99,109,125,126,127,137] KAR agonists depress evoked inhibitory postsynaptic currents (IPSCs) and reduce the frequency of miniature IPSCs as recorded in CA1 PYR neurons of the hippocampus.[125] Pertussis toxin can prevent this effect, which suggests that depression of GABA release at this synapse may occur via presynaptic KARs acting through a G-proteinâ€“coupled cellular cascade.[126] However, KARs do not always act to depress the release of GABA. In the CA1 interneurons of the hippocampus, activation of a separate population of KARs that are likely to be localized to the soma or axon can increase spontaneous GABA release by increasing action potential firing frequency.[32,52,54,106,127] Additionally, the activation of presynaptic KARs at synapses between inhibitory interneurons enhances GABA release.[30] Furthermore, presynaptic KARs have been found to exert a concentration-dependent bidirectional control of GABA release in the rat amygdala.[15]

This effect is similar to the aforementioned bidirectional control of glutamate release. These effects of presynaptic KARs on GABA release can be mediated by glutamate released from neighboring excitatory terminals under normal physiologic conditions.[99] Taken together, the control of GABA release by KARs may be heterogeneous, again ultimately depending on the properties of the GABA-releasing synapse.[78]

Pharmacology

The distinction between AMPA and kainate receptors was initially somewhat blurred because both AMPA and KA can activate both types of receptors. However, there are differences in the potency of each agonist at the different receptor subtypes. Whereas the order of agonist potency at AMPA receptors is: Quisqualate > domoic acid ~AMPA > glutamate > KA, the order for at least some molecular forms of the kainate receptor is: Domoic acid > KA > glutamate > AMPA.

Advances in the development of AMPA and KAR selective antagonists, along with the development of KAR knockout mice, have recently and dramatically increased our understanding of the structure, function, regulation, and pharmacology of these subtypes of iGluRs. In particular, the 2,3-benzodiazepines have been found to be fairly selective for AMPA receptors, and the use of these compounds have helped to reveal the functional expression of KARs on a variety of neuronal cell types. In addition, a number of decahydroxyisoquinoline carboxylate molecules have recently been developed and serve as subunit-selective KAR antagonists. However, these antagonists, (e.g., LY382884 and LY294486) are somewhat selective within the KAR family and mostly block GluR5 subunits. Thus, their utility is somewhat limited to those receptors containing the GluR5 subunit. With regard to epilepsy, a novel anticonvulsant, topiramate, in addition to its other actions on GABA receptors and sodium channels, has been found to effectively block GluR5-containing receptors in the amygdala.[58]

Many neurons that are subject to cell death following KA-induced status epilepticus also have an abundance of postsynaptic KA receptors. Perhaps the most studied synapse to date in this regard is the mossy fiberâ€"CA3 synapse of the hippocampus. CA3 pyramidal cells are highly susceptible to seizure-induced cell death in human and animal models of TLE, and have a prominent postsynaptic KAR component to the EPSC. Additionally, mossy fiber also contains presynaptic KARs. Activation of these receptors can enhance glutamate release and further contribute to excitotoxicity of CA3 cells during periods of excessive activation, as seen during seizure activity. In addition, knockout mice with targeted deletions of the GluR6 subunit are not as susceptible to the deleterious effects of kainate.[105] The CA3 neurons have a greatly reduced sensitivity to the exogenous application of kainate, and the mice are resistant to systemic KA-induced seizures and do not exhibit the same cell death patterns or astrogliosis as the littermate controls. Therefore, it is becoming increasingly clear that KA receptors play an important role in epilepsy.

Regulation of KA Receptor Subunit Expression

Anatomic Distribution.

In situ hybridization and immunohistochemical studies have led to the discovery of different distributions throughout the brain for mRNA encoding GluR5 through GluR7. In contrast to GluR5 and -6, GluR7 is not found in most of the hippocampus, although it has been found in the granule cells of the dentate gyrus.[11,12,46] GluR7 mRNA is also quite abundant in the caudate-putamen, but GluR5 is absent from this region. Of particular interest is the finding that mRNA for both GluR6 and -7 is present in high abundance in brain regions that have been found to be profoundly sensitive to destruction following KA treatment. These areas include the hippocampus, cortex, and reticular thalamic regions.

KA1 is expressed at high levels in only CA3 pyramidal cells and dentate granule cells, whereas KA2 is found in virtually all brain regions. Some evidence supports the hypothesis that the KA2 receptor is co-expressed in some areas with GluR6 and -5, and that KA1 may be coexpressed with GluR6 in the hippocampus.

KARs have been found at both postsynaptic and presynaptic locations. At many postsynaptic sites, KARs have been found to contribute substantially to the overall EPSC, thus suggesting that these receptors are colocalized with both AMPA and NMDA receptors. Activation of KARs at presynaptic sites can regulate neurotransmitter release. Activation of the receptor can open the ion channels as well as signal the G-protein, and it has recently been shown that the KA2 subunit is necessary for the G-proteinâ€“mediated effects of receptor activation at the mossy fiberâ€“CA3 synapse.[130]

Developmental Regulation.

Protein for all five KAR subunits has been identified as early as embryonic day (E)14 in the rat brain, and in situ hybridization studies have demonstrated that each of the subunits of the KAR can undergo specific changes in expression levels throughout the brain over the course of development. There is widespread and heterogeneous distribution of the receptor subunits in the adult animal, and the stoichiometry of the receptors in individual cell types is diverse and still under investigation. The GluR5 subunit is expressed at lower levels in the adult brain than in the young animal, and is ultimately found in dorsal root ganglion cells, the septum, subiculum, and a variety of cortical regions.

The GluR6 subunit is found at its highest levels in the cingulate cortex, granule cells, and CA3 and CA1 pyramidal cells in the hippocampus. GluR7 subunit expression also decreases throughout the course of development, but can be found in the striatum and throughout the cortex and hippocampus. KA1 subunit expression also decreases throughout development and is found ultimately in the CA3 pyramidal cells and subiculum. Finally, KA2 is highly expressed throughout the brain throughout development.[77]

At thalamocortical synapses, postsynaptic KARs are present early on in development, whereas postsynaptic AMPA receptors develop a little later and ultimately comprise the majority of thalamocortical synapses after postnatal day (P)7.[8] KARs have also been found on migrating axons, and the activation of these presynaptic receptors can either increase or decrease axonal motility, depending on the concentration of kainate.[77] Therefore, early expression of presynaptic KARs may have functions other than the regulation of transmitter release.

Trafficking and Associated Proteins.

Following assembly of dimers in the endoplasmic reticulum (ER), KARs are sorted and delivered to various locations within the cell. KA2 and GluR5c will remain in the ER unless paired with other subunits due to an ER retention sequence on the subunit. The C-termini of many of the KARs have PDZ-domain binding sites, which suggests that PDZ proteins such as PSD-95, GRIP/ABP, and protein interacting with C kinase 1 (PICK1) may also be involved in trafficking of these receptors to the plasma membrane and postsynaptic sites. GluR6a, GluR5b, and GluR5c contain PDZ-binding domains and, although deletion of that portion of the C-terminal does not interfere with the delivery of the receptors to the plasma membrane, it does prevent the proper insertion into the synapse.[79]

KA Receptors and Seizure Activity

Many iGluR subunits have been found to be altered in specific cell types and in selective brain regions from patients with epilepsy. Therefore, it comes as no surprise that this has been shown to be the case for KARs as well. For example, Kortenbruck and colleagues have demonstrated that there is a significantly increased editing efficiency at the Q/R site for both GluR5 and -6 receptors in patients with TLE.[74]

Recent work from Ben-Ari's laboratory[48] demonstrated that mossy fiber sprouting in the KA model of TLE results in excitatory synapses in granule cells that utilize KARs, a situation not found in the control, unsprouted granule cells. It is not clear what role in seizure generation these new synapses play, but nonetheless, the new appearance of postsynaptic KARs in pathophysiology further links these receptors to epilepsy.

NMDA Receptors

Molecular Biology

As with the non-NMDA receptors, cloning of a variety of NMDA receptor subunits has revealed a great diversity of receptors. Three subfamilies of NMDA receptors have been identified: NR1, -2, and -3. Eight splice variants of the NR1 receptor (with the presence of three inserts) have been identified, whereas NR2 has four separate subunits (Aâ€“D) encoded by four separate genes.[59] Two subunits of the NR3 family of NMDA receptors have been identified and found to be expressed in the CNS: NR3A and NR3B.[25,146]

Homomeric channels formed from the expression of NR1 mRNA are fully functional, having the typical pharmacology of NMDA receptors. That is, they require the presence of glycine for activation, and a voltage-sensitive block by extracellular magnesium ions (Mg^{2+}) occurs. However, the currents observed from homomeric channels are quite small; this has been interpreted to mean that native receptors likely have additional subunits.[41,103]

Unlike homomeric NR1 receptors, homomeric NR2 receptors do not form functional ion channels. When each of the four NR2 receptors, Aâ€“D, are individually co-expressed with the NMDA receptor (NMDR)-1 receptor, functional channels are observed with large conductances and appropriate pharmacology. Variations in both NR1 and -2 subunits have profound effects on NMDA receptor pharmacology and physiology. For example, one splice variant of NR1 confers sensitivity to polyamines. In addition, heteromeric receptors are sensitive only to the stimulating effect of polyamines if they are composed of NR1A (lacking the N-terminal insertion) and NR2B.[161] Similarly, sensitivity to the coagonist effects of glycine and Mg^{2+} are quite subtype-specific. These factors could have great implications in considering the roles of NMDA receptors in epileptogenesis and in trying to target these receptors for the development of new antiepileptic drugs.

Expression studies in human embryonic kidney (HEK)-293 cells have demonstrated that the NR3A subunit requires the expression of the NR1a subunit for proper assembly and insertion into the membrane. In addition, the presence of the NR3A subunit in combination with the NR1 and NR2A subunit results in a decrease in the single-channel conductance of the NMDA receptor.[25,36,118,146] Consistent with this finding, studies in mice lacking the NR3A gene have demonstrated that whole-cell currents induced by the exogenous application of NMDA are increased. In addition, mice lacking the NR3A subunit were also found to have an increase in dendritic spine density in cortical neurons, suggesting that the NR3 subunit can play role in the development of postsynaptic structures.[36]

Even less is known about the NR3B subunit, which has only recently been cloned.[112] This subunit is expressed in motor neurons located in the spinal cord and some brainstem nuclei. Functional channels containing this subunit occur only when both the NR1 and NR2a subunits are expressed. In a manner similar to NR3A, expression of NR3B results in a decreased conductance through the NMDA receptor.[112] Thus it would appear that the presence of either NR3 subunit will downregulate current flow through the NMDA receptor-gated ion channel. It is currently unknown whether the NR3 receptor subunits are expressed at native synapses.

Electrophysiology

At hyperpolarized membrane potentials, activation of the NMDA receptor does not result in current flow through the channel. This is because, at hyperpolarized potentials, extracellular Mg^{2+} will block the channel.[114] However, at more depolarized potentials, Mg^{2+} will be expelled from the channel, and both monovalent and divalent cations (most notably, calcium), can flow through the channel. The permeability of the channel to calcium underlies the great interest in this EAA receptor. The entry of calcium through this channel signals a biochemical cascade, resulting in the development of both LTP and LTD at many synapses (see Chapter 35). The increasing activation of the NMDA channel at depolarized membrane potentials serves as a positive feedback mechanism or amplification mechanism at excitatory synapses. As a postsynaptic cell is depolarized, more current will flow through the NMDA receptorâ€“channel and, therefore, more depolarization will result.

The behavior of the activated NMDA receptorâ€“channel complex differs dramatically from that of the non-NMDA receptors. Activation of the channel is much slower, with the time to the peak current being often tens of milliseconds. Desensitization at NMDA receptors during the exogenous application of agonist takes several hundred milliseconds to develop, whereas desensitization at AMPA receptors occurs within

5 to 10 msec. The mechanism of desensitization of this receptor (and the determination of whether the receptor desensitizes at all during synaptic events) has been controversial. Desensitization has been attributed to the absence of glycine, such that when glycine is present in high concentrations, desensitization is

prevented.[94] Other evidence, however, suggests that glycine plays no role in desensitization.[63] In addition, a calcium-dependent desensitization has also been described.[26]

Another difference between non-NMDA and NMDA receptors is the voltage-sensitive block of Mg^{2+} at the NMDA receptor. The IV relationship of NMDA receptors has a region of negative slope resistance at hyperpolarized potentials, whereas the IV relationship for non-NMDA receptors is linear. In addition, single-channel experiments have revealed that once agonist has bound to the NMDA receptor, the channel can open and close repeatedly for up to several hundred milliseconds, resulting in long-lasting currents.[81] Single-channel experiments have also revealed that the primary conductance state for NMDA channels is approximately 50 pS, although transitions to lower conductance states have been observed.[34,35]

Pharmacology

The NMDA receptor has been studied extensively, especially once it was determined that activation of this EAA receptor underlies different forms of synaptic plasticity in a number of systems. Agonists at the NMDA receptor include NMDA, glutamate, and a variety of other EAAs. As with AMPA and kainate receptors, NMDA receptors possess two agonist-binding sites.[27] Specific antagonists at the glutamate-binding site include DL-2-amino-5-phosphonovalerate (APV) and its family, as well as 3-([Â±]-2-carboxypiperazin-4-yl)propyl-1-phosphonic acid (CPP) and its structurally related family. Of particular interest to the NMDA receptors is the fact that it is the only EAA receptor that has an absolute requirement for a coagonist, glycine.[64,72] If the glycine site on the receptor is blocked or unoccupied, binding of glutamate to the receptor will not result in the channel opening. In addition, it seems that, at least in adult rat forebrain, the glycine site of the NMDA receptor is not always saturated, depending on the subunits expressed and the location of the synapse in question.[23,159] Therefore, regulation of glycine concentrations may be critical to the regulation of excitatory synapses. In addition to its coagonist requirement, the NMDA receptor has been shown to be modulated by Mg^{2+}, H^{+}, Zn^{2+}, polyamines, steroids, and an oxidationâ€“reduction site.[114,144,150,161] Modulation at all these sites represent potential therapeutic targets for the symptomatic treatment of epilepsy.

It was hoped that novel anticonvulsants could be developed to selectively target subunits of NMDA receptors. However, NMDA receptor antagonists are not generally well tolerated, exhibiting a number of adverse effects. Of the newer-generation anticonvulsants, only felbamate has been found to partially block NMDA receptors. However, felbamate is a broad-spectrum compound with multiple modes of action, so it is not felt that the NMDA antagonism can directly explain the efficacy of felbamate.

Regulation of NMDA Receptor Subunit Expression

Anatomic Distribution and Cellular Localization.

In situ hybridization studies have demonstrated that mRNA encoding the NR1 subunit is expressed in almost all neurons in the CNS, although the individual splice variants tend to be more localized.[101,103] However, the various NR2 subunits (Aâ€“D) are more differentially localized to specific brain regions. For example, the NR2A and -2B subunits are highly expressed in cortical and hippocampal regions, whereas the NR2C subunit is not expressed in these regions. The NR2D subunit is preferentially expressed in olfactory bulb and lower brainstem regions, whereas NR2C is found in the cerebellar granule cell layer.[101]

Developmental Regulation.

Although the NR1 subunit is ubiquitously present at birth, considerable developmental regulation of NR2 subunits has been described. In rats, the NR2B receptor subunit is present at birth, whereas the NR2A subunit is not expressed until sometime after the second postnatal week. The NR3A subunit has also been shown to be developmentally regulated. Expression of this subunit is high throughout the rat brain during the first few weeks of postnatal life, although in the adult animal, expression occurs only within specific nuclei of the thalamus, amygdala, and lateral olfactory tract.[25,146]

Trafficking and Associated Proteins.

Tremendous advances have recently been made in our understanding of the regulation of NMDA receptor trafficking and, not surprisingly, many of the same basic processes in play for AMPA and KARs are involved in trafficking NMDA receptors as well. Following assembly in the ER, proteins with PDZ-domain binding sites interact with the NR2 subunits to traffic the receptor to the membrane. In particular, PSD-95 is thought to bind the NMDA receptor and, through an interaction with kinesin, deliver the assembled receptors to the membrane. Delivery of the receptor appears to be NR2 subunitâ€"dependent, with NR2B subunitâ€"containing receptors delivered and inserted to extrasynaptic regions and NR2A-containing receptors delivered and inserted into the synapse. NR2B-containing receptors are free to diffuse to the synapse as needed, and the rate of exocytosis and endocytosis of these receptors is substantially higher than for receptors containing NR2A subunits.[123]

Although a vast number of proteins have been identified that directly interact with the NMDA receptor, perhaps one of the most important of the associated proteins is calmodulin-dependent protein kinase II (CamKII). Activation of this kinase is critically important for long-term plasticity to occur at excitatory synapses, and it is directly linked to signaling mechanisms involved in regulating AMPA receptor number at the synapse. The regulation of second-messenger signals subsequent to activation of NMDA receptors and Ca^{2+} influx is continuing to be studied with great interest, and future therapies for seizure disorders may ultimately involve the regulation of proteins associated with iGluRs, rather than direct modulation of the receptorâ€"ion channel complexes.

NMDA Receptors and Seizure Activity

The importance in NMDA receptors for the initiation of long-term changes in various models of synaptic plasticity, along with the ability of NMDA antagonists to block seizure activity in many animal models, has led to the suggestion that excessive activation of these receptors can underlie seizure generation. In addition, the presence of NR2B subunits at synaptic sites can lead to prolonged EPSPs with substantial calcium influx, contributing to hyperexcitability in the developing brain. Therefore, the role of the NMDA receptor in epilepsy has been extensively explored.

Recently, several groups have identified a number of changes in NMDA receptor expression and function in human tissue resected from patients with cortical dysplasia. Alterations in NMDA receptors have also been identified in several animal models of cortical malformations, leading to the hypothesis that, in some cases, altered excitatory synaptic function in these cortical circuits could contribute to the observed hyperexcitability.[4,21,33,107] Likewise, a number of alterations in NMDA receptor expression and function have been identified following kindling and in resected human tissue from patients with TLE. How these changes ultimately result in seizure activity remains to be determinedâ€"indeed, whether these changes are either compensatory or contributory still must be established. However, future work will undoubtedly contribute to our understanding of the role of the NMDA receptors to seizure activity.

Metabotropic Excitatory Amino Acid Receptors

The EAAs are also capable of activating a group of receptors that are coupled via second-messenger systems to biochemical pathways and ion channels. These have been called metabotropic glutamate receptors (mGluRs). Based on sequence homology, coupling to different second-messenger systems, and the pharmacology of presently available agonists and antagonists, three separate groups of mGluRs have been established: Groups I, II, and III. These receptors, unlike their inotropic counterparts, are not comprised of subunits that form an integral ion channel; instead, they are comprised of polypeptides that have a putative seven-transmembrane spanning domain with a large extracellular NH2 terminal region. When an agonist binds to the mGluRs, activation of a variety of G-proteins occurs. This G-proteinâ€"coupled activation then results in a diverse biochemical cascade that can result in the modulation of a variety of cellular functions, such as current flow through voltage-gated ion channels. Within the three groups of receptors, eight subtypes of the mGluRs have been cloned, and these correspond to a novel gene family of G-proteinâ€"coupled receptors.[59,110,113] In addition, a number of splice variants have been identified for mGluR1, -4, -5, -6, -7, and -8, leading to a great diversity of potential mGluRs.

Activation of this class of glutamate receptors has been implicated in a variety of CNS functions, including different forms of synaptic plasticity and excitotoxicity. However, until recently, mGluRs have been difficult to study due to the overall lack of and/or availability of specific receptor antagonists and agonists. As was the case for iGluRs, the physiologic functions of the mGluRs are beginning to be deciphered as transgenic animals become available.

This section summarizes what is presently known concerning the pharmacology, anatomic distribution, and role of the three groups of these G-proteinâ€"coupled EAA receptors in synaptic transmission, plasticity, and epilepsy. However, for more in-depth coverage of these topics, the reader is encouraged to see some excellent recent reviews.[69,113]

Group I mGluRs

Group I receptors include the mGluR1 and mGluR5 receptors. The mGluR1 receptor is further characterized by the existence of six splice variants; there are two splice variants for the mGluR5 receptor. Selective agonists, with the ranking of the relative potency, include quisqualate > glutamate > ibotenate > trans-1-aminocyclopentane-1,3-dicarboxylate (tACPD).[59] Upon binding of the ligand to the receptor, inositol triphosphate (IP3) and diacylglycerol (DAG) formation is increased, intracellular calcium is mobilized, and arachidonic acid is released. The G-proteins that couple the receptor to the effector mechanisms are pertussis toxinâ€"sensitive for mGluR1.[1,5,69]

In situ hybridization studies have revealed that the mRNA encoding for Group I mGluRs is highly abundant in the CA2 and CA3 cell layers of the hippocampus. However, although mRNA for mGluR1 is found to be highly expressed in Pur- kinje cells of the cerebellum, mGluR5 is not present at all in these cells. Likewise, although CA1 cells of the hippocampus have mGluR5 mRNA, these same neurons have virtually no detectable mRNA for mGluR1.[1,89] Although both mGluR1 and -5 are coupled to the same effector system, only activation of mGluR5 results in the induction of hyperexcitability and epileptiform activity in hippocampal brain slices. However, activation of both mGluR1 and -5 is required to maintain this electrographic behavior. It is intriguing to note that antago-nists of both mGluR1 and -5 can act as anticonvulsants[100] in a variety of animal models as well.[96,97,98]

Group II mGluRs

Group II mGluRs include the mGluR2, -3, and -8 subtypes of the receptor family. Unlike Group 1 receptors, activation of Group II mGluRs results in the suppression of forskolin-stimulated cyclic adenosine monophosphate (cAMP) accumulation.[148,149] The agonists, in the relative order of potency for this group, include: Glutamate > tACPD = ibotenate > quisqualate.[59] The actions of all members of this group are blocked by pertussis toxin. Activation of receptors in this group, as well as those of Group III, often results in a decrease in neurotransmission at both glutamatergic and GABAergic synapses. A rather specific antagonist at both Group II and Group III receptors has been identified: $^+$-Î±-methyl-4-carboxyphenyl-glycine (MCPG).[44] This antagonist can block the decrease in neurotransmission observed in the presence of tACPD.[87] Although somewhat controversial, it is believed that activation of tACPD-sensitive receptors may play a role in the development of both LTP and LTD in various regions of the brain.

In situ hybridization studies have determined that the mGluR2 receptor is abundantly expressed in Golgi cells of the cerebellum and granule cells in the accessory olfactory bulb. This receptor type is also abundant in the neocortex and hippocampus. The mGluR3 mRNA is also highly expressed in the neocortex and hippocampus.[149] In a developmental model of epilepsy, recent work using a novel Group II agonist, (2R,4R)-4-aminopyrrolidine-2,4-dicarboxylate (2R,4R-APDC), has demonstrated that the activation of these receptors can be both neuroprotective and anticonvulsant.[149]

Group III mGluRs

The mGluRs considered members of Group III include mGluR4, -6, and -7.[69,108] As with the activation of Group

II receptors, activation of those in this group results in a reduction of forskolin-stimulated increase in cAMP production.[69] However, these receptors are specifically activated by the selective agonist L-2-amino-4-phosphonobutyrate (L-AP4). These receptors are also activated following binding of both glutamate and tACPD. MCPG acts as a potent antagonist at these receptors. mGluR4-mediated activation of G-proteins is blocked by pertussis toxin, but mGluR6-mediated activation is not.

mGluR6 mRNA is found exclusively in the retina, and evidence suggests that mGluR4 is present in both the retina and cerebellum. mGluR7 is widely distributed throughout the brain. mGluR6 is involved in signal transduction from photoreceptors to on-bipolar neurons in the retina, whereas mGluR4 and -7 may be involved in regulating neurotransmitter release.[115,148] Indeed, recent evidence also suggests that agonists of mGluR4 can also be useful for protection against seizure activity.[88]

Role of mGluRs in Epileptic Activity

Many, if not all, neurons in the CNS appear to have mGluRs on axon terminals, where they mediate presynaptic modulation. In addition, activation of postsynaptic receptors may cause direct depolarization and modulation of intrinsic currents. Activation of mGluRs most often results in presynaptic inhibition and postsynaptic excitation and, thus, the net effect may be variable, brain site-specific, and may depend on the distribution of the various receptor subtypes and their cellular locations. It is not surprising, therefore, that activation or inhibition of these receptors may modulate epileptiform activity. Data suggests that mGluRs may be involved in the transition between interictal and ictal behavior in the amygdala[6] and in the maintenance of interictal activity in the hippocampus.[95] In the neocortex, mGluR activation may have both suppressive and stimulatory effects, presumably based on different receptor subtypes, and this may also be developmentally regulated.[19,20] As more is learned about the pharmacology of these receptors, as subtype-specific agonists and antagonists and as transgenic animals with targeted deletions of the mGluRs become even more available, it is possible that a new class of antiepileptic drug could emerge that would selectively enhance the suppressive effects or inhibit the stimulatory effects of mGluR activation.

Summary and Conclusions

Synaptic excitation plays a critical role in essentially every function that the CNS is designed to perform. Small transient perturbations in the efficacy of excitatory transmission or in the balance between excitation and inhibition can lead to a seizure. Permanent changes in excitatory synaptic efficacy, or changes in local recurrent excitatory circuitry, can lead to a hyperexcitable state that we call epilepsy. The molecular mechanisms that underlie excitation at the biophysical and pharmacologic levels are beginning to be unraveled. Individual AMPA, kainate, and NMDA receptorâ€"channel complexes can be analyzed, and their subunits characterized. Metabotropic glutamate receptors and their associated G-proteins, which appear to serve as modulatory elements at both excitatory and inhibitory synapses, are also being identified. The circuits within which all these receptors play their critical roles are being characterized, and changes that occur in epileptic brains are being identified. Each of these areas holds the potential for developing new strategies either to prevent the development of epileptic circuits or to target highly specific agents to interfere with the development of epileptic events, even if an epileptic propensity exists in an injured tissue.

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Chapter 23

GABA$_A$ and GABA$_B$ Receptor-Mediated Inhibitory Synaptic Transmission

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Istvan Mody

Introduction

The neurotransmitter Î³-aminobutyric acid (GABA) is the most abundant inhibitory neurotransmitter in the central nervous system (CNS). GABAergic inhibition is the primary form of fast inhibition in the forebrain, and can mediate both presyn- aptic and postsynaptic inhibition. GABA-mediated presynaptic inhibition occurs when GABAergic nerve terminals release GABA onto presynaptic nerve terminals, resulting in a reduction of neurotransmitter release. In contrast, GABAergic postsynaptic inhibition is mediated by the interaction of the neurotransmitters with specific postsynaptic receptors. GABA binds to two distinct types of GABA receptor, GABA$_{A,C}$ receptors and GABA$_B$ receptors, to produce neuronal inhibition. GABA$_A$ and GABA$_C$ receptors are ligand-gated chloride ion (Cl$^-$) channels from the cys loop family of receptors, and GABA$_B$ receptors are seven-transmembrane domain receptors from the G-proteinâ€"coupled receptor (GPCR) family. Reduction of GABAergic inhibition because of mutation of GABA$_A$ receptors has been shown to be associated with several types of idiopathic generalized epilepsies, including childhood absence epilepsy, generalized epilepsy with febrile seizures plus, and juvenile myoclonic epilepsy.[70,71] Enhancement of GABAergic inhibition is the basis of action of a number of antiepileptic drugs (AEDs).

Î³-Aminobutyric Acid

GABA is synthesized in and released from the presynaptic terminals of GABAergic neurons. Glucose is the primary precursor of GABA, but pyruvate and other amino acids can also serve as precursors when metabolized in the Krebs cycle.[79] The immediate precursor of GABA is glutamate, which can be produced from glutamine by glutamate synthetase or from Î±-ketoglutarate. Glutamic acid is then decarboxylated to form GABA. GABA is degraded by the enzyme GABA transaminase. GABA transaminase converts GABA into succinicsemialdehyde. This reaction involves removal of an amine group from GABA and transformation of Î±-ketoglutarate into glutamate. Therefore, as the GABA is degraded, its precursor molecule is formed, ensuring precursor availability for further synthesis. Succinicsemialdehyde is then degraded by the enzyme succinicsemialdehyde dehydrogenase (SSADH) to form succinic acid. This synthetic and catabolic pathway is called the *GABA shunt*. The shunt is thought to operate by an interaction with adjacent glia. GABA is released presynaptically and is taken up by high-affinity GABA transporters in nerve terminals and glia. In glia, GABA is degraded to succinicsemialdehyde, thus generating glutamate. Glutamate is then converted to glutamine by glutamine synthetase. It is believed that glutamine can then diffuse from the glia into nerve terminals, where it then again converted by glutaminase into glutamate, thus providing a substrate for GABA synthesis. GABA transaminase and SSADH are thought to be bound to mitochondria, whereas glutaminase and GAD are free in the terminal cytoplasm. Glutamine synthetase occurs free in the glial cytoplasm.

GABA$_A$ Receptors

GABA$_A$ receptors are macromolecular proteins from the cys loop family of ligand-gated ion channels that include the nicotinic acetylcholine receptor (nAChR), glycine receptor, and serotonin 5â€“HT$_3$ receptor. GABA$_A$ receptors contain multiple specific binding sites including sites for GABA, antagonists such as bicuculline and picrotoxin, AEDs including barbiturates and benzodiazepines, and the anesthetic steroids. GABA$_A$ receptors form a Cl$^-$-selective channel.[73,90]

GABA$_A$ Receptor Molecular Biology

GABA$_A$ receptors are hetero-oligomeric pentamers that form a transmembrane Cl$^-$channel. Seven GABA$_A$ receptor subunit families (Î±, Î², Î³, Î´, Ï€, Îµ, Î¸) have been identified,[90] and each subunit family is composed of one or more subtypes: (Î±1â€“Î±6), (Î²1â€“Î²3), (Î³1â€“ Î³3), (Î´1), (Îµ1), (Ï€1), and (Î¸1). In addition, several splice variants have been reported. An additional subunit, the Ï subunit, is highly homologous to the GABA$_A$ receptor subunits but primarily forms retinal receptors that have been classified as GABA$_C$ receptors. Members of the same GABA$_A$ receptor family share approximately 70% to 80% sequence homology, whereas members of different families share 30% to 40% sequence identity. The number of potential GABA$_A$ receptor isoforms that could be formed from the 12 Î±, Î², and Î³ subtypes alone is staggering. However, it has been demonstrated that not all potential subtype combinations assemble to create functional GABA$_A$ receptors,[3,4] and the Î±1Î²2Î³2 receptor is likely the dominant native benzodiazepine-sensitive isoform. The stoichiometry of native GABA$_A$ receptors has shown to be 2Î±2Î²1Î³, with an assembly pattern of Î³-Î²-Î±-Î²-Î±, as seen from the synaptic cleft.[6,26,57,110]

GABA$_A$ Receptor Structure

GABA$_A$ receptor subunits are about 450 amino acids in length and have a large N-terminus of approximately 200 amino acids that is shaped by the signature cysteine disulfide bridge and is likely an extracellular domain. The GABA binding site is at the two Î±/Î² subunit interfaces.[101] Hydropathy analysis predicted four transmembrane-spanning domains (M1â€“M4) of about 20 amino acids in length, which have the highest degree of amino acid sequence homology across subunit

families and across the cys loop family in general. The M2 domain is thought to form the GABA$_A$ receptor channel pore.[26] A short (eight amino acids) cytoplasmic segment (M1â€“M2 linker) connects M1 and M2, and a slightly longer extracellular segment (M2â€“M3 linker) connects M2 to M3. Also, a highly variable large cytoplasmic loop spans between M3 and M4 and contains consensus sequences for protein phosphorylation and proteinâ€“protein interaction that vary among subtypes. This domain is important for receptor trafficking and surface clustering through interactions with cytoplasmic proteins.

GABA Binding Site

Detailed structural information is available for the extracellular domain of cys loop receptors based on homology with the acetylcholine binding protein (AChBP),[100] which has been crystallized and solved.[21] The acetylcholine-binding pocket is formed at AChR subunit interfaces by three loops (Aâ€“C) from the positive side and three Î²-strands (Dâ€“F) from the negative side of the protomer. Using mutagenesis and the substituted cysteine accessibility method (SCAM) approach,[1,15,48,86,120] the GABA$_A$ receptor binding pocket has been shown to be similar to that of the AChBP binding pocket.

GABA$_A$ Receptor Conduction Pathway

M2 likely lines the channel, and the amino acids lining the pore are likely Î± helical[126] as is the nAChR M2.[82] Using electron microscopy of crystalline postsynaptic membranes, the nAChR channel has been shown to be tapered, as viewed from the synaptic cleft, and is formed by five Î±-helical segments.[82] The pore has a minimum diameter in the middle of M2 at residues L251 and V255, and this region has been identified as the channel gate.[82] GABA$_A$ receptors also have a 9â€²L in the middle of M2, and mutation of the M2 9â€²L causes destabilization of the closed state,[13] similar to the nAChR. Thus, the GABA$_A$ receptor gate is likely to be similar in location to that of the nAChR.

Coupling of GABA Binding to Channel Gating

Recent insights have emerged into the coupling of binding of GABA to GABA$_A$ receptors and subsequent gating of the channel. The extracellular N-terminal domain is directly connected to the membrane by M1; however, evidence from several sources has suggested that the N-terminal domain also interacts with the extracellular M2â€“M3 linker. Several disease mutations in the M2â€“M3 linker have been identified. In the nAChR, these mutations are associated with congenital myasthenic syndromes[38]; in the GABA$_A$ receptor, they are associated with a generalized epilepsy[7,14]; and in the glycine receptor, these mutations are associated with hyperekplexia.[61] All these mutations decreased receptor current, suggesting a disruption in the coupling of agonist binding to channel gating. Based on the AChBP, it was suggested that loop 2 (and possibly loop 7) interact with the M2â€“M3 linker to couple GABA binding to gating.[54] Using SCAM, gating was shown to induce a conformational change in and/or around the N-terminal half of the M2â€“M3 linker.[9] Using mutagenesis of pairs and triplets of amino acids in the nAChR Î± subunit, a network of interacting amino acid residues have been shown to connect the preM1 region, loop 2, and the M2â€“M3 loop.[64] Thus, coupling of agonist binding to channel gating may involve both direct (pre M1) and indirect (loop 2) pathways that connect to the M2â€“M3 loop. The gating process has been further clarified using electron microscopy of nAChRs.[82,116] Loop 2 of both Î± subunits is positioned such that it contacts the distal M2, just before the beginning of the M2â€“M3 loop. Binding of ACh induces both loop 2s rotate by 15 degrees about an axis passing through the disulfide bridge, normal to the membrane. The loop 2 rotations are associated with M2 rotations, which are translated down M2 to the gate, presumably causing the gate to open. Thus the major transduction of binding to gating appears to pass in the Î± subunits from loop 2 to the distal M2 and then to the M2 gate.

GABA$_A$ Receptor Desensitization

Receptor desensitization occurs when agonist-evoked current declines during continued agonist application. No clear structural basis exists for desensitization of cys loop receptors. Desensitization of nAChRs has been studied using the SCAM technique.[124] The â€œdesensitization gateâ€ was suggested to include the closed gate, but to extend further (more toward the extracellular portion) into M2. GABA$_A$ receptor subunit composition influences current desensitization rates.[37,97,117] In glycine receptors, desensitization is influenced by amino acids at the distal end of M1, leading to the hypothesis that this region and the M1â€“M2 linker served as a hinge involved in the gating of the channel.[69] Using subunit chimeras constructed with N-terminal Î´ sequence spliced to Î³2L sequence at various points within M1 and M2, and using rapid agonist application, fast desensitization was demonstrated to depend on the structure of M1 and proximal N terminus.[12]

GABA$_A$ Receptor Pharmacology

GABA$_A$ receptor pharmacology has been shown to be quite complex.[73,90] To fully activate the receptor, two molecules of GABA are required to bind to two independent sites on the GABA$_A$ receptor channel at the two Î±/Î² interfaces. In addition to GABA, a number of GABA analogs can activate the receptor, including the plant alkaloid muscimol and the synthetic GABA agonist tetrahydroisoxazolopyridinol (THIP). GABA$_A$ receptor currents can be competitively antagonized by the convulsant drug bicuculline and noncompetitively antagonized by the convulsant drug picrotoxin. GABA$_A$ receptor current can also be noncompetitively reduced by the convulsant antibiotic penicillin, which enters the GABA$_A$ receptor channel to produce a fast open-channel block. The antiepileptic benzodiazepines and barbiturates enhance GABA$_A$ receptor currents, but through different binding sites on the GABA$_A$ receptor. In contrast, the convulsant Î²-carbolines, such as methyl 6,7â€“dimethoxy-4â€“ethyl-Î²-carboline-3â€“carboxylate (DMCM), decrease GABA$_A$ receptor current. A number of compounds, including CL 218872, inverse agonist Î²-carbolines, and imidazolpyridines (zolpidem), bind to the benzodiazepine site. In addition to binding benzodiazepine receptor agonists, such as diazepam, and inverse agonists, such as DMCM, the receptor binds a benzodiazepine receptor antagonist, flumazenil, which binds to the receptor and antagonizes the actions of benzodiazepine receptor antagonists and inverse agonists but has little intrinsic activity. In addition to the preceding allosteric regulators, certain anesthetic and naturally occurring neuro- steroids, including alfaxalone, pregnenolone, and androsterone, alter GABA$_A$ receptor current. Most of these anesthetic steroid compounds bind to a specific site on the GABA$_A$ receptor to enhance current.

GABA_A Receptor Physiology

GABA binds to GABA_A receptors and evokes openings that occur in bursts.[74] When the channel opens, it opens to a main conductance level of 27 pS and to two smaller, subconductance levels.[16] GABA_A receptor channels are permeable to a number of anions and exhibit a conductance sequence of $Cl^- > Br^- > SCN^- > F^-$. GABA_A receptor channels are almost exclusively Cl selective, with a permeability ratio of potassium (K) to Cl ions smaller than 0.05. The permeability sequence for large polyatomic anions suggests that open GABA_A receptor channels have effective pore diameters of about 5.6 Ã….

Rapid application of GABA to outside-out patches from hippocampal neurons or to HEK293 cells expressing Î±1Î²3Î³2L receptors evokes rapidly rising (1â€“2 msec) currents that then decay over three to four phases of desensitization.[14,25,45] Following GABA application, the currents deactivate over two phases. GABA_A receptor subunit composition influences current desensitization rates.[14,37,97,117] For example, addition of the Î´ subunit to Î±1 and Î²3 subtypes significantly reduced both the rate and extent of desensitization relative to Î±1Î²3Î³2L receptor currents.[45]

Ensemble currents (whole cell or macropatch currents, inhibitory postsynaptic currents [IPSCs]) observed experimentally represent the summed behavior of individual channels. A complete mechanistic understanding of GABAergic inhibition requires analysis at the level of single channels. GABA_A receptor single channels exhibit complex patterns of activity. GABA increases the probability of channel opening and, after the channel opens, it closes and rapidly reopens in bursts of openings. Increasing GABA concentration increases average open and burst durations. Detailed kinetic analyses of channel behavior have been obtained for native[74,87,115,122] and recombinant[23,39,45] GABA_A receptors, demonstrating multiple open and closed states occurring in bursts. Kinetic models were proposed to account for these properties, with connections of discreet kinetic states (Markov modeling) and incorporating two sequential GABA binding sites, three open states, and ten closed states.[115]

Recombinant Î±1Î²Ï‡Î³2 receptors also exhibit multiple open and closed states.[3,39,45] However, Î±1Î²1Î´ GABA_A receptors have different gating properties, with only two open states that are similar to the two briefest open states of native and Î±1Î²Ï‡Î³2 GABA_A receptors. The model was used to interpret actions of modulators of GABA_A receptor function, including benzodiazepines, barbiturates, neurosteroids, picrotoxin, penicillin, and Î²-carbolines.[111,112,113,114] Using rapid application of GABA to outside-out patches from hippocampal neurons, Celentano and Wong[25] demonstrated three desensitization phases. Jones and Westbrook[52] demonstrated that GABA_A receptors entered long closed states and subsequently reopened, suggesting that desensitized states prolong currents evoked by brief, synaptic-like GABA applications. The combination of single-channel properties and macroscopic kinetic properties, not easily extractable from single-channel recordings (such as activation, desensitization, deactivation), led to a comprehensive GABA_A receptor model.[45]

Channel gating and desensitization have also been shown to affect GABA binding. GABA is locked onto GABA_C and GABA_A receptors by channel opening[27] and, once bound to Î±1Î²3Î³2L GABA_A receptors, GABA is â€œtrappedâ€ by open, preopen, and desensitized states.[14] This trapping of GABA on the receptor prolongs currents following brief GABA application, as occurs during IPSCs.[52] In contrast, it has been reported that ACh is not locked on nAChRs by open states.[43]

GABA_A Receptor Anatomic Distribution and Development

The widespread and overlapping distribution of GABA_A receptor subunit cDNAs identified using in situ hybridization[65,125] and the large number of subunits suggests that GABA_A receptors exist in vivo in multiple isoforms. However, the colocalization of subtype mRNAs does not provide information on subunit assembly. Immunoprecipitation has been used to determine subtypes that coassemble in vivo.[50,89,94,95,108] In the cerebellum, the most likely isoforms are Î±1Î²Ï‡Î³2, Î±6Î²Ï‡Î³2, Î±1Î±6Î²Ï‡Î³2, Î±6Î²Ï‡2Î´, and Î±1Î±6Î²Ï‡Î´ receptors. The Î´ subunit is likely to combine with the Î±6 subtype in the cerebellum and with the Î±4 subtype in the thalamus, and based on coexpression, it may also combine with the Î±1 subtype in the cortex, thalamus, hippocampus, and olfactory bulb. Characterization of GABA_A receptor subunit expression patterns using in situ hybridization has been reported in the developing[63] and adult[62,125] rodent brain. A detailed immunohistochemical study identified general anatomic patterns as well as cell-type specificity within regions and gross subcellular localization (soma versus neurite membranes).[94]

GABA$_B$ Receptors

GABA$_B$ receptors are seven-transmembrane proteins and are coupled to calcium (Ca) or K ion channels via guanosine triphosphate (GTP) binding proteins.[17,18,19] GABA$_B$ receptors are located on presynaptic terminals and on postsynaptic membranes. When activated by GABA presynaptically, GABA$_B$ receptors reduce synaptic transmitter release by decreasing presynaptic calcium entry; when activated postsynaptically, GABA$_B$ receptors produce slow postsynaptic inhibition by increasing K conductance.

GABA$_B$ Receptor Molecular Biology, Structure, and Trafficking

Two different GABA$_B$ receptor subunits have been cloned, the GABA$_{B1}$ and GABA$_{B2}$ subunits.[51,56,59,80,88,123] These subunits have an approximate length of 950 residues, and the GABA$_{B2}$ subunit has two splice variants, GABA$_{B1a}$ and GABA$_{B1b}$.[55] At the amino acid level, GABA$_{B1}$ and GABA$_{B2}$ subunits have approximately 35% identity and 55% similarity, and GABA$_B$ receptors are heterodimers composed of both GABA$_{B1}$ and GABA$_{B2}$ subunits. GABA$_B$ receptors are members of the GPCR superfamily; they have seven membrane-spanning domains and a long extracellular chain at the N terminus. Heterodimerization is required for successful trafficking of GABA$_B$ receptors to the cell surface and for effective agonist-induced activation.[24,42,77,92] The GABA$_{B1}$ subunit appears to be necessary for agonist activation, whereas the GABA$_{B2}$ subunit is involved in trafficking of the heterodimer to the cell surface. When exposed, a C-terminal arginine-based endoplasmic reticulum (ER) retention/retrieval signal, RSRR, results in the retention of unassembled GABAB$_{B1}$ subunits in the ER and prevents surface trafficking of heteromeric receptors. Interaction of C-terminal coiled-coil domains mask the RSRR retention signal motif in the GABA$_{B1}$ subunit and permit cell surface trafficking.[10,77,92] Agonist binds to the GABA$_{B1}$ subunit and produces a conformational change that permits the GABA$_{B2}$ subunit to activate G-proteinâ€“coupled signaling.

GABA$_B$ Receptor Pharmacology

GABA$_B$ receptors were initially defined as sites that were GABA sensitive but were not blocked by the GABA$_A$ receptor antagonist bicuculline.[17] Although GABA is undoubtedly the natural ligand for this receptor, a drug used to treat spasticity, Î²-p-chlorophenyl GABA (baclofen) was shown to be virtually inactive at GABA$_A$ receptors but stereo- specifically active at GABA$_B$ receptors. The active form of baclofen is the minus isoform. Since the identification of baclofen as a specific GABA$_B$ receptor agonist, a number of closely related analogs of baclofen and GABA also have been shown to be agonists. These compounds include Î²-hydroxy GABA, muscimol, 3â€“aminopropopolyphosphinic acid (3APPA), 3â€“aminopropyl (methyl)-phosphinic acid (3AMPA), and CGP44532. The phosphinic acid analogs are the most potent GABA$_B$ receptor agonists, often having affinities 10 to 100 times higher than baclofen.[4] Because GABA$_A$ receptor agonists

such as bicuculline and picrotoxin were inactive at GABA$_B$ receptors, it became important to develop specific GABA$_B$ receptor antagonists to study the effects of synaptic GABA interaction with GABA$_B$ receptors. The first GABA antagonist was the phosphonic derivative of baclofen, phaclofen. Although phaclofen is a very weak GABA$_B$ receptor antagonist, it is selective. In addition, a number of other GABA$_B$ receptor antagonists have been introduced (CGP 35348, CGP 36742, CGP 55845A, CGP 62349, and SCH50911).

GABA$_B$ Receptor Physiology

GABA$_B$ receptors have several different effector mechanisms, including the adenylate cyclase system and Ca and K channels. The actions of GABA$_B$ receptor agonists on these effectors are blocked by pertussis toxin, suggesting that GABA$_B$ receptors couple to their channel targets via a $G_{i\text{Î±}}$- or $G_{o\text{Î±}}$-type G protein (especially $G_{i2\text{Î±}}$). GABA$_B$ agonists inhibit basal and forskolin-stimulated adenylate cyclase in the brain through a G-proteinâ€“dependent pathway to reduce intracellular cyclic adenosine monophosphate (cAMP). GABA$_B$ receptor agonists also decrease voltage-gated Ca channels. Multiple high-threshold and low-threshold Ca channels have been reported.[40,81] High-threshold channels include N-type, L-type, P-type, and R-type channels. The low-threshold channel is a T Ca channel. These channels differ in the voltage range of activation and in rates of inactivation. $GABA_B$ receptor agonists have been demonstrated to reduce current flow through P/Q- and N-type Ca channels.[81] If this effect occurred at presynaptic terminals, this would result in decreased presynaptic Ca entry and, therefore, decreased release of neurotransmitter. The effect appeared to provide a basis for GABA-mediated presynaptic inhibition. These effects of $GABA_B$ receptor agonists have been shown in the peripheral nervous system and have been shown to inhibit excitatory synaptic transmission between hippocampal neurons.[98,103,109,127] It is likely that the effect of $GABA_B$ receptor agonists on reducing high-threshold transient Ca currents accounts for the reduction in synaptic transmission produced by these compounds. Activation of $GABA_B$ receptors has been shown to reduce the excitatory synaptic transmission presumably mediated by glutamate, but $GABA_B$ receptors have also been identified on presynaptic terminals of GABAergic neurons, and thus produce autoinhibition of GABA release from GABAergic nerve terminal. Thus $GABA_B$ receptors appear to be involved in the regulation of GABA release from nerve terminals and to affect the regulation of release of both excitatory and inhibitory neurotransmitters. In addition to regulation of presynaptic Ca channels, $GABA_B$ receptor agonists have postsynaptic action to enhance Kir3â€“type K conductance.[68] In a number of brain regions, including the hippocampus, cerebral cortex, thalamus, septum, and medulla, activation of GABAergic neurons produces biphasic IPSPs. A rapid early bicuculline-sensitive component is followed by a phaclofen- and CGP 35348â€“sensitive slow component. The fast component of the IPSP has been shown to be Cl-mediated, whereas the late slow phase is K-mediated.

Although all $GABA_B$ receptors appear to be heterodimers composed of $GABA_{B1}$ and $GABA_{B2}$ subunits, the role of the $GABA_{B1}$ splice variants has been unclear. Recently this issue has been clarified by the demonstration of differential compartmentalization and functions of dimers containing either the $GABA_{B1a}$ or $GABA_{B1b}$ splice variant. In hippocampal CA3â€“to-CA1 and layer 1 somatosensory cortical dendritic synapses on layer 5 pyramidal neurons, presynaptic glutamate release is inhibited by activation of $GABA_B$ receptors containing the $GABA_{B1a}$ splice variant, whereas activation of $GABA_B$ receptors containing the $GABA_{B1b}$ splice variant mediates postsyn- aptic inhibition.[93,119]

$GABA_B$ Receptor Anatomic Distribution

$GABA_B$ receptors have a widespread distribution in the central and peripheral nervous systems.[17] As has been described earlier, $GABA_B$ receptors exist on the synaptic terminal of excitatory/inhibitory neurons and on the cell bodies of neurons. In the CNS, an uneven distribution of receptors occurs, as measured by receptor autoradiography. This regional heterogeneity undoubtedly is of great importance for understanding the function of $GABA_B$ receptors. The location of $GABA_B$ receptors does not correlate with the presence of $GABA_A$ receptors. There are locations where primarily $GABA_A$ receptors are present and other locations where primarily $GABA_B$ receptors are present. The highest density of $GABA_B$ receptor binding sites appears to occur in the cerebral cortex, certain thalamic nuclei, cerebellum molecular layer, interpeduncular nucleus, and spinal cord dorsal horn.[20,29] Moderate densities of $GABA_B$ receptor sites are also present throughout the hippocampal formation. In addition, $GABA_B$ receptor binding sites have been located in the globus pallidus, habenula nucleus, superior colliculus, and amygdala. In the hippocampus, there is moderate density of binding in the stratum radiatum, dentate gyrus molecular layer, and stratum pyramidale in CA1. In contrast, there is a low level of binding in the subiculum. In the cerebral cortex, a nonhomogeneous pattern of binding is found, with high levels of binding in layers 1 to 3, and moderate levels of binding in layer 4. Thalamic binding is high in the medial geniculate and dorsal lateral geniculate, and low in the ventral lateral geniculate. In the superior colliculus, high binding occurs in the superficial gray layer and low binding in the intermediate gray layer.

Frequency-Dependent Plasticity at Inhibitory Synapses

The magnitude of the conductance change produced by a neurotransmitter or the amplitude of the synaptic potential is referred to as the *strength of synaptic transmission*. In general, the strength of synaptic transmission at most synapses is not invariant; synaptic strength may increase or decrease, commonly because of previous synaptic activity.[75,128] Alterations in the strength can be short-term increases (facilitation) or decreases (depression), or they can be long-term increases (long-term potentiation [LTP]) or decreases (long-term depression [LTD]). GABAergic synaptic inhibition is no exception, except that primarily use-dependent depression is seen at inhibitory synapses. For example, in hippocampus, inhibitory synaptic strength decreases during repetitive stimulation.[8] The basis for use-dependent depression in inhibitory synapses is unclear but could be multifactorial. The most likely mechanisms may involve postsynaptic desensitization of $\mathrm{GABA_A}$ receptors, reduction in driving force due to Cl redistribution, and a loss of the transmembrane Cl gradient or feedback inhibition of GABA release mediated by presyn- aptic $\mathrm{GABA_B}$ receptor autoreceptors. When modest stimulation protocols are employed, such as paired pulse stimulation, it is thought that the primary mechanism of GABAergic synaptic depression is due to feedback inhibition of GABA release mediated by presynaptic $\mathrm{GABA_B}$ autoreceptors.[35,84] However, it is unlikely that the activation of $\mathrm{GABA_B}$ autoreceptors is the sole explanation of synaptic depression at inhibitory synapses because not all GABAergic terminals contain $\mathrm{GABA_B}$ autoreceptors.[11,60] For example, in inhibitory synapses in area CA3 of the rat hippocampus, both $\mathrm{GABA_B}$ autoreceptor-dependent and autoreceptor-independent components of paired-pulse depression have been described. Activation of $\mathrm{GABA_B}$ autoreceptors produces *fast* paired-pulse

depression that lasts for less than 1 second, whereas a second $\mathrm{GABA_B}$ autoreceptor-independent mechanism persists for several seconds. The $\mathrm{GABA_B}$ receptor-dependent fast paired-pulse depression was shown to require activation of several presynaptic inhibitory neurons, whereas $\mathrm{GABA_B}$ receptor-independent paired-pulse depression occurred at single inhibitory synapses.[60] Thus, although GABAergic inhibition is essential for maintaining an appropriate level of excitability in synaptic circuits, under those conditions in which multiple GABAergic pathways are stimulated, GABAergic synaptic strength can be decreased by $\mathrm{GABA_B}$ receptor-dependent as well as $\mathrm{GABA_B}$ receptor-independent mechanisms, thus producing frequency-dependent depression. This phenomenon undoubtedly has significance in the acute disinhibition that may precede the development of epileptiform discharges.

Disinhibition and Epilepsy

Epilepsy is associated with hypersynchronous activation of large populations of neurons, and considerable interest has been focused on the possibility that reduction of inhibition, or *disinhibition*, is associated with the pathogenesis of some forms of epilepsy. The primary genesis for the hypothesis that modified GABAergic inhibition produces epileptiform discharge has been based on the experimental evidence that drugs that block GABAergic inhibition produced paroxysmal bursting in isolated neurons and produced partial seizures in experimental animals when the convulsants are applied topically to the cortex or hippocampus.[99] Application of GABA antagonists, including penicillin, picrotoxin, or bicuculline, produces large depolarizations because of combined giant excitatory postsynaptic potentials, thus producing paroxysmal depolarization shifts (PDSs), which are the interictal manifestation of an epileptiform event. It is thought that production of these epileptiform events requires a combination of reduced GABAergic inhibition, feed-forward excitation, and bursting properties of individual neurons.[125] It is likely that local paroxysmal bursting can spread to involve large areas of the hippocampus or generalize to the cortex when inhibition is further weakened and when other synchronizing factors occur, such as altered extracellular K and Ca concentration.

The ultimate form of disinhibition in epilepsy may be considered to be the conversion of a well-behaved GABA-mediated hyperpolarizing inhibitory event into a malicious depolarizing excitatory potential. Depolarizing or shunting inhibition has long been known to exist is neurons[2] and, depending on the threshold for action potential generation of the innervated cell, it can be inhibitory or excitatory.[106] The latter action is mainly confined to the passive phase of the synaptic potential.[44] The sign of the voltage change evoked by GABA is solely dependent on the reversal potential of the permeant ions ($\mathrm{Cl^-}$ and $\mathrm{HCO_3^-}$) through the channel. Early on during development, most cells are loaded with $\mathrm{Cl^-}$, causing GABA effects to be depolarizing[91] and thus playing a major role in shaping the development of the neurons by activating the influx of the second-messenger cation $\mathrm{Ca^{2+}}$. The depolarizing action of GABA does not last into the adulthood because, at a given stage in development, the activation of various pumps and exchangers make sure that permeant ions become extruded from the cell.[96] However, adult epilepsy is an exception. It seems that, perhaps because of the malfunctioning of some of the anion extrusion mechanisms in the epileptic brain, some principal cells become depolarized by GABA to the extent at which interictal spiking can be induced as if GABA were an excitatory transmitter.[31]

Conclusive evidence that alteration of GABAergic inhibition is involved in the pathogenesis of idiopathic generalized seizures has come from the identification of several $GABA_A$ receptor subunit point mutations in the Î±1, Î³2, and Î´ subunits; these reports have been reviewed.[70,71] The Î³2 subunit mutations include Î³2(R43Q) associated with febrile seizures (FS) and childhood absence epilepsy (CAE),[121] Î³2(K289M) associated with generalized epilepsy with febrile seizures plus (GEFS+,[5], Î³2(Q351X) associated with GEFS+,[47] Î³2(Q1X) associated with severe myoclonic epilepsy of infancy (SMEI),[47] and Î³2(IVS6 + 2T â†' G) associated with GEFS+[53]. The Î±1 subunit mutation, Î±1(A322D), is associated with juvenile myoclonic epilepsy (JME).[32] Two Î´ subunit variants, Î´(R220H) and Î´(E177A), were identified as susceptibility genes associated with GEFS+ and JME.[36]

Inhibition and Synchrony

It would be extremely simplistic to regard GABAergic neurons in the brain as only â€œinhibitory.â€ It has become exceedingly clear over the past decade and a half that the vast anatomic heterogeneity of these cells corresponds to an equal functional diversity.[41,78,83,104] It is also evident that the activity of highly specific subsets of interneurons can entrain various oscillatory rhythms in neuronal networks.[23,41,58,104] Does this action of interneurons amount to â€œinhibitionâ€? Certainly not.

One of the most elegant demonstrations of synchronization through inhibition was done in recordings from two pyramidal cells innervated by a single inhibitory basket cell.[30] If the basket cell was activated during the random and asynchronous firing of the two pyramidal cells, the two cells were both simultaneously inhibited, but started firing together for a few cycles upon their recovery from the inhibition.[30] More recent findings show that depolarizing (shunting) inhibition can serve as a â€œhomogenizerâ€ of diverse firing rates, thus greatly enhancing oscillatory activity in the Î³-frequency range.[118] In light of such synchronizing action of interneurons, the role of inhibition in epilepsies becomes much more complex than initially thought. Depending on which inhibitory interneuron survives in the epileptic tissue, and which GABA receptors suffer from plasticity, the outcome of the inhibitory changes can be pro- or antiepileptic. The general consensus seems to be that perisomatic inhibition, the type of inhibition generally thought of as being responsible for the synchronization of principal cells, is preserved in epileptic brain.[76] In contrast, the interneurons innervating the dendrites of principal cells and of other interneurons show considerably more morphologic plasticity. These GABAergic cells, which also contain various neuropeptide, are lost, sprout, and alter their synaptic contacts, thus leading to a much altered diversity of innervation in epilepsy.[76] The functional significance of these plastic changes are not well understood; one also needs to keep in mind that the morphologic plasticity is accompanied by altered $GABA_A$ receptor expression and molecular composition in epileptic brain.[67,105]

If inhibitory postsynaptic events can lead to synchrony, it is not surprising to find enhanced synaptic activation of $GABA_A$ receptors in some models of epilepsy.[7,33,89] In some epilepsy models, such as FS, the synchronizing effect of an enhanced inhibition is augmented by an increase in other voltage-gated conductances. The parallel increase in the hyperpolarization activated I_h current helps the simultaneous recovery of the principal cells from inhibition and promotes their bursting.[28]

Antiepileptic Drug Action and $GABA_A$ Receptors

There are a number of AEDs whose actions are mediated by an interaction with GABA receptor system.[72] Postsynaptic $GABA_A$ receptor currents are enhanced by barbiturates and benzodiazepines. Presynaptic GABA release is likely modified by the AED vigabatrin. The uptake of GABA has been shown to be modified by compounds such as tiagabine. Finally, valproic acid has been suggested either to enhance the release of GABA or to enhance postsynaptic GABA responses. Gabapentin was designed specifically to be a GABA analog that penetrated into the CNS. Although there are some suggestions that gabapentin may react with the GABA system to enhance GABAergic inhibition, evidence remains uncertain. Blockage of the low-threshold T Ca channelâ€“mediated Ca spike evoked by GABAergic IPSPs from the nucleus reticularis thalami (NRT) may be a mechanism of action of many drugs effective against generalized absence seizures.[34] Spike-and-wave discharges in experimental animals are blocked by $GABA_B$ receptor antagonists,[49,66,102] but the relevance of this observation to treatment of generalized absence seizures in humans remains uncertain.

Finally, felbamate has been demonstrated to enhance GABAergic inhibition, although this result requires confirmation.

Summary and Conclusions

It is quite clear that a focal reduction of GABA-mediated inhibition will produce partial epilepsy and, when produced systemically, will cause generalized seizures. Conversely, drugs that enhance GABAergic inhibition are antiepileptic. Alterations in GABAergic inhibition may be produced by several mechanisms. First, changes could occur in the morphology, axonal arborization, number, excitability, or innervation of inhibitory interneurons. Second, there could be modification of GABA release produced from individual synaptic terminals due to alterations in GABA stores or modifications of GABA-synthesizing or GABA-metabolizing enzymes. Third, a change could occur in the number, distribution, or composition or properties of postsynaptic $GABA_A$ receptors, and of the reversal potential of the permeant ions through these receptors. Fourth, mutations may be present in $GABA_A$ receptor subunits that alter the trafficking or and/or function of $GABA_A$ receptors. Finally, modified forms of GABAergic inhibition are present during development, suggesting the possibility that altered GABAergic inhibition not only is important in epilepsy but may have differential importance during development. The functions of GABAergic system are complex; they include inhibition, excitation, and synchrony. Therefore, in situ, it is difficult to predict how specific alterations in the function of GABAergic mechanisms, some of them genetically determined,[85,107] will produce epilepsy. Nevertheless, newly developed techniques for studying the specific identity of GABA receptors, properties of native GABA receptors, and behavior of GABAergic neurons and synapses should allow a more detailed understanding of the role of GABA-mediated synaptic transmission in epilepsies.

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Chapter 24

Voltage-Gated Ion Channels: Molecular Biology and Role of Mutations in Epilepsy

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Introduction

Voltage-gated ion channels have long been known to be central to the excitability of the brain. However, the recent discovery of several ion channel mutations in patients with seizure disorders (the â€œepileptic channelopathiesâ€) has led to an appreciation of the importance of the molecular mechanisms underlying ion channel function in epilepsy. These experiments of nature have provided a unique insight not only into the mechanisms of seizure initiation and propagation but also into the fundamental molecular biology of ion channel synthesis and function.

What needs to be explained?

A parsimonious description of an epileptic channelopathy attempts to account for lowered seizure threshold on the basis of whether the mutation enhances or reduces the current carried by the channel (gain or loss of function, respectively). However, it is also important to explain the inheritance pattern associated with the mutation. Most of the known mutations associated with seizure disorders are either dominantly inherited or arise de novo in sporadic cases or in the parental germ line. This finding does not necessarily mean that recessive mutations do not occur: It could simply reflect the difficulty of identifying causative genes in kindreds with recessive inheritance.

Some seemingly monogenic epilepsies show extensive variability of clinical manifestations in different members of an affected family (Chapter 18). This variability is apparent as incomplete penetrance, or as phenotypic heterogeneity within a family carrying a particular mutation. Perhaps the best example of this phenomenon is seen in the genetics of a type of epilepsy associated with mutations in genes encoding sodium (Na^+) channels. An important advance came with the demonstration that an extremely pleomorphic epilepsy syndrome, generalized epilepsy with febrile seizures (FS) plus (GEFS+), could be associated with a single mutation in a Na^+ channel subunit[109] (see the section Ion Channel Mutations in Epilepsy). GEFS+ is not a syndrome in the conventional sense because it cannot be diagnosed in an individual. Instead, it describes a spectrum of manifestations of abnormal central nervous system (CNS) excitability in different members of a family, ranging from uncomplicated FSs to malignant forms of epilepsy that can lead to profound mental and physical disabilities and premature death. At present, little is known about the relative importance of genetic and environmental factors in this variability. However, some recent efforts to identify modifying genes, summarized at the end of this chapter, provide a possible way forward.

Diversity of Voltage-Gated Ion Channels

Given the central role of ion channels in controlling neuronal excitability, and their roles as targets of several antiepileptic drugs (AEDs), it has long been speculated that inherited dysfunction of such channels may account for some of the heritability of epilepsy. Indeed, the first mutations discovered to cause epilepsy inherited in a Mendelian fashion were found in genes encoding subunits of voltage- and ligand-gated ion channels.[5,7,14,91,99,108,109] Even though monogenic epilepsies are individually rare, they have now been associated with a wide range of ion channel gene mutations. One or two new channel genes responsible for monogenic epilepsy have been reported in each of the last few years (Chapter 18).

Voltage-gated ion channels underlie both the resting and action potentials of neurons. With the exception of the chloride (Cl^-) channel CLCN2, which was recently implicated in epilepsy,[44] the voltage-gated ion channels that underlie neuronal excitability all contain pore-forming subunits that share a common motif. Indeed, the genes encoding the essential core of ion channels are all thought to be related to a common ancestral prokaryotic potassium (K^+) channel, and together comprise the third largest family in the human genome.[112] The central feature of this family is a pair of transmembrane helices joined by an extracellular loop that plunges back into the membrane and contributes to the ion-conducting pore. Most K^+ channels are composed of four such subunits, so that permeating ions travel through a tunnel lined by four symmetrical peptide chains. Among K^+ channels the largest group consists of subunits that have four additional transmembrane helices, making a total of six membrane-spanning segments, with cytoplasmic tails at either end of the peptide chain (Fig. 1). The crystal structure of a representative voltage-gated K^+ channel has now been solved[67] and is invaluable to efforts to understand the functional impact of missense mutations.

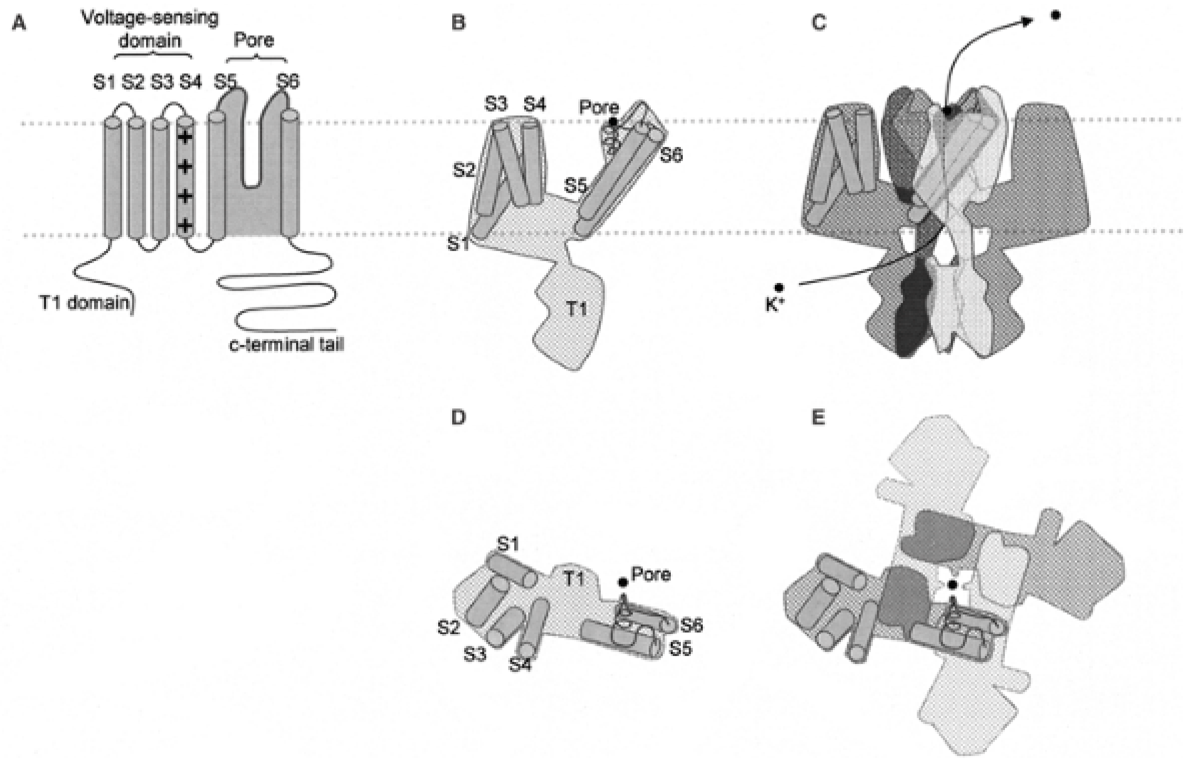

FIGURE 1. Structure of voltage-gated K^+ channels. **A:** A simplified depiction of the peptide chain of a voltage-gated K^+ channel showing the six transmembrane segments (*cylinders*) in the membrane (*dotted gray lines*). The position of the voltage sensor is indicated (+ *signs*). The loop between S5 and S6 forms the pore and selectivity filter (*shaded gray*). The outside of the cell is up, and the intracellular side is down. **B:** A representation of a single subunit of a voltage-gated K^+ channel based on the recent crystal structure.[67] The approximate positions of the helices are indicated along with the pore loop and a single potassium ion in the selectivity filter (*black circle*). The T1 domain is comprised of the N-terminal tail of the subunit and is thought to be important for subunit assembly.[85] **C:** Four subunits arranged to make a channel in the membrane. The helices are only shown in one subunit for clarity. The usual path of a K^+ ion through the lower side of the channel, and out the center of the top is indicated. **D:** A single subunit rotated and viewed from outside the cell, with the positions of the transmembrane domains indicated as in **B**. **E:** Four subunits forming the pore of a voltage-gated K^+ channel viewed looking down at the surface of a cell. The structure

determined by Long et al.[67] largely confirmed the membrane topology represented in **A**, but surprisingly, showed that the voltage-sensing domain (S1â€“S4) is offset to the side of the pore-forming segments (S5â€“S6) when the channel is viewed from above the surface of the membrane (looking into the pore of the channel). The black dot represents a K^+ ion in the pore of the channel.

The typical pore-forming subunit of a Na^+ or calcium (Ca^{2+}) channel is thought to have evolved via twofold duplication of a six-transmembrane domain (6-TM) K^+ channel gene, giving rise to a single protein containing four domains, each of which contains six transmembrane helices (Fig. 2). Although these channels exhibit distinct ion selectivities, they have the same overall topology, pore structure, and fourfold symmetry as the 6TM family of K^+ channels. The different ion selectivities exhibited by K^+, Ca^{2+}, and Na^+ channels are accounted for by a few amino acids in the pore loop. These channels also share a common mechanism of voltage sensing, which involves positively charged amino acids in the fourth transmembrane segment of each subunit (in the case of 6TM K^+ channels) or domain (in the case of Na^+ and Ca^{2+} channels). A complete native ion channel also contains one or more auxiliary subunits, which belong to a far more heterogeneous family of proteins, some of which are entirely intracellular while others contain membrane-spanning segments. These modulate the function of the pore-forming subunits, as well as helping to target them

to their correct destination in the neuron and linking them to scaffolding and signaling proteins.

In addition to their different ion selectivities, which relate the direction of ion flux to the chemical and electrical gradients across the membrane, channels have several other important features that account for their distinct roles in neuronal excitability. Notably, they activate (that is, undergo a conformational change that opens the ion-conducting pathway) at different rates and over different transmembrane voltage ranges. Many channels also inactivate in the presence of sustained depolarization, via a conformational change that is not simply the inverse of the activation event. The fast activation and inactivation kinetics of Na^+ channels, along with the positive reversal potential of Na^+ ions, underlies the upstroke of fast action potentials in almost all mammalian neurons. K^+ channels, which tend to hyperpolarize cells when they open, are largely responsible for setting the resting potential of the cells, as well as curtailing action potentials and shaping the frequency and pattern of repetitive firing. Ca^{2+} channels mediate slow action potentials in some neurons (particularly in the thalamus) but also couple depolarization with intracellular signaling, in the form of Ca^{2+} entry. One of the most important functions of Ca^{2+} channels is to trigger neurotransmitter release at synapses.

This overview of voltage-gated ion channels provides the backdrop summarized for further understanding the specialization and diversity of K^+, Na^+, and Ca^{2+} channels. Each class may be further subdivided into distinct subtypes, encoded by different genes, different splice variants, and different combinations of auxiliary subunits. This variability produces a functionally diverse population of channels with distinct patterns of expression in brain areas, among neuronal populations, and within cell compartments such as dendrites, axons, and pre- synaptic membranes.

Relating Gain or Loss of Function to Epilepsy

A simplistic view of epileptic channelopathies is that gain-of-function mutations of Na^+ or Ca^{2+} channels (that is, mutations that enhance the Na^+ or Ca^{2+} current flow when the membrane is depolarized) should enhance the excitability of neurons and circuits and therefore lower seizure threshold. Conversely,

loss-of-function mutations of K^+ channels should destabilize resting membrane potentials and predispose the brain to seizure. This view is supported, for example, by the fact that several AEDs (phenytoin, carbamazepine, and lamotrigine) are thought to act by stabilizing Na^+ channels in an inactivated state, thus rendering them more reluctant to open upon depolarization.[81] As will be seen, this view is far from providing a full account of how ion channel mutations give rise to epilepsy.

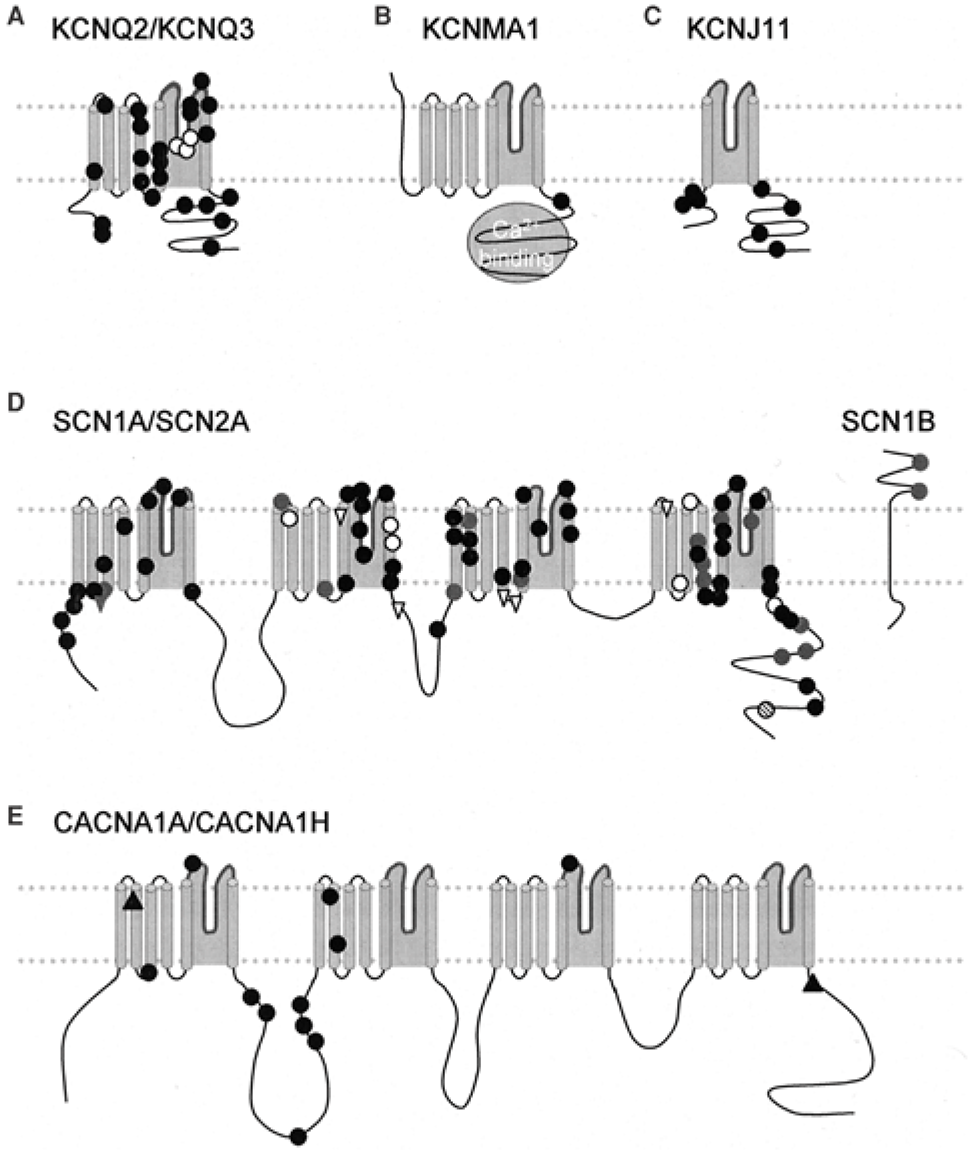

FIGURE 2. Missense mutations associated with epilepsy in voltage-gated channels. **A:** The subunits underlying the M current, the Kv7.2 and Kv7.3 subunits, encoded by KCNQ2 and KCNQ3, respectively. These subunits share the overall six-transmembrane topology of the archetypical K$^+$ channel shown in FIGURE 1A. Mutations in KCNQ2 are black circles, and KCNQ3 are white circles. (Adapted from Turnbull J, Lohi H, Kearney JA, et al. Sacred disease secrets revealed: the genetics of human epilepsy. *Hum Mol Genet*. 2005;14(Spec No. 2):2491â€“2500, with permission.[104]) **B:** The BK channel KCNMA1. This channel contains an extra TM domain before the conserved voltage-sensing domains, traditionally called S0. In addition, the channel contains a conserved Ca^{2+} binding domain (*gray circle*). The approximate position of the mutation associated with epilepsy is indicated by a black circle. Adapted from Du W, Bautista JF, Yang H, et al. Calcium-sensitive potassium channelopathy in human epilepsy and paroxysmal movement disorder. *Nat Genet*. 2005;37(7):733â€“738, with permission.[24] **C:** The approximate positions of missense mutations in KCNJ11 (Kir6.2) linked to DEND syndrome (*black circles*). The two transmembrane segments KCNJ11 are homologous to the S5 and S6 transmembrane segments in the K$^+$ channel shown in FIGURE 1A. Although KCNJ11 does not have a voltage-sensing domain, it is a member of the voltage-gated channel superfamily and likely shares an evolutionary ancestor with 6TM channels. Functional Kir6.2 channels are associated with the SUR receptor, a multitransmembrane protein. Adapted from Hattersley AT, Ashcroft FM. Activating mutations in Kir6.2 and neonatal diabetes: new

clinical syndromes, new scientific insights, and new therapy. *Diabetes*. 2005;54(9):2503â€“2513. with permission.[43] **D:** Missense mutations in Na channels linked to epilepsy. The pore-forming subunit of Na channels contains four domains each with six transmembrane segments homologous to those in the 6TM voltage-gated K^+ subunit. Missense mutations in SCN1A are associated with SMEI (*black circles*), GEFS+ (*gray circles*), intractable childhood epilepsy with generalized tonicâ€“clonic seizures (ICEGTC) (*white circles*), and infantile spasms (*hatched circle*). Missense mutations in SCN2A are linked to GEFS+ (*gray triangles*), and benign familial neonatal-infantile seizures (BFNIS) (*white triangles*). The two mutations in SCN1B linked to GEFS+ are also shown (*gray circles*) along with the membrane topology of that subunit. Many further mutations linked to SMEI are nonsense mutations; these are not shown here because they would be likely to trigger NMD, and thus their approximate position in the protein may not be relevant. Adapted from Meisler MH, Kearney JA. Sodium channel mutations in epilepsy and other neurological disorders. *J Clin Invest*. 2005;115(8):2010â€“2017, with permission.[72] **E:** Mutations in Ca^{2+} channels linked to epilepsy. The overall structure of the voltage-gated Ca^{2+} channels is similar to that of Na^+ channels, but conserved amino acid substitutions in the pore lead to selectivity for Ca^{2+} ions. Missense mutations/polymorphisms in CACNA1H (T-type Ca channel) linked to epilepsy (*black circles*), from Chen Y, Lu J, Pan H, et al. Association between genetic variation of CACNA1H and childhood absence epilepsy. *Ann Neurol*. 2003;54(2):239â€“243, with permission.[16] Mutations in CACNA1A (P/Q type Ca channel) linked to epilepsy (*black triangles*).[49,52] The mutation in the intracellular carboxyl tail of the channel is a nonsense mutation, but may escape degradation from the NMD pathway, and is therefore included with missense mutations.

Currently, missense mutations are the most common type of mutation found in voltage-gated ion channel genes associated with epilepsy. This may however be an artefact of sequencing efforts that focus on coding exons, while ignoring the introns and regulatory sequences within a gene. It may also reflect the potentially more severe impacts of nonsense mutations or mutations that disrupt the regulation of ion channels. Some mutations may not be compatible with fetal viability or with survival to adulthood.

Ion Channel Mutations in Epilepsy

K^+ Channels

For mutations of one type of K^+ channel, the simple view that relates a reduction in seizure threshold to loss of function appears to hold. Kv7.2 and Kv7.3 subunits, encoded by KCNQ2 and KCNQ3, co-assemble to form a slowly activating K^+ channel that shows little inactivation with prolonged depolarization. The subunits are widely expressed in the gray matter of the brain, including Î³-aminobutyric acid (GABA)ergic and dopaminergic neurons of the thalamus and basal ganglia.[19] The heteromeric channels consisting of Kv7.2 and Kv7.3 have the biophysical properties of the so-called *M current,*[110] which is active in many neurons close to the resting potential and is profoundly modulated by muscarinic and other G-proteinâ€“coupled receptors. The molecular identity of this conductance was only resolved with the discovery of the KCNQ2 and KCNQ3 genes. These were identified through a positional cloning effort to elucidate two loci for benign familial neonatal convulsions (BFNC) (see also Chapter 223).[7,14,91] Infants affected by this condition have brief generalized and partial seizures, with otherwise normal brain development and behavior; this topic has been reviewed.[62] The convulsions generally resolve spontaneously by the age of 6 weeks, although they can persist into adulthood in a minority of cases. All the missense mutations in KCNQ2 and KCNQ3 associated with BFNC impair K^+ flux when measured in heterologous expression experiments, mainly by reducing current density.[50,92] Loss of function can be expected to apply for the splice site, frameshift, and gene deletion mutations that have also been reported.

These findings underline the importance of the M current for setting the resting potential and firing rates of neurons that have a strategic role in seizure initiation and/or propagation.[20,63] Furthermore, the reasonably straightforward link between mutations that decrease the M current and the development of epilepsy has led to renewed interest in the experimental AED retigabine, which relatively selectively increases M currents; two reviews on this topic have been published.[20,103] Why infants carrying KCNQ2 or KCNQ3 mutations â€œoutgrowâ€ neonatal convulsions is unexplained. Because the mutations are dominantly inherited, only one allele of one of the two constituent subunits of the heteromeric channels is potentially defective in affected individuals, so there is some degree of redundancy. Moreover, a developmental increase in seizure threshold may occur during the first few weeks of life, or there may be a gradual increase in expression of the remaining, unaffected KCNQ2/3 alleles, such that a small reduction of K^+ flux may become insufficient to manifest as spontaneous convulsions. Interestingly, one missense mutation, associated with a broader syndrome that includes myokymia in adulthood, as well as neonatal convulsions, alters a voltage-sensing residue of KCNQ2.[23] This mutation produces a slowing of activation that persists upon coexpression of wild-type KCNQ2 and KCNQ3, suggesting a dominant effect on heteromeric channels.

In striking contrast to mutations in KCNQ2 and KCNQ3, mutations found in two other classes of K^+ channels associated with epilepsy lead to a gain of function. The KCNMA1 gene, which encodes the pore-forming subunit of a voltage- and Ca^{2+}-sensitive K^+ channel, has recently been linked to a syndrome characterized by generalized epilepsy and paroxysmal dyskinesia.[24] The large-conductance Big K^+(BK) channel encoded by KCNMA1 is widely expressed in the CNS. It contributes to fast neuronal repolarization following action potentials and to the early part of the afterhyperpolarization. It is also present presynaptically, where it may curtail neurotransmitter release. Surprisingly, the KCNMA1 mutation identified by Du et al.[24] in a single large family increases the open probability of these channels when expressed in vitro, such that they mediate a larger K^+ flux than wild-type channels over a range of transmembrane voltages or intracellular Ca^{2+} concentrations. A possible explanation for the occurrence of seizures and dys- kinetic paroxysms is that accelerated repolarization allows cells to fire repetitive action potentials. This is consistent with the effect of experimental deletion of an auxiliary subunit in the mouse, which paradoxically enhances BK channel function and is associated with temporal lobe seizures.[9]

Gain-of-function mutations in the KCNJ11 gene, which encodes the adenosine triphosphate (ATP)-sensitive inwardly rectifying K^+ channel Kir6.2, are associated with neonatal diabetes. Although this channel is abundant in the pancreas, where it gates the release of insulin, it is also widely expressed in the brain. Interestingly, some mutations that dramatically reduce the sensitivity of the channel to intracellular ATP (which normally closes the channels) are, in addition, associated with developmental delay, muscle weakness, and epilepsy (the DEND syndrome).[37,78,79] Mutant Kir6.2 channels tend to be open at the resting potential, so they are unlikely to lead to neuronal hyperexcitability. Why, then, are they associated with seizures? It has been suggested that ATP-sensitive K^+-channel subunits (and the sulfonylurea receptors associated with them in the native channel complex) are expressed to a greater extent in inhibitory interneurons than in pyramidal cells, and the disproportionate inhibition of interneurons by mutant Kir6.2 subunits may lead to seizures; see Ashcroft[4] and citations within.

Na^+ Channels

Many heterozygous Na^+ channel mutations are associated with epilepsy. The first missense mutation identified in a GEFS+ kindred affects the Î²1 auxiliary subunit encoded by SCN1B (see also Chapter 256). This subunit has a single transmembrane segment, and the mutation disrupts a cysteine bond within the extracellular portion of the protein, preventing it from modulating the function of the pore-forming subunit.[109] Although this represents loss of function for the SCN1B gene, the effect on Na^+ currents appears to be a net gain of function, because one of the normal roles of Î²1 is to accelerate fast inactivation. Impairment of fast inactivation represents a striking parallel with mutations in SCN4A, which encodes the pore-forming subunit of the skeletal muscle Na^+ channel, associated with hyperkalemic periodic paralysis and paramyotonia.[55] Impaired fast inactivation of muscle Na^+ channels gives rise to a persistent Na^+ current, which leads to depolarization and repetitive firing of muscle fibers.

Several mutations in SCN1A, encoding the pore-forming subunit of the brain $Na_V1.1$ channel, have since been identified in other families with GEFS+[27]; reviewed in Lerche et al.[63] Some of these have also been reported to impair fast inactivation.[69] This parallel between muscle and neuronal Na$^+$ channel mutations has, however, been challenged by several observations. First, detailed biophysical examination of several SCN1A mutations reveals effects on activation threshold and other parameters that imply that at least some of them result in loss rather than gain of function.[1,68,96] That is, depending on the pattern of membrane potential changes imposed on mutant Na$_V$1.1 channels, they may be more reluctant to open than wild-type channels. Second, disruptive mutations of SCN1A are a frequent cause of severe myoclonic epilepsy of infancy (SMEI, or Dravet syndrome).[18,100] This intractable pediatric epilepsy syndrome includes febrile and afebrile generalized and partial seizures, and is associated with episodes of status epilepticus, developmental arrest and regression, and mortality in childhood. It is generally sporadic, although it also occurs in families with a history of FSs. Indeed, an overlap occurs between GEFS+ and SMEI.[87] SCN1A mutations associated with SMEI are frequently de novo, and are typically nonsense, splice site, and frame shift mutations, although missense mutations also occur. Many of these mutations are expected to lead to complete loss of function (see later discussion). Finally, missense mutations in SCN1A have also been shown to occur in a milder pediatric syndrome, intractable childhood epilepsy with generalized tonicâ€“clonic seizures (ICEGTC),[34] with a variety of effects on activation and inactivation kinetics.[83] Notwithstanding the continued uncertainty about whether impaired Na$^+$ channel inactivation found in some GEFS+ mutations outweighs the other kinetic alterations, there is general agreement that the severe end of the GEFSâ€“SMEI spectrum is consistently associated with loss of function SCN1A mutations. In keeping with this, lamotrigine, which promotes Na$^+$ channel inactivation, can aggravate SMEI.[40]

The controversy surrounding gain versus loss of Na$^+$ channel function in GEFS+ calls for an improved understanding of the normal role of the Î²1 subunit and of Na$_V$1.1 channels in neuronal excitability. Î²1 is ubiquitously expressed and co-assembles not only with the pore-forming subunit encoded by SCN1A but also with several other Na$^+$ channels, including Na$_V$1.2 encoded by SCN2A. Interestingly, Na$_V$1.1 and Na$_V$1.2 have complementary expression profiles in many neocortical neurons, with Na$_V$1.1 predominantly expressed in the soma and dendrites, whereas Na$_V$1.2 is mainly located in the axons. Recently, heterozygous SCN2A mutations were identified in association with another pediatric seizure disorder, benign febrile neonatal/infantile convulsions (BFNIC).[45]

A possible explanation for the association of loss-of-function mutations of Na$^+$ channels with epilepsy is that they are more important for the firing of inhibitory interneurons, although this remains to be tested. Alternatively, Na$^+$ channel mutations might result in unexpected compensatory alterations in the expression of other channels, resulting in a hyperexcitable state. Genetic mouse models may provide an important insight into the consequences of deletion or missense mutations of Na$^+$ channels. The homozygous SCN1B knockout has seizures and ataxia, and exhibits subtle morphologic abnormalities in myelinated axons.[15] Interestingly, Na$_V$1.3 expression is increased in some neurons, providing some support for the hypothesis that epilepsy arises from compensatory alterations in other channels. The phenotypes of SCN1A knockin and knockout mice have not yet been reported.

Ultimately, we need to know how Na$^+$ channels behave in situ in people affected by these mutations. Although brain tissue is not accessible to detailed biophysical analysis, Bostock and colleagues have developed transcutaneous stimulation and recording methods that yield an insight into the conductances underlying action potential generation and refractoriness in peripheral nerves.[8] Neither SCN1A nor SCN2A are thought to be expressed in peripheral nerve. However, Î²1 subunits are found in motor axons. A comparison of controls and subjects with the original SCN1B mutation associated with GEFS+ reveals changes that imply a loss of excitability[59] consistent with a decreased number of Na$^+$ channels expressed in the nodes of Ranvier, rather than with a change in channel gating.[15] This again points to a loss-of-function effect, leaving unexplained the occurrence of seizures if the same phenomenon occurs in the brain.

Ca^{2+} Channels

T-type Ca^{2+} channels are unusual among Ca^{2+} channels in that they activate with relatively small membrane depolarization from resting potentials, but are also readily inactivated with maintained depolarizations. These properties mean that they mediate a transient Ca^{2+} conductance, revealed by briefly depolarizing neurons from a relatively negative potential. This can be demonstrated in thalamic neurons, which express T-type channels. These cells can be induced to fire rhythmic bursts of Na$^+$ action potentials riding on a slower T-type Ca^{2+} action potential. As each Ca^{2+} action potential terminates upon inactivation of the T-type channels, the neuron hyperpolarizes (especially if it receives a concurrent inhibitory synaptic input), following which the cycle repeats itself as the T-type channels recover from inactivation and begin a new Ca^{2+} action potential. Because of their association with rhythmic burst-firing, T-type channels have long been suspected to play a central role in spike-and-wave epilepsy, which manifests as excessive synchronous oscillations in the thalamocortical loop.

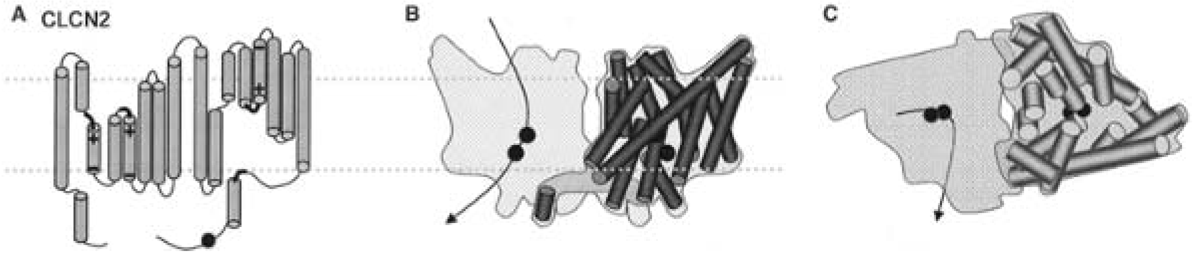

FIGURE 3. Structure of voltage gated Cl$_-$ channels. **A:** The simplified membrane topology of ClC channels. They are composed of 12 helical segments of varying lengths and have no evolutionary relationship to the voltage-gated cation channels. The pore of ClC channels is assembled from charged helices (*indicated by + and â€“ signs*) and amino acids in the loops between selected helices (*thick black lines*). The approximate position of the missense mutation in the Cl$_-$ channel ClC-2 (CLCN2) associated with IGE is indicated (*black circle*).[44] **B:** The predicted assembly of a ClC channel as resolved from crystal structure (from Dutzler R. The structural basis of ClC chloride channel function. *Trends Neurosci*. 2004;27(6):315â€“320, and Dutzler R, Campbell EB, Cadene M, et al. X-ray structure of a ClC chloride channel at 3.0 A reveals the molecular basis of anion selectivity. *Nature*. 2002;415(6869):287â€“294, with permission[25,26]). Two subunits, each containing a pore, assemble to create a functional channel. Not all helices cross the membrane, and most are tilted to give an overall rhomboid shape. Helices are only shown in only one of the two subunits for clarity, and the path of a Cl$_-$ ion into a cell is indicated with two ions shown inside each curved pore. **C:** A ClC channel viewed from outside the cell, looking down at the pores. The positions of four Cl$_-$ ions are shown inside the subunits (from Dutzler R. The structural basis of ClC chloride channel function. *Trends Neurosci*. 2004;27(6):315â€“320, and Dutzler R, Campbell EB, Cadene M, et al. X-ray structure of a ClC chloride channel at 3.0 A reveals the molecular basis of anion selectivity. *Nature*. 2002;415(6869):287â€“294, with permission[25,26]).

The pore-forming subunits of three distinct subtypes of T-type channels (Ca$_V$3.1, Ca$_V$3.2, and Ca$_V$3.3) are encoded by CACNA1G, CACNA1H, and CACNA1I, respectively.[76] Their characterization led to confirmation that ethosuximide, effective in spike-and-wave epilepsy, is a T-type Ca^{2+} channel blocker. This, together with their role in thalamic burst-firing, led to the prediction that gain-of-function mutations in T-type channels may occur in idiopathic generalized epilepsy. Several heterozygous CACNA1H polymorphisms have been identified in patients with childhood absence epilepsy (CAE).[16] However, the relationship to epilepsy requires confirmation in other populations: Some polymorphisms identified in Australian families did not segregate with epilepsy.[46] Functional characterization of the mutations in vitro has revealed several effects on activation and inactivation kinetics, which in most cases imply an increase in T-type currents.[57,58,106] However, some mutations had no detectable effect or even showed loss of function. Because some of the effects were subtle, and the polymorphisms do not cosegregate with disease in most cases, CACNA1H may be a susceptibility gene rather than a causative gene for CAE and other forms of idiopathic generalized epilepsy. Interestingly, when two polymorphisms were introduced into the CACNA1H gene, they sometimes gave rise to biophysical alterations that were not seen with either mutation on its own.[106] This calls for further work to elucidate the full impact of combinations of polymorphisms in CACNA1H and other genes encoding Ca^{2+} and other channel subunits to determine what changes in neuronal excitability are necessary to induce the disease. For the moment, as with the constellation of mutations in Na^+ channels linked to GEFS+, the link between T-type channel function and epilepsy remains incompletely understood.

High-threshold neuronal Ca^{2+} channels also exist as a triplet of subtypes ($Ca_V2.1$, $Ca_V2.2$, and $Ca_V2.1$). Of these, $Ca_V2.1$ (also known as the P/Q type channelâ€"a terminology that reflects its somewhat variable pharmacologic and biophysical properties and abundant expression in cerebellar Purkinje

neurons) is a major mediator of the presynaptic Ca^{2+} influx that leads to neurotransmitter release both in the CNS and at the neuromuscular junction. Mutations in the CACNA1A gene encoding the pore-forming subunit of the $Ca_V2.1$ channel have been linked to episodic ataxia type 2, familial hemiplegic migraine, and spinocerebellar ataxia type 6 (reviewed by Kullmann[61]). Recently, two human CACNA1A mutations have been shown to be linked to ataxia accompanied by spike-and-wave epilepsy.[49,52] One of these is a missense mutation, which leads to a radical amino acid substitution in a highly conserved transmembrane segment.[49] In this case, the main effect seems to be a decrease in total P/Q-type Ca^{2+} current in cells expressing the mutant. The location of the missense mutation in a transmembrane segment, and the reduced ability of heterologously expressed mutant channels to reach the plasma membrane, suggest that this mutation may lead to the disease not merely by a change in channel kinetics, but by a change in the folding and trafficking of the channels.

Why epilepsy should accompany loss-of-function CACNA1A mutations is far from clear. Mutations associated with episodic ataxia type 2 without epilepsy also give rise to various degrees of loss of function. Thus, it is possible that modifying genes or environmental/developmental factors also play a role in determining whether epilepsy occurs or not. Some clues as to the possible reason why seizures occur come from examining mice with $Ca_V2.1$ mutations. Several inbred strains of mice with a combination of ataxia and spike-and-wave epilepsy harbor mutations in CACNA1A and genes encoding auxiliary subunits of $Ca_V2.1$ channels.[30] Some of these mice also have unexpected increases in T-type currents in thalamic neurons, possibly as a developmental compensation.[1]

Cl_- Channels

The ClC family of voltage-gated Cl_- channels is not related to the voltage-gated cation channel superfamily. It belongs to a distinct family of channels containing two pores and consisting of two identical subunits (Fig. 3).[51] The importance of voltage-gated anionic currents in epilepsy is underscored by the discovery of five mutations in families with idiopathic generalized epilepsy (IGE) in one of these unrelated voltage-gated channel genes (CLCN2).[22,44] ClC channels are thought to have a variety of functions in many tissue types but, in neurons, they are implicated in maintaining the Cl_- gradient required to make GABAergic synapses hyperpolarizing.[51] Two of the predicted mutant sequences failed to produce any current when expressed in vitro,[44,74] and thus may reduce the inhibitory effects of GABA currents, leading to hyperexcitability. A third mutation changes a single amino acid in the CLCN2 mRNA and was shown to lead to a depolarizing shift in the voltage dependence of the current.[44] A separate study reported that this mutation changed the modulation of the channel by intracellular nucleotides.[22] Further complicating the analysis of these mutations is the presence of multiple, functionally different, alternatively spliced transcripts of the CLC2 gene,[10,17] some of which affect sequences adjacent to the missense mutation. The mutation may have different effects on different splice variants, and it is not clear which variants are expressed in neurons and which are restricted to other cell types.

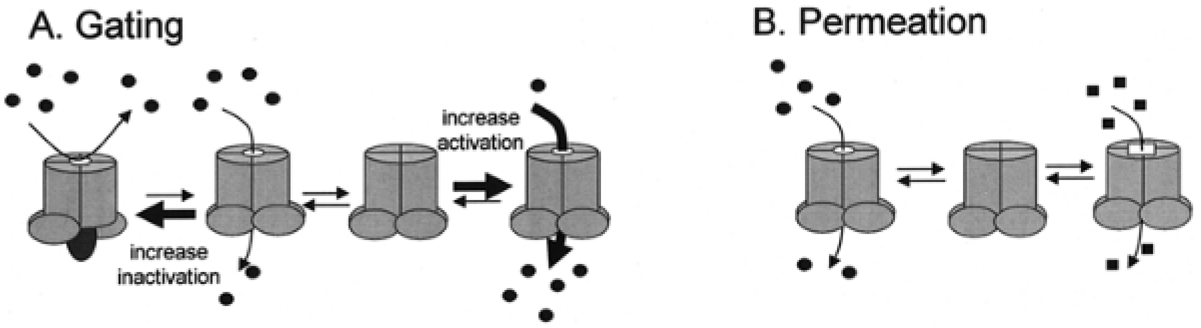

FIGURE 4. Possible effects of missense mutations on the behavior of channels. **A:** Missense mutations may change the likelihood of opening or of shutting once opened, and thus lead to increased or decreased ion conduction. In addition, missense mutations may change the rate of inactivation. **B:** Mutations may change the selectivity or permeation of channels, without changing the rate of opening. These sorts of changes are rare. More often a mutation will reduce permeation through the pore without changing the ion selectivity.

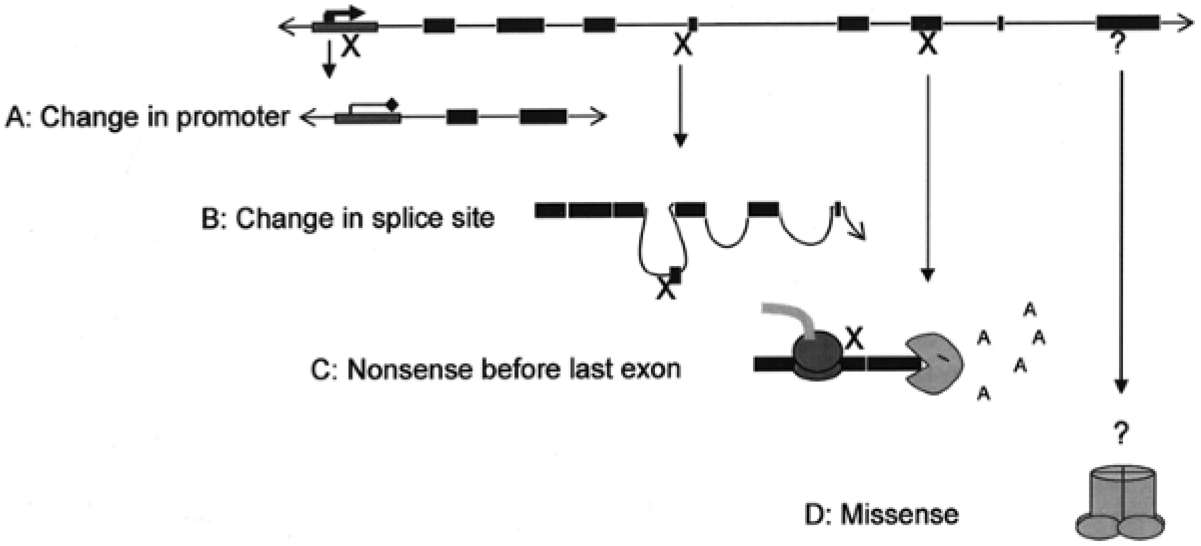

FIGURE 5. Mutations that disrupt DNA and mRNA processing. **A:** Mutations in the promoter of a gene may decrease or increase the amount of transcription from that gene, or the amount of mRNA made. **B:** Mutations in splice sites may destroy the ability of the spliceosome to recognize and excise an intron. This leads to the translation of intronic sequences and often results in nonsense and frameshift mutations. **C:** Nonsense mutations lead to nonsense-mediated decay so long as they are before the last exon/exon splice boundary. The first ribosome to translate an mRNA pauses on a nonsense codon and, unless all exon/exon boundaries have been crossed, that mRNA is destroyed by RNAses in the cell before further translation occurs. **D:** Missense mutations can have varying effects on the behavior of channels (see Fig. 4).

Ion Channel Biogenesis

The heterologous expression of mutant channel genes makes it relatively straightforward to characterize the consequences of individual mutations for the kinetic parameters of the channels (although extrapolation to clinical manifestation remains speculative, as noted earlier). However, many human channelopathies are not linked to simple missense mutations that change the gating of channels (Fig. 4). They are instead associated with mutations that have their effect on ion channels before they even reach the membrane. Mutations that disrupt the biogenesis of ion channels are much more difficult to study experimentally.

This section addresses the stages of biogenesis, starting with gene transcription (Fig. 5). Although direct evidence that all these processes are disrupted in human epilepsy is lacking, we argue that they are essential to understanding the molecular

and cellular consequences of many of the genetic defects identified in seizure disorders.

Transcription

Because DNA transcription is under the control of promoters, which play a central role in regulating the neuronal expression of ion channel genes, mutations within promoter regions might be expected to be an important disease mechanism.[84] For example, a mutation that prevents a copy of SCN1A from being transcribed might lead to the same phenotype as seen in mutations that disrupt channel biogenesis at a later stage, such as truncation. Perhaps surprisingly, no mutations in CNS ion channel promoter regions have been unequivocally associated with inherited disorders. However, this might reflect the poor understanding of promoter structures and the priority given to searching for mutations in coding regions.

Although there is very little evidence on the genetic causes of altered ion channel transcription in human disease, considerable attention has recently been given to acquired changes. Notably, axon damage can lead to changes in the transcription of several Na^+ channel genes, possibly accounting for a lowering of threshold for action potential initiation, and therefore contributing to neuropathic pain.[42] This phenomenon, called â€œtranscriptional channelopathy,â€ is reviewed by Waxman.[111] Experimental epilepsy models have been reported to alter Na^+ channel expression in vivo[66] as well as in vitro.[2] The mechanisms underlying altered transcription are poorly understood, and the consequences unpredictable. Moreover, a related

phenomenon may explain why some genetic defects are associated with the altered expression of other genes. Thus, it is possible that SCN1A mutations that should, on their own, lead to Na^+ channel haploinsufficiency could indirectly drive other promoters enough to lead to an excess of related Na^+ channel transcripts.

Mutations Leading to Faulty mRNA Processing

The importance of mRNA processing in neurologic disease is highlighted by the fact that many disease-associated mutations fall not in the coding exons, but in regions that disrupt mRNA splicing. Such mutations can result in exon skipping, or in an aberrant sequence (arising when an intronic sequence is included in the mature mRNA) and premature stop codons. Factors that regulate the stability of an mRNA or its translation can also have dramatic impacts on the level of a protein expressed. Sequences in introns and intronâ€“exon boundaries, which are not a part of the final protein and which are still poorly understood, can regulate alternative splicing and mRNA turnover and thus have an effect on the function or amount of protein produced.[35,64]

Nonsense-Mediated Decay

Mutations that insert premature termination codons in mRNAs have been estimated to account for 30% of inherited human genetic disorders.[33,107] These premature termination codons may be inserted either by a nonsense or frameshift mutation within a coding exon, or by abolishing a splice site, thus leading to translation of an intron or a frameshift in the transcript (see the section Alternative Splicing).

Most mutations that harbor premature termination codons probably do not produce a truncated protein but instead target the nascent mRNA for rapid degradation by the nonsense-mediated decay (NMD) pathway.[71,88] In some human genetic diseases, frameshifts, premature termination, and aberrant splicing often result in relatively mild defects in heterozygotes, probably because the mRNA from the mutant allele is destroyed before any potentially disruptive protein is produced. However, this generalization does not always hold: Many of the mutations linked to SMEI give rise to premature stop codons. To date, there is no direct evidence on the role of the NMD in human ion channel truncation mutations, but this may be largely because mRNA from affected tissues is not readily available for investigation.

In some cases, mRNAs containing premature stop codons can escape the NMD. An mRNA that contains a premature termination codon within about 50 bases of the final splice site fails to trigger NMD pathway and, as a result, a truncated protein is produced.[107] Similarly, a premature stop codon occurring in a gene that is transcribed from a single exon is also predicted to escape NMD and lead to translation of a truncated peptide. An example is a nonsense mutation in the KCNA1 gene, which has only one exon and encodes the Shaker-type K^+ channel Kv1.1. Mutations in this gene are associated with dominantly inherited episodic ataxia type 1 (EA1)[11] and a spectrum of related disorders ranging from muscle cramps to epilepsy.[28] A nonsense mutation in the C-terminus of the protein causes a severe drug-resistant form of the disease.[28] Expression studies show that, when the mutant allele is translated in heterologous expression systems, it exerts a dominant-negative effect on the wild-type allele.[70,82]

There are some hints that even transcripts that contain premature stop codons in exons 5â€² to the last exonâ€“exon junction can, under some circumstances, escape degradation and give rise to translated peptides. For example, radically truncated channels corresponding to fewer than the four homologous domains of neuronal Ca^{2+} channel subunits have been detected in several tissues, including the brain.[54,90] It has been argued that at least some of these peptides arise from alternative splicing rather than from posttranslational cleavage, and this might represent part of the normal variability of gene products rather than a pathologic phenomenon. Unexpectedly, experimentally truncated Ca^{2+} channels can have a dominant negative effect on full-length channels when they are co-expressed in vitro.[80] It is not known what function truncated channels may have in vivo.

Alternative Splicing

The recent completion of the human genome project has shown that humans have many fewer genes than expected on the basis of protein diversity in the brain.[41] This discrepancy is to a great extent explained by alternative splicing of mRNAs (Fig. 5). Through alternative splicing, a final gene product can contain (or lack) any of several distinct alternative amino acid sequences that confer distinct properties to the entire protein. Thus, depending on posttranscriptional splicing, individual genes can encode a range of proteins with subtle variations in function (reviewed in Lipscombe[65]). Genetic variability in splice donor or acceptor sites that control this form of mRNA processing can bias the relative proportions of the protein variants. Tate et al.[102] recently studied a common single nucleotide polymorphism falling in the splice site of an alternatively spliced exon of SCN1A, the Na^+ channel gene implicated in GEFS+ and SMEI. This polymorphism was highly significantly correlated with the maximal dose of phenytoin or carbamazepine (both of which act upon $Na_V1.1$) prescribed in a large cohort of people with epilepsy. Although the polymorphism did not appear to be correlated with the development of epilepsy per se, it appeared to have an effect on its treatment. Whether the differences in maximal dose reflected differences in seizure control or in tolerability was not determined. Interestingly, epilepsy per se also appears to affect splicing at the same site in Na^+ channels.[3,36,102] This raises the possibility that drug responsiveness and possibly biophysical properties of $Na_V1.1$ channels are affected both by inheritance and by epilepsy itself, by converging upon alternative splicing.

The mRNAs of many of the ion channels linked to epilepsy are subject to extensive alternative splicing. As yet, little is known about the expression levels of different splice variants in different cell types, and about the impact of splice variants on the function of channels. It is possible that, depending on the splice variant background, individual genetic polymorphisms may have dramatically different effects.

mRNA Editing

RNA editing in mammalian ion channels was first reported for ionotropic glutamate receptor subunits.[95] In some neurons, nearly 100% of the glutamate receptor subunit GluR2 mRNA is edited after transcription to change a single amino acid in the pore region of the channel from a glutamine to arginine. This change has profound effects on the biophysical properties of the channel,[101] as well as on its tetramerization[38] and export from the endoplasmic reticulum (ER).[39] Recently, it has been reported that genes encoding many other CNS signalling proteins undergo mRNA editing,[48] although generally to a lesser degree than does GluR2. RNA editing requires a conserved complementary sequence to form base-pairs with the region that is targeted for change. Mutations in this sequence might

be buried deep within long introns and yet could have an impact on the coding sequence of the target exon. Thus, it is possible that mutations that do not change the amino acid sequence directly still have an effect on a channel by interfering with RNA editing.

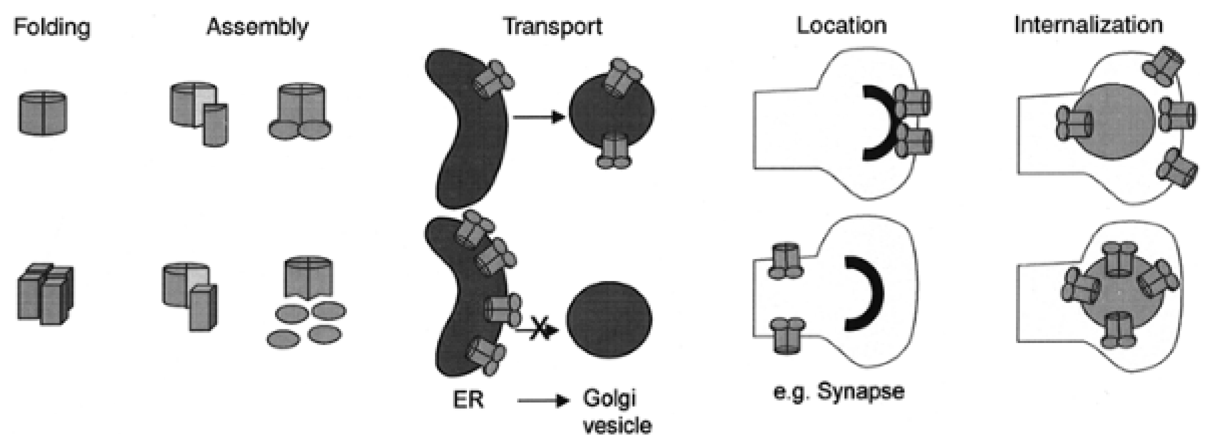

FIGURE 6. Mutations affecting protein processing. Mutations in regions that are structurally important can disrupt the folding of subunits. This can lead to the failure of subunits to assemble, the failure of accessory subunits to bind, and may trigger UPR and reduced translation and transcription. In addition, failure to assemble may prevent channels from leaving the ER or reaching the surface or the correct region of the cell. Finally, mutations may affect how long channels remain in the membrane before they are targeted for internalization and degradation.

RNA editing occurs in the human KCNA1 gene, which, as mentioned above, encodes Kv1.1,[48] a K^+ channel linked to episodic ataxia and myokymia, as well as epilepsy[28] RNA editing switches isoleucine to valine at a site in the S6 transmembrane domain lining the cytoplasmic pore that is important in fast inactivation. This residue acts as a receptor for cytoplasmic inactivating peptides that plug the pore of the channel upon sustained depolarization.[115] Interestingly, missense mutations affecting two neighboring pore-lining valine residues that also act as receptors for the inactivating peptide have been found in families with EA1.[28] Other editing sites have been reported in the N-terminus of the squid ortholog of Kv1.1, where they have a profound effect on channel assembly.[85] These observations imply that it may be important to consider an impact on RNA editing for seemingly conservative genetic variants linked to epilepsy.

Translation, Folding, and Trafficking

Some missense mutations may cause haploinsufficiency by preventing channels from reaching the surface of the cells (Fig. 6). Some SCN1A missense mutations associated with SMEI and GEFS+ have been shown to produce no current when expressed in vitro.[68] The amount of surface expression of these mutants has not been measured, so it is not known whether they reach the plasma membrane, but some channels have been shown to be retained in the ER until folded and assembled properly (see the section Subunit Assembly). Interestingly, two of the three different mutants shown in Lossin et al.[68] not to produce current were associated with GEFS+, whereas the third was associated with SMEI, a more severe clinical phenotype; yet, in the heterologous system, their effect was identical. This raises the possibility that the different mutants are processed differently in the brain, in a fashion not duplicated in vitro, such that the impact of the mutations associated with the less severe phenotype is attenuated.

Translation depends not only on the integrity of the mRNA and the ribosome apparatus but also on the ER. Misfolded proteins can jeopardize the entire cell. High concentrations of unfolded proteins can trigger stress responses implicated in the cell death associated with several neurologic disorders, including Alzheimer disease.[32] Under conditions of ER stress transcription in general is suppressed, most translation is inhibited, and protein degradation is increased[113]; collectively, these changes are known as the unfolded protein response (UPR). This provides a possible explanation for an otherwise puzzling observation: As mentioned earlier, some Ca^{2+} channel truncations, which closely mimic naturally occurring mutations associated with episodic ataxia and epilepsy, have a dominant negative effect on the wild-type allele even when no direct evidence suggests an interaction between the peptides.[52,75,80] If, as has been proposed, ion channels are in a class of â€œdifficult-to-foldâ€ proteins, a mutation in one allele that leads to an accumulation of unfolded proteins in the ER may disproportionately target other channel subunits waiting to be folded for degradation, including those encoded by the wild-type allele.

Subunit Assembly

Mutations can also potentially affect channel assembly. A cluster of missense, frameshift, and truncation mutations of KCNQ2 associated with BFNC occur in or near a C-terminal domain that affects assembly of heteromeric channels.[21,89,92] The truncation mutations are in or very near the end of the mRNA, and so are unlikely to trigger NMD. Instead, they are most likely to produce truncated or frame-shifted proteins. This C-terminal region of the subunit is located in the intracellular space and is thought to be important in subunit interactions.[89] Biochemical analysis of one KCNQ2 mutation that dramatically changes this C-terminal end of the protein has shown that the mutant subunits cannot produce current on their own, possibly because they are rapidly degraded.[94] When these mutants are allowed to co-assemble with KCNQ3 subunits, they are stabilized and able to produce currents with normal kinetics.[94] It is becoming evident that the fate of many ion channel subunits depends on their ability to assemble with the correct mixture of partners to form a complete channel.

In some cases, the subunits that are disrupted by mutations are not essential for channel function, but instead are important for modifying channel kinetics. An important example is the SCN1B mutations associated with GEFS+. SCN1B encodes the Î²1 subunit of Na^{+} channels, which accelerates fast inactivation. The first mutation identified in GEFS+ disrupts a cysteine bond in Î²1, and probably leads to degradation of the subunit.[109] The consequence is slowed inactivation, which could be interpreted as a gain of Na^{+} channel function (see the earlier section Na^{+} Channels). The simple disruption of subunit binding seems to be sufficient to cause epilepsy. In fact, it was a mutation associated with epilepsy in SCN1A that disrupted binding to the SCN1B subunit that first identified the sequence in SCN1A that mediates this binding.[97] This underscores what may be a theme in the study of channelopathies: In many cases, information from genetic disorders reveals how ion channels function, rather than the other way around.

Decay and Degradation

As we have seen (in the section on Subunit Assembly), mutations that disrupt subunit assembly can also lead to dramatic changes in channel decay rates. In the case of KCNQ2, subunits that are unable to assemble into channels seem to be targeted for decay in the proteasome. Indeed, proteasome inhibitors have been shown to prolong the half-lives of mutant channels in vitro.[94] It is quite possible that the mechanisms driving decay in heterologous systems are different from those in neurons, and consequently less sensitive to mutations affecting channel half-life. However, as yet, little is known about those factors that regulate the half-life of membrane proteins or the pathways that control their decay, either in neurons or in heterologous systems.

Modifiers of Severity: Single Nucleotide Polymorphisms (SNPs) or Mutations?

One prominent and enigmatic feature of the channelopathies associated with epilepsy is the variability of their inheritance. Mutations associated with GEFS+, for example, can lead to widely varying clinical manifestations in individuals harboring the same Na^+ channel variant.[73,98] Further illustrating this principle, a mutation found in two brothers with SMEI was also identified in their father, whose only symptom was FS.[60] A major puzzle is to determine the genetic or environmental factors that can modify the impact of a mutation so dramatically.

The importance of modifier genes is best illustrated in model animals, in which genetic backgrounds can be directly compared by selective breeding. The severity of an identical mutation in SCN2A has been shown to differ in two inbred strains of mice, with one strain developing fewer seizures later in life and living longer than another strain carrying the identical mutation.[6] Recently, a mutation that disrupts splicing in a Na^+ channel gene and causes a chronic movement disorder in one strain of mice was shown to be lethal in a second strain.[12] The difference in impact was traced to a mutation in a hitherto unknown splice factor in the second strain that reduced the amount of correctly spliced Na^+ channel below the threshold for viability.[12]

As exemplified by the CACNA1H mutations reported in CAE, polymorphisms that are not thought to be directly linked to epilepsy may affect the biophysical consequences of other genetic variants.[106] Several sequencing efforts are now underway to identify common polymorphisms in ion channels that may impact the severity of disease-causing mutations.

Relating Channel Function to Clinical Syndrome

Even when the functional consequence of a mutation in an ion channel gene is understood, explaining the phenotype and inheritance pattern can present some challenges. Clearly, it is necessary to know where the ion channel is normally expressed, its role in neuronal excitability, and the effect of perturbing signaling within a population of neurons on the behavior of the whole organism. However, several potential pitfalls exist on the road to â€œexplainingâ€ how a mutation in an ion channel can lead to a clinical syndrome, including redundancy within ion channel gene families, variations in RNA splicing, and effects of perturbed signaling on brain development.

A potentially powerful approach is to examine animal models of human channelopathies. Three types of mouse model are beginning to give significant insights. First, a number of mouse strains with spontaneous recessive mutations in ion channel genes have phenotypes that overlap with human disorders linked to the same gene (for example, CACNA1A and the glycine receptor gene GLRA1).[13,29,86] Second, targeted deletions can shed light on the consequences of nonsense mutations in channel genes.[31,53,93] And third, human mutations can be introduced into the mouse ortholog of a gene, which offers a direct test of the effects on neurons, circuits, and systems. This approach has been applied to a KCNA1 mutation associated with episodic ataxia[47] and to a CACNA1A mutation associated with familial hemiplegic migraine.[105] Although it can be highly informative, the approach suffers from the limitation that a missense mutation in a human gene might have different effects on ion channel function than the same mutation in the mouse ortholog. For example, a patient with intractable epilepsy and mental decline was found to have a heterozygous nonsense mutation in SCN2A[56]; however, mice heterozygous for a targeted knockout of SCN2A had no noticeable abnormalities, whereas the homozygotes died as neonates without obvious seizures.[77] Moreover, some genes known to be key in epilepsy, such as SCN1A, are not processed in the same way in mice and humans. The alternate exon found in human SCN1A, which contains a polymorphism that is correlated with a change in the maximal dose of AEDs is not functional in mice and rats (SS, unpublished observation). So, although mouse models may prove most helpful for exploring some of the mechanisms of ion channel mutations leading to diseases, ultimately human sequences will have to be consulted. A further limitation of mouse models is that, because of their short lifespan, subtle disorders that only manifest in adult life may not be apparent in heterozygous animals. Indeed, seizures and other neurologic disorders have generally only been reported in homozygous animals, whereas most of the human disorders are dominantly inherited.

Future Work

Although genetic studies have linked a large number of polymorphisms in ion channel genes to epilepsy, caution is advised in extrapolating from genotypes to phenotypes in humans. In most cases, it is not possible to directly examine the effects of ion channel gene polymorphisms in human neuronal tissues. However, every effort should be made to discover in what context a gene is transcribed, when transcription would be expected to result in rapid mRNA degradation or production of a truncated peptide, what splice variants and subunits are likely to be present, and how a polymorphism could affect the targeting and even removal of an ion channel. We are leaving the stage when heterologous expression of mutant cDNA is sufficient to establish the effects of the mutations on neurons. In the future, heterologous expression should be combined with

expression studies in vivo, especially when animal models might not reflect human pathologies. In the meantime, genetic studies, which have already provided a wealth of information about the functional domains of ion channels, might also lead to valuable information about the processing of mRNAs and peptides.

Summary and Conclusions

The list of voltage-gated ion channel genes harboring mutations in patients with epilepsy will no doubt continue to grow. With advances in understanding of the stages of ion channel biogenesis it will be important to focus not only on those exons which encode the protein but also on non-coding regions, in particular promoters and intronic and untranslated sequences that affect RNA processing. As the cost of DNA sequencing falls, and a larger number of ion channel genes can be sequenced, it is likely that variants will be identified where it is unclear whether they are rare non-causative polymorphisms or disease-causing mutations. Determining the functional impact of these variants will require increasingly subtle understanding of the molecular and cell biology of ion channels and neurons. Genetic variations identified in individuals may also be susceptibility factors, contributing to, but not determining fully, the risk of developing epilepsy. By extrapolation, it will be important to determine how such genetic factors contribute to the overall heritability of epilepsy in the population.

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Chapter 25

Inflammation

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Introduction

Immune and inflammatory reactions have been described in the central nervous system (CNS) in various neurologic diseases, including epilepsy. In particular, several cytokines and activated proinflammatory signaling pathways have been measured in the brain, cerebrospinal fluid (CFS), or blood after seizures induced in experimental models and in clinical cases of epilepsy (for review see Vezzani[101]).

Inflammatory reactions in the CNS appear to arise from the activation of both branches of the immune system, namely, innate and adaptive immunity. In the rodent brain, inflammatory mediators are produced during epileptic activity by microglia, astrocytes, and neurons as part of innate immune mechanisms. In human epileptic tissue, evidence suggests that both innate and adaptive immunity contribute to the induction and perpetuation of inflammation in the brain.[63] The bloodâ€“brain barrier (BBB) appears to play a crucial role in modulating the functional communication between innate and adaptive CNS immunity by tightly regulating the entry of blood-borne immune cells, antigens, and antibodies into the brain.[79]

A crucial question is whether, in the brain, inflammation is a component of the etiology of epilepsy, a consequence of seizures and cell damage, or both, and if inflammation can contribute to the progression of the disease.[76]

In the attempt to address these questions, preclinical investigations in experimental models of seizures focused first on the time-course of specific proinflammatory events occurring in the rodent brain after the induction of seizures.[101] Much effort has been devoted to describe the regional distribution and cell-specific expression of proinflammatory molecules and their signaling in brain, vis-Ã -vis the patterns of seizure spread and the associated neuronal cell loss. Second, functional and pharmacologic studies have shown that cytokines can decrease the threshold for seizure induction and/or prolong the duration of seizures. Moreover, cytokines and downstream inflammatory mediators affect neuronal survival to injury, induce glial cell proliferation, modify BBB permeability to blood-borne molecules and cells, and inhibit neurogenesis.[2] Pharmacologic evidence demonstrates that some anti-inflammatory treatments reduce seizures in experimental models and, in some instances, in clinical cases of epilepsy. All these findings support the hypothesis that inflammation in the brain plays a role in ictogenesis and, in some instances, also in neuronal cell loss, while also predicting its contribution to epileptogenesis. Direct proof for the latter is still lacking.

Several experimental findings have highlighted a dichotomous role for immune/inflammatory events in the CNS. Thus, these reactions can be also neuroprotective, and they thus constitute an adaptive, beneficial endogenous response to injury, similar to the classical immune/inflammatory responses to infection.[2,63,92] In general, the deleterious effects of cytokines or other inflammatory mediators on neuronal excitability and cell survival appear to be mediated by their ability to provoke an extracellular rise of glutamate by actions on mechanisms of neurotransmitter release and/or reuptake, to potentiate the function of ionotropic glutamate receptors, and to enhance the production of mediators of oxidative stress (i.e., arachidonic acid and nitric oxide).[2] However, cytokines can also induce the synthesis of nerve growth factor, ciliary neurotrophic factor, and insulin-like growth factor from astrocytes, all involved in brain repair.[2] Other potential mechanisms of neuroprotection induced by cytokines include stimulation of antioxidant pathways and enhanced expression of manganese superoxide dismutase or calbindin, leading to an attenuated elevation of intracellular calcium (Ca^{2+}) induced by tissue injuries. In summary, the final outcome of inflammation on brain function is highly dependent on the extent to which inflammatory mediators are produced, the length of time the tissue is exposed to inflammation, and the balance between the neurotrophic and inflammatory factors produced by the competent cells. It is also possible that the peripheral versus central origin of the cells and molecules involved in inflammation may play a role.

In this chapter, we review experimental and clinical evidence supporting the hypothesis that inflammation in brain may be a common thread playing a pro-epileptogenic role in various forms of epilepsy of different etiologies. Although the initial trigger of an inflammatory response in the brain remains still speculative (when the original description of the disease does not include the presence of specific pathogens), a large variety of insults that induce inflammation in the brain often result in the occurrence of seizures, and eventually in the onset of epilepsy, suggesting that an injury, even if subtle, occurring at birth or during lifetime may initiate a cascade of chronic inflammatory events in the CNS that contributes to the basis for the late onset of epilepsy (Fig. 1).

Understanding and awareness of the role of inflammation in epilepsy will increase our knowledge of the mechanisms underlying the etiopathogenesis of seizures and might open new perspectives for their pharmacologic treatment.

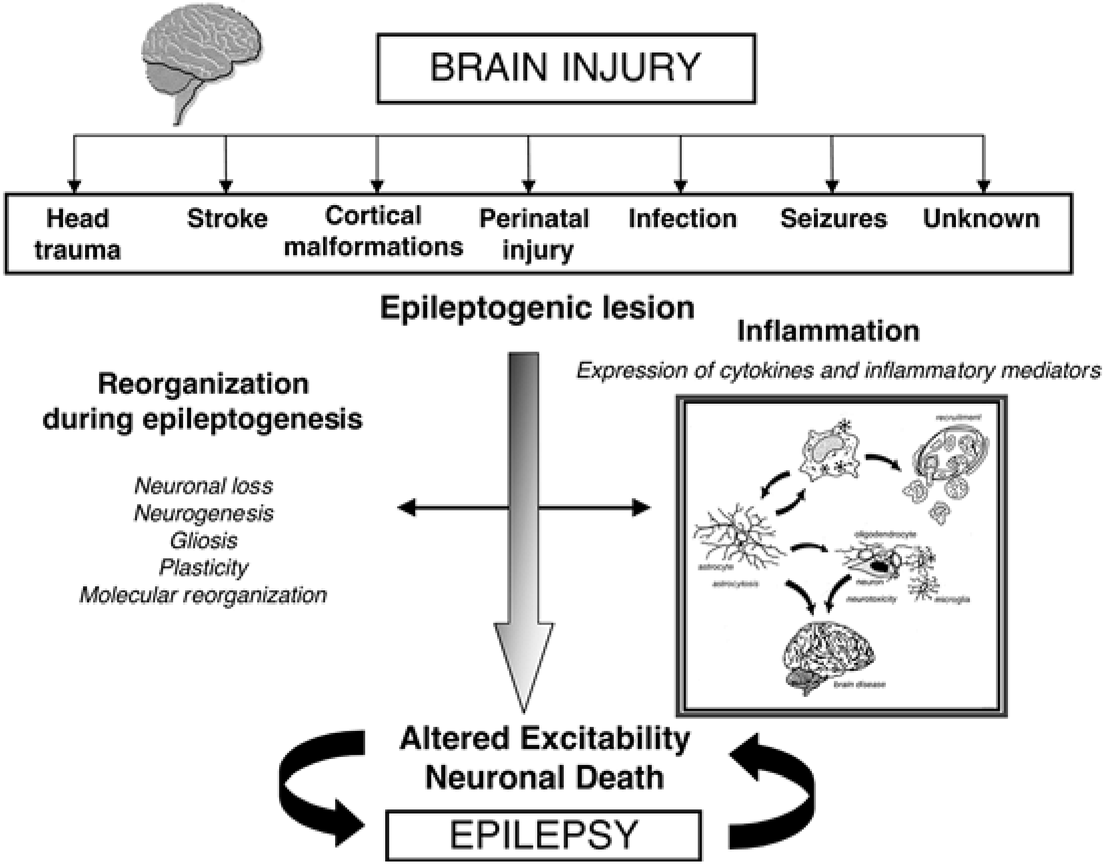
BRAIN INJURY
Head trauma
Stroke
Cortical malformations
Perinatal injury
Infection
Seizures
Unknown
Epileptogenic lesion
Inflammation
Expression of cytokines and inflammatory mediators
recruitment
oligodendrocyte
astrocyte
astrocytosis
neuron
neurotoxicity
microglia
brain disease
Reorganization during epileptogenesis
Neuronal loss
Neurogenesis
Gliosis
Plasticity
Molecular reorganization
Altered Excitability
Neuronal Death
EPILEPSY

FIGURE 1. Schematic representation of the cascade of events that may be triggered by brain injury, eventually resulting in epilepsy. A large variety of injuries, even if subtle, occurring at birth or during a lifetime, may initiate anatomic, molecular, and synaptic reorganizations as well as a cascade of chronic

inflammatory events in the brain that contribute to the late onset of epilepsy. Both innate and adaptive immune responses may play a role in initiating and consolidating inflammation in brain (exemplified in the boxed cartoon). The BBB is crucially involved in mediating the recruitment of cell components of the adaptive immune system, and alterations of the barrier properties may predispose the brain to the occurrence of seizures (see text for details).

Experimental Models of Seizures

Expression Studies

During systemic infections (mimicked in rodents through the administration of lipopolysaccharide [LPS], a component of the gram-negative bacterial wall), the brain triggers an inflammatory response mounted to protect the host against infectious microorganisms. This phenomenon consists of an early inflammatory response (innate immunity) that can eventually progress to an adaptive immune response mediated by activated lymphocytes recruited from the blood.[63,81] The CNS shows a well-organized innate immune reaction in response not only to infection but also to a variety of brain injuries. In particular, cytokines such as interleukin (IL)-1Î², tumor necrosis factor (TNF)-Î±, and IL-6, although expressed at very low levels in healthy brain tissue, are rapidly induced there following

ischemic, traumatic, and excitotoxic damage and seizures (for review see Allan[2] and Vezzani[101]). Status epilepticus (SE), or recurrent seizures induced in rodents by electrical stimulation or application of chemoconvulsants, induces a rapid increase of proinflammatory cytokines and various markers of the innate immunity (e.g., nuclear factor [NF]-ÎºB system, prostaglandins and their pathway enzymes, Toll-like receptors, chemokines, complement system) in glia and in neurons[19,60,66,97] (Fig. 2). Increased production of inflammatory molecules in the brain has also been reported in genetic models of audiogenic seizures and in kindling.[26,77] Markers of inflammation increase specifically in those brain regions involved in seizure onset and spread.

The inflammatory response observed in mouse brain following pilocarpine-induced seizures differs from that described after systemic injection of LPS[63,81,97,101]: Thus, inflammatory molecules are first and predominantly expressed after endotoxemia in circumventricular organs, the choroid plexus, the leptomeninges, and along brain microvessels whereas microglia are involved to a minor extent and with a delay of several hours. Moreover, neurons do not typically express inflammatory markers after endotoxemia. Seizures induce a massive inflammatory response in parenchymal microglia and neurons (NF-ÎºB and cyclooxygenase [COX]-2 are significantly expressed by neurons). Moreover, changes induced by endotoxemia are relatively short-lasting when compared to those observed after seizures. These observations suggest that inflammation induced by seizures in the brain results from complex neurophysiologic events that differ in their duration and in the cell populations involved from classical immune reactions triggered by infection.

The long-lasting stimulation of the innate immune response and related inflammatory reactions observed after seizures may eventually promote infiltration of lymphocytes and the establishment of acquired immunity in the CNS. Whether this phenomenon occurs is still controversial in animal models: There is indication of a late penetration of CD45$^+$ monocytes into the brain parenchyma after seizures; however, Turrin and Rivest[97] recently reported that markers of adaptive immunity, such as the production of IL-12 and interferon (IFN)-Î³ by activated T cells, are undetectable in the brain of pilocarpine-treated mice at least up to 72 hours after seizure induction. Accordingly, immunostaining for T cells, B cells, and natural killer (NK)-cells was negative in the brain of kainic acidâ€"treated rats, although granulocytes and macrophages/monocytes were detected.[21]

The Role of Inflammation in Seizures

To address the functional consequences induced by inflammatory reactions on seizures and neuronal cell death, two main experimental approaches have been taken: (a) the intracerebral or systemic application of pro- and anti-inflammatory stimuli, and (b) the use of transgenic mice overexpressing proinflammatory cytokines in glia.

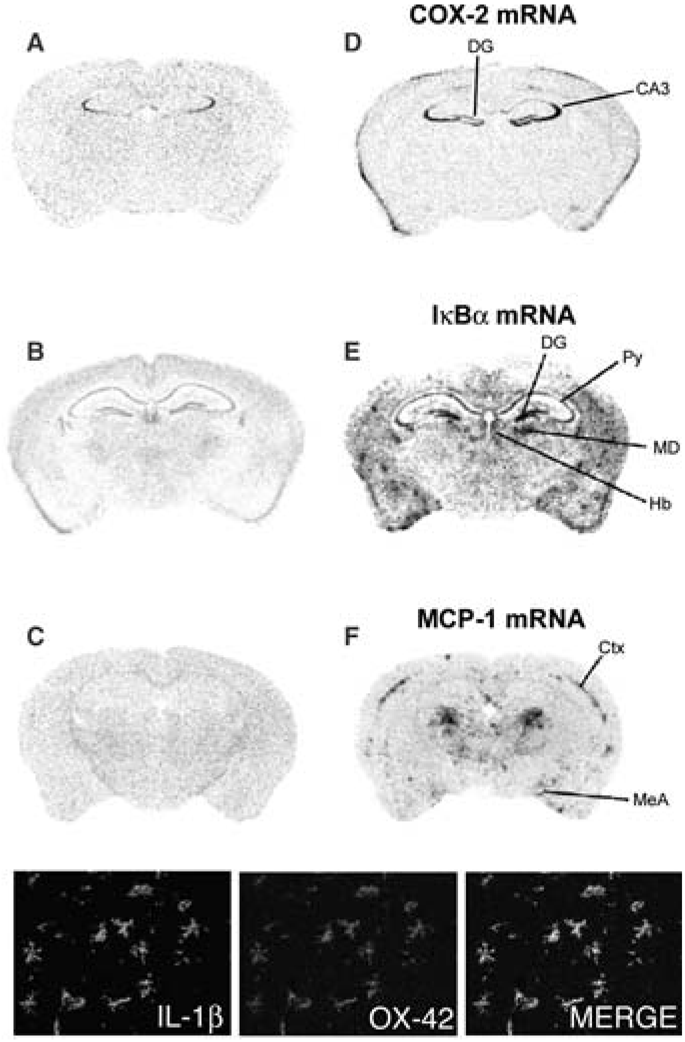

FIGURE 2. Seizure-induced expression of genes encoding proinflammatory molecules in rodent forebrain areas after seizures. Panels **D** through **F** show the increased hybridization signal of COX-2, IkBÎ±, (an index of NFÎºB activation), and the chemokine monocyte-chemoattractant protein (MIP)-1, 24 hours after seizures induced by pilocarpine in mouse forebrain sections (adapted from Turrin NP, Rivest S. Innate immune reaction in response to seizures: Implications for the neuropathology associated with epilepsy. *Neurobiol Dis.* 2004;16:321â€“334, with permission). Very low or nondetectable expression was found in basal conditions (saline-injected mice), as depicted in corresponding panels **A** through **C**. The phenotype of the expressing cells was identified using selective markers: The majority of cells expressing these inflammatory mediators were infiltrating monocytes and parenchymal microglia; in some instances also endothelial cells were positive. Neurons also overexpressed COX-2 and IÎºB mRNA. Micrographs in bottom row depict IL-1Î² and OX-42$^+$ microglia and their merged image, respectively. Ctx, cortex; CA3, pyramidal layer regions; DG, dentate gyrus; Hb, habenular nucleus; MD, mediodorsal thalamic nucleus; MeA, medial amygdala; Py, pyramidal cell layer. (See the color insert.)

IL-1Î² significantly exacerbates seizure activity when intra-cerebrally injected in rodents shortly before the induction of

hippocampal seizures or SE.[19,100,102] On the contrary, IL-1RA, a naturally occurring molecule that antagonizes the effect of endogenous IL-1Î², has powerful anticonvulsant activity,[103] and IL-1RAâ€“overexpressing mice display a reduced susceptibility to seizures.[102] These findings strongly suggest that an increase in brain levels of IL-1Î² has proconvulsant effects.

Recent data highlight the possibility that IL-1Î² signaling contributes critically to the hyperexcitability underlying febrile seizures (FS). Thus, intracerebroventricular injection of IL-1Î² reduces seizure threshold in 14-day-old mice subjected to hyperthermia[22] or in immature rats exposed to LPS-induced fever[31]; IL-1Î² receptorâ€“deficient mice or IL-1RAâ€“injected rats were resistant to the induction of this kind of seizures.

It is important to note that changes in seizure threshold or duration induced by components of the IL-1Î² system are independent of alterations in core temperature.[31] Hyperthermia-induced seizures can cause long-term effects on brain excitability in the absence of irreversible neuronal cell loss,[9] therefore highlighting the possibility that the IL-1Î² system may be critically involved in fever-induced epileptogenesis.

Biochemical studies have shown that IL-1Î² can increase glutamatergic neurotransmission, and this action may mediate its effects on seizures: IL-1Î² enhances the calcium influx induced by *N*-methyl-D-aspartate receptor stimulation in pyramidal hippocampal cells by inducing the phosphorylation of the NR2B subunit of this receptor complex[106]; IL-1Î² inhibits glutamate reuptake by astrocytes[111] and decreases the peak magnitude of Î³-aminobutyric acid (GABA)-mediated currents in cultured hippocampal neurons.[108]

The effect of TNF-Î± on seizures depends on its brain levels and the receptor subtypes primarily involved: Relatively low doses of TNF-Î± reduce seizure activity by interacting with TNF-Î± p75 receptors,[8] whereas mice overexpressing high amounts of TNF-Î± in glia show age-dependent spontaneous seizures and degenerative changes possibly mediated by p55 receptors.[1] A direct interaction between TNF-Î± and Î±-amino-3-hydroxy 5-methylisoxazole 4-propionate (AMPA) receptors has been recently demonstrated in hippocampal neurons: This cytokine acting on p55 receptors regulates the cellular trafficking of AMPA receptors by inducing their membrane expression in a molecular conformation that amplifies the glutamate responses but reduces GABA$_A$ membrane receptors.[91]

Transgenic mice overexpressing IL-6 in glia show a profound increase in their sensitivity to glutamate-induced seizures, and neuronal loss of GABA- and parvalbumin-positive neurons was constitutively found in the hippocampi of these animals.[84] Findings in transgenic mice suggest that a preexisting chronic inflammatory condition in the brain can predispose to the occurrence of seizures and promote neurologic dysfunctions. Accordingly, systemic administration of LPS to adult mice decreases their threshold to seizure induction, and this effect was blocked by anti-inflammatory drugs.[86] IL-1Î² and TNF-Î± also play an important role in the sensitization of CNS to infection-related seizures in rodents caused by *Shigella dysenteriae* or *Streptococcus pneumoniae.*[59,112]

Table 1 Inflammatory markers and anti-inflammatory treatments in experimental models of seizures

		Pharmacologic treatments	
Exp models	**Inflammatory markers**	**Anticonvulsant**	**Proconvulsant**
Chemoconvulsants	Cytokine and their receptors	Low corticosterone	High corticosterone
	Signalling pathways (NFkB;P38MAPK)	TNF-Î±/p75 receptor	High IL-1Î²

	COX-2, mPGES	IL-1RA	COX-1/2 inhibitors
	Adhesion molecules	Caspase-1 inhibitor	Aspirin (10 mg/kg)
	Chemokines	NSAID	
		Aspirin (â‰¤15 mg/kg)+	
		lipoxygenase inhibitor	
FS	IL-1Î²	IL-1RA	IL-1Î²
Infection	IL-1Î²,TNFÎ±		IL-1Î², TNF-Î±
MES	n.d.	Aspirin (100â€“500 mg/kg)	COX-1/2 inhibitors
Audiogenic seizures	IL-1Î±		
Kindling	Cytokine and their receptors	Low IL-1Î² Immunoglobulins	

Chemoconvulsions were provoked by kainic acid, bicuculline methiodide, penicillin, pentylenetetrazol, or pilocarpine. In general, the inflammatory markers were enhanced by seizures in glia and, in some instances, in neurons and in brain regions involved in the initiation and generalization of epileptic activity (see text for details). FS, febrile seizures; MES, maximal electroshock test; PTZ, pentylenetetrazol; mPGES, membrane/microsomal prostaglandin E synthase. After FS or infection, the cytokines were measured in plasma only; n.d., not determined; NSAID, nonsteroidal anti-inflammatory drugs.

Limited information exists on the role in seizures for other cytokines such as fibroblast growth factor (FGF), IL-2, IL-3, or interferon (see Vezzani[101] for details). Finally, sequential intrahippocampal infusion in rats of individual proteins of the membrane attack pathway of the complement system induced both seizures and neurotoxicity,[110] implying that complement activation in the brain may contribute to seizures and cell death in diseases such as Rasmussen encephalitis.

Anticonvulsant Effects of Anti-inflammatory Strategies

Table 1 summarizes the data available on the effects of anti-inflammatory strategies on seizures. Nonsteroidal anti-inflammatory drugs (NSAIDs) can attenuate seizures; in particular, ibuprofen and indomethacin reduced penicillin-induced electrocorticographic and motor seizures in rats[107]; a similar effect was observed with paracetamol. Aspirin also protected mice from maximal electroshock (MES)- and pentylenetetrazol-induced seizures and potentiated the anticonvulsant action of diazepam and sodium valproate.[90] In general, conflicting data are available on the effect of COX-1

and -2 inhibitors on seizures since prostaglandins can either reduce or promote seizures and affect neuronal cell survival differently depending on their specific type and receptor subtype interactions.[6,14,101]

Glucocorticoids (GCs) are potent inhibitors of the transcription of genes encoding most of the proinflammatory molecules, thus representing a critical endogenous negative feedback system with anti-inflammatory properties. Accordingly, a GC receptor inhibitor increased the inflammatory reactions induced by LPS in brain and enabled IL-1Î² and TNF-Î± to unveil neurotoxic effects. However, prolonged elevation of GCs (corticosterone) in the high physiologic range may induce a catabolically vulnerable state in neurons and result in an exacerbation of excitotoxic damage.[85] This dichotomy may explain also the paradoxical proconvulsant effects of corticosterone and dexamethasone on seizures.[51]

Interestingly, valproate inhibits the LPS-induced activation of NF-ÎºB and the subsequent production of TNF-Î± and IL-6 in monocytes and glioma cells. Carbamazepine was shown to decrease the LPS-induced production of prostaglandins and the activation of phospholipase A in rat glial cells.[39,58] This evidence suggests that part of their anticonvulsant effects may be mediated by nonconventional anti-inflammatory actions.

Inflammation and Neuronal Cell Survival

When administered individually, cytokines do not directly lead to cell death but they can have synergistic effects (e.g., IL-1 plus TNF-Î±) that result in neurotoxicity involving both necrotic and apoptotic mechanisms. IL-1 exacerbates excitotoxic injury in vivo, whereas IL-1RA reduces excitotoxic, traumatic, and ischemic brain damage.[2] Moreover, the extent of damage in the hippocampus after an excitotoxic insult appears to correlate significantly with the antecedent inflammatory cell infiltration and microglial activation, suggesting that neuronal damage can be at least in part caused by the preceding inflammation.[21]

Another cytokine effect that links them to epilepsy-related events is their inhibitory action on neurogenesis. In particular, neurogenesis is reduced by inflammation induced by radiation injury or LPS, whereas it is restored by indomethacin or inhibition of microglia activation by minocycline.[23,61]

Bloodâ€“Brain Barrier and Inflammation

During the past several years, increasing interest has arisen in the role of the BBB in epilepsy.[65] Advances in radiology have enhanced our ability to image and study the human BBB, and further developments in the research of metabolic deficiencies linked to seizure disorders, neuroinflammation, and multiple drug resistance to antiepileptic drugs (AEDs) have amplified the significance of the BBB relationship to epilepsy[5,28,42,57] (Fig. 3). Finally, a growing body of evidence has shown that inflammatory mechanisms may participate in the pathologic changes observed in the epileptic brain, with increasing awareness that blood-borne cells or signals may participate in epileptogenesis by virtue of a leaky BBB.

An indisputable correlation exists between BBB disruption and seizures. Seizures and epilepsy are commonly observed in conjunction with stroke, traumatic brain injury, and CNS infections, all conditions known to result in compromised BBB function.[7,34,83] In addition, regional patterns of BBB breakdown during epileptiform seizures induced in animal models by various convulsive agents have been quantified.[64] Unfortunately, whereas several microangiographic models are available to study the BBB in animal models, a suitable (i.e., microscopic, quantitative, and minimally invasive) technique for evaluating BBB integrity in humans does not exist. Compounded by insufficient means of investigation, a point of debate is whether (a) the BBB fails before, during, or after seizures; (b) the compromised integrity of the BBB is a component of the etiology of epilepsy or a consequence of seizures; and (c) drugs that preserve or restore BBB function (e.g., steroids or NSAIDs) can have beneficial effects.[95]

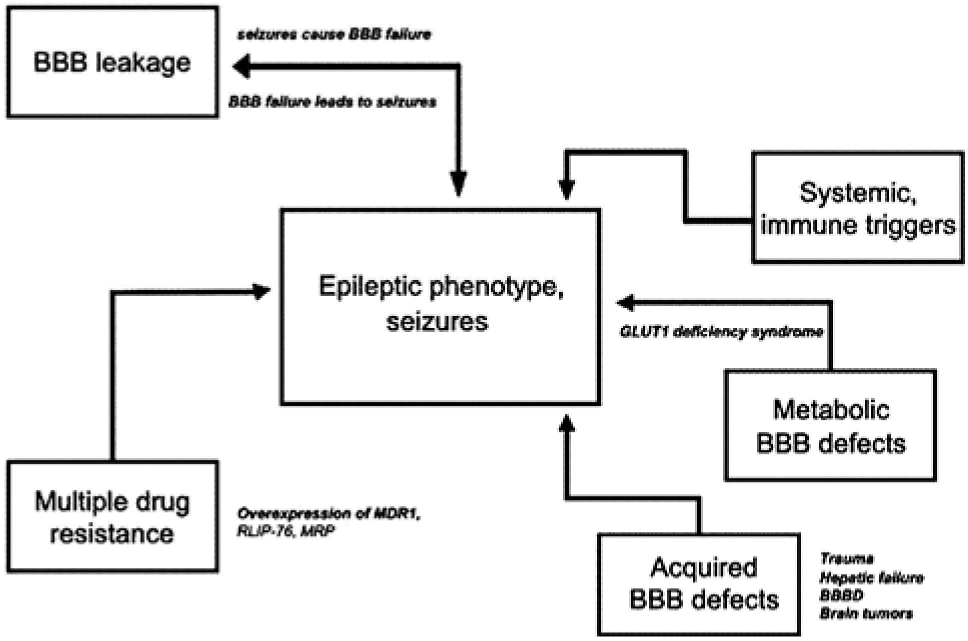
BBB leakage
seizures cause BBB failure
BBB failure leads to seizures
Systemic, immune triggers
Epileptic phenotype, seizures
GLUT1 deficiency syndrome
Metabolic BBB defects
Multiple drug resistance
Overexpression of MDR1, RLIP-76, MRP
Acquired BBB defects
Trauma
Hepatic failure
BBBD
Brain tumors

FIGURE 3. A contemporary view of the BBB's role in epileptogenesis, multiple drug resistance, metabolic epilepsies, and inflammation. See text for a review of these concepts.

BBB disruption after acute head trauma is a well-known pathologic finding in both animal studies and humans.[12,16,47]

This disruption may persist for weeks to years after the injury, and may be associated with abnormal electroencephalographic (EEG) activity.[47] Whether this abnormal activity develops into epilepsy is currently unknown, but observations have suggested that BBB disruption in conjunction with a slowing in EEG activity may be a precursor to seizures.[70]

Thus, strong evidence exists that BBB leakage may result in the development of seizures, but a clear-cut relationship and the exact nature of the offending mechanisms have remained elusive. This is likely due to the complexity of disease conditions associated with BBB leaks. These include concomitant hemodynamic disturbances (intracerebral hemorrhage or embolic stroke); loss of autoregulation of cerebral blood flow (e.g., in traumatic brain injury); and changes in intracranial pressure due to edema, inflammation, and the like. Furthermore, the lack of EEG data may actually underestimate the true impact of BBB failure on the breakdown of neuronal control.

BBB openings have been mapped for a variety of convulsive agents with different mechanisms of action (e.g., impairment of GABA transmission, increased glutamate neurotransmission, direct excitatory action).[4,41,64,78,94] Furthermore, with increased arterial blood pressure, the BBB becomes permeable to macromolecules under induced epileptiform seizures.[4,94] A direct link between the mechanism of action and the region where BBB breakdown was observed is not obvious. However, a few brain regions are easily affected by seizure activity irrespective of the means of induction.[4,41,68,70,78,94] Other regions of the brain show BBB breakdown only under the influence of specific convulsants.[64]

The results by Seiffert et al.[88] suggest that neurons tend to fire abnormally when exposed to molecules that extravasate through a leaky BBB. We studied the abnormal vasculature of rats exposed prenatally to the angiogenic inhibitor thalidomide in light of their results.[29] Abnormal neuronal development in these rats was associated with vascular malformations and a compromised BBB. Similar findings were reported by Marchi et al. for methylazoxymethanol (MAM)-treated rats.[56] A brief exposure to *intravascular* fluorescein isothiocyanate

(FITC)-albumin allowed for exploration of the integrity of the BBB and resulted in a significant accumulation of albumin in neuronal (but, surprisingly, not glial) cells. Thus, it appears that the leakage of the BBB observed in these animals was sufficient to cause extravasation of serum albumin to levels that allowed significant intraneuronal accumulation. Neuronal hyperexcitability was commonly associated with regions of abnormal cortical development characterized by protein extravasation. It is therefore possible that the altered neuronal properties of thalidomide- and MAM-treated rats are due to a combined â€œcircuitry effectâ€ (e.g., abnormal wiring of neurons) and a concomitant effect of molecules that are normally segregated into peripheral blood.

Neuroinflammation has been traditionally seen as a CNS-specific branch of immunology. Thus, a great deal of effort has been made to find immunocompetent or inflammatory cells in the brain (or spinal cord) parenchyma. It is now clear that virtually every class of brain cell has some potential or propensity to replicate immunologic or inflammatory processes. This emerging field was recently reviewed elsewhere.[99,101]

In addition to intrinsic inflammatory mechanism, it is increasingly clear that the peripheral immune system may, under certain circumstances, provoke havoc in the CNS. This is a rare occurrence, however, thanks in part to a BBB mechanism that (a) impedes or hampers cell migration across the endothelial cell monolayer and (b) prevents or reduces chemoattraction of potentially harmful macrophages. The flip-side of this is that CNS-specific antigen may be considered as non-self and thus lead to autoimmunity. Again, even when this happens, the BBB minimizes the risks associated with the presence of offending effector cells in the peripheral circulation.

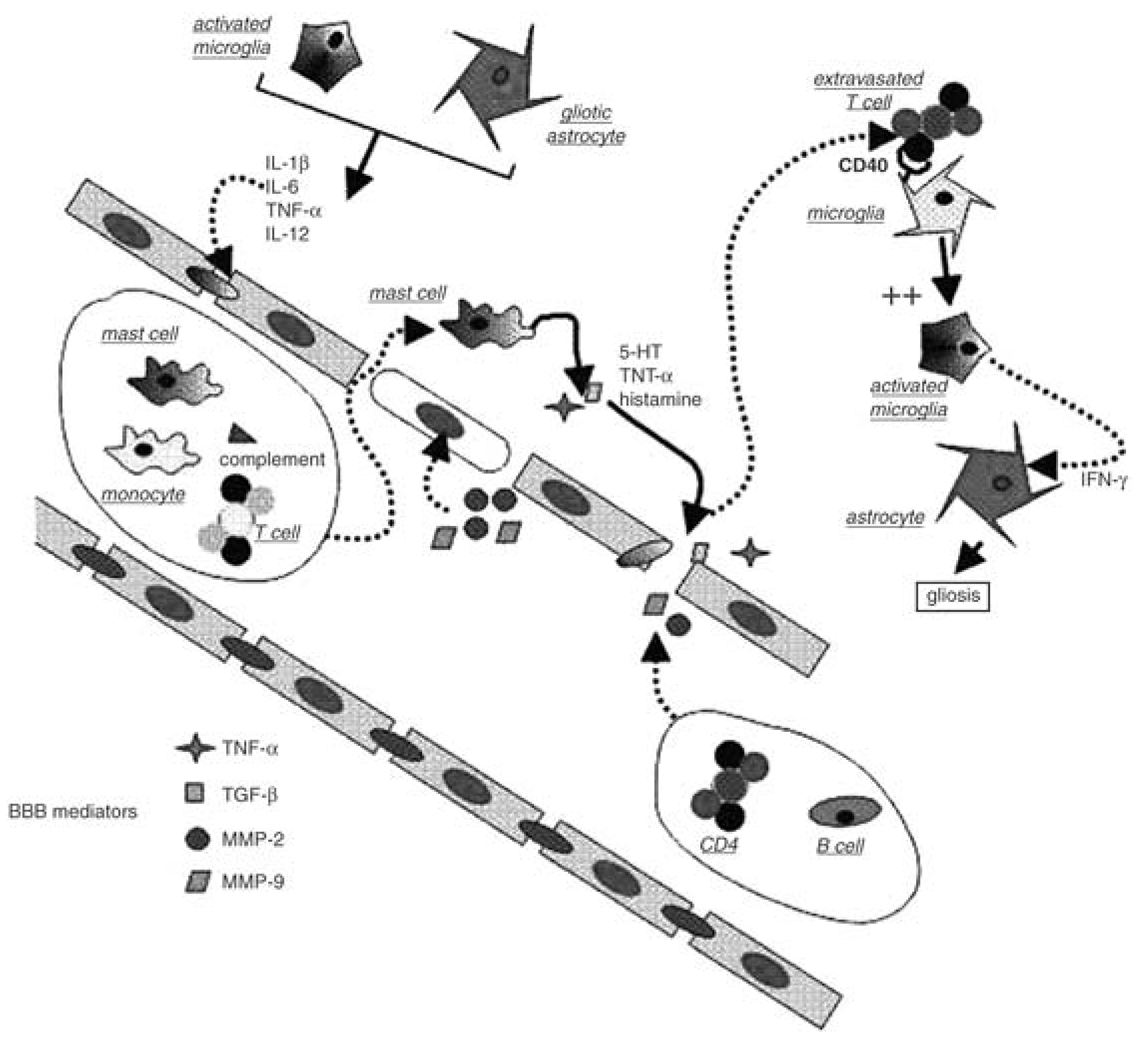
activated microglia
gliotic astrocyte
IL-1β
IL-6
TNF-α
IL-12
extravasated T cell
CD40
microglia
++
activated microglia
IFN-γ
astrocyte
gliosis
mast cell
mast cell
5-HT
TNT-α
histamine
complement
monocyte
T cell
BBB mediators
✦ TNF-α
▢ TGF-β
● MMP-2
▱ MMP-9
CD4
B cell

FIGURE 4. Schematic representation of the events that may link intraluminal inflammatory responses to

parenchymal proepileptogenic changes. Note that BBB failure is initiated by intravascular release of proteases that lead to a digestion of the endothelial cells that separate the brain parenchyma from the blood. This leads to subsequent extravasation of cellular and molecular players that ultimately may lead to abnormal epileptogenic activity.

Several potential explanations exist for the sometimes conflicting results obtained with animal models and direct comparisons to the human pathology. One of the issues that has not been fully explored is whether the increased or decreased levels of inflammatory mediators are a consequence of or are prodromic to the seizures. In addition to the temporal sequence of cause and effect, the cellular origin of inflammatory mediators is also important. It is commonly assumed that â€œbrainâ€ cytokines derive in fact from brain cells, whereas quantitatively, white blood cells are the main source of interleukins. In fact, the release of inflammatory mediators by blood cells results in focal BBB failure, and this may facilitate the extravasation of substantial quantities of cytokines.[48,49] This is likely followed by binding to CNS receptors, with a plethora of downstream effects. FIGURE 4 summarizes some of these events. An additional confounding factor is the type, duration, and intensity of seizures. All these combined may well produce opposite effects on the activation of cells either present in the brain or transmurally influenced by a number of hemodynamic changes that are associated with seizures.

In conclusion, a number of variables including the BBB must be considered and experimentally controlled before the exact nature and consequence of inflammation in animal models of seizures can be understood. In any case, as in the case of more obvious neurologic disorders based on immune overreaction (e.g., multiple sclerosis), the BBB status is likely to play an important role.

Stress and Inflammation

Seizure activity is associated with strong activation of the stress axis. Stress induces the release of corticotropin-releasing hormone (CRH), leading to the secretion of GC, which strongly influence immune and inflammatory reactions.[62] In turn, immune molecules including cytokines, stimulate CRH secretion and thus activate the hypothalamus-pituitary-adrenal axis. The secretion of CRH can affect inflammatory reactions both by activation of GC or by direct interaction with its own receptors on immune cells and in the CNS.[10] Although stress has been regarded as mainly immunosuppressive, stress hormones can have complex effects,[21,85] including the regulation of T-cell differentiation, which leads to inhibition of cellular immunity while favoring humoral immunity.[24]

Human Studies

Immunogenetics

There are several reports on the association between IL-1Î² 511 allele polymorphism and temporal lobe epilepsy (TLE). An increased frequency of homozygotes for allele 2 was described in patients with TLE with hippocampal sclerosis (TLE+HS) compared with healthy controls or TLE patients without HS.[44] In an extension study, allele 2 was most frequent in patients with a history of prolonged FS and TLE+HS.[45] However, subsequent investigations in a population of patients of European ancestry suggested that an association between the IL-1 gene variation and TLE+HS may not exist.[15,32]

Table 2 Evidence for immune activation in human epilepsy

Epilepsy type	Autoantibodies	Immune genetics	Cytokine network
Newly diagnosed epilepsy	aPLâ†‘	NA	SS IL-6â†‘ CSF/serum SE IL-6â†‘â†‘ CSF/serum
Well-controlled epilepsy	aPL Â±, AGA Â±	NA	NA
Febrile seizures	NA	IL-1Î² polymorphism	IL-6â†‘ CSF, IL-1Î² CSF
Refractory epilepsy	GADâ†‘, aPLâ†‘	IL-1Î² polymorphism	IL-6â†‘ serum interictally
	GM1â†‘	IL-1Î² polymorphism	Brain IL-1Î²â†‘
TLE+HS	GluR3â†‘	HLA DQ2â†‘	NFÎºBâ†‘
Rasmussen's encephalitis	AGAâ†‘	NA	NA
Cortical dysplasia	GluR3â†‘	NA	Brain IL-1Î²â†‘
	NA		

APL, antiphospholipid antibodies; NA, not available; SS, single seizure; CSF, cerebrospinal fluid; SE, status epilepticus; Â±, similar to controls; AGA, antigliadin antibodies; GAD, antibodies against glutamic acid decarboxylase; GM1, antibodies against GM1; GluR3, antibodies against GLUR3.

In a Finnish study, the distribution of IL-1Î± and IL-1Î² alleles was different in patients with severe localization-related epilepsy compared with control subjects; moreover, the patients who were noncarriers of the IL-1RA allele 2 were significantly more likely to be carriers of the IL-1Î² allele 2.[73] The IL-1Î² allele 2 is associated with increased production of IL-1Î², and the IL-1RA allele 2 is known to be associated with a high secretion of IL-1RA.[37] At present, the data on IL-1 polymorphism are conflicting, but new studies also demonstrate an increased frequency of haplotypes of human leukocyte antigen (HLA) such as HLA DQ2, classically associated with autoimmune disorders, in patients with mesial TLE.[67] Taken together, these findings suggest that patients with severe localization-related epilepsy may have a genetically determined predisposition for an augmented immune response (high IL-1Î² production with decreased production of IL-1RA). An increase in the frequency and the carriage of IL-1Î² allele 2 was observed also in pediatric patients with FS compared with healthy blood donors.[104]

The Activation of the Cytokine Network in Human Epilepsy: Febrile Seizures

Because IL-1Î² is both the most potent endogenous pyrogen[27] and lowers seizure threshold in animal models (see previous paragraphs), its production may be associated with the hyperexcitability underlying FS. Other cytokines such as IL-6 may also induce fever and affect seizure parameters.

Helminen and Vesikari[33] reported a significant increase in IL-1Î² production in monocytes stimulated by LPS from children with FS compared with cells from children with bacterial or viral infections without convulsions, or those with no infection, thus suggesting that peripheral cells of the immune lineage from children prone to seizures may produce more proinflammatory cytokines. A different study showed increased production of IL-6 and IL-10 by peripheral blood mononuclear cells in response to LPS in pediatric patients with previous FS compared with a control population, whereas IL-1Î² production did not differ.[93] These contradictory results on IL-1Î² are most likely due to variations in cell-stimulation protocols (Table 2).

Conflicting results were also reported when measuring cytokine levels in the CSF and blood of epileptic patients. In this respect, no significant differences were observed between mean IL-1Î² levels in the CSF and blood of patients with FS as compared with children with febrile illnesses without seizures,[50] or in the CSF and plasma concentrations of IL-6.[38] Accordingly, no differences in plasma levels of IL-1Î² were found between patients with FS and febrile controls,[105] whereas the same study showed that the plasma IL-1RA-to-IL-1Î² ratio and plasma and CSF IL-6 levels were significantly higher in FS patients. In disagreement with the above-reported studies, the mean concentration of IL-1Î² was found to be significantly increased in the CSF of patients with FS, without any changes in the corresponding IL-1Î² serum levels.[30] The discrepant findings are most likely explained by differences in the time elapsed from sample collection and the last seizure, and by the different sensitivity of the assays used for cytokine measurements. Increased levels of proinflammatory cytokines in nonfebrile conditions have been reported in patients with West syndrome.[53]

The Activation of the Cytokine Network in Human Epilepsy: Adult Patients

Activation of the cytokine network has been demonstrated after single seizures in patients with new-onset seizure disorders. Among the cytokines studied, a robust increase occurred in soluble IL-6 concentrations both in CSF and plasma, and a trend of increased IL-1RA concentrations, whereas IL-1Î², TNF-Î±, or nerve growth factor (NGF) concentrations were not changed.[72,75] The type and duration of seizures seem to determine the extent of the increase in IL-6.[52]

Although ample experimental evidence confirms the activation of the IL-1 system in the brain during seizures, clinical studies failed to consistently report changes in peripheral or CFS levels of IL-1Î², although upregulation of IL-1RA appeared to occur. This may be due to the lack of strict correspondence between the brain changes in IL-1Î² and its CFS concentrations. Thus, the autocrine/paracrine effects of IL-1Î² can be produced by very low quantities of this cytokine, but may not result in measurable changes in its CSF concentration.[87] The increase in IL-1RA and IL-6 concentrations in CSF is an indirect evidence of the activation of the IL-1 system in human epilepsy, because IL-1Î² is the most potent activator of IL-1RA, and IL-6 is also one of the best markers of enhanced IL-1Î² activity.[20]

Additional evidence for the CNS origin of the cytokines is provided by studies on therapy-resistant patients showing that, during the interictal state, plasma levels of IL-1RA and IL-6 are modified in the absence of changes in the production and secretion of cytokines from blood mononuclear cells.[36] However, at variance with this evidence, an earlier study showed a greater production of IL-1Î±, IL-1Î², and IL-6 from peripheral blood mononuclear cells in response to proinflammatory stimuli in patients with epilepsy but without seizures for 6 months preceding blood collection, compared with control subjects.[69]

Still limited but convincing evidence demonstrates the presence of active inflammation in surgically removed hippocampi from epileptic patients. Increased production of IL-1Î± has been reported in the microglia in human TLE specimens,[89] and an enhanced release of inflammatory cytokines has been measured from hippocampal slices of epileptic tissue.[18] Overexpression of NFÎºB, a transcriptional factor mediating inflammatory cascades, has been reported in hippocampal neurons and glia in TLE+HS patients.[17] Increased expression of cytokines and elevated levels of NFÎºB, TNF-Î±, and other proinflammatory markers have been described in brain samples from tuberous sclerosis; inflammatory markers have been found in dysplastic neurons and giant cells in tubers, thus suggesting that they may be related to the intrinsic hyperexcitability of cortical malformations and contribute to epileptogenesis.[54] Interestingly, high expression of IL-1Î² and its receptors, and IL-1RA was recently found in surgically resected specimens from focal cortical dysplasia and glioneuronal tumors. The number of IL-1Î² and IL-1RI$^+$ cells was positively correlated with the frequency of seizures, whereas the expression of IL-1RA was negatively correlated with the duration of epilepsy prior to surgery.[80] Other studies also document the presence of activated microglia and astrocytes in TLE.[13]

These findings indicate the activation of inflammatory cascades in human epileptic brain tissue that may be induced by recurrent seizures or even precede the onset of active epilepsy, or both.

Autoantibodies and Epilepsy

The role autoantibodies mediating inflammation in epilepsy has raised increasing interest since the first description of anti-GluR3 antibodies in Rasmussen encephalitis.[82] In subsequent studies, these antibodies have also been described in some other severe localization-related epilepsies.[55,109] Autoantibodies have also been implicated in refractory epilepsy, but their pathogenetic significance is less well established. In this respect, an increased prevalence of antiphospholipid antibodies was demonstrated among patients with epilepsy without any connective tissues disease.[3,25,71,98] Another class of antibodies with possible etiologic significance are those against GM1-gangliosides, which are a component of synaptic membrane and major regulators of ion currents. GM1 antibodies have shown to be epileptogenic in experimental studies,[46] and they have been measured in patients with therapy-resistant, localization-related epilepsy.[11] Antibodies to glutamic acid decarboxylase (GAD), an enzyme that catalyzes the conversion of L-glutamic acid to GABA, were found in patients with refractory focal epilepsy.[74] Recently, antibodies against the dietary protein gluten (contained in grains of wheat, rye, and barley) measured in patients with HLA DQ2 or DQ8 positivity were linked to TLE+HS.[43]

Treatments

In selected human epilepsies and experimental models, evidence suggests an anticonvulsant efficacy of intravenous administration of high-dose immunoglobulins (for review see Hirayama[35] and Vezzani[101]). The exact mechanisms of this action are not well established, but the modulation of circulating soluble factors, such as cytokines and antibodies, may be involved.[40] The anticonvulsant actions of adrenocorticotropic hormone (ACTH) and steroids are better documented in West syndrome and other epileptic encephalopathies (for review see Vezzani[101]). Finally, there is also evidence of anti-inflammatory actions of some antiepileptic drugs, as reported in the previous paragraphs.[39,58]

Summary and Conclusions

The hypothesis that chronic inflammation in the brain may be implicated in the etiopathogenesis of seizures is supported by experimental studies in rodent models of seizures showing that increased levels of inflammatory mediators have pro-ictogenic effects and can contribute to cell loss and BBB damage. Clinical studies support an activation of the cytokine system and downstream inflammatory events in the brain and, in some instances in blood and CSF, in pediatric and adult patients with epilepsy of various etiologies. Moreover, in some instances, anti-inflammatory or immunosuppressant treatments control seizures in otherwise drug-resistant epileptic patients.

Several issues await further investigations, including the nature of initial trigger(s) of an inflammatory response in the brain that may lead to the onset of epilepsy; to what extent seizure activity and/or injured cells may contribute to perpetuate inflammatory processes; the relative contribution of parenchymal brain cells, endothelial cells of the BBB, and peripheral immune cells to the increased levels of inflammatory mediators in the brain; and when during the epileptogenesis process these different sources of inflammatory molecules play a role.

If a relationship between inflammation and the etiopathogenesis of seizures were proven, this may suggest novel anticonvulsive treatments and possibly an innovative strategy for retarding or arresting epileptogenesis.

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Chapter 26

Astroglial Mechanisms in Epilepsy

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Nihal C. de Lanerolle

Introduction

Currently available anticonvulsant drugs and complementary therapies are not sufficient to control seizures in about a third of epileptic patients. Thus, there is an urgent need for new treatments that prevent the development of epilepsy and control it better in patients already inflicted with the disease. A prerequisite to reach this goal is a deeper understanding of the cellular basis of hyperexcitability and synchronization in the affected tissue. Epilepsy is often accompanied by massive reactive gliosis. Although the significance of this alteration is still poorly understood, recent findings suggest that modified astroglial functioning may have a role in the generation and spread of seizure activity. In the following sections we detail properties of astrocytes as well as their changes that can be associated with epileptic tissue. Our goal is to provide an understanding of the working knowledge of this cell type with the long-term view of providing a foundation for the development of novel hypotheses about the role of glia in seizure disorders.

Basic Physiology of â€œNormalâ€ Astrocytes

Before discussing details of membrane physiology of astrocytes, it is important to note that it is likely that there are different types of cells with astroglial properties within a given brain region, and that astrocyte properties may vary in different subregions. However, at this time we have only little understanding of the different properties of these cells and how heterogeneous these cell types are. In rodents, the majority of astrocytes express the astrocyte-specific protein, glial fibrillary acidic protein (GFAP); have a high resting K$^+$ conductance; are coupled in a syncytium through gap junctions, and have linear current/voltage relationships. A second type of cells, which we will also call astrocytes or astroglial cells, contains GFAP mRNA, but expresses a plethora of voltage-gated ion channels and are not coupled in a gap junction syncytium. It is likely that the functional impact of these two subtypes of cells with astroglial properties is distinct. For example, in the hippocampus the former cells express glutamate transporters, while the latter express Î±-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA)-type glutamate receptors.[80,125]

Membrane Physiology

Astrocytes express almost the same set of ion channels and receptors as do neurons,[67,108,120] although the relative strength of expression varies between the two cell types. For example, in astrocytes, K$^+$ channel density by far exceeds that of Na$^+$ channels, preventing generation of glial action potentials. Nevertheless, a glia-specific, or at least preferential expression, has been elucidated for some of these channels and carriers. Among them is Kir4.1, a subunit belonging to the family of inwardly rectifying K$^+$ (Kir) channels. In the central nervous system (CNS) this channel is predominantly localized at distant astrocyte processes surrounding synapses or capillaries.[58] Recent work suggests a colocalization of Kir4.1 with the water channel aquaporin-4 (AQP4), which in the brain and spinal cord is also expressed by astrocytes but not neurons. Increasing evidence indicates that a coordinated action of both channels is required for the astrocytes to maintain K$^+$ and water homeo-stasis in the CNS.[89,121] As illustrated in the following sections, dysfunction of these astroglial transmembrane channels appears to play a key role in epilepsy.

In contrast to the majority of mature neurons, astrocytes are usually coupled through gap junctions to form large intercellular networks. Astrocytic gap junctions are mainly formed by connexins 43 and 30 (Cx43 and Cx30) in a cell-type specific fashion. Through these networks astrocytes can dissipate molecules, such as K^+ or glutamate, a process considered important to prevent their detrimental extracellular accumulation.[116] Recent data suggest that the capacity of K^+ clearance is only partially disturbed in the absence of astrocyte gap junctions, presumably because of the existence of â€œindirectâ€ coupling of elongated astrocytic processes.[126] Connexins also contribute to the propagation of intercellular Ca^{2+} waves, presumably by enhancing adenosine triphosphate (ATP) release, rather than by providing an intercellular pathway for signal diffusion.[87] However, the pathologic impact of disturbed astroglial gap junction expression is not well understood yet.[110,110a]

Another main function of astrocytes is removal of neurotransmitters released by active neurons. Uptake of glutamate is accomplished by two glia-specific transporters, EAAT1 and EAAT2 (in rodents termed GLAST and GLT-1), the activity of which may shape the kinetics of receptor currents at some synapses.[11,32] Compelling evidence suggests that disturbed glutamate uptake by astrocytes is directly involved in the pathogenesis of epilepsy, as discussed in the following sections.

However, astrocytes can also release neuroactive agents, including neurotransmitters. Several studies revealed that such a release is critically dependent on an increase of astroglial $[Ca^{2+}]_i$. Astrocytes express a plethora of neurotransmitter receptors that are coupled through G proteins (G_q) and phospholipase C to the release of Ca^{2+} from internal stores.[56] Stimulation of neuronal afferents induces Ca^{2+} elevations within astrocytes,[33,98] which can spread to neighboring astrocytes, demonstrating the presence of an astrocyte-to-astrocyte network.[28,111] Thus, although astrocytes are electrically inexcitable, these glial cells contain a chemically based form of excitability that is bidirectionally linked to

neuronal activity.[56] Though initially discovered in 1994,[92] the past decade has seen many studies demonstrating that astrocytes release chemical transmitters (â€œgliotransmittersâ€), including glutamate, ATP, and D-serine.[56,124] Although the mechanisms underlying astroglial transmitter release are open to debate, at least part of the release seems to occur through regulated, Ca^{2+}-dependent exocytosis, a mechanism that in the CNS was previously thought to be exclusive to neurons.

What is the impact of transmitter release from astrocytes? Several reports suggested that gliotransmitters may activate receptors in neurons to modulate the strength of inhibitory and excitatory synaptic transmission[13,50,66,93,94,132,135] (reviewed by 124). Importantly, because with their fine terminal processes single astrocytes reach tens of thousands of synapses simultaneously,[25] the release of gliotransmitters may lead to the synchronization of neuronal firing patterns.[6,49] The different gliotransmitters that are released from astrocytes have quite distinct functions. Glutamate, the first identified gliotransmitter,[92] is able to modulate neuronal excitability[6,49,117] through actions on the *N*-methyl-D-aspartate (NMDA) receptor, as well as to modulate synaptic transmission.[50] D-serine is a coagonist of the NMDA receptor. Released D-serine can bind to what has been termed the glycine-binding site of the NMDA receptor and, as a consequence, enhance NMDA receptor function. In the hypothal-amus, the amount of astrocyte-derived D-serine supplied to synapses can regulate which forms of synaptic plasticity occur. In conditions where little of the coagonist is supplied a long-term synaptic depression can result, whereas when D-serine is locally supplied to the synapse long-term potentiation results.[91] The release of ATP from astrocytes can have a variety of functional actions. In cultures it has been shown that the release of ATP is important for mediating components of Ca^{2+} waves that propagate between astrocytes: During a Ca^{2+} elevation ATP is released from an astrocyte, which then has paracrine actions on neighbors, which induces further Ca^{2+} signals and ATP release.[53] Because cell surfaces express a plethora of ectonucleotidases, once ATP is released it is rapidly hydrolyzed to adenosine. As a consequence, ATP that is released from astrocytes leads to synaptic modulation mediated by adenosine.[94] In the hippocampus high-frequency activity of groups of synapses causes Ca^{2+} signals in neighboring astrocytes, which then release ATP, and after the hydrolysis to adenosine, cause a presynaptic inhibition of neighboring synapses.[94] In this manner the astrocyte coordinates the strength of synaptic signaling. As illuminating as these studies have been, we still await an understanding of the functional consequences of gliotransmission on neural network function, processes such as learning and memory and ultimately behavior. Rapid forms of neuronâ€“glia interactions seem also to be involved in the regulation of local blood flow as demonstrated in cortical brain slices where neuronal stimulation led to glutamate release, activation of metabotropic glutamate receptors (mGluRs) in astrocytes, and regulation of the tone of vessels contacted by processes of the stimulated astrocyte.[86,112,136] Emerging evidence suggests that disturbances of these mechanisms are involved in the pathogenesis of epilepsy, as discussed below.

Several important aspects of neuronâ€“glia interactions are not yet understood. Thus, as outlined above, recent studies corroborated the finding that astrocytes are heterogeneous with respect to antigen profiles and functional properties, but it is still unclear which type(s) of astroglial cells are activated and are capable of releasing transmitters, which transmitters can be released by astrocytes, which mechanisms these cells use for the release, and whether the efficiency of neuronâ€“glia signaling changes during development. Intriguingly, a recent report presented evidence that a subtype of cells with astroglial properties even receives direct synaptic input from glutamatergic and Î³-aminobutyric acid (GABA)-ergic neurons.[62] The physiologic impact of this type of interaction remains to be clarified.

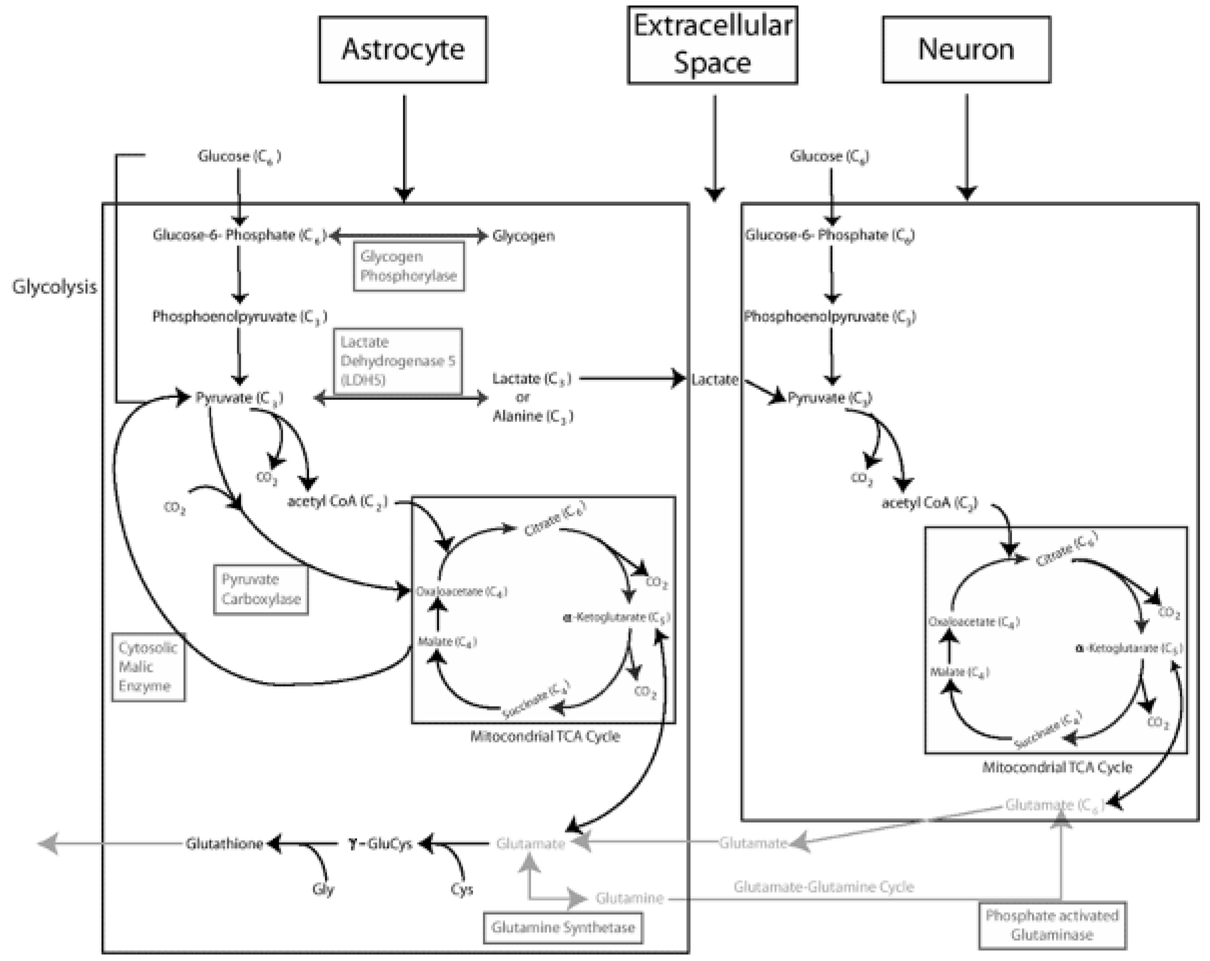
Astrocyte
Extracellular Space
Neuron
Glucose (C6)
Glucose-6- Phosphate (C6)
Glycogen
Glycogen Phosphorylase
Glycolysis
Phosphoenolpyruvate (C3)
Lactate Dehydrogenase 5 (LDH5)
Lactate (C3) or Alanine (C3)
Lactate
Pyruvate (C3)
CO2
acetyl CoA (C2)
Pyruvate Carboxylase
Cytosolic Malic Enzyme
Citrate (C6)
Oxaloacetate (C4)
α-Ketoglutarate (C5)
Malate (C4)
Succinate (C4)
Mitocondrial TCA Cycle
Glucose (C6)
Glucose-6- Phosphate (C6)
Phosphoenolpyruvate (C3)
Pyruvate (C3)
CO2
acetyl CoA (C2)
Citrate (C6)
Oxaloacetate (C4)
α-Ketoglutarate (C5)
Malate (C4)
Succinate (C4)
Mitocondrial TCA Cycle
Glutamate (C5)
Glutathione
γ-GluCys
Gly
Cys
Glutamate
Glutamate
Glutamine
Glutamate-Glutamine Cycle
Glutamine Synthetase
Phosphate activated Glutaminase

FIGURE 1. Shown schematically are similarities and differences of the energy metabolic pathways in astrocytes compared to neurons. Note the distinctive enzymes found in only in astrocytes (*in boxes*).

Astrocyte Metabolism

Astrocytes play an important role in the metabolism of the brain through their unique degradation of both glucose and glutamate.[57] The astrocyte's importance for these processes lies in their possession of some key enzymes not normally found in neurons. These enzymes are glutamine synthetase, pyruvate carboxylase, and cytosolic malic enzyme.

Glucose is the main energy source of the brain. It is a six-carbon chain molecule that is degraded to its end-products, carbon dioxide and water. The metabolism of glucose takes two stages. Glycolysis in the cytosol yields two ATP molecules and can occur in the presence or absence of oxygen, whereas oxidative metabolism in the mitochondria yields 36 ATP molecules per molecule of glucose through its conversion to acetylcoenzyme A (acetyl-CoA) and breakdown in the tricarboxylic acid (TCA) cycle.[57] Astrocytes, like neurons, are capable of metabolizing glucose through both pathways. The TCA cycle is limited by the fact that its intermediates continuously leave: Neuronal glutamate is lost to glia, glutamate is used for glutathione synthesis in astrocytes, and glutamine is used for GABA synthesis in GABAergic neurons.[57] Such a loss of carbon skeletons without replenishment can impair neuronal ability to produce amino acid transmitters and the rate of oxidative metabolism. Astrocytes alone are capable of replenishing carbon skeletons because they, rather than neurons, possess the enzyme pyruvate carboxylase, which can de novo carboxylate each molecule of pyruvate to a molecule of oxaloacetate (four carbon atoms) that can be inserted into the TCA cycle to replenish it.

The glutamate released by neurons during excitatory synaptic activity is largely removed from the synaptic cleft by astrocytic glutamate transporters (cf. above). Once in the astrocyte, glutamate is converted to glutamine by the addition of ammonia, a reaction catalyzed by the enzyme glutamine synthetase that is found in astrocytes (and oligodendrocytes) but not neurons. The glutamine thus produced is released into the extracellular space where it accumulates in high concentrations (~0.25 mM)[54] and is returned to neurons. In the neuron, glutamine is hydrolyzed to glutamate, the reaction being catalyzed by the enzyme phosphate-activated glutaminase (PAG). Several lines of evidence show that glutamine produced by astrocytes is essential for the production of neuronal glutamate.[57] This exchange of glutamate and glutamine between neurons and astrocytes is described as the glutamateâ€“glutamine cycle.

Conversion to glutamine is not the only fate of astrocytic glutamate. With high levels of extracellular glutamate, some of the glutamate taken up by astrocytes can be deaminated or transaminated to Î±-ketoglutarate and then metabolized in the TCA cycle.[82] Under conditions of high extracellular glutamate, Î±-ketoglutarate may also leave the TCA cycle as malate to be converted in the cytosol to pyruvate, catalyzed by the cytosolic malic enzyme, which is restricted to glia.[83] Pyruvate can either be reintroduced into the TCA cycle via acetyl-CoA or be converted into lactate and exported to neurons.

Glial cells, especially astrocytes, also have a prominent capacity to produce lactate in the presence of normal oxygen levels.[127] This process, also called aerobic glycolysis, is stimulated on exposure of astrocytes to glutamate.[95] Further, mobilization of glycogen reserves in astrocytes by various neurotransmitters has been shown to result in enhanced lactate release.[41] The presence of the lactate dehydrogenase 5 (LDH5) isoform in astrocytes favors conversion of pyruvate to lactate. Lactate is released into the extracellular space and used as an energy source by neurons. Thus, astrocytes act as a lactate source inside the brain, especially during enhanced synaptic activity, and the concept of an astrocyte-neuron lactate shuttle has been proposed.[96] In vivo dialysis studies in sclerotic hippocampi have demonstrated increased levels of lactate along with glutamate during seizures.[43]

Astrocytes, rather than neurons, contain the cystineâ€“glutamate exchanger.[32] This transporter helps astrocytes to accumulate cystine, which is reduced to cysteine for the production of astrocytic glutathione.[40] Synthesis of glutathione occurs primarily in astrocytes. In the process of glutathione formation, astrocytes release glutathione into the extracellular space, which is essential for providing neurons with the glutathione precursor L-cysteinyl glycine, formed from glutathione by the coenzyme Î³-glutamyl transpeptidase.

These distinctive metabolic pathways in astrocytes are summarized schematically in FIGURE 1.

Astrocytes in the Pathology of Epileptic Foci

Neurons have been the primary focus of attention in the study of the pathology of the epilepsies, because ictal activity is generated by neurons. It is, however, becoming clear that glial cells, in particular astrocytes, may play a major role in the excitability generated at seizure foci.[110a,117] With this finding in mind, re-examination of the pathology of seizure foci may indicate a significant astrocytic component in many seizure foci.

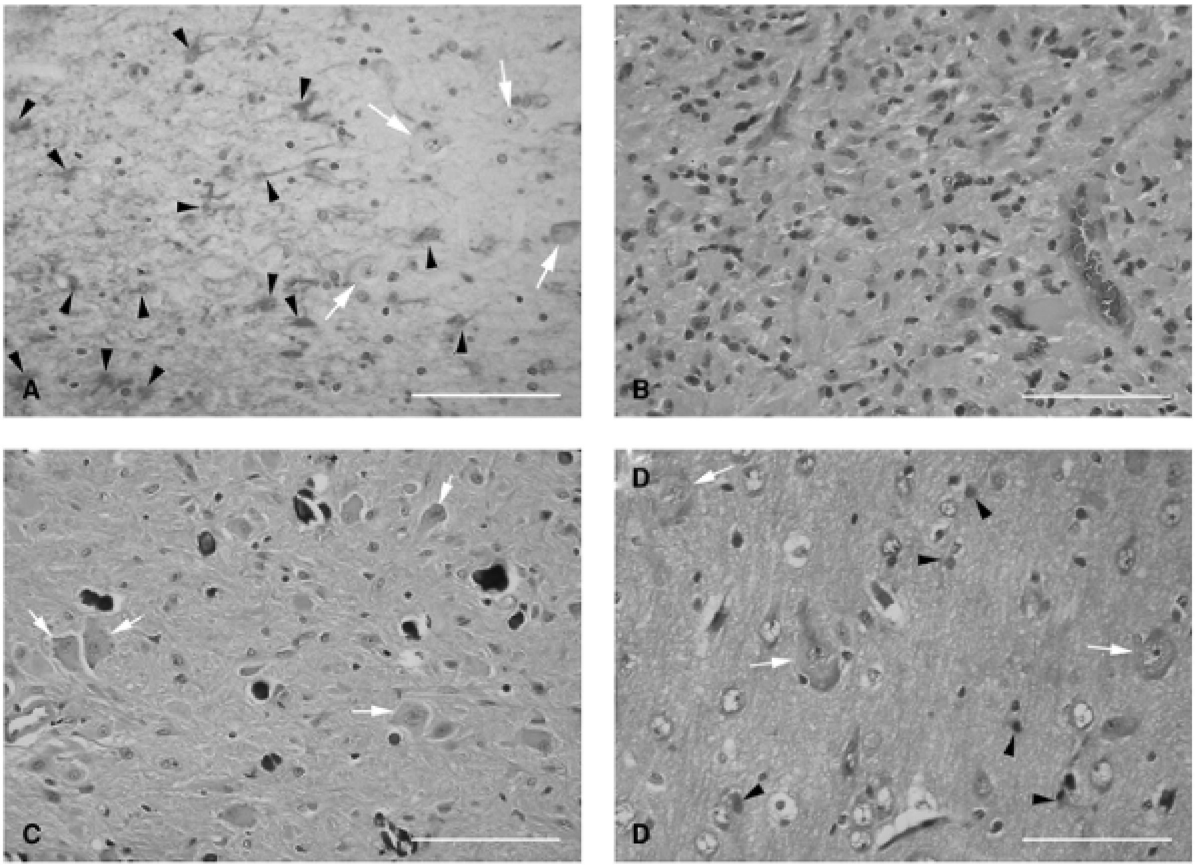

FIGURE 2. Photomicrographs of four human neuropathologic conditions associated with seizures in which astrocytes are a prominent component of their cellular composition. **A:** Hippocampal sclerosis: A portion of the hippocampus immunostained for glial fibrillary acidic protein (GFAP; peroxidase-DAB) and Nissl counterstained. The right third of the picture is area CA2 of the hippocampus showing some remaining neurons (*white arrows*). The left two thirds represent area CA1 that shows an almost complete loss of neurons, with GFAP immunopositive astrocytes (*black arrowheads*). **B:** Astrocytoma: A hematoxylin and eosinâ€"stained section of an astrocytoma showing neoplastic astrocytes with considerable variation in size and shape of individual nuclei. **C:** Tuberous sclerosis: A portion of a cortical tuber stained with hematoxylin and eosin, showing abnormal neurons (*white arrows*) in a background matrix of fibrillary gliosis. Calcification is seen as scattered black structures. **D:** Hemimegalencephaly: A hematoxylin and eosinâ€"stained portion of cortical neuropil showing large, highly anomalous neurons (*white arrows*) and astrocytes (*black arrowheads*). Scale bars, 100 Âµm. (Picture provided by kind courtesy of Dr. Jung H. Kim, Neuropathology, Yale School of Medicine.)

Temporal Lobe Epilepsy

Perhaps the most prominent seizure focus with a major astrocytic component is the sclerotic hippocampus in mesial temporal lobe epilepsy (TLE). Hippocampal sclerosis has been associated with TLE, and the prevalence of this pathology has been variously estimated. Early autopsy studies found between 30% and 58% of TLE cases presenting with hippocampal sclerosis.[20,77,109] Examination of specimens from patients who had undergone surgery for the control of medically intractable TLE showed a similar proportion. Falconer reported that about 43% to 47% of his patients suffered from Ammon horn sclerosis (AHS)[23,47]; the UCLA series of temporal lobectomies for TLE found hippocampal sclerosis in 65% of the cases.[78] In the latter two studies, patients with hippocampal sclerosis had a better surgical outcome than those without it. Careful analysis of the pathology and electrophysiology of 151 hippocampi removed in the Yale surgical series revealed that about 60% of the specimens presented with AHS.[34] After surgery, 84%

of AHS patients had an excellent (Engel class I), seizure-free outcome.

What is most striking about the sclerotic hippocampus is that it is significantly depleted of its neuronal populations but has an increased population of glia, especially astrocytes (Fig. 2A) and microglia. Anatomic and physiologic studies published to date[35,110,110a] indicate that astrocytes in the sclerotic hippocampus display many unusual characteristics compared to those of nonsclerotic hippocampi. However, neither the extent of the molecular uniqueness of astrocytes in the sclerotic hippocampus nor the molecular processes underlying their genesis and function are currently understood.

Mass Lesions

Seizures are a major clinical manifestation also of intracranial tumors, being observed in about 35% of cases.[68] The majority of primary brain neoplasms are derived from glial cells and are collectively called gliomas. Gliomas are the most common among epilepsy-related tumors and are predominantly low grade. Among the epileptogenic gliomas, astrocytomas (Fig. 2B) are most frequent, being found in 50% to 70% of cases.[68] Regardless of their type or grade, surgical removal of gliomas result in excellent seizure control (citations in 68). In hemimegalencephaly, a rare disorder closely associated with seizures, there is often diffuse proliferation of astrocytes in the cortex as well as subcortical white matter in addition to cortical neuronal abnormalities (Fig. 2D).

Tuberous Sclerosis

Tuberous sclerosis complex (TSC) is a disease that is manifested due to mutations in the TSC1 and TSC2 genes of the human genome. Epilepsy occurs in about 90% of affected individuals.[31] The pathologic substrates of TSC are also associated with astrocytes. Brain lesions of TSC are of three types: Cortical tubers, subependymal nodules, and subependymal giant cell astrocytomas (SEGAs). Cortical tubers show abnormal cortical lamination and are characterized by the presence of a proliferation of astrocytes in addition to dysmorphic neurons and eosinophilic giant cells (Fig. 2C).[37,52] Subependymal nodules are also composed predominantly of dysplastic astrocytes and mixed-lineage astrocytic or neuronal components,[37] giant cells, and, sometimes, calcium depositions.[64] SEGAs also display astrogliosis, dysmorphic neurons, and giant cells. Thus, all three pathologies are associated with astrogliosis. Even the giant cells have astrocytic properties. Yamanouchi et al.[131] divided giant cells into two subtypes: â€œNeuronlike giant cellsâ€

and â€œindeterminate giant cells.â€ The majority of the latter were positive for GFAP, vimentin, and nestin, markers expressed by astrocytes, and rarely contained neurofilaments. In conclusion, brain lesions of TSC, in addition to other alterations, also seem to be associated with defects in astrocyte biology.

Astrocyte Dysfunction Contributes to Seizure Generation in Temporal Lobe Epilepsy

The hippocampal seizure focus in TLE has been studied the most, compared to other seizure foci in the brain. Through these studies there is rapidly emerging a picture of astrocytes at the sclerotic hippocampal seizure foci as having unique structural and functional characteristics. In this section these characteristics are reviewed to exemplify some of the mechanisms through which they may contribute to seizure generation and compare them to what is known of astrocytes at other seizure foci (see Astrocyte Dysfunction at Other Seizure Foci section).

Voltage-Gated Na$^+$ and Ca^{2+} Channels

Information about changes in Na$_V$ channel expression in experimental or human epilepsy is inconsistent. Comparative patch clamp analyses were performed in hippocampal specimens with and without significant astroglial sclerosis, surgically removed from patients with intractable TLE. Two papers reported enhanced Na^+ current densities in human astrocytes from sclerotic specimens[17,18] (Fig. 3), while no increase was found in another human study[59] and in the hippocampus of kainate-treated rats, an animal model of TLE.[61] It is conceivable that this apparent discrepancy reflects subregional differences because the latter two studies investigated astrocytes in the CA1 region while the aforementioned focused on the hilus.

During seizure activity, the extracellular Ca^{2+} concentration decreases at the site of the seizure focus. Low $[Ca^{2+}]_o$, in turn, generates spontaneous epileptiform activity. In this regard it is worth considering the observation that depletion of external Ca^{2+} can induce Ca^{2+} oscillations in astrocytes. Increase in $[Ca^{2+}]_i$ is known to induce the release of the excitatory amino acid glutamate from astrocytes, a process that seems to contribute to seizure generation (see Ca^{2+} Signaling in Astrocytes: A Source of Glutamate section). Although decreases in $[Ca^{2+}]_o$ probably arise from Ca^{2+} influx into neurons, Ca^{2+} channels in astrocytes might also contribute to the depletion. Notably, immunostaining revealed an up-regulation of astrocyte L-type Ca^{2+} channels both in the kainate model of epilepsy and sclerotic hippocampal specimens from TLE patients,[38,128] suggesting enhanced glial uptake of Ca^{2+} in the lesioned CNS (Fig. 3). Besides a rapid and direct contribution to seizure generation via depletion of $[Ca^{2+}]_o$, enhanced astroglial Ca^{2+} influx is likely to stimulate synthesis and release of transmitters, cytokines, and growth factors, which may modify the architecture and activity of neural circuitry on a long term.

K^+ Channels and Water Channels

Seizure activity in vivo is characterized by elevations of $[K^+]_o$ from 3 mM to a ceiling level of 10 to 12 mM, while on the other hand, high $[K^+]_o$ levels are sufficient to trigger seizurelike events in acute brain slices. Because of its presumed importance in the regulation of excitability, properties of astroglial Kir channels have been investigated in experimental and human epilepsy. Evidence of an involvement of Kir channels in impaired K^+ buffering in sclerotic human hippocampus came from measurements of $[K^+]_o$ with ion-sensitive microelectrodes and patch clamp studies. Heinemann's group compared the effect of Ba^{2+} on stimulus-induced changes in $[K^+]_o$ in the CA1 region of hippocampal brain slices obtained from TLE patients with (AHS) or without sclerosis (non-AHS). In non-AHS tissue, Ba^{2+} significantly augmented rises in $[K^+]_o$, while this effect was not observed in AHS specimens. Since Ba^{2+} is a blocker of Kir channels, these findings suggested impaired function of these channels in the sclerotic tissue.[69] Indeed, direct evidence for a down-regulation of Kir currents in the sclerotic human CA1 region of epilepsy patients came from a comparative patch clamp study.[17,59] Together, these data indicate that in the sclerotic condition, impaired K^+ buffering through reduced expression of functional Kir channels contributes or even initiates seizure generation (Fig. 3). Preliminary data suggested an involvement of the Kir4.1 subunit in this process.[104]

Recent studies revealed a spatial overlap of Kir (subunit Kir4.1) and water channels (aquaporins) in astroglial end-feet contacting capillaries[58,89] and suggested that buffering of K^+ via Kir channels depends on concomitant transmembrane flux of water in the same cell. These parallel water fluxes are thought to be necessary to dissipate osmotic imbalances due to K^+ redistribution. In agreement with this hypothesis, clearance of extracellular K^+ is compromised upon reduction of the perivascular pool of astroglial AQP4,[4] and impaired K^+ buffering in concert with prolonged seizure duration is observed in AQP4-/- mice.[16] Hence, dysfunction of the bloodâ€“brain barrier (BBB) seems to be involved in seizure generation (see also Astrocytes and Bloodâ€“Brain Barrier Modifications at Seizure Foci section). In the sclerotic hippocampus of TLE patients, AQP4 immunoreactivity of vasculature-associated astrocyte end-feet was lower compared with nonsclerotic human epileptic hippocampi.[45] This loss of perivascular AQP4 is probably secondary, following disruption of the dystrophin complex that is necessary for anchoring of AQP4.[3] In conclusion, in the sclerotic hippocampus of TLE patients dislocation of water channels in concert with reduced expression of Kir channels in astrocytes probably underlies the impaired K^+ buffering leading to increased seizure propensity.

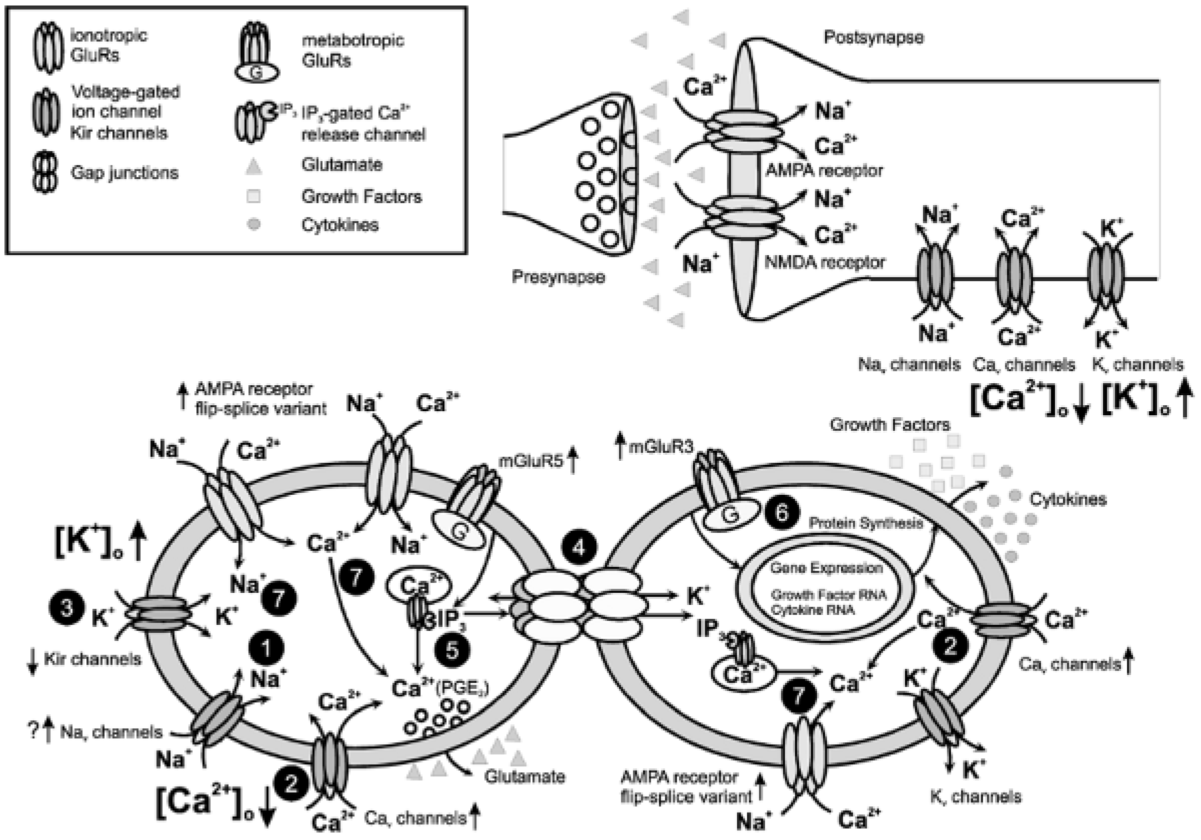
ionotropic GluRs
metabotropic GluRs
G
Voltage-gated ion channel Kir channels
IP3-gated Ca2+ release channel
Gap junctions
Glutamate
Growth Factors
Cytokines
Postsynapse
Presynapse
Ca2+
Na+
Ca2+
AMPA receptor
Na+
Ca2+
Na+
NMDA receptor
Na+
Ca2+
K+
Na, channels
Ca, channels
K, channels
[Ca2+]o↓ [K+]o↑
↑ AMPA receptor flip-splice variant
Na+
Ca2+
mGluR5↑
↑mGluR3
Growth Factors
Cytokines
Protein Synthesis
Gene Expression
Growth Factor RNA
Cytokine RNA
[K+]o↑
3
K+
K+
Na+
7
1
Na+
↓ Kir channels
?↑ Na, channels
Na+
[Ca2+]o↓
2
Ca2+
Ca, channels↑
Ca2+
7
Ca2+
IP3
5
Ca2+(PGE2)
Glutamate
4
K+
IP3
Ca2+
7
Ca2+
2
Ca, channels↑
K+
K, channels
AMPA receptor flip-splice variant↑
Na+
Ca2+
6

FIGURE 3. Temporal lobe epilepsyâ€"associated alterations of functional properties in glial cells. Neuronal hyperactivity produces enhanced release and spillover of glutamate, increase in $[K^+]_o$, and a reduction of $[Ca^{2+}]_o$. (1) Up-regulation of Na^+ channels in astrocytes of the sclerotic hippocampus might enhance $[Na^+]_i$ and modulate the activity of Na^+-dependent transporters in the glial membrane. (2) During seizure activity, $[Ca^{2+}]_o$ decreases at the focus site. Astroglial Ca^{2+} channels are up-regulated in experimental epilepsy, suggesting that part of the extracellular Ca^{2+} depletion is due to enhanced influx of Ca^{2+} into glial cells through Ca^{2+} channels. Enhanced $[Ca^{2+}]_i$ might promote the production and release of transmitters, cytokines, and growth factors from astrocytes. (3) Epileptiform activity is accompanied by an increase in $[K^+]_o$. Down-regulation of Kir channels was observed in astrocytes at the seizure site, leading to an impaired clearance of K^+ ions from the extracellular space and to stronger neuronal depolarization. (4) Glial gap junction coupling is involved in the propagation of intracellular Ca^{2+} waves, transmitter release, and neuronal activation, and thus might contribute to seizure spread. Clear evidence for a dysregulation of gap junctions in epileptic tissue is still missing. (5) Astroglial mGluR5 is up-regulated in animal models of epilepsy, which enhanced IP_3 hydrolysis, induced Ca^{2+} oscillations, and led to glutamate release through a prostaglandin E_2 (PGE_2)-dependent mechanism. This might strengthen the cascade described in (4). (6) Enhanced expression of mGluR3 was observed in astrocytes of epileptic tissue, suggesting the induction of gene expression and protein synthesis of growth factors and cytokines. Release of these factors from glial cells probably contributes to the reorganization of the neuronal circuitry. (7) Astrocytes in human Ammon horn sclerosis (AHS) primarily express the flip forms of AMPA receptors, leading to an enhanced influx of Ca^{2+} and Na^+. Coactivation of AMPA receptors and mGluRs linked to the IP_3â€"Ca^{2+} cascade stimulates Ca^{2+}-dependent glutamate release and generates Ca^{2+} waves in glial cells. The AMPA receptorâ€"mediated increase in $[Na^+]_i$ mediates an inhibition of Kir channels and reduces the K^+ buffer capacity of astrocytes. (From SteinhÃ¤user C, Seifert G. Glial membrane channels and receptors in epilepsy: impact for generation and spread of seizure activity. *Eur J Pharmacol.* 2002;447(2â€"3):227â€"237, with permission.)

Glutamate Transporters and Receptors

Several studies have suggested an involvement of glutamate transporters and receptors in seizure development and spread. Increased extracellular levels of glutamate have been found in epileptogenic foci.[51] Glutamate transporters are expressed by several CNS cell types, but astrocytes are primarily responsible for glutamate uptake. Important studies using mice with deletion[113] or antisense oligonucleotide-mediated inhibition of synthesis[102] of the astroglial transporter GLT-1 revealed that this subtype is responsible for the bulk of extracellular glutamate clearance in the CNS. GLT-1 knockout mice, but not antisense inhibition, developed spontaneous seizures and hippocampal pathology resembling alterations in TLE patients with AHS. Pharmacologic inhibition of GLT-1 reduced the threshold for evoking epileptiform activity.[26,36] Reduced GLAST and GLT-1 expression was also observed in a tuberous sclerosis epilepsy model,[130] but other animal studies were contradictory. Tessler et al.[115] investigated transporter expression on the mRNA and protein levels in human TLE specimens and found changes neither for GLT-1 nor GLAST. However, two other groups reported decreased GLT-1 protein as well as reduced[79] or increased[99] GLAST immunoreactivity in the sclerotic human hippocampus. The latter authors also noted an up-regulation of GLT-1 in the nonsclerotic epileptic hippocampus. These findings supported the hypothesis that reduced or dysfunctional glial glutamate transporters in the

hippocampus may trigger spontaneous seizures in AHS patients,[44] yet the underlying mechanisms are unclear. It has been proposed that the role of glutamate transporters in epilepsy may not be related directly to the control of excitation through synaptic glutamate concentration but rather to the glutamate-dependent metabolism.[76] In this context, the finding of a loss of glutamine synthetase in the sclerotic versus nonsclerotic hippocampus of TLE patients[46] deserves further consideration. After uptake of glutamate into astrocytes, this enzyme rapidly converts the transmitter into glutamine that is then transported to neurons, where it may be resynthesized to glutamate (see Astrocyte Metabolism section). Eid et al. did not observe epilepsy-related changes in the expression of GLT-1. They concluded that in the sclerotic tissue, down-regulation of glutamine synthetase caused a slowing of the glutamateâ€“glutamine cycling and accumulation of the transmitter in astrocytes and in the extracellular space.[46] This conclusion was compatible with findings in animal models of epilepsy and

earlier data, demonstrating slowed glutamateâ€“glutamine cycling in sclerotic human epileptic hippocampus with magnetic resonance spectroscopy.[97] Whether activation of glutamate transporters (e.g., through Î²-lactam antibiotics[103]) might be beneficial in the treatment of epilepsies remains a matter of further investigation.

A few studies addressed the potential involvement of ionotropic glutamate receptors in seizure generation. Mouse mutants with deficient GluR2 Q/R editing developed early-onset epilepsy with spontaneous and recurrent seizure activity, suggesting that enhanced Ca^{2+} influx through the Q form of the GluR2 subunit of AMPA receptors reduces seizure threshold.[22] Astrocytes also carry the GluR2 subunit, but altered glial GluR2 editing seems not to play a role in human TLE (but see Gliomas section). Rather, combined functional and single-cell transcript analyses put forward the idea that enhanced expression of GluR1 flip variants account for the prolonged receptor responses observed in hippocampal astrocytes of TLE patients with AHS.[106,107] This alteration in the splicing status of AMPA receptors predicts enhanced depolarization upon activation by endogenously released glutamate. Prolonged receptor opening will promote influx of Ca^{2+} and Na^{+} ions, and the latter plug astroglial Kir channels,[105] which will further strengthen depolarization and reduce the K^{+} buffer capacity of astrocytes (Fig. 3). It is yet unknown whether the changes in glial receptor function are causative of or result from the epileptic condition. Also, the question of how and to what extent alterations in glial GluR1 splicing contributes to seizure generation or spread requires further investigation. Astrocytes cultured from patients with Rasmussen encephalitis, a rare form of childhood epilepsy, showed spontaneous Ca^{2+} oscillations that were dependent on transmembrane influx of Ca^{2+}.[75] The authors speculated that these responses might add to neuronal hyperactivity, possibly due to autocrine ionotropic glutamate receptor stimulation by glutamate released from astrocytes. Another study suggested that the destruction of astrocytes by GluR3 antibodies plays a critical role in the progression of this autoimmune disorder.[129]

Ca^{2+} Signaling in Astrocytes: A Source of Glutamate

Under normal conditions, mGluR3 and mGluR5 are the predominant metabotropic glutamate receptor subtypes expressed by glial cells. Activation of these receptors affects cyclic adenosine monophosphate (cAMP) accumulation and leads to an increase in intracellular Ca^{2+}, respectively. The Ca^{2+} rise may oscillate and initiate Ca^{2+} wave propagation within the astrocyte network, activate Ca^{2+}-dependent ion channels, and induce glutamate release from astrocytes (see Membrane Physiology section). In experimental epilepsy, reactive astrocytes of the hippocampus persistently up-regulate mGluR3, mGluR5, and mGluR8 protein.[110] Electron microscopic inspection of hippocampal tissue from TLE patients revealed expression of mGluR2/3, mGluR4, and mGluR8 in reactive astrocytes, suggesting an involvement of these receptors in gliosis.[114] Up-regulation of astroglial mGluR2/3 and mGluR5 was also observed in epileptic specimens from patients with focal cortical dysplasia.[8] Because their activation modulates the expression of GLAST and GLT-1[7] and elevates $[Ca^{2+}]_i$, mGluRs in astrocytes might be involved in the generation of seizure foci (Fig. 3).

Over the past decade Ca^{2+} signaling mechanisms in astrocytes have received considerable attention. Of particular importance for this discussion is the novel observation that astrocytes exhibit Ca^{2+}-induced release of glutamate, which provides direct excitation to neighboring neurons (see Membrane Physiology section). Because of the observed changes in protein expression within astrocytes following injuries that lead to the development of epilepsy, it is tempting to speculate that alterations in this glial-derived excitatory pathway in coordination with reductions in glutamate uptake might provide an excitatory drive underlying seizure disorders. Recent work suggested that in chemically induced, acute epilepsy models, astrocytic Ca^{2+} oscillations and glutamate release contribute to the generation of synchronized epileptiform activity.[48,117] Future work has to elaborate whether astrocytes provide sufficient excitation to contribute to seizures and whether they indeed represent new targets for the development of antiepileptic treatments.

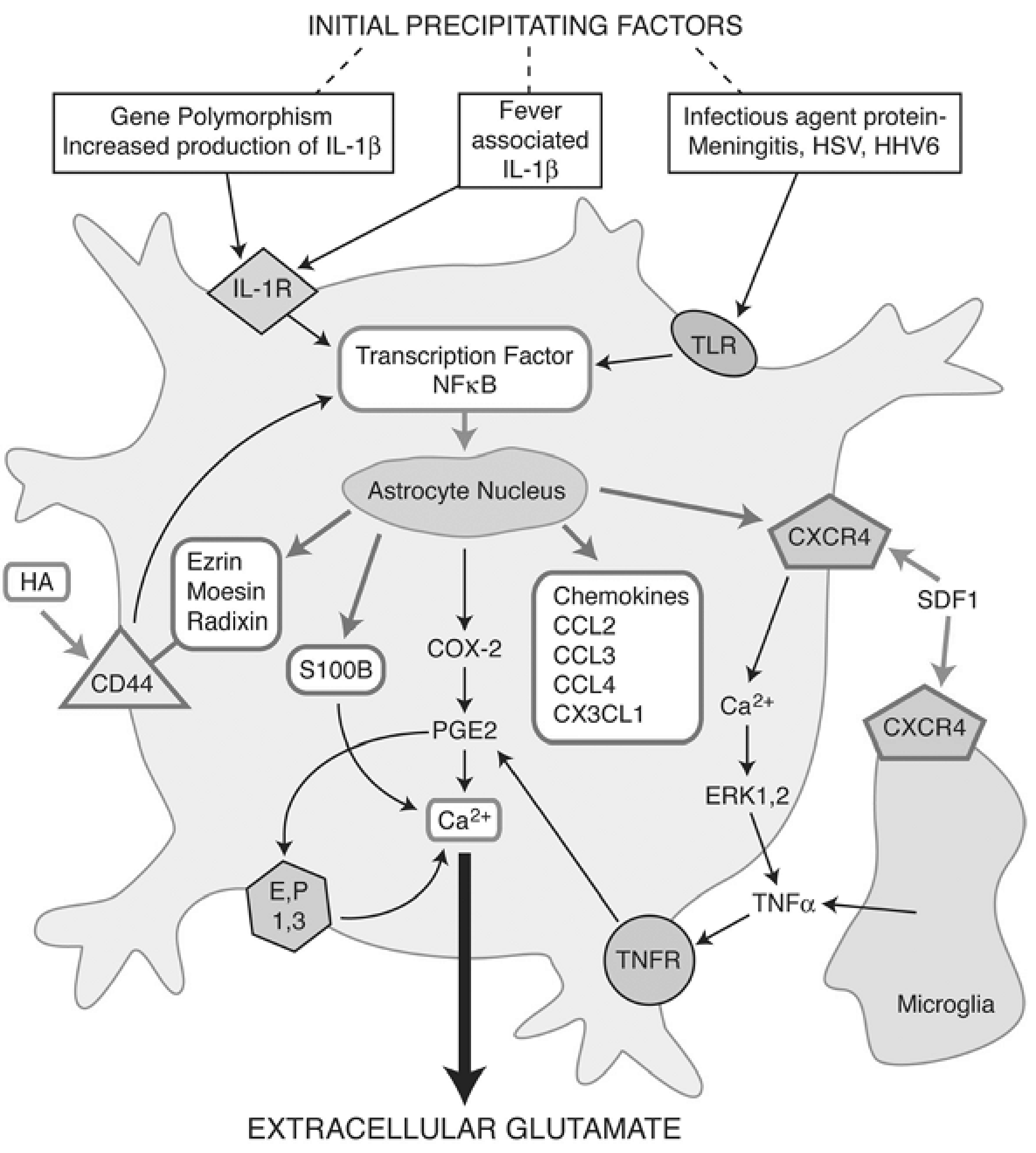
INITIAL PRECIPITATING FACTORS
Gene Polymorphism Increased production of IL-1β
Fever associated IL-1β
Infectious agent protein- Meningitis, HSV, HHV6
IL-1R
TLR
Transcription Factor NFκB
Astrocyte Nucleus
CXCR4
SDF1
Ezrin Moesin Radixin
HA
CD44
S100B
COX-2
PGE2
Chemokines CCL2 CCL3 CCL4 CX3CL1
Ca2+
ERK1,2
CXCR4
Ca2+
E,P 1,3
TNFα
TNFR
Microglia
EXTRACELLULAR GLUTAMATE

FIGURE 4. Probable molecular path-ways for glutamate release from astrocytes in the sclerotic hippocampus. This diagram is constructed on the basis of molecules produced by genes whose expression was found to increase in human temporal lobe epilepsy (TLE). The figure also shows that many of the pathways could be activated through known initial precipitating factors of TLE. CCL2, CCL3, and CCL4, CC family chemo-kines; CD44, CD44 antigen (homing function and Indian blood group system); CX3CL1, fractalkine; CXCR4, Î±-chemokine receptor; COX-2, cy-clooxygenase-2; EP1,3, calcium mobi-lizing receptors for PGE_2; ERK1,2, extracellular signalâ€"related kinases; HA, hyaluronan; IL-1Î², interleukin-1Î²; HSV, herpes simplex virus; HHV6, human herpes virus 6; IL-1R, interleukin 1 receptor; PGE_2, prostaglandin E_2; SDF1, stromal derived factor 1; TLR, Toll-like receptor; TNFR, tumor necrosis factor receptor; TNF-Î±, tumor necrosis factor-Î±. (Figure provided by courtesy of Dr. Tih-Shih Lee, PhD thesis, Yale University.)

Responses to Immune and Inflammatory Factors

Astrocytes are known to contribute to the inflammatory environment of the CNS by producing a wide range of immunologically relevant molecules. They can express class II major histocompatibility complex antigens, and produce a variety of chemokines and cytokines.[39,63] Proinflammatory cytokines have only begun to be recognized for their role in seizure disorders. Kanemoto et al. observed a strong association of a polymorphism in the IL-1Î² gene in patients with sclerosis compared to nonsclerosis patients and nonepileptic controls.[12,65] The biallelic polymorphism favors high production of IL-1Î² in patients with AHS. Other etiologic factors in TLE, such as febrile seizures, are also associated with increased IL-1Î² levels.[42,55,123]). IL-1Î² can act on astrocytic IL receptors and, via the transcription factor NFÎºB, induce the expression of a variety of molecules (Fig. 4). Immunohistochemical analysis of hippocampi removed from patients with medically intractable TLE revealed increased production of the NFÎºB-p65 subunit in astrocytes of sclerotic tissue compared to control specimens.[30]

In a recent study of differential gene expression in sclerotic hippocampi of TLE patients, several genes that could be regulated through the NFÎºB pathway were found to be up-regulated, including S100Î², ezrin, radixin, and moesin; the chemokines CCL2, CCL3, CCL4, and CX3CL1; and the chemokine receptor CXCR4[35,70] (Fig. 4). IL-1Î² can also activate cells to induce CD44 to bind to hyaluronan,[100] and interleukins may also activate microglia to express CXCR4.[14] The presence of activated microglia that express CXCR4 in the sclerotic hippocampus has been demonstrated.[70] Such activated microglia may be an important source of tumor necrosis factor (TNF) and IL-1Î².[2,88] Glutamate release by astrocytes, via a Ca^{2+}-regulated exocytosislike process, has now been established. Molecules such as S100Î², CD44, and CXCR4 might directly or indirectly activate this glutamate release pathway[10,14] (Fig. 4). Hence, up-regulation of some of the relevant molecules in astrocytes in the sclerotic hippocampus may lead to increased release of glutamate. A closer study of immune mechanisms in the pathology of TLE may hold important new insights to this disease.

Furthermore, the immunologic responsiveness of astrocytes may provide the clue as to how a variety of initial precipitating factors[78] may be associated with the common pathologic substrate of hippocampal sclerosis. It is established that early childhood febrile seizures can be predisposing for TLE,[60,72] and such febrile seizures have been shown to be associated with increased IL-1Î² levels in CNS and blood plasma.[42,55,123] High IL-1Î² levels are also associated with a genetic polymorphism.[65,122] IL-1Î² can act on astrocytic interleukin receptors and, via the transcription factor NFÎºB, might induce molecular pathways leading to Ca^{2+}-dependent glutamate release (Fig. 4).

Infections of the brain such as meningitis,[90] human herpes virus 6, and herpes simplex virus[118] were also shown to be associated with TLE, and again astrocytes might be important in this context. Human astrocytes express Toll-like receptors (TLRs),[24] which recognize pathogen-specific molecular patterns.[84] A wide range of TLRs is expressed by astrocytes, including those that respond to viruses and bacteria.[27] Both IL-R1 and TLRs induce signal transduction pathways, leading mainly to activation of the transcription factor NFÎºB[81] and possibly to enhanced release of astroglial glutamate in the sclerotic hippocampus (Fig. 4).

Astrocytes and Bloodâ€“Brain Barrier Modifications at Seizure Foci

It was reported as early as 1899[20] that there is proliferation of the microvasculature in the sclerotic Ammon horn. However, only recently has attention been paid to the role of the BBB in seizure disorders. The BBB is composed of endothelial cells characterized by extensive tight junctions, absence of fenestrations, and sparse pinocytic vesicular transport.[9] Astrocytic end-feet ensheathe blood vessels and release signals that support the formation and maintenance of the tight junctions between endothelial cells, as well as the expression of endothelial transport molecules. Astrocytes also play an active role in the short-term modulation of BBB permeability.[1]

The BBB participates in several important functions. Among them is the transport of glucose into the brain. GLUT1 is the principal glucose transporter in astrocytes. GLUT1 is found in at least two forms, a 55-kDa form in endothelial cells and a 45-kDa form primarily associated with astrocytes. There are little data on the role of GLUT1 in TLE, though in one study endothelial GLUT1 was reduced (interictally) in the temporal lobes of patients with complex partial seizures.[29]

Astrocytes play a significant role in buffering of extracellular K^+, and impaired K^+ clearance has been observed in the sclerotic human hippocampus (see K^+ Channels and Water Channels section). Kir4.1 and AQP4 water channels are predominantly located on astrocytic end-feet associated with the BBB. In astrocytes from sclerotic hippocampi, the polarity in the distribution of AQP4 is lost.[45,71] This may be associated with reduced clearance of extracellular K^+ and enhanced severity of seizures, as K^+ buffering through astrocytic Kir channels depends on a parallel flux of water.[45] In addition, there are several other molecules whose distribution along the end-foot membrane of the BBB are altered in epilepsy. These include increased expression of erythropoietin receptor,[21] increased plectin 1 (PLEC1),[73] and decreased dystrophin.[71]

Recent microarray studies,[70] while confirming the distribution of AQP4, PLEC1, and dystrophin, pointed to changes in the expression of several other molecules, including AHNAK, CD44, dystrobrevin A, CCL2, and CCL3. AHNAK is a molecule that is reported to be associated with a new type of vesicle, the â€œenlargosome,â€[19] which may contribute to enlarging the perivascular end-foot volume as reported in the brain of animal models of seizures.[4] It has been shown that human brain microvessels carry chemokine receptors CCR1 and CCR2 on the parenchymal surface of the vessels.[5] The genes for the ligands of these receptors, CCL3 and CCL2, are up-regulated in mesial TLE (MTLE). These chemokines are thought to influence the permeability of the BBB.[1] In-depth analysis of the roles of these molecules at the endothelial/astrocyte interface may provide important advances in understanding the pathophysiology of TLE.

Astrocyte Dysfunction at Other Seizure Foci

Tubers in Tuberous Sclerosis

Several lines of evidence suggest that astrocytes in tuberous cortex seizure foci may play a major role in seizure initiation and maintenance. The strongest evidence comes from astrocyte-specific TSC1 conditional knockout mice. These mice have increased numbers of GFAP-positive astrocytes, in the absence of frank cortical tubers, and more interestingly, they exhibit electroencephalographically confirmed seizures.[119] These astrocytes display impaired glutamate transport and thus may cause seizures by extracellular accumulation of glutamate[130] as shown in human TLE hippocampus.[44] Further, in these mice, the hippocampus showed the most pronounced enlargement and significant architectural disorganization, whereas the cortex was grossly normal. These data strongly suggest that changes induced in astrocytes by TSC gene mutations may be even more important for seizures than neuronal disorganization of the cortex. These features associated with TSC1 dysfunction are surprisingly reminiscent of the sclerotic hippocampus in patients with MTLE, especially regarding astrocytic proliferation. Therefore, it is possible that a common pathology of astrocytes in MTLE and TSC may explain the occurrence of seizures in these disorders.

Gliomas

Intratumoral microdialysis studies have been carried out in patients with high-grade astrocytomas.[101] These studies show that glucose tended to be lower in the tumor than in the peritumoral region, whereas lactate was significantly higher in the tumor. Only necrotic tumors displayed significantly higher glutamate levels. Human gliomas of high-grade malignancy contained reduced adenosine compared to distant tissue.[85] In a more recent microdialysis study of grade III and IV gliomas, Bianchi et al.[15] reported significantly reduced glutamate levels in the tumor compared to peritumoral and distant cortex. Moreover, they observed significantly elevated levels of taurine, GABA, phenylalanine, isoleucine, tyrosine, valine, leucine, and lysine. Only in tumors associated with epilepsy, extracellular glutamate levels were significantly decreased and glutamate concentration strongly correlated with the degree of cell proliferation.

Two main hypotheses have been put forward as to how gliomas (glioblastomas) may contribute to epileptic seizures. One of the hypotheses is based on the discovery of the underediting of the glutamate receptor subunit GluR2 at the Q/R site in human malignant gliomas.[74] The GluR2 subunit is abundantly expressed by human astrocytes,[106] and transgenic mice with a reduced rate of Q/R-site editing developed early-onset epilepsy and premature death (see glutamate transporters and receptors section). Underediting at the Q/R site results in increased Ca^{2+} permeability of the AMPA receptor, which may modulate gene expression to activate pathways and result in increased glutamate release by the glioma cells, causing excitation of surrounding neurons and resulting in seizures and excitotoxic death, which permits the spread of the tumor. A second hypothesis is suggested by the work of H. Sontheimer's group.[133,134] Studying cultures of glioma cells isolated from glioblastomas surgically removed from patients and established human glioma cell lines, they found that these cells released larger than normal amounts of glutamate. They further showed that Na^+-dependent glutamate uptake by glioma cells was up to 100-fold lower than in astrocytes. Immunohistochemistry and subcellular fractionation studies showed very low expression of the astrocytic glutamate transporter GLT-1 but normal levels of GLAST, which, however, was mislocalized to the nucleus. Thus, these cells were deficient in glutamate clearance. The unusual release of glutamate from glioma cells was shown to be due to both the reduced Na^+-dependent glutamate transporters and an up-regulation of cystineâ€“glutamate exchange.[134] It is conceivable that excess release of glutamate by tumors may generate seizure activity in peritumoral neurons.

Summary and Conclusions

Astrocytes undergo morphologic alterations in epilepsy, and recent evidence suggests that the structural changes are accompanied by variations in cellular function. Since astroglial cells have been identified as direct communication partners of neurons, their dysfunction might be involved in the pathogenesis of the disease. In fact, surgical removal of sclerotic tissue often results in a significant improvement of the epileptic condition, suggesting that gliosis contributes to seizure generation. It remains an important issue to figure out what factors initiate the dysregulation of astrocytic signaling molecules, and whether these changes are causative for the development of the disease. Moreover, the specific role different astroglial subtypes play in epilepsy still has to be elaborated. If these cell types are differently affected in epilepsy, this will likely produce distinct consequences for the excitability of neural circuitry. In fact, cells with astroglial properties differ significantly in their morphologic and functional properties, but most studies describing glial alterations in epilepsy did not identify the cellular subtype affected. Thus, it is important to appreciate that some of the changes we have discussed may represent changes in the properties of one astroglial subtype, or changes could result in modified ratios of different subclasses of astrocytes. A further understanding of the diversity of â€œnormalâ€ astrocytes, by establishing critical parameter sets allowing unequivocal subclassification, will be an essential step to help us unravel the role of astrocytes in epilepsy and other neurologic disorders. Progress made in the field over the past years suggests that this should eventually open novel rational therapeutic approaches to seizure disorders, which, so far, can only be poorly controlled.

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Chapter 27

Neuromodulation of Seizures, Epileptogenesis, and Epilepsy

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Introduction

Epilepsy is a complex disease that is influenced by a large number of diverse variables. Some of these factors, such as genes that influence seizure susceptibility, are internal. Others, which alter normal brain excitability, such as traumatic brain injury, are external.

These variables can have different and distinct effects. For example, genes may influence both the development of the disorder (epileptogenesis), or the frequency and severity of seizures after epilepsy is established. Furthermore, these same factors may also influence treatment, because they can alter the efficacy of antiepileptic drugs.

A broad range of endogenous factors include a subset that can be termed â€œneuromodulators.â€ These factors are essential components of the normal central nervous system (CNS) and play an important role in the balance of excitation and inhibition in the normal brain. Here, we review neuromodulatory compounds and principles that best exemplify those that affect seizure susceptibility, epileptogenesis, and epilepsy.

In this chapter, neuromodulators are categorized into proteins and small molecules that are (a) primarily expressed in, or released from, neurons; (b) present in the extracellular space as part of the milieu that is commonly referred to as the extracellular matrix (ECM); and (c) primarily associated with astrocytes.

This review emphasizes neuromodulators that influence excitability in the hippocampus and the adjacent parahippocampal region (including the entorhinal cortex), two brain regions known to be centrally involved in limbic seizure activity. This focus does not imply that neuromodulation is most robust in those areas, but rather reflects the fact that the majority of information in the field of epilepsy research derives from these limbic regions. This includes studies in humans, in which neuromodulation has been mostly examined using surgically resected hippocampal and parahippocampal tissue from patients with intractable temporal lobe epilepsy (TLE).

In view of the complexity of the subject matter, often involving multiple receptors as well as intricate modes of regulation of expression and release for any given neuromodulator, only specific examples will be discussed in detail in each category. Furthermore, a major message of this overview is that no single neuromodulator influences excitability in a simple manner, and that cross-talk between modulators is likely to be associated with seizure activity.

Tables 1,2,3,4 provide bulleted lists of the neuromodulator categories that have been associated with pathophysiologically or therapeutically relevant aspects of seizures or epilepsy. The selection included here should be viewed merely as a snapshot of current knowledge. There can be little doubt that additional members of these families will become relevant as well, and that novel, important neuromodulators will be identified in the future.

Neuron-derived neuromodulators

Neuropeptides

Neuropeptides comprise a variety of small proteins that were originally shown to be coexpressed with classical neurotransmitters in neurons; it was assumed that this coexpression indicated a role in synaptic transmission. Accordingly, many studies focused on the mechanism(s) by which peptides might exert their effects in concert with colocalized classical transmitters such as Î³-aminobutyric acid (GABA) or glutamate. It is widely recognized, however, that neuropeptides have effects independent of classical transmitters. These effects include an influence on ion channels, synaptic transmission, and hence excitability. Neuropeptides also affect growth, proliferation, vasculature, and neurogenesis, although these effects may only occur at a certain time during development or after an injurious insult.

A discussion of neuropeptides is particularly germane to epilepsy because many have robust effects on seizure threshold, seizure susceptibility, epileptogenesis, and epilepsy (i.e., the state of spontaneous, recurrent seizures). However, the concept that neuropeptides modulate seizuresâ€"and potentially epilepsyâ€"did not arise from studying their basic, fundamental properties as cotransmitters. Instead, it was initiated by reports that showed that seizures alter the expression of neuropeptides and their receptors. This was first demonstrated in laboratory animals,[80,138] although seizure-induced alterations in neuropeptides have also been found in surgically removed brain tissue from patients with intractable TLE.[50]

To date, it is still widely debated whether these changes in neuropeptide expression reflect a mechanism to repair the brain after seizure-induced neuronal damage or whether altered levels of neuropeptides indicate a compensatory, anticonvulsant response of the brain to prevent further seizure activity. An intriguing suggestion is that these changes are due to a pattern of genomic responses set into play to recapitulate developmental patterns.

Table 1 lists a large number of neuropeptides, organized according to the initial studies describing their expression and function throughout the body. Notably, these perspectives have evolved over time, because many of these peptides were identified in more than one brain area and found to have multiple functions.[204]

Figure 1 illustrates a focused view of these neuropeptides, using the dentate gyrus as an example. The dentate gyrus harbors a variety of GABAergic interneurons, which normally play an important role in preventing abnormal excitability. These neurons also contain one or more neuropeptides. In addition, two principal cellsâ€"the abundant granule cells and the less numerous hilar â€œmossy cellsâ€â€"use glutamate as a neurotransmitter and also express various peptides, as well as other neuromodulators. This subregion of the hippocampus plays a central role in seizure generation and propagation in animals and humans, and has been studied extensively with regard to the neuromodulatory effects of peptides in epilepsy.

Table 1 Neuropeptides

Family Member	Amino Acid #	Receptors	Convulsant Pro (+) or Anti (â€")	References
POMC-derived neuropeptides				
Adrenocorticotropin (ACTH)	39	MCR2	(-)	28

Melanocyte stimulating hormone (MSH)	13	MCR1	(-)	1
Î²-Lipotropin (Î²-LPH)	89			
Met-enkephalin	5	Âµ,Î´,Îº	Âµ: (+)	171,196
Leu-enkephalin	5	Âµ,Î´,Îº	Âµ: (+)	171,196
Î²-Endorphin	30	Âµ,Î´,Îº	(-)	229
Dynorphin	17	Âµ,Î´,Îº	(-)	196,229
Nociceptin (Orphanin FQ)	17	ORL-1	(-)	170
Tachykinins				
Substance P	11	NK1	(+)	229
Neurokinin-A	10	NK2		
Neurokinin-B	10	NK3	(+)	229
Bradykinin	9	B1, B2	(+/-)	2
Hypothalamic peptides				
Hormones				
Thyrotropin stimulating hormone (TSH)	201			
Oxytocin (OT)	9		(-)	1
Luteinizing hormone (LH)	204			
Follicle stimulating hormone (FSH)	204			

Vasopressin (AVP) or antidiuretic hormone (ADH)	9	V1A, V1b, V2	(+)	1, 37, 45
Growth hormone	191			
Releasing and inhibiting factors				
Corticotropin releasing hormone (CRH or CRF)	41	CRF1,2	(+)	
Thyrotropin releasing hormone (TRH)	3	TRH1,2	(-)	118
Growth hormone releasing hormone (GnRH)	44			
Luteinizing hormone releasing hormone (LHRH or GHRH)	10			
Somatostatin growth hormone release inhibiting hormone	14 or 28	SST (1-5)	(-)	20, 223
Gut peptides				
Motilin	22			
Cholecystokinin (CCK)	8	CCK1,2	(-)	244
Vasoactive intestinal polypeptide (VIP)-glucagon family				216
Secretin	27			
VIP	28	PACAPR type II	(+)?	39, 48
Pituitary adenylate cyclase activating peptide (PACAP)	27 or 38	PACAPR type I	(+)	37, 39

Glucagon-like peptide (GLP)-1	36	GLP-1R, rGLP-1R	(-)	58
Neuropeptide tyrosine			(-)	227
Neuropeptide tyrosine (NPY)	36	YR (1-5)		
Pancreatic polypeptide (PP)	36			
Peptide tyrosine-tyrosine (PYY)	36			
Bombesin peptides				
Bombesin (Gastrin-releasing peptide; GRP)	27	GRP R1,2	(-)	4
Gastrin	17			
Neuromedin B	10			
Galanin	29 or 30	GAL (1-3)	(-)	229
Neurotensin	13	NTSR1,2		
Calcitonin gene-related peptide (CGRP)				115
Vascular peptides				
Natriuretic hormone family				
Atrionatriuretic hormone (ANH) or atriopeptin	28	NPRA, B, C	(+)	136
Brain natriuretic hormone (BNP)	32		(+)	136

C-type natriuretic hormone (CNP)	22		(+)	136
Angiotensins Iâ€“IV	6-10	AT (1-4)	(-)	211
Placental peptides				
Prolactin Chorionic gonadotropin Placental lactogen (choriomammotropin)	198			16, 123,124

The major categories of neuropeptides are listed, with emphasis on those that have been associated with seizures or epilepsy. Peptide length refers to the number of amino acids. Receptor subtypes are shown for examples with multiple receptors. Peptides that have been shown to exert proconvulsant (+) or anticonvulsant (-) activity are indicated; mixed effects are denoted by +/-; a question mark indicates effects that are not clearly proconvulsant or anticonvulsant. References are primarily reviews, but specific citations are provided when reviews are unavailable.

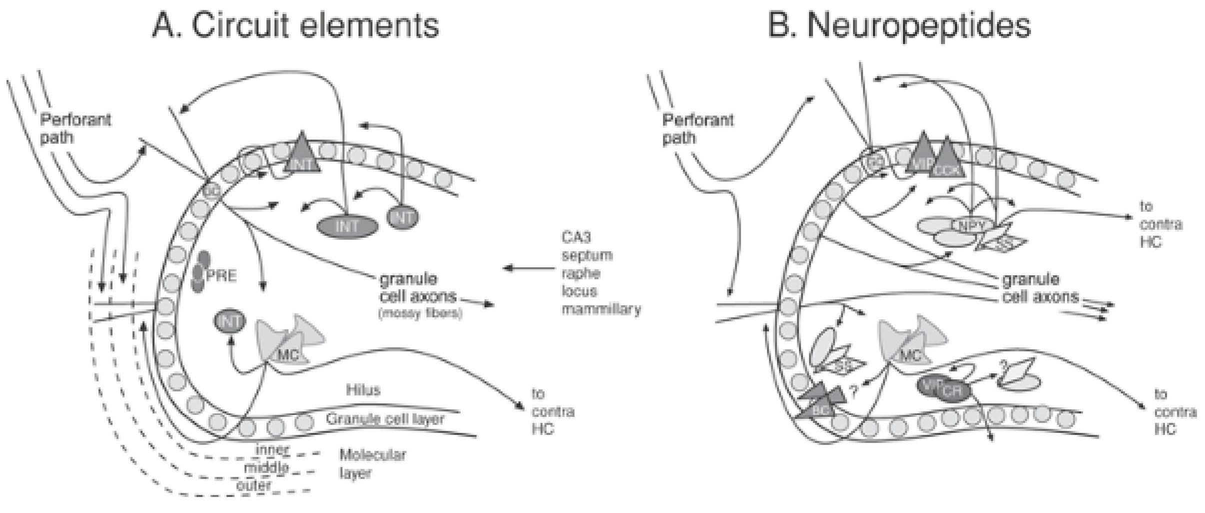
A. Circuit elements
Perforant path
GC
INT
INT
INT
PRE
INT
MC
granule cell axons (mossy fibers)
CA3 septum raphe locus mammillary
Hilus
Granule cell layer
to contra HC
inner
middle
outer
Molecular layer
B. Neuropeptides
Perforant path
GC
VIP
CCK
NPY
SS
to contra HC
granule cell axons
SS
MC
?
BC
VIP
CR
?
to contra HC

FIGURE 1. Circuit elements and neuropeptides in the rat dentate gyrus under normal conditions. **A:** Major components of dentate gyrus circuitry. These include the dense layer of granule cells (*GC*); diverse GABAergic â€œinterneuronsâ€ (*INT*), hilar mossy cells (*MC*), as well as precursors to granule cells (*PRE*) that are located in the subgranular zone. The major afferent input to the dentate gyrus is the perforant pathway, which contains the axons of neurons in the entorhinal cortex. Lateral entorhinal neurons innervate the outer molecular layer (*outer*) and medial entorhinal neurons innervate the medial molecular layer (*medial*). Mossy cells and other fibers innervate the inner molecular layer (*inner*). In addition, inputs to the dentate gyrus also arise from area CA3 pyramidal cells, the septum, dorsal raphe, locus coeruleus, mammillary bodies, and other areas. The main projections from the dentate gyrus are from the granule cell axons (the mossy fibers), which terminate locally on hilar processes and the layer containing the proximal dendrites of CA3 pyramidal

cells (stratum lucidum; not shown). In addition, mossy cells project both ipsilaterally and contralaterally to the dentate gyrus. Some GABAergic neurons also project contralaterally. Reproduced with permission from Freund TF, Buzsaki G. Interneurons of the hippocampus. *Hippocampus*. 1996;6:347â€“470; and Scharfman HE. The role of nonprincipal cells in dentate gyrus excitability and its relevance to animal models of epilepsy and TLE. In: Delgado-Esqueta AV, Wilson W, Olsen RW, Porter RJ, editors. *Basic mechanisms of the epilepsies: molecular and cellular approaches*, 3rd ed. New York: Lippincott-Raven; 1999:805-820.[77,179] **B:** Many neuropeptides are expressed in the normal dentate gyrus, and some of the most well-studied examples are shown.[77] Opiates are mainly expressed in granule cells. In contrast, other neuropeptides are primarily present in interneurons. Basket cells contain both vasoactive intestinal polypeptide and cholecystokinin; hilar neurons that innervate the outer molecular layer (as well as other targets) express neuropeptide Y and/or somatostatin; vasoactive intestinal polypeptide and calretinin that define a population that innervates the inner molecular layer, as well as other interneurons; in addition, other vasoactive intestinal polypeptide-containing cells exist and may be coupled by gap junctions.[90] Recent studies have indicated that substance P has widespread expression in interneurons.[197] (See color insert.)

Neuropeptide Y

Neuropeptide Y is the first example. This peptide is normally expressed in a subset of GABAergic neurons in the dentate gyrus. The axons of these cells project to numerous areas of the region and thus exert multiple effects (Fig. 2A). A primary effect of neuropeptide Y is to reduce excitatory transmission from granule cells to their targets, thereby decreasing the excitatory output of the dentate gyrus to hippocampal pyramidal cells. Thus, when synthetic neuropeptide Y is applied to slices of rodent dentate gyrus, it inhibits the excitatory output of granule cells by acting on neuropeptide Y receptors on the terminals of granule cell axons. This function is likely to be important in the control of seizure activity in the hippocampus since overexpression of neuropeptide Y is anticonvulsant[227] and because decreased neuropeptide Y expression leads to increased seizure susceptibility.[13]

Neuropeptide Y also has other actions in the dentate gyrus. For example, it modulates calcium entry into granule cells,[139] and also affects a specific potassium ion (K^+) channel on GABAergic neurons in the dentate gyrus.[156] The latter could influence neuronal firing and GABA release and therefore modulate the targets of GABAergic neurons.

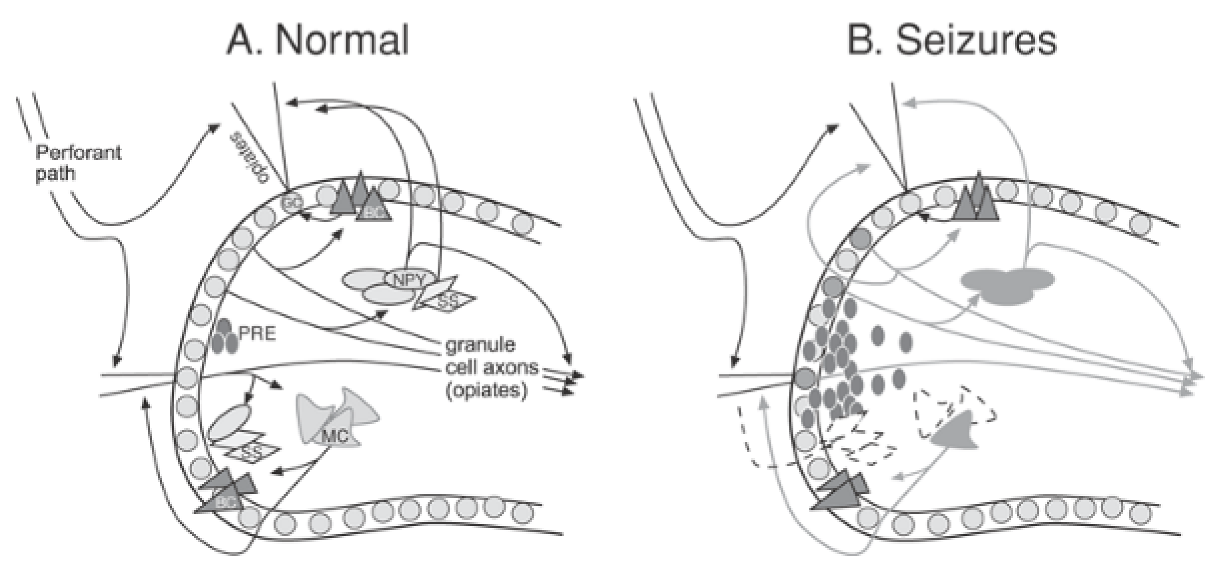

FIGURE 2. Changes in neuropeptide Y and somatostatin in the dentate gyrus after seizures. **A:** Normal circuitry and expression of neuropeptide Y and somatostatin in the rodent dentate gyrus. **B:** Alterations in neuropeptide Y and somatostatin in animal models of epilepsy are illustrated schematically. For the neuropeptide Y system, these changes include: (a) new expression in granule cells and their axons, the mossy fibers; (b) increased expression in interneurons that normally express neuropeptide Yâ€"this effect appears to develop mostly after acute rather than chronic seizures; (c) novel expression of neuropeptide Y in some mossy cells;[88] and (d) expression in newly formed granule cells, although the extent that this occurs is unclear. In addition, changes in receptors occur (not shown). For the somatostatin system, the best documented alteration is seizure-induced cell death of those interneurons that normally express this peptide. (See color insert.)

Neuropeptide Y also facilitates the proliferation of new granule cells in the adult brain, and thus influences adult neurogenesis.[88] These actions appear to be mediated by the Y1 subtype of neuropeptide Y receptors, which are situated on the proliferating cells. The source of neuropeptide Y may be the GABA/neuropeptide Y coexpressing interneurons, which have axon terminals in the subgranular zone, where the proliferating cells are located.[52]

Neuropeptide Y function may change after seizures, as initially suggested by studies showing that seizures affect the expression of neuropeptide Y in granule cells. Particularly after chronic seizures, the axons of the granule cells strongly express neuropeptide Y (Fig. 2B).[11,129]

This phenomenon may be functionally significant for two reasons: first, neuropeptide Y may exert more robust effects on the normal targets of granule cell axons; second, neuropeptide Y may have additional effects at new locations, because the axons of granule cells (mossy fibers) make new connections after chronic seizures (â€œmossy fiber sproutingâ€). Indeed, neuropeptide Y inhibits the effects of glutamate released from the sprouted axons of granule cells in epileptic rodents.[218] These data support the concept that neuropeptide Y is â€œanticonvulsantâ€ and its upregulation after seizures is â€œcompensatoryâ€ in nature. Interestingly, acute seizures, as opposed to chronic seizures, appear to have different effects on neuropeptide Y expression. Thus, a brief seizure results in a preferential, transient increase in neuropeptide Y expression in GABAergic neurons,[200] but does not cause robust changes in neuropeptide Y expression in granule cells. The functional role of the increase in neuropeptide Y within GABAergic neurons is still not clear, but it could be a way to inhibit glutamate release, which could prevent another seizure. It is important to add that this transient increase of neuropeptide Y in GABAergic neurons may be underestimated, because seizures may injure neuropeptide Yâ€"containing neurons.[29,49,212]

Additional complications arise from the fact that some, but not all, neuropeptide Y receptors change as a consequence of seizures. It appears that the predominant change is an increase in Y2 receptors. This would be likely to enhance the ability of neuropeptide Y to inhibit glutamatergic transmission, because Y2 receptors are normally responsible for this effect.[65,226]

However, other receptors do not necessarily show robust changes, or the studies to date are not in complete agreement.[12] An increase in receptors may not lead to a change in effect if neuropeptide Y is not released in sufficient concentration to activate the new receptors.

To add to the complex picture, granule cells formed after seizures, although likely to express neuropeptide Y, have distinct physiological properties and may therefore release neuropeptide Y differently. On the other hand, neurons in the epileptic brain likely release more neuropeptide Y. This may be the case for newly-formed granule cells, which typically exhibit burst discharges[181] and therefore may release neuropeptide Y.

In summary, a series of experimental studies have documented the robust influence of neuropeptide Y in the normal dentate gyrus and suggested that this peptide be considered an endogenous anticonvulsant. Moreover, neuropeptide Y expression is highly plastic and altered by seizures. These changes appear to indicate anticonvulsant properties and a compensatory inhibitory role for neuropeptide Y in epilepsy. However, the complexities of neuropeptide Y changes after seizures, and the lack of a detailed understanding of several of these changes, suggest that firm conclusions are still premature.

Somatostatin

Somatostatin is another example of a neuropeptide with robust actions in the dentate gyrus, making it another candidate to serve an endogenous anticonvulsant role.[20,223] Normally, somatostatin is preferentially expressed in a subset of GABAergic neurons in the dentate gyrus, which innervate the outer molecular layer and have collaterals in the hilus (Fig. 2A). The axonal projection to the outer molecular layer has received greatest attention because it is most dense, and because of the potential for selective modulation of the lateral perforant path, a major cortical input to the dentate gyrus, which terminates in the outer molecular layer.

In most but not all cases, somatostatin appears to depress this input when single afferent stimuli are tested.[14,178] More robust effects are observed after tetanization, which would

normally lead to long-term potentiation (LTP); somatostatin blunts this effect.[14] These data suggest that somatostatin depresses the glutamatergic activation of granule cells by an action at the site of synaptic input, and it does so preferentially after high-frequency input. In addition, somatostatin depresses calcium-mediated action potentials (calcium â€œspikesâ€) in granule cells by inhibiting N-type calcium channels. The net effect could contribute to the depression of LTP in the lateral perforant path.[14] In light of these results, it is no surprise that somatostatin inhibits seizures in animal models of epilepsy.[20] Likewise, in somatostatin knockout mice, seizures elicited by chemoconvulsants are more severe, and after discharges are longer in animals that are kindled by stimulation of the perforant path.[29]

Somatostatin may also have other actions, however. Thus, in other areas of the hippocampus, exposure to somatostatin leads to additional effects, such as modulation of the M-current.[188] This action may have numerous consequences, because M channels are located in diverse areas of the dentate gyrusâ€”not only on neuronal somata, but also on their axons.

As is the case of neuropeptide Y, somatostatin expression is dramatically changed after seizures. The decrease in somatostatin is due to the fact that somatostatin-containing neurons are extremely vulnerable to seizure-induced neuronal death (Fig. 2B). The loss of somatostatin may contribute to the change in hippocampal excitability following seizures.

However, somatostatin cell loss appears to be selective for animal models of epilepsy in which seizures are severe (i.e., models that use an initial period of status epilepticus to induce chronic seizures). Somatostatin cell loss is also evident in hippocampal tissue resected from patients with intractable TLE.[167] In contrast, animal models in which seizures are milder, such as electroconvulsive shock or kindling, do not necessarily result in the loss of somatostatinergic neurons, but lead to an *increase* in somatostatin expression within those neurons that normally express this neuropeptide.[153,186]

It is also necessary to consider that somatostatin receptors may be altered in epilepsy. In tissue resected from patients with pharmacoresistant TLE, only type 2 (i.e., the receptor known to mediate anticonvulsant effects) is altered in the dentate gyrus.[47] It appears that both the mRNA for the type 2 receptor and receptor binding increase in the granule cell layer, remain unaltered in the inner molecular layer, and decrease in the outer molecular layer. The latter changes may reflect a compensation for the loss of afferents, which degenerate due to the vulnerability of hilar somatostatin neurons. Other somatostatin receptors (types 1â€“4) in the dentate gyrus remain remarkably normal after kainic acid (KA)-induced status epilepticus, although changes occur elsewhere in the hippocampus.[162]

Taken together, the source of somatostatin and its receptor-mediated actions differ substantially between the normal and the epileptic brain. These differences are likely to alter the peptide's effects in a pathologic situation. This implies, for example, that synthetic somatostatin analogs may not be able to depress perforant path transmission in the epileptic brain because of the lack of appropriate receptor targets (see earlier discussion), and that it may be possible to design somatostatin-related therapeutic interventions that are geared specifically to the epileptic condition.

The changes in neuropeptide Y and somatostatin in the rat dentate gyrus after chronic seizures are illustrated schematically in FIGURE 2. As noted earlier, neuropeptide Y and somatostatin are just two of a long list of neuropeptides that have been studied intensively in the dentate gyrus in the context of seizures (Table 1). Thus, many neuropeptides appear to modulate excitability normally and specifically influence seizures/epilepsy in animal models of epilepsy. Most of them also have the same dual relationship with seizures as neuropeptide Y and somatostatin (i.e., they are both regulated by seizures and capable of modulating seizures). Finally, it should also be noted that there appear to be significant species differences in neuropeptide expression in the dentate gyrus. However, despite the fact that some of the peptides present in humans are not identical to those in rats or mice, the relationship of peptidergic neurons to epilepsy appears to be essentially similar in rodents and humans.

Calcium-Binding Proteins

Calcium-binding proteins have also received considerable attention with respect to their influence on the function of neurons in the dentate gyrus. Strictly speaking, this group has many members (Table 2), but those in the dentate gyrus that have received most attention are those that have the highest levels of expression. One example is calbindin D28K, which is primarily expressed in granule cells, although studies have also shown immunoreactivity in selected GABAergic neurons.[193] Other examples of calcium-binding proteins include parvalbumin and calretinin, which have been selectively localized to GABAergic neurons.[198]

The distinct distribution of these proteins naturally raises questions about their specific functions in various cell types. Interest grew after it was shown that those neurons in the dentate gyrus that appear most prone to seizure-induced damage (i.e., somatostatin-containing neurons and the glutamatergic mossy cells) lacked either calbindin or parvalbumin. However, later studies suggested a more complex relationship between calcium-binding proteins and vulnerability, because calcium-binding proteins such as calretinin were also found in susceptible neurons.[78]

Functional studies revealed that calbindin and parvalbumin have important roles in the regulation of calcium within the cell. In the granule cell, calbindin modulates calcium levels and therefore has several potential functions, including an influence on transmitter release. Indeed, overexpression of calbindin leads to alteration in granule cell transmission to pyramidal cells of CA3 due to a presynaptic mechanism at granule cell boutons. These changes are clearly important because of the dramatic alteration in hippocampal function in vivo after overexpression of the protein only in granule cells.[57] Parvalbumin also appears to have important functional roles in the regulation of calcium entry, primarily presynaptically.[40] These are likely to be substantial in their net effect in vivo, given that parvalbumin knockout mice have altered seizure susceptibility.[185] It is not clear, however, whether this is a specific defect in normal parvalbumin function or a compensatory effect.

In human tissue derived from patients with intractable TLE, calbindin expression in granule cells is reduced,[131] and the expression of parvalbumin immunoreactivity undergoes complex changes depending on hippocampal subregion and clinical features.[198,233] Some argue that these changes may be neuroprotective if intracellular calcium levels were effectively lowered by calcium-binding proteins, but others would suggest that this might not necessarily be the case.[219] In summary, the functional significance of neuromodulation by calbindin, parvalbumin, and many other calcium-binding proteins in epilepsy is still controversial and requires careful additional investigation and analysis.[35]

Table 2 Calcium-binding proteins

I. EF hand calcium-binding proteins
Î±-Actinin
Calbindin D28K

  - Calbindin D28k
  - Calretinin 20k, -22k
- Calcyphosine (p24)
- Calmodulin
  - Calmodulin
  - Calcineurin
  - Caltractin
- Calpain
  - Âµ-Calpain I, II
  - Grancalcin
  - Sorcin
- Centrin
- Neuronal calcium sensors
  - Frequenin
  - Hippocalcin
  - Neuronal calcium sensor-1
  - Neurocalcin
  - Recoverin
  - S-modulin
  - Vilip-1,2,3
  - Visinin
- Parvalbumin
  - Parvalbumin
  - Oncomodulin
- Spectrin
- S100 family
  - Calbindin D9k
  - S100A
  - S100L/S100A2
  - S100E/S100A3
  - Placental calcium-binding protein /S100A4
  - S100D/S100A5
  - Calcyclin/S100A6
  - S100A7
  - MRP-8/S100A8
  - MRP-14/S100 A9
  - p11/S100A10
  - Calgranulin C/S100A12
  - S100Î²
  - S100C
  - S100P
  - Profilaggrin
  - Trichohyalin
- Sorcin
- SPARC (osteonectin)
- Troponin
  - Troponin C
  - Tn I
  - Tn T

II. Annexins (Iâ€“XI)

III. Other

Calmegin
Calnexin
Calreticulin
Calsequestrin
Crystallins

Endogenous Trace Metals

Trace metals exert a number of biologic effects throughout the body that are caused, among other mechanisms, by the metals' ability to serve as cofactors to a large number of enzymes. They also interact directly with cell membrane and intracellular receptors, and regulate oxidation/reduction processes within

cells. Several of these properties play a role in the metals' effects on cellular excitability in the CNS. It is therefore not surprising that metals such as iron, manganese, and selenium, acting in a neuromodulatory role, may influence the development or termination of seizure activity.[85,189,208]

The endogenous trace metal zinc has been most frequently associated with seizures. This is primarily due to the observation that zinc is localized in, and can be released from, many glutamatergic neurons throughout the limbic system. Granule cells in the dentate gyrus, and especially their axon terminals, contain a particularly high concentration of zinc. Within the cell, zinc is bound to specific proteins, such as metallothioneins, or exists in presynaptic vesicles and can be released into the extracellular compartment. Extracellularly, zinc can have quite diverse effects, making it difficult to predict its net function. Thus, zinc can depress (e.g., by reducing NMDA receptor function) or enhance (e.g., by interfering with GABA$_A$ receptor-mediated inhibition) excitability.[76]

The inhibition of GABA$_A$ receptor function by zinc is particularly interesting in the context of epilepsy. The metal normally has little effect on GABA$_A$ receptors on granule cells, because the receptor subunits are not assembled in a combination that optimizes zinc sensitivity. However, these subunits change their expression patterns under epileptic conditions, resulting in reductions in the Î±1- and Î³2-subunits and an increase in the Î´-subunit; these changes greatly enhance zinc sensitivity of the receptor.[3,42,174]

Zinc may also show increased effects on GABA$_A$ receptors in the epileptic brain, because zinc-rich mossy fibers develop collaterals that innervate the proximal dendritic region of granule cells (mossy fiber sprouting). These new collaterals constitute an increased source of zinc, which may be of functional significance, because enhanced zinc release from sprouted mossy fibers may further decrease the inhibition of granule cells. In addition, the release of zinc may be greater under conditions of chronic epilepsy, given the predisposition for burst discharges.[30] Such a dampening of the normal inhibitory â€œgateâ€ function of the dentate gyrus might facilitate seizure activity in limbic circuits. Thus, zinc appears to play a critical role in the mechanisms that link changes in GABA$_A$ receptor subunits and mossy fiber reorganization in the epileptic brain to the epileptic state.

Cytoskeletal Proteins

Cytoskeletal elements are a fundamental component of nerve cells, and recent studies suggest relevance to epilepsy, particularly for the filamentous proteins. This group includes actin filaments, intermediate filaments (e.g., neurofilaments), and microtubules (such as Î±- and Î²- tubulin). In addition to this group, proteins such as clathrin and stathmin are important to consider, because they are critical to endocytosis.

Recent evidence suggests that several of these proteins may also be involved in epileptogenesis, in the response of the nervous system to seizures and, in the developing brain, in the resistance to seizure-induced neuronal damage.[126] Notably, some of the seizure-related changes in the expression pattern of cytoskeletal proteins, which may in part be due to cell swelling, have been revealed using gene profiling techniques.[127]

The involvement of cytoskeletal elements in epilepsy is probably related to their role in the intracellular movement of proteins into different cellular compartments, which, in turn, can modify neuronal excitability. Thus, cytoskeletal proteins are involved in the trafficking of neurotransmitter receptors. Proteins such as clathrin may alter excitability by changing the concentration of molecules available to the extracellular milieu. In addition, the cytoskeleton may be causally involved

in the dendritic deformation that has been described in animals with chronic seizures and in humans with TLE. For example, electron microscopic analysis indicates that cytoskeletal changes may be responsible for the unique beading of dendrites in epileptic tissue,[222] although other hypotheses that are independent of the cytoskeleton have also been suggested.[207]

Growth Factors

The term â€œgrowth factorâ€ is defined loosely here to refer to several protein families, expressed either in neurons or glia, that were originally identified for their roles in CNS growth and development (Table 3). Subsequent studies revealed that these same proteins influence neurons after maturity, and, interestingly, have striking effects in the context of epilepsy.

Growth factors influence excitability in the adult CNS both directly and indirectly.[180] Many of the effects are due to modulation by transcription factors, which in turn affect the expression of proteins that can alter excitability. Their importance to epilepsy is supported by studies showing that the expression of growth factors and their receptors is dramatically altered by seizures, both in animal models of epilepsy and in TLE.[180] Similar to the neuropeptide changes observed after seizures (see previous section), these effects may be compensatory in nature and may recapitulate developmental programsâ€"a plausible interpretation in light of the prominent role of growth factors in brain development.

Experimental interference with growth factor function can result in the withering or retraction of axonal pathways, suggesting that these proteins regulate axonal growth and maintain neuronal integrity.[206] Furthermore, growth factors influence the morphology and density of dendritic spines,[67,111] and also cause additional structural alterations of synapses.[228] All these effects may be critical in epilepsy, in which dramatic spine changes occur as a consequence of seizures,[213,235] and the axons of injured neurons degenerate. In addition, growth factors may contribute to circuit rearrangements after seizures, including axonal sprouting, formation of new synapses, and other structural alterations.[100]

Several families of growth factors can be categorized in many ways. In Table 3, the classic growth factor families are organized according to their receptors, which are primarily receptor tyrosine kinases or serine threonine kinases. These include the tyrosine kinase receptor superfamily (ephrins, epidermal growth factor [EGF] family, fibroblast growth factor [FGF] family, insulin growth factor [IGF] family, neurotrophins, and vascular endothelial growth factor [VEGF] family), and the serine threonine kinase receptor superfamily (including transforming growth factor [TGF]-Î² family). In addition, Table 3 includes two other categories critical to normal growth and development. These include axon guidance molecules (netrins, the reticulon family, semaphorins, and slit proteins) and morphogens (bone-morphogenic proteins, hedgehog family, wnt family). Inflammatory cytokines (interleukins [IL] and tumor necrosis factor [TNF] family) are discussed in Chapter 25. Chemotactic cytokines (chemokines) are also relevant, particularly in relation to the mechanisms that control axon guidance, but to date limited evidence points to their role in seizures, excitability, and epilepsy.

Neurotrophins

The neurotrophins are a family of growth factors that show robust expression in the adult CNS and are known to influence a wide variety of normal functions. They also provide some of the best examples of growth factors that have been shown to influence seizures. The dentate gyrus is useful as an example of a site in which neurotrophins are likely to affect seizure activity, because of the evidence that this region shows robust neurotrophin expression and action. Most of these studies are focused on brain-derived neurotrophic factor (BDNF) or NT-3, and much less is known about the other neurotrophins, (e.g., the prototypic member of the neurotrophin family, NGF, and the fourth major member, NT-4/5).

Figure 3 depicts the normal expression pattern of BDNF in the rodent dentate gyrus. The same pattern appears to be present in humans.[148] Thus, BDNF is mainly localized in granule cells, although a small proportion may also be contained in nongranule cells and in afferents from the entorhinal cortex (i.e., the perforant path).[41,231,242] Notably, BDNF enhances the expression of neuropeptides such as neuropeptide Y in GABAergic neurons, indicating potentially significant interactions between hippocampal neuromodulators.[134] Simply viewed, neuropeptide Y induction may limit excessive excitation by BDNF and thus prevent the development of seizures.

BDNF not only supports dendritic structure and plasticity in the dentate gyrus, but also stimulates the proliferation of cells in the subgranular zone, a major source of newly-generated dentate granule cells in the adult brain.[175] Moreover, BDNF has robust effects on the physiology of granule cells and their targets, influencing glutamatergic and GABAergic circuits.[24,116,151] These effects often involve changes in transmitter release and depend on protein synthesis.[24] In addition, BDNF depolarizes granule cells by an effect on the Nav 1.9 sodium channel.[116] Finally, BDNF may also signal via glial cells.[168]

Table 3 Growth Factors and Cytokines

	References			
Receptor tyrosine kinases	**Ligand**	**Receptor**	**Animal**	**Human**
Ephrins			239	
Ephrin A (1-8)	Ephrin A (1-8)	EphA (1-5)		
Ephrin B (1-6)	Ephrin B (1-6)	EphB (1-3)		
Epidermal growth factor family			152	
Epidermal growth factor	EGF	erbB1(HER 1)		71
Heparin-binding epidermal growth factor	HB-EGF	erbB2 (Neu, HER2)	64	51
Transforming growth factor Î±	TGFÎ±	erbB3(HER31)		
Neuregulins		erbB4(HER 4)	64	51
Neu differentiation factor	Heregulin			

ACh receptor inducting activity	ARIA			
Glial growth factor (GGF)	Neuregulin 1			
Neuregulin 2-4				
Vaccinia growth factor	VGF			
Amphiregulin	AR			
Fibroblast growth factor family (FGF) 1â€“23			79, 245	
Fibroblast growth factor 1 (acidic)	aFGF, FGF1	FGFRI (flg)		
Fibroblast growth factor 2 (basic)	bFGF, FGF2	FGFRII, III, IV		
Insulin growth factor family			104, 107	
Insulin	Ins	IR		
Insulin-like growth factor 1	IGF-1	IGFR II(M6P)		
Insulin-like growth factor 2	IGF-2	IGFR II(M6P)		
Neurotrophin family			82	
Nerve growth factor	NGF	TrkA		
VGF (nonacronymic)			172	
Brain-derived neurotrophic factor	BDNF	TrkB	21, 176	21, 176

Neurotrophin-3	NT-3	TrkC		
Neurotrophin-4/5	NT-4/5	p75		
Vascular endothelial growth factor			46	
Vascular endothelial growth factor	VEGFA	VEGFR1 (flt-1)		
	VEGFB	VEGFR2 (flk-1)		
	VEGFC	VEGFR3 (flt-4)		
	VEGFD	neuropilin 1		
	VEGFE	neuropilin 2		
Placental growth factor	PIGF			
Platelet-derived growth factor	PDGFA,B,C,D, AB	PDGFR-Î± or-Î²	135	
Serine-threonine kinases				
Transforming growth factor superfamily				
Transforming growth factor-Î²	TGF-Î² (1â€“3)	TGF-Î² (I-III)	145	
Glia-derived neurotrophic factor family			113	113
Glia-derived neurotrophic factor	GDNF	c-Ret + GFRa1		
Neurturin		c-Ret + GFRa2		

Artemin		c-Ret + GFRa3		
Persephin				
Bone-morphogenic proteins (BMP) 1â€“20	BMPs	BMPRI(A, B), II		
Growth/differentiation factors (GDF) 1â€“15				
Growth/differentiation factors	GDFs			
Activtins/Inhibins		Act RI, Act RII	217	
Axon guidance molecules				
Netrins				
Netrin 1,2		DCC/frazzled/UNC-40, UNC-5		
Reticulon family				
Reticulon	Rtn			
Nogo (A, B, C)	Nogo Aâ€“C	Nogo receptor (Ngr 1â€“3)	140	10
Semaphorins				
Semaphorin family (1â€“8)	sema 3A,3C,3F	Neuropilins 1,2	15	97
	sema 1,4D,5,7A	Plexins Aâ€“D		
Slits (1â€“3)	Slit (1â€“3)	Robo (1â€“2)		

Morphogens				
Bone-morphogenic proteins				
Hedgehog family				
Desert Hedgehog	Dhh	Patched 1		
Sonic Hedgehog	Shh	Patched 1	11	
Indian Hedgehog	Ihh	Patched 1		
Wnt (Wingless/Int-1) family (1â€“15)	Wnts 1-15	Frizzled 3	130	44
Cytokines				
Interleukins	IL-1, 2, etc.	IL-1R, IL-2R, etc.	99, 224	
gp130/Interleukin-6 family			99	
Ciliary neurotrophic factor	CNTFR	gp130/LIFR + CNTFR Î±		
Leukemia inhibitory factor	LIF	gp130/LIFR + LIFR	143	
Oncostatin-M	OSM	gp130/OSMR + OSMR		
Cardiotropin-1	CT-1	gp130/LIFR + CT-1R		
Interleukin-6	IL-6	gp130 + IL-6R		
Interleukin-11	IL-11	gp130 + IL-11R		
Tumor necrosis factor superfamily				

Tumor necrosis factor Î±, Î²	TNF-Î±, -Î²	TNFR I, II, p55, p75	9, 194	72

The major families of growth factors and cytokines are listed, including axon guidance molecules and other compounds that influence the growth-associated processes that accompany epileptogenesis. References document the influence of growth factors on seizures or epilepsy, and are divided between studies in laboratory animals (Animal) or clinical research (Human). References listed to the right of a category review members of that category. When placed adjacent to a select example, they apply only to studies of that particular growth factor or receptor.

Table 4 Extracellular matrix (ECM) and other structural proteins

- ECM
  - Collagen
  - Fibronectin
  - Laminin
  - Elastin
  - Proteoglycans
    - Chondroitin
    - Heparan
    - Keratan
    - Hyaluronic acid
    - Syndecan
  - Transmembrane glycoproteins
    - Integrins
- Cytoskeleton
  - Actin filaments
    - Microfilaments
  - Intermediate filaments
    - Neurofilaments (NF)
  - Microtubules
    - Î± and Î²-tubulin assemblies
    - Microtubule motors dynein and kinesins
- Cell adhesion molecules
  - Calcium-independent
    - Neural cell adhesion molecules (NCAMs)
    - Highly polysialylated CAM (PSA NCAM)
    - L1
  - Calcium-dependent
    - N-cadherins
    - Integrins

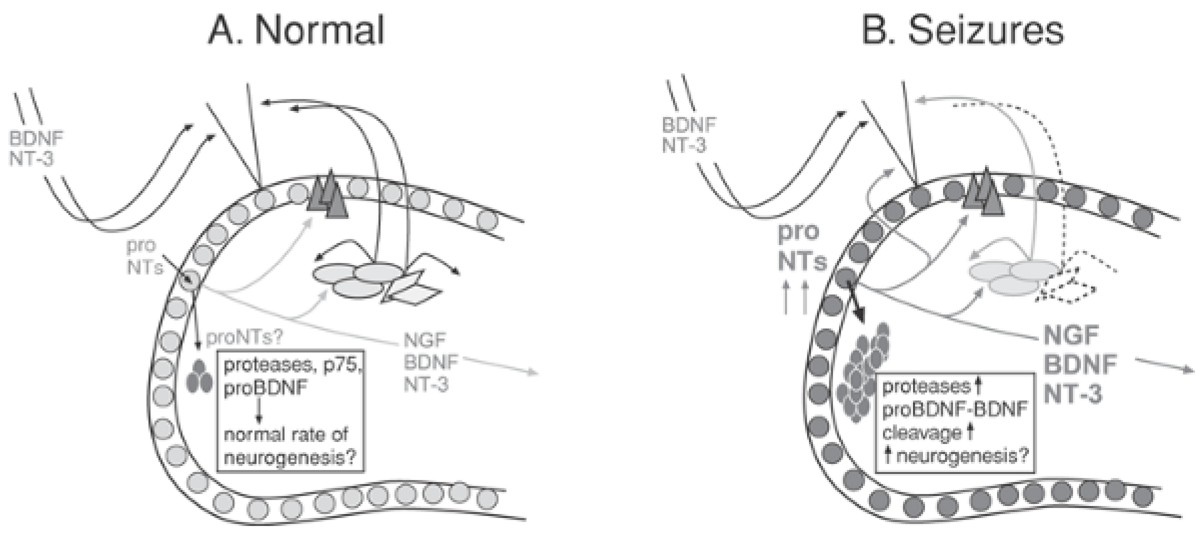

FIGURE 3. Changes in neurotrophins in the dentate gyrus after seizures. **A:** Normal pattern of expression of the neurotrophins NGF, BDNF, and NT-3. The predominant cell type expressing neurotrophins normally is the granule cell. In addition, lower levels of BDNF and NT-3 are present in perforant path axons. Proneurotrophins are present in the soma and are thought to be released in the vicinity of the soma. Proneurotrophins are typically cleaved by extracellular proteases, but can also act directly on p75 receptors to modulate survival. **B:** Changes in neurotrophins associated with chronic seizures are schematically illustrated. NGF and BDNF expression is increased in granule cells, and NT-3 levels decline; BDNF and NT-3 decline in the perforant path when seizure-induced entorhinal cell loss occurs. The altered levels of neurotrophins are likely to have diverse effects on granule cell structure and function. In addition, indirect effects may occur, such as induction of neuropeptide Y by BDNF, either in granule cells or adjacent interneurons (cf. FIGURE 2). Upregulation of proneurotrophins are also likely and, in the case of proBDNF, increased synthesis may influence seizure-induced cell death by increased activation of the p75 neurotrophin receptor, or seizure-induced neurogenesis by the increase in BDNF that would result from proBDNF cleavage. These changes, as well as alterations in receptors for neurotrophins, are likely to have a complex net effect on the excitability of the dentate gyrus. (See color insert.)

After seizures, BDNF levels rapidly increase in granule cells.[81] Judged from studies in both experimental animals and patients with intractable TLE, this effect appears to persist for weeks if the initial seizures are severe (e.g., status epilepticus).[180,182] This, and the fact that BDNF protein is also expressed in sprouted axons,[182] supports the pathophysiological relevance of BDNF in chronic epilepsy.

The neuromodulatory effects of BDNF are probably also influenced by its precursor, proBDNF. proBDNF exerts its own physiological functionâ€"for example, the regulation of cell deathâ€"through the p75 receptor.[94] This function is increased after seizures. These increases, together with elevations in mature BDNF, might contribute to seizure-induced neuronal loss. To add to the complexity, however, seizures also increase the activity of matrix metalloproteases (MMPs),[132] which are able to cleave proBDNF into BDNF.[119] This could generate BDNF at extrasynaptic locations where proBDNF, but not BDNF, is likely to be released. Extrasynaptic release of this newly formed BDNF may then influence epileptic phenomena by targeting novel receptor sites (Fig. 3).

Because of the multiple proexcitatory roles of BDNF in the dentate gyrus in physiology and pathology, it is not surprising that BDNF infusion can cause seizures, that BDNF overexpression increases seizure susceptibility, and that deficits in trkB receptors can block kindling epileptogenesis.[21] Furthermore, BDNF polymorphisms have been linked to febrile seizures,[21,176] and BDNF or trkB are frequently identified in microarray studies of genes linked to epilepsy.[128] However, analogous to the caution suggested for neuropeptide Y as an â€œanticonvulsantâ€ (see the earlier discussion), more information is needed before considering BDNF an endogenous â€œconvulsant.â€ This caveat is supported by studies that demonstrate complex and unexpected effects of trkB transgenic and conditional BDNF knockout mice.[176] In vivo infusions of BDNF, too, yield somewhat conflicting results,[176] possibly due to the fact that chronic BDNF treatment downregulates its own receptor.[240] These and related issues must be resolved before BDNF manipulation can

be viewed as a bona fide approach to ameliorate seizure disorders clinically.

Vascular Endothelial Growth Factor

VEGF was initially discovered as a protein that has robust effects on the vasculature, altering permeability and also enhancing angiogenesis.[32] Although it was not originally anticipated to have an influence in the CNS, recent studies have demonstrated that VEGF expression occurs throughout the brain, and that neurons are influenced by exposure to VEGF.

VEGF exists in more than one isoform (VEGFA-E) and has numerous receptors (VEGFR1, VEGFR2, neuropilins), leading to the potential for a variety of distinct effects. Normally, VEGF is primarily associated with glia and endothelial cells, so that many of its effects are likely to be directed at glia or blood vessels under physiologic conditions. However, in animal models of injury, VEGF expression appears to increase in various areas of the brain.[46] Interestingly, after seizures, VEGF expression also increases in neurons, and some of these changes occur in brain areas that are highly susceptible to seizures, such as the hippocampus. These findings have led to the suggestion that VEGF may have a role in epilepsy.

More evidence of a link between VEGF and epilepsy has come from functional studies. Thus, VEGF alters potassium channel function and synaptic transmission, although it is not clear whether these effects are direct or indirect.[137,241] Perhaps the most relevant of these functional studies as it pertains to epilepsy is that VEGF depresses synaptic transmission and reduces epileptiform activity in vitro.[137] The reduction in activity appears to be greater if epileptiform discharges are examined in slices from an animal with recurrent spontaneous seizures (i.e., epilepsy), as compared to slices from a normal animal that are acutely exposed to a disinhibitory agent. The results suggest potent effects in the epileptic brain relative to normal brain, possibly due to altered expression of VEGF and its receptors after recurrent seizures.

Intercellular Modulators

Components of the extracellular matrix (ECM), a scaffolding system in the interstitial space made up of glycoproteins, proteoglycans, and other molecules such as hyaluronic acid (Table 4), have begun to attract attention as modulators of neuronal function with possible links to epileptogenesis. This is in part based on the fact that the expression of several matrix molecules, such as neural cell adhesion molecule (NCAM),[149] tenascins,[25,150] and chondroitin sulfate proteoglycans such as phosphocan and neurocan, is altered in animal models of TLE. These changes are chronologically and topographically associated with the development of granule cell dispersion and mossy fiber sprouting in epileptic animals.[25,92] Gene microarray studies have confirmed and expanded the correlation between extracellular matrix components and seizures, adding cell adhesion molecules to the list of neuromodulatory proteins.[128] Notably, elevations of glycosaminoglycans and tenascins are also seen in surgical brain tissue obtained from patients with pharmacoresistant TLE. Jointly, these studies therefore raise the possibility that changes in the extracellular matrix may be *causally* involved in the cellular and synaptic reorganization seen in TLE.[7,38,92,96]

Another important aspect of the ECM that is relevant to axonal and cellular reorganization in epilepsy are changes in MMPs after seizures. These enzymes are notable because they normally degrade the ECM and appear to be altered in their expression after seizures.[83] Again the question of whether neuromodulators interact is raised, because the MMPs also cleave proBDNF to BDNF. Thus, degradation of the ECM and elevated BDNF may work in concert to facilitate changes in neural circuits, including mossy fiber sprouting. Finally, the ECM may also modulate excitability through intercellular and transmembrane proteins, like the integrins.

These proteins bind both to the ECM and to neuronal plasma membranes and can therefore activate signaling cascades that regulate neural activity.[163] Taken together, these studies suggest that the ECM, both directly and indirectly, could modulate excitability in the context of epilepsy.

Neuromodulation by Astrocytes

The abnormal appearance of non-neuronal cells in the epileptic brain has long been appreciated.[163] Until relatively recently, however, gliosis was viewed simply as a reaction to seizure-related neuronal injury or degeneration, without major functional consequences for the disease process. With a few exceptions, the conceptual and experimental approach to the primary goal of epilepsy researchâ€"that is, the elucidation of the cellular mechanisms underlying human epilepsiesâ€"was decidedly neurocentric. In functional terms, glial cells (including â€œreactiveâ€ glia) were at best regarded as sinks to buffer the abnormal, proconvulsant rises in extracellular K^+ concentrations that were known to accompany seizure activity.[98,199]

It was not until the late 1970s (first articulated comprehensively in an influential monograph of Brotchi),[27] that glial cells began to be considered as significant pathogenic factors in chronic epilepsy. The contributions of these cells to *epileptogenesis* were recognized even later. Noninvasive imaging methods, modern electrophysiologic approaches in animals and humans, the revolution in molecular biology and genetics, and the recent enthusiastic embrace of glial biology by the neuroscience community, have jointly focused the attention of epilepsy research on the pathophysiological role of glia. It is clear that glial cells participate actively in the development and maintenance of chronic epilepsy, although the involvement differs between the three major types of glial cells (microglia, oligodendrocytes, and astrocytes). Moreover, accumulating evidence suggests that abnormal glial function may also be a determining factor in the very early stages of epileptic disorders.

The role of resident and, in particular, activated microglial cells in epilepsy appears to be closely linked to the cells' function as the resident immune cells of the brain. As a major source of paracrine signals releasing pro- and anticonvulsive cytokines, growth factors and other neuroactive peptides, and proteins, the agile microglia are increasingly thought to influence not only neuronal communication in the normal brain, but also to facilitate the excessive electrical discharges characteristic of epileptic conditions.

Very few studies indicate an involvement of oligodendrocytes, the second major classes of glial cells in the brain, in seizure activity.[146,234] Normal or seizure-induced changes in oligodendrocyte function are therefore not likely to be a major, consistent feature of epileptogenesis or epilepsy. However, this conclusion is still tentative and may have to be revisited in view of recent evidence linking oligodendrocyte function to neurogenesis, a likely factor in the pathophysiology of TLE.[157,177]

Astrocytes are intimately related to neurons in terms of lineage, anatomic arrangements, and function. As indicated by the recently coined term â€œtripartite synapse,â€[5] astrocytes are now in fact considered integral players in neurotransmission. This notion, in turn, prompted a closer look into the function of these glial cells in epilepsy. It is now clear that astrocytes, and astrocyte-derived factors, play a critical role in the modulation of acute and chronic seizure activity.

Astrocyte Changes in Epilepsy

Although the â€œreactive gliosisâ€ seen in the brain of epileptic patients was long suspected to signify disease-related morphological changes in astrocytes, definitive proof for the identity of the abnormal glial cells was unavailable until relatively recently. This changed with the discovery of glial fibrillary acidic protein (GFAP), a 55-kDa member of the intermediate filament protein family, which is the major fibrous protein of astrocytes.[19] Using anti-GFAP antibodies, hypertrophied astrocytes were soon visualized immunohistochemically in excised tissue specimens obtained during epilepsy surgery[103] and in several animal models of chronic epilepsy. GFAP immuno-staining labels pathological astrocytes primarily in limbic brain areas such as the hippocampus and the parahippocampal region, which are also preferentially sensitive to seizure-induced neurodegeneration.[87,165] GFAP-positive astrocytes were therefore originally believed to be a highly selective tool to identify epileptic lesions. It turns out, however, that abnormal, GFAP-immunoreactive astrocytes are also seen in anatomic sites distant from the seizure focus.[33] Further analyses of the effects of the nature, frequency, and duration of the epileptogenic stimulus on GFAP-positive cells, the use of additional structural astrocyte markers such as vimentin and laminin, and the use of various distinct animal models, also revealed a more complex picture of astrocytic involvement in epilepsy.

Astrocytes react rapidly (within 1 hour) to strong convulsive stimuli through upregulation of glial protein synthesis,[203] but change more slowly in response to moderate seizure activity.[117,205] Although the duration of these and other seizure-related changes (see later discussion) has so far not been studied methodically, they are likely to persist in chronically epileptic animals.[84] Surprisingly, prominent brain regionâ€"specific astrocytic hypertrophy can sometimes be detected in the absence of substantive neurodegeneration. This includes kindled animals, in which the glial changes are accompanied by a reorganization of the cytoskeleton and persist for weeks after the last seizure,[108,109] and the EL mouse, in which astrocytes proliferate in the hippocampus.[55] These and a considerable number of other supportive examples indicate that a variety of seizures, ranging from single, intense convulsive insults to repetitive, mild episodes, cause regionally distinct structural astrocytic changes that are not necessarily associated with overt neuronal loss or injury. However, these microscopic data do not consider the molecular events(s) linking seizure activity to the glial reaction. They also do not address the presumed functional significance of astrocytic hypertrophy and/or proliferation, including the possible role of these reactive processes in the development and maintenance of chronic epilepsy.[7,144,166]

Astrocytes as Modulators of Extracellular Glutamate

The fact that astrocytes undergo physical changes in response to seizure activity led many investigators to examine the fate of astrocytic neurochemistry in epilepsy. The most obvious molecule of interest in this regard was glutamate, which had been speculatively associated with the pathophysiology of epilepsy as early as 1954.[91] The realization, two decades later, that glutamate is the major excitatory neurotransmitter in the brain initially suggested that enhanced *neuronal* glutamate release might be critically involved in the precipitation of epileptic discharges.[54] Although neuron-derived glutamate is still believed to play a major role in seizure activity, attention has increasingly shifted to astrocytes as the major determinants and sources of extracellular glutamate levels in both the normal and epileptic brain. Thus, the physiological concentration of glutamate in the extracellular milieu, which is in the low micromolar range, is controlled mainly by two highly efficient astrocytic glutamate transporters (GLT-1 and GLAST). These uptake sites also prevent the accumulation of convulsant, excitotoxic concentrations of the amino acid, as demonstrated in animals with a genetic deletion in either one of these proteins.[169,209,230] These studies, as well as a report showing substantial reductions in GLT-1 and GLAST expression in epilepsy-prone rats prior to seizure onset,[60] are particularly important because they provide evidence that malfunctioning astrocytes can *cause* seizure activity by elevating extracellular glutamate to pathologic levels. Interestingly, GLT-1 is also reduced as a sequela of epilepsy, thus potentially exacerbating the clinical condition.[173]

Selective transporters are not the only determinants of extracellular glutamate linked to astrocyte function. As shown originally by Haydon et al., neuronal stimulation induces a frequency-dependent calcium response in closely apposed astrocytes, which then causes these cells to release glutamate. This astrocyte-derived glutamate, in turn, modulates glutamatergic neuronal transmission.[5] It follows that any breakdown of this finely tuned interplay between neurons and astrocytes may result in enhanced glutamate release and seizure activity.[70] This hypothesis, which again indicates that astrocytes can be *causally* involved in epileptogenesis, has recently been supported by experimental manipulation of intracellular astrocytic calcium (Ca^{2+}).[214]

Within astrocytes, glutamate serves as a substrate of glutamine synthetase, an essential component of the glutamineâ€"glutamate shuttle between astrocytes and neurons.[95] This enzyme can be viewed as a precursor of potentially neurotoxic neuronal glutamate.[8] Alternatively, glutamine synthetase may function as a guardian against the accumulation of convulsive

and neurotoxic concentrations of glutamate in large astrocytic vesicles, which release their content via SNARE-dependent exocytosis to cause excitation in neighboring neurons.[105] It is therefore unclear whether inhibition of glutamine synthetase, which normally causes a *decline* in extracellular glutamate levels in the brain,[23] has pro- or anticonvulsant consequences under epileptic conditions. Measurements of glutamine formation in animal models of epilepsy[59,215] and in the brain of patients with TLE[63,201] have produced equivocal results and have so far failed to clearly define its role in seizures. Similarly inconclusive data have been obtained in nuclear magnetic resonance (NMR) spectroscopic studies in epileptic tissue, which examined the astrocyte-specific incorporation of ^{13}C-acetate into ^{13}C-glutamate and ^{13}C-glutamine.[114,141,147,155]

The external mechanisms controlling astrocytic glutamate disposition are currently only poorly understood, but are of obvious relevance for epilepsy, because unchecked glutamate release is likely to intensify both acute and chronic seizure activity. It is therefore noteworthy that hemichannels and multidrug resistance proteins[68] (i.e., proteins that regulate glutamate exocytosis from astrocytes) are upregulated in astrocytes in chronic epilepsy.[120,133,221] Notably, several subtypes of metabotropic[6,210,220] or ionotropic[192] glutamate receptors are also overexpressed in astrocytes in the epileptic brain, although the functional significance of these receptors has not been clarified so far.

Taken together, these studies leave little doubt that astrocytes, rather than neurons or other brain cells, hold the key to the role of glutamate in epileptic phenomena. Conceptually, glutamate may therefore be assigned the somewhat unorthodox function of an astrocyte-derived or astrocyte-controlled *neuromodulator*. However, because of the large number of functional proteins serving as its intra- and extracellular targets, and due to its multiple roles in cytosolic and mitochondrial energy flux and intermediary metabolism, the participation of astrocytic glutamate in epileptogenesis and chronic epilepsy is highly complex and requires considerable additional scrutiny.

Neuromodulation by Other Astrocytic Factors and Mechanisms

The role of astrocytes in seizure generation and maintenance is not only defined by the complex fate of glutamate itself but also involves several other glial products, which indirectly affect glutamate metabolism and function. This growing list of endogenous factors includes nitric oxide (NO), which is produced by nitric oxide synthase (NOS). At least two isoforms of this enzyme (neural NOS [nNOS] and inducible NOS [iNOS]) are upregulated in reactive astrocytes in response to seizures,[34,102] leading to increased NO formation, which in turn stimulates glutamatergic neurotransmission and may thus affect hyperexcitability.[71] The neuroexcitatory glutamate homolog aspartate, too, is formed in astrocytes, although it is still unclear whether glial release of this amino acid can augment or substitute for the neuronal effects of glutamate under physiological and pathological conditions. Resolution of this issue seems important in view of the fact that extracellular aspartate levels are significantly enhanced in TLE[110,195] and in animal models of epilepsy.[66,142,161] The activity of its degradative enzyme, aspartate aminotransferase, is also increased in actively spiking human epileptic cortex[110]; however, the de novo synthesis of ^{13}C-aspartate from ^{13}C-acetate is unchanged in chronically epileptic rats.[141] Notably, astrocytes also play a major role in the generation and disposition of other endogenous amino acids such as glycine and D-serine, or dipeptides like N-acetylaspartylglutamate, all of which profoundly influence glutamate function in the normal brain. These agents, sometimes cumulatively termed â€œgliotransmitters,â€ are therefore increasingly studied for their possible role in the pathophysiology of various brain diseases, including epilepsy.[43,101]

Another astrocytic product with links to glutamatergic neurotransmission is kynurenic acid (KYNA), a neuroinhibitory metabolite of the kynurenine pathway of tryptophan degradation. KYNA's preferential blockade of *N*-methyl-D-aspartic acid (NMDA) receptor function[158] probably accounts for its potent anticonvulsant and anti-excitotoxic properties.[74] Interestingly, the extracellular levels of endogenous KYNA are acutely elevated following the administration of convulsive agents.[237] Moreover, KYNA-forming astrocytes are hypertrophic, and KYNA synthesis is enhanced in the limbic brain areas of chronically epileptic animals.[56,236] Interpreted teleologically, enhanced KYNA production and release can therefore be viewed as an endogenous attempt to mobilize astrocytes for anti-epileptogenic, anticonvulsant, and neuroprotective purposes. Related to this role of KYNA, attention must also be paid to the lysine metabolite Î±-aminoadipate, which is present in the mammalian brain in micromolar concentrations and is avidly accumulated by astrocytes.[89,164] Within astrocytes, Î±-aminoadipate inhibits the biosynthesis of KYNA and may thus indirectly facilitate seizure activity.[191,238]

The active participation of astrocytes in seizure activity is not necessarily limited to molecules and mechanisms that affect glutamatergic neurotransmission directly. Thus, astrocytes express a large number of proteins that cause structural changes in the cell, alter extracellular ion concentrations, or control intra- and intercellular signalling through an array of messenger molecules. Seizure-related changes in several of these proteins have been reported in TLE and in both acute and chronic animal models of epilepsy, and may contribute toâ€"or protect againstâ€"pathology. Examples include the embryonic intermediate filament component nestin, which may remodel the glial cytoskeleton in the epileptic brain;[190] S100Î², which may be involved in structural reorganization in association with chronic seizure activity;[17] and the small heat-shock protein 27, which may actively participate in seizure-induced neurodegeneration.[18] Seizures also cause abnormal expression patterns and changes in the biophysical properties of astrocytic K^+ and Na^+ channels,[22,86,202] increase astrocytic communication by upregulating the connexin 43 gap junction protein,[73] and reduce the density of the water channel aquaporin 4, which regulates the clearance of extracellular K^+along the perivascular membrane domain of astrocytes.[62] These changes are accompanied by dysfunctional astrocytic enzymes, receptors, and transporters, which influence seizure activity through altering the metabolic fate and biologic effects of important chemical messengers such as GABA,[121,183,187] adenosine,[69] and prostaglandins.[53] Future research will need to dissect the respective contributions of these diverse impairments to disease manifestation. In addition, we must consider that the pathogenic role of microglia-derived cytokines in epileptogenesis and epilepsy, too, is at least in part dependent on the presence of astrocytes.[125,225]

Astrocyte Dysfunction: Implications for Pathogenesis and Therapy

Despite the large number of studies demonstrating astrocytic abnormalities, most of the information accumulated so far is correlative in nature and does not clarify if astrocyte impairment can in fact *cause*, rather than play an adjuvant role in, the epileptic condition.[26,93] Causality is especially difficult to establish in the chronically epileptic brain, in which astrocytes have already undergone structural and functional changes as a consequence of seizure activity. This distinction between a

primary and secondary role of astrocytes in epileptic disorders is of more than theoretical interest because it has implications for the design of therapeutic strategies. Experimentally, the question can be most unequivocally addressed by selectively manipulating astrocyte function in the normal brain and assessing the effects of the intervention on various seizure parameters. Approaches include direct or indirect interference with astrocytic glutamate function (see the earlier discussion) and the specific elimination of astrocytic proteins such as S100Î²[61] or GFAP.[154]

Other studies have successfully used fluorocitrate, an aconitase inhibitor that selectively incapacitates astrocytes by reversibly blocking tricarboxylic acid cycle activity. These experiments, which are especially instructive in view of the established dysfunction of cellular energy metabolism in epilepsy,[106] showed that transient astrocyte poisoning causes epileptiform discharges and even convulsive seizures[232] and also lowers the seizure threshold to systemically administered chemoconvulsants.[122] Taken together, all these studies provide convincing evidence that astrocyte dysfunction can singularly trigger epileptogenic events in the normal brain.

Each of the many changes in astrocytic biochemistry seen in epileptic animals and humans may play an active role in pathophysiology. As described earlier for some of the most prominent examples elaborated to date, these changes can be simplistically categorized into being either facilitatory or inhibitory of the clinical condition. It follows that it may be possible to develop novel therapeutic agents by targeting astrocytes to specifically interfere with proconvulsive mechanisms or to boost endogenous anticonvulsive principles. Exploitation of this conceptâ€"the pharmacological targeting of glial neuromodulators for the treatment of epilepsyâ€"is still in its infancy,[236] although the use of astrocytes for therapeutic purposes has received considerable attention, for example, in the area of Alzheimer disease and Parkinson disease.[36,184] Notably, this approach is not limited to those glial mechanisms known to be chronically impaired in the disease, but could also be advantageously used to influence physiological signalling processes that normally link astrocytes to neuronal and cerebrovascular function.[112,159] Any of these manipulations of astrocyte function may, in fact, play a role in the clinical efficacy of a number of currently used anticonvulsant drugs and therapies.[31,75,160,243]

Summary and Conclusions

Although often considered relatively minor role players, neuromodulators are increasingly recognized as critical factors in brain physiology. As reviewed here, their ability to modulate neuronal excitability provides a logical link to seizure activity. Indeed, studies in animals have demonstrated that virtually all neuromodulators examined so far are capable of enhancing or reducing seizure susceptibility in the normal brain either directly or indirectly. Alone or in concert, they may therefore play a significant role in seizure initiation under otherwise physiological conditions.

Perhaps more intriguing, neuromodulators appear to be critically involved in processes that are relevant to the development of epilepsy, such as neurogenesis, axonal sprouting, and, more generally, the altered expression of genes that are causally related to epileptogenesis. In turn, neuromodulatorsâ€"and neuromodulationâ€"are themselves altered once the state of chronic epilepsy is established. This and concomitant persistent alterations in receptors for neuropeptides and growth factors, as well as changes in neural circuitry, glia, and extracellular milieu, explain why the same neuromodulator may have quantitatively and qualitatively different effects in the normal and epileptic brain. In addition to being relevant for pathophysiological considerations, these differences also highlight the importance of studying animal models that approximate the epileptic condition in humans.

Despite their complexity, the neuromodulatory mechanisms summarized here provide a vast, varied, and rich resource for new potential therapeutic targets. Indeed, one could argue that a focus on modulators would constitute a superior strategy for anticonvulsant drug development, because it may minimize the side effects associated with conventional targets such as classic neurotransmitters systems (glutamate, GABA) or ion channels (sodium channels, potassium channels). Given the rapid progress in our understanding of the role of neuromodulation in the pathophysiology of epilepsy, this concept could be evaluated clinically in the not too distant future.

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Chapter 28

Gene Expression Underlying Changes in Network Excitability

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Introduction

Remarkable progress in the fields of molecular biology and molecular genetics has added a new dimension to epilepsy research. Just few years ago, studies on the basic mechanisms of epilepsy were limited primarily to anatomic, electrophysiologic, and pharmacologic analyses. However, molecular approaches have provided a more direct and specific means for studying biochemical events in the brain, leading to the recognition that seizures and other forms of injury can induce complex changes in gene expression. These changes are likely to regulate the molecular architecture of neuronal cells and circuits that contribute to longer-term process of epileptogenesis as well as seizure initiation, spread, and cessation. The application of molecular biology to investigate epilepsy can be divided into two broad categories: (a) studies on the genetic or inherited basis of epilepsies (which will not be discussed here) and (b) studies on the role of alterations in expression levels of specific genes or ensembles of genes during epileptogenesis and in epilepsy. This chapter focuses mainly on recent results of global analyses of gene expression in humans and in experimental models of epileptogenesis and epilepsy that provide new understanding of cellular and metabolic processes occurring in the brain affected by the disease.

Basic Principles of Gene Expression

This section provides a brief review of the main steps involved in the conversion of genetic information encoded by DNA into proteins (for a detailed review, see Drlica[44]).

DNA Replication

The genetic code for all cellular proteins is contained in DNA. In its native state, DNA exists as a double helix of deoxyribonucleic acids bound together by phosphate and hydrogen bonds. The hydrogen bonding between DNA strands ensures that the base adenosine (A) will pair with thymidine (T), whereas guanine (G) pairs with cytosine (C). Replication (or duplication) of DNA requires unraveling and separation of the complementary strands of DNA, attachment of DNA-binding proteins, annealing of small primer fragments, and creation of new complementary strands via DNA polymerase enzymes. Because each strand is replicated once, the process is termed *semiconservative*. DNA replication occurs prior to cell division or mitosis, but not in nondividing cells. The combination of highly specialized enzymes and the ability to â€œproofreadâ€ during the synthesis of a new strand of DNA makes this a remarkably reliable process. Even nondividing cells must constantly maintain the integrity of the DNA by using a host of scanning, editing, and repair enzymes. The double-stranded nature of DNA helps to ensure that a mutation in one strand will be rapidly detected and repaired by the cell.

Transcription

During transcription, the enzyme RNA polymerase recognizes and attaches to a specific region at the starting point of a gene. RNA polymerase synthesizes a single-stranded RNA molecule that is complementary to the DNA template, with the exception that ribonucleic acids are substituted for deoxyribonucleic acids and the base uracil (U) is substituted for thymidine in the coding scheme. Transcription continues until the enzyme reaches a termination sequence in the gene. Once the full-length gene is transcribed, segments that do not code for a specific portion of a protein (termed *introns*) are excised, and only the *exons*, which contain specific information for the coding of proteins, remain. In addition, a long tail of adenosine bases is attached to the RNA, thereby identifying it as â€œmessengerâ€ RNA (mRNA). Messenger RNA is then used to translate the genetic code from ribonucleic acids into amino acids and proteins.

The mechanisms controlling the recognition and attachment of RNA polymerase to the starting point of a gene are critical determinants of the pattern of gene expression in a cell. Specific DNA-binding proteins known as *transcription factors* can attach to a regulatory element upstream from the starting point of the gene. Depending on the type of transcription factor, this may either promote or inhibit binding of the RNA polymerase and subsequent transcription. Similarly, other upstream and downstream regions known as *enhancer* or *repressor sites* can also influence transcriptional activity. These transcription factors are critical links in the process of stimulus-induced regulation of gene expression.

Translation

Transcribed mRNA is translated into protein by an interpretive process involving ribosomes, transfer RNA (tRNA), and a variety of other proteins that facilitate the process, such as initiation factors and elongation factors. Protein synthesis begins with the attachment of the mRNA to a ribosome near the â€œstart codon.â€ A *codon* is a triplet of RNA bases that codes for either a specific amino acid or a start or stop to the translation procedure. A tRNA, which carries a particular amino acid, then joins the complex based on the complementary nucleotide sequence of the mRNA (codon) and tRNA (anticodon). The polypeptide chain is created by sequentially bringing pairs of

tRNAs together on the ribosome using the mRNA as a template. A peptidyl transferase reaction forms a new peptide bond between the two amino acids on the tRNAs. This process continues until the end of the mRNA encoding sequence is reached, and the newly formed polypeptide is released in the cell with the aid of specific release factors.

Aspects of Gene Expression Unique to the Central Nervous System

When the techniques of modern molecular biology are applied to the study of epilepsy and neural injury, certain special aspects of the central nervous system (CNS) must be taken into consideration. Although these unique characteristics do not necessarily limit the use of molecular methods in neurobiology, they do provide insight into the complexities of gene regulation that are unique to the signal processing and cellular repair mechanisms of the CNS. This section discusses several of these aspects.

One of the most notable aspects of neurons is that they are postmitotic.[92] Most mature neurons, therefore, are required to maintain their functional integrity for, ideally, the lifetime of the organism. To do this, neurons use many â€œhousekeepingâ€ functions. These functions include replacing and repairing cytoskeletal structures, replenishing membrane and membrane-associated proteins, synthesizing and packaging neurotransmitters, and maintaining integrity of synaptic contacts. If cell injury occurs, genes are activated in an attempt to restore function and to protect from further injury.[17,27,54,109,111,124,145] If cell death occurs, in certain systems new synaptic contacts are made by the surviving presynaptic neurons, presumably in response to the lost functional connectivity of the dead neuron.[110]

In addition to being postmitotic, neurons have a considerable amount of phenotypic diversity and plasticity. *Phenotypic diversity* refers to the unique characteristics of various types of neurons, such as differences in neuron size and shape, classes of neurotransmitters and peptides released, firing conditions and frequencies, and responses to stress and injury.[108,174] *Phenotypic plasticity* refers to the ability of an individual neuron to alter its function. There are numerous levels of control of phenotypic plasticity. Neurons can transiently modify the quantity of neurotransmitters they release in response to both external stimuli and intracellular signaling mechanisms, as has been suggested in certain forms of long-term potentiation.[11,116] Phenotypic plasticity is a dynamic process that is highly dependent on the molecular aspects of cellular physiology. Neurons can modulate the relative amounts and properties of proteins they express through changes in gene expression, editing of mRNA transcripts, and a variety of posttranslational modifications. For example, in response to repeated stimulation, neurons can synthesize new ion channels and membrane receptors that may contribute to long-lasting changes in membrane excitability.[42,57,98,118,126] Similarly, following stimulation or seizures, neurons may modify the response characteristics of specific voltage-dependent ion channels and membrane receptors and alter expression of mRNAs coding for various synapse-modifying proteins.[41,119] Phenotypic plasticity is an ongoing and constant component of neuronal and glial behavior and is an essential ingredient in the ability of the CNS to interact with the environment.

An especially interesting example of phenotypic diversity in neurons comes from the observation that protein synthesis may be highly localized in specific regions of the cell that are distant from the nucleus and regulated independently from translation occurring in the cell body. In most cells, translation of mRNA into protein occurs within the cell body, and newly synthesized proteins are then transported to their appropriate site based on intracellular signaling mechanisms. Most neurons are polarized cells with three fairly distinct compartments: (a) the dendritic processes, (b) a central regulatory soma, and (c) axonal projections ending with presynaptic terminals. Each of these regions has specific functions and interactions with its microenvironment.[33] mRNA can be differentially distributed and translated in dendritic processes.[13,33] Furthermore, ribosomes necessary for carrying out protein translation have also been located in dendrites. This localized distribution of mRNA and ribosomes suggests that dendrites have the capacity to support highly localized and site-specific protein synthesis. This additional level of phenotypic plasticity may prove to be an important element in the synaptic modifications implicated in activity-dependent learning. It is interesting that there is no evidence that a similar phenomenon of localized protein synthesis occurs in axons.[33] This implies that the neuron may rely on intracellular transport mechanisms, such as axoplasmic flow and microtubule systems, to deliver newly synthesized protein to the axon terminal.

Epilepsy and Alterations in Gene Expression

An â€œIntelligent Guessâ€ = Candidate Gene Approach

Changes in gene expression leading to network reorganization and neuronal hyperexcitability are crucial to understanding epilepsy and have been studied with traditional methods. Several candidate genes encoding proteins having a role in brain excitability have been tested. Obviously, much attention has been given to genes coding for proteins directly influencing electrical properties of neurons, such as receptors and channels. The other group of genes has been those coding for proteins involved in remodeling of neuronal networks, such as growth factors and their receptors, synaptic proteins, or other structural proteins. However, such studies have concentrated mostly on seizure-induced alteration and only within hours after seizures. These data were reviewed recently[49,175] and are only briefly mentioned here. Less information is available on alteration in expression of selected genes during late epileptogenesis and in epileptic tissue. In this chapter, we briefly review only data on changes in the expression of genes that are hypothesized to influence brain excitability directly or indirectly. Data from both human tissue and experimental models of epileptogenesis and epilepsy are included, but data on immediate effect of seizures or status epilepticus, reflecting influence of increased neuronal activity on gene expression, are omitted.

Traditional Methods Most Commonly Used for Studies of Gene Expression Levels

The reverse transcription polymerase chain reaction (RT-PCR) is a powerful technique for making many copies of DNA from minute quantities of RNA targets used as starting material. For gene expression analysis, the first step is synthesis of complementary DNA (cDNA) on the basis of mRNA extracted from the studied tissue using the enzyme reverse transcriptase. The PCR is then used to amplify cDNA representing the gene of interest. PCR uses an enzymatic reaction to repeatedly copy the original DNA fragment present in the reaction.

The PCR reaction mixture includes four basic components: (a) the target DNA, (b) oligonucleotide â€œprimers,â€ which are designed to hybridize the sequence of DNA to be amplified, (c) an excess of individual nucleotides (deoxyadenosine 5â€²-triphosphate [dATP], deoxycytidine 5â€²-triphosphate

[dCTP], thymidine 5â€²-triphosphate [dTTP], deoxyguanosine 5â€²-triphosphate [dGTP]), and (d) a DNA polymerase that is extremely stable at a high temperatures. With the use of an automated heating block, this mixture is cycled through a series of temperature changes that are designed to allow the polymerase to repeatedly duplicate the target DNA. Each cycle begins with a high temperature (e.g., 94Â°C) to separate the strands of target DNA (â€œstrand separation phaseâ€). The temperature is then dropped (i.e., 42Â°Câ€“60Â°C, depending on reaction conditions) to allow the oligonucleotides to anneal (â€œprimer annealing phaseâ€). Then the temperature is increased to 72Â°C, which is the optimal temperature for Taq polymerase activity, so that the DNA replication occurs using the oligonucleotides as the primers (â€œprimer extension phaseâ€). Repeated cycling through these steps results in amplification of the DNA in a highly efficient fashion.

A *Northern blot* is a method for detecting the presence of a particular mRNA transcript in a sample. RNA is isolated from tissue or cells using standard extraction procedures and separated by size via gel electrophoresis. The size-separated RNA is transferred to a membrane, and the membrane is then exposed to a radiolabeled probe. If the mRNA of interest is in the sample, the probe will specifically *hybridize* to the mRNA and produce a signal at the predicted size on the autoradiogram.

In situ hybridization provides a means of determining the pattern of mRNA expression at the cellular level. Whereas Northern analysis uses mRNA derived from homogenized tissue, in situ hybridization uses fixed tissue sections so that the cellular anatomy is preserved. Otherwise, the technique uses the same concepts described for Northern analysis. The tissue sections are mounted on slides and prepared in a way that allows the labeled probe to have access to the cellular compartments and to hybridize with the mRNA. Radioactively labeled probe is then detected with X-ray film. To obtain cellular detail, the slides are coated with photographic emulsion, such that the radiolabeled probe will expose the emulsion directly overlying the cells. The slides are then â€œdevelopedâ€ in the same manner as film, and silver grains in the emulsion seen as black specks reflect the presence of this signal, signifying the presence of the specific mRNA transcript. In case of fluorescently labeled probe, the results of hybridization are analyzed using standard fluorescent microscopy techniques.

Immediate-Early Genes

In recent decades, a class of genes termed *immediate-early genes* (IEGs) has been identified that appears to function as a vital link between acute activity-dependent events and long-term changes in gene expression.[15,31,63,88,89,102,150,154,175] By definition, induction of expression of IEG mRNAs is rapid and does not depend on protein synthesis. Protein products of IEGs often serve as transcription factors regulating the transcription of other genes (e.g., c-fos, c-jun, c-myc, jun-B, krox-20, krox-24, fra-1, zif/268, etc.).

Expression of IEGs in neurons has been shown to be induced by a wide range of stimuli, including membrane depolarization due to both physiologic[14,15,55,67,70,83,84,85,86] and nonphysiologic stimulation,[37,41,42,82,88,105,113,127,133,147,152,161] mechanical trauma,[43] and ischemia.[140] Studies using seizures induced by kindling, electroconvulsive seizures, electrolytic lesions, and chemoconvulsants have also shown that IEGs are markedly induced in specific CNS regions such as the hippocampus and cerebral cortex. Much effort has been invested in understanding molecular pathways leading to induction of IEGs expression following seizures, and the results of these studies are reviewed in detail elsewhere.[139,175]

For the purposes of this review, an important question is, what are the target genes for transcription factors (IEGs and other) participating in the development of epilepsy? Several target genes that can influence neuronal excitability and their relation to transcription factors governing their expression have been described. For example, expression of the metabotropic Î³-aminobutyric acid receptor GABA$_B$R1a and GABA$_B$R1b isoforms in hippocampal neurons is mediated by the cAMP response elementâ€“binding protein (CREB), which binds to unique cAMP response elements in the alternative promoter regions. CREB is then critical for transcriptional mechanisms that control GABA$_B$R1 subunit levels in vivo.[153] In addition, the activating transcription factor-4 (ATF4) differentially regulates GABA$_B$R1a and GABA$_B$R1b promoter activity.[153]

The DREAM transcription factor that is expressed widely in the nervous system can be induced by seizures.[29,123] Its target genes include genes related to neuronal plasticity such as c-fos and preprodynorphin.[28,29]

The AP-1 transcription factor (which is composed of proteins belonging to the Fos and Jun families) has been shown to regulate expression of nerve growth factor (NGF) after hilus lesionâ€“induced seizures[48] and proenkephalin and prodynorphin after kainic acidâ€“induced seizures.[96,143]

There are also IEGs upregulated during epileptogenesis that lack transcription factor functions and can have lasting effect on neuronal excitability. One of these proteins is homer-1, which codes for a scaffold protein anchoring metabotropic glutamate receptors to the cytoskeleton and regulates pyramidal neuron excitability.[24,141,148]

Neurotransmitter Receptors and Ion Channels

Alterations in the expression of mRNAs encoding neurotransmitter receptors and ion channels are likely candidates for affecting network excitability. Table 1 gives a summary of such changes in experimental and human epilepsy.

In the mature nervous system, GABA$_A$ receptors function as ligand-gated chloride channels that confer fast inhibitory synaptic transmission. Several studies have demonstrated abnormal GABA$_A$ receptor function in epileptic tissue.[22,64,80] Because receptor properties depend on subunit composition,[113,169] altered expression of GABA$_A$-receptor subunits can explain functional abnormalities. In fact, changes in mRNA expression for selected GABA$_A$-receptor subunits have been reported in epilepsy models induced by kainic acid[162] and pilocarpine[23,146] and electrically induced status epilepticus (SE),[103,134] as well as following hippocampal kindling.[134]

Metabotropic GABA$_B$-receptor expression has been studied in epileptic animals. Changes in the expression of mRNA encoding GABA$_B$

receptors occur in the hippocampus of patients with temporal lobe epilepsy (TLE)[60] as well as in kainic acidâ€“induced epilepsy,[59] hippocampal kindling,[134] and epilepsy following electrically-induced SE.[134]

Glutamate, the major excitatory neurotransmitter in the brain, acts on ionotropic and metabotropic receptors. Sixteen genes encoding for ionotropic receptors that belong to three functional families (Î±-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid [AMPA], kainate, and *N*-methyl-D-aspartic acid [NMDA] receptors) have been identified.[38] Alterations in the expression of AMPA receptor subunits have been demonstrated in human epilepsy[61,121] as well as in electrically-[90,173] and pentylenetetrazole-induced kindling.[46] Changes in kainate receptor subunits occur in human epileptic tissue[68] and the kainate model of epilepsy[163] as well as in amygdala and hippocampal kindling.[75,91] Changes in the expression of NMDA subunits were observed in patients with TLE,[7,121,122,130] in rats kindled with amygdala[94] or hippocampal stimulation,[100,101] and following intra-amygdala injection of kainic acid.[144]

Table 1 Summary of studies using conventional methods to demonstrate alterations in the expression of genes encoding neurotransmitter receptors, transporters, and ion channels

Authors	Model/disorder	Structure	Gene
Ionotropic GABA receptors			
Rice et al. (1996)[146]	Pilocarpine-induced SE	CA1â€“CA3	â†“Î±2, Î±5 at 1â€“2 mo
Tsunashima et al. (1997)[162]	Kainic acidâ€“induced SE	Hippocampus	â†“Î±2, Î±3, Î±5, Î²1, Î²3, Î³2, Î´; â†‘ Î±1, Î±4, Î²2 at 6â€“24 hr â†“Î±5, Î´; â†‘Î±1, Î±3, Î²1, Î²2 at 7â€“30 d
Brooks-Kayal et al (1998)[26]	Pilocaprine-induced SE	Dentate gyrus	â†“Î±1, Î²1; â†‘ Î±4, Î²3 chronically
Lauren et al. (2003)[103]	Amygdala stimulation model of TLE	CA3 CA1	â†“Î±2; â†‘Î²3 in epileptic rats â†“Î±4; â†‘Î²3 in epileptic rats
Nishimura et al. (2005)[134]	Hippocampal kindling Electrically induced SE	Dentate gyrus CA3 Dentate gyrus	â†“Î´; â†‘Î±4, Î²1â€“3, Î³2 at 7â€“30 d â†“Î±2 and Î´1â€“3 â†“Î±5 at 24 hr â†“Î´, Î±5; â†‘Î±4, Î²1â€“3, Î³2 at 7â€“30 d
Metabotropic GABA receptors			
Furtinger et al. (2003)[59]	Kainic acidâ€“induced SE	Hippocampus	â†“ GABA_{B}-1, GABA_{B}-2 acutely
Furtinger et al. (2003)[60]	Human TLE	Dentate gyrus	â†‘ GABA_{B}-1 GABA_{B}-2
Nishimura et al. (2005)[134]	Hippocampal kinding and electrically induced SE	Dentate gyrus	â†‘ GABA_{B}-2 acutely and chronically
Ionotropic glutamate receptors			

Wong et al. (1993)[173]	Seizures		â†“â†‘GluR1
Garcia-Ladona et al. (1994)[61]	Human TLE	Hippocampus	â†‘ GluR1
Kamphuis et al. (1994)[90]	Kindling	Hippocampus	â†‘ GluR1 flip up to 4 wk
Kamphuis et al. (1995)[91]	Hippocampal kindling	Dentate gyrus	â†“ GluR7 at 28 d
Bayer et al. (1995)[7]	Human TLE	Dentate gyrus	â†‘ NR2
Kraus et al. (1994, 1996)[100,101]	Hippocampal kindling	Hippocampus	â†“ NR1 splice variant at 28 d
Grigorenko et al. (1997)[68]	Human TLE	Hippocampus	â†‘ GluR6
Mathern et al. (1997)[121]	Human TLE	Dentate gyrus	â†‘ NR2
Rafiki et al. (1998)[144]	Intra-amygdalar kainic injection	Hippocampus	â†‘ NR1-2a, NR-2b, NR1-3a, NR1-3b, NR1-3b at 21 dâ€“4 mo
Mathern et al. (1997)[121]	Human TLE	Hippocampus	â†‘ GluR1
Mathern et al. (1999)[122]	Human TLE	Dentate gyrus CA2/3	â†‘ NR2A, NR2B â†‘ NR2B, NR1; â†“ NR2A
Kikuchi et al. (2000)[93]	Amygdala kindling	Frontal and temporal cortex Piriform cortex	â†‘ NR1 at 4 wk â†“ NR1 at 4 wk
Ekonomou et al. (2001)[46]	Pentylenetetrazole-induced kindling	CA1 and dentate gyrus cortex	â†“ GluR2, GluR3 at 1 wk â†‘ GluR2 at 1 mo
Neder et al. (2002)[130]	Human TLE	Sclerotic hippocampus Nonsclerotic hippocampus	â†“ NR1 â†‘ NR1
Hikiji et al. (1993)[75]	Amygdala kindling	CA3	â†‘ KA1 at 28 d
Ullal et al. (2005)[163]	Kainic acidâ€“induced SE	Hippocampus	â†“ GluR7 at 3 mo; â†‘ GluR5 at 9 mo
Metabotropic glutamate receptors			

Akbar et al (1996)[1]	Amygdala kindling	Hippocampus	â†“ mGluR5; â†‘ mGluR1 at 24 hr
Blumcke et al. (2000)[19]	Kindling Kainic acidâ€“induced SE	Hippocampus	â†‘ mGluR1
Glutamate transporters			
Akbar et al. (1998)[2]	Genetically epilepsy-prone rats	Cortex, striatum, and hippocampi	â†“ GLT-1
Ingram et al. (2000)[78]	GAERS rats	Thalamus Cortex	â†‘ GLT-1 â†‘ GLAST
Doi et al. (2000)[40]	Fe(3+)-induced epileptogenesis		â†‘ EAAC-1 up to 30 d â†“ GLAST in epileptic animals
Ingram et al. (2001)[79]	EL mice	CA3, parietal cortex	â†“ GLT-1
Crino et al. (2002)[35]	Pilocarpine-induced SE	Dentate gyrus	â†‘ EAAC1 in epileptic animals
Proper et al. (2002)[142]	Human TLE	Hippocampus	â†‘ GLT-1, EAAC1
Voltage-gated sodium channels			
Aronica et al. (2001)[4]	Hippocampal stimulation	Hippocampus	â†‘ NaCh II and III up to 3 mo
Whitaker et al. (2001)[172]	Human TLE	CA3 CA4	â†“ NaCh II â†‘ NaCh III
Ellerkmann et al. (2003)[47]	Pilocarpine-induced SE	Dentate gyrus	â†“ Nav 1.2, Nav 1.6 up to 30 d
Klein et al. (2004)[95]	WAG/Rij absence epileptic rats	Cortex	â†‘ Nav 1.1 and Nav 1.6
Calcium channels			
Hendriksen et al. (1997)[72]	Hippocampal kindling	Hippocampus CA3	â†‘ VDCC-Î±1A, -Î±1D, -Î±1E; â†“ -Î±1E during initial kindling â†‘ VDCC-Î±1B in fully kindled animals
Vigues et al. (1999)[168]	Kainic acidâ€“induced SE	Hippocampus	â†‘ Q-type Î±1A up to 7 d

Talley et al. (2000)[158]	GAERS rats	Thalamus	â†‘ T-type Î±1H, Î±1G
Blalock et al. (2001)[18]	Kindling	CA1	â†“ L-type Î± 1D
	Hyperpolarization-activated cyclic nucleotideâ€“gated cation channels (HCNs)		
Brewster et al. (2002)[25]	Rat febrile seizures	CA1 CA3	â†“ HCN1; â†‘ HCN2 at 1 wk â†‘ HCN2 at 1 wk
Bender et al. (2003)[12]	Human TLE	Dentate gyrus	â†‘ HCN1
	Pilocarpine-induced SE		

CA1, CA1 subfield of the hippocampus proper; CA3, CA3 subfield of the hippocampus proper; CA4, CA4 subfield of the hippocampus proper; EAAC, excitatory amino acid carrier; EAAT, excitatory amino acid transporter; GABAR, Î³-aminobutyric acid receptor; GAERS, genetic absence epilepsy rats from Strasbourg; GLAST, glutamate/aspartate transporter; GluR, glutamate receptor; GLT, glutamate transporter; HCN, hyperpolarization-activated cyclic nucleotideâ€“gated cation channel; KA1, kainic acid receptor subunit 1; mGluR, metabotropic glutamate receptor; NR, *N*-methyl-D-aspartate receptor subunit; SE, status epilepticus; TLE, temporal lobe epilepsy; VDCC, voltage-dependent calcium channel.

Table 2 Summary of global analyses of gene expression

Authors	Organism	Model/disorder	Tissue	Platform	Number of regulated genes	Time points
Sandberg et al. (2000)[149]	Mouse	Pentylenetetrazole-induced seizures	Cortex, cerebellum, midbrain, hippocampus	Affymetrix	>50	1 hr
French et al. (2001)[56]	Mouse	ECS-induced seizures	CA1	Genome Systems	14	1 hr
Newton et al. (2003)[132]	Rat	ECS-induced seizures	Hippocampus, choroid plexus	In-house microarray	Up to 86 (at 6 hr)	2 and 6 hr
Nedivi et al. (1993)[131]	Rat	KA-induced SE	Dentate gyrus	Differential cloning	52	6 hr
Hevroni et al. (1998)[74]	Rat	KA-induced SE	Dentate gyrus	Differential cloning	362	6 hr

Tang et al. (2002)[159]	Rat	KA-induced SE	Striatum, cortex	Affymetrix	187	1 d
Hunsberger et al. (2005)[77]	Rat	KA-induced SE	Hippocampus	In-house microarray		1 d
Lukasiuk et al. (2003)[115]	Rat	Amygdala stimulation model of TLE	Hippocampus, temporal lobe	ResearchGenetics	282	1 d, 4 d, 14 d
Hendriksen et al. (2001)[72]	Rat	Angular bundle stimulationâ€“induced SE	Hippocampus	SAGE	79	8 d
Elliot et al. (2003)[50]	Rat	Pilocarpine-induced TLE	Dentate gyrus	Affymetrix	129	14 d
Becker et al (2003)[9]	Rat, human	Pilocarpine-induced SE Human TLE	Dentate gyrus, CA1	Affymetrix	50â€“700, depending on the experimental group	3 d, 14 d, chronically epileptic
Liang et al. (2001)[106]	Mouse	Electrical kindling	Hippocampus	Differential display	26	0.5 h, 1 d, 1 wk, and 1 mo
Potschka et al. (2002)[141]	Rat	Amygdala kindling	Hippocampus	MPSS	264	2 hr
Gu et al. (2004)[69]	Rat	Amygdala kindling	Temporal lobe	Affymetrix	>200	24 hr
Arai et al. (2003)[3]	Rat	Ihara rat	Hippocampus	SAGE	21	2 mo old
Becker et al. (2002)[8]	Human	Pharmacoresistant TLE	Hippocampus	Atlas (Clontech)	21	Chronic epilepsy
Bo et al. (2002)[20]	Rat	Epilepsy-prone P77MC rat	Cortex	Atlas (Clontech)	15	Chronic epilepsy
Kim et al. (2003)[94]	Human	Intractable epilepsy	Cortical dysplasia		4	Chronic epilepsy
Crino et al. (2001)[34]	Human	Intractable epilepsy	Cortical dysplasia	In-house microarray	4	Chronic epilepsy

CA1, CA1 subfield of the hippocampus proper; ECS, electroconvulsive seizures; KA, kainic acid; MPSS, massively parallel signature sequencing; SAGE, serial analysis of gene expression; SE, status epilepticus; TLE, temporal lobe epilepsy.

There is little information about the long-term changes in mRNA expression of metabotropic glutamate receptors in

epilepsy. Kindling induced a transient decrease in metabotropic glutamate receptor mGluR5 and an increase in mGluR1.[1] Increase in mGluR1 was also observed following intraperitoneal kainate injections.[19]

Sodium channels are of particular importance for epilepsy because many epilepsies are associated with mutation in these channels, and several antiepileptic drugs (AEDs) have their site of action on sodium channels.[97] Data on the mRNA expression of sodium channels in epileptogenesis and epilepsy are sparse. Changes in mRNA levels for sodium channels were found in WAG/Rij absence epileptic rats,[95] after induction of SE with pilocarpine[47] or electrical stimulation of the hippocampus,[4] and in the human epileptic hippocampus.[172]

Various types of calcium channels contribute to increased excitability in epilepsy.[53,81,136,155] Accordingly, protein levels of subunits have been demonstrated to be altered in both experimental and human epilepsy.[39,164] The little that is known about the expression of mRNA indicates changes in Q, R, and L-type voltage-sensitive Ca^{2+} channels in kindling[18,72] and in Q-type channels in the kainic acid model.[168] It has been suggested that the epileptic phenotype in adult genetic absence epilepsy rats from Strasbourg (GAERS) may relate to elevation in the levels of mRNA encoding T-type calcium channels.[158]

Hyperpolarization-activated cyclic nucleotide-gated cation channels (HCNs) mediate the hyperpolarization-activated (I_H) currents in the brain.[135] Long-lasting changes in function of HCNs have been implicated in epileptogenesis.[25,30] It has been suggested that the normal or modified HCN channels might be involved in epileptogenic or protective mechanisms in the epileptic hippocampus.[171] Increase in HCN1 expression was observed in hippocampi of patients with TLE and in the pilocarpine model of chronic TLE in rats.[12] Alterations in HCN mRNA expression was also found in the rat model of febrile seizures.[25]

Other Genes Involved in Regulation of Neuronal Excitability

Apart from ion channels and receptors, there are also other known mechanisms that can influence neuronal excitability, including the effects of transporters, peptide neurotransmitters, growth factors, and other neuromodulators.[5,65,99,160,166] Some of these have been studied in epilepsy, but data on long-term regulation of expression of genes coding for members of these pathways are sparse.

Extracellular glutamate levels are controlled by glutamate transporters that remove glutamate from synaptic cleft. Upregulation of glial glutamate transporter GLT-1 and neuronal excitatory amino acid transporter EAAC1 has been reported in patients with TLE.[142] As summarized in Table 1, altered expression of mRNA encoding glutamate transporters also has been reported in several models of experimental epilepsy, including genetically epileptic-prone rat,[2] EL mice,[79] GAERS rats,[78] Fe^{3+}-induced epilepsy,[40] and pilocarpine-induced epilepsy.[35]

Neuropeptide Y (NPY) has a significant role in regulating seizure activity. Its presynaptic Y2 receptors are capable of suppressing seizure activity by inhibiting glutamate release from mossy fibers.[167] On the other hand, Y1 receptor antagonists have anticonvulsive potential.[62] Marked increases of NPY mRNA in hippocampal granule cells and interneurons were found in Ihara's epileptic rats and spontaneously epileptic rats.[157] In epileptic human hippocampus, NPY mRNA was increased in hilar interneurons of sclerotic and nonsclerotic specimens. Thus, together with upregulation of Y2 receptors, downregulation of Y1 receptors in the hippocampus of patients with Ammon's horn sclerosis may be an endogenous anticonvulsant mechanism.[58]

Neurotrophins can influence neuronal network excitability, and their expression following seizures has been extensively studied. Little information about their mRNA expression is available in other epilepsy-related situations. Increased expression of brain-derived growth factor (BDNF) mRNA has been observed in the neocortex of animals in which spontaneous seizures were induced following injection of tetanus toxin. At later times there was an upregulation of BDNF mRNA at the injection site and downregulation in a surrounding cortical zone. This could contribute to plastic changes in epileptic neuronal circuits and may be associated with the inhibitory surround that hampers seizure spread but facilitates the persistence of a chronic epileptic focus.[107] Epileptic patients with hippocampal sclerosis show increased granule cell mRNA levels for BDNF, nerve growth factor (NGF), and neurotrophin 3 (NT-3).[120,128]

Global Analysis of Gene Expression

Studies of gene expression in epilepsy using traditional molecular biology methods have focused on a limited number of preselected genes at a time. Recent technological developments allow the analysis of gene expression at the level of nearly the whole transcriptome, which provides an unbiased insight into molecular events that occur in the brain during epileptogenesis and epilepsy. The data derived from these studies can be expected to highlight the most prominent metabolic pathways or other phenomena that underlie reorganization of the epileptogenic circuitry and, eventually, guide our efforts at identifying candidate targets for antiepileptogenic treatments.

As described earlier, numerous studies have demonstrated up- or downregulation of a variety of neuropeptides, transporters, ion channels, and receptors in the epileptic state, as well as a host of immediate early genes and other potential effector genes. These studies demonstrate that seizures trigger transcriptional programs that can be long lasting. Unfortunately, they have not guided us to a satisfactory understanding of the molecular events underlying epileptogenesis, partly because the only genes that have been examined so far are those for which prior physiologic or anatomic study suggested their involvement. It is expected that a large array of genes may be involved in epileptogenesis, including genes involved in cell growth control, cell adhesion and migration, intracellular signal transduction, apoptosis, protein turnover, cytoskeleton, and others. Lack of information on the molecular basis of epileptogenesis directly limits the development of treatments that might prevent epilepsy from developing after, for example, traumatic brain injury.

Experiments in which global analysis of gene expression was used to study epileptogenesis and epilepsy have, to a large extent, confirmed data previously gathered with conventional methods.[34,114,116] However, large-scale studies of gene expression have provided insight into other, often unexpected metabolic pathways that may be of great importance for epileptogenesis and epilepsy. Data described in this chapter are summarized in Table 2.

Methods Used for Global Analysis of Gene Expression

Several methods have been developed for the analysis of the whole transcriptome. Here we focus on those that have been successfully used in epilepsy research.

Differential display is an RT-PCRâ€“based method used to identify differentially expressed genes. First, mRNAs from brain tissue specimen are reverse transcribed, and then they are amplified using nonspecific primers. The array of bands obtained from a series of such amplifications is separated on a sequencing gel and compared with analogous arrays from different samples. Any bands unique to a particular sample are differentially expressed. The bands can be purified from the gel and sequenced.

Serial analysis of gene expression (SAGE) is a method for comprehensive analysis of gene expression patterns.[165] It allows the quantitative and simultaneous analysis of a large number of transcripts without the need for creating a probe for each transcript. The principle of SAGE relies on the production of small cDNA tags on the basis of studied mRNA and their subsequent sequencing, counting, and assignment to corresponding genes using bioinformatic tools. The frequency of a specific tag is related to the abundance of the corresponding mRNA in the cell and allows for a comparison of mRNA expression of both known and novel genes in different samples.

Massively parallel signature sequencing (MPSS) is similar to SAGE and is capable of analyzing gene expression without *a priori* knowledge of the transcript sequence and mRNA abundance. MPSS also relies on the production of short tags. However, due to the combination of in vitro cloning of cDNA molecules on the surface of microbeads with nonâ€“gel-based high-throughput signature sequencing, a single MPSS experiment can generate >10^7 tags (100 times more than that in a SAGE experiment).[26]

DNA microarrays are increasingly popular in studies of gene expression. They enable evaluation of the expression levels of thousands of genes at the same time and thereby provide global insight into transcriptional events taking place in a studied phenomenon. The principle of DNA microarray technology is based on the hybridization of labeled cDNA synthesized on the basis of mRNA derived from the tissue of interest, applied to a microarray consisting of a large number of gene probes placed with high density on a solid surface. The strength of the hybridization signal to the particular gene probe reflects the abundance of the respective mRNA in the sample. There are two main types of microarrays: (a) spotted microarrays and (b) Affymetrix Gene Chips. For spotted microarrays, the probe (oligonucleotides or cDNA) is usually spotted on a glass surface. The sample cDNA for hybridization is typically fluorescently labeled. These microarrays offer the possibility of using cDNA from two different conditions (e.g., control vs. treated) labeled with different fluorochromes for simultaneous hybridization to the same chip. Differences in expression are detected by comparing the signal from the two fluorochromes used for labeling the examined samples. Most commercial and academic microarrays belong to this category. In the case of GeneChips produced by Affymetrix (Affymetrix, Inc., Santa Clara, CA), the oligonucleotide probes are synthesized directly onto the surface. The use of perfect and mismatch probe pairs and several probes for each gene increases the specificity and reproducibility of the quantitative results. Some methodologic issues concerning the use of microarrays in the brain have recently been extensively reviewed.[6,114,151]

The recent development of high-density cDNA or oligonucleotide microarrays has brought a new level of sensitivity and specificity to large-scale monitoring of gene expression. This technology has been most productively used in yeast, for which the sequence of every gene is known and available for analysis on microarrays. Rapid progress has occurred in the

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identification of human and mouse genes; a substantial proportion of all human and mouse genes are already available for study.

Changes in Pattern of Gene Expression in Response to Brief Seizures

One of the first studies using cDNA arrays to evaluate se-izure-induced gene expression was performed by Sandberg and colleagues.[149] The study examined whether neurobehavioral differences in mice from different strains are linked to differences in gene expression. In addition to defining the basal gene expression in different brain areas, it also examined gene expression in response to seizures in two mouse strains that display differences in susceptibility to seizure-induced damage: 129vEv (susceptible) and C57BL/6 (resistant). The seizures were evoked by subcutaneous application of pentylenetetrazole, and animals were sacrificed 1 hour after seizure. Two Affymetrix GeneChips, Mu11KsubA and Mu11KsubB, were used for gene profiling. The two mouse strains differed in their transcriptome response to seizures. Twenty-four genes were differentially expressed between the two mouse strains in all brain areas examined, and >50 genes were differentially expressed in specific brain areas.

French et al.[56] sought to identify the genes involved in plasticity in the hippocampus by using electroshock-evoked seizures as a model. Animals were sacrificed 1 hour after application of current via corneal electrodes. Control animals were exposed to the electrodes without stimulation. Samples from area CA1 of the hippocampus were profiled using the Mouse GEM1 microarray (Genome Systems). Of 9,000 genes that were present on the microarray, only 14 genes were found to have significant changes in expression following seizures. Nine were downregulated and five were upregulated. Subsequent validation of the expression changes with in situ hybridization, however, failed to detect any mRNA expression of six of the candidate genes. Upregulation in area CA1 was confirmed for only one gene (nerve growth factorâ€“induced clone B [NGFI-B]), and the authors were unable to confirm differential expression of any other candidate genes. Three genes were upregulated in the dentate gyrus. These findings suggest that, in contrast to the dentate gyrus, seizures do not appear to be accompanied by large modulation of gene expression in area CA1 of the hippocampus in the model used.

The influence of electroconvulsive seizures (ECS) on the profiles of gene expression has also been extensively studied in relation to effect of ECS on mood. Newton et al.[132] studied the expression of neurotrophic growth factors and related signaling molecules in the rat hippocampus in response to electroconvulsive seizures using a custom microarray containing 645 gene probes. They reported regulation of several genes involved in growth factor signaling and angiogenesis, which could have an important role in the molecular action of ECS.

Changes in Patterns of Gene Expression as an Immediate Consequence of Status Epilepticus

One of the first attempts to describe global changes in gene expression following SE was done by Nedivi and coworkers.[131] They used differential cloning to search for plasticity-related genes. Gene expression was studied in the dentate gyrus 6 hours after SE induced by intraperitoneal injection of kainic acid. Granule cells of the dentate gyrus are resistant to kainic acidâ€“induced neurotoxicity and display plastic changes such as axonal sprouting, growth of basal dendrites, and changes in the number and morphology of dendritic spines. About 5% of the screened genes had a change in level of expression following the seizures (candidate plasticity genes [CPG]). Fifty-two clones derived from genes showing altered expression were partially sequenced. Seventeen of those genes were previously known, with some having a link to neuronal plasticity. Five transcription factors with known role in neuronal plasticity were identified (*c-jun*, zif/268, *c-fos*, *fosB*, and cAMP responsive element modulator [CREM]). The product of another gene, TIMP (tissue inhibitor of metalloproteinase), is a component of the TIMP/matrix metalloproteinase [MMP] system, which influences neuronal plasticity by controlling enzymatic activities of metalloproteinases and regulating local proteolysis of extracellular matrix.[45] An interesting group of genes are involved in the functioning of vesicles (such as clathrin heavy chain, dynorphin, secretogranin) or in encoding the components of synapse (catechol-*O*-methyltransferase [COMT], syndecan).

Further work by Nedivi et al. identified a total of 362 candidate plasticity genes.[74] The sequencing and characterization of unknown CPGs revealed a role in the neuronal plasticity for some of them. For example, CPG15 (also known as neuritin) is an activity-induced molecule that promotes dendritic growth of projection neurons and neurite outgrowth and arborization in culture.[129] Its involvement in experience-induced neuronal plasticity has been shown in well-established models of barrel cortex plasticity and visual cortex plasticity.[71,104] The other gene, CPG2, influences synaptic properties by regulation of endocytosis of glutamate receptors.[32]

Tang et al.[159] used Affymetrix microarrays to study the genomic response in the rat striatum and cortex to a variety of brain-damaging insults including kainate-induced SE. Subcutaneous injection of kainic acid resulted in upregulation of 187 genes and downregulation of 89 genes in the parietal cortex 24 hours later. Expression of many of these genes was also changed by ischemic stroke, intracerebral hemorrhage, and hypoglycemia or hypoxia. The protein products of the regulated genes belong to a variety of functional classes, including stress-related proteins, proteases, cytoskeletal proteins, and receptors. The function of a number of genes responding to kainate treatment implicates their involvement in remodeling of neuronal networks (see earlier discussion). For example, c-jun, fos, tissue inhibitor of metalloproteinases 1 (TIMP-1), and syndecan participate in regulation of dendritic spine morphology and hippocampal long-term potentiation (LTP).[51,87]

Recently, response to kainic acidâ€“induced SE has been studied also by Hunsberger et al.[77] In this study, gene expression profiles of the rat hippocampi were characterized at 24 hours after intraperitoneal application of kainate using custom cDNA array. Kainic acidâ€“induced genes were classified into multiple functional classes such as angiogenesis, cell cycle and proliferation, cell death, extracellular matrix signaling, kinases and phosphatases, neuroprotection, neurotransmitter signaling, and transcription factors.[77] Thirty-six novel kainic acidâ€“regulated genes were found in addition to those that were discovered in previous studies, including transcription factors (CCAAT/enhancer binding protein Î´ [C/CEBPÎ´], glycoprotein 38 [gp38], and ankyrin repeat and SOCS box protein 13 [ASB13]) and those involved in neurotransmitter signaling (fibroblast growth factor receptor 4 [Fgfr4], G proteinâ€“coupled receptor 18, and L-myc-1 proto-oncogene protein [Lmyc1] transcription factor).

Lukasiuk and colleagues examined gene expression profiles during epileptogenesis at 1 day after SE induced by electrical stimulation of the amygdala using Research Genetics Rat Array (Research Genetics, Huntsville, AL) containing approximately 5,000 genes and expressed sequence tags (ESTs). One day after the induction of SE, changes were observed in the expression of 37 genes in the hippocampus (8 downregulated and 29 upregulated) and 29 genes in the temporal lobe (13 downregulated and 16 upregulated). Products of some of those genes are involved in normal metabolism, including cytochrome function, protein synthesis, and carbohydrate and amino acid metabolism. Some of these changes might reflect rescue efforts from metabolic

disturbances. Others, such as downregulation of predominantly neuronal synaptophysin or 14â€“3-3 gamma, might reflect ongoing neurodegeneration.[114,115]

Changes in Pattern of Gene Expression During Late Epileptogenesis

Hendriksen et al.[73] investigated the pattern of gene expression in the hippocampus of rats undergoing epileptogenesis that was induced by SE evoked by electrical stimulation of the angular bundle. Four hours after the stimulation, SE was stopped with pentobarbital. The hippocampus contralateral to the stimulation site was isolated 8 days after stimulation and used for gene profiling with SAGE methodology. During the latency period, rats were under continuous electroencephalographic (EEG) monitoring, and only the animals that did not express any seizure activity during monitoring were included in the study. Sequencing >10,000 tags for each group revealed 92 differentially regulated tags. Genes with altered expression were associated with expression of ribosomal proteins, protein processing, axonal growth, and glial proliferation. The authors classified 6 genes as related to axonal growth and regeneration and therefore as likely involved in the remodeling of neuronal network, including cyclophilin, glycoprotein 65, Î±-tubulin, Thy-1 antigen, thymosin Î±-10, and an expressed sequence tag highly similar to tubulin Î² chain.

Elliot et al.[50] characterized the pattern of gene expression in the pilocarpine model of rat epilepsy. SE was induced by an intraperitoneal injection of pilocarpine hydrochloride and terminated after 2 hours of convulsive SE with diazepam. Animals were sacrificed 14 days later. In this study, the authors focused on the analysis of gene expression in the dentate gyrus of the hippocampus. Expression levels were analyzed using the Affymetrix chips, and changes in level of expression were found for 129 genes. Genes altered during epileptogenesis represented a wide range of functions, with a high number of genes involved in response to injury and cell survival. The authors hypothesized that epileptogenesis shares some features with normal development of the nervous system. Therefore, they compared gene expression in the dentate gyrus of the hippocampus during development and epileptogenesis. A total of 37 genes had an altered level of expression during both epileptogenesis and development. According to functional annotations performed by authors, genes altered during epileptogenesis have functions related mainly to injury and survival, morphology, signaling, metabolism, and cell cycle. Our bioinformatic analysis of this data set that was undertaken to detect overrepresentation of functional gene groups revealed statistically significant overrepresentation of genes involved in RNA metabolism, neurogenesis, cytoskeleton organization and biogenesis, development and cell differentiation, and nerve maturation.[116] Some of these genes may be of particular interest in the context of remodeling of neuronal network. For example, internexin neuronal intermediate filament protein Î± (Inexa) may play a role in neuronal regeneration in response to injury. Bhlhb3 (basic helix-loop-helix domainâ€“containing protein class B3) has been implicated in the regulation of neuronal differentiation during development and adaptive neuronal plasticity and neurite outgrowth in the adult. Finally, protein phosphatase 1 regulatory subunit 9B (Ppp1r9b) and Ras homolog enriched in brain (Rheb) play a role in synaptic plasticity. Another gene, Synthenin, is abundant during the period of development characterized by intense growth and synapse formation and stabilization and may play a role in determining the formation and maturation of synapses.[76] Vascular growth factor (VGF) plays a key role in neuronal differentiation and survival and regulates synaptic function in hippocampal neurons, neurotrophic tyrosine kinase receptor type 2 (Ntrk2) is a receptor for brain-derived neurotrophic factor, and CD24 antigen (Cd24) may be involved in neuronal migration during development.

Becker et al.[9] also studied gene expression in the dentate gyrus and the CA1 region of the hippocampus at 3 and 14 days after pilocarpine-induced SE with Affymetrix microarrays. Increased expression of >400 genes in the dentate gyrus and 700 genes in the CA1 was observed 3 days after SE, whereas a lower number of genes was regulated at 14 days after SE: >50 genes in the dentate gyrus and 400 genes in the CA1. The authors suggested that several genes from their data set might be involved in stress reaction and structural reorganization of the hippocampus. Regulated immediate early genes include transcription factors (JE-immediate early gene, c-fos), tissue plasminogen activator (tPA; a component of the plasminogen system), as well as mitogen-activated protein kinase 1 (MEKK1) and cell division control protein 2a (cdc2a) kinases. Some genes may be linked to structural plasticity such as microtubule-associated protein 2 (map2), pentraxin, TIMP-2, glial fibrillary acidic protein (GFAP), or Thy-1 cell surface antigen. Others, like Ras-related protein Rab-3 (rab3), regulating synaptic membrane exocytosis (Rim) IÎ±, neurexin III-Î±, and neurexin I-Î², are associated with the synapse and can influence synaptic plasticity.

Lukasiuk et al. analyzed changes in gene expression in rats undergoing epileptogenesis after SE induced by electrical stimulation of the amygdala.[115] Tissue was sampled in the hippocampus and temporal lobe at 4 and 14 days after induction of SE. Four days after stimulation, 10 genes were upregulated and 2 were downregulated in the hippocampus. In the temporal lobe, 57 genes were upregulated and 98 were downregulated. Fourteen days after stimulation, there were 3 genes upregulated and 11 downregulated in the hippocampus and 17 genes upregulated and 15 downregulated in the temporal lobe. Many genes regulated during epileptogenesis are involved in basic metabolism, including energy metabolism, protein synthesis and degradation, and signal transduction. Further analysis revealed statistically significant overrepresentation of functional gene classes. At 4 days after SE there was an upregulation of genes involved in cytoskeleton organization and biogenesis (Ywhag [tyrosine 3-monooxygenase/tryp-tophan 5-monooxygenase activation protein, Î³ polypeptide], Lasp1 [LIM and SH3 protein 1], Dlc1 [deleted in liver cancer 1], and stathmin 1) and in cell differentiation (vav 1 oncogene, selenoprotein 15, Ywhag, interferon-related developmental regulator 1 [Ifrd1], bone morphogenetic protein 4, dual-specificity phosphatase 6).[116] At 14 days after SE, genes involved in electron transport and secretion were overrepresented. One of the genes that may be of particular importance for plastic changes was munc13â€“4, which encodes a protein mediating synaptic vesicle exocytosis from glutamatergic synapses.

Changes in Pattern of Gene Expression in Epileptic Tissue

Global analysis of gene expression has been used for characterization of epileptic tissue both in animal models and in surgically resected human tissue.

Several studies have dealt with global alterations in gene expression in human temporal lobe epilepsy. Becker et al.[8] studied patterns of gene expression in the resected human epileptic hippocampus with Ammon's horn sclerosis and compared them to unlesioned nonepileptic hippocampal tissue using the Atlas Human Neurobiology array. Nine genes were upregulated and 12 were downregulated in the sclerotic hippocampi. Subsequent real-time quantitative RT-PCR analysis of gene expression in laser-microdissected cells enabled identification of the genes that were differentially regulated in the neuronal and glial cell populations. For example, ataxin-3 was upregulated in neurons and GFAP (glial fibrillary acidic protein) in astrocytes. On the other hand, calmodulin expression did not differ in individual neurons sampled from sclerotic or unlesioned hippocampus, suggesting that a decrease in its expression in tissue extracts is due to the loss of calmodulin-expressing neurons.

In their further work, Becker et al. characterized and compared gene expression profiles in rat and human epileptic tissue using Affymetrix microarrays.[9] In rats, epilepsy was induced by pilocarpine-evoked SE. Gene expression was studied and compared in the CA1 and DG regions of the rats exhibiting either low or high seizure frequency. In animals with high seizure frequency, 96 genes were altered in the CA1 and 74 in the dentate gyrus. In the group with low seizure frequency, 89 genes were altered in the CA1 and 57 in the dentate gyrus. In general, fewer alterations in gene expression were detected in epileptic animals than in rats that were sacrificed for analysis at 3 or 14 days after pilocarpine application (epileptogenesis phase). Genes induced in chronically epileptic animals included neurotransmitter receptor genes (D1A dopamine receptor), channels (Kv3.2 potassium channel), and genes important for synaptic transmission such as pentraxin, Rim, and neurexins. Our analysis of this data set revealed overrepresentation of genes belonging to several functional groups, including synapse organization, response to stress, and the wounding or immune response.[116] In addition, the authors compared gene expression profiles in hippocampi of epileptic rats and hippocampi of human epileptic patients. Eighteen genes were similarly regulated in epileptic animals and in humans, demonstrating remarkable interspecies similarity in gene expression profiles. Coregulated genes are involved in cellâ€“matrix interactions, cell growth and differentiation, cellular metabolism, neuronal signaling, and regulation of transcription.

Lukasiuk and colleagues studied patterns of gene expression of the hippocampi and temporal lobes of rats that developed spontaneous seizures following SE induced by electrical stimulation of the amygdala.[115] In the hippocampus, 12 genes were upregulated and 30 genes were downregulated. In the temporal lobe, 58 genes were upregulated and 4 genes were down-regulated. It is interesting that there was little overlap between the genes regulated in epileptic animals in comparison to animals that did not have spontaneous seizures at the same time after stimulation. The regulated genes have a variety of functions, including those related to basic metabolism, cell cycle, and signal transduction.

Gene expression profiling also has been used to study genetically epileptic rats. Bo et al.[20] searched for differentially expressed genes in the cerebral cortex of genetically epilepsy-prone P77MC rats using Atlas Expression Array. They found 13 genes elevated and 2 genes downregulated in P77MC rats compared to normal Wistar rats. These genes were involved in protein synthesis, metabolism, membrane transport, cytoskeleton, and ion channels.

Arai et al.[3] studied genetically epileptic Ihara rats that have genetically programmed micodysgenesis in the hippocampus. They used SAGE to compare the expression pattern of IERs with that of control Wistar rats at 2 months of age, that is, prior to the expected manifestation of spontaneous seizure activity. They identified 21 differentially regulated genes. The genes upregulated in IER rats were involved in protein synthesis, metabolism, membrane transport, the cytoskeleton, and ion channels. Genes coding for intracellular components and neurotransmission-related proteins were downregulated. Most of these genes had not been previously implicated in epileptogenesis or epilepsy.[3]

Kim et al.[94] studied cortical dysplasia and compared gene expression in dysplastic with nondysplastic cortex. Three genes were upregulated and four genes were downregulated in dysplastic cortex. It is interesting that the majority of the genes showing altered expression were associated with apoptosis.

An earlier study of cortical dysplasia by Crino at al.[34] using targeted cDNA array revealed that GluR4, NR2B, and NR2C subunit mRNAs were increased and NR2A and GABA$_A$RÎ²1 subunit mRNAs were decreased in dysplastic neurons, whereas GABA$_A$RÎ±1, -RÎ±2, and -RÎ²2 as well as GluR mRNA levels were reduced in both dysplastic and heterotopic neurons.

Changes in Pattern of Gene Expression During Kindling

Apart from SE-induced epileptogenesis, kindling has also been used as a model to study plasticity-associated changes in trans-criptome. During kindling, repetitive application of an initially subconvulsive electrical stimulus results in development of epileptiform activity and finally generalized seizures in response to the same stimulus.[66] One advantage of this model is the absence of severe brain damage that is present in SE models. Therefore, genes that change expression level during kindling are presumably related to changes in excitability, and the data set is less likely to be contaminated by alterations related to neurodegeneration.

Liang and Seyfried[106] used RT-PCR differential display (DD) to study hippocampal tissue at 0.5 hour, 1 day, 1 week, and 1 month after rapid kindling. Out of 30,000 bands analyzed, 50 were differentially displayed. Northern blot analysis confirmed changes in 26 of these genes. Fourteen of them were known genes and 12 were novel. Only 5 genes had changed expression level for at least 1 day. Kinase Î±CaMK II, phosphatase PP2A, and GTPase-like protein Cyr 61 were downregulated, whereas King12 was upregulated for up to 1 day after kindling. Only RGS4, a GTPase-activating protein, was persistently downregulated up to 1 month after rapid kindling.

MPSS was used to study gene expression in the rat amygdala kindling model by Potschka et al.[141] Kindling by repeated electrical stimulation of the amygdala resulted in the differential expression of 264 genes in the hippocampus compared to sham controls. The most strongly induced gene was Homer 1A, an immediate-early gene involved in the modulation of glutamate receptor function. Because kindling induces overexpression of Homer 1A in the hippocampus and mice overexpressing Homer 1A exhibited retardation in kindling, this may represent an intrinsic antiepileptogenic mechanism in counteracting progression of the disease.[141]

Gu et al.[69] studied the effect of amygdala kindling on gene expression in the temporal lobe with Affymetrix microarrays. A number of genes were regulated during kindling, and the authors clustered >200 of them into 15 protein pathways or functional classes. These functional classes could reflect ongoing changes leading to increased excitability and included G-protein signaling, synaptic transmission, CA^{2+}-dependent kinases, ion channels, transcription factors, neurofilaments, microtubules, surface-linked signal transduction, and others.

Influence of Antiepileptic Drugs on Pattern of Gene Expression

Large-scale molecular profiling studies have provided opportunities to discover new mechanisms of action of AEDs that extend beyond their antiepileptic effects and can mediate their effects on neuronal recovery after epileptogenic insult. Such analyses have been performed with tissues exposed to valproic acid, lamotrigine, or phenytoin. Bosetti et al.[21] administered 200 mg/kg of valproic acid to rats for 30 days and reported that 87 of 8,799 genes on a U34A Affymetrix oligonucleotide microarray were downregulated and 35 were upregulated. The regulated genes affect a variety of molecular pathways, including synaptic transmission; ion channels and transport; G-protein signaling; lipid, glucose, and amino acid metabolism; transcriptional and translational regulation; phosphoinositol cycle; protein kinases and phosphatases; and apoptosis. The actions on these pathways might explain some of the effects of valproic acid on psychiatric conditions as well as on the recovery process after epileptogenic brain insults. One of the effects might be on angiogenesis and cell proliferation. It is interesting that valproic acid (0.25â€“1 mM) was recently reported to inhibit endothelial cell proliferation and migration as well as reduce angiogenesis in vitro and in vivo, effects that are probably mediated by the inhibition of histone deacetylase and decreased expression of endothelial nitric oxide synthase.[125] Suppressed expression of the angiogenic factors vascular endothelial growth factor and fibroblast growth factor is also proposed to contribute to the antiangiogenic actions of valproate.[176] The effect on cellular proliferation has sparked interest in valproate as an antineoplastic agent.[16] Whether trauma- or seizure-induced proliferation of neuronal and glial cells is affected by valproic acid is unknown.

Wang and colleagues[171] exposed hippocampal primary cell cultures to 0.1 mM lamotrigine for 1 week. Of 1,200 genes on the Atlas Rat 1.2 array, 8 genes were upregulated and 6 were downregulated. Regulated genes included subunits of ion channel receptors, kinases, phosphatases, and proteins involved in cell survival. The functional significance of the data has not yet been explored.

The effects of phenytoin on gene expression in human dermal fibroblasts were studied by Swamy et al.[156] Of the 18,000 elements on the cDNA microarrays, 1,500 genes were differentially expressed after exposure of cultures to 20 Âµg/mL phenytoin for up to 48 hours. The major growth factors and their receptors involved in wound healing were upregulated, as were the genes encoding proteins involved in extracellular matrix degradation (e.g., matrix metalloproteinase-1). These findings suggest a molecular basis for some peripheral effects of phenytoin, including its beneficial effects on wound healing. They are also consistent with earlier studies demonstrating that in an experimental model of wound healing, as well as in stroke patients with peripheral ulcers, phenytoin facilitates fibroblast infiltration and neovascularization.[36,137] Further investigation of the effects of phenytoin on genes encoding proteins that contribute to the reorganization of the extracellular matrix and blood vessels in neuronal tissue after brain trauma seems very worthwhile.

Gu et al.[69] studied the effect of levetiracetam on gene expression during amygdala kindling. Levetiracetam had no effect on gene expression in control rats. However, application of levetiracetam during kindling not only suppressed kindling, but also influenced gene expression patterns in the temporal lobe. Expression of some epilepsy-related genes such as neuropeptide Y, thyrotropin-releasing hormone, and DFAP was partially normalized by levetiracetam treatment. Nevertheless, a significant number of genes remained altered by kindling even on levetiracetam treatment.

Caveats in Large-Scale Profiling of Epileptic Tissue

Despite the rising number of reports of global analysis of gene expression in epileptogenesis and epilepsy, the most essential molecular players in these processes are still unspecified. The first analysis of various data sets available a few years ago led to the conclusion that there are very few common features among different studies.[114] Differences may relate to technical issues associated with large-scale gene expression analysis. Methods of global analysis of gene expression have limited sensitivity, especially when brain tissue is studied. It has been suggested, for example, that GeneChips reliably detect no more than 30% of the hippocampal transcriptome.[52] In addition, in the case of SAGE or other methods using large-scale sequencing, rare transcripts may not be detected. Furthermore, the brain is obviously not a homogeneous tissue and consists of multiple cell types. Therefore, if a particular transcript is regulated in only one cell type, this alteration may be â€œdilutedâ€ in extracts from the tissue and remain below the level of detection. In addition, techniques of global analysis of gene expression do not provide information regarding cellular localization of the detected changes in gene expression. In case of neurodegenerative diseases, some changes can be related to the disappearance of selected neuronal populations, as demonstrated by Becker et al.[8] Finally, investigators have used different animal models or human tissues as well as analyzed the pattern of gene expression at different stages of disease development and in different brain areas. As Lukasiuk et al. showed, the changes in gene expression induced by SE are dynamic and change with time.[115] Furthermore, changes in the expression of the majority of genes are often specific to the a brain area, and there is limited overlap between genes regulated, for example, in the hippocampus and the temporal lobe.[9,115] Thus, there is a great variability in genes considered to be regulated depending on the experimental model, time point, and experimental procedure used in the study. Finally, the microarray approach will not identify posttranslational events that may be critical to the process of epileptogenesis.

Global Analysis of Gene Expression in Epileptogenesis and Epilepsyâ€"Attempt at a Synthesis

To reassess the information in data sets available from epileptogenic or epileptic tissue, Lukasiuk et al. used emerging bioinformatics methods that were designed for the global analysis of gene expression to search (a) highly represented functional gene classes (gene ontology [GO] terms) within data sets and (b) individual genes that appear in several data sets and, therefore, might be of particular importance for the development of epilepsy due to different etiologies.[116] The investigators focused on two well-described models of brain insult that induce the development of spontaneous seizures in experimental animals: (a) SE and (b) traumatic brain injury (TBI). A few papers describing gene expression in rat and human epileptic tissue were included for comparison.

The analysis revealed that various epileptogenic insults induce statistically significant changes in gene expression in functionally linked genes that were predefined as GO terms (Fig. 1). The representation of statistically significant GO terms describing biologic process was time dependent. Within hours after epileptogenic brain insult, the GO term â€œregulation of transcriptionâ€ was overrepresented. It is interesting that this GO term did not become significant at any later time point. Many of the transcription factors detected by the analysis can contribute to ongoing neurodegeneration or, more generally, to cell stress. On the other hand, changes in the expression of some transcription factors might induce succeeding events that are presumably crucial for epileptogenesis, such as neuronal plasticity. Genes under the GO term â€œneurogenesisâ€ become apparent at 1 day after injury. In epileptic tissue collected from humans or animals with spontaneous recurrent seizures (i.e., the end result of epileptogenic process), the presence of the GO terms related to â€œsynaptic organizationâ€ (BDNF), â€œplasticityâ€ (BDNF), and â€œtransmissionâ€ (apolipoprotein E [APOE], synaptosomal-associated protein 25 kDa [SNAP25]) emerged. This supports the idea that neuronal plasticity occurs for a longer period of time after an insult, and can progress even after epilepsy is diagnosed.[138] It is interesting that several GO terms, including â€œimmune response,â€ â€œcell motility,â€ â€œresponse to stress,â€ â€œresponse to wounding,â€ and â€œion homeostasis,â€ are represented across different time points after an insult. Numerous individual genes change their expression in more than two models of epileptogenesis (Fig. 2). Alterations in their expression are time specific. A closer look at altered individual genes as well as GO terms indicated an involvement of many

processes previously linked with epileptogenesis such as cell death and survival, neuronal plasticity, and immune response. It is interesting, however, that only a few genes are involved in defining the electrical properties of neurons and glia. Perhaps the most striking finding was that the predominant function of genes with altered expression is related to the immune response. Although inflammation and immune response in brain trauma and epilepsy are receiving more attention, they have not been considered to have a key role in epileptogenesis and epilepsy.

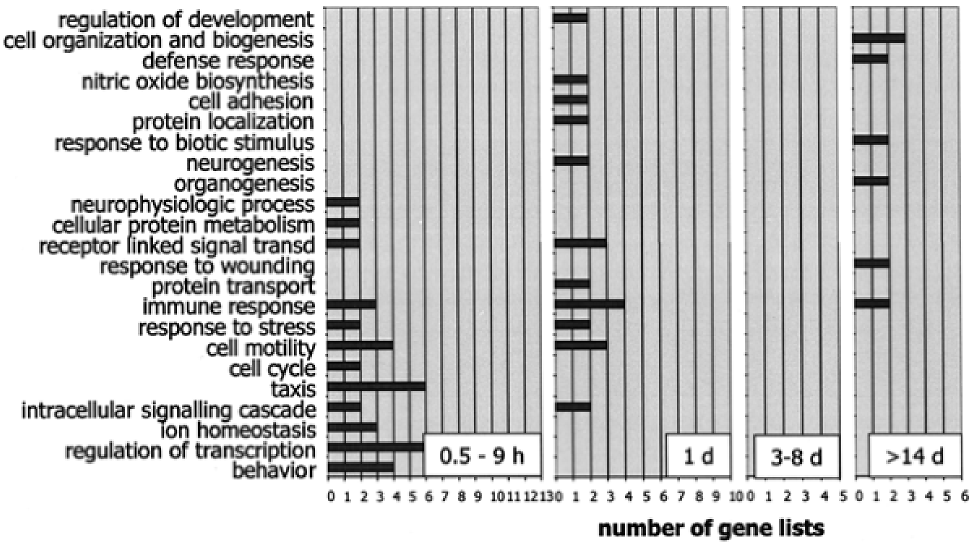

FIGURE 1. Summary of biological process gene ontology (GO) terms that are overrepresented after epileptogenic brain insults (status epilepticus or traumatic brain injury). Overrepresented functional gene classes were detected by meta-analysis of GO terms in gene lists that were generated from the data provided in selected papers using GOstat software (available at http://gostat.wehi.edu.au).[10] Only GO terms overrepresented in at least two lists within a time window are presented. For details of the analysis see Lukasiuk et al.[116] For an extended version of the results see http://www.uku.fi/aivi/neuro/research_epilepsy.shtml or http://www.nencki.gov.pl/labs/epg.htm.[116]

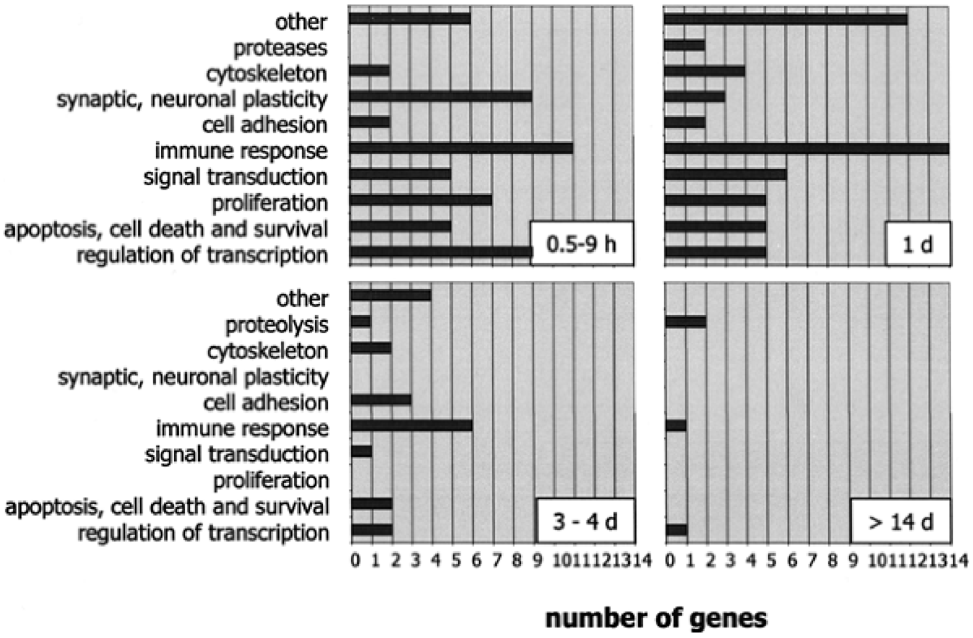

FIGURE 2. Functional classification of individual genes that appear in several data sets describing global analysis of gene expression following epileptogenic insult (status epilepticus or traumatic brain injury). transd, transduction. To find a particular gene with altered expression, data provided in selected manuscripts were reannotated and analyzed using a purpose-build relational database on a MySQL server platform. For an extended version of the results see http://www.uku.fi/aivi/neuro/research_epilepsy.shtml or http://www.nencki.gov.pl/labs/epg.htm.[116]

Summary and Conclusions

Alterations in gene expression that underlie cellular modifications leading to epileptogenesis and epilepsy have been extensively studied by using conventional molecular biology methods as well as by global analysis of gene expression. Most studies have focused on the immediate effects of seizures or SE on gene expression and therefore describe the effects of increased neuronal activity or neuronal injury on gene expression. An overall review of the studies indicates that gene lists obtained by global analysis include very few of the genes studied previously with traditional methods, such as those having a role in regulation of neuronal excitability such as receptors or channels. These observations suggest that receptor or voltage-gated channelopathies may just be some of the phenomena that occur in serial and parallel manner (possibly interacting) with other cellular changes (e.g., inflammation) that underlie the development of epilepsy and change in excitability, and these should be investigated to greater extent.

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Chapter 29

Neocortical Anatomy and Physiology

Kristen A. Richardson

Erika E. Fanselow

Barry W. Connors

Introduction

The neocortex in humans is a sheet of gray matter, 2 to 3 mm thick, with a surface area of about 2,400 cm^2, the size of a chess board. Like crumpled paper, the neocortex is folded into multiple gyri and sulci, and so fits compactly into the cranium. Gyri and sulci may be more than a solution to a packaging problem; by one view, they may also serve to compartmentalize neocortical functions.[192] Neocortex, together with the white matter that makes up its axonal connections, comprises about 80% of human brain volume.[137] Not necessary for life itself, the neocortex is essential for proper perception, motor control, memory, and cognition. Its neural circuits can adapt to a wide variety of functions, and the behavioral characteristics that define humanity can undoubtedly be ascribed to the unique expanse of neocortex enjoyed by our species. Unfortunately, possession of a neocortex comes with significant risk. The neurons and circuits that are fundamental to its normal operations can, with little provocation, produce the spectacularly disruptive activity of a seizure.

The mechanisms of clinical seizures in the neocortex are only poorly understood. However, knowledge of the basic anatomy and physiology of the neocortex is essential even to frame the questions about seizure mechanisms. Indeed, an interest in seizures has inspired many basic studies of the neocortex. The literature on neocortical biology is appropriately immense and eclectic, and numerous reviews are available.[1,25,50,57,77,125,128,129,141,194] This chapter briefly describes the structure and function of the neocortex, emphasizing those features that may contribute to its epileptic tendencies.

Basic Anatomy and Physiology of the Neocortex

The intricate structure of the neocortex has resisted explanation for at least 150 years.[95] On the one hand, all neocortexâ€"from mouse to manâ€"shares a set of common properties: The histologic appearance is comparable, the classes of neurons and the gross pattern of their connections are very similar, and the same transmitters are in use. Nevertheless, the neocortex is subdivided into many distinct areas, perhaps 50 to 100 in humans, and the number and types of areas vary widely among species. The important distinguishing features of each area include variations in cell lamination (useful for identification of the area), the patterns of axonal connections (hinting at the function of the area), and the details of neuronal structure, local interconnections, and biochemistry and gene expression (fodder for mechanistic speculations). Areas may also differ in the physiologic properties of their neurons and synapses. Nevertheless, despite knowing a tremendous amount about the general and specific structure and function of the neocortex, it is still fair to say that we cannot describe with confidence what the fundamental task of any one area of neocortex is.

Lamination as a Structural Principle

Anatomists have settled on a general six-layer nomenclature for the neocortex, although some layers can be further subdivided in many cortical areas and species.[24,104] Layering is easy to see, so the different lamination patterns of neurons, myelin, or various other structural features (glia, blood vessels, biochemical markers) have served as the basis for many schemes for neocortical parcellation. The most common approach to neocortical cytoarchitecture is Nissl staining, which highlights the cell nuclei and darkly staining clumps of material around the nuclei of neurons (Fig. 1). The Nissl-stained neocortical layers are distinguished by the density and size of their constituent neurons. In general, layer I (the â€œmolecularâ€ layer) is just below the pia and is thin and virtually neuron free. Layers II and III are hard to separate in many areas and contain medium-sized neurons in moderate density. Layer IV is the â€œgranularâ€ layer because of its densely packed, small neurons. Layer V contains the largest neurons of the neocortex and includes the output cells. Layer VI (the â€œmultiformâ€ layer) has a wide range of neuronal sizes and shapes. This general scheme has myriad variations that early anatomists, notably Brodmann, used to distinguish and define the areas of the neocortex. For example, Brodmann's area 17 (primary visual cortex) has a thick layer IV with a â€œstriatedâ€ appearance, whereas area 4 (primary motor cortex) lacks an obvious layer IV, but has exceptionally large, pyramidal-shaped neurons in layer V.

Modern anatomic methods show that the axonal connections of the neocortex are also distinctively laminated (Fig. 2). As a rule, specific neural information enters an area of the neocortex only via axons from the thalamus or other areas of cerebral cortex. Additional sources of extrinsic input include a variety of nuclei in the brainstem that project diffusely across the neocortex and deliver modulatory substances, such as norepinephrine, serotonin, acetylcholine, and dopamine.[121] Thalamic afferents from specific nuclei terminate primarily within layers III, VI, and (especially) IV. However, all other cortical layers may also receive thalamic input, depending on the area and thalamic nucleus in question.[81] Although thalamic axons are the source of input to the neocortex from the external world, they provide only a minority of all cortical synapses; even in layer IV, only 5% to 20% of synapses are from the thalamus.[142,194] Most of the rest of neocortical synapses are from the neocortex itself. Neurons in layers II and III project densely upon layers III and IV (primarily) in other areas, whereas cells in layers V and VI project to distant areas and terminate above and below layer IV.

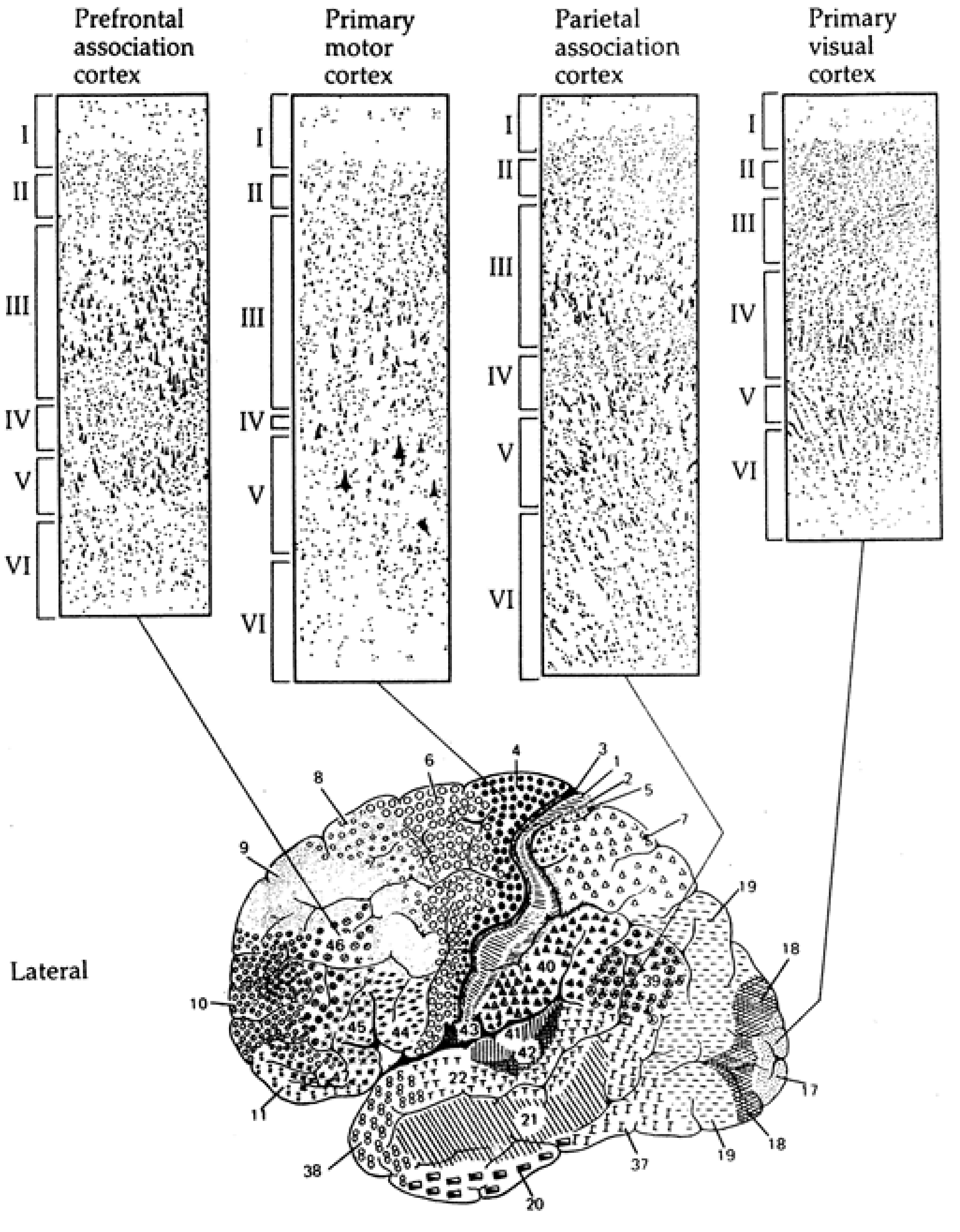
Prefrontal association cortex
Primary motor cortex
Parietal association cortex
Primary visual cortex
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FIGURE 1. Variations in laminar structure of neocortex. *Top:* Nissl-stained sections, with layers indicated. *Bottom:* Brodmann's cytoarchitectonic regions of the human cerebral cortex (lateral aspect). (From Martin JH. *Neuroanatomy: Text and Atlas*. New York: Elsevier; 1989, with permission.)

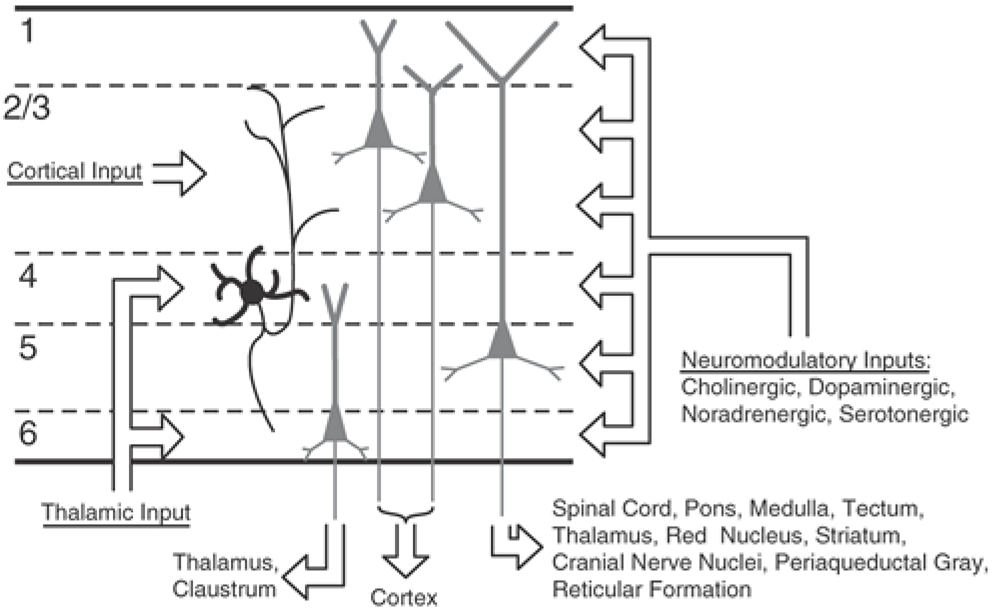
1
2/3
Cortical Input
4
5
6
Thalamic Input
Neuromodulatory Inputs:
Cholinergic, Dopaminergic,
Noradrenergic, Serotonergic
Thalamus,
Claustrum
Cortex
Spinal Cord, Pons, Medulla, Tectum,
Thalamus, Red Nucleus, Striatum,
Cranial Nerve Nuclei, Periaqueductal Gray,
Reticular Formation

FIGURE 2. Summary of the major connections to and from a generic neocortical area.

Vertical Organization of Neocortex

Nissl stains give the illusion that the neurons of the neocortex are like so many stratified grains of sand and gravel. Despite variable lamination, there is surprising uniformity of dimension. Across cortical areas and even across species, the number of neurons within a vertical column of gray matter with a surface area of 1 mm^2 is nearly identical.[148] Although some variations exist among areas,[13] the only major exception to this rule of uniformity is the primary visual cortex of primates, which has twice the neuron density of most other areas.

Nissl stains illuminate only somata, but the vast majority of each neuron's volume and surface area is in its dendrites and axons, which may stretch across layers and between areas. In the neocortex, a tendency exists for these cellular processes to extend strongly in the vertical dimension and for cells in vertical arrays to be densely interconnected. Pyramidal cells, in particular, seem to have evolved an efficient shape to collect synaptic input from a vertically oriented zone of tissue that may span several layers.[56,174] Physiologic studies show that the sensory or motor response properties of neurons in vertical â€œcolumnsâ€ of neocortex are often quite similar, whereas neighboring neurons along the horizontal dimension are relatively more different.[9,86,127,128] The widespread tendency for neocortical neurons to organize into vertical groups has prompted speculations that the neocortex is basically modular[128]; small columns form the irreducible units of neocortical organization, and new areas and functions are built up by simply adding more columnar modules. This scheme is appealing but unproven.

Systematic anatomic and physiologic measurements have suggested a basic vertical circuit for neocortex.[7,8,72] It begins in layers III and IV, where the main thalamic input arrives. Local axons of the spiny stellate cells in layer IV then excite pyramidal neurons in the upper layers, which in turn strongly excite neurons of layer V. Layer V cells synapse upon cells of layer VI, and these return excitation both to the thalamus and to layer IV. The neocortex is primarily feeding information back upon itself, which may be the single most important thing we can say about its susceptibility to seizures. If excitation were the only story, however, the cortex would seize interminably. In parallel with the loops of excitatory circuitry, Î³-aminobutyric acid (GABA)-releasing neurons also receive excitation and, in turn, inhibit pyramidal neurons, both ahead of and behind them in the circuit flow.[42,96,162]

Topologic maps of the vertical organization of neocortex have been described for many different areas and species; these reveal that, in many cases, â€œcolumnsâ€ have been misnamed. For example, in visual cortex, the zones specific for ocular dominance look, from the surface, like alternating bands or slabs, whereas the organization of neurons with similar stimulus orientation preferences resembles radiating pinwheels.[11,21] Furthermore, these two maps of visual function are coextensiveâ€”they use the same sheet of cortex simultaneously but divide it quite differently. For the most part, the anatomic underpinnings of functional columns have not yet been demonstrated in detail.[28,83] In a general way, vertical connectivity must link neurons across layers, but with a high degree of specificity.

Horizontal Organization of Neocortex

Although vertical connections received early[114] and sustained publicity, the horizontal connections of the neocortex are also widespread, complex, and essential. Their existence provides a ready set of pathways for the rampant propagation of seizures. A few generalizations about horizontal connections can be made: They vary from very short to very long, they are reciprocal, and they tend to terminate in discontinuous, patchy patterns.

In a single brain, the neocortex consists of two continuous sheets, one in each hemisphere. Horizontal connections exist between points on this sheet at very local scales (within single microcolumns), at intermediate scales between columns, within areas, between adjacent areas, and at long distances between far-flung ipsilateral areas, as well as between homologous contralateral areas via connections through the corpus callosum. In most cases, the horizontal interconnections at all scales are reciprocal; a set of connections from cell group A to cell group B is matched by a set of connections from B to A. The patchiness of interconnections is nearly ubiquitous, although there are exceptions,[185] and both the regular patterns of connections and the scale of their periodicities tend to be strikingly similar across cortical areas.[73,97,110,111]

Horizontal interconnections, especially over intermediate and long distances, are overwhelmingly excitatory, reinforcing their relevance for the spread of seizure activity. Experimental work has shown that local variations of horizontal excitatory connectivity are an important determinant of the speed and route of seizure propagation.[35,143,183] At shorter distances, on the order of adjacent intercolumn distances within one area, there may be a liberal mix of horizontal inhibitory and excitatory connections. The spatial details and relative strengths of these connections are variable with area and are probably critical in helping to determine the unique functions of each area.

Growing evidence also suggests that horizontal connections mediate some forms of experience-dependent plasticity in sensory and motor areas of the neocortex.[71,153] Cortical synapses can either strengthen or weaken, depending on their recent history of activity,[12] axons and synapses remodel dynamically[165] and, over weeks and months, cortical axons can also sprout new branches in response to chronic alterations of thalamic input.[53] It seems very likely that the grossly abnormal activity of chronic seizures could induce significant physical and physiologic changes in cortical circuitry.

Diverse Neurons of Neocortex: Morphology

At first glance, the neurons of the neocortex are dazzling in their diversity. By examining cellular morphology, connections, biochemistry, and physiology, however, order emerges.[4,195] The neurons can be divided into two major groups based on structureâ€”spiny neurons (about 70%â€“85% of the total cells) and aspiny (â€œsparsely spinyâ€ or â€œsmoothâ€) nonpyramidal neurons.[56,141,162] Spines are small (about 1â€“0.2 Âµm on average), membranous excrescences along the shafts of dendrites.

Within the cortex, spines are notable as the major site of excitatory synaptic input onto spiny cells. The spiny and aspiny morphologic categories also correspond to basic cellular functions. Spiny cells make excitatory synapses that use the excitatory amino acid glutamate; aspiny nonpyramidal neurons make inhibitory GABA-utilizing synapses. Neurotransmitters of the neocortex will not be specifically covered in this chapter, but numerous reviews are available (see Chapters 22 and 23).

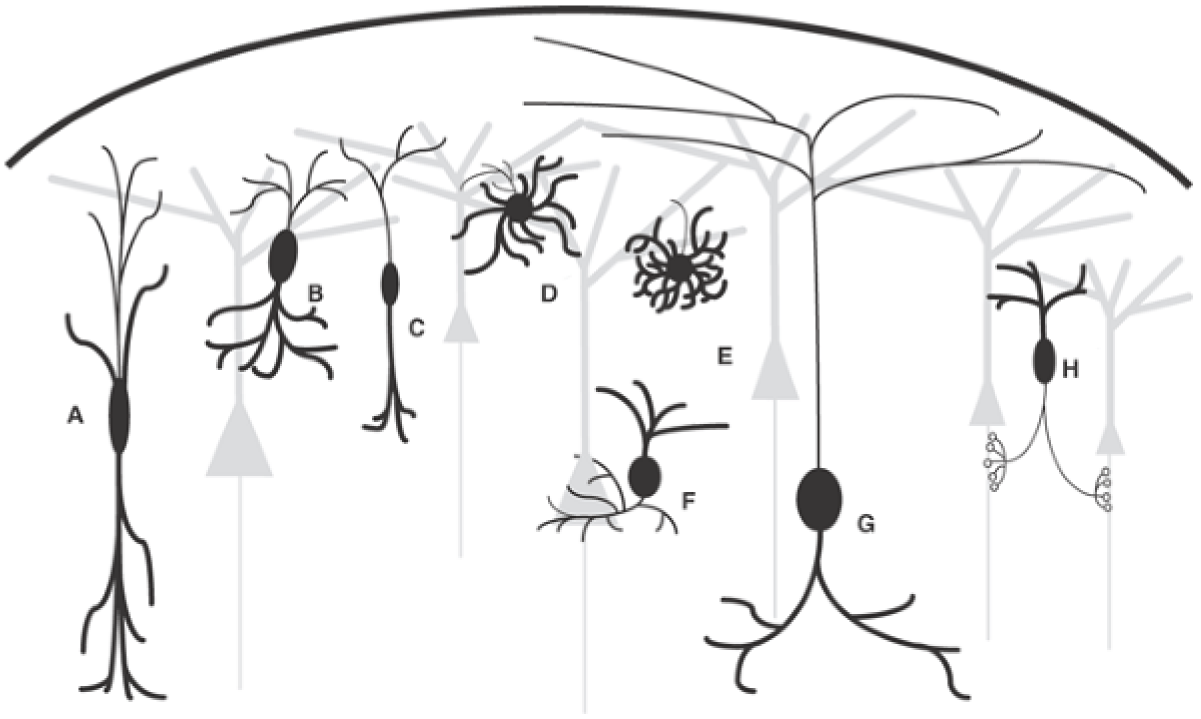

FIGURE 3. Inhibitory interneuron subtypes. **A:** Double bouquet cell. **B:** Bitufted cell. **C:** Bipolar cell. **D:** Multipolar cell. **E:** Neurogliaform cell. **F:** Basket cell. **G:** Martinotti cell. **H:** Axo-axonic/(chandelier cell). Bold lines represent dendrites, fine lines represent axons. Gray cells represent excitatory neurons.

The two major classes of cortical neurons, in turn, are subdivided. The excitatory, spiny cells include pyramidal cells and spiny nonpyramidal cells (often called *spiny stellate cells*). Pyramidal cells are the majority class of neurons in the neocortex. They have a high density of dendritic spines (rare exceptions to this rule exist), prominent apical dendrites, and an axon that projects out of the cortex, as well as locally. Pyramidal cells vary widely in size, shape, axonal structure, and their somata appear in all layers except layer I.[56] Spiny stellate (nonpyramidal) cells are relatively small neurons of layer IV, with high spine density and axons that terminate in excitatory synapses. Spiny stellate cells are distinguished from pyramidal cells by the

absence of an obvious apical dendrite, and their axons usually do not leave the cortex (although a minority may send axons out of the cortex).[188] Because of their excitatory function and spiny dendritic structure, spiny stellate cells may be considered a simple variant of the pyramidal cells. This view is supported by the development of spiny stellate cells; apparently, they begin life as pyramidal neurons, and during postnatal maturation, they gradually retract their apical dendrites.[187]

The inhibitory, sparsely spiny, nonpyramidal neurons are a very diverse group.[102,118,195] Whereas their dendritic patterns vary systematically,[37] a more useful characteristic is the pattern of their axon arbors, which do not leave the local area of cortex but which may be distinctive and specific.[61] As schematized in FIGURE 3, common morphologies for inhibitory interneurons include *double bouquet cells*, whose axons and dendrites project within a long, narrow, vertical column; *bitufted cells*, whose collaterals form two highly branched protrusions from the soma; *bipolar cells*, which have long collaterals projecting vertically above and below the soma; *multipolar cells*, which have round somata with multiple dendrites projecting radially; *neurogliaform cells*, whose dendrites form relatively tight, symmetrical spheres around their somas; *basket cells*, whose axons tend to form basket-like shapes around the somata of their target cells; *Martinotti cells*, which can have their soma in layers II to V and project their axon up to layer I, where they ramify up to several millimeters; and *axo-axonic cells*, whose dendrites terminate on the axon initial segments of target pyramidal cells, forming structures that resemble candlesticks (thus the alternative name, *chandelier cells*). Note that this is not an exhaustive list of inhibitory neuron morphologies, nor do neurons always fit clearly into one morphologic subtype.

It has been shown that somatic and perisomatic targeting cells can readily suppress action potentials,[124] suggesting that these inhibitory neurons could closely control the output of their target neurons. Because of their potentially strong control over pyramidal cell output, loss of axo-axonic cells has been implicated in epilepsy.[55] It has also been proposed, paradoxically, that axo-axonic cells actually excite pyramidal neurons because of a relatively high internal chloride ions [Cl^-] in axon initial segments.[173]

Other inhibitory neurons terminate on the dendrites of their target cells. Examples include double bouquet cells, bitufted cells, bipolar cells, neurogliaform cells, and Martinotti cells (Fig. 3Aâ€"C, E, G). The nature of the inhibition from these cells probably differs from interneurons that synapse in somatic or perisomatic regions. Dendrite-targeting inhibitory cells can alter the way their target cell integrates synaptic input within the dendrites, and it is thought that these cells can suppress dendritic calcium ion (Ca^{2+}) spikes,[106,124] decreasing the ability of excitatory inputs to propagate along the dendrites.

Classes of inhibitory cells may also be defined by interesting variations in peptide cotransmitters (in addition to the GABA that they all contain),[80] by different types of Ca^{2+} binding proteins they express,[100,184] and by their expression patterns of a wide variety of genes.[22,131,170] Three main Ca-binding proteins have been useful as markers of interneuron types: Calbindin (CB), calretinin (CR), and parvalbumin (PV). The most common neuropeptides used to identify inhibitory interneuron subtypes include cholecystokinin (CCK), somatostatin (SOM), and vasoactive intestinal peptide (VIP). Double labeling studies have shown that several of these markers tend to co-exist within cells (e.g., CR and VIP), but others never or very rarely co-exist (e.g., PV and SOM). Kawaguchi and Kubota[103] divided prefrontal neocortical inhibitory neurons in layers II through VI into four main groups based on these markers. Group I contains PV; group II contains SOM and neuropeptide Y (NPY); group III contains CR, VIP, and CCK; and group IV contains large CCK cells. However, it is not clear that these groups correlate well with specific morphologic or physiologic subcategories of inhibitory neurons. One pattern that does emerge is that PV appears to be associated with somatic/perisomatic or axo-axonic targeting cells, whereas CR is largely associated with dendritic targeting cells (reviewed in[118]).

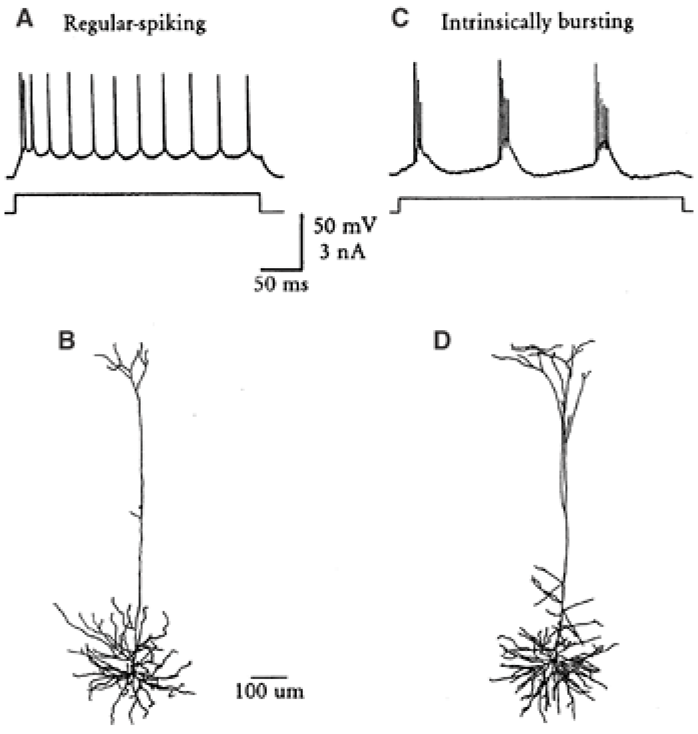

FIGURE 4. Variations of intrinsic firing patterns of layer V pyramidal cells in rodent neocortex. **A:** Regular-spiking pattern, showing spike frequency adaptation. **B:** Dye-filled regular-spiking pyramidal cell. **C:** Intrinsic bursting activity. **D:** Dye-filled intrinsically bursting cell. **A** and **C** are reprinted from Agmon A, Connors BW. Correlation between intrinsic firing patterns and thalamocortical synaptic responses of neurons in mouse barrel cortex. *J Neurosci.* 1992;12:319â€"229, with permission; **B** and **D** are reprinted from Cauller LJ, Connors BW. Synaptic physiology of horizontal afferents to layer I in slices of rat SI neocortex. *J Neurosci.* 1994;14:751â€"762, with permission.

Diverse Neurons of Neocortex: Physiology

Just as neurons vary in their shape, transmitter, and synaptic connections, they may also differ in their intrinsic physiologic properties.[46,49,112] â€œIntrinsic physiologyâ€ is defined as a neuron's inherent ability to respond to stimuli, apart from the effects of the neural network surrounding it; intrinsic physiologic properties derive from the cell's membrane (and its ion channels, primarily) and metabolic properties (such as ion pumps and control systems, second-messenger systems, and energy management). Takahashi[176] was the first to show that the intrinsic properties of neocortical cells had diverse properties. Recording from the pyramidal tract neurons of the cat, he found that axonal conduction velocities correlated with somatic spike duration, time constant, input resistance, and duration of the afterhyperpolarization. Since then, numerous studies have used methods of intracellular recording, single-cell staining, and isolated brain slices in vitro to demonstrate that the intrinsic physiology and morphology of neurons in the neocortex are related. The impact of a neuron's intrinsic properties can be appreciated from its response to simple injected current stimuli, as shown in FIGURE 4. Some cells produce a tonic, uniform spike frequency; others display strong adaptation; and still others generate periodic bursts. Clearly, when faced with the same input, each of these neurons provides a very different message to its postsynaptic targets. Myriad variations on these basic themes exist in the neocortex and in the rest of the brain.

Regular-Spiking Pyramidal Cells

The â€œregularâ€ intrinsic firing pattern[130] (regular implying most common) is that of most pyramidal cells from layers II to VI.[47,122,164] Regular-spiking (RS) cells usually fire a single spike to a threshold current pulse. Their action potentials rise at a higher rate than the rate at which they fall. These may display a combination of fast, medium, and slow afterhyperpolarizations, as well as a brief afterdepolarization.[29,47,115,155]

Repetitive firing has an initially high frequency that subsequently shows strong adaptation; that is, spike frequency declines during a sustained stimulus. Most RS cells adapt from a beginning rate of several hundred hertz to a relatively stable, but much lower, rate within about 200 msec. The adapted rates are rarely higher than 50 to 100 Hz. Some RS cells adapt steeply and often stop altogether, even as stimulus current is maintained.[2,33] One subclass of nonbursting pyramidal cell displays no frequency adaptation but generates a very rhythmic pattern of single spikes instead.[158] Near threshold, at about â€"65 to â€"60 mV, these cells can be bistable, shifting from silence to repetitive firing at low (5â€"12 Hz) rates when triggered by brief stimuli.

Intrinsically Bursting Pyramidal Cells

A particularly interesting type of cortical neuron, especially in the context of seizure generation, is the intrinsically bursting (IB) cell. Although RS cells generate a single spike to a just-threshold stimulus, the minimal response of the IB subgroup of pyramidal cells is usually a high-frequency cluster of action potentials or â€œburst.â€[47,109,122] Each burst consists of 3 to 5 spikes firing at about 150 to 300 Hz. Bursts occur either singly or in repeating patterns of bursts at 5 to 15 Hz.[2,34,158] Near firing threshold, repetitively bursting neurons of layer V can also exhibit a bistable state similar to the single-spiking cells described in the previous section. Small triggering stimuli generate long-lasting responses consisting of rhythmic bursts or burst-single spike complexes. These IB cells have been implicated in the initiation of epileptiform activity in experimental studies of neocortex in vitro.[44]

Although most physiologic studies of neurons have actually been studies of their somata, this misses most of the point for pyramidal cells; as much as 97% of their membrane area is actually dendritic,[109] and 1 mm^3 of neocortical gray matter contains a total dendritic length of about 450 m.[25] The patch-clamp method has allowed direct recordings from cortical dendrites. These have shown that the dendrites of pyramidal cells are quite excitable and express sodium (Na),[88,168] Ca,[5,106,116] and potassium (K)[94] currents that can powerfully affect the cells' ability to transform synaptic inputs. Indeed, electrically excitable dendrites are probably essential for the efficacy of many distal synaptic inputs onto the longest dendrites of neocortexâ€"synapses in layer I onto the dendrites of cells with their somata in layer V, for example.[31] In addition, just as the intrinsic physiology of neuronal somata can vary in neocortex, the physiology of long dendrites can also vary systematically from one cell type to another.[106] The properties and significance of electrically excitable dendrites are being intensively investigated.[167,191]

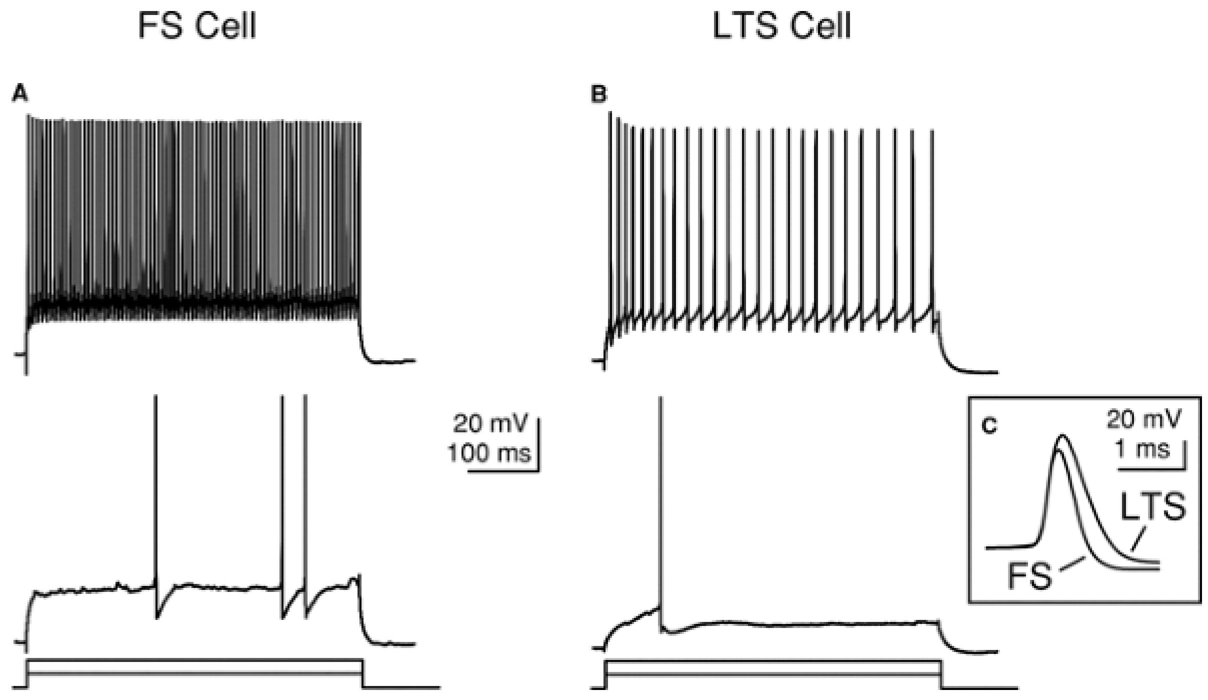

FIGURE 5. The differential responses of inhibitory neurons to pulses of injected current can be used to identify different neuronal types. **A:** Response of an FS neuron to just-threshold (*bottom*) and suprathreshold (*top*) current pulses. **B:** Response an LTS neuron to just-threshold (*bottom*) and suprathreshold current pulses. **C:** Action potentials of FS neurons are narrower than those of LTS neurons.

The density of IB cells is strikingly dependent on the cortical layer. In rodent sensorimotor cortex, their somata are most frequently observed in layer Vâ€"its deeper aspects in particular.[34,122] However, they are also seen in layer IV in some species and cortical areas.[34,47] Most or all of the layer V IB cells are subcortical projection neurons.[98,190]

Diverse Physiology of Inhibitory Interneurons

Many of the GABA-utilizing, inhibitory interneurons of the neocortex have a distinctive intrinsic physiology earning them the name fast-spiking (FS) cells. Their action potentials are exceptionally brief (<0.5 msec).[130,160,172] Intracellularly recorded, the FS cell spike has a rate of fall almost as fast as its rate of rise and a deep but brief afterhyperpolarization.[122] The inhibitory synaptic effect of FS cells has been confirmed by directly demonstrating that they make gabaergic synapses in tissue culture[87] and by showing their immunoreactivity for GABA and glutamic acid decarboxylase (GAD), the synthesizing enzyme for GABA.[99]

The most distinctive physiologic property of FS neurons is that they can fire at very high rates with little or no adaptation. When activated by coherent synaptic excitation following a single shock, FS cells are impressively responsive. They will often generate a train of spikes at relatively high frequency,[33,99,122] whereas RS cells usually fire one or two spikes. When a just-suprathreshold current step is injected into an FS cell with an intracellular electrode, the cell will often pause prior to firing, then produce the first spike after a considerable delay (Fig. 5A, *bottom*). Firing becomes repetitive with increasing stimulus amplitude, and rates can reach to >300 Hz (Fig 5A, *top*).[15,122] FS cells show little or no spike-frequency adaptation. FS cells include basket cells and chandelier cells. They often express PV.

Not all GABAergic neurons in the neocortex are FS cells. Some aspiny nonpyramidal cells in early studies of rat motor cortex[99] and human neocortex[63] described interneurons with â€œlow-threshold spikesâ€ (LTSs)â€”slow, depolarizing waves produced by low-threshold Ca^{2+} currents that can trigger one or more fast Na^+-dependent spikes at high frequency. They also show marked adaptation of firing frequency (Fig. 5B, *top*), and have wider action potentials than do FS cells (Fig. 5C). These cells often express SOM, but rarely PV, and include Martinotti cells, double bouquet cells, and bitufted cells. Similar neurons have also been referred to as regular-spiking nonpyramidal (RSNP) cells.[101]

Neocortical interneurons include cell classes with a variety of other intrinsic spiking patterns, such as bursts or irregular Spike (Is or â€œstutteringâ€) patterns. The intrinsic spiking patterns of interneurons often correlate closely with cell morphology, synaptic properties, and gene expression.[75,170]

Synaptic Physiology of Neocortical Neurons

Excitatory and Inhibitory Chemical Synapses

The functional properties of glutamatergic and GABAergic synapses in the cerebral cortex are complex and reasonably well understood (Chapters 22, 23). Within the neocortex, the strength and dynamics of chemical synaptic connections vary widely and tend to correlate with the types of neurons involved on both the presynaptic and postsynaptic sides. Thalamocortical synapses, which are the neocortex's most important source of specific information, are exceptionally strong and reliable compared to excitatory synapses that interconnect neocortical neurons.[15,68,70] Thalamocortical connections are also subject to unusually strong short-term depression when activated at high frequencies. The strength and dynamics of the synapses that interconnect different types of pyramidal cells in the neocortex also vary, although most display short-term depression.[180]

Inhibitory interneurons, befitting their diverse morphology and physiology, have input and output synapses with a wide variety of functional properties.[118,181] The FS and LTS cells illustrate this particularly well.[15,68,146] When a presynaptic excitatory neuron fires at high frequencies (>10 Hz), the EPSPs recorded in the two types of inhibitory interneurons differ in several ways. The amplitude of the initial EPSPs is relatively large and reliable in FS cells, and substantially smaller and less

reliable in LTS cells. Subsequent EPSPs are strongly depressed in FS cells but they facilitate powerfully in LTS neurons, particularly above about 20 Hz. This suggests that FS cells are ideal for responding precisely and reliably to transient neural activity. In contrast, LTS cells are not particularly responsive to brief increases in excitatory activity, but they would become strongly engaged by the sort of rapid, ongoing excitatory drive that might occur during seizure activity.

Electrical Synapses

In addition to chemical synapses, which communicate via diffusible neurotransmitters, neurons can also be connected by electrical synapses, which allow the direct flow of ionic current from one cell to the next. The substrates for electrical synapses are gap junctions: tight clusters of transcellular channels that are permeable to most physiologically relevant inorganic ions as well as to many small organic molecules (generally â‰¤1 kDa).[18]

Communication across gap junctions differs from chemical transmission in several ways. First, electrical synapses tend to be faster than chemical synapses. However, because of the capacitance of surrounding membranes, gap junctions act as low-pass filters and limit the rate at which signals can be transmitted.[67,68] Second, electrical synapses are bidirectional. The gap junction channels that interconnect neurons in the mammalian brain are essentially linear conductors, so current can flow between cells in either direction in response to voltage gradients across the gap junction.[48,69] Thus, electrical synapses can communicate signals that either depolarize or hyperpolarize neurons. Third, unlike chemical synapses in the neocortex, electrical synapses can transmit subthreshold voltage changes; electrically coupled cells can influence one another without firing action potentials.

In the relatively mature neocortex, the vast majority of electrical synapses interconnect inhibitory interneurons.[51,67,68] Remarkably, most electrical synapses appear to form selectively between interneurons of the same subtype, and only rarely between interneurons of different subtypes. This specificity of gap junctional connections reinforces the notion that there are functionally distinct subclasses of interneurons in the neocortex.[48,82] The subtypes of interneurons that form electrical synapses primarily with homologous inhibitory cells include FS cells,[67,68] LTS cells,[15,68] cannabinoid receptor subtype 1 (CB_1-IS-CCK) neurons,[66] multipolar bursting cells,[23] and late-spiking cells of layer I.[36] The specificity of interneuron gap junctions is not perfect; some electrical synapses have been described between heterologous types of inhibitory interneu-rons.[68,159] Electrical synapses are strongest between cells whose somata are within 75 to 100 Âµm of one another,[6,14,67] although dendritic gap junctions may be several hundred Âµm from a cell's soma.[64] It is estimated that one inhibitory interneuron is electrically connected to 20 to 50 others via gap junctions.[6]

Electrical synapses have not been observed between pyramidal neurons of the mature neocortex, although there is strong evidence that gap junctions interconnect pyramidal cells of the embryonic and early postnatal neocortex.[45,113,139] The functions of neuronal gap junctions during early development are unknown, although they may help to coordinate neurogenesis, differentiation, and the specification of chemical synaptic connections.[126]

Most gap junction channels in vertebrates are comprised of two hexameric hemichannels made of subunits called connexins. There are about 20 connexin isoforms. Although about half of them are expressed in the mammalian brain, only connexin36 (Cx36) has been consistently demonstrated to be an essential component of neuron-to-neuron gap junctions.[16,54,85,186] Additional gap junction proteins, in particular connexin45 and pannexins1 and 2, may also be expressed by central neurons,[26,136] but so far, no evidence suggests that they are important for electrical synapses.

Seizures of Neocortex: neurons, circuits, and architecture

Studies of seizures informed some of the earliest speculations about the functions of the neocortex. The insights of John Hughlings Jackson[177] were particularly notable. Jackson used astute clinical observations of seizures, postmortem examination of epileptic brains, and imaginative deduction to infer the locale of some motor and sensory functions in the cerebral cortex. Seizures have continued to tell us about the cortex, but there is also an urgent need to use knowledge about the cortex to enlighten our understanding of seizures. What follows is a brief survey of experimental and clinical findings that highlight links between neocortical biology and the pathology of epilepsy.

Neuronal Triggers of Seizures

Ironically, some of the characteristics of neocortical seizures that make them so devastating clinically have also made them a popular subject of experiments: Seizures are readily induced by various means, their electrical correlates are large and easily measured, and neocortical activity during seizures is very simple, compared to activity during normal functions. Detailed studies of experimental animal models of partial seizures have suggested numerous hypotheses of neocortical seizure generation.[10,58,92,144] This section focuses on one explicit proposal for the cellular origins of seizure initiation and propagation.[43]

During a seizure, the neocortex generates hypersynchronous activity that may encompass almost every neuron across a wide area. Where does the trigger for these synchronous events arise? How does that trigger spread to engulf the activity of other neurons? How does a very localized seizure propagate into adjacent areas and beyond? One simple way to induce seizures is to reduce the level of synaptic inhibition. Experiments on slices of rodent neocortex in vitro have provided a variety of evidence that certain pyramidal neurons in layer V may act as both the initiators and propagators of hypersynchronous activity. Seizure-like activity is readily induced when synaptic inhibition is depressed by applying antagonists of $GABA_A$ receptors. Even a modest reduction of inhibition, perhaps by 20%, leads to sharply synchronized, often rhythmic activity that can propagate for many millimeters across a cortical slice.[33] Under these conditions, synchronized activity is labile, changing its shape from trial to trial. When $GABA_A$ receptors are more strongly blocked, synchronized events are more stereotyped, often spontaneous, and propagate unimpeded across the cortex.[35,41,74,76,78,143] In each case, layer V is implicated as the initiation site for synchronized activity. If inhibition is eliminated, it is in layer V that epileptiform currents first appear during each event. Layers IV and V are the most sensitive to $GABA_A$ antagonistsâ€"they have the lowest threshold for event initiation, and synchronous events can be most easily blocked there by applying GABA itself.[41] With GABAergic inhibition only slightly reduced, the IB neurons of layer V are the only class of pyramidal cells that consistently generate synchronized excitatory events and spike firing; other pyramidal cells tend to be synchronously inhibited and only weakly excited.[33]

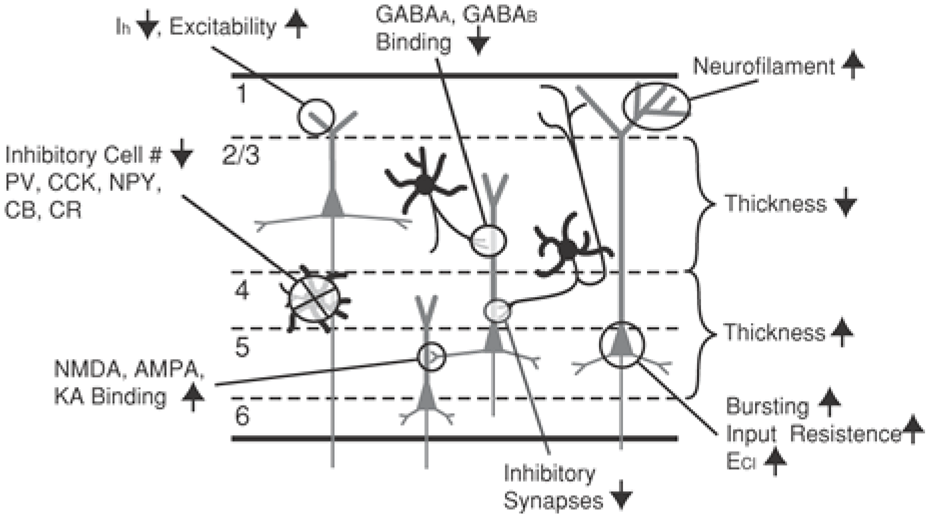

FIGURE 6. Seizure activity has been associated with a wide variety of changes in cortical cells and circuits. A summary of many of these changes are shown here. There is a general increase in excitatory tone due to increases in glutamatergic connections or due to increases in excitability of some pyramidal cells. Also observed is a decrease in inhibitory tone from cell and synapse loss as well as from changes in GABAergic function related to an increase in E_{Cl^-}. Each of these changes may or may not occur in seizing tissue depending on the epilepsy model, as described in detail in the main text.

Moreover, when slices are further dissected with horizontal cuts and bathed in low doses of $GABA_A$ antagonists, those microslices containing layer V (but not other layers) are able to support both the initiation and propagation of synchrony.[178,179] Small injections of convulsant drugs into neocortex in vivo are most effective at producing epileptiform activity when they are placed in the vicinity of layer IV.[60,84]

Synchronous activity can also be generated by boosting synaptic excitation. For example, the function of one type of glutamate receptor, the *N*-methyl-D-aspartate (NMDA) receptor, is facilitated by lowering the magnesium ion [Mg^{2+}] in the bathing solution. This reduces the voltage dependence of the NMDA receptorâ€"operated channel[134] and, in the neocortex, leads to spontaneous, highly synchronous events that occur in rhythmic epochs with 4- to 7-Hz discharges.[158,171] In horizontally dissected slices in low [Mg^{2+}], a small fragment of layer V is all that is necessary to generate the same type of rhythmic synchrony as the intact slice.[62,158] Microslices without layer V resemble intact control slices and are incapable of supporting rhythmic, synchronous activity.

Once synchronous events are initiated locally by neurons of layer V, they may propagate both vertically into other layers and horizontally into adjacent cortex.[32,35] During moderate disinhibition, the pathway of preference for horizontal movement is within layer V.[178] When inhibition is strongly suppressed, alternative pathways can be found either above or below layer V after removal of layer V. However, it is likely that the pathway through layer V remains the primary mediator of horizontal movement when the cortex is intact.[179] Layer V is also implicated in other forms of cortical synchrony, including chronic models of epilepsy (see later discussion).

Novel electrical stimulationâ€"based techniques that target the excitation thresholds of layer V pyramidal cells may prove to be an effective method of seizure control. Electric field modulation of neuronal excitability has been shown to successfully slow and even halt propagating neocortical epileptiform activity in acute preparations.[147]

In summary, layer V has neurons with the appropriate intrinsic membrane properties, intralaminar connections, neurotransmitter systems, and axonal outputs to generate highly synchronized activity and to impose it on the other neurons of the cortex. It may not be the sole synchronizing network in the cortex, but it is a major one. We do not know which properties of layer V are most responsible for its capabilities. A case can be made that intrinsically bursting neurons are likely instigators of synchrony: They are prevalent in layer V, they are exceptionally excitable, and they have the requisite local connections.[32,41,76,158] However, bursting may be only part of the answer or none of it. Unusually strong or dense interconnections between bursting cells, relatively weak inhibition, a unique complement of neurotransmitter receptors, or especially excitable dendrites could be more important. It is likely that several characteristics conspire to make layer V a uniquely excitable network in neocortex.

Seizure-Related Alterations of Neocortical Circuits

Seizure disorders have many causes. Sometimes a clear genetic basis is present (see Chapters 17, 18 and 37). Many developmental anomalies are accompanied by severe epilepsy (see Chapters 14 and 259).[3,189] Neocortical insults from tumors, trauma, stroke, and infection are also common instigators (see Section X, Epilepsy Syndromes). The origins of most seizure disorders undoubtedly lie in abnormalities of the basic biology of the cerebral cortex. Unfortunately, the large majority of human seizure syndromes cannot yet be described in cellular or molecular terms, and many cannot be described in any terms beyond their signs and symptoms.

While it has been possible to examine epileptogenic tissue resected from epileptic human patients, recording from normal, relevant control tissue for comparison is rarely feasible. Various chronic animal models of different epilepsies have therefore been developed to examine the differences between normal and epileptogenic tissue (Chapters 36,37,38,39). In general, hyperexcitable or epileptogenic neural tissue from both animal models and human epilepsy patients have demonstrable abnormalities of structure and function. These involve growth of dendritic or axonal arbors, changes in synaptic densities or transmitter receptor numbers, and either increases or decreases in specific types of neurons (Fig. 6). We highlight here a few studies of the changes in anatomy and physiology that are associated with seizure-like activity and hyperexcitability in neocortex.

Network Changes After Status Epilepticus

Malformations of cortical architecture following seizures tend to be layer-specific. For example, in the pilocarpine model of human temporal lobe epilepsy (TLE) a severe episode of status epilepticus (SE) is induced through the systemic injection of the acetylcholenergic agonist pilocarpine. Weeks after this major seizure event, spontaneous seizures begin to occur. In adult rats subjected to this protocol, the thickness of cortical layers II and III decreases, whereas the thickness of layers V and VI increases, resulting in overall neocortical atrophy.[152] More specifically, neurofilament protein increases, indicating especially increased dendritic arborization of layer V pyramidal cells into layer I. Studies of postseizure sensorimotor cortex show an overall reduction of both PV-type inhibitory interneurons specifically, and GABAergic neurons (indicated by GAD65 staining) in general.[157]

When SE is induced in relatively young animals, the resulting architectural alterations are surprisingly different from those that occur in more mature brains. PV and GAD65 immunoreactivity actually increase in layer IV of young brains, in contrast to mature brains, whereas neurofilament protein increases in tissue of both ages. Calbindin staining (which was not investigated in the adult study) is reduced after seizures, whereas calretinin staining is similar to that of control tissue.[52] These results suggest that specific subtypes of interneurons are differentially affected by seizure activity. Considering the inherent differences in the inhibitory functions of interneuron subtypes (see earlier discussion), this implies that the dynamic balance of inhibition may be altered by prior seizure experience.

Circuit Modifications in Cortical Dysplasia

Experimental models that mimic human developmental anomalies display changes in neocortical architecture and connectivity in and around the focal lesion. The agent methyl-azoxymethanol (MAM) damages dividing and migrating cells. When injected into a pregnant rat, MAM affects the neural development of gestating pups. Results from studies of MAM-induced epilepsy reveal that different types of neocortical interneurons, expressing different neuropeptide markers, are differentially affected. Neurons that express the neuropeptides SOM and VIP are apparently spared, whereas neurons that express CCK and NPY are decreased in cortical regions.[30,197] It is apparent, as in the SE, that subtypes of interneurons are differentially sensitive to MAM treatment. The exact impact of these changes on seizure dynamics is, however, unknown.

Layered microgyria can be created in rodents by inducing focal cell death with a freeze lesion during early development and neural migration.[89] In this model of cortical dysplasia, the density of inhibitory $GABA_B$ receptors is reduced in the lesioned region only, whereas excitatory NMDA receptors increase in the lesioned area and Î±-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) and kainate receptors increase within the lesion and in surrounding cortex as well[196] Jacobs et al.[89] found that PV-expressing interneurons are reduced in lesioned cortex and in layers IV and V of neighboring cortex. The levels of PV-expressing cells eventually return to control levels within the lesion, but in the paramicrogyrial region, these cells are permanently deficient.[149] Somatostatin-expressing interneurons are also reduced around the lesioned area.[138] Electrophysiologic studies indicate that epileptiform activity is more likely to be generated from cells in the paramicrogyrial region than within the lesion focus.[89] The enhanced excitability of the surrounding region may be due to an increased density of functional synapses, both inhibitory and excitatory, on layer V pyramidal cells.[90]

Intrinsic Excitability in Neocortical Epilepsies

Alterations of the intrinsic excitability of neurons can be both a cause and a consequence of seizures. Layer V pyramidal neurons from rats that have experienced chronic pilocarpine seizures show increased excitability.[152] In neocortex that has been chronically isolated from surrounding tissue, the excitability of axotomized layer V pyramidal cells is also enhanced compared to controls.[145] The mechanisms controlling the intrinsic properties of neurons after seizures are poorly understood. Neuronal excitability depends on a large variety of membrane mechanisms. One of them is the ion channel that mediates the hyperpolarization-activated cation current (I_h), which is carried by Na^+ and K^+. When activated, I_h tends to depolarize a neuron and reduce input resistance. The strength of I_h changes in several chronic seizure models. In the kainate model of TLE (which resembles the pilocarpine model), pyramidal cells in layer III of entorhinal cortex show strong and persistently reduced I_h after a single seizure. The resulting increase of dendritic input resistance leads to enhanced sensitivity to synaptic inputs.[156]

The WAG/Rij rat is genetically predisposed to absence epilepsy. Pyramidal neurons in layer II/III of these animals have abnormally low HCN1 protein, one type of I_h channel subunit.[166] This apparently leads to higher input resistances, longer-lasting EPSPs, and increased summation of synaptic inputs. Neurons also tend to show more intrinsic bursting behavior. It is possible that a deficit in I_h is responsible for seizure generation in these rats. Chronic imbalances of I_h in other parts of the brain, including the thalamus,[27,108] hippocampus, and subiculum, may also contribute to seizure-related activity.[19]

A variety of other types of ion channels has been associated with changes in intrinsic excitability following seizures,[123] including A-type K^+ channels,[19] and Ni^{2+} sensitive T-type Ca^{2+} channels.[169,193] Mutations of genes encoding voltage-gated Na^+ and other channels are the basis for several forms of epileptic phenotypes.[133]

GABA as an Excitatory Neurotransmitter

The inhibitory action of GABA is crucial for maintaining the balance of excitation and inhibition in the brain. A primary mechanism of GABAergic function is the opening of Cl^- channels following activation of $GABA_A$ receptors. The reversal potential of Cl^- is generally at or negative to resting membrane potential, so that activation of $GABA_A$ receptors usually results in an outward current that opposes excitatory influences. Shifting E_{Cl} positively can, however, render GABA excitatory, as it sometimes is early in normal brain development.[17] One of the important regulators of intracellular $[Cl^-]$ is the potassium-chloride cotransporter, KCC2, which is impaired in some animal models of epilepsy. For example, excitatory actions of GABA in the secondary focus of a unilateral pilocarpine-induced epileptic hippocampus may be related to progressive KCC2 malfunction.[105] In the chronically isolated neocortex, E_{Cl} of resting neurons is not affected, however a deficiency in the KCC2 transporter slows the extrusion of Cl^- following prolonged GABAergic activation.[93]

Studies of human epileptic hippocampus also indicate that Cl^- regulation is disrupted. In a subset of pyramidal neurons in the subiculum, E_{Cl} appears to be more positive than the resting potential, and synchronous epileptiform discharges can be blocked with the $GABA_A$ antagonists bicuculline and picrotoxin.[38]

Do Gap Junctions Play a Role in Neocortical Seizures?

Electrical synapses are a particularly effective mechanism for synchronizing neurons.[48] As described earlier, electrical synapses extensively interconnect the inhibitory interneurons of the neocortex. It stands to reason that the hypersynchronization associated with seizure activity might be facilitated by interneuronal gap junctions. It is also plausible to suggest that gap junctionâ€“mediated synchronization of inhibition would actually tend to suppress seizures.[132] Recent human genetic evidence suggests that mutations of the Cx36 gene are associated with a form of juvenile myoclonic epilepsy.[79,120] A variety of experimental studies have addressed the potential role of gap junctions in epilepsy; however, it is still unclear whether electrical synapses help or hinder seizures.

Dye-coupling is used as an indirect assay of gap junction connections. Increases in neuronal dye-coupling have been

observed in both acute (zero extracellular $[Ca^{2+}]$) and chronic (tetanus toxin injections) models of hippocampal seizures.[39,140] The interpretation of these studies is problematic because of the capricious nature of the dye-coupling technique when applied to brain slices.[48] Gap junction-blocking drugs such as heptanol, octanol, halothane, and carbenoxolone,[20,59,65,107,135,175] and manipulations of intracellular pH,[150,163] influence epileptiform bursting in both acute and chronic seizure models.[91,154,182] Unfortunately, both the drugs and pH manipulations are nonspecific,[151] so that it is not clear whether their effects on seizures were mediated by changes in gap junction function.

Mice with a null mutation for the neuronal gap junction protein Cx36 lack electrical synapses between interneurons in neocortex and hippocampus.[54,85] These animals do not have an obvious seizure disorder, although their susceptibility to seizure-inducing stimuli has not been tested. Application of the convulsant drug fampridine (4-AP) to hippocampal slices of Cx36 knockout mice yields fewer long-duration epileptiform discharges but more occasions of burst-like activity compared with wild-type mice.[117]

Chronic seizures induced by kainate treatment or kindling of the hippocampus lead to downregulation of Cx36 mRNA, although there are no clear changes in Cx36 protein levels.[40,161] In the 4-AP seizure model, however, Cx36 mRNA is upregulated along with Cx32 and Cx43, two glial gap junction proteins.[65]

Unfortunately, the importance of electrical synapses for epilepsy remains ambiguous.

Summary and Conclusions

Although the neocortex is responsible for the most complex of animal behaviors, its cellular and molecular composition is not remarkable. The enzymes, neurotransmitters, and ion channels of the neocortex are widely expressed elsewhere in the brain, and neocortical neurons and synapses are modest variations on common structures. The uniqueness of the neocortex probably derives from its elaborate interconnections and their capacity to dynamically organize, associate, and modify myriad streams of neural information.

Interconnectedness may also explain why the neocortex so readily becomes epileptogenic. Reciprocal excitatory connections, normally essential to link widely dispersed but interrelated neurons, can also mediate abnormally synchronous and spatially rampant seizure activity. Many forces goad the cortex from normal to epileptiform activity. At a broad level, these include alterations in neural and synaptic excitability, metabolic aberrations, reduced synaptic inhibition, and reordering of interconnections themselves. At a more detailed level, there may be abnormalities of the modulation or expression of channels, receptors, and enzymes.

It is clear that seizure disorders have many root causes. Determining causality for clinical seizures is complicated by the intertwined and nested nature of cortical networks and their strongly interdependent structural, electrical, and biochemical components. A deep understanding of human seizures will require a comprehensive understanding of basic neocortical biology.

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Chapter 30

Limbic Anatomy and Physiology

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Introduction

The concept of a â€œlimbic lobeâ€ was first put forth by Broca[27] as a means of labeling the various structures that surround the brainstem and form the border of the ventricular system. Broca was responsible also for the view of these structures as primarily olfactory in function (a major input from olfactory lobes)â€"i.e., as a â€œsmell brainâ€ (rhinencephalon). Based on anatomic grounds, Papez[182] proposed the existence of a network of limbic structuresâ€"including the hypothalamus, anterior thalamus, cingulate cortex, and hippocampusâ€"that was responsible for emotional behavior. The amygdala was not included in the initial description of the Papez circuit, but Maclean[139] subsequently expanded Papez's view of the anatomy of emotion to include the amygdala and several parahippocampal structures; he called this expanded network the *limbic system*. Although both Papez and Maclean viewed the hippocampus as central to the limbic system concept of emotion, we now know that emotional behavior is more strongly supported by the amygdala.[151,201,271] In contrast, the central position of the hippocampus in the limbic system has more recently focused on its role in memory[61,228,229,247] and its contributions to temporal lobe epilepsy (TLE).[74]

Of the various epileptic disorders seen in humans, the most frequently observed are those of temporal-lobe origin.[62] Considering the pathogenesis of the temporal lobe seizures, one often (but not always) finds a sclerotic lesion in one or more of the limbic or mesial temporal structures (see Chapter 13). These mesial structures form part of an olfactoryâ€"neocortical network that involves the hippocampus; the entorhinal, perirhinal, and piriform cortices; and the amygdala. The cells contained within these structures have both intrinsic properties and local connections that, when sufficiently provoked, can provide strong recurrent excitation that leads to robust seizure activity. The strong communication between these structures can amplify the seizure event and recruit cells with efferent connections that distribute widely throughout the brain. It is of little surprise, therefore, that discrete electrical stimulation in several of these same mesial structures can reproduce, in an epileptic patient, many of the features of the patient's automatism,[259] and that surgical resection of the structures can provide relief from the seizures.[63] With this evidence in mind, we briefly review both anatomic and physiologic features of the hippocampus, entorhinal cortex, perirhinal and piriform cortices, and amygdala. A description of the normal structure and function of these â€œlimbicâ€/mesial temporal structures is critical for our understanding of their roles in the development, study,[126] and expression of TLE.[73]

The Hippocampal Formation

The hippocampal formation has attracted considerable attention during the recent explosion of interest in cellular and synaptic neuroscience.[215,218] Its attraction as a focus for research stems from several considerations: (a) It is a region of the brain implicated in a number of important (and interesting) â€œnormalâ€ behaviors, such as learning and memory; (b) both functionally and structurally, the hippocampus shows an unusual degree of neuronal â€œplasticityâ€[129,172,214]; (c) it has been implicated as a focus of pathology in a number of neurologic disorders ranging from epilepsy to global ischemia,[24] Alzheimer disease,[161] traumatic head injury,[261] to psychiatric disorders[38]; (d) its unique, laminated structure has made it particularly conducive to study using in vitro brain slice preparations, an approach that has been adopted by many laboratories; (e) it can be viewed as a somewhat simplified cortex; and (f) it is richly connected to other parts of the limbic system (Fig. 1). The archicortical hippocampal circuitry has served as a â€œmodelâ€ for the more complex neocortex, and the hippocampal pyramidal cell has been studied and characterized as a model central nervous system (CNS) neuron. Given the interest and activity of so many investigators, a large store of information is available about hippocampal cell properties, structure, afferents and efferents, receptors and transmitters, and local circuits. This chapter deals primarily with major points of organization and function that have potential implications for our understanding of epilepsy-related phenomena.

Regional Connectivity

The hippocampal formation is conventionally divided into four major cell regions: Subiculum, cornu ammonis regio superior (CA1), cornu ammonis regio inferior (CA3), and the dentate gyrus (Fig. 1). Each region is defined, at least in part, by its unique patterns of input and output, as well as by the features of its principal cell population. Part of the beauty and simplicity of the hippocampus is in the early established finding that each region projects to the next through an excitatory â€œtrisynapticâ€ pathway[7] (see Fig. 1). Thus, the granule cells of the dentate gyrus send their mossy fiber axons to the CA3 region (the CA2 transition zone, by definition, receives no mossy fiber input); axon branches of the CA3 pyramidal cellsâ€"the Schaffer collateralsâ€"project to CA1; the CA1 pyramidal cells send axons to the subiculum; and the subiculum projects out of the hippocampal formation (back to entorhinal cortex as well as other cortical targets). Recent studies have suggested that this simple view of an intrahippocampal organization is unrealistic[7] and perhaps even misleading in our efforts to learn how information is processed through the hippocampus. We now know, for example, (a) that the mossy fibers also make numerous contacts within the dentate hilus and that they colocalize opioid peptides[152] and zinc,[68] along with glutamate; (b) that the CA3 cells project to contralateral hippocampus, as well as back into the ipsilateral dentate hilus, where they excite mossy cells and interneurons[65,127]; (c) that activity in the CA1 pyramidal region can influence activity in the CA3

pyramidal cells, perhaps through antidromic mechanisms[233]; (d) and that hilar neurons interconnect ipsilateral and contralateral dentate regions.[200] Further, although it appears that each of the major associational connections uses the excitatory neurotransmitter, glutamate, the nature of the evoked post-synaptic potentials in each region may be rather different. For example, the mossy fiber unitary excitatory postsynaptic potential (EPSP) onto CA3 pyramidal cells is very large (millivolts) and mediated primarily by non-*N*-methyl-D-aspartate (NMDA) glutamate receptors[270]; in contrast, the unitary EPSP produced by Schaffer collateral synapses onto CA1 pyramidal cells is more typical in size (about 100 ÂµV) and involves both non-NMDA and NMDA receptor components.[204] Finally, hippocampal â€œinterneuronsâ€ contribute a Î³-aminobutyric acid (GABA)ergic component to interregional, as well as local intraregional, information relay.[219] Thus, what was once thought to be a simple, serial, feed-forward intrahippocampal pathway is now known to be an elaborate series of interacting and parallel feed-forward and feedback circuits, involving not only principal cell axons but also specialized interneuronal interactions (Fig. 2).

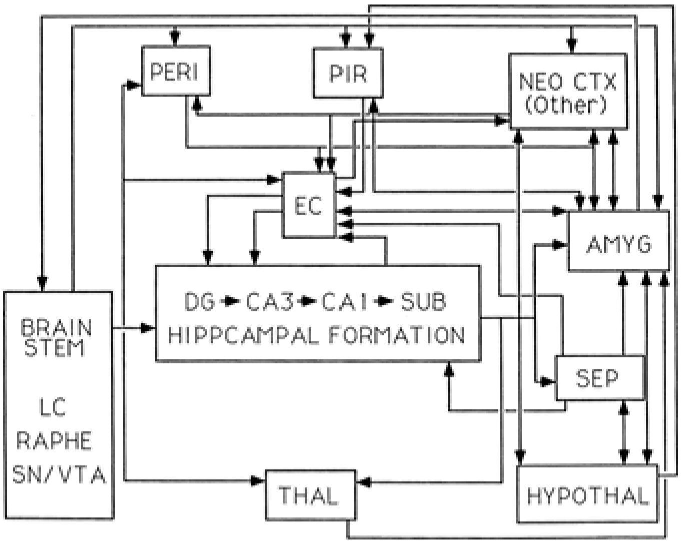
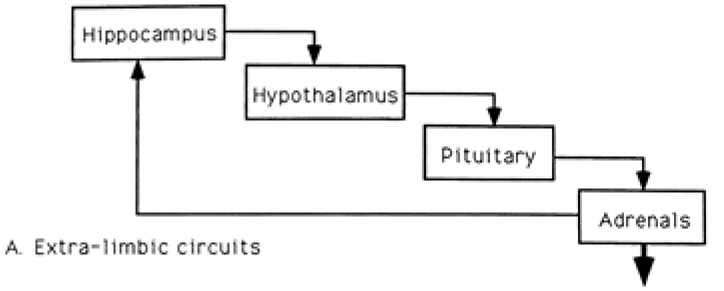
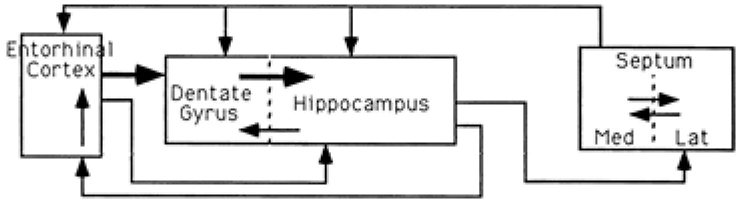

PERI
PIR
NEO CTX (Other)
EC
AMYG
DG ➞ CA3 ➞ CA1 ➞ SUB
HIPPCAMPAL FORMATION
BRAIN STEM
LC
RAPHE
SN/VTA
SEP
THAL
HYPOTHAL

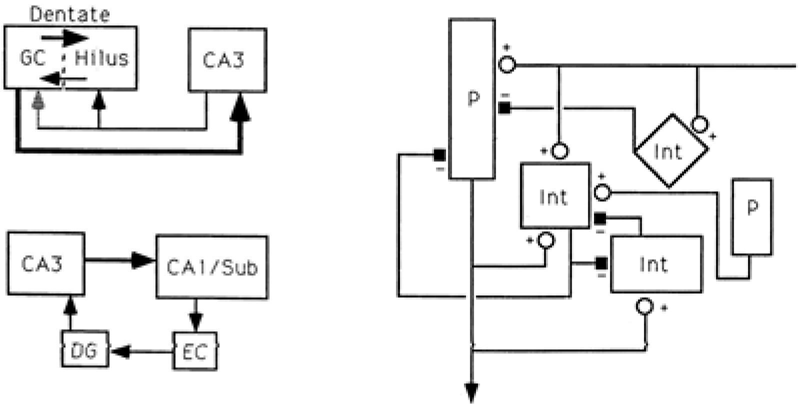
FIGURE 1. Major connections of the limbic system. Diagram of the major interconnections among principal limbic system structures, in particular, those regions described in the current review. EC, hippocampal formation, entorhinal cortex; PERI, perirhinal cortex; PIR, piriform cortex; AMYG, amygdala. Their connections are shown with: NEO CTX, neocortex (with no specification of cortical region); SEP, septum; HYPOTHAL, hypothalamus; THAL, thalamus; and brainstem structures LC, locus ceruleus; raphe; and SN/VTA, substantia nigra/ventral tegmental area.



A. Extra-limbic circuits



B. Intra-limbic circuits



C. Intra-hippocampal circuits D. Local circuits - cellular level

FIGURE 2. Feed-forward and feedback circuits. The limbic system (and its components) is entwined in a large number of feedback control circuits from interregional to local cellular levels. **A:** Hippocampal modulation of the hypothalamic-pituitary-adrenal (HPA) axis via adrenal steroid influences on hippocampal neurons. Hippocampal projections to hypothalamus help to regulate release of corticotropin-releasing hormone (CRH); hypothalamic release of CRH controls pituitary output of adrenocorticotropic hormone (ACTH); ACTH acts on the adrenal glands to stimulate secretion of cortisol. Because hippocampus has a high density of adrenal steroid receptors, the level of circulating cortisol modulates hippocampal output. **B:** Feed-forward and feedback circuits among limbic system regions. The well-studied feed-forward circuit from entorhinal cortex to dentate gyrus (DG), from DG to hippocampus proper and from hippocampus to septum is regulated by a number of feedback steps, including: (a) hippocampal projections â€œbackâ€ to the dentate gyrus; (b) septal projections to the hippocampus, dentate gyrus, and entorhinal cortex; and (c) hippocampal projections to the entorhinal cortex. **C:** Feedback circuits that modulate â€œserialâ€ processing within the hippocampus. Granule cell output to the hilus and CA3 is modulated by CA3 feedback to hilar neurons (and perhaps directly to the granule cells) and by hilar feedback from mossy cells and interneurons to the granule cells. **D:** Local feedback control within a given area of hippocampus. The principal cell (*P*) (e.g., the granule cell or the pyramidal cell) receives excitatory afferent input and sends an excitatory output, not only to the next principal cell region, but also to local inhibitory cells (*Int*). Local interneurons provide inhibitory feedback onto the principal cell and onto other inhibitory interneurons in the region.

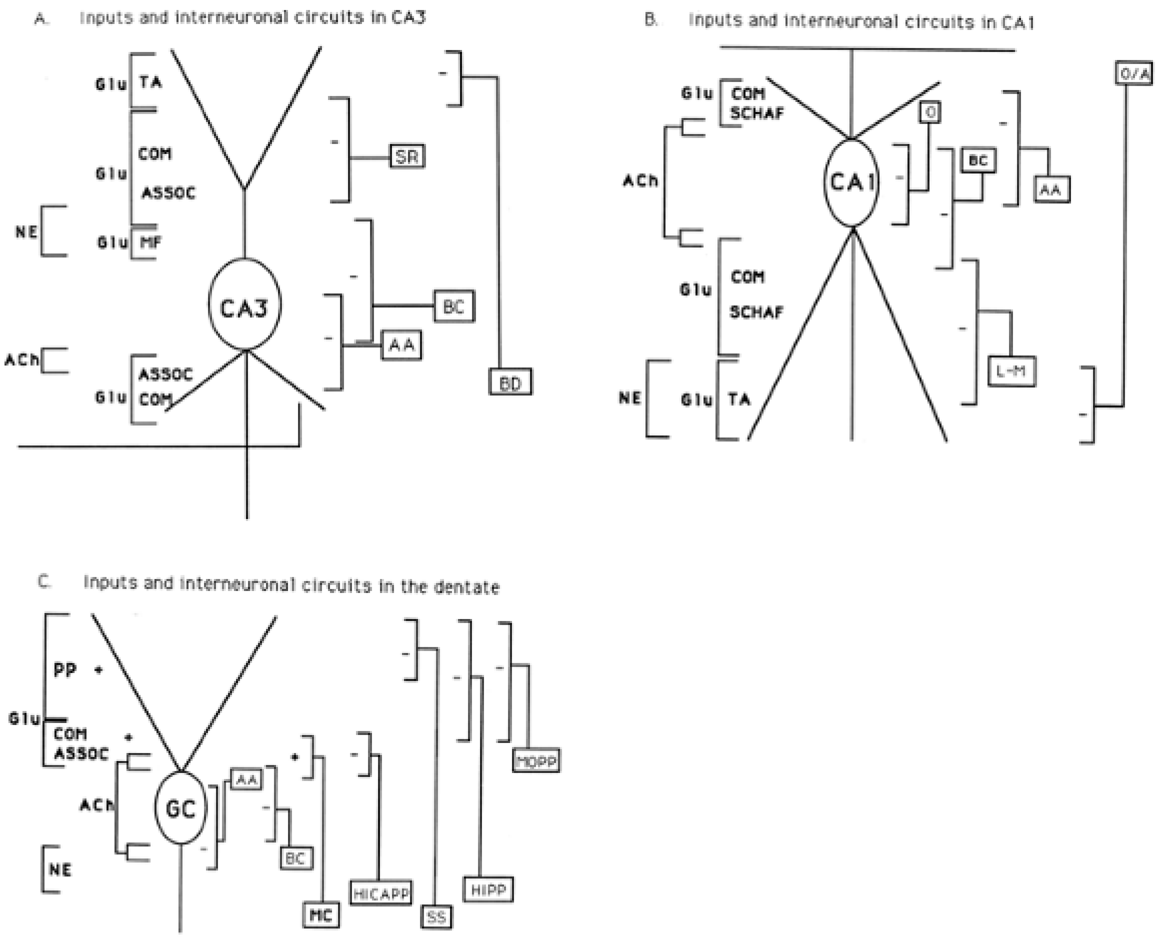

A. Inputs and interneuronal circuits in CA3
Glu TA
Glu COM ASSOC
NE
Glu MF
CA3
ACh
Glu ASSOC COM
SR
BC
AA
BD
B. Inputs and interneuronal circuits in CA1
O/A
Glu COM SCHAF
O
ACh
CA1
BC
AA
Glu COM SCHAF
L-M
NE
Glu TA
C. Inputs and interneuronal circuits in the dentate
PP +
Glu
COM ASSOC +
ACh
GC
AA
BC
NE
MC
HICAPP
SS
HIPP
MOPP

FIGURE 3. Laminar organization of hippocampal subregions. Schematic diagrams on local inhibitory interneurons and various afferent inputs (with associated transmitter type) in the CA3 region (**A**), the CA1 region (**B**), and the dentate/granule cell region (**C**). **A:** In CA3, the temporal ammonic (*TA*), commissural (*COM*), associational (*ASSOC*), and mossy fiber (*MF*) afferents all make excitatory glutamatergic (*Glu*) synapses on pyramidal cell dendrites (both apical and basal). Other inputs (e.g., from the septum and locus ceruleus) use other neurotransmitters (acetylcholine [*Ach*] and norepinephrine [NE]). Locally, inhibitory interneurons (stratum radiatum [SR] cells, basal dendritic [BD] cells, basket cells [BC], and axo-axonic [AA] cells) elaborate axons targeted to particular layers. **B:** A similar organization can be seen in CA1 with respect to both afferent inputs and to local inhibitory cell types (oriens alveus [A], oriens [O], basket cells [BC], axo-axonic [AA], and lacunosum-moleculare [L-M]); as seen in the CA3, these interneurons send axon terminals to different layers of CA1, where they make inhibitory (GABAergic) synaptic contacts. **C:** In the dentate, the perforant path (PP) input from entorhinal cortex contributes excitatory glutamatergic drive onto the granule cells. The local inhibitory cell types in the dentate include axo-axonics (AA), basket cells (BC), hilar cells of different types (HICAP, hilar cell with axon in the commissural/associational pathway; HIPP, hilar cell with axon in the perforant pathway; and SS, hilar somatostatin cell with axon in the distal dendritic layer), as well as interneurons with both soma and axon in stratum moleculare (e.g., MOPP, moleculare cell with axon in the perforant pathway). In addition, mossy cells (MC) of the hilus constitute the excitatory commissural/associational input to the dentate granule cells.

Afferents (Inputs)

Cortical Afferents

The major cortical input to the hippocampal formation arises in layer II pyramidal cells of the entorhinal cortex (EC), projects through the angular bundle pathway, and enters the ipsilateral dentate gyrus via the perforant pathway.[94,235] This excitatory input terminates largely on spines on the distal dendrites of granule cells (and on interneurons) in the outer two thirds of the dentate molecular layer (Fig. 3). The entorhinal input has been subdivided into two divisions, with fibers originating in the medial EC synapsing in the middle third of the molecular layer and fibers from the lateral EC synapsing in the outer third. Investigators continue to explore differential features of these subdivisions, some of which may be relevant to dentate seizure susceptibility. For example, the medial division is glutamatergic and evokes EPSPs with both NMDA and non-NMDA components; in the lateral division, opioid-dependent long-term potentiation[26] is supported by anatomically defined colocalization of glutamate and enkephalin, with the latter â€œtransmitterâ€ affecting regional interneurons (inhibition via Âµ- and Î´-receptors) to mediate disinhibition of granule cells[269]â€"a perhaps critical step in dentate seizure genesis.

Anatomic studies of the EC projection to the hippocampal formation have also identified an input to hippocampus proper.

This temporoammonic pathway arises in layer III cells of EC but separates from the perforant pathway to contact the most distal branches of pyramidal cells in the stratum lacunosum-moleculare of CA1 to CA3.[264] Although clearly excitatory (i.e., glutamatergic), the functional nature of this pathway has been questioned because its influence on pyramidal cell discharge has been difficult to demonstrate.[225] Recent experiments suggest that temporoammonic modulation of pyramidal cells is significant, and that this input may also differentially activate an interneuron subpopulation located in these distal reaches of the apical dendritic region (see Fig. 3).[123] It is worthwhile to note that the direction of input to cornu ammonis via this entorhinal input is opposite to that of the associational input via the major trisynaptic pathways; thus, pyramidal cell excitation and processing cannot be viewed as a one-way serial influence. The function of this pathway remains unclear but appears to provide a frequency-dependent modulatory action from the entorhinal cortex directly onto hippocampal pyramidal cells.[107]

Subcortical Afferents

A variety of subcortical fiber inputs innervate the hippocampal formation, some in very specific laminar patterns and others in a more diffuse pattern (see Fig. 3). The major subcortical projections include:

The *septohippocampal* input arises in the medial septal nucleus and diagonal band of Broca and enters the hippocampus via the fimbria/fornix.[268] This input provides the hippocampal formation with the vast majority of its acetylcholine (ACh)[131] and comprises a subcomponent of the basal forebrain cholinergic projection to cortex that has been implicated in learning and cognitive function. However, it is now very clear that this input consists of both cholinergic and GABAergic components[6]; septohippocampal lesion experiments, designed to deprive hippocampus of its ACh supply, must be carefully interpreted in light of damage to both GABAergic *and* cholinergic inputs. Acetylcholinesterase staining, which disappears almost entirely with septal lesions or with fimbria/fornix transection, shows a discrete pattern of staining in all regions of hippocampus, with a concentration in thin supra- and subcellular regions (Fig. 3). Interestingly, recent studies suggest that some interneuron subpopulations are extremely sensitive to ACh[197] and may be excited at much lower thresholds than are the principal cells. This possibility is intriguing, inasmuch as at least one form of hippocampal Î¸-activityâ€"the slow, rhythmic EEG activity that is associated with restful alertnessâ€"is mediated via cholinergic mechanisms[128] and may well depend on excitation of interneurons for synchronization of the hippocampal projection cell populations.[237] The cholinergic synaptic action in hippocampus is primarily muscarinic (blocked by atropine). The GABAergic projection from septum to hippocampus appears to have a slightly different set of targets. Although it is difficult to identify the general pattern of septal GABA fiber ramification in hippocampus (because of the large intrinsic GABA network), tracing studies have shown that septohippocampal GABA fibers preferentially synapse on GABAergic basket cells in the dentate gyrus,[69] forming a pathway for hippocampal/dentate disinhibition.

The *brainstem monoamine* pathways also provide an important, presumably modulatory, influence on hippocampal neurons. Noradrenergic fibers arising from the locus coeruleus,[135] serotonergic fibers arising from the raphe nuclei,[170] and dopaminergic fibers (although very sparse) from brainstem nuclei have been shown to ramify diffusely within all regions of hippocampus. The noradrenergic input, although generally diffuse, is most obvious in the CA3 and dentate hilar regions. However, cells in all parts of hippocampus have been shown to be sensitive to norepinephrine (NE), primarily (but not exclusively) via a Î²-adrenergic receptor mechanism[217] that leads (via cyclic adenosine monophosphate [cAMP] production) to a blockade of a hyperpolarizing potential (with loss of spike-firing adaptation) and net cell excitation.[140] Norepinephrine has been implicated in a form of long-term potentiation (LTP) in the CA3 pyramidal cell region,[97] as well as in the dentate.[232] How these noradrenergic effects on hippocampal cells are related to whole-brain hyperexcitability is unclear because lesions of the ascending noradrenergic system yield a nervous system with heightened seizure susceptibility.[153] A mouse â€œknockoutâ€ of the norepinephrine-synthesizing enzyme (dopamine Î²-hydroxylase) also shows increased seizure susceptibility.[244] In contrast to this net excitatory effect of NE in hippocampus, both serotonin 5-hydroxytryptamine (5-HT) and dopamine (DA) produce hyperpolarizing (inhibitory) responses in hippocampal pyramidal cells, mediated by G-proteinâ€"coupled mechanisms.[9,22] The role played by these potent modulators of cell excitability is yet to be well characterized. However, serotonergic fiber input, like the septal GABAergic input, has been recently traced to a specific contact with interneurons within the dentate hilus[87]; specific serotonergic effects on interneurons may well be critical in the net influence of this pathway in hippocampus. Clearly, the effects of these monoaminergic afferents in hippocampus depend on the postsynaptic receptor subtypes upon which they synapse.[10] Interneurons exhibit 5-HT3 receptors, which are colocalized with CB1 cannabinoid receptors, thus suggesting not only a specific serotonin modulation of interneurons, but also a complex interaction between 5-HT and the endocannabinoid system.[171]

Efferents (Outputs)

Cortical Projections.

The major hippocampal cortical efferents arise in the subiculum and CA1 regions and project to the lower layers of entorhinal cortex.[265] This system completes a feedback loop to the EC (through hippocampus) (see Fig. 2), because the deep cortical layers of EC then influence the output of layers II and III projection cells.[5] In addition, subicular fibers project to the perirhinal cortex, another component of the â€œparahippocampalâ€ complex. Anatomic and electrophysiologic studies show that CA1 and subiculum send axons to widespread prefrontal cortices, including the prelimbic area, cingulate cortex, medial orbital cortex, and the infralimbic areas.[102,180,258] Although the roles of these efferent projections have not yet been clearly understood, these connections are consistent with a role for parahippocampal and prefrontal cortices in cognitive processes. Further, because medial/orbital prefrontal regions have brainstem connections that modulate autonomic function, these hippocampal connections to prefrontal cortex may endow the hippocampus with a role in emotional and visceral aspects of behavior long associated with the limbic region.

Subcortical Projections.

The best studied of the subcortical hippocampal projections are the â€œreciprocalâ€ connections from CA1 and subiculum back to the septumâ€"but to the lateral, rather than medial, septal nucleus.[265] Again, because the lateral septal nucleus connects closely with the medial septal nucleus (from which hippocampal afferents arise), this projection constitutes part of still another feedback loop between the hippocampus and a related structure (see Fig. 2). The nucleus accumbens of the basal forebrain is a related projection from the same general subregions of subiculum. This structure is associated with the â€œlimbicâ€ component of the ventral basal ganglia. The subiculum also provides important connections from the hippocampal formation to the thalamus (midline nuclei), amygdala, and hypothalamus (ventromedial nucleus and mamillary body).[37,93] Although these projections â€œmake senseâ€ in terms of the old Papez circuit view of limbic system involvement in emotional and visceral behaviors, the actual role of these efferents (and of the reciprocal connections

to hippocampus, largely through septum) are still to be determined. One additional circuit of note includes the hippocampus as the component of the hypothalamic-pituitary-adrenal (HPA) axis.[76] Adrenal steroid receptor (glucocorticoid and, especially, mineralocorticoid) concentration is high in the hippocampus, and its modulation of hippocampal output may play a key role in controlling the release of corticotropin-releasing hormone (CRH) and in corticotropin release from hypothalamus (i.e., in feedback control of adrenal steroid secretion). The hippocampal efferents to hypothalamus may thus be critically involved in adrenal stress responses.[253]

Regional Characteristics

Dentate Gyrus.

The dentate gyrus is the primary target of cortical input to the hippocampal formation and consists of the granule cell region and the related dentate hilus. The granule cell region is neatly laminated,[23] with the granule cell bodies densely packed in stratum granulosum (SG) and their dendrites reaching through the stratum moleculare (SM) (see Fig. 3). The stratum moleculare is conventionally divided into thirds: The inner third is the focus of associational, commissural, and septal input; the middle third receives input from the medial EC; and the outer third receives input from the lateral EC. Partially surrounded by stratum granulosum is the hilus, home to a variety of polymorphic cells that include the excitatory (glutamatergic) mossy cells (primary source of the dentate commissural and associational connections) and inhibitory interneurons.[4] Until recently, the dentate region of hippocampus was relatively neglected by epileptologists because it appeared to have a very high threshold for seizure activity.[138] Recent studies, however, have focused more closely on this region because (a) the granule cells are relatively resistant to seizure-associated damage[224]; (b) granule cell axons show a high degree of plasticity (sprouting) in epileptic brain[42]; (c) changes in synaptic currents and voltage-dependent channels have been demonstrated in granule cells following kindling[165]; and (d) maximal activation of this region is associated with the generalization of seizure activity through the limbic system and beyond.[138] Indeed, the dentate is now sometimes considered the gatekeeper of hippocampal excitability.[91]

Granule cells are unusual because they show constant turnover throughout life, regulated in part by adrenal steroids and stress,[75] exercise,[112] and even seizures.[183] The role of newborn granule cells has been discussed with respect to behavioral function,[132] hippocampal repair,[117] and development of the epileptic state.[209] Electrical propertiesâ€"intrinsic and synapticâ€"have been extensively studied,[211,227,252] and granule cells have been found to be rather unexcitable because they maintain a very negative resting potential. Prolonged depolarization also fails to evoke rapid, repetitive firing for long periods because these cells exhibit pronounced spike firing adaptation; bursts of action potentials are followed by a large after-hyperpolarization. Activation of EC afferents to the dentate evokes a monosynaptic EPSP in granule cells; it is unclear how much of this synaptic excitation in normal hippocampus is mediated by NMDA receptors.[165] In addition, this afferent input activates a powerful inhibitory local circuit that rapidly curtails granule cell firing.[138] As elsewhere in hippocampus, at least some of the dentate interneurons are activated at a much lower threshold than are the granule cells[30]; activation of inhibitory interneurons dampens the granule cell discharge so that â€œphysiologicâ€ levels of EC input are likely to result in rather discrete and restricted dentate (i.e., granule cell spiking) output to the hilus and CA3. The granule cell axons (mossy fibers) excite hilar and CA3 neurons (both principal cells and interneurons) via glutamatergic mechanisms.[206] These cells colocalize the opioid peptide dynorphin[255] and contain a high concentration of zinc[68] in their terminals. Although the role of these colocalized substances remains controversial, evidence suggests that zinc may modulate synaptic plasticity (long-term potentiation [LTP]) at the postsynaptic cell[133]; decrease glutamate release from the presynaptic terminal,[12] and even affect GABA receptors in epileptogenic circuits.[49,169] Further, it has recently been shown that granule cells/mossy fibers also contain and release GABAâ€"an observation that has obvious implications for â€œexcitatoryâ€ neurotransmission in the adult hippocampus and also for hippocampal development in the immature brain.[80]

In addition to the granule cells, the other â€œprojectionâ€ cell type in the dentate is the hilar mossy cell, which sends its axons into the inner SM, both ipsi- and contralaterally, to make excitatory connections on granule cell dendrites. These cells receive their primary input from granule cells (another feedback circuit) (see Fig. 2), although some mossy cells have dendrites that reach into the SM to receive EC input directly.[205]

Interestingly, mossy cells are among the most vulnerable cell types in the hippocampal formation, and their death is thought to trigger the granule cell axon sprouting response into the inner SM, often seen in epileptic hippocampus.[42] It has also been hypothesized that mossy cell damage, by removing a tonic source of excitation to inhibitory interneurons, gives rise to disinhibition of the granule cells.[222] Recordings from mossy cells show them to receive a constant â€œspontaneousâ€ stream of large, non-NMDA EPSPs[206] from granule cell mossy fiber terminals that require minimal summation to trigger action potential discharge; thus, it is not surprising that mossy cells have a very low threshold for discharge and may fire in bursts of action potentials when the summed EPSP is very large.[32] Recent studies have shown that mossy cells also receive input from CA3 projecting back into the hilus.[207] Finally, it is of interest that these cells have none of the calcium binding proteins common in other hippocampal cell types (granule cells contain calbindin). It is thought that inadequate intracellular calcium buffering may contribute to mossy cell vulnerability, a possibility supported by the finding that the injection of an intracellular chelator will save these neurons from potentially toxic levels of excitation[210] and the apparent resistance to injury of calretinin-containing mossy cells in the mouse and the gerbil.[71,118]

Local circuits in the dentate, once thought to be restricted to the relatively simple feedback loop between inhibitory basket cells and granule cells, are shown to be very complex (see Fig. 3). In addition to five subtypes of dentate basket cells,[199] the dentate contains a myriad of other GABAergic interneurons. Each subpopulation appears to have a specific dendritic and axonal arborization pattern,[89] and some colocalize (with GABA) peptide neurotransmitters. For example, the somatostatin-containing interneurons in the hilus send their axons into the outer molecular layer to interact with distal granule cell dendrites and with the incoming lateral perforant path fibers.[130] Although the role played by these interneurons is not yet clear, their mode of termination (and data regarding mechanism of action of somatostatin) suggests that they may have a presynaptic inhibitory function in relation to the perforant path input. Chandelier cells, a unique interneuron cell type, make exclusiveâ€"and apparently powerfulâ€"inhibitory synapses on the axon hillock and initial segment of hippocampal cells.[33,226] Other inhibitory cell types have been described with specific axon terminal fields in the middle or inner SM,[89] and one interneuron cell type has now been found that projects to CA3 and CA1.[31] Interestingly, all these interneurons appear to contain GABA; no excitatory â€œinterneuronsâ€ have been described in the dentate (or anywhere else in hippocampus).

It is clear that each cell type has a special function, as determined by the arborization pattern of its dendritic tree, the localization of its axon terminals, and its colocalized transmitter content. However, because most interneurons synapse with each other, it is often difficult to predict what the net effect of activation of a given subpopulation might be; interneuron synapses directly onto granule cells may have a clear inhibitory outcome, but interneuron inhibition of interneurons may result in granule cell disinhibition or net excitation. Recent studies have revealed that at least one interneuron population in the dentate appears to be particularly sensitive to $GABA_B$ receptor-mediated inhibition[164]; it has been hypothesized that $GABA_B$ receptors on the terminals of GABA interneurons may, in fact, regulate the cell's release of GABA through a direct inhibitory effect by GABA on its own terminal.[173] Different interneurons, too, are differentially sensitive to excitotoxic damage; basket cells (at least those types that contain the calcium-binding protein parvalbumin) are resistant to damage,[223] and are well preserved in epileptic hippocampus (even hippocampi showing severe mesial temporal sclerosis), whereas hilar somatostatin-containing interneurons are quite vulnerable (they lack calcium-binding proteins), and their loss may contribute to the hyperexcitability of dentate exposed to high levels of prolonged stimulation.[52] Not surprisingly, the different subpopulations of interneurons express different receptor and channel combinations.[41] Finally, in interneurons, as in other cells of hippocampus, activity-dependent (seizure-inducing) changes occur in cell properties (e.g., receptor complement, channels.[186] For example, neuropeptide Y (NPY) and associated receptors are dramatically regulated by seizure activity[46,254]; these changes, plus the observation that exogenously modified NPY expression may modify seizure activity, has led to the view that the NPY system constitutes an adaptive feedback system for regulating excitability.[254]

CA3.

The CA3 region is composed of large pyramidal cells (and associated interneurons) and is the recipient of mossy-fiber input from the granule cells. The region is conventionally divided into at least three divisions: CA3a (which we shall consider together with CA2 for the purposes of this discussion) is that part of the cell band most distal from the dentate (and closest to CA1); CA3b comprises the middle part of the band, nearest the fimbria/fornix connection; and CA3c is most proximal to the dentate, inserting into the hilus.[5] Although each of these divisions may have slightly different characteristics, the region as a whole (including CA2) has been considered to be the â€œpacemakerâ€ area of the hippocampus.[267] In CA3 much of the rhythmic, synchronous bursting activity associated with interictal epileptiform activity appears to be generated. This population property is a product of the intrinsic properties of CA3 pyramidal cells and their high degree of excitatory collateral connectivity.[249] Unlike other regions of the hippocampus, CA3 pyramidal cell axon collaterals ramify extensively within the local region and make excitatory contacts with their neighbors. The unique properties of CA3 local circuitry have been implicated in a number of hypotheses regarding learning and memory processes in the hippocampus,[81] and also appear to provide a basis for oscillatory rhythms that are characteristic of hippocampus. The CA3 region (as well as entorhinal cortex) constitutes a generator of Î³-frequency (10â€“30 Hz) oscillations, a cholinergically driven pattern that depends on coupling of interneurons (and pyramidal cell axons) via gap junctions, as well as via more conventional chemical excitatory (glutamatergic) and inhibitory (GABAergic) synapses.[146,250] The CA3 region also generates sharp waves and high-frequency oscillationsâ€”EEG patterns implicated in memory consolidation.[142]

Although the excitatory output of CA3 is often damped by strong inhibitory interneuronal influences, even minor reductions in inhibitory efficacy in CA3 can result in significant synchronized bursting, due to interaction among CA3 pyramidal cells. This bursting (or oscillatory drive) is relayed to the CA1 region ipsilaterally (via Schaffer collaterals) and to CA1 and CA3 regions contralaterally (the commissural fibers of hippocampus proper). Although this output is effective in driving postsynaptic targets, it also appears to be important in inhibiting the generation of ictal activities, particularly in entorhinal cortex.[14] Because of the very extensive nature of the CA3 axon collateralization over the longitudinal extent of hippocampus,[134] there is significant divergence of this CA3 output (it is *not* laminar). Perhaps curiously, this same CA3 region is only reluctantly recruited into ictal-like seizure activityâ€”perhaps because of the strength of its inhibitory circuitry or perhaps because the mechanism of the interictal-like bursts directly antagonizes seizure genesis.[104]

The intrinsic and synaptic properties of CA3 pyramidal cells determine this unique set of epilepsy-related characteristics. Individual pyramidal cells in this region have an intrinsic burst propensity, apparently based on a relatively high density of calcium channels in their proximal dendrites.[66,266] Membrane depolarization (e.g., from incoming synaptic activity) not only may trigger conventional sodium action potentials, but also may open these calcium channels; the calcium influx causes a more prolonged depolarization of the cell, driving additional action potentials in a â€œburst.â€ Because afferent input often involves activation of both excitatory and inhibitory influences onto CA3 cells, this burst propensity is generally curtailed by the hyperpolarizing effect of the inhibition.[163] When these bursts occur, however, they provide a potent drive, not only to CA1 targets, but also to neighboring CA3 cells (via the excitatory collateral system); a gradual recruitment of CA3 neuron activity can thus lead to synchronized burst discharge. Importantly, there also appears to be a very effective mechanism for turning off these burstsâ€”the after-hyperpolarization generated by a calcium-dependent potassium conductance.[98] Thus, the very mechanism of burst generationâ€”calcium influxâ€”also involves a self-limiting process (the calcium-activated hyperpolarization). These processes presumably contribute to the reluctance of CA3 to participate in ictal-like activity, which requires prolonged depolarization and repetitive action potential discharge.

Presumably, the major trigger for CA3 discharge is afferent input from the dentate granule cells. Large mossy fiber terminals engage in very complex synapses on the proximal part of the CA3 apical dendrite in the stratum lucidum, where they contact complex dendritic spines; glutamate release from a single terminal evokes a large nonâ€“NMDA-mediated EPSP.[28] Fortunately, the baseline â€œspontaneousâ€ level of granule cell activity is relatively low, so that CA3 cells are not constantly driven at high rates. The unique features of mossy fiber input appear to account for many of the region-specific properties of CA3. Mossy fibers colocalize glutamate with high concentrations of zinc (see earlier discussion), dynorphin, and GABA. Further, the mossy fiber terminals appear to have receptors for kainate (see next section), as well as for BDNF. BDNF application to the CA3 region results in synchronized burst discharge activity.[208]

Fortunately, the same mossy fiber input that activates CA3 pyramidal cells also drives local interneurons very effectively, so that CA3 cells are tonically inhibited by a variety of interneuron subtypes[79] (see Fig. 3). The subpopulations of interneurons in CA3 overlaps with, but is not exactly the same as, those in the dentate; basket cells provide potent inhibition to the level of the cell soma, and other cell types show unique dendritic arborization patterns and region-specific targeting by axon collateral. Investigators have shown that different morphologically defined interneurons also show different electrophysiologic properties; the interneurons include both fast-spiking cellsâ€"whose inhibitory postsynaptic potentials (IPSPs) summate to produce small, smooth IPSPs in pyramidal cellsâ€"and slow-spiking cells, which produce large, fast-rising IPSPs in the pyramidal cell target.[162] As in the dentate, the dendritic region of CA3 is laminated; the most proximal apical dendrite receives mossy fibers exclusively, the mid-dendritic regions (strata radiatum on the apical side and oriens on the basal side) receive primarily associational and commissural fibers (i.e., from other CA3 cells), and the distal apical dendrites (stratum lacunosum-moleculare) receive input from the temporoammonic afferents (from EC) (Fig. 3). All these excitatory glutamatergic inputs are modulated not only by the local GABAergic circuits but also by the subcortical afferent systems. Interestingly, the mossy fiber input to CA3, because it is mediated by non-NMDA glutamate receptors, exhibits a different form of synaptic plasticity[256] from the typical LTP (or long-term depression [LTD]) so intensively studied as a cellular model of learning (and a possible contributor to kindling). The plasticity of this synapse, in contrast to the LTP produced in stratum radiatum of the same region, appears to be particularly dependent on (sensitive to) monoaminergic activation of a cAMP second-messenger system.[97] Recent studies suggest that interneurons specific to the stratum lucidum are key participants in mossy fiberâ€"induced synaptic plasticity.[184]

Seizure-related pathology in the CA3 region tends to be rather varied.[224] The neighboring CA2 transition zone, which does not receive mossy fiber input (and differs from CA3 in a few other subtle ways) is commonly identified as the â€œresistant sectorâ€ because these cells are sometimes the only CA pyramidal cells to survive in human TLE. Temporal lobe epilepsy-related â€œend-folium sclerosis,â€[147] a variation on the mesial temporal sclerosis pattern, is a pathology that primarily affects the CA3 and hilar regions, leaving surviving neurons in the surrounding granule cell layer. The kainic acid [KA] model of TLE has been used to study this pattern of cell loss because intraventricular injection of KA produces excitotoxicity, primarily among CA3 pyramidal cells.[178] Studies have suggested that the KA receptors that mediate this damage are located on mossy fiber terminals; the excitotoxic effect of KA on CA3 cells is mediated indirectly by the KA-induced release of glutamate from these terminals. Indeed, if the granule cell input to CA3 is blocked (lesioned), the CA3 population is protected from KA damage.[177]

CA1.

The CA1 pyramidal cells make up an apparently homogeneous population[103] which, together with their relatives in subiculum, comprise the primary output cells of the hippocampal formation. Their primary excitatory inputs are via the glutamatergic CA3 Schaffer collaterals (both ipsi- and contralateral), which contact spines on apical and basal dendrites in strata radiatum and oriens. An additional excitatory input (the strength of which is still unclear) is via the EC-originating temporoammonic system, which synapses in the distal apical dendrites in stratum lacunosum-moleculare.[225] Although these CA1 pyramidal cells also receive inhibitory input from a variety of interneuronal influences,[122] the strength of inhibition in CA1 seems lesser than that in dentate and CA3, and the cells, therefore, are more vulnerable to recruitment into seizurelike activity and to excitotoxic damage. This relatively low level of inhibition may also help explain why LTP is so easily induced in this region, compared with other brain regions.[110,141] Interestingly, unlike CA3, CA1 pyramidal cells appear to have relatively little excitatory interaction with each other,[248] so the basis of their synchronization rests with CA3. In general, the cell properties and circuits intrinsic to CA1 are not themselves epileptogenic (i.e., these cells are not intrinsic â€œburstersâ€); however, once provoked or recruited (e.g., by excitatory drive from CA3), their control mechanisms are insufficient to prevent seizure activity from taking over the region. In mesial temporal sclerosis, CA1 (Sommer sector) is, next to the dentate hilus, the region showing most damage[260]â€"perhaps reflecting the inadequacy of CA1 control mechanisms to reduce cell excitation. Although it is clear that CA1 can easily be driven to seizure activity, it remains unclear what role this region plays in TLEâ€"either its generation or maintenanceâ€"because these cells are often entirely absent from a hippocampus thought to be the source of seizure activity in TLE.

CA1 cell properties have been so intensively studied that CA1 cells are now often referred to as the â€œmodelâ€ CNS neuron. A variety of voltage-dependent ion channels have been characterized in the CA1 pyramidal cell membrane, including high-threshold calcium currents[227] (which are blocked by such drugs as nimodipine and nifedipine), a large number of potassium currents (delayed rectifier, calcium-activated, etc.), and even noninactivating sodium currents. These cells do not normally discharge in a burst pattern, but recent studies have shown that a subpopulation of CA1 cells tend to burst,[103] and that this proportion of cells increases as the extracellular potassium concentration increasesâ€"as might occur in epileptic tissue. Further, perhaps because of the relatively small extracellular space in CA1,[251] these pyramidal cells may be particularly sensitive to the effects of extracellular current flow as a source of ephaptic interaction and synchronization.[246] A large number of recent studies have focused on the plasticity of receptors and channels in hippocampal CA1 pyramidal cells as a function of activityâ€"both normal and pathologic.[21,48,105] Such studies have illustrated the potential for epileptogenic stimuli to induce â€œchannelopathies.â€

The major basis for local circuit communication with the CA1 region lies in the interneuronal circuitry. In CA1, a number of different inhibitory (GABAergic) interneuronal cell types have been characterized, based on (a) the laminar location of the cell body (oriens, pyramidale, radiatum, lacunosum-moleculare); (b) the shape of the soma and the pattern of the dendritic ramification (which should provide some information about the source of inputs to these cells); (c) the â€œspininessâ€ of the dendrites (many are aspinous); (d) the colocalization of transmitters/peptides with GABA (e.g., somatostatin, parvalbumin); and (e) regional specificity of its axon projection (basket cell specificity for CA1 somata, oriens/alveus cell projections to distal apical dendrites, etc.).[122] Studies have suggested that a subpopulation of GABA neurons mediates GABA$_B$ inhibitory effects[263] and that different interneuron populations are differentially sensitive to ACh[197] and norepinephrine.[56] Of particular interest is the hypothesized role played by interneurons in the generation of the rhythmic activity that is so prominent in CA1 (e.g., Î¸-rhythm), especially within the context of theories in which these rhythms provide a framework for cognitive functions.[237] Interneurons also appear to be the source (or target) of various modulatory substances that control hippocampal excitability, including opioids and endocannabinoids.[44,86,160] And recent studies implicate metabotropic glutamate receptor effects within the interneuronal circuitry as a particularly important new focus for understanding control of synaptic excitation and plasticity.[99,121,124]

This pattern of synaptic activities in CA1 has generated the most intense analysis, driven in large part by interest in the mechanisms of synaptic plasticity (LTP/LTD).[145] These studies have revealed that the EPSP in CA1 pyramidal cells has both NMDA and non-NMDA components; activation of the NMDA receptors is normally crucial for initiation of LTP-like events, but high levels of input, which activate high-threshold calcium currents, may also produce a form of LTP.[78] Studies have also confirmed the major role of intracellular calcium changes during synaptic plasticity, an issue that has been pursued with imaging techniques to follow localized changes in cellular calcium levels resulting from discrete synaptic inputs.[198] Also of considerable interest have been the studies of the various forms of inhibition in CA1 and their roles, not only in synaptic plasticity, but also in epileptogenicity. Investigators disagree about how activity-dependent changes in synaptic inhibition might occur but concur that plasticity is enhanced when inhibition is reduced. This finding is significant for epilepsy because reductions in inhibitory efficacy are clearly associated with the generation of seizure-like activity. The concept of the â€œdormantâ€ or â€œdisconnectedâ€ interneuron, originally developed within the context of epileptogenicity in the dentate gyrus, has also been found appropriate for the CA1 region.[20] For example, in the KA model, CA1 becomes hyperexcitable when the CA3 region is damaged, and a reduction of both GABA$_A$ and GABA$_B$ IPSPs occurs; curiously, the GABA interneurons (and their connections) are still intact in this model, but appear to be more difficult to activate than in the normal brain (i.e., they act as though they are functionally â€œdisconnectedâ€ from the target CA1 pyramidal cells).[67]

Subiculum.

The subiculum has been studied primarily as the major output station for the hippocampal formation. As discussed above, it receives information from the CA1 region and relays the hippocampal output to cortical and subcortical sites. Despite this apparently pivotal role in the function of the hippocampal formation, the cellular and synaptic properties of subiculum have only recently received attention. This relative neglect is even more surprising within the context of TLE; in typical mesial temporal sclerosis (MTS), the greater portion of the CA1 region is damaged (leaving few viable CA1 cells) but the subiculum remains generally intact.[11,224] Given the hypothesis that epileptic activity is generated within sclerotic hippocampus in TLE, and the knowledge that in typical MTS the CA1 region is damaged (or even absent), it may be that the subiculum is uniquely responsible for â€œprojectingâ€ the abnormal hippocampal output to other parts of the brain. How subiculum receives this abnormal hippocampal input in the face of CA1 destruction, and how it processes/modulates such excitability before sending it on to EC, prefrontal cortex, midline and anterior thalamus, amygdala, and hypothalamus remains unexplored. A number of relatively recent studies have begun to fill in the void on subiculum function, both within the context of normal â€œhippocampalâ€ function,[176] and as seen within the epileptic brain.[119,230]

What little we do know about subiculum comes from recent studies of the intrinsic and synaptic properties of subicular neurons.[148,240,245] These investigations suggest that subicular projection cells are similar to hippocampal pyramidal cells in CA1 (and CA3). Subicular pyramidal cells appear to be grouped into two categories; one category comprises cells that normally produce burst discharges (similar to CA3), and the other category consists of â€œregularâ€ firing cells (like most CA1 cells). Both types receive input from CA1 and project to EC. EPSPs with both NMDA and non-NMDA components, and complex GABAergic IPSPs, can be recorded in these cells. The mechanism of discharge in the bursting neurons appears to involve a calcium current (as in CA3 pyramidal cells); however, there is also a tendency toward burst discharge when the cell recovers from a hyperpolarizing drive (similar to the low-threshold burst seen in thalamic neurons), and the underlying basis for that burst may be activation of a low-threshold sodium current. Finally, these cells show a pronounced inward rectifier current (even more so than that in CA1) that provides a depolarizing influence on the cell when it is hyperpolarized. These characteristics would, in theory, endow the subicular neuron with the ability to support hyperexcitable, burst-like discharge generated within an abnormal hippocampus. Because so little is known about the local circuitry of the region, it remains unclear to what extent subiculum might be capable of independent epileptogenesis (e.g., when deafferentated from CA1 and CA3 in MTS).

Entorhinal Cortex

The entorhinal cortex is a relatively large area that interfaces anatomically with the hippocampus so strongly that Ramon y Cajal[196] suggested a functional solidarity between the two structures. Even today, much effort is focused on dissociating the functions of the two structures, compared with the surrounding (parahippocampal) cortical tissues. It is clear that both the hippocampus and entorhinal cortex provide modulation of many functions, particularly those associated with the declarative forms of memory.[272]

Anatomically, large portions of the neocortex project directly to the entorhinal cortex[100] and to its dorsally adjacent neighbor, the perirhinal cortex.[36,37,51] The hippocampus receives most of its cortical information from these two structures. The anterior cortical projections to the entorhinal cortex are particularly dense from the infralimbic and the orbitofrontal cortices, areas that are prominent in stimulusâ€“reward associations and other goal-directed responses.[40] Posteriorly, the orbitofrontal cortex blends first into the insular cortex, where gustatory information is processed, then into the perirhinal cortex, the functions of which are currently under study because of its role in temporal lobe amnesia[273] and its ability to propagate convulsive seizures.[95] Both of these two cortical areas, in turn, densely innervate the entorhinal cortex.[37] The cingulate cortex also innervates the entorhinal cortex,[113] and its loss significantly affects memory, especially in delayed response tasks.[60] Lastly, the subiculum interfaces between the hippocampus and the entorhinal cortex[175] and provides dense projections to both the medial entorhinal area and the perirhinal cortex.[114,265] Based on the intrinsic â€œburst firingâ€ properties of many of these subicular cells,[240] it is presumed that they provide a strong amplifying function for information to and from the hippocampus and entorhinal cortex.

The subcortical inputs to the entorhinal cortex are numerous. Prominent in this regard are several olfactory structures, including a massive input from the olfactory bulbs, which innervates the superficial layers of the entorhinal cortex, along with dense projections from all the olfactory or piriform cortex.[82] Clearly, the entorhinal cortex is privy to considerable olfactory information. Also, projecting strongly to the entorhinal cortex are the cholinergic fibers from the medial septum. It is presumed that, because these same cholinergic cells drive the rhythmic Î¸-activity pattern in the hippocampus associated with memory storage, the entorhinal activity contributes importantly to this process.[3] Emotionally colored information readily arises from the amygdala, where projections are derived from the cortical nucleus to both the medial and lateral entorhinal cortex, and the basolateral and lateral amygdala nuclei to the lateral entorhinal cortex.[18,187] From the brainstem, serotonergic afferents originate in the raphe nuclei, and noradrenergic inputs arrive from the locus coeruleus and the reticular tegmental area. Additionally, thalamic afferents to the entorhinal cortex originate in the reuniens nuclei and in the anterior thalamic nuclei.[16] Thus, the entorhinal area is broadly innervated by both cortical and subcortical structures, and clearly participates in a variety of behaviors, particularly those involving learning and memory.

Like other periallocortical and isocortical structures, the entorhinal cortex is composed of six layers, including a superficial layer I, which is comprised largely of afferents onto the apical dendrites of the cells in layers IIâ€“VI.[54,265] Its intrinsic organization is realized by prominent longitudinal pathways, much like the association pathways in the piriform cortex, with caudal levels projecting most strongly to rostral levels. Within each entorhinal area (medial and lateral), the deeper layers innervate the more superficial layers, and the superficial layers innervate other superficial layers in adjacent areas. In this regard, the entorhinal pyramidal cells of layer V receive strong input from the perirhinal cortex and the sensory cortices[25] and, in turn, project to the superficial entorhinal layer II and III cells.[58] In addition, the layer V entorhinal cells show strong interconnections via recurrent excitatory synapses, much like the CA3 cells in the hippocampus and, when appropriately provoked, are capable of firing in burst patterns.[236] This disposition clearly is important for epilepsy. Connections between the medial and lateral entorhinal areas are more sparse than their longitudinal associations and largely involve diffuse projections that arise

from the medial entorhinal cortex and project to the lateral entorhinal cortex.[54] These medial-to-lateral projections are not reciprocal.[265]

The output of the entorhinal cortex to other cortical and subcortical structures is largely reciprocal with the inputs described. However, the outputs generally arise from the deeper layers (IVâ€“VI), whereas inputs are received in the superficial layers (Iâ€“III). Thus, the entorhinal cortex innervates the olfactory and visual cortices, as well as the amygdala, septum, and thalamus, including the anterior, reuniens, pulvinar, and several â€œauditoryâ€ thalamic nuclei. The other major output of the entorhinal cortex is to the hippocampal formation. Here, the layer II entorhinal cells project to the dentate gyrus and to the CA3 cell field, constituting the well-known â€œperforant pathway,â€ whereas the layer III cells give rise to fibers that innervate the CA1 field. These two entorhinal outputs provide the hippocampus with much of its cortical information.[55]

In comparative studies, clear species differences are apparent in cortical connections with the entorhinal cortex. In the rat and cat, a very large reciprocal connection exists between the entorhinal cortex and the olfactory system, a connection that is much reduced in the primate. By contrast, the primate shows highly differentiated connections between multimodal parasensory and paralimbic cortices and the entorhinal cortex, which are not so evident in the rat and cat.[202] Also, the subiculum in both humans and other primates is considerably larger than that of other species. Perhaps, with such an increase in the size of the primate subiculum, its effect on the entorhinal cortex is enhanced proportionately.

Although the cells that comprise the entorhinal cortex are of mixed types, the majority are pyramidal in shape. Based on their intrinsic properties, most (>90%) of the layer V cells are â€œregular spiking,â€ like most other neocortical neurons,[47] with only a few â€œburst-firingâ€ cells and a few â€œfast-spikingâ€ or presumed inhibitory interneurons.[88,108] Although many of these layer V cells provide important communication routes outside the entorhinal area, the best known entorhinal output, as described earlier, is the perforant pathway. The latter originates in both the medial and lateral entorhinal areas from either â€œstellateâ€ (layer II) or small pyramidal (layer III) cells. Both of these pathways stain intensely for heavy metals using the Timm method, and they appear to use glutamate as their principal excitatory transmitter.[241] Indeed, both the superficial layers and the deep layers of the entorhinal cortex have many cells that possess glutamate receptors of both the NMDA and non-NMDA types, and repetitive stimulation at higher frequencies (as in kindling) appears to unmask depolarizing NMDA receptor-dependent responses easily, particularly in the superficial layers.[92] With this in mind, in temporal lobe tissue excised from TLE patients, an *increase* in excitatory amino acid receptors in the parahippocampal gyrus has been reported.[72] This increased expression of excitatory receptors could easily reflect much of the hyperexcitability characteristic of that TLE tissue.

Also prominent in the entorhinal cortex is the inhibitory transmitter GABA. Although the deep entorhinal cells show little evidence of slow GABAergic IPSPs, and their fast IPSPs are weak,[92] GABA is strong in superficial layers.[106] In addition, GABA antagonists applied to slices of the entorhinal cortex result in large paroxysmal depolarizations, often lasting hundreds of milliseconds; in contrast, the same treatment of the hippocampus produces a disinhibited response of only 100 msec or less. Importantly, the disinhibited entorhinal cortex response in the presence of GABA antagonists is much smaller than that arising during exposure to low extracellular Mg^{2+}.

In a horizontal slice preparation containing both entorhinal cortex and hippocampus, tissue exposure to low Mg^{2+} results in the development of protracted seizure-like events that share ionic properties with in vivo preparations. For example, the increases in $[K^+]_O$ in the slices during â€œseizuresâ€ are similar in intact animals,[231] with the larger increases occurring in the deeper layers. This large response in deep layers likely results from the seizure activity induced in the highly interconnected layer V pyramidal cells. During the seizure, much smaller increases in $[K^+]_O$ are associated with the superficial layers of the entorhinal cortex. In a similar manner, the seizure-inducing effects of low Mg^{2+} can be duplicated in the slice preparation by experimental elevation of $[K^+]_O$. This manipulation results in low-threshold burst responses in the entorhinal cortex, which are often independent of the hippocampal burst response.[17]

In the low-Mg^{2+} slice preparation, after about an hour of large-amplitude and long-duration depolarizations, the discharges change quite suddenly into shorter events. At this time, the events become synchronized throughout the various cortical structures in the slice and exhibit features similar to the late stages of status epilepticus in humans.[57] This change in recurrent discharges from an early to a late form can be blocked by increases in GABAergic activity or can be hastened by GABA antagonists. This finding suggests that reduced efficiency in GABAergic communication may underwrite the transition in the seizure discharges from an early to a late form.

It is important to note that, in low Mg^{2+} conditions, the early form of the entorhinal seizures responds well to therapeutically relevant doses of several different anticonvulsants. However, the late form of the entorhinal discharge is unresponsive to any of the clinically used anticonvulsants, similar to status epilepticus in humans; this property of the entorhinal model system may provide a means of testing agents for their therapeutic efficacy against drug-resistant seizures.[92] It is also apparent that the intrinsic and synaptic properties of the entorhinal cortex significantly contribute to the development of these drug-resistant epileptiform responses. For example, in this model system, the synaptic activation of the dentate gyrus is quite weak and rarely produces action potentials. Thus, it appears that the dentate gyrus filters both epileptic activity[109] and normal information,[77] while the CA3 cells impose an interictal profile on the network that suppresses ictal events.[13] However, with sufficient alterations to the entorhinal/hippocampal network, the dentate gyrus loses some of its filter function and begins to augment synchronized discharges, reinforcing rather than dampening abnormal activity in the entorhinal/hippocampal loop.[138] Such alterations in function would surely be associated with impairments in the normal behavior supported by this network.

Perirhinal Cortex

Lately, there has been considerable interest in the perirhinal cortex. This interest arises largely from the finding in the monkey that many of the symptoms of human temporal lobe amnesia are duplicated by perirhinal cortex lesions.[274] Spontaneous activity in the perirhinal cortex also is uniquely tied to the entorhinal cortex, which suggests a close relationship between it and the entorhinalâ€“hippocampal system that is not evident in other neocortical systems.[45] This relationship also exists at the behavioral level, at which spatial learning can be impacted in perirhinal lesions much like that seen after hippocampal lesions.[2] In addition, in the context of epilepsy, it has been shown recently that kindling of the perirhinal cortex provides the fastest rates of epileptogenesis in the forebrain, accompanied by extremely fast convulsion onset latencies (usually <1 sec). Both the rapid genesis of these kindled seizures and their brief latencies to motor expression suggest that the perirhinal cortex[154,203] and the adjacent insular cortex[168] must be intimately connected with motor areas that support convulsive expression.

Positioned laterally adjacent to the entorhinal cortex, the perirhinal cortex extends from the posterior margin of the

entorhinal area forward to the insular cortex.[36,37] Throughout its course, it forms the banks of the rhinal sulcus. The perirhinal cortex is richly innervated by cortical afferents that arise from the frontal, temporal, parietal, occipital, and piriform cortices.[51,242] Further, the subcortical afferents include the thalamus (reuniens, posterior and â€œacoustic thalamusâ€), lateral nucleus of the amygdala, claustrum, endopiriform nucleus, and dorsal raphe nuclei.[187] Although less is known about the projections of the perirhinal cortex, its efferents to the cortex tend to be reciprocal with the afferents indicated above.[265] In considering its rapid kindling rates, the dense projection from the anterior perirhinal area to the frontal motor cortex is particularly intriguing.[155] Subcortical efferents of importance include the thalamus (nucleus reuniens, posterior and acoustic thalamus), basolateral and lateral amygdala, and nucleus accumbens.[70,155,220,265]

There has been little study of the intrinsic organization of the perirhinal cortex. Cytoarchitectonically, it is agranular cortex, largely devoid of layer IV. The general excitability of the perirhinal cortex appears to parallel that of the entorhinal cortex, and indeed, there exist strong anatomical and physiological (excitatory) interactions between them.[53] With depolarizing current injection into perirhinal cells at their resting potential, most layer III pyramidal cells show regular spiking features. However, like the cells of the somatosensory and visual cortices,[43] intracellular depolarizing current into resting layer V pyramidal cells provokes burst discharges, which transform into a single-spiking profile when their membrane is held at more depolarized values.[65,174] Importantly, these bursting layer V perirhinal cells project densely to the frontal motor cortex.[156] By contrast, layer VI cells are mostly late-spiking in character, including both pyramidal and nonpyramidal cells, and are unlike any other cortical region studied to date. Recently, it has been shown that loss of the perirhinal cortex (in combination with the piriform cortex) prevents the normal development of clonic motor seizures during dorsal hippocampal kindling.[111] Similarly, extensive perirhinal/insular lesions[35] or chemical insular suppression alone,[116] but not discrete perirhinal cortex lesions alone,[212] significantly delays amygdala kindling. Thus, perhaps it is recruitment of the perirhinal/insular efferents during kindling or other forms of epileptogenesis that carries focal, mesial-limbic seizures into their generalized convulsive form. This result is clearly suggested by the recent studies of Harvey and Sloviter,[90] in which the electrographic activity and c-fos expression associated with the spontaneous seizures that occur weeks after exposure to pilocarpine-induced status epilepticus begins outside the hippocampus in parahippocampal structures like the perirhinal cortex.

Piriform or Olfactory Cortex

The piriform cortex is continuous with the entorhinal cortex anteriorly and with the perirhinal cortex ventrally (rat) or medially (cat, primate). The critical importance of the piriform cortex and the other olfactory structures for survival and reproduction in macrosomatic animals is reflected by their relatively large size. By comparison, in humans, dependency on olfactory information has been reduced considerably, along with the size of the olfactory structures, including the piriform cortex. Yet, despite its relative diminution in humans, activation of the olfactory system creates memories that are vivid and enduring, and likely provide the distinct olfactory auras experienced by some TLE patients.

The intrinsic organization of the piriform cortex involves three basic layers: The superficial plexiform layer (layer I), the cell-dense somatic or pyramidal cell layer (layer II), and the deep, diffuse polymorphic cell layer (layer III). As with the entorhinal and perirhinal cortices, layer I consists primarily of afferent inputs to the apical dendrites of deeper cells. In addition, layer I has been subdivided into layers Ia and Ib, each containing its own afferents. Layer II is densely packed with pyramidal and semilunar cells, whereas layer III contains mostly pyramidal cells in its superficial part and nonpyramidal cells in the deeper part. Many of these deep, nonpyramidal cells are presumed inhibitory interneurons and likely provide the strong recurrent inhibition shown by the piriform cortex.[82]

Fibers arising from the olfactory bulbs comprise the primary input to the piriform cortex, where they heavily innervate distal dendrites in layer Ia. Other important inputs to the piriform cortex include the anterior olfactory nucleus (to layer Ib), ventral tenia tecta (to layers II and Ib), nucleus of the lateral olfactory tract (to layer II), cortical nucleus of the amygdala (to all layers), and the insular cortex (to layer III).[19,85] Deep to layer III of the piriform cortex and laterally adjacent to the amygdala is the endopiriform nucleus. This relatively long and highly excitable structure provides dense innervation to layer Ib of the piriform cortex throughout its anterior-posterior extent.[82]

Subcortical inputs to the piriform cortex include the anterior amygdala area, substantia innominata, midline thalamus, and most of the hypothalamus. The brainstem afferents come from the dopaminergic cells in the ventral tegmental area and substantia nigra, the noradrenergic cells from the locus coeruleus, and the serotonergic cells from the raphe nuclei.[243] These brainstem afferents tend to distribute broadly in all three cell layers.

The network organization of the piriform cortex involves both vertical and horizontal dimensions. In the vertical domain, a precise ordering of fibers is present, best characterized by the segregation of afferents to the superficial layer Ia and the association fiber system to layer Ib. There is further segregation of the association fibers, in that those arising in the anterior piriform, usually from layer II, innervate the more superficial parts of the posterior piriform Ib, whereas the association fibers arising from the posterior piriform cortex do so from layer III alone and innervate the deeper part of anterior Ib.

In addition, the organization of the olfactory system is both divergent and convergent, so that activation of restricted parts of the olfactory bulb will broadly innervate the entire superficial piriform cortex, whereas inputs from all parts of the olfactory bulb will converge on discrete areas in the piriform cortex. To achieve the divergent innervation, it has been shown that a single piriform association fiber will course longitudinally for a considerable distance, making only a few contacts but with many neurons.[84] The epileptic disposition of this network of cells has been studied extensively by Haberly and colleagues, particularly with current source density analysis, and presently is a favorite structure for network modelers interested in learning and memory.[15,83]

In interfacing with several other olfactory structures, the output of the piriform cortex remains relatively restricted to much of its own association network. However, it does project densely to adjacent cortical structures, including the insular, perirhinal, and entorhinal cortices, as well as to a few subcortical structures, such as the lateral hypothalamus, ventral striatum, and dorsal medial thalamic nucleus.[85]

The importance of the piriform cortex as a seizure generator is evident in a variety of whole-animal experiments. Until superseded recently by the perirhinal and insular cortices,[154,168] the piriform cortex was thought to develop kindled seizures faster than any other structure in the forebrain.[136,156]

During kindling, the piriform cortex develops interictal spikes before all other limbic structures; when the interictal spikes are present concurrently in several structures, spikes in the piriform cortex anticipate spikes in the other structures.[191]

In the deep layers of the anterior piriform cortex, in or near the endopiriform nucleus, picomolar amounts of several convulsants (including GABA antagonists and cholinergic and glutamate agonists) have been reported to induce the rapid development of convulsive seizures.[188] Such pharmacologic sensitivity has not been observed elsewhere in the brain. A second, central area in the piriform cortex, transitional between anterior and posterior regions, provides dense expression of GABAergic neurons that are believed to broadly modulate excitability of this entire area.[137] When damaged, this expression results in facilitated kindling from the adjacent amygdala.[213]

The sensitivity of the piriform cortex to seizure activity is highlighted by its extreme vulnerability to protracted seizures. In several models of status epilepticus, the piriform cortex is the first structure to experience damage, an effect that is massive.[179]

The plasticity of the piriform cortex also has been demonstrated using in vitro experiments. In tissue slices taken from previously amygdala-kindled rats, excitability in the piriform cortex is clearly enhanced.[158] A parallel enhancement in piriform excitability is observed in control tissue when it was returned to normal Mg^{2+} perfusate after previous exposure to the seizure-inducing effects of low Mg^{2+}. The earlier exposure to low Mg^{2+} irreversibly increases piriform excitability for synaptically triggered network events mediated by changes in the deep layer III cells,[96] as well as for spontaneous events.[157] Such changes in the piriform cortex could provide the basis for alterations in olfactory experience and memories. Clearly, the powerful association system in the piriform cortex, coupled with its rich interconnections to the entorhinal and perirhinal cortices, provides it with the capability to trigger and amplify epileptic events.

Amygdala

The amygdala complex plays an important role in a variety of behaviors, including fear, aggression, learning, reproduction, and epilepsy.[1,74] Until recently, its connections with the hypothalamus were considered to be central to the expression of most of these behaviors, but it is now believed that many are realized through its connections with the sensory systems, cortex, striatum, and brainstem.[50]

The amygdala is a heterogeneous collection of nuclear groups,[150] often divided simplistically into the following divisions: The olfactory group, including the anterior area, nucleus of the lateral olfactory tract, and the cortical nucleus; the central-medial group, including the central and medial amygdala nuclei; and the basolateral group, including the lateral, basolateral, and basomedial nuclei. Not surprising, such a heterogeneous structure is matched equally by a diversity of connections.

The afferents to the olfactory group include both the olfactory bulbs and a third-order olfactory input via the piriform cortex.[85] The hippocampus provides some direct input to this group from CA1 but has more indirect influences through the subiculum and tenia tecta.[181] Important innervation also comes from the lateral entorhinal and agranular insular cortices. Subcortical afferents include cholinergic projections from the diagonal band, noradrenergic fibers from the locus coeruleus, and serotonergic fibers from the raphe nuclei.[64] Other important afferents involve the highly excitable endopiriform nucleus and several hypothalamic and thalamic nuclei.

The efferents of the olfactory group are largely reciprocal with their afferents. However, other important targets include the ventral striatum, which gives strong motor representation to the olfactory group output, and the nucleus accumbens, where reward mechanisms are influenced. This group also is well connected with the other amygdala nuclei, particularly the medial, central, and basolateral nuclei, but not with the lateral nucleus.[50]

In the medial-central group, the medial nucleus is reached by several cortical afferents, including those from piriform, agranular insular, retrosplenial, and entorhinal cortices, as well as by fibers from the subiculum and hippocampus.[149,181] Subcortical afferents arise from the hypothalamus and several midline thalamic nuclei, as well as from the brainstem structures described for the olfactory group. Efferents of the medial nucleus that might be important for epilepsy project to the entorhinal cortex and ventral striatum.[18] The hypothalamus and the brainstem also receive many efferents from the medial nucleus.[50] Although cells in the medial nucleus express many peptides such as cholecystokinin (CCK), vasoactive intestinal polypeptide (VIP), enkephalin, somatostatin, thyrotropin releasing hormone, and others, GABA is the transmitter that is particularly well represented. Perhaps this is why the medial nucleus is the slowest of the amygdala nuclei to develop kindled convulsions.[127]

By contrast, the central nucleus is the fastest nucleus to kindle.[127,167] This nucleus receives afferents from the piriform, agranular insular, entorhinal, perirhinal, and other cortices.[50] Hypothalamic afferents innervate the central nucleus, as do extensive inputs from a variety of thalamic nuclei. As with the other amygdala groups, brainstem afferents contain nor-adrenergic and serotonergic fibers. The cortical efferents from this group are Spartan, except for those to the perirhinal cortex.[51] This projection may have important implications for the generation of convulsive seizures, because the fast-kindling central nucleus is second only to the faster-kindling perirhinal cortex.[154] Important subcortical efferents include projections to the medial dorsal striatum, fundus striati, and hypothalamus.[50] Brainstem communication involves the central gray, pedunculopontine nucleus, parabrachial nucleus, nucleus of the solitary tract, dorsal motor nucleus of the vagus, and others. These brainstem structures provide considerable motor and autonomic nervous system expression for the central nucleus. Although the number of neuropeptides observed in this nucleus exceeds all others, the manner in which they contribute to the excitability of the central nucleus has not been determined.

Simplistically, the basolateral group comprises the basolateral, basomedial, and lateral amygdala nuclei. This group is distinguished by its dense connections with the neocortex, originating in the piriform, entorhinal, agranular insular, infralimbic, cingulate, orbitofrontal, and perirhinal cortices.[143,144,189,190,234] Subcortical afferents of importance include the dense cholinergic projections from the diagonal band, ventral pallidum, and substantia innominata. Further afferents reach the basolateral group from the hypothalamus and several midline thalamic structures, as well as from dopaminergic, noradrenergic, and serotonergic fibers from the brainstem.

The cortical outputs of the basolateral group are largely reciprocal with the inputs described, with the addition of a dense projection to both the somatosensory and motor cortices. The subcortical efferents of this group include projections to the dorsal and ventral striatum, as well as the nucleus accumbens and olfactory tubercle. Whereas much of the hypothalamus receives efferents from the basolateral group, projections to the thalamus are restricted to the dorsomedial nucleus.[120] Unlike the central nucleus, the basolateral group also shows limited innervation of the brainstem.

The diversity of transmitters seen in the other amygdala groups is not evident in the basolateral complex. Of course, the basolateral complex still exhibits many peptides and is highly sensitive to the classic transmitters. Indeed, most of the in vitro electrophysiologic studies of the amygdala have involved the basolateral nucleus. In this regard, it has been shown by Rainnie and colleagues[192,193,194,195] that: (a) low Mg^{2+} perfusion of the amygdala-piriform slice preparation readily results in spontaneous interictal and ictal burst discharges in the basolateral amygdala that are both NMDA- and nonâ€"NMDA-sensitive; (b) GABAergic inhibition is feed-forward to this group via the stria terminalis and direct via the lateral amygdala; and (c) previous

kindling of the amygdala results in a loss of only the stria-mediated GABAergic inhibition and is accompanied by the development of NMDA-sensitive, spontaneous burst discharges. Many of these changes in kindled tissue are evident similarly in the adjacent piriform cortex.[95,158] Thus, it appears that the development of epileptiform discharges in the amygdala-piriform area is associated with an increased sensitivity of both NMDA and non-NMDA glutamate receptors and with the loss of some GABAergic inhibition. Finally, although the basolateral nucleus is undistinguished in its kindling profile, developing convulsions at a rate intermediate between the fast-kindling central nucleus and the slow-kindling medial nucleus, it plays a critical role in the development and maintenance of limbic-based status epilepticus.[257]

When examining the amygdala in an interactive context, by comparing its kindling progression against other limbic or cortical structures concurrently stimulated by alternating between the amygdala and those other sites, an antagonism between the sites in their kindling progression becomes evident.[34,59] The amygdala kindling dominates in paired encounters with the septum, ventral hippocampus, piriform or posterior perirhinal cortices, but loses and remains undeveloped in the presence of concurrent stimulation applied to either the anterior perirhinal, insular or anterior cingulate cortices.[34,166] Clearly many dynamic interactions can be provoked in the limbic system, which can favor or disfavor epileptogenesis, depending upon their origins and timing.

Summary and Conclusions

Although Broca's[27] first description of the â€œlimbic brainâ€ was based on strictly anatomic contiguity, the idea of a limbic â€œsystemâ€ has proved very resilient, even in an age of functional emphasis. Papez[182] painted a picture of strong connectivity among various elements of the limbic brain, giving rise to a system in which sensory, endocrine, and autonomic functions were integrated to produce complex emotional behaviors. In Maclean's[139] reinterpretation of the field, the limbic brain stood interposed between the older parts of the CNS (dealing with sensing of the â€œinner worldâ€) and the newer parts of the CNS (providing sensory experience of the external world). Behavioral studies on monkeys[116] and on epilepsy patients with bilateral temporal lobe removals[216] showed this integrative system to be important in memory, as well as in emotional behaviors. These views have continued to receive support from recent studies. Many modern investigators have taken issue with the concept of a single limbic system involved in so many different (and such diverse) functions. Yet the richness of anatomic connectivity among many of these limbic brain regions and the relatedness of many of the implicated behaviors argue for some significant level of interaction among putative limbic structures.

This chapter has concentrated on a few of the most salient â€œstationsâ€ in the limbic complexâ€”salient, at least, with respect to what we know about epileptogenesis. Our omission of the hypothalamus, limbic aspects of the basal ganglia/thalamic complex, limbic (cingulate) cortex, and septal and olfactory regions from this discussion says less about their involvement in epileptogenesis than about our lack of understanding of their structure and function. Without question, however, the hippocampus, entorhinal cortex, amygdala, parahippocampal/piriform cortex, and perirhinal cortex are major players in complex partial or temporal lobe seizure syndromes. These regions display relatively low thresholds for seizure induction, tend to show some degree of damage associated with long-term (continuous) seizure activity, and are intimately connected. Seizure initiation at one site may spread rapidly to related structures. Disruption of one (or more) regionâ€”e.g., in temporal lobectomyâ€”will inevitably have consequences for function and excitability in the remaining cortices. The view of each region as an isolated entity was initially useful in attempts to characterize these structures but must be ultimately misleading with respect to both normal function and generation (initiation, maintenance) of epileptic activities. Despite the difficulties in defining a â€œlimbic system,â€ it is perhaps our inability to view these structures within the context of an interactive â€œsystemâ€ that has made it so difficult to identify the epileptogenic keys to limbic structure and function.

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Chapter 31

Thalamocortical Anatomy and Physiology

Hal Blumenfeld

Douglas A. Coulter

Introduction

The thalamus and the thalamocortical system participate intimately in the generation of generalized seizures and probably are involved in the synchronization and propagation of localization-related seizures as well.[11,13,14,108] This is due to a combination of factors that will be discussed in this chapter, including chiefly the intimate reciprocal excitatory synaptic relationship between the thalamus and cerebral cortex, and the intrinsic properties of the thalamus and associated structures that predisposes the system to generate synchronized rhythms. We will emphasize the role of the thalamocortical system in generating the spike-and-wave discharges (SWDs) seen in generalized seizures, since most work has been done with this seizure type. Continued investigations may allow similar concepts to be applied in localized epilepsy as well.

The importance of the thalamus in generation of seizures has been a subject of active experimentation for at least the past 60 years. In the 1940s, the fact that generalized spike-and-wave seizure discharges appeared virtually simultaneously throughout large areas of neocortex led investigators of the time to hypothesize that there was a â€œcentrencephalicâ€ pacemaker structure synchronizing and driving these rhythms.[112,114] Studies by Jasper and colleagues[65] and by Dempsey and Morison[39] demonstrated that low-frequency stimulation to midline thalamic structures elicited electroencephalographic responses in cortex very similar to generalized SWDs of generalized absence epilepsy. Depth recordings in patients established that the SWDs of generalized absence epilepsy were generated by an underlying thalamocortical oscillation.[5,13,52,106,113,122,126,146,147] Detailed studies of anatomic and physiologic mechanisms underlying generation of normal rhythms in the thalamocortical system have clearly delineated the underlying structures critical to the generation of synchronized rhythms in this system: the thalamic relay nuclei, the surrounding Î³-aminobutyric acid (GABA)ergic nucleus reticularis, and the neocortex. Recent work suggests that epileptic activity and altered excitability occurs in selective regions of the thalamocortical network and spares others. This selective involvement may provide more specific targets for therapeutic interventions.

Anatomy of the Thalamus

Gross Structure

The thalamus can be subdivided, based on its gross anatomy, into three main nuclear masses: anterior, medial, and lateral. They are separated by a white-matter tract called the *internal medullary lamina*. In addition, a fourth group consists of several small nuclei found within the internal medullary lamina, termed the *intralaminar nuclei,* and extends to the midline, forming the *midline thalamic nuclei*. These four groups of nuclear masses share a common embryologic origin and have collectively been termed the *dorsal thalamus*. An important functional partner of the thalamus is the nucleus reticularis thalami (NRT), which in coronal sections is a shell-shaped, thin layer of cells surrounding the thalamus on its lateral and rostral extentâ€”separated from the thalamus proper along most of its extent by the external medullary lamina. The NRT has a distinct embryologic origin from the remainder of the thalamus and has been grouped within the ventral thalamus (also comprised of the ventral lateral geniculate nucleus and zona incerta), which, unlike the thalamus proper, does not send axonal fibers to the cerebral cortex. Within each nuclear group in the dorsal thalamus, it is possible to distinguish subnuclei based on their appearance in Nissl-stained sections.

Different Nuclei

Thalamic nuclei can also be classified based on their main input and output connections (Table 1). Thalamocortical cells in the thalamic relay nuclei convey nearly all information en route to the cerebral cortex. Projections from some relay nuclei to thalamus are localized to specific cortical regions, whereas projections from other nuclei are more diffuse (Table 1). In addition, the relay nuclei receive massive reciprocal connections returning from the cortical areas to which they project. The intralaminar nuclei are distinguished by their major reciprocal connections with the basal ganglia, in addition to widespread reciprocal connections with the cerebral cortex. The NRT is unique in that it receives inputs, but sends no outputs to the cerebral cortex, and also has reciprocal connections with all thalamic nuclei.

Thalamocortical Circuits and Other External Connections

The basic synaptic circuit comprising the thalamocortical system is repeated with only modest modifications in most of the primary sensory relay nuclei. This simplified functional circuit will be employed to develop the concept and discuss the rhythm-generating functions of the thalamocortical system, the main focus of this chapter. This basic synaptic circuit is discussed in the next section and schematically depicted in FIGURE 1.

Reciprocal Connections Between Thalamus and Cortex

The principal sensory relay nuclei within the thalamus send an ordered projection to layers III and IV and to the Vâ€"VI border of cortex (synapse 1 and 2, Fig. 1) and receive a feedback

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projection from the layer VI pyramidal neurons of the same area of cortex (synapse 3, Fig. 1). Both the thalamocortical and corticothalamic projections also send axon collaterals to the surrounding NRT (synapses 4 and 5), which, in turn, provides inhibitory feedback onto the thalamus (synapse 6, Fig. 1). Both the corticothalamic and thalamocortical projections are excitatory and use glutamate or aspartate as a neurotransmitter, whereas NRT uses GABA as a neurotransmitter (Fig. 1).

Table 1 Major Thalamic Nuclei

Nuclei[â€]	Main input[â€¡]	Main outputs	Diffuseness of projections to cortex*	Proposed functions
RELAY NUCLEI **Lateral nuclear group**				
Ventral posterior lateral nucleus (VPL)	Medial lemniscus, spinothalamic tract	Somatosensory cortex	+	Relays somatosensory spinal inputs to cortex
Ventral	Trigeminal	Somatosensory and taste	+	Relays

posteromedial nucleus (VPM)	lemniscus, trigeminothalamic tract, taste inputs	cortex		somatosensory cranial nerve inputs and taste to cortex
Lateral geniculate nucleus (LGN)	Retina	Primary visual cortex	+	Relays visual inputs to cortex
Medial geniculate nucleus (MGN)	Inferior colliculus	Primary auditory cortex	+	Relays auditory inputs to cortex
Ventral lateral nucleus (VL)	Internal globus pallidus, deep cerebellar nuclei, substantia nigra pars reticulata	Motor, premotor, and supplementary motor cortex	+	Relays basal ganglia and cerebellar inputs to cortex
Ventral anterior nucleus (VA)	Substantia nigra pars reticulata, internal globus pallidus, deep cerebellar nuclei	Widespread to frontal lobe, including prefrontal, premotor, motor, and supplementary motor cortex	+++	Relays basal ganglia and cerebellar inputs to cortex
Pulvinar	Tectum (extrageniculate visual pathway), other sensory inputs	Parietotemporo-occipital association	++	Behavioral orientation toward relevant visual and other stimuli
Lateral dorsal nucleus	See anterior nucleus	â€”	++	Functions with anterior nuclei
Lateral posterior nucleus	See pulvinar	â€”	++	Functions with pulvinar
Ventral medial nucleus	Midbrain reticular formation	Widespread to cortex	+++	May help maintain alert,

				conscious state
Medial nuclear group				
Mediodorsal nucleus (MD)	Amygdala, olfactory cortex, limbic basal ganglia	Frontal cortex	++	Limbic pathways, major relay to frontal cortex
Anterior nuclear group				
Anterior nucleus	Mammillary body, hippocampal formation	Cingulate gyrus	+	Limbic pathways
Midline thalamic nuclei Paraventricular nucleus Parataenial nucleus Interanteromedial nucleus Intermediodorsal nucleus Rhomboid nucleus Reuniens (medial ventral) nucleus	Hypothalamus, basal forebrain, amygdala, hippocampus	Amygdala, hippocampus, limbic cortex	++	Limbic pathways
INTRALAMINAR NUCLEI				
Rostral intralaminar nuclei Central medial nucleus Paracentral nucleus Central lateral nucleus	Deep cerebellar nuclei, globus pallidus, brainstem, ascending reticular activating systems (ARAS), sensory pathways	Cerebral cortex, striatum	+++	Maintain alert consciousness; motor relay for basal ganglia and cerebellum
Caudal intralaminar nuclei	Globus pallidus, ARAS, sensory pathways	Striatum, cerebral cortex	+++	Motor relay for basal ganglia

Centromedian nucleus Parafascicular nucleus				
RETICULAR NUCLEUS	Cerebral cortex, thalamic relay and intralaminar nuclei, ARAS	Thalamic relay and intralaminar nuclei	None	Regulates state of other thalamic nuclei

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â€ Some additional smaller nuclei have not been included.

â€¡In addition to the inputs listed, all thalamic nuclei receive reciprocal inputs from the cortex and from the thalamic reticular nucleus. Modulatory cholinergic, noradrenergic, serotonergic, and histaminergic inputs also reach most thalamic nuclei.

*+, least diffuse (specific thalamic relay nuclei); ++, moderately diffuse; +++, most diffuse. Reproduced from Blumenfeld H. *Neuroanatomy through Clinical Cases*. Sunderland, MA: Sinauer, 2002, with permission.

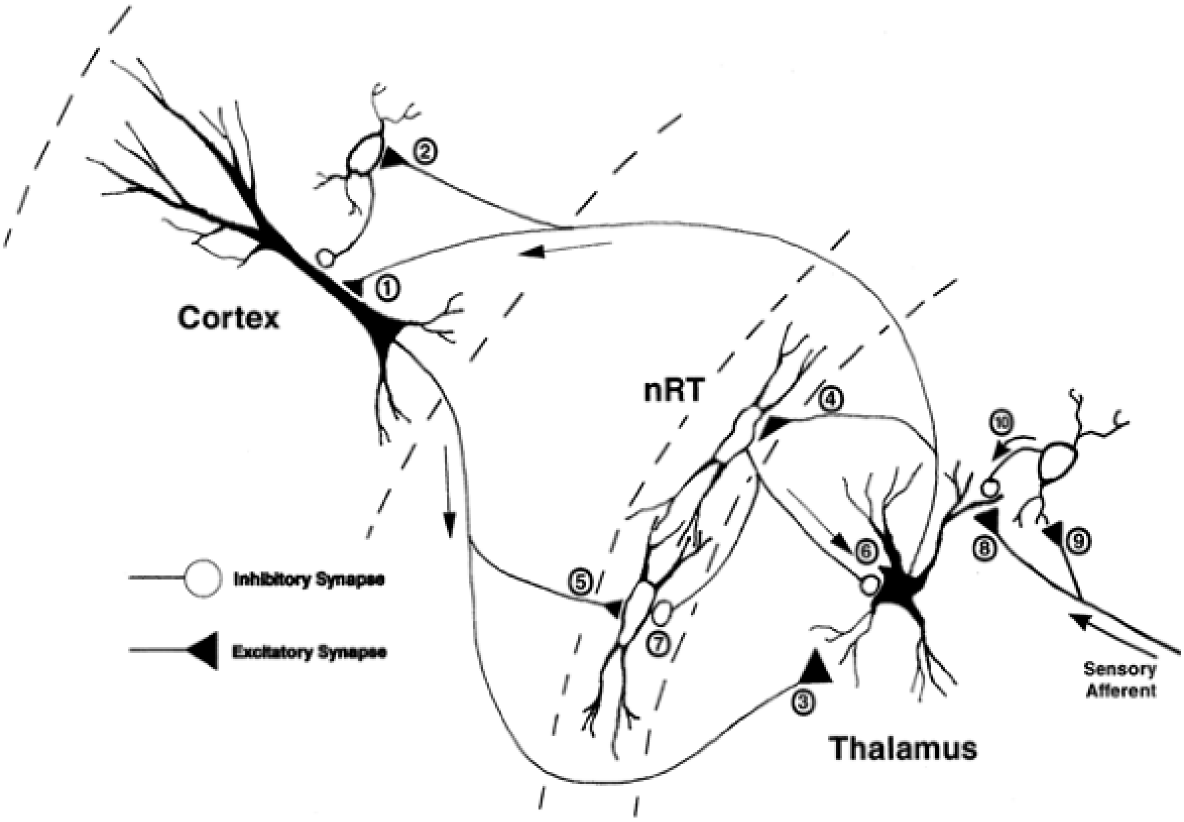

FIGURE 1. The basic thalamocortical circuit. Thalamic neurons in primary sensory relay nuclei project to layers III and IV and V and VI of the cerebral cortex. This projection terminates on both pyramidal neurons (synapse 1) and on inhibitory interneurons (synapse 2) in the cortex. Layer VI pyramidal neurons reciprocally innervate the same area of thalamus from which an ascending afferent is received (synapse 3). Both the thalamocortical and the corticothalamic projections send an axon collateral to nucleus reticularis thalami

(nRT; synapses 4 and 5). Nucleus reticularis thalami provides inhibitory GABAergic innervation to the thalamus (synapse 6) and to other NRT neurons (synapse 7). The major sensory afferents to the thalamus synapse onto the dendrites of both thalamic relay neurons (synapse 8) and inhibitory interneurons (synapse 9). The dendrites of inhibitory interneurons can function as both pre- and postsynaptic elements and can provide inhibitory innervation of thalamic relay neuron dendrites (synapse 10), as well as conventional axonal synaptic connections (synapse 10).

In contrast, the midline (intralaminar) thalamic nuclei also send projections to cortex (with a collateral projection to NRT), but this projection is much more diffuse than is the ordered projection from sensory relay nuclei, and terminates in superficial and deep layers (I and VI). These intralaminar nuclear projections are concentrated in the frontal, medial, and dorsolateral cortex, but intralaminar projections may reach all cortical areas.[56] As with the sensory relay nuclei, the intralaminar nuclei receive feedback projections from the cortex but, unlike the corticothalamic feedback projections onto principal sensory relay nuclei, intralaminar nuclei receive this projection from smaller layer V pyramidal neurons of cortex. In addition, the intralaminar nuclei project to the neostriatum and receive a feedback projection from the globus pallidus, as well as from the NRT.

Local Intrathalamic Circuits

Essentially, there are no local intrathalamic circuits involving interconnections of thalamocortical relay neurons within or between thalamic nuclei. The principal axonal target of these neurons is the ipsilateral cerebral cortex, and this projection was discussed earlier. However, there are significant populations of local circuit neurons within thalamic nuclei, and these neurons usually are GABAergic. In addition, NRT provides an extensive and powerful feedforward and feedback inhibitory projection onto relay neurons of the dorsal thalamus, and this intrathalamic inhibitory connection is of fundamental importance in the rhythm-generation capabilities of the thalamocortical system.

GABAergic local circuit neurons modulate the strength of afferent input into the thalamus. These neurons participate in a distinct form of synaptic arrangement in which dendrites of interneurons act as both pre- and postsynaptic elements in a large, glial-ensheathed synaptic aggregation that also contains the large afferent sensory terminal, dendritic appendages from relay neurons, and conventional inhibitory terminals (synapses 8â€“10, Fig. 1). The interneuron dendrite receives excitatory synaptic input from the sensory afferent terminal (synapse 9, Fig. 1), which also provides excitatory input onto the

neighboring thalamic relay neuron dendrite (synapse 8, Fig. 1). The interneuron dendrite also forms an inhibitory synaptic connection with the thalamic relay neuron dendrite (synapse 10, Fig. 1).[125] This synaptic arrangement has been termed a *synaptic triad* (Fig. 1). One of the primary functions of these synaptic specializations within the thalamus is to dramatically shorten the duration of afferent excitation of thalamic relay neurons through rapid truncation of the sensory excitatory postsynaptic potential (EPSP) before it can reach the thalamic relay neuron soma and there be transduced into action potential output to the cortex. This may serve a role in more the faithful temporal relay of sensory information to the cerebral cortex.

Brainstem Neuromodulatory Afferents

In addition to the excitatory sensory afferents that innervate the dorsal thalamic relay nuclei, other inputs reach the thalamus and cerebral cortex from various brainstem sources. These afferents release a number of different neurotransmitters. Cholinergic afferents arrive from the basal forebrain, pedunculopontine tegmental and lateral tegmental nucleus; noradrenergic afferents arrive from locus ceruleus; serotonergic afferents originate from the dorsal raphe; and histaminergic afferents originate from the tuberomammillary nucleus of the hypothalamus. Activation of these neuromodulatory afferents serves principally to maintain the thalamus in a â€œrelayâ€ mode (i.e., where afferent sensory activity is faithfully relayed to the cortex). Reduction in the activity in these afferents results, in general, in an enhancement of low-frequency oscillatory activity in the thalamocortical system.[90]

Physiology of Thalamic Neurons

Neurons in virtually all areas of the thalamus are characterized physiologically by the presence of a large-amplitude, low-threshold calcium spike.[63,64] This intrinsic membrane conductance underlies bursts of action potentials generated in thalamic neurons and plays an important amplifying role in thalamic oscillatory behavior, including sleep spindles and the spike-and-wave discharges (SWDs) of generalized absence epilepsy. In contrast to its size in other mammalian neurons, the low-threshold calcium (Ca) current is particularly prominent in thalamic neurons, where its overall peak amplitude is usually equal to or greater in amplitude than the high-threshold (dihydropyridine-sensitive) calcium current in the same cells.[30] This proportionally large low-threshold (â€œTâ€-type) Ca current influences the behavior of thalamic neurons and, in situations in which thalamic neurons are hyperpolarized from their normal waking resting membrane potentials, dominates the cellular properties of these neurons.[63] The anomalous dependence on hyperpolarization for activation of low-threshold Ca current is explained by the underlying characteristics of this current. The biophysical properties of the low-threshold Ca current are similar in many ways to those of the classical sodium (Na) current underlying action potential generation. The T current is activated at potentials very close to the resting potential of neurons, with a threshold for activation around -60 mV (Fig. 2A).[32] However, the T current is also inactivated by potentials near the normal resting potential of thalamic neurons, with virtually all the T channels inactivated at -60 mV (Fig. 2B).[30] For T-type Ca channels to be activated, the neuronal membrane potential must be hyperpolarized below -60 mV for a sufficient time to allow the channels to â€œdeinactivateâ€ or become able to be activated. Once this deinactivation process occurs, a subsequent depolarization will allow these Ca channels to open and generate the regenerative low-threshold Ca spike that is the amplifier underlying and generating oscillatory behavior within the thalamocortical system (Figs. 3 and 4). This deinactivationâ€"activationâ€"inactivation sequence of functional states of the T current underlying low-threshold Ca spikes in thalamic neurons is a fundamental process that is repeated over and over during the generation of low-frequency rhythms within the thalamus and within the thalamocortical system. Neurons within the NRT have a T current with similar voltage dependence and pharmacology but slower kinetics than those seen in thalamic neurons.[60] The genes encoding T-type Ca currents have been cloned, and three T-type Ca channels have been characterized: Cav3.1 (Î±1G), Cav3.2 (Î±1H), and Cav3.3 (Î±1H).[49,115,116] Cav3.1 is predominantly expressed in thalamic relay neurons, and Cav3.3 in NRT neurons,[132] which explains the difference in T-current properties evident in the two populations of neurons.

In addition to the T-type Ca current underlying the low-threshold Ca spike, thalamic neurons are endowed with another variety of intrinsic membrane current that significantly contributes to the propensity of these neurons to generate low-frequency rhythms. This current is a hyperpolarization-activated cationic current, I_h. This current is carried by both Na^+ and potassium (K^+) ions, and is activated by hyperpolarization to potentials more negative than -60 mV (Fig. 2C). I_h activates slowly and results in generation of a depolarizing pacemaking potential (Fig. 3A, B).[92] When the neuron is in a membrane potential range of -70 to -85 mV, this depolarizing pacemaking potential can then activate a low-threshold Ca spike, which will deactivate the h current and, upon repolarization, I_h is reactivated, once again generating a depolarizing pacemaking potential, activating another low-threshold spike, and so on (Fig. 3A, B). The rate at which I_h activates determines the frequency of low-threshold spike firing, and this, in turn, depends on the resting membrane potential of the neuron because the kinetics of I_h are voltage-dependent, with activation occurring more rapidly during greater hyperpolarizations. This combination of the T-type Ca current and the hyperpolarization-activated cationic current I_h will generate spontaneous, low-frequency oscillatory activity in thalamic neurons when in a membrane potential range of -65 to -75 mV, even in the absence of any synaptic input (Fig. 3A, B).[78,92] However, for this activity to become synchronized between cells, the synaptic network of which these thalamic neurons are members must play a critical role.

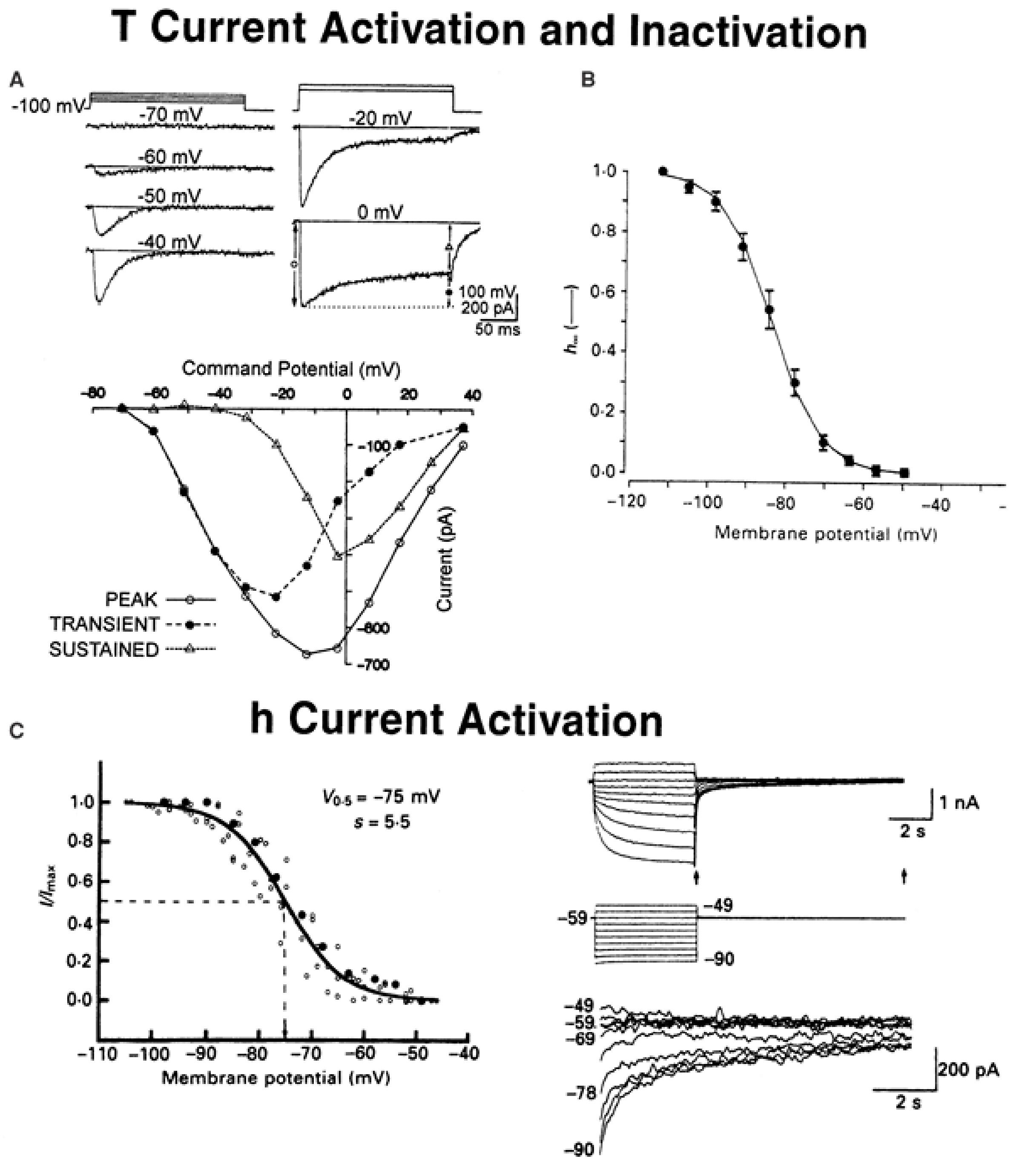

FIGURE 2. Intrinsic membrane properties of thalamic neurons that contribute to their propensity to generate low-frequency rhythms. **A,B:** Biophysical properties of the low-threshold T-type Ca current. **A:** Current voltage plot illustrating activation of the T current by depolarizing steps in an acutely isolated rat thalamic neuron. Note that the T current activates at very hyperpolarized potentials (-60 mV), and that the T current inactivates (i.e., is transient). From Coulter DA, Huguenard JR, Prince DA. Differential effects of petit mal anticonvulsants and convulsants on thalamic neurones: calcium current reduction. *Br J Pharmacol*. 1990;100(4):800â€“806, with permission.[32] **B:** Inactivation of the T current by increasingly depolarized membrane potentials in a rat thalamic neuron. Note that the T current requires the membrane potential to be hyperpolarized below -60 mV for the current to be able to be activated, and that the T current is half-inactivated at -80 mV. Modified from Coulter DA, Huguenard JR, Prince DA. Calcium currents in rat thalamocortical relay neurones: kinetic properties of the transient, low-threshold current. *J Physiol*. 1989;414:587â€“604, with permission.[29] **C:** The hyperpolarization-activated cationic current I_h. Note that

increasing hyperpolarizations activate a greater and greater proportion of the h current, which is half-activated at a membrane potential of -75 mV. From McCormick DA, Pape HC. Properties of a hyperpolarization-activated cation current and its role in rhythmic oscillation in thalamic relay neurones. *J Physiol*. 1990;431:291â€“318, with permission.[93]

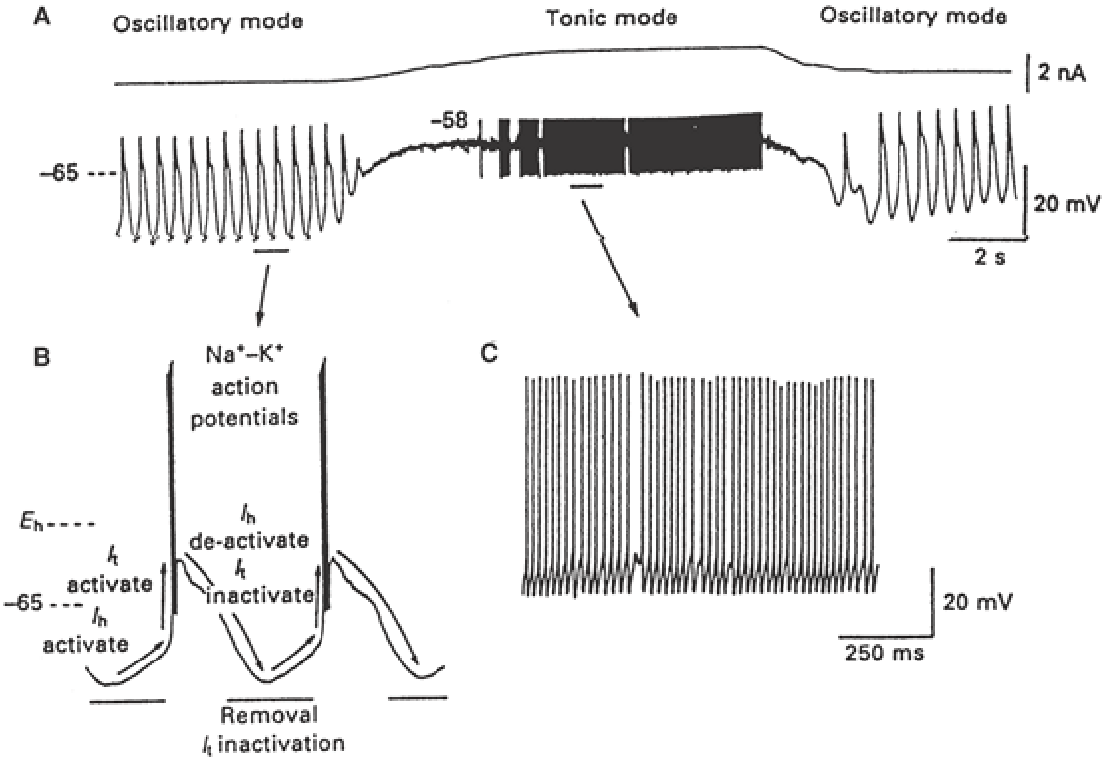

FIGURE 3. Oscillatory and tonic firing modes of thalamic neurons. **A, B:** The interaction of T current (I_t) and I_h results in the generation of spontaneous oscillations in thalamic neurons. **A, C:** Depolarization of thalamic neurons inactivates I_t, causing a transition from oscillatory firing mode to tonic relay mode. From McCormick DA, Pape HC. Properties of a hyperpolarization-activated cation current and its role in rhythmic oscillation in thalamic relay neurones. *J Physiol*. 1990;431:291â€“318, with permission.[93]

Generation of Normal Thalamocortical Rhythms

In the awake animal, thalamic neurons are maintained at a resting potential of -50 to -60 mV by the combined effects of normal afferent activity and by the ascending activating systems of the brainstem (see earlier discussion); the T current is inactivated; and the thalamus serves as a faithful relay of all types of sensory information to the cerebral cortex (Fig. 3, *tonic mode*). In this state, the thalamus transduces incoming synaptic input into a patterned action potential frequency output to cortex, with little or no loss of information content. Loss of conscious perception associated with drowsiness or sleep is associated with a marked alteration in the functional properties of the thalamus. Thalamic neurons hyperpolarize as a period of drowsiness or sleep begins,[70] due to a reduction in the neuromodulatory activity of the ascending activating systems and a decrease in normal afferent activity; the T current deinactivates in thalamic neurons, and the thalamus transitions from a faithful relay mode of firing to an oscillatory or burst mode of firing (Fig. 3, *oscillatory mode*). Because of this change in the â€œstateâ€ of thalamic neuron firing properties, during drowsiness or sleep, the thalamus serves more to disrupt and filter sensory information, and generates low-frequency oscillations during this state of reduced consciousness. Deep stages of sleep are associated with several varieties of rhythmic oscillations in the brain that are generated principally in cortical and thalamic synaptic networks. The early stages of slow-wave sleep are characterized by spindle waves recorded in the electroencephalogram (EEG). These spindle waves consist of 11- to 15-Hz oscillations that wax and wane in amplitude and are usually 2 to 4 seconds in duration, reappearing every 3 to 10 seconds. These events are triggered by an oscillatory interaction between the thalamus and NRT, and can occur spontaneously when these structures are isolated from their cortical connections[17,29,61,101,142]â€”that is, the neocortex is not required for generation of these events. Intracellular recordings in vivo have clearly shown that NRT neurons are firing in a series of bursts during spindle discharges, superimposed on a slow depolarization.[128] Synchronization of NRT may be enhanced by the presence of dendrodendritic,[40] electrical,[76,82] and conventional axonal reciprocal inhibitory interconnections between NRT neurons (synapse 7, Fig. 1). Unlike the very specific reciprocal excitatory connections between thalamus and cortex, NRTâ€“thalamic inhibitory connections tend to be much more divergent, with extensive NRT axonal arbors in the thalamus. Therefore, these bursts in NRT elicit synchronized GABAergic inhibitory postsynaptic potentials (IPSPs) in large populations of thalamic relay neurons, mediated by activation of both $GABA_A$ and $GABA_B$ receptors (Fig. 4).[17,73] Due to deinactivation and subsequent activation of T current in thalamic neurons by the IPSP-induced hyperpolarization, a large Ca-dependent spike with an associated burst of Na-dependent action potentials is generated on the rebound of the NRT-mediated IPSPs (Figs. 3B, 4B). These thalamic bursts then reactivate the NRT and activate the cerebral cortex. The reactivated NRT then rapidly reinitiates a second wave of the spindle by triggering another IPSP in thalamic neurons. In this spindle rhythm, the NRT may serve as the pacemaker because thalamic neurons do not exhibit spindle rhythms when isolated from the NRT, whereas the NRT apparently will spontaneously trigger spindles when isolated from the thalamus.[128,142] The termination of spindle oscillations may depend on progressive intracellular Ca^{2+} accumulation, which leads to persistent activation of I_h, disrupting the pacemaker potential for this rhythm.[8,84,85]

Role of Thalamus and Thalamocortical Circuits in Generating Generalized Epileptiform Discharges

Relationship Between Spindles and Spike-and-Wave Discharges

In addition to the generation of normal rhythms like sleep spindles, the thalamocortical system participates in the generation of pathologic rhythms, as well. Perhaps the best characterized of these rhythms is the 3- to 4-Hz SWD activity of absence epilepsy.[14] Unlike spindles, which can be recorded in the thalamus of decorticated animals,[29,101] intact thalamocortical connections are required for typical SWDs to be generated.[47,97] SWDs are bilaterally synchronous thalamocortical oscillations[106,122,146] and, as the name implies, consist of repetitive cycles of an early sharp spike associated with action potential firing in thalamus and cortex, followed by a slower wave associated with prolonged inhibition in cerebral cortex[118] and probably also in thalamus.[127] Several lines of evidence support the concept that similar mechanisms and

synaptic circuitry may underlie the generation of normal sleep spindle rhythms and the pathologic thalamocortical rhythms of generalized absence epilepsy. In patients with generalized absence epilepsy, Kellaway[71] has demonstrated that the occurrence of SWDs is remarkably correlated with slow-wave sleep stages. In the feline penicillin-generalized epilepsy model of generalized absence epilepsy, SWDs have been shown to evolve from spindle rhythms following intramuscular injection of penicillin. This transition from 7- to 14-Hz spindle rhythms to 3- to 4-Hz SWDs occurs gradually and is accompanied by the behavioral symptoms of absence.[47] Consistent with the hypothesis that the T current amplifies and drives both normal and pathologic thalamocortical oscillations is the finding that specific generalized absence anticonvulsants like ethosuximide (Zarontin) and trimethadione (Tridione) block the T current in thalamic neurons[30,31,32,33] and also block cloned, expressed human T-type Ca channels, including Ca3.1 to Ca3.3, when applied in clinically relevant concentrations.[49] In in vitro studies of spindle rhythms in slices of ferret lateral geniculate nucleus, blocking $GABA_A$-mediated inhibition in these slices is associated with a transition from faster, smaller, spindle-like rhythms to slower, larger, SWD-like rhythms, which are blocked by ethosuximide.[142] Huguenard and Prince[61] have also demonstrated that in vitro stimulation-evoked thalamic oscillations can be blocked by ethosuximide, a generalized absence anticonvulsant, and that this block is associated with the T-current blocking effects of this drug. Extending these studies to include the cerebral cortex in thin slices of rodent brain maintaining reciprocal connections between thalamus, cortex, and NRT, spontaneous thalamocortical oscillations can be recorded.[34] These oscillations are similar in many ways to SWD rhythms and are selectively blocked by drugs effective in the control of generalized absence epilepsy[152,153] but not by other anticonvulsants.[151] This suggests that thalamocortical circuitry is both necessary and sufficient to generate SWD rhythms, although other areas of the brain are certainly involved in the modulation of these events. Human and animal neuroimaging studies also support the role of both cortex and thalamus in spike wave seizures.[2,6,9,10,43,104,123]

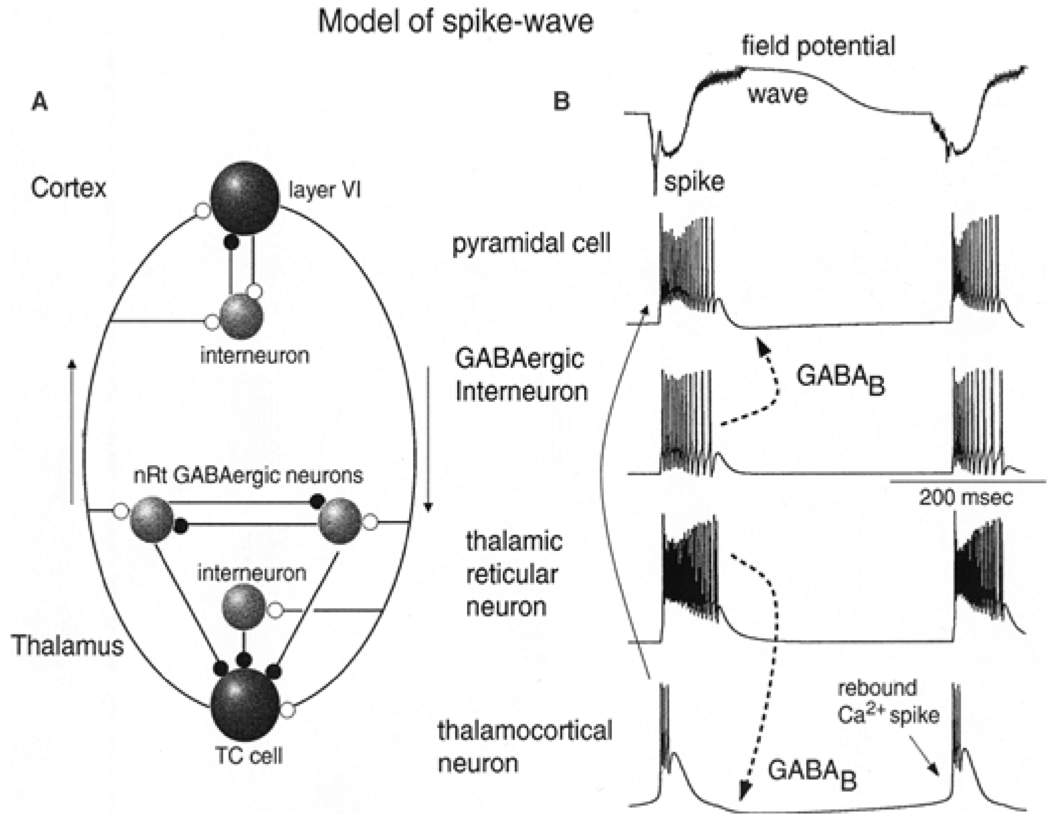

FIGURE 4. Cortical and thalamic cellular networks involved in spike-and-wave seizure generation. **A:** Simplified circuit diagram of cortical and thalamic networks shown in FIGURE 1, involved in both normal spindle wave oscillations, and spike-and-wave seizures. Cortical pyramidal neurons and thalamocortical cells form reciprocal excitatory connections (*open circles*). Inhibitory GABAergic interneurons distributed throughout the cortex and thalamus, as well as in the thalamic reticular nucleus, modulate the excitatory activity (*inhibitory synaptic connections are denoted with filled circles*). **B:** Simulation of one cycle of a SWD in corticothalamic networks. A burst of spikes in a thalamocortical neuron activates the cortical pyramidal cell through excitatory connections. This generates a strong burst of action potentials through intracortical recurrent excitatory connections. This burst strongly activates both local GABAergic neurons and thalamic reticular neurons. Activation of $GABA_B$ receptors produces a slow IPSP, leading to a rebound Ca^{2+} spike in the thalamocortical cell, 300 msec later, and initiates the next cycle of the oscillation. From McCormick DA, Contreras D. On the cellular and network bases of epileptic seizures. *Annu Rev Physiol*. 2001;63:815â€“846, with permission.

Cellular Correlates of Spike Wave Discharges of Generalized Absence Epilepsy

Steriade and Contreras[127] have physiologically characterized the cortical and thalamic cellular events that occur during the transition from spindle to seizure rhythms in anesthetized cats in vivo. In this study, it was found that during 2- to 4-Hz SWD-like activity, thalamic, cortical, and NRT neurons behave very similarly to that expected if SWDs were generated by similar underlying mechanisms to spindles (described earlier). Cortical neurons evidence increased excitatory recurrent drive during the transition from sleep to paroxysmal activity or, in some cases, a large synchronous inhibitory event could trigger the transition between sleep and epileptic activity. NRT neurons triggered large rhythmic bursts of action potentials riding a slow depolarizing wave during low-frequency thalamocortical rhythms. During 2- to 4-Hz SWD-like activity, thalamic neurons either triggered rhythmic rebound bursts following NRT-mediated IPSPs (similar to that depicted in Figs. 3,4) or exhibited prolonged periods of inhibition with no rebound activity.

Transition From Normal Sleep Spindles to Pathological Spike Wave Rhythms

The above studies, work from the feline penicillin model,[7,48] and rodent studies[96] suggest that enhanced cortical excitability can trigger a change from normal spindle oscillations to SWDs in an intact thalamocortical circuit. Dual intracellular recordings from ferret lateral geniculate nucleus slices demonstrated that brief firing of GABAergic NRT cells produced brief, approximately 0.1-second IPSPs in thalamocortical cells, mediated by GABA_A receptors.[73] In the same preparation, sustained firing of NRT cells produced longer, approximately 0.3-second IPSPs, mediated by GABA_B receptors (Fig. 4B). Under normal conditions, cortical inputs (Fig. 1, synapse 5; Fig. 4A) may produce brief firing of NRT cells, with approximately 0.1-second IPSPs in the thalamus, which sets the oscillation frequency at approximately 10 Hz or higher, as is seen in normal sleep spindles. On the other hand, pathologically enhanced cortical firing may produce sustained NRT firing, with approximately 0.3-second thalamic IPSPs setting the oscillation frequency of the whole system at 3- to 4-Hz, as is seen in typical absence seizures. Thus, the switch from spindles to spike waves may depend on enhanced cortical firing, which causes a transition from fast GABA_A to slow GABA_B receptorâ€“mediated IPSPs in the thalamus (Fig. 4B). Additional support for this mechanism has come from recordings in a stimulated thalamic slice preparation, which simulates corticothalamic and thalamocortical feedback interactions.[17,144] In this preparation, selective GABA_A or GABA_B antagonists were capable of switching the network oscillations from paroxysmal spike-and-wave rhythms to normal spindle oscillations, regardless of cortical inputs.

Phenotypic Basis for Generalized Absence Epilepsy in Animal Models

Generalized absence epilepsy is a disorder with a strong genetic basis. Elucidating the phenotypic basis of absence in rodent genetic models of this disorder has been a focus of much recent research effort. Several mechanisms that may underlie the generation of SWDs have been described in genetic animal models of generalized absence epilepsy. In a pioneering series of studies aimed at elucidating mechanisms underlying SWDs in a single-gene mutant mouse *tottering* that phenotypically expresses absencelike seizures, Noebels et al. reported a gene-linked proliferation of noradrenergic locus coeruleus axon terminals in the brain of epileptic mutants.[80] Furthermore, correction of this inherited hyperinnervation with neonatal 6-OHDA treatment prevented the expression of the absence-like phenotype, implicating noradrenergic mechanisms as being critical for expression of the epilepsy in this model.[107] Subsequent to these studies, the gene responsible for generation of seizures in *tottering* has been determined and found to be a gene encoding a high-threshold Ca-channel subunit, Cav2.1/Î±1A.[45] Similar mutations in high-threshold Ca-channel subunits have been found in several other mouse strains with absence seizures, including *lethargic* (Î²4),[24] and *stargazer* (Î³2).[79] Interestingly, these mutations in high-threshold Ca-channel subunits are all accompanied by an upregulation in low-voltage activated Ca currents in these three strains, perhaps as a compensatory mechanism, and consistent with the probable role of upregulation of T-type Ca currents in the pathophysiology of absence seizures.[25] GABA_B mechanisms have also been implicated as important in the generation of SWDs in various rodent genetic models expressing absence because systemic administration of GABA_B antagonists has a strong anticonvulsant effect, whereas localized perfusion of GABA_B agonists into the thalamus has a marked proconvulsant effect in these animals.[59,81] In addition, Hosford et al.[59] have reported an increase in the density but not the binding properties of GABA_B receptors in the thalamus and cortex of lethargic mice, a mutant strain that evidences SWDs as part of its phenotype. GABA_A receptors are important for damping overexcitation in NRT neurons; and one study found that knocking out the $GABA_A$ receptor's Î²$_3$ subunit, normally expressed selectively in the NRT, caused enhanced paroxysmal oscillations in mouse thalamic slices.[62] In the genetic absence epilepsy rat strain from Strasbourg (GAERS), it has been reported that an increased amplitude of T-type Ca current is evident in the NRT but not in thalamic neurons of GAERS, relative to control strains.[133] WAG/Rij rats, another rodent absence model, show several differences compared with control rats, including increased expression of cortical voltage-gated Na channels Nav1.1 and 1.6; decreased cortical hyperpolarization activated cation channels, HCN1; increased thalamic HCN1; increased expression of the high-voltage activated Ca-channel Ca_V2.1 (P/Q) in RTN; and altered cortical dendritic morphology.[23,69,74,129,134] Several other genetic models have known molecular defects associated with spike-and-wave seizures. HCN2 knockout mice and stargazer both have alterations in I_h,[42,83] whereas a variety of Ca-channel mutations produce spike-and-wave in mouse models.[14,36] Mutations in genes associated with other cellular maintenance functions,[68,150] and in the Na/hydrogen exchanger gene, NHE1 can cause spike-and-wave seizures in mice.[35] Given our current understanding of the mechanisms important in rhythm generation within the thalamic synaptic network, this type of phenotypic alteration could certainly contribute to an increased bias of the thalamocortical system toward generation of excessively synchronized oscillations in these epileptic rodent model systems.

The possible involvement of these experimental phenotypic mechanisms in the generation of the human epileptic condition remains to be fully determined, although recent human studies have elucidated mutations in several genes in families or individuals with absence seizures. Amino acid substitution or splice-donorâ€"site mutations in the $GABA_A$ receptor Î³2 subunit (*GABRG2*) have been associated with childhood absence and febrile seizures,[67,143] and a stop mutation in the pore-forming Î±1A subunit of the P/Q Ca^{2+} channel (*CACNA1A*) is associated with childhood absence seizures and ataxia.[66] These early examples are likely to be rare causes of absence seizures, and the search for additional genes continues. However, these findings demonstrate that changes in a number of different single genes important in neuronal signaling and excitability are capable of generating absence seizures.

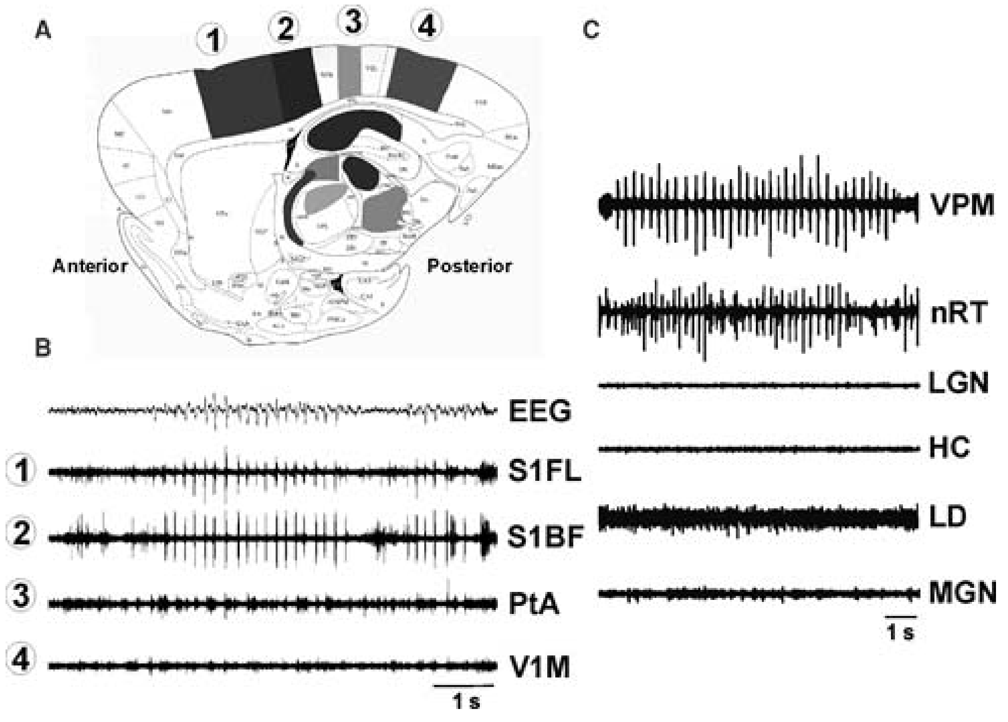

FIGURE 5. Selective cortical and subcortical network involvement in rodent spike-and-wave seizures. **A**: Regions sampled by microelectrodes, displayed on a sagittal section from a stereotactic atlas; Paxinos G, Watson C. *The Rat Brain in Stereotaxic Coordinates*, 4th ed. San Diego: Academic Press; 1998, with permission.[111] **B**: Example of recordings from cortical regions with simultaneous EEG and extracellular

multiunit electrodes during spike-and-wave seizures in the WAG/Rij rat. An array of four microelectrodes was placed along a straight line running from anterior to posterior (*contacts numbered 1 through 4*), 3.6 mm lateral from bregma. Interelectrode spacing was 2 mm. EEG (*upper trace*) was recorded with subcutaneous electrodes. S1FL, forelimb primary somatosensory cortex; S1BF, barrel field primary somatosensory cortex; PtA, parietal association cortex; V1M, primary visual cortex. **C**: Recordings from deep structures during spike-and-wave seizures. Examples are shown of recordings with individual extracellular microelectrodes placed during different experimental runs in the thalamic ventral posterior medial nucleus (VPM). nRT, thalamic reticular nucleus; LGN, lateral geniculate nucleus; HC, hippocampus; LD, lateral dorsal nucleus; MGN, ventral medial geniculate nucleus. Simultaneous recordings from frontal cortex had large amplitude SWD in all cases. Recordings were performed from WAG/Rij rats under fentanyl/haloperidol anesthesia. Modified from Nersesyan H, Herman P, Erdogan E, et al. Relative changes in cerebral blood flow and neuronal activity in local microdomains during generalized seizures. *J Cereb Blood Flow Metab*. 2004;24(9):1057â€"1068, with permission.[103]

Specific Nuclei Considered Especially Important for Generalized Epilepsy

Three main types of dorsal thalamic nuclei have been implicated as especially important in the generation of generalized seizure discharges. These are the lateral sensory relay

nuclei and the midline thalamic (intralaminar) nuclei, which are importantly involved in the generation of SWDs in animal models of absence; and the anterior and mediodorsal thalamic nuclei, which may be involved in the generation of primarily or secondarily generalized convulsive seizures, due to their extensive interconnections with the limbic system.

Lateral Thalamic Relay (Specific) Nuclei

In studies both in humans[5,13,52,106,113,122,126,146,147] and in animal models of generalized absence epilepsy,[47,97,103] the post-erolateral thalamic nuclei appear to be intimately involved in the generation of SWDs (Fig. 5). In cats experiencing feline generalized penicillin epilepsy, extracellular recordings of spike-and-wave activity are much more readily obtained from the specific nuclei than from the nonspecific midline nuclei.[94] Recordings from rodent models have shown that certain specific thalamic relay nuclei and their corresponding cortical regions are preferentially involved, whereas other thalamocortical networks are almost entirely spared[97,103] (Fig. 5).

Midline Thalamic (Intralaminar or Nonspecific) Nuclei

The midline thalamic nuclei have been reported to rarely participate vigorously in SWD generation in rodent genetic models of absence,[97] or in some chemically induced models of absence (e.g., feline penicillin generalized epilepsy).[47,94] On the other hand, more recent recordings from rodent models have shown delayed involvement of intralaminar thalamic nuclei, suggesting a role in synchronization and maintenance of SWDs.[124] In addition, these nuclei do participate in SWDs generated by systemic administration of Î³-hydroxybutyrate, and there is some evidence from depth recordings in humans that midline thalamic nuclei participate in the generation of SWDs accompanying other (nonabsence) epileptic conditions.[122] In early experiments in cats, midline stimulation of the thalamus elicited cortical EEG responses similar to SWDs, as well as some of the behavioral symptoms of absence.[39,65] It was also shown that injection of small amounts of penicillin into the midline thalamic nuclei induced a slowing of cortically recorded barbiturate spindles (8- to 12-Hz) to SWD frequencies (3- to 5-Hz), accompanied by enhanced synchronization of the rhythms,[119]

further suggesting a role for the nonspecific thalamic midline and intralaminar nuclei in the generation of SWDs.

Anterior and Mediodorsal Nuclei and Generalized Convulsive Seizures

The anterior and midline thalamic nuclei have been shown to be involved in the generation of convulsive seizures elicited by systemic pentylenetetrazol (PTZ) or bicuculline administration. In the PTZ model of seizures, EEG recordings cycle through a series of stages prior to the development of convulsive seizures. One of these activity stages appears to be SWDs, suggesting involvement of the thalamocortical system in PTZ-induced electrical activity and convulsions. Injection of $GABA_A$ or $GABA_B$ agonists into the midline thalamus will exacerbate generalized convulsive seizures induced by the systemic administration of either PTZ or bicuculline.[98,99] Furthermore, irreversible inhibition of GABA-transaminase activity with Î³-vinyl-GABA microinjections into midline thalamus elevated PTZ seizure thresholds. These data are consistent with the concept that PTZ-induced electrical and convulsant activity may involve the activation of neuronal circuitry and processes similar to those of generalized absence epilepsy (the thalamocortical system). Also compatible with this idea of PTZ's thalamocortical activation-mediating effects is the ability of generalized absence anticonvulsants to block PTZ-induced seizures. This relationship is so consistent that PTZ-induced seizures are routinely employed as a screen to test drugs for potential activity in absence epilepsy.

Further support for the role of medial thalamic nuclei in generalized convulsions comes from recent neuroimaging studies showing activation of the medial thalamus during human induced or spontaneous secondarily generalized tonic-clonic seizures.[22,137,138]

Localized Thalamocortical Networks in Generalized Seizures

Although considered a form of generalized epilepsy, it has long been recognized (based on EEG recordings) that SWDs do not involve the entire forebrain in a uniform fashion. Based on human scalp EEG, a frontal predominance in the amplitude of SWDs often is seen, maximal in the frontal midline region.[58,121,145] Recent functional magnetic resonance imaging (fMRI) studies in patients during SWDs have also shown focal involvement of bilateral frontal and parietal cortex, as well as the thalamus, with large regions of cortex relatively spared.[2,6,9,10,123] Similarly, neuroimaging of secondarily generalized tonicâ€“clonic seizures has shown focal bilateral involvement of the frontoparietal cortex and medial thalamus, with other regions relatively spared.[18,22,46,95,137,138]

Focal thalamocortical network involvement in generalized seizures has important practical implications. Selective involvement of frontoparietal association cortex may explain why patients with absence seizures often have difficulty with tasks requiring novel information processing, but continue to perform simple motor tasks during seizures.[15,75] Intense, focal involvement of the frontoparietal cortex and medial thalamus during tonicâ€“clonic seizures may explain the profound impairment of consciousness that occurs during and following this seizure type.[22,137,138]

Focal involvement in generalized seizures suggests that altered excitability in specific regions of the thalamocortical network may be crucial for seizure generation. This opens the possibility of developing more selective regional therapies, targeted at controlling altered excitability in specific regions rather than the whole brain. Work in animal models has begun to shed some light on the mechanisms of altered excitability in selective thalamocortical networks during generalized seizures. In vivo recordings from rodent models of spike-and-wave seizures have shown that seizure discharges are largest in amplitude in the more anterior somatosensory and motor cortex and corresponding thalamic nuclei, whereas the occipital cortex and thalamic visual relay areas are almost entirely spared[96,103] (Fig. 5). High-field fMRI studies in rodent models have agreed with this selective thalamocortical network involvement in generalized seizures, and may lead to the identification of other regions important in seizure generation.[104] A recent elegant study found that local delivery of ethosuximide via microinfusion to the region of somatosensory cortex most intensely involved in spike-and-wave seizures led to seizure blockade.[87] In addition, it has been found that altered expression occurs of molecules, such as Na channels, which may contribute to enhanced excitability in focal brain regions[74] (Fig. 6). An increased expression of voltage-gated Na channels Nav1.1 and 1.6 was found selectively in layers II and III of the somatosensory cortex in epileptic rats with spike-and-wave seizures, but not in nonepileptic control rats.

Pharmacologic Control of Spike-and-Wave Discharges

Generalized absence epilepsy has a unique pharmacologic profile with respect to control by antiepileptic drugs (AEDs). The efficacy (or lack thereof) of most of the currently employed AEDs can be explained, at least in part, through an understanding of how the cellular mechanisms of action of the drug interact with our current understanding of the physiologic oscillator generating SWDsâ€”the thalamocortical system. The specific generalized absence drugs ethosuximide and trimethadione, which have little or no efficacy in other forms of epilepsy, both block the T-type Ca current as one cellular mechanism of action.[31,32] Broader-spectrum anticonvulsants with absence efficacy have variable cellular mechanisms, including augmentation of GABAergic inhibition (benzodiazepines, valproate) and T-current block (methsuximide [Celontin]; valproate[72]). Both benzodiazepines and barbiturates augment GABAergic inhibition as a cellular mechanism of action, but only benzodiazepines are effective in the control of absence. This selective efficacy of benzodiazepines in controlling absence is apparently due to the selective augmentation of GABAergic neurotransmission in the cerebral cortex by these drugs, with much reduced efficacy in thalamus.[109] This may be due to regional variation in the structure and function of $GABA_A$ receptors in the brain.[62,110,117,148] Because augmenting inhibition in the thalamus is proconvulsant in absence,[47,97] the selective effects of benzodiazepines in the cortex may be consistent with their clinical utility in this seizure disorder. Barbiturates are equally effective in augmenting inhibition in the thalamus and cortex, and this could reduce their effectiveness in controlling absence seizures. In addition, differential effects on $GABA_A$ versus $GABA_B$ receptors may determine whether a medication reduces or increases absence seizures. For example, vigabatrin, by nonselectively increasing $GABA_A$ and $GABA_B$ neurotransmission, tends to increase SWDs.

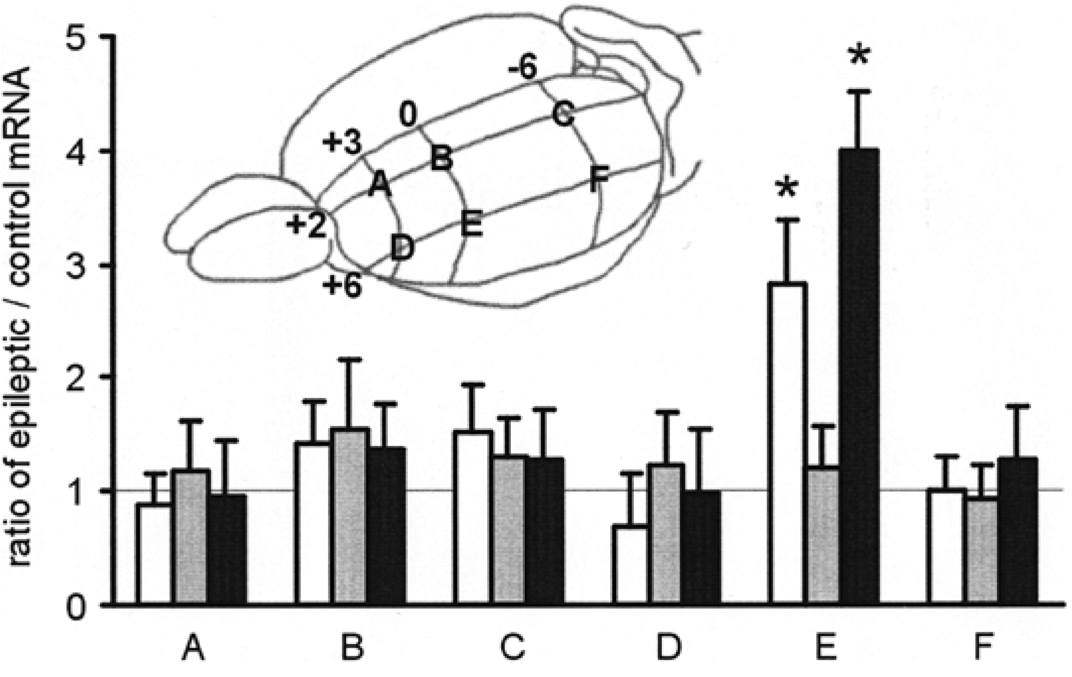

FIGURE 6. Focal increased expression of voltage gated sodium channels in region of most intense cortical spike-and-wave seizures. Na-channel mRNA was analyzed in the cortex of epileptic WAG/Rij rats and compared to nonepileptic and Wistar control rats. Anatomic locations of tissue plugs used for quantitative PCR analysis are indicated on inset drawing of rat brain. The histogram shows the ratio of sodium channel mRNA levels in the neocortex of 6-month-old WAG/Rij (epileptic) rats compared to age-matched Wistar (control) rats. At anatomical location â€œE,â€ which corresponds to the rat facial somatosensory cortex, there is a statistically significant (*$p < 0.05$) increase in the voltage-gated Na channel Nav1.1 (*white bars*) and Nav1.6 mRNA (*black bars*), but not Nav1.2 mRNA (*gray bars*), in the epileptic animals compared with control animals. From Klein JP, Khera DS, Nersesyan H, Kimchi EY, Waxman SG, Blumenfeld H. Dysregulation of sodium channel expression in cortical neurons in a rodent model of absence epilepsy. *Brain Res*. 2004;1000:102â€“109.[75]

Thalamocortical networks in localized epilepsy

The anterior thalamic nuclear group, mediodorsal nucleus, and midline thalamic nuclei have strong reciprocal limbic connections (Table 1). Because limbic cortical structures, most often in the temporal lobe, are commonly involved in localized epilepsy, interest has been growing in these limbic thalamic regions as possible therapeutic targets for localized epilepsy.

Several lines of evidence demonstrate that the thalamus participates in localized epilepsy and may be important for controlling seizure susceptibility.[108] In patients with mesial temporal lobe epilepsy, the ipsilateral thalamus shows reduced volume on MRI,[26,37,38] atrophy on pathologic study,[88] and hypometabolism on fluorodeoxyglucose positron emission tomography (PET) metabolism.[27,54,105,149] Depth electrode recordings have demonstrated thalamic involvement during seizures in patients and animal models with partial epilepsy.[11,20a,139,140] Rats with chronic spontaneous limbic epilepsy were found to have neuronal loss in the medial dorsal thalamic nucleus.[12] In addition, several 2-deoxyglucose mapping[28,50,51,93,136] and focal drug infusion studies[57,98,100] have identified the mediodorsal thalamus and midline nuclei as important for limbic and other seizure activity in animal models. These findings may reflect the known strong reciprocal connections between limbic mesial temporal structures and the medial thalamic nuclei.[1,25]

Recent fMRI and MR spectroscopy studies also suggest thalamocortical network dysfunction in localized epilepsy.[3,41,144] In addition, during seizures in patients with mesial temporal lobe epilepsy, increased perfusion occurs in the medial thalamus based on single photon emission computed tomography (SPECT),[19,77,89,130] which is highly correlated with decreased perfusion in frontoparietal association cortex.[19] Dysfunction of the frontoparietal association cortex, caused by abnormal thalamocortical network activity, may be crucial for loss of consciousness in temporal lobe seizures.[19,20,21]

Because of its participation in partial seizures, the thalamus has been investigated as a therapeutic target to reduce seizure susceptibility. In animal studies, thalamic lesions or electrical stimulation are associated with a reduction in partial seizures.[108,132] Some studies suggest that the thalamus may participate in the therapeutic modulatory effects of vagus nerve stimulation.[53,55,120,135] Work by Velasco et al. has suggested that stimulation of the centromedian nucleus in humans may reduce seizures,[141] however a trial by Fisher et al. was inconclusive.[44] Initial studies of anterior thalamic stimulation have shown promising results.[4] A large multicenter prospective trial of anterior thalamic stimulation is currently under way, and future prospects for therapeutic brain stimulation are being pursued actively.[102,132]

Summary and Conclusions

The present chapter provides an overview of the anatomy and physiology of the thalamocortical system, with a specific emphasis on how this system functions in the generation of normal and pathologic rhythms. The thalamus and cerebral cortex function in an intimately interconnected manner and, to fully understand their operation, the synaptic and intrinsic properties of both must be considered jointly. The thalamocortical system functions in two main states: a faithful relay mode, in which afferent information is relayed through the thalamus to the cortex, with little loss of information content; and an oscillatory mode, in which the system tends to spontaneously generate normal and pathologic low-frequency rhythms. The transition between these states is mediated by the degree of activity in both sensory and brainstem neuromodulatory afferents. The main oscillator driving and maintaining the rhythmic properties of this system resides in the thalamus/NRT synaptic network. In this circuit, GABAergic inhibition impinging onto thalamic neurons originating from the NRT serves as a synchronizing mechanism, and the low-threshold T-type Ca current in thalamic neurons serves as an amplifying factor. With this oscillator positioned in a tightly interconnected thalamocorticothalamic loop, the thalamocortical system is in an optimum situation to generate reverberating generalized rhythms that can be recorded in the cortical EEG. In normal situations, rhythms generated by this system include the spindle discharges encountered during drowsiness and sleep. The thalamocortical system is also critically involved in generating pathologic rhythms, including the SWDs of generalized absence epilepsy. Although little is known as yet about the etiology of absence in humans, recent studies in rodent genetic models of absence have demonstrated several candidate phenotypic mechanisms that may contribute to the generation of SWDs. Growing evidence suggests an important role for thalamocortical networks in localized epilepsy as well, with important therapeutic implications. These types of studies, coupled with our current knowledge of mechanisms involved in the generation of synchronized rhythms within the thalamocortical system, afford promise for a better understanding of the epileptogenic mechanisms underlying generalized seizures and may also have applications to understanding localized epilepsy.

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Chapter 32

Basal Ganglia and Brainstem Anatomy and Physiology

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Introduction

Seizure activity does not spread diffusely throughout the brain, but propagates along specific anatomic pathways. The particular pathways responsible for triggering and propagating a seizure determine the nature of the seizure and the pattern of the motor manifestations that accompany it. Although seizures may result from any of a broad array of brain insults, the motor concomitants of the seizures fall into only a few categories of remarkably stereotyped behaviors. This suggests that the anatomic substrates of propagated convulsive seizures in the intact organism may likewise fall into a few major categories or systems. In this chapter, some of the subcortical anatomic substrates of seizure propagation are reviewed. In addition, we identify certain anatomic circuits that are responsible for regulating seizure susceptibility and act as common modulators for multiple seizure-generating circuits. The pathways within the basal ganglia and brainstem will be the main focus of this chapter, with passing reference to other subcortical structures with which these systems interconnect.

Before considering particular anatomic substrates, it is important to recognize that brain regions and pathways may participate in the seizure process in distinctive respects. Some of the roles that a brain area or pathway may play include:

- *Epileptogenic â€œtriggerâ€ area*. A site in the brain that is capable of evoking propagated seizure activity upon focal electrical or chemical stimulation. The trigger area is analogous to a â€œswitch.â€ It sets in motion the events that result in a seizure, but it is not necessarily one of the first areas to exhibit ictal activity during seizure development.
- *Epileptogenic â€œtargetâ€ area*. A site in the brain that is especially vulnerable to the development of ictal activity, either by virtue of its anatomic inputs (e.g., from a â€œtriggerâ€ area) or by virtue of its intrinsic circuitry. This area would be one of the first areas to exhibit a pattern of ictal discharge during the initial development of a seizure, but it is not necessarily a source for seizure propagation.
- *Pathways involved in propagation of the seizure.* These include pathways connecting â€œtriggerâ€ areas and â€œtargetâ€ areas, pathways creating positive or negative feedback circuits, pathways allowing the seizure to spread to additional brain loci, and commissural pathways allowing bilateral spread.
- *Gating inputs*. Neural inputs to â€œtriggerâ€ or â€œtargetâ€ areas that modulate the excitability of these regions. Changes in the activity of the gating inputs alter seizure threshold in a predictable fashion. These inputs alone are not necessarily capable of inducing seizures.

The first three of these categories are generally specific to seizure type. Gating inputs, on the other hand, exert a common influence on many different seizure types. Brainstem circuitry is most often associated with gating functions, whereas forebrain circuitry has typically been studied for trigger and target components.[101,102,104]

Overview of Anatomy

Basal Ganglia Circuits

The basal ganglia are a collection of nuclei situated in the forebrain and midbrain that include the caudate nucleus and putamen (together referred to as â€œstriatumâ€), globus pallidus, entopeduncular nucleus (equivalent to the internal segment of the globus pallidus), subthalamic nucleus, and substantia nigra. The striatum represents the â€œreceivingâ€ end of the system, and the internal segment of the globus pallidus (entopeduncular nucleus in rat) and substantia nigra represent the output end of the system. Three major relays mediate the impact of the basal ganglia on behavior: thalamus, intermediate and deep layers of superior colliculus, and the pedunculopontine area of the caudal mesencephalic tegmentum. Some of the circuitry that interconnects these regions is illustrated in FIGURE 1.

Brainstem Projections

The midbrain and pontine regions of the brainstem contain the cell groups from which the ascending serotonin-containing pathways originate (dorsal and median raphe nuclei) and from which the noradrenergic pathways originate (locus ceruleus and nearby cell groups). Important cholinergic projections also derive from specific cell groups in the caudal midbrain and rostral pons. These monoaminergic and cholinergic projections reach widespread regions of the diencephalon and telencephalon in the forebrain (see Fig. 2). These projections play a critical role in the regulation of sleepâ€“waking states, arousal, and attention, in addition to influencing seizure susceptibility.

Independence of Seizure Generating Mechanisms in Forebrain and Brainstem

Forebrain Mechanisms

It has been demonstrated in the cat that complete transections disconnecting the forebrain from the brainstem do not interfere with the electroencephalographic seizure discharge recorded from the forebrain in response to pentylenetetrazol.[173] More recently, in the rat, Browning et al. found that electroencephalographic seizure activity evoked focally from the area tempestas, an epileptogenic site in the deep anterior piriform cortex, was not impaired by complete transections of the brainstem at the pre-, mid- or postcollicular level.[24] These observations indicate

that circuitry within the forebrain is sufficient to initiate, propagate, and sustain bilateral seizures in the absence of neural connections with the midbrain or hindbrain.

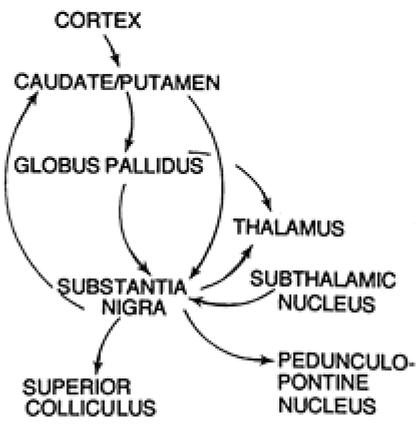

FIGURE 1. Basal ganglia and some of their interconnections, inputs, and outputs.

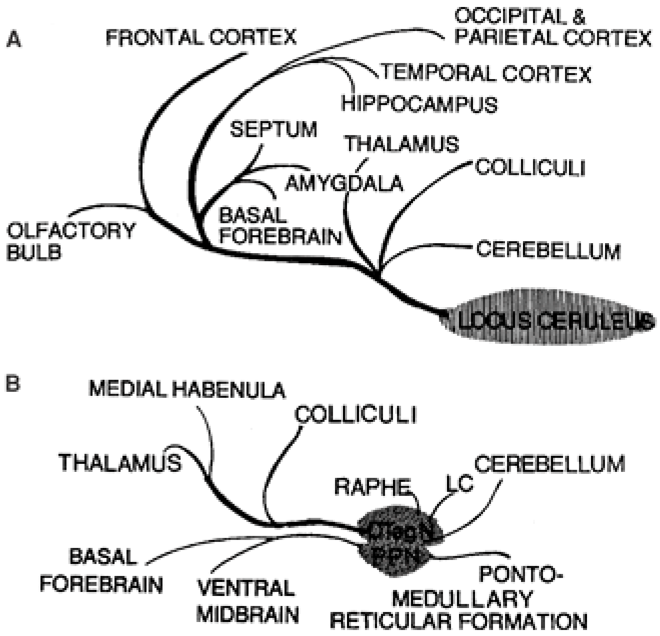
A
FRONTAL CORTEX
OCCIPITAL & PARIETAL CORTEX
TEMPORAL CORTEX
HIPPOCAMPUS
SEPTUM
THALAMUS
COLLICULI
AMYGDALA
BASAL FOREBRAIN
OLFACTORY BULB
CEREBELLUM
LOCUS CERULEUS
B
MEDIAL HABENULA
COLLICULI
THALAMUS
RAPHE
LC
CEREBELLUM
DTegN
PPN
BASAL FOREBRAIN
VENTRAL MIDBRAIN
PONTO-MEDULLARY RETICULAR FORMATION

FIGURE 2. A: Noradrenergic projections ascending from locus ceruleus. **B:** Cholingergic projections ascending from dorsal tegmental nucleus (DTegN). LC, locus ceruleus; PPN, pedunculopontine nucleus.

Brainstem Seizures That Do Not Depend on Connections with Forebrain

Although forebrain regions are crucial in many forms of epilepsy, the brainstem has multiple roles in both the triggering and propagation of certain types of seizures. A â€œbrainstemâ€ seizure model has been suggested by Gioanni et al. with regard to the quaking mutant mouse. They found that focal stimulation of multiple brainstem regions can induce tonicâ€“clonic seizures in these animals.[121] Likewise, brainstem substrates are critical in the induction of audiogenic seizures in susceptible animals, and massive ablation of forebrain structures does not prevent these convulsions.[117] Brainstem structures are also sufficient for tonic convulsions evoked by maximal electroshock or chemoconvulsants.[28] These observations indicate that, for certain seizure types, the brainstem contains the trigger areas and target areas as well as the pathways required for the full expression of the seizures.

Several animal models of convulsive seizures frequently include explosive running and bouncing characterized by vigorous clonic movements of all four limbs; a tonic component involving the flexion/extension of all limbs, and loss of righting reflex often follows. This convulsive pattern is produced by systemic administration of chemoconvulsant drugs such as pentylenetetrazol, picrotoxin, and bicuculline, as well as by acoustic stimulation of animals that are prone to audiogenic seizures.[25,103] These types of seizures have been shown to depend on neural substrates in the brainstem, and do not require the integrity of the forebrain for either their initiation, development, or expression.[25,28]

Inferior Colliculus as a Site of Seizure Initiation

Stimulation of Inferior Colliculus

The inferior colliculus is a brainstem site from which running/ bouncing clonic seizures can be triggered in rodents. Electrical stimulation of the inferior colliculus in the rat, as well as focal application of drugs that stimulate excitatory amino acid transmission in this site, elicit sudden, explosive bouts of leaping, running, and bouncing on all four limbs.[82,94,95,187,194] This behavior resembles that associated with sound-induced (audiogenic) seizures in susceptible rodent strains, and although it can also be evoked by disinhibition of periaqueductal gray neurons,[10] it is not dependent on the integrity of the periaqueductal gray for its expression. These inferior colliculus-evoked seizures in rats, which can be induced as early as 3 days of life, have been compared to human neonatal seizures. In fact, McCown and Breese suggest that many neonatal human seizures may actually be initiated in the inferior colliculus.[183]

The electroencephalographic features of seizures electrically evoked from the inferior colliculus have been well characterized by McCown et al.[187] During the wild running behavior, afterdischarges are seen in the region of the inferior colliculus, without abnormalities in the forebrain. Upon repeated stimulation of the inferior colliculus, there is a kindling-like progression to forelimb manifestations (myoclonus or tonic extension); this is associated with both afterdischarges in the region of stimulation and electrical spiking activity in the frontal cortex.

Î³-Aminobutyric Acid and Glutamate in the Inferior Colliculus

Blockade of Î³-aminobutyric acid (GABA) transmission in the inferior colliculus evokes convulsive effects similar to audiogenic seizures,[94,95] increases auditory evoked potentials, and induces susceptibility to audiogenic seizures in otherwise normal rats.[11] Faingold et al. found that infusion of baclofen (a $GABA_B$ agonist) or gabaculine (a GABA transaminase inhibitor) into the inferior colliculus of genetically epilepsy-prone rats (GEPRs) significantly reduced the severity and incidence of audiogenic seizures;[81] muscimol, a $GABA_A$ agonist, was almost twice as potent as baclofen at reducing seizures in this model. Similarly, tiagabine, a GABA uptake inhibitor that increases extracellular GABA levels, significantly reduced seizure severity in the GEPR when given either systemically or focally into the inferior colliculus. This occurred in conjunction with a reduction in neuronal firing in the central nucleus of the inferior colliculus.[85] Taken together, these observations indicate that GABAergic transmission within the inferior colliculus provides a crucial inhibitory influence on susceptibility to sound-induced seizures.

An essential role for *N*-methyl-D-aspartate (NMDA) and non-NMDA glutamate transmission in audiogenic seizure initiation was suggested by Faingold et al.[84] based on evidence that the NMDA and non-NMDA antagonists were able to block audiogenic seizures in GEPRs when focally applied to the inferior colliculus. Focal application of an inhibitor of glutamate synthesis in the inferior colliculus also blocked audiogenic seizures in the GEPR,[86] whereas focal application of glutamate agonists in this region induced runningâ€“bouncing seizures in normal rats.[82,194]

Bicuculline in the inferior colliculus evoked only submaximal seizure activity, whereas NMDA agonists fully reproduced the tonicâ€“clonic seizure seen during audiogenic seizures, suggesting that disinhibition alone, without increased excitation, is not sufficient for full seizure expression in the GEPR.[117] In the aftermath of an audiogenic seizure, depletion of excitatory amino acids in the inferior colliculus may contribute to the postictal refractory period.[243]

Interactions Between Inferior Colliculus and Other Brainstem Structures

Lesions or focal inhibition of inferior colliculus transmission interferes with the generation of sound-evoked seizures not only in the genetically epilepsy-prone rat[26,73,83,149,300] but also in DBA/2 mice[306] and in rats undergoing alcohol withdrawal.[95] Cortical, not central, inferior colliculus nuclei appear to be critical for expression of these seizures.[117]

The inferior colliculus, as part of the auditory sensory system, is probably a crucial afferent relay station for converting acoustic stimulation into convulsive discharge. Consistent with this view is the reciprocal positive transfer between kindling of audiogenic seizures and electrical kindling of the inferior colliculus[140] and the fact that subconvulsant stimulation of this region can render otherwise normal animals susceptible to audiogenic seizures.[82,194] Direct chemical or electrical stimulation of this brain region does not typically evoke *tonic* convulsions in normal rats unless ascending norepinephrine (NE) projections have been compromised by lesions or depletion of NE.[31]

Detelencephalated rats exhibit enhanced susceptibility to audiogenic seizures in the presence of bicuculline in the inferior colliculus. Therefore, the forebrain structures may normally exert some inhibitory control over these seizures.[12] The specific target areas within the brainstem engaged by the inferior colliculusâ€“evoked convulsions have not yet been elucidated, but it is likely that there are critical glutamate-mediated connections in the mesencephalic and pontine tegmentum.[193] Mid-collicular knife cuts decrease the wild running component of audiogenic seizures, indicating that inferior colliculusâ€“superior colliculus interconnections are required for some components of audiogenic seizures.[245,269] Complete blockade of audiogenic seizures has been obtained with knife cuts that separate the central and external nuclei of the inferior colliculus, suggesting that seizure activity triggered in the central nucleus propagates out of the inferior colliculus via the external nucleus.[245,269] Because corticocollicular fibers terminate mainly in the external nucleus, this region may be an important link in a positive feedback loop involving the cortex. In fact, the actual seizure discharge pattern may become organized in the network engaged by the external nucleus, because this nucleus exhibits a low threshold for bursting in disinhibited collicular slices in vitro.[233] Pierson and Snyder-Keller[233] suggest that a bidirectional excitatory loop between superior colliculus and inferior colliculus may provide for an important oscillatory interaction that sets up the seizure discharge. According to their model, an initial depolarization of external nucleus cells contributes to the epileptiform discharge that develops in the deep superior colliculus and dorsal cortex of the inferior colliculus. The bursting in superior colliculus in turn precedes the synchronous repetitive bursting that occurs in the external nucleus. Thus, the deep superior colliculus is a crucial component of this oscillatory pattern. The participation of the external nucleus and dorsal cortex of inferior colliculus, as well as the deep superior colliculus, was also indicated in vivo by the pattern of *c-fos* expression associated with audiogenic seizure development.[233]

A high degree of lateralization is present in the inferior colliculus. Unilateral kindling of the inferior colliculus sufficient to produce runningâ€“bouncing seizures and bilateral electrical afterdischarge in the rat, does not alter the de novo kindling rate of the contralateral inferior colliculus. This lateralization is supported by 2-deoxyglucose studies.[184] Thus, the progression to runningâ€“bouncing seizures is distinct for each side. This contrasts with forebrain seizures in rats; for example, unilateral amygdala kindling facilitates kindling of the contralateral amygdala.[185]

Brainstem Substrates of Tonic Extensor Convulsions

In rodent models involving maximal or supramaximal convulsive stimuli, tonic extension of the forelimbs or hindlimbs is the typical convulsive endpoint. During the tonic extensor phase of a seizure, the forelimbs are rigid and extended caudally against the ventral surface of the body, while the hindlimbs are rigid and extended horizontally and away from the prone or supine body in a caudal direction. This tonic extensor phase is characteristic of seizures evoked by maximal electroshock or high doses of chemoconvulsants and is usually maintained for 3 to 12 seconds. It is also observed in two strains of genetically epilepsy-prone rats (GEPR 9 rats) and Wistar audiogenic sensitive rats (WAS) in response to acoustic stimulation.[220,244,293]

As in the case of runningâ€“bouncing convulsions, tonic extensor convulsions require the integrity of the brainstem but not the forebrain.[28,235] However, the anatomic substrates within the brainstem responsible for generating tonic seizures have not been characterized. Neurons within the reticular formation of the caudal midbrain and pons are likely to be involved, based on the fact that stimulation of this general region triggers tonic extensor convulsions, and lesions within this area can selectively attenuate tonic convulsions.[20,29,30,157] Moreover, sustained multiunit activity in the reticular formation correlates with the tonic extensor component of seizures induced by pentylenetetrazol; this activity is not abolished following transections that disconnect the hindbrain from the forebrain at the precollicular level.[279]

The tonic extensor components of audiogenic and maximal electroshockâ€“induced convulsions are selectively suppressed by lesions of the nucleus reticularis pontis oralis (RPO) without altering clonic seizure activity.[25,30]

Furthermore, focal injections of a local anesthetic (lidocaine) directly into the RPO reversibly blocked the expression of tonic extensor convulsions.[25,30] A similar selectivity for tonic extensor seizure manifestations is seen with lesions of the superior cerebellar peduncles[25,30] or removal of the cerebellum.[237]

Interactions Between Brainstem and Forebrain

Midbrain Regulation of Forebrain Seizure Spread

At the same time that brainstem regions serve to regulate seizure susceptibility in forebrain circuits, they participate in the

development of certain changes that occur in the course of the limbic kindling process. Midsagittal section of the brainstem prior to kindling of the amygdala in rats did not alter the development of kindling at the primary (i.e., first) site but was able to prevent the positive transfer effect at the secondary site (i.e., contralateral amygdala).[137] In all intact animals, kindling of the second amygdala proceeded at a rate several-fold faster than the primary site kindling (two to five vs. nine to fourteen stimulations). In contrast, the majority of bisected rats exhibited no enhancement of the secondary-site kindling rate. These observations confirm that interhemispheric connections within the brainstem are not required for amygdala seizure development and, at the same time, suggest their importance for the *interhemispheric* transfer of susceptibility to kindled seizures. This is supported by studies in feline amygdala kindling, in which bisection of the midline brainstem from the midbrain to pons prevented the positive interhemispheric transfer effect.[130,298] It also appears that the midline brainstem participates in symmetrical patterning and electroclinical tonic expression of the kindled seizure. It is possible that the kindling process removes inhibitory influences of specific (as yet unidentified) brainstem regions and that this removal of inhibition contributes to the progressive enhancement of limbic seizure susceptibility. Presumably, brainstem structures homolateral to the primary kindling site must participate in the progression of kindling at that site via intrahemispheric projections. This notion is supported by the observation that unilateral lesions of the midbrain reticular formation markedly reduce susceptibility to seizures evoked by kindling of the homolateral amygdala in cats.[299] Apparently, the bisection of the brainstem can prevent the kindling-induced changes from occurring in the contralateral hemisphere, rendering that hemisphere â€œnaiveâ€ to the kindling stimulation.

Kindling of Brainstem Regions

The anatomic separation between forebrain and hindbrain seizures that has been repeatedly documented in experimental models is largely derived from the study of acute seizures in otherwise normal animals. Under conditions in which repeated seizure activity or *kindling* has occurred over prolonged periods, an erosion of this anatomic separation may take place. For example, repeated audiogenic seizures (daily for 2â€“3 weeks) give rise to seizures that resemble forebrain seizures, based on behavioral and electrographic characteristics. Moreover, audiogenic kindling in susceptible animals markedly accelerated hippocampal and amygdala kindling.[138,139] Data from 2-deoxyglucose, c-Fos protein expression, and functional disconnection by local lidocaine injections, indicated that the amygdala, but not hippocampus, is critical for the spread of audiogenic seizures from brainstem to forebrain.[138]

Similarly, whereas acute electrical stimulation of the inferior colliculus evokes seizures limited to the hindbrain, repeated electrical or acoustical stimulation of this structure eventually recruits forebrain circuits and induces forebrain seizure discharge.[139,140,186] Amygdala spiking has been seen after chronic inferior colliculus stimulation, indicating forebrain recruitment.[116,117] Once forebrain circuits have been recruited by repeated inferior colliculus stimulation, the focal inhibition of area tempestas (an epileptogenic region within the deep rostral piriform cortex) can suppress the limbic motor seizures that occur as a result of seizure spread into the forebrain. This suggests that the kindling-evoked spread of seizure discharge into the forebrain comes under the control of forebrain circuits that do not otherwise influence brainstemâ€“evoked seizures.[182]

Other studies demonstrate that repeated seizures in forebrain circuits can modify susceptibility to brainstem convulsions. For example, amygdala kindling was found to increase susceptibility to electroshock-induced tonic hindlimb extension, even though the kindled seizures themselves never evoked a tonic extensor response.[7]

Apparently, repetitive seizure activity in one circuit may alter the susceptibility of other circuitry to seizure induction, possibly by inducing long-term changes in structures and pathways (e.g., substantia nigra, midline thalamic nuclei, superior colliculus, ascending noradrenergic projections) that serve a general gating function (see later discussion).

Seizure-Gating Mechanisms in Basal Ganglia and Brainstem

Under this category, we describe certain pathways that influence seizure susceptibility by modulating the threshold for seizure initiation or by regulating the sensitivity of the pathways responsible for propagating the seizure activity.

In many cases, the gating substrates are relatively nonselective as to the type of seizure they can influence. Consequently, by manipulating the activity of seizure gating systems, we can exert a broad-spectrum shift in seizure susceptibility. There are, however, circumstances in which a particular pathway exerts divergent or opposing effects on different types of seizures, further reinforcing the independent nature of some of the seizure-generating networks.

Basal Ganglia and Related Structures

The earliest indications that the basal ganglia participated in seizure propagation came from subcortical ablation stu-dies[133,145] that identified the substantia nigra (SN) and the thalamic and lenticular nuclei as crucial for the generalization of chemically evoked cortical seizures. Depth recording experiments[80] showed involvement of the putamen and associated structures in the spread of seizures evoked focally from cortex or amygdala; similarly, seizures evoked from hippocampal stimulation or by systemic chemoconvulsants were observed to propagate through the SN.[134] Metabolic mapping studies reinforced the involvement of the basal ganglia in seizures by demonstrating a profound increase in 2-deoxyglucose accumulation in the SN and globus pallidus after kindled amygdala seizures.[79] More recent studies have suggested that increases in metabolic activity in basal ganglia nuclei may precede the onset of clinical seizures during epileptogenesis: SN and striatum are hypermetabolic in rats that are at the end of the latent period following lithium-pilocarpine status epilepticus (SE); that is, at a time point just prior to the development of spontaneous seizures.[71,72] Likewise in 21-day-old genetically susceptible rats (GAERS) that do not yet exhibit spike-and-wave discharges (SWDs), rates of glucose utilization are increased in the SN, superior colliculus, and globus pallidus.[221] It is possible that these changes reflect ongoing subclinical seizure activity and/or an effort of the network to retard or prevent the occurrence of seizures.

The influence of the basal ganglia on seizure propagation and generalization is not confined to the motor manifestations of the seizures. In instances in which electrographic signs of seizures have been monitored, anticonvulsant manipulations of basal ganglia structures induce a corresponding suppression of electrographic seizure discharge in cortical and subcortical structures.[112,162,192,271,272,275,276] This is consistent with a role of basal ganglia circuits in the control of cortical excitability and the regulation of neuronal discharge synchronization in widespread regions of the forebrain.

Substantia Nigra

Broad-Spectrum Seizure Protection

The caudate-putamen (striatum), globus pallidus (entopeduncular nucleus in particular), and SN are all basal ganglia components that have been demonstrated to influence seizure susceptibility in numerous experimental seizure models. The best studied of these structures is the SN, the only region that has been examined in connection with more than 10 different experimental seizure models.[100,101]

Bilateral treatments that either increase inhibitory transmission (mediated by the neurotransmitter GABA) in SN, or block excitatory transmission (mediated by glutamate or certain neuropeptides such as substance P) in the SN pars reticularis (SNpr) prevent or attenuate convulsive seizures induced by several chemoconvulsants (pilocarpine, kainic acid, bicuculline, and flurothyl, among others), maximal electroshock, kindling of amygdala, drug application into the area tempestas, acoustic stimulation in rats susceptible to audiogenic seizures (the subject of several reviews[60,100,101,105,284,289]), and spontaneously occurring in absence-like seizures in GAERS.[65] These anticonvulsant effects may be mediated largely by the rostral regions of the SNpr, because activation of GABA receptors in the caudal SNpr has been reported to be proconvulsant in the flurothyl model.[214,268,291] VelÃÅ¡kovÃ¡ and MoshÃ© have reviewed regional differences within the SNpr.[289]

Not only motor manifestations, but also electrographic manifestations of seizures are regulated by SN: Inhibition within the SNpr decreases susceptibility to nonconvulsive electrographic SWD that occur either spontaneously (in genetically predisposed strains of animals such as GAERS) or as a consequence of treatment with drugs such as pentylenetetrazol in low doses.[58,60,61,62] Although the GABA agonist muscimol in SNpr was found not to protect against seizures evoked by high doses of pentylenetetrazol[315] blockade of *glutamate* transmission in SN did protect against these seizures,[310] indicating a role for SNpr in the modulation of seizures in this model. The lack of anticonvulsant effects of intranigral muscimol found in the latter study may be due to the high doses of pentylenetetrazol employed; these doses are likely to interfere with GABA receptor function and the postsynaptic responses to muscimol in the SNpr. In fact, seizures induced by lower doses of pentylenetetrazol are attenuated by SNpr muscimol infusions.[144,222] Other pharmacologic manipulations of SNpr that are anticonvulsant include augmenting serotonergic transmission,[226] stimulating opiate receptors,[110] blocking substance P receptors,[111] and enhancing adenosine transmission.[136] The anticonvulsant effect of adenosine and the proconvulsant effect of adenosine antagonists such as caffeine and theophylline within the SN suggest that the synaptic availability of adenosine may provide a physiologic mechanism whereby seizures can be self-limiting.[136]

The SNpr is probably part of a seizure-suppressing circuit that becomes engaged by seizure discharge. For example, the SNpr of kindled animals becomes recruited into a burst-firing pattern during the afterdischarge.[21] Increased burst firing in SNpr can still be seen 1 day after a fully kindled seizure, with a significant increase in neuronal discharge rate in the posterior, but not anterior, SNpr.[120] Likewise, in GAERS, simultaneously with the occurrence of SWDs at the cortical level, SNpr neurons increase their firing rates, and action potentials become organized in bursts. However, this SN burst-firing pattern stops before or at the end of the nonconvulsive seizure.[62,63] Thus, the SN and associated nuclei of the basal ganglia may act to maintain a homeostatic balance of brain excitability, attempting to resist the development of widespread synchrony.

The SN also may be a substrate for the actions of several antiepileptic drugs. Bilateral injections of midazolam, phenobarbital, or trimethadione into the SN protect against systemic pilocarpine seizures in a rodent model. Not surprisingly, ethosuximide had no effect,[270] because the site of action of ethosuximide has been localized to the hindbrain.[176]

The integrity of the SN is not required for seizure induction, indicating that this structure is not part of a crucial seizure-conducting pathway. Bilateral destruction of the SN has been shown by Garant and Gale[109] and by McNamara et al.[192] to protect against experimentally evoked seizures by *shifting the threshold* for seizure induction. Although a later study[301] reported no effect of bilateral destruction of SN on kindled seizures (in direct contrast to the findings of McNamara et al.), the completeness of nigra damage in that study is uncertain in the absence of histologic documentation of the lesions.

Role in Genetic Predisposition to Epilepsy

The SN may be a site at which genetic abnormalities can determine seizure susceptibility. For example, it has been suggested that abnormal GABA mechanisms in the SN may contribute to the seizure susceptibility in the GEPR. Clobazam, a benzodiazepine, focally administered in the SN blocked audiogenic seizures in normal rats made susceptible to these seizures by administration of bicuculline in the inferior colliculus. However, intranigral clobazam did not block audiogenic seizures in the GEPR. Because clobazam acts by enhancing endogenous GABA transmission, this indicates that endogenous GABA transmission in the nigra of GEPRs may be deficient.[266] Moreover, intranigral injections of muscimol had no effect on audiogenic seizures in a seizure-prone strain of Wistar rat.[57] Franck and Schwartzkroin[92] found a defect in GABA receptor binding in the SN of GEPRs but did not find it in the inferior colliculus. Microdialysis studies have shown that potassium (K^+)-evoked GABA release within the SN is significantly reduced in the GEPR, as compared with controls.[69]

Role of GABA, Glutamate, and Other Neurotransmitters

The fact that GABA agonists in the SNpr reduce seizure susceptibility in seizure models in which depletion or blockade of GABA in the SNpr does not increase seizure susceptibility,[172,225] suggests that GABA release is not the only mechanism by which seizure resistance can be achieved from the SN. Enhancing 5HT transmission in SN also confers seizure resistance.[224,226] GABA and 5HT appear to work in concert with each other in the SN: Under conditions in which GABA transmission is impaired, 5HT release can increase to maintain inhibitory tone.[99] Consequently, when 5HT is depleted, the blockade of GABA receptors in the SNpr becomes proconvulsant.[225] Therefore, a defect in 5HT transmission may compromise the endogenous anticonvulsant mechanisms in the SN and predispose to epilepsy.

Consistent with the role of GABA in the SN serving a seizure gating function and not a seizure triggering function is the observation that seizures are not triggered by the blockade of GABA receptors in the SNpr,[172] even in the presence of 5HT depletion.

The only intranigral treatment that has been documented to trigger clinical seizures is kainic acid (KA). The presence of KA focally in the SN can provoke a long duration state of SE in the Sprague-Dawley rat.[171] The fact that the seizures occur following a considerable latency suggests that the KA-induced stimulation of a subpopulation of SNpr outputs is sufficient to lower seizure threshold in limbic networks to the extent that SE can develop from spontaneous (endogenous) patterns of activity in limbic circuits. Because intranigral GABA agonists are ineffective in blocking the development of seizures following intranigral KA, it appears that the kainate stimulation

overwhelms GABAergic control in this region.[171] This may explain why SE induced by systemic KA is resistant to the anticonvulsant action of intranigral GABA agonists.

Sources of Afferent Control

The activity of SN neurons can be affected by epileptogenic influences through several routes. The major route is via the striatum, which receives information converging from widespread cortical regions and communicates to the SN via the â€œdirectâ€ striatonigral projections, which are largely GABAergic and inhibitory on nigral neurons. In addition, cortico-subthalamic-nigral pathways relay cortical influences to the SN; these tend to be excitatory on SNpr neurons.[179] At the same time, ascending 5HT and noradrenergic projections from the brainstem modulate nigral activity in response to changes in arousal, pain, sleep stages, and associated fluctuations in autonomic and endocrine function.

Stimulation of various cortical regions evokes predominan-tly inhibitory responses in the SNpr, most likely reflecting transmission mediated via the cortico-striatal-nigral pathways.[152] The cells in the SNpr that respond to stimulation of the prefrontal cortex are distinct from those responsive to auditory cortex stimulation, and these populations are differentially localized in SNpr, suggesting a topographic organization and functional compartmentation within the SNpr circuitry.[152]

Striatum

Certain key structures of the forebrain and midbrain work in concert with the SN in a seizure-resisting capacity (see Fig. 1). The striatum is a major source of neural input to the SN, whereas the superior colliculus (deep layers) is an important target of neural projections coming from the nigra. One of the most prominent pathways connecting the striatum to SN is inhibitory and utilizes GABA as its transmitter.[91,132] Likewise, the SN sends an inhibitory GABA-containing projection to the superior colliculus.[67,296] Consequently, it might be expected that the stimulation of the neurons in the striatum that give rise to the GABA inputs to the SN would enhance GABA transmission in the SN and thereby exert an anticonvulsant effect. The experimental evidence supports this proposal: Electrical or drug-induced excitatory stimulation in striatum is anticonvulsant in experimental seizure models.[5,34,159,276] LaGrutta et al.[159] found that a prior conditioning stimulation to the caudate nucleus (30 c/s, 1.5 msec for 5 s, 5 V) caused almost complete inhibition of the afterdischarge in amygdala, hippocampus, and temporal cortex evoked by stimulation of a kindled amygdala.

The anticonvulsant effect of GABA blockade in striatum can be reversed by blocking GABA in the SN or entopeduncular nucleus (see discussion in next section), consistent with the concept that GABAergic efferents from striatum mediate this region's influence on seizure susceptibility.

Entopeduncular Nucleus (Globus Pallidus, Internal Segment)

The entopeduncular nucleus, also known as the internal or medial segment of the globus pallidus, is similar to the SN in function, morphology, and neuroanatomic connections. Together with the SN, this nucleus relays neuronal outputs from the striatum. It is therefore not surprising that the same treatments that suppress seizure propagation when placed in the SN exert a similar action in the entopeduncular nucleus.[51,229] However, unlike the SN, the entopeduncular nucleus does not appear to exert an influence on brainstem seizure substrates. Whereas blockade of glutamate transmission in SN attenuated audiogenic seizures in the GEPR, this manipulation in entopeduncular nucleus did not reduce audiogenic seizure activity[193] under the same conditions in which it blocked pilocarpine-induced limbic motor seizures.[229] Moreover, GABA agonist application in entopeduncular nucleus did not prevent maximal electroshock-induced tonic convulsions under conditions in which it prevented pilocarpine-induced limbic motor seizures.[141] Thus it appears that the influence of the entopeduncular nucleus may be preferentially directed at forebrain seizure circuitry, perhaps via its close connections with the habenula and other limbic structures.

Globus Pallidus: External Segment (GPe)

The indirect pathway of the basal ganglia system is a polysynaptic circuit composed of (a) GABAergic striato-pallidal neurons projecting to the external segment of the globus pallidus, (b) GABAergic neurons projecting from GPe to the subthalamic nucleus (STN)[4] and to SN, and (c) neurons projecting from the STN to SN.[4] Because the GPe sends GABAergic projections into SN, it is expected that the activation of these projections would attenuate seizures. This has shown to be the case in the GAERS model, where the *disinhibition* of GPe by local injection of the $GABA_A$ antagonist, picrotoxin, at doses devoid of behavioral effects, suppressed nonconvulsive absence seizures.[66] The antiepileptic effect obtained at the pallidal level is also linked to a decrease in glutamate levels in the rat SN measured by microdialysis,[66] suggesting that a reduction of activity in STN may also contribute to the seizure attenuation (see discussion in the next section).[66] On the other hand, disinhibition of GPe did not attenuate amygdala kindled seizures,[62] indicating that the role of this structure in seizure control may be more limited than the role of the SN. Interestingly, repeated stimulation of the GPe is effective for generating kindled seizures, suggesting that seizure suppressing actions of acute GPe stimulation are easily overridden in chronic conditions.

In sharp contrast to these results, bilateral GABAergic inhibition within the GPe, using the GABA uptake inhibitor tiagabine or a $GABA_B$ agonist, baclofen, markedly attenuated the tonic convulsions induced by acute pentylenetetrazol treatment.[39] This observation raises the possibility that $GABA_B$ receptors may exert control on a subpopulation of GPe projections that are distinct from those regulated by $GABA_A$ receptors. Thus, the role of GABAergic synapses in GPe on the development of seizures is likely to be varied and highly dependent on the nature of the seizure. The fact that GABAergic synaptic transmission in the GPe is especially sensitive to rapid frequency-dependent depression[238] may account for the conditional nature of the influence of the GPe on seizure activity.

Subthalamic Nucleus

Interactions with the Substantia Nigra

As an important component of the basal ganglia network, the STN represents a source of input into both the SN and the entopeduncular nucleus (GPi). It is therefore well positioned to regulate the outflow from these critical nuclei. Direct afferents to the STN arise from the prefrontal, premotor, and motor cortex; these projections are largely excitatory, mediated by glutamate. Inhibitory projections to STN arise form GPe; these relay the indirect influence of the cortico-striatal system.

Detailed analysis of the nature of STN interactions with the SN have largely been confined to the rat. In the rat, the STN provides a major source of glutamatergic excitatory drive that sustains the firing of nigral neurons.[247,254,256] When

activity in the rat STN is inhibited either by GABA agonists or glutamate antagonists, this results in a decreased activity of SNpr neurons.[87,247] Thus, it stands to reason that lesions or inhibition of STN could mimic the anticonvulsant action of inhibition in the SNpr. Experimental evidence in support of this proposal derives from the studies of Deransart et al. in amygdala kindled rats or GAERS,[64] Dybdal and Gale[77] in rats with seizures evoked focally or systemically with bicuculline, and VelÃÅ¡kovÃ¡ et al.[290] in rats with flurothyl-induced seizures. As in the case of SNpr inhibition, bilateral STN inhibition is required for anticonvulsant effects.[64,77,290]

A similar profile of anticonvulsant effects has been achieved in the rat using high-frequency (130 Hz) electrical stimulation of the STN.[161,277,292] This effect is frequency-dependent,[161] and the frequency-dependency is closely related to the ability of the stimulation to cause a decrease in the activity of STN neurons[263] as well as SN neurons.[180,263] Although â€œdepolarization blockâ€ has been proposed to account for the inhibitory action of the high-frequency stimulation of STN, the fact that the inhibitory action in STN is rarely complete[263] and that it is reversed by iontophoretic application of a GABA receptor antagonist[180] argues against this proposal. Instead, it appears that the stimulation in STN may activate fibers that cause the release of GABA into the SNpr.[180,307,308] These fibers could be striatonigral, pallidonigral, and/or collaterals of the SNpr GABAergic neurons themselves.

Interactions with the Frontal Cortex

An effect on SNpr may not be the only mechanism by which STN stimulation in the rat can suppress seizures. Usui et al.[277] found that *unilateral* stimulation of STN was effective in preventing the recruitment of frontal cortex into the electroencephalographic seizure discharge induced by systemic KA in rats, even though this treatment was ineffective in reducing the total seizure duration or the incidence of seizure discharge recorded from hippocampus (which was actually increased by the STN stimulation). This contrasts sharply with the more robust anticonvulsant effects observed with bilateral STN stimulation.[161,292] Because inhibition of SN must be bilateral to achieve an anticonvulsant action, it is likely that the unilateral stimulation of STN influences the seizure discharge in the frontal cortex through a mechanism not mediated by SN. In fact, in the same study, Usui et al.[277] found unilateral high-frequency stimulation in the SNpr to be ineffective, in agreement with previous observations[281] and in contrast to the anticonvulsant actions of bilateral stimulation in the SNpr.[281]

Antidromic activation of corticosubthalamic axons is one mechanism that can explain a seizure-suppressing effect of unilateral STN stimulation. It is possible that recruitment of the frontal cortex into the seizure discharge pattern was impeded by antidromic activation of STN afferent fibers coming from the frontal cortex.[179] Disruption of the activity pattern in these frontosubthalmic neurons may make it more difficult to generate hypersynchronous discharge in the frontal cortex. In support of a relationship between seizure activity in the frontal cortex and discharge in the ipsilateral STN, Dinner et al.[68] found that the activity recorded from depth electrodes in the STN mirrored both scalp EEG seizures and interictal sharp waves in patients with predominantly frontal-onset refractory epilepsy. The STN activity was consistantly lateralized to the hemisphere with the seizure activity and typically occurred after a short delay.

Deep Brain Stimulation

The success in the application of deep brain stimulation (DBS) for therapy of Parkinson disease (PD) has raised hopes that DBS can also prove effective as a therapy for intractable epilepsy. Knowing that there are endogenous neural network mechanisms for resisting seizures, it makes sense to find ways to use DBS to activate these mechanisms. Conveniently, the same region that is most often the target for DBS in PDâ€"the STN[22,166]â€"is a promising candidate for DBS therapy in patients with epilepsy.[22,35,36,107,131,166,169,297] Although evidence for an anticonvulsant therapeutic benefit is mounting, the mechanisms responsible for DBS therapy remain elusive. Once assumed to act by inactivating the neurons in the location of the high-frequency stimulation, DBS is now recognized to activate fibers of passage and collateral projections, and even to antidromically activate afferent projections.[22,166,168]

Interestingly, inhibitory treatments in the SNpr are able to reverse the akinesia caused by a loss of striatal dopamine transmission,[210,253] much as inhibition in the SNpr is anticonvulsant.[105] Therefore, the use of DBS to directly or indirectly enhance inhibition in SN would be expected to benefit PD patients as well as epilepsy patients. Moreover, the induction of dyskinesias is associated with DBS in the human STN; this is consistent with the dyskinesias that are produced by treatment in nonhuman primates when intranigral muscimol is administered in doses that are anticonvulsant.[74,75,76,107]

The fact that anticonvulsant effects using DBS in humans can be achieved in some cases with unilateral stimulation of the STN, suggests that part of this effect may be mediated by the antidromic activation of corticosubthalamic fibers (see earlier discussion). Because bilateral inhibition of the SN is required to achieve anticonvulsant effects even with seizures evoked by focal unilateral stimulation,[74,76,170] unilateral STN stimulation may depend on direct effects of the STN stimulation on the homolateral cortex, as can be achieved by back-firing cortical afferents to STN.

Evidence in favor of a combination of actions contributing to the seizure attenuation achieved with DBS in the STN comes from studies in which unilateral and bilateral stimulation was examined. Chabardes et al.[35] reported on five patients, three of whom were substantially improved by DBS in the STN. One of these patients had only unilateral stimulation, while the other two had bilateral stimulation. In one of the patients, bilateral stimulation and unilateral stimulation were compared; seizures were attenuated in both conditions, but bilateral was clearly superior to unilateral. These preliminary observations suggest that by altering corticosubthalamic activity, unilateral DBS in STN may exert seizure control; however, this control is likely to be less efficacious than that mediated via the SNpr, as may be achieved by bilateral DBS in the STN. It is also likely that the relative effectiveness of these approaches in a given patient will depend on the nature of the seizure disorder being treated and the extent of frontal cortical involvement.

If an anticonvulsant action of STN stimulation is mediated by increasing inhibitory tone in the SNpr, it remains to be determined how this occurs. As discussed earlier, it is unlikely that the mechanism is via a DBS-induced depolarization block of neuronal activity in the STN. A more likely mechanism is that stimulation in the vicinity of the STN activates GABAergic afferents to the SNpr; these afferents arise from the striatum and external GP and have axons that travel through the vicinity of the STN. It is also conceivable that GABAergic collaterals of SNpr neurons may be activated by DBS in the STN or that there may be GABAergic projections from STN to SNpr (see next section). Evidence that DBS in the STN increases the release of GABA in the SN[180,307,308] supports the possibility that DBS can exert an anticonvulsant effect by enhancing GABA transmission in the SNpr.

By enhancing inhibition in the SNpr, DBS in the STN can cause disinhibition of neurons that are the targets of the GABAergic nigrotectal projections. This has been confirmed in the rat.[23] With acute high-frequency stimulation in the STN, increased firing was observed in the majority of cells in the deep layers of the superior colliculus.[23]

Superior Colliculus

The connections and functional interactions between the SN and the superior colliculus are particularly relevant to seizure regulation. This was first demonstrated by Garant and Gale,[113] in animals in which the superior colliculus was removed bilaterally. Removal of the intermediate/deep layers of the superior colliculus, which did not impair the expression of seizures induced by electroshock or systemic convulsants, eliminated the anticonvulsant action of GABA transmission in SN.[113] In contrast, the integrity of the nigrothalamic, nigrotegmental, and nigrostriatal pathways was not required for the nigral GABA-mediated anticonvulsant action.[113] The nigrotectal pa-thway was also demonstrated to be required for the control of nonconvulsive absence seizures in GAERS,[59] and lesions of the SC enhanced the response to amygdala-kindled seizures.[216]

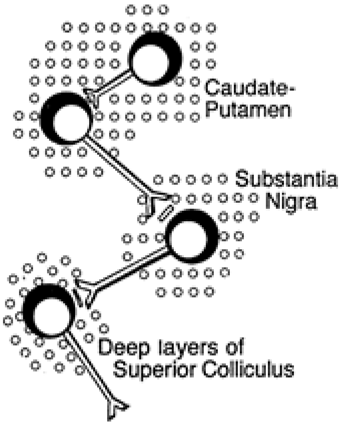

FIGURE 3. Serial inhibitory connections within the basal ganglia. All synapses shown are inhibitory and utilize GABA as their neurotransmitter. Although tonic excitatory inputs are not shown, they are present at each link in the circuit; therefore, the inhibitory terminals act to antagonize the influence of excitatory drive. When the neurons in the deep superior colliculus are *active* (*not* inhibited) enhanced *resistance* to seizure propagation results. Augmentation of GABA transmission in the SN exerts an anticonvulsant action by suppressing activity in the nigrocollicular GABA projections, thereby causing *disinhibition* (activation) of target neurons in the superior colliculus. *Blockade* of GABA transmission in caudate-putamen and superior colliculus has been demonstrated to exert anticonvulsant actions in experimental seizure models, consistent with the serial GABA interactions described.

Within the SN, inhibitory GABAergic transmission acts to suppress the activity of output projections to superior colliculus (Fig. 3). This relationship predicts that blockade of GABA transmission in the nigral projection target area of the superior colliculus should be anticonvulsant. Consistent with this expectation, blockade of GABA receptorâ€"mediated transmission in the intermediate and/or deep layers of superior colliculus is anticonvulsant against focally-evoked limbic motor seizures,[108] clonic and tonic convulsive seizures,[52] as well as against nonconvulsive spike-and-wave electrographic seizure discharge induced by pentylenetetrazol[52,108,241] or spontaneously occurring in GAERS.[56,218] Likewise, stimulation of glutamatergic transmission in the superior colliculus has also found to protect against seizures.[59] This illustrates a fundamental principle of central nervous system (CNS) organization: *disinhibition*. Inhibitory transmission within the SN acts to reduce the activity of the nigral outputs to the colliculus (which are themselves inhibitory), resulting in the withdrawal of inhibition, or disinhibition, of neuronal targets in the superior colliculus (see Fig. 3).

In detailed functional and anatomic mapping studies, Redgrave et al. identified a â€œdorsal midbrain anticonvulsant zoneâ€ (DMAZ), a region including the caudolateral intermediate/deep layers of the superior colliculus, the intercollicular nucleus, and the adjacent midbrain reticular formation. Connections between the substantia nigra pars lateralis and the adjacent peripeduncular area that project directly into this DMAZ suggest that the pars lateralis of the SN may be especially important in seizure regulation.[242]

Presently, it is not fully understood how neuronal activity within the superior colliculus acts to impede seizure progression. Some of the colliculus neurons that are activated by nigral disinhibition may be those that project to the brainstem reticular formation, where they relay with both ascending and descending neural pathways. Stimulation of certain regions of the reticular formation is capable of interfering with the development of a synchronized pattern of neuronal discharge in cortex.[267] By engaging these desynchronizing influences of the reticular formation, the superior colliculus can disrupt the generation of the synchronized neuronal bursting necessary for seizure development.

Pedunculopontine Nucleus

The pedunculopontine nucleus (PPN) is another major target of basal ganglia outflow[249] (see Fig. 1). As in the case of the superior colliculus, the PPN receives direct projections from the SNpr neurons,[249,278] and these projections have been demonstrated to be GABAergic.[41] In addition, the PPN receives direct projections from the entopeduncular nucleus.[249] Therefore, this region, like superior colliculus, may mediate the functional influence of basal ganglia structures.

Evidence for a crucial role of the PPN in the expression of nigra-evoked behavioral responses comes from studies in which the stereotyped sniffing and gnawing behavior evoked by intranigral muscimol was completely prevented by the micro-injection of muscimol into the PPN.[40,113] These observations are consistent with the concept that intranigral muscimol evokes stereotyped behaviors by inhibiting the GABAergic projections from the SN to PPN; maintaining GABA tone in PPN by the focal application of muscimol prevents this disinhibition. However, at the same time that muscimol in the PPN blocked the stereotyped behavior evoked by intranigral muscimol, it did not interfere with the anticonvulsant actions of intranigral muscimol against maximal electroshock tonic seizures.[113] This indicates that, whereas disinhibition of superior collicular neurons is crucial for nigra-evoked anticonvulsant effects, disinhibition of PPN neurons is not necessary for the anticonvulsant actions elicited from the SN.

Interestingly, in the pilocarpine-induced seizure model it appears that inhibition of PPN, by focal application of muscimol or antagonists of glutamate receptors, can exert an anticonvulsant action.[227] At first glance, this seems paradoxical, since GABA in the PPN would be expected to exert effects opposite to GABA in the SN. However, the PPN also sends afferent projections to the SN, and these appear to contain excitatory fibers.[251] Thus, inhibition of PPN neurons may also cause a reduction of excitatory input to the SN and thereby reduce seizure susceptibility. It may be relevant that pilocarpine seizures are especially sensitive to changes in glutamate transmission in the SN, as evidenced by the fact that they can be blocked by intranigral NMDA receptor antagonism and enhanced by intranigral application of NMDA[272] or depletion of GABA.[172]

Inhibition of the PPN does not protect against seizures induced by electroshock or systemic bicuculline, both of which are subject to nigral influence.[113,196] PTZ-induced seizures were unchanged[196] or enhanced by GABA agonists in the PPN and attenuated by bicuculline in the PPN.[222]

Basal Ganglia Species Differences: Rodent to Primate

Much of the functional neuroanatomy of seizure propagation and control in subcortical circuits comes from studies conducted in rat models. Although a few notable laboratories have conducted experimental epilepsy studies in cats and in nonhuman primates, only rarely are direct comparisons made to rats.

Consequently, the information derived from rodent studies cannot easily be compared to primate studies, especially because different questions are often asked. In cases in which comparisons have been made, it is clear that (a) the specific pharmacologic response profile within a given brain region can be strikingly different (and even opposite) between rat and monkey; (b) the anatomic routes via which partial seizures progress to become generalized are distinct for the rodent versus primate brain; and (c) the elaboration and topographic sorting of connections within a single nucleus, such as the SN, in the primate brain allows for rich intranuclear site specificity of far greater complexity than can be achieved (or evaluated) in the rat brain.

The most obvious difference between the progression of seizures in monkey and rat is the ease with which the focally evoked seizures become bilateral. In the rat, focally evoked partial forebrain seizures rapidly engage the hemisphere contralateral to the stimulation, mostly via commissural pathways such as those in the anterior commissure and hippocampus. Thus, in the rat, focally evoked seizures may appear bilaterally symmetrical from time of onset, as evidenced by both behavioral and cortical EEG manifestations. In contrast, in the monkey, seizure manifestations (behavioral and electrographic) stay lateralized (contralateral) longer and remain asymmetrical even as they progress to engage brainstem circuits. In fact, in the monkey, as in the human, the â€œpath of least resistanceâ€ is down the neuraxis rather than across the forebrain commissures. This is probably why the term â€œgeneralizedâ€ is used to describe seizure activity that is manifest bilaterally in the primate brain: By the time the participation of the contralateral hemisphere has been secured, it is well past the point at which the seizure networks in the midbrain and hindbrain have been recruited. In contrast, it is misleading to use bilaterality as a sufficient criterion for generalization in the rat, because partial complex seizures limited to the forebrain limbic networks are often bilateral in the absence of recruitment of brainstem seizure networks. These rat/primate differences have important implications for neural mechanisms of seizure control; compared with the rat, the primate brain may be more responsive to brainstem-evoked mechanisms of seizure protection.

Anatomically, the segregation of afferent/efferent connections according to a topographic scheme is more pronounced in the monkey SN than in the rat. This has implications for the functional impact of focal manipulations in the SN.[107] The reorganization of the functional interconnections within and between basal ganglia regions is a necessary consequence of the phylogenetic expansion and differentiation of the neocortex in the primate brain. As Beckstead and Frankfurter commented: â€œthe spatial relationships and morphological features of SNR's efferent cell populations exhibit a pattern in the monkey that does not compare well with that seen in the rat.â€[15] Thus, for example, in the rat there is great overlap in nigrotectal, nigrotegmental, and nigrothalamic projection cells, with as many as 50% of the cells projecting to both thalamus and tectum.[19,55] In contrast, little overlap in these projection cells exists in the monkey SN,[223] allowing for greater topographic discrimination of distinct outputs.

Important functional differences between the rat and the primate must also be considered when extrapolating between species. For example, the response to stimulation and blockade of GABA receptors in the monkey STN is not predicted by the neural circuitry model derived from studies in the rat. In the monkey, inhibition of the STN (using focal muscimol) was without effect,[75] whereas *blockade* of GABA inhibition in the STN by the focal application of bicuculline evoked dyskinetic and postural responses similar to those evoked by inhibition of the SN,[46,74,76] suggesting that unlike the rat STN, the monkey STN (or particular populations of neurons within the STN) may exert a net *inhibitory* influence on the SN (either directly or via projections to globus pallidus or pedunculopontine nucleus). In contrast, when applied to the SN, the same dose of bicuculline caused no dyskinetic movements but instead caused a *hypo*activity of the contralateral limb.[74,76] Thus, there is need for caution when attempting to generalize findings from the rat to the primate circuitry.

Ascending Monoaminergic Projections

Specific ascending projections from brainstem cell groups have been implicated in the regulation of seizure threshold. Best characterized in this regard are the noradrenergic projections arising from the locus coeruleus and the lateral tegmental area of the pontine tegmentum. Depletion of norepinephrine (NE) or lesions of the locus coeruleus usually causes a reduction in seizure threshold.[43,44,88,146,191] Most evidence suggests that a *deficiency* of NE increases susceptibility to a variety of seizure types. Accordingly, drugs that block CNS receptors for NE (Î±-receptors in particular) lower seizure threshold.[18,118,163] This is likely to account for the increased seizure susceptibility associated with the use of antipsychotic phenothiazines and related compounds. Depletion of NE does not in and of itself evoke seizures without a seizure-inducing stimulus; this is consistent with a modulatory or gating role of this system.

The increase in seizure susceptibility observed in animals with impaired NE transmission is not specific for seizure type. Potentiation of limbic motor seizures evoked by kindling[43] and exacerbation of explosive runningâ€“bouncing clonic and tonic convulsions evoked by focal or systemic chemoconvulsants[88,146] have been observed. Lesions of the locus coeruleus convert sporadic limbic seizures induced by bicuculline into limbic SE, suggesting that noradrenergic projections may serve to limit seizure duration.[128] Conversely, stimulation of the locus coeruleus can delay the onset of generalized seizures during kindling, an effect that is reversed by lesions of the dorsal NE bundle.[303] In addition, the suppression of kindling at one site by concurrent kindling of another site (kindling antagonism) may be mediated by release of NE.[6] Lesions of the locus coeruleus potentiated seizures evoked by kindling and maximal electroshock seizures, consistent with the NE modulation of both forebrain and brainstem seizures.[208,215] In fact, seizures evoked by acute stimulation of the inferior colliculus do not lead to tonic limb extension unless the NE projections originating in the locus coeruleus have been compromised.[31]

A genetically determined deficiency in NE contributes to the seizure susceptibility of GEPRs, and the degree of NE deficiency correlates with the severity of the audiogenic seizure response observed in different subsets of

GEPRs.[146] Conversely, drug-induced enhancement of NE transmission can protect the GEPR, as well as epileptic gerbils and seizure-susceptible mice, from seizures.[45,47,126,151] Paradoxically, the quaking mouse, which also has increased seizure susceptibility, appears to have an excess of NE neurons, and lesions that destroy NE neurons can reverse the seizure-prone phenotype of these mice.[181] Thus, the influence of the NE projections from the locus coeruleus may depend on the constellation of other neural abnormalities that coexist in the CNS of mutant strains.

Numerous brain regions may mediate the anticonvulsant influence of NE. Because the NE projections arising from the locus coeruleus diffusely innervate widespread regions of the telencephalon, multiple target regions are simultaneously regulated by this system; these targets include the entire limbic system circuitry as well as the thalamus and neocortex. In animals with lesions of the ascending NE projections, grafts of fetal NE neurons that innervate hippocampus reverse the increased susceptibility to limbic seizures caused by the lesions.[14] This effect is dependent on NE mechanisms,[163] and microdialysis studies have shown that hippocampal locus coeruleus grafts restore both basal and postconvulsive levels of NE to prelesional levels.[18] Thus, the hippocampus may be one site at which the ascending NE system may act to regulate seizure threshold (see Fig. 2A).

In addition to NE, 5HT-containing projections arise from brainstem cell groups and innervate virtually the entire central neuraxis. A defect in 5HT has been implicated in the seizure susceptibility of the GEPR, and pharmacologic evidence supports a role of 5HT in regulating seizure threshold. In particular, it has been observed that enhancement of 5HT transmission by inhibition of 5HT uptake (with fluoxetine) exerts anticonvulsant actions against explosive runningâ€"bouncing clonic convulsions and tonic convulsions[48] as well as limbic motor seizures.[236] One site of action of fluoxetine for exerting anticonvulsant effects appears to be the SN,[224,226] but in view of the extensive network of 5HT terminals throughout the brain, it is likely that additional sites of action will be identified in future studies.

In the SN, bilateral infusion of the dopamine D_1 agonist SKF-38393 potentiated pilocarpine seizures.[276] In specific subregions of striatum, the D_1/D_2 receptor agonist apomorphine was found to have anticonvulsant effects.[276] More detailed investigation suggested that D_2 agonists are anticonvulsant, whereas D_1 agonists are proconvulsant for pilocarpine seizures.[2] Lesions of ascending dopaminergic projections have been found not to significantly alter seizure threshold or severity.[44]

Cholinergic Pathways: Reticular Formation and Thalamus

The lateral dorsal tegmental nucleus of the reticular formation appears to modulate seizures via two pathways (see Fig. 2B). The cholinergic projection from lateral dorsal tegmental nucleus to the central median nucleus of the thalamus inhibits myoclonic and tonic convulsions, whereas a second ill-defined pathway may facilitate tonic seizures.[201] Substrates within the reticular formation may also explain the association between seizures and levels of arousal, because certain seizures will only occur during sleep,[195] whereas others occur during quiet wakefulness or drowsiness.[49,262] The role of the midbrain reticular formation as a crucial structure for driving the secondary generalization of seizures has been confirmed for seizures evoked unilaterally from the amygdala, hippocampus, thalamus, and visual cortex.[96,265]

Pharmacologic manipulations of the central median nucleus of the thalamus produce coupled changes in arousal states and seizure threshold, with increased arousal occurring in association with decreased seizure susceptibility.[195,196,197,198,199] Injection of either muscarinic cholinergic antagonists or GABA agonists directly into the central median thalamus depressed arousal and facilitated limbic motor seizure responses (myoclonus, facial, and forelimb clonus). This inhibition in the central median thalamus was accompanied by local suppression of neuronal activity and low-amplitude slow activity on the cortical EEG. Injections of GABA agonists into the lateral dorsal tegmental nucleus also produced a suppression of arousal and facilitated limbic motor seizure responses elicited by bicuculline or PTZ.[196] These studies suggest that a cholinergic projection from the lateral dorsal tegmental nucleus regulates both arousal and seizure susceptibility via muscarinic receptors in the central median thalamus, and that this projection and its targets are under the inhibitory control of GABA. Interestingly, the effects of inhibition of this pathway on forebrain (limbic) clonic seizure manifestations were separable from and often opposed to the effects on tonic convulsions.[196,197,199,200]

Vagal Pathways

Vagal nerve stimulation (VNS) was first used in animal models of seizures, such as those induced by electroshock,[309] and was then applied to refractory epilepsy and psychiatric depression in humans.[17,119,178] To date, VNS has been used safely for prolonged periods in over 15,000 patients worldwide.[119] VNS is indicated in the treatment of Lennox-Gastaut syndrome,[93,119,175,252] and its antiepileptic efficacy may persist for several months.[54] The effectiveness of VNS therapy increases over time of chronic treatment, and in some patients the response to VNS therapy may not appear until after a delay.[257] VNS has been shown to attenuate seizures in a variety of animal models, with the notable exception of absence seizures: VNS has no seizure-suppressing effect on nonconvulsive SWDs in GAERS and even prolongs the duration of absence seizures when applied shortly after the onset of the SWD.[53]

The fact that stimulation of the afferent vagus has been found to have therapeutic impact in treating seizures in patients with epilepsy argues that brainstem circuits (which are the direct targets of afferent vagal nerve fibers) can regulate forebrain seizure susceptibility in the human brain. The influence of VNS on epileptic seizure generation is mediated via important relays within the brainstem. Stimulation of vagal afferents generates evoked potentials in the cerebral cortex, hippocampus, thalamus, and cerebellum, and modulates EEG activity and sleep states. According to the frequency of stimulation, afferent VNS can either synchronize [weak stimulation recruiting A (0.02â€“0.2 mA) and B fibers (0.04â€“0.6 mA)],[13] or desynchronize [high stimulation recruiting C fibers (0.4â€“1.2 mA)] in the EEG.[37,38] The latter pattern can suppress strychnine-induced EEG spikes.[248] High-frequency (50 Hz) VNS has also been found to block sleep spindle occurrence during slow-wave sleep in cats.[314] Stimulation of vagal C fibers at frequencies over 4 Hz attenuated both electroshock- and chemoconvulsant-induced seizures in rodents,[309] PTZ-induced seizures in dogs,[313] and focal motor seizures in monkeys.[165] However, activation of C fibers does not appear to be necessary for an anticonvulsant action, because seizures were still suppressed in rats in which C fibers were selectively destroyed,[156] and stimulation parameters that do not recruit C fibers are clinically effective for seizure suppression.[154]

VNS is currently used to treat medically intractable complex partial seizures. The effects of ascending VNS are relayed primarily via the nucleus of the solitary tract (NTS) and its broad connections to the mesencephalic and diencephalic reticular formation, as shown by c-Fos mapping[219] and pharmacologic[302] and lesion experiments.[155] Inhibition within the NTS[302] and NTS-inhibition during VNS may be the first step in conferring seizure resistance. This inhibition, along with that of other interconnected brainstem nuclei,[219] confirms their role as a gating mechanism to impede seizure organization.[105,302] The major ascending targets of the NTS projections are the parabrachial nucleus and the locus coeruleus, from which numerous pathways project into midbrain and forebrain structures. Lesions of the locus coeruleus nullify the anticonvulsant action of VNS, suggesting that this

structure is a key relay in the seizure gating network.[155] In addition, NTS raphe-mediated activation of 5HT transmission may contribute to the anticonvulsant effects of VNS.[27,147] Within the brainstem, vagal afferents terminate in the cuneate nucleus, dorsal motor nucleus of the vagus nerve, and area postrema, in addition to the NTS.

Among the forebrain regions that receive NTS projections, either directly or indirectly via brainstem or thalamic relays, are the insular cortex, lateral hypothalamic nucleus, diagonal band nucleus, medial septum, amygdala, and hippocampus.[33] Data from imaging studies using positron emission tomography (PET) and single photon emission computed tomography (SPECT) in human subjects demonstrated VNS-induced increases in synaptic activity in structures directly innervated by central vagal structures and areas that process somatosensory information. VNS also modulates synaptic activity in multiple limbic system structures bilaterally.[13,135] VNS-induced activation of the thalamus is correlated with a favorable clinical outcome,[164] consistent with the role of the thalamus as a generator and modulator of cerebral activity.[150,246]

Most recent studies seem to agree on the primary role of the locus coeruleus and noradrenergic transmission in the effects of VNS.[122] The inhibition of the NTS triggered by VNS leads to increased activity of locus coeruleus neurons. Acute VNS at low intensities that recruit A and B fibers results in a significant increase in the discharge rate of locus coeruleus neurons,[127] causing an efflux of noradrenaline in target regions such as the amygdala.[42,155] The efficacy of VNS requires the integrity of noradrenergic neurons in the locus coeruleus, but the integrity of the latter nucleus in just one hemisphere is sufficient to maintain the anticonvulsant activity of VNS.[155] In addition to enhancing noradrenergic transmission, VNS has been shown to increase GABA levels in the cerebrospinal fluid.[17] Moreover, $GABA_A$ receptor density in the hippocampus was found to be increased in epileptic patients treated chronically with VNS, and this change was preferentially observed in responsive patients as compared with controls and nonresponders.[177] Thus, changes in $GABA_A$ receptor density may also contribute to the seizure attenuating effects of VNS; this topic has been reviewed.[128]

Cerebellum

Neurophysiological and 2-deoxyglucose studies have shown the cerebellum to be electrically and metabolically active during experimental seizure models, including focal and systemic penicillin, PTZ, and maximal electroshock seizures.[9,143,203] The cerebellum appears to have opposing effects on forebrain versus brainstem seizures. Lesions of the cerebellum *facilitate* seizures evoked focally from forebrain regions, including neocortex, and *inhibit* tonic convulsive seizures.[230,237] However, because lesions are accompanied by retrograde neuronal damage, the effects of these cerebellar lesions cannot be assumed to be due to the removal of cerebellum alone. Cooling of the cerebellum has also been shown to reversibly enhance spontaneous and sensory-evoked epileptic discharge.[70,174]

Stimulation of the cerebellum inhibits forebrain seizures while potentiating brainstem convulsions. Microinjection of high doses of picrotoxin (2 mg), a GABA antagonist, into the fastigial nucleus of the cerebellum has been reported to induce brainstem-related wild running and tonic convulsions.[50] On the other hand, electrical stimulation of the cerebellar cortex or deep cerebellar nuclei inhibits forebrain-evoked seizure induction.[9,70,143] This is consistent with the facilitatory effects of cerebellectomy on seizures evoked from the forebrain. Thus it appears that activity in cerebellar circuitry can dampen seizure susceptibility in the forebrain; this control may be mediated via relays in thalamus or via an influence on the monoaminergic projections ascending from the pontine tegmentum.

Thalamus

The thalamic nuclei are principal relay sites for both subcortical and cortical projection systems. Within the thalamus, ascending projections from the reticular formation and other brainstem cell groups impinge on pathways radiating to numerous forebrain structures, including those of the neocortex, basal ganglia, and limbic system. The role of the brainstem lateral dorsal tegmental nucleus and its projections to the thalamus was discussed in the section on cholinergic projections. At the same time, neural inputs from diverse telencephalic regions converge on thalamic nuclei from which projections descend onto brainstem neurons.[148] Accordingly, the thalamus represents a critical link in the transfer of information between cortical and subcortical structures, and between the periphery and the cortex. It is therefore reasonable to expect thalamic nuclei to be capable of regulating seizure susceptibility and influencing seizure propagation.[195]

The mediodorsal nucleus (MD) of the thalamus is a central component of the network supporting limbic seizure propagation. Blockade of excitatory transmission mediated by glutamate in the MD has been found to block systemically and focally evoked limbic motor seizures.[32,228] Moreover, MD exhibits marked increases in glucose utilization during limbic motor seizures[101,190,304] and undergoes degenerative changes following limbic SE in experimental animals[78,255,264,273] and in humans with prolonged hemiconvulsions.[211] The prominent connectivity between the MD and major limbic system regions including amygdala, hippocampus, and piriform and perirhinal cortex, as well as its connections to/from prefrontal cortex is likely to account for the pivotal position of the MD in the limbic seizure network.

Over the last several decades, the thalamus has figured prominently in the investigation of neural substrates for generating the bilaterally synchronous spike-and-wave rhythmic discharge characteristic of petit mal, nonconvulsive epileptic seizures.[89,90,123,294,305] These studies have generally provided convincing support for a crucial role of thalamic nuclei in the genesis of the 3-Hz SWD. Unilateral chemical stimulation of the ventral posterior lateral nucleus of the thalamus with kainate caused bilateral electrical disturbances within 2 hours, followed by the onset of nonconvulsive seizures at 3 to 4 hours. Interestingly, in this model, the convulsions spread bilaterally by passing via the midbrain reticular formation.[8] Glutamatergic projections from the superior colliculus to the parafascicular thalamic nucleus may be responsible for the control of absence seizures in GAERS. Disinhibition of these neurons could lead to seizure suppression and may be involved in the nigral control of this type of epilepsy.[217] Please refer to Chapter 31 for a more detailed discussion of thalamocortical substrates associated with nonconvulsive spike-and-wave seizure activity.[124,295]

The convulsive seizure paradigm used most extensively for examining thalamic involvement is the PTZ-induced model in rats. Metabolic mapping studies have shown that the neural projections from the mammillary bodies of the hypothalamus to the anterior thalamus exhibit especially pronounced increases in activity during the PTZ-induced seizures.[204] Lesions of this mammillothalamic pathway abolished both behavioral and electrographic expression of pentylene tetrazol seizures, as did focal microinjection of drugs that enhanced GABA transmission in the anterior thalamus.[204,205,207]

Studies using drug application to restricted regions of the thalamus indicated that direct stimulation of GABA receptors (using muscimol) in the dorsal midline thalamus (central median in particular) facilitated the clonic, but not the tonic, seizures induced by systemic administration of PTZ[202] and bicuculline.[198] Conversely, blockade of GABA receptors

in the central medial nucleus appeared to suppress the clonic seizures induced by pentylene tetrazol while at the same time facilitating the tonic convulsions.[197] These observations suggest that ascending influences from the central medial thalamic neurons exert a seizure-suppressing action in the forebrain, whereas descending projections from this region promote susceptibility to the tonic convulsions evoked from the brainstem. On the other hand in the ventromedial thalamus, enhancement or blockade of GABA-mediated neurotransmission was without an effect on either clonic or tonic seizures.[115]

Developmental Considerations

The immature brain has been shown to be more susceptible to seizures than the mature brain, so it is not surprising that human seizure disorders often begin during childhood.[213] In the juvenile preweaning rat, tonicâ€“clonic brainstem seizures are the hallmark manifestation in many experimental seizure models, such as those induced by chemoconvulsants.[283] It appears that the brainstem seizure circuitry matures earlier or has a lower threshold than the forebrain circuitry in young rat pups. In part, this may reflect the underdevelopment of substrates for suppression of seizure propagation in these animals. Accordingly, progression of seizure generalization during forebrain kindling is especially rapid in developing animals, and the seizures readily progress into the tonicâ€“clonic seizures of brainstem origin.[129] This is in marked contrast to adult rats, in which brainstem seizures are atypical, occurring only after hundreds of forebrain kindling stimulations.[234]

As a reflection of the reorganization of networks during development, the pattern of seizure-induced metabolic activation of the basal ganglia is age-dependent.[232] In adult rats, the SNpr consistently shows striking hypermetabolic activity during a variety of seizures.[3,16,167,221,231,287] On the other hand, during early postnatal development in the rat, the SN shows no changes in glucose metabolism regardless of seizure severity.[1,3,258] This suggests that the immature SN is not engaged by the seizure network and therefore may be less effective for seizure control as compared with its role in the mature brain. Before the third postnatal week, NMDA application into the striatum does not exert an anticonvulsant effect, despite robust NMDA receptor activation in the striatum during the early developmental period.[188] This may reflect an inability of the striatonigral pathways to recruit seizure-protective mechanisms in the SN. Thus, the gating role of the SN may not come into full swing before 21 days of age in the rat.[288]

Microinfusion studies of drugs in the SNpr have revealed an age-dependent pharmacologic profile.[259,260,311,312] For example, in the developing SNpr, instead of having anticonvulsant effects, $GABA_A$ activation by intranigral muscimol has proconvulsant effects.[260,288] This may be a result of one or more immature features of SN neurons in the pups: $GABA_A$ receptor subunit composition,[286] amount of GABA in the nigral neurons,[239] expression of the neuronal specific potassium chloride cotransporter KCC2,[97] electrophysiological properties of the SNpr GABAergic neurons,[158] or neuronal network connectivity.[214,282] However, the elevation of endogenous GABA in the SNpr protects against seizures in rat pups as it does in adults, indicating that altered receptor-specific mechanisms are responsible for the lack of muscimol-induced seizure protection in the immature SN. In fact it appears that $GABA_B$-mediated transmission in the SNpr control seizure during development, whereas $GABA_A$ â€“mediated transmission serves this purpose in the mature SN.[261,285] In 2-week-old rat pups, intra-nigral baclofen, a $GABA_B$ receptor agonist, is anticonvulsant, whereas this effect is not evident in the adult SN.[261] The relatively greater expression of $GABA_B$ receptor binding in the immature SNpr as compared to adults[114] may explain the shift in sensitivity to specific agonists. Because brain development is markedly influenced by sex hormones,[125,189] it is not surprising that the development of the seizure-controlling network in the SNpr is also influenced by exposure to testosterone and its metabolites.[98,239,240,280,282,288] The hormonal regulation of the development of this system may contribute to sex-specific differences in seizure susceptibility.

Disruption of NE innervation in immature rats has been associated with an increased rate of kindling, as has been seen in adults.[153] However, after forebrain NE lesions, the immature brain is prone to exhibit a reactive sprouting of NE innervation into the cerebellum and pons in the rat pups. When this occurs, a marked depletion of forebrain NE may have little or no impact on kindling rate.[153]

Age-specific expression of some epileptic syndromes, such as infantile spasms, probably reflects unique features of the networks in the immature brain. The possibility that the spasms may represent motor manifestations of basal ganglia outputs associated with attempts of the nigral circuitry to contain the seizure propagation, is worthy of consideration. A strong expression of a tonic phase during infantile spasms suggests involvement of brainstem in this devastating epileptic disorder.[142] Indeed, a variety of brainstem abnormalities has been found in patients with infantile spasms.[209,212,250] Maturational delays of cortico-subcortical circuits resulting in a failure of cortical regulation of the brainstem structures has been suggested as a possible pathologic substrate for infantile spasms.[160]

Summary and Conclusions

Preclinical and clinical experience dictates that the efficacy of a given therapeutic intervention depends on the type of seizure being treated. As additional therapeutic strategies develop, further refinements in distinctions between seizure types are likely to emerge. Because distinct neural circuitry underlies the epileptogenesis of different seizure types, it stands to reason that therapeutic interventions directed at specific circuitry can selectively affect the particular types of seizures that depend on that circuitry. On the other hand, therapeutic interventions directed at neural circuitry involved in â€œgatingâ€ mechanisms, such as those found in the basal ganglia, can modify susceptibility to multiple types of seizures. Thus, for example, inhibition of substantia nigra outputs can suppress tonicâ€“clonic as well as limbic motor seizures, whereas activation of cerebellar circuits reduces susceptibility to forebrain-evoked clonic seizures but enhances susceptibility to tonic extensor seizures. Vagal stimulation may represent one way of diffusely activating multiple brainstem seizureâ€“gating circuits.

Genetic or acquired predispositions to epilepsy may involve abnormalities that compromise the endogenous seizure-gating mechanisms. A better understanding of which mechanisms are compromised and which remain intact in a given seizure disorder will allow more precise and efficacious therapeutic interventions.

Systemically administered anticonvulsant drugs are likely to act on a series of mechanisms involved in the seizure-generating process. In recent years, GABAergic and glutamatergic mechanisms of seizure control have received the greatest focus. Considerations of the seizure-modulating influence of NE and serotonin projections may provide additional avenues for reducing seizure susceptibility. Multiple levels of drug action may be advantageous insofar as various anticonvulsant mechanisms may be additive or even synergistic. On the other hand, therapy that is â€œtargetedâ€ to modify a specific neural circuit may avoid many of the unwanted side effects associated with more widespread drug actions. Emerging advances in pharmacology, functional neuroanatomy, and DBS offer significant promise for such targeted approaches.

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Chapter 33

Development of Cortical Excitability

Peter B. Crino

Introduction

In the human brain, cerebral cortical development spans approximately weeks 7 to 24 of gestation and proceeds from a primordial neural tube structure containing a seemingly unspecified pseudostratified ventricular zone (VZ) epithelium to a mature layered cortex containing virtually all of the necessary cellular elements required for a functional cortex in the behaving animal. The assembly of each cortical layer is a spatiotemporally regulated process in which a series of well-orchestrated molecular events culminate in the formation of a six-layered cytoarchitecture. During this time, many early structural connections will herald functional capabilities such as the formation of synaptic connections, expression of neurotransmitter receptor subunits or ion channels, generation of axon potentials, and, ultimately, electrical activity. Indeed, it is virtually axiomatic that the development of functional electrical excitability in the cortex is necessary for virtually all cortical activity in the mature animal. One consequence of the disruption of these functional attributes is altered cellular excitability and, potentially, epileptogenesis. Thus, understanding the developmental assembly of structural elements that result in normal cortical excitability can highlight possible mechanisms leading to seizures and epilepsy. Indeed, several well-defined epilepsy syndromes result from single gene defects that alter the appropriate temporal expression of a single neurotransmitter receptor subunit or ion channel. This chapter will address the development of cortical excitability as a function of structural alterations such as neuronal cytoarchitecture and pharmacologic changes including neurotransmitter receptor and ion channel expression.

Cortical Development: Structural Changes

Early Cortical Development: Overview

At each cortical developmental epoch, there is progressive assembly of cellular, subcellular, and pharmacologic machinery necessary for mature cortical function.[37] Thus, while cells in the VZ and early cortical plate are linked by nonsynaptic electrotonic coupling (e.g., gap junctions), following the establishment of cortical laminae, the formation of axodendritic synaptic connections and transcriptional expression of many neurotransmitter receptor subunits and voltage-gated ion channels permits synaptic transmission (Fig. 1). Concurrent with this process, additional cell types such as astrocytes and oligodendrocytes appear in the cortex and refine synaptic transmission. The ingrowth of afferent fibers from brainstem monoaminergic nuclei (e.g., the locus coeruleus and raphe complexes) as well as cholinergic input from the basal forebrain contribute to modulation of synaptic function. Perhaps most interesting is that the establishment of synaptic machinery does not end with birth but continues into postnatal periods. Thus, the development of normal cortical excitability spans embryonic and postnatal periods. The implications of this time course for epileptogenesis are profound since subtle or overt disruptions in either structural assembly or pharmacologic regulation can in theory lead to epileptogenesis.

Assembly of the Cerebral Cortex

Cortical development occurs in three broad stages: Proliferation, migration, and organization. Proliferation of progenitor cells that will populate the cortex occurs in two primary sources: (a) a single layer of mitotic progenitor cells in the VZ gives rise to most excitatory projection neurons (pyramidal cells[19]) and (b) progenitor cells in the ganglionic eminence give rise to most local circuit, inhibitory interneurons.[26,34] During the proliferative phases, radial glial cells serve as progenitor cells in the VZ of the neural tube and undergo active mitosis, giving rise to daughter progeny.[19] Cells destined for a specific cortical layer are born during similar and restricted developmental epochs. Mitotic progenitors express select genes such as intermediate filaments (nestin, vimentin), transcription factors (OTX-1, Emx1, Pax6, BF1/BF2, HES-1), and markers of active cell cycle phases such as proliferating cell nuclear antigen (PCNA) and cyclins (cyclin A, D1). Daughter progeny of progenitor cells either continue to divide or exit the cell cycle (become postmitotic) and differentiate into mature neurons. At this point, cell cycle G0, expression of many â€œembryonicâ€ genes is down-regulated and a new set of â€œmatureâ€ cellular genes are turned on as cells initiate migration and lamination.

The evolving cortical plate is formed between the marginal zone (the future layer I) above and subplate below.[34,35] During the migratory phase, differentiated daughter cells exit the VZ and move radially into the cortical plate along radial glial fibers in an inside-out gradient (i.e., neurons destined for deeper cortical layers [VI] exit the VZ first, followed in succession by waves of neurons destined for more superficial laminae [V to II[26]]). Progenitor cells deriving from the ganglionic eminences follow nonradial (tangential) paths to the cortex using trophic and other guidance signals.[42] Select genes are turned on (e.g., doublecortin) that regulate physical migration of individual cells.

During the organizational phases of cortical development, upon arrival into the appropriate cortical layer, neurons extend dendrites and axons and receive a variety of afferent inputs. At this time, synaptic connectivity is initiated. At the molecular level, new expression of many distinct genes including structural proteins necessary for dendrite and axon outgrowth and synapse formation permits the generation of nascent synapses in the late embryonic and early postnatal cortex. Finally, a substantial proportion of neurons within both the cortical plate and subplate undergo apoptosis.

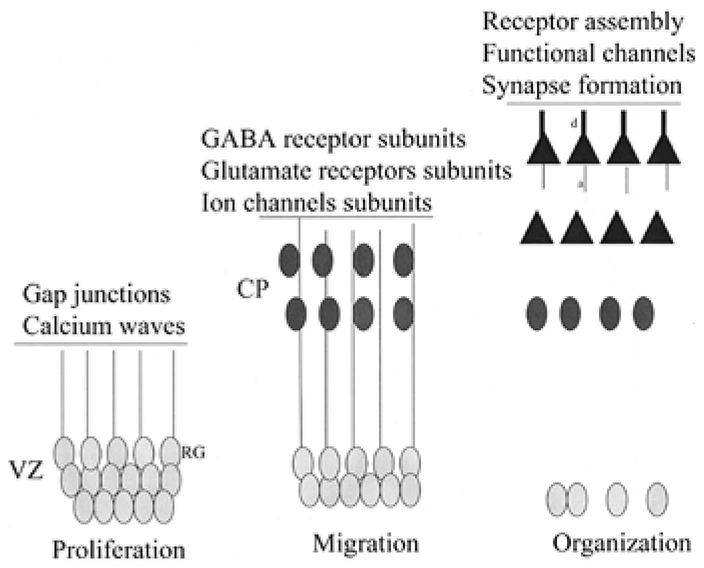

FIGURE 1. The structural assembly of the cerebral cortex during development leads to the establishment of cellular machinery necessary for normal cortical excitability. In early stages of cortical development (**left**), when cells are proliferating in the ventricular zone (VZ), electrical activity is mediated via gap junctions and through calcium waves that spread through the VZ. These electrotonic waves may be mediated largely by radial glial (RG) cells. During migratory phases (**middle**), the cortical plate is formed and there is early transcriptional expression of neurotransmitter receptor subunits and ion channels. At this stage, the establishment of resting membrane potential is a pivotal event that

heralds subsequent action potential generation. During organizational stages of development (**right**), migrating neurons have arrived in their appropriate laminar destination and have begun to extend axons (*a*) and dendrites (*d*). At this point synapses are formed, and there is coordinated expression and assembly of functional neurotransmitter receptor and ion channel subtypes. From this time forward, there are alterations in receptor subunit expression and composition as the brain moves from the late embryonic to early postnatal phases. GABA, Î³-aminobutyric acid.

In the earliest phases of cortical development, there is little spontaneous electrical activity and, in fact, the formation of synapses with subsequent synaptic transmitter release does not occur until later developmental epochs.[30,31] During migratory and early organizational phases of development, much of the structural machinery necessary for synaptic connections have not yet formed and other important components of synaptic function (i.e., glia) have not yet arrived in the cortical plate. In the VZ, there is electrotonic coupling between cells mediated largely by gap junctions.[28] Calcium waves spread selectively through the VZ, a region rich in radial glial cell bodies, and the majority of participating cells are radial glia.[40] Several investigators have demonstrated that calcium waves propagate through the proliferative zone of the embryonic cortex mediated via gap junction proteins (connexins) and intracellular calcium release.[40] In the rodent, VZ calcium waves become more robust from embryonic day 12 (E12) to E16 and coincide with increasing levels of neurogenesis. In addition to setting the stage for early electrical activity in cortex, calcium waves may be involved in modulating neurogenesis during embryonic cortical development. Thereafter, calcium waves abate in the postnatal brain and are replaced by synaptically mediated potentials in the nascent cortex.

Cajal-Retzius Cells

One exception to migratory schema of the embryonic cortex are Cajal-Retzius (CR) cells, which are present in the marginal zone before other neurons initiate migration from either the VZ or ganglionic eminences. CR cells represent a transient population of layer I cells present at early stages of cortical development that diminish during postnatal development.[24] The secreted protein reelin is released by CR cells and plays a pivotal role in permitting appropriate lamination. Layer I in the developing neocortex consists of CR and non-CR cells. Most non-CR cells are Î³-aminobutyric acid (GABA)-ergic, whereas CR cells are glutamate immunoreactive but not GABA immunoreactive.[24] CR cells also express parvalbumin and calbindin. CR cells are first observed in the preplate and later in the marginal zone. CR cells respond to various neurotransmitters and contribute to the synchronized network activity in layer I of the neocortex in which the apical dendrites of many deep and superficial layer pyramidal cells will arborize.[33] CR cells receive dense GABAergic and non-GABAergic input on cell body and dendrites.[20] CR cells express $GABA_A$ receptors and NR1/NR2B subunit-containing receptors.[33] Corticogenesis may depend on the early electrical activity of CR cells and, in fact, CR cells express functional Ca^{2+} channels. Recent calcium imaging analysis has shown that the developing layer I neurons exhibit correlated neuronal activity that could serve as the scaffold for the activity-dependent development of intracortical connections.[20]

Dendritic Development

Dendrites play a crucial role in synaptic signal integration, synaptic plasticity, and network connectivity.[32] Dendritic arborization on pyramidal and local circuit neurons occurs progressively beginning in late embryonic stages of development and extending well into the postnatal periods. Extension of dendritic arbors is a pivotal process for subsequent connectivity since synaptic connections between dendrites and incoming axonal afferents drives many of the functional properties of the mature cortex. Many dendrites of pyramidal neurons in deep layers arborize in layer IV, while some extend to more superficial layers. Pyramidal cell dendrites in layer III arborize in layer I. Thalamocortical afferents will make synaptic contact with dendrites in layer IV, while myriad other inputs will meet dendrites in layer I. The establishment of synaptic structure (see below) is in part driven by signals from incoming afferent fibers, and throughout life there is a high degree of structural and functional plasticity in axodendritic synapses. Several factors, both extrinsic and intrinsic to the neuron, are involved in the regulation of dendritic size. These factors include genetic control, electrochemical signals from incoming axons, and release of growth or trophic factors.

Synapse Formation

The generation of functional synapses in the cortex is critical for the development of cortical excitability, and a complete review of this topic is beyond the scope of any single chapter. In rodents, neocortical inhibitory synaptogenesis is a protracted process that begins in late embryonic life and matures through the first postnatal month. In man, synaptogenesis begins early prenatally and peaks a few months after birth. Perhaps the most striking physical feature of the developing cortex is the precision of its synaptic connections since these specifications herald cortical excitability.[17] In rodent, nascent synapses first appear in the late embryonic periods, but the numbers dramatically increase over early postnatal periods, coincident with the overwhelming flood of activity generated by activity and experience in the postnatal period. From a molecular perspective, the molecules governing synapse formation can be classified into at least two types: Synaptic recognition molecules that mediate choices of appropriate synaptic partners and synaptic organizing molecules that regulate maturation and differentiation of the synapse. Thus, synapse formation is driven by internal cellular programs but also in response to activity-dependent cues from incoming axons.

As axons and dendrites meet, a complex set of mechanisms set the stage for functional connectivity.[32] From a structural perspective, the pre- and postsynaptic elements fuse to form the synaptic cleft. There is rapid expression of cytoskeletal and structural proteins (e.g., cadherins, neuroligins, and GAP-43) to solidify the axodendritic contact. Subsequent expression of synaptic vesicle proteins such as syaptophsyin, synaptotagmin, and synaptobrevin permits formation of presynaptic vesicles for neurotransmitter release, whereas expression of postsynaptic proteins such as dendritic postsynaptic protein 95 (PSD95) or gephyrin are necessary for neurotransmitter receptor subunit assembly into the cell membrane. Ultimately, expression and targeting of neurotransmitter receptor to the synaptic cleft will lead to the establishment of a functional synapse.

Cortical Development: Pharmacologic Changes

Over the course of late embryonic and early postnatal development progenitor cells migrate to form cortical layers and then extend axons and dendrites. Concurrent with these events, there is the appearance of multiple and distinct neurotransmitter receptor subunits and ion channels that mediate functional synaptic connectivity (Fig. 1). The major neurotransmitter systems include the glutamate and GABA systems, and the primary ion channels include calcium, sodium, and potassium channels. Of course, other molecules such as neuropeptides, neurohormones, and unique compounds such as adenosine and nitric oxide play important though not fully defined roles in the development of cortical excitability.

The Glutamate System

Glutamate is the primary excitatory neurotransmitter in the brain and its effects are mediated via two excitatory receptor subtypes: Inotropic and metabotropic receptors (see Chapter 22). The ionotropic glutamate receptor family can be further divided into the *N*-methyl-D-aspartate (NMDA) receptor (NMDAR) and the non-NMDA receptor (Î±-amino-3-hydroxy-5-methyl-4-isoxazolepropionate [AMPA] receptor [AMPAR] and kainate receptor) subfamilies. The NMDA, AMPA, and kainate subtypes are ligand-gated, cation-selective channels consisting of multiple protein subunits. The expression of these subunits, like GABA receptors, fluctuates during embryogenesis and early postnatal development. All of these subtypes exhibit enhanced expression from embryogenesis to early postnatal life. In the rodent, AMPA and NMDA receptors exhibit a peak in expression in early postnatal life but then diminish to a relatively constitutive level with further maturity. Glutamate receptors have been implicated in synaptogenesis, learning, and memory and likely are pivotal in the establishment of normal cortical excitability.

The NMDA receptor complex consists of two NR1 subunits (which have eight splice variants) and up to two of four NR2 subunits (NR2A to NR2D). Functional NMDARs are heteromeric complexes, permissive for calcium, and composed of at least one NR1 subunit and one or more NR2A to NR2D subunits, the presence of which modulates channel functional properties. The NR2 subunits confer distinct pharmacologic and kinetic properties on the receptor. The subunit composition of all ionotropic glutamate receptors changes during development and varies in different regions of the mature brain.[27] It is likely that particular NMDA receptor subunit combinations underlie different functions of the receptor and regulate synaptic plasticity during brain development.

In the rodent, ionotropic glutamate receptors undergo rapid maturational changes.[18,27] NMDAR density peaks late in the first postnatal week in many forebrain structures, including hippocampus and neocortex, whereas AMPAR density peaks in the second postnatal week at around postnatal day 10 (P10). Both NMDA receptor and AMPA receptor expression transiently peak above adult expression levels, resulting in heightened glutamate-mediated plasticity. The ratio of GluR2 expression to that of other AMPA receptor subunits is significantly lower in immature neocortex and hippocampus compared to the adult, and AMPA receptors that lack a GluR2 subunit exhibit higher Ca^{2+} permeability than those that contain GluR2. In the human, similar developmental changes in receptor subunit expression occur over a more protracted time course. Maturational regulation of glutamate receptor subunit composition enhances their ability to mediate activity-dependent synaptic plasticity in early postnatal life. The maturational regulation of AMPA receptor composition and function also enhances glutamate-mediated plasticity in early postnatal life.

Although many synapses express both AMPARs and NMDARs, some have only NMDARs. Synaptic responses mediated only by NMDARs are more prevalent earlier in development, and the subsequent developmental recruitment of AMPARs to synapses may involve an activity-dependent process. Shortly after birth, cortical neurons exhibit relatively large and long-duration NMDAR-mediated excitatory postsynaptic currents (EPSCs). However, during postnatal development, the decay kinetics of the NMDAR become faster, there is an increase in the expression of NR2A subunits, and there is a decline in the ability of the specific NR2B antagonist ifenprodil to inhibit NMDAR function, resulting in much shorter EPSCs.[1] These changes suggest a developmental progression in the composition of the NMDAR complex from predominantly NR1/NR2B to NR1/NR2A isoforms.

Of particular interest is that both AMPA and NMDA sites are expressed largely postsynaptically and are relatively more permeable to calcium during early development. In the developing brain, electrical activity guides the formation of synaptic connections, with long-term effects on adult brain function. Many connections are organized by selective stabilization of synapses when they are activated simultaneously on the same postsynaptic cell during a sensitive period in early life. This Hebbian process often involves calcium entry through the NMDARs. The magnitude of the calcium current passed by this receptor depends on its subunit composition, which varies with age and brain region. Receptor configurations that admit large calcium currents are permissive of synaptic plasticity, and in most regions of developing brain, activity that can drive NMDA receptors initially is low and increases with maturation. As developing inputs increase in number and strength, the increasing excitatory synaptic activity in young neurons should lead to increases in postsynaptic Ca^{2+} influx through NMDA receptors. This Ca^{2+} flux is postulated to trigger a feedback system that changes the subunit composition of the NMDA receptor complex so that less Ca^{2+} enters postsynaptic cells upon NMDA receptor activation. Changes in NMDA receptor effectiveness resulting from manipulations of activity are consistent with the idea that NMDA receptor function is under the control of activity. Thus, the transition from NMDA receptors that flux large calcium currents during early periods of synaptic organization to NMDA receptor subtypes that flux less calcium as synapses become more active, more effective, and less plastic allows maturing neurons to maintain optimal levels of intracellular calcium in the face of drastic developmental changes in their inputs. Experimental observations indicate that glutamate blockade in the rodent in the immediate perinatal

period can adversely affect synaptic and neuronal development. Disruption of NMDA receptor function during development interferes with synapse elimination and sensory map formation.

In the adult nervous system, glutamatergic neurotransmission is tightly controlled by neuronâ€“glia interactions through glial glutamate reuptake by the specific glutamate transporters GLT-1 and GLAST.[36] At birth, GLT is not detectable, but GLAST is present at significant concentrations both in the forebrain and in the cerebellum. GLT is first detected in the forebrain and cerebellum in the second and third week, respectively. Both transporters reach adult levels by postnatal week 5. In somatosensory cortex, GLT-1 and GLAST are early and selectively expressed from P5 to P10. Confocal and electron microscopy confirm that the expression is restricted to the astroglial membrane. The regional distributions of both GLAST and GLT in the tissue are similar in young and adult rats, although GLT is the predominant transporter in the adult brain.[36]

The GABA System

GABA is the main inhibitory neurotransmitter in the brain, and it modulates neuronal excitability, plasticity, and network synchronization (see Chapter 23). GABAergic neurons are found in all cortical layers and account for nearly 30% of all cortical neurons.[4] Most neocortical GABAergic cells are aspiny nonpyramidal neurons whose axon terminals form symmetric synapses. Several factors are involved in GABA's postsynaptic effects: Presynaptic factors (release), factors acting at the synaptic cleft (diffusion and selective transporters), and postsynaptic factors (receptor subtypes, location, number). The inhibitory action of GABA results from interactions with the GABA$_A$ and GABA$_B$ postsynaptic receptor subtypes. These heteromeric protein complexes gate chloride ions and are widely expressed in the developing and mature brain. The GABA$_A$ site is a pentomeric complex composed of five protein subunits (e.g., Î±, Î², Î³, in multiple combinations). The GABA$_B$ site is a G-proteinâ€“coupled metabotropic receptor also composed of multiple protein subunits that is expressed primarily in the hippocampus, thalamus, and cerebellum.

There are spatiotemporal expression patterns of GABA$_A$ receptors.[5,38] Proliferating precursor cells in the neocortical VZ express GABA$_A$ receptors, as do immature postmigratory neurons in the developing cortical plate. In situ hybridization studies have shown that the transcripts for GABA$_A$ receptor Î±3, Î±4, Î²1, Î²3, Î³1, and Î³2 subunits are expressed in the VZ and embryonic cortex. Cells in the VZ may express mRNAs for GABA$_A$ receptor Î±4, Î²1, and Î³1 subunits at the premigratory stage, just after completing cell division. GABA$_A$ receptors in the VZ have a higher apparent affinity for GABA and are relatively insensitive to receptor desensitization compared with neurons in the cortical plate. GABA$_A$ receptors on VZ cells are not activated synaptically, suggesting that these receptors are activated in a paracrine fashion.[28,29] In fact, GABA-induced current magnitude increases with maturation with the smallest responses found in recordings from precursor cells in the VZ. After neurons are born and migrate to the cortical plate, they begin to demonstrate spontaneous synaptic activity, the majority of which is GABA$_A$ mediated. Expression of Î±1 and Î³2 subunits increase from birth through adulthood in the cortex.

Temporal regulation of GABA$_A$ subunit composition may account for the differences in function of GABAergic transmission in the immature and mature brain.[5,28] In early postnatal development, GABA binding to GABA receptors leads to membrane depolarization and at times to cellular excitation.[35] In contrast, in maturity, GABA exerts an inhibitory effect via an influx of chloride. These important functional differences are related also to distinct mechanisms (e.g., low expression of the chloride transporter KCC2) for chloride buffering the developing brain.[22] Uptake of Cl$^-$ by the Na$^+$-K$^+$-2Cl$^-$ cotransporter isoform 1 (NKCC1) has been shown to be pivotal for depolarizing GABA$_A$ receptorâ€“mediated responses in various types of immature neurons.[43] The ontogenetic shift to hyperpolarizing GABA action is caused by a concomitant developmental down-regulation of NKCC1 and an up-regulation of the K$^+$-Cl$^-$ cotransporter isoform 2 (KCC2). Recent studies demonstrate that NKCC1 can facilitate seizures in the developing brain.[10] In the embryonic cortex, there are high intracellular concentrations of chloride and thus, when GABA receptors are activated, chloride flows out of neurons, leading to depolarization. The net effect of temporal alterations in GABA$_A$ receptor subunit composition in the cortex and hippocampus is the development of more rapid receptor:substrate interaction kinetics and enhanced sensitivity to Î±1 agonists like zolpidem.

Similar differences in expression of the GABA$_B$ site may have functional relevance.[11] In the rodent, presynaptic expression of GABA$_{B1a}$ sites is dominant at birth but then declines by 2 weeks of age. Expression of the postsynaptic GABA$_{B1b}$ site rises from immaturity to adulthood. In addition to its role in synaptic modulation and inhibition, it appears that the GABA$_B$ site may contribute to the structural assembly of the cortex and in particular to migration of inhibitory neurons form the ganglionic eminence. Virtually all neurons migrating through the lower intermediate zone from the medial ganglionic eminence to the cortical plate express GABA$_B$ receptors (GABA$_B$Rs). Blockade of GABA$_B$Rs results in an accumulation of tangentially migrating neurons within the ventricular/subventricular zones of the cortex. Thus, GABA$_B$Rs have an important modulatory role in the migration of cortical interneurons.

GABA-mediated inhibition exerts a powerful control over cortical neuronal activity, and GABA transport contributes to modulate GABA's action.

At the synaptic cleft, high-affinity plasma membrane GABA transporters (GATs) in association with variable

GABA_A receptor subunit composition appear to modulate phasic (synaptic) and tonic (extrasynaptic) GABA-mediated inhibition.[16] Phasic inhibition reflects intermittent inhibitory postsynaptic potentials (IPSCs) and tonic inhibition plays a central role in controlling neuronal and network excitability. Four cDNAs encoding highly homologous GATs (GAT-1, GAT-2, GAT-3, and BGT-1) have been isolated in the rodent and human nervous system.[9] These sites exhibit different ionic dependencies and inhibitor sensitivities, and are differentially distributed within the cortex. GAT-1 and GAT-3 have the most relevance for cortical excitability. In the rodent, GAT-1 mRNA and protein first appear at late embryonic stages and their expression increases in the first 2 postnatal weeks. The mature pattern of expression is reached by P30.[9] Most GAT-1 expression is within axon terminals, some of which form symmetric synaptic contacts with dendrites or with somata in the early phases of development. In human temporal cortex, GAT-1 expression appears in the marginal zone by gestational week 33, and is then identified in all layers by weeks 38 to 39. GAT-3 expression appears in the marginal and intermediate zones of the cerebral cortex in late embryonic life. Colocalization studies have demonstrated GAT-3 expression in astrocytes and GABAergic neurons.

GAT-1 and GAT-3 expression follows the same pattern as inhibitory synaptogenesis, suggesting a role for GABA transport in the formation and maturation of cortical GABAergic synapses by P30. GAT-1 and GAT-3 may modulate GABA concentration in the vicinity of nascent synapses. GABA itself regulates the expression and functional properties of GABA_A receptors and chloride transporter KCC2, whose appearance correlates with the onset of GABA's inhibitory action. Local GABA transport may contribute to the maturation of GABAergic synapses and indeed, in both rodent and human cortical development, GAT-1 expression is coordinated with that of other GABAergic presynaptic proteins (i.e., the synthesizing enzyme GAD65 and the vesicular transporter VGAT) and parallels that of the Î±1 subunit of the GABA_A receptor, which participates in mature GABAergic transmission (see, for example, reference 9).

Ion Channels

Cortical pyramidal neurons are considered to be less excitable in the immature cortex than in adults. One explanation for this finding is that in addition to immaturity of functional synapses, embryonic and early postnatal cortical neurons lack the full complement of ion channel subunits necessary to initiate or propagate a viable action potential.[31] The gradual appearance of sodium (Na), calcium (Ca), and potassium (K) channels in cortical neurons coincides with the expression of neurotransmitter receptor subunits and culminates in functional maturity of the cortex. Indeed, the excitability of neurons depends largely on the movement of ions through specific membrane channels. Ion channels have been extensively investigated by means of voltage clamp recording techniques, whereas the effect of ion currents on cell membrane potential have been studied by means of single-unit current clamp recordings.

In various studies of membrane properties of the embryonic rodent neocortex, proliferating populations have been found to primarily express voltage-gated K^+, Ca^{2+}-activated K^+, and small Na^+ conductances when input resistances are sufficient to permit detection of small currents. In acutely dissociated embryonic rat cortical cells, two cell subpopulations with distinct estimated resting membrane potentials have been identified during the period of cell proliferation (E11 to E13): One at approximately -70 mV and the other at approximately -40 mV. Analysis of these two subpopulations revealed that >80% of the latter cells were in proliferative phases of the cell cycle, whereas >90% of the former cells were in postmitotic phases. Na^+ currents then increase throughout development as cells begin to migrate and differentiate. In addition, changing levels of expression of L-type, low- and high-voltageâ€“activated (LVA and HVA) Ca^{2+} currents as well as voltage-gated inactivating (IA) and delayed rectifier K^+ currents occur during both embryonic and postnatal development.

Cells in the developing cerebral cortex generate activity as early as E18, and both Na^+ and outward K^+ currents can be modulated by increasing activity. In acute slices of mouse cerebral cortex, several changes in physiologic properties occur from embryonic day 14 to postnatal day 17.[7] For example, inward $Na(^+)$ current density is up-regulated, while outward $K(^+)$ current density remains almost unchanged, input resistance drops, and a hyperpolarization-activated current appears. As a result of these changes, the action potential becomes larger and shorter in duration, and the threshold shifts to more negative potentials.[7] There is a dynamic development of resting membrane potential, with concomitant expression of K$^+$ channels and voltage-dependent Na$^+$ channels in the developing cortex as it transforms from proliferative to postmitotic cell types.[18,19] In addition, new cells arriving in the cortical plate become capable of firing repetitively and generating spontaneous action potentials.

Voltage-dependent sodium channels are responsible for the initiation and propagation of the action potential in most excitable cells, and neuronal action potentials are predominantly sodium dependent during embryonic and early postnatal ages.[6,23] The heterocomplex structure of these ion channels consists of a highly glycosylated *Î*± subunit, which is noncovalently associated with disulfide-linked *Î*²1 and *Î*²2 subunits. Furthermore, multiple isoforms of the *a* subunit have been identified, giving rise to the notation of Na$^+$ channels I, II, and III, which individually contain single *Î*± subunits and the *Î*²1 and *Î*²2 subunits. The expression of each Na$^+$ channel has been well documented in the brain and is differentially regulated depending on age, region, and cell type.[2,6,14] For example, Na channel I expression was virtually absent at E18. The expression of sodium channel I mRNA rises after a lag phase to adult levels during the second and third postnatal weeks, with stronger increases in caudal regions of the brain and in spinal cord. In the adult brain, expression of Na channel I was nearly absent in the neocortex. Sodium channel II mRNA increases steadily until the first postnatal week, keeping high adult levels in rostral regions of the brain or reaching low adult levels after the second postnatal week in most caudal regions of the brain and in the spinal cord. In comparison with types I and III, sodium channel II mRNA was the most abundant subtype at all developmental stages. Sodium channel III was mainly expressed at the embryonic stage and showed a decrease to very low levels with little regional preferences in the adult. Sodium channel III mRNA attains maximum levels around birth and decreases during the first and second postnatal weeks to reach variable low adult levels.

At least four distinct sodium channels, named NaV1.1, NaV1.2, NaV1.3, and NaV1.6, have been found, which exhibit different patterns of expression during development. In rat brain, at E15 the mRNA of NaV1.2 and NaV1.3 channels are predominant and are coexpressed at approximately equal levels. At postnatal stages all four Na$^+$ channel mRNAs were detected, but to different extents in the various brain regions. In cortex, at early postnatal stages (P1 to P7) the predominant one was NaV1.2 mRNA, and at late postnatal stages the predominant one was NaV1.6 mRNA.[2,6,14]

Calcium channels also exhibit a spatiotemporal pattern of expression regulation.[39] For example, the developmental expression of the L-type voltage-gated Ca($^{2+}$) channel is dynamic.[25] Using the *Î*±1C subunit of this channel as a marker, there is progressive increase in expression in layer V to VI pyramidal neurons from P4 onward, and in layer II to III pyramids by P9 onward. Prior to this time there is sparse expression in the L-type Ca channel in embryonic cortex. The Î³ subunit of voltage-dependent Ca^{2+} channels (VDCCs) is characterized by molecular diversity and regulation of AMPA-type glutamate receptors as well as VDCCs. The expression of the VDCC Î³1 to 8 subunit mRNAs is distinct in developing in adult mouse brains. In embryonic brains there are well-preserved spatial patterns of select subunits (e.g., Î³2, Î³5, Î³7, and Î³8), while other subunits exhibit developmental up- (Î³3) or down-regulation (Î³4). The Î³1 and Î³6 subunit mRNAs were negative or very low throughout brain development, while in adult brains, the Î³3 and Î³8 subunit mRNAs were maximal in the telencephalon and hippocampus. The developmental changes in expression of intracellular calcium release channels are dynamic. mRNA encoding the intracellular calcium release channels (e.g., inositol triphosphate receptors [IP3R] and the ryanodine receptors [RyR]) was detected in developing cortex by embryonic day 11. Expression of these proteins increases progressively throughout brain development.[12] Therefore, the spatiotemporal diversity in gene expression for individual Ca channels subunits likely reflects the functional diversity of these proteins.

K$^+$ channels play a critical role in limiting neuronal excitability, and mutations in specific voltage-gated K$^+$ channels have been associated with hyperexcitable phenotypes in both humans and animals. Using an antibody recognizing the C-terminus of the KCNQ2 channel, a progressive increase in expression in the cortex was observed from postnatal day 8 onward and gradually increased between P11 and P21. In the mouse cortex, an increasing number of KCNQ3-labeled neurons during development showed intense somatic staining beginning with P21 and leading to its maximum at P31. Colabeling with a parvalbumin antibody revealed KCNQ3N immunoreactivity in both parvalbumin-positive and -negative neurons. Expression of the KvÎ² subunit is not detected until the first postnatal week in hippocampal and cortical pyramidal cells.[12]

While the expression profiles of each ion channel subunit are variable across brain regions and through each developmental epoch, by contrast, cortical astrocytes do not show significant regional differences in their ion channel complement and essentially all astrocytes express a combination of delayed rectifying outward K($^+$) currents, transient A-type K($^+$) currents, and small Na($^+$) currents.[3] Developmentally, an increasing percentage of astrocytes express inwardly rectifying K($^+$) currents. In fact, all astrocytes contain voltage-gated ion channels that display a common pattern of expression during development.

The Development of Cortical Excitability and the Relationship to Epilepsy

As outlined above, the development of neuronal circuits in the neocortex during embryogenesis and postnatal periods is dependent on numerous coordinated processes including generation of appropriate neuronal connections, precise synapse formation, axon outgrowth, dendritic arborization, and experience and activity-dependent cues.[30] There are numerous genetic, molecular, or structural abnormalities occurring in these time epochs that can lead to dramatic dysregulation of these tightly integrated circuits. Abnormal or enhanced cortical excitability may be a consequence of these alterations and result in aberrant neuronal firing, establishment of abnormal connections, and seizures. The events leading to altered cortical excitability may have subtle effects on cortical cytoarchitecture or be dramatic abnormalities in brain structure. For example, at least ten monogenic epilepsy syndromes have been reported that result from mutations in select Na, Ca, or K channel genes. These gene mutations do not significantly alter cortical organization or structure but clearly have dramatic effects on cortical neuronal excitability. Indeed, targeted gene knockouts of select ion channels (Ca, Na, or K) leads to hyperexcitability and epilepsy but little structural disorganization. Even more interesting is that there is a temporal dimension to seizures in select channelopathies (e.g., K$^+$ channel mutations and benign familial neonatal seizures) that perhaps belie a critical period for altered excitability. In contrast, mutations in select genes that lead to malformations of cortical development (e.g., lissencephaly, hemimegalencephaly) are highly associated with intractable epilepsy. In each of these disorders, the *sine qua non* anatomic feature is a loss of normal cortical cytoarchitecture. How these structural changes lead to altered excitability is not fully understood, and it is unlikely that enhanced excitability reflects only the effects of the gene mutation. In these disorders, altered cytoarchitecture likely disrupts normal synaptic connectivity or, for example, mechanisms of inhibition in the cortex. For example, knockout of the dlx gene, a homeodomain transcription factor necessary for the production of forebrain GABAergic interneurons, leads to a reduction in inhibitory interneurons in cortex, a reduction of GABA-mediated inhibitory postsynaptic current in neocortex, and generalized electrographic seizures.[8] Thus, alterations in cortical excitability may reflect numerous mechanisms at the molecular, pharmacologic, and anatomic levels. The implications of these distinctions may have significance for the future development of targeted drug therapies that affect, for example, particular molecules in brain regions at particular time epochs.

Summary and Conclusions

The development of cortical excitability is a spatiotemporally regulated process that begins in the early phases of corticogenesis and extends well into the postnatal period. The establishment of appropriate cortical layers and, ultimately, synaptic connectivity are required for the maturation of cortical excitability. There are temporal expression gradients for gap junctions, neurotransmitter receptor subunits, uptake sites, and ion channels in the cortex that permit synaptic transmission and action potential generation. While the expression of these proteins is governed to a large extent by developmental and molecular genetic programs, experiential stimuli can obviously modulate expression as well. The expression of select glutamate and GABA receptor subtypes plays a pivotal role in the appearance of neuronal excitability, as do ion channels. Not surprisingly, alterations in the timing or integrity of how these proteins assemble or localize in neurons can have dramatic effects on cortical excitability that culminate clinically in seizures. Indeed, understanding the mechanisms through which aberrant excitatory activity can be propagated through the cortex has important therapeutic implications in epilepsy research.

The establishment of cortical excitability is a requisite process necessary for learning, sensory perception, movement, and virtually all forms of behavior. Enhancement of cortical excitability or loss of regulatory mechanisms to inhibit or dampen aberrant excitability may be pivotal mechanisms in the generation and propagation of seizures.

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Chapter 34

Early Events in the Development of the Cerebral Cortex

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Christopher A. Walsh

Introduction

There is an increasing awareness that many epileptic conditions, particularly in the pediatric age group, are associated with developmental abnormalities of the cerebral cortex. This chapter provides an overview of normal development of the cortex. The developmental description is intended to provide a context for understanding the function of genes which, when disrupted, have been shown to give rise to these malformations of cortical development (MCD). Although the genetic causes and potential mechanisms leading to the MCD are discussed, a more thorough discussion of the pathology of epilepsy is presented in several other chapters.

The cerebral cortex must undergo a series of fundamental developmental processes to create the underlying neuronal scaffolding that is responsible for the cortical organization underlying complex cognitive functions. The development of the enormous diversity of cells of the nervous system spans a series of crucial events, from (a) the division and expansion of neural precursor populations, to (b) the migration of these neurons out of the ventricular zone (VZ) into the cortical plate, and followed by (c) the differentiation of neurons into the various neuronal subpopulations that make up the six-layered cortex.[1,40] Disruption of each of these processes has been suggested to give rise to a distinct set of human disorders of cortical development. Disorders of proliferation lead to microcephaly (â€œsmall brainâ€), disorders of initial migration give rise to periventricular heterotopia (ectopic nodules of neurons located along the lateral ventricles), disorders of subsequent migration contribute to classical lissencephaly (â€œsmooth brainâ€) and subcortical band heterotopia (referring to an additional layer of neurons beneath the cortex), disorders in neuronal arrest giving rise to cobblestone lissencephaly (smooth brain with ectopic nodules of neurons on the surface of the brain), and disorders in neuronal differentiation giving rise to potential abnormal cell connectivity.[73] Many of the genes responsible for these disorders have been identified. Moreover, such genes provide an initial foundation with which to understand the normal cellular and molecular mechanisms involved in the development of the cerebral cortex and, ultimately, the mechanisms responsible for some pediatric epilepsies.

Formation of the Mammalian Central Nervous System

Neurogenesis

The oldest neurons in the human cortex appear very soon after the regional definition of the cerebral cortex, at about 33 to 42 days postovulation.[54,62] The earliest neurons derive from an epithelium that is originally pseudostratified, in which the neuroepithelial cells have attachments to both the inner, ventricular face and the outer, pial surface. The early neural progenitor cells show a characteristic nuclear movement as the cells progress through the cell cycle: Neurons in the mitotic (M) phase have their nuclei immediately lining the ependymal zone, but as the cells move into synthesis (S)-phase, when they replicate their DNA, their nuclei translocate away from the ventricular lining (growth [G] 1phase). Cells then transition from S to the growth (G) 2phase, at which time their nuclei translocate back toward the ventricular surface and into M-phase. Finally, the nuclei of precursors, which re-enter the cell cycle, move back toward the upper half of the epithelium and away from the ventricular lining during G1 phase (Fig. 1A,B). Although the majority of neurons appear to derive from the ventricular lining, a second proliferative region develops just adjacent to the epithelium, called the *subventricular zone*. Neurons are generated along the neuroepithelial lining of the ventricular zone and indirectly from intermediate progenitor cells that reside in this region.[61]

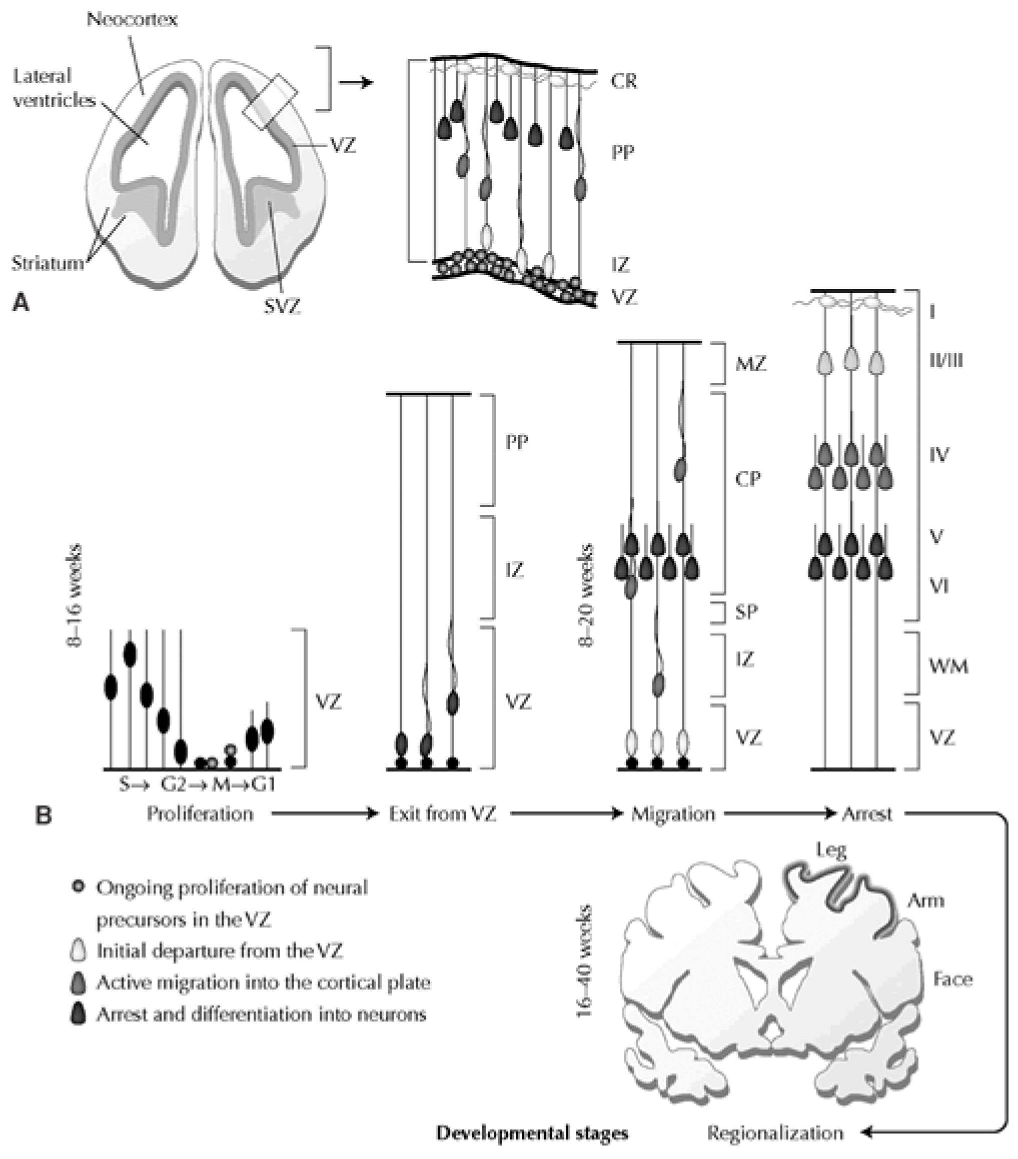
Neocortex
Lateral ventricles
VZ
Striatum
SVZ
A
CR
PP
IZ
VZ
MZ
CP
SP
I
II/III
IV
V
VI
WM
8–16 weeks
8–20 weeks
S→ G2→M→G1
B
Proliferation
Exit from VZ
Migration
Arrest
Ongoing proliferation of neural precursors in the VZ
Initial departure from the VZ
Active migration into the cortical plate
Arrest and differentiation into neurons
Leg
Arm
Face
16–40 weeks
Developmental stages
Regionalization

FIGURE 1. Diagram of the sequential developmental stages of the cerebral cortex. **A:** General anatomic overview of the developing cerebral cortex. Higher-magnification diagram (*right*) of inset (*left*) illustrates ongoing proliferation of neural precursors in the VZ (*circles*), initial departure from the VZ (*light gray*), active migration into the cortical plate (*dark gray*), and subsequent arrest and differentiation into neurons (*black*). **B:** Temporal progression of human cerebral cortical development. During the first 8 to 16 weeks of development, neural progenitors undergo proliferation, with the period of neuronal migration extending over 8 to 20 weeks. By 16 to 40 weeks, regional specification, with clear formation of sulci and gyri, is apparent. Earlier-formed neurons (*black*) become situated in deeper cortical layers (V to VI), with later-formed neurons (*light gray*) positioned more superficially in layers II to III. CP, cortical plate; CR, Cajal-Retzius cells; IZ, intermediate zone; MZ, marginal zone; PP, preplate; SP, subplate; SVZ, subventricular zone; VZ, ventricular zone. Revised with permission from Sheen VL, Walsh CA. Developmental genetic malformations of the cerebral cortex. *Curr Neurol Neurosci Rep.* 2003;(3):433â€“441.

During neural proliferation, precursors undergoing cell division in M-phase either remain as progenitors or adopt a neuronal cell fate. The neural progenitors split into two cells along a cleavage plane that is either vertical (perpendicular to the ependymal lining) or horizontal (parallel to the ependymal lining). Vertical cleavages produce identical daughter cells that resemble the original neural precursors. These symmetric divisions appear to expand or maintain the progenitor pool, because both daughter progenitors re-enter the cell cycle and their nuclei translate away from the lining during G1 phase. In contrast, horizontally dividing cells produce two types of daughter cellsâ€"one that behaves like a young migratory neuron and another that remains within the proliferative zone as a neural precursor and re-enters the cell cycle. These asymmetric divisions appear to give rise to the postmitotic neurons that will comprise the overlying cerebral cortex.[18]

Neuronal Migration

The six-layered adult cortex actually derives from three distinct populations of neurons with very different patterns of development. The oldest cortical neurons form a structure known as the *preplate* or the *primordial plexiform layer.*[52] When the earliest formed neurons of the preplate complete their final mitosis to become postmitotic, they do not actually migrate from where they are formed; instead, they translocate their nuclei through one cellular process, then retract their processes and begin differentiation into neurons (Fig. 1B).[52,54] Later-formed neurons divide the preplate into two layers, called the *marginal zone* (future layer I) and the *subplate* (future deep neurons of layer VI and the white matter) (Fig. 1B). These later formed neurons do not migrate directly to the cortex but rather display a retrograde movement toward the ventricle while in the VZ/SVZ, before migration back out into the cortical plate (Fig. 1B).[61] These neurons form the vast majority of all cortical neurons, including cells in layers VI through II, and form a third transient layer called the *cortical plate*. The cortical plate is first seen at about embryonic day (E) 52 in the human, almost 3 weeks after appearance of the preplate.[54] Studies in many different mammals have repeatedly shown that neurons within the cortical plate follow a remarkable and precise sequence of events when inserting into the preexisting preplate.[9,67] The oldest neurons of the cortical plate (future layer VI cells) cease migration nearest the subplate cells, whereas the next cohort of cortical neurons (future layer V) migrates just beyond the older layer VI cells to settle nearer the pial surface. Successive waves of cortical plate neurons then all follow the same â€œinside-outâ€ gradient of neurogenesis (Fig. 1B), with cortical neurogenesis and migration completed by about 24 weeks of embryonic development.[54] The cortical-plate neurons are formed at a later time and in the context of a larger brain than are the preplate cells; consequently, they must migrate for distances of up to millimetersâ€"equivalent to hundreds of times their cell body size. This long-distance migration appears to involve mechanisms distinct from those that operate during the formation of the preplate.

Although the neocortical excitatory neurons originate from the proliferative ventricular zone of the cortex, many of the inhibitory cortical interneurons actually appear to be derived from the germinal zone of the basal ganglia. Most of these cells derive from the medial ganglionic eminence, but may also arise from the caudal and lateral ganglionic eminences, the septal region, and the cortex itself. These interneurons follow a tangential migratory pathway from the ganglionic eminences to the cortex.[4,5,84]

Table 1 Cortical Malformations and Associated Gene Abnormalities

Gene	Phenotype	Possible Biological Role
ASPM	Microcephaly	Found in spindle poles during mitosis in proliferating brain cells

CDK5RAP2	Microcephaly	Found in centrosomes of neuroepithelial cells lining the brain
CENPJ	Microcephaly	Same as *CDK5RAP2*
Microcephalin	Microcephaly	Involved in cell cycle control and possibly in DNA repair
Filamin A	PH	Involved in regulation of actin cytoskeleton
ARFGEF2	PH	Involved in vesicle transport
LIS1	Type 1 lissencephaly	Involved in cell motility through interactions with dynein and doublecortin
DCX	Type 1 lis/ SBH	Same as *LIS1*
ARX	XLAG	Homeobox gene that activates multiple molecular pathways
Reelin	LCH	Secreted by Cajal-Retzius cells; likely extrinsic signal to migratory neuroblasts
VLDLR	LCH	Receptor on neuroblasts that interacts with Reelin
Fukutin	FCMD/ Type II lis	Involved in glycosylation of extracellular matrix proteins along the pial surface
POMGnT1	MEB/ Type II lis	Same as *Fukutin*
POMT1	WWS/Type II lis	Same as *Fukutin*
POMT2	WWS/Type II lis	Same as *Fukutin*
GPR56	BFPP	G-coupledâ€“protein expressed with neural progenitors

MeCP2	Rett syndrome	Regulates biochemical switches that control gene expression
CDKL5	Rett-like syndrome	Mediates MeCP2 phosphorylation
TSC1	TS	Tumor suppressor function
TSC2	TS	Tumor suppressor function
SCN1A,SCN2A, SCN1B, GABARG2	Generalized epilepsies with febrile seizures	Channelopathies
GABARA1	Juvenile myoclonic epilepsy	Channelopathies
KCNQ2, KCNQ3	Benign familial neonatal convulsions	Channelopathies
CLCN2	Idiopathic generalized epilepsy	Channelopathies

PH, periventricular heterotopiaâ€”type I lissencephaly is synonymous with classical lissencephaly; SBH, subcortical band heterotopia in femalesâ€”type II lissencephaly is synonymous with cobblestone lissencephaly; XLAG, X-linked lissencephaly with ambiguous genitalia; LCH, lissencephaly with cerebellar hypoplasia; FCMD, Fukuyama congenital muscular dystrophy; MEB, muscle eye brain disorder; WWS, Walker Warburg syndromeâ€”type II lissencephaly is synonymous with cobblestone lissencephaly; BFPP, bilateral frontal and parietal polymicrogyria; TS, tuberous sclerosis.

Neuronal Differentiation

Although cortical plate neurons are generated and mature gradually, the earlier formed preplate and subplate neurons achieve a high level of morphologic maturity at early cortical stages (E30â€“E50 in humans).[45] In animal models, early subplate cells have been shown to receive the earliest connections from outside the cortex (especially from the thalamus) and to form the earliest efferent connections from the cortex to subcortical sites.[3] Remarkably, the high level of morphologic and synaptic maturity achieved by the subplate is transient because these neurons regress, and most appear to die off as a normal morphogenetic process during later cortical development. The transience of the subplate has given rise to the theory that subplate cells are â€œpioneerâ€ neurons that are present to guide and direct later-formed definitive cortical connections. Thus, the regression and death of subplate connections may be a necessary, perhaps even obligatory, step in normal cortical development.[3]

Within the cerebral cortex, the progressive differentiation of a given neuron can be divided into sequential phases. Some of the steps in neuronal development include the initial neuronal specification while in the ventricular zone and several subsequent phases of postmigratory neuronal differentiation, including formation of an axon and dendrites, synthesis of synaptic machinery, and expression of ion channels. Simple invertebrate organisms with small nervous systems show specific genetic mutations that affect each sequential step in neuronal development, suggesting that the steps occur in a defined sequence.[21] Although, for any given neuron, these developmental steps occur in series; for the cortex as a whole, the developmental steps do not represent entirely separate steps because cortical neurons are also formed in sequence. Thus, the elaboration of neurites in the oldest cortical neurons overlaps in time with the specification of newer cells, and so on.

Despite the overlap in the formation of cortical neurons of different layers, cell biologic study of vertebrate cortical neurons suggests that each neuron undergoes a fairly predefined sequence of developmental steps. For example, neuronal precursors appear to receive information about the specific type of neuron they will become during their final cell division and before they migrate out of the proliferative region of the cortex. Previous transplantation studies have suggested that, once a postmitotic neuron has obtained a neuronal fate and commitment to form one particular cell type, it will carry out its developmental program and migrate to an appropriate cortical location, even if it is challenged by having to migrate through a novel cellular environment.[53] A number of transcription factors that are activated in a cortical progenitor will determine its cortical neuron phenotype and promote the repression of certain genetic sequences that would specify a different cell fate.[27] Once the neurons have obtained their laminar position, cortical pyramidal cells and interneurons make and receive efferent and afferent projections. These processes depend on the interplay between intrinsic transcriptional factors and extrinsic signaling, thereby establishing the appropriate topographic intercortical and intracortical connections and proper connectivity with the thalamus.[66]

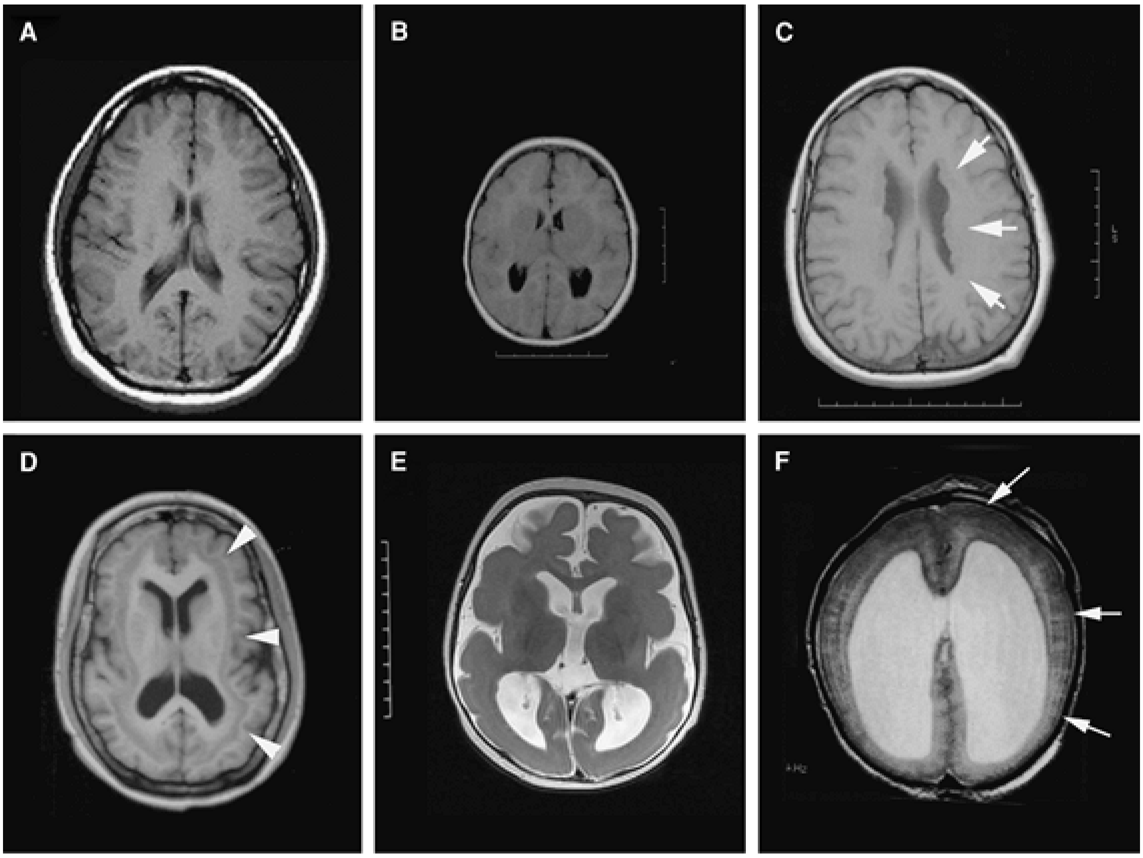

FIGURE 2. Genetically inherited malformations of cortical development. **A:** Axial T1-weighted MR image of a normal brain **B:** Microcephaly with simplified gyral pattern. The brain size is greater than two standard deviations below the norm. In microcephaly vera, the brain structures (cortical sulci and gyri, basal ganglia and fiber tracts) are normal in appearance but reduced in size. **C:** Periventricular

heterotopia due to *FLNA* mutation: The cortical layers are apparently normal, and intelligence is usually in the normal range. The heterotopia (*arrows*) consists of excessive numbers of neural cells, usually neurons, in the periventricular region. Because the periventricular region corresponds to the proliferative zones during development, the heterotopia presumably consists of neural cells that do not migrate out toward the cortex. **D:** Subcortical band heterotopia due to *DCX* mutation: The double-cortex syndrome is also known as *diffuse cortical dysplasia* and *subcortical laminar heterotopia*. In this disorder, the ependymal zone appears relatively normal, and heterotopic neurons (*arrowheads*) are found in great numbers in the subcortical white matter. The doublecortin gene that causes double cortex in females causes classical (type I) lissencephaly in males. **E:** Classical lissencephaly (*type I lissencephaly*) is characterized by the loss of the folds of the brain (sulci and gyri), an abnormally thick cortex, and loss in cortical lamination. In classical lissencephaly due to *LIS1* mutations, the spectrum of lissencephaly ranges from absent (agyria) or abnormally broad (pachygyria) convolutions. **F:** Cobblestone lissencephaly: Also termed type II lissencephaly, cobblestone lissencephaly consists of cobblestone cortex, abnormal white matter, and enlarged ventricles. A thin lining composed of ectopic neurons (*small arrows*), which have migrated beyond the superficial marginal zone, is seen on the surface of the brain. It is usually associated with eye malformations and congenital muscular dystrophy.

Malformations of Cortical Development

The complexity of proliferation, migration, and differentiation in the developing cortex make it hardly surprising that disruptions in these processes result in a number of neuropathologic disorders, including epilepsies (Table 1). Although malformations of the cortex are discussed in detail in Chapters 14 and 259, we present an overview of some genetically inherited

disorders to illustrate how our improved understanding of the basic biology of cortical development improves our insight into epileptic pathology.

Disruption of Neurogenesis

When the capacity to generate the numbers of cells needed by the developing cerebral cortex is impaired, not surprisingly, the human brain becomes microcephalic. Many genetic and nongenetic factors can result in a small brain. For example, congenital infection with toxoplasma, maternal alcohol overconsumption, as well as general disorders of cell metabolism or cholesterol synthesis can lead to a small brain. In general, however, disruption of such processes are readily apparent on examination and also affect various organ systems, leading to extra-central nervous system (CNS) manifestations.[58,63] For this reason, disorders that cause microcephaly vera (true microcephaly) have been used to more clearly delineate processes that directly affect cortical development. In such cases, the brain size is greater than two standard deviations below the norm (Fig. 2A vs. 2B). The disorder is associated with mental retardation, there is gross preservation of the brain structures (except on a smaller scale), and the disease occurs in the absence of findings outside the CNS.[57,58] Identification of the genes that cause macrocephaly vera indicates that some of them have direct relevance to neurogenesis.

Genes causal for microcephaly (*Microcephalin, ASPM*, *CDK5RAP2,* and *CENPJ*) have been suggested to play some role in neurogenesis along the ventricular neuroepithe- lium,[12,13,83] and appear to play direct roles in the mechanisms underlying cell division. *Microcephalin* is a gene that contains three BRCA1 domains that have been implicated in cell-cycle control and DNA repair.[39] Loss of DNA repair genes can lead

to increased programmed cell death, thereby suggesting that loss of *Microcephalin* function leads to increased cell loss along the ventricular neuroepithelium. More recent studies have suggested two potential roles for Microcephalin protein: One in the control of cell-cycle timing and the other in the control of DNA repair (following ionizing radiation damage).[78,85] *ASPM* (abnormal spindle-like, microcephaly-associated) is a gene that encodes a very large protein. In *Drosophila*, *ASPM* is essential for normal mitotic spindle function in embryonic neuro- blasts by stabilizing the tubulin ring complexes that organize the centrosomes.[22] CDK5RAP2 and CENPJ are also centrosomal proteins, localized to the centrosomes in interphase and to the spindle poles during mitosis.[13,38]

Although mental retardation has been a uniform feature seen in microcephaly vera,[83] seizures have not been included in the primary clinical phenotype, despite the high prevalence of epilepsy in microcephaly patients. More recent findings, however, have shown that mutations in *ASPM* can lead to epilepsy in some affected individuals. Seizures have onset at 2 to 3 years of age, and they appear focal in onset. EEGs demonstrate a generalized slowing interspersed with occasional Rolandic or central spike activity.[75] In other patients with macrocephaly, severe disruption of the gyral pattern and neuronal architecture occurs, and these conditions (known as macrocephaly with simplified gyri) are generally associated with early-onset seizures and early death; genes for these syndromes have not been identified yet.

Disruption of Migration

Malformations of cortical development that result from altered neuronal migration can best be appreciated by looking at the progressive stages of migration: The initial departure of neuroblasts from the ventricular zone, the motility required of neurons to migrate into the cortical plate, and the stop signals informing a neuron that it has reached its appropriate layer. Failure of neurons to exit from the VZ presumably gives rise to periventricular heterotopia (Fig. 2C), a malformation characterized by nodules of ectopic neurons lining the lateral ventricles.[28,42] Neurons that have delayed or impaired migration cause lissencephaly (Fig. 2E), a malformation characterized by the loss of sulci and gyri, as well as a thickened four (rather than the normal six) -layered cerebral cortex.[8,24] Disrupted migration in a subpopulation of neurons leads to subcortical band heterotopia (SBH) (Fig. 2D), a malformation characterized by heterotopic neurons positioned midway between the gyrencephalic cortex and underlying ventricular zone.[23,35] Failure of neurons to receive signals directing them to the appropriate layer can result in lissencephaly with cerebellar hypoplasia, a malformation characterized by an inverted cortex, whereby earlier-formed neurons form the superficial layers and later-formed neurons make up the deeper layers.[37] Failure of neurons to stop migration can lead to cobblestone lissencephaly (Fig. 2F), a malformation characterized by neurons that have migrated beyond the superficial marginal zone.[10,44,80,87] In each of these disorders, a failure in the mechanisms that guide migration at specific stages leads to distinct malformations of cortical development.

Neurons that fail to exit the ventricular zone during development cause periventricular heterotopia (PH). PH is characterized by continuous, bilaterally symmetric nodules of neurons, which are distributed throughout the ependymal layer and beneath an otherwise normal appearing cerebral cortex.[23] Dominant mutations in the X-linked gene *Filamin A* (*FLNA*) have been shown to result in periventricular heterotopia in females and lethality in hemizygous males.[28,70] Filamin A exists as a homodimer with a receptor and actin-binding region. Thus, the protein is believed to transduce signals from its receptor interactors onto interactions with the actin cytoskeleton, thereby regulating cell motility.[19,33] More recent studies have shown that a much rarer cause of PH with microcephaly is due to autosomal recessive mutations in the *ARFGEF2* gene.[71] *ARFGEF2* encodes an ADP-ribosylation factor (ARF) guanine exchange factor that converts guanosine diphosphate (GDP) to guanosine triphosphate (GTP), and thereby activates the ARFs. The ARFs have been implicated in vesicle transport. Although the shared mechanisms between these two genes (*FLNA* and *ARFGEF2*) are not clear, insights have been gained from studying features common to the function and expression of both genes. Namely, both BIG2 (the protein encoded by *ARFGEF2*) and filamin A are highly restricted to the ependymal lining along the ventricular zone; disruption of both genes leads to a loss in cell adhesion (with filamin A probably acting through the filaminâ€"integrin interactions, and with the guanine exchange factor (GEF) acting via impaired transport of cell adhesion molecules to the cell surface).[50,71] The overlying cortex in PH appears largely normal in both males and females,[42] suggesting that many neurons actually migrate normally into the cortex. Thus, PH may reflect a disorder of the ependymal lining in which a loss of cell adhesion may lead to a loss in neuroepithelial integrity. Alternatively, an interruption in the ependyma may disrupt the radial glial endfeet that are localized to the ventricular lining, and thereby alter the initial attachment of migratory neuroblasts onto the radial glial scaffolding.[49,74]

As neurons exit the VZ, impairments in cell motility may impede their migration into the cortical plate and cause classical lissencephaly. Classical lissencephaly (type I lissencephaly) is characterized by the loss of the folds of the brain (i.e., of sulci and gyri), an abnormally thick cortex, and loss in cortical lamination. Dominant mutations in the autosomal *Lissencephaly1*(*LIS1)* gene have been shown to cause classical lissencephaly.[48,56,68] Mutations in the X-linked *Doublecortin (DCX)* gene also cause this disorder in hemizygous males, but lead to subcortical band heterotopia in heterozygous females.[20,30] In affected females with subcortical band heterotopia, neurons are partially arrested in their migration, residing as a poorly organized layer of neurons within the white matter and beneath a relatively normal cortex. Several lines of evidence suggest that both genes (*LIS1* and *DCX*) are involved in neuronal motility. *LIS1* interactions with both dynein and doublecortin support some role in cell motility.[25,60] Moreover, neurons harboring a heterozygous *LIS1* mutation show altered dynein localization and reduced cell motility.[25] One role for DCX in neuronal migration may be through its ability to polymerize microtubules.[31] Inhibition of DCX also appears to delay or inhibit neuronal migration in rats.[6] Due to X-inactivation, neurons presumably harboring the normal DCX protein migrate into the cortex, whereas neurons harboring the abnormal DCX protein are inappropriately positioned under the normal layers of cortex.[2] Finally, a recent human case of subcortical band heterotopia was shown to involve a mosaic mutation in the *LIS1* gene, in which only some (but not all) of the cells harbored a mutation.[76] The observation that a mosaic *LIS1* mutation could result in SBH is consistent with a cell-autonomous process such as motility in giving rise to both types of cortical malformations.

Although a loss in the intrinsic capacity of neurons to migrate into the cortex can lead to lissencephaly, extrinsic molecular signals and cellular interactions are also necessary to direct neuronal migration into the cortex. Mutations in the *Reelin* gene can lead to a milder form of lissencephaly with cerebellar hypoplasia (LCH).[37] Interestingly, the causative mutation in this disorder was first described in mice that demonstrated an ataxic (reeling) gait likely secondary to the absent cerebellar folia.[16] Reelin is secreted by the Cajal Retzius cells located in the marginal zone near the surface of the brain. Presumably, Reelin provides some extrinsic signal to migratory neuroblasts. In

addition, Reelin interacts with the veryâ€"low-density lipoprotein receptor (VLDLR), apolipoprotein E receptor (ApoER)-2, integrins, and protocadherins, indicating that Reelin has some role in cell signaling and adhesion. Mice with mutations in *VLDLR* or *ApoER2* also share similar features with the reeler mice, including inversion of cortical layers and absence of cerebellar foliation.[37,79] Humans with *VLDLR* gene mutations have recently also been found to have LCH.[15] Although these interactors are known, the exact mechanisms leading to the disturbed migratory pattern remain unclear.

Disruption of the neuroepithelium along the lateral ventricles leading to PH mirrors the loss of structural integrity along the pial surface of the brain in giving rise to cobblestone lissencephaly (type II lissencephaly).[59,80,86] The autosomal recessive cobblestone lissencephalies have a gradient of severity ranging from the milder Fukuyama congenital muscular dystrophy (FCMD) that affects primarily the Japanese population, to the moderate Finnish muscle eye brain disorder (MEB), and to the most severe Walker Warburg syndrome (WWS) that leads generally to early postnatal lethality. In cobblestone lissencephaly, neurons have no inherent motility defect, but rather migrate beyond the marginal zone into the leptomeninges and through the external basement membrane during cortical development. The loss in integrity of the molecular layer leads to nodules of neurons, or heterotopia, on the surface of the brain (resembling cobblestones). Four genes have been associated with cobblestone lissencephaly (*fukutin* for FCMD, *POMGnT1* for MEB, and *POMT1* and *POMT2* for WWS)[10,44,80,87]; all are implicated in the glycosylation of the dystroglycans. Hypoglycosylation of dystroglycan abolishes binding activity for such ligands as laminin, neurexin and agrin, and thereby compromises the integrity of the dystrophin-associated extracellular matrix adhesion complex.[55] Loss of adhesion in the extracellular matrix results in a weakening of the structural integrity of the marginal zone (layer I) of the cortex, allowing migratory neurons to â€œovermigrateâ€ beyond this structural barrier onto the pial surface. Thus, the heterotopia seen along the lateral ventricles in PH reflects a similar process seen in the neuronal cobblestones seen on the outer brain surface in type II lissencephaly.

The severity of the neurologic deficits (including epilepsy) associated with these migration abnormalities appears to correspond with the severity of the neuronal migratory defect in these cortical malformations. In PH, ectopic neurons reside along the lateral ventricle with relative preservation of the overlying cortex. These heterotopic neurons do appear to extend projections, and they show some limited connectivity to other brain regions.[34] PH caused by mutations in the X-linked *FLNA* gene results in adolescent-onset seizures (up to 88% of affected individuals), which are generally not intractable and respond well to antiepileptic medications.[33,70] Consistent with the largely normal appearing cerebral cortex, affected individuals are of normal intelligence, although they may have some component of dyslexia.[17] When associated with *ARFGEF2* mutations, the onset of epilepsy in PH occurs in the early postnatal period, and infants show developmental delay and mental retardation. This increased severity of neurologic symptoms may, in part, arise from the added findings of microcephaly and delayed myelination observed in these individuals. Electroencephalographic (EEG) investigations demonstrate slowing or dysrhythmia with occasional spike and slow-wave discharges.[71,72] In SBH, the ectopic neurons reside in the white matter just beneath the cortex, suggesting a more severe malformation in cortical development. Affected individuals exhibit seizures of multiple types that usually begin in childhood and can be of varying severity and frequency.[7,23] The thickness of the ectopic band and the degree of pachygyria correlate with the likelihood of developing Lennox-Gastaut syndrome.[33] The thickness of the band also correlates inversely with the cognitive level of the patients, who demonstrate mild to moderate developmental delay, dysarthria, but minimal pyramidal signs. EEG studies usually show generalized spike-and-wave discharges or multifocal abnormalities.[7,23] Although the cortex appears relatively normal in PH and SBH, complete disruption of the normal cortical lamination seen in the type I lissencephaly usually results in more severe forms of epilepsy. Lissencephaly due to *LIS1* mutations causes seizures in over 90% of patients, with onset in the vast majority before 6 months of age. Approximately 80% of children will have infantile spasms within the first year of life, followed by mixed seizure disorders including atypical absence, drop attacks, myoclonic, partial complex, tonic and tonic-clonic seizures in later life. The lissencephaly also results in profound mental retardation, diffuse hypotonia, and later spastic quadriplegia.[32] The EEG typically shows a high Î±-Î² spike activity, which is not seen in type II lissencephaly.[46] Likewise, the severe disruption in cortical lamination seen in LCH results in seizures, severe developmental delay, and hypotonia.[37] Unlike type I lissencephaly, in which actual impairments in neuronal motility occur, the overmigration seen in cobblestone lissencephaly results in less severe epilepsy, presumably due to the fact that the cortex underlying the cobblestone heterotopia is somewhat preserved. Over 80% of patients with type II lissencephaly develop seizures; the average age of onset is in the third year of life, with seizures often occurring after a febrile event. Affected individuals have generalized tonic-clonic convulsions, followed by complex partial or secondarily generalized seizures. Less than 10% of patients go on to develop Lennox-Gastaut syndrome. The EEG studies show multifocal paroxysmal discharges superimposed on a Î¸- or Î´-wave background.[33,88] Discharges are less frequent and of lower amplitude when compared to the type I lissence-phaly.[11]

Disruption of Neuronal Differentiation

The sequential mechanisms that transform an immature neuron into the many subtypes of neurons in the cerebral cortex are not known. Furthermore, neuronal differentiation reflects a very complex process and is likely to involve a multitude of genes, including those that direct progenitors to become neurons and those that are preferentially expressed within subpopulations of mature neurons. Thus, in many ways, no simple view encompasses all the genetic mechanisms in neuronal differentiation. That said, genes involved in neuronal differentiation can be classified with respect to their function: Specifically, disrupted genes that reflect the make-up of the particular neurons and disrupted genes that direct the overall make-up of the brain.

With regard to the generalized idiopathic epilepsies, many of the monogenetic disorders have been attributed to ion channelopathies that are preferentially expressed by particular neuronal subtypes. The loss of function of certain ion channels can alter the firing properties of particular mature neurons (such as pyramidal cells, interneurons, or both) and, in this respect, the functional characteristics of such fully differentiated neurons are altered. Discussion of each of these genetic mutations can be found in Chapter 18. In summation, however, the generalized epilepsies with febrile seizures plus are attributed to mutations in sodium channels (*SCN1A*, *SCN2A*, *SCN1B*) and the Î³-aminobutyric acid (GABA) receptors (*GABARG2*). Another GABA receptor (*GABARA1*) has been associated with juvenile myoclonic epilepsy. Benign familial neonatal convulsions are caused by mutations in the potassium channels (*KCNQ2*, *KCNQ3*). Finally, mutations in the chloride channel (*CLCN2*) are thought to give rise to several idiopathic generalized epilepsies.[29] Each of these early-onset epilepsies is attributed to preferential loss of the expression and function of particular ion channels on subpopulations of neurons.

More regional and global impairments in neuronal differentiation leading to epilepsy can be seen in several neurodevelopmental disorders. Mutations in the G-proteinâ€"coupled receptor gene (*GPR56*) cause bilateral frontal and parietal polymicrogyria, with affected individuals having mental retardation, esotropia, and childhood-onset seizures.[64,65] GPR56 is preferentially expressed within cortical progenitors along the ventricular and subventricular zones. Moreover, the preferential disruption of the frontal and parietal regions would suggest that this gene plays some role in directing brain regionalization. As another example, mutations in the Methyl CpG binding protein-2 (*MeCP2*) gene and cyclin-dependent kinase-like-5 (*CDKL5*) gene cause Rett and Rett-like syndrome, characterized initially by mental retardation, ataxia, and nonpurposeful hand movement.[77,82,89] *CDKL5* encodes a nuclear protein and putative kinase whose expression in the nervous system overlaps with that of MeCP2 during neural maturation and synaptogenesis. CDKL5 also appears to phosphorylate itself and mediate MeCP2 phosphorylation.[51] Finally, MeCP2 appears to regulate many of the biochemical â€œswitchesâ€ needed to control the complex expression patterns of other genes. Failure in the activation of these gene pathways likely contributes to the progressive neuronal degeneration seen in affected individuals, leading to spastic paraparesis, vasomotor disturbances of the lower limb, and epilepsy. Thus, the capacity for some neurons to undergo appropriate neuronal differentiation is predetermined by cellular and molecular mechanisms earlier in development, thereby directing the differentiation of specific regional areas in the brain.

Disruption of Multiple Developmental Stages

Although the genetic mechanisms underlying the malformations of cortical development are conceptually easiest to understand when classified into the various developmental stages, several general observations can be made with regard to genotypeâ€"phenotype correlations. Genes involved early in development will likely influence later developmental stages. Moreover, no discrete boundary actually divides these respective developmental stages, so many of these developmentally active genes may have some overlapping functions across several developmental stages. Finally, extrinsic environmental influences can contribute to the extent and severity of these malformations.

Genes with early onset and broad function can, when disrupted, alter subsequent developmental processes. For example, another genetic cause of lissencephaly, the X-linked form of lissencephaly with abnormal genitalia (XLAG), is due to mutations in the Aristaless-related homeobox gene (*ARX*).[14,43] Homeobox genes act as transcription factors that direct the initial coordination of a cascade of genes in control of various aspects of development. In this respect, it is not surprising the mutations in *ARX* lead to a disruption of numerous brain structures: A moderately thickened cortex that has three layers, a loss in sulcal and gyral folds, and agenesis of corpus callosum. In mice, aberrant interneuron migration occurs, along with reduced brain size, loss of region-specific markers, and abnormal nerve fiber tracts.[43] Thus, a single gene responsible for early development can disrupt neuronal proliferation (microcephaly), migration (lissencephaly), and differentiation (agenesis of the callosum) in the cerebral cortex. These structural abnormalities likely contribute to the seizures and mental retardation in females, and early lethality in males. Similarly, but in a more limited sense, disruption of *LIS1* or *DCX*, while impairing neuronal motility and clearly affecting the cortical lamination, also lead to impaired differentiation. Neurons within the cortex appear dysmorphic, heterotopic in nature, and may actually be inverted.[81] The altered neuronal differentiation may in part result from the disruption in cortical lamination, causing neurons to reside in appropriate positions within the cortex, thereby interrupting the typical external signals required for appropriate connectivity.

Different developmental stages may share similar cellular and genetic mechanisms. For example, *LIS1* has a fundamental role in microtubule function, given its interactions with dynein. This interaction likely serves its role in cell motility. However, Lis1 protein also binds NUDE/NUDEL, which are regulators of cytoplasmic dynein, which is involved in organizing the centrosome in cell division.[26,60] In addition, humans with *LIS1* mutations do have microcephaly. Thus, the Lis1-dependent cytoskeletal regulation likely is required for both migration and proliferation. Another case in point is the microcephaly caused by mutation in *Microcephalin*, which has also been associated with PH.[78] Increased cell death along the ependymal lining could disrupt the integrity of the ependyma and lead to both PH and microcephaly. Similarly, individuals with PH due to

ARFGEF2 mutations also have microcephaly; presumably the GEF is involved in the vesicle transport of proteins involved in cell adhesion as well as cell proliferation along the neuroependyma lining.

The severity of some cortical malformations depends on extrinsic influences. For example, tuberous sclerosis (TS) is an autosomal dominant disorder leading to the formation of cortical tubers within the brain.[36,47] TS is caused by mutations in at least two genesâ€”*TSC1* and *TSC2â€”*which encode for hamartin and tuberin, respectively. Both hamartin and tuberin have tumor suppressor functions. Although all progenitors will have a mutation in either one of these genes, only some precursors will develop into cortical tubers. Thus, the disorder has been suggested to follow a classical Knudson â€œtwo-hitâ€ model for recessive oncogenes, in which some but not all progenitors receive a second external hit and result in a loss in cell cycle inhibition.[41]

In addition to extrinsic factors that alter gene expression and function, it is important to recognize that nongenetic insults during cortical development can give rise to cortical dysplasias and early-onset seizures. Maternal trauma, exposures to teratogens (drug and environmental poisons), infections, as well as strokes and hypoxia can all contribute to malformations of cortical development, depending on the timing and location of the insult. This topic has been reviewed.[69] Several animal models illustrate the nongenetic â€œtraumaâ€ and possible consequences on cortical development. Treatment of embryonic rodents during periods of neurogenesis using the DNA alkylating agent (methylazoxymethanol) or Î³-irradiation results in cortical thinning and cortical heterotopia, consistent with impairments in the proliferation and early migration of neural progenitors. Cortical freeze lesions on the surface of the skull of newborn rodents (at a time point after neurogenesis but during continued neuronal migration) results in a four-layered cortex reminiscent of the lissencephalic human brain, suggesting a disruption in cell migration.

Summary and Conclusions

This chapter provides a brief introduction to some of the issues that can be addressed in studying the development of the cortex. The abnormalities of cortical development frequently seen in epileptic brains represent important data that can inform the basic scientists. In turn, progress in understanding cellular and genetic regulation of cortical development may ultimately improve our understanding of the pathogenesis of epilepsy. Epilepsy is likely to be the end result of a large variety of genetic and nongenetic lesions that ultimately affect the development of the cortex. We hope that understanding these genetic mechanisms may provide several contact points for the design of improved medical therapies.

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Chapter 35

Synaptic Plasticity

Christophe Bernard

Introduction

Cognitive tasks are associated with specific firing patterns of neurons.[27,60] During learning and memory processes, a conditioning stimulus can trigger morphological and modifications at the neuronal network level to store novel information. This is known as *synaptic plasticity*. These modifications can result in changes in firing patterns in response to the same unconditioned stimulus. For example, in the cerebellum, the vestibulo-ocular reflex can be adaptively modified when vestibular-visual conditions are changed, with the triggering error signal being provided by the firing of climbing fibers.[52] The goal of this chapter is to describe the various mechanisms that have been proposed to explain how information processing can be modified via dynamic modifications at the synapse. These mechanisms are also important to consider in the context of epilepsy. First, many types of epilepsies are associated with cognitive deficits, raising the possibility that these mechanisms are compromised in patients. Second, ictal and interictal activities may activate these mechanisms to trigger further network modifications. Third, these mechanisms may themselves be involved in the construction of epileptogenic neuronal networks.

Many processes can be evoked to alter information process transiently or permanently. Because information is coded in spike trains, it is essential to understand the mechanisms responsible for changing the output firing patterns in response to given synaptic inputs. The firing pattern of a neuron usually results from the interaction between synaptic inputs and ion (voltage-gated, Ca^{2+}, ATP-gated, pH-gated, stretch-gated, etc.) channels. Any change at the synapse or ion channel level will result in a modified firing pattern. Changes in ion channels can modify firing patterns as efficiently as synaptic modifications do (in fact, both phenomena can occur simultaneously), be it during physiologic or pathologic conditions.[9,39,108,114,117,137]

Neurons use electrical and chemical processes to communicate at synapses. A chemical synapse is composed of four compartments (Fig. 1A): The presynaptic terminal, from which neurotransmitter is released; the postsynaptic terminal, which contains receptors for the neurotransmitter; the extracellular space between the pre- and postsynaptic elements; and glial cell processes, which contain various proteins, including transporters for the neurotransmitter. The arrival of an action potential in a presynaptic terminal usually results in the release of neurotransmitter that crosses the synaptic cleft to activate postsynaptic receptors. If these receptors are ionotropic, their activation leads to a flux of charged ions through the membrane. This flux of ions creates a current (I) that produces a change in membrane potential (V) (Fig. 1B). The term *synaptic plasticity* covers all of the mechanisms that ultimately result in a modification of V in response to an unconditioned stimulus (the activation of a presynaptic terminal by an action potential) following a conditioning stimulus. For example, at an excitatory glutamatergic synapse, postsynaptic depolarizing responses can be decreased on a short (short-term depression) or long (long-term depression, LTD) time scale, or increased (short-term facilitation or long-term potentiation, LTP).

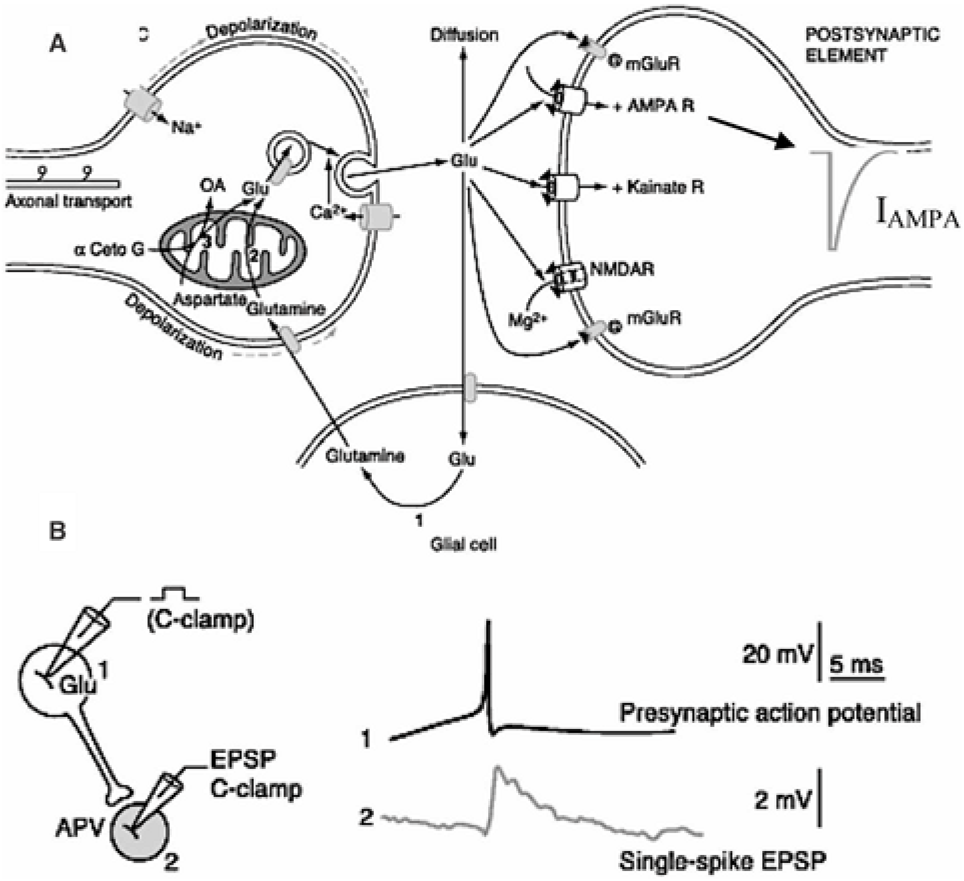
Synaptic plasticity results from modifications that can take place at all four components of the synapse.

- The presynaptic terminal, through changes in neurotransmitter release probability or the vesicular content of neurotransmitter; in this case, synaptic plasticity is said to have a presynaptic origin

- The extracellular matrix (ECM), in which molecules can be involved in synaptic plasticity
- The glial cells, which clear neurotransmitters (hence controlling the postsynaptic response) and which can release chemical messengers that can modify neurotrans-mission
- The postsynaptic element, through morphologic alterations, changes in postsynaptic receptor density, or modifications of their intrinsic properties by intracellular processes (e.g., phosphorylation, interactions with partner proteins); in this case, synaptic plasticity is said to have a postsynaptic origin

This chapter focuses on the presynaptic terminal and the postsynaptic element.

Of note, multiple ways exist to induce synaptic plasticity and the underlying mechanisms are even more diverse.[77] The goal of the chapter is not to provide an extensive review of the different mechanisms, but to provide representative examples. Synaptic plasticity mechanisms always depend on the conditioning stimulus (e.g., high- versus low-frequency stimulation), time (milliseconds to months following the conditioning stimulus), the developmental stage (e.g., mature versus immature neuronal networks), the brain region (e.g., synaptic plasticity at mossy fibers versus Schaffer collateral connections in the CA3 and CA1 hippocampal regions, respectively), and the type of neuron within a given region (e.g., Î³-aminobutyric acid [GABA]ergic interneuron versus principal glutamatergic cells).


A
Depolarization
Na+
Axonal transport
OA
Glu
Ca2+
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3
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Aspartate
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Depolarization
Diffusion
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mGluR
+ AMPA R
+ Kainate R
NMDAR
Mg2+
mGluR
POSTSYNAPTIC ELEMENT
IAMPA
Glutamine
Glu
1
Glial cell
B
(C-clamp)
Glu
1
EPSP C-clamp
APV
2
20 mV
5 ms
Presynaptic action potential
1
2
2 mV
Single-spike EPSP

FIGURE 1. Synaptic transmission at a glutamatergic synapse. **A:** The four components of the synapse are the presynaptic and postsynaptic elements, the glial cell process, and the synaptic cleft. Depolarization of the presynaptic site (e.g., by an incoming action potential) results in Ca^{2+} influx that triggers fusion of a synaptic vesicle containing the neurotransmitter glutamate with the inner presynaptic membrane. Glutamate diffuses into the synaptic cleft to reach postsynaptic receptors (AMPA, NMDA, kainate, metabotropic). Activation of AMPA receptors triggers an influx of Na^+ in the postsynaptic terminal, resulting in an inward current, $I_{AMPA.}$ Glutamate is pumped up by glial cells and presynaptic terminals by

specific transporters. **B:** Example of a recording of a connected pair of neurons. The presynaptic glutamatergic neuron (1) is connected to neuron 2. When an action potential occurs in neuron 1, the membrane of neuron 2 is depolarized. This depolarization is due to an influx of Na^+ through glutamate-activated AMPA receptors; that is, the transformation of I_{AMPA} into a change in membrane potential, following Ohm's law. Adapted from Hamon.

Presynaptic Forms of Synaptic Plasticity

The first stage of information processing at the synapse takes place in the presynaptic terminal, from which neurotransmitter is released. Demonstrating that synaptic plasticity occurs at presynaptic terminals is technically challenging, because it requires direct recordings from the presynaptic terminal, an experimental technique that is still limited to very large presynaptic structures in the central nervous system (CNS).[42] As a consequence, most presynaptic mechanisms are assessed indirectly, using recordings of the postsynaptic site. Despite this experimental constraint, presynaptic plasticity mechanisms have been established. Two forms of synaptic plasticity can be distinguished, short- and long-term.

Short-Term Plasticity

Neurons recorded *in vivo* display very different firing patterns in a brain stateâ€"dependent manner.[105,115] In addition, firing patterns are also characterized by large intrinsic variability, even during stable brain state.[105,115] The intrinsic properties of the presynaptic terminal determine how information is transmitted to the postsynaptic site. Here, the critical parameter is the interval between two action potentialsâ€"the interspike interval (Fig. 2). In response to closely spaced stimulations of a presynaptic terminal, some synapses display short-term facilitation. That is, the amplitude of the second response is larger than the first. Other synapses display short-term depression. That is, the amplitude of the second response is smaller than the first. Some synapses also display remarkable stability across a large range of interspike intervals, ensuring faithful neurotransmission (for example, the climbing fiberâ€"Purkinje cell synapse in the cerebellum).[13]

Paired-Pulse Facilitation Mechanisms

Increased intracellular calcium (Ca^{2+}) underlies paired-pulse facilitation.[139] The favored mechanism proposes that the first action potential triggers a large and rapid rise in intracellular Ca^{2+}, resulting in release of a neurotransmitter. This Ca^{2+} diffuses and equilibrates with the resting concentration of Ca^{2+} that was present before the action potential, thus giving rise to a residual Ca^{2+} concentration that will be cleared eventually. This residual Ca^{2+} facilitates neurotransmission when the second spike arrives at the presynaptic terminal (see Fig. 2).

Other, nonexclusive mechanisms have been proposed. For example, in the mossy fiber boutons of the CA3 hippocampal region, Ca^{2+} influx in the presynaptic terminal can be dynamically regulated during repetitive stimulation by presynaptic sodium (Na^+) and potassium (K^+) channels.[11,36,42]

Paired-Pulse Depression Mechanisms

The simplest model assumes a use-dependent exhaustion of the store of neurotransmitter-containing vesicles that are ready to be released in front of the postsynaptic site, but the issue remains controversial.[139] Recovery from paired-pulse depression usually takes several seconds, but this can be facilitated by Ca^{2+} accumulation during high-frequency presynaptic activity.[124] This phenomenon explains why neurotransmission does not fail totally during trains of action potentials at synapses displaying paired-pulse depression.

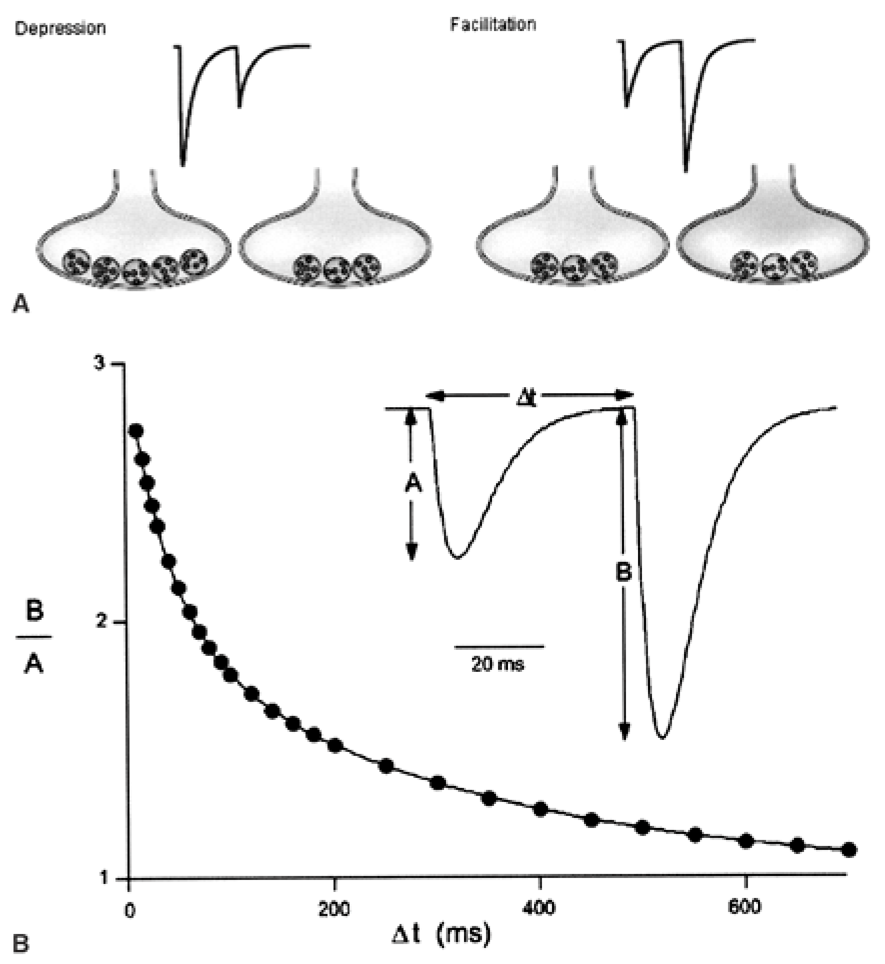

FIGURE 2. A: Paired-pulse depression and facilitation at glutamatergic synapses. A presynaptic terminal is stimulated to release glutamate, giving rise to an inward synaptic current of a given amplitude. Glutamate release is induced by a second, closely spaced, stimulation. If the amplitude of the second evoked current is smaller than the first one, the synapse is characterized by paired-pulse depression. A smaller number of vesicles ready to be released for the second stimulation may explain this phenomenon. If the second current is larger, the synapse is characterized by paired-pulse facilitation. An increased intracellular Ca^{2+} concentration (*grey shading*), thus increasing the probability of release in response to the second stimulation, may explain this phenomenon. Adapted with permission from Blitz DM, Foster KA, Regehr WG. Short-term synaptic plasticity: a comparison of two synapses. *Nat Rev Neurosci.* 2004;5:630â€“640. **B:** Simulation of paired-pulse facilitation showing that the amount of facilitation depends upon the interspike interval Î”t. When the second stimulus occurs >600 ms after the first one, the amplitude of the second response is similar to the first. Facilitation is maximum at the shortest time intervals. Adapted with permission from Zucker RS, Regehr WG. Short-term synaptic plasticity. *Annu Rev Physiol.* 2002;64:355â€“405.

Modulation of Neurotransmitter Release by Presynaptic Receptors

The two short-term forms of plasticity involve mechanisms directly linked to the machinery for neurotransmitter release. The release of neurotransmitter can also be dynamically modified by chemical messengers acting via receptors located on the presynaptic terminal. For example, consider the mossy fiber terminals, the axons of hippocampal dentate granule cells that form giant synaptic boutons with CA3 pyramidal cells. Upon repetitive activation of mossy fiber terminals, released glutamate reaches high enough concentration to activate ionotropic (kainate; KA) and metabotropic (mGlu) receptors. The result of KA receptor activation is to increase excitability,[111] thus facilitating transmitter release (i.e., directly participating in the strong paired-pulse facilitation seen at this synapse).[26,112] Activation of type 2 mGlu receptors results in a decreased probability of glutamate release, probably via inhibition of presynaptic Ca^{2+} channels, thus limiting the

amount of facilitation.[110] Other receptor types are also present on mossy fiber terminals, including adenosine A1 receptors. These receptors are tonically activated *in vitro* and result in a permanent low initial release probability of glutamate at this synapse.[82] Synaptic vesicles can contain adenosine triphosphate (ATP) that, when released, is broken down into adenosine to activate presynaptic receptors.[43] Whether A1 receptors act as autoreceptors (i.e., ATP is released by the terminal) or as heteroceptors (the source of ATP/adenosine is not the terminal[136]) is not known.

Use-dependent facilitation or inhibition of neurotransmission also involves other types of presynaptic autoreceptors, including *N*-methyl-D-aspartic acid (NMDA) receptors[51] and Î±-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) receptors[109] at glutamatergic terminals, and metabotropic $GABA_B$ receptors at GABAergic terminals.[29] Facilitation may be the result of an increase in internal Ca^{2+} concentration resulting either from direct Ca^{2+} entry through Ca^{2+}-permeable receptors (e.g., NMDA) or Ca^{2+} voltage-gated channels opened by the receptor activationâ€“induced membrane depolarization. Inhibition may result from downregulation of Ca^{2+} voltage-gated channels by G-proteins following activation of metabotropic receptors. To make things even more complex, presynaptic terminals can possess heteroreceptors that are activated by chemical messengers not released by the terminal itself. For example, repetitive activation of glutamatergic parallel fibers in the cerebellum activates GABAergic interneurons. GABA is released in large enough quantities to activate presynaptic $GABA_B$ receptors located on parallel fiber terminals contacting Purkinje cells, thus decreasing the probability of glutamate release by a Ca^{2+}-dependent mechanism.[31]

Conclusion on Short-Term Plasticity Phenomena

Presynaptic terminals are complex information-processing units. They play a crucial role in shaping postsynaptic responses by increasing or decreasing neurotransmitter release as a function of the timing of the spike train reaching the presynaptic terminal. They use multiple mechanisms to modify their output depending on the type of activity they receive, the molecular properties of their release machinery, the biophysics of their ionic channels, and the type of autoreceptors they express. Through activation of heteroreceptors, presynaptic terminals also sense the activity of neighboring terminals, which can be of a different type. The properties of a terminal depend on its origin, target, and developmental stage.[139] These properties play a very important role in information processing, for example, by allowing proper routing of information in the network by adequately shaping information transfer.[104] Any alteration in the mechanisms that control paired-pulse facilitation or depression at a given synapse will result in a dramatic change in function. Such possibilities should be considered when investigating neurotransmission and information processing in pathologic conditions.

Long-Term Plasticity

Among the many loci at which a presynaptic form of synaptic plasticity has been found, LTP at the mossy fiber has received considerable attention.[91] High-frequency stimulation (e.g., 100 pulses at 100 Hz) of mossy fibers leads to a permanent enhancement of the postsynaptic response. Three questions are in order: Where is LTP expressed: Pre- or postsynaptically? What

are the expression mechanisms (what makes the response larger after the conditioning stimulus)? and, How is this phenomenon induced by the conditioning stimulus?

Presynaptic Expression of Long-Term Potentiation

The expression of LTP at mossy fiber cell synapses is due to an increase in neurotransmitter release. As mentioned previously, presynaptic mechanisms can only be inferred indirectly, and various approaches have been used to support a presynaptic rather than postsynaptic locus. The arguments supporting the former are a decrease in paired-pulse facilitation,[132,135] a decreased failure rate,[73,132] and a change of the coefficient of variation (CV)[73,132] following LTP induction, all classical properties expected to occur if the probability of neurotransmitter release is increased. The failure rate is directly linked to release probability. Transmitter release is a probabilistic phenomenon, because an action potential does not always trigger vesicle fusion. Some synapses (such as the cerebellar climbing fiber) are reliable, having a close to 1.0 probability, whereas others have a low release probability (such as the mossy fiber, in part due to the tonic activation of A1 receptors, as described earlier). Repetitive activation of presynaptic terminals with <1.0 release probability gives rise to failuresâ€”no postsynaptic response is recorded despite the presence of an action potential in the presynaptic terminal. A decreased number of failures indicates an increased release probability. The CV is the mean postsynaptic response divided by the standard deviation of the response (using repetitive stimulation). This parameter also depends strongly on release probability. Other arguments in favor of a presynaptic mechanism have been proposed, including the measurement of postsynaptic NMDA responses,[126] and the monitoring of extracellular glutamate concentration directly[76] or indirectly using glial cells.[58]

Expression Mechanisms

The mechanisms that underlie increased neurotransmitter release at mossy fiber synapses are not fully understood and still the subject of debate.[20] A simple scheme has been proposed[91] in which the conditioning stimulus leads to increased intracellular Ca^{2+} in the presynaptic terminal,[119] activation of Î±$_{1E}$-subunitâ€“containing R-type Ca^{2+} channels.[17] The rise in Ca^{2+} would activate Ca^{2+}/calmodulin-activated adenylyl cyclase (AC)-1, which is highly expressed in mossy fiber terminals.[131] Activation of AC1 would result in a rise in cyclic adenosine monophosphate (cAMP), leading to the activation of protein kinase A (PKA). Interfering with any one of these steps alters mossy fiber LTP.[50,73,119,123,125] How this leads to enhanced neurotransmitter release, and how LTP is maintained over the long-term, remain to be established.

Induction Mechanisms

In contrast to postsynaptic expression of LTP at Schaffer collateral synapses (see the next section), the induction of mossy fiber LTP does not require activation of postsynaptic NMDA receptors.[45] The key player is Ca^{2+}, because its removal or strong buffering prevents LTP.[119] The next issue is to determine if the induction depends on a rise of Ca^{2+} in the presynaptic terminal, the postsynaptic unit, or both. Several studies have reported that a rise in postsynaptic Ca^{2+} is necessary,[128,133] whereas others have shown the opposite.[81,135] This issue is functionally important, because a postsynaptic induction mechanism implies that a retrograde messenger must be sent by the postsynaptic cell to alter synaptic release in the presynaptic terminal. A reasonable way to explain this discrepancy (and others) is that different induction mechanisms exist, and their activation depends on the experimental conditions present. The role of KA and mGlu receptors is also fiercely debated, with contradictory results regarding their direct involvement or modulatory role.[14,16,81,133]

Long-Term Depression at Mossy Fiber Synapses

Synaptic responses are enhanced at mossy fibers following tetanic stimulation, and they are decreased (i.e., LTD) following low-frequency stimulation (e.g., 15 minutes at 1 Hz).[61,122] The expression of LTD is also presynaptic, and seems to involve mirror mechanisms when compared to those described for LTP at the same synapseâ€”a decrease in adenylyl cyclase and PKA activity.[122] Using mechanisms similar to those involved in LTD, after LTP, it is possible to reverse the synaptic responses to those of preconditioning stimulus values, a phenomenon known as *depotentiation.*[48]

Target Specificity of Synaptic Plasticity

The forms of synaptic plasticity described so far concern the synapse between mossy fibers and CA3 pyramidal cells. However, mossy fibers produce small filopodial extensions that contact CA3 GABAergic interneurons.[2] Indeed, GABAergic interneurons are the main target of mossy fibers, because 10 times more filopodial extensions than mossy fiber boutons contact pyramidal cells.[2] High-frequency stimulation induces LTD at mossy fiberâ€“interneuron synapses, which express postsynaptic Ca^{2+}-permeable AMPA receptors.[67] As in mossy fiberâ€“pyramidal cell LTP, this form of LTD is NMDA receptorâ€“independent, depends on type 7 mGlu receptor and protein kinase C (PKC), and is expressed presynaptically.[68,98] However, it requires a rise in postsynaptic Ca^{2+}, which means the involvement of a retrograde messenger that has yet to be identified. This illustrates that the same experimental protocol can trigger opposite synaptic modifications onto two different targets.

To illustrate further the importance of target specificity, it is interesting to note that the same conditioning stimulus triggers a different form of LTD at those mossy fiberâ€“interneuron synapses that express postsynaptic Ca^{2+}-impermeable AMPA receptors.[67] This form of LTD requires a postsynaptic rise in intracellular Ca^{2+} via the activation of an NR2B-subunit lacking NMDA receptors.[67] The expression involves a downregulation of postsynaptic AMPA receptors.[68] (Postsynaptically expressed long-term plasticity is discussed later.)

Other Examples of Plasticity Expressed Presynaptically

LTP can be expressed presynaptically at other glutamatergic synapses (e.g., in the cerebellum at the parallel fiberâ€“Purkinje cell synapse[44] or at corticothalamic synapses[19]). Mechanisms are similar to those described previously; and require involvement of adenylyl cyclase, cAMP, and PKA.[19,44]

More complex mechanisms involve a postsynaptic induction mechanism and a presynaptic expression. The lateral nucleus of the amygdala, a structure involved in the acquisition of conditioned fear responses,[64] receives thalamic and cortical glutamatergic inputs that can be potentiated by pairing protocols. Although induction of LTP depends on activation of postsynaptic NMDA receptors and L-type voltage-gated channels, LTP is expressed presynaptically, with the involvement of adenylyl cyclase, cAMP, and PKA.[5,49] This type of LTP implies the presence of retrograde messengers, such as nitric oxide (NO), at the cerebellum mossy fiberâ€“granule cell synapse.[28] A more complex form of LTP has been described in the lateral nucleus of the amygdala.[51] In this case, repetitive activation of both cortical and thalamic inputs leads to LTP only at the cortical pathway. The mechanism involves activation of NMDA receptors located on presynaptic cortical terminals by glutamate released from thalamic presynaptic terminals.[51]

Synaptic Plasticity at GABAergic and Glycinergic Synapses

The plasticity processes described thus far involve glutamatergic synapses. GABAergic and glycinergic synapses are also involved in multiple forms of synaptic plasticity.[40] In *Xenopus* tectal neurons, LTD can be induced through visual stimulation at GABAergic synapses.[69] The induction does not depend on activation of postsynaptic NMDA receptors or on increases in postsynaptic Ca^{2+}. The expression is presynaptic, as indicated by an increase of the failure rate and an increase in the CV. The mechanism underlying LTD in this system involves activation of presynaptic NMDA receptors located on GABAergic terminals, which are activated by glutamate released during the visual stimulation.[69] This example further illustrates how different synaptic pathways cooperate to produce synaptic modification at a specific locus.

LTD can be induced at hippocampal GABAergic synapses during the early stages of development.[40] This form of LTD expression is presynaptic, but it requires a rise in postsynaptic Ca^{2+} via activation of NMDA receptors.[18] LTD can also be induced during the later stages of development, and a few mechanisms have been identified.[21] Repetitive stimulation of Schaffer collaterals (axons of the glutamatergic CA3 pyramidal cells that contact CA1 pyramidal cells) activates postsynaptic group 1 mGlu receptors, triggering the production of endocannabinoids. Endocannabinoids then diffuse to the presynaptic GABAergic terminals to activate type 1 cannabinoid receptors, resulting in a persistent decrease of GABA release.[21] This mechanism may play a very important functional role, because it may facilitate information storage.[22]

Concluding Comments on Synaptic Plasticity Expressed Presynaptically

This section has emphasized the diversity of mechanisms that can be used to change synaptic efficacy at the presynaptic terminal. These mechanisms can be very complex, sometimes involving different neurotransmitters and molecular messengers not released by the presynaptic terminal. Cooperative action is an important concept to keep in mind. Another critical feature is target-specificity, because different forms of plasticity can be triggered between a given source neuron and its various targets (e.g., principal cells versus interneurons). Finally, most studies have concentrated on synaptic plasticity at glutamatergic synapses. Comparatively, fewer studies have been devoted to GABAergic synapses. Plasticity at these synapses is undoubtedly important because of the critical role played by GABAergic neurotransmission in shaping neuronal network activity.[38,115]

Extracellular Matrix and Synaptic Plasticity

The previous section described how neurotransmitter release can be modified. The next step of neurotransmission is diffusion of the neurotransmitter through the extracellular space to its target receptors. The extracellular space, including the synaptic cleft, contains collagens, proteoglycans, and glycoproteins that compose the extracellular matrix (ECM). There is growing evidence that suggests that molecules of the ECM play a role in synaptic plasticity.[32] Many studies using transgenic animals with altered ECM molecules or their partners report alterations in long-term plasticity (mostly investigated in the CA1 region) and cognitive functions.[32] Of course, the role of ECM goes beyond the control of neurotransmitter diffusion.

A representative example is provided by heparin-binding growth-associated molecule (HB-GAM or pleiotrophin), which interacts with the cell surface receptor syndecans. Intracellular application of HB-GAM to CA1 pyramidal cells inhibited conventional NMDA receptorâ€"dependent LTP (described later), but did not inhibit either basal synaptic neurotransmission or other forms of LTP.[63] In mice overexpressing HB-GAM, LTP was reduced. At the behavioral level, animals performed better in the water maze and displayed reduced levels of anxiety in the elevated plus-maze.[97] Opposite results were found in HB-GAM-deficient mice.[97]

The ECM can be remodeled in an activity-dependent manner[89,130] and, considering the fact that ECM molecules interact with pre- and postsynaptic molecules such as neural cell adhesion molecule (NCAM),[24] it is likely that the ECM participates in morphologic remodelling, clustering of channels, and other processes.[32] For example, a change in the ECM at the synaptic cleft or perisynaptic region could alter the diffusion of neurotransmitters, thus affecting postsynaptic or extrasynaptic responses.

Glial Cells and Synaptic Plasticity

Glial cells play a critical role in information processing, both in physiologic and pathologic conditions.[90,118] For example, astrocytes can be activated by neurotransmitters released by neurons, including glutamate[103] and GABA,[56] which in turn can trigger release of glutamate via an increase of intracellular Ca^{2+}.[56,95,96]

Neurons and glial cells can be considered complex, integrative information-processing units. In the CA1 region of the hippocampus, GABA released by interneurons can activate $GABA_B$ receptors located on astrocytes, leading to a rise in intracellular Ca^{2+} that in turn result in glutamate release from the astrocytes.[56,72] Glutamate then activates kainate receptors located on GABAergic interneurons, resulting in increased GABA release onto principal cells.[72] Such modification of synaptic transmission may be involved in short-term forms of synaptic plasticity.

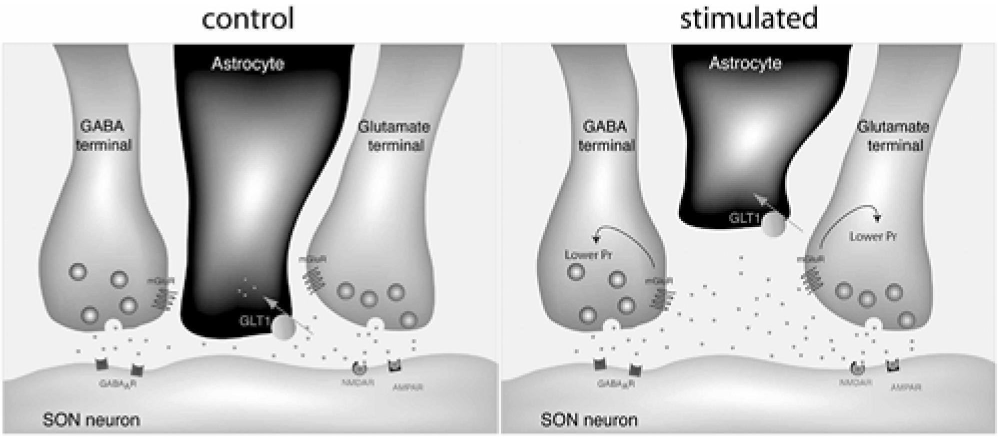

FIGURE 3. Synaptic plasticity due to astrocytic reorganization. In virgin animals (*left*), astrocytes coverage allows efficient recapture of glutamate by the glial transporter GLT1. In lactating animals (*right*), decrease of astrocytic coverage allows glutamate to diffuse and activate presynaptic mGlu receptors, resulting in lower probability of release of glutamate (homosynaptic depression) and GABA (heterosynaptic depression). S. Oliet, personal communication.

Glutamate is not the only molecular messenger released by astrocytes. High-frequency activation of Schaffer collaterals triggers a rise in intracellular Ca^{2+} in astrocytes, leading to the release of ATP, which results in decreased glutamate release from presynaptic terminals.[136] Such a short-term plasticity control system may be useful in limiting neurotransmitter release during intense periods of activity.

Glial cells are also involved in multiple forms of long-term synaptic plasticity. A good example is provided by the plastic modifications that take place in the supraoptic nucleus during lactation (Fig. 3). In virgin animals, glial processes provide a large coverage of synaptic terminals around magnocellular neurons.[94] The presence of specific transporters on glial processes ensures efficient clearance of glutamate.[8,107] In particular, glutamate cannot reach mGlu receptors located on presynaptic glutamatergic terminals. In lactating animals, the glial processes retract, decreasing synaptic coverage and allowing more glutamate to accumulate. This activates presynaptic mGlu receptors and decreases not only glutamate[94] but also GABA[99] release. This example demonstrates how a morphologic reorganization of glial cells contributes to synaptic plasticity. The freer diffusion of glutamate, results in depression of synaptic transmission at the glutamatergic terminals that released glutamate, as well as at neighboring GABAergic presynaptic terminals.

In addition to morphologic modifications, electrophysiologic responses can be modified in glial cells. For example, long-term plasticity at glutamatergic synapses can be triggered in glial cells.[41] Its induction and expression involves Ca^{2+}-permeable receptors (i.e., mechanisms different from those described at neuronâ€“neuron connections in the same region) (see the section Long-Term Plasticity). The fact that synaptic plasticity also occurs at neuronâ€“glia connections is very important, because any modification of information transfer between neurons and glial cells will also result in a change in information transfer between glial cells and neurons (via the compounds glial cells release, such as glutamate, and ATP).

Finally, glial cells appear to play a key role in controlling synaptic function when long-term plasticity is triggered at neuronâ€“neuron connections. LTP at excitatory synapses can be accompanied by heterosynaptic depression at other excitatory synapses.[75,79] The underlying mechanism involves the activation of $GABA_B$ receptors on glial cells. This is dependent on release of ATP from glial cells, which degrades into adenosine and leads to activation of A1 receptors and, thus, heterosynaptic depression.[113] Glial cells are also the source of tumor-necrosis factor (TNF)-Î±, which enables synaptic scaling.[116]

Concluding Remarks

Synaptic transmission goes beyond the linear pathway that starts at the presynaptic terminal and ends at the postsynaptic site. A given synapse, as a functioning unit, comprises the synapse itself, the ECM, glial processes, and nearby synapses. Short- and long-term modifications can occur in any of the elements the surroundings a given synapse (in particular at the ECM and glial levels), and these modifications participate directly in the way the synapse transmits information. As more investigators turn to glial cell interactions with neurons, it will be particularly interesting to determine whether activity-dependent modifications can be triggered in astrocytes.

Postsynaptic Forms of Synaptic Plasticity

The postsynaptic site is the receiving end of neurotransmission. Synaptic plasticity can take place exclusively at this location, but its expression can take many forms. Perhaps the best approach to the vast repertoire of expression is to start with the binding of the neurotransmitter to a receptor, for example, glutamate to AMPA receptors. Binding depends on the affinity of the receptor for its ligand (a biophysical property). When the receptor is activated, an influx of Na^+ ions occurs for a time determined by the biophysical properties of the channel. Other properties include desensitization (despite the presence of the ligand, the receptor remains in a closed state) and recovery from desensitisation. Many of these biophysical properties are controlled by multiple intracellular processes (e.g., phosphorylation, anchoring mechanisms, partner proteins). A conditioning stimulus may alter any of these components and change the postsynaptic response. Other modifications include the number of receptors expressed at the postsynaptic site, their 3-D localization, and their subunit composition. Finally, the flux of ions through the channel creates a current, and this current creates a change in membrane potential. If the architecture of the postsynaptic site is modified, the same receptor-induced current results in a different change in membrane potential.[101] The change of architecture can be more dramatic with the creation and elimination of the synaptic contacts. Morphologic modifications have been extensively studied at glutamatergic synapses, which usually are made on spine heads.

Spine Plasticity

Spines are characterized by a high degree of plasticity.[46,127] For example, in the hippocampus, the spine number can vary by 30% to 40% during the estrus cycle,[129] following learning,[83] or when the environment is modified.[102] In barrel cortex, dendritic spines live less than 1 month, suggesting that experience induces a reorganization at the spine level.[120] In addition, the shape and size of spines are continuously changing in an age-dependent manner (spine motility declines with age).[34,37,62]

Spine shape can also change following conditioning stim-ulus-induced long-term modifications of synaptic responses (Fig. 4). LTP is associated with an increase in spine head and shape (even splitting into two functional synapses), whereas LTD is associated with spine shrinkage.[80,93,134,138] Such changes are consistent with the modifications of the postsynaptic density associated with LTP[30] and, in general, with the modification of the number of postsynaptic receptors (see discussion in next section). In addition to morphologic alterations, LTP, LTD, learning experience, and environment changes are associated with spine formation and pruning.[88] Spine motility depends on the activity of actin,[37] a contracting molecule, and Î±-N-catenin,[1] a cadherin-associated protein.

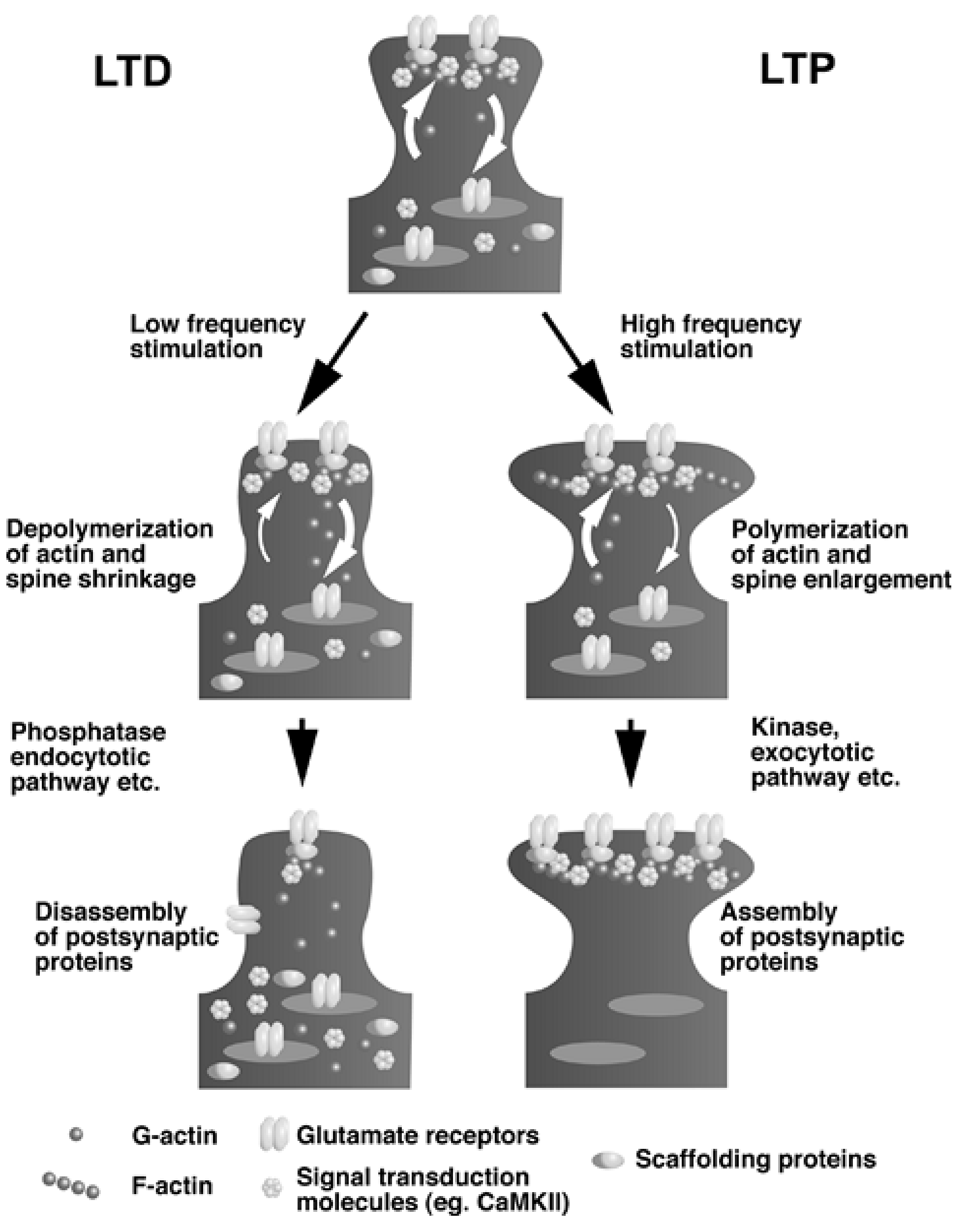
LTD
LTP
Low frequency stimulation
High frequency stimulation
Depolymerization of actin and spine shrinkage
Polymerization of actin and spine enlargement
Phosphatase endocytotic pathway etc.
Kinase, exocytotic pathway etc.
Disassembly of postsynaptic proteins
Assembly of postsynaptic proteins
G-actin
F-actin
Glutamate receptors
Signal transduction molecules (eg. CaMKII)
Scaffolding proteins

FIGURE 4. Structural plasticity during LTP and LTD. The conditioning stimulus inducing LTP triggers a morphologic modification of the spine resulting in an increase of the postsynaptic site. Various CaMKII-dependent mechanisms can be triggered, including a phosphorylation of AMPA receptors and the insertion of AMPA receptors. LTD involves reverse mechanisms. Adapted with permission from Hayashi Y, Majewska AK. Dendritic spine geometry: functional implication and regulation. *Neuron.* 2005;46:529â€“532.

What are the functional consequences of alterations in spine shape? Spine geometry affects membrane potential changes induced by synaptic currents in the spine (e.g., via a change in input resistance)[121] and postsynaptic Ca^{2+} concentration,[46] a parameter that plays a crucial role in controlling long-term synaptic modifications.

Concluding Remarks

Spine shape is important in the transfer of information between the pre- and postsynaptic terminal. Spines can be created, removed, or modified geometrically, and such changes may be spine-specific, i.e., dependent on the source, the target, and more generally on the brain region, as well as time-dependent (development, aging). Of course not all synapses are made on spines. Whether geometric modifications occur at nonspiny synapses is not known. A structural balance between excitatory and inhibitory synaptic contacts seems to be maintained

in the dendrites.[70] It is not yet known if balance is maintained structurally following a conditioning stimulus.

Long-Term Plasticity

There are multiple ways to induce long-term postsynaptic modifications in synaptic transmission. One of the best studied forms is NMDA-dependent LTP and LTD at Schaffer collateral synapses on CA1 pyramidal cells.[77] A conditioning stimulus can trigger long-term synaptic modifications, which can be separated into an early phase (~1 h) and a late, protein synthesis-dependent, phase.

Early Phase NMDA-Dependent Long-Term Potentiation

High-frequency stimulation (e.g., 100 pulses at 100 Hz) of Schaffer collaterals leads to a permanent enhancement of the postsynaptic response in a NMDA receptorâ€“dependent manner (it is blocked by NMDA antagonists).[12] As in the section on presynaptic plasticity, three questions are in order: Where is LTP expressed: pre- or postsynaptically? What are the expression mechanisms (i.e., what makes the response larger after the conditioning stimulus)? And, how is this phenomenon induced by the conditions stimulus?

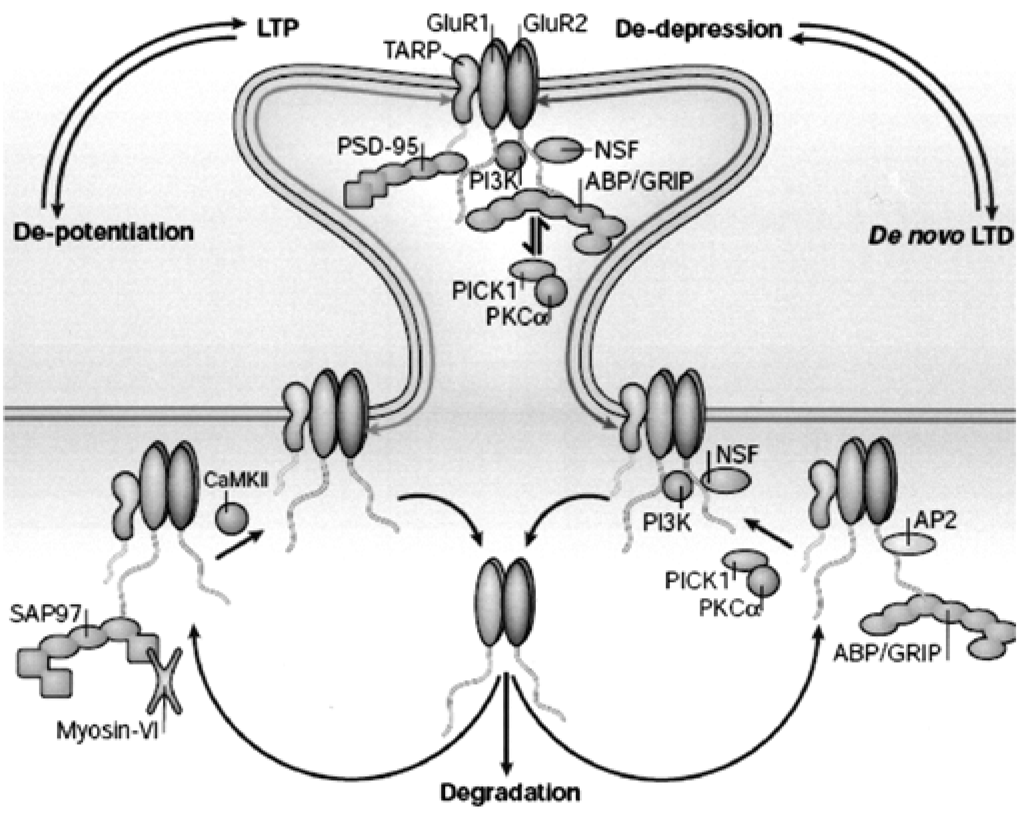

FIGURE 5. Bidirectional modifications of AMPA receptor distribution during LTP and LTD. The association between NSF and the GluR2 subunit of AMPA receptors allows their stabilization at the postsynaptic site. Its dissociation leads to receptor internaliza-tion. CaMKII may be involved in the insertion of AMPA receptors in the membrane via TARP. Depotentiation corresponds to LTD on previously potentiated synapses. Conversely, De-depression corresponds to LTP on previously depressed synapses. Adapted with

permission from Collingridge GL, Isaac JT, Wang YT. Receptor trafficking and synaptic plasticity. *Nat Rev Neurosci.* 2004;5:952â€"962.

Postsynaptic Expression of Long-Term Potentiation

Although the debate is not resolved,[23,35] many arguments support a postsynaptic locus, including modifications in receptor number and biophysical properties. However, most arguments are indirect because, as mentioned in the presynaptic section, it is very difficult to assess presynaptic modifications. Many electrophysiologic manipulations have been used to support a postsynaptic locus. First, no change in release probability occurred.[78] Second, paired-pulse facilitation was not modified after LTP.[87] Third, no modification of glial cell responses to extracellular glutamate occurred following LTP induction.[8,74] Finally, although glutamate does not have the same affinity for AMPA and NMDA receptors, if LTP is presynaptic, one would expect both responses to be increased following the conditioning stimulus (AMPA and NMDA receptors are often colocalized at the synapse). However, AMPA receptor-mediated responses were more increased than were NMDA responses.[57,86]

Expression Mechanisms

What can cause an increase in AMPA receptor-mediated responses following the conditioning stimulus? One contributing mechanism involves an increase in the conductance of AMPA receptors in a phosphorylation-dependent manner.[7] AMPA receptors at this synapse contain the GluR1 subunit, which can be phosphorylated by Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII)[4] and by PKC and PKA.[106] In that scheme, the biophysical properties are changed.

Another, nonexclusive mechanism involves the insertion of AMPA receptors (Fig. 4). A pool of AMPA receptor subunit-containing vesicles exists in the cytosol, and AMPA receptors can cycle on and off the synaptic membrane very rapidly.[15] After the conditioning stimulus inducing LTP, new AMPA receptors are inserted at the postsynaptic site in a CaMKII-dependent manner.[47] The mechanisms leading to an increase in the number of AMPA receptors are not fully elucidated. Numerous proteins that bind directly or indirectly to AMPA receptors have been identified (Fig. 5), including transmembrane AMPA receptor regulatory proteins (TARP), glutamate receptor-interacting protein/AMPA receptor-binding protein (GRIP/ABP), protein interacting with C kinase (PICK1), and N-ethylmaleimide-sensitive factor (NSF).[25,92] Whether these proteins are modulators or mediators of LTP remains to be established.

Induction Mechanisms

In the NMDA receptor-dependent form of LTP, a depolarization of the membrane during the conditioning stimulus is necessary to remove the voltage-dependent block of NMDA receptors by magnesium (Mg^{2+}).[12] This allows Ca^{2+} influx into the cell, a rise in intracellular Ca^{2+} being an absolute requirement for LTP induction.[12] However, the details of Ca^{2+} dynamics in the spine, the involvement of Ca^{2+} stores, and other issues remain to be investigated. Downstream of the Ca^{2+} increase, it is difficult to decide which intracellular cascades (CaMKII, PKA, PKC, etc.) are involved. The type of cascade may depend on the conditioning stimulus, development stage, type of neuron, and brain region.

Stabilization of Long-Term Potentiation

Early-phase NMDA-dependent LTP, which lasts 30 to 60 minutes, is translation- and transcription-independent. Late-phase LTP (>3 hours) is translation- and transcription-dependent. Dendrites and dendritic spines possess all the machinery necessary to translate mRNAs.[54] Post-translational modifications of existing proteins, which does not require de novo transcription, constitutes an efficient and rapid mechanism to control protein synthesis. Interestingly, multiple factors regulate translation at all levels (initiation, elongation, and release), pointing again at the multiplicity of pathways that can lead to LTP.[59] Activation of these translation mechanisms may allow tagging of the activated synapse for transcription and de novo protein synthesis.[100]

NMDA Receptor-Dependent Long-Term Depression

If synaptic responses can be increased, they can also be decreased. LTD can also be induced at Schaffer collateralâ€"CA1 pyramidal cell synapses. LTD can be induced by low-frequency stimulation; it requires the activation of NMDA receptors and a rise in intracellular Ca^{2+}.[33,85] How a rise in Ca^{2+} can trigger either LTP or LTD remains to be determined. The answer should depend on the spatio-temporal structure of the calcium signal and the type of NMDA receptor subunit activated during the conditioning stimulus.[71] LTD depends on the activation of protein phosphatase[84] and, in particular, on the dephosphorylation of PKA substrates.[55]

In many features, NMDA receptorâ€"dependent LTD appears to be the mirror image of NMDA receptorâ€"dependent LTP. It has a presynaptic origin, it is associated with a dephosphorylation of AMPA receptors[65] that affects the biophysical properties of AMPA receptors by decreasing its open probability,[3] and a loss of postsynaptic receptors occurs (Figs. 4 and 5). AMPA receptors can be internalized in a dynamin- and clathrin-dependent manner.[6,66] The mechanisms responsible for the late-phase LTD remain to be determined.

Concluding Remarks on Long-Term Postsynaptic Forms of Plasticity

Long-term postsynaptic forms of plasticity are not limited to NMDA-dependent mechanisms or to AMPA receptors. For example, GABAergic responses also express postsynaptic types of plasticity.[40] It is not known if all synapses are endowed with mechanisms enabling them to change postsynaptic responses. The multiplicity of the players that can act at all levels to modify synaptic transmission (shape of the spine, biophysical properties of the receptors, cycling of the receptors) is impressive. Whether these distinct mechanisms are redundant (to ensure synaptic modification) or whether they are activated under specific conditions is not known, although both proposals are not mutually exclusive. In pathologic conditions such as epilepsy, such multiplicity may guarantee the expression of LTP and LTD.[10] Alternatively, some neuronal functions may be compromised, which may explain why some patients have cognitive deficits.

Summary and Conclusions

The transfer of information between neurons can be modified in multiple ways and at different sites, from the presynaptic terminal to the postsynaptic terminal. Synaptic plasticity involves most of these modifications. Synaptic plasticity can occur on different time scalesâ€"from short-term (hundreds of milliseconds) to long-term (months)â€"and these involve very different mechanisms. While short-term plasticity is known to play a physiologic role in information processing *in vivo*, the role of long-term forms also occur *in vivo* remains to be determined. However, it is clear that LTP and LTD can be triggered at the synapse, thus demonstrating the presence of plasticity mechanisms. Another important feature is the presence of different biochemical cascades that can be activated at a given synapse to produce synaptic plasticity. This may ensure redundancy of the plasticity mechanisms as well as specificity depending on the presynaptic pathway that are activated. Synaptic plasticity also depends on the target neuron. A conditioning stimulus generated by a given source neuron will trigger different mechanisms according to its target. Plasticity mechanisms may not be evenly distributed within the network, but targeted so as to adequately respond to environmental changes.

How does synaptic plasticity relate to epilepsy? Several nonexclusive hypotheses have been proposed. First, an episode of status epilepticus may trigger synaptic plasticity and result in tissue hyperexcitability, thus leading to the construction of epileptic regions during the latent, seizure-free, period. Second, recurrent seizures may trigger synaptic plasticity and result in a further facilitation of excitability and a predisposition of seizures, in generating seizures, thus creating. Third, because of the considerable remodelling that takes place in the epileptic brain, certain biochemical cascades may be compromised, resulting in a decreased ability to express short-term and/or long-term forms of synaptic plasticity. The impact on information processing and cognitive performance remains to be assessed but it may well be disadvantageous.

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Chapter 36

Animal Models of Acquired Epilepsies and Status Epilepticus

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Introduction

In animals, epilepsies with focal seizures can be faithfully reproduced by various experimental procedures that can induce an initial status epilepticus (SE) followed after a latent period by a chronic seizure recurrence. Thus, the initial SE and the subsequent chronic epilepsy can be considered the biphasic expression of a common pathogenetic process, which is set in motion by the experimental manipulation.

This chapter reviews models for SE and for epilepsies with focal seizures obtained using experimental epileptogenic procedures in normal animals. Some procedures are relevant to both focal epilepsies and SE, whereas others are specific for either one; therefore, SE and focal epilepsy models are dealt with in two separate sections. Models of epileptogenic dysplasia are also discussed.

In principle, animals presenting with spontaneous seizures can be profitably studied to gain information on species-specific susceptibility and pathophysiologic mechanisms, but, in practice, their interest is limited by the difficulties of obtaining homogeneous populations and the obvious differences in the ability to study domesticated or laboratory species versus those in the wild.

In most domesticated species, spontaneously occurring SE has never been observed, whereas reports of spontaneous localization-related epilepsies are mostly anecdotal and do not provide a basis for defining any suitable model for systematic experimental studies. An exception is the dog, in which prevalence of epilepsy approaches that of humans.[64] Because there is evidence for genetically determined susceptibility to epilepsy and/or epileptogenic brain pathologies, canine epilepsies are not dealt with here. None of the other animal models of genetically determined epilepsies are included in this account because they also are models for generalized rather than focal epilepsies.

Reports of experimentally induced seizures in animals date back to the seventeenth century, when Robert Boyle[24] observed the occurrence of seizures in sparrows, larks, cats, and mice exposed to low air pressure in a decompression chamber. At the cusp of the nineteenth and twentieth centuries, pioneering studies by Fritsch and Hitzig,[81] Openchowski,[163] Baglioni and Magnini,[10] and later Kaufmann[109,110] revealed that other physical and chemical means were effective in inducing epileptic manifestations, including cortical electrical stimulation, freezing, and the topical application of strychnine. Other agents later shown to be effective as topical convulsants include metallic compounds, which were studied for many years by Lenore and Nicholas Kopeloff after their first report,[114] metabolic antagonists, and convulsant drugs (see Prince[172] for review). The application of intracellular recording to experimentally induced cortical foci provided an early insight into the cellular mechanisms underlying epileptogenesis,[134,135] and since then, a number of studies have considerably deepened our understanding of focal epileptogenesis in experimental animals and established a number of pathogenetic concepts that can now be reliably applied to human epilepsies.[8,173]

Experimental models provide a unique means of testing the efficacy of antiepileptic drugs and antiepileptogenic strategies, although the results may not always be generally applicable. Species-specific or mechanism-specific effects may, in fact, prevent their reproducibility in different species or in other types of experimentally induced or naturally occurring epilepsies.

Chemically Induced Focal Epilepsies

General Characteristics

Focal seizures are defined as those seizures whose symptomatology indicates the initial activation of a system of neurons limited to a part of one cerebral hemisphere.[69] Epilepsy is defined as a chronic condition of the brain characterized by an enduring propensity to generate epileptic seizures,[75] a definition that implies the tendency of recurrence of ictal manifestations over time. Thus, only animals with recurrent focal seizures can be considered as models for focal epilepsies.

In several instances, SE or closely spaced seizures are the initial event of a process leading to epileptic disorders presenting with recurrent seizures that occur spontaneously and do not require any further exogenously delivered precipitating stimulus. These characteristics correspond to those of human focal epilepsies, which are further classified as idiopathic (i.e., not preceded or caused by a neurologic disorder other than a possible hereditary predisposition), symptomatic (i.e., secondary to a known disorder of the central nervous system), or cryptogenic (i.e., secondary to a disorder whose course is hidden or occult). By definition, experimentally induced animal epilepsies fall into the category of symptomatic epilepsies because the causative factor (i.e., the experimental epileptogenic procedure) is always known.

The models reviewed in this section reproduce one important characteristic of human epilepsy, that is, its chronic course. They can be obtained by experimental manipulations that lead to a gradual development of persistent focal epileptogenic activities or by procedures capable of inducing acute epileptic manifestations that are able to set in motion a progressive epileptogenic process leading to a permanent epileptic condition. A typical example of the first possibility is topical application of alumina hydroxide gel, which induces progressive neuropathologic changes affecting cortical excitability, whereas the second possibility is best exemplified by the pilocarpine model, in which the development of a chronic epilepsy is mediated by pilocarpine-induced SE. The role of the acutely induced limbic SE or closely spaced seizures is also important although not exclusive for kainic acid, whereas afterdischarges are relevant to epileptogenesis induced by focal electrical stimulation. Whether the epileptic manifestations occurring in the early phase contribute to the development of tetanus toxin**â€"**induced chronic epileptogenesis is not clear.

Animal models of acute seizures and in vitro models are dealt with in other chapters.

Interictal and Ictal Clinical Phenomenology

Ictal clinical phenomena depend on the complex of anatomic structures involved in the generation of ictal discharges, referred to as the *epileptogenic zone*. In principle, the main types of seizures observed in human epilepsies should be faithfully reproduced in experimental animals by creating epileptogenic zones in the appropriate cortical areas. However, the evaluation of ictal phenomenology in animals is necessarily limited to external observations of animal behavior and thus provide only an indirect assessment of the subjective experience, which is an important aspect of seizures originating in cortical areas involved in sensation, emotion, and higher cognitive function.

The evaluation of experimentally induced complex partial seizures presenting with variable sequences of typical symptoms (including loss of contact) is also difficult, as is the comparison of animal and human seizures because of species-related differences in central nervous system organization. Of course, the ictal involvement of some human-specific functions such as language can never be modeled in experimental animals.

Besides these intrinsic difficulties, further problems in assessing the reproducibility of human seizures in experimental animals derive from the scanty descriptions of ictal phenomenology in some experimental studies. For instance, it is insufficient to describe a seizure as focal with elementary motor symptomatology without a qualitative (clonic vs. tonic, tonic vs. postural, positive vs. suppressive, etc.) and topographic (massive vs. segmental, stationary vs. migrating, etc.) analysis of its motor manifestations.

Neurologic, psychic, and neuropsychological persisting signs during the interictal period have been reported in patients suffering from focal symptomatic epilepsies. Interictal neurologic and behavioral studies in animals made epileptic by different experimental procedures have been performed only occasionally (see later discussion).

Interictal and Ictal Electroencephalographic Features

In human localization-related epilepsies, interictal focal â€œepileptiformâ€ electroencephalographic (EEG) activities are often seen as spikes, sharp and slow waves, fast rhythms, and so on.[53] The transition from an interictal to an ictal discharge may be represented by repetitive interictal discharges, localized fast activity (often with a recruiting character), or other rhythmic discharges not necessarily colocalized with the interictal focus (if present).[53] Similar EEG changes can be detected in animal models of partial epilepsies, although the internal frequency of interictal and ictal discharges may not be the same as that seen in humans. This may depend on both species-related differences and technical factors (the type of electrodes, interelectrode distances, etc.). In particular, the current use of bone screws or intracranial wire as recording electrodes may exclude or reduce the filtering effect of bone on fast activities. To make recordings from animals comparable with those from humans, standardized EEG methodology and terminology should be developed.[74]

Natural History

Although human focal symptomatic epilepsies depend on various progressive, stationary, or remitting brain pathologies, their course is to some extent independent of the underlying disorder. In particular, the epilepsies secondary to acute brain insults (such as traumatic, vascular, and infectious epilepsies) display a typical biphasic course that includes an early phase with single or repeated â€œreactiveâ€[68] seizures or SE, which may then subside to give rise to chronic epilepsies after a more or less prolonged interval. Some of the experimental models reviewed here have contributed significantly to clarifying the mechanisms underlying such a biphasic course.

Questions that can be Addressed by Animal Studies

Experimental studies of epilepsies try to answer various questions concerning brain physiology, pharmacology, and pathophysiology that are all basically related to the aim of gaining a better understanding of the mechanisms underlying epileptogenesis.

The characterization of a cellular hallmark of epilepsy in the â€œpenicillinâ€ focus of cat neocortex, the paroxysmal depolarization shift (PDS),[134,135] was seen as a major breakthrough that could directly lead to the unraveling of the â€œbasic mechanism of epilepsy.â€ However, it was soon realized that the analysis of this characteristic burst-discharge seen in individual neurons only partially explains the biologic basis of epileptogenesis. Moreover, it became clear that similar shifts could result from a variety of experimental manipulations differentially affecting the excitable properties of cortical neurons, thus suggesting that a unitary explanation of epileptogenesis was unrealistic.[172]

Selection of a model for study depends on the specific question being asked. However, whether designed to replicate a specific component or an overall process, the ideal model is one that most closely approximates the phenomenon or process of interest. Thus, experimental models should closely approximate behavior, electroencephalographic characteristics, and pharmacologic responses of the type of human epileptic manifestation being studied.

In considering the questions to be addressed by a given experimental model, it must be borne in mind that the answers an investigator may obtain are valid only for that specific model unless otherwise demonstrated. Therefore, the relevance that an experimentally demonstrated epileptogenic mechanism may have in relation to human epilepsies depends on the strength of the evidence of its involvement in human epilepsies. Ultimately, therefore, parallel studies in patients are required.

The following is a discussion of some of the models that have been in use for many years. Others not discussed in detail that are being developed include models of traumatic brain injury, hypoxia-induced epileptogenic encephalopathy, stroke, febrile seizures, intraparenchymal bleeding, and cerebral infection.[168]

Alumina Model

The epileptogenic effect of the topical application of alumina hydroxide gel to monkey neocortex was discovered by Kopeloff et al.[114] in the context of a study aimed at investigating

immunologic factors in epilepsy. Among the many other metallic compounds that were later shown to induce epileptic foci, alumina cream is the most suitable for inducing chronic focal epilepsy.

Methods

Autoclaved aluminum hydroxide 4% gel is injected in a few adjacent sites of the exposed neocortex using a small syringe needle.[247] Epileptogenic foci are optimally induced in primates but less consistently in dogs, cats, and guinea pigs. There are no reports of spontaneous seizures induced by intracortical alumina in lower forms. Alternatively, the systemic[76] and intracisternal[111] administration of aluminum salt or aluminum metallic powder[29] has been used to induce encephalopathy with multifocal seizures in susceptible animals (rabbits, cats, and ferrets, but not rats).

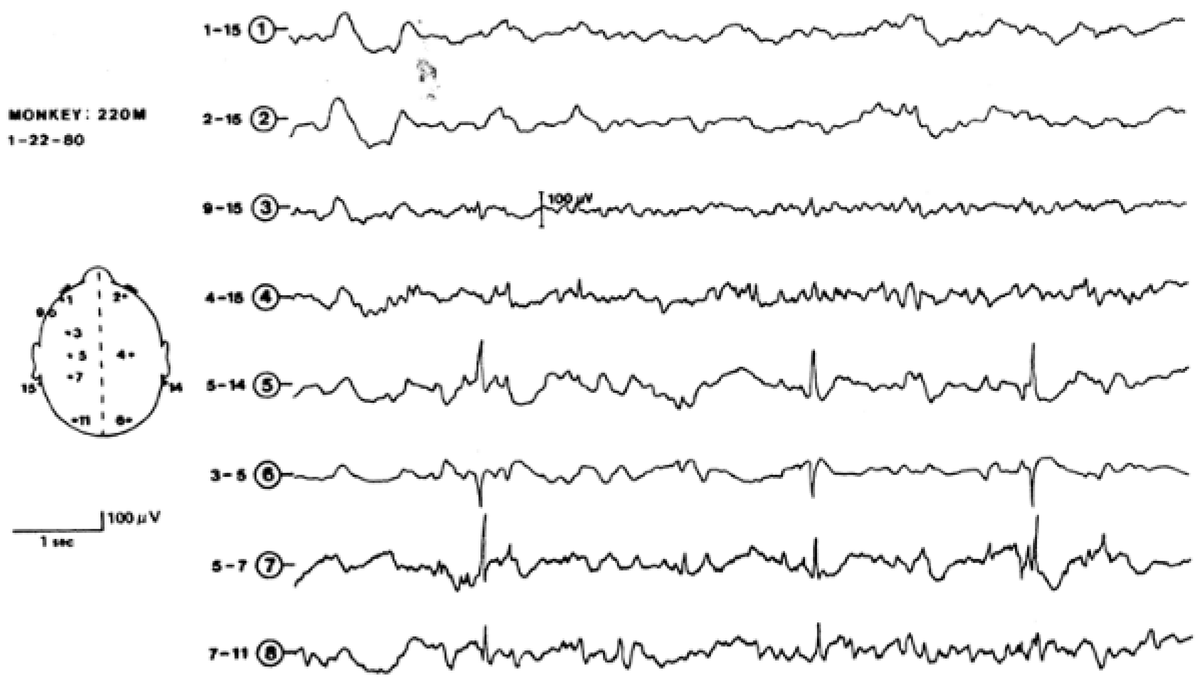


FIGURE 1. Sleep recording from a *Macaca mulatta* injected in left pre- and postcentral gyrus with aluminum hydroxide. The electrodes 1â€“8 and 10â€“13 are skull-screws. The electrode 9 is placed in temporalis muscle, and electrodes 14 and 15 are implanted in the mastoid process. Note the spike activity on the left hemisphere. (From Lockard JS. A primate model of clinical epilepsy: mechanism of action through quantification of therapeutic effects. In: Lockard JS, Ward AA. *Epilepsy: A Window to Brain Mechanisms.* New York: Raven Press, 1980;11â€“49; with permission.)

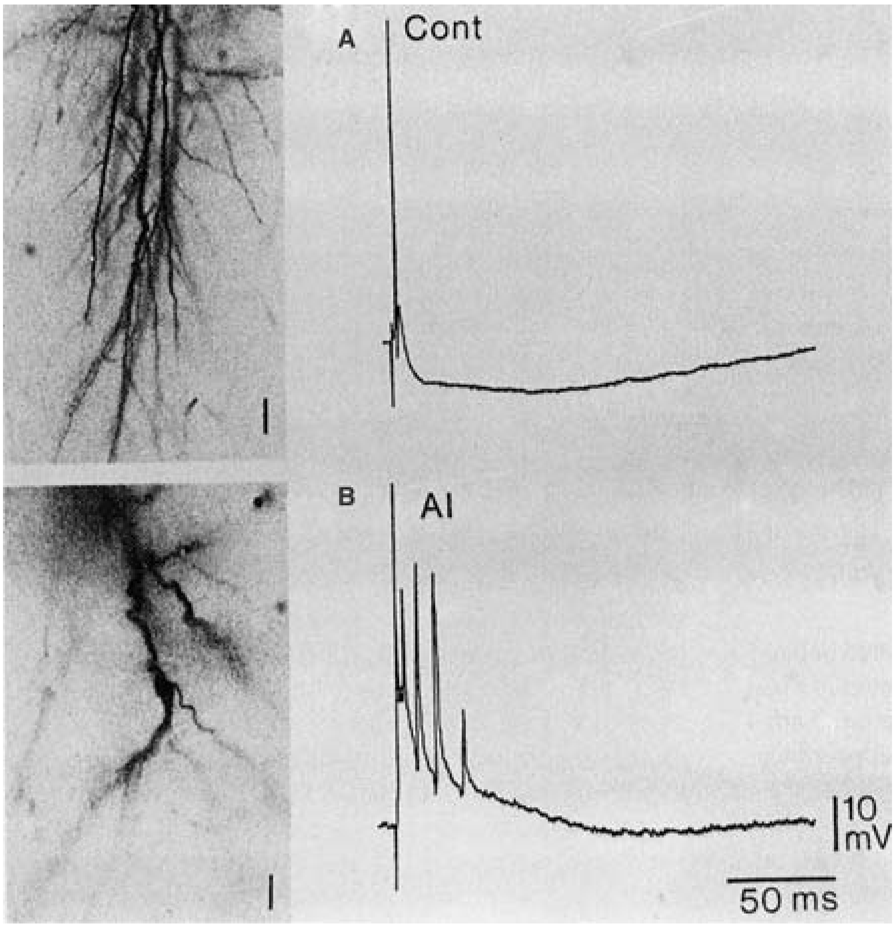


FIGURE 2. Synaptic responses of two horseradish peroxidaseâ€"injected CA1 pyramidal neurons from control **(A)** and intracysternally $AlCl_2$-injected rabbits **(B)**. Note in panel B the irregularities in dendritic size and the repetitive discharge superimposed on a prolonged depolarizing shift. (From Franceschetti S, Bugiani O, Panzica F, et al. Changes in excitability of CA1 pyramidal neurons in slices prepared from $AlCl_3$-treated rabbits. *Epilepsy Res.* 1990;6:39â€"48; with permission.)

Neuropathology

Dendritic distortion with decreased branching size irregularities and spine loss has been observed in pyramidal neurons within an alumina cortical focus.[250] These changes are due to a toxic effect leading to neurofibrillary degeneration, which has been studied in aluminum encephalopathy induced by both systemic and intracisternal administration.[29,111] The further stages of toxic degeneration lead to neuronal loss with marked gliosis, which is particularly prominent in â€œmatureâ€ alumina cortical foci.[102] A decrease in GABAergic nerve terminals at the sites of alumina foci has also been reported.[178] In most experiments, alumina has been topically applied to the sensorimotor cortex or the hippocampus; in both regions, pyramidal neurons have been found to be consistently affected after the intracisternal injection of aluminum powder.[29]

Natural History and Clinical Phenomenology

Spontaneous clinical seizures appear between 2 weeks and 6 to 8 months after intracerebral injection of alumina cream, depending on the number of injections and the width of the involved area.[247] Once established, the seizures spontaneously recur, probably throughout the life span of the animals; in monkeys, they have been observed for at least 7 years.[247] With large foci, seizure frequency may increase to status epilepticus and require antiepileptic treatment to maintain a viable preparation. The seizure patterns depend on the location of the focus. According to Ward,[247] in monkeys receiving alumina injections in the face and arm area of the somatomotor cortex, the seizures begin with contralateral facial or hand twitching, spread gradually to the entire contralateral side (mimicking a jacksonian march), and may eventually become generalized. During the seizures, muscular jerks occur at an increasing rate, which then fuse into a tonic contraction with superimposed strong generalized jerks, cyanosis, and sialorrhea. The tonic or tonicâ€“clonic phase ceases abruptly, giving place to a postictal depression with hypotonia and unresponsiveness to external stimulation of variable duration. When a particularly intense epileptogenic focus has been obtained, focal motor status epilepticus can be observed, with continuous 1/10-second jerks of the contralateral face and hand, mimicking Kojeknikoff epilepsia partialis continua. Behavioral seizures reminiscent of human complex partial seizures of temporal origin can be observed after alumina injection in the anterior part of the temporal lobe and/or in the amygdala of monkeys and cats.[83,251] Soper et al.[203] consistently obtained chronic temporal lobe epilepsy in monkeys only by means of bilateral alumina injections in the hippocampus; the clinical seizures consisted of head-turning, lip-smacking, mastication, and salivation.

Electroencephalogram

Serial recordings show the gradual development of interictal foci of slow and sharp waves, spikes, and delta activity in the region of the scalp corresponding to the underlying alumina focus (Fig. 1).[96] The transition to ictal discharge may be difficult to identify when interictal activity is sustained; otherwise, it is characterized by focal fast activity of increasing amplitude.[202] As the seizure progresses, spikes and sharp waves tend to recur rhythmically and spread to other regions. In animals with bilateral foci, ictal discharges invariably begin at the site of the older focus.[202]

Pharmacology

Antiepileptic drug efficacy on interictal EEG discharges or seizure frequency has been widely studied in correlation with pharmacokinetic parameters.[121] Phenytoin (Dilantin), phenobarbital (Arco-Lase, Bellergal-S, Donnatal, Quadrinal Mudrane, Rexatol, Solfoton), primidone (Mysoline), and carbamazepine (Atretol, Tegretol) showed a significant effect on both seizure frequency and interictal EEG discharge. The efficacy was correlated with drug plasma levels. A less clear level/effect correlation was found for sodium valproate (which improved when the correlation was evaluated on an hour-by-hour basis).

Pathophysiology

Neurons belonging to alumina foci have a high probability of burst-firing, closely associated with surface epileptiform waves.[173] These putative epilepsy-related changes are not maintained in in vitro slices prepared from monkey alumina foci, which have been found to have physiologic properties that are not significantly different from those of control tissue.[186] On the contrary, Franceschetti et al.[77] observed significant changes in the excitable properties of hippocampal pyramidal neurons in slices prepared from intracisternally $AlCl_2$-injected rabbit. These changes were accounted for by a decrease in the efficacy of Ca^{2+}-dependent K^+ conductances and GABAergic transmission and by electrotonic shortening due to dendritic debranching (Fig. 2). They were clearly detectable in the very early phases of the aluminum-induced encephalopathy, even before the manifestation of neurofibrillary degeneration, cell loss, and gliosis. On the other hand, the hypothesized epileptogenic role of the gliotic scar (which is believed to impair K^+ regulation and thus lead to K^+ accumulation in the interstitial space) is controversial[102] and could not be directly demonstrated by Heinemann and Dietzel,[100] who found that the spatial buffer capacity of gliotic tissue for K^+ was not severely impaired in cat alumina cream foci.

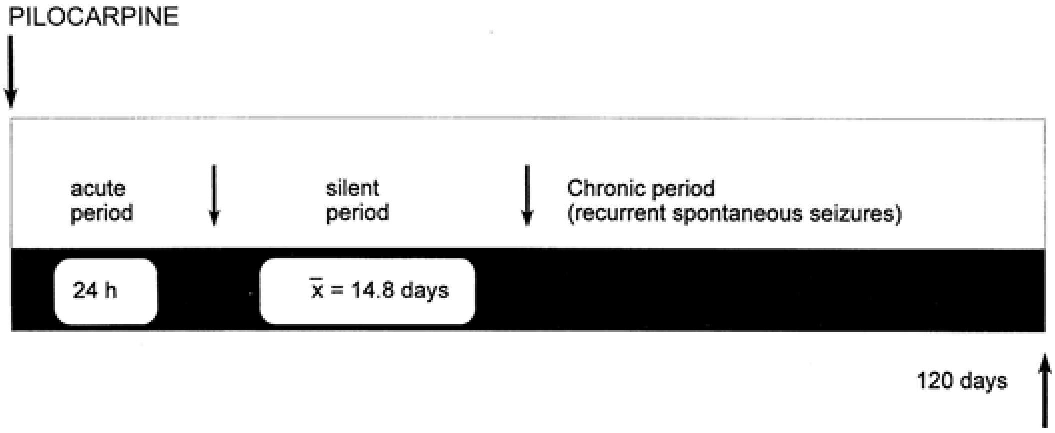


FIGURE 3. Schematic representation of temporal evolution of behavioral and electroencephalographic changes induced by an intraperitoneal injection of pilocarpine (380 mg/kg) in rats. (Redrawn from Cavalheiro EA, Leite JP, Bortolotto ZA, et al. Long-term effects of pilocarpine in rats: structural damage of the brain triggers kindling and spontaneous recurrent seizures. *Epilepsia*. 1991;32:778â€“782; with permission.)

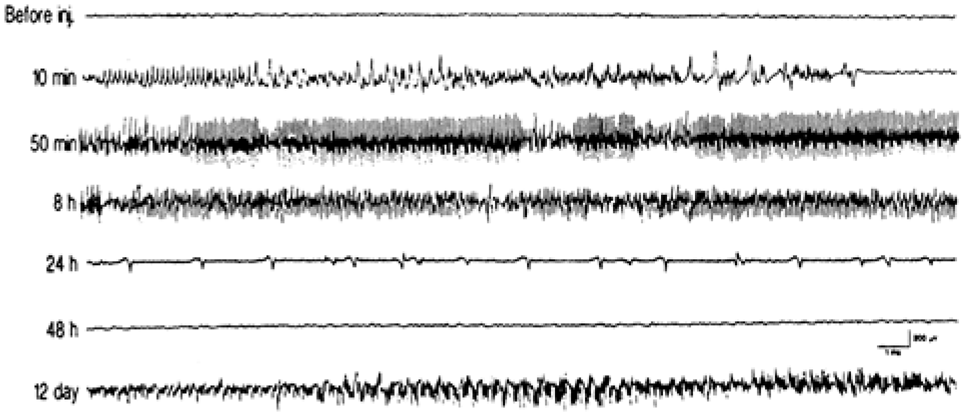


FIGURE 4. Skull-screw electrode electroencephalographic recording from frontoparietal region of a rat at different time intervals after intraperitoneal injection of pilocarpine (400 mg/kg). Continuous spike activity appeared 50 minutes after injection and lasted up to 8 hours. Isolated spikes persisted up to 24 hours, then disappeared during the latent period to show up again 12 days after injection. (From Liu Z, Nagao T, Desjardins GC, et al. Quantitative evaluation of neuronal loss in the dorsal hippocampus in rats with long-term pilocarpine seizures. *Epilepsy Res.* 1994;17:237â€“247; with permission.)

Pilocarpine Model

The first evidence that rats with brain damage induced by the cholinergic agent pilocarpine develop spontaneous recurrent seizures after a silent period of 14 to 15 days was provided by Turski et al.,[226] who were investigating the acute effects of pilocarpine treatment. As was stressed later by the same authors,[34] this natural history is reminiscent of that of human temporal lobe epilepsy, which often begins with prolonged status epilepticus in infancy and develops with recurrent seizures in later life.[89]

Methods

Thirty minutes after subcutaneous pretreatment with scopolamine, 1 mg/kg (to minimize peripheral cholinergic effects), a single high dose of pilocarpine (300â€“380 mg/kg) is injected intraperitoneally in rats and mice.[33] The acute pilocarpine-induced status epilepticus must be continuously monitored by behavioral observation and EEG recording because of the high mortality rate (30%),[33] which can be partially prevented by repeated intraperitoneal injections of diazepam 10 mg/kg plus phenobarbital 30 mg/kg[117] at 30 minutes 1, 2, and 6 hours after the beginning of the status epilepticus. Further behavioral-EEG monitoring is indicated during the silent period to detect the onset of chronic recurrent seizures.

Neuropathology

At the end of the acute phase, widespread bilateral morphologic changes appear that involve the hippocampus, amygdala, thalamus, pyriform and entorhinal cortices, neocortex, and substantia nigra.[226] These consist of massive swelling of dendrites and neuronal cell bodies with relative sparing of axons and astroglial cell swelling.[40,159] During chronic stages, there is invariably cell loss in all of the structures mentioned, including the hilus of the dentate gyrus. Clear-cut evidence of supragranular sprouting of the mossy fibers, beginning 4 days after the episode of status epilepticus and reaching a plateau after 100 days, can be found using Timm staining.[152] The severity of the chronic neuropathologic changes is proportional to the duration of the status episode[117] but not to the number of chronic seizures.[120]

Natural History and Clinical Phenomenology

The temporal evaluation of pilocarpine-induced behavioral and EEG changes is schematically illustrated in FIGURE 3. Immediately after the pilocarpine injection, the animal is hypoactive; subsequently, there is the appearance of facial automatisms, including chewing and eye blinking, followed by head bobbing and motor limbic seizures (forelimb clonus, salivation, and rearing on hind limbs). Generalized convulsions and limbic status usually occur 40 to 80 minutes after the injection, depending on the injected dose.[33,120,226] After a silent period of 4 to 44 days, the spontaneous seizures that characterize the chronic period appear and recur with a variable frequency of 2 to 15 per month, with no evidence of spontaneous remission for at least 6 months.[33]

Electroencephalogram

During the acute phase, the electroencephalographic changes evolve from early surface low-voltage fast activity correlated with a theta hippocampal rhythm to high-voltage fast activity associated with spiking in the hippocampus and, finally, surface spiking activity that correlates with head bobbing.[120] Limbic seizures are associated with high-frequency, high-voltage spike discharges that become continuous during limbic status. The EEG progressively normalizes at the end of the acute phase, although spontaneous spike discharges reappear after the silent period. The ictal electrographic discharges of the chronic period consistently originate in the hippocampus and subsequently spread to the cortical electrodes.[33] FIGURE 4 summarizes the evolution of EEG changes.

Pharmacology

Diazepam (Dizac, Valium) and scopolamine, 10 mg/kg, provide effective protection from acute seizures and limbic status.[33] Phenobarbitone 40 mg/kg/d, phenytoin 100 mg/kg/d, and carbamazepine 120 mg/kg/d have been found to be effective against the spontaneous seizures occurring during the chronic phase. Sodium valproate has been found to be effective only at very high doses (600 mg/kg/d); ethosuximide (Zarontin) 400 mg/kg/d is totally ineffective.[116]

Pathophysiology

In vitro experiments[15,16] have shown that the epileptogenic effect of cholinergic agents depends on the facilitation of burst discharges in hippocampal pyramidal neurons by means of a block of the K^+ transmembrane current I_M. This mechanism explains the massive activation of hippocampal neurons during pilocarpine-induced status epilepticus, which leads to cell death, axonal sprouting, and a synaptic reorganization of hippocampal circuitry that results in permanent epileptogenic changes.[33,35,120] The neuronal damage is not attributed to a direct toxic effect of pilocarpine, but to a seizure-related excitotoxic effect involving glutamate receptors and Ca^{2+} influx.

Tetanus Toxin

The epileptogenic properties of intracerebral tetanus toxin have been known since the end of the nineteenth century[180] but have been exploited in experimental studies of epileptogenesis only more recently after studies published by Brooks and Asanuma[28] and Carrea and Lanari[32] in cat and dog neocortex and by Mellanby et al.[152] in rat hippocampus and neocortex.[106]

Methods

Tetanus toxin is a protein with a molecular weight of 150 kDa released by *Clostridium tetani* and is now available in a purified form. It is quite stable and can be kept at 4Â°C for months. Tetanus toxin is extremely toxic and must be handled only by effectively immunized people wearing protective clothing (gloves and a mask). Tetanus toxin is active in all of the mammalian species tested[180] when very small amounts are injected in appropriate regions. The dose is usually expressed in toxicologic units that correspond to different quantities, depending on the degree of purification: 5 to 20 mouse half lethal dose (LD_{50}) has been used in rat hippocampus,[106] 2 to 30 minimum lethal dose in rat neocortex,[24] 10 to 10^3 mouse lethal dose in cat neocortex,[25] and 28 to 83 LD_{50} in dog neocortex.[32] It is important to bear in mind that tetanus toxin is very efficiently transported along axons.

Neuropathology

Early tetanus toxinâ€"induced histologic changes with minimum effective doses injected into the hippocampus are very mild and consist of a loss of neurons in the CA1 region. Much higher doses cause neuronal loss at the injection site. It is suspected that late changes in hippocampal circuitry occur, but these have not yet been systematically investigated.[106]

Natural History and Clinical Phenomenology

Animals that are injected with low doses in either the neocortex or hippocampus develop seizures 3 to 7 days after the injection.[27,106] Shorter intervals are reported with higher doses.[28] In rats receiving hippocampal injections of the toxin, there is a reduction in the number of seizures after some weeks of intense epileptic activity; the seizures eventually disappear but may relapse in the longer term.[106] In neocortex-injected rats[27] and cats,[125] tetanus toxinâ€"induced foci can be permanent. Hippocampal injections induce limbic seizures that start with a behavioral arrest, followed by vibrissal and facial twitching and forelimb myoclonus that may eventually develop into a clonicâ€"tonic seizure involving the hindlimbs. Injections in rat cortex are followed by early focal motor seizures in the jaws and/or contralateral limbs, tending to progress to generalized convulsive seizures after 16 hours.[27]

Electroencephalogram

Interictal biphasic sharp waves are recorded from the injected hemisphere 3 to 5 days after the injection and, a few days later, from the contralateral homotopic sites with synchronous or asynchronous expression (Fig. 5).[27] Ictal discharges of 3- to 20-Hz spikes and spikes-and-waves may be limited to one hemisphere or may spread rapidly to the contralateral side. The injected hemisphere leads in the early phases, but 5 to 13 days after the injection, the ictal discharge can be initiated in the contralateral hemi-sphere.[27]

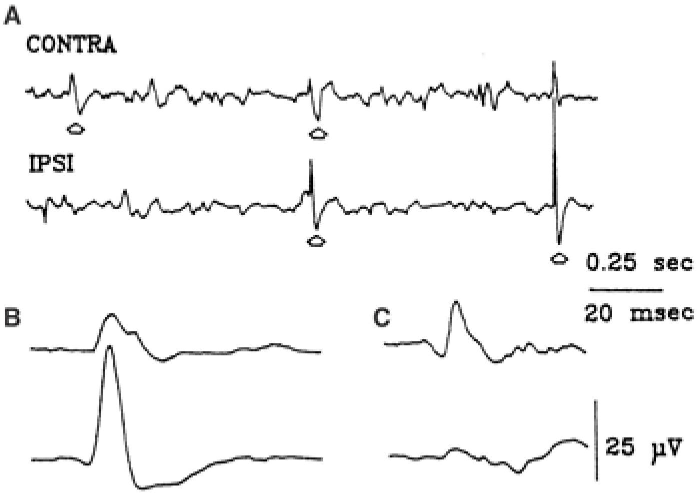


FIGURE 5. Skull-screw recording in a rat 22 days after injection of tetanus toxin. Interictal spikes occur in both injected (IPSI) and contralateral hemisphere (CONTRA) **(A)** either synchronously **(B)** or asynchronously **(C)**. (From Brener K, Amitai Y, Jefferys JGR, et al. Chronic epileptic foci in neocortex: in vivo and in vitro effects of tetanus toxin. *Eur J Neurosci.* 1991;3:47â€“54; with permission.)

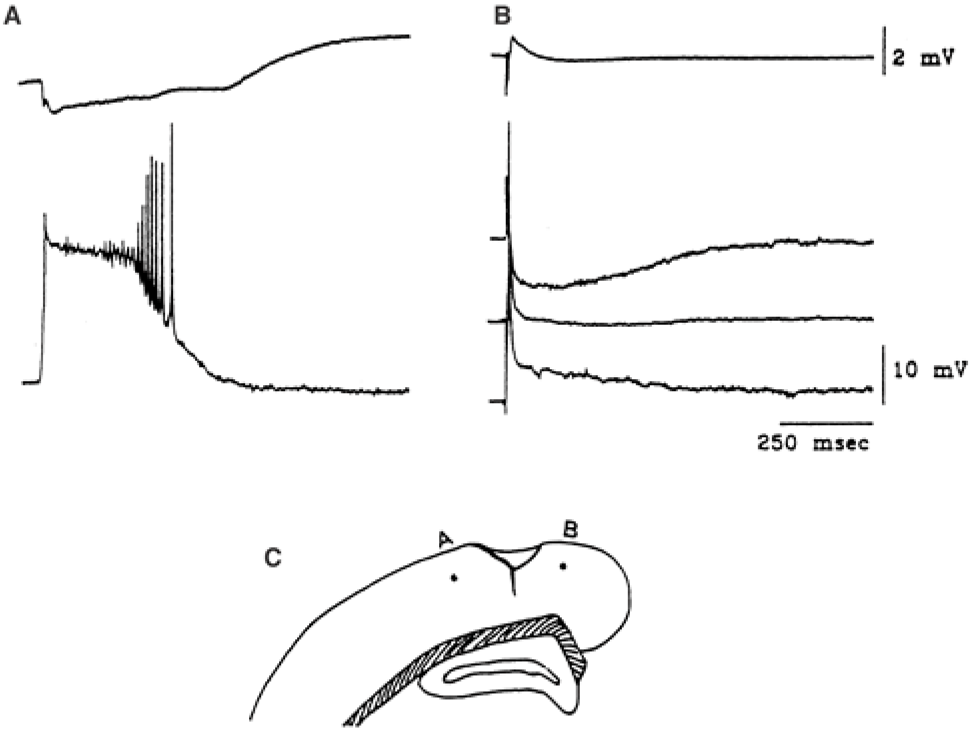


FIGURE 6. A, B: Simultaneous field (*upper trace*) and intracellular (*lower trace*) recordings made from A and B sites indicated in the schematic diagram **(C)** of a slice prepared from a rat injected with tetanus toxin in parietal neocortex 8 days before. Although the two recording points are equidistant from the injection track, site A generates epileptiform response, whereas site B appears relatively normal. (From Brener K, Amitai Y, Jefferys JGR, et al. Chronic epileptic foci in neocortex: in vivo and in vitro effects

of tetanus toxin. *Eur J Neurosci.* 1991;3:47â€“54; with permission.)

Pharmacology

Drugs effective in human focal epilepsies, such as carbamaze-pine, have also been found to be quite effective in the tetanus toxin model but not the *N*-methyl-D-aspartate (NMDA)â€“receptor antagonist 2-amino-5-phosphonopentanoic acid (APV).[106]

Pathophysiology

The tetanus toxinâ€“dependent epileptogenic process has various phases. At the very beginning, the toxin induces epileptiform discharges in the injection site as a result of a block of Î³-aminobutyric acid (GABA) release,[46] leading to the impairment of the local inhibitory circuits established by GABA interneurons in both the hippocampus and the cerebral cortex. The epileptiform neuronal aggregate is contained in hippocampal and neocortical slices prepared from the injected areas, and this has allowed a detailed electrophysiologic analysis.[67,105] In a second phase, the toxin is transported through the axons to even remote sites, where it can move transsynaptically inside local GABAergic neurons. A transport velocity of as much as 200 mm/d has been estimated in peripheral nerves,[185] and, therefore, transport-related patches of epileptiform activity can be generated in a few hours through corticocortical and callosal connections (Fig. 6). This mechanism might account for the rapid generation of mirror foci.[27] In a third chronic phase, GABA-mediated inhibition recovers, due probably to an increased RNA expression of glutamic acid dehydrogenase (GAD). The epileptic activity persisting in this chronic phase is attributed to seizure-induced plastic changes in the hippocampal or neocortical circuits, leading to the functional disconnection of GABAergic neurons or the sprouting of new excitatory axons.[106]

Kainic Acid

Kainic acid is a highly potent glutamate agonist that is obtained from the seaweed *Digenea simplex* and used as an ascaricide. Kainic acid was found to be excitatory when applied iontophoretically to rat cortex[195] and to induce seizures when injected intracranially[19,20] or systemically.[21,47,126] Olney et al.[160] highlighted its neurotoxic properties and reported its toxicity to be particularly prominent on the hippocampus, even when systemically injected. Kainic acidâ€“induced cell injury is attributed to an excitotoxic mechanism triggered by the activation of excitatory amino acid (EAA) receptors. The same mechanism is also responsible for the hippocampal seizures occurring in animals injected, either intravenously[126] or in the hippocampus,[34] with doses less than those required to produce direct cell damage.

Methods

Most of the studies with kainic acid have been done in rats. Systemic doses of 4 mg/kg[126] and local injections of 0.4 mg[8] are effective in inducing persistent seizures. Similar effects have been obtained by means of intracisternal ventricular injections in mice,[227] for which a 50% convulsive dose of 0.3 nmol has been calculated. A single intra-amygdaloid injection of 1 Âµg in cats has been found to be effective in inducing focal status epilepticus.[126,214]

Neuropathology

The systemic administration of kainic acid induces a variable pattern of cortical and subcortical damage involving the pyriform and entorhinal cortices, the hippocampus, the lateral septum, and several thalamic and amygdaloid nuclei.[159] In the hippocampus, degenerating neurons are found in the dentate hilus, CA1, and CA3.[74] A similar pattern of hippocampal degeneration has been found after local hippocampal injection during the acute phase,[133] with evidence of active cellular phagocytosis of the necrotic zone in the next active phase.

The Timm[217] sulfide silver method for heavy metals, subsequently modified,[54] shows an initial sprouting of zinc-containing mossy fibers into the inner molecular layer. This sprouting progressively increases during the latent phase, reaching its maximum at the beginning of the chronic phase, when a thick band of Timm-positive fibers is permanently found in the inner molecular layer (Fig. 7). With unilateral injection, the changes are largely unilateral, resembling human hippocampal sclerosis.

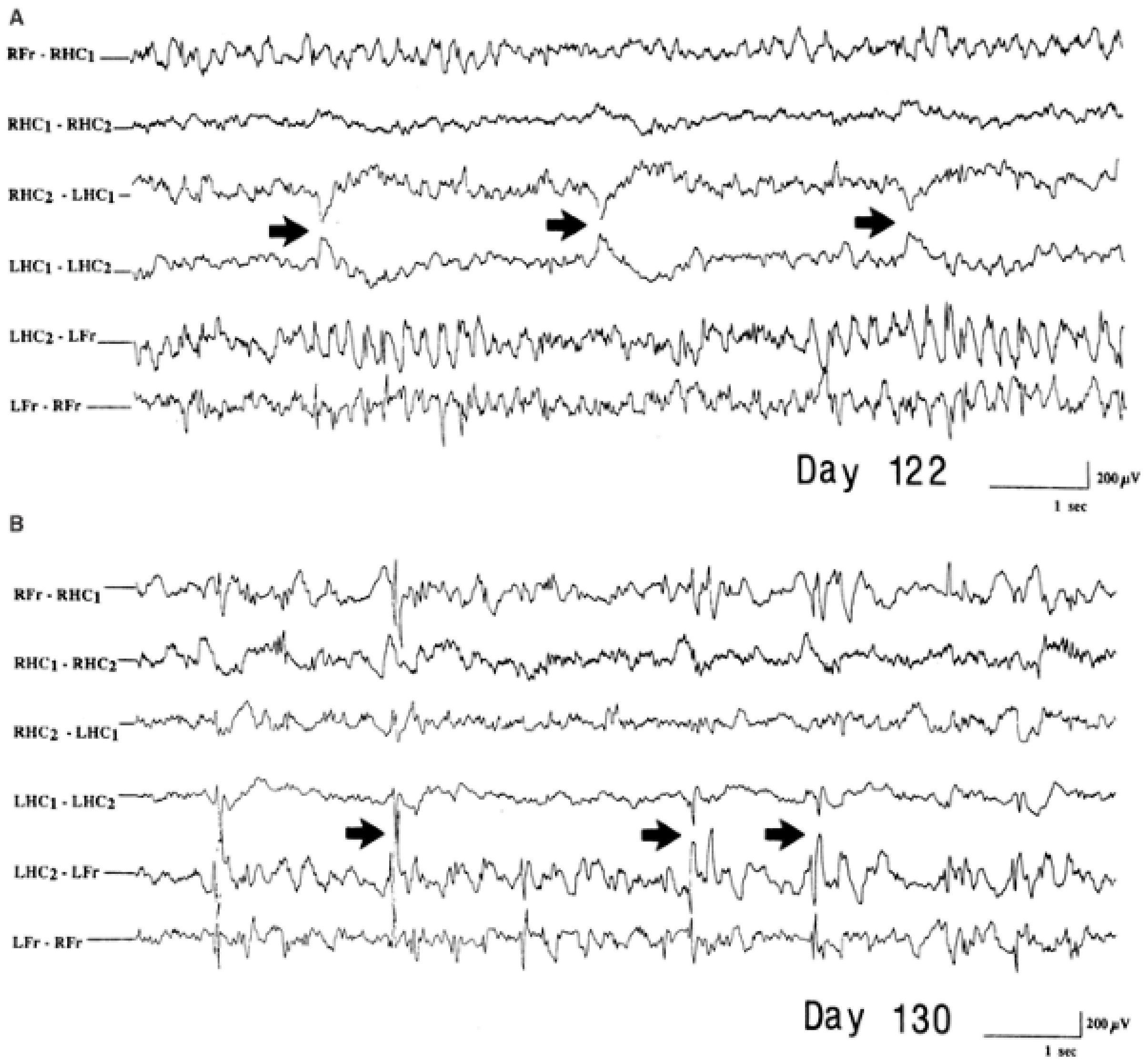


FIGURE 7. Interictal recording from a rat bilaterally injected with kainic acid in the hippocampus 122 **(A)** and 130 **(B)** days before. Fr, single wire electrodes placed into the frontal cortex; HC1, 2, double-twisted wire electrodes inserted in the hippocampus; L, left; R, right. The independent epileptiform transient (*arrows*) are seen mostly in the left hippocampus, which showed evidence of mossy fiber sprouting, as shown by Fig. 8. (From Mathern GW, Cifuentes F, Leite JP, et al. Hippocampal EEG excitability and chronic spontaneous seizures are associated with aberrant synaptic reorganization in the rat intrahippocampal kainate model. *Electroencephalogr Clin Neurophysiol.* 1993;87:326â€“339; with permission.)

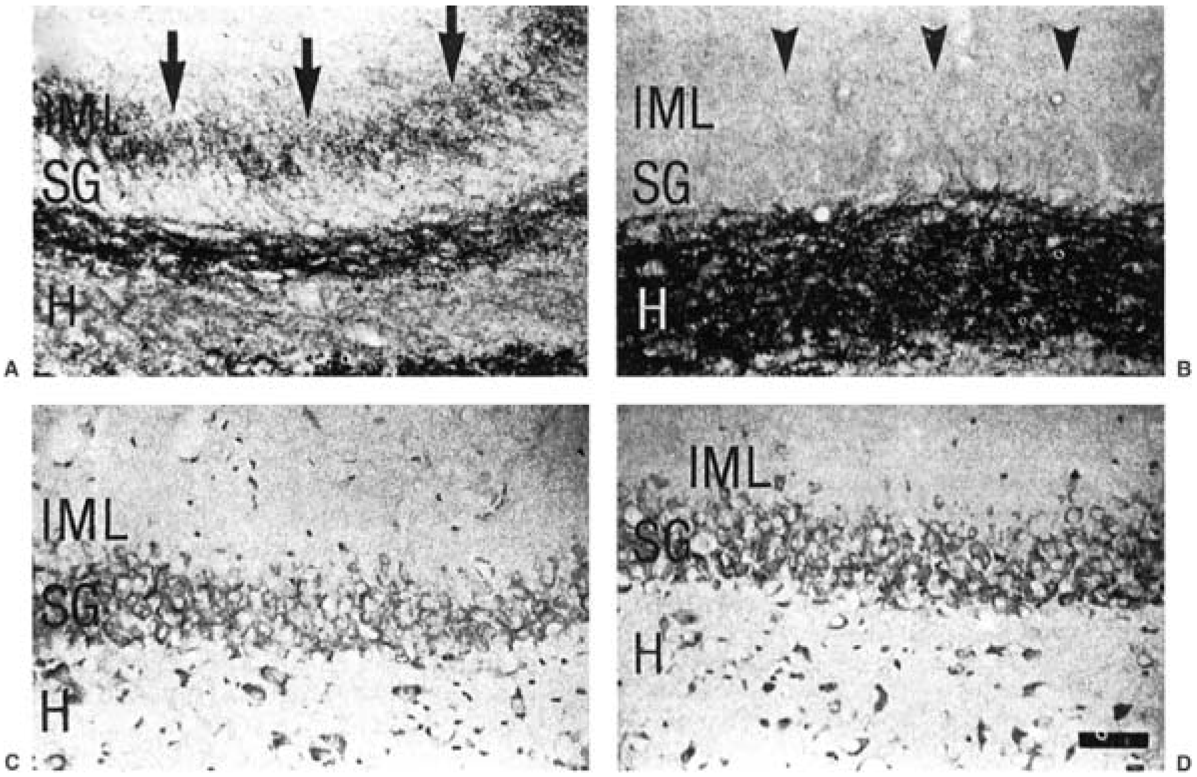


FIGURE 8. In the same animal whose electrographic recording is shown in Fig. 7, Timm-stained sections show a zinc-positive band (*arrows*) in the left **(A)** but not in the right (**B**) inner molecular layer (IML). Note that both hippocampi (**C, D**) show evidence of neuron loss in the stratum granulosum (SG) and hilus (H). (From Mathern GW, Cifuentes F, Leite JP, et al. Hippocampal EEG excitability and chronic spontaneous seizures are associated with aberrant synaptic reorganization in the rat intrahippocampal kainate model. *Electroencephalogr Clin Neurophysiol.* 1993;87:326â€“339; with permission.)

Natural History and Clinical Phenomenology

The evolution of the epileptic phenomenology and electrophysiologic correlates induced by low doses of kainic acid injected bilaterally in rat hippocampus has been longitudinally studied by Mathern et al.[133] and correlated with concomitant histologic changes. Similar asymmetric changes occur with unilateral hippocampal injections, which more accurately reproduce the predominantly unilateral condition of human mesial temporal lobe epilepsy.[25] On the basis of the clinical and electrophysiologic course, four phases have been recognized as sequentially occurring after kainic acid injection at the following approximate time intervals in days: acute (0â€“10), active (10â€“30), latent (30â€“90), and chronic. The earliest seizures characterizing the acute phase occur within 1 hour after hippocampal injection and consist of behavioral arrest; the association of sniffing and facial myoclonus is ascribed to the frontal spread of the discharge. After several hours, the seizures increase in duration and may eventually evolve into a partial status characterized by simple staring. The active phase is characterized by short-duration seizures (<1 minute) with generalized motor clonus and very rapid behavioral recovery. The seizures disappear during the latent period but relapse during the chronic phase, with characteristics similar to those of the acute stage: A motionless stare that may occasionally progress to a more complex phenomenology, including facial automatisms, forelimb clonus, and generalized clonicâ€“tonic seizures. The chronic seizures do not tend to subside, but rather increase in frequency and duration and may generalize over time.[133]

Electroencephalogram

Mathern et al.[133] and Bragin et al.[25] monitored the hippocampal activity recorded by stereotaxically implanted deep electrodes and the frontal activity derived from intracortical wires.

In the acute phase, discharges of spikes and multispikes in the hippocampus are associated with behavioral arrest and spread of the discharges toward the frontal cortex with sniffing and facial myoclonus. Postictal diffuse slowing of background activity is regularly observed and is sometimes associated with periodic lateralized epileptiform discharges (PLEDs). The active phase is characterized by interictal fast activity and polyspikes limited to the hippocampus, the transition to the ictal discharge being marked by a pronounced spike activity that rapidly generalizes. During the latent phase, there is a reduction in the interictal spikes, and background activity is almost normalized; in the late part of the latent phase, however, spikes and sharp waves are increasingly recorded, and there is a marked tendency to asynchronous expression in both hippocampi. The asynchrony of interictal spikes and sharp waves becomes more and more evident during the chronic phase, when ictal discharges limited to one hippocampus reappear in association with motionless staring episodes. A bilateral spread of discharges is observed during generalized seizures (Fig. 8). In addition to the clinical seizures, more frequent electrographic seizures can also be recorded, usually during sleep.[25] Whereas the EEG patterns during clinical seizures resemble the low-voltage fast ictal onset of human mesial temporal lobe epilepsy, the electrographic events resemble the hypersynchronous onsets usually associated with auras in patients.

More recently, microelectrode recordings from unilateral intrahippocampal kainic acidâ€“treated rats have led to the discovery of 150- to 500-Hz â€œFast Rippleâ€ oscillations identical to those recorded from human epileptic hippocampus.[25] Fast Ripples can also be recorded shortly after kainate injection and predict which rats will develop spontaneous seizures.[26] The significance of this novel finding is discussed in Chapter 13.

Pharmacology

Drug responsiveness of the kainate model is essentially the same as that for the pilocarpine model.

Pathophysiology

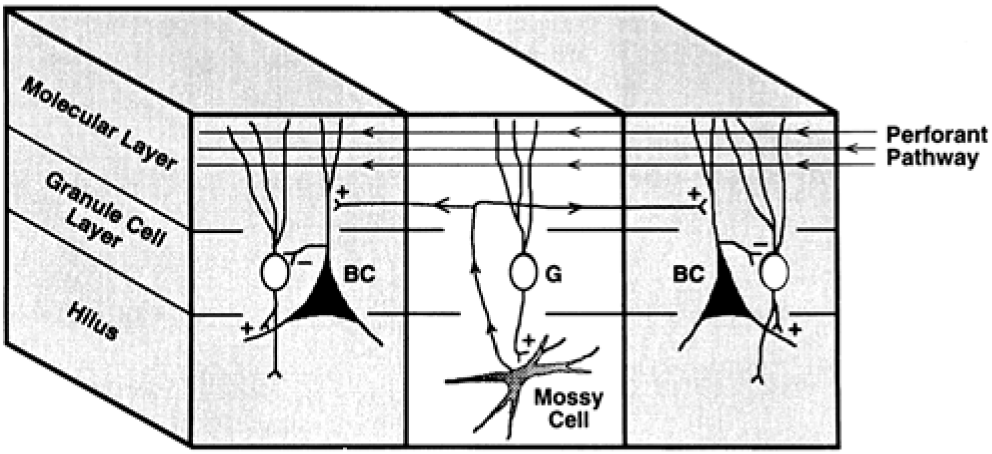


FIGURE 9. Diagrammatic representation of dentate network circuitry and the hypothesized translamellar mossy cell innervation of inhibitory basket cells. BC, basket cells; G, granule cells. (From Sloviter RS. The functional organization of the hippocampal dentate gyrus and its relevance to the pathogenesis of temporal lobe epilepsy. *Ann Neurol.* 1994;35:640â€“654; with permission.)

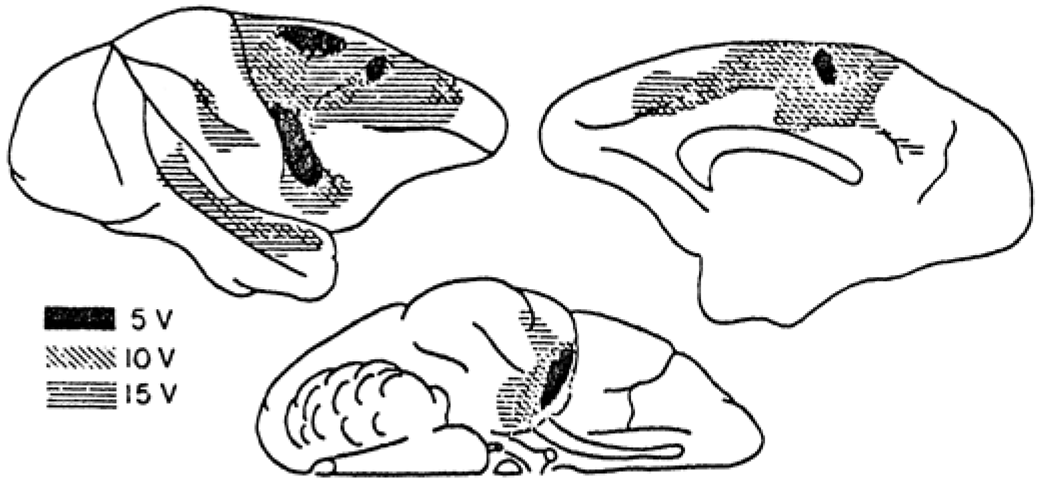


FIGURE 10. Different susceptibility to electrically induced afterdischarge in the cortex of monkey. Stimulation thresholds in volts (V) in different areas are indicated by the three coded patterns. (Originally from French et al.[80] From Ajmone Marsan C. Focal electrical stimulation. In: Purpura DP, Penry JK, Tower D, et al., eds. *Experimental Models of Epilepsy. A Manual for the Laboratory Worker*. New York: Raven Press; 1972:147â€"172; with permission.)

The early seizures occurring during the acute phase are attributed to the direct effect of the excitatory amino acid receptor agonist kainic acid, which is especially prominent in the hippocampus due to the particularly high concentration of kainic acid receptors in this region. The permanent changes in hippocampal excitability underlying chronic seizures is ascribed to neuronal damage of the vulnerable hilar mossy cells due to kainic acid excitotoxicity or the ensuing sprouting of mossy fibers. The first effect is thought to lead to a selective denervation of the neurons that mediate granule cell inhibition (Fig. 9), thus increasing their excitability.[199] On the other hand, the newly formed recurrent mossy fiber collaterals could re-excite the dentate granule cells through newly formed synapses.[215] The role of these two putative epileptogenic mechanisms will be further discussed later.

Electrical-Stimulationâ€"Induced Focal Epilepsies

Self-Sustained Status Epilepticus

The possibility of eliciting epileptic manifestations by means of the repeated electrical stimulation of discrete regions of the central nervous system has been known since the nineteenth century following the experimental studies of Fritsch and Hitzig,[81] Ferrier,[73] and Luciani.[128] The analysis of the electrographic correlates of stimulation-induced seizures showed that the associated discharge may outlast the end of the stimulation train.[3] Although self-sustained, this electrically evoked afterdischarge is still a stimulation-dependent acute epileptic phenomenon. Later, Alonso-De Florida and Delgado[5] discovered that appropriate paradigms of repeated stimulation may induce permanent changes in excitability and lead to the recurrence of spontaneous seizures. Electrogenic models of SE are discussed later in the SE section.

Methods

The optimal stimuli for the production of afterdischarges are 4- to 6-second trains of repeated (25â€"60 Hz) 2.5- to 8.0-mA, 2- to 5-msec diphasic square pulses.[4] After a first effective train, a second afterdischarge can be obtained only after a delay of at least 15 seconds. Using more prolonged and/or intense stimulating trains, Lothman et al.[126] and Handforth and Ackermann[93] overcame this refractory period and reduced the intertrain interval to 0.5 second by using a protocol currently defined as â€œcontinuousâ€ hippocampal stimulation. Focal electrical stimulation has been found to be effective in all studied species, including humans. The greatest susceptibility is in the hippocampus and amygdala. All of the neocortical areas can generate afterdischarges, the most and least prone regions being the precentral motor area and the temporal gyri (Fig. 10).[4]

Neuropathology

By definition, afterdischarges are evoked in normal tissue, which should not be directly damaged by the stimulation procedure, provided appropriate parameters are used. However, Sloviter and Damiano[201] and Sloviter[198] found that indirect damage to hilar mossy cells can be induced by the stimulation of a perforant path capable of inducing repetitive discharges in their target granule cells, which innervate the hilar mossy cells themselves. In addition, there is evidence that, during repeated stimulation, use-dependent structural rearrangements of the involved neuronal network occur (e.g., mossy fiber sprouting) that are similar to those observed in other chronic models of hippocampal epilepsy.[17]

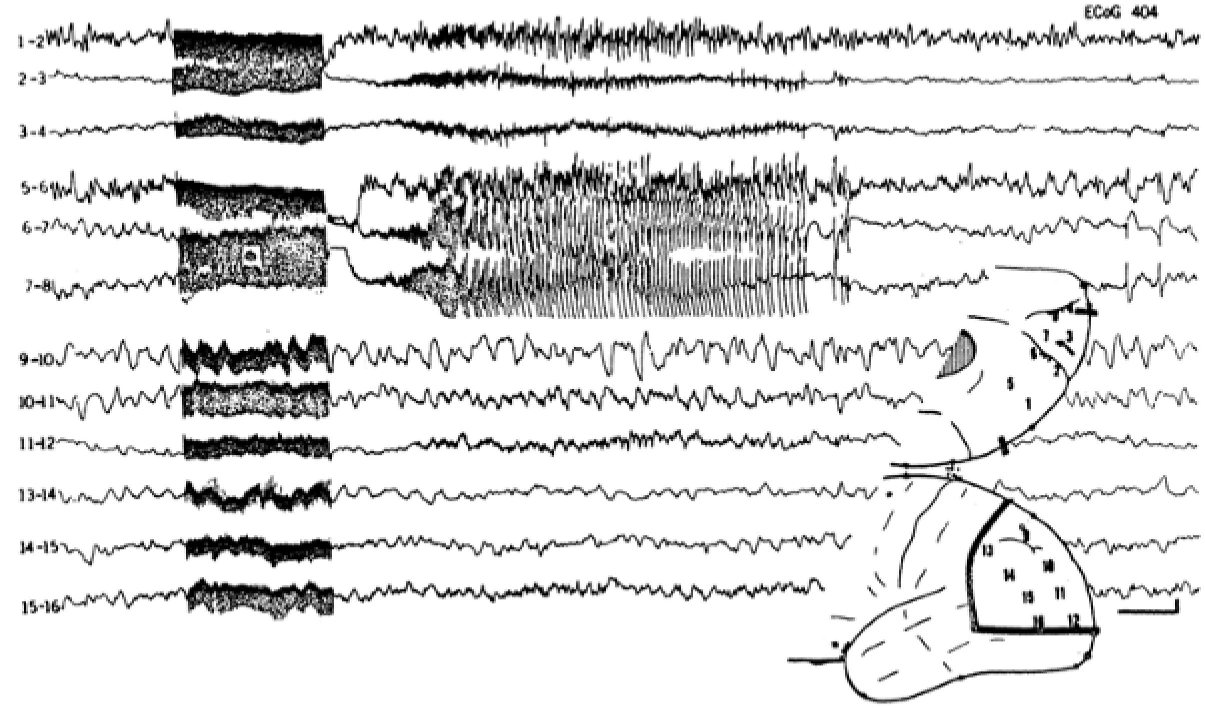


FIGURE 11. Electrocorticographic recording of a typical, relatively well-localized afterdischarge in an epileptic patient with surgical exposure of the occipital region, as indicated in brain outline with electrode position. The stimulation was delivered in the region indicated by the bent arrow. (From Ajmone Marsan C. Focal electrical stimulation. In: Purpura DP, Penry JK, Tower D, et al., eds. *Experimental Models of Epilepsy. A Manual for the Laboratory Worker*. New York: Raven Press; 1972:147â€“172; with permission.)

Natural History and Clinical Phenomenology

The stimulation-induced afterdischarge can be purely electrical or associated with clinical manifestations appropriate to the functional properties of the involved areas. Continuous hippocampal[124] or amygdala stimulation[93] leads to self-sustained epileptic states defined as â€œimmobile, exploratory, minor convulsive, and clonicâ€ according to a behavioral-electrographic hierarchy of severity.[94] After a latent period, as

with pilocarpine and kainic acid, animals exhibit spontaneous seizures.

Electroencephalogram

The electrographic activity characterizing typical afterdischarges becomes evident 1 to 2 seconds after the end of the stimulating train. It begins as 15- to 30-Hz low-voltage oscillations, which progressively increase in amplitude and decrease in frequency, leading to large voltage oscillations (Fig. 11). The episode lasts from 10 to 90 seconds and ends abruptly, giving way to a postictal depression lasting from 2 to 15 seconds.[4]

Pharmacology

The effect of antiepileptic drugs can be tested on the threshold or duration of the afterdischarge. Carbamazepine, phenobarbital, and diazepam, but not sodium valproate, ethosuximide, or phenytoin, have been found to be effective on the maximal dentate activation obtained by means of contralateral region stimulation.[209]

Pathophysiology

The self-sustained character of the afterdischarge has always been attributed to a failure in inhibitory mechanisms,[4] a view that was subsequently supported by the perforant path stimulation experiments of Sloviter and Damiano[201] and Sloviter.[198] The hyperexcitable state, leading to the facilitation of afterdischarges, electrogenic status epilepticus,[93,126] and, eventually, the epileptogenic process, is the result of complex changes involving cell excitability and circuitry rearrangements that are discussed for other models (see also next section on kindling).

Kindling

Although physiologic psychologists carrying out electrical stimulation studies in rats had noted for some time that a few eventually developed seizures, this was considered a nuisance because it disrupted their research paradigms. Goddard, however, recognized this to be an interesting phenomenon in itself and developed the concept of kindling.[90,91] Electrical kindling refers to the process of brief subthreshold brain stimulation that, when repeated, gradually results in ictal behaviors. Stimulation-induced seizures then persist indefinitely after the kindling process is discontinued. Electrical kindling, therefore, was an ideal mechanism for bringing the process of epileptogenesis under laboratory control, and it rapidly became the most commonly used animal model for studying basic mechanisms of epilepsy. Kindling as usually practiced, however, is not a model for chronic epilepsy because seizures do not occur spontaneously but need to be provoked by electrical stimulation. Although animals kindled for prolonged periods of time after maximal seizures occur eventually do develop spontaneous seizures,[165] this model of chronic epilepsy is rarely used because of the time required and the difficulty in maintaining viable animals. Consequently, although kindling remains a useful model for the study of epileptic phenomena, particularly with respect to the limbic system,[49,50,230,231,232,233,234] it has now been largely replaced by the excitotoxic and stimulation-induced self-sustained status epilepticus models that more faithfully

reproduce human mesial temporal lobe epilepsy with hippocampal sclerosis.

â€œChemical kindlingâ€ refers to the process of repeated treatments with chemoconvulsants such as metrazol or carbacol, which, like electrical kindling, eventually results in epileptic seizures in response to the chemical treatment.[87] Although chemical kindling presumably produces many of the same epileptogenic plastic changes induced by electrical kindling, the former models have been less well studied.

Methods

The classical kindling model involves electrical stimulation of the amygdala, although stimulation of hippocampus, piriform cortex, and other limbic structures results in the same epileptogenic phenomenology.[145] The time course of kindling differs depending on the site of stimulation, stimulus parameters, interstimulation intervals, and species. Kindling can also be achieved with stimulation of nonlimbic brain areas such as neocortex, thalamus, and caudate, but this is associated with a different behavioral evolution and less consistent progression than limbic kindling. Many other structures, such as brainstem and cerebellum, however, do not support kindling.

Typically, limbic kindling begins with a stimulus intensity that produces afterdischarge without behavioral effects. With repeated stimulation, the afterdischarge duration increases and ictal behaviors begin with arrest, ipsilateral eye blinking, and chewing (stage 1), followed over time by head bobbing (stage 2), then forelimb clonus (stage 3), rearing (stage 4), and falling with generalized tonicâ€“clonic movements (stage 5).[176] It is also possible to begin kindling with subthreshold stimulation intensity (below that necessary to induce afterdischarges), in which case repeated stimulation eventually produces afterdischarges, which then reiterate the electrographic and behavioral epileptogenic progression.[175] The usual stimulation parameters are 60 to 100 Hz delivered for 1 second, although slower frequencies and different durations are also effective. The time required for kindling to stage 5 depends on the area stimulated and the interval between stimulations. A typical paradigm involves stimulation for 1 second once a day, which requires approximately 2 weeks for amygdala kindling and 4 weeks for hippocampal kindling.

Neuropathology

Although limbic kindling is associated with mossy fiber sprouting, resembling this pathologic finding in human hippocampal sclerosis and chronic animal models of this disorder,[210] cell death, particularly in the dentate hilus, is minimal. Neurogenesis and astrocytic proliferations have also been reported, but there are no neuropathologic findings specific to kindling.[211]

Natural History and Clinical Phenomenology

Kindling is not a single phenomenon, but a series of phenomena that underlie a progressive epileptogenic process. With subthreshold kindling, for instance, there are changes that occur only at the tips of the stimulating electrodes that eventually result in the appearance of afterdischarge. As stimulation continues, or with classical kindling, the increase in duration of afterdischarge also involves epileptogenic plastic changes at the electrode tips, but most likely in surrounding tissue as well. The appearance of clinical signs reflects propagation of epileptiform afterdischarge to distant structures, requiring transsynaptic alterations. This process evolves to recruit primary motor cortex and other brain areas, eventually engaging brainstem systems responsible for tonicâ€“clonic seizures. The progressive transsynaptic recruitment is not merely a reflection of more intense afterdischarge at the electrode tips, but true synaptic plasticity, because stage 5 seizures, once achieved, almost always occur with any stimulation at the kindling site capable of inducing afterdischarge. Many widespread areas of the brain, therefore, develop an enduring epileptogenic potential with focal kindling. If kindling proceeds for months, spontaneous seizures eventually appear, and these typically do not originate at the site of kindling stimulation but from their efferent projection areas.[165]

Other enduring distant effects of kindling also occur. For instance, â€œtransferâ€ refers to the fact that whereas it may take 2 weeks of daily stimulation to reach a stage 5 seizure with unilateral amygdala kindling, stage 5 seizures can then be provoked with only a few stimulations of the contralateral amygdale.[144] On the other hand, contralateral kindling has an interhemispheric seizure-suppressing effect, in that it might take several additional days of stimulation to reestablish a stage 5 seizure with stimulation of the primary site.[144] Ipsilateral seizure facilitating and seizure-suppressing effects can also be demonstrated with electrical kindling. Other evidence of kindling-related seizure suppression also exists during the postictal period. There is a refractory period after kindled seizures during which time another stimulation will not generate a seizure. Animals that have been subjected to frequent seizures during a relatively short period of time develop postictal seizure refractoriness that can last weeks.[155] Investigations into this phenomenon could provide insights into natural homeostatic mechanisms that protect against recurrent seizures.

Neocortical, thalamic, and caudate kindling produces an entirely different epileptogenic progression. Rats do not go through the initial stages associated with limbic behaviors but eventually exhibit focal motor and generalized tonicâ€“clonic seizures. Whereas limbic kindling progresses consistently, once a stage is achieved, rarely does the animal backslide to a lower-stage seizure on the subsequent stimulation; backsliding is a common occurrence with neocortical, thalamic, and caudate kindling. Kindling-like phenomena can also be produced by stimulation of other subcortical structures such as nucleus accumbans, but these may not be epileptic behaviors.[207] Electrical kindling has been carried out in a variety of species, from frogs to primates.

In general, the higher the species is on the phylogenetic scale, the longer it takes to kindle. Genetic factors also appear to influence kindling rate; for instance, whereas it can take hundreds of stimulations to complete amygdala kindling in a rhesus monkey, it takes only about 70 in the *Papio papio* with genetic photosensitive epilepsy.[234]

The relationship of the various mechanisms of kindling to those of human epileptogenesis and seizure generation are unclear, but it is likely that kindling mechanisms (a) are involved in permitting subclinical electrical discharges eventually to manifest as behavioral seizures, (b) contribute to the progression of an epileptogenic abnormality, resulting in more frequent, more severe, and more pharmacoresistant seizures, (c) recruit distant structures in some forms of epilepsy, leading to secondary epileptogenesis (the development of new epileptogenic regions), and (d) induce enduring neuronal dysfunction, which could contribute to the appearance of interictal behavioral disturbances.

Electroencephalogram

As with human epilepsy, limbic kindling is associated with interictal EEG spikes that appear not only in the kindled limbic area, but also independently in other ipsilateral and contralateral limbic structures.[108] These interictal spikes appear early in the course of kindling and persist after stage 5 seizures occur. Interictal spikes are more common immediately following seizures, and there is some evidence that at least some types of postictal interictal spikes reflect mechanisms of seizure suppression.[70] Propagation of stimulation-induced ictal EEG discharges progressively recruits structures responsible for

behavioral manifestations, but there is no strict correlation between the duration of afterdischarge and the severity of the behavioral seizure. It is interesting that the very high frequency (200â€“600 Hz) oscillations associated with interictal spikes, termed Fast Ripples (FR), which in chronic animal models of mesial temporal lobe epilepsy and in the human disorder are believed to indicate tissue capable of generating spontaneous seizures, do not occur in kindled animals, perhaps because these models do not generate spontaneous seizures.[25]

Pharmacology

A number of studies over the years have been carried out to test the effectiveness of standard antiepileptic drugs as well as other compounds on kindling. It is of particular interest that drugs that are effective in preventing the development of kindling are not necessarily effective in preventing stimulation-induced seizures, whereas not all drugs effective in preventing stimulation-induced seizures disrupt the kindling process. This model, therefore, is capable of dissecting out antiepileptogenic versus anti-ictogenic properties of pharmacologic agents. Although kindling provides an effective model for screening potential antiepileptic compounds for antiepileptogenic and anti-ictogenic effects, it is much more labor intensive and expensive than the standard screening models of subcutaneous metrazol and maximal electroshock, and therefore it is rarely used. Recently, however, levetiracetam, which failed these two standard screening procedures, was tested and found to be effective against kindled seizures.[123] As a result, levetiracetam is now available as a highly effective agent against partial onset seizures.

An interesting phenomenon of contingent tolerance has been described whereby pretreatment with an effective anticonvulsant prior to, but not after, daily amygdala-kindled seizures results in a loss of efficacy.[169] Similarly, contingent inefficacy refers to the fact that pretreatment of an effective antiepileptic drug prior to daily stimulation during kindling results in the loss of effectiveness after kindling is achieved.[170] The mechanisms of contingent tolerance and inefficacy are unknown; however, they provide opportunities for studying neuronal processes underlying the development of pharmacoresistance and suggest that certain dosing schedules in patients may be counterproductive.

Chemical kindling can be achieved with a wide variety of chemical agents administered either intracerebrally or systemically.[87] Behavioral and electrographic features for most chemoconvulsants are similar to those of electrical limbic kindling, and once kindling is completed, the ability of subthreshold doses of chemoconvulsant to induce a stage 5 seizure is persistent. Reports of neuropathologic changes are variable. Crossovers among various chemoconvulsants as kindling agents, as well as between chemical and electrical kindling, suggest common mechanisms, although chemical kindling appears to involve much larger areas of the brain than localized electrical stimulation.

Pathophysiology

Although many investigations have been carried out to elucidate pathophysiologic mechanisms underlying kindling, no single underlying epileptogenic neuronal process has been revealed. This is undoubtedly due to the fact that kindling is not a unitary phenomenon but involves a great variety of alterations in cellular excitability, synaptic plasticity, neuronal loss, neurogenesis, glial proliferation, and synaptic reorganization, not only at the point of electrical stimulation for electrical kindling, but also transsynaptically in local and distant structures ultimately responsible for behavioral ictal manifestations, as well as related phenomena such as transference, the development of homeostatic seizure-protective mechanisms, and the generation of spontaneous seizures if kindling is continued. Specific fundamental neuronal mechanisms by which such changes occur are covered in more detail in other chapters in this section, and there is no indication that there are any unique to either electrical or chemical kindling.

Epileptogenic Dysplasia

The word â€œdysplasiaâ€ defines a tissue that has failed to develop perfectly during embryonic or fetal life as a result of genetic determinants[59,66] or pathogenic factors impairing the ordered sequence of maturational events, and it is known that dysplasias giving rise to macroscopic structural malformations that are clearly visible in neuroimaging studies are often associated with severe epilepsies.[13,60,163]

Genetically determined developmental brain abnormalities have been found in spontaneous mutant rodents such as dreher[189] and reeler mice,[36,71] and local[6] and bilateral subcortical neuronal heterotopias[115] have also been detected in some strains of genetically epilepsy-prone rodents. Animal models of cerebral dysplasia can also be obtained by means of embryonic exposure to physical (i.e., X-rays, freezing) or chemical teratogenic agents (e.g., ethanol, methylazoxymethanol) capable of killing neuroblasts and/or disarranging neuronâ€“glial relationships. Finally, targeted genetic manipulations can lead to a selective impairment of cortical development that may be associated with spontaneous seizures, as has been demonstrated by Acampora et al.[2] in a mouse model lacking the Otx1 gene.

However, it should be noted that most of the genetic and experimentally induced animal models of dysplasia do not present with obvious spontaneous epileptic seizures, which can only be induced by means of proconvulsant manipulations that are not effective (or significantly less effective) in control animals.

In this section, we concentrate on the models obtained by means of methylazoxymethanol (MAM), freezing, or the deletion of the orthodenticle gene (Otx1 $1^{-/-}$) and on TISH (telencephalic internal structural heterotopia) rats with laminar heterotopia.

Methylazoxymethanol Model

MAM is an alkylating agent extracted from the King Sago Palm *(Cycas revoluta)* that was found to induce cerebral dysplasia by Singh[197] and Johnston and Coyle.[107] It kills neuroblasts in mitotic phase, thus leading to a narrower and disarranged neocortical mantle. It also induces structural abnormalities of the radial glia that lead to the obstructed and misdirected migration of neocortical precursors that is responsible for subcortical heterotopias.

Methods

A single intraperitoneal injection of MAM 15 mg/kg administered to pregnant rats on embryonic day 15 (E15) regularly induces microcephaly, hippocampal heterotopias, and altered neocortical lamination in the offspring.[11,12,38,45,57,86,107,196] In addition, the double transplacental administration of MAM (15 mg/kg in the morning and, 12 hours later, the same dose injected intraperitoneally on E15) induces large heterotopic aggregates surrounding the ventricular floor (in continuity with hippocampal heterotopia) and large irregular neuronal clusters in the sensorimotor cortical area.[13,42]

Neuropathology

Morphologic analyses of MAM-treated rat neocortex show disrupted layering with evidence of a thick subpial band of heterotopic neurons in layer I. As observed in human

cortical dysplasia (see earlier discussion), the lateral somatosensory and auditory cortices contain clusters of enlarged cortical neurons positive for specific anti-SMI311 and anti-MAP2 antibody neuronal markers surrounded by a dense terminal network that is immunoreactive to antibodies against calbindin, a calcium-binding protein expressed by cortical interneurons.

The subcortical heterotopic nodules consist of normally differentiated cortical neurons randomly oriented within the nodule core with their major axis parallel to the edge of the nodule in the marginal zone. The nodule borders are characterized by a dense, GABA-positive network. In some animals, the periventricular nodules were in continuity with the overlying cortex, which was also characterized by a similar nodular structure or extended into the hippocampus and disrupted CA1 and CA2 layering.

Natural History and Clinical Phenomenology

The animals born of MAM-treated mothers show microcephaly, but postnatal developmental milestones (including eye opening, fur growth, sucking, ambulating, and grooming) are reached at the same age as controls. Spontaneous seizures and EEG changes indicating epileptic activities have never been reported, but there is evidence of increased susceptibility to epileptogenic agents or procedures such as fluorothyl,[11] hyperthermia,[86] kainic acid,[84] and kindling.[85]

Electroencephalogram

EEG monitoring reveals an increased delta frequency that positively correlates with the severity of the cortical disarrangement but no evidence of epileptiform activity.[85] Intracellular recordings from neurons located 350 to 550 Âµm below the surface of brain slices of dysplastic sensorimotor cortex show a slightly higher percentage of intrinsically bursting (IB) neurons than that found in layer V of untreated rat sensorimotor cortex.[182] Baraban and Schwartzkroin[11] reported a similar finding in the CA2 hippocampal region, with a definitely higher percentage of IB neurons in MAM-treated rats than in controls.

Aberrant firing patterns of repetitive bursts of action potentials, which gradually increase in duration and eventually merge in a long-lasting discharge, can be induced by both depolarizing current pulses[182] and an increase in extracellular K^+ concentrations.[11,12]

Pharmacology

There are no data concerning the effect of drugs on the seizures (because there are no spontaneous seizures) or susceptibility to epileptogenic agents.

Pathophysiology

The neurotoxic effect of MAM on dividing neuroblasts, which is due to the methylation of nucleic acids, affects the migrating neuronal progenitors and the radial glia along which they migrate. The results are cortical disarrangement and the formation of subcortical nodules consisting of heterotopic neurons that were originally committed to the neocortex but do not find a normally permissive environment for correct migration to their final destination.

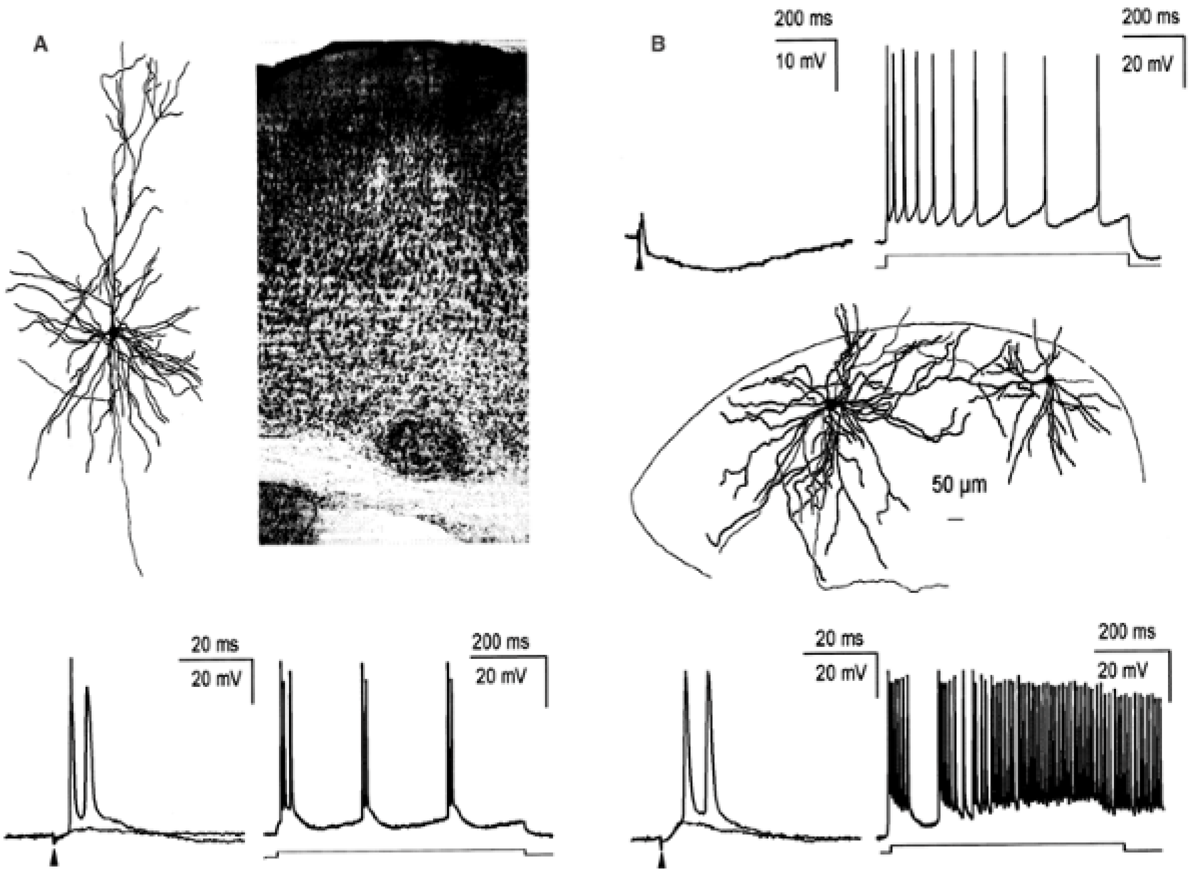


FIGURE 12. Pyramidal neurons recorded in dysplastic neocortex **(A)** and in periventricular heterotopia (PVH) **(B)** of MAM-treated rats. In panel A, the microphotograph of a thionin-counterstained slice shows abnormal neocortical layering and irregular neuronal clusters. The pyramidal neuron drawn on the left responded to both synaptic and direct activation with short burst firing. Panel B shows intracellular recordings from two PVH neurons. The left neuron shows normal responses to both synaptic and direct stimulations (*uppermost traces*), and the right neuron responds with a short burst to the synaptic activation and with an excessive bursting behavior to the direct stimulation with injection of a depolarizing pulse. (Modified from Sancini G, Franceschetti S, Battaglia G, et al. Dysplastic neocortex and subcortical heterotopias in methylazoxymethanol-treated rats: an intracelular study of identified pyramidal neurons. *Neurosci Lett*. 1998;246:181â€“185.)

Incoming inputs can affect the neurons in dysplastic neocortical areas, as well as those located in periventricular and parahippocampal heterotopias (Fig. 12). There is also evidence of reciprocal synaptic connections establishing aberrant cortico-subcortical circuitry[38,42,78,182] that is excessively susceptible to epileptogenic agents. The factors responsible for this greater susceptibility are the larger proportion of IB neurons and changes in intrinsic K^+ current-related properties,[11,182] and the possible influence of clustered GABAergic hyperinnervation should also be taken into account. The association of a smaller number of GABA-reactive neurons with a dense network of parvalbumin (PV)-immunoreactive terminals suggests that axonal sprouting of the PV-positive subpopulation of GABAergic neurons may take place during the development of MAM-treated rats. The expected functional consequence is a pacing effect due to the occurrence of highly synchronized inhibitory postsynaptic potentials in a large population of pyramidal neurons, which are then simultaneously released from inhibition and thus become prone to synchronous discharges.

Freezing-Induced Layered Microgyria in Rats

The word polymicrogyria indicates an excessive number of small and prominent convolutions separated by shallow and enlarged sulci, which give the cortical surface a lumpy appearance. Two types of polymicrogyria have been recognized: (a) unlayered polymicrogyria due to exogenous insults occurring between gestational weeks 13 and 18 or to genetic factors and (b) four-layered polymicrogyria due to a perfusion failure between gestational weeks 20 and 24. The perfusion failure causes laminar necrosis of the intermediate layers with a consequent late migration disorder and the postmigratory overturning of cortical organization. Human polymicrogyria is quite often associated with epileptic manifestations.

The application of a freeze probe to the skull of newborn rats generates a focal region of necrosis with a loss of deep layers whose basic structure is quite similar to that observed in four-layered human polymicrogyria.[62,63] The results of stimulation and lesion experiments suggest that aberrant development in the zone adjacent to the microgyrus underlies epileptogenesis.[174]

Methods

A freeze lesion is induced in rat pups 3 to 30 hours after birth by means of a freeze probe with a diameter of 1 mm to a few millimeters that is cooled to between -40Â°C and -70Â°C and applied to the skull for 3 to 8 seconds.[104,128] Neocortical slices for electrophysiologic recordings containing the lesion and the surrounding neocortex have been prepared from rats at postnatal ages ranging from 9 to 118 days.[104,128]

Neuropathology

A freeze lesion consists of an infolded cortex that creates a more or less deepening microsulcus and a surrounding mic-rogyrus that typically contains four distinguishable layers: The first and second correspond to the molecular and II/III layers of the adjacent neocortex, the third layer contains some glia and a few neurons, and the fourth layer partially corresponds to the VI layer of the adjacent neocortex (VIb).[104] The parvalbumin immunoreactive neurons normally concentrated in layers IV and Vb are completely absent in the microgyrus during the first 13 postnatal days but normalize after postnatal day 21.[179]

Natural History and Clinical Phenomenology

Scantlebury et al.[185] demonstrated increased susceptibility to hyperthermia-induced seizures in freeze-lesioned immature rats. Generalized, convulsive hyperthermic seizures were evoked by significantly lower temperatures in lesioned pups than in controls.

Electroencephalogram

No in vivo demonstration of spontaneous epileptic EEG abnormalities has been provided in rats with microgyrus, but the

ictal EEG correlates of hyperthermic seizures induced in freeze-lesioned rats show a topographic correlation between spike activity and the microgyrus.[185] In slice experiments, interictal-like epileptiform activity can be evoked from freeze-lesioned rats after postnatal day 12 and have been found until postnatal day 118, with a decreased incidence being observed after postnatal day 40 in rats lesioned on postnatal day 0 but not in those lesioned on postnatal day 1. Jacobs et al.[104] obtained evidence of decreased synaptic inhibition leading to local multiphasic epileptiform activity in neocortical areas closely surrounding the microgyri, and Luhmann and Raabe,[129] Luhmann et al.,[130] and Prince and Jacobs[175] reported similar results.

Pharmacology

The multiphasic discharges are reversibly blocked by NMDA-receptor antagonists in slices from both mature and immature freeze-lesioned rats, which suggest that they are attributable to disinhibited excitatory postsynaptic potentials mediated by the excitatory glutamate or aspartate amino acids.

Pathophysiology

Freezing interferes with cortical development through mechanisms similar to those responsible for human polymicrogyria because neuronal migration in rodents continues after birth until postnatal days 2 to 3.[187] It has been suggested that the basic mechanism supporting the increased seizure susceptibility is an imbalance between synaptically driven excitation and inhibition.[130] A number of observations suggest that aberrant synaptic connectivity develops in the rat cortex surrounding the microgyrus and causes a focal epileptogenic zone whose capacity to generate epileptiform activities does not depend on connections with the malformation itself because the evoked epileptiform activities in the paramicrogyral cortex remain unaltered if this zone is separated from the microgyrus by means of a transcortical cut in adjacent area. It has been hypothesized

that afferents originating from cortical and extracortical sites lose their targets in the region of the malformation but make appropriate laminar contacts in the cortex adjacent to the malformation and thus create an overabundance of excitatory inputs to this cortical zone. The resulting imbalance between the excitatory and inhibitory synaptic systems may be further aggravated by the loss of the parvalbumin-immunoreactive GABAergic neurons found in early developmental stages.

Otx1$^{-/-}$ Model

Mutations leading to the replication of body segments (a process called homeosis) were first observed in insects, and it has since been established that they affect a special category of genes that contain a DNA motif (or homeobox) coding for a 61â€“amino acid domain called the homeodomain. The proteins containing homeodomains act as activators or repressors of downstream target genes, thus controlling the development of body segments. The role of the Otx1 homeobox gene in mouse corticogenesis was investigated by Acampora et al.,[2] who confirmed that Otx1 is required for the development of the entire dorsal telencephalic cortex, has a more pronounced effect in the temporal and perirhinal areas, and may affect the mechanisms specifying neuronal identity. Moreover, Otx1-null mice exhibit epileptic seizures.

Methods

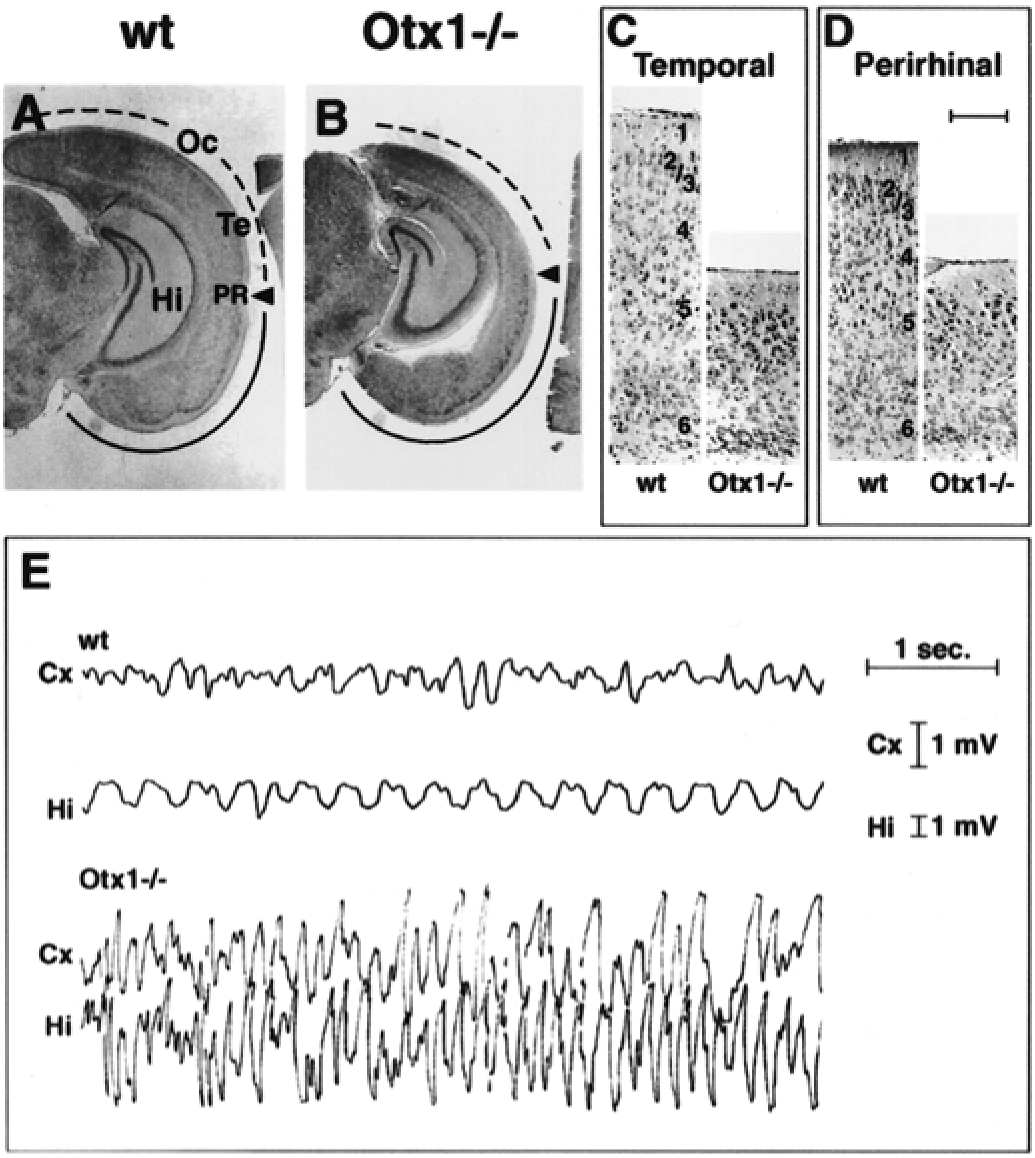
Otx1-knockout mice were generated by replacing the Otx1 gene with the *Escherichia coli* lacZ gene.[2] Heterozygous Otx1$^{+/-}$ mice are healthy and fertile, and their cross-breeding generated the homozygous mice Otx1$^{-/-}$, which are smaller and show epileptic manifestations; 30% die during the first postnatal month. Electrographic recordings from Otx1$^{-/-}$ mice have been made using screw electrodes over the occipital cortex and deep electrodes inserted in the hippocampus.[2] Intracellular recordings have been obtained from pyramidal neurons in neocortical slices prepared from Otx1$^{-/-}$ and control mice.[183]

Neuropathology

Gross examination of the brain reveals that the adult Otx1$^{-/-}$ mouse brain is about 25% lighter than that of heterozygous and wild-type mice. The overall thickness of the neocortex is reduced in the homozygous mutant, especially in the temporal and perirhinal areas, where the reduction may be as much as 40%. The sulcus rhinalis is displaced dorsally and the hippocampus is shrunken with a divarication of the dentate gyrus, whereas the volume of the colliculi is increased, and there is an additional protuberance between the superior and inferior colliculi. The cerebellar abnormalities include the presence of an additional lobule and a duplication of the rostral end of the declivus.[2] Morphologic analyses of Otx1$^{-/-}$ neocortex have shown that, despite their overall reduction in thickness, all of the cortical layers are recognizable; however, the cells appear to be more tightly packed in the mutant IV layer, whereas their density is clearly reduced in the V layer and particularly in the VA sublayer.[183] Outside of the central nervous system, Otx1$^{-/-}$ mice have no ciliary process in the eye, no lachrymal or Harderian glands, and no lateral semicircular duct in the inner ear.

Natural History and Clinical Phenomenology

Epileptic symptoms occur in all Otx1$^{-/-}$ mice but have never been observed in heterozygous Otx1$^{+/-}$ mice. The seizures are of two main types: (a) short, 30-second episodes of head bobbing and teeth chattering that may subside or evolve into (b) generalized seizures characterized by upper extremity clonus, rearing and falling, and convulsions that last for approximately 60 seconds with complete recovery or, occasionally, evolve into status epilepticus and exitus. The frequency of the seizures tends to be less in older Otx$^{-/-}$ mice, but they never disappear. In addition, Otx1$^{-/-}$ mice show nonepileptic turning behavior.


wt
Otx1-/-
A
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1
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Perirhinal
1
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4
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6
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Otx1-/-
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Cx
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Otx1-/-
Cx
Hi
1 sec.
Cx 1 mV
Hi 1 mV

FIGURE 13. Morphologic **(A, B)**, histologic **(C, D)**, and electroencephalographic (EEG) **(E)** comparison of wild-type (wt) and Otx$^{-/-}$ mice. Note the reduction of temporal (Te) perirhinal (PR) cortices and hippocampus (Hi) in Otx$^{-/-}$ mice. Representative EEG recordings from neocortex (Cx) and Hi during a convulsive seizure of Otx$^{-/-}$ mice is shown in panel E, where the EEG recording from a wild-type (wt) animal is shown for comparison. (From Acampora D, Barone P, Simeone A. Otx genes in corticogenesis and brain development. *Cereb Cortex.* 1999;9:533â€"542; with permission.) (See color insert.)

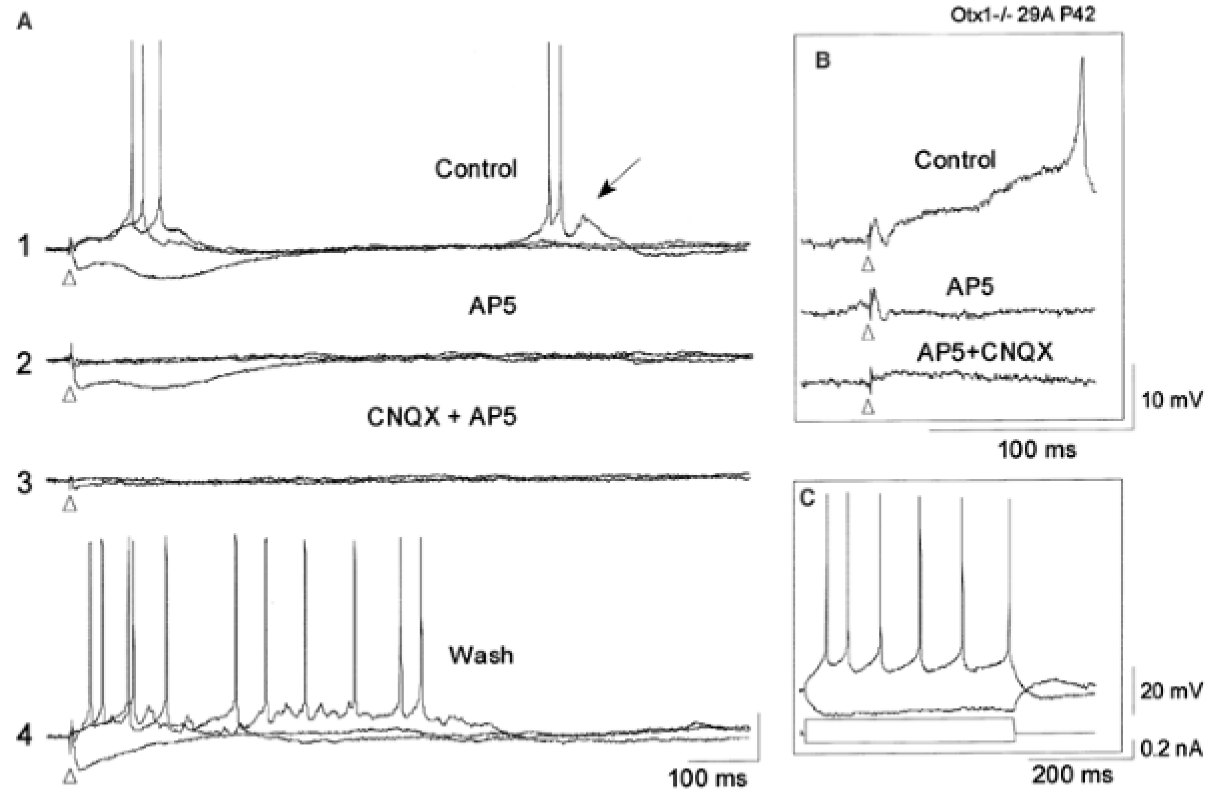

FIGURE 14. Recordings from an Otx1$^{+/Â±}$ pyramidal neuron. **A1:** Responses to two different stimulus intensities under control conditions. Note the postinhibitory depolarizing event reaching the threshold for action potential generation (*arrow*) that is abolished by the *N*-methyl-D-aspartate (NMDA) antagonist D-2-amino-5-phosphonovalerate (AP5) **(A2)**. **A3:** The addition of both AP5 and the Î±-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) antagonist 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX) led to an almost complete block of excitatory synaptic activity that was reversed after 20 minutes of washout **(A4)**. **B:** Magnification of the foremost segment of the same traces as in panels A1 to A3, showing more clearly the effect of AP5 and CNQX (the stimulus is marked by open triangles). **C:** Characterization of the tested neuron by means of low-amplitude depolarizing and hyperpolarizing current pulse injections. (From Sancini G, Franceschetti S, Lavazza T, et al. Potentially epileptogenic dysfunction of cortical NMDA- and GABA-mediated neurotransmission in Otx1$^{-/-}$ mice. *Eur J Neurosci*. 2001;14:1065â€“1074; with permission.)

Electroencephalogram

The â€œminorâ€ episodes are associated with high-voltage spikes in the hippocampus and some fast activity in the neocortex, thus suggesting that the epileptogenic discharges have a localized origin; the convulsive seizures correlate with high-voltage synchronized activity involving both the hippocampus and neocortex (Figs. 13 and 14). Electrophysiologic experiments on neocortical slices have revealed some important differences in synaptic activities, which are characterized by pronounced multisynaptic excitatory postsynaptic potentials often leading to late action potential generation and strong GABA$_A$- and GABA$_B$-mediated inhibitory postsynaptic potentials that have a pacing effect on pyramidal firing.[9] Both late excitatory postsynaptic potentials and postinhibitory excitation are selectively suppressed by NMDA-receptor antagonists but not by Î±-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) antagonists.[183]

Pharmacology

The effect of antiepileptic drugs on the seizures occurring in Otx1$^{-/-}$ animals has never been systematically tested.

Pathophysiology

The fact that the layer V neurons so far reconstructed from the mutants seem to be smaller than those of control animals suggests that neurons originally committed to the upper layers may not migrate properly but be stopped in the fifth layer, where they induce the reorganization of GABAergic circuitry.

On the basis of the foregoing data, it can be concluded that the abnormalities in $Otx1^{-/-}$ mice neocortex due to the selective loss of large projecting neurons lead to a complex rearrangement of local circuitry that is characterized by an excessive NMDA polysynaptic excitation that is counteracted by GABA-mediated inhibition in only a limited range of stimulus intensity. Prominent postsynaptic inhibitory potentials may also act as a further proepileptogenic event by synchronizing abnormal excitatory potentials.

Mutant Rats With Telencephalic Internal Structural Heterotopia

TISH rats are mutants presenting subcortical band heterotopia. They were identified by means of postmortem anatomic analyses during the course of unrelated experiments on Sprague Dawley rats by Lee et al.[116]: Spontaneous recurrent partial seizures with variable secondary generalization were present in some TISH rats.

Methods

A breeding colony was established by identifying the living relatives of deceased TISH individuals and screening them by means of magnetic resonance imaging.[116] Crosses between two affected animals produced 100% TISH progeny, whereas crosses between one affected and one unaffected animal produced no affected offspring, but their intercrossing produced 29% of affected offspring. The overall incidence of affected males and females was respectively 47% and 53%, which is

consistent with an autosomal-recessive pattern of inheritance of a single-gene defect.

Neuropathology

The brain of these mutants has a large region of heterotopic gray matter located bilaterally beneath the neocortex and extending from the frontal to the occipital lobe (Fig. 15). It is particularly prominent in the frontal and parietal cortices but is usually absent from the temporal cortex. The normotopic neocortex overlying the heterotopia is usually organized into six laminae (but thinner than in normal animals), whereas the heterotopia lacks precise lamination. Pyramidal neurons are present in both normo- and heterotopic cortices, but the apical dendrites in the latter are not consistently radially oriented and may even be inverted, and the dendrites near the edge of the heterotopic region often bend to follow the contour of the band. The heterotopia also contains nonpyramidal neurons (fusiform and stellate cells) lacking a regular tectonic organization. The normotopic cortex shows a normal laminar organization of the different cell types, but there are significantly fewer parvalbumin-positive interneurons (43% of those found in control neocortex), and the intensity of the parvalbumin plexus is likewise reduced in the neuropil of layer V.[24] Other laminar structures, such as the hippocampus and cerebellum, show a normal laminar pattern and do not contain heterotopic neurons.

Natural History and Clinical Phenomenology

Seizure activity was observed in several of the animals in the colony established in Charlottesville, Virginia, by Lee et al.[116] Chen et al.[37] made prolonged video-electrographic recordings lasting 4 to 6 months in a sample of animals and found that seizure frequency ranged from 1.5 to 15.1 events per week. The seizure phenomenology consists of twitching of the face and paws and turning to one side, occasionally followed by falling and convulsive activity; seizure duration is between 1 and 2 minutes. No seizures have been observed in animals younger than postnatal day 30.

Electroencephalogram

Electrographic recordings made using depth electrodes positioned bilaterally on both normotopic and heterotopic areas show that ictal spiking activity arises almost simultaneously in the normotopic and heteroptopic areas of one hemisphere and spreads rapidly to the homologous contralateral regions. Field potential recordings from in vitro slices bathed with epileptogenic agents show synchronous spiking activity in normo- and heterotopic areas. Making a cut between the two bands significantly decreases the threshold for epileptiform spiking in the normotopic area but significantly increases the threshold in the heterotopia. Patch-clamp recordings from identified pyramidal neurons show a consistent reduction in inhibitory postsynaptic current (IPSC) amplitude and frequency in both normo- and heterotopic cortical areas.[224]

Pharmacology

No data are available concerning the drug sensitivity of the seizures observed in TISH rats.

Pathophysiology

Injecting 5-bromo-2â€²-deoxyuridine (BrdU) to label cells in the S-phase in pregnant dams has demonstrated that the heterotopic neurons are generated during the normal period of cortical neurogenesis and that the inside-out pattern of neurogenesis is intact in the normotopic neocortex of TISH mutants.[115] Alterations in cell proliferation and migration are considered to be responsible for the TISH malformation.[115]

In relation to the mechanisms underlying epileptogenesis, electrophysiologic studies have shown that both normo- and heterotopic areas are involved in seizure activities, which are initiated by the normotopic cortex (see earlier discussion). Moreover, there is evidence that normotopic neurons have an excitatory synaptic influence on heterotopic neurons, which, conversely, have a net inhibitory effect on normotopic cortical cells. The results of Trotter et al.[224] discussed earlier provide evidence of a reduced synaptic inhibition of pyramidal neurons that may account for an epileptogenic increase in excitability.

Status Epilepticus

General Characteristics

A variety of chemical convulsants have been administered systemically to induce various forms of experimental status epilepticus (SE). Chemical convulsants used to induce experimental SE do so by either increasing neuronal excitation or decreasing neuronal inhibition. Experimental models based on systemic administration of chemical convulsants have the advantage of simplicityâ€”SE can be induced simply by parenteral administration of the convulsant agent. The disadvantage of such agents is their continuing presence once SE has been induced. Results may be confounded by the continuing presence of the inducing agent or by potential drug interactions between the inducing agent and an experimental therapeutic agent. Electrogenic models have the advantage that the status-inducing stimulus is eliminated once the stimulation has stopped, so that subsequent pathophysiologic changes or consequences of status epilepticus can be construed as being due to the seizure activity without the possible confounding effect of the initial stimulus. However, electrogenic models tend to be labor intensive, and thus do not lend themselves to large-scale studies.

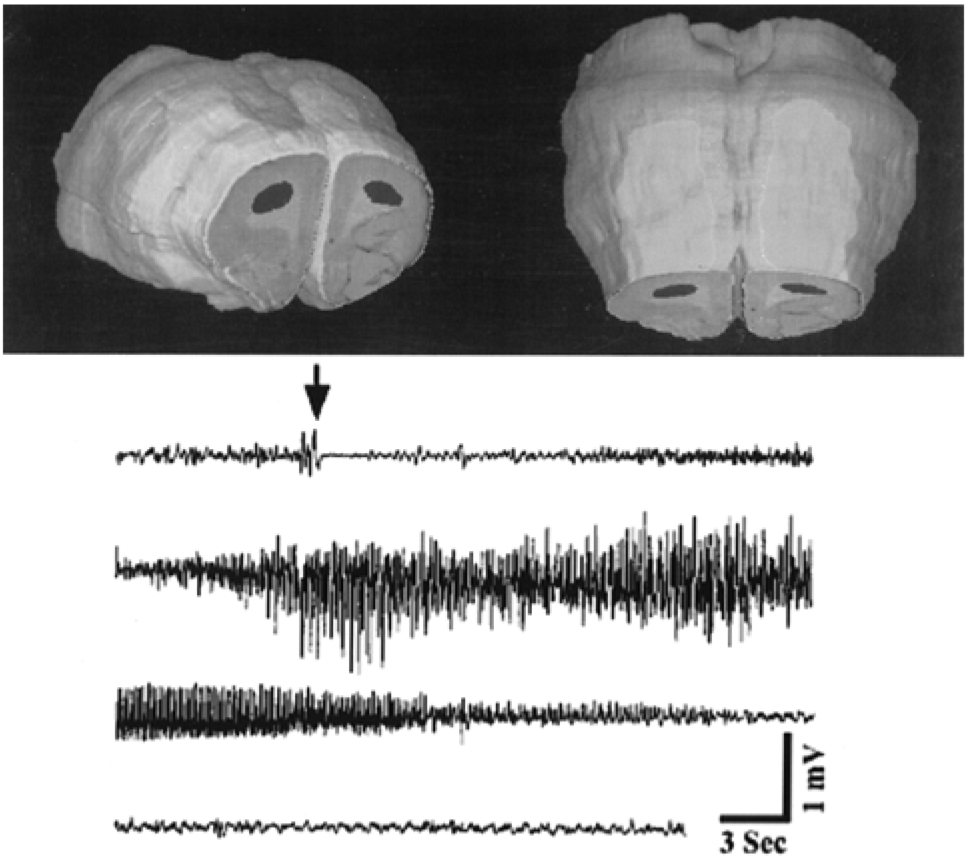

FIGURE 15. Top: Three-dimensional reconstruction of the telencephalic internal structural heterotopia (TISH) shown in red at the cut surface of the brain and in pink where it is viewed through the overlying cortex. **Bottom:** Electroencephalographic (EEG) recordings of a convulsive seizure in a TISH rat. The four lines show continuous EEG recording from a single electrode positioned in the normotopic neocortex (*arrow* indicates seizure onset). Seizure activity can be observed as changes in the frequency and amplitude of the EEG. (Modified from Lee KS, Schottler F, Collins JL, et al. A genetic animal model of human neocortical heterotopia associated with seizures. *J Neurosci*. 1997;17:6236â€“6242). (See color insert.)

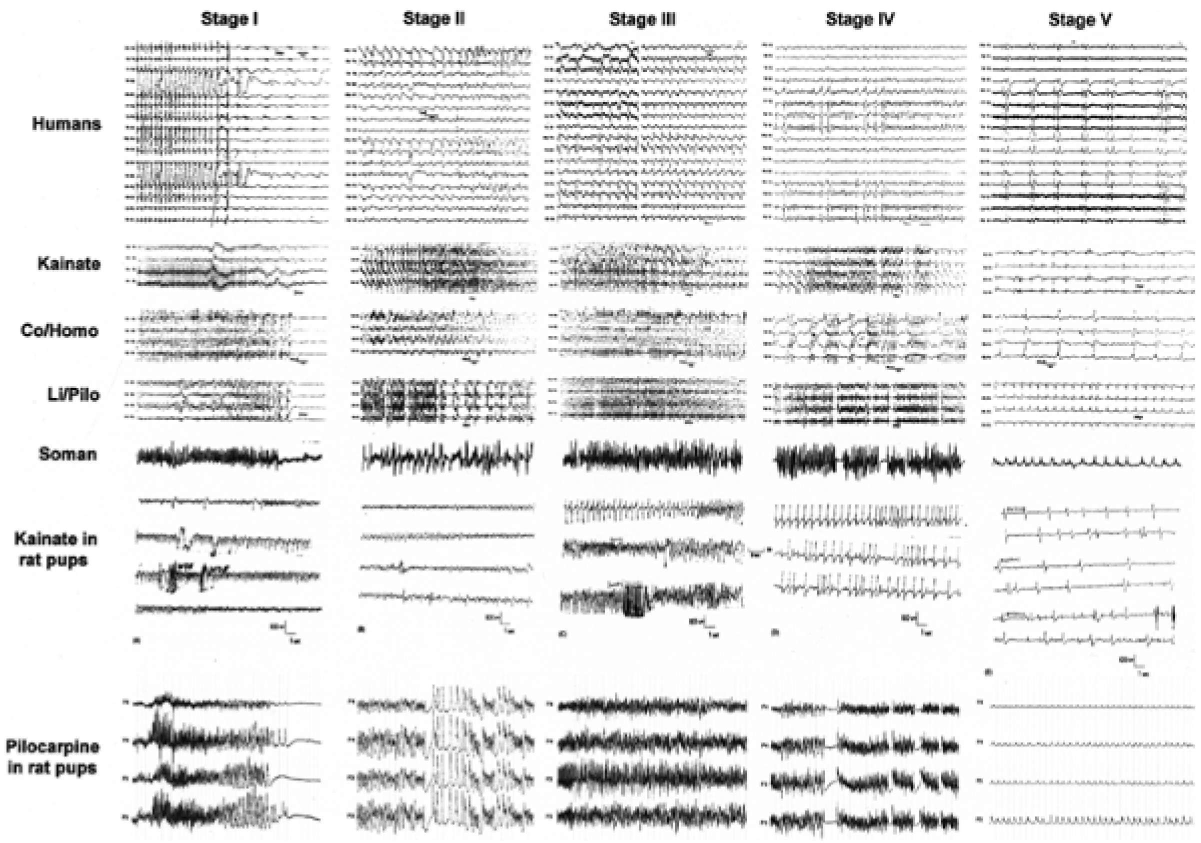

FIGURE 16. Examples of the five electroencephalographic (EEG) stages observed in human patients during generalized convulsive status epilepticus and in all animal models of experimental status epilepticus in which EEG changes over time have been systematically studied. The time required for initial appearance of epileptiform activity and for progression through the five stages varies with the model, as do details of the morphology of the ictal discharges. Nonetheless, the fundamental progression from discrete electrographic seizures (stage I), through the waxing and waning pattern (stage II), the continuous pattern (stage III), continuous ictal discharges punctuated by brief periods of relative flattening of the EEG (stage IV), to periodic epileptiform discharges on a relatively flat background (stage V) is seen in all models. See Table 1 for technical details. Co/Homo, cobalt/homocysteine; Li/Pilo, LiCl/pilocarpine.

Ictal Phenomenology

Most epileptic seizures last only from a few seconds to a few minutes. This is because seizure-terminating mechanisms operate during an isolated single seizure. A refractory period follows during which it is difficult to elicit a subsequent seizure. However, under some circumstances, the mechanisms responsible for seizure termination and the postictal refractory period fail, so that epileptic seizures recur before there has been complete recovery from the neurochemical and pathophysiologic consequences of the preceding seizure or persist beyond the usual, quite short, duration of individual seizures. This, in pathophysiologic terms, is the operational definition of SE,[218,219] whereas in clinical terms SE can be defined as â€œa condition in which epileptic seizures recur before there has been complete recovery from the consequences of the preceding seizure.â€[48,75]

Natural History

Status epilepticus is a surprisingly common[58,98] and potentially life-threatening medical emergency. There is increasing recognition that status epilepticus is a dynamic condition, with an evolution of clinical phenomenology, EEG changes, response to treatment, histopathologic changes, and behavioral consequences if it is untreated or inadequately treated.[218] Nonetheless, much remains to be learned about this disorder. The mechanisms of the transition from a single seizure to SE are not known. Our understanding of the pathophysiologic changes that cause SE to be progressively resistant to treatment is incomplete. We have only begun to understand the metabolic and pathologic consequences of sustained seizure activity; the time when permanent neuronal damage occurs during the course of SE is still not well worked out. Treatment of clinical SE is not always successful, and there remains a need for the development of more effective and less toxic drugs for this purpose. The potential role for neuroprotective agents in the clinical management of SE is unresolved, as is the cause of the differential susceptibility of young and adult brains to SE-induced neuronal damage.

Electroencephalogram

One of the major advances in the use of animal models of status epilepticus has been the recognition of a predictable sequence of electrographic changes that is common to patients experiencing generalized convulsive status epilepticus[221] and all experimental models of SE that have been carefully studied, including lithium/pilocarpine,[221,236] kainic acid in adult[221] and juvenile[153] rats, cobalt-homocysteine,[221,235] high-dose pilocarpine in adult[111] and juvenile[222] rats, three different electrogenic models,[93,95,126] soman in rats[115,140] and rhesus monkeys (McDonough, personal communication), and in an extended hippocampal slice model.[178] FIGURE 16 illustrates the sequence in a number of different models. Initially discrete electrographic seizures are seen, separated by interictal generalized slowing (stage I; Table 1). However, if the episode of SE is untreated or undertreated, the discrete seizures begin to merge together to produce a waxing and waning of amplitude, frequency, and distribution of the ictal discharges (stage II). Subsequently, the ictal discharges become continuous (stage III). This stage is usually prolonged, but eventually the continuous ictal discharges begin to be punctuated by periods of relative flattening (stage IV), which lengthen as the rhythmic ictal discharges shorten, until finally the record exhibits only periodic epileptiform discharges on a relatively flat background (stage V).

The fundamental sequence of patterns is always the same, although different models may exhibit differences in morphology within a specific stage (e.g., triphasic-like spike-wave patterns vs. rapid spiking in stage III, variable frequencies and morphologies of periodic epileptiform discharge [PEDs] in stage V), and different models may progress through the five patterns at different rates, just as has been observed in human generalized convulsive status epilepticus (GCSE) depending on the etiology of the episode of SE.

Table 1 Technical Details for the Five Electroencephalographic (EEG) Stages Illustrated in Figure 16

Model/EEG stage	Stage I	Stage II	Stage III	Stage IV	Stage V
Human[221]	39-yr-old male	64-yr-old male	68-yr-old male	68-yr-old male	64-yr-old male
Kainic acid (KA)[221]	26 m after KA	75 m after KA	103 m after KA	148 m after KA	5 hr 46 m after KA
Cobalt/homocysteine (HCT)[221]	30 m after HCT	37 m after HCT	48 m after HCT	75 m after HCT	2 hr 12 m after HCT

LiCl/Pilocarpine[221]	21 m after pilocarpine	24 m after pilocarpine	28 m after pilocarpine	109 m after pilocarpine	2 hr 19 m after pilocarpine
Soman[115]	Onset 3.1 Â± 0.5 m after soman	Onset 5.1 Â± 0.7 m after soman	Onset 19.3 Â± 3.3 m after soman	Onset 33.9 Â± 5.6 m after soman	Onset 231.4 Â± 9.5 m after soman
Kainate in rat pups[154]	P35 rat; mean onset 15 m (P15)/21 m (P35) after KA	P15 rat; mean onset 35 m (P15 and P35) after KA	P35 rat; mean onset 126 m (P15)/50 m (P35) after KA	P15 rat; mean onset 374 m (P15)/9 hr (P35) after kA	P35 rat; mean onset 10.25 hr (P15)/14.4 hr (P35) after KA
Pilocarpine in rat pups[222]	Onset 11.79 Â± 11.85 m after pilocarpine	Onset 22.78 Â± 22.11 m after pilocarpine	Onset 34.90 Â± 13.15 m after pilocarpine	Onset 61.64 Â± 21.76 m after pilocarpine	Onset 160.67 m after pilocarpine

Questions That Can Be Addressed by Animal Studies of Status Epilepticus

Experimental models have the potential of answering many of the questions posed earlier. Specifically, experimental models can be used to test drugs for the management of status epilepticus before they are tested in human clinical trials. Other questions that can be addressed using status epilepticus models include the reasons for other dynamic changes during status epilepticus, such as (a) the EEG changes discussed previously, (b) the progressive loss of motor activity as overt convulsive status epilepticus progresses to subtle and eventually nonconvulsive status, and (c) the progressively severe consequences of prolonged status epilepticus, including learning and memory deficits, neuronal damage at histology, and the development of chronic epilepsy. Models are now being used to understand the mechanisms that underlie the increasing refractoriness to treatment seen in human and experimental status epilepticus. Details of these studies are discussed in relation to the specific models described in what follows and in the chapter on generalized convulsive status epilepticus.

A number of experimental models of SE have been developed, including models in intact animals based on systemic and focal administration of chemical convulsants and focal and generalized electrical stimulation of the brain. More recently, some investigators have begun to study recurrent or sustained seizure activity in isolated neuronal circuits using slice preparations. The most useful and commonly used models of status epilepticus are discussed in what follows. Many of these models are also used for the induction of chronic epilepsy and are also discussed in the first section of this chapter. The discussion of the following models is focused on their use to further understand phenomenology and mechanisms of status epilepticus.

Bicuculline Model

Bicuculline is a highly potent alkaloid inhibitor of GABA-mediated neuronal inhibition[51,52] that has been used to induce experimental status epilepticus, initially by Meldrum and Horton in baboons.[150]

Methods

Bicuculline must be dissolved in a weak acid (0.1 N HCl) and then titrated with a weak base (0.1 N NaOH) to pH 5.6.[56] Bicuculline can be administered intraperitoneally (2â€“4 mg/kg for developing rats, 6â€“8 mg/kg for juveniles or adults)[228] or intravenously (2 mg/kg).[253]

Neuropathology

Meldrum and Brierley[149] described SE-induced ischemic-like neuronal damage in neocortex, cerebellum, and hippocampus in baboons. Similar but less severe changes were also seen in neocortex, thalamus, and hippocampus in paralyzed and mechanically ventilated baboons,[151] thus demonstrating that SE-induced neuronal damage is primarily due to ongoing seizure activity rather than to motor convulsions.

Natural History and Clinical Phenomenology

Meldrum and Horton[150] induced severe, generalized status epilepticus lasting up to 5 hours in adolescent baboons by injecting 0.4 to 1.4 mg/kg bicuculline intravenously. Seizures began with generalized myoclonic jerks that evolved within seconds to generalized flexor spasms. In rat pups, myoclonic seizures evolve to clonic and then clonicâ€“tonic seizures. After day 18, spike-wave discharges are seen, associated with motionless â€œfreezingâ€ of behavior.[253]

Electroencephalogram

A sequence of EEG changes, similar to those described by Treiman et al.[221] in generalized convulsive status epilepticus, can be observed in one figure in Meldrum and Horton's report, although the progressive nature of the EEG changes is not characterized in detail.

Pharmacology

Bicuculline-induced seizures respond readily to antiepileptic drugs, especially the benzodiazepines,[55] but the bicuculline model has not been used systematically to study potential anti-SE drugs. Peterson et al.[165] induced SE in rats pretreated with LiCl by focal injection of bicuculline methiodide into the deep prepiriform cortex. This procedure resulted in a model of SE that could be stopped with 5 mg/kg of diazepam, in contrast to the lithium-pilocarpine model.

Pathophysiology

Bicuculline induces seizures by competitive antagonism at the GABA_A receptor. More recently, blockade of K^+ channels and prolongation of Ca^{2+} action potentials has also been suggested as a possible mechanism of seizure induction by bicuculline.[190]

Cobalt-Homocysteine Model

Walton and Treiman[235] developed a model of secondarily generalized convulsive SE that closely approximates human GCSE in the natural history and characteristics of the induced seizures, the EEG changes, and the response to antistatus drugs. The model was specifically designed to test new agents for the treatment of GCSE, and a number of antiepileptic drugs have been studied in the model (see later discussion).

Methods

An epileptic lesion is created over the left motor cortex in adult male Sprague Dawley rats by placing 25 mg of powdered cobalt onto the dura when epidural screw electrodes are implanted. It is important to disrupt the dura and to pack the powdered cobalt into the screw well to reliably induce status epilepticus with the administration of the chemical convulsant, homocysteine thiolactone. When the lesion becomes electrographically active with brief focal ictal discharges and the rat is exhibiting intermittent focal motor seizures, usually about 7 days after surgery, SE is induced by intraperitoneal administration of 5.5 mmol/kg

D,L-homocysteine thiolactone.

Neuropathology

The necrotic cobalt lesion can been seen on gross inspection of the intact brain, and a profound area of encephalomalacia is

observable on histologic sections. However, the pathologic consequences of cobalt-homocysteineâ€“induced SE have not been reported.

Table 2 A comparison of the serum concentration produced by the median effective dose (ED_{50}) for control of generalized tonicâ€“clonic seizures (GTCS) in the cobalt/homocysteine secondarily generalized convulsive status epilepticus model with serum concentrations of the same drugs that have been reported to be clinically effective

Drug	Serum concentration produced by ED_{50} vs. GTCS	Serum concentration reported to be clinically effective
Phenytoin	26.2 mg/mL	23.8 Âµg/mL
Diazepam	168 ng/mL	30â€“80 ng/mL 30â€“200 ng/mL
Phenobarbital	12.8 mg/mL	8.4 Âµg/mL 18.3 Âµg/mL
Lorazepam	196 ng/mL	30â€“160 ng/mL 70â€“330 ng/mL

Modified from Walton and Treiman.[244]

Natural History and Clinical Phenomenology

Status epilepticus in this model resembles human secondarily generalized tonicâ€“clonic SE behaviorally,[235] electrically,[221,235] and pharmacologically[235,244] (Table 2), and thus fulfills criteria proposed by Walton and Treiman[235] for an ideal model of SE: (a) induced seizures should be similar in appearance to those seen in human SE, (b) electrographic patterns seen should also be like those seen in human SE, and (c) the induced SE should be responsive to the same drugs used in treating human SE. In the initial description of this model, a mean of 18.3 convulsions occurred over a mean time of 103.8 minutes after injection of homocysteine. Initially, the seizures are true, focal-onset, secondarily generalized tonicâ€“clonic seizures. However, as SE continues over many convulsions, the seizures alter in appearance and may become prominent on only one side of the body or exhibit only subtle manifestations, as has been described in humans.[218]

Electroencephalogram

SE is induced when brief focal runs of spikes with phase reversal around the left frontal electrode (the cobalt site) are evident on the EEG. Ten to fifteen minutes after homocysteine injection, these epileptiform discharges increase in amplitude, frequency, and distribution until a generalized convulsion occurs about 20 to 30 minutes after injection. Over the next 90 minutes, the EEG progresses through the five EEG stages described by Treiman et al.[221] and illustrated in FIGURE 16, although not all animals exhibit the full progression and some die before reaching stage V.

Pharmacology

Walton and Treiman[244] validated this model's ability to predict clinical effectiveness of a putative anti-SE drug by demonstrating that serum concentrations of diazepam,[235] lorazepam,[239] phenytoin,[246] and phenobarbital[237] effective at stopping generalized convulsions in this model closely approximate serum concentrations of these drugs reported to be effective in human GCSE. Subsequently, they used this model to evaluate the potential usefulness for the treatment of GCSE of other marketed and experimental antiepileptic drugs, including valproic acid,[241] tiagabine,[245] fosphenytoin,[238] NPC-17742,[242] lamotrigine,[246] and remacemide.[243]

Pathophysiology

For at least three decades, cobalt has been known to induce focal onset seizures.[43] However, the mechanism of seizure induction by cobalt remains unknown. Homocysteine appears to be an NMDA agonist, and thus the mechanism whereby homocysteine induces seizures is most likely by activation of excitatory amino acid receptors.[79]

Flurothyl Model

Flurothyl (bis-2,2,2-triflurothyl ether) is a convulsant gas[225] that has been used by a number of investigators to induce experimental status epilepticus.

Methods

Nevander et al.[159] developed a model of SE to study the effect of SE on neuronal necrosis. They induced continuous seizure activity in anesthetized (60% nitrous oxide/40% oxygen), paralyzed, mechanically ventilated rats by injecting 80 ÂµL of flurothyl directly into the rebreathing system. Additional boluses of flurothyl were used to maintain a burst-suppression pattern on the EEG during the seizure period. When flurothyl was discontinued after 15 minutes, seizure activity resolved spontaneously; a single dose of intravenous thiopental, 15 mg/kg, also arrested seizure activity. Acute seizures and SE have also been produced in initially awake, freely moving rats by dripping liquid flurothyl (1.2â€“3 mL/hr) onto filter paper suspended in a closed plastic box[252] or infusing 20 ÂµL/min into an airtight chamber. Immature rats can survive 60 minutes of such repetitive seizures without mechanical ventilation; adult rats cannot.[103,202,215]

Neuropathology

Nevander et al.[159] observed that infarction of the pars reticulata of the substantia nigra occurred in five of the six animals with seizure duration of 30 minutes and in all animals with longer seizure durations when brains were examined for histologic damage 1 week after the episode of SE. The central part of the globus pallidus was also commonly affected. Neocortical, amygdaloid, thalamic nuclear, and hippocampal pyramidal cell damage was seen in SE of longer duration. However, Sperber and Moshe[205] found no evidence of flurothyl SE-induced histologic damage when SE was induced in 14-day-old rats, suggesting that in this model, as well as others, SE-induced neuronal damage is age dependent.

Natural History and Clinical Phenomenology

The behavioral characteristics of flurothyl-induced seizures are age specific.[206] Swimming movements and tonic posturing are seen during the first week, and clonic seizures developed after P10, initially preceded by a few myoclonic jerks and then evolving into a clonicâ€“tonic seizure. By the third postnatal week, episodes of motionless staring associated with spike-wave discharges are seen. These seizures have been suggested as a model of absence seizures and the clonic and tonicâ€"clonic seizures as models of primarily generalized convulsive seizures. In adult rats, early seizures during flurothyl exposure are similar to those seen in P14 rats: myoclonic, then clonic, then tonicâ€"clonic seizures. However, because freely moving, nonventilated adult

rats cannot be kept alive during flurothyl-induced status epilepticus, there are no descriptions of the evolution of behavioral changes during status epilepticus in adult rats.

Electroencephalogram

Sperber and Moshe[205] reported discrete electrographic seizures initially, followed by a waxing and waning of seizure discharges throughout the 60 minutes of EEG recording during flurothyl-induced status epilepticus in rat pups. These descriptions correspond to what Treiman et al.[221] labeled SE EEG stages I and II. However, EEG recordings were not continued long enough in Sperber's studies to determine whether the pups would have exhibited SE EEG stages III to V. EEG changes during flurothyl-induced SE have not been described in adult rats.

Pharmacology

No pharmacologic studies have been reported using flurothyl-induced experimental status epilepticus.

Pathophysiology

Woodbury suggested that flurothyl induces seizures by opening sodium channels in neuronal membranes.[250a] More recently, antagonism of GABA-mediated inhibition[7] and activation of cholinergic transmission[65] have been proposed as possible mechanisms.

Kainic Acid Model

Kainic acid is a potent agonist for the AMPA/kainate subtype of ionotropic glutamate receptor that has been used extensively to induce status epilepticus as a means of generating a model of chronic epilepsy. Thus this model is discussed in detail earlier in this chapter. The model has not been nearly as popular for the specific study of status epilepticus. Nonetheless, it has certain advantages for this purpose, which are discussed here.

Methods

Kainic acid (KA) usually is dissolved in phosphate-buffered saline and administered intraperitoneally. Doses in the rat are age and strain dependent.[207] For rat pups, 1 to 8 mg/kg may be sufficient to induce SE; for adults, 8 to 15 mg/kg is usually necessary. The model has a relatively low efficiency. Status induction is frequently inconsistent, and acute mortality may be high. For this reason, some have advocated multiple repeated small doses tailored to the individual rat.[101,148] Focal onset SE can also be induced by direct injection of 0.4 to 1.6 Âµg into the amygdala or hippocampus.[18] It is important to use fresh kainic acid because of a loss of potency over time, which may result in high mortality when the bottle is first opened and low efficacy subsequently. Furthermore, kainic acid has been difficult to obtain at times, and is currently very expensive.

Neuropathology

See the section under chronic models for a discussion of status-induced chronic pathology. There have been no studies of the time course of neuropathologic changes during kainate-induced experimental status epilepticus.

Natural History and Clinical Phenomenology

See the section under chronic models for a discussion of the natural history and behavioral changes during kainate-induced status.

Electroencephalogram

Experimental status epilepticus induced by kainic acid injection in adult rats results in the same sequence of EEG changes originally described by Treiman et al.[221] However, in the kainic acid model, 5 to 6 hours are necessary to progress to stage V. This is similar to the time course reported for soman-induced SE, and contrasts with the 2 to 2Â½ hours required to reach stage V in the cobalt-homocysteine and lithium/pilocarpine models of experimental status epilepticus.

Pharmacology

Several compounds have been studied for their efficacy at suppressing kainate-induced status epilepticus. Nefiracetam (100 mg/kg intravenously) suppressed focal seizures induced by focal infusion of kainate into the amygdala.[97] Zonisamide (100 mg/kg intravenously) only suppressed seizure spread but not the epileptic focus.[214] MK801 [(+)-5-methyl-10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-5,10-imine] is anticonvulsant against KA-induced seizures in adult rats: It reduces their severity and protects against neuronal damage, although it may worsen electrographic seizures.[22,41,72,117] A similar effect of MK801 has been reported in lithium/pilocarpine-induced late SE.[240] In neonatal rats (P11â€“P12) pretreated with MK801, there is prevention of neither seizures nor KA-induced death.[208] Pretreatment with neuroactive steroids[113] or vigabatrin[92] prevents the development of status epilepticus, but these drugs have not been tested against ongoing SE.

Pathophysiology

Acute seizures in this model of status epilepticus are presumably due to the direct excitatory effects of kainate on AMPA/KA-type glutamate receptors, which are of greatest abundance in the hippocampus, amygdala, perirhinal cortex, and entorhinal cortex.[155]

Lithium/Pilocarpine and High-Dose Pilocarpine Models

Pilocarpine- and lithium/pilocarpine-induced SE has been used both to create models of chronic epilepsy and specifically to study various aspects of status epilepticus. Many features of the model are discussed earlier in this chapter; here we focus on elements specific to their role as SE models. Lithium/pilocarpine-induced SE is almost uniformly fatal within 24 hours and can be viewed as an experimental model of a severe form of generalized convulsive SE, perhaps approximating the clinical condition when GCSE develops as a complication of a severe systemic illness or generalized encephalopathy in patients without a prior history of epilepsy.

Methods

Status epilepticus can be induced by the intraperitoneal administration of 300 to 400 mg/kg pilocarpine (usually preceded by scopolamine 1 mg/kg given subcutaneously 30 minutes before pilocarpine to minimize peripheral cholinergic effects). Peripheral cholinergic effects can also be reduced by administering lithium chloride (3 mEq/kg) 24 hours before SE induction. With LiCl pretreatment, 20 to 30 mg/kg pilocarpine intraperitoneally is sufficient to induce SE. There is a high mortality rate, especially with lithium/pilocarpine administration, which can be largely eliminated by giving 10 mg/kg acepromazine 1 hour after the pilocarpine injection.

Neuropathology

Neuropathologic changes following pilocarpine-induced status epilepticus in the rat have been reviewed in detail by Turski et al.[226] and are summarized in the discussion of chronic models. Fujikawa[82] studied the relationship between duration of lithium/pilocarpine-induced SE and the extent and severity of pathologic changes and observed progressively severe and increasingly widespread neuropathologic changes during the initial 3 hours of the SE episode.

Natural History and Clinical Manifestations

The temporal evolution of pilocarpine-induced behavioral changes and of seizure activity is discussed earlier in this chapter. Age-related deficits in visual-spatial learning after prolonged lithium/pilocarpine-induced SE have been reported by Holmes and colleagues,[39] which, it is interesting to note, can be improved by enriched environments.[182] Marsh et al.[131] recently showed that the degree of impairment of visual-spatial learning and memory in adult rats is predicted by the EEG stage at which SE is stopped. SE that progresses to EEG stage IV or V results in profound deficits in both memory and learning when tested in the Morris water maze.

Electroencephalogram

The progressive sequence of five EEG stages originally reported by Treiman et al.,[221] which was described in detail earlier, has been observed in lithium/pilocarpine-induced SE in adult rats[221,236] and in pilocarpine-induced SE in adult[111] and juvenile[222] rats. The initial seizure activity on the EEG is seen about 20 minutes after pilocarpine injection, and stage V is reached in about 2 hours.

Pharmacology

Diazepam (5â€“10 mg/kg) is effective at stopping early lithium/pilocarpine-induced SE.[236] A cocktail of diazepam, 10 mg/kg, and phenobarbital, 25 mg/kg, can stop later SE at some stages, but is not always effective unless combined with isoflurane. Pilocarpine models of SE have not been used systematically to study pharmacotherapy of status epilepticus. The seizures are too severe and pharmacoresistant to be useful for predicting efficacy of antistatus drugs for the initial treatment of generalized convulsive status epilepticus, but they may be useful as a model for the development of drugs for the treatment of refractory status epilepticus in humans.

Pathophysiology

Pilocarpine is a muscarinic acetylcholine receptor agonist and, like acetylcholine esterase inhibitors, induces status epilepticus by its initial excitatory role. However, the inability of anticholinergic agents, such as atropine, to stop ongoing pilocarpine-induced SE suggests the recruitment of other excitatory mechanisms, so that the episode of SE becomes self-sustaining. The mechanism whereby pretreatment with lithium markedly reduces the dose of pilocarpine necessary to induce SE is not known.

Soman and Other Cholinesterase Inhibitor (Nerve Agent) Models

Soman (pinacolyl methylphosphonofluoridate) is an organo-phosphorus cholinesterase inhibitor nerve agent that causes peripheral signs of cholinergic poisoning, convulsions, central neuronal damage, respiratory arrest, and death.[44,88,147] Soman and other organophosphorus agents have been studied extensively by military research facilities because of the potential of these agents to be used in warfare or terrorist attacks.

Methods

Almost all studies of these agents have been done with rats, guinea pigs, or rhesus monkeys, and most have been conducted by military investigators. Agents studied include tabun, cyclosarin, sarin, soman, VR, and VX. Median lethal doses (LD_{50}) range from 8 to 300 Âµg/kg, depending on the agent and the species in which it is studied.[192,193,194] Administration is usually subcutaneous.[193] In pharmacologic studies, guinea pigs are usually pretreated with pyridostigmine Br (0.026 mg/kg, intramuscularly) and 30 minutes later challenged with two times the LD_{50} of the test agent, followed 1 minute later by treatment with atropine SO4 (2 mg/kg, intramuscularly) and pralidoxime chloride (2-PAM Cl; 25 mg/kg, intramuscularly).[143]

Neuropathology

After early seizures in organophosphorus-induced status epilepticus, when anticholinergics readily terminate seizures, no neuropathology is evident. However, if the seizures are not stopped early, anticholinergics become less effective, and mild neuropathology is occasionally observed. With prolonged epileptiform activity, neuropathologic changes are observed in multiple brain regions, probably due to excessive influx of calcium due to repeated seizure-induced depolarization and prolonged stimulation of NMDA receptors, as seen in other models of prolonged status epilepticus.[141]

Natural History and Clinical Phenomenology

The initial behavioral change after soman administration is purposeless chewing, followed by head tremor and then lordosis-like posturing. Seizure activity begins with rhythmic movement of the ears and facial musculature and sometimes forepaw clonus, and sometimes progresses to class IV limbic seizures.[140]

Electroencephalogram

Koplovitz and Skvorak[115] reported the same sequence of five progressive EEG changes during soman-induced experimental status epilepticus in the rat that Treiman et al.[221] initially described in humans and three experimental models of SE in the rat; they pointed out that McDonough and Shih[141] had previously described EEG changes corresponding to stages I, III, IV, and V in soman-intoxicated rats. McDonough has also observed a similar sequence of EEG changes following soman administration to rhesus monkeys (J. H. McDonough Jr., personal communication). In the Koplovitz and Skvorak study,[115] the mean time of onset of stage I after soman administration (180 Âµg/kg subcutaneously) was 3.1 minutes, and it was 231.4 minutes for stage V.

Pharmacology

Diazepam can block soman-induced convulsions, electrographic seizure activity, and neuronal damage.[99,120,132,142] Soman has been used to induce experimental SE in guinea pigs to test the ability of the anticholinergic agent scopolamine[31] and the noncompetitive NMDA-receptor blocker dizocilpine (MK-801)[204] to prevent or arrest seizure activity and thus to prevent neuronal necrosis. The dose of atropine can significantly affect the toxicity of the nerve agent and the efficacy of anticonvulsants.[195]

Pathophysiology

Organophosphorus agents are potent irreversible inhibitors of acetylcholine esterase, the enzyme responsible for degradation

of acetylcholine. Inhibition of acetylcholine esterase increases the availability of acetylcholine at all subtypes of acetylcholine receptors. Elevated acetylcholine levels in brain can be detected as early as 3 minutes after soman administration.[191] McDonough and Shih[141] proposed a three-phase â€œmodelâ€ of the neuropharmacologic processes responsible for the seizures and neuropathology produced by nerve agent intoxication. Initiation and early expression of the seizures are cholinergic phenomena. If not checked, a transition phase occurs during which the neuronal excitation of the seizure per se perturbs other neurotransmitter systems. With prolonged epileptiform activity, the seizure enters a predominantly noncholinergic phase and becomes progressively refractory to all pharmacologic treatment, as is seen in other models of status epilepticus.

Electrogenic Models

Electrogenic models of SE have the advantage that the inducing stimulus immediately ceases when the electrical stimulation is stopped. Thus, response to drug therapy and evaluation of effects of status are not compromised by an ongoing exogenous stimulus.

Although several investigators had used repeated electroconvulsive shocks to produce prolonged seizure activity to study metabolic and biochemical consequences of prolonged seizures and SE,[61,248,249] the first electrogenic models of self-sustaining SE were an outgrowth of kindling studies. Following Goddard's[90] initial description of the kindling phenomenon, Pinel and Van Oot[167] demonstrated that SE could be produced in rats when kindling stimuli were administered over several months. Subsequently, Taber et al.[213] found that by using an interstimulus interval of 1 minute applied to hippocampal electrodes they could produce long-term, self-sustained, limbic or generalized SE in mice and subsequent deficits in an inhibitory avoidance task. McIntyre et al.[146] used a kindling-based electrical stimulation model of SE in the rat to study the pathologic consequences of partial-onset SE induced by 60 minutes of continuous electrical stimulation of the amygdala. The extent of pathologic change was determined by the duration of the episode of SE. Untreated rats showed massive gliosis and neuronal degeneration of the ipsilateral hemisphere; barbiturate-treated rats demonstrated less pathology. Sloviter and colleagues[161,198,201] used electrical stimulation of the perforant pathway (the main excitatory pathway to the hippocampus) to replicate limbic SE and study seizure-induced neuronal damage independent of the metabolic effects associated with generalized convulsions. Sloviter[199] demonstrated a persistent loss of recurrent inhibition and irreversibly damaged adjacent interneurons following granule cell seizure activity. GABA-containing neurons survived, but there was a profound loss of adjacent somatostatin-containing interneurons and mossy cells, thus suggesting that seizure-induced loss of a basket cellâ€“activating system may cause disinhibition. Vicedomini and Nadler[229] also used stimulation of hippocampal afferent pathways to study the effects of prolonged seizure activity. They used a stimulus current administered through electrodes implanted in the angular bundle or fimbria to induce self-sustaining seizure activity that persisted after cessation of the electrical stimulation. In this model, the development of self-sustained seizure activity was essential for the production of neuronal damage: As little as 17 minutes of self-sustained seizure activity was sufficient to cause at least some neuronal loss, whereas as many as 759 stimulus trains (2.1 hours of evoked synaptic activity) produced no evidence of neuronal degeneration. EEG changes suggestive of a waxing and waning pattern (stage II) and of periodic epileptiform discharges (stage V) are illustrated in the description of this model, but whether continuous ictal discharges with or without flat periods (stages III and IV), as described in other models,[95,221] occurred with this model cannot be determined from the data provided. Lothman and colleagues,[125] on the other hand, described a model of self-sustained limbic SE that did exhibit the progressive EEG changes originally reported by Treiman et al.[220,221] In this model, as little as 30 minutes of continuous focal electrical stimulation of the hippocampus elicited self-sustaining SE that persisted for many hours after discontinuing the electrical stimulation. Subsequently, Bertram and colleagues,[23,171] using this model, noted that rats that progressed to stage V (periodic epileptiform discharges) were likely to develop chronic epilepsy, whereas animals in which SE stopped by early in stage III were not.

Cain et al.[30] also used a continuous stimulation paradigm as a simple and rapid procedure to induce limbic SE. These investigators administered 3-Hz biphasic square wave pulses via an electrode placed in the amygdala to reliably induce SE in almost all rats studied.

Almost all electrogenic models of self-sustained SE have resulted in limbic seizures, although occasional generalized convulsions are sometimes observed. However, Handforth and Treiman[95] described a nonpharmacologic model of limb clonic convulsions in the rat. Status epilepticus was induced by pulsed trains of suprathreshold electric current administered bilaterally to one of four forebrain sites: (a) orbital cortex, (b) medial prefrontal cortex, (c) deep prepiriform cortex, or (d) rostral caudate-putamen. Phenobarbital at very high serum concentrations stopped behavioral and electrical seizure activity; phenytoin, even at extremely high concentrations, did not. Handforth and Treiman[95] thus suggested this model for evaluation of the mechanisms and treatment of refractory SE. Mazarati, Wasterlain, and colleagues have used a perforant path stimulation model of self-sustaining status epilepticus (SSSE) in adult rats to study the response to a number of drugs. Diazepam and phenytoin are effective early, but much less so later in the episode.[137] NMDA-receptor blockers but not an AMPA-receptor blocker (NBQX) stop SSSE,[136] as does felbamate.[138] Levetiracetam in combination with diazepam appears to have some efficacy at high doses.[139] Pitkanen and colleagues developed an amygdala stimulation model of SSSE[157] and have used it to study consequences of pharmacologic treatment during status epilepticus. Treatment with diazepam within 2 hours reduces subsequent chronic epilepsy,[168] but lamotrigine does not.[158]

Summary and Conclusions

Models can be used to understand basic mechanisms of a disease process, its consequences, and its treatment. Focal or systemic administration of chemical convulsants and direct cerebral electrical stimulation have been used to create a large variety of experimental models of epilepsy and of SE. Recently, sustained seizure activity in hippocampal slices has also been used as a model of SE.[178]

The mechanisms of SE are now understood to be the result of failure of seizure-terminating mechanisms or of the mechanisms that make the brain refractory to subsequent seizures after a single discrete seizure, although many of the details of these mechanisms remain to be elucidated. Experimental models provide a method with which to study such phenomena. Furthermore, experimental models can be used effectively to test new drugs or new combinations of drugs for their utility in the treatment of chronic epilepsy and of SE before incurring the risk and expense of clinical trials.

Investigations on status epilepticusâ€"induced neuronal damage and chronic epilepsy that occur after prolonged seizure activity are contributing to a better understanding the epileptogenic mechanisms underlying focal human epilepsies. In particular, the experimental results obtained in animal models of

chronic epilepsies induced by pilocarpine, kainic acid, tetanus toxin, and focal electrical stimulation have cast some light on the mechanisms by which acute epileptic conditions can induce lesion- and seizure-dependent epileptogenic changes.

The animal models reviewed in this chapter have proven to be particularly suitable for testing the efficacy of antiepileptic drugs and may open new perspectives to the development of novel antiepileptogenic strategies.

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Chapter 37

Genetic Models of Epilepsy

Jeffrey L. Noebels

Introduction

The success of molecular genetic strategies in finding genes underlying human monogenic epilepsies has set the stage for a new generation of defined experimental genetic models to unravel the mechanisms of inherited seizure disorders. While each discovery of a causative human epilepsy gene offers the promise of an accurate molecular diagnosis, identification of the mutant gene alone is unlikely to lead to advances in medical therapy until its cellular mechanism of action is at least partially understood. This is based on two simple reasons: First, mutations can alter gene function in various ways, most notably as a loss or a gain of biologic function, each requiring entirely different strategies for pharmacologic intervention. Second, the inherited gene defect is likely to trigger epilepsy through a complex sequence of downstream cellular changes in the developing brain, leading to the emergence of a specific seizure phenotype at a particular age. This developmental plasticity means that the destabilizing action of the gene on network excitability must be isolated from many other potentially misleading structural and functional alterations.

Genetic animal models offer the opportunity to experimentally dissect these manifold effects of the inherited disease gene in the developing brain, and to precisely define which alterations in brain circuit microanatomy and physiology directly contribute to the onset of seizures. Once this therapeutic target is obtained, a rational search for pharmacologic compounds to prevent or reverse the imbalance can begin. Since many different biologic pathways have now been implicated by known epilepsy gene mutations, it is hoped that similarities among the models may point to a smaller number of common synaptic pathways and membrane excitability defects that are shared among seizure syndromes.[66] This principle of *convergent epileptogenic defects* for specific seizure types predicts that information from individually rare inherited epilepsies will one day be translatable into broad-spectrum antiepileptic drugs. In this sense, along with continuing gene discovery, the current efforts at target discovery (i.e., to precisely define the pathogenesis of epilepsy in genetic models at the molecular and cellular levels, rather than simply at the gene and electroencephalographic levels) will provide the long sought framework for major advances in the development of effective pharmacologic therapy for many inherited seizure disorders.

General Description

Two general categories of genetic models have been historically important. Over the past 50 years, the discovery of a lowered threshold to convulsant stimulation or actual spontaneous seizures in *inbred strains* of various species provided the substrate to search for brain mechanisms underlying epilepsy and to screen for anticonvulsant efficacy. Some of these original strains, which reflect the deleterious effects of many unidentified genes, have been preserved in colonies; others have been created de novo using recombinant inbred strain methods,[29] a strategy that allows the genetic propagation of randomly combined sets of hyperexcitability alleles already present but asymptomatic in the â€œwild typeâ€ genetic background. These models all possess the virtue of displaying either spontaneous electrographic and behavioral seizures or a lowered threshold to seizures evoked by various modalities, and thus share polygenic susceptibility increases resembling those that contribute to many human seizure disorders. These inbred strains provide highly reproducible laboratory models for elucidation of anatomic seizure pathways and antiepileptic intervention.

A second, more powerful approach has been to survey animals for epileptic phenotypes linked to *single locus mutations*, either those which have occurred spontaneously, or increasingly, those engineered by recombinant DNA mutagenesis techniques.[12,64,67] The latter are typically created by the insertion of additional copies of a gene to *increase the expression levels* of a gene product, the deletion of a specific gene by homologous recombination to create a *loss of function* of the targeted gene, or the alteration of a gene sequence to produce an entirely novel *gain of function*. A refinement of this approach is to replace a wild-type allele with one engineered by site-directed mutagenesis to achieve a desired effect upon the function of the protein, typically one that has been designed to exactly replicate a human mutation. Recreating the precise molecular lesion of a form of human epilepsy in another species, an *orthologous gene model,* provides an exceptional opportunity to understand the natural history of the clinical disorder.

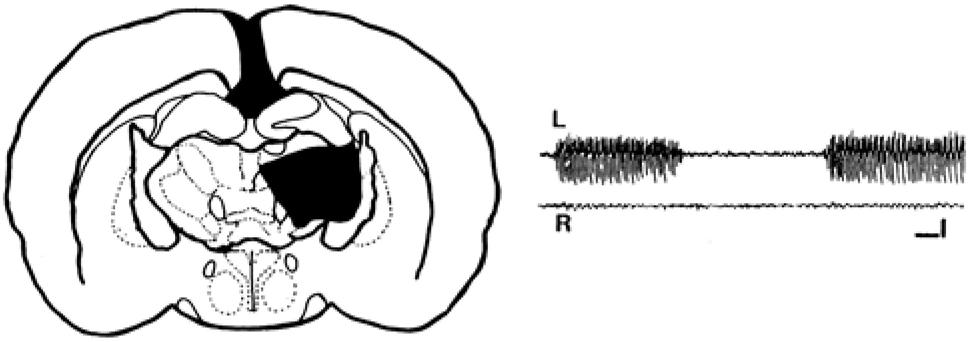

FIGURE 1. Ibotenic acid lesions of the thalamic reticular nucleus (nRT) abolish spike-wave discharges (SWDs) in the absence epilepsy model genetic absence epilepsy rat of Strasbourg. **Left:** Reconstruction of lesions induced by ibotenic acid, an excitotoxin that selectively kills neurons without affecting fibers of passage. **Right:** Electroencephalographic (EEG) recordings 4 days after unilateral nRT lesion show abolition of SWDs in the ipsilateral hemisphere, leaving only abortive low-frequency discharges. The animal was previously callosomized to prevent contralateral diffusion of the SWDs originating from the intact side. L, left EEG; R, right EEG. (From Avanzini G, Vergnes M, Spreafico R, et al. Calcium-dependent regulation of genetically determined spike and waves by the RTN of rats. *Epilepsia.* 1993;34:1â€"7.)

While many inherited human epilepsies may ultimately prove to be multigenic in origin, defects at a single gene locus suffice to produce a stereotyped seizure disorder and can be isolated and studied on many different experimental genetic backgrounds. Since the earliest electrophysiologic studies of behavioral mutants in fruitflies and mice,[36,39,68,103] spontaneous single gene mutations have contributed key examples of neuronal hyperexcitability mechanisms. *Drosophila melanogaster* hyperexcitability models of mutant ion channels, pumps, RNA binding proteins, and even KCC2-like cotransporters responsible for depolarizing GABA receptor responses continue to be described,[31,34,72] and this system shows great promise for rapidly identifying modifier gene loci,[33,88] an emerging frontier in epilepsy genetics. High-throughput mutagenesis protocols are now available to accelerate identification of relevant genes in other simple genomes, including zebrafish,[5] round worms,[101] and mice.[32] Of all of these genetic systems, defined mutations in the mouse offer the most comprehensive opportunity to identify genes linked to spontaneous, electroencephalographically proven epilepsy, and provide a powerful system to investigate the pathogenesis of single locus mutant phenotypes discovered in human mendelian pedigrees. Regardless of the species of origin, novel gene candidates for hyperexcitability discovered

through these experimental models narrow the search for genes in a linkage region mapped for human positional cloning studies, and thereby greatly facilitate human epilepsy gene discovery.

Questions That Can Be Addressed in Genetic Models of Epilepsy

Genetic animal models of epilepsy are useful to (a) define the nature, timing, and distribution of excitability changes leading to seizures in the developing brain; (b) implicate or exclude specific molecules, synapses, and networks in epileptogenesis as well as isolate gene modifiers that enhance or suppress seizures; (c) analyze the rate of progression and extent of seizure-induced neural damage during chronic epilepsy; and (d) evaluate the specificity of new antiepileptic therapies. While exact, mutation-specific (â€œknockinâ€) orthologous models of most known inherited human epilepsy syndromes are still under development, mouse models representing at least half of the known human epilepsy genes are currently available as targeted deletion (â€œknockoutâ€) or overexpression mutants. These â€œfirst generationâ€ models can mimic the overall effect of the mutation, namely, a loss or gain of function of the gene, but may not in fact reproduce the precise excitability phenotype seen in a given missense mutation of the same gene in a human proband. At the molecular level this is readily understandable, since a protein such as an ion channel that functions poorly yet continues to physically interact as a membrane protein with other channel subunits or intracellular signals often creates a different cellular defect than no protein at all. Nevertheless, these mutants provide general information on basic neural processes likely to be involved in the human clinical counterpart.

Brief Description of the Individual Models

A variety of inbred models that remain genetically uncharacterized have been of significant historical importance in the experimental analysis of epilepsy, including photosensitive baboons,[62,91] and chickens[92]; however, with a few important exceptions, including a novel unstable dodecamer expansion repeat mutation of Epm2b (Nhlrc1) identified in dogs with canine Lafora disease,[53] newer models are based on defined gene lesions in rodents. Due to the large number, this chapter will focus on recent work in a smaller number of exemplary models currently under study.

Table 1 Single Gene Models Displaying Absence Epilepsy in Mice

Mutant	Gene	Protein	Function
*Tottering**	Cacna1a	Î± subunit of calcium channel	Excitability, transmitter release
*Lethargic**	Cacnb4	Î²4 subunit of calcium channel	Excitability, transmitter release
*Ducky**	Cacna2d2	Î±2Î´2 subunit of calcium channel	Excitability, transmitter release
*Stargazer**	Cacng2	Î³2 subunit, TARP protein	AMPA receptor surface expression

mocha2j	AP3d	Adaptor protein Î´ subunit	Endosome protein trafficking
Gabrb1	Gabrb1	GABA B1 receptor subunit	GABAergic signaling
Gabrb2	Gabrb2	GABA B2 receptor subunit	GABAergic signaling
Coloboma	SNAP25	SNARE protein	Transmitter exocytosis
Swe	Nhe1	Sodium hydrogen exchanger	Intracellular pH
Hcn2[54]	Hcn2	Hyperpolarization-activated/cyclic nucleotide-gated cation channel	Membrane excitability

* Multiple alleles at these loci express spike-wave seizures.

Generalized Absence Seizure Models in Inbred Strains

Two inbred rat models of absence epilepsy, the genetic absence epilepsy rat of Strasbourg (GAERS) and the Wag-Rij rat strain, continue to serve a seminal role in defining the networks and cellular excitability mechanisms of absence seizures emerging from aberrant thalamocortical oscillations.[22,26] Inheritance of spike-wave (SW) epilepsy in these models is not due to a single gene locus, although potentially contributory gene variants can be identified that are absent in other unaffected rat strains, for example, a variant in the KCNK9 gene coding for the TASK3 (Twik-like acid-sensitive K^+) channel in the GAERS model.[35] Both inbred rat models exhibit spontaneously occurring bilaterally synchronous 5- to 11-Hz SW with behavioral arrest with a late onset at 3 to 4 months of age lasting into adulthood. The neocortex, thalamic relay neurons, and reticular thalamic nucleus are involved in the aberrant synchronous discharge, cognitive performance during the seizure is impaired, and the oscillations share major features of the circuitry and pharmacology, if not developmental onset, of slower 3/sec absence seizures in humans. Occasionally, the same discharge pattern is reported in other inbred rat strains.[84]

A number of important electrophysiologic and pharmacologic insights have been derived from these two strain models. Key among these are the involvement of the nucleus reticularis thalami in the expression of spike-wave epilepsy (Fig. 1) and the role of elevated low-voltage T-type calcium currents in this discharge.[97] Additional control over thalamic oscillations is regulated by enhanced HCN1 gene expression and decreased cAMP responsiveness of a second pacemaking current, Ih, favoring rebound excitation in these neurons.[11] Other recent findings point to regional blood flow increases,[63] cortical excitability changes in deep layer neurons,[23] a low threshold trigger zone in barrel cortex,[58] and Î³-aminobutyric acid (GABA)-ergic signaling impairments.[6] These models have served as a mainstay for the analysis of thalamocortical spike-wave seizure modulation by a variety of receptor families, as well as a wide range of antiepileptic pharmacology.[26]

Generalized Convulsive Seizure Models in Inbred Strains

The genetically epilepsy-prone rat (GEPR) is a model of experimental audiogenic seizures, a form of reflex epilepsy that has been useful in tracing the brainstem pathways mediating high decibel-induced convulsions with wild running.[41] While a rare clinical counterpart of this behavioral seizure type, *epilepsia cursiva*, has been recognized in humans,[37] the model set the stage for analysis of audiogenic mouse mutant models with defined single gene lesions, including the serotonin 5HT2C receptor,[8] the FMR1 Fragile X mouse,[105] and the JAMS1 mouse locus[59] that corresponds with a human locus for febrile seizures. Interestingly, a loss of function mutation in MASS1, another gene shown to underlie audiogenic seizure susceptibility,[86] was subsequently found within a human pedigree with febrile seizures.[61]

The *EL* mouse inbred strain is notable for the development of seizures following repeated episodes of vestibular stimulation. Susceptibility begins at 10 weeks of age, and the seizures are manifest as running fits followed by convulsions of possible cortical origin.[60,90] A variety of defects have been described in this model, and it continues to find a use in imaging GABAergic receptor signaling plasticity in chronic epilepsy.[30] Another model of convulsions evoked by stress and handling has been described in various strains of the domestic Mongolian gerbil. This model was once used extensively in neuropharmacologic testing, and more recently has been found to exhibit changes within the GABA interneuron population.[10]

The spontaneously epileptic rat (SER) was developed by crossing the *tremor* and *zitter* strains and exhibits spontaneous tonic convulsions, absencelike seizures, and spongiform encephalopathy ending in lethality by 20 weeks of age. Recent studies add abnormalities in glutamate transport to a diverse set of other neuropathologic changes resulting from coexpression of these two loci.[2] The *zitter* locus contains a splicing mutation in the gene encoding *attractin*, an enzyme with a critical role in myelination.[46] As a model displaying two distinct seizure types, it finds use in studies of antiepileptic drug profiles.[40]

An inbred rat strain with a cortical band heterotopia and convulsions resembling the human double cortex malformation syndrome, the telencephalic internal structural heterotopia (*Tish*) rat, has been described.[48] Spontaneous seizures in these animals arise nearly simultaneously in both normal and ectopic cortical circuits due to extensive interconnections between the two.[16] The genes underlying this malformation have not yet been identified; however, one epileptogenic mechanism described involves a reduction in the number of parvalbumin-containing GABAergic interneurons in *Tish* necortex.[96] This lesion is suggestive of the interneuron migratory defect seen in some targeted mouse mutants.

Absence Epilepsy in Defined Single Locus Mouse Models

Systematic electroencephalographic (EEG) screening of murine mutants for cortical excitability defects has so far revealed ten single gene loci for spike-wave epilepsy phenotypes (Table 1). All are recessive, save for the autosomal dominant *Coloboma* locus, a deletion containing the exocytosis-related SNAP25 gene, and many show additional neurologic phenotypes in the homozygous mutant. Except for the 3/sec spike-wave epilepsy mutant *Swe* lacking a functional NHE1 sodium hydrogen exchanger gene,[21] these mice express spontaneous, brief (1- to 10-second), generalized 6- to 7-Hz spike-wave discharges in the cortical EEG associated with arrest of movement. Seizures in these models typically begin in the third week of life, continue into adulthood, and respond dramatically to ethosuximide. *Swe* mice are the sole mouse model to reproduce a 3/sec spike-wave discharge in juvenile mice, disappearing in adulthood. Neurons in NHE1-deficient mice show prolonged recovery from an acid load and increased sodium ion channel expression.[104]

The *tottering* mutant develops in adolescence (postnatal day 17) a generalized 6 to 7/sec cortical spike-wave discharge with brief (1- to 10-second) bursts occurring at a mean rate of up to 60/hr. Many laboratories have now studied neuronal excitability in these classical calcium channel mutant models and their multiple alleles, and they confirm a range of cellular abnormalities in each. Loss of function mutations in the P/Q type Î± subunit of voltage-gated calcium channels reduce calcium entry through the pore; however, at many synapses, release defects are partially compensated by N-type calcium channels[77] and similar compensatory rearrangements by other related subunit genes can follow the loss of channel regulatory subunits, as seen in the *lethargic Cacnb4* mutant.[13,14] In the *tottering* mouse, several key mechanisms underlie the genesis of spike-wave synchrony, including an elevation of T-type calcium currents in thalamic neurons that precedes the onset of epilepsy (also shared by *lethargic, stargazer*, and *Coloboma* models),[107,108] and a reduction of feed-forward inhibition onto layer IV neurons in the neocortex,[80] all correlating with the onset of epilepsy. The presence of thalamic T-type currents is essential for the expression of spike-wave discharges in these models, since deleting the *Cacna1G* gene encoding T-type currents in thalamic relay nuclei abolishes the seizure phenotype.[44,87] Other downstream plasticity mechanisms are likely to modulate spike-wave epileptogenesis and may serve as additional therapeutic targets.[70] Analysis of *tottering* mice also provided the first example of a model where a potential therapeutic target may be far removed from the mutant gene itself. The *tottering* brain shows a gene-linked proliferation of noradrenergic locus coeruleus axon terminals in neocortical and thalamic regions, and neonatal correction of this inherited hyperinnervation with a selective neurotoxin prevents the expression of epilepsy.[50,65] The neuromodulatory effects of noradrenaline on the compensatory N-type calcium channel may explain why removal of this downstream target rescues the *tottering* phenotype.[51] *Lethargic* and *ducky* mice express an absence seizure phenotype similar to *tottering*, including the accompaniment of paroxysmal dystonias, but since they bear mutations of regulatory subunits that interact with multiple calcium channel Î± subunit pore proteins (not simply *Cacna1a*), they share only some of the regional profile of excitability changes.

The *stargazer* mouse bears a mutation in the calcium channel/TARP gamma 2 subunit gene (*Cacng2*) and shows an identical EEG spike-wave seizure disorder as the calcium channel subunit mutants, but lacks episodic dystonia and has a severe vestibular defect.[49,69] Like other spike-wave mutants, seizures in *stargazer* mice are immediately blocked by ethosuximide, but unlike the *lethargic* and GAERS models, GABA$_B$ receptor blockade is ineffective in preventing SW, and unlike the *tottering* mouse, no noradrenergic abnormalities are evident in *stargazer* brain, indicating that the two mutant genes produce spike-wave seizures through different intervening defects. Recent work identifying the gamma 2 subunit as a founding member of a novel family of transmembrane Î±-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) receptor regulatory proteins (TARPs) suggests a role other than calcium channel regulation. The latter proposal, initially based on its sequence homology with a subunit of muscle voltage-gated calcium channels, has been replaced with a proven role mediating AMPA receptor plasticity at dendritic spines.[71] Î³ Subunits interact with PSD-95 and other synaptic scaffolding proteins[25] and are essential for the surface expression of AMPA-type glutamate receptors, as well as two direct modulatory effects on channel function: A reduction in glutamate-evoked desensitization and an increase in the relative size of responses to the partial agonist kainate.[98]

GABA$_A$ receptor mutations linked to various human absence epilepsy syndromes have been described. One such report is a *GABRA1* truncation, which displays no current following exposure to GABA,[57] and the other is a trafficking defect in the gamma 2 subunit of GABA$_A$ receptors that reduces membrane surface expression of the receptor.[42] These defects predict that a null mutation would provide a good model of these phenotypes.

To summarize, analyses of the single locus models of absence epilepsy have revealed several general principles regarding the heredity of this cortical synchronization trait. First, a defect at a single gene locus is sufficient to produce a generalized spike-wave seizure disorder.[68] Second, the EEG pattern itself is genetically heterogeneous, and can arise from mutations in multiple independent loci that may display distinct neurologic comorbidities. Third, the intervening cellular excitability mechanisms underlying the generation of spike-wave cortical discharges are not identical, but share some features in common. Fourth, each of the mutant genes gives rise to syndromes that can differ in their seizure frequency, sensitivity to antiepileptic drugs, and severity of the associated neurologic phenotype. Fifth, due to the reproducible developmental expression of the abnormal synchronization, primary defects can be distinguished from secondary cellular alterations, and the specific patterns of these pathologic changes are linked to the inherited mutant allele.

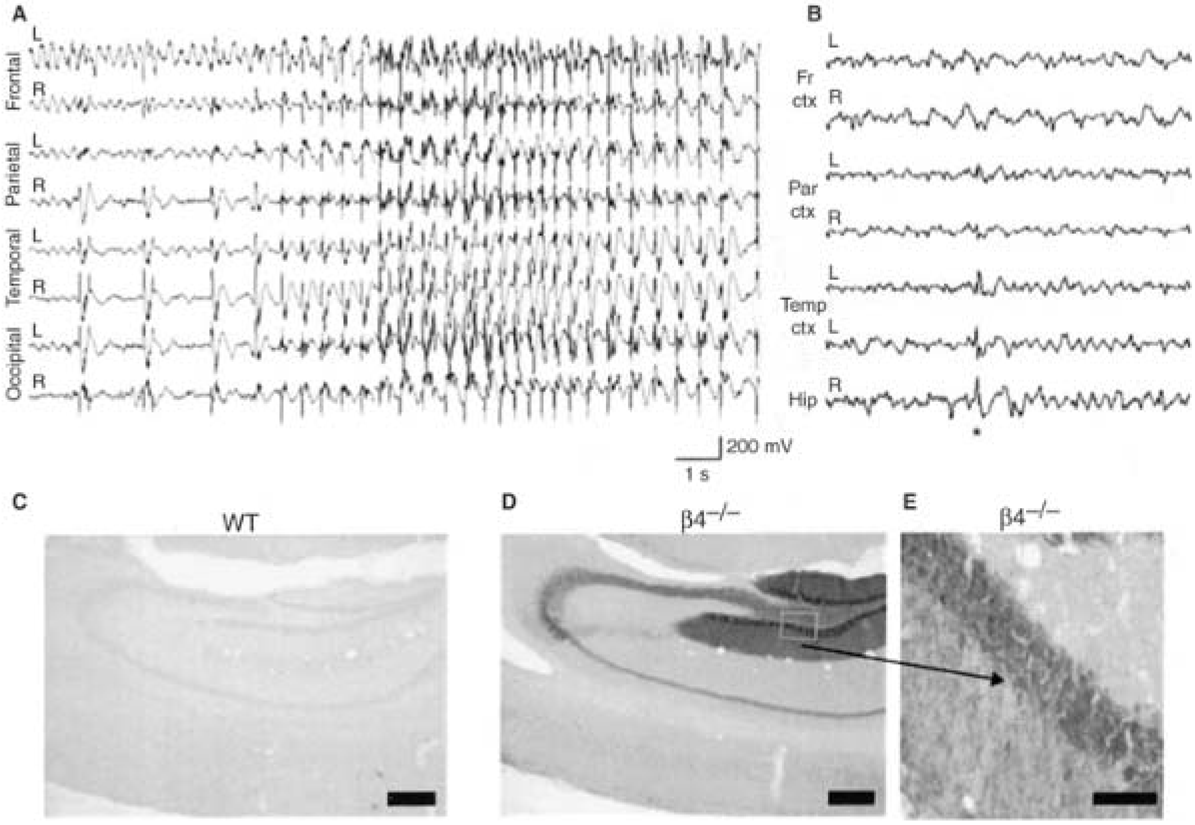

FIGURE 2. Deletion of the Î²4 subunit of BK calcium-activated potassium channels in brain causes nonconvulsive, partial-onset hippocampal seizures. **A.** Surface cortical electroencephalogram (EEG) recording shows initial interictal discharges in posterior and temporal regions with frontal spread to a generalized seizure activation pattern. **B.** Interictal spiking in depth recordings from the hippocampus (*bottom trace*). **Câ€“E.** Selective expression of Î²4 subunit in hippocampal formation and neocortex. Anti-GFP antibody shows no GFP (diffusible intracellular marker for cells deleted for Î²4 subunit expression) in wild-type mouse and strong dentate granule cell expression where the subunit gene has been deleted in mutant. (From Brenner R, Chen QH, Vilaythong A, et al. BK channel beta4 subunit reduces dentate gyrus excitability and protects against temporal lobe seizures. *Nat Neurosci.* 2005;8:1752â€“1759.)

Convulsive Seizures in Defined Single Locus Models

A variety of convulsive seizure models based on spontaneous single locus mutations have been described, and many more are certain to follow as the list of known human genes for this condition expands. At present there are over 140 mendelian syndromes that include generalized epilepsy reported in the Online Mendelian Inheritance of Man (OMIM) database.

Single Locus Models with Partial (Focal) Onset and Secondary Generalization

Using a ten-electrode recording array, Brenner et al. described a mouse model of generalized epilepsy with focal bilateral electrographic onset within temporal brain regions. This model is based on a null mutation of the BK Î²4 subunit gene (*Kcnmb4*), a negative regulatory subunit of the calcium-activated potassium channel that is expressed principally in the hippocampal formation and neurons within deeper neocortical layers (Fig. 2).[9] Loss of the braking function of the subunit that normally limits high-frequency firing patterns in dentate granule cells effectively enhances depolarizing afterpotentials and facilitates bursting in these cells in response to depolarization, thus degrading the intrinsic â€œgatingâ€ function of the dentate gyrus. The behavior of the mouse is remarkable in showing behavioral arrest in the early phase of the seizure, followed by grooming automatisms, while the EEG discharges generalize to involve the neocortex, a pattern expected of seizures in the limbic region. Interestingly, the interacting Î± subunit gene is strongly expressed in thalamus and all cortical layers, and a mutation causing a similar loss of Ca^{2+}-activated regulation of this channel has been linked in humans with childhood absence epilepsy.[28] This pair of genes is the first to differentially localize with brain circuits known to mediate these two distinct seizure types.

A second mouse model based on a mutant potassium channel is of interest due to the use of conditional genetic engineering techniques to suppress the expression of the channel gene in the brain at different developmental stages. The *Kcnq2* gene encodes a potassium channel subunit that dimerizes to form a channel mediating the M current, a strong hyperpolarizing afterpotential in hippocampal neurons, and is one of the genes linked to a human benign neonatal epilepsy (BNE) syndrome.[7,85] Mice were created with a transgene encoding a dominant-negative copy of the KCNQ2 protein that inactivates the M current. This transgene was placed under the control of

a promoter construct sensitive to the antibiotic doxycycline, and M currents were attenuated by doxycycline exposure.[74] Suppression of M currents at early developmental time points caused a mixed (partial, generalized tonicâ€“clonic, and generalized spike-wave) seizure disorder lasting into adulthood. Interestingly, genetic suppression of M currents after several postnatal weeks of age did not create a seizure phenotype, only pronounced hyperactivity and severe cognitive deficits. Neither of the models has so far provided an explanation for the disappearance of seizures in the benign human syndrome.

Primary Generalized Seizures

Disruptions in a wide variety of molecular pathways lead to the generalized convulsive seizure phenotype, including defects in neurotransmitter and receptor levels, vesicle proteins and exocytosis, transporters, and a lengthening list of transcription factors underlying programs of neuronal migration. It now appears that in a majority of cases, clear decrements in synaptic inhibition are found in regional brain networks. While GABAergic signaling may not be the sole defect, these models demonstrate that the gene mutations selectively disinhibit neural circuitry favoring epileptic synchronization. Representative examples from these categories are highlighted here.

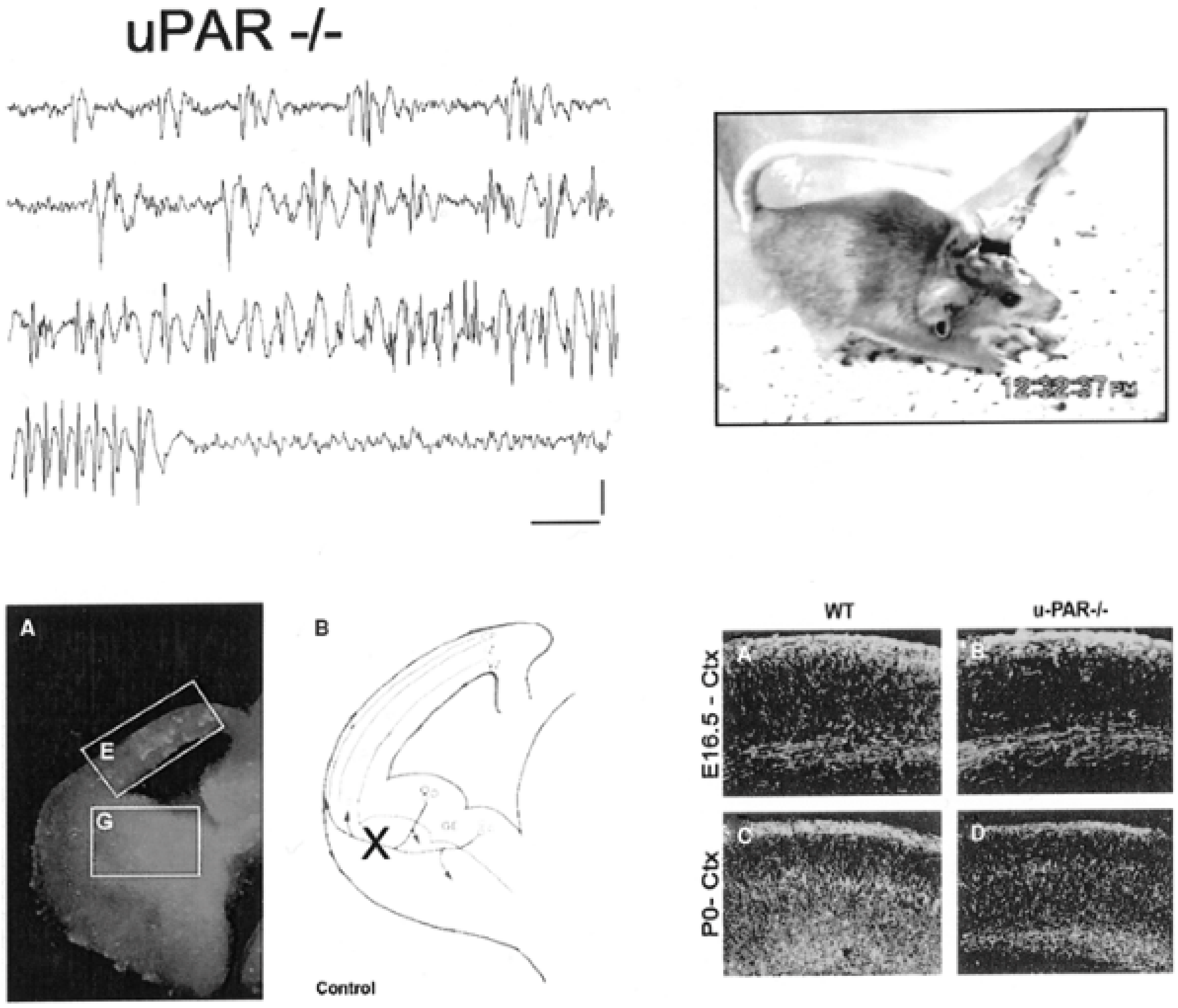

FIGURE 3. Impaired interneuron migration and myoclonic seizure activity in *upar*$^{-/-}$ mutant mice. **Above:** *At left*, Electrocorticographic monitoring of control (WT) and adult *upar*$^{-/-}$ mice reveals abnormal bilaterally synchronous interictal discharges and spontaneous seizures progressing from isolated to continuous spike and spike-wave rhythmic discharges, terminating abruptly. Representative stages of the seizure (76 seconds in duration) are shown. *At right*, posture of a *upar*$^{-/-}$ mutant mouse during the final stage of a seizure. Calibration: 500 ÂµV, 1 second. **Below:** *At left*, Absence of *upar* gene interrupts tangential migration of interneurons from birthplace in germinal eminence to neocortex, where, *at right*, relative loss of Î³-aminobutyric acid (GABA)-ergic neurons in middle cortical layers is evident at birth. (Adapted from Powell EM, Campbell DB, Stanwood GD, et al. Genetic disruption of cortical interneuron development causes region- and GABA cell type-specific deficits, epilepsy, and behavioral dysfunction. *J Neurosci.* 2003;23:622â€“631.)

Proliferation, Migration, and Maturation of GABAergic Interneurons

A primary defect in embryonic progenitor cell neurogenesis, and the first monogenic rat epilepsy model to be genetically identified, gives rise to severe seizures due to proliferation defects. The *flathead* rat is a spontaneous null mutant of the citron kinase gene, required for cytokinesis, early cell proliferation, survival, and postnatal hippocampal neurogenesis following seizures.[1] Generalized seizures in this model begin in the second postnatal week at a time when substantial apoptosis becomes apparent within cortical proliferative zones.[79] A mouse null mutant of the citron kinase gene with seizures has also been described.[27] Targeted deletion of the transcription factor NeuroD/Î²2 in the mouse creates a striking failure of proliferation of granule cell precursors in the dentate gyrus, leading to the complete absence of the granule cell layer. The adult

â€“/â€“ mouse develops spontaneous generalized electrographic discharges with partial myoclonic seizures.[52]

The ability to target genes encoding molecules essential for the correct migration of specific populations of cortical interneurons has created two important and very instructive models of epilepsy. The first, created by deletion of the *upar* gene encoding the urokinase plasminogen activator receptor, results in the arrested migration of inhibitory parvalbumin-containing interneurons in their early lateral trajectory from the medial germinal eminence to the middle layers of frontal and parietal regions in the neocortex.[75] The mice display dramatic episodes of axial clonic seizures with severely disorganized, high-amplitude polyspike-and-wave discharges (Fig. 3). A second model depleting forebrain inhibitory interneurons was generated by targeted deletion of the DLX1 gene, one of a family of five homeodomain transcription factors. Loss of DLX1 selectively reduced calretinin+ and somatostatin+ staining interneurons in the neocortex and hippocampus, leaving parvalbumin neurons unaffected.[19] Nonconvulsive generalized seizures are present in this model and were unusual in displaying electrographic-behavioral dissociation with a pattern of striking generalized EEG discharge activity while the mouse remained motionless. The developmental mechanism of this interneuronopathy is distinct from that of *upar*-deficient mice, in that loss of DLX1 affected the terminal maturation, rather than the migration of interneurons, which then undergo apoptosis following the migratory phase. Different subsets of missing interneurons were also responsible for creating either a myoclonic or absence seizure phenotype.

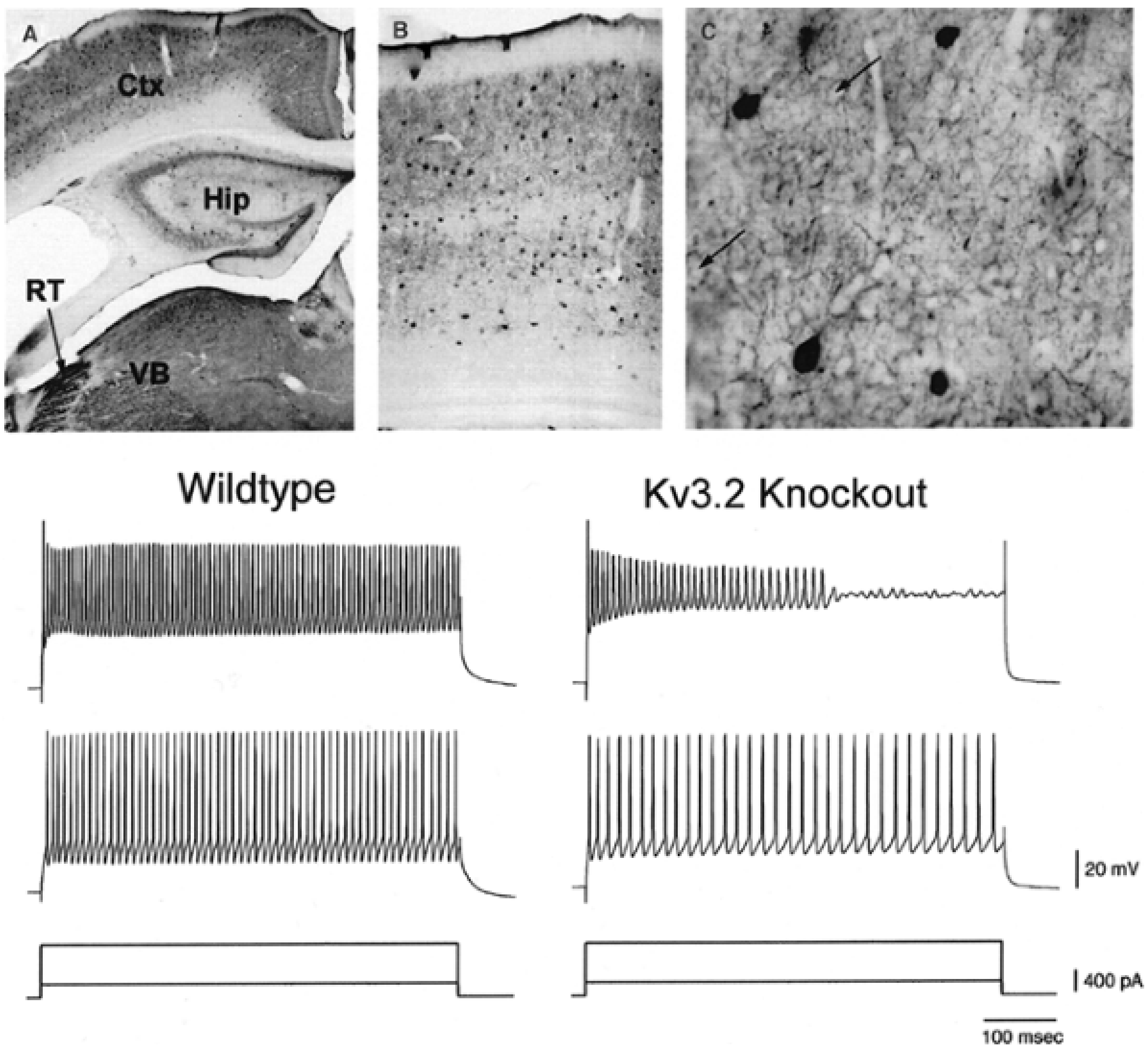

FIGURE 4. Selective impairment of high-frequency firing in inhibitory interneurons leads to generalized seizures in potassium channel Kv3.2 knockout mice. **Aâ€“C.** Kv3.2 delayed rectifier channels are expressed predominantly in parvalbumin+ staining interneurons in layers II and IV of neocortex as well as in hippocampal and thalamic networks, but not in principal excitatory neurons (**C**, *arrows*). **Below:** High-frequency firing behavior recorded from identified parvalbumin+ interneurons is limited by progressive spike adaptation during prolonged depolarization. Ctx, cortex; Hip, hippocampus; RT, reticular nucleus; VB, ventrobasal. (From Lau D, Vega-Saenz de Miera EC, Contreras D, et al. Impaired fast-spiking, suppressed cortical inhibition, and increased susceptibility to seizures in mice lacking Kv3.2 K+ channel proteins. *J Neurosci.* 2000;20:9071â€“9085.)

A variety of other developmental proliferation and migration models with epilepsy have been demonstrated, each targeting specific subsets of cells in unique patterns of the forebrain,

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for example, the SOX1 mutation impairing ventral forebrain GABArgic projection neurons.[56] Analysis of mice lacking p35, a neuron-specific activator of the cyclin-dependent kinase Cdk5, that display cortical lamination defects and seizures reveals extensive network reorganization and dystopias of hippocampal interneurons.[15,73,100] Recent evidence suggests that this molecular signaling pathway may also be disturbed in human epileptic dysplasias.[82] An entirely different pattern of reorganization is seen in the OTX1-deficient mouse that shows epilepsy, a selective loss of large cortical projection neurons, and defects in the GABAergic inhibitory system.[17]

Interneuron Excitability and GABA Release

The *Kcnc2* mouse model provides a striking example of the importance of genetic models to understand intervening mechanisms of epileptogenesis, even when the product of the mutant gene is as well understood as the potassium channel. This gene encodes the channel mediating Kv3.2, a delayed rectifier-type potassium current. Mice targeted for deletion of the Kv3.2 current encoded by the *Kcnc2* gene show generalized tonicâ€“clonic epileptic seizures.[47] In the neocortex, this channel is selectively expressed in deep-layer fast-spiking parvalbumin+ interneurons (Fig. 4). Whole cell recordings revealed that mutant cells were unable to rapidly repolarize, and that accumulating depolarization suppressed high-frequency firing upon strong depolarizations, thus effectively disinhibiting the network. This limitation of high-frequency firing is a familiar mechanism underlying antiepileptic drug mechanisms in excitatory cells,[55] yet when it acts selectively in inhibitory interneurons, it has the opposite effect.

Disproportionate reduction of the excitability of inhibitory interneurons may also explain the epilepsy arising from

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similar effects of a sodium channel mutation on firing properties in parvalbumin+ interneurons. Truncation and haploinsufficiency mutations in the *Scn1a* gene (one of five Î± subunits of voltage-gated sodium channels expressed in brain) lead to the severe myoclonic epilepsy of infancy (SMEI) syndrome,[18,89] yet the mechanisms linking network hyperexcitability with a loss of function in a subset of sodium channels remained unclear. Analysis of heterozygous *Scn1a* knockout mice whose haploinsufficiency mimics the human SMEI genetic condition revealed that loss of *Scn1a* channels in hippocampal neurons preferentially reduces membrane excitability in inhibitory interneurons compared with excitatory pyramidal cells, resulting in a net disinhibition within this network.[106] Thus, channelopathies causing *hypoexcitability in interneurons* represent a distinct category of gene mechanisms leading to inherited epileptogenesis.

The ability to rapidly release sufficient quantities of GABA in response to high-frequency stimulation is a second key feature of effective neuronal inhibition. Targeted deletion of the gene encoding the synthetic enzyme GAD65 produces viable mice with a generalized seizure phenotype.[43] GAD65 is one of two enzymes involved in GABA synthesis in the brain, and is believed to synthesize a secondary releasable pool of neurotransmitter that is drawn upon during sustained high-frequency firing.[95] Therefore, the depletion of this pool can account for the preserved whole brain GABA levels and normal GABAergic signaling in this mutant at low frequencies, as well as the early lethality of the GAD67 deletion mutant that shows severely reduced brain GABA levels.[3]

GABA Postsynaptic Response

Altered responses to GABA are the final step in the signaling pathway, and several gene models exemplify what is certain to become a well-represented category of epileptogenic mutation. Mutations in GABA$_{A}$ receptors underlie human epilepsy, and the gene for the GABA$_{A}$ *Î²*3 subunit lies within the critical chromosomal region of patients with Angelman syndrome (AS), where silencing of this gene has been proposed to contribute to the epileptic phenotype. Targeted knockout of the *Gabrab3* gene produces a mouse with severe generalized seizures,[24] and electrophysiologic analysis of these mice revealed the complete absence of inhibitory GABAergic responses in the reticular nucleus of the thalamus, where this gene is expressed, with no effects within adjacent thalamic relay nuclei, where it is not expressed.[38] This model demonstrates that suppression of intrareticular nucleus (RTN) inhibition may contribute to intrathalamic and generalized cortical synchrony in affected AS patients.

An unexpected and markedly abnormal potentiation of GABA responses have been reported in the first â€œknockinâ€ model of a human epilepsy syndrome involving the Î±4 subunit of the neuronal nicotinic acetylcholine receptor.[45] Two human mutations described in patients with the partial epilepsy syndrome of autosomal dominant frontal lobe nocturnal epilepsy (ADFLNE), CHRNA4(S252F) and CHRNA4(+L264), were genetically engineered to replace the wild-type allele of the receptor gene in two related mouse models. Both of these mutant mice showed abnormal EEG slowing and exhibited frequent generalized seizures. Electrophysiologic recordings from layer II/III cortical pyramidal cells in vitro revealed a >20-fold enhancement in inhibitory postsynaptic currents in the presence of the receptor agonist nicotine, but no effect on excitatory postsynaptic currents. The cortical excitability and seizures in the mutants were reduced by exposure to low doses of a GABA$_{A}$ receptor antagonist. These orthologous mouse models suggest that a novel mechanism contributing to the ADNFLE seizure phenotype may involve abnormally increased inhibitory synchronization of cortical networks via activation of mutant Î±4-containing nicotinic acetylcholine receptors, known to be located on the presynaptic terminals and somatodendritic compartments of cortical GABAergic interneurons.

Two other epilepsy models demonstrate epileptogenic gene mutations that may share a presynaptic site of action. Metabotropic glutamate and GABA receptors, unlike their ion channel counterparts, are G-coupled protein receptors whose activation modulates both neurotransmitter release and postsynaptic response. Deletion of the presynaptic metabotropic receptor for glutamate, mGluR7, results in an epileptic phenotype.[78] Activation of mGluR7 decreases transmitter release at excitatory glutamatergic presynaptic terminals or via heterosynaptic effects on interneuron terminals.[81] G-proteinâ€“coupled GABA$_{B}$ receptors are present at both pre- and postsynaptic sites where they prolong inhibition by reducing presynaptic calcium entry and activating postsynaptic potassium channels. Targeted deletion of *Gabarb1* and a truncation mutation of *Gabarb2* both generate mice that show handling-induced generalized seizures in the second postnatal week.[76,83,93,94] In these two models, pre- and postsynaptic GABA$_{B}$ receptor responses are abolished, resulting in loss of heterosynaptic depression, depolarizing GABA$_{A}$ receptorâ€“mediated events, and hyperexcitable network activity in vitro.

Another mechanism of postsynaptic disinhibition has been modeled by altering the chloride gradient in neurons responsible for hyperpolarizing responses to postsynaptic GABA$_{A}$ receptors. This gradient is established by the potassium chloride cotransporter KCC2, whose postnatal expression increases to convert depolarizing GABA responses in the neonatal nervous system into the hyperpolarizing inhibitory potentials seen in the adult. Depolarizing GABA responses consistent with KCC2 impairment have been reported in epileptic human cortex.[20] Deletion of the KCC2 gene *Slc12a5* in mice produces a mouse with a spontaneous generalized epilepsy phenotype.[102] The regions most affected by seizures in the mutant are in the temporal and entorhinal cortices and hippocampus, where parvalbumin+ interneurons are found to be reduced in number, suggesting the possibility that KCC2 plays a role in their development. Finally, anomalous metabolic reserves may dysregulate a large number of energy-dependent inhibitory processes in neuronal signaling, and a recent model of the human neonatal *GLUT1* deficiency syndrome reveals that knockout of the neuronal glucose transporter *Glut1* gene in mice produces a mixed seizure disorder,[109] allowing experimental exploration of the cellular mechanisms underlying the common clinical finding of hypoglycemia and neonatal seizures.

Summary and Conclusions

The last decade has witnessed a dramatic expansion of defined single gene models of epilepsy. These models play an essential role in defining the molecular anatomy and biology of epilepsy. We have learned three lessons fundamental from these models so far: First, there is a preponderance of genes that impair inhibitory processes in the brain. Second, nearly one third of all known inherited causes of epilepsy consist of mutations in ion channel subunit genes with clinically distinct epilepsy syndromes. Third, a large number of epilepsy genes alter early steps in the program for neuronal migration in the brain, producing striking changes in neocortical circuitry and highly complex compensatory excitability alterations. We have discovered that a single defective gene can give rise to multiple seizure types, that modifier genes can be mapped and isolated, and that in some instances, the brain expression pattern of a mutant gene can accurately predict the seizure phenotype, while in

others the epileptic circuit arises unpredictably from a diffuse pattern of mutant gene expression. Identifying why, where, and when the hyperexcitability phenotype will emerge during the development of inherited epilepsy remains a key challenge for each of the genes linked to epilepsy.

The next generation of genetic models will feature the application of further advances in tissue engineering, including the delivery of gene-silencing probes into specific brain networks. A major emphasis will be to faithfully replicate human mutations identified in clinical epilepsy pedigrees using knockin genetic technology (â€œhumanized mouse modelsâ€). A second strategy will be to employ conditional mutagenesis techniques permitting a selective alteration of gene function in precise regions and at various developmental ages in the brain. Combining these methods will allow us to realize the full potential of genetic models, namely, to take a single human epilepsy gene mutation and determine the correct molecular target for therapy. Completion of the rat genome sequencing project and perfecting mutagenesis strategies in the rat will also strengthen our ability to explore therapeutic strategies. In addition, a new generation of complex multigenic models of epilepsy must be developed to begin to understand the contribution of genetic modifiers in common nonfamilial patterns of idiopathic epilepsy that appear in the general clinical population. Analysis of these new kinds of mutant models will improve our understanding of the complex mechanisms that regulate the age of onset and severity of seizure disorders, and should accelerate the identification of novel treatments for inherited epilepsies in man.

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Chapter 38

Epilepsy in Vitro: Electrophysiology and Computer Modeling

John G. R. Jefferys

Introduction

Epileptic seizures and other kinds of epileptic activity are emergent phenomena from the interactions between cells organized into networks. To understand the relationship between the dynamics of cellular and local networks activity and epileptic discharges requires simplified models: This chapter outlines the use of in vitro preparations and computer models in this task. The chapter starts by describing different types of in vitro preparations and models of epilepsy, before outlining general aspects of computer modelling, and finally describing pathophysiologic mechanisms involved in epileptic phenomena.

In Vitro Preparations

Invertebrate preparations in vitro played an important role in the development of cellular studies of epilepsy, but they have largely been superseded by mammalian preparations, which are more directly relevant to the problem of epilepsy. In vitro preparations share the advantages of (a) mechanical stability, which is very helpful for cellular electrophysiology in which microelectrodes must to be precisely positioned in, on, or near neurons; (b) direct visualization, using suitable microscopes, of either general anatomic features or individual cells, both of which may be used for optical recording of Ca^{2+}, membrane potential, and other physiologic variables; and (c) simpler control over extracellular ions and drugs due to the absence of a blood–brain barrier. The following paragraphs outline the main preparations of mammalian brain tissue in vitro, starting from the simplest and going on to consider the brain slice in more detail.

- *Dissociated cell.* Neurons can be used for studies of their intrinsic properties shortly after they have been dissociated from tissue by mechanical agitation and enzymatic digestion of the extracellular matrix. This is a powerful technique for studying channelopathies in chronically epileptic tissue. Dendrites are amputated, which improves space clamp, but, of course, loses the contribution of all but the most proximal dendrites to the neuron's properties.[42,145]
- *Dissociated culture.* Neurons dissociated from pieces of brain tissue can be plated into culture dishes and maintained for several weeks. They will rewire into synaptic networks that can sustain epileptic activity. The limiting case is the single neuron culture that makes extensive connections with itself and generates spontaneous epileptic discharges.[106] Dissociated cultures are useful for those methods that take some time to work and/or need good access to neurons, such as transfection with molecular constructs to modify neuronal behavior. Non-neuronal cultured cells play a crucial role in identifying phenotypes associated with mutations found in monogenic epilepsies (see the section on chronic epilepsies). Cultured cells may also be used in the high-throughput screening of drugs with well-defined targets such as sodium channels.[23]
- *Brain slice.* This probably is the most widely used in vitro preparation in basic epilepsy research, and is the main topic of this chapter.[38] It is a section of brain tissue, a few hundred microns thick, maintained in physiologic saline or artificial CSF solution that contains the salts, glucose, and oxygen needed to sustain life. The thickness is a compromise between the need to retain the neuronal circuitry and the need to keep

the centre of the slice alive, most importantly by maintaining a high enough partial pressure of oxygen. In practice, brain slices preserve enough neuronal circuitry to sustain at least some kinds of epileptic activity. The underlying principles of brain slice preparation date back to the pioneering biochemical work of Warburg, during the 1930s. Typically, brain slices will survive several hours, perhaps a day or two.

- *Organotypic slice culture.* Slices prepared under aseptic conditions can be maintained for several weeks in appropriate tissue culture media. These slice cultures tend to flatten onto the substrate on which they are grown, which can be advantageous for visualization and manipulation.[49] They lend themselves to gene transfection and similar mid- to long-term manipulations that are much more difficult to achieve in simple slices.[12,41] One disadvantage is that the local connectivity changes as amputated axons die and surviving axons sprout, although this can be comparable to changes observed in chronic experimental and human epilepsies. Slice cultures allow the study of processes underlying damage and subsequent reorganization over prolonged periods.[76] Slice cultures lend themselves to high-throughput screening of potential anticonvulsants with a more realistic end point than the single ion channel or receptor used for similar work on isolated cells.[121]
- *Isolated brain region.* Seizures normally involve larger areas of tissue than can be preserved in a typical slice. To overcome this limitation, it is possible to cut slices in directions that preserve some longer-range pathways, for example, between the entorhinal cortex and hippocampus,[6,148] between the two hippocampi,[71] or the thalamus and cortex.[32]
- *Isolated brain.* The guinea pig brain can be isolated and perfused, providing many of the benefits of an in vitro preparation combined with in vivo connectivity.[78] Its main advantage is the maintenance of long range-connec- tions.[51] Its main disadvantage is that it is difficult (but not impossible) to maintain the tissue in good condition.

Table 1 Cellular Actions of Acute Convulsant Treatments

Drug	Action
Penicillin, bicuculline, picrotoxin	↓$GABA_A$ IPSPs
0-Mg^{2+}	↑Glutamate (NMDA) EPSPs and much more
4-Aminopyridine, dendrotoxin, MCD	↓Potassium currents →↑EPSPs; ↑IPSPs
High-K^+	↑Excitability; ↓IPSPs; ….
0-Ca^{2+}	↑Excitability, ↑nonsynaptic interactions (Ephaptic interactions; extracellular ions; gap junctions)

The choice of the most appropriate preparation depends on the question being asked. Brain slices from experimental animals have proved particularly useful for most issues addressed in this chapter, both the acute actions of convulsants and the pathophysiology of chronic models of epilepsy. It is possible to apply in vitro techniques to human tissue removed during surgery for medically intractable seizures. This method has obvious limitations on the number and consistency of samples, and controls require some ingenuity—and usually comparison with chronic animal models.[31,48,74,154] Slices from human epileptic foci usually do not produce spontaneous epileptic activity, but can generate some kinds of synchronous activity,[74] and can reveal stronger than normal responses to convulsant treatments such as increased potassium (K^+)[48] and 4-aminopyridine[5] (Table 1).

Perhaps the most commonly used brain slices in epilepsy research are from the hippocampus, and this chapter draws extensively from that literature. Similar principles, however, apply to other epileptogenic parts of the brain.

In Vitro Models of Epilepsy

In vitro models can be divided in two main groups: (a) acute convulsant treatments of normal brain tissue and (b) in vitro (or "ex vivo") studies of chronically epileptic tissue.[64] *Acute models* really model symptomatic seizures rather than epilepsy, but they have yielded major insights that can be applied to the abnormal brain tissue responsible for chronic epilepsy in vivo. Hypersynchronous epileptiform activity can be induced by perfusing normal brain slices with a variety of convulsant compounds (see Table 1).[65,67,127,128,132,137] Many of these agents block synaptic inhibition mediated by γ-aminobutyric acid $(\text{GABA})_A$ receptors, but others can work by increasing neuronal excitability, strengthening excitatory synaptic receptors, or altering synaptic release. The challenge was to find out how acute changes in synaptic or other neuronal properties can make the normal circuitry of the brain generate epileptic activity.

The prolonged exposure of hippocampal-entorhinal cortex slices to either low magnesium (Mg^{2+}) or 4-aminopyridine[22,39] results in a state characterized by recurrent epileptic discharges that are resistant to most current antiepileptic drugs. They therefore provide in vitro models of drug-resistant seizures, an area for which novel antiepileptic drugs are most urgently needed.

Chronic models are also amenable to study in vitro, simply by making the preparation from a chronically epileptic laboratory animal (or perhaps from human patients undergoing surgical resection to treat medically intractable epilepsy). The more common chronic models of epilepsy[112] can be divided into (a) those that start with status epilepticus and are associated with substantial cell loss[30] (including those using systemic or intracerebral kainic acid,[13,98] systemic pilocarpine,[140] and sustained electrical stimulation[50,84,86]); (b) those not associated with status or with early lesions (including kindling[87] and intracerebral tetanus toxin[62,66]); and (c) genetic models (most commonly of absence seizures[94,114]). Essentially all these models alter neuronal structure and function in ways that reduce seizure threshold, often to the extent that seizures occur spontaneously. A central challenge for work on these models in vitro is to determine, at the subcellular, cellular, and network levels, how the properties of neurons, synapses, and circuits have changed in chronically epileptic tissue.

Introduction to Computer Modelling of Neurons

Epileptic discharges represent an emergent property of neuronal networks. Understanding the functional relationships between the properties of individual neurons and of the networks they form is difficult on the basis of experimental observations alone. Computer modelling can play a crucial role in linking these different levels of analysis.

Computer Simulations of Single Neurons

Simulations of single neurons come in a variety of flavors. The level of abstraction depends on the questions asked. Neurons can be highly simplified to "integrate and fire" formulations. Inputs to these model neurons produce a shift in their potential, which will decay with some time constant, forming essentially a simple circuit of a capacitance and resistor; a threshold detector determines whether each cell will generate an output. Such neurons have a much more limited repertoire of firing patterns than do real cortical neurons, in which the majority are regular spiking cells, a large minority are intrinsically bursting neurons (and many of the regular firing cells can be changed to intrinsically bursting by changing the ionic environment[8]), fast spiking cells (all are interneurons), and chattering cells (in the neocortex but not the hippocampus[24]). The underlying physiology is described in more detail in Chapter 29. It is possible to create model neurons using relatively simple equations that capture these firing patterns (Fig. 1).[60] Such equations are based on neuronal physiology but do not attempt to simulate individual ion conductances. They are computationally efficient and are particularly useful for modelling large scale networks.[99a]

An alternative approach, which is the basis of most of the modelling work described here, uses equations to represent specific ion channels known to be present in particular kinds of neuron. Such realistic neuronal simulations build on the pioneering work of Hodgkin and Huxley,[57] who showed that action potentials can be described quantitatively as ion conductances that are functions of membrane potential and time, with the time-dependence usually including components for activation and inactivation. The representation of specific classes of ion channel by differential equations allows a rather direct comparison of computer model and biologic experiment by using drugs and toxins that have well-defined effects on specific ion channels. Most importantly, this allows predictions made by such realistic models to be tested, and falsified, experimentally.

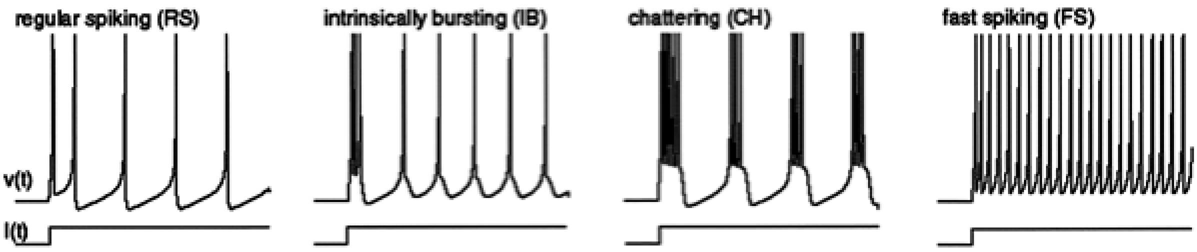

FIGURE 1. Illustration of the main classes of firing patterns of neocortical neurons as modelled by a four-parameter computational model. From Izhjikevich 2003, IEEE Trans Neural Networks, with permission. *Electronic version of the figure and reproduction permissions are freely available at www.izhikevich.com*

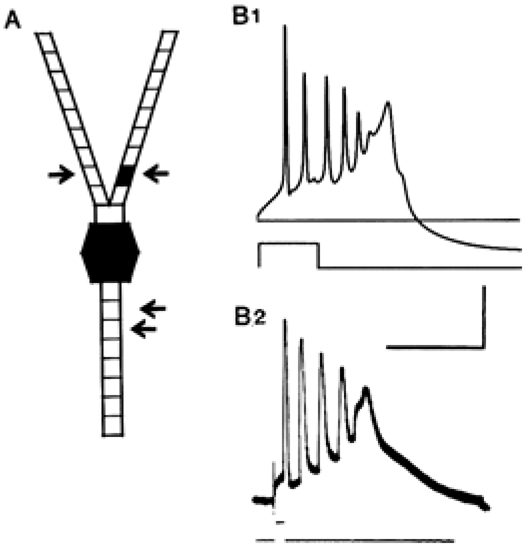

FIGURE 2. Intrinsic properties of CA3 pyramidal cells in the hippocampus. This early example of a compartmental model (*A*) with voltage-gated Na^+, K^+, and Ca^{2+}, and Ca^{2+}-activated K^+ currents in the soma (*filled hexagon*) and a single apical dendritic compartment (*filled quadrilateral segment*) reproduces (B_1) the intrinsic bursts seen in intracellular recordings from these cells recorded in the

guinea pig hippocampus (B_2). From Traub RD, Wong RKS. Cellular mechanism of neuronal synchronization in epilepsy. *Science* 1982;216:745–747, with permission.

Mammalian neurons are anatomically and physiologically much more complex than is the squid giant axon. Rall et al.[97] developed the approach of collapsing the complex anatomy of the dendrites and somata of neurons to electrically equivalent cylinders that are more amenable to computation than is the real anatomy. Traub et al.[133] developed compartmental models of hippocampal pyramidal neurons (Fig. 2), which have been refined extensively[131,134,137,138] and extended to many other types of neuron. Models of this kind include several key features:

- *Passive electrical properties* (membrane resistance and capacitance and intracellular resistance), usually of a series of linked "compartments." These are notional isopotential cylindrical segments that represent parts of the neuron, and together produce time and length constants similar to those in real neurons. The appropriate number of compartments depends on the purpose. Even those that use dozens generate new insights into dendritic function.[131] More detailed models of branched dendrites have revealed the complex processing of synaptic inputs.[73,115] Epileptic activity usually affects branches uniformly so that simpler nonbranched models often suffice.
- *Ion channels.* These are represented by equations of their dependence on voltage and time and, where appropriate, intracellular calcium (Ca^{2+}) or extracellular neurotransmitters. Individual currents, and the ion channels that generate them, are relatively well characterized. (Individual channels switch between two, or in some cases several, states; at the level of the whole neuron, however, their collective effects are more easily represented by Hodgkin-Huxley–type equations.) One complication that often arises occurs when the experimental evidence on specific currents is collected at subphysiologic temperatures; this data must be adjusted to the near-physiologic temperatures usually needed to sustain epileptic activity.
- *Distribution of ion channels* throughout the neuron, particularly on its dendrites and soma. These data are difficult to collect, but a reasonable body of work, largely from patch clamp, has been developed.[68,88] The distinct distributions of ion channels in different classes of neuron is an argument for using multiple rather than single compartments in models. A complication here is that dendritic ion channels are plastic and change in response to physiologic and pathophysiologic factors, including epilepsy.[46]

The quantitative details of ion channels usually will vary between individual real neurons,[83] and often will not be known precisely, so models should be robust to reasonable variation in their parameters; models that need very precise tuning to reproduce biologic reality need particularly critical evaluation. Once a model has been developed, it must be tested against real experimental data to ensure that its response to various kinds of stimulation and pharmacologic experiment match reality—or, perhaps more importantly, to identify where it fails so that the model can be refined or revised. Toxins and drugs exist that block or modulate most channels, and they can and should be used to test falsifiable predictions made by the model.[131] In the case of the hippocampal CA3 pyramidal cell, the intrinsic bursting depends on voltage-gated calcium channels in the dendrites, initially located in one dendritic compartment of the Traub mode 1 (see Fig. 2), but now distributed throughout the dendrites, in line with more recent electrophysiologic evidence.[88]

Just because a model reproduces the properties of a neuron does not mean it simulates how the real neuron works. In a revealing study, Prinz et al.[95] sought an alternative to "hand-tuning" model neurons. They tested a large (~1.7×10^6) database of a single-compartment model of the lobster stomatogastric neuron, in which the maxima for eight membrane conductances were varied systematically. They showed that multiple distinct combinations of ion channels could generate specific physiologic responses, and that the effects of varying a particular ion conductance could depend on the values of the other conductances in the cell. Interestingly, some neurons can adapt to changes in the expression of one ion channel, such

as I_A(an outward potassium current), by changing the expression of another, such as I_h(hyperpolarization-activated inward current).[80] Similar simulation database approaches are feasible, if more difficult, in multicompartment models. These simulation studies suggest that much more physiologic evidence is needed on the diversity of intrinsic and synaptic properties (and on their combinations within individual neurons) in both normal and epileptic tissue.

Simulation packages such as Neuron and Genesis make the building of compartmental models considerably easier than once was the case. Databases of typical models of many types of neurons are available, for example NeuronDB.[91]

Computer Simulations of Neuronal Networks

Building all but the simplest of synaptic networks remains less straightforward than making compartmental models of single neurons. Several projects exist that attempt to make relatively user-friendly packages for simulating networks, but they are not readily accessible to the nonspecialist. Several generic issues must be considered whatever the technical approach. Some form of randomization of neuronal properties across the population of model neurons is essential to avoid spurious synchronization. Real neurons will vary in their properties, both functional and structural, but experimental evidence on the extent of this variation is limited and often dismissed as experimental noise. That such variation exists is increasingly clear.[25,35,46,99,101]

Synaptic connectivity can be difficult to quantify experimentally in a statistically realistic way. Pairs of neurons will have some probability of a direct connection, but that probability will depend on distance and direction, among other variables. If these data are available, it should be fairly straightforward to generate a similar pattern of connections. A simple exponential decay of the density of excitatory synapses with distance from the parent soma reproduced many features of the propagation of epileptic activity through the hippocampus.[130] More precise information on the geometric organization of synaptic connectivity will help constrain network models.[110] The number of connections that must be modelled grows rapidly with population size, analogous with the Internet where, for example, Metcalfe's law argues that total connectivity scales as the square of the number of members of the network.

Simulations of small networks show that disparate combinations of synaptic and intrinsic properties can result in similar network dynamics,[96] and indeed, that the real networks in different animals may adopt different strategies to achieve the required output.[25] Despite such difficulties, network simulations have provided real insights into epileptic activity, as shown by the work outlined here. However, the potential for different sets of network mechanisms to result in similar emergent properties[96] emphasizes the importance of these network models to make experimentally testable, falsifiable predictions. The experimental tools are drugs and toxins, possibly applied focally, and molecular modifications (with the caveat that endogenous functional compensation can occur[80,122]).

Real neuronal networks have more complicated properties than do the models outlined so far. For example, synapses may facilitate or depress with repetitive use, with the direction of the change depending on the synapse and (critically) on the temperature.[72] Synapses may exhibit long-lasting potentiation (LTP)[17,36](see Chapter 35), and they may experience pre- and postsynaptic modulation.[33,82,113] Extrasynaptic receptors exist that, on the whole, have not been incorporated into compartmental models, but have significant impact on excitability.[77,107]

Lumped Computer Models

Compartmental models link directly with experimental neurophysiology and pharmacology in vitro, and they play a critical role in the work outlined within this chapter. Other approaches, however, can provide valuable insights. The use of simpler models of spiking neurons was mentioned earlier.[60,99] Other models use a “lumped” approach; in these models, the properties of individual neurons within a population are lumped together into equations that relate the population's net inputs to its net outputs. The lumped equations include elements for specific classes of synapse on the main types of neuron involved, and normally include a transfer function to relate the mean membrane potential of a population of neurons to their overall firing rate. This style of model has a long history (approaching five decades), back to the seminal work of WJ Freeman and others. Lumped models can, and should, make experimentally testable predictions. They have proved useful, particularly in the context of the thalamocortical system, where they have addressed issues such as the bistability of the electroencephalogram (EEG) between interictal and ictal states, and the potential therapeutic use of counterstimulation to reduce the frequency and/or duration of seizures.[120,151] Although these particular studies addressed absence seizures, mainly in vivo, such methods have also been used in vitro, for example in the hippocampal low-Mg^{2+} model, to study the dynamics of seizure-like events[120] or to model stereoencephalographic signal recorded from depth electrodes.[150]

Computer models have contributed greatly to the understanding of the underlying mechanisms of epileptic activity, particularly of the acute actions of convulsants on normal brain tissue.

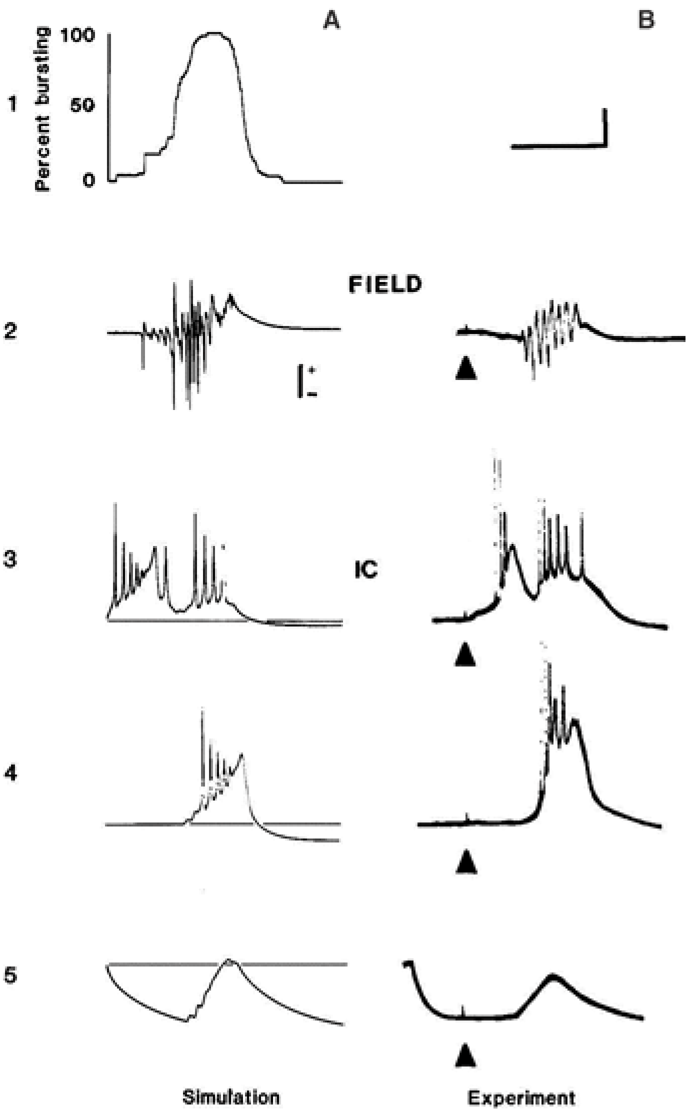

FIGURE 3. Simulation and experimental recordings of single synchronized bursts evoked by a localized stimulus in the disinhibited guinea pig hippocampal slice. The epileptic field potential (*line 2*) occurs after long latency in both simulation (*A*) and experiment (*B*). The simulation is of a network of the model neurons of FIGURE 2, sparsely connected by realistic excitatory synapses. Most cells generate PDSs synchronously with this field potential (*line 4*), and injecting hyperpolarizing current into the recorded cell reveals the underlying giant EPSP (*line 5*). A rare cell (*line 3*) fires a burst soon after the stimulus, along with another burst during the field event. The long latency corresponds to generations of exponential growth of the event; this takes time, because burst propagation can last tens of milliseconds. From Traub RD, Wong RKS. Cellular mechanism of neuronal synchronization in epilepsy. *Science*. 1982;216:745–747, with permission.

Epileptic Neurons and Mechanism of Interictal Spikes

Many acute convulsants result in brief synchronous discharges that look like interictal spikes[b] on the EEG or electrocorticogram (ECoG) from epileptic foci in humans. Some of the earliest intracellular studies in vivo (on penicillin foci) showed that these discharges were associated with substantial depolarizations and rapid action potential firing in most of the neurons in the epileptic focus. These abnormally large depolarizations were called paroxysmal depolarization shifts (PDSs) (Fig. 3B).[84]

Epileptic Neurons Versus Epileptic Aggregates (Networks)

This characteristic PDS behavior of epileptic neurons raised an intense debate several decades ago about whether it represents altered intrinsic properties of the neuronal membrane or derangement of network activity.[37]

One piece of evidence in favor of the “epileptic neuron” hypothesis is the observation that activity reminiscent of the PDS can occur in normal intrinsically bursting cortical and hippocampal neurons (see Figs. 1 and 2).[8] Intrinsic bursts in single neurons are the result of the combined operation of voltage-gated ion channels. Essentially, they depend on slow inward (depolarizing) currents, either Ca^{2+} (typical in hippocampal area CA3[102,131]; Fig. 2) or persistent sodium (Na^+) (more common in CA1[8]). These slow channels provide a depolarizing envelope that drives a burst of action potentials. Ca^{2+} entry during the burst activates the slow afterhyperpolarization mediated by K^+ currents which, with other hyperpolarizing currents, terminates the discharge.

Early in vitro studies played a key role in distinguishing the intrinsic burst from the PDS, showing that it depended on synaptic as well as intrinsic mechanisms. Johnston and Brown[67] showed explicitly that the PDS had the physiologic properties of a giant excitatory postsynaptic potential (EPSP): Both reversed at the same membrane potential and increased in amplitude with the injection of hyperpolarizing currents. The frequency of the PDSs was independent of membrane potential, implicating a synaptic network. The advent of good glutamate receptor antagonists allowed the direct demonstration of their dependence on excitatory synapses.

The question then was: Which synapses generated the PDS? In the case of the hippocampal CA3 region, the answer came from dual intracellular recordings that revealed direct (monosynaptic) excitatory connections between pyramidal cells.[7,81] The conceptual problem was that they appeared rather sparse. Extensive studies by Miles and Wong revealed monosynaptic EPSPs of ~1 mV between about 1% to 2% of pyramidal cell pairs.[90] Computer modelling of epileptic activity in these slices played a key role in determining whether this degree of synaptic connectivity was necessary and sufficient for synchronizing the epileptic discharges, and in confirming the relative contributions of the intrinsic and synaptic properties that had been found experimentally.

Computer Simulations of Interictal Bursts in CA3

In a pivotal paper, Traub and Wong[137] tested whether a network of reasonably realistic CA3 pyramidal neurons could replicate key features of experimental epileptic bursts induced by penicillin (which blocks IPSPs) in hippocampal slices. The model neurons comprised 28 compartments. Of these, the soma and one of the proximal apical dendritic compartments contained voltage-gated Na^+, K^+, and Ca^{2+} currents, and a Ca^{2+}-activated K^+ current (see Fig. 2). The individual model neurons replicated the ability of CA3 pyramidal neurons to generate intrinsic bursts. Traub and Wong replicated 100 of these neurons, connected them with synapses producing ~1 mV EPSPs so that randomly chosen pairs of neurons had a 5% probability of a direct connection, and then determined how these networks could become synchronized. No inhibitory neurons were included, because the experimental model depended on blocking inhibitory synapses, so that their activity was not relevant to the population. Exciting a small subset of these neurons (four of the 100 in the original paper) triggered a chain reaction, so that each of these neurons excited five postsynaptic neurons, which in turn each excited five more, and so on. The model explained the rather long delay between a weak stimulus and the hypersynchronous epileptic response, and predicted the existence of a minority of neurons, directly excited by the stimulus, that triggered the chain reaction (see Fig. 3).

The one notable difference between the simulation and experiment is in the detailed shape of the extracellular field (Fig. 3, row 2). The brain slice generated a more rhythmic waveform. This is due to a phenomenon not included in this model: field effect or ephaptic coupling.[61,63,129] This arises when the electrical field generated by active neurons excites neighboring neurons that are inactive, but close to threshold. The end result is that neurons that would fire in a disorganized fashion (as in the model in Fig. 3A2) become synchronized on a millisecond time scale. Their extracellular currents combine to produce the large, smooth, and relatively rhythmic population spikes seen in the experimental record (Fig. 3B2). (This kind of nonsynaptic synchronization is further explored in the section on seizure-like events.)

Further experimental evidence allowed this model of the disinhibited hippocampal slice to be refined. Experimental dissection of brain slices into progressively smaller segments showed that a minimum "epileptic aggregate" or population of neurons was necessary to sustain synchronized epileptic discharges; in the case of the guinea-pig CA3 region, this was ~1,000 to 2,000 neurons. The original estimates of synaptic connectivity (~5%[81]) were reduced to ~1% to 2% as many more dual

recordings were made.[90] Finally, it turns out that exciting a single neuron can trigger epileptic activity in both hippocampal slices and simulations.[89] Refining the model in the light of this evidence and of more detailed studies of the electrophysiology of the relevant neurons provided more realistic simulations, but the underlying principle remained a chain reaction that could take place as long as:

- Each active neuron synapses onto more than one postsynaptic neuron (divergence).
- These synapses are effective in exciting their postsynaptic targets. This not only is a product of the strength of individual synapses, but also of the physiology of the presynaptic neurons: Their ability to generate intrinsic bursts substantially increases the probability of triggering a postsynaptic burst by the process of temporal summation of EPSPs in the postsynaptic neuron.
- The size of the population of neurons exceeded a minimum aggregate, analogous to the critical mass of the nuclear chain reaction.

Similar studies of a range of acute convulsants show that the same basic ideas apply, although some details are specific to particular models, such as the relative roles of *N*-methyl-D-aspartic acid (NMDA) and non-NMDA glutamate receptors in the recurrent connectivity.[127,128,132,152] Similar approaches work in the neocortex, albeit with more complex neuronal architecture, and with the added importance of the strong connections with the thalamus.[53,120,125]

Termination of Interictal Bursts

Interictal bursts appear to be self-limiting. Several factors have been implicated in their termination, including afterhyperpolarization due to Ca^{2+}-activated K^+ currents,[27,44] GABA-mediated hyperpolarization,[132] depletion of available excitatory synaptic vesicles due to repeated release from the terminal during the epileptic burst,[118] receptor desensitization due to prolonged exposure to glutamate,[132] and presynaptic inhibition due to a variety of transmitters including glutamate, GABA, adenosine, and various neuropeptides.[82] In practice, several of these mechanisms may combine in each specific kind of epileptic activity. These self-limiting properties may contribute to the ability of interictal activity to inhibit seizures, which has been reported under at least some circumstances. Extending epileptic activity beyond the few hundred milliseconds of the interictal burst requires an excitatory mechanism that can outlast these termination mechanisms.[126]

The interictal epileptic bursts in hippocampal slices can be prolonged for up to a few seconds (resembling polyspikes on the human epileptic EEG) through the generation of repeated or "secondary" bursts (Fig. 4) following the initial "primary" burst discussed earlier (see Fig. 3). In an early simulation and experimental study of disinhibited hippocampal slices, it was found that the initiation of the primary (interictal) burst depended on non-NMDA glutamatergic receptors, but that the secondary bursts depended on NMDA receptors that could be blocked selectively.[135] The NMDA receptors did not contribute to the initiation of the primary burst because of their block with Mg^{2+} at resting membrane potentials, but the relief of that block by the PDS and the relatively slow kinetics of the NMDA receptor sustained an inward current beyond the termination of the afterhyperpolarization that normally terminated the burst. The secondary bursts then were shaped by the intrinsic properties (voltage-gated Ca^{2+} channels and Ca^{2+}-dependent K^+ channels) of the neurons, and synchronized by the glutamate released by each secondary burst acting on non-NMDA receptors (Fig. 4).[135]

Secondary bursts appear in other slice models, with slightly different mechanisms. In the case of 4-aminopyridine, the synchronization of the bursts is by non-NMDA receptors, and the sustained excitation needed for the secondary bursts may be due to depolarizing GABAergic potentials.[127]

Prolonged (Ictal) Epileptic Discharges in Vitro

Seizures in vivo are much longer-lasting than the interictal events described so far, and involve much larger areas than can easily be preserved, with their interconnections, in a slice. This is one reason why research on epilepsy in vitro should routinely be related to work in vivo. However, slices do exhibit prolonged "seizure-like" or "ictaform" events that can last tens of seconds. Such seizure-like events can be demanding—for example, submerged slices generally need rather high perfusion rates of ~4 mL/min to sustain them. One slice that does sustain seizure-like events is the combined hippocampal-entorhinal cortex slice, which is cut horizontally to include the ventral hippocampus and some relatively intact connections between these and other limbic regions (Fig. 5).[3,4,148] The entorhinal cortex and subiculum sustain such seizure-like events more easily than does the hippocampus proper,[6,34,40,154] but they can be induced in the hippocampus too, particularly in slices from young animals (Fig. 6).[19]

Enhanced Synaptic Excitation and Failure of Inhibition

The modulation of glutamatergic synaptic transmission can cause changes in excitation and promote seizure-like events in brain slices. Epileptic discharges can elicit long-term potentiation (LTP) of the synapses that sustain them,[36] increasing their efficacy and promoting epileptic synchronization (see also Chapter 35). Activating metabotropic glutamate receptors (mGluR) can promote seizure-like events in hippocampal slices: The induction of prolonged seizure-like activity depends on mGluR5, but its expression depends more strongly on mGluR1.[153] The "spill over" of neurotransmitters from the synaptic cleft may be especially important during the intense synaptic activity during epilepsy discharges, when it activates extrasynaptic receptors.[103] Furthermore, presynaptic receptors modulate transmitter release, whether in response to a presynaptic action potential[82] or not,[69] and can play a substantial role in epileptic discharges.

Equally important can be changes in inhibitory synaptic transmission. Inhibitory synapses can run down with repeated use.[123] They can become depolarizing instead of hyperpol- arizing,[117] perhaps because of impaired Cl^- homeostasis[28] or because of intracellular Cl^- accumulation due to excessive neuronal activity.[75] Depolarizing GABAergic potentials play a key role in prolonging epileptic activity in the low-Mg^{2+} model, in the CA1 region following excitation from the initial primary burst in CA3.[75] The depolarizing GABAergic activity drives a γ-band (30–100 Hz) oscillation that in turn leads to what can be termed tertiary bursts, making up a seizure-like event.

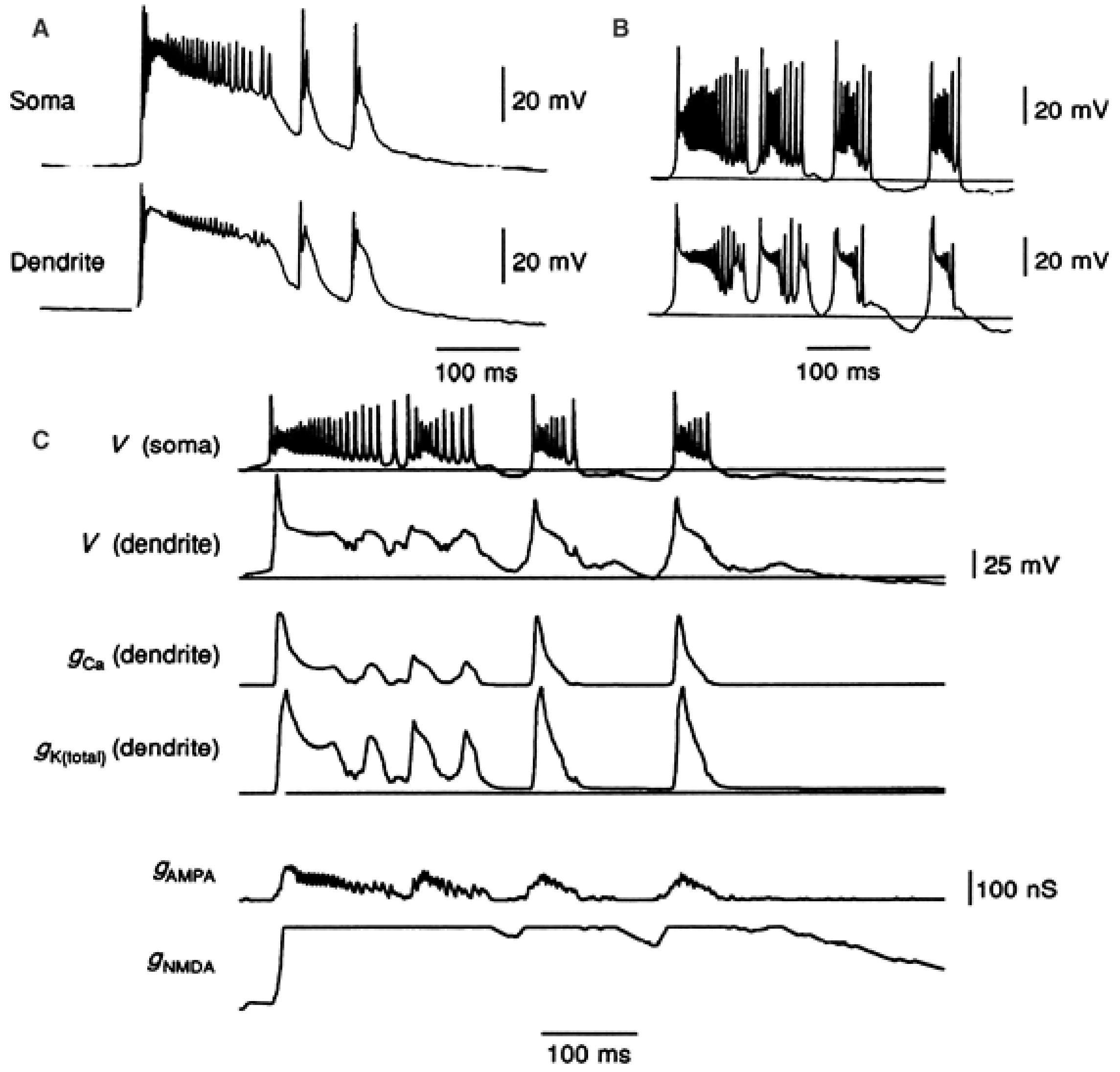

FIGURE 4. Polyspikes, or sequences of primary and secondary bursts, recorded with intracellular microelectrodes in the soma and apical dendrites of CA3 pyramidal cells in a guinea pig hippocampal slice bathed in picrotoxin (to block inhibition; (**A**) and in a simulation of a 100-cell network similar to that in FIGURE 3(**A**)). The model cells include both NMDA and non-NMDA (AMPA) glutamate receptors at the connections between the pyramidal cells, and these are shown in the summary of the model (**C**), where the dendritic data are for 0.6 space constants from the soma, the g_K term includes both medium and late AHPs. From Traub RD, Miles R, Jefferys JGR. Synaptic and intrinsic conductances shape picrotoxin-induced synchronized afterdischarges in the guinea-pig hippocampal slice. *J Physiol (Lond)*. 1993;461:525–547, with permission.

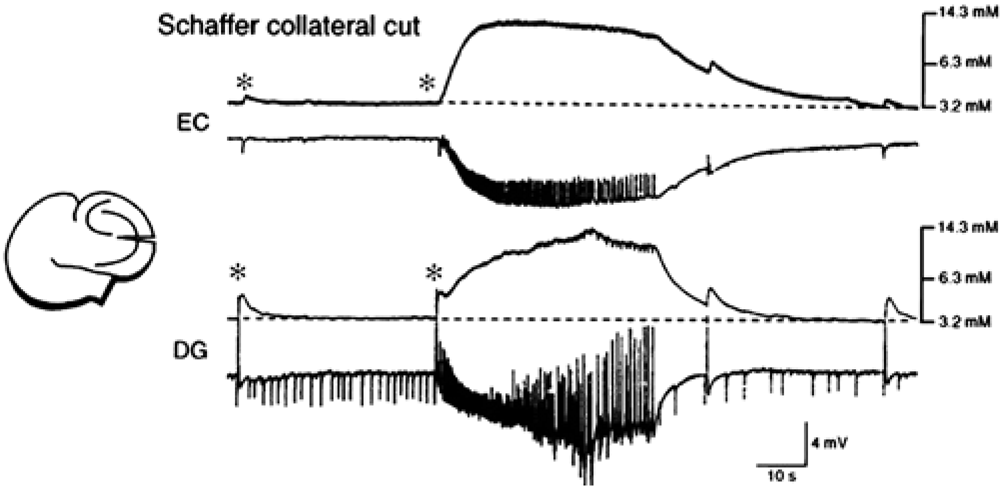

FIGURE 5. Fluctuations in extracellular K^+ measured in the rat combined hippocampal-entorhinal cortex slice exposed to 4-aminopyridine. The connection between CA3 and CA1 has been cut to remove the seizure-blocking effect of the interictal discharges generated by CA3. This allows seizure-like events to persist in entorhinal cortex (*EC*) and dentate gyrus (*DG*). Note the large, GABAergic interictal events marked by asterisks and associated with significant increases in K^+. One of these appears to trigger the seizure-like event. From Barbarosie M, Louvel J, D'Antuono M, et al. Masking synchronous GABA-mediated potentials controls limbic seizures. *Epilepsia*. 2002;43:1469–1479, with permission.

Increase in Extracellular Potassium

Epileptic discharges usually are associated with increases in extracellular K^+ from ~3 mM to a ceiling of 10 to 12 mM.[10,19,55] These increases in extracellular K^+ will feed back on the neuronal excitability in two ways: (a) by direct depolarization that results from the smaller gradient of K^+ across the membrane (and decreased repolarization after action potentials), and (b) by reducing the Cl^- gradient, as a result of the weakening of the drive to K^+/Cl^- cotransporters, thus weakening $GABA_A$ receptor–mediated inhibition.[124] These mechanisms also help explain the ability of elevated K^+ to elicit epileptic activity in brain slices in vitro[48,128](see Table 1).

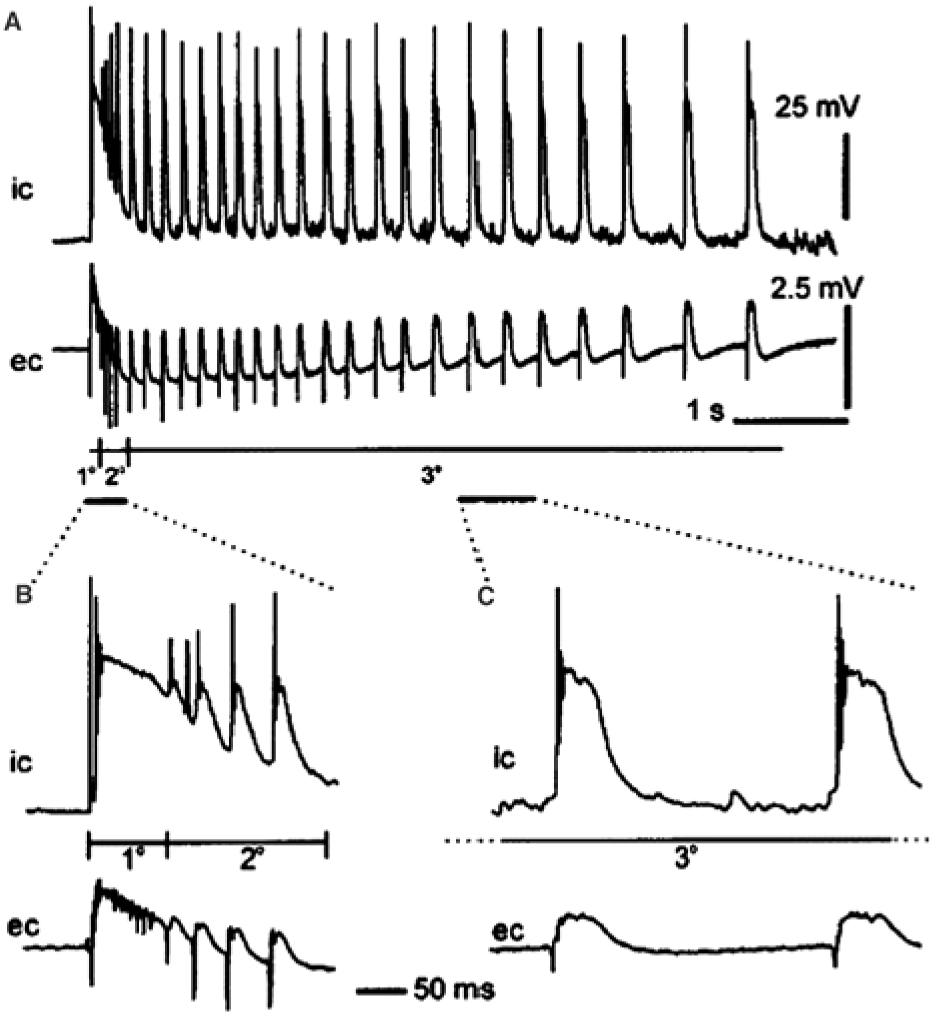

FIGURE 6. Prolongation of epileptic bursts in hippocampal slices showing primary, secondary, and tertiary bursts. The tertiary bursts occurred when extracellular K^+ reached 8 mM during an interictal event, and required both CA3 and the adjacent hilus. From Traub RD, Borck C, Colling SB, Jefferys JGR. On the structure of ictal events in vitro. *Epilepsia*. 1996;37:879–891, with permission.

At first sight, the increased neuronal firing during epileptic bursts is an obvious basis for the increases in extracellular K^+ during epileptic discharges, but the mechanisms can be more specific. For example, the combined hippocampal-entorhinal slice generates two kinds of interictal burst when exposed to 4-aminopyridine[10]: a glutamatergic chain reaction leading to minimal elevation of K^+, as described, and another mediated by GABA. The GABAergic version is associated with much bigger transients in K^+, which can trigger seizure-like events (see Fig. 5). The transporters that remove GABA from the extracellular space and Cl^- from the intracellular space both use the passive efflux of K^+ and therefore contribute to larger increases in extracellular K^+. A similar relationship between $GABA_A$ receptors and extracellular K^+ occurs in the seizure-like events seen in the low-Mg^{2+} (see earlier discussion) and tetanic stimulation models, in which depolarizing inhibitory postsynaptic potentials (IPSPs) sustain a prolonged depolarization and lead to increased extracellular K^+.[20,47,59,75]

When seizure-like events could be produced in disinhibited hippocampal slices (Fig. 6), they were associated with interictal bursts that produced increases in extracellular K^+ greater than 8 mM, suggesting that elevated K^+ provided the sustained excitation to drive the tertiary bursts in this case. In other cases, notably 4-aminopyridine, spontaneous ectopic action potentials may provide the sustained excitation needed to drive tertiary bursts.[126]

The dynamics of extracellular K$^+$ can be modelled using NEURON.[70] The movement of ions (particularly of K$^+$ ions) into a limited extracellular volume can be calculated from the currents through the various classes of ion channel. The model also needs to include elements to represent the glial compartment and the operation of ion pumps. It then can reproduce phenomena such as some kinds of epileptic seizure activity and spreading depression.[70]

Potassium is not the only ion released during epileptic activity that can modulate neuronal activity. For instance both zinc (Zn^{2+}) and hydrogen (H$^+$) can modulate postsynaptic receptors and other neuronal properties.[33,113]

Nonsynaptic Mechanism and Fast Activities in Seizure Transition

A very different kind of seizure-like event appears when Ca^{2+} is reduced to ≤0.2 mM and K$^+$ is increased to ≥5 mM. Despite the block of synaptic transmission under these conditions, hypersynchronous discharges lasting tens of seconds appear spontaneously. These are called "field bursts" (Fig. 7A).[65] These bursts exhibit at least two kinds of nonsynaptic synchronising mechanism[63]: fast synchronization, through the electric fields produced by active neurons (sometimes called ephaptic coupling); and slow synchronization, through fluctuations in extracellular K$^+$. Gap junctions also play a role.[26,136] These nonsynaptic mechanisms can operate in the presence of chemical synapses: The increase in extracellular K$^+$ associated with seizures has been known for decades, as has the sensitivity of neurons to electric fields smaller than those produced during seizures. The low-Ca^{2+} field bursts start with low-amplitude, high-frequency, irregular activity that continues for several seconds before the seizure-like event synchronizes fully (Fig. 7B).[15] Individual pyramidal neurons do not fire at these high rates (>100 Hz), but discharge on every second or third cycle (Fig. 7C), suggesting that the collective high-frequency activity is the combined consequence of multiple

small sets of synchronized neurons, and that the full seizure-like event emerges as these small sets fuse into a single large synchronous population that discharges rhythmically at ~30 Hz. The initial high-frequency activity has parallels to both the ripples and fast ripples that can be found in chronic experimental and human epileptic foci.[1,21,116]

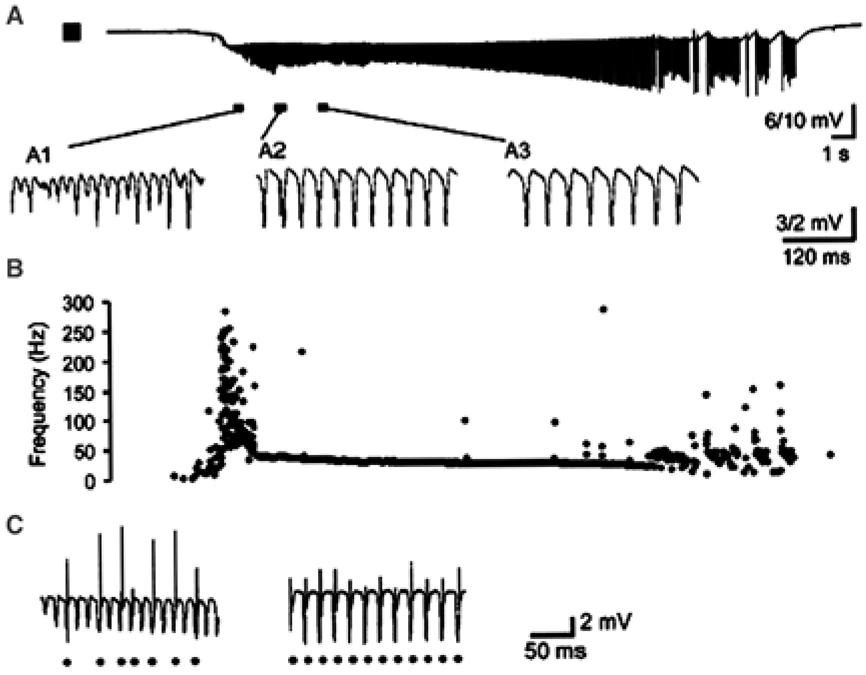

FIGURE 7. Seizure-like events, or field bursts, in rat hippocampal slices incubated in 0.2 mM Ca^{2+}. Field bursts (**A**) occurred rhythmically in these slices. They consist of a negative shift with superimposed negative population spikes (*inserts below A*). For most of the field burst, the population spikes occur at a

few tens of Hz (instantaneous frequency, or reciprocal of interspike interval is plotted in **B** at the same time scale as **A**). The very-high-frequency activity (>250 Hz) at the start of the field burst depends on the collective activity of neurons that do not fire on every cycle (**C**, *left*: Single unit produces a sharp upstroke on the negative population spikes), whereas the slower rhythmic activity later in the burst is generated by most neurons firing on every cycle (**C**, *right*: The apparently smaller size of the single unit is due to its firing close to the peak of the population spike). From Bikson M, Fox JE, Jefferys JGR. Neuronal aggregate formation underlies spatiotemporal dynamics of nonsynaptic seizure initiation. *J Neurophysiol*. 2003;89:2330–2333, with permission.

Glia

Glia are the most common class of brain cell. *Gliosis* is a consistent pathologic feature of focal epilepsies, which is most dramatic where neurons have died in substantial numbers, as in hippocampal sclerosis. Activation of microglia can occur in epileptic tissue, potentially producing inflammatory factors and contributing to epileptogenesis.[18,109] Astrocytes have long been known to play a role in K^+ homeostasis, in the "spatial buffering" hypothesis discussed earlier,[2,70,79,92,147] which is essentially an antiepileptic mechanism. Changes in K^+ currents found in sclerotic tissue in hippocampal slices from at least some patients with temporal lobe epilepsy (TLE) impair buffering and may contribute to epileptic activity.[56] More recently, the complexity of glial molecular biology and physiologic function have become much clearer. The reader is referred to several excellent reviews of the topic.[9,54,92] Astrocytes can release glutamate when their intracellular Ca^{2+} rises through mechanisms that are still under debate. Increases in intracellular Ca^{2+} can propagate through an inositol 1,4,5-trisphosphate (IP_3)-dependent mechanism throughout that astrocyte, and across the gap junctions that connect the glial syncytium. These phenomena provide plenty of scope for astrocytes to play an active role in epileptic discharges. Furthermore, astrocytes appear to play roles in synaptogenesis[111] and neurogenesis,[58] both of which are features of chronic epileptic foci.

Chronic Models Studied in Vitro

So far, this chapter has focussed on the effects of convulsant treatments on slices of normal brain. Epilepsy is by definition a chronic condition in which the brain contains abnormalities that lead to spontaneous seizures. Chronic experimental models go some way toward the clinical condition by altering brain structure and function, as discussed in Chapters 36, 39, and 40. In some chronic models, brain slices preserve epileptic activity in vitro; these can be investigated in ways similar to those used in acute models.[43,62] In other models, brain slices allow the investigation of the relationship between structural malformations and epileptic activity.[139] Perhaps the more important role of in vitro preparations made from chronic models, whether or not they preserve epileptic activity, is to find out what has changed in neuronal and network structure and function in the epileptic tissue.

Every chronic model has multiple changes in structure and function. In vitro preparations can reveal, and often quantify, many of these changes, including commonly recurring observations in chronic epileptic foci such as the sprouting of new axons and synapses, changes in neuronal excitability, and modifications in synaptic transmission.[108,144]

The sprouting of new synaptic connections is a common phenomenon in both clinical and chronic epilepsies. Mossy fibre (dentate granule cell axon) sprouting has been extensively characterised in many epilepsies, because they conveniently contain high levels of zinc and they rather specifically project to CA3 and not to the layers containing granule cell dendrites. Intracellular labelling methods in slices have shown sprouting by less easily visualised axons, such as those of CA1.[45] Physiologic methods show similar increases in connectivity. Antidromic responses evoked by focal electrical stimulation can identify the growth of axons into regions they do not normally innervate.[144] Focal application of glutamate allows an assessment of synaptic connectivity within the local circuits, without exciting afferent axons.[108] The methods used for focal glutamate application exploit the slice preparation very effectively: Pressure application through a micropipette is helped by being able to visualize the recording and application sites, whereas flash photolysis of a caged glutamate compound relies both on visualization and the ability to apply the flash to the correct zone in the tissue.

Slices allow the detailed pharmacologic and physiologic dissection of synaptic transmission that reveals many changes in chronic models, including alterations in the composition of

postsynaptic receptors,[93,141] release probability,[104] presynaptic modulation,[158] and extrasynaptic receptors.[104,105]

Changes in the properties or numbers of ion channels are common in chronic epilepsy. Several examples are known of increases in the proportion of intrinsically bursting neurons in chronic experimental models.[119,149] Given the role of intrinsic bursts in the acute models, as outlined earlier, it seems reasonable to conclude that this change contributes to epileptogenesis in the chronic models. The increase in intrinsically bursting neurons may be due to several molecular changes, including the upregulation of the low-threshold T-type Ca^{2+} channels[119] and/or changes in the properties of Na^+ channels, particularly slowing of their kinetics.[42,143] In the case of the animal models, we can be certain that the persistent Na^+ currents are related to the process of epileptogenesis, and the finding of similar changes in neurons isolated from surgically resected human epileptic tissue suggests that this applies to human cases as well.[145]

Several of the rare monogenic epilepsies are recognized as inherited channelopathies (see Chapter 18). When such a mutation is identified, the immediate question will be its functional consequences. This can be addressed by expressing the mutated gene in suitable cultured cells for subsequent electrophysiologic investigation.[11,146] Persistent Na^+ currents can drive burst firing, much as Ca^{2+} currents can,[149] but they also allow more rapid repetition of action potentials,[29] both of which are proepileptic.

In other cases, slices are essential for the analysis of ion channels, because their density varies along the dendrites: The truncation inherent in isolating individual cells can lose key epileptic changes. An interesting example comes from work on the pilocarpine model of TLE.[14] Dual whole-cell recordings from hippocampal slices showed that action potentials could invade further up the apical dendrites of pyramidal cells than normal. The pharmacology of this increased dendritic invasion (or back-propagation) showed that it could be attributed to a decrease in the density of the I_A channel.

Most of the changes outlined so far in this section are proepileptic, but work using slices in vitro and other approaches can reveal apparently antiepileptic phenomena in epileptic tissue, including changes in GABAergic transmission, neuronal excitability, glutamatergic transmission, neuropeptides, and so on.[16,52,100,142,144] Distinguishing pro- from antiepileptic changes in chronic epileptic foci remains a substantial challenge, and could suggest novel therapeutic approaches.

Summary and Conclusions

Electrophysiologic methods applied to brain tissue in vitro have provided major new insights into the cellular and synaptic mechanisms involved in epileptic activity. The strength of these methods is at the levels of ion channels, single cells, and local networks. These kinds of study benefit from quantitative computer models, especially those that can bridge the different levels of analysis, thus revealing the relationship between the properties and locations of ion channels to the firing characteristics of single neurons, or between single neurons and the emergent properties of the synaptic networks they form. Much of the benefit of in vitro preparations comes from their simplification of the problem of epilepsy, but this too is a limitation: Seizures involve interactions between multiple parts of the brain, which are not preserved with their interconnections in most preparations. In vitro preparations are important for epilepsy research, but they must be interpreted in the context of epilepsy in the intact animal or patient.

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Chapter 39

Seizure Mechanisms and Vulnerability in the Developing Brain

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Introduction

Throughout life, continuing maturational and functional changes within the brain impact seizure susceptibility and epileptogenesis. Early life is characterized by periods of excessive excitability to metabolic, electrical, and chemical stimuli as well as an inability to limit or suppress the effects of such stimuli. In humans, the incidence of seizures is highest in the first months of life, and several types of seizure disorders occur exclusively in infancy or childhood. Age-specific differences are noted in terms of motor behaviors and electroencephalographic (EEG) patterns, sensitivity to anticonvulsant treatment, and outcome. For example, in young childrenâ€"and particularly in infants and preterm neonatesâ€"behavioral and EEG phenotypes can be very subtle. Often, these seizures are missed, because of lack of motor phenomena, or considered generalized tonicâ€"clonic seizures because the features indicating focality are not overtly present. Another feature typical of early partial seizures is variability in clinical manifestations between individual seizures; the seizure phenotype is very much a function of brain developmental state. Unlike in the adult brain, focal dysfunction in the young brain can produce multifocal seizures or result in seizures with bilateral manifestations that can be loosely described as â€œgeneralizedâ€ (e.g., infantile spasms).[1]

Several factors, including altered permeability of the bloodâ€"brain barrier, continuing development of neurons and glia, and changes in neuronal connectivity contribute in many ways to developmental windows of increased seizure susceptibility. Such windows have been observed in all species in which studies of spontaneous or experimentally induced seizures have been performed, and these studies reveal differences that depend on developmental stage. To understand the mechanisms responsible for these age-related differences, it is necessary to examine developmental differences in experimental animal models of seizures. Comparisons to information from human studies can be invaluable and serve to validate the clinical significance of findings from animal studies. Animal models can also be useful in understanding the effects seizures have on brain development.

This chapter reviews experimental evidence from both in vivo and in vitro studies that demonstrate a critical period of heightened seizure susceptibility in early life. We also describe (a) age-dependent changes in the propensity for focal seizures with secondary generalization and in the expression of primary generalized seizures; (b) the age-dependent functionality of neuronal networks involved in the control of seizures, as demonstrated in animal models and human studies; and (c) the impact of seizures on brain development, including the circumstances under which early-life seizures may produce epilepsy and/or learning deficits in later life.

Critical Developmental Periods of Enhanced Seizure Susceptibility In Vivo and In Vitro

Experimental evidence shows that developmentally discrete periods of increased seizure susceptibility and expression exist. Several reviews of this topic are available.[154,183] The first period in the rat is during the first postnatal week, analogous to the preterm human infant; at this age, the immature rat brain exhibits an EEG pattern that can resemble the pattern of the preterm human.[91] Michelson and colleagues[116,117] have found that urethane-anesthetized or freely moving 7-day-old rats have the highest threshold for hippocampal afterdischarges. Mares also found elevated thresholds for hippocampal ADs in 7-day-old rats.[111] Seven-day-old rats have long refractory periods following electrical hippocampal stimulations, compared with rats in the second or third postnatal week.[11] In vitro intracellular recordings from hippocampal and neocortical slices taken during the first postnatal week have shown that action potentials routinely have slower rising and falling phases.[98,166,167] When seizures are elicited, they are far less synchronized than those recorded from tissue taken from rats 2 to 3 weeks of age.[98,167,186] Similar data have been obtained in kittens, in which electrical stimulations elicited broad action potentials and repetitive discharging was infrequent.[142,143]

During the second and third postnatal week of the ratâ€"ages roughly corresponding to human infants and young childrenâ€"peak susceptibility to focal seizures occurs. Indeed, the baseline EEG at these ages transitions from the patterns similar to the human neonate, to the infant and early childhood periods.[91] This increased excitability has been demonstrated in whole-animal experiments including neocortical focal epileptogenesis,[111] amygdala kindling,[128] hippocampal kindling,[73,118] hippocampal electrical stimulations,[193] hypoxia, hyperthermia, and systemic administration of chemoconvulsants.[127] In addition, at these same ages, numerous laboratories have demonstrated increased susceptibility to the induction of seizure-like activity using in vitro slice preparations. In most models, robust ictal events occur only during this critical period of seizures susceptibility. These ictal discharges can be readily induced by Î³-aminobutyric acid $(GABA)_A$ receptor antagonists, 4-aminopyridine, elevated extracellular potassium, hypoxia, and electrical stimulation.[43,77,78,91,186] Thus, the increased susceptibility to seizures during the second and third weeks of life is not restricted to a single structure or to a specific model, and it probably represents a widespread phenomenon intrinsic to a variety (but likely not all) of neuronal networks in the immature brain.

Mechanisms of Enhanced Seizure Susceptibility

Alterations in Synaptic Transmission

Glutamate.

The period of enhanced seizure susceptibility corresponds in time with a period of rapid axonal and dendritic outgrowth. The first 2 weeks of life in the rat and the first year of life in the human and primates are periods of dramatic increases in synaptic and spine density.[79,88,145] As the brain matures, an increase occurs in the number of excitatory synapses that use glutamate as their neurotransmitter.

Glutamate receptor subunit expression is developmentally regulated in a number of ways. There is prominent expression of the NR2B, NR2D, and NR3A subunits in rodents during the neonatal period, which gradually decreases over time, while simultaneously NR2A expression increases to as much as tenfold over levels of expression at birth.[120,158,213] The functional consequences of this â€œsubunit switchingâ€ is that, prior to the increases in NR2A expression, a net increase in excitability may be possible: NR2B results in longer current decay times,[61] whereas NR2D and NR3A expression are associated with minimal Mg sensitivity, thus resulting in an increase in both *N*-methyl-D-aspartate receptor (NMDAR) channel opening frequency and time.

Î±-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) expression is increasing simultaneously in the rat forebrain.[154,155] Furthermore, in early life, AMPAR expression is characterized by a relative lack of the GluR2 subunit in hippocampal and neocortical pyramidal neurons.[101,154,155,187,188] The lack of GluR2 allows for AMPARs to be calcium permeable, thus increasing intracellular signaling associated with glutamate receptor activation. Thus, differences in subunit composition could contribute to excitability during the critical period of neuronal hyperexcitability.

A limited number of human tissue studies confirm similar patterns of glutamate subunit expression across development. The mRNA for the NMDA receptor NR2B is expressed at high levels on principal neurons in cortex and hippocampus in the first year of life, whereas NR2A expression first appears around 1 to 2 years of age.[130] AMPAR expression is also highly developmentally regulated in the human. Immunocytochemical and Western blot analyses show that the GluR2 subunit does not appear on principal neurons in cortical gray matter until late in the first year of life,[171] suggesting that, like the rodent, immature human principal neurons express calcium-permeable AMPARs.

The changes in expression of molecular markers for glutamatergic synapses observed in early life in neocortex and hippocampus, as well as the number of synapses, most likely reflect an increase in both the number of excitatory fibers projecting from distant sites and the proliferation of local circuit connections. An example of the latter is excitatory axons that arise for CA_3 hippocampal pyramidal cells that make synaptic contacts with neighboring CA_3 neurons (both pyramidal cells and interneurons) and also project as Schaffer collaterals to CA_1 pyramidal cells. Studies on the maturation patterns of recurrent excitatory collaterals in CA_3 pyramidal cells[71] show that axon arbors are very short during the first postnatal week and, on average, branch infrequently. However, by the second postnatal week an exuberant outgrowth of these axons occurs, and branch number increases dramatically. Following this outgrowth, axon arbors appear to remodel. By adulthood, half the branches are lost, but the remaining axons increase in length concomitant with the overall growth of the hippocampus. The number of presumed presynaptic terminals increases dramatically from week 1 to week 2 and then remains unchanged into adulthood.

Alterations in Synaptic Transmission

GABA

Age-dependent differences in GABA-mediated synaptic transmission could also contribute to enhanced seizure susceptibility. In the rodent, $GABA_A$ receptors and glutamic acid decarboxylase (GAD) levels steadily increase until the third or fourth postnatal weeks, suggesting a relative lack of inhibitory tone in the immature brain compared with the adult.[27,185] Furthermore, a number of studies have shown that GABA is an excitatory neurotransmitter during early postnatal life.[42] This time period, postnatal (P)0 to P5, as originally reported, precedes the period of enhanced seizure susceptibility. Paradoxical depolarizing actions of GABA have been shown to be due to differential chloride (Cl^-) homeostasis in immature neurons compared with adult.[17,149] The immature neurons have high Cl^- concentrations since they lack the Cl^- extruding cotransporter KCC2, but have high expression of the Cl^- importer NKCC1.[57,149] Hence, GABA channel opening results in Cl^- outflow down the concentration gradient in the immature neuron, and hence to depolarization and neuronal excitation rather than the hyperpolarization and inhibition associated with Cl^- influx in mature cells. Rodent studies reveal that NKCC1 actually peaks during the first week of life, whereas KCC2 protein expression peaks between P5 and P10 (depending on rat strain) and does not reach adult levels until the end of the second week of life or even later.[17,149] The dramatic onset of expression of the Cl^- transporter, KCC2, is thought to herald a shift in the Cl^- reversal potential to a more hyperpolarized state, below the resting membrane potential.[150] Thus, during a developmental window, when recurrent excitation has become quite robust, excitatory GABA-mediated synaptic transmission in some pyramidal cells may further enhance excitability.[17,62,149] The relevance of Cl^- transporter maturation to the excitability of the immature brain is also supported by the fact that the NKCC1 inhibitor, bumetanide, can markedly attenuate seizures when administered to P7 rats.[57]

Limited parallel human data is available regarding the development of GABA systems. In human neocortex, $GABA_A$ receptors and GAD levels continue to increase into mid-childhood.[130] NKCC1 expression peaks around term.[57] In fact, KCC2 protein expression is not present in human neocortex until after 1 year of age, and rises to adult levels in early childhood.[57] Taken together, these observations suggest that, as in neonatal rodents, GABA inhibition is likely to be significantly reduced in human infancy and early childhood.

Alterations in Ion Channel Expression and Function

Developmental changes in the intrinsic properties of neurons and/or their responses to network input have been discovered and are governed to a large extent by the age-dependent expression patterns of ion channels. Indeed, work in both animal models and humans has highlighted the contribution of genetic and acquired changes in ion channel structure and function to states of hyperexcitability, seizure susceptibility, and frank epilepsy.[134,159,182,210]

Sodium channels.

Of the 13 expressed mammalian sodium (Na^+) channel genes, mutations in three subunits (Nav1.1, Nav1.2, Î²1) have been associated with epileptic phenotypes. The functional consequences of the nearly 200 different mutations identified in these genes are diverse,[115] but remarkably, the temporal evolution of the associated seizures indicates that the developing central nervous system (CNS) is particularly intolerant to these variations of Na^+ channel function. Seizures resulting from Na^+channel dysfunction commence during infancy or early childhood, and often disappear later.[163] The reasons for the developmental susceptibility to Na^+channel dysfunction are not clear. Although age-dependent expression patterns of Na^+channel subunits have been described,[14,31,72] they do not define vulnerability windows, when only a single isoform is expressed in the CNS, nor do they suggest maturation-related compensatory upregulation of nonaffected isoforms. Alternatively, the apparent age-specificity of these Na^+-channel defects may be a result of age-specific insults that interact with these channels. For example, increased temperature (fever) may unmask specific deficits of mutated Na^+ channels.[174] Consistent with this notion, sodium channel defects are particularly common in individuals with febrile seizures plus (FSP).[163]

Potassium channel superfamily.

Developmental susceptibility to seizures that is governed by the function of potassium (K^+) channels is evident from studies of dysfunction of two members, KCNQ2 and KCNQ3, that carry the M-current, a slowly activating outward current that regulates subthreshold excitability and prevents repetitive action potential firing.[218] Mutations in these lead to benign familial neonatal convulsions, seizures that occur during the first days and weeks of life and disappear later.[45] Whereas age-dependent expression of splice variants of these channels have been described,[171,190] they seem to play little role in the temporal onset and resolution of the seizures. Intriguingly, the M-current, carried by these channels, may serve as a major inhibitory mechanism during the age when GABA is depolarizing,[136] so that even a 25% reduction of the current is sufficient to induce seizures,[93] explaining the occurrence of seizures neonatally. Once the role of GABA is reversed from depolarizing to inhibitory (e.g., the second postnatal week in the rat), a new powerful inhibitory system comes into play, so that persistent dysfunction of the KCNQ channels no longer renders the neuron hyperexci-table.

HCN (or h) channels, members of the K^+ channel superfamily, contribute to the maintenance of resting membrane potential, integration of dendritic excitability, and neuronal depolarization in response to network input.[138,151] The properties of the h channels are governed by the types of HCN channel isoforms that the neuron expresses, and the expression of HCN channel isoforms (1, 2, and 4) varies drastically as a function of age.[18,26] Importantly, hippocampal maturation is associated with marked increase in the expression of the HCN1 isoform[26] that tends to dampen dendritic excitability and minimize rebound depolarization in response to hyperpolarizing input[140] and could contribute to reduced seizure susceptibility in the juvenile and adult brain.[159]

Calcium channels.

Calcium (Ca^{2+}) channels are involved in age-specific seizure vulnerability at a somewhat later age than the neonatal-infant period discussed here. In the human, dysfunction of members of the (Ca^{2+}) channel superfamily (Cav2.1, Cav3.2, Î²4) may be involved in absence seizures.[41,58,95] An elegant explanation for the age-specific contribution of the Cav2.1 subunit to seizure susceptibility has been provided in experimental models by Noebels.[134] In neonatal mouse thalamic neurons, neurotransmitter release is dependent on both N- and P/Q-type channels.[89] With maturation, this function is taken over exclusively by the P/Q-type channels, formed by Cav2.1 subunits, so that dysfunction of these channels provoked seizure vulnerability.

The understanding of the contribution of intrinsic ion channels to age-dependent seizure vulnerability is rapidly evolving. New ion channels are being discovered that are expressed in an age-dependent manner and may enhance excitability in developing neurons (e.g., NKCC1),[57] thus further highlighting the importance of function and dysfunction of intrinsic ion channels to seizure susceptibility early in life.

Alterations in Peptide Neurotransmitters

Neuropeptides are released from neurons and can influence the excitability of a neuronal network through metabotropic receptors at post- or presynaptic sites (or both). Neuropeptide Y (NPY) is expressed in developing and adult rodent hippocampus in modest amounts.[5,80,168] Interestingly, it is also found in human hippocampus, starting prenatally and persisting to adulthood.[108,217] NPY, acting via the Y2 (and possibly Y5) receptors, reduces network excitability and seizure susceptibility.[44,205] Whether the relatively low levels of NPY during early development[5] contribute to the enhanced vulnerability of the hippocampus is unknown.

Corticotropin releasing factor (CRF) or hormone (CRH) is an excitatory neuropeptide that reduces spike afterhyper-polarizations,[4] and interacts with glutamatergic neurotransmission to promote excitability in vitro.[10,83] In vivo, the administration of CRH causes age-specific seizures, especially when infused in immature hippocampus. Hippocampal CRH receptors peak during the first 2 postnatal weeks in hippocampus and amygdala.[10] Interestingly, *endogenous* CRF is much more abundant in developing compared with mature hippocampus.[39] Thus, the actions of the endogenous peptide (which is released during stress)[40] favor increased excitability and seizure vulnerability during development.

Age-Dependent Alterations in Patterns of Seizure Propagation

Kindling is one of the best models of epilepsy to study the patterns of seizure propagation.[70] Kindling, once induced, permanently changes the susceptibility of the brain to seizures.[70] Amygdala or hippocampal kindling can be produced in 8- to 15-day-old pups using frequent stimulations (e.g., every 15 minutes).[105,123] In adults, stimulations delivered every 15 minutes either significantly retard or fail to induce kindling.[70,123,139,144] Progression through the various seizures stages in young animals is different from kindled seizure stages in prepubescent and adult rats. Stages 0 to 2 represent local events, stage 3 the involvement of the hemisphere ipsilateral to the stimulation site, stages 4 to 5 bilateral (generalized) seizures, while stages 6 and 7[74] may reflect spread to the brainstem.[29,32,64] Compared to older rats, pups spend proportionally less time in the early stages of kindling (stages 0â€“2) that are associated with focal seizures.[128] Instead, there is an early appearance of bilateral, although often asynchronous, seizures, indicating a tendency for seizure generalization. Pups experience many stage 3 to 4 seizures intermixed with isolated stage 5 seizures, followed by the explosive onset of stage 6 and stage 7 seizures.[74] Spontaneous seizures occur more readily in pups compared with adults.[11,75]

Another difference between adults rats and 15-day-old rat pups involves the phenomenon of *kindling antagonism.*[7] In adult rats, concurrent kindling of two limbic foci results in the suppression of generalized seizures from one or both sites. Pups do not show kindling antagonism to the development of generalized seizures between amygdala and hippocampus, or between the amygdala.[74] These data may indicate that, early in life, different brain areas can mutually enhance their epileptogenic potential and lead to the development of multifocal epilepsy, a common clinical phenomenon in young children, especially in those with infantile spasms. The data also suggest that, during the critical period, the immature CNS is more prone to the development of secondary generalized seizures. Thus, increases in seizure susceptibility extend beyond the local generation of epileptic discharges and involve mechanisms of seizure propagation to additional structures.

Kainic acid (KA) is commonly employed to induce focal seizures with secondary generalization throughout postnatal life. Administration of this excitatory amino acid leads to the development of seizures in all ages; however, the seizure manifestations are age-dependent, with specific manifestations such as scratching and swimming-like movements occurring in rats less than 15 days of age, while â€œwet dog shakesâ€ are rare in these ages.[3] Tonicâ€“clonic seizures are regularly elicited in 7- to 25-day-old rats; however, their frequency decreases with age, especially after the third postnatal week. Rat pups are also more prone to develop status epilepticus (SE) than adult rats. In all age groups, EEG seizures start in the hippocampus; however, in young rats rapid involvement of the cortex occurs.

Age-Dependent Differences in Animal Models of Generalized Seizures

Most developmental models of generalized, predominantly motor seizures rely on the systemic administration of a chemoconvulsant, usually a GABA-related substance. The most commonly used agents are pentylenetetrazol

(PTZ), bicuculline, or picrotoxin, and glutamate agonists such as kainite.[126,192,195] After day 7, the seizures consist of motionless state (freezing), myoclonic twitches, face and forelimb clonus, and generalized tonicâ€“clonic movements. These seizure types, their latency to seizure onset, and their EEG correlates are dose dependent. The EEG correlate of motionless stare are rhythmic spike-and-wave discharges in a spindle-shaped envelope. Myoclonic body twitches are usually associated with isolated spike-and-wave discharges. Clonic and tonicâ€“clonic seizures may have similar EEG correlates consisting of fast multiple spike-and-wave discharges. The chemoconvulsant-induced phenomena are thought to be the models of different human seizures. The motionless state and its associated rhythmic EEG activity is considered to be the model of human absences. Clonic seizures are considered a model of human myoclonic seizures, whereas tonicâ€“clonic seizures may represent a model of primary generalized tonic-clonic seizures.

The expression of drug-induced motor seizures is age-dependent.[192] Thus, with PTZ, clonic motor seizures are not often observed in rat pups prior the second postnatal week, rather swimming-like movements occur, reflecting an immaturity of the motor pathways; the CD_{50} for clonic seizures remains constant after the third postnatal week. Myoclonic twitches and tonicâ€“clonic seizures occur throughout development, but the CD_{50} increases progressively with age. In rats less than 7 days old, the only seizure manifestations may be swimming movements of all four limbs, not accompanied by any EEG correlates. EEG discharges can be dissociated from behavioral seizures, and the duration of the epileptiform discharges decreases with age. Sharp waves become spikes after the second postnatal week, whereas the onset of electrographic seizures is synchronized in all areas after the third postnatal week.[165] With flurothyl, the seizure threshold increases with age. The clonic seizures become more apparent as the animal reaches the second week of life. During the first two postnatal weeks, clonic seizures in the majority of the models rapidly progress into tonicâ€“clonic seizures. Thus, clonic seizures may be masked by tonicâ€“clonic seizures.[200,203] One reason for the dissociation between behavioral and electrographic seizures may be the lack of cortical involvement in the expression of seizures in developing animals. Metabolic studies using the deoxyglucose technique have revealed that, in adults during clonic seizures, metabolic activity increases in the cortex, hippocampus, globus pallidus, and substantia nigra (SN). During tonicâ€“clonic seizures, metabolic activity increases also in the midbrain structures.[16] In contrast, in developing animals, decreases in neocortical activity occur with increases of activity in brainstem structures.[126,175,192] One notable exception is the lack of activation of the SN, a structure thought to play an important role in the control of generalized seizure.[125]

Generalized seizures can also be induced by electrical stimulation (electroshock seizures). Depending on the intensity the stimulating current, two types of seizures may occur:[110] minimal clonic seizures involving clonic movements of the head and forelimbs and maximal, generalized, tonicâ€“clonic seizures with a loss of righting reflexes. Minimal seizures probably represent a model of myoclonic seizures, and are generated in the forebrain.[107] Maximal electroshock seizures (MES) are a model of generalized tonicâ€“clonic seizures, and involve brainstem structures.[28] The mature pattern of MES emerges during the third postnatal week in the rat; younger animals show only forelimb flexion (PN 10â€“12 or earlier), or forelimb flexion followed by forelimb extension and hindlimb flexion (PN 13â€“15).[204]

Drug-induced models of absence seizures also are available.[46] The acute pharmacologic models of typical absence seizures are induced from systemic administration of a single pharmacologic compound [4,5,6,7 tetrahydroxyisoxazolo (4,5,c) pyridine 3-ol (THIP), Î³-butyrolactone, PTZ, or penicillin]. With appropriate doses, their administration leads to bilaterally synchronous spike-and-wave discharges associated with behavioral arrest, facial myoclonus, and twitching of the vibrissae. An acquired chronic model of atypical absence seizures has been derived from a timely prenatal administration of methylazoxymethanol (MAM) in combination with postnatal systemic administration of an inhibitor of cholesterol, AY-9944. For this seizure type, genetic models of absence epilepsy also are available, such as the GAERS and WAG/Rij rats, as well as various mouse mutants.[133]

Age-Dependent Activity of Brain Networks Mediating Seizure Control

Circuits involving several subcortical nuclei can regulate seizures. One such system includes a GABA-sensitive SN-based circuit. The SN and especially the pars reticulata (SNR) may be critically involved in the expression and control of bilateral, generalized seizures in rats.[125] The nigral effects are operative in both seizures of local origin (kindling) and seizures that appear to be generalized from their onset (flurothyl-induced seizures). These nigral effects on seizures are age- and sex-specific[196] and appear to involve two distinct regions within the SNR,

$SNR_{anterior}$ and $SNR_{posterior}$. The segregation occurs with maturation; before the third week of life, only one functional SNR region is present. Both GABAergic and glutamatergic systems are involved, with ample information on $GABA_A$-mediated neurotransmission available.[22,23,51,63,65,66,67,113,114,124,125,196,198,202] In male adult rats, bilateral microinfusions of muscimol into the $SNR_{anterior}$ produce anticonvulsant effects, whereas microinfusions into the $SNR_{posterior}$ are proconvulsant.[122] In male immature (less than 25 days old) rats, there is no regional compartmentalization for the SNR effects on seizures, and muscimol infusions produce only proconvulsant effects. Studies in female rats show that the effects of the SNR on seizures are sex-specific with differences in the maturation patterns and a universal lack of SNR-mediated proconvulsant effects following muscimol microinfusions.[199] Maturational changes in electrophysiologic neuronal properties, in subunit composition of $GABA_A$ receptors, expression of KCC2,[62] and in the output targets may each contribute to the emergence of pro- and anticonvulsant regions within the SNR.[194,197,198,202] The sex-specific differences appear to be under the control of postnatal testosterone and its metabolites.[69a,199,200]

Impact of Early-Life Seizures: Chronic Hyperexcitability and Epilepsy

Early-Life Status Epilepticus

Animal models have contributed significant data toward the understanding of SEâ€“related sequelae, and they offer the

opportunity to explore cellular, molecular, and functional changes following status as function of age and sex. In models, the pre-existing substrate is known, and thus changes occurring following status can be considered causally related to the status per se, although the means by which status was induced may have an impact. Combining different data sets can identify common model-independent findings. The consequence can vary depending on whether status is induced in animals with normal or abnormal brains.

Studies in animals with normal brains have shown that the immature brain is relatively resistant to SE-induced morphologic damage.[9,34,183,201] Long-lasting status, regardless of seizure origin (nonlimbic or limbic), induced by flurothyl,[176,208] pentylenetetrazol,[131] NMDA,[178] or KA,[3,15,76,179] and pilocarpine[34] is associated with little or no neuronal damage in the hippocampus or extrahippocampal regions in rats younger than 3 weeks. Synaptic reorganization in the supragranular layer of the dentate gyrus of the hippocampus does not occur following status before the third postnatal week.[19,76,157,177]. Many factors may contribute to the relative resistance of immature hippocampus to status-induced damage.[81] With maturation, the extent of hippocampal damage increases.[3,85,157]

It should be noted that several groups suggest that a degree of hippocampal or extrahippocampal injury may occur after SE during early development.[12,47,48,76,99,148,156,157,179,189,209] However, the extent of damage is far less prominent compared to status-induced changes in adulthood. Status early in life may also prime the brain to the effects of subsequent insults.[69,97] These consequences may be either detrimental to the brain or, in some cases beneficial, as is the case with the effects of 1-hour-long flurothyl status on subsequent focal ischemic insult later in life.[69]

The relationship of status to the subsequent development of epilepsy in normal immature brain is also age-dependent. In rats younger than P21 days, spontaneous seizures do not occur following KA, and are rarely observed following lithium/pilocarpine-induced SE.[157] In 21-day-old rats, spontaneous seizures occur irregularly in 10% to 73% of animals, depending on the seizure model used.[141,152,179,207] In adult rats exposed to status, the incidence of seizures reaches almost 100%.[179,207] Furthermore, 15-day-old rats exposed to KA-induced status are not more prone to develop amygdala-kindled seizures as adults than are controls; this is not the case in adults.[137] MRI changes identified within 48 hours after status can predict which 21-day-old rats will develop seizures.[152] Only rats with visible structural MRI abnormalities or without visible abnormalities, but with changes in T2 relation time, developed spontaneous seizures. Not all rats with epilepsy showed hippocampal damage. Three episodes of pilocarpine SE in 7- to 9-day-old rats produced long-term changes in epileptogenesis.[160]

Very few studies assess whether SE-induced neuronal damage may be enhanced in the setting of a compromised brain in developing rats. These studies seem to suggest that, in this scenario of a two-hit hypothesis, an augmentation of hippocampal injury occurs following status.[104,122,215]

With regard to two-hit models, a recent study by Scantlebury et al.[162] reported that hyperthermic seizures induced in P10 rats with a single freeze-lesion resulted in 86% of rats with spontaneous limbic seizures. Controls with freeze lesions were not epileptic, and a minority of those with hyperthermic seizures had abnormal EEGs.

Febrile Seizures

Febrile seizures (FS) are the most common type of seizures in infants and young children,[181] and it is important to understand their impact on the developing brain and potential contribution to epileptogenesis. To probe directly the mechanisms by which these seizures might contribute to temporal lobe epilepsy (TLE), several models are available, including one employing hyperthermia-induced seizures of 20-minute-duration evoked on postnatal day 10,[52,53,54,55,56] and those using heated water[68,121] or heated copper sheets.[86]

Early-life experimental FS produce a chronic state of hyperexcitability in an otherwise neurologically normal brain. This is manifest in vivo as an increased seizure susceptibility in animals experiencing experimental FS to convulsants given later in life, as compared with naive or hyperthermic controls,[52] the presence of interictal discharges in hippocampal EEGs in 88% of adult rats that had experienced prolonged FS early in life,[53] and the emergence of spontaneous seizures in a proportion (~35%) of FS-experiencing rats.[53] In vitro studies further localized this long-lasting hyperexcitability to the hippocampal circuit, despite increased inhibitory drive onto CA1 pyramidal cells.[37,52]

These findings raised the question of the mechanisms by which prolonged FS febrile seizures may convert a â€œnormalâ€ developing brain into a hyperexcitable or proepileptic state. The underlying mechanisms are not yet fully understood, but available evidence indicates that subtle changes of network properties rather than gross morphologic alterations play a role. Experimental prolonged FS do not kill neurons.[20,53,55,191] However, these seizures led to a significant and long-lasting change in the expression pattern of a specific ion channel, the hyperpolarization-activated cyclic adenosine monophosphate (cAMP)-regulated (HCN) channel (see the earlier discussion on ion channels). This â€œacquired channelopathyâ€ consists of coordinated, enduring changes in the expression of several subunits of this channel family, altering the current they conduct, I_h, in hippocampal pyramidal cells.[24,151,159] The mechanisms by which these changes promote hyperexcitability are discussed elsewhere.[36,159] It should be noted that, whereas transient changes in the pattern of HCN expression are found also af-ter kainate-evoked SE in the P10 rat, enduring transcriptional as well as posttranslational dysregulation of the HCN channels are unique to experimental FS,[25] and may derive from the involvement of cytokines in these, but not other seizures, during this stage of development.[54] Striking changes of the HCN channels are also found in human hippocampus from individuals with severe TLE and hippocampal sclerosis.[19]

Early-Life Hypoxia-Induced Seizures

Hypoxic encephalopathy is the major cause of neonatal seizures in the human infant.[2] Hypoxia-induced seizures can be associated with later-life neurocognitive effects and epilepsy.[21,60,132] Rats show a similar susceptibility to the epileptogenic effects of seizures in the immature period.[154]

The exposure of rats to a brief period (15 min) of global hypoxia (5%â€“6% O_2) around P7 to P12, depending on strain, results in both behavioral and electrographic seizures.[91,92] In addition, these rats exhibit increased susceptibility to chemoconvulsant seizures later in life.[92,96] Hypoxic seizures are not associated with either immediate or subacute neuronal death in forebrain structures.[92,96] However, a number of alterations in neurotransmitter receptors and signaling pathways are observed in the surviving hippocampal and cortical principal neurons. Both the mRNA and protein for the GluR2 subunit appear to downregulate within 1 to 2 days following hypoxic seizures at P10, suggesting an increase in the number and activity of calcium-permeable AMPARs.[155] In addition, activation of existing calcium-permeable receptors by hypoxia in turn activates a number of signaling cascades that result in posttranslational receptor modification.[153] Within minutes following a seizure in a P10 rat, AMPAR activation of the phosphatase calcineurin by calcium causes dephosphorylation of $GABA_A$ receptors and a decrease in inhibition.[153] Decreased inhibition due to GABA dephosphorylation and an increase in calcium

permeability due to downregulation of GluR2 may contribute to the enhanced network excitability seen in the hours to days following hypoxic seizures. It is likely that these changes are not specific to hypoxia, but that alterations of neuronal function and molecular structure occur in surviving neurons in the immature brain, given the lack of neuronal death.

Brief but Recurring Seizures

In addition to SE and seizures induced by hypoxia/ischemic episodes at birth, a clinical condition often encountered in young children is brief but recurring seizures. This is particularly true in children who are unresponsive to anticonvulsant medication. Thus studies have been undertaken to determine the effects recurrent seizures have on brain development. Particularly important is the question whether recurrent seizures in early life contribute to the epileptogenic process.[13] Do periods of repetitive seizures in early life increase neuronal excitability and/or produce epilepsy? To address this question, several animal models have been used. The tetanus toxin model, which was introduced a number of years ago in adult rats,[90] has been employed in immature animals.[103] Seizures are induced by a single unilateral stereotaxic injection of a very small quantity of tetanus toxin into the dorsal hippocampus on postnatal day 10. Tetanus toxin is known to block transmitter release by the proteolytic degradation of the synaptic vesicle docking protein, synaptobrevin.[49] However, tetanus toxin acts preferentially on inhibitory nerve terminals.[214] It is thought that by the selective blockade of GABA release, tetanus toxin is able to induce seizures. Tetanus toxinâ€“induced seizures in infant rats begin 24 to 48 hours after hippocampal injections. Long-term video-EEG (V-EEG) recording has shown that rat pups experience brief (30â€“120 sec) but recurring seizures. Seizure frequency peaks 5 to 6 days after injections, then rapidly declines. Rats are likely to experience as many as 50 to 100 seizures in the week following tetanus toxin injection.[147]

A number of studies of the tetanus toxin model have been carried out to characterize the effects of recurring early-life seizures. In this model, brief but recurring early-life seizures produce a chronic state of hyperexcitability that is most often characterized by interictal spiking on the EEG and in hippocampal slice recordings.[102,103,172] Spontaneous, electrographic seizures are far less frequent, commonly do not have a behavioral component, and likely occur in rats that have experienced very frequent seizures in early life.[6] Nonetheless, all animals appear to have an increased propensity for seizures when exposed to a convulsant.

The flurothyl model is a second model that has often been used to induce recurrent seizures in early life. Rats or mice are exposed to this volatile convulsant in an enclosed chamber. Flurothyl is thought to produce seizures by opening Na^+ channels diffusely and possibly by blocking $GABA_A$ receptors.[206] In most studies, between 25 and 50 seizures have been induced in infant rats. Spontaneous behavioral seizures have not been reported later in life in flurothyl-treated animals. Epileptiform activity has not been observed on EEG recordings.[50] However, significant decreases in seizure susceptibility have been reported later in life when the threshold to flurothyl[87,173] or pentylenetetrazol[84] have been examined. Thus, as in the tetanus toxin model, flurothyl-induced seizures appear to increase neuronal excitability long-term. However, the degree of hyperexcitabilty does not appear to be sufficient to result in overt epilepsy or interictal spikes on the EEG.

Impact of Early-Life Seizures: Learning and Memory Deficits

The catastrophic epilepsies of infancy and early childhood are often associated with learning deficits, including mental retardation.[33,82,135,170] Infantile spasms and Lennox-Gastaut syndrome (LGS) are among numerous severe childhood seizure disorders characterized by frequent seizures. It is not uncommon for a child to be developmentally normal before the onset of such seizures, only to have his cognitive abilities fail to progress or even regress in the face of unremitting seizures. This has led many to wonder if seizures contribute to cognitive decline.[112] However, it remains controversial if early-life seizures hinder learning and the formation of memories, since other factors, such as an accompanying neuropathology or anticonvulsant therapy, could be responsible for cognitive problems. However, recent results from numerous animal studies support the notion that early-life seizures may impair learning, although it was much different from that of seizures in adults.

Status Epilepticus

Since the mid 1980s, a large number of studies have examined the long-term cognitive effects of SE in the developing rats.[180] These studies varied greatly in the way in which seizures were evoked, the age at which they were induced, the age at which behavioral testing was undertaken, and the behavioral tests employed to evaluate outcome. Thus, comparison of results can be difficult. Nonetheless, in general, results reported suggest that SE in early life does not have as severe impact on cognitionâ€"particularly spatial learning and memoryâ€"as similar seizures in older animals, starting from 21 days of age.[100,109,161] One explanation for this age-dependency could be that SE incrementally induces neuronal cell deathâ€"particularly in hippocampusâ€"after 21 days of age in the rat.[109] Neuronal cell loss, especially in the hippocampus, would be expected to lead to spatial learning and memory deficits. Since neuronal loss has been more rarely reported during the first 2 to 3 weeks (see previous discussion) of life, the acquisition of spatial memories might not be expected to be as severely impaired. Nevertheless, although a prolonged seizure in early life may not kill neurons in the CNS, they appear to produce other cellular and molecular changes that result in life-long deficits in learning and memory.[109,161]

Brief Recurring Seizures

Unlike studies of SE, the effects of brief but recurring early-life seizures have consistently shown that they produce spatial learning and memory deficits later in life.[13] The majority of reports of memory and learning deficits following recurrent early-life seizures come from studies of the flurothyl model.[50,84,87,106,173] In most studies, seizures were induced beginning on the day of birth and extended through the first week of life; in some studies, seizure induction extended to postnatal 9 or 11, in order to increase the number of seizures evoked. In some studies, as few as 15 seizures were elicited; in others as many as 55. Rats could be tested for behavioral deficits as early as P24 or as late as P82. The Morris water maze and a subsequent probe test were used to assess spatial learning and memory. In all studies, the authors conclude that learning and memory were impaired. By comparing outcomes from several publications it would appear that the more seizures a rat experiences as a neonate, the more robust are the behavioral effects.

The behavioral effects of tetanus toxinâ€"induced seizures in early life have been reported to be quite robust also and comparable to the most dramatic reports from the flurothyl model.[102] This might be expected, because after a single injection of tetanus toxin, rats can experience as many as 50 to 100 seizures.[146] When these rats were 2 months of age, learning was compared across the three groups in the Morris water maze. The rats that had experienced recurrent seizures in early life were found to be markedly deficient in their ability to learn when compared with control groups. One possible confounding factor in studies of the tetanus toxin model is that, as adults, a significant fraction of the rats display epileptiform activity on the EEG (see earlier discussion). Subclinical seizures or even interictal spiking may interfere with the ability of neuronal networks to acquire new memories. To address this issue, EEG recordings were undertaken after rats were trained in a water maze.[102] Results showed that rats without interictal spikes were just as impaired in their spatial learning abilities as those that had interictal spikes. Thus, the presence of interictal discharging could not explain the poor performance in this spatial learning task. The results are also in full accord with results from the flurothyl model, in which rats have been shown not to display epileptiform activity but are learning impaired.

A febrile seizure model in which rat pups were repeatedly made hyperthermic on P10 to P12 is a third model that has been employed recently to study the effects of brief but recurrent seizures.[35] Nine seizures were induced (three each day) that were 4 to 5 minutes in duration. The Morris water maze and probe test were used to access impaired cognition beginning on P60 and, as in all the other studies reviewed earlier, rats that had experienced recurrent seizures were cognitively impaired. Additional experiments showed that the learning deficits were not produced by hyperthermia but depended on the presence of recurring seizures. Thus, results from three different animal models are fully in accord with each other and suggest that brief but recurring seizures in early life can impair an animal's ability to acquire new memories.

Underlying Mechanisms

Because neuronal death does not appear to contribute to the learning deficits in rats that have experienced seizures in infancy, identification of other potential mechanisms is important. One possible clue comes from a neuroanatomic study of hippocampal pyramidal cells in the tetanus toxin model of early-onset epilepsy.[94] Marked alterations were observed in the dendrites of CA3 neurons, which included a reduction in branching complexity of basilar dendrites as well as a decrease in spine density on both the apical and basilar dendrites. Similar observations have been made in human tissue obtained during epilepsy surgery.[184] In studies of hippocampal and neocortical foci, a decrease in length and branching complexity of dendritic arbors was observed, as well as a reduction in spine density on the remaining dendrites.[129,164] Similar observations have been made in the chronic alumina cream model of epilepsy in primates.[212] Because dendrites and dendritic spines are sites of excitatory synaptic input onto neurons, the results suggest that glutamatergic synaptic transmission may be reduced. Moreover, because these synapses are recognized sites of activity-dependent alterations in synaptic transmission (e.g., long-term potentiation [LTP]), that are thought to underlie learning and memory,

[169] studies that examine how seizures reduce dendritic arbor complexity in the brain could be an important step in understanding the mechanisms responsible for learning and memory deficits associated with early-onset epilepsy.

Two recent lines of investigations are beginning to demonstrate how seizures may impair dendritic structure and function. The first is based on the fact that seizures in early life are stressful and activate stress-mechanisms, including the secretion of the excitatory neuropeptide CRH from hippocampal neurons.[40] As mentioned earlier, both the peptide and its receptor are abundant in developing hippocampus.[8,39] Recently, Chen et al. found that even in picomolar amounts, CRH interferes with dendritic growth and differentiation.[38] Mice lacking the CRH receptor had exuberant dendritic trees, whereas hippocampal pyramidal cells exposed to CRH during the first week of life had â€œatrophiedâ€ dendrites. The relevance of the stress-evoked, CRH-mediated damage to dendritic structure for cognitive deficits was highlighted in a recent report.[30] Early-life stress led to strikingly impoverished dendritic trees of hippocampal neurons later in life, and this was accompanied by learning and memory impairment, as well as reduced synaptic plasticity (LTP). The possibility that CRH may contribute to seizure-related dendritic atrophy is exciting, because antagonists for this peptide exist, and may prove useful to prevent or even reverse these deficits.[59]

A second line of investigation emerges from the study of the effects of recurrent febrile seizures. In this study, investigators not only showed that seizures resulted in impaired learning and memory but also disrupted signaling that normally results in activation of the transcription factor, CREB.[35] When rats are tested in an inhibitory avoidance learning paradigm, normally an activation of CREB occurs by phosphorylation at Ser133. However, the investigators found that this activation is impaired after recurrent febrile seizures. This suggests a seizure-induced modification of a signally cascade upstream of CREB. To explore this possibility, the investigators treated adult rats that had experienced febrile seizures in infancy with rolipram, a specific phosphodiesterase type IV inhibitor, which results in the activation of protein kinase A (PKA) and is known to activate CREB via the mitogen-activated protien kinase (MAPK) pathway. Rolipram treatment was able to reverse the learning deficits observed in rats that had experienced recurrent febrile seizures. Because the MAPK pathway and CREB signaling are both thought to play key roles in dendritic development,[119,216] it will be important to know from future studies where in the PKA-MAPK-CREB cascade that signaling is disrupted and if these changes are initiated very early in life by seizures and possibly contribute to the dendritic abnormalities observed.

Summary and Conclusions

Critical periods of enhanced seizure susceptibility have been identified in both man and animals, and mounting evidence suggests they share underlying mechanisms. It is unlikely that only one developmental process is responsible for the marked seizure susceptibility in early life. Instead, highly dynamic alterations in synapses and ion channels temporarily converge to produce neuronal network hyperexcitability. For example, during the second postnatal week in rodents, seizure susceptibility likely arises from a transient overlap between newly formed glutamatergic networks and the remaining excitatory GABAergic systems of the neonate that have yet to disappear. The interplay between these synaptic changes and coincident developmental alterations in ion channel function will be the subject for future studies.

In addition to similarities in seizure susceptibility, animal models of experimentally induced seizures share much in common with observations made clinically. While electrical and chemoconvulsive seizures may not be considered models of chronic epilepsy, they reproduce many of the age-specific electrographic and behavioral features of seizures observed in neonates, infants, and young children, and much has been learned from these models, especially in terms of understanding circuits underlying seizure propagation and control.

In recent years, numerous chronic models have been developed. They share features in commonâ€”like precipitation by an experimental induced seizure(s) in neonatal life or infancy in normal animals or, more recently, in animals with a brain malformationâ€”the so called â€œtwo-hit models.â€ Commonly, early-life seizures do not result in the loss of neurons, although some studies have reported modest changes (compared with those produced in adults). Later in life, most models show increased susceptibility to seizure. In some models, a minority of animals become epileptic, developing spontaneous behavioral and/or electrographic seizures. Suggested underlying mechanisms vary from altered expression and/or function of several ion channels to changes in expression of the AMPAR subunit, GluR2 which may in turn diminish $GABA_A$ receptor function. Another outcome from studies of early-life SE and brief/recurrent seizures are deficits in learning and memory. Dendritic abnormalities including spine loss may contribute to these behavioral deficits.

The field of experimental childhood *Epilepsy Research* has entered an era of great promise. Although many challenges remain, opportunities abound with respect to new animal models that are availableâ€”including emerging genetic mouse modelsâ€”that should lead to a greater understanding of the molecular basis of these disorders and avenues for the development of new therapies.

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Chapter 40

The Effect of Seizures on the Brain

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Introduction

For many decades there has been an ongoing discussion about the effect that seizures have on the brain, and, although there is a rapidly expanding body of knowledge on this topic, the answers may be only partially clearer. In this chapter we review some of these data and try to draw some conclusions from as-yet-incomplete information on the overall effect of seizures on the brain. As we will show, this issue is quite complex. The clinical answer we are looking for is how repeated seizures affect the patient with epilepsy. Most of the laboratory reports over the years examining that issue have studied the effects that induced seizures have on normal brains, and a number of interesting observations have been made, many of which are outlined in this chapter. Many of the observations from these models have been equated with epilepsy or the process of becoming epileptic. However, with the availability of an increasing number of animal models of epilepsy that have spontaneous seizures and structural changes that have significant similarities to human epilepsy, we are finding that the changes associated with epilepsy are not necessarily the same as the changes that have resulted from repeated seizures in normal brains.

These observations complicate the basic question of what is the effect of seizures on the brain, and now emphasize the need to differentiate the cause from the consequence of epilepsy. To make the interpretation of the new findings more difficult, some suggest that some of the changes found in these models could represent an attempt of the system to return everything to normal, a sort of counterbalance to the changes that are interpreted as epileptogenic or pro-seizure. For this reason it is important to understand the circuitry of the seizures and place the many changes that are found throughout the circuit in the context of the overall effect these changes have on circuit function. Our understanding of the changes and the circuitry of seizure initiation and spread is not yet to the point at which we can determine the effect of the observed changes in promoting or potentially inhibiting the generation and spread of seizure activity, but we will try to place the findings into context wherever possible.

In the course of this chapter we look at three different types of seizures that either have distinctly different consequences or clinical relevance. Although we try to make the distinctions clear wherever we discuss the different models, we highlight the distinctions among the different groups here. The first group includes intermittent seizures that are induced in normal brains. Perhaps the most common model for the study of this issue is kindling, which usually involves the focal induction of a seizure through an electrical stimulation via an implanted electrode. The number of seizures can be controlled, so that the cumulative effect of the seizures can be quantified in light of an exact number of seizures. The second group comprises the models that have epilepsy. Because we do not cover absence or other generalized epilepsies, most of the models that we discuss have some form of pathologic change that contribute to the epileptic condition. For this reason it will be difficult to differentiate which changes contribute to the epilepsy from those that may be the consequence. The third group is status epilepticus. There is no question that these prolonged seizures cause brain damage and chronic changes, including, in many cases, epilepsy. Status epilepticus is not really the focus of this chapter; rather, it is used as a tool for creating animals with epilepsy, so in this chapter it is discussed primarily in that light. In the course of this chapter we review the data that are available, including the effect of repeated seizures to increase the likelihood of having another seizure, the potential result of seizures on brain structure and on behavioral function, the potential of seizures to alter neurogenesis, and the consequences of seizures on receptors and channels and, as a secondary consequence, on the pharmacology. We also review the current state of knowledge on synaptic reorganization associated with seizures and epilepsy. As will become clear, not all seizures are created equal, nor do they affect the brain equally.

Seizures Beget Seizures?

There has been a long-standing concept that the occurrence of a seizure prepares the way for the next, so that each subsequent seizure induces changes that further enhance the odds of having another.[55] To some this hypothesized process represents epileptogenesis. But what is the evidence for seizures truly begetting seizures as opposed to each subsequent recurrence of a seizure representing a symptom of an independent underlying process that is causing the seizure? In this scenario the recurrences are simply a symptom of the abnormalities that are the true source for the seizures. Although the varying natural histories of different epilepsy syndromes support the concept that seizures do not necessarily beget seizures, there are experimental data on both sides of the discussion. How do the findings apply to human epilepsy?

Before we enter into a discussion of the many observations related to the topic we should make clear what is meant by epileptogenesis because it has taken on several connotations in the epilepsy literature. A commonly used definition is that epileptogenesis is the process by which seizures gradually lengthen and behaviorally intensify with each recurrence. A common example is the kindling model, in which each repeated stimulated seizure results in a lengthening of the seizure duration and the behavioral intensity until a plateau is reached.[50,109] The other definition for epileptogenesis is the process that leads to the first spontaneous seizure after the appearance of a potentially seizure-causing abnormality, such as a traumatic lesion, a malformation, or a tumor. Whether it's through the interruption of critical neuronal pathways, the loss of particular neuronal populations, or the secretion of a proexcitatory substance (sometimes casually referred to as epileptogenic goo),

a series of structural, pharmacologic, and physiologic changes evolve during a clinically silent time known as the latent period to the point of having a seizure.[49] Although both definitions have clinical relevance, understanding the mechanisms behind the changes that take place in a brain that ultimately lead to the first spontaneous seizure will likely provide us a greater understanding of the basis for the different epilepsy syndromes.

One can find human syndromes that either support or refute the idea that seizures beget seizures because there are a number of syndromes that remit spontaneously, regardless of the number of seizures experienced, and there are others that clearly have a worsening with regard to frequency and clinical severity. Benign epilepsy of centrotemporal spikes or rolandic epilepsy is well known to remit by the teenage years independent of the number of seizures experienced.[88b] On the other hand, seizures associated with the mesial temporal lobe or limbic epilepsy syndrome sometimes start with barely perceptible subjective events and gradually progress to longer seizures with loss of consciousness that become refractory to therapy.[49] There is enough variation from individual to individual even within one of these syndromes to support the interpretation that the natural history of each epilepsy syndrome is the natural history of the underlying cause because each syndrome has a common course unique to it. Although one cannot completely exclude the possibility that in some patients with particular syndromes the seizures do cause seizure-enhancing changes in the critical circuits, it does not appear to be a universal phenomenon.

The kindling model is most frequently cited as evidence for seizures begetting seizures. Clearly with each repeated stimulated seizure there is a more intense seizure, and the seizure increases in duration.[50,109] This observation has been made in many forms of human epilepsy as well as in some of the animal models of chronic limbic epilepsy.[17,31] There are a number of additional reports that with enough stimulated seizures the kindled animals will have spontaneous seizures. This observation has been made in rats, cats, and baboons (*Papio* sp.).[130,146,164] Some investigators have indicated that this susceptibility to developing spontaneous seizures also varies with the age of the animal at the time of kindling.[58,147] However, this observation is not universal across all investigators. There are some primate species that do not fully kindle in the sense that they never show convulsions and they have never been seen to have spontaneous seizures in the course of kindling stimulation.

Genetics clearly plays a role because the baboons that have spontaneous seizures observed following kindling come from lines that are known to develop epilepsy, whereas the macaques in which spontaneous seizures are not associated with kindling have not been associated with a predisposition to epilepsy.[165] In rats, the issue is complicated by strain susceptibility, variations in the site of kindling stimulation, and many variable stimulation protocols. The number of stimulations required before spontaneous seizures are observed varies from about 150 to 300 or more.[130,136] Others (by personal report, including one of the authors) have rarely seen spontaneous seizures, even after 1,000 or more stimulations. Although it is clear that in some labs and with some stimulation protocols, spontaneous seizures can be observed following a period of extensive kindling, it is not a universal phenomenon. The real question is whether kindling to spontaneous seizures has significant implications for human epilepsy, and here the answer is unknown. It is clear that in some patients with certain types of epilepsy the seizures can progress, but this progression happens after the onset of spontaneous seizures with an underlying associated pathology. The situation of recurrent stimulated seizures in people with an otherwise normal brain is seen only with patients that undergo electroconvulsive therapy for psychiatric disorders. Among these patients epilepsy as a consequence of the convulsive therapy is extremely rare, if it occurs at all. There is a report of a patient with 1,200 induced convulsions with no evidence for progressive brain injury or the development of epilepsy.[90] There are reports of patients who do have seizures following the therapy, but the observation is clouded by the concomitant use of medications that can lower seizure threshold.[91]

So, can seizures beget seizures? The data suggest that in certain strains or species of animals the repeated induction of seizures using a particular stimulus protocol at particular ages can result in spontaneous seizures. Is this phenomenon universal? No. More important, is this phenomenon relevant for human epilepsy? It is not possible to provide a blanket statement for all epilepsies in all individuals, but certainly there is little to no evidence suggesting that repeated exogenously induced seizures lead to chronic epilepsy. Can seizures in an individual worsen over time? There is certainly good evidence that they can, but that is more of a kindling phenomenon in which the seizure duration increases and the recruitment of brain regions expands once the spontaneous seizures have started. Alternatively, it could be a symptom of a worsening of the underlying condition that is causing the epilepsy. In some of the animal models of limbic epilepsy there is good evidence for a worsening over time until a plateau is achieved, after which a relatively stable pattern is maintained.[17,51] However, in some animals, as in some people, the seizures remain fairly stable for prolonged periods of time. In most cases the seizures are â€œbegottenâ€ by an underlying pathology, and although some can clearly progress over time with repeated seizures, other syndromes can spontaneously go into remission, an observation that suggests that the evolution of the disorder depends on the underlying etiology and less on the recurrence of seizures.

As a final observation regarding seizures and epileptogenesis, there has long been a desire to prevent the development of epilepsy or to cut the disease's natural history short by means of some early intervention, and the search for an effective prophylaxis has been going on for years. The most common approaches have been to treat patients with antiepileptic drugs following an event, such as head trauma, that has a significant risk for subsequent epilepsy. To date, none of these approaches has been effective in reducing the subsequent risk of epilepsy, although immediate postinjury treatment does block the acute seizures in the first week.[157] In animal work these attempts have been divided along two lines: (a) attempts to slow or prevent the kindling process by pretreatment before stimulation and (b) attempts to prevent the development of epilepsy following status epilepticus. The former approach, the inhibition of kindling, has been most frequently studied, and there are a number of compounds with varying, and in some cases unknown, mechanisms of action that have slowed the process (which means increased the number of stimulations necessary to achieve fully kindled seizures).[108,140,149] It may be, however, that the treatments were successful at suppressing seizures but not really altering the kindling process, because as soon as the pretreatment was stopped, the animals were often at the same stage as the untreated controls. Although there are some reports that drugs such as levetiracetam, when used prophylactically during the kindling process, result in a permanent reduction in seizure duration, this phenomenon has not been regularly seen.[92] Ultimately one is left with the conclusion that treatment in kindling may slow the process slightly but is unable to prevent it.

With the more recent appearance of the postâ€“status epilepticus limbic epilepsy models (kainic acid, pilocarpine, limbic electrical stimulation), there has been an opportunity to examine possible treatments for preventing the development of chronic epilepsy. A major problem for these studies in rats has been the maintenance of potentially effective levels throughout the treatment phase, which could last several weeks or more. In the studies examining the prevention of kindling, the animals can be given the drug at a standard time before the stimulation, which for these studies is usually once daily. Maintaining therapeutic levels over a 24-hour period is not an issue in the kindling studies. Following status epilepticus, however, the latent period before the first seizure is usually several weeks to a month, and for most drugs, maintaining levels during that time is extremely difficult. There have been a few studies using antimetabolites that have reported some success in preventing anatomic features of chronic epilepsy without preventing the epilepsy.[89,168] The only studies that have been successful in preventing the development of epilepsy have been those that used treatments during the early stages of status epilepticus, usually during the first several hours, and the likely reason for success is that the intervention came early enough to stop the seizures and prevent the damage that the status epilepticus causes if left untreated.[131] Inasmuch as it is the damage that is thought to lead to the epilepsy, these interventions are likely successful because they prevent the cause rather than preventing the epilepsy once the cause has happened. Prophylaxis against the development of epilepsy following a potentially epileptogenic injury remains to be discovered.

Seizures and Brain Structure

Perhaps one of the greatest concerns in epilepsy is the question of whether repeated seizures damage the brain. The answers are confused by the mixing of different models, methods of documentation, and types of seizures. Brain damage, as evidenced by neuronal loss, gliosis, and focal atrophy, has been associated with epilepsy for as long as people have been studying the issue. As noted, the issue that is of greatest concern is which of these changes preceded the onset of the seizures and which appeared afterward, that is, what is the cause of epilepsy and what is the consequence. But there are other questions as well. Do seizures alter the structure of neurons in a way that alters their physiology? What effect do seizures have on glial cells? Do the type of seizure and the temporal patterning of the repeated seizures have different effects on the anatomy? What is the potential consequence of seizure-induced changes? Are the changes harmful or are they a protective reaction to the seizures? In this and several subsequent sections dealing with genes, channels, and neurogenesis we address these issues as best we can, given the nature of the data.

There is no question that some seizures affect the structure of the brain. There is almost universal agreement on this point. The issues are which seizures and what do they do to the brain. Absence seizures, which are brief, have a slow discharge pattern and use intrinsic brain rhythms, and they are generally considered not to have a significant effect on brain structure. At the other extreme, status epilepticus, and usually the status epilepticus associated with a progression of electroencephalographic (EEG) frequencies from continuous high-frequency activity to periodic epileptiform discharges, is unquestionably associated with significant neuronal loss and gliosis. The controversy lies in whether occasional seizures that have a tonicâ€“clonic pattern on EEG lasting for up to several minutes at a time induce neuronal loss. Furthermore, if damage does occur, does it ever plateau after a subset of vulnerable neurons is lost or does it continue to progress with each successive seizure? Clinical information is difficult to interpret in large part because it is rare to know what the structure of the brain was like before the onset of the seizures because much of the available tissue only becomes available after it has been removed surgically because of intractable epilepsy. There are a number of reports showing that patients who have more frequent or more intense seizures have more severe pathology/cell loss. Although this observation has often been interpreted to mean that more seizures or more intense seizures cause the greatest damage, this interpretation is based on the assumption that all individuals start from the same point and progress differently depending on the nature of the seizure disorder. An equally valid and more conservative interpretation is that the more severe pathology results in a worse seizure disorder. However, it is an issue that really cannot be resolved by clinical studies unless we begin collecting data well before the onset of epilepsy and watch for progression before and after the seizures begin. To study the issue under a controlled setting we have to use animal models of epilepsy.

There are several questions to answer in examining the issue of repeated seizures and neuronal loss. First, does it happen at all? Second, following the induction of an epileptogenic lesion, do the repeated spontaneous seizures cause additional loss? Two models have been used to study these questions. First, the kindling model allows us to start with a naive brain and induce seizures with an implanted electrode. We can control the number and frequency of seizures as well as the age of the animal before examining brain structure for change. The status epilepticus models result in a relatively stereotyped, but still somewhat variable, pattern of neuronal loss and gliosis. These rats then develop chronic epilepsy over a period of some weeks. The pattern of neuronal loss approximates mesial temporal sclerosis, and this model allows us to determine whether recurrent seizures on a background of preexisting pathology cause additional neuronal loss. These models of postâ€“status epilepticus limbic epilepsy are frequently compared to their human paradigm, and there are many points of similarity. One issue is not, and that is the origin of the pathology in the limbic structures. Although patients with limbic epilepsy frequently have an episode of a prolonged seizure (usually febrile) well before the onset of the seizures that are recognized as part of the symptoms of the chronic syndrome that first appear, the majority do not have a well-identified initial (and often considered precipitating) event.[12,33] Although the prolonged seizures can clearly induce neuronal loss, for those patients without a well-defined first event, the origin of the abnormality is less clear. It is possible that the precipitating event was unrecognized but still caused damage. There is some evidence to suggest that the abnormalities were present at birth because there has been frequent association with cortical dysplasias, and there is increasing evidence that genetic factors may also play a role as well.[25,87] It is also possible that the changes are the result of repeated seizures. Although the final answers are not in yet and the issue has supporters on both sides of the argument, there are a number of experimental results that are pointing in the direction of minimal loss as a result of repeated seizures.

The presence of neuronal loss is not controversial in limbic epilepsy. The questions are how it got there, and, more important, if is it progressive. It has been noted that there is considerable variability in the distribution of the pathology across patients.[102] As noted earlier, there have been a number of reports, especially quantitative magnetic resonance imaging (MRI) studies comparing volume loss and seizure severity, and the investigators have reported a relation. Some studies, however, have concluded that repeated seizures are not the cause of hippocampal atrophy seen on MRI scans.[23,24] A recent histologic study examined the relationship between the duration of the epilepsy (up to 30 years) and the severity of neuronal loss.[106] The authors found that there was a slight decrease in neuronal density over the years and that this loss was significant (see later discussion regarding the interpretation of density changes), but that there was considerable loss even among patients with a relatively short disease duration. The difference between control hippocampal densities and the neuronal density in epileptic patients was much greater than that between epileptic patients with relatively short duration and those with the longest duration. This observation suggests that most of the neuronal loss occurs either before the onset of the epilepsy or very shortly thereafter.

There has been another interesting observation with regard to seizures and brain damage. There are reports that animals with prior seizures, whether kindled or electroconvulsive, have less neuronal loss when subsequently subjected to insults that usually result in significant brain damage. This has been reported for animals that had been subjected to status epilepticus, ischemia, or adrenalectomy.[74,79,104] The duration of the protective effect is likely transient, first coming into effect about 24 hours after the â€œprotectiveâ€ seizure and lasting at least 1 or 2 weeks. The mechanism is unclear but almost certainly involves the upregulation of factors that interfere with the apoptotic cascade.

Kindling has the distinct advantage in examining the question of seizure-induced neuronal loss because intervals between seizures and the number of seizures will be controlled as desired by the experimenter. It delivers a focal electrical stimulation to the desired part of the brain, and the stimulations can follow any pattern. There have been a number of kindling-based studies, and they are generally in agreement that repeated seizures result in lower neuronal densities. There are, however, quite different opinions regarding the significance of the reduced neuronal densities and the greater reduced densities with increasing numbers of seizures. On one side of the discussion the conclusion is that the reduced density is evidence for progressive seizure-induced neuronal loss.[32] The other side of the discussion holds that the reduced density is the result of seizure-induced changes in the neuropil (e.g., increased glial activation), and that once one corrects for the expanded neuropil, there is little or no change in the absolute numbers of neurons.[3,18,19]

One of the anatomic hallmarks of the limbic epilepsy syndrome is mossy fiber sprouting, in which the axons of the dentate gyrus granule cells that normally fill the dentate hilus and project to CA3 in the hippocampus are found in the supragranular layer of the dentate gyrus.[154,156] It is seen in human limbic epilepsy as well as in the animal models of the disorder. It is also seen in kindling, with a number of reports of progression of the sprouting with successive seizures. However, the degree of sprouting seen following kindling is usually a fraction of what is seen in epileptic animals and people.[105] The primary questions surrounding this phenomenon are why it occurs and what function it serves. The mechanisms underlying the process of sprouting are clearly unknown, and it is quite likely that the mechanisms associated with sprouting in kindling are quite different than those following status epilepticus. There is some evidence that in epilepsy the degree of sprouting is linked to the severity of neuronal loss in the hilus. A potential mechanism for the initiation of the sprouting is the loss of synapses and the creation of openings for new synapses. There is some evidence that neurotrophins may also be involved in bringing the aberrant axons into the molecular layer.[64] In kindling, with a less severe level of sprouting, the presence or absence of hilar neuronal loss is under-debated, so the mechanisms for the process are less clear. However, in relative terms, the degree of sprouting is much less in kindled animals.

More important than knowing the mechanism underlying the process of sprouting is the physiologic or functional consequence of the new synapses, and there are a number of hypotheses and some data that address the issue. The issue centers on the question of whether the sprouting is part of an overall process in the granule cell that is net excitatory, net inhibitory, or part of a zero-sum process in which the final effect is that all the changes balance out to no change in overall function. What many of the studies show is that the overall response to perforant path stimulation is not profoundly different from the naive nonepileptic state.[133] The data are somewhat conflicting in that there are varying shifts in the evoked responses in the granule cells, with some showing a slight increase in inhibition in paired stimulation and some a decrease. Overall, however, the highly epileptiform evoked responses that are seen in other brain regions are not seen in the dentate gyrus either following kindling or in the epileptic animals. However, there is evidence that these fibers form recurrent excitatory autosynapses. In addition, the granule cells appear to be more sensitive to the local application of glutamate and its analogs, with a heightened excitatory response.[170] As discussed later, changes have been reported in the Î³-aminobutyric acid (GABA)â€“mediated pharmacology, and, with regard to seizure-associated neurogenesis, there are multiple new dentate granule cells generated following status epilepticus. These new cells may contribute to the sprouting, although there are data that show that sprouting occurs even when the generation of new granule cells is prevented.[126]

Seizures and Behavior

On the clinical side of epilepsy, one of the major questions remains whether seizures have an effect on overall cognitive function or behavior. Epilepsy has long been associated with a number of problems in these areas. Although the overwhelming majority of patients with epilepsy have normal cognitive and behavioral profiles on formal testing, as a group they do not function quite as high as their nonepileptic counterparts. In seeking the reason behind this apparent overall lower performance, researchers have offered a number of plausible explanations, including medications, underlying preexisting abnormalities in the brain, depression that affects a high percentage of patients with uncontrolled seizures, and the consequences of the seizures themselves. In the clinical setting it is not really possible to separate all of the factors, but there is clear evidence that medications can play a role in some (but not necessarily all or even a majority of the patients), and the identified pathology often corresponds to particular neuropsychological deficits that a patient may have. However, these correlations are difficult to separate and also limit our ability to answer the question of whether the seizures themselves are playing a harmful role.

To determine whether seizures can have a neurobiologic effect on performance long term, we have to turn to animal models because we can use them to focus on the question of seizures alone, independent of the issues of precipitating pathology, affect, or medications. The two most frequently used animal models in behavioral studies have been the postâ€“status epilepticus model with chronic limbic epilepsy and the kindling model. The postâ€“status epilepticus model is associated with significant neuronal loss, and behavioral testing, performed when the animals are in the chronic phase with spontaneous limbic seizures, have consistently revealed that there are overt abnormalities in a number of behavioral areas. However, just as with patients with epilepsy, one is dealing with the confounding issues of underlying brain pathology, seizures, and, frequently, the potential confounding effect of a postictal state.

Table 1 Factors that modulate adult hippocampal neurogenesis

Factor	Effect	Stage affected	Reference

Aging	Decreased	Proliferation/neuronal differentiation	Kuhn et al. (1996),[81] Rao et al. (2005)[132]
Stress/adrenal steroids	Decreased	Proliferation	Cameron and Gould (1994),[28] Gould and Tanapat (1999)[52]
Exercise	Increased	Proliferation/?survival /?neuronal differentiation	van Praag et al. (1999),[160] Trejo et al. (2001)[159]
Environmental enrichment	Increased	Survival	Kempermann et al. (1997, 1998),[75,76] Nilsson et al. (1999)[117]
Estrogen	Increased	Proliferation	Tanapat et al. (1999)[155]
Basic fibroblast growth factor	Increased (postnatal)	Proliferation	Wagner et al. (1999)[167]
Brain-derived neurotrophic factor	Increased	Neuronal differentiation/survival	Lee et al. (2002),[84] Scharfman et al. (2005)[138]
Vascular endothelial growth factor	Increased	Proliferation/survival	Jin et al. (2002),[71] SchÃ¤nzer et al. (2004)[137]
Insulin-like growth factor-1	Increased	Proliferation/survival /?neuronal differentiation	Aberg et al. (2002)[1]
Glutamate	Decreased	Proliferation	Cameron et al. (1995)[30]
Î³-Aminobutyric acid	Increased	Neuronal differentiation	Mayo et al. (2005),[107] Tozuka et al. (2005)[158]
Serotonin	Increased	Proliferation	Brezun and Daszuta (1999),[24] Malberg

			et al. (2000)[100]
Nitrous oxide	Decreased	Proliferation (promotes neuronal differentiation)	Packer et al. (2003)[121]
Wnt	Increased	Proliferation/?neuronal differentiation	Lie et al. (2005)[88]
Sonic hedgehog	Increased	Proliferation	Lai et al. (2003),[83] Ahn and Joyner (2005)[4]
Sox2	Increased	?Proliferation/?neuronal differentiation	Ferri et al. (2004)[46]
Stem cell niche			Song et al. (2002),[151]
Astrocytes	Increased	Proliferation/differentiation	Palmer et al. (2000),[122]
Endothelium	Increased	?Proliferation	Jin et al. (2002),[71]
Microglia	Decreased	Survival	Monje et al. (2003),[113] Ekdahl et al. (2003)[44]

It is not possible to isolate the potential effects of seizures from the neuropathology in this situation, and for this reason the kindling model may be more appropriate because the seizures can be induced in any desired pattern, at almost any age, and, although this is a controversial issue, without the overt pathology that is found in the limbic epilepsy model. Although not absolutely perfect, it may be considered a purer model for studying the effects of seizures on behavior and memory because there is much less, if any, associated neuropathology. As can be expected, the results from the kindling model are complex. Although there is no question that kindling can have a negative impact on spatial memory,[86] other studies suggest that the interactions may be more complex, with the overall effect depending on stimulation site, emotional state, and stimulation paradigm.[2,11] It is also likely that intermittent brief seizures that occur during development have an impact, although investigators point out that there may be beneficial effects as well as negative ones.[162] Overall the data suggest that seizures can have a negative effect, but that the effects may be relatively mild and are likely influenced by a number of factors in addition to the seizures themselves.

Altered Neurogenesis in Experimental Temporal Lobe Epilepsy

The dogma that neuronal production ceases after birth no longer is accepted. Evidence accumulated over the last five decades indicates that neurogenesis persists in the adult mammalian hippocampal dentate gyrus and subventricular zone (SVZ)-olfactory bulb pathway.[5,6,29,39,73,81,88a] Neuronal birth continues throughout life in every mammalian species examined, including human and nonhuman primates.[45,53,54,80a,128] In the dentate gyrus, neural stemâ€“like cells reside in the subgranular zone (SGZ) at the border of the hilus and dentate granule cell (DGC) layer. These cells express glial fibrillary acidic protein (GFAP) and nestin[42] and proliferate to generate clusters of neuroblasts that disperse and migrate a short distance into the DGC layer, where they differentiate into granule neurons.[6,29,73,81] Adult-born DGCs send axonal projections to appropriate targets in hippocampal area CA3[59,103,152,161] and acquire electrophysiologic characteristics of mature DGCs.[47,161,166]

Experimental evidence supports a role for DGC neurogenesis in learning and memory function (reviewed by Doetsch and Hen[43] and Ming and Song[110]). Stimulation of adult DGC neurogenesis with behavioral interventions such as exercise or environmental enrichment is associated with better performance on certain hippocampal learning tasks,[75,160] and the depletion of adult-generated hippocampal neurons disrupts hippocampal-dependent learning.[144,145,150] Recent work also suggests that DGC neurogenesis in the adult may be necessary for the positive effects of antidepressant medication.[135] Many physiologic states and molecular factors regulate adult hippocampal neurogenesis (see Table 1 and references therein). Aging and stress decrease DGC production, whereas exercise and environmental enrichment increase neurogenesis throughout adulthood. Most factors examined, such as growth factors, neuromodulators, estrogen, transcription factors, and the neurotransmitter GABA, increase the generation or survival of DGCs in the adult; glutamate and nitric oxide exert opposite

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effects. Cellular elements in the neural stem cell niche, including astrocytes and endothelial cells, also positively regulate neurogenesis in the intact brain.

Seizure-Induced Neurogenesis

Studies of adult rodent models of limbic epileptogenesis or acute convulsions indicate that prolonged seizures potently stimulate DGC neurogenesis.[13,56,123,125,141] In the adult rodent kainate and pilocarpine models of mesial temporal lobe epilepsy (mTLE), chemoconvulsant-induced status epilepticus (SE) increases dentate gyrus cell proliferation approximately 5- to 10-fold after a latent period of at least several days.[56,123] About 80% to 90% of the newly generated cells differentiate into DGCs. Electrical kindling of the amygdala,[125,141] hippocampus,[13] or perforant path[116] also stimulates DGC neurogenesis. Similar neurogenic effects occur after acute seizures induced by intermittent perforant path stimulation in adult rats,[123] and even single, discrete seizure-like afterdischarges induced by hippocampal stimulation lead weeks later to increased numbers of newly differentiated DGCs.[13] Although more severe seizures enhance neuronal production to a greater extent, the survival of the newborn DGCs may decrease with increased seizure severity.[111] This effect probably relates to the degree of inflammation because it is reversed in part by minocycline treatment to decrease microglial activation.[44] The increased neurogenesis after SE is a short-term phenomenon, moreover, because adult rats with chronic epilepsy show decreased DGC production 5 months after chemoconvulsant-induced SE.[60]

Functional Significance of Seizure-Induced Hippocampal Neurogenesis

A prominent abnormality involving DGCs in human mTLE is mossy fiber sprouting (reviewed by Parent and Lowenstein[123]). In the pilocarpine mTLE model, developing axons from adult-generated DGCs contribute to aberrant mossy fiber reorganization in both hippocampal area CA3 and the dentate inner molecular layer.[123] When X-irradiation is used to kill DGC progenitors after pilocarpine-induced SE, however, mossy fiber sprouting persists.[126] Thus, SE appears to induce axonal remodeling in both mature and newborn DGCs in the epileptogenic hippocampal formation.

In addition to mossy fiber sprouting, the dentate gyrus in human mTLE often shows abnormal dispersion of DGCs and the presence of ectopic granuleâ€“like neurons in the hilus and molecular layer.[57,66,127] Hilar-ectopic DGCs appear in several different experimental mTLE models and persist for at least 1 year after the initial epileptogenic insult (Fig. 1).[40,123,127,139] The cells resemble the granule-like neurons identified in surgical specimens from humans with temporal lobe epilepsy in terms of both their morphology and expression of the DGC-specific marker Prox-1.[40,127,139] Studies of neurogenesis in experimental mTLE reveal a progressive increase in hilar 5-bromo-2â€²-deoxyuridine (BrDU)â€“labeled cells, as well as chains of migrating neuro-blasts extending from the inner DGC layer to the hilus, indicating that the hilar-ectopic DGCs migrate aberrantly from the dentate SGZ to the hilus.[127]

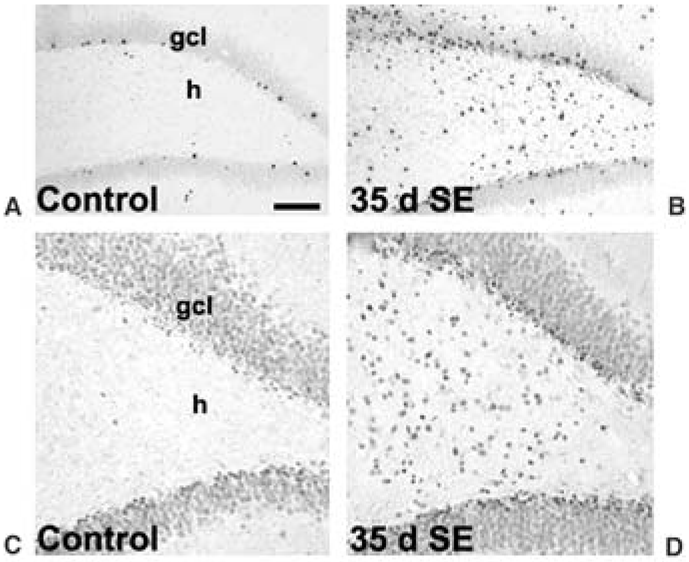

FIGURE 1. Pilocarpine-induced status epilepticus (SE) produces hilar-ectopic dentate granule cells (DGCs). Compared to a control **(A)**, bromodeoxyuridine (BrdU) labeling of proliferating cells shows increased cell proliferation in the DGC layer (gcl) and hilus (h) in an adult rat 35 days after SE (35 d SE) **(B).** BrdU was given 4 weeks earlier. **C, D:** Similar changes in hilar immunoreactivity for Prox-1, a DGC-specific marker.

Recent evidence suggests that hilar-ectopic DGCs arising after kainic acidâ€“ or pilocarpine-induced SE integrate abnormally into the mature hippocampal formation.[40,139] Using intracellular recordings in hippocampal slices from epileptic adult rats, Scharfman et al.[139] showed that the hilar ectopic granuleâ€“like cells are hyperexcitable and fire in abnormal bursts synchronously with CA3 pyramidal cells. In addition, many putatively newborn DGCs located in the hilus or hilar aspect of the DGC layer after seizures exhibit a much higher percentage of persistent basal dendrites than is normally found.[40,139] Work by Ribak and colleagues suggests that the basal dendrites of hilar ectopic DGCs receive increased excitatory input,[40] suggesting a mechanism for seizure generation or propagation. In addition, Jung et al.[72] used the antimitotic agent araC to inhibit DGC neurogenesis after pilocarpine treatment and found that treated rats developed fewer and shorter spontaneous recurrent seizures than controls. Taken together, these data suggest that hilar-ectopic DGCs integrate abnormally, are hyperexcitable, and thus may contribute to seizure generation or propagation (Fig. 2). Given the likely function of adult hippocampal neurogenesis in learning and memory, moreover, defects in neurogenesis also may contribute to the substantial and progressive memory dysfunction seen in mTLE.[62]

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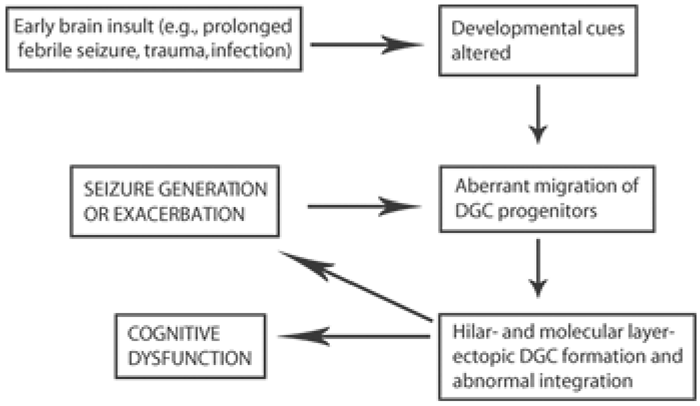
Early brain insult (e.g., prolonged febrile seizure, trauma, infection)
Developmental cues altered
SEIZURE GENERATION OR EXACERBATION
Aberrant migration of DGC progenitors
COGNITIVE DYSFUNCTION
Hilar- and molecular layer-ectopic DGC formation and abnormal integration

FIGURE 2. Aberrant neurogenesis hypothesis of hippocampal pathophysiology in mesial temporal lobe epilepsy. DGC, dentate granule cells.

Mechanisms Underlying Seizure-Induced Neurogenesis

The mechanisms by which seizure activity stimulates neurogenesis or gliogenesis are unknown. Experiments in which proliferating cells were labeled with BrdU prior to seizure induction have shown that epileptic activity stimulates dentate gyrus precursors that were proliferating prior to injury.[126] Huttmann et al.[69] used a reporter mouse in which green fluorescent protein selectively labeled nestin-expressing stemlike cells to show that kainate-induced SE specifically increases the proliferation of radial gliaâ€“like progenitors in the dentate gyrus. Seizures may act to increase neurogenesis indirectly through stimulation of astrocytosis because astrocytes stimulate hippocampal neurogenesis via wnt signaling and perhaps other mechanisms[88,151] or by inducing the death of mature DGCs, thereby leading to cell turnover in the dentate gyrus. SE also increases the expression of molecules with the potential to increase neurogenesis or gliogenesis such as growth factors[68] and neurotrophins.[70] Specific neurotransmitters or neuromodulatory systems that normally influence DGC neurogenesis (Table 1) also may be altered by seizure activity.

In terms of signals leading to hilar- or molecular-layer ectopic DGC formation, molecular factors that influence neuronal migration during development are prime candidates. The expression of one of these developmental factors, reelin, persists in the hippocampal dentate gyrus of adult humans and rodents and has been implicated in DGC layer dispersion in human TLE.[57] The expression of reelin decreases markedly after pilocarpine-induced SE (J.M.P., unpublished data), suggesting that loss of this migration guidance factor may be responsible for the aberrant migration of DGC progenitors during epileptogenesis. Another potential mechanism is loss of GABA, because this neurotransmitter influences DGC differentiation (Table 1) and decreases neuroblast migration in the other adult neurogenic region, the SVZ-olfactory bulb pathway.[22] Brain-derived neurotrophic factor (BDNF) is another good candidate. Scharfman et al.[138] showed that hippocampal BDNF infusion in adult rat increased DGC neurogenesis and led to the appearance of ectopic DGCs. Therefore, BDNF also might be involved in seizure-induced, aberrant DGC neurogenesis. The different stages of DGC neurogenesisâ€”including proliferation, migration, integration, and survivalâ€”likely are regulated by a delicate balance of multiple factors affecting DGC progenitors in the intact and epileptic hippocampal formation.

Epilepsy-induced Plasticity in Expression and Function of Neurotransmitter Receptors and Voltage-gated Ion Channels

In addition to pathologic changes in circuits due to loss or birth of neurons, epileptogenic injuries induce a multifaceted set of alterations in surviving neurons in the hippocampus, which may contribute significantly to the underlying excitability defect rendering the brain epileptic. Notable players in this plastic response to injury are alterations in neurotransmitter receptors and voltage-gated ion channels. Modification in the properties of these ion channels can contribute directly to generation of hyperexcitability within hippocampal circuits. For the purposes of the present discussion, here we summarize studies describing changes in specific responses mediated by pharmacologically or molecularly characterized receptors and ion channels. Although of interest, studies limited to examination of synaptic responses or intrinsic excitability will not be addressed in detail because the direct contribution of various subsets of receptors and ion channels is difficult to extrapolate from these types of data.

Methods for Characterizing Receptor and Ion Channel Plasticity at Cellular and Subcellular Resolution

To determine more definitively the nature of receptor and ion channel changes occurring in surviving neurons in epileptic (or epileptogenic) brain, specific sets of techniques are informative to establish the nature of changes at cellular and subcellular levels. These include immunohistochemistry (including immunogold labeling together with electron microscopy), in situ hybridization, single-cell mRNA profiling (reverse transcriptase-polymerase chain reaction [RT-PCR], antisense RNA techniques), directed pharmacology, and patch-clamp recording techniques. General immunohistochemistry, in situ hybridization, and single-cell mRNA profiling techniques provide cellular resolution when competently conducted, and immunogold/electron microscopy, directed pharmacology, and patch-clamp recording techniques can extend this cellular resolution to a subcellular level, examining changes in specific synapses and cellular compart-ments.

Alterations in Voltage-Gated Ion Channels: Focus on Dendrites

Most excitatory synaptic input impinges onto principal cells via dendritic synapses. How pyramidal cells process this dendritic synaptic input, integrate it, and generate output is an emerging area of potentially great importance in understanding mechanisms involved in seizure generation in the epileptic brain. Dendrites are endowed with a relatively unique ensemble of voltage-gated ion channels, which determine their function by regulating synaptic integration (reviewed by Magee[97]). Three ion channels in particular have a particularly prominent role in regulating dendritic processing of inputs. These are A-type (inactivating) potassium channels, hyperpolarization-activated (h-type or HCN) cationic channels, and T-type (low threshold) calcium channels. A-type potassium channels become increasingly more densely expressed in dendritic membranes as they are sampled at sites progressively more distal from the cell somata. Similarly, h-type cationic channels are densely expressed in the dendrites of pyramidal cells, resulting in a more depolarized membrane potential and decreased resistivity in dendritic plasmolemma, reducing propagation of excitatory synaptic input.[96,99] T-type calcium channels are also present in dendritic compartments, where they may serve to boost propagation of synaptic inputs.[97,98] In normal animals, propagation of distal synaptic inputs to the soma is strongly regulated by function of these ionic conductances, as well as by proximally targeted feedforward inhibition[7,97] (reviewed by Magee et al.[99]).

Several recent studies have been published demonstrating alterations in expression of all three of these dendritically prominent ionic conductances in animals rendered epileptic by a prior episode of pilocarpine- or kainate-induced status epilepticus. Of the three ion channel species that critically determine dendritic function, reductions in two (A- and h-type ion channels) and an increase in the third (T-type calcium channels) were recorded.[14,143,153] Because A- and h-type channels normally function to depress, whereas T-type calcium channels boost, propagation of excitatory synaptic input[97] (reviewed by Magee et al.[99]), all three of these changes in intrinsic voltage-gated ion channel expression are consistent with enhancement in propagation of distal synaptic inputs to the soma. This type of enhanced propagation has been described, with very distal inputs onto CA1 pyramidal neurons, assuming a markedly (>10-fold) enhanced efficacy in epileptic animals compared to controls.[8,36,41,169]

The h-type current reductions in entorhinal cortical neurons described in the foregoing were accompanied by reduction in expression of both HCN1 and HCN2 subunits, assessed using Western blots.[143] A-type potassium channel reductions were accompanied by reductions in Kv4.2 mRNA levels in CA1 pyramidal neurons,[14] and T-type calcium channel increases were accompanied by increases in Î±1H subunit mRNA.[153] These latter data provide information on the molecular identity of the proteins mediating the epilepsy-associated shift in ion channel properties, and, at least in the case of the A-type potassium and T-type calcium channel alterations (and, to a lesser extent, the h-current changes), further suggest that these alterations may be transcriptional in nature.

The impact of the ion channel alterations just described on pyramidal cell dendritic integratory responses in epileptic animals may be enhanced by the coincident loss of feedforward inhibition evident in these same animals. Feedforward inhibition is critical to constrain excessive activation of excitatory pathways and has been demonstrated to be a primary regulator of the direct cortical input to CA1 neurons, the temporoammonic pathway, which innervates these cells on their extreme distal dendrites in stratum lacunosum moleculare.[7] This feedforward inhibition is compromised in animal models of epilepsy,[8,36,41] which, combined with dendritic ion channel alterations, could lead to an explosive amplification of temporoammonic input.[8,169] Once CA1 activates due to this aberrantly regulated cortical input, it will directly innervate and reactivate both subiculum and entorhinal cortex, which constitutes a â€œshort-loopâ€ reciprocally excitatory circuit, which may facilitate seizure initiation and/or propagation.

This interaction of ion channel alterations and loss of feedforward inhibition may be further compounded by loss of the selective feedback pathway regulating temporoammonic input, the oriens alveus interneurons that project to stratum lacunosum moleculare. These interneurons normally gate temporoammonic inputs in a feedback manner[7,82,170a] and are selectively lost in epilepsy.[42,65a,114] This would remove a further check on this pathway, allowing reentrant activity to proceed unchecked and loop activity between CA1, subiculum, and entorhinal cortex to escalate.

Is there any evidence that these dendritic ion channel changes evident in spontaneously epileptic animals are mirrored in the kindling model of temporal lobe epilepsy, in which there is little or no cell death? Many of the ion channels have not been studied to the same degree in kindled animals as they have in the postâ€“status epilepticus spontaneous epilepsy models. However, where they have been studied, very little overlap is seen in terms of changes in ion channel expression. A-type potassium channels and T-type calcium channels do not appear to be altered in expression or function in CA1 neurons from kindled animals.[63,163] Other calcium currents do exhibit short- and long-term alterations,[21,45a,163] including the expression of N-type calcium channels in dendritic fields of area CA1.[15,16] However, the latter studies did not discriminate between pre- and postsynaptic loci of these changes, and so they cannot be viewed as directly supporting the concept that dendritic integration is altered following kindling. To emphasize the effects of ion concentrations on the cellular physiology, the sensitivity of the neurons to shifts in potassium concentrations are clearly different between epileptic and naive animals. When placed in increasing concentrations of potassium, the CA1 neurons from rats with limbic epilepsy begin to have spontaneous bursts of action potentials at lower concentrations than neurons from control rats.[93]

Changes in Neurotransmitter-Receptor Expression in Kindled and Epileptic Animals: Spotlight on GABA$_A$-Receptor Alterations in Granule Cells

In addition to the dendritic voltage-gated ion channel alterations described previously, which have been described primarily in pyramidal neurons, neurotransmitter receptor expression and function are also altered significantly in animal models of temporal lobe epilepsy. Much of this evidence is acquired from studies of hippocampal dentate granule cells. This preponderance of findings in granule cells may stem from two primary sources. First, granule cells are very distinct from pyramidal neuron in terms of their properties and embryonic origin, and so they respond in unique ways to stress. Second, granule cells are relatively resistant to excitotoxic death, whereas pyramidal cells are susceptible. Therefore, granule cell findings may be compared more readily between control and epileptic tissue, whereas studies in pyramidal neurons are more difficult to interpret. Any measure needs to be filtered through a background of significant cell death and accompanying gliosis contributing to apparent receptor alterations, particularly when considering in situ hybridization and immunohistochemical studies conducted at the tissue level. In addition, findings in the hippocampal dentate gyrus may assume additional importance because of the pivotal, â€œgatekeeperâ€ role that this structure may play in regulating excitability of the entire entorhinal-hippocampal loop.[61,94]

Although changes in many neurotransmitter receptor systems have been described in models of temporal lobe epilepsy, including GABA$_A$, GABA$_B$, Î±-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), *N*-methyl-D-aspartate (NMDA), and metabotropic glutamate receptors, for the most part there are divergent data when comparing kindling and postâ€“status epilepticus models. The receptor system that seems to exhibit the most uniformity in terms of changes across models is the GABA$_A$-receptor system, particularly in the dentate gyrus. For this reason, this discussion focuses on changes identified in dentate granule cells of kindled and postâ€“status epilepticus models of temporal lobe epilepsy.

$GABA_A$ receptors are hetero-oligomeric protein pentamers, with a preferred stoichiometry of two Î± subunits, two Î² subunits, and a fifth subunit, usually a Î² subunit.[95a] However, in dentate granule cells, a Î´ subunit frequently replaces the Î³ 2 subunit in subsets of receptors, which may change the subcellular location of these receptors as well as their properties. Six Î±, three Î², three Î³, one Î´, and additional families of receptor subunits have been cloned. Receptors comprising differing combinations of subunits have differing kinetic and pharmacologic properties, as well as frequently differing subcellular localization. For example, receptors containing Î± 4 subunits are insensitive to modulation by benzodiazepines, frequently also associate with a Î´ subunit, and are much more sensitive to zinc-mediated inhibition than are receptors containing an Î± 1 subunit. These Î± 4/Î´ receptors tend to be localized extra- or perisynaptically, in contrast to Î± 1/Î³ 2 receptors, which are synaptic. Additional diversity in possible receptor configurations is conferred by alternate splicing of subunits, which has been identified in members of the Î² and Î³ families.[95a] Even given the limitations associated with a preferred pentameric stoichiometry described earlier, clearly there is a potential staggering diversity in possible $GABA_A$-receptor compositions. The

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fact that $GABA_A$ receptors assemble into 10 to 20 preferred configurations in brain simplifies the situation somewhat.[107a]

Several studies have been published comparing properties and expression patterns of $GABA_A$ receptors in dentate granule cells of both postâ€“status epilepticus and kindled animal models of temporal lobe epilepsy. For the most part, these studies exhibit a remarkable consensus. The numbers of subsynaptic $GABA_A$ receptors as well as the efficacy of quantal GABAergic synaptic activation both exhibit a marked increase in both kindled animals[119,120] and epileptic animals months after status epilepticus, when rats are spontaneously seizing.[26,35,48,85] In the pilocarpine model, additional evidence has been published demonstrating that the frequency of miniature inhibitory postsynaptic currents (mIPSCs) and the amplitude of local stimulation-evoked IPSCs are reduced, reflecting a reduction in the number of GABAergic synapses associated with a loss of GABAergic neurons rather than any change in synaptic expression of $GABA_A$ receptors.[78]

Accompanying this enhancement in the number of $GABA_A$ receptors (and reduced numbers of GABAergic synapses in postâ€“status epilepticus models) are alterations in the pharmacology of $GABA_A$ receptors. These in turn correlate with and are accompanied by modification in the expression patterns of individual $GABA_A$-receptor subunits. $GABA_A$ receptors in dentate granule cells from either kindled or postâ€“status epilepticus rats exhibit enhanced sensitivity to blockade by zinc, as well as a decreased sensitivity to modulation by benzodiazepines and benzodiazepine site agonists[26,27,35,48,85,115] (reviewed by Coulter[37,38]).

These pharmacologic changes in dentate granule cell $GABA_A$-receptor responses in kindled and postâ€“status epilepticus models of temporal lobe epilepsy, in addition to being informative about possible shifts in subunit expression patterns (discussed later), may also have functional importance. Zinc is a biologically important divalent cation present in high concentrations in the central nervous system, particularly in the dentate gyrus. Zinc densely colocalizes with glutamate in synaptic vesicles of granule cells and is coreleased together with glutamate on activation of excitatory transmission. Extracellular zinc concentrations achieve concentrations of 10 to 100 ÂµM during repetitive mossy fiber activation.[10,67] Furthermore, mossy fibers sprout in epileptic hippocampus in both postâ€“status epilepticus and kindling models and reinnervate granule cells along their dendrites in the inner molecular layer.[95,156] This also occurs in the dentate gyrus of humans with epilepsy,[65,154] as does the appearance of zinc-sensitive $GABA_A$ receptors in dentate granule cells.[148] The apposition of a zinc delivery system and sprouted mossy fibers, together with the de novo appearance of zinc-sensitive $GABA_A$ receptors in granule cells of the epileptic hippocampus, has led to the formulation of the hypothesis that the combination of these two events could lead to a dynamic, zinc-mediated collapse of augmented inhibition in the dentate gyrus during seizure initiation and/or propagation. This in turn would compromise the filter or gatekeeper function of the dentate and facilitate seizures.[27,38] For these events to occur, extracellular zinc, which is released at excitatory synapses, must be sufficiently mobile to diffuse to and block neighboring GABAergic synapses. This has yet to be demonstrated either in vivo or in vitro, and at least one study has questioned whether this may occur.[112]

The pharmacologic data described here are consistent with an Î± subunit switch, which has been found to occur in dentate granule cells in both postâ€“status epilepticus and kindling temporal lobe epilepsy models. In single-cell aRNA amplification studies, Brooks-Kayal et al.[26] described a net downregulation in Î± 1 and an upregulation in Î± 4 subunit expression in individual granule cells that also showed altered $GABA_A$-receptor sensitivity to zinc and the benzodiazepine site agonist zolpidem. This switch occurred within 24 hours of status epilepticus and was permanent, manifest in animals as long as 1 year. Upregulation of Î± 4 subunit mRNA together with a downregulation in delta subunit mRNA has been found in in situ hybridization studies in dentate granule cells in both postâ€"status epilepticus and kindling models of temporal lobe epilepsy,[118] and immunohistochemical studies have corroborated this upregulation in Î± 4 and downregulation of Î´ subunits in the pilocarpine mouse model of temporal lobe epilepsy,[129] with the latter studies further demonstrating that these subunit changes are associated with a reduction of tonic GABA currents in dentate granule cells.

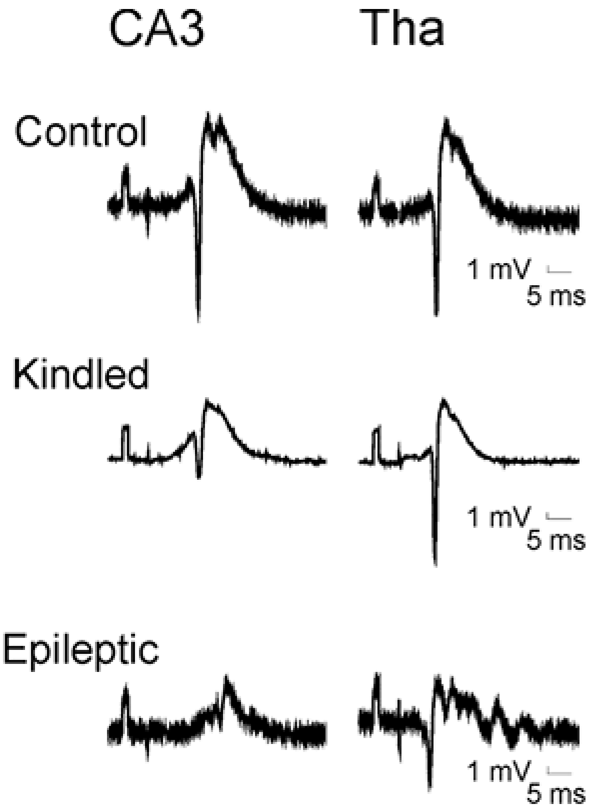

FIGURE 3. Comparison of evoked extracellular responses in CA1 following stimulation of either contralateral CA3 or the midline thalamic (Tha) region in rats. The recording site is the same for both stimulation sites. Although it is clear that there are differences based on the site of stimulation, more important are the differences across the type of animal from which the responses were obtained. Although the responses from the kindled animals are different than those from controls, these two groups are much more alike than the epileptic animals, which have much lower amplitude responses and multiple population spikes.

The consequences of the consensus finding of overall upregulation of subsynaptic $GABA_A$ receptors, reduction in tonic (extrasynaptic) GABA current, and kinetic and pharmacologic changes associated with Î± subunit switches on circuit excitability and seizure susceptibility are complex and difficult to extrapolate in either kindled or postâ€"status epilepticus temporal lobe epilepsy models. As discussed, one possible outcome is that inhibition may collapse on zinc release. A second possibility is that tonic inhibition may play a critical role in gatekeeper function of the dentate gyrus, so that reduction in this current could facilitate propagation of synchronous, epileptiform entorhinal cortical activity into the hippocampus. A third possibility is that these changes may be compensatory, a homeostatic response to hyperexcitability on the part of granule cells. In this case, alternate mechanisms, either within the dentate gyrus or in other structures, would be critical in generation of seizures, and the responses recorded in dentate would attempt to counteract these changes.

Although much of the research has been focused on the myriad of changes in the GABAergic system with an emphasis on the dentate gyrus, there is evidence for changes in the GABAergic system at other limbic sites. Furthermore, other neurotransmitter systems show evidence for alterations in the nature of drug effects as well as pharmacosensitivity. Although the work on these other regions, receptors, and channels has not come close to the depth or breadth of the studies on GABA function in the dentate, the evidence is clear. In CA1 the alterations in IPSP, including the $GABA_A$ and $GABA_B$ components, is profound, and there is evidence for changes in the presynaptic $GABA_B$ receptors as well.[101] There is evidence that the effect of drugs that work through the glutamatergic system is also profoundly different in epileptic animals. In some cases, drugs that have little effect in naive animals have a significant effect in epileptic animals, and in other cases, the opposite is true.[9,77,171,172] What is very interesting in these and other studies is that the pharmacology and physiology of kindled animals is very different from those in epileptic animals (Fig. 3).[20] This point is extremely important because it emphasizes that epilepsy is a very different condition than having experienced seizures.

Summary and Conclusions

This chapter is a complex mixture of the clinical and the scientific, crossing from the intact system to the synapse. There are several recurring themes in this data soup. First, it is essential to separate the underlying condition of epilepsy from the potential effects of seizures on the system. In this regard the message is fairly clear: The effect of the seizures on the system is not nearly as great as the changes associated with epilepsy itself. Another clear message is that there is no single change associated with epilepsy: There are changes in neuronal populations, channels, and receptors. Furthermore, there is strong and growing evidence that these changes precede the onset of epilepsy, suggesting that the contributions of seizures to the findings are limited (although there are clear contributions from the seizures). Finally, epilepsy likely has a unique pharmacology. This observation is extremely important as we continue the search for more effective therapies: We need to consider those epilepsy-specific changes so that we can develop epilepsy-specific drugs.

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Chapter 41

Basic Mechanisms of Human Epilepsy

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Introduction

Most of our views concerning the fundamental neuronal mechanisms of epileptic phenomena derive from investigations carried out on experimental animal models. An anonymous bioscientist, however, once stated, â€œThe best model of a cat is a cat, and preferably the same cat,â€ implying that the ideal approach to studying basic mechanisms of human epilepsy is actually to study patients with epilepsy. Although direct examination of the epileptic human brain has become much more feasible in recent years, experimental paradigms are severely limited by cost and ethical considerations. As a result, animal models remain an essential part of basic research into the pathophysiology of human epilepsy. Animal models are invaluable for expanding upon concepts, derived from observations of patients, that cannot be pursued with further human experimentation. Conversely, research on patients with epilepsy is essential to validate the relevance of data obtained from animal models. Both these goals are best met by designing parallel investigations involving patients with epilepsy and experimental animal preparations. Such parallel studies are greatly facilitated today by new clinical tools, such as advanced noninvasive structural and functional neuroimaging, and the unique opportunities for invasive investigations in vivo and the utilization of human tissue in vitro that exist in association with the surgical treatment of epilepsy.[38,48,102] Progress in molecular genetics promises yet another powerful means, not only for establishing similarities between specific animal models and human epileptic disorders, but also for defining epileptogenic defects in the human brain that can be precisely replicated in the animal laboratory.

There are many forms of human epilepsy, which undoubtedly reflect a variety of pathophysiologic mechanisms. In fact, a single, well-defined human epileptic condition, and even an individual epileptic seizure, involves several specific disturbances in neuronal function that occur simultaneously or in sequence before clinical manifestations appear. To carry out parallel studies in patients and animals, it is important to realize that few, if any, human epileptic conditions can be faithfully modeled in toto in the experimental animal laboratory. Consequently, it is necessary to identify and define component parts of human epilepsy that can be more easily investigated individually and replicated in animals.[33,35] This chapter, therefore, first considers one strategy for dissecting out components of epilepsy, and then examines what has been learned about the basic mechanisms of these component parts from parallel studies of the human condition and appropriate animal models.

Components of Human Epilepsy

An *epileptic seizure* is an acute event that can be a natural, albeit pathologic, reaction of a normal brain to a noxious insult. Although an epileptic seizure that has been acutely induced in an animal model may replicate certain aspects of epileptic seizures occurring in patients with epilepsy, the underlying intrinsic and enduring epileptogenic abnormality responsible for *recurrent* epileptic seizures in patients with epilepsy is missing in this situation. Consequently, investigations of acute seizures induced in otherwise normal experimental animal models provide limited information about the pathophysiologic substrates responsible for repeated *spontaneous* seizure generation in patients. Nevertheless, much information can be gained about mechanisms of ictal precipitation, ictal propagation, ictal termination, and postictal phenomena.

Epileptogenesis, or the mechanism by which an epileptic condition is acquired, undoubtedly takes many forms, but it is most evident in secondary (symptomatic) human epileptic conditions, in which habitual recurrent seizures begin many months or even years after lesions occur in the brain. Epileptogenesis has been studied in animals by introducing into the brain certain metals, such as alumina cream, and more recently by inducing status epilepticus (SE) with excitotoxins, such as kainic acid (KA) and pilocarpine, or electrical stimulation; this results in structural lesions and the development of recurrent spontaneous seizures.[95] The process of epileptogenesis has also been brought under more precise laboratory control with the various kindling models of epilepsy.[80]

Just as basic research on epilepsy made a paradigm shift with the realization that animals with chronic epilepsy more faithfully model the human condition than do epileptic seizures induced in a normal brain, investigations with animal models now requires a second paradigm shift. Given that a genetic predisposition often exists to symptomatic human epilepsies, identification of susceptibility genes and other predisposing factors should make it possible to create more realistic animal models of epileptogenesis by inducing a chronic epileptogenic lesion in a brain with these predisposing factors.[40]

The *interictal state* represents a period of relative quiescence, during which the enduring pathophysiologic disturbances that predispose to the spontaneous recurrence of epileptic seizures are minimally active, or held in abeyance by some active seizure-suppressing mechanism. These diverse phenomena can be studied in the laboratory, using animal models of chronic epilepsy in which seizures are generated spontaneously.

Ictal onset represents a functional transition from the interictal state; it can reflect a variety of processes, depending on the underlying pathophysiology and the type of ictal manifestation.[34] Increases in excitation or synchrony, decreases in seizure-suppressing mechanisms, and nonspecific precipitating factors can be studied during transition to ictus in animal models of chronic epilepsy.

Many types of seizures occur, and the *ictal state* undoubtedly reflects a variety of aberrant neuronal mechanisms involving different patterns of excitatory and inhibitory events, different synchronization processes, and different brain regions and pathways. Individual ictal events often also show evolution, involving a variety of forms of propagation of ictal discharge and resulting in variable ictal mechanisms specific to the region to which propagation has occurred. With focal seizures, this includes local spread, propagation to structures that impair consciousness when simple partial seizures evolve to complex partial seizures, and propagation to structures that generate generalized convulsive manifestations when seizures secondarily generalize. Such propagation patterns, and peculiarities of ictal discharges in particular brain regions, can be studied in the animal laboratory with acute as well as chronic models. However, pathways, and therefore ictal spread, vary across species and may not accurately replicate the human condition; for example, interhippocampal connections are strong in rats and weak in humans, a difference that can affect the manifestations of temporal lobe seizures.[121]

Ictal termination also takes many forms. It undoubtedly involves both active and passive neuronal mechanisms, which vary according to seizure type and underlying pathophysiology. Even though ictal termination can be easily investigated using animal models of acute seizures, relatively little research has been carried out on this phenomenon, compared with the attention given to ictal onset.[25]

The *postictal period* can be associated with brief or prolonged neuronal dysfunction, ranging from isolated focal neurologic deficits to coma. These clinical disturbances presumably reflect, at least in part, the enduring effects of active mechanisms that act to terminate the ictal state.[16]

Interictal behavioral disturbances can represent the enduring consequences of repeated epileptic seizures or can be produced by the underlying brain disturbance/damage that is responsible for the seizures themselves. Underlying mechanisms that have been implicated in long-term effects of epilepsy include (a) specific structural damage, which might be the result, rather than the cause, of seizures; (b) transsynaptic functional changes, such as those modeled by kindling; and (c) side effects of natural seizure-suppressing mechanisms that are necessary to maintain the interictal state. Some animal research is being carried out to elucidate mechanisms of epilepsy induced interictal behavioral disturbances. However, given the degree of clinical disability that can be attributed to these disturbances, more effort in this area of research should be encouraged.[39]

Studies of Human Epilepsy

With the preceding dissection of epileptic phenomena as a framework for organizing the approaches to research into basic mechanisms of human epilepsy, the remainder of this chapter focuses on how the results of investigations of human epilepsy confirm or contradict concepts derived from the results of studies carried out on experimental animal models.

Epileptogenesis and the Interictal State

The primary (idiopathic) epilepsies are genetically transmitted, typically have an age-related onset, and may resolve spontaneously after several years. These disorders are presumably caused by defects that manifest themselves as epileptic seizures only at vulnerable periods during cerebral development. Epileptogenesis, or the active process of creating an epileptic condition, is therefore difficult to evaluate in these conditionsâ€”although it is certainly possible that genetically determined abnormalities may be elaborated as the brain matures, and thus a process of epileptogenesis is likely to also occur in these types of epilepsies. The secondary (symptomatic) epilepsies, however, usually result from structural disturbances that become epileptogenic lesions during some finite period. In patients with epilepsy caused by metabolic diseases, congenital malformations, or intrinsic substrates such as neoplasia, the timing of this process is undeterminable; however, in others (e.g., those in whom epilepsy develops following head trauma or a cerebrovascular accident), the existence of a well-defined â€œlatent periodâ€ is well documented. Presumably, the damaged brain reorganizes during this period in a manner that ultimately predisposes to the recurrence of detectable, spontaneous epileptic seizures.

Clinical data indicate that the likelihood that epilepsy will develop after an epileptogenic insult depends on the area of brain damaged, type of damage, age at which the damage occurred, and genetic predisposition.[70] It is clear from clinical experience that mechanisms accounting for the occurrence of acute seizures at the time of, or shortly after, an epileptogenic cerebral insult are different from those accounting for the development of a chronic epileptic condition many months or years later; that is, early seizures do not necessarily predict late seizures, and the risk factors for epileptic seizures occurring at the time of head trauma or stroke are not exactly the same as those for the development of late posttraumatic epilepsy[70] (Table 1), although early seizures may indicate an increased risk of later development of epilepsy.[70] Furthermore, whereas the immature brain is more susceptible to acute seizures than the mature brain, it is less likely than the mature brain to generate subsequent spontaneous recurrent seizures, given the same initial insult.[91,101] The clinical expression of the process of epileptogenesis in the human brain (e.g., clinical seizures) following injury-associated insult can require considerable time, although this is not well understood.[55] The anatomic reorganizations that are currently hypothesized to underlie the epileptogenic process, however, cannot be the only epileptogenic factors involved, because the latent period can be much longer than expected for such changes to take place; the increased risk for epilepsy after head trauma persists for well over 10 years,[70] even though chronic epilepsy develops in more than half of such cases within the first year.

Table 1 Risk factors for epileptic seizures and epilepsy after nonmissile head trauma

Early seizures
Intracranial hematoma
Focal neurologic signs
Posttraumatic amnesia >24 hours
Any neurologic signs
Depressed skull fracture
Subarachnoid hemorrhage
Injury before 5 years of age
Linear skull fracture

Late seizures

Intracranial hematoma

Early seizures

Depressed skull fracture

Posttraumatic amnesia >24 hours

Injury after 16 years of age

Adapted from Jennet B. *Epilepsy After Non-missile Head Injuries,* 2nd ed. Chicago: William Heinemann; 1975, with permission.

It is also important to note that the brain reorganization underlying epileptogenesis (see the next section) is not necessarily a product of an epileptogenic *insult*, but may be determined by genetic factors (i.e., aberrant brain developmental processes). At the very least, it is quite clear from studies of animal models that genetics contribute significantly to epilepsy predisposition.[118]

Our current understanding of the basic mechanisms of human epileptogenesis derives largely from studies of patients with mesial temporal lobe epilepsy (TLE), perhaps the most common human epileptic condition.[103] Because mesial TLE is often medically refractory and treated preferentially by surgical resection, extensive diagnostic testsâ€"at times involving in vivo invasive electrophysiologic recordingsâ€"are carried out, and excised tissue becomes available for in vitro investigations. The pathologic substrate that is most often associated with the clinical condition known as *mesial TLE* is hippocampal sclerosis.[6,23] Microscopic examination of mesial temporal structures has further defined the kinds of lesions seen in the parts of medial temporal lobe removed from patients with hippocampal sclerosis. These include losses of neurons in almost all hippocampal regions, with a heavier loss in the hilus, CA1, and CA3, and lesser losses in CA2 and dentate gyrus (DG) granule cell (GC) layer. In addition, clear synaptic reorganization is present, with collaterals of surviving DG granule cells reinnervating the inner molecular layer of DG GC dendrites, as well as inhibitory interneurons scattered throughout the DG (see Chapter 13). It is becoming increasingly apparent that patients with this condition also have much more widespread extrahippocampal pathological changes as well.[120]

The lesions seen in mesial TLE with hippocampal sclerosis in human brain have been modeled in the animal laboratory using a variety of techniques that cause hippocampal cell loss and neuronal reorganization.[9,75,111,113,115] Whereas the progression of epileptogenic changes can be examined in these animal models, studies of patients with medically refractory mesial TLE reveal only the end results of the epileptogenic process. The pathologic changes observed in these patients could be either the cause or the effect of recurrent epileptic seizures; if the latter, they could result in further epileptogenicity or reflect natural homeostatic mechanisms acting to suppress seizure occurrence. It is also important to note that the sclerotic hippocampus, despite all our attention, may not be the primary epileptogenic region in some patients with mesial TLE. Research results are confounded by the fact that there is no adequate control tissue for human studies, because epileptiform abnormalities can be widespread and often involve both temporal lobes; in addition, evaluations are complicated by the superimposed effects of antiepileptic drugs (AEDs), which have invariably been used.[38] Nevertheless, important insights have been derived from anatomic, neurochemical, electrophysiologic, and molecular investigations of this human condition.

Hippocampal sclerosis, induced in rats by intrahippocampal injection of KA, is characterized by general cell loss but more pronounced loss of specific neurons, relative preservation of some inhibitory interneurons, and axonal sprouting resulting in the creation of aberrant circuits, gliosis, neurogenesis, and laminar dispersions of the dentate gyrus.[9,64,78,92] All these pathologic changes have been demonstrated in surgically resected specimens of human hippocampal sclerosis, suggesting that the epileptogenic process in human mesial temporal lobe epilepsy resembles that of rats injected with KA.[5,23,67,110] In addition, amygdala sclerosis has been described,[65] and some animal models show evidence for selective entorhinal cell loss.[26] Inflammatory processes also play a role in epileptogenesis in some experimental models.[116] Mossy fiber sprouting could create powerful recurrent excitatory feedback that might contribute to the development of epileptiform potentials. Such an enhanced excitatory drive is suggested by the observation of increased extracellular levels of excitatory amino acids obtained during microdialysis of human epileptic brain[29] and chronic alteration in glutamate receptors in human epileptogenic tissue.[52,53,63] Conversely, there is also evidence that a significant number of aberrant mossy fibers terminate on interneurons, which increases inhibition.[106]

Investigations of human mesial TLE have yielded inconsistent results concerning inhibitory influences. Inhibitory interneurons appear to be preferentially preserved, and sprouting of inhibitory terminals may also occur.[8,22] The results of microdialysis studies are equivocal, with evidence for both increased and decreased release of Î³-aminobutyric acid (GABA).[27] Positron emission tomography (PET) consistently reveals a reduction in benzodiazepine receptor binding in human epileptogenic regions;[60,100] this may merely reflect cell loss, but it could also indicate a selective decrease in postsynaptic inhibitory mechanisms or a receptor downregulation resulting from enhanced presynaptic inhibitory neurotransmitter release.

In vitro electrophysiologic studies of human sclerotic hippocampal slices have been difficult to perform, but there is some suggestive evidence of increased membrane excitability,[78] which may be mediated by *N*-methyl-D-aspartate (NMDA) receptors;[66] parallel animal studies also show enhanced GABA-mediated inhibition,[90] and some studies on human tissue support this.[5,50] In vivo electrophysiologic studies also indicate enhanced inhibitory influences in some areas of the human epileptogenic hippocampus and enhanced excitatory influences in others.[19,47,122] Enhanced inhibition of the epileptic hippocampus could reflect natural protective mechanisms; however, it is intriguing to note that enhanced inhibition could also predispose to the appearance of epileptiform hypersynchronization.[36] Recordings from resected human tissue in a slice chamber have been somewhat disappointing with regard to recreating the epileptiform discharges often recorded in vivo from the same tissue. Spontaneous interictal discharges are usually lacking, and seizure-like discharges can only be elicited after threshold-lowering maneuvers such as reducing inhibition or raising extracellular potassium (K).[14] More recent work suggests that recordings from parahippocampal regions (subiculum and entorhinal cortex) may more closely mimic in vivo phenomena. It has also been suggested that the enhanced excitability and increased synchrony in these regions may be related to altered intracellular chloride concentrations, such that normally inhibitory synaptic actions may become excitatory.[18]

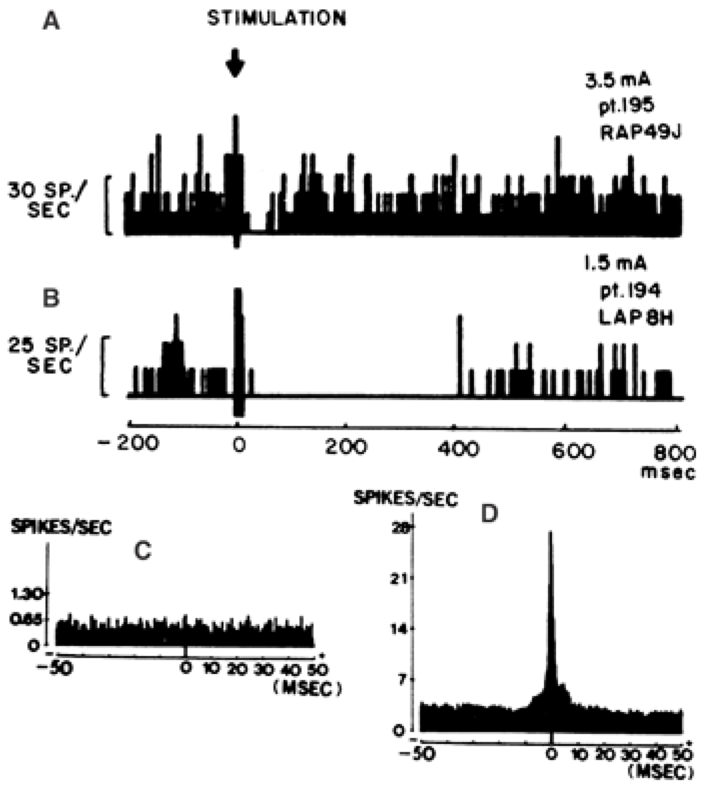

FIGURE 1. Unit histograms from human epileptic hippocampus show weak firing suppression (**A**) in

neurons that were not firing synchronously as determined by cross-correlation histograms (**C**), and strong firing suppression (**B**) in neurons that were firing synchronously (**D**). This provides indirect evidence for recurrent inhibitory circuits as a mechanism of hypersynchronization. From Isokawa-Akesson M, Wilson CL, Babb TL. Prolonged inhibition in synchronously firing human hippocampal neurons. *Epilepsy Res.* 1989;3:236â€"247, with permission.

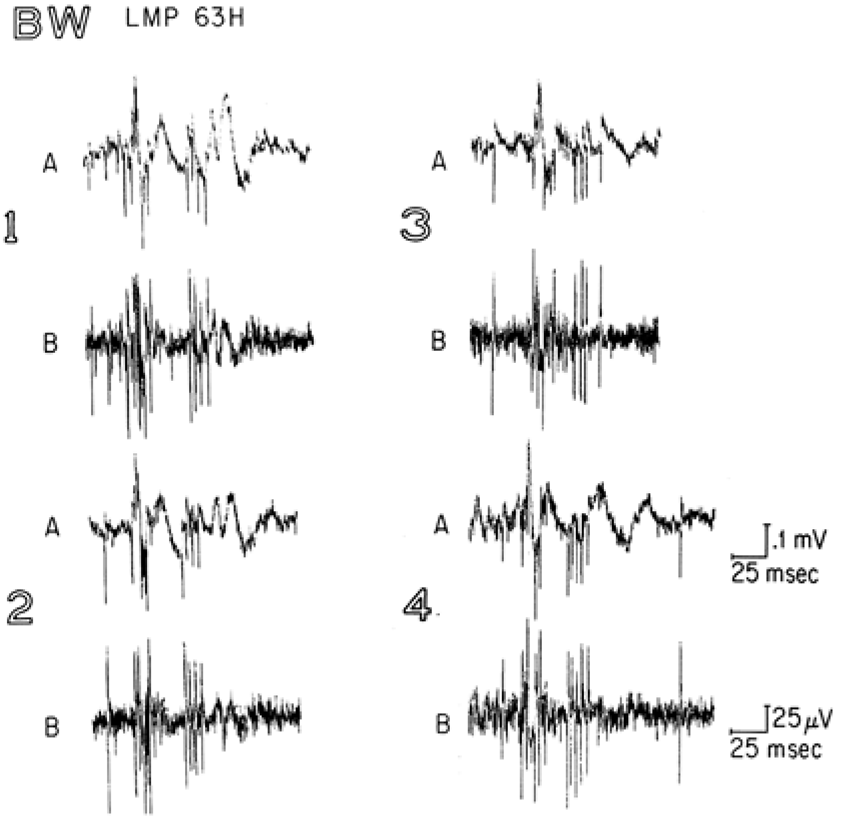

FIGURE 2. EEG spikes (**A**) and action potentials (**B**) recorded from the same microelectrode (*63H*) in the left midhippocampal pes (*LMP*) in a patient with clinical seizures originating in the LMP. *Tracings 1 through 4* were taken from the beginning to the end of the recording period and selected to have a similar EEG spike morphology, characterized by a fast rise time of the initial negative component. *Tracing A* is a wide-band recording to show the EEG spike-and-slow wave superimposed on the unit discharges. For *tracing B*, additional high-pass filtering was used to enhance the neuronal discharges. Note increased unit firing during EEG spike, and cessation of unit firing during EEG slow wave. From Babb TL, Crandall PH. Epileptogenesis of human limbic neurons in psychomotor epileptics. *Electroencephalogr Clin Neurophysiol.* 1976;40:225â€"243, with permission.

Unit recordings obtained from human epileptic hippocampus in vivo demonstrate that cells that receive strong inhibitory input are highly synchronized[68] (Fig. 1), suggesting that inhibition does play a role in the development of epileptiform hypersynchronization in TLE, just as it does in absence epilepsy[83] and in the promotion of normal rhythmic neuronal activity.[2]

The interictal state in human mesial TLE is characterized by the appearance of interictal electroencephalographic (EEG) spike-and-slow-wave discharges in the epileptogenic temporal lobe, and often independently in the contralateral temporal lobe as well. Microelectrode recordings demonstrate that the spike is associated with increased unit firing, and the slow wave with absence of unit firing (Fig. 2),[7] suggesting that this epileptiform transient reflects synchronous paroxysmal depolarization shifts and afterhyperpolarizations of neurons within the epileptogenic hippocampus, in much the same way as occurs in the experimental penicillin focus.[24] These abnormal excitatory and inhibitory events occur relatively infrequently, and the overall interictal state of the epileptogenic region in this disorder is one of relatively decreased activity, as reflected in the hypometabolism seen on PET using ^{18}F-fluorodeoxyglucose.[61] It would appear therefore that the synaptic reorganization observed in human hippocampal sclerosis are associated with a chronic state of relative quiescence, but a propensity for hypersynchronous excitatory and inhibitory discharges.

It has been suggested that hippocampal reorganization alone, and the resultant repetitive hypersynchronous ictal discharges limited to the hippocampus, is not sufficient for the clinical manifestation of epileptic seizures. In fact, these electrographic ictal phenomena can be recorded with depth electrodes, unassociated with clinical signs or symptoms.[108] Complex partial, and perhaps even simple partial, seizures would seem to require propagation of ictal discharge to adjacent and distant structures, which might be facilitated if these structures were particularly receptive and themselves epileptogenic. Secondary epileptogenesis, as occurs with kindling and the mirror focus phenomenon,[88] could conceivably account for transsynaptic changes necessary for behaviorally apparent ictal events to ensue. In primates, bilateral hippocampal lesions may be necessary before temporal lobe seizures can be observed,[107] and in patients with medically refractory TLE, some degree of bilateral mesial temporal epileptogenicity is the rule rather than the exception.[119] Patients with mesial TLE and hippocampal sclerosis often experience the recurrence of auras after radical anterior temporal removal has succeeded in abolishing the habitual complex partial seizures. Perhaps the epileptiform region is widespread from the beginning, or perhaps secondary epileptogenicity results in extension to the ipsilateral posterior hippocampus, contralateral hippocampus, or wide areas of limbic cortex in either hemisphere.

There are reasons to believe that focal epileptic conditions caused by specific structural lesions, such as neoplasms, cortical dysplasias, vascular malformations, cysts, scars, or infectious processes (so-called lesional epilepsies), involve epileptogenic mechanisms that differ from those of hippocampal sclerosis.[58] Whereas mesial TLE is usually associated with diffuse interictal hypometabolism on fluorodeoxyglucose PET, this is a rare finding with neocortical lesional epilepsy.[62] Furthermore, surgical results for mesial TLE appear to depend on the amount of adjacent entorhinal cortex removed,[105] whereas surgical cures can occasionally be achieved in lesional epilepsy by removal of the lesion alone, with the adjacent cortex left intact.[17] Therefore, for some lesional epilepsies, the lesion might produce an epileptogenic irritation that does not require reorganization of adjacent cortical neurons. This is an area that has not been very well explored in the literature. It is important to note here, however, that even with apparent â€œcuresâ€ achieved by resection of specific lesions, other regions (or lesions) that had previously been electrically innocuous may become â€œepileptogenicâ€â€”suggesting either some more diffuse abnormality and/or a subsequent epileptogenic process.[98] Focal epilepsies associated with localized areas of dysplastic cortex represent a unique category of disorder related to disturbances in neuronal migration and differentiation.[117] It is unclear whether the bizarre neurons and aberrant neuronal connections in these areas are directly responsible for seizure generation, or whether they merely represent a marker for a variety of less apparent disruptions in neuronal integration that are responsible for the appearance of spontaneous epileptic seizures (see Chapter 14). Certainly, children with extensive dysplasias also show evidence of hippocampal cell loss and abnormal axon sprouting similar to that of hippocampal sclerosis.[79] However, human[81] and animal[99] studies confirm that these dysplastic regions do have epileptogenic properties.

In a third group of secondary focal epilepsies, no association is found with a demonstrable structural lesion or hippocampal sclerosis. Presumably, these conditions are caused by structural lesions that cannot be seen using standard neuroimaging techniques or, in many cases, even using the pathologist's microscope after surgical resection of an electrophysiologically demonstrated epileptogenic region. These epilepsies might be caused by specific lesions identical to those of lesional focal epilepsies, but are too small or too disseminated to be detected; they could reflect neocortical cell loss and synaptic reorganization similar to what is seen in hippocampal sclerosis but that cannot be identified by present histopathologic technology; or they may reflect molecular changes (and related changes in gene expression) that are not manifest at the level of structural cell loss or reorganization. It is also conceivable that some forms of nonlesional neocortical focal epilepsy result from unique pathophysiologic substrates that have yet to be recognized and that might lead to entirely new concepts of human epileptogenesis.

Ictal Onset

Routine EEG recordings obtained from patients during epileptic seizures provide ample evidence of the existence of a variety of ictal phenomena. The classic *grand mal* convulsion, whether occurring spontaneously in an individual with primary generalized epilepsy or artificially induced (e.g., during electroconvulsive shock treatment for depression), typically begins with a widespread buildup of low-voltage fast activity referred to as a *recruiting rhythm*. This is distinctly different from the characteristic high-voltage, three-per-second, generalized spike-and-wave discharge seen at the onset of typical absence seizures in patients with childhood absence epilepsy and other forms of primary generalized epilepsy.[34] Although the actual generators for these ictal events have not been identified in patients, animal studies and responses of patients to various AEDs clearly indicate that they reflect different epileptogenic mechanisms. Recent studies have focused on attempting to recognize features of ictal onset so as to predict the approach of seizure activity well before the typical EEG and clinical/behavioral signs become apparent.[74] The difficulty of this enterprise, and the variable success of the different approaches (mostly based on nonlinear dynamic analysis of EEG) certainly confirm the feasibility of recognizing brain changes well before seizure onsetâ€”and also are consistent with the view that different seizures and/or seizure types are associated with significant variability (in form and underlying mechanisms) in ictal onset.

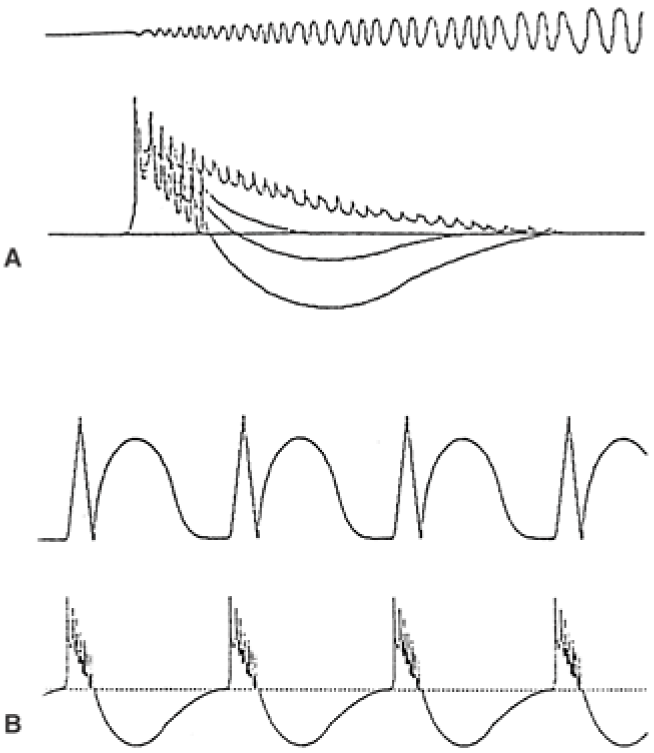

FIGURE 3. A: The neuronal mechanism of the recruiting rhythm is illustrated schematically here. The *lower trace* represents an intracellular recording of a paroxysmal depolarization shift (*PDS*); it demonstrates how the afterhyperpolarization gradually disappears to become an afterdepolarization, giving rise to continuous, high-frequency action potential discharge. The EEG in the *upper trace* increases in amplitude and slows in frequency as more and more neurons are recruited into this process and develop increasing synchrony. **B:** The neuronal mechanism of a hypersynchronous ictal discharge is schematically illustrated here. The *lower trace* shows an intracellular recording of recurrent depolarizations. As with the interictal spike-and-wave discharge, the EEG spike, seen in the *upper tracing*, represents a summation of depolarizations, whereas the EEG slow wave represents a summation of afterhyperpolarizations. In the ictal state, however, each hyperpolarization is followed immediately by another depolarization, creating a repetitive hypersynchronous discharge such as the classic three-

per-second spike-and-wave pattern of *petit mal* absences. A similar mechanism appears to underlie some partial ictal events as well. From Engel J Jr. Functional explorations of the human epileptic brain and their therapeutic implications. *Electroencephalogr Clin Neurophysiol.* 1990;76:296â€“316, with permission.

Intracellular investigations of membrane events occurring during the transition to ictus, as originally studied in the experimental penicillin focus, demonstrated a disappearance of the presumably protective afterhyperpolarization during the interictal spike-and-wave transient, and gradual appearance of an afterdepolarization accompanied by rapid action potential discharges.[24,80] These events were synchronized among many neurons in the epileptic focus and appeared in the field recordings as a transient high-frequency discharge. Therefore, such disinhibitory ictal membrane changes are consistent with the EEG recruiting rhythm of generalized convulsive seizures.

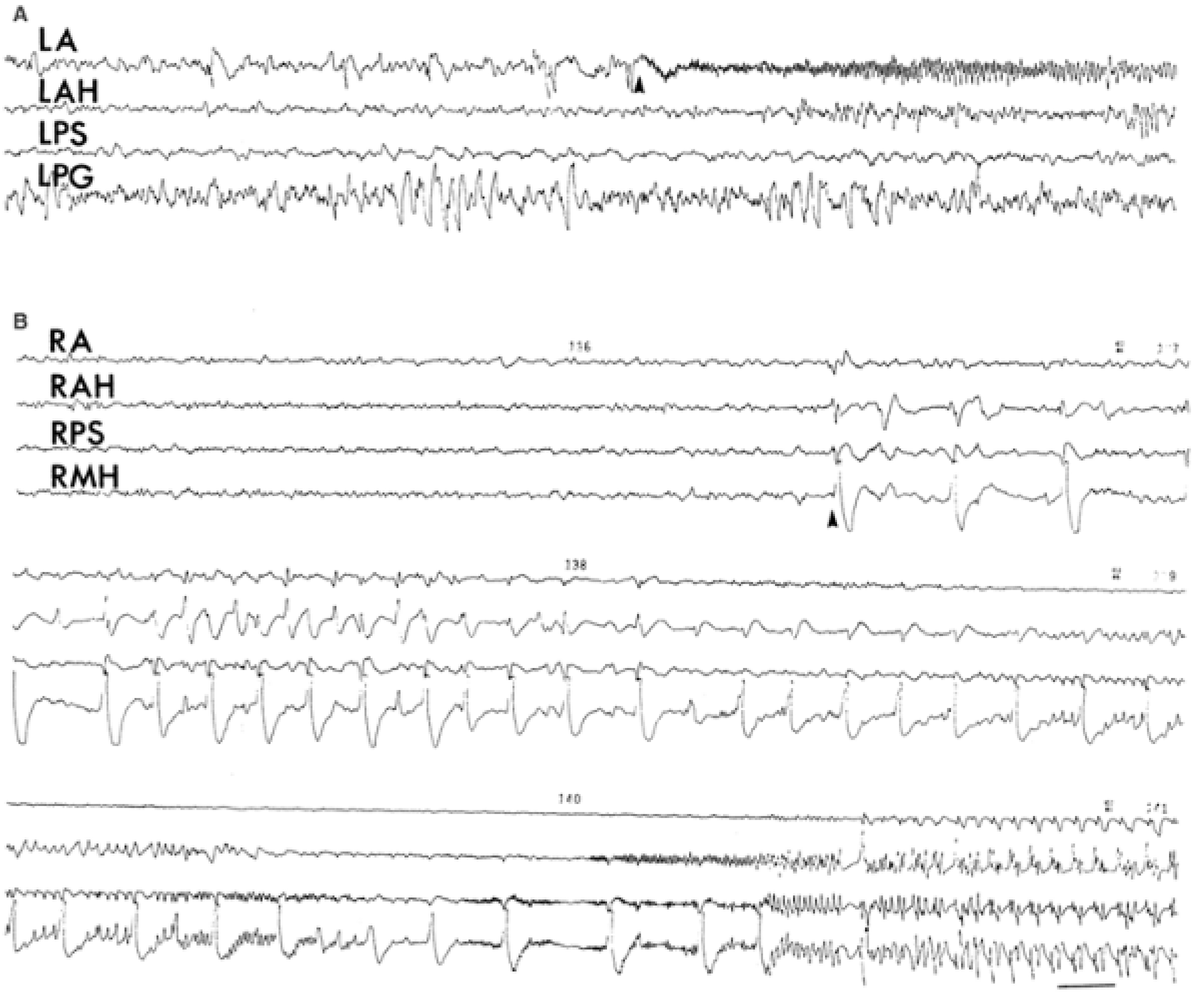

FIGURE 4. Segments of telemetry recordings from two patients showing EEG activity at selected depth electrode bipolar tips during the onset of complex partial seizures. **A:** The classic, depth electrodeâ€“recorded ictal onset consists of a buildup of low-voltage fast discharge, here beginning in a single channel (*arrow*). **B:** Three continuous segments show a more common ictal onset pattern, beginning with rhythmic, high-amplitude, sharp and slow transients (*arrow*), eventually giving way to a low-voltage fast discharge, which then evolves into higher-amplitude repetitive spikes or spikes-and-waves. *L*, left; *R*, right; *A*, amygdala; *AH*, anterior hippocampus; *MH*, midhippocampus; *PS*, presubiculum; *PG*, posterior hippocampal gyrus. Calibration, 1 second. From Engel J Jr. Brain Metabolism and Pathophysiology of Human Epilepsy. In: Dichter M, ed. *Mechanisms of Epileptogenesis: Transition to Seizure*. New York: Plenum Press; 1988:1â€“15,

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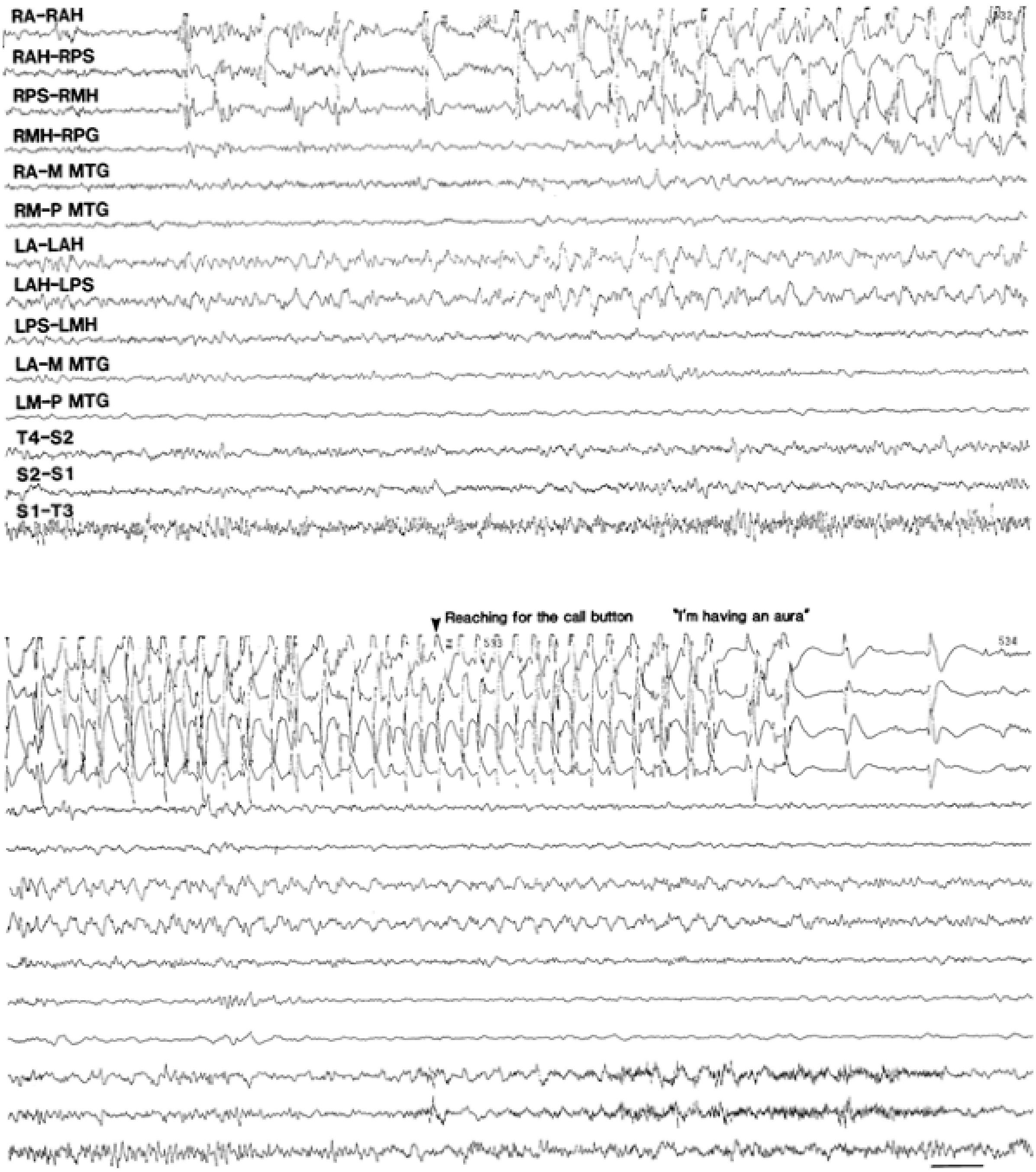
RA–RAH
RAH–RPS
RPS–RMH
RMH–RPG
RA–M MTG
RM–P MTG
LA–LAH
LAH–LPS
LPS–LMH
LA–M MTG
LM–P MTG
T4–S2
S2–S1
S1–T3
532
Reaching for the call button
"I'm having an aura"
533
534

FIGURE 5. Forty continuous seconds of an EEG recorded from depth, sphenoidal, and scalp electrodes during a simple partial seizure of the right temporal lobe. Ictal onset consists of an increase in interictal spike discharges, maximal at the right anterior hippocampal electrode (*left portion of upper panel*). After 8 to 9 seconds, these spikes become regular, eventually developing into a 3-Hz spike-and-wave pattern involving all derivations from the right mesial temporal lobe. Note that no low-voltage fast activity is seen, either initially or at any part of the ictal episode. The patient reached for the call button at the *arrow*, at which point regular slow activity is also seen in the left anterior hippocampus and in the right sphenoidal electrode. The patient then indicated an aura consisting of a sensation of fear in her stomach. Depth electrode locations indicated as in FIGURE 4. Superficial contacts from anterior (*A*), mid (*M*), and posterior (*P*) depth electrodes recorded from cortex of middle temporal gyrus (*MTG*). Calibration, 1 second. From Engel J Jr. Brain

Metabolism and Pathophysiology of Human Epilepsy. In: Dichter M, ed. *Mechanisms of Epileptogenesis: Transition to Seizure*. New York: Plenum Press; 1988:1â€“15, with permission.

By contrast, the transition between interictal and ictal states of primary generalized absence seizures, in which the prominent slow wave persists in the rhythmic spike-and-wave pattern, indicates preservation of the inhibitory afterhyperpolarization (Fig. 3). Studies of the generalized feline penicillin model, in which large doses of intramuscular penicillin in the cat produce absence-like seizures associated with rhythmic spike-and-wave discharges, demonstrate that the EEG slow wave in this animal model is a reflection of chloride-sensitive afterhyperpolarizing potentials, indicative of GABA-mediated inhibition.[54] In fact, some GABA agonists make absence seizures worse.[56] One conclusion drawn from these data is that at least some forms of human spike-and-wave absence seizures reflect abnormally enhanced inhibition, and that the enhanced inhibition helps to produce and maintain a state of epileptic hypersynchrony. Pharmacologic studies have implicated low-threshold calcium (Ca) currents in thalamic pacemaker neurons as being responsible for driving the

hypersynchronous spike-and-wave discharges of human absence epilepsy.[20] This pattern is activated by membrane hyperpolarization caused by $GABA_B$ receptor-mediated inhibitory input.[4] Typical absence seizures are associated with increased glucose metabolism, seen with ictal fluorodeoxyglucose PET,[44] consistent with evidence that GABA-mediated inhibition requires energy.[1] Furthermore, H_2O-PET studies show that thalamic blood flow is selectively increased, supporting a principal role for this structure in generating spike-and-wave discharges.[96] There are conflicting data in the literature, however, concerning the metabolic correlates of different types of human absence seizures,[45] as well as of putative experimental animal absence models, suggesting that more than one pathophysiologic mechanism likely underlies the various types of spike-and-wave ictal events.

In the past, it was widely assumed that human focal seizures were generated by neuronal mechanisms resembling the disinhibitory form of transition to ictus originally described in the experimental penicillin focus.[24,80] Indeed, EEG recordings during transition to seizures in patients with partial epilepsy often reveal a localized low-voltage fast rhythm or an attenuation of normal rhythmic activity, which presumably reflects a more distant manifestation of the same electrographic phenomenon. This buildup of low-voltage fast activity can be more readily appreciated with direct recording from the human brain, as is usually achieved with subdural grid or strip electrodes used to delineate neocortical epileptogenic regions in patients who are candidates for surgical treatment.[3] However, depth electrode recordings from human epileptic hippocampus in patients with mesial TLE undergoing evaluation for surgical therapy are more likely to reveal high-amplitude sharp, or sharp-and-slow, transients than a localized recruiting rhythm as the first electrographic ictal event[36,72] (Figs. 4 and 5). This ictal EEG pattern usually occurs during the simple partial seizure

(aura), and it can also be seen without any clinical correlate. Typically, propagation from the site of onset does not occur unless the hypersynchronous ictal discharge evolves into a recruiting rhythm.

These clinical observations suggest that there must be more than one form of transition to ictus in human partial epilepsy, and perhaps that the fundamental neuronal mechanisms underlying the generation of limbic seizures originating in sclerotic hippocampus might be different from those of some forms of neocortical epilepsy. Understanding of transition mechanisms, as indicated in the earlier discussion, requires an appreciation of the neuronal mechanisms that contribute to both excitability and synchronization. The hypersynchrony characteristic of ictal discharge can be generated by a variety of mechanisms, ranging from â€œconventionalâ€ connectivity associated with chemical synapses to less well understood interactions

based on electrical synaptic connection, changes in extracellular milieu, and abnormal reactions of local astrocytes.[11,71,89] These variables, along with differences in regional connectivities, undoubtedly can contribute in different ways to the transition to ictus. For example, connections between the two hippocampi in humans are functionally poor;[121] consequently, the fact that hippocampal hypersynchronous ictal discharges evolve into a low-voltage fast rhythm typical of some neocortical seizures before contralateral propagation could reflect a spread of activity from the hippocampus to adjacent neocortex, or it could represent a particular property of the low-voltage fast rhythm per se, which is necessary for projection along fiber tracts to distant areas of the brain. However, because hypersynchronous hippocampal ictal discharges also fail to propagate in the kainate rat model of mesial TLE, in the presence of a well-developed hippocampal commissure, it is likely that failure of this pattern to propagate reflects intrinsic properties of the involved structures that prevent spread, and not loss of commissural projections per se. It has been proposed that propagation is opposed by increased inhibition of the DG, the so-called dentate gate.[48]

If the hypersynchronous focal discharges associated with hippocampal sclerosis do require inhibitory mechanisms, then different types of inhibition with different spatial distributions would be both pro- and antiepileptogenic in the same structure. The implications of this interpretation are clear: Multiple fundamental epileptogenic disturbances can give rise not only to different types of focal seizures, but also to the different manifestations that characterize the evolution of a single focal seizure. Therefore, different therapeutic interventions may be required to prevent or terminate each of these phenomena. In fact, drugs that act to suppress one part of a seizure could conceivably exacerbate another.

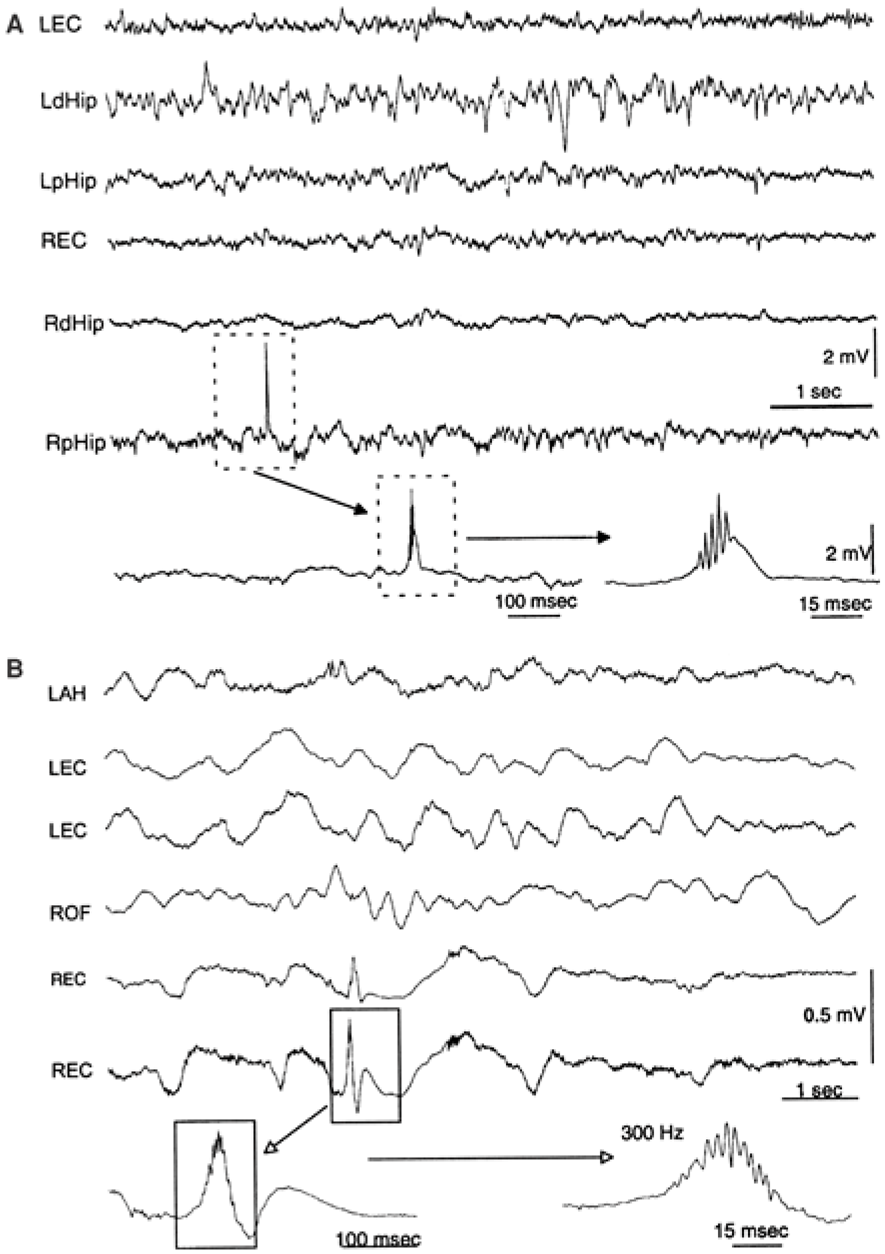

FIGURE 6. A: Example of KA-rat EEG with interictal spike with superimposed fast ripples. Abbreviations: LEC and REC left and right entorhinal cortex; LdHip and RdHip left and right dorsal hippocampus; LpHip and RpHip left and right posterior hippocampus. **B**: Interictal spike with superimposed fast ripples in the

entorhinal cortex of a patient with mesial temporal lobe epilepsy. *Arrows* indicate extension of electrical activity indicated in the box. Abbreviations: LAH, left anterior hippocampus; ROF, right orbitofrontal cortex; LEC and REC, left and right entorhinal cortex (two microelectrodes in each side). From Engel J Jr, Wilson C, Bragin A. Advances in understanding the process of epileptogenesis based on patient material: what can the patient tell us? *Epilepsia*. 2003;44(Suppl 12):60â€"71, with permission.

Although studies in patients with epilepsy and in experimental animal models have characterized disinhibitory and hypersynchronous types of ictal events, the mechanisms that precipitate these phenomena have yet to be elucidated adequately. In some types of epilepsy, sudden synchronizing influences, such as startling stimuli or repetitive photic stimulation, can induce seizures, presumably by producing synchronous neuronal discharges. Intrinsic pathways and conditions associated with synchrony, such as slow-wave sleep and activation of specific thalamic pacemakers, may also predispose to the appearance of seizures. Alternatively, convulsant drugs, withdrawal from sedative medications and alcohol, and intrinsic alterations in the extracellular ionic milieu can all result in a reduction of inhibitory influences and contribute to the precipitation of disinhibitory-type ictal events.

Recent parallel human and animal investigations have revealed the existence of abnormal high-frequency (200â€" 600 Hz) oscillations, termed fast ripples (FR), which appear to be unique to structures capable of generating spontaneous seizures[12,13] (Fig. 6). FR usually occur in association with interictal EEG spikes and are believed to reflect the field potentials of synchronously bursting neurons, perhaps the primary substrate of epileptogenicity. FR occur at the onset of both disinhibitory and hypersynchronous ictal onsets,[13] and features of the neuronal clusters that generate these high-frequency oscillations provide insight into possible mechanisms of transition to ictus. FR-generating neurons are not homogeneously distributed throughout epileptogenic mesial temporal structures, but are localized to discrete areas of hippocampus, DG, entorhinal cortex, and other parahippocampal structures embedded in tissue that does not generate FR.[14] In experimental animals, the location of these FR-generating neuronal clusters is spatially stable over time, and the frequency of spontaneous seizures is directly related to the density of these clusters.[15] Whereas surrounding nonâ€"FR-generating tissue is characterized by paired-pulse suppression indicating enhanced inhibition during the interictal state, the same afferent input results in paired-pulse facilitation within FR-generating clusters, and often the enhanced response of the second pulse is followed by an FR. Minimal disinhibition induced by small amounts of bicuculline can increase the size of these FR-generating areas.[14] It is conceivable, therefore, that minor alterations in inhibitory tone within an epileptogenic region results in an increase in size of FR-generating neuronal clusters, leading to coalescence and synchronization among them until the area involved in the hypersynchronous discharge is sufficiently large to permit propagation. This hypothetical mechanism of transition to ictus requires a reduction in some form of inhibition to expand the extent of the epileptogenic abnormality.

The currently available AEDs all appear to act on general mechanisms of excitation, inhibition, and synchronization that not only determine threshold for transition to ictus, but modulate important normal neuronal functions. Anticonvulsants such as carbamazepine and phenytoin reduce use-dependent neuronal firing, whereas others, like vigabatrin, enhance GABA-mediated inhibition. Antiâ€"petit mal drugs like ethosuximide reduce thalamically mediated hypersynchronization by blocking a specific form of the Ca channel that underlies low threshold Ca currents (T currents), whereas the GABA agonist benzodiazepines may abort absence seizures by inhibiting the synchronizing inhibitory activity of the thalamic reticular nucleus. With better understanding of the multifaceted specific epileptogenic mechanisms that predispose to the intermittent appearance of spontaneous epileptic seizures in each of the various forms of human epilepsy, additional unique interventions might be designed to reverse these primary abnormalities without interfering with normal brain function.

Ictal Termination and the Postictal State

As with EEG recordings obtained from patients during transition to ictus, recordings made during ictal termination show a number of patterns. Some generalized convulsions evolve through a clonic phase, with high-amplitude discharges interspersed with periods of suppression that increase in duration until the electrographic event ends abruptly, to be replaced by a diffusely depressed EEG pattern. This so-called â€œfit switchâ€ is by no means an invariable consequence of a generalized convulsion, however. Some convulsions have a much less prominent clonic EEG pattern, or no clonic phase at all, and the ictal discharge can gradually deteriorate with no clear delineation of the beginning of the postictal period. It is commonly assumed that generalized convulsions terminate as a result of active inhibitory processes as well as depolarization block, electrogenic pumps, or changes in the ionic environment, and that these mechanisms can account for both the intermittent EEG suppression during the clonic phase and the profound postictal EEG depression. Seizure-related pH changes (acidification) have also been proposed, as have increases in outward K currents triggered by the sodium (Na) and Ca influxes during repetitive neuronal discharge. However, very few reported studies in humans substantiate those theories, derived from research on experimental animal models, that GABA, K, opioid peptides, and adenosine are involved in ictal termination.[28,73,81,114] For example, whereas postictal EEG depression and behavioral disturbances following electroconvulsive shock and amygdaloid-kindled seizures in animals can be greatly enhanced by pretreatment with opiates and reduced by pretreatment with naloxone,[49] it has been difficult to repeat these studies in patients.[37] Studies with PET, however, have confirmed upregulation of the Âµ-opioid receptors in epileptogenic temporal lobe cortex.[51]

The hypersynchronous spike-and-wave ictal EEG discharge of absence seizures ends abruptly, with no postictal sequelae. Simple partial seizures that consist entirely of localized hypersynchronous discharges also usually are not followed by postictal EEG or behavioral disturbances. Furthermore, whereas generalized convulsions and complex partial seizures are associated with postictal hypometabolism on fluorodeoxyglucose PET, absences and simple partial seizures may not be.[42,43,44] Perhaps the termination of absence ictal events involves desynchronizing influences or the dissolution of synchronizing mechanisms, processes that do not require the release of neurotransmitters or neuromodulators that induce prolonged postictal neuronal dysfunction.

An obvious conclusion to be drawn from observations of human seizures is that many different mechanisms account for ictal termination, just as many different mechanisms underlie ictal onset and evolution. The clinical condition of epilepsia partialis continua is of interest because it illustrates that the mechanisms that act to limit the propagation of partial seizures from the primary epileptogenic region in this disorder are not the same as the mechanisms that terminate the ictal event, providing further evidence for multiple natural seizure-suppressing influences functioning in concert. Further research into the homeostatic mechanisms that limit and terminate ictal events is important, not only because these processes might be exploited to help control human epilepsy, but also because reversal of these phenomena might eliminate prolonged postictal deficits that can be an important disabling factor in some patients with epilepsy.

Research into seizure termination associated with SE must have high priority, because continuing seizure activity in this condition is associated with dramatic morbidity. Insights from clinical experience in terminating SE are at best confusing. GABA agonist approaches are often most effective in terminating SE, at least early in SE, thus suggesting that GABA-mediated inhibitory mechanisms are â€œintact.â€[76] However, as seizure activity continues, opportunities to stop seizures (short of coma induction) seem to decrease, perhaps reflecting loss (internalization) of GABA$_A$ receptors.[57] Interesting recent studies, showing that vagus nerve stimulation may sometimes be effective in terminating SE, provides a new window for developing nonpharmacological therapies.[93]

Enduring Consequences of Epilepsy

Controversy continues over the question of whether epilepsy is a progressive condition.[46,87,109] There seems to be little doubt from animal studies, such as those involving kindling and the mirror focus phenomenon, that the onset of spontaneous seizures is not necessarily the endpoint of epileptogenesis. In an acquired epileptic conditionâ€"for example, mesial TLE or posttraumatic epilepsyâ€"the epileptogenic mechanisms have presumably been under development for a period of time before the first signs of recurrent (epileptic) seizures appear. Many investigators have argued that this process continues after initiation of clinically evident ictal events, perhaps making seizures more severe or more difficult to treat, or perhaps leading to other aberrations in neuronal function that give rise to interictal behavioral disturbances. Conversely, some seizure disorders disappear with time, but the neuronal mechanisms of spontaneous reversal of the epileptogenic process have not been studied in animals or patients.

Unequivocal evidence suggests that the developmental delays associated with catastrophic childhood epilepsy can be prevented or reversed by surgical interventions that eliminate recurrent epileptic seizures.[104] Furthermore, some focal neurologic deficits, such as contralateral material-specific memory impairment, are greatly improved after successful localized resections.[97] These observations strongly suggest that some types of recurrent epileptic seizures can have an enduring deleterious effect on normal neuronal function *between* seizures, although distinguishing between postictal and truly interictal deficits in these situations can be difficult. Other clinical studies have reported an inverse relationship between the degree of seizure relief following surgical intervention and the duration of epilepsy before surgery, implying that secondary epileptogenesis can worsen the epileptic condition, or at least make it more difficult to treat surgically.[41,87]

Undoubtedly, some forms of epilepsy are more likely to be progressive than others, but it remains unclear what seizure-associated factors contribute to increasing seizure severity and related (e.g., cognitive, psychiatric) morbidity. Is it seizure severity per se (and if so, how does one measure â€œseverityâ€)? Is the key factor the occurrence of significant neuronal damage (and if so, how much damage is sufficient to lead to further seizure consequences)? Is the issue of â€œprogressionâ€ tied to the etiology of the seizure? To the age at which it appears? Benign forms of epilepsy, particularly the primary epilepsies that are age-related, may not be progressive at all and, indeed, many resolve spontaneously after several years. It is of great clinical importance to pursue research aimed at identifying the progressive aspects of human epilepsy that might be reversed or prevented, so as to determine which types of epilepsy are likely to progress and therefore require early aggressive treatment.

Future Directions

Reiterative parallel human and animal studies have been facilitated by the development of new neuroimaging techniques, such as (a) high-resolution structural magnetic resonance imaging (MRI), which has increasing capabilities for identifying small epileptogenic lesions such as migration defects in patients previously believed to have cryptogenic epileptic disorders;[10] (b) functional magnetic resonance imaging (fMRI), which has the spatial and temporal resolution to produce dynamic three-dimensional cerebral anatomic maps displaying ictal onset and propagation patterns;[69] (c) PET and single photon emission computed tomography (SPECT), which utilize a variety of tracers to localize biochemical abnormalities in the brain and characterize presynaptic and postsynaptic neurotransmitter functions;[82] (d) magnetic resonance spectroscopy (MRS), which can measure localized biochemical changes in the brain related to epilepsy;[94] and (e) magnetoencephalography (MEG), which, in association with EEG, can reliably localize current sources of interictal and ictal epileptiform events occurring deep within the brain.[30] A specific area in which these new imaging techniques may prove of extraordinary value is in the analysis of epileptogenesis in human patients. As has been discussed earlier, partial epilepsy often develops with a period of latency after some form of brain â€œinjury.â€ At the cellular and molecular level, the process of epileptogenesis is just beginning to be studied, and it is likely that observations in animal models will provide insight into comparable processes in humans. However, it is also possible, and quite desirable, to study these questions in humans, and this goal can now be approached using enhanced imaging techniques and MRS. Such studies will require detailed examination of subgroups of individuals identified with specific risksâ€"with the collaboration of population epidemiologists. Prospective studies of high-risk individuals should be developed, to look for the progression of hippocampal sclerosis and other changes in vulnerable structures that may correlate with development of the epileptic state and that may then become surrogate markers for any intervention strategy developed to suppress epileptogenesis. These studies will also benefit from the increasing resolution of novel imaging modalities that will soon provide cellular-level observations noninvasively.[85]

Another area of recent interest that also promises to produce a paradigm shift in our understanding of the development of seizures in the human brain relates to the burgeoning field of seizure prediction.[74] Recognizing that no one has yet developed an ideal model to accurately predict seizures before they occur, the demonstration that reproducible and detectable changes in brain electrophysiology occur hours, minutes, or many seconds before the ictal onset provides new sets of experimental mechanisms to investigate. Similarly, recent evidence indicating that some of these preseizure states can wax and wane without inevitably producing seizures also promises to alter the horizon for investigating seizure prediction and for understanding the network mechanisms that come into play when a chronically hyperexcitable (or perhaps â€œhyperirritableâ€) brain changes state from relatively normal, distributed activity to abnormal, hypersynchronous ictal activity. Of particular interest is that all of this work is occurring in human patients and not in animal modelsâ€"a reversal of the usual pattern of going from animal models to human studies.

There has been a growth of basic research activity in epilepsy surgery facilities, taking advantage of unique opportunities for invasive investigations utilizing in vitro microanatomy, neurochemistry, molecular biology, electrophysiology, direct brain recordings in vivo from macroelectrodes and microelectrodes,[38] microdialysis,[29] and, most recently, optical imaging.[59] All these available approaches now make it possible to design studies with patients that, in the not too distant past, were possible only in the animal laboratory.

There are several areas in which new initiatives in the analysis of human epileptic tissue promise to lead to new understanding of the pathobiology of the epileptic state and of the development of the epileptic state. The explosion of recent data regarding the molecular biology of the mammalian nervous system has defined a series of new questions that must be addressed in human epilepsy, and the development of new techniques in this field has allowed the detailed characterization of human tissue. For example, as discussed in Chapters 22 and 23, multiple subtypes of all of the neurotransmitter receptors in the central nervous system (CNS) exist, each with a specific anatomic localization and developmental pattern. Each also has a specific physiology and pharmacology, which can convey subtle, but quite important, differences in function to a given

synaptic interaction. Most receptor subtype distributions are altered after CNS injury, so it is possible, for example, that after injury to the hippocampus, a different expression pattern of NMDA receptors develops that alters the normal excitability of remaining circuits in ways that predispose to the development of epilepsy. Such altered receptors could become specific targets for new pharmacologic agents designed to dampen excess excitability while leaving normal excitability (occurring via other NMDA receptors) unaffected. Thus, tissue removed from patients with epilepsy that appears to contain the most hyperexcitable areas will need to be examined using such techniques as in situ hybridization, single-cell polymerase chain reaction,[31] or single-cell mRNA amplification[86] to analyze specific receptor changes at a cellular, as well as a network, level. Such analyses will need to be extended to many molecules involved in neuronal excitability, synaptic transmission, and neurotransmitter regulation. In addition, as is being discovered from the analysis of genetic models of both animal and human epilepsy, other molecules that are not traditionally thought to play major â€œneurobiologicâ€ roles may, when altered, produce seizures as a consequence. A new technique of single-cell mRNA amplification, which can be applied to both living and fixed human tissue,[21,31] will allow the simultaneous identification of many molecular species in identified single cells in epileptic tissue, so that coordinated changes in gene expression that may be involved in the development of the hyperexcitable state can be identified. The development of cDNA microarray technology provides a powerful tool for monitoring thousands of genes of potential interest. Recent studies suggest that one might even be able to carry out such â€œchipâ€ analyses using blood samples from patients of interest.[112]

The primary epilepsies remain an enigma with respect to basic mechanisms; invasive research on these disorders is usually not possible, because patients are not likely to be surgical candidates or to die of their disorder. Furthermore, none of the naturally occurring genetic animal models appears to reproduce human conditions adequately, although some, such as the genetic absence epilepsy rat of Strasbourg (GAERS),[77] come close. Genetic probes should provide opportunities in the future to identify the specific defects that give rise to these familial conditions and characterize their neuronal mechanisms. When specific gene defects are identified, it will be necessary to determine how these mutations affect function within neuronal circuits. It may be that this focus will require that transgenic mice be created with the mutated homolog of the human gene, so that the cellular pathophysiology of the human disease can be determined. With such transgenic models, it may be possible, by using either targeted drugs or some form of gene therapy, to rectify or correct the underlying defect. Initial attempts to modify gene expression in experimental animals, and/or to deliver genes of interest to brain regions responsible for seizure generation, are being described.[84]

Improved means of recognizing specific substrates of human epileptic disturbances should, in turn, lead to the development of better experimental animal models, particularly for those conditions that currently represent a therapeutic challenge, such as the cryptogenic partial epilepsies and the severe secondary generalized epilepsies (Lennox-Gastaut syndrome and infantile spasms), and also for specific seizure types that are difficult to treat, such as myoclonic seizures and atonic seizures. These animal models will then provide opportunities to develop and test new treatments, based on an understanding of the basic pathophysiology.

Summary and Conclusions

Many different types of human epilepsy exist, and these reflect a variety of underlying fundamental neuronal mechanisms. Even within a given epileptic disorder, there are many component parts for which unique mechanisms can be identified. Thus, basic research on a single type of epilepsy can be directed toward understanding the mechanisms of epileptogenesis, various interictal phenomena, ictal onset and spread, ictal termination, postictal disturbances, and more enduring behavioral consequences of chronic epilepsy. Although well-designed studies using experimental animal models can provide insights into the mechanisms of various epileptic conditions and their component parts, more direct research on patients can now also be carried out. In vivo studies utilize noninvasive functional and structural neuroimaging as well as invasive techniques, such as macroelectrode and microelectrode recordings and microdialysis; in vitro studies comprise electrophysiologic, neurochemical, morphologic, and molecular biologic analyses of surgically resected epileptic brain tissue. Investigations of patients with temporal lobe seizures who are candidates for surgical treatment have revealed evidence of neuronal reorganization in the epileptic hippocampus, with resultant disturbances in excitatory and inhibitory synaptic integration, leading not only to hyperexcitability but also to hypersynchronization. Inhibition as well as excitation is enhanced, which may represent natural mechanisms that maintain the interictal state and which may also contribute to certain epileptiform abnormalities and interictal behavioral disturbances. Tremendous recent technologic advances in neuroimaging and application of new concepts of molecular biology will undoubtedly lead to more direct research on patients, making possible an even greater understanding of the mechanisms underlying the various types of human epilepsy. This work should contribute to the development of better animal models designed to investigate more specifically questions that cannot be easily or ethically pursued in patients and, in turn, research in the animal laboratory will continue to yield new hypotheses, many of which can now be tested directly in human subjects.

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Chapter 42

Overview: Phenomenology

Warren T. Blume

Introduction

Accurate and complete seizure descriptions will allow the reader to elicit maximum benefit from the information contained in the chapters of this section. Ictal semiology remains the most reliable guide to the classification of the seizure disorder, localization of onset of focal seizures, and pathways of propagation.

Such meticulous descriptions will either identify these aspects with certainty or suggest the most likely possibilities, so that cogent questions can be applied to further stages of enquiry such as the neurological examination, electroencephalogram (EEG), and other tests. Attack descriptions may even identify some or all events as nonepileptic.

Aura and *epilepsy*, the two most common terms applied to seizure disorders, are good examples of the importance of accurate seizure description. The term *aura*, meaning â€œbreezeâ€ in the Greek language, was apparently first applied to initial manifestations of focal seizures by Pelops, Master of Galen (AD130â€“210), who described a seizure onset as a â€œcold breeze.â€[16] Patients often describe the succeeding ictal phase as â€œgoing into it.â€ This sensation possibly resembles the meaning of *epilepsia*, also a Greek term, as â€œa taking hold of, something seizing the subject as though that â€˜somethingâ€™ were outside himself.â€[18]

The value of ictal features in localizing involved areas of the brain was first indicated by John Hughlings Jackson, who correlated semiology with sites of lesions disclosed at postmortem pathological examination.[12] Such associations were supplemented by those disclosed by electrical stimulation of the cortex by Fritsch and Hitzig in 1870.[13] A most comprehensive description of ictal semiology and its seizure-localizing value was achieved by Penfield and Jasper in authoring *Epilepsy and the Functional Anatomy of the Human Brain* in 1954 (see further).[21]

The physician should obtain as much of the seizure description from the child or adult patient as possible, because only he may possess a detailed description of the most localizing features early in the attack. Patients who initially deny having auras may change their response if asked â€œDo you ever think you are going to have a seizure, and you don't have it?â€ If affirmed, the physician then can ask, â€œDo some of your seizures begin like that?â€ Because symptoms such as an epigastric or cephalic sensation may reflect seizure origin from one of several regions, inquiring about symptoms or signs relative to neighboring regions may refine localization possibilities. Seizures involving primary motor or sensory regions may be easier for the patient to describe and localize than those from association areas such as the limbic system. Thus, vaguely described symptoms more likely reflect involvement of such regions, rather than simply a â€œpoor historian.â€ Observations by family or associates, although of considerable value, may pertain to phenomena occurring later in the ictal sequence and therefore may represent ictal spread rather than origin. Observers may mislateralize ictal phenomena, such as automatisms or dystonia. Once they are made more aware of its clinical value, observers' scrutiny of such subsequent seizures or in-hospital video monitoring may improve the lateralizing value of such data.

Ajmone Marsan and Ralston provided further data concerning the localizing value of ictal signs and symptoms through study of EEG- and video-recorded pentylenetetrazol (Metrazol)-induced seizures in patients with focal epilepsy. They cautioned that a given semiology may represent (a) various foci among patients and (b) ictal propagation as well as origin.[1]

Interpreting The Data

Focal Seizures

Through painstaking clinical analysis and systematic electrical stimulation of the exposed cortex at operation, Penfield and Jasper[21] charted the localizing value of human epileptic semiology in a work that remains the principal source of such information. These pioneers in epilepsy surgery possessed two vital qualities: (a) a substantial interest and background in all aspects of neuroscience as understood in that era and (b) a thorough knowledge and appreciation of antecedent observations and insights by Hippocrates, Herpin, Bravais, Jackson, and others[11] who correlated ictal semiology with lesion location and defined principles of cerebral localization using this information.

Although the initial clinical phenomenon most often reflects the site of seizure initiation,[18] Carreno and Luders[8] indicate that the epileptogenic â€œzoneâ€ may not be congruent with the symptomatogenic â€œzone.â€ Rapid propagation from a clinically silent region may create the discrepancy. Although such propagation may involve adjacent areas, longer trajectories occur, such as to the mesial temporal region from the occipital lobe[7] or from the orbital frontal lobe, to the supplementary motor region from occipital and parietal lobes.[7,25] Studying scalp and subdural focal frontal seizure propagation, Blume et al.[6] found wide ranges of latency to initial propagation and its extent. Because most frontal seizures began propagation between 5 and 20 seconds from onset and remained within the frontal lobe of origin in approximately 50% of seizures, ictal semiology for frontal lobe epilepsy has at least lateralizing value in many cases. Nonetheless, instantaneous propagation of frontally originating seizures may erase any clinical features localizing or even lateralizing ictal onset within a frontal lobe.[25] Rapidly developing bisynchronous discharge occurs particularly readily with a mesial frontal onset, thus producing a complex clinical semiology.[2]

Even without measurable propagation, complex local physiology may provide multiple semiologies from a given area. Sherrington[22] obtained inconsistent motor responses when stimulating the same region of the cat motor cortex. Although refinement of stimulation techniques have limited such variability, the complexity of regional representation in the motor cortex, for example, suggests that slight variations of seizure discharge pattern in the same location may elicit a variety of semiologies.[5] The several types of neurons in one region will respond differently to identical electrical stimuli: Connors and Telfeian[10] have shown that regular spiking neurons respond with high-frequency, regularly repetitive action potentials (APs), whereas intrinsically bursting neurons respond with clusters of APs. Such variability may influence clinical seizure phenomena.

Not only can cortical stimulation in the same region elicit a variety of response patterns, but the same symptom can represent stimulation to, or a seizure from, a variety of neuronal aggregates. This well applies to the temporal lobe in humans, in which none of the responses evoked by electrical stimulation that are identical to spontaneous clinical seizures demonstrates an â€œexclusive and consistent localization to a particular structure of the temporal lobe.â€[14] Similarly, somatosensory symptoms can represent seizures from the contralateral postcentral gyrus, the second sensory area, or the supplementary sensory area.[19,20]

The foregoing examples of sensory duplication and of pathways of ictal propagation lower somewhat the localizing specificity of most sensory phenomena taken in isolation.[4,17,23] Correlative data between auras and lobes of seizure onset are difficult to summate across studies because of methodology differences. However, auras such as epigastric, somatosensory, and visual sensations each initiate more commonly temporal, parietal, and occipital seizures (respectively) than do those arising from other lobes, but exceptions are not rare. For example, Bien et al.[4] found visual auras to occasionally represent seizures arising from the temporal lobe, although they arose more commonly from the occipital lobe.

A similar duplication (or complement) endows the motor system. Paralleling clinical observations, Bender[3] obtained contralateral eye movements by stimulating the monkey frontal, parietal, or occipital lobes. Additionally, the substantial overlap in activity between the primary and supplementary motor systems, and the complex physiologic interplay between them,[24] renders difficult the assignment of some ictal motor features exclusively to one system.

Nonetheless, ictal localization is accomplished by assessing the *constellation* of auras and motor/behavioral features of a given seizure. Thus, one can agree with So,[23] who stated, in supporting the substantial achievement of Penfield and Jasper,[21] that â€œauras have localizing significance.â€ By extension, so do motor and cognitive semiology. Although unique propagation patterns could theoretically create unfamiliar semiologic juxtapositions, usual associations represent traditional spread patterns. For example, each of several motor and linguistic features of temporal lobe seizures accurately predict the side of origin in 83% to 100% of patients.[9]

Generalized Seizures

Howell[15] described the substantial variety of motor and sensory phenomena that may accompany 3 Hz bisynchronous spike-wave sequences, the sensory phenomena appearing when some awareness is preserved. Similar semiologic variabilities are described in gelastic seizures by Freeman and Olofsson (Chapter 53), febrile seizures by the Camfields and Neville, (Chapter 57), and for myoclonic attacks by Ohtahara and Ohtsuka (Chapter 62).

Summary and Conclusions

This chapter intends to help the clinical epileptologist obtain a thorough and coherent seizure description from the patient, observers and video-telemetry. Such portrayals enable more precise questions to be posed to potentially confirmatory modalities such as EEG and neuroimaging. Any *apparent* incongruity of data from these sources will more confidently lead to new associations, thus enhancing our clinical and neurophysiological knowledge base.

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Chapter 43

Classification of Epileptic Seizures

Jerome Engel Jr.

Peter D. Williamson

Anne T. Berg

Peter Wolf

Introduction

Writings about epileptic seizures date back 3,000 years to Mesopotamia and India.[18] In 400 BC, Hippocrates attributed epileptic seizures to disorders of the brain, rather than to supernatural forces and, 500 years later, Galen distinguished idiopathic seizures, which originated within the brain itself, from sympathetic seizures, which had external causes.[22] Nevertheless, throughout this time until the 19th century, very little was understood about the causes of epileptic seizures or, indeed, the variety of their manifestations. Until this time, for all intents and purposes, only generalized tonicâ€“clonic convulsions were considered to be epileptic seizures. Esquirol, in 1815, however, discriminated between grand mal and petit mal seizures[12] and, in 1827, Bravais described focal motor seizures.[5] Hughlings Jackson is credited with recognizing, in the 1860s, that a variety of focal symptomatology could be epileptic at a time when most workers considered only generalized convulsionsâ€”believed to originate in the medulla oblongataâ€”to be manifestations of epilepsy.[11,21] Jackson also recognized that it was easier to understand the mechanisms of epilepsy by studying focal ictal events, and his clinical pathologic correlations correctly established the cerebral cortex as the site of origin of focal epileptic seizures. This work helped define the location and function within the human cortex and led directly to the development of resective surgical therapy for epilepsy.[11]

With the advent of the electroencephalograph (EEG), characteristic electrographic ictal discharge patterns were identified to clearly distinguish among grand mal, petit mal, and psychomotor seizures.[14] Because linked-ear references were used, however, all these patterns were believed to be generalized until so-called *bipolar montages* revealed that the location, and not the pattern, of the electrographic discharge differentiated various focal ictal events.[16] Despite the description of hippocampal sclerosis in patients with epilepsy as early as 1826,[4] and Hughlings Jackson's observation that lesions in the hippocampal region occurred in patients with tasting movements and â€œdream state,â€[15] it wasn't until the mid-1900s that epileptologists began to accept the fact that most â€œpsychomotorâ€ seizures originated in mesial temporal structures.[17] This fact was further substantiated by the observation that psychomotor seizures could often be successfully treated by surgical resections of the temporal lobe.[2,20]

During this period, worldwide, multiple terminologies developed that made sensible discussions and communication increasingly difficult. In 1970, the International League Against Epilepsy (ILAE) created the first classifications of epileptic seizures and epilepsies.[13] They clearly distinguished ictal events from the disorders with which they were associated, and ictal and interictal EEG patterns, anatomic substrate, etiology, and age were included in this definition of seizures. Seizures were broadly divided into *partial*, beginning in a part of one hemisphere, and *generalized*, which were bilaterally symmetrical without local onset (Table 1). Partial seizures were further divided into those with *elementary* symptomatology, referring to signs and symptoms mediated by eloquent areas of neocortex, and *complex* symptomatology, referring to signs and symptoms mediated predominantly by mesial temporal limbic structures. The term â€œcomplex partial seizure,â€ therefore became synonymous with the older terms, â€œpsychomotor seizureâ€ and â€œtemporal lobe seizure.â€ This seizure classification was criticized because, at the time, insufficient anatomic and pathophysiologic information was available to provide a basis for classification, and there was controversy about some of the generalized seizure types. These perceived problems were rectified in 1981, with the second ILAE Classification of Epileptic Seizures (Table 2).[6]

1981 ILAE Classification of Epileptic Seizures

Despite persistent controversy, the 1981 Classification of Epileptic Seizures has gained general acceptance and is widely used. An ILAE Task Force has been reviewing this classification since 1997, but no new classification has yet been proposed.[7,9,10] Although flawed, it has been agreed that this useful construct should not be abandoned until a clearly better version can be devised.

The 1981 Classification of Epileptic Seizures was based on expert consensus, analyzing video-recorded seizures and considering their semiology as a sequence of ictal events developing in time. In addition to the clinical phenomenology, the ictal and interictal EEG was considered, but it was decided that there was still insufficient information about pathophysiologic mechanisms and anatomic substrates to warrant a more diagnostic approach.[6] The partial/generalized dichotomy was preserved, but the distinction between simple and complex partial seizures was based entirely on impairment of consciousness. Thus, the original intent of the concept of complex symptomatology indicating behaviors mediated predominantly by limbic structures was lost. Neocortical seizures with impaired consciousness became complex partial seizures, whereas limbic seizures without impaired consciousness became simple partial seizures. This was, and continues to be, a source of controversy and confusion. On the other hand, the 1981 classification acknowledged the evolution of partial signs and symptoms and recognized that simple partial seizures could evolve into complex partial seizures, and that both could evolve into secondarily generalized seizures. This classification also differed from the 1970 classification in that absences were divided into typical and atypical, infantile spasms were deleted because they were considered to be a syndrome and not a seizure type, and akinetic seizures were deleted because their existence was questioned.

Table 1 1970 ILAE CLASSIFICATION OF EPILEPTIC SEIZURES (defined by ictal + interictal EEG, anatomic substrate, etiology, and age)

I. Partial
    A. With elementary symptomatology
    B. With complex symptomatology
    C. Secondarily generalized
II. Generalized, bilaterally symmetrical or without local onset
    A. Absences
    B. Bilateral massive epileptic myoclonus
    C. Infantile spasms
    D. Clonic seizures
    E. Tonic seizures
    F. Tonicâ€“clonic seizures
    G. Atonic seizures
    H. Akinetic seizures
III. Unilateral or predominantly unilateral

From Gastaut H. Clinical and electroencephalographical classification of epileptic seizures. *Epilepsia.* 1970;11:102â€“113, with permission.

Table 2 1981 ILAE CLASSIFICATION OF EPILEPTIC SEIZURES

I. PARTIAL (FOCAL, LOCAL) SEIZURES

Partial seizures are those in which, in general, the first clinical and electroencephalographic changes indicate initial activation of a system of neurons limited to part of one cerebral hemisphere. A partial seizure is classified primarily on the basis of whether or not consciousness is impaired during the attack. When consciousness is not impaired, the seizure is classified as a simple partial seizure. When consciousness is impaired, the seizure is classified as a complex partial seizure. Impairment of consciousness may be the first clinical sign, or simple partial seizures may evolve into complex partial seizures. In patients with impaired consciousness, aberrations of behavior (automatisms) may occur. A partial seizure may not terminate, but instead progress to a generalized motor seizure. *Impaired consciousness* is defined as â€œthe inability to respond normally to exogenous stimuli by virtue of altered awareness and/or responsiveness.â€

There is considerable evidence that simple partial seizures usually have unilateral hemispheric involvement and only rarely have bilateral hemispheric involvement; complex partial seizures, however, frequently have bilateral hemispheric involvement.

Partial seizures can be classified into one of the following three fundamental groups:

A. Simple partial seizures
B. Complex partial seizures
    1. With impairment of consciousness at onset
    2. Simple partial onset followed by impairment of consciousness
C. Partial seizures evolving to generalized tonicâ€“clonic convulsions (GTC)
    1. Simple evolving to GTC
    2. Complex evolving to GTC (including those with simple partial onset)

Clinical seizure type	**EEG seizure type**
A. Simple partial seizures (consciousness not impaired)	Local contralateral discharge starting over the corresponding area of cortical representation (not always recorded on the scalp)

1. With motor symptoms
    a. Focal motor without march
    b. Focal motor with march (Jacksonian)
    c. Versive
    d. Postural
    e. Phonatory (vocalization or arrest of speech)
2. With somatosensory or special-sensory symptoms (simple hallucinations, e.g., tingling, light flashes, buzzing)
    a. Somatosensory
    b. Visual
    c. Auditory
    d. Olfactory
    e. Gustatory
    f. Vertiginous

3. With autonomic symptoms or signs (including epigastric sensation, pallor, sweating, flushing, piloerection, and pupillary dilatation)
4. With psychic symptoms (disturbance of higher cerebral function). These symptoms rarely occur without impairment of consciousness and are much more commonly experienced as complex partial seizures.
    a. Dysphasic
    b. Dysmnesic (e.g., dÃ©jÃ -vu)
    c. Cognitive (e.g., dreamy states, distortions of time sense)
    d. Affective (fear, anger, etc.)
    e. Illusions (e.g., macropsia)
    f. Structured hallucinations (e.g., music, scenes)

• B. Complex partial seizures (with impairment of consciousness: may sometimes begin with simple symptomatology)	Unilateral or, frequently, bilateral discharge, diffuse or focal in temporal or frontotemporal regions

- 1. Simple partial onset followed by impairment of consciousness
    a. With simple partial features as in A.1â€“4 (followed by impaired consciousness)
    b. Without automatisms
  2. With impairment of consciousness at onset
    a. With impairment of consciousness only
    b. With automatisms

• C. Partial seizures evolving to secondarily generalized seizures (This may be generalized tonic-clonic)	Above discharges become secondarily and rapidly generalized

- 1. Simple partial seizures (A) evolving to generalized seizures
  2. Complex partial seizures (B) evolving to generalized seizures
  3. Simple partial seizures evolving to complex partial seizures evolving to generalized seizures

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II. GENERALIZED SEIZURES (CONVULSIVE OR NONCONVULSIVE)

Generalized seizures are those in which the first clinical changes indicate initial involvement of both hemispheres. Consciousness may be impaired, and this impairment may be the initial manifestation. Motor manifestations are bilateral. The ictal electroencephalographic patterns initially are bilateral and presumably reflect neuronal discharge, which is widespread in both hemispheres.

Clinical seizure type	**EEG seizure type**
A. Absence seizures	
1. Typical absence	Usually regular and symmetrical 3-Hz but may be 2- to 4-Hz spike-and-slow- wave complexes and may have multiple spike-and- slow-wave complexes. Abnormalities are bilateral
a. Impairment of consciousness only[a] b. With mild clonic components[a] c. With atonic components[a] d. With tonic components[a] e. With automatisms[a] f. With autonomic components[a]	
2. Atypical absence	EEG more heterogeneous; may include irregular spike-and-slow-wave complexes, fast activity, or other paroxysmal activity. Abnormalities are bilateral but often irregular and asymmetrical.
May have: a. Changes in tone that are more pronounced than in A.1 b. Onset and/or cessation that is not abrupt	
B. Myoclonic seizures, myoclonic jerks (single or multiple)	Polyspike-and-wave or sometimes spike-and- wave or sharp and slow waves[b]
C. Clonic seizures	Fast activity (10 c/sec or more) and slow waves; occasional spike-and- wave patterns[b]
D. Tonic seizures	Low voltage, fast activity or a fast rhythm of 9â€“10 c/sec or more, decreasing in frequency and increasing in amplitude[b]
E. Tonicâ€“clonic seizures	Rhythm at 10 or more c/sec, decreasing in frequency and increasing in ampli- tude during tonic phase, interrupted by slow waves during clonic phase[b]
F. Atonic seizures (astatic)	Polyspike-and-wave or flattening or low-voltage fast activity[b]

III. UNCLASSIFIED EPILEPTIC SEIZURES

Includes all seizures that cannot be classified because of inadequate or incomplete data and some that defy classification in hitherto
described categories. This includes some neonatal seizures, e.g., rhythmic eye movements, chewing, and swimming movements.

IV. ADDENDUM

Repeated epileptic seizures occur under a variety of circumstances:

1. As fortuitous attacks, coming unexpectedly and without any apparent provocation.
2. As cyclic attacks, at more or less regular intervals (e.g., in relation to the menstrual cycle or to the sleepâ€“waking cycle).
3. As attacks provoked by:
    a. Nonsensory factors (fatigue, alcohol, emotion, etc.)
    b. Sensory factors, sometimes referred to as *reflex seizures*

Prolonged or repetitive seizures (status epilepticus). The term *status epilepticus* is used whenever a seizure persists for sufficient length of time or is repeated frequently enough that recovery between attacks does not occur. Status epilepticus may be divided into partial (e.g., Jacksonian), or generalized (e.g., absence status or tonicâ€“clonic status). When very localized motor status occurs, it is referred to as *epilepsia partialis continua*.

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[a] II.A.bâ€“f may be used alone or in combination.

[b] Combinations of II.Bâ€“F, e.g., B and F, B and D.

From Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised clinical and electroencephalographic classification of epileptic seizures. *Epilepsia.* 1981;22:489â€“501, with permission.

Table 3 PROPOSED DIAGNOSTIC SCHEME FOR PEOPLE WITH EPILEPTIC SEIZURES, AND WITH EPILEPSY

Epileptic seizures and epilepsy syndromes are to be described and categorized according to a system that utilizes standardized terminology and is sufficiently flexible to take into account the following practical and dynamic aspects of epilepsy diagnosis:

1. Some patients cannot be given a recognized syndromic diagnosis.
2. Seizure types and syndromes change as new information is obtained.
3. Complete and detailed descriptions of ictal phenomenology are not always necessary.
4. Multiple classification schemes can, and should, be designed for specific purposes (e.g., communication and teaching, therapeutic trials, epidemiologic investigations, selection of surgical candidates, basic research, genetic characterizations).

This diagnostic scheme is divided into five parts, or *Axes*, organized to facilitate a logical clinical approach to the development of hypotheses necessary to determine the diagnostic studies and therapeutic strategies to be undertaken in individual patients:

- Axis 1: Ictal phenomenologyâ€"from the Glossary of Descriptive Ictal Terminology, can be used to describe ictal events with any degree of detail needed.
- Axis 2: Seizure typeâ€"from the List of Epileptic Seizures. Localization within the brain and precipitating stimuli for reflex seizures should be specified when appropriate.
- Axis 3: Syndromeâ€"from the List of Epilepsy Syndromes, with the understanding that a syndromic diagnosis may not always be possible.
- Axis 4: Etiologyâ€"from a Classification of Diseases Frequently Associated with Epileptic Seizures or Epilepsy Syndromes when possible, genetic defects, or specific pathologic substrates for symptomatic focal epilepsies.
- Axis 5: Impairmentâ€"this optional, but often useful, additional diagnostic parameter can be derived from an impairment classification adapted from the World Health Organization (WHO) ICIDH-2.

From Engel J Jr. A proposed diagnostic scheme for people with epileptic seizures and with epilepsy: report of the ILAE Task Force on Classification and Terminology. *Epilepsia.* 2001;42:796â€"803, with permission.

Table 4 Seizure Types

Self-limited epileptic seizures

I. Generalized onset
    A. Seizures with tonic and/or clonic manifestations
        1. Tonicâ€"clonic seizures
        2. Clonic seizures
        3. Tonic seizures
    B. Absences
        1. Typical absences
        2. Atypical absences
        3. Myoclonic absences
    C. Myoclonic seizure types
        1. Myoclonic seizures
        2. Myoclonic astatic seizures
        3. Eyelid myoclonia
    D. Epileptic spasms
    E. Atonic seizures
II. Focal onset (partial)
    A. Local
        1. Neocortical
            a. Without local spread
                1. Focal clonic seizures
                2. Focal myoclonic seizures
                3. Inhibitory motor seizures
                4. Focal sensory seizures with elementary symptoms
                5. Aphasic seizures

            b. With local spread
                1. Jacksonian march seizures
                2. Focal (asymmetrical) tonic seizures
                3. Focal sensory seizures with experiential symptoms
        2. Hippocampal and parahippocampal
    B. With ipsilateral propagation to:
        1. Neocortical areas (includes hemiclonic seizures)
        2. Limbic areas (includes gelastic seizures)
    C. With contralateral spread to:
        1. Neocortical areas (hyperkinetic seizures)
        2. Limbic areas (dyscognitive seizures with or without automatisms [psychomotor])
    D. Secondarily generalized
        1. Tonicâ€"clonic seizures
        2. Absence seizures
        3. Epileptic spasms (unverified)
III. Neonatal seizures

Status epilepticus

I. Epilepsia partialis continua (EPC)
    A. As occurs with Rasmussen syndrome
    B. As occurs with focal lesions
    C. As a component of inborn errors of metabolism
II. Supplementary motor area (SMA) status epilepticus
III. Aura continua
IV. Dyscognitive focal (psychomotor, complex partial) status epilepticus
    A. Mesial temporal
    B. Neocortical
V. Tonicâ€"clonic status epilepticus
VI. Absence status epilepticus
    A. Typical and atypical absence status epilepticus
    B. Myoclonic absence status epilepticus
VII. Myoclonic status epilepticus
VIII. Tonic status epilepticus
IX. Subtle status epilepticus

From Engel J Jr. Report of the ILAE Classification Core Group. *Epilepsia*. 2006;47:1558â€"1568, with permission.

Some workers have criticized the current classification for not being purely phenomenologic.[19] To give the correct diagnosis to individual patients, EEG and other clinical information may sometimes be necessary to determine whether a brief lapse of consciousness is an absence seizure or a complex partial seizure with impaired consciousness only. An alternative, purely phenomenologic approach to the classification of individuals with epilepsy has been proposed and is used in some epilepsy centers.[19] The detailed descriptive information is particularly useful, along with other diagnostic information, in localizing the epileptogenic region when resective surgery is being considered, but this type of descriptive detail is usually not necessary for determining diagnosis, treatment, or prognosis for most patients with epilepsy.[8] It should also be noted that the ILAE Classification is a taxonomy and not intended to be a diagnostic manual.[23] Although distinguishing between partial and generalized epileptic seizures has clinical value with respect to the differential diagnosis of underlying etiologies, this is not an absolute dichotomy. It can be difficult to determine whether some ictal phenomena are partial or generalized, or to account for the continuum from discrete focal, to diffuse hemispheric, to multifocal bilateral, to bilaterally symmetrical epileptogenic abnormalities.

Proposals for Improving the Classification

The ILAE Task Force has acknowledged the usefulness of a detailed description of ictal phenomenology under certain circumstances. Thus, the first axis of a proposed five-axis diagnostic scheme for describing individual patients (Table 3) consists of ictal phenomenology.[7] To standardize the use of this axis, a glossary of descriptive terminology has been published.[3] This axis, however, is considered optional, because the degree of detail needed for clinical purposes varies greatly from one patient to another.

The second axis of the diagnostic scheme introduces a new concept: a seizure type as a diagnostic entity.[7] The Task Force believes that sufficient information now is available about the pathophysiologic mechanisms and anatomic substrates of many ictal events to permit identification of epileptic seizure types that are unique diagnostic entities, having within themselves etiologic, therapeutic, and prognostic implications. In any given patient, therefore, the diagnostic evaluation, treatment, and prognosis of these entities may be determined from the diagnosis of a specific seizure type, when a diagnosis of an epilepsy syndrome is not possible. The Task Force is currently attempting to establish scientifically rigorous criteria for the identification of specific epileptic seizure types that include not only pathophysiologic mechanisms and neuronal substrates, but also response to antiepileptic drugs (AEDs), ictal EEG patterns, propagation patterns, postictal features, and the epilepsy syndromes with which the seizure type is associated.[9] Clinical semiology is not a necessary criterion, nor is the anatomic location per se. For example, an epileptogenic abnormality due to a unique pathophysiologic mechanism could be considered a class of seizures regardless of whether the epileptogenic region were in the posterior frontal cortex (giving rise to motor signs), or in the occipital cortex (giving rise to visual symptoms). Conversely, similar ictal behaviors could reflect different classes of seizures; as noted earlier, a brief loss of consciousness could be a â€œgeneralizedâ€ absence, or a focal limbic seizure due to entirely different pathophysiologic mechanisms acting on entirely different anatomic substrates.

The ultimate objective is to pattern a new ILAE classification after other biologic classification systems; that is, to establish reasonable, rigorous objective criteria for recognizing epileptic seizure types as unique natural classes that can be reproducibly distinguished from all other natural classes.[1] This is an ambitious goal, but the field is just beginning to have the capacity to evaluate more than signs, symptoms, and EEG discharges, and to consider fundamental concepts of pathophysiology. A list of seizure types has been compiled (Table 4) and is discussed herein. Each type classification should be considered as a testable working hypothesis, subject to verification, falsification, and revision.[9] Evidence-based methodology can be used to reevaluate, revise, or discard seizure types, and changes are also anticipated as new information becomes available. The revision and refinement of this list of seizure types, as well as any future organization into one or more diagnostic manuals, is an ongoing dynamic process.

The Task Force has proposed replacing the term â€œpartial seizureâ€ with â€œfocal seizure,â€ which remains in common use, with the understanding that this does not imply a small, discrete area of epileptogenicity.[7] A description of focal-onset seizures has presented a particular problem for identifying unique diagnostic entities. They represent dynamic events, usually involving propagation, so that clinical manifestations do not necessarily reflect the site of onset. Focal seizures due to discretely localized lesions must be distinguished from focal seizures due to more distributed network disturbances, for example those occurring in patients with benign childhood epilepsy with centrotemporal spikes. Maturational factors, mode of precipitation, structural pathology, pathophysiologic mechanisms, location, and progressive disturbances all need to be taken into consideration. A suggested approach to defining focal seizures, therefore, is shown in Table 4[9] and discussed below. Although impairment of consciousness is a clinically important manifestation of some ictal events, this parameter is poorly defined and often difficult to determine. Aspects of altered consciousness, therefore, are not considered as a factor for defining *seizure types* here, but rather should be assessed as part of the *phenomenologic description* in individual patients. Finally, any new classification of epileptic seizures must take into account continuous epileptic seizure types or *status epilepticus*. As yet, no agreed-upon classification for status epilepticus exists, but a list of forms of status proposed by the ILAE Task

Force is shown in Table 4[9] and discussed below.

Discussion of ILAE-Recognized Seizure Types

The following discussion is adapted from the work of the ILAE classification committee, with permission.[11]

Self-Limited Epileptic Seizure Types

I. **GENERALIZED ONSET**

A. **Seizures with tonic and/or clonic manifestations**

1. *Tonic-clonic seizures*: involve brain stem, possibly prefrontal, and basal ganglia mechanisms. Ictal initiation of primarily bilateral events are predominantly disinhibitory, but other mechanisms are responsible for ictal evolution to the clonic phase, involving gradual periodic introduction of seizure-suppressing mechanisms. Several discrete types might be identified: Future investigation is needed to determine which of these types represent unique phenomena.

   - Reactive GTCS (acutely provoked seizures)
   - GTCS of idiopathic generalized epilepsies
   - GTCS of symptomatic generalized epilepsies
   - GTCS evolving from myoclonic seizures (e.g., clonic-tonic-clonic seizures in Juvenile myoclonic epilepsy (JME) and Epilepsy with myoclonic astatic seizures)
   - GTCS evolving from absence seizures

   And several questions can be raised:

   - Do patients with idiopathic focal epilepsies have primarily generalized as well as secondarily generalized seizures? Some data suggest that GTCS in Benign childhood epilepsy with centrotemporal spikes (BCECTS) are secondarily generalized, although some patients with this condition may have primarily generalized GTCS as well.
   - What are clonic-tonic-clonic seizures? Are GTCS that evolve from myoclonic seizures the only form, or are there also true clonic-tonic-clonic seizures (as may be seen in forms of progressive myoclonus epilepsy [PME])?
   - How should we regard hemi-generalized seizures which manifest unilaterally in the immature brain due to poor myelinization of the corpus callosum? In this case the disorder is bilateral, but the onset is clearly unilateral. Do these only occur in infants, or do they also occur in children and adults? In some infants, hemi-generalized seizures have focal onset.

   Some experimental evidence suggests that the mechanisms of ictal initiation could be different for some or even all of these subtypes of GTCS, and that there may even be more than one mechanism of initiation within each of the subtypes.

2. *Clonic seizures*: Clonic seizures are fast rhythmic events (1â€“2 Hz), associated, or not, with impaired consciousness. Mechanisms are different from those of the clonic phase of GTCS. In the latter, the clonic phase represents the phasing in of seizure-suppressing mechanisms, whereas in clonic seizures, the repetitive discharges appear to be due primarily to rhythmic excitatory discharges. There may be several types of generalized clonic seizures.

3. *Tonic seizures*: The mechanism of tonic seizures is probably not the same as that of the tonic phase of GTCS. Generalized tonic seizures typically occur in Lennox-Gastaut syndrome and occasionally in Epilepsy with myoclonic astatic seizures.

B. **Absences**

1. *Typical absences*: Although the pyknoleptic manifestations of typical absences in Childhood absence epilepsy (CAE) have been suggested to differ by shorter duration from the longer-duration, less frequent absences of Juvenile absence epilepsy (JAE), based upon what we currently know, it seems likely that they do not represent two mechanisms, but merely the evolution of a single mechanism as the brain matures. Phantom absences also are likely to be a result of brain maturation. A working group will be convened to study whether absences of CAE and JAE represent two seizure types or a spectrum of the same seizure type, and to better define associated motor components.

2. *Atypical absences*: There are variable manifestations of this ictal event, some involving hypotonia and atonia. Better criteria for characterizing atypical absences will also be discussed by the working group on atonic seizures.
3. *Myoclonic absences*: The myoclonic components of these seizures are rhythmic (2Â½â€“4Â½ Hz) clonic rather than myoclonic and have a tonic component. The seizure type should be called something else, but there is no agreement on another name at this time.

C. **Myoclonic seizures types**

1. *Myoclonic seizures*: The distinction between myoclonic seizures and clonic seizures is not clear. Classically, clonic seizures are rapid rhythmically-recurrent events, whereas myoclonic seizures are single, or irregularly recurrent events. The prototype of generalized myoclonic seizures are those occurring with JME. These are typically bilateral and symmetrical, but localized reflex myoclonus can also occur. The slowly rhythmic events of Subacute sclerosing panencephalitis (SSPE) used to be considered epileptic myoclonus but are more accurately epileptic spasms, those with biPEDs (bilaterally synchronous PLEDs) in comatose patients also are not necessarily epileptic, and their cause is usually not clearly defined. Differential diagnosis between myoclonic and clonic seizures can be difficult because a single jerk can be a fragment of a clonic seizure.

   Working groups will be convened to specifically evaluate myoclonic epileptic phenomena, including negative myoclonus and atonic seizures, compare them with nonepileptic myoclonic phenomena, and develop uniform criteria and terminology for these diagnoses.
2. *Myoclonic astatic seizures*: These seizures occur typically in Epilepsy with myoclonic astatic seizures. There is a question as to whether the astatic component is an atonic seizure.
3. *Eyelid myoclonia*: The degree to which these recurrent events (5â€“6 Hz) are associated with impairment of consciousness has not been adequately documented, and should be. In some patients they can be provoked by eye closure. The seizure type, however, does exist as a unique entity.

D. **Epileptic spasms**: The mechanism of infantile spasms is unknown. The semiology and pathophysiology of epileptic spasms in the more mature brain need to be better defined.

E. **Atonic seizures**: A number of seizure types involve an atonic component, some of which may be variants of atypical absences, others of which can have an initial brief tonic or myoclonic component. When these events are very short, they have been referred to as negative myoclonus. A working group will be convened to review videotapes of various types of atonic seizures, and to develop criteria to distinguish between negative myoclonus, atonic seizures, and perhaps some atypical absences.

II. **FOCAL ONSET**

The anatomical substrates of a substantial number of focal seizure manifestations have now been sufficiently established to include this information in their description. Because focal seizures represent dynamic events that usually involve propagation, and clinical manifestations can reflect discharges at the site of ictal onset, and/or sites of propagation, the organization of focal seizures here takes into account the various patterns of ictal propagation. In addition, a number of factors will need to be investigated in order to develop more definitive criteria for distinguishing between different types of focal seizures. These include:

- Factors that might distinguish between focal seizures due to discretely localized lesions, as occur with focal symptomatic epilepsy, and focal seizures due to more distributed network disturbances, as might occur with some focal idiopathic epilepsies (e. g., those responsible for the transverse dipole of BCECTS), or even in idiopathic generalized epilepsies.

- Maturational factors
- Modes of precipitation, as in reflex seizures
- Pathology, i.e. focal seizures due to various malformations of cortical development may be different from each other and from those due to other lesions.
- Pathophysiologic mechanisms, e. g., hypersynchronous ictal onsets, which most commonly occur in hippocampus, vs. low voltage fast ictal onsets, which most commonly occur in neocortex. These electrophysiological features clearly reflect different pathophysiologic mechanisms of seizure initiation, which may not be absolutely correlated with location, and there may be other ictal onset patterns indicative of other initiating mechanisms that have not yet been well-described.
- Location, not with respect to differences in ictal semiology that reflect differences in the normal function of cortex, but to differences in neurophysiologic properties and anatomical connections unique to specific areas of cortex, e. g., those that cause brief and clustered seizures with little or no postictal disturbances and nocturnal predilection typical of some frontal areas, as compared to longer, less frequent events with profound postictal disturbances in other areas, and those that cause fast distant propagation from some areas and localized, slower propagation in others.

Factors influencing seizure-induced progressive disturbances in neuronal function and structure at the site of, and downstream from, ictal onset.

Local

1. *Neocortical*
    a. Without local spread
        1. *Focal clonic seizures* are brief focal motor events that are distinguished from focal myoclonic seizures by their rhythmic repetition. Localization to the primary motor cortex is implied.
        2. *Focal myoclonic seizures* most likely consist of many types. These events, including *multifocal myoclonus*, will be discussed by the working group on myoclonus. There is no unanimity of opinion as to whether the myoclonic events in PME which have no EEG correlate are epileptic. At least in Lafora, there is evidence to suggest a cortical site of initiation.
        3. *Inhibitory motor seizures* are not a unique seizure type. The clinical manifestation merely represents the function of the involved cortex, just as focal motor seizures and unformed visual hallucinations reflect seizures in precentral gyrus and calcarine cortex.
        4. *Focal sensory seizures with elementary visual, somatosensory, vestibular, olfactory, gustatory, or auditory symptoms* manifest themselves as a variety of sensory phenomena that can be produced by activation of primary sensory cortices.
        5. *Aphasic seizures* can consist of inability to speak when Broca's area is principally involved, or more complex disturbances of

speech production or reception when other language cortical areas are principally involved.

    b. With local spread
        1. *Jacksonian march seizures* refers to the clinical manifestations of the slow ephaptic propagation of epileptic discharge along the motor cortex, although similar progression can sometimes be seen in other primary cortical areas as well.
        2. *Focal (asymmetric) tonic seizures* can be associated with seizure origin from practically anywhere in the neocortex. In their purest form, focal tonic seizures are seen in the

    explosive motor seizures of supplementary motor area origin.

    3. *Focal sensory seizures with experiential symptoms* are those with complex, usually formed, distorted and/or multimodal, sensory symptoms implying seizure initiation in association cortices, such as the temporo-parieto-occipital junction, with connections to multiple sensory areas.

2. *Hippocampal and parahippocampal seizures* almost always require local spread for clinical manifestation, which may involve insula, amygdala, hypothalamus, and other limbic structures. Autonomic features such as a sensation of epigastric rising is common, as well as emotional experiences such as fear, dysmnesias, focal sensory seizures with olfactory or gustatory symptoms, and vague bilateral sensory phenomena such as tingling.

With ipsilateral propagation to:

1. *Neocortical areas*
    a. Same manifestations as II.A.1.a. and b.
    b. *Hemiclonic seizures* occur early in development before myelinization of the corpus callosum and do not necessarily have localizing value. They can alternately affect both hemispheres, as in Dravet syndrome and ischemic encephalopathy, or only one hemisphere in the case of focal disturbances.
2. *Limbic areas*
    a. Same manifestations as II.A.2.
    b. *Gelastic seizures* are clearly unique ictal events when they are initiated in relation to structural abnormalities of the hypothalamus, which are usually hamartomas. The mechanism is unknown, but initiation, at least, is distinct from gelastic seizures arising from other areas, such as mesial temporal lobe and cingulate.

With contralateral spread to:

1. *Neocortical areas*

   Hyperkinetic seizures, also referred to by some as *hypermotor seizures*, involve bilateral forceful limb movements, sometimes with vocalizations. Frontal lobes are implicated in these behaviors.

2. *Limbic areas*

   Dyscognitive seizures with or without automatisms (psychomotor) are not exactly synonymous with the current term â€œcomplex partial seizures,â€ which were defined on the basis of impaired consciousness only and do not necessarily involve limbic areas. This new term, as well as the term â€œpsychomotor,â€ conforms more to the original intent of the term â€œcomplex partial seizuresâ€ in the 1970 ILAE Classification of Epileptic Seizures.â€[13] It is implied that mesial temporal limbic areas and their immediate connections are involved in the clinical manifestations, although seizures may have been initiated elsewhere.

Secondarily generalized

1. *Tonic-clonic seizures* that are secondarily generalized probably consist of multiple types and may involve different pathophysiologic mechanisms and anatomical substrates, at least initially, than generalized tonic-clonic seizures with generalized onset.
2. *Absence seizures* can rarely represent propagation from localized cortical areas, usually in the frontal lobe. There may be a continuum between these events and generalized atypical absences.
3. Although *epileptic spasms* can occur in infants with focal lesions, the mechanism by which these generalized events are generated is unknown.

III. **NEONATAL SEIZURES**

Neonatal seizures: Although the components of neonatal seizures can be described in terms of the seizure types itemized above, they often display unique organizational features. Therefore, a study group will be created to more completely define and characterize the various types of neonatal seizures.

Status Epilepticus

Mechanistically, status epilepticus represents the failure of the natural homeostatic seizure-suppressing mechanisms responsible for seizure termination. Although an operational definition of status epilepticus has been proposed and is in common use in the clinical and epidemiological literature, it does not adequately reflect the underlying mechanisms involved in status epilepticus, nor is it always useful for clinical purposes. Regardless of the specific operationalized definition, however, the mechanisms involved in initiation and spread of the various types of status epilepticus are, in general, similar to those of self-limited ictal events, but additional factors that need to be considered in determining criteria for classification include:

- Different mechanisms that can prevent seizure termination, e.g., mechanisms that prevent active inhibition, desynchronization of hypersynchronous discharges, and depolarization block.
- Progressive features that contribute to subsequent functional and structural brain disturbances.
- Maturational factors

I. **EPILEPSIA PARTIALIS CONTINUA (EPC) OF KOJE- VNIKOV**

This is a combination of focal seizures with continuous twitching in the same area. The clinical and EEG features permit distinction of 3 conditions that correlate with etiology.

As occurs with Rasmussen syndrome. EPC in this subacute lateralized encephalitis of unknown cause (half the cases show the clinical expression of this encephalitis) combines focal myoclonus and focal seizures affecting various areas of the same hemisphere, with or without clear EEG correlation of the myoclonic jerks, and at times persistence of the jerks in sleep. There is progressive slowing of the background EEG activity on the affected side.

As occurs with focal lesions. Various dysplastic, vascular or tumor lesions produce EPC lasting a few days, weeks or months before the patient returns to baseline. EPC is also seen with nonketotic hyperglycemia. The jerks affect the same area as the focal seizures, and have an EEG correlate; they do not persist in sleep.

EPC is also a component of several inborn errors of metabolism. Various conditions affecting energy metabolism, namely Alpers disease or Myoclonus epilepsy with ragged red fibers (MERRF), produce uni- and then bilateral rhythmic jerks that persist in sleep, with EEG correlates.

II. **SUPPLEMENTARY MOTOR AREA (SMA) STATUS EPILEPTICUS:** Frequently repeated seizures from the SMA usually present as a type of focal status epilepticus with preserved consciousness and individual tonic motor seizures occurring every few minutes all night long. Another type of SMA status epilepticus consists of secondarily generalized seizures that evolve into repetitive asymmetrical tonic motor seizures with profound impairment of consciousness.

III. **AURA CONTINUA:** Aura continua is a rare but well described manifestation of focal epilepsy. The symptoms depend on the localization. The attacks are usually without impairment of consciousness. The symptoms wax and wane, often for hours, and may be associated with a motor component, depending on the spread. Dysesthesia, painful sensations and visual changes are examples. Limbic aura continua is the most common clinical pattern. Fear, an epigastric rising sensation, or other features may recur every few minutes for many hours, or more than a day without going on to seizures with impairment of awareness. Electrographic correlation is variable. Diagnosis must be entertained, particularly in patients with well-established epilepsy.

IV. **DYSCOGNITIVE FOCAL (PSYCHOMOTOR, COMPLEX PARTIAL) STATUS EPILEPTICUS**

Mesial temporal: Focal status epilepticus predominantly involving mesial limbic structures consists of serial dyscognitive focal ictal events without return of clear consciousness in-between. Onset can be limited to one side, or can alternate between hemispheres.

Neocortical: Focal status epilepticus originating in various neocortical regions can present with a wide variety of unpredictable clinical patterns. Status epilepticus from some frontal foci can resemble absence status or generalized tonic-clonic status. It can present as repetitive descrete behavioral seizures. To some extent, this type of status epilepticus can reflect the neocortical region of origin. For example, occipital status epilepticus might present with unexplained blindness while dysphasia or aphasia could represent focal status in language cortex.

V. **TONIC-CLONIC STATUS EPILEPTICUS:** Generalized tonic-clonic status epilepticus can be an acute symptomatic event; it can be primarily generalized in idiopathic and symptomatic generalized epilepsies; and it is commonly secondarily generalized from focal epilepsies. Occasionally the manifestations can be unilateral.

VI. **ABSENCE STATUS EPILEPTICUS**

Typical and atypical absence status epilepticus: When absence status epilepticus occurs in the idiopathic epilepsies, it has features similar to atypical absence and can be terminated by antiepileptic drugs. In the generalized symptomatic epilepsies, there is overlap with focal status epilepticus due to lesions of certain frontal lobe areas. The absence status epilepticus occurring in elderly patients without a prior history of epilepsy, as well as drug-induced and drug-withdrawal absence status epilepticus, have been characterized and most likely represent similar mechanisms; however, there may be several different types of typical and/or atypical absence status epilepticus.

Myoclonic absence status epilepticus: Myoclonic absence status epilepticus consists of proximal, predominantly upper extremity myoclonic jerks corresponding with 3 Hz spike-wave discharges in the EEG. It can last hours or even days and is usually very resistant to therapy.

VII. **MYOCLONIC STATUS EPILEPTICUS:** Myoclonic status epilepticus consists of irregular, usually bilateral or generalized myoclonic jerking without interference with consciousness. Duration may be up to hours. It is most often seen in patients with insufficiently controlled JME, Dravet syndrome, and in non progressive myoclonic epilepsy in infancy, particularly Angelman syndrome. In myoclonic-astatic epilepsy, it predominates in the extremities of the upper limbs and around the mouth, the areas most represented in the precentral gyrus.

VIII. **TONIC STATUS EPILEPTICUS:** Tonic status epilepticus most commonly occurs in patients with symptomatic generalized epilepsy, but may occur in patients with idiopathic generalized epilepsy. In some of these patients, there appears to be an overlap of symptoms of idiopathic and symptomatic generalized epilepsy. Characteristically, when the patient is lying down, the neck is flexed, the arms are flexed at the elbow, and slightly elevated. The tonic spasms are brief and can continue at brief intervals for hours. In symptomatic generalized epilepsy the duration of the status epilepticus can be much longer.

IX. **SUBTLE STATUS EPILEPTICUS:** This has become an accepted concept, although its accurate diagnosis is often controversial. It refers to an end stage of prolonged generalized tonic-clonic status epilepticus characterized by focal or multifocal myoclonic movements, coma, and pseudoperiodic lateralized epileptiform discharges (PLEDs) against a slow low-voltage background on EEG. The myoclonic movements reflect severe brain damage caused by prolonged status epilepticus and may not be epileptic in nature.

Summary and Conclusions

The 1981 International Classification of Epileptic Seizures has been under review by the ILAE for the past 8 years. A diagnostic scheme for describing individual patients has been proposed that treats epileptic seizure types as diagnostic entities with etiologic, therapeutic, and prognostic implications. This concept is particularly useful when syndromic diagnoses cannot be made. This diagnostic scheme also recognizes the need for a separate detailed phenomenologic description of epileptic seizures in some patients. Although minor changes in the 1981 classification have been recommendedâ€”most importantly replacement of the term â€œpartial seizureâ€ with â€œfocal seizureâ€â€”no new classification has been proposed. As a first step, however, a list has been prepared of recognized epileptic seizure types that are currently believed to be unique diagnostic entities based on knowledge of pathophysiologic mechanisms, anatomic substrates, response to AEDs, ictal EEG patterns, provocative factors, postictal features, and epilepsy syndromes with which the seizure types are associated. Impairment of consciousness should be noted as part of the clinical description of individual patients' seizures, but is not a factor for defining unique seizure types as diagnostic entities. Scientific principles and hypothesis testing will be applied to the process of classification of these seizure types. Each will be subject to evidence-based verification, falsification, and revision, as new information becomes available. Experience with the application of these seizure types and their subsequent classification will also lead to modifications. Continuous review and revision of seizure types will be needed to ensure that they adequately and accurately reflect current knowledge, as well as the needs of clinicians and scientists working in the field of epilepsy.

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Chapter 44

Simple Motor Seizures

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Introduction

Focal motor seizures have been recognized since Hippocrates first noted them, beginning contralateral to the side of head injury. Hemiplegic epilepsy was first actually described by Bravais in 1827.[62] Jackson pointed out that focal epileptic seizures were due to a â€œsudden and excessive discharge of gray matter in some part of the brainâ€ and that the symptoms of the seizure depended on the â€œseat of the discharging lesion.â€ Fritsch and Hitzig demonstrated that electrical stimulation of the motor cortex in animals gave rise to focal muscular contractions in the contralateral limb.[38] In 1887, Charcot proposed the term *jacksonian epilepsy* to describe seizures with a â€œmarchâ€ of symptoms.[59] Another term â€œBravais-jacksonian seizuresâ€ has been used by some to indicate a similar march of symptoms. The term *aura* has been in use since Galen's time; its literal meaning â€œbreeze of airâ€ refers to the altered sensations experienced by the patient with epilepsy at the start of a seizure. Erastus pointed out that an aura was the start of the seizure itself.[48] Electrical stimulation of the brain[100] and detailed observations of spontaneous and metrazol-induced seizures[3] have provided much of the basis for our current knowledge of focal motor seizures.

Definitions

The International Classification of Epileptic Seizures divides simple partial motor seizures into those with or without a march, versive, postural, and phonatory seizures.[30,31] Consciousness is retained during these seizures; however, occasionally, a seizure discharge may remain localized and still produce alterations of consciousness.[46] The epileptogenic zone in the involved hemisphere may be very restricted or quite large, even though terms such as â€œpartialâ€ or â€œfocalâ€ are employed. A more recent seizure classification is based on clinical symptomatology and is independent of electroencephalographic (EEG), neuroimaging, and historical information. In this classification, terms such as *focal clonic, focal tonic,* or *versive* are used, and evolution during the course of the seizure is indicated by arrows, for example somatosensory aura â†' left arm clonic seizure â†' left versive seizure.[8,81,82]

Epidemiology

In a series of 8,938 patients admitted to the University Hospital of Lyon over a 10-year period from 1965 to 1975, 1,158 (12.9%) patients had focal motor seizures without march, 199 (2.2%) patients had focal motor seizures with march, 582 (6.5%) had hemiconvulsions, and 461 (5.2%) had adversive seizures.[89] In a population-based study of 1,054 patients from Denmark, Wagner found that 17% of epileptic patients had simple partial seizures.[124] Loiseau reported that out of 200 patients with partial seizures, 71 (35.5%) had partial motor symptoms, of whom 10 patients exhibited a march.[76]

Anatomic Pathways and Pathophysiology

Simple partial seizures with motor manifestations are due to ictal onset within or near the pre- and postcentral gyri of the contralateral hemisphere. The somatotopic motor and sensory representation of various regions of the body has been documented by the pioneering work of Penfield and Jasper[100] and others[75] (Fig. 1). It is believed that the relatively large representation of the face and fingers is accounted for by the majority of focal motor seizures starting in those brain regions. Holowach noted that 25 of 50 jacksonian seizures in children began in the face, 17 from the hand, 7 from the arm, and 9 from the leg.[60] Penfield and Jasper also noted that the angle of the mouth was involved first in seizures affecting the face; upper-extremity seizures began in the thumb and index finger, whereas lower-extremity seizures often began in the great toe.[100] Another factor is the seizure threshold of various regions of the homunculusâ€"the trunk not only has the smallest cortical representation[87] but also a higher threshold to electrical stimulation.[37] Jacksonian seizures show an orderly â€œmarch,â€ beginning, for example, in the thumb, then involving other fingers, the wrist, forearm, proximal arm, shoulder, and then the face (usually the orbicularis region first). At times, the march may skip certain areas, perhaps because of different seizure thresholds in various regions.[4] Sensory phenomena may occur in about one third of patients with focal motor seizures;[27] this may be caused by involvement of pre- and postcentral regions by the epileptogenic lesion or preferential pathways for spread of the ictal discharge.[36,112] Clonic seizures were reported in 29% of 24 patients with frontal lobe epilepsy.[113] Noachtar and colleagues examined seizure phenomena preceding and following clonic movements in a group of patients with frontal lobe epilepsy: Clonic seizures were usually preceded by behavioral arrest or tonic movements and were the initial manifestation in one third.[93] Motor symptoms also occur in seizures starting elsewhere and spreading to the sensorimotor cortex, such as the parietal lobe,[114,126] occipital lobe,[83,127] or even the temporal lobe.[17]

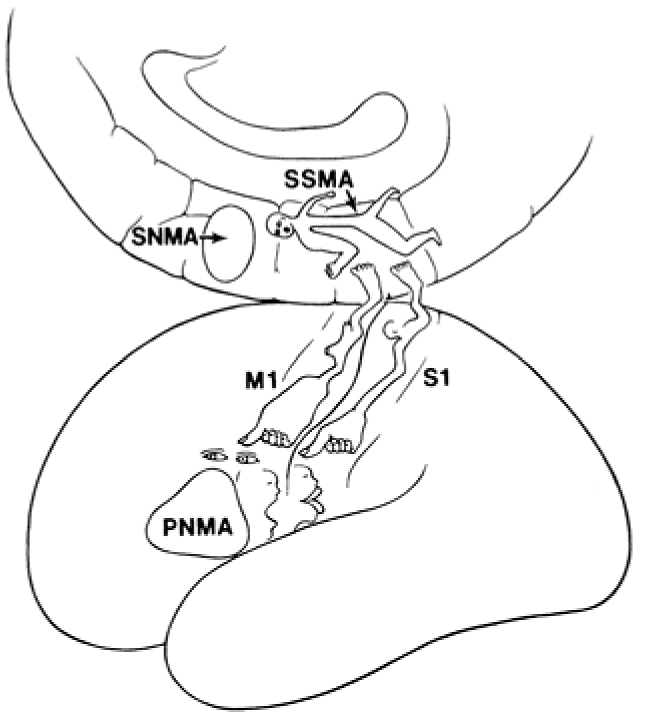

FIGURE 1. Motor and sensory homunculi. The lateral convexity homunculus was simplified from Penfield and Jasper (1954); the supplementary sensorimotor area (SSMA) homunculus was prepared based on stimulation findings by Lim et. al (1994).

The output of the primary motor area (PMA) goes to the corticospinal and corticobulbar tracts, as well as to the supplementary motor area and homologous areas in the opposite hemisphere via the corpus callosum. The PMA gives rise to only one third of the corticospinal and corticobulbar tract fibers, another third come from the premotor cortex and supplementary motor area (SMA), while another third arise from the parietal lobe.[5] Ictal single photon emission computed tomography (SPECT) scan findings in patients with frontal and parietal lobe epilepsy show good agreement with data from electrical brain stimulation studies and invasive EEG recordings.[28,54,58,84,92]

Very rarely, focal seizures have been reported in patients with cerebellar, brainstem, or spinal lesions.[52,55] In

Harvey's patient, localized hyperperfusion on ictal SPECT and ictal discharges were noted in the vicinity of the lesion, and the seizures disappeared after surgical removal of the lesion.

Clinical Features

Ictal

The hallmark of simple motor seizures is focal motor activity that may be expressed as clonic, tonic, postural, or phonatory activity. The international classification of seizures divides simple partial motor seizures into clonic, tonic, postural, and phonatory seizures.[30,31]

Clonic seizures consist of jerky, usually rhythmic movements and are usually seen with seizures starting from the sensorimotor cortex. The clonic movements may remain restricted to one region or spread in a jacksonian manner. As mentioned earlier, jacksonian seizures begin and spread in characteristic ways. Hemiconvulsions are clonic seizures affecting one side of the body. These often occur in the setting of infantile hemiplegia.[2,19,43,47] Most clonic seizures are brief, lasting less than 1 or 2 minutes. Focal myoclonus has also been reported in infants and young children with dysplastic lesions of the motor cortex.[71]

Persistent, stereotyped, periodic, or quasi-periodic clonic activity may occur, and different types are described.[42] Kojevnikov gave the label *epilepsia partialis continua* (EPC) to repeated jacksonian seizures characterized by a march of clonic seizures. Between such attacks, patients have persistent, stereotyped focal myoclonic episodes.[67] The twitching typically affects the thumb or big toe, and individual jerks occur no more than 10 seconds apart.[119] Another type consists of repeated, stereotyped clonic seizures without a march. The usual etiology for EPC is a lesion involving the sensorimotor cortex resulting from stroke, tumor, trauma, metastasis, or hypoxic ischemic encephalopathy.[98,119] EPC is frequently seen in the setting of Rasmussen encephalitis, in the subacute type of measles encephalitis, and in mitochondrial disorders such as mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS).[22] EPC cases have also been reported in nonketotic hyperglycinemia affecting adults and in some patients with subcortical lesions.[24]

Tonic motor seizures produce sustained contraction of a limb and result in assumption of various postures. Tonic motor seizures are believed to implicate a wider area of cortex including the SMA and premotor region.[34,44,100,128] The M2e posture described by Ajmone-Marsan is seen in seizures arising from the SMA region. It consists of abduction, elevation, and external rotation of the contralateral arm with the elbow slightly flexed; the head and eyes deviated as if to look at that arm, while both lower extremities may be slightly flexed at the hips and knees or extended. Even in patients where tonic posturing appears unilateral, a bilateral increase or decrease of tone occurs.[1]

Postural seizures refer to tonic contraction affecting more than one limb and the trunk or headâ€"typically these are bilateral tonic movements affecting the proximal muscles more than the distal muscles. Rarely, motor seizures are manifested by focal weakness instead of tonic or clonic activity.[45,51,100,122] Consciousness is retained during SMA seizures in 72% of attacks.[3] A prolonged continuous or interrupted vocalization may occur in seizures involving the supplementary motor or lower rolandic area from either hemisphere.

Versive seizures are characterized by predominantly tonic contraction of head and eye muscles resulting in sustained, forceful deviation to one side (invariably contralateral).

Consciousness is often lost by the time a patient experiences version; at other times, however, patients are conscious of forced eye and head deviation;[26,90] often the angle of the mouth is also deviated to the same side, and the neck is extended.[63] In Wyllie's study, version was accompanied by clonic or posturing arm movements or facial clonic movements on the side of contraversion. The versive movement was smooth in 65% and jerky in 35% of seizures.[129] Rasmussen and Penfield found that stimulation of the precentral gyrus immediately anterior to the central sulcus (area 8) resulted in contralateral eye deviation;[107] less often ipsilateral deviation or upward deviation and convergence occurred. However, stimulation of more anterior sites always resulted in contraversion.[117] Version may also occur upon stimulation of the occipital lobe.[10,104,120,129] Version occurs on the same side as dystonic posturing[68] and is usually but not always followed by a secondarily generalized tonicâ€"clonic seizure.[13,21,68,129] Version occurs in partial onset seizures originating from a number of different locations that spread to the premotor cortex. Chee et al. found that version occurred earlier than 18 seconds in extratemporal seizures and later than 18 seconds in the vast majority of temporal lobe seizures.[21] This is, of course, due to more rapid spread to the prefrontal cortex in extratemporal seizures (the majority starting from the frontal lobe). Ipsilateral forced eye and head deviation occurs in frontal lobe seizures; later in the seizure, contralateral version occurs just prior to secondary generalization. Some authors reported forceful head turning occurring ipsilaterally to the focus;[44,95,109] these could be due to (a) seizures beginning in the area where Penfield and Rasmussen found ipsiversive movements, (b) rapid contralateral spread to homotopic frontal eye fields, or (c) disruption of normal pathways due to structural lesions.[16] In our experience, version occurring just prior to a secondary generalization has always been correct in lateralizing the side of ictal onset.[13,21] At the end of the generalized convulsion, Wyllie et al. have noted ipsilateral head and eye deviation (ipsiversion), which is presumed to reflect activation of the opposite hemisphere and neuronal exhaustion on the side of seizure onset.[130] Ictal SPECT scans in versive seizures show localized hyperperfusion in the region of the sensorimotor cortex.[54,92,125] Asymmetric tonic limb posturing, sometimes referred to as the â€œFigure 4 sign,â€ occurs in the course of secondarily generalized tonicâ€“clonic seizures, and is usually contralateral to the side of ictal onset.[69]

Phonatory seizures are thought to result from activation by the ictal discharge of the primary motor cortex or the SMA. Phonatory movements have been elicited upon stimulation of the SMA or the primary motor cortex below the tongue or lip area.[100] Vocalization in SMA seizures is more often sustained than interrupted,[64] whereas seizures involving the primary motor area tend to produce interrupted sounds. Speech arrest (inability to speak during the seizure in spite of conscious attempts by the patient) may result from involvement of the primary motor cortex on either the dominant or nondominant hemisphere.[40] Conversely, Broca aphasia results from involvement by the ictal discharge of the Broca area immediately anterior to the face area in the dominant hemisphere. This can be reproduced by electrical brain stimulation.[40,56,80,116]

Interictal

In the interictal state, patients who have structural lesions involving the sensorimotor cortex may exhibit contralateral hemiparesis or sensory disturbances on that side of the body, for example in the setting of Rasmussen encephalitis, infantile hemiplegia, or the hemiconvulsions, hemiplegia, epilepsy (HHE) syndrome. In the HHE syndrome, infants between 6 months to 2 years of age develop prolonged unilateral convulsions in the setting of a febrile illness. The convulsions last from an hour to several days, and are followed by the onset of hemiparesis and jacksonian motor, complex partial seizures or secondarily generalized tonicâ€“clonic seizures arising from the contralateral rolandic region or the temporal lobe.[43] Cases of HHE syndrome are much less common these days since the introduction of effective medications to terminate status epilepticus.

Postictal

Postictally, a functional neurologic deficit that lasts from minutes to as long as 48 hours may be seen.[122] This may be a worsening of a previous focal deficit, or a new one may appear. Todd paralysis, as it is commonly referred to, is related to the duration of the seizure, and is thought to represent postictal neuronal hyperpolarization,[85,86] the inhibitory effect of ictally released endogenous peptides, or cortical ischemia resulting from functional arteriovenous shunting.[131] It may be accompanied by postictal slowing on the EEG, contralateral to the side of weakness. Computed tomography (CT) and magnetic resonance imaging (MRI) scans may show transient cerebral edema.[29,115] The side of Todd paralysis is useful in lateralizing the hemisphere of seizure origin in over 90% of patients, especially when it can be documented in the epilepsy monitoring unit.[65]

Electroencephalographic FINDINGS

Interictal

Detection of interictal spikes by scalp EEG electrodes depends on the extent of the epileptogenic zone as well as the orientation of the dipole. A critical area of 6 cm^2 must be involved before changes can be detected at the scalp.[39] Quesney et al. examined surface and subdural recordings from 34 patients with frontal lobe epilepsy rendered seizure-free after resection of the epileptogenic focus. Focal spiking was noted in 9% of patients, whereas nearly 60% had more widespread or generalized spiking. Nearly 12% had no detectable spikes on scalp recordings. Subdural recordings revealed either regional spiking over two or three gyri, extensive spiking all over the grid electrodes, or less often, an absence of interictal spikes.[103]

Ictal

Scalp recordings of ictal onsets may disclose regional seizure patterns; however, the patterns are more extensive or difficult to lateralize compared to temporal lobeâ€"onset seizures. From subdural electrode recordings, evidence for a focal onset is found in a relatively small number of patients; more often a diffuse regional onset is seen.[103] Devinsky et al. reported good correlation between the localization of the ictal onset with semiology. Furthermore, subdural electrodes detected ictal changes that were not apparent at the scalp in some cases.[28] In epilepsia partialis continua, irregular 0.5- to 3-Hz slowing is seen in the frontocentral region, along with a reduction in the Î²-activity. If progression to a more involved seizure occurs, a well-defined seizure pattern may become evident. Interictal epileptiform discharges were noted in only 8 of 36 (22%) of patients with EPC[24] (Fig. 2).

Diagnostic Considerations

Simple motor seizures are usually easily diagnosed by history alone. The history of focal tonic or clonic features is usually unmistakable. Seizures arising from the SMA however, can sometimes be mistaken for generalized tonicâ€"clonic seizure or psychogenic seizures. SMA seizures are brief, stereotyped seizures with variable responsiveness, which often involve the proximal limbs bilaterally. Video-EEG (V-EEG) monitoring is helpful in ambiguous cases; after reducing or stopping the patient's antiepileptic medications one may note a progression to focal clonic activity, version, or secondary gene- ralization.

Differential Diagnosis

The differential diagnosis of simple motor seizures includes nonepileptic myoclonus,[101] tic disorders, tremor, myokymia, and paroxysmal dystonic and kinesogenic choreoathetosis; a normal outpatient routine EEG does not exclude the possibility of simple motor seizures. Home videotape recordings, when available, are extremely helpful; otherwise, prolonged V-EEG monitoring may be indicated if the attacks are occurring with some frequency. In this setting, ambulatory EEG is not particularly helpful, especially if no ictal changes are seen. Good-quality videotape recordings of the events are essential in making a diagnosis.

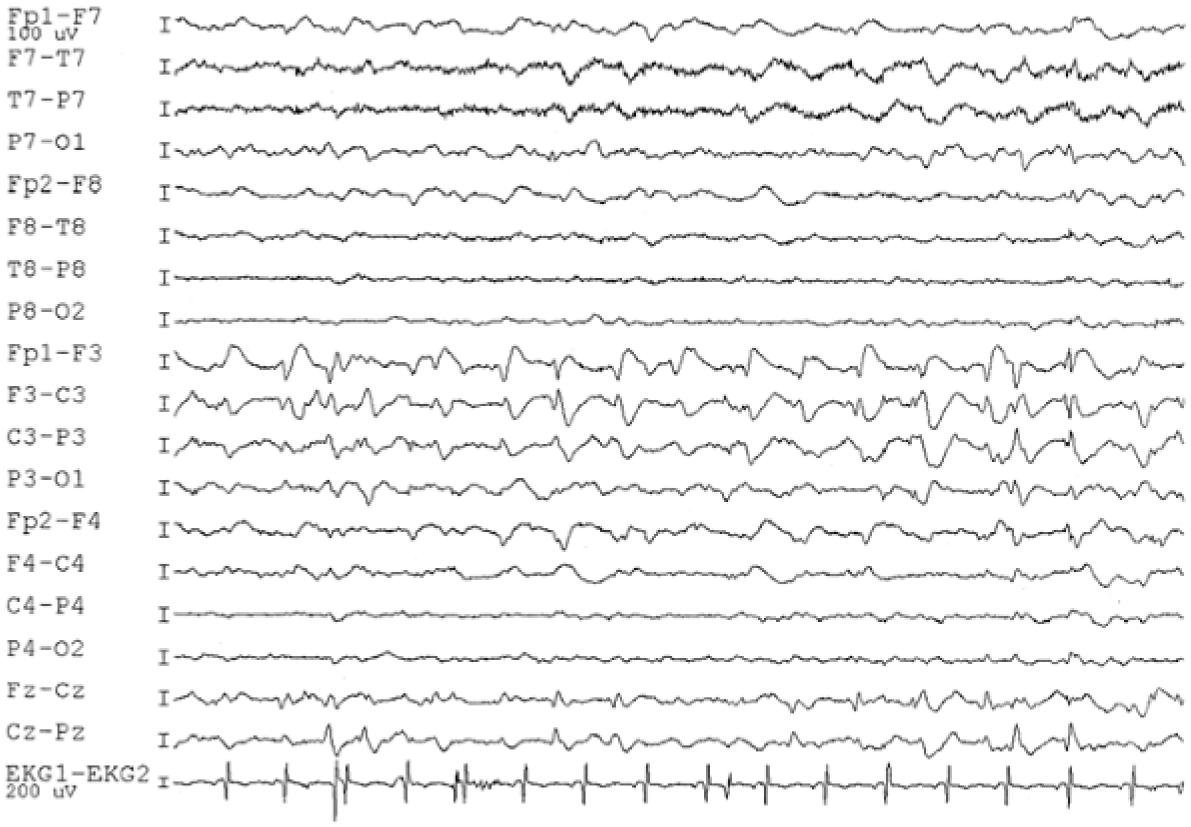

FIGURE 2. EEG recording in a 12-year-old girl with epilepsia partialis continua affecting the right hand secondary to Rasmussen encephalitis. Repetitive sharp waves and continuous slowing are noted in the left frontocentral region; these were noted to coincide with the jerks.

Specific Syndromes

Rasmussen Encephalitis

In Rasmussen encephalitis, young children, usually between 6 and 10 years of age, develop intractable focal motor seizures with frequent bouts of focal status or epilepsia partialis continua on one side of the body. Within months of onset, the child develops a progressive hemiparesis, hemisensory loss, or even hemianopsia, as the involved hemisphere undergoes progressive neuronal cell loss, gliosis, and atrophy. This is accompanied by intellectual decline and behavior disturbances. The course is progressively worsening, with death occurring in most of the children within a decade; a few patients appear to stabilize over time, a condition known as â€œburnt-out Rasmussen.â€[96,105]

CT and MRI scans show progressive atrophy starting in the region of the sylvian fissure and slowly affecting other areas of that hemisphere. Changes in signal intensity may also be seen in the deep gray and white matter.[118] Pathologic examination shows signs of inflammation, with glial nodules and perivascular infiltrates containing plasmocytes, lymphocytes, and glial cells.[49,61,110] Diagnostic criteria for making the diagnosis of Rasmussen syndrome were recently published.[12] In situ hybridization techniques were reported to show most Rasmussen patients to have neurons with cytomegalic inclusion virus;[102] this, however, has not been confirmed by others.[7] Autoantibodies to the glutamate receptor GluR3, functioning as a glutamate agonist, have been reported in some patients.[111] T-cellâ€“mediated cytotoxicity may also play a role.[35] Following cleavage of the GluR3 protein by granzyme B, the immunogenic section of the GluR3 protein becomes exposed to the immune system.[41] For reasons that are not yet known, Rasmussen encephalitis is essentially a unilateral disease. Because the seizures do not respond to medical treatment, surgical removal of the epileptogenic cortex is done when hemiparesis has resulted (usually when useful finger movement has been lost). This consists of a functional or complete hemispherectomy. The surgical procedure should be done relatively early in the course, prior to involvement of the opposite hemisphere. Some authors have recommended intravenous immunoglobulins, high-dose steroids, or plasmapheresis; patients with recent onset of the disease showed a significant improvement.[6,23,32,53] However, medical treatment does not appear to produce a lasting improvement. A trial of tacrolimus was found to slow the rate of neurologic deterioration, but it did not improve seizure frequency.[11]

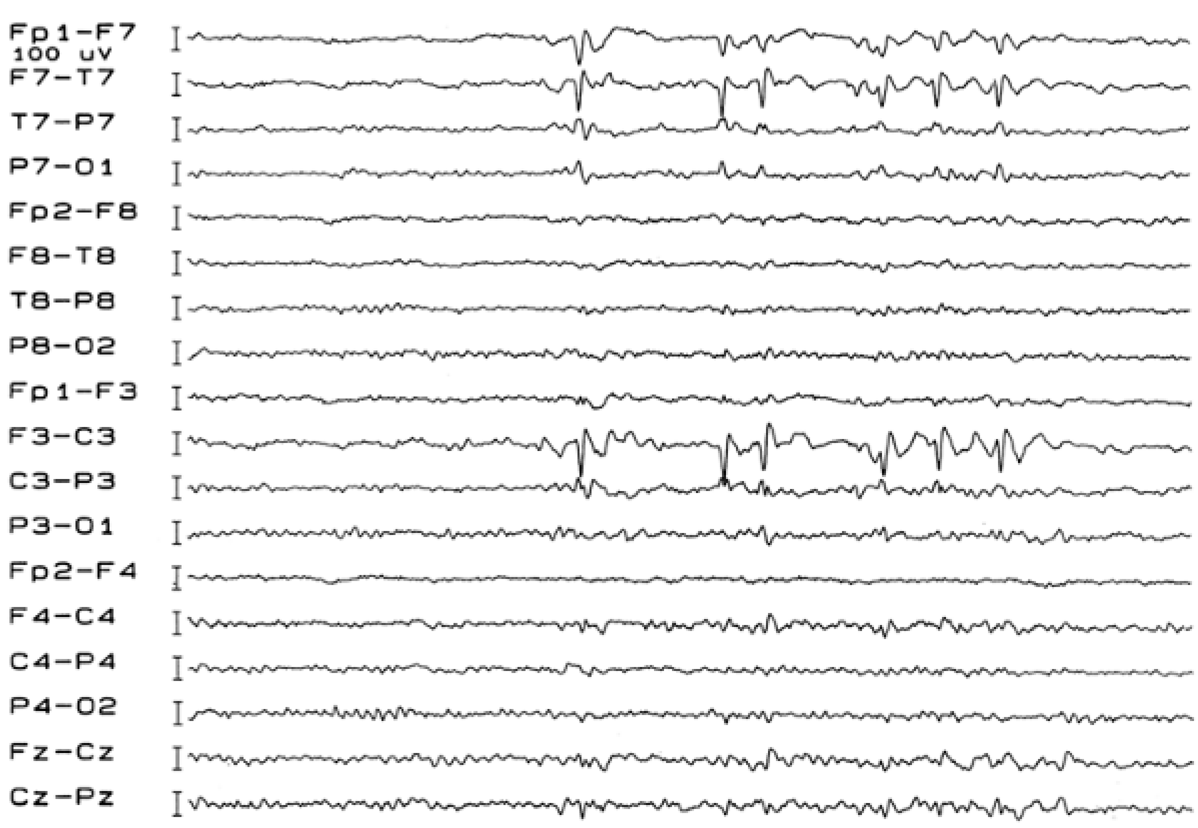

FIGURE 3. Typical benign focal epileptiform discharges of childhood in the left central-temporal distribution.

Benign Focal Epilepsy of Childhood

Also known as *benign rolandic epilepsy* or *benign epilepsy with centrotemporal spikes*, benign focal epilepsy of childhood (BFEC) is the commonest epilepsy in children, accounting for 15% to 25% of childhood epilepsies.[57,73] Its usual age of onset is between 2 and 12 years, followed by eventual remission in all typical cases before the age of 16.[77] Genetic factors are believed to play a role; it is thought to be autosomal dominant with variable penetrance.[18,57] It has been calculated that only about 8% to 10% of children with the typical EEG picture will actually manifest seizures.[79] It is thought to have a diffuse epileptogenicity affecting the brain in an age-dependent expression.[79] Children typically present with simple motor seizures affecting the face and arm (sometimes accompanied or preceded by somatosensory auras) that occur shortly after falling asleep or upon awakening. Younger children may instead have secondarily generalized tonicâ€“clonic or hemiclonic seizures. The EEG findings in this syndrome are diagnostic.[9,15,57,73,79,91] Sharp waves with a characteristic morphology and polarity occur in the centrotemporal region; at times multifocal sharp waves are seen in other areas as well (Fig. 3). The typical sharp waves may not be seen on awake recordings, but are abundant, sometimes in long runs as soon as the child falls asleep. Seizures in BFEC are readily controlled by most antiepileptic medications. Approximately half the children will have fewer than five seizures; the remainder can be readily controlled by medications such as oxcarbazepine, carbamazepine, phenytoin, or gabapentin.[9,15,73,78] After a seizure-free period of 2 or 3 years, children can be successfully tapered off medications. Another syndrome of benign partial seizures affecting adolescents has been reported; however, the epileptiform discharges do not have a typical morphology.[66]

Partial seizures during the first 2 years of life often manifest tonic posturing (either symmetric or asymmetric), eye deviation, and asymmetric clonic jerking. This contrasts with auras, restricted clonic movements, automatisms, and dystonic posturing that become increasingly frequent after the age of 6 years.[94] Some of these infants will also develop infantile spasms following or preceding the partial seizures.[97] The entity of *malignant migrating partial seizures of infancy* begins before the age of 6 months, with nearly continuous focal seizures arising independently from shifting foci in both hemispheres. These seizures may be clonic, tonic, versive, or autonomic. Interictal EEG shows multifocal sharp waves and background slowing, whereas ictal recordings demonstrate monomorphic rhythmic Î¸-discharges arising from shifting foci. These infants show developmental regression and have high morbidity and mortality risk.[25,50]

Response to Treatment

After the occurrence of several partial or secondarily generalized tonicâ€“clonic seizures, the need for treatment with antiepileptic medications becomes evident. Sodium channel blocking agents such as oxcarbazepine, carbamazepine, and phenytoin are most often used. Other antiepileptic drugs (AEDs) that are also effective include levetiracetam, topiramate, zonisamide, lamotrigine, gabapentin, pregabalin, vigabatrin, and primidone. The response to treatment becomes clear by the end of the first year in most cases, provided that the seizure type and medication used are correct.[33] Elwes found that approximately 73% of those with partial seizures had a 1-year seizure-free period during 5 years of follow-up; the remaining patients have medically intractable seizures.[33,108] Recent studies indicate that failure to respond to two or three AEDs is a very strong indicator of medical intractability.[72] Such patients may benefit from a presurgical evaluation to determine if they can benefit from focal cortical resection.[70] Partial onset seizures occurring in association with periodic lateralized epileptiform discharges (PLEDS) may be more difficult to control; however, few of these patients go on to develop chronic epilepsy.[74] Seizures occurring in the setting of focal lesions, such as focal dysplasia or tumor, seem more resistant to therapy. Patients with medically intractable seizures should be evaluated for epilepsy surgery. Results after focal cortical resection are much better for those with localized lesions than for those without.[123] Unless evidence shows the epileptogenic focus to be far removed from functional areas, invasive EEG recording and electrical brain stimulation are necessary in most patients. Children with Rasmussen chronic encephalitis almost always have a progressively worsening course. Functional hemispherectomy should be considered when useful finger movements have been lost in the affected hand. Hemispherectomy is also useful in

patients with chronic epilepsy and infantile hemiplegia.[19] In the case of BFEC, in which some children have only occasional simple motor seizures at night, the child's physician and parents may decide not to use daily antiepileptic medications, which may have potential side effects.

Summary and Conclusions

The study of simple partial seizures has provided us with valuable insights into the organization of the sensorimotor cortex. BFEC, the most common epilepsy in children, is easily recognized thanks to its typical presentation; seizures are infrequent and readily controlled with antiepileptic medications. At the other end of the spectrum, Rasmussen encephalitis is an infrequent but catastrophic disease with inexorable progression. Medical treatment offers no lasting benefit, and hemispherectomy is usually necessary. Approximately 25% of patients with simple partial seizures become medically intractable and may need evaluation for epilepsy surgery.

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Chapter 45

Neocortical Sensory Seizures

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Introduction

Simple sensory seizures represent challenging clinical phenomena. Neurologists readily accept that a patient's sensory symptoms prior to the appearance of motor symptoms or alteration of consciousness represent part of the patient's clinical seizure semiology and provide valuable localizing information. A challenge appears when a patient has only simple partial sensory seizures. Simple partial seizures are a relatively common seizure presentation among the childhood epilepsies, but motor seizures are predominant.[47] The paucity of psychic or sensory symptoms may reflect the child's inability to describe internal experiences in a way that is easily interpretable to adult observers. Since simple sensory seizures have no overt ictal behavior, the subjective description of the seizure symptomatology is the only clue that can lead to a proper clinical evaluation and treatment. Some patients react to sensory seizures in a stereotypic fashion. For example, a painful simple partial sensory seizure of the hand may result in hand rubbing or vocalization about the pain. Occasionally, physicians encounter patients who have simple partial seizures for many years prior to the appearance of more clinically apparent seizures. When patients with pure sensory seizures also have psychiatric complaints, the chances for misdiagnosis or delay of diagnosis are high.[121]

Simple sensory seizures were originally underrecognized as epilepsy.[35] While auras were known in ancient times as an event preceding seizures,[122] it was not until the early 19th century that partial seizures were clearly related to localized brain disease. Fritsch and Hitzig described localization of function in 1870, which led to modern concepts of cortical specification.[38]

Jackson also promoted the hypothesis that abnormal electrical activity in a localized region of cortex could cause symptoms such as those seen in epilepsy.[51,52] In the early 1900s, the work by Brodmann[18] and other neuroanatomists showed that the cerebral cortex had regional histologic variations often corresponding to different cerebral functions. Penfield, Jasper, and others made major contributions to mapping the localization of cerebral function and defining motor and sensory areas of the brain, as well as areas without obvious effect on sensory, motor, or speech activity.[83,85]

Definitions

Sensory seizures were defined by Penfield and Jasper separately from simple seizures with autonomic symptoms or psychic symptoms:[85]

â€œSensory seizures. Discharge in an area of sensory representation produces a sensation that may serve as a warning (aura) of a motor or psychical seizure. Actually, the sensation constitutes, in itself, a seizure. Under this heading we have taken up the sensory attacks that involve the trunk, head, and extremities (somatosensory), and the special senses (visual, auditory, vertiginous, gustatory, and olfactory).

1. Somatosensory seizures. Sensation of this type may be transient, or it may be continuous over a considerable period of time. The quality of sensation is tingling, numbness, sense of movement, desire to move, or, very occasionally, pain. A detailed march of sensation may occur from one somatic part to the

next in a manner similar to the Jacksonian motor march. The discharge, which produces this, usually occurs in the postcentral gyrus. There is a tendency for the sensory march to stop and to spread across the Rolandic fissure so as to produce movement in the same member. Spread in the reverse direction from motor to sensory representation, thus producing sensation after movement, is quite rare.

A somatosensory seizure may also be produced by discharge in the second sensory area on the upper bank of the fissure of Sylvius. Furthermore, peculiar body sensations may result from discharge in the supplementary motor area within midsagittal fissure.

2. Visual seizures result from discharge in one or the other occipital lobe. Lights, which may be colored, appear before the patient, or there may be dimming of vision and complete blindness even though the discharge originates in one occipital lobe. Complicated visual hallucinations and alterations in the interpretation of things seen are not included in this group, but are discussed under the heading of psychical seizures.
3. Auditory seizures are characterized by a simple sound, usually described as buzzing or drumming, and often referred by the patient to the opposite ear, or opposite side of the head. Like a visual seizure, there is nothing elaborate about it. Hallucinations of music, for example, are classified as dreamy states or psychical seizures and are discussed below.
4. Vertiginous seizures. What is called by the patient dizziness or unsteadiness is frequently reported, but there is rarely any recollection of direction of rotation as there is in the sudden dizziness of Meniere syndrome.
5. Olfactory seizures have been called uncinate fits because of the demonstration by Jackson of involvement of the uncinate gyrus in cases in which an aura of disagreeable odor constituted the initial feature. The localization of discharge is doubtless in or near the uncinate gyrus.â€

Penfield and Jasper's classification of simple partial sensory seizures has withstood the test of time since the international classification[26] of simple partial seizures with somatosensory or special sensory symptoms is nearly identical to the original description except for lack of description of gustatory seizures (Table 1). It is unlikely that another sensory modality will be discovered and change the classification further.

Table 1 Simple Partial Seizures with Somatosensory or Special Sensory Symptoms[a]

Somatosensory
Visual
Auditory
Olfactory
Gustatory
Vertiginous

[a] Simple hallucinations (e.g., tingling, light flashes, buzzing).

Penfield and Jasper recognized the difficulty of separating a simple sensation from a more complicated hallucination, for example, separating simple visual hallucinations from more complicated formed illusions. Occasionally one finds more complicated hallucinations with intraoperative stimulation, but more reliably localizing are the simple hallucinations of rather elementary sensory perceptions. A conscious patient may attach many complex descriptions to simple hallucinations, and since we observers have nothing to observe other than the patient's subjective description, sometimes there may be a fine line between a classification of simple partial sensory seizure and a simple partial psychic seizure with prominent sensory complaints.

Epidemiology

Ideally, understanding the epidemiology of simple partial seizures would require evaluation of a large population in which patients with epilepsy are identified accurately and their seizures and epilepsies are classified based on a thorough clinical and laboratory investigation. Such studies are usually based on patients referred to specialized epilepsy centers. Focal epilepsy occurs in approximately 60% of patients with epilepsy, and 10% to 21% of these patients have simple partial seizures alone.[40] Detection of simple partial seizures can be difficult. Some patients with simple partial sensory seizures may be undiagnosed or unaware that their symptom represents epilepsy unless the seizure progresses into a more disabling seizure type. In patients with obvious epilepsy and more severe types of seizures, only a careful history will elicit remote sensory complaints that may no longer occur, as in several cases reported by Williamson et al.[123]

Isolated simple partial sensory seizures are uncommon in patients referred to major epilepsy centers. Among the focal epilepsies, temporal lobe and frontal lobe foci predominate in surgical series.[119] Parietal and occipital cases are rare because those epilepsies are either rare, rarely intractable, or rarely brought to surgery. For example, occipital epilepsy was identified in only 12 of 502 nontumoral epilepsy cases by Bidzinski et al.[12] Williamson et al. reviewed reports of occipital lobe epilepsy in the literature and found that <2% of focal epilepsy is occipital.[124] They found only sporadic reports when they reviewed parietal lobe epilepsy.[123]

These surgical data are typically grouped by lobe, not seizure type. It is likely that the epidemiology of simple partial sensory seizures differs from the lobar distribution of surgical cases. A review of the initial signs of seizure onset in data adapted from Penfield and Kristiansen showed that in 222 patients, 55 had somatosensory auras, 11 had visual auras, three had auditory auras, one had an olfactory aura, and two had gustatory auras.[62] Penfield and Perot noted visual hallucinations in 41 of 1,132 (3.6%) patients with focal epilepsy; 21 had only visual hallucinations.[87] Mauguiere and Courjon found somatosensory epilepsy in 127 of 8,938 (1.4%) patients with epilepsy when evaluated after age 3 years.[72] Young and Blume reported painful seizures in 24 of 858 (3%) epileptic patients[129] and Hausser-Hauw and Bancaud noted that 30 of 718 (4%) intractable epileptics had gustatory hallucinations.[43] West and Doty reviewed olfactory auras in epilepsy and concluded that prevalence is unknown but published estimates ranged from <1% to >30% depending on the epilepsy syndrome and pathology.[122]

The advent of magnetic resonance imaging (MRI) technology has further complicated matters. Patients with lesions identified in known sensory cortical regions may not volunteer information on sensory symptoms until thoroughly interrogated about an aura. At times, only with inpatient video-electroencephalography (V-EEG) and MRI can sensory symptoms be suspected and assessed. This is especially true in patients with sensory symptomatology at seizure onset that progresses to loss of consciousness and amnesia for the aura. These patients often have more intense seizures and EEG changes are usually bilateral.[103] Additionally, sensory symptoms may result from spread of a seizure from an unexpected location; for example, many patients with supplementary motor seizures complain of a somatosensory aura even when lesions are not near the sensory cortex.[106] Gustatory hallucinations may also represent seizure spread.[43] Visual hallucinations have been reported with frontal lesions,[102] as have jacksonian sensory seizures from a prefrontal lesion.[118] Thus, at this time, there is still need for adequate epidemiologic studies of localization-related epilepsies and partial sensory seizures using modern technology and appropriate clinical information.

Anatomic Pathways and Pathophysiology

Understanding neocortical anatomy and regional interconnections has led to a better understanding of seizure semiology and evolution. The neocortex is a repository for all primary sensory input for somatosensory, visual, auditory, and gustatory senses, while olfaction mostly utilizes portions of the limbic system and is the only special sense without thalamic relays.[21] Within the cerebral cortex, sensory functions are not so discreetly organized that there are sharp boundaries; for example, the sensory responses obtained by Penfield and Rasmussen[88] and Uematsu et al.[116,117] showed that sensory responses could be recorded from the precentral gyrus (see reference 85, p. 58, Fig III-12). Motor responses show similar dispersion. Penfield reported that removal of the precentral gyrus did not prevent motor responses from the postcentral gyrus, suggesting that activation of the postcentral gyrus alone could result in movements during seizures.

The sensory homunculus (see reference 85, p. 70, Fig III-15) must be considered as an artist's schematic diagram of data obtained by Penfield and Jasper on many patients; it is not entirely accurate for each patient. However, the homunculus does show significant organization of the cerebral cortex in an anatomically meaningful way (see reference 85, p. 71, Fig. III-17).

Some body parts (e.g., the tongue and hand) have large cortical sensory areas. Picard and Olivier have extensively reviewed the anatomy of the sensory tongue cortex in humans. The language-dominant hemisphere had a larger sensory cortical tongue representation and the tip of the tongue had more extensive representation than the middle or back portions of the tongue.[89] Most cortical representation was contralateral to somatic localization, but ipsilateral and bilateral responses to stimulation were reported, suggesting possible stimulation of the secondary sensory area, located at the base of the perirolandic cortex.

Penfield and Rasmussen[88] found a human second sensory area in the region of the termination of the motor strip in the frontoparietal operculum (see reference 85, p. 79, Fig III-21). When stimulated, the second sensory area on the superior bank of the frontoparietal sylvian fissure produces bilateral, contralateral, or ipsilateral sensations, often of the perioral regions (see reference 85, p. 79, Fig III-21). Ipsilateral inputs are less numerous as shown by Adrian in cats.[1] LÃ¼ders et al. recorded evoked potentials from the second sensory area that were of lower amplitude than primary sensory potentials.[67]

Other primary sensory cortices show highly organized anatomy; for example, the visual cortex deep within the calcarine fissure is organized so that the occipital pole is innervated polysynaptically by the macula and therefore is activated by the central visual field, whereas more rostral portions of the calcarine cortex contain representations of more peripheral visual fields.

The auditory cortex in the Heschl gyrus of the temporal lobe is tonotopically organized as shown by evoked potential mapping of longer-latency responses with magnetoencephal- ography.[82,115,119,120] Vestibular cortex is also in the superior temporal gyrus rostral to the auditory cortex, but stimulation does not produce anatomically specific symptoms, just mild vertigo.[85]

Taste is represented in the parietal operculum and possibly near the insula,[85] though Hausser-Hauw and Bancaud's detailed depth electrode studies point primarily to the parietal operculum.[43] Olfaction initially involves pathways from the olfactory epithelium through the cribriform plate to the olfactory bulbs, olfactory tracts, and lateral stria. These areas project to the anterior perforated space, prepiriform cortex, lateral olfactory gyrus, periamygdaloid cortex, entorhinal cortex, amygdala, septal nuclei, and hypothalamus.[122] Thus, most olfactory centers are located in the mesial temporal region and adjacent structures.

While a description of epileptogenesis is beyond the scope of this chapter, clearly any structural lesion, whether seen by MRI or not, involving a sensory cortex or adjacent area may provide the necessary and sufficient changes for chronic localization-related epilepsy to develop. The concept of the epileptogenic zone, as interpreted by Penfield and Jasper[85] and Ajmone-Marsan[4] and reviewed by LÃ¼ders and Awad,[65] implies that the locations in the cortex where symptoms are produced, where seizures are generated, where interictal spikes occur, and of any structural lesions all may contribute to epileptogenesis or to the symptom expression during seizures. It is certainly possible for sensory cortex to become activated late in a seizure and thus produce symptoms after the actual EEG onset in a silent cortical area. To experience somatosensory, visual, or auditory symptoms, white matter pathways, association cortices, and brain structures regulating attention and consciousness all play a role.

Epileptogenesis producing sensory seizures and focal epilepsy may occur without brain lesion or injury from peripheral nervous system injury. Spiller et al. reported three cases with soft tissue injuries to the hand where sensory seizures developed within months in the injured limb and all cases eventually had secondarily generalized tonicâ€“clonic seizures. The authors postulated that the injury resulted in cortical reorganization that was epileptogenic.[109]

Clinical Features

Simple sensory seizures show a wide variety of phenomenology and represent some of the most interesting seizures reported. Patients can have prolonged symptoms[70] and can relate elaborate descriptions of their seizure. Since sensory cortices are located in adjacent lobes, it is not surprising that multimodality sensory seizures are frequently reported in addition to sensory seizures from one modality.[72]

Seizures of the primary sensory cortex typically produce contralateral positive or negative symptomatology. Unilateral symptoms thought to originate in or near the contralateral postcentral gyrus include tingling, numbness, sense of movement, desire to move, somatic pain, heat or cold, electric shock sensations, agnosia for a body part, and phantom sensations.[60,72,85,99,123,129] The hand and fingers are most often involved initially.[72] Symptoms may be stationary or have a sensory march. Somatosensory seizures may be interpreted as motor activity by the patient, even when there is no visible movement seen. This can often lead to misinterpretation of seizure localization by a physician taking the history. Cephalic pain, occasionally migrainous in nature,[19] even if unilateral, may not have localizing value, while abdominal pain usually originates from the temporal lobe.[129] Genital pain probably originates at the mesial parietal termination of the sensory strip and is not necessarily associated with orgasmic seizures.[98,110,128] Attacks of limb agnosia (sudden loss of sensation for a body part) and phantom limb sensations (sense that the limb is in a position that is not the true position) probably originate in the posterior parietal region.[41,72,99] Ajmone-Marsan gives Foerster credit for pointing out that a postcentral-area seizure can be distinguished from the precentral seizure since motor symptoms stop earlier when the seizure originates in the postcentral gyrus and that the convulsing muscles are often more limited in distribution than when the primary motor cortex is seizing. Additionally, when a motor seizure occurs after activation of the sensory cortex, a tremor may be seen before true clonic spasms, if clonic spasms occur.[4] Russell and Whitty observed that somatosensory auras often spread quickly to involve at least the entire limb and that prolonged sensory seizures, comparable to the epilepsia partialis continua of motor seizures, were not observed in their 85 cases. Motor seizures rarely progress to a simple somatosensory seizure, while the reverse is common. Sensory seizures often end abruptly, unlike the gradual cessation typical of focal motor attacks.[99]

Seizures from the second sensory area may produce ipsilateral or bilateral symptoms that are identical in character to symptoms occurring in the primary sensory cortex (e.g., numbness and tingling). Affected body parts can be diffuse or axial but often symptoms localize to the fingertips, feet, lips, or tongue.[2,6,11,13,61,85,93,123] Second sensory-area seizures can arise from the frontoparietal operculum or the inferior parietal lobule.[126] It is also possible to have ipsilateral sensations with seizures originating near the supplementary motor area since there may be a corresponding supplementary sensory region adjacent to the primary sensory foot area.[85] Arseni and Maretsis' case 3 may have had ipsilateral seizures from this location.[6]

Somatosensory auras have been reported in temporal lobe epilepsy, usually with bilateral or unilateral tingling. Pain and numbness were also noted in Erickson et al.'s report and most symptoms were in the limbs but could involve the head or trunk.[36]

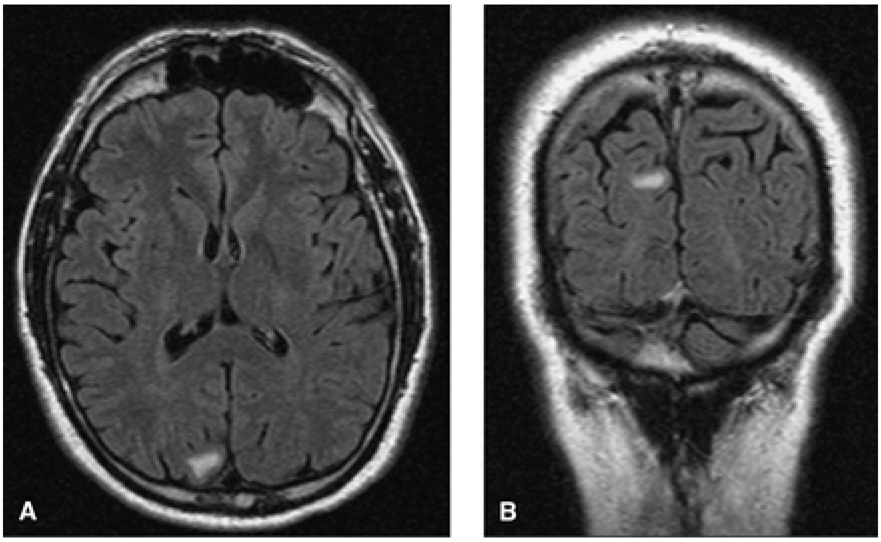

FIGURE 1. Poststroke occipital epilepsy. **A, B:** This is a magnetic resonance image of the brain in a 53-year-old male smoker and drinker with a right occipital infarct, mild left homonymous visual scotoma, and complex partial seizures with an aura of autonomic symptoms of epigastric sensation, facial flushing, and dizziness associated with â€œgraying outâ€ of his vision prior to loss of consciousness. Routine electroencephalography was normal and seizures are controlled by carbamazepine.

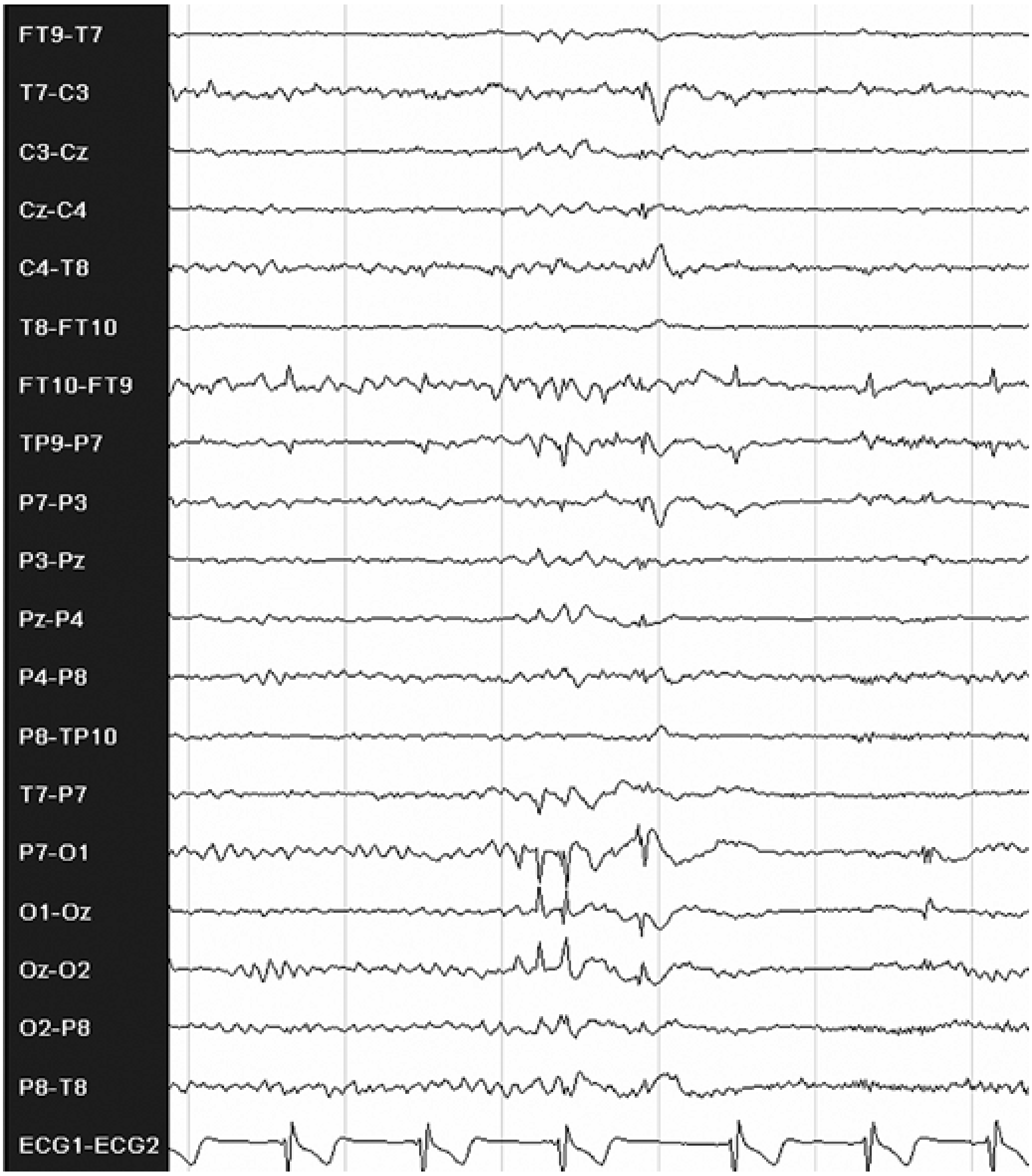

FIGURE 2. Interictal electroencephalogram showing left occipital spikes in an 18-year-old, right-handed male patient with a history of seizures since age 5, starting 3 months after a mild head trauma. He has an aura of right-sided flashing lights, then vertigo, followed by a subjective feeling of right arm twitching and then loss of consciousness. After that he turns his head to the right, raises his right arm, and progresses into a secondarily generalized tonicâ€“clonic seizure. Magnetic resonance imaging of the brain was normal. The patient became seizure free after adding levetiracetam to his monotherapy carbamazepine regimen.

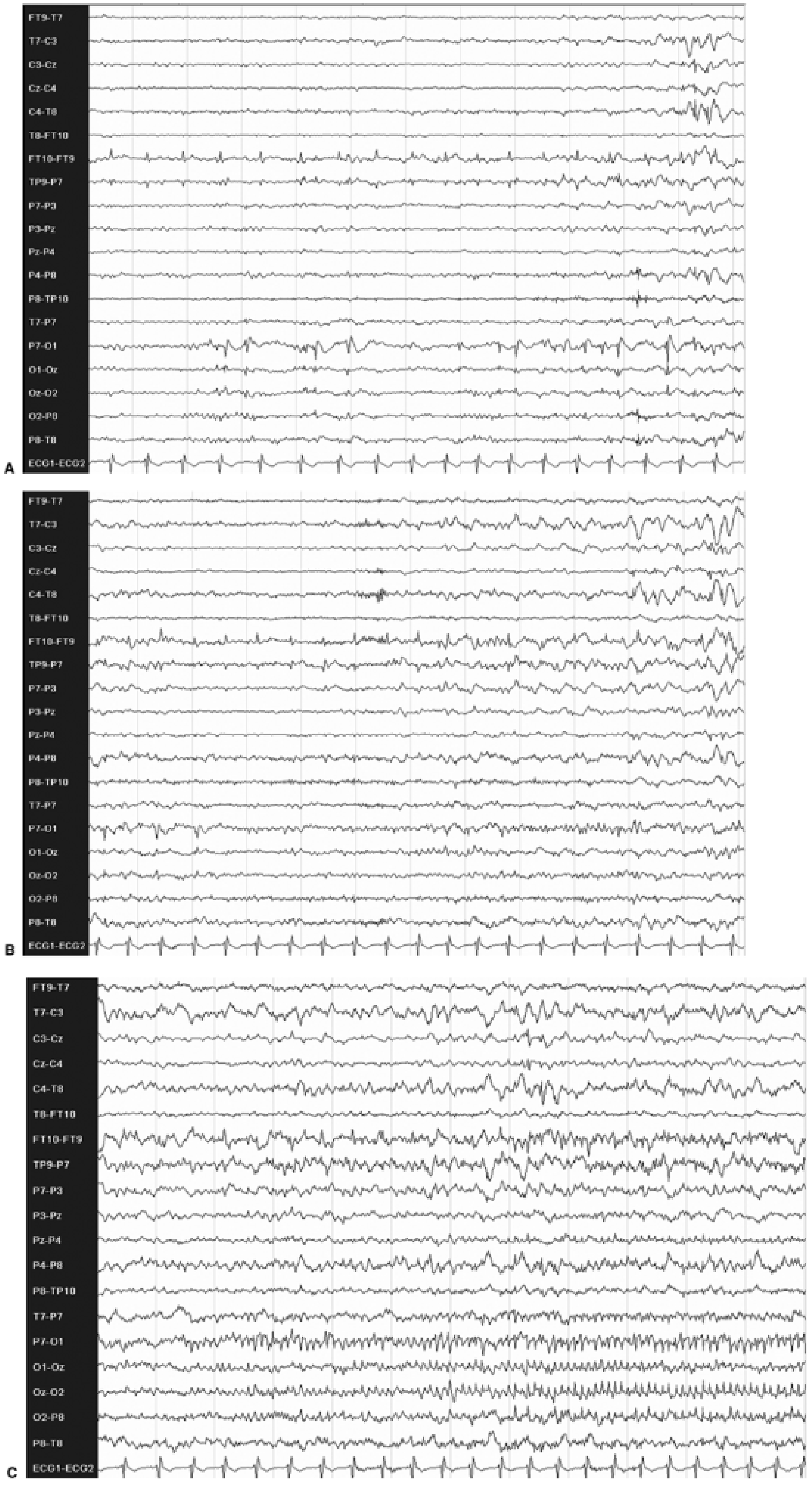
FT9-T7
T7-C3
C3-Cz
Cz-C4
C4-T8
T8-FT10
FT10-FT9
TP9-P7
P7-P3
P3-Pz
Pz-P4
P4-P8
P8-TP10
T7-P7
P7-O1
O1-Oz
Oz-O2
O2-P8
P8-T8
ECG1-ECG2
A
FT9-T7
T7-C3
C3-Cz
Cz-C4
C4-T8
T8-FT10
FT10-FT9
TP9-P7
P7-P3
P3-Pz
Pz-P4
P4-P8
P8-TP10
T7-P7
P7-O1
O1-Oz
Oz-O2
O2-P8
P8-T8
ECG1-ECG2
B
FT9-T7
T7-C3
C3-Cz
Cz-C4
C4-T8
T8-FT10
FT10-FT9
TP9-P7
P7-P3
P3-Pz
Pz-P4
P4-P8
P8-TP10
T7-P7
P7-O1
O1-Oz
Oz-O2
O2-P8
P8-T8
ECG1-ECG2
C

FIGURE 3. A: Same patient as in FIGURE 2, 16 seconds after ictal onset showing the electroencephalographic onset of a left occipital seizure. Patient reported seeing flashing lights to his mother prior to this time. **B:** Left occipital seizure 28 seconds after clinical onset showing O1 spikes and later rhythmic fast activity. **C:** Same seizure, 40 seconds after clinical onset. Note the rhythmic sharp waves maximally over the left occipital region. The seizure subsequently spread and secondarily generalized, not ending until 88 seconds after clinical onset.

Simple sensory visual seizures' semiology includes positive symptoms and unilateral or bilateral negative symptoms.[49,101] Seizures of the calcarine cortex produce elementary visual hallucinations such as flashing or flickering lights, spots, colored lights, weaving patterns, zigzag lights, or visual field deficits such as scotoma or ictal amaurosis.[85,100,101,124] Other seizure symptoms attributed to the occipital lobe include eye movement sensations, sensations of object movement, ictal nystagmus, eye deviation, early forced blinking, and inversion of the visual field.[57,93,101,124] Some cases with autoscopic hallucinations where a person sees him- or herself without a mirror may be due to epilepsy.[63,100] Eye movements can complicate the clinical picture; for example, if a patient sees a bright light, he or she may look toward that light and yet the light continues to move away as his or her eyes deviate, giving a sensation of movement. Nystagmus may also occur and complicate the symptomatology. The patient may see colored lights. Negative symptoms can include loss of a visual field or quadrant; some patients complain of transient blindness. Ictal blindness probably results from seizure spread to the contralateral occipital lobe.[9] The visual symptoms often occur in areas of scotoma or other visual field defect.[58,100] While the simplest visual phenomena probably relate to involvement of the calcarine cortex,

adjacent areas may also participate, and occasionally patients with posterior temporal lesions or parietal lesions may report a visual aura with or without other disturbances. Formed or complex visual hallucinations, including remembered scenes[95] or distortions such as micropsia, macropsia, or changes in object shape, and blindness or hemianopia probably originate in the visual association cortex or adjacent parietal or temporal lobe[100] and are more often seen from the right or nondominant posterior temporal region.[87]

Auditory seizures were reported by Holmes as early as 1927.[46] Penfield and Kristiansen found only three patients, suggesting that this condition is rare.[86] The auditory symptoms can occur without dizziness. Certainly more complicated auditory hallucinations can occur, such as hearing words or music, but these seizures usually are classified as psychic, rather than just as sensory seizures, because of accompanying experiential phenomena. Simple sounds such as buzzing, drumming, or single tones, often contralateral, are typical of seizures from the auditory cortex.[85] One localizing sign noted occasionally with an auditory seizure consists of plugging an ear or placing the hand over the ear. This seems to correlate with an auditory aura that originates contralateral to the plugged ear in the auditory cortex.[25]

Simple partial olfactory sensory seizures (uncinate seizures) are relatively infrequent considering the large number of patients with temporal lobe epilepsy seen at most centers. These seizures may originate from the orbitofrontal cortex as well as the mesial temporal region. Howe and Gibson reported that there is not an increased incidence of tumors in patients with olfactory aura,[48] contrary to reports in other series (see reference 122 for review). Olfactory symptoms have also been reported in occipital- or central-area epilepsy by King and Ajmone-Marsan,[55] but seizure spread may explain at least some of the more unusual localizations. The odor is often but not exclusively unpleasant or disagreeable.[28,85,122] Daly described two types of olfactory phenomena. Hallucinations may be crude or elaborate with other sensory modalities involved, while illusions distort or alter the character of normal olfactory stimuli. Illusions were also noted interictally or postictally.[28]

Gustatory seizures are usually associated with temporal lobe epilepsy, often due to tumors. Daly reported that the sensations, though often unpleasant, can be acidic, bitter, salty, or sweet. Often a metallic taste is experienced.[28,29] The taste of bile or cigarette smoke has been reported.[43] Penfield and Jasper believed that gustatory symptoms result from seizures originating in or near the insula,[85] although Bornstein believed that the parietal operculum may also produce these seizures.[15] Rosetti et al. reported a case with dysgeusia and contralateral sensory symptoms from the insula in a case well documented with subdural ictal EEG recordings.[97] Hausser-Hauw and Bancaud reviewed their experience with gustatory hallucinations. Seizures originated in the parietal and temporal lobes in 20 of 30 patients with adequate ictal localization. Electrical stimulation of the parietal and/or rolandic operculum produced gustatory hallucinations and spontaneous seizures produced symptoms by spread to the opercular region.[43]

Seizures with vestibular symptoms, or vertigo, when isolated, are notoriously difficult to diagnose since these patients are often initially evaluated and treated for peripheral vestibular dysfunction. Symptoms include true vertigo, vague dizziness, or unsteadiness, with spinning most common.[56,85,86,105] Smith's study of 120 cases described rotation around the vertical or sagittal axis but not the coronal axis. Horizontal and vertical movements and also a sense of body or room tilting were described.[105] Lesions have been reported near the temporal parietal occipital junction as well as the superior temporal gyrus by Penfield and Kristiansen,[86] and Eviatar and Eviatar[37] have shown vertiginous symptoms in patients with frontal lobe epilepsy. Kogeorgos et al. found that 7 of 30 cases also had generalized tonicâ€"clonic seizures and 15 of 30 had absencelike episodes, while only two had auditory hallucinations with vertigo.[56]

Postictally, a variety of neurologic deficits can occur analogously to the classical Todd paralysis or postictal amaurosis or visual field deficits.[34,101] Patients with central-area epilepsy may have sensory deficits postictally that gradually improve, and these may only affect higher cortical sensory functions, such as graphesthesia or two-point discrimination. Olfactory sensitivity decreases postictally for several hours.[122] A severe seizure is not necessary to produce Todd paralysis and the process probably involves active inhibition of function rather than neuronal exhaustion.[34] Holmes found prominent postictal impairment infrequently in children with simple partial seizures.[47]

Electroencephalographic Findings and Clinical Correlations

Since sensory seizures can originate in a variety of brain regions, it is not surprising that a variety of interictal EEG abnormalities can be seen (Figs. 1, 2, and 3). Interictal changes could include changes in amplitude or frequency (e.g., focal slowing), particularly if there is a known structural lesion. Focal fast activity is less commonly seen with lesions. Interictal spikes may occur, but should be interpreted cautiously.

Blume et al. reported that 4 of 44 focal epilepsy cases that localized with ictal EEG had ictal onset clearly distant from the area of principal interictal spiking.[14] Temporal lobe spiking can occur in cingulate, frontal, parietal, and occipital lobe epilepsy.[107] Some authors report that ictal patterns are occasionally difficult to interpret in patients with seizures originating in the parietal or occipital region.[123,124] This is certainly true when seizures rapidly generalize and obscure the EEG record or muscle and movement artifact prevail. However, it is also recognized that some patients will have well-defined interictal spikes or ictal onsets from the occipital,[49,69] parietal, or central area[72] while clinical symptoms are recorded. Activation procedures can increase focal spiking and occipital spikes may be enhanced by eye closure or darkness.[69] Kogeorgos et al. found 28 of 30 patients with epileptic dizziness had abnormal interictal EEG, and localization was in the posterior temporal lobe unilaterally or bilaterally with sharp waves or focal slowing.[56]

Devinsky et al. studied the prevalence of scalp EEG changes in patients with simple partial seizures and found that when sensory symptoms alone predominate, only 15% of patients have EEG changes, whereas if motor symptoms are present, 33% will have EEG changes.[30] However, Bare et al. found that extra scalp electrodes improved the EEG yield in sensory seizures to 27%.[8] Sperling et al. reported that EEG changes may be absent in patients with simple partial seizures in presumed temporal lobe epilepsy when recording with bitemporal depth electrodes, and even in patients where postoperative seizure outcome was excellent.[108] The limited neocortical coverage with bitemporal depth electrodes may miss simple partial seizure ictal patterns from neocortex.

Kaibara and Blume studied postictal EEG changes.[53] Thirty-seven percent of cases had polymorphic delta, 29% had attenuation of background, 31% had immediate return to normal background, and 25% had spike activation. Some patients had more than one postictal pattern. All 51 patients in the study had focal seizures. The changes seen could be prolonged. When postictal EEG changes occur, one may appreciate postictal spiking or slowing that was not evident before the seizure occurred, and these findings may have some localizing value.

Diagnostic Considerations

As with any focal epilepsy, the history from the patient or reliable observer is very important for proper diagnosis. It may be helpful to ask the patient to watch for certain symptoms during subsequent seizures so that a more detailed description can be obtained later. Onset, evolution, postictal features, postictal deficits, patterns of occurrence, and precipitating factors should be thoroughly explored. The stereotypic nature of a seizure is also helpful in confirming a diagnosis of epilepsy.

MRI and routine EEG will often support a diagnosis of epilepsy, but negative initial MRI studies may require alternative MRI scanning protocols tailored for specific clinical situations such as cortical dysplasia or other neocortical lesions. Initially, nondiagnostic EEG studies should be repeated with prolonged recordings, or with sleep and other appropriate activation procedures. V-EEG monitoring may be quite helpful in patients when the diagnosis of epilepsy is uncertain or when seizures are medically intractable.[62] Other medical or neurologic disorders can result in epilepsy and should be considered during the evaluation process. Several genetic forms of focal epilepsy have been characterized, including autosomal dominant partial epilepsy with auditory features,[80] so it is likely that commercial testing for these syndromes will become available.

Differential Diagnosis

As alluded to earlier, pure sensory seizures can occasionally be confused with other nonepileptic conditions, such as cerebrovascular disease or psychiatric disorders.[61,121] Sensory symptoms due to ophthalmologic, otolaryngologic, or vestibulocochlear disease or to peripheral neuropathy need to be excluded. A thorough evaluation is warranted to avoid missing a more serious medical problem that is leading to the symptoms.

Specific Syndromes Incorporating the Seizure Type as an Integral Feature

In the 1989 proposed classification of the epilepsies,[27] one can identify a variety of epilepsy syndromes in which sensory seizures may occur; for example, in benign childhood epilepsy with centrotemporal spikes, sensory symptoms may be noted when partial seizures occur.[64] Seizures involving the central area may exhibit somatosensory symptomatology. Seizures of the temporal lobe can present with auditory or vertiginous sensations, as well as olfactory sensations.

The International Classification does not significantly address the issue of parietal lobe epilepsies. Seizures are clinically diverse and do not always include sensory auras.[123] Recently, Ho et al., using ictal single photon emission computed tomography (SPECT) and MRI, have described an anterior parietal syndrome with sensory symptomatology being quite prominent, whereas a more posterior parietal syndrome was characterized by psychoparetic complex partial seizures.[45]

Occipital lobe epilepsies can be divided into those with symptoms that are supracalcarine or infracalcarine, depending on the location of the visual hallucinations. Depth electrode studies have documented specific seizure spread patterns. Infracalcarine seizures, for example, more often manifest with a temporal lobe seizure spread pattern, whereas supracalcarine occipital lobe seizures may spread to the parietal and central area producing focal motor or even generalized seizure activity.[7,112] Not all occipital epilepsies produce appropriate visual auras.[68,124] Williamson et al. reported that 88% of their series of 25 occipital epilepsy patients had visual symptoms,[124] while only 73% of the Montreal series of 42 patients reported by Salanova et al. had a visual aura.[101] Childhood epilepsy with occipital paroxysms and the syndrome of migraine and seizures are often manifested by seizures that have visual symptomatology, simple or more complex.[27,39,78]

Some reflex epilepsies are associated with partial seizures rather than generalized seizures. Partial seizures of various

types are reportedly induced by startle, somatosensory input, proprioception, music, sounds, voices, hot water immersion, eating, reading, and other language functions.[94] Simple sensory seizures are infrequent manifestations of reflex epilepsy and usually develop after similar seizures develop spontaneously. Ritaccio believed that this represents postafferential facilitation of a preexisting condition.[94] Reading epilepsy can have seizures with a sensation of jaw movement, though often jaw clonic movements predominate.[94] Sutherling reported sensorimotor seizures triggered by music.[111] Caloric vestibular stimulation can produce temporal lobe seizures with auras of tinnitus and vertigo.[10,20] Ricci and Vigevano described stroboscopic provocation of occipital seizures with simple visual hallucinations in four cases and complex hallucinations in one patient;[92] however, most patients with photosensitive epilepsy have generalized seizures.[17,94] Brinciotti et al. found that pattern (checks or stripes)-sensitive seizures were more often associated with localization-related epilepsies.[17] Duncan et al. reported a case with gaze-evoked seizures in nonketotic hyperglycemia.[32] Reder and Wright described a 13-year-old boy whose seizures included ictal sensory loss in one arm provoked by using cutlery while eating. Accidental finger amputation resulted in seizure control.[91]

A wide variety of childhood epilepsy syndromes may exhibit simple sensory seizures, though motor seizures dominate the clinical picture. For example, cortical dysplasia can cause simple partial seizures with motor symptomatology that is extremely resistant to medical therapy.[81] Just as with motor seizures, status epileptics may present with sensory symptomatology. Chronic focal encephalitis typically presents with epilepsia partialis continua in association with unilateral progressive cortical atrophy.[5] Mitochondrial encephalopathy with lactic acidosis and strokelike episodes (MELAS)[74] has a similar, but more acute presentation. Epilepsia partialis continua is common in children with Alper disease[16] and focal cerebral vasculitis. In all these syndromes, sensory seizures, if present, are often relegated to a minor role in the complete clinical syndrome.

Responses to Treatment

A thorough discussion of medical and surgical management of epilepsy is beyond the scope of this chapter. However, if the epilepsy syndrome is focal, drugs used for partial seizures should be used first. These include carbamazepine, phenytoin, gabapentin, lamotrigine, topiramate, tiagabine, oxcarbazepine, levetiracetam, zonisamide, pregabalin, primidone, and phenobarbital. In suspected cases of pure sensory simple partial seizures without EEG changes, a blind trial of antiepileptic drugs may support the diagnosis;[127] however, a definitive treatment end-point is necessary to avoid prolonged unnecessary therapy.

The success of pharmacotherapy for simple sensory seizures is not well described in the literature, though some patients do respond well to medical therapy. At times, more severe seizure types will be eliminated by antiepileptic drugs but simple sensory seizures will persist as auras with minimal disability. Often patients will choose occasional auras over antiepileptic drug toxicity when higher doses are tried. Still, some patients claim severe disability from sensory seizures, resulting in medication changes and dose escalation until intolerable dose-related toxicity develops. These cases may benefit from counseling, treatment of comorbid underlying depression, and consideration for a surgical procedure.

The benign childhood epilepsy syndromes may resolve spontaneously, so lifelong therapy is unwarranted. When seizures persist in benign focal epilepsies, particularly benign rolandic epilepsy, one should consider alternative diagnoses.

If neuroimaging studies have shown specific lesions, such as tumor or vascular malformation, particularly when there is a risk of progression, specific surgical or nonsurgical therapy may help seizures, particularly in cases where the lesion is adjacent to important sensory cortex, rather than in the functional zone.

Surgery for patients with sensory seizures should proceed with caution to avoid significant postoperative deficits. Sufficient disability from seizures should exist. For example, careful thought should be given before suggesting surgery in an individual with sensory seizures alone, unless an underlying lesion was serious enough to require surgical intervention in any case. Careful mapping of ictal foci and cerebral function may be needed to plan a safe resection.[12,22,42,71,75,76,77,79,96,113,114,119,125] Functional MRI offers hope for noninvasive functional mapping.[50] Subdural electrodes[66] are preferred by most epilepsy centers because of potentially better localization and less risk of hemorrhage compared to depth electrodes[113,114] or epidural electrodes.[42] Still, selected cases with subcortical lesions, such as a cortical dysplasia case reported by Privitera et al., are better evaluated with intracerebral depth electrodes.[90] Subdural electrodes are more convenient for functional mapping by direct cortical stimulation or with evoked responses for various sensory modalities. Additionally, the use of subdural electrode recordings can help with decisions on the need for intraoperative electrocorticography and cortical mapping during awake craniotomies.

The role of magnetoencephalography is controversial, since the technique is better for interictal epileptiform discharge localization. Magnetoencephalography data should be considered complementary to scalp EEG. No randomized controlled studies exist to show superior surgical outcomes with the use of magnetoencephalography.

Subpial transection gained favor as more reports appeared in the literature demonstrating safety and efficacy.[31,76,77,104] Theoretically, subpial transection can spare sensory cortex and function, yet still help relieve seizures. However, deficits have been reported after this technique and a pathologic study suggested that subpial transection may produce small confluent lesions rather than disconnection.[54]

Lesionectomy can also decrease risks of sensory deficits and help seizures long term in about half of the cases.[23,24] Gamma Knife radiosurgery may be appropriate in selected patients.[44]

At times, resection of primary cortex is needed for seizure control and the sensory deficits may be acceptable to the patient. It is possible to remove portions of primary sensory or motor neocortex without producing a lasting neurologic deficit.[73] Lehman et al. reported that the disability was quite limited with resection of the sensorimotor face region in the lower central area.[59]

With reflex seizures, avoidance of the stimulus can play a role in management. In some patients, biofeedback or sensory input may also reduce seizures, as in Efron's remarkable case.[33] Aird reviewed alternative epilepsy therapies in 500 refractory patients with various forms of epilepsy and found that 43% benefited from lifestyle modification in areas such as hydration, central nervous system excitation, sleep habits, and anxiety.[3]

Safety concerns should also be considered if the seizures produce any disability. While most simple partial seizures with sensory symptomatology alone may not be very disabling, many have complex partial or secondarily generalized seizures also. Safety concerns are justified if a patient has a job where sudden, complete or partial loss of vision or disturbance of sensation could result in injury. Each case must be assessed individually for safety concerns.

Summary and Conclusions

Simple sensory seizures can occur in a variety of epileptic syndromes. Many patients have other seizure types that make

the diagnosis more obvious. Caution is recommended in those patients with subjective sensory symptoms alone, particularly without supportive EEG or neuroimaging findings. The chances for misdiagnosis are high, and these patients may require a more thorough investigation before nonepileptic, medical, or psychiatric conditions are diagnosed.

The epidemiology of simple partial seizures is incomplete. Evidently, these seizures are seen in a minority of patients with epilepsy. Identifying patients with simple sensory seizures can help localize structural lesions. Prolonged clinical manifestations are occasionally reported by patients. Postictal neurologic abnormalities should be sought in the history and examination. Scalp EEG, while not highly sensitive, can be diagnostic. Treatment is similar to treatment in other localization-related epilepsies.

The possibility of developing treatment strategies that could specifically inactivate seizures by altering sensory function transiently requires further exploration. Additionally, patients with well-defined sensory phenomena may be good candidates for studying treatment methods that rely on advance warning of an impending seizure. Since consciousness is maintained, at least during the patient's simple partial seizure, these patients would make ideal study subjects.

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Chapter 46

Limbic Seizures

Jerome Engel Jr.

Peter D. Williamson

Introduction

In 1970, after a 4-year effort, the Commission on Classification and Terminology of the International League Against Epilepsy (ILAE) presented a scheme for classifying epileptic seizures, in which the term â€œpartial seizures with complex symptomatologyâ€ was introduced.[54] This term was used to denote a type of seizure that was clearly described almost 100 years earlier by Hughlings Jackson,[74] who noted a relationship between lesions in the mesial temporal lobe and seizures characterized by olfactory hallucinations and a â€œdreamy state,â€ which he referred to as â€œuncinate fits.â€ Since then, myriad signs and symptoms, both psychic and motor, have been identified with this seizure type. In 1937, Gibbs et al.[56] proposed the term â€œpsychomotorâ€ to define these phenomena. Subsequently, the Montreal school, through their pioneering invasive recording and surgical treatment efforts, repeatedly demonstrated the clear association between psychomotor seizures and temporal lobe pathology, changing the terminology to â€œtemporal lobe seizures,â€ as part of a condition known as *temporal lobe epilepsy* (TLE).[75,104] Because the limbic system primarily involves mesial temporal lobe structures, the specific condition is now known as *mesial temporal lobe epilepsy* (MTLE).[140]

The advent of long-term video electroencephalographic (video-EEG) recording allowed routine electroclinical correlation and documentation of habitual seizures, permitting detailed analysis of ictal semiology. It became recognized that not all seizures of temporal lobe origin have psychomotor features; some seizures have psychic symptoms without motor signs, and others have motor signs without psychic symptoms; seizures originating outside the temporal lobe can propagate into limbic areas, producing ictal events that are indistinguishable from temporal lobe onset seizures; and seizures originating outside the temporal lobe could have complex symptomatology without involving temporal limbic structures. Whereas the 1970 International Classification essentially used the term *complex partial seizure* (CPS) as synonymous with â€œpsychomotor seizureâ€ or â€œtemporal lobe seizure,â€[54] the revised 1981 Classification[21] chose to define terms purely on the basis of phenomenology and to avoid any implication of anatomic substrate. Consequently, CPSs were defined as partial seizures associated with impairment of consciousness, as opposed to *simple partial seizures* (SPSs), which are partial seizures with preserved consciousness.

Now that more is known about the pathophysiologic mechanisms and anatomic substrates of various epileptic seizure types, it is recognized that classical temporal lobe seizures, beginning in mesial temporal limbic structures, can be simple or complex partial, whereas ictal impairment of consciousness can occur during partial seizures that arise from the neocortex and never involve mesial temporal limbic structures.[147] Because modern electrophysiologic and neuroimaging technology now permit accurate anatomic localization of ictal events in many patients under evaluation for surgical treatment, it has become common to distinguish between limbic partial seizures and neocortical partial seizures based on their characteristic ictal semiology. Consequently, the ILAE has now recommended that SPS and CPS not be used in a future classification, but have accepted the term â€œlimbic seizuresâ€ to describe ictal clinical manifestations of epileptic activity in mesial temporal limbic areas and their efferent projections.[37,39]

Definitions

Although the current 1981 International Classification of Epileptic Seizures appeared to satisfy many of the needs of the epileptology community, confusion and lack of acceptance persisted among some practicing neurologists because highly complicated and sometimes bizarre seizures in which consciousness was not impaired were, by definition, simple partial seizures. Conversely, patients with partial seizures who have only a motor arrest with impaired consciousness, by definition, have CPS, which can be mislabeled as petit mal. Finally, although the term â€œcomplex partial seizuresâ€ has been universally accepted, it continues to be abused by reversal to the meaningless term â€œpartial complex seizure.â€[3,44,71,72,103]

Defining consciousness is difficult.[11,57,58] For example, seizures can present with a relatively pure reversible Wernicke aphasia. In this situation, the patient would appear alert and awake. Speech would be jargon, and commands would not be followed. On the other hand, patients can present with seizures consisting of pure word muteness or aphemia,[146] during which the patient would be able to follow commands and perform all other language-related functions, but simply could not speak. Are these examples of CPS or SPS? The latter should be considered simple partial seizures, but the former could be difficult to classify when impairment of receptive language function complicates testing consciousness. Amnesia for the ictal event is another criterion that can be used to define CPS.[33] Amnesia, however, whether complete or partial, can be as difficult to document as altered consciousness. Careful testing by trained observers during and after seizures is the only method that can define these issues,[141] but in practice, this has not been standardized, nor is it universally performed in all centers where seizures are recorded. Although recognition of whether consciousness is impaired is of clinical importance in individual patients, the ILAE has recommended that this difficult-to-assess clinical manifestation not be used as a criterion for classifying seizure types in the future.[37,39] For purposes of describing the ictal manifestation of cognitive dysfunction, the ILAE has now recommended the term â€œdyscognitive.â€[11]

The term â€œlimbic seizureâ€ is used in this chapter to describe ictal events in which the clinical manifestations result from epileptic activity within the mesial temporal limbic network and structures to which it projects. Limbic seizures can be initiated by epileptogenic regions within this limbic network, or from epileptogenic regions in any neocortical area that projects to it and gives rise to the same clinical manifestations. Epileptic activity will preferentially propagate to mesial temporal limbic structures from the temporal neocortex, orbital frontal cortex, mesial frontal regions such as the anterior cingulate, and

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occipital cortex ventral to the calcarine fissure. Certain sensory, psychic, and autonomic manifestations of limbic seizures do not usually involve impairment of consciousness, and so would currently be classified as SPS.

Epidemiology

Most prevalence studies estimate that approximately 60% of the adult population with epilepsy and 40% to 50% of children with epilepsy have focal seizures.[18,24,25,50,55,68,79,80,89,103] The earlier Rochester study by Hauser and Kurland reported that CPS were the most prevalent of any single type of seizure, constituting 42% of focal seizures and 26% of all seizures. Another earlier study reported that 40% of patients with epilepsy had CPS as the predominant seizure type.[55] Epidemiologic studies from developing countries usually report much lower percentages of patients with CPS.[2,28,47,64,77,118,126] The reasons for this discrepancy are not entirely clear but probably reflect such factors as diminished diagnostic accuracy and different etiologies. However, the inherent difficulties of seizure classification exist at any level of societal development.[92,102,132]

CPS are not all limbic seizures and not all limbic seizures are CPS; therefore, attempts to further subclassify focal seizures based on limbic system involvement are at best an estimate. By necessity, such approximations come from epilepsy surgery centers, where ictal substrates are most thoroughly and precisely evaluated and where surgical results give credence to the localization of seizure origin. This introduces an undeniable referral bias that cannot be avoided. Of those patients referred for surgical consideration, patients with limbic seizures of temporal lobe origin are by far the most common, constituting approximately 70% of the referrals.[138,151] Of the other 30%, approximately two thirds are patients with different varieties of frontal lobe seizures, with the remaining 10% divided among seizures originating in other lobes of the brain.[107,139,143,150] Some of these patients also have seizures generated by the limbic system, even though they do not originate in limbic structures.

Many pathologic conditions, idiopathic as well as symptomatic, primarily involving limbic structures or occurring in distant neocortex, can be associated with limbic seizures as the predominant ictal features. These conditions are discussed in detail in Chapters 246 and 247. The most common pathologic substrate associated with limbic seizures is hippocampal sclerosis (HS) (Chapter 13), which can now be detected in most patients using high-resolution magnetic resonance imaging (MRI).[73,83] Another indication of the prevalence of limbic seizures, therefore, can be derived from two large longitudinal outpatient studies, one in Paris that included tertiary referrals,[116] and the other at a primary clinic in Glasgow.[128] In the Paris study, half the patients had a diagnosis of TLE and, in both studies, approximately a quarter of the patients had hippocampal atrophy documented by MRI. In both studies, the seizures in patients with hippocampal atrophy were the most refractory. In the Paris study, only 11% were seizure-free in the previous year, and with dual pathology (hippocampal atrophy plus another MRI abnormality), only 3% were seizure free in the preceding year.[117] Although there is no way to accurately assess the true prevalence of limbic seizures and the burden of disability due to epilepsy that limbic seizures represent, it is reasonable to assume that they are the most common, and are certainly among the most refractory epileptic seizure types.

Anatomic Pathways and Pathophysiology

Because patients with TLE are the most common candidates for surgical treatment,[45,46] and often require invasive V-EEG monitoring, many more limbic seizures have been explored with stereotactically implanted depth electrodes in TLE than any other seizure type. It is clear from these recordings that ictal activity that remains confined to hippocampus and parahippocampal structures can have no clinical manifestations at all,[125] and that the classical signs and symptoms of limbic ictal events reflect propagation, both ipsilaterally and contralaterally, to frontal and temporal neocortex, insula, hypothalamus, basal ganglia, and other subcortical structures. Although limbic and neocortical propagation patterns have been explored with depth electrodes,[81,85,87,124] and thalamic and basal ganglia involvement has been inferred from ictal behavior as well as structural and functional neuroimaging,[8,13,70,101] the contribution of other subcortical structures to the typical signs and symptoms of limbic seizures in the human cannot be directly studied.

Both animal and human investigations suggest that the pathophysiologic mechanisms responsible for seizure initiation in the hippocampus, and perhaps parahippocampal structures, may be different from those of seizures originating in neocortex;[16,114,133] this is discussed in Chapter 41.

The limbic anatomy and physiology responsible for the elaboration of clinical signs and symptoms of limbic seizures are described in Chapter 30. As previously mentioned, ictal discharges restricted to hippocampus alone are often devoid of noticeable clinical manifestations.[125] Ictal symptoms that occur in clear consciousnessâ€"the typical limbic aurasâ€"result from usually ipsilateral projections. Autonomic symptoms and emotions such as fear most likely reflect propagation to hypothalamus and insula, whereas complex multimodal sensory psychic experiences result from neocortical projection, particularly the temporal parietal occipital junction.[59,129] Limbic structures responsible for memory, as well as taste and smell appreciation, give rise to dysmnesias and olfactory and gustatory auras. More complex motor symptomatology, characteristic of limbic automatisms, however, is almost always associated with impaired consciousness and usually involves contralateral propagation. Bilateral hippocampal involvement accounts for ictal amnesia, although unilateral ictal discharge can produce amnesia when the contralateral hippocampus is severely dysfunctional. Oroalimentary automatisms derive from the temporal and frontal operculum but the specific origin of more complicated gestural automatisms has not been clearly defined.

Studies in animal models of MTLE with HS reveal strong inhibitory mechanisms within the hippocampus that suppress contralateral propagation.[91] A similar resistance to contralateral propagation exists in patients, as evidenced by the common observation that depth-recorded limbic ictal discharges remain unilateral for long periods of time and may never involve the contralateral side.[85,87] The existence of intrinsic mechanisms that permit ictal discharges within the limbic system to remain unilateral for extended periods of time without propagation likely accounts for the clinical observation that auras in patients with limbic seizures of mesial temporal origin commonly occur in isolation; these patients typically experience auras that do not progress to behavioral seizures. In contrast, neocortical auras rarely occur in isolation because of the propensity for neocortical discharges to rapidly project contralaterally across the corpus callosum. When contralateral propagation occurs, it is usually indirect via either temporal or frontal ipsilateral neocortex.[81,85,86,87,124] Because ictal discharges can be seen in contralateral mesial temporal limbic structures before involvement of contralateral neocortex, the route of contralateral propagation may not be callosal. Furthermore, it is not possible to explain how bilateral automatisms can occasionally occur in clear consciousness without amnesia.

The neuronal networks responsible for the manifestations of limbic seizures involve neocortical and subcortical areas.

Extensive extrahippocampal cortical and subcortical gray matter atrophy may be apparent on MRI,[8,13] and positron emission tomography (PET) often reveals unilateral thalamic and basal ganglia hypometabolism ipsilateral to the side of ictal onset in patients with limbic seizures.[70] Unilateral basal ganglia hyperperfusion on single-photon emission computed tomography (SPECT) is associated with contralateral ictal dystonic posturing, suggesting that the basal ganglia are involved in this clinical behavior.[101]

Impairment of consciousness, which is a feature of bilateral limbic seizures and the hallmark of CPS, is difficult to define, and can also be difficult to document in individual patients. Consciousness is a multidimensional phenomenon. The ILAE has recommended referring to *cognition* rather than *consciousness,* and has defined *dyscognitive seizures* as involving at least two of five components of cognition: perception, attention, emotion, memory, and executive function.[11] Consequently, it is unlikely that a single pathophysiologic mechanism or anatomic substrate is responsible for dyscognitive ictal manifestations. Unilateral electrical stimulation of human limbic structures can produce signs and symptoms of limbic seizures that typically occur in clear consciousness, but impairment of consciousness does not occur in the absence of contralateral discharge.[59,66] Although this suggests that at least some dyscognitive features of limbic seizures require bilateral hippocampal or other limbic involvement in the epileptic discharge, it does not rule out the possibility that certain unilateral subcortical structures that receive preferential input from the limbic system mediate other aspects of dyscognitive behavior.[149] Accurate descriptions of the various types of cognitive dysfunction that occur during limbic seizures, and their neurobiologic basis, cannot be elucidated from research with animal models of MTLE and will require further studies in patients.

The evolution of epileptogenesis in the limbic system, as well as propagation patterns during individual limbic seizures, have been studied in detail in animals using procedures such as amygdala kindling[22,23,60,106] or chronic models of hippocampal sclerosis following status epilepticus induced by neurotoxins or electrical stimulation.[105] In these models, the limbic ictal manifestations often secondarily generalize, and in amygdala-kindled animals, once the initial stages of limbic ictal manifestations progress to involve the generalized stages of rearing and falling, subsequent stimulation almost always results in the fully developed kindled seizure.[106] In contrast, limbic seizures only relatively rarely secondarily generalize in patients, despite the fact that ictal discharges often commonly become bilateral. This could possibly be attributed to the fact that patients are treated with antiepileptic drugs (AEDs), which are much more effective at preventing secondarily generalized seizures than they are at preventing limbic ictal events, or inherent protective mechanisms could account for failure of propagation to brainstem structures responsible for more generalized ictal manifestations. The latter interpretation is consistent with the observation that some rat models of MTLE with HS (that are not treated with AEDs) continue to have frequent localized limbic seizures that only rarely progress to involve more generalized ictal semiology.[15] When limbic seizures secondarily generalize, the motor manifestations are usually asymmetrical.[93] Increasing evidence suggests that the responsible subcortical mechanisms are not exactly the same as those that give rise to primarily generalized tonicâ€“clonic seizures, which are invariably symmetrical.[76]

Recent studies provide converging evidence that the clinical expression of limbic seizures involves large neural networks with both inhibitory and excitatory functions.[5,12,34,35,135] Understanding these networks might provide new targets for AEDs.[48] Also, careful network analysis might explain some of the reasons for surgical failures in limbic epilepsy.[115] This, in turn, could lead to more effective surgical approaches.

A final consideration with respect to the ictal network responsible for the manifestations of limbic seizures concerns the unlikelihood that this will be clearly defined as a group of interrelated structures that are necessary and sufficient for limbic seizures to occur. The central nervous system is extremely redundant, and decades of animal research with limbic kindling has revealed that no forebrain lesions, including destruction of the amygdala itself,[78] can completely prevent the progression of limbic epileptogenesis.[22,23,97] Although these studies have identified specific structures that undoubtedly are important in limbic epileptogenesis, because specific lesions can delay the progression of ictal manifestations, eventually alternate pathways are found and kindling proceeds to completion. Given the fact that the human nervous system is much more complex than that of the lower animals used for kindling experiments, it is reasonable to assume that there are multiple overlapping neuronal networks capable of mediating the clinical behaviors characteristic of limbic ictal events. On the other hand, animal experiments suggest that some areas of the limbic system, apart from the hippocampus, are exquisitely epileptogenic and may be more important than others in promoting limbic epileptogenesis and epileptogenicity, such as the prepiriform, perirhinal, and entorhinal cortices.[53,67,98] In fact, a postoperative MRI study of patients who underwent amygdalohippocampectomy for MTLE demonstrated that seizure freedom is related specifically to the amount of entorhinal cortex, not hippocampus, removed.[119]

Clinical Features

Clinical features of limbic seizures encompass a rich and diverse spectrum of signs and symptoms. Some of these reflect the region of seizure origin, some reflect spread patterns, whereas others are nonspecific. Although many of the clinical characteristics of limbic seizures have been recognized for over 100 years,[63,74,130] the advent of closed-circuit video and EEG monitoring has allowed repeated detailed studies of many seizures from large numbers of patients.[61,65]

This section briefly describes the classical clinical features of limbic seizures that occur with MTLE. Limbic seizures that result from propagation of epileptic discharges originating in neocortical epileptogenic regions outside the mesial temporal lobe area often, but not always, begin with signs or symptoms that reflect the unique functioning of the cortex of origin. These variations are described in detail in Chapter 246.

Early attempts to subclassify limbic seizures based on anatomic substrates have not stood the test of time,[29,137] although they did help direct attention to different clinical manifestations. Nevertheless, it is now recognized that most limbic seizures begin in mesial temporal structures.[33,138,150] This observation, combined with specific clinical features and a distinctive hippocampal pathology, serves to define a syndrome of MTLE with HS,[140] the subject of Chapter 247. A generic description of a typical mesial temporal lobe seizure (MTLS) is included here.

Table 1 Clinical Features of Simple Autonomic Seizures

Abdominal sensations
Apnea
Arrhythmias/bradyarrhythmias
Chest pain
Cyanosis
Erythema
Flushing
Genital sensations/orgasm
Hyperventilation
Lacrimation
Miosis/mydriasis/hippus
Palpitations
Perspiration
Pilomotor excitation
Tachycardia
Urinary urgency/incontinence
Vomiting

From Liporace JD, Sperling MR. Simple autonomic seizures. In: Engel J. Jr., Pedley TA, eds. *Epilepsy: a comprehensive textbook.* Philadelphia: Lippincottâ€“Raven Publishers, 1997:549â€“555.

Table 2 Principal Ictal Psychic Phenomena

- (a) Perceptual hallucinations/illusions
    - Visual
    - Auditory
    - Olfactory
- (b) Mnemonic
    - DÃ©jÃ vu
    - Jamais vu
    - Memory recall
    - Memory gaps/amnesia
- (c) Emotional
    - Fear
    - Sadness
    - Pleasure
    - Sexual emotion
    - Emotional distress
    - Anger
- (d) Other
    - Change in reality
    - Depersonalization
    - Feeling of a presence (â€œas if someone is nearbyâ€)
    - Forced thinking
    - Distortion of body image

From Fish DR. Psychic seizures. In: Engel J. Jr., Pedley TA, eds. *Epilepsy: a comprehensive textbook.* Philadelphia: Lippincottâ€“Raven Publishers, 1997:543â€“548.

Most, but not all, MTLS begin with an aura, which is an SPS. The most common limbic aura is a visceral sensation of gastric rising, although a wide variety of autonomic signs and symptoms, complex multimodality psychic experiences, dysmnesias, emotions (fear being particularly frequent), and gustatory, olfactory, or nonspecific somatosensory symptoms occur. Clinical features of simple autonomic seizures are listed in Table 1,[88] and principal ictal psychic phenomena are listed in Table 2.[49] Olfactory and gustatory auras are typically, but not always, unpleasant. Limbic somatosensory seizures have nonspecific anatomic localization, such as tingling or paresthesias, that are bilaterally diffuse, perioral, or at the bridge of the nose. Experiential phenomena involve multiple sensory modalities as well as appropriate emotions and can be quite vivid.[59]

Sensory distortions and bizarre hallucinations are also encountered, all of which reflect propagation from mesial temporal structures to neocortex, particularly the temporal parietal occipital junction.[59,66,129] Although limbic auras can evolve from one type to another, they are almost always stereotyped, with the same static or evolving pattern appearing with each occurrence. A characteristic feature of limbic auras, when they occur, is that they occur in isolation, and they precede the typical limbic seizure with impaired consciousness and automatisms. Auras in isolation typically occur more frequently than do behavioral limbic seizures, and they can persist after surgical resection that eliminates disabling seizures.

The behavioral limbic seizure begins with impaired consciousness, widened palpebral fissures (fixed stare), and dilated pupils. Early in the seizure, oral-alimentary automatisms occur consisting of lip smacking, chewing, tooth grinding, or swallowing. Patients can continue with ongoing motor activity, react to their surroundings in a semiappropriate fashion (reactive automatisms), or develop repetitive motor behavior that is similar during each seizure in a given patient (stereotyped automatisms). Ictal head and eye deviations, tonic/dystonic postures, unilateral automatisms, and hemiparesis have lateralizing significance that is discussed further in Chapters 246 and 247. MTLSs rarely last longer than 1 to 2 minutes and have a definite postictal period of variable duration, with longer durations associated with seizure origin on the language-dominant side. Ictal automatisms can stop abruptly at the end of the ictus and the beginning of the postictal period, or they can persist for variable lengths of time into the postictal stage. Clear postictal aphasia is seen after seizures beginning in the language-dominant temporal lobe.

EEG Manifestations and Clinical Correlation

EEG findings in patients with limbic seizures are highly variable. Routine recordings often are normal or display nonspecific findings.[82] Continuous monitoring of the EEG when the patient is awake and through all stages of sleep increases the yield of abnormal findings.[30] AED reduction during continuous monitoring further increases detection of both ictal and interictal events.[65,94]

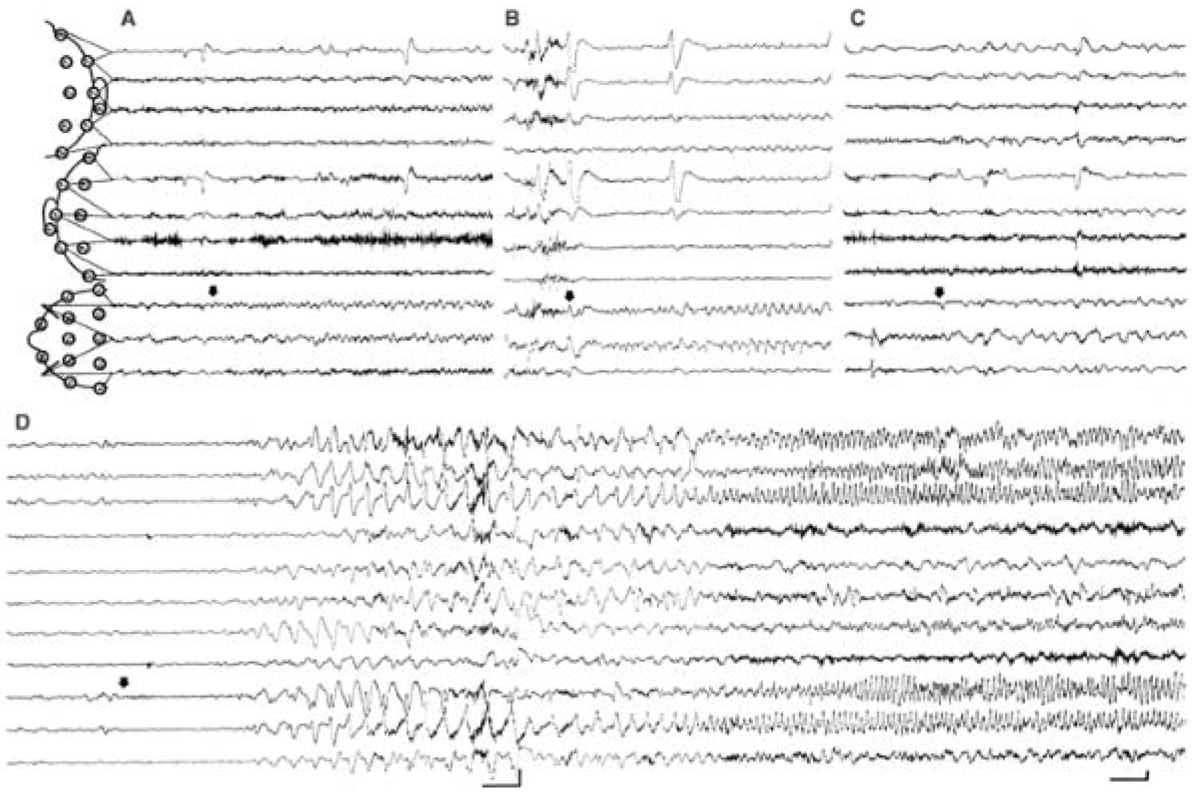

FIGURE 1. Examples of EEG telemetry-recorded ictal onsets from four patients with complex partial seizures. **A:** Low-voltage 5- to 7-c/sec rhythmic activity appears at the right sphenoidal electrode (*arrow*) 5 seconds before it is seen over the right temporal convexity. **B:** After a diffuse burst of muscle and eye movement artifact, low-voltage fast activity is recorded by the right sphenoidal electrode (*arrow*). This becomes progressively slower, and the amplitude increases; 5 seconds later, it is seen diffusely over the right hemisphere. **C:** Irregular, sharply contoured slow waves demonstrate phase reversal at the right sphenoidal electrode (*arrow*) and are reflected as low-amplitude Î´-waves, without phase reversal, over the right hemisphere. **D:** In this lateralized but not localized ictal onset, voltage suppression and low-voltage fast activity occur over the right frontotemporal area and are best seen at the right sphenoidal electrode (*arrow*). This precedes by 3 seconds the appearance of diffuse 3-c/sec spike-and-wave discharges, which are prominent from the right frontotemporal and sphenoidal derivations. After 10 seconds, this latter activity evolves into high-voltage 7-c/sec rhythmic activity, which phase reverses at the right sphenoidal electrode and laterally at the right anterior to midtemporal region. Patterns shown in **A** and **B** (initial focal onsets) and **D** (delayed focal onset) have more reliable localizing significance than the irregular Î´-pattern shown in **C**. Calibration: 1

second, 100 ÂµV. Note that sensitivity is the same for **A, B**, and **C** and the first half of **D**, but decreased to half in **D** at the first calibration mark. From Engel J Jr, Crandall PH, Rausch R. The partial epilepsies. In: Rosenberg RN, Grossman RG, Schochet S, Heinz ER, Willis WD, eds. The clinical neurosciences, Vol. 2. New York: Churchill Livingstone, 1983:1349â€“1380, with permission.

Interictal

Depth electrode studies show that hippocampal interictal spikes cannot usually be seen on scalp or sphenoidal EEG recordings unless they have propagated to neocortex. Therefore, interictal EEG abnormalities in patients with focal epilepsy do not necessarily reflect either maximum interictal spike activity, or the region of seizure origin. In a series of surgically verified patients with MTLS origin, the vast majority had interictal epileptiform abnormalities on scalp EEG monitoring.[145] The interictal abnormalities consisting of spike, sharp, and slow complexes were usually located in the anterior temporal derivations, but some were not; one third had bilateral, independent, anterotemporal, paroxysmal findings, results consistent with other studies.[4,9,20] Bilaterally synchronous temporal paroxysmal activity was conspicuously absent. Rarely occurring frontopolar sharp waves in patients with temporal lobe seizures are considered clinically insignificant.[111] There is general agreement that lateralized anterior temporal or sphenoidal interictal spikes in patients thought to have temporal lobe seizures are relatively reliable indicators of side and site of seizure origin.[4,9,10,20,82,100] Investigations of mesial versus lateral interictal spike relationships have shown latency changes in either direction.[6,127] Reconciliation of these different mesialâ€“lateral interictal findings from extracranial studies and intracranial data is difficult considering the common observations that abundant interictal paroxysmal activity occurs independently and dependently in mesial and lateral temporal structures during invasive monitoring.[120,122]

Patients with extratemporal limbic seizure origin often have unreliable interictal EEG findings. Frontal lobe onset limbic seizures can be associated with normal or nonspecific interictal EEGs.[142,147] When epileptiform abnormalities occur, they

can be bilateral or temporal.[147] Absent or temporal interictal EEG findings are common in patients with parietal and occipital lobe seizure origin.[14,17,112,144,148] Typical anterior temporal interictal spikes, therefore, do not rule out an extratemporal origin of limbic seizures.

Ictal

Limbic seizures without impairment of consciousness typically are unassociated with ictal EEG changes, although interictal spikes can disappear. This phenomenon is usually not appreciated unless interictal spikes are frequent. The classical ictal EEG onset pattern begins at the time consciousness becomes impaired and is a 5- to 7-Hz rhythmic discharge, maximal in basal electrodes over the side of seizure origin[42,43,109,145] (Fig. 1). Although correlation between simultaneous depth and sphenoidal electrode recordings revealed that this unilateral ictal-onset EEG pattern does not usually appear until the electrographic discharge in deep mesial temporal structures is bilateral, it indicates the side of hippocampal onset in 83% of seizures.[109] This is true regardless of whether the 5- to 7-Hz pattern is the initial ictal EEG change, or whether it follows another ipsilateral or bilateral ictal pattern within 30 seconds.[109] This pattern is not lateralizing, however, if the initial ictal changes occur contralaterally. Nonspecific ictal onset patterns include unilateral or bilateral slowing, rhythmic Î´-waves, loss of ongoing activity including interictal spikes, low-voltage fast, and no discernible change other than muscle artifact.

No systematic studies of ictal scalp EEG have been performed in extratemporal onset seizures. Most reports comment on the nonspecificity or paucity of ictal findings, particularly in frontal lobe seizures.[17,134,142,143,147,150,151]

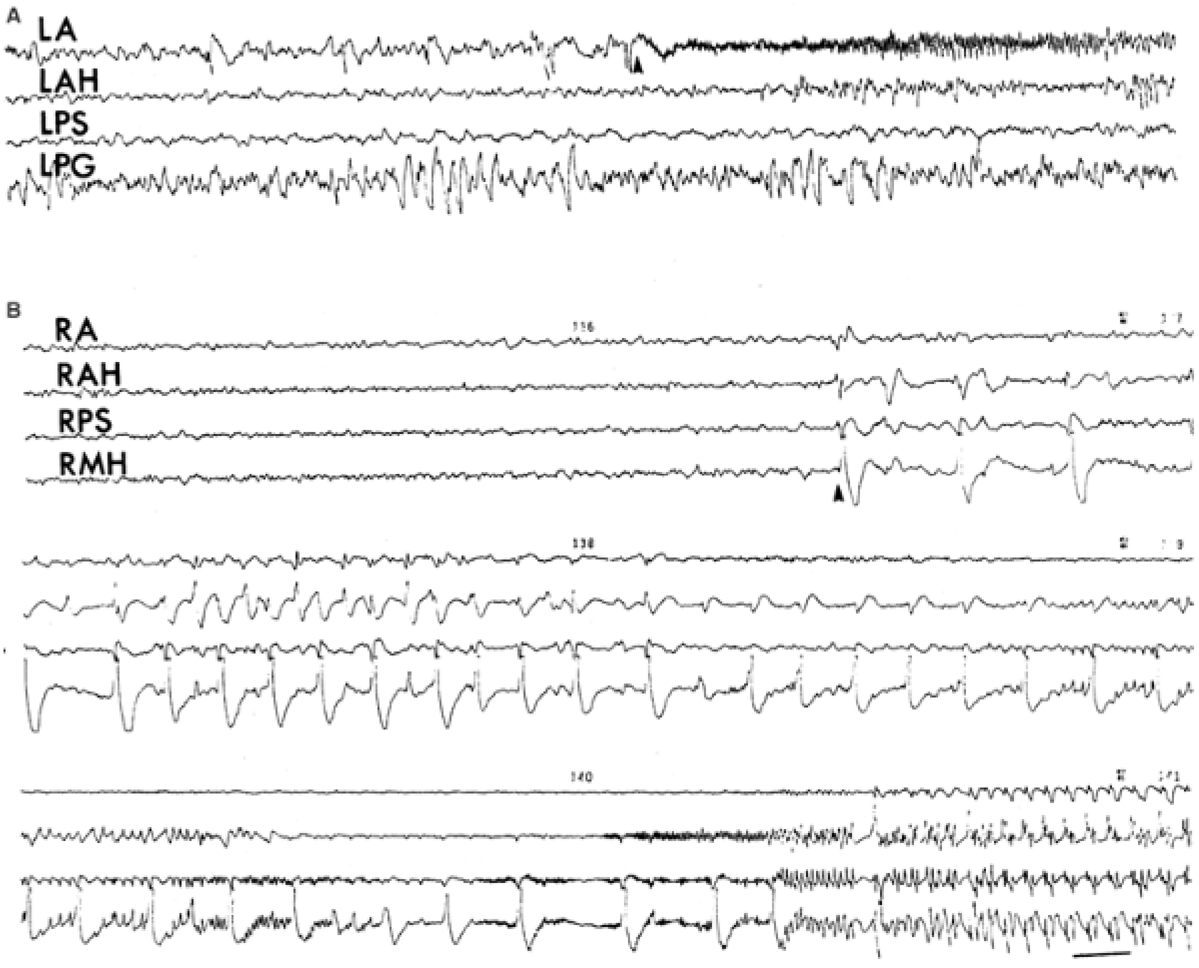

FIGURE 2. Segments of telemetry recordings from two patients showing EEG activity at selected depth electrode bipolar tips during the onset of complex partial seizures. **A:** The classic, depth electrodeâ€“recorded ictal onset consists of a buildup of low-voltage fast discharge, here beginning in a single channel (*arrow*). **B:** Three continuous segments show a more common ictal onset pattern, beginning with rhythmic, high-amplitude, sharp and slow transients (*arrow*), eventually giving way to a low-voltage fast discharge, which then evolves into higher-amplitude repetitive spikes or spikes-and-waves. *L*, left; *R*, right; *A*, amygdala; *AH*, anterior hippocampus; *MH*, midhippocampus; *PS*, presubiculum; *PG*, posterior hippocampal gyrus. Calibration 1 second. From Engel J Jr. Brain metabolism and pathophysiology of human epilepsy. In: Dichter M, ed. Mechanisms of epileptogenesis: transition to seizure. New York: Plenum Press, 1988: 1â€“15, with permission.

Postictal

Postictal EEG changes have rarely been specifically examined. In documented temporal lobe seizures, lateralized postictal slowing, when present, could be a lateralizing finding.[145] Localized interictal spiking often increases in the postictal period[62] and, in some patients, this may be the only localized EEG abnormality.

Intracranial EEG

A variety of ictal onset patterns can be recorded using depth electrodes from hippocampal and parahippocampal struc- tures;[32,34,121,131] these have implications for basic mechanisms, which are discussed in Chapter 41. Limbic seizures of hippocampal origin typically begin with hypersynchronous discharges that remain relatively restricted; they may be associated with an aura or have no associated behavioral signs or symptoms.[34,131] If this ictal activity progresses to a behavioral limbic seizure with impairment of consciousness, it typically converts to a low-voltage fast pattern before propagation to contralateral mesial temporal structures (Figs. 2 and 3).[32] Contralateral propagation, when it occurs, usually is slow (>5 seconds), whereas contralateral propagation of neocortical onset seizures is usually rapid.[85,87] MTLS can also begin with low-voltage fast activity, but this is more likely to be diffuse than focal, and could indicate that the initial site of ictal origin is not within the range of the recording elec- trodes.[32,34,131]

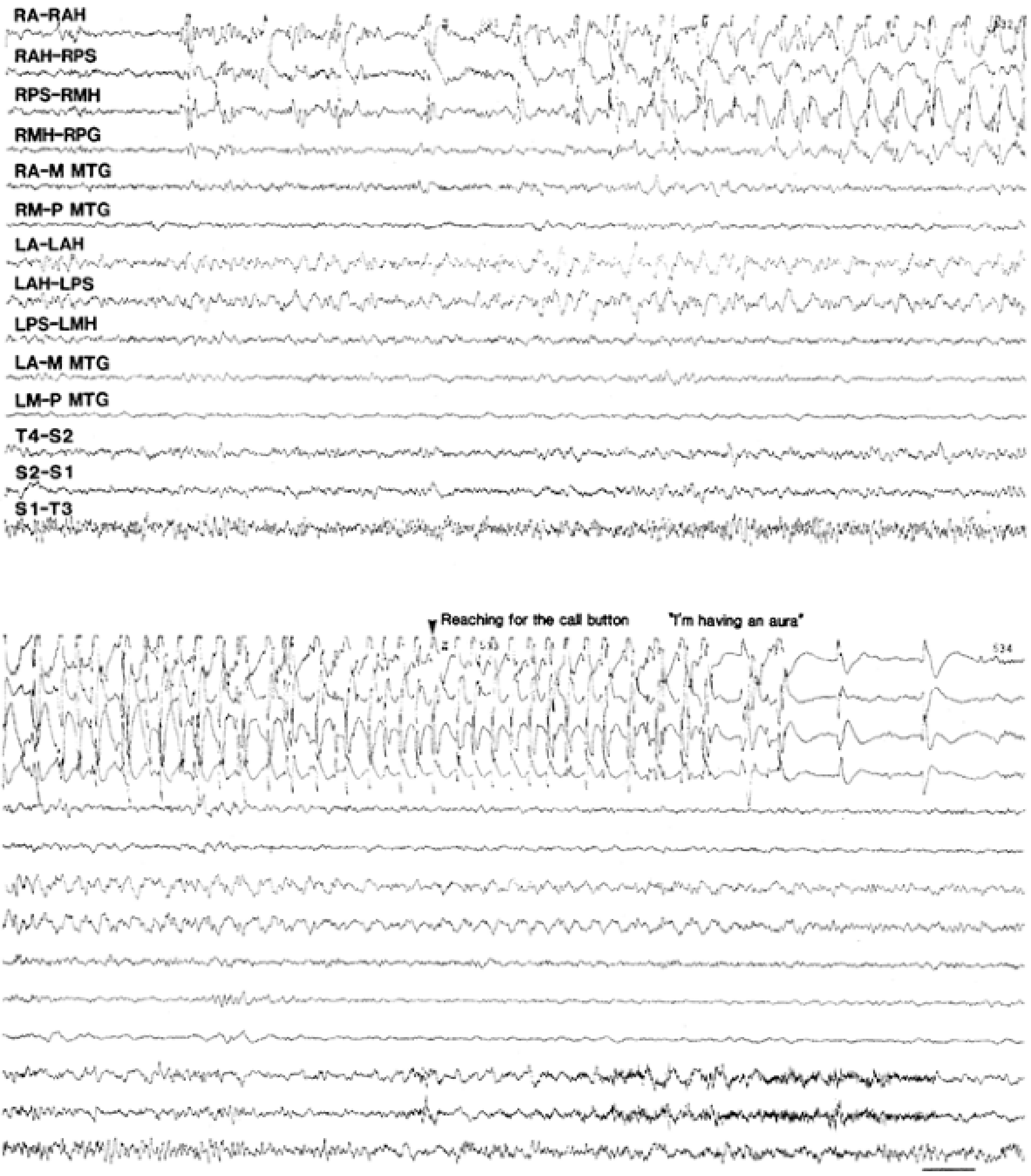

FIGURE 3. Forty continuous seconds of an EEG recorded from depth, sphenoidal, and scalp electrodes during a simple partial seizure of the right temporal lobe. Ictal onset consists of an increase in interictal spike discharges, maximal at the right anterior hippocampal electrode (*left portion of the upper panel*). After 8 to 9 seconds, these spikes become regular, eventually developing into a 3-Hz spike-and-wave pattern involving all derivations from the right mesial temporal lobe. Note that no low-voltage fast activity is seen, either initially or at any part of the ictal episode. The patient reached for the call button at the arrow, at which point regular slow activity is also seen in the left anterior hippocampus and in the right sphenoidal electrode.

The patient then indicated an aura consisting of a sensation of fear in her stomach. Depth electrode locations indicated as in Fig. 1. Superficial contacts from anterior (*A*), mid (*M*), and posterior (*P*) depth electrodes recorded from cortex of middle temporal gyrus (*MTG*). Calibration 1 sec. From Engel J Jr. Brain metabolism and pathophysiology of human epilepsy. In: Dichter M, ed. Mechanisms of epileptogenesis: transition to seizure. New York: Plenum Press, 1988: 1â€"15, with permission.

Considerable experience has been gained over many decades from ictal depth electrode recordings of limbic seizures from

patients who have been evaluated for surgical treatment.[35,38] Data are not only important for devising more effective surgical therapies (see Chapters 166,167,168,169,170,171,172,173,174,175,176,177,178,179,180,181,182,183,184,185), but for investigating the pathophysiologic mechanisms and anatomic substrates of limbic system epileptogenicity (see Chapters 30 and 41). A detailed description of indications and uses of invasive monitoring, however, is beyond the scope of this discussion. Suffice to say that these techniques are justified only during evaluation for possible resective epilepsy surgery. The distinction between limbic seizures that originate within those mesial temporal structures that are removed in a standardized anteromesial temporal resection, and those that originate

from temporal or extratemporal neocortex, can be exceedingly difficult.[1,84,120,122,123,142,143,152,153,154]

Diagnostic Considerations

As with the diagnostic approach to any patient with intermittent behaviors that could represent epileptic seizures, the primary concerns are to determine whether the events in question are epileptic, whether they constitute a chronic condition justifying the diagnosis of epilepsy, and whether a treatable underlying cause exists. A description of the ictal semiology by the patient and reliable observer is extremely important for classifying ictal events as limbic seizures. A description of the typical auras, oroalimentary and other automatisms, and postictal features discussed earlier in this chapter, and elicitation that auras, when present, commonly occur in isolation, makes a diagnosis of mesial temporal onset limbic seizures highly likely. This diagnosis of seizure type is further supported when (a) the history yields information typical of MTLE with HS, such as a family history of epilepsy, prolonged febrile seizures, or initial precipitating insults early in life; (b) neurologic examination is normal with the exception of verbal or nonverbal memory deficit; (c) and other features discussed in Chapter 247 are present. When a history suggestive of MTLE with HS is missing, limbic seizures could still reflect MTLE due to another type of mesial temporal lesion, or an epileptogenic abnormality in an area of neocortex that preferentially projects to mesial temporal limbic structures. Features of the history, neurologic exam, and initial ictal signs and symptoms then help to localize the neocortical epileptogenic region (see Chapter 246), although the limbic seizure itself, including the aura, can be identical to one originating in mesial temporal limbic structures.

Routine EEG is an essential part of the diagnostic evaluation, and the presence of unilateral or bilateral independent anterior temporal interictal spikes supports a diagnosis of limbic seizures. Although an interictal EEG spike focus outside the temporal lobe suggests that the limbic seizures do not originate within mesial temporal structures, the absence of such findings does not rule out this possibility.

High-resolution MRI is now the most effective diagnostic test for identifying the structural epileptogenic lesions responsible for limbic seizures, and the most common finding is unilateral hippocampal atrophy and increased T2 signal, including fluid-attenuated inversion recovery (FLAIR).[83] Other lesions can also be seen in mesial temporal structures, and neocortical lesions outside this area suggest that limbic seizures represent propagation from neocortex. Many patients with limbic seizures have normal MRI scans. Structural imaging is normal when lesions are below the resolution of MRI, as occurs early in MTLE with HS,[113] and in most patients with idiopathic familial MTLE.[19]

Neurocognitive testing often documents material-specific memory and learning deficits in association with limbic seizures due to mesial temporal lesions,[108] but memory also can be secondarily impaired when frequent limbic seizures result from neocortical projections. FDG-PET has been used to study patients with limbic seizures for over 25 years.[41] Ictal SPECT, functional MRI (fMRI), magnetic resonance spectroscopy, and magnetoencephalography (MEG) are increasingly employed to localize the epileptogenic lesion in patients with limbic seizures, as discussed in Chapters 246 and 247.

Differential Diagnosis

Limbic auras and seizures can be confused with a variety of psychiatric conditions, including nonepileptic psychogenic events. Clinically, the former can usually be easily diagnosed by their stereotypical features, whereas psychiatric experiences (Chapters 284, 285, 286), and nonepileptic psychogenic seizures (Chapter 283) are less likely to be stereotyped and can continue for prolonged periods. Other nonepileptic events that might be confused with limbic seizures include sleep disorders, particularly the parasomnias (Chapter 277) and migraine phenomena (Chapter 275). A differential diagnosis of limbic seizures from nonepileptic seizures that is not obvious by careful description of the ictal events can usually be achieved by routine EEG showing interictal spikes, and/or demonstration on MRI of structural abnormalities that are likely to be epileptogenic. It is important to bear in mind, however, that epileptiform-appearing transients on EEG or structural abnormalities on MRI, in themselves, do not make a diagnosis of epilepsy, and inpatient video-EEG monitoring may be necessary to make a definitive diagnosis.

Differential diagnosis between limbic seizures and other seizure types that involve bizarre behaviors with and without impaired consciousness is important only when diagnosis affects management. A typical situation would be the differential diagnosis between a limbic seizure consisting of impairment of consciousness only and the typical absence seizures seen with idiopathic generalized epilepsies. This distinction is usually easily made based on the clearly different clinical contexts of these two conditions, as well as the fact that patients with typical absence have bilaterally synchronous spike-and-wave on EEG and normal MRIs. Differential diagnosis between the seizures described here that utilize the mesial temporal ictal limbic network and certain frontal lobe seizures can be more difficult. Frontal lobe seizures tend to be more frequent, briefer, occur in clusters, and have a nocturnal preponderance. Supplementary motor area seizures can be confused with limbic seizures because they are bilateral and do not always show the classical tonic posturing, but consciousness is usually preserved. Hyperkinetic seizures mediated by frontal lobe structures, but at times originating in other neocortical areas, have sudden onset and offset without postictal confusion, and are characterized by vocalization, marked bilateral motor manifestations with a bizarre hysterical appearance and, occasionally, sexual automatisms. Differential diagnosis in these situations is important when seizures are refractory to medication and surgical treatment is being considered. In this situation, ictal EEG, neuroimaging, and characteristics of the ictal behavior are all important for localization, as discussed in Chapter 246.

Specific Syndromes Incorporating the Seizure Type as an Integral Feature

Limbic seizures are the predominant seizure type associated with MTLE with HS (Chapter 247), but are also the predominant seizure type of MTLE caused by other mesial temporal lesions, as well as other symptomatic focal epilepsies caused by neocortical lesions that preferentially propagate to mesial temporal limbic structures (Chapter 246). They also occur in association with gelastic seizures with hypothalamic hamartoma (Chapter 250), and in familial TLEs (Chapter 248).

Responses to Treatment

Any discussion of the medical management of limbic seizures must recognize that there are no population studies using currently available diagnostic methods to document pharmacoresistance of specific seizure types. Furthermore, no such studies are likely to occur because the vast majority of extensive evaluations are conducted in specialized epilepsy units as part of a presurgical investigation in patients who are deemed medically intractable. Whereas most large drug trials are carried out on patients with CPS, not all of these meet the criteria

discussed here for a diagnosis of limbic seizuresâ€"that is, seizures for which the ictal manifestations reflect activity in the limbic system and its efferent projections.

One comprehensive double-blinded study has compared the efficacy of four major AEDs (phenytoin, carbamazepine, primidone, and phenobarbital) on CPS and, secondarily, on generalization convulsions.[95] This multicenter cooperative study found phenytoin and carbamazepine to be superior, with the latter having a statistically insignificant edge. What was not intuitively obvious was that all drugs were equally efficacious once established. The problem with primidone and phenobarbital was intolerance to side effects at the time of drug initiation. In a similar study comparing carbamazepine and valproate, carbamazepine was found superior for controlling CPS, whereas both were equally efficacious for treating secondarily generalized seizures.[96] New AEDs are typically given as add-on trials in patients who are refractory to standard medications. In this situation, antiepileptic potency can easily be obscured. No data suggest that any of the new AEDs is more efficient against limbic seizures than carbamazepine or phenytoin, although their side-effect profiles are different and in some cases more acceptable to many patients.[26,27,51,52]

Numerous studies have documented that CPSs are not satisfactorily controlled with AEDs.[26,27,31,68,95,99,110,116] When these are limbic seizures associated with MRI-documented MTLE with HS, only 11% were adequately controlled in one study in a tertiary outpatient clinic,[117] and 46% in a primary outpatient clinic.[128] In both cases, this was the most pharmacoresistant condition. In the latter case, most of the patients were new onset, and recent evidence confirms the clinical impression that MTLE has a â€œstutteringâ€ course; limbic seizures are initially easily controlled, and it may take many years before they become pharmacoresistant.[7] This suggests that limbic ictal events could have progressive structural or functional consequences that make seizures more severe, or more difficult to treat. Indeed, evidence suggests that these ictal events could also be responsible for long-term interictal behavioral dysfunction, including progressive memory impairment and even psychiatric disturbances such as depression.[40]

One explanation for the relative refractoriness of limbic seizures, compared to primary generalized tonicâ€“clonic and absence seizures, is that virtually all potential AEDs, until recently, were screened against experimental models of the latter seizure types: maximal electroshock and subcutaneous metrazol. Consequently, many pharmacologic compounds that might have been highly effective against limbic seizures could have been discarded because they did not have anticonvulsant or antiabsence properties. One of the newer AEDs, levetiracetam, did fail these two screening tests, but was brought to market because it was found to be effective against amygdala-kindled seizures, a model of human limbic seizures.[90] Levetiracetam has proved to be highly effective clinically against limbic seizures, although not necessarily more effective than several other AEDs.[26,27,51,52] Although this proves that compounds without anticonvulsant or antiabsence properties can have clinical efficacy against limbic seizures, and that animal models of limbic seizures should be employed when routinely screening potential antiepileptic compounds, it does not provide evidence that such screening will significantly reduce the percentage of patients with limbic seizures who are currently pharmacoresistant.

Fortunately, most patients with limbic seizures have surgically remediable epilepsy disorders, such as MTLE, that can be effectively treated with excellent results.[36,46,136] Surgery, therefore, should not be considered a last resort; rather, patients with surgically remediable syndromesâ€”those conditions with seizures resulting from a known pathophysiologic disturbance and that have a high likelihood of being pharmacoresistant and progressiveâ€”should be referred for surgical treatment early, before the disabling social and psychological consequences of recurrent seizures become irreversible.[36,46]

Summary and Conclusions

Limbic seizures are ictal manifestations resulting from epileptic discharges within a specified neuronal network consisting of the limbic system and its efferent projections. Limbic seizures can be caused by epileptogenic abnormalities within this mesial temporal limbic network, such as occurs with MTLE with HS, MTLE due to other structural lesions, or idiopathic familial MTLE, or they can be the predominant seizure type in patients with epileptogenic regions in areas of neocortex that preferentially project to mesial temporal limbic structures. Limbic seizures are the single most common type of seizure and among the most pharmacoresistant. They present with a wide variety of signs and symptoms, most of which, alone or in combination, can reliably localize and, in some instances, lateralize the region of seizure origin. However, numerous exceptions exist. When accurate seizure onset localization is required before planned surgical intervention, the clinical characteristics of a patient's limbic seizures should never be examined in isolation, but only as one important part of the data in a comprehensive evaluation. However, the concept that clinical seizure characteristics are not useful for localization is not valid.

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Chapter 47

Generalized Tonicâ€“Clonic Seizures

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Introduction

The generalized tonicâ€“clonic seizure (GTCS) has been known since antiquity. The earliest descriptions appear in Egyptian hieroglyphics before 700 B.C.[99] From the mid-19th century, when notions of cerebrovisceral sympathy were discarded and all epilepsy was recognized as originating in the brain, the GTCS was considered the cardinal manifestation of genuine or idiopathic epilepsy due to a predisposition to have seizures. GTCS was described as *grand mal,*[49] a term that is still encountered. This predisposition was, in turn, believed to be associated only with generalized seizures (reviewed in Gastaut[42]). Although the history of clinical epileptology has been marked by the differentiation of nonconvulsive seizures as epileptic events, progressively more exact descriptions of seizure types and epileptic syndromes, the development of surgery (usually for intractable partial seizures), and progress in childhood seizure disorders, the GTCS is still the hallmark of epilepsy for the general public. It remains a dramatic and often frightening event for patients, families, and onlookers. For most neurologists, however, the generalized convulsion is a rarely witnessed clinical event, albeit a common reason for consultation the history of which can be frustratingly difficult to obtain. It may be an isolated event in the setting of an acute encephalopathy, a symptom of serious brain disease, or a manifestation of several epilepsy syndromes of generally good prognosis.

Definitions

The current International Classification of Epileptic Seizures[23,30] defines GTCS within the group of generalized convulsive or nonconvulsive seizures. Unlike the conceptual approach of the classification of epileptic syndromes,[24] this classification of seizures is based on observed events, specifically, the seizures themselves as documented during intensive monitoring, and the electroencephalogram (EEG). As a group, in generalized seizures, â€œThe first clinical changes indicate initial involvement of both hemispheresâ€¦. Motor manifestations are bilateral. The ictal electroencephalographic patterns initially are bilateral, and presumably reflect neuronal discharge which is widespread in both hemispheres.â€ The classification, however, treats the term *tonicâ€“clonic seizures* as self-explanatory. In the last proposal by the International League Against Epilepsy (ILAE) Task Force,[33] the Glossary of descriptive terminology for ictal semiology describes a tonicâ€“clonic seizure as â€œa sequence consisting of a tonic followed by a clonic phase. Variants such as clonicâ€“tonicâ€“clonic may be seen.â€ Dreifuss[29] provides a useful description:

â€œThe majority lose consciousness without any premonitory symptoms. There is a sudden sharp tonic contraction of muscles; when this involves respiratory muscles, there is a cry or moan. The patient falls to the ground â€¦tonic contraction inhibits respiration.â€¦ The tongue may be bitten.â€¦ This tonic stage then gives way to clonic convulsive movements that last for a variable period of time.â€

Cyanosis, salivation, tongue biting, and incontinence are frequent, and the postictal state includes a variable period of unconsciousness.

There is at present no provision in the international classification for subclassifying GTCS with preceding bilateral myoclonic jerks or absence attacks. Sequences such as a brief clonic attack before the tonic phase (clonicâ€“tonicâ€“clonic seizure) are also well known to epileptologists, and the glossary indicates this possibility. The classification makes it clear, however, that the term *generalized convulsive seizure* is restricted to convulsive seizures that are generalized from the start and excludes partial seizures that may become secondarily generalized so quickly as to look like GTCS, as is seen in some frontal lobe seizures.[93] Generalized tonicâ€“clonic (convulsive) seizures are manifestations of idiopathic generalized epilepsies (IGEs) and epilepsy syndromes, as these have been defined and, in the most recent proposed classification of epileptic syndromes,[33] would be associated with the generalized epilepsies with variable phenotypes: These are discussed in detail elsewhere in this book.

Seizures that often differ from classic tonicâ€“clonic convulsions can occur when partial seizures become generalized. Distinguishing these from GTCS due to an IGE syndrome is a common problem of vital importance in daily practice. Especially in seizures arising in the temporal lobe, clinical spread is not immediate, and the complete seizure pattern (see â€œDiagnosis,â€ below) may aid in diagnosis. These seizures are classified under partial seizures as partial seizures evolving to GTCS, although the seizure pattern is often different from that of GTCS. An isolated seizure or brief flurry of seizures clinically indistinguishable from GTCS may occur with an acute diffuse encephalopathy. These are classified as situation-related seizures in the classification of epilepsies, because they do not constitute a separate seizure type. Childhood febrile convulsions, probably the most common form of convulsion, are similarly classified.

It is important to emphasize that, although generalized convulsions may occur in the generalized cryptogenic and symptomatic epilepsies and syndromes, they are not the predominant or defining seizure type and usually happen relatively late in the course of the disease. Generalized seizures manifested only by a tonic phase are, however, quite different from GTCS and are common and often intractable in these syndromes. True GTCSs are not frequent in young children but can occur, particularly in epilepsy with myoclonicâ€“astatic seizures,[27] severe myoclonic epilepsy of infancy (Dravet syndrome),[28] and in some progressive myoclonic epilepsy varieties in children and adults, such as Jansky-Bielschowsky disease[94] and Unverricht-LÃ¼ndborg disease.[68]

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Epidemiology

Tonicâ€“clonic seizures may be the most common afebrile seizure type in the general population. However, until recently, epidemiologic studies included patients with clinically generalized seizures of partial onset and did not specify the epilepsy syndromes in which GTCSs occur. The occurrence of GTCS is also age-related. Although epilepsy begins much more commonly in infants, children, and the elderly than in middle life, other seizure types are more common in young children, related in part to incomplete synaptic development and myelination, especially of interhemispheric connections.[2] Generalized convulsive seizures are uncommon in infants and rarely, if ever, occur in neonates. In the elderly, seizures usually reflect localized brain lesions. Thus, GTCSs are rare in the first few years of life, although myoclonic and tonic seizures are not, whereas partial seizures with secondary generalization are common in the elderly. Typical GTCSs are common, however, in later childhood, adolescence, and young adult life, with the onset of IGEs. Studies based on seizure descriptions without EEG or imaging results or which refer to GTCS in very young children will, thus, overestimate their occurrence. Studies from specialized epilepsy centers that concentrate on patients with intractable seizures and candidates for epilepsy surgery risk underestimating the prevalence of GTCS. It should also be noted that not every subject with a generalized epilepsy syndrome has GTCSs.

Hauser and Kurland,[56] using the unique medical records system in Rochester, Minnesota, reported that the prevalence of patients with only GTCS was 20.6% of patients with epilepsy. Patients with GTCS also accounted for 23%[54] of the incidence of epilepsy. Incidence estimates for all recurrent afebrile seizures in children and adolescents are roughly similar in different studies, from 50 to 100 new cases per 100,000 per year.[55] A study of clinical and EEG data[61] estimated that about 39% of patients with epilepsy have a generalized epilepsy syndrome. As discussed later, GTCSs occur in several of these syndromes. Patients with absences commonly develop GTCS, particularly if absences begin relatively late, in preadolescent years: This occurs in about 35% of patients with absences in general, but in 90% of patients with later-onset absences (reviewed in Aicardi[3]).

A genetic component is evident in many different types of epilepsy. However, the common epilepsies do not usually behave as simple Mendelian disorders, and several lines of evidence suggest multifactorial inheritance.[5] The genetics of juvenile myoclonic epilepsy (JME), in which GTCSs often occur, have been recently reviewed.[110] Relatives of patients with idiopathic epilepsy have a higher risk for epilepsy than do those of patients with symptomatic epilepsy.[86] Population studies show an increased risk of unprovoked seizures in close relatives of patients with idiopathic age-related epilepsy syndromes of childhood. The relative risk ranges from 2.5 (95% confidence interval [CI] 1.3â€“4.4] for siblings to 3.4 (95% CI 2.1â€“5.1) for offspring. However, the risk for offspring of parents with GTCS, about 5%, is not higher than that for offspring of parents with partial seizures, the difference being accounted for by the much higher risk to offspring if a parent has absences.[7,86] Twin studies in IGEs, reviewed by Berkovic et al.,[12] provide further evidence for a large inherited component and show a high rate of concordance in monozygous twins for specific syndromes, including those with GTCS as a major feature. Other risk factors[80,92] include a history of febrile convulsions (odds ratio 13.75, 95% CI 3.49â€“54): This may indicate a lower convulsive threshold and cannot be taken as the cause of later GTCS. Some familial epilepsies are associated with specific ion channel defects (Chapter 18), but single gene defects are a rare cause of common epilepsies. This information is, however, in keeping with a polygenic inheritance for common epilepsies.

Anatomic Pathways and Pathophysiology

Different forms of convulsive seizures in animals depend on independent anatomic regions and pathways. Models of convulsive seizures using drugs such as bicuculline and pentylenetetrazol, kindling studies, and animals genetically prone to generalized epilepsy at times with reflex triggers, have implicated brainstem structures (reviewed by Browning[19] and Moraes[82]) in the genesis and, clearly, in the modulation of convulsive seizures; including the lateral geniculate body, which produces GTCS when kindled in the cat[96]; ascending pathways through the mamillary bodies and anterior thalamus; the substantia nigra, including a nigrotectal Î³-aminobutyric acid (GABA)ergic projection[38]; and diffuse increased noradrenergic innervation of the cortex from the locus coeruleus.[84] The three principal concepts of generalized epilepsy, thus, each implicate a different mechanism: an abnormal response of hyperexcitable cortex to initially normal thalamic input, a primary subcortical trigger, and abnormal cortical innervation from subcortical structures. Subcortical mechanisms would play at least a modulating role. Any or several of these may operate in the clinically and genetically different syndromes with GTCS in humans (for a review with EEG emphasis, see Binnie[14]). It should be emphasized that GTCS models in rodents and fowl are clinically quite different from human epilepsy; feline, canine, and primate models may be closer approximations.

Studies in the Senegalese baboon *Papio papio*, which has both photosensitive and spontaneous generalized motor seizures, suggest that the substantia innominata participates in the mechanism of generalized convulsions by modulating excitability of the hemispheric motor mechanisms. In partial seizures that spread from limbic structures, the claustrum participates in activating the ipsilateral hemispheric motor mechanisms. Bilateral spread of partial motor seizures requires the anterior two-thirds of the corpus callosum. These studies (reviewed in Wada[103]) are of particular interest because, despite some important differences, the photosensitive baboon is believed to be a closer model of human epilepsy than are lower animals such as rodents and fowl.

Regulation of the seizure threshold and of seizure spread in different animal seizure types depends on seizure-gating pathways, which themselves are not pathways for seizure spread. Gating mechanisms include the substantia nigra and related circuits, ascending noradrenergic pathways, thalamic circuits, and some arising in the cerebellum (for a review see Gale[37]).

Intracellular events during GTCS have not been studied extensively, but neocortical neurons recorded during convulsive seizures induced by focal penicillin application show prolonged depolarization coinciding with the tonic phase, followed by sequential rhythmic depolarization and repolarization during the clonic phase. Gloor[46] noted that GTCSs are associated with activation of *N*-methyl-D-aspartate (NMDA) receptors, which would permit calcium (Ca^{2+}) influx into the neuron, and that many deleterious intracellular events follow the massive Ca^{2+} influx associated with convulsive seizures, some of which depend on activation of second messengers and some of which are direct. These can be transitory and manifested clinically by symptoms such as postictal stupor or Todd paralysis. However, irreversible cell damage or cell death may occur, especially with prolonged seizures or with status epilepticus (SE).[57]

Clinical Features

Ictal

Generalized convulsive seizures occur in several distinct epilepsy syndromes. Although the convulsion seems stereotyped, details of the seizure onset are important in the diagnosis of the related epilepsy syndrome. These may not be obtained from witnesses: video-EEG monitoring may be needed to document clinically relevant features, such as partial onset of a secondarily generalized event. Frontal lobe seizures particularly may imitate GTCSs (see the next section), and GTCSs may imitate focal seizures.[36]

Some patients reliably report a *prodrome*, premonitory symptoms hours or days before a seizure. It is surmised that these represent changes in cortical excitability or manifestations of some factor that also alters the seizure threshold. These are not auras; that is, they are not simple partial seizures that come immediately before more elaborate partial seizures, and they do not indicate a focal seizure onset. Common prodromes include mood changes, sleep disturbances, lightheadedness, anxiety, difficulty concentrating, and irritability.

GTCSs may begin with myoclonic jerks (Fig. 1) or, rarely, with absences.[78,83] Before the tonicâ€“clonic phase, versive movements of the head and eyes may occur. Although controversial and usually considered typical of partial seizures, versive movements clearly occur at or near the onset of some seizures which, as far as can be known, are generalized from the start.[21,85,91] More complex circling behavior has also been documented.[39,70] GTCSs can also occur at the onset, in the midst of, or at the end of absence status.[6]

The tonic phase[40] begins with a brief flexor spasm of axial muscles that spreads quickly to the arms and legs, accompanied by loss of consciousness. The eyes deviate upward, the pupils dilate, and the jaw is rigid and partly open. This is followed by more prolonged tonic extension, spreading from axial muscles to the limbs. The initial closing of the mouth often results in tongue biting or other trauma, and the strong tonic contraction of respiratory muscles results in the characteristic cry. Apnea begins at the very onset of the tonic phase and can cause progressive cyanosis. Autonomic signs are prominent: Pulse and blood pressure rise, and profuse sweating and tracheobronchial hypersecretion are common. Although urinary bladder pressure rises, voiding does not occur because of sphincter muscle contraction.

The clonic phase begins gradually as a diffuse tremor (European authors often refer to this as *vibratory*), which slows from 8 to 4 Hz. It then emerges with cycles of inhibition interrupted by reappearance of the tonic contraction, producing atonia alternating with repeated violent flexor spasms. Each spasm is accompanied by pupillary contraction and dilation. The atonic periods gradually become longer until the last spasm. Voiding may occur at the end of the clonic phase as sphincter muscles relax. The convulsion typically lasts 1 to 2 minutes.

Postictal

Respiration returns almost at once after the last clonic jerk. Usually, the muscles are relaxed postictally, but a diffuse tonic state may return, resembling decerebrate rigidity and possibly causing further injury. The patient gradually awakens, often after a period of stupor or sleep, and is often confused, with some automatic behavior. Headache and muscle pain are common. The patient does not recall the seizure itself.

Complications of GTCS include trauma to the tongue, lips, and cheeks from trismus; head trauma due to a fall or to repeated banging of the head against hard surfaces during the clonic phase; vertebral compression fractures (usually asymptomatic); aspiration pneumonia; and, infrequently, neurogenic pulmonary edema, which may be related to the intense autonomic activity during the seizure. Sudden death in epilepsy, an uncommon but well-known event, may be related to an immediately preceding seizure. A GTCS can, rarely, be lethal[74] (this topic is extensively reviewed in Lathers[72]). Langan et al.[71] found that sudden death was more likely if GTCS had occurred in the previous 3 months (odds ratio 13.8, 95% CI: 6.6â€“29.1) (see Chapter 189). Pulmonary edema, apnea, cardiac arrhythmia, and aspiration with asphyxia have been proposed as mechanisms (see Chapter 10). Transitory metabolic changes after GTCS are usual. Changes in circulating hormone levels are also common.[90] They are summarized in Tables 1 and 2. The elevation of plasma prolactin reaches its zenith of 5 to 30 times the upper limit of normal about 20 minutes after the seizure and, if present, almost certainly excludes pseudoseizure as the cause of a clinical episode. The postictal value should be compared to a control value obtained 24 hours later with no intervening seizure. Other hormone levels also rise after a seizure, but the relatively minor diurnal variation of prolactin levels and the relative ease of measuring them make this a practical test for clinical use. A prolonged convulsion may be associated with a minimal increase in the cerebrospinal fluid (CSF) cell count of 1 to 2 cells/mm^3 and SE with a greater pleocytosis, but whatever the number of seizures, a cell count of more than 10 cells/mm^3 should be taken as evidence of intracranial inflammation until proven otherwise.[32]

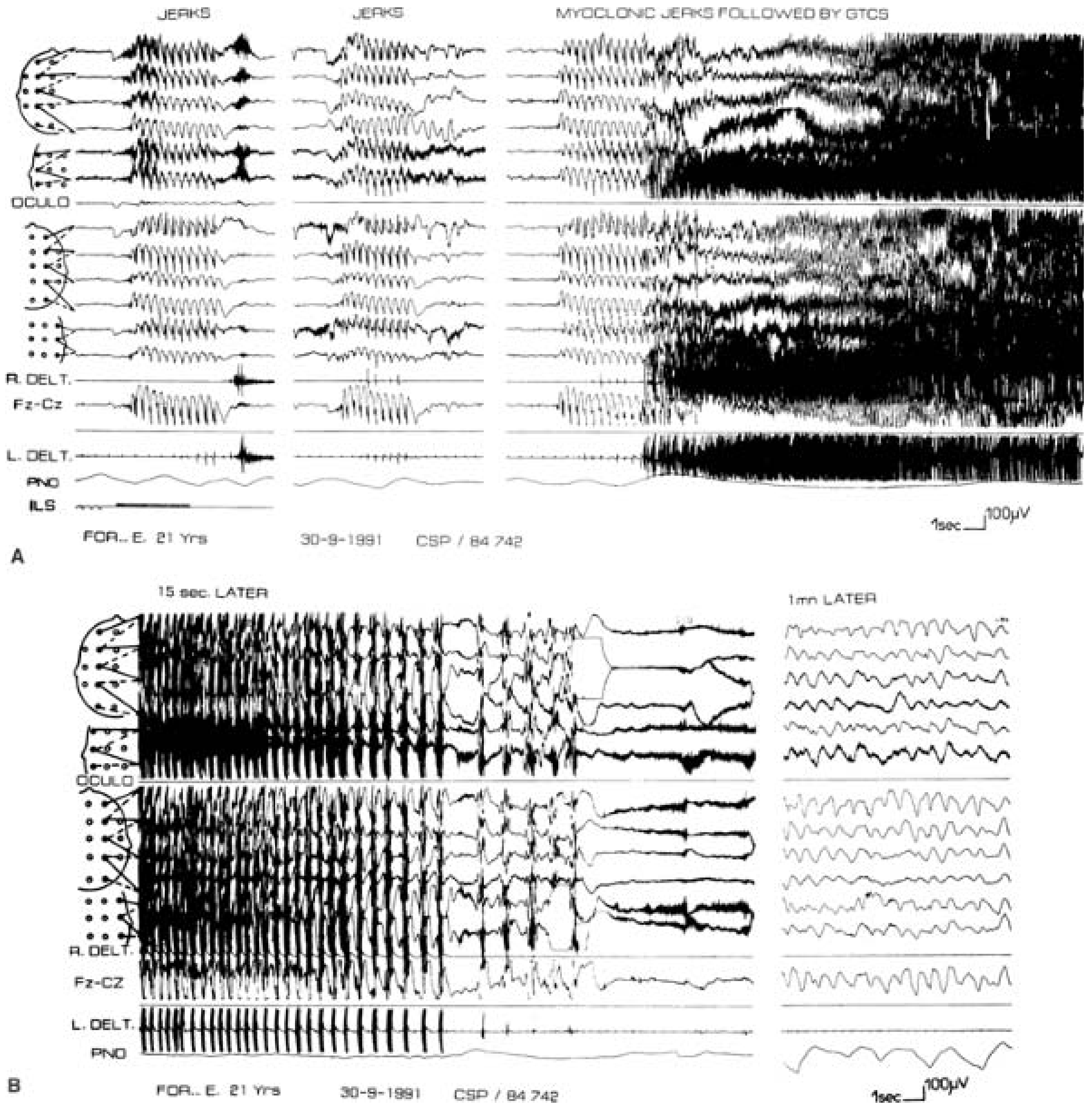
JERKS
JERKS
MYOCLONIC JERKS FOLLOWED BY GTCS
OCULO
R. DELT.
Fz-Cz
L. DELT.
PNO
ILS
FOR.. E. 21 Yrs
30-9-1991
CSP / 84 742
1sec
100µV
A
15 sec. LATER
1mn LATER
OCULO
R. DELT.
Fz-CZ
L. DELT.
PNO
B
FOR.. E. 21 Yrs
30-9-1991
CSP / 84 742
1sec
100µV

FIGURE 1. A generalized tonicâ€“clonic seizure preceded by myoclonic jerks in a 21-year-old with juvenile myoclonic epilepsy. **A:** Three salvos of myoclonic jerks on awakening, the first elicited by intermittent photic stimulation. The others occur spontaneously, and the third is followed immediately by the tonic phase of the generalized convulsion. **B:** Clonic phase and end of the convulsion. Bilaterally synchronous jerks of decreasing frequency are recorded in the deltoid muscle EMG, followed by relative flattening of the EEG, partly masked by EMG artifact caused by postictal tonic spasm. Diffuse delta activity is recorded 1 minute later. The respiratory monitor records apnea during both the tonic and clonic phases of the seizure. R. delt, right deltoid; L. delt, left deltoid; PNO, pneumogram; ILS, intermittent light (photic) stimulation.

EEG Manifestations and Clinical Correlations

Interictal

The waking EEG of patients with only GTCS is often normal.[17] Slight nonspecific abnormalities of background activity may occur, and antiepileptic drugs (AEDs) may cause mild diffuse slow activity, especially at high levels. Barbiturates and benzodiazepines commonly cause diffuse increased Î²-wave activity. Some patients, especially those with a history of absences, may have some paroxysmal frontal intermittent rhythmic delta activity. Although abnormal in the EEG of the awake adult, this pattern reflects only a nonspecific disturbance of cerebral activity and is not considered epileptiform (reviewed in Zifkin[109]).

Generalized EEG interictal epileptiform abnormalities consist of spikes, sharp waves, polyspikes, and polyspike or spike-and-wave complexes (SWCs). Hyperventilation is often effective in bringing out generalized epileptiform activity, especially typical SWCs. Sleep recordings, ideally obtained without sedation, often increase the yield of epileptiform activity. Epileptiform activity may be reduced or abolished by chronic treatment with certain AEDs, especially valproate and the benzodiazepines. The type of interictal epileptiform activity can be related to the syndrome in which GTCS occurs:

- Typical generalized bilaterally synchronous 3-Hz SWCs are associated with typical absence attacks: Whether this is really interictal is a subject of debate.
- Irregular bilateral SWCs may be seen with IGE and GTCS but may also be recorded in different metabolic encephalopathies and drug withdrawal.
- Fast spike-and-wave activity at 4 to 5 Hz is most often associated with GTCS. In the resting EEG in wakefulness, this is typical of JME and can also be seen with

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epilepsy with myoclonic absences, in which subjects are also typically photosensitive.

- Polyspikes or polyspike-and-slow-wave complexes are usually seen with JME, often on eye closure.[8]

All these are usually predominant over anterior head regions; they may be seen only over these areas but may occasionally be predominant posteriorly in children. They are commonly asymmetric: This should not be interpreted to indicate a focal or regional seizure onset without additional evidence such as convincing local or regional nonspecific abnormalities. During non-REM sleep, the epileptiform bursts are usually more frequent but briefer and fragmented. They become much less frequent in REM sleep.[95] Patients with GTCS are more likely to have an epileptiform response to intermittent photic stimulation than are those with partial seizures. Routine photic

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stimulation may induce generalized epileptiform activity in about 25% of patients with IGE and, if strictly defined, this activity is rare without a personal or family history of epilepsy.[14]

Table 1 Transitory changes following a generalized convulsive seizure

Tissue	Value	Change
Arterial blood	pH	Decrease (usually >7.0)
Serum	Glucose	Increased up to 12 mmol/L (decreases in status epilepticus)
Serum	Creatine kinase	Increased

Serum	Lactate	Increased
CSF	Cell count	Usually normal. Consider inflammation if elevated after a single seizure or >10 cells/mm^3 after any number of seizures.

Table 2 Circulating hormone changes following GCS

Hormone	Change
Prolactin	Increased
ACTH	Increased
Cortisol	Increased
Vasopressin	Increased
Growth hormone	Increased
Î²-Endorphin	Increased
TSH	Inconsistent change

Ictal

Much of the ictal EEG of a GTCS is usually obscured by muscle and movement artifact. Computer analysis shows that the EEG seizure onset is usually asynchronous, with small time differences between the hemispheres (Figs. 1, 2). These are minor and usually inconsistent,[48] and if there is no focal interictal epileptiform activity, the current classification of seizures treats such attacks as generalized, although this is now a subject of debate. Certain stereotyped patterns of seizure onset have been observed. Some patients have one or a few bilateral myoclonic jerks before the tonic phase begins, usually associated with EEG artifact, although individual high-amplitude bilateral anterior predominant spikes may be recorded with each jerk. Absences may progress to GTCS[78,83]: The ictal EEG shows a transition from the spike-and-wave activity of the absence through a sudden bilateral relative flattening of the EEG with low-amplitude Î²-wave activity, followed by the GTCS. Perioral myoclonia with absences may also be accompanied by GTCS.[9]

The convulsion itself is characterized during the tonic phase by progressively higher amplitude and lower frequency ictal epileptiform activity, reaching about 10 Hz, which is the epileptic recruiting rhythm.[41] This then becomes slower, mixed with bilateral high-amplitude spikes, and a progressively greater amount of high-amplitude rhythmic Î´-wave activity. These are slow, progressively developing into repetitive complexes of high-amplitude spike-and-slow-wave activity associated first with the tremor, then, with further slowing of the repetitions, with the violent jerks of the clonic phase. This pattern is held to be the result of progressively greater inhibition.

The postictal EEG may be briefly isoelectric at routine gains or may show diffuse, very low-amplitude slow Î´-wave activity. This corresponds to sustained hyperpolarization.[105] The seizure ends not by exhausting the brain but by an active mechanism. Baseline activity returns in minutes to hours, but a mild, nonspecific postictal disturbance may persist for a day or more in adults and longer in children. The postictal EEG may occasionally show only subtle nonspecific change; this appears to represent different mechanisms of ictal termination, but the basis for it is unknown.

Diagnostic Considerations

The diagnosis of GTCS requires first establishing that a seizure, not usually observed by the physician, is indeed an epileptic event, then whether it is a manifestation of an IGE, another form of epilepsy or epileptic syndrome, or an isolated seizure. The rarity of true GTCS in very young children should not be forgotten, nor should the likelihood that a first generalized convulsion in middle adult life and later is much more likely to be due to a symptomatic focal brain lesion or other encephalopathy than to an IGE syndrome. Even with an apparent cause such as alcohol withdrawal, full investigation of a first seizure is required. The patient does not remember the seizure, so the history should also be obtained from witnesses whenever possible. Factors such as sleep deprivation, alcohol withdrawal, and nonmedical drug use should be explored, as well as more specific triggers such as television or cognitive performance. Eliciting a history of the sequence of the tonicâ€“clonic convulsion without leading the witness is important. Family members can also often provide details of prenatal, perinatal, developmental, and family history. A GTCS is not usually captured during routine EEG recording, and the interictal EEG, even if it contains epileptiform activity, provides only suggestive evidence for the diagnosis of a given event. Patients with GTCS and IGE typically have no evidence for any localized, regional, or diffuse brain abnormality on history, physical, or neurologic examination; clinical laboratory testing; EEG; or imaging studies. Focal or asymmetric regional EEG epileptiform abnormalities are not rare, especially in JME.[110] A history of simple febrile convulsions or of familial epilepsy may be obtained: These are recognized risk factors for the development of GTCS.

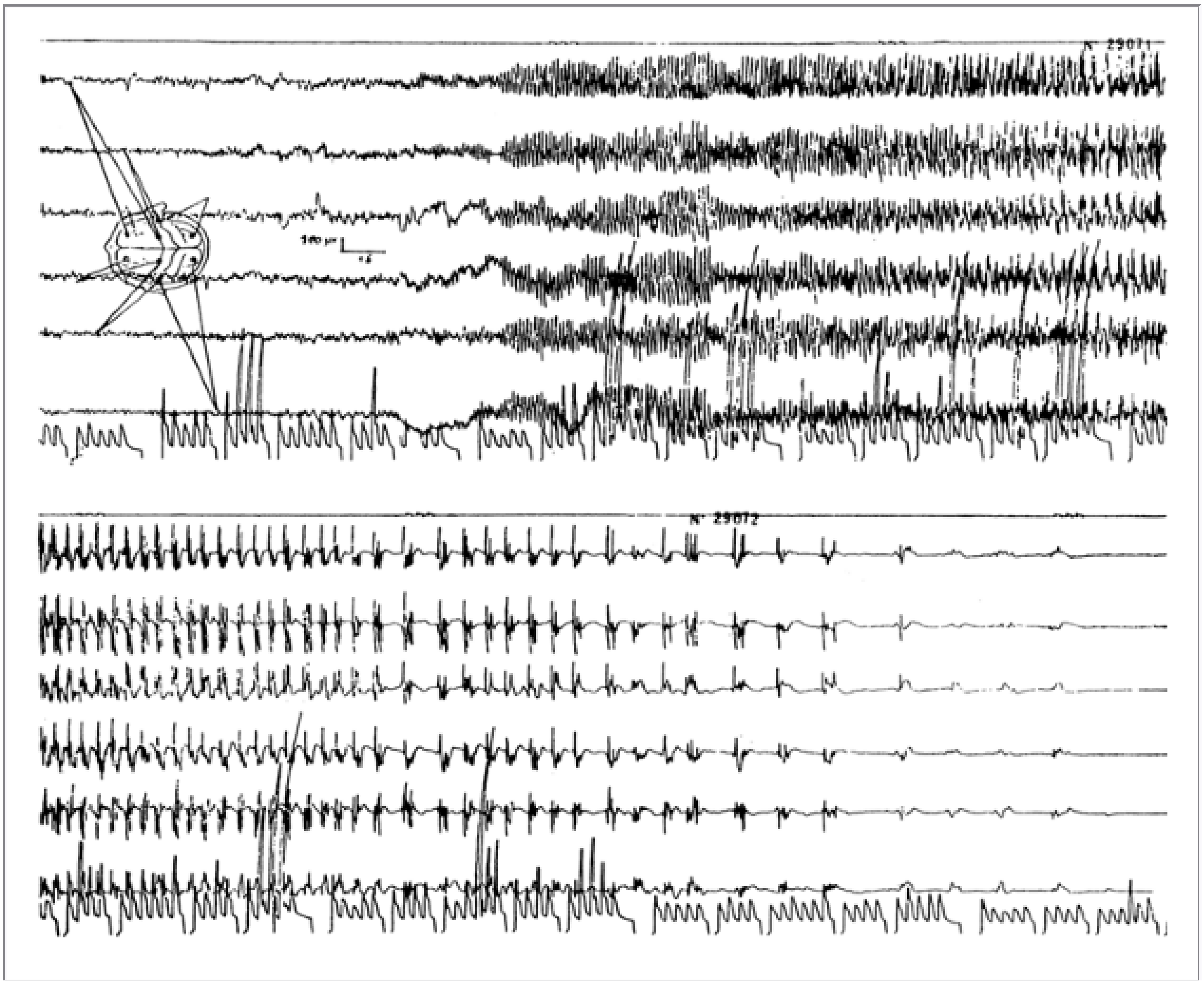

FIGURE 2. The first 10 seconds of EEG are recorded prior to the clinical seizure. The seventh channel (*bottom*) is the output of a Grey-Walter frequency analyzer. The recording was obtained with partial muscle relaxation after injection of curare and is less contaminated by muscle artifact than are present-day ictal scalp EEGs. The second 10 seconds corresponds to the tonic phase, with prominent 9- to 10-Hz rhythmic activity throughout, the epileptic recruiting rhythm. Note the increase in amplitude, followed by the vibratory period of transition to the clonic phase with the development of increasing theta activity. The lower fragment of the tracing shows the clonic phase. The repetitive and rhythmic 3-Hz polyspike and slow-wave complexes slow progressively and are followed by periods of relative flattening, between which bursts of polyspikes appear. From Gastaut H, Broughton R. *Epileptic Seizures. Clinical and Electrographic Features, Diagnosis and Treatment*. Springfield, IL: Charles C. Thomas, 1972, with permission.

Evidence that the generalized convulsion may have been secondarily generalized and a manifestation of a symptomatic localization-related epilepsy must be carefully sought. Suggestive historic elements of possible importance include prenatal, perinatal, and neonatal difficulties; prolonged or

atypical febrile convulsions; partial seizures at an early age; head trauma; intracranial infection; and developmental or physical disability. Examination between seizures may reveal subtle lateralized or bilateral motor disturbances or asymmetries of the face, hands, or feet. Detailed sensory testing may also show asymmetry of two-point discrimination over the face or hands. The seizure pattern can also be highly suggestive. Whereas the initial history from a frightened witness may suggest a seizure generalized from the start, a detailed history may disclose an aura that may lateralize or localize the clinical seizure onset or deviations from the very stereotyped pattern of the typical GTCS described earlier. Intensive monitoring of patients with intractable partial seizures shows that, when these seizures generalize, especially from the temporal lobe, the result is not a typical GTCS. Seizures arising in the temporal lobe often follow various sequences of lateralized dystonic posturing or adversion before generalization (extensively discussed in Kotagal[67]). The generalized seizure in these cases occurs late in the sequence of ictal events and usually in the longer seizures observed during monitoring. Kirton et al.[65] reviewed some of the clinical differences between primary and secondarily generalized seizures in childhood. In all cases with focal onset, the mouth either remained open or repeatedly opened and closed rather than slamming shut. In 77% of cases with focal onset, late motor activities were seen after the clinical and EEG seizure was over.

Partial seizures arising in the frontal lobe, although of several clinical types, are notorious for their rapid onset, prominent motor activity, and tendency to generalize rapidly (see Kellinghaus and LÃ¼ders[64] for review). Such patients often have apparently generalized convulsions, but the focal onset may be apparent on history or video monitoring. The posturing of supplementary motor area attacks may be disclosed by informed questioning of witnesses or by video monitoring. Similarly,

transient postictal findings, such as hemiparesis or dysphasia, are of diagnostic importance. Whereas patients with frontal seizure onset often have supporting clinical and paraclinical evidence, the differentiation of their attacks from generalized seizures can be extremely difficult and can require extensive and, at times, invasive monitoring. Nocturnal paroxysmal dystonias are unusual events that, although not GTCS, are usually frontal lobe epileptic seizures, but monitoring may be required to make the diagnosis.[98]

The typical childhood seizure patterns of idiopathic localization-related epilepsies with rolandic or occipital spikes may not be elicited, and these may present as apparently generalized convulsions in sleep. History and examination are normal, but the EEG is characteristic (see Chapters 73, 236, and 238). Reports differ as to the frequency with which rolandic epilepsy is manifested by generalized convulsions, but at least a quarter of affected children are reported to show this,[77] possibly because the seizure onset was not observed by sleeping parents. Benign epilepsy of childhood with occipital spikes and other occipital epilepsies of childhood (reviewed in Aicardi[4] and Gastaut[43]) may also generalize, but these typically progress from the characteristic visual aura, and postictal migraine symptoms are common.

Generalized tonic seizures typically occur in patients with diffuse encephalopathies and developmental delay, as part of symptomatic generalized epilepsy syndromes. These may occur in prolonged sequences during sleep,[40] which might be confused with GTCS, but the clinical context is different. Brief tonic seizures in wakefulness, responsible for disabling drop attacks,[31] are not usually associated with GTCS. A sleep video recording may help diagnosis if doubt persists. Some GTCSs with a very brief tonic phase could be confused with purely generalized clonic seizures. The use of the EEG and of imaging in differential diagnosis is discussed elsewhere in this book.

Historic, laboratory, and EEG data may help in the diagnosis of an isolated GTCS related to acute or chronic metabolic encephalopathies, an event not considered diagnostic of epilepsy, although the seizure itself is clinically not different from an epileptic event. Common causes include alcohol and other drug withdrawal, hyponatremia, hypoglycemia, and drug toxicity.

Differential Diagnosis

Nonepileptic Conditions

The differential diagnosis of GTCS from nonepileptic conditions is different in children and adults. In infants, apneic syndromes including gastroesophageal reflux, jitteriness of the newborn with various encephalopathies and metabolic disorders, and paroxysmal abnormalities of tone such as opisthotonic posturing and clonus, can be mistaken for GTCSs, which are very rare in early childhood. In toddlers and young school-age children with paroxysmal disorders during wakefulness, simple faints, breath-holding spells, and pallid syncope are common causes of diagnostic confusion, especially if brief convulsive movements occur (convulsive syncope is reviewed by Lin[76]). Syncope of various types is probably the most common source of diagnostic error in older children and adults. Elements suggesting syncope include the typical precipitating factors such as pain, fear, prolonged standing, or heat; the presyncopal, gradually increasing feeling of lightheadedness, blurred vision, and clamminess over several seconds; and pallor followed by collapse. EEG and imaging studies are normal or noncontributory. The diagnosis of syncope should not be taken lightly, and potentially life-threatening cardiac disease such as cardiomyopathy, prolonged QT syndrome, and other arrhythmias should be considered in children and adults.[73,87,97] Hyperventilation and electrolyte imbalances may cause tetanic attacks that could also be confused with GTCS.

Nocturnal paroxysmal events in adults and children include sleep apnea, night terrors, and nocturnal paroxysmal dystonias. Cardiac arrhythmia and resulting brain ischemia followed by a seizure can occur with severe sleep apnea. This seizure is not diagnostic of epilepsy but reflects the acute encephalopathy. Night terrors are stereotyped and unlikely to be confused with GTCS. Nocturnal paroxysmal dystonic attacks are often frontal lobe seizures.

Psychogenic nonepileptic seizures are unusual in young children but are a common diagnosis among patients referred to epilepsy centers for intractable seizures. The belief that many such patients also have epileptic seizures has not been confirmed.[75] Whereas routine clinical evaluation can usually distinguish among the disorders described here, especially if an adequate history can be obtained, the diagnosis of psychogenic nonepileptic seizures is often difficult and may require intensive monitoring, particularly when there has been strong iatrogenic reinforcement of the diagnosis of epilepsy. Measurement of serum prolactin[90] and creatine kinase[108] levels following a seizure can be helpful but also requires a hospital setting to collect blood at the appropriate time. Vinton et al.[101] suggest that detailed evaluation of the rhythmic muscle artifact can distinguish GTCS from convulsive nonepileptic events: The nonepileptic attacks showed a stable, nonevolving frequency that is different from the evolving pattern seen during an epileptic seizure.

Specific Syndromes Incorporating the Seizure Type as an Integral Feature

A further step in differential diagnosis is determining whether the GTCS forms part of a defined epilepsy syndrome. This has implications for the prognosis and response to medication. Different syndromes also have different genetic substrates. Generalized convulsive seizures, strictly defined as a manifestation of IGE, occur in these syndromes, which are described in detail elsewhere in this book.

Febrile Convulsions

This syndrome is classified as situation-related seizures, rather than as epilepsy (see Chapter 57).

Juvenile Myoclonic Epilepsy

JME[50,88,110] is discussed in Chapter 244.

Epilepsy with Generalized Tonicâ€“Clonic Seizures on Awakening

The diagnosis of this syndrome is usually made by specialist epileptologists, and there are disagreements as to its frequency and nosologic usefulness as a separate syndrome distinct from JME (compare reports by Berkovic[13] and Janz[59]). The current proposal would include it under generalized epilepsy syndromes with variable phenotypes.

Juvenile Absence Epilepsy

Juvenile absence epilepsy, beginning around puberty or shortly before, is characterized by absence attacks that are clinically similar to, although less frequent than, those of childhood onset (pyknoleptic) absence epilepsy. The juvenile onset syndrome is much more often associated with GTCS than is childhood-onset absence epilepsy, and the EEG spike-and-wave activity may be slightly faster (see Chapter 239).

Reflex-Induced GTCS

Individual patients with reflex-induced GTCS are sensitive to different epileptogenic stimuli. Those with only reflex seizures are considered to have reflex epileptic syndromes. Certain stimuli affect specific cortical regions but induce attacks that are clinically and electroencephalographically generalized from their onset. These are typically absences or GTCSs, and the patients may also have spontaneous generalized seizures: They are often considered to have an IGE. The prototype for this phenomenon is pattern-sensitive epilepsy, in which a localized occipital trigger is responsible for the apparently generalized or bilateral EEG abnormality and generalized seizures.[106] It is also observed in seizures induced by thinking[47] and by reading.[10] These uncommon but well-defined clinical events raise essential questions about the underlying nature of apparently generalized epilepsy and GTCS (reviewed in Ferlazzo et al.[35]).

Responses to Treatment

GTCSs respond to most AEDsâ€”except ethosuximideâ€”at least partially. However, GTCSs are part of different syndromes in which other seizure types may occur, and we must emphasize that some AEDs can aggravate other seizure types such as myoclonus and absences that may occur in patients with GTCSs. Therefore, it is also necessary when deciding on treatment to consider the syndrome diagnosis. Treatment will not be the same for an IGE and a focal epilepsy. This is, for example, particularly so for carbamazepine and lamotrigine, which should be avoided in some syndromes.[100]

Valproate is the first-line drug for GTCS. It can be used in every idiopathic generalized syndrome because it is effective against GTCS, myoclonus, and absences, isolated or repeated in status.[11,107] In JME, it is effective in up to 90% of patients.[60,89] Side effects such as weight gain can limit its use, particularly in adolescents and in women. Endocrine adverse effects and an association with polycystic ovaries are currently under study. Teratogenicity (neural tube defects[22]) must be considered in women of child-bearing age. In these patients, it can be replaced by another AED. However, the teratogenic potential of newer appropriate drugs is not yet clear, and it is also possible to give valproate at the lowest effective dose of the sustained release formulation, with folate supplementation before conception and detailed ultrasound monitoring during pregnancy. Valproate is also indicated in secondary generalized GTCS after a focal onset.

Lamotrigine,[18,102,104] topiramate,[1] and levetiracetam[69] are useful alternatives with broad efficacy for the other seizure types often associated with GTCSs. However, several cases of JME worsened by lamotrigine have been reported,[15,20,79] as well as deterioration in IGE patients with only GTCSs.[25] Lamotrigine can aggravate myoclonus in other situations, particularly in severe myoclonic epilepsy in children.[53] Thus, we consider lamotrigine indicated for GTCS, but we prefer to avoid it for JME when possible. Topiramate is useful for GTCS in both primarily and secondarily generalized seizures.[1,51,81] However, in JME, results obtained are good for GTCS but less so for myoclonic and absence seizures.[16] Although rare, the possible occurrence of ophthalmologic side effects (eye pain, redness, glaucoma) needs close monitoring because they are reversible after topiramate withdrawal.[8] Other side effects are more frequent and may require discontinuation (language and cognitive disturbance, psychotic episodes, weight loss, nephrolithiasis, dehydration). Paresthesia is usual and transient when starting treatment. Thus, we prefer TPM for refractory secondarily GTCSs rather than idiopathic GTCSs.

Levetiracetam is a promising drug for GTCS, whatever the associated seizure type and syndrome.[63] It may thus be a very useful alternative drug for JME. Even if there are no randomized controlled studies of patients with GTCS, small open-label studies and case reports provide preliminary information suggesting efficacy in both secondarily and idiopathic GTCS and myoclonic seizures.[45,69] The drug is usually well-tolerated, but behavioral toxicity such as aggressiveness and psychosis, usually in patients with known psychiatric symptoms, are reported.[66]

Carbamazepine or oxcarbazepine may be used if absences or myoclonus have not occurred, but there are different practices in different countries. These two drugs have been proved to aggravate every type of epilepsy with myoclonic components, including JME.[62,44] Thus, in Europe, experts believe that an accurate syndromic diagnosis must be established to exclude syndromes such as JME before prescribing them in patients with GTCS, and they should be restricted to patients who have secondary GTCS and given in the sustained-release formulation whenever possible to minimize side effects and improve compliance. Moreover, carbamazepine should also be avoided in GTCSs related to idiopathic rolandic (mid-temporal) epilepsy in children, because it could be responsible for a worsening of epilepsy, triggering negative myoclonus[52] and, exceptionally, continuous spike-and-wave activity during slow-wave sleep.[26,34] Patients may be referred for IGE syndromes with GTCS and already are taking such drugs that are not recommended for these conditions. If seizure control is complete and without side effects, we would not change drugs at once in these patients, although it would be useful to verify with detailed questioning and EEG that no myoclonic seizures are present. Outside Europe, carbamazepine and oxcarbazepine are more widely used, even for GTCS with IGE syndromes.

In patients with generalized or partial seizures, the side effects, interactions, and complex pharmacokinetics of phenytoin make it a second- or third-choice monotherapy drug except for parenteral use in convulsive SE or when enteral administration is temporarily impossible, and it should be avoided in JME.

Phenobarbital is an effective drug whose usefulness is limited by side effects, which may be inapparent, and by drug interactions. Its long half-life can be an advantage in cases of poor compliance, as in young adults, for example. The same considerations are valid for primidone, which was previously the treatment of choice in JME.[58] Phenobarbital remains popular, especially in developing countries, because it is very inexpensive and because it is believed to be relatively innocuousâ€"comment on these issues would be beyond the scope of this chapter. In IGEs with absences, it must be used with ethosuximide because it does not control absence seizures.

Benzodiazepines, mainly clobazam, are popular outside the United States as add-on treatment active against all seizure types, and they sometimes achieve complete seizure control. Clobazam is effective against photosensitivity. Unfortunately, many patients develop tolerance after a delay of weeks or months, with seizure reappearance. Clobazam can be given intermittently in cases of periodic seizure exacerbations as in catamenial epilepsy, in case of clusters and threatening SE, or in triggering situations (sleep deprivation, stress, etc.).

GTCSs usually occur in idiopathic syndromes with a generally good prognosis for seizure control and normal development, and adequate seizure control should mean *no seizures at all* in most cases, although very long-term treatment, possibly lifelong, is needed in JME and in seizures upon awakening. If an IGE syndrome with inadequate seizure control is diagnosed, and the patient is not taking valproate, it should be added if there are no contraindications, and a switch to valproate monotherapy should be considered. Although refractory cases exist, the diagnosis should be reevaluated if seizures persist despite optimal medical management. The possibility of rapidly generalized seizures arising in one frontal lobe should also be considered in these patients (see earlier discussion).

Because GTCSs can be triggered by factors such as sleep deprivation and alcohol withdrawal, and because patients are often adolescents or young adults, comprehensive treatment involves not only the right diagnosis and choice of AED, but also explanation and encouragement of the changes in habits that may be necessary.

Summary and Conclusions

Generalized convulsive seizures are common and dramatic manifestations of common IGE syndromes. It is very important to identify patients whose apparently generalized seizures arise from secondary generalization of a partial seizure. Idiopathic generalized convulsive seizures typically begin in later childhood, adolescence, and early adult life in otherwise normal subjects, but a history of febrile convulsions and a family history of epilepsy are risk factors. Interictal EEG abnormalities may be scanty, especially in treated patients, but generalized polyspike or spike-and-wave activity is typical, and many patients may be photosensitive. Recognition and appropriate treatment of idiopathic GTCSs offer a good prognosis for seizure control and intellectual development. Many patients with idiopathic GTCS have myoclonic jerks or absence attacks, and valproate used alone is the drug of choice. Successful treatment also requires attention to factors that may provoke the seizures, notably, sleep deprivation and alcohol withdrawal.

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Chapter 48

Generalized Clonic and Hemiclonic Seizures

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Masakazu Seino

Introduction

The generalized convulsive seizure has been known since antiquity, and the earliest descriptions appear in Egyptian hieroglyphics before 700 BC.[48] From the mid-19th century, the generalized convulsive seizure was considered the cardinal manifestation of genuine or idiopathic epilepsy caused by a predisposition to have seizures. The generalized convulsive seizure was described as *grand mal,*[26] a term that is still encountered. Whereas a great amount of literature has been dedicated to this seizure type, which corresponds to the generalized tonic-clonic seizure (GTCS), the distinction between GTCS and purely generalized clonic seizure (GCS) did not appear clearly before the mid-20th century. The first use of this distinction was in the original international classification of epileptic seizures proposed by the International League Against Epilepsy (ILAE),[23] in which they were a type of generalized convulsive seizure different from the tonicâ€“clonic, myoclonic, and tonic seizures. They were considered as observed especially in children.

In the same classification, the authors described a category of unilateral seizure including unilateral clonic seizures, also known as hemiclonic seizures (HCS), occurring almost exclusively in very young children. The existence of unilateral motor seizures with possible permanent hemiplegic sequelae, if the seizures are prolonged, has long been recognized.[4,17,26,37,47,51] However, the combination of seizure observation and recording and the study of a large series of cases with status epilepticus (SE), with or without hemiplegia and/or permanent epilepsy, enabled Gastaut et al.[22] to define precisely the electroclinical details of these unilateral seizures.

Definitions

These two seizure types, GCS and HCS, were better defined in the 1970 proposal.[19] The generalized seizures were â€œthose in which the clinical features do not include any sign or symptom referable to an anatomical and/or functional system localized in one hemisphere and usually consist of initial impairment of consciousness, motor changes which are generalized or at least bilateral and more or less symmetrical and may be accompanied by â€˜en masseâ€™ autonomic discharge; in which the electroencephalographic patterns from the start are bilateral, grossly synchronous and symmetrical over the two hemispheres; and in which the responsible neuronal discharge takes place, if not throughout the entire grey matter, then at least in the greater part of it and simultaneously in both sides.â€[19]

The unilateral seizures were â€œthose in which the clinical and electroencephalographic aspects are analogous to those of the generalized group, except that the clinical signs are restricted principally, if not exclusively, to one side of the body and the electroencephalographic discharges are recorded over the contralateral hemisphere. Such seizures apparently depend upon a generalized or at least very diffuse neuronal discharge which predominates in, or is restricted to, a single hemisphere and its subcortical connections. They are characterized by clonic, tonic or tonicâ€“clonic convulsions, with or without an impairment of consciousness, expressed only or predominantly in one side. Such seizures sometimes shift from one side to the other but usually do not become symmetrical.â€[19]

One epileptic clonic seizure is a form of generalized seizure peculiar to early childhood and characterized by (a) clinical loss of consciousness, one massive autonomic discharge, and more or less rhythmically repeated, bilateral clonic contractions, distributed more or less regularly throughout the entire body; (b) an associated mixture of rapid rhythms and slow waves realizing more or less regular images of spike-and-waves and polyspike waves in the electroencephalogram (EEG).[20]

However, 11 years later, the ILAE commission, in a new proposal, maintained the category of GCS, but withdrew that of unilateral clonic seizures (as well as all other unilateral seizure types), deeming them â€œputative syndromic seizures.â€[8] The definition of generalized seizure has changed. These seizures are now defined as â€œthose in which the first clinical changes indicate bilateral involvement of both hemispheres. Consciousness may be impaired and this impairment may be the initial manifestation. Motor manifestations are bilateral. The ictal electroencephalographic patterns initially are bilateral, and presumably reflect neuronal discharge which is widespread in both hemispheres.â€[8]

Finally, the last ILAE commission has proposed a completely new approach to the seizure classification, which can be found at its Web site (www.ilae-epilepsy.org). The glossary now defines *generalized seizure* to mean â€œa seizure whose initial semiology indicates or is consistent with more than minimal involvement of both cerebral hemispheres.â€ In the list of seizure types, generalized clonic seizures are not described, and the hemiclonic seizures are placed among focal seizures with no additional description.

In the semiologic classification proposed by LÃ¼ders et al.,[30] based on a purely clinical description of the seizures, the definitions are the same but expressed differently. Clonic seizures are simple motor seizures, consisting of a series of myoclonic contractions that regularly recur at a rate of 0.2 to 5 per second. Their different subtypes are indicated by the use of â€œmodifiers.â€ These seizures are *generalized* when the manifestations occur over a relatively widespread distribution, with approximately equal involvement of both sides and of the distal and proximal segments of the brain. These seizures may also be *localized*; in that case, different modifiers are used according to the somatotype localization, such as â€œleft-hand clonic seizure.â€ Unilateral seizures are not considered in this classification. Hemiclonic seizures may be described as â€œunilateral, left or right clonic seizuresâ€ or â€œleft or right hemibody clonic seizures.â€

These variations reflect our lack of knowledge of the true physiopathology of generalized and unilateral seizures, despite the progress in technical advances in all fields of investigation. In practice, no clear-cut borderline exists between generalized and unilateral clonic seizures in many cases, making it difficult, if not impossible, to classify them. Moreover, the two types can have a focal onset that is often hidden because of the rapid secondary generalization. Sometimes the generalized clonic seizure can begin with a very short tonic phase, but continue with all the characteristics of the purely clonic seizure. Outside of cases of SE, these seizures are not usually observed by the clinician, and most onlooker descriptions are not detailed enough to definitively classify them as generalized or unilateral in an infant or a young child. The observation of a postictal hemiparesis is in favor of ictal unilaterality.

As in GTCS, clonic and hemiclonic seizures may be an isolated event in the setting of an acute encephalopathy, a symptom of serious brain disease, or a manifestation of several epilepsy syndromes of differing prognoses.

Epidemiology

GCSs and unilateral clonic seizures or HCSs are rarely described in the literature, and they are not considered apart from GTCSs in epidemiologic studies. However, GCSs are probably rare, unlike HCSs, which are reported primarily in papers concerning the pediatric population because of their relative frequency in infancy and childhood.

In one single Spanish study,[36] GCSs are not specified, but the following data were reported for unilateral seizures, without distinction between HCSs and the other types: Among 5,000 patients consecutively recruited between1966 and 1990, 346 (6.92%) presented with unilateral seizures; 13.29% of them were febrile seizures and 18.21% developed during status; 53.17% started before 2 years, 80% before 6 years and only 2.02% after 18 years. The unilateral seizures were the initial seizures of generalized epilepsies in 7.5% of the patients, of focal epilepsies in 23.4%, and of undetermined epilepsy if generalized or focal in 65.9% (the majority).

In a previous series of 3,000 patients,[35] the same author found 151 patients (5%) with HCSs, separated into four groups. In the first group, 39 patients went on to a diagnosis of temporal lobe epilepsy (TLE). In the second group, 32 patients had Lennox-Gastaut syndrome (it is important to note that severe myoclonic epilepsy was not recognized as an epilepsy type in this study). In the third group, six patients had an idiopathic generalized epilepsy. In the fourth group, 74 patients had only HCSs.

In a pediatric French regional population-based study,[31] GCS had an incidence of 5.8 per 100,000 children younger than 10 years, in comparison with 8 per 100,000 with GTCS. HCSs were not counted because they did not appear in the 1981 international classification. Conversely, HCSs appeared in a pediatric Yugoslavian regional population-based study[42] in which they represented 6% of patients born between January 1, 1967 and December 31, 1984, aged less than 18 years, versus 0.3% for GCS and 38.8% for GTCS.

One could also indicate that, due to their propensity manifest during SE, HCSs have been often considered within epidemiologic studies of SE, whereas generalized clonic statuses are rarely separated from generalized tonicâ€“clonic seizures. Thus, Aicardi and Chevrie,[1] among 239 cases of SE, reported 102 cases with GCS status and 94 with HCS status. Congdon and Forsythe[9] reported 17 cases of SE treated by clonazepam, in which 14 were GCS status but none HCS status.

Clinical Features

Generalized Clonic Seizures

All authors recognize that clonic seizures are predominantly observed in infants and children, and very often tend to be lateralized. So, the descriptions usually given correspond to HCSs or GCSs evolving to HCSs or vice versa. We did not find many descriptions of seizures that were only generalized. In 1973, Gastaut[20] defined their characteristics: â€œLoss of consciousness, massive autonomic discharge, and bilateral clonic contractions more or less rhythmically repeated and more or less irregularly distributed in all the body parts. The ictal EEG shows a mixture of rapid rhythms and slow waves realizing more or less regular images of spike-waves and polyspike-waves.â€

A good description was reported by Gastaut and Broughton.[21] The attacks begin with loss of consciousness associated either with sudden hypotonia or, conversely, with a brief generalized tonic spasm, sometimes so abbreviated that it could be considered as massive bilateral myoclonus. Either causes falling. The child then remains on the floor for 1 minute or longer and is seized by a series of bilateral myoclonus, usually generalized, although often asymmetrical and predominating on one side or in one limb. Subsequently, the variability of amplitude, frequency, and spatial distribution of these jerks from one moment to the next may become quite extraordinary. The most unlikely combinations are observed. Rapid low-amplitude twitching of facial muscles, for example, may be associated with infrequent but very intense jerks of the upper limbs and with such rapid myoclonus of the lower limbs that virtual tetanic contraction results. In some children, particularly those 3 years of age or younger, the myoclonus remains bilaterally synchronous and massive throughout the attack, rather than showing such complex and unstable patterns. The autonomic changes are relatively unimportant, except during very prolonged seizures in which accumulated bronchial secretions may cause respiratory distress. Resumption of consciousness is rapid after brief seizures. Those of long duration, however, may be followed by a confusional or even comatose state with generalized muscular hypotonia and areflexia.

Other forms of clonic seizures, seen in older subjects, are more properly considered as absence status with marked myoclonus, often rhythmic, or prolonged myoclonic absences with the jerks repeated at 3 Hz.

Hemiclonic Seizures

Conversely, HCSs have been well studied. Here we report their description by Roger et al.,[43] completed by our own observations.

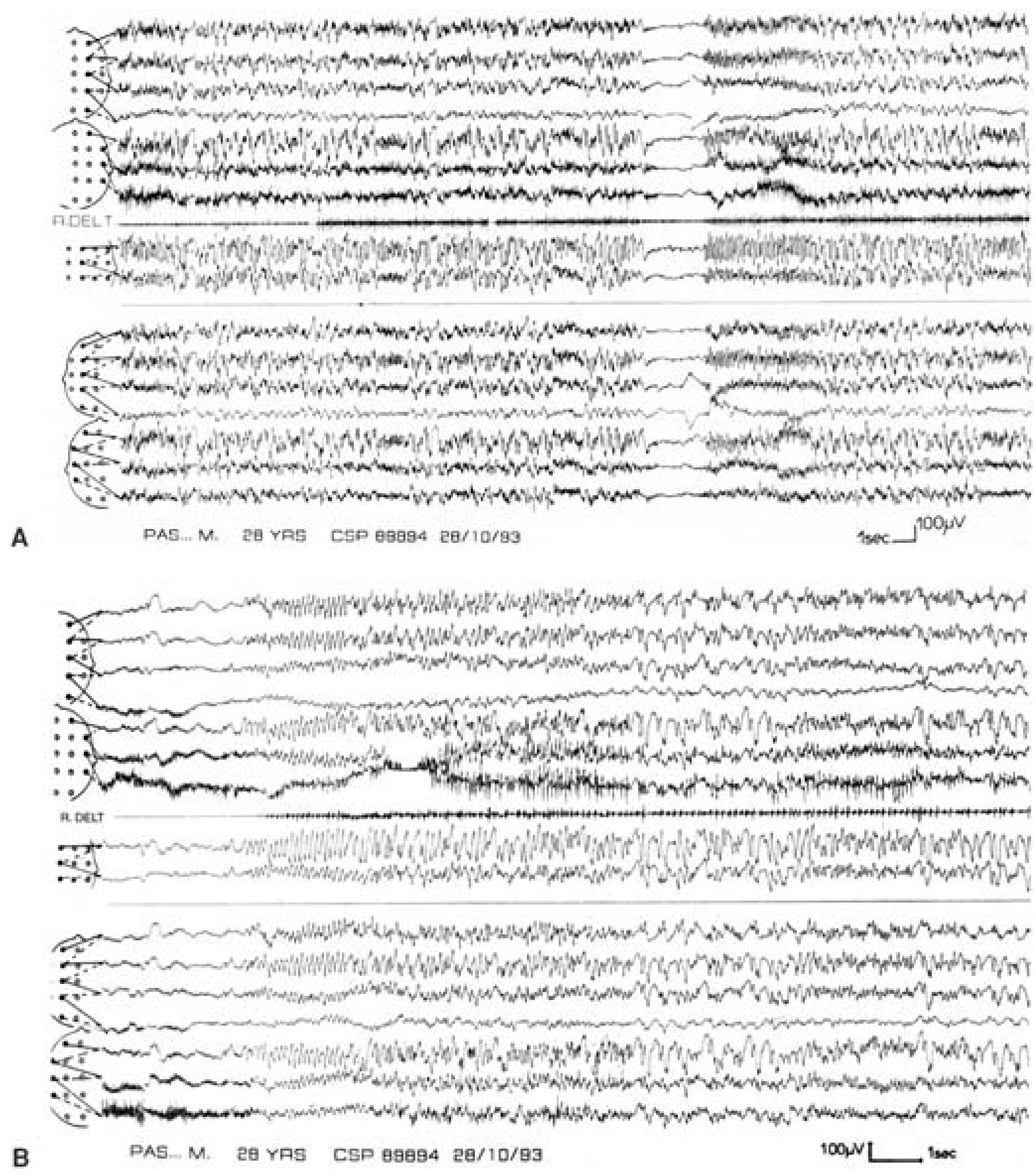
R.DELT
A
PAS... M. 28 YRS CSP 89894 28/10/93
1sec 100µV
R. DELT
B
PAS... M. 28 YRS CSP 89894 28/10/93
100µV 1sec

FIGURE 1. A: Generalized clonic seizure recorded in a 28-year-old woman suffering from an Angelman syndrome. Onset occurred 20 minutes before start of EEG. The irregular mixture of bilateral spikes and slow waves is well visible. The myoclonic jerks recorded in the right deltoid are extremely rapid. During a 2-second interruption of the jerks, a flattening of the EEG occurs. **B:** Another fragment of the same seizure recorded at 30 cm/sec. This better illustrates the variations of EEG patterns and myoclonus.

When observed, the onset is variable. Sometimes HCSs present as repeated clonic jerks or twitching of the eyeballs, followed by a deviation of the head to the same side. These are followed rapidly by hemifacial myoclonus that spreads to the upper and lower limbs. In other cases, the clonic jerks involve the entire side from the onset. In some cases, the clonic phase is preceded by a general discomfort, with abdominal pain, pallor, and loss of contact. Many children are discovered while already convulsing. More often, the seizures are of long duration (minutes, hours, even days). In such cases, the jerks show continuous changes in frequency, rhythm, and amplitude in the different body areas involved. This gives a pattern of erratic seizures. They may, for instance, disappear in the lower limb while continuing in the upper limb or the face, and then spread to the entire side of the body again, thereby

creating patterns of considerable complexity. At times they affect both sides of the body, either simultaneously as generalized seizures, or successively, as alternating epileptic seizures, so-called â€œsee-saw epileptic seizuresâ€ or *crises Ã bascule*. They also can affect one upper limb and the opposite lower limb together, as *crossed seizures*. Another eventuality consists of a seizure reduced for some minutes to the loss of consciousness with only slight jerks localized to a small muscular segment or with lateral deviation and slight clonic jerks of the eyeballs. The state of consciousness is variable and often difficult to assess. Either initial complete loss of consciousness occurs, or consciousness is little, if at all, impaired and may fluctuate while the seizure develops. Most often, there is a loss of contact, and the clouding of consciousness increases with the duration of the seizure, as do the autonomic manifestations (hypersalivation, pallor, cyanosis, vomiting). The end of the seizure usually is sudden, immediately followed by a flaccid hemiplegia, with or without Babinski sign, in the side involved; this is of variable duration, depending in part on the duration of the seizure. This aspect is difficult to determine in a child in coma with unilateral SE. The side of the hemiplegia gives a good indication for the lateralization of the seizure, which is not always easy to define in small infants, particularly when the seizure is not directly observed by a doctor. Spontaneous postictal recovery is progressive with an agitation phase whereas, after seizure interruption by a drug injection, the child may sleep quietly. However, when the seizure has been protracted (>1 hour) there is a risk for a definitive hemiplegia, first flaccid then spastic; this sequence constitutes the hemiconvulsion-hemiplegia (HH) syndrome, usually followed by epilepsy and manifesting as hemiconvulsion-hemiplegia-epilepsy (HHE) syndrome.[6] This syndrome has become rare with the advent of prompt, efficient treatment that shortens the duration of febrile seizures. The risk remains, however, for the development of later mesial TLE. It has been established by various authors that patients with mesial TLE often have had a long febrile seizure in early childhood.[5] The exact type of this seizure is generally not indicated by the authors, but we think a high probability exists for HCS, because this seizure type is most prone to be of very long duration, and we have found it in the history of our own patients.

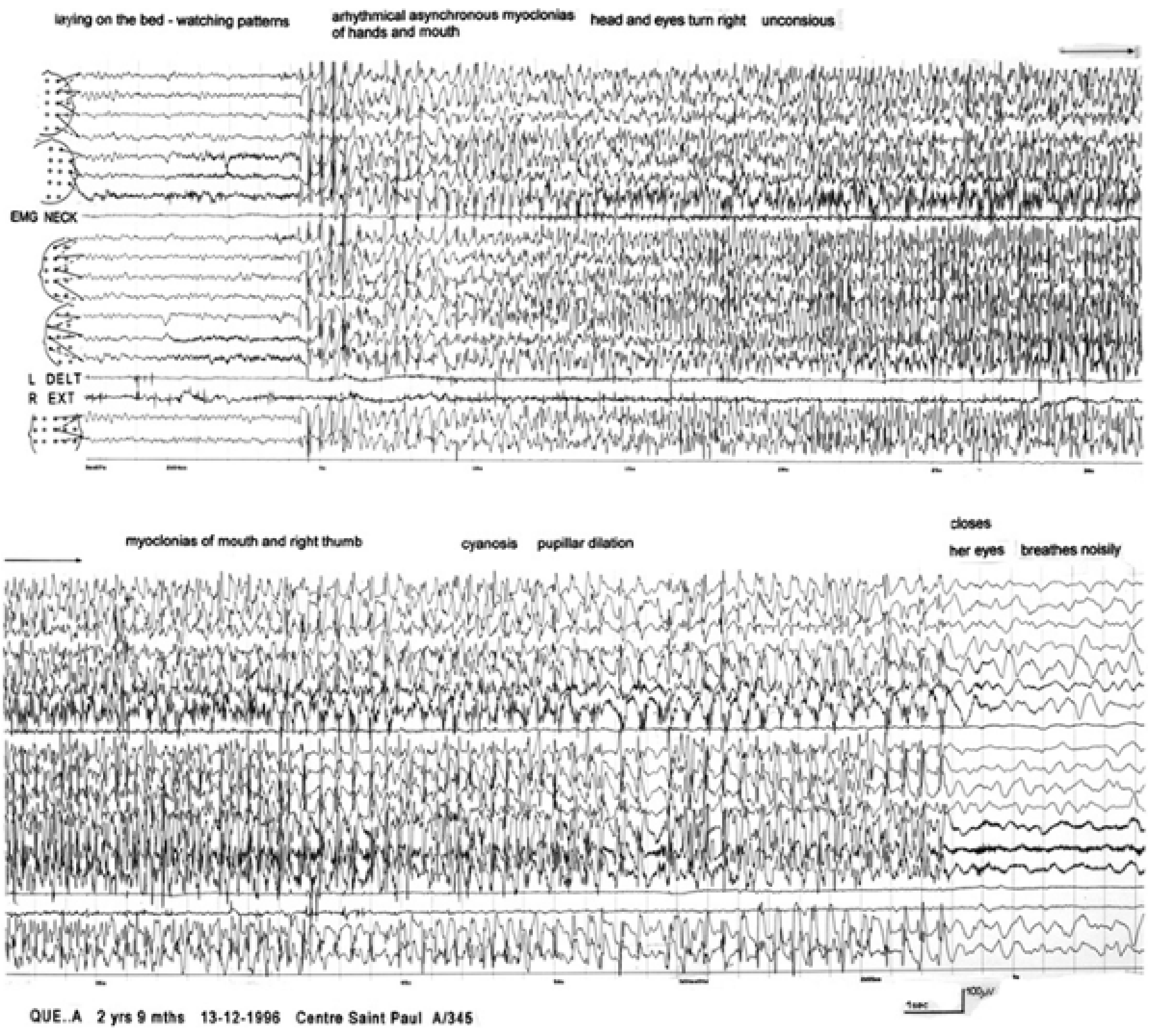
laying on the bed - watching patterns
arhythmical asynchronous myoclonias of hands and mouth
head and eyes turn right
unconsious
EMG NECK
L DELT
R EXT
myoclonias of mouth and right thumb
cyanosis
pupillar dilation
closes her eyes
breathes noisily
QUE..A 2 yrs 9 mths 13-12-1996 Centre Saint Paul A/345
1sec
100µV

FIGURE 2. Right hemiclonic seizure recorded in a 33-month-old girl suffering from severe myoclonic epilepsy

in infancy. EEG shows an onset of a burst of generalized spike-and-wave discharges (6 sec), progressively mixed with bilateral rapid activities prominent in the left hemisphere (30 sec), and followed by bilateral rhythmic spike-and-wave discharges of higher voltage in the left. After the end, bilateral Î´-waves and relative left depression are noted. Clinically the child presents with, unconsciousness, small myoclonic jerks that are arrhythmic in the hands and the mouth but rhythmic in the head (EMG), eyes and head deviation to the right, cyanosis, and brief postictal right motor deficit.

EEG Features

In GCSs, the ictal EEG patterns are generalized over the entire scalp and are often of considerable complexity (FIGURE 1). An epileptic recruiting rhythm at 10 Hz is intermingled with slower activity of changing frequency. The two activities are mixed from the start, giving a very complex discharge of

irregular spike-and-wave type. As in myoclonus, the EEG pattern can be extremely variable in time, with the relative predominance of rapid or slow activity over a given region of the scalp usually fluctuating from moment to moment. Simultaneous recording of EEG and electromyogram (EMG) shows no constant relationship between the hypersynchronous muscular potentials of a given body region and the presence of spikes (i.e., the sharp waves of the recruiting rhythm) over the contralateral scalp region. After the seizure, a transient period of diffuse slow-wave activity occurs without the phase of postictal electrical silence after a GTCS.

The interictal EEG can be normal or show only generalized discharges with normal background. More often, the interictal EEG findings depend on the etiology (discussed in the next section). In some cases, these findings are highly characteristic for a metabolic (hepatic, renal, hypoglycemic encephalopathy) or a degenerative disease (Lafora disease).

In HCSs, the clinical phenomena are concomitant with an ictal EEG discharge of bilateral slow waves, at around 2 to 3 Hz, greater in amplitude over the hemisphere contralateral to the seizure and associated there with a rapid recruiting rhythm discharge that generally predominates in the posterior scalp regions (FIGURE 2). Complex EEG patterns occur due to the unceasing changes in phase, frequency, and topography of the two components, such as rhythmic slow waves, or spike-and-wave, or polyspike-and-wave discharges, variable in frequency and distribution. At times, the discharge and myoclonus are interrupted for several seconds. The polygraphic recording shows no constant correlation between the muscular and the EEG phenomena. Immediately after the seizure, depression

of electrogenesis is noted over the contralateral scalp regions, followed by slow-wave activity of variable duration. The latter is not always correlated with the duration of the seizure. No depression occurs in the hemisphere ipsilateral to the attack, and normal EEG patterns are rapidly restored.

The interictal EEG findings vary according to the mechanism of the seizures. In infants and young children, when HCSs are the peculiar expression of a generalized epileptic process, the EEG shows only generalized discharges and a more or less normal background. In patients who have HCSs due to a symptomatic focal epilepsy, the EEG can show focal interictal anomalies corresponding to the underlying lesion. Sometimes it shows only an asymmetric background, for example, in patients who have a hemiplegia due to HHE syndrome. In other patients, EEG anomalies are multifocal, associated or not with generalized discharges, as in severe myoclonic epilepsy.

Anatomic Pathways and Pathophysiology

There are no specific studies separating GCSs from GTCSs, and mechanisms are probably the same as discussed in Chapter 47.

According to Gastaut and Broughton,[21] HCSs result from an excessive neuronal discharge limited to or predominating in a single hemisphere. The attacks either may originate in brainstem structures and be *unilateral from the start* or result from propagation of a local cortical discharge to brainstem structures and so be *unilateral of local onset or secondarily hemigeneralized.*

As with generalized seizures, unilateral attacks may be categorized into two groups depending on whether they result from a primary discharge involving the brainstem and its cortical connections, or from a distant focus propagating secondarily to the brainstem structures. In the latter group, the discharge is first localized in one hyperexcitable intrahemispheric neuronal population but then spreads very quickly to involve the entire ipsilateral hemisphere. Such an attack consists of a partial (focal) seizure with *secondary hemigeneralization* or a *unilateral seizure of local (focal, partial) onset*.

Why HCSs only or predominantly involve one hemisphere is not well known. In the first group, it is apparently due to asymmetries of neuronal excitability resulting from physiologic and pathologic factors still poorly understood.[2,52] In the second group, it could be due to an insufficiency of commissural transmission. Because they occur almost exclusively in early infancy, this insufficiency has been related to the structural and functional immaturity of the corpus callosum. This hypothesis is supported by the results of experimental animal studies that have demonstrated the role of the corpus callosum in the synchronization of ictal discharges in feline generalized epilepsy[33] and in Senegalese photosensitive epileptic baboons (*Papio papio*).[34]

Diagnostic Considerations

Obviously, the first step is to determine the epileptic nature of the paroxysmal event. Rarely, as regard to other seizure types, nonepileptic manifestations can mimic GCSs and HCSs. However, when the seizure has not been directly observed, it is mandatory to have a precise description of the symptoms from the onset to the end of the event, of the circumstances, the triggering factors, the previous history of the patient, and other pertinent details. In young children, for example, a febrile context is highly suggestive of an epileptic event. The diagnosis may be uncertain between repeated myoclonic jerks, either physiologic during drowsiness or pathologic, and a GCS in neonates, or between a syncope followed by a brief clonic phase and a GCS in infants, children and adults.

Concerning the diagnosis of the seizure type, we would like to underline a terminology problem raised by Porter,[41] who wrote that â€œmyoclonic is often used interchangeably with â€˜clonic,â€™ especially when used to describe fragments or â€˜myoclonic componentsâ€™ of a seizure.â€ Thus, it is sometimes difficult to differentiate between a long myoclonic absence with strong myoclonic jerks and a GCS. Indeed, the duration of the event is much shorter in absences, rarely exceeding 1 minute, and the rate of repetition is much higher (several a day). The same criteria can be applied to those cases in which myoclonic jerks are grouped in bursts and repeated at brief intervals, with full consciousness (as in juvenile myoclonic epilepsy), often early in the morning.

According to Treiman et al.,[49] a generalized convulsive SE that either has not been treated or has been treated inadequately evolves to one phase they have named â€œsubtle generalized convulsive status,â€ in which the clinical manifestations are reduced to loss of consciousness and subtle twitching of the fingers, abdominal muscles, or face, or nystagmoid jerks of the eyes while the ictal EEG discharges persist. This electroclinical picture could be diagnosed as a purely clonic or myoclonic status.

The *differential diagnosis* between GCS and HCS should be easy in adulthood. At this age, GCSs are more frequent than HCSs, and the semiology is clear enough to be described without ambiguity. The main question is whether the seizure is primarily or secondarily generalized. That information is obtained from eyewitness accounts of seizure onset. A careful neurologic examination may find interictal signs of localization, actually rarely present. The interictal EEG may also give good information when asymmetry or focal anomalies are present.

In infants and young children, we have seen that GCSs and HCSs are not well differentiated, sometimes having the same generalized basis, as in severe myoclonic epilepsy. The best way to understand the ictal semiology is to use video-EEG and polygraphic recordings, rarely available in a clinical situation. If this is not possible, the diagnosis can be aided by the search for a transitory postictal lateralized motor deficit, which can be obvious after one diazepam injection. A postictal recording is still useful in demonstrating the presence (or absence) of a clear asymmetry of the background activity. In that case, the etiologic workup will be orientated toward a localized origin, even if it is known that a diffuse pathologic process (e.g., metabolic disease) cannot be eliminated a priori.

Specific Syndromes Incorporating the Seizure Type as an Integral

Feature

GCSs and HCSs are the expression of either primarily generalized seizures or generalized seizures secondary to a focal onset, and they may occur in many various clinical situations.

Simple febrile seizures more often manifest as tonic and tonicâ€"clonic in nature, but they sometimes present a GCSs.[15,16] It is important to differentiate them from massive myoclonias because they do not have the same meaning. In *complex febrile seizures*, HCSs occupy a predominant place and constitute a situation of emergency due to the risk of occurrence of HH syndrome, which occurs in about 4% of patients.

Pyridoxine dependency in infants causes various seizure types, including GCSs and HCSs, which are severe and often result in SE. Antiepileptic drugs (AEDs) are not efficacious, and only pyridoxine, first given intravenously then orally, allows recovery.

In our own experience, GCSs are observed in various *metabolic disturbances*, and *anoxic and toxic encephalopathies* in children as well as adults.[38,44] In one study, PoirÃ©[40] reported an extensive and deep analysis of hypoglycemia-induced epileptic seizures in a psychiatric ward where Sakel's cure was regularly applied. He showed the seizures could feature all the different aspects of generalized convulsive seizures, from isolated myoclonic jerks, grouping of massive myoclonias, and purely clonic fits to, more rarely, full tonicâ€"clonic seizure. Data are scanty in the recent literature, but Dulac,[15] in one review, confirmed that GCSs sometimes occur in children in hyponatremia, hypoglycemia, or hypocalcemia. The report by Dalla Bernardina et al.[10] on hypernatremia give additional details. Other authors who have reported seizures in metabolic encephalopathies in adults mentioned generalized seizures only, and it was impossible to know if they were GTCSs or GCSs.[18,45]

GCSs are one of the seizure types observed in most of the *progressive myoclonus epilepsies*.[24] In Unverricht-Lundborg disease, they often present as a sequence of clustered massive myoclonic jerks triggered by voluntary movement. They may develop into full GCS with impairment of consciousness. A brief tonic component may be inserted between the two phases, producing a clonicâ€"tonicâ€"clonic seizure.

GCSs and HCSs are also a part of the epilepsy present in some *chromosomal disorders*. Although in Angelman syndrome the most typical seizures are long myoclonic status, we have observed true generalized clonic seizures, sometimes evolving to SE, in patients presenting with this syndrome, in accordance with other authors.[10,28] HCSs are rarely signaled in this syndrome.[32] GCSs and HCSs were also reported in patients with 4p-syndrome.[3,25]

GCS can occur in *epilepsy with myoclonic astatic seizures (Doose syndrome)*, in association with generalized tonicâ€"clonic seizures and drop attacks.

HCSs are observed in *idiopathic focal epilepsies* in childhood. They appear in *benign epilepsy with centrotemporal spikes* in children aged 2 to 5 years. These seizures sometimes last more than 30 to 60 minutes and are followed by a transient homolateral deficit, generally not including the face.[12]

In *early-onset benign childhood occipital epilepsy (Panayiotopoulos syndrome)*, HCSs occur in 25% of patients in a context of behavioral (irritability) and autonomic symptoms (pallor, sweating, nausea, vomiting), usually with impairment of consciousness.[39] They are only nocturnal in 66% of patients. Their duration is variable, from minutes to hours. When prolonged, they are followed by a transient hemiparesia.[50] HCSs may also occur in 43% of patients presenting with *late-onset childhood occipital epilepsy (Gastaut type)*, in which the visual symptoms and headache are more characteristic.

Rare cases of idiopathic generalized epilepsy with hemiconvulsive seizures within the framework of *juvenile myoclonic epilepsy* have been reported.[29] These patients presented with bouts of grouping myoclonic jerks lateralized on one hemibody; these seizures were of brief duration (from seconds to few minutes), occurring without loss of consciousness and repeated several times a day. Ictal and interictal EEGs showed generalized 3-Hz spike-and-wave discharges, asymmetrical during the attack. This type of seizure seems to be myoclonic rather than truly hemiclonic. HCSs have been reported as initial seizures in the syndrome of *electrical status epilepticus during slow sleep (ESES or CSWS)*,[46] related to a focal epilepsy preceding the syndrome.

HCSs are the hallmark of *HH syndrome*, occurring mostly in young children, and they may continue later in life, during the course of HHE syndrome. They are more extensively described in Chapter 233 (Arzimanoglou et al.). It is noteworthy that, in developed nations, this situation has dramatically declined over the last quarter century, and is either exceptional or absent in the recent series of SE studies[27]; it persists, however, in developing countries where prompt control of SE may be lacking.

We have observed a HHE syndrome in one diabetic patient presenting with undiagnosed hypoglycemic coma and followed by focal epilepsy. Three children presenting with HHE syndrome due to hypoglycemia were reported by Christiaens et al.[7] HCS in hypoglycemia and hypocalcemia are also mentioned by Dalla Bernardina et al.[11]

Hemispheric brain malformations are a relatively frequent etiology of HCS, as it is observed in corpus callosum agenesia, hemimegalencephaly, or Sturge-Weber disease. In the latter, repeated and prolonged HCSs lead to the risk of a permanent hemiplegia and represent a strong indication for an early pharmacologic treatment and, if not efficacious, early surgery.

HCSs of focal onset can occur in *many other situations* that provoke epileptogenic lesions (e.g., head trauma, subdural hematoma, intracerebral hemorrhages, meningitis, ischemia). They are more frequently due to lesions in the frontal lobe, but they can originate in the occipital or parietal lobe by spreading of the discharge above the sylvian fissure. This evolution is less frequent for the temporal localization of the lesion.

We have described a group of patients[13] whose epilepsy began in childhood (between 1 and 5 years) and was always characterized by HCSs during its course, with a strong tendency to evolve into SE. It included subjects with and without signs of brain damage. It represented a peculiar type of focal epilepsy, which should be acknowledged because its treatment raises specific problems.

GCSs and HCSs are also the hallmark of *severe myoclonic epilepsy in infancy (Dravet syndrome)*, which begins in the first year of life with the occurrence of these seizures, with or without fever, in a previously normal infant. They were fully described by Dravet et al.[14] (see Chapter 231). We would like to underline their variable aspects in this syndrome. The clinical phenomena can be generalized from the onset and remain during the entire seizure event. At other times, they can be initially localized, mainly in the facial muscles, before becoming unilateral or generalized. In other seizures, a fluctuation occurs from one side to the other, and from one body part to another. The clonic jerks can be associated with a tonic muscular contraction of variable intensity during the event. The EEG abnormalities correlate with these fluctuations, giving the impression of â€œfalsely generalized seizures.â€ We have postulated that these seizures were the expression of multifocality in infants having a very low epileptic threshold. True HCSs may also occur in this syndrome, often with a tonic component (FIGURE 3). They can affect both sides of the body successively in the same seizure and from one seizure to another one, this variability being a strong argument for the diagnosis of Dravet syndrome.

Responses to Treatment

GCSs and HCSs are often prolonged seizures, with a risk of SE, and they require rapid and vigorous treatment. They respond well to rectal or intravenous benzodiazepines. If seizures continue or cease only transiently, treatment for SE should be started. A diagnostic workup for etiology (EEG, biology, CT scan) must be started simultaneously in the emergency ward, in order to treat the immediate cause when possible (e.g., hyperthermia, infection, metabolic disturbance).

After the episode ends, treatment depends on the circumstances and etiology. Except in case of simple febrile seizures, usually an antiepileptic treatment must be initiated and continued as long as the diagnosis remains uncertain. When the seizure is symptomatic of an acute disease, treatment is adapted to the nature of this disease and, sometimes, rapidly interrupted. In other situations, treatment must be tailored in accordance with the electroclinical picture.

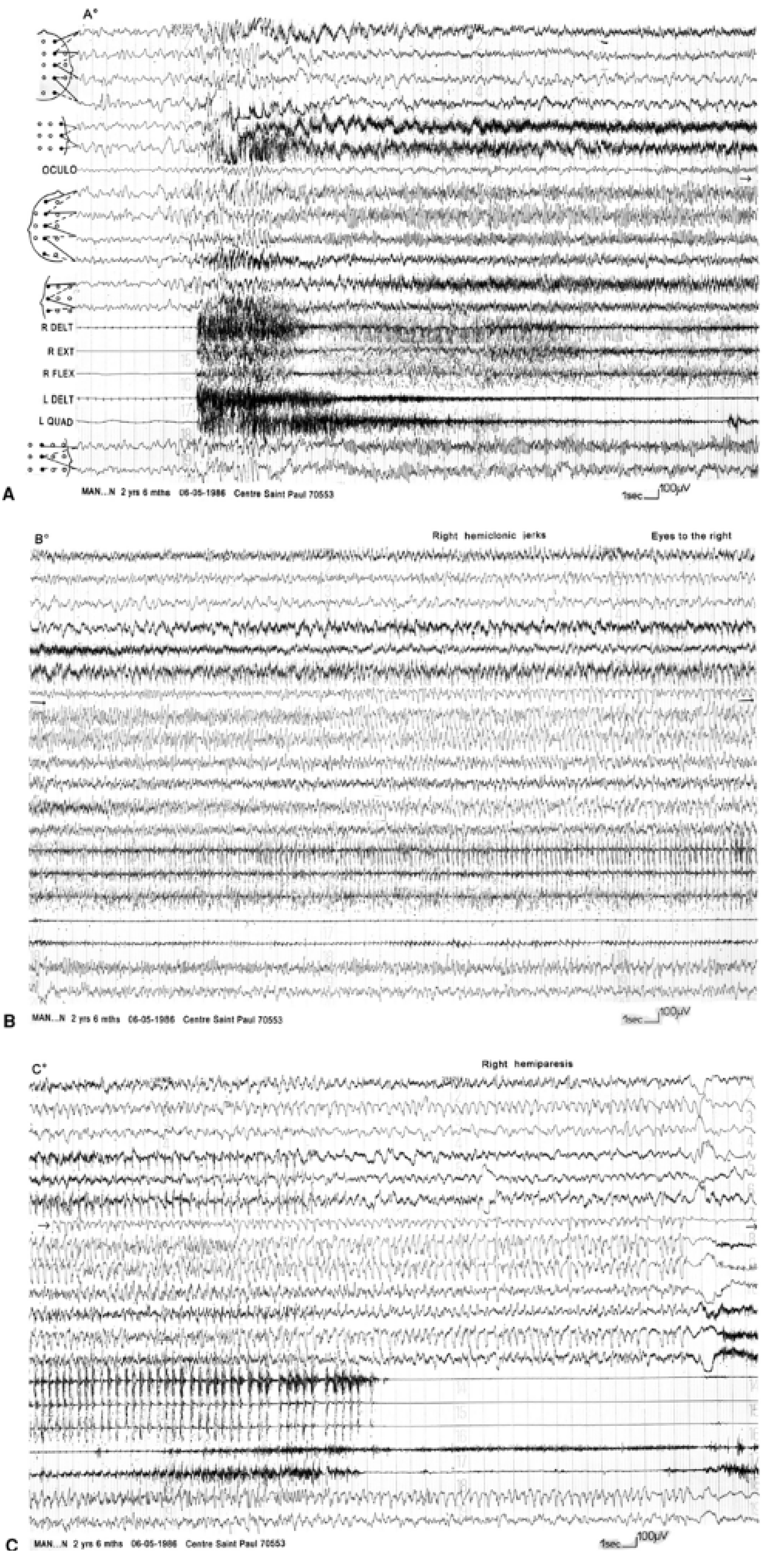
A°
OCULO
R DELT
R EXT
R FLEX
L DELT
L QUAD
A
MAN...N 2 yrs 6 mths 06-05-1986 Centre Saint Paul 70553
1sec 100µV
B°
Right hemiclonic jerks
Eyes to the right
B
MAN...N 2 yrs 6 mths 06-05-1986 Centre Saint Paul 70553
1sec 100µV
C°
Right hemiparesis
C
MAN...N 2 yrs 6 mths 06-05-1986 Centre Saint Paul 70553
1sec 100µV

FIGURE 3. A right hemiclonic seizure recorded during SE in a 30-month-old boy suffering from severe myoclonic epilepsy in infancy. **A:** The EEG shows onset with a bilateral burst of slow and sharp waves, beginning in the left frontocentral channels; after 7 seconds, a discharge of fast, high-voltage activity develops on the left hemisphere for about 30 sec. **B:** This activity then is mixed with slow waves, which become rhythmic at 2 to 2.5 Hz at the end of the seizure. (**C**): All these activities are present on the right hemisphere with a much lower amplitude. The EMG shows brief bilateral tonic contraction (6 sec), followed by extremely rapid myoclonic jerks on the right muscles associated with a slight tonic muscular background; at the end (**C**), the jerks slow down and stop abruptly while the EEG discharge persists. Myoclonic jerks of very low amplitude are also present on the left quadriceps (**B**). A right hemiparesis is observed after the end of the seizure.

As indicated earlier, GCSs and HCSs are related to many various epilepsy types, more often symptomatic than idiopathic, and the treatment will be established for every specific syndrome. All classical and modern AEDs active against generalized convulsive and focal epilepsies can be used, none being more efficacious than another in this seizure type. Their indication depends on the generalized or focal nature of the seizure. Only the AEDs specifically used against absences should be avoided, unless the patient has absences associated with convulsive seizures.

When febrile or afebrile GCSs or HCSs occur in an apparently normal infant and are repeated during the first year of life without known reason, the diagnosis of severe myoclonic epilepsy may be suggested, and it is reasonable to quickly institute a chronic treatment to minimize the risk of SE and delayed psychomotor development.

Summary and Conclusions

GCSs are a type of generalized convulsive seizures that present at every age in different etiologic contexts. In adults, they are often observed within the framework of acute metabolic pathologies and in progressive myoclonic epilepsies. They have a trend to be prolonged and to develop into SE. In childhood, they occur also in various situations, such as febrile seizures, metabolic diseases, and generalized epilepsies (Doose and Dravet syndromes).

HCSs are a particular seizure type, much more frequent in children than in adults. They can be related to either a generalized or focal epilepsy. They have a strong tendency to be prolonged and to produce SE, which can be followed by a definitive hemiplegia and further epilepsy (HHE syndrome). When they occur in a febrile context, they can be responsible for later TLE. Thus, these seizures represent a pediatric emergency, and they must be treated as soon as possible using intrarectal or intravenous diazepam, to avoid hemiplegia and TLE. They also can be the first manifestation of Dravet syndrome, especially when their lateralization changes during the seizure and from one seizure to another one.

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Chapter 49

Typical and Atypical Absence Seizures, Myoclonic Absences, and Eyelid Myoclonia

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Introduction

The first clinical description of generalized absence seizures was by Poupart, in a report to the Académie Royale des Sciences in 1705: "At the approach of an attack the patient would sit down in a chair, her eyes open, and would remain there immobile and would not afterward remember falling into this state. If she had begun to talk and the attack interrupted her, she took it up again at precisely the point at which she stopped and she believed she had talked continuously." Later in the eighteenth century, Tissot used the terms *grands accès* ("great attacks") and *petits accès* in describing a 14-year-old child whose intervals between generalized convulsive seizures were punctuated with "a movement of the eyelids which at first seemed to be a tic, but which was soon recognized as convulsive."[15,115] Adie[1] later described the characteristic features of a form of epilepsy with a good prognosis occurring in children. Neurophysiologic investigations in patients with epilepsies and impairment of consciousness by Gibbs and Gibbs[42] proved for the first time that spike-and-wave paroxysms were the electroencephalographic (EEG) correlate of absence seizures. The clinical correlates of absence seizures during spike-and-wave paroxysms in the EEG also were described by Lennox and Davis.[65] Although the terms *petit mal* and *absence* have been used interchangeably to describe this distinctive seizure type since the early part of the nineteenth century, it has been only with the advent of video-EEG (V-EEG) monitoring and careful studies utilizing that technique[87] that the clinical spectrum of the absence seizure has come to be understood.

Definitions

Generalized absence seizures may be defined as a paroxysmal loss of consciousness of sudden onset and sudden end that is associated with bursts of bilaterally synchronous spike-and-wave discharges recorded on the EEG. Behaviorally, absence seizures are characterized by a sudden clouding of consciousness, usually associated with a motionless stare and cessation of ongoing activities. The beginning and end of the seizure are abrupt, and no aura or postictal state is observed. In addition to the clouding of consciousness, mild motor and automatic symptoms may occur. Brief absences may be detected only by cognitive testing during the seizure itself. Frequency of seizures in absence epilepsy varies from daily to weekly.

Absence seizures may be "typical" or "atypical." Typical absence seizures are the most common, and are characterized by a loss of consciousness that is time-locked with bursts of bilaterally synchronous 3 cycles per second spike-and-wave discharges (SWD). Little if any cognitive impairment is observed with typical absence seizures, which generally respond well to pharmacologic treatments. This is in contrast to atypical absence seizures, which are less common, respond poorly to treatment, and are often associated with severe neurologic impairment.[7,16] Although the pharmacologic profile of the two absence types is the same,[25] four features may be used to distinguish typical from atypical absence seizures. The first is the neural circuitry involved in the

SWD. In typical absence seizures, the epileptiform activity is constrained within thalamocortical circuitry.[6,101] In contrast, there are experimental,[21] clinical,[41,53,91] behavioral,[19] and neuroimaging[36] data for the involvement of both thalamocortical and limbic circuitry in atypical absence seizures.

The second defining feature relates to the frequency of the spike-and-wave discharge. In typical human absence epilepsy, the frequency of the SWD is 3 Hz, while in atypical absence epilepsy the frequency is typically 1- to 2-Hz, and the background rhythms are slow for age.[81] In rodent experimental models of typical and atypical absence epilepsy, the SWD frequency is similarly disparate, being 7- to 9-, and 4- to 6-Hz, respectively.[20,21,22,101]

The third major difference concerns voluntary behavior during the ictus. The ictal behavior in typical absence has an abrupt onset and offset that is time-locked with the spike-wave discharges. In contrast, voluntary movement and at least partial consciousness is maintained during the ictus in atypical absence seizures, in which the ictal behavior is gradual in onset and offset and is not time-locked to the spike-wave discharge.[7,16,21,39,53,68,81,101]

The final distinguishing feature is that a major difference in outcome occurs between children with typical versus atypical absence seizures. Children with typical absence seizures generally have a good outcome and are spared major cognitive deficits. This may relate to the restriction of the SWD to the thalamocortical circuitry in typical absence epilepsy. In distinct contrast, atypical absence seizures are associated with a severely abnormal cognitive and neurodevelopmental outcome in children.[35,81] Similar cognitive deficits are observed in experimental models of atypical absence seizures.[19] Therefore, whether absence seizures are typical or atypical is often used as a predictor of outcome in children with absence epilepsy.

Epidemiology

The annual incidence rate of absence seizures has been estimated to be 1/10,000.[49] The estimation of the prevalence of absence seizures varies from 2.3%[65] to 37.7%.[64] Cavazzuti[17] observed absence seizures in about 8% of epileptic children of school age. In absence epilepsies among children, absences are more frequent in girls than in boys. Absence seizures are

more often seen in childhood epilepsy, and predominantly occur in children of school age;[84] however, absence seizures also are seen in adults,[32] albeit less commonly.

A family history of epilepsy is found in 15% to 44% of patients with generalized absence seizures,[65] and an inherited factor in human absence seizures was first recognized by Metrakos and Metrakos.[77] Genetic factors play a predominant role in the etiology of idiopathic generalized epilepsies with typical absence seizures.[11,66,67] Because the concordance for absence seizures in monozygotic twins does not reach 100%, acquired factors also probably play a role in the causation of this type of seizure.[10,11] Myoclonic absence is a rare seizure type with a male preponderance. The mean age of onset is 7 years (range: 9 months to 12 years).

Recently, the γ-aminobutyric acid $(GABA)_A$ receptor γ-2 subunit mutation R43Q has been reported to be an autosomal dominant mutation associated with childhood absence epilepsy and febrile seizures.[62,71] This mutation appears to impair $GABA_A$ receptor function by compromising $GABA_A$ receptor trafficking and reducing surface expression.[62]

Anatomic Pathways and Pathophysiology

The current thinking about the pathogenesis of absence seizures dates to the landmark experiments of Jasper and Droogleever-Fortuyn,[58] who demonstrated that electrical stimulation of the midline and intralaminar nuclei of the thalamus in cats at a frequency of 3 cycles per second could produce bilaterally synchronous spike-and-wave discharges in the cortical EEG of those animals. The relevance of this finding to human epilepsy was demonstrated in 1953, when Williams,[120] utilizing depth-electrode recordings from the thalamus of a child with absence seizures, demonstrated that bilaterally synchronous spike-and-wave discharges with a frequency of 3 cycles per second arose from that structure. During the next 20 years, a debate ensued in the literature as to which region was preeminent in controlling the bilaterally synchronous spike-and-wave discharges characteristic of absence seizures: the cortex,[3,70,116] the thalamus,[88] or both.[43] During the last 10 years, studies using several available animal models of generalized absence seizures coupled with sophisticated in vitro electrophysiologic techniques that allow investigation of cortical and thalamic networks have begun to shed light on the basic neurobiologic mechanisms of generalized absence seizures.

In 2002, Mereen et al., using the WAG/Rij rodent model of typical absence seizures, showed that a functionally intact thalamocortical network is required for the generation of spike-and-wave discharges.[75] By investigating the corticothalamic interrelationships in this model with nonlinear association signal analyses of multiple SWDs, those authors showed a consistent focus within the perioral region of the somatosensory cortex. From this focal activity, generalization took place rapidly over the cortex. During the first cycles of the seizure, the cortex appears to drive the thalamus, followed by the cortex and thalamus driving each other, thus amplifying and maintaining the rhythmic discharge.[76]

The fundamental underlying mechanism of absence seizures involves thalamocortical circuitry and the generation of abnormal oscillatory rhythms from that particular neuronal network.[28,29,38,73,74,77] Biochemical mechanisms operative within thalamocortical circuitry during this neuronal oscillation seem to entail phase-locked inhibition mediated by $GABA_B$ (γ-aminobutyric acid) alternating with glutamate-mediated excitation. The basic cellular mechanism operative within this tension between excitation and inhibition appears to involve low-voltage activated or T-type calcium (Ca^{2+}) currents, activation of which within thalamocortical circuitry plays a critical role in the development of the thalamocortical network oscillations that underlie absence seizures.[23,73] Of the three α1-subunits of the T-type Ca^{2+} channels, the α1G-subunit is critical to the genesis of spontaneous absence seizures.[102,122]

Local circuitry within the thalamus may influence the oscillatory rhythms that characterize absence seizures by $GABA_A$-mediated inhibition.[55] Pharmacologic factors that play a role external to the thalamocortical circuitry in the genesis of absence seizures include cholinergic, dopaminergic, and nor-adrenergic mechanisms.[72] Pathways utilizing these various neurotransmitters project onto the thalamus, cortex, or both from sites distant to those structures and may modulate the process either up or down. Perturbation of one or more of these neuronal networks, particularly those involving the basal ganglia[27,99] and the superior colliculus,[79] may lead to abnormal neuronal oscillatory rhythms within the thalamocortical circuitry, with resultant generation of the bilaterally synchronous SWDs that characterize generalized absence seizures.[100]

Although these mechanisms may explain the alteration of consciousness that occurs with absence seizures, the pathophysiologic mechanisms of the motor symptoms that so often accompany absence seizures are not as clear. Many of the mild motor phenomena of absences consist of turning and rotating movements around the vertical body axis, raising and lowering of extremities, or even episodes of decreased tone. These movements belong to the motor activity controlled by the phylogenetically old system that mediates posture and locomotion, the so-called *eneirismatic motor system.*[51] Hassler[48,49] has shown that different brainstem structures are involved in the performance of this kind of motor activity. The brainstem, truncothalamic projecting pathways and extrapyramidal cortical areas, supplementary motor area, and anterior part of the gyrus cinguli are all known to play a major role in inciting and coordinating complex movements such as those seen in some types of absence seizures.[3,112]

Table 1 Clinical features of absence seizures

Cognitive impairment: staring gaze, change of facial expression: 94%	
Type 1: **ocular motor productive (89%)**	*Type 2:* **nonocular sporadic motor (11%)**
Rhythmic lid/eye clonic tonic retropulsive predominance oral and nonoral automatisms (march)	Sporadic myoclonic tonic without oral automatism

EEG: background normal generalized >>>regional ictal: fast rhythmic SW duration long (often 5–15 s or even longer)	Slowing focal abnormalities generalized>regional slow rhythmic SW duration low (often <10s)

SW, spikes and waves.

Clinical Features

Ictal

V-EEG split-screen studies of generalized absence seizures show that, in addition to cognitive impairment, staring and a change of facial expression occur in 94% of investigated absence seizures[108] (Table 1). Therefore, cognitive impairment, staring, and a change of facial expression represent the most common and important signs of absence and are common to all types of this seizure disorder (Table 1). In an attempt to differentiate absence seizures based on ictal clinical symptomatology, two types have been suggested: type 1 (*ocular motor productive*) was described in 89% of all absence seizures, and type 2 (*nonocular sporadic motor absence*) in 11%. The typical ocular motor productive absence seizure was characterized by predominantly ocular motor activity at the beginning of or during the seizure. The motor activity consisted of mild, rhythmic lid or eye clonic activity, tonic retropulsion of the eyes and head, or both. Oral automatisms were often combined with the ocular activity, and if the duration of the absence seizure was prolonged, nonoral (gestural) automatisms sometimes occurred. The motor activity often showed a "march" from ocular or facial regions to the extremities (Fig. 4). The atypical nonocular sporadic motor absence seizure was associated with sporadic myoclonic jerks, primarily of the head and extremities, and occasional oral automatisms.[108]

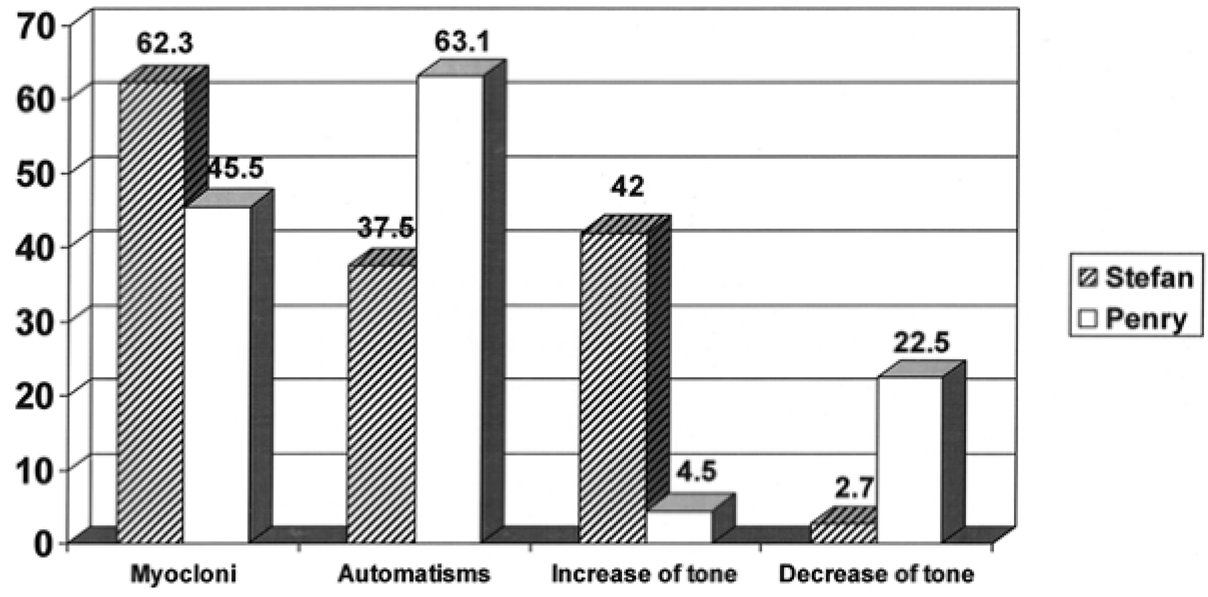

FIGURE 1. Comparison of frequency of different mild motor symptoms during absence seizures as documented by V-EEG recordings. From Stefan H, Burr W, Hildenbrand K, et al. Computer-supported documentation in the video analysis of absences. Preictal-ictal phenomena: Polygraphic findings. In: Dam M, Gram L, Penry JK, eds. *Advances in Epileptology: the XIIth Epilepsy International Symposium*. New York: Raven Press, 1981, with permission.

In addition to the phenomenologic description of clouding of consciousness during absence seizures, Janz[57] described subtle motor symptoms and differentiated absences according to the direction in which these motor symptoms progressed: retropulsive, propulsive, and adversive absences; those with no predominant direction; and those with no motor symptoms. Up to this time, automatisms had rarely been noted. However, subsequent investigations[8,24,40,87,90,103] showed that automatisms were not an uncommon occurrence in absence seizures. Penry et al.[87] took a further important step by using V-EEG monitoring to analyze the frequency of different absence components according to the criteria of the International Classification of Epileptic Seizures. V-EEG analysis of absence seizures showed clearly that absences with impairment of consciousness only, so-called *simple absences*, were rare.[53,86,87,107] For example, in 59 patients with 528 absences, only two cases of simple absence were recognized.[107] During a simple absence seizure, no ocular movements occur. Absences with ocular movements show mild tonic or clonic movements. In addition to upward ocular movements during an absence seizure, adversive movements of the eyes may occur (mild tonic, clonic, or both). An analysis of ictal signs in typical absence seizures has shown that mild myoclonic or clonic phenomena and automatisms are a common adjunct to clouding of consciousness. The studies of Penry et al. and Stefan et al. are compared in FIGURE 1.

Patient No														25								26																					40
Seizure No		1	2	3	4	5	6	7	8	9	10	11	12	POS	1	2	3	4	5	6	7	POS	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	POS
Myocloni sporadic	lid			●		●								●																													
	face																																		●					●			●
	bulb																																										
	head-lowering					●								●																													
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	head-turning																	●				●																					
	trunc																																										
	arms																																●	●									●
	legs																																	●									●
	anything			●		●								●			●	●				●											●	●	●					●			●
Myocloni rhythmic	lid		●				●							●		●				●		●	●	●	●		●	●			●	●	●	●	●		●	●	●	●			■
	face																																		●								●
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Tone	lid		●	●	●	●		●	●	●	●	●	●	■			●					●	●	●	●	●	●				●	●	●	●	●		●	●	●		●	●	■
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Auto-matisms	non oral			●	●	●	●		●		●	●	●	■					●			●																		●			●
	oral		●	●	●	●	●	●	●	●	●	●	●	■							●	●	●																				●
	anything		●	●	●	●	●	●	●	●	●	●	●	■					●		●	●	●																	●			●
Automatic phenomena					●	●	●							●																													

● low
◆ medium
■ high

FIGURE 2. Profile of symptom activity of mixed absences (POS). Left side of figure shows different absence components. The first row contains the patient number, the second row the absence number. Vertically, the occurrence of symptom in each absence is marked by a *star*. All absences of one patient are combined as an aggregate of the seizures of that patient. The results are shown in the *shaded columns*, the "profile of symptoms." Patients 25, 26, and 40 have mixed absences with myoclonic, tonic, and automatic components. The activity of components occurring in not more than 33% of the absences of a patient is defined as low (marked on the graph by a *point*), between 33% and 66% as medium (marked by a *rhomboid*), and above 66% as high (marked by a *rectangle*). The POS of patient 26, for example, shows a low level of all the components;

the POS of patient 25 shows a high level of the combination of light myoclonus and increase of tone. Cluster analysis of the motor symptom activity of all V-EEG–documented absences indicates a continuum from low to high activity. From Stefan H, Burr W, Hildenbrand K, et al. Computer-supported documentation in the video analysis of absences. Preictal-ictal phenomena: Polygraphic findings. In: Dam M, Gram L, Penry JK, eds. *Advances in Epileptology: the XIIth Epilepsy International Symposium*. New York: Raven Press, 1981, with permission.

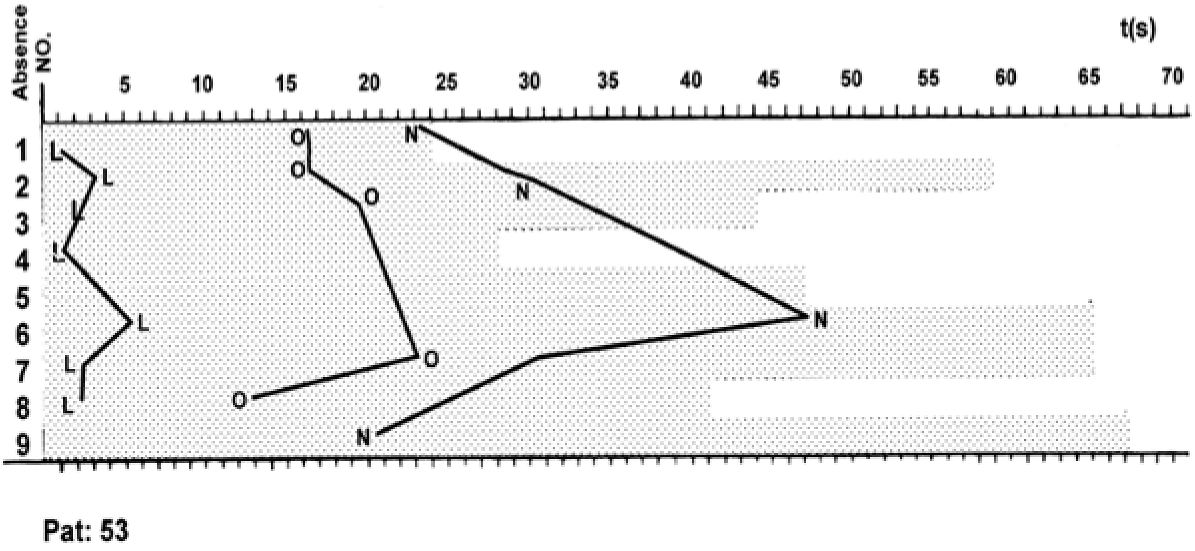

FIGURE 3. Correlation of mild motor signs and spike-and-wave duration in absences. Onset of lid activity and oral and nonoral automatisms in nine absences in one patient. *L*, myoclonic or tonic activity of lids, eyes, or both; *O*, oral automatism; *N*, nonoral automatisms; *dotted vertical lines*, end of EEG paroxysm. From Stefan H, Burr W, Hildenbrand K, et al. Basic temporal structure of absence symptoms. In: Akimoto H, Kazamatsuri H, Seino MD, et al., eds. *Advances in Epileptology: the XIIIth Epilepsy International Symposium*. New York: Raven Press; 1982:55–60, with permission.

The high percentage of patients with mixed absences in these studies indicates that many combinations of components are found in each patient. These data suggest that the existing classification of absence seizures is perhaps oversimplified. The simple enumeration of the various components without emphasizing one of them does not suffice to characterize absences precisely. The proposed criteria of the International Classification should therefore be more detailed, with other components added. Absences are characterized not only by myoclonic, tonic, or automatic events, but also by the directions of ictal movements and their lateral symmetry. For example, a profile of symptom activity (POS) of patients with mixed absences is shown in FIGURE 2. Various types of absences can be better differentiated phenomenologically if symptoms are weighted by defining accompanying behavior using the POS. In this way, even mixed absence seizure types can be differentiated by an analysis of the predominance of ictal behaviors. In the experience of Stefan et al.,[107] 74% of absence seizures are associated with two or more ictal signs in combination.

The recognition of this phenomenon and the subclassification of absence seizures according to the predominance of characteristic motor symptoms would seem reasonable in lieu of the current classification system, which provides for a somewhat static description of absence seizures with multiple clinical presentations and fails to weigh the predominant motor symptom activity. Myoclonic absences are characterized by:

- Impairment of consciousness, which varies from mild, in which the patient can continue with normal activities such as playing with toys, to severe.

- Motor manifestations consisting in rhythmic myoclonic jerks, primarily of the the shoulders and arms, and occasionally of the legs.
- In connection with shoulder symptoms, simultaneous jerks of the head can be seen.
- Eyelid twitching is absent or rare, whereas perioral myoclonias may be frequent.
- Due to coinciding tonic contractions, the arms can be lightly elevated.
- The jerks and tonic contractions are usually bilateral but may be unilateral or asymmetric.

- In about two-third of cases, other seizures such as simple absences and generalized tonic–clonic seizures can be seen.
- Autonomic manifestations may occur as arrest or as change of respiration and urinary incontinence.
- The seizures are usually extremely therapy resistant.

A further analytical approach to analysis of the phenomenologic structure of absences may be found in studies of time course. Based on the results of Rabending,[90] who described a succession of rhythmic myoclonic adversive symptoms and automatisms, Stefan[103,109] investigated the time course of the progression of myoclonic and tonic motor phenomena, automatisms, and autonomic changes during absence seizures by means of V-EEG monitoring. This dynamic approach seemed necessary to understand better the mosaic of events that characterize generalized absence seizures. Analysis of time course revealed the presence of a complex sequence of behaviors during absence seizures. For example, in some patients the absence was heralded by initial elevation of the eyelids. This was followed by eye deviation, chewing and licking, subtle tonic spasms of the extremities, and discrete automatic movements of the hand. In other absence seizures in the same patient, only single elements of the complex movement pattern occurred. In other words, the different elements of the whole complex movement pattern, which were completely visualized in one absence seizure, were only incompletely present (like fragments of motor pattern) in other absence seizures in the same patient.

A constant latency was found for each patient from the beginning of the spike-and-wave paroxysms to movements of the eyelids, eye deviation, chewing, and perioral myoclonus (Fig. 3). The latency for automatisms of the arms and legs was generally longer from onset of the SWDs. Studies of ocular lid movement (L activity), oral automatisms (O activity), and nonoral activity (N activity) in different absences often revealed a highly constant relation between the onset of an EEG paroxysm and the onset of L, O, and N symptoms (Fig. 4). It is of interest that the time interval between the L, O, and N symptoms during long-lasting seizures was prolonged compared with that in absences of shorter duration, indicating a compressed or prolonged time course of the same ictal complex of motor behaviors, depending on the duration of the ictal event.[108] Different types of oral automatic phenomena (swallowing, licking, smacking) could be recognized during the time course of an absence seizure, occurring most often during the earlier part of a seizure, whereas simple movements of the mouth (mouth opening, or “carp mouth phenomenon”) were more evenly distributed throughout the course of the seizure. Ictal motor patterns correspond to archetypal elements of movement.[61] They are contained in normal motor schemes and are controlled by higher coordinating mechanisms. Their occurrence is possibly related to an isolated demand of stored elementary motor acts of a complex motor behavior. At the beginning of the seizures, staring gaze, change of facial expression (such as an anatomic facial palsy), and stopping of the rhythmic motor movement may be related to negative motor mechanisms. After this, the proximal-axial sequence of time-ordered involuntary motor events may indicate a disturbance of initiation and programming of motor activity.[37,92]

The V-EEG analysis also showed an interesting time course for autonomic phenomena during absence seizures. These include a change of respiratory rate at the onset of spike-and-wave paroxysms, followed by a reduction of heart rate and skin resistance response (see Fig. 4).

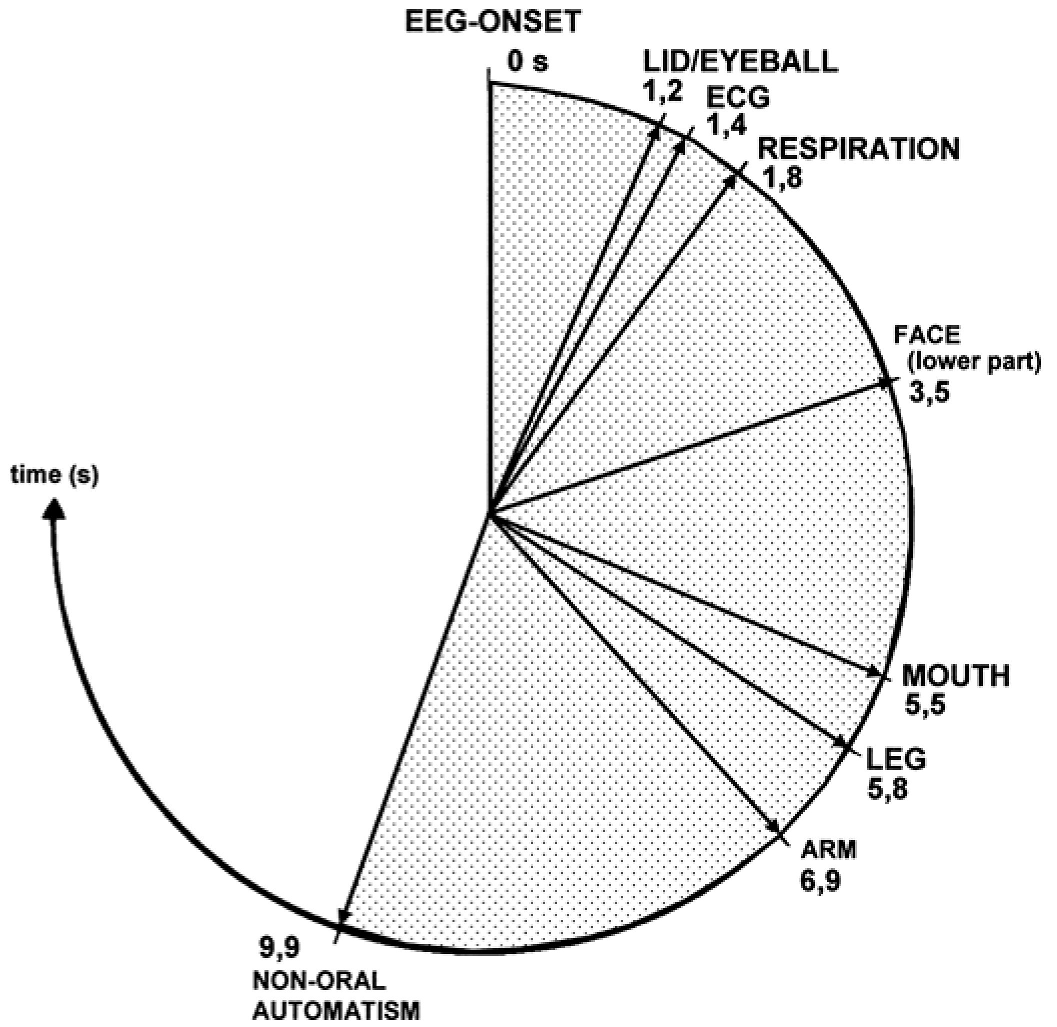

FIGURE 4. Temporal occurrence of motor and autonomic symptoms during absence seizures related to the beginning of generalized spike-and-wave paroxysms in the EEG. From Stefan H, Burr W, Hildenbrand K, et al. Basic temporal structure of absence symptoms. In: Akimoto H, Kazamatsuri H, Seino MD, et al., eds. *Advances in Epileptology: the XIIIth Epilepsy International Symposium*. New York: Raven Press; 1982:55–60, with permission.

Analysis of the time course of behaviors during generalized absence seizures suggests a spread of motor involvement in a craniocaudal direction, from the ocular region to the perioral area, thence to the upper and lower extremities, which is somehow analogous to the jacksonian march of partial elementary motor seizures. However, in absences variations occur as far as a somatotopic predominance of the ocular region is concerned in the case of craniocaudal descent to the extremities.

Frequently, after initial activity of the head and ocular region, the lower extremities show discrete myoclonic or tonic motor signs, but also motor pattern fragments occur. The craniocaudal march may indicate the involvement of frontolateral as well as frontomesial regions (e.g., premotor region, supplementary motor area, or gyrus cinguli) with excitatory and inhibitory interactions. These data support the suggestion of Berkovic et al.[9,10,89] that extremely careful analysis of ictal V-EEG recordings is necessary to classify absence seizures correctly, because of the continuum that exists between partial and generalized epilepsy.

Cluster analyses of motor symptomatology of absence seizures[103] have shown no clearly defined separation of seizure types with regard to the motor signs of absence. These findings support the hypothesis of Gloor[43,44,45] and Gloor et al.[46,47] concerning a continuum of absence seizure signs that are manifested in both genetic and diffuse symptomatic epilepsies. Along these lines, Gloor has suggested that, in absence seizures, there exists a spectrum of pathophysiologic disturbances that may involve the cortex, reticular projection system, or thalamus, with the primary abnormality not originating in any single structure. At one end of this spectrum are the frequently observed ocular motor productive absences, which might also be considered typical absences, with normal interictal EEG findings, no neurologic findings, and no demonstrable pathologic process; at the other end of the spectrum are the ocular motor unproductive absences, often associated with abnormal interictal EEG patterns, neurologic findings, and hints of diffuse central nervous system pathology. Holmes et al.[53] have suggested that the most likely causes of absence seizures of the first type are genetically determined, whereas in the second type, the seizures are likely to be a consequence of diffuse cerebral pathology. The normal interaction between cortex and subcortical projection mechanisms of reticular origin is probably disturbed in both types of absence.

Postictal

Generalized absence seizures usually stop abruptly. The patient immediately recovers mental function and can resume ongoing activities with no appreciable delay. The accumulation of a series of absences can cause a so-called *discontinuous nonconvulsive status*, or a prolonged absence can result in a continuous nonconvulsive absence status. Impairment of consciousness can vary quantitatively from slight dizziness to stupor.

EEG Manifestations and Clinical Correlations

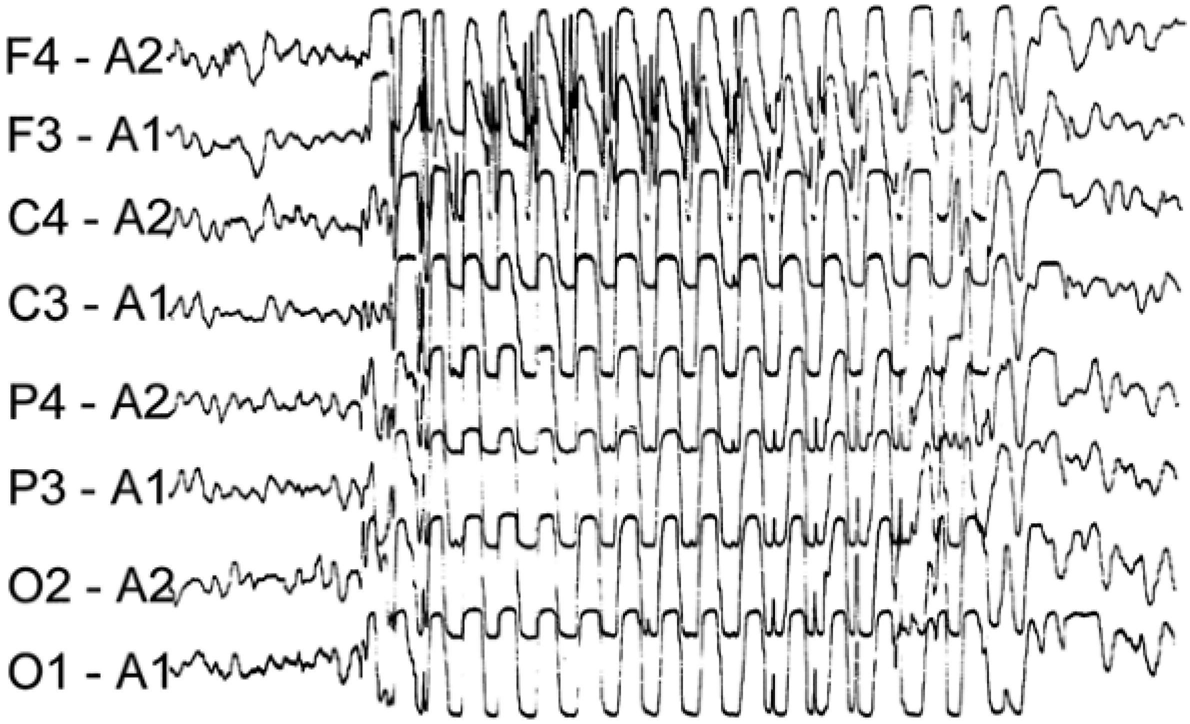

FIGURE 5. Generalized 3-cycle per second spike-and-wave paroxysms during an absence seizure with discrete accentuation in frontal brain regions. From Stefan H. *Epilepsien—Diagnose und Behandlung*. New York: Chapman & Hall, 1995, with permission.

Interictal

In patients with typical absences, the EEG demonstrates bilaterally synchronous and symmetric SWDs at 3 cycles per second, with normal background activity. The EEG for ocular motor productive absence seizures shows normal background activity with predominantly generalized spike-and-wave or polyspike-and-wave discharges, sometimes also mixed with focal or predominantly regional activity. Even bilateral independent interictal focal frontal spikes can occur in typical absence epilepsy.[103] This may be caused by accentuated projection in the thalamocortical network system or by a focal frontal onset, such as in the frontobasal or mesial regions.[54] Encephalographic and magnetoencephalographic (MEG) recordings show an early MEG spike component and a later EEG negative spike element. By means of dipolar analysis, the main sources were shown to be in the frontopolar, premotor, or mesiobasal regions.[82,93] The coregistration of EEG and functional MRI indicates functional activation of the anterior or posterior cingulate cortex during generalized spike-and-wave paroxysms.[2,117] This result raises questions concerning the source of discharges in presumptive generalized epilepsies. The electro-clinical findings suggest that absence seizures may not be truly generalized but rather involve selective cortical networks,[54] as do the regional epilepsies, with participation of thalamocortical networks. In atypical absences, the background activity frequently shows abnormal findings (diffuse slowing, interictal spikes), and the SWDs are irregular, with a frequency below 2.5 cycles per second or above 3.5 cycles per second. The reason for the slower rhythms in this disorder is not clear, but in atypical absence seizures the bilaterally synchronous activity is not constrained by thalamocortical circuitry, but involves in all likelihood thalamocortical hippocampal circuitry.[19,21,118]

Ictal

Absence seizures are usually characterized by generalized, bilaterally synchronous, predominantly frontal SWDs having a frequency of 3 to 4 cycles per second and lasting less than 30 seconds[53,87](Fig. 5). Statistically, clinical manifestations are more likely to occur with spike-and-wave paroxysms lasting longer than 3 seconds. However, cognitive functional disturbances may occur during shorter spike-and-wave paroxysms. These cognitive lapses may be measured by means of neuropsychologic testing during the absence seizure by V-EEG monitoring.[13,78] Initial SWDs faster than 3.5-seconds occur more frequently in absence seizures accompanied by complex motor phenomena. In addition, regional frontal ictal onsets may sometimes occur.[103]

The ictal EEG for atypical nonocular sporadic motor absence seizures shows a tendency toward slower spike-and-wave rhythms of 2.5 to 3 cycles per second duration, often lasting less than 10 seconds.

The ictal EEG in myoclonic absences comprises rhythmic generalized and bilateral synchronous and symmetric 3 cycle per second spike-and-wave activity as can be seen in typical absence seizures. Occasionally, these classic discharges may be intermingled with polyspikes.

Postictal

In typical absences, the postictal EEG usually is normal. Single or brief discharges of bilateral SWDs are frequent, especially during non-REM sleep.

Diagnostic Considerations

For an accurate diagnosis of generalized absence seizures to be made, a careful description of the seizure is very important. This should include the presence or absence of an aura, the clinical events that transpire during the seizure itself, the presence or absence of a postictal event, and the duration and frequency of the seizure. In addition, EEG findings, family history of epilepsy, and developmental history are important.

EEG recordings should be recorded predominantly in the morning, between 8 and 10 AM. In previously untreated

patients with typical absences, generalized SWDs are most often seen at that time of day. If the routine EEG fails to detect SWDs, sleep deprivation, hyperventilation, and photic stimulation may activate them. The results of the neurologic examination and neuroimaging studies usually are normal in generalized absence epilepsy. Myoclonic absences are usually typical, and the diagnosis is mainly based on careful clinical observations and V-EEG studies with polygraphic recording (electromyelography [EMG] of various shoulder and arm muscles).

Differential Diagnosis

Absence seizures may sometimes be misdiagnosed as nonepileptic disturbances of behavior and concentration in school. In addition, clouding of consciousness with ocular and oromotor automatisms may occur in partial seizure disorders and generalized epilepsies other than absence epilepsy. The "absence" is no more than a short description of a clinical condition that evolves from physiologically different mechanisms. Thus, a careful history of the seizure is very important. A generalized absence seizure is characterized by an abrupt onset with no aura, a short duration of less than 30 seconds, and no postictal state. The appearance of a patient having a complex partial seizure may be similar, with staring, lip smacking, and motor automatisms of varying complexity. However, complex partial seizures are frequently heralded by an aura, usually last longer than a minute, and are commonly followed by postictal confusion.

Seizures arising from the frontal lobe may be more difficult to differentiate from absence seizures, because they appear to be nonfocal. Bancaud et al.[4,5] showed that mild stimulation of the frontal cortex produced absence-like seizures, and stimulation with higher intensity produced tonic–clonic seizures. Therefore, absence seizures might represent a minimal expression of epileptogenicity in the frontal lobe. Frontal lobe seizures generalize extremely rapidly, which may lead to the impression of a primary generalized epilepsy. Seizures originating in the frontal lobe are characterized by short duration and abrupt onset and termination of clouding of consciousness, in approximately the same time span as absences in generalized spike-and-wave epilepsy. In addition, seizures of frontal lobe origin occur rather frequently. Therefore, the differentiation of frontal lobe epilepsy from primary generalized absence epilepsy may prove very difficult in clinical practice.

The EEG findings are helpful in differentiating generalized absence seizures from complex partial and frontal lobe seizures only if they are abnormal. Normal EEG findings are not helpful. If the index of suspicion is high for an epileptic event, and the behaviors are frequent, V-EEG monitoring with capture of the event in question is the gold standard for differentiation of an epileptic from a nonepileptic event and for precise clinical definition of the type of seizure involved. In generalized absence epilepsy, the presence of generalized, bilaterally synchronous SWDs or of photosensitivity indicates the diagnosis of absence seizures. Focal spikes suggest complex partial seizures. The ictal EEG in frontal lobe epilepsy may show nothing but bilateral slowing if the frontal lobe onset is deep.

The rhythmic myoclonic movements in myoclonic absences can be overlooked due to tonic contraction of arm, or if the intensity of the myoclonias can be reduced through treatment. In such cases, simple absences may be suspected. When the motor manifestations are asymmetric, focal seizures may be considered. It has been proposed that resistance to conventional treatment for simple absences with a 3 cycle per second spike-and-wave activity is an indication of myoclonic absences, and adequate investigation should be performed.

Specific Syndromes Incorporating Absence Seizures as an Integral Feature

The term *absence* refers to seizures, not epilepsies; however, several epilepsies or epileptic syndromes incorporate absence seizures as a major feature and are commonly referred to as *absence epilepsies*.

Many genetic, pharmacologic, and semiologic data suggest that epilepsy with typical absences is not a homogeneous entity.[52,83,90] Animal studies support this hypothesis, because they suggest that chromosomal mutations may correlate with phenotypic variations of seizures, particularly in regard to frequency and duration.[80] The heterogeneity of the absence epilepsies has been recognized by the Commission on Classification of the International League Against Epilepsy, which describes four epileptic syndromes with typical absences: childhood absence epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy, and myoclonic absence epilepsy. To this list has been added eyelid myoclonus with absences; perioral myoclonus with absences; absences with single, nonrhythmic myoclonus; late-onset absence status and phantom absences; reflex absences; and symptomatic and secondarily generalized typical absences.[83]

Childhood Absence Epilepsy

This is an idiopathic generalized epileptic syndrome with onset of simple and complex absence seizures at 4 to 8 years of age. The seizures may be accompanied by upward deviation of the eyes and retropulsion of the head and trunk. Generalized tonic–clonic seizures develop in 30% to 40% of the cases.[69]

Juvenile Absence Epilepsy

The age of onset is around the time of puberty, and the absences are the same as those observed in childhood absence epilepsy, except that retropulsive movements are less common. Seizure frequency is lower than in childhood absence epilepsy. Generalized tonic–clonic seizures are common; they usually occur on awakening and may precede the appearance of absences. The patients may also have myoclonic jerks, and the prognosis for seizure control is said to be poorer than in childhood absence epilepsy.

Juvenile Myoclonic Epilepsy

Absence seizures occur in one third of patients with juvenile myoclonic epilepsy. Early-onset absence seizures may predate myoclonic jerks, generalized tonic–clonic seizures, or both by many years in this disorder, which requires lifelong treatment with antiepileptic drugs.

Myoclonic Absence Epilepsy

Absence seizures associated with rhythmic myoclonic jerking of the shoulders, arms, and legs and tonic contractions around the shoulders were first described as a specific syndrome by Tassinari et al.[113] and reviewed by Tassinari and Bureau.[114] The rhythmic (clonic) jerking is stronger in intensity than that seen in typical absence seizures. The duration of the myoclonic absence varies between 10 and 60 seconds. EMG activity during

the myoclonus correlates with the 3-cycle per second spike-and-wave bursts. The prognosis for seizure control in myoclonic absence seizures is less favorable than that in typical absences. Moreover, myoclonic absence epilepsy may be associated with an encephalopathy.

Eyelid Myoclonus with Absences or Jeavons Syndrome

The characteristic seizure, mainly occurring after eye closure, is a brief episode of marked jerking of the eyelids, often associated with jerky upward deviation of the eyeballs and sometimes associated with retropulsion of the head. The EEG shows generalized SWDs, which are inhibited by total darkness. All patients are photosensitive. Impairment of consciousness may occur. Sometimes, generalized tonic–clonic seizures in connection with sleep deprivation or fatigue have been reported. The prognosis for seizure control is poor. The seizure manifestations can initially be misinterpreted as a behavior disturbance with tics. The clinical manifestations were originally described by Jeavons.[59,60] The syndrome was recognized by Duncan and Panayiotopoulos.[34] This type of absence epilepsy has also been called *eye-closing seizures.*[12,119] Some patients may precipitate nonconvulsive status epilepticus with eye closure.[110]

Perioral Myoclonus with Absences

This is a syndrome with onset in childhood or adolescence, characterized by frequent typical absences associated with jaw and lip myoclonus. These patients are said to be at high risk for absence status. Moreover, generalized tonic–clonic seizures usually occur in conjunction with this type of absence epilepsy. The disease is said to be lifelong, like juvenile myoclonic epilepsy. There is no photosensitivity.

Other Classification Schemes

Hirsch et al.[52] analyzed 570 absences in 43 patients and were able to differentiate four groups of patients on the basis of clinical presentation and response to treatment, coexistence of generalized tonic–clonic seizures, and the nature of precipitating events.

Based on their experience, Hirsch et al.[52] have suggested that the only reliable clinical criteria by which one may predict the course of absence epilepsy are the early onset of generalized tonic–clonic seizures and the nature of the precipitating factors, that is, hyperventilation or intermittent photic stimulation. Moreover, these authors have questioned the usefulness of more and more syndromic subcategories of absence seizures, either in guiding treatment or establishing prognosis. Further, it is the belief of this group that the terms *childhood absence epilepsy*, *juvenile absence epilepsy*, and *eyelid myoclonus with absence* are misleading. Rather, they propose a simplification of the classification scheme for absence epilepsy with just three categories: (a) “pure” absence epilepsy, (b) generalized epilepsy with absences and tonic–clonic seizures, and (c) generalized epilepsy with photosensitive absences and tonic–clonic seizures.

Doose[30] described absences in patients with myoclonic astatic epilepsies of early childhood. If generalized tonic–clonic seizures occurred before the fourth year of life, and absences were also later observed, the prognosis for control of absences with drug treatment was poor.

There is strong evidence of causal heterogeneity within the disorder. Polygenic inheritance and multifactorial influences may explain the wide range of manifestations.[31,32]

Responses to Treatment

The drugs of choice for typical absence seizures are ethosuximide, valproate, or lamotrigine. Ethosuximide has been successful in controlling seizures in 70% of patients with absence seizures who are drug-naïve.[94] The initial dosage is 15 mg/kg/day. This dose can be gradually increased to a daily maintenance dose of 20 to 40 mg/kg.

If the patient continues to have absence attacks, has atypical absence seizures, or absence seizures with generalized tonic–clonic seizures or other seizure types, valproic acid or lamotrigine should be used; these broad-spectrum anticonvulsant agents are expected to be effective against both absence and generalized convulsive seizures.

The maintenance dose of valproic acid in children is 20 to 40 mg/kg/day in two divided doses. The enteric-coated formulation of valproic acid reduces the frequency of gastrointestinal complaints, but it does not lessen the fluctuations in serum concentrations.[18] If the sprinkle formulation is used in monotherapy, however, the drug may be given every 12 hours in children.[18] To avoid side effects in children given valproic acid, the initial dose is usually one third of the maintenance dose; this is increased by one third every 4 to 5 days until the full maintenance dose is reached. Some exceptional patients who do not respond to doses of 60 mg/kg may respond to doses as high as 80 to 100 mg/kg/day. These “supramaximal” doses of valproic acid are most effective when given as monotherapy.

In previously untreated adult patients, a dose of valproic acid of 15 to 20 mg/kg/day may be sufficient for seizure control. In these cases, a once-daily administration in the evening is often effective and well tolerated.[14,106] Dosing more than twice a day is rarely necessary.

Lamotrigine can be a choice in especially older girls and women. The initial dose in children under 12 years is 0.6 mg/kg/day in two divided doses for the first 2 weeks, and for the next 2 weeks 1.2 mg/kg/day. The dose is titrated with 1.2 mg/kg every or every second week up to a maintenance dose of 5 to 15 mg/kg/day or a maximum of 400 mg daily. If the child also is treated with valproic acid, the titrating doses are 50% of those mentioned, and the maintenance dose is 1 to 5 mg/kg/day or a maximal daily dose of 200 mg.

In children over 12 years and in adults, the dose is 25 mg/day during the first 2 weeks and 50 mg/day during the next 2 weeks. The dose is increased by 50 mg/week or every second week up to a maintenance dose of 200 to 400 mg/day. In combination with valproic acid, the corresponding doses are 25 mg every second day, 25 mg/day, and the increasing dose 25 to 50 mg/week or every second week with a maintenance dose of 200 mg/day.

If no therapeutic response to monotherapy occurs with either ethosuximide or valproic acid, a combination therapy, such as that already described for valproic acid and lamotrigine, may be of benefit.

For intractable absence seizures unresponsive to a combination of the mentioned drugs, other drugs may be tried (e.g., topiramate, lamotrigine, clobazam or, zonisamide, if there is no seizure control). Further details concerning side effects of treatment are discussed in the special literature.[26,33,56,60,63,85,89,95,96,97,98,104,111,121,123]

Summary and Conclusions

Absence seizures are primarily a disorder of childhood. They are neurophysiologically and pharmacologically unique and comprise the primary seizure type in a number of different

absence epilepsy syndromes. The underlying mechanism of SWD bursts that characterize generalized absence seizures involves thalamocortical modulation of spindles and recruiting responses of the cerebral cortex. Generalized absence seizures represent a perturbation of neocortical rhythmicity in favor of the rhythmic burst firing mode.

Although they are a seemingly heterogeneous group of disorders, all absence seizures have an abrupt, brief loss of consciousness without an aura or postictal state, and with or without motor or autonomic automatisms; all are associated with a burst of bilaterally synchronous SWDs, usually at a frequency of 2.5 to 3.5 cycles per second. No universal agreement exists regarding the best way to characterize the absence epilepsies; however, it is generally accepted that the coexistence of generalized tonic–clonic seizures, myoclonic jerks, or both with absence is considered unfavorable for ultimate seizure control. Clinical genetics may, in the future, hold the key to syndrome classification.

The drug of choice for typical absence seizures is ethosuximide and valproate. Valproic acid is the drug of choice for all other types of absence seizures, absence seizures with proven intractability to ethosuximide therapy, or absence seizures that occur in association with generalized tonic–clonic seizures. For lamotrigine and topiramate evidence class 2 for treatment efficacy exists in addition. From experience, drugs like carbamazepine and phenytoin should be avoided.

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Chapter 50

Generalized Myoclonic Seizures and Negative Myoclonus

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> Signa epilepsiae remotoria sunt jactatio et cetera. (Heberden, 1804)

Introduction

"The term and concept of myoclonus have been a longstanding source of confusion and debate. Myoclonus should be used in its strictly etymological sense, referring to any brief muscular contraction, as would have been wished by Muskens, the first neurologist to do detailed clinical and experimental studies of it."[42]

The development of the concept of myoclonus and its application to epileptic seizures is closely connected with the history of description and conceptualization of progressive myoclonus epilepsy (PME) and other myoclonic epilepsies. Dubini (1846)[35] described a cohort of patients with possibly different conditions who had involuntary jerky movements that he named *electric chorea*. Delasiauve (1854), Reynolds (1861), Féré (1890), Binswanger (1899), and Gowers (1902) described sudden starts or jerks as expressions of motor prodromes, auras, or abortive seizures (*petit mal moteur*) in their monographs on epilepsy. They did not, however, differentiate them semiologically or nosologically. Credit for the first exact and comparable description of these phenomena belongs to Herpin (1867),[59] who described them as: "this variety of [seizure] prelude is a jerk [*secousse*] which runs through the entire body like an electric current." His twenty-fourth observation was the first description of juvenile myoclonic epilepsy (JME), in a 14-year-old child, the son of a doctor. His jerks were called *commotions* or *impulsions*.

"At the beginning of the seizure, the movements or jerks were limited to the upper part of his body; they later became generalized. If the boy were to stand or walk, he might fall, although this is rare. He stands up again immediately [after the seizure]. He throws or drops what he is holding, particularly if he is holding it with his right hand. He says that he cannot see at the moment of the movement, but that he recovers immediately afterwards. His mother called these events (*accidents*) shakes (*tremblement*) and the father jerks (*secousses*)."

In 1881, Friedreich[40] described a case, the diagnosis of which has remained unclear until today, and named it *paramyoclonus multiplex*. Many publications followed his observation, but they were comparable only in that they were dealing with involuntary jerks. From the "chaos of motor neuroses and from the cloudy pool of many publications," Unverricht[116] crystallized a unique disease entity from his 1895 study of members of two families and named it *familiäre myoclonie*. This disease started between the ages of 7 and 15 years, and consisted of a combination of nocturnal convulsive seizures and "lightning-like, arrhythmic, isolated jerks of individual, functionally unrelated muscles of both sides of the body. The jerks occurred less frequently when strained, but more frequently during psychic excitement, and stopped completely during sleep." Unverricht seemed to have not observed any relationship between the phenomena he named *myoclonie* and the preparoxysmal or interval jerks of epileptic patients that, at that time, were still called *secousses*.

In 1899, both Dide[27] and Rabot,[90] at almost the same time, introduced the concept of *myoclonie* to the vocabulary of epilepsy—Dide from a semiologic viewpoint ("La myoclonie dans l'épilepsie") and Rabot from a nosologic view ("De la myoclonie épileptique"). Rabot confirmed Herpin's observation and emphasized that the "jerks" might precede major convulsive seizures for many years, usually occur in the morning after awakening, are prone to recur in series, and occur more frequently days before major convulsive seizures and disappear thereafter for a while, as if switched off.

Some years later, Clark and Prout[19] proposed the concept of myoclonus epilepsy for their cases of Unverricht myoclonie, which they had described as *paramyoclonus multiplex associated with epilepsy* in 1900. When, in 1903, Lundborg[76] sought an appropriate term for the disease he observed in 18 members of a Swedish farm family, he noticed the same nomenclature for two different diseases. He then proposed to describe one, which was "identical with the Unverricht's myoclonie," as *progressive familial myoclonus epilepsy*—from which later the term Unverricht-Lundborg myoclonus epilepsy developed—and the other, which was "standing near the essential epilepsy," as *intermittent sporadic myoclonus epilepsy* (Rabot's type). This was described by Lecasble in 1958 as "épilepsie generaliseé avec des myoclonies intermittentes et sporadiques" and by Castells and Mendilaharsu[18] in the same year as "la epilepsia mióelonia bilaterally cosciente" to differentiate it from the epilepsy beginning with partial myoclonus. Janz[66,67] as well as Lennox[73] tried to replace the vague but accepted concept of myoclonus with the descriptive terms—at least for the jerks of JME—*impulsive-petit mal*[67] (from the Latin impulsio, "jerk") and jerk epilepsy.[73] During the 1970s, a syndromic approach to the problems of myoclonic epilepsies occurred, with a new importance given to electroencephalographic (EEG) findings and to elements of etiology and prognosis. The Marseille school, among others, established several well-accepted syndromic entities using the adjective myoclonic, such as *benign* and *severe myoclonic epilepsy in infancy*, and *epilepsy with myoclonic absences.*[44]

Recently, myoclonus has been the subject of intensive research using advanced technologies. Electrophysiologic studies, especially, have brought new insights into the pathophysiomechanism of myoclonus.[102] The recent advances in molecular genetics have also helped achieve an understanding of the different conditions that cause myoclonus.

Clinical Manifestations

Myoclonus consists of involuntary, quick movements distinctive for their abrupt, lightning-like character, occurring in a mild or vehement manner, spontaneously or in stimulus-sensitive conditions, affecting the entire body or in regional or localized distal or proximal parts of the body. It may be diffuse, predominating symmetrically in the axial muscles and the upper limb (*massive myoclonus*), or segmental, affecting randomly the different parts of the body, although the most involved muscles are those of the extremities, face, and trunk (*erratic myoclonus*); if the legs are involved, the person may be thrown to the ground. Myoclonus can be asymmetrical or even focal, limited to a restricted part of one limb or the face (*epilepsia partialis continua*).[36] It may occur at random over time, or at more or less fixed interval, and in sporadic or rhythmic fashion. Most myoclonia are caused by abrupt muscle contraction (positive myoclonus); rarely, a brief interruption of ongoing activity may be observed (negative myoclonus, previously named *asterixis*).[1] No distinguishable, even momentary, loss of consciousness occurs with single jerks, but if jerks occur in rapid succession or in the form of myoclonic status epilepticus, there may be a blurring of awareness.

Phenomenologically, epileptic myoclonus cannot be distinguished from the brisk, nonepileptic movements associated with physiologic or pathologic conditions. The classification of seizures as an epileptic manifestation requires knowledge of the clinical context and/or electrophysiologic confirmation, although physiologic correlates are not always demonstrable. Hallett[54] proposed to define epileptic myoclonus as an elementary electroclinical manifestation of epilepsy involving descending neurons, whose spatial or temporal amplification can trigger overt epileptic activity.

In this chapter, we use the term *myoclonic seizure* as synonymous with epileptic myoclonus. The term *myoclonus* was coined by Friedreich.[55] *Myos* means muscles, *clonus* means tumult or a quick movement, and (myo)clonia is the plural. Because a myoclonic movement is a jerk, the term myoclonic jerk is redundant.[42]

Stimulus Sensitivity

Myoclonus is often stimulus-sensitive, being elicited by stimuli of a single or multiple modalities. Tendon tap, posturing, passive or voluntary movement, visual and acoustic stimuli, and cognitive and emotional experiences may precipitate myoclonus. Myoclonus can also be facilitated by various physiologic factors such as the sleep–wake cycle and fatigue.

Rhythmicity/Periodicity

Myoclonus usually occurs irregularly; however, it occasionally appears to be rhythmic. Bilateral, rhythmic, virtually continuous myoclonus can be observed in Angelman syndrome. Guerrini et al.[46] suggested that small areas within the motor cortex are able to independently produce hypersynchronous, rhythmic neuronal discharges recruiting muscle activity similar to tremor. Cortical tremor, in the form of postural or action tremor, and showing the neurophysiologic characteristics of reflex cortical myoclonus, can be observed in patients with PME and with benign adult familial myoclonic epilepsy (BAFME).[60,111]

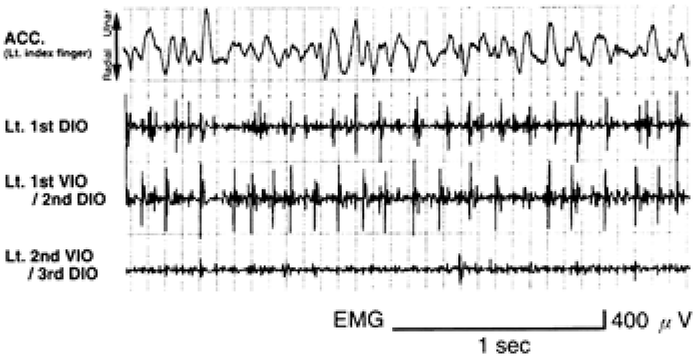

FIGURE 1. Polygraphic EMG records and accelerogram (ACC) in a patient with cortical myoclonus, obtained while the patient maintained the posture of finger extension. Each EMG activity lasted less than 50 msec. EMG discharges are relatively rhythmic. The ACC, therefore, demonstrates relatively sinusoidal wave corresponding to so-called “cortical tremor.” From Terada K, Ikeda A, Mima T, et al. Familial cortical myoclonic tremor as a unique form of cortical reflex myoclonus. *Mov Disord.* 1997;12:370–377, with permission.

Epilepsia partialis continua is another example of the rhythmic, periodic, or arrhythmic recurrence of myoclonus. The cortical site of origin of the spike discharges and the site of origin of the associated focal myoclonic seizures do not necessarily coincide.[22]

Pathophysiology

The term epileptic myoclonus implies a central nervous system origin, presumably accompanied by neuronal depolarization shifts with subsequent hyperpolarizing potentials. To clarify the underlying pathophysiologic mechanisms of myoclonus, electrophysiologic studies are useful (i.e., electromyogram [EMG], somatosensory evoked potential [SEP], C-reflex, and jerk-locked back averaging [JLA]). Hallett et al.[54,57] divided epileptic myoclonus into three categories: cortical reflex myoclonus, primary generalized epileptic myoclonus, and reticular reflex myoclonus. Guerrini et al.[48] also divided this disorder into cortical, thalamocortical, and reticular form.

From an EMG point of view, myoclonus appears as short bursts of synchronized activity, which may involve agonist and antagonist muscles at the same time. The duration of EMG burst during epileptic myoclonus ranges between 10 and 100 msec, usually less than 50 msec (Fig. 1), and that of the EMG silent period of epileptic negative myoclonus from 50 to 400 msec (Fig. 2).[44] By recording the EMG, the nature of myoclonus can be described (i.e., positive or negative myoclonus, duration of EMG burst, rhythmicity and periodicity, synchrony of agonist and antagonist muscles, distribution of myoclonus, spreading pattern of myoclonus, and so on).

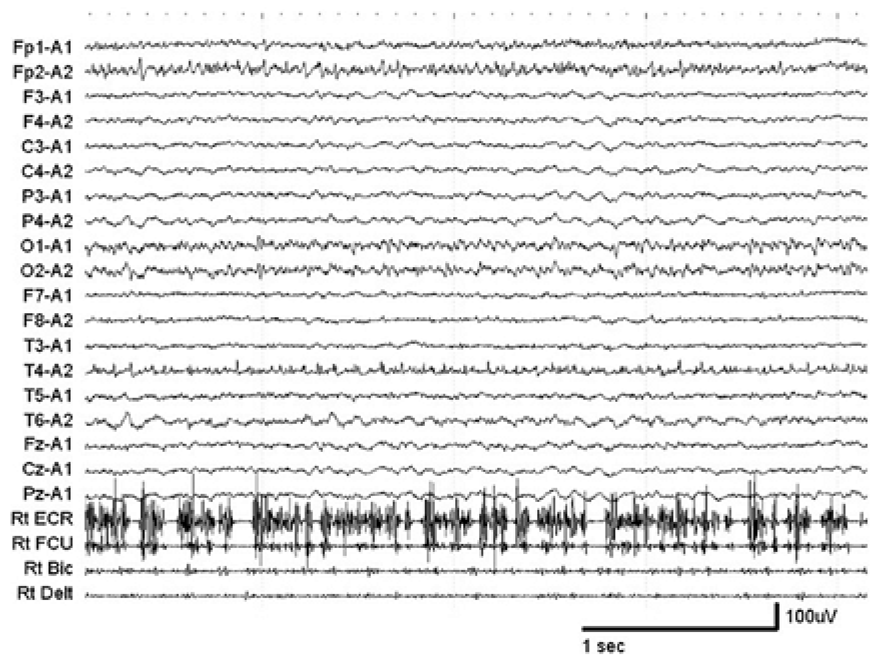

FIGURE 2. Polygraphic EEG/EMG records in a patient with ENM. The record was obtained while the patient maintained an extended posture of right wrist. SPs are seen in the right wrist extensor (ECR) and flexor (FCU) muscles synchronously. They are sometimes preceded by positive myoclonus. EEG shows no clear spikes in association with the jerks in this polygraphic recording.

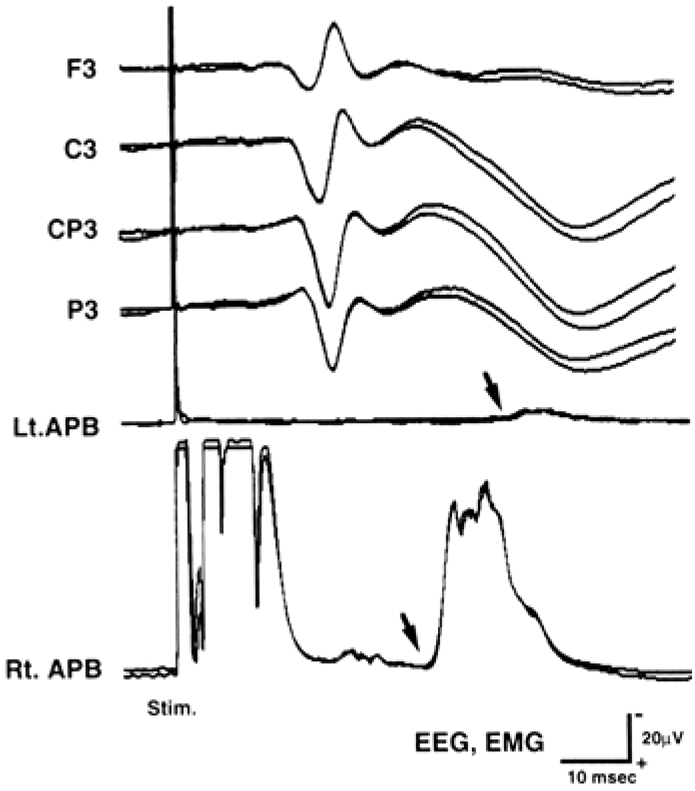

FIGURE 3. SEP and C-reflex following electric stimulation of the right median nerve in a patient with cortical myoclonus. The amplitudes of all SEP components except for N20 are abnormally large. Enhanced C-reflex is seen not only on the stimulated but also on the contralateral side. The arrows indicate the onset of C-reflex in abductor pollicis brevis (APB) muscles on each side. FromTerada K, Ikeda A, Mima T, et al. Familial cortical myoclonic tremor as a unique form of cortical reflex myoclonus. *Mov Disord.* 1997;12:370–377, with permission.

Cortical Myoclonus

Cortical myoclonus reflects impulses that originate in the sensorimotor cortex and travel down the brainstem. Cortical myoclonus is typically seen in progressive myoclonus epilepsy. Muscles involved tend to be distal more than proximal and flexor more than extensor, and to involve more the face and upper extremities than the rest of the body. Cortical myoclonus is more commonly encountered in a multifocal form, presenting with multifocal spike discharges. If myoclonus is triggered by stimuli, the term *cortical reflex myoclonus* is used. If myoclonus occurs periodically, the term *epilepsia partialis continua* is used. The neurons in the sensorimotor cortex may be primarily hyperexcitable, or may be driven by abnormal inputs from the neurons of other brain parts. Therefore, cortical myoclonus occasionally is called *fragmented epileptic convulsion*.

In patients with cortical reflex myoclonus, the cortical components of median-nerve SEP showed abnormally large amplitude (Fig. 3). Usually, the initial peaks (N20/P22) are not large, and the following components become higher. This giant SEP is thought to indicate hyperexcitability of the sensorimotor cortex. Abnormally large evoked potentials were also reported by photic stimulation.[104]

When the peripheral nerve is stimulated, the stimulus goes up the spino-thalamo-cortical tract and, after excitation of the pyramidal neuron, it goes down the cortico-spinal tract, resulting in muscle contraction (long-loop reflex). In normal subjects, long-loop reflex can be recorded only when subjects maintain muscle contractions. In patients with cortical reflex myoclonus, however, this reflex can be recorded even while resting (C-reflex) (see Fig. 3). The latency of C-reflex for median nerve stimulation is about 40 to 45 msec, which is almost double of the latency of N20 to the median nerve stimulation. When the C-reflex is recorded from the contralateral limbs to the stimuli, the latency delay is about 10 msec to the ipsilateral limbs, which corresponds to the traveling time of the transcallosal pathway. This stimulation-locked muscle contraction is believed to share the same underlying mechanism with cortical reflex myoclonus.

Some EEG correlates are time-locked to cortical myoclonus. However, because of the relatively smaller amplitude of the EEG spikes in comparison with the background activities, the physiologic correlates of myoclonus can only be detected by using jerk-locked (EEG or magnetoencephalograhic [MEG]) averaging (JLA of jerk-locked magentic field [JLF]) (Fig. 4) or coherence analysis method.[46,102] In JLA, EEGs are averaged with respect to the EMG onset, to reduce the non–time locked background EEG activities. Positive peak of the EEG spikes is 15 to 20 msec prior to the myoclonus for the upper limbs, and 25 to 40 msec for the lower limbs. Spikes are located around the contralateral primary motor cortex.

As such, cortical reflex myoclonus is caused by hyperexcitability of the primary sensorimotor cortex. However, because giant SEPs are not always present in patients with cortical reflex myoclonus (as in dentatorubral-pallidoluysian atrophy [DRPLA]), some other pathophysiologic mechanisms may exist.

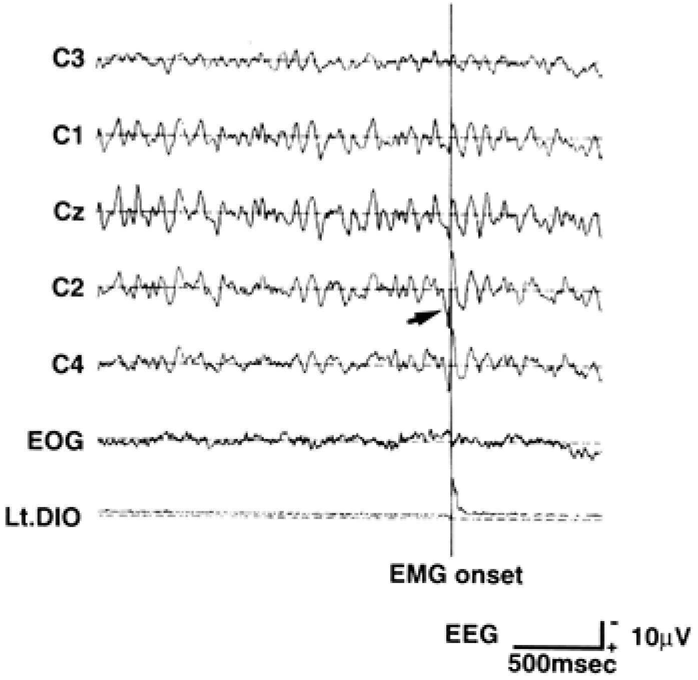

FIGURE 4. Waveforms of cortical discharge demonstrated by jerk-locked back averaging time-locked to the involuntary EMG activity of the left dorsal interosseus muscle (DIO) in a patient with cortical myoclonus. The positive/negative biphasic spike (*arrow*) is maximal at the right central area (C2), which precedes the EMG onset by about 30 msec. From Terada K, Ikeda A, Mima T, et al. Familial cortical myoclonic tremor as a unique form of cortical reflex myoclonus. *Mov Disord.* 1997;12: 370–377, with permission.

In Lennox-Gastaut syndrome (LGS), myoclonus is rare and disclosed only in those cases with a cortical lesion affecting the rolandic area;[12] thus, myoclonus appears to be produced by a secondary generalization of focal cortical myoclonus. They also present with arrhythmic, distal small focal jerks, leading to the individual tiny finger movements unaccompanied by premyoclonic potentials on JLA that Wilkins et al.[119] proposed to call *minipolymyoclonus*. Brown et al.[14] indicated that the major role of facilitation of inter- and intrahemis-pheric spread of cortical myoclonic activity is through trans-callosal or intrahemispheric corticocortical pathways in producing generalized or bilateral myoclonus. Therefore, bilateral jerks may not be synchronous in patients with cortical myoclonus.

Thalamocortical Myoclonus

Thalamocortical myoclonus or idiopathic generalized epileptic myoclonus represents the common type of myoclonus in various epileptic syndromes. Myoclonia are often spontaneous, predominantly arrhythmic and axial with varying severity, and associated chronologically with an EEG pattern of diffuse polyspikes or (poly) spike-and-wave discharges. A hyperexcitable cortex is thought to be driven diffusely and synchronously by ascending subcortical inputs that trigger the paroxysmal events. As a consequence, muscles from both sides are activated, and muscles innervated by the cranial nerves are involved through a rostrocaudal manner.

Electrophysiologically, SEP usually does not show giant SEP, and C-reflex may be recorded at rest. A negative peak of the generalized spike (30–100 msec duration) precedes the jerk (<100 msec duration) by 20 to 75 msec. The latency of the spike is relatively longer, and the temporal relationship is looser than in that of cortical myoclonus. The underlying mechanism of the thalamocortical myoclonus is still uncertain. The myoclonus of benign myoclonic epilepsy of infancy, myoclonic-astatic epilepsy, and JME belongs to this category.[46]

Myoclonus observed in patients with Dravet syndrome is not straightforward: Patients may exhibit massive myoclonus combined with a generalized spike-wave (rarely in infancy, mostly in childhood),[32] and erratic myoclonus, particularly during episodes of myoclonic status, in which the patient is drowsy with diffuse slow wave activity and few spikes. The generator remains unidentified.

Reticular Reflex Myoclonus

Reticular reflex myoclonus originates in a hyperexcitable caudal brainstem reticular formation, giving rise to a widespread pattern of muscle activation with proximal and flexor predominance, spontaneous or induced by various stimuli. The impulses may travel up the brainstem. Reticular reflex myoclonus may be present simultaneously with cortical myoclonus.

Reticular reflex myoclonus is not time-locked to EEG discharges, and the sensory evoked potentials are not enhanced. Myoclonus is triggered by stimuli, but the temporal relationship is variable between the stimuli and the myoclonus, whereas it is constant in patients with cortical reflex myoclonus. The EMG discharges start in the areas of lower cranial nerves (sternocleidomastoid muscle, trapezius muscle). They go up to the facial muscles, down to the upper limbs, then to lower limbs. Therefore, it was speculated that the stimuli excited the reticular formation and that abnormal electrical activity then spread from it to the upper brainstem and the spinal cord.[56]

Other Myoclonus

Epilepsy generally does not occur with these other conditions. In spinal myoclonus, the jerks are generated in the spinal cord. Propriospinal myoclonus, nocturnal myoclonus, and periodic leg movements may be involved in this category.

Psychogenic myoclonus is also considered when other organic disorders are ruled out.[81] In patients with psychogenic myoclonus, readiness potentials are present preceding the myoclonus, indicating underlying mechanisms similar to voluntary movements.[112]

Clinical and Electrographic Features of Myoclonic Seizures

Patients may refer to their myoclonus as a jerk, shock, jump, start, involuntary movement, or even stiffness and numbness. Patients may describe being thrown down, as though pushed by someone. Usually, patients do not notice any warnings, but sometimes smaller seizures serve as precursors to more severe ones. Myoclonus may be predominant in axial muscle groups or in the distal ones. Injury caused by falls or by striking a nearby object with a hand or limb may occur during an attack. Myoclonus occurs spontaneously, sometimes predominantly on awakening, and may be precipitated by various internal or external, simple or complex stimuli. Myoclonus may occur in isolation or in patients experiencing generalized tonic–clonic seizures (GTCs) or other forms of epileptic attacks.

In the following section, we describe the clinical and electrographic features of myoclonus in generalized forms. Because the clinical characteristics and EEG expressions of myoclonus are distinct in accordance with the epileptic syndromes, the descriptions accompany the syndromic classification. Detailed descriptions of the individual syndromes can be found elsewhere.[92]

Myoclonic Epilepsies of Infancy and Early Childhood

Harper[58] called attention to the fact that myoclonic seizures occur in childhood, just as in adolescence or adulthood; he described true myoclonic epilepsy in childhood in the age group of 3 to 7 years. Aicardi[3,4] further argued that approximately two thirds of the myoclonic epilepsies occur during the first 5 years of life, and that the true myoclonic epilepsies of childhood—which should be delineated from epilepsies with other types of brief axial motor seizures, such as epileptic spasms and tonic seizures of the LGS—might be subdivided into several forms. International classification of epilepsies and epileptic syndromes[21] covers several distinctive syndromes occurring in infancy and early childhood in which myoclonus is a main seizure type.

Early Myoclonic Encephalopathy

Clinical Features

Massive or axial bilateral myoclonus is the myoclonic feature of early myoclonic encephalopathy, a rare syndrome with several causes occurring during the first 28 days of life (see Chapter 224). In addition, erratic myoclonus frequently repeats as the earliest and main clinical events, with a tendency to shift incessantly from one part of the body to another in an anarchic and asynchronous way.[5,7] Events may be restricted to a very small territory, such as a finger or eyebrow, but sometimes may involve a whole limb. Focal motor seizures and, in the later stage, epileptic spasms or tonic seizures also may appear. Affected infants have severe neurologic abnormalities along with therapy-resistant seizures, and more than half of them die by the age of 1 year.

Electrophysiologic Features

The EEG activity consists of complex bursts of asynchronous spikes and irregular, arrhythmic sharp waves and slow waves lasting 1 to 5 seconds and alternating with flat periods of 3 to 10 seconds (suppression-burst pattern). Normal background activity is absent. The paroxysmal bursts are sometimes synchronous with bursts of bilateral myoclonus. The EEG may later evolve toward atypical hypsarrhythmia.

Myoclonic Status in Nonprogressive Encephalopathies

Clinical Features

This condition is characterized essentially by the recurrence of atypical status combined with an impairment of contact and continuous jerks in infants suffering from a nonprogressive severe encephalopathy with profound cognitive deficit and hypotonia.[23] The myoclonus is more or less rhythmic, asynchronous, and multifocal, affecting periorbital, perioral, and distal muscles. It may be followed by a brief silent period but, in some patients, a negative myoclonus may be predominant. This electroclinical picture is usually observed in children with Angelman syndrome and with 4p-syndrome, allowing an early diagnosis of these disorders.

Other seizure types are focal motor seizures, myoclonic absences, and rare generalized or unilateral clonic seizures. The recognition of this condition is important to exclude the assumption of progressive disease and to allow an adequate treatment against the worsening of the cognitive impairment.

Electrophysiologic Features

The EEG shows bursts of more or less diffuse, more or less synchronous, rhythmic or arrhythmic discharges of diffuse slow spike-waves, often fluctuating, during wakefulness and sleep. Between these bursts are inserted periods of variable duration without obvious paroxysmal discharges but with θ-wave activity of variable amplitude involving both central regions subcontinuously.[23] Bilateral jerk may be time locked with a cortical spike.

Benign Myoclonic Epilepsy in Infancy

Clinical Features

Myoclonus in this rare syndrome occurs during the first or second years of life in normal children who often have a family history of seizures or epilepsy. The seizures are characterized by frequent, brief, mostly symmetrical myoclonus isolated or grouped in clusters and involving the axis of the body and limbs. These seizures provoke a head drop and an upward-outward movement of the upper limbs, with flexion of the lower limbs and sometimes a rolling of the eyeballs.[30,31] They may repeat pseudorhythmically. They occur at any time of day but may be enhanced by drowsiness. In some patients, myoclonus can be triggered by photic stimulation, or by a sudden noise or contact. The myoclonus represents the only seizure type, except for occasional febrile convulsions and GTCs, that occasionally develops later during adolescence. Seizures do not occur in series, and flexion of the entire body, tonic seizures, or absence seizures are never observed. Myoclonus is easily controlled by appropriate medical treatment but psychomotor development may be delayed; hence, the term “benign” is disputed.

Electrophysiologic Features

On EEG, myoclonus is accompanied by a discharge of bilateral spike-wave or polyspike-wave (Fig. 5) that sometimes occurs in rapid succession at more than 3 Hz. The background activity is normal for the child's age, and drowsiness and the early stage of sleep may activate bilateral spike-waves. Myoclonus of about 100 msec duration consists of symmetric, rostocaudal muscle activation, and a premyoclonus negative spike precedes a jerk by about 30 msec.

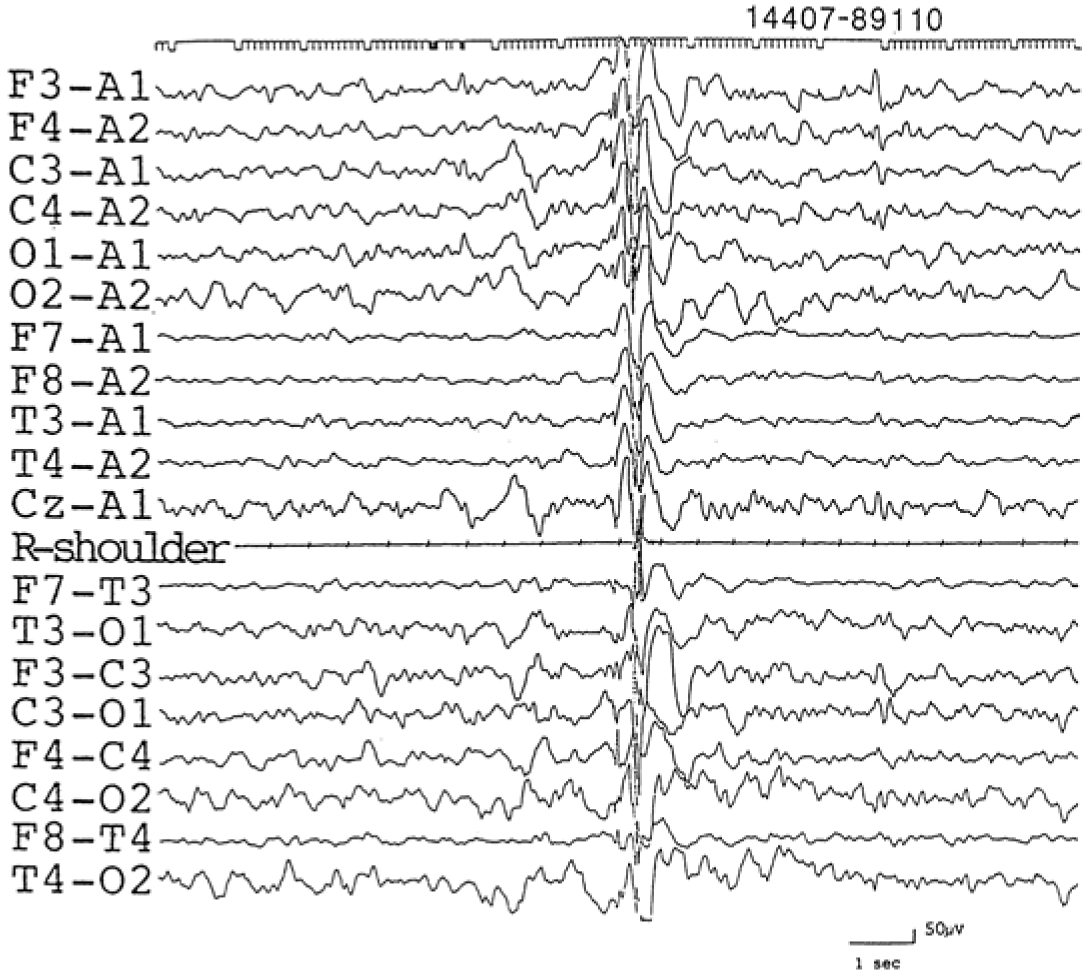

FIGURE 5. An EEG correlate of a myoclonus recorded in a boy, aged 2 years and 11 months, of benign myoclonic epilepsy in infancy. A brief burst of bisynchronous and symmetrical high-amplitude slow waves, maximal in the anterior head part and notched with small spikes, preceded the occurrence of

muscle potentials of the right shoulder. The boy experienced daily axial myoclonus accompanied with abduction of the upper extremities starting at age 2 years and 8 months.

Severe Myoclonic Epilepsy in Infancy (Dravet Syndrome)

Clinical Features

Dravet syndrome (see Chapter 230) is characterized by isolated or grouped axial-dominant bilateral myoclonus, which may lead to throwing of objects the child is holding and to falling. It is one of the typical features of severe myoclonic epilepsy in infancy. Symptoms appear between the ages of 2 and 5 years and occur very frequently, especially on awakening or in the hours preceding a major seizure. In the course of the disease, frequent, distally predominant and perioral erratic myoclonus that exists at rest but increases with movement may be seen, combined with drowsiness and drooling, in the context of nonconvulsive status epilepticus.

As a rule, this syndrome begins with a generalized or unilateral, often prolonged, febrile convulsive seizure before 1 year of age in normal infants.[33,34] The seizures consist of myoclonic, clonic, or clonic–tonic–clonic seizures, atypical absences—often with clonic components—and complex

partial seizures. The seizures are extremely difficult to control, but myoclonus decreases and may disappear in the long-term course. Psychomotor development is retarded from the second year of life onward. This is accompanied by neurologic signs such as ataxia and slight pyramidal signs.

Myoclonus may be induced by variations in illumination, closure of the eyes, and fixation on patterns that can produce an autostimulation phenomenon.

Electrophysiologic Features

Myoclonus is accompanied by a burst of bisynchronous spike-waves or multiple spike-waves (Fig. 6), and appears to originate from spread of cortical myoclonus, whereas distal erratic myoclonus is often without EEG correlates, even on JLA.[4,46] Photosensitivity, including pattern sensitivity, is rather common, and a photoconvulsive response may appear during the first 2 years of life—even as early as 4 or 5 months of age. The EEG background activity fluctuates, depending on the number and duration of the clinical seizure events. Paroxysmally, rhythmic θ-activity at 4 to 5 Hz appears in the centroparietal areas, as do fast bilateral spike-waves, which may be associated later with variable focal or multifocal abnormalities. This syndrome represents an epileptic encephalopathy with diffuse hyperexcitability of the brain, as revealed by sodium channel dysfunction.

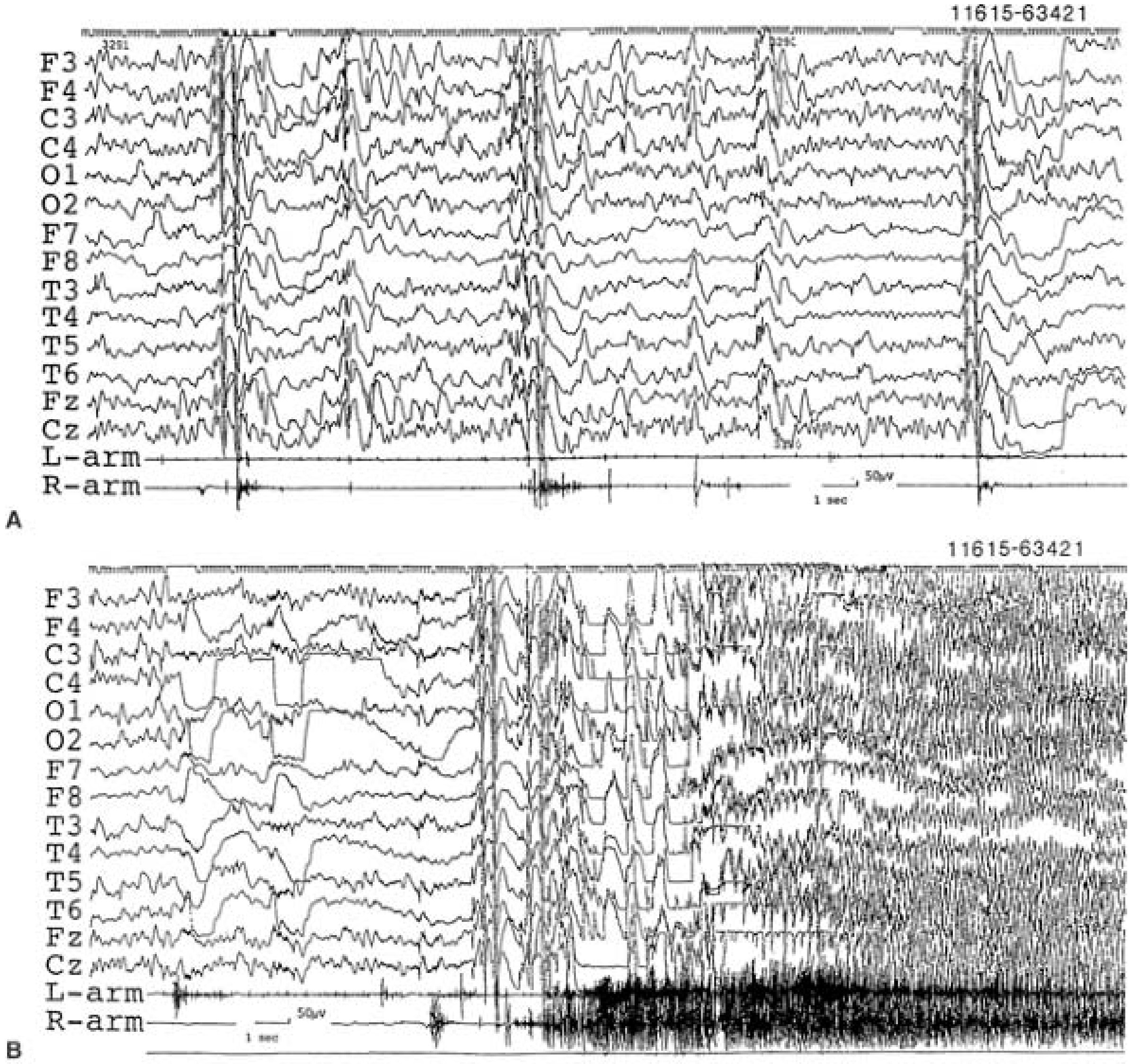

FIGURE 6. A: Frequent myoclonia shown as muscle potentials of arms concurrently occurring with bisynchronous and almost symmetrical polyspike-waves in EEG recorded in a 3-year-old boy. **B:** The myoclonus eventually cumulated into a generalized clonic–tonic–clonic seizure. He suffered from severe myoclonic epilepsy in infancy from 5 months of age on. Myoclonus became prominent from the age of 1 year and 2 months.

Lennox-Gastaut Syndrome

Clinical Features

This syndrome is discussed more completely in Chapter 241. The myoclonic jerks of LGS are generally bilateral and symmetrical (massive), commonly occur upon falling asleep and awakening, and lead preferentially to a flexion of the trunk and abduction of the arms. Bilateral myoclonus followed by an atonic state may lead to abrupt falling and injury, although injuries occur less frequently than in tonic falling.[62] In LGS, myoclonus is never the predominant symptom. Gastaut et al.[43] originally described the rarity of massive myoclonus. Rather, atypical absences and axial tonic seizures occur frequently and sometimes, in series, predominate. Aicardi[6] found that myoclonus was present in 11% to 28% of the patients with this syndrome. Those cases in which myoclonus is observed, called a myoclonic variant of LGS by some authors,[4,43] cannot be distinguished from myoclonic-astatic epilepsy (MAE);[68] (an unfavorable course in which the patients develop myoclonic status lasting several months and are left with tonic seizures in sleep). Indeed, the concept of myoclonic variant of LGS was developed before the nosology of MAE was clarified. The presence of myoclonus in LGS indicates some lesion in the rolandic cortex.[12]

This syndrome generally starts before the age of 8 years, with a peak between 3 and 5 years of age, in children with or

without neurologic antecedent. It is frequently followed by a disturbance of psychomotor development.

Electrophysiologic Features

The ictal EEG of the myoclonus consists of bilateral and symmetrical spikes or sharp waves of brief duration followed by one or several slow waves (Fig. 7). Bonanni et al.[12] reported that the epileptic myoclonus in LGS originates from a stable generator in the frontal cortex, with spread to contralateral and ipsilateral cortical areas. The background EEG is often slow and poorly structured, with bursts of diffuse slow spike-wave patterns of 2 to 2.5 Hz and runs of widespread rhythmic spike discharges at around 10 Hz during sleep. Multifocal spikes and spike-waves may also be recorded.

Epilepsy with Myoclonic-Astatic Seizures

Clinical Features

This recently identified condition is characterized by symmetrical brief jerking involving more proximal muscles, such as of the shoulders and arms; these are isolated or replicated in short series, often with nodding of the head, with or without a subsequent abrupt loss of muscle tone.[28,29] Violent jerks or jerks followed by atonia may lead to abrupt falling and subsequent injury. In severe cases, irregular twitching of the upper extremities and facial muscles, especially of the mouth and tongue, may occur. In rare cases, photostimuli precipitate the myoclonus. Myoclonus may appear in a status form with focal erratic jerks on distal and facial muscles. Other seizure types occurring in this syndrome are atonic seizures, short absences, and febrile and afebrile generalized tonic–clonic seizures.

This syndrome starts mostly between 2 and 5 years of age, in normal children with a high incidence of seizures and/or abnormal EEGs in relatives. For further information, see Chapter 232.

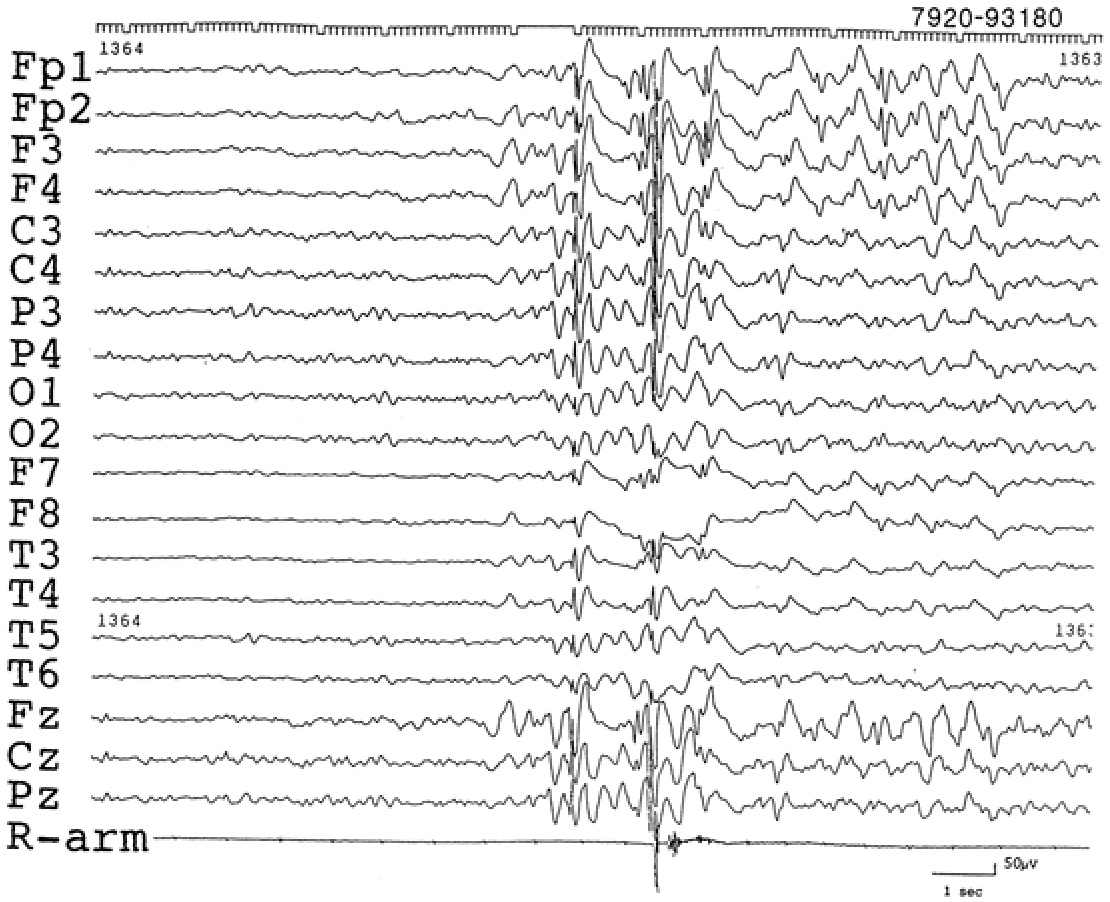

FIGURE 7. A 16-year-old patient suffering from Lennox-Gastaut syndrome. Seizures consisted of tonic seizures with or without falling, atypical absences, generalized tonic–clonic seizures, and myoclonus since the age of 4 years and 3 months. The EEG findings were recurrent bursts of bilateral diffuse spike-waves of 2.5 to 3 Hz, high-voltage waves of about 4 Hz, polyspike-waves, and diffuse fast spike rhythms. The figure represents an axial myoclonus occurring many times a day.

Electrophysiologic Features

The ictal EEG typically shows short paroxysms of bilateral synchronous spike-waves and polyspike-waves (Fig. 8) with an interside latency of 2 to 4 msec.[12] The myoclonus has a duration

of <100 msec, is synchronous on both sides of the body, and time-locked to the negative EEG potential, with a mean latency of around 30 msec. The erratic myoclonus during the status could be of cortical origin, according to JLA,[51] although it is difficult to conceive that the same patient starts with thalamo-cortical myoclonus, then develops cortical myoclonus. This contrast illustrates the difficulties in identifying the determinants of myoclonus based on neurophysiologic studies. The interictal EEG pattern may vary according to seizure type in that, in cases with mainly astatic seizures, irregular 2- to 3-Hz spike-waves predominate. The presence of the interictal θ-rhythm over the centroparietal areas is a feature of this syndrome.

Epilepsy with Myoclonic Absences

Clinical Features

The distinct feature of this syndrome is the rhythmic bilateral myoclonus mainly involving the muscles of shoulders, arms, and legs, associated with a mild axial tonic contraction that results in progressive elevation of the upper extremities (15 and Chapter 240). When the face is involved, myoclonus is more evident around the chin and mouth. Consciousness is cloudy, but not completely interrupted. Falling is uncommon, but a backward or forward oscillation is frequently seen. The duration of myoclonic absence ranges from 10 to 60 seconds, slightly longer than usual absence, and the seizure occurs many times daily. Other types of seizures are rare. The seizure onset is around 7 years of age.

Electrophysiologic Features

The ictal EEG consists of rhythmic, bilateral, synchronous, and symmetric spike-waves at 3 Hz. The onset and end of the discharges are usually abrupt. Myoclonus appears at the same frequency as the spike-waves, and later accompanies a tonic contraction that is maximal on the shoulder and deltoid muscles and responsible for the elevation of the arms. Each spike is followed by a myoclonus with a latency of 15 to 40 msec (proximal muscles).[15] Interictal EEG may show generalized or, rarely, focal spike-waves.

Myoclonic Epilepsies of Late Childhood and Adolescence

The best-known epileptic syndrome belonging to this age group is JME. Other forms of idiopathic generalized epilepsy, such as juvenile absence epilepsy and epilepsy with GTCs on awakening, may also display myoclonus, but far less often. Patients with myoclonus induced by photic stimulation in the environment or laboratory are also discussed in this section, although some of them have onsets in earlier childhood.

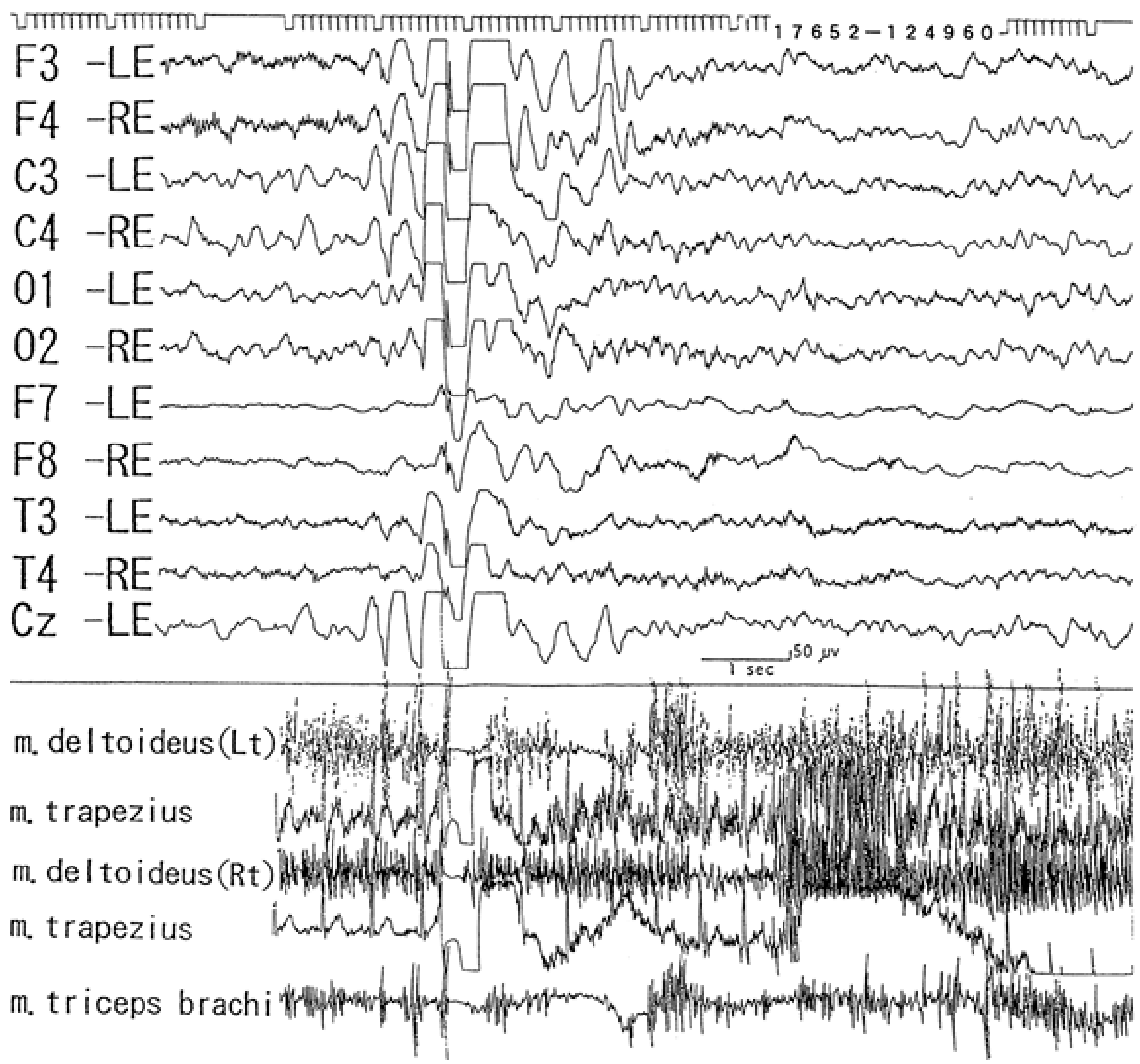

FIGURE 8. A myoclonus immediately followed by a brief atonia leading to a fall, recorded at the age of 2 years and 8 months in a boy with myoclonic-astatic seizures of Doose. Myoclonus precipitated by a high fever began at the age of 2 years. At age 2 years and 7 months, astatic seizures that consisted of either

myoclono-atonia or atonia started in addition to GTCs and absences. The interictal EEG showed an irregular slow background activity of 4 to 6 Hz and paroxysms of bisynchronous high-amplitude slow waves.

Juvenile Myoclonic Epilepsy (Janz Syndrome)

Clinical Features

A complete discussion of JME can be found in Chapter 244. The cardinal symptom of JME, the myoclonus, is characterized by very short, bilateral, symmetrical, and synchronous

jerks affecting mainly the shoulders and arms. The jerks may occur singly or in close succession in clusters at irregular intervals; they may vary in frequency and intensity. They are sometimes perceived only inwardly, as a mild electrical shock, but may also lead to such violent movements that the patient may throw down things he is holding. Because the jerks occur preferentially after waking, irrespective of whether the patient has risen or is still lying in bed, the objects thrown are usually those connected with the patient's morning toilet or breakfast. If the jerks are violent, the patient may drop to his knees or, in rare cases, may fall, but stand again immediately. In some cases, the jerks occur only in one arm and, in rare cases, the jerks are both monolateral and bilateral. Occasionally, especially if the patient continues activities and does not lie down immediately, the jerks may occur in a protracted series or may lead to a true myoclonic status. A status of this sort is reminiscent of a chorea, with more or less violent jerks at irregular intervals. The series and status usually end in a GTC. Unlike absences, the jerks occur while the patient is fully conscious. Only a sharp knock may cause the patient to appear momentarily “in a fog” or briefly “miles away.”

Myoclonus produces contractions of synergistic groups of muscles, with the effect of moving entire limbs. Janz and Christian[67] opted for the purely descriptive name of *impulsive petit mal* for these jerks, harking back historically to Herpin.[59]

The seizures are precipitated by sleep withdrawal and most commonly occur shortly after awakening. According to Touchon,[114] half the patients he observed had manifestation peaks after awakening in the morning, and one third at nocturnal awakening. Some peaks were in the evening relaxation period and during sleep. Some patients report seizure precipitation by intermittent light stimuli. Occasionally, the jerks can be reflectively induced by mental activities connected with manual movements, psychic tension, and decision-making (praxis induction). Even the ideation of action can induce the jerks.[64] Frequent seizure occurrence while using a toothbrush or handling a table knife or a fork might indicate a seizure induction by such actions that could be in line with the praxis. Matsuoka et al.[77] pointed out the usefulness of “neuropsychological EEG activation.” Mayer et al.[78] reported perioral (mostly single, lightning-like oro-linguo-facial) myoclonus induced by talking, which is often underestimated in patients with JME.

Additional generalized tonic–clonic seizures often occur, less often absences, usually of infrequent repetition. Onset of the seizures is pre- to postpuberty. The response to appropriate

antiepileptic drugs (AEDs) is good, but relapse after discontinuation of therapy is high.[65]

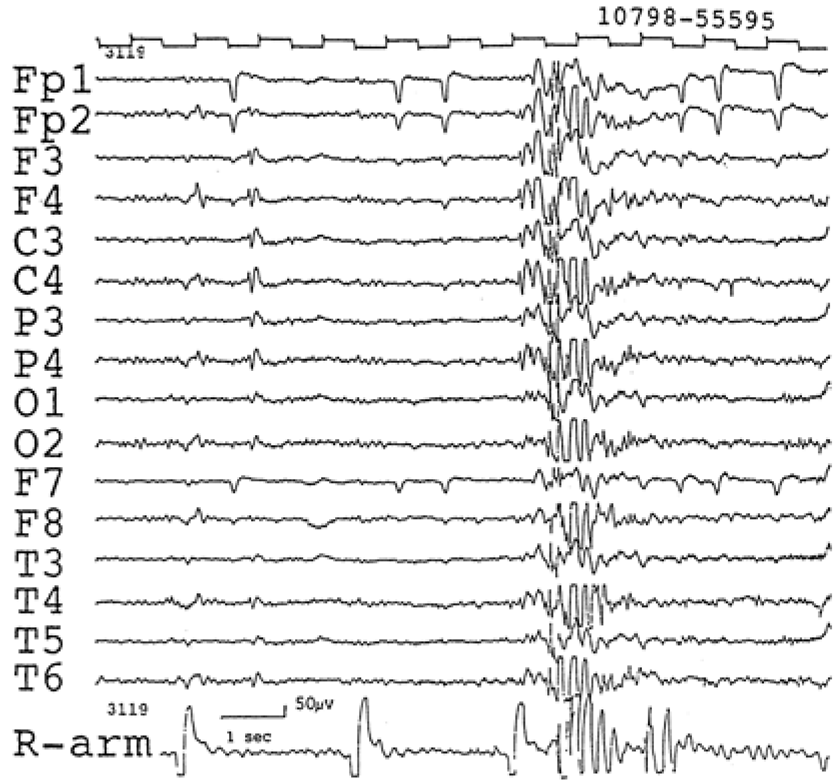

FIGURE 9. Myoclonus of a 47-year-old patient with JME. The seizures occurred predominantly on awakening, but were also provoked when practicing tasks requiring complex mental and manual activities.

Electrophysiologic Features

The characteristic EEG of jerks in JME is bilaterally symmetrical, frontocentrally accentuated polyspike-waves, with the number of spikes ranging from 5 to 20 (Fig. 9). A burst of spikes suddenly occurs with the jerks and is followed by slow waves of varying frequency of 10 to 16 Hz. Interictal polyspike-wave patterns usually display fewer spikes and are often restricted to the frontal leads. Usui et al.[117] found focal clinical or EEG features or both in a substantial number of patients with JME. In 14% of patients with JME, giant SEP were observed.[96] Panzica et al.[89] investigated the myoclonus of JME with JLA, and concluded that the ultimate mechanism responsible for myoclonus is largely similar to the cortical myoclonus in PME.

Myoclonic Epilepsies of Non–Age-Related and Special Conditions

The progressive myoclonus epilepsies (PME) and benign adult familial myoclonic epilepsy (BAFME) are included within this group. In Creutzfeldt-Jakob disease and subacute sclerosing panencephalitis, the duration of the jerks is clearly over 100 msec, and they do not therefore correspond to myoclonus *stricto sensu.* Metabolic diseases (e.g., hepatic encephalopathy, uremia, Hashimoto encephalopathy, drug-induced encephalopathy, toxic encephalopathy, and so on) and cortico-basal degeneration sometimes show jerks, the characteristics of which are often not determined precisely; generalized tonic–clonic seizure is not a typical feature.

Progressive Myoclonus Epilepsy

Clinical Features

PME is commonly hereditary and characterized by myoclonus and generalized convulsions. Patients with PME frequently demonstrate cerebellar ataxia, mental deterioration, pyramidal signs, and rigidity. These symptoms start in late childhood or adolescence, progress slowly, and are fatal in many instances. This category comprises different forms such as Unverricht-Lundborg disease, Lafora disease, myoclonic epilepsy with ragged red fibers, neuronal ceroidlipofuscinosis, sialidosis, and dentatorubral-pallidoluysian atrophy. The clinical picture involves a combination of parcellar or segmental, arrhythmic, asynchronous, asymmetric myoclonus, and massive myoclonus. The myoclonus is often precipitated by action, posturing, or various sensory stimuli. A long build-up of myoclonus may culminate in a tonic–clonic seizure.

Other seizure types, including tonic–clonic, clonic, absence, and focal seizures, as well as their intensity, vary depending on the etiology.

Electrophysiologic Features

The EEG shows generalized polyspikes and spike-waves, frequently induced by photic stimulation. The background EEG activity becomes progressively slower. Giant SEP, C-reflex at rest, and premyoclonus spike are often observed, indicating the underlying mechanisms of cortical reflex myoclonus. However, because the findings may differ among various types of PME, the other mechanisms could overlay it.

Benign Adult Familial Myoclonic Epilepsy

Clinical Features

In patients with familial cortical reflex myoclonus, some demonstrate rare epileptic seizures, but do not present with the ataxia, mental deterioration, or progression seen in PME. Clinical symptoms start between 18 and 64 years. Family history indicates autosomal dominant traits. Magnetic resonance imaging (MRI) results are usually normal. Many reports come from Japan, and the terms *cortical tremor,*[60] *familial essential myoclonus and epilepsy*,[63] *familial benign myoclonus epilepsy of adult onset*,[86] *familial cortical myoclonic tremor*,[111] and *familial cortical myoclonic tremor with*

epilepsy[118] were used in addition to the term benign adult familial myoclonic epilepsy.[120] A similar disease was reported from Europe as *autosomal dominant cortical myoclonus and epilepsy* (ADCME).[47] However, patients with ADCME have mental retardation and partial seizures, which are not typically seen in patients with BAFME. Linkage analysis demonstrated a map on chromosome 8q23.3–q24.1 in Japanese (BAFME) and on 2p11.1–2q12.2 in European pedigrees (ADCME). Negative linkage analyses also were reported in BAFME;[26,37,71] this syndrome therefore may be hetero- geneous.

Electrophysiologic Features

The background EEG is normal. Generalized polyspikes and spike-waves may be demonstrated, frequently induced by photic stimulation. Giant SEP, C-reflex at rest, and premyoclonus spike are often observed.

Delineation from Other Seizure Types

The delineation of myoclonus from other types of seizures is sometimes difficult. Tonic seizures characterized by more or less sustained increased muscle tone and atonic seizures characterized by sudden loss of axial (or appendicular) muscle tone can be easily confused with myoclonus, especially when the seizures are short and abrupt. However, the EEG pattern is entirely different: In tonic seizures, commonly a synchronous recruiting activity occurs before any spike-and-wave activity develops. Polygraphic recording helps to sort out the differences. Myoclonus is manifested as biphasic or polyphasic EMG potentials of 20- to 100-msec duration, whereas tonic seizure indicates an inferential muscle discharge of longer duration that may be of crescendo pattern at onset, similar to that in voluntary contraction. During atonic seizures, EMG shows suppression of normal tonic activity in the involved muscles. Myoclonus may be followed by sustained residual tonic contractions or by a brief period of inhibition of muscle tone that may be sufficient to produce head nodding or even a fall. Episodes of myoclonus may be preceded by a tonic seizure.

Confusion of myoclonus with epileptic spasms is possible on clinical grounds, and the distinction may require video-EEG recording. Particularly in early infancy, the distinction between early epileptic encephalopathy and neonatal myoclonic encephalopathy may be a challenge that has etiologic and therapeutic implications.

Etiologic and neurobehavioral correlates, and their responses to AEDs, are also of importance for differentiation.

Subcortical negative myoclonus is usually characterized by rhythmic, EMG silent periods occurring at a rate of 6 to 11 Hz, without any detectable EEG correlate, even by using the technique of silent period-locked averaging. Early cortical components of SEPs are not enhanced.[100] The subcortical NM may appear as a bilateral, although not perfectly synchronous, phenomenon, affecting both hands. NM in toxic-metabolic encephalopathies—that is, "asterixis" —displays the characteristics of subcortical NM, although, in some cases, the demonstration of a cortical correlate by means of averaging the EMG–EEG signal[2,8,115] and the evidence of giant SEPs and a C-reflex[113] support a cortical origin. Finally, subcortical NM has been obtained through electrical stimulation of the human internal capsule.[87]

Negative Myoclonus

The first description of sudden, irregular lapses interrupting a tonic contraction dates back to 1949, when Adams and Foley[1] used the term "asterixis" to describe the brief, involuntary jerky movements on the maintenance of posture that occurred in patients suffering from hepatic encephalopathy. In 1963, Lance and Adams[72] reported lapses of postural control in the postanoxic intention myoclonus syndrome as a result of a muscular silent period (SP), whether preceded by myoclonus or not, in relation to a spike-and-slow-wave complex. Periods of muscular inhibition, strictly and only related to a diffuse or focal spike, without preceding myoclonia, were defined as "spike-related epileptic silent periods."[105,107] The term "*negative myoclonus*" was introduced by Shahani and Young in 1976;[99] they analyzed the clinical and EMG characteristics of posthypoxic intention myoclonus and asterixis, and concluded that "because these synchronous brief pauses, which occur at irregular intervals in the ongoing voluntary EMG activity, produce movements that appear clinically to be myoclonic, one may characterize this as *'negative myoclonus.'"* Indeed, at present, NM encompasses all the above-mentioned phenomena, and is extended to define any brief, jerky interruption of tonic muscular activity that causes a sudden postural lapse.

NM is a nonspecific motor disorder that can be observed in a variety of physiologic as well as pathologic conditions. NM of epileptic nature, such as *epileptic negative myoclonus* (ENM)[49,106,108] identifies an interruption of tonic muscular activity, time-locked to a spike on the EEG, without evidence of an antecedent myoclonus. Recently, the Task Force of the International League Against Epilepsy on Classification and Terminology has recognized NM as a seizure type,[38] defining it as an "interruption of tonic muscular activity for < 500 msec without evidence of preceding myoclonia."[11]

Clinical Manifestations

NM appears as a shock-like involuntary jerky movement caused by a sudden brief interruption of muscular activity. As proposed by Young and Shahani,[121] "asterixis" is a type of NM that occurs typically in toxic-metabolic encephalopathies, often associated with reduced alertness; it can also be observed during the recovery phase following general anesthesia with sedative drugs. Obeso et al.[83] considered as a separate form of NM the *postural lapses* that can be observed in posthypoxic action myoclonus, characterized by interruptions of the tonic muscular activity of postural muscles (neck, trunk, proximal leg muscles) lasting 200 to 500 msec, and usually following a myoclonic potential.[72] A similar phenomenon can be observed also in other diseases such as progressive myoclonus epilepsies (Lafora disease, Unverricht-Lundborg syndrome), torsion dystonia, cerebellar ataxia, and Huntington disease. In these conditions, a combination of positive myoclonus and NM can often be observed; however, NM seems to be the most disabling disturbance, significantly affecting the ability to stand or walk.

In epileptic patients, ENM can be either unilateral or bilateral.[108] In some instances, this disorder can be a clinically very mild or almost undetectable motor event, giving rise to an "instability." More often, ENM can cause dropping of objects from the hands, "tremulousness" of a limb with difficulties in writing and feeding, head nodding or, at times, gait instability and falls.[20,24] Despite the relatively short duration, ENM can be so frequent as to lead to a severe motor disturbance resembling motor neglect of the affected arm. Capovilla et al.[17] reported two children suffering from partial benign epilepsy and presenting with sudden falls and episodes of fecal incontinence related to ENM in one lower limb and the pelvic floor muscles.

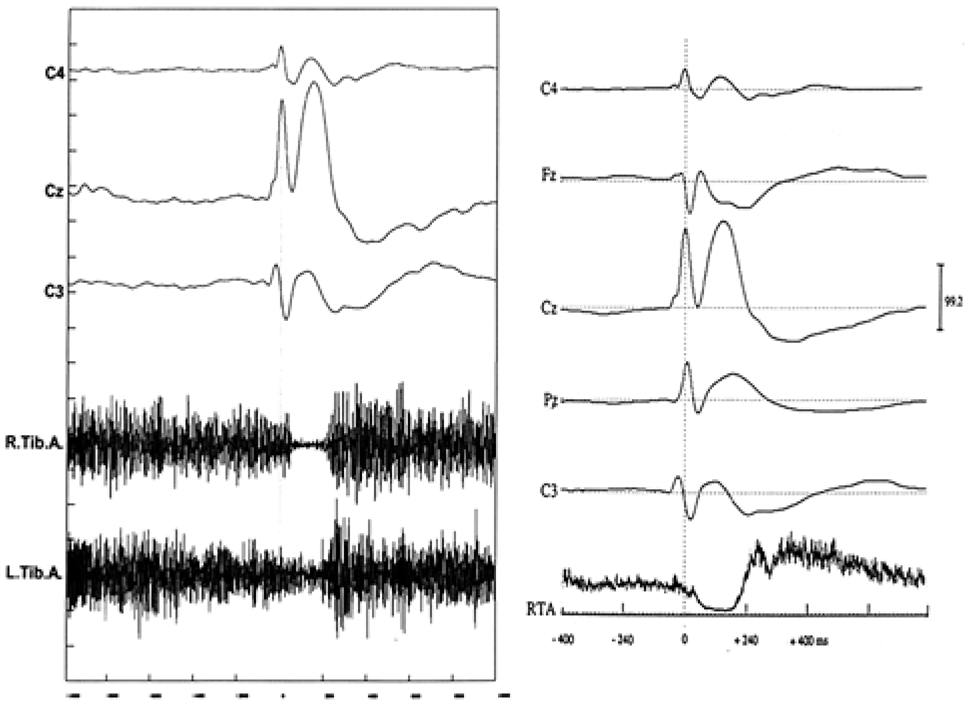

FIGURE 10. Epileptic negative myoclonus (ENM) in a child with idiopathic partial epilepsy. *Left panel*: A spike-and-wave complex on Cz is associated with a brief interruption in a tonic contraction in the right tibialis anterior. *Right panel*: Average of 20 spike-complexes, triggered from the peak of the spike, showing that the muscular suppression of ENM is not preceded by a positive myoclonia; moreover, the onset of the EMG SP precedes the onset of the slow wave in Cz.

Syndromes and Diseases in Which ENM Occurs

ENM is a nonspecific motor disorder that can be observed in a wide variety of epileptic conditions. It is classified according to etiologic criteria as idiopathic, symptomatic, or cryptogenic.[108] In the idiopathic form, it is usually detected in children suffering from partial epilepsy of childhood (including benign epilepsy with rolandic spikes).[16,17,24,69,84,85,108] ENM as an isolated

clinical manifestation has never been reported; seizures associated with ENM can be partial motor (often of the rolandic type), absences, or atonic. The evolution of both ENM and epilepsy in this group of patients is usually benign. In the pediatric group, ENM can be observed in the *epileptic encephalopathy with electrical status epilepticus during sleep* or ESES syndrome. In this condition, ENM is associated with various seizure types and impairment of higher functions, such as language regression, behavioral disturbances, and ataxia.[110] The mechanism of drop attacks may be challenging, especially if masked by benzodiazepines.[9] Gambardella et al.[41] described a patient with photic-induced negative myoclonus suffering from a form of idiopathic generalized epilepsy.

ENM can occur in pediatric as well as adult patients in symptomatic epileptic conditions such as mitochondrial diseases, birth anoxia, vascular malformations, progressive myoclonus epilepsies, epileptic encephalopathies, and neuronal migration disorders. Seizure types associated with ENM in these epileptic conditions can vary from simple to complex partial seizures, tonic seizures, spasms, and generalized tonic–clonic seizures. Occurrence of ENM in a newborn with Ohtahara syndrome and hemimegalencephaly has been recently reported.[52]

Finally, NM is not infrequently induced as the side effect of various anticonvulsive drugs.

Pathophysiology

Classifications based on the possible site of the generator have distinguished *subcortical* and *cortical*

NM.[83,100,109] Focal NM has been observed in patients presenting with focal brain lesions involving subcortical structures such as thalamus, internal capsule, midbrain, and pons, and cortical structures such as the parietal lobe and medial frontal cortex.[13,25,70,88,91,121]

In cortical NM, EMG SPs are usually longer in duration (100–400 msec) as compared to subcortical myoclonus; the resulting falls are "progressive" and rarely responsible for any injury. Cortical NM of epileptic nature (i.e., ENM) is associated with an EEG event such as an epileptic spike[49,105,108] or a low-amplitude EEG transient.[108] Tassinari et al.[105,107] showed that the onset of the EMG SP was related to a negative component of the spike on the EEG, occurring before the slow-wave (Fig. 10). The fact that NM can be evoked by intracranial cortical stimulation using single electric pulses lends support to the hypothesis of a NM related only to a spike event.[95] The involvement of cortical mechanisms has been clearly demonstrated in cortical reflex negative myoclonus, described by Shibasaki et al.[103] in progressive myoclonus epilepsies. In these patients, electrical stimulation of the median nerve during sustained tonic contraction caused a postural lapse at the wrists, with an EMG SP ranging from 100 to 400 msec. A C-reflex could precede this stimulus-induced NM. The occurrence of an induced EMG SP and giant SEPs were significantly correlated. Furthermore, recovery of function of the N33 component was slow and similar to the duration of the induced EMG SP. Summarizing this evidence, the authors concluded that this form of stimulus-induced NM occurred via a transcortical reflex mechanism, hence the definition of "cortical reflex negative myoclonus." Shibasaki[101] hypothesized that the generation of ENM requires an enhanced inhibitory activity in the primary motor cortex. Excessive inputs into the motor cortex, as may occur following spontaneous epileptic activity in the premotor or postcentral areas, or due to enhanced excitability of the sensory cortex, can activate the already hyperactive inhibitory motor system, thus suppressing the cortico-spinal volley to the spinal motoneurons and producing the EMG SP that results in clinical NM. The hypothesis of cortical inhibitory mechanisms mediating ENM was further supported by the inability of transcranial magnetic stimulation to elicit a motor evoked potential when magnetic stimuli were delivered during the EMG SP of ENM.[108] Preserved spinal excitability in ENM was demonstrated by recording normal F waves during the period of muscular inhibition.[108]

It is also possible that some NM might be caused by excessive excitation of a group of cortical neurons that activate inhibitory interneurons at the spinal level.

Rubboli et al.[95] described a frontal EEG potential encompassed in spikes and associated with ENM preceding the onset of the interruption of the tonic muscular activity. Baumgartner et al.,[10] by combined use of EEG and single photon emission computed tomography (SPECT)-MRI coregistration, and Meletti et al.[80] provided further evidence supporting a role for frontal cortical regions in the generation of ENM. These findings may be supported by intracerebral

electrical stimulation results in epileptic patients demonstrating the existence, in the lateral and mesial aspects of the frontal lobes, of cortical areas whose activation can produce motor inhibition.[74,75] The involvement of postcentral parietal areas has been suggested by Noachtar et al.,[82] who showed the association of epileptic spikes in the postcentral cortex, recorded by subdural grids, with ENM in the contralateral upper limb.

The role of premotor cortex, primary motor and somatosensory cortex, and supplementary motor area in the generation of NM was investigated by means of single-pulse intracerebral electrical stimulation.[61,93] In particular, Rubboli et al.[93] observed that NM could be obtained by stimulating all these cortical areas; however, its occurrence by activation of premotor, primary motor, and primary somatosensory cortex depended on the intensity of stimulation—NM could be observed mainly at low stimulus intensity, whereas higher stimulation evoked a motor evoked potential followed by a SP. On the contrary, supplementary motor area stimulation induced only NM regardless of stimulus intensity.

Hypotheses suggesting that positive myoclonus and NM are two distinct motor events (with positive myoclonus requiring the involvement of the primary motor cortex and NM depending on the activation of cortical inhibitory areas), or two aspects of the same phenomenon (both resulting from an altered sensory-motor cortex output producing different degrees of positive or negative effects on the motor system) have been proposed.[113] It might be that both phenomena are associated more often than expected: Indeed, for NM to become apparent, a tonic contraction is required that could masquerade a preceding or following muscular burst; on the other hand, a myoclonic jerk at rest can be easily appreciated, whereas an associated SP would not be observable due to the lack of muscular tone.

This concept of a cortical inhibitory area is unlikely to apply to all types of NM. Indeed, in idiopathic focal epilepsy that never undergoes intracranial recordings, video-polygraphic recordings show the strict correspondence of the myoclonus and the slow wave of the spike-wave complex.[39] The corresponding clinical condition often comprises continuous spike waves in slow sleep (CSWS). It is remarkable that, in symptomatic conditions with CSWS, a series has highlighted the frequency of thalamic lesions,[53] a remarkable feature related to the frequent effect of ethosuximide.

Diagnosis

The incidence and prevalence of ENM are underestimated because this sometimes mild and transitory disorder often is overlooked. Polygraphic recording is the essential neurophysiologic tool used to define ENM. Only simultaneous EEG-EMG monitoring, recording activity from the agonist and antagonist muscles of the body segment affected by ENM, can allow the diagnosis of this motor disturbance by showing a brief interruption of a tonic EMG activity not preceded by a positive myoclonus.

The clinical features of NM—a sudden involuntary jerk—may make it difficult to distinguish from positive myoclonus. In addition, in certain conditions, both disorders are commonly observed in the same patient. It must be pointed out that to unveil NM, a tonic contraction of the affected muscle is necessary; the diagnosis of NM requires the exclusion of a positive myoclonus preceding the onset of the EMG SP.

NM can occur in a continuous fashion, rhythmic or arrhythmic, as soon as the patient maintains a posture: In this case, the affected limbs look “tremulous.” Depending on the frequency of this “tremulousness,” it may be difficult to differentiate it from true tremor. In NM, polygraphic recording demonstrates the simultaneous interruption of EMG activity in agonist and antagonist muscles, whereas in tremor, the muscular contractions in the two muscular groups tend to occur in an alternate fashion.

In epileptic patients, sudden postural lapses leading to a fall may be caused by ENM involving axial and leg muscu- lature.[17,94,101]

Responses to Medical Treatment

The drugs used to treat conditions with myoclonus include valproic acid (VPA), benzodiazepines, piracetam, levetiracetam (LEV), phenobarbital or primidone, acetazolamide, ethosuximide (ESM), topiramate (TPM), and zonisamide (ZNS).

VPA is the drug of choice in many conditions with myoclonus. In patients with epilepsy with myoclonic-astatic seizures and with a syndrome of myoclonic absences, ESM or benzodiazepines may be added to VPA. Stiripentol or TPM may be used in combination with VPA and clobazam in Dravet syndrome, although bromide or a ketogenic diet may also be instituted.[97] LEV, benzodiazepines, TPM, or ZNS can be used in JME instead of, or in addition to, VPA, although benzodiazepines may not reduce GTCs.[79] ENM may be successfully treated by ESM.[16,85] In progressive myoclonus epilepsy, in addition to medical treatment using conventional or newer antiepileptic agents such as VPA, benzodiazepines, piracetam, phenobarbital, LEV, or ZNS, various other treatments may be applied according to the etiology.

Some drugs may aggravate myoclonus, such as carbamazepine, oxcarbazepine, phenytoin, gabapentin, vigabatrin, and tiagabin.[98] Lamotrigine should be used with caution because, in high doses, it may initiate myoclonus or even myoclonic status, particularly in Dravet syndrome.[50] The inhibition of carnitine uptake when using VPA should be taken into account in the treatment of progressive myoclonus epilepsy with ragged red fibers.

Summary and Conclusions

Myoclonus is characterized by coordinated or synergic movements of the limbs or the trunk. It is an involuntary, quick, and often arrhythmic positive or negative movement. It typically presents spike- or polyspike-wave patterns in EEG and short bursts or interruptions of synchronized activity involving both agonist and antagonist muscles in EMG.

Differentiation of myoclonus from other seizure types such as brief tonic seizures and atonic seizures and from brisk non- epileptic movements associated with physiologic or pathologic conditions requires a knowledge of clinical, etiologic, and electrophysiological contexts.

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Chapter 51

Atonic and Myoclonic-Atonic Seizures

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Introduction

Atonic and myoclonic-atonic seizures represent specific seizure types whose definition implies a characteristic physiopathologic mechanism and a well-defined electro-clinical pattern that may be demonstrated only by polygraphic and video-polygraphic recording. Therefore, these seizures cannot be diagnosed only on the basis of the clinical history, which may usually reveal recurrent "falling" seizures, associated or not with minor motor events. Falling seizures, otherwise termed *epileptic drop-attacks* or *astatic seizures,*[5] are a heterogeneous group of epileptic seizures in which the fall represents the main or only clinical feature, with no major motor phenomena (e.g., convulsions) occurring.[58,82] Falling seizures may represent a variety of seizure types (either generalized or focal) and mechanisms, including widespread myoclonic jerks, tonic contraction, pure atonic events, or the combinations of motor phenomena, as in the case of myoclonic-astatic seizures. These observations may explain the controversies in the terminology of epileptic falls and the high number of terms used in the past (akinetic, atonic, astatic, static, drop, apoplectic, inhibitory).

Atonic and myoclonic-atonic seizures are usually classified among generalized seizure types.[24] However ictal atonic events may be also recognized in focal seizures, such as drop-attacks of frontoparietal origin,[75] focal inhibitory seizures,[39] and negative myoclonus.[84,85]

History

Seizures characterized by a sudden fall have been known for a long time. Apart from early clinical notes by Tissot and Newman dating back to the 18th and 19th centuries, respectively, the first detailed description of atonic seizures was given by Hunt in 1922, who called the condition "static epilepsy"—that is, a "form of epilepsy characterized by sudden losses of postural control."[40] In 1945, Lennox proposed the term *akinetic seizures* for attacks of this type, which he rebaptized *astatic* in 1951.[47,48] These seizures were considered to belong to the electro-clinical group of petit mal absences: Lennox suggested the term *petit mal triad* to include absences, myoclonic jerks, and akinetic attacks.[49] In 1966, Gastaut et al.[29] described the *Lennox-Gastaut syndrome*, in which falling seizures were a characteristic seizure type, and also reported a few cases of polygraphically studied atonic seizures.[30] In the same years, there was the first polygraphic demonstration of a specific seizure type with a combination of myoclonus preceding atonia, which was termed *myoclonic-astatic* seizure by Kruse.[42] In 1981, the Commission on Terminology and Classification of the International League Against Epilepsy (ILAE) established the term *atonic seizure* for falling attacks with loss of tone.[11] Last, in 2001, the Task Force on classification and terminology of the ILAE included atonic seizures and myoclonic-atonic seizures within an accepted list of generalized seizures.[24]

Definitions

Atonic seizures are currently defined as epileptic attacks characterized by a sudden loss or diminution of muscle tone, which may be confined to a segment (limb, jaw, head), or involve all postural muscles, leading to a slumping to the ground.[5,11,28] In atonic seizures, the loss or diminution of muscle tone is "pure," without apparent preceding myoclonic or tonic events.[5]

Myoclonic–atonic seizures may be defined as epileptic attacks in which the atonia is preceded by a myoclonic jerk (i.e., a sudden and brief—<100 msec—involuntary contraction of muscle groups of variable topography).[5]

In the recent glossary of descriptive terminology for ictal semiology,[5] it has been also stated that "falling seizures" are better termed *astatic*, this term implying "loss of erect posture that results from atonic, myoclonic or tonic mechanism"; drop attack would be a synonym.

Epidemiology

Because of controversies in terminology and the need of a polygraphic recording to perform a reliable diagnosis, exact figures for the incidence of these seizure types are not available. Atonic seizures have been quoted to occur in at least 50% of cases of Lennox-Gastaut syndrome and probably in 2% to 3% of an epileptic population.[60] However the introduction of video-polygraphic systems in the analysis of "astatic" seizures has clarified that seizures characterized by pure diminution or loss of tone (atonic seizures) are distinctly rare, accounting for only a minority of epileptic drop attacks. Gastaut et al.[30] found atonic seizures only in 3 out of 2,000 epileptic patients followed at the Centre St. Paul in Marseille. Myoclonic astatic seizures are likely to reflect the prevalence of myoclonic–astatic epilepsy, accounting for 1% to 2% of all childhood epilepsies.[17]

Anatomic pathways and pathophysiology

Because of the variety of seizures featuring atonia as the main clinical and polygraphic event, it is likely that different mechanisms are implicated, involving cortical and subcortical structures.

Gastaut and Broughton[27] considered "epileptic drop attacks" to be related to very brief but intense inhibitory mechanisms, suggesting the importance of motor cortex participation. Data from electrical stimulation of human cerebral cortex reveal the existence of frontal regions whose activation produces inhibition of voluntary movement.[52,53,54] These regions, defined as "negative motor areas", have been localized in the superior bank of the sylvian fissure near the

rolandic representation of the face ("primary negative motor area")[52,70] and in the rostral portion of the supplementary motor area (SMA), in a region immediately anterior to the primary motor cortex ("supplementary negative motor area").[50] The importance of these cortical inhibitory areas is well established in the genesis of focal atonic seizures and negative myoclonus[72,76,84] but is only presumed in the origin of atonic falling seizures.[75] An alternative explanation is that epileptic discharges in the primary sensorimotor cortex can produce negative motor phenomena via direct inhibition of the spinal motoneuron pool, as suggested in humans by means of direct cortical stimulation through subdural electrodes[36] or ictal electrocorticogram.[55]

Gloor[32] stressed the importance of recurrent cortical inhibition (mediated via the thalamocortical volleys) leading to interference with cortical function during the spike-and-wave discharges (SWDs) of absence seizures. Oguni et al.[64] suggested that atonic seizures associated with generalized SWDs may have a neurophysiologic mechanism in common with absence seizures, with the atonic phenomenon being only the expression of a stronger disruption of cortical activity.

The good results of callosotomy in the treatment of epileptic drop attacks in the context of partial epilepsies suggest that bilateral synchronization of the epileptic discharge via the corpus callosum is a crucial mechanism.[65] Whether this may lead to a bilateral activation of inhibitory cortical areas or of cortical regions projecting downward to brainstem structures is not known.

The brainstem has also been considered to play a role in the origin of atonic seizures, both generalized and partial.[10,23,41,89] In the brainstem, the direct or indirect (via the corticoreticular efferents) activation of the pontomedullary reticular formation, which is responsible for atonia or inability to move in rapid eye movement (REM) sleep and in cataplexy, could produce a motor inhibition and underlie atonic seizures.[44]

Electroclinical features

Atonic and myoclonic–atonic seizures have been mostly documented in large clinical series of generalized epilepsies of infancy, such as Lennox-Gastaut syndrome or myoclonic astatic epilepsy.

Gastaut et al.[30] studied the electroclinical features of 300 "*effondrements epileptique*" by using video-polygraphic methods in three young patients with Lennox-Gastaut syndrome. Egli et al.[23] recorded 239 "drop seizures" both by radiotelemetered electroencephalographic (EEG) split-screen videotaping and polygraphically in 45 patients suffering from "secondary generalized epilepsy."

Similarly, Ikeno et al.[37] recorded 48 epileptic falls in 15 children, captured by a self-tracking video monitoring system. Oguni et al.[62] studied 36 drop seizures in five patients with myoclonic–astatic epilepsy of early childhood with simultaneous split-screen video recording and polygraph. By using the same technique, Yaqub[90] also recorded falling seizures in 21 patients with Lennox-Gastaut syndrome.

Dravet et al.[20] reported the various types of epileptic drop attacks in eight children whose seizures were recorded by polygraphy and simultaneous video.

Oguni et al.[63] described the video-EEG (V-EEG) and video-polygraphic findings of myoclonic, atonic, and myoclonic–atonic seizures in 30 children with myoclonic–astatic epilepsy.

The analysis of these studies has clarified some of the complexities of the falling or astatic seizures, which have been found to encompass four different seizure types: pure atonic seizures, myoclonic–atonic seizures, myoclonic seizures, and tonic seizures (including axial spasms).[77,82].

Moreover atonic seizures may have a generalized or focal origin.

Generalized Atonic Seizures

Clinical Features

Only a few polygraphically documented atonic seizures are available in the literature: atonic seizures were present in one of 15 children studied by Ikeno et al.,[37] in nine of 45 patients observed by Egli et al. with epileptic falls,[23] in 10 of 30 patients studied by Oguni et al.,[63] and in three children described by Gastaut et al.[30]

From clinical observation, two forms of atonic seizures have been recognized[30]

- *Brief atonic seizures* (also called *effondrements epileptiques*), in which loss of tone may be restricted to the head (head drop) or involve all postural muscles, leading to a slumping to the ground. If consciousness is lost, this loss is extremely brief. The patients are able to stand up immediately after the fall.
- *Prolonged atonic seizures* (also called *akinetic seizures*), in which the loss of consciousness and the generalized atonia last for 1 to several minutes. The patient falls to the ground and remains mute and motionless.

Gastaut et al.[30] studied the clinical features of the brief atonic seizures by video recording and found that the patients fall to the ground in less than 1 second, with a typical sequence of events being (a) head drop (lasting for 250 msec) and (b) trunk and legs drop (from 250 to 800 msec) (Fig. 1).

After an intermediate period of about 1 second, patients recover a normal standing position in about 2 seconds. Oguni et al.,[62] by examining the video-polygraphic features of 69 "atonic epileptic drop attacks" recorded in two patients with myoclonic–astatic epilepsy, observed that the clinical manifestations ranged from collapsing and landing on the buttocks to head nodding only. Detailed video analysis of the drop attacks with the patient in standing position demonstrated the first manifestations to be flexion at the waist and knees, followed by further knee flexion, leading to falling straight down and landing on the buttocks. More recently, the same authors recorded atonic seizures in 11 children while they were either in a sitting or standing position.[63] When in a standing posture, patients fell straight downward, landed on their buttocks, and recovered immediately. When sitting, the patients fell forward or backward depending on the position of their center of gravity. The polygraphs, corresponding to the atonic seizures, showed sudden interruptions of ongoing electromyographic (EMG) potentials confined to the upper trunk when seizures were mild, and extending to the lower antigravity muscles when they were intense. The duration of EMG silence extended to 400 msec, which indicated rapid recovery, either immediately after or possibly during the fall.

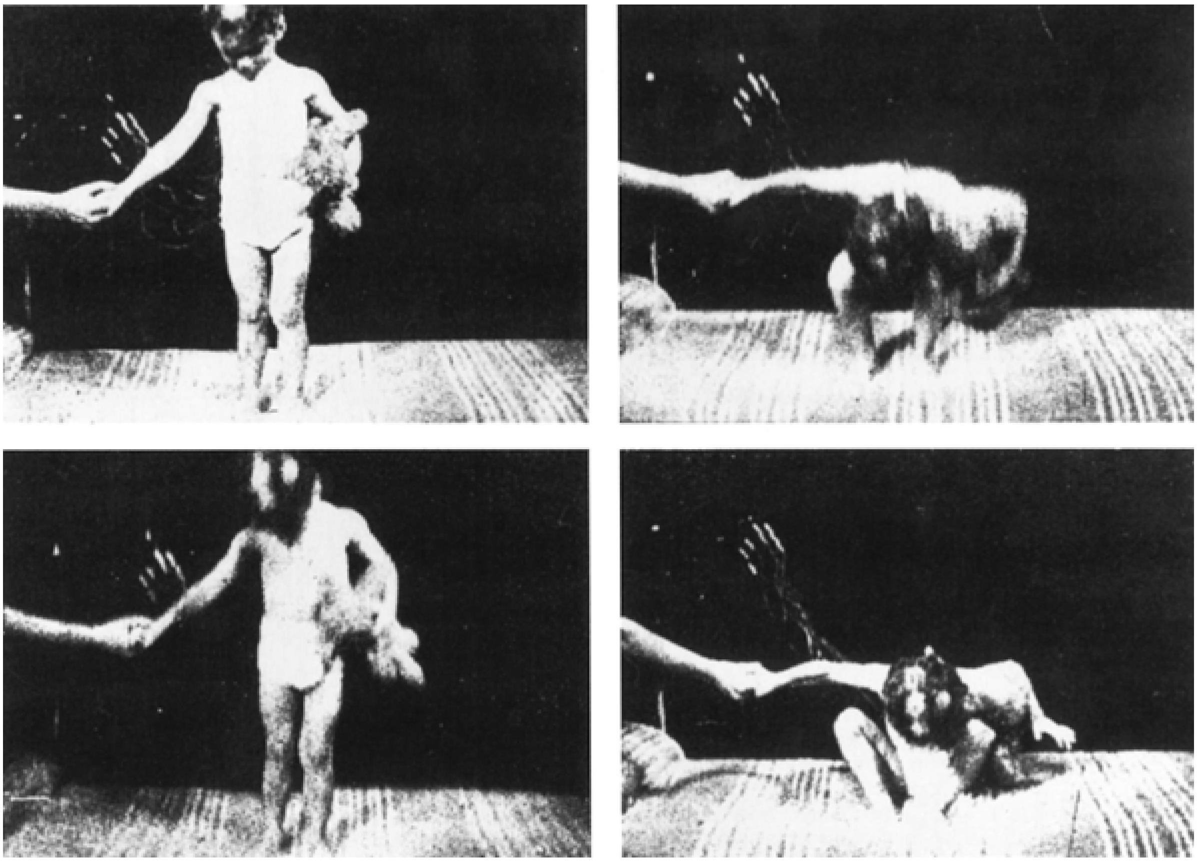

FIGURE 1. Brief atonic seizures ("effondrement atonique epileptique"). Video recording of a very brief atonic seizure, showing a typical sequence of events: initial head drop (*left*) and subsequent trunk and leg drop (*right*). It is interesting to note that the fall occurs exactly on the body axis, and the arms are not involved by tonic or myoclonic phenomena. These features may help in identifying an epileptic atonic fall on direct clinical observation. From Gastaut H, Tassinari CA, Bureau-Paillas M. Etude polygraphique et clinique des "effondrements atoniques epileptiques." *Rev Neurol.* 1966;36:5–21, with permission.

Electroencephalographic Findings

Interictal EEG findings are not specific and consist of bursts of slow spike-and-wave activity or polyspike-and-wave (PSW) complexes.

The ictal EEG of atonic seizures discloses a generalized PSW discharge, with loss of tone usually being associated with the slow wave component of the spike-and-wave complexes (Figs. 2A, 3, and 4). Other ictal patterns include low- or high-voltage fast activity, flattening, or a burst of polyspikes followed by generalized spike-and-wave activity. Polygraphic recording may reveal additional subtle clinical signs, such as bradycardia or brief arrest of respiration.

Generalized Myoclonic–Atonic Seizures

Clinical Features

Myoclonic–atonic seizures represent the main seizure type in myoclonic–astatic epilepsy of early childhood of

Doose,[16,18,21] and are probably more frequent than previously believed (see Chapter 232). These seizures have been documented in nine of 45 patients studied by Egli et al.,[23] in three of 15 children reported by Ikeno et al.,[37] and in four of 21 patients described by Yaqub.[90] They have also been reported in detail by Gastaut and Broughton[27] and Dravet et al.[20]

Surprisingly, in a video polygraphic study performed in myoclonic–astatic epilepsy of early childhood, Oguni et al.[62] recorded 36 drop seizures in five children, and found that most patients had pure atonic attacks without a myoclonic component. However, in these patients, the clinical impression was noted of minimal myoclonic contraction of facial muscles or extremities preceding the falls. More recently, the same authors reported a larger group of 30 children with myoclonic–astatic epilepsy studied by means of video-polygraphy and found myoclonic seizures in 16 cases, atonic seizures with or without preceding minor myoclonus in 11 cases, and myoclonic–atonic seizures in three.[63]

From the clinical point of view, myoclonic–atonic seizures are characterized by a sudden fall preceded by some degree of jerky movement (of the face, trunk, or arms).

Electroencephalographic Findings

Interictal EEG findings are not specific and show generalized slow spike-and-wave complexes.

The ictal EEG shows generalized slow spike-and-wave or PSW discharges (at 2–3 Hz), with the spike usually being associated with myoclonia and the slow wave with the ensuing atonia (Fig. 2B).

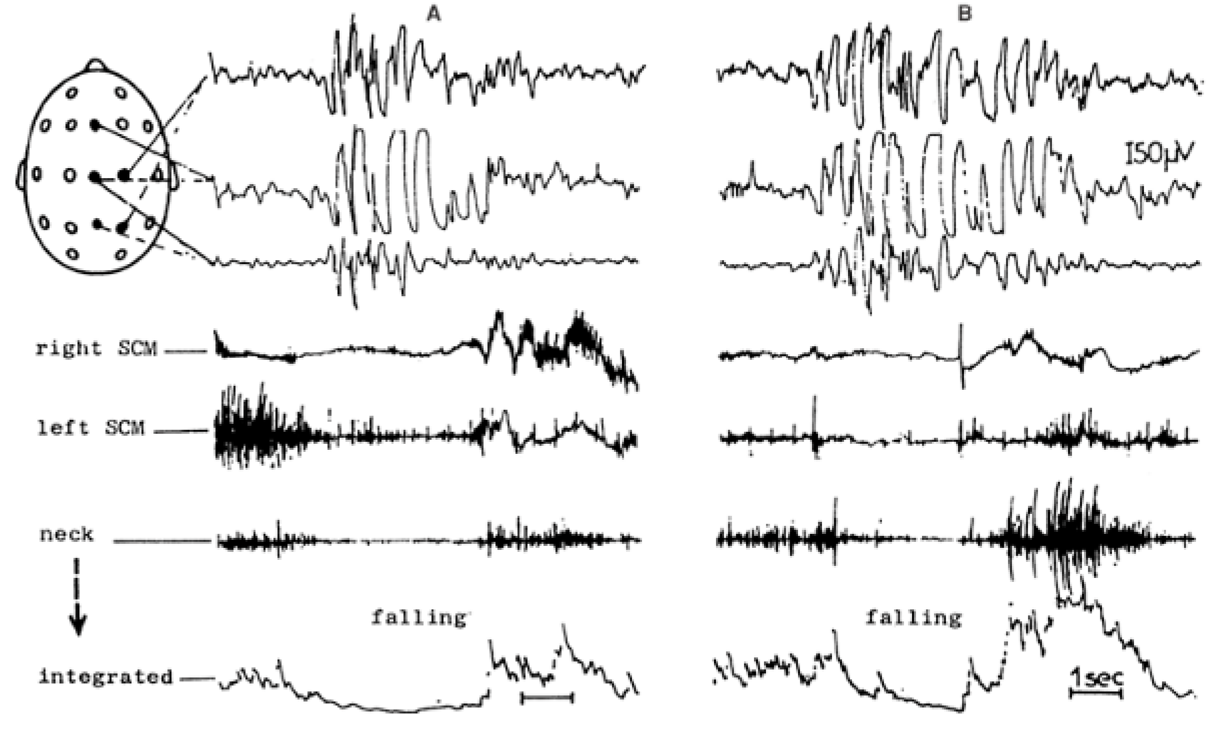

FIGURE 2. Falling seizures (atonic and myoclonic–atonic seizures). In the first drop attack (**A**), a rather irregular multiple SWD is associated with abrupt and complete loss of postural tone, which is very quickly regained at the end of the discharge; the patient returns immediately to an erect position. In the second episode (**B**), the drop is preceded by a brief myoclonic jerk, and postural tone returns before the end of the discharge. SCM, sternomastoideus muscle. From Gastaut H, Broughton R, Roger J, Tassinari CA. Generalized Non-convulsive Seizures without Local Onset. In:Vinken PJ, Bruyn GW, eds. *The Epilepsies-Handbook of Cinical Neurology, Vol 15.* Amsterdam: North-Holland Publishing; 1974:130–134, with permission.

Focal Atonic Seizures

At least three types of ictal atonic phenomena may be seen in focal seizures[76]: drop attacks, focal inhibitory seizures, and negative myoclonus.

Epileptic drop-attacks or falling seizures may occur in the context of focal epilepsies, being usually due to symmetric or asymmetric tonic stiffening caused by discharges involving the frontal lobe or SMAs.[82,88] More rarely, falling seizures of focal origin are considered to result from atonic mechanisms, and video-polygraphic demonstration is available only in few cases of the literature.[75,77] These seizures are also called drop attacks to emphasize their short duration and semiology—"like a bolt from the blue without any preceding sign."[51] Satow et al.,[75] however, provided polygraphic evidence that the epileptic falls were slow (2–5 sec in duration) in two patients with frontal and parietal lobe epilepsy exhibiting atonic seizures. Paroxysmal diminution of muscle tone mainly involved the axial muscles in both patients. Ictal EEG records showed low-voltage fast activity in the fronto-central area, followed by repetitive spikes at the midline in the patient with frontal lobe epilepsy and rhythmic spikes in the left central area in the patient with parietal lobe epilepsy. Interictal FDG-positron emission tomography (PET) disclosed hypometabolic regions consistent with the clinical and EEG findings.

Landolt[45] and Caffi[7] coined the term *temporal lobe syncope* to define individuals who have psychomotor seizures and drop attacks. This term, however, is unsatisfactory in that patients may not necessarily have a temporal lobe origin for their seizures, nor have they obviously fainted. Delgado Escueta et al.[14,15] considered drop attacks of this type to be an ictal behavioral manifestation of so-called type III complex partial seizures and suggested that these may be the product of bitemporal or extratemporal foci. Clinically, they are characterized by a rapid and abrupt fall, without preceding or accompanying sign, and followed by a complete recovery within a few seconds or minutes.[38,69] Gambardella et al.[26] reported the stereo-EEG recording of a drop attack in a patient with temporal lobe epilepsy, showing initial involvement of the left amygdaloid and hippocampal regions, with rapid spread to the right hippocampal and both orbitofrontal regions. Unfortunately, the EMG recording was not available.

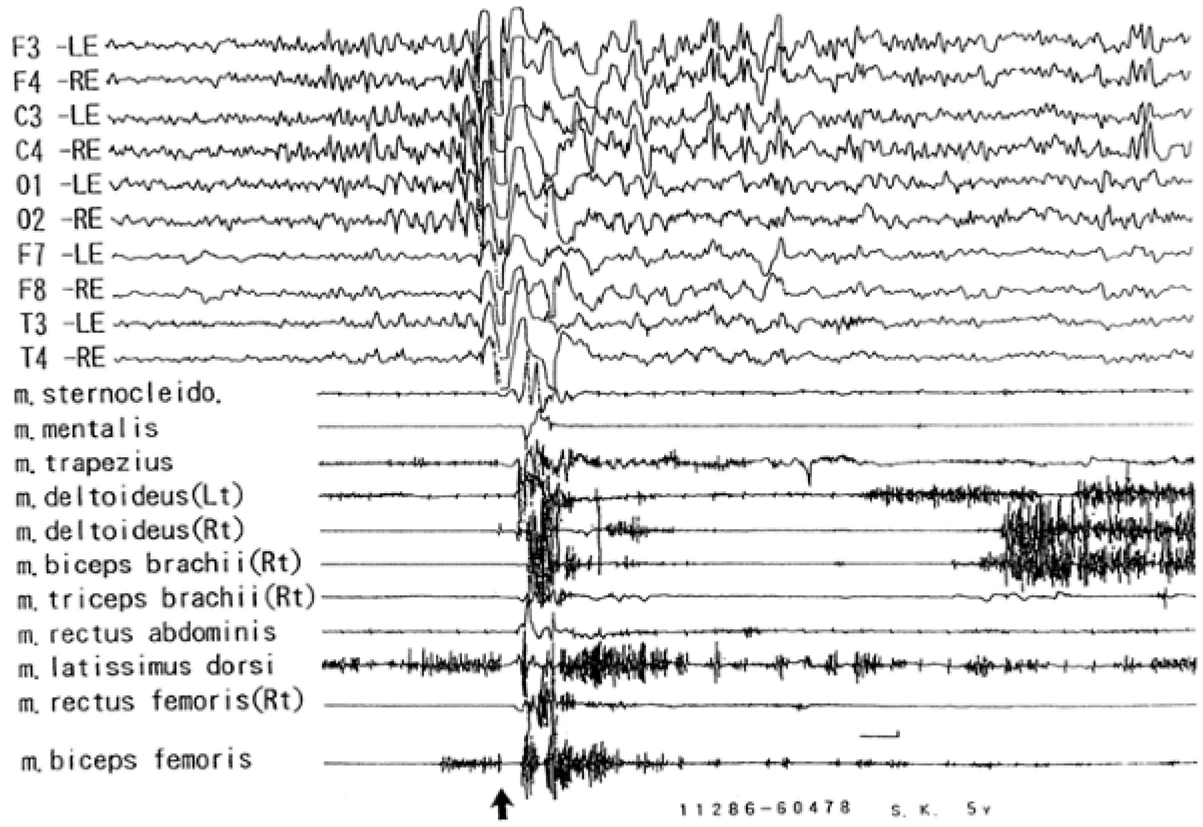

FIGURE 3. Atonic epileptic fall (epilepsy with myoclonic-astatic seizures). This 5-year-old child, who was the younger brother of monozygotic twins, had a history of febrile and afebrile convulsions. Since the age of 4

years, myoclonic seizures, drop attacks, and atypical absences appeared. He had mental retardation, and brain computed tomographic (CT) scan showed mild cortical atrophy. His co-twin was normal. Interictal EEGs demonstrated diffuse bilateral spike-and-wave, polyspike-and-wave, and monorhythmic θ activity over parieto-occipital areas. The figure shows the ictal polygraphic EEG recording of an atonic seizure: The disappearance of the myographic potentials (*arrow*) coincides with the wave component of the generalized SWD. (H. Shigematsu and M. Seino, personal observation.)

More recently, particular attention is being paid to apparently "atonic" seizures occurring in focal epilepsies in which the falls are the result of true syncopes caused by asystole triggered by the epileptic discharge.[73]

Focal inhibitory seizures are partial seizures with ictal paresis or paralysis of one or more parts of the body, which must be distinguished from the more common postictal Todd paralysis. Several reports in the literature, using V-EEG documentation of these seizures, are available.[39,46,57,87] Clinically, the ictal paralysis (usually hemiparesis) may be preceded or accompanied by a somatosensory aura affecting the same side of the body that subsequently develops focal atonia. Focal atonic seizures may have a long duration (>30 min) and therefore may present as status epilepticus (SE).[6] Ictal EEG was recorded in 30 patients and showed spike-and-wave or slow-wave discharges (53%) or rhythmic ictal activity (47%) in frontal or centroparietal areas (63%), the temporal lobe (20%), or distributed over a wide scalp region (17%) contralateral to the paralyzed limb.[35] In the only two patients with ictal electrocorticogram did the seizure discharges involve the mesial frontal or the primary sensorimotor cortices.[55,61] Isolated focal atonic seizures, particularly when of new onset, cannot be reliably distinguished from focal cerebral ischemia without EEG proof that an accompanying ictal discharge is present.

Negative myoclonus is an interruption of tonic muscular activity for <500 msec without evidence of antecedent myoclonia[5,24,84] (Fig. 5). Clinically, the negative myoclonus may be unilateral or bilateral, and it is manifest by brief lapses in tone that interfere with motor coordination.[9,33,81] At times, it may be a very mild or almost undetected motor event, giving rise to an "instability"; more often, it causes dropping of objects from the hands, head nodding, or falls.[81,84] Negative myoclonus can occur in a variety of extremely different epileptic conditions, including idiopathic and symptomatic entities.[9,66,83,84] From a neurophysiologic viewpoint, the negative myoclonus consists of an EMG silent period of 50 to 400 msec duration, time-locked to an EEG sharp wave or spike in the contralateral centroparietal cortex that precedes the EMG silent period by 15 to 50 msec for the upper limbs.[84,85]

Diagnostic considerations

Because many seizure types and different mechanisms may be responsible for epileptic falling seizures, video-polygraphic monitoring is mandatory to achieve a correct diagnosis. Indeed, what may resemble an atonic fit on clinical observation may turn out to be a myoclonic–atonic seizure or a tonic spasm on polygraphic examination. By disclosing the basic mechanism of the fall, video-polygraphic monitoring is crucial for a correct semiology of falling seizures and is likely to improve and clarify the terminology and classification in this field of epileptology.[58,82]

Ancillary diagnostic tools may be considered for specific purposes. Magnetic resonance imaging (MRI) is needed in drop attacks of focal origin or in generalized atonic seizures to disclose specific etiologies, such as cortical malformations.[34] Stereo-EEG recording and ictal single positron emission computed tomography (SPECT) may be required in partial atonic seizures of symptomatic or probably symptomatic etiology when a surgical therapy is postulated.

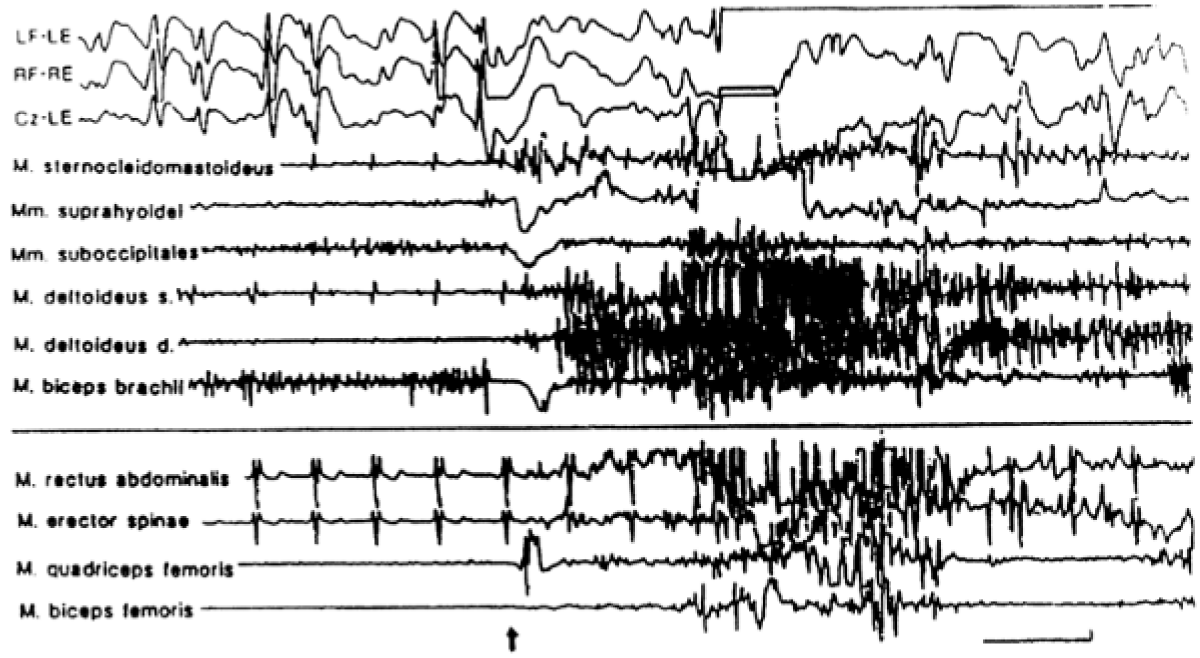

FIGURE 4. Atonic epileptic fall (Lennox-Gastaut syndrome). This 7-year-old boy with a family history of febrile convulsions had suffered from head nods since the age of 1 year. Tonic seizures, drop attacks, and atypical absences appeared at 5 years, 3 months. He had severe mental and motor retardation. Interictal EEGs showed diffuse spike-and-wave and polyspike-and-wave activity. The figure shows the ictal polygraphic EEG recording of an atonic seizure: Immediately before the appearance of the initial sign of the fall (*arrow*), bilateral double spikes were recorded in the frontal regions. EMG tracings support the presence of a very brief atonia, most clearly shown in the biceps muscle. From Ikeno T, Shigematsu H, Miyakashi M, et al. An analytic study of epileptic falls. *Epilepsia.* 1985;26:612–621, with permission.

Differential Diagnosis

Aside from pure atonic or myoclonic–atonic seizures, epileptic drops and falls may be caused by myoclonic seizures and, more frequently, tonic seizures (including axial spasms).

Myoclonic seizures causing sudden falls have been exceptionally documented by polygraphic studies. Dravet et al.[20] reported one such case in which head drops or true violent falls to the ground were associated with polygraphically proven axial myoclonic jerks. Oguni et al.[62] also described myoclonic drop attacks in one child with myoclonic–astatic epilepsy who had a propulsive flexion of the body at the waist and a forward thrust of the upper body due to myoclonic seizures or spasms. More recently, the same authors identified myoclonic seizures in 16 out of 30 patients with myoclonic–astatic epilepsy and found that six of them had a history of drop attacks.[63] Similarly Yaqub[90] described myoclonic seizures without loss of tone involving limbs, trunk, or neck and causing sudden falls.

From the EEG viewpoint, the jerks were associated with generalized SWDs at 3- to 3.5-Hz in these cases.

Tonic seizures represent the most common cause of sudden fall to the ground in children with Lennox-Gastaut syndrome.[20,23,37,78] From the clinical viewpoint, tonic seizures may be axial, axorhizomelic, or global. They are characterized by sudden flexion of the neck and body, rising of the arms in a semiflexed position, extension of the legs, contraction of facial muscles, rolling of the eyes, apnea, tachy- or bradycardia, dilated pupils, enuresis, and facial flushing. Tonic seizures may be either symmetric or asymmetric and diurnal or nocturnal.[78]

Two types of tonic seizures associated with falls ("tonic drop seizures") have been described, namely *short* tonic seizures and *prolonged* tonic seizures.

Short tonic seizures, or axial spasms, resemble those of infantile spasms and are characterized by an abrupt and widespread increase of tone, maximal in the neck and shoulder girdle. The ictal EEG shows either generalized slow waves or no changes, or occasionally a slight attenuation.[23,37]

Prolonged tonic seizures are characterized by an overt and sustained increase of tone over the axial and segmental muscles, over both agonist and antagonist muscles. The ictal EEG expression is either a run of low-voltage, fast activity, or a brief burst of generalized spike-and-wave or PSW activity.[20,78]

Tonic posturing and stiffening is also responsible for the vast majority of epileptic falls occurring in localization-related epilepsies.

Video-polygraphic monitoring may be needed also to exclude drop attacks of nonepileptic origin. Meissner et al.[56] analyzed the diagnosis in 108 consecutive patients with a history of drop attacks and found the following etiologies: unknown (64%), cardiac (12%), cerebrovascular insufficiency (8%), combined cardiac and cerebrovascular disease (7%), seizures (5%), vestibular (3%), and psychogenic (1%). Other conditions to be included in the differential diagnosis include cataplexy, syncopes, and breath-holding spells.

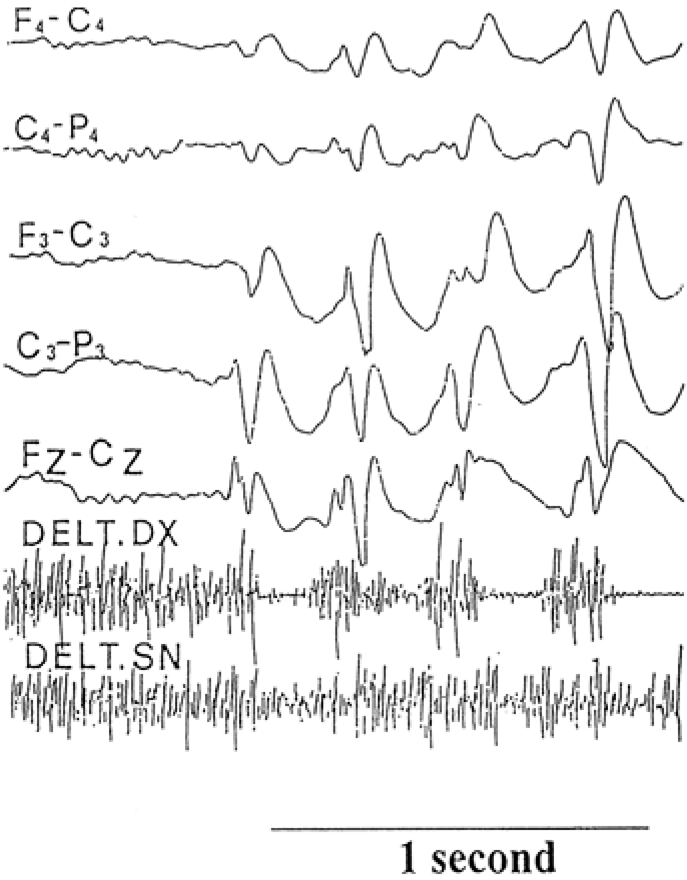

FIGURE 5. Negative myoclonus. An EEG polygraphic recording of a 4-year-old child suffering from benign partial epilepsy with centrotemporal spikes. The patient was holding arms outstretched. The appearance of triphasic spikes (*left central region*) is accompanied by a sudden interruption of the EMG activity on the right deltoid (*Delt. Dx*). Note that when the spikes become more diffuse and also involve the right central regions, brief decrements of EMG amplitude are also seen on the left deltoid (*Delt. Sn.*). From Tassinari CA, Rubboli G, Parmeggiani L, et al. Epileptic Negative Myoclonus. In: Fahn S, Hallett M, Lüders H, Marsden CD, eds. *Advances in Neurology*, Vol. 67. *Negative Motor Phenomena*. Philadelphia: Lippincott-Raven,1995;181–197, with permission.

Specific syndromes incorporating atonic and myoclonic–atonic seizures as an integral feature

Epileptic falls and head nodding of pure atonic or myoclonic–atonic origin have been mainly described in myoclonic–astatic epilepsy (also known as Doose syndrome; see Chapter 232) and Lennox-Gastaut syndrome (Chapter 241).[18,62,63] Myoclonic, atonic, and myoclonic–atonic attacks are usually responsible for falling in Doose syndrome, whereas tonic seizures or axial spasms are more frequently involved in the Lennox-Gastaut syndrome. At variance with what was defined in the present international classification,[12] myoclonic–astatic epilepsy is considered an idiopathic generalized epilepsy in the proposed diagnostic scheme,[24] because it includes only children with myoclonic–atonic seizures who are otherwise normal with no discernible causes other than a strong genetic background. Myoclonic–atonic seizures may be also observed, however, in epileptic encephalopathies of infancy such as Dravet syndrome,[19] Lennox-Gastaut syndrome,[2] and atypical benign epilepsy of childhood.[1]

In epilepsy with electrical SE during slow sleep, atypical absences with atonic components, epileptic falls, and negative myoclonus have been described in subgroups of patients,[13,79] formerly reported under the heading of atypical benign epilepsy of childhood.[1]

In severe myoclonic epilepsy of infants or Dravet syndrome, seizures begin during the first year of life in the form of generalized or unilateral febrile clonic seizures, with the secondary appearance of myoclonic jerks and often partial seizures; in these patients, falling seizures result from either vide supra, myoclonic jerks or partial seizures with atonic pheno- mena (see Chapter 230).[19]

“Epileptic drop-attacks” are also described in focal epilepsies, particularly of frontotemporal origin and with marked bilateral synchrony.[31,69,88] In these cases, however, the falls are usually associated with tonic stiffening, and polygraphic documentation is scanty. Satow et al.[75] reported pure atonic seizures in two patients with localization-related epilepsy (of frontal and parietal origin) studied by means of prolonged V-EEG monitoring. Epileptic “drop-attacks” have been found to be a very frequent seizure type in localization-related epilepsies caused by focal neuronal migration disorders, especially when they involve the central cortical regions[34,43,68] or in the context of the epileptic syndrome linked to hypothalamic hamartomas.[4]

Whatever the origin and mechanisms of falling seizures in localization-related epilepsy, their occurrence often represents an ominous sign because they are frequent, resistant to therapy, physically dangerous, and portend personality changes.

Response to treatment

Medical Treatment

The medical treatment of atonic and myoclonic–atonic seizures remains empirical. Valproic acid associated with lamotrigine and a benzodiazepine is usually considered the treatment of choice, either in generalized or focal epilepsies exhibiting epileptic drop attacks.[22,86] Ethosuximide, alone or in combination with the above drugs, has also been demonstrated to improve atonic seizures and negative myoclonus.[8,67] Some of the new antiepileptics, particularly lamotrigine, felbamate, and topiramate have shown some promise for the treatment of the Lennox-Gastaut syndrome, with atypical absences and “astatic” seizures being particularly improved.[25,59,74] However, these results await confirmation in large multicenter studies.

Some compounds, on the other hand, should be given with extreme caution because they may contribute to worsen atonic, myoclonic–atonic, and negative myoclonus, particularly in generalized syndromes of infancy. These dangerous drugs include carbamazepine, oxcarbazepine, phenytoin, vigabatrin, and phenobarbital.[71] Instances of tonic SE precipitated by intravenous administration of benzodiazepines have been documented in children with Lennox-Gastaut syndrome.[80]

Surgical Treatment

Callosotomy is widely considered the surgical treatment of choice in patients with falling seizures who are not candidates for classical resective surgery.

From the review of the literature, it appears that patients with tonic or atonic falls had a reduction of about 80% in seizure frequency after callosotomy, although in most cases complete or permanent control of other seizure patterns did not occur.[3] The aim of callosotomy is to limit the spread of convulsive discharges from one hemisphere to the other, and therefore, patients with mainly lateralized foci with secondary generalization should benefit most. Indeed, in the Montreal experience,[65] patients with lateralized EEG abnormalities tended to have a better result than did those without lateralization, but patients with synchronous and symmetric SWDs also benefited. Partial seizures, often inconspicuous before surgery, may emerge after callosotomy in some patients.

Summary and conclusions

Atonic and myoclonic atonic seizures are specific seizure types whose identification rests on an accurate video-polygraphic analysis of the ictal events. Atonic seizures are characterized by sudden and pure loss of tone, whereas myoclonic–atonic seizures show an initial myoclonic potential, sometimes in sequence, followed by muscle silence. Both seizure types are accompanied by generalized/diffuse spike-and-wave and PSW complexes, with the slow-wave component usually being associated with atonia in atonic seizures and the spike with myoclonia in myoclonic–atonic seizures. Both seizure types are a common cause of epileptic falls or drops in childhood epileptic encephalopathies, such as Lennox-Gastaut syndrome, Dravet syndrome, and atypical idiopathic localization-related epilepsy of childhood,[2] as well as in idiopathic generalized syndromes—namely, myoclonic-astatic epilepsy of Doose. Moreover, these seizures must be distinguished from tonic and myoclonic seizures, which also account for falling in epileptic encephalopathies of childhood. Tonic seizures of very brief duration (axial spasms) are responsible for most epileptic falls in Lennox-Gastaut syndrome, whereas

myoclonic–atonic seizures are more frequently encountered in Doose syndrome. Atonic seizures may also have (vide supra) a focal origin, and may be classified into three main focal seizure types:

- Epileptic drop attacks, usually in the context of frontal or frontotemporal or parietal epilepsies, sometimes with outstanding secondary bilateral synchrony on the EEG.
- Focal inhibitory seizures, with ictal paresis or paralysis of one or more parts of the body, sometimes accompanied by a somatosensory aura. These seizures may have a long duration and are associated by a discharge usually involving the centroparietal areas.
- Negative myoclonus, defined by an interruption of tonic muscular activity for <500 msec without evidence of antecedent myoclonia, causing unilateral or bilateral drops, head nodding, falls, or brief lapses in tone that interfere with motor coordination.

The pathophysiology of atonic seizures or the atonic components of seizures is largely unknown, but subcortical and cortical mechanisms have been proposed to explain the ictal loss of tone. Medical treatment is often unsatisfactory, but some of the newer antiepileptic drugs such as lamotrigine, felbamate, and topiramate have shown encouraging results. Callosotomy may be helpful in selected cases of falling seizures of tonic or atonic origin, with the best results being obtained in patients with lateralized EEG discharges.

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Chapter 52

Generalized Tonic Seizures

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Introduction

Generalized tonic seizures are convulsive events in which the tonic component is predominant and not followed by clonic jerks. Actually, the majority of convulsive generalized seizures have both tonic and clonic components, especially in generalized epilepsies. Also, in partial epilepsy a secondary generalized seizure usually manifests a clonic phase.[53] On the basis of experimental animal models of epilepsy, there is evidence that different circuits are responsible for tonic and clonic seizures and indicate that the anatomic substrate for tonic seizures could be in the brainstem.[58] Possibly due to their intrinsic pathophysiology, which heavily involves the brainstem, tonic seizures are a common manifestation in pediatric age and especially in symptomatic/lesional epilepsies, in which a forebrain/brainstem dysfunction could be more easily hypothesized. In the neonatal period tonic seizures are recorded in early infantile epileptic encephalopathy (EIEE), in early myoclonic encephalopathy (EME) (see Chapters 224 and 225), and in severe symptomatic neonatal seizures, especially those due to hypoxic-ischemic perinatal injury, which account for 50% of such seizures.[2] During infancy, tonic seizures are observed in refractory infantile spasms, especially after the first year of life and are sometimes associated with epileptic spasms (tonic-spasm epileptic seizure).[14] Tonic seizures are the main seizure type in symptomatic generalized epilepsy associated with an inverted duplication of chromosome 15[49] and in Lennox-Gastaut syndrome.[3] Among the partial epilepsies, tonic events are the main type of seizures recorded in startle-induced epilepsy, in which the tonic seizure is often generalized, despite the focality of the underlying lesion. Although rare, there are also reports of tonic seizures belonging to idiopathic generalized epilepsies[32] and in this case they follow the same course as generalized tonic–clonic seizures.

Definitions

Tonic seizures are classified among the generalized seizures and described as follows: “a rigid, violent muscular contraction, fixing the limbs in some strained position, with usually deviation of the eyes and of the head toward one side.” Thus, we consider a seizure as purely tonic when the hypertonia, mainly involving the axial muscles, is not followed by clonic jerks. This is independent of the symmetry or the extention nature of the contraction.

The glossary of descriptive terminology for ictal semeiology describes, among the generalized events, the tonic seizure as “a sustained increase in muscle contraction lasting a few seconds to minutes.”[10]

On the basis of a single case, Jackson and Barnes[28] and Jackson and Singer[29] accurately described tonic seizures as “the axial type,” which were considered immature grand mal seizures. Lennox[35] described tonic seizures as convulsive variants, involving brief muscle rigidity without subsequent clonus. Detailed clinicoelectroencephalographic studies of tonic seizures were later conducted by Ouachi et al.[43] and Gastaut et al.,[22] mainly on the tonic seizures of Lennox-Gastaut syndrome. A clear distinction between tonic and tonic–clonic seizures was made. Following these studies, tonic seizures were classified as a separate type of generalized epileptic attack.[7,18] However, the tonic seizure may also be a clinical manifestation of localization-related epilepsies, especially of those originating from frontal lobe areas.[11]

From a clinical point of view, and especially where only historical information is available, it is not always easy to distinguish clearly between pure tonic and tonic–clonic seizures. Unfortunately, the distinction between the two types of seizure are not always clear in the literature as well.

Epidemiology

Epidemiologic data about tonic seizures are difficult to identify outside the context of the epileptic syndrome in which they occur. However, in recent years more attention has been given to the epidemiology of each epileptic syndrome, and some data about the prevalence of Lennox-Gastaut syndrome, refractory infantile spasms, EIEE, and focal epilepsies are now available.[32,34,54] In the population-based study conducted using a multiple-source surveillance system for epilepsy and developmental disability by Trevathan et al.,[54] the prevalence among Atlanta children of Lennox-Gastaut syndrome was 4% of all children with epilepsy. In the study reported by Kramer et al.,[32] the relative frequency and age of onset of the different seizure types were analyzed in a 20-year cohort of a pediatric neurology outpatient clinic in Tel Aviv. Lennox-Gastaut syndrome accounted for 1.5%, EIEE for 0.2%, and generalized tonic seizures not otherwise specified for 6.6%. In a subsequent study by Kwong et al.[34] performed in a cohort of 309 Chinese children, Lennox-Gastaut syndrome prevalence was 3%, but the prevalence of tonic seizures was not specified separately.

Previously, data regarding only Lennox-Gastaut syndrome showed that tonic seizures, as reported in papers by Gastaut et al.[20] and other authors,[6,39] were experienced in 55% to 60% of cases. Gastaut et al.[23] reported that such a percentage probably underestimates the real incidence of tonic seizures in Lennox-Gastaut syndrome, as the incidence of tonic seizures rises to 92% at the Centre Saint-Paul, a specialized institution in which the patients are under constant observation and are usually recorded during sleep.

More difficult to estimate is the prevalence of reflex tonic seizures in startle-induced epilepsy. The papers on tonic reflex seizures come mainly from laboratories specializing in the surgical treatment of medically resistant lesional startle-induced epilepsies, which, therefore, have limited epidemiologic value. Kramer et al.[32] reported that startle-induced epilepsy in their cohort accounted for 0.2% of cases.

Anatomic Pathways and Pathophysiology

There is relative agreement on the brainstem involvement or origin of tonic seizures, both in Lennox-Gastaut syndrome and in EIEE or EME, whereas a cortical circuit is presumed to be involved in tonic seizures of startle-induced epilepsy. In animal models, the tonic extensor convulsion is the characteristic motor pattern of seizures evoked by maximal electroshock and high doses of chemoconvulsants.[16] As demonstrated by Tanaka and Mishima[50] and later by Browning and Nelson,[5] in animal models a tonic convulsion requires the integrity of the brainstem but not the forebrain. However, the anatomic substrates within the brainstem responsible for generating tonic seizures have not fully been characterized. The reticular formation of the lower midbrain and pons are surely involved, as stimulation of these regions triggers tonic convulsions, and a lesion can attenuate them.[17] As a result of these experiments and the similarity between clinical tonic seizures and those induced in animals, a role for the brainstem in the initiation of convulsive seizures has long been suspected. However, as pointed out by Velasco and Velasco,[56] the literature on the role of the brainstem in the initiation and propagation of seizure activity is very contradictory. Velasco et al.[57] recorded ictal discharges of various types of generalized seizures within the centromedian thalamic nucleus (CM) and the cerebral cortex in children with intractable generalized seizures related to Lennox-Gastaut syndrome. Ictal CM discharges were consistently correlated with widespread surface cortical electroencephalographic (EEG) activities and symptoms in all patients and all types of generalized seizures. Fast spike discharges in the CM correlated with onset of tonic and tonic–clonic generalized seizures. Ictal EEG activity occurred simultaneously in the right and left CM and the surface at the onset of all seizure types of a generalized nature, with the exception of myoclonic seizure. Velasco et al.[57] maintain that simultaneous thalamic and cortical activation depends on epileptic discharges arising from cerebral structures outside the thalamocortical system. They postulate that the presence of abnormalities in the brainstem close to the red nucleus noted in MRI scans of all children with Lennox-Gastaut syndrome imply that epileptic discharges may arise from the brainstem.[55] The fact that tonic seizures occur more frequently during slow-wave sleep than during rapid eye movement (REM) sleep, modify sleep organization,[27,45,62] and raise the level of vigilance[36] also support the hypothesis that tonic seizures originate in the brainstem. Recently Veliskova et al.[58] provided evidence from animal studies that the anatomic substrate for tonic seizure could be in the brainstem, suggesting that different circuits are responsible for tonic and clonic seizures. In a previous animal study, excitation of the brainstem reticular formation produced convulsive seizures in decerebrated rats and cats, demonstrating that reticular neuronal circuits are independent of cortical networks in seizure generation.[33] Rodin et al.[47] used Metrazol and Megimide to produce seizures. He hypothesized that different functional states of the animal were a significant variable in the distribution of seizure activity. In paralyzed and unanesthetized animals, epileptic discharges were evident in the thalamus and cortex, whereas they were mainly in the brainstem reticular formation in freely moving animal.

A cortical origin for tonic reflex seizures seems to be likely, based on neuroimaging and neurophysiologic studies performed in surgery centers. Such data support involvement of the supplementary motor area in generation of this seizure type.[38,40] Gates et al.[25,26] and Courtney et al.[8] described the effectiveness of corpus callosotomy in patients with refractory tonic seizures. Disappearance of reflex tonic seizures after callosal section (which prevents the spread from one unilateral focus to the contralateral homotopic motor center) is not completely unexpected. More difficult to explain is how seizures believed to originate from brainstem structures are improved by a callosal section. Though there is both, speculation[26] and controversy[24] concerning the efficacy of corpus callosotomy in controlling generalized tonic seizures, clinical and experimental evidence currently available indicates that seizure activity can spread and generalize in humans and experimental animals via both the corpus callosum and the reticular formation.[12]

Clinical Manifestations

In newborns with EIEE or EME, tonic seizures are a predominant feature. In EIEE the prevailing initial seizure type is tonic seizures, whereas in EME tonic seizures develop in the course of the disease. Interestingly, Djukic et al.[9] pointed out that the two conditions represent a continuum of progressive pathology and dysfunction and that the presence versus absence of tonic seizures indicates the severity of the brainstem pathology or dysfunction at the time the syndrome presents. If the EEG shows a burst-suppression pattern, tonic seizures usually correlates with the burst (Fig. 1). In such cases prognosis remains poor. Clinically tonic seizures involve axial and limb muscles are of brief duration, and may present with abrupt onset resembling an epileptic spasm or epileptic myoclonus. However contractions persist and last longer than either spasms or myoclonus. Focal signs consisting of asymmetric contraction or unilateral head or eye deviation may be present, depending on the presence of an underlying structural lesion.

Although spasms and tonic seizures are two clearly distinct types of epileptic events, they may appear closely associated in the so-called tonic-spasm seizure, a particular form of generalized tonic seizure (Fig. 2). The beginning of this type of seizure is marked by a real “spasm,” with flexor contraction of trunk and limbs lasting about 1 second. Immediately afterward, there is a tonic contraction lasting a few seconds that makes the patient maintain the position assumed during the spasm. This type of seizure has two characteristics in common with spasms: They appear in series that can last several minutes, and a tendency to occur mostly upon awakening. Tonic-spasms seizures are mainly observed in children with drug-resistant infantile spasms of unknown cause, who then develop an epileptic encephalopathy with cognitive impairment and multifocal EEG abnormalities.

In Lennox-Gastaut syndrome, tonic seizures manifest mainly during phases 1 or 2 of non-REM sleep. At times they are associated with minimal clinical signs, such as opening the eyes and apnea, and at times with a more violent behavior with sustained diffuse contractions, usually of brief duration. The seizures tend to persist until the sleep phase changes into slow-wave sleep. They present again in the same phase of each cycle over the course of the night. The characteristics of tonic seizures are the following: Rapid, mostly flexor contraction of muscles extending from the body axis to the upper or lower extremities; when awake the patient, may fall if standing and lose consciousness. If muscle tone is tested during the seizures, it is impossible to move the body parts involved. Tonic contractions may be symmetric or asymmetric. Seizure duration varies from several seconds to a minute (most last for 5 to 20 seconds). Seizure frequency varies from patient to patient, ranging from once a month to several dozen times a day. Occasionally, seizures are so frequent that status epilepticus occurs. Regarding the topography of the contractions, Gastaut et al.[19,23] divided tonic seizures into three types: Tonic “axial” seizures, tonic “axorhizomelic” seizures, and tonic “global” seizures. Tonic “axial” seizures are characterized by tonic contraction of the neck muscles, causing either fixation of the head in an erect position or slight displacement of the head, depending on the relative predominance of flexor or extensor muscle groups. Contraction of the superior

facial muscles and the frontal muscles causes the elevation of the eyebrows and eyelids (Fig. 3). Respiration often accelerates or ceases (apnea). Tonic “axorhizomelic” seizures begin like tonic axial seizures but are accompanied by involvement of the proximal musculature of the upper limbs. Thus, contraction of the trapezius and deltoid muscles follows contraction of the neck muscles, resulting in elevation of the shoulder (Fig. 4). During tonic “global” seizures, the contraction spreads from axial muscles axis to all muscles of the upper and lower limbs (Fig. 5). The upper limbs are in abducted and semiflexed; the lower limbs are flexed or, more infrequently, in extension, also with trunk extension. The different contraction patterns of muscles of the lower limbs and trunk can cause the patient to fall forward or backward. Contraction of the respiratory muscles causes apnea.

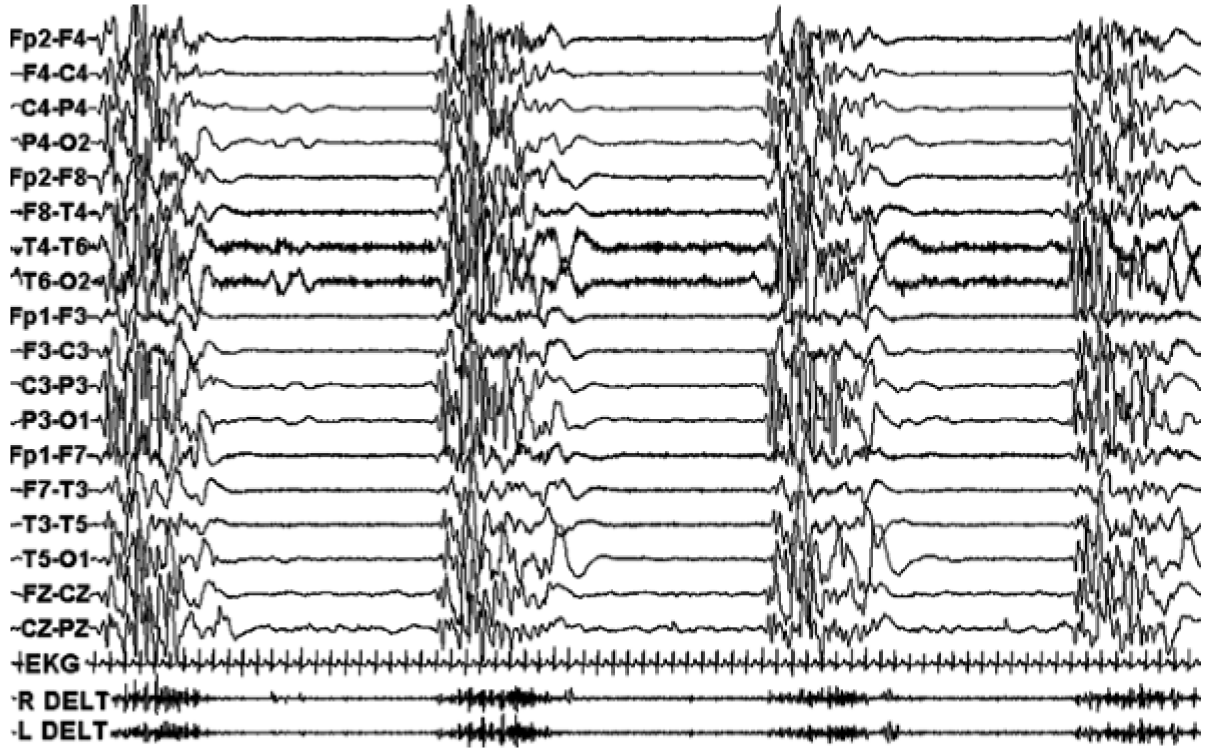

FIGURE 1. Burst-suppression pattern in a 1-month-old boy: The burst is strictly correlated with the appearance of brief tonic seizures recorded over both the deltoids.

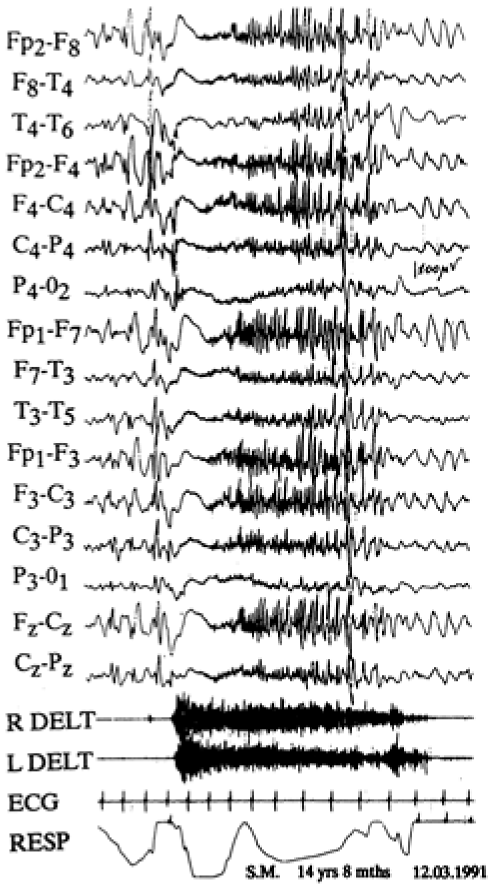
Fp_2-F_8
F_8-T_4
T_4-T_6
Fp_2-F_4
F_4-C_4
C_4-P_4
P_4-0_2
Fp_1-F_7
F_7-T_3
T_3-T_5
Fp_1-F_3
F_3-C_3
C_3-P_3
P_3-0_1
F_z-C_z
C_z-P_z
R DELT
L DELT
ECG
RESP
S.M. 14 yrs 8 mths 12.03.1991

FIGURE 2. Tonic-spasm seizures in a 14-year-old boy who began having infantile spasms resistant to treatment in the first year of life. The spasms progressively transformed into tonic-spasm seizures. The ictal electroencephalogram is characterized by a diffuse high-amplitude slow wave, followed by a fast rhythm of increasing amplitude. Recording from the deltoid muscles shows first a contraction similar to a spasm, then a prolonged tonic contraction.

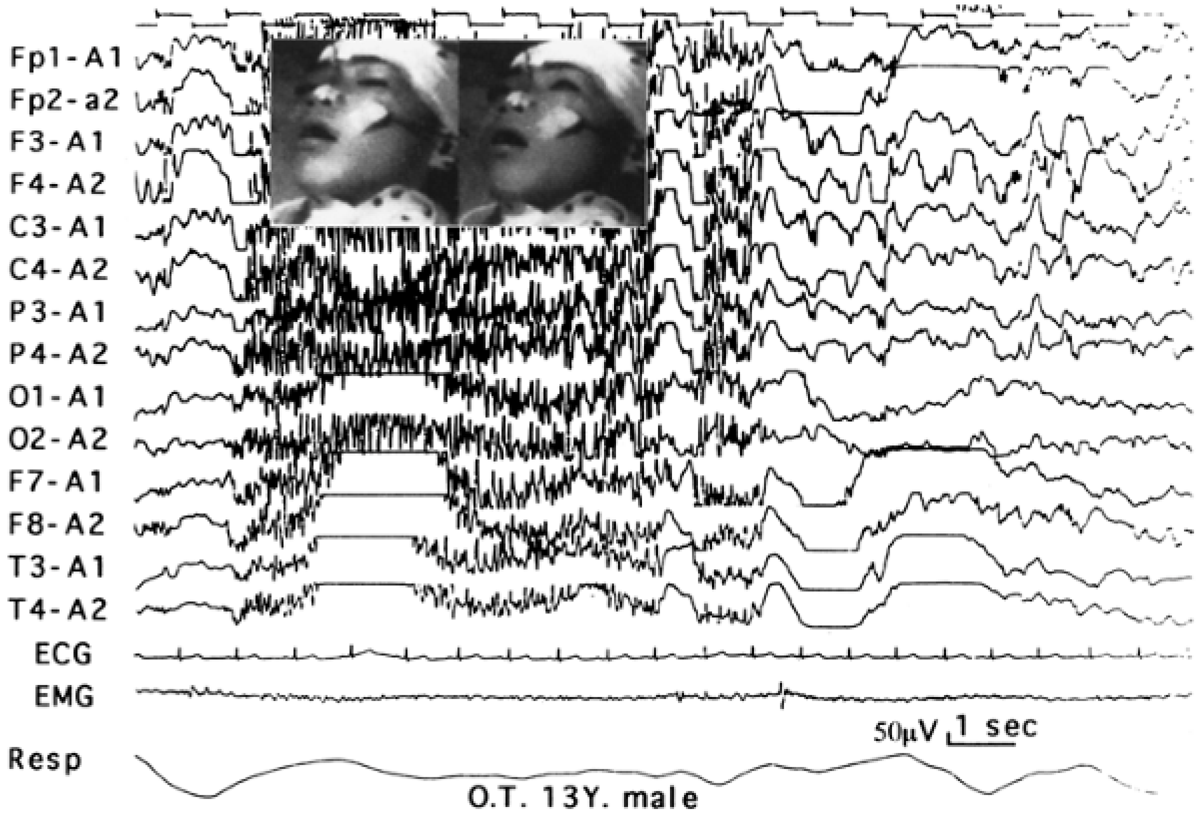
Fp1-A1
Fp2-a2
F3-A1
F4-A2
C3-A1
C4-A2
P3-A1
P4-A2
O1-A1
O2-A2
F7-A1
F8-A2
T3-A1
T4-A2
ECG
EMG
50μV 1 sec
Resp
O.T. 13Y. male

FIGURE 3. An axial tonic seizure in a 13-year-old boy with Lennox-Gastaut syndrome. The clinical manifestations are eye opening due to the elevation of both eyelids, suppression of respiration, and slight acceleration of heart rate. The electroencephalogram shows high-voltage fast discharges at about 14 Hz.

Tonic seizures are commonly accompanied by autonomic symptoms, including alteration of depth or frequency of respiration, tachycardia or bradycardia, pupillary dilation, and facial flushing. Seizure intensity varies greatly from patient to patient or from one seizure to another in the same patient. Seizures vary from rapid, massive contraction of trunk and limb muscles with apnea and cyanosis to ones limited to raising the eyebrows, mild contraction of the shoulder muscles, and minimal variation in respiratory rhythm. These latter seizures are observed especially during sleep. Postictal symptomatology is related to seizure intensity: The more violent seizures are followed by drowsiness and sleep, whereas the less intense ones may have no postictal symptom.

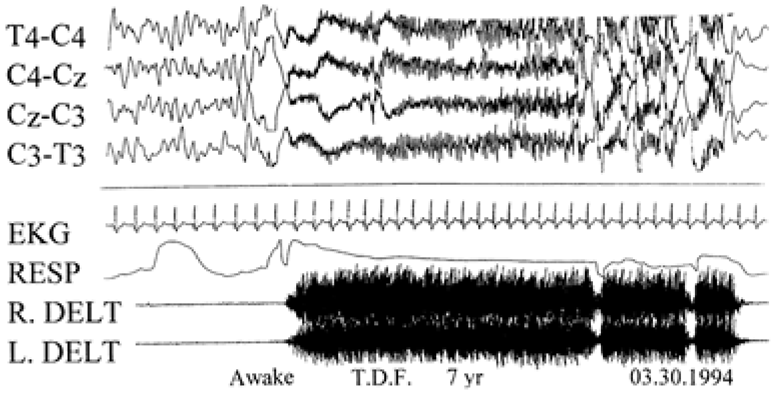
T4-C4
C4-Cz
Cz-C3
C3-T3
EKG
RESP
R. DELT
L. DELT
Awake
T.D.F.
7 yr
03.30.1994

FIGURE 4. An axorhizomelic tonic seizure while awake in a 7-year-old boy with Lennox-Gastaut

syndrome. The tonic seizure involves deltoid muscles. During the seizure, the heart rate accelerates and respiration is suppressed. The electroencephalogram shows fast discharges at about 20 Hz of increasing amplitude.

In startle-induced epilepsy, the tonic seizures are generally a kind of global seizure, but the contraction involves mostly the postural muscles, to the extent that the patient assumes particular postures. The seizure is provoked by acoustic or sometimes proprioceptive stimuli and is observed in severely motor-impaired children. At times the tonic seizures may show focal signs, such as an asymmetry in tonic contraction, depending on the unilaterality of lesion. In fact, startle-induced tonic seizures are usually observed in the context of perinatal or infantile brain damage and contralateral hemiplegia,[40] and have

been attributed to a focus arising in the frontal lobe (Fig. 6). Although startle-induced epilepsy with motor seizures could be observed even in children without motor area lesions (mostly due to the unilateral or bilateral forebrain lesion, although the extent of brainstem involvement is unclear), subdural grids studies have repetitively shown that such a seizure derives from the supplementary motor area of one hemisphere and therefore should be considered a kind of partial event.[42,48] From a clinical point of view, startle-induced tonic seizure quickly arises after the stimulus and rapidly involves the axial and limb muscles, with impairment of consciousness that is often difficult to evaluate. Whatever the underlying pathophysiology, and especially in severely mentally retarded patients, startle-induced tonic seizures represent a kind of generalized motor seizure, which is often an emergent problem, as it is drug refractory and there is frequently self-injury.

Electroencephalographic Manifestations and Clinical Correlations

The ictal EEG of tonic seizures usually consists of rhythmic spiking.[30] The frequency and amplitude of the spikes vary widely. Frequency ranges between 10 and 25 Hz, and amplitude ranges from a very low-amplitude, desynchronized rhythm to more than 100 µV (Fig. 5). An initial brief flattening may precede fast activity, especially in startle-induced tonic seizures. Moreover, Gastaut et al.[23] described an ictal EEG of diffuse slow-wave discharges at theta and delta frequencies in subjects whose background EEG activity is very slow, and only during status epilepticus of tonic seizures in Lennox-Gastaut syndrome. Polygraphic recordings[61,62] have demonstrated how in tonic seizures there is a muscle contraction of increasing intensity that within 1 to 2 seconds can reach a level that then remains constant for the rest of the seizure. The muscle contraction occurs more slowly than in myoclonus or spasms.[13]

In EIEE and in EME, tonic seizures are a counterpart of the burst of burst-suppression pattern, especially in the neonatal and infantile period. The burst-suppression pattern tends to disappear by 6 months of age and is replaced by a hypsarrhythmic pattern in about 75% of cases.[41] Tonic seizures

have been then replaced by epileptic spasms or focal seizures. Although clinically a sleep–wake cycling is observed, neurophysiologically no differentiation between the wake state and sleep is recorded. In fact, the burst-suppression pattern is unchanged. As tonic seizures are strictly associated with the burst period, they are as frequent as the burst is (Fig. 1). However, although the burst-suppression pattern continues during sleep, tonic seizure does not, suggesting a forebrain involvement in the genesis of the phenomenon.

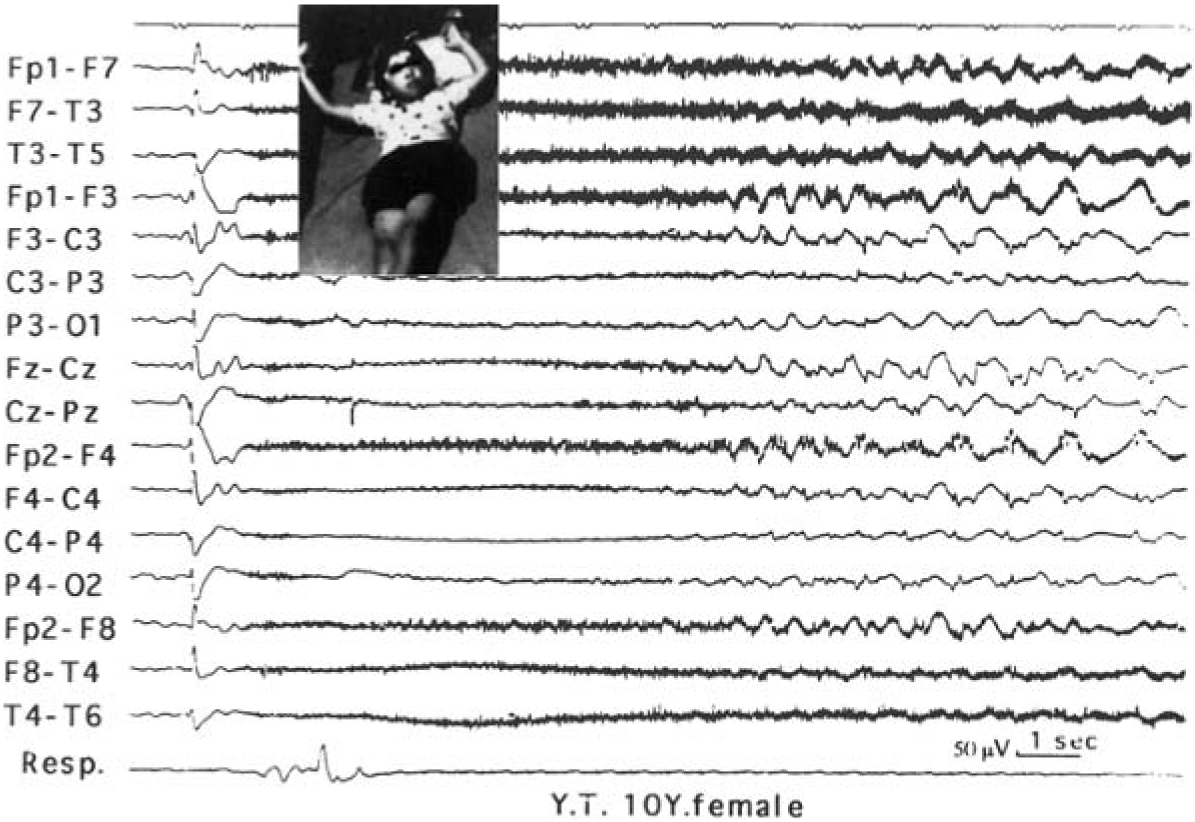
Fp1-F7
F7-T3
T3-T5
Fp1-F3
F3-C3
C3-P3
P3-O1
Fz-Cz
Cz-Pz
Fp2-F4
F4-C4
C4-P4
P4-O2
Fp2-F8
F8-T4
T4-T6
Resp.
50 μV 1 sec
Y.T. 10Y.female

FIGURE 5. A global tonic seizure in a 10-year-old girl with Lennox-Gastaut syndrome. The manifestations are abrupt elevation of both arms, followed by a tonic state in both sides of the upper and lower extremities and trunk. The electroencephalogram shows high-voltage sharp waves and flattening upon jerking both upper extremities, then low-voltage fast discharges upon entering the generalized tonic state.

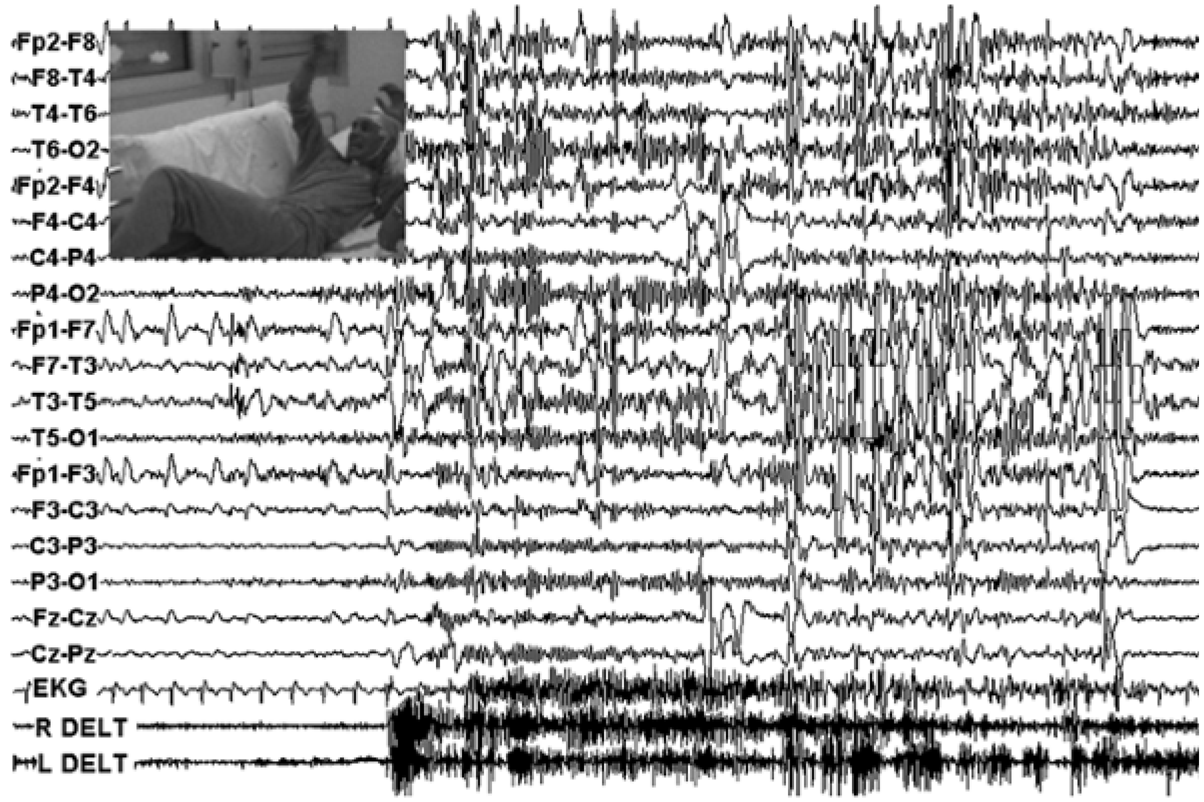

FIGURE 6. Startle epilepsy in a 15-year-old boy with a left porencephaly. This boy experiences many tonic startle seizures per day. The electroencephalogram pattern is characterized by the presence of a flattening of the cerebral activity over the frontocentral areas of the left hemisphere, which is then substituted by the recurrence of rhythmic spikes sometimes obscured by muscular artefacts.

The polygraphic pattern of tonic-spasm seizures is particularly characteristic (Fig. 2). On EEG, the seizure begins with a diffuse slow wave of high amplitude, positive over the vertex central regions, lasting 0.5 to 1 second. This is followed by a rapid rhythm of 10 to 15 Hz, with increasing amplitude lasting from 5 to 10 seconds. The polygraphic recording is characterized by a rhomboid pattern, as observed in spasms, that coincides with the wide slow wave. Immediately afterward there is a muscle contraction of increasing intensity that coincides with the rapid rhythm. This ictal pattern tends to occur in series lasting several minutes, with seizures every 20 to 30 seconds; the duration of the tonic phase can vary from one seizure to another in the same series.

The interictal EEG characteristics are strictly related to the epileptic syndrome in which the seizures occur.

Diagnostic Considerations

Based only on an anamnestic account, it is sometimes difficult to understand precisely whether the convulsive seizure of a patient is a real tonic seizure. From a semeiotic point of view, detailed questioning of eye witnesses to the seizures about the clinical manifestations can help to distinguish a real tonic seizure from other convulsive seizures. The presence of jerks at the beginning or end of the seizure permits the differentiation from clonic or tonic–clonic seizures. The presence of clear focal elements at the beginning of the seizures, such as focal hypertonia, focal clonus, or marked eye or head deviation, as well as jerks at the end of the seizure, permits the differentiation from partial seizures with prompt generalization. As an indirect element of diagnosis, it should be remembered that Lennox-Gastaut tonic seizures occur more often during sleep, whether in the afternoon or at night. The Lennox-Gastaut tonic seizures appear prevalently during the first sleep cycle, in the non-REM stage; they can also occur in quick succession, with intervals of only a few minutes, and be of varying intensity. From an etiologic point of view, the underlying epileptic syndrome should be assessed as precisely as possible. In Lennox-Gastaut syndrome, cerebral MRI scan should exclude or support a symptomatic etiology. Because Lennox-Gastaut syndrome appears after West syndrome in about half of the cases, it is necessary to remember that the etiologies associated with West syndrome are also the same as half of the cases of Lennox-Gastaut syndrome (see Chapter 241).

Differential Diagnosis

Differential diagnosis is made in relation to other epileptic seizures and to nonepileptic events.

Epileptic Seizures

Tonic–Clonic Seizures

Tonic seizures must be differentiated from generalized tonic–clonic seizures (GTCSs). Gastaut et al.[22] described GTCSs as follows: (a) their duration is usually longer than 1 minute; (b) their tonic phase is more intense and more generalized than the contraction of tonic seizures and rapidly ends with a general contraction and extension; (c) they have a clonic phase of gradually decreasing frequency that lasts twice as long as the initial tonic phase; (d) they are always followed by a stertorous phase, by residual muscular contractions, and by deep sleep; and (e) their EEG manifestations never consist of flattening of the tracings or of low-amplitude rapid synchronization during the tonic phase, but rather consist from the start of an epileptic recruiting rhythm at 10 Hz that quickly becomes associated with slow waves of inhibition during the clonic phase and always shows electrographic silence (cortical extinction) after the seizure.

Infantile Spasms

Infantile spasm is a particular type of seizure characterized by a complex flexor-extension movement of the trunk and limbs, and lasting about 1 second. As seen in the chapter dedicated to spasms, the EEG and polygraphic picture of the spasm differs substantially from that of the tonic seizure.[13] The ictal EEG of the spasm is characterized by a diffuse, slow wide wave or by a brief rapid rhythm, but never by a recruiting rhythm or by a prolonged fast activity of 20 Hz. The spasm is characterized polygraphically by a muscle contraction that lasts about 1 second and reaches a peak more rapidly than does a tonic seizure; it then decreases quickly and appears as a kind of “rhombus.” The tonic seizure, instead, shows a prolonged muscle contraction of growing intensity.

Focal Seizure of Frontal Lobe Origin

The tonic postural seizures originating from the mesial frontal lobe and heavily involving the supplementary motor area manifest with tonic contraction of axial and limb muscles as in generalized tonic seizures.[60] The main differential pattern regards the consciousness that is lost in generalized tonic seizures and preserved or slightly impaired in partial tonic seizures. In fact, although the partial seizures of the frontal lobe show a bilateral body involvement, as the supplementary motor area has a bilateral motor representation, the ictal discharges remain confined to the unilateral frontal lobe, usually preserving consciousness.

Nonepileptic Seizures

Tonic Seizures in Hyperekplexia

Hyperekplexia is a disease characterized by an accentuation of the “startle response.” Most cases are of autosomal dominant inheritance, although cases have been reported as having acquired brainstem lesion.[31] Children with this disease have myoclonic jerks as a reflex to tactile or acoustic stimulation. Furthermore, mostly in the early months of life, they can have prolonged stiffness seizures evoked by the same stimuli.[1] The child suddenly has a diffuse muscle contraction with limb extension; consciousness is preserved; the seizure causes respiratory arrest and cyanosis; if it lasts more than 2 to 3 minutes, the seizure can produce cardiac arrhythmia or sometimes death. The EEG does not show an ictal discharge, but only muscular artifacts. Whereas this seizure cannot be stopped by intravenous administration of antiepileptic drugs, it can be stopped by abrupt flexing of head and limbs to the trunk.[59] This movement permits a correct diagnosis.

Dystonic Seizures

Children with brain damage or epilepsy sometimes have dystonic movements with sustained muscle contractions that can be mistaken for epileptic seizures. In these dystonic events, the patient has a slow contraction of the trunk in dorsal extension, with deviation of the head to one side; the limbs contract in extension; consciousness is preserved; and the child often cries.

Such paroxysms can last from 3 to 10 seconds. The EEG does not show any ictal sequence. Such events are more frequent when the child has fever or feels pain.

Repetitive Sleep Starts in Neurologically Impaired Patients

Repetitive sleep starts occurring in clusters at the onset of sleep in neurologically impaired children have been reported as non-epileptic tonic or myoclonic manifestations.[15] Children who present with repetitive sleep starts have tetraparesis, and pyramidal or extrapyramidal features. Often they previously had a diagnosis of epilepsy in the first year of life. The onset of repetitive sleep starts is in the second year of life. Video-EEG recordings of the events during sleep show the presence of clusters of massive tonic contractions, resembling prolonged sleep starts, in the transition phase between wakefulness and sleep stage I, with the EEG counterpart being unremarkable. The clusters last from a few to 15 minutes. The duration of each muscle contraction is from 500 msec to 5 seconds, depending on the type of the contraction, which can be more or less tonic. No epileptiform pattern is observed as a counterpart of the clinical event. Muscle contraction is usually massive, involving more trunk than limbs, and onset is sudden and usually spontaneous but can be induced by acoustic and tactile stimulation. Clinical characteristics are similar to a startle.

Benign Myoclonus of Infancy

In 1977, Lombroso and Fejerman[37] described benign nonepileptic myoclonic manifestations in healthy children 6 to 12 months of age. While awake, the child has a brief tonic contraction, called myoclonus by the authors. This is actually a tonic contraction lasting 1 to 2 seconds that resembles a shiver. This phenomenon can happen several times a day, especially when the child is excited or tired. Consciousness is preserved and there are no postictal phenomena. The EEG is normal during the episode.

Specific Syndromes Incorporating Tonic Seizures as an Integral Feature

Generalized tonic seizures constitute one of the principal features of EIEE with suppression burst and of Lennox-Gastaut syndrome. Tonic seizures, not always generalized, constitute the main seizure type of the startle-induced epilepsy. In other syndromes, tonic seizures could be one of the several seizures presented. Epileptic tonic-spasms have been observed mostly in generalized symptomatic epileptic encephalopathy, independently from the underlying etiology. Tonic seizures are also the seizure type reported in epilepsy associated to some chromosopathy,[49] although a unifying syndromic picture has not yet been defined in these congenital conditions.

Response to Treatment

Tonic seizures are generally resistant to the commonly used antiepileptic drugs. Medications that make patients sleepy or lower their level of vigilance worsen tonic seizures, especially in Lennox-Gastaut syndrome, as the seizures occur more frequently during sleep than while awake. Consequently, a general principle of treatment is to consider all antiepileptic drugs, the only precaution being to avoid lowering the patient's vigilance level.[44]

Phenytoin can be effective for the treatment of tonic seizures and tonic status epilepticus, though it has side effects, including gingival hypertrophy, hypertrichosis, leukopenia, and disturbance of liver function.

Phenobarbital, primidone, and carbamazepine are at times effective for tonic seizures. Carbamazepine is particularly effective in the treatment of tonic postural seizures.

Sodium valproate is currently regarded as the drug of first-choice in Lennox-Gastaut syndrome. However, its effectiveness for tonic seizures is limited. Lamotrigine is an alternative initial therapy: It seems particularly effective in reducing falls and improving cognition and quality of life. Benzodiazepines such as clonazepam, nitrazepam, and clobazam are often used to treat tonic seizures. When a benzodiazepine is not effective, it should be withdrawn slowly to avoid withdrawal seizures or tonic seizure status epilepticus. Clobazam is useful in the treatment of Lennox-Gastaut syndrome because its side effects are much less marked than those of other benzodiazepines.[21] However, the development of tolerance is a problem with clobazam, as well as with other benzodiazepines.

Some authors have reported that intravenous injection of diazepam can induce tonic status epilepticus in patients with Lennox-Gastaut syndrome.[46,51]

Felbamate is indicated as adjunctive therapy in the treatment of generalized seizures associated with Lennox-Gastaut syndrome in children.[52] However, indications for its use are restricted because of recent data suggesting increased risks of developing aplastic anemia or liver failure in patients taking felbamate. In Japan, zonisamide is regarded as an effective drug for tonic seizures.[63]

Topiramate has been effective in some open and controlled trials, and anecdotal experience with levetiracetam suggests that this drug could also be effective in the treatment of tonic seizures. Vigabatrin could be very useful in the treatment of the tonic-spasm seizure moreover when the etiology is demonstrated to be symptomatic, although the risk:benefit ratio should be carefully considered.

Callosotomy has not been proven to be effective in the treatment of tonic seizures but is performed as a palliative measure. More clearly defined case selection and longer follow-ups are needed to fully evaluate its effectiveness.[4]

Summary and Conclusions

Tonic seizures are defined as such on the basis of a clinical phenomenon that actually includes different etiologies and pathophysiologic mechanisms. These occur mostly in patients with symptomatic epilepsies, but also in patients with cryptogenic epilepsies and, more rarely, in idiopathic epilepsies. Although there is the common element of tonic muscle contraction, it is possible to recognize shades of difference in the semiology that separate the various types of tonic seizures. It is probable that different types of tonic seizures utilize different anatomic pathways. Subcortical structures are surely involved, as are some cortical regions, especially the frontal lobe.

An element common to all the tonic seizures is their particular relation to sleep: Sleep and sleepiness facilitate tonic seizures. Another element, unfortunately common to all tonic seizures, is frequent drug resistance. Studies proposing to increase the knowledge of the pathophysiologic mechanisms of tonic seizures would permit a better treatment, both pharmacologic and neurosurgical, of this type of seizure in the future.

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Chapter 53

Gelastic Seizures

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Introduction

It has long been recognized that laughter may be an epileptic phenomenon. Authors have cited different examples of the first mention of epileptic laughter, including the patient described in 1581 by Erastus and cited by Chen and Forster,[15] the patient of Trousseau published in 1873 and cited by Loiseau et al.[48] and Gascon and Lombroso,[29] the observations of Gowers in 1881 cited by Daly and Mulder,[16] and the report of Féré in 1898 cited by Druckman and Chao.[24] Daly and Mulder coined the term "gelastic epilepsy," from the Greek word *gelôs* meaning joy or laugh, to describe seizures in which laughter was an integral part.[16]

Gelastic seizures have most often been described in association with hypothalamic hamartoma, and there is good evidence that the gelastic seizures in those patients originate within the hamartoma itself (see later discussion). Gelastic seizures, however, are also described in patients without hypothalamic hamartoma, in whom a proven or suspected seizure focus lies in the frontal or temporal lobes, or where the origin of the seizures remains undetermined.

Definitions

After an earlier attempt by Gumpert et al.,[32] Gascon and Lombroso[29] suggested the following criteria for the diagnosis of gelastic epilepsy: Stereotyped recurrence of pathologic laughter; absence of external precipitants; concomitance of other manifestations generally accepted as epileptic (such as tonic or clonic movements, loss of consciousness, automatisms); presence of interictal and, where it can be recorded, ictal electroencephalographic (EEG) epileptiform discharges; and absence of other neuropathology that could explain pathologic laughter. Loiseau et al.[48] insisted on the now-accepted distinction between a seizure symptom or type and an epilepsy syndrome, arguing that there was no basis for the concept of "gelastic epilepsy," an example, in their opinion, of the futility of classifications based on a single symptom.

Epidemiology

Gelastic seizures are rare. The childhood prevalence of hypothalamic hamartoma with gelastic seizures was estimated at 0.5 per 100,000,[11] and although there are no estimates of the prevalence of gelastic seizures in patients without hypothalamic hamartoma, the number of cases reported in the literature is considerably smaller.

Clinical Features

Ictal Features

Laughter is the principal clinical manifestation and defines the gelastic seizure type. Whether there are features of the laughter or other ictal manifestations that can distinguish between different gelastic seizure foci has been a matter of much discussion, and the issue remains controversial. Gascon and Lombroso[29] noted that patients with probable temporal lobe seizure origin had either a pleasurable aura or a mirthful quality to their laughter, and Loiseau et al.[48] agreed that the laughter in such cases was an expression of emotion. Exceptions have been noted, however, including patients with temporal lobe tumors whose ictal laughter either sounded forced or did not have an infectious quality.[4,64] Conversely, gelastic seizures of frontal lobe origin are said to present a more uniform picture, in which laughter sounds unnatural, appears forced, is devoid of emotional content, and is not associated with feelings of mirth.[8,71] The clouding of consciousness and impairment of memory that often accompany gelastic seizures of temporal and frontal lobe origin make separation of the affective and motor components of ictal laughter fraught with difficulty. Furthermore, previous reviews of gelastic seizures not associated with hypothalamic hamartoma have included many cases described before the use of magnetic resonance imaging (MRI) and in which localization of the ictal onset zone was based primarily on scalp EEG abnormalities.[71] As is discussed further in Chapter 250, localized interictal EEG abnormalities and even invasive ictal recordings can be misleading in patients with hypothalamic hamartoma.[13] In addition, the diagnosis can easily be missed with computed tomographic imaging.[1,34,49]

The laughter in gelastic seizures associated with hypothalamic hamartoma has been described variously as “unnatural,”[21,69] “mechanical,”[13,70] “mirthless,”[44] “bubbling,”[20] “pleasant,”[5,70] or “normal.”[1] Delay in diagnosis of gelastic seizures in patients with hypothalamic hamartoma (see Chapter 250) attests to the fact that the laughter may sound real[11] and be indistinguishable from the person's normal laughter.[1,3,54] The best-known example of this is the patient reported by Berkovic et al.[5] who won a happy baby contest. As the patient grows older, however, the quality of the vocalization may become increasingly less like normal laughter.[5]

As to the question of mirth associated with gelastic seizures in hypothalamic hamartoma, reports are limited in number because of the typically young age of patients and the frequent presence of intellectual impairment. Striano et al.[67] observed that older patients do not feel amused during gelastic seizures but, rather, are so embarrassed that they try to conceal them (e.g., by feigning a sneeze). On the other hand, Sturm et al.[68] described three adult patients who experienced a strong desire or “pressure to laugh” either separately from or just prior to typical gelastic seizures; one described this as a pleasant and emotional feeling in the chest, and another said it was a pleasant, nonsexual feeling that made him happy and would allow himself to laugh when this was socially appropriate.

Gelastic seizures may be closely related to seizures with epileptic crying, termed “dacrystic”[56] or “quiritarian.”[64] Ictal crying has been noted in many patients with gelastic- seizures, mostly in association with hypothalamic hamar-toma[12,31,41,47,60,65,67,72,73] and less often associated with other localized pathology.[64] By contrast, dacrystic seizures have rarely been reported in the absence of gelastic seizures.[17,18]

Gelastic seizures in patients with hypothalamic hamartoma are typically brief, lasting <30 seconds and often are just a few seconds in duration. Consciousness is said to be preserved during these brief events.[71] This appears to be based on the rapid resumption of previous activity in infants and young children and from interviews with adult patients; ictal cognitive testing, however, has not been undertaken. By contrast, laughter is said to be longer lasting in patients with frontal and temporal gelastic seizures and is associated with impairment of consciousness in temporal gelastic seizures.[71] Very frequent gelastic seizures that occur in wakefulness and from sleep are typical of infants with hypothalamic hamartoma.[22,62,65] Occasional cases of gelastic status epilepticus or “status gelasticus” have been reported, both in patients with hypothalamic hamartoma[55,59,73] and in one without it.[30]

Associated with the ictal laughter are other motor manifestations that have not been well characterized. Facial contraction resembling a grimace or smile is reported,[47,61] as are clonic buccal, palpebral, and ocular movements, producing a grimacing appearance.[20] Autonomic features including facial flushing, lacrimation, and pupillary dilation are known to occur in patients with hypothalamic hamartoma,[5,68] but whether these are unique to patients with hypothalamic hamartoma is uncertain. Cerullo et al.[14] demonstrated a rise in systolic and diastolic blood pressure, increased heart rate, facial flushing without diaphoresis, flattening of the plethysmogram, and modification of respiratory activity during gelastic seizures of two patients with hypothalamic hamartoma.

Interictal Features

Interictal clinical features in patients with gelastic seizures depend on the underlying syndrome diagnosis. There is insufficient knowledge of such clinical features in patients with gelastic seizures due to temporal or frontal lobe epilepsy. The interictal clinical features associated with hypothalamic hamartoma are discussed in relation to diagnostic considerations later in this chapter and in Chapter 250.

Postictal Features

Postictal features of gelastic seizures have not been well characterized. In older patients with hypothalamic hamartoma, gelastic seizures may be associated with impaired consciousness. In addition, gelastic seizures in hypothalamic hamartoma may be followed by nongelastic seizures, and the postictal features of these other seizure types may dominate the clinical picture. Whether these nongelastic seizures represent seizure spread from the hypothalamic hamartoma[13] or are otherwise "triggered" by the gelastic seizure[41] is unresolved, but both situations are possible.

Electroencephalographic Findings

Interictal Findings

Interictal EEG findings in patients with gelastic seizures necessarily depend on the associated syndrome diagnosis and, in patients with hypothalamic hamartoma, the degree of epileptic progression. In patients with hypothalamic hamartoma and gelastic seizures alone, particularly during infancy and early childhood, the interictal scalp EEG may be normal,[5,27] and the subsequent appearance of scalp EEG abnormalities coincides with the development of other seizure types and clinical features (see Chapter 250 for more details). Stereotactic depth EEG studies in some patients with hypothalamic hamartoma have demonstrated interictal discharges produced within the hamartoma,[43,46] but these do not coincide with scalp EEG discharges.[41] Recently, in vitro studies with surgically resected hypothalamic hamartoma tissue slices and single cells have demonstrated intrinsic pacemaker-like properties of GABAergic hamartoma neurons.[74] It is speculated that attachment of the hamartoma to the mammillary bodies enables seizure propagation via connection with the mammillothalamic tracts to other limbic areas and may facilitate progression of the epileptic syndrome and the development of widespread interictal epileptiform discharges, including slow spike-wave discharges, in a process akin to secondary epileptogenesis.[26,27,54]

Ictal Findings

Ictal EEG findings of gelastic seizures depend on the location of the ictal onset zone and patterns of seizure propagation. It is now widely accepted that the gelastic seizures associated with hypothalamic hamartoma originate within the intrinsically epileptogenic hamartoma.[6] The most important contribution to our understanding of the role of the hamartoma in the genesis of seizures came from the stereotactic depth EEG studies of patients conducted by Munari, Kahane, and colleagues in Grenoble.[40,41,42,43,54] They demonstrated that gelastic seizures are associated with an ictal discharge within the hamartoma itself and that electrical stimulation of the hamartoma can reproduce the patients' clinical symptoms. Kuzniecky et al.[46] replicated these results and performed ictal single photon emission computed tomography (SPECT) studies that demonstrated hyperperfusion in the region of the hamartoma. Confirmation of the intrinsic epileptogenicity of the lesion then formed the basis for the various forms of surgical treatment now offered to patients with hypothalamic hamartoma and refractory epilepsy (see Chapter 250). Propagation of the ictal discharge to the cingulate gyrus was also demonstrated with depth EEG.[54]

Scalp ictal EEG patterns during gelastic seizures associated with hypothalamic hamartoma may be absent.[3,57,65,70] When an ictal EEG pattern is noted, the most consistent finding is diffuse EEG desynchronization, which may be followed by diffuse or lateralized low-voltage fast activity.[5] Desynchronization of the EEG and cessation of the interictal epileptiform discharges may also be produced by depth electrode stimulation of the hamartoma.[41]

Diagnostic Considerations

The association between hypothalamic hamartoma and gelastic seizures is so strong that almost all patients with the hypothalamic hamartoma syndrome have gelastic seizures at some point in the course of their epilepsy.

Therefore, hypothalamic hamartoma should be considered in any person with ictal laughter.

The mechanisms by which the clinical manifestations of gelastic seizures are produced are poorly understood, and it is uncertain whether ictal clinical features can distinguish between patients with and without hypothalamic hamartoma. Regarding the functional anatomy of mirth and laughter in humans, Arroyo et al.[2] presented a hypothesis drawing on their own observations, reports in the literature of conditions associated with pathologic laughter, and electrophysiologic aspects of laughter, including both stimulation experiments and ictal EEG recordings. They concluded that the cingulate and basal temporal cortex were important contributors to mirth and laughter, and suggested that the anterior cingulate was of primary importance in relation to motor aspects, whereas the basal temporal cortex was involved in processing emotional aspects; the hypothalamus was presumed to subserve the autonomic nervous system response. Involvement of the hypothalamus in normal laughter has been implied by the association of various hypothalamic lesions with pathological laughter,[2,37] yet depth EEG studies in patients with hypothalamic hamartoma indicate that the hypothalamus proper is spared by the ictal discharge.[54]

Biraben et al.[8] suggested that ictal laughter might be produced by one of three mechanisms: (a) a simple reaction to a modified cognitive process, (b) an automatic behavior, or (c) a forced action. They argued that the latter two mechanisms are indistinguishable clinically but could have different anatomic and physiologic bases. Fried et al.[28] reported electrical stimulation of laughter in a girl who underwent subdural monitoring for epilepsy but did not have laughter as part of her ictal semiology. The area stimulated was in the left superior frontal gyrus, at the lateral limits of the supplementary motor area, and the resultant laughter was accompanied by a sensation of merriment or mirth. The patient offered a different explanation for it each time, attributing the laughter to whatever external stimulus was present. Fried et al. suggested a close link between the motor, affective, and cognitive components of laughter and that these components are represented in a neuronal network capable of parallel distributed processing, in which the entire network is activated as a whole by the stimulation of any of its constituent units.

Using $H_2{}^{15}O$ positron emission tomography (PET), Iwase et al.[38] investigated differences in brain activation between smiling produced voluntarily and that produced in response to comic stimulation in healthy subjects. They found that emotional smiling activated visual association areas, the left anterior temporal lobe, left uncus, left orbitofrontal cortex, and right medial prefrontal cortex, as opposed to voluntary smiling, which activated primary and supplementary motor cortex as well as bilateral parietal and insular cortex. According to Arroyo et al.,[2] the orbitofrontal cortex is a region responsible for inducing laughter associated with mirth.

Interictal clinical features and the circumstances surrounding the expression of gelastic seizures may be of greater use in distinguishing between patients with and without hypothalamic hamartoma. Gelastic seizures in patients with hypothalamic hamartoma usually begin in infancy or early childhood. Neonatal onset is common, and onset from the very first day of life is well known.[5,20,22,46,58,65] In patients with onset in early childhood, other seizure types characteristically appear in a delayed fashion along with worsening of the interictal EEG and cognitive deterioration.[5,27] In contrast, gelastic seizures in patients without hypothalamic hamartoma are said to have a later age of onset, and, if other seizure types occur, they do so concurrently or pre-date the gelastic seizures.[71] Onset of gelastic seizures in adult life, however, is known to occur in patients with hypothalamic hamartoma,[52] and other seizure types may present before gelastic seizures in both children and adults with hypothalamic hamartoma.[53] Central precocious puberty is associated with hypothalamic hamartoma and may be the presenting symptom in children[26]; it is not uncommon for the diagnosis of epilepsy to be made only after investigation for precocious puberty if gelastic seizures have been unrecognized. Hypothalamic hamartoma is usually an isolated and sporadic cerebral malformation, but gelastic seizures are reported in patients with Pallister-Hall syndrome,[45] an autosomal-dominant condition associated with hypothalamic hamartoma and insertional polydactyly.[7,10]

Continuous video-EEG monitoring is an essential investigation for characterization of gelastic seizures and the associated epilepsy syndrome. In patients with gelastic seizures not associated with hypothalamic hamartoma, useful information about the ictal onset zone may be obtained. In patients with hypothalamic hamartoma, characterization of gelastic seizures and other seizure types, along with evaluation of the interictal EEG in wakefulness and sleep, allows for assessment of the degree of epileptic progression, if any, on which treatment decisions may be predicated.

MRI examination of the brain with an appropriate high-resolution epilepsy imaging protocol is a mandatory investigation in patients with gelastic seizures but also when there is any component of laughter noted on history or video-EEG recording of seizures, including patients with a mirthful aura or a feeling of "pressure to laugh." In addition, attention should be drawn to the region of the hypothalamus by the referring physician in such cases. We have seen several patients in whom a small intrahypothalamic lesion was overlooked despite an adequate imaging study having been performed. In patients without hypothalamic hamartoma, MRI may disclose a tumor, focal cortical dysplasia, or other lesion. Although patients with hypothalamic hamartoma only rarely have associated potentially epileptogenic lesions elsewhere in the brain,[26] MRI studies should be of sufficient quality to detect such lesions in consideration of epilepsy surgery.

Other investigations, including functional brain imaging (SPECT, PET, or functional MRI), neuropsychological evaluation, and invasive EEG monitoring, may be indicated in patients with gelastic seizures in whom surgical management is entertained. In patients with hypothalamic hamartoma, however, functional imaging and invasive monitoring are now generally considered unnecessary for proving the origin of gelastic seizures.[35] Exceptions are rare cases with associated potentially epileptogenic lesions elsewhere in the brain.

Differential Diagnosis

The differential diagnosis of gelastic seizures includes pathologic laughter associated with other conditions of the nervous system, including progressive supranuclear palsy, multiple sclerosis, amyotrophic lateral sclerosis, and psychiatric illness, to name but a few.[9,37,50] The distinction between epileptic and nonepileptic pathologic laughter is generally made in accordance with the criteria of Gascon and Lombroso[29] and may be facilitated by the use of video-EEG monitoring. Narcolepsy-cataplexy has been mistaken for gelastic-atonic seizures in one case,[25,39] and this particular diagnosis may be challenging in cases of Niemann-Pick disease type C.[63]

The most difficulty, however, arises in distinguishing between normal laughter or crying and gelastic or dacrystic seizures in children with hypothalamic hamartoma, often resulting in late presentation and sometimes in diagnostic delay after medical attention is sought. There are several reasons for this. There is little appreciation among parents and doctors that laughter in the neonatal period is developmentally precocious and should be regarded as abnormal.[5,66] Unexplained crying in infancy is common and considered normal or attributed to other conditions such as infantile colic.[61] Gelastic seizures in infancy are not typically accompanied by "other manifestations generally accepted as epileptic," and interictal scalp EEG recordings of infants with hypothalamic hamartoma are usually without abnormality. Most importantly for the neurologist and epileptologist, ictal EEG patterns may be absent during gelastic seizures.[3,57,65,70] Therefore, a high index of suspicion in an infant with unexplained episodic laughter or crying in whom the episodes are unprovoked, brief, and stereotyped in appearance will lead to further investigation and correct diagnosis.

Specific Syndromes

Other symptomatic focal epilepsies are the next-most-common category of syndromes associated with gelastic seizures and may be further classified according to location

and etiology. The locations associated with gelastic seizures are the temporal lobe, with particular emphasis given to the basal temporal cortex[64] or the lateral convexity[48]; and the frontal lobe, with particular emphasis given to the cingulate gyrus[2,51] and the mesial forebrain.[48] The pathology reported in these cases has included tumors of various types and grades, including meningioma,[48] astrocytoma,[64] ependymoma,[16] oligodendroglioma,[4] and cavernous haemangioma[2]; focal cortical dysplasia[19,51]; and less specific findings including hemispheric atrophy or dilation of the lateral ventricular horns.[29] Probable symptomatic cases with normal MRI examinations and focal origin of seizures demonstrated with video-EEG monitoring and ictal SPECT are also reported.[8,67]

Gelastic seizures have been reported in association with other symptomatic (or probable symptomatic) epilepsy syndromes, including West syndrome,[11,23,24,27,53] tuberous sclerosis,[33,75] measles encephalopathy,[15] and Niemann-Pick disease type C[15,63] and in patients with widespread cerebral malformations such as lobar holoprosencephaly and lissencephaly.[36] By contrast, gelastic seizures have only rarely been described in patients with presumed idiopathic epilepsy syndromes.[36]

Response to Treatment

The prognosis for patients with gelastic seizures depends entirely on the associated epilepsy syndrome and the underlying etiology. Gelastic seizures associated with the hypothalamic hamartoma syndrome are typically refractory to medical treatment but may be amenable to surgical treatment (see Chapter 250). No particular prognostic significance is attached to the occurrence of gelastic seizures in other epilepsy syndromes or conditions associated with epilepsy. The management of patients with gelastic seizures also depends on the associated epilepsy syndrome and underlying etiology. Management of gelastic and other seizure types associated with the hypothalamic hamartoma syndrome is discussed in Chapter 250, and the management of symptomatic focal epilepsy syndromes, other epilepsy syndromes, and other causative conditions mentioned earlier are beyond the scope of this chapter and are discussed elsewhere.

Summary and Conclusions

Gelastic seizures are an uncommon seizure type in which ictal laughter is the principal manifestation and defining feature. The hypothalamic hamartoma syndrome is strongly associated with gelastic seizures and should be considered in all patients with ictal laughter, although there are frontal and temporal lobe epilepsy patients with various underlying pathologies and other, mostly symptomatic epilepsy syndromes in which gelastic seizures are reported. Interictal clinical features may be of more use than ictal clinical features in distinguishing between patients with and without hypothalamic hamartoma, whereas MRI is an indispensable diagnostic investigation.

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Chapter 45

Neocortical Sensory Seizures

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Introduction

Simple sensory seizures represent challenging clinical phenomena. Neurologists readily accept that a patient's sensory symptoms prior to the appearance of motor symptoms or alteration of consciousness represent part of the patient's clinical seizure semiology and provide valuable localizing information. A challenge appears when a patient has only simple partial sensory seizures. Simple partial seizures are a relatively common seizure presentation among the childhood epilepsies, but motor seizures are predominant.[47] The paucity of psychic or sensory symptoms may reflect the child's inability to describe internal experiences in a way that is easily interpretable to adult observers. Since simple sensory seizures have no overt ictal behavior, the subjective description of the seizure symptomatology is the only clue that can lead to a proper clinical evaluation and treatment. Some patients react to sensory seizures in a stereotypic fashion. For example, a painful simple partial sensory seizure of the hand may result in hand rubbing or vocalization about the pain. Occasionally, physicians encounter patients who have simple partial seizures for many years prior to the appearance of more clinically apparent seizures. When patients with pure sensory seizures also have psychiatric complaints, the chances for misdiagnosis or delay of diagnosis are high.[121]

Simple sensory seizures were originally underrecognized as epilepsy.[35] While auras were known in ancient times as an event preceding seizures,[122] it was not until the early 19th century that partial seizures were clearly related to localized brain disease. Fritsch and Hitzig described localization of function in 1870, which led to modern concepts of cortical specification.[38]

Jackson also promoted the hypothesis that abnormal electrical activity in a localized region of cortex could cause symptoms such as those seen in epilepsy.[51,52] In the early 1900s, the work by Brodmann[18] and other neuroanatomists showed that the cerebral cortex had regional histologic variations often corresponding to different cerebral functions. Penfield, Jasper, and others made major contributions to mapping the localization of cerebral function and defining motor and sensory areas of the brain, as well as areas without obvious effect on sensory, motor, or speech activity.[83,85]

Definitions

Sensory seizures were defined by Penfield and Jasper separately from simple seizures with autonomic symptoms or psychic symptoms:[85]

â€œSensory seizures. Discharge in an area of sensory representation produces a sensation that may serve as a warning (aura) of a motor or psychical seizure. Actually, the sensation constitutes, in itself, a seizure. Under this heading we have taken up the sensory attacks that involve the trunk, head, and extremities (somatosensory), and the special senses (visual, auditory, vertiginous, gustatory, and olfactory).

1. Somatosensory seizures. Sensation of this type may be transient, or it may be continuous over a considerable period of time. The quality of sensation is tingling, numbness, sense of movement, desire to move, or, very occasionally, pain. A detailed march of sensation may occur from one somatic part to the

next in a manner similar to the Jacksonian motor march. The discharge, which produces this, usually occurs in the postcentral gyrus. There is a tendency for the sensory march to stop and to spread across the Rolandic fissure so as to produce movement in the same member. Spread in the reverse direction from motor to sensory representation, thus producing sensation after movement, is quite rare.

A somatosensory seizure may also be produced by discharge in the second sensory area on the upper bank of the fissure of Sylvius. Furthermore, peculiar body sensations may result from discharge in the supplementary motor area within midsagittal fissure.

2. Visual seizures result from discharge in one or the other occipital lobe. Lights, which may be colored, appear before the patient, or there may be dimming of vision and complete blindness even though the discharge originates in one occipital lobe. Complicated visual hallucinations and alterations in the interpretation of things seen are not included in this group, but are discussed under the heading of psychical seizures.
3. Auditory seizures are characterized by a simple sound, usually described as buzzing or drumming, and often referred by the patient to the opposite ear, or opposite side of the head. Like a visual seizure, there is nothing elaborate about it. Hallucinations of music, for example, are classified as dreamy states or psychical seizures and are discussed below.
4. Vertiginous seizures. What is called by the patient dizziness or unsteadiness is frequently reported, but there is rarely any recollection of direction of rotation as there is in the sudden dizziness of Meniere syndrome.
5. Olfactory seizures have been called uncinate fits because of the demonstration by Jackson of involvement of the uncinate gyrus in cases in which an aura of disagreeable odor constituted the initial feature. The localization of discharge is doubtless in or near the uncinate gyrus.â€

Penfield and Jasper's classification of simple partial sensory seizures has withstood the test of time since the international classification[26] of simple partial seizures with somatosensory or special sensory symptoms is nearly identical to the original description except for lack of description of gustatory seizures (Table 1). It is unlikely that another sensory modality will be discovered and change the classification further.

Table 1 Simple Partial Seizures with Somatosensory or Special Sensory Symptoms[a]

Somatosensory
Visual
Auditory
Olfactory
Gustatory
Vertiginous

[a] Simple hallucinations (e.g., tingling, light flashes, buzzing).

Penfield and Jasper recognized the difficulty of separating a simple sensation from a more complicated hallucination, for example, separating simple visual hallucinations from more complicated formed illusions. Occasionally one finds more complicated hallucinations with intraoperative stimulation, but more reliably localizing are the simple hallucinations of rather elementary sensory perceptions. A conscious patient may attach many complex descriptions to simple hallucinations, and since we observers have nothing to observe other than the patient's subjective description, sometimes there may be a fine line between a classification of simple partial sensory seizure and a simple partial psychic seizure with prominent sensory complaints.

Epidemiology

Ideally, understanding the epidemiology of simple partial seizures would require evaluation of a large population in which patients with epilepsy are identified accurately and their seizures and epilepsies are classified based on a thorough clinical and laboratory investigation. Such studies are usually based on patients referred to specialized epilepsy centers. Focal epilepsy occurs in approximately 60% of patients with epilepsy, and 10% to 21% of these patients have simple partial seizures alone.[40] Detection of simple partial seizures can be difficult. Some patients with simple partial sensory seizures may be undiagnosed or unaware that their symptom represents epilepsy unless the seizure progresses into a more disabling seizure type. In patients with obvious epilepsy and more severe types of seizures, only a careful history will elicit remote sensory complaints that may no longer occur, as in several cases reported by Williamson et al.[123]

Isolated simple partial sensory seizures are uncommon in patients referred to major epilepsy centers. Among the focal epilepsies, temporal lobe and frontal lobe foci predominate in surgical series.[119] Parietal and occipital cases are rare because those epilepsies are either rare, rarely intractable, or rarely brought to surgery. For example, occipital epilepsy was identified in only 12 of 502 nontumoral epilepsy cases by Bidzinski et al.[12] Williamson et al. reviewed reports of occipital lobe epilepsy in the literature and found that <2% of focal epilepsy is occipital.[124] They found only sporadic reports when they reviewed parietal lobe epilepsy.[123]

These surgical data are typically grouped by lobe, not seizure type. It is likely that the epidemiology of simple partial sensory seizures differs from the lobar distribution of surgical cases. A review of the initial signs of seizure onset in data adapted from Penfield and Kristiansen showed that in 222 patients, 55 had somatosensory auras, 11 had visual auras, three had auditory auras, one had an olfactory aura, and two had gustatory auras.[62] Penfield and Perot noted visual hallucinations in 41 of 1,132 (3.6%) patients with focal epilepsy; 21 had only visual hallucinations.[87] Mauguiere and Courjon found somatosensory epilepsy in 127 of 8,938 (1.4%) patients with epilepsy when evaluated after age 3 years.[72] Young and Blume reported painful seizures in 24 of 858 (3%) epileptic patients[129] and Hausser-Hauw and Bancaud noted that 30 of 718 (4%) intractable epileptics had gustatory hallucinations.[43] West and Doty reviewed olfactory auras in epilepsy and concluded that prevalence is unknown but published estimates ranged from <1% to >30% depending on the epilepsy syndrome and pathology.[122]

The advent of magnetic resonance imaging (MRI) technology has further complicated matters. Patients with lesions identified in known sensory cortical regions may not volunteer information on sensory symptoms until thoroughly interrogated about an aura. At times, only with inpatient video-electroencephalography (V-EEG) and MRI can sensory symptoms be suspected and assessed. This is especially true in patients with sensory symptomatology at seizure onset that progresses to loss of consciousness and amnesia for the aura. These patients often have more intense seizures and EEG changes are usually bilateral.[103] Additionally, sensory symptoms may result from spread of a seizure from an unexpected location; for example, many patients with supplementary motor seizures complain of a somatosensory aura even when lesions are not near the sensory cortex.[106] Gustatory hallucinations may also represent seizure spread.[43] Visual hallucinations have been reported with frontal lesions,[102] as have jacksonian sensory seizures from a prefrontal lesion.[118] Thus, at this time, there is still need for adequate epidemiologic studies of localization-related epilepsies and partial sensory seizures using modern technology and appropriate clinical information.

Anatomic Pathways and Pathophysiology

Understanding neocortical anatomy and regional interconnections has led to a better understanding of seizure semiology and evolution. The neocortex is a repository for all primary sensory input for somatosensory, visual, auditory, and gustatory senses, while olfaction mostly utilizes portions of the limbic system and is the only special sense without thalamic relays.[21] Within the cerebral cortex, sensory functions are not so discreetly organized that there are sharp boundaries; for example, the sensory responses obtained by Penfield and Rasmussen[88] and Uematsu et al.[116,117] showed that sensory responses could be recorded from the precentral gyrus (see reference 85, p. 58, Fig III-12). Motor responses show similar dispersion. Penfield reported that removal of the precentral gyrus did not prevent motor responses from the postcentral gyrus, suggesting that activation of the postcentral gyrus alone could result in movements during seizures.

The sensory homunculus (see reference 85, p. 70, Fig III-15) must be considered as an artist's schematic diagram of data obtained by Penfield and Jasper on many patients; it is not entirely accurate for each patient. However, the homunculus does show significant organization of the cerebral cortex in an anatomically meaningful way (see reference 85, p. 71, Fig. III-17).

Some body parts (e.g., the tongue and hand) have large cortical sensory areas. Picard and Olivier have extensively reviewed the anatomy of the sensory tongue cortex in humans. The language-dominant hemisphere had a larger sensory cortical tongue representation and the tip of the tongue had more extensive representation than the middle or back portions of the tongue.[89] Most cortical representation was contralateral to somatic localization, but ipsilateral and bilateral responses to stimulation were reported, suggesting possible stimulation of the secondary sensory area, located at the base of the perirolandic cortex.

Penfield and Rasmussen[88] found a human second sensory area in the region of the termination of the motor strip in the frontoparietal operculum (see reference 85, p. 79, Fig III-21). When stimulated, the second sensory area on the superior bank of the frontoparietal sylvian fissure produces bilateral, contralateral, or ipsilateral sensations, often of the perioral regions (see reference 85, p. 79, Fig III-21). Ipsilateral inputs are less numerous as shown by Adrian in cats.[1] LÃ¼ders et al. recorded evoked potentials from the second sensory area that were of lower amplitude than primary sensory potentials.[67]

Other primary sensory cortices show highly organized anatomy; for example, the visual cortex deep within the calcarine fissure is organized so that the occipital pole is innervated polysynaptically by the macula and therefore is activated by the central visual field, whereas more rostral portions of the calcarine cortex contain representations of more peripheral visual fields.

The auditory cortex in the Heschl gyrus of the temporal lobe is tonotopically organized as shown by evoked potential mapping of longer-latency responses with magnetoencephal- ography.[82,115,119,120] Vestibular cortex is also in the superior temporal gyrus rostral to the auditory cortex, but stimulation does not produce anatomically specific symptoms, just mild vertigo.[85]

Taste is represented in the parietal operculum and possibly near the insula,[85] though Hausser-Hauw and Bancaud's detailed depth electrode studies point primarily to the parietal operculum.[43] Olfaction initially involves pathways from the olfactory epithelium through the cribriform plate to the olfactory bulbs, olfactory tracts, and lateral stria. These areas project to the anterior perforated space, prepiriform cortex, lateral olfactory gyrus, periamygdaloid cortex, entorhinal cortex, amygdala, septal nuclei, and hypothalamus.[122] Thus, most olfactory centers are located in the mesial temporal region and adjacent structures.

While a description of epileptogenesis is beyond the scope of this chapter, clearly any structural lesion, whether seen by MRI or not, involving a sensory cortex or adjacent area may provide the necessary and sufficient changes for chronic localization-related epilepsy to develop. The concept of the epileptogenic zone, as interpreted by Penfield and Jasper[85] and Ajmone-Marsan[4] and reviewed by LÃ¼ders and Awad,[65] implies that the locations in the cortex where symptoms are produced, where seizures are generated, where interictal spikes occur, and of any structural lesions all may contribute to epileptogenesis or to the symptom expression during seizures. It is certainly possible for sensory cortex to become activated late in a seizure and thus produce symptoms after the actual EEG onset in a silent cortical area. To experience somatosensory, visual, or auditory symptoms, white matter pathways, association cortices, and brain structures regulating attention and consciousness all play a role.

Epileptogenesis producing sensory seizures and focal epilepsy may occur without brain lesion or injury from peripheral nervous system injury. Spiller et al. reported three cases with soft tissue injuries to the hand where sensory seizures developed within months in the injured limb and all cases eventually had secondarily generalized tonicâ€“clonic seizures. The authors postulated that the injury resulted in cortical reorganization that was epileptogenic.[109]

Clinical Features

Simple sensory seizures show a wide variety of phenomenology and represent some of the most interesting seizures reported. Patients can have prolonged symptoms[70] and can relate elaborate descriptions of their seizure. Since sensory cortices are located in adjacent lobes, it is not surprising that multimodality sensory seizures are frequently reported in addition to sensory seizures from one modality.[72]

Seizures of the primary sensory cortex typically produce contralateral positive or negative symptomatology. Unilateral symptoms thought to originate in or near the contralateral postcentral gyrus include tingling, numbness, sense of movement, desire to move, somatic pain, heat or cold, electric shock sensations, agnosia for a body part, and phantom sensations.[60,72,85,99,123,129] The hand and fingers are most often involved initially.[72] Symptoms may be stationary or have a sensory march. Somatosensory seizures may be interpreted as motor activity by the patient, even when there is no visible movement seen. This can often lead to misinterpretation of seizure localization by a physician taking the history. Cephalic pain, occasionally migrainous in nature,[19] even if unilateral, may not have localizing value, while abdominal pain usually originates from the temporal lobe.[129] Genital pain probably originates at the mesial parietal termination of the sensory strip and is not necessarily associated with orgasmic seizures.[98,110,128] Attacks of limb agnosia (sudden loss of sensation for a body part) and phantom limb sensations (sense that the limb is in a position that is not the true position) probably originate in the posterior parietal region.[41,72,99] Ajmone-Marsan gives Foerster credit for pointing out that a postcentral-area seizure can be distinguished from the precentral seizure since motor symptoms stop earlier when the seizure originates in the postcentral gyrus and that the convulsing muscles are often more limited in distribution than when the primary motor cortex is seizing. Additionally, when a motor seizure occurs after activation of the sensory cortex, a tremor may be seen before true clonic spasms, if clonic spasms occur.[4] Russell and Whitty observed that somatosensory auras often spread quickly to involve at least the entire limb and that prolonged sensory seizures, comparable to the epilepsia partialis continua of motor seizures, were not observed in their 85 cases. Motor seizures rarely progress to a simple somatosensory seizure, while the reverse is common. Sensory seizures often end abruptly, unlike the gradual cessation typical of focal motor attacks.[99]

Seizures from the second sensory area may produce ipsilateral or bilateral symptoms that are identical in character to symptoms occurring in the primary sensory cortex (e.g., numbness and tingling). Affected body parts can be diffuse or axial but often symptoms localize to the fingertips, feet, lips, or tongue.[2,6,11,13,61,85,93,123] Second sensory-area seizures can arise from the frontoparietal operculum or the inferior parietal lobule.[126] It is also possible to have ipsilateral sensations with seizures originating near the supplementary motor area since there may be a corresponding supplementary sensory region adjacent to the primary sensory foot area.[85] Arseni and Maretsis' case 3 may have had ipsilateral seizures from this location.[6]

Somatosensory auras have been reported in temporal lobe epilepsy, usually with bilateral or unilateral tingling. Pain and numbness were also noted in Erickson et al.'s report and most symptoms were in the limbs but could involve the head or trunk.[36]

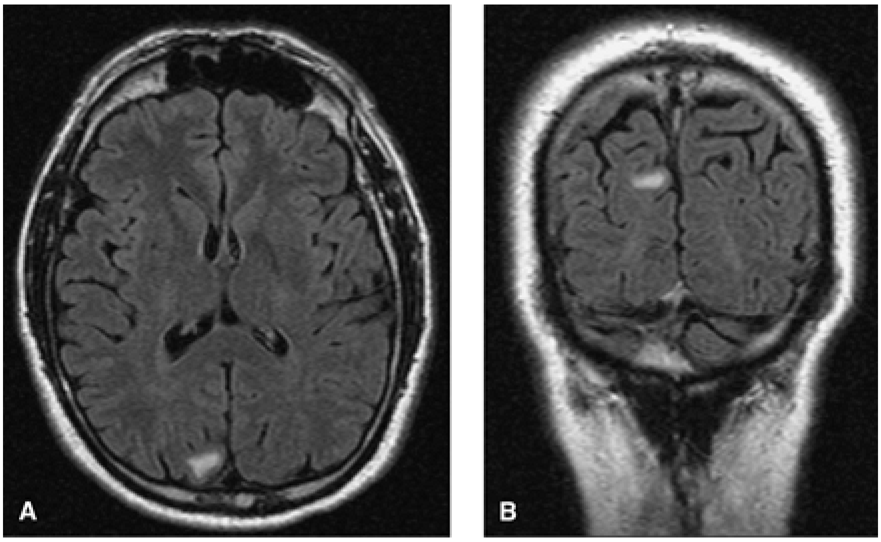

FIGURE 1. Poststroke occipital epilepsy. **A, B:** This is a magnetic resonance image of the brain in a 53-year-old male smoker and drinker with a right occipital infarct, mild left homonymous visual scotoma, and complex partial seizures with an aura of autonomic symptoms of epigastric sensation, facial flushing, and dizziness associated with â€œgraying outâ€ of his vision prior to loss of consciousness. Routine electroencephalography was normal and seizures are controlled by carbamazepine.

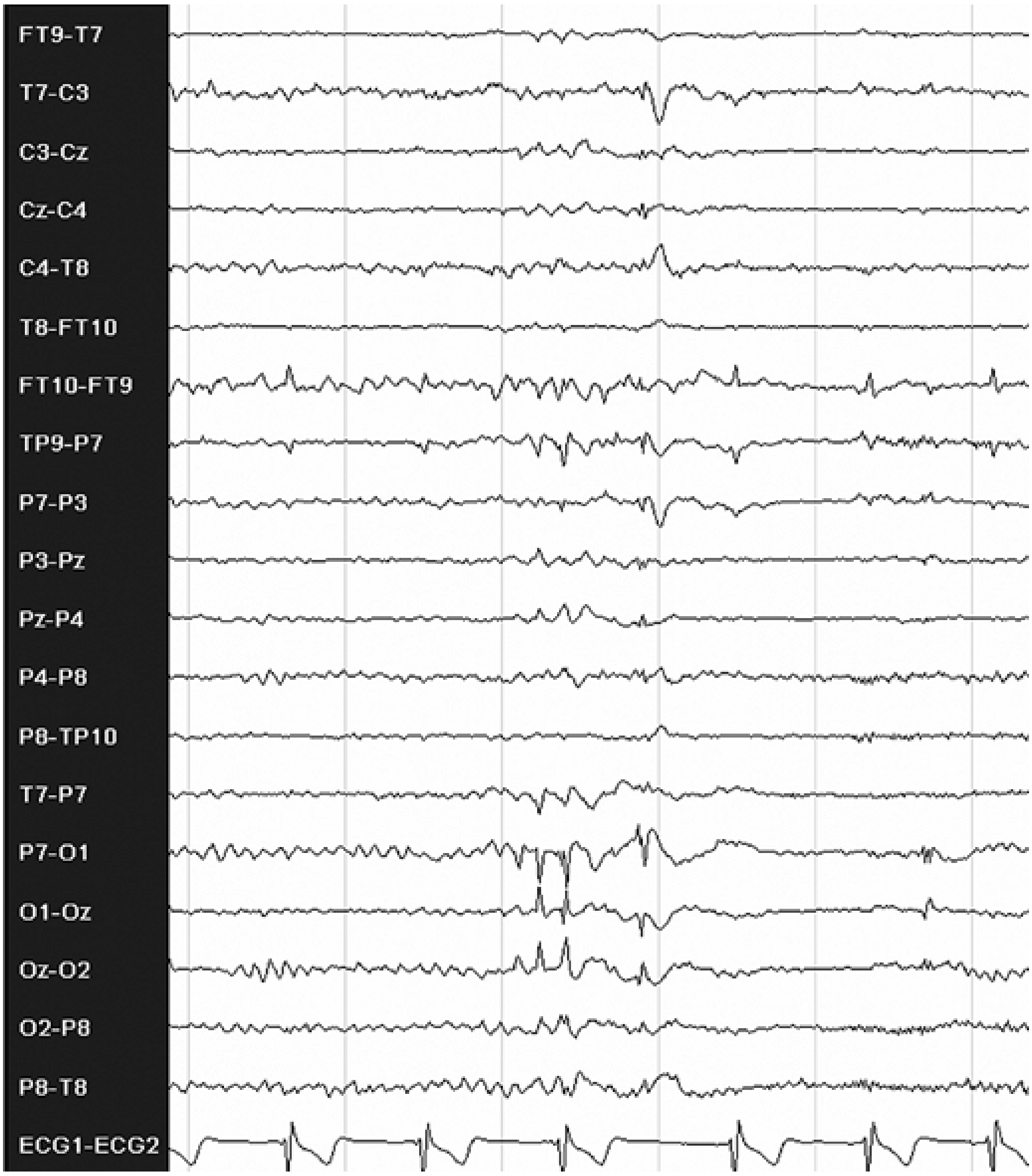

FIGURE 2. Interictal electroencephalogram showing left occipital spikes in an 18-year-old, right-handed male patient with a history of seizures since age 5, starting 3 months after a mild head trauma. He has an aura of right-sided flashing lights, then vertigo, followed by a subjective feeling of right arm twitching and then loss of consciousness. After that he turns his head to the right, raises his right arm, and progresses into a secondarily generalized tonicâ€“clonic seizure. Magnetic resonance imaging of the brain was normal. The patient became seizure free after adding levetiracetam to his monotherapy carbamazepine regimen.

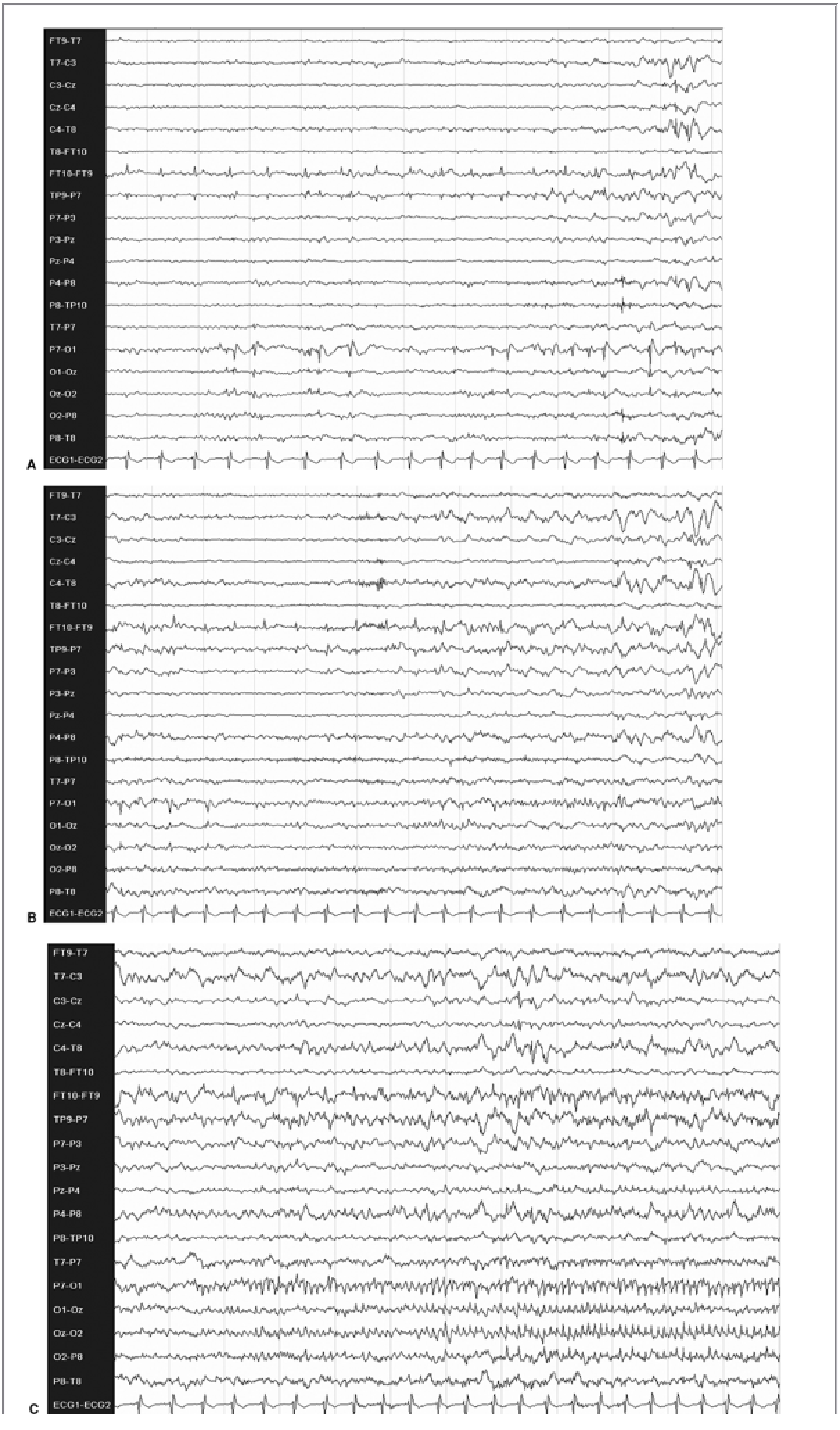
FT9-T7
T7-C3
C3-Cz
Cz-C4
C4-T8
T8-FT10
FT10-FT9
TP9-P7
P7-P3
P3-Pz
Pz-P4
P4-P8
P8-TP10
T7-P7
P7-O1
O1-Oz
Oz-O2
O2-P8
P8-T8
ECG1-ECG2
A
FT9-T7
T7-C3
C3-Cz
Cz-C4
C4-T8
T8-FT10
FT10-FT9
TP9-P7
P7-P3
P3-Pz
Pz-P4
P4-P8
P8-TP10
T7-P7
P7-O1
O1-Oz
Oz-O2
O2-P8
P8-T8
ECG1-ECG2
B
FT9-T7
T7-C3
C3-Cz
Cz-C4
C4-T8
T8-FT10
FT10-FT9
TP9-P7
P7-P3
P3-Pz
Pz-P4
P4-P8
P8-TP10
T7-P7
P7-O1
O1-Oz
Oz-O2
O2-P8
P8-T8
ECG1-ECG2
C

FIGURE 3. A: Same patient as in FIGURE 2, 16 seconds after ictal onset showing the electroencephalographic onset of a left occipital seizure. Patient reported seeing flashing lights to his mother prior to this time. **B:** Left occipital seizure 28 seconds after clinical onset showing O1 spikes and later rhythmic fast activity. **C:** Same seizure, 40 seconds after clinical onset. Note the rhythmic sharp waves maximally over the left occipital region. The seizure subsequently spread and secondarily generalized, not ending until 88 seconds after clinical onset.

Simple sensory visual seizures' semiology includes positive symptoms and unilateral or bilateral negative symptoms.[49,101] Seizures of the calcarine cortex produce elementary visual hallucinations such as flashing or flickering lights, spots, colored lights, weaving patterns, zigzag lights, or visual field deficits such as scotoma or ictal amaurosis.[85,100,101,124] Other seizure symptoms attributed to the occipital lobe include eye movement sensations, sensations of object movement, ictal nystagmus, eye deviation, early forced blinking, and inversion of the visual field.[57,93,101,124] Some cases with autoscopic hallucinations where a person sees him- or herself without a mirror may be due to epilepsy.[63,100] Eye movements can complicate the clinical picture; for example, if a patient sees a bright light, he or she may look toward that light and yet the light continues to move away as his or her eyes deviate, giving a sensation of movement. Nystagmus may also occur and complicate the symptomatology. The patient may see colored lights. Negative symptoms can include loss of a visual field or quadrant; some patients complain of transient blindness. Ictal blindness probably results from seizure spread to the contralateral occipital lobe.[9] The visual symptoms often occur in areas of scotoma or other visual field defect.[58,100] While the simplest visual phenomena probably relate to involvement of the calcarine cortex,

adjacent areas may also participate, and occasionally patients with posterior temporal lesions or parietal lesions may report a visual aura with or without other disturbances. Formed or complex visual hallucinations, including remembered scenes[95] or distortions such as micropsia, macropsia, or changes in object shape, and blindness or hemianopia probably originate in the visual association cortex or adjacent parietal or temporal lobe[100] and are more often seen from the right or nondominant posterior temporal region.[87]

Auditory seizures were reported by Holmes as early as 1927.[46] Penfield and Kristiansen found only three patients, suggesting that this condition is rare.[86] The auditory symptoms can occur without dizziness. Certainly more complicated auditory hallucinations can occur, such as hearing words or music, but these seizures usually are classified as psychic, rather than just as sensory seizures, because of accompanying experiential phenomena. Simple sounds such as buzzing, drumming, or single tones, often contralateral, are typical of seizures from the auditory cortex.[85] One localizing sign noted occasionally with an auditory seizure consists of plugging an ear or placing the hand over the ear. This seems to correlate with an auditory aura that originates contralateral to the plugged ear in the auditory cortex.[25]

Simple partial olfactory sensory seizures (uncinate seizures) are relatively infrequent considering the large number of patients with temporal lobe epilepsy seen at most centers. These seizures may originate from the orbitofrontal cortex as well as the mesial temporal region. Howe and Gibson reported that there is not an increased incidence of tumors in patients with olfactory aura,[48] contrary to reports in other series (see reference 122 for review). Olfactory symptoms have also been reported in occipital- or central-area epilepsy by King and Ajmone-Marsan,[55] but seizure spread may explain at least some of the more unusual localizations. The odor is often but not exclusively unpleasant or disagreeable.[28,85,122] Daly described two types of olfactory phenomena. Hallucinations may be crude or elaborate with other sensory modalities involved, while illusions distort or alter the character of normal olfactory stimuli. Illusions were also noted interictally or postictally.[28]

Gustatory seizures are usually associated with temporal lobe epilepsy, often due to tumors. Daly reported that the sensations, though often unpleasant, can be acidic, bitter, salty, or sweet. Often a metallic taste is experienced.[28,29] The taste of bile or cigarette smoke has been reported.[43] Penfield and Jasper believed that gustatory symptoms result from seizures originating in or near the insula,[85] although Bornstein believed that the parietal operculum may also produce these seizures.[15] Rosetti et al. reported a case with dysgeusia and contralateral sensory symptoms from the insula in a case well documented with subdural ictal EEG recordings.[97] Hausser-Hauw and Bancaud reviewed their experience with gustatory hallucinations. Seizures originated in the parietal and temporal lobes in 20 of 30 patients with adequate ictal localization. Electrical stimulation of the parietal and/or rolandic operculum produced gustatory hallucinations and spontaneous seizures produced symptoms by spread to the opercular region.[43]

Seizures with vestibular symptoms, or vertigo, when isolated, are notoriously difficult to diagnose since these patients are often initially evaluated and treated for peripheral vestibular dysfunction. Symptoms include true vertigo, vague dizziness, or unsteadiness, with spinning most common.[56,85,86,105] Smith's study of 120 cases described rotation around the vertical or sagittal axis but not the coronal axis. Horizontal and vertical movements and also a sense of body or room tilting were described.[105] Lesions have been reported near the temporal parietal occipital junction as well as the superior temporal gyrus by Penfield and Kristiansen,[86] and Eviatar and Eviatar[37] have shown vertiginous symptoms in patients with frontal lobe epilepsy. Kogeorgos et al. found that 7 of 30 cases also had generalized tonicâ€“clonic seizures and 15 of 30 had absencelike episodes, while only two had auditory hallucinations with vertigo.[56]

Postictally, a variety of neurologic deficits can occur analogously to the classical Todd paralysis or postictal amaurosis or visual field deficits.[34,101] Patients with central-area epilepsy may have sensory deficits postictally that gradually improve, and these may only affect higher cortical sensory functions, such as graphesthesia or two-point discrimination. Olfactory sensitivity decreases postictally for several hours.[122] A severe seizure is not necessary to produce Todd paralysis and the process probably involves active inhibition of function rather than neuronal exhaustion.[34] Holmes found prominent postictal impairment infrequently in children with simple partial seizures.[47]

Electroencephalographic Findings and Clinical Correlations

Since sensory seizures can originate in a variety of brain regions, it is not surprising that a variety of interictal EEG abnormalities can be seen (Figs. 1, 2, and 3). Interictal changes could include changes in amplitude or frequency (e.g., focal slowing), particularly if there is a known structural lesion. Focal fast activity is less commonly seen with lesions. Interictal spikes may occur, but should be interpreted cautiously.

Blume et al. reported that 4 of 44 focal epilepsy cases that localized with ictal EEG had ictal onset clearly distant from the area of principal interictal spiking.[14] Temporal lobe spiking can occur in cingulate, frontal, parietal, and occipital lobe epilepsy.[107] Some authors report that ictal patterns are occasionally difficult to interpret in patients with seizures originating in the parietal or occipital region.[123,124] This is certainly true when seizures rapidly generalize and obscure the EEG record or muscle and movement artifact prevail. However, it is also recognized that some patients will have well-defined interictal spikes or ictal onsets from the occipital,[49,69] parietal, or central area[72] while clinical symptoms are recorded. Activation procedures can increase focal spiking and occipital spikes may be enhanced by eye closure or darkness.[69] Kogeorgos et al. found 28 of 30 patients with epileptic dizziness had abnormal interictal EEG, and localization was in the posterior temporal lobe unilaterally or bilaterally with sharp waves or focal slowing.[56]

Devinsky et al. studied the prevalence of scalp EEG changes in patients with simple partial seizures and found that when sensory symptoms alone predominate, only 15% of patients have EEG changes, whereas if motor symptoms are present, 33% will have EEG changes.[30] However, Bare et al. found that extra scalp electrodes improved the EEG yield in sensory seizures to 27%.[8] Sperling et al. reported that EEG changes may be absent in patients with simple partial seizures in presumed temporal lobe epilepsy when recording with bitemporal depth electrodes, and even in patients where postoperative seizure outcome was excellent.[108] The limited neocortical coverage with bitemporal depth electrodes may miss simple partial seizure ictal patterns from neocortex.

Kaibara and Blume studied postictal EEG changes.[53] Thirty-seven percent of cases had polymorphic delta, 29% had attenuation of background, 31% had immediate return to normal background, and 25% had spike activation. Some patients had more than one postictal pattern. All 51 patients in the study had focal seizures. The changes seen could be prolonged. When postictal EEG changes occur, one may appreciate postictal spiking or slowing that was not evident before the seizure occurred, and these findings may have some localizing value.

Diagnostic Considerations

As with any focal epilepsy, the history from the patient or reliable observer is very important for proper diagnosis. It may be helpful to ask the patient to watch for certain symptoms during subsequent seizures so that a more detailed description can be obtained later. Onset, evolution, postictal features, postictal deficits, patterns of occurrence, and precipitating factors should be thoroughly explored. The stereotypic nature of a seizure is also helpful in confirming a diagnosis of epilepsy.

MRI and routine EEG will often support a diagnosis of epilepsy, but negative initial MRI studies may require alternative MRI scanning protocols tailored for specific clinical situations such as cortical dysplasia or other neocortical lesions. Initially, nondiagnostic EEG studies should be repeated with prolonged recordings, or with sleep and other appropriate activation procedures. V-EEG monitoring may be quite helpful in patients when the diagnosis of epilepsy is uncertain or when seizures are medically intractable.[62] Other medical or neurologic disorders can result in epilepsy and should be considered during the evaluation process. Several genetic forms of focal epilepsy have been characterized, including autosomal dominant partial epilepsy with auditory features,[80] so it is likely that commercial testing for these syndromes will become available.

Differential Diagnosis

As alluded to earlier, pure sensory seizures can occasionally be confused with other nonepileptic conditions, such as cerebrovascular disease or psychiatric disorders.[61,121] Sensory symptoms due to ophthalmologic, otolaryngologic, or vestibulocochlear disease or to peripheral neuropathy need to be excluded. A thorough evaluation is warranted to avoid missing a more serious medical problem that is leading to the symptoms.

Specific Syndromes Incorporating the Seizure Type as an Integral Feature

In the 1989 proposed classification of the epilepsies,[27] one can identify a variety of epilepsy syndromes in which sensory seizures may occur; for example, in benign childhood epilepsy with centrotemporal spikes, sensory symptoms may be noted when partial seizures occur.[64] Seizures involving the central area may exhibit somatosensory symptomatology. Seizures of the temporal lobe can present with auditory or vertiginous sensations, as well as olfactory sensations.

The International Classification does not significantly address the issue of parietal lobe epilepsies. Seizures are clinically diverse and do not always include sensory auras.[123] Recently, Ho et al., using ictal single photon emission computed tomography (SPECT) and MRI, have described an anterior parietal syndrome with sensory symptomatology being quite prominent, whereas a more posterior parietal syndrome was characterized by psychoparetic complex partial seizures.[45]

Occipital lobe epilepsies can be divided into those with symptoms that are supracalcarine or infracalcarine, depending on the location of the visual hallucinations. Depth electrode studies have documented specific seizure spread patterns. Infracalcarine seizures, for example, more often manifest with a temporal lobe seizure spread pattern, whereas supracalcarine occipital lobe seizures may spread to the parietal and central area producing focal motor or even generalized seizure activity.[7,112] Not all occipital epilepsies produce appropriate visual auras.[68,124] Williamson et al. reported that 88% of their series of 25 occipital epilepsy patients had visual symptoms,[124] while only 73% of the Montreal series of 42 patients reported by Salanova et al. had a visual aura.[101] Childhood epilepsy with occipital paroxysms and the syndrome of migraine and seizures are often manifested by seizures that have visual symptomatology, simple or more complex.[27,39,78]

Some reflex epilepsies are associated with partial seizures rather than generalized seizures. Partial seizures of various

types are reportedly induced by startle, somatosensory input, proprioception, music, sounds, voices, hot water immersion, eating, reading, and other language functions.[94] Simple sensory seizures are infrequent manifestations of reflex epilepsy and usually develop after similar seizures develop spontaneously. Ritaccio believed that this represents postafferential facilitation of a preexisting condition.[94] Reading epilepsy can have seizures with a sensation of jaw movement, though often jaw clonic movements predominate.[94] Sutherling reported sensorimotor seizures triggered by music.[111] Caloric vestibular stimulation can produce temporal lobe seizures with auras of tinnitus and vertigo.[10,20] Ricci and Vigevano described stroboscopic provocation of occipital seizures with simple visual hallucinations in four cases and complex hallucinations in one patient;[92] however, most patients with photosensitive epilepsy have generalized seizures.[17,94] Brinciotti et al. found that pattern (checks or stripes)-sensitive seizures were more often associated with localization-related epilepsies.[17] Duncan et al. reported a case with gaze-evoked seizures in nonketotic hyperglycemia.[32] Reder and Wright described a 13-year-old boy whose seizures included ictal sensory loss in one arm provoked by using cutlery while eating. Accidental finger amputation resulted in seizure control.[91]

A wide variety of childhood epilepsy syndromes may exhibit simple sensory seizures, though motor seizures dominate the clinical picture. For example, cortical dysplasia can cause simple partial seizures with motor symptomatology that is extremely resistant to medical therapy.[81] Just as with motor seizures, status epileptics may present with sensory symptomatology. Chronic focal encephalitis typically presents with epilepsia partialis continua in association with unilateral progressive cortical atrophy.[5] Mitochondrial encephalopathy with lactic acidosis and strokelike episodes (MELAS)[74] has a similar, but more acute presentation. Epilepsia partialis continua is common in children with Alper disease[16] and focal cerebral vasculitis. In all these syndromes, sensory seizures, if present, are often relegated to a minor role in the complete clinical syndrome.

Responses to Treatment

A thorough discussion of medical and surgical management of epilepsy is beyond the scope of this chapter. However, if the epilepsy syndrome is focal, drugs used for partial seizures should be used first. These include carbamazepine, phenytoin, gabapentin, lamotrigine, topiramate, tiagabine, oxcarbazepine, levetiracetam, zonisamide, pregabalin, primidone, and phenobarbital. In suspected cases of pure sensory simple partial seizures without EEG changes, a blind trial of antiepileptic drugs may support the diagnosis;[127] however, a definitive treatment end-point is necessary to avoid prolonged unnecessary therapy.

The success of pharmacotherapy for simple sensory seizures is not well described in the literature, though some patients do respond well to medical therapy. At times, more severe seizure types will be eliminated by antiepileptic drugs but simple sensory seizures will persist as auras with minimal disability. Often patients will choose occasional auras over antiepileptic drug toxicity when higher doses are tried. Still, some patients claim severe disability from sensory seizures, resulting in medication changes and dose escalation until intolerable dose-related toxicity develops. These cases may benefit from counseling, treatment of comorbid underlying depression, and consideration for a surgical procedure.

The benign childhood epilepsy syndromes may resolve spontaneously, so lifelong therapy is unwarranted. When seizures persist in benign focal epilepsies, particularly benign rolandic epilepsy, one should consider alternative diagnoses.

If neuroimaging studies have shown specific lesions, such as tumor or vascular malformation, particularly when there is a risk of progression, specific surgical or nonsurgical therapy may help seizures, particularly in cases where the lesion is adjacent to important sensory cortex, rather than in the functional zone.

Surgery for patients with sensory seizures should proceed with caution to avoid significant postoperative deficits. Sufficient disability from seizures should exist. For example, careful thought should be given before suggesting surgery in an individual with sensory seizures alone, unless an underlying lesion was serious enough to require surgical intervention in any case. Careful mapping of ictal foci and cerebral function may be needed to plan a safe resection.[12,22,42,71,75,76,77,79,96,113,114,119,125] Functional MRI offers hope for noninvasive functional mapping.[50] Subdural electrodes[66] are preferred by most epilepsy centers because of potentially better localization and less risk of hemorrhage compared to depth electrodes[113,114] or epidural electrodes.[42] Still, selected cases with subcortical lesions, such as a cortical dysplasia case reported by Privitera et al., are better evaluated with intracerebral depth electrodes.[90] Subdural electrodes are more convenient for functional mapping by direct cortical stimulation or with evoked responses for various sensory modalities. Additionally, the use of subdural electrode recordings can help with decisions on the need for intraoperative electrocorticography and cortical mapping during awake craniotomies.

The role of magnetoencephalography is controversial, since the technique is better for interictal epileptiform discharge localization. Magnetoencephalography data should be considered complementary to scalp EEG. No randomized controlled studies exist to show superior surgical outcomes with the use of magnetoencephalography.

Subpial transection gained favor as more reports appeared in the literature demonstrating safety and efficacy.[31,76,77,104] Theoretically, subpial transection can spare sensory cortex and function, yet still help relieve seizures. However, deficits have been reported after this technique and a pathologic study suggested that subpial transection may produce small confluent lesions rather than disconnection.[54]

Lesionectomy can also decrease risks of sensory deficits and help seizures long term in about half of the cases.[23,24] Gamma Knife radiosurgery may be appropriate in selected patients.[44]

At times, resection of primary cortex is needed for seizure control and the sensory deficits may be acceptable to the patient. It is possible to remove portions of primary sensory or motor neocortex without producing a lasting neurologic deficit.[73] Lehman et al. reported that the disability was quite limited with resection of the sensorimotor face region in the lower central area.[59]

With reflex seizures, avoidance of the stimulus can play a role in management. In some patients, biofeedback or sensory input may also reduce seizures, as in Efron's remarkable case.[33] Aird reviewed alternative epilepsy therapies in 500 refractory patients with various forms of epilepsy and found that 43% benefited from lifestyle modification in areas such as hydration, central nervous system excitation, sleep habits, and anxiety.[3]

Safety concerns should also be considered if the seizures produce any disability. While most simple partial seizures with sensory symptomatology alone may not be very disabling, many have complex partial or secondarily generalized seizures also. Safety concerns are justified if a patient has a job where sudden, complete or partial loss of vision or disturbance of sensation could result in injury. Each case must be assessed individually for safety concerns.

Summary and Conclusions

Simple sensory seizures can occur in a variety of epileptic syndromes. Many patients have other seizure types that make

the diagnosis more obvious. Caution is recommended in those patients with subjective sensory symptoms alone, particularly without supportive EEG or neuroimaging findings. The chances for misdiagnosis are high, and these patients may require a more thorough investigation before nonepileptic, medical, or psychiatric conditions are diagnosed.

The epidemiology of simple partial seizures is incomplete. Evidently, these seizures are seen in a minority of patients with epilepsy. Identifying patients with simple sensory seizures can help localize structural lesions. Prolonged clinical manifestations are occasionally reported by patients. Postictal neurologic abnormalities should be sought in the history and examination. Scalp EEG, while not highly sensitive, can be diagnostic. Treatment is similar to treatment in other localization-related epilepsies.

The possibility of developing treatment strategies that could specifically inactivate seizures by altering sensory function transiently requires further exploration. Additionally, patients with well-defined sensory phenomena may be good candidates for studying treatment methods that rely on advance warning of an impending seizure. Since consciousness is maintained, at least during the patient's simple partial seizure, these patients would make ideal study subjects.

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Chapter 55

Seizure Semiology in Infants with Localization-Related Epilepsy

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Elaine Wyllie

Introduction

The clinical manifestations of seizures in infants differ from those in older children and adults.[11,16] These clinical differences relate, at least in part, to factors intrinsic to the immature brain that bestow unique electrophysiologic characteristics. These factors, which underlie normal brain development, include the topography of brain metabolism, the development of myelinated connections, and the properties of ion channels and their associated ion gradients. Differences probably also relate to the causes of seizures themselves, which in some sense could be viewed as extrinsic factors. The etiology of infantile seizures, when compared to that in older patient populations, is more likely to be due to disorders of cortical formation, intrauterine pathology, channelopathies, or inborn errors of metabolism. Some of these disorders may result in widespread or multifocal pathology that strongly influences the clinical and electrographic expression of seizures, but even when restricting the comparison to the relatively homogeneous category of localization-related epilepsies, key differences remain.

As the child matures, the intrinsic properties of brain physiology change and thereby alter the expression of seizures. Gradually, seizures take on characteristics seen in adults. These changes occur in an orderly fashion, so that an ontogeny of ictal semiology can be described, just as one can characterize and predict normal child development.[17] We believe that a general understanding of these key differences and some detailed knowledge of the electroclinical correlation of infantile seizures allow the examiner to ask better questions during the medical interview, aid the evaluation for epilepsy surgery, and increase the chances of making a correct epilepsy syndrome diagnosis.

Unique Features of Infantile Seizures

Several unique features of infantile focal seizures are seen as a result of the differences in the physiology and etiology of localization-related epilepsies. These can be summarized into several key points (Table 1).

Infantile Seizures Are Often Subtle

Many infantile seizures are subtle and lack declarative features seen in adults.[8] This is particularly true of those arising from the temporal lobe: The infant may pause ongoing behaviors, appear to suddenly stop movement, and exhibit simplistic automatisms such as mouthing movements.[23] These are sometimes referred to as behavioral arrest, behavioral change, or hypomotor seizures. Oxygen desaturation may accompany these events, and if the child is connected to an oxygen saturation monitor, the change in the tone of the monitor may be the first sign alerting observers to the presence of the seizure. Parents reliably and quickly detect the peculiar change in the infant's behavior, but others unfamiliar with the child's habitual behavior may have difficulty identifying the onset of the event. There are almost never other declarative features of mature temporal lobe seizures: The infant is unable to vocalize the presence of an aura, cannot be asked about his or her experiences during the event to determine consciousness, does not exhibit contralateral dystonic hand postures, and does not show ipsilateral fine hand automatisms. Well-developed secondary generalization with synchronized clonic activity of both sides of the body is rare, particularly in the symptomatic epilepsies.[14]

Duchowny studied 14 infants <2 years of age with focal seizures and lateralized ictal electroencephalographic (EEG) abnormalities.[9] Seizure semiology most frequently included behavioral arrest with forced head turning and tonic extension of the arms, sometimes accompanied by chewing, sucking, mouthing, or blinking. Yamamoto et al. compared focal seizures in 15 infants <2 years old with those in 23 children 3 to 13 years old.[25] They noted that the seizures in the infants were longer in duration and had simpler, predominantly oral automatisms.

Automatisms during partial seizures in infants and young children are usually subtle and predominantly oral, sometimes with simple gross motor movements of the proximal extremities.[3] These contrast with the more complex fine motor behaviors seen in older patients. Jayakar and Duchowny noted an age-dependent evolution, with complex fine motor automatisms first appearing in their preschool group (2–6 years old).[12] A similar ontogeny was reported by Nordli et al.[17] Karbowski et al. proposed the term *temporal pseudoabsences* to emphasize that decreased behavioral activity was more prominent than were automatisms in their infants with temporal lobe epilepsy.[13] All of these results suggest a continuum in development of automatisms during childhood from simple to complex.

Table 1 Semiology of Focal Seizures

Feature	Infants	Adults
Auras	Absent	Sometimes present
Behavioral arrest	Promiment, often isolated	Present, but often with other specific features
Clonus, limb	Present	Present
Cyanosis, perioral	Prominent, particularly with temporal lobe seizures	Sometimes present
Dystonic posture	Absent	May be present
Hand automatisms	Absent	May be present
Loss of consciousness	Difficult or impossible rigorously to determine	Often present, can be reliably determined
Myoclonus, diffuse	Sometimes seen at the start or end of a focal seizure	Rare
Secondary generalization	Rare	Common

Spasms	May be concurrent with focal seizures	Absent
Tonic postures, symmetric	Frequent	Unusual

The Terms "Simple" and "Complex" Are Difficult to Apply

It can be extraordinarily difficult reliably to determine alteration of consciousness in most infants. For these reasons, the terms "simple" and "complex" are difficult to apply with any degree of certainty to most infantile seizures. The gold standard in adult monitoring units for assessing consciousness is to ask the patient to follow commands, repeat phrases, and recall test items. None of these can be performed in the preverbal child. Inattentiveness, such as not turning the head to alerting stimuli, is not the same as altered consciousness.

Dravet and colleagues studied children with partial epilepsy that began before 3 years of age and used the term *undetermined partial seizures* for three patients in whom they experienced difficulty with this assessment.[7] Duchowny accepted the term *complex partial* in this setting, under the assumption that some disturbance of consciousness must have occurred, based on unsuccessful attempts to influence attention by various maneuvers.[9] In a study at the Cleveland Clinic Foundation of videotaped seizures from infants <2 years old with localization-related epilepsy, the authors found it impossible to be as confident about level of consciousness, despite similar attempts.[1] Nordli et al.[16] reached the same conclusions, and Ohmori et al.[18] found it difficult to apply the labels "simple" or "complex" definitively.

Infantile Focal Seizures May Have "Generalized" Clinical Features

Apparently generalized features are relatively common and do not necessarily imply a diffuse or generalized epileptic diathesis. Two of the most important features in this category also are diffuse tonic postures and infantile spasms. Diffuse tonic postures, even symmetric ones, are common during infantile focal seizures. Brockhaus and Elger[3] studied age-related features of complex partial seizures in children and adolescents with temporal lobe epilepsy defined by EEG or magnetic resonance imaging (MRI). They compared 6 younger children (18 months to 6 years old) with 23 older children (8–16 years old) and found that the older children had seizure semiology similar to that of adults, including aura, arrest of activity, simple and complex automatisms, versive movements, and dystonic posturing. In contrast, the younger children lacked auras and complex automatisms, and instead often had symmetric motor phenomena. The authors concluded that some young children may be appropriate candidates for temporal lobe resections despite "atypical" seizure semiology.[3] Bilateral tonic stiffening or clonic or myoclonic movements may be seen during partial seizures in infants. Dravet et al. also observed that several children had "apparently generalized seizures" (flexor spasms, atonic or tonic seizures) with localized EEG ictal and interictal abnormalities.[7] These results illustrate that seizure semiology in infants may give limited clues to the localization-related nature of the epilepsy. In these infants, the ictal EEG findings are critical to clarifying the localized onset of the seizures. However, for some infants, interictal EEG features such as focal slowing, attenuation, or both can be even more illustrative.

Shields, Chugani, and associates at the University of California at Los Angeles emphasized the critical role of high-resolution MRI and positron emission tomography (PET) in identifying potentially resectable cortical lesions in children with infantile spasms and hypsarhythmia.[19] A similar experience was reported from the Cleveland Clinic.[24] The most commonly reported epileptogenic lesion in surgical series of children with infantile spasms is focal cortical dysplasia, especially in the temporal-parietal-occipital region, but frontal or temporal lobe tumors have also been noted.[2,22]

The observation that infantile spasms can result from a focal cortical lesion forces us to broaden our concept of localization-related epilepsy beyond that defined only by seizure semiology and ictal EEG. The 1989 classification of epilepsies and epileptic syndromes from the International League Against Epilepsy left room for this by defining localization-related (focal, local, or partial) epilepsies as those "in which seizure semiology or findings at investigation disclose a localized origin of the seizures."[6] For some infants, the critical diagnostic findings may be those of neuroimaging, either anatomic or functional, rather than ictal EEG. Recent observations from the Cleveland Clinic have further shown that this phenomenon (generalized EEG and nonlocalized seizure semiology) may also be seen in older children with surgically remediable focal epilepsy due to extensive focal or hemispheric brain lesions that are congenital or acquired early in life, especially malformations of cortical development or perinatal infarction.

Table 2 Common Manifestations of Infantile Focal Seizures

Spasms, asymmetric or combined with focal seizures
Behavioral arrest with version (hypomotor)
Focal clonic
Focal tonic
Others

Difficulty Lateralizing Based on Clinical Features

The ictal semiology provides fewer clues to the laterality of the seizure in infants when compared to older children or adults. This is largely due to the paucity of declarative features such as contralateral limb dystonia, ipsilateral hand automatisms, auras, and orderly secondary generalization. In addition, the presence of diffuse postures or spasms obscures some other features and makes it difficult to discern subtle asymmetries.

Types of Infantile Focal Seizures and their Electroclinical Correlations

Given the limitations of what one might deduce from the ictal semiology of an infantile seizure, it can be useful to record the event with simultaneous video-EEG recording to further characterizing the seizure. One study reviewed 2,112 patients and found 109 distinct seizures in 77 infants.[15] Overall, 13 seizure types were identified, of which 10 were seen in the localization-related epilepsies. The findings of this study can be combined with other observations to provide common descriptive elements of the most frequent infantile seizures.[1,7,8] Five of these account for the majority of focal seizures seen in infants (Table 2).

Spasms With Focal Features

Among the most common manifestations of infantile focal seizures are spasms. These can occur either as diffuse spasms accompanied by independent focal seizures or as spasms that with markedly asymmetric features, either clinical or electrographic. The focal seizures that accompany spasms may take a variety of forms and arise from nearly any region. Focal clonic and focal tonic manifestations are the most common.[15]

Behavioral Arrest With Version

Behavioral arrest seizures are characterized by a sudden cessation of ongoing behavior, often with associated staring. The infant abruptly stops his or her activity but does not demonstrate limb automatisms, dystonic posture, or clonus. In addition to the prominent behavioral arrest, these seizures also show pronounced version of the head, eyes, or both.[20] These seizures are associated with rhythmic ictal patterns often arising from the temporal, parietal, or occipital, but more diffuse hemispheric involvement at onset can also be seen. Capovilla et al. recorded seizures in infants with a benign form of localization-related epilepsy with similar clinical features but with prominent interictal vertex spikes.[4]

Focal Clonic Seizures

Focal clonic seizures are characterized by unilateral or bilateral asymmetric jerks of the limbs. The electrographic onset is always focal and most often involves the contralateral central region. Often, the EEG pattern of these seizures is distinctive, with a localized "crescendo" of rhythmic spikes or sharp waves in the central region followed by a "decrescendo" of ictal activity.

Focal Tonic Seizures

Focal tonic seizures are characterized by a predominant asymmetric tonic posture. The EEG ictal correlate of these seizures is diverse in terms of both pattern and focus.

Other Seizures

Rarely, seizures can be recorded in infants that arise in a focus and then secondarily spread into a more diffuse or generalized pattern. If the onset is not carefully observed, these seizures might be mistaken for generalized tonic–clonic seizures.[21] Other rare seizure types seen include those with prominent agitated behavior (hypermotor activity), focal tonic–clonic manifestations (involving just one side or part of the body), and migratory patterns in which the ictal discharge appears to wander from one cortical region to the other without any clear secondary generalization.

Further Comments on Infantile Seizure Classification

Even though there is a more limited repertoire of seizure semiology in infants than in adults, the immature nervous system still can produce a myriad of subtle variations in the particular clinical features of focal seizures. It is clearly an oversimplification to characterize seizures simply in broad categories as we have done, but at a minimum, this semiology-based classification allows for a quick means of communication and does correlate grossly with electrographic patterns. This should not, however, preclude more complete descriptions of seizures with detailed sequences of clinical events for surgical planning or other clinical circumstances.

Important Implications for Surgical Selection

The key elements indicating possibilities for epilepsy surgery include medically refractory epilepsy, the presence of a localized epileptogenic zone, and low risk for new postoperative neurologic deficits. In infants and children, definition of the epileptogenic zone is especially difficult and requires a different approach than that typically used to develop surgical strategy for adults. Challenges include the absence or paucity of localizing or lateralizing features in seizure semiology and often also on ictal and interictal EEG. Brain lesions that are congenital or acquired early in life—the typical etiologic substrate of catastrophic epilepsy in infants—may manifest with generalized EEG patterns and seizures that provide few or no clues to the focal nature of the epileptogenic process. In infants, the manifestation is often epileptic spasms with hypsarrhythmia; in older children, the electroclinical phenotype may resemble other forms of symptomatic generalized epilepsy, including Lennox Gastaut syndrome.

It has become clear that generalized features on seizure semiology and EEG should not necessarily contraindicate epilepsy surgery in an infant or child with *a very clear and extensive* congenital or early-acquired epileptogenic lesion seen on MRI.[6,10] However, the italics are added to emphasize the critical importance of strong MRI findings to clarify a surgical strategy in the absence or paucity of localizing features on semiology and EEG. If MRI does not show a single clearly defined potentially resectable epileptogenic lesion such as a malformation of cortical development or encephalomalacia due to pre- or perinatal arterial infarction, *and* localizing or lateralizing clues are absent from seizure semiology and EEG, then any strategy for epilepsy would be weak. In cryptogenic cases with normal or equivocal MRI findings or in children with bilateral or multifocal MRI abnormalities, clearly localized findings on ictal and interictal EEG assume critical importance for surgical planning. Focal clonic activity ipsilateral to the lesion would be an important indicator of noncongruency. Whether the surgical plan is based on clearly localized EEG or MRI or both, however, the seizure semiology in infants with surgically remediable epilepsy may lack localizing features typically associated with focal epilepsy in adults. Referral of such children to specialized centers for pediatric epilepsy surgery is warranted, and systematic long-term follow-up is important to further clarify appropriate strategies for identification of pediatric candidates for epilepsy surgery. Severe medically refractory epilepsy and detailed parental informed consent are prerequisites for an ethical approach to epilepsy surgery in these difficult cases.

Summary and Conclusions

The semiology of infantile localation-related epilepsies, though different from seizures seen in adults and older children follows some predictable ontogenic patterns. In general, the repertoire is less complex in the immature, and there are fewer declarative features keeping with the limited connectivity of brain regions. Seizures in children less than one year of age seldom have recognizable distal automatisms, dystonic hand postures, orderly secondary generalization and ascertainable changes in consciousness. Instead, primitive oral automatisms, restless body movements, behavioral arrests, prominent autonomic features including oxygen desaturation and eye version are seen. Both symmetric and asymmetric tonic postures may be observed with infantile focal seizures. About one third or more of children with infantile spasms may have concurrent focal seizures.

In terms of electroclinical correlations some generalizations are possible. Focal clonic seizures lateralize well to the contralateral rolandic region and are usually characterized by runs of rhythmic spikes, sharp waves, or focal spike-wave complexes. Seizures with behavioral arrest may arise from any location, though ictal rhythmic “crescendo" patterns from the temporo-parietal-occipital region often present this way, manytimes combined with version. Symmetric infantile spasms and tonic postures can belie a true focal process and have unpredictable EEG correlates. Video-EEG recordings are useful in any infant with refractory epilepsy, but particularly in those with infantile spasms, tonic seizures or behavioral arrests. A detailed knowledge of the infantile seizure semiology should improve our ability to elicit a complete history, define the epilepsy syndrome, and screen for potential candidates for epilepsy surgery.

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Chapter 56

Neonatal Seizures

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Introduction

Neonatal seizures may represent the first, and perhaps only, clinical sign of a central nervous system (CNS) disorder in the neonate. They prompt immediate concerns related to their etiologic diagnosis and management and future concerns relevant to the long-term outcomes of those who experience them. Our traditional understanding of neonatal seizures continues to evolve. It was recently believed that neonatal seizures, although easily provoked by acute injury in the immature brain, imparted little or no permanent anatomic or physiologic sequelae. Current research in both animal models and humans challenge this traditional view, and it is now believed that neonatal seizures may leave a permanent mark on the developing CNS.

Despite recent basic and clinical research of neonatal seizures there still remain considerable gaps in knowledge in areas that relate to diagnosis, pathophysiology, etiology, therapy, and prognosis. Although such work continues, the clinician is left with the task of developing strategies in diagnosis and management with limited scientifically confirmed data. The following discussion is based on both the best available data and, in their absence, clinical practice. This discussion has in part been presented elsewhere and is now updated and expanded.[31,113,114,119]

Controversies related to the characterization and classification of neonatal seizures have for the most part been definitively addressed. However, data relating to treatment and prognosis have not. While the debate continues in the basic neuroscience literature as to whether and how seizures cause significant brain injury in the developing brain, even less information is available concerning whether these findings are applicable to human newborns and whether the degree of injury, if present, is clinically significant. Resolution of these issues will ultimately guide antiepileptic drug (AED) therapy in neonates and more clearly define factors that predict long-term outcome.

The more practical approach is to consider the notion that the overriding determinant of outcome is seizure etiology. Seizure occurrence may indicate the presence of a potentially treatable etiology and should prompt an immediate search for this cause and institution of appropriate therapy. Seizures themselves may require emergent therapy because they may, directly or indirectly, disrupt the infant's homeostasis or contribute to additional brain injury. Seizure occurrence, and particularly the type of seizures, may have predictive value in determination of outcome.

The approach to the clinical management of an infant thought to have experienced a seizure is defined by the orderly consideration of issues that will improve long-term outcome: Accurate seizure characterization and classification, maintenance of infant homeostasis, urgent search for a treatable etiology, appropriate application of electroencephalography, institution of etiologic-specific treatment, thoughtful consideration of acute and then chronic AED treatment, and consideration of risk factors that predict outcome in order to plan for long-term care.

Definitions

The use of the term “seizure” to describe paroxysmal clinical events in the neonate represents a unique challenge. Early clinical investigations assumed that all such events were of epileptic origin; that is, such clinical events were generated by coincident electrographic seizures, composed of abnormal, excessive hypersynchronous discharges of networks of cortical neurons. Later studies suggested that, although most clinical seizures can be viewed in this way, some may be generated by nonepileptic mechanisms. Although it is appropriate to generically call all abnormal paroxysmal clinical events "seizures," more detailed classification can relegate most of them to either epileptic or nonepileptic categories. These distinctions become most important clinically when considering AED therapy. However, the terms also become cumbersome in discussing neonatal "seizures" as a whole. Thus, in the discussions that follow, the term "neonatal seizures" will generally encompass those events of epileptic origin. There are, however, a few exceptions that will be specified.

The definition of an electrographic seizure also becomes important. This will be discussed in detail later. In brief, it is an abnormal electrical ictal event consisting of evolving, rhythmic activity of at least 10 seconds' duration—with or without accompaniment of a clinical seizure.

Definitions of the age of the infant are also relevant, since they provide a measure of the degree of brain maturation. The neonatal period is defined as the first 4 weeks (28 days) of life. Legal age (LA) refers to the number of weeks the baby has been alive since birth. Estimated gestational age (EGA) refers to the duration of pregnancy prior to birth. The gestational age plus the chronologic age defines the age since conception or conceptional age (CA). The CA is a useful metric that benchmarks brain maturation, regardless of whether the infant was born prematurely or at term. Thus, the electroencephalogram (EEG) of 1-week-old (LA), 39 weeks EGA infants (CA of 40 weeks) should match that of a premature baby of EGA 34 weeks who is now 6 weeks old (LA).

Epidemiology

The neonatal period is one of greatest periods of seizure hazard during the human life span. The incidence of seizure occurrence is greatest in childhood,[77,182] especially in the first month of life. Reported incidence rates of neonatal seizures range from 1.5 to 5.5 per 1,000 neonates[10,51,147,148,153,172] depending on the study methodologies and the populations investigated. Most neonatal seizures first appear within the first week of life.[87] It has also been suggested that seizure incidence varies with specific risk factors such as birthweight, degree of illness, and possible etiology. Lanska et al.[87] reported "seizure" occurrence, based solely on clinical recognition, to be greatest in preterm or low-birth-weight infants compared with term infants. They reported an incidence of clinically

suspected seizures in all neonates to be 3.5 per 1,000, but 57.5 per 1,000 in very–low-birth-weight (<1,500 g) infants, 4.4 per 1,000 in low-birth-weight (1,500–2,499 g) infants, and 2.8 per 1,000 in normal-birth-weight (2,500–3,999 g) infants. Scher et al.[158,159] reported that seizures occurred in 3.9% of neonates of less than 30 weeks' conceptional age and 1.5% in neonates older than 30 weeks. Similarly, Kohelet et al.[82] found an overall incidence of seizures in a cohort of very–low-birth-weight infants to be 5.6 per 1,000. However, the incidence of 57.5 per 1,000 in very–low-birth-weight infants reported by Lanska et al.[87] may be skewed by the inclusion of nonepileptic clinical events in the very premature population studied.

The International League Against Epilepsy (ILAE) has used the terms "acute reactive" or "symptomatic" to describe the trigger of most neonatal seizures. The ILAE has also designated *unprovoked* neonatal epileptic syndromes: Benign neonatal convulsions, benign familial neonatal convulsions, early myoclonic encephalopathy (EME), and early epileptic encephalopathy (EIEE).[32,33,114,182] Acute reactive or symptomatic seizures are very frequent, whereas, in contrast, the occurrence of specific neonatal epileptic syndromes, as defined by ILAE, are rare.

Clinical Features

Ictal Features

Seizures in the neonate have clinical features that are unique compared with those occurring in older infants and children. Such features include: Fragmentation, disorganization, unusual patterns of spread, and simultaneous, but asynchronous multiple regions of involvement. Some of these differences are based on mechanisms of epileptogenesis and the state of early development in the immature brain. Other differences are based on the relative importance of nonepileptic mechanism of "seizures" generation in this age group. Some similarities also are noted between neonatal seizures and those of older infants and children. These include the types of movements that characterize the events, such as clonic, tonic, and myoclonic seizures.

A number of methods have been used to classify neonatal seizures: According to clinical features, the relation between clinical seizures and electrical seizure activity on the EEG, seizure pathophysiology, and epileptic syndromes. Each classification has some clinical utility, and each provides some further insight into the clinical problems of diagnosis and management.

Clinical Classification

Efforts over the years to characterize and classify neonatal seizures[49,94,117,150,152,156,189,190,196] demonstrate an evolution of thought and also underscore the importance of the ground-breaking work of French investigators reported over 40 years ago.[49] Early classification schemes focused on the differences between neonatal seizures and those of older children: Neonatal seizures were reported to be clonic or tonic, not tonic–clonic, and, when the seizures were focal, they were characterized as unifocal or multifocal. Later classifications included myoclonus.[150]

Early investigators also identified clinical events that had less of a traditional organization of motor activity, considered an important distinction between seizures of the neonate and older children.[49,111,152] These seizures were initially characterized as "anarchic"[49] and later as "subtle"[189] or "minimal."[94] These descriptions included events of oral-buccal-lingual movements such as sucking and chewing; movements of progression, such as bicycling of the legs and swimming movements of the arms; and random eye movements. Although these events were initially considered to be epileptic in origin, others later suggested that they were exaggerated reflex behaviors and referred to them as "brainstem release phenomena" or "motor automatisms."[117] Table 1 lists the clinical characteristics of neonatal seizures according to a current classification scheme.[118] This scheme can be applied through clinical observation of the neonate. The basic classification includes seizures characterized as: Focal clonic, focal tonic, myoclonic, spasms, generalized tonic, and motor automatisms (also referred to as "subtle seizures").

Paroxysmal changes related to the autonomic nervous system have also been reported to be manifestations of seizures. These events include alterations in heart rate, respiration, and blood pressure as well as flushing, salivation, and pupillary dilation.[53,58,98,196,197] Any of these findings occurring as isolated epileptic events are rare. When they do occur, they do so most consistently in association with other clinical manifestations of seizures.[117]

Classification According to Temporal Relation to Electrical Seizure Activity

Although the classification scheme just described is based on the clinical characteristics of the seizures, other codification schemes consider the temporal relation of clinical events to the occurrence of electrical seizure activity on EEG. An "electroclinical" seizure occurs when the clinical event overlaps in time with electrographic seizure activity. A seizure is referred to as "clinical only" when it occurs in the absence of any EEG seizure activity. A seizure is referred to as electrographic "only" if the electrical seizure occurs without any coincident clinical seizure activity.

Table 1 Clinical characteristics, classification, and presumed pathophysiology of neonatal seizures

Classification	Characterization
Focal clonic	Repetitive, rhythmic contractions of muscle groups of the limbs, face, or trunk

	May be unifocal or multifocal May occur synchronously or asynchronously in muscle groups on one side of the body May occur simultaneously, but asynchronously on both sides Cannot be suppressed by restraint or repositioning Pathophysiology: Epileptic
Focal tonic	Sustained posturing of single limbs Sustained asymmetric posturing of the trunk Sustained eye deviation Cannot be provoked by stimulation or suppressed by restraint Pathophysiology: Epileptic
Generalized tonic	Sustained symmetric posturing of limbs, trunk, and neck May be flexor, extensor, or mixed flexor/extensor May be provoked or intensified by stimulation May be suppressed by restraint or repositioning Presumed pathophysiology: Nonepileptic
Myoclonic	Random, single, rapid contractions of muscle groups of the limbs, face, or trunk Typically not repetitive, or may recur at a slow rate May be generalized, focal, or fragmentary May be provoked by stimulation Presumed pathophysiology: May be epileptic or nonepileptic
Spasms	May be flexor, extensor, or mixed flexor/extensor May occur in clusters Cannot be provoked by stimulation or suppressed by restraint Pathophysiology: Epileptic
Motor automatisms Ocular signs	Random and roving eye movements or nystagmus (distinct from tonic eye deviation) May be provoked or intensified by tactile stimulation Presumed pathophysiology: Nonepileptic
Oral-buccal-lingual movements	Sucking, chewing, tongue protrusions May be provoked or intensified by stimulation Presumed pathophysiology: Nonepileptic
Progression movements	Rowing or swimming movements Pedaling or bicycling movements of the legs May be provoked or intensified by stimulation May be suppressed by restraint or repositioning Presumed pathophysiology: Nonepileptic
Complex purposeless	Sudden arousal with transient increased random activity of limbs

movements	May be provoked or intensified by stimulation Presumed pathophysiology: Nonepileptic

From Mizrahi EM, Kellaway P. *Diagnosis and Management of Neonatal Seizures*. Philadelphia: Lippincott-Raven; 1998:181, with permission.

Classification According to Pathophysiology

Seizures may also be classified according to their pathophysiology: Epileptic or nonepileptic in character (Table 2). This was suggested by Mizrahi and Kellaway,[117] who reported their findings of neonates experiencing seizures during video-EEG monitoring. These authors classified neonatal seizures based on clinical characteristics, the relation between EEG and clinical events, and also on presumed pathophysiology. They suggested that a group of behaviors, previously referred to as "subtle" seizures, had features more consistent with reflex phenomena rather than epileptic seizures. They demonstrated that the paroxysmal clinical events in some could be provoked by tactile stimulation of the infant; that the intensity of the response could be proportional to the intensity of the stimulus (both in terms of intensity at a single site of stimulation or consistent intensity with increasing sites of stimulation); that the response could spread to regions of the body distant from the site of stimulation; and that the clinical events could be suppressed by restraint of the infant. These were considered features of reflex behaviors.

When the concept of nonepileptic seizures is discussed in the literature, the absence of electrical seizure during clinical seizure activity is strongly emphasized by some.[191] These discussions speculate that electrical seizure discharges can be generated in "deeper" cortical or even subcortical regions and thus may not be visible by conventional EEG recorded at the scalp surface. Data from human adults and mature animal studies are provided to support this concept. Although this possibility cannot be discounted in human neonates, there is no supportive evidence of its occurrence. In addition, ictal single photon emission computed tomography (SPECT) performed in neonates with "nonepileptic" events (brainstem release phenomenon) have failed to demonstrate the characteristic hyperperfusion hallmark of genuine epileptic seizures.[7] Finally, the lack of associated EEG seizure activity is not the only finding that suggests a nonepileptic pathophysiology; rather, the similarity of the events to the experimental models of reflex behaviors provides additional compelling data (Table 3).

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Seizures of Epileptic Origin

Current research reveals that some clinical seizures can be confidently classified as epileptic in origin based solely on their clinical characteristics. Some seizures may be confidently classified as "epileptic" in nature just by their clinical appearance. The clinical events that are most clearly epileptic in origin are: Focal clonic, focal tonic, some types of myoclonic seizures, and spasms (Tables 1 and 2). These seizure types can be recognized and characterized at the bedside by the visible features of the spontaneous event. In addition, during the event, the clinician can attempt to suppress the motor behavior by holding the affected limb; a continuation of rhythmic muscle contractions indicates the epileptic basis of the event. These seizures occur in close association with EEG seizure activity, and the clinical event cannot be provoked by stimulation nor suppressed by restraint of the infant. When EEG is utilized, seizures characterized as electrical-only seizures are also considered, by definition, epileptic in origin. Specific features of the developing brain enhance acute seizure initiation, maintenance, and propagation. Similar factors promote a greater predisposition to epileptogenesis, the development of long-term, postnatal epilepsy in the wake of acute, reactive neonatal seizures. These properties include enhanced cellular excitation, enhanced synaptic excitation, and a tendency to promote propagation of an epileptic discharge.[62,68,121,144,161,179]

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Table 2 Classification of neonatal seizures based on electroclinical findings

- Clinical seizures with a consistent electrocortical signature (pathophysiology: Epileptic)
  - Focal clonic
    - Unifocal
    - Multifocal
    - Hemiconvulsive
    - Axial
  - Focal tonic
    - Asymmetrical truncal posturing
    - Limb posturing
    - Sustained eye deviation
  - Myoclonic
    - Generalized
    - Focal
  - Spasms
    - Flexor
    - Extensor
    - Mixed extensor/flexor
- Clinical seizures without a consistent electrocortical signature (pathophysiology: Presumed nonepileptic)

  - Myoclonic
    - Generalized
    - Focal
    - Fragmentary
  - Generalized tonic
    - Flexor
    - Extensor
    - Mixed extensor/flexor
  - Motor automatisms
    - Oral-buccal-lingual movements
    - Ocular signs (aside from sustained eye deviation)
    - Progression movements
    - Complex purposeless movements
- Electrical seizures without clinical seizure activity

From Mizrahi EM, Kellaway P. *Diagnosis and Management of Neonatal Seizures*. Philadelphia: Lippincott-Raven; 1998:181, with permission.[118]

Seizures of Nonepileptic Origin

Other seizures are best considered as nonepileptic in origin.[77,117] Clinical events classified as nonepileptic in origin include some types of myoclonic events, generalized tonic posturing, and motor automatisms such as oral-buccal-lingual movements, movements of progression, and some ocular signs (Tables 1 and 2). These events occur in the absence of electrical seizure activity, but more importantly, have clinical characteristics similar to reflex behaviors. These clinical events can be provoked by stimulation of the infant. Both the provoked and spontaneous events can be suppressed by restraint or by repositioning the infant during the event. In addition, the clinical events may increase in intensity with the increase in the repetition rate of stimulation (temporal summation) or the sites of simultaneous stimulation (spatial summation).

Table 3 Reflex physiology demonstrated in animal models compared with generalized tonic seizures and motor automatisms (so-called nonepileptic) seizures in human neonates

Animal models	Neonates
Decortication	Cortical depression, obtundation, or coma EEG background depressed and undifferentiated or electrocerebral silence
Reflex movements	Spontaneous or elicited movements
Progression	Motor automatisms
Posturing	Tonic posturing
Response to stimulation	Response to stimulation
Temporal summation	Temporal summation
Spatial summation	Spatial summation
Irradiation of the response	Irradiation of the response
Response to restraint	Response to restraint
Arrest of behavior	Arrest of behavior

From Kellaway P, Mizrahi EM. Neonatal Seizures. In: Luders H, Lesser RP, eds. *Epilepsy: Electroclinical Syndromes*. New York: Springer-Verlag; 1987:13–47[78], based on data from Sherrington CS, Creed RS, Denny-Brown DE, et al. *Reflex Activity of the Spinal Cord*. London: Oxford, University Press, 1932[166]; Lindsley DB, Schreiner LH, Magoun HW. An electromyographic study of spasticity. *J Neurophysiol*. 1949;12:197–205[93]; Starzl TE, Taylor CW, Magoun HW. Collateral afferent excitation of reticular formation of the brain stem. *J Neurophysiol*. 1951;14:479–496[176]; and Sprague JM, Chambers WW. Control of posture by reticular formation and cerebellum in intact, anesthetized and unanesthetized and in decerebrated cat. *Am J Physiol*. 1954;176:52–64[173], with permission.

Syndromic Classification

Most neonatal seizures are classified as acute reactive or symptomatic by the ILAE.[3,33,182] They occur as a consequence of a specific external trigger, such as hypoxic ischemic encephalopathy.[120] However, four specific neonatal epileptic syndromes also are identified by the ILAE. Two are relatively innocuous: Benign neonatal convulsions and benign familial neonatal convulsions; two others are associated with poor outcomes: Early myoclonic encephalopathy[5] and early epileptic encephalopathy.[128] The syndromes of neonatal seizures are discussed in detail in the following sections. A discussion also is included concerning other disorders that may have a consistent constellation of findings that may also suggest syndromic classification, including epilepsy in focal cortical dysplasia in infancy.[97]

Interictal Feature

Neonates who have experienced seizures have no typical clinical features, except for those with specific epileptic syndromes as defined by ILAE (these will be discussed in detail later).

However, clinical interictal findings in individual infants are significant. The interictal state of consciousness will vary depending on the etiology of the seizures, from alert to comatose. Often, these clinical findings may suggest cause and prognosis. The state of alertness usually correlates with the EEG background activity. In addition, focal neurologic signs may suggest focal brain lesions. Dysmorphic features may suggest genetic or developmental etiologies.

Postictal Features

Clinical and electroencephalographic postictal features are also not consistent. Usually, few, if any, postictal changes are present, particularly in neonates with more benign etiologies. They enjoy a rapid return to their baseline clinical and electrographic state. Prolonged focal paralysis is unusual and, if present, should suggest a structural brain lesion. In addition, a prolonged altered state of conscious is also unusual following individual neonatal seizures. Infants with severe acute encephalopathies often have abnormal levels of tone, activity, and awareness before seizures with little noticeable change in the postictal state.

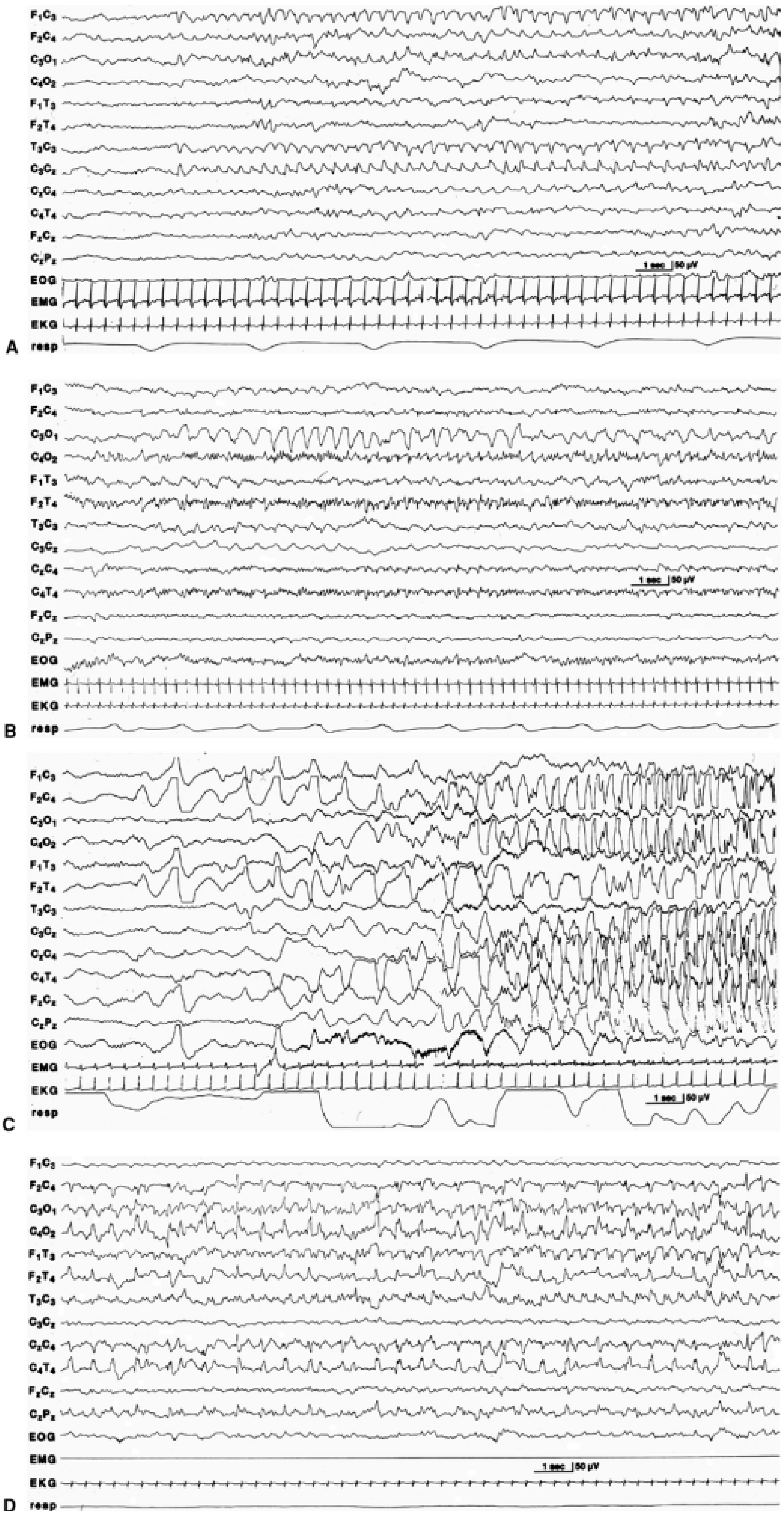
A
F1C3
F2C4
C3O1
C4O2
F1T3
F2T4
T3C3
C3Cz
CzC4
C4T4
FzCz
CzPz
EOG
EMG
EKG
resp
1 sec 50 μV
B
F1C3
F2C4
C3O1
C4O2
F1T3
F2T4
T3C3
C3Cz
CzC4
C4T4
FzCz
CzPz
EOG
EMG
EKG
resp
1 sec 50 μV
C
F1C3
F2C4
C3O1
C4O2
F1T3
F2T4
T3C3
C3Cz
CzC4
C4T4
FzCz
CzPz
EOG
EMG
EKG
resp
1 sec 50 μV
D
F1C3
F2C4
C3O1
C4O2
F1T3
F2T4
T3C3
C3Cz
CzC4
C4T4
FzCz
CzPz
EOG
EMG
EKG
resp
1 sec 50 μV

FIGURE 1. Electrical seizure activity may be varied in frequency, morphology, voltage, and onset. **A:** Rhythmic sharp waves in the left central region, remaining confined to that region (2-week-old, 40-week gestational age). **B:** Rhythmic sharp and slow wave activity in the left occipital region (6-day-old, 40-week gestational age). **C:** High-voltage, repetitive, slow, sharp waves arising in the right frontal region, later appearing as faster and sharper activity spreading to the right central region (3-day-old, 40-week gestational age). **D**: Initial rhythmic, moderate-voltage, sharp-wave activity arising in the right central-temporal region, which remains unchanged as another seizure arises independently from the left temporal region with a complex morphology (2-day old, 39-week gestational age). From Mizrahi EM, Kellaway P. *Diagnosis and Management of Neonatal Seizures*. Philadelphia: Lippincott-Raven: 1998:181, with permission.[118]

Electroencephalographic Findings

The EEG is the most important laboratory examination to assist in the diagnosis of neonatal seizures. However, its application differs in the neonate when compared with older children and adults.

Interictal Findings

Interictal Focal Abnormalities

Focal sharp waves may be present interictally in the neonatal EEG, but are not considered epileptiform. Some focal sharp waves are normal, developmentally determined findings, such as frontal sharp transients (*encoches frontales*) and temporal sharp waves that occur randomly, that are low or moderate in voltage, and are present in transitional or light sleep.[116] Focal sharp waves that are persistent, excessively numerous, high amplitude, present in wakefulness and sleep, and have complex morphology suggest focal injury. Multifocal sharp waves may suggest diffuse dysfunction, such as might occur in meningitis or hypoglycemia. Focal spikes may suggest focal injury, such as localized stroke, or may have uncertain diagnostic significance.[73] In the neonate, interictal focal sharp waves and spikes are not considered direct evidence or confirmation that an individual has had or will have electrographic seizures. A similar conundrum arises in some older infants and children. A small percentage of nonepileptic infants have an incidental finding of interictal spikes or sharp waves. In others, unmistakable seizures can arise from an interictal background that lacks identifiable spikes or sharp waves.

Interictal Background EEG

The degree of abnormality of the interictal background activity may provide information concerning the extent and type of CNS dysfunction associated with seizures. The nature of the interictal background activity may also suggest the risk individual infants have in experiencing a seizure.[88] Infants with initial normal background activity are less likely to eventually experience electrographic seizures than are those with persistent diffuse background abnormalities. In addition, the extent, degree, evolution, and rate of resolution (if any) of background EEG abnormalities can suggest prognosis. An EEG with normal background activity recording within the first 24 hours of life may suggest a good outcome,[72] whereas EEG background activity with abnormal features that persist or resolve slowly suggests a poorer outcome.[73]

Ictal Findings

Although not clearly defined, it appears that electrical seizure activity in neonates is rare before 34 to 35 weeks. As previously noted,[87] suspected clinical seizures are reported with great frequency in very-low-birth-weight infants, but few of these have confirmed simultaneous EEG ictal patterns. When electrical seizure activity is recorded, its manifestations on EEG can vary widely.[116,135,156] Frequency, voltage, and morphology of the seizure discharges may change within an individual seizure, between seizures in an individual infant, or among infants (Fig. 1). The minimum duration has been designated to be 10 seconds,[28] but the duration of seizure discharges varies widely. The electrical events are predominantly focal and well circumscribed. They frequently arise from the central or centrotemporal region of one hemisphere and less commonly in the occipital, frontal, or midline central regions (Fig. 1). Although seizures may arise focally and remain confined to that region, they may also spread to other regions (Fig. 2): As a gradual widening of the focal area, by an abrupt change from a small regional focus to involvement of the entire hemisphere (a finding that characterizes a hemiconvulsive seizure), or by migration of the electrical seizure from one area of a hemisphere to another or from one hemisphere to another.[118]

Unique Neonatal Ictal Patterns

Two ictal patterns are relatively unique to the neonatal period; both are typically associated with severe encephalopathies and their associated abnormal background EEG. *Seizure discharges of the depressed brain* are typically low in voltage, long in duration, and highly localized (Fig. 3).[77] They may be unifocal or multifocal and show little tendency to spread or modulate. They are typically not associated with clinical seizures, even in the untreated infant. Seizure discharges of the depressed brain occur when the EEG background is depressed and undifferentiated, and their presence suggests a poor prognosis.

α-Seizure activity is characterized by a sudden appearance of paroxysmal, rhythmic activity of the α frequency (8–12 Hz), typically in the temporal or central region.[80,197,199] This pattern may evolve from the more typical seizure discharges or may appear de novo. As with seizure discharges of the depressed brain, clinical events usually do not occur with α-seizure discharges. The presence of an α-seizure discharge usually indicates the presence of a severe encephalopathy and poor prognosis (Fig. 4). Electrical seizure activity that is persistently focal may be consistent with a focal lesion in the corresponding region,[97] for example focal cortical dysplasia (Fig. 5).

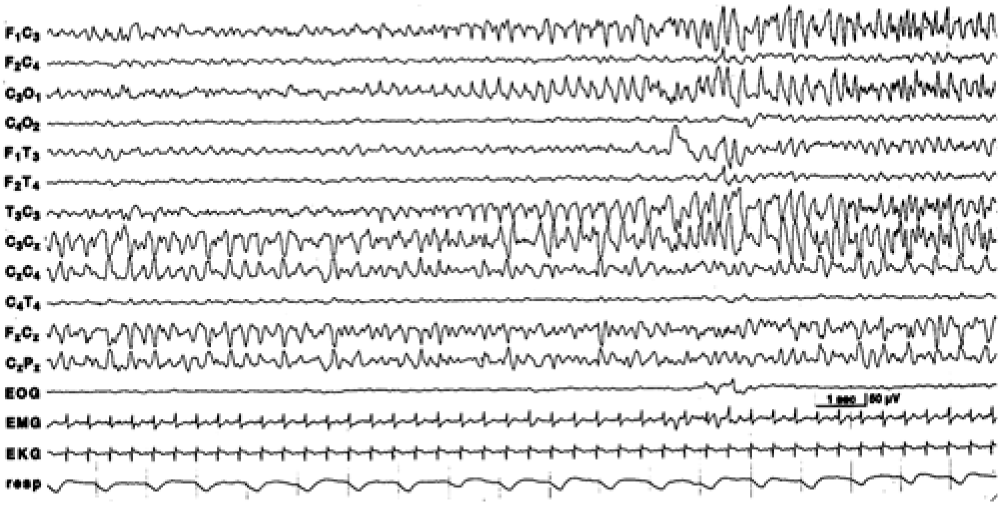

FIGURE 2. Migration of electrical seizure activity that begins in the midline region (CZ) and shifts to the left central region (C3) as the CZ region becomes less involved. This EEG was recorded from a 4-day-old, 40-week gestational age female infant with hypoxic–ischemic encephalopathy and suppression-burst EEG background. No clinical seizures were present during the electrical seizure activity. From Mizrahi EM, Kellaway P. *Diagnosis and Management of Neonatal Seizures*. Philadelphia: Lippincott-Raven: 1998:181, with permission.[118]

Video-EEG Monitoring

Video-EEG monitoring is a powerful tool in the diagnosis and management of neonatal seizures and initially had been the basis of clinical investigations that addressed seizure classification, therapy, and prognosis.[17,21,30,112,117] It is becoming increasingly more available at many centers for routine use, and is more widely employed in neonatal intensive care units.[27] However, its increasing popularity should not detract from the fact that attended EEG can provide important clinical information, when the recorded infant is observed by a trained electroneurodiagnostic technologist (ENDT) who can carefully observe an infant's behavior and characterize the events.

Computer-Assisted EEG Analysis of Neonatal Seizures

Computer-assisted analysis of EEG to detect and quantify electrical seizure activity has been utilized reliably in long-term EEG monitoring of older children and adults in epilepsy monitoring units. EEG seizure detection in neonates is more challenging because of variability of the electrographic events. More recently, such programs have been developed and may provide reliable data, particularly if the recordings are attended by a trained ENDT.[59,122] There has also been renewed interest in the use of cerebral function monitors (CFMs), such as amplitude integrated EEG (aEEG), to detect neonatal seizures.[63,162,185] This technique is limited in terms of its ability to provide data from all brain regions and its reliance on nonexpert health care professionals. A recent study reports that, using CFMs, up to 50% of neonatal seizures were misclassified or unrecognized.[146] However, advocates suggest that the ability to monitor specific brain regions for long periods may, in some ways, balance the limited localization capability of the technique.[44] Another recent study examined 851 electrographic neonatal seizures detected in 125 conventional, full-array EEG recordings. A one-channel EEG (C3 → C4) was digitally created to simulate the contemporary use of single-channel EEGs for seizure detection by CFMs.[165] Although 78% of the seizures were visible in the single-EEG channel, the seizures were briefer and lower in amplitude, and less than half were diagnosed by aEEG based on the C3 → C4 channel.

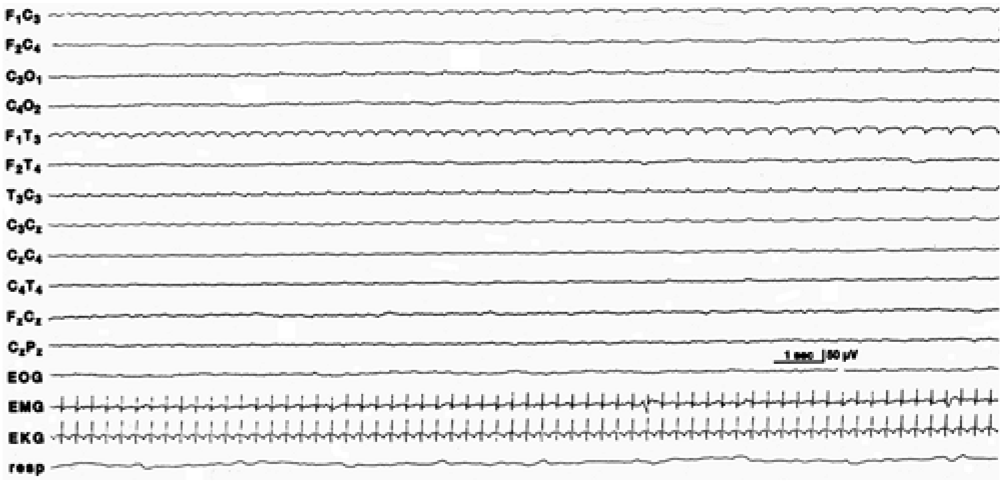

FIGURE 3. Seizure discharge of the depressed brain in the left temporal region occurring in the EEG of a 2-day-old, 38-week gestational age female infant with hypoxic–ischemic encephalopathy. The EEG background is depressed and undifferentiated. No clinical seizures ac-companied the electrical seizure activity. From Mizrahi EM, Kellaway P. *Diagnosis and Management of Neonatal Seizures*. Philadelphia: Lippincott-Raven: 1998:181, with permission.[118]

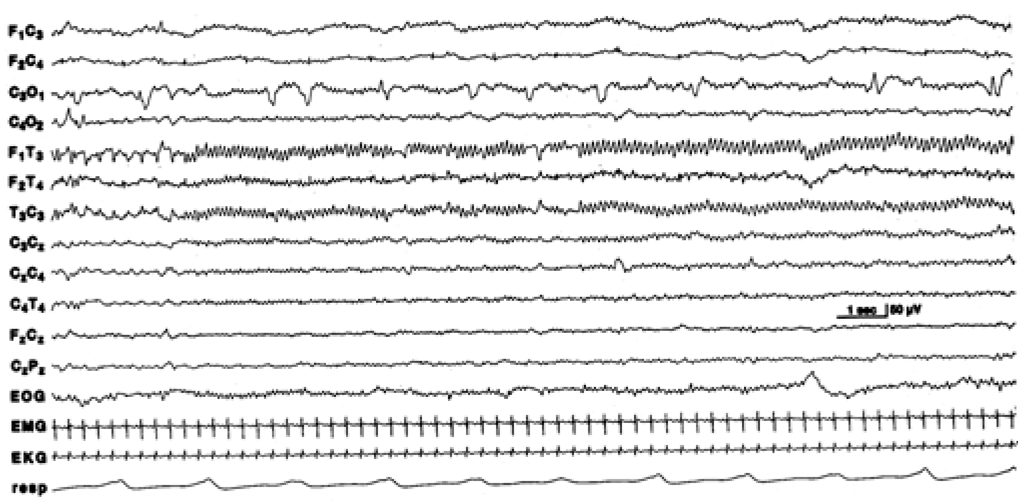

FIGURE 4. α-Seizure discharge in the left temporal region is characterized by sinusoidal 10- to 11-Hz rhythmic activity that evolved from rhythmic sharp-wave activity. There is also an independent, repetitive, slow, sharp transient in the left occipital region. The EEG background activity is depressed and undifferentiated. This EEG is recorded from a 4-week-old, 38-week gestational age male infant with pneumococcal meningitis. No clinical seizures occurred with these electrical seizure discharges. From Mizrahi EM, Kellaway P. *Diagnosis and Management of Neonatal Seizures*. Philadelphia: Lippincott-Raven: 1998:181, with permission.[118]

Diagnostic Considerations

Etiology

The occurrence of neonatal seizures indicates the presence of CNS disease and, in clinical practice, prompts a thorough evaluation for etiology and, if found, the institution of etiologic-specific therapy. A large number of potential causes exist for neonatal seizures. This, coupled with the susceptibility of the immature brain to injury may account for the high incidence of acute neonatal seizures and chronic postnatal epilepsy in this population. Although the list of potential etiologies is extensive,[118] most causes can be broadly categorized as hypoxia–ischemia, metabolic disturbances, CNS or systemic infections, and structural brain lesions. Table 4 lists the most frequently identified etiologies of neonatal seizures in the order of their relative occurrence.

Symptomatic Neonatal Seizures

The presence of hypoxic–ischemic encephalopathy (HIE) can be difficult to establish because diagnostic criteria have not been uniformly established or accepted. In addition, some proposed criteria have been so restrictive that infants with encephalopathy may not meet all of them but still carry the diagnosis of “suspected HIE.” In other proposed schemes, the criteria are too lenient and may not predict the occurrence of long-term neurologic sequelae.[123,134] The American College of Obstetricians and Gynecologists, in association with the American Academy of Pediatrics, have provided guidelines for HIE diagnosis.[34] At some centers, current practice is directed toward identification of measures of asphyxia that have predictive value in the occurrence of long-term sequelae.[137] This strategy has resulted in less restrictive criteria for HIE. Both approaches, however, include the tabulation of delivery room Apgar scores, blood gases, need for resuscitation, recognition of clinical aspects of encephalopathy including seizures, and confirmation of multisystem involvement. There is also an emerging discussion of the use of computer-assisted analysis of EEG, including aEEG, to aid in the staging of the severity of HIE,[163] although this is still considered investigational.

Metabolic disturbances ranging from electrolyte imbalances to inborn errors of metabolism may also be associated with neonatal seizures. This category of etiologies represents an important group of potentially treatable disorders and include hypocalcemia, hypomagnesemia, and hypoglycemia. Much less frequent is the finding of an inborn error of metabolism, such as an aminoaciduria, urea cycle defect, or organic aciduria. Other rare causes of medically refractory neonatal seizures that are potentially treatable include pyridoxine and biotinidase deficiency and others.

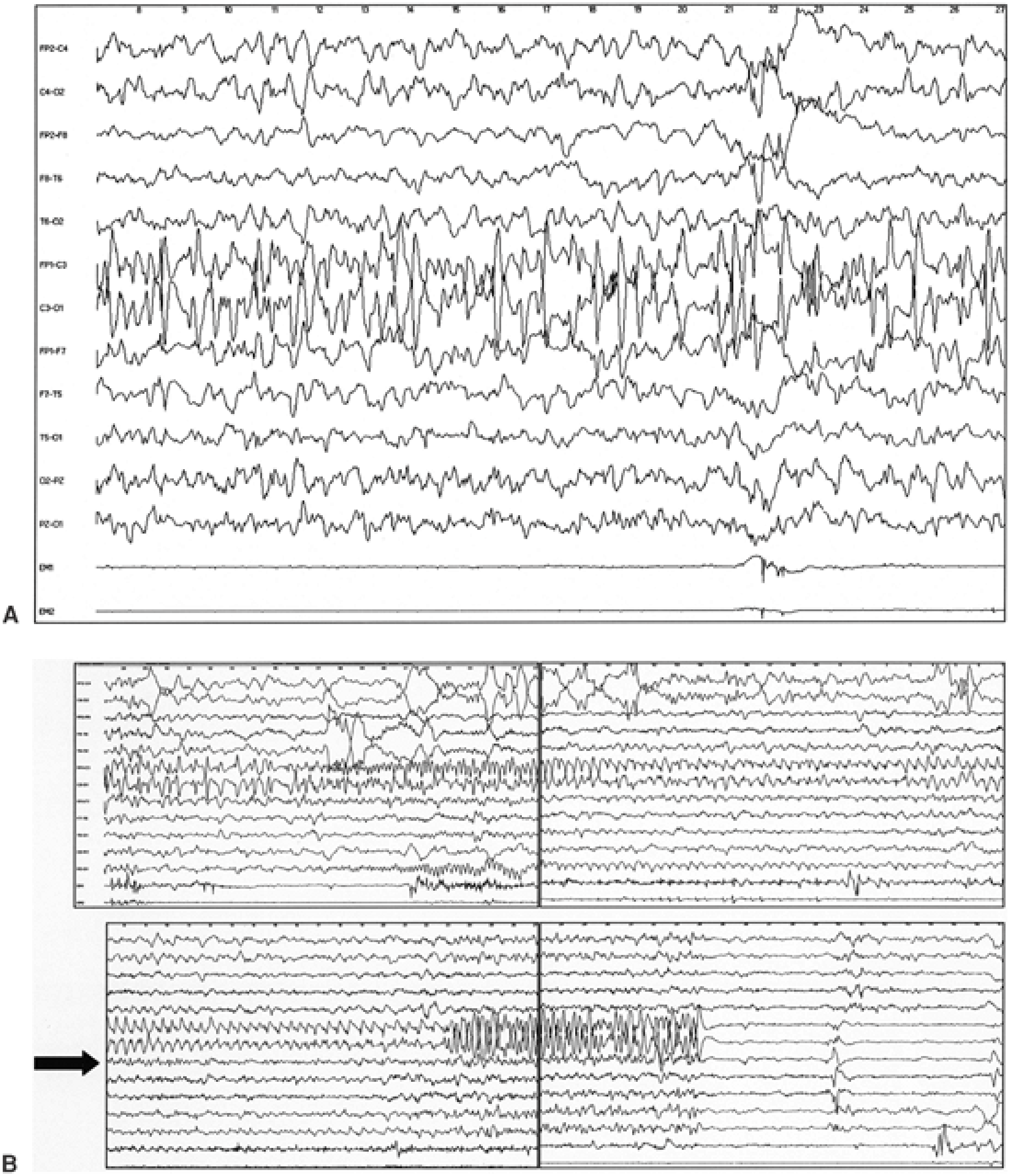

FIGURE 5. Interictal and ictal seizure activity associated with focal cortical dysplasia. **A:** Interictal high-voltage sharp waves are present in the left central region of this recording of a 1-month-old infant. **B:** Four sequential and continuous segments of the EEG from the same infant in **A** demonstrating, in the first panel, the transition from interictal to ictal seizure activity and then the evolution of the electrical seizure all confined to the left central region. (Note in this example post-ictal depression of the EEG occurs, a relatively unusual finding in neonatal seizures). From Lortie A, Plouin P, Chiron C, et al. *Epilepsy Res*. 2002;51(1–2):133–145, with permission.[97]

Both bacterial and viral agents can be causes of CNS infection in the neonate that are associated with seizures, to the extent that almost all neonates with new-onset seizures are investigated for such infection. Some viral infections, such as herpes simplex encephalitis, may be treated empirically at clinical presentation prior to confirmation of the diagnosis. In addition, prenatal *t*oxoplasmosis, *o*ther agents, *r*ubella, *c*ytomegalovirus, *h*erpes simplex (TORCH) infections can be risk factors for neonatal seizures.

Structural brain conditions associated with neonatal seizures include acquired conditions such as stroke or hemorrhage and developmental anomalies of the brain. Congenital brain malformations may range from highly localized focal dysplasias to catastrophic defects such as holoprosencephaly. Some malformations, such as lissencephaly, are associated with specific genetic disorders.

Special circumstances also arise in which neonates may be at risk for seizures, providing opportunities for increased surveillance and development of preventative therapies. Clancy et al.[30] prospectively studied neonates undergoing cardiac surgery that required deep hypothermic circulatory arrest. They found that 19% of all infants with nonhypoplastic left heart syndrome experienced a postoperative acute neurologic event, including seizures and coma.

Table 4 Most frequently occurring etiologies of neonatal seizures

- Hypoxia–ischemia
- Intracranial hemorrhage
  - Intracerebral
  - Intraventricular
  - Subarachnoid
  - Subdural
- Infection—CNS
  - Encephalitis
  - Intrauterine
  - Meningitis
- Infarction
- Metabolic
  - Hypocalcemia
  - Hypoglycemia
  - Hypomagnesemia
- Chromosomal anomalies
- Congenital abnormalities of the brain
- Neurodegenerative disorders
- Inborn errors of metabolism
- Benign neonatal convulsions
- Benign familial neonatal convulsions
- Drug withdrawal or intoxication

Main categories are listed in relative order of frequency (subcategories listed alphabetically). Not listed is “unknown” etiology, which is encountered in approximately 10% of cases (although some in this category may be benign neonatal convulsions). From Mizrahi EM, Kellaway P. *Diagnosis and Management of Neonatal Seizures*. Philadelphia: Lippincott-Raven; 1998:181, with permission.[118]

Prognosis

In clinical practice, the long-term outcome of neonates with seizures is predominantly determined by the etiology underlying seizure onset. However, two other specific issues frequently arise in discussion of prognosis: The possibility that the seizures themselves contribute harm to the developing brain, and the possibility that AED administration may adversely affect the neonate.

Adverse Effects of Seizures on the Developing Brain

For many years, it was believed that, even though the immature brain was more likely to develop seizures in response to injury than was the more mature brain, the immature brain was either more resistant to seizure-induced injury or that any seizure-related alterations were either transient or not clinically significant. However, emerging evidence suggests that seizures in early life result in permanent anatomic and functional

alterations and enhanced epileptogenicity. However, a full understanding of the mechanisms of these seizure-induced dysfunctions has not been clearly delineated.[69,71,180,192,195]

A number of mechanisms of seizure-induced injury have been investigated. Seizures may cause direct neuronal injury through the sustained release of glutamate receptors,[170] even though this type of injury is age-dependent, with the immature brain less vulnerable than the mature one.[175,184] Although the otherwise healthy immature brain may be relatively resistant to glutamatergic excitotoxicity, seizures may cause a greater degree of neuronal damage in previously immature abnormal brains, thus raising the possibility that a recurrence of seizures after neonatal seizures may be associated with cell death. This so-called “double-hit” clinical scenario may be common in neonates.

It has also been hypothesized that seizures in the immature brain impair subsequent brain growth. Experimental data suggest that prolonged seizures may uncouple energy production and utilization; decreased energy supply eventually depletes energy stores which, in turn, inhibits DNA and protein synthesis and dissociates polysomes. However, these findings appear transiently and are followed by a period of “catch-up” brain growth.[75,99,108,194]

Seizures may have an adverse effect on the structure and function of the hippocampus, resulting in an increased susceptibility to seizures and perhaps, chronic epilepsy.[22,23] It has been hypothesized that, in mature animals, hippocampal damage caused by seizures is manifested by synaptic reorganization and selective cell death through a number of proposed mechanisms including: (a) the “sprouting” hypothesis, (b) seizure-induced cell death, (c) aberrant growth of axons and reorganization of excitatory synapses,[178] and (d) the “dormant interneuron” hypothesis, based on the suggestion that seizures lead to dysfunction of γ-aminobutyric acid (GABA)-containing cells, rendering them nonfunctional or dormant, and thus contribute to a state of decreased inhibition.[169] All these effects may be age-dependent, with the immature brain more resistant than the mature brain. In addition, seizures in the immature brain may alter synaptic connectivity during brain development, alter the morphology of individual pyramidal cells, and alter ion channel subunit composition. Collectively, these disturbances promote hyperexcitability.[35,106,180,183]

Epileptic activity may adversely impact the immature brain and the subsequent development of CNS networks and pathways. To achieve precise patterns of connections within the normal mature brain, axons typically grow toward an established synaptic contact with their appropriate target; this is achieved first by the establishment of a relatively imprecise projection pattern, followed by a process of “fine-tuning.” This depends on normal electrical patterns of neuronal activity.[79,161,164] Grigoinis and Murphy[61] investigated the effect, in immature animals, of epileptic activity on the visual system, including occipital cortex and associated corpus callosal projections. Epileptic activity in the occipital cortex early in life stabilized immature projections that were normally eliminated during development, suggesting that epileptic-induced maintenance of such immature projections in the eventually mature brain may interfere with normal cortical functions later in life. Thus, seizures may create artificial functional pathways that interfere with the intended and necessary pruning of neuronal networks.

Recent findings indicate that seizures in immature animals do not, in the immediate post-seizure period, result in significant alterations of learning, memory, or activity levels. However, when animals who had been exposed to seizures early in life were compared with those exposed when mature, the immature animals demonstrated impairments and alterations in learning and behavior.[70,72,124,171,174] Adverse effects of seizures are more apparent when animals exposed to prolonged seizures early in life are then exposed to seizures when mature.[81,155] Lado et al.[85] suggest that subtle age-specific changes are present following the initial bout of prolonged seizures, but manifestations of actual symptomatic damage and behavioral effects required a second insult for expression. Holmes et al.[68,69] note that prolonged seizures in immature animals result in minimal behavioral consequences when the animals are studied later in life and are associated with minimal morphologic changes. However, in describing the "two-hit" hypothesis, they report that early-onset seizures result in changes in the brain that make it more vulnerable to the development of cognitive impairment when animals are exposed to post-neonatal seizures.

Table 5 Outcome at 24 months of Term and Near-term Neonate with Seizures

Study population	
Number enrolled	207
Number of survivors	149
Number of survivors evaluated at 24 months	127 (84.7%)
Outcome	**Percent**
Death	28.0
Abnormal neurologic examination*	42.7
MDI <80*	55.2
PDI <80	49.6
Post-neonatal epilepsy**	26.0

From Mizrahi EM, Clancy RR, Dunn JK, et al. Neurologic impairment, developmental delay and postnatal seizures 2 years after EEG-video documented seizures in near-term and term neonates: Report of the clinical research centers for neonatal seizures. *Epilepsia*. 2001;42:102, with permission.[115]
*Outcome for survivors 2 years following neonatal seizures: Standard neurologic examination, Bayley Developmental Assessment of Mental Development Index (MDI), and Psychomotor Developmental Index (PDI).

Clinical Considerations in Prognosis

The outcome of infants with neonatal seizures has been assessed in terms of survival, neurologic disability, developmental delay, and post-neonatal epilepsy. Ortibus et al.[130] reported that 28% of those with neonatal seizures died, 22% of survivors were neurologically normal at an average of 17 months of age, 14% had mild abnormalities, and 36% had severe abnormalities. In a prospective study of full-term infants 2 years following neonatal seizures, Mizrahi et al.[115*] found that 28% died; in survivors, 42.7% had abnormal neurologic examinations, 55.2% had a Bayley Developmental Assessment of Mental Development Index score of less than 80, 49.6% had a Bayley Developmental Assessment of Psychomotor Developmental Index score of less than 80, and 26% had post-neonatal epilepsy[115*] (Table 5). Brunquell et al.[19] found that 30% of those with neonatal seizures died and 59% of survivors had abnormal neurologic examinations, 40% were mentally retarded, 43% had cerebral palsy, and 21% had post-neonatal epilepsy when

followed up to a mean of 3.5 years. Most recently, Tekgul et al.[181] found that 7% of neonates who had experienced seizures died and, of the survivors, 28% had a poor outcome.

Ellenberg et al.[50] studied post-neonatal epilepsy in more detail. They found that approximately 20% of those who survived neonatal seizures experienced one or more seizures within 7 years of age, and that nearly two-thirds occurred within the first 6 months of life. Similar rates were found by Scher et al.[158] (17%–30%), Ortibus et al.[130] (28%), Bye et al.[21] (21%), Mizrahi et al.[115] (26%), Brunquell et al.[19] (21%), and, most recently, Da Silva et al.[37] (22% at 12-month follow-up and 33.8% within 48 months). Clancy and Legido[29] found a much higher rate of post-neonatal epilepsy. However, entry into this study required that at least one EEG seizure be captured on a brief, routine EEG examination. It is thus likely that many of these patients actually had numerous seizures or status epilepticus, which is known to further increase the rate of subsequent epilepsy. Seizure types that characterize post-neonatal epilepsy include both partial and generalized. Watanabe et al.[198] considered in detail a selected population of infants with neonatal seizures that persisted beyond the neonatal period and that could be classified as epilepsy of neonatal onset. For most of those infants with severe encephalopathy syndromes such as EIEE and EME, their initial epileptic syndrome evolved to West syndrome, with a fewer number evolving to symptomatic localization-related epilepsy.

The management of neonatal seizures includes accurate diagnosis, expeditious determination of etiology, rapid administration of etiologic-specific therapy, and successful AED treatment. The goal is to improve long-term outcome and prevent adverse sequelae. However, it is not clear which of these management components is critical to achieving the goal of maximizing outcome. It may appear that seizure duration may influence outcome, because infants who experience brief and infrequent seizures may have relatively good long-term outcomes, whereas those with prolonged seizures may not do as well. However, easily controlled seizures or self-limited seizures may be the result of transient, or more benign CNS disorders, whereas medically refractory neonatal seizures may be the result of more sustained, refractory, or more severe brain disorders. Recently, McBride et al.[105] demonstrated that a relation exists in infants with perinatal asphyxia between a greater amount of EEG seizure activity and subsequent relative increased mortality and morbidity. Other investigators, utilizing proton magnetic resonance spectroscopy in neonates, found an association between scores of seizure severity and impaired cerebral metabolism measured by lactate/choline and compromised neuronal integrity measured by *N*-acetylaspartate/choline. These investigators suggested this as evidence of brain injury not limited to structural damage detected by magnetic resonance imaging (MRI).[110]

Table 6 Prognosis of neonatal seizures according to neurologic disorder

Neurologic disorder	Normal development (%)(a)
Hypoxic–ischemic encephalopathy	50
Intraventricular hemorrhage (b)	10
Primary subarachnoid hemorrhage	90

Hypocalcemia	
Early onset	50(c)
Late onset	100
Hypoglycemia	50
Bacterial meningitis	50
Developmental brain defect	0

Prognosis is for those with the stated neurologic disease when seizures manifest (thus, value usually differs from overall prognosis).
(a) Values are rounded to the nearly 5%.
(b) Usually severe intraventricular hemorrhage associated with major periventricular hemorrhagic infarction.
(c) Represents primarily the prognosis of complicating illness; prognosis approaches that of later onset hypocalcemia if no or only minor neurologic illness present.
From Volpe JJ. Neurology of the Newborn. In: *Neonatal Seizures*.
Philadelphia: WB Saunders, 2001, with permission.[191]

However, it is currently thought that the dominant variable that predicts neurodevelopmental outcome may be the underlying cause of the seizures, rather than the presence, duration, or degree of brain involvement of the seizures themselves. Mizrahi and Kellaway[118] analyzed a number of clinical studies indicating that normal outcomes occurred with increasing frequency in association with the following etiologies: HIE, infection, hemorrhage, hypoglycemia, and hypocalcemia.[10,78,95,103,107,150] In discussing prognosis, Volpe[191] emphasized gestational age and etiology on outcome (Table 6). Mortality increases with the greater degree of prematurity, and specific etiologies are associated with varying degrees of developmental delay. Most recently, Tekgul et al.[181] suggested that seizure etiology and background EEG patterns remain powerful prognostic factors.

It has been suggested that clinical seizure type may also predict outcome,[117] although this too may reflect etiology or the degree of associated brain dysfunction at the onset of seizures. Focal clonic and focal tonic seizures were associated with a relatively good outcome primarily because these seizure types are typically associated with relatively confined, nondiffuse brain injury and significantly spared CNS function. Generalized tonic posturing and motor automatisms were associated with a poor outcome because they are associated with diffuse CNS dysfunction. Recently Brunquell et al.[19] demonstrated similar findings in long-term studies.

Multivariant analyses factors that were considered as predictors of outcome have included features of the interictal EEG from one or serial recordings, the ictal EEG, the neurologic examination at the time of seizures, the character or duration of the seizures, etiology, findings on neuroimaging, conceptional age, and birth weight. Multiple, rather than single factors, appear to be most accurate in predicting outcome. For example, Ortibus et al.[130] found that the predicted outcome is less reliable when based solely on EEG variables from a single recording obtained at seizure onset than when based on a combination of imaging findings and clinical and EEG data. Pisani et al.[139] also considered several different independent variables and found the character of the EEG background activity predictive of developmental outcome. However, in these studies, all variables related to a single factor: The degree of brain injury at the time of seizure occurrence, and this, in turn, related to etiology.

Differential Diagnosis

The differential diagnosis of generic clinical "seizures" is diverse and ranges from normal movements to abnormal, but nonseizure, activity. Normal movements of neonates may at times appear "paroxysmal," such as abrupt stretching of the extremities or trunk, squirming, sucking, and sudden jerking movements, which may occur during sleep. Infants may also experience spasmodic coughing and hiccups. Jitteriness and tremor may also occur in normal infants, although they may also be present in abnormal newborns. Unforeseen changes in the parameters of autonomic dysfunction such as heart rate, respirations, and blood pressure have been described as features of neonatal seizures. However, more often these changes are nonseizure in origin —physiologic changes that can be present in normal neonates or abnormalities related to the systems themselves. Some abnormal, nonseizure movements may be age-dependent. For example, the extreme premature infant may experience random, erratic movements resembling fragmentary myoclonus. The clinical significance of these movements is not clear.

Specific Very–Early-Onset Epilepsy Syndromes

Epileptic seizure syndromes are characterized by recognizable constellations of clinical signs, symptoms, and laboratory findings. These features include seizure type, age of onset, etiology, anatomy (including neuroimaging findings), precipitating factors, severity, ictal and interictal EEG, duration of the seizure disorder, associated clinical features, chronicity, diurnal and circadian cycling, response to AEDs, and prognosis.[48] In its Classification of Epilepsies and Epileptic Syndromes, the ILAE has designated only a few syndromes in the neonatal period,[33,200] although their recognition in clinical practice is important. These syndromes are benign neonatal convulsions, benign neonatal familial convulsions, early myoclonic encephalopathy and early infantile epileptic encephalopathy. These have been reviewed by Mizrahi and Clancy.[114] The first two are associated with a relatively good prognosis, whereas the others suggest a poor outcome and have been included among the catastrophic pediatric epilepsy syndromes.[86]

Benign Neonatal Convulsions

The syndrome of benign neonatal convulsions has also been referred to as "benign idiopathic neonatal convulsions," because of the lack of an identifiable etiology,[140] and "fifth day fits," because of their timing of onset.[41] This syndrome is characterized by focal clonic seizures or, rarely, focal tonic seizures in an otherwise normal neonate. There is no family history of neonatal seizures. Infants are typically full term with a history of an uncomplicated, normal pregnancy, labor, and delivery. Seizures usually occur between the fourth and sixth day of life and are typically brief (1 to 3 minutes) although, rarely, the seizures can be prolonged. The seizure disorder is self-limited in that seizures may recur during a 24- to 48-hour period after onset, although, rarely, seizure disorder can also be prolonged. The clinical seizures are usually unifocal clonic and may be associated with apnea. The infants are neurologically normal prior to, between, and after the occurrence of seizures.[141] A critical feature for diagnosis is that no etiology for the seizures can be identified. In the past, this disorder has been associated with a finding of rotavirus in stool but not in cerebrospinal fluid (CSF)[65] and with acute zinc deficiency in CSF.[57] These findings are now considered of doubtful etiologic relevance. The ictal EEG is characterized by focal, rhythmic, recurrent sharp wave or spike activity that is closely correlated with the clinical seizures. The background EEG is typically normal, although it has also been reported that, in up to 60% of neonates with this syndrome, the interictal EEG pattern referred to as *θ pointu alternant* may be present.[141] This is characterized as a discontinuous nonreactive background with rhythmic (4 to 7 Hz) θ-wave activity within the bursts, which may be mixed with sharp waves that alternate between hemispheres. More recently, this pattern has not been considered diagnostic for this disorder.[143] Although the clinical seizures may spontaneously resolve within a short period, it has been reported that the θ pointu alternant EEG pattern may persist for up to 2 weeks.

This syndrome is a diagnosis of exclusion, because the initial clinical presentation may resemble that of infants with symptomatic focal clonic seizures. Thus, a thorough evaluation for an etiology is conducted to identify a potentially treatable cause of seizures, even though the diagnosis of benign neonatal convulsions may be considered at the onset. Plouin[141,142,143] has proposed the following diagnostic criteria for the disorder: Normal pregnancy and delivery, full-term gestation, appropriate for gestational age birth weight, Apgar score greater than 7 at 1 minute, typical interval between birth and seizure onset (4–6 days), normal neurologic examination before seizures and interictally, normal laboratory findings (including, but not limited to metabolic studies, neuroimaging, and lumbar puncture), and no family history of either neonatal seizures or post-neonatal epilepsy.

Treatment for this disorder is controversial. Most frequently, the seizures are treated with phenobarbital. However, because the seizures tend to be brief and infrequent, it can also be argued that AED therapy may not be needed. If AEDs are used, they are typically discontinued once the seizures subside.

The prognosis for infants with benign neonatal convulsions is considered to be generally good.[142,143] However, one group of investigators has found transient psychomotor delays in infants[41]; another found neurodevelopmental deficits at 2 years of age in 50% of those with this syndrome, and the incidence of post-neonatal epilepsy—0.5% of patients—is slightly higher than in the population of those without neonatal seizures.[142,143]

Benign Neonatal Familial Convulsions

This syndrome is characterized by early-onset focal clonic or focal tonic seizures in a neonate with a family history of neonatal seizures and with no other neurologic findings.[20,66,138] There is an autosomal dominant pattern of inheritance with incomplete penetrance,[36] with two known chromosomal loci: One on chromosome 20q13[89,90] and one on chromosome 8q.[92,151,177] All the families with benign neonatal familial convulsions provide sufficient data for linkage to chromosome 20q; only one family has provided data for linkage to chromosome 8q. Recently, the genes for this disorder have been identified. These are potassium channel genes, referred to as *KCNQ2* for the chromosome 20q gene[11,25,168] and *KCNQ3* for the chromosome 8q gene.[177] It has been suggested that the KCNQ2/3 channels might be the molecular basis of the M-current, a slowly activating and deactivating potassium conductance channel that may play a critical role in determining the subthreshold electrical excitability of neurons.[11,193] Only a slight loss of channel activity will lead to neuronal hyperexcitability and resultant seizures.[193] A novel mutation in *KCNQ2* has been reported that is associated with the diagnosis of benign neonatal familial convulsions, but also with drug-resistant epilepsy and mental retardation.[14]

The clinical seizures are best characterized as focal clonic or focal tonic. Seizure onset is between the first few days and 1 week of life,[145] although there have been reports of onset as late as the second month of life. The various ages of onset may be developmentally determined, because infants who are born prematurely with this disorder will have seizure onset at an older chronologic age than will infants born at term. The seizures may be brief, but can recur up to 2 to 3 months of age, when they will remit spontaneously. The interictal EEG is typically normal, although θ pointu alternans pattern has also been reported to occur in these infants. Although the outcome is generally good, there is a higher incidence of post-neonatal seizures in affected infants later in life, ranging from 11% to 16%.[141,149] It has been reported that phenobarbital therapy is successful, although some investigators use valproate as an alternative.[142,143]

Early Myoclonic Encephalopathy

Early myoclonic encephalopathy is a relatively rare syndrome characterized by the onset of erratic, fragmentary myoclonus in the first month of life and with the eventual development of both focal seizures (originally described as partial motor seizure) and infantile spasms.[1,4,5] The associated EEG is characterized as a periodic, suppression-burst pattern.[102] This syndrome has also been referred to as neonatal myoclonic encephalopathy,[187] myoclonic encephalopathy with neonatal onset,[24] neonatal epileptic encephalopathy with periodic EEG bursts,[104] and early epileptic encephalopathy.[39,40]

Aicardi[1,4] reviewed in detail the clinical expression of the ictal events in 39 cases. These seizure types included fragmentary or partial erratic myoclonus; massive (or generalized) myoclonus, simple partial (or focal) seizures; and infantile spasms with a sustained tonic component. These clinical events were not all present at onset of the disorder. Typically, the erratic myoclonus appeared first, sometimes within the first few hours of life. Myoclonic movements could involve very circumscribed regions of the limbs or face; they are typically repetitive or virtually continuous, shift persistently from one body region to another in an anarchic and asynchronous manner, and may persist in sleep. Either with the onset of erratic myoclonus or shortly thereafter, generalized myoclonus and partial seizures may develop. The generalized myoclonus may involve all extremities synchronously and bilaterally, or may involve axial musculature. The partial seizures have been reported to consist of deviation of the eyes associated with limb or face clonic activity, or autonomic phenomena such as flushing or apnea. Although the appearance of general myoclonus and partial seizures may occur early with, or shortly after, the onset of erratic myoclonus, infantile spasms typically develop later in the course of the disorder, usually between 3 and 4 months of age.

The EEG is characteristic and considered an essential criteria for the diagnosis of this syndrome. The background activity is a suppression-burst pattern. The bursts occur periodically and are characterized by generalized and multifocal, high-voltage spikes and sharp and slow wave complexes (Fig. 3). (There are other disorders in which suppression-burst may be present; thus this finding alone is not diagnostic of early myoclonic encephalopathy.) The pattern usually persists during wakefulness and sleep. There is typically no specific EEG correlate to the fragmentary or erratic myoclonus, except that the myoclonus usually occurs during the burst periods of the EEG. When partial seizures occur, their EEG correlate is no different from other infants with focal seizures. When infantile spasms occur, they may eventually be associated with high-voltage, slow, sharp transients and/or episodes of generalized voltage attenuation. Over time, the suppression-burst pattern may take on features that may allow it to be characterized as atypical or modified hypsarrhythmia.

Aicardi[1,3] notes that the neurologic status of infants with early myoclonic encephalopathy is always abnormal either at birth or at the onset of clinical seizures. Most often, the infants are hypotonic and poorly responsive; this latter feature is consistent with the clinical diagnosis of an encephalopathy. This early onset of abnormal neurologic status makes further neurologic deterioration difficult to assess.

When the syndrome is encountered, a metabolic etiology is most often given initial consideration as an etiology, including nonketotic hyperglycinemia, propionic acidemia, D-glyceric acidemia, and methylmalonic acidemia.[18,38,60,96,188]

Therapy is typically symptomatic, directed toward the specific inborn error of metabolism, if present. AEDs or hormonal therapy typically utilized for infantile spasms are often tried, with little success.

The outcome for infants with early myoclonic encephalopathy has been consistently reported as poor. There is a high incidence of death within the first few years of life. Some survivors have been reported to remain in a vegetative state, and others show significant developmental delay. As noted, there is some debate concerning the course of neurologic impairment. Some suggest that there is a gradual deterioration or arrest of development with onset of the disorder,[39,40] whereas others suggest that, because of the severity of impairment at onset, subsequent development cannot be quantified.[1,4,5]

There has been an ongoing discussion concerning the relationship of early myoclonic encephalopathy and the syndrome of early infantile epileptic encephalopathy, described by Ohtahara et al.[4,126,127] and discussed below. Kellaway et al.[73] suggested that these syndromes represented a continuum of a single disorder. Aicardi[1] indicated that the two syndromes "have too many points in common to assume that they are completely different syndromes, and they may, at least in some cases, simply be two different aspects of a single basic process." However, others suggest that these represent two distinct syndromes.[128,160] The syndromes are compared in Table 7.

Table 7 Comparison* of early myoclonic encephalopathy (EME) and early infantile epileptic encephalopathy (EIEE)

	EME	EIEE
Age of onset	Neonatal period	Within first 3 months

Neurologic status at onset	Abnormal at birth or at seizure onset	Always abnormal even prior to seizure onset
Characteristic seizure type	Erratic or fragmentary myoclonus	Tonic spasm
Additional seizure types	Massive myoclonus, simple partial seizures, infantile spasms (tonic)	Focal motor seizures hemiconvulsions, Generalized seizures
Background EEG	Suppression-burst	Suppression-burst
Etiology	Cryptogenic, inborn errors of metabolism, familial	Cerebral dysgenesis, anoxia, cryptogenic
Natural course	Progressive impairment	Static impairment
Incidence of death	Very high, occurring in infancy	High, occurring in infancy, childhood, or adolescence
Status of survivors	Vegetative state	Severe mental retardation, quadriplegia, and bedridden
Long-term seizure evolution	Infantile spasms	West syndrome, Lennox-Gastaut syndrome

Based on data from Aicardi J. Early Myoclonic Encephalopathy (Neonatal Myoclonic Encephalopathy). In: Roger J, Bureau M, Dravet C, et al., eds. *Epileptic Syndromes in Infancy, Childhood and Adolescence*, 2nd ed. London: John Libbey; 1992:13[1]; Aicardi J. Overview: Neonatal Syndromes. In: Engel J Jr, Pedley TA, eds. *Epilepsy: A Comprehensive Textbook*. Philadelphia: Lippincott-Raven; 1997:2243[3]; and Ohtahara S, Ohtsuka Y, Yamatogi Y, et al. Early-Infantile Epileptic Encephalopathy with Suppression-Bursts. In: Roger J, Bureau M, Dravet CH, et al., eds. *Epileptic Syndromes in Infancy, Childhood and Adolescence*, 2nd ed. London: John Libbey;1992:25.[128] Reprinted from Mizrahi EM, Clancy RR. Neonatal seizures: Early-onset seizure syndromes and their consequences for development. *Ment Retard Dev Dis Res Rev*. 6;2000:229–241, with permission.[114]

Early Infantile Epileptic Encephalopathy

Cases of early infantile epileptic encephalopathy were first reported by Ohtahara et al., with additional cases reported by that group beginning a short time later.[125,126,127,128] In addition, they proposed that the syndrome of early infantile epileptic encephalopathy represents one of three so-called “age-dependent epilepsy encephalopathy syndromes,” which also included West syndrome and Lennox-Gastaut syndrome.[125,128,129,202] The characteristics of early infantile epileptic encephalopathy include onset in early infancy (neonatal period through the first few months of life), tonic spasms (brief tonic seizures) as the predominant seizure type, suppression-burst EEG background, severe psychomotor retardation, medically intractable seizures, poor prognosis, no single etiology characteristic for the disorder, and evolution to West syndrome (i.e., infantile spasms, retardation, hypsarrhythmia on EEG).[4,128,129]

The predominant seizure type is described as a tonic spasm. These are brief episodes of limb and axial stiffening, with each event lasting longer than a general myoclonic event, but shorter than a typical tonic seizure. Tonic spasms may occur in clusters, but in some may be solitary events. In most patients, they occur during wakefulness or sleep, and their daily frequency may be very high. In addition to tonic spasms, about a third also experience other seizure types including focal motor seizures, hemiconvulsions, alternating hemiconvulsions, and generalized seizures.

As previously noted, the EEG is also characterized by a suppression-burst pattern that is not modulated by wake–sleep cycles. This distinguishes its pattern from other hypsarrhythmic EEG variants that feature suppression burst. During a clinical spasm, the EEG is characterized by generalized voltage attenuation.

A number of etiologic factors have been associated with this syndrome. In a series of 15 cases, Ohtahara et al. reported cryptogenic factors in four and symptomatic factors in 11. The symptomatic patients included four with HIE; two with Aicardi syndrome; and porencephaly, cerebral atrophy, or dysgenesis in the remaining subjects. None had a recognized metabolic disorder.

These infants are often treated with hormonal therapy (typically adrenocorticotropic hormone [ACTH]). However, this therapy is considered less effective for early infantile epileptic encephalopathy. In addition, other AEDs have been utilized, also with limited success, including clonazepam, nitrazepam, valproate, and pyridoxine.[128]

The prognosis for early infantile epileptic encephalopathy is poor. In a series by Ohtahara et al.,[128] seven of 15 infants died between 6 months and 11 years (with four deaths occurring within the first 2 years of life). All survivors were characterized as severely mentally and physically disabled when last evaluated between 4 and 17 years of age All but two were described as quadriplegic and bedridden. In six of the eight survivors, seizures were either controlled or resolved. In a surviving 7-year-old, tonic seizures persisted; focal motor seizures continued in a 14-year-old. The degree of both mental and physical impairment appears to be static over time.

Table 8 Etiology-specific therapy for neonatal seizures of metabolic origin

	Acute therapy	Maintenance therapy
Glucose, 10% solution	2 mL/kg, IV	Up to 8 mg/kg/min IV
Calcium gluconate, 10% solution (9.4 mg of elemental Ca/mL)	2 mL/kg IV over 10 min (18 mg of elemental Ca/kg)	8 mg/kg/day IV* (75 mg of elemental Ca/kg/day)
Magnesium sulfate, 50% solution (50 mg of elemental Mg/mL)	0.25 mL/kg IM	.25 mL/kg IM repeated every 12 hrs until normomagnesemia
Pyridoxine	100 mg IV	

*After restoration of normocalcemia, tapering dosage may help prevent rebound hypocalcemia. Diagnosis of hypoglycemia, hypocalcemia, and hypomagnesia may vary between laboratories and is dependent on neonate's gestational age (with preterm infants tending to tolerate lower physiologic levels). Administration of metabolic correcting solutions requires careful monitoring of infant's systemic homeostasis, including EKG monitoring during administration of calcium.[76,83] From Mizrahi EM, Kellaway P. *Diagnosis and Management of Neonatal Seizures*. Philadelphia: Lippincott-Raven; 1998:181, with permission.[118]

Although there was a high incidence of death in the series by Ohtahara et al.,[128] their data from all patients formed the basis for an interesting discussion and the development of hypotheses concerning the evolution of seizure types and syndromes and their relationships to brain development. They note that, for many patients, an evolution of the EEG occurs from a suppression-burst pattern, to a hypsarrhythmic pattern, then to that of diffuse slow-spike and slow-wave activity. They propose that this evolution follows brain development, with periods of transition characterized by the emerging pattern when the infant is awake and the resolving pattern persisting in sleep. The evolution of the EEG is an objective marker of and parallels the sequential emergence of the age-dependent epileptic encephalopathies: Early infantile epileptic encephalopathy (associated with suppression-burst activity), West syndrome (associated with hypsarrhythmia), and Lennox-Gastaut syndrome (associated with generalized slow-spike and slow-wave activity). In general, this complete evolutionary development occurs in only a very small number of infants, because the occurrence of early infantile epileptic encephalopathy is rare. Thus, while this sequence may be observed in those with early infantile epileptic encephalopathy, the vast majority of those with West syndrome or Lennox-Gastaut syndrome do not experience an antecedent early infantile epileptic encephalopathy.

Epilepsy in Focal Cortical Dysplasia in Infancy

Epilepsy in focal cortical dysplasia (FCD) in infancy is not currently recognized as a specific syndrome by ILAE, although it falls into the broad category of symptomatic neonatal seizures. However, emerging data suggest that infants with this disorder have a fairly characteristic constellation of features. Lortie et al.[97] reviewed the features of 28 infants with FCD presenting at two specialized centers. Semiology depended on the topography of the dysplasia (for example, abnormal eye movements in all cases of posterior FCD). Almost half the infants eventually developed infantile spasms, mainly asymmetric. All but one patient in the series exhibited abnormal neurodevelopmental findings. Of those studied, 15 patients underwent surgery; eight became seizure free and in seven, their neuro-developmental status improved. It was suggested that the early identification of this disorder may prompt early surgery and improved outcome.

Response to Treatment

The basic principles of general medical management of the critically ill infant are naturally relevant to the comprehensive therapy of neonatal seizures because in some, both seizures and acute AED administration may be associated with depression of respirations, heart rate, and blood pressure. Ensuring airway patency and access to the circulatory system are considered critical early in the course of treatment.

Assessment of the cause of seizures is often conducted in parallel to the initial phase of AED therapy. If remediable causes of seizures are identified for which specific treatments are available, this therapy is initiated. This may be essential in management because it not only may directly treat the underlying disorder but also because some seizures may not be controlled effectively with AEDs unless the underlying cause is treated. This is particularly evident when seizures are caused by metabolic disturbances such as hypocalcemia, hypomagnesemia, and hypoglycemia. Etiologic-specific therapies for these disorders are listed in Table 8. Although treatment of some etiologies may not immediately affect seizure occurrence, therapy is still critical because it may limit the degree of CNS injury.

Decision to Initiate AED Therapy

The decision to initiate AED therapy should be based on several considerations. Because AEDs are utilized to treat neonatal seizures of epileptic origin, initial considerations are given to the clinical and EEG features of the events. When EEG examinations are available, electroclinical seizures and "electrical only" seizures are clearly candidates for AED therapy. When clinical observation alone is the basis for management, AED treatment should be considered for those clinical seizures that are most likely coupled to EEG seizures. These primarily include focal clonic and tonic seizures. In contrast, clinical events characterized as generalized tonic seizures and motor automatisms (provoked by stimulation and suppressed by restraint) are considered nonepileptic in origin and unlikely to require or respond to AED administration.

Table 9 Dosages of first-line, second-line AEDs in the treatment of neonatal seizures

Drug	Dose		Average therapeutic range	Apparent half-life
	Loading	Maintenance		
Diazepam	0.25 mg/IV (bolus), 0.5 mg/kg (rectal)	May be repeated 1–2 times		31–54 h
Lorazepam	0.05 mg/kg (IV) (over 2–5 min)	May be repeated		31–54 h
Phenobarbital	20 mg/kg IV (up to 40 mg)	3–4 mg/kg in 2 doses	20–40 μg/L	100 h after day 5–7
Phenytoin	20 mg/kg IV (over 30–45 min)	3–4 mg/kg in 2–4 doses	15–25 μg/L	100 h (40–200)

Based on Fenichel GM. *Neonatal Neurology*, 3rd ed. New York: Churchill-Livingstone, 1990[53]; Aicardi J. Neonatal Seizures. In: *Epilepsy in Children*, 2nd ed. International Review of Child Neurology Series. New York: Raven; 1994:217[2]; and Volpe JJ. Neurology of the Newborn. In: *Neonatal Seizures*. Philadelphia: WB Saunders, 2001.[191]
Table from Mizrahi EM, Kellaway P. *Diagnosis and Management of Neonatal Seizures*. Philadelphia: Lippincott-Raven; 1998:181, with permission.[118]

There has also been discussion concerning the need to treat all neonatal seizures of epileptic origin because some are brief, infrequent and self-limited, occurring only in reaction to an acute CNS insult. In these instances, AEDs may not be warranted, and the infant need not be exposed to acute and chronic AED therapy. On the other hand, some neonatal epileptic seizures are long in duration, frequent, and not self-limited. These should be treated acutely and vigorously with AEDs. It is difficult to predict at the onset of seizures which infants will have self-limited, frequent, or prolonged events. Clinical difficulties arise in the management of those infants whose seizures have characteristics that fall between these two extremes. In clinical practice, almost all neonatal epileptic seizures within this intermediate category are treated.

Initial AED Therapy for Acute Seizures

First-line AEDs and dosing schedules are listed in Table 9. The pharmacology of some of some these individual drugs has been well studied in neonates, particularly phenobarbital and phenytoin. However, few comprehensive clinical trials have been conducted to determine the most effective regimen for the treatment of neonatal seizures.[26] The most established strategy is

to acutely treat seizures with an AED that can be subsequently given as maintenance therapy; most often this is phenobarbital. It is given first as a loading dose then with additional boluses titrated to response until the maximum tolerated dose or serum levels in the high therapeutic range are reached. Boylan et al. prospectively assessed the efficacy of phenobarbital utilizing video-EEG monitoring[17] and found that only four of 14 infants completely responded with a cessation of all electroclinical seizures. The others experienced a reduction in electroclinical or clinical seizures, but continued electrical seizures.

After phenobarbital, phenytoin is the AED most often used, now typically initiated with fosphenytoin because of reports of reduced adverse effects with acute administration.[136] Again, as with phenobarbital, phenytoin administration is increased to the maximum tolerated dose or high therapeutic serum levels. Painter et al.[133] compared the relative efficacy of the acute administration of phenobarbital and phenytoin in seizure control and found no significant difference between the two medications. However, neither drug proved as efficacious as generally hoped or believed.

An alternative strategy of acute seizure management is the intravenous administration of benzodiazepines (midazolam, diazepam or lorazepam) until seizures are controlled, thus avoiding chronic AED therapy.

When the clinician begins AED therapy, this should be accompanied by establishment of criteria to determine whether acute therapy has been successful. Control of the clinical and electrical seizures is ideal, but often difficult to determine or unattainable. A typical response by electroclinical seizures to acute AED therapy is the initial control of the clinical seizures with the persistence of the electrical seizure activity, referred to as “uncoupling.”[117] With additional doses, the electrical seizures may be controlled.[157] However, there are common instances in which the EEG seizures cannot be controlled despite increasing doses of the initial AED and addition of other AEDs.

Current practice usually consists of acute AED administration (most commonly, phenobarbital) until clinical seizures are controlled. This often requires the achievement of serum levels in the high therapeutic range or maximum tolerated dose followed by a second drug if needed (commonly phenytoin or a benzodiazepine). If EEG is utilized, the same AED strategy is followed, although the AEDs are ideally titrated to eliminate the electrographic seizures. Since the electrical seizure discharges are often acutely resistant to AED therapy, additional drugs are administered cautiously to avoid adverse effects without significant benefit.

Some aspects of the pharmacology of phenobarbital and phenytoin in the neonate are useful to consider in the treatment of neonatal seizures because pathologic conditions can alter the availability of active drug given at standard doses in sick neonates.[43,91,100,131] Because phenobarbital is a weak acid and is protein bound, infants with acidosis may have less active AED available. Those with hypoalbuminemia may have greater unbound or active drug available. Both conditions may be found in sick neonates. Phenobarbital is eliminated by the liver and kidney, so that infants with impaired hepatic or renal function, including those with HIE, may have a reduced rate of elimination and, therefore a potential for unexpectedly high serum levels and clinical toxicity using standard dosing. Phenobarbital has a longer half-life in preterm compared with term infants and, in term infants, it is reduced during the first month of life. Thus, in preterm infants there exists a potential for higher serum levels with standard doses and the potential for toxicity; as the infant becomes older, there is the potential for identical doses to result in lower serum levels, thus creating the potential for breakthrough seizures with no other change in the infant's clinical condition. Overall, monitoring serum level trends, rather than day-to-day fluctuations, is more useful in the management of phenobarbital therapy.[47,55,132,191]

Important pharmacologic characteristics of phenytoin include nonlinear pharmacokinetics,[15,46] a variable rate of hepatic metabolism, a decrease in elimination rates during the first weeks of life, and a variable bioavailability of the drug in various generic preparations. In addition, a redistribution of the AED occurs after the initial dose, resulting in a drop in brain concentrations after the first dose. These pharmacologic characteristics indicate that phenytoin use requires individualization of dosing after the initiation of therapy.

Adjuvant AED Therapy for Acute Seizures

The use of so-called second-line, or adjuvant, AEDs falls into two categories: Those agents used to control acute seizures and those administered for otherwise medically refractory seizures. Agents in both classes have been utilized either intravenously or orally with variable success. Those given intravenously and primarily as alternatives to acute therapy include clonazepam,[8] lidocaine,[64,186] midazolam,[74,167] and paraldehyde (not available in the United States).[84] One recent study reported success with continuous midazolam infusion in the treatment of otherwise uncontrolled neonatal seizures,[74] although infants experienced treatment-related hypotension that required medical management. Lidocaine is another medication that has been the topic of renewed interest. Boylan et al.[16] reported limited success with lidocaine in refractory neonatal seizures. Another recent investigation reported that, during the use of lidocaine (initial loading dose of 2 mg/kg over 10 minutes followed by a continuous infusion of 6 mg/kg per hour), 4.8% of infants experienced a cardiac arrhythmia but all responded to lidocaine discontinuation.[186] Other agents, which are given orally to control medically refractory seizures, include carbamazepine,[101] primidone,[154] valproate,[54] vigabatrin,[6] and lamotrigine.[109] The success of this latter group of AEDs is difficult to assess because they have been used in conjunction with other AEDs and well into the course of illness.

Chronic AED Therapy

The use of chronic AED therapy for neonates after the acute seizures have been controlled is not well studied or standardized. There are no well-defined criteria for maintenance AED treatment. When chronic therapy is considered, either phenobarbital or phenytoin is given in maintenance doses of 3 to 5 mg/kg/day and serum levels are monitored. There are also no well-established criteria for discontinuation of maintenance AED therapy. Reported schedules range from 1 week up to 12 months after the last seizure,[13] although a currently utilized and successful schedule is to withdraw AEDs 2 weeks after the infant's last seizure.[52] At some centers, an EEG is also performed at the end of this 2-week period to assess for electrical seizure activity not associated with clinical seizures.

Potential Adverse Effect of AED Therapy

There has been much concern about the potential adverse effects of AEDs on the developing brain. Early animal experiments suggested alteration in cell growth and energy substrate utilization,[9,45] although the applicability of these findings to humans has been called into question.[191] There have been few studies of clinically significant adverse effects of acute AED therapy. However, over vigorous acute AED administration can result in transient CNS depression, hypotension, bradycardia, and respiratory depression. Any of these clinical events represent a risk for secondary CNS hypoxia or ischemia.

More recently, Ikonomidou et al. assessed the effect of phenytoin, phenobarbital, diazepam, clonazepam, vigabatrin, and valproate on apoptotic neurodegeneration in the developing rat brain in plasma concentrations relevant for seizure control in humans. The basis of their study was the consideration that AEDs work via three mechanisms: Limitation of sustained repetitive neuronal firing via blockade of voltage-dependent sodium channels, enhancement of GABA-mediated inhibition, and blockade of glutamatergic excitatory neurotransmission. However, they hypothesized that these blocked mechanisms are also features of an endogenous neuroprotective system in the brain that is crucial for neuronal survival during development. They concluded that AEDs may impair survival-promoting signals and an imbalance between neuroprotective and neurodestructive mechanisms in the brain, which, during a developmental period of ongoing programmed neuronal death, will promote apoptotic neurodegeneration. However, the proapoptotic effects of these AEDs appears to be species specific in research animals, and it is unclear if these results can be extrapolated to human newborn infants. In addition, recent data from the same group show that another AED, topiramate, lacks the toxicity seen with the other drugs.[56]

Summary and Conclusions

The occurrence of seizures in a newborn infant strongly indicates the presence of a CNS disorder. Clinical management is based on accurate characterization and classification of the clinical events and, if available, appropriate correlation of the interictal and ictal EEG. Etiologic factors are wide-ranging, although, hypoxic-ischemic encephalopathy continues to be a prominent cause. Etiology-specific therapy is critical to minimizing any adverse effects of the seizures. Although a number of potential AED regimens exist, phenobarbital and benzodiazepines are used most consistently. There are only a few well-defined, specific neonatal epileptic syndromes including benign neonatal seizures, benign familial neonatal seizures, early myoclonic encephalopathy, and early infantile epileptic encephalopathy. The prognosis of neonatal seizure is generally associated with the nature and severity of the underlying etiology, but this may be modulated by the burden of associated neonatal seizures and possibly the administration of the AEDs themselves, both fertile areas for future research.

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Chapter 57

Febrile Seizures

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Introduction

Febrile seizures are the most common convulsive disorder through the lifecycle. In the United States and Western Europe, about 4% of children under the age of 5 years experience a febrile seizure[47,65]; the frequency has been reported to be higher in some Asian populations (8% in Japan and 14% in Guam).[58,64] Febrile seizures are characterized by their benign prognosis.

Historical Perspectives

Until the mid-19th century, febrile seizures were not recognized as distinct from other seizures. Before that time, infantile convulsions were thought to be the result of irritation of the central nervous system (CNS). Presumed causes included gastrointestinal irritation, teething, improper diet, and fever. Treatment was nonspecific and focused on relieving the symptoms. By the mid-19th century, this began to change, and treatment was directed at underlying causes rather than symptoms. Beginning in the latter part of the 19th century, fever came to be regarded as a primary factor in producing infantile convulsions. This emphasis on fever may have been related to the introduction of the thermometer into clinical use around this time.[26]

Throughout the late 19th and early 20th centuries, any infantile convulsion was considered to be serious and potentially fatal. This was because of a failure to separate febrile from neonatal and other symptomatic seizures.

By the turn of the century, as it was gradually understood that seizures were a symptom and not a disease, treatment of the underlying cause became important. Unfortunately, very few effective treatments were available.

In the mid-20th century, studies focused on febrile seizures were published by Lennox[40] and Livingston.[41] These investigators found that a benign outcome was predicted by onset between 1 and 3 years, generalized seizure of short duration, single or few episodes, family history positive for febrile convulsions, male sex, and normal findings on the electroencephalogram (EEG). Increased likelihood of later epilepsy was associated with onset before 1 year of age, prolonged or partial convulsions, multiple seizures, abnormal birth history, family history of epilepsy, female sex, and abnormal EEG findings. Subsequent studies have confirmed many of these factors as predictive, albeit not very accurate predictors.

By the 1970s, three large population-based studies had been published that demonstrated a much lower risk for epilepsy following febrile seizures than previously proposed. These studies had very similar results, and formed the foundation for our current understanding of febrile convulsions. In their study of 18,500 children, van den Berg found a 2% incidence of febrile seizures with a 3% rate of later epilepsy.[65] In 1976, the National Institute of Neurological Disorders and Stroke (NINDS) Collaborative Perinatal Project, which followed 54,000 infants prospectively, found an incidence of almost 4% for febrile seizures.[47] The developmental outcome was unaffected, and the overall incidence of later epilepsy was relatively small (2%). Verity followed a British cohort of 14,676 children.[70] The incidence of at least one febrile seizure was 2.7%, and 2.3% of those with febrile seizures later developed epilepsy.

Definitions

In 1980, the National Institutes of Health (NIH) Consensus Panel defined febrile seizures as "An event in infancy or early childhood, usually occurring between three months and five years of age, associated with fever but without evidence of intracranial infection or defined cause. Seizures with fever in children who have suffered a previous nonfebrile seizure are excluded. Febrile seizures are to be distinguished from epilepsy, which is characterized by recurrent nonfebrile seizures."[21]

This definition excludes any seizure that occurs in the presence of neurologic illness, such as encephalitis, meningitis, or toxic encephalopathy. The prognosis for such seizures is different from that of febrile seizures, because the underlying illnesses can potentially cause CNS sequelae. Seizures caused by mild encephalopathies may be included within this definition, such as those associated with *Shigella*, a bacterium that produces a neurotoxin. Febrile seizures are difficult to define in malaria-endemic areas where all children are infected from time to time, many have elevated temperatures, and the severity of brain involvement is often measured by severity of the seizure disorder as well as level of consciousness.[48]

Simple febrile seizures are those that last less than 15 minutes and are generalized. Complex febrile seizures are prolonged, multiple within 24 hours, or partial. Seizures in either of these subgroups may be accompanied by a pre-existing neurologic abnormality or a family history of either febrile or afebrile seizures.

Febrile status epilepticus follows the usual definition of 30 minutes of continuous or intermittent convulsive phenomena without the return of consciousness.

Discussion remains about the age range used in the NIH Consensus Panel definition. Many experts feel that ages between 3 and 6 months is rather young for the onset of a first febrile seizure. In fact, it may herald the onset of Dravet syndrome, a recently described epilepsy syndrome. As well, children have febrile seizures beyond the fifth birthday, and it has been suggested that the upper age limit be the sixth birthday. Another area of contention is a standard definition of "fever" and how a child's temperature should be measured (i.e., oral, rectal, axillary, or tympanic measurement). Based on the childhood vaccine trial literature, our definition of an elevated temperature is 38°C per rectum or 38.5°C orally. However, we recognize that such accuracy is not always available.

Seizures are not considered to be "febrile seizures" when they occur with fever but in the context of exposure to proconvulsant drugs such as diphenhydramine, tricyclic antidepressants, amphetamines, and cocaine.

Table 1 Predictive Factors in Febrile Seizures

- **For a first febrile seizure**
    - Family history of febrile seizures
    - Low plasma ferritin level
    - Slow development
    - Day care
    - Higher temperature
    - Delayed neonatal discharge
- **For recurrences**
    - "Complex" first febrile seizures
    - Family history of febrile seizures
    - High number of febrile episodes
    - Low fever
    - Short duration of fever before seizure
- **For epilepsy**

  - Young age at onset
  - Abnormal development before first seizure
  - Family history of epilepsy

It has been suggested that febrile seizures should be categorized as acute symptomatic because of the coincident febrile

illness. We feel this is misleading. It is our opinion that fever is a systemic trigger that provokes the seizure, as contrasted to the underlying severe brain dysfunction found in most conditions included in the acute symptomatic category. In addition, the outcome for febrile seizures is so much better than for seizures associated with many acute symptomatic causes that it is misleading to lump them together.

Epidemiology

In the United States, South America, and Western Europe, febrile seizures are experienced by 2% to 5% of all children before the age of 5 years.[28,47] They are reported to be even more common in certain Asian countries.[58,64]

The first febrile seizure is complex (lasting more than 15 minutes, partial, or multiple within 24 hours) in about 30% to 40% of cases.[69] The peak incidence is in the second year of life, with the average age of onset between 18 and 22 months. Febrile seizures are slightly more common in boys.

Risk factors for a first febrile seizure have been studied in comparison to febrile controls without seizures (Table 1). A higher temperature was a risk factor for febrile seizures in two studies,[9,52] and a history of febrile seizures in the immediate family was noted in another study.[15] Low plasma ferritin, reflecting poor iron status, also increased the risk. When both febrile and afebrile children were used as controls, in addition to a family history of febrile seizures, neonatal discharge at 28 days or later, parental report of slow development, and day care attendance were also risk factors.[16]

Approximately 40% of children with a first febrile seizure will experience one or more recurrences. The risk of a second seizure after a first is about the same as a third febrile seizure after a second. Most recurrences (75%) are within 1 year of the first febrile seizure. Four major risk factors for recurrence have been identified: (a) a young age (<12–18 months)[17,69]; (b) a family history of febrile seizures[16,52,66]; (c) a low temperature at the time of seizure[12]; and (d) a short duration of fever before the first seizure.[12] The recurrence risk for those with none of the four factors was 14%, with one factor 23%, with two 32%, with three 62%, and with all four 76%.[13] In a meta-analysis, young age of onset and a family history of febrile convulsions were the strongest predictors of recurrence[11] (see Table 1). A family history of afebrile seizures has inconsistently been associated with risk for recurrence.[12,47,49,69] “Complex” febrile convulsions and neurologic dysfunction do not influence the chance of febrile recurrences.[12,47,69]

Genetics

There is an important genetic predisposition for febrile seizures, and genetic factors exist that may be either causative or protective. It is natural to consider the possibility of a genetic propensity for the occurrence of a febrile seizure; however, there may also be protective gene(s) in those who never experience a febrile seizure. These protective gene(s) might raise the seizure threshold.

Although the exact mode of inheritance is not known, febrile seizures tend to run in families. An autosomal recessive mode of inheritance is not likely, because there is an excess of affected parents and the risk to siblings is less than 25%. Either a polygenic mode of inheritance or dominance with incomplete penetrance is more likely.[3,63] Afebrile seizures or epilepsy may be more common in families of children with febrile seizures, but the evidence is controversial. When a child has a first febrile seizure, the risk for younger siblings is in the range of 10% to 20% and even higher if a parent reports having had a febrile convulsion.[6]

Two unique epilepsy syndromes always include seizures with fever: generalized epilepsy with febrile seizures plus (GEFS+)[54] and Dravet syndrome (severe myoclonic epilepsy of infancy).[22] GEFS+ is an autosomal dominant epilepsy syndrome with 80% penetrance and is associated with heterogeneous clinical phenotypes (see Chapter 257).[20] In a given family, about one third of those affected have one or more febrile seizures that often persist beyond the usual age of 5 years. About one third have febrile seizures and then afebrile generalized tonic–clonic seizures in adolescence that usually remit. A final third have other epilepsy syndromes, usually, but not always, generalized syndromes (myoclonic-astatic epilepsy, typical childhood absence, and even Dravet syndrome). Several gene mutations have been identified involving voltage-gated sodium channels of *SCN1A* and the γ2 subunit of ligated-γ-aminobutyric acid (GABA)-2 receptor.[20]

Dravet syndrome (Chapter 230) begins in the first year of life with prolonged, often unilateral febrile seizures precipitated by relatively low-grade fever. Development stagnates or regresses around 1 year of age, when other seizure types develop (myoclonic, atypical absence, or partial). Ataxia and important behavior problems (hyperactivity) are very common. Dravet syndrome may occur within families with GEFS+ and with the identical gene defect, but in approximately 50% of cases, no de novo missense or truncating mutations of the *SCN1A* subunit are present.[20]

The complete genetic story of febrile seizures is still incomplete. More than seven chromosome linkage sites have been associated with febrile seizures, suggesting locus heterogeneity. In addition, at least five genes have been identified as causal for epilepsy syndromes that include febrile seizures, including GEFS+.[73] These findings may provide insights into the biology of age-limited temperature-dependent seizure susceptibility.

Etiology and Basic Mechanisms

"Everyday" infections, such as tonsillitis, upper respiratory infections, otitis media, roseola infantum, or *Shigella* gastroenteritis are often implicated as the cause of fever in children with febrile seizures. Unfortunately, there are no recent studies of the epidemiology of these infections, since vaccines against *Haemophilus influenzae*, varicella, pneumococcus, meningococcus and influenza are in widespread use and have likely

changed the panorama of childhood febrile illness. Seizures occurring soon after immunization with whole-cell diphtheria-pertussis-tetanus (DPT) and measles vaccines should not be regarded as a direct adverse effect of the vaccine.[30] Such seizures are believed to be "ordinary febrile seizures" triggered by fever induced by the vaccine. Their subsequent clinical course is identical to other febrile seizures,[29] with no increased risk for subsequent afebrile seizures or abnormal neurologic development.[7] The frequency of febrile seizures after DPT or measles vaccination is six to nine, and 24 to 25 per 100,000 children vaccinated, respectively. Newer acellular pertussis vaccines rarely induce a febrile reaction and, since their introduction in Canada, there has been a 79% decrease in hospital admissions for DPT vaccine related febrile seizures.[38]

The pathophysiology of febrile seizures is unknown. The role of activation of the cytokine network is presently being studied. There appears to be increased susceptibility to febrile seizures associated with specific interleukin alleles.[36,43,62,71] Circulating toxins, immune reaction products, and viral or bacterial invasion of the CNS have been implicated, together with relative lack of myelination in the immature brain and increased oxygen consumption during the febrile episode.[30] Immaturity of thermoregulation and a limited capacity to increase cellular energy metabolism at elevated temperatures have been suggested as contributory factors.[32]

Recent reports indicate that human herpes virus type 6 (HHV6), which causes roseola, is strongly associated with febrile seizures.[8] HHV6 infection was identified in eight of 42 children with a first febrile seizure.[60] In children with multiple febrile seizures, HHV-6 DNA was detected in the cerebrospinal fluid, but not in controls without febrile seizures. It was postulated that viral invasion of the brain might occur during roseola, with reactivation by fever during subsequent illnesses, thus provoking recurrent febrile seizures.

In a survey of general practitioners throughout the Netherlands, a significant relationship was noted between recurrent febrile seizures and influenza A[67]; therefore, vaccination against influenza A may be considered after a first febrile seizure as a strategy to reduce the risk of recurrences.

Clinical Presentation

A febrile seizure is often the first sign that a child is ill, and it usually occurs early in the course of a febrile illness.[69] It is commonly assumed that a rapid rise in temperature is an important trigger, but this has not been proven.[9] The most common seizure type is tonic–clonic, but the seizure may be partial or atonic, having the appearance of a sudden collapse. Prolonged febrile seizures are often focal, and a Todd paresis may follow a partial seizure.

Other possible seizure types are described as staring accompanied by stiffness or limpness, rhythmic jerking movements without prior stiffening, or focal stiffness or jerking only. Most seizures do not last beyond 6 minutes; in a large study, fewer than 8% were longer than 15 minutes.[47] Therefore, the child with a febrile seizure is usually not brought to medical attention until after the seizure has ended.

Febrile seizures are generally divided into either simple (single, brief, and generalized) and complex (partial, prolonged, or repeated in the same illness). About 60% to 70% of febrile seizures are simple, and 30% to 40% are complex.[10,47] A Todd paresis occurs in 0.4%.[47] In a prospective cohort study of first febrile seizures, 35% of 428 children had one or more features of a complex febrile seizure.[10] A retrospective study reported similar findings.[39] Postictal unconsciousness lasting more than 30 minutes, although rare, has been associated with seizures that are focal and/or last longer than 5 minutes.[50]

Diagnostic Evaluation

As soon as the child is brought to medical attention following an apparent febrile convulsion, it is important to identify whether any medical condition is present that requires treatment. The history should include possible symptoms of infectious illness, trauma, medication taken, exposure to toxins, developmental level, and any previous or family history of seizures, either febrile or afebrile. Whenever possible, a complete description of the seizure from start to finish should be obtained from an eyewitness. This history may be unreliable because caretakers are often very frightened by the seizure.

A general physical examination should note the level of consciousness and presence or absence of meningismus, tense or bulging fontanelle, Kernig or Brudzinski signs, and focal differences or abnormality in muscle strength and tone. Urgent attention must be given to exclude the presence of meningitis and status epilepticus.

For children with many febrile seizures, it is important to consider a chronic infection or immune deficiency.

Two practice parameters prepared for the American Academy of Pediatrics, based on peer-reviewed publications about simple febrile seizures,[4,5] have concluded that very little investigation is warranted.

Routine Blood Work

Routine blood work has not been shown to be of value. Two studies have suggested that low serum sodium after a first febrile seizure is associated with a significant risk of a recurrent febrile seizure within that illness[33,37]; however, another more robust study failed to confirm this association.[61] Because rates of bacteremia (2%) and other serious bacterial illnesses are low (2%), blood cultures and complete blood count are not routinely necessary.

Lumbar Puncture

The main controversy in the evaluation of febrile seizures continues to be the lumbar puncture (LP). About 15% of children with meningitis will have seizures, but virtually none are neurologically normal shortly after the seizure.[27] Once a febrile seizure has stopped, excluding meningitis/encephalitis becomes a critical task for the physician.

A LP is indicated if meningitis is suspected clinically, even if a source of infection outside the CNS has been found, such as otitis media. If the infant has been receiving antibiotics, partially treated meningitis should be considered.

In infants younger than 12 to 18 months, clinical signs of meningitis may be absent, and a LP should be strongly considered.[72] However, this clinical truism has not been critically assessed. The American Academy of Pediatrics Committee on Quality Improvement Committee practice parameter states: “The clinical evaluation of young febrile children requires skills that vary among examiners. In all children younger than 12 months, performance of a lumbar puncture should be strongly considered.”[5] In the slightly older child, the practice parameter maintains: "In a child between 12 to 18 months of age, a LP should be considered because clinical signs and symptoms of meningitis may be subtle."

The LP should not be omitted solely on the basis of age or family history, and it should be considered even in a child who has had several previous febrile seizures. If increased intracranial pressure is suspected, the decision to perform a LP should be made by an experienced physician who is able to weigh the

risk of delaying a possible diagnosis of meningitis against the risk of LP.

It is clear that meningitis is incredibly unlikely if a child older than 18 months of age appears well shortly after the seizure. The American Academy of Pediatrics Committee on Quality Improvement Committee stated, "In a child older than 18 months, although a lumbar puncture is not routinely warranted, it is recommended in the presence of meningeal signs and symptoms. In addition, if the child has previously been treated with antibiotics, the clinician should be aware that the signs and symptoms of CNS infection may become masked, and lumbar puncture should be strongly considered in such cases."[5]

In one series, of 503 children with meningitis, none had a simple febrile seizure.[27] Offringa studied 309 children who had an LP after presenting to an emergency department with a seizure associated with fever.[49] Ten cases had meningitis (bacterial or viral), and all had major signs pointing to serious illness. Six other children had the same signs but did not have meningitis. Therefore, only 16 of 309 "needed" an LP to exclude a CNS infection. An older study by Lorber suggested that an experienced pediatrician could avoid many LPs without missing cases of meningitis.[42] Such a selective approach implies that the physician assessing the child is experienced with the kinds of symptoms that are associated with meningitis in children. This judgment seems to be based on "the child appeared more ill than the physical signs suggested; had photophobia, neck stiffness, or a positive Kernig sign; had continuing pyrexia without obvious cause; or deteriorated in hospital."[49] The contention that "lack of experience by junior doctors does not justify routine lumbar puncture" must be tempered by what is realistically possible.[42] We suggest following the practice parameter recommendation (noted earlier) to perform a LP if the child is less than 12 months of age, unless an experienced pediatrician is available to assist.

Neuroimaging

The published evidence indicates no proven benefit for neuroimaging in children with either simple or complex febrile seizures. Neuroimaging would appear justified only when special evidence points to an underlying structural lesion such as focal neurologic abnormalities, significant developmental delay, neurocutaneous lesions or abnormal head circumference.[5] Anxiety about complex febrile seizures does not justify routine imaging, especially considering that this group involves 30% to 40% of all first febrile seizures. No abnormalities were found in one study of computed tomography (CT) scans in 44 hospitalized febrile seizure patients.[46]

Electroencephalograph

Routine electroencephalography (EEG) is not justified after a first simple febrile seizure, either at the time of presentation or within the following month.[5] Even though EEG is often requested, no consistent evidence suggests that routine EEG predicts febrile seizure recurrence or subsequent epilepsy.[45,57] Furthermore, studies of children with complex febrile seizures have not shown the EEG to be predictive of the development of epilepsy.

The one special feature of the EEG and febrile seizures is hypnagogic spike-wave. This discharge consists of short bursts of irregular high-voltage δ-waves with a few buried spikes as the child drifts off to sleep. It has a peak expression at about 3 to 4 years of age—long after the peak age of febrile seizures—and apparently may be seen in the majority of children with febrile seizures.[2,56,63] Many authorities view hypnagogic spike-wave as an expression or marker of the febrile seizure tendency but, in any case, it carries no long-term negative connotations. The value of EEG in children with repeated febrile seizures has apparently not been extensively studied.

Differential Diagnosis

Rigors due to fever, febrile myoclonus, breath-holding, and syncope triggered by illness must be differentiated from febrile seizures.[51,59] It is possible that many febrile seizures are febrile syncope, a diagnosis that should be suspected on the semiology of reflex asystolic attacks accompanied by sudden pallor and atonic collapse or tonic extension.

A new scenario of an afebrile seizure associated with minor infection was described by Lee.[39] The age group is similar to those with febrile seizures, and a high prevalence of family history of febrile seizures is noted. Children with this disorder frequently have febrile seizures on other occasions. The seizures occur in children who are afebrile (temperature <37.8°C), have definite signs or symptoms of illnesses (cough, coryza, vomiting, or diarrhea), and have normal metabolic and cerebrospinal fluid findings and no other obvious cause for seizures. Nearly 25% of the 125 children had more than one recurrent seizure within the next 24 hours. After a follow-up of 6 years, the risk of recurrence of an afebrile seizure was 7.8%, as compared with 1.6% followed having a first unprovoked (regular) febrile seizure. There is an overlap in presentation between febrile and illness-provoked seizures. We are not convinced that including them within the acute symptomatic group is appropriate, as mentioned previously. The appropriate initial evaluation for cause of seizures is similar, as is the supportive care, counseling, and long-term management. The “afebrile-febrile seizure” scenario was also noted in a recent study of 39 children from Seattle, Washington.[74]

Long-Term Prognosis

Risk for Epilepsy

A population-based study and a large case series determined that febrile seizures precede 15% of all cases of childhood-onset epilepsy.[14,17] The majority of these children had experienced simple, generalized febrile seizures. On the other hand, epilepsy develops in fewer than 5% of all children with febrile seizures.[53] The reported rate of epilepsy after a febrile seizure is higher in populations from selected sources, such as patients admitted to hospitals or referred to specialists.[47]

The number of recurrent febrile seizures does not increase a child's risk for later afebrile seizures.[47] Factors that increase the risk for one or more afebrile seizures are history of abnormal development before the first febrile seizure, abnormal findings on neurologic examination, a history of afebrile seizures in a parent or sibling, or a “complex” first febrile seizure (see Table 1).[3,47] In a large prospective study, 66% of children with febrile seizures had none of these risk factors (“simple febrile seizures”), and only 2% of those with simple febrile seizures had an afebrile seizure by the age of 7 years. Of the 34% with one risk factor, one or more afebrile seizures occurred in 3%, and if a child had two or more risk factors, the afebrile seizure rate was 13%. Therefore, most children with risk factors do not develop epilepsy. Identification of a risk factor for subsequent afebrile seizures generally does not mandate a change in long-term management.

Annegers in Rochester, Minnesota, noted that, when epilepsy follows a simple febrile seizure, it is usually generalized epilepsy. In the 2% to 4% of children who develop subsequent epilepsy after a complex febrile seizure, partial epilepsies

tend to follow.[3] The significance of these observations must be tempered somewhat because these conclusions are only based on a long follow-up of 687 children with febrile seizures of whom only 32 developed epilepsy (or at least one unprovoked seizure) following a febrile seizure. Again, the clinician following a child with a complex febrile seizure must remember that the vast majority never develop epilepsy. Even those with a partial, prolonged febrile seizure repeating within the same illness have only a 15% chance of developing epilepsy.[47]

The Sequence of Prolonged Febrile Seizures Followed by Intractable Temporal Lobe Epilepsy Secondary to Mesial Temporal Sclerosis

Although it has been argued that febrile seizures may predispose a child to the later development of partial seizures of temporal lobe origin, the evidence for a cause-and-effect relationship remains controversial. Studies of patients with intractable complex partial seizures who have a history of prolonged febrile convulsions show an increased rate of mesial temporal sclerosis.[18] However, population-based studies find this sequence to be rare—about 1 in 150,000 children.[17]

The initial observations of Falconer, based on a series of 100 children having surgery for intractable temporal lobe epilepsy (TLE), suggested two main ideas.[25] First, the etiology of TLE often appeared to be mesial temporal sclerosis (MTS); in 41 of his 100 cases, it was the only pathology. Second, a 30% of those with mesial temporal sclerosis had preceding prolonged febrile seizures (compared with 6% in the group with other pathologies). A cause-and-effect relationship was postulated, and further confirmation came from work with status epilepticus in adolescent baboons, in which very severe status caused damage to the mesial temporal structures.[44] It is likely that these baboons were too mature to accurately reflect the human circumstance (see Chapter 39). Recent evidence in rats suggests that a prolonged febrile seizure may not be sufficient to cause later epilepsy by itself, but rather may permanently lower the seizure threshold, which in turn allows the expression of a second independent injury.[23]

In many cases, at the time of surgery “dual pathology” is found in the temporal lobe; for example, a small area of malformation plus mesial temporal sclerosis.[31] A single published magnetic resonance imaging (MRI) study documents two completely normal children with no perinatal difficulties who had febrile status with initial unilateral hippocampal swelling and then volume loss in mesial temporal structures.[68] More frequently, investigators have found bilateral hippocampal swelling following febrile status, which usually resolves completely.[55] No prospective studies document a normal MRI, then a prolonged febrile seizure, then unilateral hippocampal swelling, followed by mesial temporal sclerosis and intractable TLE. Additional longitudinal prospective studies are presently underway that will help to answer this question.

The link between a very common condition causing a significant problem is very difficult to demonstrate prospectively. We have estimated that the sequence of febrile status followed by mesial temporal sclerosis and intractable TLE occurs in only 1 of 75,000 to 150,000 children.[17] However, regardless of how rare or complicated, the syndrome of prolonged febrile seizures associated with unilateral mesial temporal sclerosis and intractable TLE has an excellent surgical outcome in 80% to 90% of cases (see Chapter 247 for further discussion).[1,34,35]

Intellectual Development

Two large cohort studies have firmly established that febrile seizures do not affect later intellectual ability. The National Perinatal Collaborative Study followed more than 54,000 babies identified prenatally to age 7 years.[47] There were 1,706 with at least one febrile seizure. Of these, 431 children had a sibling without febrile seizures. At age 7, the intelligence and school performance of those with febrile seizures was the same as their unaffected siblings.[24] Of the 16,163 children in the British National Birth Cohort Study, 381 with a history of febrile convulsions were no different from other children with regard to behavior, height, head circumference, or academic progress, behavior, or performance on simple intellectual tests.[69] In two other large prospective studies, academic performance was not impaired in children of school age with a history of febrile seizures.[47,53]

Chang utilized a prospective, population-based, case-control method to assess the learning, spatial, and sequential working memory of 87 school-aged children with a previous febrile seizure and 87 randomly selected age-matched control subjects.[19] The febrile seizure group performed significantly and consistently better than control subjects on mnemonic capacity and had more flexible mental processing abilities than their age-matched controls.

Summary and Conclusions

Febrile seizures are essentially benign. They are determined by genetic factors and an age-related susceptibility to fever that is outgrown by about 6 years of age. Although febrile seizures may be extremely frightening to parents, they resolve without appreciable risk of sequelae. There is no later effect on intellectual or behavioral ability. Epilepsy later develops in only a small minority of children with febrile seizures and, unless the seizure is exceedingly long, there is no evidence of any risk for neurologic consequences in the future. The most important determinant of neurologic status after a febrile seizure is the child's neurologic status before any seizure occurred. Although the sequence of prolonged febrile seizures followed by intractable TLE secondary to mesial temporal sclerosis occurs, this appears to be an infrequent event.

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Chapter 58

Generalized Convulsive Status Epilepticus

David M. Treiman

Introduction

Generalized convulsive status epilepticus (GCSE) is the most common and most dangerous type of SE. The earliest mention of SE in the medical literature—in a Babylonian medical text from the first millennium before the Common Era[165]—referred to what we now know as *generalized tonic-clonic SE*,[109] *major motor SE*,[110] *generalized status epilepticus*,[74] *GCSE*,[135] or *grand mal status epilepticus*.[101] The first modern description of GCSE was provided by Calmeil in 1824,[17] who wrote, “There are cases where, as soon as one attack is barely over, another begins, so that there is a succession of up to as many as 40 or 60 uninterrupted attacks. This is what the patients amongst themselves call *etat de mal*. The danger is urgent; many patients die.” Detailed descriptions of GCSE subsequently were provided by Bourneville,[12] Trousseau,[152,153] and Clark and Prout.[25,26,27] However, it was not until the Marseilles Conference[42] that GCSE was clearly distinguished from other types of SE. In 1984, Treiman et al.[143] introduced the term *subtle GCSE* to describe a late and subtle presentation of GCSE. At that time, subtle GCSE was not generally recognized, although Bourneville[12] and later Clark and Prout[25,26,27] had recognized the dynamic character of GCSE as a disorder with “progressive clinical stages.”

Definitions

Generalized convulsive SE classically has been defined as recurrent generalized convulsions without full and complete recovery of consciousness between seizures or as a single prolonged convulsion without the characteristic evolution of a single discrete seizure. Thus, recurrent primarily and secondarily generalized tonic–clonic seizures without recovery of consciousness between seizures are both forms of GCSE. However, it is now recognized that at least secondarily GCSE is a dynamic state[137,138,139,141] (evidence for dynamic changes during primarily generalized convulsions is sparse). If recurrent convulsions are allowed to persist without treatment or with inadequate treatment, a progressive diminution of convulsive activity occurs, so that the motor manifestations of GCSE become increasingly subtle.[33] Subtle GCSE is defined as a condition in which a patient exhibits profound coma, convulsive activity consists of only subtle twitches of the extremities or trunk or nystagmoid movement of the eyes, and bilateral (although frequently quite asymmetric) ictal discharges are present on the electroencephalogram (EEG).[137] Although the clinical and EEG characteristics of GCSE are different in early (usually overt) GCSE and late (usually subtle) GCSE, there is a continuum between these two presentations, and subtle GCSE may progress to complete cessation of motor activity, even though ictal discharges continue on the EEG. Treiman[141] termed this presentation of GCSE electrical GCSE and suggested that this represents the final stage in the progression from overt GCSE. Electrical GCSE, sometimes following more overt GCSE, has also been reported by others.[33,34] Many investigators have used the term *nonconvulsive SE* for such profoundly comatose and severely ill patients.[13,33,102,160] Treiman[137] suggested that what others have called *myoclonic SE* (in patients with anoxic or other severe encephalopathies) is really subtle GCSE, even though there may be only one or two (or occasionally no) generalized convulsions before the appearance of signs and symptoms of subtle GCSE. This is an area of controversy, and some epileptologists are not convinced that the subtle convulsive activity and periodic epileptiform discharges sometimes seen in severe hypoxic encephalopathy should be considered SE.

The definition presented also distinguishes subtle GCSE from true nonconvulsive SE (a category that includes both complex partial SE and absence SE), in which the characteristic clinical feature is an epileptic twilight state, although, as noted, the increasingly common use of the term nonconvulsive SE in comatose patients adds confusion to the literature. A progression from overt to subtle motor activity has not yet been described for primarily GCSE.

The definition of GCSE must also deal with generalized convulsive activity that occurs as a single prolonged episode rather than as repeated discrete behavioral seizures. Such a situation is common in the later stages of GCSE, when convulsive movements tend to be subtle, but it may also occur early in an episode of GCSE, especially in children. Here the convulsive movements are more likely to be overt. Most authors have suggested that seizure activity should persist for at least 30 minutes before the diagnosis of SE is made. However, data from Theodore et al.[130] confirming the widely held clinical impression that single convulsions that are not part of an episode of SE do not last >2 minutes (discussed later) suggest that 30 minutes of continuous convulsive activity is far too long to be a good operational criterion for the diagnosis of GCSE. For practical clinical purposes, 10 minutes of continuous behavioral or electrical seizure activity, without the evolution of the ictal discharges typical of a discrete generalized convulsion, is a more realistic criterion. Lowenstein et al.[75] suggested 5 minutes' duration as the definition of SE, but this may be too short, especially because discrete generalized convulsions in children may persist for >5 minutes.

Epidemiology

Generalized convulsive SE is the most common type of SE, especially when subtle presentations of GCSE are included. However, in many older reports, GCSE is not clearly distinguished from other types of SE. Hauser[47] suggested that there are approximately 65,000 cases of SE in children and adults in the United States each year. However, DeLorenzo et al.[32] estimated that there are approximately 150,000 cases of SE in the United States each year, based on extrapolation of data from their community-based study in Richmond, Virginia. About 70% of both adults and children in the Richmond series exhibited GCSE. Shorvon,[118] on the basis of a careful review of hospital-, clinic-, and population-based studies, estimated an annual incidence of GCSE of 180 to 280 per million persons in the United States and the United Kingdom. He emphasized that this probably represents an underestimate of the true incidence of GCSE, which almost certainly is still higher in developing countries. In the last decade, eight major population studies of the epidemiology of status epilepticus have been reported, six of which were reviewed by Chin et al.[22] Data from all eight studies are summarized in Table 1. Five included all ages,[28,32,48,63,166] two included only adults,[157,158] and one included only children.[21] Six covered all types of status epilepticus; two only included convulsive SE.[21,166] Overall, the reported incidence of status epilepticus ranges from 10.3 to 61/10^5, but the incidence is much higher in the very young (<1 year: 135–156/10^5) and the elderly (>60 or 65 years: 14.6–86/10^5). Generalized convulsive status epilepticus (including both primarily and secondarily generalized convulsions) accounted for 33.3% to 71% of the cases when all types of SE were included. These numbers can be extrapolated to give an estimate of at least 2 million cases of GCSE in the world each year.

Etiology

Older series of cases of SE that tabulated etiologies usually included all varieties of status, but the majority of such cases were GCSE. A summary of these data is provided in the first edition of this book.[140] However, even when newer studies are reviewed, the etiology of GCSE has not changed substantially. Ten case series in the last decade have been limited to generalized convulsive status epilepticus (Table 2). Most of these studies used variations on a classification of etiology that includes acute symptomatic and remote symptomatic causes, prolonged febrile seizures, and de novo epilepsy. Hauser[47] suggested that 12% of patients with new-onset epilepsy will present in status epilepticus. Over the last decade, 10, mostly prospective, studies of the etiology of GCSE have been reported (Table 2). The etiology of GCSE is quite variable, depending on age and whether the patient has a previous history of epilepsy, as are events precipitating specific episodes of SE. In adults, the most common causes are remote symptomatic, and discontinuation of antiepileptic drugs is the most common cause of SE in patients with chronic epilepsy. Head trauma, central nervous system infection, and cerebral infarction or hemorrhage are frequent causes of SE occurring de novo. In the one series of patients with subtle GCSE,[148] life-threatening medical illnesses, including hypoxic encephalopathy, accounted for more than half of the cases. In children, prolonged febrile seizures account for up to 40% of the cases.

Pathophysiology

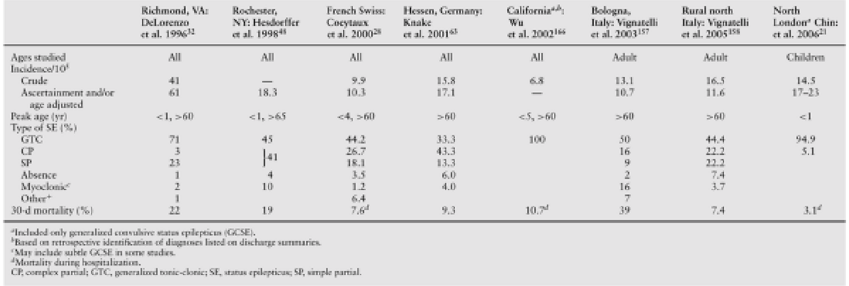
Most convulsive seizures are of short duration, and the convulsive activity almost always terminates within 2 minutes. Theodore et al.[130] studied the convulsive portion of 120 generalized tonic–clonic seizures recorded in a monitoring unit at the National Institutes of Health. The mean duration of the generalized tonic–clonic phase was 62.2 seconds, with a range of 16 to 108 seconds. Thus, mechanisms exist that terminate isolated epileptic seizures within a short period of time. Furthermore, in many patients there is a refractory period lasting for minutes, hours, or days before another seizure occurs. However, under some circumstances, seizure-terminating mechanisms fail and seizure activity either persists or recurs before full recovery of physiologic and neurochemical homeostasis. This, in physiologic terms, is the operational definition of SE. Neuronal inhibitory mechanisms that may contribute to seizure termination include Ca^{2+}-dependent K^+ currents, blockade of *N*-methyl-D-aspartate (NMDA) channels by Mg^{2+}, and the inhibitory effects of adenosine, opioid peptides, and γ-aminobutyric acid (GABA). Kapur et al.,[59] using a paired-pulse technique in an electrogenic model of experimental SE, showed that a marked deterioration of GABA-mediated inhibition occurs during continuous hippocampal stimulation, and Treiman et al.[151] reported similar findings in hippocampal slices obtained during various EEG stages in lithium/pilocarpine-induced SE. Furthermore, NMDA receptors become activated during continuous hippocampal stimulation,[8] and NMDA antagonists block the deterioration of GABA-mediated inhibition.[58] Wasterlain and colleagues reported a 50% reduction in synaptic $GABA_A$ receptors and increase in synaptic NMDA receptors per granule cell synapse after 1 hour of experimental SE.[20,88] On the basis of these observations they propose that alterations in receptor trafficking can explain the transition from isolated seizures to SE and the progressive refractoriness of ongoing GCSE to treatment, especially with GABAergic drugs such as benzodiazepines and barbiturates.

Although it is frequently difficult to sort out cause and effect, there is abundant evidence for profound neuropathologic changes occurring as a consequence of GCSE, starting with Pfleger's detailed pathologic study of a patient dying in SE.[100] Neuronal damage, involving principally the neocortex, hippocampus, thalamus, and cerebellum, has been observed in brains of children and adults dying shortly after an episode of SE.[29,40,92,116,167] However, neuronal damage observed after SE could be caused by the initial insult to the central nervous system that precipitated the episode of status rather than by the SE seizure activity itself. DeGiorgio et al.[31] attempted to test this possibility with a case-matched control study. These authors studied hippocampal neuronal density in the brains of five adult patients who died shortly after an episode of GCSE; five patients who were as closely matched as possible for parameters such as age, underlying central nervous system insult, and underlying medical conditions, including epilepsy, but who had not had an episode of GCSE; and five age-matched controls with no history of central nervous system insult or epilepsy. In five regions of the hippocampus, the patients with SE had the lowest neuronal counts, the case-matched controls the next lowest, and the central nervous system controls the highest.

Animal studies also provide evidence for SE-induced neuronal damage in previously normal subjects, even when the animals are paralyzed and artificially ventilated.[83] Observation of neuronal changes in well-ventilated animals in which adequate glucose levels have been maintained suggest that although systemic complications such as hypoxia, hypoglycemia, lactic acidosis, and especially hyperpyrexia may exacerbate the neuronal damage occurring as a result of sustained seizure activity,[9,76,83,120,126] the ongoing seizure activity itself substantially contributes to the neuronal damage.[30,43,54,70,89,90,93,154,155] Fujikawa[41] detected neuronal damage after only 20 minutes of ongoing pilocarpine-induced experimental SE. There was a progression of distribution and intensity over the 3 hours of observation. Both animal and human studies have shown that the immature brain may be less susceptible to seizure-induced neuronal damage, although it is more susceptible to seizures.

Clinical Features

Generalized convulsive SE is characterized by paroxysmal or continuous motor activity. The motor activity may be of the tonic or clonic type or a combination of both; it may be symmetric or asymmetric, and overt or subtle. However, it is always associated with a marked impairment of consciousness and with bilateral (although frequently asymmetric) ictal EEG discharges.[137] In what Treiman et al.[148] called *overt GCSE* the episode usually begins with a series of discrete generalized convulsions in which tonic or clonic motor activity, or a combination thereof, is associated with EEG discharges that evolve during the course of the convulsion. At this stage, the clonic phase of a discrete generalized convulsion stops abruptly, coincident with the end of the electrographic seizure. Typically, there is a gradual recovery of consciousness following each convulsion, but if the patient has not recovered fully to baseline—usually a fully alert state with no residual confusion or other neurologic symptomatology—before the next convulsion occurs, the patient is considered to be in GCSE. If GCSE is not treated or is inadequately treated, the motor manifestations become increasingly subtle as the episode of SE persists.[137] Eventually, only subtle twitching of the fingers, abdominal muscles, or face or nystagmoid jerks of the eyes may be seen. Finally, if GCSE continues for a prolonged period of time, all motor activity may cease, although ictal discharges on the EEG persist. This condition is then called *electrical GCSE*. Such a term is not an oxymoron because GCSE is a dynamic state in which the clinical and electrical manifestations change with time, as discussed in the Definition section. Thus, the evolution of untreated or undertreated GCSE is usually from overt GCSE to subtle GCSE to electrical GCSE. However, in some patients the encephalopathic insult is so severe (e.g., anoxic encephalopathy) that only one or two generalized convulsions (or sometimes even none) occur before subtle convulsive activity develops or the patient progresses to electrical GCSE.[24,156]



	Richmond, VA: DeLorenzo et al. 1996[32]	Rochester, NY: Hesdorffer et al. 1998[48]	French Swiss: Coeytaux et al. 2000[28]	Hessen, Germany: Knake et al. 2001[65]	California[a,b]: Wu et al. 2002[166]	Bologna, Italy: Vignatelli et al. 2003[157]	Rural north Italy: Vignatelli et al. 2005[158]	North London[a] Chin: et al. 2006[21]
Ages studied	All	All	All	All	All	Adult	Adult	Children
Incidence/10^5								
Crude	41	—	9.9	15.8	6.8	13.1	16.5	14.5
Ascertainment and/or age adjusted	61	18.3	10.3	17.1	—	10.7	11.6	17–23
Peak age (yr)	<1, >60	<1, >65	<4, >60	>60	<5, >60	>60	>60	<1
Type of SE (%)								
GTC	71	45	44.2	33.3	100	50	44.4	94.9
CP	3	41	26.7	43.3		16	22.2	5.1
SP	23		18.1	13.3		9	22.2	
Absence	1	4	3.5	6.0		2	7.4	
Myoclonic[c]	2	10	1.2	4.0		16	3.7	
Other[+]	1		6.4			7		
30-d mortality (%)	22	19	7.6[d]	9.3	10.7[d]	39	7.4	3.1[d]

[a] Included only generalized convulsive status epilepticus (GCSE).
[b] Based on retrospective identification of diagnoses listed on discharge summaries.
[c] May include subtle GCSE in some studies.
[d] Mortality during hospitalization.
CP, complex partial; GTC, generalized tonic-clonic; SE, status epilepticus; SP, simple partial.

Table 1 Incidence of status epilepticus

Table 2 Etiology of generalized convulsive status epilepticus

	Nijmegen, Holland: et al. 1994[115]	U.S. VA Hospitals: Treiman et al. 1998[148] Overt GCSE	U.S. VA Hospitals: Treiman et al. 1998[148] Subtle GCSE	Ismir, Turkey: Sagduyu et al. 1998[111]	Santander, Spain: Minambres et al. 2001[87]	California hospitals: Wu et al. 2002[166]	Tampere, Finland, Children: Metsaranta et al. 2004[85]	Hong Kong Elderly: Hui et al. 2005[52]	Bangkok children: Visudtibhan et al. 2006[159]	North London Children: et al. 2006[21]
Number of cases	346	384	134	66	57	15,882	279			176
Etiology (%)										
Acute symptomatic		27.3	37.3				3.9	56.3		33.0
Hypoxia/anoxia	1.7	6.3	38.1			8.0		7.5		
Brain trauma	2.6			3.0	5.3			2.5		
Brain tumor	3.5			6.1	12.3	1.8		6.3	3.1	
CNS infection	1.7			10.6	5.3	0.6		5.0	6.3	
Acute CVA	8.4			3.0	22.8	1.6		43.8	3.1	
Subarachnoid hemorrhage						0.4		17.5		
Encephalopathy									3.1	
Toxic/med/drug	6.1	6.3	5.2	7.6	15.8	8.7		6.3		
Alcohol		6.5	0.7			8.1		3.8		
Drug withdrawal	0.3			48.5	36.8	3.8				
Otitis media						2.8				
Life-threatening med		32.0	56.7							
Febrile SE						2.5	41.9			31.9
Systemic infection	1.4									
Exhaustion	0.9									
Idiopathic/unknown	2.3			21.2	1.8	32.6	26.2		15.6	18.8
Progressive symptomatic	0.9					1.0				
Remote symptomatic	70.2	69.5	34.3				28.0		96.9	16.5
Prior vascular event								7.5		
Prior TBI										

Prior structural insult						10.8			18.8	
Hydrocephalus						1.4				
Static encephalopathy						16.0			12.5	
Prior epilepsy (%)	69	42.4	12.7	72.7	51.8		14	18.8	84.4	40.3
Mortality (%)	11	27	64.7	21	36.8	10.7	0		6.3	3

CNS, central nervous system; CVA; cerebrovascular accident; drug, drug abuse; GCSE, generalized status epilepticus; met, metabolic; SE, status epilepticus; TBI, traumatic brain injury; VA, Veterans Administration.

Interictal symptomatology depends on the stage to which GCSE has progressed. Discrete seizures typically evolve from initial generalized tonic stiffening to clonic jerks, which increase in amplitude and decrease in frequency until further clonic activity ceases abruptly and completely. At this point, the patient remains comatose and motionless. If the patient is truly in an interictal state, low-voltage slow activity without epileptiform discharges are seen on the EEG. Following a discrete seizure the comatose state lightens gradually and the EEG gradually normalizes. However, even though the patient may largely recover to a full state of alertness, if the behavior and the EEG do not return completely to the preictal baseline before the next seizure, the patient operationally is considered to be in GCSE. As GCSE evolves from overt to increasingly subtle motor manifestations, the EEG and associated behavioral abnormalities progressively become continuous and the patient no longer exhibits any periods that can be considered interictal.

A number of physiologic changes occur during the course of GCSE. Physiologic changes during SE have been summarized recently by Simon[121] and Young.[167] Meldrum,[79] Brown and Hussain,[14,15] and Walton[161] emphasized the importance of differentiating between early and late physiologic changes during SE. The initial physiologic response is a massive release of epinephrine and norepinephrine into the circulation.[7,123] This increase in circulating catecholamines results in increased systemic, pulmonary, and left atrial blood pressure, heart rate, and plasma glucose concentration[7,9,10,11,19,50,53,66,67,81,82] and an increase in cardiac arrhythmias.[39,68,81] Several investigators have suggested, on the basis of experimental evidence from animal studies, that hyperglycemia may exacerbate SE-induced neuronal damage.[9,103,131] Therefore, glucose administration during SE should be avoided unless true hypoglycemia has been established.[131]

Respiratory function is frequently impaired in early SE.[6,98] Pulmonary edema is a common finding in experimental[60,122] and clinical[39] SE and has also been seen at autopsy following clinical episodes of SE.[94] Acidosis is seen frequently during GCSE, both in animal models[56,81,124] and in human patients.[1,35,163] Much of the acidosis is caused by a combination of respiratory failure and release of systemic lactate during generalized convulsive activity. However, some degree of acidosis is present even in paralyzed and artificially ventilated animals.[83,124]

It has long been recognized that of all the systemic physiologic changes occurring during early SE,[12,25,26,27] hyperpyrexia is the most important cause of poor outcome following an episode of SE.[1] In their studies of bicuculline-induced SE in baboons, Meldrum and colleagues[80,83] reported that cerebellar damage following status occurred exclusively in animals whose core temperatures remained >40°C for prolonged periods. Temperature elevations >41°C cause hippocampal epileptic damage in rats and hypothermia protects against damage.[76] Hyperthermia lowers the seizure threshold to kainic acid, and prolonged seizures result in greater brain damage.[71] Sustained hyperpyrexia during GCSE also has been shown to produce permanent cerebral damage in humans.[120]

White blood cell counts may also be elevated in GCSE.[2,35,129] When patients also exhibit hyperthermia, clinicians may mistakenly presume an infectious etiology for the episode of status when no such infection exists. A low-grade pleocytosis in the cerebrospinal fluid (CSF) may also be observed following an episode of GCSE.[1,3,114] Barry and Hauser,[3] however, recently reported that the CSF white blood cell count in their study of 138 episodes of SE was never >30/mm^3 unless there was another cause for the CSF pleocytosis.

In late GCSE (usually after ≥30 minutes of seizure activity), many physiologic parameters return to baseline values or even drop below baseline. After an initial period of hypertension, blood pressure begins to decline after 15 to 30 minutes of experimental SE and may be markedly low after 2 hours of continuous seizure activity.[7,54,81,82] Plasma glucose concentrations may also decline to hypoglycemic levels.[11,38,84] Renal failure may develop as a result of rhabdomyolysis with resultant myoglobinuria[44,62,113,125] but has also been reported to be caused by intense vasoconstriction, even without myoglobinuria.[99]

Increased intracranial pressure occurs, at least transiently, with all epileptic seizures. However, if increased intracranial pressure persists when blood pressure drops during late SE, generalized cerebral edema may develop, especially in children.[14] Focal cerebral edema may also occur in GCSE and may be mistaken for other pathologies on cerebral imaging studies.[5,65,108,112] One recent report found evidence of hippocampal edema associated with prolonged febrile seizures but not in nonfebrile generalized SE.[117] Two recent reports[69,127] suggested, on the basis of MRI acute and chronic data, that mesial temporal sclerosis (MTS) may follow prolonged febrile convulsions, but other contributing factors for MTS, including genetic predisposition, have also been proposed.[18]

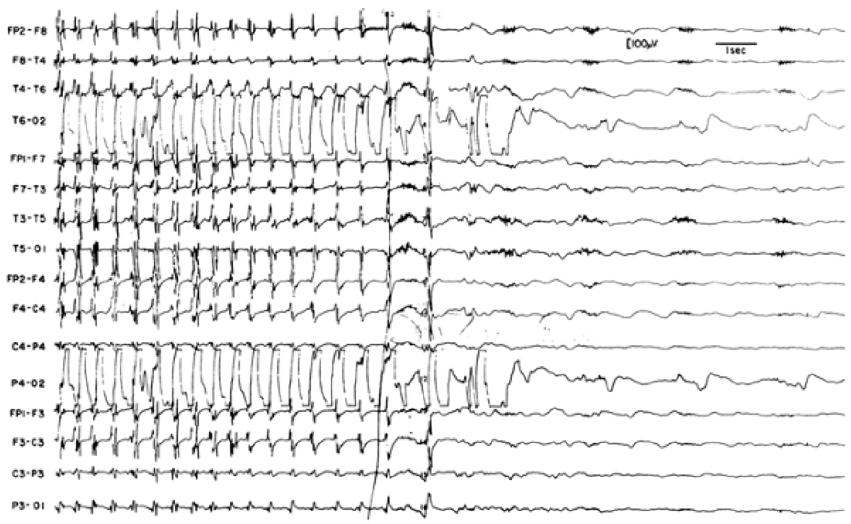


FIGURE 1. Discrete generalized tonic–clonic seizures with interictal slowing, recorded before treatment in a 39-year-old man. The example shows the end of the clinic phase of the seizure and the appearance of postictal slowing. (From Treiman DM, Walton NY, Kendrick C. A progressive sequence of electroencephalographic changes during generalized convulsive status epilepticus. *Epilepsy Res*. 1990;5:49–60; with permission.)

Diagnosis

Overt GCSE is operationally defined as two or more generalized convulsions without full recovery of consciousness between seizures or as a single prolonged convulsion. The diagnosis of overt GCSE is not difficult when recurrent convulsions occur, but a common error is to fail to diagnose SE because the patient appears to be recovering consciousness before the next seizure occurs. Any residual impairment of consciousness—any state short of full alertness—is an indicator that seizure-induced pathophysiologic changes persist and that therefore, by definition, the patient is in SE when seizure activity recurs under such circumstances. Furthermore, the clinical presentation of GCSE and the ictal patterns observed on the EEG may be asymmetric. Physicians might erroneously make a diagnosis of focal motor (simple partial) SE when a patient with impaired consciousness exhibits only unilateral convulsive movements. Such patients should be considered to be in GCSE with an asymmetric or unilateral presentation unless they are fully alert during the motor convulsions.

Although the initial diagnosis of GCSE is usually based on clinical criteria, the EEG has an important role in the diagnosis and management of GCSE. A predictable sequence of five patterns of EEG discharges has been reported by Treiman and colleagues in human patients (Figs. 1,2,3,4,5) and six experimental models of SE in the rat.[46,61,145,150] Subsequent to Treiman et al.'s initial description[144] the same sequence also has been observed in four additional models of experimental SE.[64,73,86,104] Initially, the EEG exhibits discrete electrographic seizures associated with overt generalized convulsions. If GCSE is allowed to progress without adequate treatment, the discrete seizures merge to form a waxing and waning pattern of rhythmic ictal discharges that ultimately become monomorphic and continuous. This continuous seizure activity, which may take the form of continuous spike or spike-and-wave patterns, rhythmic sharp waves, or rhythmic slow waves, is then punctuated by periods of relative flattening that become progressively longer as the ictal discharges shorten. Finally, the patient exhibits periodic epileptiform discharges on a flat background. Recognition of any of these ictal patterns in a comatose patient should lead to the diagnosis of GCSE, even in the presence of extremely subtle convulsive movements. However, some investigators continue to question whether such patterns as periodic epileptiform discharges should be considered as electrographic evidence of status epilepticus.[13]

There is a growing consensus that most cases of SE should be managed using simultaneous EEG recording, although initiation of treatment should never be delayed while the physician is waiting for the EEG. However, not all neurologists share this view. Certainly, if clinical seizure activity stops and the patient clearly is recovering consciousness, EEG monitoring is not necessary. However, if after convulsive movements have stopped the patient does not rapidly regain consciousness, cessation of all electrical seizure activity should be verified by EEG. Furthermore, if a patient has a single convulsion but fails to recover consciousness, emergency EEG recording is essential. Such a patient is likely to be in subtle GCSE following the single convulsion.

Subsequent diagnostic evaluation after the initial treatment of GCSE should be directed toward determining the cause of the episode. In patients in whom GCSE develops as a complication of a preexisting seizure disorder, the precipitating cause of the episode—low serum concentrations of antiepileptic drugs, intercurrent infection, progressive neurologic insult—should be determined by obtaining blood for serum chemistries, complete blood cell count, and assays for toxic agents. A history of intracranial mass may require magnetic resonance cerebral imaging to detect recurrence or enlargement. If the episode of GCSE is a first seizure, the patient should be evaluated for causes of new-onset epilepsy or for the possibility of an underlying systemic illness or encephalopathy that has been complicated by the development of GCSE. Depending on age, central nervous system infection, cerebral infarction or mass lesion, systemic metabolic disorder, or substance abuse or presence of other toxins must be considered.

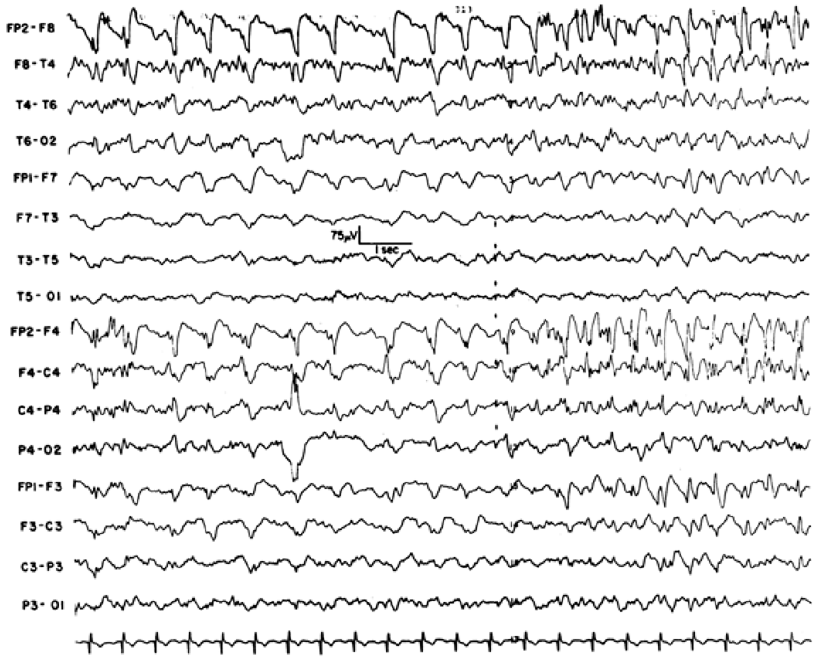


FIGURE 2. Merging of discrete seizures, recorded before treatment in a 64-year-old man. Ictal discharges are continuous but exhibit waxing and waning of frequency and amplitude. An increase in frequency and amplitude can be seen beginning on the right side of the recording. (From Treiman DM, Walton NY, Kendrick C. A progressive sequence of electroencephalographic changes during generalized convulsive status epilepticus. *Epilepsy Res*. 1990;5:49–60; with permission.)

Differential Diagnosis

Although psychogenic SE is not common, it has been described by a number of investigators in adults and children.[4,16,36,45,49,51,55,95,96,97,106,107,119,128,132,164] Psychogenic SE is seen frequently in some epilepsy-monitoring units. Some patients who exhibit psychogenic seizures, even in the context of SE, can be extremely convincing. Four characteristics of genuine epileptic seizures are helpful in the identification of psychogenic seizures[23,136,137]: (a) evolution of behavior during the seizure, (b) stereotyped seizures, (c) sustained convulsive activity without pauses, and (d) eyes open during the seizure. Typically, generalized convulsive seizures exhibit a stereotypic evolution of first tonic and then clonic movements. Overt clonic jerks followed by tonic stiffening and then cessation of convulsive activity is never seen in a true epileptic seizure, although some patients may exhibit mild clonic jerks at the onset of a clonic–tonic–clonic seizure. Clonic jerks at the end of a clonic seizure, a typical tonic–clonic seizure, or a clonic–tonic–clonic seizure tend to decrease in frequency but increase in amplitude as the seizure progresses, and they usually stop abruptly. When motor seizure activity spreads in seizures of partial onset, the pattern of spread should be consistent with the organization of the homunculus on the motor cortex. If a seizure does not evolve in a typical pattern, this raises the question of a possible psychogenic seizure. However, some convulsions, particularly those of frontal lobe origin, may involve bizarre behavior, including strange vocalizations, flailing of the arms, head jerking from side to side, and sexually suggestive pelvic thrusting. If such seizures are stereotypic in their behavioral manifestations, it is likely they are true epileptic seizures despite their bizarre presentation. Psychogenic seizures, on the other hand, may exhibit variable behavior patterns from event to event. Furthermore, motor activity during a psychogenic event is likely to be punctuated by pauses for brief periods of rest, whereas during true epileptic convulsions, tonic, clonic, or tonic–clonic activity is usually sustained without pauses until the end of the seizure. A conscious patient having psychogenic generalized tonic–clonic seizures cannot ordinarily sustain continuous intense clonic or even tonic muscle contractions without at least brief periods of rest.

Ultimately, the EEG recording is the definitive way to differentiate between epileptic seizures and psychogenic seizures.[139] Well-modulated alpha activity in the posterior regions during or immediately following apparent seizure activity is good evidence for psychogenic seizures. After true generalized convulsions, there should be postictal slowing, at least initially, although patients with seizures of frontal lobe origin rapidly recover consciousness and their EEGs rapidly normalize.

Response to Treatment

Response to treatment in GCSE is largely determined by the duration, EEG pattern, and clinical presentation at the time treatment is initiated and by the underlying etiology. The longer an episode of status is allowed to persist, the more refractory to treatment it will be.[37,78,146,148] In both experimental SE[57,162] and human GCSE,[149] the later the EEG stage, the less responsive is the subject. In a Veterans Administration (VA) cooperative study that compared the efficacy of four treatments of GCSE, overall only 56% of patients with overt GCSE and only 15% with subtle GCSE responded to the initial treatment.[148] There was little further response to a second or third treatment. Only intravenous general anesthesia exhibited efficacy in a substantial number of patients who failed the first drug. The outcome of this study is discussed in more detail in Chapter 126.

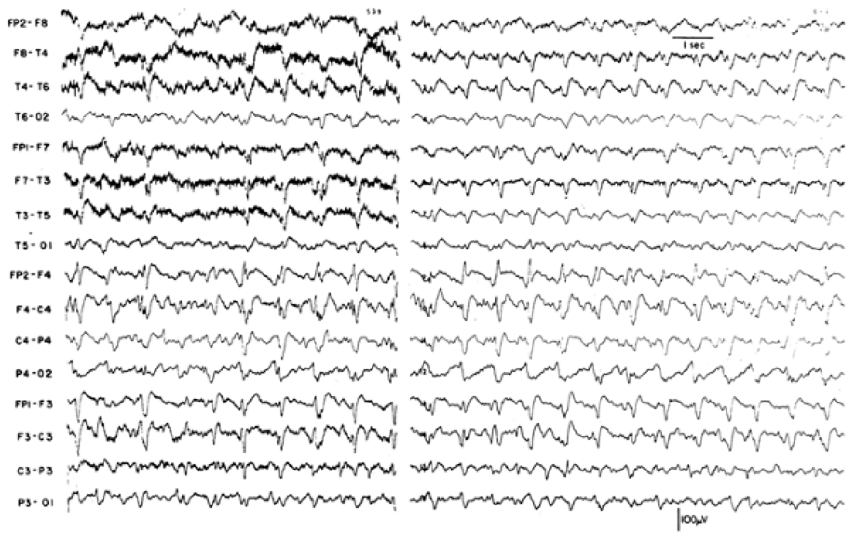
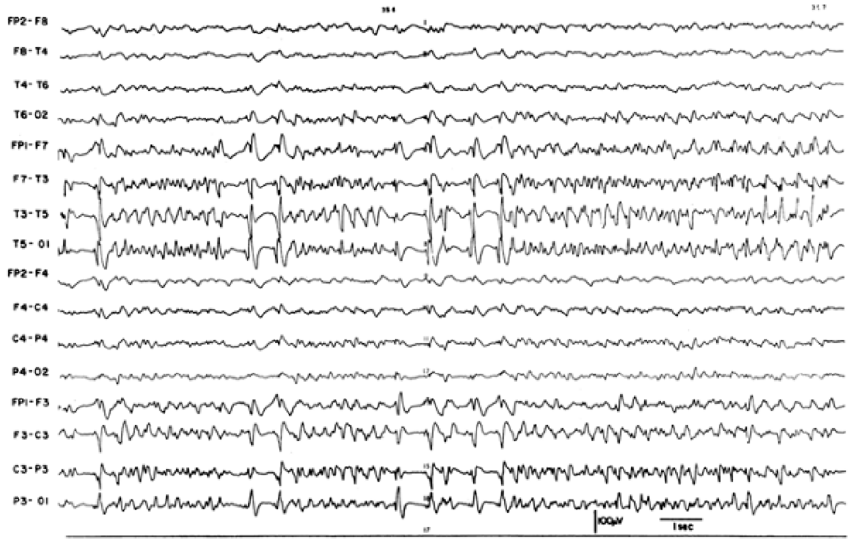

FP2-F8
F8-T4
T4-T6
T6-O2
FP1-F7
F7-T3
T3-T5
T5-O1
FP2-F4
F4-C4
C4-P4
P4-O2
FP1-F3
F3-C3
C3-P3
P3-O1
1 sec
100µV

FIGURE 3. Continuous ictal discharges recorded before treatment in a 68-year-old man. Examples are 16 minutes apart. Continuous ictal activity persisted for 101 minutes, stopping only after phenytoin infusion was completed and 4 minutes after the end of lorazepam infusion. (From Treiman DM, Walton NY, Kendrick C. A progressive sequence of electroencephalographic changes during generalized convulsive status epilepticus. *Epilepsy Res*. 1990;5:49–60; with permission.)


FP2-F8
F8-T4
T4-T6
T6-O2
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T3-T5
T5-O1
FP2-F4
F4-C4
C4-P4
P4-O2
FP1-F3
F3-C3
C3-P3
P3-O1
100µV
1 sec

FIGURE 4. Continuous ictal discharges with flat periods recorded before treatment in a 68-year-old man. The seizure focus is clearly in the left hemisphere, but the spread of ictal activity to the right hemisphere can be seen as well. (From Treiman DM, Walton NY, Kendrick C. A progressive sequence of electroencephalographic changes during generalized convulsive status epilepticus. *Epilepsy Res*. 1990;5:49–60; with permission.)

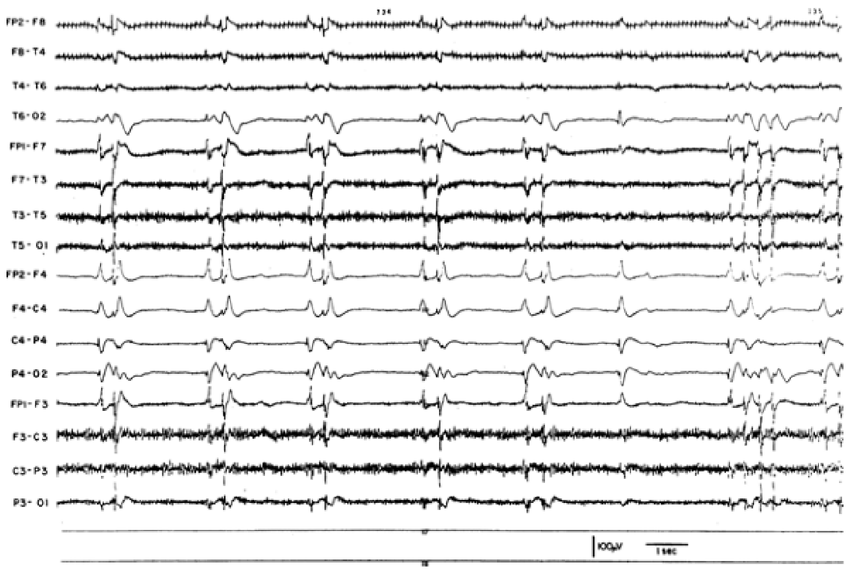

FIGURE 5. Periodic epileptiform discharges on a flat background recorded before treatment in a 64-year-old man. (From Treiman DM, Walton NY, Kendrick C. A progressive sequence of electroencephalographic changes during generalized convulsive status epilepticus. *Epilepsy Res*. 1990;5:49–60; with permission.)

Consequences

Morbidity and mortality in GCSE are largely determined by the underlying etiology of the episode, but they may be substantially increased by inadequate treatment. When treatment is delayed or inadequate, prolonged duration of GCSE is associated with a high morbidity and mortality.[35,77,148] However, in a systematic review of the outcome of pediatric convulsive SE, Raspall-Chaure et al. found the etiology is the main determinant of outcome and the effect of age or duration is difficult to separate from the underlying cause.[105] In fact, Hauser[47] suggested that mortality directly caused by SE itself occurs in no more than 1% to 2% of SE cases, even though recent series have reported mortality rates of 10% to 12%. Mortality rates of 5% to 50% have been reported.[142] Morbidity and mortality rates are substantially higher in hospital-based studies than in community-based studies. For instance, in the VA study mentioned earlier, the percentage of patients dying within 30 days of the episode of status was 26.8% for overt GCSE and 64.9% for subtle GCSE.[148] In this study, several predictors of mortality were identified. Both acute central nervous system insult and severe systemic disorder predicted poor outcome, whereas a remote central nervous system insult, whether or not an acute insult also occurred at the time of GCSE, predicted a better outcome.[147] In a community-based study in Richmond, Virginia, mortality was also defined as death occurring within 30 days following the episode of SE. Towne et al.[134] reported a mortality rate of 21% in patients with generalized SE, most of whom had GCSE. In Rochester, Minnesota, acute mortality after SE was 19%.[72] Table 2 summarizes mortality data from recent series of GCSE.

Summary and Conclusions

Generalized convulsive SE has been recognized since Babylonian times. This presentation of SE is characterized by recurrent or prolonged generalized convulsions, profound impairment of consciousness, and ictal discharges on the EEG. More than 150,000 cases of SE occur in the United States each year, most of which are cases of GCSE. Generalized convulsive SE is a dynamic state, and a predictable progression from overt to increasingly subtle motor manifestations occurs if GCSE persists without treatment or with inadequate treatment. A predictable sequence of progressive EEG changes also occurs from the beginning to the end of GCSE. Generalized convulsive SE includes what is sometimes mistakenly called *focal motor status* when motor activity is markedly asymmetric in a comatose patient. Psychogenic SE is not common but can be suspected by variability of seizure presentations during an episode, brief pauses for rest occurring during tonic or clonic motor activity, or persistent eye closure. Generalized convulsive SE must be treated early to achieve the greatest probability of success. The later the episode, the subtler the presentation, and the later the EEG stage, the more refractory to treatment the episode will be. Morbidity and mortality are largely determined by underlying etiology, but poor treatment further worsens a poor prognosis.

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Chapter 59

Complex Partial Status Epilepticus

Peter D. Williamson

Introduction

Nonconvulsive status epilepticus (SE) is divided into two categories: absence SE (ASE) (spike-wave stupor, petit mal status) and complex partial SE (CPSE).[4,71,102,114,117] ASE is discussed in detail in the following chapter (see Chapter 60). ASE will be examined here only in comparison to CPSE. Until relatively recently, CPSE has been considered very rare. Twenty-three years ago, Ballenger[4] reviewed the literature and concluded that there were only 17 well-documented cases of CPSE. Subsequently and certainly related to the exponential growth in epilepsy centers, there has been a significant increase in reports critically examining nonconvulsive SE and CPSE.[14,18,44,62,91,114,115,116,127,129,133] This includes several studies in which CPSE was studied using intracranial electrodes.[53,129,133] Even so, the limits and definitions of nonconvulsive SE in general, and CPSE in particular are still imprecise.[125] Consequently, controversies over several important issues persist. As will be discussed, differentiating the two types of nonconvulsive SE is often difficult and sometimes not possible at the time of initial clinical presentation.

The term "complex partial" has recently been called into question by the ILAE Task Force on Classification and Terminology.[9] This was largely based on the difficulty encountered when trying to define consciousness. The term "dyscognitive" was suggested to replace "complex partial." Dyscognitive SE would greatly simplify the condition and overlook many of the complicated and complex characteristics of the condition. This is even further confounded by a recent recommendation of a new classification of SE in which dyscognitive status is further subdivided into three subcategories.[93] For the purposes of this discussion, the term CPSE will be retained in the hopes of avoiding confusion. This is consistent with the recommendations of the ILAE task force.

History

CPSE with electroencephalographic (EEG) documentation was first reported by Gastaut et al.[38] in 1956. Almost 70 years earlier, however, during his Tuesday lectures, Charcot provided a fascinating and colorful account of a patient he had examined who had multiple, prolonged, ambulatory fugue states.[16,41] Charcot was convinced that this form of poriomania was indeed an example of epileptic fugue and, as such, would now be considered a type of nonconvulsive SE. Although an argument has been presented implying Charcot's case was an example of ASE,[41] an equally strong case could be made for CPSE. Jackson[50] also described cases of prolonged twilight states presumed to be epileptic. Whether these and other descriptions found in scholarly writings from ancient times up to Gastaut's report in 1956 are examples of nonconvulsive SE can only be conjectural, since most modern authorities would agree that EEG criteria are needed to make the diagnosis.[14,17,30,45,53,91,114,115,124]

SE of any type was only rarely described before the 19th century,[110] but as reviewed by Shorvon,[102] isolated early descriptions of fatal convulsive SE date from the neo-Babylonian era. In ancient times, it can be assumed that most nonconvulsive varieties of SE were not recognized as epilepsy. For example, a patient with probable nonconvulsive SE is described in *The Sacred Illness* written by an unknown student of Hippocrates, but this manifestation was specifically excluded as a form of epilepsy.[110] Hunter[49] made the ironic observation that descriptions of SE increased with the introduction of bromide therapy, implying a causal relationship between the introduction of effective antiepileptic drug (AEDs) and the increased frequency of SE, presumably a consequence of withdrawal of medication.

Definitions

SE is defined as "a condition characterized by epileptic seizures that are sufficiently prolonged or repeated at sufficiently brief intervals so as to produce an unvarying and enduring epileptic condition."[36] Although this definition is generally accepted, it has some definite drawbacks and limitations. What constitutes "enduring"? Time constraints were suggested only after the definition was proposed and have since generated considerable debate and controversy. Although the duration of convulsive SE may have prognostic significance, it is of much less importance in most cases of nonconvulsive SE, even in extreme examples.[18,77,133] In a study of patients with CPSE reported from the Yale epilepsy program,[133] several patients had repeated flurries of partial seizures, some lasting for less than 30 minutes and others lasting for hours. No fundamental difference was noted between the longer and the shorter episodes in terms of clinical seizure manifestations or intracranial electrographic findings. Are patients with prolonged postictal confusion examples of SE? The answer to this question depends on specific circumstances. Most examples of prolonged postictal states following complex partial seizures are exactly that—prolonged nonepileptic disturbances of cortical function following a discrete seizure. As such, this should not be considered SE. Occasionally, however, prolonged "postictal" states are due to continued seizure activity, either localized or diffuse, following a typical discrete complex partial seizure[53] (see patient 2 in case descriptions). This latter possibility clearly constitutes an enduring seizure state and is a form of SE.

Similarly, "unvarying" in the definition of SE is misleading. Some examples of nonconvulsive SE are very unvarying, whereas others present with widely variable clinical features. Some patients within a single episode of CPSE have stereotyped as well as highly variable clinical and electrographic manifestations.[127,129,133] The definition of SE therefore must be less restrictive to encompass a wide variety of types.

Shorvon[102] reviewed the limitations and proposed the following definition: "SE is a condition in which epileptic activity persists for 30 minutes or more, causing a wide spectrum of clinical symptoms, and with a highly variable patho-physiological, anatomical, and aetiological [sic] basis."

Although this avoids most of the limitations of the traditional definition of SE, there have been objections to the time constraints for nonconvulsive SE, for the reasons cited earlier. Also, this definition implies continuous seizure activity which is clearly not true in many examples of SE. Recently, the recommendations for minimal seizure duration in nonconvulsive SE have been 10 minutes.[103] This seems in much better agreement with clinical observations.

Gastaut[37] stated that there are as many types of status as there are types of epileptic seizures. The traditional separation of nonconvulsive SE into ASE and CPSE has, however, been questioned.[102,114,115] The definition of CPSE must be re-examined, and this will be done when describing clinical and electrographic seizure activity.

Epidemiology

Considering that the concept of CPSE is evolving and has yet to be defined precisely, the fact that there are no good epidemiologic studies of the condition should come as no surprise.[125] Although earlier studies concluded that CPSE was very rare, almost a medical curiosity,[4,71,74,117] more recent investigations report that CPSE is under-reported and more common than previously thought.[18,102,114,115,133] The current belief that CPSE is not rare is undoubtedly related to improved methods of detection, particularly through the use of intensive monitoring.[45] Although it is admittedly a crude approximation, Shorvon[102] estimates that CPSE occurs in 35 per 1,000,000 persons in the general population. Nonconvulsive status in the mentally handicapped population was similarly calculated at 100 to 200 per 1,000,000 persons.[102] In one hospital-based population study, an incidence of nonconvulsive SE was 1.5 per 100,000 per year.[114] Approximately half of these patients were thought to have CPSE. Two studies found that 19% to 25% of all types of SE were nonconvulsive, but the majority were considered ASE.[15,25] DeLorenzo et al.[24] attempted a prospective study of all types of SE. CPSE was very uncommon. This is not in agreement with other recent reports, which indicate that it can no longer be considered rare.[114,116,133] Treiman[116] notes that over 200 well-documented cases of CPSE have been reported. Furthermore, CPSE is probably even more common if, as suspected, the condition is under-reported.[14,24,56,102,114,133] Finally, as discussed later, many examples of what appear to be ASE occur in patients with localization-related epilepsy and are therefore examples of CPSE.[49,91,102,115,116,117] Nonconvulsive SE, in general, is estimated to comprise one third of all types of SE.[133] A PubMed search of "complex partial SE" from 2000 to present yielded 666 citations.

Etiology

The etiologies of CPSE are many and varied. Approximately one third to one half of patients with CPSE are initially seen without an antecedent history of epilepsy.[102,114] In one study of nonconvulsive SE that included CPSE, the most common precipitants were generalized tonic–clonic (GTC) seizures and changes in AEDs, either due to noncompliance or under medical direction.[114] A recent study related CPSE to increased levels of carbamazepine-10,11-epoxide secondary to comedication.[108] Other causes of CPSE include various acute diseases of the nervous system, including encephalitis and stroke.[62] A case of alcohol-induced CPSE has been reported.[35] Nonconvulsive SE has also been precipitated by intrathecal metrizamide during myelography and electroconvulsive therapy.[122,123] CPSE has been described in several reports of patients with presumed benign childhood rolandic epilepsy.[19,32,54] A type of autonomic status is characteristic of Panayiotopoulos syndrome,[59,66,81] and recurrent refractory CPSE is a component of the ring chromosome childhood epilepsy syndrome.[3] Over 30 reports relate tiagabine with the development of new CPSE.[58] CPSE has even been reported to occur after temporal lobectomy,[12] but this may have been in a patient with two separate types of epilepsy.

The causes of CPSE in patients with known focal seizures are the same as the causes of localization-related epilepsy. These include gliotic scars, tumors, vascular malformations, cerebrovascular disease, hamartomas, and congenital malformations. Precipitants include drug and alcohol withdrawal, physical and emotional stress, sleep deprivation, and metabolic disturbances. CPSE can produce transient abnormalities on neuroimaging studies that may or may not have etiologic and localizing significance.[5,61,96,109,113]

The anatomic site of seizure origin may be important in the development of SE. Until recently, CPSE was equated with temporal lobe SE.[30,37,74,98,102] In many cases, temporal lobe seizure origin was diagnosed on the basis of interictal scalp recording or simply implied because of clinical seizure characteristics. However, except for the four cases described by Wieser,[127,129] and several patients who have benefited from temporal lobectomy,[18,48] there have been very few well-documented examples of CPSE of temporal lobe origin (also see patients 1 and 3 in case descriptions). In one report, CPSE was recorded in eight of 87 patients with medically intractable localization-related epilepsy who were undergoing presurgical evaluations with intracranial electrodes.[133] Seizure origin was extratemporal in these eight patients, whereas CPSE developed in none of the 60 patients from this series with seizure origin in the medial temporal lobe. Extratemporal seizure origin and CPSE has been observed by others.[73,102] The association of frontal lobe epilepsy and convulsive SE has been the subject of several reports.[15,51,85] A similar association of nonconvulsive SE and frontal lobe seizure origin has also been reported.[7,10,13,41,114,115,130,134] In conclusion, CPSE is not analogous to temporal lobe SE, but is often related to extratemporal seizure origin, possibly with a frontal lobe preponderance.

Pathophysiology

Less is known about the pathophysiology of SE than of isolated seizures. Although the onset of isolated seizures and the initiation of an episode of SE are probably an expression of the same physiologic mechanisms, exactly how seizures start is not known. Even less is known about the mechanisms of seizure termination, but here is undoubtedly the key to understanding SE. It is known that the cessation of status per se is not due to energy failure, but presumably is related to the activation of those systems that stop single seizures.[33,34,86] The development of SE must represent failures of different systems, producing a cascade of neurophysiologic, neurochemical, and probably neuroanatomic changes that serve to perpetuate and prolong the epileptic process.[75,101] Self-sustaining feedback loops have been postulated in limbic status.[120,121] At the neurochemical level, depletion of γ-aminobutyric acid (GABA) during nonconvulsive status was reported,[126] but these results could not be duplicated in other studies.[105] Status-induced cell damage and the role of excitotoxins is discussed elsewhere in this volume, but the experimental evidence of CPSE-induced cell death must be described briefly because of its effects on long-term prognosis. In the kainic acid (KA) model of limbic SE, disseminated brain damage occurs, particularly in the hippocampus.[82] Pretreatment with diazepam abolishes this effect, thus demonstrating that cell damage is not due to the direct excitotoxic effect of KA.[6] Remote hippocampal damage occurs following prolonged perforant pathway stimulation.[104,106] Hippocampal cell damage does not occur following multiple (thousands of) single seizures.[8] How these observations relate to clinical CPSE is discussed in the sections on treatment and consequences.

Clinical Features

The initial descriptions of CPSE using EEG documentation defined two types: one with clinically apparent recurrent seizures, and another that exhibited a continuous seizure state.[30,39,69,74] Treiman and Delgado-Escueta,[117] after reviewing the literature and examining cases of their own, concluded that epileptic twilight states consisted of continuous and cyclic varieties of seizures, with CPSE being of the latter type—that is, all examples of CPSE consisted of recurrent complex partial seizures with incomplete clearing between episodes. The continuous type was thought to be ASE. This was in disagreement with previous reports (including one of their own), and is not supported by other studies. For example, Wieser[127] described a patient, studied using depth electrodes, who, during an episode of CPSE had continuous and discontinuous clinical and electrographic seizure activity. Subsequent reports of patients with CPSE, some studied using intracranial electrodes, confirmed the existence of both cyclic and continuous varieties, with some patients exhibiting both types of CPSE in single or different seizures.[14,92,114,115,129,133] Treiman,[116] in a recent communication, described CPSE presenting as a continuum between continuous altered conscious and recurrent discrete complex partial seizures, and he believed that CPSE originating in the medial temporal lobe structures was more likely to be of the cyclic variety, whereas frontal lobe CPSE was more likely to be continuous. However, this concept had been refuted by intracranial electrode studies.[129,133] Finally, variable or cyclic clinical patterns have been described in patients with ASE.[114,115] CPSE, therefore, does not always present with consistent or readily identifiable clinical characteristics, but rather is associated with a wide variety of clinical patterns, some of which may be indistinguishable from ASE. Others may mimic psychiatric disease.[53,91]

Recurrent focal EEG seizure activity was said to be typical and diagnostic of CPSE.[117] This pattern is said to exist at the onset of most, if not all, episodes of CPSE.[116] However, this has not been substantiated in patients who developed CPSE during intracranial electrode studies.[127,129,133] Cyclic and continuous ictal EEG activity can both occur in the same patient. Cyclic EEG activity has also been observed during intracranial recording without corresponding recurrent clinical activity.[133] Scalp EEG recording sometimes did not distinguish between cyclic and continuous seizure patterns in these same patients. When recurrent electrographic seizures occurred through episodes of CPSE, they tended to simplify with time, in terms of electrographic seizure discharge,[133] (see patient 2 in case descriptions). Finally, there are reports of patients with continuous diffuse spike-and-wave EEGs resembling ASE who have localization-related epilepsy.[7,40,44,114,115,116] Periodic lateralized epileptiform discharges (PLEDs) can be associated with prolonged but reversible alterations of neurologic function.[19,29,111] Some metabolic and single photon emission computed tomography (SPECT) studies indicate that PLEDs in some patients are a reflection of partial SE.[1,21,46] The EEG in patients who present with EEG patterns typical of ASE may have focal electrographic patterns only at the onset of the episode, thereby promoting diagnostic error[44,114,115] (also see patient 5 in case descriptions). Both scalp and intracranial EEG, analogous to the clinical seizure characteristics, can display a wide variety of different patterns during CPSE. The only diagnostic pattern would be clear, recurrent, localized electrographic seizures.

Given the many different clinical and EEG presentations, it is not surprising that clinical descriptions of CPSE cover a very broad range. By definition, impairment of consciousness must occur. This can vary from mild clouding of consciousness to unresponsive obtundation.[68,73,77,95,114,115] The accompanying behavior can range from bland confusion, either continuous or fluctuating, to agitated unresponsiveness with bizarre, almost psychotic activity.[37,79,91,133] Specific examples include prolonged reversible Wernicke aphasia,[60] recurrent unilateral atonic seizures in children with benign rolandic epilepsy,[54] and confusional states with PLEDs in the elderly.[46,111]

The concept of epileptic fugues lasting several days or longer has been disputed, with most such examples attributed to psychiatric disease.[76] Recent reports, however, describe well-documented examples of CPSE lasting months,[18,77,92,102] suggesting that prolonged fugues due to CPSE can occur. One of the earliest examples of prolonged nonconvulsive SE with EEG documentation is the frequently cited case of Henriksen.[48] A neurotic woman with well-established, discrete, complex partial seizures of presumed temporal lobe origin was described; she had a prolonged episode of recurrent auras of fear and a visceral sensation followed by acute anxiety with corresponding EEG changes. After 4 months, the episode was terminated with a left anterior temporal lobectomy. Because impairment of consciousness was not mentioned in the report, this would currently be classified as simple partial SE or aura continua.[97] Mikati et al.[77] describe a previously healthy 11-year-old boy who was first seen with several right focal motor and secondarily generalized convulsions; a protracted confusional state then developed, with EEG-documented recurrent localized seizures interspersed with acute psychotic behavior. While the recurrent electrographic seizures continued, he exhibited progressive obtundation that culminated in a catatonia-like state; eventually he required a gastrostomy feeding tube. AEDs were ineffective. After the third month of illness, he began to slowly improve. Nine months after illness onset, he was fully recovered and off all medications. An addendum to this report describes a similar case. Shorvon[102] mentions CPSE lasting 2 years in one of his patients, but does not provide further information. CPSE lasting 18 months is included in a report of recurrent CPSE.[18]

The following brief descriptions are selected from the author's series to illustrate some of the points made in this section:

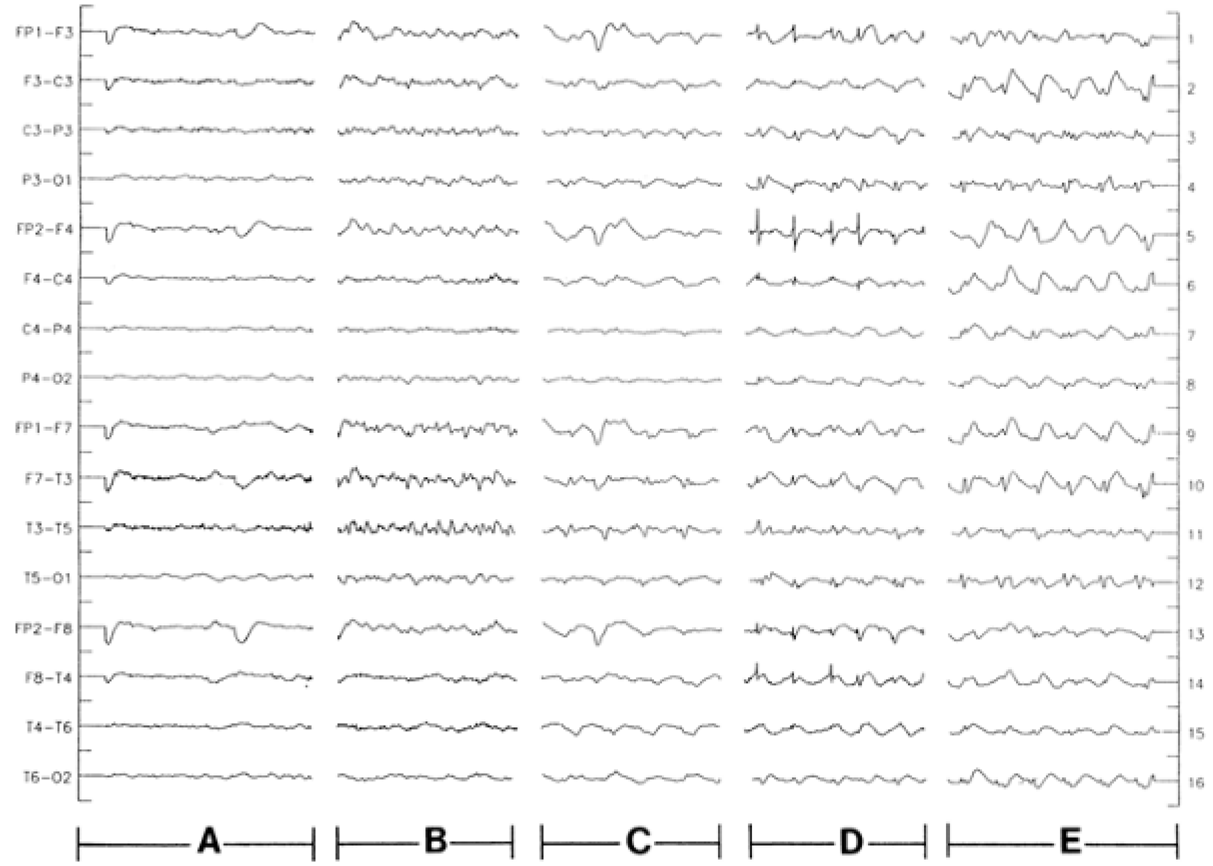


FIGURE 1. Patient No. 1. Segments of scalp EEG during prolonged, continuous seizure. **A:** Clinical seizure onset; no EEG changes. **B:** Rhythmic sharp wave buildup over left mid temporal region. **C,D:** Transition from localized to generalized seizure pattern, culminating in diffuse sharp-slow activity **(E)**.

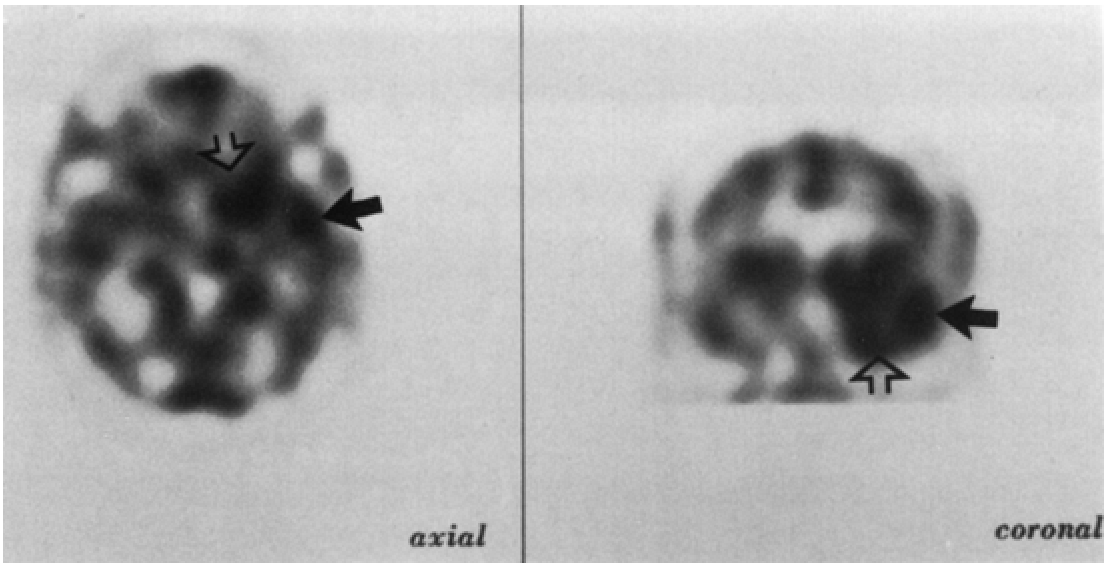


FIGURE 2. Patient No. 1. Ictal SPECT. Axial and coronal views showing increased activity in left medial (*open arrows*) and lateral (*closed arrows*) temporal lobe.

Case Study: Patient1

This 23-year-old man began having seizures at age 7. They consisted of several minutes of confusion and abnormal behavior. After 6 years of control, seizures became refractory to all antiepileptic medications, alone or in combination. Seizures occurred in a very cyclic fashion every 3 to 4 weeks. Typically, he would awaken in the morning, experience a salty taste in his mouth, and the smell of a sea breeze. He would utter “I am not going to make it! I am going to die!” and then lose contact and utter nonsense speech. He would continue in a variably confused state, fading in and out of contact throughout the rest of the day. He would then remain well for 3 to 4 weeks and have another day-long episode of recurrent seizures.

The patient was admitted for video and EEG monitoring. Medications were withheld to precipitate seizures. Interictal recording revealed left anterior temporal sharp-slow complexes and very infrequent left frontal sharp and slow complexes. He had recurrent seizures over a 74-minute period. The EEG progressed through a series of localized and generalized ictal patterns (Fig. 1). Approximately 30 minutes after onset, the entire process repeated itself, and was followed by a third similar cycle.

Clinically, during the first cycle, he initially appeared alert but was confused and unable to respond. He gradually became more responsive but did not return to baseline. His head and eyes then deviated to the extreme right, after which a tonic–clonic seizure ensued. The second cycle consisted primarily of unresponsiveness followed by brief, complete clearing, during which the EEG transiently normalized. This was followed by repetition of the same clinical and EEG sequence seen in the first cycle.

Findings on magnetic resonance imaging (MRI) were normal, but ictal SPECT obtained during one of his habitual flurries demonstrated increased signal in the left anterior lateral and medial temporal lobe (Fig. 2).

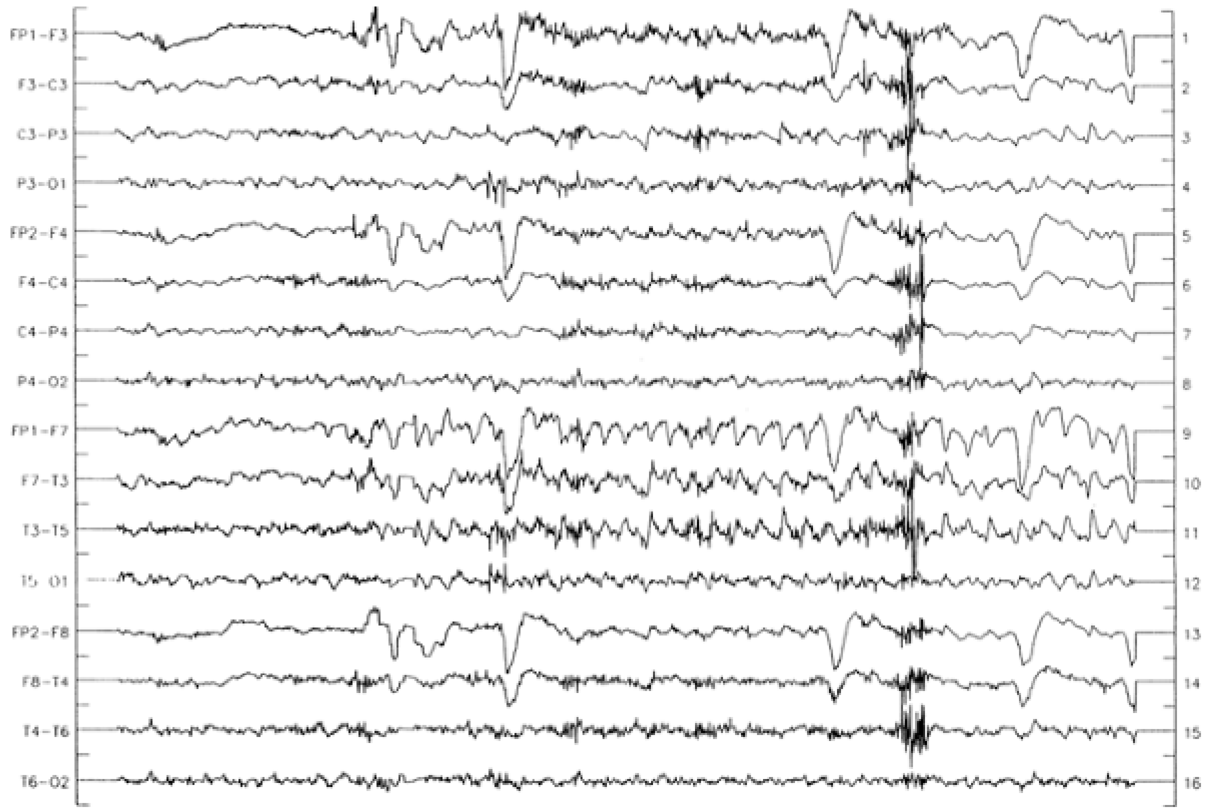


FIGURE 3. Patient No. 1. Scalp EEG during serial seizures showing rhythmic buildup over left midtemporal to anterior temporal region.

He was subsequently readmitted during one of his habitual seizure flurries, but this time while taking therapeutic doses of AEDs. Ten serial seizures were recorded. Clinically, they were repeated episodes of receptive aphasia. The EEG demonstrated left midtemporal buildup of seizure activity during each episode (Fig. 3). Anticipating seizure origin in the lateral temporal neocortex, subdural electrode grids were placed over the left frontal convexity and left lateral temporal lobe. Additional subdural strip electrodes were placed subtemporally on the left and over the right lateral temporal and frontal lobes. Habitual seizures occurred with seizure build-up in the anterior portion of the left lateral temporal lobe followed by posterior spread, but without a clear localized onset. The first EEG changes were subtle rhythmic changes in the subtemporal strip electrode placed over the uncus. A multicontact depth electrode was then stereotactically placed to sample the length of the left hippocampus. Subsequent recorded seizures had a clear hippocampal onset that preceded EEG changes elsewhere by over 20 seconds (Fig. 4). He underwent a selective hippocampectomy. Pathologic examination revealed mesial temporal sclerosis. He remained completely seizure-free 12 months following surgery. Then he began to have very infrequent dysphasic seizures without loss of consciousness, usually related to noncompliance or sleep deprivation.

Comment

This is an example of both clinical and electrographic features suggesting ASE and CPSE in the same patient. During the first admission, the episodes, recorded after he had been taken off medications, had more generalized than partial features, whereas the reverse was true in the second monitoring admission during a habitual seizure flurry when he was on antiepileptic medication. It is also a demonstration of the potential utility of ictal SPECT during CPSE. Finally, what was thought to be an example of temporal neocortical seizure origin proved to be unexpected hippocampal seizure origin.

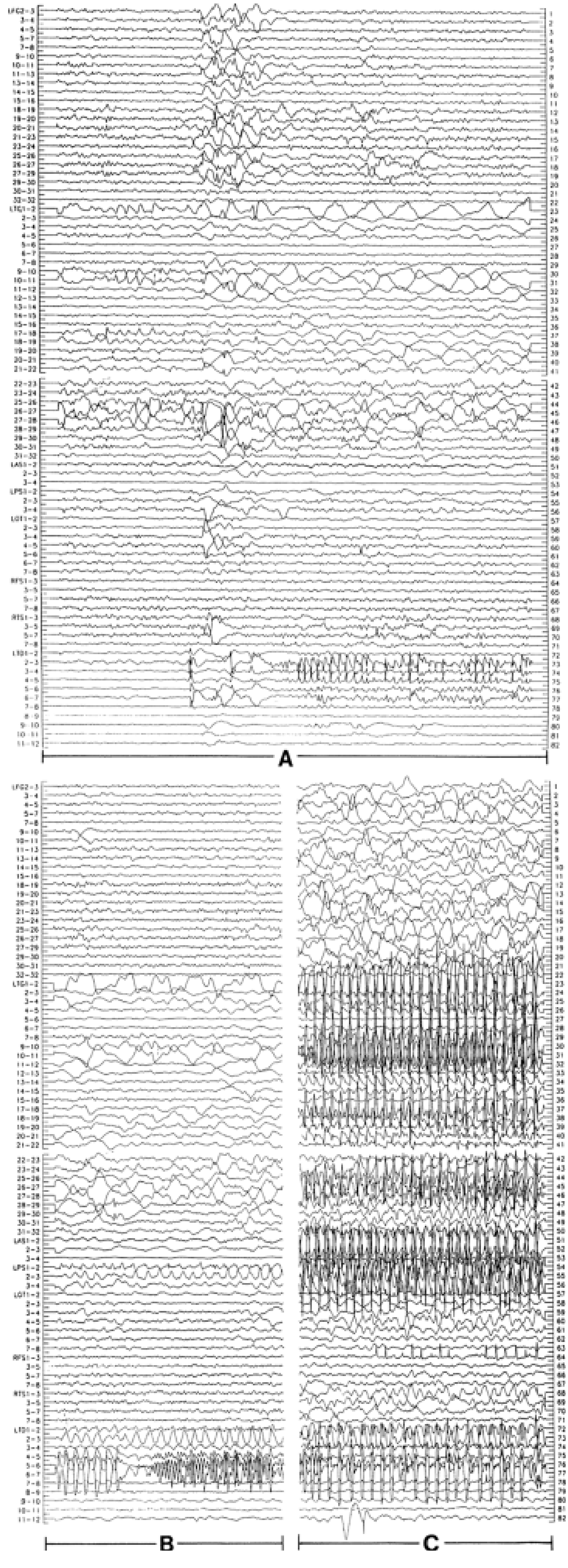

LFG2-3
LTG1-2
LAS1-2
LPS1-2
LOT1-2
RFS1-3
RTS1-3
LTD1-2
A
B
C

FIGURE 4. Patient No. 1. Segments of depth and subdural electrode recording of typical seizure showing onset and spread pattern. **A:** Ictal EEG onset in left hippocampus (depth electrode contacts *LTD 2 to 6*). **B:** Twenty-eight seconds later, ictal pattern continues in left hippocampus and rhythmic activity first occurs in subdural recording over left uncus (*LPS 2*). **C:** After another 20 seconds, seizure activity spreads to anterior left lateral temporal neocortex subdural contacts (*LTG 1 to 32*; lower numbers in each of four rows of eight contacts more anteriorly situated) and left subtemporal subdural contacts (*LAS 1 to 4* and *LPS 1 to 4*) but does not spread to frontal subdural contacts (*LFG 1 to 32*) or to right side (*RFS 1 to 8* and *RTS 1 to 8*).

Case Study: Patient 2

This 17-year-old man had several brief tonic–clonic febrile seizures beginning at 1 year of age. Afebrile seizures with tonic stiffening and falling backward began at 6 years of age. His parents thought his early seizures began with right arm stiffening and head deviation to the right, but they were not certain. After puberty, seizures increased in frequency, occurring weekly, with a nocturnal preponderance of up to ten seizures per night. He claimed to be fully awake during seizures, but was unable to speak or control his muscles. Seizures were preceded by a brief aura of a floating, "spacey" feeling.

Medications failed to control seizures, and he was evaluated for epilepsy surgery. MRI was normal. Interictal scalp EEG had rare right frontal spikes and bilateral frontal polar spike-and-wave activity. Ictal EEGs revealed some mild bifrontal slowing but were mostly obscured by muscle artifact. Clinical seizure characteristics consisted of shouted expletives and the sudden assumption of an extreme tonic posture with fists clenched, arms flexed, and legs extended. His head initially deviated to the right in several seizures, but most seizures were symmetrically tonic with some superimposed vibratory tremulousness. They lasted about 45 seconds, and stopped as suddenly as they started. He was mentally clear within several seconds. An ictal SPECT revealed increased activity on the left posterior high frontal convexity. Subdural grids were implanted interhemispherically to cover both supplementary motor areas (SMAs). Additional subdural electrodes were placed to cover the frontal convexities and frontal polar regions.

He had a series of seizures spanning an 8-hour period. The first seizure was a typical habitual seizure. The next three seizures were typical seizures that secondarily generalized into tonic–clonic convulsions. They occurred 1 hour apart, with complete clearing in between. Similar seizures began to occur more frequently without clearing between episodes. They gradually became less symmetric, culminating in a CPSE consisting of first left and then bilateral supplementary motor area ictal EEG activity occurring repeatedly for over an hour (Fig. 5). During and between seizures, the patient was unresponsive. He would elevate his right arm with each brief electrographic seizure. Status was terminated with 400 mg of intravenous phenobarbital. Other isolated habitual seizures had bilateral SMA ictal EEG activity without consistent lateralization, but cumulative findings from the entire evaluation favored left SMA seizure origin. He underwent a selective left SMA resection. Pathologic examination of the resected cortex was unremarkable. During the first 3 months following surgery, he had several flurries of very brief tonic seizures, but then became and has remained seizure-free for 12 years.

Comment

This is an example of secondarily generalized convulsive seizures evolving first into convulsive SE and then CPSE. It is also an example of the progressive simplification of electrographic and clinical seizures in a patient having recurrent partial seizures.

Case Study: Patient 3

This 15-year-old girl had her first febrile seizures at 9 months of age. These consisted of three to four separate 15-minute episodes. Three similar febrile seizure clusters occurred during the next 6 months. Seizures without fevers began at age 2, and have persisted. Seizures consist of an aura of a "butterfly" feeling in her epigastrium and a tingling feeling in her scalp, followed by partial loss of contact and automatisms. She could remain confused for up to an hour. When seizures proved medically intractable, she was evaluated for surgery. Right hippocampal atrophy was revealed by MRI (Fig. 6).

Six typical seizures were recorded during video-EEG (V-EEG) monitoring. They all started with her aura; prominent lip-smacking was then followed by dystonic posturing of her left hand and arm. She remained partially responsive throughout this part of the seizure, which lasted approximately 1 minute. One typical seizure appeared to end clinically, but she remained only partially responsive for the next 15 minutes. During this time, repeated brief left head and eye deviation was noted. At the end of the seizure, left head and eye deviation progressed into a left-sided tonic–clonic seizure followed by a dense left Todd paresis. The EEG demonstrated no change during her aura, and then went through the progression of ictal changes illustrated in FIGURE 7. Another seizure was almost identical, but ended after 20 minutes without focal motor seizure activity. At the completion of the evaluation, right medial temporal seizure origin seemed established, and she underwent a right anterior temporal lobectomy and hippocampectomy. Pathologic examination showed mesial temporal sclerosis. During the first 2 postoperative weeks, she had several focal motor seizures, but then became and has remained seizure-free for 3 years before being lost to follow-up.

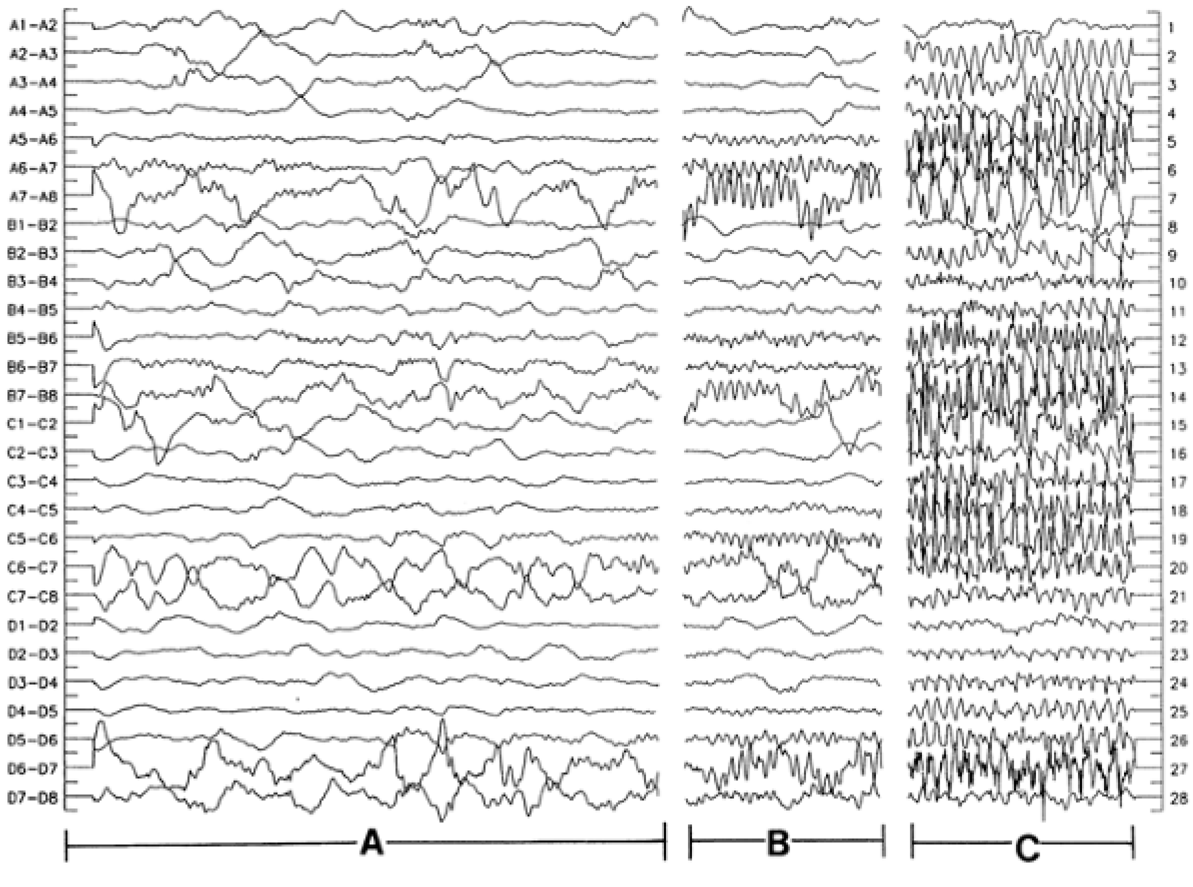


FIGURE 5. Patient No. 2. Segments of interhemispheric subdural recording of single event during CPSE.*A,B*: Contacts over left interhemispheric region. *C,D*: Contacts over right interhemispheric region.) **A:** Seizure begins with rhythmic activity in left SMA (*A7,B7*). **B:** Seizure spreads to right SMA (*C7,D7*). **C:** Seizure more extensively involves left and right interhemispheric regions. Left and right frontal convexity subdural contacts are not illustrated but were not involved in the seizure.

Comment

This is an example of what might have been considered prolonged postictal confusion following a typical right medial temporal lobe seizure. The EEG revealed continuous but variable ictal activity culminating in a lateralized spike-and-wave pattern. This case is an illustration of medial temporal lobe onset seizures leading to CPSE with continuous EEG ictal activity.

Case Study: Patient 4

This 39-year-old man with mild mental retardation has had seizures at least since age 2 years. Nothing is known about his birth and early development. He has lived in a sheltered and supervised environment all his life. Seizures occur on a daily basis and consist of loss of contact, with the sudden assumption of an asymmetrical tonic posture. This lasts for 30 to 40 seconds, after which he exhibits bimanual automatisms. The patient could have recurrent seizures of this type for hours.

He was evaluated for epilepsy surgery. Results of MRI revealed a large area of encephalomalacia in the left frontal lobe corresponding to the distribution of the anterior cerebral artery (Fig. 8). Neuropsychological testing documented IQ scores in the low 70s and diffuse moderate cognitive impairments. He had a very mild right hemiparesis.

During V-EEG monitoring, numerous seizures were recorded. There were isolated seizures and episodes of CPSE lasting up to 40 minutes. The CPSE consisted of asymmetrical tonic seizures followed by automatisms and confusion; these recurred repeatedly without clearing between episodes. Both the clinical and the electrographic seizures became progressively simpler and more subtle over time (Fig. 9). A subsequent study with subdural strip and grid electrodes over both frontal lobes failed to adequately lateralize frontal lobe seizure origin. An anterior two-thirds callosal section was done. Seizures recurred but were less frequent and less severe, but he remains disabled due to seizures.

Comment

This is an example of the relationship between frontal lobe epilepsy and CPSE. It also again demonstrates the simplification of electrographic and clinical seizures seen in some cyclic forms of CPSE. Anterior callosal section in patients with unlateralized frontal lobe seizures is an example of a not widely recognized indication for disconnection surgery.[88,131,132] Unfortunately, it did not prove very beneficial in this patient.

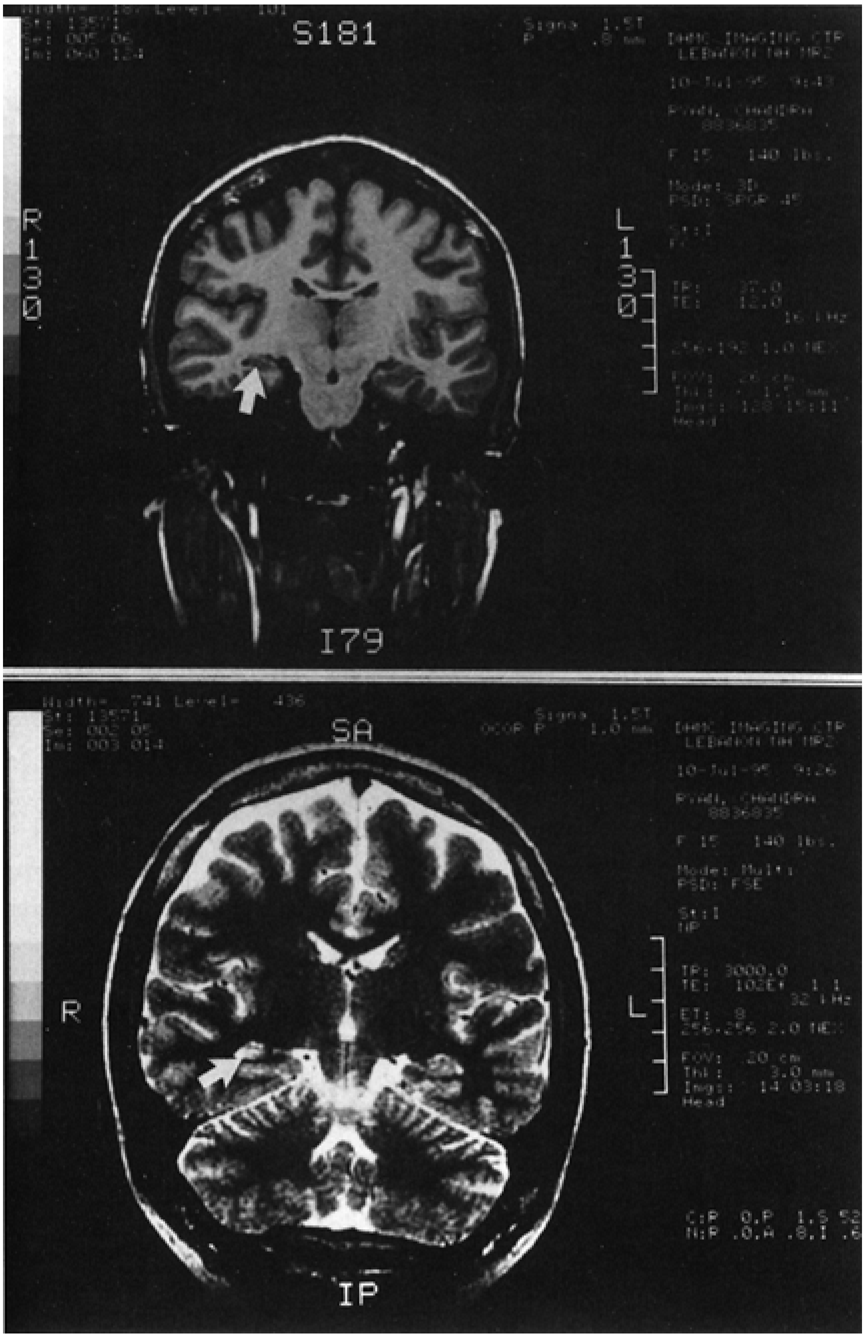


FIGURE 6. Patient No. 3. SPGR sequence (*top*) and T_2-weighted MRI (*bottom*) showing atrophy of right hippocampus and signal enhancement (*arrows*).

Case Study: Patient 5

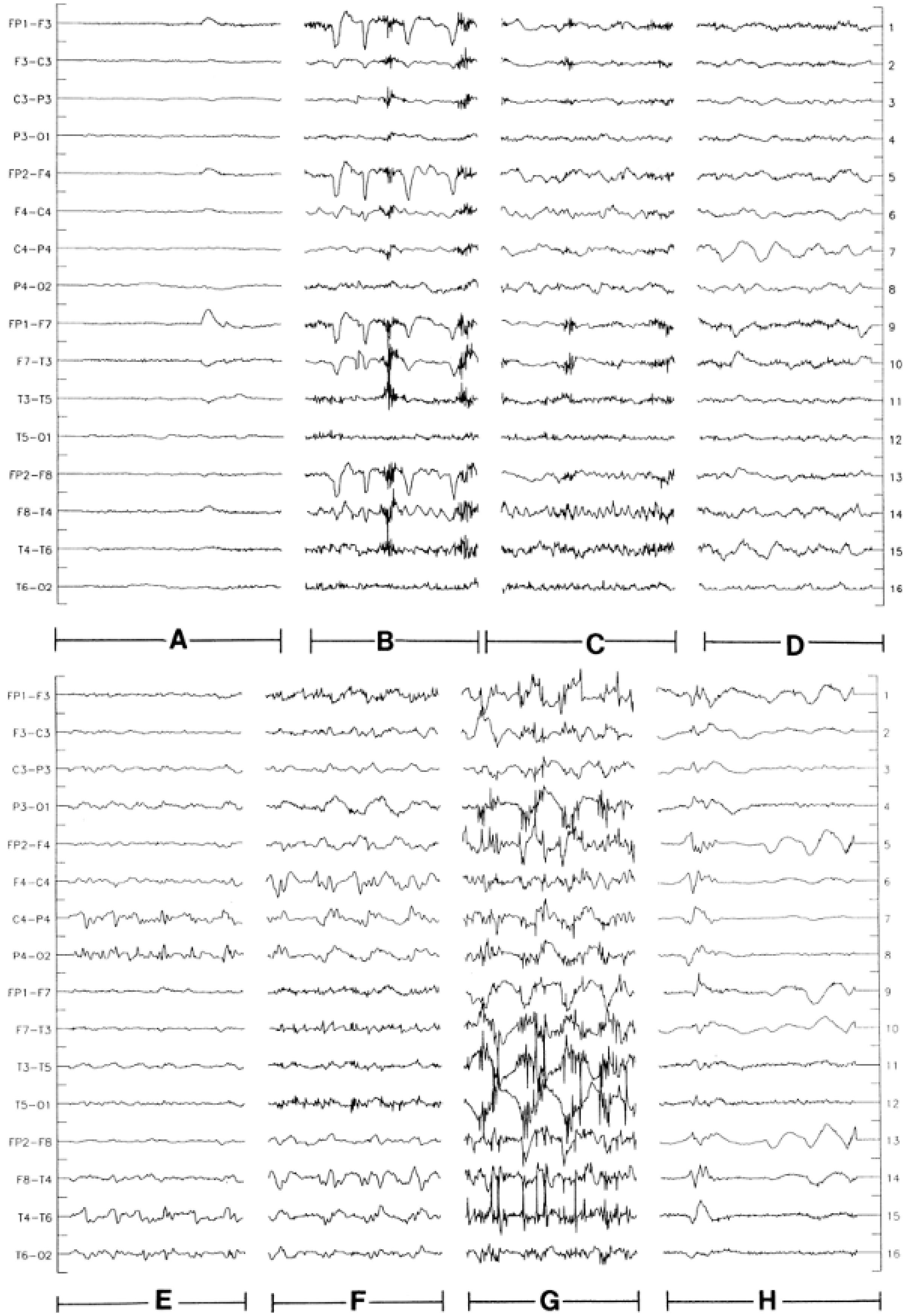
This 41-year-old woman had epilepsy diagnosed when she was 33 years old. Prior to that time, she reported rare episodes of "blacking out" beginning at 8 years of age. Treatment with AEDs produced little benefit. She had "grand mal seizures" every 2 to 3 months, with as many as eight major motor seizures in 1 day. She also described episodes lasting several hours, during which she was observed behaving as if she were in a trance but responsive when questioned. She claimed total amnesia during these trance-like episodes. There were no risk factors for epilepsy. The results of neuroimaging studies and numerous EEGs were normal.

She was admitted for diagnostic monitoring with the impression she had psychogenic nonepileptic seizures. Medications were withdrawn to determine whether she had epilepsy. The results of the initial 24-hour EEG monitoring were normal. Subsequently, her EEG became progressively abnormal,

starting with rare right frontal spikes and culminating with a pattern suggesting spike-and-wave stupor (Fig. 10). Later episodes of nonconvulsive status later terminated with left adversion followed by convulsive seizures with increasing frequency, necessitating urgent medical treatment. Although she was not specifically examined when the EEG exhibited continuous spike-and-wave activity, she did respond appropriately on several occasions when the nurse questioned her. She later said she was totally amnestic during the 12-hour period when recurrent episodes of nonconvulsive status were occurring. Subsequent adjustment of medications resulted in complete seizure control.

Comment

This is an example of a patient in whom the diagnosis of epilepsy had been questioned; however, during the course of evaluation, she developed nonconvulsive SE. Unequivocal focal EEG features and adversive seizures established localized seizure origin. However, had she been evaluated with an EEG only during the portion of her nonconvulsive SE associated with generalized spike-and-wave discharges, a diagnosis of ASE would likely have been made.


FP1–F3
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C3–P3
P3–O1
FP2–F4
F4–C4
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FIGURE 7. Patient No. 3. Segments of scalp recording during typical prolonged clinical seizure. **A:** Seizure onset with aura; no EEG changes. **B,C:** Starting at 20 seconds after clinical seizure onset, progressive buildup of right midtemporal to anterior temporal rhythmic activity. **D:** At end of typical temporal lobe seizure, there

is marked EEG slowing, most pronounced on right. At end of typical temporal lobe seizure, there is marked EEG slowing, most pronounced on right. This evolves into right posterior quadrant rhythmic sharp and polysharp activity. **(E,F). G:** At 18 minutes after seizure onset, right-sided activity becomes more diffuse and intense during tonic-clonic activity of left side of the body. **H:** At end of motor activity, diffuse right-sided rhythmic sharp activity develops on EEG before terminating 22 minutes after clinical seizure onset.

Diagnosis

Once the diagnosis of CPSE has been considered, an EEG should be obtained early in the course of the evaluation. Considering the rich variety of possible clinical presentations of CPSE, EEG confirmation and documentation is considered mandatory to make the diagnosis, except in the most obvious of cases.[14,30,114,115,117] Unexplained persistent alteration of mental status is one of the few relatively urgent indications for an EEG. The results usually have an immediate impact on further management. EEG findings are usually dramatic, varying from PLEDs to diffuse spike-and-wave patterns.[40,43,107,111] Only rarely will the EEG patterns in CPSE be subtle.[133] As discussed previously, however, the EEG findings in CPSE cover a wide range of abnormal patterns that, although indicative of an

epileptic basis for the problem, are not always able to differentiate between the two categories of nonconvulsive SE.[102,114,115]

After the diagnosis of nonconvulsive SE has been documented using EEG, further evaluation will depend on what is already known about the patient. If the patient has a previous diagnosis of epilepsy with partial seizures and a known lesion in one frontal lobe, it is entirely reasonable to assume that the diagnosis is CPSE, regardless of what particular pattern the EEG shows. Similarly, if an otherwise healthy young adult with known idiopathic generalized epilepsy exhibits confusion and a diffuse spike-and-wave pattern on EEG, the diagnosis is ASE. Between these two extremes are many diagnostic possibilities, a complete discussion of which is beyond the scope of this chapter. Suffice it to say that when information about a patient with possible CPSE is limited, diagnostic considerations include infections, metabolic disorders, toxic exposures, withdrawal conditions, and structural brain lesions, acute and chronic. Further diagnosis and management will depend on results of initial evaluations.

If a patient with clinical localization-related epilepsy presents with CPSE, and no acute, potentially hazardous, coexisting problems exist, a window of opportunity exists. This is particularly pertinent in the absence of known structural lesions. MRI or computed tomography (CT) during or shortly after CPSE can reveal transient signal abnormalities that might have diagnostic and localizing implications.[5,61,67,95,109,113,137] Ictal SPECT, a logistically difficult test to perform with isolated seizures, but with potentially localizing information not otherwise obtainable, can be done with relative ease during CPSE.[47,62,63,72,78,79,94] Because CPSE can masquerade as ASE, ictal SPECT could provide crucial diagnostic information in atypical cases.[34] CPSE also offers a unique opportunity to obtain an ictal positron emission tomography (PET) scan, which could provide localizing information in addition to research data.[28,46]

If the initial assessment suggests a deteriorating or urgent situation, such as a transition from nonconvulsive status to convulsive SE, treatment with intravenous AEDs should be initiated without delay. Because (with some exceptions, as discussed later) CPSE alone is usually not associated with enduring neurologic sequelae, treatment can usually be safely delayed to obtain important diagnostic tests.[18,57,62,77,82,109,133] Treatment itself can be diagnostic. Intravenous diazepam is said to control ASE rapidly in most cases, whereas CPSE responds more gradually.[102] Furthermore, intravenous diazepam may unmask focal EEG features in some patients with generalized ictal discharges.[44] One report also describes a diagnostic intracarotid sodium Amytal test in a patient with CPSE.[11]

Differential Diagnosis

CPSE is included in the differential diagnosis of the unresponsive or confused patient.[68,102] A critical step in the diagnosis of CPSE is to consider it in the appropriate clinical setting. Although this statement might seem self evident, doubtless CPSE is often not considered, and the diagnosis is therefore missed.[18,115,133] Unexplained obtundation during an acute

illness could be unrecognized CPSE.[107] Psychiatric disorders sometimes are erroneously diagnosed in patients with CPSE.[60,91,102,133] CPSE with very subtle alterations in consciousness and behavior can easily be missed.[73] Although CPSE is more common in the adult population between 20 and 40 years of age,[18,102,115] it can occur in the elderly or very young. ASE in the elderly has been associated with focal frontal onset, justifying the diagnosis of CPSE in some patients.[112] A diagnosis of CPSE should therefore be considered whenever there occurs the acute or subacute onset of persistent unexplained alteration of consciousness and behavior, regardless of the patient's age or whether a history of epilepsy is present.[91,124]

CPSE must be differentiated from true absence status because of different treatment strategies. When nonconvulsive status occurs in a patient with known idiopathic generalized epilepsy, the correct diagnosis is obvious. Clinically, however, the two types of status can be indistinguishable.[112,133] Even the EEG findings will not always separate the two. Therefore, in certain situations, additional clinical information will be needed to make the correct diagnosis.

Treatment and Outcome

How aggressive the management of CPSE should be is a controversial issue. During the past 20 years, most well-documented reports of CPSE describe favorable neurologic outcomes despite whether medical treatment is successful.[18,77,102,114,133] This appears to be true in extreme, very prolonged, medically refractory examples of CPSE lasting months.[18,77,92] Severe focal neurologic deficits and localized cerebral edema can occur after CPSE and may be long lasting, but completely reversible.[96] During an ictal PET study, a patient with CPSE had hypermetabolism in the occipital region and hypometabolism in the same region when seizures stopped.[28] After CPSE, a new homonymous hemianopsia was detected that gradually cleared over 15 months. Partial resolution of the hypometabolism corresponded with the neurologic improvement. Two often-cited earlier reports describe enduring neurologic deficits following CPSE.[20,96] These two studies report three patients with memory impairment after CPSE, but one patient also had convulsive status during the episode and another had a short follow-up. A study[49] of CPSE-related complications is flawed, because seven of the ten patients reported had acute systemic or neurologic disorders that could account for the morbidity and mortality. Three patients, however, with previously diagnosed epilepsy did develop mild-to-moderate cognitive impairments following CPSE. Another report describes a permanent hemiparesis following CPSE in a patient with frontal lobe epilepsy.[7] There have been several recent studies of nonconvulsive status in the critical care setting.[17,62,135] Reports of morbidity and mortality from acutely ill patients, not surprisingly, are associated with a poor prognosis. This can be misleading, because all such reports find that the poor prognosis is related to the underlying etiology of the serious medical condition present in the majority of patients. Only exceptionally was a poor outcome due to

epilepsy per se and, in at least some of these patients, it was due to complications of aggressive treatment.[56,101] In summary, CPSE is not associated with increased neurologic deficits in most patients.[55]

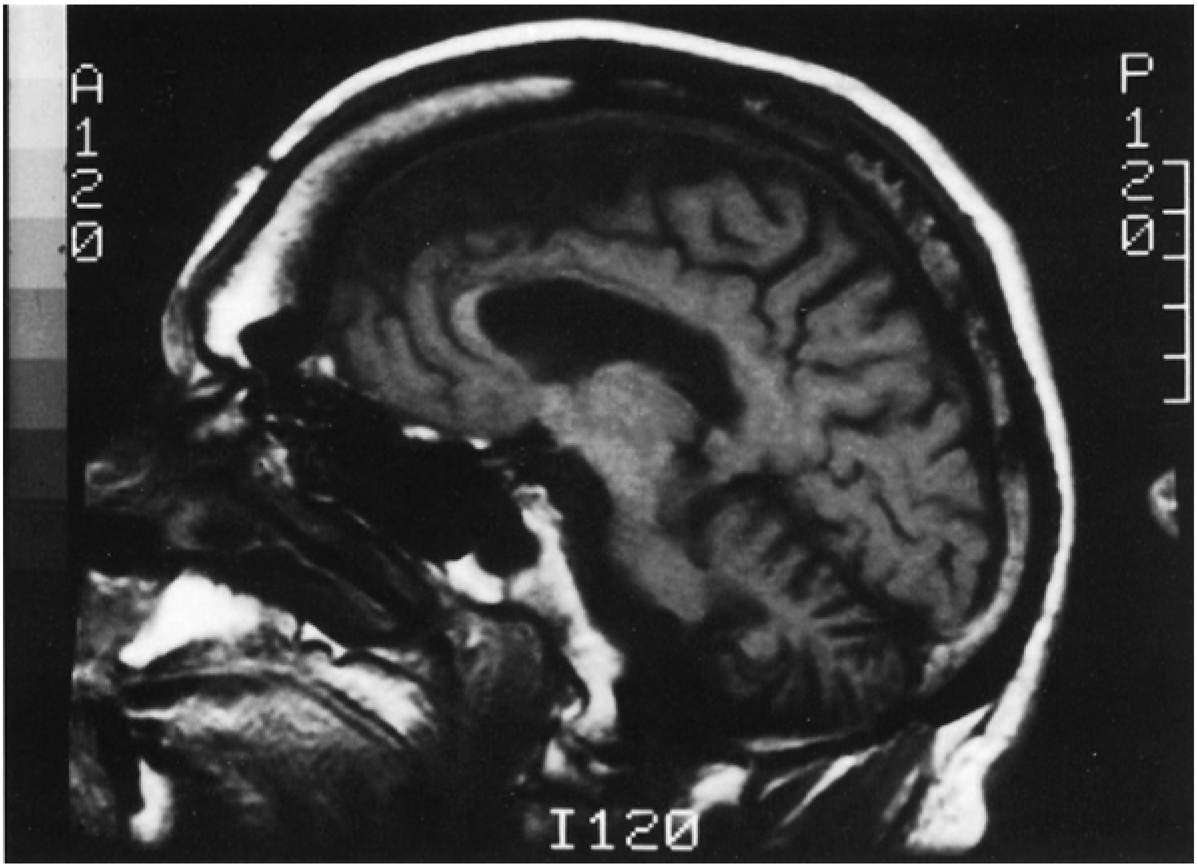

FIGURE 8. Patient No. 4. Midline sagittal MRI showing encephalomalacia in the left medial frontal region.

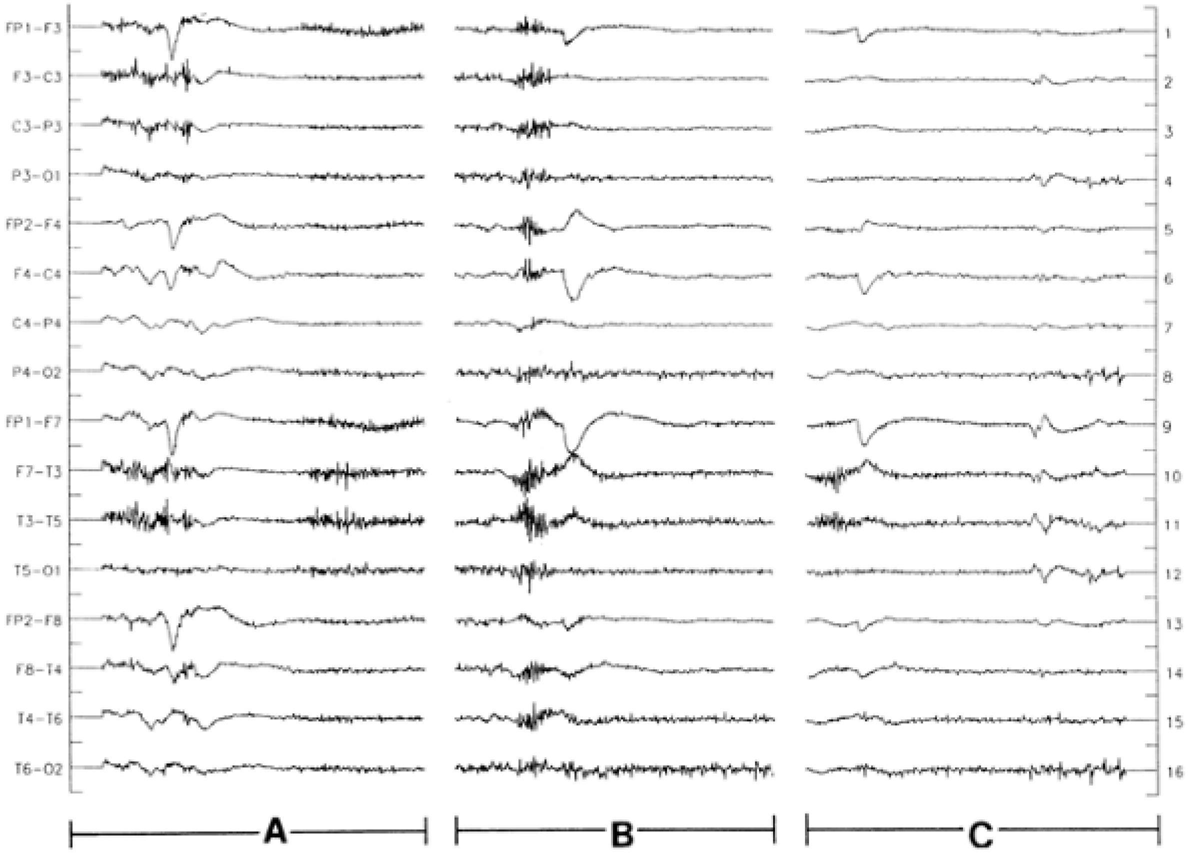
FP1-F3
F3-C3
C3-P3
P3-O1
FP2-F4
F4-C4
C4-P4
P4-O2
FP1-F7
F7-T3
T3-T5
T5-O1
FP2-F8
F8-T4
T4-T6
T6-O2
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FIGURE 9. Patient No. 4. Scalp EEG of three separate asymmetric tonic seizures during an episode of CPSE. **A,B:** Onset only with voltage suppression of two seizures at beginning of CPSE. These seizures lasted 15 to 20 seconds. **C:** Entire seizure lasting under 3 seconds towards end of CPSE.

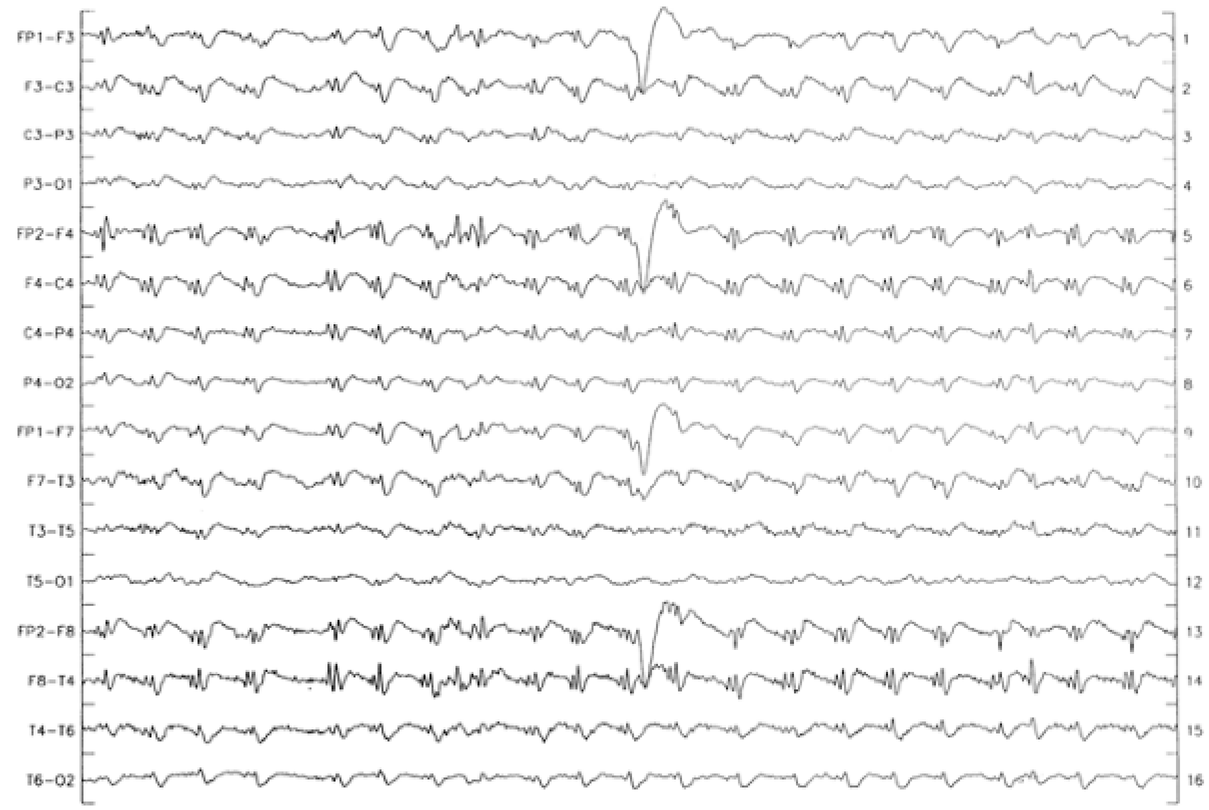

FIGURE 10. Patient No. 5. Scalp EEG during prolonged episode of diffuse sharp-slow activity.

This is in contrast to studies of partial SE in laboratory animals where, as discussed in the pathophysiology section and elsewhere in this volume, permanent brain damage is frequently observed. At present, no identified features predict an unfavorable neurologic outcome following CPSE except when it occurs during comorbid medical conditions.

CPSE is a disabling condition and, as such, it should be treated. The treatment of CPSE is no different than that for other varieties of SE. Drugs to treat CPSE should be given intravenously. Benzodiazepines, such as diazepam, lorazepam, or midazolam, are often first-line choices, followed by a longer-acting medication, such as phenytoin.[23] An alternative method is to use intravenous phenobarbital as the sole drug for treating CPSE. The only study comparing the efficacy of phenobarbital with diazepam/phenytoin for treating SE found phenobarbital superior.[99] Although the methodology used in this study was criticized,[84] the authors' reply satisfactorily addressed the criticisms.[100] Either treatment will be effective in most cases of CPSE, but the occasional patient with CPSE will be resistant to conventional therapy.[18,77,92] As discussed previously, the issue of aggressive medical therapy in CPSE is controversial. Although pentobarbital coma has been recommended for refractory cases of SE,[119] this can be associated with serious complications.[83,90,138] The same is true of intravenous anesthesia using propofol.[52,56,80] As suggested earlier, an alternative method for treating refractory CPSE is to initiate therapy with intravenous phenobarbital and continue with this drug. This approach has scientific rationale. In tests of antiepileptic efficacy, phenobarbital is many times more potent than pentobarbital.[2,70,89] Very high doses of phenobarbital, with serum levels exceeding 300 ng/mL, have been used to successfully treat refractory status in children.[20] The concerns related to profound sedation, respiratory depression, and hypotension are largely unfounded. If hypotension does occur, it can be treated with low doses of pressor drugs without major reductions in the dose or level of phenobarbital. A recent report emphasizes the efficacy and safety of phenobarbital in general.[65]

Most patients with CPSE have a prior history of epilepsy. Many will have medically intractable, localization-related epilepsy. These patients should be considered for surgical intervention, because it can be very beneficial.[18,27,42,48,128,133,134] A current review of the use of phenobarbital in SE provides favorable data in support of its use.[31]

Long-Term Prognosis

The long-term prognosis of CPSE is, to some extent, related to the cause. In many acute situations, such as intoxication and adverse drug reactions (e.g., to metrizamide, tiagabine),[58,87,123] the process is self-limited. In patients who develop CPSE in association with systemic disorders, the outcome is often determined by the course of the systemic disease and not the CPSE.[62] As noted previously, there are a few isolated reports of long-lasting neurologic deficits following CPSE,[10,26,30,62] but most patients suffer no ill effects; when neurologic deficits do occur, they are usually completely reversible.[18,56,95,96] Whether repeated episodes of CPSE can take a neurologic toll over time is not known, but it is probably unlikely. There are reports of full recovery following recurrent, prolonged, and incapacitating episodes of CPSE.[18,77] Patients, however, who present with unprovoked CPSE or have CPSE as part of their chronic epilepsy are very likely to have recurrence of CPSE.[18,92,102,115] Finally, as noted previously, in patients with medically intractable partial epilepsy who have CPSE, successful surgical intervention can eliminate both.

Summary and Conclusions

Previous descriptions and definitions of CPSE have proven to be too restrictive. Broadening the definition of CPSE to include all cases of localization-related epilepsy with episodes of prolonged, continuous, or repetitive seizures during which consciousness is impaired will increase the numbers of patients in whom CPSE is diagnosed. By doing this, many patients with clinical and electrographic features of ASE will receive the correct diagnosis and treatment for CPSE. As a result of these concepts, coupled with vastly improved diagnostic capabilities, CPSE will become recognized as one of the more common types of SE.

The issue of enduring neurologic deficit following CPSE has not been resolved. The fact that most patients with CPSE, even when subject to prolonged CPSE, recover completely does not negate the occasional observations of permanent neurologic deficit following CPSE. Do these few examples of CPSE-induced deficit dictate aggressive, potentially hazardous management of those cases of CPSE who do not respond readily to standard medical management? Probably not, but there will be exceptions. Criteria defining these exceptions have yet to be identified. Fortunately, most cases of CPSE will respond to the intravenous administration of standard AEDs, without resorting to drug-induced coma.

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Chapter 60

Absence Status Epilepticus

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Introduction

Status epilepticus (SE) may be classified for practical purposes into convulsive SE, which must be rapidly stopped to prevent death or neurologic sequelae, and nonconvulsive SE (NCSE) in which the diagnosis is not obvious and must be confirmed by urgent EEG recording. NCSE may be further classified into nonconfusional and confusional forms.[85] Nonconfusional NCSE is characterized by various somatosensory, visual, auditory, psychic, or vegetative symptoms that occur, by definition, with no impairment of consciousness. This is in contrast to confusional NCSE, which is characterized by some degree of clouding of consciousness. NCSE is also classically divided on the basis of the ictal EEG into absence SE (ASE) and complex partial SE (CPSE). CPSE is discussed in Chapter 59.

ASE, a diagnostic challenge, is a heterogeneous clinical and EEG condition that associates impaired consciousness and predominantly symmetrical bilaterally synchronous ictal discharges. On a historical perspective, Charcot, in one of his Tuesday lectures of January 1888, described a healthy 37-year-old delivery man with episodes of prolonged automatisms during which he walked from place to place throughout Paris. Charcot believed that this prolonged ambulatory fugue state was related to an epileptic breakdown of consciousness[28] and later proposed a trial of potassium bromide, an early antiepileptic drug (AED).

Concept of Absence Status, Definitions, and Classification

In 1938, W.G. Lennox recorded periods of continuous spike-and-wave discharges (SWDs) and altered level of consciousness after insulin-induced hypoglycemia in one of his cousins, a child with absence epilepsy. Lennox believed that this represented very brief absences in rapid succession without a return to the usual level of consciousness and, in 1945, suggested the term *petit mal status* to describe this condition.[99] This term implied a clinical picture limited to prolonged or serial typical absence attacks that were sufficiently close together to give rise to a prolonged disturbance of consciousness and an EEG pattern limited to the classic ictal 3-Hz spike-and-wave pattern on a syndromic absence-epilepsy background. However, it soon became clear that these forms of SE could occur in patients whose epilepsy was manifested by seizures other than absences and who had no history of idiopathic generalized epilepsy (IGE).

In the mid-1960s, Niedermeyer and Khalifeh,[116] then Lob[104] reported that, during ASE, the alteration of consciousness seemed to be less profound than that observed during typical absence attacks. Similarly, the EEG expression of ASE also was atypical, consisting of SWDs that were neither as regular nor as continuous as those of absence seizures. Also, these epileptic confusional states could appear in patients with severe epilepsy associated with mental retardation. These authors preferred the less specific and more descriptive term *spike-wave stupor* rather than petit mal status. The problems arising from the use of this latter term may explain the extraordinary development of new eponyms, described by Shorvon[144] as a “nosographic labyrinth” for what were very similar clinical entities (Table 1).

Typical and Absence Status Epilepticus

In 1970, in an attempt to unify the concept, the Classification and Terminology Commission of the International League Against Epilepsy retained the term *absence status,* which Gastaut had proposed in October 1962 during the tenth Marseilles Colloquium[60,61]: "a prolonged or repeated absence seizure, thus representing SE. Clinically, ASE is essentially or exclusively characterized by impairment of consciousness of varying intensity, persisting hours to days, occasionally leading to an epileptic fugue. The EEG findings exceptionally consist of continuous or discontinuous rhythmic 3-Hz SW discharges similar to those encountered in typical absence seizures; more often one finds more or less rhythmic SW or polyspike-wave (PSW) discharges sometimes interrupted by slow background activity".

In a further attempt at clarification, Gastaut suggested at the 1983 Santa Monica Colloquium a new classification of ASE,[62] distinguishing "typical" ASE as having an excellent prognosis, occurring in patients with IGE, and characterized by a simple confusional state with rhythmic 3-Hz SWDs; "atypical" ASE is characterized as occurring mainly in patients with symptomatic and/or cryptogenic generalized epilepsy. This atypical variety could be conceptualized as a transient exacerbation of the epileptic symptomatology superimposed on a chronic epileptogenic encephalopathy, such as the Lennox-Gastaut syndrome.[13] Episodes of atypical ASE were characterized by periods of confusion accompanied by more marked tonic or myoclonic manifestations, and associated with SWDs or PSW discharges slower than 3 Hz, with a variable rhythmicity and regularity.[62] Moreover, these atypical ASEs were clearly distinguishable from "typical" ASE by their associated clinical features, including pseudoataxia and/or pseudodementia, their prolonged duration (several days or several weeks), their tendency to recur, and their pronounced resistance to treatment—benzodiazepines (BZ) being usually ineffective.[25,40,57,122]

New Cases of Uncertain Classification

During the 1970s, newly reported cases that could not be correctly classified added yet further difficulties. These events were occasionally encountered in patients with localization-related epilepsy[123] and were characterized by electroencephalographic (EEG) patterns with focal features that were considered too significant to justify their classification within the group of generalized epilepsies.[59,75,115] This "imperfectly generalized" ictal pattern was compared to the focal ictal discharges of CPSE and contributed to blur the margins between the two entities. New pathophysiologic mechanisms were discussed, mainly based on the works of Tükel and Jasper in Montreal, and on depth electrode studies by Bancaud and Talairach in Paris, who demonstrated that a single epileptic focus could give rise to secondary bilaterally synchronous discharges.[9,175]

Several authors had indeed emphasized the similarities between these ASE forms and CPSE of temporal or, especially, frontal origin.[3,59,137,168,171] These similarities are probably not fortuitous: Several reports show the transformation from CPSE with fronto-polar focal ictal discharges into an ASE with a perfectly bilateral and symmetric EEG pattern.[2,97,115,139,164,168] These occasional but well-documented reports may explain the development of ASE with "generalized" discharges during the course of an extratemporal localization-related epilepsy, particularly of frontal lobe origin.[97]

Table 1 Absence Status Epilepticus: Some Published Synonyms

Petit mal status[99]
Prolonged epileptic twilight state with almost continuous wave-spikes[192]
Prolonged alterations in behavior associated with a continuous EEG spike-and-dome abnormality[21]
Epilepsia minoris continua[56]
Simple epileptic confusional state[63]
Prolonged behavioral disturbance as ictal phenomena[67]
Spike-wave stupor[116]
Minor SE[23]
Centrencephalic condition of prolonged disturbance of consciousness[73]
Isolated petit mal status presenting de novo in middle age[141]

Borderline petit mal status[75]
Ictal psychosis[186]
Absence status with focal characteristics[115]
Prolonged confusion as an ictal state[48]
Senile petit mal epilepsy[119]
Acute prolonged ictal confusion[179]
De novo minor SE of late onset[11]
Toxic ictal confusion in middle age[177]
Generalized nonconvulsive SE[71]
De novo absence status of late onset[167]

De Novo Absence Status Epilepticus of Late Onset

A further group of patients was described in which ASE first occurred in elderly subjects with no previous history of seizures. In 1971, Schwartz and Scott[141] published reports on four patients with ASE appearing "de novo" in middle-aged or elderly adults. They suggested that these cases could represent the "the extreme end of a continuum of Petit Mal epilepsy extending from childhood to middle age."[141] However, later observations show that this is not usually so. Since 1971, about 100 such patients have been described in the literature; a review is available.[165] The average age of the patients is in the sixth decade, and there is a preponderance of women. Many of the subjects have preexisting psychiatric symptoms. In two thirds of the cases, the ASE occurs with a toxic or metabolic systemic disorder.[166,178] Among triggering factors, psychotropic drugs appear to be prominent and were present in a series of 79 such patients.[164] The ASE may occur with high doses of psychotropic drugs or with a sudden withdrawal of the medication: Several reports have emphasized the role of BZ withdrawal.[45,52,83,167] A combination of factors, such as a simultaneous toxic and metabolic encephalopathy, is characteristic. These data indicate that "de novo" ASE is more often an acute symptomatic epileptic event rather than the late resurgence of a childhood absence epilepsy, and is probably best designated as "situation-related SE."[31,177]

Electrographic Status Epilepticus in Coma

In recent years, several intensive care unit series tend to lump together "subtle" SE, ASE, CPSE, and EEG patterns suggestive of NCSE in comatose patients.[82,96,101,138] For example, Mayer et al. included seven patients with "nonconvulsive SE" in "comatose or obtunded patients"[111] and among the comatose patients studied by Towne et al.[172] 8% had "an EEG pattern suggestive of SE," a pattern whose validity has been challenged by Benbadis et al.[15] This conceptual extension appears to have been caused by some degree of misinterpretation in EEG findings. Prominent generalized paroxysmal activity in comatose patients is usually the expression of a severe encephalopathy of the hypoxic/anoxic type, rather than of NCSE.[117] As proposed by Kaplan,[87,88,89,90] the term *electrographic SE in coma* seems more appropriate, in its neutrality, to characterize generalized seizure activity in deeply obtunded patients with severe brain injury. Similarly, "subtle" SE,[173] the extreme end of an insufficiently treated generalized tonic–clonic SE must not be confused with ASE because context of occurrence, clinical features, prognosis, and treatment are dramatically different. Severe mental confusion in ASE may express itself as catatonia,[100,107] but this presentation is radically different from a comatose state.

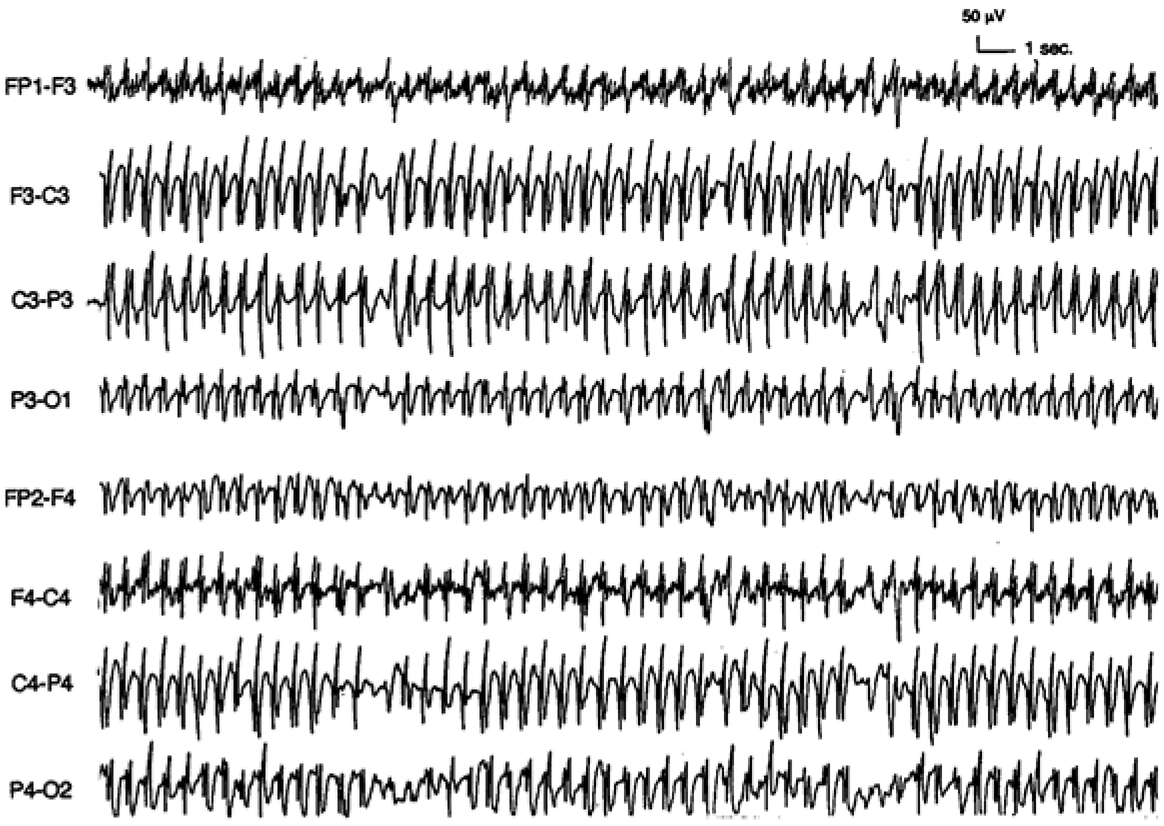

FIGURE 1. Typical absence status in a 13-year-old girl with juvenile absence epilepsy. ASE followed withdrawal of valproate and administration of carbamazepine. Patient had an isolated, permanent, mild-to-moderate confusional state. The EEG shows continuous, generalized 3-Hz spike-and-wave activity with little variation in amplitude and frequency.

Clinical Classification of Absence Status Epilepticus

We believe that four types of ASE may be recognized: typical ASE, atypical ASE, ASE with focal features, and “de novo” ASE of late onset. A number of cases appear to be transitional forms between these better defined clinical entities.

Typical ASE (Fig. 1) occurs as part of an IGE most often characterized by absences. Isolated impairment of consciousness, at times with subtle jerks of the eyelids, is the essential symptom. The EEG correlates with repetitive absence seizures and shows symmetric and bilaterally synchronous spike-and-wave or PSW complexes faster than 2.5 Hz, but this pattern is often not strictly maintained as the event continues. The immediate prognosis is excellent: An intravenous BZ injection stops the ASE.

Atypical ASE (Fig. 2) occurs in patients with symptomatic or cryptogenic generalized epilepsies and is characterized by a fluctuating confusional state with more prominent tonic, atonic, myoclonic, and/or lateralized ictal manifestations than occur in typical ASE. There is often no clear-cut onset and offset of the ictus. The EEG shows continuous or intermittent diffuse irregular slow spike-and-wave or PSW complexes. The immediate prognosis is guarded, as these episodes tend to recur and to be resistant to medication.

ASE with focal features (Fig. 3) occurs in subjects with a preexisting or newly developing localization-related epilepsy, most often of extratemporal origin. The EEG shows bilateral, but often asymmetric ictal discharges. Many of these cases may represent the natural evolution of CPSE of frontal lobe origin,

and the EEG may not conclusively distinguish these from ASE, especially late in the episode. The immediate prognosis is variable.

In middle-aged or elderly subjects with no previous history of attacks, “de novo” ASE of late onset (Fig. 4) is characterized by toxic or metabolic precipitating factors leading to seizures. Patients often have a history of psychiatric illness, with multiple psychotropic drug intake. The electroclinical characteristics and the immediate prognosis are variable. These episodes of ASE generally represent acute symptomatic seizures and may not recur if the triggering factors can be controlled or corrected. Long-term AEDs thus may not be needed.

Epidemiology

Lob et al.[104] found that of 148 patients with ASE collected by 1962, 93% had preexisting epilepsy, and 92% of these patients had a form of IGE. Nevertheless, 16% of these patients had only absence seizures, and 11 patients had no history of epilepsy. Porter and Penry[130] found that 85% of patients with ASE had preexisting epilepsy. Of the patients discussed by Rohr-Le Floch et al.[137] 78% had preexisting epilepsy, and all of these had IGE. Dalby[35] found that 6.2% of patients with IGE had had episodes of ASE. Patients with absences more often had ASE (9.3%), than those who did not (3.4%). In patients with childhood- and adolescence-onset absence epilepsy, the incidence of ASE has varied: 3% of patients according to Cascino and Hauser,[27,74] 5.8% for Loiseau and Cohadon,[105] 9.9% for Livingston and Brown,[103] 28.3% for Lorentz de Haas and Magnus,[106] and 37.7% for Oller-Daurella.[124] A reasonable estimation is to consider that almost 10% of adults who continue to have absence seizures that began in childhood will have an episode of ASE, and that its incidence appears to increase with the frequency of absence attacks. However, with a 100 per million prevalence of absence epilepsy and a 1% occurrence of ASE in these patients, Shorvon estimated the annual incidence of typical ASE to be very low, occurring in about 1 per million persons in the general population.[144]

ASE has been reported in epileptic encephalopathies, such as the Lennox-Gastaut syndrome, in 15% to 40% of patients.[41] Other studies[13,42] show that almost all these patients have periods of epileptic confusional states at one time or another. In a mentally handicapped population, the annual incidence of ASE can be estimated to be 100 to 200 cases per million.[144]

No reliable data are available to estimate the occurrence of “de novo” ASE of late onset. Studies from emergency wards of general hospitals in which immediate EEG is available, generally in cities of one million or more, describe two to five new cases per year.[137,140,170]

Clinical Features

The cardinal clinical sign of ASE is variable clouding of consciousness, ranging from subtle subjective impairment of thought processes to severe stupor with incontinence. Subtle motor signs are seen in half the patients. In 90% of cases, the confusional symptoms fluctuate. This is an important clue in favor of the ictal nature of the confusional state, this fluctuation being most marked when the level of consciousness is well preserved. However, impairment of consciousness in ASE

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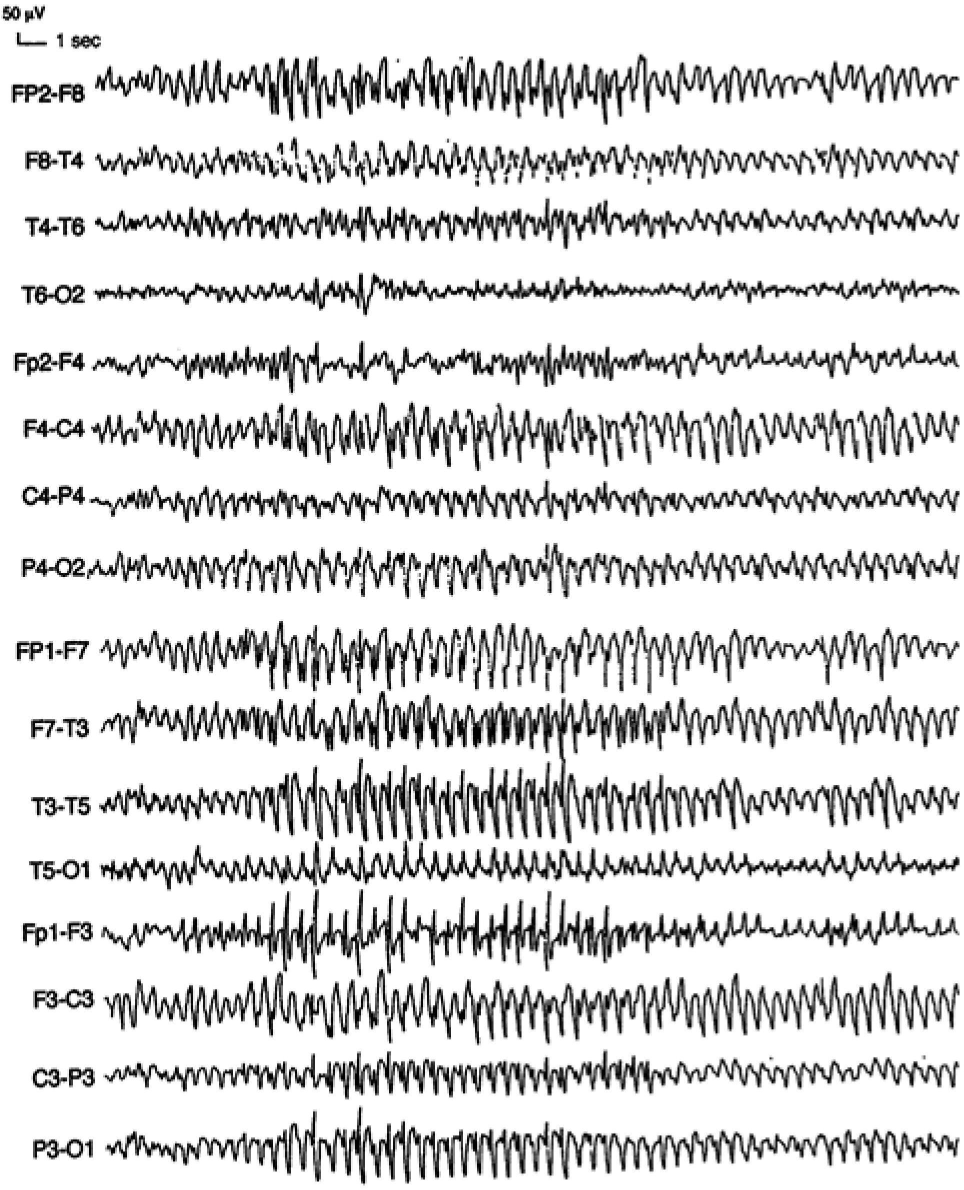
is never clearly organized in a cyclic and a discontinuous way, as may be observed in some patients with CPSE of presumed amygdalo-hippocampal origin.[173]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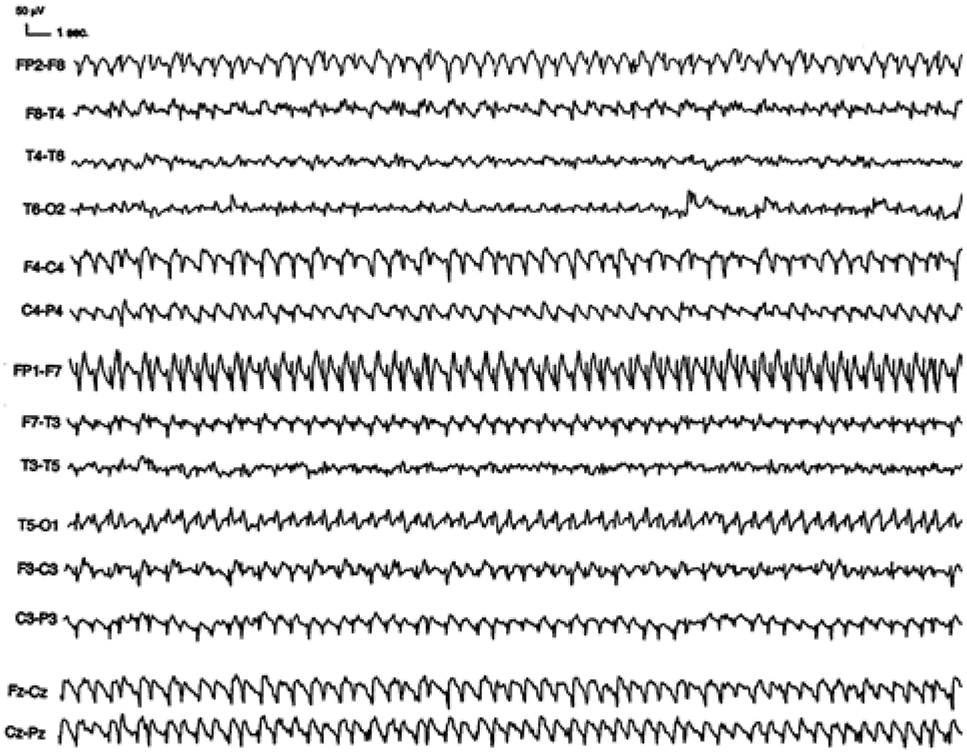
FP1-F7
F7-T3
T3-T5
T5-O1
Fp1-F3
F3-C3
C3-P3
P3-O1

FIGURE 2. Atypical absence status in a 15-year-old boy with Lennox-Gastaut syndrome. His head and eyes were slightly turned to the right, and he was moderately confused, with periocular myoclonia and hypersalivation. The EEG shows almost continuous irregular bilateral 2-Hz spike-and-wave complexes with left centrotemporal predominance. Intravenous benzodiazepines were ineffective.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T3-T5
T5-O1
F3-C3
C3-P3
Fz-Cz
Cz-Pz

FIGURE 3. Absence status with focal characteristics in a 55-year-old woman with cryptogenic left frontocentral epilepsy. Patient was moderately confused, with some disinhibition, echolalia, and palilalia. The EEG shows bilateral 1.5-Hz slow spike-and-wave complexes with a clear left frontotemporal predominance.

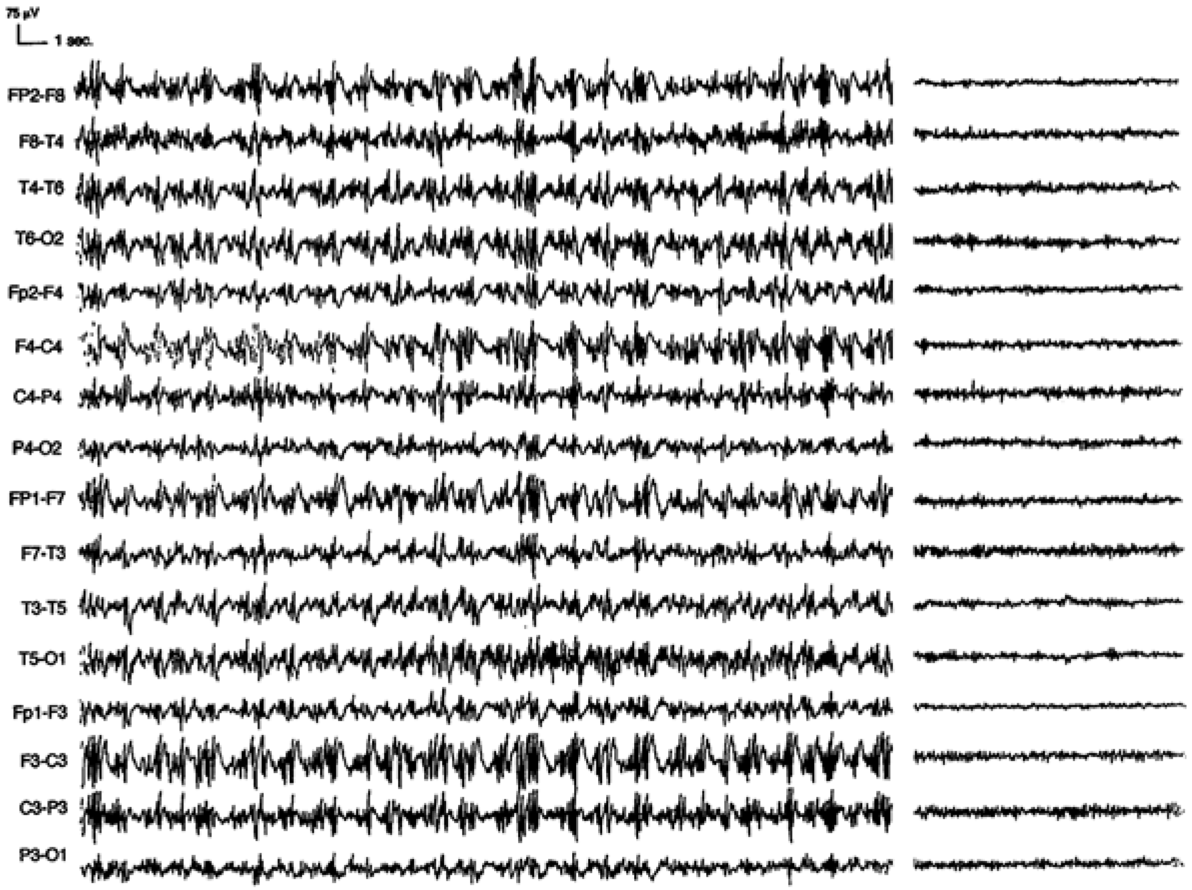

FIGURE 4. A positive diagnostic and therapeutic trial of intravenous benzodiazepines in an 82-year-old woman with "de novo" absence status of late onset, related to multiple psychotropic drugs intake and withdrawal. The EEG shows continuous irregular polyspike and slow wave activity, which stops 140 seconds after injection of 1 mg of clonazepam. Her level of consciousness returns to normal.

Clouding of Consciousness

Although the alteration of consciousness in ASE is best represented by a continuum,[6] recognition of four grades of severity in disturbance of consciousness[104,136] may be useful in clinical practice. This classification was based on the largest series of ASE, the 148 cases collected at the time of the 1962 Marseilles Colloquium.[60]

Slight clouding of consciousness is present in 19% of cases. This consists of simple slowing of thought processes and expression, often so subtle that only the patient himself can recognize it. There is often no true mental confusion.[7,129] Patients with recurrent ASE may learn to recognize these periods, which may be defined as "bad days" often described to "a lack of efficiency" or "the inability to perform at a normal level."[6] Patients with the mildest degree of disturbance have no apparent psychological disturbance and may be able to speak fluently. Although these patients are able to carry on with typical activities of daily living, they are unable to normally perform complex intellectual tasks involving choices, strategy, planning, or initiative. Formal neuropsychological testing, in one report including dichotic listening,[55] may be necessary to document mild degrees of altered consciousness in ASE.[118,184] Neuropsychological deficits may also suggest a more localized disturbance,[65] typically with sparing of language, unlike some cases of CPSE. Shorvon[144] noted the frequent and striking dissociation between these mild clinical manifestations and the impressive ictal EEG abnormalities.

Marked clouding of consciousness is most typical and is reported in 64% of cases. A frank confusional state occurs with disturbance of alertness, attention, memory, judgement, language, and with some agnosia and apraxia. The patients are severely disoriented. They are usually calm, immobile, indifferent, with little or no spontaneous language or motor activity. Simple commands are only obeyed after repeated requests, often correctly, but very slowly and after some delay. Patients usually are unable to follow more complex commands. Language is reduced to fragmented, hesitant, and at times irrelevant responses interrupted by long pauses. Echolalia and palilalia may be present. Motor tasks are performed clumsily and slowly, and sequential tasks are usually interrupted more because of attention difficulties than because of a true apraxia. Many have spontaneous or environmentally induced automatisms of variable complexity. Simple gestural automatisms are frequent. More elaborate motor patterns, which appear to represent a combination of complex automatisms and the behavioral disturbance caused by the clouding of consciousness, are associated with perseverative and compulsive features, a highly suggestive feature of ASE.

Profound clouding of consciousness is reported in 7% of cases. Even with vigorous stimulation, only very brief and limited motor or verbal responses can be elicited. The patients remain motionless, cannot move without help, and are unable to feed themselves.

Lethargic stupor is reported in 8% of cases. This resembles catatonic stupor, with apparent suspension of all psychic activity.[100] Patients are motionless, with eyes turned upwards,

and incontinent of urine and stool. They are completely dependent and react only to strong painful stimulation.

Associated Signs

Myoclonus is the most frequent and most suggestive associated sign, occurring in about half the cases.[137] It is an important diagnostic clue, because as it does not occur in CPSE.[137] ASE with myoclonic components could be associated with less impairment of consciousness.[57] It is characterized by bilateral jerks of the eyelids or face, most often subtle and intermittent, and more easily diagnosed with the patient's eyes closed.[109] Myoclonic jerks occasionally may involve the arms and hands. These may be asymmetric, falsely suggesting a localization-related SE.[136] Rarely, they may be so marked as to dominate the presentation, overlapping clinically with myoclonic SE.[163,176] A history of myoclonic episodes associated with confusion can suggest a retrospective diagnosis of ASE especially in patients with preexisting IGE.[78,92] Epileptic negative myoclonus may also be intermingled with the positive myoclonic jerks (Thomas, unpublished personal observation).

Complex automatisms occasionally may be responsible for prolonged fugue states, or *poriomania*. At times, some of these behaviors can cause legal problems (e.g., in the case of compulsive masturbation[81] or destructive behavior[6]). Psychiatric manifestations have been reported in atypical ASE. These include hallucinations, illusions, experiential phenomena, psychotic depression,[6,54,68] and acute pathologic neurologic laughter.[22] These symptoms are very unusual and, if present, never as marked as those which occur in CPSE.[137]

Natural History of Absence Status Epilepticus Episodes

The spontaneous duration of each episode of ASE is variable and ranges from about half an hour to several weeks.[63,84] Most episodes last from 6 to 72 hours, only exceptionally exceeding 1 week.[34] In most typical cases, spontaneous cessation of the ASE is sudden, with a striking clinical improvement. Some patients fall asleep and awaken normal. Typically, the episode most often ends in a tonic–clonic convulsion.

Electroencephalographic Findings

Emergency EEG with a therapeutic trial of BZs is the key to confirming the diagnosis of ASE.[91]

Electroencephalographic Characteristics of Absence Status Epilepticus

The essential EEG feature of ASE is a bilateral, synchronous, and symmetric epileptiform activity that is unreactive to sensory stimulation. The most characteristic tracings show continuous trains or frequently repeated bursts of polyspike and slow-wave complexes or slow spike-and-wave complexes that are diffuse, rhythmic, and nonreactive.[171] Nevertheless, the EEG manifestations may be so variable that Porter and Penry[130] noted that “virtually any generalized continuous or nearly continuous abnormality could be a substrate for this syndrome.” Roger et al.[136] found that half of cases of ASE in patients with IGE had continuous, usually rhythmic, bilaterally synchronous and symmetric SWDs or PSW discharges with a bifrontal predominance and a frequency between 1.5 and 3 Hz. Less commonly, the discharges were discontinuous and broken up into bursts separated by more or less normal background rhythms. Continuous spike-and-wave activity could also become discontinuous during the same EEG recording.

Only rarely does the spike-and-wave activity occur at precisely 3 Hz. In 80% of cases, it ranges from 1 to 2.5 Hz. Granner and Lee[69] reported 59 patients with ASE whose paroxysmal activity ranged in frequency from 1.0 to 3.5 Hz, with a mean of 2.2 ± 0.6 Hz. Only 7% had an ictal EEG pattern of typical absence. One quarter of the patients showed some focal predominance of their paroxysmal activity.

Occasionally, the spike-and-wave activity may be unusually rapid, from 4 to 6 Hz,[59] or unusually slow, slower than 1 Hz.[75] Other variants of the ictal epileptiform activity include irregular slow spike-and-wave activity,[16] slow waves with sporadic spike-and-wave complexes,[169] and rhythmic triphasic slow waves.[187] In these unusual EEG presentations, correct identification of ASE is a challenging problem, given the fact that "any rhythmic EEG rhythmic activity recorded during a confusional state does not inevitably correspond to ASE."[15]

No clear correlation exists between the degree of altered consciousness and the EEG. Stupor may however be more frequently associated with the pattern of continuous, rhythmic, 3-Hz spike-and-wave activity.[144]

Therapeutic Trial of Benzodiazepines

The intravenous injection of a BZ during the EEG recording is mandatory to confirm the ictal nature of the episode. Difficulties may indeed arise in distinguishing true ictal epileptiform EEG patterns from interictal or nonictal EEG discharges,[90] such as, for example, runs of triphasic sharp waves in hepatic encephalopathy. The injection must be given slowly, in successive boluses over 30 to 60 seconds each, and must produce rapidly progressive disappearance of the paroxysmal activity, leading to normalization of the EEG; SWDs or PSW discharges are typically replaced by low-amplitude diffuse β activity (see Fig. 4). The effective doses are usually relatively low, and typical ASE responds to diazepam 0.2 to 0.3 mg/kg, clonazepam 1 to 2 mg (0.5 mg in children), or lorazepam 0.07 mg/kg (0.1 mg/kg in children). An average of 3.8 mg of diazepam has been reported effective in adults.[69] Normalization of the EEG must also be associated with disappearance of the confusion, which may be dramatic when immediate or may take minutes or even hours in elderly patients. For a therapeutic trial to be considered successful, both EEG and clinical normalization must occur.[53] Recording must be continued for at least 60 minutes after EEG normalization to detect any early recurrence of ASE, and follow-up recording is needed if any later alteration of consciousness occurs, to diagnose any possible recurrence of ASE.

If intravenous access is not available, or if there is a high risk of respiratory depression in a disabled patient, a single oral dose of 1 mg/kg of clobazam, a rapidly absorbed BZ, has been proposed as an alternative.[64] With this regimen, clinical and EEG improvement is often noticeable after approximately 10 minutes, and complete cessation of the ASE usually occurs within 15 to 30 minutes. There are usually no noticeable effects on vigilance, and respiratory depression does not occur. Other AEDs may be used with similar results, including intravenous lorazepam,[84] parenteral valproate,[29,66,79,86] and, in ASE associated with the Lennox-Gastaut syndrome, propofol.[32] Intravenous valproate may avoid some of the morbidity of repeated doses of BZ or prolonged infusions of propofol: for children in ASE, a loading dose of 20 mg/kg has been suggested followed by maintenance infusion of 1 mg/kg/h in noninduced patients and 2 mg/kg/h in those on multiple drugs.[77] Although phenytoin[5] and phenobarbital[104] have been reported to be useful in the treatment of ASE, these drugs are not generally recommended because they are not only ineffective against absence seizures, but are known to exacerbate both clinical and experimental absence.[156] The potential neurologic morbidity of ASE, which is most often a relatively benign event especially with typical ASE, must be weighed against the possible morbidity of intravenous AEDs, and overtreatment must be avoided.[88]

A paradoxical worsening of the electro-clinical picture has been reported in the atypical ASE of the Lennox-Gastaut syndrome after BZ injection.[102]

Table 2 Differential Diagnosis of Absence Status Epilepticus

1. Other types of nonconvulsive SE

Complex partial SE (temporal origin)

Complex partial SE (frontal origin)

Confusional state with PLEDs

2. Other seizure-related causes of altered mental state

Prolonged postictal confusion

Prolonged postictal encephalopathy

Idiosyncratic reaction to AEDs

Interictal psychosis

3. Metabolic encephalopathy

Hypoglycemia

Hyperammonemia

4. Toxic encephalopathy

Psychotropic drug overdose

Psychotropic drug withdrawal

Amnesia or automatisms related to a short acting

benzodiazepine

5. Psychiatric syndromes

Depression

Psychosis

Hysteric conversion reaction

Catatonia

6. Neurologic disorders

Transient global amnesia

Frontal lobe stroke

Aphasia

Dementia

Creutzfeldt-Jakob disease

Transient unresponsiveness in the elderly

Diagnostic Considerations

EEG and BZ therapeutical trial prove the ictal nature of the confusion and settle issues of differential diagnosis. In most cases,[53,72,85,107,170,171] nonictal events are suspected initially (Table 2). Among ictal events, ASE may be completely indistinguishable from CPSE[108] or from a prolonged postictal encephalopathy.[19] The main practical problem is to think of the diagnosis and to obtain a rapid EEG: Kaplan notes that in most instances, "the diagnosis was all too evident in retrospect, and frequently missed or delayed initially."[84] In a single study,[78] remote risk factors for seizures, severely impaired mental state, and ocular movement abnormalities were the most sensitive indicators for an emergency EEG.

When a reliable clinical history can be obtained, and the beginning of the confusional state is reportedly sudden, its epileptic nature may be suspected.

Another diagnostic point is that the EEG at the time of the ictal event should represent a definitive change from the preictal state. Such a change is more clear-cut in typical ASE, in which the interictal EEG is not as replete with ongoing paroxysmal abnormalities as that seen in a patient with epileptic encephalopathy in whom there is a diagnostic question of atypical ASE. In these latter cases, it may be far from clear that the atypical ASE represents a change from their baseline condition either clinically or electrographically.

Primary or secondarily generalized tonic–clonic seizures may appear at the beginning[12,50] or, more classically, at the end of ASE.[6] When the seizures occur at the onset, the unusually long duration of the presumed postictal confusional period should raise a suspicion of the diagnosis, and an urgent EEG should therefore be obtained.

The delay in diagnosis is often long. Rohr-Le Floch et al.[137] found that the correct diagnosis was made at the time of initial clinical examination in only four of 60 cases (7%). In 18 of 60 cases (30%), the diagnosis was that of a prolonged postictal state. In recent series,[90,164] delays in diagnosis ranged from 8 hours to 4 days. As noted by Kaplan,[84] in adults, the altered mental status of ASE may be attributed to a metabolic disturbance or to excessive psychotropic drug use or withdrawal, each of which may also induce ASE. In these cases, impaired consciousness can result a combination of ASE and encephalopathy, and it may be impossible to assess the relative part played by these two factors.

Etiologic Factors in Absence Status Epilepticus

Endocrine factors appear important in women of childbearing age. The catamenial period,[114] pregnancy,[46] the immediate postpartum period,[14] and menopause[136] have all been implicated.

Drug-related factors are clearly important in many cases, particularly, but not exclusively in "de novo" ASE of late onset. Many authors[45,71,132,164,167,177] suggest an etiologic role for psychotropic medication either taken in excess, alone, or in association with other drugs, or during rapid drug withdrawal.[51] Many psychotropic drugs have been implicated, in order of frequency and probable causality: BZ, neuroleptics (especially butyrophenones), tricyclic antidepressants (especially amitriptyline), lithium, meprobamate, viloxazine, methaqualone, barbiturates, and monoamine oxidase inhibitors.

Many cases have also been reported to occur in relation to other drugs. Only some of these are known to lower the convulsive threshold: bemegride and metrazol,[104] theophylline,[180] cyclosporin,[37] ifosfamide,[145,187] baclofen,[191] metformin,[71] cimetidine,[177] cefepime,[131] and ceftazidine.[93]

A number of cases have been reported with the use or withdrawal of AEDs, including one during a valproate-related encephalopathy, which was partially reversed by flumazenil.[159] Therapeutic concentrations of carbamazepine and/or phenytoin may exacerbate IGE in the specific form of ASE.[125,158] Patients with absence seizures appear to have a heightened risk for this paradoxical response, underscoring the value of an adequate syndromic approach.[125] Tiagabine has been implicated in episodes of atypical ASE.[47,49,146] Although this has been challenged as a valid phenomenon,[142] the exacerbation of experimental absence seizures by all γ-aminobutyric acid (GABA)ergic agonists, be they direct $GABA_A$ receptor or $GABA_B$ receptor agonists or indirect GABA agonists (GABA transaminase inhibitors, such as vigabatrin) and GABA uptake inhibitors, such as tiagabine[76,153,156] is well established. As well, a clinical correlate exists for the exacerbation of absence seizures and potential triggering of ASE by GABAergic drugs other than tiagabine, such as baclofen[191] and vigabatrin.[127,190] However, in most cases, EEG data were not really convincing of the ictal nature of the disorder, and this issue remains controversial.[142] True syndromic aggravation related to tiagabine use also has been associated with typical ASE in IGE[94] and in ASE with focal features in lesional focal epilepsy.[182] Replacement of valproate with lamotrigine precipitated ASE in a

single patient.[174] Levetiracetam has also recently been implicated in two patients with symptomatic partial epilepsy.[8]

Metabolic disturbances, either isolated or associated with drugs are frequently reported to be associated with ASE: hyponatremia,[48,98] hypocalcemia,[181] hypoglycemia,[71] decompensated chronic renal or hepatic failure,[48] hyperthyroidism,[160] psychogenic polydipsia with metabolic imbalance,[48] electroconvulsive therapy,[70] and cobalamin deficiency.[2]

Metrizamide and other contrast-enhancing products deserve special mention. A number of ASE case-reports have been documented following the use of these agents during myelography.[4,120,121,134,183,184] One case occurred after carotid angiography.[180] Another single case was described after intrathecal fluorescein injection.[30]

Other nonspecific triggering factors have also been reported occasionally (these have been reviewed[165]), but the mechanism by which they lead to ASE is speculative: alcohol, hyperventilation, intermittent photic stimulation, stress, grief, fatigue, disturbances of the sleep–wake cycle. Cases have also been reported following surgery, mild head trauma, severe head trauma, fever, paraneoplastic syndrome,[43] and neurosyphilis.[133] Genetic factors may also be implicated.[24]

In contrast to the number and variety of possible etiologic factors, no focal lesions have been documented in

ASE on imaging studies. However, in elderly patients with frontal mild to moderate cortical-subcortical atrophy of vascular and/or degenerative origin, it has been suggested that various toxic and/or metabolic factors may express themselves more easily in brains structurally damaged by such nonspecific lesions.[59]

ASE has been associated with other neurologic syndromes: Inoue et al.[80] reported six cases of ring chromosome 20 (RC 20) and epilepsy with prolonged confusional states resistant to AEDs associated with bilateral high-voltage ictal slow waves occasionally beginning with focal frontal EEG activity. These authors proposed that this constitutes a new syndrome.[80,128] ASE was also described in a child with the congenital bilateral perisylvian syndrome,[161] in patients with the eyelid myoclonia with absences syndrome,[185] in the perioral myoclonias with absences syndrome,[1,18] and in another syndrome of idiopathic generalized epilepsy with phantom absences of undetermined onset.[126] An isolated case report of atypical ASE has been reported in the context of a syndrome of increased intracranial pressure and transient MRI abnormalities.[26] Another patient with new-onset ASE[164] had unilateral frontal hyperperfusion on ictal single photon emission computerized tomography (SPECT). SPECT images were similar to those found in patients with focal NCSE.[95,168]

Long-Term Treatment and Prognosis

ASE generally has no effect on the natural history of any preexisting epilepsy, although Wirrell et al. have suggested that it is a factor predicting that childhood absence epilepsy will not remit.[188] In IGE, the occurrence of ASE appears to have no appreciable effect on subsequent seizure frequency, and the patients' cognition and mentation remain normal, as reviewed by Drislane.[44]

The influence of atypical ASE on the cognitive prognosis in epileptic encephalopathies is not as clear. It probably relates more to the encephalopathy that gives rise to the epilepsy than to the atypical ASE itself: In most instances, ASE does not appear to have any significant effect.[136] However, Doose and Völzke believe that repetitive ASE may aggravate intellectual deterioration in children with myoclonic-astatic epilepsy,[41] and Manning and Rosenbloom reported 13 children with atypical ASE followed by a deterioration of their mental handicap.[110] In NCSE, some adult patients were reported to show a significant increase of neurospecific enolase, a marker of neuronal damage,[36,135] but a recent study showed normal values in ASE.[143]

ASE has an inconsistent tendency to recur. Most patients have a single ASE, some have a few episodes, while others have a marked tendency to recur despite AEDs: Andermann and Robb reported a man with IGE who had more than 500 episodes of ASE between ages 40 and 65 years.[6] When ASE occurs with a preexisting IGE, the drug of choice to prevent recurrence is valproate[17]: In a series of 18 patients with IGE, the rate of recurrent attacks during a 4.4-year period was reduced with valproate from 5.7 to 0.6 attacks per year. Trimethadione, ethosuximide, phenytoin, barbiturates, and carbamazepine also have been used with less favorable results.[6] In elderly patients, the identification and correction of probable triggering factors may be sufficient to prevent recurrence.[166]

Pathophysiology

The fundamental underlying mechanisms of absence seizures have been delineated as well as any mechanism of human epileptogenesis. GABA-mediated inhibition and low-voltage activated or T-type calcium current activity becomes phase locked with glutamate-mediated excitation within thalamocortical circuitry, with resultant abnormal oscillatory rhythms that characterize absence seizures.[33,39,58,112,113] However, it is unknown whether these same mechanisms are operative in ASE. Perhaps a more important question is: What is the mechanism by which absence seizures usually are self limited, lasting only seconds? In this regard, some evidence shows that the α_4 subunit of the $GABA_A$ receptor complex may be involved in the maintenance and termination of absence seizure activity in the γ-hydroxybutyric acid (GHB) animal model of absence seizures.[10] These data raise the possibility that, in some instances, perturbation of the α_4 subunit of the $GABA_A$ receptor might lead to generalized ASE in a brain predisposed to absence seizures.

Very few animal models are available that might help us to understand the pathogenesis of epileptogenesis in ASE. However, the few experimental preparations of ASE that have been reported all have in common the prolongation of GABA agonist–induced absence seizures.[150,151,152,153] For example, based on the low-dose pentylenetetrazole model of absence seizures,[155,156] Wong et al.[189] administered repetitive low doses of pentylenetetrazol to create a rodent model of ASE that showed no evidence of immediate pathologic damage.

Of interest is the fact that, in those experiments, Wong and colleagues were able to induce ASE only in adult animals, but not in developing rats. In addition, Snead[153] has shown that if one superimposes a $GABA_B$ receptor agonist, baclofen, on the GHB model of absence seizures,[154] ASE results.

In another series of experiments using the prodrug of GHB, γ-butyrolactone (GBL)[157] in conscious marmoset monkeys, Tenney et al.[162] confirmed earlier work showing GHB-induced absence seizures in monkey[148,149] and also demonstrated functional magnetic resonance imaging activation of both thalamus and sensori-motor cortices concomitant with the GHB-induced SWDs. In a recent positron emission tomography study,[20] $^{[18F]}$fluoro-L-DOPA uptake was significantly decreased bilaterally in the putamen and caudate nucleus of 14 patients with ring chromosome 20 and epilepsy, suggesting that a reduction of striatal dopamine plays a key role in seizure interruption in some ASE patients. These clinical data comport with experimental data that implicate nigrostriatal and corticostriatal pathways in the pathogenesis of absence.[38,147,152]

Summary and Conclusions

ASE forms a major heterogeneous subgroup of NCSE. The clinical hallmark is an altered mental state with eyelid myoclonus

associated on emergency EEG with concomitant, bilaterally synchronous electrographic SWDs or PSW discharges. The literature indicates that four types of ASE may be recognized. Typical ASE occurs as part of an IGE most often characterized by typical absences, and immediate prognosis is excellent after BZ injection. The major defining feature of atypical ASE is that it occurs in the context of a preexisting neurologic abnormality, usually an epileptic encephalopathy. Therefore, atypical ASE is more difficult to treat and has a poorer prognosis than typical ASE in terms of long-term neurodevelopment and seizure control.

ASE with focal features occurs in patients with a localization-related epilepsy, most often of extratemporal origin. Ictal features tend to overlap with CPSE of frontal lobe origin. “De novo” ASE of late onset is a situation-related condition precipitated by toxic or metabolic factors in elderly subjects with no epileptic antecedents. ASE appears to be a rather benign condition: intellect, memory, behavior, and worsening of preexisting epilepsy do not appear to deteriorate from baseline even after recurrent attacks. Finally, the pathogenesis of ASE is virtually unknown, although some experimental data point to perturbation of GABA-mediated inhibition as playing a potential mechanistic role in this phenomenon.

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Chapter 61

Simple Partial Status Epilepticus and Epilepsia Partialis Continua of Kozhevnikov

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Introduction

Literature reports of simple partial status epilepticus (SPSE) seem to be relatively rare in comparison with those of generalized convulsive SE, complex partial SE (CPSE), and absence SE. One reason may be that SPSE very often progresses to CPSE, so that many overlaps between SPSE and CPSE exist in the literature, and cases are finally categorized according to their full-blown semiology, that is, as CPSE, even though for a certain time they might fulfill the criteria of SPSE (for definitions, see later discussion). Moreover, some subjective forms of SPSE have been described under the recently rediscovered term “aura continua”[285] and nonconvulsive SE (NCSE),[121] although levels of alteration of consciousness in the latter are often difficult to assess.

Among the multiple potential subtypes of SPSE, certain manifestations (which are readily accessible to the patient's awareness or physician's observation) seem to predominate, such as SPSE with motor symptoms and with certain sensory symptoms. Numerous studies have dealt with the pathophysiology of epilepsia partialis continua (EPC), whereas few have been devoted to SPSE with the expression of emotional/affective and subtle vegetative-autonomic symptoms only. Apart from the problem of the so-called interictal personality and behavioral syndrome[271] and other described peculiarities of personality, there remains the question of the boundaries of SPSE being expressed through very localized, ongoing epileptic discharges in “relatively silent” brain regions (e.g., nondominant frontal lobe) that might not be associated with any overt symptom at all but might be detected only with subtle decreases in very sophisticated neuropsychological test performance.

In contrast to the history of epilepsy, SE was infrequently recorded until the dissertation of Louis Calmeil,[40] where the expression *état de mal* is first found, but still in reference to convulsive generalized SE only. The proceedings of the Xth Marseilles Colloquium of 1962 represent the first monograph (*Les états de mal épileptiques*)[94] on this subject. At the Marseilles Colloquia of 1962 and 1964, definitions and classifications of seizures and of SE were proposed with the obvious notion that there are *as many types of status as there are types of seizures*.

The modern conceptual basis of SE as having an “etymologic definition” and the notion that this term is to be used “whenever a seizure persists for a sufficient length of time [subsequently defined as at least 30 minutes] or is repeated frequently enough to produce a fixed or enduring epileptic condition” has been widely accepted and enshrined in the WHO *Dictionary of Epilepsy*[90] as well as in the *Handbook of Clinical Neurology*[210] and the *Handbook of Electroencephalography and Clinical Neurophysiology*.[95] The first international classification of seizure types[88,89] and its revision[58] divided partial seizures into “simple” and “complex” according to whether consciousness was retained or lost. The subsequent classification of epilepsies and epileptic syndromes[59] included a few syndromes that might conform to the widened definition of status (e.g., EPC, CSWS, Landau-Kleffner) but otherwise lacked a synoptic view. A major review of SE occurred at the Santa Monica, California, conference in 1980, which was published in 1983.[66]

In the new proposal,[74] *continuous seizure types* are divided into *generalized status epilepticus* (including generalized tonic–clonic SE, clonic SE, absence SE, tonic SE, and myoclonic SE) and *focal status epilepticus* (epilepsia partialis continua of Kozhevnikov,[284] aura continua,[285] limbic SE [psychomotor status[283]], and hemiconvulsive status with hemiparesis). The division of partial seizures into "simple" and "complex" is not retained. In addition, the terms "partial" and "localization-related" have met with criticism, and a task force proposed that these terms be replaced by the older term "focal."

Pathophysiologically, a clear distinction should be made between the terms *epilepsia partialis continua* (EPC), or so-called *Kozhevnikov syndrome*, and *Rasmussen encephalitis* (see section Pathophysiology). Clinically, Bancaud's EPC type 2 largely corresponds with Rasmussen encephalitis.

Epilepsia partialis continua was first described by Kozhevnikov in 1894 as a "peculiar form of cortical epilepsy" that consisted of localized continuous jerks intermingled from time to time with spreading jacksonian seizures.[129,130] In his 4 cases, the seizure disorder continued for 3.5 to 5 years in the same part of the body. Kozhevnikov postulated a localized inflammation of the brain involving the motor strip. Omorokow reviewed 42 cases of "Kozhevnikov syndrome" in the literature and described a further 52 cases from his Siberian clinic, recognizing that this form of epilepsy may be due to Russian spring-summer tick-borne encephalitis.[174,175] In 1958, Rasmussen et al.[206] described 3 cases of persisting focal epilepsy due to chronic focal encephalitis. By 1988, a total of 48 Rasmussen chronic encephalitis cases had been identified and described,[205] differing in many ways from those of Russian spring-summer tick-borne encephalitis.[7] Since the first descriptions of EPC, many localized cerebral disturbances have been found to give rise to similar patterns of ictal behavior,[219] and the definition and nomenclature of EPC has become a subject of controversy.[29] In 1966, Juul-Jensen and Denny-Brown[120] pointed out that in various papers, the definition of EPC was not the same. They asked for a differentiation between true EPC with "clonic muscular twitching repeated at fairly regular short intervals in one part of the body for a period of days or weeks" and "focal epilepsy with motor seizures with frequent recurrence and with 'Jackson march' or progression from tonic to clonic phase." Gastaut and Broughton[92]

commented that "certain authors now also include chronic localized myoclonus without intercurrent somatomotor seizures or, conversely, recurrent somatomotor seizures without local myoclonus. Other authors also include the subacute episodes of localized myoclonus observed during certain syndromes of diffuse hemispheric ischemia." Later authors characterized EPC as a "partial somatomotor SE for a minimum of 1 hour and recurring in intervals of no more than 10 seconds"[249] and as "spontaneous regular or irregular clonic twitching of cerebral cortical origin sometimes aggravated by action or sensory stimuli (reflex component) confined to one part of the body and continuing for a period of hours, days, or weeks."[171] In 1989 the International League Against Epilepsy (ILAE) Commission defined EPC (Kozhevnikov) syndrome as a specific form of partial somatomotor seizure disorders involving the rolandic area of the motor cortex.[59] Schomer used EPC and focal SE as synonymous terms.[219]

Definition

For the purpose of this chapter, we suggest the following operational definition: SPSE is an epileptic condition (defined by clinical and electroencephalographic signs and symptoms) of at least 30 minutes' duration with a large spectrum of clinical manifestations and encompassing subtle clinical signs, as well as at least some behavioral disturbances and psychosis-like states, in particular, elementary and complex (polymodal) hallucinations, without loss or severe alteration of consciousness (in other words, "with preserved consciousness" in the sense of an [operationally defined] adequate reactivity and response). Furthermore, we add the criterion that observed symptoms should fit with the known functional anatomy and, thus, with localization of the electroencephalographic (EEG) discharge, and, in the case of more diffuse and difficult-to-describe personality and behavioral changes, that there be a clear-cut relationship in time of the particular subtle signs and symptoms with epileptic EEG activity.

Epidemiology

Incidence

There exist no population-based studies on SPSE. Until very recently, computations of frequency were restricted to generalized tonic–clonic SE, but even here, only vague guesses could be given, at best. At a conservative and approximate estimate, status syndromes, including West syndrome, neonatal and childhood status syndromes, EPC, other SPSE, and absence status in the elderly, contribute to the annual incidence of status no more than 5 to 10 cases per one million persons in the general population. SPSE is, thus, very rare, but this statement might require revision if the boundary syndromes (mentioned earlier) are included.

Prevalence

Hauser[112] attempted to break down SE by seizure type into the categories *generalized* (23%–51%), *unilateral* (39%), *partial motor* (24%–72%), *partial, secondary generalized* (5%–62%), *other* (5%), and *nonconvulsive* (5%–33%), based on the studies of Aminoff and Simon,[5] Celesia,[42] Hauser,[111] Aicardi and Chevrie,[2] and Forster et al.[81] Unfortunately, no precise mention is made in these studies of the incidence and prevalence (or definite absence) of SPSE. Brett[35] reported 22 children with "minor epileptic status" and differentiated this from "petit mal status" by the presence of myoclonus and less frequently occurring spike-wave patterns in EEG.

There seems to be a consensus that SPSE with motor phenomena is at least as common as SPSE without motor phenomena, that is, SPSE with sensory and/or autonomic signs and symptoms and SPSE with disturbances of language and higher cortical functions.

Epilepsia partialis continua is a condition with a wide range of underlying pathologies. Articles about EPC include case reports or small series of patients. For this reason, no epidemiologic data exist. Based on their survey of all registered cases in the United Kingdom during 1993, Cockerell et al.[53] estimated the prevalence of EPC to be <1 per million.

Etiology

No specific etiology leading to SPSE is known, and a large spectrum of underlying causes has to be considered (See also section Differential Diagnosis).

Myoclonic seizures progressing into status ("myoclonic storm"), in general, may be due to a wide variety of etiologies (essential hereditary myoclonus epilepsy, lipidosis of the central nervous system, acute encephalitis, subacute sclerosing panencephalitis, acute cerebral anoxia, Creutzfeldt-Jakob disease, and renal insufficiency with uremia) and may occur in various epileptic conditions (common generalized epilepsy, Lennox-Gastaut syndrome, infantile spasms).[167] Benign idiopathic neonatal convulsions, described in the literature as "fifth day fits," present often as lateralized clonic seizures and may lead to a SE lasting about 20 hours (from 2 hours to 3 days).[199] Some subtypes of the early infantile epileptic syndromes with suppression-burst must be considered here also. They can be viewed as falling into two main categories: (a) the Aicardi syndrome,[1,3] which is, in essence, a complex malformation syndrome, and (b) an inborn metabolic disease, nonketotic hyperglycinemia.[63] The majority of these patients have an EEG showing suppression-burst, for example, 98 of 146 in the Aicardi syndrome.[50] Suppression-burst was also described in other metabolic or malformation syndromes, such as olivary dysplasia,[109,207] hemimegalencephaly,[177,250,267] Menkes disease,[56,194] D-glyceric acidemia,[100] methylmalonic acidaemia,[152] propionic acidaemia,[268] and sulfite oxidase deficiency.[17] In early myoclonic encephalopathy (neonatal myoclonic encephalopathy), segmental and erratic myoclonias are usually the earliest ictal events (accompanied later by one or more of the other seizure types, such as massive myoclonias, simple partial seizures, and infantile spasms of the tonic type) and can recur frequently, so that they present as a status.[1]

Cases of *epilepsia partialis continua* (EPC) or *Kozhevnikov syndrome* have been a posteriori attributed to Russian spring-summer encephalitis.[219] A Russian spring-summer tick-borne virus has been isolated from monkey brain after several months of incubation, supporting the hypothesis of a slow-viral disease.[304] Dereux,[67] reviewing a series of 102 cases of Kozhevnikov syndrome, found that >50% were caused by an "encephalitic process," as were 31% of 85 pathologically verified cases in the review published by Löhler and Peters in 1974.[141] In a study of 36 cases by Cockerell et al.,[53] 7 patients had Rasmussen encephalitis, 9 had vascular diseases, 4 had a "multisystem" disease, 4 had neoplastic diseases, 2 had perinatal injury, 1 had trauma, 1 had hyperglycemia, and 1 had Creutzfeldt-Jakob disease.

Rasmussen encephalitis roughly corresponds to Bancaud's type 2 epilepsia partialis continua.[19,20,21] In the statistics published by Oguni et al.,[172] EPC developed in only 56% of the cases of Rasmussen syndrome as they evolved. In a recent Indian study of 20 patients,[180] type 1 and type 2 EPC were found in respectively 55% and

45%; infectious etiologies were found in 60% (Rasmussen encephalitis in 25% of these, or 3 cases) and vascular etiologies in 25%, with the remaining 15% consisting of 1 mitochondrial disorder and 2 undetermined causes.

Creutzfeldt-Jakob disease (CJD) rarely presents with epilepsia partialis continua with subacute progression in which the EEG shows focal epileptiform activity and neuroimaging is negative.[183]

Patients with human immunodeficiency virus (HIV) infection may present new-onset EPC as an early manifestation of progressive multifocal leukoencephalopathy (PML).[25,79]

Cerebral tumors, such as astrocytomas, hemangiomas, lymphomas, and metastases, have been reported as causes of EPC. In fact, these tumors are associated with EPC because of their anatomic location near the central sulcus and probably not because of their neoplastic nature. The same relation may exist in cases of EPC in multiple sclerosis[115,240,244] and in the earlier American[120] and recent Indian cases[180] with infectious mass lesions, especially of tuberculosis.

The vascular etiologies reported were occlusive, embolic, or hemorrhagic stroke; arteriovenous malformations; cortical venous thrombosis; and vasculitis in lupus and in Sjögren syndrome.[23]

Traumatic lesions are present in many series.[22,53,141,249]

Cortical dysplasias, especially hemimegalencephaly, can present with EPC, as well as tuberous sclerosis, linear sebaceous nevus syndrome, and Sturge-Weber syn-drome.[83,84,68,133,150,151,165]

EPC may be associated with widespread gliomatosis cerebri[224] and paraneoplastic recurrent multifocal encephalitis[164] and was seen in cat scratch disease.[202] It can be observed in hemiconvulsion, hemiplegia, epilepsy (HHE) syn-drome.[45]

EPC and SPSE can occur as a complication in nonketotic hyperglycemia in children and adults, including elderly patients (>50 years).[176,214,234] Such a condition may show progressive development over days. Clinical symptoms associated at the beginning are polydipsia, loss of appetite, simple partial seizures with motor symptoms, and a mild-to-moderate psycho-organic syndrome. In a hyperosmolar nonketotic coma, glucose values are often very high, and osmolarity may be >320 mmol. Because phenytoin can reinforce hyperglycemia, it is contraindicated. Renal failure giving rise to *uremia* in older patients is particularly often associated with frequent myoclonic jerking. In renal insufficiency, the EEG becomes frequently abnormal and is characterized by excessive slowing. Not infrequently, EEG abnormalities are enhanced during and after hemodialysis.

EPC has been described in mitochondrial disorders such as Leigh syndrome,[72] mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes,[9,51] subacute measles encephalopathy in immunosuppressed children, and Alpers disease with, in the case of Bourgeois and Aicardi,[32] a deficiency of cytochrome c oxidase.

Iatrogenic partial motor SE has been reported after exposure to penicillin, azlocillin, or cephotaxime[301] and after diagnostic use of metrizamide.[229]

Somatomotor SPSE occurs about 50% of the time as a first manifestation in otherwise nonepileptics, is usually seen in the elderly, and often reflects an embolic but otherwise asymptomatic ischemia (sylvian or suprasylvian). The so-called *somatomotor SPSE* accompanying severe brain lesions in nonepileptics presents differently, with periodically repeated, about 1/sec localized myoclonus involving, as a rule, a proximal part of limbs or one side of the trunk or flank. It is nearly exclusively observed in elderly patients, most often representing infarction in watershed territories (so-called interterritorial infarction), or, less frequently, metastatic brain tumor or brain contusion.[44,166] The EEG most often shows corresponding periodic lateralized epileptiform discharges (PLEDs; Figs. 1 and 2). In vascular cases, Gastaut[91] referred to the "initial myoclonic phase of interterritorial infarction" in such a situation, to avoid the term *status*.

PLEDs may be an ictal EEG pattern in SPSE. Ictal PLEDs are often associated with corresponding jerks in the sense of EPC. In addition, PLEDs can be associated with recurrent and prolonged episodes of a confusional state associated with psychic and neurologic manifestations. Terzano et al.[248] reported seven elderly (>60 years of age) patients with PLEDs and prolonged confusional states. In these seven patients, the EEG became normal when the ictal episodes subsided, either spontaneously or following intravenous diazepam. More often, however, PLEDs are viewed as an "interictal" pattern that can last as long as 3 months to 2.5 years[274] and can occur in a variety of disorders. Snodgrass et al.,[238] for example, found PLEDs most often in acute unilateral lesions (vascular, 35%; mass lesion, 26%; infection, including herpes simplex encephalitis, 6%; anoxia, 2%), but also in other conditions (22%), such as alcohol withdrawal and toxic-metabolic disorders. They are also seen with chronic seizure disorders or with old static lesions when associated with recent seizures.

The determination of whether such a periodic EEG pattern, if not associated with obvious ictal signs and symptoms, reflects an interictal or ictal state (in the sense of an ongoing ["sub-clinical"] electrographic status) has important implications for antiepileptic therapy. Single photon emission computed tomography (SPECT) studies strongly suggest that PLEDs may be ictal in some patients. Whereas Treiman[253] feels that treatment is appropriate until all EEG discharges are gone, Lothman et al.[142] and Brenner and Schaul[34] suggested that a stable periodic pattern may represent underlying pathology with neuronal damage rather than seizure activity and does not demand antiepileptic treatment.

Pathophysiology

Why and how epileptic discharges can remain restricted to a given cortical (or corticothalamic sector) region without noteworthy propagation, over long periods of time to produce SPSE might be related to (a) certain pathologies, (b) the localization of the lesion, and (c) sufficiently preserved inhibition to limit the epileptic process in space.

In general, the pathophysiology of SPSE is poorly understood. Considerable knowledge, however, has been accumulated on EPC. Bancaud's classification of EPC into types 1 and 2 is clinically useful.[22] In type 1, the myoclonias correspond to a focal structural lesion in the contralateral rolandic cortex. This type does not show any age dependence, the continuous myoclonias are restricted, and the EEG usually also shows a sharply delineated spike focus. The clinical course and the prognosis are determined by the underlying pathology. The unaffected brain regions are often and remain, as a rule, more or less normal. Type 2, also called *Rasmussen syndrome*,[6,10,172,206] is a progressively evolving "chronic encephalitis" with a predominance in children and a peak around the sixth year of life.[101,205] (see Chapter 243.) In about two thirds of cases, there is a history of a preceding nonspecific infection. Often, the disease starts with a grand mal seizure or several simple partial motor seizures and eventually includes complex partial seizures. In about 50% to 60% of patients, EPC develops and is then the predominating seizure type.[172] Seizures are usually resistant to antiepileptic drugs, and extensive resective surgery was the only known effective treatment.

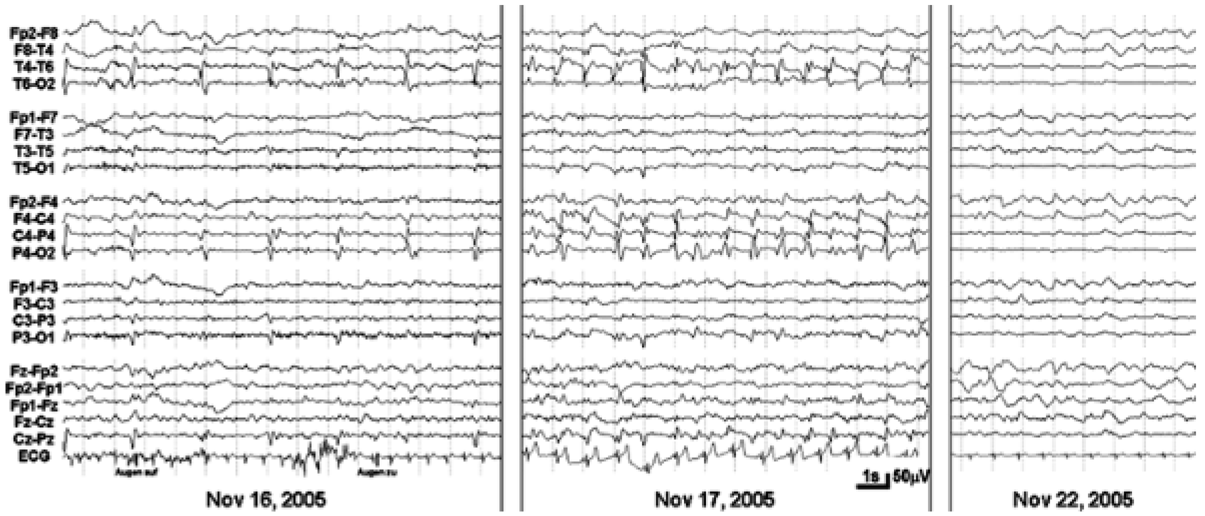

FIGURE 1. Illustration of periodic lateralized epileptiform discharges (PLEDs) followed for 1 week. On November 16, 2005 **(left),** there was a periodicity of sharp waves at T6 and P4 of about 0.4/s with an intermingled seizure discharge (see Fig. 2). Valproate was administered. One day later, the PLEDs showed a periodicity of 1/s, and there were now seizure discharges. Five days later, PLEDs were no longer present, but there was a flattening at T6 and P4. One day before admission (November 15, 2005), the patient experienced a left hemiplegia due to a new hyperintense magnetic resonance imaging lesion in the right crus cerebri. This

was diagnosed as new plaque within the diagnosed chronic-progressive multiple sclerosis (since 1985). The patient also suffered from schizophrenia-like psychosis and anorexia nervosa. She had had several seizure-like episodes (falls during the last year but without the clear diagnosis of epilepsy).

In relatively well-preserved brain areas, perivascular lymphocytic cuffs and glial nodules, and in later stages microcystic degeneration with marked neuronal fallout but without evidence of inflammatory elements, are typical histologic findings.[208] It is fair to say that the nature of this disease remains obscure, although in recent years an autoimmune process has been postulated, as prompted by various reports.[11,211,257] Autoantibodies in sera from patients with active Rasmussen encephalitis and experimentally induced antibodies in rabbits seemed to act as agonists for glutamate receptors consisting of or containing GluR3 subunits. Agonist activity of autoantibodies on a glutamate receptor subunit suggested their role as pathogenetic factors, potentially as highly specific excitotoxins or neuromodulators. Our search, however, for the presence of anti-GluR3 antibodies in sera and cerebrospinal fluid of four patients with typical histologic findings of Rasmussen encephalitis yielded negative results.[252] In other patients with Rasmussen encephalitis, autoantibodies against the glutamate receptors (GluR3, GluRepsilon2) were detected,[131,211,246,247,257] suggesting an autoimmunologic etiology in a subgroup of this syndrome. Preliminary data with plasma exchange therapy in some patients with Rasmussen's encephalitis seem also to support this etiology.[221,291]

The definite proof for a cortical origin of EPC was provided by three studies using depth-electrode recordings (Fig. 3).[21,39,287] An experimental model of EPC was achieved by injections of aluminum hydroxide into monkey motor cortex.[46] Using this experimental model, Chauvel and associates proved the role of the long-loop reflexes for generation of the cortical myoclonus.[47] Thermocoagulation of the thalamic nucleus ventro-lateralis posterior (VPL) oralis disrupted the reflex loop and led, in the majority of cases, to a cessation of the myoclonus.[48] The participation of the (presumably) ventrolateral and intralaminar thalamic nuclei[119] in the epileptic process was illustrated on fluorodeoxyglucose (FDG)-positron emission tomography (PET) by a simultaneous metabolic increase in both the cortical and the ipsilateral thalamus in a patient with an EPC.[106]

On the other hand, absence of epileptogenic EEG abnormalities in some patients with EPC[189] and presence of subcortical brain lesions with preserved cortex[31,120] led to the hypothesis of a subcortical origin of the EPC in at least some patients. A recent report even implicates a cerebellar lesion as possible cause for EPC.[263]

In 1985, Hallett introduced three types of epileptic myo-clonus: (a) cortical reflex myoclonus as a fragment of partial epilepsy, which represents hyperactivity of a focal area of cerebral cortex; (b) reticular reflex myoclonus as a fragment of generalized epilepsy with hyperactivity of medullary brainstem reticular formation; and (c) primary generalized epileptic myo-clonus as a fragment of primary generalized epilepsy, which may represent a generalized hyperactive response of cortex to subcortical input.[107] (For further discussion of myoclonus, see Chapter 277.)

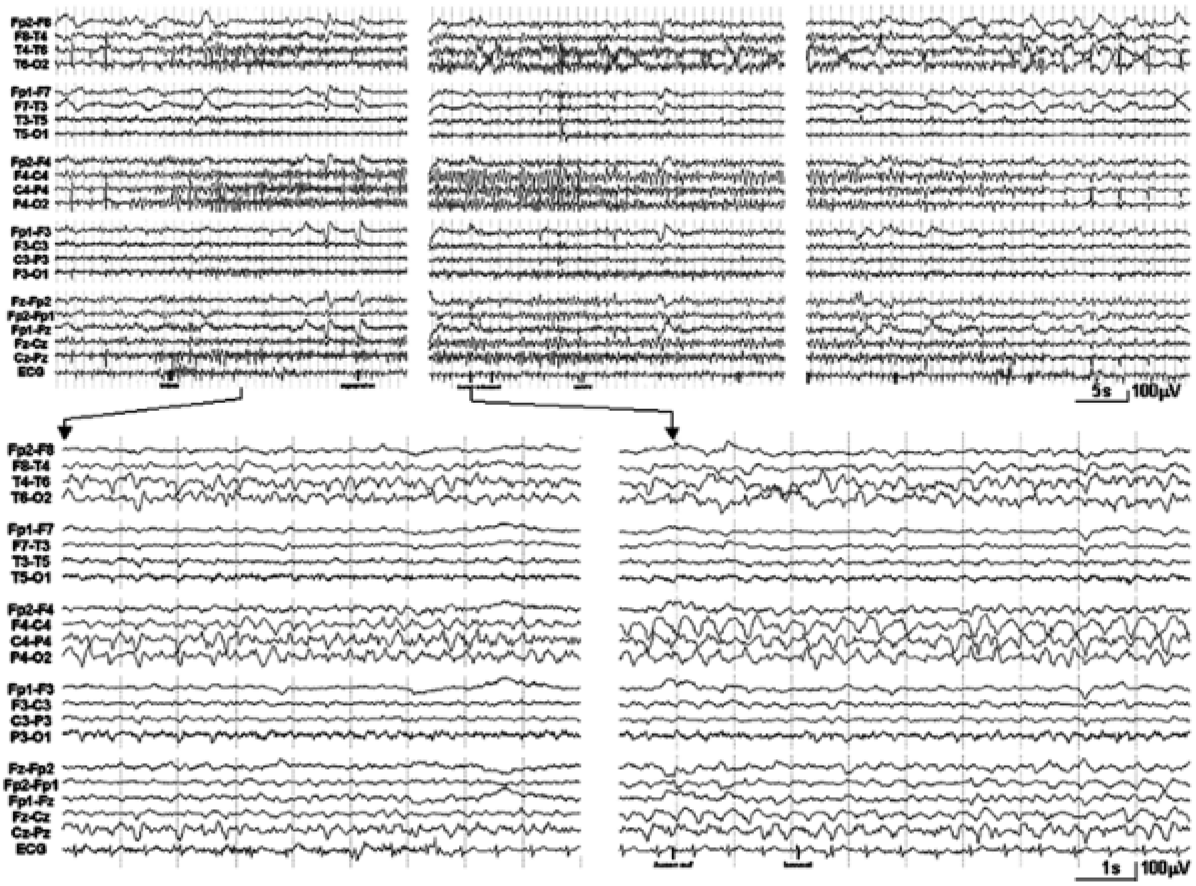

FIGURE 2. Same patient as in FIGURE 1. During the electroencephalogram (EEG) recorded on November 16, 2005, with periodic lateralized epileptiform discharges of a periodicity of sharp waves at T6 and P4 of about 0.4/s, the depicted seizure discharge occurred with evolving slow rhythmic activity at the right temporo-parieto-central region. **Upper rows:** Sections showing the beginning, height, and the end of the seizure. **Lower row:** Corresponding EEG sections (indicated) with better time resolution.

In cases with cortical reflex myoclonus, the epileptogenic focus is localized in the contralateral rolandic cortex, and the EEG may show spikes related to the myoclonic jerks. In cases without a clear-cut temporal relation between epileptic events and myoclonus in the EEG, the back-averaging technique identifies the spikes preceding the myoclonus.[227] Somatosensory-evoked potentials of the rolandic cortex are abnormally enlarged.[228] Tight relations between the afferent volley evoking abnormal evoked potentials in the primary motor cortex itself and triggering of focal myoclonus have been demonstrated by depth recordings in patients with EPC.[49]

Without such proof of the cortical origin of the myoclonus by neurophysiologic methods, a subcortical or even spinal origin of the myoclonus has to be considered. Cockerell et al. suggested that the diagnosis of EPC should be confined exclusively to cortical myoclonus.[53] They proposed the term “myoclonia continua” for myoclonus that arises extracortically.

In cases of EPC in which the jerks are associated with other seizures, the physiologic characteristics of the jerks are identical to those of cortical myoclonus.[230] In this sense, cortical myoclonus is cortical epilepsy, that is, a hypersynchronous discharge from a group of cortical cells. By employing different physiologic methods, such as back-averaging of EEG recordings in relation to the jerks, evoked potentials, and electromyographic recordings of the sequence of recruitment of muscle

groups in a myoclonic jerk, a distinction of myoclonus into cortical, brainstem, and spinal myoclonus is possible in most cases. Typically in cortical myoclonus, the EEG cortical generator potentials precede the jerks; sensory-evoked potentials are enlarged; and the myoclonus may be spontaneous and action or stimulus sensitive with a rostrocaudal pattern of muscle recruitment and antagonist and agonist cocontraction. In stimulus-sensitive myoclonus, the reflex timings are compatible with a cortical loop. Obeso et al.[171] reported patients showing a spectrum of spontaneous and stimulus-sensitive myoclonus, EPC, jacksonian seizures, and generalized seizures, all with similar physiology. In these cases, EPC is repetitive cortical myoclonus. In cases without seizures, however, jerks resemble EPC clinically but not neurophysiologically. In such cases the jerks might be of subcortical origin. Menini and Naquet[149] called this variant type C myoclonus with suggested origin in the brainstem. It is, however, fair to say that this variety is neither as common nor as well studied as the cortical myoclonus, and its exact nosologic position is not clear.

The neurophysiologic criterion for a cortical generator of myoclonus is the presence of a preceding potential in the central region contralateral to the jerk. However, many circumstances, related to the rate of occurrence of myoclonus or presence of a lesion modifying the geometry of the cortex or volume conduction, can impair the reliability of jerk-locked averaging. Applying methods that analyze EEG-electromyograph (EMG) and EMG-EMG relations in the frequency domain, several studies have demonstrated functional coupling between cortical and muscular activity during myoclonus even when back-averaging was negative.[37,38,146,154] Distinction between the pathologic corticomuscular coupling and the physiologic one might be only quantitative, and polygraphic EMG recordings remain essential for identifying pathologic drives to muscles.[104,261] In addition, an exaggerated coupling in the efferent pathway does not preclude the existence of putative generators upstream of the motor cortex.

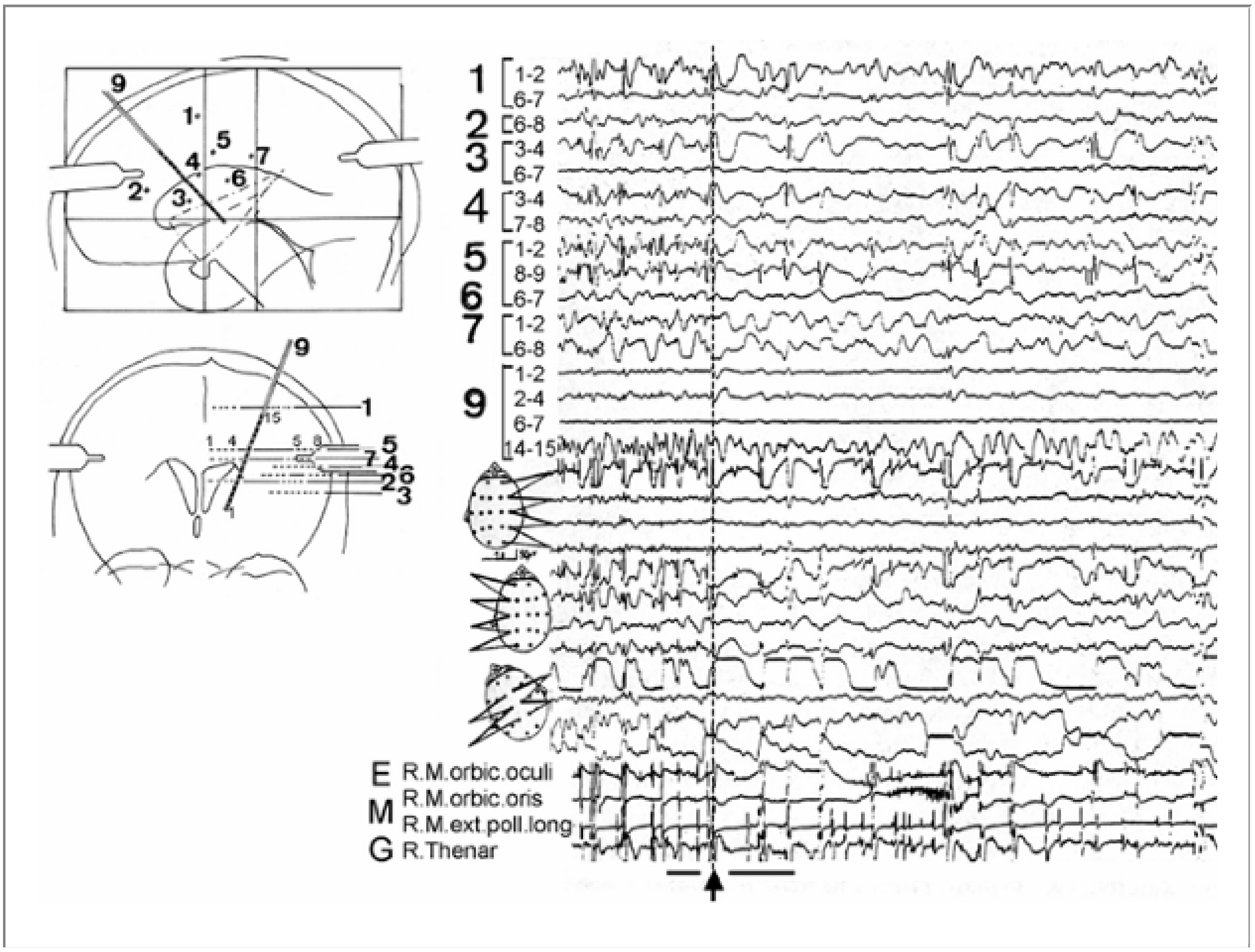

FIGURE 3. Stereo-electroencephalogram in a patient with epilepsia partialis continua recorded by eight left-hemispheric, 8-contact stereotactically inserted depth electrodes (of the "chronic" type) and by an additional rigid 15-contact electrode (#9) with its tip in the ventrolateral thalamus. Note the correspondence of left central spikes with the corresponding electromyographically (EMG) recorded muscle jerks and the different time scales (the paper speed was doubled at the time indicated by the vertical line). The patient underwent thermocoagulation of the ventrolateral thalamus with initially good, but in the long-time course moderate, therapeutic effect (follow-up >20 years; no definitive histologic diagnosis).

Clinical Features

Ictal Signs and Symptoms

SPSE can be described from a practical standpoint within the following categories[91]:

1. Somatomotor SPSE, which, according to Passouant et al.,[186] accounts for approximately two thirds of all cases of partial SE occurring in known epileptics. Somatomotor SPSE can be further divided into the following categories:

    a. One subtype that occurs during the course or at the onset of somatomotor partial epilepsy, that is, somatomotor SPSE stricto sensu.
    b. Epilepsia partialis continua (Kozhevnikov).
    c. So-called somatomotor SPSE accompanying severe brain lesions in nonepileptics ("initial myo-clonic phase of interterritorial infarction with PLEDs"[91]).
    d. Another special subtype, adversive SPSE, in particular, the oculoclonic form.

2. The less frequent sensory SPSE can be divided into the following subtypes:
    a. SPSE with dysesthesia
    b. SPSE with visual phenomena
    c. SPSE with acoustic phenomena
    d. SPSE with olfactory or gustatory phenomena
    e. SPSE with vertigo
3. SPSE with autonomic phenomena, with a special subtype in children—abdominal SPSE—might be classed separately.
4. Dysphasic or aphasic SPSE may be divided into intermittent versus continuous and into receptive ("fluent aphasia") versus expressive ("aphemia") types. The Landau-Kleffner syndrome and CSWS are sometimes listed in this context. Whether this is appropriate is a matter of controversy. Arguments against it are that the core symptoms do not immediately resolve after cessation of seizures and disappearance of spikes.
5. French authors also have used a category *erratic*. Other rare manifestations of SPSE and boundary conditions can be subsumed under this category.
6. Finally, we have SPSE with psychic and emotional phenomena.

Somatomotor SPSE is characterized by frequently repeated typical somatomotor seizures with or without jacksonian march and with more or less pronounced EEG discharges in the rolandic region. Consciousness is well preserved, and there are no marked vegetative signs. EPC is a particular subtype with localized segmental myoclonus.

Adversive SPSE is briefly reported by a few authors[43,209] but might be exceptional if we exclude cases with secondary generalization and tonic status with predominantly unilateral seizures and accompanied by head and eye turning. *Oculoclonic SPSE* with occipital discharges and *epileptic nystagmus*[87,93,236] and *palatal tremor*[168] are other rare manifestations of motoric phenomena of SPSE.

Epilepsia partialis continua is characterized by almost continuous, rhythmic muscular contractions affecting a limited part of the body for a period of hours, days, or even years. The myoclonic jerks have a frequency of about 1 to 2 per second and may persist during sleep.[22,193,287] About 60% of the

patients exhibit other types of seizures in addition to an EPC,[53] such as secondary generalized seizures and complex partial seizures. In addition to muscle twitching, patients may show varying degrees of muscle weakness, sensory loss, or stretch reflex changes.

The presentation of the disorder depends on the underlying cause (see section Etiology). Patients with localized neoplastic, vascular, or infectious brain lesions may have neurologic deficits and isolated seizures prior to the onset of the focal SE.[19] With metabolic causes, however, such as nonketotic hyperglycemic diabetes mellitus, or hypersensitive reactions to certain drugs such as penicillin or metrizamide, the onset of focal SE is sudden.[219]

In the Russian patients, the epilepsy usually developed 3 to 4 months after a febrile illness, associated with a hemiplegia or monoplegia in 30% of cases. In this condition, the jerks typically affect agonist and antagonist muscles with a rhythmic quality, in short bursts of 1 to 2 seconds' duration alternating with quiescent phases 2 to 4 seconds long, persisting in sleep and worsened by action or stress. Motor seizures with jacksonian march or generalized epileptic seizures are almost invariable accompaniments, although they have a strong tendency to improve over time. The jerking, often highly focal, continues relentlessly for years. Sensory symptoms occur in about one fifth of cases, and 80% have a persisting hemiparesis. EPC associated with Rasmussen encephalitis manifests itself in children in the majority of cases (mean age 6.8 years, with 85% being <10 years of age). All children present with epileptic seizures, often generalized tonic–clonic, although focal simple or complex partial seizures also occur as a first manifestation of the disease. In Rasmussen encephalitis, about one half of the patients exhibit episodes of EPC, usually within 3 years of onset with epilepsy. These episodes last hours to years and are often discontinuous. The condition is progressive, and after a highly variable period of 3 months to 10 years, fixed focal deficits develop, notably hemiplegia, hemianopia, and (depending on the hemisphere) aphasia, as well as progressive intellectual impairment. After an initial progressive course in which the focal motor seizure activity is often multifocal, the disease process appears to eventually burn itself out, at least in a substantial proportion of Rasmussen encephalitis patients.[162]

With regard to localization, EPC is a particular form of rolandic partial epilepsy that involves the motor strip of one hemisphere and usually has a clinically localized appearance. In Rasmussen encephalitis, the disease process seems to be more widespread, with diffuse patchy inflammatory changes in the cortex and white matter (microglial nodules, perivascular cuffs of small lymphocytes and monocytes, multifocal neuronal loss, and some spongy degeneration) depending on the features of the disease activity. (See also Robitaille,[208] who classified the Montreal specimens into four groups of disease activity.)

Current views are that the physiologic characteristics of the jerks in most cases of EPC are identical to those of cortical myoclonus (see section Pathophysiology). The myoclonic jerks in EPC can affect any muscle group. They may be confined to a single muscle or muscle group or they may be widespread. Face, upper limb, and trunk predominate. The distribution of jerks can vary over time. Agonists and antagonists are affected together, and distal muscles are affected more often than proximal ones. Isolated clonic twitching of the abdominal muscles due to a metastatic cortical lesion and considered as a rare manifestation of EPC has been described.[78] Jerks are unilateral. Bilateral cases have been included,[141,249] but it is questionable whether such cases should be described within the category called EPC. Takahashi et al.[245] studied EPC of childhood involving bilateral brain hemispheres; Ashkenazi et al.[16] described a bilateral focal motor status epilepticus with retained consciousness after stroke; and Lim et al.[140] described a generalized myoclonus evolving into EPC due to a cingulate gyrus venous angioma.

Familial alternating EPC with chronic encephalitis as another variant of Rasmussen syndrome has been described by Silver et al.[233]

Sensory SPSE was described by Scott and Masland[222] as a possible “continuous symptom” based on the notion that such an "aura continua" reflects the intrinsic epileptogenic properties of an epileptogenic focus that remains "well controlled" without further recruitment, that is, without increase of the number of epileptically involved neurons. A hippocampal epileptic focus causing electrographic focal SE may be limited to a volume of <1 cm in diameter.[77,288] Metaphorically speaking, one assumes that the "critical mass" necessary for the spread of the discharge is not reached in such a condition. A pure sensory aura continua, or SPSE, is rare. Not infrequently, in our experience, it is seen in relation to a marked increase in antiepileptic medication, in particular, with drugs preventing spread, or after surgical removal of parts of the primary epileptogenic area mediating seizure spread along preferential pathways. Although pure *localized* (*or hemi-*) dysesthesia as a cortical phenomenon of ongoing ictal discharges is likely to exist, convincing evidence—support by clear-cut EEG findings—is scanty. *Unilateral symptoms* point to the contralateral postcentral area and include tingling, numbness, sense of movement or desire to move, somatic pain, heat or cold, electric shock, agnosia for a body part, and phantom sensation.[138,189,191,212,259,260,303] Bilateral somatosensory symptoms often affecting fingertips, feet, lips, or tongue (perioral region) point to the second sensory area localization (termination of the motor strip of the frontal parietal operculum and superior bank of the frontoparietal sylvian fissure).[191]

Pain as an epileptic aura[275] and painful epileptic seizures are uncommon but have been described.[232,297,303] Direct evidence that long-lasting pain is a special form of SPSE is scanty, but this possibility should not be discarded. Indeed, Seshia and McLachlan[223] reported two patients with long-lasting aura continua and "pain" (patient no. 1: 21 years old, with nose pain for 2 years; left temporal seizure origin; symptom abolished after surgery; without pathology in the resected tissue; patient no. 3: 43 years old, with epigastric pain; right temporal seizure origin; symptom abolished after surgery; glioma). Certain forms of pain per se might be closely linked to epileptic basic phenomena,[82] and the positive therapeutic effect of antiepileptic drugs in such circumstances is well known. The so-called abdominal aura continua (abdominal epilepsy, recurring abdominal pain) has been described, particularly in children,[153,192,217] and has been found to be associated with amygdalar discharges.[76]

Hemicrania epileptica is a rare ictal phenomenon[116,292] (for a review, see Andermann and Lugaresi[8]), which may last >30 minutes and, therefore, can then be labeled as a form of SPSE.

Gastaut reported *simple partial status epilepticus with elementary visual phenomena only*,[91] and Sowa and Pituck described prolonged complex visual hallucinations.[239] FIGURE 4 gives an example of this type of SPSE. *Status epilepticus amauroticus* was described by Ayala[18] and Barry et al.[24] Hadjikoutis and Sawhney[105] described a case with occipital seizures presenting with bilateral visual loss. Ictal visual hallucinations with reversible postictal hemianopia with anosognosia have been reported by Barry et al.[24] and Spatt and Mamoli.[241] Sheth and Riggs[226] reported an unusual case of a clinically silent occipital electrographic SE persisting for >3 years in a 13-year old girl. Calcarine and pericalcarine occipital cortex are the principal localizations.[213,216]

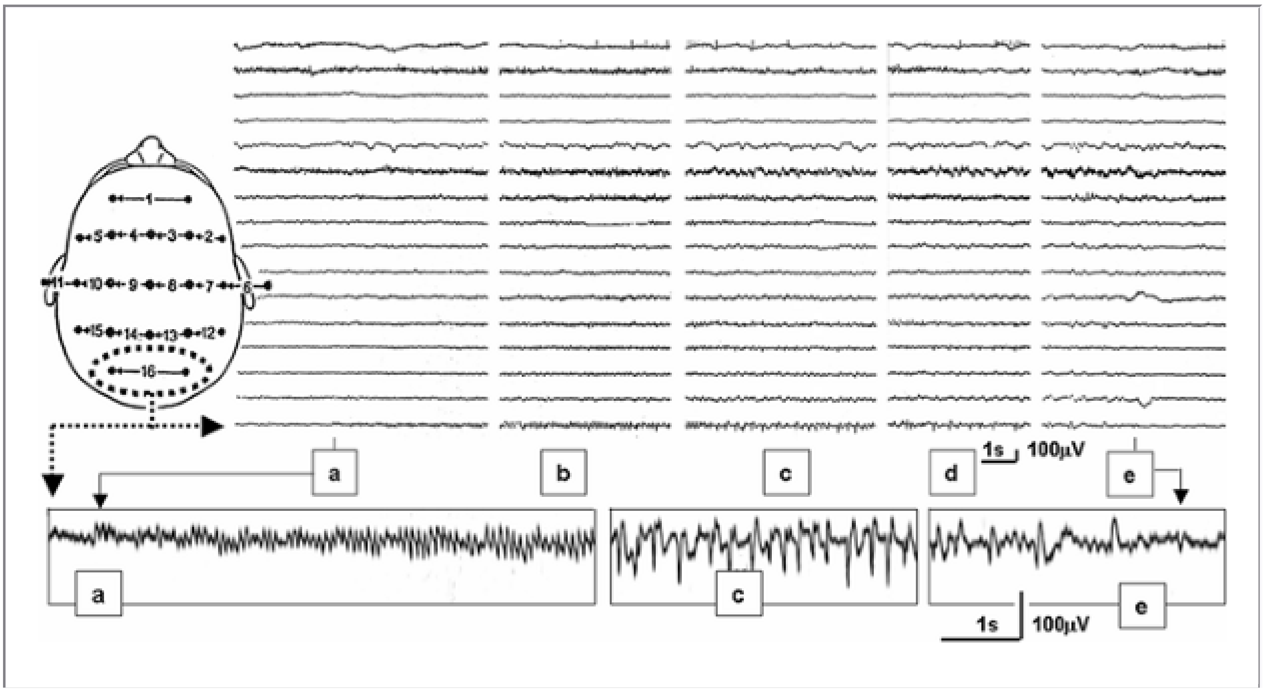

FIGURE 4. A very localized posterior simple partial seizure with elementary visual hallucinations (flickering lights) during simple partial status epilepticus (SPSE) with frequently recurring seizures of this type. This patient had a history of occipital venous thrombosis following a splenectomy at age 8 years (1963). After some initially generalized seizures, he developed severe drug-resistant partial epilepsy with frequently recurring psychomotor seizures. He underwent presurgical evaluation with stereo-electroencephalogram (SEEG) (with electrodes in the occipital and temporal lobes) in January 1980 and underwent selective amygdalohippocampectomy in March 1980 because his seizures originated at these structures. Postoperatively the patient was seizure free with the exception of two grand mal seizures during a safari in Africa. In the last months of 1994, during slight reduction of antiepileptic drug monotherapy, he experienced "funny flickering lights" similar to what he had had before operation as one of several aura symptoms. Although no headache was associated with the SPSE, he was believed to suffer from migraine and referred for a control with EEG, which showed the epileptic nature of his visual disturbances. He responded well to an increase of the dose of his carbamazepine treatment, without further disturbances of this type during more recent years.

Simple partial status epilepticus with auditory hallucinations only has been observed[277] but was published under the heading CPSE. This because the SPSE with stereo-EEG–documented discharges restricted to Heschl's gyrus and accompanied by musical hallucinations (the patient experienced a song well known and familiar to her) in "endless repetition"

finally spread to the ipsilateral mesiobasal limbic structures, resulting in alteration of consciousness. FIGURE 5 illustrates the onset of this electrical status activity that was accompanied at the beginning by musical hallucinations only. Schiffter and Straschill[218] reported on a case with aura continua musicalis. Most cases with simple auditory hallucinations described in the literature, however, do not fulfill the criteria of an aura continua.[123,190] Blanke et al.[30] described a patient with epilepsy (secondary to left parietotemporal brain damage) suffering from the paroxysmal unilateral experience of hearing a person in her near extrapersonal space associated with a deficit in spatial auditory perception and other paroxysmal disorders of somatognosia.

Simple partial status epilepticus with *olfactory symptoms* is rare but has been documented.[279] FIGURE 6 gives an example of long-lasting kakosmia associated with fronto-orbital discharges. Jackson and Beevor[117] and Jackson and Stewart[118] reported olfactory sensations with the mesial temporal lobe ("uncinate fits"). Projection areas for olfaction include the anterior perforate, prepiriform and lateral olfactory gyri, amygdala, periamygdalar and entorhinal cortices, and septal nuclei as well as hypothalamus

"*Gustatory aura continua*" was the leading symptom of case 4 of the 1985 paper of Wieser et al.,[288] with electrical left hippocampal status activity in the EEG. The parietal operculum near insula and the anterior insula have been classically implicated in taste.[113,189] In our case, the gustatory SPSE was also associated with subtle higher cognitive deficits detected with a tachistoscopically presented lexical decision task (Figs. 7 and 8). Seshia and McLachlan[223] reported one pati-ent with long-lasting metallic taste for 2 years (patient no. 6: 46 years old; left temporal seizure origin; symptom abolished after surgery; oligodendroglioma) and another with foul taste for 5 years (patient no. 2: 34 years old; right temporal seizure origin; symptom abolished after surgery; mesial temporal sclerosis).

Whereas complex or simple partial seizures *with autonomic symptoms* as the leading feature are well known,[295] evidence is less convincing for SPSE with autonomic signs and symptoms only. An exception might be *umbilical sensations in children*[262] and autonomic seizures and *autonomic SE in Panayiotopoulos syndrome*.[178] In this syndrome with good prognosis, which is now recognized in the new classification scheme of the ILAE, seizures start with autonomic symptoms, mainly emesis, while the child is fully conscious. Half of the seizures last >30 minutes, constituting autonomic SE.[179]

Long-lasting borborygmi and long-lasting episodes with widened pupils (or hippus pupillae), pilomotor phenomena, goose-flesh, periodic shivering, and so on were described,[36,102,243,276,280,281,294,296] but often they were accompanied by certain peculiarities of personality and behavior, and, therefore, they were often described in the context of "limbic dyscontrol syndrome."[97,293]

Under the category *nonconvulsive status epilepticus*, Rabending and Fischer[203] described ictal bradycardia and asystole. Zijlmans et al.[305] determined the prevalence of heart rate changes and electrocardiogram (ECG) abnormalities during epileptic seizures in 281 seizures in 81 patients. ECG abnormalities were found in 26% of seizures (44% of patients), and long seizure duration increased the occurrence of ECG abnormalities.

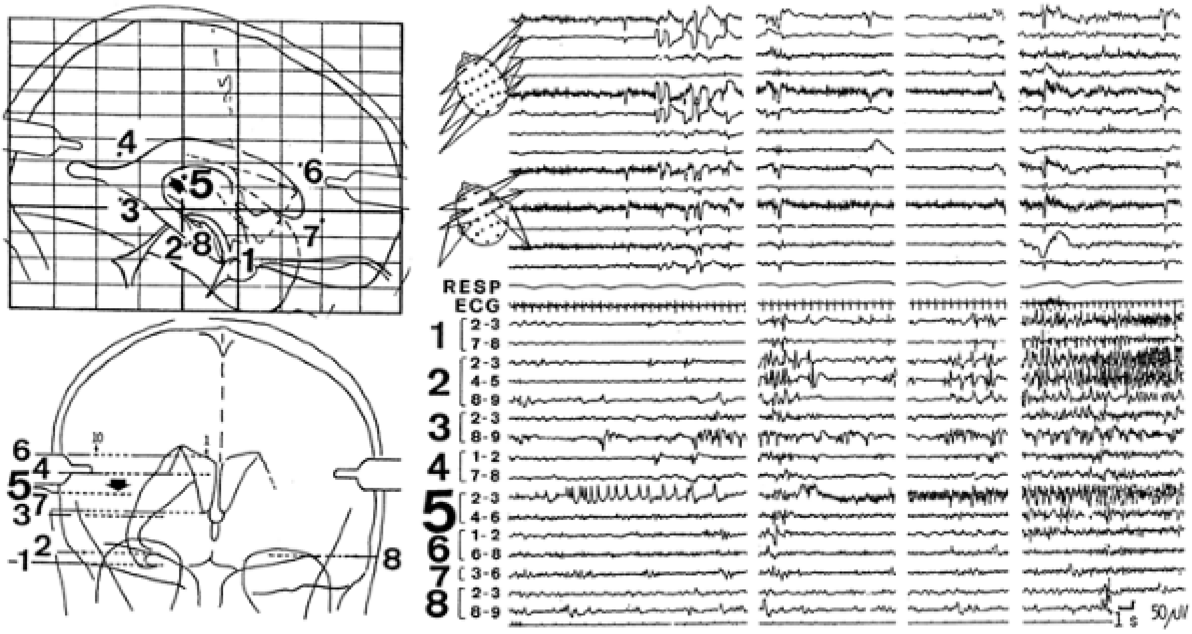

FIGURE 5. Onset of a partial status epilepticus with long-lasting discharges at the right gyrus of Heschl (5/2-3) and with subsequent spread to the right mesiobasal temporal lobe structures (hippocampal formation, 2/2-3; and amygdala, 1/2-3). At the onset of this electrical status activity this 22-year-old Portuguese woman experienced a hallucination of music (the Portuguese song “Santa Maria”) in “endless repetition.” Initially, she reported a “good quality of the record”; after 3 hours, the quality was reported to become worse and worse, with the voice of the singer ceasing and the drums becoming more prominent. Later, she entered a complex partial status epilepticus. (See detailed case report in Wieser.[277])

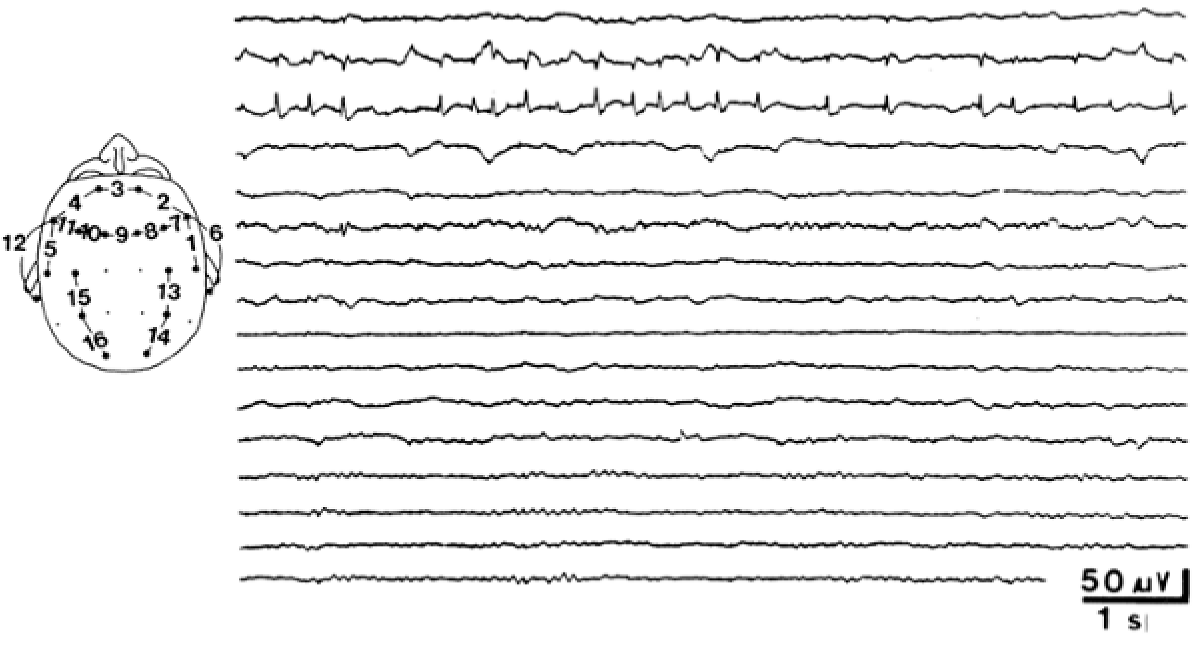

FIGURE 6. Surface electroencephalogram (EEG) in a 42-year-old man with a history of repeated simple partial status epilepticus with long-lasting kakosmia as the sole symptom. During such an episode, the EEG showed continuously repetitive spike discharges right frontal. Single photon emission computed tomography (Tc^{99m}-pertechnetate) revealed a hyperactivity right frontal. A tumor was suspected but could not be verified with computed tomography. There was good response to antiepileptic drug treatment. (For a more detailed case report, see Wieser,[279] pp. 79–80.)

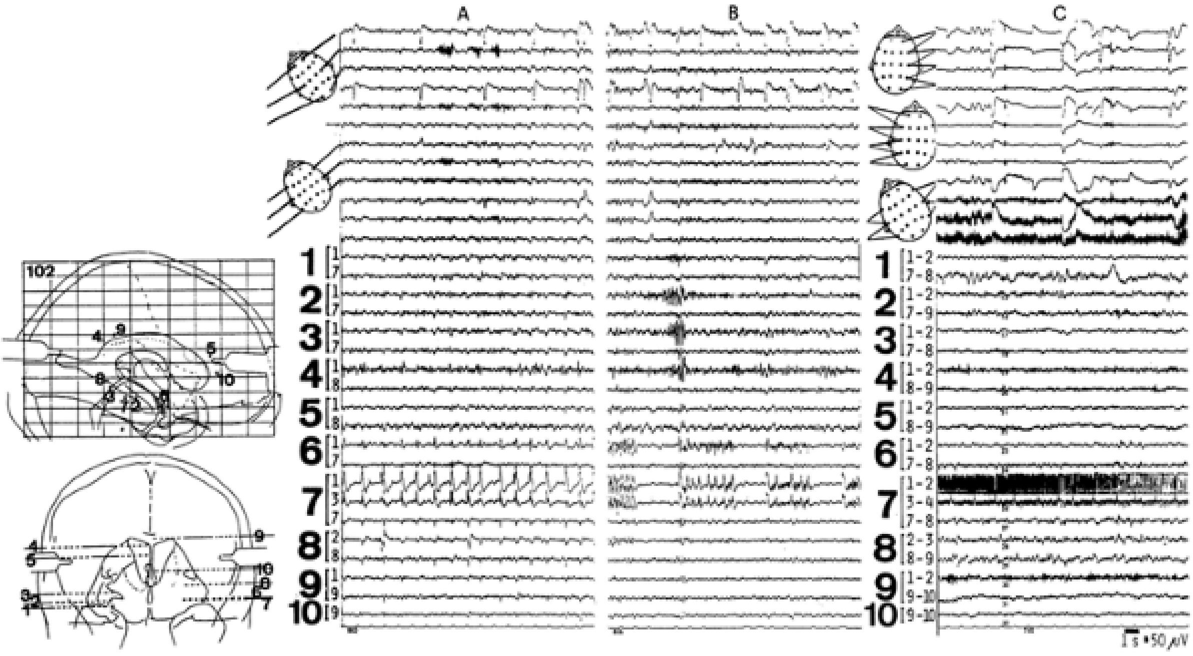

FIGURE 7. A left hippocampal electrical status activity (case no. 4 of Wieser et al.[288]). Combined surface and depth electroencephalogram (EEG) shows the epileptic discharge patterns of the left hippocampus (inner contacts of electrode 7) during the limbic status. **A, B:** Common average reference. Panel A shows a slow clonic and panel B shows a tonic–clonic discharge pattern. **C:** Bipolar surface and depth EEG recordings show tonic discharges in the left hippocampus. Note that the surface EEG does not pick up the hippocampal epileptiform activity. In panels A and B, there is moderate propagation to the homolateral amygdala (6/1-2), and this synchronized activity also affects the common intracerebral average reference, giving rise to some "erroneous" activity with opposite polarity in the scalp EEG, best seen in panel B (far left). (For a more detailed description, see Wieser et al.[288])

With regard to *SPSE with psychic and emotional phenomena*, we believe that autonomic phenomena usually are associated with overt or subtle behavioral changes, such as irritability, fear, panic, and sometimes existential emptiness or some other form of pathologic self-perception. Seshia and McLachlan's[223] aura continua patient (patient no. 5) suffered from epigastric fear for 8 years, which started after surgery (left temporal seizure origin; mesial temporal sclerosis).

Ictal depression and anxiety in temporal lobe disorders is frequent,[272] and *SPSE with fear as the outstanding clinical expression* was described by Henriksen[114] and McLachlan and Blume.[148] A large literature exists on this topic (for recent reviews see Smith et al.[235] and Trimble and Bolwig[255]). *Ictal aggression* seems to be rare.[65]

Limbic encephalitis may be associated with long-lasting, usually fluctuating signs and symptoms of disturbed self-perception, altered states of mood, emotion, and autonomous signs, and perturbations of higher cognitive functions,[124] not classed as SPSE. Pilomotor SE has been recently reported in a case with voltage-gated potassium channel antibody-positive, non-paraneoplastic limbic encephalitis.[296]

Dysphasic or aphasic SPSE is rare but well documented as the sole manifestation of focal status epilepticus.[52,69,70,103,108,110,127,163,185,201,204,256,258,266,273] A few cases were labeled as CPSE, although aphasia was reported as the sole manifestation.[70,127] In other described cases, persistent aphasia followed repeated partial seizures.[270] Dysphasic or aphasic SPSE is characterized by an episode of aphasia, sometimes associated with alexia and agraphia. Several subtypes have been identified, depending whether (a) receptive or expressive language is predominantly affected and (b) language recovers within short interictal intervals. If language recovers between the attacks, which recur every 2 to 3 minutes with aphasia of 10 to 20 seconds' duration, the true nature or even the disturbance itself might be missed. Most cases had left posterior temporal discharges[70] or seizure foci and presented with fluent (Wernicke type) aphasia,[127,237] but prolonged epileptic aphemia also has been described.[188] Kirshner et al.[126] described aphasia secondary to partial status epilepticus of the basal temporal language area. Single photon emission computed tomography revealed hyperperfusion in the left temporo-occipital[302] or left temporoparietal region.[139] It is fair to say, however, that in many of these cases the question remains open whether the persisting dysphasias were really ictal or were postictal.

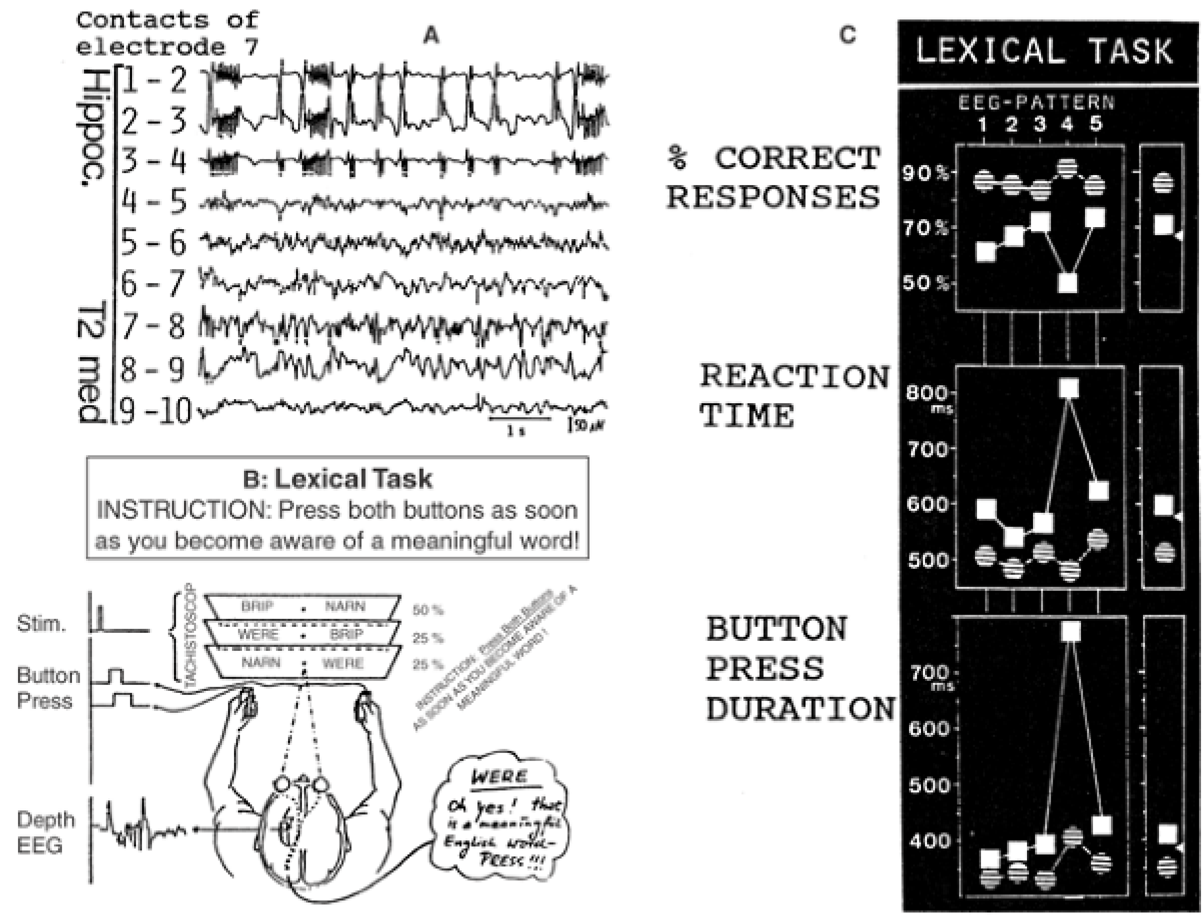

FIGURE 8. A: Bipolar derivations along the 10 contacts of electrode 7 (case no. 4 of Wieser et al.[288]) (see also FIGURE 7) of patient SEEG #102, showing that the epileptic discharge pattern is restricted to the left hippocampus (contacts 1–3) and illustrating the "tonic–clonic" electroencephalogram (EEG) pattern labeled 5 in FIGURE 7C. **B:** The test situation during the tachistoscopically presented lexical decision task. Fifty percent of the stimuli consist of two matched nonsense words (example: BRIP–NARN), and 50% of the stimuli pairs consist of a nonsense word and a matched meaningful high-frequency filler word, either in the left (25%) or in the right (25%) visual half-field (example: WERE). **C:** Results of lexical decision task of patient SEEG# 102 during left hippocampal status activity. Overall result (1–5, right) and breakdown according to the left hippocampal EEG pattern (1, normal and flat; 2, slow "clonic" sharp-waves <1/sec (see Fig. 7A); 3, fast "clonic" sharp-waves >1/sec; 4, high-frequency "tonic" spike discharge (as illustrated in Fig. 7C); 5, tonic–

clonic [as illustrated in Figs. 7B and 8A]). Note that the number of correct button presses during tonic discharges drops to chance level (50% correct responses) when stimuli addressed the left hemisphere with its hippocampus epileptically discharging (*white rectangle*, right visual half-field stimuli), whereas the percentage of correct responses to stimuli addressing the right hemisphere (*shaded circles*, left visual half-field) in general was high (87%) and even showed a kind of compensatory improvement during left hippocampal tonic discharges (EEG pattern 4). Measurement of reaction time and button press duration (mean of both hands) likewise resulted in a marked increase, but only for stimuli addressing the epileptically disturbed left hemisphere during tonic hippocampal discharges. The right column shows the mean of all stimuli. (For a more detailed analysis, see Wieser et al.[288])

According to the review of Beaumanoir,[27] overt SE of various types occurred in about 15% of children suffering from the syndrome of *acquired epileptic aphasia*.[135,300] In this disorder, aphasia develops in more or less tight correlation with usually left temporal focal high-voltage spike or spike-wave discharges,[181,231] with remarkable activation in slow-wave sleep, evolving then into continuous electrographic ("bioelectric") status. Overt epileptic seizures are manifest in only about 70% of cases and are usually mild. Although >200 cases have been reported,[230] the etiology, pathogenesis, and pathophysiology are unknown.[134] Family history is usually negative, and

children (male preponderance of about 2:1) have previously developed normally. Neuropathology findings consist of nonspecific gliosis (two lobectomy specimens[57]), encephalitis (one biopsy[144]), and isolated arteritis (four patients, angiographic findings[184]).

The similarities of the Landau-Kleffner syndrome with CSWS are obvious. Although in CSWS the EEG changes are essentially generalized, some authors have included cases in CSWS with relatively focal abnormalities. According to the review of Morikawa et al.,[161] CSWS is present in 0.5% (of 12,854) children with epilepsy, and about 20% to 30% have identifiable brain pathology (e.g., previous meningitis, birth asphyxia, cytomegalovirus infection), 3% have a family history of epilepsy, and 15% have a history of febrile seizures.

Diagnosis

Essential Clinical Features

The diagnosis of SPSE should be made only if clinical signs and symptoms that last for >30 minutes are accompanied by clear-cut localized epileptiform discharges in the corresponding brain region. In an operationally defined sense, consciousness must be retained. Symptoms and signs are manifold[64,73,96]

and can combine, although often they consist of localized somatomotor symptoms. Isolated sensory symptoms are less frequent.

Electroencephalography

Not infrequently, the conventional scalp EEG is uncharacteristic or even normal. If it is abnormal, the EEG in SPSE may exhibit localized high-frequency "tonic" discharges, but more often the epileptiform discharges consist of rhythmic clonic patterns with sharp-slow-wave complexes of about 0.3 to 3/sec with a peak about 1/sec. Waxing-waning, as well as paroxysmal pattern changes ("paroxysmale Umschaltungen"[196,282]), can occur. Waxing-waning may be seen not only in terms of time (i.e., appearance and disappearance, or at least amplitude reduction, of epileptiform patterns), but also in terms of enlargement and diminution of the epileptogenic area (i.e., the volume). Both phenomena might be interrelated and most probably are a function of the specific properties of the neuronal population pathologically recruited into the epileptiform discharges. Specific seizure-suppressing maneuvers might exert a recognizable effect on the formal aspects of the EEG discharges.[277,286]

Prolactin, Luteinizing Hormone, and Creatine Phosphokinase in Blood

These were reported to show a good correlation with seizure frequency,[26,137] and it has been suggested that an increase in prolactin would be helpful for the diagnosis of epileptic seizures and SE. Further studies, however, have shown that the absence of elevated prolactin levels does not exclude SE—not even grand mal status, and certainly not SPSE, CPSE, or absence status.[80,251] Therefore, prolactin, luteinizing hormone, and creatine phosphokinase do not contribute much to the diagnosis of SPSE.

Diagnostic Workup of Simple Partial Status Epilepticus and Epilepsia Partialis Continua

Every case with SPSE and EPC requires a general medical and neurologic evaluation to search for a metabolic or hereditary disorder and a structural imaging with magnetic resonance imaging (MRI), which often reveals a brain lesion. Functional neuroimaging with SPECT, PET, or functional MRI (fMRI) may be helpful (Fig. 9).[306] The EEG may show focal spikes and slowing, but there are no characteristic EEG patterns that aid in diagnosis. In EPC cases without a conclusive EEG, the back-averaging technique may help to identify the spikes preceding the myoclonus. In Rasmussen encephalitis, the documentation of a progressive atrophy of usually one hemisphere is important. A moderately to severely abnormal EEG with progressive slowing and spiking is the rule. It is important to note that in Rasmussen encephalitis, cerebrospinal fluid (CSF) may be abnormal with elevation of protein and lymphocytes, but a normal CSF does not rule out the presence of Rasmussen encephalitis.

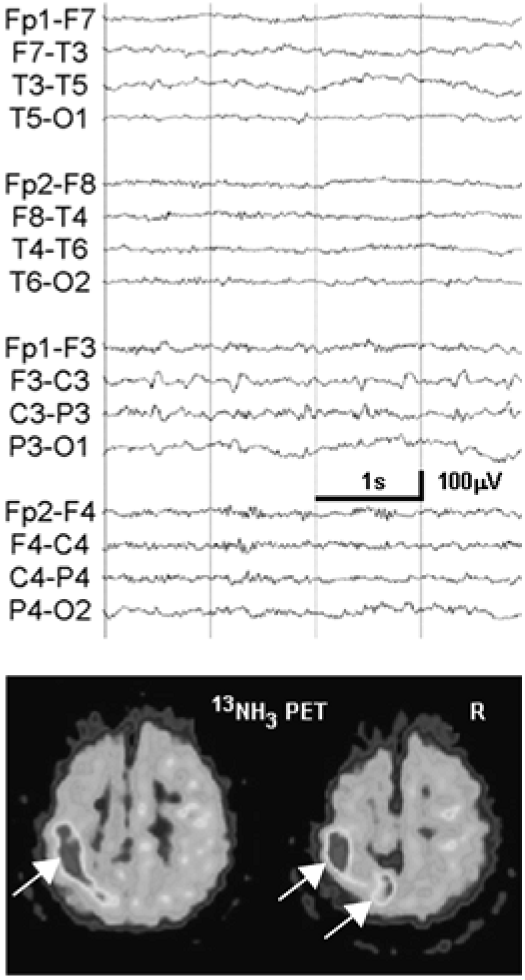

FIGURE 9. $^{13}NH_3$ positron emission tomography (PET) and conventional electroencephalogram (EEG) (performed within 4 hours of each other) in a 25-year-old woman with a 2-year history of epilepsia partialis continua (EPC) due to histologically proven Rasmussen encephalitis with mild right spastic hemiparesis with rhythmic jerks of about 2/s. Note the periodic sharp wave complexes at C3 and the corresponding PET focus (*arrows*). A focal cortical resection of the left sensorimotor hand area, which showed continuous ictal discharges at intraoperative electrocorticography, was performed, which

aborted EPC but not isolated focal seizures. (For details, see Zumsteg et al.[306])

Kim et al.[125] studied seven children with Rasmussen syndrome in a prospective longitudinal MRI study with three to eight MRIs per patient performed between 12 months before and 9 months after the onset of EPC; the most common region of initial MRI signal change was the frontocentral region (six patients). From their findings of three patterns of neuroimaging abnormalities, they concluded that the differences in these neuroimaging patterns might reflect inherent differences in the pathogenesis of Rasmussen syndrome. MR spectroscopy in patients with EPC revealed increased ratio of lactate to creatine and reduced ratio of *N*-acetyl-aspartate to creatine in the affected hemispheres.[182]

Differential Diagnosis

Differential diagnosis of SPSE might be difficult, even in *somatomotor SPSE*, if the surface EEG does not show corresponding epileptiform abnormalities. A variety of disorders, such as endocrine (hypoglycemia, porphyria), cardiac, cardiovascular, and gastrointestinal disorders and carcinoid, pheochromocytoma, limbic encephalitis, panic attacks, and paroxysmal autonomic dysfunction, have to be considered.

As has been repeatedly reported, very circumscribed epileptogenic generator zones in the depth of the rolandic fissure might escape detection in the routine scalp EEG, despite a clear-cut cortical origin of epileptiform spikes that correlate well with the myoclonic jerks when intracranial (i.e., subdural or intracerebral depth-electrode recordings) and special back-averaging techniques are employed.[287] In other cases with a more favorably located generator zone, the temporal relationship between cortical frontorolandic spikes and the myoclonic jerk can be extremely intimate and convincing.[278] A corresponding slow-wave focus might be demonstrated with mapping techniques.[289]

Subcortical as well as *spinal myoclonus* and certain tremor forms must be excluded by special neurophysiologic examinations. As already mentioned, in *EPC*, the two types 1and 2 should be differentiated. Careful examinations are necessary in type 1 EPC with a view toward the detection of a lesion amenable to successful curative surgery. EPC of the abdominal muscles may pose diagnostic difficulties.[78]

In EPC, the differential diagnosis depends on its definition. If the diagnosis of EPC is based on the presence of cortical myoclonus, the diagnosis requires electrophysiologic verification. If the diagnosis of EPC is based on the clinical appearance alone, a differentiation between cortical and subcortical origin is not possible. Rasmussen encephalitis is usually considered a distinct syndrome from Kozhevnikov EPC. Fifty percent of Rasmussen encephalitis patients exhibit EPC.

A major step in the diagnosis of EPC is to differentiate between type 1 and type 2.[20] These two clinical forms differ by their clinical signs, EEG patterns, and mode of evolution. Type 1 may start at any age, and its clinical and EEG characteristics are more focal and unilateral. Background EEG is generally unaltered. Myoclonus is limited to a group of muscles, but it may spread to neighboring muscles and even initiate a simple and then a complex partial or a secondary generalized seizure. Type 2 is much more variable; myoclonus is often multifocal and bilateral, and multiple seizure types may be seen. Background EEG is slow; its characteristics evolve rapidly with time, with extensive paroxysmal activities and frequent subclinical ictal discharges. The delay between the first seizure and the onset of myoclonic jerking is shorter in type 2 than in type 1. Seizure frequency is higher in type 2 than in type 1. Progressive neurologic deficit (at least hemiparesis) and neuropsychological impairment with evolution occur in type 2; deficit, if any, is stable and depends on etiology in type 1. Type 1 corresponds to a local and nonprogressive lesion in or near the central cortex. Type 2 is part of the clinical manifestations of a progressive inflammatory lesion of the central nervous system (CNS), typically in Rasmussen encephalitis.

It is generally accepted that EPC may be associated with focal, multifocal, and diffuse brain lesions and may include numerous syndromes (see section Etiology). For the differential diagnosis of EPC, the age of the patient should be considered and whether EPC occurs as the first clinical manifestation. In *children*, besides Rasmussen encephalitis, the other main causes for an EPC are as follows: (a) infections, such as subacute measles encephalitis, viral encephalitis or meningoencephalitis, or infective granuloma[15]; (b) developmental malformations, such as cortical dysplasia (see Chapter 259); (c) genetic causes, such as mitochondrial cytopathies, in particular mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episode (MELAS),[9,12,41,156,265] or mitochondrial encephalopathy with ragged red fibers and MELAS plus syndrome[195] (see Chapter 262); (d) metabolic causes, such as nonketotic hyperglycemia and diabetic ketoacidosis (see Chapter 267); and (e) gliomatosis cerebri (see Chapter 264).[224]

In *adults*, EPC is most frequently related to cerebrovascular diseases (embolic or thrombotic ischemic stroke, cerebral venous thrombosis, cerebral hemorrhage, arteriovenous malformations) and tumors (metastatic tumors, gliomas). Less frequent causes are metabolic disturbances, such as diabetic ketoacidosis, nonketotic hyperglycemia,[55] particularly nonketotic hyperglycemia associated with hyponatremia,[234] renal and hepatic encephalopathy,[160] and cortical dysplasia.[62,68,150,165,169] EPC has also been observed with multiple sclerosis.

EPC as the first clinical manifestation has been described in progressive cerebral degeneration of childhood with liver disease (Alpers Huttenlocher disease),[298,299] with cytochrome oxidase deficiency,[299] as well as in a patient with a missense mutation in the mitochondrial DNA CO I gene encoding the cytochrome c oxidase subunit I[264] and in association with a homoplasmic mitochondrial tRNA [Ser(UCN)] mutation.[220] EPC also has been observed as a new manifestation of anti-Hu–associated paraneoplastic encephalomyelitis,[200,225] in Creutzfeldt-Jakob disease,[136,183] and following bone marrow transplants.[14] It was observed as an atypical presentation of cat scratch disease,[170,202] in association with type 1 diabetes mellitus and elevated anti-GAD65 antibodies,[173] in ketotic and nonketotic hyperglycemia,[198,215] and in HIV-infected patients.[25,79] Kufs disease has also presented as late-onset EPC.[85] EPC has also been found in progressive multifocal leukoencephalopathy as a motor cortex isolation syndrome[28] and in benign epilepsy of childhood with centrotemporal spikes. Metrizamide, penicillin, and azlocillin-cefotaxime may also induce this disorder.[219]

Due to its typical course, the *diagnosis of Rasmussen encephalitis* is usually not too difficult in latter stages but might be difficult at the beginning.

Somatomotor SPSE in nonepileptics often accompanies severe brain lesions and very often represents, at least in the elderly, the "initial myoclonic phase of interterritorial infarction,"[91] usually associated with PLEDs in the EEG.[86] Restless leg syndrome and other periodic movements during sleep might require video monitoring and polygraphic night sleep recordings.[157]

The *dys-/aphasic SPSE* is more difficult to diagnose if it presents in the intermittent form with recovery of speech between seizures. The *Landau-Kleffner syndrome* has similarities with CSWS and other syndromes of "bioelectric status."

Sensory and autonomic SPSE expressing itself with strange and unusual phenomena might be difficult to diagnose in the absence of clear-cut EEG findings. As discussed and illustrated in previous sections, convincing ictal discharges are frequently not seen without intracranial recordings, and such invasive techniques, of course, are justified only in the context of epilepsy surgery. Particular problems are represented by long-lasting autonomic phenomena and peculiarities of behavior and personality in which the mesial temporal lobe and insular cortex are candidate areas for suspected discharges. Discharges at such a location are difficult to detect in routine scalp EEG. Whereas humoral changes—in particular, prolactin—are not very helpful in such conditions for differentiating SPSE of these types from psychiatric disorders or from other nonepileptic neurologic disorders, PET and SPECT might significantly contribute to the correct diagnosis; for example, SPECT can be extremely helpful in separating the focal status from nonepileptic conditions.

CPSE and prolonged postictal confusional states are by definition easily differentiated from SPSE because of altered consciousness. Nevertheless, there exist convincing SEEG-documented cases, including our observations, with prolonged focal "afterdischarges" in some brain regions following well-elaborated seizures in whom "postictal" confusional status or only "minor symptoms" persist because of ongoing focal electrical status activity.[280]

Epileptic behavioral disturbances and psychosis-like states might sometimes be due to prolonged seizure discharges.[293] Usually, epileptic psychosis is classed into ictal, postictal, and interictal categories, each with distinctive features.[255] Whereas the postictal psychosis is, as a rule, associated with delirium, altered consciousness, and amnesia, the interictal psychosis is characterized by clear consciousness, retained memory, and less severe behavioral disturbances. The ictal psychosis with fluctuating or frequently recurring focal electrographic epileptic discharges arising in temporal or extratemporal regions pres-ents most often as a confusional state with variable productive (i.e., "positive") signs and symptoms. Extratemporal—in par-ticular, frontal—focal status has less cycling symptomatology,

and confusion is less pronounced in comparison with limbic (psychomotor) SE.[123] Fronto-orbital polar status epilepticus may be particularly "poor" in clinical symptoms.[290]

Response to Treatment

In general, response to high-dose antiepileptic drug (AED) treatment can be used in the differential diagnosis, but there are well-documented cases in which classic AEDs of first choice, such as diazepam, did not completely suppress the localized discharges associated with SPSE.[277] In addition, there is the problem that diazepam can also arrest nonepileptic signs and symptoms, particularly psychiatric ones. EPC and somatomotor SPSE associated with PLEDs and severe vascular brain damage are known to respond only moderately, if at all, to AEDs. If hyperglycemia is the reason for EPC, it can be stopped by insulin.[132] Rasmussen encephalitis associated with EPC almost never can be controlled by available AEDs, but was reported to respond to plasma exchange (see earlier discussion) and to immunoglobulin therapy.

Focal SE, according to the literature,[230] is controlled by *diazepam* in 88% of 67 patients. Lorazepam and midazolam, an imidazobenzodiazepine, are considered AEDs of first choice. Midazolam is short acting and, therefore, can be well titrated on prolonged infusion. The recommended regimen is for one or two bolus injections of 0.1 to 0.3 mg/kg followed by an infusion of 0.05 to 0.4 mg/kg per hour. Mild bradycardia and a slight fall of arterial blood pressure may occur at conventional doses. Apnea has not been reported in SE, but this is clearly a potential risk because in anesthetic practice with higher doses for the induction of anesthesia, apnea occurred in 10% to 77% of patients (71).

Treatment of Epilepsia Partialis Continua

Treatment of EPC should concentrate on the underlying cause when possible. The management of iatrogenic and metabolic disturbances is apparent.[132] The major antimyoclonic drugs are piracetam, valproate, ethosuximide, and benzodiazepines (clonazepam). AEDs such as sulthiame and carbamazepine may be effective in treating EPC associated with benign childhood epilepsies and centrotemporal spikes. Other causes of Bancaud type 1 EPC tend to be refractory to AEDs. In single case reports, therapeutic success was achieved by nimodipine, a calcium-channel blocker,[33] and clonazepam.[219] In addition to conventional AED therapy, steroid administration may be indicated in EPC. In Cockerell's study of 36 patients, EPC resolved in 4 patients and persisted in the remaining 32. In cases with Bancaud type 1 EPC and a lesion, the appropriate therapy is surgical excision of the structural lesion. When the epileptogenic region involves the primary motor cortex, multiple subpial transection may be an option. Multiple subpial transection can eliminate seizures without inducing severe additional neurologic deficit.[155,159,187,242] Repetitive transcranial magnetic stimulation has been tried in an attempt to dampen hyperactive cortical regions in EPC.[98,151,158]

In Rasmussen encephalitis, many authors consider functional hemispherectomy as the only effective treatment (hemispherotomy[269]). Usually, however, it is only performed at a relatively late stage, that is, not before a hemiparesis already exists. Lozsadi et al.[144] used botulinum toxin A to improve involuntary limb movements in Rasmussen syndrome. Based on the assumption that the cause of Rasmussen encephalitis is either infective, probably viral, or the result of an autoimmune process, ganciclovir, zidovudine, high-dose interferon, high-dose steroids and immunoglobulins, and plasmapheresis have been tried. A beneficial influence of plasmapheresis observed in two studies[11,211] led us to introduce a combined treatment with plasmapheresis and CSF filtration in two patients with some initial but no long-lasting effect.[291]

Antozzi et al.[13] reported that long-term selective immunoglobulin G immunoabsorption improves Rasmussen encephalitis; Dabbagh et al.[61] were able to stop seizures by intraventricular interferon-alpha in one case of Rasmussen encephalitis. In the case of Olson et al.,[173] with the diagnosis of type 1 diabetes and anti–glutamic acid decarboxylase 65 antibodies in serum and cerebrospinal fluid, antiepileptic agents did not improve seizures, but high-dose steroids, plasmapheresis, and intravenous immunoglobulin resulted in decreased anti–glutamic acid decarboxylase 65 antibody levels and resolution of seizures.

When the diagnosis of Rasmussen encephalitis is being considered, it is important to rapidly exclude other causes of EPC. Although there are no good data from randomized trials of different immune-related therapies, treatment with immunoglobulin G (IgG), steroids, or plasmapheresis is advocated as first-line therapy. It is not unreasonable to institute at least two treatment options (e.g., IgG followed by plasmapheresis) if response to the first treatment is poor.[60,99]

Prognosis and Complications of Epilepsia Partialis Continua

The long-term prognosis of EPC depends on the underlying disorder. When it appears early in the course of a metabolic disturbance, the condition may be benign. Iatrogenic EPC induced by certain antibiotics and metrizamide disappears with removal of the offending agent. EPC associated with benign childhood epilepsy syndromes with rolandic foci usually responds to treatment with AEDs. EPC due to Rasmussen encephalitis has an almost invariably poor outcome with respect to the function of the affected hemisphere. There seems to be a progressive phase (mean of 5.3 years in one series of 48 patients), and the condition then becomes static.[172] Death is exceptional because eventually the condition stabilizes, although with severe disability. In many cases with EPC due to Rasmussen encephalitis, a functional hemispherectomy is the only effective treatment option. In a few exceptional patients, the EPC disappeared after some months to years, suggesting that the disease can "burn out." These few observations are in opposition to the opinion that in very rare cases Rasmussen encephalitis may also affect the opposite hemisphere (see Chapter 243).

Other forms of EPC, although not progressive, also usually respond poorly to AED medication but may disappear with time or resolve with surgical excision of a focal lesion. There may be associated weakness in muscle groups involved in the clonic activity, which can persist when the EPC abates. It is unclear to what extent this is due to the persistent epileptic discharges and to what extent the residual neurologic deficit is due to the underlying lesion. In the retrospective series of Thomas et al.[249] of 26 patients with EPC of various causes, 11 patients were alive and 15 had died after a follow-up of 1 to 18 years. Outcome was largely determined by the underlying cause, and seizures were more likely to remit in patients with stroke or other acute insults than in encephalitis cases.[249]

In contrast to convulsive generalized SE and various other age-dependent syndromes of SE in neonates and in childhood, morbidity and mortality are low in nonmotor SPSE of the adult. In *nonmotor SPSE*, there is no mortality, and there is no convincing evidence that this condition results in secondary brain damage. This contrasts with psychomotor status, in which the situation is less clear. Although most reported cases with psychomotor status have returned to baseline

neurologic function,[54,147] several well-described patients have had prolonged memory deficits.[75,254] Patients with electrographic SE in the setting of serious medical illness have a poor prognosis, but this is due most often to the underlying serious cerebrovascular or other medical illnesses.[4,121] In SPSE with EPC type 2 (Rasmussen encephalitis) and the initial myoclonic phase in severe brain damage and in the elderly, associated with PLEDs, the prognosis is usually poor. Long-term follow-up of 1 to 18 years in EPC revealed that 58% of patients had died, and the survivors had severe neurologic deficits: 96% had severe unilateral weakness, 49% had homonymous field defect, 29% had cortical sensory loss, 23% had dysarthria, and 18% had dysphasia. In addition, 85% showed mild to severe mental retardation.[230]

Factors identified as influencing outcome in general are (a) underlying etiology, (b) duration of status, (c) complications (cardiorespiratory failure, autonomic disturbance, hyperthermia, hypoxia, and medical and systemic complications not infrequently due to therapy), and (d) age of the patient (strongly interrelated with the first factor, i.e., underlying etiology). (See also Maegaki et al.[145])

Summary and Conclusions

Simple partial status epilepticus is relatively rare if borderline or boundary conditions (such as continuous spike-wave discharges during sleep, the Landau-Kleffner syndrome, neonatal convulsions, early infantile syndromes with suppression burst, and early myoclonic encephalopathies) are excluded. Whereas the separate classification of these borderline and boundary conditions can be well justified and actually was accepted for the purpose of this book, a discussion of SPSE without considering these boundary conditions with malformations and metabolic as well as special etiologic syndromes remains unsatisfactory because it does not take into account the growing evidence that status epilepticus is a condition (or a group of conditions) with distinctive pathophysiologic features and not just an iterative version of ordinary epilepsy. Consequently, the borderline and boundary conditions, including PLEDs, have been briefly discussed in this chapter.

Simple partial status epilepticus, in a narrow sense, is divided into somatomotor and sensory SPSE with the additional special categories of autonomic-vegetative SPSE and dysphasic/aphasic SPSE. Whereas considerable knowledge has accumulated on epilepsia partialis continua, and completely new pathophysiologic insights have appeared on the horizon suggesting that Rasmussen encephalitis is an autoimmune disease, the characterization of several other types of SPSE remains limited to anecdotal case reports. This is particularly true for SPSE with autonomic signs and symptoms. Some evidence has been provided for the intriguing possibility that some abnormal mental states, including peculiar personality and behavioral changes (commonly described under the category of "limbic dyscontrol syndrome"), are due to prolonged seizure activity in certain limbic or paralimbic areas. It is unknown, however, to what extent the generality of "interictal behavioral peculiarities" might be associated with such "subclinical status" in deep structures.

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Chapter 62

Myoclonic Status Epilepticus

Shunsuke Ohtahara

Yoko Ohtsuka

Introduction

There are as many types of status epilepticus as there are types of epileptic seizures. Myoclonic status epilepticus is defined as a condition in which generalized myoclonic jerks are repeated continuously or occur in clusters lasting for a sufficiently long period, usually >30 minutes.

Myoclonic status is divided into two types—pure and symptomatic.[12,31] The former is observed in epileptic patients. The latter is associated with degenerative encephalopathies, that is, the dyssynergia cerebellaris myoclonica of Ramsay-Hunt, progressive myoclonus epilepsy, and, especially, Lafora disease; with various lipidoses or metabolic (hepatic and renal) encephalopathies; with toxic encephalopathies; and with severe anoxic encephalopathies. However, Treiman[42] argued that symptomatic myoclonic status epilepticus should be considered a subtle presentation of generalized convulsive status and that the term "myoclonic status epilepticus" should be used only for pure myoclonic status. Therefore, this chapter discusses only pure myoclonic status epilepticus.

Definition and Classification

Pure myoclonic status epilepticus is seen in patients with generalized epilepsy, especially in types that exhibit myoclonic seizures. Pure myoclonic status is further subclassified into primary and secondary forms.[12]

Primary myoclonic status epilepticus is regarded as the prototype of myoclonic status epilepticus and is observed in patients with one of the primary (idiopathic) generalized epilepsies, such as juvenile myoclonic epilepsy.[3]

Secondary myoclonic status epilepticus occurs in children with one of the secondary (symptomatic) generalized epilepsies,[12] such as myoclonic-astatic epilepsy, Lennox-Gastaut syndrome, and epilepsy with myoclonic absences. This secondary form has also been reported as minor epileptic status[5,6,36] and has been observed in myoclonic epilepsy ("myoclonic status") in nonprogressive encephalopathies,[8] and in association with obtundation status in severe myoclonic epilepsy in infancy.[10] Status epilepticus associated with negative myoclonus is also classified as a type of secondary myoclonic status epilepticus and is seen in epilepsy with continuous spike-waves during slow-wave sleep (CSWS)[40] and its related epilepsies.[22,26,29] The Commission on Classification and Terminology of the International League Against Epilepsy classifies severe myoclonic epilepsy in infancy and epilepsy with CSWS into "epilepsies and syndromes undetermined whether focal or generalized."[7]

Epidemiology

Although the incidence and prevalence of the primary and the secondary types of myoclonic status epilepticus have not been precisely delineated, the primary type is regarded as relatively rare.[11,12] In contrast, the secondary type of myoclonic status is far more frequent.[12]

Etiology (Mechanism)

There are various etiologies of pure myoclonic status epilepticus, and the underlying pathophysiology of myoclonic status epilepticus is unclear.

Recently, seizure aggravation by antiepileptic drugs (AEDs), especially a worsening of seizures resulting from an inappropriate choice of an AED, has been attracting much attention.[13,30] Although in this case AEDs may provoke aggravation by a purely pharmacodynamic mechanism, the precise biological mechanisms involved are unclear. Aggravation by AEDs is probably more common in children than in adults.[13,30] Potential AEDs include carbamazepine, phenytoin, phenobarbital, vigabatrin, lamotrigine, gabapentin, and tiagabine.[13,30] Generalized seizures such as myoclonic seizures and absences are aggravated,[30,35,37] sometimes evolving into nonconvulsive status epilepticus such as myoclonic status.[13] Although such aggravation usually occurs in generalized epilepsies, it is also observed in severe myoclonic epilepsy in infancy,[10] in epilepsy with CSWS and its related epilepsies,[22,26,29] and even in localization-related epilepsies.[28,35,37]

Clinical and electroencephalogram (EEG) findings suggest that perhaps the secondary type of myoclonic status epilepticus should be considered a modified form of atypical absence status.[12] In some cases diagnosed as absence status, however, myoclonus constitutes the main symptom rather than a consciousness disturbance.[41,43] Differentiation between myoclonic status epilepticus with absence features and absence status epilepticus with myoclonic features remains a problem in the classification of status epilepticus.

Pathophysiology

Several investigators have attempted to classify myoclonus based on its pathophysiology.[17,18,23] Electrophysiologic examinations of myoclonus, such as jerk-locked averaging, somatosensory-evoked potentials (SEPs), enhanced long-latency reflexes (C reflexes), magnetoencephalography, and transcranial magnetic stimulation, have been performed to investigate the pathophysiology of myoclonus.[33,34]

Shibasaki et al.[33,34] classified myoclonus into three types (cortical, subcortical, and spinal myoclonus) based on the presumed physiologic mechanism underlying its generation. They emphasized the existence of cortical reflex myoclonus in which a myoclonus-related cortical spike was detected by jerk-locked averaging, and a giant SEP accompanied by an enhanced C reflex was observed. They speculated that the sensory and motor cortices mediated the occurrence of cortical reflex myoclonus. However, the pathophysiology of myoclonic seizures in epilepsy has not been fully elucidated.

In cortical myoclonus, the EEG usually shows multifocal or generalized spike-wave or multiple spike-wave discharges with or without associated myoclonus. On the conventional polygraph, however, the temporal and spatial relationships between myoclonus and its EEG correlate are often difficult to determine quantitatively.

Simultaneous EEG and electromyogram (EMG) polygraphic recording demonstrates that muscular inhibition, namely, negative myoclonus, can arise from the central nervous system in addition to positive myoclonus, which refers to sudden, brief, shock-like involuntary movements caused by muscular contractions. Negative myoclonus of cortical origin also can be associated with an EEG spike or spike-wave complex. Again, however, it is difficult to determine precisely the temporal and spatial relationships between the EMG silent period and the associated EEG spike on the conventional polygraph. Furthermore, because the silent period tends to be preceded or followed by an abrupt EMG discharge (positive myoclonus),[46] it is often difficult to judge whether the detected EEG spike is directly related to the positive component or the negative component of the EMG discharge. Myoclonic status epilepticus characterized by negative myoclonus has also been described.[22,26,28,29]

Clinical Features

In the primary type of myoclonic status epilepticus, consciousness is basically preserved in spite of long-lasting seizures. A polygraphic recording of the myoclonic jerks[31] shows brief muscular contractions of 100- to 200-msec duration repeated at a rate of 3 to 6 per second. These contractions are diffuse, predominating over the proximal muscles of the extremities, and they are bilaterally synchronous in homologous regions.

The secondary type of myoclonic status epilepticus is characterized by myoclonic jerks, which, although bilateral, are often asymmetric, asynchronous, and of small amplitude. A variable extent of impairment of consciousness is characteristic in this condition and can dominate the clinical picture.[12]

As outlined, several epileptic conditions and syndromes can develop the primary and secondary types of myoclonic status epilepticus, and each shows characteristic electroclinical findings. They are described as follows.

Myoclonic Status Epilepticus in Juvenile Myoclonic Epilepsy

Juvenile myoclonic epilepsy (JME) is an idiopathic generalized epilepsy characterized by myoclonic seizures. Often, generalized tonic-clonic seizures occur, and less often, infrequent absences. Myoclonic seizures can occur as myoclonic status. Although Asconapé and Penry[3] reported that 5 of 12 JME patients experienced at least one episode of myoclonic status, it is believed that myoclonic status is rare in JME.[11,12] Myoclonic status epilepticus in JME can last for a few hours, when the myoclonic jerks recur every few seconds, either isolated or in clusters of three to five jerks.[3] Consciousness is maintained,[3] or change in mental status, such as confusion, can be associated.[11,32,41,43] Sleep deprivation or other precipitants are usually present. Recently it has been reported that AEDs, especially carbamazepine, have aggravating effects on patients with JME. Aggravation is mostly in the form of increased myoclonic jerks, including myoclonic status.[14]

Nonconvulsive Status Epilepticus in Eyelid Myoclonia With Absence

Eyelid myoclonia with and without absences are the characteristic seizure types of this epileptic syndrome, which is one of idiopathic generalized epilepsies starting in childhood and persisting into adulthood. These seizures can be very frequent: Sometimes hundreds occur every day. Seizures are readily precipitated by eye closure in an illuminated room. All patients are highly photosensitive.

It was reported that some patients with eyelid myoclonia with absence experience status epilepticus, especially nonconvulsive status epilepticus.[1,45] During status epilepticus, some of these patients were confused, resulting in limitations in their daily activities. In others, however, absences were extremely brief and mild, in spite of severely persistent eyelid myoclonia. A patient reportedly could continue riding a bicycle safely for 20 minutes during status epilepticus.[1] We also experienced a patient who told her mother after walking down a stairway that she had continued to have eyelid myoclonia for >10 minutes without an impairment of consciousness.

During status epilepticus, EEG shows generalized poly-spikes or polyspike-waves concomitant with eyelid myoclonia.

Minor Epileptic Status

Minor epileptic status was proposed by Brett in 1966.[5,6,36] Many of his reported cases would now be categorized as Lennox-Gastaut syndrome; the remainder fit into other syndromes. This condition may last for hours, days, or even weeks. The patients are obtunded and drool, and speech is absent or slurred. They cannot understand or obey commands (pseudodementia). Symmetric and asymmetric jerks are seen in the limbs, the trunk, and the face to variable degrees. Sudden atonia may occur, resulting in head nodding, flexion of the trunk, or falls. The gait is lurching and unsteady (pseudoataxia).

The EEG shows multifocal continuous spikes or sharp waves or even continuous irregular slow waves without spikes. Minor epileptic status is a heterogeneous condition that includes atypical absence status and myoclonic status.

Myoclonic Epilepsy ("Myoclonic Status") in Nonprogressive Encephalopathies

Dalla Bernardina et al.[8] reported a peculiar type of symptomatic myoclonic epilepsy characterized essentially by the recurrence of atypical status combined with an impairment of attention and continuous jerks in infants suffering from a nonprogressive encephalopathy, and they considered that it constitutes a peculiar syndromic entity.

The electroclinical manifestations during myoclonic status are characterized by brief bursts of diffuse slow spike-waves accompanied by myoclonic jerks and mixed with other continuous and polymorphous abnormal movements. Sometimes the myoclonic jerks are rhythmic, bilateral, continuous, and strictly related to EEG discharges. Frequently, in the same patients, however, they are continuous but asynchronous in the different muscles without the definite one-to-one relationship between the jerks and paroxysmal EEG discharges. Besides paroxysmal discharges, the EEG often displays continuous theta activity (4–6 c/s), which is relatively monomorphous but varying in amplitude. During the status, positive and negative myoclonus is nearly continuously observed. In some cases, negative myoclonus is predominant, continuously fragmenting the voluntary movements and inhibiting the maintenance of any fixed antigravitary posturing.

Dalla Bernardina et al.'s series[8] included 18 cases of Angelman syndrome, 2 cases of 4p- syndrome, and 1 each of Rett syndrome and Prader-Willi syndrome. Other researchers[24,27,38,44] also reported the frequent occurrence of a peculiar epileptic status in Angelman syndrome. In our 11 cases of this syndrome, 10 presented with nonconvulsive status epilepticus[27] characterized by reduced alertness associated with brief atonias and erratic myoclonus.

Obtundation Status in Severe Myoclonic Epilepsy in Infancy

Obtundation status was reported in severe myoclonic epilepsy in infancy.[10] It consisted of an impairment of consciousness that was variable in intensity; the presence of fragmentary and segmental, erratic myoclonus of low amplitude, involving the limbs and the face; and sometimes a slight increase of muscular tone. It persisted for several hours or even several days.

The EEG is characterized by diffuse dysrhythmia of slow waves intermixed with focal and diffuse spikes, sharp waves, and spike-waves, of higher voltage in the anterior regions and the vertex without correspondence between the spikes and the myoclonic jerks except during the epileptic myoclonic seizures.

A clouding of consciousness characterizes the obtundation status, but its degree is variable. In some cases, myoclonus may dominate the clinical picture. Dravet et al.[10] classified this peculiar status among atypical absence status.

AEDs such as lamotrigine sometimes induce a worsening of seizures and can cause myoclonic status, namely, obtundation status.[10]

Myoclonic Status in Myoclonic-Astatic Epilepsy and Lennox-Gastaut Syndrome

The status of myoclonic astatic seizures accompanying absences is especially characteristic of myoclonic-astatic epilepsy.[9] The condition is characterized by apathy or even stupor. Careful observation reveals irregular twitching of the facial muscles and the extremities. Astatic seizures and head nodding can appear serially. The status epilepticus may last for hours or even days, but the status of pure myoclonic seizures seems to be extremely rare.

During the status of myoclonic astatic seizures, the EEG shows 2- to 3-c/s spike-waves and, especially, in younger children, very irregular polymorphous hypersynchronous activity, sometimes resembling hypsarrhythmia. In very rare cases with myoclonic status, the EEG is dominated by polyspike-waves.

The status in myoclonic astatic epilepsy can rapidly lead to dementia. The younger the children when the status epilepticus appears, the higher is the risk of dementia.[9]

Status epilepticus is not rare in Lennox-Gastaut syndrome.[4,19] It is composed of tonic status epilepticus and atypical absence status (including so-called minor epileptic status).[25] Myoclonic status in a strict sense has rarely been reported in typical Lennox-Gastaut syndrome.[21] However, myoclonic status may appear in the myoclonic variant of Lennox-Gastaut syndrome. Myoclonic status following high-dose lamotrigine therapy was reported in a patient with Lennox-Gastaut syndrome.[15]

Epilepsy With Myoclonic Absences

Status epilepticus has rarely been reported in epilepsy with myoclonic absences. According to Tassinari et al.,[39] 1 of their 36 cases presented a status with diffuse spike-waves and rhythmic myoclonic jerks interrupted after 20 minutes by an intravenous injection of diazepam. Two other cases had myoclonic absences repeated at close intervals. In myoclonic absence, myoclonic seizures constitute the constant characteristic feature, and a tonic component is often associated. An impairment of consciousness is of variable degree.

Status Epilepticus Associated With Negative Myoclonus

Epilepsy with continuous spike-waves during slow sleep (CSWS)[40] and its related conditions sometimes exhibit status with frequent myoclonic seizures and/or negative myoclonus. Nonconvulsive status epilepticus with epileptic negative myoclonus (NSENM),[26] which we originally named "a peculiar type of nonconvulsive status epilepticus,"[22,29] and atypical benign partial epilepsy (ABPE)[2] both have partial or generalized motor seizures as clinical seizure types. The former is also characterized by frequent "brief atonic episodes" and the latter by frequent "atonic fits" and myoclonic seizures. In NSENM, transient "paresis" is sometimes observed in the upper limb, where frequent "brief atonic episodes" occur. Neuropsychologic abnormalities and even mental deterioration are observed transiently during the status episode and can persist in long-term follow-up as in epilepsy with CSWS.[22,26,29] In contrast, ABPE is associated with neither neuropsychologic abnormalities nor mental deterioration.[2] Guerrini et al.[16] also reported five patients with partial epilepsy of diverse etiology who presented with very frequent epileptic negative myoclonus in one or more somatic segments. Three of them displayed a higher-order brain dysfunction that closely resembled motor neglect. This consisted of a reduction in spontaneous movements of affected segments of the body that could not be attributed to deficits in strength or sensation, a phenomenon similar to "paresis" observed in NSENM.

On the waking EEG, multifocal spikes, especially rolandic spikes, are seen in NSENM,[22,26,29] and rolandic spikes in ABPE.[2] In both, diffuse spike-waves are also seen. The sleep EEG demonstrates continuous focal spike-waves with a tendency to generalization, and diffuse spike-waves appear as in epilepsy with CSWS, but the spike-wave index is not usually as high as in typical epilepsy with CSWS.[22] Polygraphic recordings reveal that "brief atonic episodes" and "atonic fits" are both negative myoclonus. This occurs simultaneously with spike-waves on the EEG. On the other hand, spike-waves on the EEG do not always accompany negative myoclonus clinically. In all patients with frequent epileptic negative myoclonus reported by Guerrini et al.,[16] sleep activated continuous epileptiform EEG activity—central in three and diffuse in two.

Diagnosis

Essential Clinical Features

Essential clinical features are myoclonic jerks that are repeated continuously or that occur in clusters lasting for a sufficiently long period—30 minutes or more. Myoclonic jerks are mainly generalized bilateral synchronous in the primary type of myoclonic status, but asymmetric or asynchronous myoclonic jerks are often observed in the secondary type of myoclonic status.

Electroencephalography

In the primary type of myoclonic status epilepticus, simultaneous EEG recordings show multiple spikes closely related to, and usually preceding, the myoclonic jerks; these spikes are generalized with predominance over the anterior region of

the head.[31] Background activity is normal during the interictal period.

In contrast, the EEG of the secondary type of myoclonic status epilepticus does not always show generalized and synchronous multiple spike-waves, but rather arrhythmically repeated spike-waves interspersed with high-amplitude delta activity mixed with bursts of theta waves and epileptic recruiting rhythms.[12] Background activity usually shows slow-wave dysrhythmia.

Differential Diagnosis

Pure myoclonic status should be differentiated from symptomatic myoclonic status associated with acute or subacute brain disorders in nonepileptics. These disorders include various types of degenerative, toxic, and severe anoxic encephalopathies. The patients with symptomatic myoclonic status have the characteristic clinical and laboratory findings of each disorder. The EEG is useful in the differential diagnosis. The EEG of symptomatic myoclonic status can manifest the specific findings of each disorder. Because myoclonus in symptomatic myoclonic status is usually nonepileptic, it is not accompanied with spikes on the ictal EEG. However, epileptic myoclonic seizures are sometimes observed in such cases along with nonepileptic myoclonus.

With regard to pure myoclonic status epilepticus, differentiation from absence status epilepticus is important. As mentioned earlier, the secondary type of myoclonic status is sometimes difficult to differentiate from absence status. The secondary type of myoclonic status often shows a slight disturbance of consciousness along with myoclonus. In such cases, however, myoclonus constitutes the main symptom, but in absence status, an impairment of consciousness dominates the clinical picture. The fundamental EEG finding of absence status is bilateral synchronous generalized spike-wave discharges at about 3 c/s, appearing more or less continuously, but that of myoclonic status epilepticus is generalized multiple spike-waves. However, there are a significant number of cases without the typical EEG findings in both absence status and myoclonic status. The differential diagnosis of myoclonic status from absence status should be made by the overall clinical and electroencephalographic picture.

Response to treatment

Intravenous injections of benzodiazepines, especially diazepam and clonazepam, may be effective at stopping myoclonic status epilepticus. Intravenous valproic acid was reportedly effective for myoclonic status in JME.[32] However, the secondary type of myoclonic status epilepticus is often refractory. Even if it is once suppressed, relapse is common. Adrenocorticotropic hormone (ACTH) may sometimes control the secondary type of myoclonic status.[6,9] An oral administration of valproate and ethosuximide can also be effective.[8,20]

Consequences

Prognosis depends on the type of myoclonic status epilepticus. Basically, the primary type enjoys a favorable prognosis, but the secondary type shows poor mental prognosis. Furthermore, prognosis in the secondary type is closely related to the type of epilepsy and also to the length and frequency of the myoclonic status.

Summary and conclusions

Myoclonic status epilepticus consists of pure myoclonic status epilepticus and symptomatic myoclonic status epilepticus. This chapter described only pure myoclonic status epilepticus, which mainly appears in patients with generalized epilepsy. Pure myoclonic status epilepticus is further divided into the primary type and the secondary type. The former is relatively rare and is seen in patients with primary generalized epilepsy, namely idiopathic generalized epilepsy. The latter is much more frequent, especially among children, and is mainly observed in patients with symptomatic or cryptogenic generalized epilepsy who have myoclonic seizures. Because the secondary type of myoclonic status epilepticus is usually associated with various degrees of disturbance of consciousness, the differential diagnosis from absence status is difficult. The position of this type of myoclonic status epilepticus in the classification of status epilepticus is a future problem.

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Chapter 63

Febrile Status Epilepticus

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Introduction

Febrile seizures (FS) are acute symptomatic seizures that occur in 2% to 5% of children, making them the most common form of childhood seizures. About 5% of FS can be classified as febrile status epilepticus (FSE). Due to the long-debated relationship between prolonged FS, mesial temporal sclerosis (MTS), and temporal lobe epilepsy (TLE), there is currently a great deal of interest in the causes, effects, and long-term prognosis of FSE.

Definitions

The International League Against Epilepsy defines a FS as a seizure in association with a febrile illness in the absence of a central nervous system (CNS) infection or acute electrolyte imbalance in children older than 1 month of age without prior afebrile seizures.[20,21] FSE is defined as a FS of 30 minutes' duration or greater, or a series of FS lasting more than 30 minutes, between which the infant does not return to normal level of alertness.[20,73] FS, and by extension FSE, are also divided into those without prior neonatal seizures and those with prior neonatal seizures. No upper age limit is specified; however, FS, and also FSE, are most common between 6 months and 3 years of age, with peak incidence at about 18 months of age.

Epidemiology

Although the majority of FS are simple, approximately 5% are of sufficient duration to be classified as FSE. In a study of 428 children with a first febrile seizure, 14% had duration of longer than 10 minutes, 9% of longer than 15 minutes, and 5% of longer than 30 minutes or FSE.[8] Although only 5% of FS are FSE, these seizures nevertheless account for approximately 25% of all childhood status epilepticus (SE)[23,74] and more than two-thirds of cases of SE in the second year of life. FSE can also be classified as partial (focal) or generalized, depending on the presence or absence of focal features in the ictus. The age distribution of FSE is identical to that of simple FS, with 74% of episodes occurring younger than 2 years and 96% at ages younger than 5 years.[73]

Anatomic Pathways and Pathophysiology

Anatomic Pathways

The site of origin and pathways of propagation of electrical seizure activity underlying FS and FSE are unknown. Generalized delta waves, spikes, and polyspikes have been seen in simple FS recorded fortuitously in human infants (Morimoto et al 1991; Maehara 1988). The electroencephalographic (EEG) sources and propagation patterns during FS will very likely depend on the type of seizure (e.g., focal vs. generalized) and on the genetic susceptibility factors in each case. There are a few anecdotal case reports of EEGs recorded during FSE, one showing ictal activity over a temporal lobe and several showing diffuse bilateral but asymmetric ictal activity during FSE.[57,77] Interestingly, in these few cases, MTS was ultimately documented by follow-up magnetic resonance imaging (MRI) in the temporal lobe ipsilateral to the predominant ictal EEG activity.

More information is available on the EEG correlates of hyperthermia-induced seizures in rats used to model FS in human infants. Hyperthermia to approximately 42°C core temperature reliably induced 20-minutes' duration seizures in 10- to 11-day-old rats with electrodes placed on the cortex, and in the hippocampus and amygdala. The clinical seizure activity suggested limbic origin, and the EEGs documented onset in the amygdala or, less often, in the hippocampus.[6] Others have also found evidence of limbic origin of hyperthermia-induced seizures in infant rats.[67] The paucity of information on anatomic pathways associated with FSE prevents any firm conclusions, however.

Pathophysiology

The pathophysiology of FS has been studied only to a limited extent in animals, and even less is written on models of FSE. To model FS, investigators have induced hyperthermia in rats using radiant heat, hot air, or hot water immersion. A consistent finding has been that hyperthermic seizures in infant rats result in lowered seizure thresholds when the affected rats are adults.[25,39] The most intensely studied model exposes 10-day-old rat pups to heated air, consistently evoking hyperthermic seizures of about 20 minute duration, apparently arising in the hippocampus or amygdala.[6] Within about 24 hours and up to about 2 weeks following these seizures, silver staining revealed argyrophilic neurons in the central nucleus of the amygdala and in CA3 and CA1 sectors of the hippocampi in these rats.[76] Ultimately, the argyrophilia resolves, and no cell loss is noted when cell counts are done at later age.[7] Nevertheless, hippocampal excitability is permanently altered, and the threshold for chemically induced seizures is permanently decreased.[25] This persistent decrease in seizure threshold after infantile hyperthermic seizures has been noted by prior investigators also.[25,39] Although the limbic seizure threshold is reduced, there is a paradoxical increase of perisomatic γ-aminobutyric acid $(\mathrm{GABA})_A$ inhibition due to increased pre-synaptic GABA release.[19] In addition, a permanent alteration occurs in the properties of the hyperpolarization-activated cation current (I_h) in hippocampal CA1 and CA3 pyramidal cells.[18] I_h is a depolarizing current carried by sodium (Na) and potassium (K) that is normally activated by hyperpolarization of the cell and tends therefore to counteract hyperpolarization and to return the cell to a more depolarized level following

hyperpolarization. After rat pups have experienced hyperthermic seizures, hippocampal I_h is activated at more depolarized levels, resulting in mild resting depolarization of pyramidal cells and an enhanced posthyperpolarization rebound with depolarizing overshoot and a resultant burst of spikes. Therefore, when a brief tetanic train of stimuli is applied to the pyramidal neurons, the enhanced GABA_A inhibition produces a hyperpolarization that is followed by a depolarization and burst of spikes due to the enhanced I_h. This tendency for bursting may underlie the reduced seizure threshold. The altered I_h properties result from a change in relative expression of isoforms of these channels that persists into adulthood.[12]

The only structural alteration so far noted in these animals is mildly increased mossy fiber density in the granule cell and molecular layer of the dentate gyrus.[7] It is very interesting that many of these rats develop spontaneous limbic seizures in adulthood even though the prolonged hyperthermic seizures they suffered as infants did not produce hippocampal sclerosis.[26] Thus, this model raises the possibility that a single prolonged febrile seizure in a human infant could permanently alter hippocampal seizure threshold and even predispose to TLE in the absence of obvious structural alteration.

Many investigators have proposed that both prolonged FS and the epilepsy that occasionally develops after these seizures may be a result of preexisting brain pathology. A few animal studies have combined induced brain anomalies with hyperthermic seizures to test this concept. Rat pups exposed to methylaxozymethanol (MAM) during gestation display extensive cortical and hippocampal dysgenesis and a heightened vulnerability to hyperthermia-induced seizures.[37] Hyperthermia induced cortical electrographic seizures in both the MAM-treated and the control pups. However, the MAM-exposed pups had a higher incidence of behavioral (clinical) seizures, probably due to increased spread of seizure activity. Significant pyramidal cell loss, independent of seizure activity and presumably due to hyperthermia alone, was documented in the CA1 and CA3/4 hippocampal subfields of MAM rats 4 weeks after exposure to hyperthermia. It was concluded that extensive dysgenesis lowers the threshold for hyperthermia-induced behavioral seizures and irreversible neuronal injury. In a different model, more restricted neocortical freeze lesions causing a focal microgyrus have also been shown to predispose infant rats to more severe hyperthermia-induced seizures.[66] These lesions reduced the latency to hyperthermia-induced generalized convulsions, and the convulsions themselves were followed by prolonged electrographic seizure activity compared with hyperthermic seizures induced in controls. Finally, video-EEG recordings from the same rats as adults revealed a high incidence of spontaneous limbic seizures in the rats with both lesions and hyperthermic seizures but not in lesion-only or hyperthermic seizure–only rats.[66] As was the case in the pure hyperthermia model,[6] the spontaneous limbic seizures occurred without any obvious evidence of hippocampal sclerosis induced by the hyperthermic seizures experienced in infancy. These animal studies support the hypothesis that preexisting brain abnormalities could predispose to prolonged FS and subsequent epilepsy in human infants.

Contribution of Magnetic Resonance Imaging to Understanding Pathophysiology of Febrile Status Epilepticus

FSE is an uncommon and unpredictable event and generally does not recur. Therefore, studies of pathophysiology of FSE are quite limited and consist of tests such as EEGs and MRIs that can be done during or shortly after the acute and emergent presentation of the affected infants.

Animal Models

A brief review of MRI changes observed with animal models of SE will help put the human data in perspective. MRI analyses of SE in rats usually employ limbic SE evoked by kainic acid (KA) or pilocarpine, and hence the anatomic distribution of abnormalities reflects the regional specificity of these agents, with changes being seen most commonly in the amygdala, piriform cortex, and hippocampus as well as in extralimbic areas of the neocortex and thalamus. Six to 24 hours following lithium-pilocarpine–induced SE in adult rats, the apparent diffusion coefficient for water (ADC) is usually reduced in the amygdala and piriform cortex, and thalamus and cortex if affected.[31,34] Along with ADC changes, T2 signal intensity is increased in amygdala, piriform cortex, hippocampus, and often in thalamus and cingulate cortex. The areas of increased T2 signal intensity have, in general, correlated with areas of neuronal injury, neuronal loss, and tissue edema on histologic analysis.[31,62] Acute ADC changes in the hippocampus in these models have been inconsistent. Some have seen an increase in ADC initially using pilocarpine,[31,34] and in others no significant change using KA.[52,60,75] When the hippocampal MRI changes have been followed beyond the acute phase for 2 or more weeks, increased ADC and increasing T2 signal have been seen along with atrophy and cell loss.[59,63,75] Acutely increased piriform and entorhinal cortex T2 intensity and T2 relaxation times were predictive of ultimate development of spontaneous seizures and increased hippocampal T2 signal in a study of pilocarpine SE in 21-day-old adolescent rats.[63] Thus, in adult and adolescent rats, MRI changes following status reflect tissue damage and may be surrogate markers for the development later of MTS and limbic epilepsy.

The significance of MRI abnormalities is less clear in hyperthermic seizures of shorter duration studied in infant rats. There is only one MRI analysis of prolonged hyperthermic seizures in infant rats using P10 rat pups exposed to heated air and suffering approximately 20-minute-long seizures. These are relatively brief seizures, compared to the 2- to 4-hour-long SE typical of the kainate or pilocarpine models. Nevertheless, transiently increased T2 signal was noted in the dorsal hippocampus, amygdala and piriform cortex at 24 hours in six of eight rat pups and at 8 days in seven of eight with the hippocampal changes lagging behind the other areas. However, Fluoro-Jade staining failed to reveal evidence of dying neurons in these areas at 1, 2, 4, and 7 days after the hyperthermic seizures.[27] Recently, the same group has shown that their model of P10 prolonged hyperthermic seizures results in about a third of the rats developing spontaneous limbic seizures by 3 months or more of age.[26] Therefore, in these 10-day-old infant rats, transient acute postictal T2 hyperintensity did not correlate with cell death or persistent MRI abnormality.

Human Magnetic Resonance Imaging Studies

There are only a few MRI studies of human infants performed soon after an episode of FSE, and these have emphasized abnormalities in the hippocampus. Vanlandingham et al.[77] described 27 infants with FSE, the majority of whom were imaged within 4 days of the episode of FSE. Of 15 with lateralized seizures, six had definite hippocampal MRI abnormalities. Presumed chronic hippocampal injury with atrophy and increased T2 signal bilaterally were seen in two subjects with histories of perinatal asphyxia and evidence of periventricular leukomalacia. In the other four, presumed acute abnormalities of increased T2 signal and increased volume were seen on the side of presumed seizure origin. Of note in the lateralized group was the longer average seizure duration of 99 minutes in subjects with swollen, bright hippocampi versus 41 minutes in those without these findings.

There were 12 infants with generalized FSE, and only one had subtle bilateral increase of hippocampal signal and size. The authors concluded that both chronic and acute hippocampal abnormalities could be seen following FSE, and that focal and prolonged FSE was more likely to be associated with these abnormalities. Follow-up MRIs have demonstrated that hippocampi with definite increased size and T2 signal on acute imaging developed atrophy with persistently increased T2 signal months to years later, a picture consistent with MTS.[45]

A more recent study of this type[68] carefully analyzed hippocampal T2 signal relaxation times and volumes in 21 infants with presumed generalized FSE. Visual assessment of the MRIs was normal in 16, three appeared to have hippocampal asymmetry (of which two were confirmed by volumetry), one had a left temporoparietal arachnoid cyst, and one had poor gray-white differentiation in the left midtemporal gyrus. Unlike the Vanlandingham study,[77] there were no hippocampi with grossly increased T2 signal intensity on visual inspection. However, the group mean calculated T2 relaxation time was increased compared with controls in those imaged within 2 days of the event but not in those imaged later at 3 to 5 days after FSE. In addition, the mean hippocampal volumes of the FSE group were increased compared with an age-matched control group. Follow-up imaging of 14 of these infants from 4 to 8 months later[69] showed that there was no longer any difference between mean T2 relaxation time or mean hippocampal volume when compared with the controls. However, the hippocampal volumes of the subjects had decreased from the initial studies, and the hippocampal asymmetry had increased and was outside the 95% of control limits in five of the 14. In one of these five, the asymmetry was visually apparent. The conclusion was that FSE could produce transient hippocampal edema and in some cases perhaps neuronal loss.

Grunewald et al.[38] looking at MRI findings in 10 infants imaged within 2 weeks of FSE found abnormal hippocampal volume ratios in nine when compared with volume ratios of controls. Because no abnormalities of hippocampal T2 signal or T2 relaxation time constants were found, the authors concluded that the abnormal right to left volume ratios could not be ascribed to edema. No follow-up scans were reported. However, based on the findings of Scott et al.[68] that increased T2 signal tended to reverse by several days after FSE, the MRIs done an average of 11 days after FSE in the Grunewald study might have been too late to detect increased T2 relaxation times.

Very few data are available on hippocampal ADC changes in FSE in human infants. The ADC data in theory could help determine if the structural changes seen soon after FSE were acute or chronic. ADC maps of chronic hippocampal injury—MTS—have consistently shown increased ADC.[5,65] As discussed previously, acute reductions of ADC have been reported in the animal models of limbic status in amygdala and piriform cortex during the phase of cellular swelling and death, although hippocampal changes have not been uniform. In humans, acute changes in ADC are rarely reported and certainly have not been studied in an organized prospective fashion in large samples of infants with FSE. A report of five infants imaged following SE is the largest series thus far.[33] Although four of the five had low-grade fevers during the status, it is not clear that these were straightforward episodes of FSE, because the initial status was quickly followed by recurrent seizures of uncertain nature in four subjects. Four subjects imaged within 2 to 3 days of status had hippocampal increased T2 signal and size on the affected side and 5% to 20% reductions of ADC in the affected hippocampus compared with the unaffected side. Follow-up MRIs months later in four cases showed increased ADC in the abnormal side along with hippocampal atrophy. Two other case reports noted similar findings acutely after SE[29] and single temporal lobe seizures in established TLE.[41] A tenuous suggestion exists, therefore, that in human limbic status epilepticus, acute reduction of hippocampal ADC might be found immediately postictally followed later by increased ADC if the initial injury results in MTS. More animal and human data will be needed before the changes in ADC can be used to gauge the age and nature of hippocampal abnormalities following FSE.

Differing conclusions about the type and significance of hippocampal abnormalities associated with FSE very likely reflect both differences in subject groups and pathogenesis. Detection of FSE-induced T2 abnormalities may require prompt postictal imaging. Scott et al.[68] documented that subtle increases in T2 signal returned to normal after 2 to 3 days following FSE, and some animal data demonstrates that T2 may transiently return to normal 2 to 4 days following FSE.[60,63] Generalized FSE may have a lower incidence of acute MRI abnormalities than does focal FSE.[77] Finally, extremely prolonged and focal FSE lasting 90 minutes or more may be required to produce striking hippocampal abnormality such as that reported by Vanlandingham et al.[77]

These initial MRI studies raise more questions that remain to be answered regarding the relationship of FSE to hippocampal injury.[45] How often and under what circumstances does hippocampal injury occur during FSE?

What determines whether the initial injury is reversible or evolves instead to MTS? What are the clinical parameters and MRI findings in FSE that are predictors of MTS? Do infants with obvious acute hippocampal abnormalities and subsequent MTS develop TLE? Do infants with subtle hippocampal MRI abnormalities, even those below visual threshold, ultimately develop TLE? Can acute injury be differentiated from preexisting hippocampal abnormality using diffusion weighted imaging (DWI), subsequent hippocampal growth curves, or other techniques? Assuming that hippocampal injury can occur in FSE, what are the mechanisms of neuronal injury and subsequent epileptogenesis? What other brain abnormalities detectable on MRI can be found in children with FSE? Can pharmacologic intervention to prevent neuronal death and epileptogenesis reduce subsequent TLE?

Clinical Features

No distinguishing ictal or postictal features of FSE differentiate these seizures from other acute symptomatic or cryptogenic prolonged seizures except for the association with febrile illness. Given that this is an acute symptomatic seizure type triggered by febrile illness, there are no persisting distinguishing interictal features either.

By definition, the duration of these seizures is 30 minutes or more; however, detailed studies of FSE have shown that many are much longer. Of 180 cases of FSE, Shinnar et al.[73] found 58% lasting from 30 to 59 minutes, 24% from 60 to 119 minutes, 15% from 120 to 239 minutes, and 3% over 240 minutes. If the FSE was focal, as it was in 64 subjects (35%), the distribution of seizure durations was similar, with about half lasting 30 to 59 minutes and the other half more than 60 minutes. This breakdown was similar whether the bout of FSE presented as the first febrile seizure event or after an initial shorter FS. Comparing the FSE group to a group of complex FS not including FSE, the proportion of focal seizures to generalized was similar. However, focal features were more common in the FSE group than in a comparison group of 244 unselected, prospectively identified children with FS.

As an interesting corollary to the animal studies linking brain lesions with severe hyperthermic seizures, preexisting neurodevelopmental abnormalities were more common in subjects with FSE than in the comparison group. Twenty-one percent of the FSE group had previously documented neurologic abnormalities compared with 5% of the comparison group.

The question of whether an episode of FSE makes subsequent FSE more likely or not has clear clinical implications

when deciding on future management. One episode of FSE does not seem to increase the risk of recurrence of a FS in general.[10] However, if the initial FS is prolonged, a recurrent FS is also more likely to be prolonged.[8]

Response to Treatment

No studies have specifically addressed the response to treatment of FSE as opposed to other causes of SE. However, as with SE of any etiology, prompt and aggressive treatment is clearly indicated.[24]

After the FSE episode, the question of preventative therapy arises. The indications and choice of subsequent preventative therapy following FSE are not clearly determined and may be controversial. Physicians may be more inclined to place an infant on prophylactic medication following an episode of FSE than following an initial complex FS of lesser duration or following a simple FS. However, in this situation, when the major concern is recurrent prolonged FS, the therapy can be designed not to prevent FS but to limit their duration, as in the use of rectal diazepam.[43] Rectal diazepam has been demonstrated to be effective in terminating FS,[58,70] and it is widely used in Europe, Canada, Japan, and United States. Children at high risk for prolonged or multiple FS and those who live far from medical care would be candidates for this approach.[56] Intranasal midazolam has also been used in treating acute childhood seizures, including prolonged FS, with some success.[4,11,35] However, it should be noted that to date there is no true intranasal preparation, and the data come from using the intravenous preparation intranasally.

Long-Term Consequences

Relationship to Epilepsy

Retrospective studies from epilepsy surgery centers demonstrate that adults with intractable TLE commonly have a history of prolonged or atypical FS in childhood.[1,16,17,22,32,40,47,48,49,64] The animal studies discussed earlier also indicate that prolonged FS may be associated with long-term changes in hippocampal excitability,[25,76] and that induced cerebral dysgenesis predisposes to hyperthermic seizures that are more severe than those seen in animals with normal brains.[37,67] Despite these observations, population-based studies have failed to find a consistent causal link between FS and brain injury or TLE.[13,14,44,53,54,61,78] Camfield et al.,[13] with access to data encompassing the entire population of Nova Scotia, concluded that the sequence of prolonged FS to MTS to TLE was highly unusual and might occur only once in 75,000 children. Lee et al., in Denmark, also concluded that TLE was not a consequence of FS.[44] On the other hand, Rocca et al.[61] looked at the population of subjects with complex partial seizures (with two case controls for each subject) drawn from the population of Rochester, Minnesota, and concluded that FS was more common in the histories of the subjects (20%) than in controls (2%). Complex FS was also more common in the subjects with complex partial seizures. Again, however, it was not clear whether FS increased the risk of complex partial seizures or whether both were due to common preceding risk factors. It is a common dilemma that, if an association of partial seizures and prolonged or complex FS is found, one cannot determine whether this is a causal relationship or an association based on some common underlying predisposition. In addition, the partial seizures are usually not further characterized, thus preventing any determination of an association with TLE specifically.

However, when considering FSE specifically, the evidence for a link to later partial epilepsy does become more convincing. In the longest follow-up study available[3], the relative risk for epilepsy following FS was assessed in a group of 687 subjects who had FS, but with no prior apparent neurodevelopmental abnormalities identified from the medical records linkage of the Rochester Epidemiology Project. These were followed for a first afebrile, unprovoked seizure for an overall average follow-up duration was 18 years. The overall relative risk for unprovoked seizures was only about fivefold that of a control cohort, or an individual cumulative risk of 0.024 for an unprovoked seizure by age 25 years. However, focal seizures, prolonged seizures, and multiple seizures within 24 hours markedly increased risk. For seizures that were focal, the risk was 0.081; for seizures of 30 minutes or more in duration, the risk was 0.065; and for repeated seizures in 24 hours, the risk was 0.064. Multiple risk factors characterizing the same seizure markedly increased the risk. Focality and a duration 30 minutes or more combined carried a risk of 0.215 and, if these seizures were also repetitive, the risk increased to 0.49 or a 50% chance of later unprovoked seizures by age 25 years. The unprovoked seizures that occurred in this focal prolonged group were classified as partial seizures; however, the lobe of origin was not determined. In the study of Berg and Shinnar,[9] each complex feature of duration, focality, and multiple occurrences was also predictive of unprovoked seizures, but the presence of multiple complex features in a subject did not increase the risk. The predictive value of focality and prolonged duration for later epilepsy, and the observation that focality and long duration are correlated in complex FS,[8] may indicate that in these children, the complex FS are a manifestation of an underlying brain abnormality predisposing to both focal FS and partial epilepsy. Alternatively, the recent MRI studies (discussed earlier) suggesting acute hippocampal abnormalities following FSE argues that the FSE itself, whatever its cause, may contribute injury that adds to the later tendency for epilepsy. Other prospective studies have confirmed that, of children suffering FS, those experiencing focal and/or prolonged seizures are much more likely to develop epilepsy than are those without these features.[47,68,78,81] Unfortunately, the detailed analysis needed to determine if the epilepsy that develops following FSE is indeed TLE is missing from the large prospective studies.

Given the multiple and careful studies just discussed, we are still unable to clearly define the relationship between FSE, severe and prolonged FS, and TLE. This remaining ambiguity reflects the inherent difficulties of demonstrating the relationship between FSE and subsequent epilepsy. First, only 5% of FS meet criteria of FSE and, of these, somewhere between only 14%[51] and 42%[73] are over 60 minutes' duration. Based on what little evidence we have in infants,[77] FSE may need to be of greater than 60 minutes' duration to be associated with clear MRI evidence of hippocampal injury. Not only are such long FS rare, but hippocampal injury is probably exceptional even given adequate duration. Second, hippocampal injury and MTS are clinically silent and therefore detection of FSE-induced brain injury requires MRI imaging, a method not readily applicable to large cohort studies. Finally, the latent period between initial insult, in this case FSE, and subsequent TLE is often over a decade, requiring long follow-up of subjects. Also, once unprovoked seizures are detected in a subject, these must be clinically and electroencephalographically characterized and assigned to a specific epilepsy syndrome using published criteria.[20] The requisite study would therefore require a very large number of subjects with FSE, available MRI facilities for initial and follow-up imaging, and very long follow-up with detailed seizure characterization. The population studies of FS available thus far have not been designed to meet these criteria, and therefore they cannot answer definitively the question of a relationship between FSE and TLE. An ongoing prospective multicenter study of FSE that is attempting to address this question has to date recruited over 100 children and is finding a high rate of acute MRI hippocampal abnormalities.[46,71]

Neurodevelopmental Outcome

Relatively few studies have addressed the long-term neurodevelopmental outcome of FSE. Early publications described higher rates of neurologic and intellectual morbidity following SE and FSE in infants[2,15,36] than do more recent studies. Reasons for the higher morbidity have been given such as lack of modern emergency transportation and care, retrospective studies of hospitalized subjects more likely to select severe cases, and less effective drug treatment. Recent studies of FSE in childhood are more optimistic.[50,73] Of 180 infants with FSE recruited prospectively, none were left with new neurodevelopmental defects following FSE, based on neurologic examinations, mental status exams, and parental reports.[73] Ellenberg and Nelson[30] examined 431 sibling pairs, one of each with a history of FS, using Wechsler Intelligence Scales for Children and Wide Range Achievement Tests. This sample included 27 children whose FS lasted longer than 30 minutes. There were no differences in cognitive function at 7 years of age between affected and siblings. Specifically, there were no differences considering the group with status alone or considering a group of 14 whose status was greater than 1 hour in duration. This is in agreement with other studies reflecting low morbidity and mortality.[23,28,80] In the British Cohort Study, there were no differences between 5-year-olds with or without FS, even when the analysis was limited to complex FS.[79,80] Verity et al.[80] reported outcomes in 19 subjects with FSE whose seizures lasted longer than 1 hour in most cases. Using British ability scales, standardized mathematics, and reading tests, 12 were tested at 10 years of age and were normal, three were tested at 5 years of age and were normal. One whose seizure was 4 hours long was abnormal, and two were documented to have been abnormal prior to the FSE. One was not tested.

In adults with MTS and TLE, memory impairment has been well documented.[42,55] If hippocampal injury were significant in FSE, one would expect memory dysfunction to be detectable in a sufficiently large sample of children following FSE. Presently, detailed memory testing data are not available in children who experienced prolonged FS.

Summary and Conclusions

FSE is a common cause of SE in infants. FSE is, in general, a one-time event; hence, studies of the pathophysiology of FSE in humans have not been done. The pathophysiology of FSE as studied in animal models of hyperthermia-induced seizures suggest that hyperthermia-induced seizures in infant rats originate in limbic brain areas, and that preexisting brain abnormalities are associated with prolonged hyperthermic seizures. It is demonstrated that prolonged hyperthermic seizures in rats can cause lifelong reduced limbic seizure threshold and, in a fraction of affected animals, the development of spontaneous limbic epilepsy. This occurs in the absence of the classical pathologic picture of MTS.

The relationship of FSE to hippocampal injury, MTS, and TLE is gradually being addressed in human studies but answers remain elusive. MRI-based studies of human infants are also demonstrating hippocampal abnormalities following FSE. These abnormalities vary from subtle and visually unapparent to gross signal and size abnormalities that often evolve in a manner suggesting that the injury was acute and due to the FSE. The ultimate significance of these MRI findings remains to be determined.

Although it remains a serious and common medical emergency in infancy, FSE appears to have a low morbidity and mortality, in large part due to rapid and aggressive medical management, and serious brain injury is probably an infrequent occurrence. Prospective studies in progress may provide more data on the relationship between FSE and TLE.

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Chapter 64

Acute Physiologic Changes, Morbidity, and Mortality of Status Epilepticus

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Introduction

Status epilepticus is a relatively infrequent but serious manifestation of epilepsy. In population-based studies, annual incidence rates have been shown to vary between 9.9 and 41 per 100,000.[18,25,26,27,28,29,30,31,32,44,49,51,56,85,88,99,106] The highest annual incidence rate (41 of 100,000) was found in the prospective population-based study carried out by De Lorenzo et al. in Richmond, Virginia (Fig. 1). The age distribution of the frequency of total status epilepticus events per year and the incidence of status epilepticus are presented in FIGURE 2. Extrapolating these data, 102,000 to 152,000 individuals would be affected each year in the United States (with 126,000 to 195,000 status epilepticus episodes), and over 22,000 to 42,000 deaths per year occurred in patients with status epilepticus. From hospital studies, Hauser[44,45] estimated that status epilepticus occurs in 50,000 to 60,000 individuals in the United States annually: One third of these patients present with status epilepticus (SE) as a first unprovoked seizure; one third present with established epilepsy; and one third present with no previous history of epilepsy. Recent cost studies from the Richmond group have developed estimates of the cost of SE in an urban hospital.[76] The estimate from this data indicated that the cost for care of SE in the United States per year is approximately $3 billion to $4 billion. Projecting the population of the United States to the world would suggest that SE would cost more than $70 billion to $93 billion per year on an international basis.

The differences in these incidences may reflect the different methods of data collection and the ability to correctly identify cases of SE from the medical record. Analysis from the Richmond study indicates that it is very difficult to identify cases of SE from International Classification of Diseases (ICD)-9 codes, discharge summaries, and retrospective chart reviews.[26,27] The higher incidence in the Richmond study may in part be due to the prospective nature of this study and the ability of this study to detect nonconvulsive SE cases. Nonconvulsive SE is often not detected unless aggressive electroencephalographic (EEG) monitoring is conducted on all comatose patients. Nonconvulsive SE was found in 8% of comatose patients in the Richmond study.[98] In addition, environmental, genetic, racial, and other differences may contribute to the ranges in incidences for SE in these studies. Race is a significant contributing factor in determining the incidence of SE.[26,27] Studies from Richmond had an incidence of SE of 41 per 100,000.[28] This incidence was about one to four times that of SE in the predominantly white (Caucasian) populations of other studies.[18,44,45,49,51,56,85,88,99,106] The incidence of the white population in Richmond was 19 per 100,000,[28] which compared well to several other predominantly white populations.[44,45,51,56,88,106] However, the nonwhite, African American population in Richmond had a much higher incidence of SE, 57 per 100,000.[28] Since Richmond is over 50% African American, the higher incidence in this group accounted for the higher incidence in the overall Richmond population. Correcting the Richmond data for the higher percentage of African Americans in the population gives an incidence very close to the Rochester[44,45] and Hessen[51] studies. Further investigations are needed to more fully evaluate the effects of genetic factors and race on the incidence of SE. It is essential to further evaluate these ethnic disparities in the incidence and mortality of SE around the world.

Status epilepticus can cause cerebral damage in various ways.[30] The damage caused by physiologic changes that are a direct consequence of seizure activity ("excitotoxic" damage) is usually considered the most important mechanism of damage, although status epilepticus can cause other physiologic changes that also may result in cerebral damage. The drug therapy of status epilepticus also carries risks. The situation is complex and these variables are often interrelated, and skillful medical management is essential to minimize the physiologic changes, morbidity, and mortality. Most studies have been carried out in tonic–clonic status epilepticus, and it is clear that the risk of morbidity and mortality is highest in this form. In this chapter, only this form of status epilepticus will be considered.

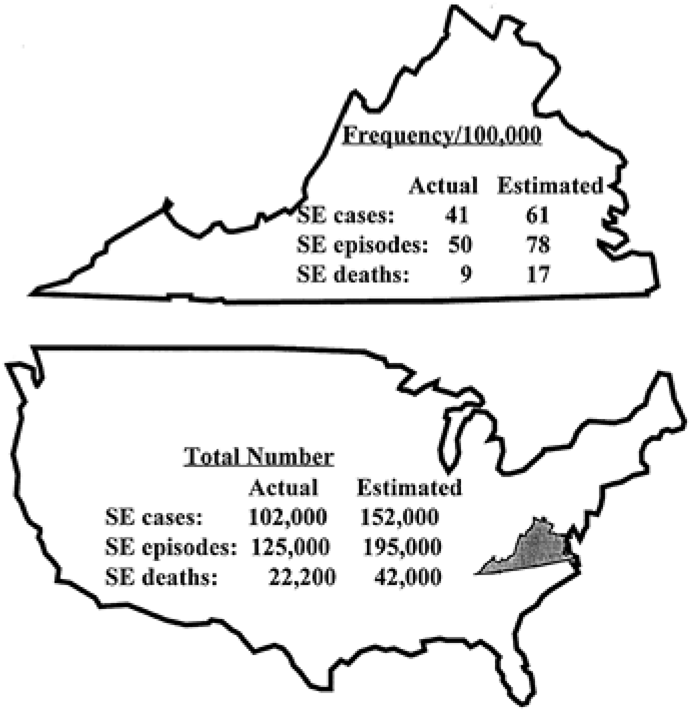

FIGURE 1. Schematic representation of the frequency and total number of status epilepticus (SE) episodes and status epilepticus deaths in Richmond, Virginia **(top),** and the United States **(bottom).** "SE cases" represents the number of patients presenting with one episode of status epilepticus in a year. "SE episodes" represents the number of occurrences of status epilepticus per year. "SE deaths" represents the number of deaths associated with status epilepticus per year. The data represent the actual and estimated values based on the validation of the case ascertainment studies in Richmond (see Materials and Methods). The estimates projected for the United States assume that Richmond, Virginia, is a representative population for the country. Further corrections for the distribution of factors such as age, race, and etiologic variations between Richmond and the United States are necessary to make more accurate projections. Studies are in progress at the VCU/MCV Comprehensive Epilepsy Institute to obtain more accurate estimates of the rates of occurrence and mortality for status epilepticus in the country and the world. (Reprinted with permission from Towne AR, Pellock JM, Ko D, et al. Determinants of mortality in status epilepticus: a retrospective study of 292 adult patients. *Epilepsia.* 1994;35:27–34.)

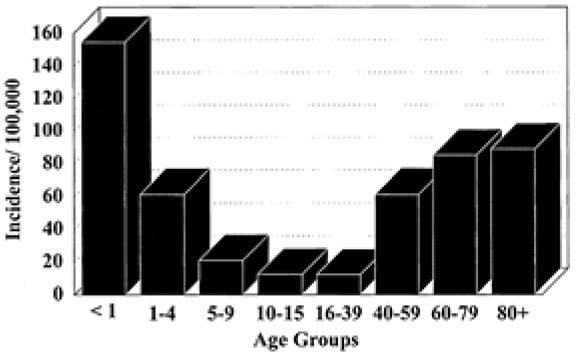

FIGURE 2. Age-specific distribution of the incidence of status epilepticus per year per 100,000 population in Richmond, Virginia. Incidence of status epilepticus represents the number of patients who developed a first episode of status epilepticus in Richmond per year per 100,000 population in each age group. These data do not include recurrent episodes of status epilepticus. The population for each age group was obtained from the 1990 U.S. Census Bureau for Richmond, Virginia. (Reprinted with permission from Towne AR, Pellock JM, Ko D, et al. Determinants of mortality in status epilepticus: a retrospective study of 292 adult patients. *Epilepsia*. 1994;35:27–34.)

Systemic Physiologic Changes in Status Epilepticus

These have been reviewed in detail elsewhere.[10,22,30,64,85] The majority of information comes from tonic–clonic SE, but some data exist from other types of SE. Below we list the changes that can influence outcome in tonic–clonic status epilepticus. Monitoring and skillful management of these changes are vital.

Blood Pressure and Heart Rate

Generalized seizures in animals and humans result in elevated systemic arterial pressures. Similar changes occur in the early phases of convulsive status epilepticus and levels occasionally reach those encountered in hypertensive encephalopathy. In the 21 patients of White et al.,[103] whose blood pressures were recorded during pentylenetetrazol-induced seizures, the mean elevation in systolic pressure was 85 mm Hg and in diastolic pressure 42 mm Hg (maximum changes over baseline were 120 mm Hg for systolic and 100 mm Hg for diastolic, with the minimum changes being 25 and 10 mm Hg, respectively). The time course of seizure-induced hypertension has been studied more thoroughly in animals.[65,90] In the setting of bicuculline-induced status epilepticus in sheep, systemic pressure, heart rate, and plasma epinephrine/norepinephrine concentrations each peaked within the first minute of seizure activity (Fig. 3). Systemic pressure elevations of approximately 150% then returned gradually to baseline over the first 60 minutes of status epilepticus, whereas epinephrine and norepinephrine concentrations as well as heart rate showed only modest attenuation. Benowitz et al.[8] speculated that the mechanism responsible for the decline in blood pressure despite persistent sympathetic activation during status epilepticus was desensitization of vascular adrenergic receptors or hypovolemia induced by vasoconstriction with the resultant movement of blood volume into extracellular spaces. Plasma catecholamine levels after spontaneous single seizures[89] in humans are presented in FIGURE 4. With single seizures or a flurry of seizures, systemic hypertension occurs as well. Again, the peak pressures occur within the first minute, and the maximum level reached is not different between one seizure, a flurry of seizures, or status epilepticus[7] (Fig. 5).

With prolonged status epilepticus, blood pressure decreases to levels below baseline.[8,63] The risk of cerebral hypoperfusion then arises due to the inhibition of cerebral autoregulation during seizures due to a decrease in cerebral vascular resistance.[78] In experimental primates, boundary zone lesions occurred in the cortex and cerebellum when blood pressure was <75 mm Hg during the final 30 minutes of status epilepticus.[65] Drug therapy can also greatly lower blood pressure, and this is a common clinical problem, for instance, with the use of bolus doses or prolonged infusion of anesthetic agents, barbiturates, phenytoin, and benzodiazepines. Pressor agents are often required during anesthesia in status epilepticus, and blood pressure must be carefully monitored.

Cardiac Effects

Status epilepticus can have significant effects on cardiac function. The Richmond study has provided direct evidence in humans of the effects of SE on cardiovascular function.[11,12] These studies indicate that during or immediately after control of SE, patients exhibit a high frequency of electrocardiographic (ECG) abnormalities when compared with expected rates of abnormalities in control populations. Several ECG abnormalities, including ischemia, conduction defects, prolongations of the QTc interval, the presence of latent potentials on sinoatrial ECGs, and the absence of the expected sinus tachycardia during SE, correlated significantly with mortality.[12] Monitoring patients after SE and up to the time of death with cardiac monitoring, it was found that at the time of death after SE, two distinct cardiovascular patterns of mean arterial pressure (MAP) and heart rate (HR) were observed.[11] One group of patients manifested a gradual decline in MAP and/or HR (GDP), and the other group showed sudden death with an acute cardiac decompensation pattern (ADP). These studies represent the only large comprehensive, prospective, population-based data to evaluate central nervous system (CNS) and cardiac factors in the mortality of generalized tonic–clonic, partial complex, and nonconvulsive SE in humans.

Acidosis

A severe lactic acidosis is a prominent accompaniment of status epilepticus in humans and animals[5,64,72] (Fig. 6). Arterial pH measurements in 70 spontaneously ventilating patients with status epilepticus ranged from 6.28 to 7.5; the pH was <7.35 in 59 patients and <7.0 in 23 patients.[5] A respiratory component to the acidosis was found in 30 patients, of whom 13 had a recorded PCO_2 over 60 mm Hg. The decrease in blood pH is rapid (from 7.33 to 6.83 within 4 minutes in rats),[91] reaching minimal levels within 15 to 20 minutes of status epilepticus in baboons (6.47 to 6.86).[65] The rapid rate of decrease of pH is also demonstrable by the similar pH values found after a single seizure: 6.86 to 7.36.[72] A respiratory component to the acidosis in a single seizure also was seen (PCO_2 range 31 to 65 mm Hg). The pH then normalizes over 60 minutes as the causative agent, lactic acid, is metabolized. Other potential causes of acidosis include an acceleration of glycolysis, tissue hypoxia, and catecholamine release. Seizure-induced acidosis is markedly attenuated by treatment with neuromuscular paralysis,[67,91] showing that anaerobic metabolism in muscle is the major source of lactate accumulation. In well-ventilated and paralyzed patients, acidosis is not usually a major clinical problem, and although the administration of bicarbonate can be helpful, this is not usually required and should not be given routinely.[85]

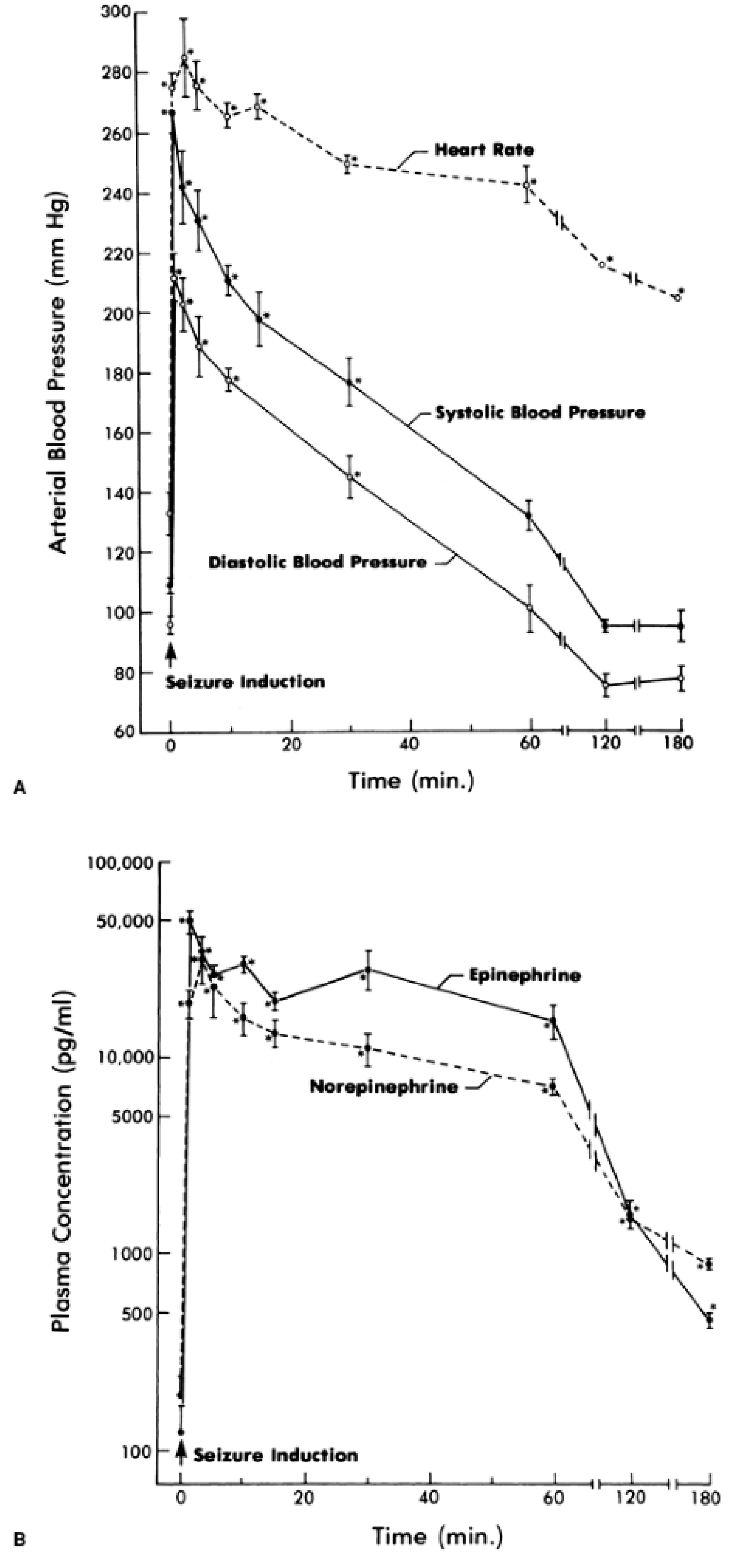
Arterial Blood Pressure (mm Hg)
300
280
260
240
220
200
180
160
140
120
100
80
60
Heart Rate
Systolic Blood Pressure
Diastolic Blood Pressure
Seizure Induction
0
20
40
60
120
180
Time (min.)
A
Plasma Concentration (pg/ml)
100,000
50,000
10,000
5000
1000
500
100
Epinephrine
Norepinephrine
Seizure Induction
0
20
40
60
120
180
Time (min.)
B

FIGURE 3. A: Responses of systemic arterial blood pressure and heart rate to status epilepticus induced by bicuculline injection (time 0). Seizure activity persisted for the duration of the experiment in paralyzed sheep. Data points represent mean (± standard error of the mean [SEM]) of five animals, except for heart rate at 120 and 180 minutes, which represent data collected from two animals. Asterisks indicate a significant difference from pressurized value ($p < 0.05$). **B:** Plasma norepinephrine and epinephrine response to status epilepticus (mean ± SEM). Asterisks indicate a significant difference from pressurized value ($p < 0.05$). (From Aminoff MJ, Simon RP. Status epilepticus. Causes, clinical features and consequences in 98 patients. *Am J Med.* 1980;69:657–666.)

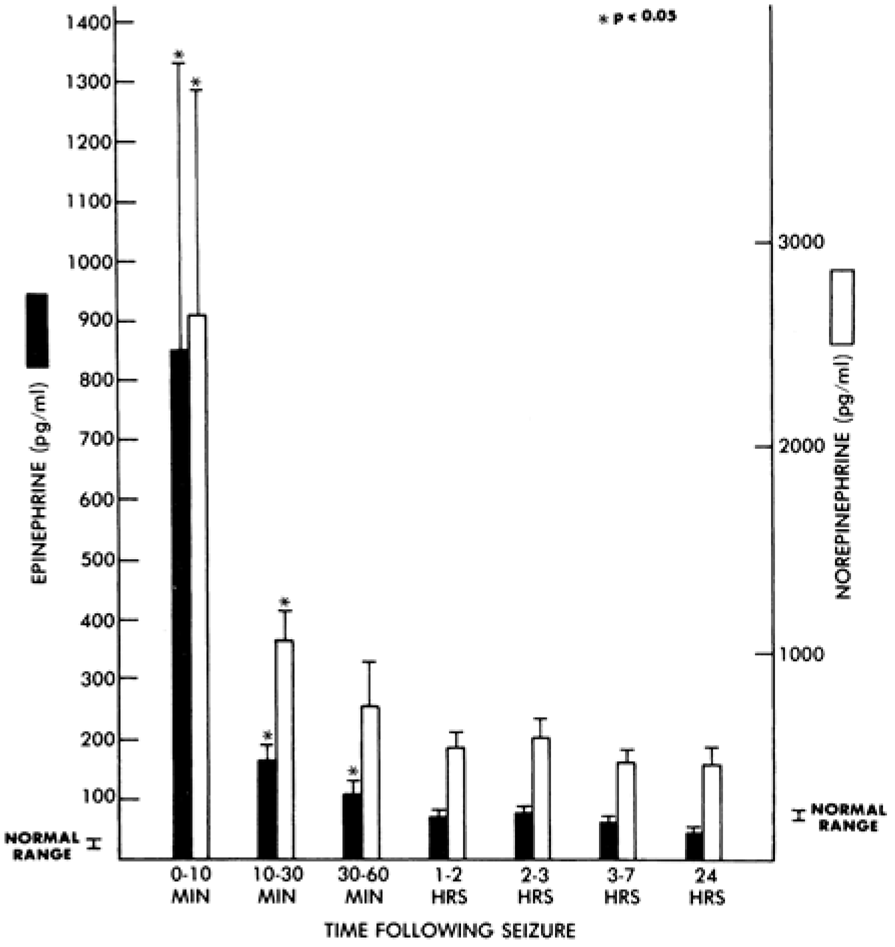

FIGURE 4. Plasma epinephrine and norepinephrine concentrations after a single generalized tonic–clonic convulsion. Data expressed as geometric means (± status epilepticus). (Reprinted with permission from Simon RP, Aminoff MJ, Benowitz NL. Changes in catecholamines after tonic clonic seizures. *Neurology.* 1984;34:255–257.)

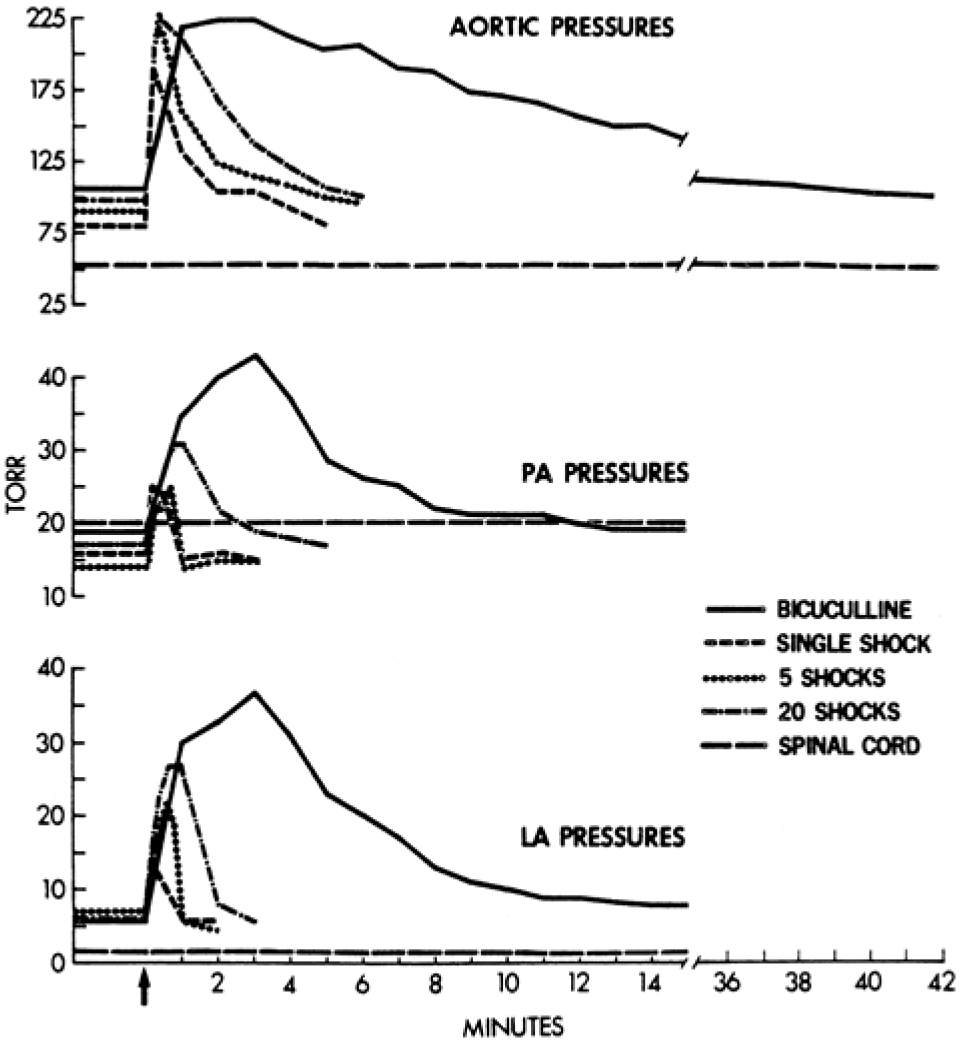

FIGURE 5. Vascular pressure elevations during seizures in sheep; mean values, plotted at 10-second intervals. "Spinal cord" refers to animals with cervical spinal cord transection before seizures. "Single shock," "5 shocks," and "20 shocks" refer to numbers of electroconvulsive seizures induced. "Bicuculline" refers to bicuculline-induced status epilepticus. PA, pulmonary arterial; LA, left atrial. (Reprinted with permission from Bayne LL, Simon RP. Systemic and pulmonary vascular pressures during generalized seizures in sheep. *Ann Neurol.* 1981;10:566–569.)

The induced acidosis is not thought to be generally correlated with the degree of neuronal injury in status epilepticus. In the classic studies of Meldrum and Brierley,[64] the mean arterial pH during the last 30 minutes of status epilepticus was 6.92, 7.08, and 7.14 in animals with no, moderate, or severe CNS damage, respectively. Using heat shock protein immunocytochemistry as a marker of neuronal injury in experimental status epilepticus, acidotic animals (paralyzed and ventilated with 10% CO_2) had less neuronal injury than did animals with normal pH. However, the apparent protective effect was due to attenuation of seizure duration in the acidotic animals.[79] It is also worth noting that acidosis has a strong anticonvulsant effect (a fact underpinning the use of the ketogenic diet in epilepsy, for instance).[104]

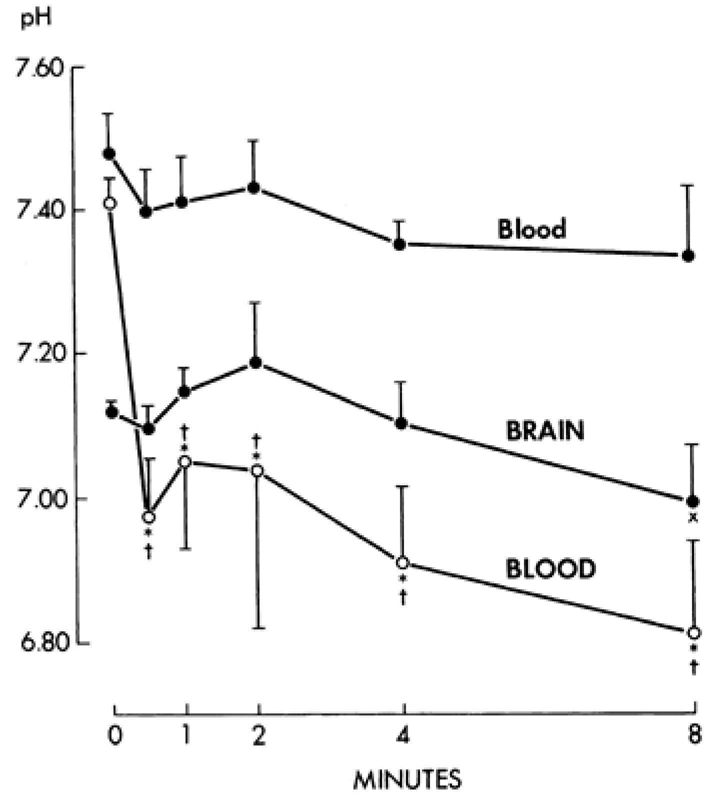

FIGURE 6. Blood and brain pH during status epilepticus. •, paralyzed–ventilated animals; ○, nonparalyzed (freely convulsing) animals (brain pH not determined in freely convulsing animals). Status begins at time 0. Data plotted as means ± standard deviation. *$p < 0.001$ control value (time 0) versus each time point for blood pH in freely convulsing seizures. $p < 0.001$ blood pH paralyzed versus nonparalyzed animals at each time point. ×$p < 0.005$ brain pH, time 0 versus all time points. (Reprinted with permission from Simon RP, Aminoff MJ, Benowitz NL. Changes in catecholamines after tonic clonic seizures. *Neurology.* 1984;34:255–257.)

Hypoxia

Arterial oxygen tension decreases modestly in status epilepticus.[64,65,80] The mean arterial PO_2 values were 58 to 68 mm Hg in experimental primates that showed no moderate or severe neuropathic change.[64] Results of human and experimental studies support the concept that hypoxia alone does not induce brain damage, at least in the early stages of status epilepticus.[13,42] In fact, there is some evidence that hypoxia may be neuroprotective during seizures. Blennow et al.[10] demonstrated that a reduction of arterial PO_2 to 50 mm Hg during the 2 hours of experimental status epilepticus protected animals from neuropathic damage in the cortex hippocampus and striatum; prominent ischemic cell change occurred in animals with induced status epilepticus without hypoxia. Blennow suggested that its protection was due to an attenuation of seizure intensity as measured electroencephalographically. Amano et al.[4] also noted the ameliorative effect of hypoxia (8.5% oxygen with balanced nitrogen) upon seizure induction and excitotoxic injury resulting from intravenous kainic acid. On the other hand, maximal oxygenation (ventilation with 100% oxygen) does not exacerbate neuropathic change in experimental status epilepticus.[94] As status epilepticus proceeds, however, it is likely that prolonged hypoxia does carry a risk of serious damage via many potential mechanisms including free radical release, rupture of lysosomes, and the induction of intracellular acidosis and apoptotic cascades. The increased demands for oxygen are not confined to cerebral tissue, and there are impressive metabolic demands from convulsing muscles. The protection of respiratory function and administration of oxygen is an important element of the emergency management of convulsive status epilepticus.

Pulmonary Edema

Status epilepticus affects not only inspiratory and expiratory effort, but also the passage of fluid across the pulmonary capillary bed. The barrier to this movement is at the pulmonary capillary. The major clinical problem is the occurrence of pulmonary edema. This was found in 15 of 41 patients who died during status epilepticus[71] and in eight patients with the diagnosis of epileptic sudden death.[95] Repetitive seizures or status epilepticus are more likely to be followed by pulmonary edema than by a single seizure.[20] The best experimental studies have been carried out in sheep, and status epilepticus resulted in increases in pulmonary arterial pressure of up to 685% of that in resting states.[7] The greater the number or the longer the duration of seizures, the higher are the increases in intravascular pressures (Fig. 6), and the fall in pulmonary arterial pressure after seizures lags behind that of the systemic arterial pressure. These pulmonary arterial pressures are well in excess of the osmotic pressure of blood, and the lung capillaries also suffer from stretch injury. These marked increases in intravascular pressure in the pulmonary capillaries cause a doubling of pulmonary lymphatic drainage, an increase in transcapillary albumin conductance, and an alteration in pulmonary capillary permeability[90] (Fig. 7).

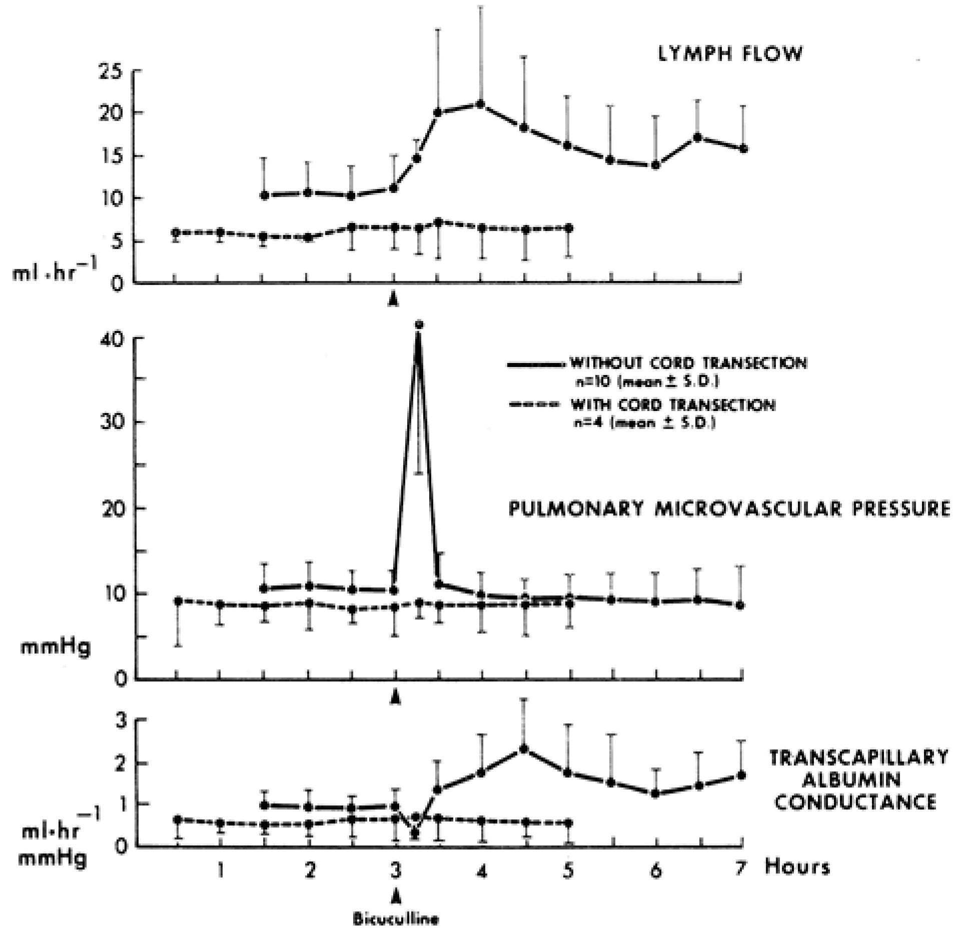

FIGURE 7. Pulmonary lymph flow, calculated pulmonary microvascular pressure, and calculated pulmonary transcapillary albumin conductance before and during bicuculline-induced status epilepticus in ten paralyzed, halothane-anesthetized sheep (*solid line*) and four sheep with cervical spinal cord transection (*broken line*). Values are presented as means ± standard deviation. *Arrowheads* indicate administration of bicuculline. (Reprinted with permission from Simon RP, Bayne LL, Tranbaugh RF, et al. Elevated pulmonary lymph flow and protein content during status epilepticus in sheep. *J Appl Physiol.* 1982;52:91–95.)

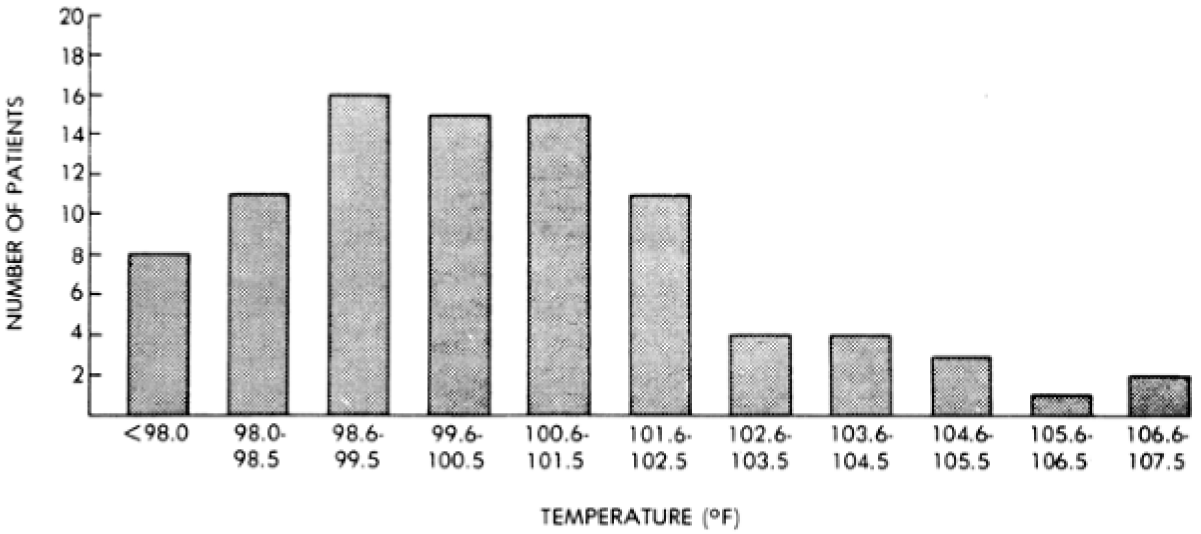

FIGURE 8. Rectal temperatures recorded between seizures or immediately after institution of treatment in 90 patients with status epilepticus. (Reprinted with permission from Aminoff MJ, Simon RP. Status epilepticus. Causes, clinical features and consequences in 98 patients. *Am J Med.* 1980;69:657–666.)

Body Temperature

Hyperthermia is a very common accompaniment of major motor status epilepticus. The convulsing muscles and the sympathetic overactivity due to the heat produce the rise in temperature. The importance of the latter is shown by the increase in body temperature in paralyzed animals.[100] In baboons paralyzed at the onset of status epilepticus, a mean temperature

increase was 2.05°C (range 1.0 to 2.7) over a 7-hour period of observation. In freely convulsing experimental primates, a core temperature of >40°C, persisting for more than 3 hours, was associated with neuronal damage, greater than that predicted from the seizure duration alone.[64,100] The neuronal damage was most prominent in the cerebellum. In these animals, the temperature elevation of 40°C was reached within 60 to 90 minutes of status epilepticus onset.[100]

In 90 patients in status epilepticus, hyperthermia was found in 75, with core temperatures reaching 107°F (42°C) (Fig. 8). The highest temperatures were found in patients with prolonged status epilepticus (more than 9 hours) and were

associated with brain injury.[5] The duration of hyperthermia persisting after status epilepticus cessation can be estimated from reports of temperature elevation after single seizures. Most patients remained febrile at 12 hours, but only 3 of 27 were febrile at 48 hours.

Leukocytosis

An elevation in the peripheral white blood cell count in status epilepticus is common, possibly due to the rapid elevation in plasma catecholamine concentrations. Such demarginated leukocytes resulted in white blood cell counts of 12,700 to 28,800 cells/mm^3 in 50 of 80 patients in status epilepticus in whom there was no evidence of infection.[5] A polymorphonuclear predominance was found in 17 of these patients, a lymphocytic predominance in 11, and a differential cell count with a normal distribution in 15.

Rhabdomyolysis and Renal Failure

Prolonged or violent convulsive movements during generalized tonic–clonic status epilepticus can cause muscle necrosis and acute rhabdomyolysis.[105] Anoxia due to decreased muscular vascular supply in decubitus comatose status epilepticus patients can contribute to severe muscle damage and rhabdomyolysis. Although severe rhabdomyolysis is uncommon in status epilepticus, it can be a serious complication because myoglobinuria can result in renal failure from acute tubular necrosis.[43,93] Renal damage due to tubular necrosis from myoglobinuria or dehydration can lead to fulminant renal failure in extreme cases. Use of artificial ventilation and muscle paralysis in the intensive care unit can minimize the extent of rhabdomyolysis.

Cerebrospinal Fluid Changes in Status Epilepticus

A rise in cell count in the spinal fluid in the absence of an infectious process is rare after single seizures but is common in status epilepticus. Such a phenomenon was found in 12 of 65 cases (18%) reported by Aminoff and Simon.[5] The cell counts were often maximal the day after the status epilepticus. The rise in cells is usually modest, and in the series of Aminoff and Simon[5] was above 70 cells/mm^3 in only 2 out of 70 cases (3%). Personal cases have occasionally been encountered with cell counts of up to 100 cells/mm^3. Cell counts normalize over a few days, with polymorphonuclear predominance yielding to mononuclear cells as the pleocytosis resolved. Modest elevations in protein content can be seen as well (maximum 62 mg/100 mL). Cerebrospinal fluid (CSF) glucose concentrations in the series of Aminoff and Simon[5] were modestly elevated (range 52 to 204), reflecting the elevation in plasma glucose levels. Similar observations have been made subsequently by others.[6,82]

Other Physiologic Changes

A wide range of other physiologic changes and systemic complications can occur in status epilepticus,[83] and the incidence and risk rises the longer the status persists. Changes include disseminated intravascular coagulation (DIC) and multiorgan failure. Various mechanisms may predispose to this including rhabdomyolysis, hypoxia, acidosis, thromboplastin release, hyperpyrexia, and drug renal or hepatic failure.[21,37] The use of valproate or lamotrigine may also increase the risk.[80] Electrolyte disturbances (of many types) and renal failure can occur in status epilepticus due to dehydration, systemic hypoxia, hyperpyrexia, drug therapy, or rhabdomyolysis. Hepatic failure seems, at an anecdotal level, to be more common and again may be induced by drug therapy (particularly valproate) or the underlying cause of the status epilepticus—a particular issue in Alpers syndrome or other mitochondrial diseases. Vomiting; acute pancreatitis[70]; excessive sweating, salivation, and tracheobronchial secretions; inhalation and asphyxia; trophic and skin changes; bed sores; limb fractures[75]; infection; thrombophlebitis; and peripheral ischemia are other complications of status epilepticus that interfere with management and can worsen outcome.

Central Nervous System Physiologic Changes in Status Epilepticus

Oxygen and Glucose Utilization in Status Epilepticus

Cerebral oxygen and glucose utilization is probably greater in epileptic seizures than in any other cerebral activity. In the early stages of status epilepticus, the cerebral cellular metabolic rate and the demand for oxygen and glucose are profoundly increased. This has been clearly demonstrated in human studies with positron emission tomography and metabolic analysis.[38,39,62,87] It has been recognized that the capacity of cerebral tissue to cope with these metabolic demands deteriorates over time. Initially, the increased demands are compensated for by greatly increased cerebral blood flow. This initial physiologic state is referred to as stage I of status epilepticus (stage of compensation).[14,100,101] During this time, because the demand for oxygen and glucose is matched by supply (from the markedly increased cerebral blood flow), no damage occurs.

As status epilepticus continues, the supply of oxygen and glucose begins to fail, and stage II (the stage of decompensation) develops. Cerebral cellular hypermetabolism recedes, and indeed, in late status epilepticus, hypometabolism and ischemia are common. The time taken for stage I to evolve into stage II depends on factors such as etiology, duration and severity of seizure activity, the site of seizure activity, and the treatments used. One factor probably key to this process is the fall in cerebral blood flow. This falls over time as systemic blood pressure falls, and the failure in cerebral perfusion is probably critical in the transition from stage I to stage II, although evidence is contradictory. Siesjo's group[87] showed that in stage II, cerebral blood flow was no longer increased to meet the increased demand of the elevated cerebral metabolism, thus resulting in neurologic injury. In contrast, however, Meldrum[62] found that during stage II of status epilepticus, cerebral blood flow did not decrease, and suggested that a mismatch between metabolism and blood flow was not critical for brain damage. He suggested that a toxic chemical or chemicals are released during status epilepticus and that these compounds are responsible for brain injury. In addition, decreased glucose levels and oxygenation can be observed in very late stages of status epilepticus if patients are not properly ventilated, further contributing to cerebral hypoxia and anoxia. More human and animal studies are necessary to fully understand the relationship of blood flow

and oxygen and glucose utilization during the very late stages of status epilepticus.

Excitotoxic Cellular Damage

Meldrum,[62] based on his classic experimental studies of status epilepticus, suggested that excessive accumulation of intracellular calcium ions in neurons during status epilepticus precipitates a cascade that leads to cell damage. This *excitotoxic* cellular damage is thought now to contribute most to cellular damage in tonic–clonic status epilepticus, and it is because of this risk that urgent intravenous therapy is required.[30] The cerebral cortex, hippocampus, and cerebellum are the cerebral areas most affected by excitotoxic damage. Both apoptosis and necrosis occur and the resultant histologic changes include neuronal loss, atrophy, and gliosis.

Intracranial Pressure Changes and Cerebral Edema

Intracranial pressure during spontaneous seizures in children has been shown to increase by 30 to 40 mm Hg, and this elevation has been shown to persist for up to 20 minutes after seizure cessation.[68] Intracranial pressure during status epilepticus increases in a linear relationship with arterial pressure.[66] During pentylenetetrazol-induced seizures in humans, the mean intracranial pressure elevation was 549 cm H_2O (42 mm Hg), with a range of 270 to 800 cm H_2O or 21 to 61 mm Hg.[68] Electroshock-induced seizures in dogs[46] produced intracranial pressures of approximately 80 mm Hg over baseline. In this study, the elevation in blood pressure (150 mm Hg) was greater, however, resulting in cerebral perfusion pressure that remained above baseline values. In human status epilepticus, the intracranial pressure is often elevated, especially in the early stages. As systemic blood pressure falls, the intracranial pressure can also fall. Cerebral edema is a common occurrence in tonic–clonic status, especially in children, and is often the result of changes in intracranial pressure, low cerebral perfusion, and systemic hypoxia. However, localized cerebral edema in the seizure focus is commonly shown on imaging[47] and so edema can be produced presumably by local membrane changes related to seizure activity as well as any general rise in intracranial pressure. In generalized tonic–clonic status epilepticus, intracranial pressure monitoring is often indicated, especially in children, to anticipate and prevent cerebral edema and ischemia. Raised intracranial pressure is associated with a poor outcome, and this has been well studied particularly in status epilepticus due to infection (Japanese B encephalitis or malaria).[19,69]

Blood–brain Barrier Changes

Cerebral blood vessels are lined with endothelial cells that allow less molecular transfer across the wall of the blood vessels than elsewhere in the body. This blood–brain barrier prevents the entry of certain blood compounds into the brain tissue. Only small molecules or ions with specific transfer systems or highly lipid-soluble molecules can normally easily enter the brain.[89] During severe status epilepticus, the blood–brain barrier is compromised[41] and more compounds gain entrance to the brain. This exposes brain tissue to risk of injury and damage and adds potentially to the morbidity and mortality of status epilepticus. The extent to which blood–brain barrier injury does contribute to morbidity in human status epilepticus is unknown. The increased local permeability of the brain in epileptic foci may in fact aid the distribution of therapeutic agents (e.g., phenobarbital) to these foci.[92]

Cerebral Vascular Changes

Cerebral arterial hemorrhage and infarction, cortical venous thrombosis, and other vascular catastrophes are well recorded in status epilepticus and are a reflection of poorly controlled metabolic and physiologic changes. Vascular changes have also been implicated in cerebral edema, and infarction due to coning can occur.

Electrophysiology Changes

There are several important EEG[32,48] and evoked potential (EP)[89] electrophysiologic changes that have been shown to occur following SE. These changes have been shown to be predictive of both morbidity and mortality in SE.[32,48,89] Abnormal EP changes following SE indicate neuronal injury and were observed in both cortical and subcortical structures following both tonic–clonic SE and partial SE.[89] DeLorenzo et al. have shown that 1 hour after the successful treatment of convulsive SE, 67% of SE cases were still in coma either due to medication effects or underlying medical problems. Continuous EEG monitoring of patients in coma for more than 2 hours after the successful treatment of clinical convulsive SE demonstrated that 14% of the comatose patients were still in nonconvulsive SE[32,48] and an additional 40% manifested persistent after SE ictal discharges.[32] These results demonstrate the pronounced effects of both tonic–clonic and partial SE on the central nervous system.

Acute Morbidity of Status Epilepticus

The morbidity of human status epilepticus has been surprisingly poorly studied. The main sequelae among survivors of tonic–clonic status epilepticus are intellectual dysfunction, permanent neurologic deficits, and continuing recurrent seizures.[1,16,59,86] Neuropathologic studies in animals by Meldrum and others have demonstrated conclusively that prolonged epileptic activity, even if blood sugar and oxygen are maintained at normal levels, can result in irreversible neuronal damage.[63,64,67] These were the first studies to show that the duration of the seizure activity is a crucial factor in determining outcome, and this finding has been confirmed repeatedly both in experimental and human studies. They showed that seizures lasting <1 hour may produce neuronal changes that are reversible, but longer-lasting seizures produce permanent neuronal injury.[63] Similarly, in human status epilepticus, many studies have shown that the longer the seizure duration, the worse the outcome in terms of both mortality and morbidity.[25,26,27,31,86,96] Several other clinical parameters also have been associated with morbidity and mortality. Studies have suggested that prognosis depends on the interval of time allowed to elapse between the onset of status epilepticus and the start of effective treatment.[3] Almost all clinical studies have shown also that the underlying etiology is an important determinant of morbidity and mortality.

Most studies have been of children and concentrated on neurologic deficits. There are few studies of psychometric changes after status epilepticus, in spite of the common clinical experience of cognitive and particularly memory deficits in the aftermath of status epilepticus, albeit often transitory.[33,34,35] Furthermore, it has proved extremely difficult to disentangle the effects of status epilepticus per se from the effects of the

precipitating cause (e.g., encephalitis, vascular insult, etc.). This issue has bedeviled studies in this field. The longer-term morbidity in terms of mental impairment and neurologic deficit are discussed in Chapter 65.

The main acute deficit caused by status epilepticus in children has been termed the HH and HHE syndromes (initials referring to the permanent hemiplegia or hemiparesis, mental retardation, and chronic epilepsy [in about three quarters]). This is usually the result of a prolonged asymmetric or unilateral febrile convulsion in a child under 4 years of age (usually under 2 years).[1] Many of these children have some neurologic dysfunction before the SE, and the SE may be of greater severity than usual, reflecting this. The damage is probably due to a mixture of vascular and excitotoxic mechanisms. It used to be a relatively common sequela to febrile SE,[1,2,3] and indeed was present in 25 of 79 children with status lasting 1 hour or longer in a Japanese series published in 1979.[40] Nowadays, however, with rapid and effective early therapy, HH and HHE are rare occurrences in developed countries, although they are still frequent and preventable in the developing world. This improvement is very likely to be the consequence of more rapid and urgent control of convulsive and febrile SE.

There is equally little information available on the rate of morbidity associated with status epilepticus in adults. There are a number of old studies from a period when drug treatment was more limited and when therapy was not administered with the same degree of urgency as is current practice. Rowan and Scott[80] examined 42 patients with tonic–clonic status epilepticus and indicated that 26% had neurologic sequelae but did not provide details. Their study indicated that greater deterioration related to longer periods of status epilepticus. The first modern study of outcome among 86 patients was carried out by Oxbury and Whitty.[73,74] They demonstrated that 2% of the patients without a specific neurologic etiology deteriorated with adverse personality and intellectual changes after status epilepticus. Aminoff and Simon[5] evaluated 98 patients with histories of tonic–clonic status epilepticus in a retrospective study and demonstrated that approximately 8% of the patients had diffuse encephalopathy and intellectual impairment after status epilepticus. Their study also indicated that longer episodes of status epilepticus were associated with a greater degree of impairment. The risk of epilepsy following status is discussed in Chapter 65.

Acute Mortality of Tonic-Clonic Status Epilepticus

Status epilepticus results in significant mor-tality.[16,17,22,23,24,25,26,27,28,29,30,31,32,36,52,54,55,56,57,59,60,73,74] Case fatality rates as high as 50% have been reported, but the more recent studies have reported rates between 8% and 32%.[16,22,23,24,25,26,27,28,29,30,31,32,56,57,59,73,74] The rates reported in large hospital series have varied considerably, depending on the type of population evaluated, whether all types of SE were included, and the referral base of individual hospitals.[16,22,23,24,25,26,27,28,29,30,31,32,56,57,59,73,74] The variability in mortality rate also relates to the distribution of underlying etiologies within each series, as well as to the duration of follow-up of patients in the acute versus late stage of mortality after status epilepticus. The mortality rate for status epilepticus has decreased over the past 60 years, probably being related to more rapid and aggressive treatment of this condition. The mortality rates in more recent population-based studies have been reviewed[57] and have reported case fatality rates of between 7.6% and 39%. Much of the variation is due to the inclusion or exclusion of patients with myoclonus due to acute anoxic encephalopathy within the rubric of status epilepticus. Series in which such cases are excluded[18,51] show a low mortality, whereas studies in which they are included have much higher rates.[28,29,30,31,32,56,57] Rates have also been found to be higher in white Americans compared to black Americans (31% vs. 17%) in one study.[28] A largely consistent finding has been the higher mortality in status epilepticus due to acute brain disorders. In the Rochester study, for instance, 90% of all deaths were in the acute symptomatic group and no deaths occurred in the idiopathic group,[56,57] and this reiterates the similar findings of studies over the previous decades (see 85 for a review). The importance of the underlying cause is shown in the meta-analysis of series up to 1989[85] in which the overall mortality rate of 1,686 cases was 18%, of which only 2% were attributable to the status epilepticus itself.[85] A large study from Waterhouse et al. has evaluated the interaction between SE and the underlying etiology or symptomatic conditions associated with SE.[102] In this study it was shown that there was a synergistic interaction between the underlying etiology, cerebral vascular event, and SE in causing mortality. The mortality of SE alone or the cerebral vascular event was much less than the mortality due to a combination of SE and stroke. This study controlled for the size and severity of the cerebral vascular event. These results indicate that the combination of SE and an underlying etiology have a complex effect on mortality, and this important area needs further investigation.

Classic studies by Aicardi and Chevrie[2] reported in 1970 indicated that the mortality rate in children approached 11%, and in half of these cases, death was due to status itself. Many of these children had febrile status epilepticus. These studies stressed, for the first time, the importance of early therapy and were very influential. The more urgent approach to therapy greatly improved mortality rates, and a subsequent study by Maytal et al.[61] described 193 children of whom only seven died after status epilepticus. Similarly, in 1989, Philips and Shanahan[77] reported their study, designed to revisit those of Aicardie and Chevrie, of 218 episodes of childhood status epilepticus in patients admitted to a pediatric intensive care unit over a 5-year period, among whom there was an overall mortality rate of only 6%. The importance of early therapy continues to need to be stressed, as the outcome of status in children remains poor in developing countries, where access to early therapy may not be available.

The mortality rate in adults is consistently reported to be higher than that in children. Nineteenth-century studies, conducted before effective therapy (other than bromide) was available, estimated that 30% to 50% of adults with status epilepticus died.[9,15,58] A series of studies between 1970 and 1990 reported mortality rates in adults between 14% and 35%.[85] In more recent studies, Towne et al.[96] in a series of 256 patients demonstrated an overall mortality rate in adults of 22%. De Lorenzo et al.[23,24,25,26,27,28,96,97,98] studied mortality in a population-based prospective study from Richmond, Virginia. This is the largest and most comprehensive clinical investigation of status epilepticus carried out and has provided very important data (Figs. 9,10,11,12). The overall mortality rate associated with status epilepticus in the entire population was 22%. The mortality rate of status epilepticus at different ages is shown in Figures 9 and 10. Mortality rates increase with age, and the highest rates were seen in the elderly (38%). The rate in children was 3% and among young adults 13%. The Richmond studies also compared mortality rates in generalized and partial status epilepticus[31,96] and no significant differences were found. Seventy-three percent of patients had generalized status epilepticus and 27% had partial status epilepticus (Fig. 11A). Of those patients with partial status epilepticus, the mortality rate was 30.4%. Patients with generalized tonic–clonic seizures had a mortality rate of 20.7% (Fig. 11B). The lack of difference probably reflects the importance of the underlying etiology in

determining mortality, and those presenting with focal neurologic lesions, such as stroke or infection, in this study are classified as partial status epilepticus.

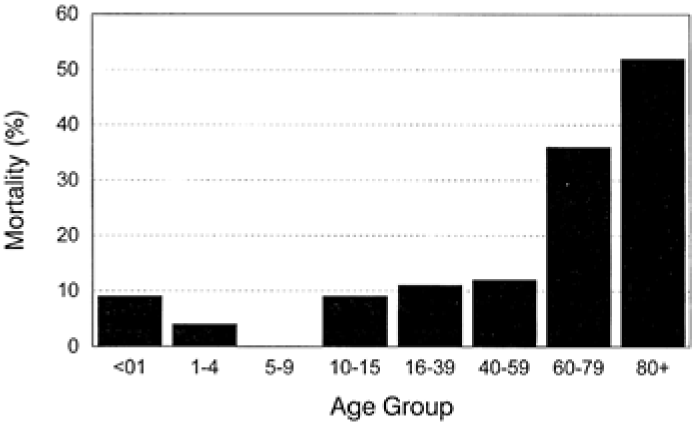

FIGURE 9. Mortality of each age group in the Medical College of Virginia population. Data represent the mortality for each age group. (Reprinted with permission DeLorenzo RJ. Clinical and epidemiologic of status epilepticus in the elderly. In: Rowan AJ, ed. *Seizures and Epilepsy in the Elderly.* Newton, MA: Butterworth-Heinemann; 1996:191–205.)

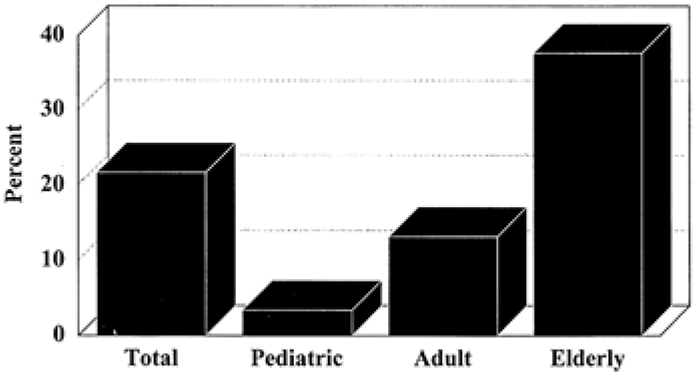

FIGURE 10. Mortality of status epilepticus in Richmond for the total, pediatric, adult, and elderly populations. Data represent the percentage mortality for each age group in the population. Mortality is expressed as the number of status epilepticus–associated deaths in each age group and as a percentage of the number of patients that died in each age group. (Reprinted with permission from Towne AR, Pellock JM, Ko D, et al. Determinants of mortality in status epilepticus: a retrospective study of 292 adult patients. *Epilepsia.* 1994;35:27–34.)

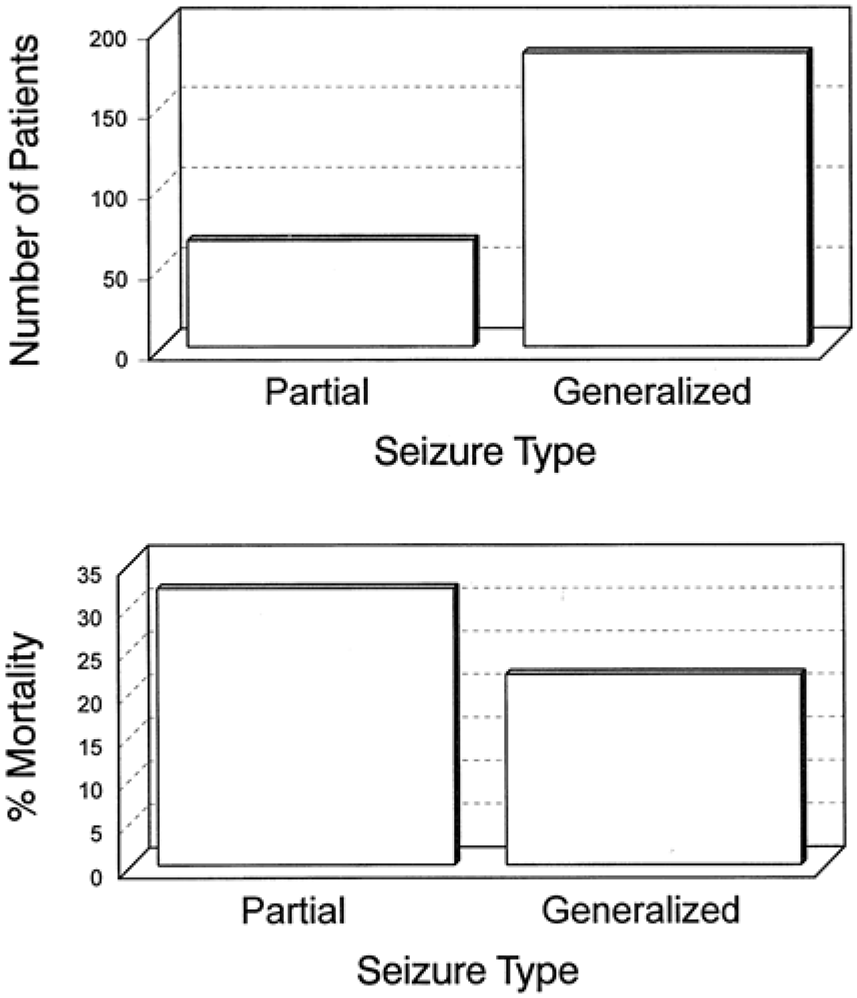

FIGURE 11. Seizure type and mortality. **A:** Seizure type as a function of the number of patients. Most patients had generalized seizures. **B:** Patient mortality rate for partial and generalized seizures. (Reprinted with permission from Towne AR, Pellock JM, Ko D, et al. Determinants of mortality in status epilepticus. *Epilepsia.* 1994;5:27–36.)

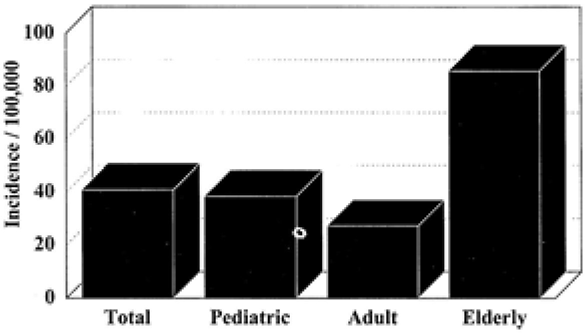

FIGURE 12. Incidence of status epilepticus for the total, pediatric, adult, and elderly populations in Richmond. Data represent the incidence of status epilepticus per year per 100,000 population in each age

group. (Reprinted with permission from Towne AR, Pellock JM, Ko D, et al. Determinants of mortality in status epilepticus. *Epilepsia.* 1994;5:27–36.)

The etiology of status epilepticus has an overriding influence on mortality, and indeed in modern practice, the fatality rates of status itself are under 5%.[5,26,27,28,44,45,53,56,57,81,85,96,97] The etiologies of status epilepticus in pediatric and adult patients in the Richmond Study are shown in Table 1. The major cause of status epilepticus in children was systemic, non-CNS infections, which accounted for more than 51% of status epilepticus cases in children. This was the only cause resulting in death. In the adult population, major etiologies included lowered antiepileptic drugs (34%), stroke (22%), alcohol-related disorders (13%), metabolic disorders (15%), and anoxia/hypoxia (18%). The mortality rates in children and adults are shown in Table 1. Rates are higher in adults and are highest in cases due to acute anoxia and hypoxia (71% and 53%, respectively) and are significant for cerebrovascular disease (33%), tumor (30%), and metabolic (30%) etiologies. Lowered antiepileptic drugs (4%) and alcohol-related disorders (20%) had lower mortality rates.

Table 1 Etiology and Mortality Rates for Pediatric and Adult Cases of Status Epilepticus (SE)

	Pediatric		Adult	
Etiology	**% of SE cases**	**Mortality**	**% of SE cases**	**Mortality**
Anoxia	0	0	5	71
Hypoxia	5	0	13	53
CVA	10	0	22	33
Hemorrhage	0	0	1	0
Tumor	0	0	7	30
Infection	52	5	7	10
CNS infection	2	0	3	0
Metabolic	7	0	15	30
LAEDs	21	0	34	4
Drug OD	2	0	3	25

Etoh	0	0	13	20
Trauma	0	0	3	25
Remote	38	0	25	14

CNS, central nervous system; CVA, cerebrovascular accident; LAED, lowered antiepileptic drugs; OD, overdose.

Summary and Conclusions

Status epilepticus is a major medical and neurologic emergency that is associated with acute physiologic changes that can be severe enough to cause significant morbidity and mortality. SE has significant effects on blood pressure and heart rate and also can cause marked acidosis. Hypoxia and impairment of respiratory function are also associated with SE. Hyperthermia and leukocytosis are prominent features seen in association with SE. Violent convulsive movements during SE can lead to rhabdomyolysis and renal failure. Increased intracranial pressure and CSF pleocytosis also have been described in this condition. Breakdown of the blood–brain barrier and changes in oxygen and glucose utilization and supply may also contribute to the morbidity and mortality associated with this condition. Morbidity associated with SE has been difficult to study, but the condition has been clearly associated with significant morbidity in adults and some, but reduced, morbidity in children. Further research on the acute and chronic morbidity associated with SE is necessary to fully establish the effect of SE on brain function. SE has been associated with significant rates of mortality in adults, ranging from 20% to 25%. The mortality rate in children is much less significant and in well-treated cases is <5%. Seizure duration, age, and etiology have been shown to influence morbidity in SE. Recent studies demonstrate that another 102,000 to 152,000 individuals are affected with SE in the United States every year. Approximately 22,000 to 42,000 deaths per year are associated with SE in the United States. Thus, SE represents a significant public health problem. Partial and generalized SE is associated with approximately the same mortality rate. The mortality rate is much higher in the elderly. The pronounced physiologic effects of SE on the CNS and the body contribute to the significant morbidity and mortality associated with this condition.

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Chapter 65

Long-Term Sequelae of Status Epilepticus

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Introduction

Status epilepticus (SE) is a common neurologic emergency that can result in significant morbidity and mortality. Convulsive status epilepticus is the most common and potentially detrimental form of status, but long-term sequelae have been reported even following nonconvulsive status. Three major population-based prospective studies investigated the epidemiology of SE. The annual incidence of SE around Richmond, Virginia, was 41/100,000 individuals.[37] It was 27/100,000 for young adults and 86/100,000 for the elderly. The mortality rate was also higher in the elderly: 14% for young adults and 38% for the elderly, but only 3% in children. The annual incidence from two prospective studies in Europe was 17.1/100,000 in Germany[76] and 10.3/100,000 in the French-speaking part of Switzerland.[31] These findings are close to the incidence of 18.1/100,000 found in an early retrospective study of SE from 1965 to 1984 in Rochester, Minnesota.[72]

It is estimated that, in the United States alone, status epilepticus affects 100,000 to 150,000 individuals each year, approximately half of whom are children. In >50% of the cases, there is no prior history of seizures.[40,67] Status epilepticus can occur either as part of an established seizure disorder or in the context of an acute illness. Approximately 10% of children and adults who have epilepsy initially present with status epilepticus.[15,40,67,142]

In the past, status epilepticus was associated with a high morbidity and mortality. This has changed dramatically, especially in children. Recent clinical data (see Chapter 126) indicate that with proper treatment, the acute morbidity and the mortality of status per se is quite low, particularly in children. The adult data still show a significant morbidity and mortality, much of which is related to the underlying etiology.[3,36,40,45,46,64,92,166,171] This chapter reviews the potential long-term sequelae of status epilepticus with an emphasis on the issue of whether status epilepticus results in a chronic seizure disorder. The old definition of status epilepticus was a condition in which epileptic seizures are sufficiently prolonged or repeated at sufficiently brief intervals to produce "an unvarying and enduring epileptic condition."[60,126] More recent data suggest that if this occurs in humans, it is not very common. In this context we also review the association between status epilepticus, particularly in early life, and mesial temporal sclerosis.

Cognitive Deficits Following Status Epilepticus

In animal models, status epilepticus has been associated with neuronal changes, particularly in the adult animals.[32,95,96,97,126,127,131,132,157,158] In humans, chronic intractable seizure disorders have been associated with cognitive deficits and in some cases even intellectual decline.[38,54,125] Isolated case reports of cognitive impairment following status epilepticus, whether convulsive or complex partial or even absence, are frequent,[41,135] but none gives a sense of how commonly this occurs. In an entity associated with a significant morbidity and mortality, one would expect that cognitive impairment might occur. However, much of the morbidity and mortality of status epilepticus is associated with the precipitating acute neurologic insult.[3,36,39,40,45,46,64,66,92,116,166,171] The morbidity and mortality have dramatically declined over the last 50 years, especially in children, and other sequelae may have decreased as well.[2,3,4,7,36,40,45,46,64,92,127,166,171] Therefore, the high rate of adverse sequelae reported in the older series are probably not representative of the current reality.[39,40,64] In this section we address the issue of whether status epilepticus per se results in long term-cognitive impairment.

To answer this question, we need to identify the appropriate group of patients. This turns out to be a very difficult task. Status epilepticus is often seen in the context of an acute brain insult such as trauma, stroke, or encephalitis.[3,39,40,92] In this setting, it is difficult if not impossible to differentiate cognitive impairment due to prolonged status epilepticus from that caused by the acute brain injury itself. Status epilepticus also occurs in the context of chronic intractable epilepsy. In this setting it may be difficult to separate the effect of status epilepticus from the cumulative effects of many briefer seizures. Ideally, one would look at patients who had an isolated episode of status epilepticus near the onset of their epilepsy. This is a not an infrequent occurrence. Approximately 10% of patients who present with a first unprovoked seizure or with newly diagnosed epilepsy present with status epilepticus.[11,16,64,67,68,69,70,91,139] However, very few of these patients have had neuropsychological testing before their episode of status. Thus, when a subtle deficit is found, it is difficult to know whether it was a result of status or preexisted. These considerations apply to both adults and children. In children, there is the additional difficulty that status epilepticus most often occurs in very young children, with half the cases under age 15 years occurring under age 3 years.[92] At this young an age it is very difficult to get an accurate estimate of premorbid intellectual function unless the child was very severely impaired.

The data regarding cognitive impairment following status epilepticus were reviewed by Dodrill and Wilensky.[39] They excluded case reports and reviewed 14 studies of status.[3,7,29,38,42,46,47,48,58,59,66,81,92,117,127] They noted that most studies are of children, and few studies of children or adults used any formal psychological testing. In addition, many studies were retrospective. Of the 14 studies reviewed, the more recent and prospective ones were the ones that reported the lowest morbidity, including cognitive outcomes. This may be attributable to less skewed patient samples in prospective

studies, an improved ability to identify etiologies (e.g., some older studies included cases of meningitis in the category of febrile status epilepticus), and perhaps improved treatment in the modern era.

There are some excellent prospective data on adults. Dodrill and Wilensky performed complete neuropsychological testing on 143 adults on two occasions 5 years apart.[39] Of these, 9 had a definite episode of status epilepticus in the 5-year period, including cases of both generalized tonic–clonic status and complex partial status. These were compared to matched controls that had not experienced an episode of status in the 5-year period. The group with status epilepticus had lower IQ scores and performed worse on a variety of cognitive measures. However, some of these differences were present at the baseline testing prior to the episode of status. This is consistent with the epidemiologic data that status epilepticus is more common among those who are neurologically abnormal.[40,66,67,68,92] The authors concluded that most investigators described at least a few adverse changes attributable to SE rather than to underlying neurologic disease. However, in general, status epilepticus has only a modest adverse effect on cognitive abilities and in many individuals no effects are discernible.[39]

The data on children are even more difficult to tease out. However, data from the National Collaborative Perinatal Project (NCPP) suggest that status epilepticus per se has few if any adverse effects on the young child. Ellenberg and Nelson examined 27 children with febrile convulsions lasting >30 minutes and found no differences in cognitive function at 7 years of age between them and their siblings.[47] They also found no evidence of decline in cognitive function in children with onset of epilepsy between ages 4 and 7 years who had cognitive testing as part of the NCPP at ages 4 and 7 years.[48] The group included 8 children who experienced status. Dunn[46] and Maytal et al.[92] also found few long-term sequelae following status epilepticus in children unless it was associated with an acute or progressive central nervous system (CNS) insult. Animal data also suggest that the immature CNS, while more susceptible to developing status epilepticus, is more resistant to adverse sequelae.[6,21,27,33,65,73,74,75,83,102,103,105,112,116,150,151,152,167,168]

In summary, there are case reports that document the occurrence of cognitive deficits following status epilepticus in both children and adults. These deficits may occur not only following convulsive status, but also following complex partial status and perhaps absence status. However, in large studies the morbidity of status epilepticus is primarily a function of the underlying etiology. Patients with status epilepticus are more likely to have had prior cognitive deficits. The incidence of demonstrable cognitive deficits following an episode of status appears to be low. More studies are needed to address this issue.

Hemiconvulsion-Hemiplegia-Hemiparesis Syndrome

A particular neurologic syndrome frequently found in the older series of convulsive status in children was an acquired hemiplegia, the so-called hemiconvulsion-hemiplegia-epilepsy syndrome (HHE).[3,59,61] In one series, the syndrome was present in 25 of 79 children with convulsive SE lasting >1 hour.[59] The association is well established in the older literature.[3,5,28,59,61,126] These cases of acquired hemiplegia were also almost invariably associated with subsequent intractable seizures.

However, more recent studies report not only a much lower acute morbidity and mortality of status epilepticus,[36,40,45,46,64,67,92,166,171] but also a lower rate of adverse sequelae. The syndrome of HHE is notably absent from studies of status epilepticus over the last two decades.[36,40,45,46,64,67,92,166,171] Whether this is a result of improved therapy or of other factors remains a matter of speculation. However, it does coincide with the decrease in mortality and other acute and long-term adverse sequelae of status epilepticus.

Status Epilepticus and the Development of Future Seizures

The textbook definition of status epilepticus as "a seizure of such duration as to create a fixed epileptic condition"[60,126] might lead one to assume that all cases of status epilepticus are inevitably associated with a subsequent chronic seizure disorder. Indeed, if "seizures beget seizures" as has been argued by some authors,[49,62,122,123] then one would expect that the occurrence of a prolonged seizure such as status epilepticus would inevitably result in subsequent seizures. However, the epidemiologic data do not support this conclusion.[15,17a,67,69,70,106,130,137,139] This section reviews the data regarding the development of a subsequent seizure disorder following an episode of status epilepticus.

Experimental Data

Status epilepticus–induced epileptogenesis is a widespread phenomenon that reproducibly occurs in the vast majority of animals after many types of experimental status epilepticus. The majority of subjects develop spontaneous recurrent seizures after status epilepticus induced by kainate, pilocarpine with or without lithium, tetanus toxin, stimulation of excitatory pathways such as the perforant path, or stimulation of limbic structures such as amygdala[111] or ventral hippocampus in a number of animal species.[20,22,79,82,129,133,160] Acutely, neuronal loss in the dentate hilus and CA1 and increases in diffusion-weighted and T2-weighted imaging (by magnetic resonance imaging [MRI]) are seen in hippocampus.[50,124] Chronically, an increased T2 signal reveals hippocampal cell loss coupled to gliosis, a combination that is reminiscent of human medial temporal sclerosis.[124] The respective role in epileptogenesis of loss of GABAergic interneurons[115,147] and of sprouting of excitatory fibers[154,155,169] is debated. In immature animals, SE can lead to spontaneous recurrent seizures and chronic epilepsy, although the immature brain is more resistant than the adult brain.[71a,71b,132,133] However, this epileptogenicity is highly model dependent: Whereas the lithium-lipocarpine model is highly epileptogenic,[133,153] the perforant path model of status epilepticus generates spontaneous recurrent seizures in only about 15% of subjects.[134,169]

Domoic acid (a close analog of kainic acid) ingested from mussels induced status epilepticus in a man who later developed chronic epilepsy, and this case may offer the closest human approximation to the animal models.[26]

Status Epilepticus as a First Unprovoked Seizure

Approximately 10% of patients who come to medical attention with a first unprovoked seizure present with SE.[11,16,40,64,67,68,69,70,91,139] The majority of these have a cryptogenic or idiopathic etiology. In both children and adults, the risk of seizure recurrence following a cryptogenic/idiopathic first unprovoked seizure is not influenced by the duration of the initial seizure.[11,15,69,70,139,142,143,143a] This is true whether one

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examines seizure duration as a continuous variable or compares those with status epilepticus as their first unprovoked seizures with those who presented with a brief first seizure. These studies, which include follow-up periods of >15 years, support the view that status epilepticus per se does not create a permanent seizure disorder.[70,142,143,143a]

In both children and adults who present with status epilepticus as their first unprovoked remote symptomatic seizure, the risk of recurrence is increased.[16,69,70,139] As discussed later, these patients are at increased risk not just for recurrent seizures, but also for recurrent status epilepticus.[15,43,140,143a] However, it should be noted that status epilepticus as the initial seizure is relatively uncommon in this group. In one study of childhood status epilepticus, 29 (63%) of 46 children with idiopathic status epilepticus had no prior history of seizures, whereas 34 (75%) of 45 children with remote symptomatic status had a prior history of seizures.[92] The fact that status epilepticus is a risk factor for subsequent seizures in remote symptomatic cases but not in idiopathic ones suggests that either it is a marker for epilepsy in those cases or that the already compromised brain is more susceptible to injury as a result of status. More research is needed on this point, and animal models are being developed to address this issue (see Chapter 36).

When one looks at long-term outcomes following an initial episode of status epilepticus, the epidemiologic data in children also do not show long-term adverse effects of an isolated episode of status epilepticus. The occurrence of status epilepticus does not influence long-term remission rates in children who present with status epilepticus as their first unprovoked cryptogenic seizure.[141a,142] In a case–control study of predictors of intractability in children with newly diagnosed epilepsy, the occurrence of status epilepticus was found to be a marker for future intractability.[18] The best predictor, however, was the presence of an underlying neurologic abnormality. Furthermore, of the four children believed to have cryptogenic epilepsy whose presentation included an episode of status epilepticus, one was later diagnosed as having a brain tumor, one had retardation, and one had a progressive neurologic disorder. Thus, status in this population seems to be a marker for an abnormal brain, which is known to be a predictor of future intractability.[18] Similarly, in Sillanpaa's study, the occurrence of status epilepticus was more common in remote symptomatic cases, which are also more prone to recurrent status. However, it had an only modest effect on long-term outcome once one controls for etiology.[145,146] Few data are available on this question in adult-onset epilepsy.

Epilepsy Following Febrile Status Epilepticus

The literature regarding this issue is confusing. Retrospective studies from tertiary epilepsy centers reported that many adults with intractable temporal lobe epilepsy had a history of prolonged or atypical febrile seizures in childhood.[1,19,24,25,52,53,58,84,86,87,88,89] However, population-based studies failed to find this association, nor did prospective studies of febrile seizures.[8,10,48,90,108,163,164] In this section we review some of the data as they relate to the association of prolonged febrile seizures and subsequent epilepsy.

One must be careful to distinguish between very prolonged febrile convulsions, which are the extreme end of the complex febrile seizure spectrum,[107] and status epilepticus associated with fever. The latter term often includes cases of encephalitis, meningitis, and other forms of acute brain injury as well as children with already established epilepsy who decompensate in the context of an acute febrile illness. These are discussed in the section on acute symptomatic status epilepticus. This section focuses on the data on the consequences of prolonged febrile seizures (for a more detailed discussion see Chapter 63).

Studies that limit themselves to children with prolonged febrile seizures uniformly report a low morbidity and mortality.[8,10,36,40,45,46,48,64,67,89,90,108,163,164,166,171] As with all forms of complex febrile seizures, there is a somewhat higher risk of epilepsy compared to children with a simple febrile convulsion.[8,10,17,40,48,51,89,90,108,163,164] In a study of a British cohort of 16,004 children born during a single week in April 1970, the proportion of those who developed afebrile seizures was 3.4% after febrile convulsions lasting <30 minutes but 21% after febrile convulsions lasting >30 minutes.[164] This increased risk may express itself many years later.[8,10,164] At highest risk are those whose febrile seizures are both prolonged and focal[10] and those who are already neurologically abnormal prior to the febrile seizure.[10,16,90] In children who were previously neurologically abnormal, even the short-term risks of developing epilepsy are substantial.[90]

The difficulty in interpreting the data centers on whether the febrile seizures are markers for subsequent epilepsy or a cause of the epilepsy. Those who argue that there is a causal relationship point to the retrospective studies of temporal lobectomy patients, autopsy studies,[1,19,24,25,32,51,52,53,58,84,89,172] and adult animal data on the sequelae of status epilepticus.[83,95,96,97,148] On the other hand, there are those who would argue that febrile seizures are simply an age-specific marker for subsequent epilepsy.[141] Namely, those patients with a predisposition to epilepsy based on a genetic predisposition or based on underlying structural abnormalities will, at the age-specific developmental window, also be more likely to experience febrile seizures, possibly even prolonged ones. The data in favor of this view include the fact that the risk of subsequent epilepsy is highest in those with focal seizures or prior neurologic abnormality.[8,10,17a,90,108,139a,163,164] The risk of epilepsy is also high in those with four or more febrile seizures even if they are brief.[10] This population tends to have a high incidence of generalized spike-and-wave abnormalities on the electroencephalogram (EEG) when older, pointing again to probable genetic causes.[42,139a,161] Finally, in the study of Annegers et al.,[10] which provided the longest follow-up, those with generalized status developed a generalized seizure disorder, whereas those with focal status developed a focal disorder, which is what one would expect if the prolonged febrile seizure were a marker for subsequent epilepsy.[10] By contrast, if one proposed a causal relationship between status per se and later epilepsy, then one would expect a high rate of focal seizure disorders regardless of whether the initial episode of status was generalized or focal.

In reviewing the data from retrospective series of epilepsy surgery candidates,[1,19,23,24,25,32,52,53,58,84,86,87,88,89] one must keep in mind that these are highly selected patient groups. Many of these patients had complex febrile seizures or at least seizures associated with fever, but few actually had status epilepticus. It is often very unclear whether they truly had febrile seizures or if seizures were associated with fever in patients who may have had an acute brain insult such as encephalitis or in patients with a preexisting epilepsy. Atypical febrile seizures of the latter type have been associated with a worse prognosis for remission[18,138,141] but should not be confused with febrile seizures. If febrile seizures are simply a marker for seizure susceptibility, then quite possibly those most susceptible will experience more frequent and/or more prolonged febrile seizures.[139a] Note that complex febrile seizures in general and very prolonged febrile seizures in particular are much more common in children who are already neurologically abnormal and are most likely to be focal, suggesting prior focal pathology.[10,28,47,108,163,164] Current prospective studies on the long-term outcomes of febrile SE with an emphasis on the development of mesial temporal sclerosis and epilepsy will provide the answer to these questions, but given the long latency, it will be some time before the precise relationships between

febrile SE and subsequent epilepsy are defined (see Chapter 63).

Epilepsy Following Acute Symptomatic Status Epilepticus

A proportion of patients with acute symptomatic status epilepticus develop a seizure disorder at some time in the future. This proportion varies and is a function of the severity of the underlying insult. In most cases it is on the order of 15% to 30%. However, the seizure disorder may not develop for several years.[9,68,71,156] There are few data that support prophylactic antiepileptic drug (AED) treatment to prevent the subsequent development of epilepsy in acute symptomatic seizures.[56,104,137,156] There is some evidence that acute symptomatic seizures, including status epilepticus, are associated with an increased risk of subsequent epilepsy in patients with acute CNS injury. However, it is unclear whether patients with acute symptomatic status epilepticus have a higher risk than other patients with briefer acute symptomatic seizures.[66,67,70,71] The majority of patients with acute symptomatic or febrile status epilepticus do not have unprovoked seizures later, even with long follow-up periods.[8,10,56,66,67,68,90,108,156,163,164]

Recurrent Status Epilepticus

Although not clearly a sequela of status epilepticus, the issue of recurrent status is best dealt with in this chapter because it is closely related to the issue of status epilepticus and subsequent seizures. Most of the available data in this regard are in pediatric series, which are discussed first. Pediatric studies report that 11% to 25% of children with status epilepticus experience at least two episodes.[3,43,46,92,140] These studies included both prospective and retrospective cases. Shinnar et al.[140] followed 95 children from the time of their first episode of status. Sixteen children (17%) experienced recurrent status, including 5 with three or more episodes. All but 2 of the 16 had prior neurologic abnormalities. The risk of recurrent status epilepticus in the remote symptomatic and progressive encephalopathy group was almost 50%, compared with only 3% in children who were otherwise neurologically normal. The neurologically abnormal group constituted 32 (34%) of the 95 children, but they accounted for 14 of 16 (88%) of children with recurrent status epilepticus and all 5 children with three or more episodes of status epilepticus.

It is of interest that the increased risk of recurrent status epilepticus for neurologically abnormal children was present not only in the remote symptomatic and progressive encephalopathy group, but also in the febrile[92,140] and acute symptomatic group. Driscoll et al.[43] reported similar findings in a retrospective review. Thus, it would appear that the risk of recurrent status epilepticus is primarily in children with preexisting neurologic abnormalities. This is also the population that is at higher risk for developing seizures[14,68,71,109] and status epilepticus in the first place.[3,36,40,45,46,64,67,92,166,171] These data support the notion that status epilepticus is primarily a marker for an abnormal or injured brain destined to be epileptic rather than the cause of an injury sufficient to produce an epileptic condition. In adults there is one study with similar conclusions.[13]

More recently, there is an accumulation of data that suggest that there is a subgroup of children with a predisposition to prolonged seizures.[17,18a,18b,31a,139,143,143a,146a] These children are not necessarily at risk for frequent or intractable seizures, but are at increased risk for prolonged seizures. The evidence comes from several studies. In children with febrile seizures, an initial prolonged febrile seizure is not associated with an increased risk of recurrent febrile seizures. However, if another febrile seizure does occur, it is likely to be prolonged.[17] Similarly, in children with a first unprovoked seizure who are neurologically normal, a prolonged first seizure including status does not increase the risk of recurrence, but if a recurrence does occur, it is likely to be prolonged.[139,143,143a] In the Finnish childhood onset epilepsy cohort, the majority of cases of status occurred early in the disorder. If status did occur, there was a high likelihood of recurrent status. However, if there was no episode of status in the first few years of the disorder, then status did not occur even if there was a continuing active seizure disorder for many years.[146a] In the Connecticut study, the majority of cases of status also occurred early, but there were more late cases.[18a,18b] Finally, genetic studies of twins have shown that, if one twin has status, there is an increased risk of not just seizures, but also status in identical but not fraternal twins.[31a]

Status Epilepticus and Mesial Temporal Sclerosis

The pathological entity of mesial temporal sclerosis is described in detail in Chapter 13. In this section we review the data regarding whether MTS is a sequela of status epilepticus, particularly in early childhood (see also Chapter 65).

Falconer et al. described the pathologic findings in temporal lobes obtained from 100 patients with intractable temporal lobe epilepsy.[53] Forty-seven percent had mesial temporal sclerosis, varying from loss of cells in Sommer (H1) sector of the hippocampus to more widespread involvement of the temporal lobe. Of those with MTS, 40% had a history of prolonged convulsions in infancy. The major controversy regarding mesial temporal sclerosis is whether it is a sequela of status epilepticus, particularly of prolonged febrile seizures in early life or due to some other cause.[128] We review the data for and against the hypothesis that MTS is a sequela of status.

In favor of this hypothesis are the elegant experiments in adult animals that have produced MTS with a variety of models of status including kainic acid, pilocarpine, and fluorothyl.[21,83,95,96,97,102,103,105,150,151,152] Meldrum et al. showed that in the adult monkey, even if one paralyzes the animal and adequately ventilates and oxygenates it, neuronal changes occur as a sequela of status.[95,96,97] Such changes are readily produced in the adult rat as well.[21,83,102,103,105,150,151,152]

In patients with refractory complex partial seizures who undergo epilepsy surgery and are found to have mesial temporal sclerosis, a substantial number have a history of complex febrile seizures in early life, although, as discussed previously, not necessarily of status epilepticus.[1,19,24,25,32,51,52,53,58,84,89,172]

A number of imaging studies found cerebral edema acutely, and atrophy chronically, after convulsive or nonconvulsive status epilepticus,[30,77,78] but others did not.[129] One 5-year-old patient had a normal brain MRI before and atrophy after nonconvulsive status epilepticus,[119] and neuronal loss was found at autopsy in areas that became atrophic after his bout of status epilepticus.[113] Focal atrophy has been reported to develop in areas of intense seizure activity,[57,100,101] supporting a mechanistic explanation. However, the problem with these studies is that although they establish that sequelae can occur, they do not give any sense of how common the event is.[136]

Although this view of a causal relationship between prolonged seizures in early childhood and subsequent MTS has become entrenched in the literature, there is a large body of data that do not support this view. The animal and clinical data simply do not match in this regard. The clinical

data from adults evaluated for epilepsy surgery suggest that MTS is associated with an insult or seizure onset in early childhood but not in adult life.[1,12,24,25,58,85,86,87,88,89] The animal data indicate that although the immature CNS is more susceptible to seizures in general and status epilepticus in particular, it is far more resistant to its sequelae.[6,21,27,33,65,73,74,75,83,102,103,105,112,116,150,151,152,167,168] In many, although not all, animal models of status, rat pups who experience an episode of status do not develop MTS. This is true in a variety of models, including kainic acid, pilocarpine, flurothyl, and kindling.[102,103,104,105,150,151,152] Reversible hippocampal injury has been shown in the infant rat using the kainic acid model.[27] Based on the use of Timm staining, aberrant reinnervation has been demonstrated following status in the adult rat, but it only occurs in some models in the rat pup.[133,134,150,151,152] Rat pups that experience kainate status and are allowed to reach adulthood have the same seizure threshold as control adult animals using the kindling model,[116] but in other models, after status epilepticus at P15, a majority of animals show spontaneous recurrent seizures.[153]

The pathologic data show that MTS is often associated with developmental abnormalities such as migration defects, suggesting that there is preexisting pathology.[12,80,86,87,93] The association of MTS with brain tumors of the adjacent temporal lobe, particularly when these tumors are adjacent to the hippocampus, also points to preexisting pathology as a frequent correlate of MTS.[12,89] Using autopsy material of patients who died following an episode of status epilepticus is problematic because these are extreme cases, which do not necessarily represent the effects of status per se, which has a low mortality, but rather probably represent the results of acute brain injuries associated with status epilepticus.[55,94,149,172]

The clinical data are also problematic. MTS is most common in cases with childhood onset. However, MTS is not diagnosed in childhood but many years later. In fact, documentation of MTS under age 6 years is uncommon.[44,110] Whether this is because MTS occurs later in the course of the epilepsy or is simply due to lack of early diagnosis is unclear. Recent data indicate that mesial temporal sclerosis, similar to that found in adults, can be seen in children with intractable mesial temporal lobe epilepsy.[88]

Radiologic evidence of hippocampal damage is reported primarily in adults. An example is a paper in which five adults with status had magnetic resonance imaging with fast spin echo techniques demonstrating reversible abnormal hyperintensity and swelling of the hippocampus and amygdala.[159] Two of these patients subsequently had evidence of hippocampal atrophy. In children, the data are sparse. One case report of a very young child with status epilepticus followed by MTS has been reported.[114] The child was neurologically abnormal previously, had focal status suggesting focal pathology, and had almost no latent period between the status and the intractable seizures. Although this case is interesting in demonstrating that MTS can occur early in life, it is hardly a demonstration of the proposed paradigm of a prolonged seizure followed by a silent interval and then complex partial seizures. In fact, most childhood intractable epilepsy is extratemporal.[44,104,110] Although temporal lobe epilepsy does occur in children and can be associated with MTS, other etiologies such as cortical dysplasia and developmental tumors are more common.[44,63,170] Status epilepticus is actually much more common in frontal lobe epilepsy and in Lennox-Gastaut syndrome, neither of which is associated with MTS. The clinical data regarding the association of prolonged febrile seizures and subsequent MTS or temporal lobe epilepsy were discussed previously.

More recently a number of case reports and series have shown that febrile SE can cause increased T2 signal in the hippocampus, which in some cases is associated with subsequent hippocampal volume loss.[80a,80b,101,144,162] Some of those radiologic findings were confirmed at autopsy.[113] Recent animal data from rats with hyperthermic seizures have also indicated increased T2 signal,[43a] although in that model it was not associated with cell death. Thus, it is now clear that febrile status epilepticus can lead to hippocampal atrophy, although the frequency with which this occurs and the required seizure duration are unclear.[135a,136] For a detailed review of this important topic see Chapter 63.

Mathern et al. have tried to document the relationship between mesial temporal sclerosis and various preceding insults.[84,85,86,87,88,89] They found that an injury prior to age 5 years, whether or not associated with a seizure, was most likely to be associated with MTS. Those with MTS were most likely to have initial precipitating injuries, including trauma and encephalitis. In addition, severe hippocampal neuronal losses (hippocampal sclerosis) were often associated with mesial temporal lesions or masses adjacent to the body of the hippocampus.[89] Longer durations of temporal lobe epilepsy were associated with some secondary neuron losses. The data "support the hypothesis that the etiology of hippocampal sclerosis is an acquired injury to the hippocampus and that the pathogenesis is a combination of acute, subacute, and progressive changes following the initial injury."[86] Note that the initial injury need not necessarily be a seizure.

The entire field is being rewritten as newer studies with better imaging techniques are leading to a better understanding of the relationship of very prolonged febrile seizures and subsequent MTS. For a better discussion, see Chapter 63.

Other Pathologic Sequelae of Status Epilepticus

In postmortem examinations of five children who died after status epilepticus associated with a febrile illness, Fowler described neuronal necrosis in the cerebral cortex, basal ganglia, and cerebellum.[55] The exact etiology of these seizures, which lasted from 1 to 6 hours, is unclear, although the children were febrile. Similar findings were described in several other reports.[94,149] Of particular interest is the case of a 20-year-old who died following prolonged focal status epilepticus associated with fever and had unilateral pathology.[149] It is unclear whether the pathologic changes were due to hypoxia as suggested by Fowler, to the underlying brain insult, or to the status epilepticus. Cell loss in the cerebellum has also been described in patients with long-standing seizure disorders even without a history of status epilepticus.[12] Brain damage is often seen in children or adults who died from SE,[32] although the complexity of clinical situations usually makes it very difficult to tell whether damage resulted from the seizures themselves or from medical complications such as hypoxia or hypotension. DeGiorgio et al.[34] found decreased hippocampal neuronal densities in five patients who died after complex partial status epilepticus. Given the overall low morbidity and mortality of SE per se, it is difficult to extrapolate from these postmortem findings to those who survive an episode of SE, particularly when it is not associated with an acute neurologic insult.

What Further Studies are Needed

Further studies are needed in several areas. Prospective long-term follow-up studies after episodes of status epilepticus are needed to determine whether status epilepticus is associated with subsequent mesial temporal sclerosis and, if so, how often

this occurs. These studies should take into account differences in etiology and age that may affect outcome. Given the recent association of mesial temporal sclerosis with migration defects, studies are needed on whether preexisting brain abnormality or injury makes the brain more susceptible not only to developing status epilepticus, but also to sustaining damage as a result. Modern imaging techniques should also allow for better studies of pathologic changes associated with status epilepticus in humans as well as in animal models. Animal and human studies are also needed on ways to not just stop the seizures, but also to prevent the damage. The role of *N*-methyl-D-aspartate antagonists and other agents that may prevent secondary neuronal damage following brain injury is being evaluated in animals but not yet in humans.

Summary and Conclusions

The morbidity and mortality of status epilepticus have declined significantly in the last two decades. In the absence of an acute or progressive CNS insult, the morbidity and mortality of status epilepticus are low, particularly in children. Long-term sequelae are also difficult to document in the absence of an acute associated neurologic insult. Motor and cognitive sequelae, although they may occur, are rare. The epidemiologic data do not support the idea that status epilepticus is necessarily associated with a subsequent chronic seizure disorder. Status epilepticus is most common in young children. However, although the immature brain is more prone to develop status epilepticus, both human and animal data suggest that it is more resistant to its adverse sequelae.

Textbook definitions of status epilepticus that imply that it is always associated with subsequent chronic epilepsy need to be revised. The relationship between status epilepticus and mesial temporal sclerosis also needs further study. Defining the precise role of status epilepticus in human epileptogenesis requires further research.

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Chapter 66

Introduction to the Epilepsies

Anne T. Berg

Introduction

> This alleged divine character is only a shelter for ignorance and fraudulent practice…. Epilepsy is not more divine than other diseases are. Like all diseases, it is hereditary; its cause lies in the brain, a brain over-flowing with the superfluity of phlegm. When the phlegm rushes into the blood vessels of the body it causes all the symptoms of the attack. (Hippocrates, ~400 BCE[51])

More than 2000 years ago, epilepsy was recognized as a physical disease arising in the brain. Despite the enlightened approach reflected by the Hippocratic authors, the prevailing views about epilepsy were that it was due to supernatural forces—demonic possession or divine retribution. Some held that epilepsy was contagious. These attitudes largely account for the tremendous stigma associated with epilepsy, a stigma that still lingers to a greater or lesser extent.

The establishment in the mid- to late 1800s of specialized centers for the care and treatment of "epileptics" represented a shift from the highly stigmatized views of epilepsy as due to evil, supernatural forces to one in which epilepsy was regarded as a medical disorder. With the concentration of people with epilepsy in these specialized centers, early neurologists began to describe epilepsy from the medical perspective. This led to the characterization and long-held belief that epilepsy was a uniformly progressive, nonremitting disorder. Sir William Gowers wrote one of the most famous and influential dissertations on epilepsy, in which he said, "The tendency of the disease is toward self-perpetuation; each attack facilitates the occurrence of another by increasing the instability of the nerve elements…. The spontaneous cessation of the disease is an event too rare to be reasonably anticipated."[28] Since then, our understanding of how to study the natural history of a disorder and of epilepsy in particular has developed. This has been in large part due to conceptual and methodological contributions from two very different areas—epidemiology and "syndromology."

Epidemiology

The first development to be described here was greatly facilitated by the advent of modern epidemiologic and statistical principles and techniques and their application to the study of epilepsy in the overall population. This helped to lead to the recognition that findings based on the most severely affected patients seen in tertiary referral centers were of limited value in treating and counseling the vast majority of patients in the population, whose epilepsy was often mild enough not to require treatment at such centers. In other words, the earlier observations suffered from multiple and severe forms of bias.[49] The early epidemiologic efforts were largely due to Mayo Clinic investigators led by Leonard Kurland and later by W. Allen Hauser and J. Fred Annegers.[30,31,39] The epidemiologic approach cast a broad net and provided invaluable information about the frequency, risk factors, and overall outcomes in the population at large.[1,2,3,6,7]

The early epidemiologic studies yielded valuable information about the prognosis of epilepsy. They provided an overview by providing an understanding at the population level of the frequency of epilepsy, the distribution by age at onset and gender, and an assessment of the various factors that cause it. In general, however, epilepsy itself was treated as relatively undifferentiated disorder. Although the epidemiologic studies identified some broad categories with important prognostic significance (e.g., presence of an underlying symptomatic factor likely responsible for the epilepsy, the age at onset, and whether the seizures were of generalized or focal onset), these were viewed as factors that modified a single disorder much as height and weight can vary among members of a single species.

Syndromology

The other major development that occurred was the recognition that epilepsy, much like cancer, was not a single disorder but a term used for a wide range of disorders. The endeavors in this area have been and still are at the heart of efforts to identify and investigate individual forms of epilepsy, often called syndromes. This movement has largely come from the European schools of pediatric neurology. Among these the French investigators have been the most prolific and productive, with many notable and important contributions coming from German, Italian, and Japanese investigators as well. Efforts to apply this approach to adult-onset epilepsy are hindered perhaps by the relative lack of distinctive diversity within these forms of epilepsy.

The concept of an epilepsy syndrome was defined in 1985 as "an epileptic disorder characterized by a cluster of signs or symptoms customarily occurring together. The signs and symptoms may be clinical or findings detected by ancillary studies. In contradistinction to a disease, a syndrome does not necessarily have a common etiology or prognosis. Some epileptic syndromes are, however, of great prognostic importance."[18] An updated definition was provided recently: "A complex of signs and symptoms that define a unique epileptic condition."[25]

Contrary to the epidemiologic approach, individual forms of epilepsy, from this vantage point, represent complete, integrated disorders. Epilepsy is not a single disorder with a variation in prognosis statistically defined based on circumstances and risk. Traditionally, the epidemiologic approach would require an individual to have had at least two unprovoked seizures on separate days for the condition to qualify for the label of epilepsy.[20] From the syndromic perspective, it is not clear why it is necessary to withhold the diagnosis of the epileptic disorder in someone who, for example, has had a

single unprovoked seizure and whose underlying disorder can be clearly identified or in a child who presents with febrile status epilepticus and is shown to have a functional SCN1A gene mutation. In fact, to the extent that early identification of the nature of the disorder influences choice of treatment and management options, and to the extent that the correct choice may lead to better outcomes, it seems it would be irresponsible to insist on waiting for two unprovoked seizures to diagnosis and treat the underlying epileptic disorder.

With a syndromic approach, a disorder such as febrile seizures, which, for good practical reasons, has been distinguished from epilepsy proper,[6,21,41,42,43] might reasonably be reintegrated into the spectrum of epilepsy. The same might be said of benign nonfamilial neonatal seizures. In doing this, however, the older notion of epilepsy as a uniformly nonremitting, progressive disorder must be abandoned and the very broad spectrum of manifestations, duration, outcomes, and consequences of the wide variety of epilepsies acknowledged. In particular, without denying or forgetting the severe end of the epilepsy spectrum, we need a widespread recognition that, at least from the perspective of seizure control, many forms of epilepsy are actually quite mild, easily treated, often resolve on their own, and are associated with minimal consequences.

Concepts in classifying seizures and epilepsies

In the 1989 proposal for the classification of the epilepsies, two key axes were identified, one for generalized versus localization-related conditions and another for etiology (idiopathic, symptomatic, and cryptogenic).[19] Currently, these are well-accepted terms for organizing syndromes and epilepsies.

Generalized Versus Localization-Related Conditions

These concepts are used in relation to both seizures and types and syndromes of epilepsy. In relation to seizures, "generalized" has traditionally meant that both cerebral hemispheres are involved simultaneously and symmetrically during the actual seizures. By contrast, "localization related" (sometimes "partial" or "focal") indicates that the activity arises from a more discrete, lateralized region, usually in the cortex, regardless of later spread (see Chapter 43).

As applied to syndromes, these terms have been used in essentially the same manner, with the syndrome type being classified based on its predominant seizure types. Although this dichotomy is convenient, it obscures important gradations between the two extremes—generalized and partial.

The prototype for a generalized syndrome is childhood absence epilepsy. The syndrome is characterized by a typical age of onset of between 4 and 10 years, peaking around 5 to 6 years, with a preponderance of girls relative to boys. The hallmark absence seizure is accompanied by a highly recognizable bilaterally symmetric, 3-Hz spike and wave discharge with symmetric bilateral onset and offset. This is the description according to leading reference books.[46,48] In fact, our current understanding of generalized absence seizures is that they involve thalamocortical networks with projections predominantly involving the frontal lobes. Thus, the term “generalized” does not preclude the involvement of regional or even of relatively discrete, “focal” mechanisms or structures, including subcortical structures, such as the reticular nucleus of the thalamus. In fact, although the ideal is still that recognizable onset be bilateral and symmetric, there is likely a considerable variation in the extent to which this bilateral symmetry is expressed, and discernible asymmetric onset on the electroencephalogram (EEG) is not at all uncommon.[46]

The term “generalized” is also used in reference to a group of often difficult forms of epilepsy largely restricted to onset during infancy and early childhood. Disorders such as West and Lennox-Gastaut syndromes are among the better known. Although these disorders are characterized by “generalized” seizures, they can be associated with focal and multifocal pathology. Multifocality seen in the EEG tracing is not uncommon, and partial or focal onset seizures may occur. The application of the concept “generalized” to these syndromes is quite different from that to the idiopathic generalized epilepsies. It might ultimately be more useful to think of these in terms of diffuse or multifocal disorders and abandon a label that linguistically implies a similarity or relationship to the idiopathic generalized epilepsies.

Crossing over to the more focal side of the spectrum, there are syndromes such as benign rolandic epilepsy (BRE) and autosomal-dominant nocturnal frontal lobe epilepsy (ADNFLE), which involve more discrete and predictable areas of the cortex. For a given patient, at least in BRE, the activity observed on the EEG might alternate between left and right sides.[46] For such syndromes the term “localization related” seems particularly apt because the epileptic disturbance is functionally linked to a location or region. This is in contrast to epilepsies linked to a discrete structural lesion. In these latter instances, the term “focal” might be more precise.

Even within the nonidiopathic focal epilepsies, however, there is probably little that the condition is strictly focal. Mesial temporal lobe epilepsy, the most common form of epilepsy treated with surgical resection, might be considered the ideal focal epilepsy. Yet, our best understanding is that complex and extensive limbic networks are involved in this form of epilepsy.

The 1989 classification of the epilepsies includes a category for “undetermined.” This contains two distinct subcategories. The first is for syndromes in which both focal and generalized features occur. Some of the better-known disorders in this category are Landau-Kleffner syndrome and Dravet syndrome.[48] As the generalized versus partial dichotomy is relaxed, it may ultimately be more reasonable to incorporate these syndromes within that spectrum rather than keep them apart. For example, the characteristic generalized EEG features, myoclonic seizures, and the generalized tonic–clonic seizures seen in Dravet syndrome might suggest that it fits in well with the concept of generalized/diffuse epilepsies. The focal features associated with this syndrome (e.g., focal febrile status epilepticus) would not preclude such a designation. The localization-related nature of Landau-Kleffner syndrome and apparent similarities between it and benign rolandic epilepsy invite speculation and, more important, investigation into commonalities between these nonlesional functional forms of epilepsies.

Use of the second subcategory under the label of “undetermined” reflects a diagnosis of ignorance, and by and large is intended for unclassified forms of epilepsy. It is important, however, to distinguish between someone who has been appropriately and competently evaluated and for whom it is unclear whether the seizures and underlying epilepsy represent a generalized versus a more localized process and the case in which information is simply missing. For example, someone who has one or more generalized tonic–clonic seizures without evidence of partial onset (seizures were reasonably well witnessed, post-ictal state is well described, etc.) and had a normal or uninformative EEG and a normal magnetic resonance imaging (MRI) study can reasonably be diagnosed as having an undetermined form of epilepsy without clear generalized or focal signs. By contrast, the patient who never had so much as an EEG and whose seizure description is obtained from a notation by a general practitioner in the medical records has been inadequately evaluated for the purposes of accurate diagnosis of his or her type of epilepsy.

Etiology: Idiopathic, Symptomatic, and Cryptogenic

The early epidemiologic studies defined the term "remote symptomatic" to be used in reference to epilepsy that occurred in the presence of a preceding but remote (not acute) insult or condition, the occurrence of which had been demonstrated to be associated with an increased risk of epilepsy.[31] In fact, Gowers's writing reflects an awareness of these distinctions.[28] The list of potential conditions and insults is always subject to modification as knowledge changes. Some of the more salient factors include stroke, head trauma, intracranial infections, and what at the time were termed "congenital disorders." This group contains individuals with cerebral palsy and mental retardation but in whom no specific causative agent has been identified. An updated list was provided in 2001.[25]

The early epidemiologic studies also used the term idiopathic to mean "not remote symptomatic." The classification of the epilepsies, however, identified and reserved this term to be used specifically for well-characterized forms of epilepsy, primarily occurring in childhood and adolescence, and believed—although often not demonstrated—to have a genetic basis.[19] This distinction was later adopted by the International League Against Epilepsy (ILAE) Commission on Epidemiological Standards in Epilepsy.[20] The term "idiopathic" comes from the Greek and means sui generis, and refers to a disorder arising from itself in the sense that the seizures represent the direct and primary manifestations of the disorder. "Idiopathic" has often been inappropriately equated with the concept of benign, perhaps because, relative to epilepsy secondary to a remote symptomatic cause, seizures are typically well controlled and other outcomes are relatively good.

Finally, the term "cryptogenic" has had a contentious history. The Commission on Classification and Terminology in 1989 used it to mean "probably symptomatic."[19] The basis for the "probably" was not elaborated on and left the supposition up to individual variability in interpretation. When it adopted the Classification and Terminology Commission's definition of "idiopathic," the 1993 Commission for Guidelines for Epidemiological Studies defined cryptogenic neutrally as meaning "nature or cause unknown."[20] It was used in cases in which the epilepsy did not clearly fit the criteria of a defined idiopathic condition and there was no evidence (by exam or history) of a remote symptomatic cause. The use of the term reflects an absence of knowledge and relative uncertainty regarding the nature of the epilepsy. This is important to bear in mind because there have recently been several "idiopathic" syndromes identified from among epilepsies that were previously called "cryptogenic." These include Panayiotopoulos syndrome and autosomal-dominant nocturnal frontal lobe epilepsy. Whether the term cryptogenic is used or a separate term is coined, a label is needed to identify those individuals for which the nature of the underlying cause of their epilepsy is truly unknown. It may be symptomatic or it may be idiopathic.

Updated Understandings of Etiology

The terms symptomatic, idiopathic, and cryptogenic have been particularly meaningful and useful for both research and clinical purposes; however, the distinctions they represent are increasingly more complex. At this juncture, there is debate over whether the words should be retained but with modified meanings or whether new terminology, free from the baggage of the old, should be introduced. Several issues need to be considered, as follows.

Idiopathic Versus Symptomatic

The distinction between idiopathic and symptomatic is increasingly difficult to justify. In reality, all epilepsy is symptomatic of something, and idiopathic epilepsies have causes and consequences too. Mounting evidence demonstrates that idiopathic epilepsies as well as epilepsies that are considered cryptogenic are associated with a number of other neurologic disorders and that these other disorders precede the onset of seizures. Factors associated with new-onset epilepsy include behavioral disorders,[9,45] school problems,[13] attention deficit disorder,[33] and psychiatric disorders.[34,35,37] These findings suggest that whatever are the underlying mechanisms involved in idiopathic and cryptogenic epilepsies, they are not limited just to causing seizures. Thus the original meaning of the term idiopathic as "sui generis" really does not seem to be strictly applicable to any form of epilepsy. As we relax the association between idiopathic and benign, it seems reasonable to consider that some rather severe forms of epilepsy such as Dravet syndrome might best be thought of in terms of "idiopathic." In fact, Doose syndrome, as it was initially conceived, was considered a form of idiopathic generalized epilepsy. The 1989 classification moved it to the group of cryptogenic or symptomatic generalized syndromes. Now it is again being associated with the idiopathic generalized syndromes. Ultimately, as knowledge develops, epilepsies may be identified according to their fundamental mechanisms and not surface impressions or increasingly outmoded concepts.

Diversity Within Remote Symptomatic Causes

The initial distinction between remote symptomatic (predisposing abnormality clearly present prior to the onset of seizures) and idiopathic/cryptogenic is of tremendous significance, convenience, and value for clinical research purposes as well as for clinical decision making, especially early in the course of the disorder. It invites a certain degree of complacency especially in epidemiologic (both population-based and clinical) studies, however, in that it groups together forms of epilepsy that likely have very different underlying mechanisms. As with the "idiopathic" epilepsies, a future classification may better reflect fundamental mechanisms rather then convenient but broad categories.

Risk Factor Versus Cause

The link between a risk factor (a potential symptomatic cause) and epilepsy is almost always based on statistical knowledge of the association and not necessarily a demonstration of cause and effect through specific mechanisms in any specific instance. There is always the possibility that someone would have developed epilepsy even had he or she not had a particular predisposing condition or insult. When the risk is greatly increased in the presence of the risk factor, we generally accept a causal interpretation. For example, the relative risk of epilepsy associated with cerebral palsy is on the order of 30.[8] From that, we can calculate that the attributable risk (the increase in risk above background) is about 97%. This would mean that, of 100 individuals with cerebral palsy and epilepsy, about 3 of them would have had epilepsy regardless of the cerebral palsy and 97 have epilepsy secondary to the factors that caused the cerebral palsy in the first place. When the association between a risk factor and epilepsy is much weaker, it is less clear how to handle assessment of etiology. For example, mild head trauma is associated with a relative risk of epilepsy of 3.1 within the first year after the injury.[3] This indicates that about 32% of individuals who developed epilepsy within a year of experiencing a mild head trauma would have developed epilepsy regardless of the head trauma and about 68% developed it in (presumed causal) association with the head trauma. We cannot necessarily

distinguish cases attributable to the trauma from those not attributable to it. This information is valuable on a population level, it can sometimes be useful for public health purposes, and it identifies groups appropriate for intervention studies. It does not provide precise information at the individual level because in assigning mild head trauma as the cause of epilepsy, one would be wrong about one in three times.

Competing Causes

Causes do not have to be mutually exclusive. It is not unheard of for a child with mild retardation or who has a neurocutaneous syndrome (both considered symptomatic risk factors for epilepsy) to have a form of idiopathic generalized epilepsy. Whether the symptomatic cause further contributes to the expression of seizures (e.g., lowers the threshold for expression of the trait) or whether it might in any way modify the presentation or course of the disorder is generally not known. In fact, it may be the cause of a second and relatively independent form of epilepsy in a single individual. Exclusion of such complicated or ambiguous cases is common so as to keep the phenotype pool as clean as possible. However, adherence to rigorous definitions necessary for research may discourage certain interesting questions from being addressed.

Epileptic Encephalopathies

The concept of epileptic encephalopathies is intuitively appealing and seems to encompass a difficult group of epilepsies largely occurring in infancy and early childhood. Epileptic encephalopathies are forms of epilepsy in which it is believed that, as a result of interactions between the seizures, perhaps their underlying causes, and the ontogenetic backdrop of the developing brain, irrevocable alternations in brain development and brain function occur.[24] Children with these disorders usually develop signs of diffuse and severe neurologic compromise such as autism and mental retardation. A direct demonstration of the mechanisms by which epileptic encephalopathies realize their effects on the brain has yet to be made. Our ability to determine whether an infant is truly neurologically intact before the onset of seizures is impaired by the infant's limited behavioral repertoire relevant to assessing the integrity of later higher cortical and particularly intellectual functioning. Thus, we simply do not know whether the roots of the resulting mental retardation, autism, and other behavioral disorders observed later predated the onset of seizures or were the result of them or factors related to the seizures. Nonetheless, the label of epileptic encephalopathy meaningfully identifies and seems to describe an inherent aspect of disorders such as West, Lennox-Gastaut, Landau-Kleffner, and Dravet syndromes among others. Of note, many children with these disorders do not have a remote symptomatic cause. Dravet syndrome has been closely linked to mutations in several genes but particularly the gene coding for the SCN1A subunit of the sodium channel, thus raising the possibility that it might be reasonably construed as representing the dark end of the idiopathic spectrum.[26,38]

Landau-Kleffner syndrome typically has no identifiable symptomatic cause. Again, the similarities it can occasionally seem to share with benign rolandic epilepsy raise questions about whether it too may represent the more severe end of an idiopathic localization-related spectrum.[22] At this point, it would be more satisfying and useful to classify with greater precision the underlying causes and mechanisms rather than rely on broad and increasingly less meaningful category names such as “idiopathic."

Practical Gray Areas in Classifying Etiology

How does one classify the etiology in a patient who does not have a clear remote symptomatic cause when nonetheless one just “knows” the epilepsy is “symptomatic.” From the perspective of scientific research, definitions must be respected, and a clear a priori approach to such situations is needed. On the other hand, rigid adherence to the notion that the etiology is cryptogenic if a hard symptomatic cause or sign is not demonstrated can diminish the value and the credibility of the research. Neither of these last two statements should be taken as a justification to do whatever seems convenient, but rather they should be used together to balance the need for rigorous research standards with common sense. From the clinical perspective, not all of medical practice is based on scientific evidence. Where that evidence is missing or inadequate, experience and intuition must take over. It is such areas that are fertile grounds for future research.

Classification: Technology, natural history, and selection

Identification and classification of any of these aspects of seizures or epilepsy depend on adequate information and knowledge. In the ideal world, an individual would be thoroughly and accurately diagnosed right from onset. In reality, this is not always feasible for a number of reasons, some having to do with availability of technology, some having to do with the natural history of the disorder, and, related to that, some reflecting appropriateness in using medical care and procedures.

Technology

The concept of unknown cause depends on the adequacy of the evaluation and our understanding of causes. Early epidemiologic studies included patients who were evaluated before the advent of the computed tomography (CT) scan, let alone MRI. Video EEG technology was not available, nor were functional imaging techniques. Today, studies are done in developing countries in which routine access to such evaluations is not possible. Patients evaluated in such settings and who otherwise appear normal on exam and have no history of a remote symptomatic cause might be considered to have epilepsy of unknown (cryptogenic) nature or cause. In fact, some, perhaps many, of such individuals, had they been adequately evaluated, would have been shown to have demonstrable brain lesions likely contributing to their predisposition to seizures. The adequacy of evaluation is a moving target, however. In 10 to 20 years, current technology will be outmoded, and similar caveats will be leveled at studies done today.

Natural History and Related Factors

Clear, precise observations from the patient or other observer are key to accurate diagnosis, particularly for determining the seizure semiology. Such information may not always be readily available at initial presentation. For example, in one community-based cohort study of children, 11.6% of patients were considered unclassified at initial diagnosis (typically they had normal EEGs and only partially observed tonic–clonic seizure). Two years later, about one third of those whose form of epilepsy was initially unclassified received more precise diagnoses, largely because of new information from subsequent EEGs and more detailed descriptions of subsequent seizures.[12] Some of the newly appearing EEG abnormalities may reflect developmental changes in expression of the underlying epileptic traits, variation in quality and thoroughness of the EEGs, or variation in sampling the EEG tracing.

Certain forms of epilepsy may be particularly difficult to identify at the outset. This appears to be the case with mesial temporal lobe epilepsy (MTLE). In adult surgical groups, the majority of cases have onset during childhood and adolescence. Mesial temporal sclerosis (MTS) is rarely seen in either newly diagnosed children[15,23] or adults[29,50] but appears to develop over time. Although typically considered a form of symptomatic epilepsy, it is unclear how the initial epilepsy can be symptomatic of a lesion that has yet to develop, at least as best as can be visually determined. Whether a vicious (progressive) cycle ensues is unknown. As with idiopathic epilepsies, MTLE with MTS is certainly symptomatic of something, but the best characterization of exactly what remains elusive. For example, the APOE-4 allele is well established as a factor increasing the susceptibility to Alzheimer disease.[27] It also modifies the progression of mild cognitive impairment to Alzheimer disease[47] and modifies the risk and age of onset of Parkinson disease.[40] A full listing of the association with APOE-4 is beyond the scope of this chapter. A recent report, however, linked the presence of the APOE-4 allele to younger age at presentation of MTLE.[16] Overall, these observations invite speculation that more basic host mechanisms not specific to epilepsy proper might play an important role in the natural history of this and possibly other disorders.

Selection Factors

We often know far more about those who do poorly than about those who do well. For those who have multiple seizures, seizure descriptions are more detailed and likely more accurate. Witnesses learn what to look for and how to report that information. For the patient who has only a few seizures, the information is, by comparison, rather thin and can often be of doubtful accuracy. The initial (and maybe only) seizures also create an emotionally charged situation for the witness and may affect accuracy of reporting. Medical evaluations are also not uniformly performed on all patients. Although a several-day in-hospital video monitoring EEG might seem ideal for diagnosing everyone right from initial presentation, it is not feasible for two primary reasons. First, it is prohibitively expensive and simply not justified at the initial presentation. Second, the differential yield over a standard EEG is likely to be minimal. Many newly diagnosed patients may have no detectable EEG abnormalities, and most would probably not have a seizure during monitoring. This unevenness in the quality and extent of information can severely limit our ability to study the natural history of different forms of epilepsy. If certain forms of epilepsy can only be identified when they become intractable (e.g., MTLE), then only intractable forms of that epilepsy are ever recognized and that epilepsy then becomes known as a uniformly intractable disorder. Identifying only those instances of the disorder that become intractable might place serious constraints on studying and ultimately understanding the mechanisms behind intractability.

Purpose and Use of a Classification of the Epilepsies

The quality and value of the syndromic work are evident in the worldwide acceptance and use of this approach. Syndromic diagnoses are incorporated into clinical practice, they serve as the basis for many research endeavors, and they have vastly facilitated effective and rapid communication among investigators and clinicians worldwide. The syndromic approach to epilepsy, especially in children and adolescents, is of tremendous utility for clinical purposes. Its application in large-scale clinical and population-based studies further demonstrates it practicality and utility.[14,17,36,52] Although some argue that it is of limited value because not all forms of epilepsy fall into well-defined syndromic groups,[44] this is simply not a valid argument. For one, identifying, studying, and treating separately those well-defined forms of epilepsy from currently “nonsyndromic” forms allows both clinicians and researchers to be more precise and tailored in their evaluations, recommendations, and investigations. It is hard to imagine arguing that one should use a multivariate equation to determine the risks and consequences of epilepsy based on age at onset and seizure type when one can clearly identify syndromes such as childhood absence and West syndrome (both occurring in childhood and both characterized by generalized seizures). Second and related to that, by separating forms of epilepsy that meet clear criteria for specific syndromes, we can then focus efforts on forms of epilepsy that are not readily classified and that are clearly an important next horizon for future research.

Scientific classifications and other approaches to classifying epilepsy

Despite the enormous success of the syndromic approach, in fact because of its success, a paradigmatic shift is needed in how we classify epilepsy. The classification of the epilepsies largely has been based on descriptive work and expert opinion. With increasing efforts to identify the genomic and other mechanistic bases of the epilepsies and the need for more precise characterization of the epilepsies that have not conveniently conformed to the current approach for syndromic diagnoses, the importance of biologically relevant phenotypes is paramount.[10,11] Whereas useful broad or distinctive patterns can be and have been discerned, it is time that the field of epilepsy adopted a more structured and scientifically rigorous approach to recognizing epilepsy syndromes. A previous comparison of classification to evolutionary biology and phylogenetic systematics pointed out that, in the classification of species, and really for any scientific classification, one must have three components: (1) a rigorous conceptual and operational definition of the end node to be classified (species or syndrome)—one that is biologically relevant; (2) methods for collecting, analyzing, and interpreting data; and (3) a process or processes guiding the analysis and interpretation. This is the next set of logical steps needed to provide a structure and direction to facilitate future efforts to determine the root causes (especially genetic) of the diverse disorders called epilepsy. This in turn has the potential to open avenues to more effective treatment and perhaps, one day, prevention.

Summary and Conclusions

Epilepsy is an umbrella term used to refer to a complex set of disorders with different causes, manifestations, consequences, and outcomes. Both epidemiologic and syndromic approaches have contributed to general knowledge, treatment, and management of epilepsy. Both have also made important and extensive contributions to standardizing language and establishing concepts that have formed a basis for and facilitated communication internationally. The epidemiologic work has provided the broad view of the forest and thus a critical initial framework for approaching the incidence of epilepsy in the population. The syndromic approach has given us a very detailed understanding of the individual forms of epilepsy (the trees), something of tremendous clinical relevance to individual patients, as well as being an initial framework for a more precise and mechanistic approach to investigating and treating epilepsies.

Concepts developed and accepted over the last 30 to 50 years are now proving to be more complex than previously appreciated. Simple “generalized” versus “focal” and “idiopathic” versus “symptomatic” dichotomies, distinctions that are well engrained within epileptology, are increasingly less meaningful, or at least less apt. Whereas a common language facilitates communication, it can also constrain thought.[53] Consequently, some changes may be appropriate in the future. In addition, the syndromic approach has rested on description and expert opinion. Another challenge, in conjunction with carefully considered modification of terminology, will be to ensure that phenotypic characterizations of epilepsies are as biologically relevant as possible so as to facilitate investigation into their underlying causes.

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Chapter 67

Classification of the Epilepsies

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Introduction

Although epilepsy is an ancient disease, described in writings of ancient Mesopotamia and India,[12] recognition that there are many forms of epilepsy is a fairly recent development. Petit mal and focal seizures were distinguished from grand mal seizures by nineteenth century neurologists,[3,9] and Hughlings Jackson noted that there could be many causes of epilepsy[16]; however, there was no universally accepted classification of epilepsy syndromes until the late twentieth century. Even in 1970, when the International League Against Epilepsy (ILAE) proposed the first international classification of epileptic seizures, the accompanying classification of the epilepsies merely divided them broadly into partial and generalized types (Table 1).[14] This classification further distinguished between primary generalized epilepsies, which were associated with epilepsy alone, and secondary generalized epilepsies, in which the seizures were symptoms of an identifiable cerebral disorder that itself could produce other signs and symptoms as well. At the time, it was thought that all partial seizures were symptomatic.

With the increasing description of reasonably well defined epilepsy syndromes, the ILAE made its first attempt to organize them into a coherent classification in 1985.[4] The 1985 classification retained the partial/generalized dichotomy but deleted the term “partial” because it seemed an inappropriate term for diseases and created misunderstandings when secondarily generalized tonic–clonic seizures were the only seizure type. The possible term “focal” was not chosen because the idiopathic epilepsies of childhood with focal seizures do not present stable foci but may have seizures coming from alternate sites and sides. “Localization related” was proposed instead as the preferred term. The primary/secondary dichotomy was retained, but these two groups were now referred to as idiopathic and symptomatic because “secondary generalized epilepsies” had become confused with “secondarily generalized seizures.” The term “idiopathic,” from the Greek word “*idios*,” meaning self, referred to epilepsy as the disorder itself, or epilepsy sui generis. This classification recognized the fact that some localization-related epilepsies are idiopathic and, for the first time, listed specific syndromes within each of the categories. For generalized epilepsies, a category of “idiopathic and/or symptomatic” was included, as was a category of “epilepsies and syndromes undetermined as to whether they are focal or generalized,” together with a category of special syndromes. The International Classification of Epilepsies and Epileptic Syndromes was again revised in 1989, and this is the classification in current use[5] (Table 2).

The 1989 Classification of Epilepsies, Epileptic Syndromes, and Related Seizure Disorders

The 1989 classification retained the localization-related/generalized and idiopathic/symptomatic dichotomies but introduced the term “cryptogenic” to define conditions in which the cause of the disorder is “hidden or occult."[5] The term “cryptogenic epilepsies” was intended to be used for conditions presumed to be symptomatic but without definitive evidence for the etiology. The use of this term became ambiguous, however, as a result of a 1993 report of the ILAE Commission on Epidemiology and Prognosis in which it was recommended that the term “cryptogenic epilepsies” be used to define “patients who do not conform to the criteria for the symptomatic or idiopathic categories."[6] As a result, there is considerable confusion regarding the use of the term "cryptogenic," and a more recent report of the ILAE Task Force on Classification and Terminology recommended that this term be discarded and replaced by "probably symptomatic" when this is the intent, or "unknown as to whether idiopathic or symptomatic" when this is the intent.[7] It should also be noted that, whereas the ILAE classification is a taxonomic classification,[18] the problem addressed by the term "cryptogenic" is more relevant to a diagnostic scheme intended to describe individual patients. The task force also made several other recommendations. Because the term "localization related" is cumbersome and not used by everybody, it was recommended that it be replaced with the commonly used term "focal," with the understanding that focal epilepsies do not usually result from a small, discrete cluster of epileptogenic neurons. The term "focal," however, is particularly inappropriate in this respect for the idiopathic localization-related epilepsies, which are distributed disorders. The words "convulsion" and "convulsive" were also felt to be imprecise, and it was recommended that they not be used to define specific syndromes.

Much of the 1989 classification of the epilepsies is derived from initial work done in children and adolescents, that is, age groups in which highly distinct and diverse forms of epilepsy occur. The use of epilepsy syndromes in children and adolescents has had tremendous utility for clinical as well as research purposes. Large-scale community-based and specialized centers–based studies have demonstrated that, within this young age group, 50% to 60% of children can be assigned a specific syndromic diagnosis.[2,11,17] Remaining cases carry diagnoses of less well-defined and less specific entities, namely symptomatic or cryptogenic focal epilepsy and undetermined (essentially unclassified) epilepsy. The focal epilepsies are generally defined based on localization from semiology, electroencephalogram (EEG), or neuroimaging and by the presence or absence of an identified underlying cause. Many entities identified within the focal epilepsies do not conform to current concepts of what is meant by the term syndrome in the same way that, for example, childhood absence epilepsy or West syndrome do. The vast majority of adults have these latter forms of focal epilepsy and only about 10% or 15% meet the diagnostic criteria for other highly specific epilepsy syndromes.[11] This had led some to criticize the 1989 classification for attempting to include all epilepsies in a rigid classification structure. An alternative proposal maintains that it is sufficient to define individual patients by describing their ictal phenomenology in detail.[13] This is again relevant to diagnostic schemes or manuals and not to taxonomy, which only makes sense when it includes all recognized conditions, be they rare or frequent. Taxonomic classifications, however, need to be accompanied by diagnostic manuals.

Table 1 The 1970 ILAE Classification of the Epilepsies

I. Generalized
    A. Primary
    B. Secondary
    C. Undetermined
II. Partial (focal, local)
III. Unclassified

These were defined by clinical and electroencephalographic criteria but were not listed as syndromes.
Source: From Merlis JK. Proposal for an international classification of the epilepsies. *Epilepsia.* 1970;11:114–119; with permission.

An alternative or supplementary approach taken by the ILAE Task Force is to create a list of epileptic seizure types as diagnostic entities that, by themselves, have etiologic, therapeutic, and prognostic implications.[8,19] These seizure types, based on pathophysiologic mechanisms and anatomic substrates, information that was inadequately available to be used in the 1981 ILAE Classification of Epileptic Seizures, can be used to determine the diagnostic evaluation, treatment, and prognosis in patients for whom a syndrome diagnosis is not possible.

Although the 1989 classification represented an expert consensus based on thorough and discriminatory literature reviews,[15] another criticism is that it does not clearly enough distinguish between syndromes that are well-accepted and those that are controversial or lack sufficient data for verification. The ILAE Task Force is currently using methods of accepted biologic classification that use measurable objective criteria for recognizing natural classes that can be reproducibly distinguished from all other natural classes.[1] Each epilepsy syndrome should be a unique diagnostic entity, similar to a natural class in biologic classification. The Task Force has defined an epilepsy syndrome as

> a complex of signs and symptoms that define a unique epilepsy condition. This must involve more than just the seizure type: thus frontal lobe seizures per se, for instance, do not constitute a syndrome. An epilepsy syndrome must be distinguished from an epilepsy disease, defined as: a pathologic condition with a single specific well-defined etiology. Thus, Progressive myoclonus epilepsy is a syndrome, but Unvericht-Lundborg is a disease.[7]

(It is important to point out that syndromes can be used for diagnostic manuals that are applied to individual patients as well as constitute taxonomic classes. Most syndromes are both, but some are not. Progressive myoclonus epilepsy is useful for diagnosis of individual patients but not for taxonomic purposes.) Criteria used to identify specific syndromes as unique diagnostic entities include their seizure type, age of onset, progressive nature, interictal EEG findings, associated interictal signs and symptoms, pathophysiologic mechanisms, anatomic substrates, etiologic categories, and genetic bases.[8,10] A tentative list of syndromes that meet these criteria is shown in Table 3. These syndromes should be considered testable working hypotheses subject to verification, falsification, and revision. Evidence-based methodology will be developed to evaluate syndrome hypotheses on an ongoing basis, making syndrome classification a dynamic process.

The next step will be to arrange these syndromes into a logical format that is useful for a variety of purposes, including clinical discussion, teaching, epidemiologic studies, drug trials, and basic research. In the process of organizing diagnostic entities as natural classes into coherent groupings, a benign epilepsy syndrome has been clarified as “a syndrome characterized by epileptic seizures that are easily treated, or require no treatment, and remit without sequelae."[7] The specification “without sequelae” makes this definition different from other fields of medicine, for example, brain tumors, in which “benign” is a relative term comparing conditions that are still potentially serious and not always remediable with similar ones that take a much more deleterious course. In addition, a category of “epileptic encephalopathy” is now defined as “a condition in which the epileptic processes themselves are believed to contribute to the disturbance in cerebral function."[7] A “reflex epilepsy syndrome” is defined as

> a syndrome in which all epileptic seizures are precipitated by sensory stimuli. Reflex seizures that occur in focal and generalized epilepsy syndromes that also are associated with spontaneous seizures are listed as seizure types [but would in fact require the introduction of a new category of “traits” because the seizure semiology is not different from spontaneously occurring seizures]. Isolated reflex seizures also can occur in situations that do not necessarily require a diagnosis of epilepsy. Seizures precipitated by other, special circumstances, such as fever or alcohol withdrawal, are not reflex seizures.[7]

Table 2 International Classification of Epilepsies and Epileptic Syndromes

1. Localization-related (focal, local, partial)
    - 1.1 Idiopathic (with age-related onset)
      At present, the following syndromes are established, but more may be identified in the future:
        - Benign childhood epilepsy with centrotemporal spikes
        - Childhood epilepsy with occipital paroxysms
        - Primary reading epilepsy
    - 1.2 Symptomatic
        - Chronic progressive epilepsia partialis continua of childhood
    - 1.3 Cryptogenic (presumed to be symptomatic but with unknown etiology)
      The symptomatic and cryptogenic categories comprise syndromes of great individual variability that are based mainly on:
        - Seizure types (according to the International Classification of Epileptic Seizures)
        - Anatomic localization
            - Temporal lobe epilepsies
            - Frontal lobe epilepsies
            - Parietal lobe epilepsies
            - Occipital lobe epilepsies
            - Bi- and multilobar epilepsies
        - Etiology (in symptomatic epilepsies)
        - Specific modes of precipitation
2. Generalized
    - 2.1 Idiopathic (with age-related onset, in order of age)
        - Benign neonatal familial convulsions
        - Benign neonatal convulsions
        - Benign myoclonic epilepsy in infancy
        - Childhood absence epilepsy (pyknolepsy)
        - Juvenile absence epilepsy
        - Juvenile myoclonic epilepsy (impulsive petit mal)
        - Epilepsy with grand mal (GTC) seizures on awaking
        - Other idiopathic generalized epilepsies not defined above
        - Epilepsies with seizures precipitated by specific modes of activation
    - 2.2 Cryptogenic or symptomatic (in order of age)
        - West syndrome (infantile spasms, Blitz-Nick-Salaam-Krämpfe)
        - Lennox-Gastaut syndrome
        - Epilepsy with myoclonic-astatic seizures
        - Epilepsy with myoclonic absences
    - 2.3 Symptomatic
        - 2.3.1 Nonspecific etiology
            - Early myoclonic encephalopathy
            - Early infantile epileptic encephalopathy with suppression-burst
            - Other symptomatic generalized epilepsies not defined above
        - 2.3.2 Specific syndromes (see Table 3)
3. Epilepsies and syndromes undetermined as to whether focal or generalized
    - 3.1 With both generalized and focal seizures
        - Neonatal seizures
        - Severe myoclonic epilepsy in infancy
        - Epilepsy with continuous spike-waves during sleep

        - Acquired epileptic aphasia (Landau-Kleffner syndrome)
        - Other undetermined epilepsies not defined above
    - 3.2 Without unequivocal generalized or focal features (e.g., many cases of sleep-grand mal)
4. Special syndromes
    - 4.1 Situation-related seizures (Gelegenheitsanfälle)
        - Febrile convulsions
        - Isolated seizures or isolated status epilepticus
        - Seizures due to acute metabolic or toxic factors such as alcohol, drugs, eclampsia, nonketotic hyperglycemia, and so on

Source: From Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. *Epilepsia*. 1989;30:389–399; with permission.

Table 3 List of Syndromes

Epilepsy syndromes and related conditions

Neonatal period

- *Benign familial neonatal seizures (BFNS)*: This may be a disease and not a syndrome.
- *Early myoclonic encephalopathy (EME)*: Although this may be different from Ohtahara syndrome, the clinical distinction can be difficult.
- *Ohtahara syndrome*: See above.

Infancy

- *Migrating partial seizures of infancy*: This has been sufficiently described by several independent investigators to merit recognition as a syndrome.
- *West syndrome*: This is a clearly defined syndrome based on specific clinical features and age of onset.
- *Myoclonic epilepsy in infancy (MEI)*: Because this is not benign in some infants, the word “benign” was removed from the name. It was initially introduced to distinguish it from Severe myoclonic epilepsy in infancy (SMEI), which is now called Dravet syndrome. Seizures may occasionally be reflex (i.e., touch).
- *Benign infantile seizures*: Whereas BFNS and Benign (nonfamilial) neonatal seizures clearly represent two distinct syndromes because of differences in seizure type and age of onset, the familial and nonfamilial forms of Benign infantile seizures are identical except for the family history. Consequently, the sporadic form cannot be considered a separate syndrome, and both should be combined into a single syndrome, unless subsequent information indicates otherwise.
- *Dravet syndrome*: Because many of these children do not have myoclonic components to their characteristic seizures in infancy, it cannot be called SMEI, and we should retain the eponym.

- *Myoclonic encephalopathy in nonprogressive disorders*: There is sufficient evidence to support this as a syndrome. It is important as a form of epileptic encephalopathy.

Childhood

- *Early onset benign childhood occipital epilepsy (Panayiotopoulos type)*: The consistency of localization remains controversial in this syndrome.
- *Epilepsy with myoclonic astatic seizures*: This syndrome is now well defined but the course is variable. Many are epileptic encephalopathies.
- *Benign childhood epilepsy with centrotemporal spikes (BCECTS)*: This condition also is not always benign, although nonbenign forms occur in only a small percentage of patients, and may represent related conditions.
- *Late onset childhood occipital epilepsy (Gastaut type)*: There was concern because this condition is rare and there has been a paucity of recent confirmatory reports. More data are needed.
- *Epilepsy with myoclonic absences*: This syndrome needs further study in the context of the work to be done on myoclonic seizures.
- *Lennox-Gastaut syndrome (LGS)*: This syndrome is clearly defined by clinical and EEG features and by age of onset.
- *Epileptic encephalopathy with continuous spike-and-wave during sleep (CSWS) including Landau-Kleffner syndrome (LKS)*: It was decided that there is insufficient evidence for mechanistic differences between LKS and CSWS to warrant considering them separate syndromes. It is unknown whether these conditions are idiopathic, symptomatic, or both.
- *Childhood absence epilepsy (CAE)*: Further deliberation and research will be needed to clarify the distinction between this syndrome and JAE, and to define the relationship of this syndrome to the other idiopathic generalized epilepsies such as JME.

Adolescence

- *Juvenile absence epilepsy (JAE)*: See above.
- *Juvenile myoclonic epilepsy (JME)*: See above.
- *Progressive myoclonus epilepsies (PME)*: This group is different from the others in that it consists entirely of specific diseases, and might be considered under diseases with epilepsy rather than epilepsy syndromes. However, because it is a very helpful concept for diagnostic purposes when it is not possible to reach a more specific diagnosis, it is still included in this list.

Less specific age relationship

- *Autosomal-dominant nocturnal frontal lobe epilepsy (ADNFLE)*: All affected family members have nocturnal frontal lobe seizures. In some families, mutations in neuronal nicotinic acetylcholine receptor genes are found, but in many families the genetic etiology is unknown.
- *Familial temporal lobe epilepsies*: There are a number of forms that are being defined. Division into lateral and mesial temporal types based on the predominant seizure semiology is useful. The lateral temporal type (also known as Autosomal-dominant partial epilepsy with auditory features) is associated with mutations in the LGI1 gene in about half the families. The mesial group is heterogenous within and between families in terms of epilepsy severity, association with febrile seizures and presence of hippocampal sclerosis.

- *Mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE with HS)*: This condition probably consists of more than one syndrome, and it is not certain whether features of patients with HS clearly differentiate them from those with other mesial temporal lesions.

- *Rasmussen syndrome*: There continues to be a question as to whether this is best characterized as a syndrome or a disease; that is, whether there may be multiple etiologies for this inflammatory process.
- *Gelastic seizures with hypothalamic hamartoma*: This may be a disease and not a syndrome.

Special Epilepsy conditions

- *Symptomatic focal epilepsies not otherwise specified*: Disorders due to epileptogenic lesions that are localized, diffuse but limited to one hemisphere, or multifocal do not constitute syndromes per se, but can be defined according to the seizure type, the underlying pathophysiologic disturbance, if known, and the location of the lesion(s), if they do not fit into a described syndrome.
- *Epilepsy with generalized tonic-clonic seizures only* is not a syndrome, and the Core Group was unable to agree on any syndrome with this feature: The consistent diurnal pattern of seizures in some patients needs further investigation. Whether epilepsy with generalized tonic–clonic seizures on awakening exists as a distinct entity is unclear.
- *Reflex epilepsies*: Although Idiopathic photosensitive occipital lobe epilepsy, Primary reading epilepsy and Hot water epilepsy in infants are syndromes, it is unclear whether other reflex epilepsies constitute unique syndromes.
- *Febrile seizures plus (FS+)*: This is a condition that is part of the familial syndrome known as GEFS+. The latter is broader than a single generalized syndrome and may be a useful category for future classifications.
- *Familial focal epilepsy with variable foci*: This syndrome cannot be diagnosed in a single individual. Recognition depends on the occurrence within a family of individuals with different seizure patterns (commonly temporal or nocturnal frontal); each individual has a single seizure pattern.

Conditions with epileptic seizures that do not require a diagnosis of epilepsy

- The reasons for not considering some syndromes to be epilepsy seem to be more political than scientific. Two syndromes exist in this group.
- *Benign neonatal seizures (BNS)*: These are self-limited events without sequelae.
- *Febrile seizures (FS)*: Classically, the seizures that constitute this condition consist of two forms: simple and complex; however, many different types undoubtedly exist. This condition may eventually be understood to encompass many different entities.

Source: Adapted Engel J Jr. Report of the ILAE Classification Core Group. *Epilepsia*. 2006;47:1558–1568, with permission.

Future Directions

The work of the ILAE Task Force will be continued by a new commission, charged with preparing new flexible and dynamic systems of taxonomic classification and diagnostic manuals for epilepsy syndromes. A revised or new classification will need to take a critical look at the two basic dichotomies. For instance, even as the terms idiopathic and symptomatic seem to be straightforward, epileptogenesis is often complex, and there is no clear demarcation between idiopathic and symptomatic epilepsies, whatever this means for a taxonomic classification. It also is not likely that any form of epilepsy is truly generalized, and perhaps few, if any, are truly focal. However, because these terms have important implications in clinical practice and there is no simple way to replace them, they will be retained where useful, as in the description of certain idiopathic generalized epilepsies and certain idiopathic and symptomatic focal epilepsies. The border between "generalized" and "focal" idiopathic epilepsies seems to be dissolving in view of newer findings with some common reflex epileptic traits[19] and with functional imaging of both groups. These may eventually be considered variants of functional system disorders of the brain in the same sense as system disorders in neurology in which preexistent subsystems of the central and peripheral nervous system are involved in the pathologic process. What is now a major dichotomy would then become a distinction between subgroups of nosologically related disorders.

A variety of other logical groupings for categorizing epilepsy syndromes include autosomal-dominant epilepsies and the generalized and focal conditions related to generalized epilepsy with febrile seizures (GEFS+), which could constitute a group of syndromes sharing specific susceptibility genes, perhaps even including mesial temporal lobe epilepsy. Ultimately, a multivariate approach could be used to construct an organization of syndromes in diagnostic schemes and taxonomic classifications for variable purposes, allowing some syndromes to be represented in more than one grouping and others to be represented in none. Mechanisms will be provided to repeatedly reevaluate the contributions of new developments in clinical research, genetics, molecular neurobiology, and pathophysiology to the organization of the classification system(s), as well as the functional utility of the classification, so that it can be updated on an ongoing basis.

Summary and Conclusions

The ILAE has critically reviewed the 1989 Classification of the Epilepsies, but has not yet made recommendations for its replacement. The distinction between a taxonomic classification, which considers the entire field of epilepsy, and diagnostic manuals, which provide schemes for describing individual patients, is important for understanding the work that needs to be done to improve the current efforts to improve the 1989 classification. A proposal for a diagnostic scheme that includes epileptic seizure types as diagnostic entities as well as syndromes was proposed by the ILAE in 2001, but this does not constitute a new classification. A more recent report describes an evidence-based approach to identifying epilepsy syndromes as unique diagnostic entities, different from all other diagnostic entities, in the same manner that biologic classifications identify natural classes. Criteria for identifying discrete epilepsy syndromes have been established, and a list of syndromes that superficially appear to meet these criteria has been published. It is now necessary to apply evidence-based methodology to confirm these syndromes and to construct one or more new taxonomic classifications and diagnostic schemes for variable purposes. It is envisioned that these will be dynamic and flexible constructs, subject to verification, falsification, and revision as new research data become available and as practical experience is obtained from their use.

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Chapter 68

Differential Diagnosis

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Introduction

Patients presenting with transient alteration of neurologic function offer neurologists the opportunity to do what they do best: Solve a medical mystery and make a diagnosis. In general, the history will provide the essential clues, with ancillary testing providing only a modicum of additional assistance.

A careful history in the setting of a possible first seizure will frequently disclose prior spells that provide important diagnostic clues. Often, however, patients will not have recognized the relevance of these previous symptoms, and the neurologist must ask about them specifically. In fact, many typical epileptic phenomena such as déjà vu and morning myoclonus ("I'm just clumsy when I first get up") may be considered normal by the person experiencing them or, alternatively, not neurologic in origin (e.g., "panic attacks"). A history that clearly indicates alteration of awareness is very helpful, but many patients—perhaps most—do not recognize brief changes in the degree of awareness.

Relatively few patients with epilepsy are able to recall all of their seizures, and a substantial number cannot remember any of them. Blum et al.[6] prospectively determined seizure awareness in 31 patients admitted to an epilepsy monitoring unit. Twenty-three had epileptic seizures, but only 26% of these were aware of all of their seizures (regardless of seizure type), and 30% were not aware of any. Thus, obtaining additional information from observers is crucial. For recurrent spells, video-electroencephalogram (EEG) recording in an epilepsy monitoring unit is the best way—and sometimes the only way—to make a definitive diagnosis. Health professionals who have spent substantial time in one of these units know that findings can be surprising, and can include unexpected psychogenic spells, subclinical seizures, or substantial impairment of awareness during "auras," to name a few.

Any highly stereotyped, recurrent, brief alteration of neurologic function without an obvious alternative explanation can be of epileptic origin. Table 1 lists some of the disorders that can mimic epilepsy in adults along with the clinical features that are most useful diagnostically. Table 2 provides similar information for children and adolescents. The most important condition to consider and recognize promptly is syncope, especially cardiac syncope due to a life-threatening arrhythmia that may be fatal in a subsequent spell.[31] Table 3 compares the clinical characteristics of syncope and seizures to assist in distinguishing the two.

Table 1 Common seizure mimics and useful clinical features for diagnosis

Diagnosis	Clinical features suggestive of diagnosis
Syncope	Trigger usually identifiable, with autonomic

	symptoms/pallor; no aura or unilateral symptoms; loss of consciousness <20 s with rapid return to normal; jerking/posturing, if present, is brief and occurs after the loss of consciousness; see also Table 3
Transient ischemic attack	Variable presentation depending on area involved; with any neurologic deficit, consider focal seizures if symptoms are recurrent and stereotyped with no signs of infarct on brain imaging
Migraine (especially basilar)	Slow march of neurologic symptoms over >5 min and prolonged duration (usually 20–60 min); posterior circulation symptoms; scintillating scotomata; subsequent headache (may be absent)
Transient global amnesia	Prolonged spell (hours) with normal behavior except for amnesia; personal identity always intact (if not, suspect psychogenic etiology)
Psychogenic nonepileptic seizures	Psychiatric history, especially somatization; history of physical or sexual abuse; eyes closed and normal vital signs during spell; recurrent spells not responding to treatment; precipitation by hyperventilation or other suggestive techniques
Panic attack, hyperventilation	Often with environmental trigger; severe fear; hyperventilation with perioral cyanosis, bilateral hand paresthesias, carpopedal spasm; loss of consciousness not complete; dyspnea; palpitations; >5 min in duration (seizures are shorter); associated depression and phobias (95%), especially agoraphobia; onset in young adulthood
Cataplexy	No loss of consciousness; triggered by emotion, especially laughter; other features of narcolepsy usually present (daytime somnolence, hypnagogic hallucinations, sleep paralysis)
Sleep disorders (somnambulism, night terrors, confusional arousals, enuresis, REM behavior disorder, hypnagogic hallucinations, periodic limb movements, paroxysmal nocturnal dystonia)	Sometimes difficult to distinguish from seizures without video-electroencephalographic monitoring, polysomnography, or both, especially if no reliable witness; paroxysmal nocturnal dystonia is a manifestation of epilepsy in most if not all cases; slow-wave-sleep parasomnias are usually in the first one third of the night; see Table 2
Staring/behavioral spells in patients with static encephalopathy or	Difficult to distinguish from seizures without video-encephalographic monitoring

dementia	
Hypoglycemia	Long prodrome; on treatment for diabetes (or insulinoma, rare)
"Drop attacks"	Can be due to cataplexy, cervical spine disease, basilar ischemia, vertigo attack (Ménières), seizures (myoclonic, tonic, atonic; rarely complex partial), or syncope (especially cardiac)

Source: Adapted with permission from Hirsch L, Ziegler D, Pedley T. Seizures, syncope and their mimics. In: Rowland L, ed. *Merritt's Neurology*, 11th ed. New York: Lippincott Williams & Wilkins; 2005:13–20.

Misdiagnosis

An incorrect diagnosis of epilepsy creates a significant problem with serious consequences.[23] About one fourth of patients with a diagnosis of epilepsy have been misdiagnosed[29,30]; the rate of misdiagnosis is higher in children.[37] One should always remain open to the possibility that the initial diagnosis was incorrect, especially when antiepileptic drug treatment is ineffective, and take full advantage of future spells to help confirm or modify the diagnosis. The majority of patients misdiagnosed as having epilepsy are eventually found to have either psychogenic nonepileptic seizures (PNES) or syncope.[11,25,29,30,40] Misinterpretation of EEG findings or overreliance on the EEG frequently contributes to misdiagnosis.[11,30] The presence or absence of interictal epileptiform discharges on EEG is not definitive and may be misleading.[5,19] Interictal epileptiform discharges (IEDs) occur in about 0.5% of healthy adults and in 1.9% to 3.5% of normal children.[26] Multifocal IEDs and IEDs occurring over the frontal and anterior temporal regions are highly correlated with clinical seizures,[10,18] but only about 40% of children with central-midtemporal spikes and 50% with occipital spikes had seizures in one study.[18] When EEGs are interpreted by physicians without special training, a number of benign or normal patterns are commonly misinterpreted as epileptiform. These include benign epileptiform transients of sleep (also termed small, sharp spikes), wicket spikes, hyperventilation-induced high-voltage paroxysmal slow waves, various artifacts (such as overfiltered muscle potentials), repetitive vertex waves, especially in children, and the 6/sec "phantom" spike-wave phenomenon.[38] One study reported that 54% of patients referred to an epilepsy center with a previous diagnosis of epilepsy and wicket rhythms on EEG did not have epilepsy on further evaluation.[19] Benbadis et al. reported 15 patients who were eventually diagnosed with PNES but had previously carried a diagnosis of epilepsy based on EEGs misinterpreted as epileptiform.[5] Of the 15 records reviewed, the patterns that were incorrectly considered epileptiform were wicket spikes ($n = 1$), hypnagogic hypersynchrony ($n = 1$), and hyperventilation-induced slowing ($n = 1$). In the other 12 records, simple fluctuations of sharply contoured baseline background activity and fragmented alpha activity, not identifiable specific variants, were misinterpreted as epileptiform. Repeating the EEG or having it reinterpreted at a tertiary epilepsy center by a certified electroencephalographer can be helpful in problematic cases. It is also important to remember that EEGs can never rule out epilepsy. Even with repeated EEGs or prolonged monitoring, a significant number of patients with epilepsy (10% to 19%) will have no interictal epileptiform discharges[26]; even ictal recordings may not have an identifiable scalp correlate in many frontal lobe seizures, as well as in simple partial seizures from any location.

Zaidi et al.[40] investigated the utility of noninvasive cardiovascular tests (including head-up tilt test and carotid sinus massage during continuous electrocardiography, EEG, and blood pressure monitoring) in 74 patients with apparent treatment-resistant epilepsy. An alternative diagnosis was found in 31 (41.9%) patients, including 13 (36.1%) of 36 patients taking an antiepileptic drug (AED). The most common alternative diagnosis was vasovagal syncope (25.7% of patients), followed by carotid sinus hypersensitivity (9.5%). At follow-up at about

10 months, all patients in whom an alternative diagnosis was made had subjective improvement, and 61.3% were symptom free. Of the 13 patients who were taking AEDs and for whom an alternative diagnosis was identified, 11 had successfully stopped their medications. These findings underscore the importance of cardiovascular testing early in the evaluation of a patient with "blackouts." This is especially true in patients with cardiac risk factors, in whom it is essential to exclude cardiac arrhythmias.

The most challenging and most common alternative diagnosis in epilepsy monitoring units is PNES. Approximately 20% to 40% of patients admitted to such units have PNES,[3,4,13] including a substantial portion of those referred for epilepsy surgery. If seizures do not respond to trials of two AEDs, the patient should be referred for video-EEG monitoring, both for definitive diagnosis and, if epilepsy is confirmed, initial surgical evaluation. The chance of complete seizure control after failing two AEDs is <10%.[22]

The following sections discuss differential diagnosis based on clinical presentation. Because PNES can manifest with any of these presentations, they are addressed separately at the end and more extensively in Chapters 207 and 282.

Table 2 Common Seizure Mimics in Infants and Children

	Relative incidence with age			
Symptoms/signs	**0-2 yr**	**2-8 yr**	**8-18 yr**	**Description**
Unusual movements				
Infantile masturbation	•••			Can be confused with seizure activity, especially in young infants; can almost always be aborted by distracting stimulus
Shuddering	•••	•	•	No risk of developing epilepsy later in life, normal EEG; may have family history of essential tremor
Benign sleep myoclonus	•••	•	•	Most common seizure mimic in neonates; not stimulus sensitive; normal EEG; no association with a higher incidence of epilepsy/abnormal neurologic development in later life
Startle disorder/hyperekplexia	••	••	•	Rare familial disorder; infant becomes rigid when handled; forceful repetitive jerks on falling asleep; spells can lead to hypoxia
Spasmodic torticollis	•	••		May be due to labyrinthine imbalance or

				neuroleptic drugs; sometimes manifestation of focal dystonia; normal EEG
Self-stimulating behaviors	••	•••	••	Hand-shaking, head-rolling, head-banging, body-rocking; more common in children with mental retardation or autism
Tics		•	•••	Can be confused with myoclonus; unlike myoclonus, they almost always disappear in sleep; preferentially involve face; premonitory urge and transiently suppressible
Chorea/choreoathetosis		•	••	At times may be indistinguishable from multifocal myoclonic jerks
PNES		•	••	May present in a variety of ways; for more details see section in text on PNES
Unusual eye movements	•••	••	•	For example, spasmus nutans (triad of nystagmus, head-nodding, and head tilt)
Overflow movements (synkinesis)	••	••		Defined as "extra" motor activity seen during performance of a complex motor task due to underdevelopment of inhibitory neural circuitry; seen in children with ADHD, and persists into late childhood/adolescence
Sandifer syndrome	•••	••	•	Association of torsional dystonia (mainly neck and upper extremities) with esophageal reflux or hiatal hernia; spasms/posturing seen shortly after feeding
Loss of tone or consciousness				
Syncope		••	•••	See text and Table 3
Drop attacks		•	•	See text and Tables 1 and 5
Cataplexy		•	•	Usually with other symptoms of narcolepsy; see text and Table 1

Disorders of respiration				
Apneic attacks	•••			May occur alone or as part of triad (apnea, staring, and flailing), often with gastroesophageal reflux
Breathholding	•••	•		Attacks of respiratory arrest following fright or minor injury; may be pallid or cyanotic; cyanotic spells feature vigorous crying, LOC (<1 min) and return to normal activity; pallid spells are longer (LOC >1 min), child rarely cries, may rarely result in a postanoxic seizure
Hyperventilation		•	•	Associated with anxiety/panic; may have perioral and bimanual paresthesias, carpopedal spasm
Deliberate syncope		•	••	Also known as the “fainting lark”; hyperventilation + straining + sudden standing = fainting (usually self-induced by children as dare or entertainment or for avoiding an undesirable task)
Behavioral disorders				
Head-banging	••	•		Mainly in infants, usually resolves by age 10; if persists longer, it is usually associated with mental retardation or autism; occurs as child falls asleep; no association with emotional disturbances; normal EEG
Night terrors	•	•••	•	May be confused with CPS, especially of frontal lobe origin; occur during first 3 h of sleep, in stage 3 and 4 (slow-wave) sleep; child screams and sits up, often with increased sympathetic activity; typically has no recollection of the event; normal EEG
Nightmares		••	••	Occur primarily during REM sleep, usually later in night; child is restless during dream but usually does not scream; often recalls nightmare and develops a fear of sleeping alone; normal EEG

Sleepwalking	•••	••	May be confused with automatisms of CPS; trance-like episodes of walking from and back to bed; eyes open, rarely violent; child may mumble; has no recollection of event; usually in slow-wave sleep or associated with incomplete arousal
Rage	•••	••	Associated with other conduct/personality disorders, directed to source; behavior can be modified during episode; differentiate from ictal rage (rare, seen in frontal/temporal lobe epilepsy; unprovoked and not focused on a particular object/individual)
Fear	•	•••	Occurs as feature of chronic anxiety disorder or in depressed or schizophrenic patients; distinguish from "ictal fear" (often followed by CPS)
Daydreaming/attention deficit	•••	•••	Brief (30–60 sec) loss of contact with environment; generally responds to touch; daydreamers never interrupt their own speaking to stare ahead and lose track of time; a child who stops speaking in mid-sentence with staring almost always has a seizure disorder
Migraine			
	•	•••	See text and Table 1 ; 3%–7% of children with migraine may have coexisting epilepsy
• Basilar			• Initial symptoms of brainstem/occipital lobe dysfunction (especially vertigo/bilateral visual loss) or less often LOC; one third have occipital spike-and-wave complexes between episodes on EEG
• Confusional			• Confusion, with or without delirium, is seen in confusional migraine, more common in adolescents; often no headache, may have past history of more typical migraines or family history

	of migraines
• Migraine equivalents	• Episodic nausea and vomiting can be from seizures (almost always with complex partial seizure, usually nondominant temporal onset) or can be a migraine equivalent, especially in younger children; brief, stereotyped, recurrent paroxysmal epigastric discomfort can be epileptic auras, most commonly temporal lobe

ADHD, attention deficit hyperactivity disorder; CPS, complex partial seizures; EEG, electroencephalogram; LOC, loss of consciousness; PNES, psychogenic nonepileptic seizures; REM, rapid eye movement. *Source*: Adapted and expanded from Prensky AL. An approach to the child with paroxysmal phenomena with emphasis on nonepileptic disorders. In: Pellock JM, Dodson WE, Bourgeois BFD, eds. *Pediatric Epilepsy: Diagnosis and Therapy*, 2nd ed. New York: Demos; 2001:97–116.

Table 3 Syncope Versus Seizure: Useful Distinguishing Features

	Syncope	Seizure
	Before spell	
Trigger (position, emotion, Valsalva)	Common	Rare
Sweating and nausea	Common	Rare
Aura (e.g., smell, déjà vu)	Rare	Common
Unilateral symptoms	Rare	Common
	During spell (from eyewitness)	
Pallor	Common	Rare
Cyanosis	Rare	Common

Duration of loss of consciousness	<20 sec	>60 sec
Movements	A few clonic or myoclonic jerks; brief tonic posturing (few seconds); duration <15 sec; always begin after loss of consciousness	Prolonged tonic phase (~30 sec), then prolonged rhythmic clonic movements (~30–60 sec); duration >1 min; may begin at onset of loss of consciousness or before; unilateral jerking (partial seizure)
Automatisms	Occasional	Common (in complex partial and secondarily generalized seizures)
Tongue biting, lateral	Rare	Occasional
Frothing/hypersalivation	Rare	Common
EEG (during event)	Nonspecific slowing	Ictal EEG pattern
	After spell	
Confusion/disorientation	Rare; <30 sec	Common; several minutes or longer
Diffuse myalgias	Rare, brief, usually upper body	Common, hours to days
CK elevation	Rare	Common (especially after 12–24 h)
EEG (between events)	Normal	Epileptiform discharges common
Features that are not helpful for differentiating	Incontinence, prolactin level, dizziness, fear, injury other than lateral tongue biting, eye movements (rolling back), brief automatisms, vocalizations, visual or auditory hallucinations	

CK, creatine kinase; EEG, electroencephalogram.
Source: From Hirsch L, Ziegler D, Pedley T. Seizures, syncope and their mimics. In: Rowland L, ed. *Merritt's Neurology*, 11th ed. New York: Lippincott Williams & Wilkins; 2005:13–20.

Table 4 Differential diagnosis of transient alteration of consciousness or awareness

Presentation	Possible etiologies
Blackout/faint	Seizures (multiple types)
	Syncope
	Sleep attack
	Vertebrobasilar transient ischemic attack
	Hypoglycemia
Confusional or fugue states	Nonconvulsive status epilepticus (absence or complex partial)
	Postictal state
	Acute toxic/metabolic encephalopathy
	Acute porphyria
	Hypersomnia (sleep drunkenness)
	Parasomnias
	Intermittent psychosis
	Transient global amnesia
	Psychogenic fugue
	Basilar artery migraine
	Flumazenil-responsive recurring stupor
	Stroke
Amnesia	Seizures, especially temporal lobe
	Transient global amnesia

	Daydreaming
	Sleep attack
	Alcoholic blackout
	Drugs
Hallucinations	Seizures, occipital (simple visual) or temporooccipital (formed visual)
	Drugs/hallucinogens
	Delirium tremens
	Toxic encephalopathies
	Peduncular hallucinosis
	Hypnagogic hallucinations
	Schizophrenia and other psychoses
Anxiety/rage	Seizures, especially temporal lobe
	Panic attacks
	Hyperventilation/anxiety attacks
	Intermittent explosive disorder (episodic dyscontrol)

Note: Psychogenic seizures can present under any category. *Source*: Partly adadpted from So NK, Andermann F. Differential diagnosis. In: Engel J, Pedley TA, eds. *Epilepsy:* A Comprehensive Textbook. Philadelphia: Lippincott-Raven; 1997:791–797; and NICE guidelines: the epilepsies: clinical practice guideline, October 2004, available: http://www.nice.org.uk/page.aspx?o=229389.

Transient Alteration of Consciousness, Awareness, or Mental State

Table 4 lists some of the possible causes for transient alteration of awareness; only the more common causes are discussed in detail here. As already mentioned, the most common differential diagnosis involves distinguishing seizure from syncope (Table 3; see also Chapter 271). *Syncope* (“fainting” or “blackout”) is defined as transient alteration of consciousness and loss of muscle tone from an acute, reversible global reduction in cerebral blood flow.[16] The two most important types of syncope are neurally mediated reflex syncope ("neurocardiogenic" syncope) and cardiac syncope. Neurocardiogenic syncope includes vasovagal syncope, situation-related forms of syncope such as micturition and cough syncope, and carotid sinus

hypersensitivity. All of these types of syncope tend to have an identifiable trigger, occur most often while standing, and usually have a prodrome consisting of lightheadedness and dimming or "closing in" of vision (often described as tunnel vision). Patients appear pale and usually have profuse sweating (which is rare with seizures). The period of unconsciousness is usually only a few seconds unless the patient is held upright. It is not unusual to have brief tonic posturing, and it is even more common to have a few clonic or myoclonic jerks, referred to as "convulsive syncope." In a study of normal young adults with videotaped self-induced syncope, 90% had myoclonic jerks following the loss of consciousness.[24] In seizures, jerks may either precede or follow loss of consciousness. With syncope, consciousness returns rapidly, in marked contrast to generalized tonic–clonic seizures. Cardiac syncope is similar, but it may not have a prodromal phase or trigger, and the duration of loss of consciousness can be variable depending on the duration of the arrhythmia. A cardiac cause of syncope is especially important

to consider because 5-year mortality in this group can exceed 50% and is often preventable.[31] For patients with infrequent but recurrent syncope or possible syncope, subcutaneous implanted loop electrocardiogram recorders can be used to make a definitive cardiac diagnosis; these can be left in place for >1 year when necessary. Other features that suggest a generalized tonic–clonic seizure rather than syncope are lateral tongue biting, frothing, cyanosis, and subsequent headache and diffuse myalgias (Table 3). An aura other than dizziness or lightheadedness is helpful if present. It is important to note that incontinence and elevated prolactin level are not rare with syncope and, as a result, are not helpful in distinguishing syncope from seizure.[7,17]

Transient ischemic attacks (TIAs) can occasionally be confused with seizures. Vertebrobasilar TIAs occasionally present as drop attacks, but these are almost always associated with additional brainstem, cerebellar, or occipital lobe symptoms. Seizures manifesting with isolated aphasia are usually misdiagnosed as hemispheric TIAs until spells become recurrent and stereotyped with no evidence of ischemia or infarct. Global or atypical aphasia without hemiparesis or visual field deficit and negative magnetic resonance imaging with diffusion-weighted imaging should favor the likelihood of seizure, even with the first attack. We have referred to these spells as "transient global aphasia." Limb-shaking TIAs are rare, and are characterized by nonrhythmic, coarse, 3- to 12-Hz shaking of the arm (with or without leg involvement) contralateral to severe carotid stenosis.[1,32] These patients may experience symptoms on standing due to hemodynamic insufficiency in the distal carotid field (see also Chapter 275).

An *acute confusional state* can occur due to a number of causes, many of which are treatable (Table 4). It is important to rule out nonconvulsive status epilepticus, a condition that can occur in patients with or without a history of seizures. Delay in diagnosis of nonconvulsive status epilepticus is associated with lower likelihood of response to treatment and worse neurologic outcome, independent of etiology.[39] Intermittent episodes of confusion or altered behavior can be very difficult to diagnose definitively without video-EEG monitoring, particularly in patients with dementia or a static encephalopathy. On rare occasions, an intermittent or episodic nature is not noticed at all, and patients present with dementia. This situation has been termed "*epileptic pseudodementia.*"[33] When fluctuations in the confusional state are present, nonconvulsive seizures are a more obvious consideration. Treating the seizures improves cognition and may restore a normal mental state.

Table 5 Differential diagnosis of abnormal paroxysmal movements

Presentation	Possible etiologies

Bilateral motor activity	Epilepsy: primary or secondarily generalized, or supplementary motor
	Convulsive syncope
	Startle disorders (hyperekplexia)
	Myoclonus
	Paroxysmal dyskinesias
	Other movement disorders
	Decorticate and decerebrate rigidity/posturing
	REM behavior disorder
	Other parasomnias
	Rabies
	Tetanus
	Strychnine and camphor poisoning
Unilateral/focal motor activity:	Focal motor seizures
• Twitching	Myoclonus
• Jerking	Tics
• Shaking	PLMS
• Posturing	Tonic spasms of multiple sclerosis
	Limb-shaking TIAs
	Esophageal reflux (Sandifer syndrome) in children

Facial muscle and eye movements	Partial seizures
	Hemifacial spasm
	Oculogyric crisis
	Dystonia
	Tics
	Other movement disorders
Episodic phenomena during sleep	Normal physiologic movements
	Epilepsy, especial frontal lobe
	Paroxysmal nocturnal dystonia (may be seizures)
	Pathologic fragmentary myoclonus
	Restless leg syndrome/PLMS
	Parasomnias
	Sleep apnea
Paralysis	TIAs
	Hemiplegic migraine
	Alternating hemiplegia of childhood
Drop attacks	Seizures: atonic, tonic, myoclonic or astatic
	Syncope
	Vertebrobasilar TIA
	Metabolic disorders

	Cataplexy

Note: Psychogenic seizures can present under any category PLMS, periodic limb movements of sleep; REM, rapid eye movement; TIA, transient ischemic attack. *Source*: Partly adapted from So NK, Andermann F. Differential diagnosis. In: Engel J, Pedley TA, ed. *Epilepsy:* A Comprehensive Textbook. Philadelphia: Lippincott-Raven; 1997:791–797; and NICE guidelines: the epilepsies: clinical practice guideline, October 2004, available: http://www.nice.org.uk/page.aspx?o=229389.

Basilar migraine (see Chapter 274) occasionally causes alteration of consciousness, but associated symptoms and its slow evolution usually allow it to be readily distinguished from a seizure. *Transient global amnesia* (TGA) produces abrupt memory loss but does not involve alteration in consciousness or awareness. Episodes of TGA last several hours but almost always <1 day. Patients appear bewildered and anxious, ask repeated questions as a result of their memory loss, but are otherwise normally alert and interactive. Seizures only rarely cause transient amnesia in isolation ("epileptic amnesia"); usually there are other indications of complex partial seizures, although these can be quite subtle.

Panic attacks can be confused with partial seizures, with errors occurring in both directions. Panic attacks have several features not usually associated with seizures. They tend to be triggered by known stressors, last >5 minutes, and are associated with dyspnea, palpitations, trembling, and intense fear. There may be some sense of detachment, but there is no loss of consciousness or responsiveness. Some patients hyperventilate, which can lead to oral and bimanual paresthesias, carpopedal spasm, and dizziness. Almost all patients with panic attacks (95%) have associated anxiety disorders, phobias, or depression. Features suggesting seizures are absence of a consistent trigger, short duration (<5 minutes), amnesia for parts or all of the spell, an observed period of unresponsiveness, and prominent oral or hand automatisms. Differentiating the two conditions is sometimes difficult and may require video-EEG monitoring for definitive resolution.

Table 6 Differential diagnosis of paroxysmal sensory disturbances

Presentation	Possible etiologies
Somatosensory attacks/parasthesias	Seizures: parietal onset
	Transient ischemic attack
	Multiple sclerosis
	Peripheral neuropathy
	Restless leg syndrome
	Hyperventilation/anxiety attack

	Hypnagogic hallucinations
	Schizophrenia
Visual symptoms	Seizures: occipital or temporooccipital
	Migraine with aura
	Transient ischemic attack
	Ocular disorders
	Disorders of optic pathway (phosphenes/photopsias)
	Hypnagogic hallucinations
	Schizophrenia
	Drugs
Auditory symptoms	Seizures: posterior temporal neocortical
	Ear disorders (including Ménière disease)
	Cranial bruits
	Palatal myoclonus
	Drugs
Vertigo	Seizures: temporoparietal
	Vestibular disorders (including Ménière disease)
	Basilar artery migraine
	Brainstem disorders
Abdominal sensation	Seizures: variable onset, most commonly limbic

	Migraine Drugs: side effects Gastrointestinal disorders
Autonomic disturbances: • Flushing • Pallor • Sweating • Palpitations	Seizures: most commonly limbic onset Panic attacks Presyncope Hypoglycemia Pheochromocytoma Carcinoid syndrome Mastocytosis

Note: Psychogenic seizures can present under any category. *Source*: Partly adapted from So NK, Andermann F. Differential diagnosis. In: Engel J, Pedley TA, eds. *Epilepsy:* A Comprehensive Textbook. Philadelphia: Lippincott-Raven; 1997:791–797; and NICE guidelines: the Epilepsies: clinical practice Guideline, October 2004, available: http://www.nice.org.uk/page.aspx?o=229389.

The symptoms of *hypoglycemia* can also mimic epilepsy, usually in individuals being treated for diabetes mellitus. On rare occasions the hypoglycemia may be due to an insulinoma.[2] Insulinomas present with an insidious onset of transient neurologic (usually motor) deficits, confusion, lethargy, personality change, and autonomic disturbances. Diagnosis is

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often delayed because other neuropsychiatric diagnoses tend to be considered first.[15] *Idiopathic recurrent stupor*[36] is a controversial syndrome thought to be due to excessive endogenous benzodiazepine levels causing recurrent episodes of prolonged stupor and prominent rhythmic beta activity on EEG (identical to what is seen in patients taking benzodiazepine drugs). Symptoms respond to flumazenil, a benzodiazepine antagonist. Some investigators have suggested that this syndrome is due to unrecognized exogenous benzodiazepine use.[14]

Paroxysmal Abnormal Movements

Convulsive syncope and limb-shaking TIAs were discussed in a previous section. *Myoclonus* (see Chapter 277) can be epileptic or nonepileptic (Table 5). When it is epileptic, jerks are associated with generalized spike-wave or polyspike-wave discharges on EEG; other seizure types are usually present but can be absent. Myoclonic seizures in idiopathic generalized epilepsy are

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usually part of the syndrome of juvenile myoclonic epilepsy. They tend to be most frequent in the morning shortly after awakening and present during adolescence or in early adulthood and are exacerbated by recent alcohol intake or sleep deprivation. Nonepileptic myoclonus is not associated with other seizure types or epileptiform discharges in the EEG. Patients with multiple sclerosis can have "*tonic spasms*" that appear similar to epileptic tonic seizures, and these often respond to antiepileptic drugs.

Paroxysmal movements in sleep usually require video/EEG/polysomnographic monitoring for definitive diagnosis. Even with such testing, the nature of *paroxysmal nocturnal dystonia* is often unclear. Some authorities have argued that it is a movement disorder, whereas others have shown that, in many cases, it is a manifestation of localization-related epilepsy.[35,41] We believe that it is usually or always epilepsy. Regardless, it is quite responsive to AEDs such as carbamaze-pine.

Sometimes seizures present with purely "negative" symptoms such as weakness or numbness, thereby mimicking a TIA. The brief, recurrent, stereotyped and reversible nature of these events or their eventual spread to areas that result in positive phenomena usually leads to the correct diagnosis. On occasion, the negative ictal phenomenon is followed by postictal migraine (especially common in occipital epilepsy, but not rare in any epilepsy syndrome), mimicking migraine with aura, hemiplegic migraine, or other complicated migraine attack. The reverse—a seizure triggered by a migraine aura, possibly due to cortical spreading depression—can also occur, although this is much less common. To make matters more confusing, there are rare families with both seizures and familial hemiplegic migraine. In fact, mutations in the same calcium-channel gene on chromosome 19 can cause familial hemiplegic migraine, epilepsy, episodic ataxia, chronic ataxia (SCA-6), or some combination of these.[21,27,34]

Drop attacks are sudden falls with or without momentary loss of consciousness. They can occur due to syncope (discussed previously), cataplexy, Ménière disease, vertebrobasilar TIAs, or seizures. Seizures that cause sudden falls can be myo-clonic, tonic, atonic, or combinations of these. These seizures are usually part of an epileptic syndrome with multiple seizures types in neurologically abnormal children, most commonly with Lennox-Gastaut syndrome. On rare occasions, temporal lobe seizures can cause drop attacks, but virtually always late in the course of chronic temporal lobe epilepsy.[12] Focal seizures (temporal and frontal, more often left hemisphere) can also lead to asystole with cardiac syncope, fortunately a relatively rare occurrence.[8,28]

Cataplexy is usually triggered by strong emotions, especially laughter, and is eventually associated with other symptoms of narcolepsy such as sleep attacks, hypnopompic or hypnagogic hallucinations, and sleep paralysis in the majority of cases. In vestibular drop attacks associated with *Ménière disease*, there is almost always a history of previous attacks of more typical vertigo (without sudden drops), usually accompanied by tinnitus, ear fullness, and hearing loss. Patients often describe a sensation of being pushed suddenly to the ground. Historically, consciousness is not lost with these falls, although momentary loss of consciousness may not be recognized or recalled by patients with drop attacks from any cause. Vertebrobasilar TIAs have already been discussed; they are rare causes of isolated drop attacks. In some elderly patients, a firm diagnosis is elusive. As with syncope, cardiac arrhythmia is the most important entity to diagnose quickly because life-threatening ventricular arrhythmias (particularly a prolonged pause or asystole) can present as drop attacks.

Paroxysmal Sensory Disturbances

Paroxysmal sensory disturbances are listed in Table 6, and several have already been discussed. Paroxysmal visual disturbances are likely encountered most often and are clinically the most important. Simple visual hallucinations are common in both migraine with aura and occipital lobe seizures (see Chapters 237, 238, and 274). The most reliable differentiating feature is the time course: Migraine auras almost always last >5 minutes, typically 20 to 30 minutes, whereas seizures are almost always <5 minutes and typically <2 minutes in duration. Occipital seizures are often followed by a typical migraine headache. Thus, a migraine with a visual aura that lasts <5 minutes is likely to be caused by, or associated with, a seizure. Migraine auras tend to be black and white or glittery, have straight lines with sharp angles, and march across a visual field quite slowly (over several minutes). Occipital seizures include colors and circles or dots and march across a field quickly (seconds).

Psychogenic Nonepileptic Seizures

Psychogenic nonepileptic seizures are found in 20% to 40% of patients referred to epilepsy centers[3,4,13] (see also Chapters 207 and 282). Episodes of PNES are variable in presentation, and strong emotional or psychological elements are common precipitants. A history of physical or sexual abuse or a personal or family history of psychiatric disease is often obtained in patients with PNES, but a definite diagnosis on the basis of history alone is usually not possible. Repeatedly normal interictal EEGs in the presence of medically refractory seizures also raise the possibility of PNES. Incontinence and injuries are unusual but can occur.

Violent flailing or thrashing of arms and legs, side-to-side head movements, and pelvic thrusting are common in patients with PNES, although similar phenomena can be observed in partial seizures of frontal lobe origin. Preserved consciousness with sustained bilateral motor activity of the limbs is rare in epilepsy but occurs in some patients with frontal lobe seizures, especially those involving the supplementary motor area. Other features suggestive of PNES include variability from spell to spell, lack of spells occurring during sleep, spells in the physician's office, prolonged spells, starting and stopping of symptoms or movements, motionless state with eyes closed, lack of tachycardia, and a slow-motion, neurasthenic state with hypophonia during recovery. Even the most experienced observers cannot always distinguish epileptic from psychogenic spells. A definite diagnosis of PNES can be made only with video-EEG recording. A negative ictal EEG alone does not prove a nonepileptic etiology because a significant proportion of simple partial seizures and a small number of complex partial seizures (predominantly those of extratemporal origin) do not have identifiable scalp EEG correlates. In these cases, clinical semiology, stereotypy, and spells arising from EEG-documented sleep allow proper diagnosis.

To complicate matters further, PNES and epileptic seizures may coexist in the same patient.[3,9,20] Therefore, recording nonepileptic attacks in a patient with uncontrolled seizures does not prove that all the patient's seizures are psychogenic. Before reaching a final conclusion, one must verify with the patient and family that the recorded events are typical of the habitual spells experienced at home.

The AAN Therapeutics and Technology Assessment Subcommittee recently reported on the use of serum prolactin in differentiating epileptic seizures from nonepileptic seizures.[7]

Data from one Class I study and seven Class II studies supported the use of serum prolactin levels measured at 10 to 20 minutes following the event as an adjunct test for differentiating generalized tonic–clonic or complex partial seizures from PNES in adults and older children. These levels should then be compared with interictal baseline prolactin levels drawn on a different day at the same time. With epileptic generalized tonic–clonic seizures, prolactin levels are elevated to at least three times baseline. An epileptic etiology is also more likely if there is a prominent but transient metabolic acidosis and elevated creatine kinase after 12 to 24 hours.

Summary and Conclusions

Almost any condition manifesting with recurrent, stereotyped, and episodic symptoms can represent epileptic seizures. The extent to which other conditions are considered in the differential diagnosis of epilepsy depends on the nature of the symptoms and the age of the patient. A detailed history is the cornerstone of diagnosis because few patients have seizures in the office or clinic. It is important to bear in mind that many patients are unaware of some or all of their seizures or do not realize that they are associated with impaired awareness. Although ancillary tests are necessary and usually helpful, they can also be misleading. Incidental findings on brain imaging or misinterpretation of benign EEG patterns or artifacts can result in misdiagnosis. Dual diagnoses are not unusual, and having a nonepileptic condition does not preclude the possibility of coexisting epilepsy. Some of the most common coexisting illnesses with paroxysmal features are migraine and psychogenic nonepileptic seizures.

Cardiac syncope is the most important alternative diagnosis to consider in a patient with transient loss of consciousness because lack of appropriate and timely treatment can be

fatal. A few myoclonic jerks and transient posturing occur in a significant number of patients with syncope. Neurally mediated reflex syncope, the most common type, is characterized by an identifiable stimulus or set of circumstances, a characteristic prodrome, pallor, diaphoresis, and rapid return to normal. In contrast, a seizure is suggested if the loss of consciousness is followed by postictal symptoms that clear gradually, lateral tongue biting, myalgias, and, on the following day, elevated creatine kinase. Incontinence and elevated prolactin levels can be seen in both conditions and are therefore not helpful in differentiating between them.

Panic attacks are often confused with partial seizures, but they are usually longer and associated with psychological stress and do not involve complete loss of awareness. Paroxysmal movements in sleep usually require EEG-video monitoring or polysomnography for definitive diagnosis. EEG-video monitoring is also required to make a firm diagnosis of PNES. Serum prolactin levels drawn 10 to 20 minutes after a spell and compared to baseline levels drawn at the same time on a different day can be helpful in differentiating between generalized tonic–clonic or complex partial seizures (elevated prolactin level in many but not all cases) and PNES (no change in prolactin).

Anyone whose spells persist despite reasonable treatment or remain of uncertain etiology should be referred to an epilepsy monitoring unit. With the widespread availability of EEG-video monitoring systems, polysomnography, autonomic function laboratories, and other diagnostic tests, it should be possible to make a definitive diagnosis in nearly all patients with recurrent spells.

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Chapter 69

Overview: Diagnostic Evaluation

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Introduction

Because epilepsy is a group of conditions and not a single homogeneous disorder, and because seizures may be symptoms of both diverse brain disorders and an otherwise normal nervous system, it is neither possible nor desirable to develop inflexible guidelines for what constitutes a "standard" or "minimal" set of diagnostic tests. Furthermore, it is not always clear from the history that the patient has even had a seizure or has epilepsy. Thus, the role of the physician is threefold: (a) to determine whether epilepsy or seizures exist and not some alternative diagnosis; (b) to define, if possible, an underlying cause; and (c) to optimize treatment.

The Clinical Data

Epilepsy is primarily a historical diagnosis, and the initial assessment and approach to management are based, in large part, on the clinical history, especially on an accurate description of the event in question. Information should be obtained from the patient when possible, as well as from other individuals (especially family members) who have observed typical attacks. Memory is always highly selective, however, and the abrupt and unexpected nature of seizures—especially the first—may render witnessed accounts unreliable. The patient's recollection may also be limited by alteration of consciousness and postictal amnesia. Important focal features may be overlooked, and estimates of seizure duration are almost invariably exaggerated. Auras are often particularly difficult to characterize from the patient's description because the subjective experiences are only vaguely recalled ("a feeling in my head") or conveyed using terms that different individuals use to mean quite different things (e.g., dizzy, shaking, chill, numbness, spacey). Finally, there are important age-related differences in seizure semiology that physicians must take into account. Even with these limitations, physicians must train themselves to take a systematic history that does not overlook important features (Table 1). Family members of patients who have recurrent episodes may succeed in capturing one or more of them on videotape, and this can provide invaluable information not otherwise available. As Aicardi and Taylor conclude (Chapter 70), "Clinical diagnosis is an intellectual process whereby all available sources of information, from the purely clinical to the highly technical, are integrated with a view to arrive at a meaningful conclusion."

Laboratory Tests

The clinical data from the history and physical examination should allow a reasonable determination of probable diagnosis, seizure and epilepsy classification, and the likelihood of an underlying pathologic condition of the brain. Based on these considerations, diagnostic testing should be undertaken selectively. Thus, a normal child with brief lapses of attention whose symptoms can be reproduced in the office by hyperventilation is a very different patient than is a middle-aged man who has developed partial seizures and seems to be getting progressively worse. It must be remembered, too, that diagnostic testing is never a substitute for clinical judgment and observation through follow-up and reexamination.

A great number of both routine and highly specialized diagnostic tests are available to aid physicians in the evaluation of patients with known or suspected seizures. Routine blood tests are rarely diagnostically useful in healthy children and adults but are necessary in newborns and in older patients with acute or chronic systemic disease to detect abnormal electrolyte, glucose, calcium, and magnesium values and impaired liver or kidney function.

Monitoring antiepileptic drug (AED) levels depends on the clinical situation. Leppik (Chapter 71) suggests that levels be determined at steady state after good seizure control has been attained to establish a useful benchmark. This can be repeated at annual follow-up as needed, for example, at the time of renewal of a driver's license, to ensure that adequate levels are being maintained. Other times when AED levels may be indicated are when a patient has breakthrough seizures, experiences toxicity, or is being treated with other drugs known to influence AED metabolism (especially when such comedication is altered).

The electroencephalogram (EEG) remains the most useful diagnostic test when a seizure disorder is considered (Chapters 73,74,75). An EEG should generally be obtained in every case as an aid to diagnosis or to assist in classifying the type of seizure or epilepsy syndrome. In some instances, EEG findings will aid in prognosis and in determining the need for treatment. Buzáki and Traub (Chapter 72) provide an excellent discussion of the physiologic basis of EEG activity and introduce new concepts concerning EEG oscillatory patterns. They suggest that the term *desynchronization* is misleading and that synchronous EEG activities should be characterized in terms of slow and fast oscillatory patterns. The same oscillatory patterns may be responsible for generating both interictal (Chapter 73) and ictal (Chapter 74) discharges. Bleck et al. (Chapter 75) discuss the greatly expanded use of EEG in intensive care unit (ICU) settings, which has led to major improvements in ICU care. Tassinari and Rubboli (Chapter 77) advocate the use of polygraphic recordings in selected patients to help differentiate sleep-related phenomena from epileptic seizures. Visual qualitative analysis of seizure-related EEG discharges has relied mainly on the experience and expertise of the electroencephalographer. Wong and Lopes da Silva (Chapter 76) describe and advocate the use of quantitative methods to characterize electrical and electromagnetic signals responsible for interictal and ictal discharges. The magnetoencephalogram (MEG) (discussed in Chapter 78) can provide additional information concerning the spatial features of the epileptogenic brain region, although it is unlikely that MEG will ever be routinely available. These and other quantitative analyses are complementing traditional visual assessment of EEG and other physiologic data and providing additional information that is clinically useful in selected situations. Long-term monitoring (Chapters 92 and 93) with simultaneous collection of EEG data and videotaped behavior has allowed improved characterization of seizure semiology and definitive separation of epileptic from nonepileptic behaviors. It has also opened the possibility of surgical intervention to far greater numbers of patients. LeVan and Gottman (Chapter 95) summarize the essential role played by computers in data reduction and analysis of physiologic data obtained during both routine EEG and long-term monitoring.

Table 1 important historical features of epileptic seizures

First event in the seizure (aura, initial movement, or sensation)

Subsequent evolution of the seizure

Postictal manifestation [focal (e.g., Todd paresis) vs. diffuse nonspecific]

Is there more than one seizure type?

Has there been a change in the seizure pattern?

Date and circumstances of first attack

Subsequent precipitating or triggering factors (alcohol, sleep deprivation, hormonal)

Age of onset, average frequency of attacks, and longest seizure-free interval

Response to previous medication (doses, blood levels, cominations)

Family history (parents, offspring, siblings)

Is there a history of neonatal seizure or febrile seizures?

Is there a history of previous brain injury?

Is there personal or family history of other neurologic, mental, or systemic disease?

The modern era of structural brain imaging—first with computed tomography (CT), then with magnetic resonance (MR)—has revolutionized our ability to identify epileptogenic brain lesions (see Chapter 79). With high-resolution MR scans, a wide variety of pathologic lesions can now be diagnosed routinely and noninvasively. These include mesial temporal sclerosis, well-differentiated gliomas, gangliogliomas, cavernous malformations, neuronal migration defects, and dysembryoplastic neuroepithelial tumors. Fewer seizure disorders are now justifiably classified as "idiopathic" or even "cryptogenic." The identification of lesions that are potentially surgically resectable has added a new dimension to treatment and given hope to many patients with medically intractable epilepsy. Functional brain imaging, such as positron emission tomography (PET) (Chapter 80), single photon emission computed tomography (SPECT) (Chapter 81), and magnetic resonance spectroscopy (Chapter 82), is providing additional and often critical information about the extent of metabolic changes and alterations in regional cerebral blood flow associated with seizures, and graphically illustrates how widespread can be the disruptive effects of an epileptogenic brain region. Indeed, surgical decisions in infants with seizures may actually rely more on functional characterization of the epileptogenic "focus" than on delineating structural pathology. Chapter 83 describes the current and future uses of functional MRI, and Chapter 84 addresses the use of computational anatomic studies to characterize structural abnormalities in patients with epilepsy.

Chapters 92 and 93 describe how to organize an effective monitoring unit that meets both technical requirements and patients' needs for a pleasant environment that can be tolerated for relatively long inpatient stays. Due to quality-of-life and fiscal restraints, it is important to maximize the yield of meaningful data obtained within a reasonable time frame. Drug withdrawal and activation techniques (Chapter 94) increase the yield of epileptiform EEG abnormalities and facilitate recording clinical events in compressed time intervals. Neuropsychological testing (Chapters 90 and 91) provides measurements of a patient's intellectual capacity as well as insights into the effects that epilepsy is having on an individual's cognitive functioning and psychosocial adjustment. In addition, neuropsychological assessment is an essential part of the pre- and postsurgical evaluations. The particular tools used, as well as data interpretation, are highly age dependent.

Even with all of these diagnostic aids, there are many patients in whom the epileptogenic mechanisms, including even where in the brain seizures originate, are poorly understood. In the previous edition of this book, we identified MR spectroscopy and functional MRI as exciting new directions. Both these methods are now used routinely. In this second edition, new directions that we have chosen include the remarkable possibility of seizure prediction (Chapter 85); optical imaging (Chapter 86), which may provide physiologic data that can be compared to the biochemical data obtained with in vivo microdialysis (Chapter 87); transcranial magnetic stimulation (Chapter 88); and cellular and molecular imaging (Chapter 89).

Summary and Conclusions

Many of the newest diagnostic methods are most readily applicable to older children and adults. Because of various social, ethical, and practical constraints, the newest ancillary tests are not routinely used in infants and very young children, and the role of these technologies in the youngest age groups remains to be determined. Nonetheless, it is readily apparent that the ability of physicians to diagnose, classify, and intervene rationally in epileptic disorders has improved dramatically, to the overall benefit of their patients. Comprehensive epilepsy centers, with their multidisciplinary teams, are probably best positioned to make optimal (including cost-effective) use of the various clinical and investigative diagnostic tools available in the management of patients with complex or intractable seizure disorders.

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Chapter 70

History and Physical Examination

Jean Aicardi

David C. Taylor

Introduction

Careful and detailed history taking remains the cornerstone of accurate diagnosis of epilepsy,[13] the prototype of diseases for which the diagnosis rests entirely on clinical grounds and especially on historyâ€"the diagnosis is as good as the history.[16] Therefore, history taking and physical examination should be performed in a comprehensive and methodic manner, although flexibility in their practical modalities is an absolute requirement in the examination of children, especially younger ones. The investigation of any disorder should be scaled in proportion to the severity of the problem. Epilepsy has a tremendous impact on patients' lives, both physically, because it is a threatening and dangerous condition, and psychosocially, because of its chronicity, the fears it generates, and the still-present prejudice against affected persons. Therefore, patients with a suspected diagnosis of epilepsy should be investigated using all means necessary for making a definitive diagnosis, establishing a prognosis, and planning the proper treatment. The necessary investigations vary with the clinical presentation and need not include much in the way of laboratory or other ancillary examinations. However, the process often requires considerable time and is best completed from onset. A succession of fragmentary assessments that may initially seem to save time often results in delaying the diagnosis, sometimes with disastrous consequences, and usually turns out to represent a considerable waste of time.

Taking a history of a paroxysmal disorder demands a proper technique of medical interrogation and a good knowledge of the protean manifestations of the disorder. The aim is to determine as precisely and reliably as possible the objective characteristics and course of a sudden, brief, and unexpected event that has occurred in a highly emotional context and is only partially recalled, often in a biased manner, by both the patient and witnesses. The objective of physical examination is to look for any evidence of an underlying cause, whether limited to the brain or involving other systems as well, as is the case with neurocutaneous disorders, chromosomal abnormalities, and some systemic illnesses.

History Taking

Background

History taking cannot follow strict rules and has to be adapted to each individual case and person. It is often wiser to take advantage of opportunities that may arise during conversation with the person relating the history than to try to maintain a chronologic and logically constructed questioning.

As previously indicated, history should be scaled in detail in proportion to the seriousness of the illness; therefore, it should be meticulously detailed for epilepsy. In some cases, apparently casual details are of tremendous importance.

Although the basic aims of history taking are fundamentally the same, there may be some variation depending on the position of the person taking the history, and the emphasis may not be the same for primary physicians and those in secondary or tertiary care. More importance may variably be given to clearing previous diagnostic confusion, to assessing overall life situation, or to reviewing treatment. History taking is also the first act of the doctorâ€“patient relationship, with long-lasting consequences for the subsequent development of this relationship.

Some physical conditions of the room in which the history is taken are important. Information cannot be properly exchanged in impossible situations. Seating and lighting arrangements should be meant to favor communication, and disturbing factors, such as telephone calls or the repeated entrance of a secretary or colleagues, should not interfere with the exchange. It is essential that patients have the feeling that their personal history is being listened to and given the importance it deserves. This is one of the reasons that sufficient time should be allowed, even for relatively simple cases, and even if the doctor feels that questioning has been thorough. Time is also essential to gather information about fine details, which may constitute valuable cues. It may take a very long time to disentangle the threads of a history and reweave them into a true likeness to the event.[16] Indeed, more than one session is often necessary. An additional advantage is that both patient and doctor can think again about the case and possibly come up with new questions or newly remembered details.

With children, the history is usually obtained mainly from parents or guardians, and such third-party questioning poses special problems. The child's account, if any can be given, should be particularly facilitated. Older children and adolescents can contribute information on subjective phenomena that are unobtainable from any other source; such information may prove crucial for the diagnosis and be important to the young patients in coming to terms with their illness. One of the difficulties of third-party questioning is the increasing risk for biased and overrehearsed accounts, with the description of the attacks conforming more and more to a preconceived, once-and-forever established idea of what they are like, without the possibility of rectification on the basis of phenomena personally felt by the patient.

Another risk is to give credence to only one parent's account, usually the mother's, and ignore the other's. Listening to both parents, however, might result in contradictory statements. A decision of which account is more credible must be made, which may be in part arbitrary. For these reasons, a fresh history and not a simple repetition of previously given accounts should be obtained at each new consultation. Accepting previous accounts uncritically is a major source of diagnostic errors. Jeavons[10] emphasized the trap represented by a previous

diagnosis of known epilepsy often based on a history that may not have been properly obtained. Such a diagnosis may nonetheless remain accepted for years, thus delaying the true diagnosis. Doctors' and nurses' accounts are potentially of great value. In some cases, however, they can also be misleading because professionals often have a tendency to describe attacks as they should theoretically be rather than as they are. Whoever the witnesses, critical scrutiny of their accounts is essential. A distinction should be drawn between first-hand versus second-hand witnesses and between witnesses who have been able to observe the whole of a seizure and those who saw only a part of it. An assessment of the degree of reliability of the witnesses has to be done. It should not be based only on how articulate they are; attempts at checking the veracity of their accounts (e.g., by gathering details that indicate whether they were really in a position to observe some reported phenomena) are important.

The style of history taking depends on individual patients and physicians. With some patients it may be best to listen first to their own account with minimal interference and later ask precise questions about specific points. With others, more directed questioning may be necessary to avoid garrulous, irrelevant, and interpretative accounts. In such cases, it is useful to formulate direct questions about uninterpreted events that are to be answered as yes or no. The meaning of terms has to be made clear and medical terms avoided as much as possible. It is often helpful to offer patients several simple words that are synonymous with medical terms, among which they can choose. Stephenson gave a useful list of such words.[16] Questioning several witnesses may permit some cross-checking of data, and going back to the history to gain more and finer details can clarify some issues.

Obtaining a description of the paroxysmal events is the most important part of history taking, and it requires a high degree of attention and considerable time. The history, however, is not limited to this description. Such events occur in individual persons who react in their own way and in a given setting. Thus, there are two approaches to history takingâ€”obtaining a history of the complaint and obtaining a history of the person.

History of the Complaint

It is often very useful and always recommended to ask for a description of specific attacks. This should especially include *the last attack actually witnessed* because it is better remembered. The physician should not forget that there may be two or several types of seizures. In such cases, efforts should be made to obtain a description of the most recent seizures of every type.

A description of the *first* seizure is also of great interest because it not infrequently differs from subsequent attacks. For example, it may have been a febrile convulsion followed by complex partial seizures. In addition, the impact it had on the patient's life and the way the patient reacted to the first epileptic event can tell much with regard to later adjustment to the illness.

A description of the *worst* attack is also to be sought. It provides indications about the capacities for adjustment under maximal stress and about the scale of the clinical problem and the risk to life. The circumstances of occurrence, duration, and possible presence of postictal phenomena, such as Todd's hemiplegia or aphasia, can give valuable clues to lateralization and localization.

The *setting* in which the attacks occurred may be of considerable significance. Epileptic attacks or nonepileptic paroxysmal events that simulate seizures are often nonrandom phenomena, and the circumstances of occurrence can be important for differential diagnosis and planning of investigations. Points of particular interest include the temporal relation of events to the sleepâ€“waking cycle; for example, was the patient awake or asleep, and, if asleep, did the attack occur at onset of sleep, before or shortly after awakening, or in the middle of the night? In the case of daytime attacks, the following should be determined: Whether the attacks usually occur at a particular time (morning or evening) or apparently at random; the type of activity in which the patient is engaged at the time of seizures (resting, exercising, in bed, at school, playing, in a bath, eating or fasting, standing or reclining, using a computer, watching television or playing a video game, bored, emotionally disturbed, or engaged in a pleasant occupation); and the patient's general state of health (concomitant or recent febrile or other systemic disease). In the case of a child taking antiepileptic drugs on a long-term basis, the temporal relationship of fits to drug ingestion, the possible failure to take one or several doses, and events such as vomiting or other digestive disturbances that may have interfered with absorption of ingested drugs should all be noted.

A *prodrome* is a long-term indication of a forthcoming attack. Prodromes (e.g., changes in behavior, such as irritability, sleepiness, feelings of hunger, sweating, hypothermia, distant feeling, and the like) are mostly absent or of secondary importance. Behavioral changes are more often seen before migraine attacks than before epileptic seizures; hunger and hypothermia can suggest hypoglycemia.

The search for a *stimulus* regularly associated with the occurrence of attacks is of extreme diagnostic interest and consequently should be systematic and thorough. Identification of the regular association of attacks with an immediate stimulus is often of greater value than even a description of the attacks. The significance of the fit may also be better pointed to by the type of stimulus than by the clinical phenomenology of the paroxysm. The *regular* precipitation of attacks by such stimuli as the sight of blood, blood letting, or injections, prolonged standing in hot or confined places, holding breath, or pain from minor trauma, such as bumping one's head, is practically diagnostic of â€œanoxic seizures,â€[15] even when the induced attack is difficult or virtually impossible to differentiate from a convulsive generalized epileptic seizure, as in convulsive syncope.[7,11] Conversely, such precipitating factors as flashing lights or startle strongly favor a diagnosis of epilepsy after such rare conditions as hyperekplexia have been excluded.[3] Certain maneuversâ€”for example, Valsalva's maneuverâ€”can induce attacks that are very difficult to distinguish from seizures but are easily recognizable when the initial phenomena are well described.[2]

The *analysis of the aura* or first symptom of the seizure is so important that detailed questioning is required; the patient and witnesses should be asked to concentrate on that moment. A wide range of symptoms, from vague sensations (especially abdominal and visceral) to highly elaborate motor, sensory, and psychosensorial phenomena, occurs in epileptic seizures,[9,17] but auras can occasionally precede attacks of other types, such as migraine (especially visual aura) or syncope.[4,16] In addition, no description of auras is available with young children. The occurrence of an aura can sometimes be deduced from a child's observed behavior, such as screaming, appearing terrified, and running to his or her mother, or suddenly stopping any ongoing activity and assuming an appearance of preoccupation and concentration. Although such events are often fairly vague, their regular presence indicates that a seizure is probably of localized origin or that any more apparent first symptom is not in fact initial and can be misleading if interpreted without knowledge of previous phenomena.

Reconstitution of the *ictal sequence* itself is difficult because most seizures are brief events with rapidly changing and multiple symptoms. So many things take place in so short a time that even the best witnesses are unlikely to be able to describe all

aspects of the whole sequence. For that reason, monitoring with video in a hospital or, more easily, at home is extremely helpful. It is not, however, a substitute for history taking because it often does not allow a full view of the patient and provides no information on essential clues such as awareness, responsiveness, memory of events, and any cognitive or language involvement. Inquiry about ictal incontinence and tongue biting is traditional, but the presence of these symptoms is neither necessary nor specific for a diagnosis of epilepsy. Although lateral tongue biting is unusual in disorders other than epilepsy, it has been reported occasionally in syncope.[11] The subjective estimation of the *duration* of a paroxysmal attack is very often exaggerated. The person taking the history should attempt to obtain temporal clues, such as the time elapsed before taking the child to the hospital or calling a neighbor for help or phoning the doctor. It is imperative to separate the duration of the active seizure itself from that of the immediate postictal coma, confusion, or sleep and therefore to ask specific questions in this regard. Very often, the duration initially reported includes the whole of the ictal and immediate postictal phases.

The manifestations of the postictal phase and their duration are of interest because they can provide useful lateralizing or localizing clues and indications about the severity of the ictal phase.

Asking witnesses to complement descriptions by miming seizures is often more informative than a purely oral account. Often, miming reveals features that would have easily gone unrecognized, such as asymmetry of posture. The doctor's miming of features of seizures can be of considerable help to witnesses in distinguishing between jerks and vibratory tremor and understanding what an oro-alimentary automatism or different types of head turning look like. Certain types of seizures, such as infantile spasms or other minor seizures, are difficult to recognize, and parents often recognize them only when their features are demonstrated.

Finally, the rate of repetition of the attacks should be carefully recorded, as well as the regularity or irregularity of repetition and the occurrence of clusters. This should be done for each type of seizure.

Patient History

This includes the patient's life and developmental history; aspects of social, behavioral, and cognitive functioning; and the family history, especially of seizures and other neurologic disorders.

Developmental History

Developmental history is recorded along traditional lines, with special emphasis on the perinatal period; milestones, such as age of independent walking and first talking; and school performance, which in older children is particularly useful for the assessment of cognitive functions. A precise history of previous diseases, especially meningitis, encephalitis, and febrile convulsions, including attempts to determine their length, possible lateralization, and the presence of any localized postictal deficit or other episodes of loss of consciousness, is of obvious importance. Any severe or unusual disease should be recorded. It should be remembered that a previous history of seizures or central nervous system disease, however significant, does not necessarily indicate that subsequent paroxysmal events are epileptic.

History of Epilepsy

A history of the epilepsy (once the epileptic nature of the child's seizure has been *authenticated*) should be reconstructed in great detail. Age of onset, initial manifestations, change in frequency and type of seizures, occurrence of episodes of status, presence of deterioration or stagnation (cognitive, behavioral, or both), and any previous investigations should be determined. A precise drug history is of particular importance for a rational treatment, but this is difficult to obtain. It requires considerable effort to collect old prescriptions and determine the duration of drug trials. When available, blood levels of drugs can give precisely dated indications of the adequacy of previous treatments; these should be correlated with the presence and frequency of attacks as well as side effects during the corresponding periods. Family history of neurologic diseases and especially of seizures may be important for diagnosis and prognosis, but it is often difficult to elicit, and the significance of paroxysmal events that occurred many years earlier is often impossible to assess. If medical records, electroencephalographic reports, or other results are available, they should be scrutinized carefully because some types of epilepsy have a strong genetic component.

The Person With Epilepsy

It is essential that the physician gain a sufficient knowledge of the patient as a person. Therefore, the patient's life history, personality, and interests should be reviewed. This will help in assessing the degree of disturbance caused by epilepsy, which varies considerably depending on preferred activities. Persons with active lifestyles, such as athletic individuals, may well find themselves more handicapped than individuals more inclined to reading or a sedentary lifestyle, at least in terms of physical risk. The type of personality may help to predict how a patient will respond to the challenge of epilepsy. The social background will in part determine the sort of explanation and advice given. Assessing the family background and trying to determine to what extent the family may help or represent an additional problem are also important; the attitudes of any other group to which the patient belongs will also be significant. All this information will influence the manner of addressing the patient, the way of conducting the investigations, and the expectation of success in treatment.

The impact of epilepsy on a patient's emotional, professional, and social status is extremely variable, depending on the combination of disease manifestations and the patient's personality and manner of living. Assessment of this impact will largely determine a number of essential decisions, for example, the respective indications of medical and surgical treatment. With children, the disorder affects both the patient and the family. The attitude of parents regarding the risks they are ready to accept and their level of expectations greatly affects their way of coping with the disease. For children and adolescents, school is not only a major part of their present life, but is also a critical determinant of the rest of their existence. Inquiring about school performance is therefore of the utmost importance. Moreover, children with epilepsy who have a satisfactory cognitive level and reasonable capacity for paying attention may be capable of attending a school for normal children, but the real learning problems of some well-behaved children may be overlooked.

Physical Examination

Neurologic Examination

The neurologic examination should take into account the interval since the last seizure. If it is performed within minutes

or occasionally hours after a fit, the physician should look for postictal signs, especially focal signs such as Todd's hemiparesis, even of a minor grade. Transient aphasic symptoms are also important to detect. Care should be taken to separate postictal confusion from true aphasia. Postictal symptoms and signs of localizing or lateralizing significance are not uncommonly the clue to the localized origin of a seizure otherwise reported by witnesses as generalized. When the examination is performed after some time has elapsed since the last seizure, the main objective is to determine whether there are signs of permanent nervous system dysfunction, favoring a diagnosis of symptomatic epilepsy, and if there is evidence for a focal brain lesion. Signs of increased intracranial pressure should be looked for but are rather uncommon. Only undoubted neurologic abnormalities are of value. The so-called soft signs cannot be accepted as sole evidence of brain damage. Additional neurologic signs of interest include language difficulties and possible evidence of drug toxicity such as nystagmus, ataxia, diplopia, or tremor. When appropriate, tests for laterality should be performed because patients with epilepsy related to brain damage have an unusual incidence of left-handedness or mixed laterality, in contrast to patients with idiopathic epilepsy.[14]

General Medical Examination

Skin Examination

Examination of the skin is of particular importance because neurocutaneous syndromes are a frequent cause of epilepsy in children. The presence of cutaneous features of tuberous sclerosis, such as depigmented nevi, fibrous plaques, shagreen patches, or facial angiofibromas, or the presence of a facial flat angioma in the region of the trigeminal nerve, characteristic of Sturge-Weber syndrome, is particularly important. Linear nevus of the face, cutaneous signs of neurofibromatosis, and abnormal pigmentation, as in incontinentia pigmenti or Ito's disease, are also significant.[8]

The growth and general appearance of patients can also provide diagnostic clues. Epilepsy is a major manifestation of many dysmorphic syndromes, for example, Angelman's disease.[18] Body asymmetries are of particular importance. Epilepsy is not rare in association with hemihypertrophy. Facial asymmetry has been reported to be associated with temporal lobe epilepsy.[5,17] Unusual shape and especially size of the skull may suggest craniosynostosis, hydrocephalus, chronic subdural hematoma, or arachnoid cysts.

Eye and Visual Examination

Eye and visual examination should aim to detect papilledema and field cuts associated with focal brain lesions. Ocular motor abnormalities might suggest involvement of the brainstem or floor of the third ventricle. Intrinsic abnormalities such as cataracts, glaucoma, or corneal opacities may indicate the etiology of seizures.

Visceral Examination

Visceral examination should never be neglected and should include a particularly careful cardiovascular examination. The presence of heart arrhythmias or murmurs can suggest syncopal rather than epileptic attacks. Electrocardiographic recording is indicated in selected cases, and measurement of the PR interval should then be performed. Measurement of blood pressure, although often neglected in children, may be the only way of attributing seizures or status epilepticus to arterial hypertension.[6]

Brief Assessment of Cognitive, Social, and Behavioral Functioning

An opinion about the overall level of the patient's functioning in these areas is formed during examination and questioning. It is useful to assess systematically, although informally and rapidly, the more important components of the patient's mental state. The possibility of latent anxiety or depression, even psychosis, should be kept in mind. The level of attention and hyperkinesis is important to judge, as is the general fund of knowledge. The patient's overall behavior and manner of relating to the physician and the attributes of the patient's spouse or family are all very important in terms of diagnosis and therapeutic orientation and should be carefully recorded. They may be of considerable value in planning treatment and in assessing the effects of intervention. A more formal neuropsychologic evaluation is not necessary in most children if school performance and familial behavior are not affected. When there is suspicion of change or deterioration, it is important that a precise baseline be established to allow later comparisons.

Summary and Conclusions

Clinical diagnosis is an intellectual process whereby all available sources of information, from the purely clinical to the highly technical, are integrated with a view to arrive at a meaningful conclusion.[1]

In all fields of medicine, history and physical examination form the essential bases of diagnosis, even though additional information might be required from other sources, such as neurophysiologic and imaging studies and biochemical or other laboratory tests. Such additional information should not be requested in either a predetermined or a haphazard manner, but according to a hypothesis founded on clinical grounds. In this way, time is saved and the costs of investigationâ€"not only in terms of money but also of inconvenience and possible suffering for patients and their familiesâ€"can be considerably reduced while results are improved.

The principles that apply in other fields of medicine are relevant to an even greater degree in epilepsy and other paroxysmal disorders; history taking is by far the most important step in the diagnosis of paroxysmal disorders. Several series give figures of 20% to 30% for false diagnoses of epilepsy.[12] This represents a considerable burden of unnecessary suffering, caused above all by less-than-optimal history taking.

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Chapter 71

Laboratory Tests

Ilo E. Leppik

Introduction

Laboratory testing for persons with epilepsy is needed for two reasons: (a) measuring antiepileptic drug (AED) concentrations and (b) monitoring for adverse side effects. Therapeutic drug management is based on the rationale that knowledge of the AED concentrations is necessary to identify the appropriate dose and concentration for an individual patient and monitor treatment to maintain stable therapeutic levels. Measurements of AED concentrations can improve care by avoiding breakthrough seizures, and unnecessary toxicity. AED concentrations can be influenced by a number of factors: (a) pharmacologic, such as changes in product formulation and use of comedications; (b) alterations in physiologic states, such as pregnancy, illnesses, and aging; and (c) noncompliance with AED treatment. The rationale for routine laboratory monitoring for systemic adverse events is based on the assumption that subclinical hepatitis or hematopoietic dysfunction can be detected in asymptomatic patients. However, the cost of performing routine laboratory testing is considerable. As the public becomes increasingly concerned about the cost of health care, physicians can expect to feel more pressure to cut expenses, especially in the area of routine laboratory testing. In facing these pressures, physicians must also consider the overall cost to both patients and society of not performing laboratory tests when they are necessary. This chapter describes a rational approach to the use of laboratory testing in patients with epilepsy.

Monitoring Antiepileptic Drug Treatment

Measurement of antiepileptic drug concentrations is necessary to manage the treatment of epilepsy. Routine measurement of AEDs without a specific purpose is not cost effective and not recommended. There must be a reason for ordering each test. One useful approach is to obtain an AED level when the patient has been titrated to his or her therapeutic goalâ€"no or the fewest seizures with no toxicity. This level then serves as that individual's therapeutic range and is much more useful than the published ranges, which are population derived. Serial AED concentrations in compliant, healthy patients usually do not vary by more than 20%. Thus, if a person has a therapeutic target of 13 mg/L, a level of 10.4 to 15.6 mg/L would fall within this range. However, a level of 18 mg/L, although within the published therapeutic range, may be unnecessarily high. Measurement of a level during a breakthrough seizure can then be very informative. If the level was <10 mg/L, a cause for the decreased concentration must be identified. However, if the breakthrough was associated with a level of 13 mg/L, a lowering of the patient's seizure threshold by worsening of the epileptogenic process or a lowering of the seizure threshold (i.e. use of excitatory substances, sleep deprivation) must be considered, and appropriate changes in management can be initiated. Table 1 lists appropriate times at which to measure AED concentrations.

A number of devices exist for measuring drug concentrations in plasma, serum, saliva, and other biologic samples.[9,12,30] To be approved by the U.S. Food and Drug Administration (FDA), a device for therapeutic drug monitoring must be able to perform with a coefficient of variation of <5%. Although all marketed devices meet this standard under strict testing conditions, the potential for error exists, and unusual results should be repeated.

In the United States, there are laboratories within clinics and within hospitals, as well as central national laboratories. Clinics and hospitals can usually measure concentrations of the older AEDs, usually within hours for emergency situations. Tests are available for all of the new AEDs through central laboratories, but results are usually not available for a few days. Every laboratory in the United States has relations with national laboratories, and so physicians in, say, Minot, North Dakota, or other remote locations can have access to these laboratories. Routine tests measure only the total (bound plus unbound) concentrations. For some highly bound AEDs such as valproate (VPA) and phenytoin (PHT), unbound or â€œfreeâ€ levels may be more informative.

The rationale behind measuring levels is that the serum concentration, specifically the unbound (free) fraction, is in equilibrium with the receptor-site concentrations. This has been verified for the older AEDs, for which serum levels and brain concentrations in animal and human specimens (obtained during surgery) showed close relationships.[10,18,24] However, these relationships have not been established for the newer AEDs. Indeed, for some of these, there appears to be very strong, and in some cases irreversible, binding with the pharmacologically active site. This appears to be the case for vigabatrin and perhaps levetiracetam, for which the pharmacodynamic half-life appears to be much longer than the plasma half-life.

Although a single measurement at steady state when the person with epilepsy has attained the therapeutic goal sets the individual's therapeutic range, subsequent monitoring is for the purpose of assuring that these levels are being maintained in this range. Serial measurements are needed to identify variations from the target AED concentration over time. These can be attributed to pharmacokinetics, changes in physiology, and/or compliance issues.

Table 1 Use of blood tests in monitoring patients with epilepsy

For antiepileptic drugs

1. At steady state, good seizure control, and no toxicity, to obtain a target level[a]
2. Annually, to monitor compliance
3. When a patient has a breakthrough seizure
4. When a patient experiences toxicity
5. When a substance known to affect metabolism is added or removed
6. When there is a change in a patient's physiologic state (pregnancy, burns, renal failure)

Hematologic/hepatic

1. At initiation of therapy
2. Once during the first few months
3. Whenever clinical symptoms occur
4. Annually or less often

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[a] Trough measurements are primarily useful for pharmacokinetic studies. Levels drawn for target levels and compliance should be obtained at similar times of day, within 1 to 2 h of each other.

Variability Due to Pharmacokinetics

A number of pharmacokinetic factors can influence the absorption and elimination of antiepileptic drugs. For example, changes in product formulation can markedly alter the absorption of phenytoin. If the preparation is more bioavailable, phenytoin concentrations can increase to levels at which toxic reactions occur.[21,30]

Alteration of gastric or intestinal absorption by food or other drugs may influence the time or extent of absorption. If a product's bioavailability is affected by food,

lowered levels and seizures may occur. This appears to be the case for phenytoin as well.[3,32] Changes in hepatic or renal blood flow can modify the rate of clearance and affect drug concentrations only to a small degree.[6]

Time of sampling can contribute to variability for some AEDs. In general, AEDs with long absorption and elimination characteristics vary little, regardless of time of sampling. Phenytoin has a relatively long absorption time (time to maximal concentration of 9 to 12 hours) because it is absorbed only in the small intestine. It also has a long half-life and nonlinear kinetics (slower elimination at higher concentrations). Thus, the absorption and elimination phases overlap during one dosing cycle, and the concentration differences are small, usually <2 mg/L, between peak and trough levels. On the other hand, carbamazepine and valproate both have shorter absorption times and, during long-term therapy, have elimination half-lives of 6 to 14 hours. This can lead to differences between peak and trough concentrations of as much as 50% or more. Sustained-release preparations for these products have lengthened the absorption phase and have decreased the peak and trough variations.

To be most useful, blood samples should be drawn at the same time relative to dosing. In a clinical setting, this can be accomplished by always scheduling appointments for the same time of day. A reasonable limit is Â±1 hour, which can be attained most of the time. For example, a person with a 3 PM examination usually has blood drawn by 3:30 PM, but any time between 2:30 PM and 4:30 PM is acceptable. Trough concentrations can be quite misleading, especially for AEDs with short serum half-lives. In one institution, it was mandated that carbamazepine levels needed to be >4 mg/L for carbamazepine, and physicians were requested to increase its dose if levels were below this value. Unfortunately, all levels were measured as morning fasting or trough levels, and the mandated dose increases sometimes led to toxicity. The problem was solved by simply changing the time of sampling to approximately 2 hours post morning dose. Through levels for AEDs are widely used, but for therapeutic management of AEDs they can be misleading for agents with short half-lives such as carbamazepine, valproate, and levetiracetam.

Concentrations of AEDs that are metabolized can be altered by the addition or removal of other drugs that are also processed by the liver. These may be other AEDs, drugs used for other disorders, or herbal supplements and foods. For example, St. John's wort, a popular herbal purported antidepressant, is a powerful inducer of cytochrome P3A4, the major isozyme responsible for carbamazepine metabolism, and can significantly lower concentrations of prescription drugs.

Variability Due to Altered Physiology

Any change in homeostasis can alter the absorption or elimination of AEDs. The most commonly encountered situation is that of a woman who becomes pregnant. Of the older AEDs, phenytoin concentrations decrease the most, beginning in the first trimester and decreasing to the lowest levels before labor. Carbamazepine and valproate levels also decrease but to a lesser degree. Of the newer AEDs, lamotrigine levels decrease dramatically, by as much as 200%.[30] There are no specific guidelines for monitoring AED concentrations during pregnancy, but it may be reasonable to obtain a minimum of one measurement at the onset of pregnancy, during the second trimester, and near the time of delivery, or at any time that breakthrough seizures occur or there are symptoms of toxicity.

Phenytoin clearance can be accelerated during various febrile illnesses and also after vaccination.[14,16] Because many AEDs are metabolized by the liver, any condition affecting this organ can influence the concentrations of AEDs. Very little research has been done in this area, and so knowledge of basic principles of metabolism and clinical judgment rather than evidence-based medicine must be relied on when caring for patients with hepatic disease. Burns extensive enough to require admission to a burn unit significantly influence phenytoin, phenobarbital, and diazepam levels.[2] Valproate concentrations can be influenced by head injury.[1] The newer AEDs have not been studied in this regard.

Renal disease or the normal decline in renal function in the elderly necessitates the measurement of AEDs whose elimination is mainly through the kidneys. The formulas that are given to calculate creatinine clearance to adjust doses for gabapentin and levetiracetam cannot substitute for actual measurement of levels. This is because in the elderly, decreases in muscle mass lower the amount of creatinine in the blood, and levels may be in the normal range even when the kidney function is less than in younger persons. In addition, protein binding is greatly affected by renal disease, and the unbound (free) concentration must be measured for highly bound AEDs (phenytoin, valproate).

Table 2 Types of behavior in noncompliance

Medication ingestion
Consistent overcompliance Consistent undercompliance Irregularity Irregularly irregular Sporadically irregular Cyclically irregular Filling prescriptions Medical appointments
Lifestyle
Sleep patterns Alcohol use Psychological stress Exposure to music, strobe lights Drug abuse Adherence to regulations
Intentionality of compliance (patient controlled)
Rational Pregnant women afraid of teratogenicity Compensation related Irrational Fear of medicine Superstition
Structural
Memory deficit Financial problems

Variability Due to Compliance Issues

Noncompliance with antiepileptic drug treatment is a major factor in the recurrence of seizures in patients with epilepsy (Table 2). As many as 50% of all patients with epilepsy are noncompliant to a degree that interferes with optimal treatment.[17,27] Studies using electronic monitors to measure compliance indicate that what might appear to be sporadic seizures can be attributed to missed doses of prescribed drugs.[5] Consequently, proper management of epilepsy requires physicians to identify noncompliant patients, determine the extent of the problem, and devise and monitor an appropriate intervention strategy.

A number of studies have evaluated the variability of serial concentrations of phenytoin and carbamazepine in various settings. In a study of phenytoin, patients in a residential facility were found to have values for the coefficient of variation of <10%.[13] In compliant patients in an outpatient study of bioavailability during which samples were obtained every 2 weeks and compliance was monitored by pill counts,[13] a few of these patients reported missing an occasional dose several days before the blood sample was taken. This did not significantly affect the coefficient of variation. In the same study, sequential patients at the epilepsy clinic were asked about compliance; a strong correlation was noted between reported noncompliance and a high coefficient of variation. Data from rigorous studies indicate that in most compliant patients the coefficient of variation for carbamazepine is <20%.[8] My experience indicates that similar fluctuations can be expected with valproate.

Based on this experience, use of the percentage of deviation from the mean of two or more levels has been adopted to aid in the evaluation of noncompliance. Although calculation of the coefficient of variation is more accurate, a determination of the percentage of deviation is simpler and more practical for clinical use. In general, deviation of 20% or less from the mean of previous phenytoin, carbamazepine, or valproate concentrations is evidence for adequately compliant behavior. A patient can attain the 20% limit even if an occasional dose is missed. Values between 20% and 45% should raise strong suspicions of noncompliance. Values deviating more than 45% are almost always associated with noncompliance. The larger the percentage, the more marked is the noncompliance (assuming the absence of any factors altering pharmacokinetics, such as a new drug, illness, or altered bioavailability). The percentage of deviation from the mean can be used as a general measure of the degree of noncompliance. For example, a patient with a deviation of Â±25% is less severely noncompliant than one with a deviation of Â±45%, which would have to be considered when assessing the need for intervention to improve compliance.

Serial measurement of AEDs levels is a relatively useful tool for detecting noncompliance. With increasing legal pressure on physicians to certify the safety of a driver's license or a particular work place for a patient with epilepsy, it becomes critical to know that a patient is compliant. Thus, if a patient's antiepileptic drug concentrations fall within the usual therapeutic range but vary from the high to the low end, noncompliant behavior must be suspected. That patient might also be at increased risk for intermittent toxicity or seizures.

Serial measurement of blood levels is relatively crude compared with devices that record each opening of a container of medication daily. Such devices can detect noncompliant behavior lasting only a few days between clinic visits or blood level measurements.[5] However, use of this method is limited to clinical research because of its cost.

Table 3 Laboratory parameters: normal ranges and threshold (â€œpanicâ€) values for antiepileptic drugs

	Normal range	â€œPanic valuesâ€
	Hematologic	
White blood cell count, total	4500â€“10,000/mm^3	<2.0/mm^3

Neutrophils	1500â€“6700/mm^3	<1.0/mm^3
Platelets	150,000â€“350,000/mm^3	<50/mm^3
Hemoglobin	11.5â€“15.0 g/dL	<10.0 g/dL
Hematocrit	34%â€“44%	<28%
	Hepatic	
Transaminase (SGOT)	15â€“40 U/L	>100 U/L
Transaminase (SGPT)	9â€“31 U/L	>100 U/L
Lactate dehydrogenase	60â€“200 U/L	>600 U/L
Alkaline phosphatase	30â€“115 U/L	>300 U/L
Î³-Glutamyl transpeptidase	0â€“65 U/L	None
Bilirubin, total	0.2â€“1.2 mg/dL	>1.5 mg/dL
	Other	
Sodium	135â€“145 mEq/L	<128 mEq/L

SGOT, aspartate aminotransferase; SGPT, alanine aminotransferase.

Table 4 Idiosyncratic reactions to antiepileptic drugs: approximate rates of occurrence[a]

Reaction	CBZ	PHT	VPA	Other AED
Aplastic anemia	2/575,000 (*n* = 65 [61 adults])	A (n [asymptotically	A(*n* = 1â€“2)	A(*n* = ?)

		equal to] ~35)		
Hepatitis	A (*n* [asymptotically equal to] 30)	A (*n* = ~60)	See Table 5	A (*n* [asymptotically equal to] 20)
Pancreatitis	A(*n* = a few)	A (*n* = a few)	A (*n* [asymptotically equal to] 10)	A(*n* = 0)
Exfoliative dermatitis ~30)	A (*n* [asymptotically equal to] 30)	A (*n* [asymptotically equal to] 30)	A (*n* <5)	A (*n* [asymptotically equal to] 30)

AED, antiepileptic drug; CBZ, carbamazepine; PHT, phenytoin; VPA, valproate. [a]Data are based on a review of the literature and hearsay. Data are very incomplete, except for hepatitis related to CBZ and VPA and hematologic disorders related to CBZ. A, <1/100,000 treated patients.

Laboratory Testing for Adverse Reactions

Serious reactions to antiepileptic drugs are rare. They include hepatotoxicity, bone marrow suppression, pancreatitis, exfoliative dermatitis, and other conditions that, if not detected in time, can be fatal. Much emphasis has been placed on routine monitoring of hepatic and hematopoietic factors to detect these serious reactions. However, routine monitoring is expensive and has been discouraged.[22,23] This policy might be appropriate in the case of all antiepileptic drugs except felbamate.

The popularity of laboratory monitoring is based on the assumption that subclinical hepatitis or hematopoietic dysfunction can be detected. However, slight elevations of hepatic enzymes are not unusual, and mild leukopenia is a common side effect in patients treated with antiepileptic drugs. Thus, in addition to being costly, laboratory testing can be misleading, provoke further testing, or lead to inappropriate discontinuation of medication. Table 3 lists the â€œpanicâ€ levels my colleagues and I use as an indication to take immediate action.

The cost of performing routine laboratory testing is considerable. If one assumes that 2.8 million persons are being treated for epilepsy in the United States, that a set of hematologic and hepatic tests costs $50 (conservatively), and that the test is repeated three times a year for each patient, the cumulative cost can be projected to be $420 million. Nevertheless, in the United States reluctance is great to abandon routine laboratory monitoring for two reasons. First, there is the perception that such testing can detect a serious adverse event early enough to prevent a fatal outcome. Second, there is the real concern regarding the medicolegal consequences of not following community practice standards. However, support is growing in the literature for the abandonment of routine monitoring.[4,23]

The precise frequency of serious drug effects from antiepileptic drugs is difficult to determine because of inadequate postmarketing surveillance. Most of the information comes from two sources: (a) reports in the medical literature and (b) information from drug manufacturers supplied to the FDA. A recent search of the Medline database revealed 424 references regarding hepatitis and/or phenytoin, valproate, carbamazepine, phenobarbital, or other antiepileptic drugs. Most of these consisted of isolated case reports, often involving other major complicating factors. A much shorter list of references was generated for hematologic problems.

Tables 4 and 5 list the approximate number of cases, derived from the medical literature, of life-threatening reactions attributable to specific antiepileptic drugs in the United States. These numbers are crude, but they underscore the relatively infrequent occurrence of serious reactions.

Felbamate is the antiepileptic drug with the highest risk for aplastic anemia.[19] During 1994, 32 cases of aplastic anemia were reported in a population of approximately 130,000 to 150,000 treated individuals. Approximately two thirds of these patients recovered. Severe hepatitis developed in approximately 12 to 14 persons. Many neurologists are comfortable with testing every month or two after the first few months of treatment and every 3 months after a year of treatment. There is no evidence that routine monitoring is of any definite benefit. Indeed, if clinical symptoms develop shortly after a normal set of laboratory values has been obtained, retesting is essential.

Carbamazepine was considered to be associated with a high risk of aplastic anemia shortly after its introduction. In a thorough review using an estimated number of persons exposed per year,[26] a rate of two cases of aplastic anemia and one fatality for 575,000 treated persons was calculated. It is interesting that 61 of the 65 reported cases of agranulocytosis or aplastic anemia occurred in adults. Similar data are not available for phenytoin, but such cases have been reported in the literature. Aplastic anemia has rarely been reported in association with valproate use, and well-documented cases of aplastic anemia with phenobarbital or other antiepileptic drugs are rare. Thus, it would appear that the highest risk for aplastic anemia is found in adults exposed to felbamate, and after that in patients taking carbamazepine, but this conclusion must be tempered by lack of reliable data for the other drugs. Even then, the risk of the group at highest risk is very low.

A pattern emerges for the incidence of hepatitis. The group at highest risk comprises infants exposed to valproate in the context of polypharmacy.[7] This may be a consequence of the fact that valproate metabolism depends on both cytoplasmic and mitochondrial systems, and the relative production of hepatotoxic metabolites is influenced by the amount of drug passing through each system. The proportions of cytoplasmic and mitochondrial metabolism can be influenced by comedication and age-related factors. In addition, the existence of metabolic or neurologic disorders poses a significant risk.[33] The actual number of fatal cases of hepatitis attributable to phenytoin is difficult to determine, but the overall number may be approximately 50. Carbamazepine and other antiepileptic drugs appear to be associated with a lower rate of occurrence of hepatitis. Thus, infants given valproate are the only group at major risk[25]; adults receiving valproate or other antiepileptic drugs are at very low risk.

Other potentially fatal adverse reactions include pancreatitis, serum sickness reaction, Stevens-Johnson syndrome, and other rare complications. Routine laboratory testing for pancreatitis is unnecessary because clinical symptoms of abdominal pain and anorexia are dramatic and lead to specific confirmatory tests.[28] For the other reactions, clinical skills are more diagnostic than laboratory findings.

Table 5 Approximate rate of occurrence of fatal hepatitis from valproate

Monotherapy	Polytherapy	Age
1/7,000	1/500	Infant
1/9,000	1/6,500	Child

0	1/22,000	Adult

Source: Dreifuss FE, Langer DH, Moline KA, et al. Valproic acid hepatic fatalities, II. U.S. experience since 1984. *Neurology.* 1989;39: 201â€“207.

Problems of False Positives

Table 3 is a list of laboratory tests performed routinely. The â€œpanicâ€ values are those that trigger an immediate response from the laboratory and are often grounds for discontinuation of a drug.

Use of antiepileptic drugs often leads to values outside normal laboratory ranges. A study of 610 persons with epilepsy between 20 and 40 years of age evaluated the effect of long-term treatment on various laboratory parameters.[11] The findings were that leukocyte counts were significantly lower, with a specific lowering of lymphocytes. In addition, persistent macrocytosis without anemia was noted. In a review of approximately 2,500 white blood cell (WBC) counts in a population of >1,100 patients with epilepsy receiving primarily valproate, phenytoin, carbamazepine, or a combination of these, >17% had WBC counts <4,000/mm^3 and 8 had a WBC count <2,500 (1,800 to 2,400)/mm^3.[15] The 8 cases with â€œpanicâ€ values were reviewed; all were clinically asymptomatic, and in 2 cases the physician discontinued carbamazepine based on laboratory findings. In 1 case, zidovudine was discontinued and the WBC count normalized. In 5 cases, no change was made in treatment. The lowest WBC count was 1,800/mm^3. Other reports documented transient leukopenia in up to 12% of adults and children treated with carbamazepine.

Gamma-glutamyltranspeptidase (GTT) levels are markedly elevated in patients with epilepsy and do not signal hepatic dysfunction. Levels of serum glutamic oxaloacetic transaminase (SGOT; same as aspartate transaminase [AST]) might be more reliable. In one study,[15] approximately 33% of values for >1,100 patients were above normal; in 12 cases the SGOT (AST) values were >100 U/L (normal, 10 to 35). In 8 cases, the elevations were sporadic, that is, the values were in the usual range when the test was repeated. In 4 cases, all on valproate, the drug dose was decreased, and in 1 it was discontinued. All 4 had had clinical symptoms of loss of appetite, malaise, or nausea, which had alerted the clinician to possible problems that led to testing.

Thus, from one study of >5,000 visits involving >1,100 patients who were followed for 24 months, approximately 2,500 measurements of WBC counts and SGOT levels were obtained.[15] The incidence of WBC counts of <2,500/mm^3 was 6.6/1,000 patients, and in only 2 cases was an antiepileptic drug changed based on low WBC count. The rate for â€œpanicâ€ SGOT elevations was higher. Nevertheless, clinical symptoms led to tests that uncovered abnormal values. Thus, overall, routine testing alone uncovered only 2 asymptomatic cases with â€œpanicâ€ values that led to discontinuation of therapy. The approximate total cost of these tests was $125,000 in 1990. It is reasonable to conclude that the cost effectiveness of routine laboratory testing is very questionable. This conclusion is reinforced by the fact that most â€œpanicâ€ values represented false positives, in the sense that they did not lead to modification of treatment but only to additional testing.

Camfield et al. reported similar results from a smaller series.[4] They performed serial testing at initiation of treatment, at 1, 3, and 6 months, and then every 6 months. There were no serious clinical reactions, but laboratory testing was repeated in 6% of cases to confirm abnormal but clinically insignificant results. In a study of 662 adults in whom treatment was initiated with phenytoin, carbamazepine, phenobarbital, or primidone, no clinically significant abnormalities were detected after 6 months.[20]

Antiepileptic drugs, in addition to the major complications listed in Tables 4 and 5, can cause other problems that may be associated with clinical symptoms. Valproate can be associated with thrombocytopenia. This in itself may not be problematic if undetected and asymptomatic. However, the risk for bleeding during injury or surgery might be increased. Carbamazepine is associated with hyponatremia in a substantial number of patients but causes symptoms only occasionally. Elevated ammonia levels can be associated with valproate, but they are often not significant in the absence of clinical symptoms or other laboratory signs of liver failure.

Alternatives to Routine Blood Monitoring

Screening laboratory testing should be obtained to detect any underlying problems before initiating therapy with antiepileptic drugs. These tests can uncover specific problems that, if they developed further, might be incorrectly attributed to the drug. Rarely, however, do they contraindicate use of a medication. Table 6 lists recommended tests.

It can be useful to order a complete blood cell count to check for leukopenia in patients on carbamazepine or a platelet count in patients on valproate 2 to 6 months after onset of treatment. Routine blood or urine monitoring after initiation of therapy is probably unnecessary if the patient is asymptomatic.

Patients in a high-risk group and those unable to communicate must be monitored more closely. The most efficient monitoring system is a high degree of awareness of symptoms that portend serious complications, patient awareness of these symptoms, and rapid assessment of any problems that suggest a rare but potentially fatal complication. However, wide acceptance of less routine testing might be offset by continued liability in the rare but unfortunate cases of serious adverse effects.

Summary and Conclusions

Monitoring antiepileptic drug levels is not necessary at each clinic visit. It is prudent to determine levels at steady state after good seizure control has been attained to establish a benchmark. This target level can be followed annually, especially at the time of renewal of a driver's license, to ensure that adequate levels are being maintained. Other appropriate times to measure are when a patient is having breakthrough seizures or experiencing toxicity. In addition, whenever therapy with other drugs known to affect antiepileptic drug metabolism is modified, measurement of blood levels should be considered.

For systemic toxicity, the recommendations in the current *Physicians Desk Reference* are less strict than those in previous editions. Screening laboratory testing should be obtained to detect any underlying problems before therapy with antiepileptic drugs is initiated. It might be useful to order a complete blood cell count to check for leukopenia in patients on carbamazepine or a platelet count in patients on valproate 2 to 6 months after onset of treatment. Routine blood or urine monitoring after initiation of therapy is probably unnecessary if the patient is asymptomatic. Patients in a high-risk group and those unable to communicate can be monitored more closely. For patients on felbamate, monthly determination of laboratory parameters is suggested at initiation of therapy and, then at each clinic visit or if symptomatic.

Table 6 Blood tests to be done before initiating treatment with antiepileptic drugs

All patients
Hematology
Complete blood cell count, platelet count, differential
Prothrombin time, partial thromboplastin time (optional)
Serum chemistry
Glucose
Blood urea nitrogen
Calcium
Phosphorus
Magnesium
Creatinine

Urate
Bilirubin
Alkaline phosphatase
Aspartate aminotransferase
Alanine aminotransferase
Total protein Albumin

Specific high-risk patients (based on clinical findings)

Lactate, pyruvate, arterial blood gases
Urine metabolic screen, organic acids
Ammonia
Carnitine
Specific tests for suspected underlying disease

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Chapter 72

Physiologic Basis of the Electroencephalogram and Local Field Potentials

GyÃ¶rgy BuzsÃ¡ki

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Introduction

Analyses of electric and magnetic fields and imaging energy production in brain structures are the principal instruments in the arsenal of contemporary neuroscience for noninvasive studies of the brain. Three fundamental methods can provide high temporal resolution of neuronal interactions at the network levelâ€"electroencephalogram (EEG), magnetoencephalogram (MEG),[31] and, in invasive experiments, voltage-sensitive, dye-based optical imaging[28] (see Chapters 74, 75, 76, 77, 80, 87, and 90). Each of these methods has its advantages and shortcomings. A common major obstacle of clinical EEG, MEG, and optical imaging methods is that their â€œviewsâ€ are confined mostly to surface events (although MEG, in principle, can provide information about depth events as well[62,63]). However, most network interactions occur in the depth of the cortex. Although imaging methods provide significant spatial resolution, including deep structures in the brain, all of these â€œglobalâ€ methods face the same fundamental questionâ€"the â€œreverse engineeringâ€ problem of signal interpretation.[62] The signals measured by EEG and MEG reflect the cooperative actions of neurons. Therefore, full understanding of the signals recorded by these methods is possible only after their cellular-synaptic generation is explored. Nevertheless, even without a full deciphering of the origin of the recorded signal, EEG and MEG provide useful information about brain operations in health and disease, and EEG evaluation remains the essential method for the diagnosis of epilepsy.

Membrane currents generated by neurons pass through the extracellular space. These currents can be measured by electrodes placed outside the neurons. The field potential (i.e., local mean field) recorded at any given site reflects the linear sum of numerous overlapping fields generated by current sources and sinks distributed along multiple cells. This macroscopic state variable is referred to as local field potential (LFP) if measured by a small electrode in the brain, an electrocorticogram (EcoG) if measured by, for example, subdural grid electrodes, and EEG if recorded from the scalp, or an MEG as monitored with magnetosensor semiconductor quantum interference devices (SQUIDs). LFPs provide experimental access to the spatiotemporal activity of afferent, associational, and local operations in a given structure. Field potential measurements provide the best experimental and clinical tools for assessing cooperative neuronal activity at high temporal resolution. However, without a mechanistic description of the underlying neuronal processes, the mean fields recorded by these methods are a gross correlate of brain activity rather than a predictive descriptor of the specific functional/anatomic events.

Scalp recordings offer only limited information about the structures and neuron groups from which the electrical activity emanates, and the inverse problem does not have a unique solution. The difficulty of source localization using scalp EEG has to do with the low resistivity of neuronal tissue to electrical current flow, the capacitive currents produced by the lipid membranes, and the distorting and attenuating effects of glia, blood vessels, pia, dura, skull, scalp muscles, and the skin. As a result, the EEG recorded by a single electrode becomes a spatially smoothed version of the local field potentials under a scalp surface on the order of 10 cm^2, and under most conditions has little discernible relationship with the specific patterns of activity of the neurons that generate it.[62] The spatial resolution can be improved with intracranial electrodes such as subdural grid electrodes. Nevertheless, because current density, that is, the spatial derivative of current, is sensitive mainly to superficial sources, the signals recorded by scalp or grid electrodes sample mostly the electrical activity that occurs in the superficial layers of the cortex. The contribution of deeper layers is scaled down substantially, whereas the contribution of neuronal activity from below the cortex is, in most cases, virtually negligible. This â€œfish-eye lensâ€ scaling feature of EEG is the major theoretical limitation for improving its spatial resolution.

A straightforward approach to deconvolving the surface-recorded event is simultaneously to study electrical activity on the surface and at the sites of the extracellular current generation in experimental situations. LFP measurements (sometimes referred to as â€œmicro-EEGâ€[68]) combined with recording of neuronal discharges is the best experimental tool available for studying the influence of cytoarchitectural properties, such as cortical lamination, distribution, size, and network connectivity of neural elements, on electrogenesis. However, large numbers of observation points combined with decreased distance between the recording sites are required for high spatial resolution and for making interpretation of the underlying cellular events possible. Progress in this field has been accelerated by the availability of micro-machined silicon-based probes with numerous recording sites.[12,92] The information obtained from the depth of the brain can then assist with the interpretation of the surface-recorded events.

In principle, every event associated with membrane potential changes of individual cells (neurons, glia) contributes to the perpetual voltage variability of the extracellular space. Until recently, synaptic activity has been viewed as the exclusive source of extracellular current flow or EEG. As will be discussed, however, synaptic activity is only one of the several membrane voltage changes that contribute to the measured field potential. Progress during the last decade has revealed numerous sources of relatively slow membrane potential fluctuations not directly associated with synaptic activity. Such nonsynaptic events also may contribute significantly to the generation of local field potentials. Accordingly, this chapter focuses on the cellular origin of the extracellular fields. The reviews by HÃ¤mÃ¤lÃ¤inen et al.[31] and Okada et al.[64] provide detailed theoretical background for MEG and SQUIDs and compare EEG and MEG signal detection problems.

Measuring extracellular current flow: A TUTORIAL

Although a variety of sources can contribute to the extracellular current flow (see later discussion), for simplicity, we consider only synapse-mediated events in this section. For the transmembrane potential to change in a given neuron, there must be a transmembrane current, that is, a flow of ions across the membrane. This is the event that one has to spatially localize for the interpretation of the extracellular current or voltage. Opening of membrane channels (or more precisely, an increase in their open-state probability) allows transmembrane ion movement, that is, current flow. LFP (i.e., local mean field) recorded at any given observation point reflects the linear sum of numerous overlapping fields generated by current *sources* (e.g., current from the intracellular space to the extracellular space) and *sinks* (current from the extracellular space to the intracellular space) distributed along multiple neurons.

The term â€œfieldâ€ is often used differently by electrophysiologists and physicists. For the physiologist the field or local field typically means extracellular potential, whereas in physics the gradient of the field is referred to as electric potential. The field is defined at every point of space from which one can derive the force â€œfeltâ€ by an electric charge at that point. The field can be transmitted through volume and is known as volume-conduction. Lower-frequency currents produce, or correspond to, transmembrane currents over larger spatial extent of membrane than are fast signals, partially because the space constant of the dendritic cable is shorter for high frequencies than low frequencies. Furthermore, because the lipid membrane of neurons, glia, and other cells in the brain acts as a capacitive low-pass filter, it offers an easier passage to low-frequency signals than to high-frequency signals. As a result, slow signals, such as postsynaptic potentials, can propagate much farther in the extracellular space than can spikes. In addition, longer-duration events (e.g., excitatory and inhibitory postsynaptic potentials [EPSPs and IPSPs]) have a much higher chance of occurring in a temporally overlapping manner than do the very brief action potentials. Finally, many more neurons display EPSPs and IPSPs than fast spikes in a given temporal window because only a very small minority reaches the spike threshold at any instant in time. For these reasons, the contribution of action potentials to the LFP and especially to the subdural ECoG or scalp EEG in the normal brain is practically negligible. This is not necessarily the case under epileptic conditions, however, when neurons can synchronize within the duration of action potentials. The synchronously discharging neurons create local fields, known as compound or â€œpopulationâ€ spikes.

Excitatory currents, involving sodium (Na^+) or calcium (Ca^{2+}) ions, flow inwardly at an excitatory synapse (i.e., from the activated postsynaptic site to the other parts of the cell) and outwardly away from it. The passive outward current far from the synapse is referred to as a return current from the intracellular milieu to the extracellular space. Inhibitory loop currents, involving chloride (Cl^-) or potassium (K^+) ions, flow in the opposite direction. Viewed from the perspective of the extracellular space, membrane areas where current flows into or out of the cells are termed sinks or sources, respectively. The current flowing across the external resistance of the extraneuronal space sums with the loop currents of neighboring neurons to constitute the local mean field or LFP. In short, extracellular fields arise because the slow EPSPs, IPSPs, voltage-gated active currents, and other intracellular events (see later discussion) allow for the temporal summation of currents of relatively synchronously activated neurons.

Depending on the size and placement of the extracellular electrode, the volume of neurons that contributes to the measured signal varies substantially. With very fine electrodes, LFPs reflect the synaptic activity of tens to perhaps thousands of nearby neurons only. LFPs are, therefore, the electric fields that reflect a weighted average of input signals on the dendrites and cell bodies of neurons in the vicinity of the electrode. If the electrode is small enough and placed close to the cell bodies of neurons, extracellular spikes can also be recorded. Not surprisingly, in such a small volume of neuronal tissue, one often finds a statistical relationship between local field potentials, reflecting mostly input signals (EPSPs and IPSPs), and the spike outputs of neurons.[42] The reliability of such relationship, however, progressively decreases with increasing electrode size, by lumping together electric fields from increasingly larger numbers of neurons. This is why the ECoG or scalp EEG, the spatially smoothed version of the LFP at numerous contiguous sites in a volume, often has a poor relationship to the spiking activity of individual neurons.

In deciphering the current sourceâ€“sink origin of the local fields, we have to go â€œbackwardâ€ from LFP measurement to cellular-synaptic current sources.[57] Current density is the current entering a volume of extracellular space. The current flow between two recording sites can be calculated from the voltage difference and resistivity using Ohm's law, provided that information about the conductance (inversely proportional to resistivity) of the tissue is available. The conductance is a factor of both conductivity and the specific geometry of volume. If at least three linearly spaced electrodes are placed in the brain tissue, one can measure the voltage between the middle electrode and the two side electrodes and calculate the current flow between the pairwise sites. The difference between the respective current flows (i.e., the change over distance) is proportional to current density. More precisely, the current density is a vector reflecting the rate of current flow in a given direction through the unit surface or volume (measured in amperes/m^2 for a surface and amperes/m^3 for a volume).[25,56,60]

To illustrate the utility of the foregoing approach, consider a distant current source relative to the three equally spaced recording sites (Fig. 1). Each electrode will measure some contribution of the field (due to the passive return currents that pass through the extracellular space) from the distant source. Because the source is outside of the area covered by the electrodes, the voltage difference will be the same between the middle and side electrodes. Taking the difference between the voltage differences (voltage gradient), we get a value of zero, an indication that the measured field did not arise from local activity but was volume-conducted from elsewhere. In contrast, if the three electrodes span current-generating neuron groups, the voltage gradients will be unequal and their difference will be large, indicating the local origin of the current. By placing more microelectrodes closer to each other, one can more precisely determine the maximum current source density (CSD) and, therefore, the exact location of the maximum current flow.

Unfortunately, from CSD measurement alone, one cannot conclude whether, for example, an outward current close to the cell body layer is due to active inhibitory synaptic currents or reflects the passive return loop current of active excitatory currents produced in the dendrites. Without additional information that can clarify the nature of the current flow, the anatomic origin is ambiguous. The missing information can be obtained by simultaneous intracellular recording from representative neurons that are part of the population responsible for the generation of the local current. Alternatively, one can record extracellularly from identified pyramidal cells and interneurons and use the indirect spike-field correlations to determine whether, for example, a local current is an active,

hyperpolarizing current or a passive, return current from a more distant depolarizing event. Only after taking these extra steps one can pin down the current sources and sinks and make hypotheses about their synaptic-cellular origin. The combined information is very useful because it provides clues about the synaptic inputs to the same set of neurons whose outputs (i.e., spiking) can also be simultaneously monitored, provided that the recording electrodes are small enough. Once we have information about both the input and output of a small collection of neurons working together, we can begin to understand the transformation rules governing their cooperative action. This approach is the next best thing to the ideal condition when all inputs (synapses) and outputs of each cell are monitored simultaneously and continuously.

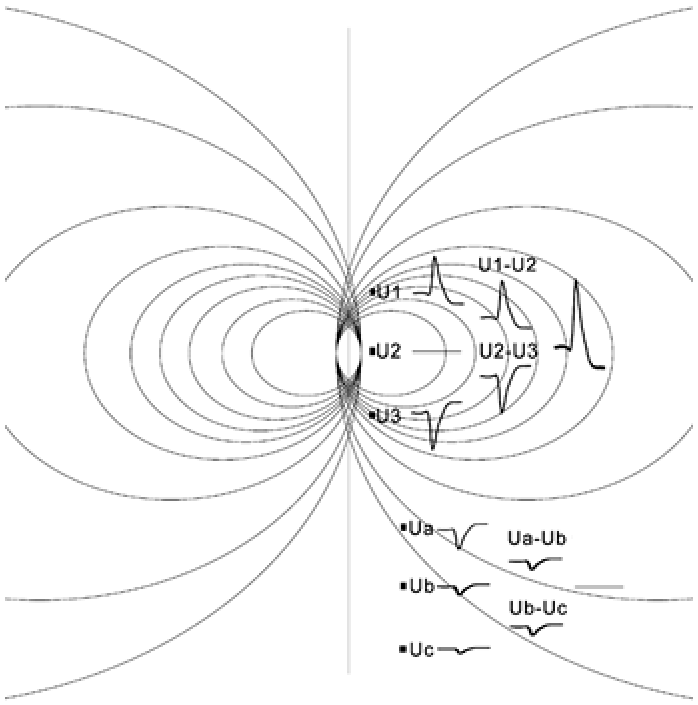

FIGURE 1. Identifying current sources. Current sourceâ€“sink dipole imbedded in a homogeneous and isotropic conductive medium. The density of lines reflects density of currents. The potential generated by the active dipole decays in the medium as the inverse square of the distance (not properly shown proportionally here, for illustrative purposes). The potentials measured at equally spaced locations, relative to an ideal infinite site (reference), are shown as U1, U2, and U3 close to the dipole, and Ua, Ub, and Uc far from the dipole. The differences of the potentials are shown in the middle row and the difference of the differences on the right. In a nonhomogeneous, nonisotropic medium, such as the brain, the current is flow is calculated as the ratio between the voltage (difference) and tissue conductivity (according to Ohm's law). Although dipole-induced voltages can be measured far from the source, calculation of current density by three simultaneously recorded sites is spatially confined and can help to identify the anatomic location of the dipole.

Figure 2 illustrates the necessary steps in the identification of network mechanisms of evoked and spontaneous field events. The example is taken from the hippocampus because it is a simple, three-layered structure consisting of orderly arranged principal cells (pyramidal and granule cells) and interneurons. Therefore, the synaptic interpretation of the extracellular current is simpler than in multilayered structures. Activation of the excitatory associational input by electrical stimulation will depolarize the mid-apical and basal dendrites of pyramidal cells (shown in blue in FIGURE 2). The passive return current will flow out of the cells at the level of the neuronal bodies and distal apical dendrites (shown in red in FIGURE 2) specify where exactly (Figure D or 2E). This change in voltage is reflected by the characteristic depth distribution of field potentials. The extracellular voltage is negative close to the excitatory synapse and positive in the cell body layer. The reason for this is the large depolarization of the dendrite and the gradual decrease of intracellular depolarization toward the soma. This synaptic activityâ€"induced intracellular voltage difference between the dendrites and soma (a â€œdipoleâ€) will result in a current flow across the resistive membrane (arrows in FIGURE 2F). Simultaneous events in many neighboring pyramidal cells will linearly sum and produce an extracellular voltage fluctuation that can be measured with closely spaced electrodes. After determining the resistivity (impedance in case of an alternating current signal) characteristics of the extracellular space, we can calculate the local currents and current densities from the voltage measurements.[25,60]

Increased afferent discharge also activates interneurons, some of which terminate on the cell bodies of the pyramidal cells. For example, the discharging basket cells release gamma-aminobutyric acid (GABA) and activate Cl^- channels, which allows the entrance of the negatively charged ion with resulting hyperpolarization of the pyramidal cell somata. Somatic hyperpolarization, in turn, creates a voltage gradient between the soma and dendrites (inhibitory dipole). The created intracellular voltage difference is the driving force of charges across the cell membrane and the consequent spatially distributed current flow in the surrounding extracellular fluid (FIGURE 2). Note that the direction of current flow is the same as in the case in which the driving force is apical dendritic depolarization (active sink). Because the direction of current flow is identical for dendritic excitation and somatic inhibition, the excitatory and inhibitory currents will sum in the extracellular space, resulting in large-amplitude field potentials. Because the excitation-concurrent somatic inhibition may prevent the depolarization of the axon initial segment and, consequently, the occurrence of action potentials, large-amplitude extracellular current flow can be associated with no spike output from pyramidal neurons. Thus, the relationship between dendritic excitation and spike output of pyramidal cells is highly nonlinear, and is largely determined by the state of inhibition.

Provided that dendritic excitation is strong enough to override somatic inhibition, the cells may discharge. In the simplest case, a Na^+ spike will be generated in the initial segment of several neighboring pyramidal neurons. The large inward current associated with the spikes is reflected by a negative change of the extracellular voltage at the level of the axon initial segment/cell body accompanied by a smaller-amplitude, extracellular positive deflection out in the dendritic regions for the same reasons as described previously for the EPSPs. However, because the spatial location of this event is opposite to the afferent excitation of dendrites, the direction of the extracellular current flow will also be opposite. The contribution of fast spikes to the extracellular mean field is due to the hypersynchronous discharge of many pyramidal neurons (population spike) as a result of artificial stimulation of an afferent bundle. Interpretation of the extracellular events after the population spike is not straightforward, however, due to complex feedback effects of the network and other nonsynaptic events (see later discussion).

Once a circuit, such as that shown in FIGURE 2, has been â€œcalibratedâ€ by electrically evoked potentials, one can move to the next stepâ€"network-level description of the generation of spontaneous EEG events. The tutorial example we use is an intermittently occurring, large-amplitude hippocampal sharp wave (SPW). SPWs are present during immobility, consummatory behaviors, and slow-wave sleep. It is important that the events to be analyzed are clearly separable from other waveforms. After extracting the invariable features of this EEG pattern by averaging or other pattern recognition methods, we convert the

simultaneous voltage measurements into a CSD map (Figures 2D and 2E). Note that the distribution of the sinks and sources of SPWs is strikingly similar to the potentials elicited by stimulation of the associational/commissural inputs to the pyramidal cells. Comparison of the spontaneous and evoked events, therefore, allows the conclusion that activation of the same afferent pathways and neurons brings about both events. Indeed, independent experimental work revealed that SPWs in the hippocampus arise from the quasi-synchronous discharge of CA3 pyramidal neurons, the source of associational and commissural afferents to the CA1 region.[11,16] Temporally overlapping activation of converging activity on single CA1 pyramidal cells results in a large depolarization of the dendrites, similar to the depolarization of these cells when the associational pathways are electrically activated. These extra- and intracellular events therefore provide circumstantial evidence that the same neuronal machinery is activated during spontaneously occurring SPWs as during electrical stimulation of the associational afferents.

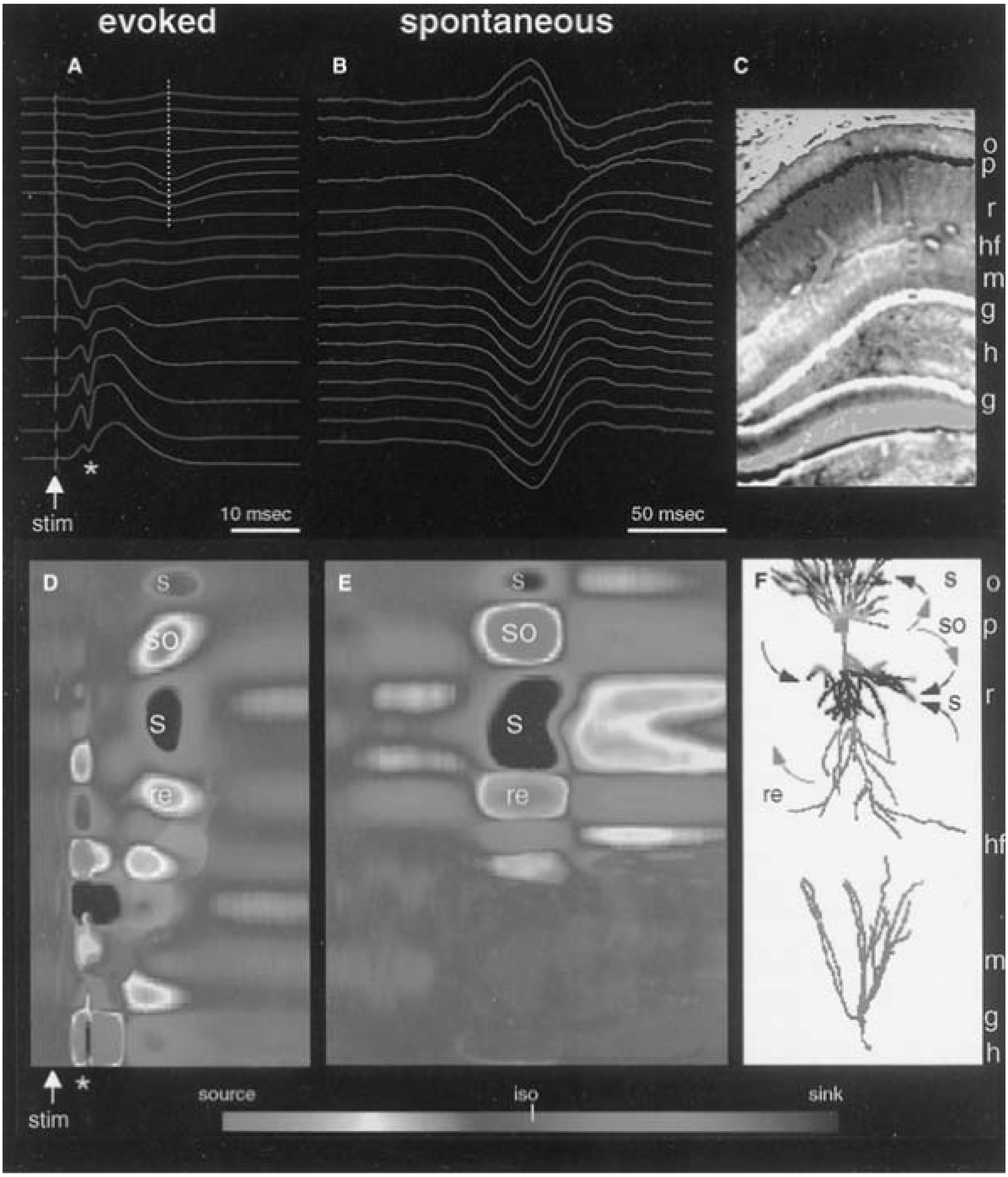

FIGURE 2. Generation of extracellular field potentials. **A:** Simultaneously recorded evoked field responses in the CA1-dentate gyrus axis of the rat hippocampus in response to stimulation of the entorhinal input (stim). The asterisk indicates the population discharge of the monosynaptically activated granule cells. Their discharge, in turn, activates CA3 pyramidal cells (not shown), whose associational collaterals depolarize CA1 pyramidal cells and interneurons. This trisynaptic activation of CA1 pyramidal cells is reflected as a late field event (vertical dotted line). **B**: Spontaneously occurring sharp wave recorded during immobility. The traces are averages of 40 individual events. **C**: A frontal section of the hippocampus indicating the contact sites of the recording silicon probe (*small squares*). o, stratum oriens; p, pyramidal layer; r, stratum radiatum; hf, hippocampal fissure; g, granule cell layer; h, hilar region. **D**, **E**: Current-source density (CSD) maps of evoked

field responses to perforant path stimulation (**D**) and of the spontaneous SPW pattern. Sinks (s, inward currents) and sources (so, outward currents) are indicated by cold and warm colors, respectively. iso, zero-current flow. The time scales in panels A and D, and B and E, are the same. **F**: Interpretation of the current sinks and sources on the basis of anatomic connectivity. Recorded layers are shown on the right of the pyramidal cell (**above**) and granule cell (**below**). Putative active currents are indicated on the right, and passive return (re) currents on the left of the pyramidal neuron. Note identical current sinkâ€“source distribution of the evoked and spontaneous events in the CA1 region (compare panels D and E). Sinks in stratum radiatum and oriens reflect excitation of the apical and basal dendrites of CA1 pyramidal cells, respectively, by the associational (Schaffer) collaterals of the CA3 region. The large source in the pyramidal layer is a combination of active outward current due to hyperpolarization of the soma by the simultaneously activated basket cells (not shown) and passive return currents from the sinks generated in the basal and apical dendrites. The source in the distal apical dendrites (re) is assumed to represent a passive return current due to the active sink in the middle of stratum radiatum. In addition to excitatory postsynaptic potentials, dendritic Ca^{2+} spikes may also contribute to the sinks in strata oriens and radiatum (see FIGURE 4). (From BuzsÃ¡ki G, Traub RD. Generation of EEG. In: Engel J Jr, Pedley TA, eds. *Epilepsy: A Comprehensive Textbook.* Lippincott-Raven Press; 1996, with permission).

The contribution of $GABA_a$ receptorâ€“mediated inhibitory currents is generally believed to be small, based on the assumption that because the Cl^- equilibrium potential is close to the resting membrane potential, the change of the transmembrane voltage is limited. However, in actively spiking neurons, when the cell body is depolarized, the transmembrane potential mediated by $GABA_a$ receptors can be large. Another cautionary note is that inhibition operates also on the dendrites, causing current flow opposite to the direction of excitatory currents. For the identification of excitatory and inhibitory components, represented by the extracellular current flow, a precise knowledge of the anatomic network is essential. Detailed physiologic experiments, including recordings from anatomically identified interneurons and pyramidal cells as well as differential pharmacologic blockage of the excitatory and inhibitory synapses, can provide further knowledge necessary for the proper interpretation of the observed sinks and sources (Fig. 3).[43,44,74] Only when all this knowledge is in place can the extracellular events be interpreted unambiguously.

The strategy just described is, in principle, applicable to any other a priori identified rhythmic or sparse EEG event. Complications arise when several dipoles are involved in the generation of the same EEG patterns, especially when these dipoles are phase-shifted, as is the case in the generation of numerous neocortical patterns (Fig. 4).[14,76,80] Nevertheless, the described strategies have been successfully used in the identification of evoked and spontaneous EEG patterns in the neocortex as well.[18,39,56]

Origin of extracellular currents

Fast (Na^+) Action Potentials

The largest-amplitude intracellular event is the sodium-potassium spike, referred to as the fast (Na^+) action potential intracellularly and as unit activity extracellularly. Individual fast action potentials are usually not considered to contribute significantly to the scalp-recorded EEG, mainly because of their short duration (<2 msec), the low degree of synchrony of spikes in the normal brain, and the high-pass frequency filtering (capacitive) property of the extracellular medium, which attenuates spatial summation of high-frequency events. However, when a microelectrode is placed close to the cell body layer of cortical structures the recorded field potentials contain both extracellular units and summed synaptic potentials. Furthermore, when action potentials from a large number of neighboring neurons occur within a short time windowâ€" for example, during highly synchronous epileptic activityâ€"â€œpopulation spikesâ€

can be recorded even with relatively large electrodes and in a larger volume (Fig. 2).[3,11,16]

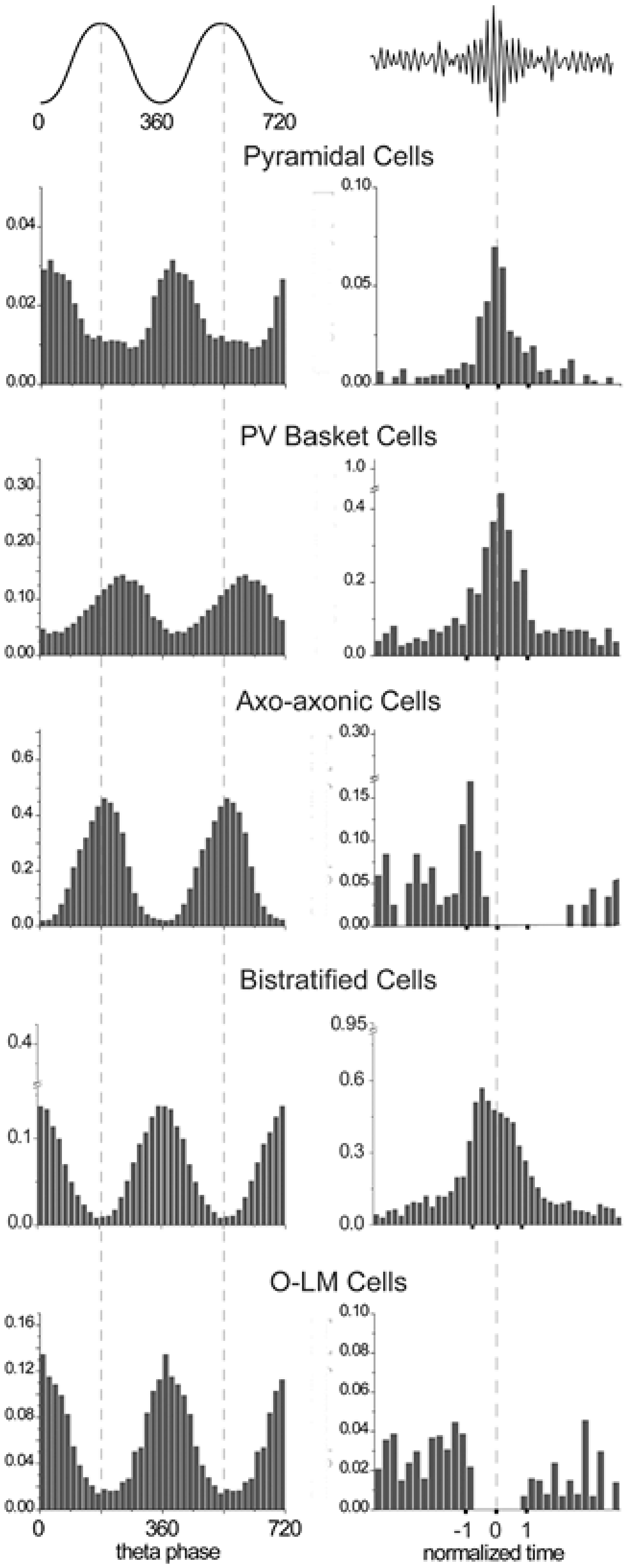

FIGURE 3. Relationship between circuit (axonal targets) and function properties of interneuron classes in the hippocampus. Mean firing probabilities of different cell types during theta (**left**) and sharp-waveâ€"related fast â€œrippleâ€ oscillations (**right**). Distinct classes of anatomically defined interneurons contribute differentially to either theta phase or ripple patterns. O-LM, stratum oriens

interneurons projecting to stratum lacunosum-moleculare. (Adapted from Klausberger T, Magill PJ, Marton LF, et al. Brain-state- and cell-type-specific firing of hippocampal interneurons in vivo. *Nature.* 2003:421:844â€“888; and Klausberger T, Marton LF, Baude A, et al. Spike timing of dendrite-targeting bistratified cells during hippocampal network oscillations in vivo. *Nat Neurosci.* 2004;7:41â€“47; with permission.)

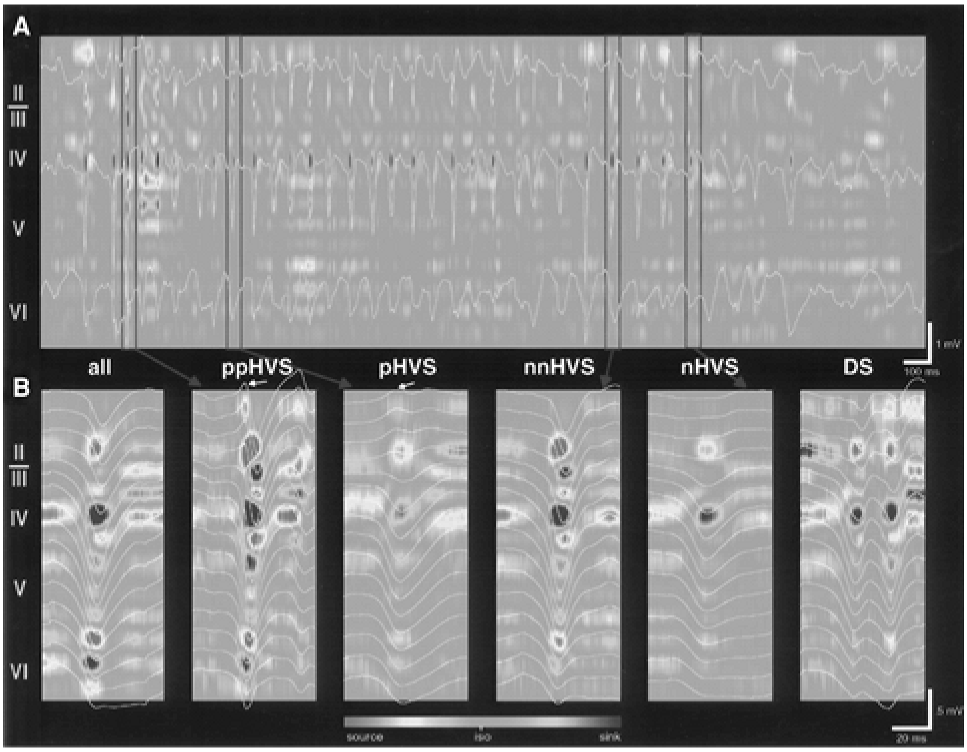

FIGURE 4. Variations in the voltage-versus-depth profiles and current-source density (CSD) maps of high-voltage spike-and-wave patterns (HVSs) in the awake rat. **A**: CSD map of a single HVS episode (3-second sweep). The superimposed field traces were recorded from layers II, IV, and VI, respectively. Note the consistent presence of the layer IV sink but the large variability of sinks and sources at other depth locations. **B**: Selected averages of HVS traces and corresponding CSD maps. all, averages of 200 successive events; ppHVS, average HVS with prominent surface-positive spike component; pHVS, average HVS with less pronounced surface-positive component; nnHVS, average HVS with dominant surface-negative spike component and large sink in layers IIâ€“III; nHVS, average HVS with negative spike component in layer IV; DS, average HVS with double spike components at short interspike intervals. Note a prominent delayed sink in layers IIâ€“III in ppHVS and nnHVS. Averages from 40â€“50 traces selected from a 5-minute recording session. Representative single events of the averages are indicated by vertical lines in panel A. iso, baseline isopotential. (From Kandel A, BuzsÃ¡ki G. Cellular-synaptic generation of sleep spindles, spike-and-wave discharges and evoked thalamocortical responses in the neocortex of the rat. *J Neurosci.* 1997;17:6783â€“6797; with permission.)

Synaptic Activity

In most physiologic situations, synaptic activity is the most significant source of extracellular current flow or EEG. The notion that synaptic potentials contribute to the generation of EEG stems from the recognition that for the summation of extracellular currents from numerous individual compartments, the events must be relatively slow.[61] The dendrites and soma of a neuron form a tree made up of an electrically conducting interior surrounded by a relatively insulating membrane with tens of thousands of synapses on it. Each synapse acts as a small battery to drive current, always in a closed loop. Depending on the chemical nature of the neurotransmitter released in the synaptic cleft, the postsynaptic membrane is depolarized (EPSP) or hyperpolarized (IPSP). Excitatory currents, involving Na^+ or Ca^{2+} ions, flow inwardly at an excitatory synapse (i.e., from the activated postsynaptic site to the other parts of the cell) and outwardly away from it. Such an outward current is referred to as a passive return current from the intracellular milieu to the extracellular space. Inhibitory loop currents, involving Cl^- or K^+ ions, flow in the opposite direction. The current flowing across the external resistance of the cortex sums linearly with the loop currents of neighboring neurons to constitute a local mean field (Fig. 2).

Calcium Spikes

Beside the fast Na^+ spike, an important nonsynaptic event in neurons is a wide Ca^{2+}-mediated action potential. These Ca^{2+} spikes are generated in the dendrites and do not necessarily propagate to the soma.[93] Their major role is believed to be to boost synaptic inputs and assist in the plastic modification of synapses.[52,54] The Ca^{2+} spikes represent an inward dendritic current and are large in amplitude (10 to 50 mV). They can occur synchronously with dendritic EPSPs, and for this reason they cannot be simply revealed or separated from EPSPs with extracellular recordings. Because Ca^{2+} spikes are activated by a voltage-dependent mechanism, dendritic depolarization can trigger them.

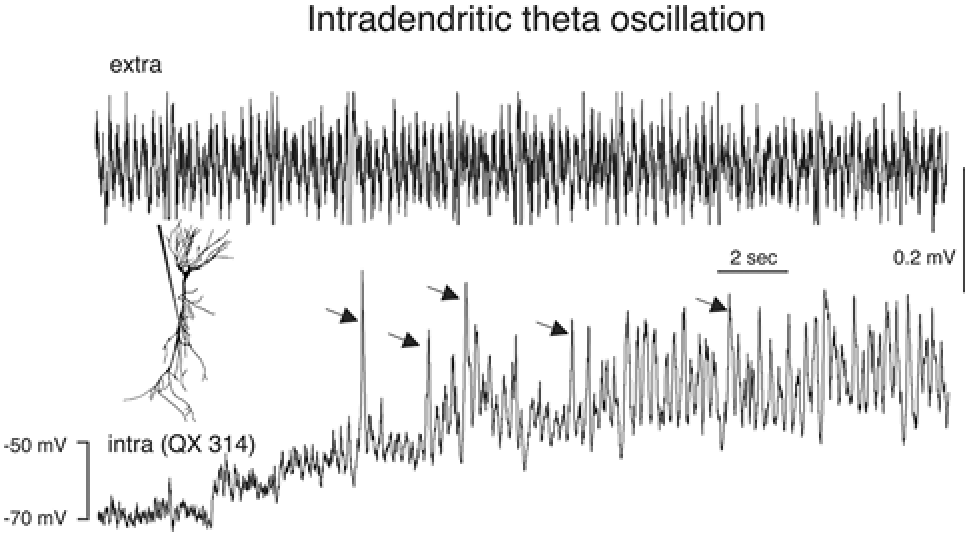

FIGURE 5. Nonsynaptic currents also contribute to the local field potential. Voltage dependence of theta-frequency oscillation in a hippocampal pyramidal cell dendrite. Continuous recording of extracellular (extra) and intradendritic (intra) activity in a CA1 pyramidal cell. Holding potential was manually shifted to progressively more depolarized levels by intradendritic current injection (0â€“0.8 nA). The recording electrode also contained QX-314 to block Na^+ spikes (20 mM). Note the large increase of intradendritic theta oscillation amplitude on depolarization. Some of the putative high-threshold calcium spikes to the phase of extracellular theta in the CA1 pyramidal layer is indicated by arrows. (From Kamondi A, AcsÃ¡dy L, Wang XJ, et al. Theta oscillations in Somata and dendrites of hippocampal pyramidal cells in vivo: activity dependent phaseprecession of action potentials. *Hippocampus*. 1998;8:244â€“261; with permission).

Figure 5 illustrates in vivo recording from a distal dendrite of a hippocampal CA1 pyramidal neuron during theta oscillation.[38] As the dendrite is progressively depolarized by intracellular current injection, the rhythmic synaptic potentials are superimposed on large-amplitude Ca^{2+} events. Are such Ca^{2+} spikes triggered by physiologic stimuli? Recent evidence indicates that this might well be the case. Patterned stimulation of the visual system evoked putative Ca^{2+} events in layer V pyramidal neurons of area 17.[33] Furthermore, intradendritic recordings during spontaneous sharp wave bursts revealed that the amount of physiologic depolarization brought about by the converging active presynaptic afferents to CA1 pyramidal cells is sufficient to trigger voltage-dependent Ca^{2+} spikes.[37]

Such new information, of course, indicates the need for the possible reinterpretation of the extracellular events illustrated in FIGURE 2. Provided that Ca^{2+} spikes occur simultaneously in several neurons near the recording electrodes, these large inward currents can contribute significantly to the field sinks observed in the dendritic layers. The quantitative contribution of dendritic Ca^{2+} spikes to the field EEG has not been determined. They might be quite important in highly synchronous events, such as epilepsy, because synchronous Ca^{2+} spikes in neighboring neurons may be reflected in the field as large sinks. A complicating factor is that, in contrast to EPSPs, Ca^{2+} spikes can actively propagate. Therefore, large dendritic segments and dendritic locations distant from the initiating site might be also involved.

Voltage-Dependent Intrinsic Oscillations

Experiments similar to that shown in FIGURE 5 revealed that when intradendritic depolarization is sufficiently strong, the resonant property of the membrane can give way to a self-sustained oscillation of the voltage, even in the absence of network-driven rhythmic activity. Intrinsic, voltage-dependent slow oscillations and theta frequency resonance have been observed also in somatic recordings of hippocampal pyramidal cells,[48] thalamocortical neurons,[65] stellate cells of the entorhinal cortex,[1] and layer V-VI pyramidal cells of the neocortex.[73] In stellate cells, the main driving force of the oscillation is a persistent Na^{+} current,[1] whereas another depolarizing current (I_h) in conjunction with the low-threshold Ca^{2+} current (I_T) is responsible for the maintenance of cellular rhythms in thalamic neurons.[5]

Voltage-dependent oscillatory activation of ionic channels has been shown also in the gamma frequency range. The membrane potential of sparsely spiny inhibitory interneurons in cortical layer IV can sustain a 40-Hz oscillation by sequential activation of a persistent sodium current followed by a slowly inactivating K^{+} conductance.[50] Similar intrinsic oscillatory properties have been shown in the intralaminar thalamocortical and GABAergic neurons of the nucleus reticularis neurons in vivo[78] and in the dendrites of hippocampal pyramidal cells.[67] Although these oscillatory membrane currents are small in amplitude, they can nevertheless significantly contribute to the extracellular field.

In most neurons, the voltage-dependent oscillation is below the threshold needed to trigger action potentials. However, when action potentials do occur, they are phase-locked to the depolarizing portion of the oscillatory cycle. Because these intrinsic, oscillatory membrane fluctuations can occur simultaneously in a number of nearby neurons, their contribution to the extracellular EEG can be substantial. This is perhaps best illustrated in the â€œlow-Ca^{2+}, high Mg^{2+}â€ model of epilepsy, when all synaptic activity is completely blocked, and the large, rhythmic extracellular field potentials are exclusively due to the voltage-dependent fluctuation of pyramidal cells, coordinated by ephaptic transmembrane or other nonsynaptic effects.[29,82]

Intrinsic Spike Afterhyperpolarizations

In addition to voltage changes, perturbation of the intracellular concentration of one ion species may trigger influx of other ions by activation of ligand-gated channels. The large Ca^{2+} influx, in association with a dendritic Ca^{2+} spike, is followed by the suppression of fast spikes and hyperpolarization of the membrane due to activation of $Ca2^{+}$-mediated increase of K^{+} conductance in the somatic region.[34,71] These burst-induced afterhyperpolarizations (AHPs) are frequently larger in amplitude and of longer duration than synaptic events. A logical progress of thought is to conclude that they should also be considered as an important source of the extracellularly recorded EEG potential.

Large-amplitude, slow delta waves (1 to 4 Hz) are among the most frequently studied neocortical EEG patterns. These irregular, semirhythmic or rhythmic patterns are most frequently observed during stage 4 sleep in the normal brain. Delta waves occur with largest amplitude in deep (layer V) cortical layers, and they are recorded as negative waves on the neocortical

surface or the scalp. Depth profile measurements in the neocortex of the cat,[17,36,69,70] rabbit,[6,69] and rat[14,90] revealed that surface-negative, deep-positive delta waves during slow-wave sleep correlate with the suppression or cessation of discharges of layer V pyramidal neurons. Intracellularly, the deep-positive waves are correlated with hyperpolarization of pyramidal cells.[2,19] Although the depth profile of the slow delta waves and the associated unit activity are compatible with the hypothesis that the extracellularly recorded delta waves reflect inhibition of pyramidal cells mediated by GABAergic interneurons,[2] all putative, physiologically identified, neocortical interneurons decreased their firing rates during the deep-positive slow waves.[14] An alternative, nonsynaptic explanation of the origin of delta wave generation is based on the summation of long-lasting AHPs of layer V pyramidal neurons.[14,77] During sleep, pyramidal cells of the neocortex often fire bursts in response to rhythmic thalamic volleys,[21,78] and these bursts, in turn, can trigger Ca^{2+}-mediated K^+-conductance changes. The long-lasting nature of AHP combined with disfacilitation from the network favors the summation of outward somatic currents of individual pyramidal cells, resulting in a local positive field in deep layers. Such extracellularly summated currents were hypothesized to form the basis of slow delta EEG waves recorded during sleep.[14] Using whole-cell recordings in vivo, Metherate and Ashe[55] could differentiate between IPSPs and AHPs in cortical neurons of the intact brain. First, they showed, by intracellular injection of Cs^+, that a large part of the delta EEG results from a K^+ current. Second, stimulation of the cholinergic nucleus basalis mimicked the cesium effect. Third, Cs^+ injection blocked the nucleus basalis stimulation effect. These findings support the suggestion that delta waveâ€“concurrent hyperpolarizations result partly from the calcium-activated K^+ current rather than by $GABA_a$ receptorâ€“mediated IPSPs. Overall, these examples illustrate that knowledge of the intrinsic properties of the neurons is as important for the identification of sources of the extracellular ion flow as knowledge of synaptic potentials and anatomic circuitry.

Nonsynaptic Neuronal Effects

Synchronous discharge of large neuronal populations is often associated with large-amplitude extracellular potentials (millivolts to tens of millivolts) and steep voltage versus depth gradients. These large field currents, in turn, can influence the activity of nearby neurons by changing their transmembrane voltage (ephaptic effects). Measurement of transmembrane potential changes (as opposed to potentials relative to a distant ground) indicated that such extracellular current loops can depolarize neurons to spike threshold under certain conditions.[29,82] Computer simulations of multiple neurons embedded in a conductive medium show that such a mechanism is plausible with observed estimates of extracellular resistivity.[83,88] It is important to note that the voltage gradient across pyramidal cell bodies during physiologic SPWs and especially during epileptic or interictal spikes is larger than the experimentally induced voltage gradients that are known to affect cellular excitability. Although direct experimental support is not available yet, one might expect that ephaptic effects could recruit neurons to fire that are otherwise not, or not sufficiently, activated by synaptic inputs alone.[11,24,29]

Gap junctions or electrical synapses[7,20,40] between neurons allow for direct charge transfer not involving the extracellular space. Nevertheless, direct electrical communication can greatly enhance neuronal synchrony and, therefore, network patterns detected by extracellular electrodes. Gap junctions have been suggested to be critical in numerous oscillations, including alpha,[35] gamma,[9,84,86] and high-frequency (150 to 600 Hz) rhythms in both hippocampus and neocortex.[6,83,84,85,94]

Neuronâ€“Glia Communication

The glial syncytium (astrocytes) is connected through gap junctions, which allows the direct spread of current and the diffusion or transport of small molecules. Although the role of concerted changes in membrane potentials of glia in the generation of extracellular current under physiologic conditions has not been studied extensively, recent work on neuronâ€“glia interactions indicates that the glial syncytium can contribute to the slow field patterns in several important ways. Intercellular coupling through gap junctions is required for both propagating Ca^{2+} waves and spreading depression.[58,59] The traveling Ca^{2+} waves, in turn, can trigger calcium influx into neurons.[59] The gliaâ€“neuron dialogue in vivo may be responsible for postictal depression.[8,23,30,32]

The increased $[K^+]_o$ resulting from intensive neuronal activity during epileptic afterdischarge may trigger propagating waves in the astrocytic network reflected by the slowly spreading sustained potentials. In turn, astrocytes at the front of the propagating depolarization wave release more K^+,[46] resulting in a large depolarization of neurons. The ensuing depolarization block of spike generation contributes to the termination of the afterdischarge and is regarded as the cause of the consequent â€œpostictal depressionâ€ of the EEG.[8,81]

DC current fluctuations or ultraslow change of the extracellular voltage cannot be recorded with conventional EEG devices with high-passâ€“filtered inputs. Sensory-evoked responses in scalp recordings with DC amplifiers and nonpolarizing electrodes often contain reliable and relatively long-lasting DC changes, usually referred to as *Bereitschaftpotenzial*[45] or contingent negative variation (Walter). The relatively quick changes in the DC level, such as epilepsy-associated spreading depression,[8] could be identified mistakenly as a slow delta or faster â€œwaveâ€ due to the differential effect of the high-pass filters. These slow potentials may arise from glia, gliaâ€“neuron interaction, or vascular events.[91]

Thus far, we have considered only â€œwell-behavedâ€ single events and provided a bottom-up approach to explaining the extracellular fields from the activity of the neuronal constituents. In the working brain, however, a multitude of (mostly unknown) patterns exists. The bottom-up approach assumes linear operations, and therefore it can be limited in addressing the complex nature of cortical waves. Explanations at the level of networks and systems are also needed.

A system of oscillations is responsible for perpetual EEG activity

A main challenge in cortical neurophysiology is to understand how a useful computation implemented by a relatively small network at a given stage of evolution can be continually implemented when the size of the network grows. The essence of this â€œscaling problemâ€ has to do with the relatively slow conduction velocities of axons and the space and energy limitations of neuronal connections.[47] Growing neuronal networks do not appear to scale linearly, but appear to scale by hitherto unidentified rules.[75] In light of these limitations, a remarkable feature of centrally organized rhythms is their frequency preservation throughout mammalian evolution. All known oscillations in humans have homologous counterparts in monkeys, carnivores, and rodents, and although the frequency ranges can differ somewhat, the variation is within the same order of magnitude. The respective cortical oscillations have similar behavioral correlates, drug sensitivity,[90] and heritability,[72,89] suggesting that they arise from similar mechanisms. Many of the cortical rhythms can sustain high, albeit typically transient, coherence over large spatial distances[10,22,76] despite a

several-hundredfold increase in the volume of the neocortex from mouse to human. Understanding the spatial scale-invariant preservation of cortical oscillations is a challenging issue for future experimentation and modeling.

Cerebral cortical oscillations range from very slow oscillations with periods of minutes to very fast oscillations with frequencies exceeding 500 Hz, covering a frequency range of at least five orders of magnitude.[41] The neighboring bands often overlap, and boundaries of human scalp EEG bands have been drawn artificially for pragmatic-clinical needs.[79] The historically agreed on frequency bands were largely confined by the limitations of early recording technology. The widely used mechanical recorders limited the upper border of frequencies, and electrode polarization and movement artifacts prevented low-frequency observations.[91]

A useful taxonomy of brain oscillations requires that the individual oscillatory classes represent physiologic entities, that is, that they are generated by distinct mechanisms. A particularly important step in this direction was the discovery of a lawful relationship among brain oscillators: Discrete oscillation bands form a geometric progression on a linear frequency scale and a linear progression on a natural logarithmic scale (Fig. 6).[14,66] An implication of this relationship is that the bandwidth (accuracy of the mean) of the oscillator is proportional to its mean frequency. The numerous brain oscillators fill all frequency bands from ultra slow to ultra fast frequencies without gaps. This noninteger (e ~ = 2.17; the Napierian logarithm, or ln) relationship within the family of brain oscillators has an important consequence. Because e is an irrational number, the phases of coupled oscillators of the various bands vary from cycle to cycle instead of entraining each other for extended periods. Cortical oscillators constantly but only transiently couple and decouple, allowing for an exchange of neuronal information in different regions.[27] In the jargon of nonlinear dynamics, the oscillators are not locked together by a fixed point or attractor (phase), but they attract and repel each other according to a quasiperiodic or weakly chaotic program. Locally emerging stable oscillators are constantly being pushed and pulled by the global dynamics. In reciprocally interconnected networks, temporal ordering of neuronal activity by way of phase-locking can direct the flow of propagation of neuronal activity. The oscillatory network whose neurons discharge earlier can drive the neurons of the trailing network oscillator. By simply reversing the phase offset, the direction of drive can also be reversed without any changes in the connectivity between the networks. The wavelength of a particular oscillation determines the temporal window of processing and, indirectly, the size of the neuronal pool involved. Therefore, different frequencies favor different types of connections and different levels of computation. In general, slow oscillators involve many neurons in large brain areas, whereas the short time windows of fast oscillators facilitate local integration, largely because of the limitations of the axon conduction delays. This anatomic-physiologic limitation can provide an explanation of the observation that a given frequency *f* is spatially correlated over a distance *L(f)* that increases as *f* decreases.[26,62,63]

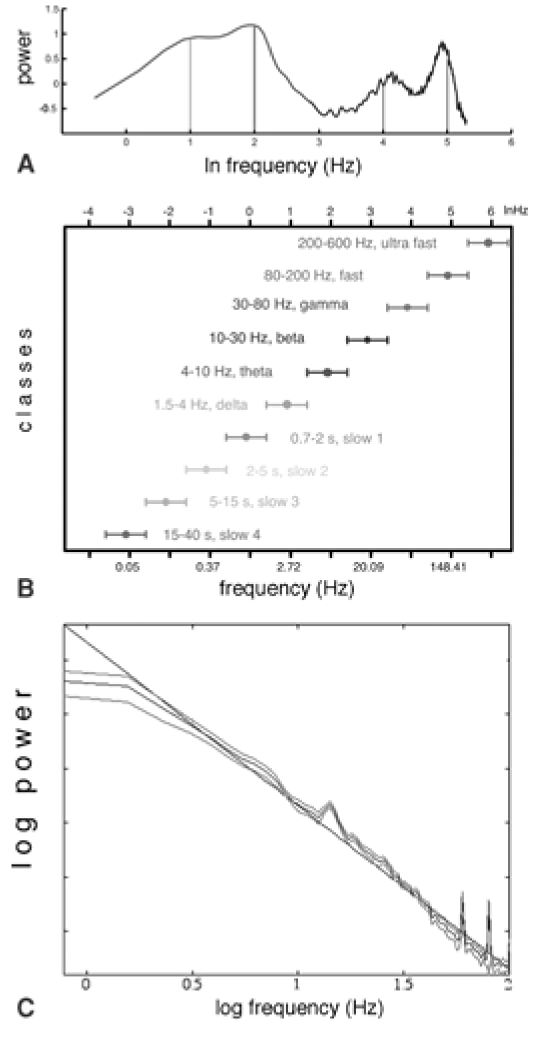

FIGURE 6. An interacting system of brain oscillators. **A**: Power spectrum of hippocampal electroencephalogram (EEG) in the mouse during sleep and waking periods. The spectrum was â€œwhitenedâ€ by removing log slope (see panel C). Note four peaks close to ln integers. Color code band peaks as in panel B. **B**: Oscillatory classes in the rat cortex. Note the linear progression of the frequency classes on the ln scale. For each band the range of frequencies is shown together with their commonly used terms. **C**: Power spectrum of EEG from the right temporal lobe in a sleeping human

subject. Subdural recording. Note near linear decrease of log power with increasing log frequency from 0.5 to 100 Hz. (Adapted from BuzsÃ¡ki G, Draguhn A. Neuronal oscillations in cortical networks. *Science.* 2004;304:1926â€“1929; with permission.)

The ln logarithmic relationship of cortical oscillators gives rise to a perpetual motion of cortical activity. This perpetual activity is nicely reflected by the power law (*1/f*) relationship between frequency and power in all forebrain structures of mammalian brains (Fig. 2).[26] In the frequency-domain (Fourier) plot, the amplitude (square root of power) *A* increases as the frequency *f* decreases, as expressed by the inverse relationship *A* ~ 1/*f*$^{\text{Î±}}$, where Î± is an exponent. The inverse relationship between frequency and its power is an indication that there is a *temporal* relationship between frequencies: Perturbations of slow frequencies can cause a cascade of energy dissipation at all frequency scales.[4] One can only speculate that this interference dynamics is the essence of the global organization of the cortex at multiple spatial and temporal scales.[15] The 1/*f* scale-invariant feature of the EEG is referred to as â€œpink noiseâ€ or â€œcomplex noiseâ€ in physics, a behavior halfway between disorder with high information content (high entropy, â€œwhiteâ€ or random noise) and certainty or predictability with low information content (low entropy, e.g., harmonic oscillation). It is also the mathematical tell-tale sign of self-organization, implying that the dynamics of the cerebral cortical operations is in a â€œcritical state.â€[3] The physiologic implication of this postulated metastability is that even a very weak transient local perturbation (input) can invade large parts of the network and exert a long-lasting effect, whereas myriads of other inputs remain ignored, depending on the past history of the cortical networks.

The complex (pink) noise view of the EEG implies that the cerebral cortex primarily generates noise. However, as discussed earlier, cortical networks gives rise to several, physiologically defined rhythms in the same frequency range within which the 1/*f* power law applies. In addition, the 1/*f* behavior of the power spectrum is a result of calculating power over a long time epoch. However, at any given moment one or few oscillators may dominate, but the frequency versus time orthogonality of the power spectrum does not reveal this. An alternative explanation of the 1/*f* behavior of cortical activity is that it is a result of the perpetual interference of the multiple cortical oscillators. If these oscillators were independent, spectra with multiple peaks would be expected. On the other hand, if the oscillators interact with each otherâ€”an inevitable consequence of the interconnectedness of cortical networksâ€”the frequency, amplitude, and recurrence variability of the oscillators and their interactions might account for the smoothness of the power spectrum constructed from long recordings without a need for generating extra noise. The advantage of such construction is that cortical networks can switch from highly sensitive, scale-free (pink-noise) dynamics to the predictive oscillatory mode that can provide transient autonomy of the involved cell assemblies. The ability rapidly to shift from the metastable state to a highly predictable oscillatory state and back is perhaps the most critical feature of cortical brain dynamics.

It is important to point out that only particular architectures, such as the cerebral cortex, can give rise to spontaneous, self-organized activity with complex dynamics. Self-organization requires regenerative feedback and long-range connectivity. The neocortex with its â€œsmall world-likeâ€ connection architecture[74] and the hippocampus with its random graph-like connectivity[49] meet these criteria. Losing the ability to shift flexibly between the critical state and rhythmicity, these architectures may give rise to hypersynchronous epileptic discharges and the loss of conscious brain operations. In the cerebral cortex, paroxysmal states such as epilepsy usually (but may be not always) depend on recurrent synaptic excitation. Paroxysmal states do occur in other parts of the brain, but of course if there is no recurrent synaptic excitation in those parts, then other mechanisms must be involved.[13]

Summary and Conclusions

The cerebral cortex generates a consortium of interdependent oscillators whose interference pattern appear as spontaneous brain activity. Synchrony of neuronal population is brought about by either external inputs or the self-generated oscillations. Synchronous cooperation of sufficient number of neurons generate extracellular current flow that can be measured by extracellularly placed microelectrodes, subdural electrodes or scalp electrodes. Understanding the processing that give rise to the field requires close monitoring of the neuronal and glial constituents that give rise to the field. Membrane potential fluctuations in all cells can contribute to the field, including EPSPs, IPSPs, voltage-dependent oscillations, afterpotentials and dendritic spikes. Understanding the mechanisms of EEG generation is a central problem because field patterns reflect state changes and provide important clues to the computational â€˜modesâ€™ of the underlying networks.

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Chapter 73

Interictal Electroencephalography

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Introduction

In spite of the many advances in imaging, digital analysis, and other techniques, routine interictal electroencephalography (EEG) remains central in the diagnosis and management of epilepsy. This should not be surprising. Epilepsy is a disorder of cortical excitability, and interictal EEG remains the most convenient and least expensive way to demonstrate cortical hyperexcitability. Findings indicating abnormal cortical excitability have not changed since the early descriptions. Interpretation of these patterns, however, has evolved in tandem with increased understanding of the natural history of different types of epilepsy, improved study designs, and the issues and opportunities that have emerged in the contemporary care of people with epilepsy. Initial concerns revolved mainly around the relationship between the interictal epileptiform discharge (IED) and the clinical diagnosis of epilepsy. This was usually framed as a problem of sensitivity and specificity, and a thorough understanding of this issue remains important in EEG interpretation. As we learned to view seizures in patients more globally as epilepsy syndromes, EEG findings in patients and close family members became central components in establishing a syndromic diagnosis. As we gained greater understanding of the longer-term course of epilepsy, it became clear that interictal EEG was very helpful in addressing other, nondiagnostic questions that commonly arose. Thus, even in an era of epilepsy care marked by high-resolution anatomic and functional imaging, information provided by routine EEG is more important than ever.

This chapter reviews how interictal EEG is used to address diagnostic and management questions encountered in clinical care of people with epilepsy (Table 1). We discuss how EEG is used to help classify epilepsy syndromes in a general fashion, emphasizing commonly encountered issues and leaving details to the specific chapters describing each syndrome. We also discuss other situations encountered during the treatment of epilepsy in which EEG provides important information.

Electroencephalography in the Diagnosis of Epilepsy

When a patient presents with an unusual spell, the first question the clinician must address is whether the event in question is an epileptic seizure or something else. Although the diagnosis of epilepsy remains a clinical judgment, interictal EEG, interpreted in the context of other clinical data, is often pivotal in answering this question. Two broad ideas must be kept in mind when interpreting interictal EEG in this situation. First, different EEG findings have different degrees of association with epilepsy. Clinicians may encounter any of the finding when considering a diagnosis of epilepsy: interictal epileptiform discharges (IEDs), periodic lateralized epileptiform discharges, generalized periodic epileptiform discharges, focal slowing, diffuse slowing, temporal intermittent rhythmic delta activity and (often) a normal EEG. Of these patterns, only IEDs, the relatively uncommon temporal intermittent rhythmic delta activity, and perhaps periodic lateralizing epileptiform discharges are associated with epilepsy at sufficiently high rates to strongly support the diagnosis of epilepsy. Therefore, understanding specificity and predictive value of the IED is important. Second, lack of these abnormalities or even an entirely normal EEG does not “rule out” the possibility of epilepsy. Therefore, understanding factors affecting likelihood of recording IEDs (sensitivity) is important. These ideas are to some extent affected by the age of the patient and associated clinical condition.

The Interictal Epileptiform Discharge

Definition

IEDs are difficult to describe precisely. However, consensus is widespread that the IED should meet at least the following criteria[20,100]:

1. It must be paroxysmal. This means that it must be clearly distinguished from background activity.
2. There must be an abrupt change in polarity occurring during several milliseconds. This gives the IED its sharp contour and is commonly referred to as the "spikiness" of the IED.
3. Duration must be <200 msec. The Committee on Terminology[20] distinguishes between spikes, which have a duration <70 msec, and sharp waves, which have a duration between 70 and 200 msec. It is not clear that this distinction has clinical utility.
4. The IED must have a physiologic field. Practically, this means that the IED is recorded by more than one electrode and has a voltage gradient across the scalp. This requirement helps distinguish IEDs from artifacts. However, IEDs may have very restricted fields in certain situations (e.g., neonates and the central IEDs seen in benign rolandic epilepsy).

Table 1 Uses of Electroencephalography for Diagnosis and Management of Epilepsy

Diagnosis

Is the paroxysmal event an epileptic seizure?
Is seizure onset focal or generalized?
What epilepsy syndrome best describes the patient's seizure disorder?

Management

What is the risk of recurrence after the first unprovoked seizure?
Is change in behavior due to nonconvulsive status epilepticus?
Is the patient a candidate for epilepsy surgery? What is the area of seizure onset?
How likely are epileptic seizures to recur after antiepileptic drugs are discontinued?

In addition to these necessary criteria, the great majority of IEDs have negative polarity, and many IEDs are followed by a slow wave in the delta range. These two features, although not required, are frequently present and help to distinguish IEDs from other forms of paroxysmal activity. Within the limitations discussed later, IEDs as defined in this manner are highly correlated with epilepsy and rarely seen in normal populations.

Sensitivity: How Often Are Interictal Epileptiform Discharges Seen in Patients With Epilepsy and Seizures?

Prevalence of Interictal Epileptiform Discharges in People With Epileptic Seizures

Sensitivity is an important measure of clinical utility of a test finding. For our purposes, sensitivity of IEDs can be defined as the prevalence of IEDs in people with a diagnosis of seizures or epilepsy determined by other means. Many studies have addressed these issues and allow some general conclusions. However, many factors affect sensitivity, and these must be considered when making clinical decisions.

In three studies of large groups of mostly adult patients evaluated at epilepsy centers, the initial routine EEG demonstrated IEDs in 29% to 55% of patients.[2,50,108] However, serial EEGs performed during varying periods of time ultimately demonstrated IEDs in 80% to 90%.[2,108] Of those patients who had IEDs recorded at some point, 90% had such findings by the fourth EEG.[2,108] If the first EEG demonstrated nonspecific abnormalities but no IEDs, subsequent EEGs were more likely to demonstrate IEDs.[108] Another investigation[135] continuously screened adult patients undergoing video-EEG monitoring for IEDs with standard IED-detection software. Analysis was confined to patients with recorded seizures, allowing a secure diagnosis that was not influenced by the presence of IEDs. No IEDs were detected in 19% of patients, although EEG was screened continuously for an average of 6.9 days.

Studies of patients with single seizures or patients in whom antiepileptic drugs are being discontinued provide some information about the prevalence of IEDs in patients with infrequent seizures (Table 2). Such studies are less likely to be affected by selection bias. From 12% to 50% of this population have IEDs recorded during the initial routine EEG. Nonepileptiform abnormalities are noted in 4% to 45%, and 43% to 74% have normal EEGs. Only one study[131] examined the yield of repeated EEGs in patients with single seizures. Twelve percent of a mostly adult group had IEDs recorded with the first EEG. Electroencephalography was repeated in almost all of those with an initially nonepileptiform study, and an additional 14% had IEDs, resulting in a total yield of 26% after two EEGs. The wide variability in the prevalence of IEDs in these groups with infrequent seizures can be related to a variety of factors, including the study of different populations at different centers and the use of different criteria for the detection of IEDs. The prevalence of normal EEGs was less variable, with five of seven studies finding that about 50% of patients had normal initial EEGs.

Factors Associated With Presence of Interictal Epileptiform Discharges

Interictal epileptiform discharges are recorded more frequently in children than in adults.[2] Furthermore, IEDs are more frequent when epilepsy begins earlier in life.[2] IEDS are more prevalent and more persistent in some epilepsy syndromes such as hypsarrythmia, Landau-Kleffner syndrome, untreated childhood-onset absence, and benign rolandic epilepsy. However, the interictal findings usually form a critical component of diagnosis in these cases, and so such statements may constitute circular reasoning. In adults with partial epilepsy, IEDs are more common when seizures originate in the temporal lobes than when seizures originate elsewhere.[2,135]

Some antiepileptic drugs appear to affect the likelihood of recording IEDs in certain situations.[6,112] Benzodiazepines and barbiturates consistently decrease the prevalence of IEDs acutely. These effects appear to wane with long-term therapy. Withdrawal of barbiturates may be accompanied acutely by the appearance of generalized epileptiform activity or the appearance of noncharacteristic foci of seizure onset. Variable effects on IEDs have been reported with long-term administration of phenytoin and carbamazepine, and no clear trend has emerged. Valproate dramatically suppresses generalized IEDs. In a series of studies, valproate decreased the number of generalized spike-wave discharges in 76% of patients 10 weeks after the drug was started, and the number of generalized spike-wave discharges was still decreased in 57% of patients 1 year after therapy was begun. Photoparoxysmal response was eliminated in 25% of patients with this finding 10 weeks after treatment and in 75% at 1 year after treatment; it is interesting that suppression of photoparoxysmal response persisted even after valproic acid was discontinued and serum levels were no longer detectable. Activation of generalized spike-wave activity with hyperventilation was not affected by treatment at 10 weeks but was eliminated in about half of patients with this finding at 1 year after initiation of treatment.[16,133] Although treatment with benzodiazepines, barbiturates, or valproic acid clearly affects the number of IEDs recorded in certain situations, these drugs are not usually discontinued when no IEDs are recorded and epilepsy is suspected. Atypical IEDs are often seen when barbiturates or benzodiazepines are withdrawn, and the suppressive effect of valproic acid is probably too lengthy to allow safe discontinuation for diagnostic purposes in most cases.

Table 2 Yield of initial electroencephalogram in patients with infrequent seizures

Study	Number of	Age group	With	With IEDs (%)	Normal

	patients		**non-IED**	**abnormalities (%)**	**(%)**
Patients with first unprovoked seizure					
Hopkins et al.[61]	408	Adults	26.8	26.8	46.4
FIRST Group[41]	397	Mixed	50	6	44
Van Donselaar et al.[132]	157	Adults	12	45	43
Shinnar et al.[116]	283	Children	28	10	63
Kawkabani et al.[70]	177	Adults	34		
Scotoni et al.[115]	213	Children	18	4	78
Patients withdrawing from antiepileptic drugs					
Callaghan et al.[17]	92	Mixed	—	—	74
Shinnar et al.[117]	88	Children	18	—	49
Emerson et al.[36]	68	Children	—	—	50
Specchio et al.[121]	225	Mixed	18	53	29

IED, interictal epileptiform discharge.

Seizure frequency was associated with greater likelihood of recording IEDs in one study,[2] but the opposite was found in another.[135] The first series included many children, whereas the second studied only adults, which may account for the discrepancy. Contemporary studies agree that IEDs occur more frequently in the period immediately after epileptic seizures.[52] Nonetheless a small minority of people with a clear diagnosis of epilepsy will lack IEDs in spite of several routine EEG recordings. There are several potential explanations. IEDs may be infrequent and therefore not detected, even with aggressive sampling. They may be present but not detectable with traditional scalp electrode arrays. IEDs are frequently recorded with intracranial electrodes when results of simultaneous scalp recordings are normal.[1,125] More than 10 cm^2 of brain surface must be involved with an IED before the IED can be detected at the scalp, and fields of IEDs recorded with intracranial electrodes often occupy a smaller area.[1,125] Furthermore, many areas of the cortex, such as the basal frontal and medial temporal regions, are not directly accessible to scalp recording, and IEDs

originating in these regions may not be detected by scalp electrodes. Finally, some patients with epilepsy may have no IEDs even with intracranial recording, although experience suggests that this situation is rare, at least in intractable epilepsy.

Increasing the Likelihood of Recording Interictal Epileptiform Discharges

The yield of IEDs can be increased by activation methods (sleep, sleep deprivation, hyperventilation, photic stimulation, and others; see Chapter 94), by longer EEG recordings, and by employing more electrodes than the routine number used with the 10-20 International System. Each of these may increase sensitivity of interictal EEG in supporting the diagnosis of epilepsy.

The increased yield of IEDs after sleep recordings has been accepted since the early reports of Gibbs and Gibbs.[45] Several reviews provide detailed information.[26,29,35,110] An EEG recorded during sleep will demonstrate IEDs in 40% or more of people with epilepsy in whom EEGs recorded during wakefulness reveal no IEDs. Chloral hydrate is most commonly used to hasten sleep onset. There is no evidence that spontaneous sleep is more effective than sedated sleep; however, sedative drugs, including chloral hydrate, may affect EEG background activity. The majority of studies have shown that 24 hours of sleep deprivation further increase the yield of IEDs by 20% or more after accounting for the increased yield expected with sleep and multiple EEGs.[35] Furthermore, activating effects of hyperventilation and photic stimulation are consistently potentiated by sleep deprivation. Many laboratories employ lesser amounts of sleep deprivation, even though these have not been proved to be as effective.

The occurrence of IEDs and changes in IED distribution and morphology differ depending on epilepsy syndrome and sleep stage. Hypsarrythmia is usually potentiated by sleep, and the EEG becomes increasingly abnormal with deeper stages of sleep; however, the EEG pattern often reverts to normal during rapid eye movement (REM) sleep. Rates of slow spike-wave activity, centrotemporal discharges, and 3-c/s spike-wave activity all increase during deeper stages of sleep. The activating properties of sleep are considered so profound in some of these syndromes that most epileptologists do not consider the EEG evaluation for infantile spasms, Lennox-Gastaut syndrome, Landau-Kleffner syndrome, or benign rolandic epilepsy complete unless a reasonable amount of sleep was recorded. In contrast, the polyspike-wave bursts seen in juvenile myoclonic epilepsy may decrease with sleep and are especially prominent on forced arousal from sleep. Although all studies agree that temporal IEDs are more frequent in non-REM sleep than in wakefulness or REM sleep, there is controversy as to whether frequency is higher in deep or light sleep.[81,109]

Hyperventilation increases the frequency of generalized spike-wave activity in 50% to 80% of patients with absence seizures and often precipitates overt absences, especially in untreated patients.[111] However, altered clinical responsiveness can occur during hyperventilation in the absence of a spike-wave discharge and is a nonepileptic phenomenon observed even in normal children.[39] In contrast, hyperventilation increases the yield of focal IEDs in <10% of patients.[26]

Photic stimulation induces IEDs in 10% of people with epilepsy.[142] More than 80% of such patients have childhood absence epilepsy, juvenile absence epilepsy, juvenile myo-clonic epilepsy, or epilepsy with tonic–clonic seizures on awakening.[142] When partial seizures are activated, clinical features usually suggest a posterior cerebral onset.

An incidental photoparoxysmal response in people without other IEDs or a clear history of seizures can be difficult to interpret. Photoparoxysmal response must be distinguished from the photomyoclonic response and potentiated visual-evoked responses, which are not associated with an increased risk for seizures.[26,79,105,142] Initial studies reported that photoparoxysmal responses persisting beyond the period of photic stimulation were associated with epilepsy, whereas while those limited to the period of photic stimulation were not.[105] However subsequent work has not found this distinction to be useful.[65,120] The very large studies of highly selected airplane crew members report a prevalence of <0.3%.[54] Few adults with an incidental photoparoxysmal response eventually develop epilepsy.[54,114,120] Twin studies of the photoparoxysmal response indicate a concordance of virtually 100%, so the family history should be scrutinized if a photoparoxysmal response is found in someone without seizures. Consequently, most clinicians interpret an incidental photoparoxysmal response conservatively and do not recommend treatment on this basis alone.

IEDs may occasionally be provoked by tactile stimuli; these do not necessarily imply potential epileptogenicity.[76]

Increasing the number of EEGs clearly increases the likelihood of recording IEDs. Salinsky et al.[108] found that approximately 60% of patients studied with up to seven EEGs demonstrated IEDs. About half of these had IEDs in the first EEG, and 90% of these had them after four EEGs. Walczak et al.[135] studied a similar population with continuous detection of spikes and seizures and obtained a somewhat higher yield of 80%. No study has compared the yield of continuous IED detection with that of serial routine EEGs.

Additional electrodes may provide useful information when IEDs are not recorded with the standard 10-20 International System array. This is especially relevant with temporal IEDs. Nasopharyngeal electrodes, true anterior temporal electrodes, and sphenoidal electrodes are all positioned closer to the anterior temporal lobe than are the $F_{7/8}$ electrodes. Several studies[50,51,60,106,107,122] have compared how often temporal IEDs are recorded with these four electrodes. In patients in whom IEDs were recorded at some point during the study, IEDs were recorded in 43% to 58% with the standard electrode array, in 57% to 69% with nasopharyngeal electrodes, in 81% to 90% with true anterior temporal electrodes, and in 75% to 100% with sphenoidal electrodes. More artifacts were seen with nasopharyngeal recordings than with other electrode types. Consequently, nasopharyngeal electrodes have been largely abandoned in favor of anterior temporal electrodes. Sphenoidal electrodes are often used during evaluation for epilepsy surgery but are rarely used during routine EEG. Orbitofrontal electrodes help to record from the frontal pole and nasoethmoidal electrodes from the frontal operculum,[102] and these may be helpful when seizures are thought to originate in the frontal lobe. It is not clear how often such electrodes record IEDs that would not be detected by the standard 10–20 International System electrode array.

Specificity: Interictal Epileptiform Discharges in Nonepileptic Patients

Prevalence of Interictal Epileptiform Discharges in Nonepileptic Patients

Specificity is another important measure of the clinical utility of a test finding. Strictly speaking, the specificity of an IED is defined as the number of individuals not having a diagnosis of epilepsy that do not have IEDs. However, IEDs are rare in people without epilepsy, and so prevalence of IEDs in people without epilepsy is often discussed. All studies of EEGs in large numbers of normal individuals indicate that IEDs are seen in rare individuals without a clinical history of seizures. The likelihood of epilepsy developing in such people appears to be increased, although the likelihood is much less than in patients with paroxysmal clinical episodes who have IEDs. Prevalence of IEDs in nonepileptic individuals is influenced by age, general condition, and recording conditions, among other factors. Only one community-based study is available.[19] Some degree of selection occurred in the remainder.

Table 3 summarizes the available information. Although the studies are few in number and have many limitations, several trends tentatively emerge. In healthy individuals, IEDs are more common in children (2.2% to 3.5%) than in adults (0.2% to 0.5%). Seizures appear to develop eventually in a higher percentage of healthy children with IEDs.[127] In the single study reporting results in hospitalized adults without neurologic or psychiatric disease, prevalence of IEDs was similar to that found in healthy persons.[8] The higher rate in the frequently quoted study of Zivin and Ajmone-Marsan[144] may be attributable to the inclusion of patients who had cerebral neoplasms and underwent craniotomies. The similar rate reported among psychiatric inpatients[15] may be related to the inclusion of patients who were withdrawing from barbiturates or who had anorexia. Interictal epileptiform discharges are more frequent in these conditions and are not necessarily associated with epilepsy.

Types of Interictal Epileptiform Discharges in Nonepileptic Individuals

The types of IEDs seen in normal individuals appear to differ from the types seen in large series of people with epilepsy. Centrotemporal IEDs, generalized IEDs, and the photoparoxysmal response account for the great majority of IEDs found in normal individuals, especially children.[8,19,33,54] On the other hand, focal or multifocal IEDs, especially temporal IEDs, predominate in series of people with epilepsy.[2,37,71] The types of IEDs observed in most nonepileptic subjects with IEDs appear to have a lower association with epilepsy than do other types of IEDs. Centrotemporal IEDs appear to be a heritable EEG pattern with incomplete and age-dependent penetrance.[56] Only approximately 40% of patients with centrotemporal IEDs had epileptic seizures in one large retrospective study.[71] Generalized IEDs occur in approximately 10% of parents and 35% of other family members of probands with both tonic–clonic seizures and generalized epileptiform discharges.[91] The photoparoxysmal response accounts for as many as 63% of IEDs found in individuals without epilepsy.[54] Most studies indicate that seizures develop infrequently in patients with this pattern (see earlier discussion).

Sharp waves or transients are frequently seen in normal neonates and appear to be a normal part of cerebral maturation as revealed by EEG. Frontal sharp transients are isolated sharp waves first present at 34 weeks of conceptional age, with maximum expression at approximately 36 weeks of conceptional age and then with gradual diminution in number and voltage following 44 weeks of conceptional age, and so they are rarely present following 6 weeks postterm. Frontal sharp transients are bilaterally synchronous and symmetric from the time of their first appearance. Focal sharp waves, especially midtemporal sharp waves or sharp slow complexes, can also be normal in premature neonates and perhaps as late as 44 weeks of conceptional age. In normal neonates these are rare in number, random in occurrence, and without persistent focality. The following features suggest that focal sharp waves are abnormal in this age range[23,72,95]: (a) The amplitude of abnormal sharp waves is higher; (b) normal sharp waves occur randomly over the two hemispheres, whereas abnormal sharp waves occur in repetitive runs; (c) normal temporal sharp waves are typically mono- or diphasic, whereas abnormal sharp waves are typically polyphasic with aftergoing slow waves; (d) sharp waves with positive polarity are abnormal, whereas negative sharp waves may be normal; and (e) whereas normal temporal sharp waves may occur in any wake-sleep state in premature infants, they are more common turning transitional sleep in term infants. Temporal sharp waves present in awake term infants are probably abnormal, especially if they are persistent. Overall, the association between IEDs and epilepsy appears to increase as the neonate transitions into infancy and further. There is no information indicating the approximate age at which the degree of association between IEDs and seizures reaches that found in adults, and this is likely to vary depending on the type of IED.

Table 3 Prevalence of interictal epileptiform discharges[a] in individuals without epilepsy

Study	Total number	Age (yr)	General condition	Number with IEDs (%)	Number with IEDs who develop seizures (%)
Eeg-Olofsson et al.[33]	743	1–15	Highly screened normal individuals	14 (1.9)	Not reported
Cavazzuti et al.[19]	3,716	6–13	Screened community-based	131 (3.5)	7/131 (5.3)
Bennet[8]	424	Adults	Healthy flight personnel	2 (0.5)	0/2 (0)

Gregory and Wong[53]	13,658	17–25	Healthy flight personnel	69 (0.51)	1/38[b] (2.6)
Bennet[8]	1,541	Adults	Hospitalized patients; no neurologic illnesses	5 (0.3)	0/2[b] (0)
Zivin and Ajmone-Marsan[145]	6,497	1–74	Hospitalized patients; including neurologic illness	127 (2.0)	20/127 (1.6)
Bridgers[15]	3,143	11–85	Psychiatric inpatients	81 (2.6)	Not reported

IED, interictal epileptiform discharge.

[a] Patients with 6 c/s spike-wave activity were not included, but patients with a photoparoxysmal response (see text) were included in some studies.

[b] Follow-up was not available in all patients with IEDs.

In children, the association between IEDs and epilepsy appears to vary by location, distribution, and morphology. Available studies are retrospective and tainted by selection bias. Nonetheless, the available information and clinical experience indicate that multifocal independent spikes and spikes occurring over the midline, frontal, and anterior temporal regions

are highly associated with epilepsy. Epilepsy occurs in 75% to 95% of cases with such IEDs.[34,71] On the other hand, only about 40% of centrotemporal IEDs and only 50% of occipital IEDs were associated with a history of seizures in a large retrospective study.[71] Occipital IEDs occur after the onset of blindness in infancy; 15% of patients with occipital IEDs were blind in one study.[118] Finally, IEDs tend to cease during follow-up studies in both normal[19] and sick[71,80,129] children who have IEDs; this appears to occur less commonly in adults.[64] Thus, the "cerebral irritability" that seems to be associated with IEDs appears to change with cerebral maturation in many pediatric patients. Clearly, the precise EEG findings and the clinical situation must be carefully considered when the presence of IEDs is used to support the diagnosis of epilepsy in infants and children.

Nonepileptic Conditions Associated With Interictal Epileptiform Discharges

Electroencephalograms recorded during periods of metabolic dysfunction may occasionally reveal IEDs. Triphasic waves, seen in a variety of metabolic encephalopathies, may be difficult to distinguish from generalized epileptiform activity. Focal spikes, multifocal spikes, and diffuse spikes or sharp waves without typical triphasic morphology have been reported in dialysis dementia and hypocalcemia. Seizures are fairly common in these conditions as well, but some such patients with IEDs do not report seizures.[132] Interictal epileptiform discharges may be recorded in nonepileptic patients treated with chlorpromazine, lithium, or clozapine, especially at higher doses. Seizures develop in some, but not all, such patients. The discharges disappear when doses are decreased. These agents also increase the number of IEDs recorded in patients with epilepsy. Electroencephalograms recorded during withdrawal of short-acting barbiturates in nonepileptic patients occasionally demonstrate generalized IEDs or prolonged photoparoxysmal response. This appears to be uncommon with the longer-acting barbiturates.[47] Finally, IEDs in patients without a history of seizures are occasionally seen in cases of cerebral mass lesions, especially abscesses and slow-growing neoplasms.[26] Interictal epileptiform discharges in such situations presumably indicate a higher risk for seizures, but confirmatory follow-up studies are not available.

Summary: Determining the Meaning of the Interictal Epileptiform Discharge

The available information indicates that IEDs are rare in healthy persons and hospitalized patients without neurologic disease and are common in patients with epilepsy. Different types of IEDs appear to have different levels of association with epilepsy, especially in neonates and children. The association between epilepsy and IEDs increases with age. Interictal epileptiform discharges in nonepileptic individuals tend to occur in situations associated with an increased risk for seizures, and seizures subsequently develop in more persons with these findings than in the general population. Clearly, the physician must consider the type of IED and the age and condition of the patient before deciding how much diagnostic significance to attribute to an IED. Furthermore, the "increased seizure tendency" presumably associated with IEDs in some clinical situations may be temporary and not inevitably associated with a long-term risk for seizures, although little information is available to guide the clinician here. Understanding the sensitivity and the specificity of the IED and the factors affecting them will allow proper application of this finding to the individual situation faced by the clinician.

Other Electroencephalographic Findings in Epilepsy

Three paroxysmal patterns meeting criteria for IEDs described earlier have a somewhat lower association with epilepsy than IEDs. Periodic lateralizing epileptiform discharges (PLEDs) consist of sharp waves that are lateralized to one hemisphere

and occur every 1 to 2 seconds. This pattern is usually seen in the setting of an acute irritative structural lesion. The PLEDs attenuate and cease altogether as the patient recovers from the acute event. Seizures occur in about 70% of patients with PLEDs during the acute period.[119] However, at least 20% of such patients have preexisting epilepsy.[119] In three small studies,[113,136,143] epilepsy developed in 23% to 66% of patients without preexisting epilepsy after they recovered from illness associated with PLEDs. Bilateral independent periodic lateralized epileptiform discharges (BIPLEDs) consist of periodic lateralized sharp waves occurring independently and at different rates over the two hemispheres. These are recorded during acute presentation of bilateral or multifocal cerebral disease. In 55% of patients with BIPLEDs, seizures occur during the acute course, and 22% have preexisting epilepsy.[28] Mortality is high, and there is no information on how often epilepsy develops in those who survive. Generalized periodic sharp waves consist of periodic sharp waves occurring synchronously over the two hemispheres. The pattern is recorded in the setting of acute severe bilateral brain damage that is often irreversible. Anoxia is probably the most common etiology; the pattern is also commonly seen in Creutzfeldt-Jacob disease and the late stages of status epilepticus.[128] Association of epilepsy with this pattern is unknown. No data regarding subsequent occurrence of seizures are available because this pattern is associated with a poor prognosis. Epilepsy would appear to be more common in diseases associated with this pattern than in the general population. However, overall occurrence of seizures during or after acute presentation appears to be lower than with PLEDs or IEDs.

Several paroxysmal patterns meet many of the criteria for IEDs but are not associated with an increased prevalence of epilepsy. These include benign epileptiform transients of sleep (BETS), 6-c/s phantom spike-wave, 14- and 6-c/s positive bursts, rhythmic midtemporal theta bursts of drowsiness, subclinical rhythmic electrographic discharge of adulthood, and the midline theta rhythm. A recent review details morphology and clinical associations.[137] Benign epileptiform transients of sleep and 14- and 6-c/s positive bursts occur in >20% of a highly selected normal population and somewhat less frequently in patients with epilepsy. The remaining patterns occur in <3% of referral populations. Controlled studies of these infrequent patterns indicate no association with epilepsy. An experienced electroencephalographer can usually distinguish these patterns from IEDs by careful consideration of morphology, sleep and awake states, and background rhythms. Occasionally, distinguishing between benign epileptiform transients of sleep and temporal lobe spikes, or between 6-c/s phantom spike-wave and the fast spike-wave seen in juvenile myoclonic epilepsy, may be difficult.

Focal slowing or generalized slowing of background rhythms is commonly seen in patients with partial seizures. However, these findings are so common in other neurologic diseases that they cannot be used to support the diagnosis of epilepsy. When continuous focal polymorphic delta activity is present in adults, a focal structural lesion is found approximately two thirds of the time. From 12% to 17% of cases with focal polymorphic delta activity have a history of epilepsy and no structural lesion.[46,87] In children with focal polymorphic delta activity, focal structural lesions are found only half of the time. Twenty-three percent of children with focal polymorphic delta activity have a history of epilepsy and no structural lesion.[89]

Temporal intermittent rhythmic delta activity (TIRDA) is a particular form of focal slowing. In contrast to continuous or intermittent polymorphic delta described previously, monomorphic slow waves of <3 cps occur in brief bursts over the temporal regions. TIRDA is found in only 0.3% of studies recorded in a general EEG laboratory[98] but in more than one fourth of patients evaluated for temporal lobe resection.[44] In contrast to polymorphic focal slowing, TIRDA is highly associated with temporal lobe epilepsy.[44,98,104]

In neonatal EEG, a number of abnormal but nonepileptiform findings are associated with an increased risk of seizures. These risks are not as well quantified as those associated with the IED in adults. Temporal sharp waves, when persistently focal, suggest a lesion or area of focal dysfunction that may be potentially epileptogenic. Similarly, unilateral depression of background can suggest a focal intracranial lesion that increases seizure risk. Central positive sharp waves (also known as positive rolandic sharp waves) suggest periventricular leukomalacia, which is associated with increased incidence of seizures.[12,24] Finally, degree of abnormality of interictal background EEG in neonates is a predictor of seizure risk, especially in high-risk infants[77]; infants with normal background activity are less likely to eventually experience seizures than those with persistent background abnormalities. Of special note is a pattern of modified hypsarrhythmia that can be present in the neonatal period—the suppression-burst variant.[62] This is characterized by periodic bursts of asynchronous high-voltage activity mixed with multifocal spikes and sharp waves. Infants with this pattern experience infantile spasms as well as fragmentary myoclonus, and most eventually develop tonic seizures.

Role of Electroencephalography in the Diagnosis of Epilepsy Syndromes: An Overview

Diagnosis of an epilepsy syndrome is critical for determining correct treatment and prognosis. After a detailed history has been taken, EEG is the most important test in making such a diagnosis. The chapters on the various epilepsy syndromes and other reviews[106,141] discuss specific EEG findings associated with each syndrome in detail. Here we discuss the general principles underlying the use of EEG in diagnosing epilepsy syndromes, briefly summarize important features of various epilepsy syndromes, and describe three common situations in which clinically important distinctions among epilepsy syndromes are based on EEG findings.

General Principles and Summary of Findings

The International Classification of Epilepsy Syndromes is based on two distinctions: (a) between localization-related and generalized epilepsies and (b) between idiopathic and symptomatic epilepsies. The EEG can help to establish which of these categories pertains in a particular case of epilepsy and thus to facilitate the diagnosis of an epilepsy syndrome. Focal IEDs suggest localization-related epilepsies, whereas generalized IEDs suggest generalized epilepsies. The location of the focal IED loosely corresponds to the site of onset of seizures in the localization-related epilepsies; however, there are exceptions (see later section, Role of Interictal Electroencephalography in Evaluating Patients for Epilepsy Surgery). Focal background abnormalities or focal slowing occur in symptomatic epilepsies. Persistent significant attenuation or polymorphic delta activity suggests a structural lesion as the etiology for the symptomatic epilepsy. Diffuse background abnormalities suggest symptomatic epilepsies, whether generalized or localization related. On the other hand, normal background activity argues for an idiopathic epilepsy syndrome. Electroencephalographic findings in the common epilepsy syndromes are summarized in Table 4.

Table 4 Electroencephalographic features of some epilepsy syndromes

Syndrome	Type of IED	Background	Other

Otahara	Burst suppression	Slowed, attenuated	
Infantile spasms	Hypsarrythmia (multifocal IEDs)	Hypsarrythmia (no parietooccipital rhythm, high-amplitude random focal slow waves); other variants common	Electrodecremental response during infantile spasms
Lennox-Gastaut	Generalized slow spike-wave activity (<2.5 c/s); focal IEDs less common	Diffuse slowing and disorganization	Generalized paroxysmal fast activity during sleep
Absence epilepsy	Generalized 3-c/s spike-and-wave	Usually normal; occasional rhythmic posterior delta activity	Generalized spike-wave activity; activation by hyperventilation
Benign rolandic epilepsy	Rolandic (centrotemporal) spikes; generalized or occipital IEDs occasionally seen	Normal	
Benign occipital epilepsy	Bilateral synchronous occipital spikes or spike-wave activity; amplitude lateralization common	Normal	IEDs activated by eye closure; no activation by photic stimulation
Electrographic status epilepticus during sleep	Continuous slow spike-wave activity during sleep, usually generalized; much less frequently, focal IEDs while awake	Mild diffuse slowing	May be difficult to distinguish from Lennox-Gastaut syndrome by electroencephalogram alone
Landau-Kleffner	Independent bitemporal IEDs	Independent bilateral focal slowing and diffuse slowing	
Juvenile myoclonic	Generalized polyspike wave,	Probably normal; some authors	Photic activation of IEDs common

epilepsy (of Janz)	often >3 c/s	report a midline theta rhythm of questionable specificity	
Progressive myoclonus epilepsy	Generalized spike, polyspikes and waves; also focal or multifocal IEDs in some syndromes	Progressive slowing of background frequencies, especially when dementia is present	Photic activation in some syndromes
Temporal lobe epilepsy	Temporal IEDs; independent bitemporal IEDs in about 25%	Focal temporal slowing; mild slowing of parietooccipital rhythm	
Frontal lobe epilepsy	Frontal IEDs, secondary bilateral synchrony; occasional anterior temporal, multifocal, or no IEDs	Focal slowing uncommon; mild slowing of parietooccipital rhythm	
Occipital lobe epilepsy	Occipital IEDs, independent bioccipital IEDs; occasional temporal IEDs	Focal attenuation of parietooccipital rhythm may occur	Photic activation of seizures may occur

IED, interictal epileptiform discharge.

Clinical Utility of Electroencephalography in Diagnosing an Epilepsy Syndrome: Three Common Situations

Seizures Consisting of Quiet Staring

Staring with unresponsiveness but without automatic activity is a common presentation of epilepsy. These seizure manifestations can be seen in classic absence epilepsy, in the atypical absence of Lennox-Gastaut syndrome, and in complex partial seizures. EEG can provide critical information that aids in diagnosis and treatment. Generalized 3-c/s spike-wave activity (Fig. 1) and a normal background supports the diagnosis of absence epilepsy; slow (<2.5-c/s generalized spike and wave; Fig. 2) together with a slow background supports the diagnosis of atypical absence and suggests Lennox-Gastaut syndrome. Multifocal epileptiform activity, generalized paroxysmal fast activity, and focal paroxysmal fast activity are also common and provide further diagnostic clues.[7,86] Developmental delay and other seizure types may not be very prominent in this syndrome, and so interictal EEG is often very helpful. Finally, a temporal spike or sharp wave (Fig. 3) indicates the presence of complex partial seizures, probably of temporal lobe origin. The medical treatment, surgical options, and prognosis are very different in these three syndromes, so that a correct diagnosis is critical.

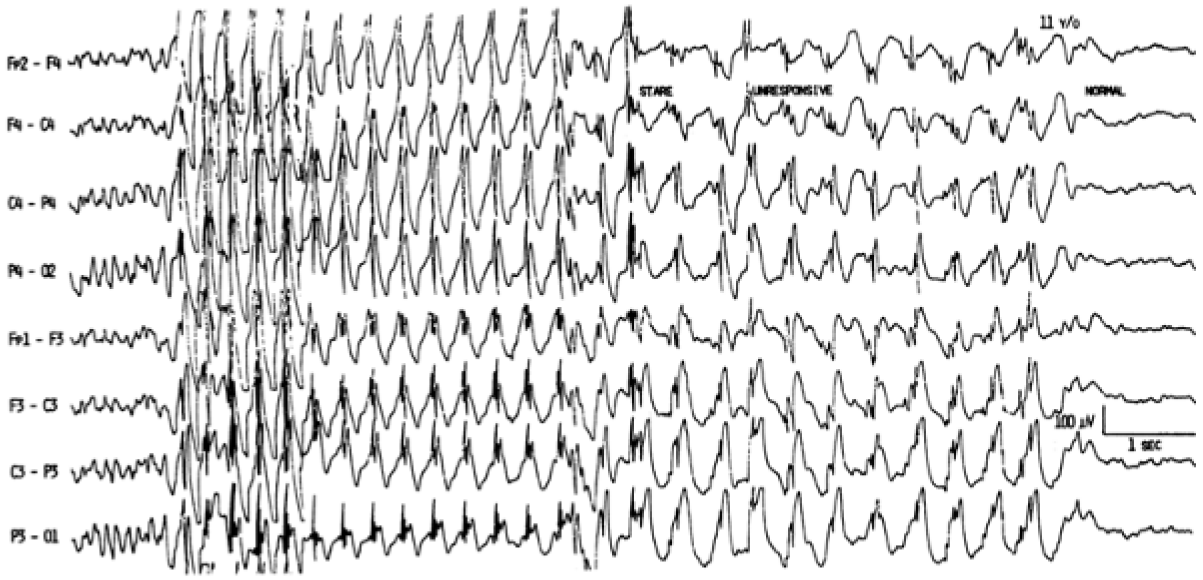
Fp2 - F4
F4 - C4
C4 - P4
P4 - O2
Fp1 - F3
F3 - C3
C3 - P3
P3 - O1
11 y/o
STARE
UNRESPONSIVE
NORMAL
100 µV
1 sec

FIGURE 1. Ten-second absence seizure in an 11-year-old with staring spells. Generalized spike-wave activity at 3 to 4 c/s is seen at the beginning of the seizure. The rate gradually slows toward the end of the seizure. The patient was asked to follow a simple command and was unable to do so during the spike-wave discharge. (Courtesy of Dr. Timothy A. Pedley, Columbia University, New York City.)

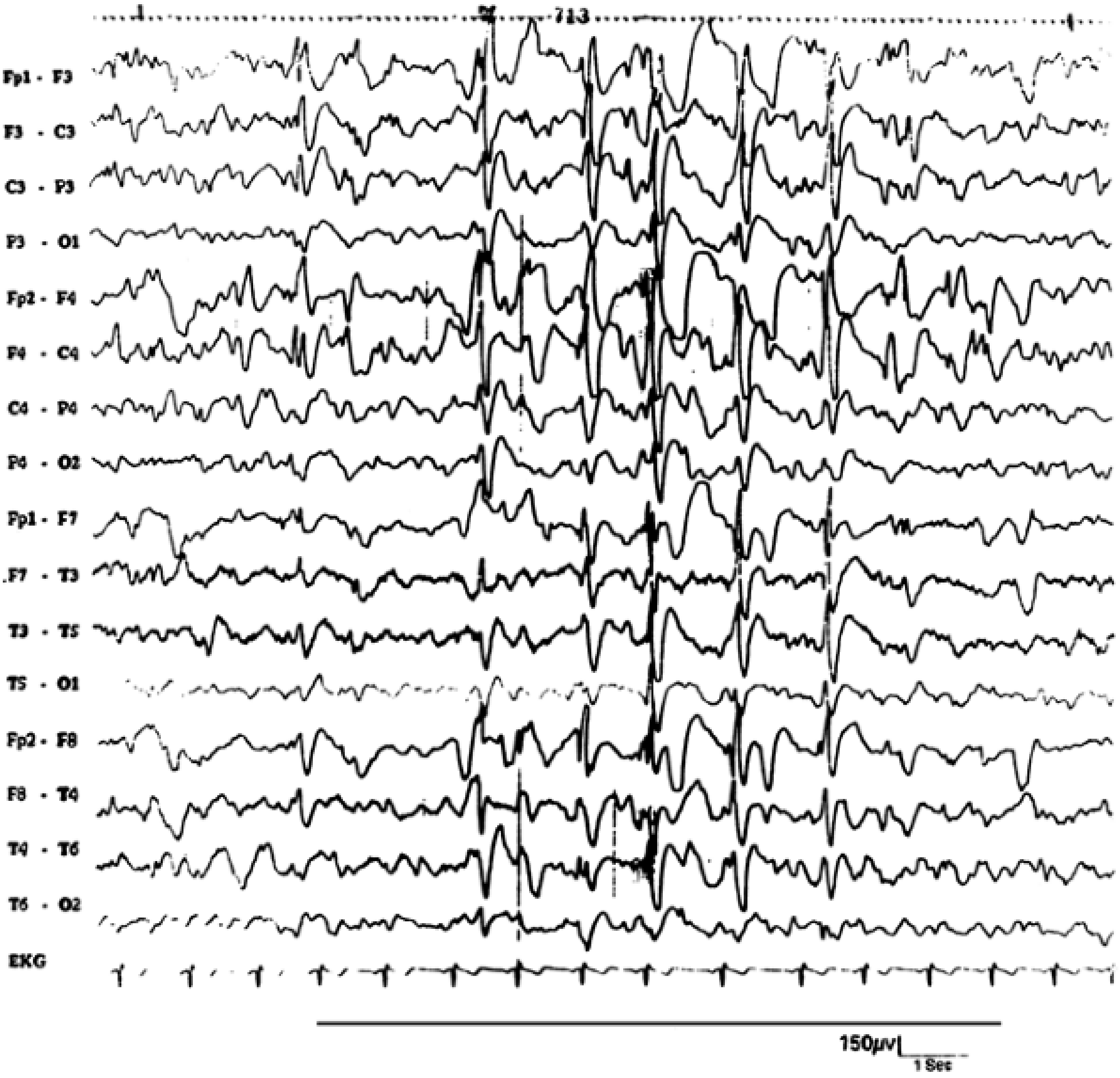
713
Fp1 - F3
F3 - C3
C3 - P3
P3 - O1
Fp2 - F4
F4 - C4
C4 - P4
P4 - O2
Fp1 - F7
F7 - T3
T3 - T5
T5 - O1
Fp2 - F8
F8 - T4
T4 - T6
T6 - O2
EKG
150µv
1 Sec

FIGURE 2. Generalized sharp-slow wave ("slow spike-wave") activity.

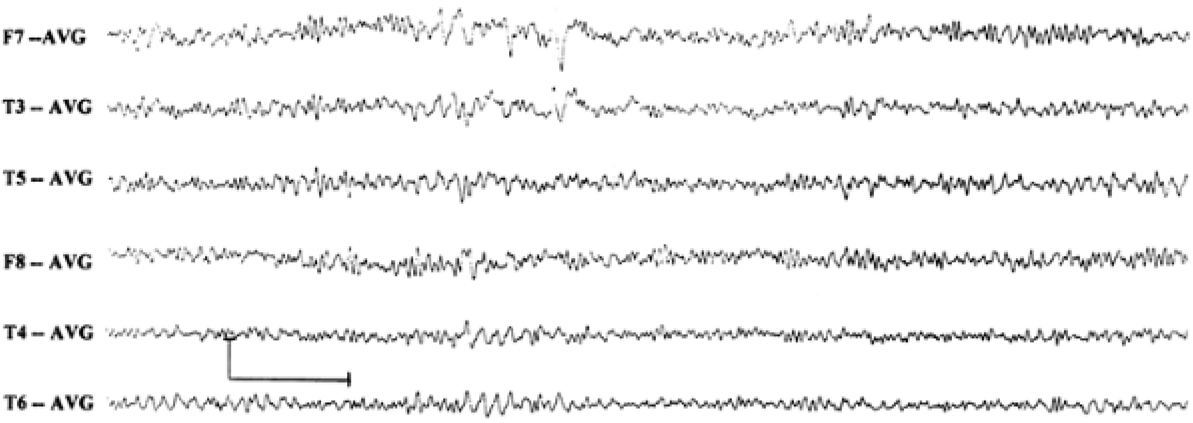
F7 – AVG
T3 – AVG
T5 – AVG
F8 – AVG
T4 – AVG
T6 – AVG

FIGURE 3. Left anterior temporal spikes. Average reference montage is employed, and only temporal channels

on both sides are displayed. Horizontal bar, 1 second; vertical bar, 70 µV.

Primary Generalized Versus Secondarily Generalized Tonic–Clonic Seizures

Epilepsy often comes to medical attention only after a tonic–clonic seizure. Initial manifestations of a seizure are often not witnessed or forgotten. The distinction between primary generalized epilepsy and partial seizures with secondary generalization is clinically important and often cannot be made confidently on clinical grounds alone. Again, EEG provides critical information. Generalized IEDs indicate a generalized epilepsy, and features of the generalized IED suggest specific generalized epileptic syndromes. Focal IEDs indicate localization-related epilepsy. Treatment approach and prognosis differ in these two groups of epilepsy syndromes, and so a correct diagnosis is important.

The EEG distinction between generalized spike-wave activity and secondary bilateral synchrony from one or multiple foci (Fig. 4) is occasionally difficult. The first pattern implies a bilateral synchronous abnormality and an idiopathic generalized epilepsy. The second pattern implies a more focal onset with rapid generalization and raises the possibility of a structural lesion. Shifting focal fragments of the generalized spike-wave often appear during sleep, and this can be misinterpreted as secondary bilateral synchrony. Generalized spike-wave bursts are occasionally recorded in benign rolandic epilepsy or in childhood epilepsy with occipital paroxysms, which can also cause confusion. The following criteria have been offered to distinguish secondary bilateral synchrony from generalized IEDs[100]: (a) Focal IEDs, when present, occur persistently on one area; (b) morphology of the focal IED differs from that of the generalized IED; and (c) focal IEDs clearly and consistently precede and initiate the generalized IEDs or IED bursts. Because secondary bilateral synchrony appears to be less common than primary generalized epilepsy, conservative interpretation is indicated. Simple procedures, such as increasing paper speed, occasionally will make possible the distinction between generalized spike-wave activity and secondary bilateral synchrony. Subtle time differences between IEDs in different regions can be emphasized by with special montage designs, such as reference subtraction.[66]

Nocturnal Attacks With Drooling in Children

Children are occasionally seen with a history of drooling, facial twitching, and unresponsiveness occurring at night. Diagnostic possibilities include the rolandic seizures of benign rolandic epilepsy and complex partial seizures of temporal lobe epilepsy. Drooling and facial twitching often occur during the latter. A careful history taken from an alert child or parent occasionally indicates that consciousness was preserved, that unresponsiveness was a consequence of anarthria, or that peculiar oral sensations preceded the seizure. All of these features would favor a diagnosis of rolandic seizures. However, such a precise description is rarely available. Once again, EEG provides critical information. A centrotemporal spike focus (Fig. 5) supports the diagnosis of benign rolandic epilepsy, whereas an anterior temporal focus usually indicates temporal lobe epilepsy. The distinction is important because the prognosis differs significantly in the two syndromes.

Not all patients with centrotemporal spikes have benign rolandic epilepsy,[31,57,71,88] although how often centrotemporal IEDs indicate symptomatic localization-related epilepsy is unclear. Both classic descriptions[57,82] and computerized analysis of voltage topography[53] indicate that the IED of benign rolandic epilepsy is oriented tangentially. The negative pole typically lies near the junction of the rolandic and sylvian fissures, and the positive pole is more broadly distributed over the frontal regions bilaterally. Gregory and Wong[53] confirmed that the IEDs of benign rolandic epilepsy have this sort of tangential distribution, whereas the IEDs of partial symptomatic seizures have a radial distribution. Others have noted that the IEDs of benign rolandic epilepsy are stereotyped, whereas centrotemporal IEDs of symptomatic localization-related epilepsies demonstrate greater variability in field. Focal background abnormalities are common in symptomatic epilepsy[89] and are not present in benign rolandic epilepsy. These differences, age of the patient, and the clinical situation usually allow a distinction between "benign" and "malignant" centrotemporal IEDs. Nor is the distinction between centrotemporal IEDs and midtemporal IEDs with some suprasylvian representation always straightforward with routine electrode arrays. The $T_{3/4}$ electrodes of the 10-20 International System actually lie near the junction of the sylvian and rolandic fissures. Recording to inactive reference always demonstrates that the amplitude of

IEDs seen in benign rolandic epilepsy is maximal over $C_{3/4}$ or $C_{5/6}$ rather than $T_{3/4}$.[79] Electrodes below the standard temporal 10-20 placements may allow more direct recordings from the temporal cortex and help to make this distinction as well.

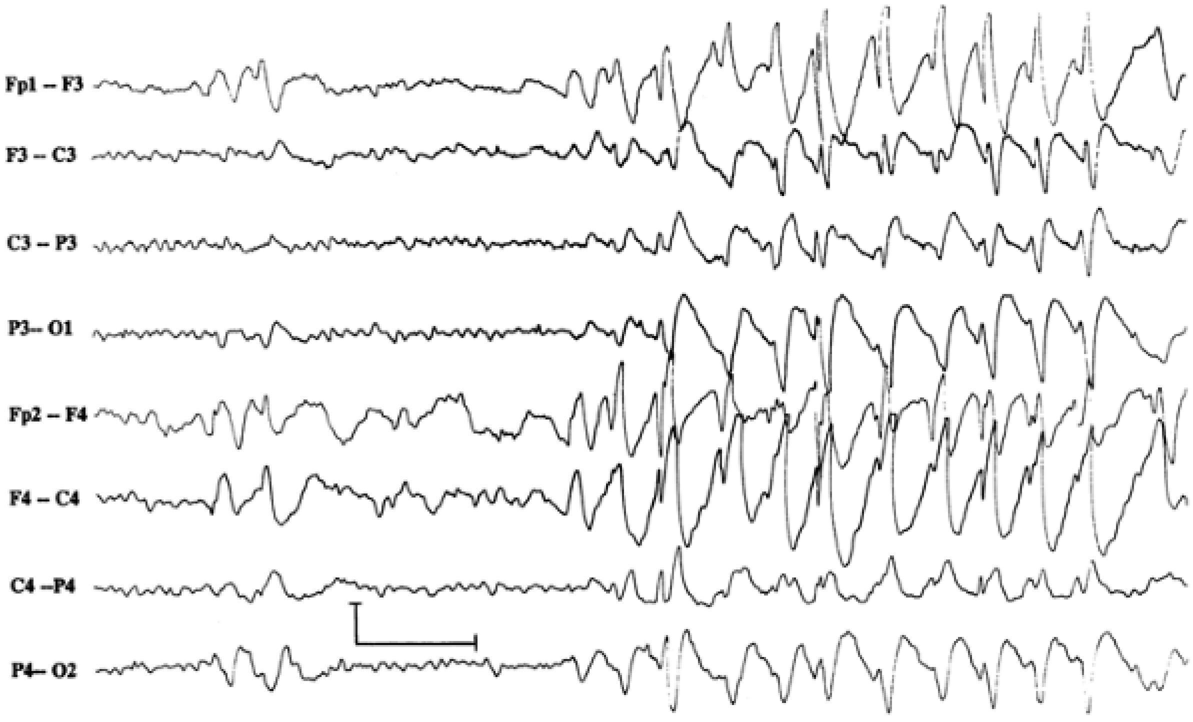

FIGURE 4. Secondary bilateral synchrony. Right frontocentral slowing and an independent right frontocentral sharp wave are noted. The next frontocentral sharp wave leads into a burst of secondary bilateral spike-wave activity, which is better organized over the right hemisphere. The patient had sustained traumatic injury to both frontal lobes, and posttraumatic epilepsy subsequently developed. Horizontal bar, 1 second; vertical bar, 70 μV.

Role of Electroencephalography in Assessing Cognitive Decline in People With Epilepsy

Electroencephalography can also be useful in distinguishing various causes of cognitive decline in people with epilepsy. Possible causes include antiepileptic drug toxicity, development of a degenerative syndrome associated with epilepsy, evolution of a neoplasm, or nonconvulsive status epilepticus. If baseline EEG is available, development or worsening of background slowing over time suggests either antiepileptic drug toxicity or the development of a degenerative syndrome (e.g., progressive myoclonic epilepsy). The appearance of new focal polymorphic delta activity raises the possibility of a new structural lesion. Both focal and diffuse slowing can be seen postictally. In large groups of patients, these changes almost always revert to baseline within 1 hour[69]; encephalopathic changes lasting as long as 10 days, however, have been rarely reported.[11] Previous EEG findings must be reviewed before focal delta activity can be considered significant in people with epilepsy because 12% to 23% of recordings in these patients demonstrate focal slowing without structural lesions.[46,87,89] Finally, nonconvulsive status epilepticus must always be suspected when responsiveness or alertness deteriorates in a person with epilepsy. Only EEG can confirm this diagnosis. Electroencephalographic evaluation is especially useful when postictal impairment is unduly prolonged because nonconvulsive status epilepticus or frequent subclinical seizures are more likely in this situation.

In children, IEDs may occur very frequently, blurring the differentiation between interictal and subclinical electrographic seizures. Such EEG abnormalities are often associated with adverse developmental and cognitive, behavioral, or psychiatric symptoms. It is not clear that treatment with antiseizure medications directed at decrease of IEDs is helpful. However, more definitive treatment of underlying etiologies (e.g., focal malformations of cortical development or hypothalamic hamartoma) is widely recognized as improving these comorbidities. The association between IEDs and autistic/behavioral dysfunction in general and the role of antiepileptic medications in treatment are even less well defined.[101,126]

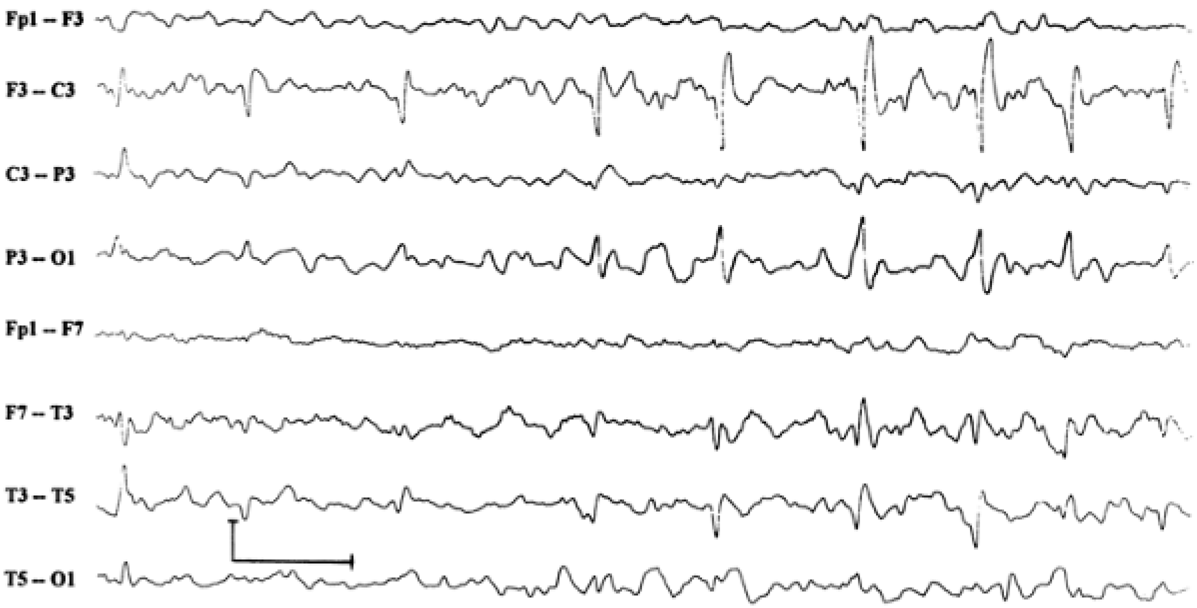

FIGURE 5. Centrotemporal spike in a 12-year-old with a clinical diagnosis of benign rolandic epilepsy. Only left hemispheric electrodes are displayed. Horizontal bar, 1 second; vertical bar, 70 µV.

Role of Interictal Electroencephalography in Evaluating Patients for Epilepsy Surgery

Adults

Resective epilepsy surgery aims to remove the area of seizure onset if it is safe to do so. Interictal EEG defines the irritative area, that is, the cortical area capable of generating IEDs. There is some overlap between irritative areas and areas of seizure onset, and so interictal EEG is used to find potential areas of seizure onset. Temporal lobe epilepsy is the most common localization-related epilepsy; consequently, anterior temporal lobectomy is the most commonly performed resective epilepsy surgery. In large surgical series, 74% to 92% of patients with unilateral anterior temporal IEDs had remission or significant improvement.[30,134] In these patients scalp interictal EEG appears reliably to define the area of seizure onset. However, unilateral anterior temporal IEDs by themselves can be misleading.

First, the duration of EEG sampling and sleep stage, among others,[21,109] determine the likelihood that IEDs are unilateral. Second, up to 25% of surgical candidates who have independent bitemporal seizure onsets found with intracranial recordings also have unilateral anterior temporal IEDs with scalp EEG.[58] Finally, anterior temporal IEDs have been reported in patients with seizure onset in lateral temporal neocortex[32] or orbitofrontal neocortex.[103,139] Voltage distribution with dipole modeling[32] or the use of sphenoidal electrodes[103] can help to distinguish between these possibilities. However, limited studies of these additional techniques have not yielded clinically useful rules.

More than 25% of potential candidates for resective epilepsy surgery have independent bitemporal IEDs.[58,103,134] In these patients, the probability that seizures originate independently from the two temporal lobes appears to be higher.[21] Nonetheless, 73% to 83% of patients with independent bitemporal IEDs recorded with scalp EEG have all seizures emerging from one temporal lobe after seizures are recorded with intracranial electrodes. Independent bitemporal seizures are more much likely when lateralization of temporal IEDs is <80%.[21,120]

IEDs appear to be less useful for localization in extratemporal epilepsies. In one study of 34 patients with intractable epilepsy cured by frontal lobe resection, only 9% had focal IEDs, and only 33% had regional IEDs that were thought to point to the frontal lobe.[103] Multifocal IEDs or secondary bilateral synchrony were common. Localization and lateralization appeared to be even less accurate in children. Other studies report similar findings.[40,85] Less information is available regarding seizures with occipital lobe onset. In three series of patients with seizures thought to emerge from the occipital regions (total 70 patients), occipital IEDs were seen 32%, 50%, and 63% of the cases, respectively.[13,78,140] Anterior temporal IEDs and secondary bilateral asynchrony were common. Independent bitemporal IEDs occurred in 31% to 40% of cases.[13,140] Similarly, in parietal lobe epilepsy, IEDs are localized to the parietal regions in less than half of the cases and are rarely the only abnormalities. Diffuse or bilateral independent temporal IEDs are common.[74,138]

Why are IEDs less localizing in the extratemporal epilepsies? There are several reasons. Opercular and interhemispheric cortex accounts for proportionally more of extratemporal cortex and is further removed from scalp electrodes than dorsal convexity. Cortical regions generating the IED may be larger, more variable, and overlap with seizure-onset area less well in the extratemporal epilepsies. Finally, white matter pathways mediating IED propagation may be more extensive and variable in extratemporal epilepsies.[37,103] A better understanding of the electrical pathophysiology of the IED in the various epilepsy syndromes would help in interpreting the localizing information that IEDs provide.

The usefulness of nonepileptiform focal changes in defining the seizure onset area has been less extensively examined. One study found that focal polymorphic delta was highly lateralizing in patients with unilateral mesial temporal sclerosis being evaluated for epilepsy surgery but was less useful in patients with bilateral mesial temporal sclerosis.[43] Temporal intermittent rhythmic delta appears to have a higher lateralizing and localizing value (see earlier discussion). Others have examined asymmetries of beta activity induced by intravenous barbiturates.[38,73] Such asymmetries occur in 23% to 66% of patients evaluated for epilepsy surgery and 37% to 54% of patients with mesial temporal sclerosis. False lateralization appears to be rare with visual assessment of scalp recordings.

Children

There is consensus that an EEG must be interpreted in the context of a child's cerebral development. Although partial seizures in children of school age that are associated with a localized epileptogenic zone are generally approached in the same manner as seizures in adults, the situation is different in early childhood. Maturational changes may lead to migration of the focus or appearance of new ones, and serial EEG studies are required to demonstrate consistency of the focus.[25]

Table 5 Electroencephalographic predictors of recurrence after first unprovoked seizure

Study	Population	IEDs	Non-IED abnormalities	Any abnormality	Comments
Annegers et al.[4]	Mixed	NR	NR	+	In idiopathic seizures only
Hopkins et al.[61]	Adults	0	0	0	

Shinnar et al.[116]	Children	0	NR	+	Trend toward IED predicting recurrence
Hauser et al.[56]	Mixed	+	0	0	Only generalized IEDs predicted recurrence
FIRST Group[41]	Mixed	+	NR	NR	
Van Donselaar et al.[132]	Adults	+	+	+	
Scotoni et al.[115]	Children	+	NR	+	

IED, interictal epileptiform discharge.
+, factor associated with increased risk; 0, factor not associated with increased risk; NR, effect of factor on risk not reported.

Multifocal epileptiform discharges raise concern about potentially multiple areas of seizure onset, but some of these

children may still be good surgical candidates. Typical examples are children with tuberous sclerosis, in which seizures may arise from a single tuber even when IEDs are multifocal and magnetic resonance imaging (MRI) reveals many tubers. Runs of repetitive IEDs may help to identify the candidate tuber in this situation.[75]

Another important scenario in early childhood occurs when focal lesions are associated with multifocal independent IEDs, diffuse IEDs, or even hypsarrythmia. Resection of lesions may eliminate the IEDs,[103] leading to the conclusion that IEDs in this situation do not represent multiple areas of increased seizure tendency. Rather, the IEDs appear to represent a functional electrical irritability of the whole cortex that is induced by the focal lesion and is apparently related to a particular stage of cerebral development. Thus, multifocal or diffuse IEDs do not appear to argue as strongly against a single area of seizure onset in immature abnormal cortex as they do in older children and adults.

A note of caution is warranted in a heterogeneous group of focal epilepsies in childhood that are not amenable to surgical care. These include genetically based partial epilepsies and those associated with progressive neurologic disorders requiring specialized investigations. Interictal EEG plays an important role in defining these situations.

Electroencephalographic Findings and Risk of Recurrent Seizures

The likelihood of seizure recurrence is the most important issue in deciding whether to treat with antiepileptic drugs after the first seizure. Five of six representative studies (Table 5) found that EEG abnormalities of any sort are associated with an increased risk for seizure recurrence. Three of the five studies found that presence of IEDs was associated with an increased risk for recurrent seizures. In one other study, a trend toward increased recurrence was noted in patients with IEDs. The risk for recurrence with the various types of IEDs was separately reported in only two studies. Hauser et al.[56] found that only generalized IEDs were associated with increased risk for recurrence. Shinnar et al.[116] did not find that different types of IEDs carried different levels of risk. A meta-analysis found that EEG findings provide useful prognostic information beyond that obtained by diagnosis of epilepsy syndrome, which is itself strongly influenced by EEG results.

These statements are not correct, however, when considering risk of unprovoked seizures following a febrile seizure. Nonspecific EEG abnormalities, usually generalized slowing maximal in the occipital regions, are common following a febrile seizure. Neither generalized slowing nor IEDs increase risk for further febrile seizures, unprovoked seizures, or subsequent epilepsy.[42,127,130] EEG has no demonstrated role in evaluating children with typical febrile seizures.

Likelihood of seizure recurrence is also a central issue when a suitable seizure-free period has elapsed and discontinuing antiepileptic drugs is being considered (see Chapter 7). It is reasonable to expect that EEG abnormalities are associated with an increased risk for relapse after discontinuation of antiepileptic drugs. It is not clear what features of the EEG evaluation would be most helpful. Results at time of first seizure, results at time of antiepileptic drug withdrawal, or change between these two could be considered. Again, it is reasonable to expect that IEDs would be more predictive than presence of other abnormalities. Finally, it is reasonable to ask whether the EEG provides unique information, separate from the diagnosis of the epilepsy syndrome.

Available information partially answers these questions. Electroencephalographic abnormalities increase risk for seizure recurrence in almost all studies (Table 6), although the strength of the effect ranged widely. Several studies examined risks associated with different types of IEDs. In the Medical Research Council study of antiepileptic drug withdrawal,[90] only generalized IEDs in patients with tonic–clonic seizures indicated increased risk for relapse significantly (relative risk, 1.37). Similarly, when antiepileptic drugs were discontinued following 3 years of seizure control in a group of children, generalized IEDs recorded immediately prior to discontinuation doubled the risk of seizure recurrence but centrotemporal IEDS did not.[3,14] However, another pediatric series[117] found that focal or diffuse slowing or IEDs were associated with relapse in univariate analysis. With multivariate analysis, four of six variables predicting relapse were EEG-related: (a) an association between age at first seizure and slowing, (b) presence of IEDs of any type, (c) presence of slowing, and (d) improvement in EEG at withdrawal compared with EEG at diagnosis.

It is not immediately obvious whether the value of EEG in determining whether to discontinue antiepileptic drugs comes from its contribution to the diagnosis of epilepsy syndrome or from its ability to measure “seizure susceptibility” at the time of medication discontinuation. Recent multivariable analyses simultaneously considering EEG findings at the time of medication withdrawal, previously established epilepsy syndrome diagnosis, and other factors suggest that IEDs at time of discontinuation predict the risk of recurrence independent of epilepsy syndrome, at least in children.[14,117]

Table 6 Electroencephalographic predictors of relapse after withdrawal from antiepileptic drugs

Study	Population	Abnormality at withdrawal	With abnormality who relapsed (%)	Definition of abnormality
MRC Trial[90]	Mixed	+	NR	Features analyzed individually
Callaghan et al.[17]	Adults	+	70%	IEDs, focal slowing

Shinnar et al.[117]	Children	+	35%	Features analyzed individually
Emerson et al.[36]	Children	+	57%	IEDs, "paroxysmal slowing"
Andersson et al.[3]	Children	+	43%	IEDs
Specchio et al.[121]	Mixed	+	NR	IEDs

IED, interictal epileptiform discharge.
+, factor increases risk for relapse; NR, information not reported.

Summary and Conclusions

Even in the era of high-resolution imaging, interictal EEG provides unique and critical information in the evaluation of people with known or suspected seizures. Interictal epileptiform discharges are highly correlated with epileptic seizures in the great majority of patients. Situations in which the presence of IEDs should be interpreted more cautiously are relatively uncommon and fairly well defined. Types of IEDs and other EEG abnormalities are somewhat less specific when the purpose is diagnosis of an epilepsy syndrome. This is in part because the epilepsy syndromes are often not precisely defined and because interictal EEG plays a critical role in the definitions that have become generally accepted. The usefulness of EEG in predicting seizure relapse is increasingly clear. Finally, limitations of interictal EEG in defining seizure onset area are becoming better defined so that the information provided by interictal EEG during evaluation for epilepsy surgery can be properly used.

It is remarkable that the EEG provides so much useful information. The fact that much of our knowledge is empiric—that is, derived from observed associations between easily recognizable waveforms and certain clinical situations—can be attributed to our imperfect understanding of the pathophysiologic underpinnings of the different forms of epilepsy and the associated cerebral electrical abnormalities. We do not understand exactly how damaged brain generates an IED or a sustained epileptic seizure, and so it should not be surprising that the relationship between epilepsy and IEDs is imperfectly defined. As further studies delineate the electrical, neurochemical, and genetic underpinnings of human epilepsy, empiric EEG investigations will become more focused. Contemporary digital and statistical techniques can then be applied more effectively so that interpreting clinicians can make full use of the wealth of information available in the interictal EEG.

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Chapter 74

Ictal Electroencephalogram

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Introduction

This chapter reviews the electroencephalographic features of seizures. The electroencephalogram (EEG) is an indispensable tool for studying seizures and is often the only means by which a diagnosis of epilepsy can be unequivocally established or seizures accurately classified. It supplies unique information about seizures that is not provided by any other physiologic method. Depending on the EEG technique, the spatial resolution ranges from 1 mm to several centimeters. Its recording characteristics allow the resolution of brief transients lasting a few milliseconds, yet comfortably allow the examination of events like seizures that last for minutes or hours.

Several questions about seizures can be answered using the EEG. The EEG verifies that the event in question is an epileptic seizure and not something else. It helps to classify the type of seizure, defining whether it is partial or generalized. Often, the EEG helps to pinpoint where seizures arise in the brain. The frequency of seizure occurrence and the effectiveness of therapy can be gauged with EEG.

This chapter first discusses the rationale and methods for recording seizures, then illustrates and describes the types of seizures seen in neonates, children, and adults. The EEGs shown here have mainly been recorded with scalp electrodes because seizures recorded with intracranial electrodes are amply illustrated in a subsequent chapter.

Rationale for Recording Seizures

Differential Diagnosis

There are many types of episodic events (see Chapter 68). Some are seizures, whereas others might be pseudoseizures, syncope, paroxysmal movement disorders, transient ischemic attacks, night terrors, somnambulism, narcolepsy, fugue states, or transient global amnesias, among others.[23] Although the medical history often helps to establish the diagnosis, it is not always adequate for the task. The history at times is misleading, and data must be obtained from other sources to arrive at a diagnosis. Ultimately, one can be confident of the diagnosis only when the episode is witnessed and physiologic recordings are made. Interpretation of the EEG recording is generally enhanced by simultaneous analysis of the behaviors that occur during the spell, although that is not always necessary.

Because seizures are characterized by paroxysmal changes of the brain's electrical activity, the diagnosis of a seizure can be confirmed with certainty by demonstrating those changes during the event in question. Seizures that produce impairment in consciousness or bilateral movements such as tonic–clonic seizures, tonic seizures, and complex partial seizures nearly always appear in the scalp EEG. However, there are certain circumstances in which the electrical signature of a seizure is not seen in the scalp EEG, even if a seizure has occurred:

1. During some seizures, the brain's electrical activity may be completely obscured by muscle and movement artifact. Whereas this sometimes prevents physicians from reaching a firm conclusion, the diagnosis of an epileptic seizure can still be offered if the pattern of muscular contractions is stereotyped (as in tonic–clonic seizures) or if it is followed by postictal slowing of EEG frequencies.
2. The scalp EEG usually does not show ictal discharges during simple partial seizures because of their

restricted potential fields.[21,69] Whereas this is especially true of simple partial seizures arising in medial, basal, and interhemispheric cortex, this is often true of convexity simple partial seizures as well. Even when simple partial seizures produce bilateral movements (e.g., supplementary motor seizures), a scalp EEG correlate is often lacking.

3. The scalp EEG, on rare occasion, also fails to detect ictal discharges during complex partial seizures, particularly when they originate in a frontal lobe.[38,78] Intracranial EEG generally eliminates these problems, and with adequate spatial sampling, seizures should appear in the EEG recorded by electrodes directly in contact with the cortex from which the seizures originate.

Occasionally, it is useful simultaneously to record other physiologic parameters along with the EEG when trying to diagnose episodic events. For example, the electrocardiogram (ECG) may reveal a primary cardiac rhythm disturbance, which then secondarily produces changes in the EEG. Blood pressure, muscle, and eye movement can also be studied if they might be helpful. Finally, the events in question can be provoked to help arrive at the diagnosis. For example, suggestion can be used to elicit a pseudoseizure while simultaneously recording the EEG, or tilt-table testing might reproduce vasodepressor syncope.

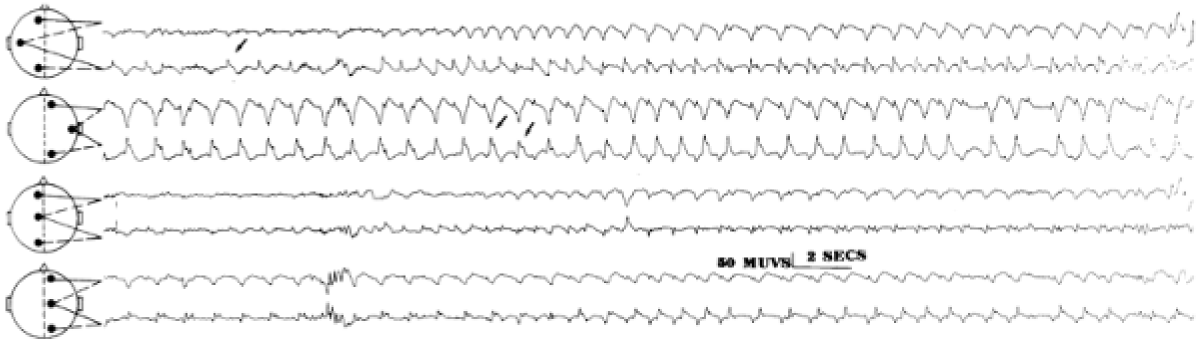


FIGURE 1. Neonatal seizure. This electroencephalogram was recorded from a 1-day-old, full-term infant boy who showed an acute neonatal encephalopathy, including seizures after a placental abruption. Two ongoing, independent electrographic neonatal seizures are apparent in the temporal-central regions (see text for details). The calibration mark in this and subsequent neonatal rhythm strips is 7 μV/mm and 2 seconds.

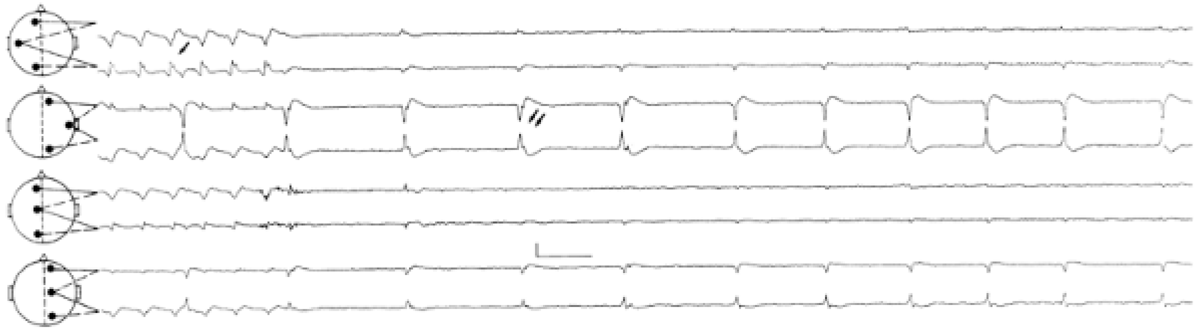


FIGURE 2. Neonatal seizure. This electroencephalogram was recorded from the same patient as in FIGURE 1, at a slightly later time. The very end of an electrographic neonatal seizure appears at T3, and periodic

lateralized epileptiform discharges recur invariantly at T4-C4 (see text for details).

Case Report

A 19-year-old woman had a history of absence seizures since the age of 12 years. They had never been completely controlled and, at the time of her latest evaluation, occurred three to four times daily. They came without warning and had no postictal confusional state, and she believed that they lasted between 10 and 20 seconds. She had taken ethosuximide (Zarontin) for the previous 7 years. She had normal developmental milestones and intelligence, and was a college student at a prestigious university at the time of her evaluation. Her medical history was significant only for well-controlled asthma, and no one in the family had a history of seizures. The neurologic examination was entirely normal. Her interictal EEG showed brief, 3- to 4-Hz generalized spike-and-wave bursts, mainly in light stages of sleep.

A decision was made to try to stop the seizures because of her dissatisfaction with her condition. First, the dose of ethosuximide was increased without benefit. She next tried valproic acid (Depakene) alone, then a combination of ethosuximide and valproic acid, then valproic acid and methsuximide (Celontin), then valproic acid and acetazolamide (Diamox), then valproic acid and clonazepam (Klonopin), and then trimethadione. With each drug or combination, she complained of persistent seizures and often had sedation, tremor, or some other side effect. Midway in the course of adjusting her medication, another EEG was obtained. This again showed interictal generalized spike-and-wave discharges.

Because therapy had failed, she had continuous EEG recording to study the seizures. During a 4-hour morning session, she complained of two absence seizures. Although she appeared briefly to stare, the EEG remained normal. She was informed that her seizures were not epileptic in nature, and psychogenic seizures were diagnosed. Ethosuximide was restarted and psychotherapy begun. Her complaints of seizures stopped, and she had no further complaints of seizures for the next 4 years of follow-up. After the seizures resolved, her asthma became more severe, requiring several hospitalizations in the next few years.

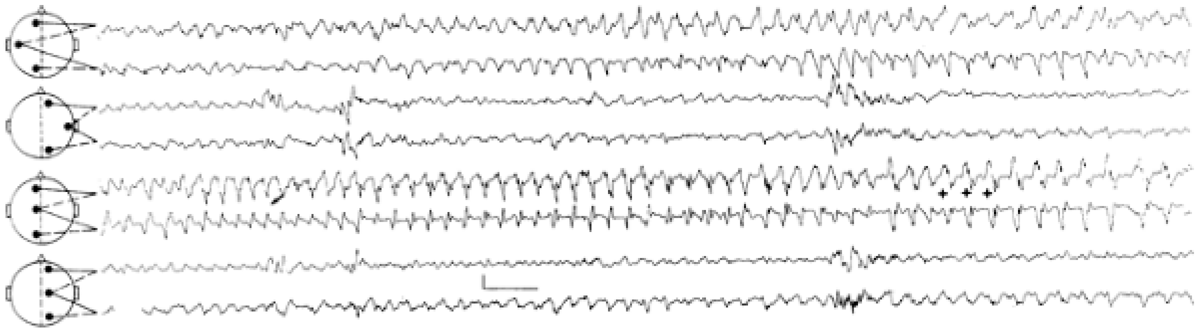
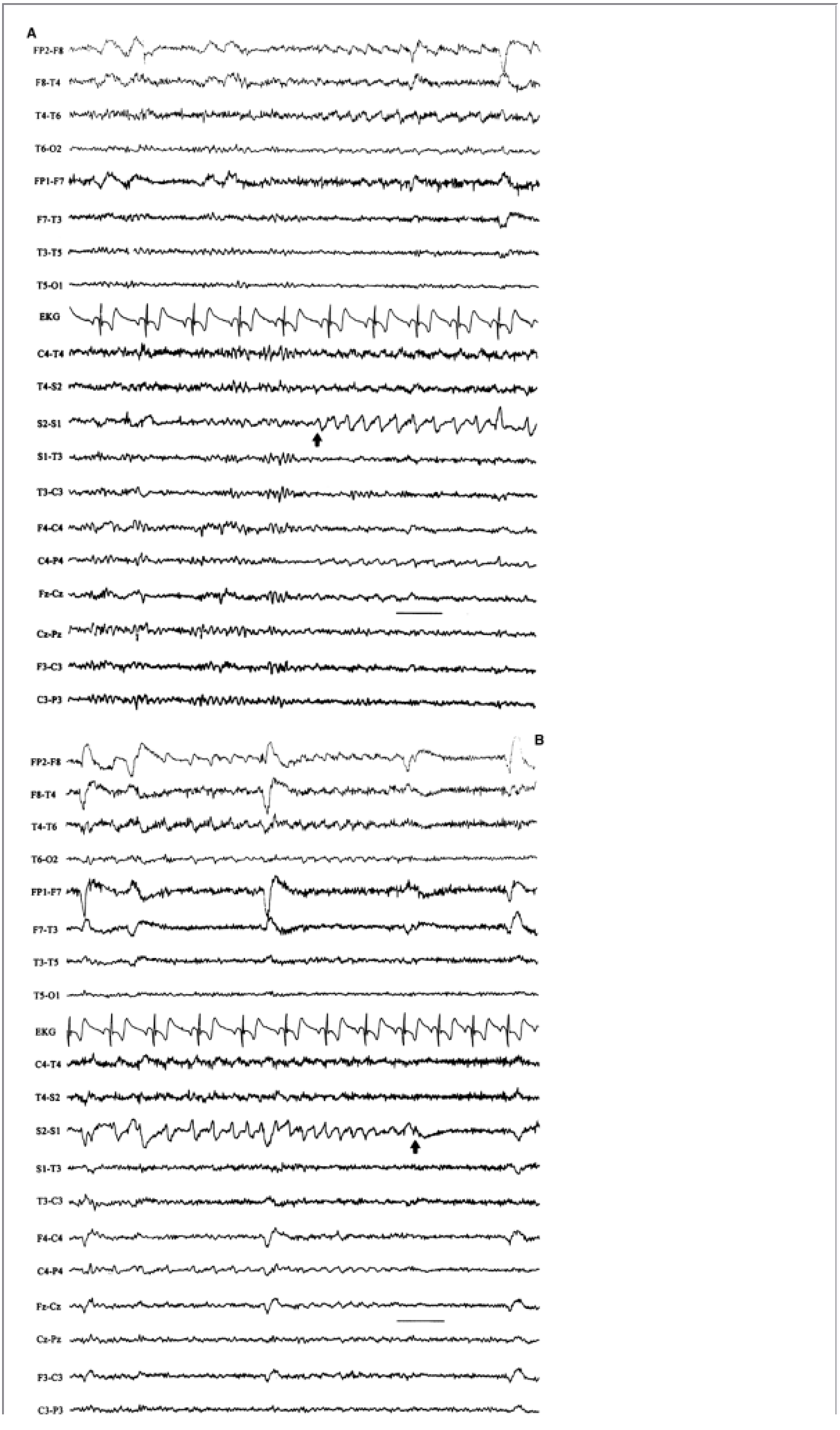


FIGURE 3. Neonatal seizure. This electroencephalogram was recorded from a comatose, 1-day-old, full-term infant boy who was being treated by extracorporeal membrane oxygenation for severe respiratory distress syndrome due to meconium aspiration syndrome and perinatal asphyxia (see text for details.)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EKG
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T4-S2
S2-S1
S1-T3
T3-C3
F4-C4
C4-P4
Fz-Cz
Cz-Pz
F3-C3
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T6-O2
FP1-F7
F7-T3
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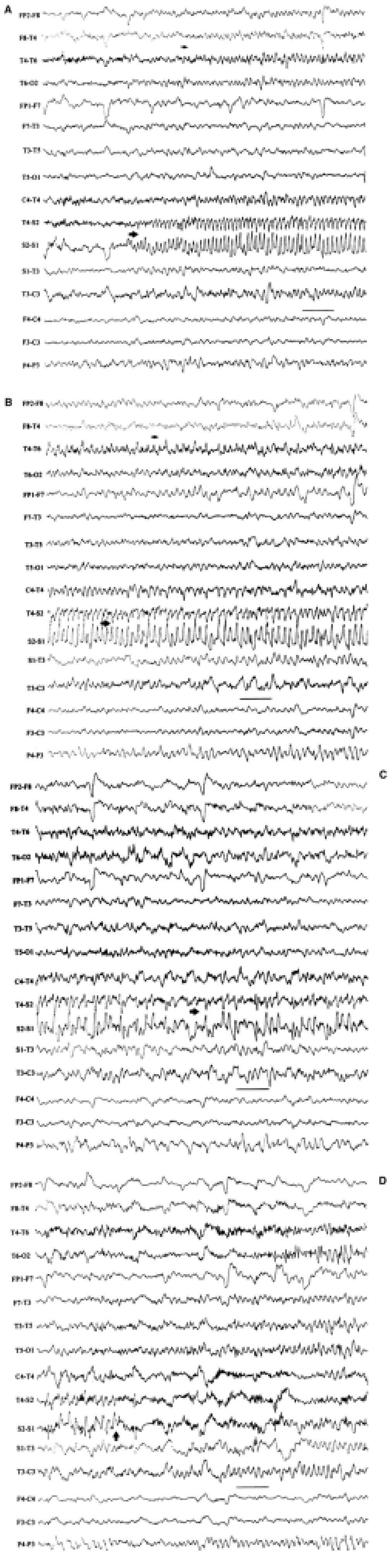
T4-S2
S2-S1
S1-T3
T3-C3
F4-C4
C4-P4
Fz-Cz
Cz-Pz
F3-C3
C3-P3

FIGURE 4. Simple partial seizure of right temporal lobe origin. **A:** The record begins with the patient awake, with eye blinks and frontalis muscle artifact. Midway through the page, rhythmic sharp waves appear in the right temporal region at approximately 3 Hz. In the anterior to posterior chain (channels 1–4), they phase-reverse at F8 (between channels 1 and 2). In the transverse chain, the phase reversal is less well defined, although it is apparent between channels 10 (C4-T4) and 12 (S2-S1). The sharp waves progressively increase in amplitude while simultaneously diminishing in frequency. When they appear, a bilateral desynchronization and attenuation of the alpha rhythm are seen, probably related to arousal. **B:** As the seizure continues, the sharp waves evolve in frequency and amplitude while the spatial extent of the field remains relatively constant. The discharge increases in frequency in the 5 seconds prior to seizure termination (*arrow*). The ictal activity does not spread to the contralateral hemisphere, and the patient remains conscious and in full contact during the entire seizure. Note the subtle increase in heart rate during the course of the seizure, due to either hypothalamic activation or heightened arousal. Although this patient felt this aura midway through the surface electroencephalographic (EEG) manifestation, awareness may precede, coincide, or follow its scalp EEG appearance in others. (Note: bar = 1 second in this and all subsequent figures.)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S1-T3
T3-C3
F4-C4
F3-C3
P4-P3
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F8-T4
T4-T6
T6-O2
FP1-F7
F7-T3
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T5-O1
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S1-T3
T3-C3
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T6-O2
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T3-T5
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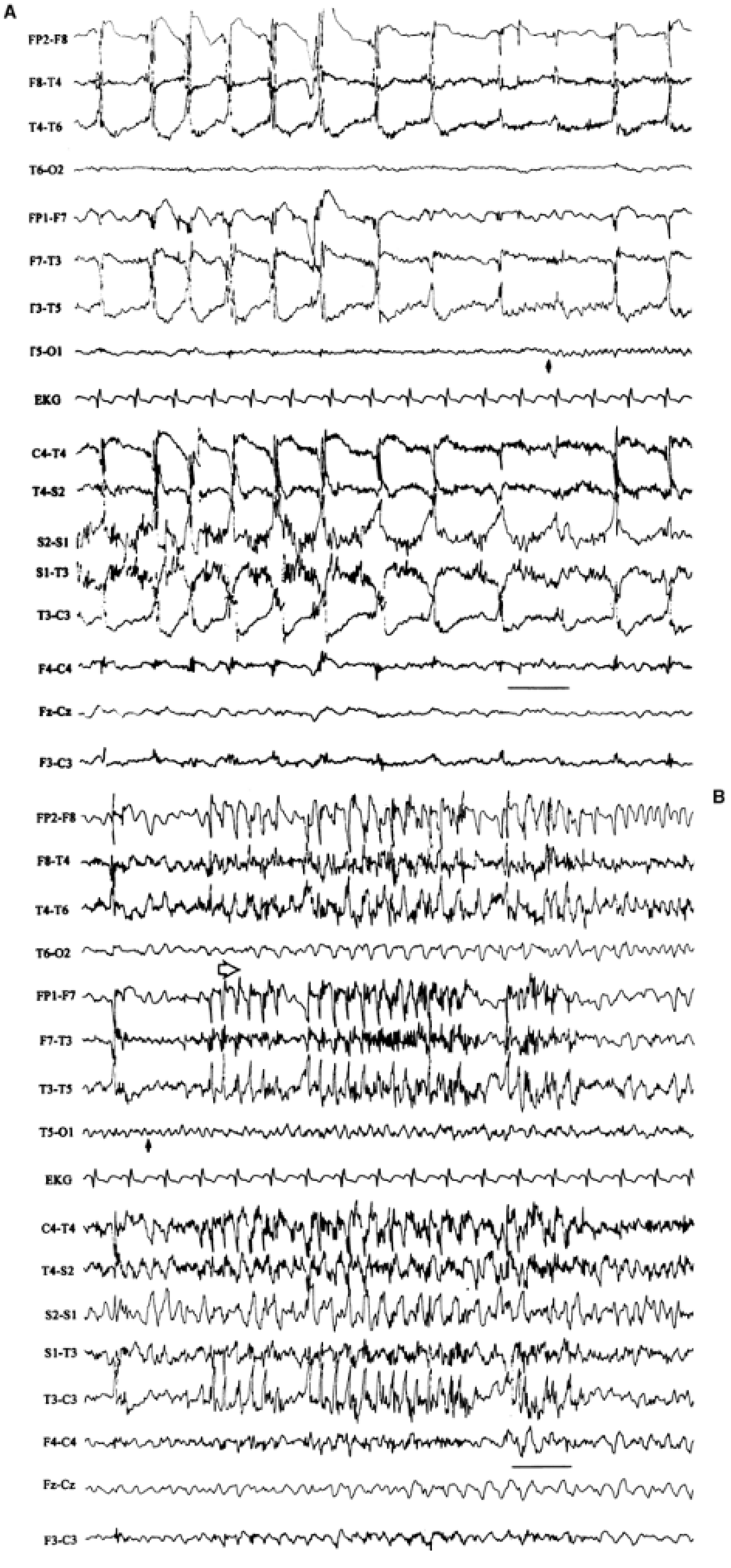
C4-T4
T4-S2
S2-S1
S1-T3
T3-C3
F4-C4
F3-C3
P4-P3

FIGURE 5. Complex partial seizure of right temporal lobe origin. **A:** This sequence illustrates a typical complex partial seizure of temporal lobe origin. The seizure begins with rhythmic 8- to 8.5-Hz sharp waves in the right basal temporal region, with a crisp right sphenoidal phase reversal (*arrow*). Because of the steep field gradient between T4, S2, and S1, the activity is best seen in the transverse chain. The same activity, although much reduced in amplitude, is seen in the anterior-to-posterior chain as well (channels 1–4), and it becomes clearer toward the end of this page. Note the progressive increase in amplitude of the sharp waves as the seizure continues. There is a subtle increase in the amount and rhythm of the theta- and alpha-frequency waves in the left hemisphere leads at the same time. This probably reflects invasion of the ictal discharge in that hemisphere. **B:** The seizure continues (*arrow*) with a gradual slowing of the sharp wave frequency, seen best in T4-S2 and S2-S1. In the anterior-to-posterior chain, the rhythmic sharp waves phase-reverse between channels 1 and 3 or 1 and 2 as the field varies, which is characteristic of mesial temporal lobe seizures. The ictal activity in the left hemisphere is subtle compared with the right, but rhythmic alpha-frequency waves are present that were not seen in the interictal state. **C:** On this page, the right sphenoidal sharp waves vary more in amplitude and frequency (*arrow*), and semirhythmic delta activity becomes prominent in the right hemisphere, although it is noted in the left-sided derivations also. **D:** The rhythmic sharp waves stop early in this page (*arrow*), marking the end of the seizure. Immediately afterward, lateralized postictal slowing, consisting of prominent delta activity in the right temporal region, appears. This last page also illustrates how physiologic artifact from eye blinks and muscle contraction help to diagnose a seizure and to characterize the behavior. This last page contains at least eight eye blinks in 7 seconds after the seizure stopped. In contrast, no eye blinks are seen on the first two pages once ictal activity appears, and only two blinks are seen in panel C. This lack of blinking correlates with a motionless stare, noted during some complex partial seizures. The high-frequency activity in channels containing the right temporal leads (F8, T4, T6, S2) is muscle artifact, which reappeared immediately after seizure cessation. It had been present before the seizure early in panel A and disappeared once the seizure began. Hence, the seizure produced a decrease in muscle tone, further confirming concomitant behavioral change, had no observer been present.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EKG
C4-T4
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S2-S1
S1-T3
T3-C3
F4-C4
Fz-Cz
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T4-T6
T6-O2
FP1-F7
F7-T3
T3-T5
T5-O1
EKG
C4-T4
T4-S2
S2-S1
S1-T3
T3-C3
F4-C4
Fz-Cz
F3-C3

FIGURE 6. Left occipital complex partial seizure. **A:** This seizure begins with low-amplitude 9-Hz waves (*arrow*). The patient was eating prior to seizure onset, and the record shows muscle artifact caused by chewing. **B:** The seizure continues with an occipital alpha-frequency discharge (*small arrow*). Several seconds after the start of the page (*large arrow*), higher-amplitude sharp waves appear in the temporal regions, with mid- to anterior temporal phase reversal. This represents anterior spread of the seizure and the development of an independent ictal discharge in the temporal lobes at a different frequency from that of the occipital lobe.

This case illustrates the usefulness of EEG recording to clarify a diagnosis. In retrospect, it would have been prudent to perform EEG recording of her seizures much earlier. Her physician was swayed by the abnormal interictal EEG, and, in all likelihood, she did have epilepsy at one time and may still have had a tendency for seizures. Arriving at a diagnosis of pseudoseizures allowed for institution of appropriate therapy.[37] The subsequent worsening of the asthma reveals the need for illness that motivated the complaints of absence seizures, and it may be suggested that ongoing psychotherapy is required.

Classification

Once seizures are diagnosed with certainty, the type of seizure should be determined. The classification of seizures and the epilepsies is reviewed elsewhere, and here it suffices to remind the reader that seizures typically fall into one of two categories—generalized or partial. Generalized seizures begin more or less simultaneously throughout the cortex, whereas partial seizures begin focally and spread to a variable extent. This distinction is important because it helps to determine which of the epilepsy syndromes a particular patient has, influences the choice of medication, and ultimately affects prognosis. The history and interictal EEG usually suffice for reasonable diagnostic confidence. However, should a patient fail to respond to therapy or experience adverse side effects to a number of medications, recording of seizures with EEG not only can confirm the diagnosis of epilepsy, but it also can establish the classification to ensure that appropriate therapy is prescribed. EEG recording, particularly when behavior is studied, greatly furthers this aim.

Generalized seizures begin with a number of character-istic patterns that are apparent in the scalp EEG: Typically, generalized spike-and-wave discharges (e.g., absence or tonic–clonic seizures), generalized paroxysmal fast activity (e.g., tonic seizures), a diffuse electrodecremental response (e.g., atonic seizures), or a generalized frontally predominant slow wave (e.g., atonic seizures). Because partial seizures begin focally, one

might reasonably assume that the EEG shows a focal onset in a frequency domain when they begin. This often happens and, in theory, should always be present. However, technical limitations in recording methods make demonstration of a focal seizure onset either impractical or unattainable. Some seizures spread so quickly —within a few milliseconds—that localized onset cannot be demonstrated, despite the best of modern technology. Other seizures begin in “buried cortex,” that is, cortex hidden from the recording electrodes. These seizures are detected only once they have spread elsewhere in the brain, and the propagation may be so diffuse that a focal start cannot be seen. Fortunately, the EEG patterns of partial seizures

usually differ sufficiently from those of generalized seizures that they are diagnosed with reasonable confidence, even though a focal onset is not seen. Nevertheless, there still remain some occasions when seizures cannot be definitively classified.

Case Report

A 22-year-old man complained of seizures that began at the age of 15 years. He had a prior history of an uncomplicated febrile convulsion. His seizures began with a feeling of lightheadedness lasting several seconds, and then he became unresponsive and motionless for approximately 20 seconds. He had been treated unsuccessfully with phenytoin (Dilantin) since his seizures began and still had several per month. No one in his family had a history of seizures. Neurologic examination was normal, and an interictal EEG was normal.

The phenytoin was discontinued and carbamazepine (Atretol, Tegretol) was begun. The seizures continued unabated, perhaps slightly increased in frequency. Another interictal EEG was normal. Because of nausea at higher doses, the carbamazepine was stopped and phenobarbital (Arco-Lase, Bellergal-S, Donnatal, Quadrinal, Mudrane, Rexatal, Solfoton) was begun. The seizures continued.

He then had continuous EEG recording to capture seizures. During one of his typical seizures, the EEG showed a prolonged run of generalized, 4- to 5-Hz spike-and-wave discharges. Valproic acid was then begun, and his seizures stopped.

This case illustrates how ictal recording, by classifying seizures, can help. Once it was realized that this patient had generalized epilepsy, appropriate medical therapy could then be used successfully to treat the seizures.

Localization

There are two reasons to localize seizures. The first reason is scientific. By directly studying seizures and characterizing how they begin, spread, and end, one can better understand epilepsy. Planning for epilepsy surgery provides the main clinical reason to localize seizures. If a surgical procedure is planned, it is first necessary to establish whether all seizures come from one region and, if so, to identify the specific region of cortex that gives rise to the seizures. Whereas evaluation for epilepsy surgery involves performing a variety of tests, recording seizures with either scalp or intracranial EEG still offers the most direct means of identifying the tissue to be resected. Seizures can be localized either with scalp (extracranial) electrodes or with intracranial electrodes. It is important to recall that both extracranial and intracranial EEG can be misleading with regard to localization. Just as partial seizures might not appear to be localized in some EEG recordings or might not appear at all (as discussed previously), a "clear-cut" localization can at times be misleading if the propagation of an ictal discharge is seen first, rather than its initiation. For example, a seizure might start in the occipital lobe but spread rapidly to the temporal lobe and falsely appear to begin in the temporal lobe in the scalp EEG.

Quantification

The last of the major clinical reasons to record seizures is to quantify their rate of occurrence. Many people do not know when they have had a seizure or how often they occur. A prolonged recording session can define how often seizures occur, thereby providing a gauge of the effectiveness of therapy. For example, absence seizures may occur dozens of times per day in small children, and a 24-hour recording can establish whether medication levels are sufficient. Examination can be made of the relationships between seizure occurrence and the time of day or month, the different stages of sleep, and medication levels, among other factors.

Methods for Recording Seizures

Electrodes

Extracranial Electrodes

Most types of EEG electrodes that are employed for interictal EEG recording are also suitable for recording seizures. The only requirements are that the electrodes be suitably placed to detect the electrical activity of the brain and that they be reasonably secured so that they do not fall off or move too much during a seizure. The electrodes most often used for extracranial recording are attached to the scalp (placed in the 10/20 system, its intermediate placements, or more inferiorly).[61] Collodion should be used to maintain optimal contact and minimize movement. Sphenoidal electrodes are inserted medially beneath the zygoma to record from basal temporal structures[67] and are sometimes useful for detecting basal temporal lobe spikes and localizing temporal lobe seizures.[57] Nasopharyngeal electrodes are too unstable to use for recording seizures. Extracranial electrodes are subject to significant limitations. These include limited spatial resolution and inability to detect activity from deep cortex (such as basal cortex, including basal orbitofrontal, temporal, and occipital cortex; interhemispheric cortex; and activity within the depths of sulci).

In addition, EEG electrodes record some physiologic artifacts that may sometimes aid in diagnosis. These include characteristic patterns of muscular contraction, changes in heart rate, and alteration in eye blinking. For example, whereas the muscle artifact of a tonic–clonic seizure may completely obscure the EEG, the pattern of muscular contractions is so stereotyped that the EEG is diagnostic. Subtle increases or decreases in tonic muscle activity help to establish whether electrographic seizures have an associated subtle change in behavior. The cessation of eye blinking often heralds the onset of many temporal lobe complex partial seizures; this observation is readily made in the EEG. Most seizures induce an increase in heart rate, sometimes even before the seizure produces a conscious response, and this is often recorded in the EEG.

Intracranial Electrodes

These are used to localize the source of seizures when noninvasive methods are inadequate.[27,40] They lack many of the limitations of scalp and other extracranial electrodes and are discussed at length in a separate chapter. Briefly, they include electrodes that can overlie the dura, known as *extradural electrodes*; electrodes that overlie the pia and are beneath the dura, known as *subdural electrodes*; and electrodes that enter the substance of the brain, known as *intracortical* or *depth electrodes*. Electrodes may also be inserted through the foramen ovale to record from the mesial temporal lobe from an epidural location. They are more sensitive to small field potentials than with scalp EEG and serve to localize seizures when noninvasively obtained data are inadequate. They may often show a well-localized seizure onset, even when scalp EEG recording is nonlateralizing.[40] A more complete discussion can be found in Chapter 171.

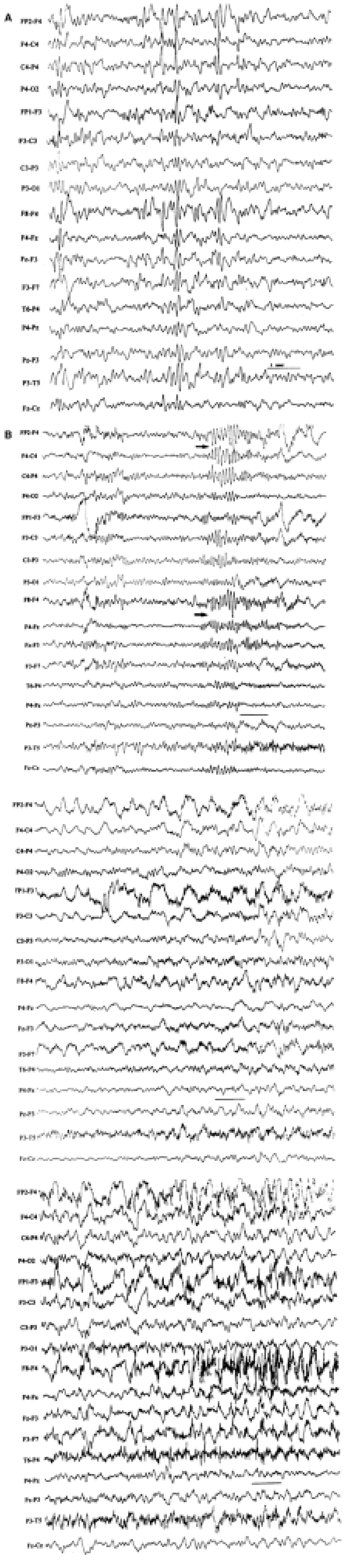
Other Electrodes

Electrocardiography (ECG) recording is usually done along with EEG. At times, an electromyogram (EMG) may be recorded, using surface electrodes glued to the skin. These help to define artifacts in the recording environment and so assist in interpreting the EEG.

Electroencephalographic Recording

The EEG should be recorded using standard filter settings (low-frequency filter, 1.0–1.6 Hz, and high-frequency filter, 70 Hz). If excessive movement is present, the low-filter settings can be increased to reduce sway; reducing the high-frequency filters rarely clarifies the situation. Montages should incorporate at least 16 channels and should include bipolar montage configurations in anterior-to-posterior and transverse directions (at times, referential montages are useful supplements). Paper records should be displayed at 30 mm/s. When digitally recording the EEG, the sample rate should be at least 200 Hz.

Seizures can be recorded in the EEG in a routine laboratory setting, on an outpatient ambulatory basis, or in an inpatient unit. Routine laboratory recording allows for behavioral testing but suffers from technical and time constraints. Ambulatory recording eliminates the time limitations, but video is not available, and technical problems are not immediately remediable. An inpatient unit permits the most comprehensive and technically satisfactory recording, although at greater expense than the other methods. Automatic spike and seizure detection programs employed during long-term monitoring reduce the amount of EEG that must be directly reviewed by the electrophysiologist and, therefore, are useful means of performing data reduction while simultaneously enhancing detection capabilities.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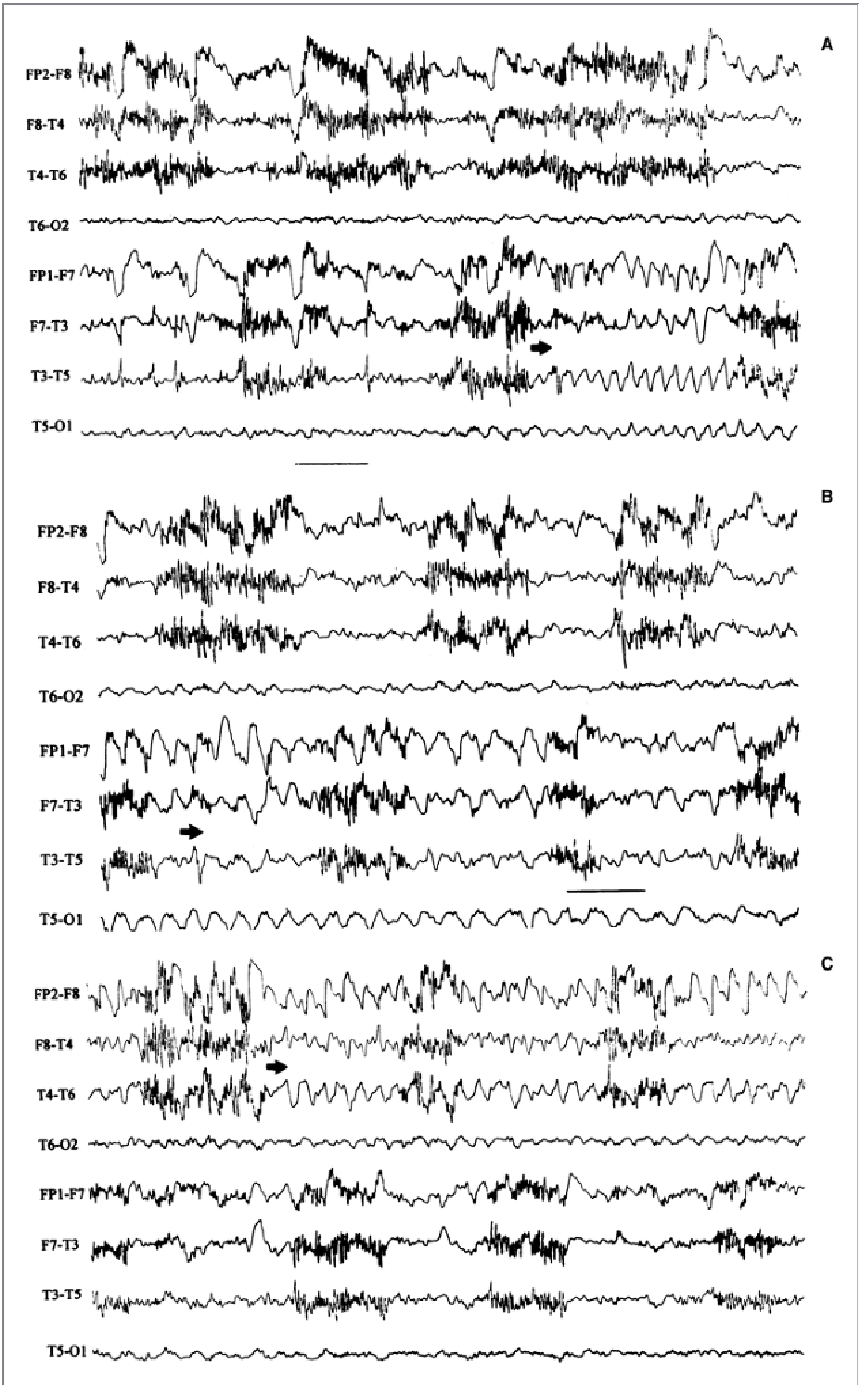
Fz-F3
F3-F7
T6-P4
P4-Pz
Pz-P3
P3-T5
Fz-Cz

FIGURE 7. Frontal lobe complex partial seizure. **A:** This page immediately precedes seizure onset. Frequent interictal sharp waves are present at F4, C4, and F3. These wane in the last 2 seconds of this page. **B:** The sharp waves are replaced by irregular theta and delta discharges in the first several seconds of this page. In the last few seconds, an obvious ictal discharge consisting of rhythmic 9- to 10-Hz sharp waves appears (*arrow*), maximal at F4, suggesting right frontal localization. **C:** The seizure continues, but no definite ictal discharge is seen in the electroencephalogram. Toward the end of this page, high-amplitude rhythmic delta discharge appears. This is accompanied by a notable increase in tonic muscle artifact, indicating a behavioral change. **D:** The seizure continues with rhythmic theta- and delta-frequency activity. Contractions of the temporalis muscles show as phasic muscle artifact in the latter portion of the page.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T6-O2
FP1-F7
F7-T3
T3-T5
T5-O1
C
FP2-F8
F8-T4
T4-T6
T6-O2
FP1-F7
F7-T3
T3-T5
T5-O1

FIGURE 8. “Ping-pong" complex partial seizure of temporal lobe origin. **A:** The seizure begins with rhythmic theta-frequency activity in the left temporal derivations (*arrow*). **B:** The seizure continues with rhythmic theta and delta activity in the left temporal region, which diminishes toward the end of this page. **C:** The left temporal ictal discharge has stopped. However, rhythmic 3- to 4-Hz waves develop in the right temporal region as the seizure continues in that lobe, despite having ceased in the temporal lobe of origin.

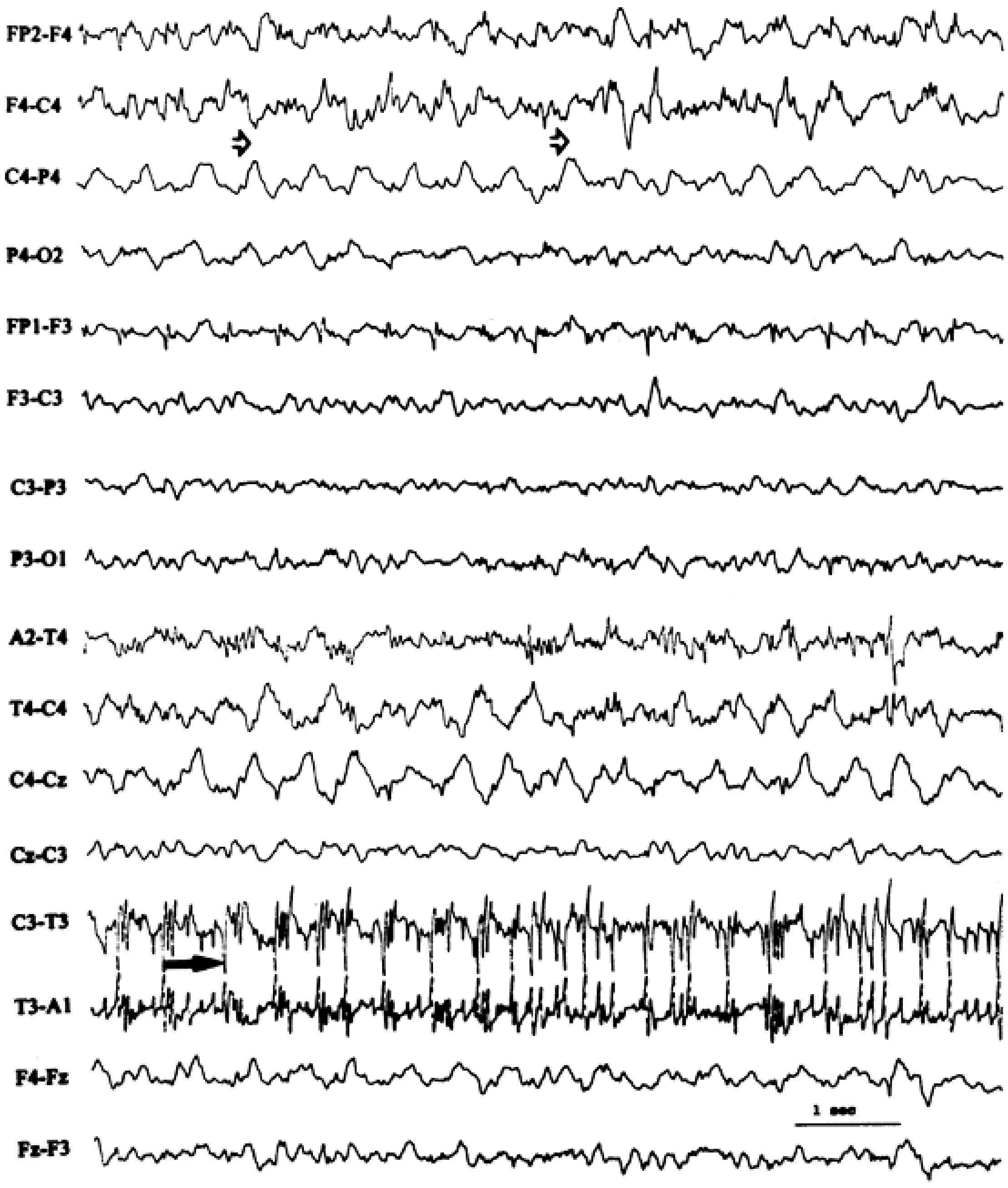
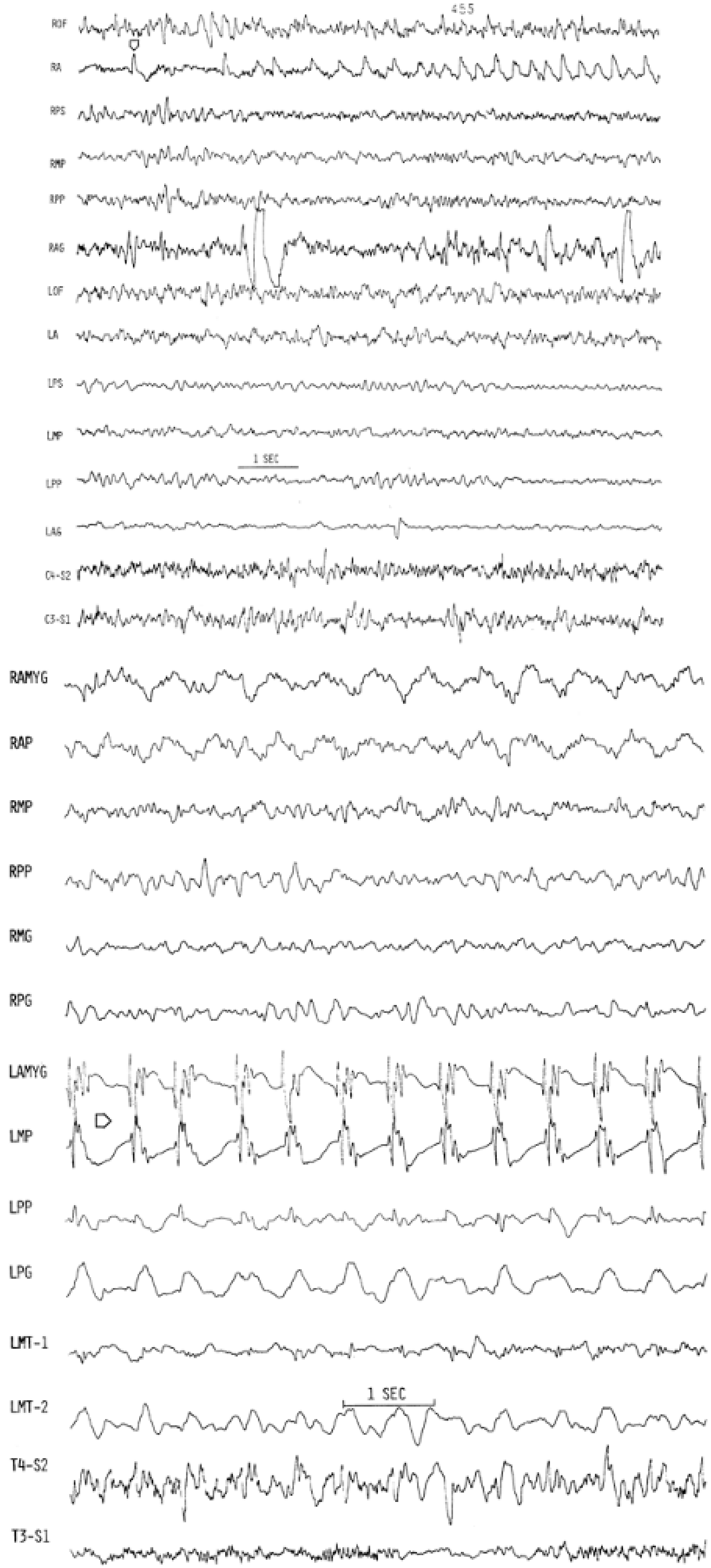


FIGURE 9. Electroencephalogram (EEG) of epilepsia partialis continua. The channels containing T3 show irregular muscle twitch artifact (*solid arrow*). Nonevolving semirhythmic delta activity that phase-reverses at C4 (*hollow arrows*) is the electrographic feature of this seizure. Note the lack of relationship between twitch rate and EEG frequency.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LMP
LPP
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LMT-1
1 SEC
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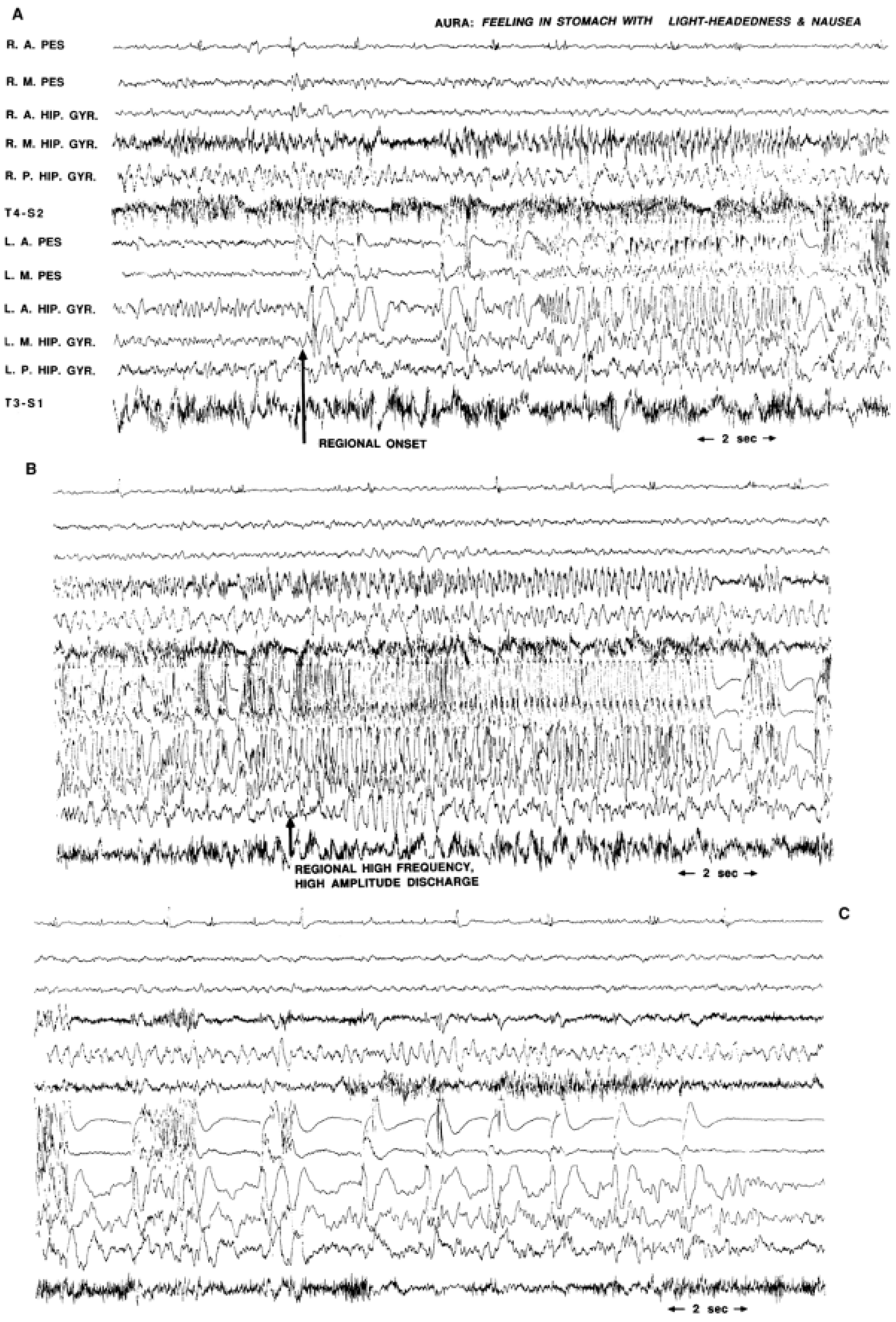
T4-S2
T3-S1

FIGURE 10. Seizure onset demonstrated with intracranial electroencephalogram. **A:** A discrete (focal) seizure onset is seen in the right amygdala (*arrow*). The seizure begins with rhythmic triangular sharp waves that are confined to the amygdala. **B:** This regional onset seizure contrasts with the previous seizure in that a more widespread onset is seen in both amygdala and hippocampus. Rhythmic spiking (*arrow*) is seen in electrodes recording from amygdala and mid pes hippocampus, with some reflection of the spikes in the posterior pes electrode and reflection of the slow wave in the parahippocampal gyrus. AMYG, amygdala; AP, anterior pes hippocampus; L, left; MG, mid parahippocampus gyrus; MP, mid pes hippocampus; MT, middle temporal gyrus; PG, posterior parahippocampus gyrus; PP, posterior pes hippocampus; R, right.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R. M. PES
R. A. HIP. GYR.
R. M. HIP. GYR.
R. P. HIP. GYR.
T4-S2
L. A. PES
L. M. PES
L. A. HIP. GYR.
L. M. HIP. GYR.
L. P. HIP. GYR.
T3-S1
REGIONAL ONSET
← 2 sec →
B
REGIONAL HIGH FREQUENCY, HIGH AMPLITUDE DISCHARGE
← 2 sec →
C
← 2 sec →

FIGURE 11. Mesial temporal simple partial seizure recorded with intracranial electrodes. **A:** The seizure begins with regional high-amplitude spiking (*arrow*) for several seconds. This is followed by the development of regional fast activity in the latter portion of the page. **B:** The regional discharge progressively slows in

frequency while increasing in amplitude. The extracranial channel (*bottom channel*) shows a rhythmic pattern, although the fast spiking present in the depth electrodes cannot be seen. Toward the end of the page, the discharge is interrupted by transient suppressions. The seizure does not spread to the contralateral hemisphere but remains confined to the left mesial temporal lobe. **C:** The pattern of ictal fast activity and suppression continues initially, although the fast activity is then replaced by spikes. The seizure ends with flattening in the anterior mesial channels. A. HIP. GYR., anterior hippocampus gyrus; A. PES, anterior pes hippocampus; L, left; M. HIP. GYR., mid hippocampus gyrus; M. PES, mid pes hippocampus; P. HYP. GYR., posterior hippocampus gyrus; R., right.

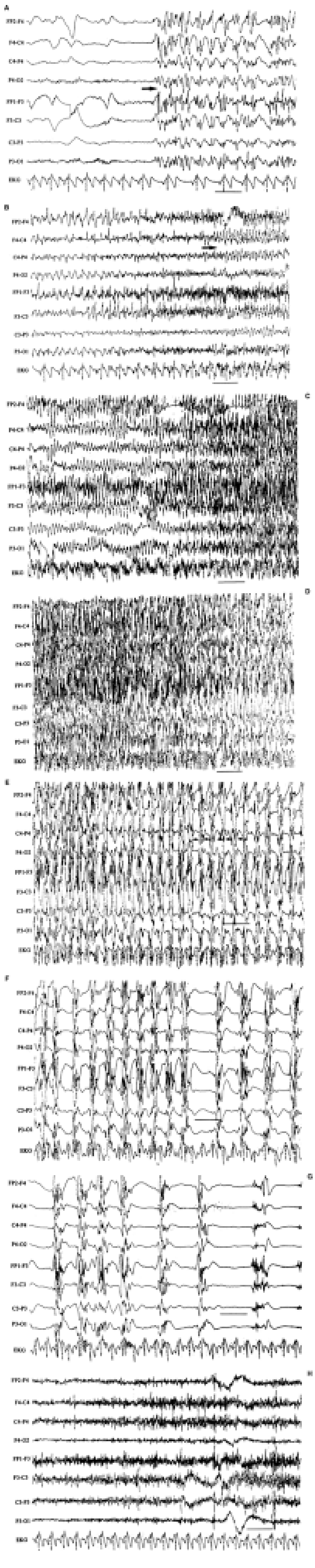
A
B
C
D
E
F
G
H
FP2-F4
F4-C4
C4-P4
P4-O2
FP1-F3
F3-C3
C3-P3
P3-O1
EKG

FIGURE 12. Generalized tonic–clonic seizure. **A:** The seizure begins with a generalized spike-and-wave burst (*arrow*) that is replaced by polyspike and wave. **B:** The polyspike and wave is succeeded by generalized continuous fast activity, which is the start of the tonic phase of the seizure. The latter half of this page begins to show tonic muscle artifact indicative of a generalized increase in continuous muscle contraction. **C:** The fast activity, at 8 to 10 Hz, continues with progressive increase in muscle artifact. **D:** During this segment, the tonic phase continues. The electroencephalogram cannot be seen because it is completely obscured by muscle artifact. Slow waves start to appear in the last second of this page, heralding the onset of the clonic phase. **E:** The clonic phase now predominates. Bursts of muscle contractions are interrupted by pauses (coexistent with the slow wave), with a gradual diminution of the frequency of muscle contractions. **F:** The clonic phase shows increasing intervals between contractions, with occasional long pauses between jerks. **G:** The clonus becomes less frequent, and suppressions of increasing duration are seen. **H:** The seizure is now mostly ended. This page shows a mild tonic phase that lasted 30 to 40 seconds in this patient. This subtle tonic phase typically follows tonic–clonic seizures and is succeeded by loss of muscle artifact and profound background amplitude attenuation and slowing.

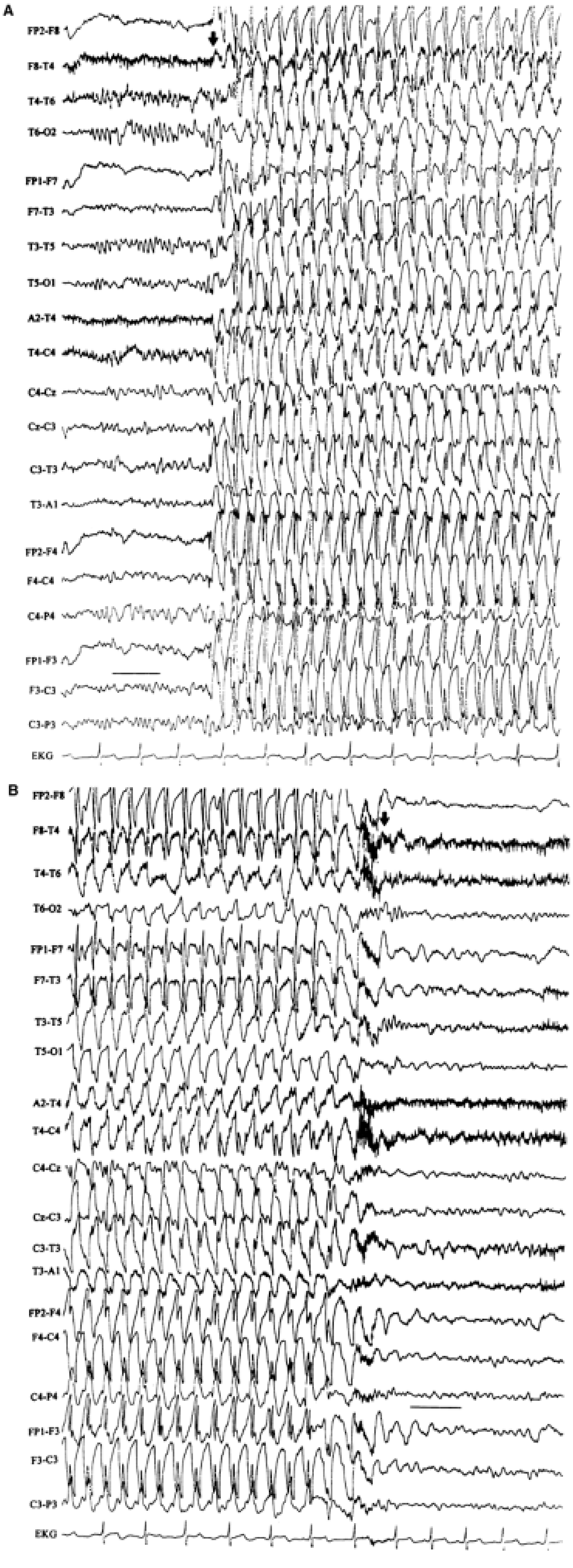
A
FP2-F8
F8-T4
T4-T6
T6-O2
FP1-F7
F7-T3
T3-T5
T5-O1
A2-T4
T4-C4
C4-Cz
Cz-C3
C3-T3
T3-A1
FP2-F4
F4-C4
C4-P4
FP1-F3
F3-C3
C3-P3
EKG
B
FP2-F8
F8-T4
T4-T6
T6-O2
FP1-F7
F7-T3
T3-T5
T5-O1
A2-T4
T4-C4
C4-Cz
Cz-C3
C3-T3
T3-A1
FP2-F4
F4-C4
C4-P4
FP1-F3
F3-C3
C3-P3
EKG

FIGURE 13. Absence seizure. **A:** This absence seizure begins abruptly with a generalized spike-and-wave discharge at 3.5 Hz (*arrow*). The discharge continues with a slight diminution in frequency. **B:** As the seizure continues, the frequency of the discharge gradually slows, and the seizure terminates with a series of slow waves (*arrow*), seen best in the channels in the lower half of the page.

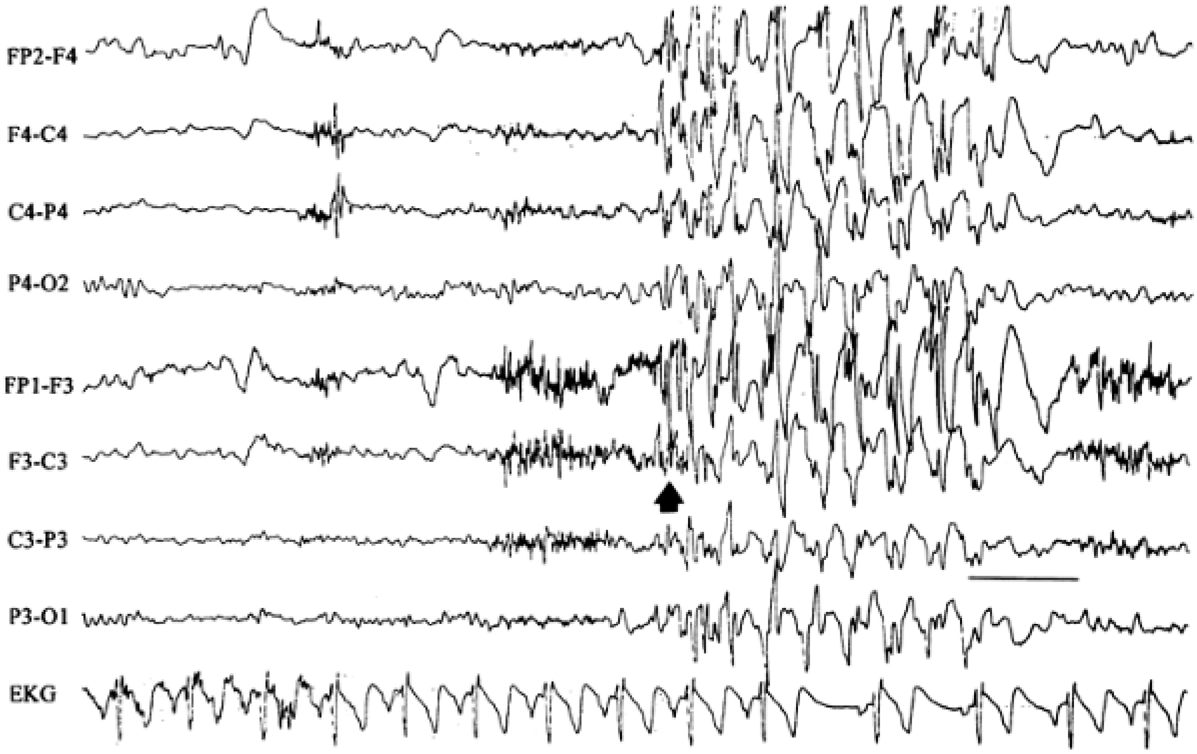

FIGURE 14. Atypical absence seizure. This brief seizure begins with a burst of generalized polyspikes (*arrow*) that are interrupted at irregular intervals by slow waves. This seizure lacks the regularity of the preceding absence seizure (Fig. 11), with its machine-like spike-and-wave repetition rate.

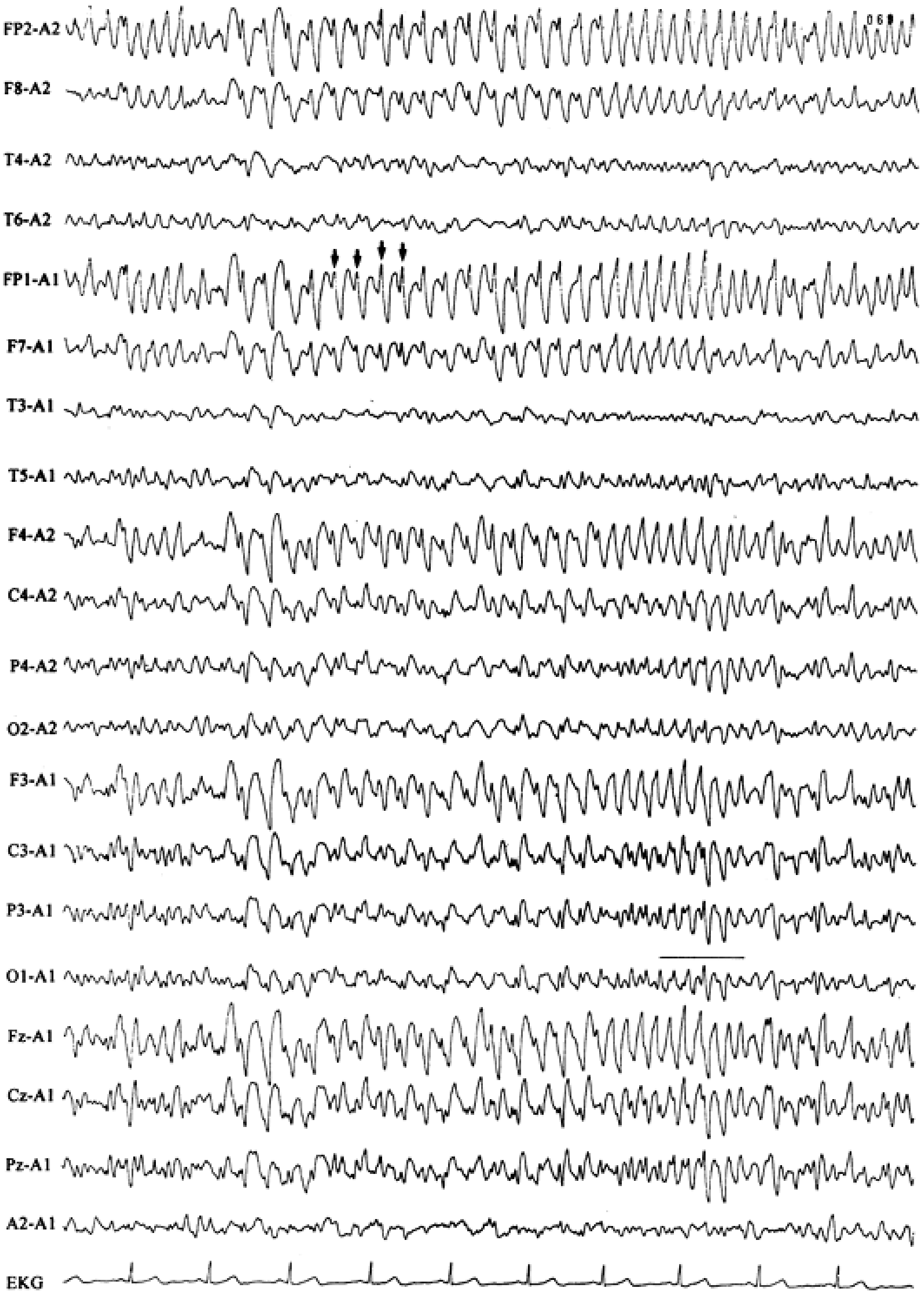
FP2-A2
F8-A2
T4-A2
T6-A2
FP1-A1
F7-A1
T3-A1
T5-A1
F4-A2
C4-A2
P4-A2
O2-A2
F3-A1
C3-A1
P3-A1
O1-A1
Fz-A1
Cz-A1
Pz-A1
A2-A1
EKG

FIGURE 15. Continuous spike-and-wave state (absence status; spike-wave stupor). Spike-and-wave discharges at 4 Hz occupy part of this page (arrows highlight the spikes), whereas rhythmic theta at approximately 5 Hz predominates at other times.

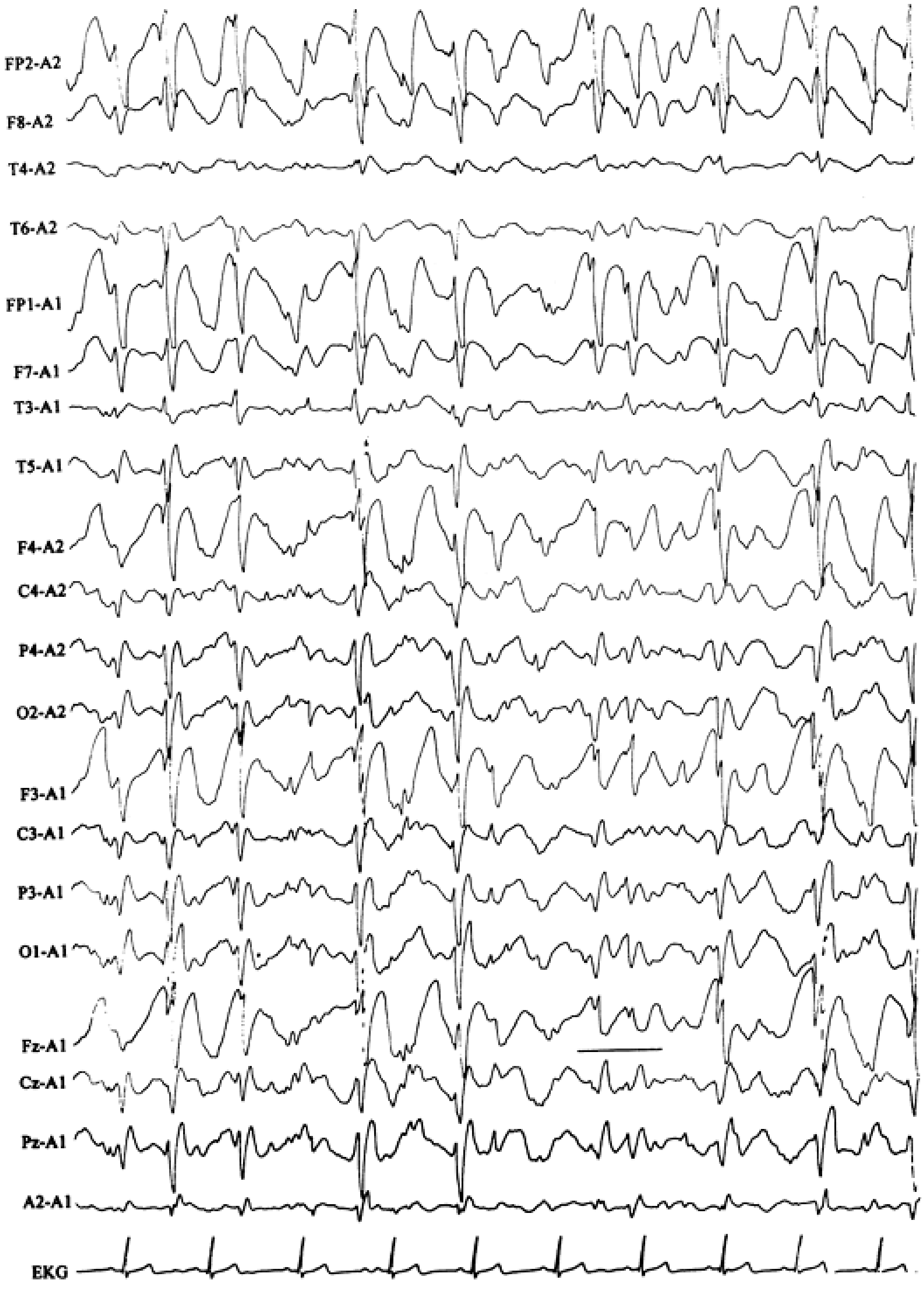
FP2-A2
F8-A2
T4-A2
T6-A2
FP1-A1
F7-A1
T3-A1
T5-A1
F4-A2
C4-A2
P4-A2
O2-A2
F3-A1
C3-A1
P3-A1
O1-A1
Fz-A1
Cz-A1
Pz-A1
A2-A1
EKG

FIGURE 16. Interictal electroencephalogram from a patient with symptomatic generalized epilepsy. This shows high-amplitude generalized slow spike-and-wave discharges arrhythmically and at 1.25 to 2.0 Hz superimposed on a diffusely slow background.

Limitations of Electroencephalographic Recording

Seizures often produce abnormal movements such as blinking, chewing, jerking, and stiffening, among others. These movements can obscure portions of the EEG recording and sometimes may render an EEG uninterpretable. Scalp EEG suffers from other limitations. When recording from scalp electrodes, the EEG signal is filtered variably, depending on frequency (fast frequencies are attenuated more than slow frequencies);

spatial signal averaging takes place; volume conduction occurs; and signals from perpendicularly oriented superficial cortex predominate.[52] To be visible with scalp electrodes, a large volume of cortex must display synchronized activity. The scalp and skull serve as spatial averagers, further hindering EEG interpretation. In addition, deep cortex (e.g., interhemispheric, basal frontal, temporal, and occipital cortex) is often too distant for scalp electrode detection of potentials. Finally, the orientation of the dipole in EEG is critical, so that only orthogonally oriented potentials are visible.[52] Consequently, the standard scalp EEG may record from as little as one third of the cortex. For all of these reasons, many EEG events, including some interictal discharges and seizures, do not appear in the scalp EEG.

Using intracranial EEG eliminates muscle and movement artifact, but these electrodes suffer from “tunnel vision.” They record from a limited amount of cortex, and the electrode placement biases the results.[27] For example, a seizure can be localized only to the cortex in which electrodes have been placed; because it is impossible to put electrodes everywhere, mislocalization must occasionally occur.

Enhancing Seizure Occurrence

Because seizures usually occur infrequently and unpredictably in most people, the EEG must often be recorded for a long time before a seizure occurs. Certain methods can be used to increase the likelihood of seizure recurrence. Stress, either emotional or physical (e.g., sleep deprivation), sometimes helps to

bring on a seizure. Anticonvulsant medication taper more reliably induces seizures, so this is commonly employed. This is safest when reserved for the inpatient setting. It should be performed cautiously to avoid status epilepticus and secondarily generalized seizures.

Neonatal Seizures

The behaviors and activities of the newborn infant are regulated by a variety of innate neurobiologic mechanisms that govern the natural rhythms of life. Sleeping, waking, feeding, crying, and quiet visual exploration wax and wane as the infant's biobehavioral state cycles through an orderly progression of predictable state changes that appear and evolve as the nervous system matures from the preterm to the term infant and beyond. Healthy newborn infants possess an inherently modest repertoire of motor activities and behaviors commensurate with their limited maturity. There are also a number of paroxysmal behaviors that the healthy newborn can display, such as tremors, jitteriness, benign apnea-bradycardia, rapid eye movement sleep activities, and startles. These arise suddenly and unexpectedly against the background of the normal unfolding of the activities and behaviors dictated by the infant's biobehavioral state. Neurologically compromised neonates may also display an assortment of abnormal paroxysmal postures, movements, or behaviors that must be distinguished from their innocent counterparts.

Neonatal seizures are a common phenomenon encountered in the care of the newborn infant.[3,15,17,73,74] Historically, neonatal seizures were diagnosed on clinical grounds alone and were classified by their most visually conspicuous features as subtle, clonic, tonic, myoclonic, or autonomic. In more recent times, there has been a growing appreciation of the limitations of diagnosing neonatal seizures on clinical grounds alone and an increased recognition of the role of EEG in confirming and characterizing epileptic-based seizures in the newborn infant.[22,36,41,51,74] Specifically, not every clinical “neonatal seizure” is simultaneously accompanied by a coincident electrographic seizure, and, conversely, many electrographic seizures recorded in the newborn arise subclinically.[13,18,48,77] Such occult electrographic seizures, those subclinical electrographic seizures unaccompanied by simultaneous clinical seizures, constitute a significant fraction of recorded electrographic seizures.[77] Furthermore, there are common circumstances in the newborn nursery in which the use of neuromuscular blocking agents such as pancuronium bromide (Pavulon) renders the patient clinically neurologically unassessable due to the iatrogenic paralysis. EEG examinations performed to provide a measure of neurologic assessment during therapeutic paralysis may capture electrographic seizures that were clinically unexpected.[28] Consequently, the electroencephalographer must be familiar with the basic characteristics of the electrographic neonatal seizure (ENS) and alert to their possible presence when reviewing neonatal EEGs performed for any reason.

Common Scenarios to Recording Neonatal Seizures

The majority of clinically witnessed neonatal seizures appear in the acutely ill newborn.[43,45,58] As such, they are examples of *reactive* seizures that arise in the context of intercurrent medical or neurologic illnesses that provoke the many signs of an acute neonatal encephalopathy. In this context, EEGs may be performed to provide a measure of neurologic assessment because the degree of EEG background abnormality may serve as a useful, accurate barometer of neurologic outcome.[2,5,14,30,33,39,50,54,56,63,64,70,71,72] EEG

examinations may also be conducted to understand the nature of clinically witnessed neonatal “seizures.”[19] That is, the EEG may confirm whether certain abnormal clinical paroxysms (“seizures”) are founded on a specific epileptic mechanism.[48] Clinical “seizures” that are uniquely time-locked to electrographic seizures thus may be regarded as examples of “*epileptic*” neonatal seizures.[76] On the other hand, clinical “seizures” that do not coincide with electrographic seizures may be regarded as a type of “*nonepileptic*” seizure, including so-called automatisms, brainstem release phenomena, and other poorly understood abnormal reflex behaviors.

Infants who require the use of neuromuscular blocking agents are usually acutely ill and may have experienced significant episodes of hypoxia or ischemia.[28] Because the clinical neurologic examination is unfruitful in this setting, the EEG is employed to measure the reaction of the cortex to the illness at hand. Electrographic neonatal seizures are not uncommon in this setting and must be carefully searched for in the interpretive process.

Although the majority of neonatal seizures are provoked by intercurrent illness, there are examples of *very early onset epilepsy* in the sense that these conditions feature unprovoked seizures in the absence of an underlying trigger. These infants are prone to recurrent attacks of epileptic seizures due to a persistent underlying “lowered seizure threshold.” For example, certain forms of cerebral dysgenesis may announce their presence, with or without accompanying outward somatic signs of multiple congenital anomalies, by unprovoked neonatal seizures. Thus, this version of the “well neonate with seizures” may actually be harboring pachygyria or a form of holoprosencephaly. Some neurocutaneous disorders may also feature very early onset seizures. When tuberous sclerosis penetrates the individual deeply and severely, the result can include conspicuous neonatal neurologic dysfunction and seizures from the earliest hours of life. The organoid nevus syndrome, another neurocutaneous disorder, also possesses a very broad spectrum of penetrance and may appear in an extreme form in the neonatal period featuring neonatal seizures.

There are two dramatic but relatively rare epilepsy syndromes of the neonate that merit special mention.[1] Both are regarded as examples of “malignant” forms of epilepsy, in that they feature multiple types of refractory and debilitating seizures in the setting of pronounced psychomotor retardation and may lead to early death. Early myoclonic epileptic encephalopathy (EMEE) is characterized by early-onset

unprovoked neonatal seizures, stimulus-provoked myoclonus, other clinical seizure types, bulbar dysfunction, and a very abnormal EEG background. The syndrome known as *early infantile epileptic encephalopathy* (EIEE) features tonic seizures as the core clinical ictal phenomenon, a markedly abnormal EEG background, early transformation into a form of infantile spasms with hypsarrhythmia, and a possible association with overt cerebral dysgenesis. There are other examples of less notorious unprovoked neonatal seizures, such as *benign familial neonatal seizures*, that also represent a kind of neonatal-onset epilepsy and underscore the rich variety of disorders that may rise to the surface in life's earliest moments.[4,44,60]

Ideally, the neonatal EEG should be interpreted with this general background of information at hand. Furthermore, knowledge of the physical condition of the patient is an immense aid to an understanding of the confounding influences of rhythmic artifacts, such as mechanical ventilation, extracorporeal membrane oxygenation (EMCO), or even the nurse “patting” the baby.

Background Cerebral Electrical Activity

In neonatal EEG, the background activity refers to the ongoing, moment-to-moment unfolding of the electrographic activities and rhythms generated by the cerebral cortex. The EEG background changes substantially, depending on the infant's biobehavioral state. Thus, there are dramatic differences in the visual appearance of the neonatal EEG, depending on whether the infant is awake, dream sleeping, or quietly sleeping. This is no different in principle from the more familiar EEG state changes recorded in adults or older children.

The EEG background may also be affected by the presence of any disorder that disturbs the functional integrity of the central nervous system (CNS). During the evolution of conditions such as bacterial meningitis, the degree of EEG background abnormality may range from a minimal amount to an advanced abnormal state, such as burst-suppression or isoelectricity. Several schemes for organizing observed EEG background abnormalities have been suggested, but they differ somewhat on exact classifications.[14,39,50,64,74,77] However, most distill the wide range of observed findings into the broad categories of "normal to mildly abnormal," "moderately abnormal," and "markedly abnormal." Although these broad groupings are not very specific from the viewpoint of the etiology or identity of the disorder, they are useful for gauging the severity of the impact that the disorder has imposed on the CNS.

Electroencephalographic Seizures

The EEG background is the stage on which the *process* of the electrographic seizure conducts itself. The electrographic seizure is an *event* in which abnormal EEG patterns and waveforms evolve in time and location. In many patients, it is also possible to describe the *behavior* of electrographic seizures. In this sense, many infants' seizures behave as a *series* of relatively brief (i.e., a few minutes) attacks separated from each other by variable-length periods of interictal EEG background.[12] Because most neonatal seizures arise in acutely ill, encephalopathic infants, it is quite common to encounter abnormalities of the interictal EEG background, ranging in degree from minor to severe.

An electrographic seizure is a discrete event with a definable beginning, middle, and termination.[12] Consequently, it can be considered as a transient phenomenon that can wax and wane. However, in the field of neonatal EEG, the concept of so-called EEG transients actually refers to a wide array of specific, short-lived, named waveforms in the premature and term neonate. Delta brushes, rhythmic temporal theta activity, encoches frontales, positive rolandic sharp waves, and positive temporal sharp waves are all—strictly speaking—examples of EEG transients that convey markedly different kinds of information about the functional condition of the cortex.[6,10,11,16,34,46,53] The distinction between the electrographic seizure as a transient event and these other individual waveforms as EEG transients should remain in mind.

There is a variety of descriptors that helps to define and quantify the ENS, including location(s), duration, morphology, and amplitude. These attributes are distinctive in the newborn, but some have analogous counterparts in the "mature" EEG.

Location

A fundamental observation about ENSs is that they essentially always arise *focally*. The ENS is, by its nature, a partial seizure. Although it is true that generalized, synchronous and symmetric, spike-and-slow wave discharges have been rarely encountered, they are an extreme exception to the rule. The exact site of origin of an individual ENS may vary within an individual. The midtemporal regions (T3 and T4) are probably the most common locations of origin of ENSs. Certainly, ENSs have been recorded from all brain regions, and so care must be exercised to ensure that the chosen neonatal montage is spatially comprehensive, including sampling from the midline vertices (Fz, Cz, and Pz).

Electrographic neonatal seizures that always originate from the same, single location are called *unifocal*. There is usually no special information conveyed by the knowledge of the location of onset of such a single focal seizure. It does not necessarily indicate the existence or location of a restricted brain abnormality. However, if repeated ENSs always arise from the same single location, it is fair to question whether a focal or lateralized structural CNS lesion exists. For example, in the setting of an embolic neonatal stroke, a brief wave of repetitive seizures often arises, such that all of the individual electrographic seizures have their spatial origin in the same location. In other neonates, multiple seizures originating from different brain regions are recorded, illustrating the case of "multifocal" onset seizures. For the purpose of an operational definition, the description *multifocal* should require at least three independent generators involving both hemispheres. For example, the locations Fp3, O1, and T4 satisfy the criteria for "multifocality."

Electrographic neonatal seizures are not always spatially stationary. Once they arise, they may leave their site of origin and migrate to remote locations, even to the contralateral hemisphere. This is commonly matched with an evolution of the morphology of the ictal waveforms as they progress from one location to another. Some neonates display the interesting phenomenon of simultaneous but independent focal electrographic seizures. In this instance, careful examination of the tracing shows two or more coincident electrographic seizures arising from independent foci and evolving at their own pace.

Duration and Temporal Profile

The typical duration of an individual ENS is about 2 to 3 minutes.[12] There is much variability in seizure duration within and between individuals, but most are relatively brief. Occasionally, a single, extremely long, uninterrupted seizure is encountered, such that the strict conventional definition of electrographic status epilepticus (i.e., ≥30 minutes) is satisfied. The minimal duration of an event that qualifies as an electrographic seizure is debatable.[65] Certainly, many agree that a single, sharp EEG transient, even if it implies a "lowered seizure threshold," would not be adequate to be designated as an actual seizure. How long does the event have to last to be considered a seizure? In common practice, a minimum duration of 10 seconds has been specified in several published studies, but this duration

was chosen as much for convenience as for any substantial neurobiologic reason.[12,63,65]

Because of the variable and often very high rate of subclinical electrographic seizures in the neonate, the true temporal profile of neonatal seizures' abundance as a function of time has not been studied by clinical observation. Unfortunately, there has been no universal definition or criteria for neonatal *status epilepticus* adopted into general use by neonatal neurologists or electroencephalographers. The usual definition of status epilepticus requires an uninterrupted seizure lasting at least 30 minutes or recurrences of seizures between which the patient's mental status remains abnormal. Surely, determination of mental status in the neonate is elusive and not a suitable clinical endpoint for the definition of status epilepticus. Furthermore, by their nature, most ENSs tend to behave as relatively brief but recurrent events. One study offered a reasonable but arbitrary definition of electrographic status to be present if 50% or more of the tracing was occupied by an electrographic seizure. Status was present, by that definition, in 27% of the 81 infants studied.[31] Because most examples of neonatal

seizures arise in acutely ill infants, it is common to observe an initial burst of seizures in the first 2 to 3 days of the illness.[8,32,35,75] The seizures gradually wane (usually in parallel with the administration of an antiepileptic drug [AED]) during the first week of the illness and eventually terminate completely. It is certainly true that many of those affected eventually develop chronic postnatal epilepsy in the conventional sense, but the acute seizures tend to disappear, even after an initially explosive beginning. Consequently, a significant number of critically ill neonates are actually experiencing electrographic status epilepticus for days, perhaps at a time when they have just suffered a serious acute encephalopathy. There is no suitable information on the natural history of neonatal seizure abundance during the first days and weeks of an acute illness. This would require continuous video-EEG monitoring for many days without the administration of an AED. Instead, most current data are culled from much briefer samples of video-EEG recordings obtained randomly in the early hours of the illness. The emphasis should remain on the fact that although the term *neonatal seizures* is commonly used, the real situation is actually "electrographic status epilepticus" in many more patients than is widely appreciated.

Morphology

The morphology of the ENS is noted for its rich variety. Ictal waveforms can assume many appearances, ranging from simple sinusoidal waveforms of any frequency (i.e., beta, alpha, theta, or delta activity) to complex, bizarre ictal patterns.[80] One of the hallmarks of the genuine article is the *evolution* of morphologies demonstrated within an individual seizure or between seizures. In contrast, one of the clues that a suspected "electrographic seizure" is artifactual is the recognition that the morphology is fixed and invariant. Such monotonous, albeit rhythmic, patterns commonly arise from noncerebral sources such as repetitive electrode "pops" (capacitance discharges), pulse artifact, ballistocardiographic effects, mechanical pumps, respirators, or even "patting" the baby.

Amplitude

The typical ENS evolves in amplitude as well as in waveform morphology. It is common for the seizure to first appear at relatively low voltage and gradually to increase as the event unfolds. In contrast, the termination of a seizure may be abrupt, and the voltage may precipitously truncate from a high value to zero. On the other hand, some seizures gradually wind down and show an orderly progression of lower voltages until their final termination.

Examples of Neonatal Seizures

The principles that describe the usual properties and behaviors of the ENS can be illustrated by several specific examples. FIGURE 1 is a rhythm strip that features a number of electrographic properties of a typical ENS. The most conspicuous feature of this tracing is the presence of two simultaneous but independent ENSs. In the left midtemporal and occipital regions (T3 and O1), the beginning of one ENS is shown (*arrow*) as surface-negative, low-voltage, sharply contoured slow waves that quickly evolve in frequency, amplitude, and waveform morphology. Notice that the waveform morphology becomes more complex with the passage of time, especially in channel T3-O1, and that the frequency slows as the amplitude

progressively builds, a very common property of the ENS. At the same time, another ENS is in progress that is most conspicuous in the right midtemporal area (T4) (*double arrows*). The second rhythm strip on the same patient at a slightly later time (Fig. 2) shows the last 6 seconds of an ENS at T3 (*arrow*), whereas periodic lateralized epileptiform discharges (PLEDS) appear invariantly at T4-C4 (*double arrows*). Careful inspection of their homologs (T3-C3) show faint, low-amplitude, surface-positive potentials that are time-locked to the main negative deflections, creating a positive–negative dipole across the cortical surface. Surface-positive EEG activity can appear in a variety of forms in the neonate but is rarely encountered in EEGs recorded from more mature individuals. In general, PLEDs are not considered to be an electrographic seizure per se in neonatal electroencephalography but convey the same connotation as PLEDS in older individuals, namely, the presence of a relatively acute, destructive CNS lesion.[47,62]

Another example of an ENS is provided in FIGURE 3 to show an evolving complex waveform at C3-T3 (*arrow*). As the seizure progresses, the ictal pattern becomes progressively more complex, and the seizure converts polarity from surface-negative to surface-positive. Notice also that the seizure is confined to the left hemisphere. The EEG background in the right hemisphere is largely unperturbed by any seizure activity but does show markedly excessive discontinuity and a paucity of richness of the normal background patterns and rhythms anticipated in healthy neonates of this conceptional age.

Partial Seizures in Children and Adults

Seizures Recorded With Scalp Electrodes

Many of the basic definitions and rules hold true once an individual has matured past the neonatal stage. Seizures still represent paroxysmal discrete events with beginnings, middles, and ends, although the duration might sometimes be measured in hours or days rather than in seconds or minutes.

Temporal and spatial evolution of the ictal discharge is usually seen, and seizures may give rise to changes in either behavior or perception, or may remain subclinical and asymptomatic. Seizure onset may be described as discrete (or focal), regional, hemispheric, or nonlateralized. Discrete (focal) onset is that confined to a single scalp electrode or to one or two intracranial electrode contacts; these imply a highly restricted area of seizure origin. Regional onsets when using scalp electrodes refer to a lobar onset but with a spatial extent of several centimeters. Hemispheric onset refers to an ictal discharge that is clearly lateralized but whose broad voltage field maxima make further localization impossible. A nonlateralized seizure is one in which ictal discharges appear at seizure onset in both hemispheres, with approximately equal vigor in the scalp EEG or simultaneous onset in both hemispheres with intracranial EEG, without regard for amplitude or frequency of the ictal discharge.

A variety of EEG features are present during seizures that aid in classifying and defining them.[24,26,68] Partial seizures have a number of distinctive characteristics. Often, a focal onset to the seizure is seen in the scalp or intracranial EEG, but this is not a constant feature. Many partial seizures propagate so rapidly that the initial detection of localized ictal activity with conventional methods is not possible; in these cases, the earliest observed ictal changes may be widespread over either an entire hemisphere or within both hemispheres. Nonetheless, the pattern of electrical activity during the seizure usually provides a clear sign that the seizure is partial and not generalized, as shown in this section. Partial seizures may begin with ictal discharges of any frequency (delta, theta, alpha, or beta) and are sometimes heralded by either an increase or a decrease in interictal spike rate.[26,79] The initial ictal activity may be focal or diffuse. The typical pattern is one of waxing and waning frequencies, subtle or prominent lateralized amplitude maxima during parts of the seizure, and postictal slowing of background frequencies.

Simple partial seizures have a restricted field that favors detecting a localized abnormality. However, most do not appear in the scalp EEG[21,40,69] because the summated background activity tends to overshadow the small fields of such seizures. Intracranial EEG has a higher yield, yet nearly half of simple partial seizures are not detected with modern techniques.[69] FIGURE 4 shows a simple partial seizure from the temporal lobe that does appear in the extracranial EEG. This has many of the characteristics of a partial seizure. It begins focally in one temporal lobe, with sharp waves that evolve in frequency while remaining confined to one hemisphere. It is also relatively brief—most simple partial seizures last less than 1 minute.

In contrast, complex partial seizures typically show a more complicated picture.[7,24,79] They nearly always spread to the contralateral hemisphere, so that bilateral ictal changes are seen, usually last longer (often 2–3 minutes), display more spatial evolution, and more often produce postictal slowing. FIGURE 5 shows a well-localized temporal lobe complex partial seizure. This begins with an alpha-frequency discharge, and although it would be considered localized and discrete, it is obvious that the contralateral hemisphere contains abnormal frequencies indicative of subtle ictal invasion. Very often, by the time the scalp EEG shows the ictal discharge in a temporal lobe seizure, the seizure has spread beyond the hemisphere of origin.[67] The characteristic evolution of frequencies occurs in this seizure. The lateralized postictal slowing is also a common feature of partial seizures. A relatively slow frequency at onset (in theta and slow alpha ranges) is more characteristic of temporal lobe seizures of mesial temporal origin. In contrast, neocortical seizures often start with higher frequency activity in the alpha or beta bands in the scalp EEG.

Figure 6 shows a complex partial seizure with a subtle ictal onset and prominent secondary distant propagation. The seizure begins with low-amplitude alpha-frequency activity in the left occipital lobe (the source of seizures in this patient). Once the seizure spreads anteriorly to the temporal lobes, a more vigorous ictal discharge pattern appears, with prominent bilateral temporal activity, maximal on the right. This temporal lobe discharge appears at a different frequency than the

simultaneously occurring occipital discharge, demonstrating that the different lobes of the brain may seize somewhat independently during a seizure. Had the early occipital activity not been noted, temporal lobe localization of the seizure might otherwise have been suggested. Other complex partial seizures differ from the two previous examples in that the initial activity is not well localized at onset. The same type of rhythmic activity, although present, is bilateral in distribution, without clear laterality or with only subtle asymmetry. The lack of clear localization in the ictal scalp or intracranial EEG recording simply reflects the technical limitations of current of EEG technology and does not preclude the presence of a focal restricted epileptogenic zone. The EEG does not always permit the precise demarcation of the time of seizure onset, and EEG patterns during seizures may not always appear to be "ictal." Moreover, the scalp EEG may sometimes suggest misleading localization of the site of seizure origin.

Figure 7 illustrates these points. It shows cessation of actively firing interictal sharp waves before the seizure starts, but the seizure appears to develop gradually over several seconds without a clear-cut demarcation between interictal and ictal states. The ictal activity, once apparent, phase-reverses at F4, suggesting right frontal localization. As this seizure progresses, the conspicuous ictal rhythmic discharge (Fig. 7B) is replaced with irregular delta and theta activity (Fig. 7C) that is not obviously ictal, although subsequent pages show more rhythmic and clearly ictal activity. This patient was ultimately studied with intracranial electrodes, which showed seizure onset in the left frontal lobe; resection of that area eliminated seizures. Consequently, the early right frontal localization suggested by the scalp EEG was misleading. It is important to note that this "localized" activity was present several seconds after seizure onset and reflected ictal propagation.

The variability of seizure propagation is further illustrated in FIGURE 8. This seizure begins in the left temporal lobe. After approximately 10 seconds of a left temporal ictal discharge, the seizure terminates there. However, the ictal activity then continues in the right temporal lobe, to which the seizure had spread before stopping on the left side. This “ping-pong” effect is more often seen with intracranial EEG recording and further emphasizes the caution with which scalp seizure patterns should be viewed.

As noted, the EEG may not always show an obvious ictal discharge during portions of some seizures. During other partial seizures, no conspicuous ictal discharge may ever be seen, even though a localized abnormality is present. Epilepsia partialis continua serves as a prototype for this, with only irregular slowing in the EEG, despite ongoing focal motor seizures. FIGURE 9 demonstrates this finding. The clinical manifestation in this patient was left facial twitching, yet irregular, semirhythmic delta and theta discharges were the sole EEG manifestations. The segment shown here was taken from a time when the delta activity was at its most rhythmic, yet it still never exhibited temporal or spatial evolution, and the rate of twitching never correlated with EEG frequencies.

Seizures Recorded With Intracranial Electrodes

These are discussed more fully in Chapter 171 and are the subject of a comprehensive review elsewhere.[66] In addition to conventional visual analysis, computerized techniques have been applied to the intracranial EEG to aid in its analysis.[20,29] A few examples of seizures recorded with intracranial electrodes are shown here to further illustrate some key points. As noted previously, intracranial electrodes are less subject to physiologic artifact and, being closer to the source, show a fuller picture. Intracranial electrodes have much greater spatial resolution and can demonstrate a highly localized seizure onset if one is present. In FIGURE 10A, the seizure begins focally (discrete onset) in the right amygdala, without concurrent ictal discharges 5 mm distant in the presubiculum or in other hippocampal areas or parahippocampal gyrus. FIGURE 10B shows a regional seizure onset, with more widespread ictal spiking in amygdala and hippocampus. Although it is not restricted to a few millimeters like the previous example, this seizure is still localized far more accurately than would be possible with extracranial electrodes. Many patients have well-localized seizures like these, yet their scalp EEG may be nondiagnostic.

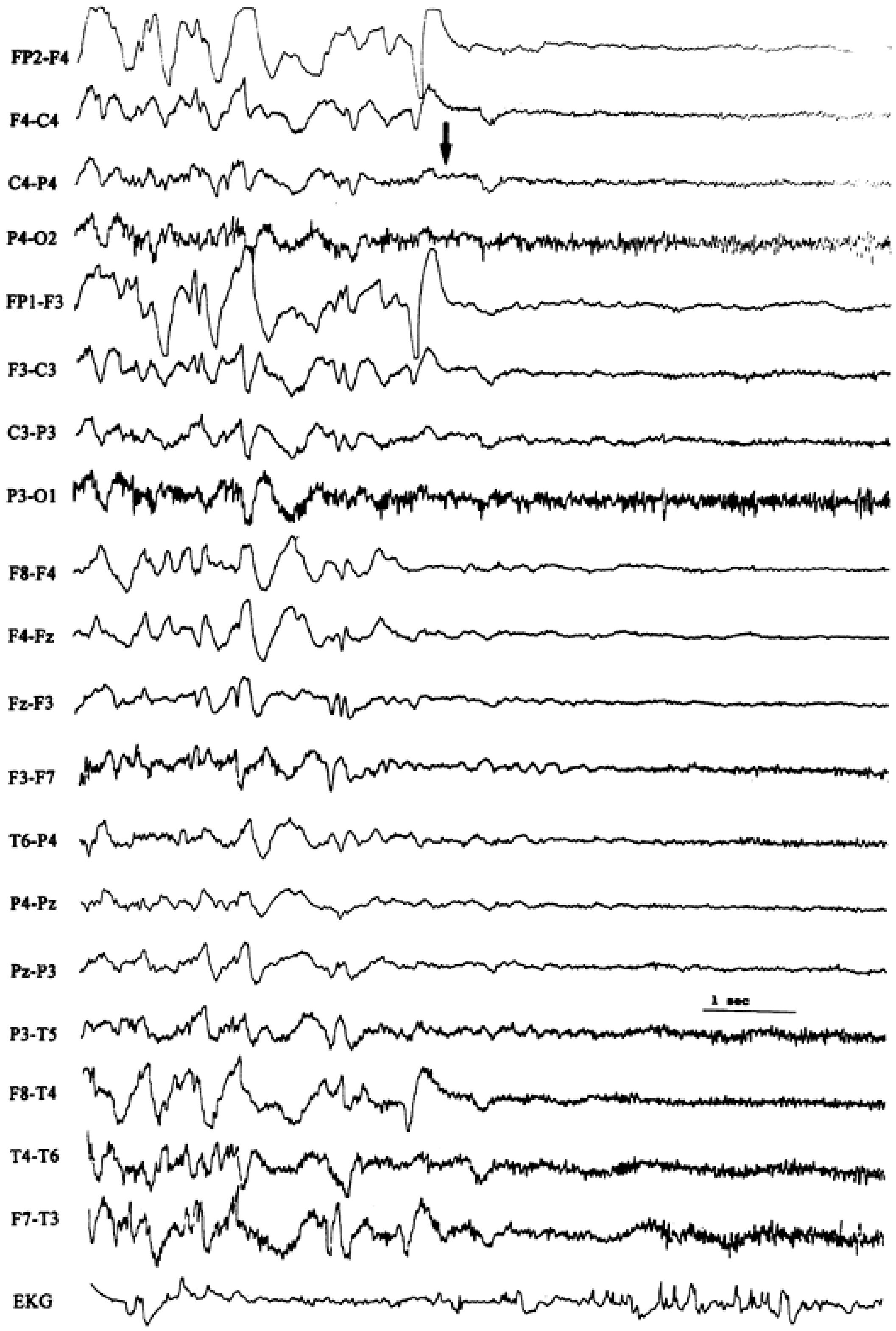
FP2-F4
F4-C4
C4-P4
P4-O2
FP1-F3
F3-C3
C3-P3
P3-O1
F8-F4
F4-Fz
Fz-F3
F3-F7
T6-P4
P4-Pz
Pz-P3
1 sec
P3-T5
F8-T4
T4-T6
F7-T3
EKG

FIGURE 17. Atonic seizure characterized by sudden loss of posture and falling. The electroencephalogram shows a diffuse attenuation (*arrow*) following an eye blink. The amount of muscle artifact is somewhat reduced compared with that present before the seizure, and the accompanying clinical behavior was a loss of postural tone. It should be noted that a complete loss of scalp muscle activity is not required to diagnose an atonic seizure because tone in postural muscles may not mimic that of all scalp muscles.

Figure 11 shows a simple partial seizure, recorded with intracranial and extracranial electrodes. The EEG shows the early and clear localization made possible by intracranial EEG

recording. In contrast, the extracranial derivations (midtemporal and sphenoidal leads) contain a large amount of muscle artifact, which hides the first half of the seizure. Moreover, the evolution of the ictal discharge can be readily seen without interference from muscle artifact or the scalp's spatial averaging of extraneous potentials. This seizure also highlights the difficulty of determining precisely when some seizures begin. Standard interpretation would place seizure onset in FIGURE 11A at the time when the rhythmic spiking first appears because the background was previously quiescent. This type of activity in other circumstances, however, might be indistinguishable from interictal spike discharges, and the development of fast activity several seconds later might be considered firmer evidence of a seizure. This figure shows the progressive changes in frequency and amplitude of the electrographic discharge. Note the similarities of the EEG activity in this seizure to the pattern of muscular contractions in FIGURE 12. The profound flattening in the EEG in the anterior and middle pes hippocampus commonly follows even brief seizures and usually lasts less than 1 minute.

Generalized Seizures

Generalized seizures involve large parts of both hemispheres more or less at once and do not have a localized onset. They presumably reflect a generalized disturbance of cortical function, either on a genetic basis or from diffuse injury (discussed elsewhere). Several distinct EEG patterns appear in generalized seizures that are related to the underlying cause of the epilepsy. Seizures arising in patients with idiopathic generalized epilepsy usually begin with generalized spike-and-wave discharges or a burst of generalized polyspikes. Patients with symptomatic generalized epilepsy have a broader variety of ictal onset patterns, although a generalized spike and slow wave, generalized slow wave, generalized fast activity, or generalized attenuations

are usually seen. Subsequent ictal EEG findings depend on the seizure type. During absence seizures, the spike-and-wave pattern continues; during tonic seizures, the generalized fast activity persists. Tonic–clonic seizures show an evolving spike pattern consonant with the muscular contractions.

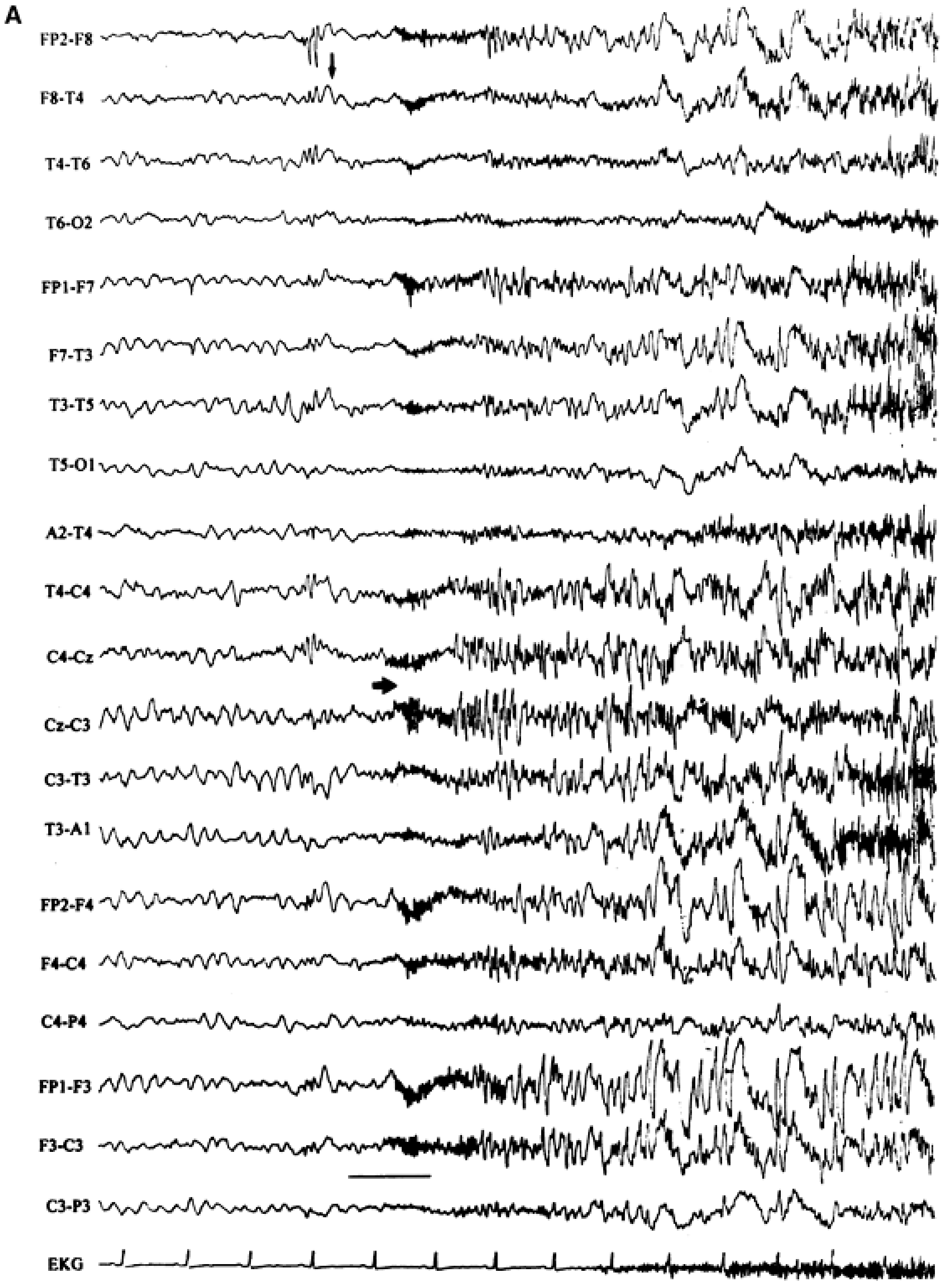
A
FP2-F8
F8-T4
T4-T6
T6-O2
FP1-F7
F7-T3
T3-T5
T5-O1
A2-T4
T4-C4
C4-Cz
Cz-C3
C3-T3
T3-A1
FP2-F4
F4-C4
C4-P4
FP1-F3
F3-C3
C3-P3
EKG

FIGURE 18. Tonic seizure. **A:** The seizure begins with a sudden amplitude attenuation (*small arrow, top*), which lasts <1 second. An immediate buildup of beta activity then occurs (*large arrow, middle*). This progressively increases in amplitude and slows in frequency. Muscle artifact appears in the last 2 seconds of the page. **B:** This page continues where the other stopped. It shows the rapid increase in muscle artifact consistent with a generalized increase in muscle tone. The muscle contraction lasts for approximately 4 seconds, then ceases for 2 seconds. The muscle artifact resumes, but the patient is no longer stiff and begins to move about, although he is confused. The underlying electroencephalographic background shows excess delta at this time, although the large amount of movement artifact hampers interpretation of the record.

Figure 12 shows a typical tonic–clonic seizure in a patient with idiopathic generalized epilepsy with a strong family history of epilepsy. The seizure begins with a generalized spike-and-wave burst that is replaced by repeated polyspike and wave discharges. This is followed by the tonic ictal discharge with continuous spikes. Slow waves of progressively longer duration gradually intrude and interrupt the spikes for the clonic phase of the seizure. The seizure ends with profound background suppression and slowing in both hemispheres. After the first 10 seconds or so, muscle artifact fills the EEG, and cerebral activity cannot be seen. The pattern of muscular contraction is so characteristic of an epileptic seizure as to be diagnostic; this evolution of activity cannot be voluntarily produced.

Absence seizures have varying characteristics.[42,55] Typical absence seizures (Fig. 13) usually begin with a generalized, frontally predominant spike-and-wave discharge at 3.5 to 4 Hz that gradually slows to 2.5 Hz by the end of the seizure.[59] Absence seizures often show increasing spike amplitude in the first two or three discharges, as shown here. Seizure offset, while relatively quick, also often reflects a "build down," with one to three rhythmic slow waves of diminishing amplitude following the last spike discharge. There is no significant postictal slowing of the background after absence seizures, corresponding to immediate regaining of full control of mental faculties. Atypical absence seizures may show somewhat more irregular spike-and-wave or polyspike-and-wave discharges, sometimes at initial higher frequencies. FIGURE 14 demonstrates an atypical absence in a patient with juvenile myoclonic epilepsy, a generalized polyspike initiating the seizure. Myoclonus may also be accompanied by a brief (<0.5 second) generalized spike-and-wave discharge identical to that seen at the start of the atypical absence seizure.

A less common form of absence seizure is that of the continuous spike-and-wave state. Episodes of "absence status" or "spike-wave stupor"[25,42] occur in the juvenile and childhood absence epilepsies. Patients in this state display impairment of consciousness ranging from stupor to full alertness with only subtle cognitive defects. FIGURE 15 shows the EEG of a patient in a continuous spike-and-wave state who displayed only mild confusion. The EEG oscillated between 4-Hz spike-and-wave and a rhythmic theta state for many hours.

Patients with symptomatic generalized epilepsy and multifocal brain injury often have atonic or tonic seizures.[9] These seizures are usually relatively brief, lasting from 5 to 30 seconds. The interictal EEG in these individuals characteristically shows diffuse background slowing, generalized slow spike-and-wave (frequency <2.5 Hz), and multifocal spikes[9] (Fig. 16). Atonic seizures may begin with a generalized spike or sharp wave (with or without a slow wave), a generalized slow wave, or simply a diffuse attenuation of the background EEG with or without low amplitude fast activity. FIGURE 17 illustrates an atonic seizure, starting with the last pattern, a generalized attenuation without increased fast activity. In contrast, a characteristic feature of tonic seizures is the progressive buildup of generalized fast activity (15–30 Hz), which may be preceded by a spike-and-wave or a slow wave or may appear without antecedent. The seizure is usually followed by a brief period of postictal background slowing. FIGURE 18 illustrates the typical evolution of a tonic seizure, with a progressive increase in amplitude of generalized fast activity and muscle artifact accompanied by the gradual slowing of the frequency of the ictal discharge. The tonic phase may be followed by a brief (10- to 20-second) period of confusion with diffuse background slowing in the EEG or generalized arrhythmic slow spike-and-wave discharges.

Summary and Conclusions

The EEG has enabled us to gain valuable insights regarding the fundamentals of epilepsy and has proven invaluable in diagnosing and treating patients. The ictal EEG remains irreplaceable for many clinical questions. However, much remains to be learned, and more investigative studies are needed. Whereas careful EEG studies must still be done, the addition of newer physiologic methods should improve our understanding of seizures and their treatment.

Acknowledgments

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Chapter 75

Electroencephalography in the Intensive Care Unit

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Lawrence J. Hirsch

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Introduction

Intensive care units (ICUs) employ physiologic monitoring equipment to detect potential problems, aid in rapid diagnosis, and guide therapy. Although the equipment available in most general ICUs allows sophisticated monitoring of cardiac and pulmonary variables, the most important organ for functional outcome, the brain, is typically monitored only by physical examination. Additional monitoring devices are used in special circumstances. Intracranial pressure (ICP) monitoring has been available since the 1960s and brain tissue oxygen and brain temperature monitoring since the 1990s. Microdialysis of the brain extracellular fluid can be performed, but the time lag between the equilibration of dialysate and the generation of results prevents changes in management in real time. Other devices, such as probes that provide continuous regional measurements of cerebral blood flow, are becoming available in a few research centers. By far the most widely available techniques for monitoring the brain, however, are electrophysiologic, primarily electroencephalography (EEG), but also including evoked potentials (EPs) and event-related potentials (ERPs).

The most common current indication for electrophysiologic monitoring is refractory status epilepticus (RSE).[1] Once a patient fails to awaken after first-line therapy for status epilepticus (SE), EEG monitoring becomes necessary because a substantial percentage of patients will enter a state of electrical-mechanical dissociation in which motor activity ceases but the EEG continues to show ongoing seizure activity. It is no more conscionable to attempt treatment of RSE without EEG monitoring than to treat complex cardiac arrhythmias without electrocardiographic monitoring. In the coming years, neurologists should ensure that such monitoring is available in all centers that treat such patients.

Technical Considerations

Performing EEGs in ICUs using standard EEG equipment has long been viewed as a challenge for both the technologist and the interpreter. The electrical environment of the ICU is commonly viewed as hostile because the large number of devices produces electrical interference, mechanical artifacts, or both. Attention to detail, however, such as keeping electrode wires parallel to each other and away from cables carrying mains current can reduce many artifacts. Technologists may not be able to eliminate all physical artifacts, such as those produced by mechanical ventilation, but they can provide the interpreter with accurate information about the timing of extracerebral events so that they are not misinterpreted as being of brain origin. Simultaneous video recordings are helpful for identifying artifacts and avoiding misinterpretation. In the modern era, fears about compromising patient electrical safety are largely unfounded because all devices attached to a patient are electrically isolated, and the ground electrodes placed on the patient's skin are virtual grounds that are not physically connected to the equipment chassis or the earth. Thus, there is no longer a prohibition against placing more than one ground electrode on a patient (assuming that all of the devices are properly isolated). ICU staff members involved in patient care still need to understand the possibility of microshock hazard, but they should also be aware that contemporary vascular devices that could provide a current path through the heart are also electrically isolated.

The large numbers of tubes, catheters, and other devices attached to the patient may seem intimidating to EEG technologists accustomed to working in the EEG laboratory, but with assistance from the patient's nurse, it is almost always possible to achieve good electrode attachment with acceptable scalp impedances. Many patients will have scalp wounds or monitoring devices that may require some creativity in electrode placement. In such circumstances, it is often not possible to position all electrodes at standard International 10–20 System locations. If the interpreter is aware of the alternate location, this does not pose a significant problem. For brief studies, saline paste is adequate unless the patient is very diaphoretic. For longer recordings, electrode attachment using collodion or similar substances is preferred. However, EEG electrodes produce artifacts in computed tomographic (CT) and magnetic resonance (MR) images, and the presence of any wire loops inside the MR magnet may cause inductive heating, with the attendant risk of burns. Although several groups are developing CT- and MR-compatible EEG electrodes,[16,19] there are still no readily available and practical MRI-safe and non–image-distorting electrodes.

Several types of devices are available that can record EEG activity in some manner. The standard against which these should be judged is the regular digital EEG machine, recording activity from at least the 18 usual locations of the International 10–20 System. The device employed should store the raw EEG signal recorded against a common reference electrode so that montages of choice can be reformatted off-line. Simultaneous recording of the electrocardiogram (ECG) is crucial, and the system should also be capable of recording other polygraphic variables such as airflow, chest movement, electromyographic (EMG) signals, and eye movements. Video recording capability is important for the identification of artifacts, especially during prolonged recordings when a technologist will likely not be present for the bulk of the recording. A reliable system for recording medications and other interventions is also a necessity. Having the data automatically downloaded to a network server for analysis and archiving is very useful.

A variety of less capable devices have been developed with a view toward use in both the operating room and

the ICU. One of the earliest, the cerebral function monitor, provides a single channel of EEG for visual analysis. The signal is derived from two electrodes, usually placed over the parietal regions, and filtered to diminish low (<2 Hz) and higher (>15 Hz) components. The device displays the amplitude of the signal remaining after filtering. The tracing is displayed on a chart recorder at a low paper speed. The effect of seizures on this signal is unpredictable, and the manufacturer (Lectromed) does not suggest its use for seizure monitoring.

Later versions of the small EEG monitor include the amplitude-integrated EEG (aEEG) monitor (Brainz Instruments) and the BIS monitor (Aspect Medical). The aEEG device is designed for neonatal intensive care units; it displays and stores two channels of EEG along with the corresponding amplitude-integrated tracings at a lower sweep speed. The current version of the BIS monitor provides displays of EEG and EMG activity as well as a number calculated from the EEG, derived from a single bipolar frontopolar derivation. The algorithm for calculation of this “BIS number” is proprietary, but it appears to be heavily influenced by the presence of periodic suppressions in the EEG. According to the manufacturer, a normal waking EEG should produce a number of 100; surgical anesthesia produces a number between 60 and 40; a suppression-burst pattern causes the number to fall to near 20; and an isoelectric EEG yields a number of 0. Similar devices are now in development, and their ultimate role in ICU monitoring will require study and experience. None of these devices is intended to detect seizures; rather, their purpose is to assess and track EEG background activity.

The Moberg Neurotrac was an eight-channel EEG monitor that could display and store raw EEG along with a variety of computed parameters. The most useful of these was the compressed spectral array (CSA), discussed later. Its flexible display and its ability to store 24 hours of EEG on a removable hard drive made it a very useful device, but the slow microprocessors of the 1990s prevented its wide adoption.

Although continuous monitoring of all ICU patients with altered awareness may be the ideal, compromises are usually necessary because of too few monitoring devices, technologists, or electroencephalographers. Claassen and colleagues showed that nearly 20% of the ICU patients they monitored had seizures, and >90% (101/110) of these had purely nonconvulsive activity that would have been missed without EEG monitoring.[8] Eighty-eight percent of these seizures were detected in the first 24 hours of monitoring and another 5% on the second day.

Data Analysis and Management

Recording 24 hours of continuous multichannel EEG with simultaneous video is now a trivial matter, but it poses substantial challenges in monitoring, interpretation, and data archiving. EEG *monitoring* implies that someone knowledgeable is observing either the raw EEG or the results of some computer program running in real time designed to detect events or trends of possible pathophysiologic significance. Such events may be seizures, but they could also be runs of focal slow waves, periods of voltage attenuation, or a change in a derived value such as the ratio of delta to alpha activity, which appears to be valuable in the prediction of vasospasm in patients with subarachnoid hemorrhage (SAH). Such observation needs to be done in real time to provide the intensive care staff with the timeliest information with which to manage the patient. However, becoming a skilled electroencephalographer requires years of training and experience. In addition, patients being monitored in ICUs often display EEG activity that is not commonly seen in other settings and may thus present interpretive difficulties.

Seizure detection software is sometimes used to assist the bedside staff in determining whether changes in the EEG are ictal in origin. Because such software was not developed with the ICU patient in mind, it may have difficulty with either the EEG consequences of many of the drugs administered in the ICU or with some of the unusual rhythmic artifacts that may occur in the unit. Furthermore, seizures in encephalopathic patients tend to have more gradual onsets and offsets and slower frequencies, characteristics that make them more difficult to distinguish from background EEG, particularly the abnormal backgrounds found in these patients. Thus, the output of this software cannot substitute for experienced analysis of the EEG. Other analytic approaches involve data reduction at the bedside using CSA or density spectral array (DSA) displays to aid ICU staff in detecting seizures. In contrast to routine EEG practice, CSA is often able to detect seizures in patients being treated with sedative drugs for SE or to improve their ability to tolerate mechanical ventilation. In such patients, the spectral edge frequency (the frequency envelope that includes 95% of the power in the EEG) is often in the range of 1 to 2 Hz. A seizure may shift the spectral edge frequency to 10 Hz, which causes an obvious change in the activity displayed, thus alerting the staff. One must have access to the raw EEG, however, to confirm that this was actually a seizure rather than an artifact or a transient emergence from sedation.

Because an experienced electroencephalographer is usually not available much of the time in most ICUs, many units rely on a combination of ICU physician and nursing interpretation at the bedside, with later off-line review by an electroencephalographer. The diagnostic accuracy of this approach is unknown. To decrease the time between data acquisition and interpretation, network transmission of the EEG from the ICU to the EEG laboratory, or the EEG reader's office or home, is very useful. However, this off-line interpretative service only constitutes a retrospective check when therapies have been altered based on the local interpretation. Thus, it is incumbent for the critical care staff to become as proficient in EEG interpretation as they can.

The vast amount of data generated by continuous video-EEG monitoring creates archiving problems. The percentage of the acquired data that contains events of interest is usually small, but the time involved in selecting and archiving these events is often prohibitive. Although the cost to archive the data to DVD media is relatively low, the space eventually consumed to store the DVDs suggests that in routine practice some attempt should be made to preserve only clinical or electroencephalographic events of note. As memory storage capability continues to improve, it may soon become practical to simply store all EEG data on large servers.

The Electroencephalogram in Status Epilepticus

The electroencephalographic appearance of SE varies with the type of SE and its duration. Unfortunately, attempts to classify the types of SE have not yet yielded a consensus. Table 1 presents one classification, which will be used in this chapter.

Table 1 Classification of Status Epilepticus (SE)

Type of SE (synonyms)	Characteristics	Comments
Generalized	May begin with discrete seizures	Partial seizures with secondary

convulsive SE (GCSE)	that progress through a reasonably predictable sequence (see Table 2)	generalization are typically included here rather than adding another category
Simple partial SE	Focal SE with retained awareness, such as continuous focal jerking of one limb (epilepsia partialis continua)	The focus may be too small or deep to be detected with standard scalp electroencephalogram
Myoclonic SE		May be the consequence of diffuse anoxia or the end-stage of a progressive myoclonus epilepsy
Nonconvulsive SE (*subtypes in italics*)		Encompasses all other forms of SE
Complex partial SE	Continuous or repetitive complex partial seizures	Sometimes manifested as rhythmic theta activity over the temporal regions without sharp activity; may become generalized later
Absence SE	Long runs of generalized 3-Hz wave and-spike activity (electrographic characteristics may vary slightly with the nature of the underlying epilepsy)	Seen in those with chronic epilepsy with absence seizures; in contrast to absence syndromes in general, the SE form often occurs in adults
Subtle SE	Slight clinical manifestations such as nystagmus	Perhaps a consequenc of a long duration of ictal activity prior to detection or in those with an underlying encephalopathy

Table 2 Electroencephalographic stages of generalized convulsive status epilepicus

Stage	Description	Likelihood of response to initial veterans therapy in the administration cooperative Trial (%)
1. Discrete seizures	Typical generalized seizure (with or without focal onset) followed by	75

	postictal slowing	
2. Waxing and waning activity	The frequency and amplitude of ictal activity increases and decreases but it is not replaced by postictal slowing	30
3. Continuous seitzure activity	The frequency and amplitude of the discharge are constant	24
4. Continuous seitzure activity punctuated by flat periods	Periods of suppression interrupt the ictal activity	8
5. Periodic discharges	An endstage with single bisynchronous generalized sharp waves occurring at approximately 1, usually on a relatively flat background	7

Treiman and colleagues derived the stages listed in Table 2 by observations in humans and confirmed them in experimental models of SE.[24] Although there has been considerable controversy about the development of periodic discharges as the end-stage of human SE and their clinical significance, others have made similar observations.[11] Some patients with periodic discharges have suffered severe diffuse anoxic injury, and rare patients with this finding have prion diseases or subacute sclerosing panencephalitis. The most reasonable approach appears to be to treat patients who present with periodic discharges after resuscitation who do not have clinical or electrographic seizures for their anoxic injury (e.g., considering induced hypothermia[21]) and to reserve treatment for SE for those patients with clinical or electrographic seizures. As can be seen in Table 2, SE patients who have a periodic pattern are very unlikely to respond to conventional anticonvulsant drugs, so therapy would require agents typically used for RSE.[2] However, this question has not been answered by an appropriately designed and powered clinical trial. Furthermore, anoxic patients being treated with hypothermia may seize while receiving neuromuscular junction blockade, which suggests that EEG monitoring should be performed in this group.[22] Although a periodic pattern after anoxia has often been held to augur a poor prognosis, this may not be true with therapeutic hypothermia.[15] The same is probably true of myoclonic SE after an arrest, which has commonly been said to mark a very poor prognosis[28]; this contention needs reexamination with contemporary therapy.

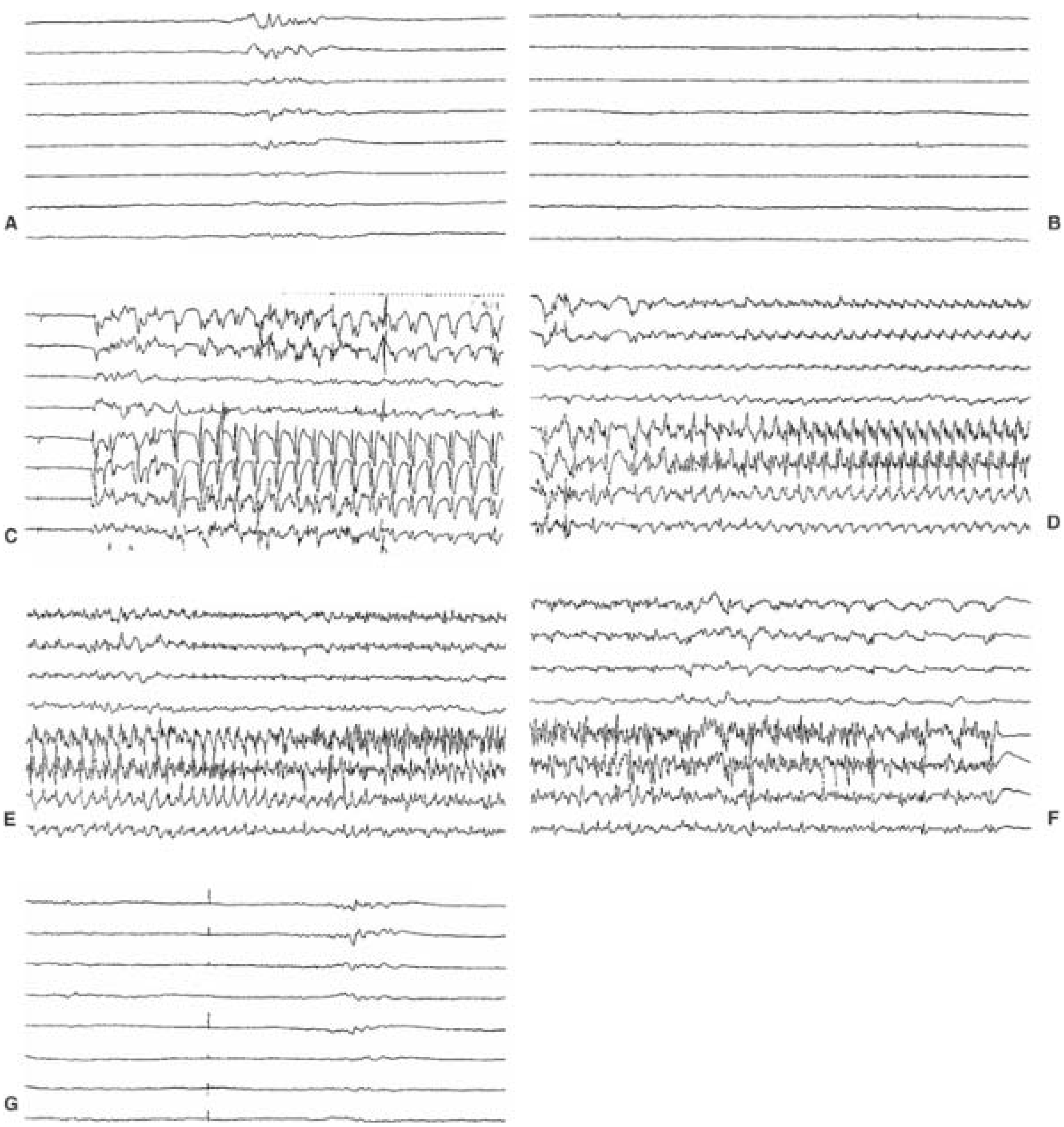


FIGURE 1. Seizure occurring in the setting of a suppression-burst background. Seventy seconds of continuous electroencephalogram recorded from a motionless patient receiving pentobarbital for refractory status epilepticus. Bipolar anteroposterior montage; channels 1–4, left temporal; channels 5–8, right temporal. Each panel displays 10 seconds.

In the past, some authors suggested that the physiology underlying the suppression-burst background pattern, typically when induced by high-dose barbiturates, prevented the generation and propagation of a seizure. When such patients are continuously monitored, however, subclinical seizures are often discovered. One such example is presented in FIGURE 1. Seizures can even arise from complete suppression.

Table 3 presents some suggested criteria for a definitive diagnosis of nonconvulsive seizures; in clinical practice, there are many equivocal cases.

As continuous EEG monitoring has become technically easier, a baffling array of previously rare or unknown electrographic findings has been recorded from ICU patients. A classification of those that appear potentially ictal has been proposed for research purposes[12]; the reader is encouraged to consider this classification for clinical use as well.

Table 3 Criteria for Nonconvulsive Seizures

Any pattern lasting at least 10 s satisfying any one of the following three primary criteria:

Primary criteria

1. Repetitive generalized or focal spikes, sharp waves, spike-and-wave, or sharp-and-slow wave complexes at ≥3/s.
2. Repetitive generalized or focal spikes, sharp waves, spike-and-wave, or sharp-and-slow wave complexes at ≥3/s and the secondary criterion.
3. Sequential rhythmic, periodic, or quasiperiodic waves at ≥1/s and unequivocal evolution in *frequency* (gradually increasing or decreasing by at least 1/s, e. g., from 2/s to 3/s), *morphology*, or *location* (gradual spread into or out of a region involving at least two electrodes). Evolution in amplitude alone is not sufficient. Change in sharpness without other change in morphology is not adequate to satisfy evolution in morphology.

Secondary criterion

Significant improvement in clinical state or appearance of previously absent normal electroencephalograptic (EEG) patterns (such as posterior dominant rhythm) temporally coupled to acute administration of a rapidly acting antiepileptic drug. Resolution of the "epileptiform" discharges leaving diffuse slowing without clinical improvement and without appearance of previously absent normal EEG patterns would not satisfy the secondary criterion.

Source: From Chong DJ, Hirsch LJ. Which EEG patterns warrant treatment in the critically ill? Reviewing the evidence for treatment of periodic epileptiform discharges and related patterns. *J Clin Neurophysiol*. 2005;22:79–91. This is a modification of the criteria initially proposed by Young et al.[29]

One characteristic of electrographic seizures is their repetitive nature, even when the activity itself is not clearly ictal. FIGURE 2 presents such a case. Some electrographic events may be triggered by sensory stimuli, causing confusion regarding their nature as ictal, evidence of a change in the patient's level of consciousness, or artifactual.[13] It is now quite clear that unequivocal electrographic seizures, and less commonly focal clinical seizures, can be repetitively triggered by nonspecific alerting stimuli in many encephalopathic patients (Fig. 3).

The Electroencephalogram in Other Critical Neurologic Illnesses

In recent years, EEG monitoring has been applied to larger groups of critically ill patients; in addition to detecting previously unrecognized seizures, this monitoring provides information of substantial therapeutic and prognostic significance.[3] Table 4 presents some suggested indications for EEG monitoring in the ICU.

Subarachnoid Hemorrhage

Labar and colleagues reported that early forms of quantitative EEG monitoring (single-channel CSA and trend analysis) could predict the development of delayed ischemia (cerebral vasospasm) in patients with subarachnoid hemorrhage (SAH).[18] Subsequent work by Vespa and colleagues has extended these observations, focusing on the variability of relative alpha activity in the continuously monitored quantitative EEG.[25] Their observations suggest that cerebral vasospasm can be detected by EEG about 2 days before clinical symptoms appear and about 1 day earlier than an increase occurs in the transcranial Doppler blood flow velocity measurement. Quantitative EEG changes preceded transcranial Doppler or angiographic detection of vasospasm by at least 2 days in 10 of 14 patients, and quantitative EEG was 100% sensitive for angiogram-defined vasospasm (19/19) with a positive predictive value of 76%.

Claassen and colleagues studied this and other quantitative EEG parameters in SAH patients and found that the most useful quantitative EEG measure was the poststimulation alpha/delta ratio.[7] They also detected nonconvulsive SE (NCSE) in at least 8% of unresponsive SAH patients and noted the poor outcome in this group.[10] Other findings carrying a poor prognosis are periodic epileptiform discharges and the absence of sleep architecture.[6]

Phenytoin is commonly administered for seizure prophylaxis in SAH patients. In this setting phenytoin, however, is associated with a plethora of complications.[20] EEG monitoring represents a reasonable way of detecting and treating subclinical seizures in this group of patients rather than relying on a prophylactic approach.

Head Trauma

Vespa and colleagues studied 94 patients with moderate or severe head trauma and found seizures in 22%; 6 developed SE.[26] Seizures were exclusively nonconvulsive in just more than one half of the patients with seizures.

Intracerebral Hemorrhage

Intracerebral bleeding raises serious concerns for long-term epileptogenesis because of irritative effects of iron on the cortex. Because the majority of intracerebral hemorrhages (ICHs) occur in subcortical structures, however, the utility of prophylactic approaches in this population is also uncertain. In a study of 63 patients with ICH, Vespa and colleagues detected electrographic seizures in 28%; a comparison group of patients with large ischemic strokes had a 6% incidence of electrographic seizures.[27] Seizures in the ICH group were associated with increased periclot edema and midline shift and a trend toward worse outcome, even after controlling for ICH size.

Complications of Nonneurologic Critical Illnesses

Clinically apparent seizures complicate about 3% of nonneurologic critical illnesses.[4] In one unselected series of comatose patients in a medical intensive care unit without any clinical suspicion of seizure activity, Towne and colleagues found that 8% were in nonconvulsive SE as diagnosed by a standard EEG.[23] Using continuous EEG monitoring, Connell and colleagues determined that 20% of infants in a neonatal ICU were having seizures; almost half had no clinical manifestations.[9] The percentage of pediatric or adult ICU patients in which altered awareness is due to intermittent seizure activity, often superimposed upon some other type of encephalopathy, is unknown.

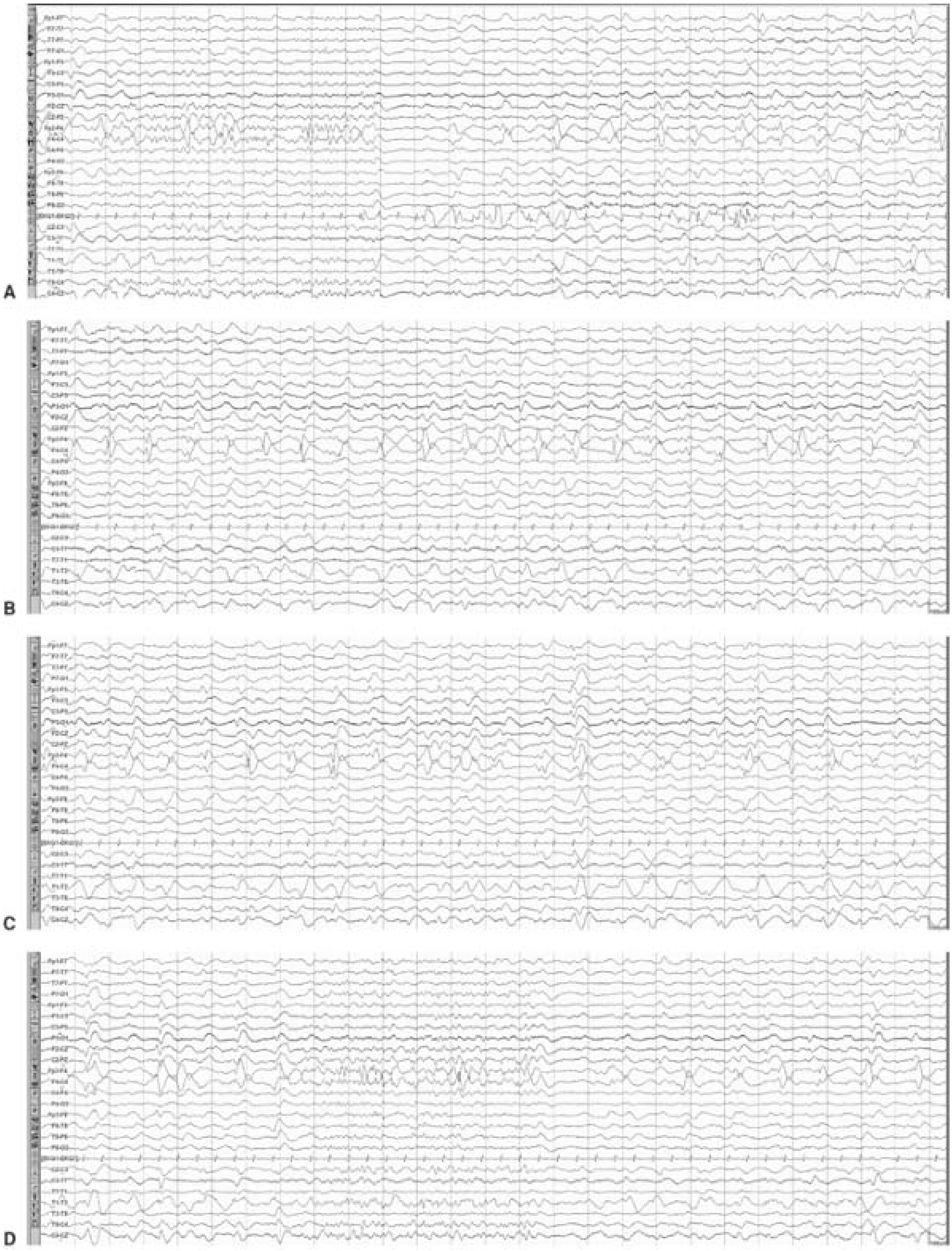
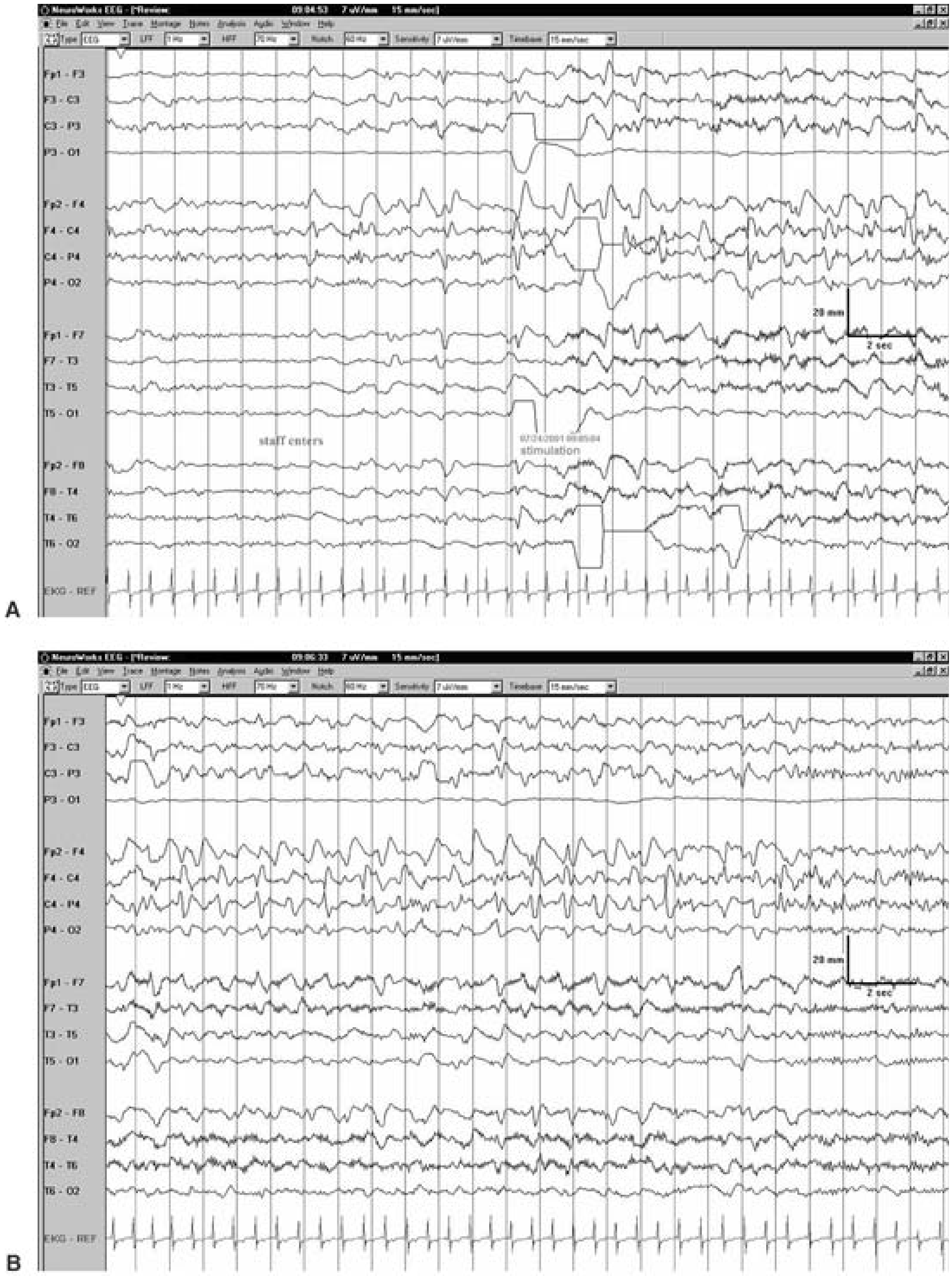


FIGURE 2. Repetitive seizures arising from the right frontal region in a patient with encephalitis. The onset consists of fast activity near F4 (panel A, repeated in panel D); after 8 seconds, there is widespread desynchronization, with the subsequent evolution of periodic sharp activity, which spreads to involve the entire cortex. The pattern then repeats itself until terminated with propofol.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7 uV/mm
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Fp1 - F3
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C3 - P3
P3 - O1
Fp2 - F4
F4 - C4
C4 - P4
P4 - O2
Fp1 - F7
F7 - T3
T3 - T5
T5 - O1
Fp2 - F8
F8 - T4
T4 - T6
T6 - O2
EKG - REF
staff enters
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B

FIGURE 3. Stimulus-induced rhythmic, periodic, or ictal discharges (SIRPIDs). **A:** Before and during stimulation. **B:** After vigorous stimulation (80 seconds after A). A 61-year-old patient with a recurrent right frontal glioblastoma multiforme. Stimulation consistently elicited periodic lateralized epileptiform discharges, maximal at C4 (right central), with some underlying rhythmic delta and bilateral spread. After vigorous or repetitive stimulation, this pattern often became a focal ictal-appearing pattern, as shown in panel B. There was no clinical correlate. [From Hirsch LJ, Claassen J, Mayer SA, et al. Stimulus-induced rhythmic, periodic, or ictal discharges (SIRPIDs): a common EEG phenomenon in the critically ill. *Epilepsia*. 2004;45:109–123.]

Summary and Conclusions

The most common indication for EEG monitoring in the ICU is refractory status epilepticus. Technical improvements in EEG machines and software make monitoring safer and easier to interpret, but skilled technologists are still essential. The electrographic patterns of status epilepticus, as well as transient events and background activity, are often different in the ICU patient population compared with other patient groups.

Patients with particular critical illnesses may specifically benefit from EEG monitoring. The development of vasospasm in subarachnoid hemorrhage is often suggested by EEG changes a day or more before clinical changes are noted or other modalities yield abnormal findings. Patients with head trauma or intracerebral hemorrhage develop nonconvulsive seizures more frequently than had previously been suspected. Nonconvulsive status epilepticus contributes to coma in about 8% of ICU patients without previously suspected neurologic disease.

Table 4 Indications for Continuous Electroencephalographic Recording

1. Detection of subclinical seizures
    a. Fluctuating mental status
    b. Unexplained alteration of mental status
    c. Acute or remote supratentorial brain injury with altered mental status
    d. After convulsive status epilepticus
2. Characterization of spells
    a. Episodic posturing; other paroxysmal or repetitive movements
    b. Subtle twitching, nystagmus, eye deviation, hippus, chewing
    c. Paroxysmal autonomic spells including tachycardia or hypertension
3. Assessment of level of sedation and following trends
4. Management of burst-suppression in anesthetic coma
5. Detection of ischemia (particularly if continuous electroencephalographic review and alarms are utilized)
    a. After subarachnoid hemorrhage
    b. During and after vascular neurosurgical or interventional neuroradiologic procedures
    c. In patients with hemodynamic lesions and borderline flow
    d. in other patients at risk for in-hospital acute ischemia
6. Prognostication

Source: Modified from Jette N, Hirsch LJ. Continuous electroencephalogram monitoring in critically ill patients. *Curr Neurol Neurosci Rep.* 2005;5:312–321.

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Chapter 76

Electroencephalogram Mapping and Dynamic Analysis

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Introduction

In its simplest use, mapping of the scalp electroencephalogram (EEG) provides a convenient display of instantaneous scalp topography, usually that of resting background or interictal spike activity. In more complex forms, the scalp EEG data are subjected to mathematical manipulation as prescribed by a theoretical model. The result is a variety of parameters capable of characterizing the input data, albeit always within limitations imposed by the model. In between these two approaches is a large variety of methods using quantitative analysis.

In the clinical arena of epilepsy diagnosis, EEG analyses seek maximally to extract information pertaining to the epileptic discharge so as to facilitate the understanding of the underlying focus and its current and future behavior. The final purpose is then to use such information for earlier and more accurate diagnosis, which, in turn, can facilitate appropriate treatment and management. This is of particular importance when surgical resection is contemplated.

With spike discharges, the routine EEG tracing provides good visual information regarding spike morphology, scalp localization, and temporal changes (see Chapter 73). It is generally accepted that more useful information might be available but undiscovered. This drives the search for better and more productive display techniques, usually based on computer software algorithms. However, there is no consensus on what technical approaches are useful or acceptable. It is appropriate to observe that newer algorithms and theoretical models tend to be viewed with skepticism. This view has some valid basis, in part generated as a reaction to schemes that purport to make instant clinical diagnoses of various kinds based only on scalp recordings, without the need for clinical assessment. Such computerized diagnostic "aids" have been proposed for differentiating depression from dementia, for example. One is well advised to exercise caution with any such device.

We hope that by increasing the understanding and knowledge base of prospective users, choice of methodology and utilization can be made based on sound neurophysiologic considerations. Toward this end, this chapter reviews selected techniques and results.

Methodology

General Aspects: Electroencephalography and Magnetoencephalography

Electroencephalographic signals reflect the dynamics of the electrical activity generated by populations of neurons (see Chapter 72). This activity is caused by ionic currents flowing through neuronal (and glial) membranes between the intra- and the extracellular space. These signals can be measured at a considerable distance from the sources when two conditions are satisfied: (1) the responsible neurons are regularly organized in space and (2) they are activated in a rather synchronized fashion. As regards the first condition, the cortical neurons form the main sources of EEG potentials because they are arranged in palisades perpendicular to the cortical surface and are activated by synapses distributed in a regular way along their soma-dendritic membranes. According to this spatial organization, their synaptic activation causes the generation of potential fields with a dipole layer configuration. The second condition, synchronization of neuronal populations, is important because in this way, potential fields can be generated that are sufficiently strong to attain the necessary signal-to-noise ratio to be recordable at a distance. The main factor responsible for the synchronous activity of populations of neurons also has a structural basis. It consists of the fact that the neurons within these populations form interlocked networks through excitatory and inhibitory synaptic connections. These populations of interconnected neurons form the macroscopic sources of EEG signals. The neuronal ionic currents not only generate electric fields; they also give rise to magnetic fields. The latter constitutes the magnetoencephalogram (MEG) (see later discussion and Chapter 78).

Although EEG and MEG are caused by the same elements, in practice the two types of signals differ: (1) The EEG is a relative measurement needing a reference electrode; this does not apply to the MEG; (2) the MEG is a signal that consists of the magnetic fields oriented perpendicular to the skull that are caused by current dipoles tangential to the cortical surface, whereas the radial components do not contribute significantly to the MEG signal; the EEG signal is a measure of both tangential and radial components; (3) the MEG pattern of activity is more focal than the corresponding EEG pattern because the former is much less dependent on variations in resistivity of the volume conductor.

Sampling in Time and Space

Electroencephalographic signals are continuous variations of electrical potential as a function of time and space. The same applies to the variations of magnetic fields that form the MEG signals. In practice, these signals must be digitized to be quantified and analyzed. First we consider this question in terms of the variable *time*. This implies that the signals have to be sampled at a certain rate and that their amplitude has to be quantified. These operations must take place in such a way that all important information contained in the signals is preserved. Accordingly, the Nyquist sampling theorem has to be satisfied: If the signal has a frequency spectrum with an upper limit f_N, the signal should be sampled at a frequency at least equal to

$2f_N$. This means that care should be taken that the signal does not contain frequency components $>f_N$ to avoid aliasing, that is, all frequency components $>f_N$ should be zero. Thus, before sampling, all frequency components $>f_N$ should be eliminated by appropriate filtering. For most EEG-MEG signals, a quantitization into 4096 amplitude levels (i.e., 12-bit precision) is appropriate and commonly available. In practice, however, the Nyquist criterion, although a minimally necessary condition, is not sufficient for displaced signals, and a sampling frequency of $>3f_N$ should be used.

Another aspect of the temporal properties of EEG-MEG signals that has to be taken into consideration here is that the statistical properties of these signals can change as a function of time (i.e., nonstationary properties). However, they can be subdivided into representative segments, or epochs, that are quasistationary. A precise definition of the duration of these epochs cannot be given in general terms because it depends on the subject's condition. Nevertheless, it has been shown[20,30] for EEG signals recorded in a general population that 90% had time-invariant properties for epochs of about 20 seconds, whereas <75% remain time invariant after 60 seconds. This means that it is, in general, safe to choose epochs with a duration of 10 to 20 seconds to avoid deviations from stationary behavior.

Sampling in space must obey the same general rules as sampling in time. However, it is much easier to grasp the meaning of a frequency component in the time domain than one in the spatial domain. What is the spatial frequency of a given EEG signal? This can be accounted for by considering a model of a source within a volume conductor, which will cause a potential distribution at the surface of the conductor. Using Fourier analysis, we can represent this potential distribution as a spectrum of spatial frequencies. The sharper the potential distribution, the higher are the corresponding spatial frequencies. It is important to know the upper limit of this spatial frequency spectrum to estimate how sampling in space should take place in an optimal way. If the sampling in space is not appropriate, an aliasing error will be introduced. In general terms, the traditional 10–20 system can be sufficient to sample in space most potential distributions that are rather widespread and smooth, but not those distributions that are highly focal and change abruptly with distance. Some practical questions posed by sampling this kind of potential distribution, in which a high spatial resolution has to be achieved, are discussed later.

Two other fundamental issues need to be further understood—volume conduction and the “inverse problem.” The former is a physical phenomenon that smears or blurs the EEG signal as a result of the different layers of tissues interspersed between source and electrode (brain, cerebrospinal fluid, skull, muscle, fat). The result is added uncertainty about the EEG source. The "inverse problem" refers to the process of inferring the source characteristics from the recorded EEG signal. Fundamentally, this problem has no clear or unique mathematical solution, and is the reason for the general skepticism about dipole localization methods (DLMs; see later discussion). Certain mathematical simplifications that are implicit (e.g., the number of sources, the configuration being small and localized rather than as a layer) might not be clinically appropriate. Experience with application to known problems (e.g., somatosensory-evoked potentials, visual-evoked potentials, known epileptogenic lesions) allows some general understanding of its capabilities and limitations, which can guide its use under certain circumstances.

The detection of specific signals in the background EEG, whether occurring spontaneously, such as epileptiform spikes, or evoked by sensory stimuli, is not only an important general problem in electroencephalography, but it is also relevant for the estimation of the parameters of the equivalent dipole sources. This is a classic problem of detection of signals in noise. The background EEG represents the noise term. To optimize the detection, it is important to know the statistical properties of the noise, that is, the background EEG. Knowledge of these statistical properties is necessary to estimate the confidence limits of equivalent dipole parameters and to design optimal noise filters to improve the signal-to-noise ratio. The spatiotemporal covariance matrix of the background EEG differs with frequency band. For the frequency bands 5 to 8 Hz and 13 to 30 Hz, it was found experimentally that the variance is a function of electrode distance that is compatible with a generator model consisting of random dipoles with a spherically symmetric distribution. However, for the alpha (9 to 12 Hz) frequency band, such a distribution is not adequate, and a localized model consisting of one or more clustered dipoles has to be assumed. These estimates of the statistical properties of the background EEG have practical implications because they allow the construction of maximum likelihood estimators for evoked potentials/magnetic fields based on the spatiotemporal covariance matrix of the background signals.[7]

High-Resolution Electroencephalography and Magnetoencephalography

The condition in which the highest possible spatial frequencies are achieved can be represented by a source consisting of a radial dipole situated in the cortex, that is, close to the surface of the volume conductor. This may correspond to the source of an epileptiform spike located in the cortex. If one uses the traditional 10–20 system (interelectrode distance of about 4.5 cm), the aliasing error in such a case is 6%. To reduce this error to the more adequate level of 1%, one must reduce the interelectrode distance to 3.2 cm, which corresponds to at least 64 electrodes.[49] Gevins and Bressler[14] indicated that sampling with 128 electrodes (interelectrode distance of 2.25 cm) might be indicated in some cases. A comprehensive system, called the *10% system*, includes electrodes halfway between each of the principal 10–20 system electrodes.[6,61] Electroencephalographic signals recorded according to such a system using a large spatial sampling frequency are called *high-resolution EEGs*.

The technique, developed by Gevins et al.,[15] combines large spatial sampling (>100 electrodes) with a method that minimizes the blur distortion that takes place in the transfer from the cortical surface to the scalp. For the deblurring operation, these authors use a realistic finite-element model of the subject's head using the structural information provided by the magnetic resonance imaging (MRI).[37] The scalp and skull volumes are approximated by tetrahedral finite elements having the physical properties characteristic of the different layers of the head. These authors' algorithm searches for the optimal potential distribution at the cortex that provides the best-fit forward solution to the measured scalp distribution, using this volume conductor model. Deblurring is equivalent to a high-pass filtering operation in the spatial domain. Therefore, it can enhance high spatial frequencies and introduce spurious results; this can be avoided by applying spatial filtering techniques (smoothing) to the scalp recordings.

Static and Propagated Fields

In the earlier discussion, we considered EEG-MEG signals as being generated by static sources. However, this is not necessarily the case. Particularly in epilepsy, we can encounter evidence for the propagation of electrical activity over the cortex. We can distinguish two main problems that arise when the propagation of epileptiform activity from a focal area must be analyzed: The first is to determine whether there are multiple independent sources; the second is to determine, in case that related sources exist, whether the activity of one source occurs in a fixed time sequence in relation to that of another source. In the latter case, a time delay can be expected between the signals due to the finite propagation velocity of electrical activity in the brain.

A classic way to estimate the degree of association between two signals and the corresponding time delay is to calculate the correlation coefficient as a function of time shift between the two signals. This is called the *cross-correlation function*. Alternatively, we can deal with this problem in the frequency domain by estimating the coherence and phase functions. In short, the coherence function expresses how each frequency component of one signal is related to the corresponding frequency component of the other signal. The delay can be estimated by calculating the slope of the phase spectrum. This method was used in electroencephalography to analyze the propagation of epileptic seizure activity, initially by Brazier[4] and in a systematic way by Gotman,[18,19,20] Gotman et al.,[22] and Lieb et al.[45,46]

A limitation of these methods is that they provide unambiguous results only if the relationship between the signals is linear. This is not necessarily the case for epileptic seizure activities. Therefore, methods have been proposed that are not restricted to the case of linear relationships. One of these uses the average amount of mutual information, which was introduced into the analysis of epileptiform activity by Mars and Lopes da Silva[50] and Mars et al.[51] Later, Pijn et al.[63,65] introduced a method for estimating the relationship between two signals that always applies, regardless of whether or not it is linear. This is a form of nonlinear regression analysis because it describes the dependence of a signal on another one in a general way, independent of the type of relation between the two signals. This measure was called h^2. If the relationship is linear, h^2 approximates the cross-correlation coefficient r^2. This method was applied to EEG signals recorded during epileptiform seizures by Fernandes de Lima et al.[13] and Pijn et al.[63] A particularly interesting application of this method is in the analysis of epileptiform seizures recorded from simultaneous intracranial electrodes, with the aim of estimating the localization of an epileptogenic focus and the spread of seizure activity in patients being assessed for a possible surgical intervention. Typically, at the beginning of a seizure, considerable differences were encountered between r^2 and h^2, indicating the presence of nonlinear relations between signals recorded from different sites. In practice, it is appropriate to apply the following procedure to estimate the degree and type of interdependence between EEG and MEG signals recorded simultaneously. First, compute the values of r^2 and h^2 as a function of time delay for a number of representative epochs. From these values, we can draw conclusions regarding the linearity or nonlinearity of the relationship. Second, estimate the corresponding time delays. In this way, we can obtain a valid interpretation of the EEG-MEG signals regarding the presence of propagated epileptiform activity.

Simple Voltage Maps: Spike Topography

An example of interictal spikes can be found in children with benign epilepsy with central temporal spikes (BECTS). A similar term, *benign rolandic epilepsy of childhood* (BREC), was used in the past to refer to the same syndrome. This syndrome occurs from 3 to 16 years of age and has an EEG focus in the centrotemporal or rolandic region. There is a particular topography displayed by the peak of the negative spike, namely, a pattern with simultaneous negativity and positivity in a distinctly tangential pattern.[24] Further analysis of this patient population led to the observation that there were two subgroups, depending on the clinical presentation. One subgroup tended to have a more benign presentation, whereas the other tended to have one that was less benign.

It was also observed that the spike topography was correlated with these groupings: A tangential field was associated with the benign group, whereas a nontangential (or radial) field was associated with the less benign group. For convenience, these two subgroups will be labeled *typical* and *atypical BECTS* because the former fulfills the criteria of typical BECTS, whereas the presence of abnormal neurologic findings in the latter coexists with otherwise typical seizure symptoms and EEG features.

Figure 1 illustrates spikes from both groups. Gregory and Wong[25] studied 366 children with rolandic spikes to determine whether the tangential field had any clinical significance. Clinical factors studied included development history, school performance, intelligence, total number of seizures, and neurologic findings. Patients with nontangential spikes tended to show a greater degree of abnormality in the aforementioned clinical areas. That study was based on a visual determination of spike topography from the tracing, without requiring more sophisticated computer hardware. It was speculated that such tangential discharges might represent a benign functional focus whose identification can be differentiated from those rolandic spikes associated with nonbenign clinical presentation.

In a study of 48 children with an EEG rolandic spike but no other EEG abnormalities outside of the rolandic region and no diffuse or progressive brain disorder, van der Meij et al.[53] analyzed the rolandic spike with respect to whether there were associated seizures and, if so, what type of seizures they were. Using dipole source analysis parameters, they did not find any differences in the rolandic spike-and-wave complexes. If they took into account the presence (in some cases) of an initial spike preceding the rolandic spike-and-wave complex, they were able to conclude that this pattern was associated with a greater probability of seizures. On this basis, they hypothesized that this preceding spike is generated by a group of neurons that cause seizures and that the rolandic spike-and-wave complex is not strongly related to clinical symptomatology. More recent results have suggested that this syndrome may not be adequately modeled by a simple fixed point source.[27]

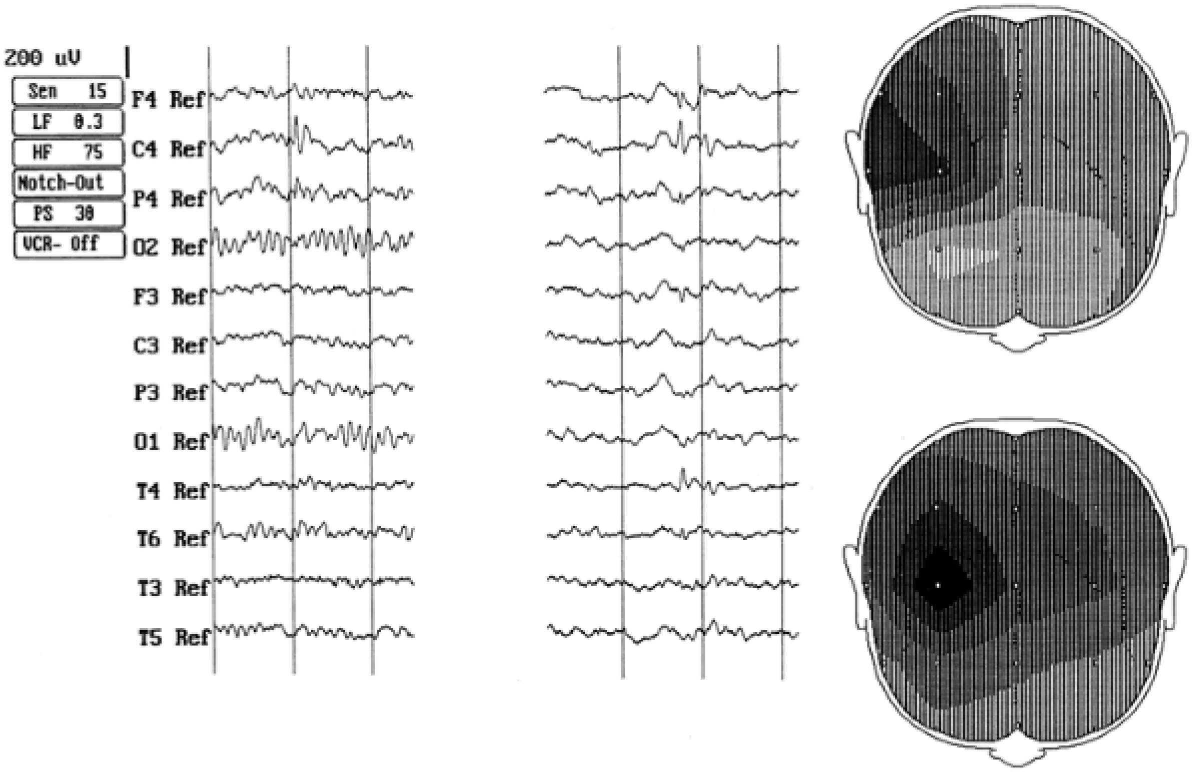

FIGURE 1. Examples of electroencephalogram s and maps of radial and tangential spikes. Tracing: left, radial; right, tangential; grid lines 1 second apart; ref, linked cheeks; negative up. Maps: top, tangential (T4-F4); bottom, radial (C4); nose-down vertex view; right, patient's left. Color scale: white, positive; black, negative.

Decomposition of Spikes

A segment of scalp EEG containing a single spike discharge might represent the aggregate of electrical activity from more than one source. In the presence of a high signal-to-noise ratio, as may be present with averaged spikes,[24] it is possible to decompose this aggregate using mathematical techniques. The assumption is that such objective mathematical decomposition can represent separate physiologic sources, with no guarantee that such an interpretation is accurate or even appropriate. Nevertheless, the results can be useful in providing a measure of the electrical characteristics of the spike generators or sources. On this latter point, Wong[84] reviewed the use of source behavior information in distinguishing populations of epileptic foci. FIGURE 2 is an example of an analysis using singular value decomposition (SVD).[26] Principal component analysis can also be used to achieve substantially similar results, although SVD makes spatial displays more directly available.

From FIGURE 2, one can see that the original spike segment shows a complex topography over the right frontocentrotemporal area, with the predominant negative spike peaking earliest at F4, then slightly later at C4, then still later at T4. Simultaneously with the F4 negative peak is a smaller, positive peak at T6. Under such careful scrutiny, there are, therefore, tangential and radial components within the single spike, lending to the suspicion that this was a complex spike, with perhaps complicated multiple generators. The decomposed features (1 and 3) provide mathematical (and objective) evidence of two separate sources, overlapping spatially but with distinct topography (tangential and radial). These two presumed separate sources might well originate from cortical areas with different clinical symptomatology.

Notwithstanding the cautionary note regarding the interpretation of each component as being from a separate source, such a hypothesis could be generated and tested against collected patient populations for verification, with particular emphasis on the clinical symptomatology and electroclinical correlations.

Kobayashi et al.[33] reported being able to isolate separate epileptic components from spike and slow wave complexes using independent component analysis (ICA). They proposed that these components might represent separate cortical regions. Such a possibility would be of interest in the identification and surgical resection of the presumed neocortical focus. However, Unsworth et al.[74] defined the criteria for the EEG data required for the ICA procedure to be reliable and interpretable. They concluded that it was not appropriate to apply ICA or source localization from independent components in four common types of childhood epilepsy. They also listed some preconditions before such analysis can be valid.

Source Models

The technique of source modeling (or the *dipole localization method* [DLM]) can be applied to interictal spikes (see also Chapter 78). Here, the implicit assumptions are that there is a limited number of well-defined electrical generators whose mass occupies a small volume in space (i.e., discrete source) and whose electrical signals are accurately recorded by the scalp electrode array. Generally speaking, DLM is an exercise in force-fitting the mathematical model onto the recorded scalp data, the objective being to achieve the best mathematical fit (based on a goodness-of-fit measure). Either a particular time point or a segment of EEG can be chosen for this fitting process. The former produces a moving dipole solution, whereas the latter is a spatiotemporal solution.[8,9,10,11,83,84,85,89,90] Evoked potential waveforms have similarly been analyzed.[1,68,86,87]

It has to be borne in mind that DLM has limitations based on its assumptions. A common pitfall is to use an inordinately large number of sources in the model, which will guarantee a “perfect” mathematical fit. Mathematical adequacy does not guarantee accurate or physiologically appropriate results from DLM. Thus, the choice of the number of dipoles in the model should be made on appropriate electroclinical grounds. In reality, multiple dipole models are inherently more difficult to execute and less amenable to valid physiologic interpretation.

Constraints on the mathematical computation using anatomic knowledge can be extremely helpful in restricting solutions and in increasing the chances of meaningful results. Knowledge of the exact head and brain shapes, skull thickness, tissue layers, presence of foramen, and so on improves the quality and accuracy of the model. Gevins et al.[15] used corrected and aligned MRI images to recreate a realistic head model, which was used to calculate cortical current flow patterns. These closely approximated actual cortical surface recordings made during surgery. Nunez[60] discussed an approach to realistic models and experience with DLM. Such realistic head models allow mathematical models to follow closely the brain volume but do not provide further detail, for example, at the gyrus and fissure level.

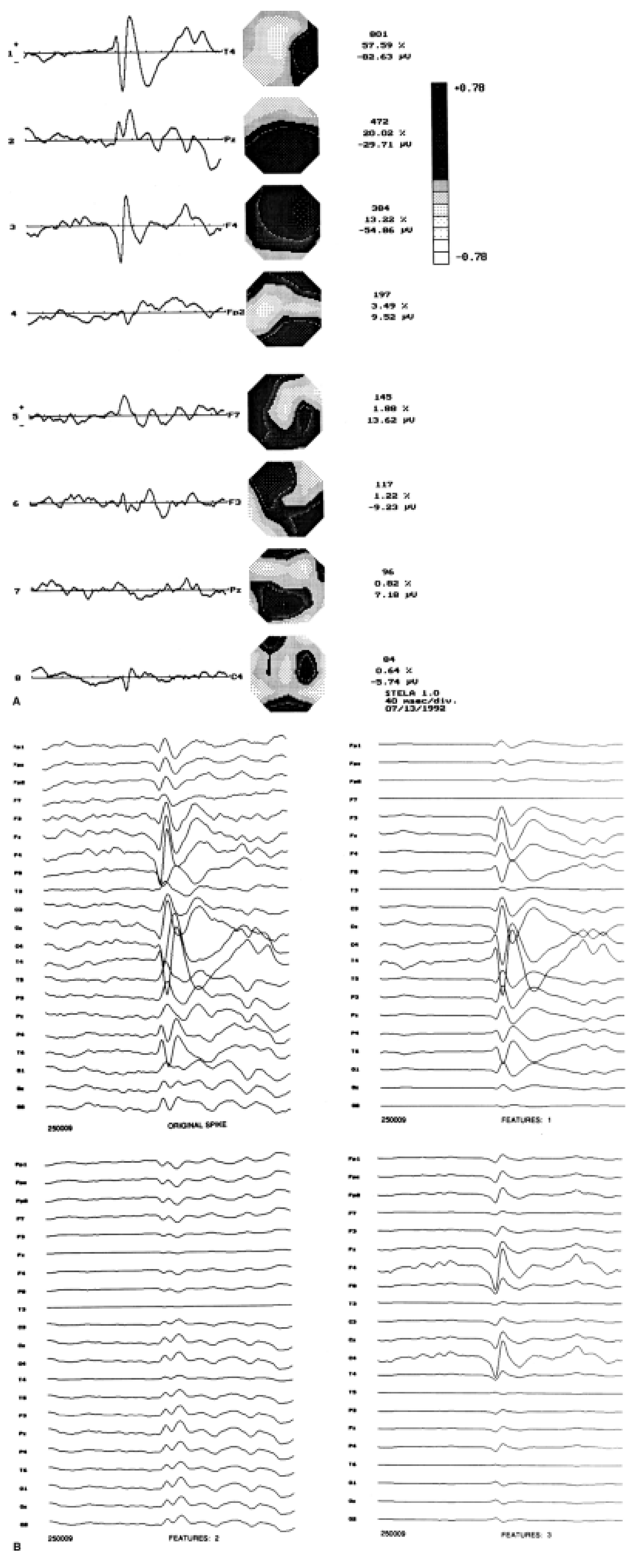
1
T4
801
57.59 %
-82.63 µV
+0.78
-0.78
2
Pz
472
20.02 %
-29.71 µV
3
F4
384
13.22 %
-54.86 µV
4
Fp2
197
3.49 %
9.52 µV
5
F7
145
1.88 %
13.62 µV
6
F3
117
1.22 %
-9.23 µV
7
Pz
96
0.82 %
7.18 µV
8
C4
84
0.64 %
-5.74 µV
STELA 1.0
40 msec/div.
07/13/1992
A
250009
ORIGINAL SPIKE
250009
FEATURES: 1
250009
FEATURES: 2
250009
FEATURES: 3
B

FIGURE 2. Singular value decomposition (SVD) example from an averaged scalp spike. **A:** Decomposition into eight features or components in descending order of magnitude, positive up; the spatial distribution of each feature is shown in the map; arbitrary magnitude color scale—white, positive; black, negative contribution. **B:** Top left, original spike segment; feature 1 (top right) shows a tangential spike maximal at the right centrotemporal area; feature 2 (bottom left) is a nondescript, broad midline posterior waveform; feature 3 (bottom right) is a radial spike over the right frontocentral area, mathematically distinct from feature 1, although spatially overlapping. Montage: Fp1, Fpz, Fp2, F7, F3, …, F8, T3, C3, …, T4, T5, …, T6, O1, Oz, O2, referred to linked cheeks. (Software courtesy of Dr. Richard Harner.)

Such localization applied to the somatosensory-evoked potential has produced good anatomic and physiologic agreement. Results with interictal spikes have been less ideal, likely attributable to the less-defined source configuration present in different epileptic foci. By careful selection of patient material, particularly partial epilepsy (while avoiding generalized discharges like spike-and-wave complexes), the assumption of a discrete generator can be adequately satisfied. Under these circumstances, DLM can serve not only as an acceptable localization tool, but also as an objective measure to characterize the electrical properties of the focus. Ebersole and Wade[11] used the inclination angle of the calculated dipole in patients with complex partial seizures as a measure of improvement after temporal lobectomy. Their hypothesis was that this angle reflects the location of the generator (mesial temporal or lateral temporal cortex), and thus has predictive value for postsurgical outcome.

In BECTS, calculated sources showed a clustering at the rolandic area, as expected. A study of the variability of source locations (i.e., their stability index) indicated that the "typical" group had a greater stability index than did the "atypical" group.[82] If the individual components of these spikes were separately analyzed (i.e., the initial sharp negativity and positivity, and the aftercoming slow wave) using a single-dipole model, the goodness of fit of each component showed an interesting profile. For the typical group, all three components were adequately fitted by a single-dipole model. For the atypical group, the negative and positive peaks were adequately fitted by a single dipole, but the slow wave was not.[84] This singular behavior of the slow wave in the atypical group suggests a different source configuration, one that requires the assumption of a widespread or diffuse source, an extended dipole sheet, or even multiple sources. It could not have been generated by a single discrete source. Regardless of which explanation is correct, the results suggested that source configurations of the interictal spike can differentiate between typical and atypical groups.

In this manner, mathematical models can supply additional information on the interictal focus. The computed solution provides a measure of source characteristics that can be very helpful in the formulation of a hypothesis regarding the epileptic focus.

More recently, the use of accurate MRI images with gyral pattern information has been explored, lending hope to a "realistic gyral model" to provide a finer degree of anatomic realism amenable to mathematical solutions.[1] Potentially, this technique can greatly enhance the accuracy achieved by a large variety of mathematical imaging techniques. These are not yet in common use. Other recent developments include new modeling approaches.[88]

The experience with multichannel MEG is now considerable. Stefan[70] reported that magnetic source localization compared favorably with EEG and electrocorticography (ECoG) recordings and volumetric MRI measurements. Further analysis of focal epileptic activity was made using "dipole cluster quantification," demonstrating additional useful information on the spatial distribution of the underlying excitation process—in their case, in the temporal lobe. Such information was found to be useful in the workup of presurgical candidates, particularly to guide the implantation of invasive recording electrodes.

Methods for the automatic analysis of large numbers of spontaneously occurring epileptiform paroxysms on MEG records based on spike clustering combined with averaging of similar spikes and subsequent dipole modeling can simplify the laborious work of manual spike classification and yield useful results regarding the clinical neurophysiologic assessment of epileptic patients.[76]

Nakasato et al.[58] compared MEG, EEG, and ECoG methods for seizure localization in complex partial epilepsy. By studying a large number of interictal spikes in each modality, they concluded that MEG was superior to EEG (more consistency), by virtue of better agreement with ECoG, MRI lesion location, and surgical outcome. Generally, when viewing such comparative studies it is important to ensure that the same recording parameters had been used for both MEG and EEG. An obvious one is spatial sampling density (number of recording sensors used) because it is obvious that comparing results from 128-channel MEG with 32- or 64-channel EEG would be inappropriate.

Dynamic Analysis: Linear and Nonlinear Correlations

The classic method for the quantification of background EEG signals is by way of frequency spectra, usually based on Fourier analysis. Accordingly, the relationships between simultaneously recorded EEG signals are analyzed by way of cross-correlation functions or coherence and phase spectra. Incidentally, higher-order spectra (e.g., bispectra) are used to estimate nonlinear interactions.

However, these methods do not take into account the possibility that EEG signals are generated by neuronal networks with nonlinear dynamical properties. The hypothesis is that the irregular patterns presented by EEG signals can correspond to the expression of complex nonlinear dynamical systems. This is interesting because it is known that systems with complex nonlinear properties that are both deterministic and low dimensional can exhibit complex oscillations, which in some cases can be considered chaotic. Whether the latter correspond to deterministic chaos is, in most cases, neither mathematically proven nor relevant to the specific problem under discussion here. What is important is to note that EEGs are, in general, muitivariable, nonstationary, and complex nonlinear signals.

Mathematicians have developed quantitative measures for identifying these kinds of systems. These measures include, among others, the correlation dimension and the Lyapunov exponents. Most commonly, the algorithm of Grassberger and Procaccia[23] has been used to find evidence for the presence of nonlinear dynamics in EEG records. This algorithm provides an estimate of the correlation dimension and has been widely used in EEG analysis (see Pritchard et al.[67] for review). Although the initial investigations have led to the claim that normal EEG signals can have low-dimensional chaotic dynamics, the application of more sophisticated techniques has shown that under normal conditions, most EEG signals, recorded under normal conditions, cannot be distinguished from filtered noise.[73]

Nevertheless there is evidence for nonlinear dynamics in EEGs recorded *during epileptic seizures* in animals and humans, obtained by comparing the correlation dimension of the real EEG signals with that of surrogate data obtained by randomizing the phases of the corresponding Fourier coefficients.[3,5,64,65,66,75,79] Thus we can state, in general terms, that seizure activity, in most cases, is highly nonlinear and low dimensional, whereas interictal EEG is high dimensional and only weakly nonlinear.[71] Therefore, the change in correlation dimension occurring at the beginning of an epileptiform seizure, which differs from that of normal EEG epochs, might indicate a transition in the dynamic state of the underlying networks.

How the transition between interictal and ictal takes place is a question of paramount importance in epilepsy. Stam[71] noted that there are two aspects of this transition: (1) changes in local dynamics and (2) changes in interregional coupling. The former may reflect one or more bifurcations from a high-dimensional dynamical state characteristic of the normal state to another,

low-dimensional state typical of an epileptic seizure. The transition may occur according to different scenarios: (1) abruptly, as in the case of absence seizures arising “out of the blue”[72]; (2) induced by an external stimulus, as in reflex epilepsies[62]; and (3) in a gradual way by a series of bifurcations culminating in a pre-ictal and, finally, an ictal state.[37,38,39,77,78,80] Regarding the second aspect of the transition, the general assumption is that an increase in coupling between brain areas is characteristic of seizures.[40] However, in some types of seizures a decrease in coupling can initially occur.[57,59,81] The studies carried out in patients, mostly with temporal lobe epilepsy, suffer from the important limitation of being based on a relatively small number of electrodes that, in general, do not provide satisfactory spatial sampling of the brain areas involved in the epileptic process. Thus, more detailed analyses of these brain systems based on adequate sampling in space and time are necessary to obtain a reliable insight into the evolution of the coupling between different brain areas at the onset and during epileptic seizures.

An even more controversial issue is whether the dynamical state of the brain systems involved in the generation of epileptic seizures, as revealed in EEG recordings, may provide a reliable indication of a *pre-ictal state*. The question, in practice, is whether measures derived from these EEG recordings could be used to anticipate or predict seizures. Assuming that epileptic seizures correspond to a state of increased synchronization, at least between some brain sites, one might expect that this increase of synchronization can gradually evolve in the pre-ictal state, and this gradual change might be detectable by appropriate analysis methods. After some early studies reporting that nonlinear dynamical EEG measures (e.g., Lyapunov exponents) might change some time before the onset of a seizure,[28,29] in the late 1990s a number of papers reporting that epileptic seizures could be predicted using nonlinear EEG measures appeared that had a large impact in the scientific and clinical communities,[12,52] leading even to an editorial comment in *Nature Medicine*.[69] A considerable number of studies followed these seminal papers, which were reviewed by several authors involved in this research line.[28,40,42,43,47,48] The initial perspectives were, however, too optimistic. One of the limitations of the early studies is that they were based on small sets of selected EEG data and did not include solid statistical evaluations of sufficiently long records. Furthermore, many of these studies used only specific EEG measures and did not analyze a comparative assessment of different methods of EEG analysis. Recently an issue of *Clinical Neurophysiology* (March 2005) published a useful collection of papers on this issue. The study of Mormann et al.[57] reports a second-generation study attempting to evaluate in a comprehensive way the predictability of seizures using 30 EEG measures, both linear and nonlinear, applied to long-term intracranial EEG recordings lasting over days. The authors concluded that a *pre-ictal period* can be identified and that a combination of univariate (e.g., Hjorth mobility and complexity) and bivariate (e.g., cross-correlation coefficient, Hilbert mean phase coherence, wavelet mean phase coherence) measures offers the most promising approach in seizure anticipation. It is important to emphasize that the direction of the change of the phase coherence, a measure of synchronization, can vary with electrode site, and it can increase at some sites while it decreases at adjacent sites. In addition, in an analysis of intracranial long-term EEGs in patients with mesial temporal lobe epilepsy Le Van Quyen et al.[40] found that phase synchronization can be used to characterize a pre-ictal state, although this is controversial.[31]

Recently the issue of the changes in dynamical properties of the EEG in the course of the process of transition toward an epileptic seizure has been explored using a different approach. Instead of analyzing the spontaneous EEG, the activity evoked by stimulating with bursts of pulse trains, applied intermittently during long periods lasting even days by way of intracranial electrodes, was used.[32] The EEG measure that showed the most significant performance was a quantitative measure of spectral phase demodulation, the relative phase clustering index (rPCI). In interictal periods, large values of rPCI recorded from specific sites were correlated with the most probable seizure onset sites, and large values of rPCI from certain locations were correlated with shorter time intervals to the next seizure, whereas small values were associated with much longer time intervals. This indicates that this approach might be relevant to estimating the probability of occurrence of epileptic seizures within a given time, at least in patients with mesial temporal epilepsy.

The studies of dynamical changes in EEG recorded in the course of the transition from the interictal to the ictal state, however, have been empirical without an appropriate theoretical framework, based on solid experimental data indicating how the activity of neuronal networks responsible for epileptic behavior develops in the course of time. This is an important limitation. A promising theoretical approach in this respect is that of Wendling et al.,[80] who proposed relevant models of such neuronal networks. More work along these lines is needed.

Generator Considerations

In the clinical consideration of seizures, it is important to ask whether the ictal generator is different from the interictal one(s). Conventional epileptology teaches that these generators are different and that the only reliable localization is by the study of ictal data, often from invasive recordings (cortical grids and depth electrodes). In practice, discussion usually proceeds to involve other possible foci, areas that were not recorded from. This issue is bound to arise, and a satisfactory resolution can be achieved only when there is convincing and converging evidence toward a particular generator/focus or, conversely, of multiple foci, so as to render focal surgical resection nonviable. The complexity of ictal localization is compounded by the fact that the focus might initiate a seizure accompanied by very low amplitude signals that can be recorded only by nearby depth electrodes. If no electrodes had been placed there, such signals would be lost. The first recorded ictal signals, then, might well be secondarily generated as a result of propagation. Such a scenario might well be present with temporal lobe foci, in which the seizures originate from the deep hippocampus or amygdala and propagate to the superficial temporal cortex.

There is evidence that the generators responsible for interictal discharges might overlap with ictal generators; this line of reasoning has been particularly supported by the findings of Ebersole[8] and Ebersole and Wade.[11] In fact, this should not come as a complete surprise if one considers that seizure surgery (temporal lobectomy and cortical resection) is guided by intraoperative interictal spike discharges. The obvious difficulty here is that there may be different types of interictal discharges recorded in a given patient from multiple scalp locations. This is in part a by-product of the ease of obtaining interictal spikes as compared with ictal episodes. Perhaps if one were to always insist on having an equally large number of ictal episodes, one would well appreciate the diversity of ictal patterns in the same given patient. Of course, this is not easily accomplished because ictal recordings usually require expensive hospitalization for many days under the direct supervision of skilled personnel using sophisticated equipment.

Expanding the horizons for the foregoing discussion, one can consider how other modalities image a seizure focus—computed tomography (CT) or MRI atrophy, positron emission tomography (PET) hypometabolism, single-photon emission tomography (SPECT) hypervascularization, functional MRI (fMRI) enhancement, and so on. Each modality demonstrates a particular and unique aspect of the (interictal) behavior of the epileptogenic area. Therefore, it is not surprising that each modality might describe different aspects of this common epileptogenic area and that the resultant localizations from these techniques might not overlap completely. It follows that localization by interictal spikes falls into the same situation and should not be treated differently. It is necessary for any localization technique to have its measurement result well defined (i.e., variability and reproducibility). Therefore, serial scalp recordings must have been done with a complete cataloging of all interictal foci, their spike topography, and their morphology. For scalp recordings, quantitative descriptions are superior to qualitative descriptions and can be based on one of the aforementioned mathematical techniques.

In the final analysis, it is not relevant how localization is determined and whether mathematical models are "accurate" (whatever this means) when compared with a given standard. Rather, it is physiologic parsimony of model with clinical observations that is relevant, so that all available clinical information can be explained. The clinician can then confidently use the model (whether it be derived from MRI, PET, EEG, etc.) to make a diagnosis, infer behavior, and predict future outcome.

Such multimodality models require the coregistration of findings into real brain space. Currently, each modality obtains data and displays results in a particular manner, and it is difficult to make comparisons: Scalp EEG might be displayed using a two-dimensional flattened-scalp topography, whereas PET and CT create three-dimensional images of brain slices. Magnetic resonance imaging is a true three-dimensional anatomic display due to its resolution and software capabilities.

Recently, the co-registration of EEG and fMRI has become technically possible.[2,16,17,21,34,44] Nevertheless co-registration of different techniques poses difficult problems of interpretation. The goal should be for brain regions or structures to be identified with confidence when comparing across modalities, and not pixel locations, as shown on the computer screen from each modality. For other recent examples of co-registration see Moran et al.[56] and Mirkovic et al.[55]

A note of caution: There are readily available mathematical models that purport to yield source localization accuracy to within millimeters. These models claim to be able to identify activity as coming from very specific and small brain structures, based on parameters (e.g., 20 recording EEG electrodes) that most electrophysiologists would not associate with such accuracy. Lantz et al.[35] demonstrated the level of caution required before making conclusions from such analyses (see also Lehmann et al.[41] and Michel et al.[54]).

Summary and Conclusions

Quantitative analyses allow objective characterization of electromagnetic signals from spontaneous interictal spike discharges and ictal patterns. Such techniques are still being developed, but they appear at least to have good electroclinical correlations, which is encouraging. Current techniques lend themselves to the formulation of specific hypotheses and their application to clinical studies. There is still tremendous potential for making significant advances in the recovery of more information from the EEG-MEG signals.

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Chapter 77

Polygraphic Recordings

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Introduction

Polygraphy is a general term that refers to the simultaneous recording of multiple physiologic measures. The main purpose of polygraphic investigations is to provide a correlation between the phenomenology of a behavioral manifestation and a set of physiologic parameters. The polygraphic study must be tailored to each clinical problem to select the parameters relevant to the nature and the characteristics of the manifestation being investigated. Several books and chapters have reported a list of the different variables that can be monitored polygraphically.[38,56,104,133]

In the study of epilepsy, polygraphy helps to determine the occurrence and characteristics of the modifications of different physiologic functions associated with changes in the electroencephalogram (EEG) and the temporal relationship with the EEG events. Data obtained by means of polygraphy can be extremely useful for describing the symptomatology of epileptic seizures, defining the clinical characteristics of different epileptic conditions, clarifying the physiopathogenetic mechanisms of epileptic conditions, establishing and verifying diagnostic hypotheses, and monitoring and evaluating the action of drugs. This chapter outlines some applications of polygraphic techniques to the study of epilepsy—in particular, its motor manifestations.

Technical Aspects

Currency

Polygraphic recordings are usually performed using modified EEG apparatus. An appropriate number of channels is required, either to collect sufficient information to localize abnormalities or to adequately record polygraphic data. Standard EEG machines usually employ a set of alternating current (AC) amplifiers to collect the data. However, this type of amplifier limits the possibility of recording constant or slowly varying signals (such as those produced by blood pressure, respiratory parameters, or electrodermal resistance). The availability of one or more direct current (DC)-coupled amplifiers can allow the collection of signals whose magnitudes or frequency characteristics range outside those provided by the standard EEG AC machines.

Methodology

The following parameters are relevant to epileptic seizures that can be monitored by means of polygraphic recordings.

Electroencephalogram

Data are collected following the standard procedure for EEG recording. The number of recording channels and the montage used depend on the characteristics of the clinical situation being investigated.

Electromyogram

Surface electromyogram (EMG) activity is obtained by applying two electrodes over the muscular belly of the recorded muscles. To allow collection of high-frequency EMG signals, a short time constant (0.03 second or less) to reduce artifacts caused by movement or sweating and minimum filtering are necessary. Simultaneous EEG and EMG recording can provide useful information to verify the existence of correlations between cortical and muscular events. Analysis of latency between EEG and EMG events, which was once difficult and imprecise by visual inspection of data on paper, can be performed more precisely and reliably by using computerized polygraphic systems that collect the neurophysiologic signals in a digital format and allow off-line processing and analysis of the data. Recording of EMG activity from antigravity muscles can be useful for investigating modification of the muscular tone associated with paroxysmal discharges. Disorders such as tremor or myoclonia require the monitoring of muscular activity of both agonist and antagonist muscle groups.

The inherent limitations of surface EMG, including difficulty recording from a deep or a single muscle without the interference of nearby muscles, loss of high-frequency muscular activity, and inability to obtain single-motor-unit activity, mean that there is only a gross correlation between the EEG and the compound activity of a single muscle. For analysis of the effect of epileptic activity on the single motor unit, needle EMG recording is indicated.

Electrooculogram

Eye movement recording is usually performed by placing two electrodes at the outer canthi to record horizontal movements and one electrode above and the other below one eye to record vertical movements.

When only one electrooculogram (EOG) channel is available, two electrodes can be used, one placed above the outer canthus of one eye and the other placed below the outer canthus of the opposite eye. Other systems have been proposed, including using infrared-detecting cells mounted on a spectacle frame together with an infrared-emitting diod[43] or employing piezoelectric sensors.[53] Electrooculography is particularly useful for detecting artifacts induced by eye movements, investigating lambda waves, studying ocular manifestations correlated with EEG paroxysms, such as in cases with epileptic nystagmus,[58,103] and scoring sleep stages in polysomnography. Computerized methods for removing the EOG artifacts using the EOG signal have been extensively described by Barlow.[5]

Electrocardiogram

Electrocardiograms (ECGs) can be easily recorded with an EEG device by placing two electrodes on the chest wall or—to obtain a lead I derivation—on the right and left arms. Sensitivity must be adjusted by switching from microvolts per millimeter to millivolts per millimeter; bandwidth ranges from 0.8 to 60 Hz. Simultaneous recording of EEG and ECG allows the detection of pulse and ECG artifacts contaminating the EEG tracing.

Respirogram

Respiratory activity can be monitored either by measuring the changes in thoracic volume due to respiratory movements or by detecting the flow of air through the nostrils and the mouth. Modifications of chest volume can be measured using a strain gauge attached to a piece of elastic forming a band around the chest. Variations of chest circumference due to respiration stretch the elastic band, causing a change in resistance in the strain gauge. Change in resistance can be measured by means of a DC-excited Wheatstone bridge circuit. This system requires that the patient remain still because chest size in moving individuals can change independently from respiration.

Another method for monitoring respiratory activity is to detect the air flow through nostrils and mouth by means of a thermocouple, which generates a current whenever warmed, or by a thermistor, which requires a constant-current source and reproduces changes of temperature as variations of resistance. Both thermocouples and thermistors must be placed between the nostrils and the mouth to detect differences in temperature between inspired and expired air. All of these methods require a long time constant (0.6 or 1 second) and filtering of high frequencies.

Electrodermal Response or Electrodermogram

Electrodermal (EDG) response, also referred to as *electrical skin resistance*, *galvanic skin reflex* or *response*, and *psychogalvanic reflex*, is a change in resistance and the generation of a potential between areas containing many sweat glands and areas almost devoid of them, due to modifications of sweat gland activity. Change in resistance is also called the *Fere effect*; the generation of a potential is called the *Tarchanoff response*. The Fere effect and the Tarchanoff response are probably two measures of the same phenomenon, both being affected by cholinergic modulation.[70]

Measurement of EDG response is performed by placing one electrode in the palm of the hand or on the sole of a foot and another in an area without sweat glands (such as the back of the hand). Another method is to place both electrodes on the dorsal surface of the forearm 5 to 6 cm apart. Recording must be performed using the longest time constant available with the maximum high-frequency filtering. Measurement of the skin potential, which appears as a DC potential (Tarchanoff response), is quite easy; however, it is unstable due to the possible occurrence of an offset potential at the electrode–skin interface and is difficult to control and distinguish from the EDG. For these reasons, measurement of change in skin resistance is more appropriate.

In normal individuals, resistance recorded from two electrodes on the hand ranges from 20 kΩ to perhaps 0.2 MΩ. If the autonomic nervous system is malfunctioning, resistance can reach values of >1 MΩ. Variations of EDG by measuring the Tarchanoff response during sleep in normal individuals and in patients with epilepsy have been described by Broughton et al.[16] Arousal is associated with a decrease in resistance and relaxation with an increase in resistance. Evident EDG modifications were observed—especially during sleep—and were associated with temporal lobe interictal discharges and brief generalized discharges of polyspikes (Fig. 1).

Blood Pressure Monitoring

Blood pressure can be monitored invasively by introducing a microcatheter in the radial artery. The microcatheter is connected with a pressure transducer to polygraph preamplifiers. DC recording is required. It is possible, via microcatheter, to obtain blood samples for blood gas measurements. A preferable method for monitoring blood pressure is a noninvasive assessment based on the computerized processing of instantaneous blood pressure modifications, which are collected by a plethysmographic system applied, usually, to the middle finger of the hand.

Micturition Recorder

A micturition recorder is a device that allows the detection of enuresis or loss of urine due to a convulsive seizure. Broughton[37] designed a system consisting of two long electrodes, in separate nylon sheaths, placed parallel with and close to one another in a serpentine shape close to the urinary meatus. The signal recorded, using a high upper-frequency response and a short time constant, is a 50-Hz artifact (60 Hz in North America). As soon as the patient urinates, the first drops of urine create a conductive path between the two electrodes that causes the disappearance of the artifact.

Body Movement Detectors

Systems for signaling body movements are usually based on displacement transducers, accelerometers, or actigraphy monitors. These systems can be applied to the bed of the patient—especially when the aim is to detect seizures during sleep[131]—or to body parts. A wrist accelerometer can be extremely useful for monitoring movements during sleep,[60] identifying different types of movements (tremors, myoclonia),[72] and differentiating EEG activity from movement artifacts.[18] Actigraphs are small, wrist-worn devices (usually about the size of a wristwatch) that measure movements; they are equipped with a microprocessor and an on-board memory that can allow off-line analysis and display. Actigraphy monitoring is particularly useful in the study of sleep and circadian rhythms.[2,64]

Gastrointestinal Activity Monitoring

Motility of the gastrointestinal tract was studied by means of EMG recording of the duodenal activity[116] using bipolar platinum electrodes. This study investigated modifications of duodenal motility in relation to wakefulness, sleeping (Fig. 2), and ictal activity (Fig. 3). Cherubini et al.[20] polygraphic techniques, including monitoring of EMG activity of intestines in cats, to investigate the effects of pharmacologically induced generalized epileptic seizures on intestinal motility.

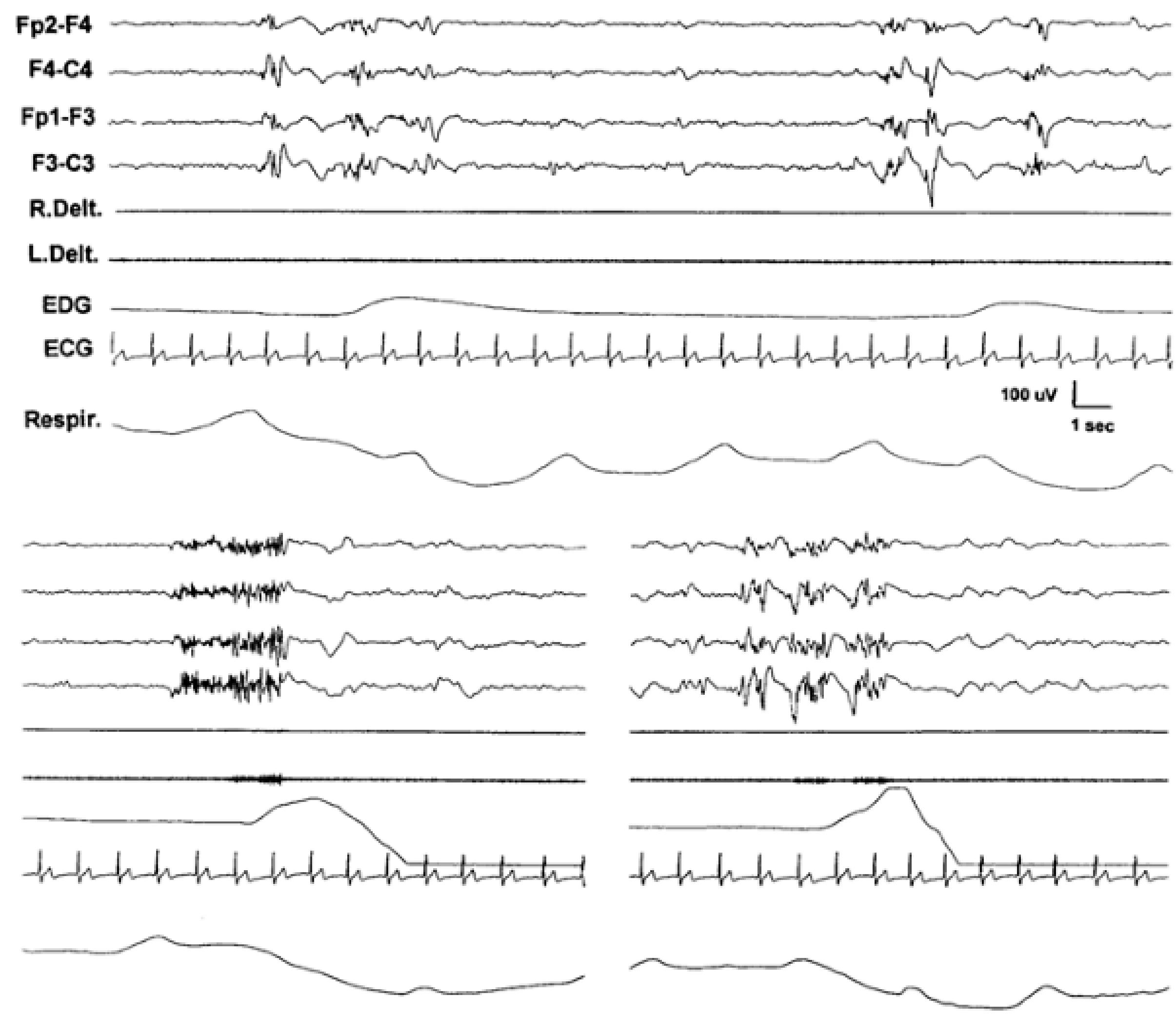

FIGURE 1. Modifications of electrodermogram (EDG) associated with paroxysmal electroencephalogram (EEG) activity during sleep. **Upper:** Slight EDG changes, indicating a modification of skin potential (Tarchanoff effect), occur as the only manifestation associated with diffuse polyspike-wave activity (note the absence of EMG changes in the deltoids and of modifications of electrocardiogram [ECG] and respiratory rate). **Lower:** Fast rhythmic activity of polyspikes accompanied by a more significant EDG modification, mild contraction on the left deltoid, and change of respiration. L. Delt, left deltoid; R. Delt., right deltoid; Respir., thoracic respiration.

Polysomnography in Patients With Epilepsy

The term *polysomnography* refers to polygraphic recordings of sleep/wake cycle in subjects with sleep disorders. Technical or methodologic aspects of these techniques applied to the study of sleep have been addressed in specialized books and monographs.[15,59,61,128] In patients with epilepsy, the role of sleep in facilitating seizures and in activating interictal EEG paroxysmal abnormalities is well known. On the other hand, epileptic seizures can be responsible for modifications of sleep architecture. The relevance of the relationship between epilepsy and sleep has been acknowledged.[28,102,132] Sleep polygraphic studies in epilepsy can be extremely useful for diagnosis and for understanding some of the physiopathologic mechanisms of sleep and epilepsy.[5a]

In epilepsy, polysomnographic studies can be indicated for two reasons: (a) to investigate the presence of disturbances of vigilance or sleep in patients with epilepsy and (b) to identify and analyze paroxysmal interictal activities, detect nighttime seizures, and evaluate the influence of epilepsy on sleep.

Altered alertness in patients with epilepsy can be due to several factors that are either related or unrelated to the epilepsy. Frequent nocturnal seizures altering sleep structure, antiepileptic treatment, and epileptogenic lesions affecting anatomic structures related to vigilance can cause excessive sleepiness in patients with epilepsy. Polysomnographic studies can document the possible occurrence of sleep disorders, such as sleep apnea, and other respiratory disorders, nocturnal myoclonus, or restless leg syndrome.

When the goal of polysomnography is to document nighttime seizures or to investigate the relationship between sleep and epilepsy, a higher number of EEG channels is required than for standard polysomnography. Overnight polysomnography can be helpful to discriminate between epileptic and nonepileptic nocturnal episodes,[12,37,49,55,74,77,101,120] characterize and classify nocturnal epileptic seizures,[8,75,110] establish the occurrence of electrical status epilepticus during sleep,[107,108] identify the primary focus in localization-related epilepsy by investigating topography of paroxysms during rapid-eye-movement (REM) sleep,[71,89] and analyze the behavior of interictal discharges during sleep.[8,25,27,33,36,66,84,125,126]

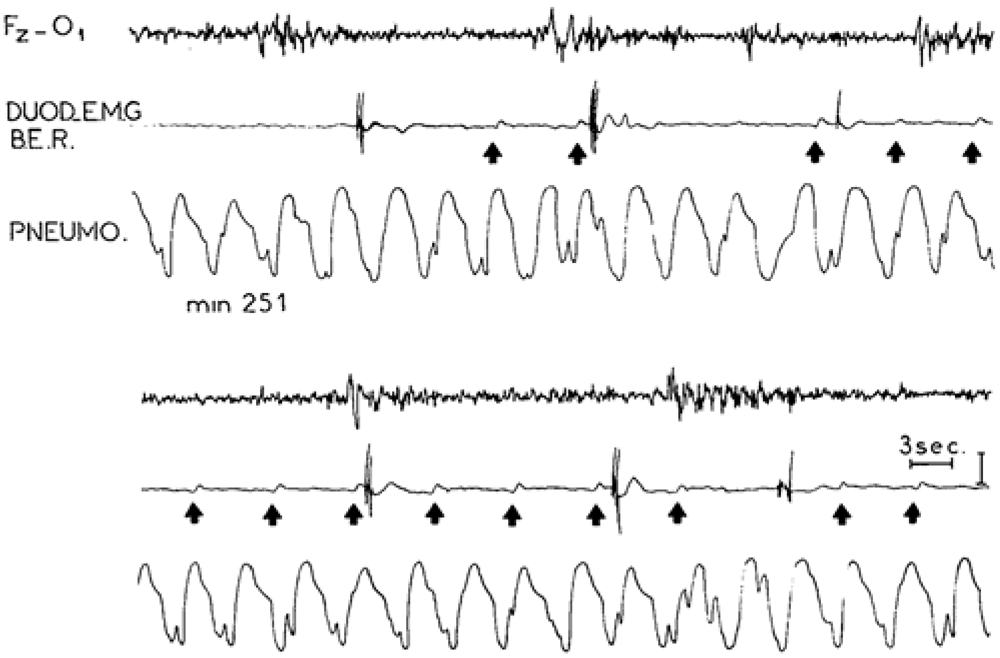

FIGURE 2. Sleep polygraphic tracing with duodenal electromyogram (EMG) recording in a normal individual. Basal electrical activity can be associated with bursts of muscular potentials accompanying duodenal contractions (*arrows*). No constant relation is observed between duodenal electrical activity and K complexes. DUOD E.M.G. BER, duodenal EMG demonstrating basal electrical activity; PNEUMO., respirogram.

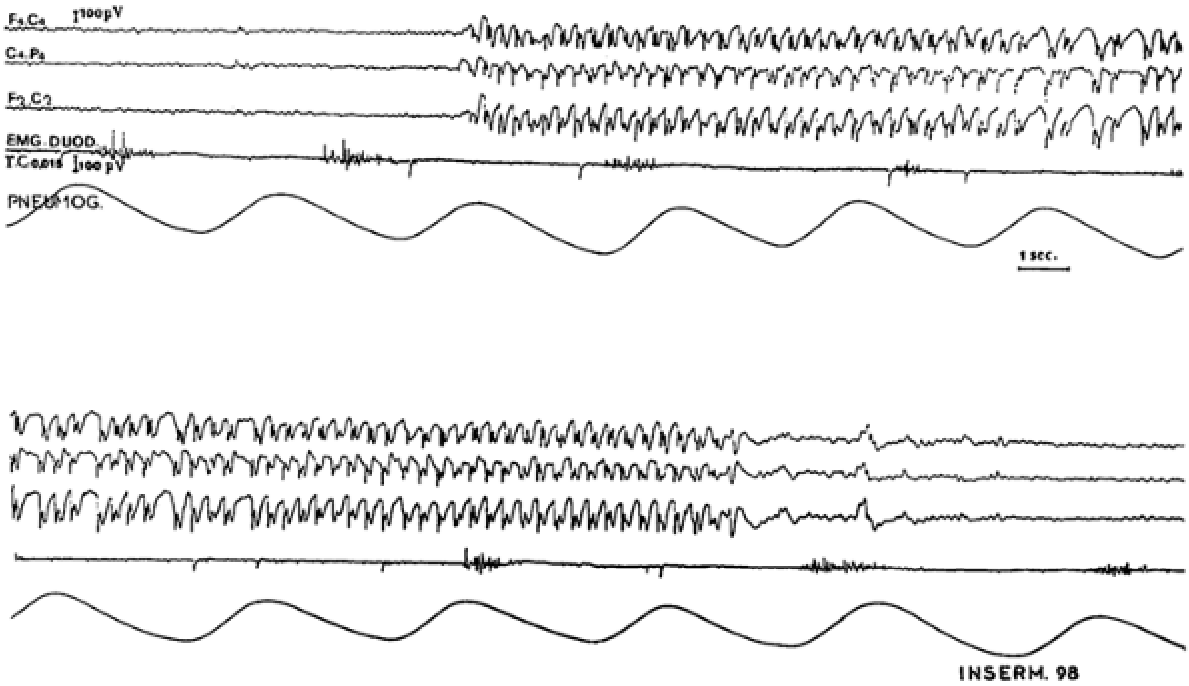

FIGURE 3. Duodenal electromyogram (EMG. DUOD.) activity persisted unmodified (or, possibly, slightly decreased) during spike-and-wave discharges; PNEUMOG., respirogram.

Polygraphic Studies in the Investigation of Epileptic Motor Manifestations

Motor phenomena are often the most overt clinical aspects of an epileptic seizure. However, when one is relying solely on clinical data, the patterns of muscular activations can be difficult to characterize and analyze. Mild contractions or sporadic muscle twitchings can often be missed by an observer. Polygraphy with recording of surface EMG activity can be extremely

useful in identifying and characterizing even subtle and apparently subclinical muscular manifestations and correlating these movements with EEG activities.

Analysis of Motor Phenomenon

Surface EMG recording can provide information regarding the modality of muscular contraction, which can allow distinctions to be made among different types of motor phenomenon. All of the following types of muscular phenomena can occur, either in isolation or in various combinations, to constitute the clinical manifestations of the different types of epileptic seizures.

Myoclonus

A positive myoclonus is characterized by a massive, shock-like muscular contraction involving one or more body segments. It appears in the EMG as a brief burst of muscular potentials (Fig. 4), synchronous on agonist and antagonist muscles, with or without an EEG correlate. The opposite phenomenon, a "negative" myoclonus, is a brief interruption of a tonic muscular contraction (Fig. 4), sometimes clinically indistinguishable from the positive myoclonus.[94,123] When associated with a paroxysmal EEG event, a *negative myoclonus* is defined as "epileptic negative myoclonus" (Fig. 5).[48,106,122] Negative myoclonus, defined as an interruption of tonic muscular activity for <500 msec without evidence of preceding myoclonia, was recognized in 2001 as a seizure type by the Task Force of the International League Against Epilepsy on Classification and Terminology.[13]

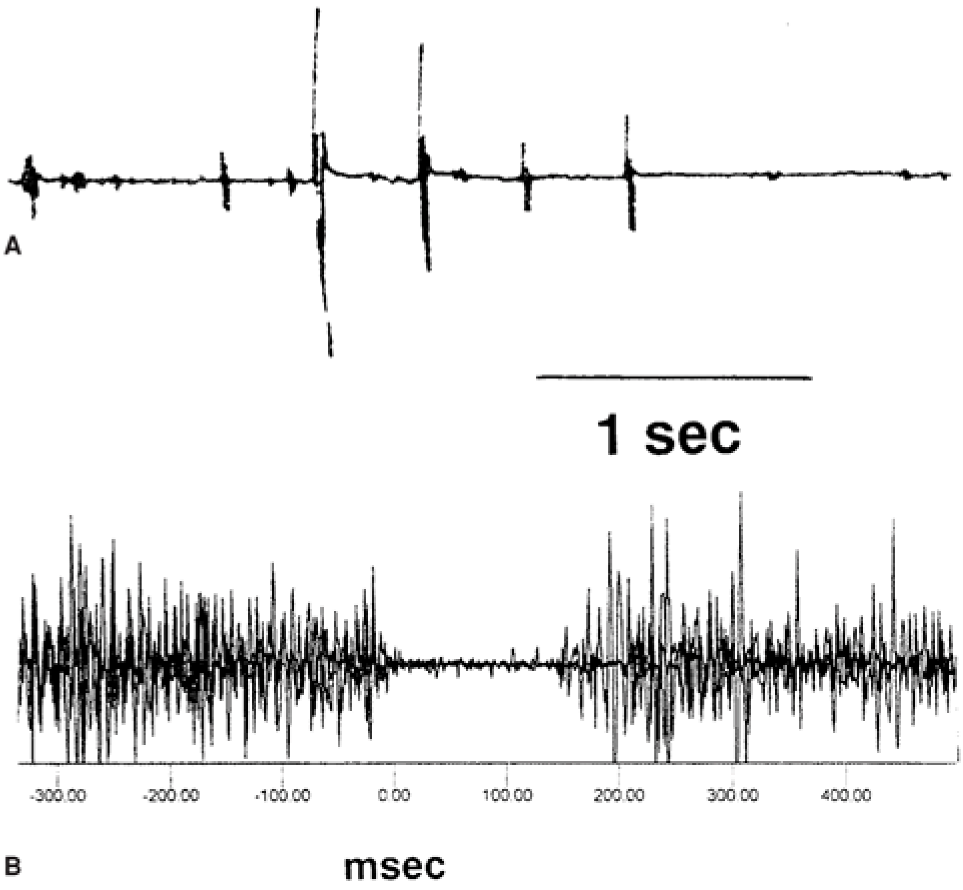

FIGURE 4. A: Positive myoclonus. **B:** Negative myoclonus.

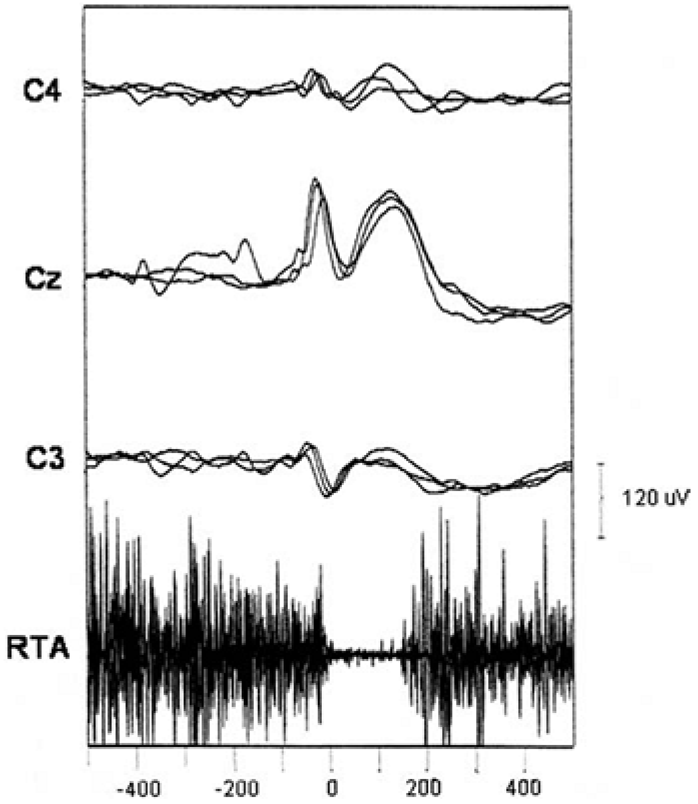

FIGURE 5. Epileptic negative myoclonus. Superposition of three polygraphic segments illustrating a spike-wave complex on Cz, slightly spreading to C3 and C4, associated with epileptic negative myoclonus in right tibialis anterior (RTA), in a child with benign partial epilepsy of infancy. The onset of the electromyogram silent period in RTA precedes the onset of the slow-wave component on Cz, suggesting that the muscular inhibition is related to the spike and not to the slow wave.

Spasm

A spasm, which appears as a massive but slow contraction reaching a climax and progressively decreasing, more often than not involves axial and proximal muscular groups. Indeed, polygraphic recordings with multiple EMG leads have demonstrated that epileptic spasms can occur with a complex pattern of muscular activation, with the involvement of cranial as well as limb and axial muscles. This complex pattern of contraction can appear clinically similar in different spasms, although with variable sequences of muscular recruitment (Fig. 6).[10,134] On the EEG, spasms can be devoid of any modification of tracing or they can be associated with flattening, diffuse low-voltage fast activity,[42] or a slow wave.[34,46]

Tonic Contractions

Tonic contractions consist of slow, sustained contractions maintained over time and involving several muscular groups. They are usually associated with fast recruiting EEG activity.

Clonic Contractions

Clonic contractions are characterized by a series of jerks, appearing on the EMG as hypersynchronous muscular potentials. They can vary in amplitude, symmetry, frequency, and topography and are often related to contralateral EEG spikes.[42]

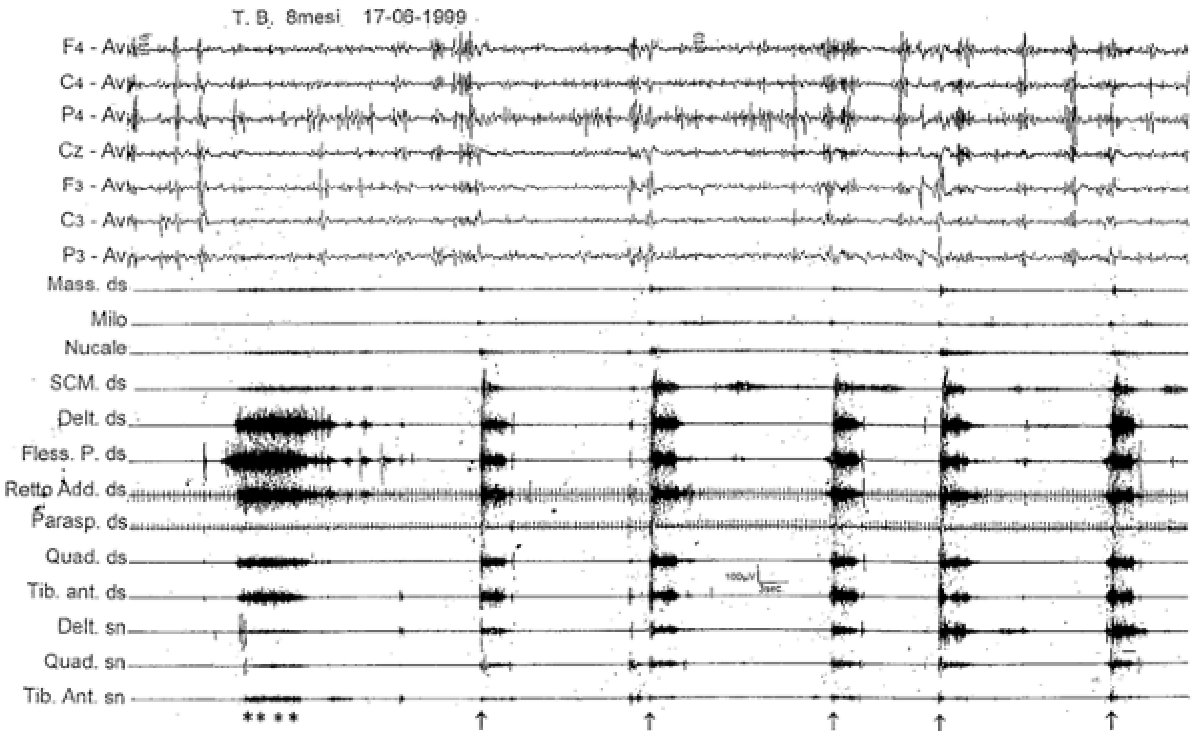

FIGURE 6. Polygraphic recording of a cluster of spasms (*arrows*) following a brief tonic seizure (*asterisks*) in

an 8-month-old child with severe epileptic encephalopathy associated with cortical dysplasia. The multichannel electromyogram recording shows the involvement of cranial, trunk, and limb muscles with a quite reproducible pattern. A slow complex associated with the spasms is detectable in the electroencephalogram (horizontal time scale: 3 s). Delt., deltoid; ds, right; Fless. P., wrist flexor; Mass., masseter; Milo, mylohyoideus; Nucale, splenium capitis; Parasp, paraspinal muscles; Quad., quadriceps; Retto Add., rectus abdominis; SCM., sternocleidomastoideus; sn, left; Tib.ant., tibialis anterior.

Atonic Phenomena

Atonic phenomena can appear as a sudden global or focal loss of muscular tone, characterized polygraphically by an abrupt flattening of the EMG activity. They are associated with different types of EEG paroxysmal discharges (generalized spike- or polyspike-and-wave, diffuse fast rhythmic spikes, bilateral synchronous fast waves intermixed with slow waves) or with no EEG changes at all.[42]

Analysis of Motor Pattern

Polygraphy can be extremely relevant for defining the characteristics of a motor manifestation during a seizure in terms of (a) the relationship with the concomitant EEG activity, (b) muscular groups involved in the seizure, (c) the temporal succession and the time course of the activation of motor patterns during the seizure, and (d) the presence of a stereotypic motor pattern across different seizure types.

Generalized Tonic–Clonic Seizures

Polygraphic recordings make it possible to characterize the complex manifestations of generalized tonic–clonic seizures, which are composed of a more or less stereotyped sequence of motor phenomena.[9,29,38,40] This sequence consists of an initial tonic phase of sustained muscular contraction lasting 10 to 20 seconds and involving all skeletal muscles. This phase is responsible for the characteristic body attitude (a flexion followed by a longer extension phase). A diffuse vibratory contraction follows this initial phase, and clonic manifestations follow next. The clonic manifestations consist of brief, maximal flexor contractions of the whole body, with the interval between the jerks becoming progressively longer. It is interesting that polygraphic recordings have demonstrated that, just a few seconds after the last clonic jerk, a new tonic phase usually reappears, as intense as the first one but with different topographic distribution, involving mainly facial and masticatory muscles.[42]

The EEG correlates of a tonic–clonic seizure are usually represented by an initial desynchronization, sometimes preceded by generalized bursts of polyspike-and-waves, followed by a recruiting rhythm. These are intermixed with slow waves of decreasing frequency and increasing amplitude that correspond, at a certain point, with the interruption of the tonic massive contraction and with the onset of the clonic manifestations. A flattening of the EEG activity follows, which represents the phase of “cortical extinction” and lasts several seconds (see Chapters 47 and 74).

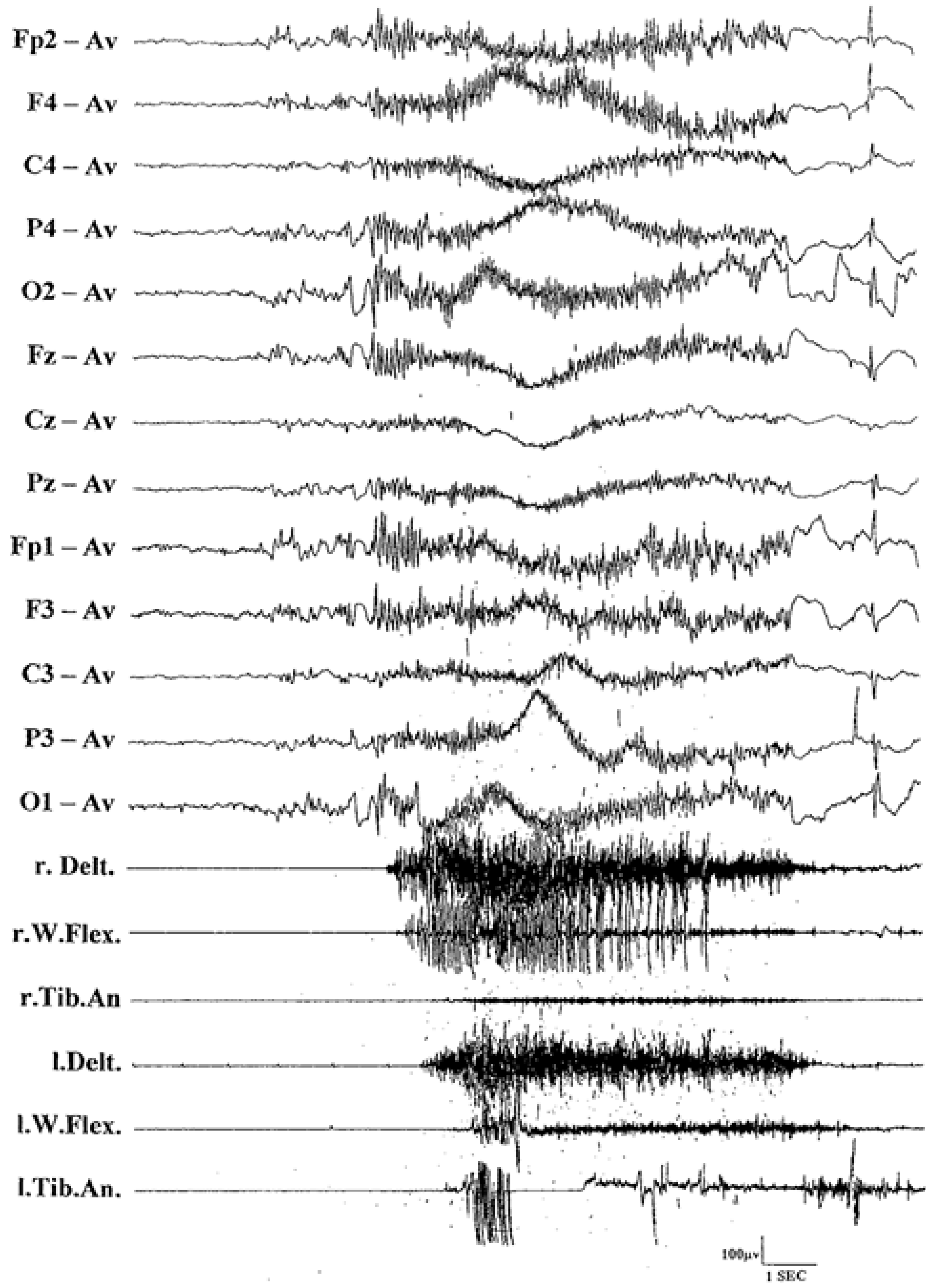

FIGURE 7. Tonic seizure. The bilateral tonic contraction, more prominent in both deltoids, is associated with a fast rhythmic polyspike activity. Delt., deltoid; l, left; r., right; Tib. An., tibialis anterior; W. Flex., wrist flexor.

Tonic Seizures

Clinical features of tonic seizures consist of a brief (5 to 20 seconds) muscular tonic contraction accompanied by impairment of consciousness and involving, with varying degrees of intensity and extension, distinct muscular groups (i.e., the head and trunk or the limb girdles and, to a lesser extent, the legs) or the whole body.[19,40,41,42] The associated polygraphic findings are represented by different EEG patterns such as (a) flattening of the tracing, (b) fast activity (around 20 Hz) of progressively increasing amplitude, and (c) recruiting rhythmic discharge at about 10 Hz, sometimes of high amplitude from the onset. The EMG leads show an interference pattern in all involved muscles corresponding to the tonic contraction (Fig. 7). Different patterns of muscular activation can be observed according to the duration of the seizure: When it lasts a short time, the contraction is maximal at the onset, then decreases; when it is of longer duration, a progressive increment of the muscular activity reflects the increasing intensity of the contraction. In global tonic seizures, an axial preponderance of the muscular activation is evident. Asymmetry of the tonic contraction or the occurrence of myoclonia at the end of the tonic manifestation can be observed. Tonic seizures are often associated with autonomic changes, such as modifications of heart and respiration rate, mydriasis, vasomotor phenomena, increase in intravesicular pressure, and positive electrodermogram responses (see Chapter 52).[19,40]

Myoclonic Absences

In myoclonic absences, the appearance of a generalized 3-c/s spike-and-wave discharge lasting up to several seconds is associated with myoclonic jerks (see Chapter 240). These jerks are particularly evident in the upper limbs and are polygraphically characterized by myoclonic potentials that, a few seconds after the beginning of the discharge, are superimposed on a progressively increasing tonic muscular contraction, which mainly involves the shoulders and the deltoids and results in the abduction and elevation of the upper limbs (Fig. 8).[109,118] With extra leads, facial muscles and the mentalis and orbiculus oris muscles can be observed for twitchings synchronous with the spike-and-wave complex. Oscilloscopic analysis of the EEG/EMG correlation has demonstrated that the positive transient of the 3-c/s spike-and-wave complex[137] is correlated with the appearance of the myoclonic jerks. Latency between the myoclonic jerk and the spike on the EEG is 15 to 40 msec for the upper limbs and 50 to 70 msec for the lower limbs. The myoclonic bursts are followed by a brief (60 to 120 msec) silent period that interrupts the tonic contraction (Fig. 9).[109]

Juvenile Myoclonic Epilepsy

Polygraphy can be extremely useful for supporting a diagnosis of juvenile myoclonic epilepsy, in which brief myo-clonic jerks—particularly in the upper limbs—are associated with polyspike-and-wave complexes at a frequency of 3 to 3.5 c/s (see Chapter 244).[54,99] Computerized polygraphic recordings have shown that myoclonic potentials in juvenile myoclonic epilepsy are related to a cortical positive potential encompassed in the polyspike discharge of the polyspike-wave complex.[73]

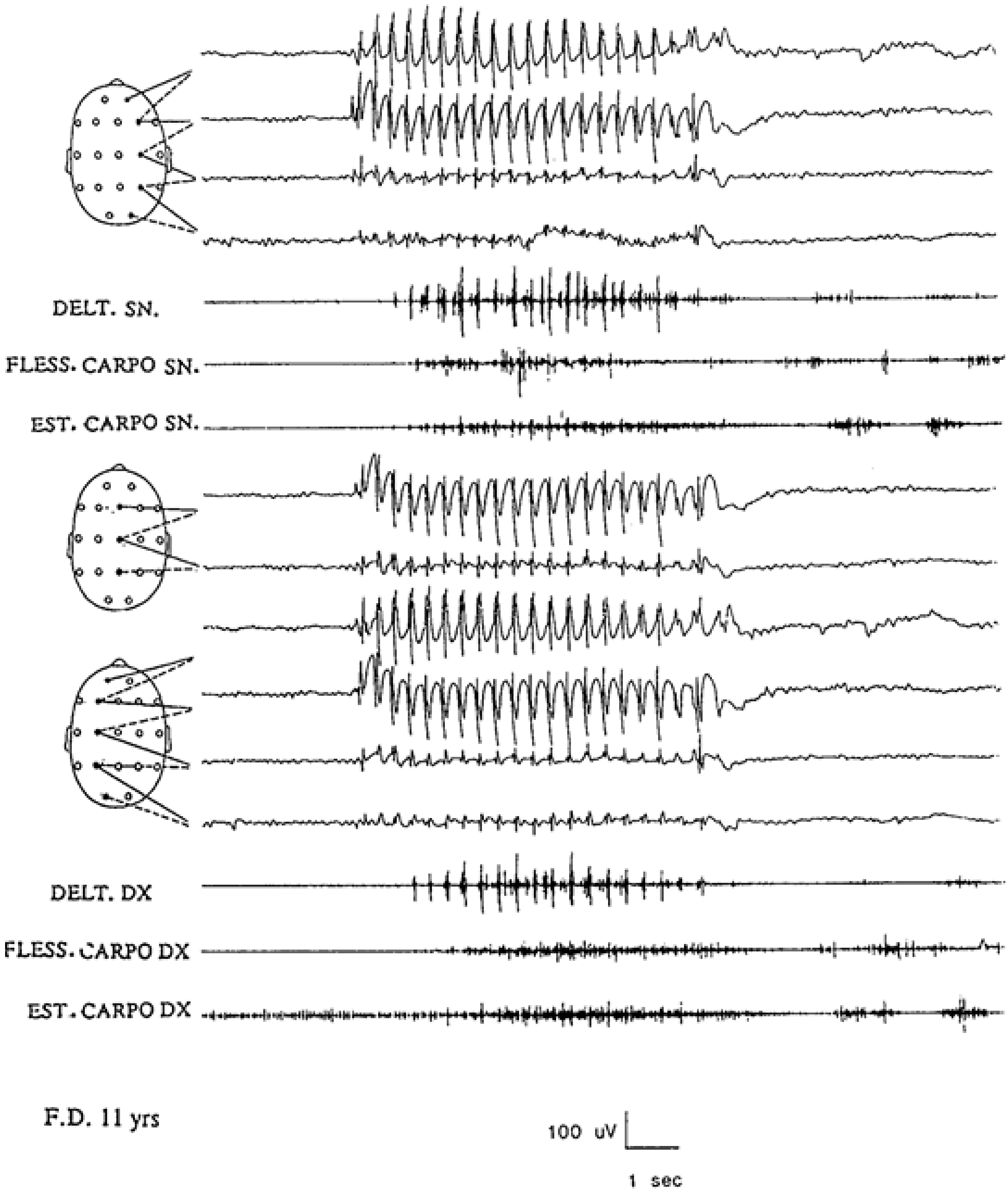
DELT. SN.
FLESS. CARPO SN.
EST. CARPO SN.
DELT. DX
FLESS. CARPO DX
EST. CARPO DX
F.D. 11 yrs
100 uV
1 sec

FIGURE 8. Myoclonic absence. A 3-c/s generalized spike-and-wave discharge is accompanied by rhythmic myoclonic jerks in the upper limbs, particularly evident on the deltoids, occurring at the same frequency of the spike-and-wave complexes and progressively associated with a tonic contraction. DELT. SN. and DELT. DX., left and right deltoid, respectively; EST CARPO SN. and EST. CARPO DX, left and right extensor carpi, respectively; FLESS. CARPO SN. and FLESS. CARPO DX, left and right flexor carpi, respectively.

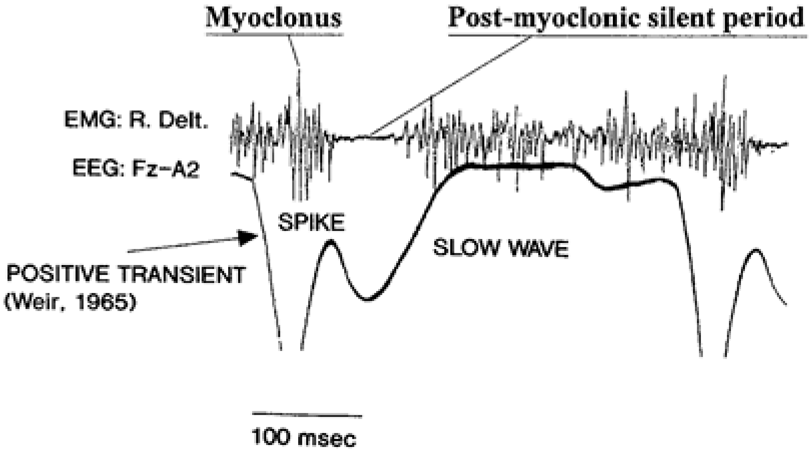

FIGURE 9. Electroencephalographic (EEG)/electromyo-graphic (EMG) correlation on oscilloscope of the spike-and-wave complex and associated muscular events in myoclonic absences. The myoclonic potential is associated with a positive transient preceding the spike and is followed by a postmyoclonic EMG silent period. R. Delt., right deltoid.

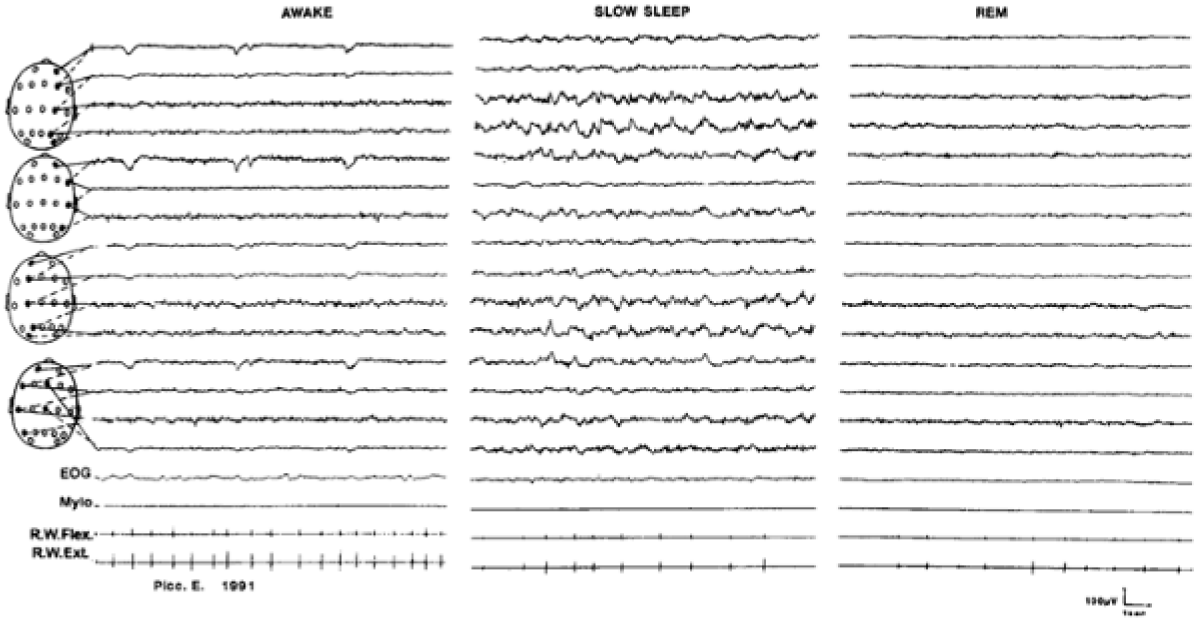

FIGURE 10. Rhythmic contractions of the right upper limb in a case of epilepsia partialis continua. No evident electroencephalographic activity was correlated with the myoclonic jerks. Note the persistence of myoclonia, although with some modulation of frequency, during sleep. EOG, electrooculogram; Mylo, mylohyoideus; R.W. Ext., right wrist extensor; R.W. Flex, right wrist flexor; REM, rapid eye movement.

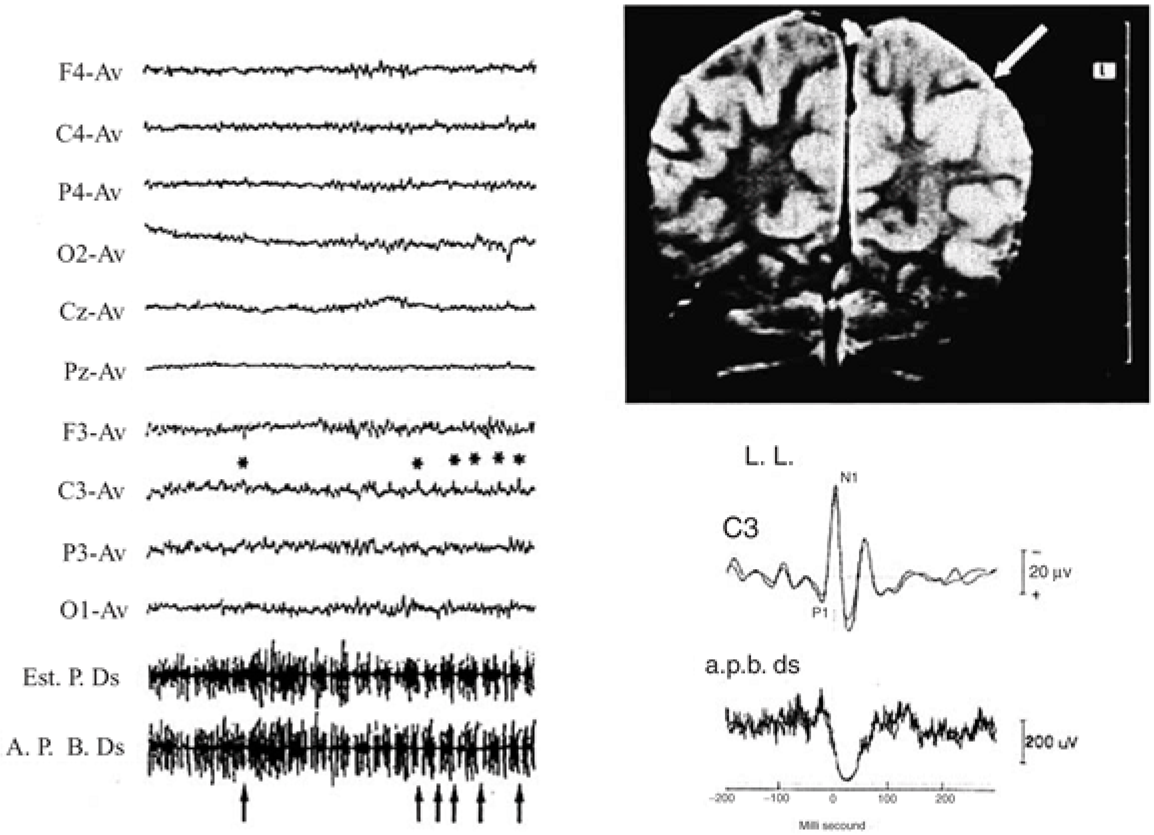
F4-Av
C4-Av
P4-Av
O2-Av
Cz-Av
Pz-Av
F3-Av
C3-Av
P3-Av
O1-Av
Est. P. Ds
A. P. B. Ds
L
L. L.
N1
C3
P1
20 µv
a.p.b. ds
200 uV
−200
−100
0
100
200
Milli secound

FIGURE 11. Left: Subcontinuous epileptic negative myoclonia (*arrows*) in the right wrist extensor (Est.P.Ds) and right abductor pollicis brevis (A.P.B.Ds) associated with small-amplitude spikes (*asterisks*) in the left central region in a patient with focal epilepsy associated with left parietal focal cortical dysplasia (indicated by the arrow in the magnetic resonance image shown in the right upper panel). **Lower Right:** Average of the C3 spikes triggered at the peak of the spike and rectified electromyogram (EMG) of the right abductor pollicis brevis (a.b.p. ds). No positive myoclonia precedes the onset of the brief EMG silent period associated with the C3 spike.

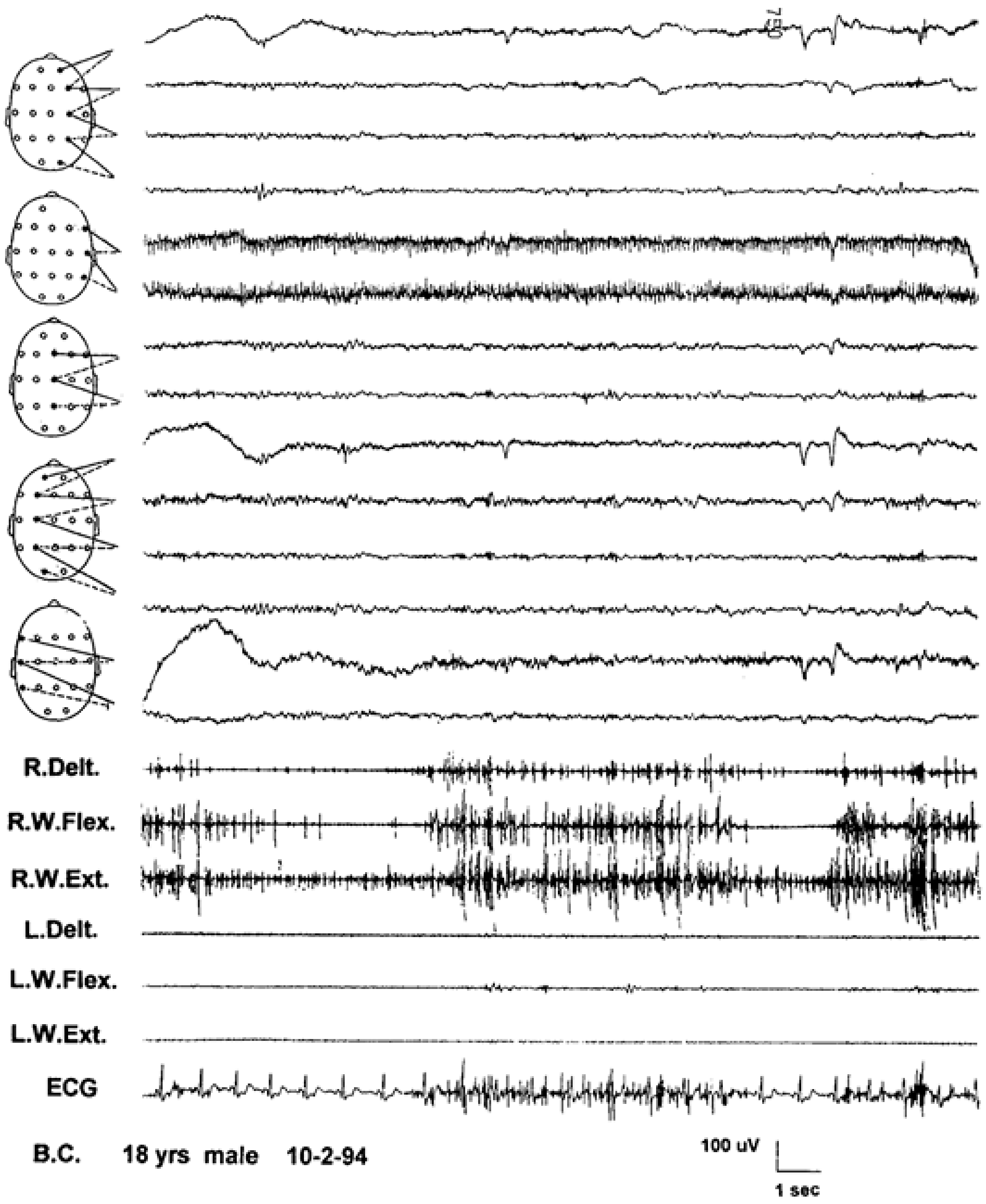

FIGURE 12. Action myoclonus in the right upper limb of a patient with progressive myoclonus epilepsy. The patient was asked to touch with his right index finger the tip of the index finger of the examiner. Muscular contraction in the right arm is fragmented by myoclonic potentials, intermixed with brief silent periods. No evident electroencephalographic modifications were associated. L. Delt., left deltoid; L.W. Ext., left wrist extensor; L.W. Flex., left wrist flexor; ECG, electroencephalogram; R.Delt. right deltoid; R.W. Ext., right wrist extensor; R.W. Flex., right wrist flexor.

Epilepsia Partialis Continua

In cases of epilepsia partialis continua, polygraphic study allows the analysis of the rhythm, intensity, rate, and distribution of the muscle jerks.[127] Myoclonic EMG potentials can be associated on the EEG with slow focal abnormalities, focal paroxysmal discharges, or no evident paroxysmal activity (Fig. 10) (see Chapters 61 and 243).

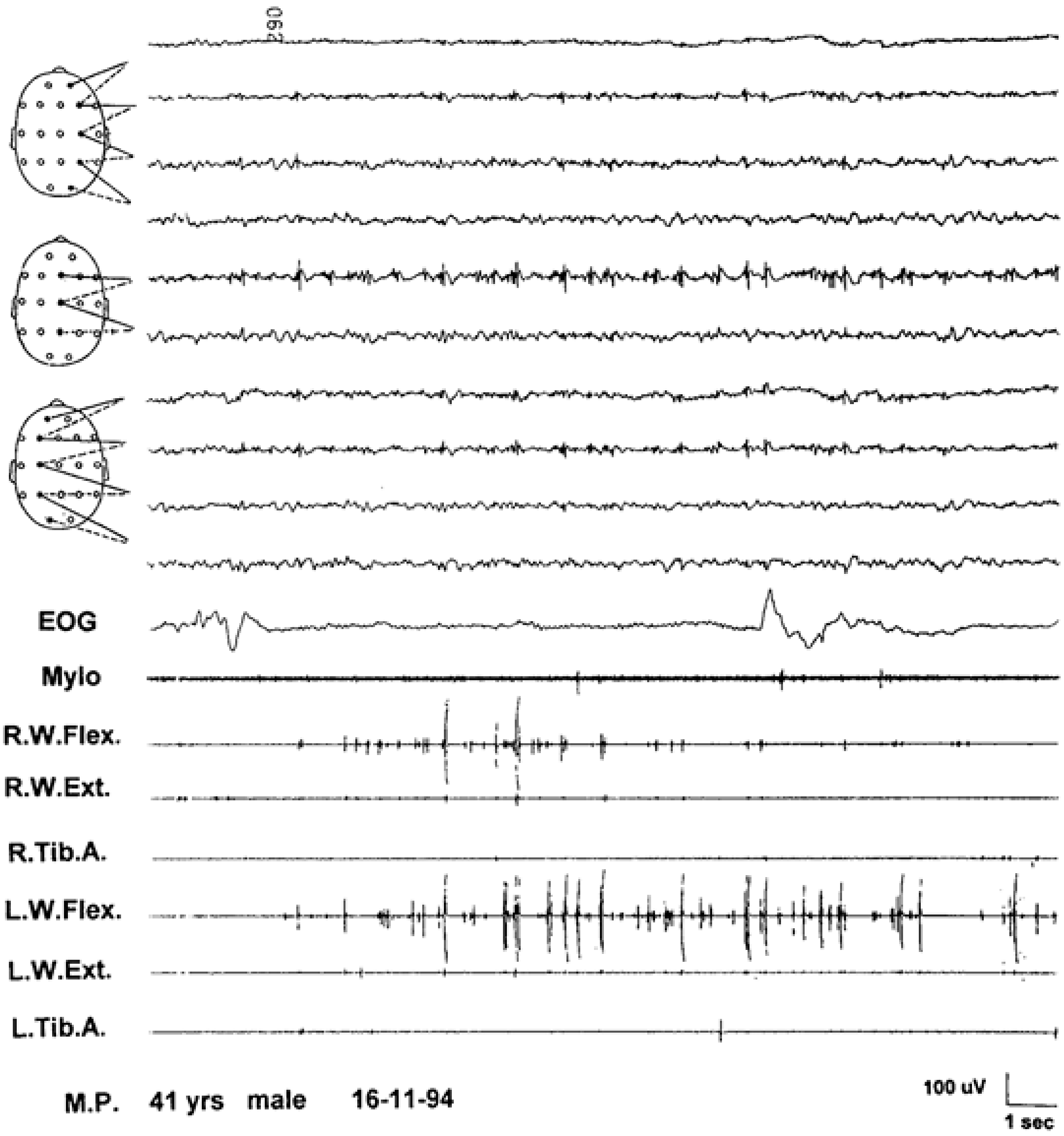

FIGURE 13. Polygraphic recording during rapid-eye-movement (REM) sleep in a patient with Unverricht-Lundborg disease. The tracing is characterized by fast spikes at the vertex, diffusing to parasagittal regions, and abundant, erratic myoclonic jerks, inconstantly related to the vertex spikes. EOG, electrooculogram; L.W. Ext., left wrist extensor; L.W. Flex, left wrist flexor; L. Tib. A., left tibialis anterior; Mylo, mylohyoideus; R.W. Ext., right wrist extensor; R.W. Flex, right wrist flexor; R. Tib. A., right tibialis anterior.

Epileptic Negative Myoclonus

Some patients with epilepsy can present with a clinical picture resembling epilepsia partialis continua, characterized by frequent, subcontinuous jerks, evident when the patient maintains a posture, or by a tonic contraction (Fig. 11). Polygraphic recordings can be crucial in defining the exact nature of this motor disorder, which can be caused by subcontinuous epileptic negative myoclonia (i.e., brief lapses of the muscular activity time-locked to paroxysmal EEG activity).[48,106,122] In epileptic negative myoclonus, the interruption of the muscular activity occurs synchronously on agonist and antagonist muscles; when epileptic negative myoclonus is focal, involving one or both limbs on the same side of the body, it is usually associated

with a contralateral EEG spike located in the centroparietal region. Epileptic negative myoclonus can be found in a wide spectrum of epileptic conditions—idiopathic, cryptogenic, and symptomatic (see also Chapter 277).[122]

Progressive Myoclonic Epilepsies

The polygraphic features of progressive myoclonus epilepsies, such as Unverricht-Lundborg disease, consist of constantly present action myoclonus, characterized by high-amplitude EMG potentials of short duration (20 to 30 msec), which are synchronous on agonist and antagonist muscles. These are followed by an EMG-silent period lasting 40 to 120 msec (rarely up to 300 msec) **(**Fig. 12). The myoclonic bursts and the silent periods are inconstantly related to EEG spike-and-waves and polyspike-and-waves.[113] Myoclonic seizures in Unverricht-Lundborg patients are characterized by generalized myoclonia, predominant proximally in the upper limbs, with varying rhythm and associated with generalized, symmetric polyspikes or polyspike-and-waves. Lafora disease is characterized polygraphically by the presence of abundant, asymmetric, asynchronous, subtle myoclonia at rest, diffuse to all muscular groups, usually without an EEG correlate.[81,110] In the progressive myoclonus epilepsies, intermittent photic stimulation is very effective in eliciting fast polyspikes and polyspike-and-waves associated with massive myoclonic jerks (see also Chapter 252).[81,112]

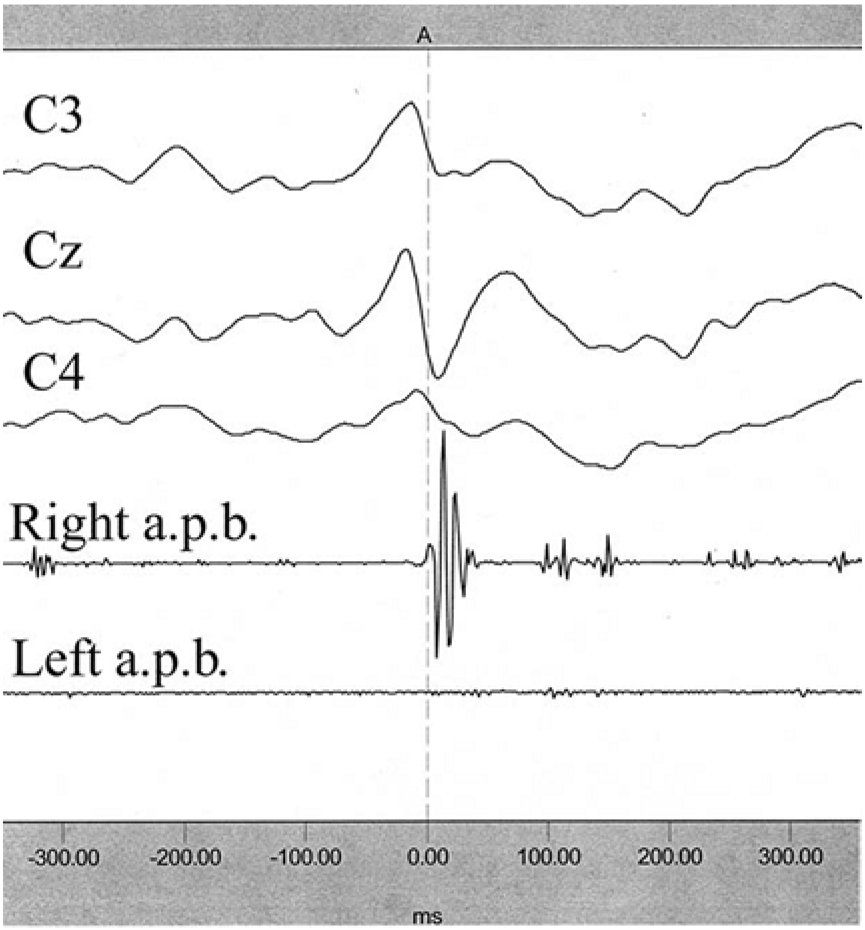

FIGURE 14. A patient with Lafora disease. Jerk-locked averaging triggered from the onset of the myoclonic potential in the right abductor pollicis brevis (Right a.p.b.) showing a premyoclonic electroencephalographic potential in the left central region and on the vertex (number of averaged myoclonia = 125). Left a.p.b., left abductor pollicis brevis.

Evolution of Motor Manifestations in Relation to Sleep–Wake Cycle

Epileptic manifestations are entrained to the sleep–wake cycle in a consistent number of epileptic conditions (see Chapters 187 and 188). Accordingly, epileptic motor phenomena can show modifications in the transition from wakefulness to sleep. Photosensitivity and light-induced myoclonus are decreased in non-REM sleep,[23,69,80] whereas discordant results—perhaps due to differences in medications and stimulation procedures and indicating either a decrement or an increment of

photosensitivity-related myoclonus in REM sleep—have been reported.[23,52,69,90,135]

Lennox-Gastaut Syndrome

In patients presenting with Lennox-Gastaut syndrome (see Chapter 241),[41] nocturnal tonic seizures can recur so frequently during non-REM sleep that they produce a tonic status epilepticus, which is characterized polygraphically by a progressive attenuation of tonic motor manifestations, paralleled by a worsening of the vegetative parameters and by an impairment of consciousness between seizures. The situation can deteriorate into a coma-like state, with autonomic derangement and mild motor phenomena, such as raising of the hands and slow eye movements. An adequate polygraphic monitoring can be of utmost importance for the diagnosis and treatment of such a condition. Patients with Lennox-Gastaut syndrome can also show minor nocturnal seizures, which are associated with eye-opening spells, head nodding, and changes in cardiac and respiratory rate. Sometimes these seizures are uncovered only by means of polygraphic recording, represented by generalized polyspikes, fast recruiting rhythms, or slow spike-and-wave discharges.[4,19] A disruption of sleep architecture has been reported in patients with Lennox-Gastaut syndrome.[1,4]

Epilepsia Partialis Continua

Polygraphic studies during sleep have demonstrated modifications of myoclonic phenomena in different pathologic conditions. Epilepsia partialis continua is usually characterized by the persistence of focal myoclonic jerks, which modulate only in intensity and frequency, across all sleep stages (see Fig. 10).[65]

Unverricht-Lundborg Disease

In Unverricht-Lundborg disease, sleep studies demonstrate (a) lack of activation of generalized paroxysmal discharges and (b) appearance of focal multiple fast spikes occurring in repetitive bursts, localized over the midline and centroparietal regions, and occurring more frequently during REM sleep, particularly when eye movements are abundant. These fast spikes can be time-locked to myoclonic jerks, particularly in those muscles that show a striking action myoclonus during wakefulness (Fig. 13).[111,113,120]

Lafora Disease

In Lafora disease, sleep organization is extremely altered, with the different stages barely recognizable: paroxysmal activity does not seem to increase during sleep; diffuse multiple fast spikes show variable amplitude and topography and can be intermixed with fast activity, and posterior spikes persist during slow sleep and can show an enhancement during REM sleep.[112,120]

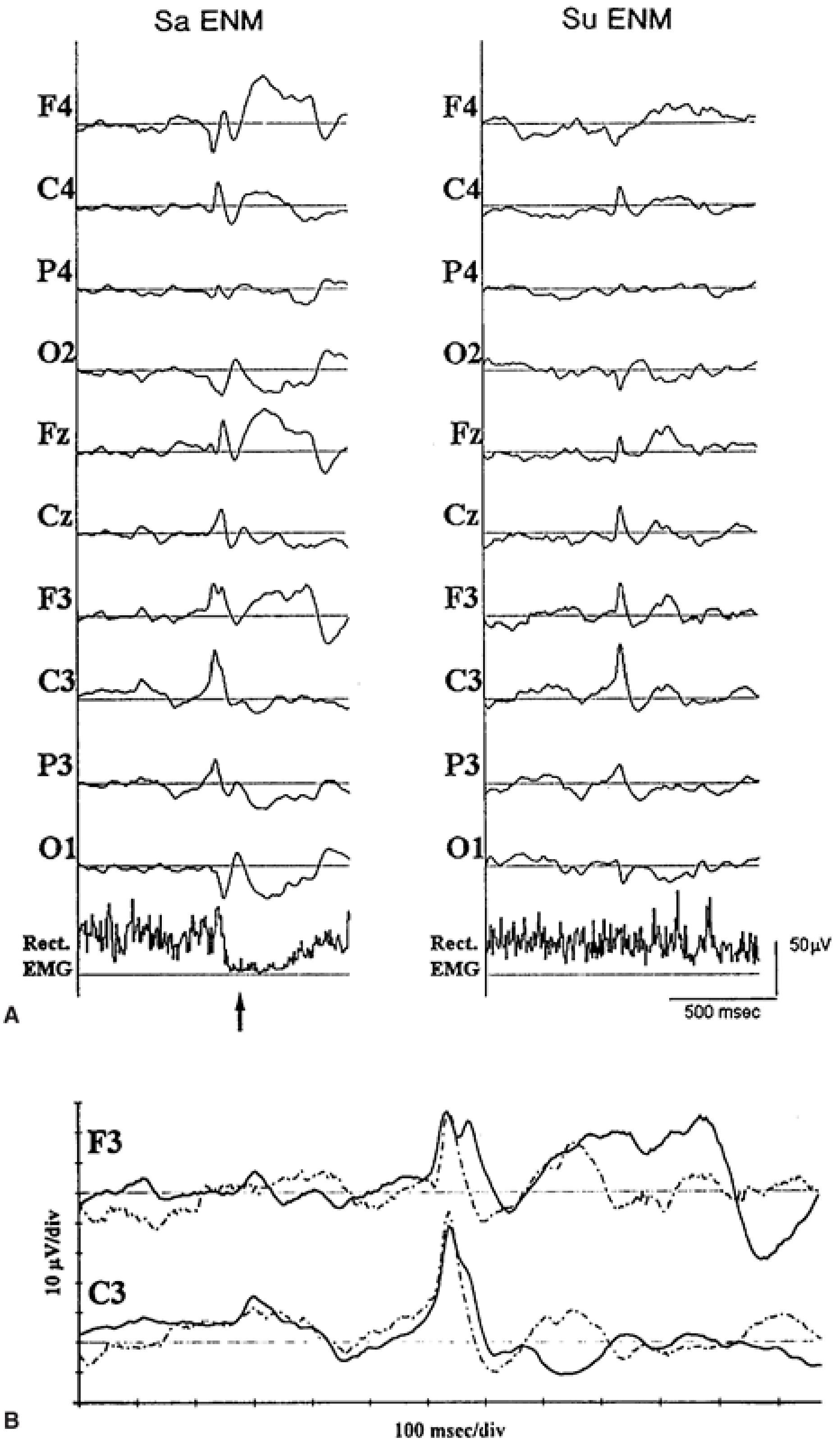

FIGURE 15. Digital electroencephalographic (EEG)/electromyographic (EMG) recording in a patient with epileptic negative myoclonus in the right upper limb. **A:** On the left, averaged spikes ($n = 25$) associated with epileptic negative myoclonus (Sa ENM); on the right, averaged spikes ($n = 22$) unrelated to epileptic negative myoclonus (Su ENM). The bottom channel shows rectified EMG activity of the right wrist extensor. Epileptic negative myoclonus appears as a brief flattening of EMG activity (*arrow*). **B:** Superposition of averaged Sa ENM (*solid line*) and of averaged Su ENM (*broken line*) at F3 and C3. Note the presence in Sa ENM of a “double spike” in F3 due to a frontal component related to the occurrence

of epileptic negative myoclonus absent in Su ENM. Negative is up. Average potential reference montage. (From Rubboli G, Parmeggiani L, Tassinari CA. Frontal inhibitory spike component associated with epileptic negative myoclonus. *Electroencephalogr Clin Neurophysiol*. 1995;95:201–205, with permission.)

Myoclonic Encephalopathies

Myoclonic encephalopathies can be properly investigated by means of sleep polygraphy to detect myoclonus during sleep when other associated abnormal movements that occur in wakefulness disappear.[27] In patients presenting with myo-clonic epilepsy with ragged red fibers (MERRF), sleep polygraphic studies showed the occurrence of vertex and central spikes, absence of physiologic EEG elements of stage II sleep, and persistence of generalized paroxysmal activity as in wakefulness.[82] Sleep polygraphic investigations can be relevant in the study of aminoacidopathies, in which multifocal paroxysmal abnormalities and suppression burst patterns are inapparent during wakefulness but are unveiled by sleep.

Computer-Assisted Analysis of Polygraphic Signals

The introduction of computerized techniques has provided new tools for the analysis of polygraphic data. The main field of application in epilepsy has been the simultaneous collection and processing of EEG and EMG signals. This allows for detection of cortical correlates associated with muscular phenomena not identifiable with standard polygraphic techniques and for more precise determination and quantification of the temporal relation between cortical and muscular phenomena.

Jerk-Locked Averaging

One such technique, a computerized EEG averaging technique called *jerk-locked averaging*, was applied to polygraphic data by Shibasaki and Kuroiwa.[95] Jerk-locked averaging is triggered by an EMG pulse, which is represented by a myoclonic potential, and permits cortical correlates associated with muscular events to be extracted from background EEG activity (Fig. 14). This allows different types of myoclonus to be characterized in terms of presence or absence of a cortical correlate and according to the latency between the cortical correlate and the myoclonic jerk.[96,97]

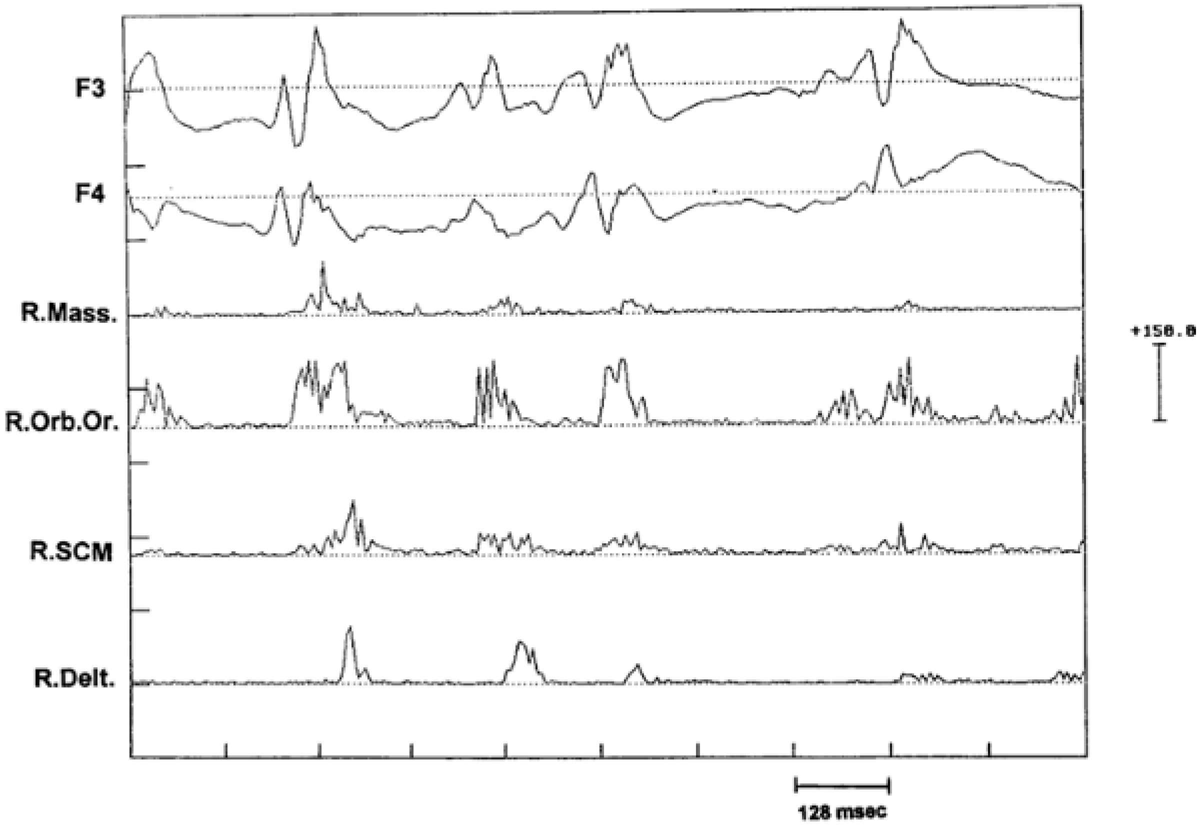

FIGURE 16. Single sweep (1,280 msec) of prolonged computerized electroencephalographic (EEG)/electromyographic (EMG) recording showing myoclonic potentials associated with a spike-and-wave discharge. Each spike-and-wave complex is associated with a myoclonic contraction. Note the sequential activation of the right orbicularis oris, followed by the right masseter, the right sternocleidomastoideus, and the right deltoid, in each myoclonic jerk. EEG activity is recorded with average potential reference. EMG activity is rectified. Negative is down. R.Delt., right deltoid; R.Mass., right masseter; R.Orb.Or., right orbicular oris; R.SCM., right sternocleidomastoideus.

Silent-Period Locked Averaging

A similar technique, triggered not by a myoclonic jerk but by the onset of an EMG silent period on a background of a tonic contraction, was introduced by Ugawa et al.[130] Known as *silent-period locked averaging*, this technique allows different types of negative myoclonus, including asterixis, to be identified and associated with cortical events.

Spike Averaging

Spike activity associated with different muscular events can be investigated by means of EEG computerized systems with an extra channel for polygraphic signals and displaying the topographic distribution over the scalp of the EMG related-cortical potentials. These techniques have been adopted to investigate paroxysmal activities associated with epileptic negative myoclonus.[57,88] Through the finding of a frontal spike component that suggests the involvement of inhibitory frontal areas in the generation of negative motor phenomena (as subsequently demonstrated by intracerebral electrical stimulation[86]), spike-averaging procedures have demonstrated that spikes associated with epileptic negative myoclonus differ from spikes without epileptic negative myoclonus (Fig. 15).[88]

Quantitative Analysis of Electromyography

A quantitative analysis of EMG signals can be performed by rectification and integration of EMG wave forms.

These techniques allow the area between the EMG tracing and the baseline to be calculated. The area varies according to modification of amplitude, frequency, and duration of the potentials, which provides a quantification of EMG activity.

Multichannel Electromyography

Multichannel computerized EMG recordings with only a few EEG channels can analyze the pattern of sequential activation of different muscular groups that participate in a sudden motor event (i.e., a massive myoclonic jerk) (Fig. 16) or in the complex motor manifestations characterizing focal seizures involving motor areas[67] (Fig. 17). Analysis of the temporal sequence of the onset of contraction in different cranial and limb muscles has allowed a distinction to be proposed between cortical and reticular myoclonus.[50,51,85]

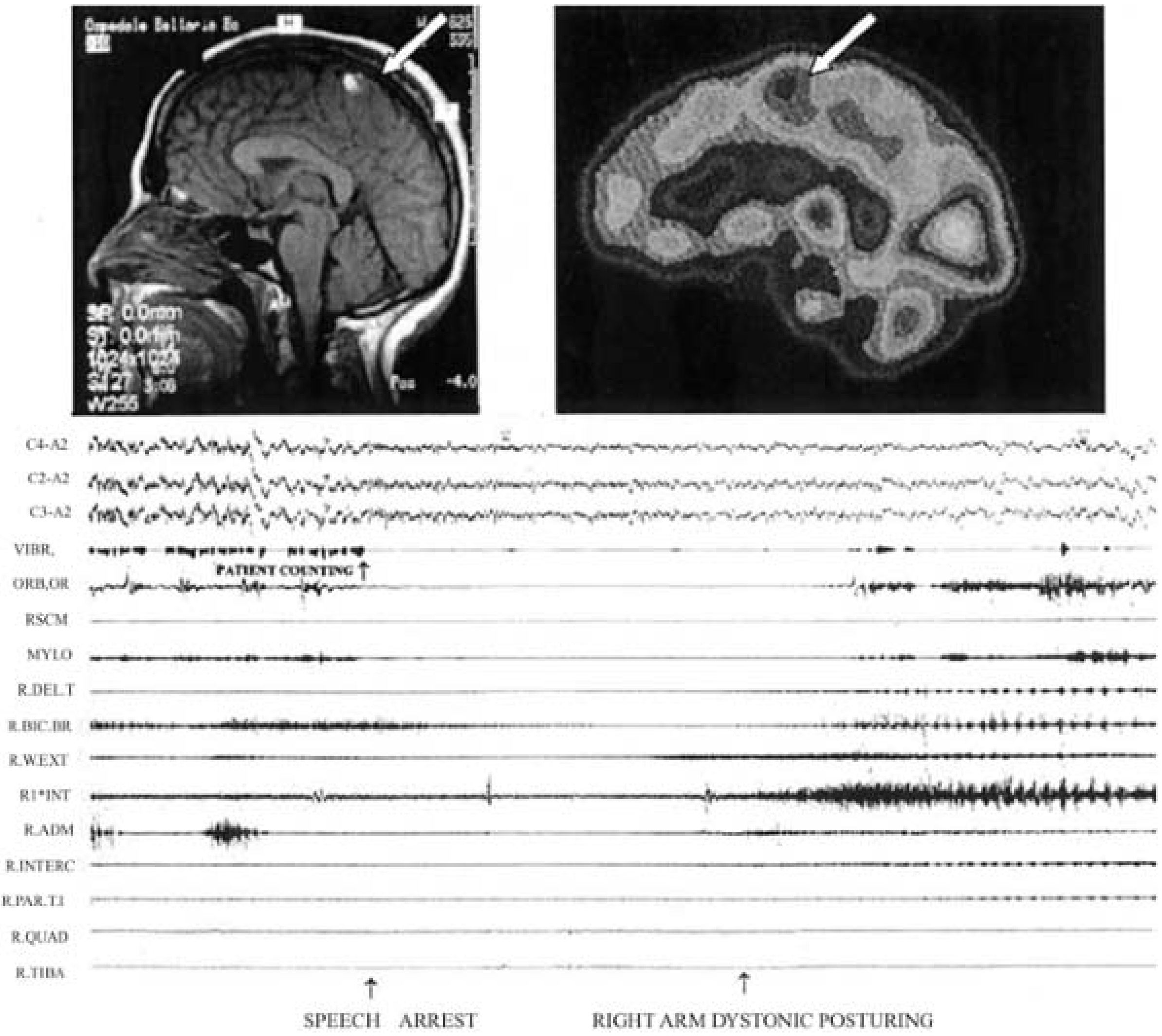

FIGURE 17. Polygraphic recording of a focal seizure originating from the left frontomesial region in a patient with left frontomesial neoplasia (indicated by the arrow in the magnetic resonance image in the left upper panel). Ictal single-photon emission computed tomography showed focal hyperperfusion in the mesial aspect of the frontal lobe just anterior to the neoplastic lesion (*right upper panel*). Polygraphic recording showed, as soon as the electroencephalographic activity at the vertex and central leads was modified by the paroxysmal discharge, a speech arrest (the patient stopped counting aloud) and muscular inhibition in all the electromyographic channels, suggesting early involvement of frontomesial "negative" motor areas. Then a tonic contraction (evident in the right wrist extensor and first interosseus muscles) associated with a dystonic posturing of the right arm appeared, followed by clonic contractions in the right upper limb and trunk muscle.

1st INT, first interosseus; ADM, abductor digiti minimi; BIC.BR, biceps brachii; DELT, deltoid; INTERC, intercostalis; MYLO, mylohyoideus; ORB.OR., orbicularis oris; PAR.T-L, m. paraspinalis at the thoracolumbar level; QUAD, quadriceps; R., right; SCM, sternocleidomastoideus; TIB.A, tibialis anterior; VIBR., microphone; W.EXT, wrist extensor. (Courtesy of Dr. S. Meletti.)

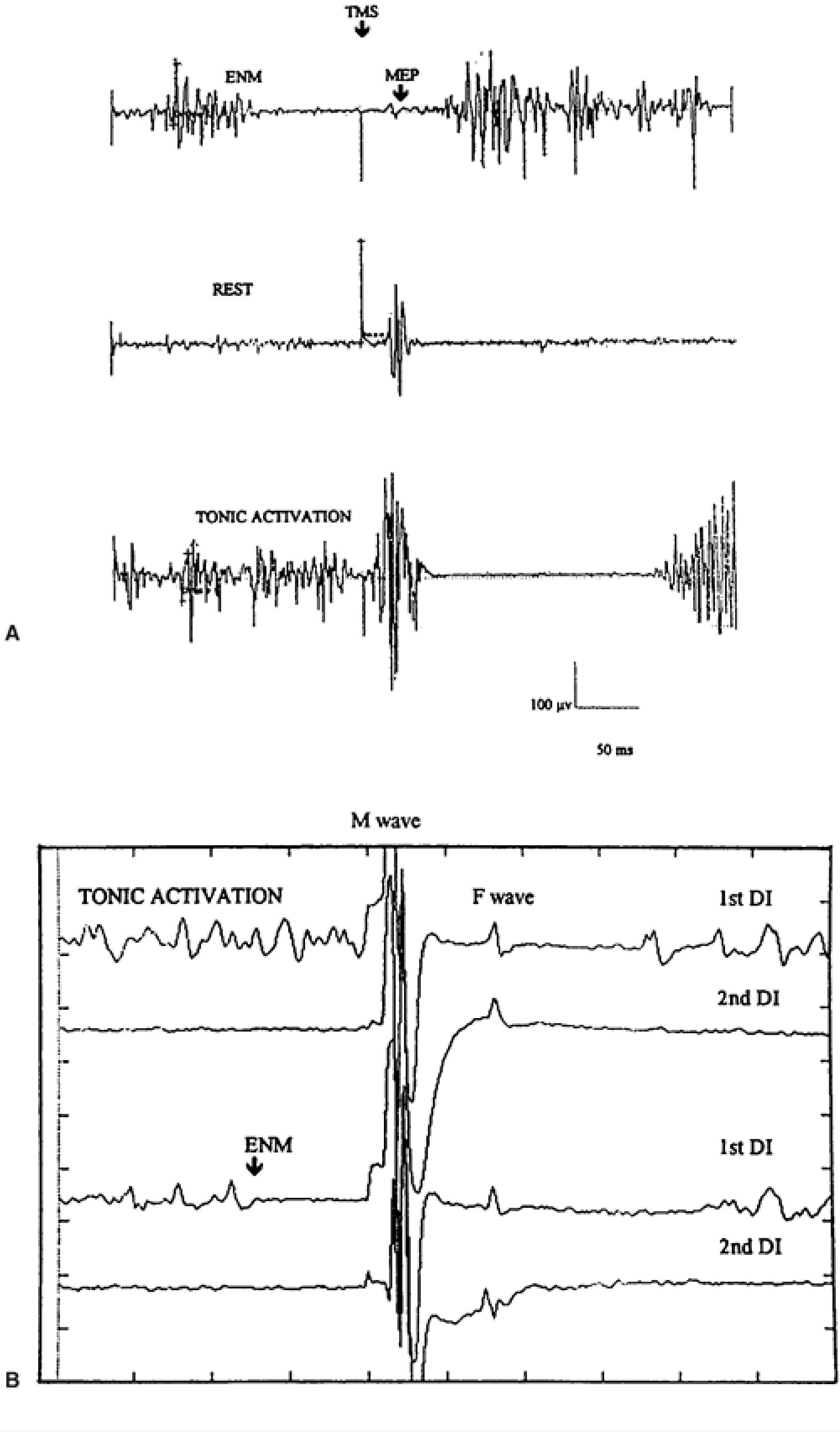

FIGURE 18. A: Cortical excitability during epileptic negative myoclonus (ENM) assessed by transcranial magnetic stimulation (TMS). During ENM, motor-evoked potentials (MEPS) were consistently depressed as compared with rest and tonic activation conditions. **B:** Spinal excitability during ENM evaluated by F-wave study. The upper pair of traces show M response and F wave during tonic activation, recording from the first and second dorsal interosseus (DI); the lower pair of traces demonstrate preservation of F wave during the EMG silent period of ENM, suggesting an unaltered spinal excitability. (From Tassinari CA, Rubboli G, Parmeggiani L, et al. Epileptic negative myoclonus. In: Fahn S, Hallett M, Marsden CD, eds. *Negative Motor Phenomena. Advances in Neurology*, vol. 67. New York: Raven Press; 1995:181–197, with permission.)

Combination Recordings

Investigations on the modulation of the motor system during ictal and interictal paroxysmal discharges can be performed by combining polygraphic recordings with techniques able to assess cortical (e.g., transcranial magnetic stimulation) and spinal (e.g., H reflex, stretch reflex, F wave) excitability. During epileptic negative myoclonus, an inability of transcranial magnetic stimulation to evoke a motor response, associated with the preservation of the F wave, suggests a cortical origin for this motor disorder (Fig. 18).[122] In patients with severe partial epilepsies and falling seizures, H-reflex and motor-evoked potentials are unmodified during slow spike-and-wave complexes, whereas they appear to increase during subclinical fast polyspike discharges. A similar facilitation can be observed at the beginning of tonic seizures, when the EMG is silent. During the ensuing tonic contraction, H-reflex and motor-evoked potentials are further enhanced, decreasing consistently only in the postictal phase. In contrast, 3-c/s spike-and-wave discharges of typical absences or evoked by intermittent photic stimulation do not alter motor-evoked potentials or the stretch reflex.[124]

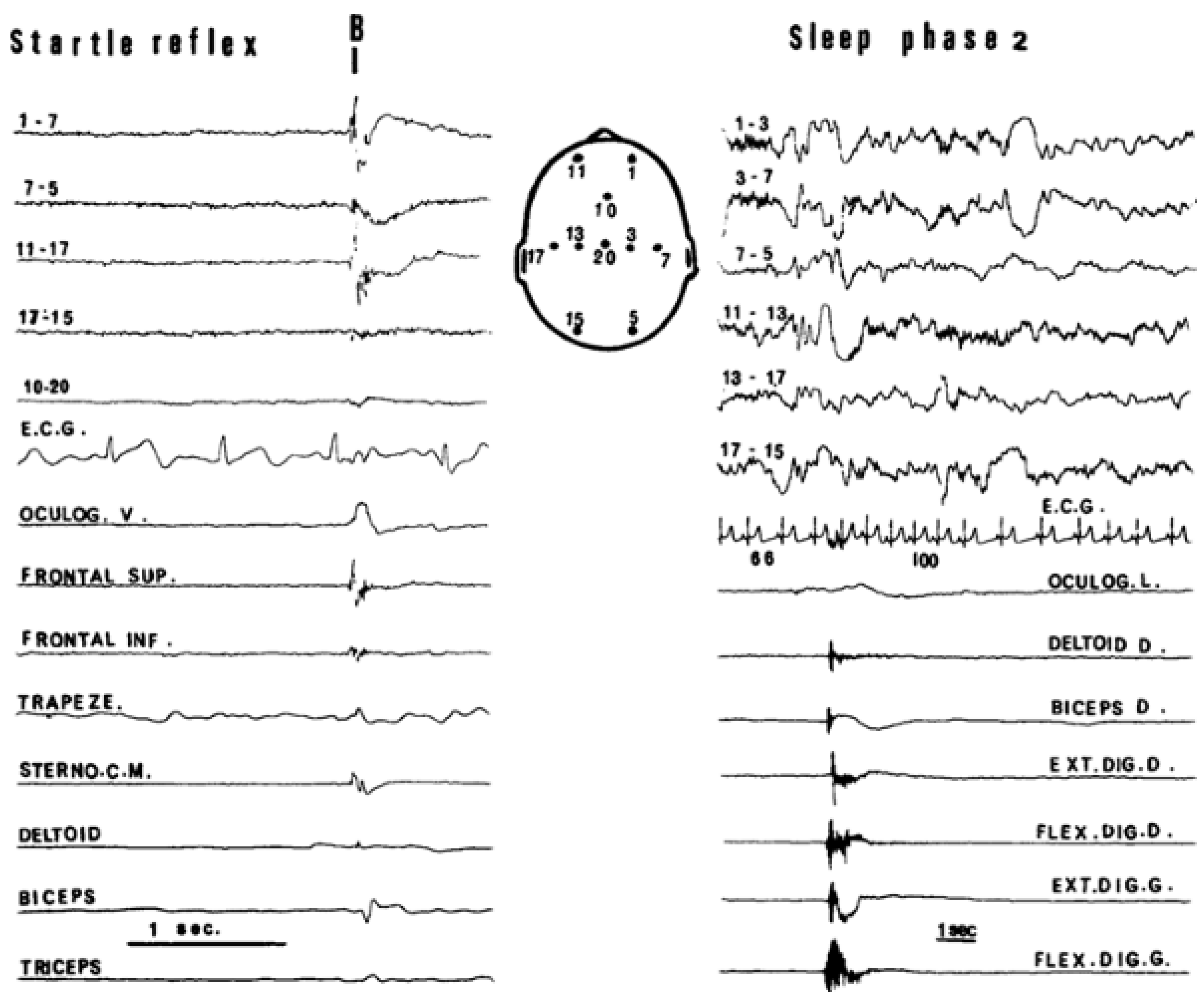

FIGURE 19. Left: Physiologic startle response during wakefulness; B indicates a sudden loud noise. **Right:** Spontaneous startle during sleep. Both tracings were recorded in a normal individual. Note the simultaneous activation of all muscles recorded without electroencephalographic (EEG) correlate. BICEPS D., right biceps; DELTOID D., right deltoid; E.C.G., electrocardiogram; EXT. DIG. D and G., right and left extensor digitorum, respectively; FLEX. DIG. D. and L., right and left flexor digitorum, respectively; FRONTAL INF., inferior frontal muscle; FRONTAL SUP., superior frontal muscle; OCULOG. L., lateral oculogram; OCULOG. V., vertical oculogram; STERNO.C.M., sternocleidomastoideus; TRAPEZE., trapezius.

Polygraphic Investigations in the Study of Reflex Epilepsy

In reflex epilepsies, seizures are elicited by some specific stimuli or events (see Chapter 257).[6,68,121] Polygraphy can be useful in defining the stimulating factor and documenting the correlation between the triggering condition and the seizure. Arseni et al.[3] documented the role of proprioceptive stimuli in eliciting and blocking convulsive seizures. Scollo-Lavizzari and Tassinari[91] provided polygraphic evidence in one patient of simple partial motor seizures involving body parts that had been actively or passively moved. Polygraphy can be a useful aid in discriminating between movement-induced seizures and attacks of paroxysmal choreoathetosis and in proving the nonepileptic nature of a startle response (Fig. 19).[76,79] Polygraphy has also documented seizures related to the act of eating a meal and characterized by occurrence of myoclonic jerks or head drops.[21,32]

Tassinari et al.[124] presented a polygraphic demonstration of the mechanism of induction of seizures by hand waving in a patient with self-induced seizures. In this patient, the intermittent light stimulation resulting from the rhythmic movement of the hand in front of the eyes elicited a bilateral spike-and-wave discharge. Photic reflex myoclonus in progressive myoclonus epilepsies has been investigated with jerk-locked averaging techniques applied to computerized polygraphic recordings showing the combined participation of the visual and motor cortex in the genesis of this type of reflex myoclonus.[87,96]

The occurrence of extreme somatosensory-evoked potentials following tapping of the extremities of the four limbs has been reported[116]; polygraphic recordings, including a marker channel reporting the tapping artifact, allow observation of the correlation between the tactile stimulus and the cortical spike.

Polygraphy as an Aid in the Differential Diagnosis of Epileptic and Nonepileptic Episodes

Recurrent and transitory episodes of cerebral disturbance are not necessarily epileptic. Definition and characterization of the episodes by means of polygraphic techniques can help to determine the etiology and pose the correct diagnosis. Two main groups of episodes can mimic epileptic seizures: (a) episodes of syncopal or cardiac nature and (b) pseudoseizures.

Syncope and Cardiac Dysrhythmia

Because syncope and epileptic seizures can share some common characteristics (e.g., loss of consciousness, dilation of pupils, opisthotonus, clonic jerking, salivation, incontinence),[35,39] clinical description alone is inadequate in identifying the correct etiology. Polygraphic studies with simultaneous recording of EEG and ECG, therefore, can be helpful for differential diagnosis.[35] Twenty-four-hour ambulatory recording systems that can monitor EEG and ECG activity in unrestrained conditions can be extremely effective in demonstrating the cardiac nature of syncopal episodes (Fig. 20).[14,30,62]

Because of the longer duration of EEG recording, ECG monitoring during EEG recording has a higher probability of detecting cardiac abnormalities than does routine ECG.[31] Monitoring of ECG during EEG recording, therefore, should be encouraged in a routine setting. If an altered ECG is found, episodic cerebral symptoms due to cardiac arrhythmia can be suspected. However, because cardiac arrhythmia can represent a secondary event associated with epileptic seizures, the finding does not necessarily imply that the patient suffers from syncope rather than epilepsy.[129] It should also be remembered that when prolonged ECG monitoring is performed, there is a relatively high incidence of cardiac dysrhythmia in an asymptomatic population.[22]

Ambulatory cassette EEG/ECG systems can allow the investigation of the instant heart rate by measurement of the R-R interval during spontaneous seizures. Smith et al.[100] observed impressive seizure-to-seizure similarities in heart rate profiles when multiple partial seizures were recorded. In long-duration records, identification of heart rate profile changes could be useful in detecting seizures that are either not indicated by the event marker or not accompanied by overt EEG modifications. Analysis of the ECG tracing in the polygraphic recording and its modifications and correlations with EEG can be an important diagnostic aid in cases of Q-T interval prolongation,[47,105] Jervell and Lange-Nielsen syndrome,[93] and Romano-Ward syndrome.[83,136]

Pseudoseizures

Recognition of pseudoseizures has always been and continues to be a diagnostic challenge for epileptologists. A number of clinical features of pseudoepileptic and true epileptic (particularly complex partial) seizures are similar, rendering diagnosis based solely on clinical observation extremely difficult. Unequivocal documentation of EEG epileptic modifications associated with the episodes, therefore, is necessary. A normal routine EEG does not exclude epilepsy, nor does it confirm pseudoseizures. Although recording of a pseudoseizure during EEG can be crucial for the diagnosis, this is an infrequent occurrence. Therefore, diagnosis of pseudoseizures often requires intensive monitoring. Ambulatory cassette EEG can allow for prolonged recording in the patient's environment and quantification of the episodes.[78] However, several drawbacks (e.g., reduced spatial sampling over the scalp due to a limited number of channels, lack of patient and family cooperation, artifacts, or poor-quality recording) can render analysis of the recording unreliable.

Intensive monitoring with closed-circuit video-polygraphic systems can help in the differential diagnosis of pseudoseizures. Pseudoseizures usually last longer than do epileptic seizures, and alpha activity can persist throughout the episode.[63,92] Surface EMG channels show muscular activity corresponding to the gross and polymorphous movements that occur during pseudoseizures. Although true epileptic seizures can present bizarre and chaotic clinical manifestations as well, compared to pseudoseizures, they tend to show a more stereotyped clinico-polygraphic pattern. In the postictal phase, an immediate recovery of alpha activity and an abrupt arrest of the muscular artifacts are clues that the nature of the episode is nonepileptic. Simultaneous EEG/ECG recording, either during ambulatory cassette EEG or video-polygraphic monitoring, can provide additional helpful information. Whereas tachycardia or bradycardia can occur during epileptic seizures, only tachycardia has been reported in pseudoseizures.[92]

Polygraphic Monitoring of the Effects of Antiepileptic Drugs

Polygraphic monitoring can be useful when drugs are parenterally administered, especially during intravenous treatment for status epilepticus. Recording of EEG activity is necessary to evaluate the effectiveness of treatment and the rapidity and duration of its effect. Some drugs, such as benzodiazepines and phenytoin, require monitoring of vital functions when given by injection.

Because benzodiazepines have been reported to cause hypotension or respiratory depression, several authors,[7,17] recommend blood pressure and respiration monitoring during administration. However, these adverse effects are probably more likely to occur when benzodiazepines are given in conjunction with another central nervous system depressant or with concomitant organic cerebral damage.[115]

Another reason to use polygraphy with benzodiazepines is that the drug can uncover focal paroxysmal activities. Electroencephalographic recording after benzodiazepine administration, therefore, can provide information about the localization of the epileptic focus. Polygraphic recording is mandatory when benzodiazepines are injected to treat clusters of tonic seizures in patients with Lennox-Gastaut syndrome. A paradoxical effect consisting of precipitation of tonic status epilepticus has been reported following benzodiazepine injection.[11,117]

Intravenous administration of phenytoin requires monitoring of blood pressure, ECG, and respiration due to the possible occurrence of hypotension, heart block, and respiratory depression, especially when injected rapidly in elderly patients.[24,44] Polygraphy has also been used to document antimyoclonic effects of alcohol intake in patients with progressive myoclonic epilepsy.[45]

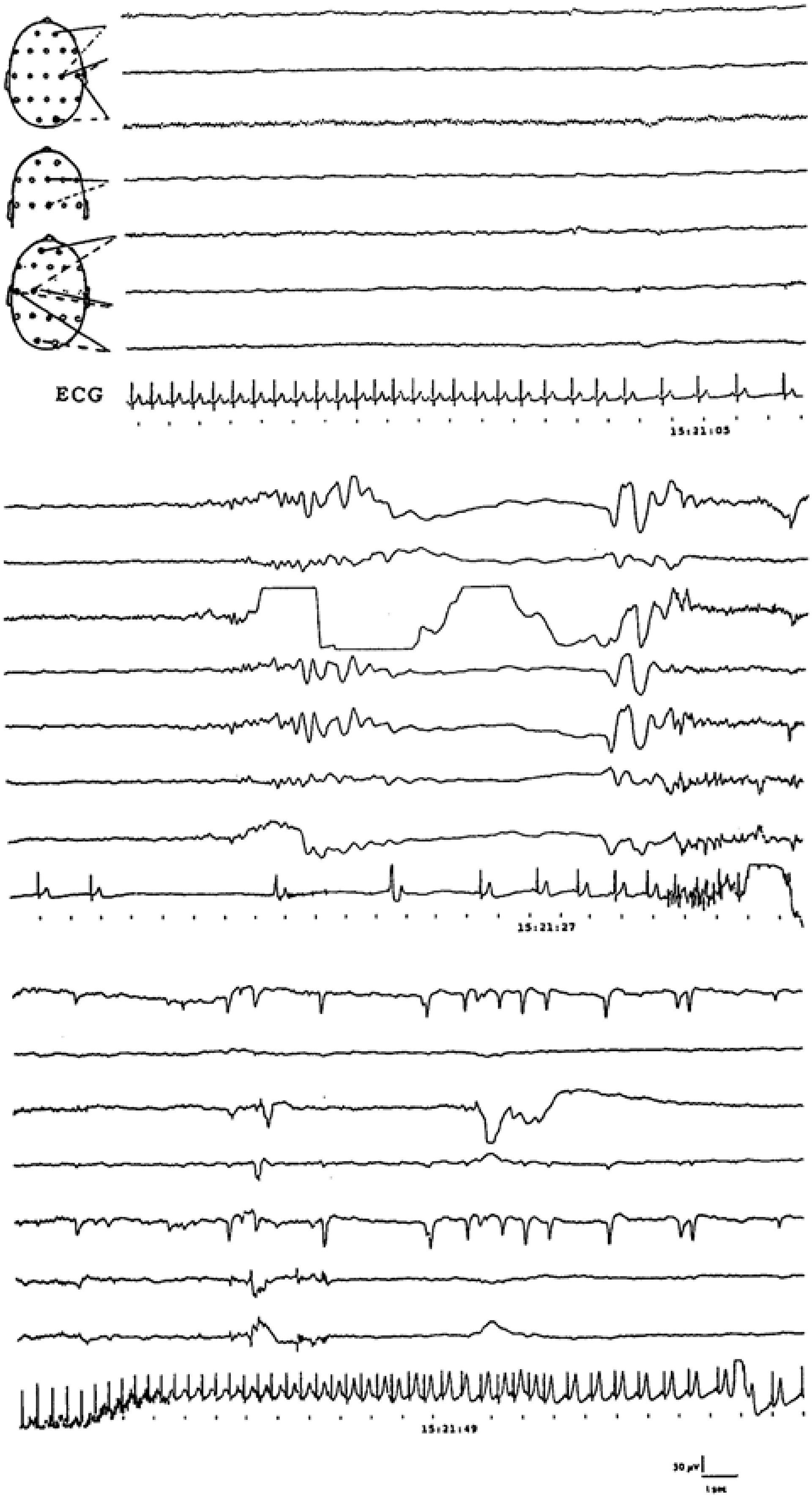
ECG
15:21:05
15:21:27
15:21:49
30 µV
1 sec

FIGURE 20. Ambulatory cassette electroencephalographic (EEG) /electrocardiographic (ECG) recording of a convulsive syncope during tilt test. **Upper:** A slowing of the heart rate begins (right). **Middle:** Heart

beats cease for a few seconds, followed by a flattening of the EEG activity and by movement artifacts due to massive jerks; then heart beats restart, and EEG alpha activity reappears. **Lower:** Tachycardia is evident a few seconds after resumption of cardiac activity.

Summary and Conclusions

Polygraphic recordings are essential tools in investigating physiologic parameters of epileptic phenomena and in providing relevant data for diagnostic and therapeutic purposes. Polygraphy is particularly useful in defining the various motor manifestations of different epileptic seizures and syndromes. Indeed, subtle motor phenomena—such as the diffuse myoclonia of Lafora disease that sometimes can be barely appreciable on clinical examination—can be detected only by polygraphy; their distribution can also be described. Complex motor patterns involving several muscular groups can be analyzed, and the existence of a stereotypic sequence of muscular activation can be investigated. It is possible, therefore, to describe not only "what moves first," but also "how it moves." In conditions such as epileptic negative myoclonus, polygraphy is essential to prove the effect of paroxysmal activity, demonstrating that an apparent "interictal" epileptic abnormality can actually be "ictal," depending on the state of the patient (relaxed or maintaining a muscular contraction) and on the methodology used to investigate the phenomenon (simultaneous EEG/EMG recording).

Rapid technologic progress will no doubt continue to provide new tools for collecting and processing different physiologic parameters, thereby increasing our ability to explore the relationships among distinct anatomic/functional systems during an epileptic event.

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Chapter 78

Electroencephalographic and Magnetoencephalographic Source Modeling

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Hermann Stefan

Christoph Baumgartner

Introduction

Many patients who suffer from medically uncontrolled partial seizures are candidates for epilepsy surgery. A significant rate-limiting factor in delivering this care is the evaluation necessary to determine whether the epileptogenic focus is localized to a resectable brain region. Significant additional delay, expense, and some morbidity are incurred if intracranial electroencephalographic (EEG) monitoring is necessary. Accordingly, there has been great emphasis recently on improving noninvasive presurgical localization of focal epileptic activity and functionally important cortical areas. Although various imaging techniques are now playing a significant role, we continue to rely on the analysis of interictal spikes and ictal patterns recorded by scalp EEG for functional localization. However, the information obtained in this regard from traditional visual inspection of the EEG has not changed much over the last 20 years. Localization is often limited to defining the electrode with greatest spike amplitude or clearest seizure pattern. These data have, at best, an imperfect relationship to the underlying cerebral source. Visual inspection of the EEG is, in fact, mainly used to lateralize the most epileptogenic area rather than to localize it. If our understanding of the clinical neurophysiology of epilepsy is to advance, we must go beyond simple description of EEG waveforms and pursue the physiology and location of the underlying generators. Visual inspection and qualitative impressions should be replaced by quantitative characterization. Among the noninvasive approaches, source localization techniques applied to epileptiform EEG potentials and magnetoencephalographic (MEG) fields appear to be particularly promising. This chapter reviews the principles behind and the clinical applications of EEG and MEG dipole and other source models.

Electroencephalographic Dipole Source Modeling

Principles of Voltage Topography

Neuronal excitation and inhibition are accompanied by current flow across the membrane of and through affected cells. From these, secondary currents and a voltage potential field are generated in the extracellular space. The orientation of an EEG voltage field is orthogonal to the surface of the generating cortex because it is aligned with the pyramidal cells that are thought to produce it. Most epileptiform transients are initially negative when recorded from electrodes on or above the cortical surface. Electrodes on the opposite side of the generating cortical layer, whether in underlying white matter or even on the scalp at the other side of the head, would record a positive potential. The scalp voltage fields that we measure, therefore, have dipolar configurations, that is to say, two maxima—one negative and one positive (Figs. 1 and 2). Thus, what a given electrode records is very dependent on the orientation as well as the location of the source relative to the sensor. In general, it is the complete contour of the spike voltage field over the head that provides information about the location and orientation of its cerebral generator.

Cerebral sources that generate epileptiform potentials that can be recorded at the scalp are quite large, usually consider-ably larger than the 6 cm^2 often quoted in the literature.[29] Recent measurements of simultaneous intracranial and scalp EEG have shown that cortical spike sources commonly encompass 10 to 30 cm^2 (Figs. 3 and 4).[34,36.161] Voltage fields from opposing walls of individual sulci tend to cancel each other, leaving the major lobar outline of gyral crowns to predominate in producing the net voltage field. Spike sources may recruit adjacent cortex into discharging. The net geometry of activated cortex becomes different at different times during the course of this propagating spike, which, in turn, produces a change in field maxima position or shape. Thus, temporal evolution of the scalp voltage field provides information about changes in source geometry due to sequential cortical activation or propagation (Figs. 2 and 4).

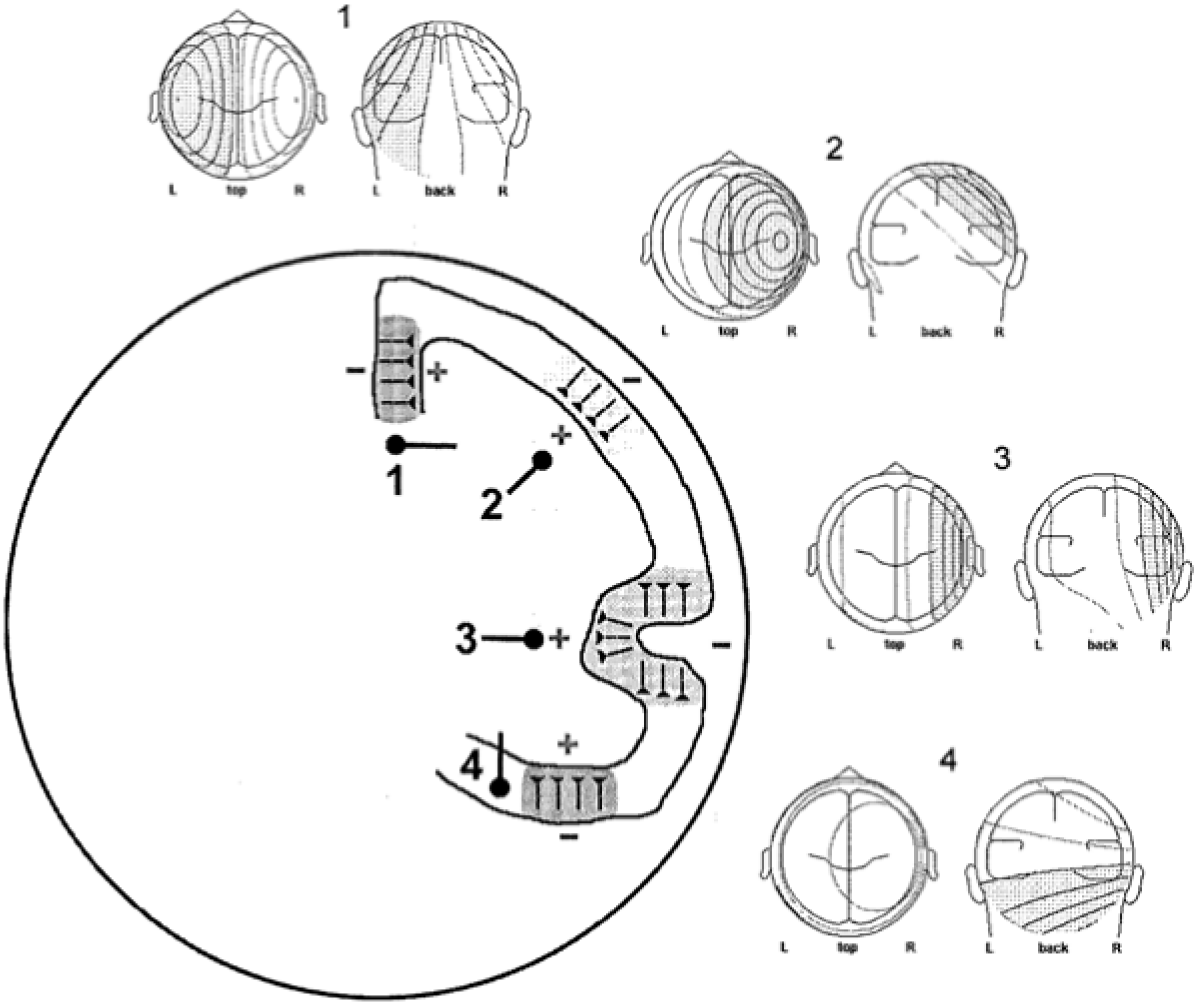

FIGURE 1. Example cortical sources 1–4 depicted in a schematic head/brain in coronal cross section. Typical pyramidal cell orientations are shown for each source. Resultant scalp voltage field topography for superficial laminar depolarization is displayed above each source as isopotential lines of field strength (*speckled*; negative; *clear*, positive). Typical dipoles modeling these sources are depicted beneath each source. Note that simple and more complex cortical convexity sources (1 and 2, respectively) produce radial fields with negative maxima directly above them and positive maxima contralaterally. Radial dipoles deep to the cortex model these sources. Interhemispheric source 3 and temporal base source 4 produce tangential fields with negative and positive maxima displaced on either side of the source and essentially no potential directly above them. Tangential dipoles deep to the cortex model these sources.

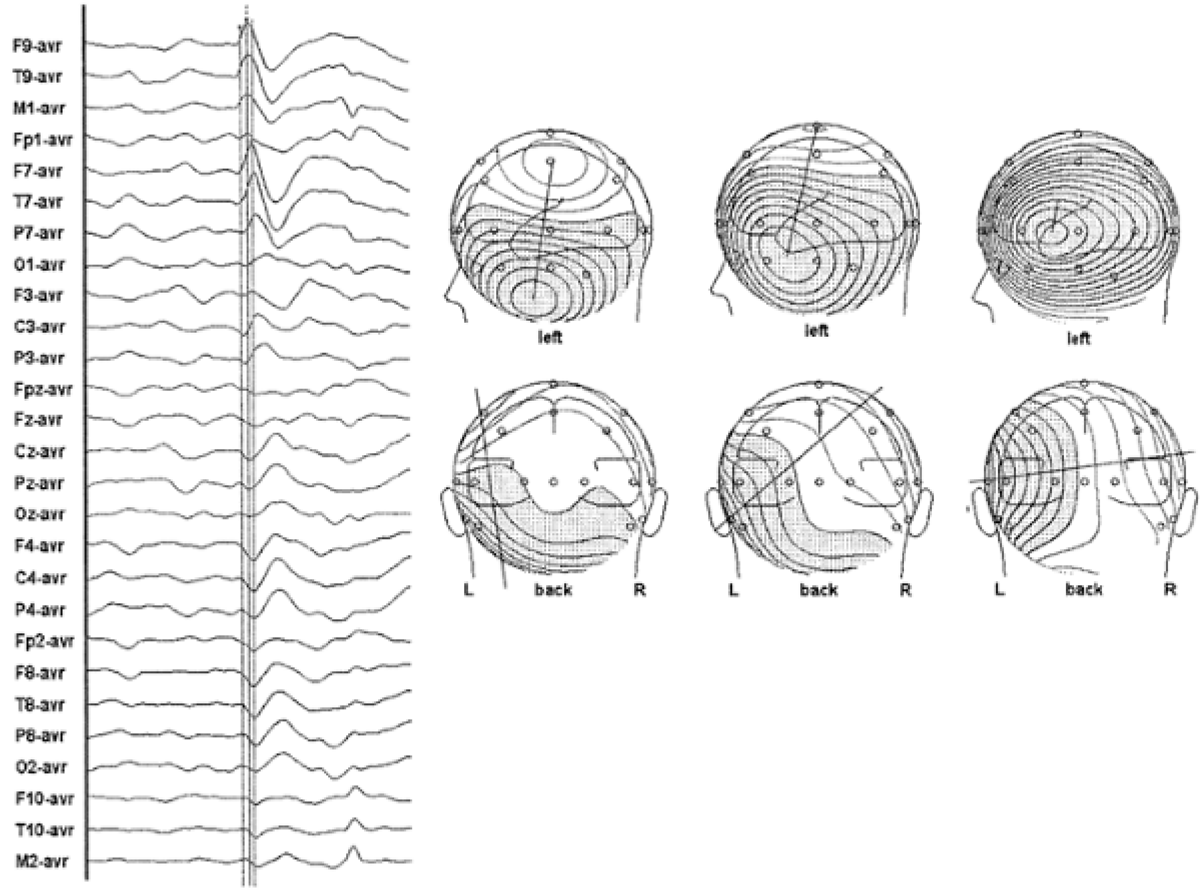
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FIGURE 2. A scalp electroencephalogram (EEG) of a left temporal spike is shown at the left. In this and subsequent figures scalp EEG is illustrated in common average reference. Cursors mark three time points on the rising phase of this spike. Topographic maps depict the scalp voltage fields at these three points in isopotential lines. In this and subsequent figures voltage field negativity is shown as a speckled region and positivity as a clear region. A three-dimensional line defining field orientation connects the two maxima. Note that early in the spike the field is vertical and tangential. Later it is oblique, and at the spike peak the field is horizontal and radial. Such changes in the location of voltage field maxima and field orientation are the result of spike propagation across basal and into lateral temporal cortex.

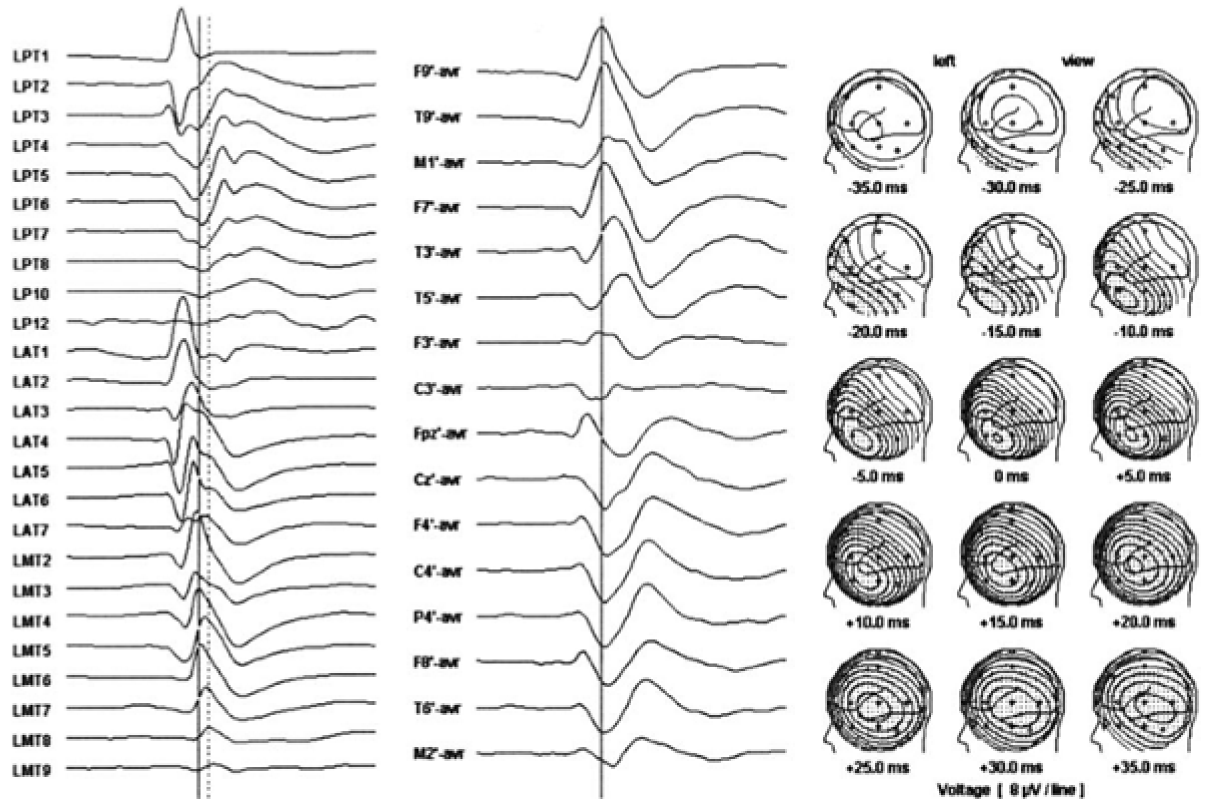

FIGURE 3. Simultaneous intracranial and scalp electroencephalogram of a left temporal spike. Topographic maps at the right show the evolution of the spike voltage field over 70 msec. Cursors denote the time point 0 msec. Note the progressive increase in spike potential latency across subdural strip electrodes LAT 1–7 and LMT 2–8 and across scalp electrodes F9 to T5. Note also the progressive movement of spike field maxima.

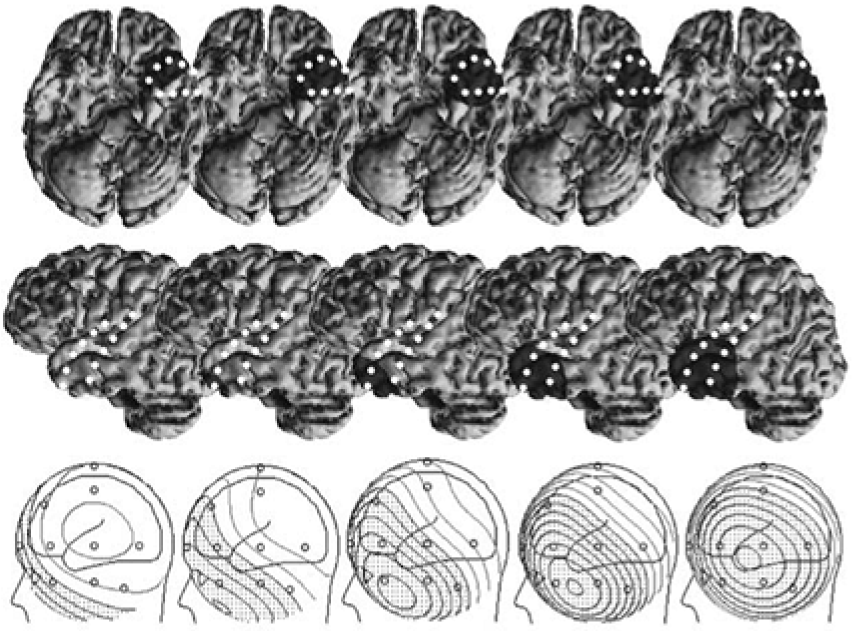

FIGURE 4. Subdural strip electrodes LAT (left anterior temporal) and LMT (left mid temporal) depicted on a three-dimensional reconstruction of the patient's brain. Voltage topography of the same temporal

spike as in FIGURE 3 at five time points is illustrated at the bottom. Location and area of the cortical spike source at each time point is shown as a shaded region. Sources were estimated from the subdural electrodes recording active spike depolarization at that time point. Note the progressive propagation of the source from the inferior temporal tip to the anterolateral temporal cortex and the associated movement of the negative spike field maximum. Note also the enlarging area of the cortical source.

Principles of Electroencephalographic Dipole Modeling

Dipole localization techniques are based on electric field theory applied to volume conduction that was developed by Helmholtz[66] in the mid-nineteenth century. Nearly 100 years later, electroencephalographers began to consider the physical relationship between electric fields on the scalp and their underlying sources within the brain.[20,60,148,151] At the same time, Wilson and Bayley[169] developed a method for calculating the voltage field generated on a spherical volume conductor by a known dipole. In simple terms, if the location, orientation, and strength of a dipolar source within a spherical and homogeneous conducting medium is known, one can predict the shape and magnitude of the potential field that is measurable on its surface. The answer to this type of problem has been called the "forward solution," and it is unique. There is only one field that can be generated by a given dipole. However, the usual clinical problem is the opposite, namely, trying to locate the intracerebral generator, having measured the topography of a

scalp potential. The answer to this is called the "inverse solution," and, unfortunately, for any given voltage field there is no unique answer. Rather, there are multiple possibilities because the fields of sources in a volume conductor sum linearly (the principle of superposition). Therefore, the field measured by a given electrode array may well be a composite from a number of different sources.

Certain assumptions are necessary to apply these principles to human EEG. First, the brain is usually modeled as a sphere of uniform conducting material,[25] and concentric shells are added around this to imitate the skull and scalp.[32,33,75,128,146] The brain and scalp are usually considered to be of equal resistivity, and the intervening skull is considered to have a resistivity that is 80 times greater. In addition, for ease of modeling, the source of the field is considered to be a point-like dipole. Obviously, the generators of scalp spikes are not point sources, but rather large aggregates of neurons that extend over 10 to 30 cm^2. However, the combined activity of such a generator region can be modeled effectively by a single dipole. That is, the field that would be produced by this "equivalent dipole" is very similar to that of the real source. As a first approximation, the equivalent dipole should reside close to the center of the real generator area and have a similar net orientation (Fig. 5).

Single Moving-dipole Model

The most common form of source localization is the instantaneous single-dipole inverse solution. This procedure takes the voltage values from all electrodes at a given instant in time and searches, using iterative minimization techniques, for an equivalent dipole within a spherical head that could generate such a field.[32,33,67,75,141,146] This method defines a single equivalent source for a voltage field at one point in time. Regardless of the complexity of the real cerebral sources, the resultant compound activity is simplified into that of a single-dipole generator.

Spike voltage fields evolve over time, but the instantaneous single-dipole technique models the field at only one instant. Temporal evolution of a voltage field can be described, however, by a series of sequential single dipoles that can move in position and orientation over time, and these can be displayed in

one image as a "moving" dipole.[35,36] For some spikes, repeated dipole solutions are very consistent during the course of the potential, varying only in magnitude and little in position or orientation (Fig. 6). A single-dipole model fits these types of data well and suggests a discrete cerebral generator or nearly synchronous activation of several generator regions. For other spikes, sequential solutions over the potential's time course show progressive drift in dipole location and rotation of vector orientation (Fig. 7). Such behavior of the dipole model is incompatible with a single generator region and suggests asynchronous activation of different cortical areas. The direction of dipole movement can convey useful information about likely spike propagation, as long as it is simple and unidirectional. Moving dipoles that spiral in a loop or make sudden turns in direction or position are usually the result of fields created by superposition of early source repolarization and later source depolarization or several different asynchronous sources. Therefore, one-dipole solutions can be misleading, particularly at later latencies when propagation is likely to have occurred, resulting in increased source complexity. Accordingly, several investigators recommend modeling the rising phase of the spike rather than the spike peak or later potentials.[72,88,89,139] However, a different technique is required to model successfully several simultaneously active sources.

Interpretation of Single-dipole Models

Unfortunately, solutions for an equivalent-dipole source seldom reflect precisely the location of actual cerebral generators. Clinical interpretation requires an appreciation for

the weaknesses in the modeling assumptions and the complexity of source geometry and physiology. Equivalent dipoles are usually located deep to the true source cortex. Dipole localization techniques are least accurate in depth determinations because this estimation depends on the size of the generator region. Single-dipole solutions provide a reasonable approximation for superficial cortical sources if their diameter is smaller than 2 cm, such as with somatosensory-evoked potentials.[50,132] Activation of a larger area of cortex, which is likely in the case of epileptiform spikes, produces a more diffuse scalp field that would be modeled as a deeper equivalent dipole. A large area of activated cortex also means that tangential fields from opposing sulcal walls will often cancel one another, allowing radial components to predominate. A reasonable simplification for interpreting spike dipole models is to consider only sources on the major outline of brain lobes. Accordingly, a tangentially oriented dipole is more likely to reflect an appropriately oriented major cortical surface or fissure, such as the temporal lobe base or sylvian fissure, rather than an individual sulcus. Dipole orientation is often more useful than is dipole location in determining which area of cortex in a given lobe is the likely generator.

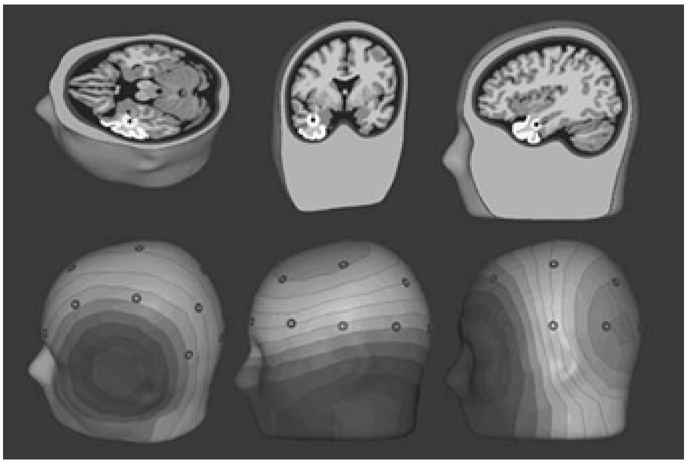

FIGURE 5. Shown as whitened cortex are the three most common types of temporal lobe spike sources, their resultant scalp voltage fields, and equivalent dipole models. Left to right: lateral temporal cortex, temporal base cortex, temporal tip cortex. Note that all the dipole models are located in temporal lobe white matter, but the dipole orientations differentiate the sources. Horizontal radial = lateral cortex source; vertical tangential = basal cortex source; horizontal anterior-posterior tangential = tip cortex source. Note also that dipole orientation is orthogonal to the net orientation of the source cortex.

Patients with complex partial seizures of temporal lobe origin have been found to have spike voltage fields that could be

categorized into one of two patterns, termed type 1 and type 2.[46,47] Type 2 spikes have a lateral temporal negative field maximum and a contralateral temporal positive field maximum. These spikes are well modeled by a single equivalent dipole located in the temporal lobe that has a radial and horizontal orientation (Figs. 6 and

8B).[35,36] Type 1 spikes possess an inferior temporal negative field maximum and a vertex positive field maximum. They are modeled by a similarly located single equivalent dipole that has instead a vertical tangential to oblique orientation (Figs. 7 and 8A).[35,36] In keeping with the foregoing interpretive guidelines, the horizontal, radial nature of type 2 spike dipoles suggests sources in lateral temporal cortex, whereas the more vertical and tangential orientation of type 1 spike dipoles suggests inferior and basal temporal cortex sources.

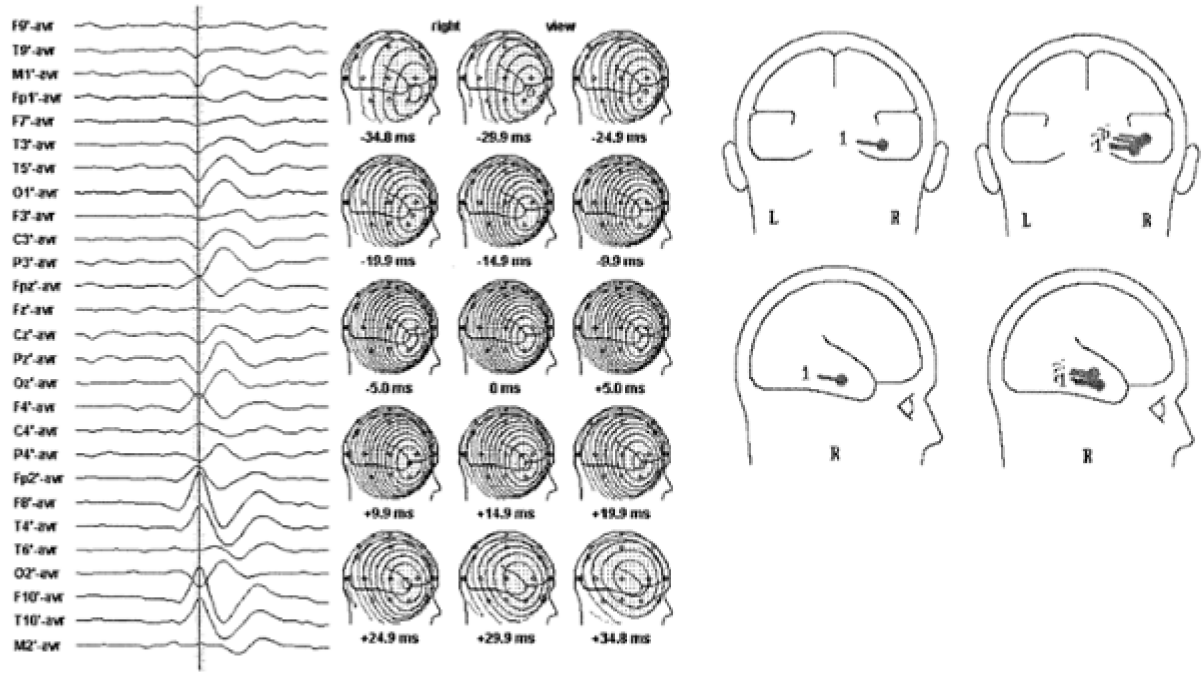
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FIGURE 6. A scalp electroencephalogram of a right, type 2 temporal spike. Cursor denotes 0-msec latency. **Middle:** Sequential voltage topography of the spike. Note the stable shape of the fields over 70 msec. **Right:** Single- and moving-dipole models of the spike. Note that voltage field stability and the tight cluster of the moving dipole model suggest a simple source for which a single-dipole model is appropriate.

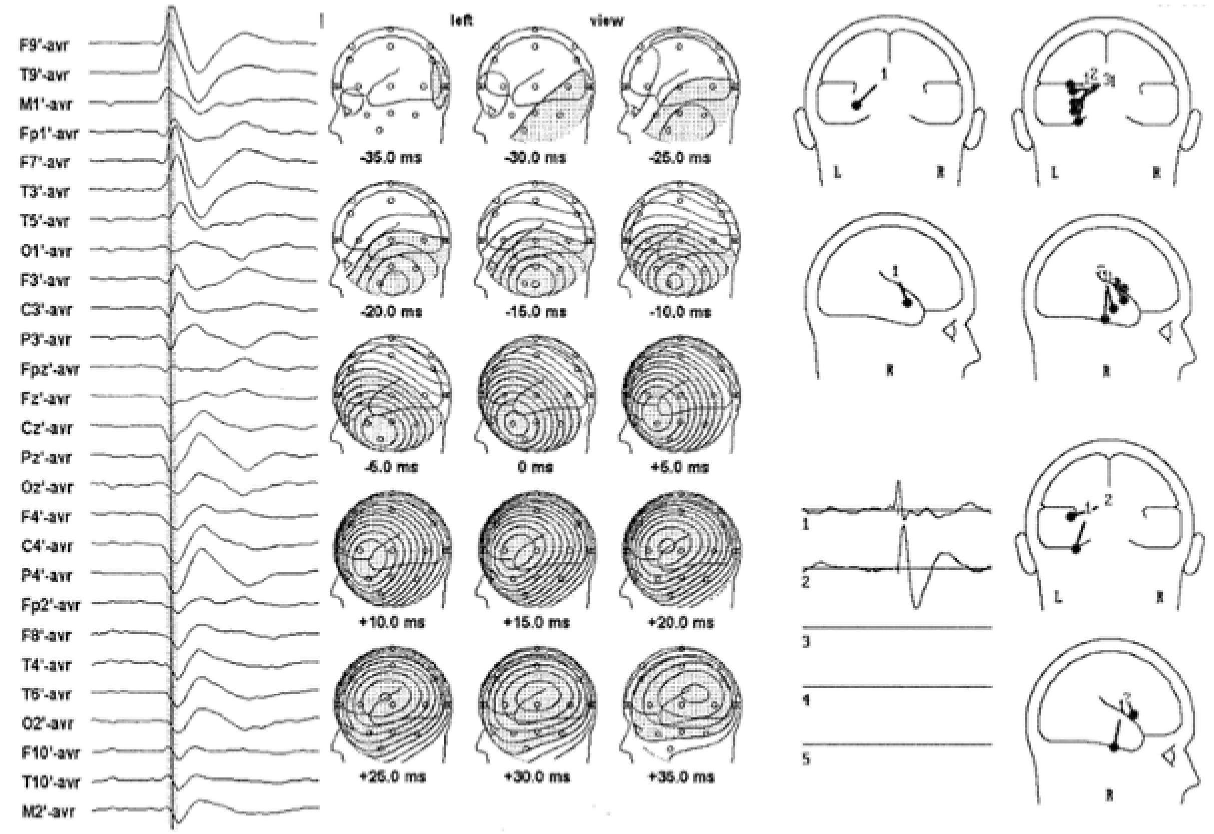
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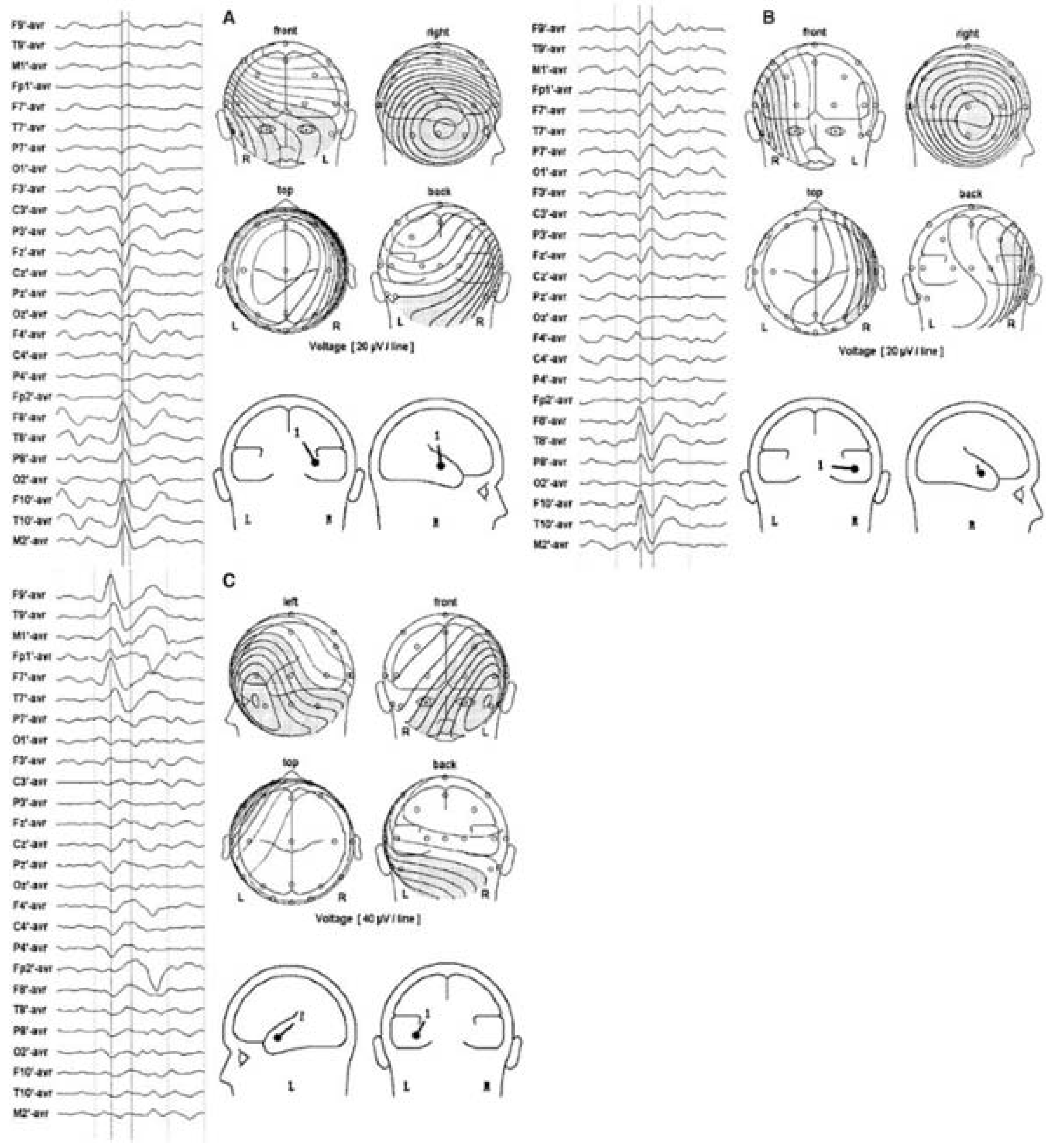
FIGURE 7. A scalp electroencephalogram of a left, type 1 temporal spike. The cursor denotes 0-msec latency. **Middle:** The progressive change in the sequential voltage topography of the spike is evident. **Right:** Single-dipole, moving-dipole, and spatiotemporal dipole models of the spike. The single dipole at the spike peak is oblique in orientation, whereas the moving-dipole model shows a progression in dipoles from the vertical tangential to the horizontal radial. The spatiotemporal model requires two dipoles to explain the field over time—the first vertical tangential and the later horizontal radial. Both the moving-dipole and the spatiotemporal dipole models suggest spike propagation.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C4'-avr
P4'-avr
Fp2'-avr
F8'-avr
T8'-avr
P8'-avr
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Voltage [40 µV / line]

FIGURE 8. A scalp electroencephalogram, voltage fields, and single-dipole models of **(A)** type 1, **(B)** type 2, and **(C)** tip temporal spikes.

Spatiotemporal Multiple-dipole Model

It is overly simplistic to think that small brain regions are activated briefly in sequence when spikes propagate. It is more reasonable that adjacent cortical areas are activated for a longer period but not synchronously. Source modeling with single instantaneous dipoles cannot take into consideration such an overlap of activity of multiple generators, nor can it decompose the voltage fields produced by this superposition. Spatiotemporal source modeling is, however, an approach based on this rationale.[133,138,139] Dipoles are fixed in location and orientation but can vary over time in strength and polarity to explain the temporal evolution of a voltage field. Sufficient degrees of freedom are obtained to calculate multiple dipoles from this positional constraint and from modeling over several time points. The solution for a given data set reveals not only a best-fit location for the model, but also the putative activity of each dipole over time in the form of a source potential (Fig. 7).

Because there is no unique solution when trying to identify several sources that may underlie a voltage field that is a composite, it is necessary to use modeling strategies to constrain the solutions to those that are most realistic. Two major categories of strategies include those based on sequential temporal activation of adjacent generator areas and those based on the orientation of the cortical areas likely to be involved

in the process. Implicit in the "temporal" strategy is the idea that the earliest part of a spike waveform is more likely to be the product of a single source than are later segments. Accordingly, one should first attempt to model the early part of the field evolution as a single dipole rather than the spike peak, for example. Additional dipoles are used in sequence to model the residual field left unexplained by the preceding dipole(s). If the initial equivalent source explains, in spatiotemporal terms, the entire spike field evolution, the generator is rather discrete or simple in character. Commonly, however, two or sometimes three dipoles are necessary to explain "focal" spike data. The spatiotemporal technique attempts to find the fewest number of fixed equivalent sources that can explain field evolution by a temporal overlap of activity among them.

Several different patterns of multiple dipole models have emerged in applying this technique to the spikes of patients with presumed temporal lobe epilepsy.[17,19,35,36,37] Spikes with a type 1 topography usually require two or more dipoles to be modeled adequately (Fig. 7). One of these dipoles typically has an orientation that is vertical and tangential to the lateral skull convexity, whereas the other is horizontal and radial. The tangential dipole is usually deeper than the radial one. Type 1 spike topography is the result of the superposition of fields from both sources when their activity overlaps in time. Source analysis of type 1 spikes from different patients has shown tangential source activity leading, lagging, or being synchronous with radial source activity. The pattern of voltage field evolution for a particular spike thus depends on the temporal relationships of its various source components. Information about the direction of spike propagation is conveyed by the sequence in which dipole sources become active. Simultaneous intracranial and scalp EEG recordings have validated previous assumptions that the vertical tangential dipole models activity from basal temporal lobe cortex and the horizontal radial dipole models activity from lateral temporal cortex.[42,137] Spikes confined to the hippocampus produced no scalp-recognizable voltage field. However, when these spikes propagated to basal cortex, which was common, sufficient cortex was activated to result in a scalp potential. Basal to lateral cortex propagation and vice versa, suggested by timing differences in dipole source components, have also been confirmed.

The majority of spikes with type 2 topography require only one horizontal radial dipole to be modeled (Fig. 6); in approximately one third of patients, however, two or more dipoles are needed. In these cases, the dipoles usually differ in azimuth orientation and anteroposterior position yet continue to be predominantly radial. Differences in timing between these sources can suggest anterior to posterior or, less commonly, posterior to anterior propagation along the lateral temporal convexity.

More recently, dipole modeling has identified a third major cortical source contributing to typical temporal spike fields.[40,41,137] Synchronous activity of anterior temporal tip cortex results in a field with a negative maximum recorded from frontopolar and frontotemporal electrodes because of its net forward-facing orientation. Dipoles modeling this activity are horizontal but have a distinct anterior-posterior (AP) vector (Fig. 8C). Occasionally, spikes have just this dipole solution, but usually the tip component is present in combination with other temporal source components in more complex spikes that exhibit propagation.

Modeling strategies using anatomic constraints can also be useful. Unconstrained inverse-solution mathematics considers any position within the spherical head model and any orientation of dipole vector to be equally likely as a source. This is obviously not true biologically. Spikes arise from cortex that has limited and definable locations and orientations. Of the two, it is more useful to specify the orientation of possible

equivalent sources. As noted previously, it is reasonable to consider for purposes of modeling only the orientations of major lobar surfaces. For the temporal lobes, these orientations are horizontal radial for the lateral convexity cortex, vertical tangential for the basal cortex and superior temporal plane, and AP horizontal tangential for the temporal tip (Fig. 4). One approach in using this strategy for the temporal lobes is to create a priori a multiple spatiotemporal dipole model of major lobar surfaces based on specific orientations obtained from brain imaging studies and to note from the source potentials the extent to which each dipole can contribute to explaining spike voltage fields over time.[2,3,136,137]

Dipole Modeling in Clinical Investigations

By the mid 1990s several investigators began to apply EEG dipole modeling to the evaluation of epilepsy surgical candidates. In general they confirmed findings from earlier studies. In a series of investigations, Boon et al.[19,20,21,22,23] demonstrated that patients with medial temporal lesions had EEG spikes and early seizure rhythms that were modeled by dipoles having an elevated orientation above the horizontal (a combination of radial and tangential) similar to Ebersole's type 1 spike, whereas patients with lateral temporal or extratemporal lesions had EEG spike and early seizure rhythms that were modeled by dipoles having a radial orientation similar to Ebersole's type 2 spike. In a series of studies using simultaneous scalp and intracranial EEG recordings, Lantz et al. confirmed that dipole orientation was the major distinguishing factor in distinguishing spikes originating from basomesial temporal sources from those of lateral temporal origin.[86,90,92] Merlet and Gotman[99,100] in a pair of papers validated dipole models of spikes or seizures with a later combination of intracranial and scalp EEG. They concluded that only simple cortical sources could be well modeled by one dipole and that spike modeling yielded better and more frequent results than seizure modeling. Numerous other publications began appearing in the late 1990s that confirmed a good correlation between spike dipole models and other localization tools such as intracranial EEG,[69,106] positron emission tomography,[145] single photon emission tomography,[124,145] and magnetic resonance imaging (MRI) lesions in both adults and pediatric patients.[83]

Dipole Modeling of Seizures

Dipole modeling can also be applied to seizure rhythms with some modifications in the protocol used for spikes.[19,20,21,22,23,37,38,40,41,100] The earliest recognizable seizure potentials should be preferentially modeled because they are more likely to reflect the seizure origin than are later rhythms, which usually evolve only after significant propagation. In most instances, the EEG must be filtered with a narrow band pass covering those frequencies that represent the cerebral seizure activity and not the accompanying artifact. For partial seizures of the temporal lobes, this is approximately 2 to 10 Hz. For extratemporal seizures that commonly have a beta frequency component, this is a broader 2 to 20 Hz.

Because ictal onset rhythms are typically of low amplitude and are commonly confounded with movement and muscle artifacts, averaging successive potentials might be necessary to increase the signal-to-noise ratio. The key is to average seizure waveforms with similar voltage topographies (Fig. 9); only these reflect the same source configuration. These periods of stable fields might last only a few seconds. Alternatively, spatiotemporal modeling can be performed over this stable epoch. One or more fixed dipoles possessing cyclic variations in the magnitude and polarity of their source potentials can often explain the repeating evolution of an ictal voltage field. Temporal and orientation strategies are applicable in seizure modeling, just as in spike modeling. Modeling sequential epochs during the course of the seizure can provide insight about seizure propagation.

The orientation of dipole models of ictal waveforms carries the same significance as those of spikes, and it is most useful in identifying sublobar temporal lobe sources.[2,19,20,21,22,23,37,38,40,41] Temporal lobe seizures modeled by dipoles with dominant horizontal radial, vertical tangential, or horizontal tangential AP orientations are most likely associated with lateral temporal, hippocampal/basal, or temporal tip seizures, respectively (Fig. 10). In addition, many temporal lobe seizures are modeled best by dipoles having an anterior oblique orientation, that is, a combination of all three of the previous orientations (Fig. 10). In this case the ictally active cortical region includes inferior, tip, and lateral temporal cortex. Multiple fixed-dipole models can also be used to identify the contribution of various sublobar cortical areas to seizure potentials. This technique has recently been used to determine temporal lobe seizure origins and to predict surgical outcome following standard temporal lobectomy.[2,3]

Ictal EEG dipole models have been correlated with intracranial EEG and surgical outcome.[2,1923,37,38,40,41] The results are similar to those found with spike dipole modeling. Patients with seizures modeled by horizontal radial dipoles, which suggest a lateral cortex origin, do less well following a standard anteromesial resection and should be considered candidates for invasive monitoring and possibly tailored temporal lobe resections. Patients whose seizures are modeled best by dipoles with a vertical, horizontal AP, or anterior oblique orientation have seizures originating probably in baso-mesial, temporal tip, and anterior inferior temporal cortex, respectively. All of these patients do well following surgery because these cortices are customarily removed in the standard temporal lobe resection.

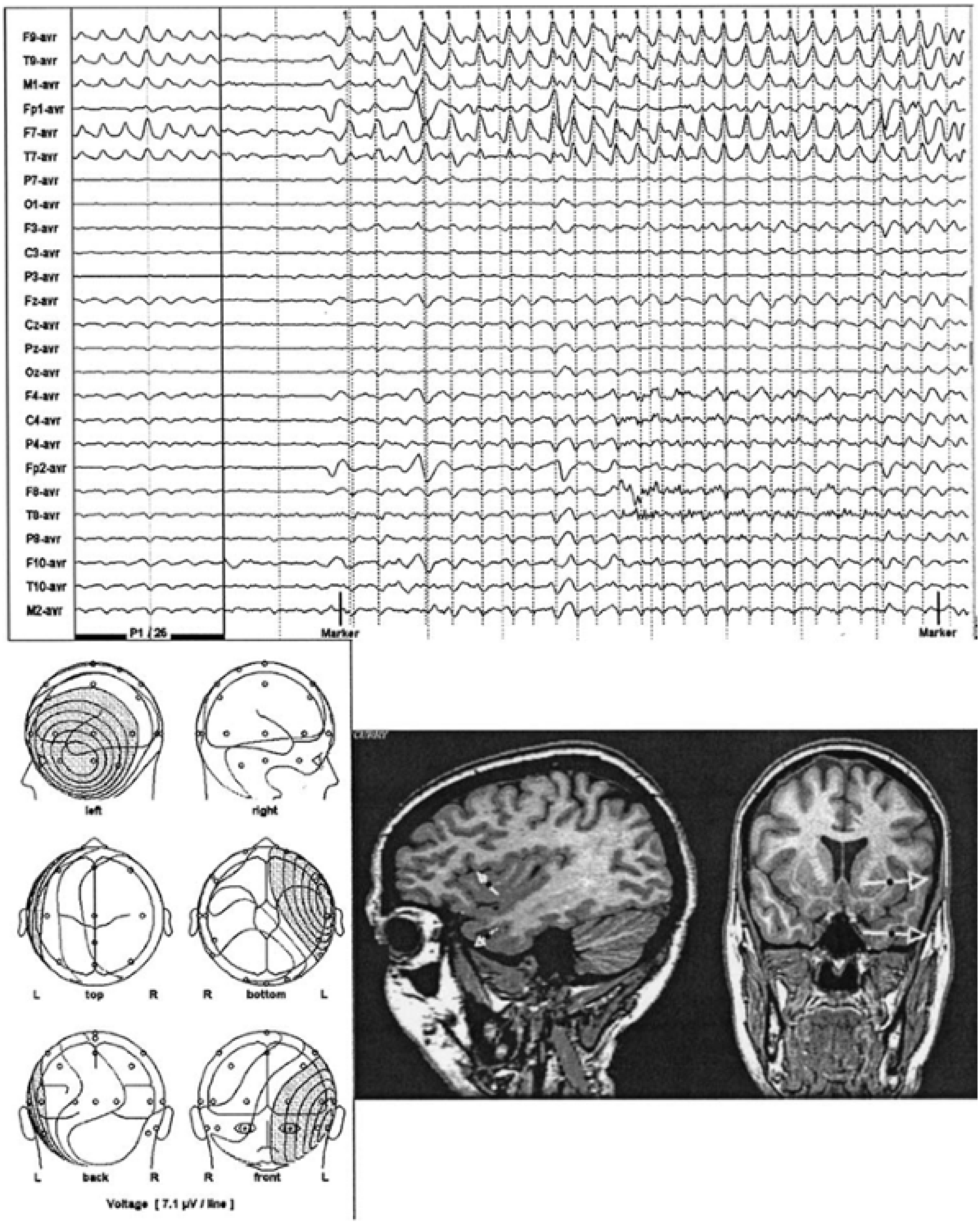
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FIGURE 9. Scalp electroencephalogram of a left temporal seizure is illustrated at the *top right*. Cursors mark individual ictal potentials that are averaged to produce the ictal potential at the *top left*. Note the improved signal-to-noise ratio. The voltage field of the averaged ictal potential is shown at the *bottom left*. Single-dipole models of the ictal potential are coregistered with the patient's magnetic resonance image at the bottom right. Inverse solutions were obtained using a spherical head model (upper dipole) and a boundary element method (BEM) realistic head model (lower dipole).

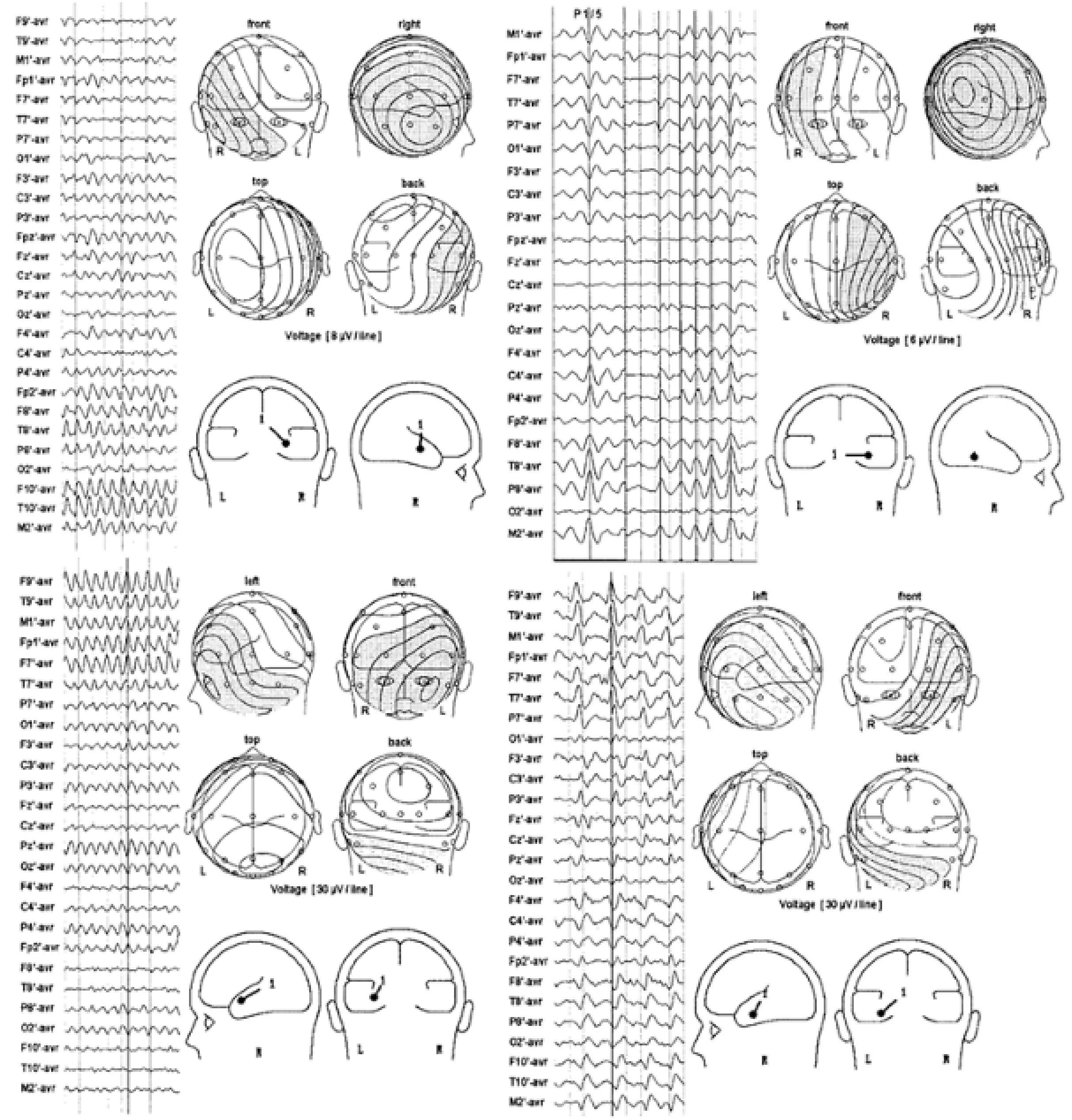

FIGURE 10. Scalp electroencephalogram, voltage fields, and single-dipole models of **(A)** type 1, **(B)** type 2, **(C)** tip, and **(D)** oblique temporal seizures.

Improvements in Recording and Modeling Techniques

With the advent of volumetric computed tomography (CT) and MRI, detailed anatomic information about an individual's head and brain has become readily available. However, only recently have these data been combined with EEG to provide "functional imaging" of the brain's electrical activity. Three-dimensional reconstructions of MRI have demonstrated the geometric relationship between standard scalp electrode positions and the underlying brain.[38,85] The standard International 10–20 temporal electrode chain passes across the superior aspect of the temporal lobe. Supplementary inferior temporal electrodes are necessary for properly recording the negative field of spikes and seizures from the basal cortex of frontal, temporal, and occipital lobes. Sphenoidal or the so-called anterior temporal electrodes, T1 and T2, are useful in this regard, but a broader spatial sampling of lower-head voltage fields is better for modeling purposes than simply one or two positions. Digitizing the scalp electrode locations and certain head fiducials, such as the nasion and preauricular points, in 3-space makes it possible for the topography of the scalp EEG fields to be coregistered with and superimposed on a three-dimensional (3D) MRI reconstruction of the patient's head or brain. In similar fashion, calculated dipole models can be coregistered with the same 3D brain image (Fig. 11).[38]

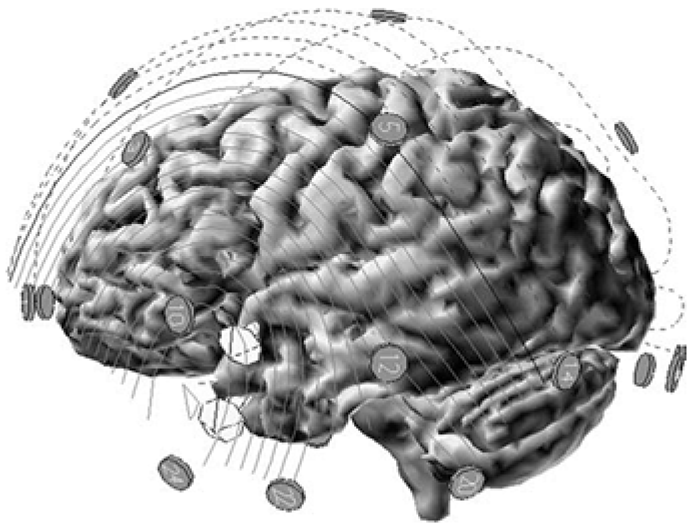

FIGURE 11. Three-dimensional coregistration of a patient's brain, scalp electrode positions, voltage field of a left temporal spike, and dipole models of that spike. Inverse solutions were obtained using a spherical head model (upper dipole) and a boundary element method (BEM) realistic head model (lower dipole).

Some have proposed on theoretical grounds that high-resolution EEG requires hundreds of electrodes,[63] whereas others have concluded that the gain beyond 40 to 64 electrodes is negligible.[84,176] This is particularly true for epileptogenic spike and seizure sources that tend to be large spatially and produce

voltage fields of low spatial frequency. Lantz et al.[87] recorded spikes from patients with epileptogenic lesions with 128 electrodes and performed source modeling with various downsampled arrays. An increase in electrode number from 31 to 63 resulted in significantly improved localization, whereas only minimal additional precision was achieved with an increase in electrode number to 128.

The spherical model commonly used to calculate EEG dipoles is a mathematically convenient approximation for the shape of a head. Although the superior convexity of the head is rather spherical, the base of the brain/skull is not. Realistic head models created by the boundary element method (BEM) are the most commonly used (Fig. 12). This type of model accounts for the individual, nonspherical shape of the main intertissue boundaries of the brain, skull, and scalp.[52,54,96,178] Each of these is discretized into triangular elements to form a mesh. The effects of conductivity inhomogeneities across the boundaries are modeled by so-called “secondary dipoles” that are placed in the center and perpendicular to each of the surface elements. The strength of these secondary dipoles is proportional to the conductivity difference and the electrical potentials, which are assumed to be constant over each surface element. BEM head

models have two shortcomings. Conductivity is assumed to be piecewise constant and isotropic, whereas cranial tissues are inhomogeneous and show anisotropy. Finite-element methods can overcome these problems but require considerably more computational effort.[26] In addition, the detailed conductivity information needed to construct such a model is not known. Accordingly, BEM realistic head models are a reasonable compromise. Recent investigations have also shown that the accuracy of source solutions can be further improved if an increase in the density of the triangulation mesh is made in the region of the source.[175,176]

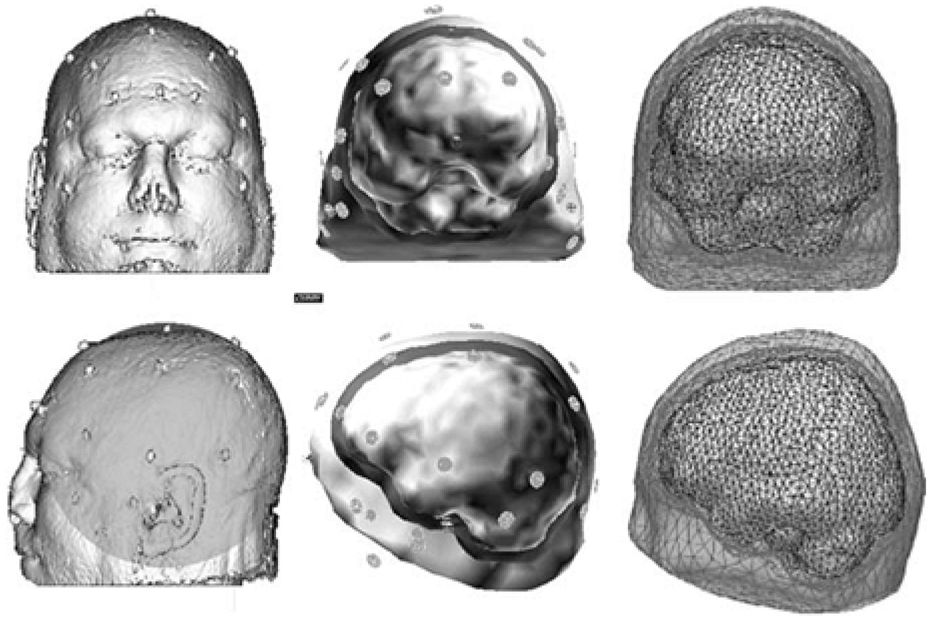

FIGURE 12. Middle: Realistic boundary element method (BEM) head model illustrating inner and outer surfaces of skull and scalp derived from three-dimensional magnetic resonance imaging reconstructions. **Right:** Tessellation of these surfaces into a triangular mesh. **Left:** The shaded circle on the patient's head depicts the typical shape of a spherical head model. Note the divergence of the brain and skull base from this spherical shape.

Systematic errors in dipole location introduced by spherical head models have been identified.[30,31,140] Roth and colleagues[126,127] first simulated and then studied real EEG sources in the temporal and frontal lobes to compare the effects of spherical versus realistic head models on dipole solutions. They noted location errors in the spherical models of 1 to 3 cm that were worse in the vertical or Z direction. Yvert et al.[175,176,177] and Fuchs et al.[52,54,56] simulated EEG dipole sources throughout the brain and found that spherical head modeling errors were worse for basal regions and in the Z direction. These results were also confirmed using temporal lobe spike and seizure foci as the source and validating the true location of these foci with intracranial EEG.[40]

Fig. 13 illustrates dipole solutions for a temporal lobe spike calculated with both spherical three-shell and BEM head models. Dipoles using a spherical model were misplaced on the average of 2 to 3 cm upward from those of a BEM model and their true temporal lobe source. In several patients, this gave the false impression that the spike/seizure sources were of superior temporal or frontal rather than anterior-inferior temporal lobe origin. Others have confirmed these observations.[68] It is apparent that realistic head models should be used whenever dipoles are coregistered with MRI for interpretation. This is particularly true for basal frontal, temporal, and occipital sources, where brain cortex and skull departs most from a spherical shape.

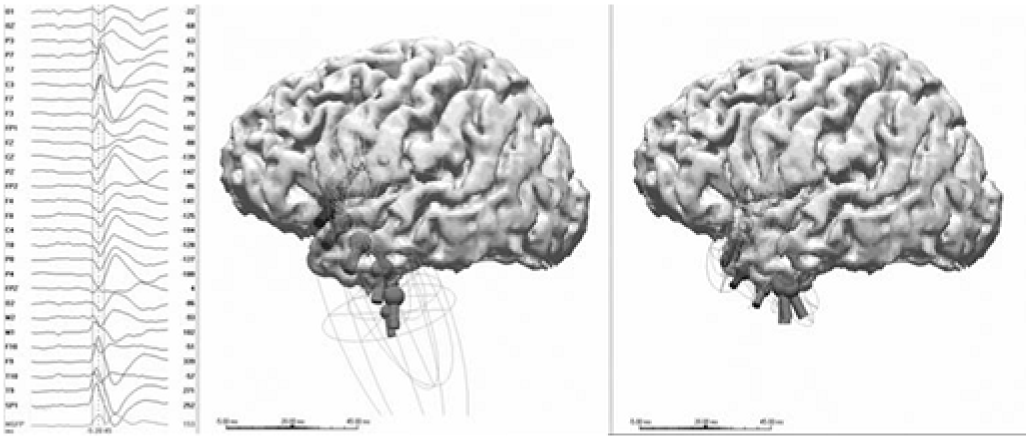

FIGURE 13. Moving-dipole model of a propagating left temporal spike calculated with a three-spherical-shell-head model **(left)** and a boundary element method (BEM) realistic head model **(right)**. Note that dipole solutions using a spherical model begin below the temporal lobe and end in the frontal operculum, whereas those using a realistic model all reside within the temporal lobe. Confidence volumes (displayed as ellipsoids) are largest with early and late dipoles and smallest with the best signal-to-noise ratio at the spike peak.

Fuchs et al.[53] described the use of a standardized BEM head model derived from an averaged MRI data set (Montreal Neurological Institute) to provide simple access to realistically shaped volume conductor models for source reconstruction. They compared dipole modeling accuracy using spherical head models, individually derived realistic head models, and the standardized realistic head model in both source simulations and epileptic spike data. Spherical head models resulted in dipole mislocation errors at the base of the brain, as previously noted. Standardized and individualized BEM head models resulted in more accurate and comparable dipole solutions. By using a standardized head for the BEM setup, an easier and faster access to the benefits of a realistically shaped volume conductor models can be achieved.

Recently, Kobayashi et al.[82] tested the accuracy of dipole models when applied to simulated EEG derived from cortical patches of different location and area. They demonstrated that dipole models of small sources (6 cm^2) or very large sources (>100 cm^2) were misleading, whereas dipole modeling sources between 18 and 36 cm^2 were consistent and accurate. Dipoles are thus a reasonable source model for focal spikes, given that Tao et al.[158] showed that epileptic potentials appreciated on scalp EEG commonly had source areas of 10 to 30 cm^2.

Other Electroencephalographic Source Models

Within the last 5 years there has been considerable development of new techniques for expanding the use of source modeling

in the evaluation of epilepsy patients. Many of these involve new mathematical approaches to the decomposition of the data or to the reconstruction of a source model. Because the number of cortical sources is not known when modeling spike or seizure potentials, some investigators feel that decomposing the data by a variety of techniques is worthwhile before attempting to model them. Several have chosen to use singular value decomposition[27] or independent-component analysis.[79,80,81] The likely number of component sources, or at minimum the dominant component, can be estimated and their contributions to the voltage field and waveform separated without prior knowledge. Others have devised techniques for systematically scanning the entire brain space for possible sources.[108,109]

Although the dipole is a useful concept from which practical diagnostic information can be obtained, it is anatomically not very realistic. Brain sources of spikes or seizures are extended cortical patches, not isolated points. Clinicians, in particular, are more comfortable seeing regions of cortical activation, such as displayed in positron emission tomography (PET), single photon emission computed tomography (SPECT), or functional MRI (fMRI) images, regardless of the physiologic soundness of these representations. There has been considerable effort recently to go beyond dipole source models to more realistic extended-source models. These take a variety of approaches; a common form of source reconstruction works on the hypothesis that brain currents are located only at specified locations. Using the cortical surface, for example, can afford a powerful reconstruction parameter because it restricts the search space to a surface that can be defined further by local orientation information.

Algorithms have been devised that can calculate discrete approximations of the current density distribution on a defined surface. This is an ill-posed problem, however, if many local sources are to be calculated from measurements at relatively few electrode locations. Regularization is necessary to proceed in these circumstances. This represents a compromise between the demands to explain the measured data and to meet certain source or boundary conditions. One such boundary condition is the minimum norm criterion, in which the source constellation of lowest electrical power is calculated. Variations include the L2 or L1 norms[54] and or the minimum spatial Laplacian, also called low-resolution tomography (LORETA).[101,121] Additional techniques for estimating multiple sources or a single extended source include LAURA and EPIFOCUS[64,103] and VARETA.[129] The usefulness of these techniques, however, needs to be proven with clinical data and further validated by intracranial EEG recording. One investigation demonstrated no advantage of current density reconstruction over source modeling with dipoles.[167] However, a recent study of 44 patients with partial epilepsy using 123 channels of EEG demonstrated that an extended-source model (EPIFOCUS) was capable of correct lobar localization in 90% of patients and correct sublobar localization in 79% when compared to the eventual surgical resection site that eliminated the patient's seizures.[102]

Another very recent approach to the problem of unrealistic point-like dipoles is the use of a “dipole patch” model. It is composed of many individual dipoles that are constrained to follow the surface of the patient's cortex, derived from 3D MRI reconstructions, in both position and orientation. This model, which has an adjustable spatial extent, was tested with data from eight surgical candidates with complex partial seizures.[65] Dipole patch solutions for EEG spikes and seizures were compared to single-dipole models and to the location and extent of cerebral sources recorded with intracranial electrodes. Physiologically reasonable dipole patch solutions were obtained for spikes or initial seizure rhythms in all patients. The location of dipole patches was accurate at a sublobar level when compared to underlying cerebral sources, as validated by intracranial EEG. Dipole patches with a diameter of 3 to 5 cm most accurately simulated the spatial extent of real cortical sources (Fig. 14). Single-dipole solutions usually fell within the boundary of the dipole patch or its underlying white matter, but often they did not lie at the geometric center of the patch. In this technique, the localization accuracy achieved with a dipole model using a realistic boundary element head model is enhanced by the spatial extent and realism of an extended generator area that is constrained to cortical anatomy. Other extended-source models, such as those employing current source density estimations, are not limited to realistic source areas, nor are they constrained to anatomically contiguous cortex. This EEG source model is probably this best one for comparisons with other functional imaging techniques, such as fMRI.

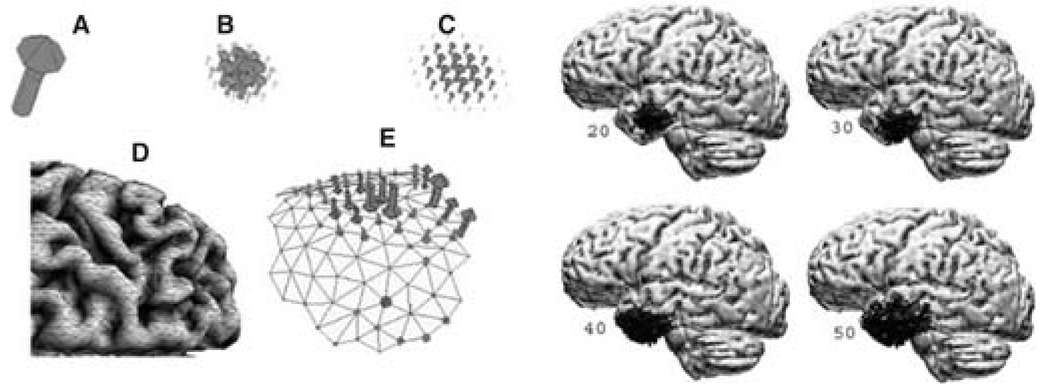

FIGURE 14. Source models of spikes or seizures do not have to be only single dipoles **(A)**; they also can

be arrays of dipoles **(B, C)**. Cortex can be tessellated into triangles **(D)** that have both location and orientation information. Dipole arrays or "patches" can follow the shape of tessellated cortex **(E)**. "Dipole patch" models have an adjustable extent that encompasses the physiologic range of sizes of cortical sources of scalp-recordable electroencephalogram potentials. Diameters of 20 to 50 mm are illustrated at right.

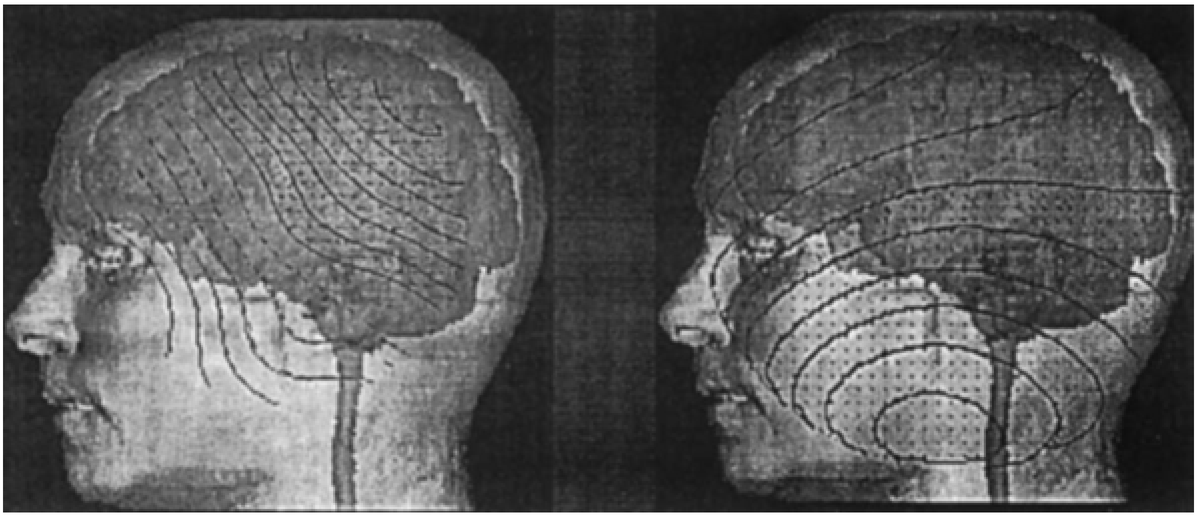

FIGURE 15. Isofield and isopotential contour lines of the magnetic field **(left)** and electrical field **(right)** of a type 1 spike projected onto a three-dimensional magnetic resonance imaging reconstruction of a patient's head to illustrate their spatial relationships. Dotted regions depict magnetic fields emerging from the head or electrical field negativity. Maps illustrate the fields at a time when source activity is principally from a vertical tangential dipole. Note that the magnetoencephalographic field is orthogonal to and more compact than the electroencephalographic field.

Magnetoencephalographic Dipole Source Modeling

Magnetoencephalography is the measurement of extracranial magnetic fields produced by electrical currents, mostly intracellular, within the brain. These magnetic fields are extremely weak, on the order of one-billionth that of Earth's, and can be measured only by superconducting quantum interference devices (SQUIDs). Current within the cell is called source current; the return current outside is called volume current. MEG, like EEG, is principally produced by aligned pyramidal cells oriented perpendicular to the surface of the cortex. The magnetic field associated with a neuronal current dipole encircles the cell at right angles to its direction. The SQUID gradiometer outside the head is usually oriented perpendicular to the head and is sensitive to the component of the magnetic field that is perpendicular to the head surface. Such a field is generated by tangentially oriented current dipoles. In contrast, EEG measures

principally volume currents associated with both radial and tangential dipoles.

Magnetoencephalography may be better for the localization of epileptogenic foci, or at least the source of epileptiform potentials, for several reasons relating to the physical properties of the signal. First, magnetic fields pass through the skull and scalp unperturbed, unlike EEG potentials, which are attenuated and smeared. Thus, the picture of underlying brain activity should be clearer, and a simple one-shell, rather than a three- or four-shell, head model can be used. In addition, because MEG represents nearly pure tangential source activity rather than an indeterminate mixture of radial and tangential components, as is the case for EEG, the modeling of MEG by inverse dipole methods should be easier and the results more accurate.

Principles of Magnetoencephalographic Dipole Modeling

If one assumes, as in EEG dipole modeling, that the cerebral generator of interest is reasonably discrete and can be modeled as a current dipole, the character of this source should be obtainable from the magnetic fields it produces. Magnetic fields from tangentially oriented brain sources exit the head at one location and reenter at another, producing two magnetic extrema of opposite sign at the surface. Once the magnetic field map is measured, three-dimensional characterization of the source can be done. Note that the MEG extrema should be and usually are orthogonal to EEG dipolar potential distribution on the head (if the EEG potential at that point is principally tangential and not a mixture). Note also that the magnetic extrema are approximately one-third closer together than are the EEG extrema, which are farther apart and smeared, due principally to the influence of the skull (Fig. 15).[28]

Because MEG signals are not perturbed by the skull and scalp, simpler modeling schemes have been used to localize ce- rebral sources. An infinite half-space model assumes that the source lies below the surface of the head, halfway between the two extrema and at a depth equal to their separation distance divided by two. More commonly, inverse solutions using iterative least squares methodology are now employed, in much the same way as with EEG dipole modeling. Research using implanted electrodes to produce artificial current dipoles has determined that volume currents may confound the magnetic field produced by cerebral source near the base of the brain and

lead to some inaccuracies.[7] Thus, even for MEG, in these instances more realistic head models may be useful in improving localization accuracy.

A serious limitation to successful clinical MEG recording is the magnitude of the signal. Epileptiform spikes and sharp waves typically have amplitudes of only one to several picoteslas (10^{-12} Tesla). In contrast, magnetic fields generated by wall power lines and room lighting, for example, are 10^5 to 10^6 times larger. These extraneous magnetic fields can be partially canceled by placing both patient and recording sensors in a magnetically shielded room and by using gradiometer detector designs. Such measures are expensive and limit patient studies to a fixed location where there is a shielded room.

Inadequate spatial sampling over the head was a serious limiting factor for MEG epilepsy studies until the introduction of the new large sensor arrays. The relative infrequency of interictal and, certainly, ictal events continues to be a major problem in MEG data collection. Patients have to lie or sit quietly and without motion under the MEG dewar for proper signal recording. Recording sessions of longer than several hours are impractical. Unlike long-term EEG monitoring, which may be continuous for several days or weeks to record spikes and seizures, MEG recording is restricted to one or more relatively shorter time periods. Consequently, recording ictal events is uncommon unless the patient is having very frequent seizures, and an adequate sampling of interictal spikes may require several recording sessions if they are infrequent.

Evolution of Clinical Magnetoencephalographic in the Evaluation of Epilepsy

Multiple early studies showed that dipole analysis of MEG spikes could estimate the character and location of the cerebral sources. Barth et al.[9,10,11] and Sutherling et al.[155,156] demonstrated that MEG localization agreed well with lesions, depth electrode data, electrocorticographic (ECoG) findings, PET, and postoperative follow-up. Magnetoencephalographic spikes were recorded in the absence of scalp EEG spikes and vice versa. They concluded that MEG and EEG data are complementary because the techniques are sensitive to spikes of different source orientation. However, magnetoencephalography may be less sensitive to deep spikes, according to their data. Modena et al.[107] and Ricci et al.[123] concluded that MEG was a better localizer of spike foci than was EEG. They too reported that some MEG spikes were without a scalp EEG transient. Sato and Smith[130] showed that the phase relationships between MEG and EEG and the timing of spikes recorded simultaneously from both were not always constant. Ricci et al.[123] correlated MEG with lesions and found better localization for centro-parietal-occipital foci than for frontal and, particularly, for temporal foci. It appears that both EEG and MEG modeling suffer in the basal frontal and temporal regions. Nonspherical, nonconcentric changes in conductivity in this region can produce secondary sources, and volume currents can add to the MEG field.

Sutherling and Barth[154] (154) as well as Stefan et al.[152] later studied spike propagation using MEG and demonstrated lateral to mesial spread in the temporal lobe. Barth et al.[9] applied multiple-source modeling to more complex MEG spikes, which probably involved several generator areas of cortex. Later, Nakasato et al.[110] compared the source localization provided by simultaneous MEG and EEG dipole modeling of spikes from patients with neocortical seizures, using ECoG as the "gold standard." They concluded that MEG localization was consistently more accurate.

Further steps in the development of MEG concerned the use of increasing numbers of channels and its coregistration with MRI.[151] The development of large-array biomagnetometer systems capable of simultaneously sampling the magnetic field pattern over a large region of the head has greatly reduced the previous equipment-related limitations of MEG in epilepsy. Several groups demonstrated that with such instruments it is possible to record enough of the magnetic field of individual epileptiform spikes[58,112,117,118,119,151,152,159,164,174] or slow waves[59,165] to model single events without moving the sensors. Most of these studies were performed with a 37-channel, one-hemisphere, flat or concave sensor array.[112,152,153,174] With such systems, recordings are necessary from only two or three sensor positions over each hemisphere. Routine studies typically require 2 to 3 hours, depending on the frequency of spike activity.

In a series of reports Stefan et al.[151,152,153] observed a close correlation between MEG spike localizations and regions of functional abnormality noted by both PET and SPECT, temporal/hippocampal atrophy, or lesions. They concluded that MEG could help to reduce the need for invasive monitoring in partial epilepsy. In a group of 50 surgical candidates, Smith and et al.[147] found MEG to be most helpful in patients with nonlesional, cerebral convexity foci of temporal, frontal, parietal, and occipital lobes. Eliashiv et al.[49] compared MEG spike source locations with irritative and ictal onset zones in nine patients determined from depth and subdural electrodes. The lateralization and localization of MEG sources were most concordant with invasive EEG findings in patients with extratemporal seizure onset. By comparison, Ebersole et al.[43] studied 30 epilepsy surgery candidates with a bihemispheric 74-channel MEG system and found focal MEG spikes, which were localized to sublobar areas of temporal or frontal lobes. Nearly half of these patients had MRI/CT studies without focal abnormalities, including no hippocampal atrophy.

Interpretation of Magnetoencephalographic Dipole Models

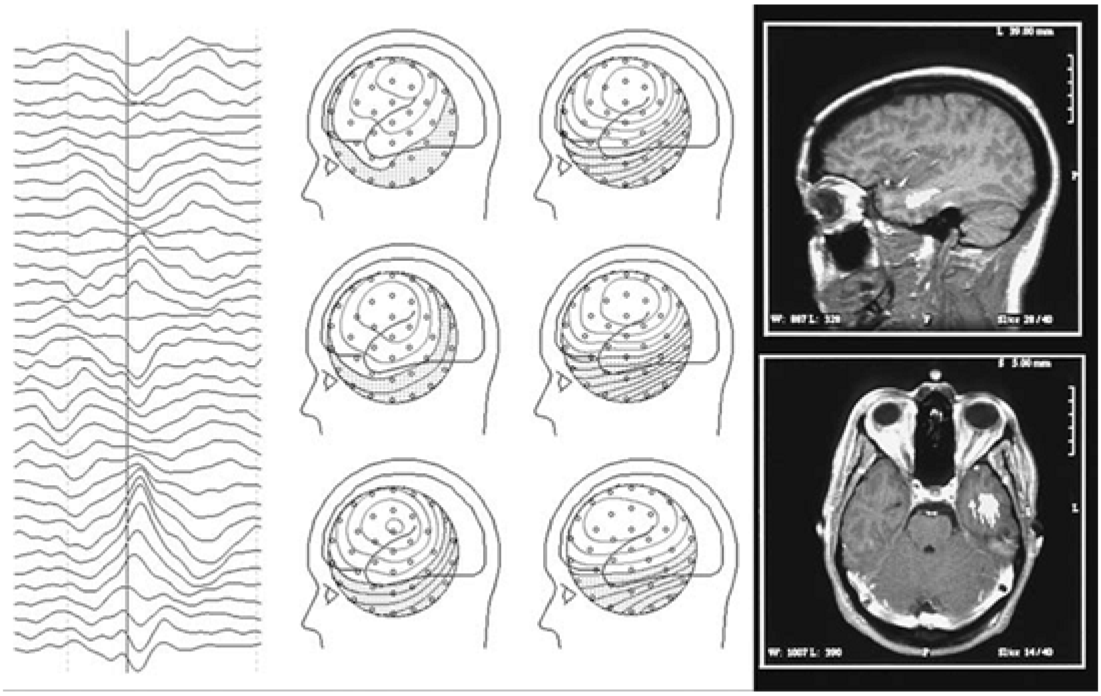

FIGURE 16. Left temporal spike recorded with 37-sensor magnetoencephalography. Note that the magnetic field is relatively stable in location and shape during the course of the spike. Dipole models of several such spikes are depicted at right and are of the anterior temporal anterior-posterior horizontal

type.

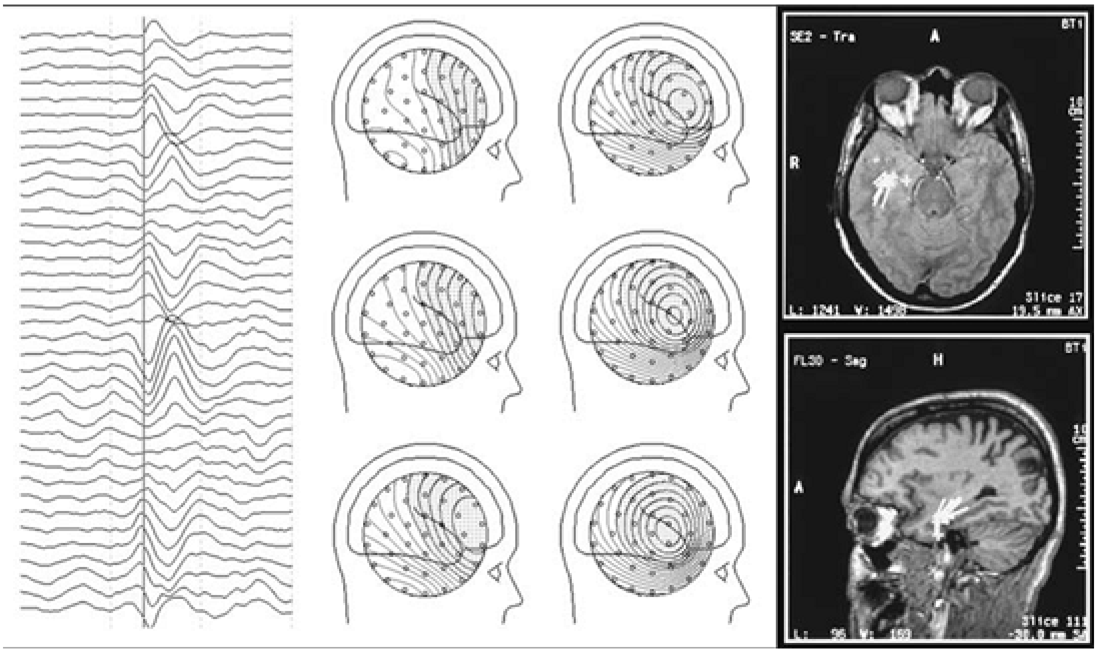

FIGURE 17. Right temporal spike recorded with 37-sensor magnetoencephalography. Note that the magnetic field maxima change considerably in location and shape during the course of the spike. A moving-dipole model of this spike has solutions that progress from vertical to horizontal in orientation. This suggests propagation from the base to the tip of the temporal lobe.

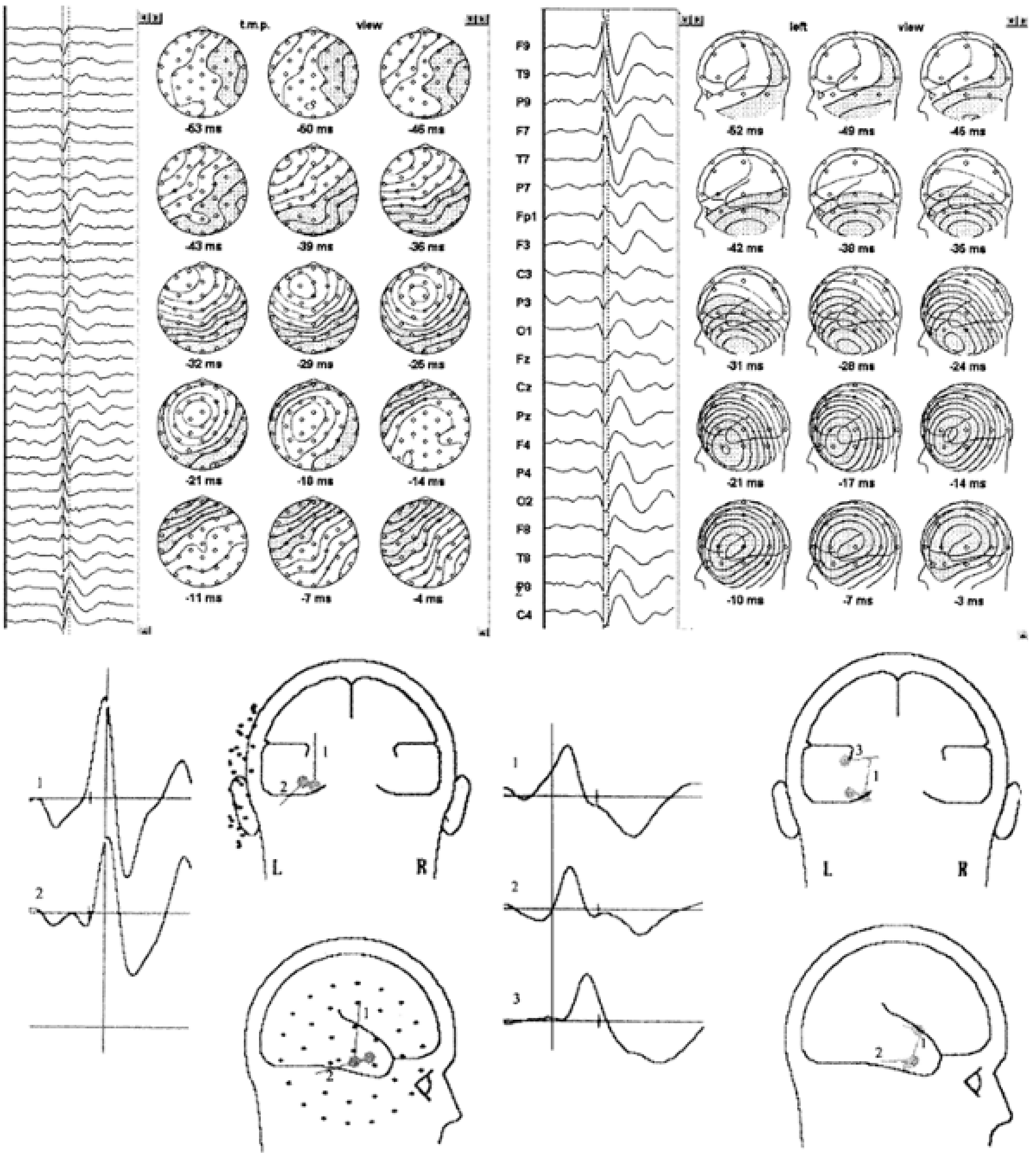
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FIGURE 18. Simultaneously recorded magnetoencephalographic (MEG) **(left)** and electroencephalographic (EEG) **(right)** spike from the left temporal lobe. Maps of both MEG and EEG show movement of field maxima during the spike. A spatiotemporal model of the MEG spike reveals two component dipoles, an initial vertical tangential (1) followed by an anterior-posterior (AP) horizontal tangential (2). A spatiotemporal model of the EEG spike shows the same initial two component dipoles (1, 2) plus a later horizontal radial dipole (3). These source models suggest propagation from temporal lobe base to tip to lateral surface. MEG could not identify the last source because its orientation was radial.

In a series of 32 patients with complex partial epilepsy, Ebersole et al.[44] recorded simultaneously 37-channel MEG and 21-channel EEG to make direct comparisons between their respective dipole models for the same interictal spike. As in the case of EEG, they found that patients can have multiple types of MEG spikes when parameters of dipole orientation and evolution over time are taken into consideration along with location. Sorting spikes by these additional criteria led to tighter clusters of spike dipoles that were more likely modeling the same source. Many of the earlier MEG epilepsy studies calculated only equivalent dipole location, possibly resulting in a more heterogeneous sample.

When investigating MEG fields over the duration of the spike, Ebersole et al.[44] found that the majority were relatively stable in contour, reflecting a simple source character (Fig. 16). However, as more commonly noted in EEG, as many as 30% of spikes in a given patient possessed magnetic fields that changed over their time course (Fig. 17). This means that generator geometry is changing, probably from spike propagation. In these cases, instantaneous single-dipole modeling is not adequate, as explained earlier, and spatiotemporal multiple MEG dipole modeling is appropriate (Fig. 18). This type of analysis has provided good explanations for evolving MEG fields. Usually, two or, at most, three sources with temporally overlapping activity result from the modeling. Propagation within the temporal lobe from basal to anterolateral cortex and vice versa has been demonstrated in such modeling. It is important, therefore, to assess dipole stability before

attributing a spike to a single source. The earliest active source contributing to a spike is more important clinically than is a later source activated by propagation. Modeling just the peak of a spike or a single time point when the field is maximally dipolar may result in erroneous localization of spike origin.

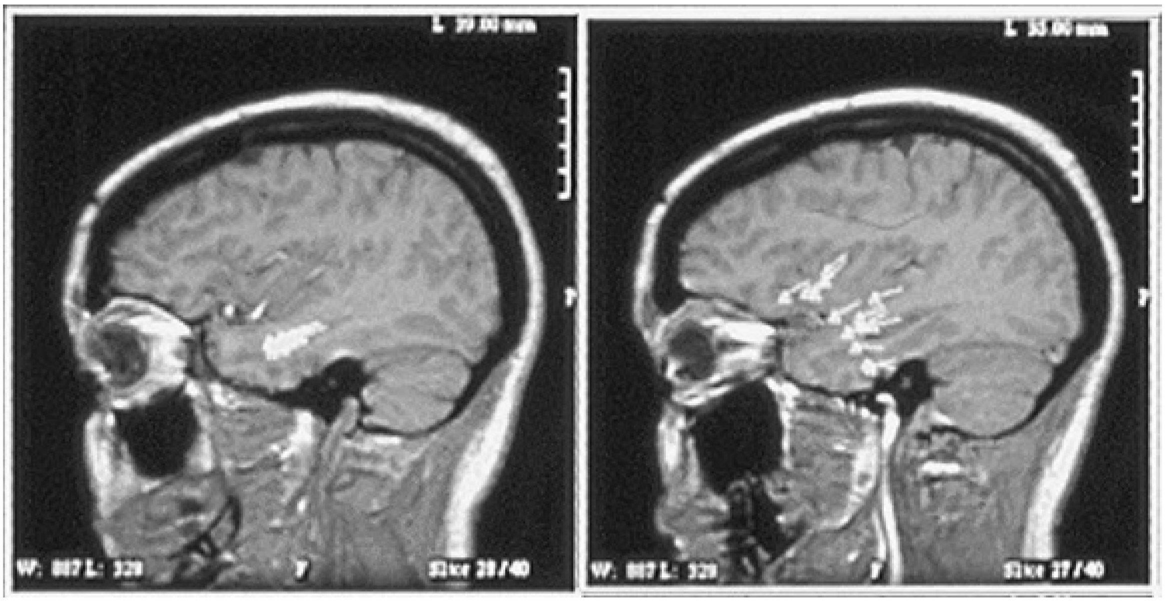

FIGURE 19. Left: A tight cluster of dipoles (anterior-posterior horizontal) modeling a series of magnetoencephalographic (MEG) spikes is coregistered with the magnetic resonance imaging of a patient with temporal lobe epilepsy. **Right:** electroencephalographic (EEG) dipole models of the same spikes. Note that the EEG dipole scatter is greater and that several of the dipoles fall outside of the temporal lobe.

When MEG and EEG dipole models of the same spike population were compared, several trends emerged across all patients. First, the MEG dipoles formed tighter, anatomically more restricted clusters than did counterpart EEG dipoles. Second, the EEG dipole clusters were usually higher and somewhat deeper in the head. When projected into the patients' MRIs, the MEG dipole clusters were confined to localized regions of the temporal lobe, whereas the more diffuse EEG dipoles were commonly scattered among temporal, frontal, and parietal lobes (Fig. 19). These patients were all presumed or later proven to have temporal lobe epilepsy by intracranial EEG monitoring. Ebersole et al.[44] concluded that MEG spike dipole localization was more accurate and anatomically reasonable

than that of EEG. Factors that probably contributed to the poorer performance of EEG dipole modeling included the smaller number of recording channels and the spherical head model, which was vulnerable to error in the temporal area. Scheler et al.[131] also showed, in data collected from 100 patients, that EEG results scattered significantly more than MEG results.

Detection Sensitivity of Magnetoencephalography

Baumgartner found that synchronized epileptic activity of about 4 cm^2 restricted to the most mesial temporal electrodes covering the parahippocampal gyrus did not produce a detectable MEG spike, whereas activity of about 8 cm^2 involving mesial plus more lateral electrodes overlying the fusiform gyrus could clearly be identified on MEG.[15] Other investigations with simultaneous subdural EEG and MEG recordings validated that temporal basal sources must be >4 cm^2 in area to be detected by MEG.[104] In the case of lateral neocortex, however, only 3 to 4 cm^2 of synchronized epileptic activity involving the lateral neocortex was necessary to produce a detectable MEG signal at the scalp,[15,104,113] which is smaller than the 10 cm^2 of spiking cortex found by Tao et al. to be necessary to generate a measurable scalp-EEG spike.[158] Thus, MEG appears be more sensitive than scalp-EEG for the detection and delineation of the irritative zone in neocortical epilepsy involving superficial cortex.

Diagnostic Yield of Magnetoencephalography

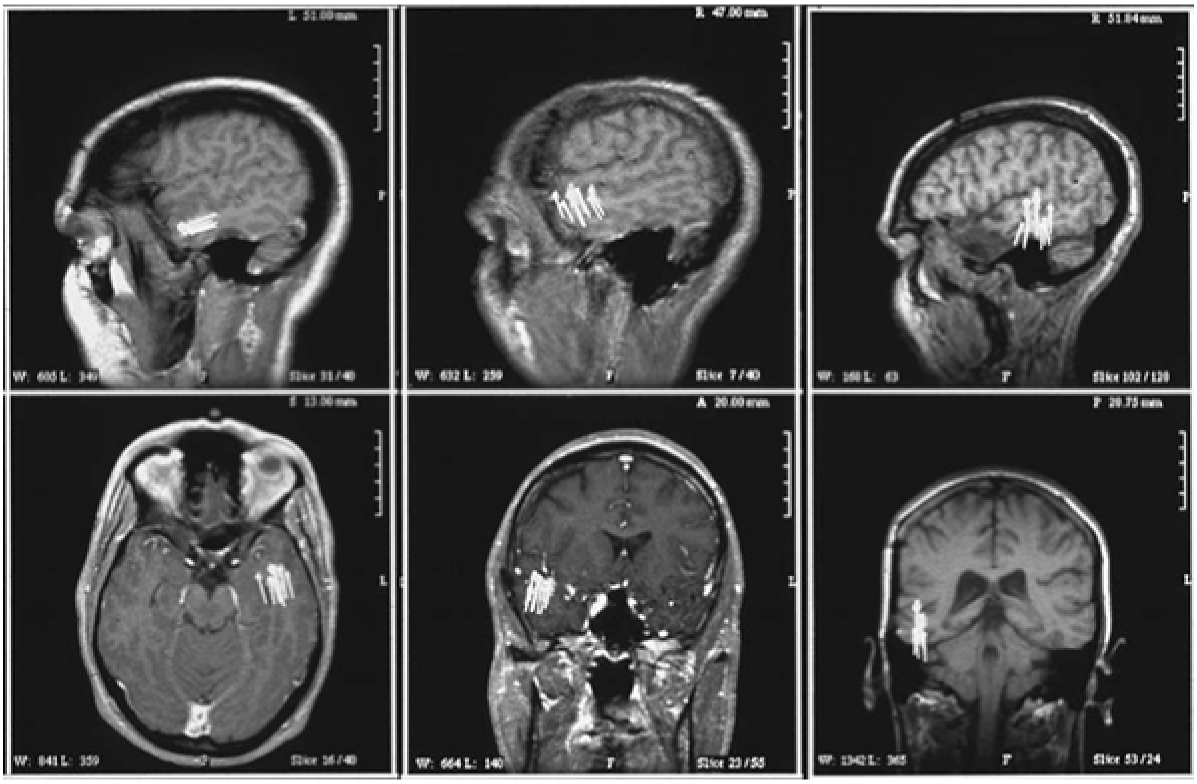

FIGURE 20. Three patterns of magnetoencephalographic (MEG) spike dipoles noted in patients with temporal lobe epilepsy. **Left:** Anterior temporal anterior-posterior horizontal. **Middle:** Anterior temporal vertical tangential. **Right:** Posterior temporal vertical tangential.

In many early MEG studies patients were selected because they had frequent spiking on prior EEGs. When randomized patients were evaluated, the yield for MEG spikes suitable for modeling using a single 2- to 3-hour study varied from 73% of cases[77] to 53.1% in patients with temporal lobe epilepsy.[18] Iwasaki et al.[74] blindly reviewed simultaneous MEG and EEG data from 43 consecutive patients with temporal lobe epilepsy. They found spikes in MEG alone in 8 and in EEG alone in 1. The remaining patients had spikes in both, with an overall agreement in 25 of 43 patients between the two modalities. They found that MEG was slightly more sensitive than EEG by 55.8% to 49.7%.

Interictal MEG spikes are more readily recorded from patients with neocortical seizures as compared to mesial temporal lobe seizures. Thus, the diagnostic yield was 92% for neocortical epilepsy versus 50% for mesial temporal lobe epilepsy in one study[77] and 73.3% for neocortical versus 42.3% for mesial temporal lobe epilepsy in another.[18] Park et al.[120] blindly reviewed simultaneous MEG and EEG data from 12 consecutive patients with neocortical epilepsy. All patients had spikes seen by both modalities; however, MEG spikes without an associated EEG potential represented from 5.9% to 97.9% of the total spikes in a particular patient, whereas spikes unique to EEG were seen in only 0% to 35% of spikes.

Intracranial Validation of Magnetoencephalographic Source Models

As in the case of EEG dipole analysis, validation of postulated source character and location requires either direct invasive measures, such as intracranial EEG, or a large controlled study of indirect measures, such as other noninvasive tests or surgical outcome. In numerous studies, MEG dipole localizations showed good agreement with the results obtained from subsequent invasive EEG recordings.[76,77,78,105,110,115,117,125,147,152,155,156] However, the problem with many attempts at validation has been a lack of confirmation that the activity recorded from the brain was the same as that recorded by MEG. It is well known that most interictal spikes recorded from invasive electrodes are not recordable with scalp EEG and probably not with MEG. Therefore, it is not adequate simply to show that there are interictal spikes arising from a brain region identified by a dipole model; rather, it must be shown that the spikes arising from this region are of sufficient size and extent to produce the EEG and MEG signals that were recorded at the scalp. Such proof requires at least simultaneous intracranial

and scalp EEG recording, if not simultaneous intracranial EEG and extracranial MEG recording.[44] This has been performed simultaneously in only in a limited number of patients.[15,77,104,113,150]

Magnetoencephalographic Dipole Modeling in Temporal Lobe Epilepsy

Several studies investigated the use of MEG in distinct subtypes of temporal lobe epilepsy (TLE)—mesial, nonlesional, and lesional TLE.

In classic mesial TLE, two patient subgroups could be identified. One group possessed spikes modeled by anterior temporal vertical (ATV) dipoles and the other had spikes modeled by anterior temporal horizontal (ATH) dipoles.[18,122] Whereas ATV dipoles indicate epileptic activity in the medial basal temporal, ATH dipoles are compatible with epileptic activity in the temporal pole and adjacent parts of the lateral temporal lobe. In patients with ATV dipoles, interictal and ictal EEG changes recorded during prolonged video-EEG monitoring were localized consistently to the ipsilateral temporal lobe. On the contrary, up to 50% of patients with ATH dipoles showed bitemporal spikes and/or seizure onsets.[122] Surgical outcome after selective amygdala-hippocampectomy was slightly better in patients with ATV dipoles than in those with ATH dipoles, which could serve as an argument for performing larger resections in the latter patient group, whereas a selective amygdala-hippocampectomy should be sufficient in the former.

In nonlesional TLE, MEG dipole localizations agreed reasonably well with invasive EEG recordings. One pattern of spike source localization and orientation (anterior temporal AP horizontal) correlated well with mesial temporal lobe seizure onset. Another pattern (anterior temporal vertical) was correlated with anterior, and perhaps mesial, temporal lobe onset. A third (posterior temporal vertical) correlated well with lateral or nonlocalized onset (Fig. 20).[18,39] MEG therefore may be helpful to noninvasively differentiate mesial from lateral neocortical epileptogenic zones in patients with nonlesional temporal lobe epilepsy.

In lesional TLE, MEG helped to resolve the relationship between structural lesions and the seizure-onset zone. In a study on patients with neocortical temporal lesions, lesionectomy produced a seizure-free outcome in patients in whom MEG spike dipole localizations corresponded to the lesion.[73] In patients with diffuse MEG spike dipole localizations, on the contrary, invasive EEG recordings documented a mesial temporal seizure onset distant from the lesion.

Magnetoencephalographic Dipole Modeling in Extratemporal Epilepsy

Patients with medically refractory extratemporal epilepsies pose major problems for presurgical evaluation and surgical treatment because lesions frequently cannot be identified on MRI scans and surgical outcome is worse than in temporal lobe epilepsy. MEG provided useful information during the evaluation of patients with extratemporal epilepsies in several recent studies, which found excellent agreement between MEG spike dipole localizations and the results of invasive recordings.[115,142,148,149] MEG helped to localize the irritative zone in patients with normal MRI scans, to define the relationship of epileptic activity with respect to large lesions and eloquent cortex, and to decide which of multiple lesions was the epileptogenic one.[148] With this information the correct placement of invasive electrodes could be improved significantly.[148] MEG also provided unique information during a second presurgical evaluation leading to a successful second resective surgery.[148] Finally, resection of the MEG-defined irritative spike

zone had prognostic implications for postoperative seizure control.[62,115]

Ictal Magnetoencephalography

Consistent regional interictal epileptiform discharges can add confirmatory evidence for identifying the area of seizure onset; however, regional ictal epileptiform discharges preceding or simultaneous with the patient's habitual seizures are considered the most reliable localizing sign in presurgical evaluation. Recently several studies presenting data on ictal MEG recordings in patient series were published.[4,8,48,157,160] Whereas some studies showed good concordance between interictal and ictal MEG localizations in most patients,[4,157,160] one study found ictal MEG clearly superior to interictal MEG.[48] Ictal MEG localizations could be confirmed by subsequent intracranial recordings in selected cases.[4,8,48] Nevertheless, ictal MEG recordings are impractical in a routine clinical setting for several reasons. First, the patient must have frequent seizures for an event to be captured during the restricted time of the MEG recording session. Second, the patient is required to stay in a fixed position in relation to the magnetometer over a prolonged time period, which is stressful and uncomfortable and can be achieved only with very cooperative patients. Third, seizures usually are accompanied by movement and associated artifacts, which make MEG data difficult to interpret. Finally, several seizures have to be recorded to localize the seizure onset zone reliably. Barkley et al.[8] reported one patient who had one seizure during MEG that colocalized to one of three zones of interictal MEG spikes. When this patient later had invasive EEG monitoring, all three zones of interictal MEG spiking were found to be zones of ictal onset. Thus, further technological improvements are necessary to facilitate long-term MEG recordings.

Clinical Utility of Magnetoencephalography in Presurgical Evaluations

A number of investigations have attempted to quantify the usefulness of MEG in the evaluation of patients who are being evaluated for epilepsy surgery as compared to other diagnostic studies. MEG was second only to invasive video-EEG in correctly localizing the epileptogenic focus in the patient series studied by Wheless et al.[170] Later Stefan et al. demonstrated that interictal MEG localized to the lobe where the resection was performed in 71% of seizure-free patients, as compared to 43% using ictal scalp EEG.[149] In a study of temporal lobe epilepsy patients, those with anterior temporal (AT) MEG spike localization (defined as >70% of spike dipoles located in the anterior temporal lobe) had a different surgical outcome from patients with non-AT localizations.[73] All AT-localized patients became seizure and spike free after anterior temporal lobectomy with amygdala-hippocampectomy, whereas patients with non-AT MEG spike localizations faired less well, indicating either non–medial temporal lobe epilepsy or spike propagation to the posterior and extratemporal neocortex. In another study on 26 patients with TLE, MEG dipole locations and orientations provided useful localizing information about the seizure onset zone.[5] Twenty-three patients with ATV and ATH dipoles became seizure free after anterior-medial temporal lobectomy or selective amygdala-hippocampectomy; however, the remaining 3 patients with lateral vertical dipoles became seizure free after restricted neocortical temporal resections. In lesional frontal lobe epilepsy, complete resection of the MEG-defined irritative zone correlated with a favorable surgical outcome.[62] Finally in a study of 33 patients, successful surgical outcome was correlated with (a) MEG dipole ellipsoids being in the surgical resection volume, (b) a small distance separating the center of the MEG dipole ellipsoid and the center of the resection volume, and (c) a homogeneous distribution of MEG dipole localizations, thus supporting the prognostic implications of MEG in epilepsy surgery.[51]

Simultaneous Magnetoencephalographic and Electroencephalographic Dipole Modeling

There are few studies in the medical literature that compare dipole models of both MEG spike fields and EEG spike potentials that were simultaneously recorded. Early investigations with small sensor arrays showed that both MEG and EEG dipole modeling gave good results relative to ECoG findings, but most researchers felt that

MEG was superior.[34,78,110] Recent investigations with whole-head systems have emphasized that in individual cases spike localization may be better with one or the other technique.[12,13,94,122,173] All concluded that using data from both MEG and EEG is better than using either alone. This is easily understandable, given the complimentary strengths of each type of recording.

Future of Magnetoencephalographic/Electroencephalographic Dipole Modeling

As noted, investigators have concluded that future successes of source modeling in epilepsy evaluations may lie in combining the strengths of MEG and EEG. Several researchers have developed methods for combining EEG and MEG data in one source model.[6,76] They too claim that these combined-source models are superior to either MEG or EEG model alone and can provide information not present in either. Directions of highest sensitivity for MEG and EEG are orthogonal to each other—tangential and radial, respectively. MEG data are simpler, less ambiguous, and easier to model, but they are incomplete. Electroencephalographic data are more complete, but they are more complex and less clear. Combining MEG and EEG makes great theoretical sense, but exactly how to do this is an incompletely solved question, particularly given the considerable influence of the volume conductor on the EEG. Significant advances in the EEG component will come with further implementation of high-density sampling and realistic head models. Magnetoencephalography has been enhanced by whole-head systems. Technological advances in the future may dramatically reduce the cost of MEG equipment. This includes the elimination of shielded rooms and the development of sensors based on high-temperature superconductivity. Both techniques will benefit from a more complete understanding of brain/head anatomy, conductivity, and anisotropy. These will enhance both data display and provide parameters/constraints that can be used to improve source modeling. Certainly it is likely that there will be continued development of cortex-constrained extended-source models. These will probably replace simpler dipole models in the near future.

Summary and Conclusions

Spatiotemporal analysis of EEG and MEG by means of voltage and magnetic field topography and dipole and extended-source modeling can reveal a wealth of information beyond that routinely obtained from scalp EEG. Pattern recognition, as the foremost form of EEG analysis, will soon be supplanted by a more sophisticated appreciation for EEG and MEG source characterization that is now available with modern computer-analysis techniques. It is likely that these sensitive measures will

also allow us better to understand the relationships between brain function and dysfunction. Improved noninvasive characterization of the epileptogenic focus and of functionally important cortical areas in surgical candidates will likely be the first beneficiary of these diagnostic developments.

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Chapter 79

Structural Neuroimaging

Graeme D. Jackson

Ruben I. Kuzniecky

Introduction

The magnetic resonance imaging (MRI) study has become part of the basic assessment of patients with epilepsy and is of equal importance to the electroencephalogram (EEG). The assessment of the problem of seizures requires knowledge of the clinical details and features of the seizures, the functional abnormality in the brain as shown on the EEG, and the structural assessment of the brain with an MRI study optimized for epilepsy.

Several commissions of the International League Against Epilepsy have considered which patients with epilepsy should have an MRI study. It is becoming increasingly clear that a basic MRI study now has a similar status to the EEG as part of the basic assessment of epilepsy (Table 1).

Because there is the option of a surgical excision of the â€œseizure focus,â€ which may cure the patient, the detection of a focal abnormality of the brain is important for the formulation of the reason for the seizures and the options available for treatment. Knowledge of the brain abnormalities early in the course of treating the patient greatly helps the management of each individual. Magnetic resonance imaging is indispensable in many areas of neurology. The challenge to epileptologists is that the problem of epilepsy is a special one, which requires optimized protocols dedicated to it. In this chapter, we explain the essential elements of this issue and give a broad overview of what imaging options are available for the investigation of the patient with epilepsy from the perspective of the practicing epileptologist.

MRI studies should fit into the overall assessment of the patient. To understand the basis of the epileptic disorder, we first need to define and understand the epileptic events (clinical and EEG, ictal single photon emission computed tomography [SPECT]), the structural abnormalities in the brain, and the clinical context in which seizures occur.

In this chapter, we first deal with the need to define and understand the structural brain abnormalities by acquiring appropriate epilepsy-focused MRI of high quality and diagnosing the important lesions with high sensitivity and specificity. The clinical context, seizure features, and interpretation of the imaging, with full knowledge of the hypothesized basis of each individual's epilepsy, are the keys to proper use of imaging. MRI interpretation is different when used in a screening way and when viewed in the context of other investigations. This is particularly important when the patient has partial seizures and may be considered for surgical treatment.

In Epilepsy, â€œNormalâ€ and â€œAbnormalâ€ are Diagnoses That Require Certainty: â€œSuspiciousâ€ is Equally Important and Different

It is important to identify suspicious as well as definitely abnormal areas. In the interpretation of the MRI in epilepsy, it is not enough to evaluate the images as â€œabnormalâ€ or, by default, â€œnormal.â€ The diagnosis of â€œnormalâ€ should be an active and positive one. If there is any change that is suspicious but not definitely abnormal, the diagnosis of normal is not appropriate. This â€œin-betweenâ€ assessment can be very important in deciding how further investigations progress.

Most centers that deal with epilepsy spend a great deal of time in ensuring the quality of their EEG and EEG interpretation. However, unless there is a radiologist with an interest in epilepsy or an epileptologist who spends time with radiologic colleagues, it can be difficult to establish good epilepsy-focused MRI with appropriate sequences, radiography, and interpretation (Table 2).

Technical Issues

An â€œEpilepsy Protocolâ€ Is Essential

An epilepsy MRI is not just a â€œroutine MRI.â€ This is because the lesion of hippocampal sclerosis (HS) is hard to diagnose without using a dedicated epilepsy protocol, and it is essential to be confident about this in the basic assessment of the patient with epilepsy.

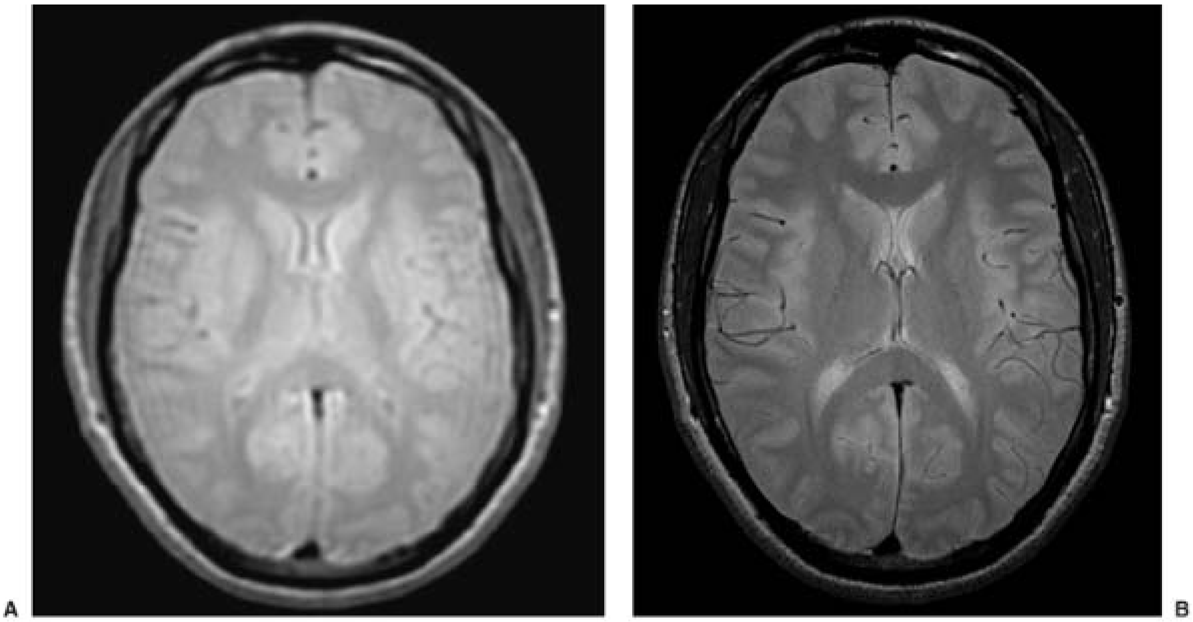


FIGURE 1. Spatial resolution. An optimal magnetic resonance study needs to optimize spatial resolution contrast and imaging time. Low spatial resolution is shown on the left and high resolution with longer scan time is shown on the right. All other imaging parameters are identical between these images.

MRI acquisition and interpretation need to be focused on the problem of epilepsy (Table 2). An optimal MR study needs to deal with the issues of partial volume, which can blur the edges of a structure such as the hippocampus, as well as have good spatial resolution, good signal-to-noise ratio, good contrast, and short imaging time. To deal with this issue of partial volume effects, often very thin images are acquired. This can lead to increased noise in the images, which can defeat the purpose of having these thin slices. This interplay between spatial resolution and signal-to-noise ratio is illustrated in Figures 1 and 2. (For a review of the physical principles of imaging see Jackson et al.[8] and references therein.)

T1-Weighted Images

T1-weighted images are usually presented so that cerebrospinal fluid (CSF) is black, gray matter is gray, and white matter is bright. Generally these images are used to assess brain morphology. Different sequences give different types of T1-weighted images. FIGURE 3A shows an inversion-prepared, gradient-echo, echoplanar image. Sequences like this are fast, give good brain coverage, and often allow reasonably thin slices to avoid â€œpartial volumeâ€ effects. FIGURE 3B shows a true inversion recovery image. This gives better grayâ€“white matter contrast, improved contrast for gliosis, and also better delineation of the internal features or architecture of the hippocampus. These images take longer and have thicker slices and often incomplete brain coverage, but they can be extremely helpful in difficult cases.

Table 1 The three most important tests in assessing the patient with epilepsy

A good clinical history
A good electroencephalogram
Epilepsy-protocol magnetic resonance imaging

T2-Weighted Images

T2-weighted images usually show the CSF as white and the gray matter of higher signal (brighter) than the white matter. These images typically show pathology as areas of increased signal and are used to assess whether the tissue is abnormal (Fig. 4). As with T1-weighted images, there are many choices of sequence that one can use. Fast spin echo is a sequence that allows high-resolution images with good contrast in a short time (Fig. 5).

Fluid-Attenuated Inversion Recovery Images

Table 2 Epilepsy magnetic resonance imaging involves a team

The epileptologist must be involved in imaging
The radiologist must understand clinical needs
The radiographer must deliver high-quality epilepsy-focused images
Training and development must be ongoing between radiology and neurology
The members of the team all need to understand some of the technical issues

Fluid-attenuated inversion recovery (FLAIR) images can be thought of as T2-weighted images in which the CSF, through clever tricks applied during imaging, has been made to look dark. Pathology still looks high in signal (bright, Fig. 6). It is often much easier to see the pathology in these images, largely because there is no concern that the signal change can be attributed to partial voluming of the CSF and also because it is visually easier to identify. Some lesions that with a practiced eye can be seen on T2-weighted images become obvious on FLAIR images because of this issue of CSF partial voluming (Fig. 7). FLAIR images are not good for looking at morphology and may produce some artifactual signal increases in some areas. In the case of epilepsy, the issue of most concern relates to subtle signal changes in the mesial temporal regions on coronal images, in which these artifacts need to be interpreted with an experienced eye.

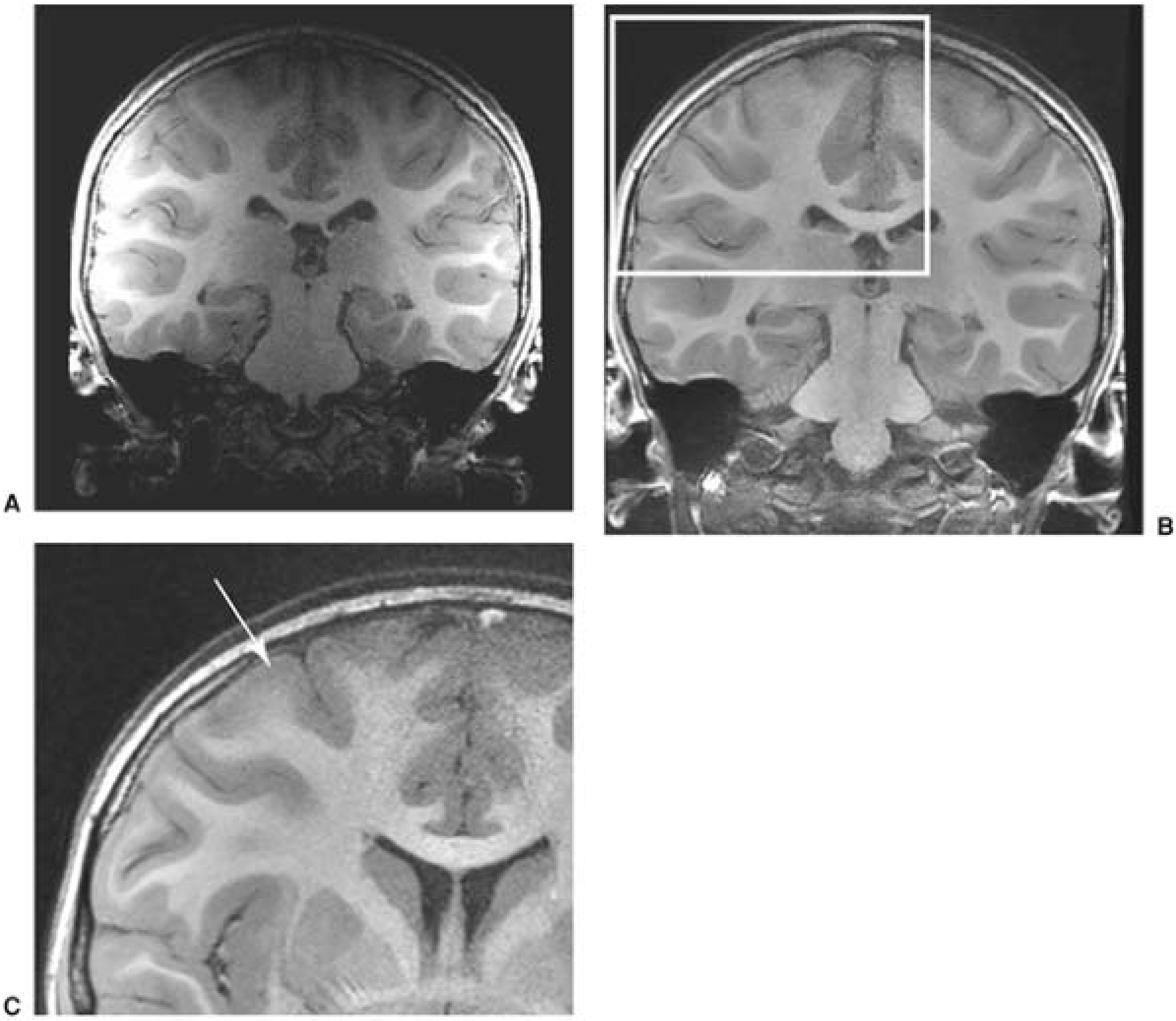


FIGURE 2. Signal-to-noise ratio. The issue of signal-to-noise ratio is well illustrated by this image, which was obtained using temporal surface coils. There is high signal-to-noise ratio close to the surface coils (bright in panel A). The image intensity is corrected in panel B and expanded in panel C. The consequences of low signal-to-noise ratio are easily seen here. Laterally, the grayâ€“white matter junction is crisp and well defined. In the medial frontal region the image appears â€œspeckledâ€ and the grayâ€“white matter junction is harder to define. An optimal signal-to-noise ratio may be somewhere in the area shown by the arrow.

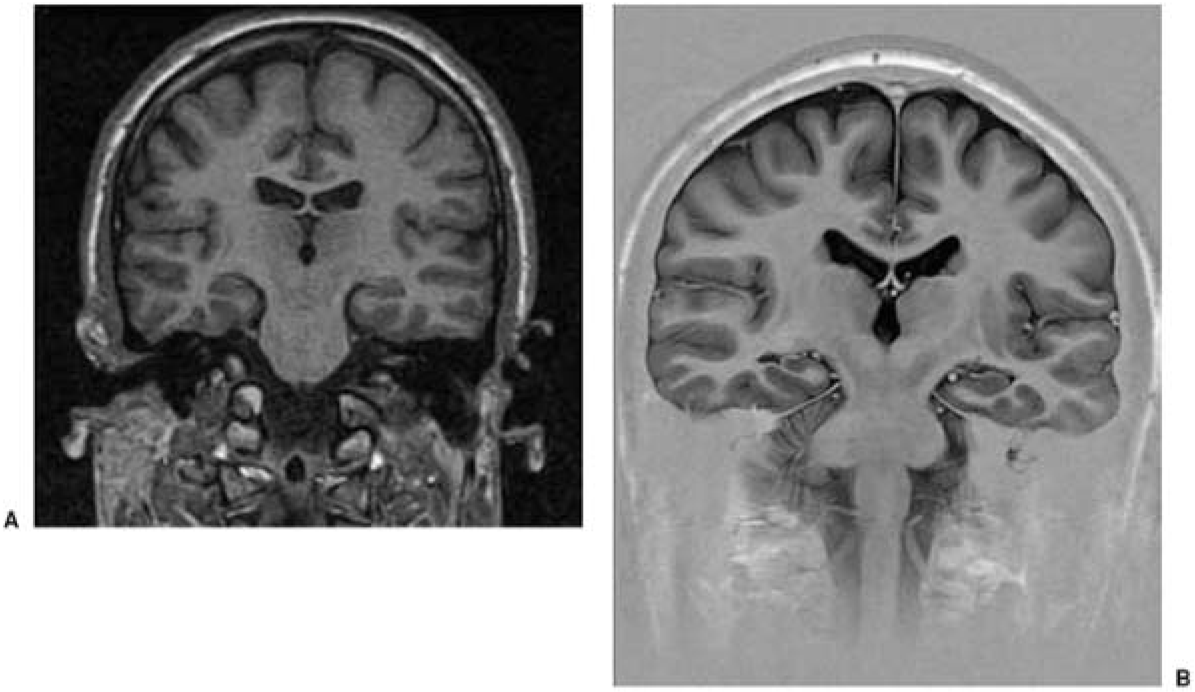


FIGURE 3. Different sequences give different types of T1-weighted images. **A:** An inversion-prepared, gradient-echo echoplanar image. **B:** A true inversion recovery image. The image in panel B shows right hippocampal sclerosis with a small right hippocampus and loss of the normal internal architecture (CA1 is not seen).

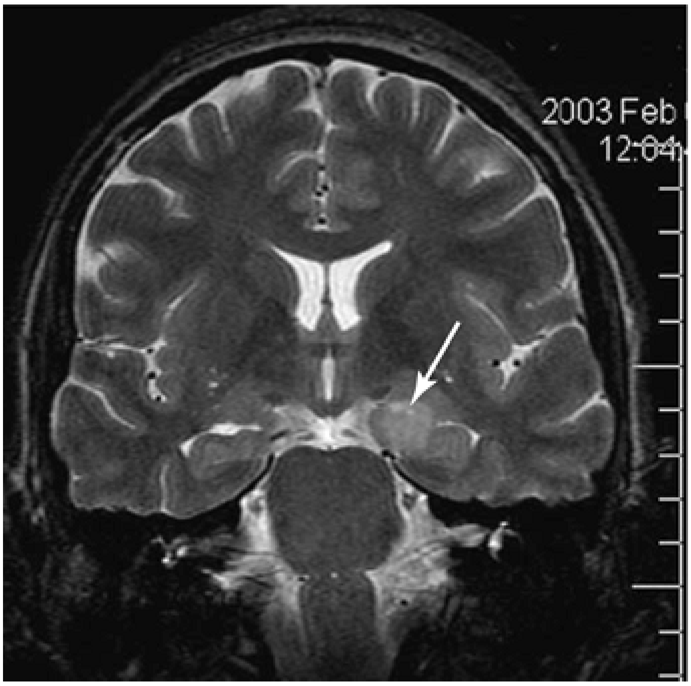


FIGURE 4. This T2-weighted image shows a dysembryoplastic neuroepithelial tumor in the mesial temporal region, involving the amygdala and the hippocampus on the left side (*arrow*).

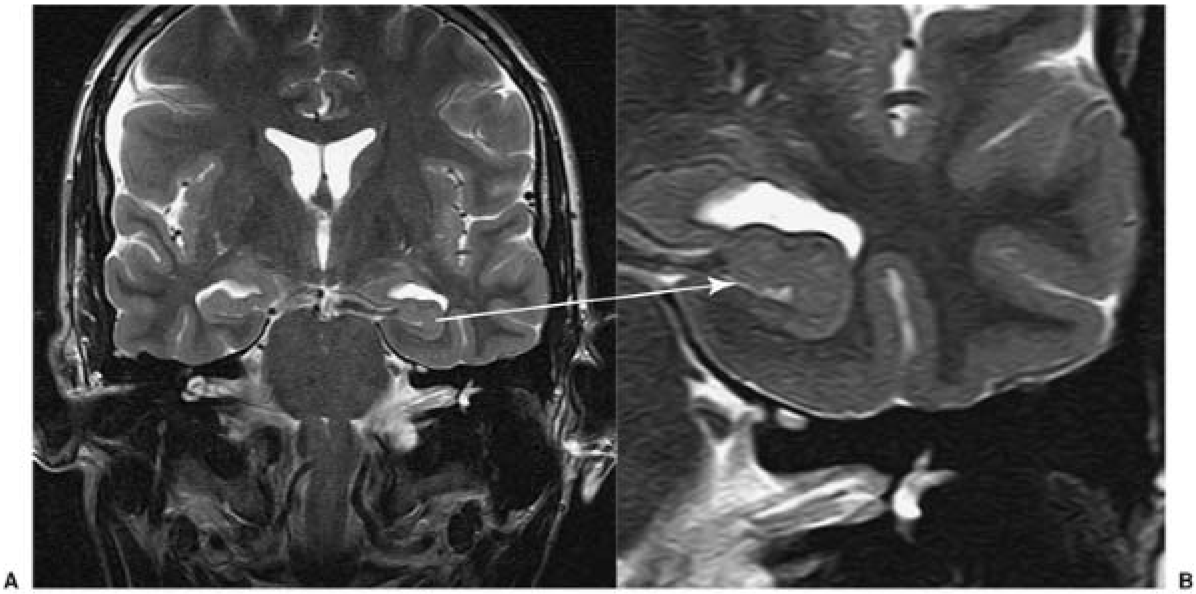


FIGURE 5. Fast spin echo = faster or higher resolution. The internal structure of the hippocampal head can be seen in these fast spin echo images.

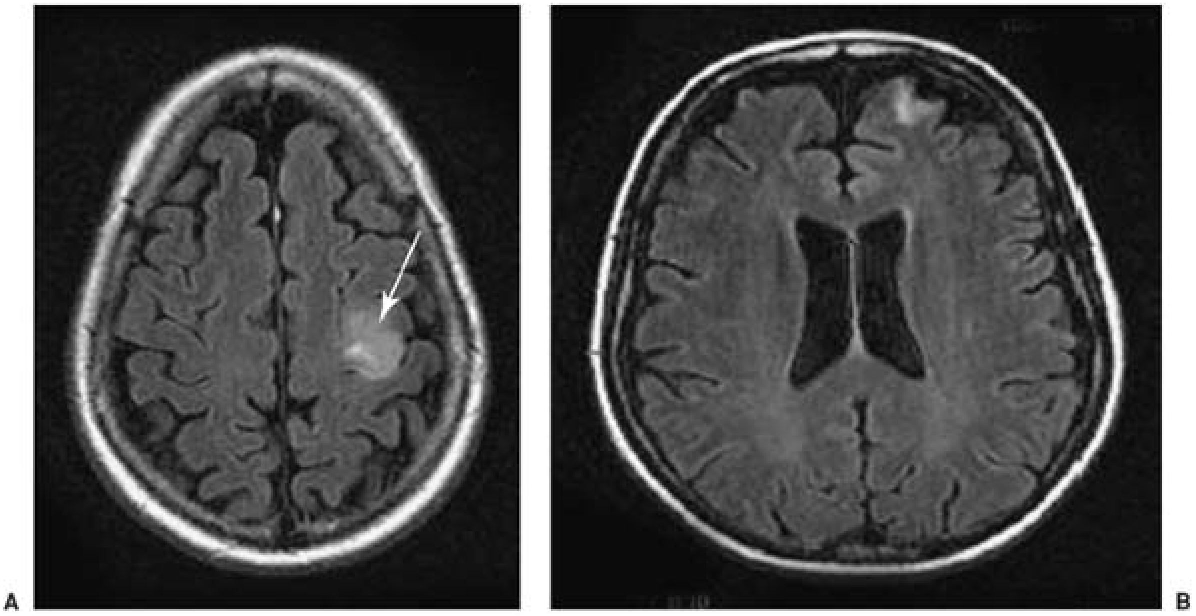


FIGURE 6. Fluid-attenuated inversion recovery (FLAIR) images can sometimes make lesions easier to see. This image shows a focal lesion in the middle frontal gyrus (*arrow*, panel A). This would be seen easily on a

routine T2-weighted sequence, but note the additional abnormality in the left frontal pole (*unmarked,* panel B). When signal change from pathology is close to a cerebrospinal fluid (CSF) boundary, it can sometimes be hard to identify. FLAIR images are not good for looking at morphology and may produce some artifactual signal increases in some areas, but they are excellent for identifying non-partial-volume signal changes that cannot be due to CSF.

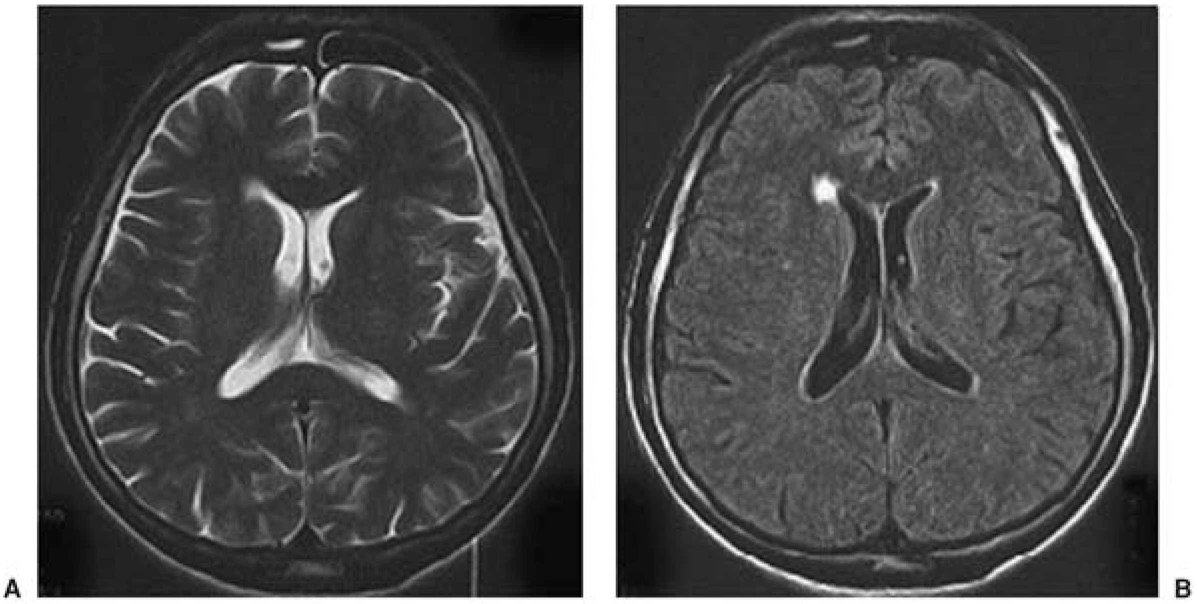


FIGURE 7. The same lesion on T2-weighted **(A)** and fluid-attenuated inversion recovery (FLAIR) **(B)** images. To the experienced eye, the lesion is easily seen on the T2-weighted images, but it is much more apparent, more easily noticed, and more confidently diagnosed with the FLAIR sequence.

Figure 8 shows the practical importance of this. This patient had severe intractable frontal lobe epilepsy, and the MRI had been reported as normal over a long period of time. A repeat imaging study using these principles revealed a focal cortical dysplasia in the right frontal lobe that led to a clearly defined surgical option. Recognition of these subtle lesions is the fundamental skill toward which the optimization of epilepsy imaging and interpretation is directed.

Radiography

For epilepsy protocol images, the orientation of the imaging plane must be according to â€œein-brainâ€ landmarks. This means that the radiographer must understand the hippocampal axis and ensure that all imaging is in this plane (Fig. 9). Some centers still acquire images in the â€œmachine axis,â€ which is in terms of the x, y, and z directions of the bore of the MRI system. Because patients lie in the MR system at different angles, this gives images of inconsistent orientation. This is most important to keep in mind if one is to interpret the pathology of the hippocampus. Because one will need to compare structures on the left and the right, the angulation of the imaging in the coronal plane must also be symmetric, based on in-brain landmarks. In older MRI systems, this angulation caused some problems or was not possible. With new MR systems, this is easily done, but old habits may carry over from previous practice. Images can also be reconstructed in this appropriate axis from three-dimensional (3D) data sets. It is important that the epileptologist review and be satisfied with the quality of the imaging.

Figure 9 shows the basic orientation for an epilepsy protocol.[6] The image sequence in this case gives axial and coronal images as shown. This is possibly the most important message of this chapter. Without understanding of the importance of this, the rest does not follow. The whole of the hippocampus is seen in a single slice (top right image), and there is little partial voluming of the hippocampus (lower left image). Because the diagnosis of abnormalities in the mesial temporal region is fundamental to the assessment of any patient with epilepsy, this imaging plane must be part of any effective epilepsy protocol imaging.

Interpretation

Even when imaging is excellent, the correct interpretation of subtle changes needs to be based on a clear understanding of the features of the abnormality that has been looked for. In the case of epilepsy, the major difficulty that confronts the radiologist, and one with which the epileptologist must also be confident, is the reliable diagnosis of HS and subtle malformations of cortical development (MCDs).

The features of HS are altered signal in a small hippocampus and loss of the normal internal architecture (Table 3, and Figs. 10 and 11).[6] Not all asymmetry is HS, and abnormal signal in a large hippocampus is usually hippocampal dysplasia rather than sclerosis. If one only looks for atrophy or asymmetry, the wrong hippocampus may be diagnosed as abnormal.

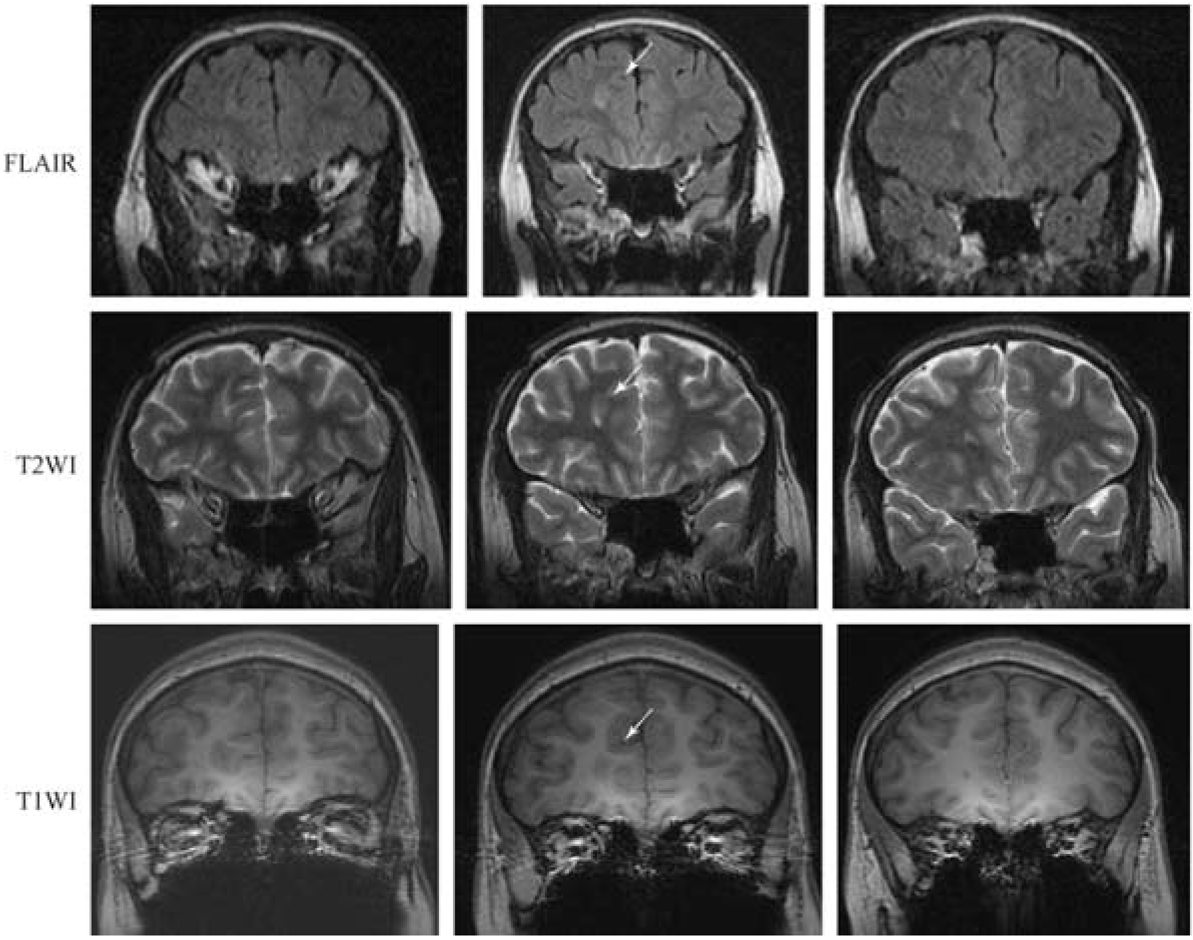


FIGURE 8. A typical imaging sequence (*arrow*). Note that the focal cortical dysplasia is visible in all sequences but is much easier to identify in the fluid-attenuated inversion recovery (FLAIR) sequence because of the easily seen abnormal and focal signal. T1WI, T1-weighted image; T2WI, T2-weighted image.

Requests

MRI is like the EEG in terms of requirements for basic study, sleep-deprived study, extra electrodes, or video-monitored

study. One can acquire many different bits of information using MRI that give different degrees of assessment of the brain (Table 4). This also involves having the patient potentially in the scanner for a long time. Although basic MRI is needed in nearly all patients, further studies need to be clinically driven and aimed at solving a specific problem. The epileptologist needs clearly to understand what information is needed and what can be obtained. The more focused the question that is asked of the radiologist, the better focused will be the assessment of the images. This is often the weak link in otherwise excellent MR imaging. Effort to focus the request is well rewarded.

There are many levels of information that can be acquired using MRI. In many ways this is similar to the EEG: It is familiar practice to order a routine EEG, a sleep-deprived EEG, or prolonged video monitoring studies. In addition, it is understood that a routine EEG may be associated with activations such as hyperventilation and photic stimulation.

The indication and interpretation of an MR depend on the electroclinical findings and are assessed along with other examinations, such as video-EEG telemetry, positron emission tomography (PET), and SPECT. The correct application and interpretation of MR imaging also depend on knowledge of the brain anatomy (see Kuzniecky and Jackson[10] for detailed review and further discussion of these issues).

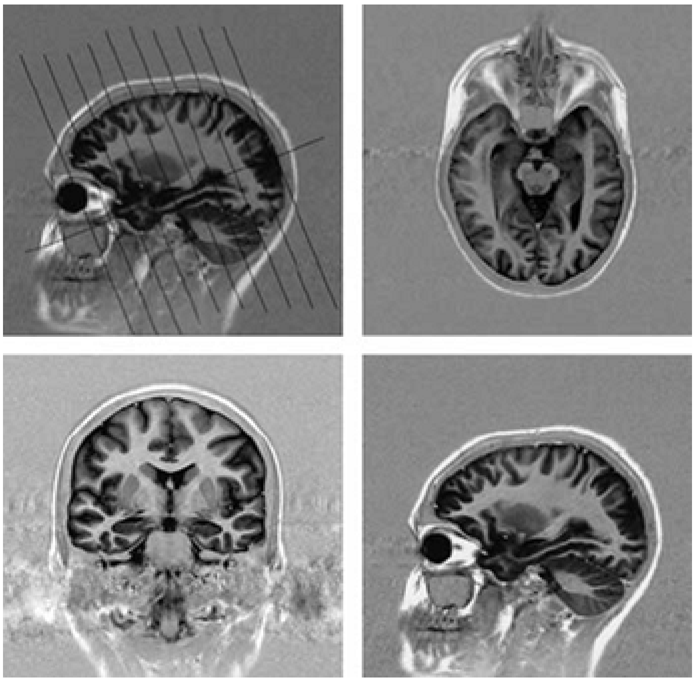


FIGURE 9. Epilepsy magnetic resonance imaging basics â€”the â€œhippocampal axis.â€ This image shows the basic orientation for an â€œepilepsy protocol.â€ The image sequence in this case gives axial and coronal images as shown. The whole of the hippocampus is seen in a single slice **(top right)**, and there is little partial voluming of the hippocampus **(lower left)**. Because the diagnosis of abnormalities in the mesial temporal region is fundamental to the assessment of any patient with epilepsy, this imaging plane must be part of any effective epilepsy protocol imaging.

Typical Imaging Sequences for an Optimized Epilepsy Protocol

A typical clinical scanning protocol for a patient with refractory epilepsy may include T1-weighted imaging, T2-weighted imaging, FLAIR imaging, and 3D volume acquisition sequences. T1-weighted imaging (short repetition time [TR] and echo time [TE]) is commonly used to initially define the brain anatomy. In T2-weighted images (long TR, long TE), many types of brain pathology are discernible. On FLAIR images, the CSF appears dark, which helps to identify lesions with long T2-relaxation times. A high-resolution 3D volume acquisition provides a useful degree of T1-weighted contrast between gray and white matter and helps greatly in the identification of subtle abnormalities, such as those associated with malformations of cortical development. The 3D data are made up of contiguous slices and allow characterization of the spatial extent of anatomic structures. Common 3D acquisition sequences include magnetization-prepared rapid acquisition gradient echo (MPRAGE) and 3D fast spoiled GRASS (3D-SPGR) imaging, where GRASS stands for gradient recalled echo acquisition at steady state. These sequences use a combination of short TR and TE to improve the time efficiency of the acquisition.

Table 3 Magnetic resonance imaging features of hippocampal sclerosis

Altered morphology (structure): Atrophy
Altered abnormal signal (tissue property)
High T2
Low T1
Abnormal internal structure with loss of CA1 microarchitecture

Based on multiple acquisitions with a variety of these pulse sequences acquired in optimized imaging planes, it is possible to detect low-grade tumors, vascular malformations, infarction, inflammation, or trauma as sources of seizures. The application of contrast agents is indicated if there is suspicion of a primary or metastatic tumor, infection, or inflammatory lesion.

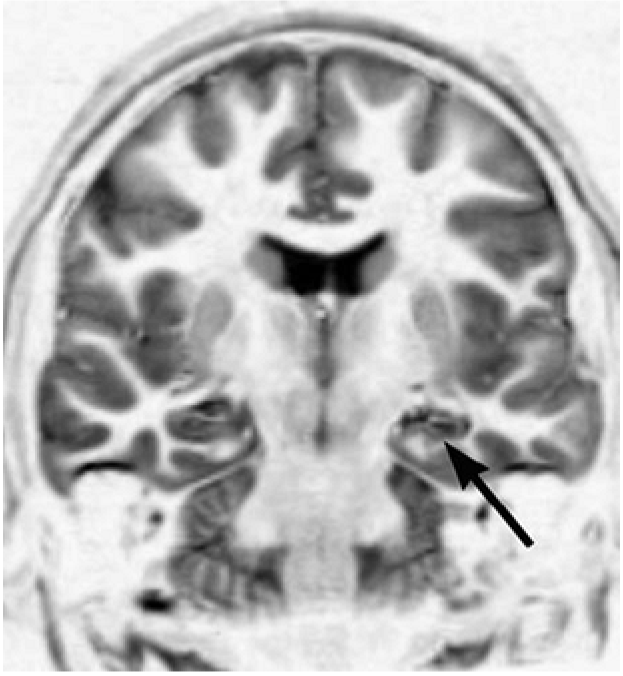


FIGURE 10. Classic hippocampal sclerosis (HS). Note the small hippocampus, with abnormal T1-weighted signal (*dark*) and no normal internal features (*arrow*). The hippocampus on the other, contralateral, side shows clearly demonstrated internal features. In this case the CA1 and dentate show decreased signal. This is also the case in heavily T1-weighted images in normal controls, suggesting that these neuronal parts have special imaging properties. In this case, this is more than is usual, suggesting that there may be minor changes in the contralateral hippocampus in these areas. This patient had a prolonged febrile convulsion at the age of 9 months and now has temporal lobe epilepsy.

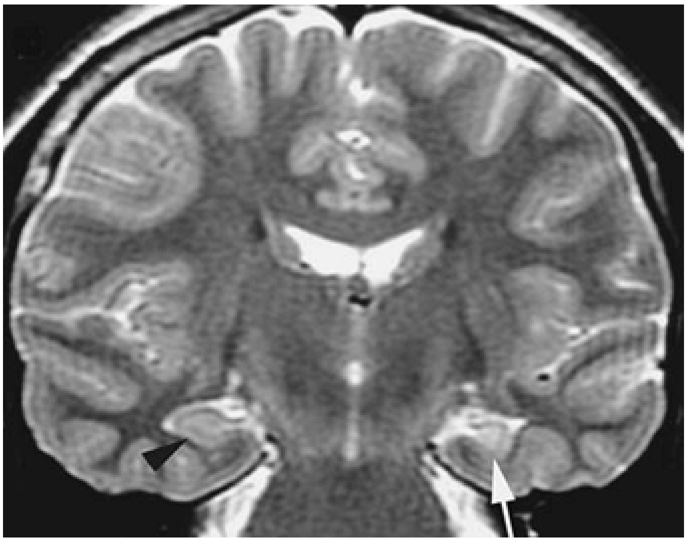


FIGURE 11. This 24-year-old woman had left temporal lobe epilepsy. The coronal T2-weighted images show increased signal and reduced volume (*white arrow*). The contralateral hippocampus is normal

(*black arrow*).

One should think good â€œepilepsy MRIâ€ not â€œMRI.â€ To achieve this, knowledge of MRI is needed not only by the radiologist, but also by the neurologist and epileptologist. It is this continuing interaction that enables optimized imaging to be obtained (Table 5).

Table 4 Types of magnetic resonance imaging studies and information acquired

Type of study	Information	Aim
Basic screening study	Structural information with good morphology and signal data	Detect all obvious lesions, evaluate hippocampal sclerosis and suggestive areas of gyral abnormality
Further assessment	Special studies, e.g., volumes, T2 relaxometry, further analysis of images, magnetic resonance spectroscopy, diffusion-weighted imaging, diffusion tensor imaging, quantitative methods, reconstructions	Support other investigations, detect subtle structural changes not easily seen on visual inspection
Intensive investigation	Functional studies, e.g., language and memory, functional magnetic resonance imaging (fMRI) MR physiology Simultaneous electroencephalogram/fMRI	
	MR physiology	
	Simultaneous electroencephalogram/fMRI	

Table 5 Dedicated imaging protocol for epilepsy

Imaging must be in the â€œhippocampal axisâ€
There must be a high-quality T1 and T2 sequence
Fluid-attenuated inversion recovery (FLAIR) images must be part of the protocol
Good signal-to-noise ratio is as important as thin slices

In epilepsy centers, it must be possible to diagnose hippocampal sclerosis with high sensitivity and specificity with visual analysis.

Quantification of Volumes and T2 Relaxometry in Epilepsy

High-resolution T1-weighted 3D volume sequences can be used quantitatively to measure the volume of any particular regions of interest. In the case of epilepsy this is usually the hippocampus.[7] Volumetric measurements require a significant investment in learning the hippocampal boundaries and depend on a large number of variables that need to be understood and controlled for in image analysis and acquisition. Volumetric assessment can be done manually or with half- or fully-automated software (Fig. 12), and increasingly advanced methods of anatomic analysis are being developed and

implemented. Longitudinal studies are possible, and this makes it possible to assess the progression of volumetric changes and may begin to help unravel the effects of the primary disease from the secondary effects of seizures.

T2 relaxometry is the quantitative determination of the T2 relaxation time. To achieve this, several T2-weighted images are acquired at different echo times, and in each voxel the resultant values are fit with an exponential decay curve to estimate the T2 decay rate of the imaged tissue. T2 relaxometry has been established as a reliable tool that is stable over time. In contrast to elaborate volumetric assessment, the T2 relaxometry is a quick technique with small variance and can be implemented in large-scale studies (Fig. 13).[7]

In epilepsy patients with HS, signal increase on T2-weighted images is typically observed in the hippocampus. The measured values of the hippocampal volume and the T2 time are correlated with each other, indicating that a marked volume loss is associated with a significant increase in T2 relaxation, reflecting the complex pathology that is HS.

Diffusion-Weighted Imaging

A diffusion-weighted signal reflects the molecular motion of water in the extra- and intracellular environments. The extent of this motion depends on the microscopic environment, and is therefore tissue dependent. In tissues with a linear arrangement of myelinated fibers, such as white matter tracts, the molecular motion is restricted to the axis along the white matter tracts. This is known as anisotropic diffusion. In other tissue components, such as CSF, molecular motion is not restricted in any direction, and this is known as isotropic diffusion. Diffusion-weighted MR techniques are frequently used to assess early signs of cerebral ischemia. Diffusion changes similar to those observed in ischemia may also be present in tumors or infection. Diffusion imaging requires postprocessing, which allows the measurement of summary parameters such as diffusivity and fractional anisotropy. It is also possible to visualize the path of the white matter tracts using tractography techniques. This is a computationally intensive technique and is in the process of being refined.[5]

Advanced Analysis Techniques

There are a number of methods for analysis of images. Voxel-based methods such as voxel-based morphometry (VBM), voxel-based relaxometry (VBR), and voxel-based diffusivity (VBD) can use statistical methods to demonstrate the areas of the brain that differ from control values. This approach is particularly powerful when examining the effects between groups (such as patients with temporal lobe epilepsy [TLE] and controls) (Fig. 14).[2]

Major Findings on Magnetic Resonance Imaging

The major findings on MRI can be thought of in a fairly simple way as being the obvious lesions, HS, malformations of cortical development, or, at least after the initial epilepsy protocol imaging, normal (Table 6).

Obvious Lesions

In several series, detailed analysis of MRI images has revealed a high percentage of abnormalities that can be detected in the brains of patients with intractable partial epilepsy (see Kuzniecky and Jackson[10] for review and more details).

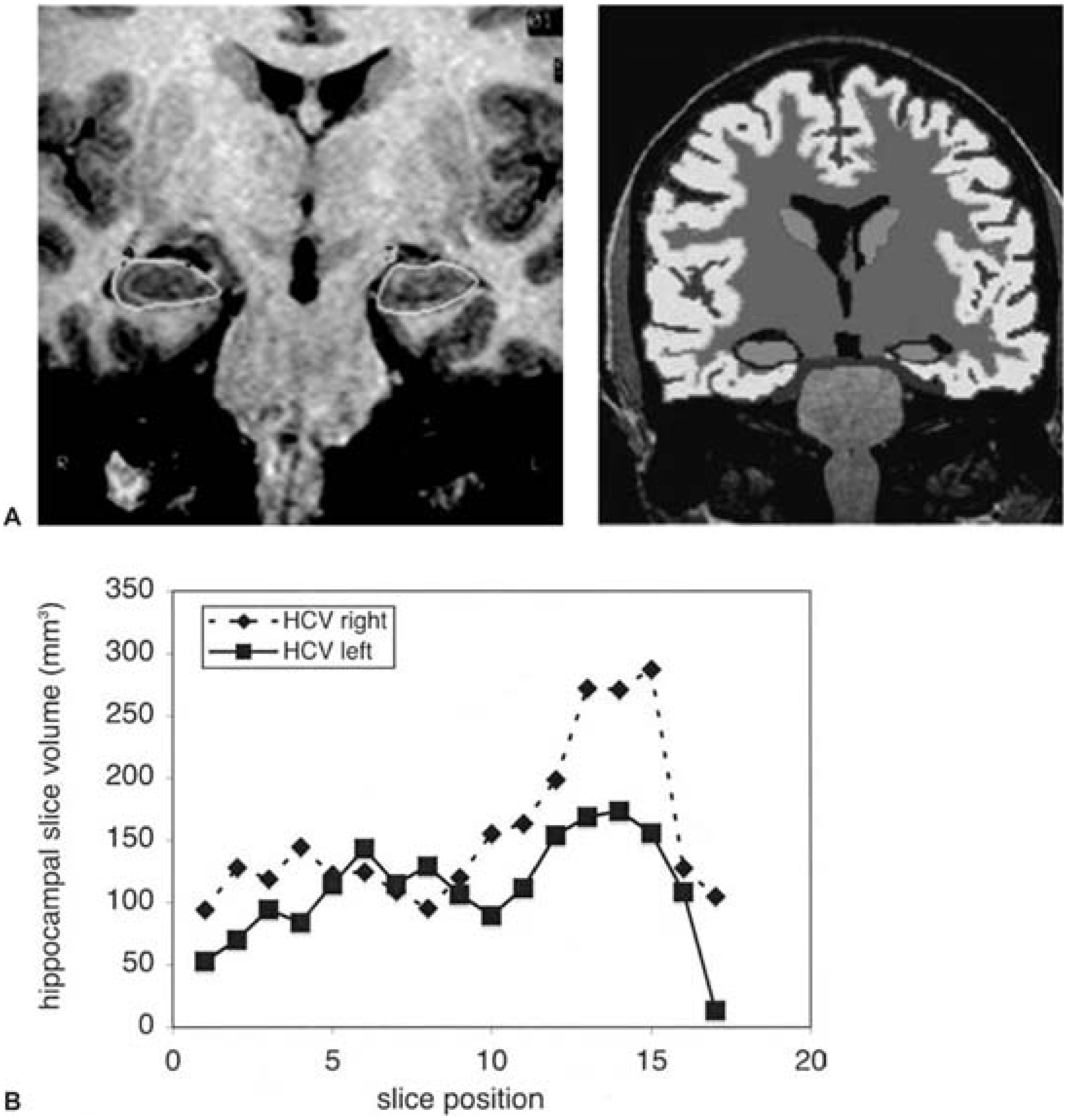

A
hippocampal slice volume (mm³)
350
300
250
200
150
100
50
0
HCV right
HCV left
0
5
10
15
20
slice position
B

FIGURE 12. Hippocampal volumes can be measured, and this quantification can be useful for distinguishing subtle abnormalities that may not be visually apparent. This can be done by drawing the boundaries of the hippocampus manually **(left, A)** or semiautomatically **(right, A)**. The cross-sectional area of each slice measured can be plotted to give a shape curve **(B)**. In this case, atrophy of the left hippocampal head is easily appreciated.

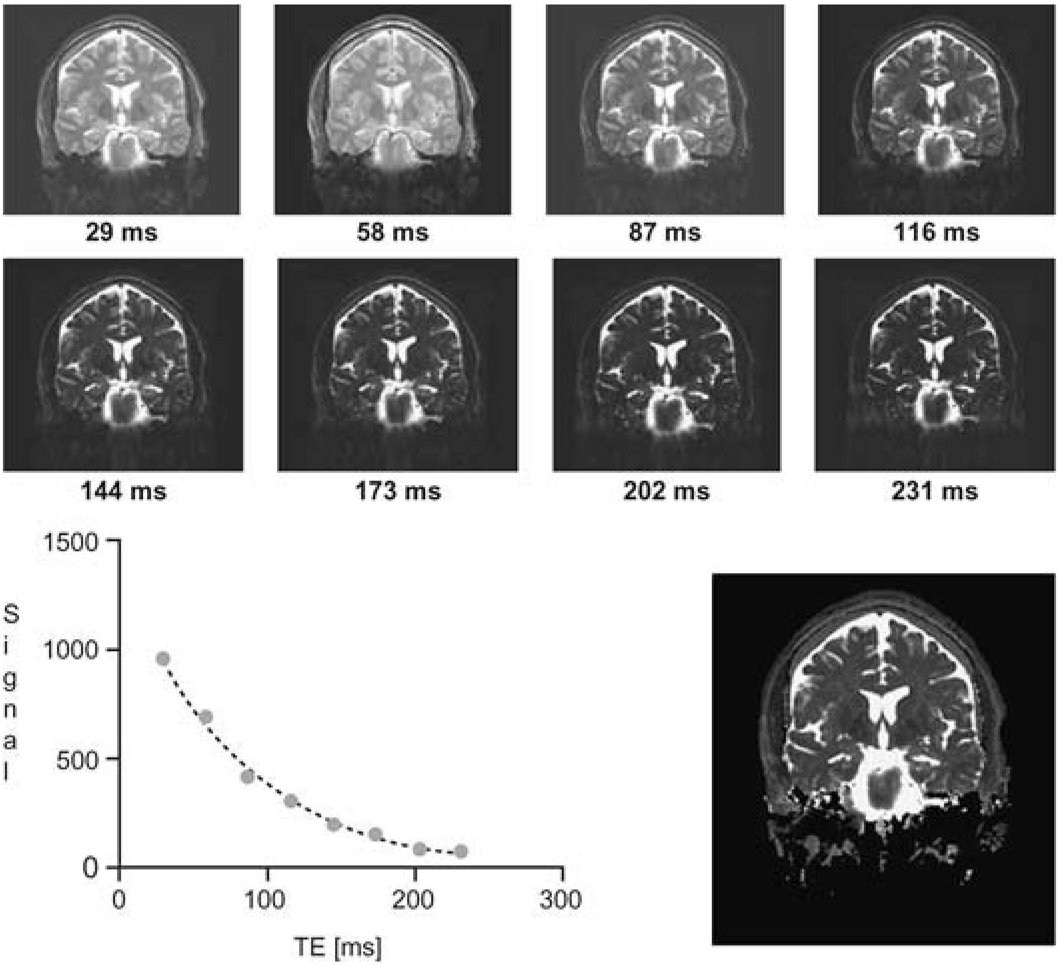


FIGURE 13. T2 relaxometry is a quantitative way of measuring the signal changes in tissue. The upper sequence of images shows how the T2 characteristics of the magnetic resonance image changes as a function of echo time. If one plots the signal change in a voxel or region of interest, the T2 decay curve is seen **(bottom left)** as the reduction of signal intensity as a function of echo time. The measured values can then be presented as a T2 map **(bottom right)**. The T2 time of any region of interest can be determined from this map. This information can also be used in a voxel-based way with statistical analysis of signal changes compared to a control group, in a similar way to voxel-based morphometry.

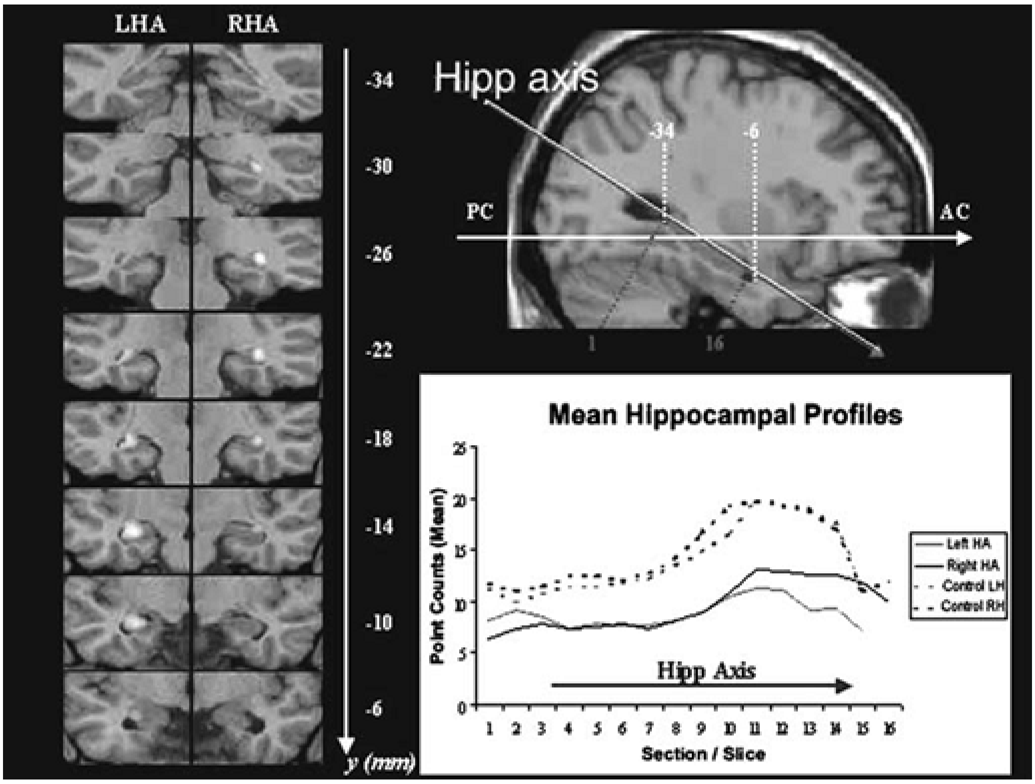

LHA
RHA
-34
-30
-26
-22
-18
-14
-10
-6
y (mm)
Hipp axis
-34
-6
PC
AC
1
16
Mean Hippocampal Profiles
Point Counts (Mean)
0
5
10
15
20
25
Hipp Axis
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
Section / Slice
Left HA
Right HA
Control LH
Control RH

FIGURE 14. Quantitative measurement of the hippocampus. The volume can be measured in the cross-sectional coronal images obtained in the hippocampal axis. This can be extracted to give a shape analysis. The left panel shows this data in a statistical way by using voxel-based morphometry to show how the patient groups differ from a control group. LHA, left hippocampal axis; RHA, right hippocampal axis. (Figure courtesy of Gaby Pell, Brain Research Institute, Australia.)

Table 6 Findings on visual assessment of magnetic resonance images

Type of finding	Comments
â€œObviousâ€ lesions	Basic magnetic resonance imaging is appropriate and will demonstrate these; tumors, vascular lesions, and obvious malformations of cortical development will be seen on any MR imaging protocol
Hippocampal sclerosis	Must have a dedicated epilepsy protocol
Malformations of cortical development	Images must have optimal signal-to-noise ratio and spatial resolution; advanced analysis may be appropriate; need good imaging and interpretation skills

Nothing	Advanced methods of imaging and analysis might be considered for further investigation; quantitative analysis can reveal subtle abnormalities

Besides from mesial temporal sclerosis, other epileptogenic lesions commonly seen in the temporal lobes of patients with epilepsy include tumors, vascular malformations, and traumatic and developmental lesions. In general, these lesions constitute approximately 10% to 15% of the focal abnormalities found in partial epilepsy.

Neoplasms

Astrocytic Tumors.

Astrocytic tumors constitute about 20% of those epilepsy patients with â€œalienâ€ or â€œforeign tissueâ€ lesions and often involve the parahippocampal gyrus and the amygdala. Fibrillary astrocytomas are most common. MRI typically demonstrates homogeneous masses, with calcifications present in up to 20% of cases. The location is variable, with cortical lesions having extension into the white matter, and they are poorly demarcated. MRI features are not specific. Anaplastic tumors or glioblastomas are the most frequent astrocytic tumors; they do not constitute a significant number of patients referred with intractable epilepsy because they usually present as a primary tumor problem. Pilocystic astrocytomas are more frequent in children. On MRI these lesions are sharply demarcated and often lobular. Contrast enhancement is typically present due to prominent vascularity. Edema is rare, and calcifications are not seen.

Xanthoastrocytomas usually occur in the first decade of life and have a good prognosis. Cystic components are common in this tumor, which usually occurs in the temporal or parietal region.

Oligodendrogliomas.

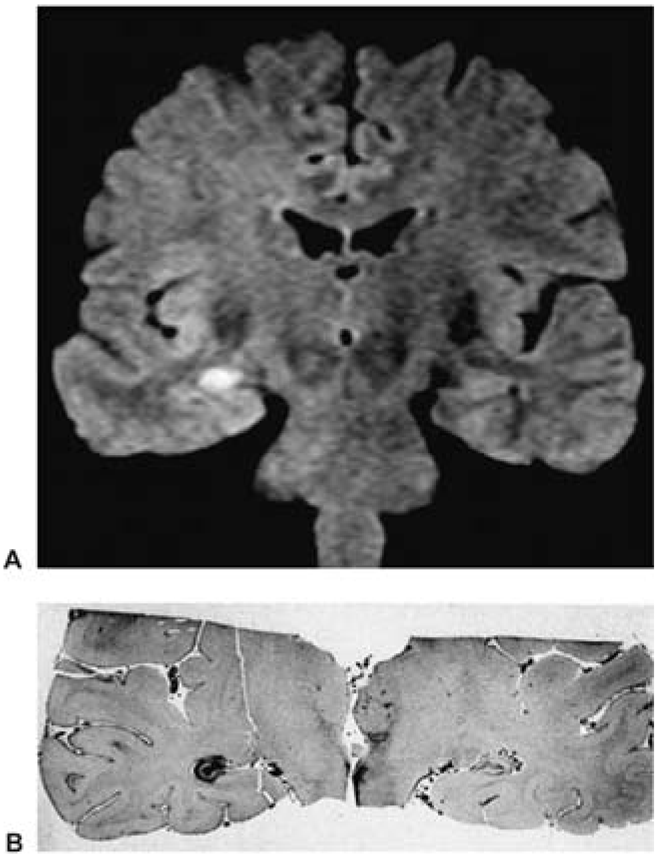


FIGURE 15. A: Fluid-attenuated inversion recovery (FLAIR) image in a patient with hippocampal sclerosis (HS). **B:** A pathologic specimen from a different patient reported by Meencke and Veith. It is a histologic specimen with Nissl stain. In both cases the degree of hippocampal atrophy was symmetric. (From Meencke HJ, Veith G. Hippocampal sclerosis in epilepsy. In Luders H, ed. *Epilepsy Surgery*. New York: Raven Press; 1991:705â€"715; with permission.)

Oligodendrogliomas are histologically characterized by the presence of compact groups of large, rounded cells with empty cytoplasm, often also with mixed glial components. These tumors are less frequent than astrocytomas and uncommon in patients referred for intractable epilepsy, but, when present, they are located within the temporal lobe and tend to involve the amygdala and the uncus and parahippocampal gyrus, with sparing of the middle and inferior temporal convolutions. The underlying white matter often shows tumor infiltration.

Mixed Glial Lesions

Mixed glial lesions are a common tumor type in epilepsy (about 5% of foreign tissue lesions). Calcifications are often present. Seizures begin typically in childhood. These tumors are predominantly seen in young patients (younger than age 14 years). Gangliogliomas tend to spare the lateral temporal neocortex and primarily involve the mesial structures.

Dysembryoplastic Neuroepithelial Tumors

Dysembryoplastic neuroepithelial tumors (DNETs) are a common tumor type in patients with intractable partial seizures. These tumors are usually located in the temporal region or, less commonly, the frontal region. These represent about 10% of all tumors removed in patients with intractable epilepsy. Cysts are uncommon. DNETs involve both gray and white matter. Imaging findings are quite characteristic. They commonly involve the temporal lobes (Fig. 4). The MR characteristics, although not pathognomonic of this condition, should strongly suggest the underlying abnormality.

Metastatic Disease

Metastatic spread of tumor to the brain is common and comprises approximately 20% of brain neoplasms. Seizures are the presenting symptom in about 30% of patients with cerebral metastasis. Metastases have fairly stereotyped localization (grayâ€“white matter junction) and often have peripheral edema.

Vascular Malformations

Although seizures and epilepsy are frequent presentations of vascular malformations of the brain, these lesions are less common (1%â€“2%) among the alien lesions in patients with intractable epilepsy referred to epilepsy surgery. These abnormalities are less frequent in the temporal lobes than in other regions and can be divided into arteriovenous malformations, cavernous angiomas, capillary telangiectasia, and venous angiomas. Capillary telangiectasias and venous angiomas are rarely associated with chronic seizure disorders.

Cavernous angiomas constitute a distinct vascular malformation. In the majority of patients with intractable seizures, cavernous angiomas constitute the most common vascular abnormality, particularly with multiple lesions. The MRI features of cavernous angiomas are fairly characteristic. The lesions have a central core with mixed signals indicating blood byproducts of different stages. Within the core, methemoglobin appears as high signals often intermixed with lower signals. Typically, a complete rim of hypointensity surrounds the central core. This rim is usually hypointense on both long and short echoes, with marked hypointensity in the longer echo. These lesions are void of mass effect or surrounding edema, and they should be easily recognized. Venous angiomas are probably the most common vascular malformation, but they are rarely the cause of chronic epilepsy.

Posttraumatic Lesions and Stroke

Trauma to the brain can cause epilepsy. This includes injuries of all sorts, including percussive injuries and those due to vascular disease (stroke). In general the presence of blood products is highly epileptogenic. Reorganization of damaged tissue after injury of any kind can also lead to epilepsy. The imaging of these disorders is primarily a radiologic issue rather than an epileptologic one, and these are included here for the sake of completeness. It is worth noting that contusions commonly affect the temporal lobes, and the brain injury is often bilateral and multilobar, even if the abnormalities seem very focal on MRI.

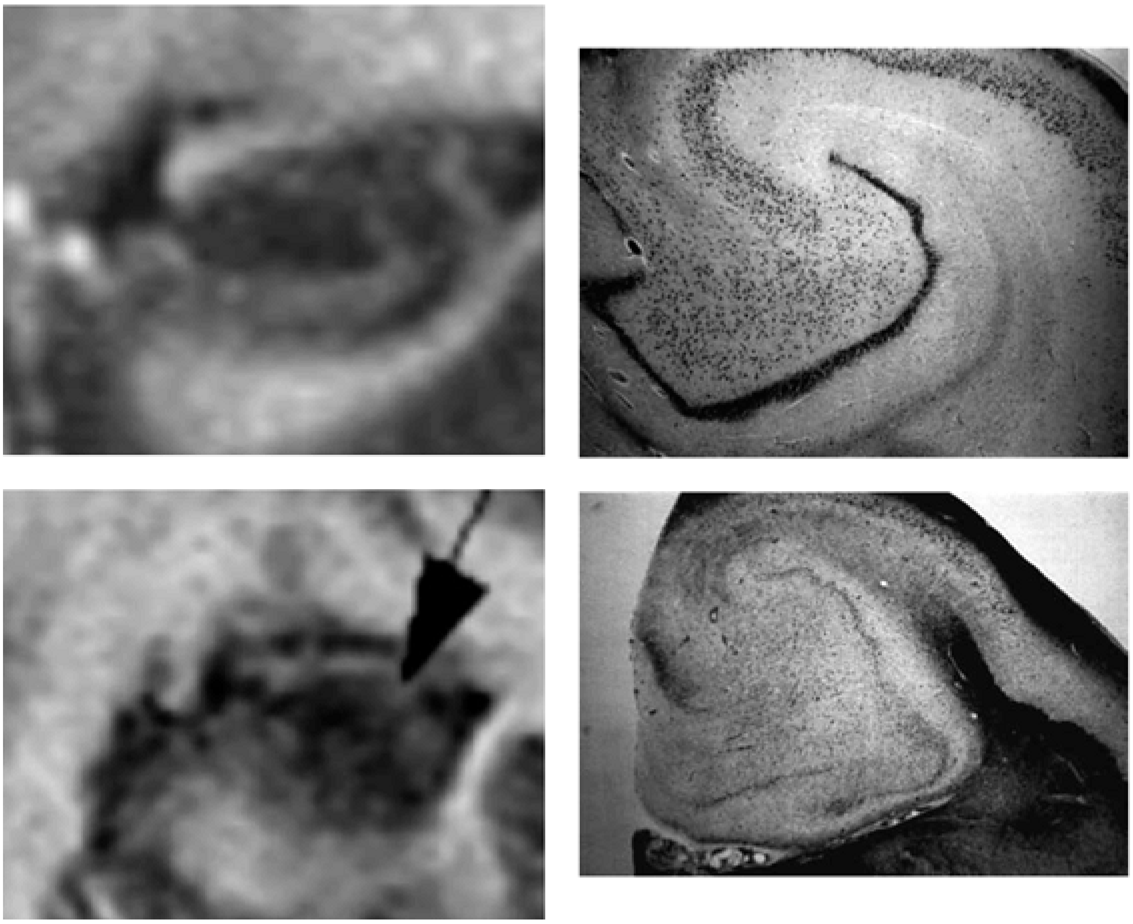


FIGURE 16. Magnetic resonance and pathology images of a normal hippocampus **(top row)** and hippocampal sclerosis **(bottom row)**. Different sequences show these features to varying degrees, but a heavily T1-weighted sequence, such as an inversion recovery sequence, seems to reveal contrast in the CA1 and dentate gyrus that parallels the distribution of the pyramidal cells. The basis of this magnetic resonance image contrast is not known. (From Kuzniecky RI, Jackson GD. *Magnetic Resonance in Epilepsy: Neuroimaging Techniques*, 2nd ed. London: Elsevier; 2005; with permission.)

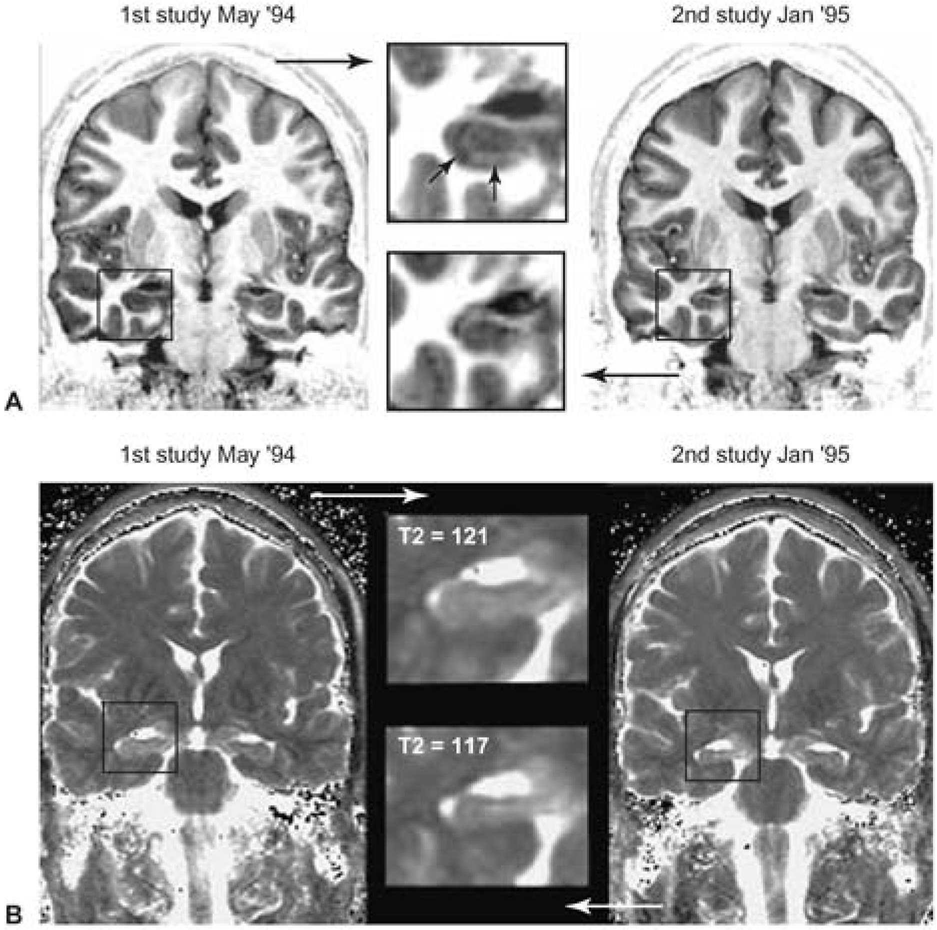


FIGURE 17. Progressions of hippocampal sclerosis. This 25-year-old man presented with three tonicâ€“clonic seizures. Note that the internal architecture of the hippocampus (*arrows* in panel A) is clearly seen in the first study but is absent in the second study. There is atrophy of the hippocampus in the second study in the areas that showed abnormal signal in the first study. In panel B, the right hippocampus shows high signal in both the first and the second study. This was confirmed on T2 relaxometry studies (numbers).

Hippocampal Sclerosis

Methods of Detecting Pathology Using Magnetic Resonance

As described earlier, the detection of pathology by MRI in general, and of mesial sclerosis in particular, can be performed in three ways:

1. The visual detection of abnormal tissue quality by *contrast* between normal and abnormal tissue. Tissue characteristics that reflect the pathology of abnormal tissue composition can be identified by alterations in signal intensity, T1 or T2 relaxation times, magnetic resonance spectroscopy (MRS), diffusion-weighted imaging, or other methods.
2. The visual detection of *morphologic changes* of a structure that can demonstrate changes in size or appearance that correlates with underlying pathology.

3. Advanced quantitative and statistical image analysis methods.

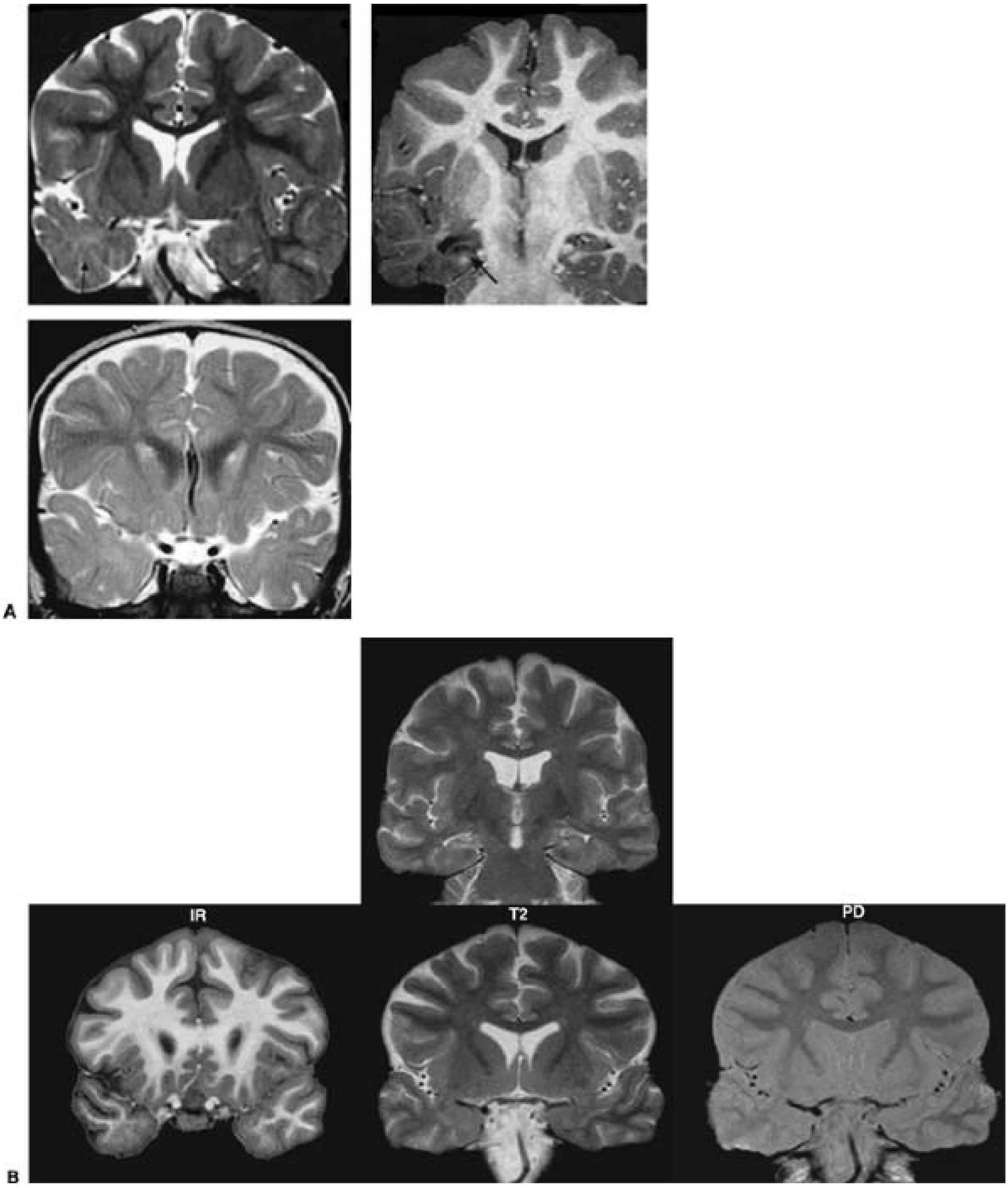


FIGURE 18. A: Magnetic resonance findings in a 10-year-old boy with intractable temporal lobe epilepsy emanating from the right. He suffered a very prolonged febrile convulsion at 12 months of age. The features of hippocampal sclerosis (HS) and mesial temporal sclerosis are clearly seen. The hippocampus is small, with abnormal signal and absence of normal internal architecture (*arrow*). There are also changes in signal in the white matter of the temporal lobe, seen on both T2- and T1-weighted images. The whole temporal lobe is small. The temporal lobe essentially shows the features of an arrest in development at the 12-month stage. For comparison, the lower left panel shows the findings in a normal 12-month-old without epilepsy. (From Mitchell LA, Harvey AS, Coleman LT, et al. Anterior temporal changes on MR images of children with

hippocampal sclerosis: an effect of seizures on the immature brain? *Am J Neuroradiol*. 2003;24:1670â€“1677; with permission.) **B:** Hippocampal sclerosis and anterior temporal lobe changes. HS is often associated with changes in the anterior temporal lobe. These images show the typical constellation of features associated with HS. HS is present on the right, and there is increased signal in the anterior temporal pole white matter. In some cases the gray matter also seems to show some change in signal. In this case no pathologic cause for these changes was apparent on careful assessment. It has been suggested that this is due to abnormalities in myelin or an arrest of development in the immature temporal lobe. For a review of this issue, see Ryvlin et al.[12] and references therein. It is clear that these changes are different than and can be distinguished from focal cortical dysplasia. IR, inversion recovery; PD, proton density-weighted; T2, T2-weighted.

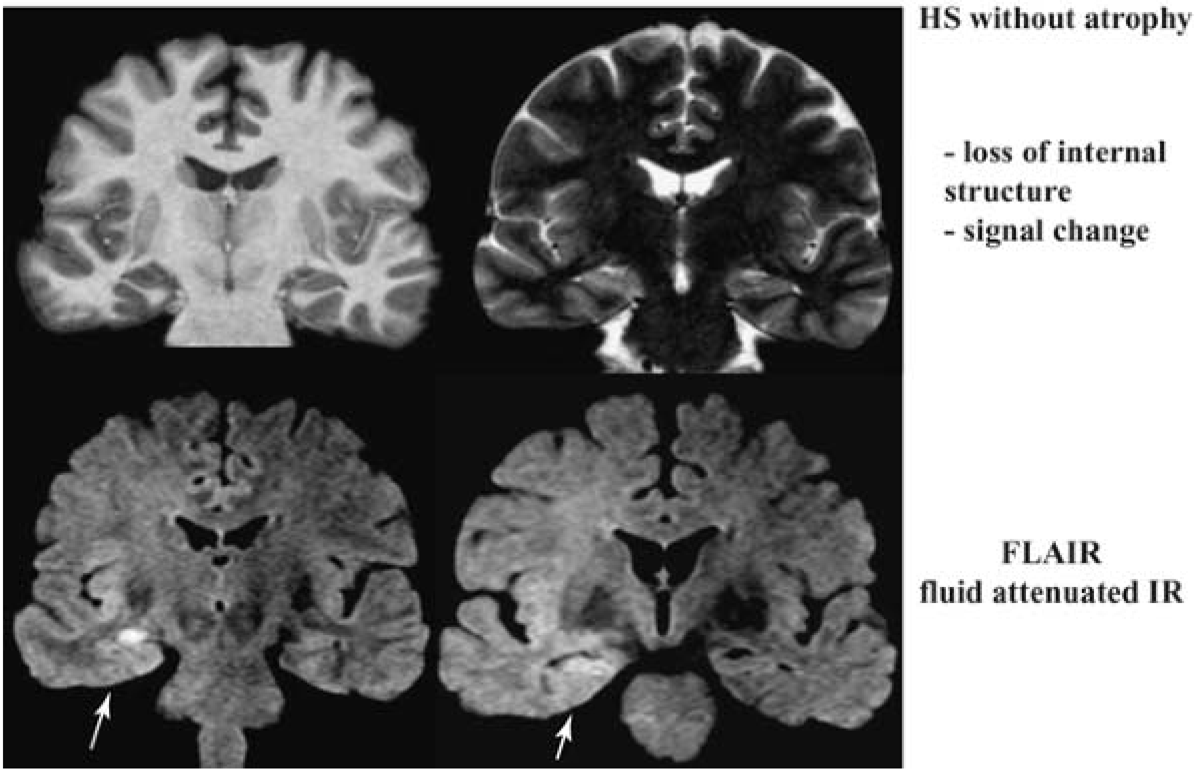


FIGURE 19. Atrophy of the hippocampus is not apparent in this case of hippocampal sclerosis (HS). There is signal change in the hippocampus that may be considered to be subtle. When assessed with fluid-attenuated inversion recovery (FLAIR) imaging, the signal change is dramatic, and there is a suggestion of changed signal more extensively throughout the hemisphere. The latter subtle change should be interpreted with care because FLAIR imaging can give a variety of artifacts. In this case this was confirmed on T2 relaxometry studies. (See also Fig. 18.)

Optimized imaging of the hippocampus and temporal lobe structures depends on image orientation and image sequences optimized to display the anatomy and signal abnormality of hippocampal sclerosis and temporal pathology (Fig. 9).[6]

Abnormal Signal in the Hippocampus

Using optimized T2-weighted sequences (orientation and sequence), including CSF nulled sequences such as the FLAIR sequence, one can easily detect the presence of increased signal from the hippocampal body. The high signal is localized to the hippocampal gray matter and usually can be seen in the middle of the structure if one uses the corresponding T1-weighted image for definition of anatomic detail (Figs. 10,11,12,13,14).

Although the abnormal T2 signal is a reliable finding for hippocampal sclerosis, one needs to be aware of a number of common problems. A problem may arise from the presence of normal dilation of the hippocampal fissure. Although this may be incorrectly diagnosed as a high signal from the hippocampus, it should rarely be mistaken for hippocampal sclerosis. Bilateral hippocampal T2 signal abnormalities may be present, which may create difficulties. These and other problems are usually resolved by using clearly defined criteria for the diagnosis of hippocampal sclerosis in optimized images or by using more advanced methods of analysis or quantitation when doubt exists. These criteria have proven to be very reliable and sensitive for the detection of hippocampal sclerosis in experienced hands. The quantification of T2 relaxation times has also confirmed that T2 signal abnormality is almost invariably present with hippocampal sclerosis even when this cannot be seen by visual analysis.

The use of a heavily T1-weighted sequence is, in our experience, a valuable approach to studying hippocampal sclerosis. Currently, despite the time and coverage issues, we still routinely use IR as part of our epilepsy protocol because we believe that it provides information not seen on our 3D or other T1-weighted sequences. It would be reasonable, however, to only run this sequence if the hippocampus looks normal or equivocal on other sequences in the context of a diagnosis of TLE. The atrophic hippocampus more often demonstrates decreased signal with a dark appearance (Fig. 10).

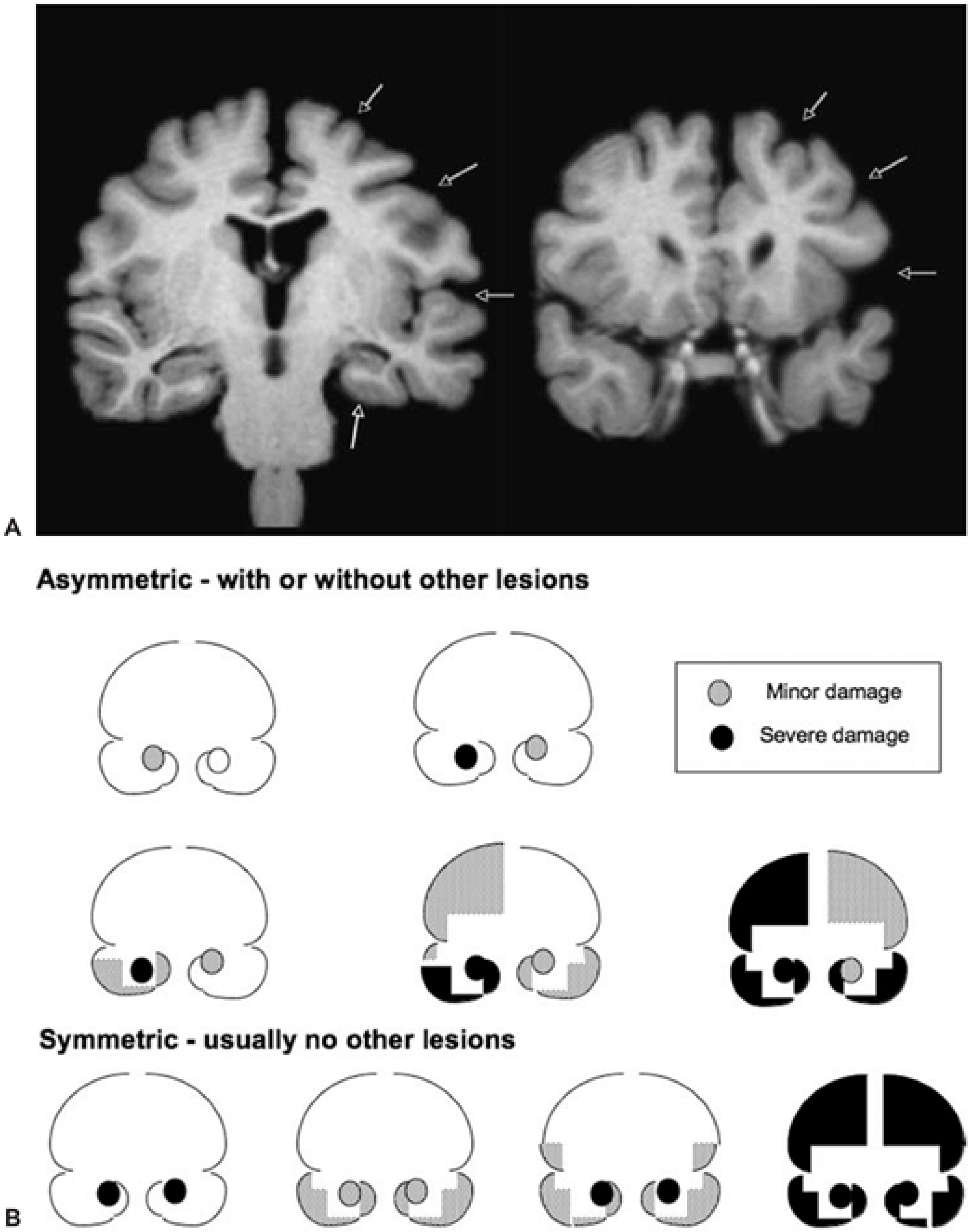

A
Asymmetric - with or without other lesions
Minor damage
Severe damage
Symmetric - usually no other lesions
B

FIGURE 20. A: Hippocampal sclerosis and hemiatrophy. Hippocampal sclerosis can be associated with more extensive changes, usually throughout the ipsilateral hemisphere. This case shows hippocampal atrophy in the context of hemispheric atrophy. **B:** The types of hippocampal sclerosis seen on magnetic resonance studies. These patterns can be conceived of as being caused by seizure or other damage that is either lateralized **(upper rows)** or generalized **(lower row)**. (From Kuzniecky RI, Jackson GD. *Magnetic Resonance in Epilepsy: Neuroimaging Techniques*, 2nd ed. London: Elsevier; 2005; with permission.)

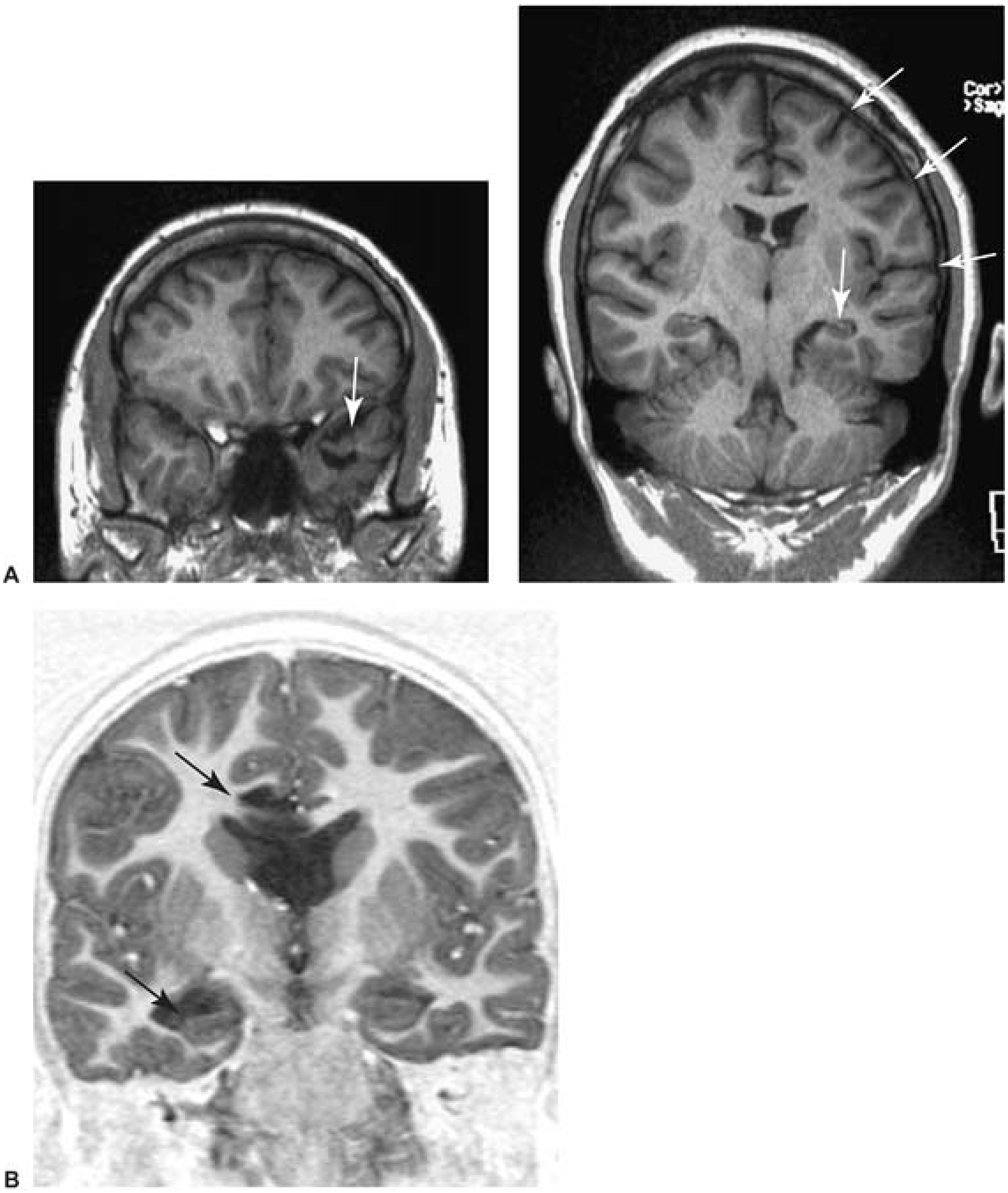


FIGURE 21. A: This 49-year-old patient has temporal lobe epilepsy, with no childhood antecedents and onset of epilepsy at age 11 years. She has an abnormality in the anterior temporal pole, with a deep sulcus and abnormal gyral pattern, suggesting a malformation of cortical development (MCD) (left panel). She has an atrophic hippocampus on the ipsilateral side, and the whole hemisphere is small (*small arrows*, right panel). A proposed sequence of events is that the MCD initiated the first seizure and the changes in the hippocampus are secondary to this. The hippocampus can then become the primary epileptogenic lesion. **B:** Dual pathology. Hippocampal sclerosis (HS) is present on the right, and a lesion is seen in the right cingulate gyrus. Dual pathology is usually ipsilateral to the HS and is likely to be pathogenically important in the genesis of unilateral HS.

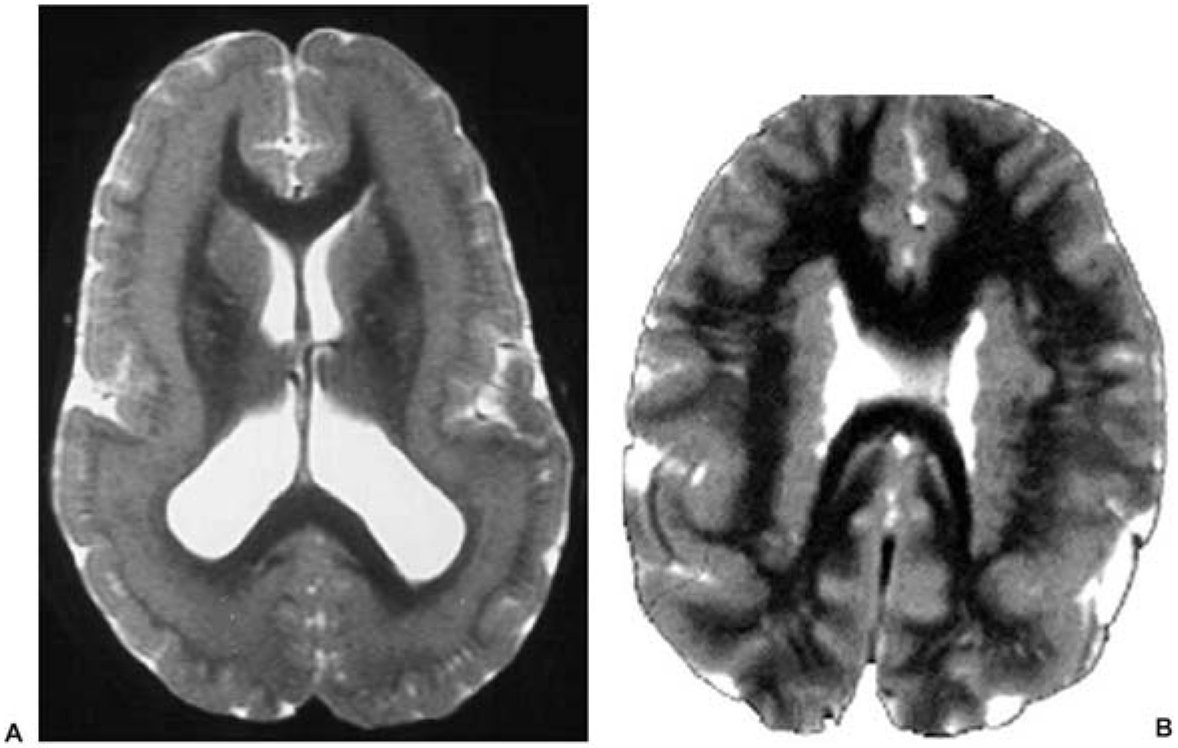


FIGURE 22. Malformations of cortical development can be dramatic. The heterotopia may be subcortical **(A)** or periventricular **(B)**. The overlying cortex is abnormal.

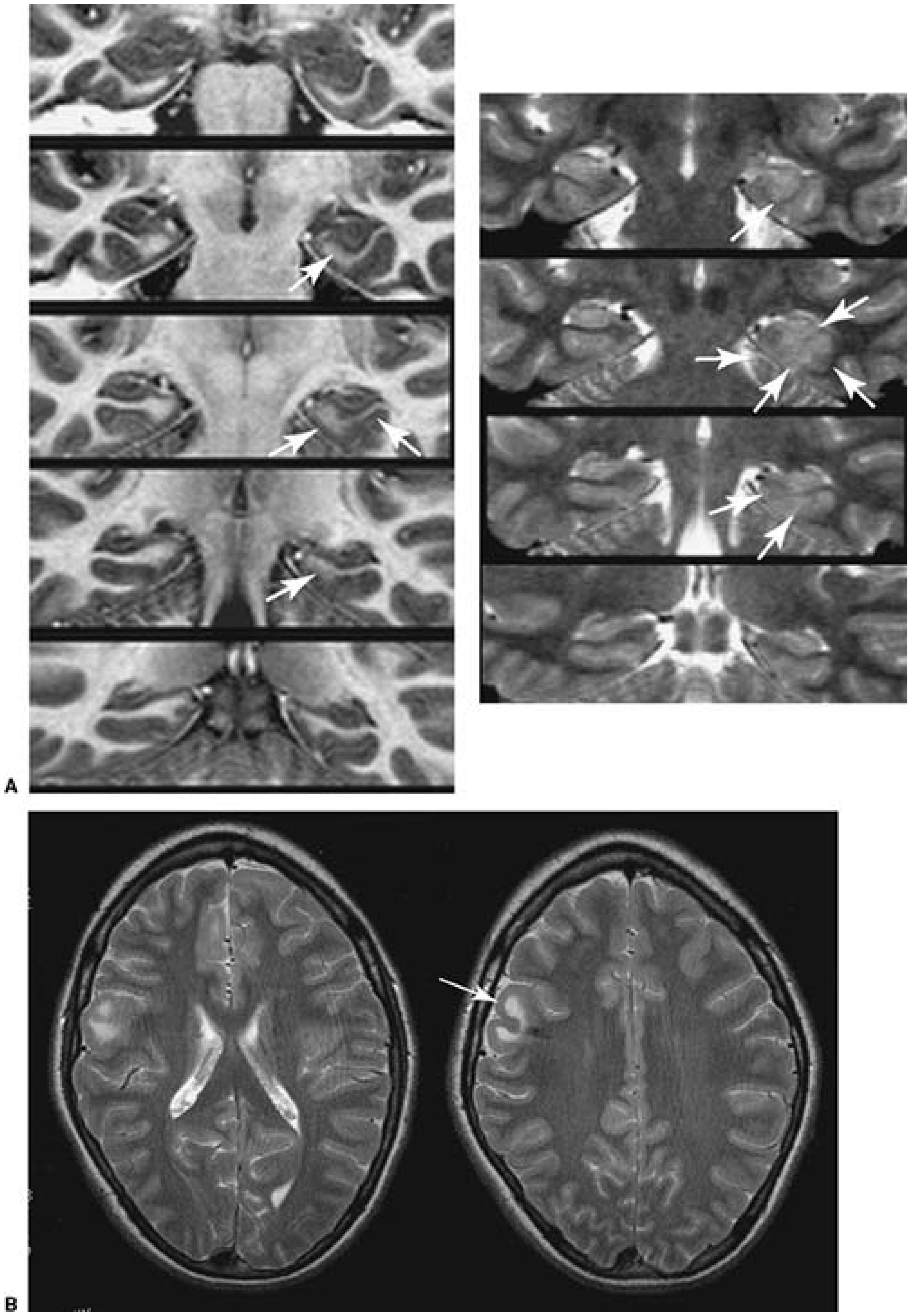


FIGURE 23. A: This 31-year-old woman with epilepsy demonstrates one of the problems of seizure localization in the mesial temporal lobes, particularly in the parahippocampal gyrus. This woman had confusing lateralization of her temporal lobe seizures. Depth electrodes were implanted in the mesial temporal region anteriorly, and these showed independent bilateral seizures more from the right. The ictal single photon emission computed tomography also showed bilateral seizures more from the right. Eventually a resection of this lesion was performed, and she became seizure free with persisting auras. In general, when there is disparity of the electroencephalographic data and an apparently epileptogenic lesion, we believe that seizure freedom is rarely achieved without resection of the lesion. The obvious and difficult issue is to recognize when lesions are truly incidental and irrelevant to the epilepsy. **B:**

Tuberous sclerosis. Tuberous sclerosis is often best appreciated by the changes in the white matter. Although the gray matter may appear to be normal in these magnetic resonance images, the pathology is of dysplasia. Just because the lesion appears to be in the white matter does not mean that is not epileptogenic. (Image courtesy of Simon Harvey, Royal Children's Hospital, Melbourne, Australia.)

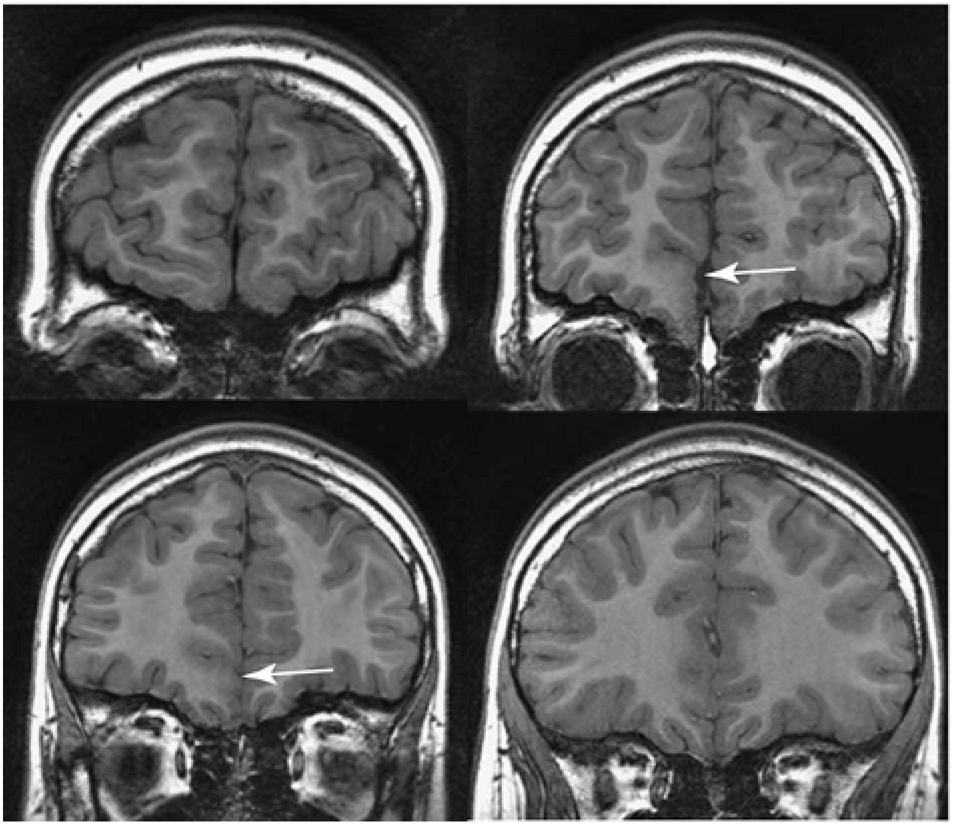


FIGURE 24. Subtle lesions require reliable boundaries between gray and white matter. These images show a focal cortical dysplasia in the medial and inferior aspect of the frontal lobe. The patient had frontal lobe epilepsy with lateralization to the right on ictal electroencephalogram. The identification of this lesion with concordant ictal single photon emission computed tomography led to focal resection of the lesion with good outcome without the need for implantation of subdural electrodes. The key to the recognition of this subtle lesion is the good signal-to-noise ratio of the imaging, which gives a clear grayâ€"white matter demarcation.

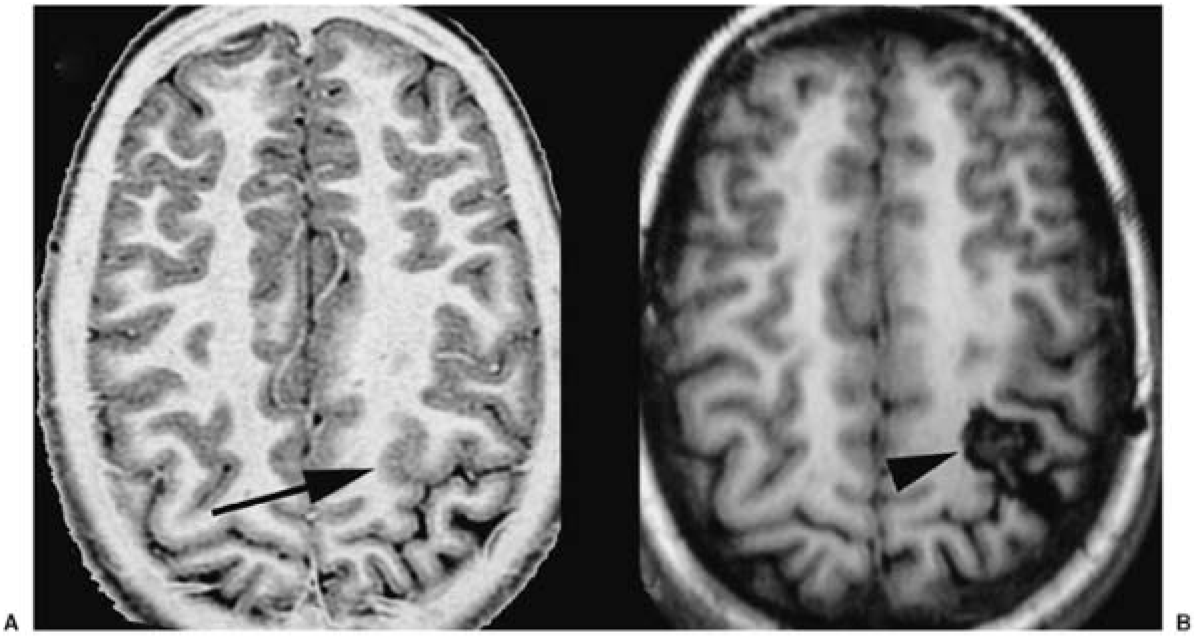


FIGURE 25. â€œBottom of the sulcusâ€ dysplasia. This 30-year-old man had very intractable epilepsy, and a large right frontal resection was proposed because the precise onset was hard to determine. A small abnormal gyrus extending from the hand area of the central sulcus was identified **(A)** that had subtle blurring of the grayâ€“white matter junction. A focal resection was performed **(B)**, and the patient has now been completely seizure free for >5 years. Finding and correctly identifying subtle abnormalities such as this may make a large difference to treatment options.

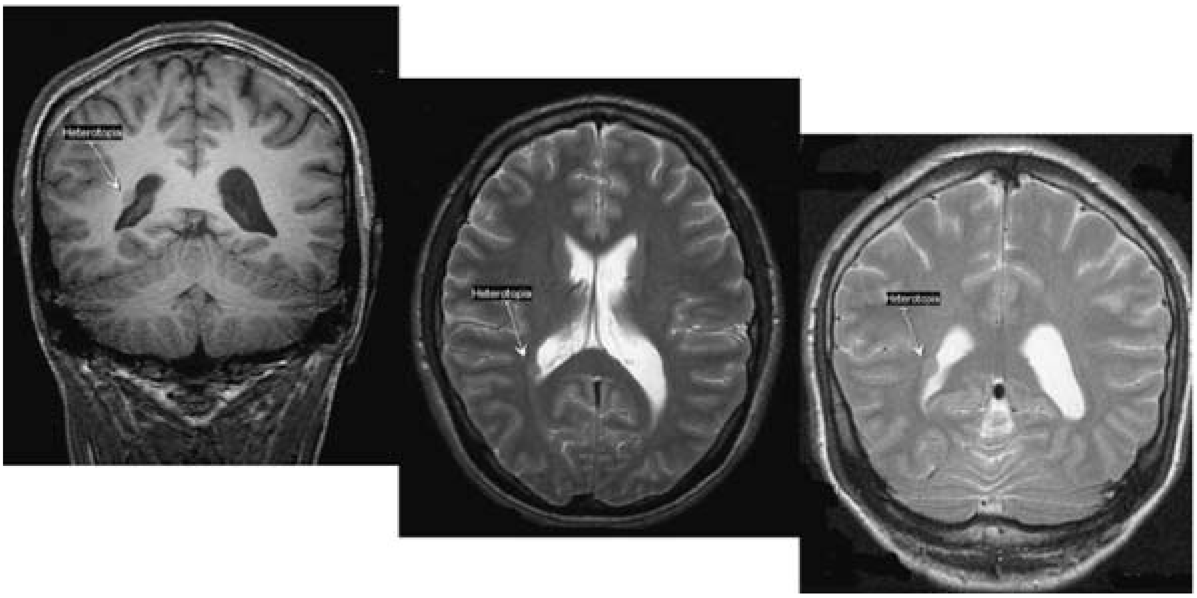


FIGURE 26. Periventricular nodular heterotopia can easily be missed. It is important because it is a poor prognostic feature for focal resections in localized epilepsy. (Images courtesy of Simon Harvey, Royal Children's Hospital, Melbourne, Australia.)

The signal change can sometimes be best seen on FLAIR images. There can sometimes be artifacts in the mesial temporal region, and interpretation of subtle changes without confirmation on the T2 sequences can be problematic, but real signal change can sometimes be dramatically emphasized with this imaging contrast (Fig. 15).

Hippocampal Atrophy

Hippocampal atrophy remains the best-known feature of HS in radiologic assessment. It is important that this be seen only as part of the complex of findings that give the correct diagnosis and avoid errors. Nonetheless, when severe, this is the most dramatic feature of HS, and often where visual screening starts. It is essential to use the appropriate imaging planes to correctly visualize these structures. It must be remembered that the hippocampus is indeed like a sea horse in shape, curving around the mesencephalon with a superior rostrocaudal angulation of approximately 30 to 35 degrees (Fig. 9). Using MRI, the assessment of the cross-sectional size of the hippocampus must be made in images obtained in the coronal axis that transects the hippocampus at right angles, often now known as the â€œhippocampal axis.â€ Using this angulation largely avoids partial volume effects, in particular in the posterior sections of the body and tail of the hippocampus. Although assessment of epilepsy has adopted this coronal plane in most centers, axial imaging is usually ignored. Axial images or reconstructions should also follow the long axis of the hippocampus, thus avoiding similar problems.

Visual assessment of hippocampal atrophy is reliable in experienced hands and with optimal imaging sequences. Hippocampal volume measurements and T2 relaxometry objectively and quantitatively confirms that these features are present in specific cases (Figs. 12 and 13) and can be useful in helping to train the epileptologist and radiologist in the degree of abnormality in the visually assessed images that can be confidently diagnosed. It must be remembered that these abnormalities might be considered to be subtle to the radiologist used to looking at â€œobviousâ€ pathology. In addition, the mesial temporal region is an area where signal change from flow artifacts in the adjacent major intracranial vessels can generate doubt in the mind of the reporting specialist. The key is the anatomic â€œexactnessâ€ of where the changes are. This means that good knowledge of the mesial temporal anatomy is the most important skill in diagnosis.

Table 7 Malformations of Cortical Development

Malformations due to abnormal neuronal *proliferation*
Malformations due to abnormal neuronal *migration*
Malformations due to abnormal neuronal *organization*

Loss of Definition of Internal Microarchitecture of the Hippocampus (Loss of the Normal Internal Structure)

Normal internal morphologic structure of the hippocampus is produced by the alveus, the molecular cell layer of the dentate gyrus, and the pyramidal cell layer of the cornu ammonis, and can be seen on optimized coronal MR images. In hippocampal sclerosis, the loss of this normal internal structure is a consequence of neuronal cell loss and replacement of normal anatomic layers with gliotic tissue. It is difficult to describe precisely this feature because, even in severe cases, the alveus can give the appearance of structure in the hippocampus. Once recognized, it is important for confidence of diagnosis in cases in which other features are only mildly abnormal. As imaging is becoming better, this is a more important feature. The degree of T1 weighting is important here, however, and inversion recovery images demonstrate this better than other T1-weighted sequences (Figs. 16 and 17).

Anterior Temporal Lobe Changesâ€"The Temporal Pole

Hippocampal sclerosis is often associated with changes in the anterior temporal lobe (Fig. 18). The typical constellation of features associated with HS can be considered to

include changes in other parts of the brain. This includes hemisphere atrophy (see Figs. 20A and 21A), and white matter changes in the anterior temporal lobe. When HS is present there also can be increased signal in the anterior temporal pole white matter. In some cases the gray matter may also show some change in signal, suggesting that this is not simply a myelin effect. In careful studies no pathologic cause for these changes has been found. Meiners[10a] suggested that this is due to abnormalities in myelin and Mitchell and Blumke[3a,10b] that it is an arrest of development in the immature temporal lobe, which includes immaturity of the myelin as well as persistence of immature cells and the overall structure of the temporal lobe into adult life. It is clear that these changes are different than and can be distinguished from focal cortical dysplasia.

Anterior temporal lobe white matter changes are probably due to delayed development and early insult. They are rarely due to â€œdysplasia.â€ This issue and its associated controversies are well reviewed by Ryvlin et al.[12]).

Hippocampal Sclerosis With Minimal Atrophy

Sometimes HS can exist without significant atrophy. Usually when there is high signal in a large hippocampus, this reflects hippocampal dysplasia, and this is one of the key reasons why asymmetry between hippocampi should not be accepted as HS on the side that may be interpreted as being small, in the absence of assessment of the signal in that hippocampus (Fig. 19). It is always important to assess the signal and the internal structure as well as the size of the hippocampus.[7]

Not Just Damage to the Hippocampus in Hippocampal Sclerosis

There are various degrees of asymmetric damage that has the hippocampus as the most obvious part. The presence of hemisphere atrophy is common and perhaps underappreciated in many of these cases (Figs. 20 and 21A). As the ipsilateral damage becomes more severe, it is more likely that one finds regional and contralateral damage of lesser degrees. In the case of the symmetric hippocampal sclerosis, the degree of damage equally involves regional structures on both sides. These patients are not the same as the unilateral cases that have well-lateralized HS and unilateral TLE and are seen in adult surgical series. Often the seizure disorder is severe, or this is associated with devastating loss of function in children who show impairment after a bout of uncontrolled seizures. This suggests that there might be two fundamentally different mechanisms that cause the full spectrum of hippocampal damage. It may be that a severe insult or some property that causes sensitivity of the subject to the effects of seizures might determine the final outcome.

In the case of predominantly unilateral HS, one can conceive of a mechanism by which seizures are sustained and maximal unilaterally.

The range of imaging findings that can be seen in association with MRI is shown in FIGURE 20. Note the concept that there are bilateral and symmetric changes associated with HS, as well as the more usual lateralized cases that are more commonly associated with intractable seizures in epilepsy surgery centers.[7]

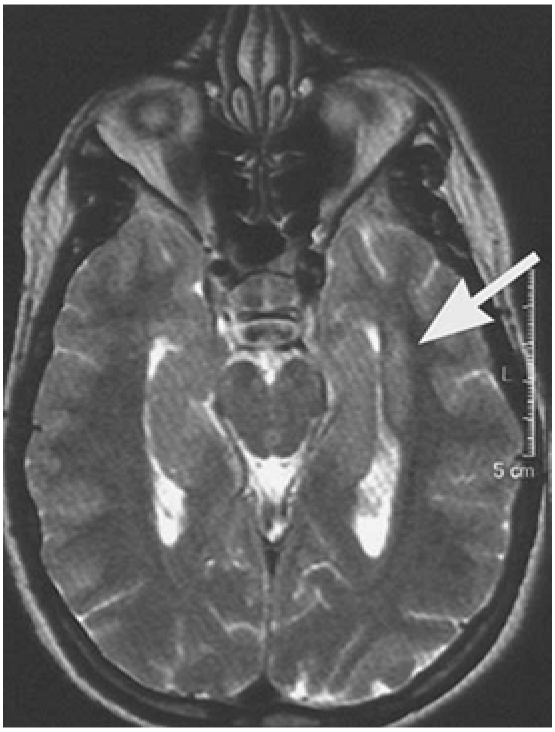


FIGURE 27. Mesial temporal dysplasia. This 15-year-old female had â€œdÃ©ja-vuâ€ events. There is a periventricular dysplasia in the left mesial temporal region (*arrow*). (Image courtesy Simon Harvey, Royal Children's Hospital, Melbourne, Australia.)

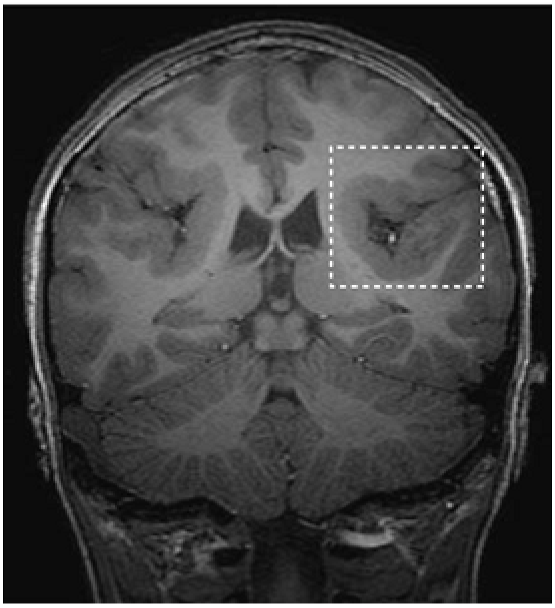


FIGURE 28. Bilateral perisylvian polymicrogyria. Perisylvian polymicrogyria can be easily missed if the thickened gray matter is not appreciated. These lesions may be better appreciated in the parasagittal images, and these need to be reviewed in all cases in which no other lesion is identified.

Dual Pathology

The incidence of dual pathology in TLE with HS is common. It is nearly always ipsilateral (Figs. 21A and 21B). Dual pathology is present in at least half of all cases of HS. There are two sorts of dual pathology. In the obvious case, there is a lesion, clearly unrelated to the HS, and it is usually on the same side as the HS. It is easy to imagine that this may be causally related to the existence of HS by causing predominantly unilateral seizures. The other sort of dual pathology occurs when the MRI shows changes in other parts of the brain that might be related to a

common injury that caused both the HS and changes such as unilateral atrophy or anterior temporal lobe changes.

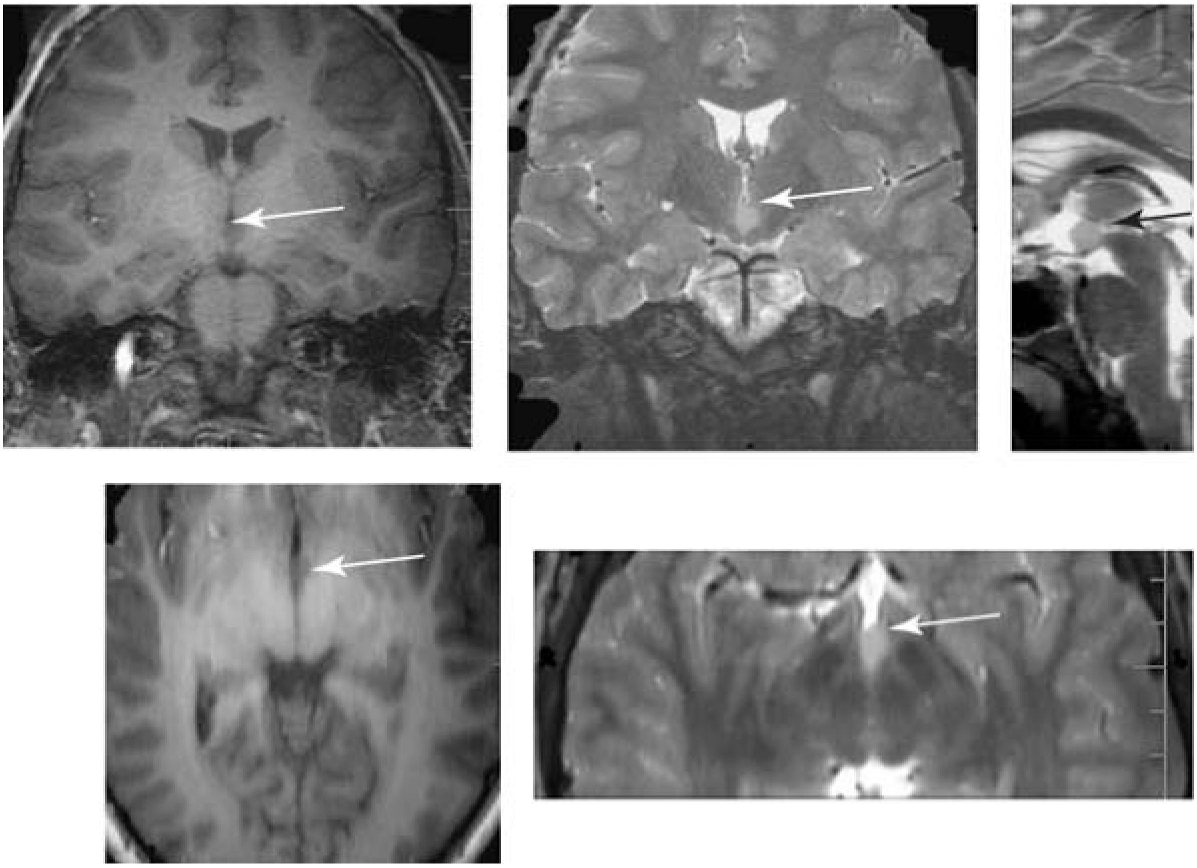


FIGURE 29. Hypothalamic hamartomas can be seen in the third ventricle. They are small and can easily be missed. They should be specifically looked for in all cases of temporal lobe epilepsy or partial epilepsy in which the magnetic resonance imaging is otherwise considered to be normal. (Image courtesy of Simon Harvey, Royal Children's Hospital, Melbourne, Australia.)

Malformations of Cortical Development

Under this term we include a number of pathologic entities that result from derangements of normal cortical development (Table 7).[1] These malformations are usually manifest in childhood. They can sometimes be dramatic, and knowledge of these abnormalities can greatly assist in understanding the patient (Fig. 22). Here we briefly address some particular forms of focal developmental lesions. These lesions are not exclusive to the temporal lobes, but in our opinion they merit separate discussion because of some distinctive clinical and imaging features.

Cortical dysplasia has been classified into what is now known as Taylor-type dysplasia characterized by the presence of balloon cells, and often the abnormality extends from the ventricle to the cortex. Focal cortical dysplasia (FCD) is a disorder of cortical organization and does not contain such bizarre cell types and hamartomas of the temporal lobe. Clinically, patients with cortical dysplasia of either type and temporal lobe epilepsy do not have striking clinical differences when compared to those with mesial temporal sclerosis. The frequency of childhood febrile convulsions is lower (20%â€“30%) in this population. Sometimes these can be subtle, and the abnormality appears to be predominantly in the white matter on MRI (Figs. 8 and 23). Tuberous sclerosis has imaging features that are similar to those of Taylor-type dysplasia (Fig. 23B).

Although MRI findings are abnormal in many patients with focal dysplasia, often the findings are subtle, and sometimes they are not seen on MRI, even with ideal imaging (Figs. 24 and 25). The MRI features range from abnormal signal changes to subtle abnormalities.

In contrast to cortical dysplasia, hamartomas are defined as abnormal proliferation of neuronal, meningeal, glial, or any combination of these cell types without evidence of neoplastic changes.

Periventricular nodular heterotopia is another important finding that can be easily missed (Fig. 26). When this is present, focal resections usually do not lead to a good outcome, regardless of how localized the cortical EEG activity is. The basis of the epileptogenicity is still controversial. It has been argued that the overlying cortex must be the source of the epileptogenic focus, but recently, epileptogenicity within the hamartoma has been demonstrated in at least a few cases. It is not clear whether resection of these lesions will lead to seizure freedom in an analogous way to the situation with regard to hypothalamic hamartomas.

Dysplasia in the mesial temporal region can also give seizures indistinguishable from mesial TLE from HS. In some cases these lesions can be subtle, and sometimes they are associated with ipsilateral HS (Fig. 27).

Bilateral perisylvian polymicrogyria can be easily missed if the thickened gray matter is not appreciated. These lesions are often better appreciated in the parasagittal images, and these

need to be reviewed in all cases in which no other lesion is identified (Fig. 28).

Hypothalamic hamartomas are highly epileptogenic. The seizures are typically partial, and they may appear to originate from the temporal lobe. Temporal lobe resections do not lead to seizure freedom. These lesions need to be looked for in all cases of cryptogenic TLE. Resection of the hamartoma can lead to seizure freedom (Fig. 29).

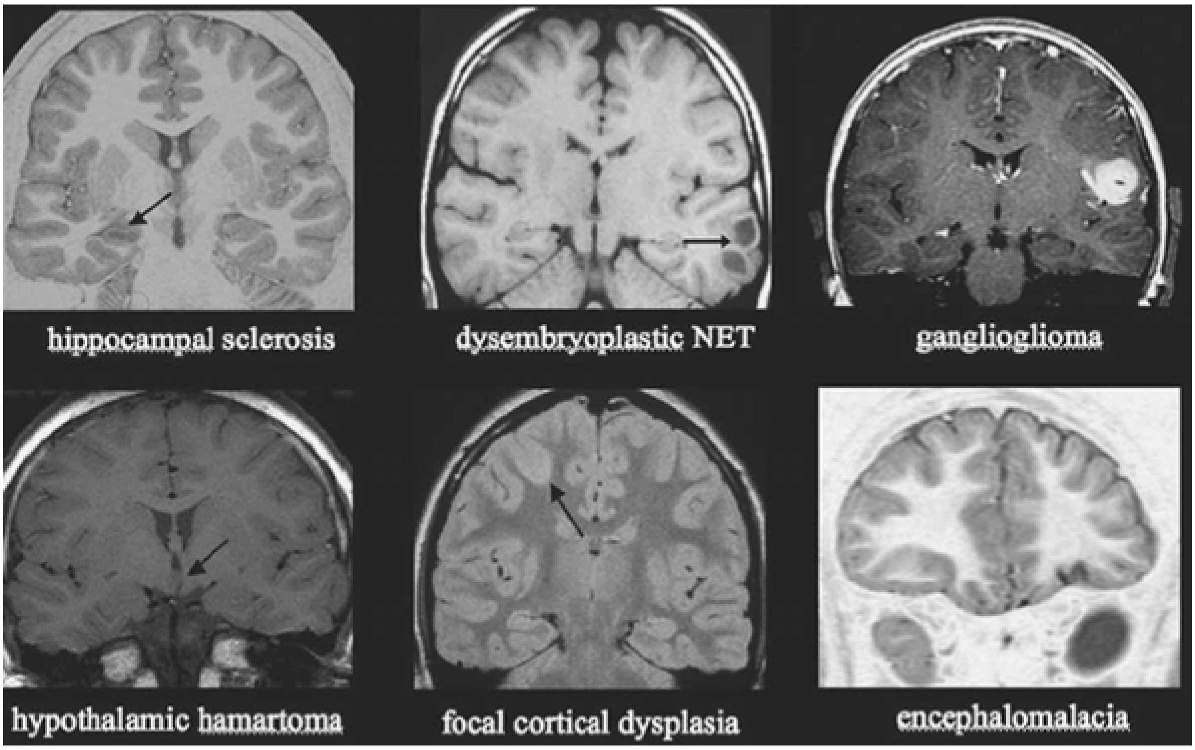


FIGURE 30. A range of the common causes of focal epilepsy that are essential to diagnose. NET, neuroepithelial tumor. (Courtesy of Simon Harvey, Royal Children's Hospital, Melbourne, Australia.)

There are a number of abnormalities that can be easily missed if not specifically looked for (Table 8 and Fig. 30). Conversely, some lesions can be overdiagnosed in inexperienced hands (Table 9).

A number of lesions that are highly significant for epilepsy are found at the â€œbottom of the sulcus.â€ In some cases there is a fine tract from the ventricle to the sulcus. These lesions are often the hardest to see on MRI, but small resections

(Fig. 30) can render the patient seizure free. We propose that the mechanism of the development of these lesions may be a small injury or MCD on the surface of the brain that ends up at the bottom of the sulcus because of the continuing growth of the brain (Table 10) and the formation of gyri (after 20 weeks of gestation). The brain grows a great deal even after birth (Table 10).[13] This may be an explanation of the â€œabnormal gyriâ€ or â€œstrange-looking gyral patternâ€ that is

nonspecific but with which all who deal with epilepsy are familiar (Fig. 31).

There is a range of abnormalities that give rise to diffuse pathology in the hemisphere. These are usually readily identified (Fig. 32).

Table 8 Subtle lesions that can be missed on magnetic resonance imaging

Focal cortical dysplasia

Mild or bilateral hippocampal sclerosis
Small hypothalamic hamartoma
Polymicrogyria
Subcortical band and periventricular nodular heterotopia
Mild tuberous sclerosis

Curvilinear surfaces can be of great help in visualizing abnormalities of gyral pattern and understanding the anatomic location of an abnormality that may be hard to appreciate in standard imaging planes (Fig. 33). The curvilinear surface maintains information about the gray and white matter and can be more useful than a simple surface-reconstructed image. There are a number of nonstandard investigations that can be requested that might help in particular cases (Table 11).

Other Imaging Techniques in The Context of The Anatomic Magnetic Resonance Imaging Study

Although it might be desired to perform all studies in all patients, the proliferation of imaging technologies means that we have entered an era in which appropriate selection of imaging is required. This is partly a cost-effectiveness problem as well as an issue of how much imaging is reasonable for a patient to undergo.

Electroencephalogram Simultaneous With Functional Magnetic Resonance Imaging

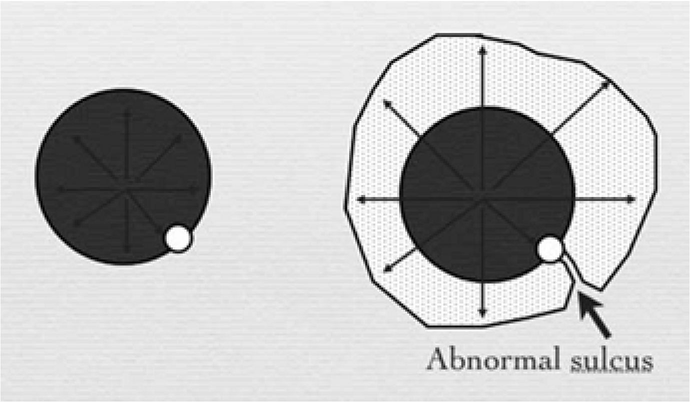


FIGURE 31. Why small focal dysplasias may be at the â€œbottom of the sulcus.â€ The brain grows a great deal after birth, and any abnormality that is on the cortical surface may not grow as much, leading to folding of the cortex in a slightly unusual way and leaving the abnormality at the bottom of the folded sulcus.

Idiopathic generalized epilepsies (IGEs) have been believed to have normal imaging. With advanced methods, one can now find structural and functional abnormalities in these cases using MRI methods. In childhood absence epilepsy, simultaneous EEG and functional MRI (fMRI) can show that electrographic bursts of spike and wave are associated with intense blood oxygenation levelâ€"dependent (BOLD) â€œactivationâ€ of the thalamus bilaterally (Fig. 34).

Table 9 Magnetic resonance imaging lesions that can be overdiagnosed

Hippocampal sclerosis (e.g., asymmetric temporal horns, artifactual signal increase, shape asymmetry)
Temporal pole dysplasia (e.g., anterior temporal lobe changes with hippocampal sclerosis)
Periventricular heterotopia

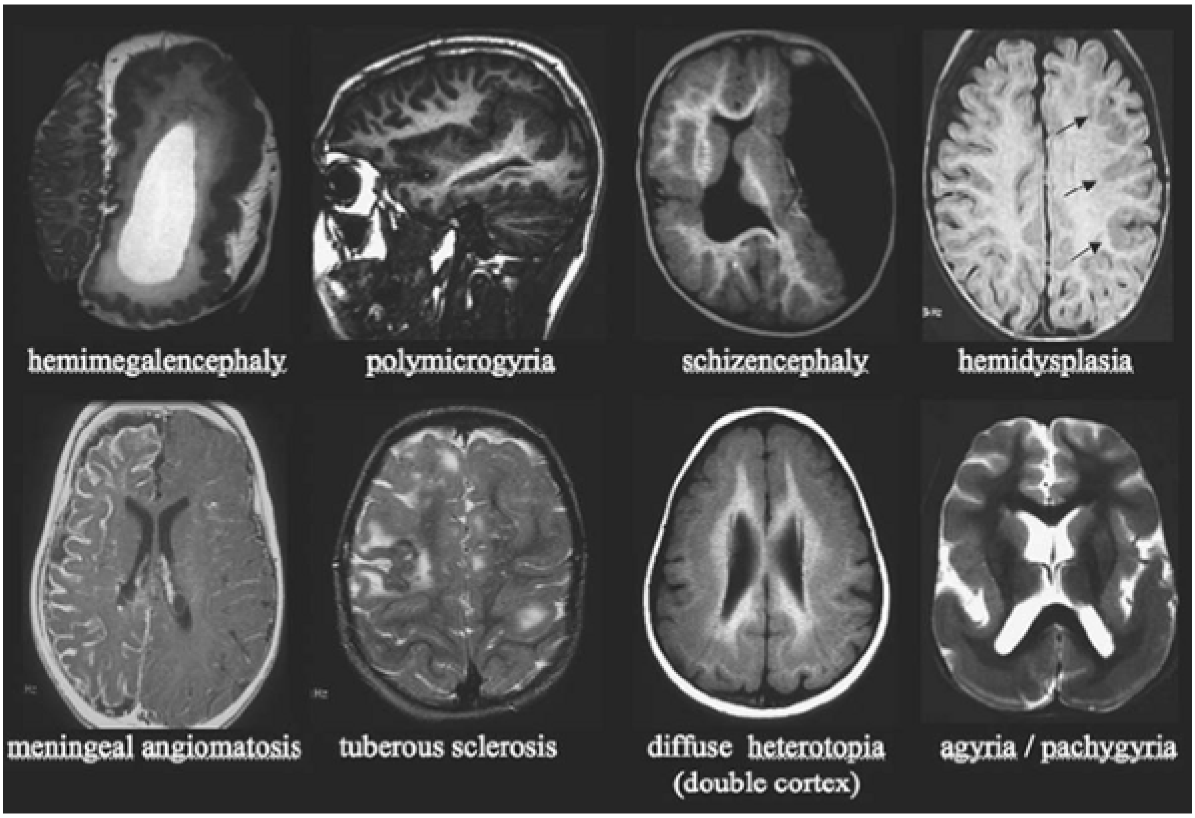

hemimegalencephaly
polymicrogyria
schizencephaly
hemidysplasia
meningeal angiomatosis
tuberous sclerosis
diffuse heterotopia (double cortex)
agyria / pachygyria

FIGURE 32. A range of diffuse pathologies that can be seen on magnetic resonance imaging that are the cause of epilepsy. Perisylvian polymicrogyria is usually best appreciated on the parasagittal images.

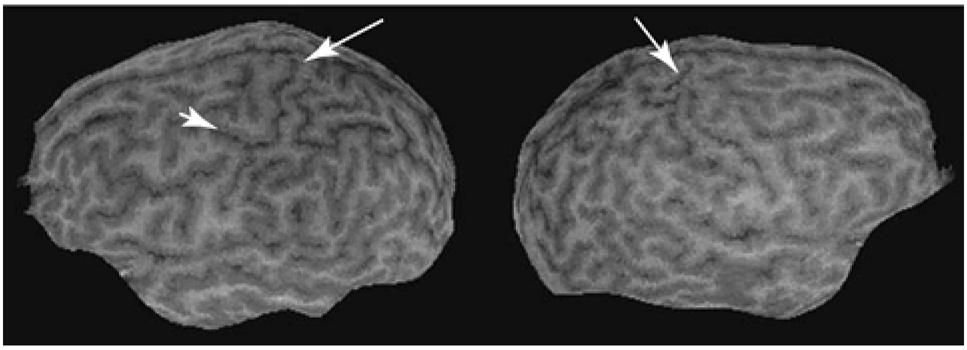


FIGURE 33. This curvilinear surface is obtained in Brainsightâ„¢ (Rogue Research, Montreal) and shows an abnormal sulcus extending anteriorly from the central sulcus on the left side in a patient with reading epilepsy.

Table 10 Brain growth in weight, by developmental stage

Developmental stage	Average brain weight (g)
20 wk of gestation	100
Birth	400
18 mo	800
3 yr	1,100
Adult	1,300â€"1,400

Table 11 Special techniques for special problems

T2 relaxometry
Volume measurements
Voxel-based morphometry, voxel-based relaxometry
Diffusion-weighted imaging

Functional magnetic resonance imaging (fMRI) for language and memory
Electroencephalogram/fMRI
Positron emission tomography
Ictal single photon emission computed tomography
Magnetic-resonance-imaging surface coil studies

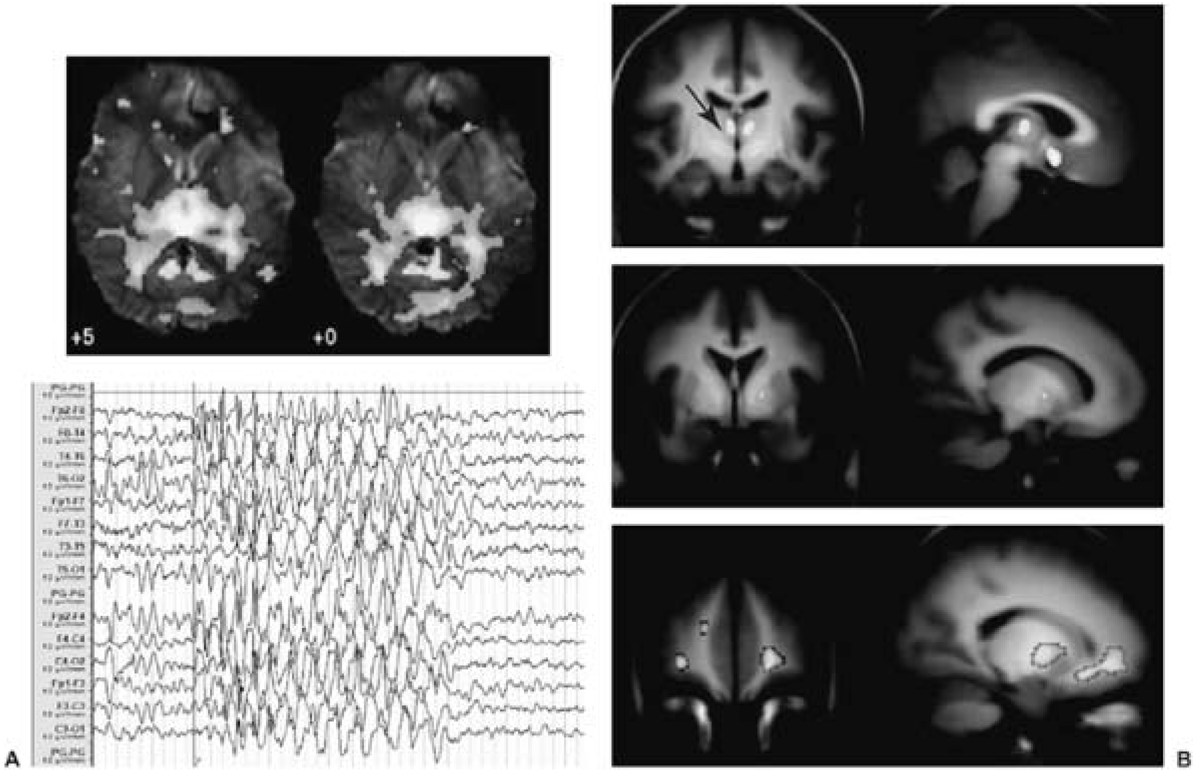


FIGURE 34. In childhood absence epilepsy, simultaneous electroencephalography and functional magnetic resonance imaging can show that electrographic bursts of spike and wave are associated with intense blood oxygenation levelâ€“dependent â€œactivationâ€ of the thalamus bilaterally **(A)**. In a group study, there is atrophy of the thalamus in these patients when compared to controls **(B)**. These advanced methods give insight into the structural and functional changes that occur in these epilepsies.

Focal activation low in the rolandic region can be seen in benign epilepsy with centrotemporal spikes (BECTS) with quite specific localization on the EEG/fMRI study (Fig. 35).

Structure can be correlated with function using a range of techniques in absence epilepsy (Fig. 36). Diffusion imaging and tractography can also reveal important aspects of the microarchitecture of the brain that is important in understanding the networks of the brain that may be altered in epilepsy (Fig. 37).

In addition to defining the structural basis of epilepsy, important aspects of brain function can also be identified with MRI. Functional MRI and EEG/fMRI can reveal remarkable aspects of brain function. Language fMRI using BOLD is a robust technique for the lateralization of language, and this is in common use in epilepsy centers. For the issue of lateralization of language function, in our center we have the opinion that fMRI provides better and more robust information than the Wada test. The combined use of these techniques can suggest hypotheses about the nature of the pathophysiology of brain function in epilepsy and its consequences that no other data can provide (Fig. 38).[3,14]

Positron Emission Tomography

The typical finding that can be very helpful in the localization of focal epilepsy is an area of hypometabolism that raises the question of whether this might be related to the seizure focus. This role in extratemporal epilepsy is very important. This then can direct further investigations if it is supported by the clinical context and seizure semiology. In the case of temporal lobe epilepsy, positron emission tomography (PET) study usually confirms the other imaging finding, and although it might make a useful contribution to assessing outcome, the decision for surgery is only occasionally affected by fluorodeoxyglucose (FDG) PET findings (Fig. 39) in centers such as ours.

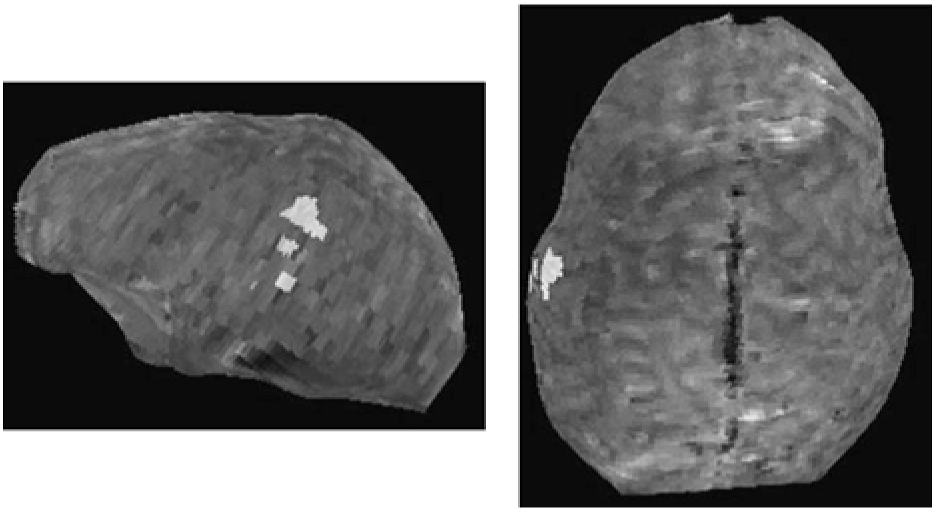


FIGURE 35. Blood oxygenation levelâ€“dependent functional magnetic resonance imaging (fMRI) activation in a child with classical benign epilepsy with centrotemporal spikes (BECTS), electrographically coming from the left. The fMRI study uses the â€œspikesâ€ as events. The activation is focal and in the postcentral gyrus, mostly in the anterior bank from the level of the inferior frontal gyrus, extending into the sylvian fissure and contiguously including the opercular bank of the postcentral gyrus on the left. The activations are shown on curvilinear reconstructions in Brainsight.

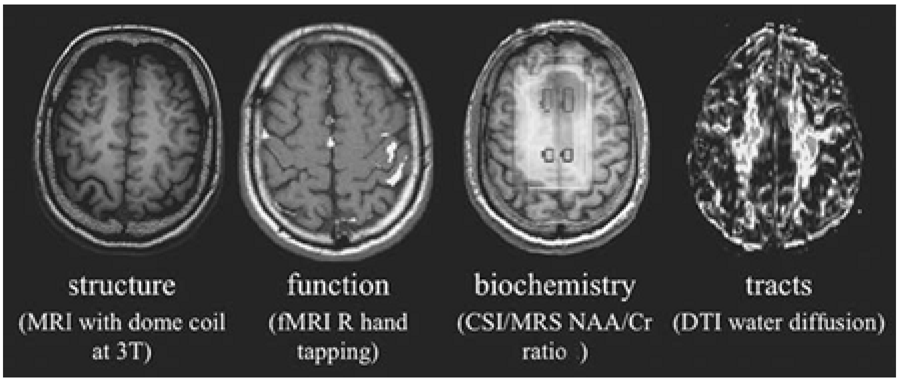


FIGURE 36. Advanced magnetic resonance imaging (MRI) in epilepsy. A range of advanced methods is

available. Functional MRI (fMRI) can reveal the localization of functions such as language or, in this case, hand function, biochemistry (using chemical shift imaging [CSI]), and aspects of the microstructure of the brain such as white matter with diffusion imaging. Cr, creatine; DTI, diffusion tensor imaging; MRS, magnetic resonance spectroscopy; NAA, *N*-acetyl aspartate; R, right.

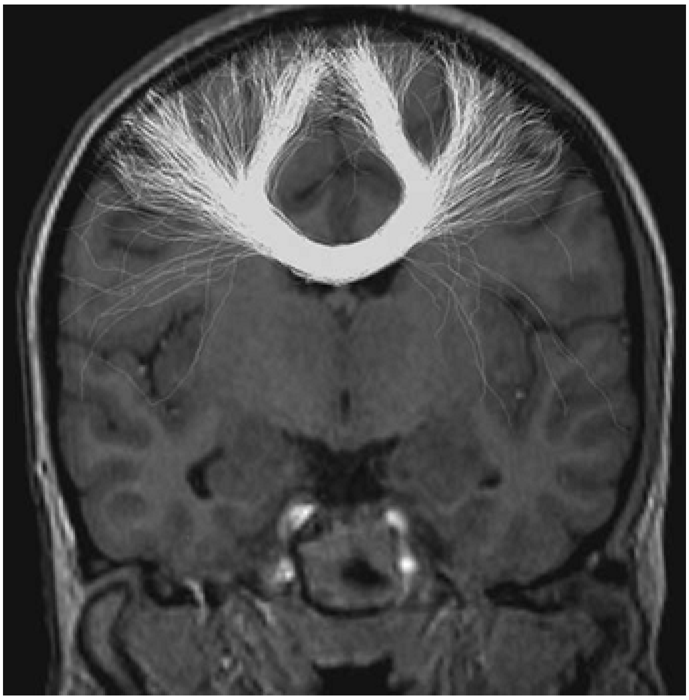


FIGURE 37. White matter tracts delineated using diffusion-weighted magnetic resonance imaging (MRI) fiber tracking, superimposed on a T1-weighted coronal MR image. The tracks were generated from a seed point in the body of the corpus callosum, using a probabilistic streamlines tracking algorithm. To allow tracking through crossing fiber regions, the directional information was obtained from the diffusion-weighted images using constrained spherical deconvolution (CSD). (Image courtesy of J-Donald Tournier, Brain Research Institute, Melbourne, Australia.)

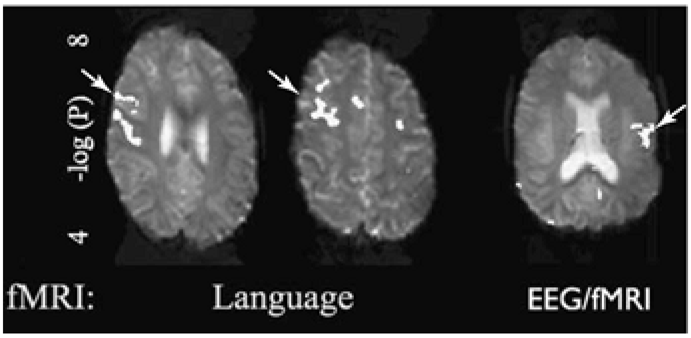


FIGURE 38. Physiologic and pathologic function. In the case shown here, there is right-sided language lateralization in a right-handed individual with no family history of sinistrality. The magnetic resonance imaging (MRI) was structurally normal, and seizures were partial and left hemispheric. Language functional MRI (fMRI) shows right-sided function in inferior and middle frontal gyri, suggesting atypical lateralization of language. The electroencephalographic/fMRI study localized the blood oxygenation levelâ€“dependent response from the interictal events to the left inferior frontal gyrus. We propose that this is likely to be the reason that language function is on the right, away from an area of epileptic activity. This patient's seizure onset was in early childhood.

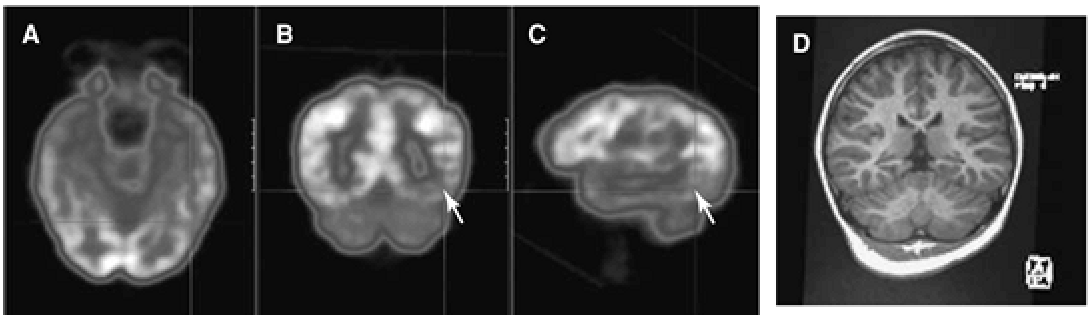


FIGURE 39. An area of decreased glucose uptake in the floor of the left temporal lobe (*arrows*) in a patient with photosensitive epilepsy and complex partial seizures **(Aâ€“C)**. In this case the magnetic resonance imaging was normal **(D)**. (Image courtesy of Sam Berlangieri, Austin Health, Melbourne, Australia.)

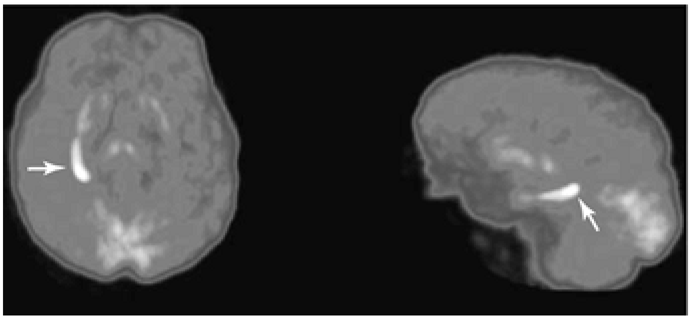


FIGURE 40. The positron emission tomography images show increased glucose uptake in the left hippocampus, consistent with limbic encephalitis. No obvious cause was identified despite extensive investigations.

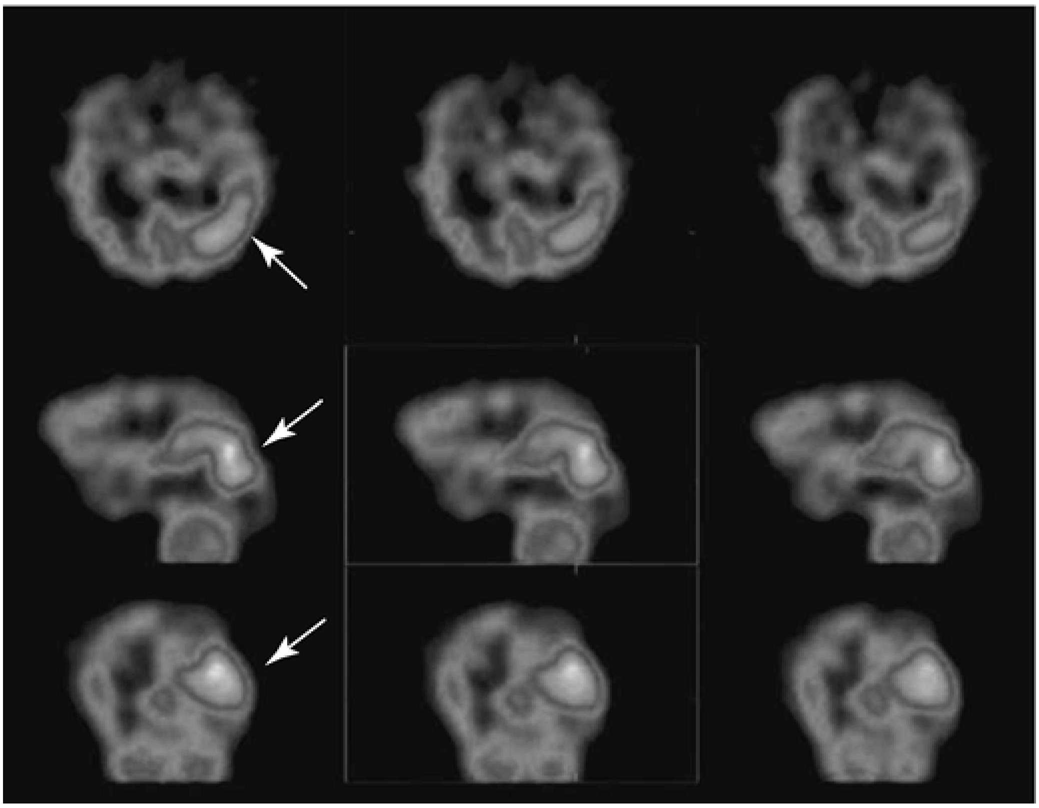


FIGURE 41. Injection of a single photon emission computed tomography radioligand during a seizure can show dramatic focal increase in perfusion in the posterior temporal region, suggesting seizure origin in this area.

In many such cases there is also some hypometabolism in the temporal lobes (first image). The presence of temporal hypometabolism in this clinical context is nonlocalizing, and the concept that the temporal lobe is a â€œsinkâ€ that is affected secondarily by lateralized partial seizures may be important.

PET images can give remarkable insights into epilepsy in some cases. When MRI is normal, it can give localizing information that will inform a more detailed review of the structural images. In some cases it suggests processes that could not have been determined from other information. For example, there are cases in which the structural images are normal, and yet there can be dramatic regional or hemispheric hypometabolism. Rarely, focal status or other dramatic findings may give unique insight into the epilepsy problem (Fig. 40).

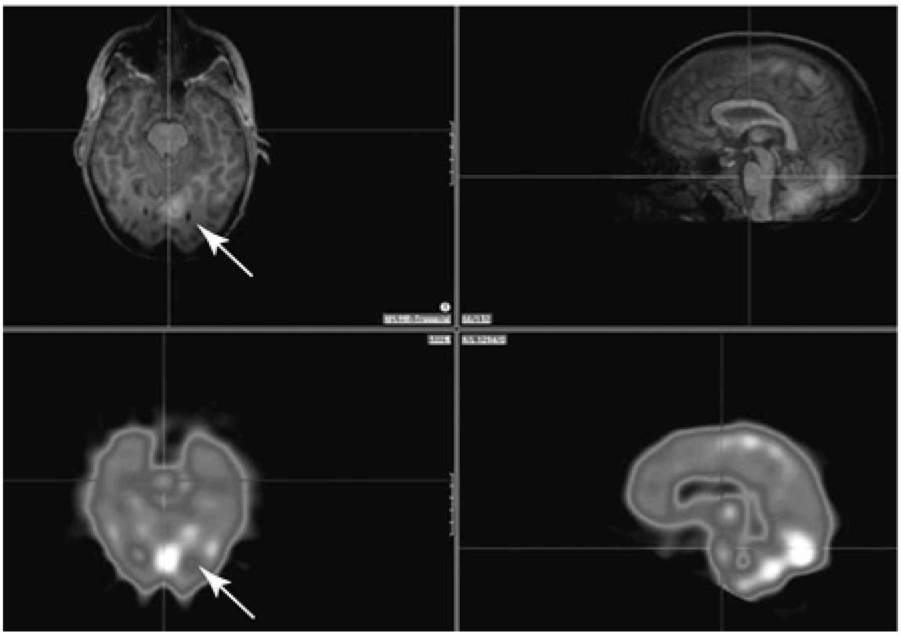
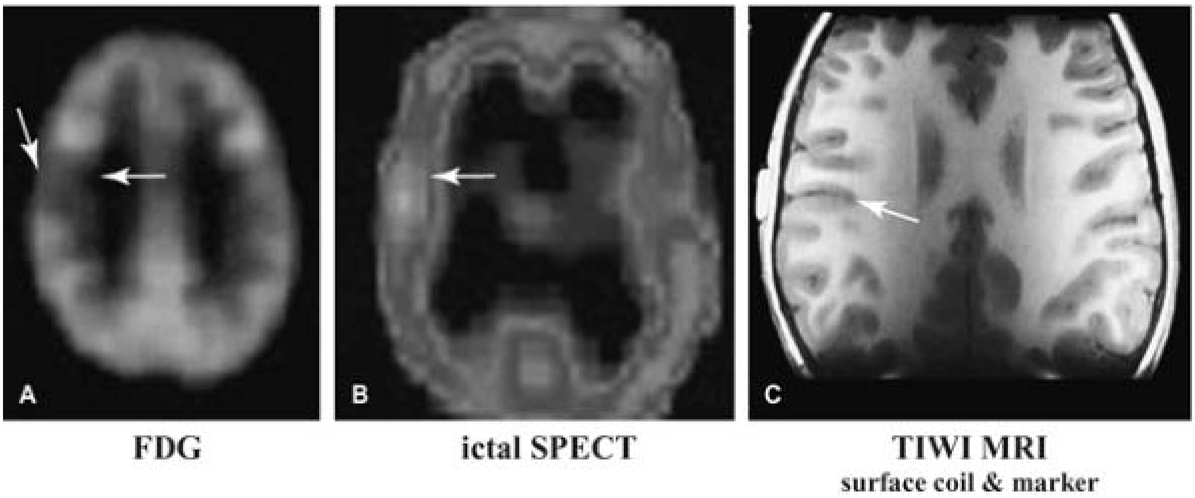


FIGURE 42. Early injection can suggest areas that should be further investigated. An early injection in a patient with apparent temporal lobe epilepsy suggests that there is early activity in the mesial occipital region. The top panels show the activation coregistered and superimposed over the magnetic resonance imaging anatomy, the lower panels show the single photon emission computed tomography image only.



FDG

ictal SPECT

TIWI MRI
surface coil & marker

FIGURE 43. Simple partial seizures with right face sensation and jerking. In many cases of partial epilepsy the initial magnetic resonance imaging shows no abnormality. The patient had simple partial seizures with a sensation in the right face and jerking of the face. Fluorodeoxyglucose (FDG) positron emission tomography (PET) **(A)** showed a clear focal abnormality that accords with the increased perfusion on ictal single photon emission computed tomography (SPECT) **(B)**. Careful analysis of the magnetic resonance imaging (MRI) and a further surface coil study with a fiducial marker **(C)** revealed a focal abnormality. In this case a small â€œbottom of the sulcus dysplasiaâ€ was identified. Surgery of this small focal area led to seizure freedom. T1WI, T1-weighted imaging. (Case courtesy of Simon Harvey, Royal Children's Hospital, Melbourne, Australia.)

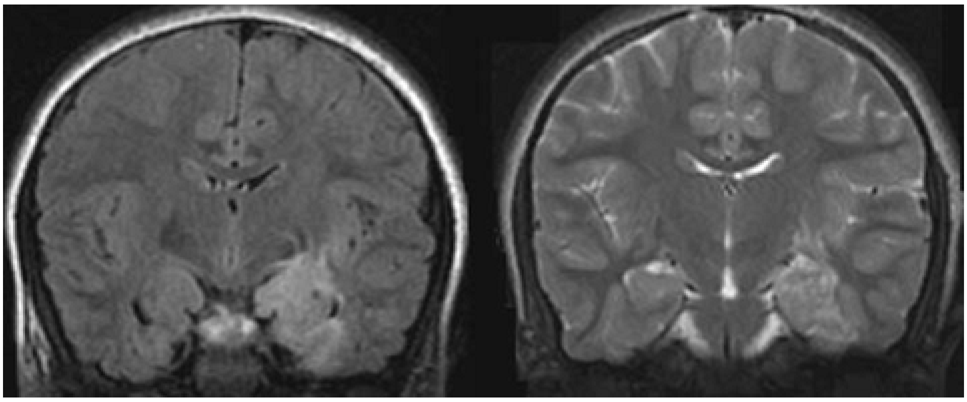


FIGURE 44. Dysembryoplastic neuroepithelial tumors in the temporal lobe are an important cause of epilepsy. Lesions such as these are â€œobviousâ€ on most imaging, regardless of epilepsy optimization. The relationship of the lesion to other mesial temporal structures is most easily seen in images acquired in the hippocampal axis.

Probably the most exciting use of PET is the development of techniques for the evaluation of receptor-specific aspects of epilepsy such as the role of serotonin in tuberous sclerosis.[9]

Single Photon Emission Computed Tomography

Ictal single photon emission computed tomography is technically very demanding and requires a high degree of organization within the epilepsy monitoring unit and good collaboration with the nuclear medicine department. The effort is certainly of benefit, and in some cases this is an essential investigation that allows understanding of the epilepsy origins or the ability to offer surgery without the need for intracranial implantation (Fig. 41). Early injection and comparison to the interictal study are the keys to using this method. It is essential to interpret these studies with knowledge of the timing of the injection relative to the clinical and electrographic events of the seizure, and this must be done with video monitoring. Early injection can be revealing (Fig. 42).

Ictal SPECT is a very important tool in understanding the localization of epileptic seizures.[11] It is important for two reasons. First, it can identify a region that gives focus to more detailed assessment with structural imaging studies. The best outcome in epilepsy surgery occurs when the functional studies showing seizure origin are concordant with a focal lesion. In the absence of an identified focal structural lesion, outcome is worse. Second, ictal SPECT shows information that is primarily about the paroxysmal events that are the basic complaint of the patient with epilepsy. Conceptually, structural imaging, and even PET, shows abnormalities that are present in the brain all of the time. Although they might be the basis of the paroxysmal seizure events, ictal SPECT is a way of actually imaging these events. Therefore it provides data that are of a different nature than those from other imaging methods and adds to the understanding of the cause of an individual patient's epilepsy.

Ictal SPECT must be interpreted in conjunction with an interictal study. This can be done visually by comparison of the two studies or with advanced processing methods such as subtraction ictal SPECT coregistered to MRI (SISCOM). When these findings suggest a focal area, the MRI and structural studies should be reviewed, and further imaging might be indicated to specifically interrogate these areas. Finding a focal area of abnormality gives great confidence that focal resection will be associated with a good outcome from surgery (Fig. 43).

Summary and Conclusions

MRI studies are an essential component of the overall assessment of why a patient has epilepsy. This requires us to define and understand the epileptic events, the structural abnormalities in the brain, and the clinical context in which seizures occur. Unless high-quality information is obtained in all three of these domains, the basis of the epilepsy in any individual has not been fully assessed.[4]

In this chapter, we have dealt with the need to define and understand the structural brain abnormalities by acquiring appropriate epilepsy-focused MRI of high quality and diagnosing the important lesions with high sensitivity and specificity because this is fundamental to good epileptology, albeit often difficult to implement in practice. The clinical context, seizure features, and interpretation of the imaging, with full knowledge of the hypothesized basis of each individual's epilepsy and the other investigations, are the key to the proper use of imaging.

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Chapter 80

Positron Emission Tomography

Thomas R. Henry

Harry T. Chugani

Introduction

Positron emission tomography (PET) generates physiologic images that are complementary to brain structural magnetic resonance images (MRI) in numerous epilepsy research applications and also in a major clinical application (planning epilepsy surgery). Epilepsy research with PET has used various radiopharmaceutical tracers to measure cerebral blood flow, glucose metabolism, neurotransmitter synthesis, receptor density, kinetics of antiepileptic drugs, and effects of antiepileptic drugs and therapeutic neural electrostimulation (Table 1). Cerebral glucose metabolic mapping, using PET and 2-deoxy-2-[^{18}F]fluoro-D-glucose ([^{18}F]FDG), has been extensively studied in the epilepsies. Regions of interictal glucose hypometabolism are highly associated with cerebral sites of seizure generationâ€“propagation in partial epilepsies and in West syndrome. Localization of interictal hypometabolism in planning epilepsy surgery is widely accepted as a clinical application of PET. This chapter reviews essential principles of PET (Table 2) methodology and emphasizes epilepsy research and presurgical epilepsy evaluations using clinical PET.

Methodology

Interictal [^{18}F]FDG PET is readily available in clinical PET centers, whereas research centers typically provide [^{18}F]FDG and multiple other radiopharmaceutical agents. Clinical PET centers are financially supported mainly by whole-body [^{18}F]FDG PET, which is used to screen for metastases of solid tumors. The relatively long half-life of ^{18}F (about 2 hours), the common use of highly standardized protocols for synthesizing [^{18}F]FDG, and the availability of high-resolution tomographic cameras all serve to make [^{18}F]FDG imaging practical and affordable in an advanced oncology center. Epileptologists can easily arrange for brain [^{18}F]FDG imaging in a clinical PET center, which provides the multidisciplinary expertise required for safe and accurate PET imaging. Clinical epileptologists need to understand essentials of PET methodology and [^{18}F]FDG physiology to apply [^{18}F]FDG images in presurgical epilepsy evaluations. Following intravenous injection of radiolabeled [^{18}F]FDG, patients are observed for 30 to 45 minutes, and then scanning is performed. During the observation period after [^{18}F]FDG injection, the labeled [^{18}F]FDG circulates through cerebral arterioles and capillaries, with diffusion into brain tissue; [^{18}F]FDG is taken up by neurons and other cells and is phosphorylated, as is glucose; unlike glucose, [^{18}F]FDG does not enter the rest of the Krebs cycle and remains in place as ^{18}F decays and emits positrons.[146] The tomograph detects oppositely directed high-energy photons produced in positron decay. Image data usually are reconstructed into a set of axial [^{18}F]FDG activity images, which are viewed and interpreted by a nuclear medicine physician.

Research studies with PET also use the sophisticated physics (for generation of positron-emitting radionuclides), neurochemistry (for radiopharmaceutical preparation), and computing (for image reconstruction and analysis) widely available in nuclear medicine facilities. Clinical cyclotrons can produce positron-emitting isotopes of fluorine (^{18}F, half-life of 110 minutes), carbon (^{11}C, half-life of 20 minutes), nitrogen (^{13}N, half-life of 10 minutes), and oxygen (^{15}O, half-life of 2 minutes). Radiochemists have perfected reaction sequences rapidly to incorporate these radionuclides into a wide variety of labeled organic molecules, which can be administered intravenously in high purity to image many neurochemical sites and brain processes of interest to epileptologists. The accuracy of PET measurement and anatomic display is determined by the biochemical and physical properties of the selected radiopharmaceutical tracer (Table 1) and its mathematical model, performance characteristics of the tomographic instrument, scanning procedure, and other factors. Several reviews have covered general and epilepsy-related aspects of PET methodology in detail.[49,50,71,219,220]

Table 1 Positron-emitting radiopharmaceuticals used in Positron emission tomography studies of epilepsy

Function	Radiopharmaceuticals
Glucose metabolism	2-[^{18}F]fluoro-2-deoxyglucose (FDG)
Oxygen metabolism and oxygen extraction ratio	[^{15}O]O_2
Cerebral blood flow	[^{15}O]O_2, [^{15}O]H_2O, [^{15}O]CO_2, [^{13}N]NH_3
Central benzodiazepine receptor distribution	[^{11}C]flumazenil (formerly [^{11}C]RO15-1788)
Muscarinic cholinergic receptor distribution	[^{11}C]*N*-methyl piperidyl benzilate
Opiate receptor distribution	[^{11}C]Carfentanil (Âµ-receptors)
	[^{18}F]Cyclofoxy (Âµ-/Îº-receptors)
	[^{11}C]Diprenorphine (Âµ-/Îº-/Î´-receptors)
Serotonin synthesis	[^{11}C]Î±-methyl tryptophan
Serotonin-1 Aâ€“receptor distribution	[^{11}C]WAY100635, [^{18}F]FCWAY, [^{18}F]MPPF
Drug distribution	[^{11}C]Phenytoin
	[^{11}C]Valproate
Monoamine oxidase B distribution (glial density)	[^{11}C]Deuterium-deprenyl

[^{11}C]WAY100635, [*O-methyl*-^{11}C]-*N*-(2(4(2-methoxyphenyl)-1-piperazinyl)ethyl)*N*-(2-pyridinyl) cyclohexanecarboxamide trihydrochloride; [^{18}F]FCWAY,

[^{18}F]*trans*-4-fluoro-*N*-2[4-(2-methoxyphenyl)piperazin-1-yl]ethyl]-*N*-(2-pyridyl)cyclohexanecarboxamide; [^{18}F]MPPF, 2â€²-methoxyphenyl-(*N*-2â€²-pyridinyl)-*p*-[^{18}F]fluoro-benzamidoethylpiperazine.

Table 2 Indications for FDG PET in presurgical evaluation of epilepsy

Indications	Temporal lobe epilepsy	Extratemporal partial epilepsy	Infantile spasms and Sturge-Weber syndrome
Lateralization and regionalization of interictal hypometabolism for possible resection without prior intracranial electrophysiologic ictal monitoring	Requires PET concordance with scalp-sphenoidal EEG ictal onsets, with any cortical abnormalities on MRI, and with any other localized epilepsy-associated cerebral dysfunction	No established role for PET	Requires PET concordance with any lateralized or focal features on ictal scalp EEG recordings, with any cortical abnormalities on MRI, and with absence of significant cerebral dysfunction beyond the intended margins of resection
Regionalization of interictal temporal or extratemporal hypometabolism for direction of intracranial electrode placement	Requires correlation of PET with semiologic, interictal, and ictal extracranial EEG, MRI, and other noninvasively acquired data	Requires correlation of PET with semiologic, interictal, and ictal extracranial EEG, MRI, and other noninvasively acquired data	No established role for PET
Prognostication of surgical outcome with regard to seizure control	Presence of temporal hypometabolism and absence of extratemporal cortical hypometabolism predict best outcome	No established role for PET	No established role for PET

EEG, electroencephalogram; FDG, 2-[^{18}F]fluoro-2-deoxyglucose; MRI, magnetic resonance imaging; PET, positron emission tomography.

The performance of each PET tracer and PET scanning system must be considered in four dimensions of physiologic imaging: (a) process, (b) temporal, (c) contrast, and (d) spatial resolutions. *Process* resolution is the accuracy of a tracer kinetic method in measuring the intended biochemical process. *Temporal* resolution is the duration of brain function represented in any PET data set. *Contrast* resolution (â€œsignal-to-noise ratioâ€) is determined by the ability of a PET system accurately to measure the activity of positron-emitting tracer within the object scanned. *Spatial* resolution is determined by the ability of an imaging system to detect subdivisions of the object scanned to support image reconstruction that renders the subdivisions in accurate position and shape. Each dimension of a volume of tissue must be at least twice the linear resolution of the imaging system if the volume is to be accurately resolved in space and functional intensity on the image.[126] Structures smaller than this will have their functional activity averaged with those of adjacent structures (the partial volume effect). The higher spatial resolution of current PET tomographs compared with those reported in earlier [^{18}F]FDG imaging research has been shown to generate more sensitive and accurate detection of hypometabolism, with greater ability to correlate [^{18}F]FDG image coordinates with brain MRI locations.[72] Epileptologists who use MRI in research are accustomed to spatial resolution and signal-to-noise ratio in determining which reported findings are supported by the imaging techniques. Results of PET-based epilepsy research must be critically analyzed with respect to all four dimensions of resolution in physiologic imaging.

Evaluation of [^{18}F]FDG images is complex with respect to temporal resolution, but otherwise it is fairly straightforward. The [^{18}F]FDG kinetics generates a nonlinear temporal resolution, in that glucose metabolism is averaged over about

40 minutes, with earlier periods during scanning weighted more heavily in this average. The tracer kinetic model of [^{18}F]FDG requires steady-state conditions for absolute measurements of glucose metabolic rate, and so only relative comparison of metabolism within different regions of the image set can be made if a single seizure occurs during [^{18}F]FDG imaging.[146] Ictal [^{18}F]FDG PET studies cannot be quantified because glucose metabolism is not at steady-state.[146] Dynamic [^{15}O]H_2O PET imaging of cerebral blood flow (CBF) is in theory superior for ictal scanning of single seizures to either

[^{18}F]FDG PET or single photon emission computed tomography (SPECT) techniques due to its superior temporal resolution and the possibility of fully quantifying CBF (without requirement of correction for nonlinear activityâ€“CBF relationships, as occur with SPECT agents). In practice, the short half-life of ^{15}O and the usually unpredictable timing of seizure onsets render ictal [^{15}O]H_2O PET impossible except for the study of reflex seizures. Relative increases and decreases in ictal regional metabolism have been observed with [^{18}F]FDG PET.[127] Ictal [^{18}F]FDG studies are most useful when the duration of continuous seizure activity approximates the duration of [^{18}F]FDG uptake and phosphorylation following bolus [^{18}F]FDG injection, that is, when seizures last 10 minutes or longer. Epilepsia partialis continua is required for â€œpurelyâ€ ictal [^{18}F]FDG scanning.[59] Occurrence of a brief complex partial seizure shortly after [^{18}F]FDG injection may actually be associated with false normalization of apparent [^{18}F]FDG activity, presumably due to averaging of interictal hypometabolism and ictal hypermetabolism in the same region.[71]

Many centers perform continuous scalp electroencephalographic (EEG) monitoring immediately prior to and following [^{18}F]FDG administration, including for outpatient PET. Continuous EEG is useful in determining wakeâ€“sleep state, frequency of interictal epileptiform discharges, and occurrence of electrographic seizures. Scalp electrodes do not significantly attenuate or scatter the high-energy (511 keV) photons that are produced by positron annihilation. Some centers do not routinely perform EEG monitoring because this slightly increases the cost of [^{18}F]FDG scanning and because some believe that subclinical or unreported seizures rarely occur in the imaging suite and that single seizures do not alter [^{18}F]FDG images.[6] The latter point has been disproved (see, e.g., the case presented by Henry et al.[71]). Nonetheless, the costâ€"benefit ratio of continuous EEG during clinical [^{18}F]FDG studies has not been established. Continuous EEG monitoring is standard in PET research protocols, not only for [^{18}F]FDG, but also for other radiopharmaceuticals; focal seizures cause marked focal increases on cerebral blood flow and therefore cause marked increases in delivery of any PET ligand to areas of maximal seizure involvement, resulting in altered physiologic images.

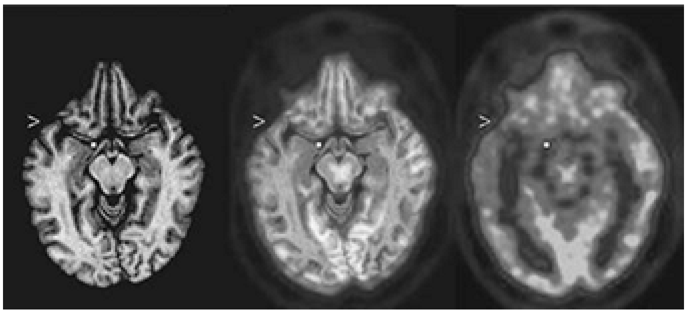

FIGURE 1. Coregistered axial image plane of magnetic resonance imaging (MRI) and interictal 2-deoxy-2-[^{18}F]fluoro-D-glucose ([^{18}F]FDG) positron emission tomography (PET) images of a limbic temporal lobe epilepsy (TLE) patient. The gray-scale MR image **(left)** and the color PET image **(right)** are coregistered in the center image. The MRI and PET data were reoriented parallel to a line through the anterior and posterior commissures. A widespread area of reduced [^{18}F]FDG activity is evident on the left side of the PET image; inspection of the PET image alone does not clarify whether the reduction extends from mesial structures (at the dot internal to the brain FDG image) of the temporal lobe into the basal frontal lobe, nor whether the lateral temporal hypometabolism (at the arrowhead) extends above the sylvian fissure. The dot and arrowhead appear at the same coordinates in the MRI and the coregistered MRIâ€"PET images as in the PET image, clarifying that all sites with severe hypometabolism are confined to the temporal lobe. (See the color insert.)

Structural imaging data should guide anatomic analysis of PET images. An individual's MRI and PET images can be coregistered and then viewed side by side or with superimposition of the functional and structural images (Fig. 1). Accurate PETâ€"MRI coregistration permits comparison of anatomically specific metabolic measurements of the individual with normal subjects' means and variances of regional metabolism.[34] Statistical parametric imaging detects some abnormalities that cannot be appreciated with qualitative interpretation. For example, unilateral temporal lobe epilepsy often causes bilateral temporal hypometabolism with marked asymmetry of temporal metabolism (with lower [^{18}F]FDG activity on the epileptogenic side). Bilateral but asymmetric temporal lobe hypometabolism can be detected readily with statistical parametric imaging techniques, but it usually appears only as unilateral temporal hypometabolism on visual interpretation. Quantitative analyses that determine an asymmetry index also will fail to detect bilateral temporal hypometabolism, although the temporal lobe with relatively greater metabolic decrease will be accurately noted as the more hypometabolic. Issues regarding the construction of regions of interest for regional sampling of [^{18}F]FDG activity have been previously discussed.[71] Despite the advantages of statistical parametric imaging techniques, visual interpretation and quantification of asymmetry remain useful in current clinical applications because unilateral TLE often has asymmetric, bilateral temporal hypometabolism interictally.

Research Findings in the Epilepsies

Mesial Temporal Lobe Epilepsy: Glucose Metabolism and Cerebral Blood Flow Studies

Interictal [^{18}F]FDG PET usually demonstrates hypometabolism of one temporal lobe (Figs. 2,3,4) or bilateral temporal hypometabolism with more severe hypometabolism of one temporal lobe (Fig. 5) in adults and children with refractory mesial temporal lobe epilepsy (TLE).[1,3,10,11,39,40,41,42,60,61,67,71,72,74,75,98,106,108,118,137,151,164,165,167,168,186,187,189,197,204,208,210,212,215] Qualitative visual analysis of [^{18}F]FDG scans obtained with high-performance tomographs detects unilateral (or bilateral, but asymmetric) temporal lobe hypometabolism in >70% of refractory TLE patients. Higher-resolution tomographic systems support a higher detection rate for hypometabolism, and greater concordance among readers, in qualitative interpretation of [^{18}F]FDG imaging in localization-related epilepsies.[72] With quantitative analysis, detection of significant temporal lobe hypometabolism may exceed 90% in this group.[92,98,216]

Temporal lobe hypometabolism usually extends over mesial and lateral portions of an interictally dysfunctional temporal lobe on [^{18}F]FDG scans in mesial TLE.[72,74,167,215] Regional hypometabolism in mesial TLE typically is diffuse, with graded demarcations from adjacent areas of normal metabolism and a relatively large area of hypometabolism. Even in the presence of a temporal lobe foreign-tissue lesion, patients with refractory mesial temporal seizures usually have widespread temporal lobe hypometabolism rather than focal hypometabolism restricted to the site of the lesion. When using older tomographs with lower spatial resolution, the lateral temporal hypometabolism often appeared more severe than the mesial temporal hypometabolism of an affected temporal lobe on qualitative scan interpretation and even with quantification.[72,167] Using an ultra-high-resolution tomograph, however, one study of mesial TLE found that small volumes of anterior mesial

temporal structures were more severely hypometabolic than were any other temporal or extratemporal areas in many mesial TLE patients.[215] As shown in FIGURE 3, current tomographs more often provide [^{18}F]FDG scans that show mesial temporal greater than lateral temporal hypometabolism of the affected temporal lobe. This suggests that partial-volume averaging of severe hypometabolism in the epileptogenic amygdala-hippocampus together with less depressed metabolism of adjacent basal temporal areas may cause the mesial temporal areas to appear less severely hypometabolic than they actually are when older clinical PET systems are used. In contrast to lateralized temporal lobe predominance of metabolic dysfunction most often observed in refractory TLE, some TLE patients have symmetric hypometabolism of both temporal lobes (Fig. 6).[10,93] Normal interictal metabolism also occurs in refractory mesial TLE, but normal [^{18}F]FDG scans are more common in nonrefractory than in refractory mesial TLE.[55,124]

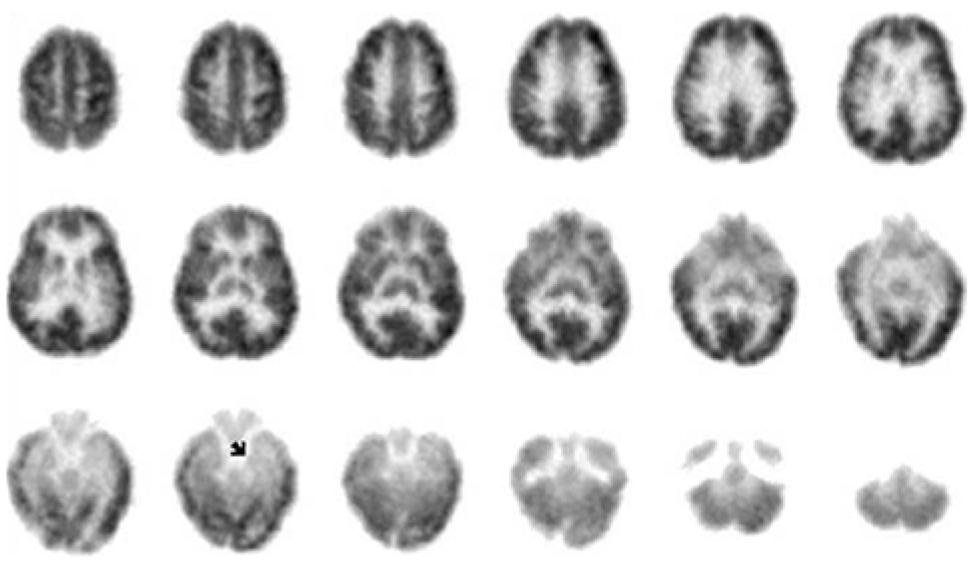

FIGURE 2. Interictal 2-deoxy-2-[^{18}F]fluoro-D-glucose ([^{18}F]FDG) positron emission tomography (PET) images of a limbic temporal lobe epilepsy (TLE) patient. These transaxially oriented images show anterior hippocampal hypometabolism (*arrow*), which is more severe than reduction in [^{18}F]FDG activity in the adjacent inferior-lateral temporal regions. No extratemporal abnormalities are evident. The patient's brain magnetic resonance imaging (MRI) was normal. Mild hippocampal sclerosis was present in tissue resected on the side of hypometabolism and of extracranially recorded electroencephalographic (EEG) ictal onsets. Seizures ceased after resection.

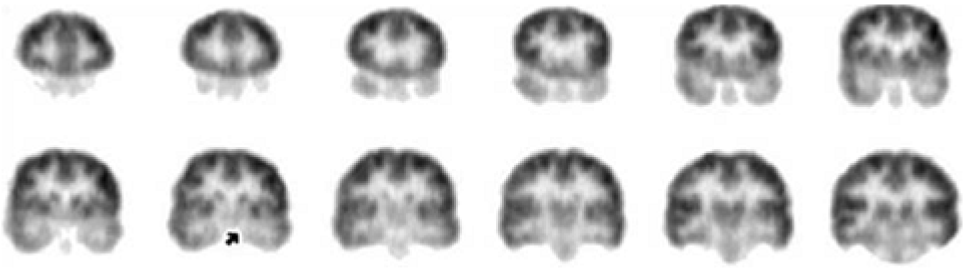

FIGURE 3. Interictal 2-deoxy-2-[^{18}F]fluoro-D-glucose ([^{18}F]FDG) positron emission tomography (PET) images of a limbic temporal lobe epilepsy (TLE) patient. These coronally oriented images were reconstructed from the same [^{18}F]FDG data as shown in FIGURE 2. It is evident that mesial is greater than lateral temporal hypometabolism (at arrow and on adjacent planes). On each row, the coronal images are arranged with the most anterior plane to the left and 4 mm spacing. Subject left is displayed on image right.

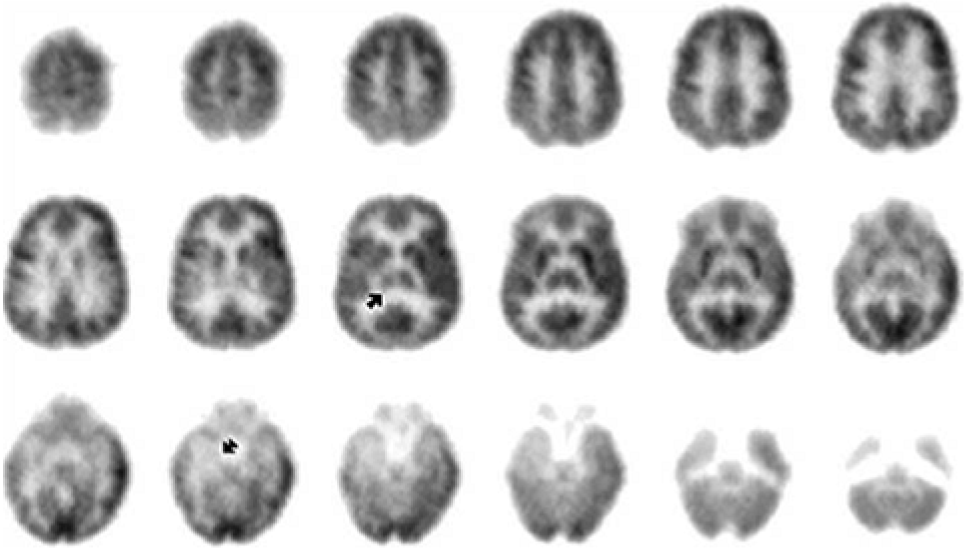

FIGURE 4. Interictal 2-deoxy-2-[^{18}F]fluoro-D-glucose ([^{18}F]FDG) positron emission tomography (PET) images of a limbic temporal lobe epilepsy (TLE) patient. These images show severe hypometabolism of the anterior hippocampus (*arrow*) and moderate hypometabolism of the ipsilateral temporal neocortex and thalamus (*arrow*). Mild hypometabolism is seen diffusely over the dorsolateral frontal and parietal cortex ipsilaterally. The patient's brain magnetic resonance imaging (MRI) showed mild bilateral hippocampal atrophy. Moderate hippocampal sclerosis was present in tissue resected on the side of hypometabolism and of intracranially recorded electroencephalographic (EEG) ictal onsets. Seizures ceased after resection.

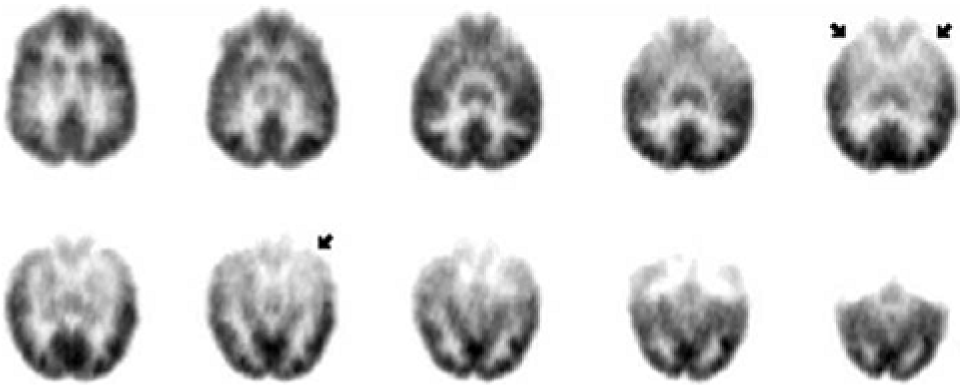

FIGURE 5. Interictal 2-deoxy-2-[^{18}F]fluoro-D-glucose ([^{18}F]FDG) positron emission tomography (PET) images of a limbic temporal lobe epilepsy (TLE) patient. These images show bilateral mesial temporal hypometabolism (arrows on image at upper right), which is more severe on the left (arrow on image in lower row). The patient's brain magnetic resonance imaging (MRI) showed mild left hippocampal atrophy. Moderate hippocampal sclerosis was present in tissue resected on the side of hypometabolism and of intracranially recorded electroencephalographic (EEG) ictal onsets. Seizures ceased after resection.

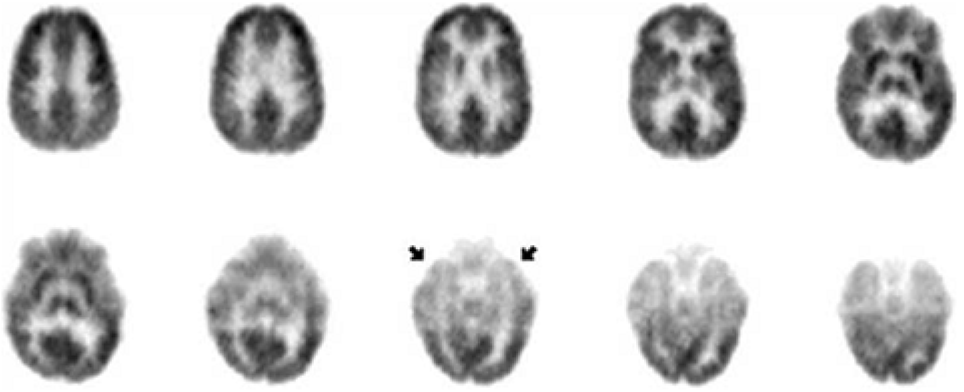

FIGURE 6. Interictal 2-deoxy-2-[^{18}F]fluoro-D-glucose ([^{18}F]FDG) positron emission tomography (PET) images of a limbic temporal lobe epilepsy (TLE) patient. These images show bilateral mesial temporal hypometabolism (arrows on image at upper right), which is symmetric. The patient's brain magnetic resonance imaging (MRI) was normal. Extracranially recorded electroencephalographic (EEG) ictal onsets were artifactually obscured, in some instances with prolonged right temporal ictal discharges seen in later periods during complex partial seizures. Intracranially recorded EEG ictal onsets occurred independently over each hippocampus in approximately equal numbers. Resective surgery was not performed.

Many TLE patients have unilateral frontal, parietal, thalamic, or basal ganglial hypometabolism ipsilateral to temporal hypometabolism, but occipital hypometabolism is rare in mesial TLE.[3,11,72,74,161,168,186] The temporal hypometabolism is nearly always more severe than is any extratemporal hypometabolism. The thalamus ipsilateral to the affected temporal lobe is the extratemporal site most likely to demonstrate hypometabolism in limbic TLE.[72,74] Thalamic asymmetries in [^{18}F]FDG activity are mainly dorsal (Fig. 4), and in some cases are associated with dorsal thalamic hypovolemia on structural MRI. The ipsilateral putamen is significantly more likely to be interictally hypometabolic in patients whose complex partial seizures involve dystonic posturing than in patients without ictal hemidystonia.[161] The cortical hypometabolic area typically is contiguous across its entire temporal and extratemporal extent (Fig. 4). In particular, the insular and inferior frontal regions are most often the portions of the ipsilateral frontal lobe that are hypometabolic in association with temporal lobe hypometabolism.[3,11,72,137] Bilateral cerebellar hypometabolism is common.[203] Thus, interictal [^{18}F]FDG PET in refractory mesial TLE usually reveals unilateral diffuse regional hypometabolism of one mesial-lateral temporal area, with or without ipsilateral extratemporal cortical hypometabolism or contralateral temporal hypometabolism; ipsilateral extratemporal hypometabolism almost always appears to be less severe than does the temporal lobe hypometabolism.

The pathophysiologic basis of regional hypometabolism imaged with [^{18}F]FDG interictally in TLE is unclear. Ablative structural lesions must contribute to localized decreases in glucose metabolism. Nonetheless, it has been recognized for some time that the volume of hypometabolism is greater than the volume of associated structural lesions in localization-related epilepsies.[39] Acute-subacute cerebral infarction is associated with hypometabolism at the site of neuronal loss, and additional extra-infarctional sites of hypometabolism are considered to represent â€œdiaschisisâ€ as passive and usually impersistent effects of a focal insult on remote brain regions that receive projections from the insulted area. Neuronal loss and diaschisis were considered the causes of the anatomically distributed interictal hypometabolism in TLE patients with hippocampal sclerosis. This hypothesis was refuted, however, by a study of quantified preoperative [^{18}F]FDG PET in patients whose resected temporal tissue underwent quantitative neuronal volumetric densitometry.[67] Subsequent studies, using different methodologies, confirmed this observation.[15,33,47,112] Similarly, several studies of MRI volumetry and interictal [^{18}F]FDG PET found that hippocampal atrophy and temporal lobe hypometabolism are not highly correlated in mesial TLE.[53,99,139,205] Furthermore, MR spectroscopic determination of the neuron-specific peaks of *N*-acetylaspartate (NAA) also found limited association of mesial temporal glucose hypometabolism and NAA decreases.[2,97] Although neuronal loss and diaschisis probably cause some of the disseminated glucose metabolic depression in mesial TLE, other factors must also influence regional metabolism interictally. Indeed, surgical ablation of epileptogenic temporal lobe tissue might be expected to increase diaschisis effects on extratemporal glucose metabolism. Instead, comparisons of preoperative and postoperative [^{18}F]FDG scans have shown postoperative increases in [^{18}F]FDG activity of the contralateral temporal lobe and of ipsilateral thalamus and frontal sites.[37,61,183] Several pathophysiologic processes other than diaschisis have been proposed, including reduced transmembrane glucose transport rates and reduced mitochondrial glucose oxidation of viable neurons in sites of ictal onset and habitual propagation.[155,217] On comparing the anatomic distributions of ictal hyperperfusion (using SPECT) and interictal glucose hypometabolism (using [^{18}F]FDG PET) within individual TLE patients, it is evident that many TLE patients have an identical or highly similar distribution of ictal hyperperfusionâ€“interictal hypometabolism that predominates in the temporal lobe and thalamus ipsilateral to the epileptogenic site (including but extending beyond the electrographic ictal onset zone), often with less severe involvement of ipsilateral frontoparietal and basal ganglial sites and of contralateral temporal cortex[76]; one exception is the occipital hyperperfusion often observed in the absence of occipital hypometabolism in TLE. Possibly long-duration postictal dysfunctions may underlie some of the reduction in [^{18}F]FDG activity, as suggested by differential associations of specific distributions of extrahippocampal hypometabolism with specific patterns of electrographic seizure propagation in groups with unilateral hippocampal sclerosis, for example, patients with bitemporal hypometabolism having earlier spread of ictal discharges from one hippocampus to the other.[16,171] Altered energy use in neurotransmitter metabolism might mediate such spatial relationships between ictal dysfunctions and postictal dysfunctions, as suggested by a study using MR spectroscopic determination of the glutamate-glutamine peaks in which localized interictal decreases and ictal increases of [^{18}F]FDG activity and glutamate-glutamine peaks were coupled.[144] Dual pathology undetectable with MRIâ€”specifically, microscopic cortical dysplasia accompanying some but not all cases of hippocampal sclerosisâ€”might generate some of the heterogeneity of [^{18}F]FDG topography in TLE.[32] The diagnostically robust patterns of interictal glucose hypometabolism in TLE are not fully explained by macrostructural, microstructural, and biochemical alterations.

Peri-ictal [^{18}F]FDG PET studies have shown a complex time course of changes in regional cerebral metabolic rate of glucose utilization (CMRGlc) following seizures. In a group of patients with complex partial seizures who had PET at different intervals following the most recent seizure, quantified regional metabolic changes evolved for >48 hours after a single complex partial seizure.[116] The most severe regional hypometabolism occurred >48 hours after the seizure, the least severe hypometabolism occurred at 24 to 48 hours postictally, and metabolism was intermediate in the first 24 hours postictally. In a study in which [^{18}F]FDG studies were performed on average <60 hours after the most recent seizure, the type of seizures that preceded the scan had a strong influence on the regional distribution of hypometabolism.[171] In general, the most localized ictal discharges preceded scans with the smallest volumes of hypometabolism, and secondarily generalized seizures preceded scans with the most widespread patterns of unilateral hypometabolism. In both lesional and nonlesional partial epilepsies, the volume of hypometabolism expands with increasing numbers of seizures over the course of the epilepsy, even with nonprogressive lesions,[88,124] and in limbic TLE, the severity of mesial temporal hypometabolism increases with increasing duration of epilepsy.[209]

Focal mesial temporal *hyper*metabolism sometimes occurs interictally in children with mesial TLE, but it rarely occurs in adults with localization-related epilepsies.[23,41,210] Continuous or repetitive focal mesial temporal seizures, which are subclinical and not detectable with scalp electrodes, may cause â€œinterictalâ€ deep temporal hypermetabolism.[185] Alternatively, there may be interictal epileptogenic processes that are peculiar to childhood and that generate greater glucose metabolism interictally. The latter speculation is encouraged by the presence of interictal regional hypermetabolism in some young children with Sturge-Weber syndrome or with infantile spasms, which does not occur in older children with Sturge-Weber syndrome or with Lennox-Gastaut syndrome (a common â€œendpointâ€ for patients with infantile spasms earlier in life), the older children having exclusively hypometabolism or normal metabolism interictally.

Ictal or peri-ictal (representing mixed ictalâ€“postictalâ€“interictal states during the [^{18}F]FDG uptake period) [^{18}F]FDG scans are difficult to obtain and interpret. True ictal imaging with [^{18}F]FDG is restricted to status epilepticus due to the relatively poor temporal resolution of the [^{18}F]FDG method. Occurrence of a single complex partial seizure during the [^{18}F]FDG uptake period may be associated with the usual interictal findings of unilateral temporal hypometabolism. In one reported case, a partial seizure occurred about 2 minutes after [^{18}F]FDG injection and the scan appeared normal; the same patient later had marked hypometabolism of the epileptogenic temporal lobe on an interictal [^{18}F]FDG scan.[71] Presumably, ictal hypermetabolism was averaged with interictalâ€“postictal hypometabolism over the temporal lobe to cause â€œnormalizationâ€ of [^{18}F]FDG activity on the peri-ictal scan. In another case, a TLE patient had repeated complex partial seizures following [^{18}F]FDG injection, and the scan showed hypermetabolism over the epileptogenic temporal lobe, with ipsilateral frontal and thalamic metabolic increases.[44] Alterations on ictal and peri-ictal [^{18}F]FDG images likely reflect ictal dysfunction at the site of ictal onset, but they also reflect dysfunctions in areas of ictal propagation and interictal and postictal dysfunction in these areas. It is difficult or impossible to sort out the relative contributions of these various dysfunctions to a single set of [^{18}F]FDG images.

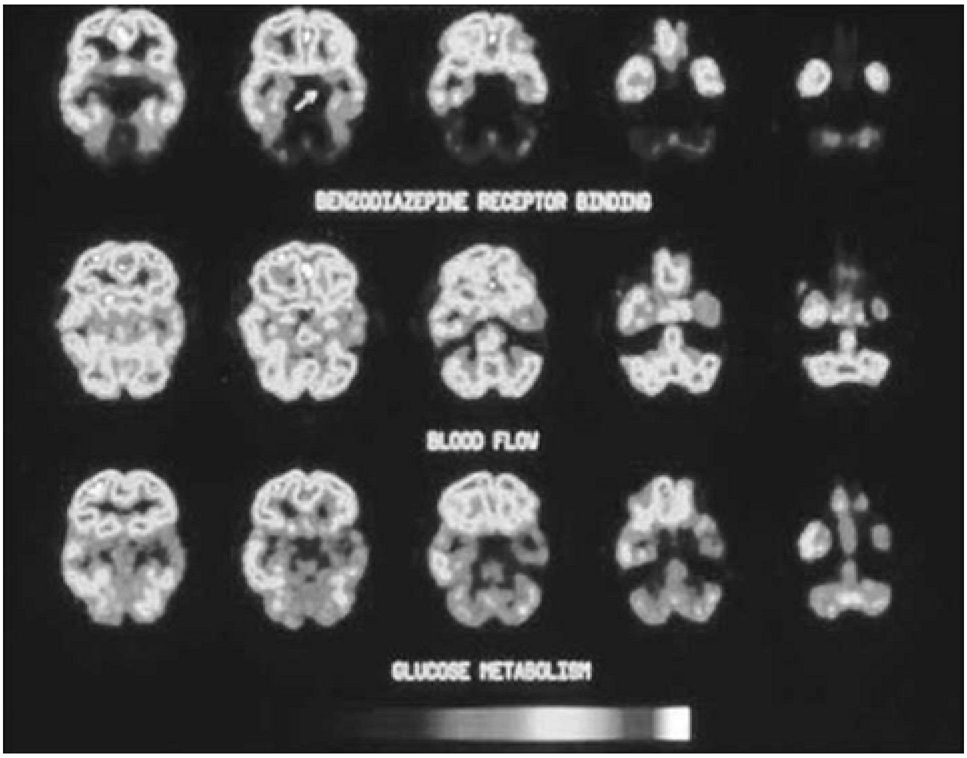

FIGURE 7. Coregistered interictal [^{11}C]flumazenil and 2-deoxy-2-[^{18}F]fluoro-D-glucose ([^{18}F]FDG) positron emission tomography (PET) images of a mesial temporal lobe epilepsy (TLE) patient. Flumazenil transport rate is determined predominantly by regional cerebral blood flow. Flumazenil distribution volume is determined by the regional density of central benzodiazepine receptors. Five adjacent image planes are displayed for each modality. The more superior image plane is to the left of each row. The subject's left is on the right of each image. Images of glucose metabolism and flumazenil transport rate show a widespread left mesial and lateral temporal decrease. Images of flumazenil distribution volume show a highly localized left anterior mesial temporal decrease (*arrow*). The specimen at efficacious temporal lobectomy demonstrated sclerosis of the left anterior hippocampus. (From Henry et al. with permission.) (See the color insert.)

Cerebral glucose metabolism and CBF normally are â€œcoupledâ€ (increasing and decreasing in parallel with changes in synaptic activity within each region of cortex), but interictal PET measurements show uncoupling of CBF and [^{18}F]FDG activity in TLE.[53,114] Interictal CBF imaging with PET often shows â€œdiffuseâ€ regional hypoperfusion, consisting of a relatively large area of hypoperfusion with indistinct boundaries from adjacent areas of normal CBF and with inhomogeneous severity of hypoperfusion.[9,48,108,118] Interictal regional CBF decreases often occur predominantly contralateral to the ictal onset zone in mesial TLE.[118,206] Ictal CBF imaging of complex partial seizures with [^{15}O]H_2O is nearly impossible to obtain, given the 2-minute half-life of [^{15}O], except with seizure induction by proconvulsant drugs or during complex partial status epilepticus.[196] For these reasons, ictal imaging and resting

interictal imaging with [^{15}O]H_2O have no clinical role in presurgical evaluation. It has been suggested, however, that detection of regional glucose metabolicâ€"CBF uncoupling might be more sensitive in detecting epileptogenic tissue than is [^{18}F]FDG mapping alone.[226]

Mesial Temporal Lobe Epilepsy: Neuroreceptor and Other Ligand

Studies

Imaging of the GABAergic Inhibitory System in Temporal Lobe Epilepsy

The Î³-aminobutyric acid A (GABA_A) receptors in temporal lobe epilepsy have been examined using $[^{11}\text{C}]$flumazenil ($[^{11}\text{C}]$FMZ), a high-affinity, highly selective ligand of central benzodiazepine receptors (BZRs) that are consistently present in the GABA_A-receptor complex.[28,62,63,73,90,91,101,102,103,105,162,163,172,173,176,177,178,193,194] The doses of $[^{11}\text{C}]$FMZ required for PET receptor studies do not have detectable pharmacologic effects. The first study in TLE reported averaged imaging data of six patients; it showed unilateral temporal lobe decreases in receptor density that were significantly different from averaged normal control values, whereas calculated receptor affinity was normal.[176] Subsequently, individually quantified $[^{11}\text{C}]$FMZ scans showed that in mesial TLE patients, highly focal decreases in BZR density were usually limited to the anterior mesial temporal lobe.[73,75] Cerebral MRI studies in some of these patients showed significant decrease in hippocampal volume. Quantitative analysis of coregistered $[^{11}\text{C}]$FMZ PET and MRI showed that hippocampal atrophy did not account for the decreased hippocampal BZR density.[73,105,113,193]

Decreased hippocampal BZR density is evident on autoradiography of resected hippocampi in mesial TLE,[14,87] including that resected from patients who had anterior mesial temporal decreases in $[^{11}\text{C}]$FMZ activity on preoperative PET.[102] These autoradiographic observations support the assertion that focally decreased anterior mesial temporal activity on $[^{11}\text{C}]$FMZ PET, in fact, represents a decrease in anterior hippocampal BZR density. Nonetheless, it appears that $[^{11}\text{C}]$FMZ binding on PET studies can be altered by recent or increased seizures shortly before PET data acquisition.[13,177] Such seizure-related temporal changes may not only alter the quantitative measurement of $[^{11}\text{C}]$FMZ PET, but it may also rarely even cause false lateralization of $[^{11}\text{C}]$FMZ PET abnormalities in refractory TLE.[163] Furthermore, developmental changes in the composition and regional density of GABA_A receptor complexes are detectable with $[^{11}\text{C}]$FMZ PET.[18] Many patients who have focal anterior mesial temporal BZR decreases on $[^{11}\text{C}]$FMZ PET are shown on $[^{18}\text{F}]$FDG PET to have widespread temporal and extratemporal hypometabolism (Fig. 7), but TLE patients with mesial temporal $[^{11}\text{C}]$FMZ reductions sometimes have more restricted mesial temporal hypometabolism or normal metabolism interictally.[73,173] In addition to unilateral mesial temporal $[^{11}\text{C}]$FMZ reductions, ipsilateral thalamic, insular, and neocortical regions sometimes show reduced $[^{11}\text{C}]$FMZ binding in mesial TLE.[63,73,91] Although extratemporal $[^{11}\text{C}]$FMZ reductions appear to be less common and less widespread than are $[^{18}\text{F}]$FDG reductions, on comparing these PET modalities in refractory TLE, all of these factors pose complexities in possible clinical application of $[^{11}\text{C}]$FMZ PET.

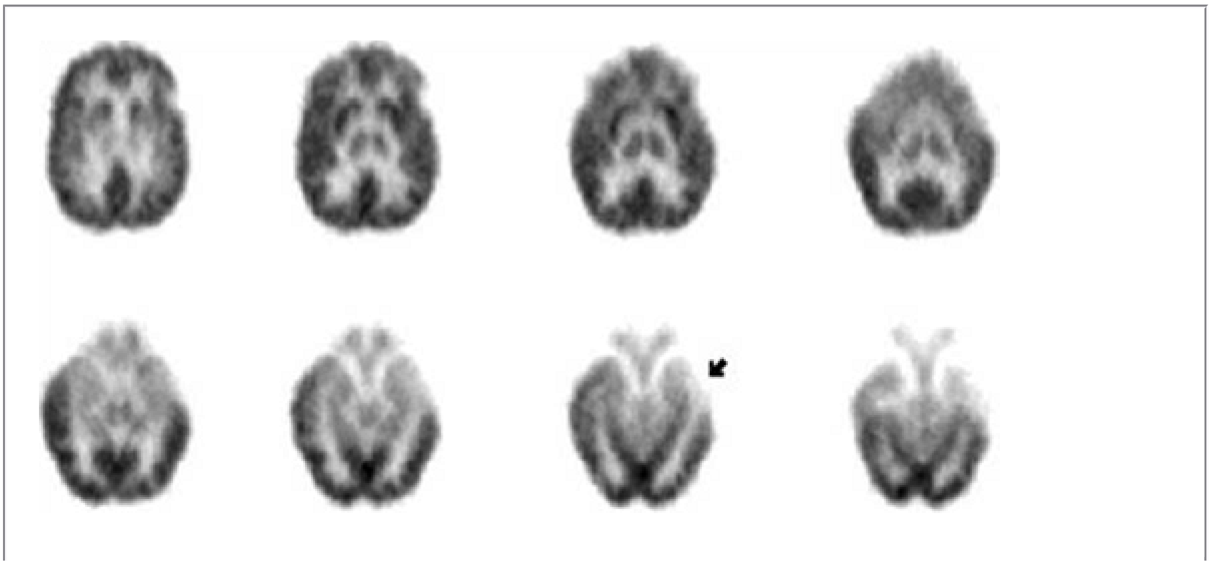

FIGURE 8. Interictal 2-deoxy-2-[^{18}F]fluo-ro-D-glucose ([^{18}F]FDG) positron emission tomography (PET) images of a neocortical temporal lobe epilepsy (TLE patient). These images show severe hypometabolism of the lateral and inferior temporal neocortex (*arrow*), and moderate hypometabolism of the ipsilateral mesial temporal structures. The patient's brain magnetic resonance imaging (MRI) was normal. Focal cortical dysplasia was present in tissue resected at the site of severe hypometabolism and of intracranially recorded electroencephalographic (EEG) ictal onsets. Seizures were reduced by >90% after resection.

Focal BZR decreases in mesial TLE show a high rate of concordance with the ictal onset zone determined by intracranial ictal EEG monitoring and other studies in unilateral TLE, despite the complexities in pathophysiologic interpretation of [^{11}C]FMZ decreases.[28,162] It is important to note that focal mesial temporal [^{11}C]FMZ decreases are detectable and are highly associated with the ictal onset zone in patients whose brain MRI is normal.[101] Although some consider the evidence of clinical utility of [^{11}C]FMZ PET in presurgical evaluation of refractory TLE to be adequately established, widespread clinical application of [^{11}C]FMZ PET in presurgical evaluation has not occurred. Possibly the difficulty in preparing and administering [^{11}C]FMZ with ^{11}C labeling will remain excessive with respect to clinical utility. An exciting possibility is that an ^{18}F analogue of [^{11}C]FMZ such as [^{18}F]fluoroethylflumazenil[119] will have similar accuracy in central BZR imaging to that of

[^{11}C]FMZ and will be less expensive to use in clinical settings. This compound is biochemically distinct from [^{11}C]FMZ, however, and so full safety and other validation studies will be required before large-scale clinical trials can be planned.

Imaging of the Excitatory Amino Acid System in Temporal Lobe Epilepsy

Glutamatergic excitation may be expected to increase during partial-onset seizures, but one PET study suggested that TLE patients might have decreased *N*-methyl-D-aspartate (NMDA) receptor density at the ictal onset zone. Binding at the NMDA receptor was reduced in the epileptogenic temporal lobe of patients studied with [^{11}C]ketamine and PET.[110] This study did not determine, however, whether this regional reduction in [^{11}C]ketamine retention was due to reduced receptor density, reduced receptor affinity for ketamine, or higher regional endogenous ligand concentration. Furthermore, the kinetic modeling did not determine the tracer input function, and so reduced regional blood flow might account for the observed local reduction in [^{11}C]ketamine binding. At this time, it cannot be stated with certainty that [^{11}C]ketamine PET has fully established the existence of decreased NMDA receptor density in epileptogenic hippocampus.

Imaging of the Opiate System in Temporal Lobe Epilepsy

Opiate receptors have been imaged in TLE with several ligands selective for different receptor subtypes. Mu-opiate receptor activity, measured with [^{11}C]carfentanil PET, frequently demonstrates marked increases in [^{11}C]carfentanil binding over the lateral temporal neocortex.[52] Amygdalar and hippocampal [^{11}C]carfentanil binding shows a smaller increase.[125] Lateral temporal glucose metabolism and [^{11}C]carfentanil binding have a significant inverse relationship.[52] Combined Âµ- and Îº-opiate receptor binding, measured with [^{18}F]cyclofoxy PET, also has shown greater mesial and lateral temporal binding on the epileptogenic side.[200] Combined Âµ-, Îº-, and Î´-opiate receptor binding, measured with [^{11}C]diprenorphine PET, shows no asymmetry among various temporal regions in unilateral TLE.[125] Thus, different opiate receptor subtypes appear to have differentially distributed binding alterations in TLE. The relevance of these complex findings to epileptogenesis and the interictal behavioral disturbances of TLE have not been clarified.

Imaging of Other Neurochemical Systems in Temporal Lobe Epilepsy

Serotonin synthetic capacity has been imaged in TLE patients, using [^{11}C]Î±-methyl-L-tryptophan and PET.[135] Serotonin-1Aâ€“receptor binding has been imaged in TLE patients, using PET with

2â€²-methoxyphenyl-[(*N*-2â€²-pirydynyl)-*p*-[^{18}F]fluorobenza-midoethylpiperazine ([^{18}F]MP-PF),[128,129] with [^{18}F]*trans*-4-fluoro-*N*-2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl]-*N*-(2-pyridyl)cyclohexanecarboxamide ([^{18}F]FCWAY),[214] and [*O-methyl*-^{11}C]-*N*-(2-(4-(2-methoxyphenyl)-1-piperazinyl) ethyl)- *N*- (2-pyridinyl) cyclohexanecarboxamide trihydrochloride **(**[^{11}C]WAY100635).[174]

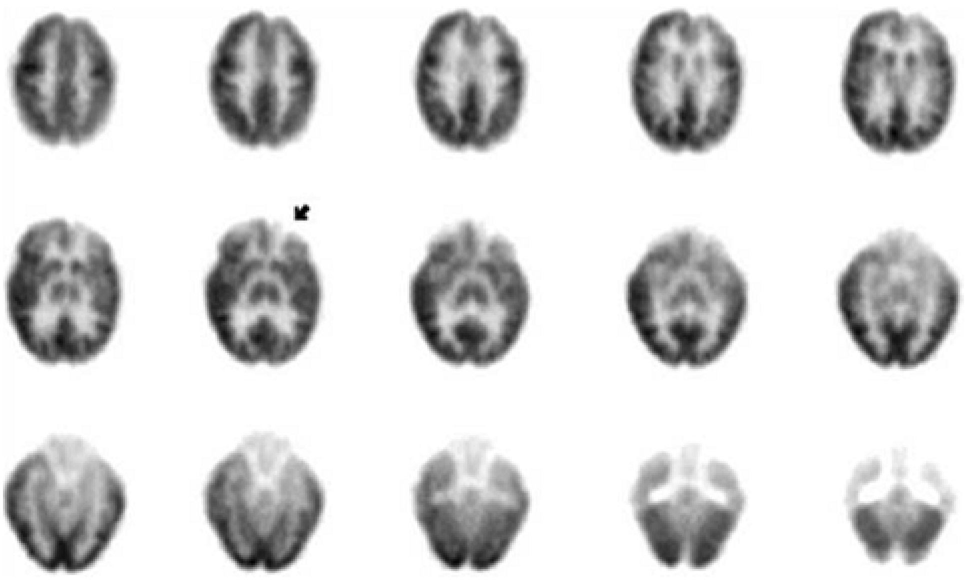

FIGURE 9. Interictal 2-deoxy-2-[^{18}F]fluo-ro-D-glucose ([^{18}F]FDG) positron emission tomography (PET) images of a lesional frontal lobe epilepsy patient. These images show a left frontopolar FDG defect (*arrow*) and left anterior temporal hypometabolism. The patient's brain magnetic resonance imaging (MRI) was normal within the anterior temporal lobes but showed an apparent cavernous malformation of the left frontal pole. Extracranially recorded electroencephalographic (EEG) ictal onsets showed left temporal maxima. Intracranially recorded EEG ictal onsets showed earliest changes near the MRI lesion, with rapid propagation to the ipsilateral temporal lobe and delayed spread contralaterally. Seizures ceased after resection of a histopathologically confirmed cavernoma.

Muscarinic cholinergic receptor density has been imaged in TLE patients, using [^{11}C]*N*-methyl piperidyl benzilate and PET.[143] Muscarinic receptors were reduced predominantly over the anterior mesial temporal lobe, in a distribution similar to that of BZR decreases imaged with [^{11}C]flumazenil PET.[143]

Hippocampal sclerosis causes increased local deprenyl binding (at the monoamine oxidase B sites on glia), which can be detected with [^{11}C]deuterium-deprenyl and PET.[109]

Other Localization-related Epilepsies

Interictal [^{18}F]FDG PET often demonstrates a region of pathologic hypometabolism in adults and children with refractory partial seizures of extratemporal origin or of neocortical (extralimbic) temporal origin.[60,61,71,78,151,186,189,202] In patients with a single neocortical site of ictal onset, interictal [^{18}F]FDG PET usually demonstrates a single region of hypometabolism (Fig. 8), but normal metabolism also is frequently observed. Compared with nonlesional limbic TLE, nonlesional neocortical epilepsies are much more likely to have normal interictal [^{18}F]FDG PET studies.[78,152] Interictal focal neocortical areas of *hyper*metabolism may occur in early childhood epilepsies[23] but have not been reported in adults. In many lesional neocortical epilepsies, the hypometabolic region is small, sharply circumscribed, and colocalized with a focal structural lesion detected with MRI (Fig. 9); a similar relationship of â€œmatchingâ€ focal PET hypometabolism and focal MRI lesion rarely is observed in limbic TLE.[78] Many individuals with lesional or nonlesional neocortical localization-related epilepsies have a more widespread hypometabolic zone, which has graded transitions from areas of severe hypometabolism to areas of normal metabolism, similar to patterns of hypometabolism in limbic TLE. When associated with a lesion, a diffuse hypometabolic area of neocortex often is much larger than any associated

structural imaging abnormality and than any histopathologic lesion (Fig. 8), as also is observed in limbic TLE. In the absence of a structural lesion on MRI, the volume of diffuse regional hypometabolism sometimes is fairly small in neocortical epilepsies. Larger areas of hypometabolism often include mesial temporal, thalamic, and basal ganglial hypometabolism ipsilateral to the neocortical site of hypometabolism. Hypometabolism over an entire hemisphere is rare, as is symmetric bilateral hypometabolism, in unilateral neocortical epilepsies. The degree of hypometabolism usually varies across a region of diffuse hypometabolism. The zone of most severe hypometabolism, excluding the site of a foreign-tissue lesion, usually contains the electrophysiologically defined ictal onset zone.[71]

Children with frontal lobe epilepsies may demonstrate interictal frontal hypometabolism more often than do adults with frontal lobe epilepsies. When onset of frontal lobe seizures is in the neonatal period or in infancy, an underlying structural lesion is almost always present, even when the MRI is normal. Under these circumstances, [^{18}F]FDG PET can be quite useful in defining an area of hypometabolism that correlates both with the extent of microdysgenesis[24] and with the area of epileptogenicity.[141]

Ictal and peri-ictal [^{18}F]FDG imaging during simple partial seizures of neocortical frontal origin demonstrate patterns of increased and decreased (or normal) [^{18}F]FDG uptake, which likely reflect neuronal activity at the site of ictal onset, in areas of ictal spread, and in regions involved in postictal depression. Epilepsia partialis continua can be associated with a small volume of cortical hypermetabolism or hypometabolism when the ictal discharge remains limited, or more diffuse unilateral cortical and thalamic hypermetabolism or hypometabolism when intrahemispheric spread occurs.[43,44,48,59] In one patient with epilepsia partialis continua manifested as left arm and leg clonus, right frontal hypermetabolism and other bilateral regions of hypermetabolism were present.[43,44] In other cases of epilepsia partialis continua, [^{18}F]FDG scans have revealed focal frontal hypermetabolism with ipsilateral thalamic or contralateral cerebellar hypermetabolism or widespread hypometabolism without detectable areas of hypermetabolism. In several patients with epilepsia partialis continua, [^{15}O]O_2 scans showed increased blood flow, increased oxygen metabolism, and decreased oxygen extraction fraction in widespread areas of one cerebral hemisphere, which was contralateral to the focal motor seizure; frontal lobe abnormalities were quantitatively more severe than those of other regions.[48]

Partial epilepsy of motor cortex origin was studied with [^{11}C]flumazenil PET interictally.[176] The activity of the likely epileptogenic zones, averaged over sets of images in three subjects in this early study, was interpreted as showing decreased central benzodiazepine receptor density but normal receptor affinity. The contralateral frontal areas and extrafrontal areas on either side showed apparently normal receptor density and affinity. In a more recent report of [^{11}C]flumazenil PET, each of six patients who had intracranial EEG localization to the frontal lobe were reported to have focal BZR decreases in the ictal onset zone.[179] A patient with occipital seizures had decreased benzodiazepine receptor density limited to the epileptogenic occipital lobe.[176] Lesional and nonlesional partial epilepsies of extralimbic origin consistently demonstrate FMZ abnormalities as reductions in FMZ activity except for malformations of cortical development, which may demonstrate either increased or decreased FMZ binding.[64,88,133,156,157,158,159]

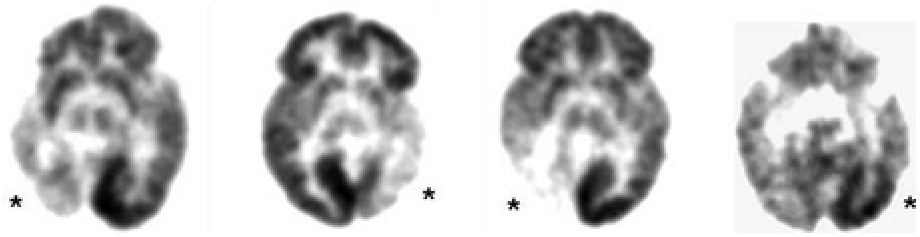

FIGURE 10. Interictal 2-deoxy-2-[^{18}F]fluoro-D-glucose ([^{18}F]FDG) positron emission tomography (PET) images of four patients with Sturge-Weber syndrome. These transaxially oriented images show considerable variability in extent and severity of hypometabolism of cortex underlying the vascular malformation in three patients (*single asterisks*). A fourth patient had paradoxical hypermetabolism interictally in cortex underlying the malformation (*double asterisks*).

Sturge-Weber Syndrome

The Sturge-Weber syndrome of unilateral encephalotrigeminal angiomatosis is highly associated with partial epilepsy, although some have secondary generalized epilepsy or no seizures. In children and adults with advanced Sturge-Weber syndrome, PET typically reveals unilateral diffuse regional hypometabolism ipsilateral to the facial nevus (Fig. 10) in a distribution that extends beyond the abnormalities depicted on computed tomography (CT) or MRI. As the cerebral injury progresses during childhood in this condition, early periods of unilaterally increased [^{18}F]FDG activity give way to profound and extensive unilateral hypometabolism.[115,145] In contrast, infants with Sturge-Weber syndrome and recent seizure onset show a paradoxical pattern of increased glucose utilization in the cerebral cortex of the anatomically affected hemisphere on interictal PET.[22] Metabolism appears to correlate with the course of progressive cerebral dysfunction in some Sturge-Weber patients (Fig. 11). In Sturge-Weber syndrome patients with refractory epilepsy, PET has been useful both in guiding the extent of focal cortical resection (i.e., correlating better with intraoperative

electrocorticography than with CT or MRI) and in assessing candidacy for early hemispherectomy.[22] Children with cutaneous anomalies similar to those of Sturge-Weber syndrome but without intracranial angiomas have normal cerebral [^{18}F]FDG PET.[22] Thus, PET provides a sensitive measure of the extent of early cerebral involvement in Sturge-Weber syndrome patients, a means of monitoring disease progression, and information useful in guiding resective surgery.

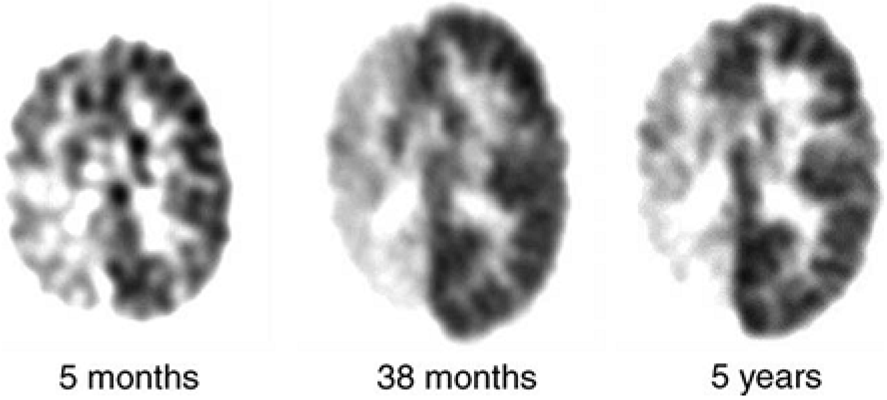

FIGURE 11. Serial 2-deoxy-2-[^{18}F]fluoro-D-glu- cose ([^{18}F]FDG) positron emission tomography (PET) images of a patient with Sturge-Weber syndrome. These transaxially oriented images, which were acquired interictally at the indicated ages, demonstrate progression from mild to severe hypometabolism diffusely over the involved hemisphere. Despite severe right hemispheric metabolic dysfunction, the cognitive outcome was good.

Idiopathic Generalized Epilepsies

Presurgical evaluations with PET have not been used to exclude primary generalized epilepsy patients from consideration of surgery because clinical histories and interictal and ictal scalp EEG recordings usually have established the diagnosis. Even when history and EEG might not entirely distinguish atypical primary generalized epilepsy from secondary generalized epilepsy, interictal [^{18}F]FDG imaging would not be helpful. Interictal [^{18}F]FDG studies are normal in primary generalized epilepsies.[45,140,199] Some patients with symptomatic generalized epilepsies and some with localization-related epilepsies also have normal interictal [^{18}F]FDG imaging,[21,75,211] and so the finding of normal interictal cerebral glucose metabolism is not useful in syndromic classification.

On the other hand, thalamic CBF is increased to a greater extent than is cortical CBF during absence seizures studied with [^{15}O]H_2O and PET.[148]

Interictal [^{11}C]flumazenil PET detected significantly decreased central benzodiazepine receptor densities within the thalami and significantly increased receptor densities within deep cerebellar nuclei bilaterally but normal receptor densities in cerebral cortex, cerebellar cortex, and basal ganglia in eight primary generalized epilepsy patients.[104,149,150,175,180]

Combined Âµ-, Îº-, and Î´-opiate receptor density was normal in all brain regions interictally in eight childhood and juvenile absence epilepsy patients who had [^{11}C]diprenorphine PET.[147] During absence seizures, endogenous opiate release was shown to be increased, based on displacement of [^{11}C]diprenorphine, but the increase was limited to frontoparietotemporal association cortex and did not involve visual or sensorimotor cortex or the thalamus.[7] Serotonin-1Aâ€"receptor binding has been imaged in juvenile myoclonic epilepsy patients, using PET with [^{11}C]WAY100635.[130]

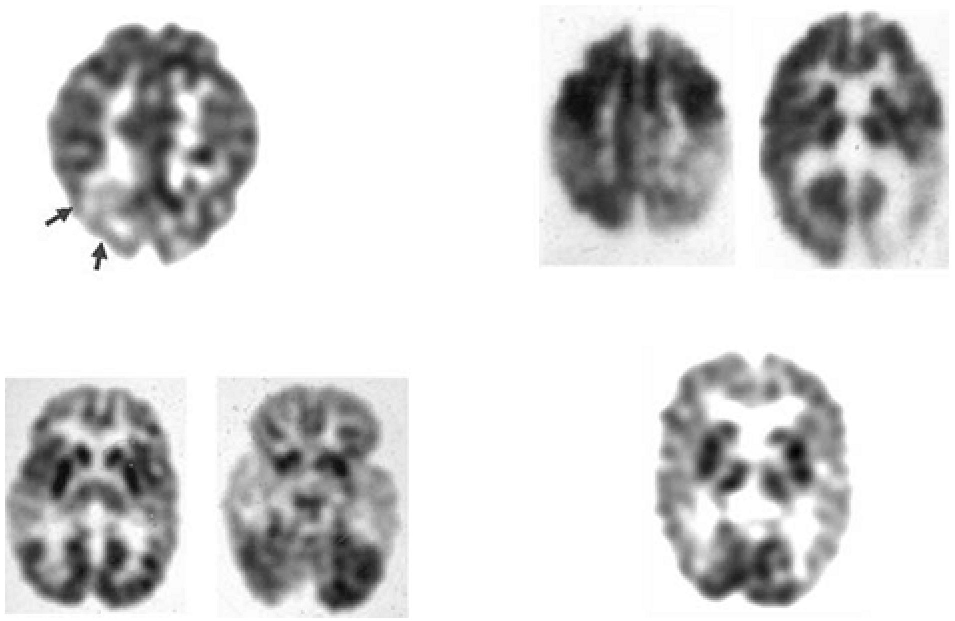

FIGURE 12. Interictal 2-deoxy-2-[^{18}F]fluo-ro-D-glucose ([^{18}F]FDG) positron emission tomography (PET) images of West syndrome patients. These fours sets of transaxially oriented images, acquired in four different patients, demonstrate the most common spatial distributions of interictal metabolic dysfunction in patients with refractory infantile spasms. The unifocal pattern occurs in about 20% of patients and is the only pattern associated with consistently good epilepsy and developmental responses to surgical intervention. The multifocal, bitemporal, and generalized patterns occur in approximately 65%, 10%, and 5% of patients, respectively. The bitemporal pattern is more strongly associated with autism, whereas the generalized pattern is more associated with neurogenetic syndromes, than are the other patterns.

Lennox-Gastaut Syndrome

Patients with the Lennox-Gastaut syndrome usually have multiple regions of bilateral cortical hypometabolism interictally on [^{18}F]FDG scans, but they sometimes have predominantly unilateral hypometabolism (Fig. 10) when pati-ents with structural lesions are included.[21,58,85] When only Lennox-Gastaut patients with no lateralizing findings on neurologic examination and with normal cranial x-ray CT scans were imaged with [^{18}F]FDG interictally, most patients had symmetric generalized cortical and thalamic hypometabolism, although a few had symmetric generalized cortical hypermetabolism.[211]

A series of 32 children with â€œcryptogenic epileptic encephalopathies,â€ which presumably included mainly children with symptomatic generalized epilepsies, demonstrated generalized metabolic dysfunction in most cases (usually hypometabolism, but hypermetabolism in some), regional metabolic dysfunction in some cases, and normal metabolism in only 2 cases.[46] The [^{18}F]FDG scans in this series detected thalamic hypometabolism in 90% of cases, which was usually bilateral, but thalamic metabolism was lower on the side of more severe cortical hypometabolism.

Mutations causing deficiency of the glucose transporter Glut1 result in epilepsy and developmental delay. In these patients, the cortex and thalami show generalized reduction in [^{18}F]FDG activity on PET but relatively high [^{18}F]FDG activity in the basal ganglia.[142] In the presence of normal brain MRI, this peculiar [^{18}F]FDG pattern should lead to genetic studies in early symptomatic epilepsy.

Unilateral focal or multifocal sites of hypermetabolism during sleep, with more nearly normal cerebral glucose metabolism during waking, are typical of electrical status of slow wave sleep.[123] The sites of metabolic dysfunction mainly were found in association cortex. This childhood syndrome of continuous generalized spike-and-wave discharges during slow wave sleep, usually with dementia or progressive aphasia, and with clinically evident epileptic seizures, thus provides another example of a symptomatic generalized epilepsy in which generalized EEG phenomena are associated with focal or multifocal cortical metabolic dysfunction.

Infantile Spasms

Patients with infantile spasms have been extensively studied with [^{18}F]FDG imaging in both research applications and presurgical evaluation. Unilateral cortical metabolic dysfunctions (hypo- or hypermetabolism) are relatively common in West syndrome[19,20,25,27] (Fig. 12). Bitemporal hypometabolism is less common, occurring in approximately 15% of infants with spasms in Chugani's series. In this series, bitemporal hypometabolism was never associated with a single predominant zone of structural imaging or electrophysiologic abnormality, and so surgery was never performed; most of these infants later developed autism.[20] (Bitemporal hypometabolism also has been reported in autistic children who had partial status epilepticus early in life,[31] but these children had evidence of hippocampal sclerosis on MRI.) By contrast, approximately 20% of infants with refractory spasms had [^{18}F]FDG studies showing unilateral cortical regions of metabolic dysfunction; those who underwent unilateral cortical resection, which usually included large volumes of cortex, often had cessation of seizures and normal or near-normal cognitive development.[26] In a recent study, [^{18}F]FDG PET showed prognostic value following initial therapy of West syndrome, in that patients who had normalization of earlier cerebral [^{18}F]FDG abnormalities on initiation of medical therapy were later observed to have better seizure control and less developmental delay than were those with persisting cerebral [^{18}F]FDG abnormalities.[86]

Many infants with West syndrome have both unilateral cortical metabolic dysfunction, and bilateral lenticular and brainstem metabolic dysfunction.[25] Chugani hypothesized that infantile spasms begin with a focal cortical abnormality, which induces brainstem activities that are projected symmetrically to the basal ganglia and spinal cord.[25] This theory is consistent with the observations that infantile spasms are generalized from onset and that unilateral cortical resection can result in cessation of the spasms.[27] Such patients often have cortical dysplasias in resected tissue, and in some of these cases, brain MRI did not detect the malformation.[26]

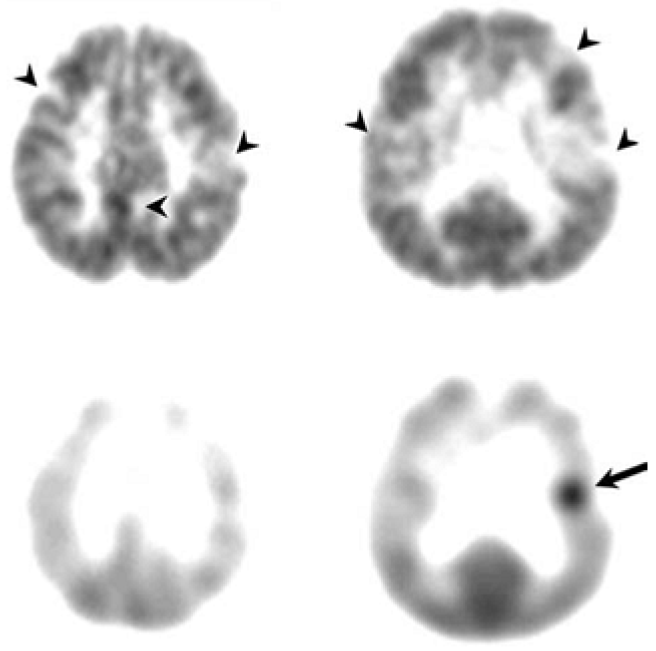

FIGURE 13. Interictal 2-deoxy-2-[^{18}F]fluoro-D-glucose ([^{18}F]FDG) positron emission tomography (PET) and [^{11}C]Î±-methyl tryptophan ([^{11}C]AMT) PET images of a patient with tuberous sclerosis. These transaxially oriented images show multiple foci of glucose hypometabolism (*arrowheads*) and a single site of increased [^{11}C]AMT activity (*arrow*) in a patient with refractory seizures. The image planes are coregistered at higher **(left)** and lower levels **(right)**. Resection of cortex at the site of increased AMT uptake resulted in improved seizure control.

High-resolution PET tomographs permit detection of focal cortical regions of decreased or increased glucose utilization in many infants who previously were diagnosed as having idiopathic West syndrome. Chugani reported a series of 140 cases of infantile spasms, including 7 who had neurogenetic syndromes and 29 who had lesions on structural imaging; among the patients without lesions or neurogenetic syndromes, [^{18}F]FDG imaging detected regional metabolic dysfunction at one cortical site in 30 cases and at multiple cortical sites in 62 cases.[19] The patients in this study were biased by referral pattern toward infants with refractory spasms and without a structural lesion on MRI. Nonetheless, one might logically conclude that infantile spasmâ€“associated malformations of cortical development are more likely to be detected as metabolic dysfunction than as structural lesions during infancy. Chugani suggested that in infants the normal absence of myelination of subcortical white matter may render MRI less sensitive in detecting subtle neuronal heterotopia and other dysplastic features compared with the high MRI sensitivity to dysplasias in children and adults with completed myelination.

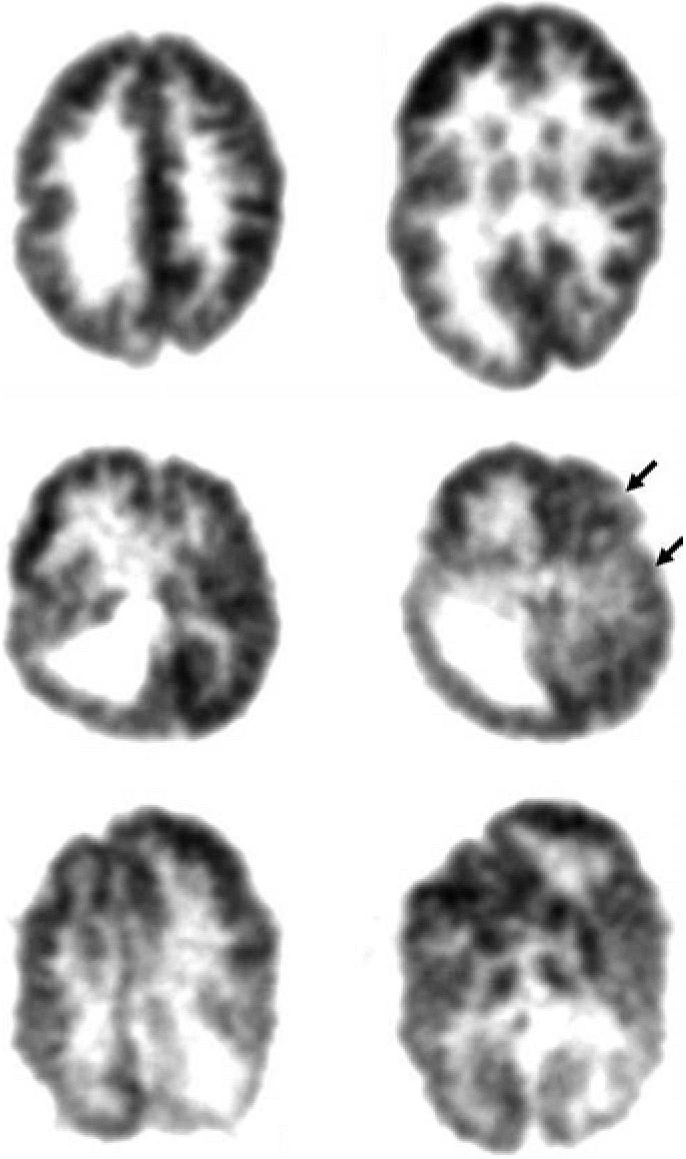

FIGURE 14. Interictal 2-deoxy-2-[^{18}F]fluoro-D-glucose ([^{18}F]FDG) positron emission tomography (PET) images of three patients with hemimegalencephaly. These transaxially oriented images show marked variability in extent and severity of hypometabolism within the malformed hemisphere (the right hemisphere in the first two cases, shown as a pair of images for each patient, on the upper and middle rows, and on the left hemisphere for the third patient, on the lower row). The second patient (middle row) also has mild hypometabolism of the frontotemporal opercular area (*arrows*). The third patient (lower row) also has marked hypometabolism diffusely over the contralateral hemisphere. The subject's left is on the right of each image.

Tuberous Sclerosis

Cortical tubers in tuberous sclerosis appear as hypometabolic areas (Fig. 13) on the interictal PET scan,[191] presumably due to the simplified dendritic arborization within tubers. When the PET study is performed ictally, the tuber is seen as a hypermetabolic zone. Some hypometabolic regions on PET do

not correspond to abnormalities on CT and MRI scans and may either represent small tubers or be related to epileptogenic mechanisms.

Î±-Methyl tryptophan with ^{11}C labeling often demonstrates one tuber that has increased serotonin synthetic function among other tubers with decreased serotonin synthesis.[17,89]

Other Childhood Epilepsy Syndromes

Hemimegalencephaly is a rare developmental brain malfor-mation characterized by congenital hypertrophy of one cerebral hemisphere and ipsilateral ventriculomegaly. The distribution of glucose metabolic dysfunction on [^{18}F]FDG PET is quite variable across different patients with hemimegalencephaly (Fig. 14). When the epilepsy is medically uncontrolled, cerebral hemispherectomy is recommended. Irrespective of seizure control postoperatively, however, hemimegalencephalic children, as a group, have a worse developmental outcome than children who have been hemispherectomized for Sturge-Weber syndrome or chronic focal encephalitis of Rasmussen. PET studies of cerebral glucose metabolism have indicated that the worse developmental outcome in hemimegalencephaly is related to the presence of focal areas of cortical dysfunction in the remaining hemisphere and that preoperative assessment of the integrity of the less affected hemisphere with PET may provide important prognostic information with regard to cognitive outcome, despite seizure control.[160]

An [^{18}F]FDG PET study during sleep in three children with acquired epileptic aphasia (Landau-Kleffner syndrome) confirmed the general notion that this condition is heterogeneous. Metabolic disturbances consisting of hypermetabolism or hypometabolism were seen during sleep in the temporal lobes and were right-sided, left-sided, or bilateral.[122]

Research in Therapeutic Mechanisms

Antiepileptic drug (AED) research using PET techniques has mainly focused on mechanisms of AED toxicity and to a lesser extent on AED kinetics and AED effects on specific neurochemical systems.[65] Several PET investigations also have examined effects of vagus nerve stimulation and of resective epilepsy therapy on CBF or glucose metabolism.

Mechanisms of adverse or unintended effects of specific therapies have been studied with PET in healthy and epileptic individuals. Barbiturates, benzodiazepines, phenyt-oin, carbamazepine, and valproate globally depress absolute values of cerebral metabolic rate for glucose without significant regional variability in reduction of [^{18}F]FDG

activity.[117,197,198,201,204,218,222] Phenobarbital depresses cerebral glucose metabolism to a greater degree than does valproate, and carbamazepine and phenytoin have lower effects on cerebral glucose metabolism when these AEDs were in chronic steady state at serum levels commonly used in clinical practice. The severity of thalamic hypometabolism induced by lorazepam has been shown to correlate significantly with the degree of drowsiness induced by the drug.[218] Valproate causes global cerebral decrease in CBF, but thalamic CBF is decreased to a greater degree than is cortical CBF.[56] The basis of relatively greater thalamic (than cortical) hypoperfusion due to valproate effect is unclear, as is the question as to whether other AEDs would show a similar pattern. Another [^{18}F]FDG PET study suggested that severe AED intoxication might cause enduring ataxia and cerebellar hypometabolism, although groups of patients with and without histories of AED intoxication were studied with PET only many years after the episodes of intoxication.[181]

Cerebral kinetics of phenytoin and of valproate were mapped using ^{11}C-labeled AED and PET. Following intravenous administration, [^{11}C]phenytoin rapidly entered cerebral gray matter and equilibrated within 20 minutes on dynamic PET imaging.[4] The early kinetics of [^{11}C]phenytoin did not differ between the epileptogenic region and its contralateral homologue. No other AEDs have been similarly studied. Intravenously administered [^{11}C]valproate was distributed equally to gray and white matter in a flow-dependent fashion in primate PET studies, but kinetic modeling did not fully determine the radiotracer input function, and therefore valproate-specific distribution parameters could not be calculated.[153]

The effects of AEDs on GABAergic and serotonergic systems have been reported. Chronic valproate therapy was associated with generalized cerebral decreases in [^{11}C]flumazenil binding, but interictal [^{11}C]flumazenil activity was normal in patients with absence seizures who were receiving AEDs other than valproate.[149] This observation suggests that valproate may act to increase cerebral endozepine concentration, which would reduce the availability of central benzodiazepine receptors to bind flumazenil at the $GABA_A$â€“chloride ionophore complex; reduced affinity of the receptor for flumazenil or reduced neuronal expression of the receptor (or of the entire $GABA_A$ complex) is less likely to explain the association of valproate use and [^{11}C]flumazenil activity reduction. Chronic phenytoin, carbamazepine, valproate, lamotrigine, oxcarbazepine, and levetiracetam use did not appear to be associated with altered serotonin-1Aâ€" receptor affinity for [^{18}F]FCWAY or of the cerebral density of serotonin-1A receptors[207]; however, several AED exposures significantly altered the free serum fraction of [^{18}F]FCWAY to an extent that PET measures of cerebral serotonin-1Aâ€“receptor binding would be rendered inaccurate in the absence of mathematical modeling to correct for this effect.

Mechanistic studies of therapeutic vagus nerve stimulation (VNS) have used [^{18}F]FDG PET in rodent studies[29] and CBF PET in humans to map sites of VNS-induced activation and deactivation of synaptic activity.[68,69,79,100] Acute VNS-activation PET studies (performed within the first 24 hours after VNS therapy began) found synaptic activations in the dorsal medullary complex of the vagus, the central pons and midbrain, inferior cerebellum, hypothalami, and thalami, and also showed a combination of activations and deactivations in amygdalae, hippocampi, insulae, and other neocortical sites bilaterally.[69] Somatosensory system responses to VNS were unilateral, as might be expected in patients experiencing exclusively left-sided cervical paresthesias during VNS. Chronic VNS-activation PET studies (performed after 3 months of ongoing VNS therapy) showed synaptic activations in the same brainstem, cerebellar, and diencephalic sites as were observed acutely, but cortical effects were markedly reduced on chronic as compared with acute CBF imaging.[68] Acute VNS-activation PET findings were compared with response to seizures during 3 months of VNS without AED changes.[79] Patients who had greater bilateral thalamic activation went on to experience significantly greater seizure reduction during VNS than those who had little or no thalamic activation. In this study other sites of acute VNS-induced CBF changes also tended to occur more often in VNS responders, but these trends did not achieve statistical significance. Chronic VNS-activation PET studies also showed that bilateral thalamic activation was significantly associated with greater seizure reduction.[68] The metabolic mapping in rodent studies produced rather different findings than observed in human CBF mapping of VNS effects, although numerous differences in the study conditions are apparent.[29] Two functional MRI (fMRI)-based studies found greater seizure reduction in patients who had greater thalamic CBF activation during VNS.[120,134] The PET and fMRI studies suggest that VNS acutely and chronically alters thalamic processing in some way so as to antagonize partial-onset seizures.

Effects of epilepsy surgery on cerebral function have been studied by comparing preoperative and postoperative [^{18}F]FDG PET imaging within individuals. Among patients who become seizure free following anterior temporal lobectomy, [^{18}F]FDG activity increases in the contralateral (unresected) temporal lobe and in the ipsilateral thalamus and frontal cortex.[37,61,183] Similarly, after efficacious temporal resection in several patients who had preoperative FMZ PET, relative increases in FMZ binding at sites of earlier seizure propagation were found.[172] These observations are highly relevant to understanding the pathophysiology of hypometabolism and altered GABAergic physiology interictally in TLE, as discussed earlier, but have yet to be adequately explored in relevance to postoperative improvements in cognition and other cerebral functions.

Presurgical Evaluation

Planning Surgery of Localization-related Epilepsies

Single regions of interictal hypometabolism on [^{18}F]FDG PET are highly associated with the region that can be resected to control seizures in localization-related epilepsies. In the syndrome of medically refractory limbic TLE, strong support for anterior temporal resection *without* prior intracranial EEG monitoring is provided by the presence of most severe dysfunction in one temporal lobe on interictal [^{18}F]FDG PET if other noninvasively acquired data support this localization. Specifically, unilaterally predominant hypometabolism supports temporal resection in the absence of intracranial EEG recordings when (a) extracranial EEG recordings show temporal ictal onsets exclusively on the side of functional imaging abnormality, (b) MRI is normal, or nonspecifically abnormal, as in the case of puncta of subcortical white matter abnormalities, or MRI shows hippocampal atrophy, malformation of cortical development, or foreign-tissue lesion or encephalomalacia in the same temporal lobe, and (c) other noninvasively acquired data are not discordant with this localization.[40] When brain MRI is normal in the syndrome of refractory mesial TLE, interictal [^{18}F]FDG PET can detect temporal lobe hypometabolism.[15,72,98] In the syndrome of limbic TLE, when interictal [^{18}F]FDG PET shows most severe abnormality in one temporal lobe, this does not alone establish that all seizures are arising from that temporal lobe (as discussed later). Thus, intracranial EEG is necessary when [^{18}F]FDG or ictal CBF abnormalities are not supported by ictal extracranial EEG localization and when [^{18}F]FDG or ictal CBF abnormalities contradict other localizing abnormalities.

In extratemporal epilepsies and in localization-related epilepsies that cannot be fully characterized by electroclinical manifestations, ictal CBF and interictal [^{18}F]FDG abnormalities cannot be used to determine the margin of cortical resection but can be used with other data to determine sites that should be monitored with intracranial electrodes.[78,182] Current evidence demonstrates that PET and SPECT data are not redundant with electrophysiologic data nor with structural imaging data. These functional imaging modalities sometimes provide evidence of falsely localized extracranial ictal EEG data or evidence that EEG and MRI falsely suggested unifocal ictal onsets in patients who actually have two independent ictal onset zones.[77] The cost effectiveness of performing one of these functional imaging modalities in all patients before resective epilepsy therapy is unknown. Based on the available information, it is reasonable to perform either interictal [^{18}F]FDG PET or ictal/interictal SPECT in all patients with localization-related epilepsies before resective surgery, in addition to ictal recordings with extracranial EEG, MRI, and neuropsychometric studies.

Unilateral temporal lobe hypometabolism is â€œfalsely lateralizedâ€ (located contralateral to the intracranially recorded site of ictal onset in patients with single ictal onset zone) in approximately 1% to 2% of patients in series in which potential sources of imaging artifact and unreliable forms of quantitative analysis were excluded. Prior intracranial surgery, including depth electrode placement, can produce temporal hypometabolism that is falsely lateralized with respect to intracranially recorded temporal lobe ictal onsets and to the side of subsequent, efficacious resection.[40] Imaging artifacts also can be produced by unrecognized errors in cranial positioning, errors of improperly aligned images in attenuation correction, and other aspects of imaging; visual image analysis should be used to exclude these artifacts prior to any automated quantitative image analysis. Volume-of-interestâ€“based quantitative analysis should sample regions whose volumes are in the range of the usual volume of the interictally hypometabolic area of TLE, and techniques that do not use predefined volumes of interest, such as statistical parametric mapping, should use a volume threshold to avoid detection of potentially misleading, tiny foci of statistically significant hypometabolism, at least for application in presurgical evaluation. Continuous EEG monitoring can be performed during [^{18}F]FDG scanning and sometimes can exclude unintentional ictal scanning that could lead to misinterpretation of [^{18}F]FDG images.[71] Sperling et al.[185] reported a patient who did not have subjective or objective clinical changes or scalp EEG changes during â€œinterictalâ€ [^{18}F]FDG scanning, which appeared to show falsely lateralized temporal hypometabolism. In fact, the scan probably showed correctly lateralized ictal hypermetabolism. Subsequent intracerebral recordings showed frequently recurrent seizures confined to one hippocampus (without subjective or objective behavioral change and without scalp EEG change). Visual interpretation relies on detecting asymmetry, and so hypermetabolism on one side may appear to represent hypometabolism on the other side. Sperling suggested that relative quantification of temporal lobe and occipital lobe metabolism might support distinction of temporal hypermetabolism on one side from temporal hypometabolism on the other side. As is true of all noninvasive means of localizing the epileptogenic zone, presurgical application of interictal [^{18}F]FDG PET in partial epilepsies should be limited to correlation with other studies used to regionalize the ictal onset zone.

Cerebral MRI is essential in detection of hippocampal sclerosis, neoplasia, vascular malformations, other foreign-tissue lesions, ablative lesions, and malformations of cortical development.[36,111] Cerebral structural abnormalities are highly but not completely correlated with the epileptogenic zone. In some cases, a small foreign-tissue lesion may be located distant from the ictal onset zone, although most cerebral lesions are located near ictal onset zones, and this topographic relationship is especially strong in the case of cavernomas. In cases of a large area of encephalomalacia, porencephaly, or cerebral maldevelopment, the ictal onset zone may be much smaller than the lesion; even when extracranial EEG recordings suggest that the ictal onset zone is near the lesion, it often is not desirable or necessary to resect the entire lesion when the exact location of the ictal onset zone is unclear; sometimes such lesions are distant from the region of ictal onset. In groups of patients with tuberous sclerosis and other conditions with longstanding multifocal lesions, individual patients can have a single ictal onset zone, multiple independent ictal onset zones, or even generalized-onset seizures. Optimal choice of intracranial electrode placements is necessary for successful localization of the electrophysiologic ictal onset zone when noninvasive data do not suffice. Interictal metabolic and ictal perfusion information may be combined with other data to direct intracranial electrode placement to sites of possible ictal onset.[131] Regional hypometabolism or ictal hyperperfusion can suggest otherwise unsuspected possible sites of ictal onset to avoid intracranial monitoring procedures that record ictal propagation patterns but fail to record earliest ictal onset patterns (evidenced by absence of ictal discharges recorded during earliest behavioral manifestations). The absence of any hypometabolism obviously does not rule out localization-related epilepsy. Similarly, regional hypometabolism strongly suggests that seizures may begin somewhere within the region of hypometabolism, but it does not rule out multiple areas of ictal onset both within and beyond the hypometabolic cortex. Many epilepsy surgery programs offer temporal resection to a patient who has refractory complex partial seizures with semiology characteristic of mesial TLE, without prior physiologic imaging or intracranial EEG monitoring, if the patient has unilateral temporal lobe spikes interictally and ictal onsets on extracranial EEG and has hippocampal atrophy or specific mesial temporal lesions ipsilaterally on MRI, in the absence of contradictory information on neuropsychometric or other standard studies. In some programs, confirmatory information is sought with interictal [^{18}F]FDG PET or ictal SPECT in such a patient, although no detailed costâ€"benefit analysis of this additional physiologic imaging has been reported.

Unilateral temporal hypometabolism has been reported in patients who have bilateral independent hippocampal ictal onsets recorded with intracranial electrodes during habitual complex partial seizures, and most of these patients also had exclusively unilateral MRI abnormality.[48,77] Furthermore, ictal scalp-sphenoidal EEG recordings are much more likely than are MRI or PET images to show evidence of bilateral TLE among patients who subsequently have intracranial recording of bilateral independent hippocampal ictal onsets during complex partial seizures.[77] Alternatively, some patients who had bilateral independent temporal ictal onsets on extracranial EEG with unilateral temporal abnormalities on MRI and PET or on PET only have been shown to have exclusively unilateral hippocampal intracranial EEG onsets that were on the side of the imaging abnormality (and of efficacious temporal lobectomy). On the other hand, bilateral hippocampal atrophy on MRI sometimes is observed in patients who have unilateral temporal hypometabolism interictally, unilateral hippocampal ictal onsets, and good surgical outcome.[98] All focal ictal onset patterns on extracranial EEG, all focal cerebral gray matter lesions on MRI, and all regions of cortical hypometabolism on PET should be considered when planning intracranial electrode placements.

Imaging of ictal CBF with SPECT and imaging of interictal CMRGlc with PET have similar roles in evaluations for epilepsy surgery. Both ictal CBF SPECT and interictal [^{18}F]FDG PET can detect definite abnormalities when structural ima-ging is normal or nonspecifically altered.[80,81,94,164,166,184,188,223] Overall sensitivity and specificity of ictal SPECT and interictal [^{18}F]FDG PET are similar in large series of partial epilepsies; studies of the two techniques in the same sets of patients report sensitivity to functional abnormality of >70% (and usually â‰«70%), with specificity to the ictal onset zone >90%.[12,80,84] In fact, a relatively greater sensitivity of ictal SPECT (over [^{18}F]FDG PET) in detecting extratemporal epileptogenic zones may be obscured in series that include all forms of partial epilepsy, due to the predominance of temporal lobe epilepsy over other partial epilepsies and to the profound glucose metabolic dysfunctions of temporal lobe epilepsy. Quantitative statistical image analysis may significantly increase the sensitivity and specificity of [^{18}F]FDG PET in detecting evidence of neocortical (lateral) temporal and extratemporal ictal onset zones compared with standard clinical interpretation.[95,96]

Interictal regional hypometabolism also is useful in predicting the outcome of temporal resection with respect to seizures. Greater severity of preoperative hypometabolism of the resected temporal lobe is associated with significantly better postoperative seizure control, using either qualitative or quantitative definitions of severity of hypometabolism.[30,38,121,138,151,169,212,213,224] The high correlation of temporal hypometabolism and seizure outcome is independent of the pathologic diagnosis. Uncal or temporal pole metabolism, analyzed quantitatively, may provide the most accurate correlation with seizure outcome.[38,121] Qualitatively severe *extra*temporal cortical or thalamic hypometabolism, however, is associated with a higher incidence of postoperative seizures.[136,190] Symmetric, severe, bilateral temporal hypometabolism also is associated with a higher incidence of postoperative seizures, even when other data suggest that all seizures originate in one temporal lobe.[10] A site of reduced [^{18}F]FDG activity that is distinct and noncontiguous with a cavernous angioma is highly associated with recurrent seizures after lesionectomy.[107,165] Temporal lobe hypometabolism contralateral to intracranially recorded ictal onsets also is reportedly associated with recurrent seizures after resections of the electrophysiologically defined focus,[8] although individual cases with good outcome of resection contralateral to temporal lobe hypometabolism have been reported.[132] Interictal CBF imaging with [^{15}O]H_2O PET is not useful in predicting seizure outcome.[206]

Cognitive activation CBF PET or [^{18}F]FDG PET studies might be useful in predicting the outcome of temporal resection with respect to language and memory function, although fMRI has the potential to do so without exposure to ionizing radiation. Both activation PET and fMRI appear likely to be able to lateralize hemispheric language specialization.[51,69,221] Specific deficits of delayed recall may be associated with severity and distribution of glucose hypometabolism interictally in TLE.[82,154,170] These [^{18}F]FDG PET abnormalities, however, have not been used to provide the presurgical memory prognostication afforded by the Wada test.[57,81,170] Full application of activation PET or fMRI in presurgical evaluation will require many studies to determine the answers to many areas of uncertainty, including the following issues: (a) whether fMRI techniques can be developed to permit speech-related cranial motion during imaging, and whether it is essential to assess patient effort with analysis of verbal responses (given that patients may not comply with instructions during silent cognitive task performance, as apparently do paid, healthy volunteers in studies of normal cognitive activation), (b) how results of activation PET and fMRI compare with current clinical tools such as the Wada test and direct cortical electrical stimulation mapping, and (c) whether modification of resection based on functional imaging results actually improves functional outcome of surgery.

In the future [^{11}C]flumazenil PET and, in patients with tuberous sclerosis, [^{11}C]Î±-methyl tryptophan (AMT) PET, may prove useful for noninvasive determination of the epileptogenic zone when concordant with other data. The more focal distribution of the [^{11}C]flumazenil PET abnormality than the [^{18}F]FDG PET abnormality and the specificity of increased [^{11}C]AMT activity for epileptogenic tubers are particularly attractive in these potential applications. Randomized clinical trials have not been completed to evaluate these potential applications.

Planning Surgery of Symptomatic Generalized Epilepsies

Single regions of interictal hypometabolism on [^{18}F]FDG PET are highly associated with the region that can be resected to control seizures in West syndrome, Sturge-Weber syndrome with generalized-onset seizures, and other secondary generalized epilepsies of early childhood.[24,25,26,27] In addition to the generalized interictal and ictal EEG phenomena, these early childhood secondary generalized epilepsies frequently have focal scalp EEG abnormalities,[26] which often correspond to the PET focus in patients with infantile spasms. When a single region of abnormal glucose utilization is apparent on PET corresponding to the EEG focus and the seizures are intractable, surgical removal of the PET focus results not only in seizure control, but also in complete or partial reversal of the associated developmental arrest. This is in contrast to the expectation of moderate to severe retardation based on preoperative developmental decline.

Neuropathologic examination of the resected tissue in West syndrome in patients who underwent surgery reveals that the epileptogenic zone is typically a previously unsuspected area of cortical dysplasia.[26,27] It is recommended that any patient considered to have cryptogenic medically refractory infantile spasms following extensive evaluation, including metabolic studies and structural neuroimaging, should have a PET study of glucose metabolism. About 20% of these refractory cases will show a single focal lesion and be candidates for cortical resection. The remainder will show multifocal abnormalities on PET, usually corresponding to bihemispheric epileptogenicity on the EEG.

In Sturge-Weber syndrome patients with refractory epilepsy, PET has been useful both in guiding the extent of focal cortical resection (i.e., correlating better with intraoperative electrocorticography than CT or MRI) and in assessing candidacy for early hemispherectomy.[22] Children with cutaneous anomalies similar to those of Sturge-Weber syndrome but without intracranial angiomata have normal cerebral [^{18}F]FDG PET. Thus, PET provides a sensitive measure of the extent of early cerebral involvement in Sturge-Weber syndrome patients, a means of monitoring disease progression, and information useful in guiding resective surgery.

Normal metabolism or complex regional metabolism bilaterally on [^{18}F]FDG PET might be proposed as indirect support for corpus callosotomy. Further investigation will be required to establish a specific role for PET in precallosotomy evaluation.

Summary and Conclusions

Positron emission tomography permits in vivo measurement and whole-brain anatomic mapping of a wide variety of brain functions in healthy and epileptic individuals. Glucose metabolic imaging has revealed unexpected patterns of interictal cerebral dysfunction in most forms of epilepsy. In localization-related epilepsies, the zone of interictal metabolic

dysfunction is often more lateralized than is interictal electrophysiologic dysfunction, but it is typically much larger than the electrophysiologically determined ictal onset zone and larger than any associated structural lesion. Mesial temporal reductions in central benzodiazepine receptors exceed the degree of hippocampal atrophy and only rarely extend beyond the anterior mesial temporal regions in mesial TLE. Mu-opiate receptor density is increased over the entire temporal lobe in mesial TLE. In patients with infantile spasms, focal cortical dysplasias are often associated with unilateral cerebral metabolic dysfunction and with bilateral lenticular nuclear and brainstem dysfunction. This suggests that the cortical dysfunction influences the brainstem and lenticular nuclei symmetrically to account for the generalized spasms and hypsarrhythmic EEG. In absence epilepsies, cerebral metabolism and opiate receptor density are normal interictally. During absence seizures, metabolic increases are generalized, but increased endogenous opiate release is limited to frontoparietotemporal association cortex. In tuberous sclerosis with partial-onset seizures, epileptogenic tubers often demonstrate significantly greater serotonin synthesis than is present in nonepileptogenic tubers. Cerebral blood flow PET imaging revealed that bilateral thalamic activation was associated with antiseizure effects of vagus nerve stimulation. These and other PET findings have expanded our understanding of neurochemical alterations and interictal disturbances in human epilepsies and to some extent have elucidated therapeutic mechanisms.

Interictal metabolic imaging with [^{18}F]FDG PET has been extensively applied in presurgical evaluations of refractory seizures. Primary clinical applications have been correlative with ictal electrophysiologic and structural magnetic resonance findings for the following purposes:

1. Increasing certainty that the ictal onset zone has been accurately determined by noninvasive studies prior to anterior temporal lobectomy, hemispherectomy, or multilobar resection.
2. Optimizing selection of intracranial electrode placement sites for ictal monitoring.
3. Prognostication with regard to seizure control.

With further clinical trials, PET imaging and other functions may support future applications in planning epilepsy surgery.

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Chapter 81

Single Photon Emission Computed Tomography

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Introduction

One of the primary goals of neuroimaging in epilepsy is to identify the epileptogenic zone. The epileptogenic zone is the focus of the brain that is necessary and sufficient to generate seizures, and the focus that, when resected, would render the patient seizure free. The phenomenon of increased blood flow at the time and location of seizure activity has long been observed and studied.[13] Single photon emission computed tomography (SPECT) is a functional imaging test that can provide a semiquantitative map of cerebral blood flow changes associated with the epileptogenic zone. The SPECT radiotracer is rapidly taken up by the brain within 40 to 60 seconds after its injection.[25] When the radiotracer is injected during seizure activity (ictal SPECT), it can provide a â€œsnap shotâ€ of the transient hyperperfusion at the region of the focal seizure activity. This is the major advantage of ictal SPECT because it can image the dynamic ictal state, unlike other imaging modalities, such as positron emission tomography (PET) and magnetoencephalography (MEG), which give information about the static interictal state. If the seizure had ended by the time the radiotracer is injected (postictal SPECT), blood flow SPECT can image the pattern of intensely reduced perfusion that is frequently present for a few minutes at the seizure.[28] Furthermore, the radiotracer can also be administered during the interictal nonseizure state (interictal SPECT) to image the pattern of persistent but low-grade hypoperfusion that is detectable at some seizure foci.

An additional advantage of SPECT is that it is widely available and relatively inexpensive to perform. A cyclotron is not required for the production of SPECT radiotracers. Therefore, blood flow SPECT has been an important tool for localizing the seizure focus for epilepsy surgery. It has also been used to detect seizure spread patterns in different forms of epilepsy. This chapter discusses the principles, techniques, and clinical applications of blood flow SPECT studies and interpretation in epilepsy evaluation.

Radiotracers for Blood Flow Single Photon Emission Computed Tomography

The acquisition of images by the SPECT camera is based on the detection and localization of an internal source of **Î³**-energy rays emitted by the radiotracer that has been administered to the patient.[25] The basic images acquired by the camera when it is stationary in one position are termed planar images. Modern SPECT technique uses computer-aided mathematical reconstruction of multiple planar images taken at different rotational angles to produce a series of thin cross-sectional two-dimensional images of a three-dimensional object.

The properties of a radiotracer that is ideal for SPECT imaging in epilepsy are as follows:

1. Stability for at least several hours in vitro, without need for further reconstitution, so that it can be ready near the patient for immediate intravenous injection as soon as seizure activity is detected.

2. Rapid brain uptake that is linearly proportional to blood flow at all physiologic and pathologic blood flow rates and minimal backdiffusion after uptake. This ensures that the relative concentration of the radiotracer (and therefore the intensity of the Î³ radiation emitted) will closely reflect the relative regional cerebral blood flow.
3. Minimal extracerebral uptake and rapid blood clearance, thereby maximizing the contrast between cerebral and noncerebral structures.

Although no currently available radiotracer completely fulfils these criteria, modern blood flow SPECT radiotracers are compounds that have high first-pass brain extraction and are rapidly metabolized to hydrophilic compounds, so that back-diffusion is minimal. Therefore, the radiotracers become trapped in the brain in an amount that is closely proportional to the regional cerebral blood flow at the time of their uptake. Two technetium-based radiotracers have been in widespread clinical use in epilepsy studies: ^{99m}Tc-HMPAO (hexamethyl propylene-amine-oxime) and ^{99m}Tc-ECD (ethyl cysteinate dimer). The principal disadvantage of ^{99m}Tc-HMPAO is that it is chemically unstable in vitro and it has to be used within 30 minutes of preparation. Therefore, the radiotracer has to be reconstituted immediately prior to its injection. Preparing the radiotracer delays its injection when the onset of a seizure is recognized. Because ^{99m}Tc-HMPAO was the radiotracer used in most early SPECT studies in epilepsy, results of those studies are not comparable with those of more recent studies that used stabilized ^{99m}Tc-HMPAO or ^{99m}Tc-ECD, both of which do not require reconstitution immediately prior to their injection.[16] ^{99m}Tc-HMPAO has relatively high uptake in the extracerebral soft tissues (10%â€“30%) and a slow urinary clearance of 40% in 48 hours.[42] This results in poor cerebral-to-extracerebral contrast, which makes extraction of the brain surface for surface matching coregistration algorithms particularly difficult. ^{99m}Tc-ECD has been observed to have better brain-to-background contrast. There is controversy, however, regarding the superiority of one radiotracer over the other in sensitivity for detecting the seizure focus.[1,18,32]

Interictal Blood Flow Single Photon Emission Computed Tomography

Earlier SPECT studies in patients with intractable partial epilepsy were interictal studies. For interictal SPECT, the radiotracer should ideally be injected following a seizure-free

period of at least 24 hours and without immediate postinjection seizure activity, including that of auras. Concurrent electroencephalographic (EEG) recording during the radiotracer injection is ideal for ensuring that the SPECT study is truly interictal, although it is not routinely practiced. The injection should be performed in a quiet room with the lights dimmed and the patient calm, to minimize the activation of cerebral regions by environmental factors.

Results of interictal SPECT studies varied widely among different institutions, with reported sensitivity ranging from 36% to 96% and specificity from 36% to 94%.[14,30,50,53] Most studies have a small number of patients. Comparing the results of different series is difficult because of the wide variation in patient population, SPECT instrumentation, type of radiotracer used, concurrent EEG monitoring, and the criteria for determining the correct localization (i.e. EEG, magnetic resonance imaging [MRI], pathology, or surgical outcome). Spencer[50] combined the results of 23 series of interictal blood flow SPECT studies in 539 patients and found sensitivity of 66% and specificity of 68% for lateralizing temporal lobe seizures to the side localized by ictal scalp EEG. Devous et al.[6] performed a meta-analysis of 13 series of interictal SPECT studies in 247 patients and found a mean sensitivity of 44% and a false-positive rate of 7.4%. These results are lower than those for PET or volumetric MRI.[41]

Interictal SPECT is particularly disappointing in nonlesional epilepsy and extratemporal epilepsy patients. Interictal SPECT studies using ^{99m}Tc-HMPAO correctly localized the epileptogenic zone in only 20% to 47% of nonlesional temporal lobe epilepsy (TLE) patients.[41,44,50] Many studies of interictal SPECT in extratemporal epilepsy found poorly localizing results.[17,22,51] In a study that used ^{99m}Tc-HMPAO in pediatric frontal lobe epilepsy (FLE) patients, only 9% had focal hypoperfusion that corresponded to EEG or MRI abnormality.[9] Similarly, Ho et al.[11] found that interictal SPECT was localizing in only 4 of 14 parietal lobe epilepsy patients, compared with localizing ictal SPECT finding in all of the patients. It is now generally accepted that the main role of interictal SPECT images is as a baseline for comparison with ictal SPECT images.[6]

Peri-ictal Cerebral Blood Single Photon Emission Computed Tomography

Peri-ictal SPECT studies include both ictal and postictal SPECT studies. Attempts at ictal injection of the radiotracer might not always be successful, and the seizure might have ended by the time the radiotracer is injected. Earlier reports of peri-ictal SPECT in the literature consist mostly of postictal SPECT studies. Immediate injection of the radiotracer during seizure activity was impractical because of the need to reconstitute older radiotracers and the lack of continuous video-EEG monitoring for prompt recognition of seizure onset. The radiotracer injection technique has now been refined, however, to allow earlier injection times in the ictal or immediate postictal period, and video-EEG monitoring is now widely available. It is well known that earlier ictal injection time improves the sensitivity and the specificity of SPECT in localizing the seizure focus, particularly in extratemporal epilepsy, in which seizures are often brief in duration but rapid in their spread to other regions of the brain.[7,26]

Technique of Peri-ictal Single Photon Emission Computed Tomography Injection

It is essential that the peri-ictal SPECT injections be performed while the patient is undergoing video-EEG monitoring. Interpretation of the perfusion patterns on the SPECT images requires knowledge of the injection timing relative to the clinical and EEG seizure activity. The dose of ^{99m}Tc to be injected is typically 20 mCi for either HMPAO or ECD. Accurate calibration of the radioactive decay dose is needed to ensure that the correct dose is administered.[24] All persons who handle the radiotracer must have formal training on safe handling of radioactive materials. If the patient has childbearing potential, a pregnancy test must be performed. An intravenous indwelling catheter is inserted to provide ready access for injecting the radiotracer. The catheter must be checked regularly to ensure patency. Ideally, the person responsible for injecting the radiotracer must be experienced in recognizing on the video-EEG screen, the clinical and the EEG manifestations of seizure activity. The radiotracer is then injected immediately into the indwelling intravenous catheter. The person injecting the radiotracer must indicate the instant when the plunger of the syringe is completely depressed and the radiotracer has been completely injected. One way to indicate this time of injection is to say â€œinâ€ so that the timing of the injection relative to the time of the seizure onset can be determined accurately by reviewing the video-EEG recording. The catheter is then immediately flushed with intravenous normal saline, and the injected extremity is elevated to help clear the radiotracer from the injection site into the systemic circulation.

There are other factors that enhance the likelihood for successful ictal SPECT injection. The number of hours in a day when the injection could be performed is often determined by the availability of the radiotracer and the staff in the video-EEG, nursing, and nuclear medicine departments. Radioactivity half-life of SPECT radiotracers requires that the radiotracer be replenished every few hours. The chance of injecting during a seizure is hampered if the injection and subsequent scan can be done during only a limited of hours in the day. To increase the likelihood of seizure occurrence so that ictal SPECT can be accomplished, antiepileptic drugs (AEDs) are often withdrawn and the patient deprived of sleep. Triggers of seizures can be employed if the precipitants of habitual seizures are known.

SPECT injection is problematic in patients whose seizures occur usually during sleep at night when the SPECT procedure is typically not available. One strategy for addressing this situation is to have the patient stay up at night and sleep in the daytime or at a time when it is possible to do the SPECT study. If seizure frequency is high, as is the case of many FLE patients, arrangements can be made for the staff and the radiotracer to be at the patient's bedside for immediate SPECT injection when a seizure occurs. This arrangement is especially important when seizures are brief, as often is the case with FLE. It is also preferable to inject during a seizure without secondary generalization because the sensitivity of ictal SPECT is reduced by seizure generalization.[31,38] Because the likelihood of seizure generalization is increased by AED withdrawal, AEDs should be withdrawn more cautiously if the patient's history suggests that habitual seizures have a tendency to generalize.

Peri-ictal Single Photon Emission Computed Tomography Perfusion Patterns

To be able to recognize focal ictal or postictal perfusion changes that are attributable to the seizure activity, ictal or postictal SPECT images have to be compared with interictal SPECT images. Peri-ictal SPECT studies in TLE have shown a characteristic pattern of evolving blood flow changes at the site of seizure activity (Fig. 1). Ictal blood flow changes consist of focal hyperperfusion at the mesial and anterolateral regions of the temporal lobe.[7,28] Within 1 to 5 minutes following the termination of seizure activity, the lateral temporal neocortical region becomes intensely hypoperfused while the mesial temporal region remains slightly hyperperfused. Over the next few minutes, the hypoperfusion becomes more diffuse in both the lateral and the mesial temporal areas. The pattern of conversion from ictal hyperperfusion to postictal hypoperfusion has been termed â€œpostical switch.â€[28] The degree of this focal hypoperfusion gradually lessens over the next 15 minutes or so until it reaches the interictal state of mild hypoperfusion.

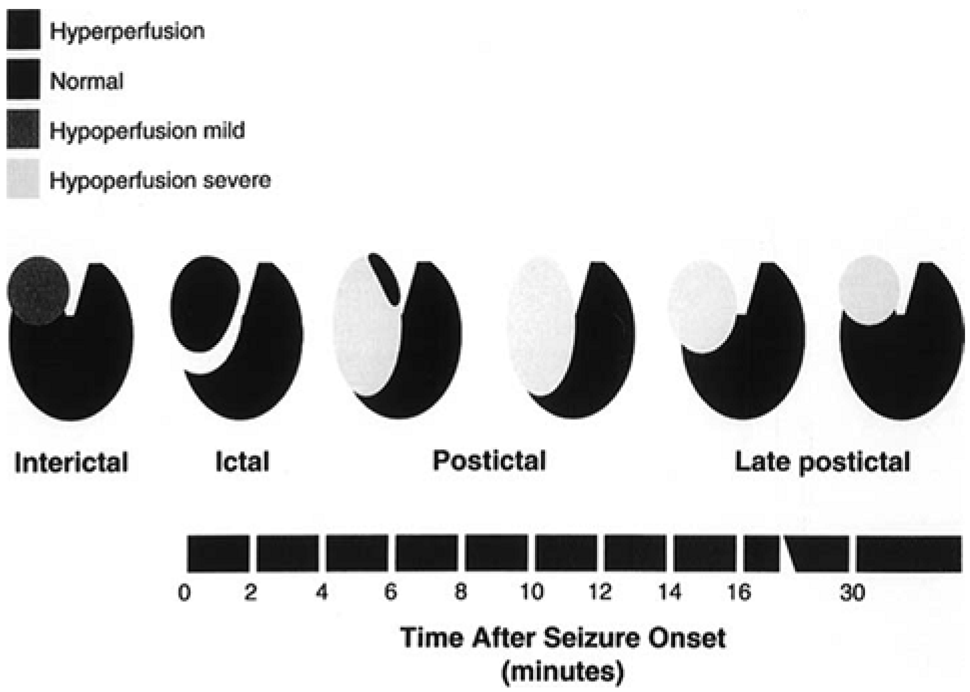

FIGURE 1. Single photon emission computed tomography of temporal lobe seizures according to timing of the radiotracer injection in relation to epileptic seizure activity. (From Rowe C, Berkovic S, Austin M, et al. Patterns of postictal cerebral blood flow in temporal lobe epilepsy: qualitative and quantitative analysis. *Neurology*. 1991;41:1096â€"1103, with permission.)

The timing of the postictal switch cannot be accurately predicted. Postictal switch of perfusion may occur earlier in extratemporal seizures that are short in duration, but SPECT studies are still useful for these seizures if seizure activity persists for 10 to 15 seconds after the injection. Therefore, it is prudent to look for both focal hyperperfusion and hypoperfusion abnormalities regardless of the timing of the radiotracer injection relative to the seizure onset.

Techniques in Single Photon Emission Computed Tomography Image Analysis and Interpretation

Clinical interpretation of peri-ictal SPECT studies typically requires comparison of the peri-ictal (ictal or postictal) SPECT images with the interictal SPECT images. The comparison has conventionally been made by side-by-side visual comparison of the images, but more modern methods use computer-aided techniques for image analysis, display, and interpretation. One method subtracts the interictal from the peri-ictal images and then registers the difference image on the MRI image (subtraction SPECT). Another method statistically compares the degree of peri-ictal perfusion changes in the patient with control values derived from aggregates of interictal studies or nonepileptic volunteer studies (statistical parametric mapping [SPM]).

Conventional Single Photon Emission Computed Tomography Analysis and Interpretation

Clinical Usefulness of Conventional Ictal Single Photon Emission Computed Tomography Studies

Several studies have demonstrated the superiority of ictal SPECT studies over interictal SPECT studies in lateralizing seizure onset in patients with known temporal lobe epilepsy. Sensitivity reported for ictal SPECT in these patients ranged from 75% to 97%, whereas specificity ranged from 71% to 100%.[10,50,53] Devous et al.[6] conducted a meta-analysis of series of peri-ictal SPECT studies that met the following criteria: (a) localization-related epilepsy with at least interictal EEG-documented epileptiform abnormality, (b) at least six adult patients in each series, and (c) a study population that is not highly selected. Only three series with total of 51 patients met the criteria, of whom 42 were from one institution.[22,27,51] The calculated sensitivity for ictal SPECT for TLE in these studies was 96% with a false-positive rate of 1.5%, but Devous et al. cautioned that the number of patients in each series is small.

Most older series of peri-ictal SPECT studies involved patients whose TLE focus had been well localized with interictal scalp EEG, ictal video-EEG, or MRI. The outcome of epilepsy surgery in these patients would be expected to be very good. For new diagnostic tests such as SPECT to have an important role in the presurgical evaluation of partial epilepsy patients, they must provide localizing information that is additional to that provided by current standard tests. This is particularly important in patients with extra-temporal lobe epilepsy, nonlesional epilepsy, or poorly localized seizures.[48,52,55] Surgical outcome in these patients is often poor. Ictal SPECT has been reported to have a sensitivity of 81% to 95% and specificity of about 93% in extratemporal epilepsy.[9,50] Ho et al.[11] found that ictal SPECT localized seizures in all 14 patients with parietal lobe epilepsy. Using ictal SPECT to guide intracranial EEG studies, Siegel et al.[45] obtained good postsurgical seizure outcome in 83% of patients with nonlesional epilepsy. In a

study by Markand et al.,[21] ictal SPECT correctly lateralized the EEG focus in 87% of MRI-negative patients, compared with 82% with PET. Therefore, ictal SPECT appears to have a useful role in identification of the nonlesional epileptogenic zone.

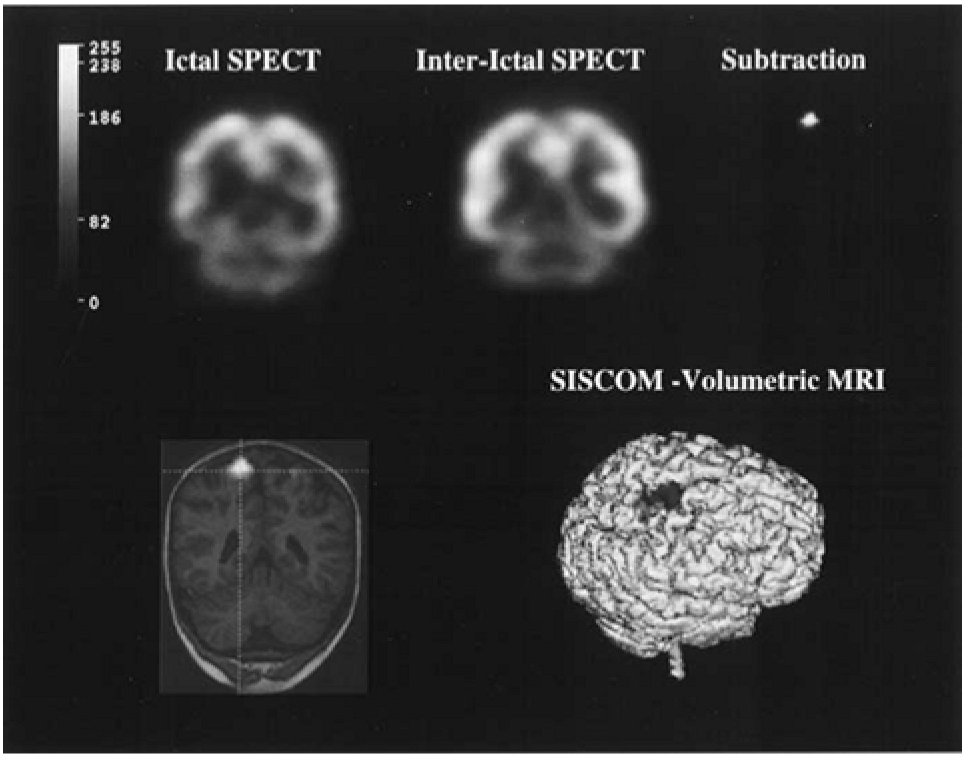

FIGURE 2. Steps to obtaining subtraction ictal SPECT (single photon emission computed tomography) coregistered to MRI (magnetic resonance imaging) (SISCOM) image. Ictal (*upper left*) and interictal (*upper middle*) SPECT images are obtained. After normalization of their mean intensities and coregistration with each other, subtraction is performed to obtain a â€œdifferenceâ€ image (*upper right*). The difference image is then coregistered with MRI at specific planes (*lower left*) or on the surface of a three-dimensional MRI (*lower right*). (From So E. Role of neuroimaging in the management of seizure disorders. *Mayo Clin Proc*. 2002;77:1251â€“1264, with permission.) (See the color insert.)

Clinical Usefulness of Conventional Post-ictal Single Photon Emission Computed Tomography Studies

Clinical interpretation of postictal SPECT is more difficult than that of ictal SPECT.[7,29,40] Most studies have reported a lower sensitivity and specificity for postictal SPECT in lateralizing TLE than for ictal SPECT, although the sensitivity and specificity are still better than those for interictal SPECT.[6,29,50] Meta-analysis involving four series of postictal SPECT studies in 69 patients showed sensitivity of 75% and false-positive rate of 1.5%, but most series had a small number of patients.[6]

Subtraction Single Photon Emission Computed Tomography With Magnetic Resonance Imaging Coregistration

The conventional method of SPECT interpretation by side-to-side visual comparison of peri-ictal and interictal SPECT images is beset with a number of technical limitations, including (a) image intensity differences, which depend on the radioisotope dose injected and the time between injection and scanning, (b) differences in slice level and orientation of the images, which depend on the position of the patient's head in the scanner when the images were acquired, and (c) the fact that the exact anatomic location of perfusion abnormalities can be difficult to determine because of poor spatial resolution and structural detail of SPECT images compared with MRI images. To overcome these limitations, a few investigators introduced computer-aided subtraction of peri-ictal SPECT data from interictal SPECT data and subsequent registration of the difference data as images on brain MRI.[8,56] At the Mayo Clinic, we have developed, validated, and applied a method of subtraction ictal

SPECT with coregistration on MRI (SISCOM) for epilepsy evaluation.[33]

SISCOM involves five steps that are semiautomated and can now be performed in <10 minutes (Fig. 2). First, the interictal SPECT is coregistered and transformed into the three-dimensional space of the ictal SPECT by either surface matching or a voxel-based method. Second, the intensities of both images are normalized to a standard value (most commonly the mean cerebral intensity). Third, the normalized and coregistered images are subtracted to derive a difference (activation) image of cerebral blood flow related to the partial seizure activity. Fourth, the difference image is threshold to display only pixels with intensities greater than two standard deviations above (for hyperperfusion) or below (for hypoperfusion) zero. Finally, the resulting image is coregistered onto the brain MRI. Each of these steps has been validated by using both phantom and patient studies.[33]

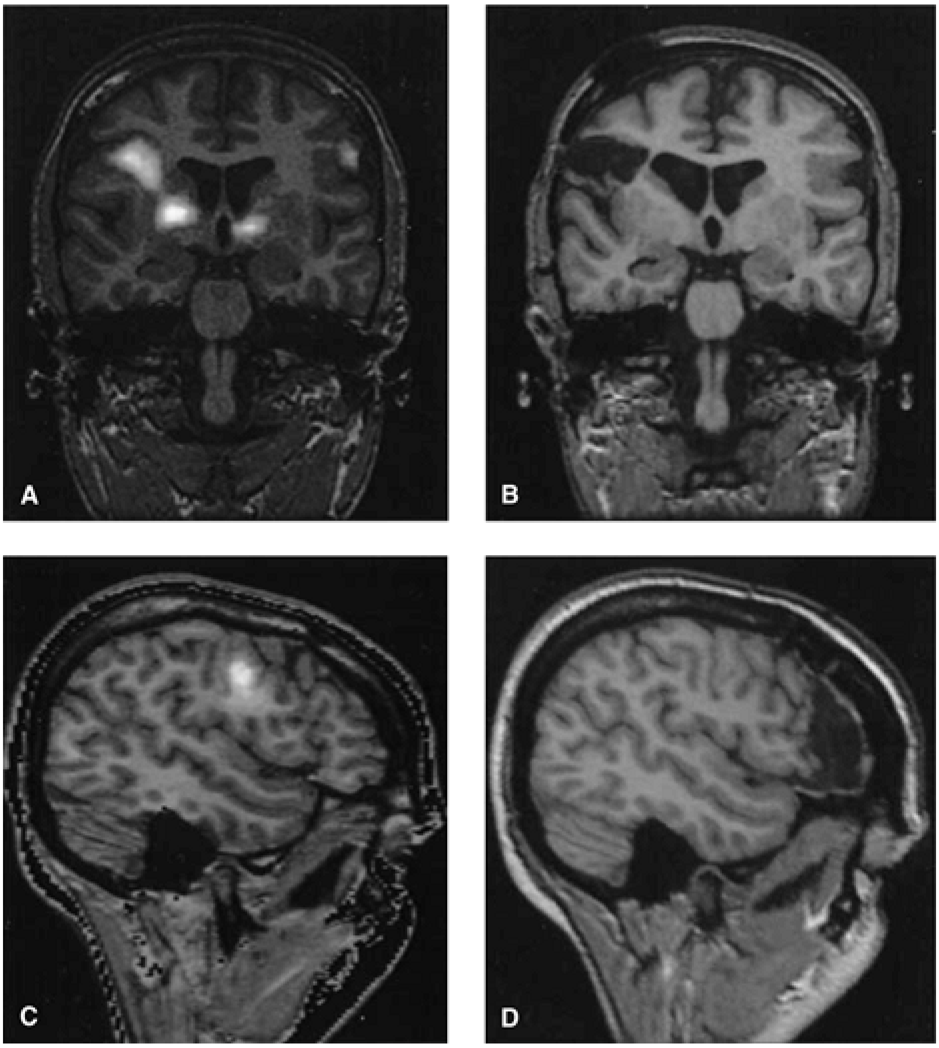

FIGURE 3. Preoperative subtraction ictal SPECT (single photon emission computed tomography) coregistered to MRI (magnetic resonance imaging) (SISCOM) images (A and C) and postoperative MRI (B and D). **A, B:** Complete resection of neocortical region underlying SISCOM focus. **C, D:** Nonresection of neocortical region underlying SISCOM focus. (From O'Brien T, So E, Mullan B, et al. Subtraction peri-ictal SPECT is predictive of extratemporal epilepsy surgery outcome. *Neurology*. 2000;55:1668â€"1677, with permission.) (See the color insert.)

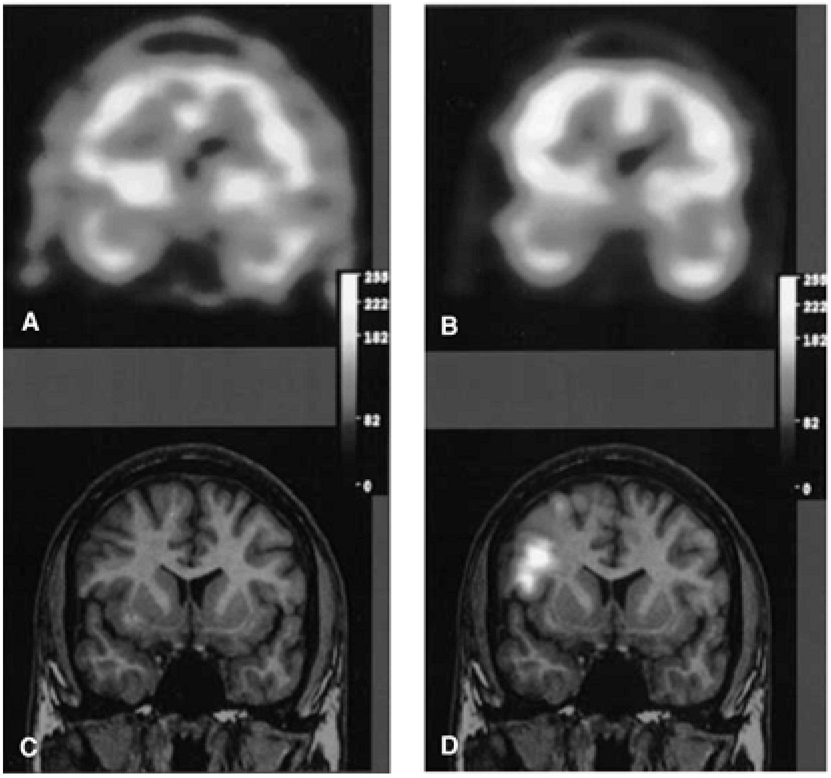

FIGURE 4. Subtraction ictal SPECT (single photon emission computed tomography) coregistered to MRI (magnetic resonance imaging) (SISCOM) with â€œpositiveâ€ subtraction for detecting hyperperfusion focus and â€œnegativeâ€ subtraction for detecting hypoperfusion focus. **A:** Postictal SPECT image obtained from radiotracer injection at 88 seconds after seizure termination. **B:** Interictal SPECT image. **C:** â€œPositiveâ€ subtraction shows no hyperperfusion focus. **D:** â€œNegativeâ€ subtraction shows a hypoperfusion focus at the right frontal region. (See the color insert.)

Clinical Usefulness of SISCOM in Epilepsy Evaluation

SISCOM was clinically validated in 51 patients whose seizure focus could not be adequately localized by standard tests for epilepsy surgery.[35] Study reviewers detected a hyperperfused SISCOM focus in 88% of patients, compared with only 39% with the conventional visual comparison method. The agreement rate between blinded reviewers was significantly better with the SISCOM method (84% vs. 42%). Postsurgical outcome was better when the SISCOM focus was present and included in the surgical resection than when it was not (excellent seizure outcome in 63% vs. 20%; Fig. 3).

We also used the computer-aided subtraction and coregistration technique to detect the phenomenon of reduced focal perfusion that occurs typically during the postictal state (Fig. 4).[37] Two thirds of the 35 postictal SISCOM studies disclosed a hypoperfusion focus, whereas one third still showed a hyperperfusion focus. Hogan et al.[12] also showed that hyperperfusion abnormalities can persist into the postictal period. Because of these observations, we have been performing both â€œpositiveâ€ subtraction for detecting hyperperfusion abnormalities and â€œnegativeâ€ subtraction for detecting hypoperfusion abnormalities regardless of the timing of radiotracer injection. When reviewed independent of each other, 66% of the postictal â€œpositiveâ€ subtraction SISCOM disclosed a hyperperfusion focus, whereas 74% of the postictal â€œnegativeâ€ subtraction SISCOM showed a hypoperfusion focus.[37] Combined use of â€œpositiveâ€ and â€œnegativeâ€ subtraction SISCOM images, however, detected a focus of perfusion abnormality in 83% of the postictal injection studies. We observed that the intensity is less and the distribution is wider with hypoperfusion abnormalities than with hyperperfusion abnormalities. To adjust for these observations, the difference image that results from the subtraction has to be threshold to display the pixels separately at one and at two standard

deviations above (hyperperfusion) and below (hypoperfusion) the baseline.

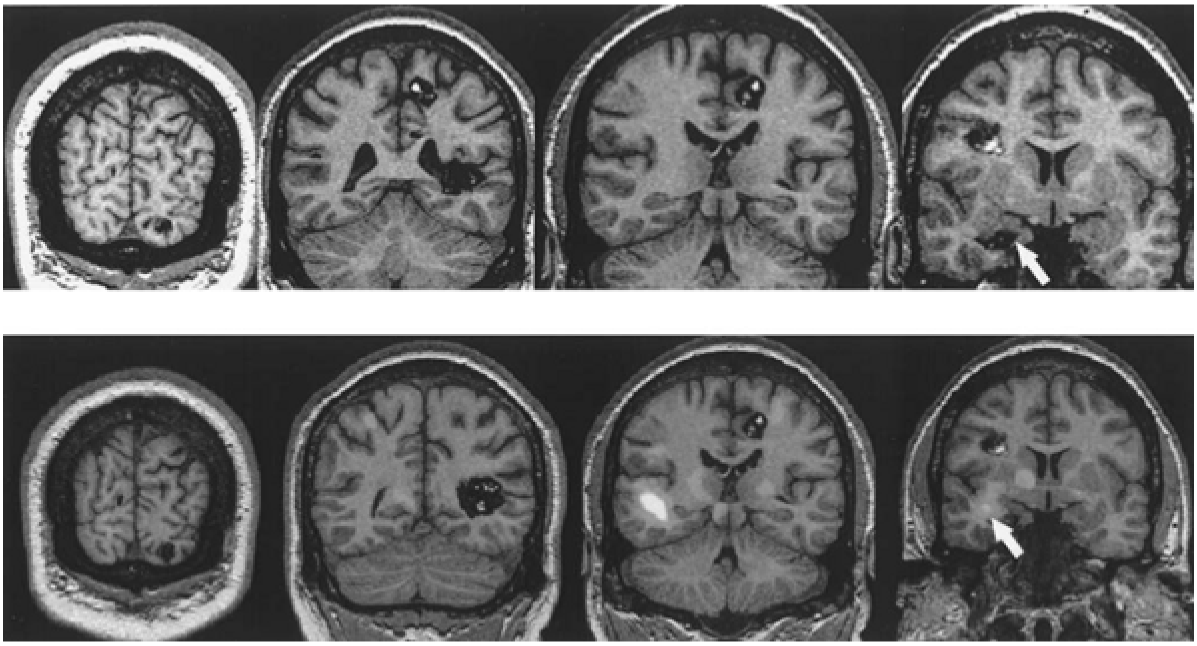

FIGURE 5. Coronal MRI (magnetic resonance imaging) (*top row*) and subtraction ictal SPECT (single photon emission computed tomography) coregistered to MRI (SISCOM) (*bottom row*) images of a patient who had medically refractory partial epilepsy associated with multiple cavernous angiomas. Electroencephalography did not localize seizure onset. SISCOM shows ictal hyperperfusion focus at the right mesial temporal angioma, and seizure semiology was compatible with right temporal onset seizures. Resection of the right temporal angioma and its immediate surrounding tissues resulted in seizure freedom. (See the color insert.)

The combined use of â€œpositiveâ€ and â€œnegativeâ€ subtraction SISCOM images is helpful in evaluating patients whose seizures are especially difficult to localize. In lesional and nonlesional extratemporal epilepsy, the presence of a SISCOM focus that is subsequently resected has a better probability for postsurgical seizure control than when the SISCOM is either unresected or absent (58% vs. 18%).[37] In our study, the rate of excellent postsurgical outcome was 100% for complete resection of the extratemporal SISCOM focus, 60% for partial resection, and 20% for nonresection. In patients with malformations of cortical development, the inclusion of the SISCOM focus in the surgical resection is also associated with better postsurgical outcome than its absence or exclusion.[34] Moreover, peri-ictal SISCOM was localizing in 86% of patients with malformations of cortical development. As for patients who had failed prior epilepsy surgery, peri-ictal SISCOM study showed a hyperperfusion focus in 80%. Fifty percent of the patients had favorable outcome when repeat epilepsy surgery did include the SISCOM focus, compared to none when the surgery did not.[54] Another application of peri-ictal SISCOM is in patients with multiple potentially epileptogenic lesions such as multiple cavernous angiomas and tuberous sclerosis. Peri-ictal SISCOM may help to identify the lesion that is responsible for the patient's habitual seizures (Fig. 5). Finally, peri-ictal SISCOM is helpful in guiding the location and extent of intracranial electrode implantation.[46,49]

SPECT injection in children is sometimes easier to anticipate and perform than in adults because many children have frequent seizures, including daily multiple seizures. Some children may require sedation for SPECT scanning following injection of the radiotracer. The usefulness of SISCOM in children is comparable to that in adults.[4,5,15,39]

Single Photon Emission Computed Tomography with Statistical Parametric Mapping Analysis

Statistical parametric mapping is more commonly used in the analysis of activation images in PET and functional MRI studies. Few studies have applied SPM to analyze SPECT data. Lee et al.[19] analyzed ictal SPECT with SPM and correctly lateralized seizures in 18 of 21 mesial temporal lobe patients, compared with ictalâ€“interictal subtraction studies that correctly lateralized seizures in 16 patients and falsely lateralized seizures in 1. More recently, McNally et al.[23] used a method of ictalâ€“interictal subtraction SPECT analyzed by SPM (ISAS) in patients with well-localized epilepsy. All SPECT studies were of seizures that did not generalize. They identified seizure onset in five of seven mesial temporal lobe epilepsy patients and in five of six neocortical epilepsy patients. There were no false-positive localizations. It should be noted that with the ISAS method, SPM analysis is applied to the difference between ictal and interictal SPECT data, whereas Lee et al. analyzed only ictal data with SPM. Between the two methods, ISAS has the theoretical advantage of avoiding the phenomenon of â€œpseudonormalization,â€ in which the ictal hyperperfusion is only relative to a more intense degree of interictal hypoperfusion at the same site. In such a situation, SPM analysis of the ictal data alone may disclose perfusion that approximates the control values but does not exceed them to produce the characteristic hyperperfusion finding.

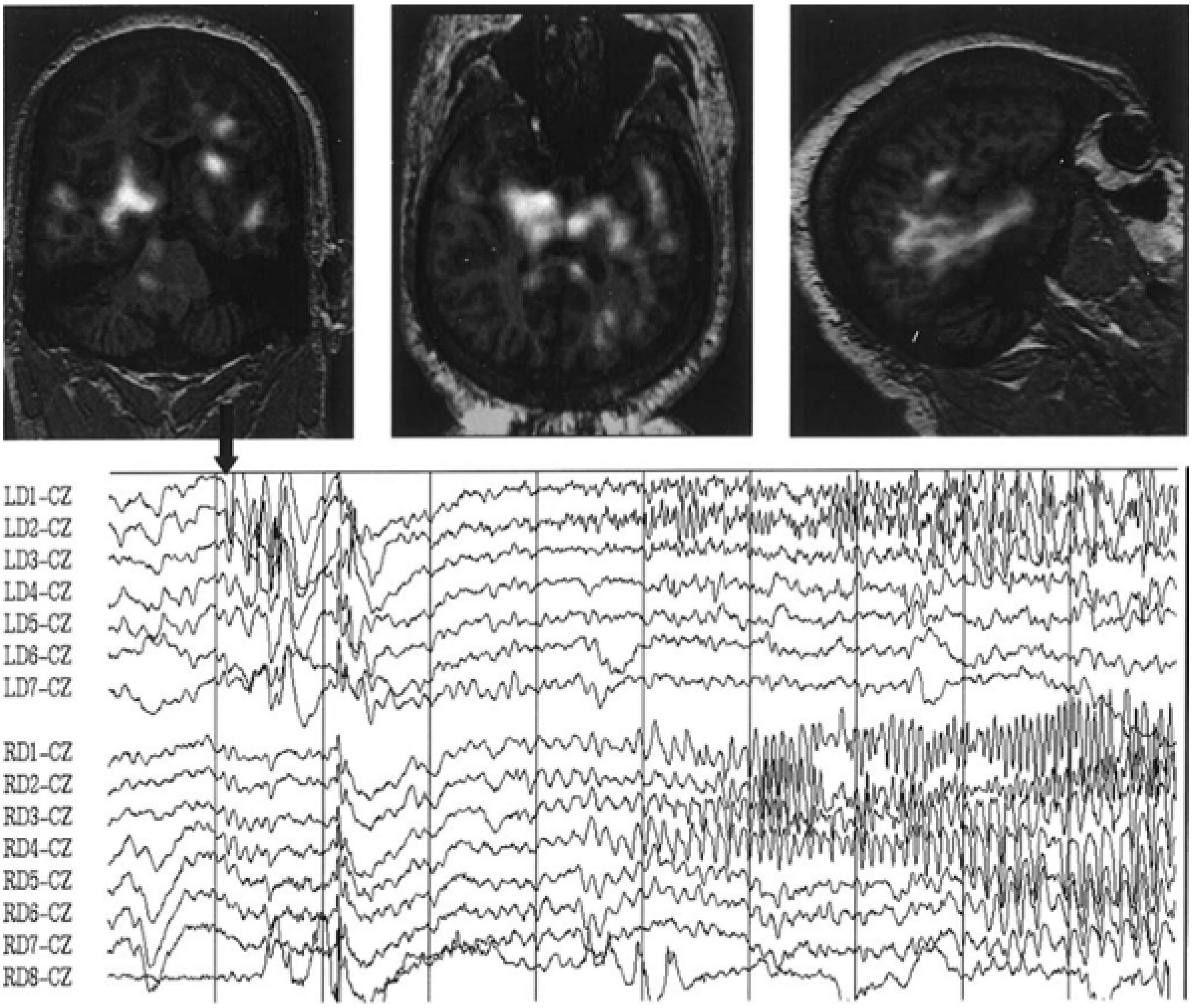

FIGURE 6. Subtraction ictal SPECT (single photon emission computed tomography) coregistered on MRI

(magnetic resonance imaging) (SISCOM) images (*top*) and bilateral mesial temporal depth electrode recordings (*bottom*) in a patient with left mesial temporal sclerosis and seizure onset. SISCOM shows dominant hyperperfusion focus involving the right mesial temporal and thalamic regions (*upper left* and *middle*). There is also a streak of less intense hyperperfusion at the left temporal region (*upper right*). Left mesial temporal depth electroencephalogram (LD1â€“7 referred to Cz) shows seizure onset (*arrow*) with subsequent rapid spread to involve the right mesial temporal depth electrodes (RD1â€“8 referred to Cz). (See the Color insert.)

Limitations of Single Photon Emission Computed Tomography

Regardless of the technique of image analysis, SPECT should always be used in conjunction with clinical information and other laboratory tests to confirm the seizure focus for epilepsy surgery.[46,49] Seizure localization in epilepsy surgery evaluation is rarely based on one modality alone; convergence of localizing information must be sought to ensure accurate delineation of the epileptogenic zone. When SPECT localization is incongruent with other information, the possibility of SPECT false localization must be considered. False localization by any type of SPECT image analysis can be due to procedural or biologic factors. Late ictal or postictal injection may result in hyperperfusion changes in a region that is distant from the focus of seizure origin (Fig. 6). SPECT interpretation should always be made in the context of seizure semiology, ictal EEG, and latency of radiotracer injection (time between injection and time of seizure onset and offset). Late ictal or postictal injection may also result in hypoperfusion instead of hyperperfusion abnormalities. As discussed earlier, image processing and analysis must be made in every study to detect these two types of perfusion abnormalities. If both intense hypoperfusion and hyperperfusion foci are present in the same study, it is probable that the hypoperfusion focus represents earlier and possibly originating seizure activity and the hyperperfusion focus represents late or propagated seizure activity.

A SPECT study provides information about the seizure that was occurring when the injection was performed, but the particular injection and images derived do not evaluate other seizure foci in patients with multifocal epilepsy. We routinely show the video recording of the injected seizure to the patient's family or friend to help establish that the injected seizure is representative of the patient's single or dominant habitual seizure type. Other than the injected seizure, several seizures should be recorded and analyzed to confirm that the seizures are stereotypic and relevant to the patient's burden from the epilepsy. This is especially important when there is evidence to suggest the possibility of multifocal epilepsy (i.e., multiple clinical seizure types, multiple MRI lesions, or multiple EEG abnormalities).

It should be noted that the abnormal conventional or subtraction SPECT focus localizes seizure activity to a region rather than a specific anatomic structure. This is especially true of an abnormal hypoperfusion focus, which tends to be more widespread than a hyperperfusion focus. SPECT focus often appears at the lateral temporal region in patients with mesial temporal onset epilepsy. Therefore, intracranial electrode recording may be needed when surgical resection requires more accurate delineation of the electrophysiologic abnormalities and eloquent function associated with the region of SPECT abnormality.

Research Applications in Single Photon Emission Computed Tomography

Techniques of quantifying the degree of peri-ictal blood flow change have been used to study perfusion patterns and their corresponding locations in different seizure types or modes of seizure propagation.[2,20,43] Other than SPM, objective detection of blood flow changes that are statistically significant and clinically meaningful should continue to be developed and assessed. Brinkmann et al.[3] developed the voxel variance method, which takes into account the expected baseline variation between two nonactivated or interictal images when analyzing a patient's ictalâ€“interictal subtraction SPECT image. Instead of thresholding the patient's subtracted image at two standard deviations as in SISCOM, the voxel variance method detects and displays only pixels in the patient's subtracted image that differ from the expected baseline variation to a statistically significant degree. Preliminary application of this method in a small group of patients showed that images generated by the voxel variance method were rated higher in quality than SISCOM images, but the localization rates were the same between the two methods.

The precise relationship between injection timing and the pattern of peri-ictal blood flow changes remains to be defined. Improvements in radiotracer injection techniques, including use of automated injection systems, may help in studying this relationship. The logistics in performing ictal SPECT injections is complex and expensive, and many institutions are not performing SPECT studies on a regular basis.[24] New types of radiotracers and new methods for their delivery may simplify and widen the use of peri-ictal SPECT, thus making it also possible for multicenter studies to be conducted with a uniform protocol to further define the usefulness of SPECT in epilepsy evaluation.

Summary and Conclusions

Ictal SPECT has been established in the last two decades as a useful test to help identify the surgical seizure focus. Subtraction SPECT methods such as SISCOM has also been shown in the last decade to improve the usefulness of ictal SPECT in both lesional and nonlesional temporal and extratemporal focal epilepsies. More advanced methods using SPM have been reported with encouraging results, but further clinical experience is needed to better define their usefulness and limitations. Regardless of the method of SPECT acquisition and post-acquisition data analysis used, the principles and limitations of SPECT studies must be fully appreciated to avoid poorly localizing or false positive results. Prompt injection of the SPECT radioligand early during the seizure must be attempted to improve the yield of the study. Moreover, SPECT results have to be integrated with other data of seizure localization from the clinical history, neurological examination, seizure semiology, ictal EEG, and structural and functional imaging tests.

Acknowledgments

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Chapter 82

Magnetic Resonance Spectroscopy

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Introduction

In this chapter we review the application of magnetic resonance spectroscopy (MRS) to the investigation of the epilepsies in humans from both research and clinical perspectives. Initially we deal with proton MRS of the major metabolites that are detectable in vivo in focal and generalized epilepsies. We then consider the measurement of glutamate, glutamine, and Î³-aminobutyric acid (GABA). Finally, we address the use of phosphorus MRS interictally and postictally and the effect of therapies on the spectra.

Hydrogen (Proton) Magnetic Resonance Spectroscopy

The principal signals, measured using long-echo-time (TE) proton (^1H) magnetic resonance spectroscopy, include the singlet resonances of *N*-acetyl aspartate (NAA) (2.01 parts per million [ppm]), creatine plus phosphocreatine (CR; 3.0 and 3.9 ppm, respectively), choline-containing compounds (Cho; 3.2 ppm), and lactate (Lac; doublet signal centered at 1.35 ppm). The long TE suppresses signals from most other brain metabolites and macromolecules (lipids, proteins, and glycoproteins). N-acetyl-aspartate is the most concentrated organic metabolite unique to the central nervous system (CNS). The singlet resonance from the three hydrogen atoms of the terminal methyl group of the *N*-acetyl portion of NAA serves as a useful marker of normal adult nervous tissue (Fig. 1). The epileptic state appears to be characterized by a widespread though modest decrease in NAA, which is centered on the seizure onset zones in the focal epilepsies. Paradoxically, the loss of neurons in the epileptogenic focus exceeds the modest decrease in NAA, which suggests that NAA levels are above normal in the remaining cells, predominantly glia, but the area of NAA reduction may be more extensive.

The Acute Effects of Seizures

Relatively few patients have been studied during or soon after seizures using MRS. A recent review has summarized these case reports involving patients with partial status epilepticus.[15] Lactate levels were increased and NAA levels reduced in the acute phase of the seizure. The difficulty in interpretation lies in distinguishing the contribution of neuronal injury from the metabolic effects of the prolonged seizure. Two epilepsy centers reported MRS studies of patients measured soon after mesial temporal lobe seizures.[18,19] Lactate levels were elevated in the epileptogenic mesial temporal lobe obtained during complex partial seizures or within 4 to 24 hours after the seizures. Although NAA levels were below normal in all patients, there was no difference in NAA levels among serial spectra taken in the ictal, postictal, and interictal states. Generalized seizures were not associated with raised ictal lactate levels or decreased NAA levels. A significant decrease in the magnetization transfer ratio (MTR) of Cho was seen after seizures. Reduced MTR of Cho indicates a shift from a bound to a more mobile fraction. These changes might indicate membrane perturbation in areas of seizure spread.[44]

N-Acetyl Aspartate Levels of the Temporal Lobe Epilepsies

Several series of 30 to 100 patients with temporal lobe epilepsy (TLE) report that NAA and NAA/Cr ratios are decreased in the epileptogenic temporal lobe.[17,21,28,46,57,122] In TLE, low NAA levels are often widespread and can affect the temporal lobe contralateral to the epileptogenic hippocampus and correlate with interictal hypometabolism measured using positron emission tomography (PET).[80,96,102,113] The widespread changes seen using PET and MRS are attributed to diaschisis. Low NAA levels in the contralateral temporal lobe often herald a poor outcome from surgery in terms of seizures and cognitive function.[47,92] Below-normal NAA levels can provide evidence of temporal lobe or hippocampal abnormalities in patients with TLE who show no abnormality on magnetic resonance imaging (MRI).[29,111,167,183] Lesser decreases in NAA levels are seen in the temporal lobe contralateral to the epileptogenic one. About half of the patients with newly diagnosed TLE and unremarkable MRI have low NAA/Cr ratios.[97] There may be subtle decreases in neuronal density in a hippocampus that appears normal on MRI.[33]

What Is the Impact of Seizure Frequency on N-Acetyl Aspartate Levels in Temporal Lobe Epilepsy?

The NAA/Cr ratios of the mesial temporal lobe ipsilateral to the seizure focus correlated with seizure frequency but not with the duration of the epilepsy.[50] Similar findings were reported for frontal lobe epilepsy. Mesial temporal NAA levels and the NAA/(choline plus creatine) ratios were normal in patients with neocortical epilepsy, from which the authors inferred that repeated neocortical seizures did not cause secondary damage to the hippocampus.[185] However, 5 of 10 patients with neocortical epilepsies had low NAA/(creatine plus choline) ratio in the mesial temporal lobe ipsilateral to the seizure focus, which suggests that seizure activity arising elsewhere in the same cerebral hemisphere may reduce hippocampal NAA levels and, by inference, neuronal function.

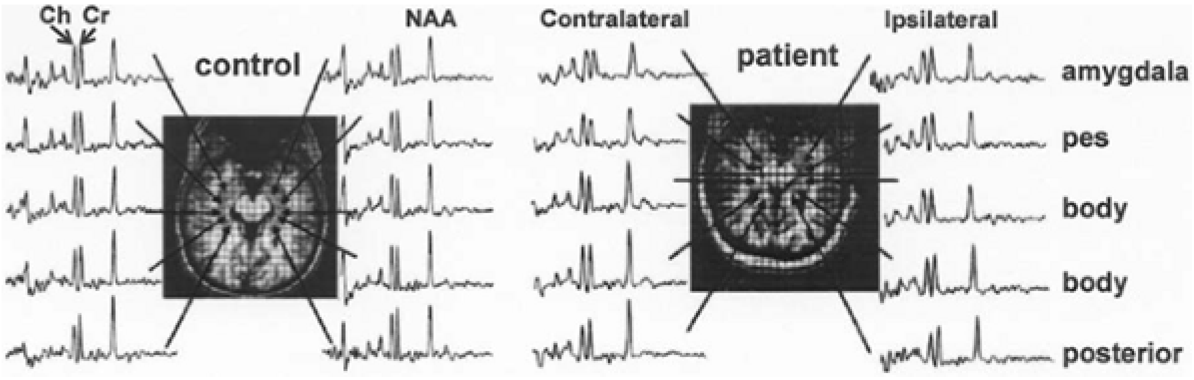

FIGURE 1. Long-spin-echo time (TE = 72 msec) proton magnetic resonance spectroscopic imaging of the human hippocampus at 4 T with intermediate spin-echo time (TE = 50). **Left:** A healthy volunteer. **Right:** A patient with mesial temporal lobe epilepsy (MTLE). Signals from the methyl groups (singlets) of *N*-acetylaspartate (NAA), creatine (Cr), and choline (Ch) are seen clearly. The spectra ipsilateral to the epileptogenic hippocampus have lower NAA signals and a lower NAA/creatine ratio than the contralateral side and the control subject. (Adapted from Cohen-Gadol AA, Pan JW, Kim JH, et al. Mesial temporal lobe epilepsy: a proton magnetic resonance spectroscopy study and a histopathological analysis. *J Neurosurg*. 2004;101:613â€"620.)

What Is the Impact of Interictal Epileptiform Discharges on N-Acetyl Aspartate Levels?

There have been several correlations of MR spectroscopic imaging (MRSI) with interictal epileptiform discharges (IEDs). In 9 patients with TLE and five with frontal lobe epilepsy there was a negative association between IED frequency and the decrease in NAA/Cr ratios, and the NAA/Cr ratio of the voxels nearest to the surface electrode with the highest IED frequency tended to be lowest.[159] In 31 patients with TLE there was a high degree of concordance between unilateral IED and the number of voxels with below-normal NAA/Cr ratios and a moderate concordance between the distribution of NAA abnormalities and the field of the IED.[106] In patients with lateralized NAA abnormalities and lateralized ictal EEG onset, however, the data were discordant in 6 of 22 (27%). In 32 patients with mesial temporal sclerosis (MTS), the NAA/Cr ratios in the ipsilateral medial temporal lobe were significantly lower than in the contralateral side and NAA/Cr ratios of both mesial temporal lobes. There was no significant correlation between the NAA/Cr ratio and IED frequency on the side with MTS, but there was a significant inverse correlation between IED and NAA/Cr contralaterally. The clinical significance of these data are unclear, but they suggest a relationship between IED and lower NAA levels in hippocampi that appear normal on MRI.[123] Alterations in NAA levels also were reported in focal areas of IED, which were identified by magnetoencephalography (MEG), in nonlesional temporal lobe epilepsy.[163] The NAA/choline ratios were decreased significantly in the spike zone compared with the contralateral homologous region but did not correlate with IED frequency.

Do N-Acetyl Aspartate Levels Progressively Decline in Temporal Lobe Epilepsy?

NAA/CR ratios were lower with longer duration of epilepsy in refractory TLE, both ipsilateral and contralateral to the epileptogenic temporal lobe.[10,34,176] Declining NAA levels ipsilateral to the seizure focus may be attributed to neuronal loss. The decline in NAA/Cr ratios in the contralateral mesial temporal lobe is not as easily attributed to neuronal loss alone. Axonal injury can contribute to decreased NAA levels in the absence of neuronal loss.[45,145] Frequent seizures spreading to the contralateral hippocampus potentially could reduce NAA levels in the contralateral hippocampus. Patients with TLE and a history of secondarily generalized tonicâ€“clonic seizures are more likely to have bilaterally low NAA levels than are patients who have infrequent generalized seizures.[92] Other, smaller studies have not found a significant relationship between duration of the epilepsy and NAA levels.[16,37,185] Several groups have reported further, age-related decreases in hippocampal NAA levels in healthy volunteers, and so inclusion of an age-matched control group is essential to interpreting findings in those with epilepsy.[175]

N-Acetyl Aspartate Levels and the Pathology of the Epileptogenic Hippocampus

It is not clear whether decreased NAA levels in the mesial temporal lobe reflect hippocampal neuron loss. Initial studies attributed the low NAA/Cr ratio of the epileptogenic temporal lobe to neuronal loss and the accompanying loss of neuropil and axons.[65] A study of the epileptogenic human hippocampus resected at surgery reports that NAA content is significantly lower in â€œsclerotic glioticâ€ specimens than those that are â€œhistologically unremarkable.â€[126] Another semiquantitative study suggested that there is an association between low NAA levels measured in vivo with MRS and the severity of hippocampal sclerosis.[34] There was no association between the hippocampal Cr/NAA ratios measured in vivo by MRS and neuron/glia ratios of the portion of the resected hippocampi.[87] It was suggested that metabolic alterations associated with seizure activity contributes as much as altered neuron/glia ratios to the NAA/Cr ratio. Hippocampi with severe neuronal loss and gliosis had the same or higher NAA levels as did hippocampi with little neuron loss. This would appear to suggest that NAA levels, although lower than normal, are much higher in hippocampi in MTS than would be anticipated from nonepileptogenic hippocampi with similar degrees of neuronal loss, for example, Alzheimer disease or stroke. A recent surgical series found no significant associations between hippocampal neuron loss and the cellular content of NAA despite a more than a threefold difference in neuron loss and a twofold increase in glial density.[140,142] The modest decrease in NAA levels and the NAA/Cr ratios of the hippocampi with >70% neuron loss and a doubling of glial density were unexpected. The NAA

content, measured in hippocampal sclerosis with TLE, was too high for the degree of neuron loss with the attendant loss of NAA synthetase expression. In the adult nervous system, NAA appears to be localized to neuronal cytosol; it would appear to be unlikely that the intracellular NAA content is increased two-to-threefold in the remaining neurons of the most gliotic hippocampi. A more probable explanation is that the glial cells contain significant amounts of NAA. One hypothesis is that NAA is synthesized by glial precursor cells or abnormal glia. Enzyme and transporter expression, function, and localization are altered in the epileptogenic human hippocampus with sclerosis. In cell cultures, the NAA and total creatine content of O2A-oligodendrocyte precursor cells are higher than in cerebellar neurons.[178] A recent study shows that â€œmature oligodendrocytesâ€ grown in cell culture with ciliary neurotrophic factor (CNTF) contain high levels of intracellular total creatine and NAA, comparable to levels reported in a variety of neuronal cultures.[13]

Spectroscopic imaging at 4 T before surgery found that NAA/CR ratios decrease from 78% of normal values in the posterior hippocampus to a nadir of 68% of normal in the anterior epileptogenic hippocampus in patients with MTS.[61] The contralateral hippocampus also had lower NAA/CR ratios ranging from 80% of normal in the posterior hippocampus to 86% to 87% of normal in the anterior hippocampus. There was no significant correlation between NAA/Cr in the epileptogenic hippocampus, measured in vivo before surgery, and neuronal counts of the resected hippocampus. There was, however, a significant correlation between NAA/Cr and reactive glial counts averaged over CA1-CA4 and the dentate. There was no significant correlation between glial fibrillary acidic protein (GFAP) staining and neuronal counts. This suggests that in TLE, reductions in the hippocampal NAA/Cr ratios inversely correlate with the presence of reactive astrocytes, an accepted marker for injury, rather than with the loss of neurons, and that reactive glia are able to metabolize NAA to some degree. An alternative hypothesis is that there is a pool of NAA in astrocytes with a very slow turnover rate and both oligodendrocytes and astrocytes avidly take up NAA.

N-Acetyl Aspartate Levels Recover Following Successful Temporal Lobe Resection

In regions with low levels prior to surgery, NAA can recover to nearly normal values following successful temporal lobe resection.[20,66,172,186] Most of the recovery occurs within 6 months and 95% by 2 years.[160] The recovery of NAA following surgery indicates that neuronal loss probably is not the main cause of low NAA levels in the nonepileptogenic hippocampus. Seizure activity may inhibit mitochondrial synthesis of NAA; in addition, frequent seizures may enhance neuronal release of NAA with subsequent enhanced glial catabolism. It is not clear whether decreased NAA levels are an adaptive response to seizure activity, which may downregulate hippocampal excitability. Some investigators have suggested that improved NAA levels may contribute to improved cognitive functions with seizure freedom, perhaps through improved neuronal functioning.

N-Acetyl Aspartate Levels of the Nonlesional, Focal Neocortical Epilepsies

Nonlesional neocortical epilepsies are defined by a normal-appearing MRI; the epileptogenic region of the neocortex is defined usually by surface or intracranial video-electroencephalographic (EEG) monitoring. Spectroscopic imaging to measure NAA levels, NAA/Cr ratios, or NAA/choline ratios may be useful for localizing the epileptogenic zone.[49,56,104,114,173] Findings in nonlesional neocortical epilepsies parallel those reported for nonlesional TLE. Seizure frequency correlates with the magnitude of the decrease in NAA/Cr ratios in the seizure focus in several studies. Decreased NAA levels also were seen in regions outside of the seizure onset zone in most patients, including the ipsilateral hippocampus in nearly half.[56,92,114,173]

N-Acetyl Aspartate Levels of Epileptogenic Focal Cortical Dysplasia

Several studies have measured interictal NAA levels or NAA/CR ratios of epileptogenic focal cortical dysplasia.[85,104,187] Mean NAA levels of the dysplasia were lower by 17% to 27%, and the mean NAA/CR ratios decreased to 71% to 79% of normal. One study reported MRSI and quantitative cell counts for focal cortical dysplasia.[85] The mean neuron-to-glia ratio was the same in the autopsy control and the patients. There was no evident correlation between the rate of IED and the NAA/CR ratios. However, the ratios were lower in patients with frequent seizures. The metabolic abnormalities closely correlated with the location of the epileptogenic focus among patients with focal cortical dysplasia with normal NAA/CR ratios in other cortical areas.

Spectroscopic Imaging of Heterotopia and Polymicrogyria

Malformations of cortical development (MCD) include diverse pathologies. The mean lesional NAA/CR ratios are variably altered in epileptic patients with heterotopia and polymicrogyria.[95,115,195] There are many reports of no significant differences in the mean NAA/CR ratio between the heterotopia and the cortex or white matter of control sub-jects.[85,116,192] Others have reported small decreases in the lesion.[72,95,171,195] Similarly, there are reports of no significant metabolic alterations in the regions affected by polymicro-gyria,[72,85,192] and others report significant decreases in the mean NAA/Cr ratio.[171] MRSI studies have reported considerable heterogeneity within the volume involved with the MCD or the perilesional brain.[95,115,195] NAA and creatine levels and their ratios may be decreased in one voxel within the lesions seen by MRI and increased in another voxel, with much of the lesion having normal levels. What is unclear is the relationship between these metabolic alterations and the seizure focus. Quantitative histopathology correlated to the metabolic measurements remains to be published. The clinical value of MRSI in addition to conventional MRI in this context remains to be assessed.

N-Acetyl Aspartate Levels in Idiopathic and Cryptogenic Epilepsies

Overall, the mean hippocampal NAA/CR ratio of children with rolandic epilepsy was increased by 12% to 14% compared with healthy children matched for age and development.[103] However, lateralization of the lower NAA/CR ratios was concordant with the lateralization of the IED in 10 of 13 children. The mean NAA/CR ratio of the hippocampus contralateral to the IED was 20% above normal. The ipsilateral ratio was in the normal range (6% higher). In cryptogenic occipital lobe epilepsy, NAA

levels and NAA/CR ratios measured in the occipital lobe (61% cortical grey matter) were reported as normal.[167] There have been several studies of idiopathic generalized epilepsies (IGEs), primarily of patients with juvenile myoclonic epilepsy (JME) or generalized tonicâ€“clonic seizures (GTCS).[11,19,110,155,156,169] Overall, the mean NAA/CR ratios have been about 10% below normal in the thalamus, 5% below normal in the frontal lobes, and within the normal range in the occipital lobes of those with idiopathic generalized epilepsies.

Summary on the Utility of N-Acetyl Aspartate Measurements in the Human Epilepsies

Measurements of NAA levels using MRSI appears to be most useful in focal epilepsies without lesions seen using conventional MRI. Low NAA levels and NAA/Cr ratios are widespread, with the lowest values associated with the areas most frequently and intensively involved by the seizures. NAA imaging may offer clues to the regions where the seizures start or those areas that facilitate the spread of the seizure to more normal cortex. Detailed NAA images may complement EEG- and MEG-based maps of epileptogenic networks. NAA images may help lateralize mesial TLE, but bilateral abnormalities are common. Based on the use of single voxels, the reported sensitivity of the NAA/CR ratio in determining the epileptogenic hemisphere was 60% to 65%.[28,92] With the use of MRSI, the lateralization improves to 85% to 98%.[17,21,83,86,98] More important, severe bilateral hippocampal involvement appears to be associated with less desirable surgical outcomes. Combined measurements of NAA/CR with MRSI and volumetric MRI correctly predicted the surgical outcomes of 39 of 52 (75%) patients with TLE who became seizure free and of 21 of 29 (72%) patients who did not.[2] Combined measurements of the NAA/Cr ratio in the ipsilateral midtemporal region, asymmetry of the NAA/Cr ratio in the ipsilateral midtemporal region, ipsilateral hippocampal volume, and hippocampal asymmetry correctly predicted the surgical outcomes of 92% of patients who experienced a >90% reduction of seizure frequency and 63% of patients who did not. The biology of the lesion appears to interact with seizure frequency to affect NAA levels in focal cortical epilepsies with lesions evident by MRI. Further studies at higher field strength may offer the spatial resolution needed to distinguish the epileptogenic regions from the metabolic changes produced by the biology of the anatomic abnormalities. When there are multiple lesions, this approach may reveal the epileptogenic abnormalities. In patients with extensive cortical malformations, detailed NAA images may offer insights into the pathophysiology of these epilepsies. Overall, the spectroscopic imaging of NAA has not offered much insight into idiopathic generalized epilepsy. The interictal changes in NAA metabolism are small, with the greatest involvement localized to the thalamus.

Glutamate Metabolism

Glutamatergic neurons contain 80% to 88% of total brain glutamate, GABAergic neurons contain 2% to 10%, and astrocytes contain about 10%.[68] Decreases in brain glutamate content, therefore, usually primarily reflect the loss of glutamatergic neurons and synapses.[59] The glutamate content of human white matter is lower than that of gray matter.[32,130] In normal brain, glutamate is known to be in high concentration in neurons, and astrocyte glutamate concentrations have been estimated in vivo to be comparatively low (<1 mM).[118] The low intraglial glutamate concentrations are maintained primarily by the conversion of glutamate and ammonia into glutamine by glutamine synthetase.[39] In addition, glutamate is oxidized by glutamate dehydrogenase (GDH) and enters the tricarboxylic acid (TCA) cycle. Neuronal glutamate is lost during glutamate transmitter release and is taken up by glia, where it is recycled by glutamine synthetase.[31] Glutamate lost from the neuron is replaced through phosphate-activated glutaminase (PAG) acting on glutamine synthesized in the glia and transported into neurons.[89,181] All glutaminases, including neuronal PAG, produce glutamate and ammonia. Ammonia is a mitochondrial toxin and is detoxified primarily by glial glutamine synthetase. If there is no neuronal loss, changes in tissue glutamate content reflect changes in neuronal glutaminase activity and indirectly the net synthesis of glutamate from glucose.

Proton Spectroscopy of Glutamate in the Human Epilepsies

The signals from glutamate and glutamine are difficult to measure because of low signal-to-noise ratios and spectral crowding. Investigators using 1.5-T clinical spectrometers and short-TE pulse sequences have used the broad signals located between 2.1 to 2.5 ppm, which comprise resonances from glutamate, glutamine, NAA, various macromolecules, and, to a lesser extent, GABA, succinate, homocarnosine, glutathione, and *N*-acetylaspartylglutamate (NAAG), as a surrogate for glutamate plus glutamine (GLX) signals. Initial studies suggested that GLX might be useful in focal epilepsies with a normal MRI.[154,194] GLX signals and the GLX/NAA ratios were reported to be above normal in the MRI-negative epileptogenic hippocampus (Fig. 2) or the epileptogenic areas of the nonlesional neocortical epilepsies. Subsequent studies reported greater variability of the GLX signals and GLX/NAA ratios, which were the same as or above normal values in various regions outside of the presumed seizure focus, that is, frontal lobes or contralateral hippocampus in TLE.[44,167,190] The GLX signals showed considerable inter- and intrasubject variability in patients with MCD or Rasmussen encephalitis.[191,195] Studies of patients with idiopathic generalized epilepsy suggest that the GLX signals and the GLX/NAA ratios of the frontal lobes are above normal.[168,169] Stronger magnetic fields, reduced magnetic field inhomogeneity (shimming), better receiver design, and advanced pulse sequences facilitate the measurement of glutamate and glutamine by improving the signal-to-noise ratio, reducing spectral crowding, and ensuring a flat baseline.[8,32,73,121,149]

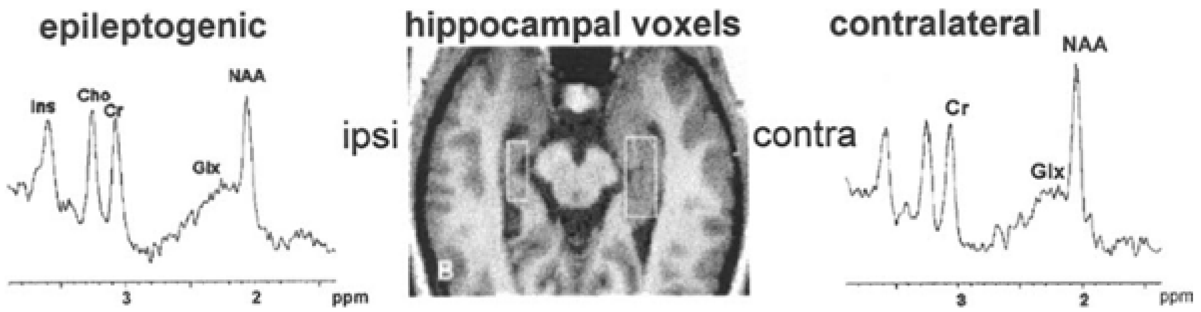

FIGURE 2. Left: Magnetic resonance spectroscopy using a short spin-echo sequence at 1.5 T with the voxel

size tailored to the epileptogenic human hippocampus with mesial temporal sclerosis (MTS). The spectrum of the contralateral hippocampus is shown on the right. In MTS, mean GLX (glutamine, Î³-aminobutyric acid, and glutathione) values are 95% of the values of control subjects and contralateral GLX values are also low (93%). In magnetic resonance imagingâ€“negative patients, mean GLX values are above normal (108%) ipsilateral to seizure onset. Cho, choline compounds; Cr, total creatine; Ins, myo-inositol; NAA, *N*-acetyl aspartate. (Adapted from Woermann FG, McLean MA, Bartlett PA, et al. Short echo time single-voxel 1 H magnetic resonance spectroscopy in magnetic resonance imagingâ€“negative temporal lobe epilepsy: different biochemical profile compared with hippocampal sclerosis. *Ann Neurol*. 1999;45:369â€“376.)

The glutamate content of gray matter, which contains a high density of synapses, is higher than values for white matter, which has less water content, more myelin, and few synapses.[130] The glutamate concentrations of extracellular fluid (ECF) and cerebrospinal fluid (CSF) are 10,000-fold lower than neuronal intracellular values. Parsing each voxel into gray matter, white matter, and CSF (segmentation) helps to reduce variability in metabolite measurements.[32,121] As expected, voxels that contain a greater fractional volume of gray matter have higher glutamate levels than those containing more white matter. In vivo measurements show that the glutamine content of white matter appears to be 50% to 60% of gray matter values. Biopsy material, however, has shown a uniform glutamine content between lateral temporal neocortex and subjacent white matter.

The Effects of Antiepileptic Drugs on Cortical Glutamate and Glutamine Levels

Antiepileptic drugs may contribute to the variability in GLX, glutamate, and glutamine levels in patients who take these medications.[131,134,136] Measurements made in the visual cortex of patients with refractory complex partial seizures, primarily temporal or frontal lobe epilepsies, suggest that glutamate levels are modestly but significantly increased in patients taking carbamazepine, phenytoin, or gabapentin and are low in patients taking phenobarbital or primidone. Whether barbiturates lower tissue glutamate content remains to be determined. Cortical glutamate content decreases by 16% to 28% with pentobarbital anesthesia.[124,165] Valproate and vigabatrin increase human brain glutamine levels by 50% to 80%. Valproate increases blood ammonia levels through its effects on human kidney glutamine metabolism. Vigabatrin is an irreversible inhibitor of GABA-transaminase and may inhibit, albeit to a lesser degree, the other transaminases, including ornithine aminotransferase, thereby raising ammonia levels.[62] Whether the use of valproate contributes to the increase of frontal lobe GLX levels in patients with idiopathic generalized epilepsy remains speculative.

Hippocampal Glutamate Content in Temporal Lobe Epilepsy

In a surgical series of 151 patients, there was >60% cell loss in MTS and 23% loss in nongliotic hippocampi.[33] The large glutamatergic principal cells are primarily lost in TLE, whereas specific populations of interneurons are preserved and undergo complex synaptic reorganization.[105] Histopathologic studies show greater cell loss and synaptic reorganization in the more anterior portions of the hippocampus.[144] The glutamate content of the resected epileptogenic hippocampus with MTS is significantly less than values measured in the nongliotic ones.[126,140] It is surprising, however, that the glutamate content in MTS, despite the 67% neuronal loss, is not significantly less than the mean values measured at autopsy (8.2 mM) or in vivo (8.0 and 8.8 mM) of nonepileptic subjects.[73,108,121] Similarly, the hippocampal glutamine content in MTS is at the lower end of normal, despite an 82% increase in glial density.[141] The neuron-to-glia ratios are significantly altered in the epileptogenic hippocampus, yet both glutamate and glutamine concentrations remain nearly normal. These findings suggest that the intracellular concentration of glutamate of the remaining cells must be markedly increased because of the loss of glutamatergic neurons and synaptic density that characterizes MTS. The loss of glutamine synthetase expression and activity in the setting of increased GFAP expression in MTS suggests that astrocytes probably contain the excess glutamate.[38,182]

Spectroscopic imaging of MTS at 4 T showed that mean hippocampal glutamate content was 30% below normal ipsilateral to the seizure focus.[121] The glutamate content of the contralateral hippocampus, which appeared normal by MRI, was 12% below normal. NAA levels were 20% lower than normal ipsilateral and the same as normal contralateral to the sclerotic, epileptogenic hippocampus. The glutamate/NAA ratios were the same for all three groups, which suggests, but does not prove, that glutamate and NAA are colocalized in the same cell type. The reductions in glutamate and NAA content were surprisingly small in view of the >60% neuron loss and >80% increase in glial density that are the hallmarks of MTS (Fig. 3).

Spectroscopic Methods for Measuring Î³-Aminobutyric Acid

Continuing MRS development has resulted in techniques for the measurement of intracellular GABA and its major metabolites noninvasively in the brain of healthy human subjects.[76,150,162,177] Recently, MR methods have been developed to image GABA.[70,161] Because of low tissue concentrations (about 1 mM), spinâ€“spin interactions (multiplet resonances), and resonance overlap (spectral crowding), quantitative measurements of GABA require specialized receiver coils and advance pulse techniques.[23,58,67] Although GABA signals may be detected using a 1.5-T clinical imager with a whole-head volume transceiver, the signal-to-noise ratios are insufficient to measure small changes in GABA content. The availability of stronger magnetic fields of 3, 4, and 7 T for human subjects, which improve the signal-to-noise ratio two- to fivefold, simplify spinâ€“spin interactions, and reduce spectral crowding, has led to more robust quantitative measurements of brain GABA.

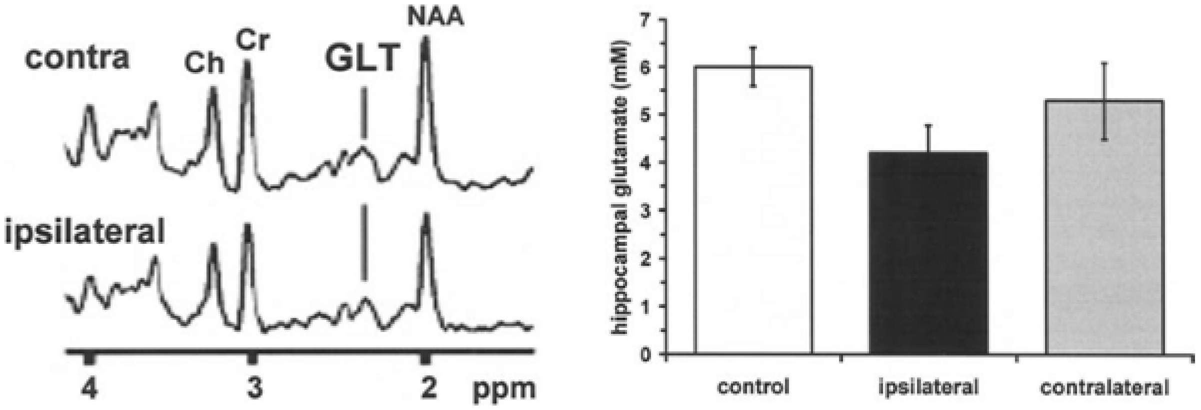

FIGURE 3. Left: Spectra obtained from the voxels marked on the image, which sampled the epileptogenic (ipsi) and the contralateral (contra) hippocampus. **Right:** The mean hippocampal glutamate content with standard error bars for 10 control subjects and 5 patients with mesial temporal lobe epilepsy. Ch, choline compounds; Cr, total creatine; GLT, glutamate; NAA, *N*-acetyl aspartate. (Adapted from Pan JW, Venkatraman T, Vives K, et al. Quantitative glutamate spectroscopic imaging of the human hippocampus. *NMR Biomed*. 2006;19:209â€“216.)

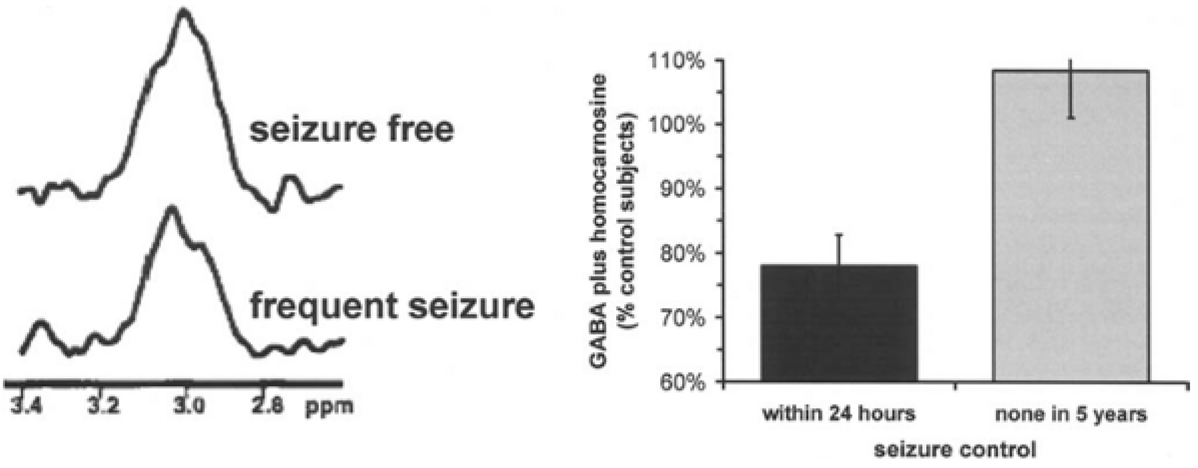

FIGURE 4. Left: The edited Î³-aminobutyric acid (GABA) spectra of two patients made from a voxel centered on the visual cortex. **Right:** Mean GABA plus homocarnosine content of the occipital lobe is below normal when measured within 24 hours of a complex partial seizure originating from the temporal or frontal lobes. (Adapted from Petroff OAC, Rothman DL, Behar KL, et al. Low brain GABA level is associated with poor seizure control. *Ann Neurol*. 1996;40:908â€"911.)

Tissue Î³-Aminobutyric Acid Levels and Seizure Activity

An increase in cytosolic GABA will enhance both vesicular and nonvesicular GABA release during seizures and slow clearance of GABA from the synaptic cleft, thereby prolonging its effects.[51,53] GABA release is decreased in the epileptogenic human hippocampus compared with the contralateral one.[35] The deficiency of GABA release was attributed in part to a dysfunction of the GABA transporter system (GAT).[36,125] However, low cytosolic GABA levels could contribute to the deficiency. Synaptic and extrasynaptic (tonic) GABA concentrations serve critical roles in modulating cortical excitability.[14,148,189]

Studies using MRS have found reduced cellular GABA plus homocarnosine levels in the human visual cortex in focal epilepsies. Two thirds of patients with refractory, focal epilepsy treated with traditional antiepileptic drugs have below-normal occipital lobe GABA levels.[136] Below-normal GABA levels in the visual cortex are associated with poor seizure control (Fig. 4).[132] Whether low GABA levels facilitate the spread of seizures from the seizure onset zone to the occipital neocortex or reflect the result of frequent generalized seizures involving the occipital cortex is unknown. Low cellular GABA levels in the visual and somatosensory cortex contribute to enhanced cortical excitability and therefore to the potential for seizures.

In patients with TLE, GABA-plus/CR ratios in the occipital lobe ipsilateral to the seizure focus were lower than the

levels measured contralateral to the epileptogenic hippocampus. Whether the lower GABA-plus/CR ratios reflect functional downregulation of net GABA synthesis or a loss of GABAergic neurons and synapses of the occipital cortex is unknown.[112] After accounting for proportion of gray matter in voxels, GABA levels were not significantly different from controls in the occipital lobes in occipital lobe epilepsy or IGE or in the frontal lobes in IGE.[168,169]

The Effects of Interictal Epileptiform Discharges on Î³-Aminobutyric Acid Metabolism

Intracellular GABA plus homocarnosine levels measured in the visual cortex remote from the presumed seizure focus in the temporal or frontal lobes are lowest in those patients with interictal epileptiform discharges on

EEG.[132] The associations between the interictal EEG and cellular GABA plus homocarnosine are similar to the associations between the EEG and the likelihood that seizures will recur. Low cortical cellular GABA levels could contribute to increased cortical excitability that allows the focal seizure to spread and become generalized. Some studies have shown that patients with IED recorded soon after a seizure are more likely to have another seizure within 2 years than are patients with normal EEGs.[179] The presence of IEDs extending beyond the area of resection correlates with poor surgical outcome in patients with extrahippocampal epilepsy.[7] These IEDs probably reflect increased cortical excitability and serve as a biomarker of epileptogenicity. Low cellular GABA plus homocarnosine, as measured by in vivo MRS, could become a useful marker for epileptogenicity.

Cortical Î³-Aminobutyric Acid Levels Increase With Electroconvulsive Seizures

Serial MRS of patients with severe depression before and after a 2-week course of electroconvulsive therapy showed that occipital GABA plus homocarnosine levels increase by 56%.[152] The finding is similar to the MRS-based observations made using an amygdala-kindled rat model, which reported a 22% increase in GABA content of the epileptogenic hippocampus and a 14% increase contralaterally 2 weeks after the onset of stage 5 seizures.[164] The increase in cortical and hippocampal GABA levels with recurrent electrically induced seizures is the opposite to the finding of decreased cortical GABA seen in patients who had a seizure within 24 hours of the MRS measurement (see earlier comments).[132] Studies of epilepsy patients that measured the rate of GABA increase following inhibition of GABA catabolism with the GABA-transaminase inhibitor vigabatrin suggest that patients with lower occipital GABA content have slower rates of GABA synthesis.[141]

Antiepileptic Drugs Have Different Effects on Human and Rodent Î³-Aminobutyric Acid Metabolism

Human and rodent GABA metabolism differs considerably in the response to gabapentin, topiramate, and lamotrigine. In healthy human subjects, gabapentin, topiramate, or lamo-trigine increased occipital cortical GABA levels within hours of the first dose.[88] These changes are sustained over 1 month of daily medication. Similar large increases in occipital cortical GABA levels were observed with the start of gabapentin, topiramate, or vigabatrin in patients with epilepsy.[135,137,138] Studies in rodents using a dose of gabapentin, topiramate, or lamotrigine several orders of magnitude greater failed to show any significant effect on cortical GABA content.[1,30,43,166] Gabapentin, however, does not increase the cortical GABA content of rat or mouse forebrain.[43,91] Gabapentin increased intracellular GABA content in human neocortex brain slices but did not increase the GABA content of rat neocortex slices prepared in the same way.[42] Caution, therefore, must be used in extrapolating negative results obtained in rodent models to the human situation, and animal models must be validated by patient-based studies. Valproate increases brain GABA in a number of animal models.[100] In patients with epilepsy, valproate is not associated with increased brain GABA.[134] Clonazepam reduced GABA plus homocarnosine levels by 24% in 90 minutes.[52] Several other drugs, including citalopram, fluoxetine, and pramipexole, have been shown to increase GABA levels in humans.[12,151,174] The observed differences between human and rodent responses to clonazepam, gabapentin, topiramate, lamotrigine, valproate, and other medications have profound implications for the use of rodent models in the development of new drugs affecting GABA metabolism.

Homocarnosine and Human Epilepsy

Homocarnosine is a dipeptide of histidine and GABA unique to brain.[79,127] Intracellular homocarnosine concentrations are higher in human brain (0.3â€“1.6 mM) than in the brains of nonprimate mammals (<0.07 mM). Human CSF total GABA levels consist of micromolar concentrations of homocarnosine and pyrrolidinone (the internal lactam of GABA), small amounts of other GABA-containing peptides, and only nanomolar quantities of unconjugated (free) GABA.[55] Rodent models contain virtually no homocarnosine and little pyrrolidinone. Homocarnosine comprises ~40% of the total GABA and histidine activity measured in human CSF and has been proposed as an inhibitory neuromodulator.[69] The reasons for the uniquely elevated intracellular and extracellular concentrations of homocarnosine in human brain remain unknown.

The Effects of Antiepileptic Drugs of Human Homocarnosine Metabolism

Few studies have addressed the in vivo regulation of brain homocarnosine concentrations. Virtually all published studies have stimulated homocarnosine synthesis by increasing brain GABA concentrations by inhibition of GABA-transaminase, thereby reducing GABA catabolism.[54] Cerebrospinal fluid GABA and homocarnosine increase in parallel following a single dose of the irreversible GABA-transaminase inhibitor vigabatrin (50 mg/kg). Human CSF homocarnosine concentrations remain elevated for >1 week.[9] Cortical homocarnosine levels increase within 4 hours of the first dose of vigabatrin (3,000 mg). A second dose 2 days later had no significant impact. Daily doses of vigabatrin (3,000 mg) increased intracellular homocarnosine levels twofold (Fig. 5).[135]

Other drugs that are not direct GABA-transaminase inhibitors also increase human intracellular homocarnosine.[137,138] Topiramate, gabapentin, and levetiracetam increase cortical homocarnosine concentrations by mechanisms that are unknown. Unlike vigabatrin, none of these drugs alters intracellular GABA concentrations in rodent models.[43,101,166] Topiramate and gabapentin increase human

cortical GABA levels within 2 hours of the first dose and homocarnosine levels rise after 1 day (with topiramate) to 1 week (with gabapentin) of daily use. Levetiracetam has been studied only after 2 weeks of treatment.

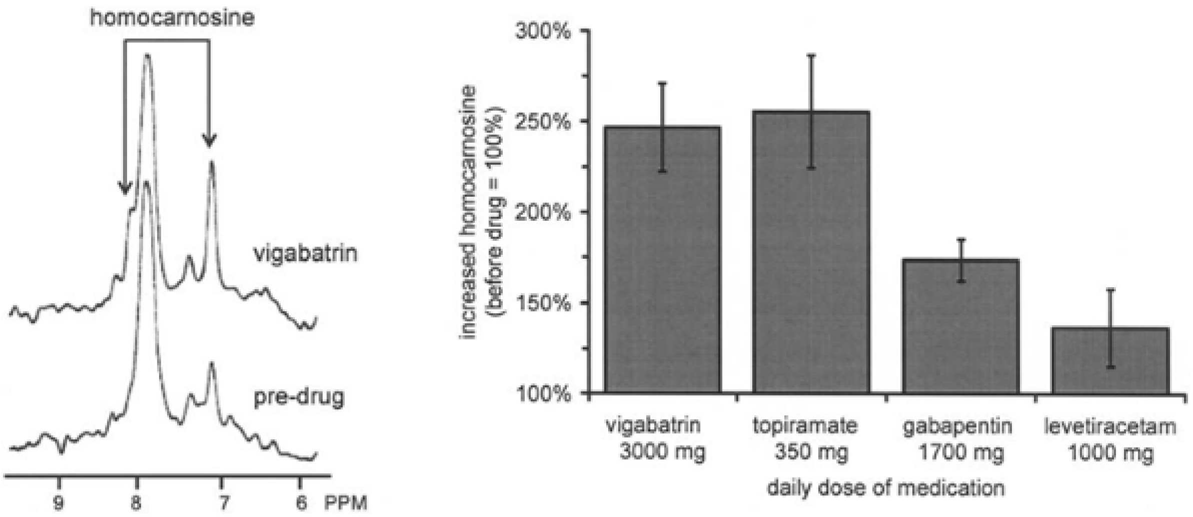

FIGURE 5. Serial spectra on the left show the increase in the signals from the histidyl resonances of homocarnosine after the start of vigabatrin. Daily add-on therapy with vigabatrin, topiramate, gabapentin, or levetiracetam increases occipital homocarnosine levels. (Data from Petroff et al.[135,137,138])

Homocarnosine and Seizure Control

Increased cortical levels of intracellular homocarnosine appear to be associated with decreased cortical excitability. Low intracellular homocarnosine and GABA levels measured in the occipital lobe using MRS are associated with frequent complex partial seizures in patients treated with valproate or lamotrigine. Patients with juvenile myoclonic epilepsy with excellent seizure control and treated with the same drugs usually have high homocarnosine levels but very low intracellular GABA levels.[139] What is unknown is whether higher levels of intracellular homocarnosine are a characteristic of patients with idiopathic generalized epilepsies, perhaps compensating for the low intracellular GABA levels and contributing to better seizure control, or low intracellular homocarnosine levels reflect frequent seizures. Patients with refractory complex partial seizures with better seizure control have higher homocarnosine levels than those with poor seizure control.[133,143] Cortical intracellular GABA levels are the same in patients who responded compared with those who failed to benefit. The findings again suggest but do not prove that homocarnosine may decrease cortical excitability. The alternative explanation is that frequent seizures may decrease the synthesis of homocarnosine or enhance its catabolism. Taken as a whole, these findings suggest but do not prove that homocarnosine may decrease cortical excitability.

Phosphorus Magnetic Resonance Spectroscopy

Cerebral metabolites detectable by phosphorus spectroscopy (^{31}P-MRS) that are relevant to epilepsy include compounds related to high-energy phosphate and phospholipids metabolism, such as adenosine triphosphate (ATP), phosphomonoesters (PME), phosphodiesters (PDE), phosphocreatine (PCr), and inorganic phosphate (Pi). ^{31}P -MRS is the best method for measuring high-energy phosphates because it completely avoids disrupting the energy state of the tissue being investigated. Because ^{31}P -MRS is completely noninvasive, serial observations are easily made, allowing dynamic measurements of the response to repeated physiologic perturbations.[146,147,158] Magnetization transfer experiments can be used to measure the rates of ATP and phosphocreatine synthesis and utilization using ^{31}P -MRS or imaging (^{31}P -MRSI).[22,93,109] Using the information provided by the chemical shifts of Pi and ATP, we can use ^{31}P -MRS to measure brain pH and intracellular magnesium concentrations in healthy and diseased conditions.[5,6,147] Dynamic measurements of phosphocreatine, inorganic phosphate, and pH using ^{31}P -MRSI complement EEG, evoked potentials, functional MRI, and other types of MRS studies, which can be made simultaneously or using an interleaved design.

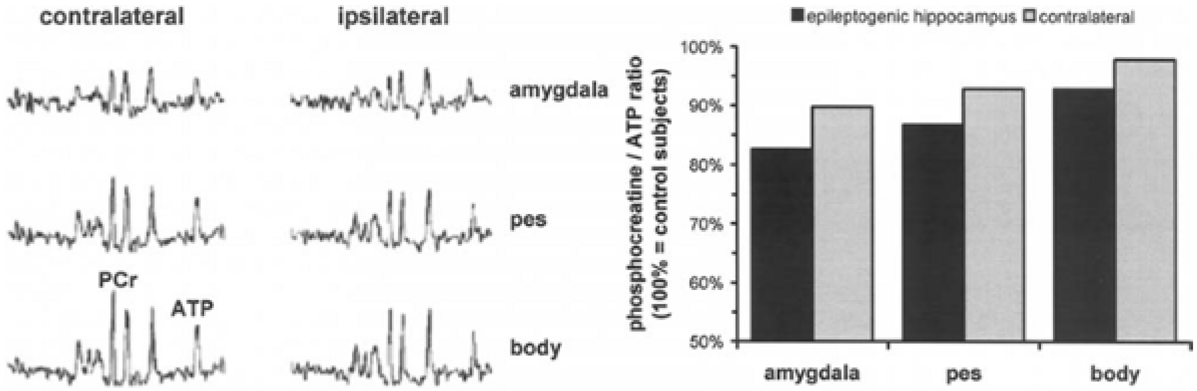

FIGURE 6. In the interictal state, the phosphocreatine/adenosine triphosphate (ATP) ratios are decreased in the epileptogenic hippocampus compared to the contralateral one. The decrease in energy state is worse in the anterior portions of the hippocampus compared with the body. (Adapted from Hetherington HP, Kim JH, Pan JW, et al. 1 H and 31P spectroscopic imaging of epilepsy: spectroscopic and histologic correlations. *Epilepsia*. 2004;45(Suppl 4):17â€“23.)

Energy Metabolism and the Creatine Kinase Equilibrium

Phosphorus spectroscopy provides quantitative data on ATP, phosphocreatine, and inorganic phosphate, which can be used directly to evaluate changes in cerebral high-energy phosphate compounds, primarily phosphocreatine and ATP. Inorganic phosphate has a chemical shift that is pH dependent. At neutral pH, Pi exists principally as HPO_4 and H_2PO_4, with an equilibrium constant (pK_a) of 6.77 in brain tissues.[129] The pH measure in vivo reflects the weighted average of the pH of all intracellular (neurons, glia, etc.) and extracellular compartments, including blood.[78] All neurons and glia express creatine kinase (CK), the enzyme that catalyzes the equilibrium among phosphocreatine, ADP, creatine, and ATP.

Through the creatine kinase equilibrium, phosphocreatine preserves a high-energy ratio of ATP to ADP by maintaining low ADP concentrations.[27,117,184] The ratio of phosphocreatine

to ATP therefore reflects the availability of phosphocreatine and serves as a marker of the energy state of the brain using ^{31}P-MRS if brain pH remains constant. The phosphocreatine-to-inorganic phosphate ratio (PCr/Pi) directly mirrors alterations in energy state (thermodynamic free energy) during pathologic conditions involving acidosis, low magnesium, or low total creatine content.

In the brain, the primary role of phosphocreatine is to shuttle energy from the mitochondria to areas of high rates of energy (ATP) consumption.[184,188,196] Phosphocreatine diffuses through the cytosol considerable faster than ATP, which may be important for the neuronal dendrites and spines and the processes of astrocytes.[75,99] Saturation transfer experiments using ^{31}P-MRS directly measure the rates of ATP synthesis, ATP utilization, and metabolite flow through the creatine kinase.[22,63,153] The forward flux from phosphocreatine to ATP doubles during seizures, which indicates that mitochondrial oxidative metabolism doubles during bicuculline-induced status epilepticus. ATP levels remained essentially the same from barbiturate anesthesia through to status epilepticus. The ^{31}P-MRS saturation and inversion transfer experiments involve applying magnetic label to the frequencies of the phosphate precursors of metabolic reactions and observing the appearance of the magnetic label in the product of the reaction.[93,109] This type of spectroscopy is used to study fast chemical reactions because the magnetic label rapidly decays after it is transferred to the new metabolite.

Phosphorus Spectroscopy During Epileptic Seizures

Ictal studies in human patients are rare.[197] Seizures cause a 33% decrease in brain phosphocreatine and a 50% decrease in the phosphocreatine-to-inorganic phosphate (PCr/Pi) ratio. Focal seizures cause lateralized decreases in the PCr/Pi ratio; generalized seizures cause bilateral decreases. Postictal spectra show increased PCr/Pi ratios, presumably due to postictal inhibition. One patient's seizures were successfully treated with intravenously administered phenobarbital during MR data acquisition, causing an immediate increase in the PCr/Pi ratio from 0.7 to 1.2. No significant alteration in intracellular pH is seen. A decrease in PCr without a change in pH implies a significant increase of ADP. Both ADP and Pi are important modulators of energy metabolism, stimulating glycolysis and mitochondrial metabolism.[41,77]

Interictal Phosphorus Spectroscopy

An altered energy state characterizes the interictal state of the involved brain regions of focal seizures. Initial interictal studies using ^{31}P-MRS found a 73% increase in inorganic phosphate and an increase in brain pH (mean alkalosis of 0.11 and 0.17 units) ipsilateral to the seizure focus without significant asymmetries between ipsilateral and contralateral temporal lobe concentrations of ATP, PCr, or PDE.[64,60,180] In a later study of eight patients with frontal lobe epilepsy, increased pH in all eight and decreased PME in seven were found in the epileptogenic frontal lobes, but no alterations in Pi levels were detected.[48] These three studies indicate that energy state (PCr/Pi ratio) is reduced in the epileptogenic region. Another group reported that the PCr/Pi ratios were lower in the ipsilateral than the contralateral temporal lobe of the patients and lower in both sides than the control data.[84] Subsequent studies also reported widespread alterations in bioenergetic parameters (decreased PCr/Pi and PCr/ATP ratios), but failed to show any alteration in brain pH (Fig. 6).[24,25,60] No significant decreases in ATP levels were reported. Phosphorus spectroscopic imaging (^{31}P-MRSI) showed that the maximal decrease in cerebral energetics appears to be centered in the epileptic focus. Reduced PCr/ATP or PCr/Pi ratio of the temporal lobe was predictive for the side of the seizure focus in >70% of patients studied.[85]

Recently, it has been shown that PCr/ATP was reduced to the greatest extent in the amygdala ipsilateral to the seizure focus, followed by the ipsilateral pes, hippocampus, and thalamus with decreasing severity. A similar pattern was seen in the contralateral hemisphere, albeit to a lesser extent.[61,120] These data are consistent with a network connecting the thalamus, hippocampus, and bilateral striatum. These observations suggest that the epileptic state is characterized by widespread mitochondrial dysfunction, particularly in regions involved in the epileptic network as defined by EEG and alterations of cerebral glucose and oxygen metabolism.

Hippocampal Excitability and Low Phosphocreatine Levels

The 5% to 15% decreases of the PCr/ATP ratios observed in the epileptogenic human hippocampus using ^{31}P-MRSI appear to have significant electrophysiologic consequences, which can be measured using a standard brain slice preparation made from the resected tissues.[193] A significant negative correlation was seen between the ability to fire multiple spikes in response to single synaptic stimulation applied to the hippocampal slice and PCr/ATP ratios measured before surgery. This type of increased â€œburstingâ€ response is rarely seen without extensive hippocampal cell loss and synaptic reorganization and is characteristic of granule cells obtained from patients with MTS. An increased bursting score that is seen with low PCr/ATP ratios reflects increased excitability of the brain slice and presumably the hippocampus in vivo. There was, however, no correlation between the frequency of spontaneous excitatory activity and PCr/ATP ratios. These data are consistent with the hypothesis that baseline asynchronous activity is not impaired by a modest reduction in the PCr/ATP ratio, but that evoked stimulation, which activates numerous presynaptic and postsynaptic elements and activates mitochondrial metabolism to restore ionic homeostasis, becomes uncontrolled with a 10% to 15% decrease in the PCr/ATP ratio. Another test of the functional reserve in the hippocampus also fails with low PCr/ATP ratios. There was a strong correlation between PCr/ATP ratios and the recovery of the membrane potential following a stimulus train, with low PCr/ATP being associated with prolonged recovery times. More-normal PCr/ATP ratios were associated with rapid rates of recovery of membrane potential following a 10-Hz, 10-second train electrical stimulus. In summary, low PCr/ATP ratios were associated with those measures of increased excitability that are associated with a high energy demand. A marker of inhibitory function in the hippocampus, inhibitory postsynaptic potential (IPSP) conductance (GIPSP), is impaired by a 5% to 10% reduction in the presurgical PCr/ATP ratio. The strength of inhibition is positively associated with PCr/ATP ratio. The fact that both bursting score and GIPSP correlated inversely with PCr/ATP ratio supports the hypothesis that both abnormal excitatory and inhibitory physiologic responses depend on altered energetics.[71]

Improved Seizure Control and Improved Phosphocreatine Levels with the Ketogenic Diet

Serial ^{31}P-MRS measurements show that successful use of the ketogenic diet improves PCr/Pi and PCr/ATP ratios toward normal as seizure control improves.[119] Whether improved mitochondrial function and energy state reflects the metabolic effects of the ketogenic diet directly or is an epiphenomenon of improved seizure control remains to be determined. However, low phosphocreatine levels or low PCr/ATP ratios clearly are associated with poor seizure control.

Creatine Supplementation Treats the Epilepsy Associated with Creatine Deficiency

Three genetic causes of creatine deficiency are known, which are associated with various forms of epilepsy.[94,157,196] All are characterized by exceedingly low or absent phosphocreatine concentrations in the brain measured using ^{31}P-MRS. Neurologic symptoms associated with creatine deficiency have some variability but present overall as mental retardation, developmental regression, behavioral problems, and epilepsy, which varies from intractable seizures in guanidinoacetate methyltransferase (GAMT)â€“deficient patients to febrile convulsions with arginine:glycine amidinotransferase (AGAT) deficiency and mild epilepsy in X-linked creatine transporter (CrT1)â€“deficient patients. When oral creatine supplementation raises brain phosphocreatine levels, monitored using serial ^{31}P-MRS, seizure control improves in parallel with rising brain phosphocreatine concentrations. Improvement in seizure control with creatine supplementation was documented in an adult patient who was diagnosed with guanidinoacetate methyltransferase deficiency at age 26 years.[158]

Phosphocreatine is Low in Mitochondrial Diseases

Epilepsy is part of the phenotype of several mitochondrial cytopathies.[81,170] The observations reported in focal epilepsies are similar to those reported in the mitochondrial cytopathies, including low phosphocreatine levels and low PCr/ATP and PCr/Pi ratios measured using ^{31}P-MRS.[3,4,40,107] Phosphocreatine levels, measured in the occipital lobe using ^{31}P-MRS, decreased with photic stimulation in patients with mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke (MELAS).[74] The response in patients with chronic progressive external ophthalmoplegia (CPEO), who did not appear to have overt CNS involvement, was more complicated.[147] Under basal conditions, the PCr/ATP and PCr/Pi ratios and brain pH were normal. In control subjects, phosphocreatine levels and the PCr/Pi ratio remained unchanged during photic stimulation and increased during the recovery following photic stimulation. Patients with CPEO differed from the control subjects in that the PCr/Pi ratio dropped during the recovery period.

Summary of the Usefulness of Phosphorus Spectroscopy in the Human Epilepsies

The interictal state appears to be characterized by low phosphocreatine levels with normal ATP levels and normal pH. The lowest phosphocreatine levels are measured in the epileptogenic regions of the brain. With the onset of seizure activity, phosphocreatine levels decrease further and an acidosis develops.[128] The low phosphocreatine levels reflect mitochondrial dysfunction, which is a potential cause of epileptic seizures. Impairment of mitochondrial function is present in the seizure focus of human and experimental epilepsy. Low phosphocreatine levels, which are seen in the epileptogenic human hippocampus, are associated with specific changes in excitatory and inhibitory neuronal responses to synchronized synaptic inputs.[193] Mutations of mitochondrial DNA that lead to the inhibition of mitochondrial oxidative phosphorylation selectively in epileptogenic areas of the human brain are associated with epileptic phenotypes.[81] Treatments that raise phosphocreatine levels improve seizure control in some patients.[119,158]

Summary and Conclusions

Multivoxel spectroscopy consumes at least 30 to 60 minutes of instrument time and requires skilled personnel for acquisition and interpretation, limiting the utility of MRS in the clinical setting. Scheduled interictal studies, rather than ictal studies that are inherently inefficient, are the most practical, unless a dedicated imager-spectrometer is available. Spectroscopic imaging

is useful when conventional neuroimaging fails to detect a lesion. N-acetyl-aspartate measurements using MRSI can lateralize the epileptogenic hemisphere with a sensitivity of 85% to 98%. Low NAA level can lateralize mesial TLE, but bilateral abnormalities are common. Severe bilateral hippocampal involvement is associated with poor surgical outcomes from anterior temporal lobe resection. Combined MRSI and volumetric MRI correctly predicted the surgical outcomes of 75% to 92% of patients with TLE who became seizure free and 63% to 72% of patients who did not.

Spectroscopic imaging of phosphocreatine and ATP can localize the epileptogenic regions and map the epileptogenic network. However, phosphorus spectroscopy requires a dedicated set of transceiver arrays and amplifiers that are not widely available. Low levels of NAA and PCr reflect interictal mitochondrial dysfunction that is characteristic of regions of the brain that are involved most frequently and intensively by seizures. NAA and PCr imaging offers clues as to where the seizures start and the areas that facilitate the spread of the seizure.

With the dissemination of 3-Tesla imager-spectrometers, lactate images may prove most useful in localizing regions of the brain that were most involved with the seizure. Lactate levels rapidly rise with seizure onset and slowly decline over many hours; post-ictal spiking further slows the decline of lactate. High lactate levels reflect populations of glia that are activated by depolarizing stimuli including extracellular potassium, glutamate, cytokines and other stimulators of glial metabolism rather than merely reflecting focal cerebral hypoxia.

Spectroscopic measurements of glutamate, glutamine, GABA, homocarnosine, glutathione and N-acetyl-aspartyl-glutamate require high-field (3-, 4-, 7-, 9-Tesla) spectrometer-imagers for quantitative measurements and should therefore be considered experimental. Similarly, dynamic spectroscopic measurements using stable (non-radioactive) isotopes of carbon (13C), nitrogen (15N) and oxygen (17O) should be considered experimental too. In vivo tracer studies using substrates labeled with these stable isotopes have revolutionized our understanding of cerebral metabolism by providing new insight into the dynamics of neural-glial signaling.

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Chapter 83

Functional Magnetic Resonance Imaging

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Introduction

The signal derived from magnetic resonance has dynamic properties that make it possible to derive physiologic information from a series of otherwise static images. The field of functional magnetic resonance imaging (fMRI) encompasses the study of such time series to interrogate otherwise covert brain processes. In both the clinical management of epilepsy and in understanding its fundamental etiology, fMRI has become an important component of the epileptologist's toolkit. In particular, fMRI applications using cognitive activation paradigms include attempts to determine language laterality, measure hippocampal function in the affected and unaffected hemisphere, and contribute to diagnosis of the epileptic focus. A growing interest in multimodality imagingâ€"particularly in combining fMRI with electroencephalographic (EEG) measuresâ€"suggests the potential for functional identification of epileptogenic zones while maintaining the MRI advantage of a relatively simple, quick, and noninvasive diagnostic procedure that is cost effective when placed in the context of other available tests. This chapter offers an introductory explanation of the fMRI method and reviews its use in clinical practice. It then addresses the likely directions for technical improvements that may ultimately make fMRI a truly comprehensive method for seizure focus localization, offering both guidance to neurosurgery and perhaps a proxy measure for medical treatment without surgery.

Static (structural) imaging by magnetic resonance imaging is capable of showing diagnostic features in the epileptic brain such as polymicrogyria, cortical dysplasias, and atrophic change in the more common mesial temporal lobe (MTL) epilepsies with great precision and resolution and is an essential part of the workup for any surgical intervention and indeed for considering the possibility of resective treatment at all.

Functional MRI is now a well-accepted method that takes advantage of the coupling between neuroelectric activity and blood flow to offer a window into the spatial distribution of brain activity. It is used widely in the cognitive neurosciences to characterize the engagement of various brain regions in tasks from visual perception to abstract cognition and ethical decision making. The sensitivity of fMRI is such that it is also possible to localize eloquent cortex at the single-subject level, making it an attractive means of performing clinical diagnostic examinations. Increasingly, fMRI has become an integral part of the surgeon's planning for resection of tumors or arteriovenous malformations because it offers reliable guidance as to which structures must be avoided to retain maximal normal brain function. Coupled with structural imaging by MRIâ€"and often an integral portion of the same examâ€"fMRI greatly improves the safety and confidence with which epilepsy can be surgically managed.

Structural images, however, frequently are not on their own sufficient either to identify any abnormality at all or to distinguish epileptogenic zones from other brain abnormalities that might be without clinical sequelae. Even quantitative analyses of MRI parameters such as T2 relaxation times or analogous analyses such as spectroscopic quantification of *N*-acetyl aspartate often are inadequate for this purpose for many reasons. For example, bilateral atrophic changes may be present in the MTL, whereas only one side may contribute directly to the seizure disorder, and bilateral resection would clearly be unacceptable. There is thus a need for improved imaging that might help to identify functional markers that can distinguish pathologic from normal brain. It is likely that advances in fMRI will be able to fill that role, effectively bridging the structural and functional data collections.

The Physiologic and Physical Bases of Functional Magnetic Resonance Imaging

We focus on functional signal interpretation in MRI because many excellent resources exist for learning the basic principles of magnetic resonance imaging. Nevertheless, it is useful to present a short review of the general MRI method to provide a better understanding the fMRI technique.

Hydrogen protons and several other atomic nuclei carry a small magnetic moment that gives them a preferential alignment to an applied external magnetic field. Furthermore, the nuclei have angular momentum, known as â€œspinâ€ (a quantum property), which is conserved and causes them to rotate or â€œprecessâ€ about any applied magnetic field at a rate governed by the â€œgyromagnetic ratio,â€ which for protons is about 42.58 Ã— 10^6 Hertz per tesla of applied field. These two properties are exploited in collecting the magnetic resonance signal.

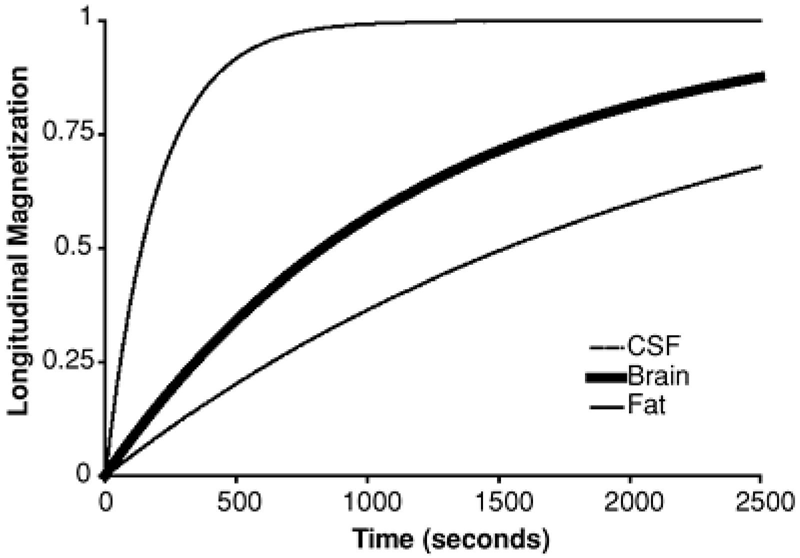

FIGURE 1. Tissues become magnetized (i.e., the proton magnetic moment reaches equilibrium) over an extended period of seconds. This so-called longitudinal relaxation rate can be characterized by a single time constant. CSF, cerebrospinal fluid.

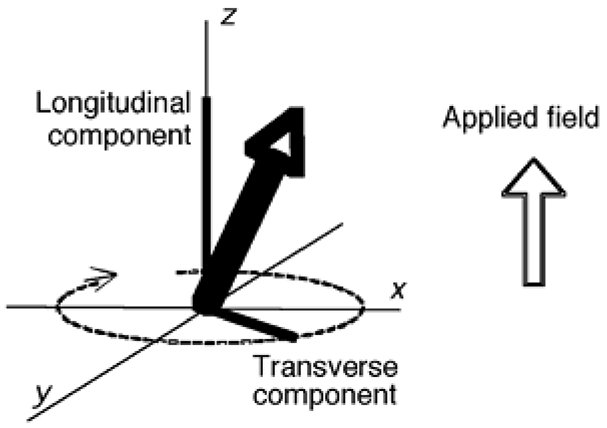

FIGURE 2. When protons are placed in a magnetic field, their angular momentum causes their magnetic moment to precess about that field. Conventionally, it is convenient to decompose the net proton magnetization into a stationary, *longitudinal*, component aligned in the direction of the applied magnetic field and a rotating, *transverse*, component that precesses about it.

When a sample, or a patient, is placed into a magnetic field, the protons immediately realign to the new field such that their precession is about the axis of the applied field (which is conventionally called B0). However, this is not an equilibrium condition because half of the protons will have their net magnetic moment in the same direction as the applied field (spin â€œupâ€) and half will be lined up opposed to it (spin â€œdownâ€), which is a lower energy state. Instead, there is a relaxation process (similar to thermal cooling) that takes some time to occur. The approach to the new equilibrium state follows an exponential time course (Fig. 1). The rate at which a tissue or other material approaches its equilibrium is considered to be characteristic of that sample and differs widely among human body tissues. The relaxation time (which is the inverse of the rate) can be conveniently and often very accurately described by a single parameter known as T1. The parameter T1 itself depends on factors such as the magnetic field strength, the temperature,

and micro and nanostructural physical properties, as well as on the presence of other magnetic or paramagnetic materials.

This approach to equilibrium is known a longitudinal relaxation. At equilibrium each of the individual protons will be precessing about the axis of the applied field in either the up or down direction (Fig. 2), such that the longitudinal components of their orientation are parallel. As the protons spin, however, their horizontal or transverse component is rotating within the plane orthogonal to the applied field and will be different for each of the spins in the sample. If we examine the vector sum of all of these magnetic moments, there will exist only a stationary vector in the longitudinal direction.

However, it is possible to create a condition in which the transverse components are aligned. This is performed by applying a second magnetic field (B1) rotating about the B0 field at the same rate as the spins are precessing. If the B1 field is left on for the correct duration at the correct amplitude, this can create a condition essentially equivalent to having rotated the longitudinal magnetization of the entire sample into the transverse plane, where it precesses about at a frequency determined by the gyromagnetic ratio. This time-varying signal can be detected easily by its induction of an electrical current into any nearby conductor. Typically, the signals in clinical imagers are in the range from tens to hundreds of megahertz, where they are detectable as radio energy. The B1 pulse is also therefore a â€œradioâ€ signal. When applied, it moves the sample out of equilibrium (because the longitudinal component is reduced when it is rotated into the transverse plane), and it is therefore called an â€œexcitation pulseâ€ or an â€œexcitatory RF (radiofrequency) pulse.â€ When the longitudinal component is rotated completely into the transverse plane, it is reduced to zero; this condition is known as a 90Â° pulse.

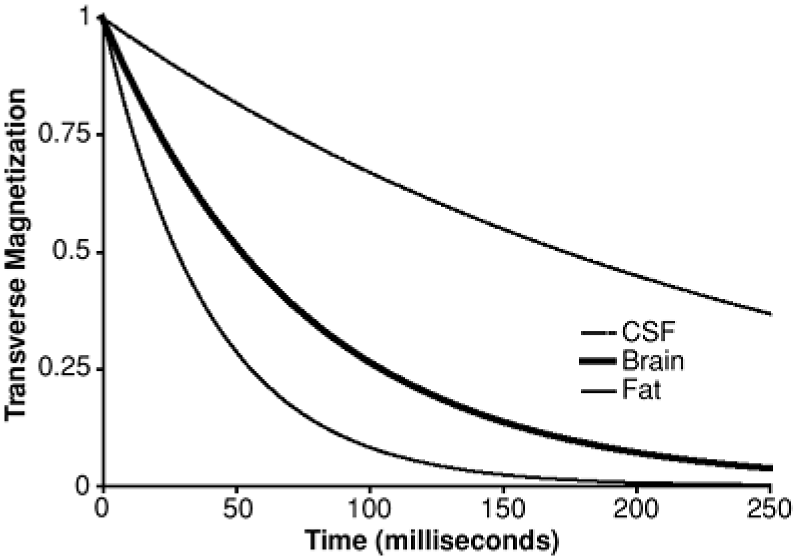

FIGURE 3. The loss of transverse coherence of multiple proton spins results in an exponential decay of the resultant magnetic resonance signal. The decay rate, T2, is tissue dependent, such that the T2 of cerebrospinal fluid (CSF), for example, is >10 times that of fat.

Even very tiny spatial variations in the magnetic field make the condition of transverse coherence unstable because over time the differences in spin frequency cause individual spins to precess more or less rapidly than their neighbors, so that the net summed magnetic moment decays over time. Like T1, this magnetic decay rate differs among tissues and can be described efficient by a single rate constant (for each tissue), known as T2 (Fig. 3).

Because the signal strength depends on the coherence of the transverse orientation of individual spins, the process of transverse decay results in a decrease in MRI signal. The time from RF excitation to signal detection is called TE and offers a means to adjust image contrast. Specifically, with a te near zero, the signal from all tissues is independent of T2, whereas when te is increased, the signal is increasingly dominated by the tissues with the longer T2; thus, adjusting te adjusts the T2-dependent contrast.

It is also possible to adjust the degree of T1-dependent contrast in MR images. Consider the case of a series of 90Â° pulses. After each, no longitudinal magnetization remains. Thus, the longitudinal relaxation process must start anew. If the time between excitatory pulses is short (compared to T1), the longitudinal equilibrium will not be reached by the time of the next RF pulse, and thus the MRI *signal* (whose magnitude is determined by the longitudinal magnetization prior to the pulse) will be reduced. The term â€œtrâ€ is used to describe the time between repeated RF pulses. In general, this means that tissues whose T1 is long compared to will have less signal (and will appear dark) compared to those whose T1 is short.

Functional Magnetic Resonance Imaging Contrast

Both T1 and T2 can be used to expose brain activity; at present, however, fMRI procedures that exploit changes in transverse

relaxation (T2) rates are most common. We present the physical principles of both methods in brief here.

Like positron emission tomography (PET), single photon emission computed tomography (SPECT), and autoradiography, the ability of fMRI to detect brain activity depends on the empirical fact that increases in synaptic activity are followed by localized increases in blood flow. Current thinking is that for excitatory synapses the relationship between electrically coupled synaptic activity and blood flow is approximately linear.[11,34,52] Although the deviations from linearity of the fMRI response overall are important,[9,17,51,53,64] they will not be considered in detail here. Although the biophysics that couples neuronal firing and blood flow is still the matter of some controversy (see, e.g., Villringer[72]), the basic findings are very robust.

In its most commonly used form, fMRI is performed by using imaging protocols that confer a moderately strong T2 sensitivity to the image contrast. (More precisely, T2â€² contrast is used, which emphasizes signal losses from local perturbances of the magnetic field rather than from interactions among the nuclear spins. For more detail, see, e.g., Buxton,[12] Jezzard et al.,[43] or the older review by Cohen and Bookheimer.[18]) It is well known that in its deoxygenated state, hemoglobin has a magnetic moment equivalent to four unpaired nuclear spins; when oxygen is bound to hemoglobin, there is a significant reduction in the magnetic moment (to zero).[58] When deoxyhemoglobin is present, the magnetic field is disturbed locally, so that nearby spins precess more rapidly than those at a greater distance, causing the MR signal to decay rapidly and the apparent T2 of adjacent tissue to be shorter: Deoxyhemoglobin thus causes the magnetic resonance images to be slightly darker.

It is believed that the effects of neural activity on the magnetic resonance signal are coupled indirectly, as follows. When the energetic needs of the brain parenchyma are increased secondary to neural signaling, oxygen substrate (and possibly other factors) is delivered by the capillaries to the brain. As a result, the intraluminal oxygen tension is reduced and more of the capillary hemoglobin is in the deoxygenated state. The vascular system responds by increasing blood flow to the affected region, which keeps the substrate concentration in the blood higher in order to deliver more to the brain parenchyma. However, in the case of increased flow, the net result in the postcapillary arterioles is for the oxygen content to *increase*.[13] Because the oxygenated hemoglobin disturbs the magnetic field less, the transverse relaxation times are increased and the magnetic resonance signal is stronger. Thus, the consequence of increased neural activity is a brighter MR image. This method overall has been called blood oxygenation levelâ€“dependent (BOLD) fMRI.

The neuronally driven signal changes in MRI are typically 1% to 2% of the background signal level, depending on factors such as field strength as well as on experimental conditions, such as the magnitude of the stimulus that drives the neuronal signal. In practice, with only a few data points, this change is readily detectable when images are compared in active and baseline conditions. A series of MRI pictures acquired even from a nonliving subject, however, will show small signal intensity fluctuations from noise. Biologic baseline processes, such as respiration and cardiac pulsation, further vary the signal. On top of these, there appear to be spontaneous changes in the neurovascular signal itself, so that on average, the baseline signal fluctuates by 1% or so. Thus, statistical means ordinarily are used to detect the fMRI signal by assessing the significance of the change in mean signal when a series of images is acquired under rest and active conditions.[6] There are many tools for efficient statistical analysis of fMRI data, but they will not be considered further here. Note, however, that this method generally requires the comparison of MRI signal in two (or more) conditions to get a single result that localizes neuronal activity. Practiced in this manner, BOLD fMRI cannot show baseline metabolic state.

An alternative use of MRI exploits changes in apparent T1 during neural firing. Although it is currently less popular, it was actually presented at the time of the very first BOLD studies.[47] When a *slice* of tissue is subjected to repeated RF excitation pulses at TR short compared to T1, the recovered signal is less than at long TR (or short T1), which imparts T1-dependent image contrast, as noted earlier. If the excitatory pulses are presented slicewise, however, the replacement of blood within the slice by blood that flows in from elsewhere results in an overall stronger MR signal because the inflowing blood has its full magnetization at the time of the excitatory RF pulse, whereas the stationary tissue does not. T1-weighted imaging thus provides a means of visualizing blood flow more directly (as opposed to through its secondary effects on oxygen tension).

Consider now a different experiment, in which the blood outside of the target slice is â€œlabeledâ€ by exposing it first to an excitatory RF pulse. In this case, the replacement blood in the slice can be distinguished from the stationary tissue. It is important that under a variety of more or less tenable assumptions, the images derived from these flow-dependent strategies are in principle quantitative, expressing absolute perfusion in units convertible to milliliters of flow to milligrams of tissue. Several methods of arterial spin labeling (ASL) have been presented in the current MR literature, and they have been sparking a great deal of research interest.[21,24,26,77,79]

Functional MRI by BOLD and ASL share several important features. First and foremost, they rely on entirely endogenous mechanisms for contrast, unlike PET and SPECT, which require the patient to receive radioactive tracers either intravenously or by breathing. fMRI may therefore be performed repeatedly on single subjects without fear of inducing tissue or genetic damage. The fMRI methods may be performed on existing MRI devices, generally without any modification, making the technique widely available in hospital and university settings. Because the same instrument is used for fMRI and for structural MRI studies, the burden to the patient and clinical staff are much reduced and the cost is consequently less as compared to scheduling separate functional studies by alternative means such as PET, SPECT, magnetoencephalography (MEG), or others.

Applications of Functional Magnetic Resonance Imaging to Epilepsy

Surgical Planning

fMRI holds tremendous promise in the presurgical evaluation of patients with epilepsy. In principle, fMRI has the potential to augment or replace the Intracarotid Amytal Procedure (IAP, or Wada test) and electrocortical stimulation mapping in presurgical and intraoperative testing of eloquent cortex. However, fMRI differs in a fundamental way from these methods, in that both involve disruption of an ongoing process, thus reflecting brain regions that, if lesioned, should produce clear deficits. In contrast, fMRI reveals all regions associated with task performance, some of which may be involved in but not critical to task performance, or which may have redundant systems that can compensate after resection. In general, although numerous fMRI studies show associations between fMRI results and those of invasive methods at the group level, very few demonstrate the sensitivity and specificity of these techniques. Fewer still have examined a sufficient number of patients with atypical language organization to claim adequate reliability in these cases. Considering that numerous factors specific to the imaging center will affect the generated results (such as MRI field strength, stability, choice of paradigm, analysis approach, to

name a few), the routine use of clinical fMRI to make independent clinical decisions is probably not warranted at this time. Here we discuss some of the recent studies using fMRI for surgical planning and the outstanding problems that remain to be solved.

Language Lateralization

fMRI holds the promise of replacing some of the more invasive diagnostic procedures in patients with epilepsy, specifically the intracarotid Amytal procedure (IAP) and intraoperative electrocorticography. One hurdle in developing the technology is that of finding a reliable way to determine language laterality. Numerous language activation studies in normal volunteers (see Cabeza and Nyberg[14] for a review) present paradigms that reveal a lateralized response at the group level consistent with left hemisphere language in normal right-handers. Several studies have used fMRI during language activation in normal volunteers to demonstrate hemispheric dominance.

Binder et al. performed fMRI on 22 epileptic patients who also received a sodium Amytal (Wada) test to determine language lateralization. For the Wada test, participants performed four language tasks: (a) object naming, (b) repetition, (c) following commands, and (d) reading sentences. The authors determined language lateralization by rating both task performance and paraphasic errors for each hemisphere, generating a laterality index. During fMRI, they used a different set of language tasks, previously reported in normal volunteers: (a) tone discrimination (control condition) and (b) a semantic judgment task, determining whether a heard word was â€œnative to the U.S.â€ or â€œused by people.â€ A correlation analysis identified voxels significantly associated with task performance. Based on the number of voxels in each hemisphere that exceeded threshold, they calculated a laterality index. The authors reported that all patients showed concordant fMRI and Wada results. Eighteen of the 22 patients had strong left hemisphere dominance on both fMRI and Wada test. The remaining 4 patients showed less strong or atypical language dominance on fMRI; 3 of these patients had a right hemisphere language bias. Although the authors reported that these patients also showed â€œlessâ€ or â€œatypicalâ€ laterality on Wada measures, it is unclear whether, categorically, these patients were felt to have right hemisphere dominance on either measure. The question of mixed dominance was also not addressed directly. Although patients showing less strong laterality did so on both measures, whether this represented â€œbilateralâ€ representation or some other pattern is not clear. Because these are the very patients who are at risk for postoperative deficits, characterization of their results on both fMRI and

Wada might shed light on language organization in such patients.

Another study compared fMRI with Wada testing in seven patients with intractable seizures. Based on the Wada test, four patients were determined to have left hemisphere (LH) dominance, and three had right hemisphere (RH) dominance. During fMRI, participants were presented words visually and had to make a perceptual versus a semantic decision for each stimulus, and these images were subtracted. The authors found activation in frontal language areas that corresponded to language lateralization as determined by the Wada test, suggesting that fMRI can be used in lieu of the Wada exam to determine language lateralization. The regions activated in this study were similar to those observed in word generation studies performed in normal volunteers, and the method appears to support the use of such a paradigm to determine the lateralization of frontal language areas. In contrast to the Binder et al. paradigm, the semantic judgment task produced no activation of the posterior language areas. This is unfortunate because mixed-dominance patients may show differential laterality of anterior versus posterior language areas.[57] Neither study mentioned the basal temporal language area. Located in the inferior temporal gyrus, this region is close to the resection zone in many temporal lobe surgical procedures and is consequently an important region to study. Artifacts in the basal temporal area are accentuated in susceptibility-weighted imaging and may interfere with the ability to measure functional activation in this region. The largest fMRI study examining language laterality was reported by Woermann and Jokeit.[78] They scanned 100 epilepsy patients, all of whom underwent an IAP. The fMRI paradigm used a covert word generation task using 10 activation and rest blocks. Results were analyzed by visual inspection and rated as typical (left), atypical (right or bilateral), or artifactual. They found a 91% concordance rate in scans that were not artifactual, four cases in which lateralization was discordant (4%), and four in which either the fMRI or the IAP was not lateralizing. Notably, with this paradigm, 82% of patients with fMRI lateralization showed bilateral activation interpreted as greater on one side. The authors also noted a high failure rate of correct fMRI lateralization in patients with extratemporal epilepsy (25%).

Choice of Task

There is little agreement on which task is best to use for language lateralization in fMRI. Many studies have used a covert word generation task that has been studied repeatedly in normal controls. This paradigm has the advantage of requiring little in the way of presentation devices; however, it is acknowledged to be a poor activator of Wernicke's area. Indeed, a prior PET study showed that this task actually produces signal decreases in posterior temporal cortex.[28,68] A semantic decision task was compared to tone discrimination, finding a high degree of left lateralization among normal volunteers and patients with epilepsy; bilateral activity was found in most participants. They used a lateralization index (LI) approach, which compared all voxels in the two hemispheres.

Lehericy et al.[49] compared three language tasks in their correlation with IAP laterality across a range of regions. Different tasks produced different LIs across these regions; a fluency task showed a reliable L:R ratio of the number of voxels activated in the frontal lobe in the strongest of the word generation tasks (semantic fluency); other tasks, including story listening and silent repetition, showed less fMRI asymmetry in frontal cortex and correlated less well with IAP results. Compared to frontal cortex, activations in the temporal lobe regions did not lateralize as well and were less correlated with the IAP results; this may have reflected the inclusion of auditory cortex, which is bilaterally represented.

Although most of these studies use a single fMRI task to determine language laterality, a recent study[29] argued that a task-panel approach improves the predictive value of fMRI in determining laterality. Participants performed between three and five different tasks, including a generation task, reading comprehension, and auditory comprehension. The scans were interpreted by raters looking at the thresholded images rather than through a predetermined algorithm for calculating LI. Although agreement was somewhat better than reported in other studies, in several cases, fMRI results appeared to be bilateral to all raters when the IAP was unilateral, and there was 1 case of 26 in which a left-dominant fMRI result was at odds with the bilateral IAP. However, in no case did the fMRI yield unilateral data that contradicted a unilateral IAP, suggesting that the use of multiple activation tasks may indeed improve clinical utility of fMRI for determining laterality.

Metrics of Laterality

Most investigators calculate the number of voxels exceeding a statistical threshold to enter into a formula for laterality indices. This metric does not take into account the magnitude of the blood flow response or how tightly the fMRI changes correspond to the ideal function describing response to the task. One study comparing these metrics found that the number of voxels above a statistical threshold was an extremely unstable metric, with a standard deviation of 74% in primary visual and motor cortices, where the greatest stability would be expected.[19] In contrast, the slope of the regression line between the modeled time course and the data (the beta value) was far more stable (SD 14%). Thus, the most commonly used approaches, although effective in group statistics, may be considerably more problematic when drawing interpretations at the single-subject level.

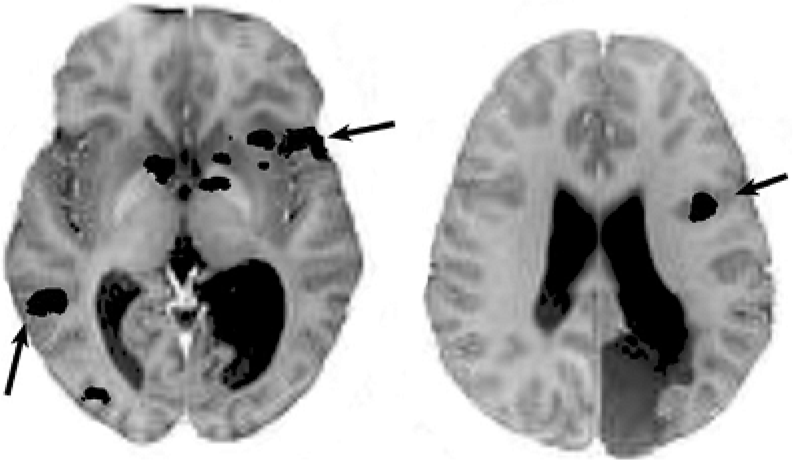

FIGURE 4. Congenital left hemisphere lesion shows anterior left, posterior right, hemisphere activation on functional magnetic resonance imaging.

The location of regions of interest (ROIs) chosen for determining laterality indices will also affect their validity. For instance, whole-hemisphere ROIs given a single task will include regions irrelevant to language function such as visual or auditory areas; because these are bilaterally organized, they will tend to reduce true interhemispheric differences in the LIs. Other brain regions involved in but not essential to language may include dorsolateral prefrontal cortex, which is involved in working memory but is also engaged when the task is challenging, may not correlate with language laterality but may be mistaken for nearby language areas.

Calculated laterality indices to obtain a single number to determine hemispheric dominance, whether in regard to Wada testing or fMRI, tend to assume a model of language in which language is either in one hemisphere or is bilateral. In our experience, bilateral or mixed-dominant language is rarely suggestive of overlapping representations in both hemispheres. Rather, patients tend to have one aspect of language, for example, expression or initiation of speech, in one hemisphere with comprehension in the other.

Such a case is presented in FIGURE 4. Here, a developmental lesion (arteriovenous malformation [AVM]) in Wernicke's area led to language reorganization. The fMRI shows left-dominant activity in the inferior frontal lobe but RH activity in the posterior temporal lobe. Such mixed dominance is usually found in cases with a clear structural lesion in eloquent cortex involving only one language area, and suggests that reorganization in a patient with genetic left hemisphere language will tend to be specific for the function that cannot be performed in the dominant hemisphere rather than global. Simple laterality indices will not capture such patients and can lead to incorrect interpretation of fMRI data. An alternative is separately to measure laterality in anterior versus posterior regions. Such an approach was taken by Pouratian et al.[59] in a group of AVM patients with preoperative fMRI and intraoperative validation with electrocortical stimulation mapping (ESM).

Whereas left hemisphere language dominance is virtually assured in right-handed, normal volunteers, there is a much higher incidence of right hemisphere or mixed language dominance among patients with temporal lobe epilepsy.[54,57] Only a few patients with atypical language organization have been studied. This sample is too small to determine language dominance in the more difficult cases using fMRI alone. Another issue that has not been explored well is the effect of language impairment on fMRI results. How language deficits might influence the magnitude and perceived direction of laterality is not known. Most patients with right hemisphere or mixed dominance have reorganized language because of a lesion, and patients with lesions in the left hemisphereâ€"whether or not language has movedâ€"may have deficits in language processing.

Base Rates and Right Brain Speech

Although many studies have reported large cohorts of individuals with Wada and fMRI concordance, few have had sufficient numbers of participants with confirmed right brain speech (RBS) to establish sensitivity and specificity figures in these cases. The base rate of RBS in the normal population is estimated to be quite low (<5%), but it is significantly more common among left-handers and among patients with epilepsy of either handedness. A study by Sabbah et al.[65] recruited left-handed epilepsy patients with a high rate of RBS; they compared fMRI and IAP laterality indices in 20 epileptic patients, of whom 11 were left-handed. On the Wada test, 7 of the left-handers and 2 of the right-handers had RBS. Using a word generation paradigm (both semantic and letter-cued), they compared the number of all supratentorial voxels in the hemispheres to derive an LI based on the fMRI results. The authors chose an arbitrary cutoff threshold LI of 20 (scale from -100 to 100), which correctly classified 19 of 20 individuals as having concordant fMRI and IAPs; 1 individual with RBS had an equivocal laterality index on fMRI, and several others were correctly categorized but had relatively low laterality indices. The Wada analysis did not appear to allow for mixed-dominant patterns, and there are no studies examining IAP/fMRI concordance in this population. Nonetheless, results from these studies do suggest that the larger majority of epilepsy patients show strong fMRI laterality using a variety of fMRI approaches; these cases show very high concordance with IAP laterality. Thus, for the purpose of establishing language laterality in epilepsy, especially mesial temporal epilepsy, a high laterality index is probably as reliable as the Wada test. In cases of neocortical epilepsy, space-occupying lesions, or more moderate laterality indices, fMRI has less potential for determining language laterality definitively.

Performance and Brain

Cortical stimulation studies typically use stimuli that the patient can perform accurately at baseline; consequently, errors during stimulation are sufficiently anomalous that they can easily be attributed to the stimulation. In activation imaging studies, task difficulty and performance variables affect the magnitude of the blood flow response; consequently, if performance levels and their effects on blood flow are not well characterized, results are interpretable. Consider, for an example, an early PET study. In this study, individuals were presented visual stimuli at different repetition rates. The magnitude of the blood

flow changes was proportional to the amount of motor activity: The harder the person worked, the greater did the blood flow change. Cognitively challenging tasks have been found to show greater changes in blood flow than simple tasks.[10] Given multiple trials of the same word generation task, Raichle et al. found differences in the magnitude and patterns of regional cerebral blood flow (CBF) using PET.[62] This finding has important implications for patients with epilepsy: There are typically neuropsychological impairments associated with the seizure focus, and consequently there may be performance impairments during the fMRI procedure. Tasks that are too simple may fail to produce sufficient signal changes; tasks that are overly practiced may show changes in areas other than those of interest; and tasks that are too difficult may result in negative results if the target cognitive skills are not sufficiently engaged. Therefore, to draw useful clinical conclusions about the function of a target brain region, one must know which tasks produce CBF changes in the target cortical region, which experimental parameters affect the expression and magnitude of those CBF changes, and how variations in task difficulty and subject performance affect the hemodynamic responses.

Memory Patency

Although fMRI applications for determining language laterality in epilepsy are rapidly moving toward clinical applicability, significantly less research has supported a role for fMRI in determining memory patency for presurgical evaluation. Because most centers use the IAP for both language and memory determination, the possibility of replacing the IAP with fMRI depends on valid and reliable memory activation paradigms that are predictive at the single-subject level. Although no studies have clearly developed an fMRI memory test with the sensitivity for within-subject interpretation, a rapidly increasing number of studies have explored memory lateralization paradigms at the group level leading toward this goal.

The first fMRI study to demonstrate significant memory-related activation of the medial temporal regions used a novel picture-encoding paradigm[69] in which participants viewed complex visual scenes in comparison to viewing two scenes repeated throughout the experiment. Although the results were primarily observed in the parahippocampal gyrus (PHG), and the resolution was not sufficient to disentangle PHG from hippocampus (HC) proper, the study provided the first strong indication that memory-related activity could be observed with fMRI.

This paradigm was adapted in several studies of patients with epilepsy.[61] An initial report of 10 epilepsy patients undergoing fMRI and IAP found asymmetry indices in the same direction for all patients, including 2 whose asymmetry was opposite to that predicted by the seizure focus (in contrast, normal volunteers had equal left and right activation). However, in a larger series of 36 patients undergoing fMRI, 27 of whom also underwent IAP exams, fMRI correlated with the IAP but the magnitude was relatively low (0.35), and the congruence between modalities was only moderate.

Richardson et al.[63] used groupwise activation data to create a valid region of interest, which was then applied to within-subject data using an aversive-word-encoding paradigm in an event-related design. During a retrieval condition, they presented a longer list of words and asked participants whether the words were on the encoding list, and, if they were, could they recall the encoding episode or did they have a â€œfeeling of knowing,â€ which is not associated with hippocampal activity.[25] These data were then used to evaluate fMRI activity for Remember versus Know items during encoding. Although visual inspection of the fMRI maps suggested that they were too noisy clearly to identify a lateralized memory response, the ROIs derived from the group data distinguished patients from controls. Across the group, LH activity predicted memory decline after surgery in a subset of patients who had surgical resections. Although the study did not determine, on a single-subject basis, which HC supported memory or whether a resection was possible, it does suggest a general approach to improving the predictive validity of fMRI in temporal lobe surgery; moreover, the results indicate that the most sensitive area for encoding is the left mid-anterior HC proper.

Using an imagery-guided navigation task, Jokeit et al.[44] studied activation in the left and right medial temporal regions in controls and patients with unilateral temporal lobe epilepsy (TLE). Although controls did not differ in lateralization, the patients showed decreased MTL activity in the side of the seizure focus (this activity was predominantly in the PHG rather than the HC); 90% of patients showed this pattern. However, two patients with left TLE and one with right TLE were misclassified. Furthermore, the magnitude of the lateral asymmetries was very small in many patients, suggesting that this approach, although promising, was not sufficient to avoid performing an IAP in most patients.

As paradigms evolve that produce activation of the normal hippocampus during memory processing, it will again be necessary to determine the relationship between performance and activation in patients with hippocampal damage.[76] One recent study in Alzheimer patients, who also have HC damage and atrophy, showed that when performance was controlled (by post hoc sorting of individual responses), AD patients showed as much activation as controls, whereas typically they show much less. Thus, paradigms that fail to account for performance may incorrectly show below-threshold activation. Furthermore, imaging memory activation in the hippocampus may be especially difficult in patients in whom the hippocampus is atrophic. Because the signal magnitude is proportional to the amount of tissue in each voxel, there may be a smaller proportion of potentially activating hippocampus in these patients. Thus, there is a greater risk of false-negative effects, a potentially dangerous error for with-in subject fMRI.

In summary, determining memory patency using fMRI is a critical step toward replacing the Wada test, but there remain serious concerns with the potential to cause harm. The base rate of Wada failure due to patients failing the memory test is quite low in our experience; thus a large degree of concordance between the Wada and fMRI memory evaluation is expected. The critical test for fMRI, however, is its ability to identify the Wada failures with essentially perfect sensitivity. A large sample of patients who have failed the Wada test is therefore needed, and no studies to date have a sufficient sample of such patients to allow meaningful conclusions as to the value of fMRI for this purpose.

Prediction of Seizure Focus and Clinical Outcome

Memory performance on the Wada test has been shown to predict seizure focus.[80] Bellgowan et al.[7] used fMRI to differentiate known right and left TLE patients, using a semantic-encoding paradigm in which they made a semantic decision about auditorally presented words in comparison to a tone discrimination task. The discrimination was made on the basis of the responses in the right TLE group, who showed significant left hippocampal activation in comparison to right hippocampus; the left TLEs did not show MTL activity. This study suggests the potential for fMRI to add to seizure focus localization in TLE.

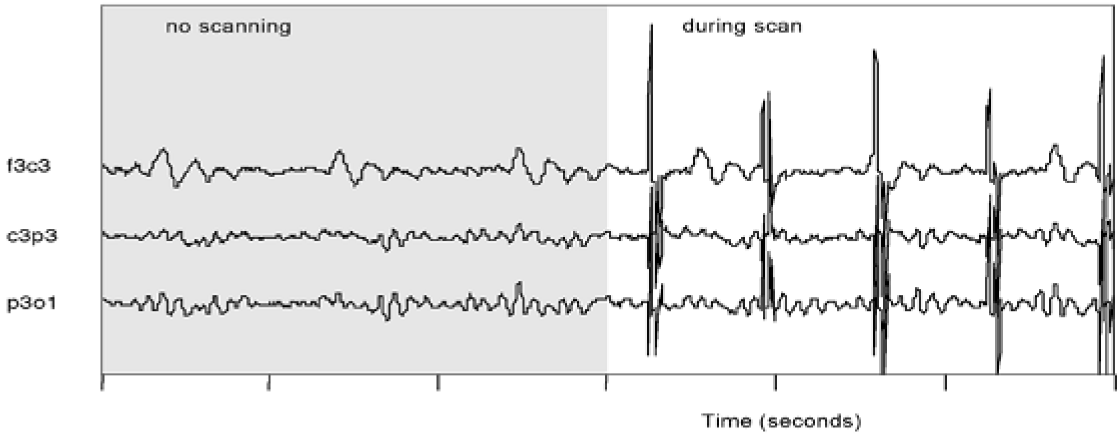

FIGURE 5. Electroencephalogram (EEG) recorded in the magnetic resonance imaging device contains artifacts from multiple sources. **Left:** Recordings from three electrode pairs, as indicated, while the patient rests within the scanner, but during a period when there is no acquisition taking place. **Right:** The EEG record during scanning. Note the prominent artifact in the left panel with a period of about 1 second, which derives from the ballistocardiogram. The scanning periods show a much larger artifact (already attenuated by spectral filtering) that derives from the switching of magnetic field gradients required for image formation.

Rabin et al.[61] used fMRI during a picture-encoding para-digm to determine whether asymmetric activation in a broad MTL region including HC, PHG (encompassing entorhinal and

perirhinal cortex as well), and fusiform, or a selective HC region, correlated with postsurgical memory outcome. Asymmetry in activation in the broader MTL region significantly correlated with memory performance on the fMRI task postsurgically. Although these predictions were made at the group level, the possibility that memory fMRI may add to clinical decision making in assessing postoperative risk is an important new step toward this goal.

Imaging Abnormal Tissue

Can abnormal cortex be eloquent? A recent study of five patients with polymicrogyria in language or motor cortex showed significant fMRI signal increases within the abnormal cortex.[4] AVMs or large tumors creating a mass effect may decrease the magnitude of the blood flow response, in some cases making laterality of language difficult to determine.

It is not clear how common pathologies in epilepsy such as medial temporal sclerosis affect fMRI activation, what degree of cell loss is necessary to change the fMRI response magnitude, or how great this decrease must be to conclude that the tissue is nonfunctional.

Intrahemispheric Localization of Language

In many patients, the seizure focus is known, and the critical diagnostic question becomes, What functions are subserved by this brain region? Eloquent cortex mapping relies on our preexisting hypotheses about what functions should be near this cortical region based on our knowledge of functional locations because we cannot practically test all known or putative brain functions for a given region. Not surprisingly, the best functional mapping is done in well-characterized functional regions such as primary motor and primary visual cortex.

Only a few cases have been reported that used functional MRI in epileptic patients for intrahemispheric functional mapping. Morioka et al.[56] used fMRI to determine function in a patient with en epileptogenic lesion in the central sulcus. They mapped both sensory and motor function using fMRI, MEG, and transcranial magnetic stimulation. All images were mapped onto MRI to determining colocalization of the functional zones. Both motor and sensory maps from fMRI matched those of the other techniques in this patient.

Puce et al.[60] mapped extrastriate cortex in 12 patients with epilepsy using fMRI. Patients were presented human faces in multiple trials, interspersed with presentations of scrambled versions of the same stimuli. They looked for cortical regions responding specifically to human faces. The authors found face-sensitive regions in the fusiform and inferior temporal gyri in 75% of their patients, with additional regions of activation in several occipital and superior temporal regions. Although this study did not report direct comparisons of fMRI findings with those from other techniques, previous work by this group in epilepsy patients identified face-processing regions in the same cortical zones, using electrical stimulation mapping.[3] The inferior temporal lobe is often resected in surgical treatment of medial temporal lobe epilepsy, although face-processing deficits are rarely associated with surgery (by some accounts, bilateral damage is required to produce prosopagnosia[67]). Nonetheless, this study indicates that fMRI may yield a high degree of functional specificity outside of primary sensory cortices.

Seizure Focus Localization

As noted earlier, most fMRI exams are performed by examining the blood flow response to a task challenge. Used in this way, they can efficiently identify the regional associates of normal brain function and identify brain areas that must be avoided in resective surgery. At least as useful, however, will be a method that might identify the epileptogenic zones directly.

Electroencephalogramâ€“Functional Magnetic Resonance Imaging

At some level, the seizure is essentially an electrical phenomenon, and it is rational to imagine that the electrical disturbance visualized in the EEG should offer both spatial and temporal localizing information useful in the planning of resective surgery. Unfortunately, the scalp EEG alone seldom offers great precision in locating the epileptogenic brain regions. However, the possibility of combining EEG with more precise imaging measures is extremely attractive. Thus, several teams have put substantial effort into the development of techniques suitable for such joint recordings.

From a purely technical perspective, combining EEG and MRI has proven extremely challenging. Both Ives and Huang-Hellinger reported early that such recordings were possible, but noted that large-amplitude artifacts were present in the EEG recordings.[36,37,38] The origin of these is well understood: The imaging process requires the creation of large-amplitude, time-varying magnetic fields from both the RF excitation pulse and the electromagnetic coils required to localize the magnetic resonance signal in space. These are coupled inductively to the recording loop created by the active and reference leads used in the EEG recording; such artifacts can be tens to hundreds of millivolts in amplitude and are therefore on the order of 1,000 times larger than the scalp EEG and the interictal epileptiform discharges (IEDs), making it difficult to discern the scalp signal during the imaging process. A second disturbance of the EEG recording results from the so-called â€œballistocradiogramâ€ (Fig. 5). With each heartbeat there is a displacement of the head of perhaps 100 Âµm. Although this might seem tiny, it results

in a motion of the EEG leads within the large magnetic field of the imager that produces an artifact of about 100 ÂµV that is highly variable with the patient. The features of this artifact cloud the interpretation of the

EEG.

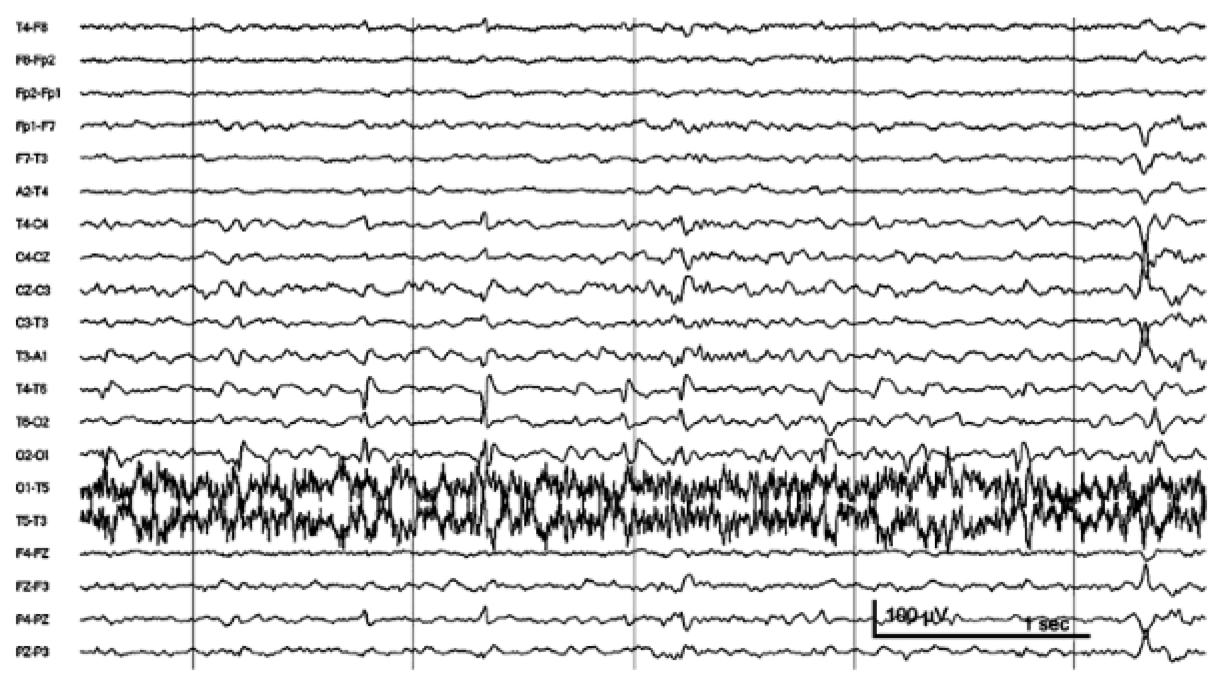

FIGURE 6. Multichannel electroencephal-ogram (EEG) recording made during magnetic resonance imaging (MRI) recording, after suitable artifact suppression (electrode T5 made poor contact in this session). Paroxysmal interictal spikes are evident in these recordings and may be used to drive data analysis of combined EEG-functional MRI data.

Several variably effective means have been developed to mitigate these artifacts, the most effective being those that use statistical means to create a template of each of the characteristic artifact types. Allen and colleagues used a purpose-built EEG system that digitizes the EEG signal at an unconventionally high rate. An accurate template can be created by using an adaptive correction method that provides a progressive interpolation between acquired points.[2] An alternative method was developed by Cohen and Goldman, using a sampling system that is synchronized to the MR scanner itself.[20,30] Both methods, and a variety of others,[8,40,55] (e.g., 8) are capable of producing essentially artifact-free EEG recordings during continuous high-data-rate fMRI (Fig. 6).

As discussed elsewhere in this volume, the presence of paroxysmal IEDs in the scalp EEG of the epileptic patient is a common finding, although it is not universal. Studies have indicated that resective surgery of the anterior temporal lobe results in significant improvement, or cure, of up to 92% of patients showing IEDs.[23,74] Generally, these EEG features are prominent and relatively easy to detect. A computer-aided means of IED detection was developed, for example, by Gotman[27,31,32] that can identify these features with good accuracy. The power of the IED in seizure focus localization, however, is limited. For example, in two studies it was shown that in the overwhelming majority of patients with IEDs that localize bitemporally, the seizures originate from only one temporal lobe.[16,35] Walczak and Jayakar noted that the IEDs suggest that the entire cortex may display an electrical irritability in the epileptic brain that is a consequence of the presence of a focal lesion.[73] Nevertheless, it is likely that the IEDs themselves originate in the epileptogenic zone. This interpretation is supported by the finding that IEDs may be reduced or eliminated following successful surgery, although this finding, too, is complex because IEDs may also be increased after surgical intervention.[15]

Based on the hypothesis that the IED recorded at the scalp may be a distant or propagated reflection of a disturbance that originates in the generative zone for seizures, several investigators have attempted to use the timing of the IEDs as independent variables in the fMRI analysis, studying the fMRI signal changes that follow these spike discharges. Warach et al.,[75] using an MRI-compatible EEG system designed by Ives et al.,[38] compared MRI scans taken immediately after IEDs to those presumably acquired during periods of normal EEG and noted areas of focal signal increase. Of the two patients studied, one showed such focal signal change despite a history of generalized epilepsy. Although these authors speculated that the method might well detect true focal abnormalities in patients that generalize, this pattern is extremely rare,[42] and an alternative interpretation is that the spiking behavior may either be dissociated from the seizure or that the coupling between IEDs and fMRI signal is somehow variable. As noted later, the linkage between IEDs, focal fMRI signal, and seizure disorder has not been definitively established and remains an area of active research and some controversy.

One way to assess the reliability of the IED-fMRI correlations is to perform repeated studies of single patients to see whether the effects are in fact reproducible. Symms et al. reported, for example, that similar patterns of MRI signal were observed in one patient studied on four separate occasions.[71] Another approach is to determine whether the source localizations determined by dipole solutions to the scalp EEG colocalize with the fMRI data. Lemieux et al. performed such a study on six patients and noted that the localizations were reasonably consistent and that the discovered sites were frequently in proximity to abnormalities visible in the structural scans.[50] These results and others were sufficiently encouraging that there have now been several reasonably large-scale studies.

Using the newer EEG-MRI methods, it is possible to examine the fMRI responses to IED discharges over a relatively broad range of discharge rates and scalp topographies.[66] There have been several studies that address the potential of the combined method in terms of both its practical limitations and its added utility in diagnosis.[1,5,33,45] As noted in all of these reports, the method of IED-fMRI has a few technical limitations that restrict its application. In particular, even using optimal continuous data collections, patient data frequently must be excluded because spike activity is absent during the limited window of the scanning session; the sample by Al-Asmi et al. is the largest reported to date.[1] In their work, using patients selected based on the presence of frequent interictal spikes, some 25% of patients studied with continuous EEG monitoring could not be analyzed for this reason. Motion artifacts are a well-understood contaminant in fMRI studies.[18] Although there are remarkably effective postprocessing tools available to mitigate these problems, data loss to motion is a substantial problem in the epilepsy studies (on the order of 15% across reported studies). Other problems include patient compliance related to discomfort from wearing the electrode array during scanning and the presence of artifacts from materials such as dental work that are common to all fMRI studies. Even with technically adequate data there are still many studies that fail

to result in the identification of focal signal fMRI changes. Using spike-triggered acquisition with carefully selected patients with pharmacologically induced control states, Lazeyras et al. reached a 73% positive yield in a study of 11 patients.[48] Intracranial recordings confirmed the concordance of the fMRI localization of the epileptogenic zone in 5 of 6 patients on which it was performed. Al-Asmi et al. reported a lower yield of 50% in their study of 24 patients.[1] A study by JÃ¤ger et al. showed a 50% yield, although certain aspects of the data analysis were unusually liberal.[41] Overall, then, the combined IED-fMRI method is extremely promising as technical data quality continues to improve and as investigators gain a better understanding of the patient selection criteria that might make this an effective diagnostic means.

There have been scattered reports of fMRI data collection during ictus. Perhaps the first was that observed by Jackson et al. in 1994,[39] who showed that repeatable areas of focal signal increase were present during five consecutive seizures in a 4-year-old boy. Others have reported similar findings.[22,46,48,70] Although the diagnostic yield may well be higher during seizures, there are added practical problems. In a few cases, it may be possible to induce controlled seizures, but more generally it is unlikely that patients could be observed for long periods in the MRI device while waiting for seizures to occur. Because any subject motion can make data analysis impractical, only a subset of seizures not involving gross movement are amenable to study.

Summary and Conclusions

Functional MRI is now an established non-invasive tool for the study of human brain structure-function relationships, and thus of obvious interest in the diagnosis, characterization, and surgical management of the epilepsies. In surgical planning, it has been used with excellent success to guide surgeries that spare eloquent cortex, identify language lateralization with high accuracy and augment or replace the invasive Intracortical Amytal Procedure. While fMRI is superior in understanding complex patterns of language dominance, and the lack of a well-validated fMRI memory procedure means that the IAP will continue to have an important role. Newer methods are under development to detect and epileptogenic brain tissues by combining fMRI and electrophysiogic recording, and may provide an excellent avenue of access to restricted surgical resections for the management of seizure disorders.

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Chapter 84

Computational Anatomy

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Introduction

Improvements in magnetic resonance imaging (MRI) technology have significantly improved signal-to-noise characteristics, allowing in vivo visualization of brain anatomic structures at relatively high (<1 mm) resolution. With the use of mathematical modeling in computational anatomy, these high-resolution images can be manipulated to detect subtle differences in neuroanatomy beyond what is possible qualitatively with the human eye.[4]

Previously, quantitative magnetic resonance tools have focused on manually delineated volumes to assess brain size and regions of interest such as the hippocampus and the amygdala.[9,21] Volumetric changes may not be sensitive in detecting early or subtle changes. Even when volumetric changes are detected, these methods lack regional specificity because they cannot map the exact location of structural abnormalities. Region-of-interest studies can only evaluate the specific brain area in question, without assessing other structurally or functionally connected regions. Finally, volumetric studies cannot provide information relating to the change in shape of the neuroanatomic structure that maybe vulnerable to the underlying epileptic disease process.

With the advances in computational speed and automated image analysis, the emerging field of computational anatomy has recently been employed in epilepsy. Computational anatomy is the effort to develop algorithms that use mathematical techniques such as differential geometry, numerical analysis, and partial differential equations to model anatomic structures in brain image data.[46] Some of these techniques can be applied to the entire brain without a priori bias to study global changes associated with epilepsy.[10,11,30] Other techniques extend previous region-of-interest volumetric studies to map the precise location of atrophy and shape deviation in selected structures, such as the hippocampus.[25,33] These algorithms detect cross-sectional differences between an epilepsy group and appropriately matched controls or prospective changes over time. The regional-specific changes can also be related to clinical variables to elucidate the underlying structureâ€“function relationship. These studies provide a better understanding of the widespread cerebral changes associated with epilepsy, clinical factors that correlate with these anatomic differences, and anatomic predictors of surgical outcome. In this chapter, we review some of the basic algorithms of computational anatomy and discuss specific computational methods that have been employed in epilepsy. Finally, we highlight some of the important clinical findings resulting from these efforts.

Overview of Algorithms

Algorithms in computational anatomy can be divided into methods that evaluate whole brain or cortical structures versus those used to assess subcortical structures. Most whole-brain or cortical algorithms have all or some of the following steps in common: (a) brain extraction (remove voxels containing brain tissue from nonbrain voxels), (b) tissue classification (partition the voxels into gray and white matter and cerebrospinal fluid [CSF]), and (c) spatial normalization or registration. The great variability in human brain anatomy presents a particular challenge in developing strategies to average and compare brain structures across individuals. This is precisely the goal of spatial normalization, a pivotal step that differs greatly in different brain-mapping algorithms. Voxel-based morphometry and cortical pattern matching illustrate two potential approaches to some of these issues.[2,50] When studying subcortical structures such as the hippocampus, computational anatomists are no longer satisfied with volumetric information alone. Large-deformation, high-dimensional brain mapping (HDBM-LD) is a method for assessing morphologic shape changes such as inward or outward deviations that may give subtle but important clues to the underlying pathophysiologic process.[17,26] Surface-based anatomic mapping is another technique that maps the precise location of the atrophy pattern.[33,52] Specific disease processes may preferentially affect more vulnerable anatomic regions, and detailed visualization may further our understanding of the pathology. Diffusion tensor imaging (DTI) with probabilistic tractography allows the assessment of individual white matter bundle structural integrity that is not possible with conventional structural imaging.

Most computational methods require high-spatial-resolu-tion MRI with clear tissue differentiation among gray and white matter and CSF. Typically, T1-weighted, three-dimensional (3D) MRI such as spoiled-gradient-echo (SPGR) or magnetization-prepared rapid gradient-echo sequence (MP-RAGE) acquired on a 1.5- or 3-T magnet and 1-mm isotropic voxels across the entire cranium provides sufficient anatomic resolution for these analysis. These T1-weighted raw images can be improve with MR sequences using centric phase encoding rather than linear phase encoding.[18] Radiofre-quency inhomogeneity can be further corrected with a special excitation pulse to compensate these effects.[19] More recently, the development of the multichannel head coil array (iPAT-coil) has allowed parallel acquisition of independently reconstructed images, thus reducing scanner time and improving signal-to-noise characteristics.[56]

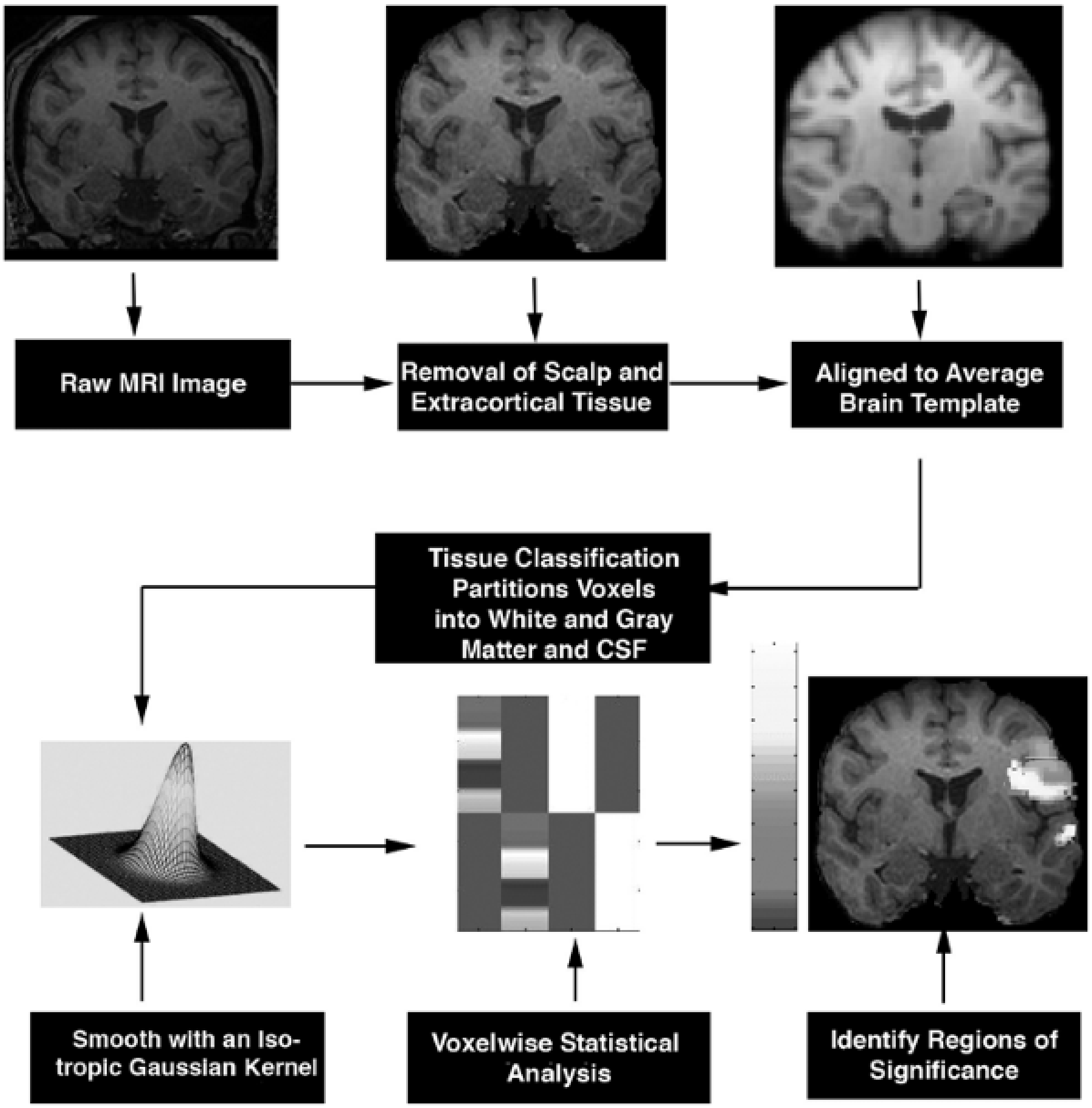
Raw MRI Image
Removal of Scalp and Extracortical Tissue
Aligned to Average Brain Template
Tissue Classification Partitions Voxels into White and Gray Matter and CSF
Smooth with an Isotropic Gaussian Kernel
Voxelwise Statistical Analysis
Identify Regions of Significance

FIGURE 1. Steps in voxel-based morphometry. Scalp and extracortical tissues are removed from raw images, and the resulting brain images are normalized to a standard template. Gray and white matter and cerebrospinal fluid (CSF) are automatically classified based on voxel intensity values. Normalized images are smoothed with an isotropic Gaussian kernel. Voxelwise statistical analysis based on generalized linear model is applied to the images to identify regions of significance. MRI, magnetic resonance imaging. (See the color insert.)

Because temporal lobe epilepsy is the most common form of epilepsy, studies are particularly interested in defining lateral and mesial temporal lobe structural deficits. However, the temporal lobe, particularly the medial aspect, is partially surrounded by bone and tissue interfaces such as nasal sinuses, ear cavities, and perforated bone and thus is prone to susceptibility artifacts. Magnetic susceptibility differences between tissue/air and bone/tissue interfaces result in magnetic field gradients, which lead to intravoxel phase dispersion and image distortion. These susceptibility artifacts can affect computational results,

and steps have been proposed to compensate for this static field effect. Spiral acquisition sequences use shorter TE and a single-shot acquisition, which can reduce geometric distortion.[23] Another approach to reducing local background gradient is to use Z-shimming, in which slice refocusing gradients are collected and combined.[22] More recently multiple array parallel image techniques have been employed to reduce susceptibility artifact and increase signal-to-noise characteristics (8).

Voxel-Based Morphometry

Voxel-based morphometry (VBM) is a whole-brain analysis tool in which voxelwise statistical comparisons of local gray matter concentrations are made between two groups of subjects.[2] VBM algorithms involve spatial normalization, tissue segmentation, smoothing, and finally application of statistical analysis to localize and infer group differences (Fig. 1). Spatial normalization involves the transformation of all of the subjects' images to the same stereotactic space to remove global brain difference between subjects. This step is important because the goal of VBM analysis is to detect regional brain tissue concentration, and, therefore, it must first remove global differences. Spatial normalization is achieved by registering the images to a standard template, such as the 152 normal data set from Montreal Neurological Institute (MNI152), using linear and nonlinear mathematical transformation based on prior knowledge of normal variability of brain size and correction for nonlinear shape differences.

More recently, an optimized VBM technique has been introduced that incorporates additional spatial processing steps in an attempt to improve image registration and segmentation. In this technique, instead of using a standard template such as the MNI152, a study-specific template created by averaging the spatially processed images of patients and controls is used to normalize the individual brain image. VBM spatial

normalization steps do not attempt to match every cortical feature, but merely correct for intersubject global brain differences. Tissue classification partitions voxels into gray and white matter and CSF based on voxel intensity values. This model assumes that each tissue class fits in a mixture of intensity values with a Gaussian (normal) distribution and assigns the voxel with the highest probability of belonging to that particular class. Separate gray matter images can be derived after tissue classification. These images are then smoothed with an isotropic Gaussian kernel, rendering each voxel in the smoothed image to contain the average amount of gray matter from around the voxel. This is defined as the gray matter concentration at which the relative amount of gray matter in each voxel can be compared to that in another voxel in the same stereotactic space. Smoothing allows the data to be more normally distributed, increasing the validity of the parametric statistical tests. It also helps to compensate for the inexact nature of the spatial normalization. Whenever possible, the size of the smoothing kernel should be selected to reflect the expected regional tissue differences between the two study groups. The final step of this process is to use voxelwise statistical analysis based on a general linear model to discover regions of significance. This method identifies clusters of tissue with increased or decreased concentrations that are significantly related to the covariates under study, such as the differences between patient and control brains, duration of epilepsy, or epilepsy risk factors.

VBM offers a number of advantages in brain mapping. Many steps in this algorithm are automated, and, thus, inter- and intrarater errors and labor-intensive manual segmentation are reduced. It allows whole-brain analysis of both cortical and subcortical structures without preconceived bias for a particular structure. Because it uses voxel-by-voxel comparisons, this method can be modified to evaluate not only gray matter differences, but also white matter segmented images and indices of diffusion tensor images.[48a] However, spatial normalization is the most important step in this algorithm, and misregisteration of the image of interest to the template can produce systematic errors.[3,12] Furthermore, the gray matter concentration measurements in VBM are sensitive to losses in gray matter, increases in CSF volume, and differences in cortical surface curvature, which cannot be distinguished from each other.[13]

Cortical Pattern Matching

Cortical pattern matching is a technique that measures the topologic variability of the cortex. The wide anatomic variability among individual brains, especially gyral patterns of the cortex, presents a significant challenge when comparing brain structures across subjects.[49,54] By explicitly matching cortical gyral patterns, this technique eliminates much of the confounding anatomic variance when pooling data across subjects and increases the power to detect group differences.[51] Similar to VBM, all MR images are first globally aligned to a standardized anatomic template. Tissue classification algorithms then partition the aligned images into gray and white matter and CSF based on voxel intensity. Unlike VBM, additional steps are performed using parametric surface-based methods to generate a geometric 3D model of the cortex with deformation maps that explicitly associate corresponding cortical region across subjects (Fig. 2). A three-dimensional cortical surface model consisting of discrete triangular tiles is extracted from each individual brain image. Thirty-eight sulcal curves on the lateral and medial surface of each hemisphere are manually traced from each individual 3D cortical model (this protocol is available on the Internet at http://www.loni.ucla.edu/~khayashi/Public/medial_surface/). The cortical models along with the manually delineated sucal landmarks are flattened. A warping technique uses these sulcal landmarks to constrain the mapping of one cortex onto another by driving individual sucal features into correspondence with the average set of sulcal curves. This creates a flatten map that contains the average set of sulcal curves derived from many people. The warped images are averaged across subjects and decoded to produce an average cortical model for each group. Similar to VBM, a general linear model is applied to each cortical point to map regions that correlate with clinical variables.[53,55]

Although flattening the brain into a two-dimensional surface allows the explicit matching of the brain features across subjects, the deflation and inflation process also produce errors associated with compression and stretching of a three-dimensional structure. Several methods have been proposed to minimize these distortions. In the cortical pattern matching method, points on the flattened map contain color codes (red, blue, green) representing x, y, z coordinates in the original three-dimensional space.[54] Principles of continuum mechanics are applied to minimize distortion as one flat map is averaged onto another flat map. The average warped images can be inflated into a three-dimensional brain structure by decoding the embedded colored coordinate system. Another way of minimizing distortion of a flat map is to make a number of cuts in the medial surface of the three-dimensional brain, such as the corpus callosum, calcarine sulcus, and temporal poles.[20] Analogous to mapmaking, in which a spherical globe is transformed into a flat plane, these cuts remove most of the intrinsic curvature of the brain surface and allow it to be flattened with minor distortions. Geodesic metrics are used to calculate the shortest distances between vertices of the original folded surface. The cortical manifolds are unfolded onto a target surface and assigned normal vector fields with consistent orientation. The potentially large distortion from such a transformation is removed by a mathematical solution that minimizes the energy needed to unfold the original structure to the desired flattened shape. Thus, converting the brain into a two-dimensional plane allows topologic exploration of a highly folded and curved structure. However, computational solutions must be found to minimize distortion and maximize preservation of the original structural integrity.

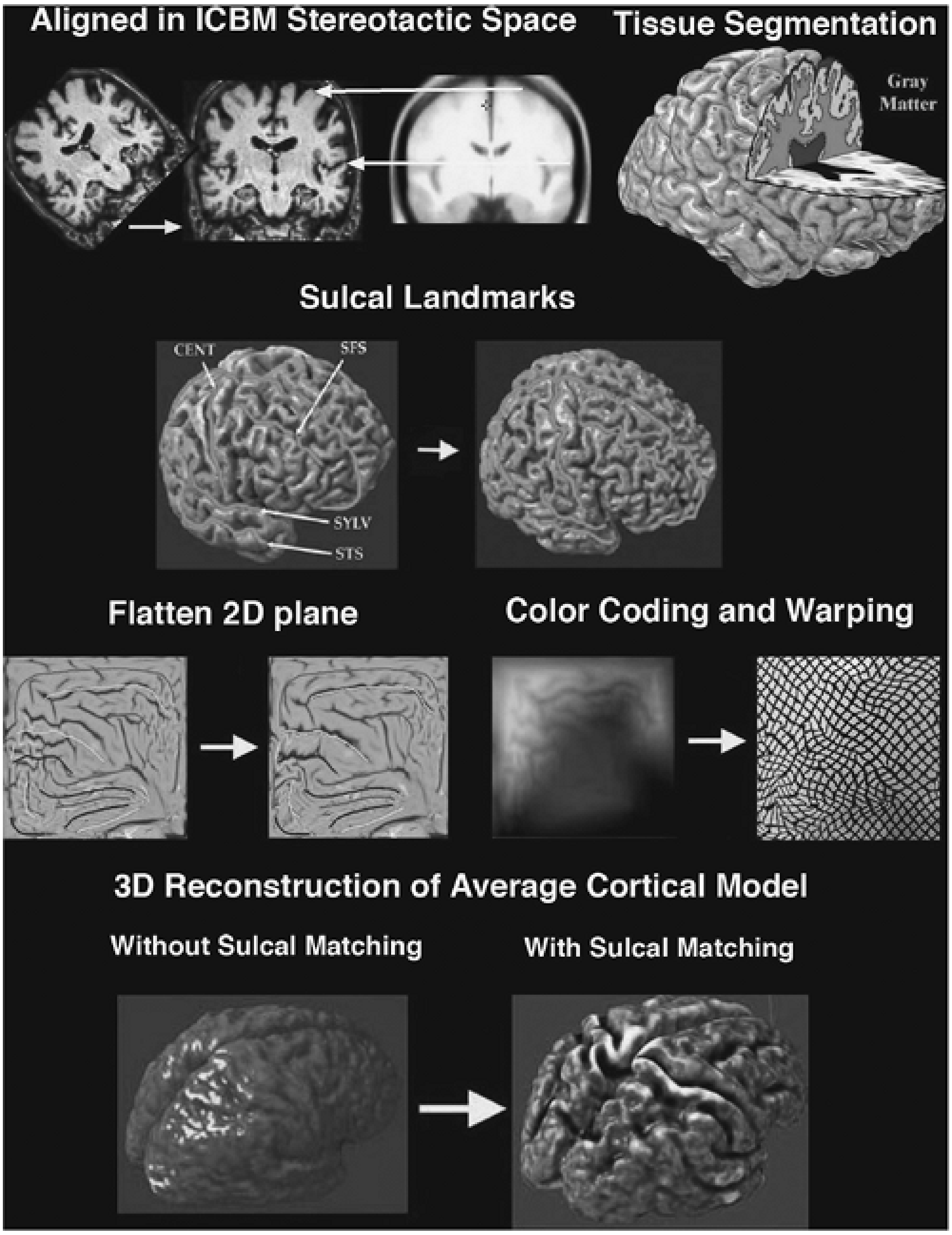
Aligned in ICBM Stereotactic Space
Tissue Segmentation
Gray Matter
Sulcal Landmarks
CENT
SFS
SYLV
STS
Flatten 2D plane
Color Coding and Warping
3D Reconstruction of Average Cortical Model
Without Sulcal Matching
With Sulcal Matching

FIGURE 2. Steps in cortical pattern-matching algorithm. Raw images are first globally aligned to a standard template. Tissue classification partitions the image into gray and white matter and cerebrospinal fluid based on voxel intensity. A three-dimensional (3D) cortical model is extracted from each scan, and sulci are traced and labeled directly on the surface model. A geometric flattening process transforms the cortical model into two-dimensional (2D) space with retained sulcal landmarks. A color-coding system with intensities of the red, blue, and green corresponding proportionally to the x, y, z location of the three-dimensional cortical model plot the original coordinates onto the flat map. A warping technique uses the sulcal landmarks to constrain one cortical region onto another. The result produces an averaged cortical model for each group across subjects. ICBM, International Consortium for Brain Mapping; CENT, Central Sulcus; SFS, Superior Frontal Sulcus; STS, Superior Temporal Sulcus; SYLV-Sylvian Fissure. (See the color insert.)

Large-Deformation High-Dimensional Brain Mapping

HDBM-LD is a diffeomorphic mapping technique that analyzes subtle shape variations in subcortical brain structures.[17,29,37] This method has been applied to such enclosed structures as the hippocampus in epilepsy.[25,26] In this method, the typical brain structure is represented as a template and its variabilities determined by probabilistic diffeomorphic transformations applied to the template. A diffeomorphic transformation produces a map between topologic spaces that is constrained by laws of continuum mechanics while allowing all data points independent freedom to match. This allows the geometric properties of the neuroanatomic substructures to be preserved. The algorithm begins with semiautomatic segmentation of the hippocampus. Individuals with expert anatomic knowledge first manually segment a template hippocampus.[25] Brain images from target scans are then globally aligned to the template image with standard landmarks from a coordinate system such as that of Talairach and Tournoux.[47a] Hippocampal-specific landmarks such as the head and tail define the long axis of the hippocampus in the target scan. Several additional landmarks are placed in cross sections along the axis. Using these manually defined hippocampal

boundaries, a mapping algorithm generates transformation fields from template images to the target images, thus automatically defining the hippocampus. More important, the diffeomorphic transformation fields and the matrices derived from them contain information defining the composite shape and volume of the structure. Statistical tests can be applied to determine the degree of shape and volume change between groups and within individuals over time. The initial steps of defining the brain structure of interest in the template image and landmarks in the target images require knowledge of neuroanatomy. Once the template structure has been delineated and target boundary points have been chosen, this algorithm relies solely on the transformation to apply the neuroanatomic information to a large number of individual target scans.

Anatomic Surface Modeling

This method uses surface-based mesh modeling combined with surface-based statistics to map the three-dimensional profile of an enclosed structure such as the hippocampus or ventricle.[33,52] Images are first linearly aligned and manually registered to the average template stereotaxic space (Fig. 3). A standard neuroanatomic atlas is used as a guide to manually segment the hippocampus. Hippocampal models are then delineated in continuous coronal brain MR sections, including the hippocampus proper, dentate gyrus, and subiculum. Based on the use of interactive segmentation software, anatomic landmarks are followed by viewing images in all three orthogonal planes simultaneously. An anatomic mesh modeling method is used to match equivalent hippocampal surface points obtained from manual tracings across subjects and groups. Three-dimensional parametric surface mesh models are generated from manually segmented hippocampal tracings. This allows one to match the digitized points in the parametric surface model in each brain volume, and these corresponding surface points can be compared statistically in three dimensions. This surface matching method also allows the calculation of average hippocampal morphology across individuals belonging to a group and the variance among corresponding surface points relative to group averages.

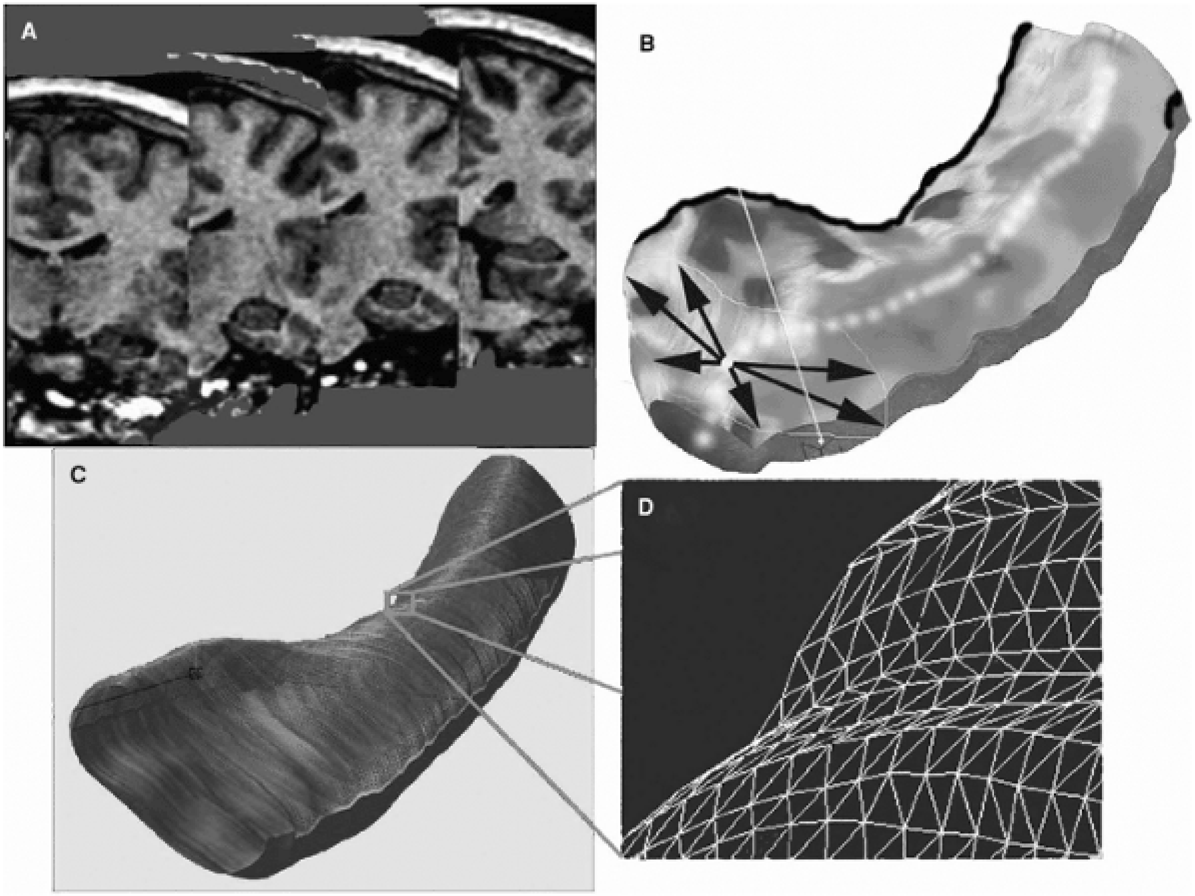

FIGURE 3. Steps involved in three-dimensional (3D) hippocampal modeling. Each individual's hippocampus is traced in consecutive coronal magnetic resonance imaging sections **(A)** and converted to a 3D parametric surface **(B)** in which the radial size of the hippocampus is measured from a centerline and plotted in color on the surface to index radial atrophy. These meshes are averaged across subjects **(C)**, and atrophy relative to control means is computed at each surface grid point **(D)**. (See the color insert.)

The 3D parametric mesh models of each hippocampus are analyzed to compute the average region-specific volume difference among groups. To measure the patterns of regional hippocampal atrophy, a â€œmedial curveâ€ is defined for each individual hippocampus as the 3D curve traced out by the centroid of the hippocampal boundary in each section. Radial distances from homologous hippocampal surface points to the central core of each surface model are determined to assess the radial distance of each hippocampal boundary point. These numerical distances assigned to each hippocampal boundary point can be thought of as a map of hippocampal radial volume. The radial measures can be compared across groups or within a group over time to generate region-specific maps of change. Multiple regressions are carried out to assess the extent of hippocampal change associated with clinical characteristics. The

resulting maps are visualized and their significance assessed by permutation to correct for multiple comparisons within each statistical map. This method measures the boundary changes relative to the medial core of an anatomic object. Thus, it is sensitive in localizing regional atrophy patterns but is not confounded by overall shift or rotation of the structure.

Defining Anatomic Boundaries of The Hippocampus

Both HDBM-LD and anatomic surface modeling require individuals with expert knowledge in anatomy and radiology to segment the hippocampus because the anatomic boundary is difficult to determine on MRI studies.[28] Earlier volumetric studies used variable landmarks to delineate the anterior and posterior boundaries of the hippocampus, with certain groups excluding the head[5,47] and another group excluding the tail.[27] Most recent work has traced the entire hippocampus by following a protocol such as that of Watson et al.[60] Even with similar protocols, differences in hippocampal morphometry still exist because the boundaries are determined by neighboring structures such as the crura of the fornices to delimit the posterior landmark and thus are prone to intra- and interrater errors. A small difference in how close an operator manually traces the in-plane hippocampal boundaries results in large differences in the eventual segmented structure. These discrepancies affect the computational results of any study that relies on manual hippocampal parcellation. Thus, it is imperative that each study follows well-defined anatomic boundaries with high inter and intrarater reliability.

Diffusion Tensor Imaging and Probabilistic Tractography

DTI is a relatively new MR sequence that provides a measure of the structural integrity of white matter tracts by measuring the diffusion of water and its directionality in three-dimensional space.[7,40] A medium that lacks a barrier to water diffusion, such as the cerebrospinal fluid, is isotropic. Membranes perpendicular to neuronal structures that have a highly parallel organization direct water diffusion. These structures have diffusion tensors aligned with their long axis, resulting in an anisotropic environment. Thus, fractional anisotropy can be quantified by assigning values between 0 (isotropic) to 1 (anisotropic). Due to the cylindrical geometry of white matter fibers, anisotropy is higher than in gray matter, where the cellular geometry is more globular. Thus, lower anisotropy values in white matter are indicative of poor structural organization of white matter tracts because highly organized fiber bundles constrain the motion of water molecules in a preferred direction parallel to the orientation of the fibers.

Probabilistic tractography has been developed to assess individual white matter bundles. The goal of tractography is to reconstruct the three-dimensional trajectories of white matter

tracts by following the continuous path of greatest diffusivity.[14] A commonly used method uses line-propagation algorithms by assuming that the orientation of the largest component of the diffusion tensor (principal eigenvector) represents the dominant axonal tracts.[39] Based on anatomic knowledge, a seed point is place as a starting point in a region of interest (e.g., the fornix at the level where fusion is visible).[16,59] A linear propagation model is used to convert the tensor information in each voxel to a continuous tracking line. Lines are terminated based on their anisotropy value and angle of curvature. Because gray matter has low anisotropy compared to white matter (typically 0.1â€“0.2), a line can be terminated if the anisotropy of the voxel falls below a preset threshold (e.g., 0.2 or 0.3). Large-angle transitions from one voxel to the next create large errors in the linear propagation model. In addition, the curvature violates the assumption that diffusion along an axis is normally distributed. Therefore, the tract will be terminated if consecutive voxels have a curvature greater than the predetermined threshold (typical range is from 50 to 70 degrees). Probabilistic tractography can delineate regions of interest based on fiber orientation and integrity.

Applications of Voxel-Based Morphometry and Cortical Sulcal Matching In Epilepsy

Previous MRI morphometric studies focused on manually segmented volumes derived from single brain regions such as entire cerebral cortex or its lobes.[38,48] Inferences from these data are limited, in that one cannot assess the precise localization of the abnormality within the delimited volume. For example, if a frontal lobe volume difference is found between two groups, it is impossible further to define whether the difference is localized in the orbital frontal or lateral frontal regions. Such differences may have important implications for associated functional or behavioral deficits. Furthermore, one cannot determine the relationship to other neuronal connected structures not under study. These image analysis procedures are also labor-intensive and suffer from difficulties related to defining reliable anatomic boundaries.

Voxel-based morphometry and cortical sulcal matching techniques permit whole-brain and cortical analysis of brain images, respectively. Most of the studies in temporal lobe epilepsy patients used VBM to evaluate extrahippocampal structural abnormalities associated with this epilepsy syndrome, although it is also sensitive in detecting hippocampal deficits.[31] In temporal lobe epilepsy, most studies show that structural deficits extend beyond the hippocampus and involve multiple neocortical regions. Patients with temporal lobe epilepsy exhibit marked white matter reduction, predominately in the temporal lobe ipsilateral to the presumed epileptogenic zone and in the corpus callosum.[10,36] In addition, VBM studies consistently have found gray matter reduction in bilateral frontal regions and the thalamus.[10,11,30] Both Keller's and Boniha's groups showed gray matter involvement bilaterally in the parietal-occipital regions,[30,11] whereas Bernasconi and coworkers only found decreases in the occipital regions of left temporal lobe epilepsy patients.[10] Different investigators have reported conflicting results in the temporal lobe neocortex, with some suggesting increases in gray matter concentration,[30] whereas others have reported decreases in this region.[10,11] These discrepancies may result from different VBM tissue registration and segmentation techniques. As previously noted, spatial registration is a critical step in VBM. In attempting to ensure that the same brain regions are comparable among different individuals, matching of an individual brain to the template may transform the shape of the brain, resulting in inflation and deflation of brain regions. These studies used different spatial registration techniques, which may in part account for the differences in detecting temporal occipital parietal deficits. Keller et al. compared standard and â€œoptimizedâ€ VBM and showed that â€œoptimizedâ€ VBM, which incorporates additional spatial processing steps to improve image registration and conservation of tissue volumes after normalization, yielded increased sensitivity in detecting extrahippocampal structural abnormalities in temporal lobe epilepsy.[31]

More recently, cortical pattern matching techniques have been applied in mesial temporal lobe epilepsy.[33a] As previously noted, this method allows the explicit matching of consistent neuroanatomic structures in the neocortex (i.e., sulcal landmarks and cortical surfaces) across subjects, thus enhancing the signal-to-noise ratio for detecting group differences. In fact, the sulcal pattern alignment results in a higher-dimensional alignment of brain structure across subjects than is typically achievable using automated nonlinear registration approaches. An algorithm has been developed to estimate gray matter cortical thickness in millimeters from T1-weighted MRI scans.[41,55] Compared to healthy controls, both right and left mesial temporal lobe epilepsy (MTLE) patients show regions with up to a 30% bilateral decrease in average cortical thickness. Significant thinning of the cortical ribbon is found in the bilateral frontal poles, frontal operculum, orbital frontal, lateral temporal, and occipital regions. In both MTLE groups, cortical thickness was also reduced in the right angular gyrus and primary sensorimotor cortex surrounding the central sulcus. Furthermore, longer seizure duration was correlated with decreased cortical thickness in the superior frontoparietal regions, including the primary sensorimotor cortex and the parahippocampal gyrus ipsilateral to the side of seizure onset.

For many years, functional studies such as interictal positron emission tomography (PET) have demonstrated widespread metabolic changes associated with temporal lobe epilepsy.[24] By visualizing the entire cerebrum, VBM and cortical pattern-matching techniques have determined that the presence of the structural deficit pattern in chronic unilateral temporal lobe epilepsy patients also extends to multiple cortical and subcortical regions. These regions are primarily located in the efferent limbic neocortical pathway. MR tractography studies have visualized the direct connectivity between limbic structures such as the hippocampus and neocortical areas such as temporal, orbitofrontal, and extrastriate occipital lobes.[45] A similar limbic neocortical network has also been demonstrated in patients with complex partial seizures using interictal and ictal single photon emission computed tomography (SPECT).[58] Thus, many authors have proposed that these deficits are due to limbic efferent disconnection from the chronic epileptogenic temporal lobe.[10,11] However, conclusions about disease progression and cause and effect issues between epilepsy and brain damage are limited in these cross-sectional studies.[34] A cross-sectional study cannot differentiate the underlying etiology of the structural changes, which may include acute damage associated with an initial precipitating injury, such as febrile seizure or head injury, that triggered epileptogenesis, chronic progression of damage caused by the initial insult, or possible damaging effects of recurrent seizures.[43]

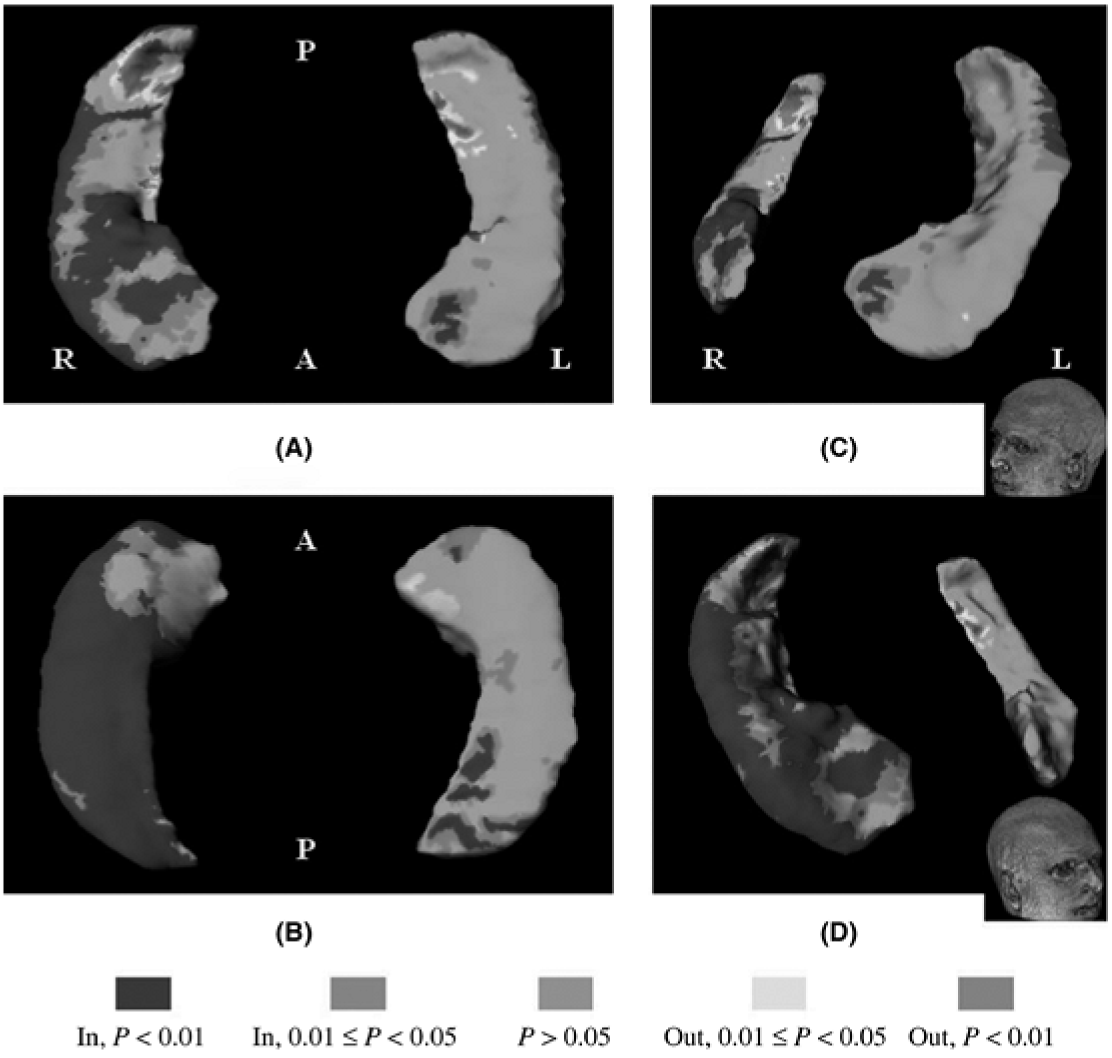

FIGURE 4. Large-deformation, high-dim-ensional brain mapping reveals bilateral hippocampal deformity in right mesial temporal lobe epilepsy patients. Similar bilateral changes were found in left temporal lobe epilepsy patients. Inward deviation is shown in purple (*p* <.01) and turquoise (.01 = *p* <.05). Outward deviation is shown in red (*p* <.01) and yellow (.01 = *p* <.05). **A:** View from above. **B:** View from below. **C:** View from a perspective slightly above and to the left of a midline plane, showing the top side. **D:** View from a perspective slightly above and to the right of a midline plane, showing the top side. A, anterior; L, left; P, posterior; R, right. (From Hogan RE, Wang L, Bertrand ME, et al. MRI-based high-dimensional hippocampal mapping in mesial temporal lobe epilepsy. *Brain*. 2004;127:1731â€“1740, with permission.) (See the color insert.)

A recent prospective longitudinal study examined the progression of neocortical damage in epilepsy.[35] This study used a voxel-based approach to examine neocortical changes in patients with focal and generalized epilepsy in a 3.5-year time span. Because this was a prospective study in which all subjects were scanned twice at two different time points, an image subtraction method was developed to detect differences over time. Thus, voxels of individual repeat scans were subtracted from the baseline scan to generate a difference image. However, to reduce false-positive results due to artifacts such as pulsation within the temporal lobe, a separate spatially

normalized structural noise map was generated from difference images of healthy controls. This structural noise map was used as a threshold against the difference map in epileptic patients to define the genuine pathologic change. The resulting difference maps of epileptic patients were visually assessed by two raters to determine whether the changes in voxel pattern between the two scans were focal or generalized. Focal or generalized neocortical volume losses were found in 54% of patients with chronic epilepsy, 39% of patients with newly diagnosed epilepsy, and 24% of controls. The most common pattern of structural change was generalized volume loss, which was observed in both focal and generalized epilepsy syndromes. Generalized volume loss was associated with age and more commonly seen in patients with increased exposure to antiepileptic drugs. The less common pattern of focal neocortical changes was not related to the epilepsy syndrome, having been seen in both types of epilepsy.

Applications of Large-Deformation, High-Dimensional Brain Mapping In Epilepsy

Underlying neuronal connections influence neuronal anatomic shape during morphogenesis. For example, during early development, neurons migrate to the cortical plate along radial glial cells and emanate axons that connect target regions. The physical forces of these interconnecting regions affect the ultimate shape of the neuroanatomic structure.[57] Shape changes may be a particularly sensitive index of disturbances in the underlying anatomic connections and offer another window for analyzing a disease process.[17] This method has been applied this technique to evaluate hippocampal shape deformation in mesial temporal lobe epilepsy patients.[26] Compared to normal controls, the hippocampus with mesial temporal sclerosis (MTS) has large regions of significant inward deviation mapped to the CA1 subfield and the subiculum (Fig. 4). The hippocampus contralateral to MTS also showed significant inward deviation, but the pattern was markedly differently relative to the MTS hippocampus. The contralateral hippocampus showed smaller and more regional inward deviation in the medial hippocampal head and the inferior and lateral aspects of the hippocampal body. More important, the contralateral hippocampal volumes showed no difference between control and MTLE subjects. Thus, hippocampus shape change appears to be a more sensitive measurement of neuronal disturbance in this epilepsy syndrome. In the future, this technique may be useful in epilepsy surgical evaluation to help to define subtle anatomic abnormalities of the hippocampus that are not apparent by visual inspection or volumetric analysis.

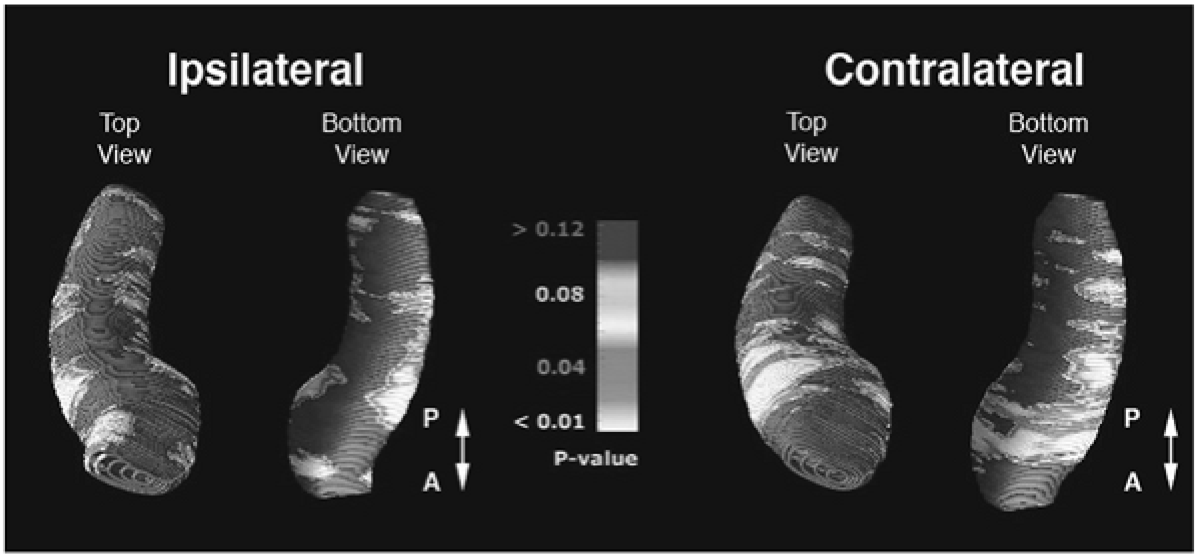

FIGURE 5. Maps identifying regions where seizure-free (SF) and not-seizure-free (NSF) surgical outcome groups differ in their degree of atrophy. Group difference maps show mean hippocampal volume differences ipsilateral **(left)** and contralateral **(right)** to the side of seizure onset. Areas of significant atrophy between the two surgical outcome groups are plotted as a map of *p* values. The NSF groups show significantly greater diffuse atrophy in the ipsilateral hippocampus, whereas the contralateral side shows a more region-specific

atrophy pattern. The maximal atrophy is seen in the anterior and lateral aspects of the contralateral hippocampus. A, anterior; P, posterior. (Adapted from Lin JJ, Salamon N, Dutton RA, et al. Three-dimensional preoperative maps of hippocampal atrophy predict surgical outcomes in temporal lobe epilepsy. *Neurology*. 2005;65:1094â€“1097, with permission.) (See the color insert.)

Application of Anatomic Surface Modeling In Epilepsy

Anatomic surface modeling combined with surface-based statistics has been applied to preoperative MRI studies of patients with MTLE to isolate hippocampal deficit profiles that are associated with better or poorer surgical outcome.[33] All patients had well-localized MTLE based on seizure semiology and ictal EEG and had preoperative MRI showing unilateral hippocampal atrophy. They underwent anteromesial temporal resection and were followed for at least 2 years. Three-dimensional hippocampal profiles of seizure-free (SF) patients were compared to those who continued to have seizures (NSF). Direct comparison of the ipsilateral and contralateral hippocampi between the SF and NSF group showed that the NSF group had greater bilateral hippocampal atrophy, but the distribution of the atrophy was markedly different between the two hippocampi. The NSF group showed greater hippocampal atrophy in a relatively uniform pattern in the ipsilateral hippocampus when compared to the SF group (Fig. 5). However, the contralateral hippocampus showed a more regional atrophy pattern maximally involving the anterior hippocampus.

The visualization of a three-dimensional hippocampal atrophy map provides greater insight into the underlying mechanisms of hippocampal damage that may be associated with surgical outcome. The greater contralateral hippocampal involvement may suggest further disease progression in the NSF group, in which the sclerotic ipsilateral hippocampus would already be diffusely damaged (i.e., a floor effect), whereas the contralateral hippocampus may exhibit damage only in regions with the greatest susceptibility for epileptogenesis. In animal studies, the ventral hippocampus, analogous to the human anterior hippocampus, has much greater seizure susceptibility.[1] In human surgical specimens, there is greater neuronal cell loss in the anterior compared to the posterior hippocampus.[6] Seizure propagation from one hippocampus to the other over time may lead to damage first in the most vulnerable areas of the contralateral hippocampus.

Applications of Diffusion Tensor Imaging and Tractography In Epilepsy

Probabilistic tractography has permitted virtual in vivo dissection of white matter fasciculi by reconstructing three-dimensional trajectories of white matter tracts. Once these tracks are identified, the integrity of the white matter bundles can be evaluated with DTI indices such as fractional anisotropy. DTI analysis with fiber tracking has been applied to detect axonal degeneration in the fornix and cingulum in a group of temporal lobe epilepsy patients with MTS.[15] Previously, volumetric studies of the fornix in mesial temporal lobe epilepsy only revealed unilateral fornix atrophy concordant to side of hippocampal sclerosis.[32,42] Based on the use of DTI measurements, bilaterally symmetric reductions in fractional anisotropy were observed in the fornix and cingulum of patients with unilateral MTLE (Fig. 6). The presence of these bilateral abnormalities in unilateral temporal lobe epilepsy patients is an unexpected finding based on previous volumetric studies and may indicate that DTI is a more sensitive determinant of structural integrity. However, the clinical implication of the bilateral DTI abnormality in MTLE is limited because structureâ€“function relationships were not studied.

Another application of DTI tractography is for the identification of anatomic structures that are difficult to delineate on conventional MRI and have great variability in the normal population. Visual field defects are a significant morbidity associated with a minority of patients who undergo anterior temporal lobe resection for drug-resistant epilepsy due to disruption of Meyer's loop. Defining the preoperative location of this white matter tract and identifying those patients who are at risk for visual field defects has proved to be a challenge. Powel et al. used probabilistic tractography to define the optic tract and overlaid these results onto the postoperative anatomic MRI to assess the location of Meyer's loop in relation to the region of surgical resection.[44] Compared to a patient without postoperative complications, a patient with visual field defect had a Meyer's loop that extends more anteriorly and inferiorly, encroaching into the resection region and surgically disrupting this tract (Fig. 7). DTI tractography may help to define individual optic radiation anatomy and identify patients at risk for visual field defects after temporal resection.

Summary and Conclusions

Computational anatomy has been increasingly applied to characterize structural abnormalities in patients with epilepsy. Comparison of anatomic structures in terms of manifolds of points, curves, and surfaces governed by probability laws allows statistical inferences of group differences. Morphometric techniques such as VBM and cortical pattern matching have detected systematic differences in gray matter distribution in the frontal regions and the thalamus and white matter distribution in the temporal lobe and corpus callosum in TLE. More variable gray matter deficits have been found in the temporal,

parietal, and occipital regions, which may in part due to different spatial registration methods. Mapping of these neuroanatomic deficits in the three-dimensional space of the entire cerebrum have permitted greater understanding of the distributed network involved in the epileptogenic process. Metrics other than overall volume have been used to localize deficit patterns and assess changes in shape of a subcortical structure such as the hippocampus. Alterations in the shape of a structure may precede volumetric changes, reflecting more subtle disturbances in neuronal organization. Localizing the region-specific hippocampal atrophy patterns based on clinical outcome groups has allowed more precise characterization of anatomic changes associated with each disease state and provides clues to potential underlying pathophysiology. DTI tractography provides a sensitive measurement of white matter tract integrity and permits assessment of specific fasciculi that are not visible on conventional MRI. Thus, computational anatomy has already offered new approaches to investigating subtle neuroanatomic disturbances in epilepsy. With continuing improvement in computational algorithms, these tools will be further applied in epilepsy to study neuroanatomic markers of genetic variability, disease progression, and clinical outcome.

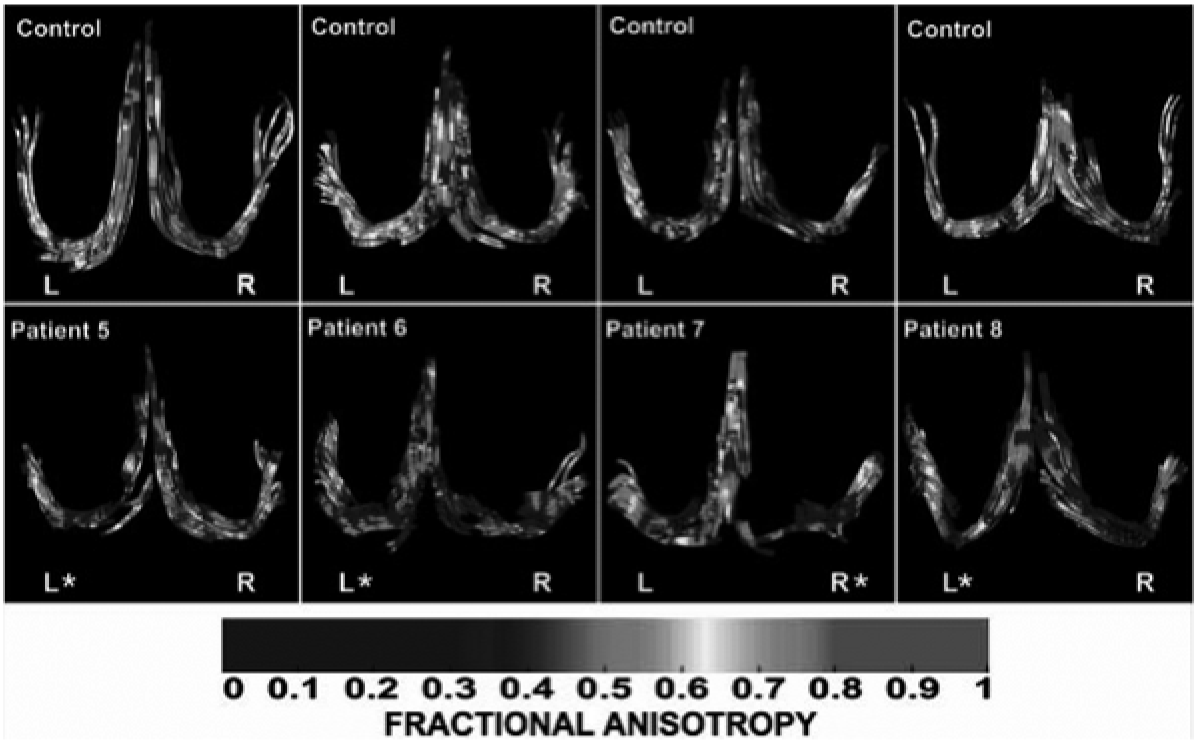

FIGURE 6. Diffusion tensor imaging tractography mapped the integrity of the fornix in four healthy controls

and four patients with unilateral mesial temporal lobe sclerosis (MTS). Fractional isotropy for each voxel is color coded, with higher values denoting greater structural organization. Fornix of patients with MTS has lower anisotropy and less continuous tracts. Asterisk indicates the side of MTS. L, left; R, right. (From Concha L, Beaulieu C, Gross DW. Bilateral limbic diffusion abnormalities in unilateral temporal lobe epilepsy. *Ann Neurol*. 2005;57:188â€“196; with permission.) (See the color insert.)

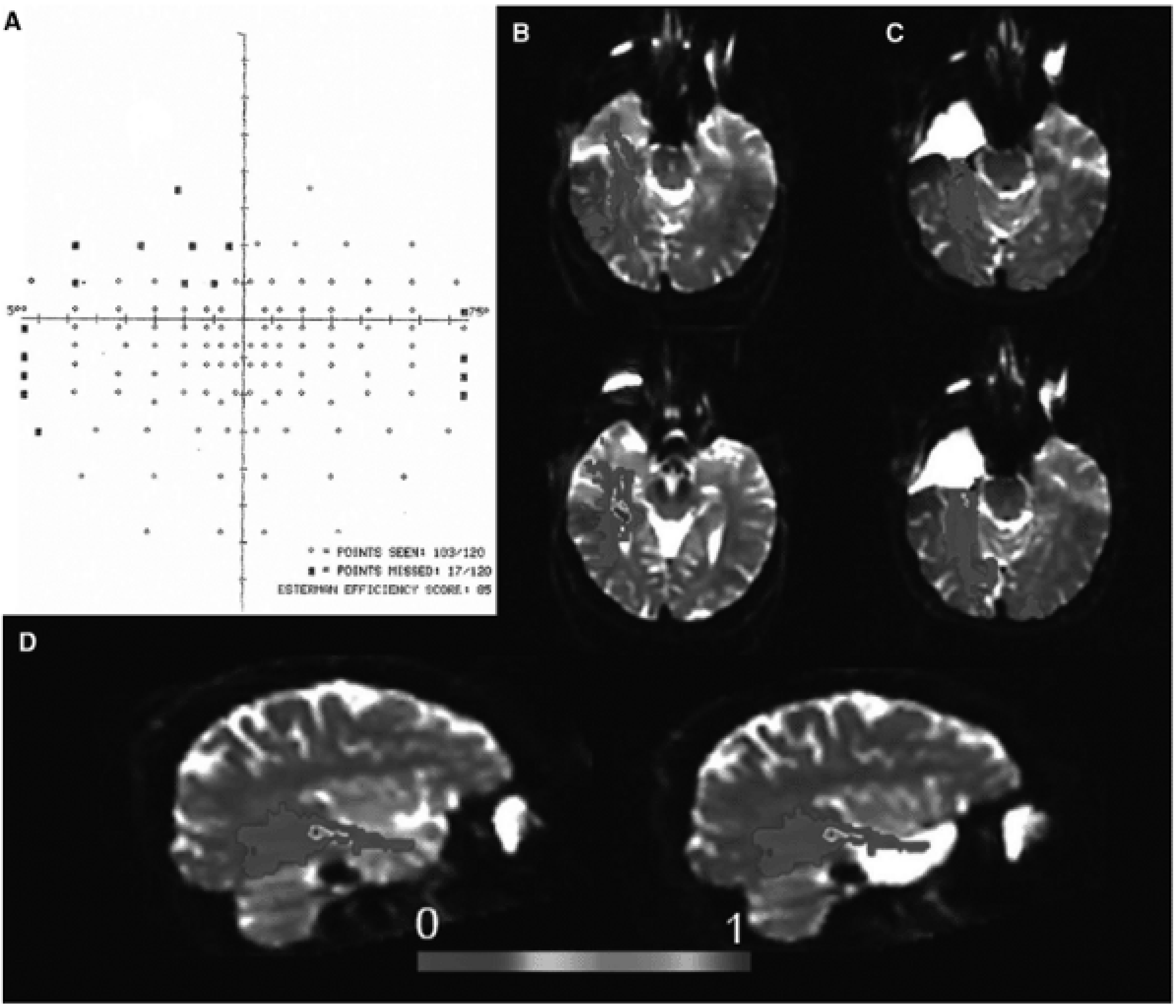

FIGURE 7. Postoperative visual field demonstrates a superior homonymous quadrantanopia **(A)**. Preoperative right optic radiation overlaid on preoperative axial **(B)** images; postoperative right optic radiation overlaid on postoperative axial image **(C)**; preoperative optic radiation overlaid on preoperative sagittal **(D, left)** image and postoperative optic radiation overlaid on postoperative sagittal **(D, right)** image. These images show that the preoperative tract overlies the resected anterior temporal lobe, resulting in postoperative visual field deficit. (From Powell HW, Parker GJ, Alexander DC, et al. MR tractography predicts visual field defects following temporal lobe resection. *Neurology*. 2005;65:596â€“599; with permission.) (See the color insert.)

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Chapter 85

Seizure Prediction

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Introduction

Seizure prediction, anticipation, or forecasting (despite their different meanings, these terms are currently used interchangeably) is a field of great interest in the clinical and basic neuroscience communities. This is not only because of its potential clinical application in warning and therapeutic antiepileptic devices, but also for its promise to increase our understanding of the mechanisms underlying epilepsy and seizure generation. The motivation for research into the predictability of seizures is straightforward. The fact that seizures occur without warning in the majority of cases is one of the most disabling aspects of epilepsy. If it were possible to predict seizures with high sensitivity and specificity, even seconds before their onset, therapeutic possibilities would change dramatically.[50] One might envision a simple warning system capable of decreasing both the risk of injury and the feeling of helplessness that results from seemingly unpredictable seizures. Side effects from treatment with antiepileptic drugs, such as sedation and clouded thinking, could be reduced by on-demand release of a short-acting drug[48,197] or electrical stimulation[62,175,213] during the pre-ictal state. Paired with other suitable interventions, such as focal cooling[70] or biofeedback operant conditioning,[56,170,198] such applications could reduce morbidity and mortality, and greatly improve the quality-of-life for people with epilepsy. In addition, identifying a pre-ictal state would greatly contribute to our understanding of the pathophysiologic mechanisms that generate seizures.

In most patients seizures appear to occur unpredictably, with no discernible pattern, while in others, seizures appear to be entrained to biologic rhythms, such as menstrual or sleepâ€“wake cycles. Clustering patterns, where one seizure appears to increase the likelihood of subsequent seizures, also appear common in clinical practice. Despite these observations, analyses of long-term patterns based upon seizure diaries[4,11,16,74,115,147,204] have yielded inconsistent findings. While some authors conclude that the timing of seizure recurrence is random, others hypothesize that seizures occur in a probabilistic nonlinear fashion. Because of this inconsistency, based upon clinical observations, the transition to a seizure has generally been thought of as an abrupt phenomenon, occurring without warning. Nevertheless, there is physiologic support for the idea that at least certain types of seizures are predictable.

Several seizure-facilitating factors are known. Lennox[125] defined seizure facilitation as the input of sensory, metabolic, emotional, or other yet unknown factors that â€œfill up some reservoir until it overflows,â€ which in turn results in a seizure. State of consciousness, sleep deprivation, being tense, disturbances of electrolytes and acidâ€“base balance, sensory stimulation, and exposure to certain drugs are factors known to potentiate seizures. Apart from the rare exception of sensory-evoked or reflex epilepsies, however, these factors are rather nonspecific and highly variable, since they depend on individual habits, susceptibility, and daily routine.

Clinicians who care for patients with epilepsy have long known that individual patients can identify periods when seizures are more likely to occur, though they can rarely specify an exact time when seizures will happen. Rajna et al.[174] found that the vague sensations that characterize these periods, called â€œclinical prodromes,â€ occurred in more than 50% of 562 investigated patients, though the reliability of these reports was not evaluated prospectively. Reported sensations included mood changes, irritability, sleep problems, nausea, and headache. There are also physiologic studies in small numbers of patients, usually collected serendipitously before seizures, that support the existence of a pre-ictal period. Weinand et al.[216] detected a significant increase in blood flow in the epileptic temporal lobe that started 10 minutes before seizure onset that spread to both temporal lobes 2 minutes before seizure onset. Similarly, Baumgartner et al.[14] demonstrated increased blood flow in the epileptic temporal lobe in two patients, 11 and 12 minutes, respectively, before seizure onset. Using near-infrared spectroscopy in three patients, Adelson et al.[2] reported an increase in cerebral oxygen availability that began more than 13.5 hours, and was identified as early as 1.5 hours, before documented seizure onset. Pre-ictal changes in other variables, such as Râ€“R interval on the electrocardiogram (ECG)[40,95,159] may also have predictive value, perhaps as epiphenomena related to seizure precursors, in some types of epilepsy. More recently, functional magnetic resonance imaging has demonstrated changes in perfusion prior to seizure onset.[55]

During recent years, a variety of potential ictogenic (seizure-generating) mechanisms have been identified in experimental models of focal epilepsy, including alterations in synaptic and cellular plasticity and changes in the extracellular milieu (see Section II). However, it is still a matter of debate whether these mechanisms can be regarded as specifically ictogenic, apart from their critical role in normal brain function. On the level of neuronal networks, focal seizures are assumed to be initiated by abnormally discharging neurons (so-called *bursters*[21,22,34,182,208]; see reference 226 for an overview) that recruit and entrain neighboring neurons into a critical mass. This build-up might be mediated by an increasing synchronization of neuronal activity that is accompanied by a loss of inhibition, or by processes that facilitate seizures by lowering the threshold for excitation or synchronization. In this context the term â€œcritical massâ€ might be misleading in the sense that it implies an increasing *number of neurons* that are entrained into an abnormal firing pattern. This *mass* phenomenon would be easily accessible to conventional electroencephalogram (EEG) analysis, which, to date, has failed to detect it. Rather, the seizure-initiating process might better be visualized as a process in which an increasing number of critical interactions between neurons in a focal region and connected units in an abnormal functional network unfold over time. Indeed, there is now converging evidence from different laboratories that quantitative analyses appears to be capable of characterizing this collective neuronal behavior from the gross EEG, allowing definition of a transitional pre-ictal phase, in a high percentage of cases.

History of Seizure Prediction

As early as 1975, researchers considered analysis techniques such as pattern recognition, analytic procedures of spectral data,[44,189,214] or autoregressive modeling of EEG data[179,181] for the prediction of seizures. Their findings indicated that EEG changes characteristic for a pre-ictal state may be detectable a few seconds before their actual seizure onset on EEG. None of these mostly linear techniques has been implemented clinically.

Since spikes in the EEG are usually considered the hallmark of an epileptic brain, their possibly altered pre-ictal occurrence was investigated in several studies. Sherwin[188] noted increased correlation of epileptiform activity (spikes) between two adjacent cortical sites in the 15 to 20 minutes prior to EEG onset of focal seizures in a cat model of epilepsy. In 1983, Lange et al.[107] demonstrated a similar correlation of interictal spikes between the side of the seizure focus and the â€œnormalâ€ temporal lobe within the 20 minutes prior to EEG seizure onset in patients with temporal lobe epilepsy. While other authors reported a decrease or even total cessation of spikes before seizures,[63,64,221] re-examination did not confirm this phenomenon in a larger test set.[94]

With the advent of the physical-mathematical theory of nonlinear dynamics (colloquially termed *chaos theory*) in the early 1980s, new analysis techniques were developed to characterize apparently irregular behaviorâ€”a distinctive feature of the EEGâ€”and thus to extract features from the EEG that are not obvious to the human eye (see references 12, 45, 84, 118 for an overview). During the last two decades, these techniques have generated a large body of evidence for the existence of a pre-ictal state. The earliest attempts to use nonlinear time series analysis (see reference 91 for an overview) were started in the 1990s using the â€œlargest Lyapunov exponentâ€ to describe changes in brain dynamics.[78,79,83] The investigators observed transient drops in the temporal evolution of this measure several minutes prior to seizures and proposed that the EEG became progressively less chaotic as seizures approached. The first studies to describe characteristic changes in the EEG shortly before an impending seizure in a larger group of patients used the â€œcorrelation dimensionâ€ as an estimate for neuronal complexity[51,53,117,119,121,124] and the â€œcorrelation density.â€[141] These studies were followed by others using measures such as dynamical similarity index,[108,111,112,113,157] Kolmogorov entropy,[153,210,211] or marginal predictability.[43,126,127] In parallel, other techniques have focused on extracting neurophysiologic features from the EEG associated with epileptiform activity in human and animal physiology, such as bursts of complex epileptiform activity, slowing, chirps, and changes in signal energy.[60,133,158,225] Other methods focused on defining pre-ictal states include catastrophe theory,[25,26] self-organized criticality,[128,224] recurrent neural networks,[167] and simulated neuronal cell models.[186] Similar to the studies using the largest Lyapunov exponent, all of the above studies showed characteristic changes minutes to hours prior to seizure onset on the EEG, and were interpreted by their authors as defining pre-ictal states of various durations, some lasting hours.

A problem with most of these studies is that the measures used to characterize the EEG are difficult to interpret in terms of their physiologic correlate. Also, since almost all of these measures are univariate (i.e., related to only a single recording site), they fail to reflect any interactions between different regions of the brain. The epileptogenic process, on the other hand, is commonly accepted to be closely associated with changes in neuronal synchronization in a network of components that may be spatially distributed. The analysis of synchronization in the EEG can therefore a priori be regarded as a promising approach for the investigation of the spatiotemporal dynamics of ictogenesis. Based on newly developed physical-mathematical concepts for synchronization (see reference 169 for an overview), some researchers have focused on bivariate or, more generally, multivariate measures over the last 5 to 6 years that permit assessment of synchronous activity from multiple sites.[61,212] These measures include nonlinear interdependence,[9,110] measures for phase synchronization and cross-correlation,[28,76,109,149,150,152] the difference of the largest Lyapunov exponents of two or more channels,[27,75,80,82] nonlinear causality,[29] a classification approach based on a fusion of multiple EEG features from multiple sites.[38,133]

Results obtained indicate that seizures are not random events, but rather are related to ongoing dynamical processes that may begin minutes to hours to days beforehand (for an overview, see references 73, 132, 134, 192, 193). The fact that most of the approaches result in different prediction horizons indicates that they may reflect different aspects of ictogenesis, but it is likely that none of these techniques appears to depict the process fully. As many of these studies suggest, seizure precursors may wax and wane in attempts to ignite a clinical event, but the forces both driving and suppressing seizure generation remain hidden. Other concepts abstracted from the above body of work indicate that seizure precursors may begin locally and then expand spatially, and even â€œentrainâ€ other brain structures before reaching the critical mass required to initiate a clinical seizure. Patterns appear to be patient specific, within a finite range of pattern types, and it appears that different approaches may be required to predict seizures with clinically useful accuracy in different individuals or in different epilepsy syndromes. This may be a function of individual physiology or potentially confounding variables such as electrode placement and the amount and speed of medication taper during inpatient video-EEG monitoring.[132,134]

Scrutinizing the Field: The First International Collaborative Workshop on Seizure Prediction

At the beginning of the new millennium there was great enthusiasm for the ability of a variety of analysis methods to define the pre-ictal state. By that time work in the area had also extended to scalp EEG,[43,71,77,110,173] though the majority of researchers confined their investigations to intracranial EEG recordings. Careful review of the literature at that time, however, revealed considerable contradiction in results from different research groups. Of even more concern was that despite over a decade of excellent work in the field, convincing evidence demonstrating unequivocal seizure prediction in blinded, prospective, randomized clinical trials, with appropriate statistical validation, remained elusive. Central to the problem was the challenge of developing algorithms to detect unknown patterns associated with seizure generation, a process that remains poorly understood. Much of the EEG data analyzed in studies up to that time were highly selected and restricted with regard to seizure type, patient state, signal:noise ratio, duration of recordings, artefacts, etc. In addition, there were no standardized methods or nomenclature for marking continuous EEG data, no accepted methods for assessing algorithm performance, and no agreement on acceptable test data. Even clear definitions of exactly what constitutes seizure onset, seizure prediction, anticipation, and the definition of ictal events either clinically or by EEG were nebulous. For these reasons, beginning with an impromptu meeting at the American Epilepsy Society Meeting in Los Angeles, California, in 2000, the International Seizure Prediction Group (ISPG) was formed to provide an informal structure for the major groups working in this area to share data and ideas.

The ISPG was established with the specific goal of moving the field of seizure prediction forward from â€œproof of principleâ€ experiments into validated, well-understood methods that could be applied to both basic science and clinical applications. The first international workshop of this group was held in Bonn, Germany, in 2002, funded by grants from the German Section of the International League Against Epilepsy, the German Section of the International Federation of Clinical Neurophysiology, and the American Epilepsy Society. At the core of the workshop was an assessment of the state of the field at that time by having each major group apply its methods to predict seizures from a shared set of continuous intracranial EEG data.[122] Findings obtained from applying a large number of analysis techniques are summarized in eight peer-reviewed articles published together in the journal *Clinical Neurophysiology*.[38,54,66,81,86,88,114,151] Although substantial efforts were made to provide uniform data in terms of disease type, conditions, and recordings, the results of all these investigations were inconsistent and at times contradictory. Three studies had positive results, predicting seizures for different time horizons; four studies had negative results; and one had both, depending upon which techniques were employed. In none of the investigations, even those with positive findings, could seizures be predicted with any exact timing. Rather, a state of increased seizure likelihood lasting up to several hours was identified. There was agreement that, at present, none of the EEG analysis techniques was sufficient for broad clinical application, and that there were major practical problems to overcome. Nevertheless, much was learned from the exercise, particularly with regard to the need for standardization of analyses, data requirements, performance criteria, and nomenclature. Some of the results were encouraging, while other results illustrated that certain approaches are unlikely to be worthwhile. The current impact of the latter point is stressed by recent controversies about the relevance of nonlinear approaches for the prediction of epileptic seizures[140,144,145,150,151] and by studies raising doubts about the reproducibility of previously reported claims.[10,39,67,105,106,123] These contradictory findings emphasize the need for reliable methods for evaluating the performance of seizure prediction techniques.

Overview of Electroencephalogram Analysis Techniques Used to Predict Seizures

Over the last three decades two main categories of analysis techniques have been used to extract pre-ictal information from the EEG: Linear and nonlinear techniques. Depending upon whether EEG data from two or more sites are analyzed independently, or for possible interactions, these techniques can further be divided into univariate and multivariate approaches. All techniques permit reduction of large amounts of EEG data to a small number of parameters for downstream processing.

Linear EEG analysis techniques (see reference 135 for an overview) are important contributors to understanding physiologic and pathophysiologic conditions in the brain. Nonparametric linear methods comprise analysis techniques such as evaluation of amplitude, interval or period distributions, and estimation of auto- and cross-correlation functions, as well as analysis in the frequency domain (using the Fast Fourier Transform or other time-frequency transformations) such as power spectral estimates, cross-spectral functions, or linear coherence.[23] Parametric linear methods include, among others, autoregressive (AR) and autoregressive moving average (ARMA) models,[57,87,88] and provide an alternative way to estimate properties of the power spectrum. These main branches are accompanied by pattern recognition methods involving either a mixture of techniques mentioned above or, more recently, taking features extracted from neurosignals and inputting them into a variety of novel classifiers, such as probabilistic artificial neural networks. Since linear methods provide only limited information as to the dynamical aspects of the EEG, it is argued that they cannot fully characterize the complicated, apparently irregular behavior of the complex nonlinear dynamical system *brain*. In this system, nonlinearity is introduced already on the cellular level, since the dynamical behavior of individual neurons is governed by integration, threshold, and saturation phenomena. There is evidence, that the epileptic process enhances the nonlinear deterministic structure in the EEG.[6,8,24] In order to allow for an improved characterization of complex dynamics, nonlinear analysis techniques have been developed that provide a methodologically different approach to EEG analysis. Within this framework, the dynamical behavior is embedded in a so-called *state space*. This generally high-dimensional cartesian space is spanned by all state variables (i.e., the number of degrees of freedom) of a system, and the system dynamics generate a *trajectory* through this space. Properties of the trajectory in state space can then quantitatively be characterized by nonlinear measures (see below). When embedding EEG time series, the number of state variables (i.e., the number of degrees of freedom of the system brain) are unknown. Fortunately, the theorem of Takens[202] allows to reconstruct a so-called *equivalent state space* even from a single time series using the so-called method of delays (*time-delay embedding*) (see also references 164 and 183). Here the basic assumption is that a single but long enough and accurate measurement of a stationary dynamics is sufficient to capture all the relevant system properties necessary to reconstruct the state space. In terms of EEG analysis, one may assume that an EEG signal reflects the influence of the multiple variables participating in brain dynamics.[49,143] The reconstruction of an *m*-dimensional state space (here *m* is the so-called *embedding dimension*) requires the generation of *m* time-delayed versions of an EEG time series; that is, each version consists of successive points of the original time series separated by a fixed time delay (Ï„). A variety of techniques have been proposed that allow one to estimate either *m* or Ï„ from a measured time series, assuming, however, that the other parameter has been chosen appropriately beforehand. Because of this mutual dependence, the time-delay embedding of an EEG time series in a high-dimensional state space is regarded as a crucial point in nonlinear EEG analysis. An improper state space reconstruction is a common source of errors and can lead to a mischaracterization of the dynamics. In case of multichannel EEG recordings, an alternative embedding scheme would be to use each channel as an axis of the cartesian space. In this case the embedding dimension *m* is fixed and equals the number of recording channels. Although this *spatial embedding* is regarded to be the more natural scheme, several assumptions have to be made beforehand that might lead to similar problems as with the time-delay embedding and are matter of debate.[103,172] These problems include the optimal distance between different recording sites, which is usually fixed, among others. It remains to be established whether the combined use of techniques (so-called *spatial-temporal embedding*[141]) can be regarded as more appropriate for EEG analysis.

Table 1 Studies on Seizure Prediction Using Different Univariate and Bivariate Measures Comprising Both Linear and Nonlinear Approaches along with the Observed Mean Prediction Times

Authors	Characterizing Measure	Mean Prediction Time (min)
Iasemidis & Sackellares, 1991[79]	Lyapunov exponent	up to 10
Lehnertz & Elger, 1998[119]	Correlation dimension	12
Martinerie et al., 1998[141]	Correlation density	3
Le Van Quyen et al., 1999[111]	Similarity index	6
Le Van Quyen et al., 2000[108]	Similarity index	4

Le Van Quyen et al., 2001[113]	Similarity index	7
Iasemidis et al., 2001[75]	Dynamical entrainment	49
Litt et al., 2001[133]	Accumulated energy	19
Lehnertz et al., 2001[117]	Correlation dimension	19
Navarro et al., 2002[157]	Similarity index	8
Schindler et al., 2002[186]	Simulated neuronal cells	83
Hively et al., 2003[71]	Dissimilarity measures	52
Mormann et al., 2003[149]	Synchronization/correlation	86/102
Mormann et al., 2003[150]	Phase synchronization	4â€“221
Niederhauser et al., 2003[158]	Sign periodogram transform	<1.4
ChÃ¡vez et al., 2003[28]	Phase synchronization	>30
Hively & Protopopescu, 2003[71]	Dissimilarity measure	35
D'Alessandro et al., 2003[37]	Feature selection	3
Iasemidis et al., 2003[80]	Dynamic entrainment	100
van Drongelen et al., 2003[211]	Kolmogorov entropy	21
Drury et al., 2003[43]	Marginal predictability	30
D'Alessandro et al., 2005[38]	Feature selection	2
Esteller et al., 2005[54]	Accumulated energy	85

Iasemidis et al., 2005[81]	Dynamic entrainment	78
Le Van Quyen et al., 2005[114]	Phase synchronization	187
Navarro et al., 2005[156]	Similarity index	>13
Chaovalitwongse et al., 2005[27]	Dynamic entrainment	72

Studies that did not report prediction times were not included.

In order to characterize dynamics in state space, a number of univariate and bivariate approaches are available. Quantities such as an effective correlation dimension, correlation density, entropy-related measures, or Lyapunov exponents allow one to draw inferences about the number of degrees of freedom (or *complexity*), the amount of order/disorder, or the degree of *chaoticity* or predictability in a single time series. Other univariate measures aim at discriminating between deterministic

and stochastic dynamics[92] or provide an estimate of the amount of nonstationarity.[36,176,177,178]

Bivariate measures such as the similarity index,[111] phase synchronization,[104,109,152,203] nonlinear interdependency,[9,110,138] and other measures for generalized synchronization allow one to estimate dynamic interactions between two time series; some of these approaches can even provide information about the direction of interdependence.[9,29,180,190] A full description of the physical and mathematical concepts underlying these quantities along with their implementation details for EEG analysis is beyond the scope of this chapter. Instead, we summarize in Table 1 the various measures, concepts, and achievements of univariate and bivariate approaches used for seizure prediction.

Further details can be found in a number of tutorials, conference proceedings, or text books on nonlinear time series analysis.[1,45,49,52,58,65,69,84,90,91,93,118,134,163,171,187,195]

Despite their great potential for a detection of subtle changes in brain dynamics, both linear and nonlinear analysis techniques must be painstakingly applied, and the results obtained should be interpreted with great care. Many techniques place great demands on the recorded time series with respect to the precision of the data and the absence of noise. Almost all techniques assume the underlying dynamical system from which the recordings were taken to be stationary. None of these requirements, however, can be exactly fulfilled in practice. With respect to nonlinear EEG analysis, numerous studies have identified factors that might alter the absolute value of a measure: Properties of EEG electrodes, the precision of the analog-to-digital converter, amplifier and filter settings, and different recording montages might all strongly influence nonlinear measures. Finally, problems specific to the individual algorithms have to be taken into account. Based on these potential limitations, we feel that it is advisable to avoid claims on the existence of chaotic behavior in the EEG, and instead to use nonlinear measures as tentative indexes of different brain states when analyzing EEG data.

Statistical Considerations

The current state of seizure prediction is that there is strong evidence from several methods for identifiable precursors preceding partial-onset seizures. This conclusion, however, is based on retrospective analyses of mostly intracranial EEG data recorded during presurgical evaluation of patients during evaluation for resective surgery. Up to the time of this writing, no study has been published that demonstrates unequivocal seizure prediction in blinded, prospective, randomized clinical trials. Reasons for this become apparent when considering the major methodologic steps involved in seizure prediction algorithms along with problems posed by respective study design.

Typically, the first step in a retrospective seizure prediction study consists of calculating a certain characterizing measure from the EEG using a moving-window technique. The length of the time window is chosen so that there is a reasonable trade-off between approximate stationarity of the EEG signal and sufficient number of data points to characterize the EEG dynamics. The resulting temporal evolution of the measure (*measure profile*) is then scanned for prominent characteristics that can be related to the actual seizure times. These features might be

drops or peaks (e.g., quantified as threshold crossings) or any other distinct pattern in the measure profile. In a second step the measure's capability to distinguish the pre-ictal state from the inter-ictal interval is evaluated with test statistics quantifying the occurrence of these features relative to the seizure times, which results in some kind of performance value. A high performance value is assumed to reflect the existence of a pre-ictal state and the capability of the applied measure to detect it.

The first question that arises from these types of analyses is which of all the characterizing measures presented above is the best, though with their different time horizons and processing methods they constitute different ways of viewing the same process. As some studies have demonstrated, it appears that some combination of measures will probably be required to carry out reliable seizure prediction tailored to individual patients.[38,117] Usually, algorithm performance requires optimizing numerous computational parameter choices and sometimes the choice of an estimation algorithm. Upon close inspection, these choices often rely on a posteriori knowledge, which interposes significant risk of in-sample overtraining. Certainly, what is true for a single measure holds also for a larger number of different measures. The application of a huge variety of measures to the EEG might yield seemingly good results just by chance (particularly on a limited database), if appropriate methods for dealing with statistical issues of multiplicity are not implemented. The resulting explosion in computational degrees of freedom emphasizes the need for control tests and independent validation. This is necessary to avoid the potential for fitting results to the data and to enable independently reproducible results. Many measures have a clear physical meaning since they are derived from mathematical-physical theories that allow one to characterize complex spatiotemporal dynamical systems. However, due to a huge number of influencing factors and constraints associated with analyzing EEG data, strict interpretation of particularly nonlinear measures (e.g., in terms of attractor dimensions, deterministic chaos, or entropy) is rarely justified. Nevertheless, many classical measures can still be used as tentative indexes of different brain states, and more recently developed measures often allow less ambitious but more straightforward interpretation. Ongoing research will clarify whether a meaningful physiologic interpretation in terms of underlying brain dynamics can be achieved.

The next issue concerns the EEG recording. Taking into account that epilepsy is a heterogeneous disorder, what constitutes an optimum spatial and temporal sampling of the ictogenic process? How to select optimum data acquisition parameters such as sampling rate, filter settings, resolution of the analog-to-digital converter, and electrode montage is not straightforward, and may depend on things that are currently unknown, such as the temporal and spatial resolution of physiologic events critical to seizure generation. How many electrodes are necessary? Is a noninvasive recording sufficient or does a good seizure prediction technique require the higher frequency components only available in intracranial recordings? More importantly, what constitutes a *good* data set for testing sensitivity and specificity (see below) of a seizure prediction algorithm? Many of these more technical issues have not been satisfactorily addressed yet, and there may be a number of reasons for this. Data acquisition parameters like sampling rate and filtering have to follow the demands of the sampling theorem, and have traditionally been based on analog paper-and-pen EEGs and the requirement that they allow for good visual inspection of the EEG. With modern digital equipment, cheaper computer storage, and recent interest in single unit recording, acquisition rates of tens of kilohertz per channel are now possible, but deriving meaning from terabytes of such data is a daunting prospect, particularly when searching for unknown patterns. Traditionally, acquisition parameters are chosen to allow adequate sampling of target waveforms, balanced with the need to keep data storage capacity as small as possible. Almost all EEG data sets that have been studied up to now were recorded with data acquisition parameters set by clinical EEG systems, without specific regard to prediction study requirements. It is well known that these parameters affect virtually all characterizing measures, and it still remains an open issue whether they must be regarded as potentially confounding variables in seizure prediction studies. The placement of EEG electrodes typically follows roughly common protocols, guided by the demands of the presurgical evaluation and limited by the need to protect patients, but there is little standardization from center to center in this regard. Without understanding more about seizure generation in the epileptic network, there is no way to know what might be optimal spatial sampling for seizure prediction studies. Clearly, more sensors would be better, including those placed into deep integrating structures, such as the thalamus, but this type of spatial sampling is currently only possible in animal studies, because of patient safety concerns. Even with the number of channels available from implanted electrodes in humans, the spatial information available for measuring the ictogenic process has been used insufficiently. Most researchers have confined analyses to at most one or several electrodes, relying on a posteriori knowledge as to location and extent of the ictal onset zone. At best, data from sites distant from the ictal-onset zone are included in these studies only for comparison to more â€œnormalâ€ regions. Others have developed optimization schemes that allow one to select certain electrodes out of a large number of electrodes[27,37,75,76,80,114] relying on a posteriori knowledge as to the dynamics of the ictogenic process. Due to the availability of more powerful computers, it is only recently that EEG data from all electrode sites have entered seizure prediction studies. Interestingly, some studies reported that the site selected as best for prediction was not in close vicinity to the epileptic focus but could be located in remote or even contralateral brain structures.[38,89,114,150,151,156] This seemingly counterintuitive finding may indicate the importance of brain outside of the ictal-onset zone but within the â€œepileptic networkâ€ in generating clinical seizures (see also references 218 and 219). This is also in accordance with findings showing that the synchronization of specific populations in relation to the epileptic focus may be of crucial importance to determine whether a seizure is likely to occur and to spread.[114,149,150,151] On the other hand, it may also indicate a rather nonspecific phenomenon whose temporal proximity to seizure onset was just by chance. Obviously, correct site selection would be a practical problem in instances where electrode contacts are limited. At present, it is not clear at all whether optimum recording sites can be identified.

Large amounts of well-documented, continuous, prolonged, multichannel EEG data are very difficult to acquire in a busy clinical environment, and storage of a diverse archive of data is an expensive prospect. Many institutions store short-lasting (typically a few minutes only) inter-ictal and/or peri-ictal epochs for documentation purposes or because of legal requirements for medical records and results. It is therefore not surprising that many past studies lack reference to the interictal state in terms of insufficient control data or baseline epochs. In other words, many studies have focused merely on sensitivity without considering specificity of the applied techniques. Maiwald et al.[140] reviewed 14 seizure prediction studies published between 1998 and 2003 and concluded that in only half of these studies was the performance of the applied seizure prediction technique tested against interictal control data. Proper selection of control data poses another problem, that even during the interictal period the epileptic brain is different from â€œnormal,â€ and that there may be abnormal dynamical changes that are not necessarily followed by a seizure. Other nonstationary variables such as sleepâ€"wake cycles or different cognitive states must definitely be regarded as potential

confounding variables in seizure prediction studies. In addition, during presurgical monitoring an artificially high seizure frequency (0.15 seizures per hour, or 3.6 seizures per day[68]), seizure clustering, and atypical seizures may occur due to the reduction of anticonvulsive medication. Under normal conditions, patients with pharmacoresistant focal epilepsy have a seizure frequency of about three seizures per month, that is, 0.0042 seizures per hour.[13] In order to thoroughly evaluate the suitability of possible seizure prediction techniques, reference to continuous, prolonged, multichannel EEG data must be regarded as indispensable.

EEG data accompanying clinical information must be as complete as possible to account for other factors that may modulate seizure generation. Relating mathematical approaches to clinical, video, and neurophysiologic data, a massive undertaking, has begun only recently.[148,156] There are now attempts to identify and mark the broad range of physiologic and pathophysiologic changes that occur in these measures interictally and at seizure onset in a standardized and clear-cut manner. Given imperfect methods for determining exact clinical and EEG onset times for seizures, at present, reference to EEG onset of seizures, as opposed to clinical seizure onset, is preferred.[122]

The above considerations indicate that seizure prediction studies have to be designed with great care, and with an acute awareness that as we delve deeper into seizure generation we may be confronted with other, yet unforeseen problems. A thorough evaluation of potential predictors and potentially confounding variables requires large, high-quality, meticulously collected and annotated data archives that are well characterized and represent the heterogeneity of patterns and patients found in human epilepsy. Equally important, a review of the literature points to the need for proper statistical validation in order to assess the performance of seizure prediction algorithms. This is a major issue in the field at present, and one that has been neglected by many past studies.

Assessing the predictive performance for a given algorithm usually involves analysis of the so-called receiver operating characteristics (ROC) curve that is based on quantities such as sensitivity and specificity. *Sensitivity* is defined as the ratio of true positive classifications (or predictions, detections, or warnings) to total number of (true and false) positive classifications. *Specificity* is defined as the ratio of true negative classifications to total number of negative classifications. The *false-positive rate* is defined as the average number of false classifications per unit time, and is one accepted measure of specificity. Finally, *performance* can be defined as the square root of squared sensitivity plus squared specificity. Let us assume that a seizure prediction method requires adjustment of a parameter (e.g., some threshold). With ROC, values of the parameter are continuously varied, and the sensitivity of the classification for these parameter values is plotted against 1 minus the corresponding specificity. The resulting curve is termed the ROC curve, and each point on the curve corresponds to a different parameter value. An ideal classifier has a curve that goes from the bottom left corner to the top left and then from the top left to the top right (two perpendicular lines). An unspecific, random classifier produces a ROC curve that is a diagonal line.

The aforementioned considerations indicate the tight dependence between sensitivity and specificity (a high sensitivity may be achieved at the expense of a poor specificity, and vice versa) and the need to evaluate both quantities together[161,162] in order to achieve a meaningful estimate of the performance of a seizure prediction method. Many past studies have reported on the sensitivity of a given method only, and it appears that the mostly positive results had been achieved by an in-sample overoptimization of parameters and by using insufficient control data. Recently, Winterhalder et al.[222] suggested what they call the *seizure prediction characteristic* to evaluate seizure prediction methods. The authors proposed to extend the ROC approach (i.e., investigation of sensitivity and false prediction rate) by including additional assessment criteria that are based on clinical and statistical considerations. Since, at present, none of the current prediction methods is able to indicate the exact point in time when a seizure is to occur, the authors suggest considering this uncertainty by referring to the â€œseizure occurrence period,â€ defined as the period of time during which a seizure is to be expected. In addition, to render a therapeutic intervention possible, they refer to an important interval as the minimum window of time between an â€œalarmâ€ raised by the prediction method and the beginning of the seizure occurrence period. They and other investigators refer to this interval as the â€œseizure prediction horizon.â€ Due to the interdependence between sensitivity and specificity, and that it may not be possible to avoid false alarms completely, the authors suggest using a maximum false prediction rate as a measure for algorithm performance. This quantity can be derived from the average seizure incidence, which determines sensitivity. Finally, the authors propose to compare the achieved sensitivity values with those obtained from random and periodical prediction methods. Using this framework, the same group shows that the achieved performance values of three previously proposed prediction methods (dynamical similarity index, accumulated energy, and effective correlation dimension) are significantly better than the performance of unspecific methods.[140] They conclude that this finding indicates the existence of specific â€œpredictiveâ€ information in pre-ictal epochs and that the investigated methods are sensitive to this information. The resulting seizure prediction characteristics, however, were judged as not yet sufficient for clinical application.

Studies like these are important since they clearly point to deficiencies in current seizure prediction methods. Showing that a method is sensitive enough to detect a pre-ictal phenomenon is only the first step in developing a seizure prediction method. Unfortunately, a high sensitivity does not prove that the method is suitable for clinical applications. Even a highly sophisticated performance estimation, as the one above, is confronted with a number of problems for which there are currently no satisfactory solutions. Many quantities that enter performance evaluation tests require parameter optimization or a choice of parameter ranges. As an example, seizure prediction methods usually require adjustment of some threshold (or reference) level, and a deviation of some characterizing measure from this threshold is assumed to (truly or falsely) indicate a pre-ictal state. The threshold level is usually derived from analyses of control (also called baseline or reference) data that should represent all conditions and states of consciousness from which seizures can emerge (which again calls for large, high-quality, and meticulously annotated data archives). In this context, it should be mentioned that there is now consensus among the major groups in the field that choice of short reference periods, even if done randomly, could exert great influence over results. It is important to note that a properly designed study based upon randomly chosen data epochs could be made statistically sound, if strict statistical criteria are met that dictate a sufficient number of randomly chosen interictal segments. Unfortunately, there would still be concern that all patient states might not be adequately represented. Because of these considerations, recommendations from the First International Collaborative Workshop on Seizure Prediction include that it would be best to avoid the use of short reference periods.[122]

When calculating a threshold level, the question arises as to whether one should consider it as constant or whether one should account for possible slow drifts in dynamics (e.g., due to changing antiepileptic drug levels during medical tapering,[120] changes in vigilance states,[54,116,133] or other circadian fluctuations[101]) and use an adaptive threshold level instead. The latter makes a prospective implementation of an

algorithm for seizure prediction a nontrivial problem. Closely related to appropriately selecting a threshold level is the problem of defining false classifications, which requires a clear-cut delineation of a pre-ictal state from the inter-ictal state. Currently available information indicates that a pre-ictal state might last from minutes to hours to days. An *inappropriately* selected duration would lead to an increased number of false classifications. More importantly, the model of a pre-ictal state assumed by a prediction algorithm has enormous potential impact upon its performance. For example, the interictal-to-pre-ictal transition is usually assumed to follow some rectangular function, with a sharp boundary between states. If, however, this transition follows another function (e.g., linear or exponential or log-periodic), very early or intermittently occurring precursors would wrongly be classified as false positives. The situation becomes even more complicated when taking into account the spatial distribution of the interictal-to-pre-ictal transition. From their synchronization studies, Mormann et al.[152] concluded that an epileptic seizure might be interpreted as the climax of a process of changes in brain dynamics that starts long before the seizure. In an attempt to relate these dynamic changes to EEG-based physiology, Litt et al.[133] suggested a possible evolution of waxing and waning events, such as bursts of complex epileptiform activity, subclinical seizurelike bursts (chirps), and alterations in neuronal activity measured by energy changes that might characterize this process. Unfortunately, we still lack the physiologic or dynamic understanding to delineate a pre-ictal state both in time and space, particularly not from a level that relates to neurophysiology on the cellular and network level. Of interest, a recent study by Kalitzin et al.[89] indicates that important clues for possible dynamical scenarios that lead to epileptic seizure onsets may be obtained from analyzing the so-called phase demodulation of intracranial EEG recorded interictally during intermittent electrical stimulation.

The above considerations clearly indicate that assessing the performance of a seizure prediction algorithm strongly relies on assumptions of a model of seizure generation, including the spatiotemporal characteristics of the process and, more importantly, on the existence of a pre-ictal state. When reviewing the seizure prediction literature, it is important to note that if a pre-ictal state does not exist (null hypothesis), no information predictive of an impending seizure could be extracted from the EEG, but many algorithms could still perform better than an unspecific, or random, prediction algorithm. This is because any measure tested on recorded data will likely contain fluctuations, generating a nonzero probability of attaining any course within its range of definition. Even though this probability may be very small, the large number of potentially confounding variables discussed above is likely to lead to an increased probability for finding a combination of them, which then leads to a nonzero performance value. The influence of the different degrees of freedom on the statistical significance of the obtained results is difficult, if not impossible, to estimate on a theoretic basis. Hence, it is difficult to decide whether a given performance value indicates the existence of a pre-ictal state or whether it is consistent with the null hypothesis stated above. Although there are statistical methods for addressing these issues, these require careful sampling of distributions of feature values amassed over time, and only with adequate amounts of continuous data allow definition of expected measurement error and requirements for statistically significant results.

In order to address this ambiguity, Andrzejak et al.[7] proposed an alternative approach to the problem, using the concept of *seizure time surrogates*. In this method, original seizure onset times are replaced with â€œsurrogateâ€ times randomly chosen from the interictal intervals. Specified properties of the original sequence (such as total number of seizures, distribution of intervals between consecutive seizures, and clustering of seizures) can be imposed as constraints on the surrogate seizure onset times. A seizure prediction algorithm is then applied to the original seizure time sequence and the surrogates. Assuming that a pre-ictal state exists, and that the algorithm is able to detect it, the performance should be higher for the original seizure times than for the surrogate times. Alternatively, Kreuz et al.[101] proposed the concept of *measure profile surrogates,* in which the seizure onset times are kept fixed and instead a constrained randomization of a measure profile is performed using the method of simulated annealing. Using this method, the amplitude distribution of a measure and the autocorrelation function (accounting, for example, for circadian fluctuations) of the measure profile are preserved. As with the seizure time surrogate concept, a seizure prediction algorithm is applied to the original measure profile and the surrogates, and the highest performance is expected for the original measure profile, provided that a pre-ictal state exists and the algorithm is able to detect it. Both methods have conceptual advantages and disadvantages, and the concept of measure profile surrogates has a greater computational burden. Both concepts are based on null hypothesis tests, and the nominal size is determined by the number of surrogates. It is important to keep in mind, however, that the fact that the null hypothesis cannot be rejected does not prove its correctness. Rather, there may be alternative explanations for this result.

Taking into account the above considerations, and using the concept of seizure time surrogates, Mormann et al.,[151] within the scope of the First International Seizure Prediction Workshop, investigated the predictability of seizures by retrospectively analyzing multiday intracranial recordings from five patients recorded at different epilepsy centers comprising 51 seizures and a total recording time of 311 hours. They compared the performance (based on ROC statistics) of 30 univariate and bivariate measures, comprising both linear and nonlinear approaches, in terms of their ability to distinguish between the interictal state and the pre-ictal state. Using different evaluation schemes that take into account the majority of potentially confounding variables discussed so far, they were not able to detect a pre-ictal state, if one assumes a consistent effect on the EEG at all electrodes in all seizures of a patient and across patients, without comparison to some adaptive threshold level. If, however, one allows variable effects such as recording sites selected as best for prediction, a prolonged pre-ictal state (up to hours) could be detected using bivariate measures. Their findings suggest that a prospective seizure anticipation system is, in principle, possible and would perform better than random. Whether this is sufficient for a clinical application would need to be decided on an individual basis.

Studies in Animal Models of Epilepsy

In order to gain deeper insights into the neurobiologic mechanisms underlying pre-ictal dynamical changes, approaches that are based on experimental models of epilepsy are highly desirable. Although there is a considerable bulk of literature on animal models of epilepsy, the phase of transition to the seizure state is not yet fully explored. Early work on the neurophysiology of the interictal-to-ictal transition can be found as early as the late 1960s, in the work of Dichter and Spencer.[41,42] In a penicillin model of epilepsy, these studies demonstrate a progression in the complexity and amplitude of interictal discharges during the interictal-to-ictal transition. While other studies have demonstrated similar changes, it was not until more recently that in vivo studies in acute and chronic animal models reported distinguishable preseizure EEG patterns several minutes prior to seizure onset.[59,129,165,168] Other investigators[201] have showed seizure predictability from

stochastic models of temporal interdependence between the ictal and interictal states. Studying four pharmacologic epilepsy models, Widman et al.[220] reported on a reduced dimensional complexity of in vitro hippocampal recordings in the seconds to minutes prior to the manifestation of paroxysmal depolarization shifts in xanthine and penicillin models. The authors went on to demonstrate that there was no preceding loss of complexity in low-magnesium and veratridine models. In contrast, Chiu et al.[32] recently analyzed in vitro hippocampal recordings from a low-magnesium model using wavelets and artificial neural networks and claimed prediction of seizurelike events as early as 60 seconds before, and with more than 75% accuracy within a 30-second precision window.

Although these studies indicate that discernible pre-ictal patterns can be detected, at least in some experimental models of epilepsy, they must, at present, be regarded as â€œproof of principle studies,â€ since most lack a sound statistical validation, suffering from the same limitations of the human studies discussed above. In addition, a number of the studies used for seizure prediction from animal tissue, both in vivo and in vitro, have focused on acute seizure models whose behavior is not clearly analogous to spontaneous seizures in humans. These studies in animal models of epilepsy have considerable potential to address questions regarding the mechanisms regulating seizure generation; however, fundamental questions about underlying cellular mechanisms still remain unanswered. Earlier in vitro studies of ictogenesis suggested that the pre-ictal transition may reflect gradual changes in network excitability during the interseizure interval. In the 30 to 60 seconds preceding a seizurelike event, induced by high extracellular potassium, the excitability of CA1 pyramidal cells appeared to increase gradually to some threshold level, at which point the next incoming interictal burst precipitates a seizure.[209] These pre-ictal changes in neuronal excitability are hypothesized to reflect the slow recruitment of an increasing number of excitatory interconnected neurons into synchronous discharges.[146]

In chronic epilepsy, it is known that an increased propensity for hypersynchronization is associated with neuronal loss and synaptic reorganization that can be observed in human mesial temporal lobe epilepsy, and in kindling and kainic acid models.[15] The transition to ictal activity, however, is often attributed to a breakdown of the interneuronal inhibitory control, which is assumed to be the major factor responsible for ictogenesis in human temporal lobe epilepsy and analogous animal models of epilepsy. This assumption is supported by early animal model studies that indicate that the inhibition of neuronal activities peripheral to the epileptic focus can be of crucial importance in determining whether or not a seizure is likely to occur and to spread.[142]

A more recent hypothesis[17,97] suggests that a pre-ictal imbalance between inhibition and excitation might be due to some transient excitatory effect of GABAergic (*Î³*-aminobutyric acid) function, resulting in repetitive high-frequency epileptiform bursts. Supporting this hypothesis, the prolonged repetitive activation of inhibitory neurons has been shown to induce an intracellular accumulation of chloride in principal cells, leading to a transient disinhibition of the local networks and, thus, to a decreased threshold for subsequent epileptiform discharges and ictal events.[99] The potential ictogenic effect of GABA-mediated depolarization has also been observed in other studies[33] (for a review, see reference 35). Finally, slow changes in extracellular ion concentrations are assumed to contribute to the gradual depression of inhibitory mechanisms. In particular, some seizures are preceded by an increase in the extracellular potassium concentration,[166] and in vitro studies have confirmed a corresponding pre-ictal depolarization of the neuronal membrane potential.[85]

More recently, the cellular basis of pre-ictal changes has been investigated using a hippocampalâ€“entorhinal brain slice preparation exposed to high extracellular potassium[47] and to low magnesium concentrations.[98] In this network, predictable alterations in interictal activity were shown to precede the transition to ictal-like activity. These pre-ictal changes were characterized by alterations in the origin and spread of CA3 epileptiform discharges. Spectral analysis of the interictal epileptiform activity preceding the transition to ictal-like activity revealed a prominent increase in the high-frequency range (200 to 400 Hz). In a very active related area of research, microelectrode studies in vivo in the hippocampus of kainate-treated rats and depth EEG recordings from patients with mesial temporal lobe epilepsy have also revealed 200- to 400-Hz oscillations, termed â€œfast ripples,â€ which have been hypothesized to identify microscopic regions important to seizure generation.[18,19] These oscillations may uniquely occur in areas that generate spontaneous seizures, and may reflect pathologic hypersynchronous population spikes of bursting pyramidal cells.[46] In rat models of chronic epilepsy, fast ripples are seen during the latent period between the occurrence of an initial epileptogenic insult and the onset of recurrent spontaneous seizures.[20] These oscillations may thus be a possible marker of alterations in interictal activity that precede the transition to ictal activity.[207,208] Further investigations at a cellular level during the preseizure state are necessary to validate these hypotheses in humans.[194]

Applications: Clinical and Basic Science

In addition to its scientific appeal, two main motivations for seizure prediction research are (a) its potential to control therapy in antiepileptic devices and (b) to elucidate mechanisms underlying seizure generation. Initial research into antiepileptic devices demonstrated that open-loop stimulation (e.g., paradigms that stimulate in a set â€œonâ€“offâ€ cycle regardless of underlying brain activity) can reduce seizure frequency and severity.[72,96,131,139,205] While initial results are promising, this strategy has not yet made many patients seizure free, and none of these devices has achieved sustained clinical use.[72,131,215] One device, targeting the anterior thalamic nucleus, is in active clinical trials, and no definitive performance results are available as of this writing. Open-loop devices are attractive because of their relative simplicity; their analogy to successful cardiac devices, such as early pacemakers; and their modern origin in successful devices to treat movement disorders (e.g., Parkinson disease, tremor, etc.). While this research continues, focusing on different central targets and stimulation paradigms, an interest in more â€œintelligentâ€ responsive devices, designed using strategies similar to implantable cardiac defibrillators, is under way.

Over more recent years, research into responsive, closed-loop antiepileptic devices, which read and respond to features extracted â€œon the flyâ€ from implantable sensors and processors, has proceeded actively. This is primarily motivated by an attempt to improve upon results from open-loop devices.[100] While trials of these first-generation devices demonstrate proof of principle well, specifically that clinical seizures can be successfully stopped by electrical stimulation triggered after seizure onset is detected, these devices are not yet ready for widespread clinical deployment. Recent results from an initial safety trial, not designed to test efficacy, suggest that responding to seizure onset can reduce seizures by 50% or more in over 40% of refractory epilepsy patients. This result, however, also indicates that this method might not be the most effective path to making patients seizure free (Worrell et al., unpublished). The current state of these responsive devices suggests a significant potential role for therapy triggered in advance of seizure onset on the intracranial EEG, perhaps controlled by seizure prediction algorithms.

The case that seizure prediction is a better method for controlling antiepileptic brain stimulation than seizure detection can be made on two fronts, though, unfortunately, there is not yet class one evidence to support this hypothesis. First, there is evidence from a number of seizure prediction studies quoted above[38,114,150,151] that there is considerable evolution of quantitative features in multiple channels, including changes in synchronization in the epileptic network, prior to the time of detectable seizure onset on the intracranial EEG. Given that abnormal brain activity is often broadly distributed by the time seizures are detected, it seems unlikely that stimulation over a limited region, as is the standard technique with first-generation responsive devices, will be effective in suppressing clinical events. Clinical evidence to support this conjecture is more difficult to come by, as there is little information published in peer-reviewed journals about experience to date with responsive antiepileptic devices. There are anecdotal reports of widespread stimulation, grouping four or more electrode contacts together to form one pole for stimulation of distributed electrodes. To date, only two groups have reported results from responsive stimulation in humans, and were lead by NeuroPace, Inc., and Osorio et al.[100,161] (Worrell et al., unpublished). Because of intense activity in industry to perfect effective antiepileptic devices and bring them to market, current concepts are largely shaped by anecdotal clinical experience, conference abstracts, lectures, posters, and personal communication. With clinical trials currently in progress, it is anticipated that publication in this area should increase substantially over the next 12 to 24 months.

Initial reports indicate that when detection algorithms are tuned to high sensitivity and short detection latencies, so that stimulation is triggered not only by seizures, but also by bursts of epileptiform and rhythmic oscillatory activity often found to occur during periods of increased probability of seizure onset, seizure frequency declined (Pless, unpublished). In addition, under this paradigm, subclinical seizurelike bursts, which appear to increase prior to seizure onset in some patients, have been reported to greatly increase in number but not lead to seizures when repetitively suppressed by responsive stimulation. This result, observed by several investigators, suggests a drive to seize that might be somewhat suppressed by electrical stimulation. An additional explanation might include a critical amount of energy or some other quantity that might need to be dissipated in order to interrupt the process of seizure generation. Again, in the absence of controlled, randomized clinical trials in an adequate number of patients, this information is suggestive, at best, that intervention based on seizure â€œprecursorsâ€ may be useful in suppressing clinical events. In responsive stimulation studies by Osorio et al.,[161] prediction paradigms were not tested in human stimulation trials.

While discussing the clinical application of seizure prediction algorithms, it is instructive to consider how such an algorithm might function in a responsive antiepileptic device. Since current thinking is that seizure generation is likely a probabilistic phenomenon, most investigators agree that prediction algorithms will, at best, be able to identify periods of increased probability of seizure onset. The most important factor governing application of prediction algorithms for device control is the nature of the therapy being administered. If the treatment has few or no side effects, then high false-positive rates can be tolerated, as administering therapy when seizures are not imminent carries little or no penalty. If the algorithm is able to calculate the probability of an impending seizure at a given time, then the intensity of therapy can be increased in proportion to the likelihood that a seizure is going to occur. This scheme would also make sense if seizures are more difficult to pre-empt as they progress in the generation process. Finally, therapy is administered more intensely and perhaps over a broader geographic area as seizure generation progresses and the probability of onset continues to rise, until a seizure is detected, and maximal therapy is administered. At this point it might be reasonable to issue an alarm to the patient that a seizure is imminent. Should therapy not be immediately effective, it is possible for the antiepileptic device to broadcast an alarm, perhaps over a broadband communications link, or contact some central station to call for help unless the patient deactivates this process, demonstrating that awareness has returned. While this is only one way in which a predictive antiepileptic device might be deployed, it gives some sense of how prediction algorithms might be translated into a practical therapy.

One important aspect of implantable antiepileptic devices is the potential, in some models, to provide data vital to understanding the process of seizure generation. Some current devices have the capability for storing EEG information at different points in the seizure cycle, a capacity that might be possible to expand. This capability provides, for the first time, a way for investigators to look at intracranial EEG data acquired in the steady-state human condition, in the absence of proximate surgery or medication taper. Though the buffering capacity of these devices is likely small, the ability to download information from them over time provides an unprecedented opportunity to observe the natural seizure cycle in human patients. The authors are hopeful that these data will eventually become available for analysis by groups using a variety of different techniques. More confined data downloads at different times in relation to seizures might also be used to reconstruct the process of seizure generation, but as discussed above, relying on fragmented data is a more challenging task than analyzing prolonged, continuous data streams.

The utility of seizure prediction in understanding mechanisms underlying seizure generation also remains largely uncharted territory. While a number of investigators have attempted to predict seizures in a variety of mechanism-driven experiments, this body of work suffers from the same statistical and methodologic limitations as the more clinical studies noted above. Primary knowledge from prediction studies with macroelectrodes that could be extremely useful in understanding ictogenesis are such things as the period of time over which seizures are generated, what components of the epileptic network are necessary for clinical events to occur, how seizure precursors are temporally and spatially distributed in brain, and what effective intervention strategies for modulating this process are. The answers to these questions might guide basic science investigations to specific mechanisms. For example, if the seizure prediction horizon turned out to be on the order of seconds, then mechanisms related to ion channel or neurotransmitter function might be areas of focus for seizure generation experiments. Longer periods of time, perhaps minutes, might point to slower second messenger systems for study. More prolonged periods of seizure generation, perhaps minutes to hours or longer, could point to protein transcription, synaptic plasticity, and other mechanisms that might better fit into this time frame. If the pre-ictal state is found to be a permissive one, waxing and waning between false starts that back to the interictal period and then only occasionally to seizures, this finding might point to some oscillating pathologic process that is *gated* by another, perhaps unrelated mechanism.

These same types of ideas might also better elucidate the functional structure of the epileptic network. For example, if very high-frequency precursor events are found that spread very rapidly through local cellular regions, mechanisms involving ephaptic conduction and gap junctions might be implicated. If precursor spread is measured in longer intervals, it might be attributed to more typical synaptic conduction. Lateral cortical spread versus dispersion of signals via large fiber tracts are

also questions that could be answered by appropriately crafted seizure prediction studies. These are just a few ways in which seizure prediction algorithms and study might contribute to our basic knowledge of seizure generation, and perhaps to the development of better therapies.

Challenges

The science of seizure prediction is now approximately 15 years old, and maturing. The overt initial enthusiasm that resulted from finding changes in â€œchaoticâ€ measures reliably associated with periods prior to seizure onset has now given way to careful introspection. There is now a focus on meticulous data acquisition, annotation, study design, and rigorous statistical design of prediction studies and validation of results. The last 5 years has seen established groups and methods come under increasing scrutiny, as new investigators enter the field and newer techniques are developed to benchmark algorithms against random predictor performance and against the null hypothesis that there is no pre-ictal state. There is also pressure to get an answer and develop methods ready for clinical deployment. This is driven by a keen awareness that patients are likely to benefit considerably through second-generation responsive antiepileptic devices if researchers can field working algorithms for seizure prediction and validate them in blinded, prospective, clinical trials. There is great need for establishing convincing, iron-clad evidence for the existence of a pre-ictal state and an appropriate model for its behavior in human epilepsy. Researchers are acutely aware of the heterogeneity of epilepsy and the fact that one model may not work in all epilepsy syndromes. An improved mathematical modeling of the dynamics underlying the transition to seizures[130,136,137,199,200,217,218,219] may help to test various hypothesis concerning pre-ictal brain dynamics and its relation to endogenous and exogenous control parameters. There is also a great need for new analysis methods, using multivariate techniques[5,30,155,184,185,223] to analyze data streams from multiple sensory sites simultaneously, and even to sample at multiple temporal and spatial scales, from single neurons to ensembles, local then global networks, to investigate the physiologic substrate for larger-scale quantitative observations. Along with these observations will come improvements in our ability to collect, store, and analyze longer, more complete, and broader-band data sets. This work is already under way as a collaborative effort through the International Seizure Prediction Group. Following initiation of an international collaborative working group in this area, in Bonn in 2002, the task of establishing an extensive archive of high-quality, broadband, meticulously collected and annotated data archive from humans and animal models of epilepsy is getting under way. New hardware and software platforms[154] will likely provide more computational power, such as through VLSI implementation of algorithms,[31,102,191] while an effort to reduce the complexity of algorithms continues.[196] Finally, more work on developing and understanding spontaneously seizing animal models of epilepsy for use in prediction research will allow us access to deep brain structures and other locations in the epileptic network that cannot be explored in human studies, due to safety concerns. Characterizing and verifying the clinical presentation, reliability, and reproducibly of these models will be vital to interpreting results involving these animals. All of these factors promise increasing progress in the field of seizure prediction, now tempered by experience and a knowledge that this is a complex, long-term problem. Most importantly, we are starting to appreciate exactly what the task is that we are trying to accomplish, including articulating the benchmarks required for knowing when we've succeeded in predicting epileptic seizures.

Summary and Conclusions

In this chapter we have tried to give a broad overview of the field of seizure prediction and its history, accomplishments, controversies, and potential for future development. In a work of this scope it is inevitable that some contributions may be over- or underemphasized, depending upon the points to be made in the text. Seizure prediction remains an exciting field, with the potential to have significant impact upon the quality of life of our patients with epilepsy, in the form of newer and more effective treatments and in expanding our knowledge of how seizures are generated in the brain. What is clear, after the seminal contributions of a few insightful research groups over 15 years ago, is that the problem is large, and will require the collaborative efforts of a dedicated international group of investigators to solve it. We are hopeful that the pace of discovery in this relatively new field will continue to accelerate, as we begin to deal with our growing appreciation of the complexity of the problem.

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Chapter 86

Optical Imaging of Seizure Activity

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Introduction

Recent advances in imaging techniques have provided the clinician with new methods to identify epileptic foci, rolandic cortex, and eloquent language areas. The best method for understanding how these imaging techniques, such as magnetoencephalography (MEG), positron emission tomography (PET), single photon emission computed tomography (SPECT), functional magnetic resonance imaging (fMRI), and optical imaging, fit together is to examine briefly their temporal and spatial resolutions.[11,14,18,30,31,53,55,57] Accurate maps of brain function and the spread of epileptiform activity require excellent spatial resolution to identify interictal activity and the site of onset of ictal activity and to find the source of the epileptic activity and the pathways by which the seizure activity spreads.[13,47,49] Unfortunately, although each of these new methods holds significant promise, none stands alone to provide the unique answer for identifying epileptic foci and mapping functional activity. PET (Chapter 80) provides three-dimensional information regarding functional activity but has a temporal resolution of only 40 seconds and a spatial resolution of 5 to 7.5 mm^2, limiting its ability to identify ictal onsets and individual interictal activity.[1,38,41] SPECT has similar limitations, although newer imaging compounds have allowed identification of epileptic foci and ictal-onsets zones.[14,53] Functional MRI (Chapter 83) is rapidly advancing, and provides three-dimensional identification of rolandic cortex and has been shown to have the potential to localize eloquent regions, especially Broca area; however, identification of epileptic foci and seizure spread awaits further advancements.[2,11,14,55] MEG (Chapter 78) has the fastest temporal resolution, which is necessary to identify epileptic foci, but is somewhat limited by its overall spatial resolution and the methods necessary to identify rolandic cortex and eloquent regions.[15,18] Optical imaging is one of the latest imaging techniques to be used on human cortex with potential advantages of being the only technique used for intraoperative localization of epileptic foci, rolandic cortex, and eloquent language regions.[26,38,44] This chapter focuses on the use of optical imaging in identifying epileptic foci and the spread of seizure activity in human patients undergoing epilepsy surgery.

Background Studies in Optical Imaging

The foundational work that allowed optical imaging to be used in the operating room to identify speech and sensory cortical regions began more than 50 years ago. Using the nerve trunk of the crayfish, Hill and Keynes[27] found optical changes in the nerve trunk that correlated with stimulation of the nerve. The â€œintrinsic signalâ€ changes (without any voltage-sensitive dyes) in the nerve trunk recorded by a photocell showed an increase in the transmission of light during stimulation and a more prolonged undershoot following the stimulation. The potential uses of optical recordings have been advanced during the last 20 years by the work of a small group of investigators including, but not limited to, Waggoner, Davila, Salzberg, Grinvald, Ross, and Orbach.[7,8,9,10,16,19,36,41] These investigators have made vital contributions to the techniques of optical imaging by screening and developing optical probes of membrane potential (voltage-sensitive dyes) as well as by pioneering different technologies for their use.

Blasdel and Salama[5] expanded on these techniques by using a television camera to obtain greater spatial resolution (120 Ã— 100) than had been previously possible with the standard photodiode arrays (24 Ã— 24) by previous investigators. Blasdel went on to use optical imaging and voltage-sensitive dyes to visualize functional domains of visual cortex in nonhuman primates such as ocular dominance columns and orientation preferences.[3,4] Frostig et al., Grinvald et al., and Ts'o et al.[16,19,54] were later able to identify similar functional regions in the primate visual cortex without voltage-sensitive dyes by using the intrinsic signal changes in the optical reflectants from the cortical surface. These advances led to the first human epileptiform and functional images of language and sensory cortex obtained by Haglund et al.[26] There are a vast number of questions that can be addressed with optical imaging techniques; however, this chapter focuses on the basics of the technique and how the technique can be used to identify epileptic foci and follow the spread of seizure activity across neocortex. The use of optical imaging to localize rolandic cortex of cortical regions involved in higher cognitive functions such as language, memory, or phrase processing is not covered in this chapter and has been reviewed by Pouratian et al.[38] and Suh et al.[50]

Fundamentals of Optical Imaging

Much of the fundamental work on optical imaging concerns the correlation of optical changes observed with voltage-sensitive dyes and electrophysiologic changes.[3,4,5] The voltage-sensitive dyes were known to bind to cell membranes and their absorption properties change when the cell membrane voltage changes. The work on the invertebrates established that the optical changes observed with voltage-sensitive dyes were tightly correlated with action potential depolarization recorded by the means of intracellular electrodes. Correlation of optical changes to functional regions in cortex was developed from work on the rat somatosensory cortex with the identification of individual barrels using single-unit recordings and optical images.[32,34] Blasdel and Salama added to the correlative information on optical imaging and single unit recordings by demonstrating that in the intact nonhuman primate visual cortex, the peak optical changes for the specific orientations correlate with peak optical imaging changes

for that specific orientation stimulus. Anatomic studies also confirm that these optical changes correlated with anatomic boundaries.[3,4,5]

The understanding of the mechanism underlying the intrinsic signals still awaits more detailed studies, but some information has been presented in the last several years. Initially, Frostig et al.[16] demonstrated in a monkey visual cortex that ocular dominance orientation preferences that correlated with anatomic substrates could be found using the intrinsic signal. These studies have shown that the intrinsic signal changes can be used for mapping functional activity during visual-evoked changes.[12,46,47,48,54,56] Using an in vitro slice preparation, MacVicar and Hochman[33] have shown that there was a broad range of wavelengths over which the intrinsic signal changes allow more light transmission through the slice when the Schaffer collaterals are stimulated in the hippocampal slice. They went on to show that the intrinsic signal depends on a Na-K-2Cl cotransport mechanism, which is blocked by furosemide. Because the intrinsic signal is abolished by the Na-K-2Cl cotransport inhibitor, the mechanism underlying the intrinsic signal in the bloodless brain slice preparation appears to be a consequence of cellular swelling. However, Frostig et al.[16] have shown that the intrinsic signal also depends on blood volume and oxygen delivery changes. More recent studies from Haglund and Hochman[23,24] demonstrated that in the human neocortex, the changes in the intrinsic signal could be either due to blood volume or blood oxygenation changes, depending on the wavelength used. Using a wavelength at the isobestic point for hemoglobin (535 nm), changes in the negative direction (the tissue getting darker) are localized to pial arterioles that are dilating during functional or epileptic activity. In contrast, imaging done at a wavelength where the oxy-deoxy-hemoglobin absorption curves are maximally separated shows blood oxygenation changes restricted mainly to the draining veins. These blood oxygenation changes are more likely to go along with the BOLD (blood oxygen levelâ€“dependent) signal that is part of the fMRI imaging paradigms.[29,31,37,40] Using this technique, Haglund and Hochman were able to demonstrate spontaneous ictal activity in the human cortex and more recently interictal activity in the human cortex that correlated with intrinsic signal changes. The most localized changes appear to go along with the blood volume at the isobestic point for hemoglobin (green light, 535 nm).

Optical Imaging of Epileptiform Activity in Animal Models

Visualization of the spread of epileptiform activity has been accomplished in the brain slice preparation.[52] In neocortical slices, stimulation of the white matter demonstrated a certain area of cortical activation in an area increased in its spatial extent when bicuculline, a Î³-aminobutyric acid (GABA_A) antagonist, is added to the bathing medium. These studies point toward a baseline inhibition that leads to a larger area of activation when the slice is disinhibited. However, most of these studies do not demonstrate localization of the seizure focus or how the seizure activity spreads from its site of origin. Intact neocortical preparations have shown an increase in the area of cortex activated when GABA_A antagonists are superfused in the cortex. These studies do not specifically address localization of the epileptic focus or the spread of ictal seizure activity. Grinvald et al.,[20] using a photodiode array and voltage-sensitive dyes (with high temporal resolution but limited spatial resolution), showed the rapid spread of interictal spikes (paroxysmal polarization shift) across the cortical surface. With the advent of CCD (charge coupled device) cameras for identifying functional areas of visual cortex,[4] Haglund and Blasdel[22] used the visual cortex as a model for localizing acute epileptic foci. After the optical imaging of voltage-sensitive dyes was used to map the ocular dominance column (Fig. 1B), an acute epileptic focus was created by placing a 0.5-mm^2 pledget of bicuculline-soaked Gelfoam on the cortical surface for 5 minutes at site No. 5 (Fig. 1A). This application of the convulsive bicuculline created an epileptic focus that persisted for 2 to 3 hours and was well localized to the area of application. By activating the visual cortex with the moving grading for 250 msec, which resulted in the single large interictal spikes, the area of epileptic discharge was identified (Fig. 1C). The area surrounding the epileptic focus was hyperpolarized, consistent with surround inhibition. When the cortex was activated with visual stimulation for 500 msec, multiple interictal spikes occurred and an interesting pattern of alternating hyperexcitability and inhibition was evident (Fig. 1D). The development of an acute epileptic focus is shown in FIGURE 2. A new epileptic focus was created at site No. 6 (Fig. 2A). Five and 10 minutes after bicuculline application, the site could be identified (Fig. 2B,C). However, 30 minutes after the epileptic focus was created, brief stimulation of the visual cortex elicited a pattern of depolarization in the epileptogenic region (Fig. 2D) with an area of probable surround inhibition.[39] Spreading out from the epileptic focus were alternating patterns of excitation and inhibition. These patterns are reminiscent of the patterns previously found with intercortical stimulation.[17,21,57] Whether these patterns are spreading via the horizontal connections involving the color blob system, which is known to run orthogonal to the ocular dominance columns, awaits further study. These preliminary studies demonstrate the power of the high spatial resolution of optical maps. The entire images shown in Figures 1 and 2 with a spatial resolution of 120 Ã— 100 pixels would most closely represent a single voxel in an individual PET scan. The pattern of seizure activity in the optical imaging map suggests the complexity that would not be appreciated with other imaging modalities, such as PET or SPECT, because of their lesser temporal resolution. These studies in nonhuman primates led to attempts to identify seizure onset and spread of human cortex during neurosurgical procedures in awake patients for the treatment of intractable epilepsy. The human studies could be performed on a much larger scale (4 to 5 cm^2) compared to the primate studies, which were carried out in an area of 0.6 to 0.8 cm^2. The spatial resolution for these optical imaging studies is on the order of 100 Âµm^2 per pixel.

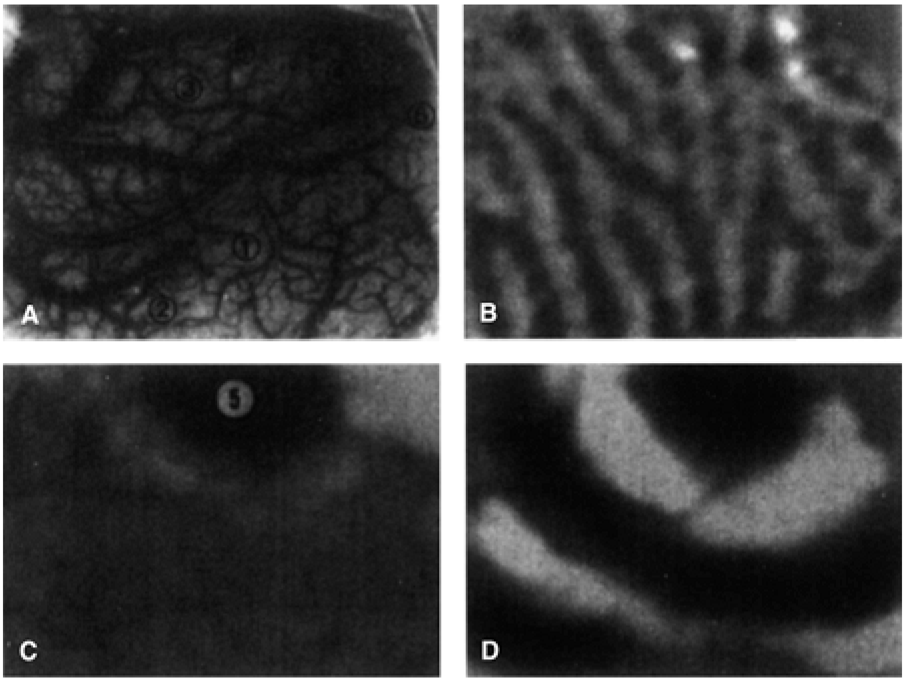

FIGURE 1. A: A 6 Ã— 8-mm area of monkey primary visual cortex with the bottom region just behind the lunate sulcus, such that ocular-dominance columns should intersect perpendicular to that region. The numbers in circles represent regions where epileptic foci were created. **B:** Ocular-dominance columns obtained by staining the cortical surface with merocyanine voltage-sensitive dye and stimulating the right eye for 3 seconds and then the left eye for 3 seconds. After six trials of right- and left-eye stimulation, the optical images collected during left-eye stimulation (1,000 frames) are subtracted from the right-eye images and the pattern of ocular-dominance columns is shown. Note that the width of the image is 8 mm, and there are approximately eight right-eye columns (*black*) and eight left-eye columns (*white*). **C:** After creation of an epileptic focus at site No. 5 **(A)**, stimulation of only the right eye for 250 msec evoked a single large interictal burst; after six stimulations were averaged, the baseline control images were subtracted from the stimulation images. The black area represents areas of intense activation, whereas the white surrounding regions represent areas below baseline. **D:** If the stimulation of the right eye is prolonged (500 msec) to elicit multiple interictal bursts, an interesting pattern of alternating excitation and inhibition is evoked. See text for further details.

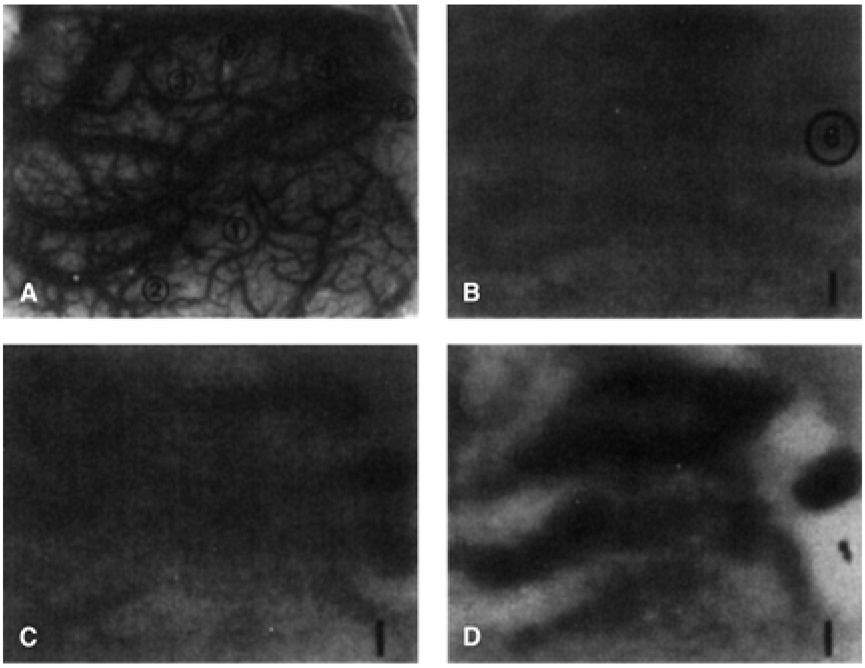

FIGURE 2. A: Same area of monkey visual cortex as for FIGURE 1, except a new epileptic focus has been created at site No. 6. The development of the epileptic focus is followed for 5, 10, and 30 minutes after its creation. **Bâ€"D:** The stimulations of the right eye were carried out for 125 msec, just enough to elicit a single interictal burst. After the epileptic focus is well established **(D)**, the area of the seizure onset is noted with its surrounding inhibitory region and the alternating pattern of excitation and inhibition.

Optical Imaging of Epileptiform Activity in Humans

By using the intrinsic signal in human cortex and stimulating at just above the afterdischarge threshold, seizure activity can be elicited and recorded by a surface electrode (electroencephalogram [EEG]) (Fig. 3Aa). In a large area of cortex (4 cm^2), stimulating electrodes separated by 1 cm (Fig. 3Ab) evoked either short afterdischarges (lower left, Fig. 3B) or a longer series of seizure activity (lower right, Fig. 3B). The optical imaging changes at baseline (one control image subtracted from another) demonstrate the noise present in the system (Fig. 3Ab). At the end of the stimulation during the shorter seizure episode, the area of optical changes is shown in FIGURE 3Ac, whereas a much greater spatial extent of cortex activation is found in the more intense seizure episode (Fig. 3Ad). In addition to examination of the spatial extent of activation, the magnitude of optical changes during the seizure episode can be measured. The sites at FIGURE 3B correlate with the regions of interest in

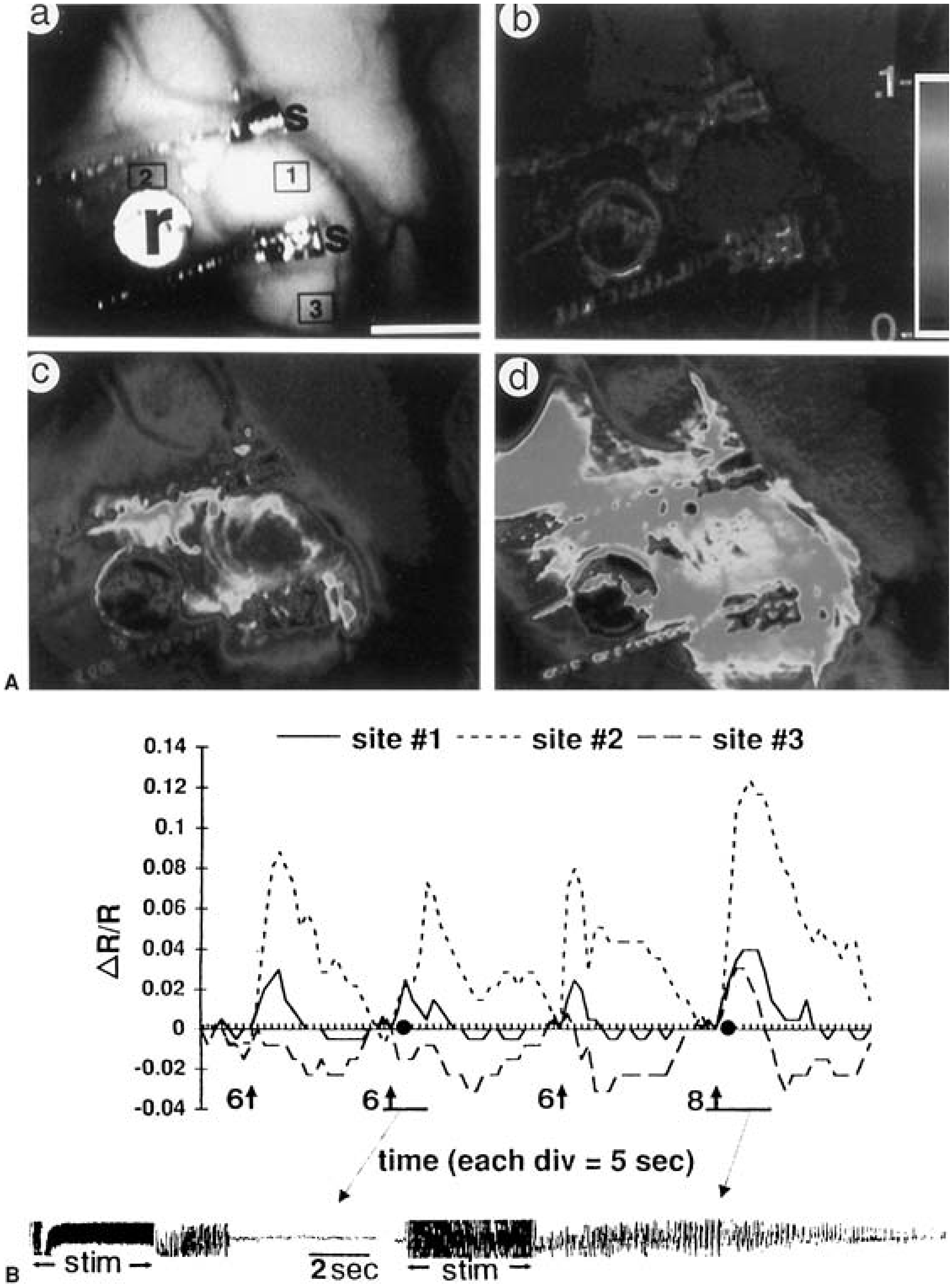
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FIGURE 3. A: Human frontal cortex exposed at the time of a neurosurgical procedure for treatment of medically intractable epilepsy. Recording surface electroencephalographic (EEG) electrode is represented by *r*, the two stimulating electrodes by *s*. *Boxes 1, 2, and 3* are regions of interest where the optical changes in the intrinsic signal were measured for FIGURE 3B. Scale bar = 1 cm. **Ab:** Control image subtracted from another control image showing the baseline noise. The pseudocolor scale bar (*right*) shows the intensity of the optical changes, with black being below baseline, blue near baseline, and red maximal. **Ac:** Optical changes at the end of the second stimulation at 6 mÃ…, which evoked a

short seizure â€œafterdischargeâ€ episode. The peak changes are near the recording electrode with a surrounding region that is black, suggesting that the optical changes in that region are below baseline. **Ad:** Optical changes after the fourth stimulation are at 8 mÃ…, which evoked a more prolonged and intense seizure episode compared with the other intense optical change. **B:** The optical changes from the three boxes shown in FIGURE 3Aa are shown, as well as the surface EEG recording from the second stimulation (optical changes in Fig. 3Ac; *lower left*) and the surface EEG recording from the second stimulation (optical changes in Fig. 3Ad; *lower right*). From Haglund MM, Ojemann GA, Hochman DW. Optical imaging of epileptiform and functional activity from human cortex. *Nature*. 1992;358:668â€“671, with permission. (See color insert.)

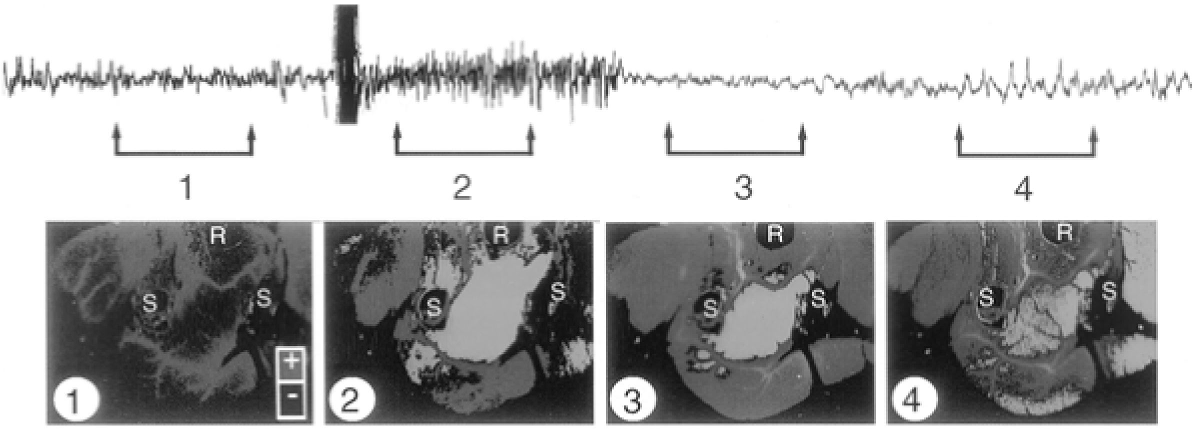

FIGURE 4. Upper trace: Surface electroencephalographic (EEG) trace from the recording electrode (*r* in the *lower images*). The brackets represent the period during which the optical images in the *lower panel* were collected and a baseline image was subtracted from each of the images. The four brackets show the baseline, seizure, postictal, and recovery electrical recordings, respectively. **Lower panel:** Optical changes before and after electrical stimulation at the afterdischarge threshold (stimulating electrodes represented by *s*). The optical changes are shown in a two-color scheme, so positive changes correlated with increases in neuronal activation are shown in red, whereas optical changes in the intrinsic signal below baseline are shown in blue. The optical changes in the positive direction correlate with the increases in electrical activity, especially the seizure activity in bracket No. 2. The optical changes also correlate with the quiescent postictal surface EEG recording in bracket No. 3, where the optical changes are below baseline. (See color insert.)

Figure 3Aa. Site No. 1 represents the area between the stimulating electrodes and shows the positive change in optical signal during four stimulations. The first three stimulations were performed at 6 mAA and the last stimulation at 8 mAA. Of the three stimulations at 6 mAA, the first seizure episode was the longest electrically, whereas the second and third were of shorter duration and intensity. The last stimulation at 8 mÃ… led to the longest and most intense seizure episode as measured by the surface EEG electrode. The optical changes near the recording electrode are measured at box No. 2, mimicking the electrical changes, with large darkening of the optical changes occurring after the four stimulations (Fig. 3B, lower right).

Of interest, but still without clear mechanisms, are the surrounding opposite changes measured at box No. 3. During each of the first three stimulations, the optical changes are in the opposite direction of neuronal activity activation, whereas during the fourth and most intense seizure episode, the change is initially along with neuronal activation but then goes in the opposite direction. Whether these intrinsic signals in the opposite direction from a neuronal activation actually represent surround inhibition as seen in the monkey visual cortex or is some type of surrounding shunting of cellular swelling or blood volume changes needs to be studied with more detail. However, studies in the ferret neocortex have shown that the surrounding intrinsic signal changes are active inhibition.[42,43,50]

Closer comparison of the electrical and optical changes can be accomplished by studying surface EEG activity in different stages of seizure activity. In FIGURE 4, the surface electrode (red) measures the baseline No. 1, the seizure No. 2, postseizure quiescent No. 3, and return to baseline No. 4 activities while the optical imaging was performed. By comparing those areas colored red, associated with increases in neuronal activity, and those colored blue, having a decrease in neuronal activity, the optical changes can be compared with a concomitant surface EEG recording. During baseline activity, the region around the recording electrode is black, whereas during the seizure episode, the area is clearly activated (red). During the postseizure period, when the electrical activity is quiescent compared with baseline, the area around the recording electrode shows a signal in the opposite direction of activation (blue), which gradually returns to near baseline in the last image (No. 4). These preliminary studies indicate that those changes associated with neuronal activity also correlate with increases in electrical activity, whereas changes in the opposite direction correlate with decreases in the baseline electrical activity.

Recent advances have allowed investigators to image the neocortical surface in the operating room during spontaneous seizures and interictal activity. By using specific wavelengths, Haglund and Hochman[23] were able to compare optical changes during a spontaneous seizure in the neocortex. These changes were confirmed clinically and the intrinsic signal changes at the blood volume wavelength (535 nm) and the blood oxygenation wavelength (660 nm) were compared. The blood volume changes were closely associated with the site of the seizure activity, whereas the blood oxygenation changes were more variable. It appears that the blood volume wavelength will be more precise in localizing epileptic foci, while the blood oxygenation wavelength may be more variable and have more to do with the draining venules from the area than localizing the exact site of neuronal activity.

Summary and Conclusions

The use of optical imaging to identify epileptic foci and the spread of seizure activity in the operating room is still in its earliest stages.[28,38,49] However, if it is to be used in a noninvasive manner, infrared cameras and lasers will likely be required. Optical imaging of rat and monkey visual cortex has been accomplished through a thin skull,[6,34,35,45,46,47,50,54] and implanted brain tumors have been identified through the rat skull by means of optical imaging.[25] Since these technologies can be carried out noninvasively, the potential exists for using optical imaging to identify sources of epileptic activity.

The most significant application of optical imaging is its capacity to identify functional regions intraoperatively that are important to preserve and localize the epileptic focus and the pathways of seizure spread. By using these optical imaging techniques, the more precise surgical treatment of medically intractable epilepsy could be performed. As optical imaging emerges from being a purely research tool, the technique will fulfill its future potential as an adjunct to three-dimensional fMRI and PET techniques. Additional advantages over PET and fMRI include the capacity be formed intraoperatively,

better spatial and temporal resolution than PET, and functional maps that have been compared with precise electrical stimulation maps of language and higher cognitive functions.[1,2,51,55]

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Chapter 87

Microdialysis

Idil Cavus

Charles L. Wilson

Introduction

Microdialysis is a method that allows continuous in vivo sampling and neurochemical analysis of brain extracellular fluid (ECF) for extended periods of time. Although brain extracellular (EC) space comprises only 15% of brain volume, the neurochemical changes in this compartment are critical for the functioning of the various cellular receptors and transporters. Brain microdialysis was first introduced in animal research in the 1970s[32,125] and applied to human research in the 1990s. This method has been used in numerous animal models of disease, including epilepsy, to measure the EC levels of ions, drugs, neurotransmitters, and other small molecules and peptides under anesthetized as well as awake behaving conditions. In humans, brain microdialysis is used primarily to monitor or study the neurochemistry of brain injury related to trauma, stroke, or ischemia in neurointensive care and tumors in the neurosurgical setting, and it has also been used during intracranial electroencephalographic (EEG) monitoring of epilepsy patients (for reviews, see Benjamin et al.[11] and Hillered et al.[51]). Recently, significant advances in clinical microdialysis research have allowed the technique to be used not only for the study of disease neurochemistry, but also as a bedside monitoring and diagnostic tool in neurointensive care patients.[10]

Microdialysis Methodology

The microdialysis setup is relatively simple, involving a probe/catheter, a perfusion pump, and a collection system. The microdialysis probe (~1 mm in diameter) consists of a concentric or side-by-side dual catheter with a semipermeable membrane attached to its tip and connected to inlet and outlet tubing. The probe membrane is usually 1 to 3 mm long in rodent studies and 5 to 30 mm in humans, with typically 10- to 20-kDa molecular weight cutoff. Microdialysis membranes with small pore sizes have the advantage of acting as an additional barrier to likely infectious agents, and may be preferable in human research. A recently introduced probe for human research with 110-kDa molecular cutoff,[54] however, allows for sampling of larger proteins and can be useful in studying the proteomics of the brain microdialysate.[70] A microdialysis probe with even larger membrane cutoff (3,000 kDa) has been used in tumor patients to sample neurotrophins and inflammatory factors.[136] Usually, the commercially available CMA 70 (molecular cutoff 20 kDa; CMA Microdialysis, North Chelmsford, MA) has been the probe of choice for human research in brain trauma, stroke, and tumor patients. In human epilepsy research, however, in which stereotaxic placement and simultaneous electrophysiologic monitoring are desired, probes with smaller diameters and longer shafts are preferred. The earlier homemade designs[35] have been replaced by custom-made probes. These probes can be inserted inside the depth electrode (Spencer probe) for simultaneous EEG[35] or single unit activity monitoring.[43] In human epilepsy research, patients with refractory epilepsy who are evaluated with intracranial electrodes for localization of their seizure onset site are implanted with microdialysis or Spencer probes after obtaining institutional review board approval and the necessary informed consents.

Spencer probes can be stereotaxically implanted into the brain area of interest and their position confirmed with magnetic resonance imaging (MRI) and computed tomography (CT). The probe is perfused with sterile artificial ECF through the inlet at relatively slow rates (usually 0.1â€“2.5 ÂµL/min) allowing for diffusion of molecules across the membrane down their concentration gradient. The dialysate fluid is collected either manually or automatically (typical sampling rates 1â€“60 min) and can be analyzed on-line or off-line using high-performance liquid chromatography (HPLC), mass spectroscopy, or enzyme-based methodologies.[78] The more recently developed and highly sensitive capillary electrophoresis analysis allows for relatively high (5â€“60 seconds) temporal resolution,[71,80] which is more useful in tracking fast neurochemical changes during seizures.

The amount of brain chemical recovered in the dialysate represents only a fraction of its actual interstitial concentration. This relative recovery depends on many factors, including the molecular weight, charge, uptake, and metabolism of the measured compound, diffusion, tortuosity factors in the interstitial microenvironment, length and composition of the dialysis membrane, flow rate, temperature, and composition of the perfusion fluid.[12,15] Usually, higher relative recovery is obtained at lower perfusion rates and with longer membranes.[123] The absolute EC concentration of the measured neurochemicals can be estimated using quantitative microdialysis methods such as no-net-flux[65] and extrapolation-to-zero-flow methods.[55] These methods have been rarely used in clinical research, for example, in epilepsy patients,[1,20] and in neurointensive care,[53,62] because of their cumbersome nature.

The insertion of the microdialysis probe causes local tissue damage, transient disruption in the bloodâ€“brain barrier, and gliosis around the probe tract.[13,134] Some of this damage is attributed to the relatively large, nonsterile probes inserted in small animals' brains. Postmortem studies in sheep brain using sterile probes approved for human use reveal minimal disturbance to the cerebral parenchyma.[134] Similarly, implantation of small, flexible, sterile catheters in epileptic patients[35] has been reported to leave only a small track with minimal gliosis in the brain tissue. After the probe insertion, there is an initial period of disturbed metabolic function that can last up to 24 hours.[12,14] The disruption in the bloodâ€“brain barrier usually heals within 2 hours,[15,52] although a widespread leakage of albumin into the rat brains 24 hours after probe implantation has been also reported.[131] In humans, several clinical studies cite stabilization of dialysate levels within 20 to 60 minutes of probe insertion.[52] In contrast to microdialysis in rodents, in which dynamic exchanges across the dialysis membrane are lost relatively rapidly after probe implantation and in which experiments frequently must be conducted on the same day as the

probe implantation, human microdialysis parameters appear remarkably stable over many days. This stability is attributed to the minimal tissue damage and gliosis associated with the implantation procedure, which is most likely due to the use of sterile, relatively small, and flexible probes that are floating rather than rigidly secured to the skull, decreasing the trauma to the brain parenchyma.[35]

In epilepsy patients, microdialysis can be performed intraoperatively or during the intracranial EEG monitoring phase, on an intermittent or continuous basis (usually up to 2 weeks). In our experience, continuous bedside microdialysis for several days at low flow rates can be used safely in epilepsy patients and in neurointensive care.[10,49,50,81] The microdialysis probe can be also used for drug delivery to the brain (reverse dialysis), and this technique is often used in animal experimentation. In humans, drug delivery through microdialysis has been used for local brain tumor therapy[96] and for research purposes in epilepsy[37,38] and stroke patients.[58] Microdialysis can be applied simultaneously with other methods, such as positron emission tomography (PET)[41,52] and Doppler flowmetry,[56] to study the relationship between the neurochemical changes in the EC milieu and changes in brain metabolism and blood flow.

The Cellular Origin of the Dialysate Neurotransmitters

Microdialysis typically samples neurochemical changes and volume transmission in the immediate vicinity of the probe, and it may provide information only indirectly on the changes within the synapse.[12,34,133] The probe is much larger than the synaptic cleft, and the time resolution is orders of magnitude slower than that for synaptic events. The extrasynaptic concentration of a transmitter reflects a balance between its rate of neuronal and glial release and reuptake, together with its diffusion outside the synapse. In addition, these parameters are affected by the neuroanatomic location and density of terminals, receptors, and transporter molecules. As such, the measured ambient neurotransmitter levels may be most relevant for the function of the extrasynaptic receptors.

Although there is evidence that dialysate dopamine, norepinephrine, serotonin, and acetylcholine are primarily of neuronal, calcium-dependent origin, the cellular origin of glutamate and Î³-aminobutyric acid (GABA) has been disputed.[117,132] In most cases, glutamate and GABA in dialysate are insensitive to tetrodotoxin and to calcium depletion, raising the possibility of glial metabolic release.[117] Indeed, recent evidence indicates that glia are capable of releasing both glutamate and GABA through a variety of mechanisms, calcium dependent and independent, including tonic nonvesicular release and transporter reversal, via the cystine/glutamate antiporter and in response to neuronal stimulation.[9,19,31,89] Thus, the basal microdialysate levels of glutamate and GABA may be most relevant to our understanding of volume transmission and the regulation of tonic excitation and inhibition through activation of the extrasynaptic receptors, which can in turn affect excitability.[19,31,88] EC glutamate and GABA may be also of neuronal origin, particularly in response to stimulation. Synaptically released glutamate and GABA can spill over into the EC space and become accessible to the microdialysis probe during intense physiologic and electrical stimulation, particularly when glial reuptake or coverage is reduced.[3,34] Improvements in microdialysis method (smaller probes, increased temporal resolution, minimal tissue trauma) and in analytical procedures may enhance the detection of synaptically released neurotransmitters.[34,87]

Role of Microdialysis Studies in Animal Models of Epilepsy

Although the primary utility of microdialysis in animal models has been to further our understanding of the basic mechanisms of epilepsy, these studies have also provided data that may have potential diagnostic value for patients.[17] Measurement of brain anticonvulsant levels in animal models and their effect on electrographic, neurochemical, and behavioral expression of seizure activity only provides approximations of effective brain levels of antiepileptic drugs (AEDs) because of differences in AED absorption and breakdown between rodents and humans.[130] Although the effective levels may differ, the mechanisms of action can more easily be determined in animal models of epilepsy, which provide important information for identification of AED targets by measurement of neurotransmitters and transporters that are modulated by seizures. This provides a means for evaluating the potential for effective use of an AED in patient treatment[25,26] or identification of receptor agonists or antagonists with anticonvulsant potential by providing in vivo data complementary to in vitro electrophysiology.[109]

Initial in vivo microdialysis studies of neurotransmitter modulation in epilepsy published in the 1980s and 1990s largely focused on the amino acids (AAs) glutamate, aspartate, taurine, and GABA in attempts to determine their role in seizure genesis as reflected by changes in AA release in rodent brain during seizures evoked by excitotoxins or stimulation (for review, see Chapman[21]). The use of microdialysis specifically in animal epilepsy research has increased from about 90 studies in the first 10 years of its use to >170 animal studies in an equivalent period since 1997, and these studies have focused on an ever-wider range of topics related to a variety of epilepsy-related neurotransmitters and neuromodulators, receptor agonists, and antagonists, as well as AEDs.

The animal models employed in these microdialysis studies are extremely varied but can be roughly divided into acute, chronic, and genetic. Acute models (such as systemic, intra-cerebral, or reverse dialysis administration of substances that induce depolarization, afterdischarge, and status epilepticus) are useful for evaluation of anticonvulsants, whereas chronic models (such as kindling models, which usually require several weeks of electrical or chemical stimulation; the status epilepticus model; and the genetic models) have the potential of identifying antiepileptic properties of drugs and perhaps more faithfully simulate the interictal and ictal clinical expression of epilepsy.

Microdialysis Research in Epilepsy in Animal Models

Amino Acid Studies

Investigation of the roles of excitatory and inhibitory amino acids in seizure generation has been a primary focus of microdialysis research. Naive rats generally show little change in AAs in response to a single acute electrical stimulation or chemical administration of picrotoxin (PTX), bicuculline (BMI), pentelynetetrazol (PTZ), or kainate (KA).[74,106] Systemic administration of 4-aminopyridine (4-AP)[72] is effective in evoking a two-to sixfold increase in hippocampal glutamate or glutamine, and local reverse dialysis of pilocarpine produces significant release of glutamate as well as dopamine,[108] accompanied by seizures. Seizure-related increases in EC glutamate similar to the ones observed in humans[39,135] have been observed more reliably in chronic models of epilepsy, such as kindling with electrical stimulation[120] or intrahippocampal[135] or amygdalar KA injection.[119] Paradoxically, in a PTX kindling model, ictal

discharges were associated with initial decrease in glutamate and aspartate,[104,105] which was followed by delayed, long-lasting increase in glutamate,[107] again indicating the need for rapid measurement to detect transient glutamate change and suggesting an important role for glia in slower glutamate modulation.

Repeated bursts of high-potassium stimuli in the rat hippocampus[118] or electrical stimulation in kindled rats[121] were associated with graded increases in glutamate release, suggesting that repeated short-term increases in EC glutamate levels results in enhancement of excitatory neuronal systems, causing propagation of seizure activity and culminating in secondary generalized seizures. In KA-kindled rats, the hippocampus had elevated interictal glutamate, which increased sharply in response to potassium-induced depolarization,[119] findings that were again similar to reports in humans.[20,39] Ueda and colleagues[119] identified a parallel downregulation in hippocampal glial glutamate transporters GLAST and GLT-1 as the basis of the increased interictal basal glutamate levels.

Not only are kindling models more responsive, but chronic rat models and genetic models also show AA increases that are absent in naive rats.[64,83,99,113] Changes in metabotropic glutamate receptors have also been identified as important mediators of AA release.[22,76,109]

Amino Acid Transporter Studies

Given the normally rapid reuptake of glutamate by its transporters and the resistance to glutamate elevation during transient evoked seizures in normal rat brain,[63,73] the observation of glutamate elevation with microdialysis during spontaneous seizures in the human hippocampus[37,39,135] has generated interest in the possible reduction or loss of glutamate transport in epilepsy. The glutamate transporters GLAST, GLT-1 (glial), and EAAC1 (neuronal) have received substantial study using the combination of microdialysis to detect changes in glutamate or GABA levels and quantitative immunoblotting or in situ hybridization to measure changes in transporters that might be associated with seizure models.[73] The genetically epilepsy-prone rat (GEPR) shows reduced GLAST, GLT-1, and EAAC-1 mRNA but not protein,[5] whereas results of kindling in normal rats have been variable depending on the measure used,[6,44,75,120] but usually showing less change in GLT-1. Rats receiving chronic administration of antisense oligonucleotide probes, which drastically reduce the expression of glial glutamate transporter GLT-1, respond with elevated EC glutamate levels and signs of excitotoxic neuronal degradation, whereas rats receiving antisense probes against the neuronal glutamate transporter EAAC-1 show no elevation of EC glutamate but do develop seizures.[97] Chronic KA[119] or iron chloride[100] rat models are consistent in showing reduced GLT-1, and although most glutamate uptake is mediated by GLT-1 into glia, GLT-1 also transports glutamate into neuronal terminals,[112] making interpretation of transporter data more complex.

Antiepileptic Drug Pharmacokinetics and Effects on Neurotransmitter Release

Microdialysis has been used for pharmacokinetic analysis of AEDs,[46,129,130] and methodologic issues related to such studies have been discussed extensively by de Lange et al.[28,29,30] Studies using microdialysis in rat models of epilepsy to investigate the change in glutamate and GABA levels in response to AEDs usually report decreased glutamate levels and variable effects on GABA.[3,4,57,61,98,107] Monoamine response to AEDs has also been investigated[4,27,79] to determine whether increases in serotonin or dopamine may be associated with AED efficacy. Although changes in serotonin have been associated with action of these AEDs, dopamine's role is less clear. Monoaminergic changes were preceded and are generally secondary to the role of GABA increase or Na^+ channel blockade by AEDs.

Monoamine Modulation of Epileptic Activity

The most heavily studied endogenous neuromodulator that might have antiepileptic properties is serotonin. A good deal of work has been done in the GEPR rat by Dailey and Jobe in a long series of studies with a number of coauthors (see review by Dailey et al.[27]). They found that both norepinephrine and serotonin are reduced in GEPRs, and that administration of serotonin agonists reduces seizures, whereas serotonin depletion prevents the anticonvulsant effects of agonists.[141] Recently, a rat seizure model using reverse dialysis of pilocarpine has been used to evaluate anticonvulsive effects of focal microdialysis perfusion of serotonin and dopamine.[24,25] Both serotonin and dopamine suppressed pilocarpine seizures, but the effect was lost when glutamate was coperfused prior to seizures.[23] The authors concluded that although increase in glutamate does not necessarily induce seizures, interictal or preictal elevation in glutamate can exacerbate seizure activity, even in the presence of monoaminergic protection.

Microdialysis Evaluation of Other Neuromodulators

In addition to the studies of adenosine release during seizures in humans described earlier, Michotte and colleagues used their pilocarpine rat model to test the anticonvulsant effect of adenosine A1 receptor agonists in hippocampus,[59,60] finding a decrease in glutamate release but only a small degree of seizure suppression. Other studies showed that seizures evoked by PTZ, KA, or bicuculline evoke a small but significant adenosine release,[16] and perforant path kindling was reported to increase hippocampal adenosine and its metabolites xanthine and hypoxanthine.[2]

Several studies using microdialysis in rats have found increases in opioid peptides,[92,93,94] nociceptin/orphanin FQ opioid peptides,[8] and somatostatin[68] in response to kindling or chemical induction of seizures, changes that may have differential influences in excitability depending on the receptor type activated. Microdialysis has been also used to evaluate the relation of nitric oxide (NO) or NO synthesis to seizure generation or glutamate levels in a variety of models.[7,90,122,142]

Wu, Schwarcz, and colleagues[137,139] used in vivo microdialysis to investigate the role of kynurenic acid, an endogenous agonist of the glycine site of the *N*-methyl-D-aspartic acid (NMDA) receptor, in suppressing epileptic activity. Recently, they reported that although poor brain penetration of kynurenate limits its use as an anticonvulsant, systemic administration of its precursors in the pilocarpine rat with chronic seizures causes increase in the kynurenate levels in epileptic brain regions, likely through increased synthesis due to astroglial incursion.[138]

New Directions in Use of in Vivo Microdialysis in Animal Models of Epilepsy

Several recent studies have shown the potential of in vivo microdialysis for evaluating diverse antiepileptic approaches. For example, the antiepileptic mechanism of anterior thalamic electrical stimulation in epileptic patients has received little study, but catecholamine release during thalamic deep brain stimulation was evaluated in the rat during PTZ administration, and significant differences in norepinephrine, serotonin, and 5-hydroxyindolacetic acid (5-HIAA) levels were found between controls and stimulated animals.[144] In seeking more effective antiepileptic drugs, administration of selective antagonists of the GLU_{K5}(GlutamateR5) kainate receptor subunit was found to block seizures induced by intrahippocampal pilocarpine in rats[108a]. Microdialysis monitoring showed that pretreatment with the GLU_{K5} antagonists LY377770 and LY382884 both prevented the pilocarpine administrationâ€"associated increases in glutamate and GABA and blocked the electrographic seizures.

Microdialysis has been used extensively to measure AED levels in the epileptic hippocampus, where AEDs are found to be significantly reduced in the presence of endogenous P-glycoproteins and multidrug-resistant transporters (MDRs).[85,91] Reviews of the effects of MDRs in reducing the effectiveness of AEDs have been published by Loscher and Potschka,[66,67] and a complete description of these investigations can be found in Chapter 115.

Microdialysis in Humans

Clinical Applications

The most common clinical use of microdialysis is in neurointensive care patients following severe head trauma, subarachnoid hemorrhage, and occlusive stroke (for review, see Hillered et al.[51]). Most commonly, hypoxia/ischemia events have been associated with dramatic and persistent (hours to days) release of excitatory AAs and changes in the markers of glucose metabolism. In these settings, massive increase in EC glutamate can result from hypoxia/ischemiaâ€"related cellular depolarization or damage, leakage across the bloodâ€"brain barrier, and inhibition or reversal of the glutamate transporters. The changes in the microdialysate glucose and its metabolites (profound decrease in glucose, and increase in lactate, lactate/pyruvate, and lactate/glucose ratios) have been interpreted to indicate decreased glucose delivery and utilization, increased anaerobic glycolysis, and energy failure in the affected hypoxic/ischemic tissue. Seizures in patients with traumatic brain injury are a cause for even higher increases in EC glutamate that can last for hours[128] and to additional membrane injury as reflected by elevated EC glycerol levels.[127] In general, the extent of glutamate release and the disturbance in glucose metabolism appear to correlate with the severity of the pathology and the clinical outcome (reviewed by Hillered et al.[51]). Conversely, therapeutic interventions such as barbiturate coma[45] and hypothermia[140] result in decrease in the pathologically elevated glutamate and lactate levels. In recent years, microdialysis has moved from preclinical evaluation and validation to clinical applications. Ungerstedt and colleagues[110,111,124] pioneered the use of bedside around-the-clock microdialysis analysis as a tool for monitoring the clinical development in neurotrauma and stroke patients. This monitoring has allowed the detection of neurochemical changes in the brain hours before their clinical manifestation, thus allowing for early therapeutic intervention.[101,110,111,126] The Swedish clinical experience with neurotrauma and stroke patients confirms that neurochemical changes in the human brain can be detected with microdialysis long before the clinical signs of a disease. No similar studies to investigate markers heralding the development of epileptogenicity, however, have been performed.

Microdialysis Studies in Epilepsy Patients

Intraoperative Studies

Several centers have carried out acute microdialysis in patients undergoing epilepsy surgery under generalized anesthesia and maintained on their usual antiepileptic pharma-cotherapy.[18,47,95,114,115,116] Equilibration and sampling periods were necessarily short to conform with the surgical procedure. First, Hamberger et al.,[47] using a dialytrode (an early version of microdialysis probe) placed on exposed cortical surface, reported that several AAs (glutamate, alanine, glycine, serine, and phosphoethanolamine) are higher interictally at the epileptiform cortical regions compared to the nonepileptic regions. More recently, Thomas et al.,[116] using simultaneous intraoperative electrocorticography (ECoG) and microdialysis in hippocampus in a limited number of patients, related the increase in glutamate, aspartate, and GABA levels to increased epileptiform activity. Another group[18,95] measured the amino acid changes during spontaneous or electrically evoked seizures (following a standard clinical electrical stimulation protocol to verify the location of the epileptogenic focus) in the epileptic cortex or hippocampus of seven intraoperative patients. Both spontaneous and electrically evoked seizures were associated with sharp rises in the EC levels of aspartate and glutamate, as well as in glycine, serine, and lactate.

Microdialysis in Ambulatory Epilepsy Patients

The group led by Dr. Dennis Spencer at Yale has been pioneering microdialysis in ambulatory patients with refractory complex partial epilepsy (CPS) undergoing intracranial EEG monitoring, with continuous perfusion and sample collection for up to 16 days to determine interictal steady-state levels of AAs and neurometabolites and their elevation with spontaneous seizures.[1,20,36,37,38,39,69,102,103] Table 1 shows EC levels of various neurochemicals measured with microdialysis in the nonepileptic brain areas of awake patients with refractory epilepsy and comparisons obtained from animal studies. In patients with bilateral hippocampal probes, the epileptogenic hippocampus had higher glutamate at baseline. With the onset of seizure, there was a sharp increase in dialysate glutamate in both sides, with much larger and more prolonged (up to 18 minutes of sampling) increase in the epileptogenic hippocampus. Dialysate GABA also increased with seizure bilaterally; the GABA increase in the epileptogenic hippocampus was small and short lasting, however, compared to the nonepileptogenic site. The large seizure-related glutamate release together with relatively small GABA increase (high glutamate/GABA ratio) was proposed to lead to neurotoxicity and further seizures in the hippocampus. This first observation of seizure-related glutamate release in the human hippocampus was very significant because such elevations were seen in some but not all animal models of epilepsy. Wilson et al.[135] at UCLA replicated the study in a group of ambulatory patients and noted that the seizure-related glutamate increase was not seen in all of them; they speculated that the extent of glutamate release may depend on the extent of the hippocampal sclerosis. Furthermore, they verified that the same AAs (aspartate, glutamate, GABA, and taurine) that increase with spontaneous seizures in the human hippocampus increase with seizures in a chronic kainate rat model of temporal epilepsy, which also has evidence of mossy fiber sprouting in the dentate gyrus. Thus, for the large and prolonged EC glutamate transients to occur, a certain degree of chronic axonal and synaptic reorganization over long periods of time may be necessary. It is of interest that the increase in glutamateâ€“which is usually thought to be of neuronal originâ€“is seen paradoxically in patients with pronounced hippocampal sclerosis in which a majority (70%â€“90%) of the neurons are lost. The origin of the increased glutamate efflux in the epileptogenic hippocampus both at baseline[20] and with seizures remains to be elucidated.

Table 1 Brain extracellular neurotransmitter and neurometabolite levels

Substance	Species	Brain area	Extracellular fluid concentration	Method	Authors
Glutamate	Rat	Hippocampus	2.9 Â± 0.4	Recirculation	Lerma et al. 1986[63a]
	Rat	Striatum	1.8 Â± 0.2	Ultra-low flow	Kennedy et al. 2002[58a]
	Human	Hippocampus	2.6 Â± 0.3	Zero flow	Cavus et al. 2005[20]
	Human	Cortex	2.4 Â± 0.3	Zero flow	Cavus et al. 2005[20]
Aspartate	Rat	Hippocampus	1.7 Â± 0.2	Recirculation	Lerma et al. 1986[63a]

Glutamine	Rat	Hippocampus	193 Â± 11	Recirculation	Lerma et al. 1986[63a]
	Human	Hippocampus	700 Â± 130	Zero flow	Cavus et al. 2005[20]
	Human	Cortex	617 Â± 81	Zero flow	Cavus et al. 2005[20]
GABA	Rat	Hippocampus	0.8 Â± 0.15	Recirculation	Lerma et al. 1986[63a]
	Rat	Striatum	0.3 Â± 0.04	Ultra-low flow	Kennedy et al. 2002[58a]
	Human[a]	Hippocampus	0.2. Â± 0.07	Zero flow	Cavus et al. 2004[19a]
	Human[a]	Cortex	0.1 Â± 0.03	Zero flow	Cavus et al. 2004[19a]
Glycine	Rat	Striatum	4.6 Â± 1.1	Ultra-low flow	Kennedy et al. 2002[58a]
Adenosine	Human	Hippocampus	1.8	Estimate from in vitro recovery	During and Spencer 1992[38]
Glucose	Rat	Hippocampus	1.7 Â± 0.3	Estimate from in vitro recovery	Abi-Saab et al. 2002[1]
	Human	Hippocampus	1.6 Â± 0.8	Zero flow	Abi-Saab

					et al. 2002[1]
	Human	Hippocampus	2.2 Â± 0.2	Zero flow	Cavus et al. 2005[20]
	Human	Cortex	1.6 Â± 0.3	Zero flow	Cavus et al. 2005[20]
Lactate	Rat	Hippocampus	2.7 Â± 0.8	Estimate from in vitro recovery	Abi-Saab et al. 2002[1]
	Human	Hippocampus	5.1 Â± 1.4	Zero flow	Abi-Saab et al. 2002[1]
	Human	Hippocampus	4.6 Â± 0.4	Zero flow	Cavus et al. 2005[20]
	Human	Cortex	4.7 Â± 0.5	Zero flow	Cavus et al. 2005[20]

Values (mean Â± SEM) are expressed as ÂµM, except for glucose and lactate (mM). Human values are from the nonepileptogenic brain areas in awake patients with medication-resistant epilepsy. GABA, Î³-aminobutyric acid.

[a] Values in men.

Subsequent microdialysis experiments in patients with CPS have explored the basis of the diminished seizure-evoked GABA release in the epileptogenic hippocampus.[37] In a unique set of experiments, potassium (56 mM, 30 minutes) and glutamate (5 mM, 30 minutes) in a calcium-free or physiologic calcium medium were perfused through the microdialysis probe to investigate the mechanism of GABA release in the human hippocampus. Results suggested that although the calcium-dependent, potassium-induced GABA release in the epileptogenic hippocampus is intact, the glutamate-induced, calcium-independent GABA release is diminished. Parallel studies in amygdala-kindled rats that had 50% reduction in their GABA transporters further suggested that the glutamate-induced GABA release is nonvesicular (calcium independent) and mediated by transporter reversal. Thus, the authors concluded the diminished GABA release with spontaneous seizures in the epileptogenic hippocampus is largely due to the decrease in the transporter-mediated nonvesicular GABA release limiting inhibition and contributing to epileptogenicity in human temporal lobe epilepsy.

Other studies in epilepsy patients implanted with bilateral hippocampal probes showed large transient increases in adenosine[38] and lactate[36] with the onset of spontaneous seizures. The persistent bilateral (larger in the ipsilateral hippocampus) increase in adenosine, a potent inhibitory neuromodulator with anticonvulsant activity, was proposed to mediate the seizure arrest and the postictal refractoriness in epilepsy patients. However, interictal baseline adenosine levels have not been found to differ between the mesial temporal lobe of seizure onset and the contralateral side.[143] Lactate, a product of nonoxidative glucose metabolism, is released from both neurons and glia with increased cerebral activity.[33] Lactate, monitored with an online method (lactography) in patients with CPS, fluctuated with the interictal spiking rate and increased sharply with seizure onset in the ipsilateral hippocampus for up to 60 to 90 minutes.[36] This prolonged rise in lactate was proposed not only to be a product of increased nonoxidative glycolysis with seizures, but also to endogenously mediate the seizure arrest and postictal refractoriness through acidification of the EC compartment.

Lactate has been also proposed as an alternative energy source in the brain.[42,82] Using the zero-flow microdialysis method in a group of fasting, medication-resistant epilepsy patients, Abi-Saab et al.[1] reported that although brain glucose levels are only 30% of that found in the plasma, brain lactate is much higher than brain glucose or than in the plasma, suggesting that lactate is synthesized locally in the brain. During a hyperglycemiaâ€“hypoglycemia insulin clamp in the same patient population, the change in brain glucose lagged behind the change in the plasma by 20 to 30 minutes, which may be protective to the brain during hypoglycemia.

Epilepsy has been associated with impaired energy metabolism,[48] decreased glutamateâ€“glutamine cycling,[84] and decreased glutamine synthase levels in the epileptogenic hippocampus.[40] Cavus et al.[20] used the zero-flow microdialysis method to estimate the absolute interictal in vivo concentrations of glutamate, glutamine, and the energy metabolites glucose and lactate in the epileptogenic and nonepileptogenic cortex and hippocampus of 38 awake patients with medically refractory CPS. The epileptogenic hippocampus had significantly higher basal glutamate levels (12.1 Â± 3.4 ÂµM, mean Â± SEM; in some cases up to 35 ÂµM), low glutamine/glutamine ratio (~100 vs. 350 in the nonepileptogenic sites), and high lactate levels. Higher EC glutamate correlated with higher EC glucose only within the epileptogenic hippocampus in which basal glutamate was elevated, suggesting that glucose utilization, which is driven by glutamate reuptake,[82] is also impaired. The authors concluded that interictal energy deficiency could result in poor glutamate reuptake, lower glutamine synthesis, and increased glial glutamate release. This could lead to glutamate-induced glial and neuronal toxicity, as well as to cellular deprivation of glutamate and glutamine as substrates

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for energy, and to poor utilization of the available glucose and lactate. Thus, a cycle of events triggered by energy deprivation could lead to worsening of energetics in mesial temporal lobe epilepsy.

Microdialysis Assessment of Antiepileptic Drug Pharmacokinetics in Humans

Whereas peripheral microdialysis (e.g., probe insertion into subcutaneous adipose layer) has become a relatively common procedure for evaluating drug pharmacokinetics,[77] central nervous system microdialysis evaluation of AEDs in epilepsy patients has been very limited. Early studies measuring the absolute ECF brain levels of carbamazepine, phenytoin, and valproate with zero-flow microdialysis in a limited number of refractory epilepsy patients chronically implanted with microdialysis probes reported that brain interstitial drug levels closely mirrored their unbound plasma concentrations.[69,102,103] Recently, to explore the hypothesis that drug resistance in epilepsy is related to lower interstitial concentrations of AEDs mediated by upregulated drug efflux transporters in affected brain regions,[66,67] Loscher and colleagues[66] measured the concentrations of several AEDs in the epileptic neocortex that was to be resected using intraoperative microdialysis in a series of 22 patients with refractory epilepsy. Although the EC AED levels showed great intraindividual and interindividual variability, they appeared significantly lower than their cerebrospinal fluid levels. The limitations of the study, however, which included lack of control data obtained from nonepileptic cortex and inexact determination of the absolute EC drug concentration, precluded any conclusions related to the authors' hypothesis.

Summary and Conclusions

It is evident from this brief review that microdialysis has provided a wealth of information from both animal and human studies that have aided in the investigation of basic mechanisms of brain physiology relevant to epilepsy as based on measurement of neurotransmitters and neuromodulators in the extracellular space. Although microdialysis has found clinical application in stroke and neurotrauma rather than epilepsy, the use of microdialysis for understanding both transient and chronic changes in epileptic brain tissue has been fruitful in several areas of study. These include rapid measurement of glutamate and GABA increases associated with concurrent EEG recording of spontaneous seizures in humans, as well as long-term differences in levels of these neurotransmitters measured interictally. Similar in vivo microdialysis measures in both the human and rodent brain of the participation of catecholamines, monoamines, purines, peptides, and other endogenous neuromodulators have enhanced our understanding of their roles in epilepsy.

In addition, microdialysis has been used to study glutamateâ€“glutamine cycling and glucose/lactate levels in relation to chronic impaired energy metabolism in the epileptic human cortex and hippocampus. These investigations provide evidence in human epilepsy for reduced glutamate uptake and glutamine synthesis and increased glial glutamate release that may be responsible for glutamate-induced neuronal toxicity. As newer techniques for rapid in vivo measurement of neurotransmitter release are developed, increased understanding of the role of phasic excitatory and inhibitory neurotransmitter participation in the preictal evolution of seizure genesis and subsequent ictal events may also be anticipated.

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Chapter 88

Transcranial Magnetic Stimulation

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Introduction

Transcranial magnetic stimulation (TMS) depolarizes neural elements through electromagnetic induction. It might more properly be called â€œtranscranial electromagnetic stimulation.â€ However, emphasizing the magnetic component distinguishes TMS more clearly from direct electrical stimulation and highlights the easy penetration of the magnetic field through skin, skull, and cerebrospinal fluid. TMS provides unique, non-invasive measures of neurologic function, along with the possibility of focally augmenting or inhibiting cortical activity.

Principles of Transcranial Magnetic Stimulation

The fundamental principles of electromagnetic induction are that an electric current produces a magnetic field B and a *changing* magnetic field induces a flow of electric current in nearby conductorsâ€" including human tissue. A static magnetic field, however large, produces no current in the brain. Thus, the key parameter for a magnetic stimulator is not the absolute magnetic field strength in teslas but its first time derivative, dB/dt, combined with the duration of the stimulating pulse. Typical magnetic stimulators operate at a few thousand volts and several thousand amperes per pulse. Peak power output is measured in megawatts and lasts a few score microseconds. The very high peak currents are obtained by discharging a large capacitor directly into the stimulation coil (Fig. 1).

The resulting pulse waveforms are determined by the resonant frequency of the capacitor plus coil. These waveforms fall into two categories: (a) monophasic and (b) biphasic. â€œMonophasicâ€ magnetic pulses have the general shape illustrated in FIGURE 2A, with a large initial peak and a much smaller, longer-lasting tail that presumably has no biologic effect. Biphasic pulses form a cosine wave, as shown in FIGURE 2B, with the later peaks smaller than the first because of energy losses in the circuitry.

These induced voltage waveforms mirror the voltage across the stimulation coil during the course of the discharge cycle. They do not reflect the actual coil current, which lags the coil voltage by 90Â°. The biphasic waveform appears to stimulate neurons maximally at the second (downgoing) shaded region, which represents the longest epoch of induced voltage across neuronal membranes.

Monophasic pulses have prominent directional effects, which may be important for some applications. They can be produced with circuitry that is lighter and cheaper than that needed for biphasic pulses. However, simple monophasic stimulators dissipate the entire capacitor charge with every pulse, incurring a high energy cost. This power loss translates into additional heating of the stimulation coil and other components, making monophasic stimulators more difficult to adapt for sustained repeat stimulation. Biphasic stimulators conserve energy by recapturing much of the original charge in the capacitor, and the biphasic wave shape has somewhat greater biologic effect for a given output voltage. This makes biphasic stimulators three to four times more efficient than monophasic devices, and the most practical choice for rapid repetitive stimulation.

TMS pulses may be single, paired, or repetitive (rTMS). rTMS can be fast (more frequently than once per second) or slow (less than once per second). Paired-pulse TMS most commonly involves passing two separate pulses through the coil within a few milliseconds. The large capacitors used for TMS cannot be recharged that rapidly, so paired-pulse stimulation requires two separate power modules coupled to a single coil.

Transcranial Magnetic Stimulation Coils

Circular Transcranial Magnetic Stimulation Coils

The simplest TMS coil is a circular loop. As shown in FIGURE 3, the changing current in the coil loop induces an antiparallel current flow of opposite direction in the underlying brain. Although the magnetic field is maximum directly under the center of the coil, the induced current is maximum near the outer edge of the coil. This discrepancy is an occasional source of confusion and may lead to the erroneous assumption that the site of magnetic stimulation is beneath the coil center.

Large circular TMS coils have good penetration to the cerebral cortex. They are commonly placed at the cranial vertex, where they can stimulate both hemispheres simultaneously. However, the effect on motor cortex tends to be asymmetric, especially with monophasic pulse waveforms. The main drawback of circular coils is their lack of focality. Not only does the circumference of the coil overlie a large area of brain, but in addition the radius of strongest stimulation is difficult to specify.

Figure 8 Transcranial Magnetic Stimulation Coils

If two round coils are placed side by side so that the currents flow in the same direction at the junction point, the induced electric fields will add together and be maximum below the junction (Fig. 4). This design, known as a â€œfigure-8,â€ â€œbutterfly,â€ or â€œdouble-Dâ€ coil, allows focal stimulation at a limited and clearly definable location. Because of this greater focality, figure-8 coils are chosen much more often than round coils for research and clinical applications. In typical use, the area of stimulated cerebral cortex is several square centimeters and its contours resemble an oval or rounded rectangle. The long axis of the rectangle parallels the junction of the two coils.

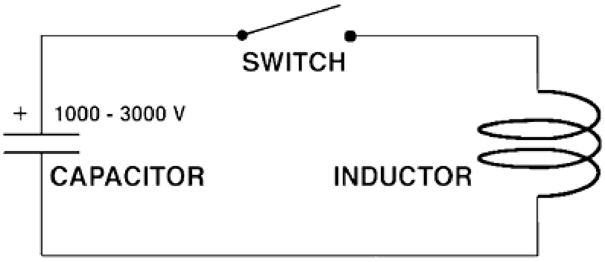

FIGURE 1. Simplified transcranial magnetic stimulation (TMS) circuit. The capacitor is first charged to a high voltage and then is discharged into the inductor (the stimulation coil) when the switch is closed. Additional components are needed to shape monophasic TMS pulses and to stop biphasic TMS pulses after a single cycle.

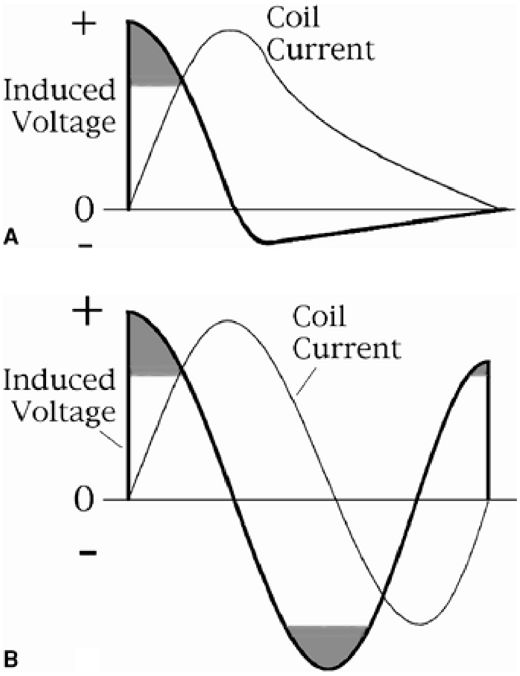

FIGURE 2. Monophasic **(A)** and biphasic **(B)** transcranial magnetic stimulation waveforms. Darker curves represent the induced voltage in the brain, and lighter curves the simultaneous current in the stimulation coil. Shaded areas are the periods of highest induced voltage, when neuronal membranes are most likely to be depolarized.

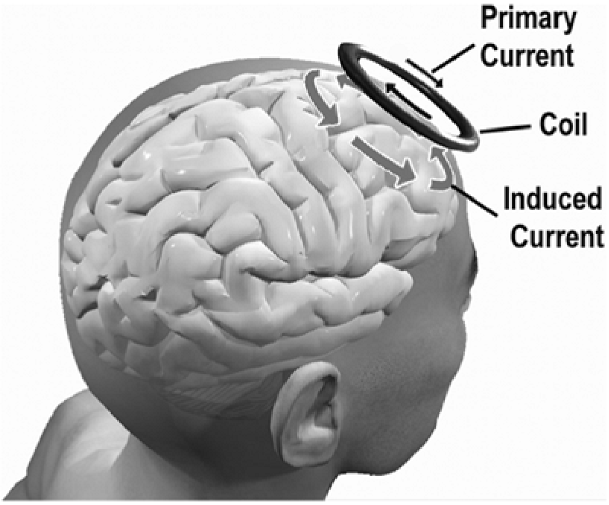

FIGURE 3. Round transcranial magnetic stimulation coil. Small dark arrows show the primary current in the coil. Large arrows show the path of maximum induced current, which lies below the outer coil edge.

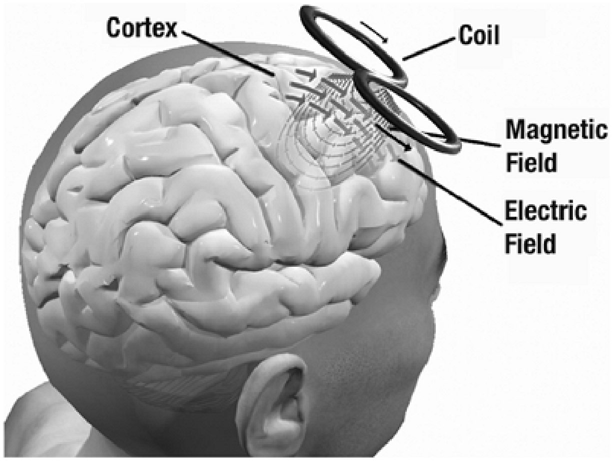

FIGURE 4. Figure-8 type transcranial magnetic stimulation coil. Small dark arrows show the primary current in the coil. Very small gray arrows (forming loops and penetrating into the brain) show the position and orientation of the maximum magnetic field, which lies perpendicular to the coil junction. Larger gray arrows show the position and orientation of the maximum electric field, which lies parallel to the junction and largely tangent to the cortical surface.

Iron-core Transcranial Magnetic Stimulation Coils

The efficiency of energy transfer from TMS coils to tissue is extremely small, on the order of 0.0001%. This striking inefficiency is responsible for the high power requirement of magnetic stimulation, bulky power supplies, and an annoying tendency to overheat with repeated firing. Ferromagnetic cores have much greater magnetic permeability than air, and consequently produce equivalent magnetic fields with much lower coil currents, increasing efficiency by a factor of four and reducing heat production by a factor of 5 to 10. In return for this improved performance, iron-core coils may be several pounds heavier.

Sham Transcranial Magnetic Stimulation Coils

The need for placebo stimulation in TMS research has led to the development of sham TMS coils, which are intended to prevent the subject and even the operator from knowing whether a given session involves real or sham stimulation. Ideally, sham stimulation should reproduce the external appearance of the coil and lead wires, the auditory click and mechanical tapping when it fires, and the complex sensations of scalp muscle contraction and electrical paresthesias that accompany real TMS, without actually projecting a magnetic field into the brain. The most advanced sham coils are integrated with scalp electrodes, which deliver a small current and produce subjective scalp paresthesias at the moment of sham stimulation. Most

placebo coils have been less complex. Properly designed experiments rely in part on presenting real and sham stimulation to different subjects, or at widely separated times to the same subjects, so that any difference is difficult to detect.

The Site of Transcranial Magnetic Stimulation Activation

The electric currents induced by TMS in brain are strongly constrained to lie parallel to the superficial surface of the cerebral cortex. Evidence from varied sources suggests that TMS induces depolarization of myelinated axons that are aligned parallel to the cortical surface, and lie near the grayâ€"white matter junction. The sites of activation are likely to be branch points or bends, where induced transmembrane currents will be largest. In motor cortex the depolarized axons belong primarily to interneurons, although the axons of large motor neurons can be activated directly in some experimental paradigms.

Transcranial Magnetic Stimulation and the Neurophysiology of Epilepsy

A large number of studies have investigated cortical excitability in epilepsy by means of TMS to gain new insight into the physiopathology of this disorder. As discussed in a subsequent section, however, antiepileptic drugs (AEDs) can influence TMS parameters. Therefore, the optimal methodologic approach to investigating epileptic processes by TMS is to evaluate untreated patients or, if this first-choice approach is not possible, design TMS studies to evaluate at best the possible effects of AED treatment. In this section the results of TMS studies investigating cortical excitability are separated into two main subsections according to the generalized or focal nature of the epilepsies included in the TMS trials.

Generalized Epilepsies

In a group of untreated patients with IGE, Reutens et al.[72,73] found an abnormal motor threshold (MT) reduction. This finding was interpreted as an index of motor cortical hyperexcitability due to the epileptic process. In contrast, Gianelli et al.[39] reported increased MT in untreated patients suffering from idiopathic generalized epilepsy (IGE) with typical absence seizures. Another group found no MT abnormality in IGE patients.[7,52]

Finally, MT increase has been reported in a group of untreated patients who experienced a first generalized tonicâ€"clonic seizure in the previous 48 hours, this finding having been interpreted as a postictal â€œprotective effect.â€[21] The differences reported in these studies may be related to the clinical heterogeneity of IGE patients. In accordance with this view, Reutens et al.[73] found that MT was lower in patients with myoclonic seizures than in patients suffering from absence seizures. In an unusual group of patients with IGE and versive, circling seizures, the interhemispheric difference of the MT was significantly higher than in IGE patients without circling and in normal controls, suggesting an explanation for the clinical phenomena.[3] The cortical silent period (CSP) was found to be increased or normal in untreated patients with IGE.[21,54,63]

According to the finding of increased excitability as demonstrated by MT in generalized myoclonic seizures, an abnormal intracortical inhibition (ICI) reduction and a normal intracortical facilitation (ICF) were found in both treated and untreated patients with juvenile myoclonic epilepsy (JME).[10,42,56] ICI suppression suggests impaired functioning of inhibitory circuits in JME, which may result in hyperexcitability of the corticospinal pathways. Increased facilitation at interstimulus intervals of 200 to 300 msec, but not at 100 to 150 msec, corresponds to the mean interdischarge interval of spike-wave activity on the electroencephalogram (EEG).[7,54] Patients with progressive myoclonus epilepsies (PMEs) have reduced long-ISI paired-pulse inhibition[47,94] as well as exaggerated facilitatory effect of peripheral stimulation on motor-evoked potential (MEP), suggesting a markedly increased influence of afferent input on motor cortical excitability.[73] Digital stimulation markedly facilitated conditioned MEPs, suggesting cortical and subcortical components of abnormal sensorimotor integration in addition to hyperexcitability of the sensory and motor cortex.[54]

Focal Epilepsies

Normal MT was reported in untreated patients with benign rolandic epilepsy (BRE)[53] and cryptogenic focal epilepsy (FE),[61] as well as in a group of patients with focal seizures in which AED treatment was discontinued at least 48 hours prior to TMS as part of an evaluation for epilepsy surgery.[103]

Alterations in MT and CSP prolongation have been reported, mostly in patients suffering from seizures involving the motor cortex. In these cases, CSP prolongation may indicate that the mechanisms underlying CSP contribute to the compensatory phenomena in the interictal phase. In contrast, CSP has been shown to be usually normal in FEs localized outside the motor cortex.[8,15,17,103] Nevertheless, in a patient with FE due to a lesion within the supplementary motor area[19] and in two patients with FE secondary to cortical dysgenesis not involving the motor cortex,[16] the CSP was greatly lengthened in the contralateral hand, this effect being more likely related to the structural brain lesions rather than to the epileptic process. One study reported a shortened CSP after high-intensity TMS of the affected hemisphere in a group of patients with cryptogenic focal epilepsy, whose characteristics indicated that the epileptogenic area did not correspond to the motor cortex.[14] More recently, a single- and paired-pulse TMS study performed in 23 patients with focal epilepsies not including the primary motor area disclosed that CSP was shorter in epileptic hemispheres of extratemporal epilepsies than in controls, suggesting that FEs chronically influence distant cortex, leading to decrease inhibition in the ipsilateral motor cortex even when the epileptogenic zone is apart from it.[42]

In FE, studies of ICI and ICF have led to inconsistent findings that may be due to subject heterogeneity and AED fluctuations. Overall, most studies have reported ICI reduction and ICF increase in FEs involving or not the motor cortex but without any clear lateralization value.[8,37,95,103,104]

Studies Performed by Stimulating During the Seizures

Single-pulse TMS performed during the seizures captured by long-term EEG monitoring may disclose a variety of alterations of MT and MEP amplitudes, which are likely to reflect the influences of different seizure types on the motor system.[86] In four IGE patients, Gianelli et al.[39] compared the size of MEPs following test magnetic pulses delivered during normal EEG segments and during typical 3-Hz spike-and-wave EEG complexes. MEP size was reduced when TMS was time-locked to the slow-wave component, suggesting a transient decrease in excitability of corticospinal pathways.

In a group of BRE patients presenting extreme somato-sensory-evoked potentials, an abnormal MEP facilitation was seen when the test magnetic pulse was delivered during the ascending phase and the peak of the spike evoked by electrical digital nerve stimulation.[54] In contrast, peripheral nerve stimulation produced no abnormality of MEP size modulation in IGE patients.[74]

Effects of Anticonvulsants

Although TMS can be a useful method for evaluating a patient with epilepsy, it is crucial to note that anticonvulsants have a major influence on brain excitability and, therefore, TMS effects. Hence, it is necessary to understand these effects in order to interpret TMS studies. In fact, some of the information on mode of action of anticonvulsants was actually determined in part from TMS studies.

Before looking at anticonvulsant effects, we review the types of information that can be obtained from TMS studies. Virtually all the data come from stimulation of the primary motor cortex, where TMS produces MEPs in muscles topographically related to the site of stimulation.[1,41,88] Stimulation can excite the descending axons from M1 directly, called the D-wave, and indirectly by a series of intracortical synaptic influences that produce a number of indirect or I-waves.[23] At lowest stimulation intensity, typically the earliest effect comes from the first I-wave, I1.

The *threshold* for producing an MEP reflects the excitability of a central core of neurons that arises from the excitability of individual neurons and their local density. It can be influenced by drugs that affect Na and Ca channels, and must indicate membrane excitability. Because the MEP is small, the threshold measure reflects the influence of mainly the I1 wave. Threshold can be measured with the muscle at rest, rMT, or with an active background contraction of the muscle, aMT.

The *recruitment curve* is the growth of MEP size as a function of stimulus intensity and/or background contraction force. This measurement is less well understood because there are many effects, but it must involve neurons in addition to the core region activated at threshold. These neurons have higher threshold for activation because either they are intrinsically less excitable or they are spatially further from the center of activation by the magnetic stimulus. These neurons would be part of the â€œsubliminal fringeâ€ and contribute to I2 and later I-waves. D-waves are also recruited with higher intensities of stimulation.

Intracortical inhibition and facilitation are obtained with paired-pulse studies and reflect interneuron influences in the cortex.[108] In such studies, an initial conditioning stimulus is given, enough to activate cortical neurons but small enough that no descending influence on the spinal cord can be detected. A second test stimulus at suprathreshold level follows at a short interval (Fig. 5). Intracortical influences initiated by the conditioning stimulus modulate the amplitude of the MEP produced by the test stimulus. At very short intervals, <5 msec, there is inhibition, and at intervals between 8 and 30 msec, there is facilitation. ICI is likely largely a GABAergic effect, specifically Î³-aminobutyric acid A (GABA$_A$).[24] This type of inhibition is also referred to as â€œshort ICIâ€ or SICI to contrast it with ICI studied at longer time intervals, called LICI.[78]

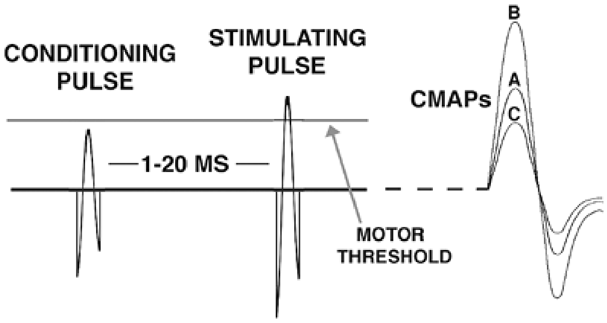

FIGURE 5. Intracortical inhibition and facilitation with paired-pulse stimulation. The first, conditioning pulse is just below motor threshold; the second, stimulating pulse, is just above. Depending on the time interval between the two pulses, the recorded compound muscle action potential (CMAP) may be **(A)** normal, **(B)** facilitated, or **(C)** inhibited.

The *silent period* (SP) (or cortical silent period, CSP) is a pause in ongoing voluntary EMG activity produced by TMS. Although the first part of the SP is due in part to spinal cord refractoriness, the latter part is entirely due to cortical inhibition. There is evidence that this type of inhibition is mediated by GABA$_B$ receptors.[102] SICI and the SP reflect different aspects of cortical inhibition.

Intracortical inhibition can also be assessed with paired suprathreshold TMS pulses at intervals from 50 to 200 msec. This is called LICI to differentiate it from SICI as noted previously. LICI and SICI differ, as demonstrated by the facts that with increasing test pulse strength, LICI decreases but SICI tends to increase, and that there is no correlation between the degree of SICI and that of LICI in different individuals.[78] In addition, LICI appears to inhibit SICI and shows some interaction of inhibitory mechanisms within the human motor cortex.[78] The mechanisms of LICI and SP may be similar.

Short afferent inhibition (SAI) is produced at short latency by somatosensory stimulation of the hand.[24] This has been demonstrated to be mediated by muscarinic synapses because it is selectively blocked by scopolamine.

The data on the influence of anticonvulsant drugs on TMS measures were reviewed in depth by Ziemann.[106] Only the highlights are addressed here and summarized in Table 1. As he noted, the literature is not completely consistent, and the acute and chronic effects of these agents may differ, which makes the interpretation of the literature a bit more complex.

Certain anticonvulsants affect mainly Na channels and thus should influence the threshold for the MEP selectively. This is true of carbamazepine (CBZ),[106] phenytoin (PHT),[11] and la-motrigine (LTG).[106] These agents do not affect MEP recruitment, SP, SICI, or ICF.

Some anticonvulsants, such as lorazepam[107] and diazepam,[67] appear to facilitate the action of GABA$_A$ in a straightforward fashion. These drugs do not influence the motor threshold, but they suppress MEP recruitment, increase SICI, and depress ICF. On the other hand, a more recent finding is that these two agents have different effects on SAI.[26,27] Lorazepam decreases SAI and diazepam increases it. This result shows how complex interneuronal networks are and that even similar compounds might have differing effects.

Other anticonvulsants that are supposed to facilitate GABA do not have the fully expected effect. Valproate was initially reported to elevate MT in patients with primary generalized epilepsy,[73] but in subsequent studies it had no clear influence on any measure.[109] In one study, vigabatrin suppressed ICF but did not affect SP or SICI.[106] In another study, vigabatrin increased LICI and SP but not SICI.[70] This result would be compatible with a selective effect on GABA$_B$ receptors. Tiagabine has paradoxical effects in suppressing SICI and facilitating ICF, but it does lengthen the SP.[102] This suggests that its inhibitory effect is also mediated largely by GABA$_B$ effects.

Table 1 Effects of AEDs on TMS Measures

AED	MT	SICI	LICI	SAI	ICF	REC	sp
Carbamazepine	â†‘						
Lamotrigine	â†‘						
Phenytoin	â†‘						
Levetiracetam	(â†‘)					â†“	
Lorazepam		â†‘		â†“	â†“	â†“	
Diazepam		â†‘		â†‘	â†“	â†“	
Tiababine		â†“			â†‘		â†‘
Gabapentin		â†‘			â†“		â†‘
Vigabatrin			â†‘		â†“		(â†‘)
Valproate		(â†‘)					
Topiramate		â†‘					

Some anticonvulsants have unknown, incompletely known, or multiple modes of action. In this situation, the TMS studies can give some information about how they might have their most important actions. Gabapentin has several modes of action, including increasing GABA synthesis, and its effect is consistent with facilitating GABA effects in that it increases both the SP and SICI and suppresses ICF but has no effect on threshold.[106] Topiramate also has several modes of action, but its effect on TMS measures is limited to increasing SICI, which likely indicates a prominent $GABA_A$ influence.

Levetiracetam has an uncertain mode of action, although some basic studies suggest an effect at the GABA synapse. Multiple TMS measures in one study revealed only a suppression of MEP recruitment and no effect on threshold, SP, ICI, or ICF.[81] As noted earlier, this is difficult to interpret in isolation. Another study, however, did find an elevation in rMT.[71] Levetiracetam was also studied in a special way, via a motor learning task, which might be a method for assessing long-term potentiation.[82] Pinch force and acceleration and motor cortex excitability were studied before and after 30 minutes of pinch practice at 0.5 Hz. Either 3,000 mg of levetiracetam or placebo was administered 1 hour before the experiment. After practice, pinch acceleration was significantly increased with placebo but not with levetiracetam. All other measures showed no significant change. The finding is consistent with a negative influence on long-term potentiation.

Given the influence of anticonvulsants on the brain, it should be possible to use TMS as a functional measure of drug levels. In some ways, this makes more sense than just the serum level of a drug. On the other hand, there needs to be some caution because the anticonvulsant efficacy may not be linearly related to a TMS effect. This has been attempted in several studies. For example, the relationships among LTG oral doses, serum levels, and rMT were assessed by TMS.[90] With a single dose, rMT elevation showed a poor but significant correlation with serum levels, but with a graded dose, serum levels as well as rMT increased in a dose-dependent fashion with significant linear correlation. However, there was a high interindividual variability in the relationship, resembling a sigmoid correlation.

Another study investigated the correlation between serum levels of CBZ and several different measures of motor excitability in patients at the beginning of antiepileptic treatment.[93] Recording sessions were performed before treatment and after 7, 15, and 60 days. There was a progressive increase in rMT and aMT until the serum levels of CBZ reached a steady-state condition. On the other hand, no significant changes were observed in MEP amplitude, SP, SICI, and ICF. This study confirms both the selective effect of CBZ as well as the correlation with serum levels. A third study examined TMS measures and relationship to serum levels with both LTG and CBZ during drug administration and withdrawal.[51] rMT increased with increasing total and free CBZ and LTG levels during drug administration. After acute drug withdrawal, rMT elevation persisted in most individuals with CBZ despite undetectable plasma levels, whereas there was a rapid normalization with LTG. Another interesting finding was that acute drug withdrawal resulted in a transient decrease in rMT in 3 of 10 individuals with CBZ and 2 of 10 with LTG. The authors concluded that plasma levels provide information on motor cortical function during active treatment phases but not during drug withdrawal, and noted that the transient decrease in rMT associated with acute drug withdrawal could represent a physiologic substrate contributing to drug withdrawal seizures.

Induction and Inhibition of Seizures

The potential role of TMS in inducing or inhibiting seizures has long been debated, and a number of experimental studies have been devoted to this issue. In this section we discuss the induction and inhibition properties of TMS separately, as well as the effects of single-pulse (sp), paired-pulse (pp), and repetitive (r) TMS.

Transcranial Magnetic Stimulation and Induction of Seizures

Single-pulse and Paired-pulse Transcranial Magnetic Stimulation

At the time of its introduction in clinical practice, the use of sp TMS was limited by the hypothetical risk of inducing epileptic seizures.[2] However, there are only a few reports dealing with the accidental induction of seizures in patients with neurologic disorders of the brain, while the causative role of TMS remains questionable in most of these cases.[34,43,50] Only Homberg and Netz[43] reported a stroke patient who had his first tonicâ€“clonic seizure during the stimulation procedure.

Table 2 Maximum safe duration (in seconds) of single trains of repetitive transcranial magnetic stimulation based on the National Institute of Neurological Disorders and Stroke experience

Frequency (Hz)	Intensity (% of motor-evoked potential threshold)												
	100	**110**	**120**	**130**	**140**	**150**	**160**	**170**	**180**	**190**	**200**	**210**	**220**
1	>1,800	>1,800	360	>50	>50	>50	>50	27	11	11	8	7	6
5	>10	>10	>10	>10	7.6	5.2	3.6	2.6	2.4	1.6	1.4	1.6	1.2
10	>5	>5	4.2	2.9	1.3	0.8	0.9	0.8	0.5	0.6	0.4	0.3	0.3
20	2.05	1.6	1.0	0.55	0.35	0.25	0.25	0.15	0.2	0.25	0.2	0.1	0.1
25	1.28	0.84	0.4	0.24	0.2	0.24	0.2	0.12	0.08	0.12	0.12	0.08	0.08

Numbers preceded by > are the longest durations tested. No afterdischarge or spread of excitation has been encountered with single trains of repetitive transcranial magnetic stimulation at these combinations of stimulus frequency and intensity.
From Wassermann EM. Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5â€“7, 1996. *Electroencephalogr Clin Neurophysiol*. 1998;108(1):1â€“16.

Single-pulse TMS has not been shown to induce seizures consistently in epileptics.[58,59] In 1990, Tassinari et al.[85] studied 58 patients with recurrent seizures (either partial or generalized) resistant to AEDs. The patients were subdivided into three groups according to seizure frequency (rare, weekly, or daily seizures). Each patient received an average of 25 stimuli, ranging in intensity from 50% to 90% of the maximum stimulator output, with a rate not exceeding one shock every 10 seconds. Neither the short-term (for 2 hours after TMS) or long-term (for 2 months after TMS) clinical monitoring disclosed any TMS seizure-triggering effect in any group of patients. Only one patient with 5 to 10 complex partial seizures (CPS) a day experienced one of his habitual seizures during the TMS investigation. Similarly, Hufnagel et al.[45] reported that 2 of 53 patients with three to five spontaneous CPS a day had a typical seizure during the course of the TMS investigation. Other cases of seizures temporally related to sp TMS in epileptics have been reported,[29,44,46] but these ictal events may have been coincidental. For at least one patient, however, there is clear-cut evidence of focal seizures triggered consistently and reproducibly by single-pulse TMS.[19] Recently, Schrader et al.,[79] reviewing published data and their own experience with three additional seizures in epilepsy patients, estimated that the crude risk of a TMS-associated seizure ranges from 0.0% to 2.8% for sp TMS and from 0.0% to 3.6% for pp TMS in patients with epilepsy. Medically intractable epilepsy and lowering AEDs were associated with increased incidence. In most cases, however, the patients experienced their characteristic seizure semiology, and doubt was expressed in the original reports as to whether the seizures were induced or merely coincidental.

Repetitive Transcranial Magnetic Stimulation

By the end of 1996, six seizures had been elicited by rTMS in 6 nonepileptic individuals (5 volunteers and 1 with depression). Four of these seizures occurred in 4 of 250 volunteers studied at the National Institute of Neurological Disorders and Stroke (NINDS) during the program of clinical development of the technique.[68,97,99] On the basis of these induced seizures and safety studies that monitored the occurrence of post-TMS EMG activity and spread of excitation,[12] limits of stimulation parameters were recommended and proposed for a correct and safe use of the technique in clinical practice (Table 2). These safety margins supplemented and outweighed those previously published by Pascual-Leone et al.[69] on the basis of their studies on spread of cortical excitation along the motor cortex.

Although high-frequency rTMS may induce accidental seizures in normal subjects, it has been rarely associated with seizures in epileptics. So far, only three epileptic patients have been reported to experience a seizure during rapid rTMS procedures (Dhuna et al.[22]; Cohen, personal communication;

Michelucci, Valzania, and Tassinari, personal communication). In view of the seizures occurring in normal subjects, the difficulty of producing seizures in epileptic patients seems paradoxical, especially given that many studies used combinations of settings that were outside of the safe zone (Table 2). A possible explanation is that all of the epileptic subjects were treated with anticonvulsants at the time of stimulation. Special epileptic conditions, however, seem more prone to develop seizures following rTMS. Of 60 patients with various types of epilepsy studied by means of rTMS, Tassinari et al.[87] observed apparently rTMS-induced seizures in 2 of 10 patients with PME and in 1 of 4 patients with epilepsia partialis continua. Persistent jerking of the contralateral arm following cessation of motor cortex rTMS, indicating the presence of afterdischarges, was reported by Michelucci et al.[60] in 2 patients with cryptogenic FE.

Transcranial Magnetic Stimulation and Inhibition of Seizures

In normal subjects, application of low-frequency trains of rTMS produces a relatively long-lasting suppression of cortical excitability.[13] In addition, 0.5-Hz rTMS prolonged the latency for development of pentylenetetrazol-induced seizures in rats.[4] These data provide a rationale for using low-frequency rTMS to treat patients affected by epilepsy and epileptic myoclonus.

In an open pilot study, Tergau et al.[89] investigated the effects of 0.33-Hz rTMS delivered on five consecutive days in nine patients with drug-resistant FE (two temporal, seven extratemporal). Each day, two trains of 500 pulses at 100% of the RMT were applied by means of a large circular coil placed over the vertex. During the follow-up period (4 weeks before and 4 weeks after the rTMS application) the AED treatment was kept constant. Seizure frequency was significantly reduced in the postintervention period compared with the preintervention period.

In a patient with intractable partial seizures due to a focal cortical dysplasia in the left parasagittal parietal region, Menkes and Gruenthal[57] used 0.5-Hz trains of 100 subthreshold magnetic stimuli twice a week for four consecutive weeks. rTMS was delivered by a round coil. During the month of observation, the seizure frequency and the interictal spikes were reduced by 70% and 77%, respectively. Similarly, Fregni et al.[38] observed a significant antiepileptic effect after one session of 0.5-Hz trains of 600 pulses in eight patients with refractory epilepsies due to malformations of cortical development.

These effects of 0.3- to 0.5-Hz rTMS on seizure frequency have yet to be replicated in randomized, blinded trials. In contrast, a controlled study was performed to assess the therapeutic potential of 1-Hz rTMS.[91] Twenty-four FE patients were randomized to blinded active or placebo stimulation delivered

for 15 minutes twice daily for 1 week. Active stimulation was administered at 120% of MT using a figure-8 coil placed over the EEG focus. For the â€œplaceboâ€ stimulation, the coil was angled at 90 degrees away from the scalp. A trend toward a short-term reduction of seizure frequency was observed in the active group, whereas placebo stimulation had no effect. However, this difference was not significant. These findings do not necessarily indicate that the seizure reduction observed in the previous reports was merely due to observer expectations and placebo effects. For instance, distinct effects of different rTMS frequencies (0.3â€“0.5 vs. 1 Hz) could also explain this discrepancy. Cincotta et al.[18] provided evidence that suprathreshold 0.3-Hz rTMS but not 0.9- to 1-Hz rTMS produces a relatively long-lasting enhancement of the inhibitory mechanisms responsible for CSP.

A preliminary report suggested that low-frequency rTMS could reduce epileptic cortical myoclonus.[101] However, the same group performed a sham-controlled study of a larger case series and found no significant beneficial effect with 10 days of 1-Hz rTMS of the motor cortex.[100] In patients with epilepsia partialis continua due to cortical dysplasia, 0.5- to 1-Hz rTMS applied over the motor area induced a marked reduction or temporary disappearance of the jerks.[62,75] In conclusion, the available data are too preliminary to establish whether low-frequency rTMS may be an effective adjunctive treatment in epileptic processes. Randomized trials with realistic shams reproducing as far as possible the physical sensation of the active stimulation should test different rTMS parameter combinations (frequency and intensity of stimulation, train duration, number and frequency of applications, focal vs. nonfocal stimulation). Larger and homogeneous case series are essential to increase sensitivity and to identify the specific epileptic conditions that could be alleviated by rTMS. Finally, appropriate endpoints and long-term follow-up are necessary to evaluate the clinical relevance of the results.

Mapping Speech, Language, and Memory

From the time of its introduction, many researchers in TMS have focused on replicating or replacing the intracarotid amobarbital test (Wada test).[96] The requirements for doing so are straightforward. The new procedure should be safe, tolerable, and robust, producing obvious effects in virtually all subjects and allowing test paradigms that epilepsy patients can comply with in the face of anxiety, medications, and structural encephalopathies. Finally, of course, the new procedure should have excellent concordance with Wada test results, and when discordant, should be at least as good at predicting surgical outcomes. TMS has provided a wealth of information about language and memory mechanisms but has not yet fully satisfied the requirements for a clinical language test.

Initial attempts to affect language with rTMS were hampered by the use of round stimulation coils and colored by the belief that stimulation parameters should match those used in operative electrocorticography. Prior to the existence of safety guidelines,[99] stimulation frequencies ranged up to 50 Hz; stimulator output was commonly set between 80% and 100% of maximum, with stimulus trains up to 10 seconds in duration. Pain, crying, and even seizure were among the outcomes.[20,35,48,60,69] Pascual-Leone et al.[68] reported lateralized interference with speech output using TMS in 6 of 6 epilepsy patients; all results matched the Wada test. Others found speech disruption difficult to induce with round TMS stimulation coils. Jennum et al.[48] achieved complete speech arrest in only 7 of 14 subjects, whereas Michelucci et al.[61] reported 14 of 21. Epstein et al.,[30] using a more focal figure-8 coil, induced speech arrest with frequencies as low as 4 Hz and train durations of 5 seconds or less. These stimulation parameters produced more consistent results while reducing the discomfort of rTMS and allowing compliance with safety guidelines.

TMS-induced speech arrest is now safe and robust enough to produce obvious effects in almost all epilepsy patients and normal volunteers. However, it appears to represent a disruption of motor speech output rather than a true aphasia and to occur in the vicinity of facial motor cortex.[32] Like simple speech arrest in the Wada test itself, it is not fully accurate for language lateralization.[6] Jennum et al.[48] and Epstein et al.[32] each reported a patient with left hemisphere language lateralization by Wada testing but apparent right lateralization by rTMS speech arrest. We have encountered a third such patient in the course of additional testing. When compared directly in 17 epilepsy surgery candidates, rTMS showed a significant correlation with the Wada test but also showed a significant bias toward right hemisphere or bilateral lateralization.[32] Most patients in this series underwent resection of the epileptic focus; the Wada results corresponded more closely than TMS with postoperative language deficits.

In retrospect, it might have been predicted that TMS speech effects would be obtained most easily over motor cortex. Ojemann's classic studies of verbal interference sites during electrocorticography show the most common locus to lie at the foot of the precentral sulcus.[66] In these studies, there is no evidence for a more anterior cluster of speech arrest sites corresponding to Broca's area. Furthermore, despite occasional observations of transient aphasic phenomena, it has not been possible for TMS to produce consistent Broca's or Wernicke's aphasia.

Stewart et al.[84] demonstrated in normal volunteers that magnetic stimulation of two different, nonoverlapping inferior frontal sites could result in speech arrest. Stimulation of the more posterior site was accompanied by mentalis muscle activity; stimulation of the more anterior site was not. The anterior, nonmotor site was more clearly lateralized to the left hemisphere but was also more uncomfortable and more difficult to activate in all subjects. The finding of two separate sites for TMS speech interference has been replicated,[5] but it is not yet clear whether the anterior site represents interference with language as opposed to simply motor speech.

A large number of studies have in fact demonstrated TMS effects on language function. Most of these effects have been subtle, however, consisting of group changes in reaction time rather than accuracy of performance. Picture naming and a variety of other language tasks can be both delayed and facilitated by rapid rTMS over left posterior temporal, left superior temporal, dorsal frontal, and inferior frontal lobes.[9,28,63,76,77,83,92] It is interesting that some of the facilitatory effects can be obtained from stimulation of the nondominant hemisphere[65,100] and can be demonstrated in aphasic patients.[64]

In the present era, lateralization of memory function probably has greater practical importance than lateralization of speech. A few TMS studies have shown interference with verbal memory by TMS over the temporal lobe.[29,40,69] However, the hippocampus represents a daunting target for TMS. Focal stimulation of such deep structures without overstimulation of overlying cortex remains a technical challenge. The granular cortex of the prefrontal lobe is now known to be intimately involved in both working memory and encoding of novel stimuli and represents a far more accessible target. Several reports have described interference or facilitation of episodic memory encoding by TMS over dorsolateral prefrontal cortex. In general, the results are consistent with classic models of hemispheric specialization: Verbal encoding is disrupted by stimulation over the left prefrontal region, and nonverbal encoding is impaired by right prefrontal stimulation.[9,33,36,49,63,77,80] Virtually all of these studies have been carried out in normal volunteers, for

which the required intensity of stimulation is generally quite tolerable.

New, noninvasive techniques for determining the lateralization of memory function remain desirable for epilepsy practice and research. Recent approaches to memory testing with TMS show promise of eventual clinical application.

Summary and Conclusions

Most of our understanding about the mechanisms of TMS comes from studies of the motor cortex, where the major site of activation appears to be myelinated axons of cortical interneurons, aligned parallel to the cortical surface. TMS findings in different epileptic phenotypes are complex and sometimes contradictory, with the most consistent being decreased MT and ICI in some forms of IGE. Such studies are complicated by time of testing in relation to seizures, the possibility that patients with similar clinical conditions may have different underlying disorders, and the independent effects of AEDs. The AED effects, while occasionally inconsistent, are sufficiently reliable that they can be helpful in exploring AED mechanisms of action and tracking central nervous system changes over time. Application of TMS to mapping language and memory is promising, but not yet sufficiently robust and accurate for general clinical application. Preliminary reports of TMS efficacy in activating and suppressing seizures have yet to be substantiated in clinical trials.

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Chapter 89

Cellular Imaging of Epilepsy

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Introduction

We are at the start of an imaging revolution that is transforming our view of the brain. The techniques and technology continue to develop, and the benefits are self-evident when studying such a complex network phenomenon as a seizure. Indeed, the complexity of epileptiform activity and our inability to record it with sufficient detail at an appropriate temporal and spatial resolution have been major obstacles to progress in the field. Imaging permits detailed measurements (e.g., membrane potential or calcium [Ca^{2+}] dynamics) to be made at many locations simultaneously, and it has already proved a significant adjunct to traditional electrophysiologic recordings.

Our main goal in this chapter is to present the possibilities that imaging affords, with a focus on imaging neural activity. We start with a brief description of some of the tools of the trade. We then provide an overview of various imaging techniques and their relevance to epilepsy, and we finish with some thoughts on possible future research.

Imaging Hardware

Technological developments have both fed and driven the burgeoning field of imaging in biology. It is tempting to draw comparison with how developments in making lenses fuelled new ways of looking at nature (both literally and metaphorically) at the start of the scientific revolution in the seventeenth century.

Key among these recent developments is the continual improvement in light sensors and cameras. The importance of the camera is obviously in part to make a permanent record of the biology, but also to record things that are not necessarily visible to the naked eye. There are two facets to thisâ€"enhancement of the view, which involves creating an image from light that lacks sufficient contrast or has spectral characteristics beyond visible light (e.g., infrared [IR] or ultraviolet [UV]); and intensification, which involves boosting the signal when the light levels are too low, which is especially important in fluorescence microscopy because it permits much less intense illumination of the specimen.

Most imaging today involves recording fluorescent emissions. There are three main optionsâ€"epifluorescent, confocal, and two-photon microscopy (TPM). Of these, epifluorescent microscopy has been the most conventional and affordable. Its limitation is that the signal of interest, located at the plane of focus, is contaminated with fluorescence from molecules above and below this plane. Consequently, the signal-to-noise level is low, necessitating intense illumination to improve the signal. The intensity of illumination is a severe problem because it causes photobleaching and phototoxicity. Furthermore, these effects occur throughout the path of illumination.

This problem is partly solved by confocal microscopes. The key feature of these microscopes is a pinhole at the confocal plane (the plane of focus of the image located at the other side of the objective lens to the specimen; the pinhole effect also can be achieved with a tilting mirror) through which both the illumination and the fluorescent emission have to pass. Thus, any fluorescence emission from molecules out of the plane of focus will fail to pass back through the pinhole. Consequently, the only signal arises from the focal plane. This is known as focal sectioning. Focal sectioning provides a much-improved signal-to-noise ratio and thus permits lower illumination. Unfortunately, there is still photobleaching and phototoxicity in the path of illumination.

Two-photon microscopy (TPM) produces the least photobleaching and phototoxicity because the excitation of the chromophore occurs at a single point in the plane of focus. The essential physics for understanding TPM is that if a fluorescent molecule can be activated by a single photon at a given wavelength, then it can also be activated by the near-simultaneous absorption of two photons of approximately double the wavelength. However, the intensity of light required to get two photons to hit the same molecule is staggeringly high and is only achieved at the focal point with illumination using a pulsed laser.

The benefit of illumination with long wavelengths (roughly twice the wavelength for two-photon excitation) is that the light is less scattered and consequently penetrates tissue much better, causing less damage as it passes through. One can therefore monitor activity far deeper into slices and, crucially, perform in vivo imaging. This ability is further aided by the fact that fluorescence occurs at a single point, and so all emissions, no matter how scattered, can be attributed to that point. Indeed, it was possible to image dendritic spines on pyramidal cells in vivo without even doing a craniotomy.[15]

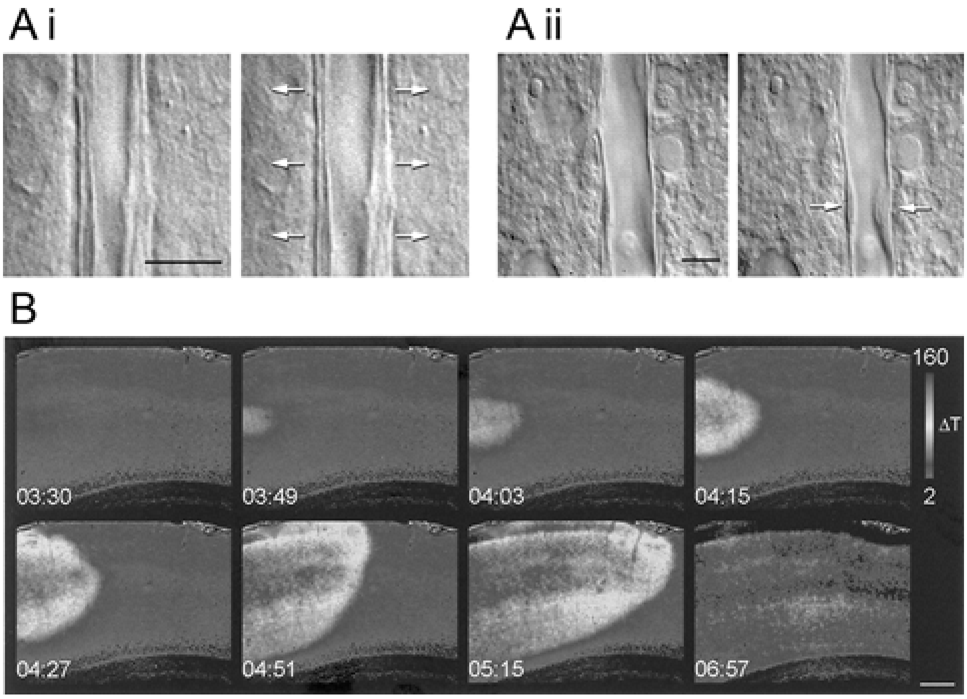

FIGURE 1. Imaging without stains. **A:** Regulation of vascular tone by interneuronal activity. Differential interference contrast images of microvessels before and after electrical stimulation of (**i**) a vasoactive intestinal peptide (VIP)-positive interneuron and (**ii**) a somatostatin-positive interneuron. The stimulated interneurons were not in the field of view but were characterized electrophysiologically and, post fixing, with immunocytochemistry. (From Cauli B, Tong XK, Rancillac A, et al. Cortical GABA interneurons in neurovascular coupling: relays for subcortical vasoactive pathways. *J Neurosci.* 2004;24(41):8940â€“8949; with permission.) **B:** Spreading depression in a neocortical slice viewed using intrinsic optical imaging. The spreading depression was triggered by perfusion of 100 ÂµM ouabain. (From Basarsky TA, Duffy SN, Andrew RD, et al. Imaging spreading depression and associated intracellular calcium waves in brain slices. *J Neurosci.* 1998;18(18):7189â€“7199; with permission.)

One further use for TPM is laser uncaging of various biologically active species (e.g., glutamate and Ca^{2+}).

The main drawback of TPM is the slow rate of imaging acquisition. Because only one point is being illuminated at any given time, to get an extended two-dimensional image, the laser has to be scanned through the whole field of view. This usually takes about 1 second, which is clearly a serious impediment when trying to monitor rapidly evolving network activity. Recently, however, the problem of slow image acquisition has been solved in three different ways. The first involves splitting the laser beam into multiple beams.[14] There is a cost in signal-to-noise ratio and possibly spatial resolution and depth of imaging (due to scatter of emitted light), but the potential benefit is, in principle, a doubling in imaging rate each time the beam is split. The second solution is to direct the laser only to those points in the field of view that are of interest. For instance, one maps the location of the neuronal somas with an initial scan, and then directs the laser only to those points.[20] The resulting laser trajectory is a fraction of that in normal raster mode. A

third option is to use acoustooptic scanners, which could be as much as 1,000 times faster than mechanical scanners.[17]

It is important to remember that all modes of imaging entail photobleaching and phototoxicity, the only difference being one of degree. Thus, there is a general overriding principle that applies to all imaging methods: To optimize the protocol so as to reduce the illumination intensity to a minimum. This demands an understanding of the nature of the biological phenomenon being studied and the properties and sensitivity of the tools being used to examine it. Out of necessity, we have given a narrow and simplistic view of the field, and we encourage interested readers to consult more-specialized texts.[10,13,16,37]

Nature of Cellular Imaging

In the following sections we cover the main techniques used to study neural activity. We also introduce some techniques that, although not yet applied to epilepsy, show promise for future research.

Floyd Bloom wryly noted that â€œthe gain in brain lies mainly in the stain.â€ Certainly our ability to visualize and understand biology has been transformed by green fluorescent protein (GFP), Ca^{2+} dyes, and many other labeling methods, and we discuss these in due course. It should be remembered, however, that there are also means of observing brain processes that do so without the potential invasiveness of loading the tissue with dye.

Imaging Without Stains

Brain tissue is not colored, but cells (either isolated or in slices) can be visualized using differential interference contrast (DIC) imaging. In slices, the view is limited effectively to the soma and dendritic stems of neurons, but this has proved to be an excellent way of visualizing neurons for patch clamping. Blood vessels are also easily seen, permitting a beautiful demonstration of the interaction between interneurons and the vasculature (Fig. 1A).[6]

A similarly simple technique is intrinsic optical imagingâ€” the recording of subtle changes in reflectance of the tissue (see Chapter 86). The reflectance changes are secondary to neural activity and are thought to arise from changes in cellular volume and, for in vivo studies, changes in blood flow and hemoglobin oxygenation. In vivo intrinsic imaging has been used to show a prominent inhibitory annulus surrounding a neocortical ictal focus during interictal events and a preceding inhibition in advance of a propagating wave.[27] In vitro imaging of slices has demonstrated activity-induced swelling of neurons,[2] swelling of astrocytes secondary to potassium (K^+) uptake,[22] spreading depression[5] (Fig. 1B), and ischemic depolarization.[4] The limitation of the technique is that it gives only an indirect measure of activity recorded on a relatively slow time scale, but on the plus side, it provides large-scale views of neuronal activity without indicator dyes.

Finally, a handful of biological molecules autofluoresce when illuminated at the appropriate wavelength.[36] Probably the most useful of these is the reduced form of nicotinamide adenine dinucleotide[7](NADH) (other examples include retinol, indoleamines, and collagen), the oxygenated form of which (NAD^+), does not fluoresce. Thus, changes in NADH autofluorescence reflect shifts in the ratio of NADH to NAD^+, which in turn reflect the metabolic state of the cell.[7]

Seizure-like activity or persistent stimulation in vitro causes an initial drop in NADH fluorescence (trough at around 10 seconds) followed by a subsequent overshoot peaking at around 60 seconds.[21] A further in vitro study, using GFP and immunofluorescently labeled astrocytes, identified the early flux as arising from oxidative metabolism in neuronal dendrites, whereas the late rise in NADH occurred in astrocytes (rich in glycolytic enzymes but poor in mitochondria).[19] There is, however, one significant caveat to this interesting metabolic relationship between neurons and glia: Experiments in vivo fail to show the late rise in NADH fluorescence unless the local blood supply is impaired.[18] It seems that in the normal brain, any oxygen debt incurred by neuronal activity is more than offset by an increased supply of oxygen through dilated blood vessels.

Anatomic Stains

Perhaps the most widely discussed imaging development arose from molecular biologyâ€"the ability to genetically engineer green fluorescent proteins. The developments continue apace,

as illustrated by the Gensat project (http://www.gensat.com). This online resource is striving to characterize expression patterns for all genes known to be expressed in the mouse brain, by creating mouse strains in which individual promoters are used to drive GFP expression. In principle, one can then visualize the temporal and spatial pattern of expression by the presence of GFP.

This facility might allow the expression of key genes to be followed during the evolution of ictogenic foci in vivo, for example, following a head injury. Of course, there are easier means of identifying candidate genes ex vivo (e.g., immunolabeling fixed tissue, gene expression profiling using microarray analysis), but the availability of the relevant GFP mouse line would permit detailed analysis of the temporal and spatial patterns of gene expression in living samples.

A further use for anatomic stains is that they provide easy, noninvasive cell identification. One can then target those cells for patching or for characterizing cell-class-specific patterns of activity using Ca^{2+} dyes.

Finally, epileptic activity might induce morphologic changes that can be followed in labeled cells. For instance, dendritic spines, the site of excitatory drive on to pyramidal cells, are known to be restructured by activity, although the degree to which this happens is the subject of intense debate.[15,33] Studies of post mortem tissue have shown reductions in spine density following seizures. However a recent TPM in vivo study of pilocarpine-induced epileptic activity failed to find evidence of spine remodeling, except secondary to other pathologic changes in the dendrites.[25]

Voltage-sensitive Dyes

Optical monitoring using voltage-sensitive dyes has been used to record activity in a single neuron at many locations in the dendritic tree or to record population activity in a bulk-loaded preparation. The signals are rapid, but they are also small. Measurements from a single cell require intense illumination, but the dyes are then very phototoxic, and the cells usually die after firing a handful of action potentials. In population studies, the signal is too weak to record from individual neurons.

An additional problem in interpreting the signal is that it is an average from all neural structuresâ€"axons, somas, and dendrites. This problem is well illustrated by attempts to study epileptiform propagation in neocortical slices. These studies seemed to indicate that activity spreads primarily in the supragranular layers,[1,29,35] in contrast to other work, which concluded that the earliest recruited pyramidal population were the large layer 5 neurons.[8,31] A resolution to this contradiction may come from simultaneous somatic and dendritic patch recordings,[26] which show that the peak membrane potential deflection during a paroxysmal depolarizing shift (PDS) is 10 mV greater in the apical trunk (i.e., supragranular location) than at the soma. This is also consistent with the anatomy of neocortical networks because we know that the most powerful reciprocal lateral connections are in the supragranular layers 2 and 3.[11]

Ca^{2+} Imaging

We come finally to what may prove to be the most useful imaging tool for epilepsy research. Most Ca^{2+} indicators are derivatives of the Ca^{2+} buffer 1,2-bis(*o*-aminophenoxy)ethane-*N*,*N*,*N*â€²,*N*â€²-tetraacetic acid (BAPTA) and thus are exquisitely sensitive to Ca^{2+}. They work by chelating the ion, with the bound form having different fluorescent properties from the unbound form. A key property is therefore the dissociation constant for Ca^{2+} binding, K_d, which determines the dynamic range of the dye (typically 0.1 to 10 times K_d). The K_d, however, is influenced by temperature, pH, protein binding, the presence of other ions (especially magnesium [Mg^{2+}]), and a number of other factors. Consequently the K_d measured in vitro and that in situ can be rather different. The most useful dyes for monitoring firing patterns have an in vitroâ€“measured K_d in the range 100 to 350 nM and include fura-2, indo-1, Oregon green 488 BAPTA-1 (OGB1), and fluo-4.

Calcium indicators can be loaded into neurons directly via the recording pipette, and this method has been used to explore the role of Ca^{2+} in the PDS during bicuculline-induced events.[26] Ca^{2+} enters primarily through *N*-methyl-D-aspartate (NMDA) receptors and voltage-gated Ca^{2+} channels, and the cytosolic concentration is further boosted from intracellular stores.[26] This rise in Ca^{2+} activates the nonspecific cation channel I_{can}, which is the crucial for sustaining the PDS.

Bulk loading, on the other hand, uses the acetoxymethyl (AM) ester derivatives of the various dyes. These freely cross the cell membrane, and the AM group is then cleaved by intracellular esterases to produce the functional dye. Fura-2 has been the dye of choice for our in vitro studies[3,9,30] for several reasons:

1. It affords a good signal-to-noise ratio, with Ca^{2+} increases causing a drop in emission; thus the quiescent cell is clearly visualized, allowing easy localization of the somas.
2. It can be used in tandem with GFP; the dyes have different absorption and emission spectra.
3. It yields preferential loading of neurons over glia; we estimate that with good loading, about 95% of labeled cells are neurons.

OGB1 also gives good neuronal labeling (70% to 90% neuronal, with glia being easily distinguished using the astrocyte-specific label SR101[23]; see Fig. 2). Brief loading with fluo-4-AM can give good neuronal loading (30% to 70% neuronal), but with longer incubations, the loading is preferentially of glia. The reason for the differential pattern of loading is not clear, but it is most likely caused by some combination of the following: Differences in the intracellular esterases, differences in the internal milieu influencing the effective K_d, and differences in the Ca^{2+} rise triggered by action potentials in different neuronal populations.

Our bulk-loading experiments use what appears to be a universal feature of spiking neurons, which is that their somatic Ca^{2+} levels rise following an action potential. The Ca^{2+} change is detected as a sharp change in fluorescence, occurring in less than 17 msec (one time frame imaged at 60 Hz: Fig. 2). The subsequent decay has a time constant of about 0.5 second, so the signal persists for some time, allowing action potentials to be captured at relatively slow imaging speeds.

How fast can one usefully capture population dynamics with Ca^{2+} imaging? Low-power imaging necessarily reduces the numbers of pixels collecting signal for an individual soma, and consequently the spatial averaging is limited. Furthermore, lower-power objectives have lower numerical apertures, and hence they have poorer focal sectioning and produce a somatic signal contaminated by neuropil signal. The neuropil signal can be large during intense network activity such as epileptiform events. These factors lower the signal-to-noise ratio. Increasing the intensity of illumination helps, but at a cost of increased phototoxicity and bleaching. A second option is to image at higher powers but with a smaller field of view. The final option is to collect each image over a longer period, that is, to image more slowly. For these reasons, we believe that Ca^{2+} imaging of bulk-loaded slices is unlikely to discriminate activation times of neurons activated within much less than 10 msec of each other.

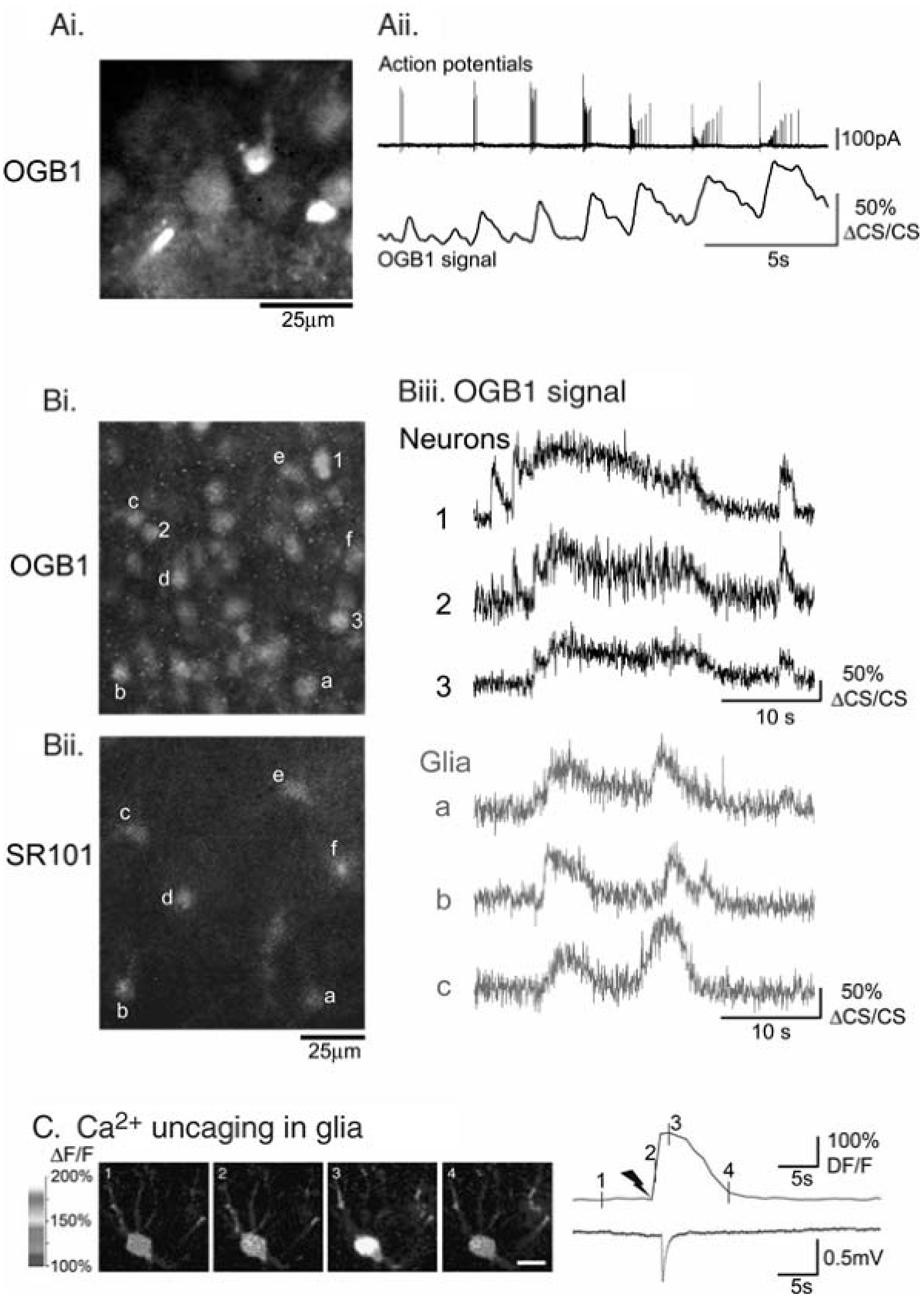

FIGURE 2. Ca^{2+} imaging of epileptiform activity. **A:** Ca^{2+} indicators give a reliable record of action potential trains. A loaded pyramidal cell (**i**, *center*) was recorded in cell-attached mode (electrode is the white flash,

lower left) during the transition into a full ictal event. We know from other recordings that the action potential barrages occur on the crest of successive paroxysmal depolarizing shifts (the PDSs themselves are not apparent in cell-attached recordings). **B:** Neuronal and glial activity. Both neurons and glia take up the Ca^{2+} indicator OGB1 (**i**), but only glial cells take up SR101 (**ii;** glia labeled aâ€"f). **(iii)** The Ca^{2+} fluorescence for three of the glia (aâ€"c) and for three representative neurons (1â€"3). Glia have slower and delayed Ca^{2+} rises compared to the neuronal signal. (From Tian GF, Azmi H, Takano T, et al. An astrocytic basis of epilepsy. *Nat Med.* 2005;11(9):973â€"981; with permission.) **C:** Two-photon uncaging of Ca^{2+} in glial cells provokes glutamate-dependent DC shifts in the local field recordings. The glia were also labeled with the Ca^{2+} dye fluo4. The four sequential micrographs were taken at the times shown in the traces (*right*). The rise in the glial Ca^{2+} consistently was followed by a local network event recorded here using a field electrode.

These techniques have shown patterns of activity in cortical slices bathed in nonepileptogenic artificial cerebrospinal fluid (ACSF),[9] and we have extended these studies to various in vitro models of epilepsy.[3,30] The most interesting results are the propagation patterns of the first epileptiform waves following washout of Mg^{2+} from the bath. The wave propagates by stepwise recruitment of local populations of neurons, seemingly regulated by the local inhibitory elements.[34]

Calcium imaging has also highlighted prominent Ca^{2+} dynamics in glia (Fig. 2). Epileptogenic conditions induce a marked increase in the incidence of large oscillations of intracellular Ca^{2+} in glia.[30,32] These are associated with synchronized NMDA-mediated events in local pyramidal populations. Furthermore, uncaging Ca^{2+} in glia can cause these local depolarizing events.[12,32]

Further evidence of a role for glial Ca^{2+} waves in epilepsy derives from in vivo experiments that demonstrate a surprising action of three different anticonvulsants. Valproate, gabapentin, and phenytoin were all found to reduce the amplitude of glial Ca^{2+} waves triggered by either 4-aminopyridine or ATP.[32] This effect implies that the crucial anticonvulsant action of these drugs, long thought to be mediated through neurons, may in fact be mediated through glia. The ATP-induced waves provide the strongest evidence because ATP is thought to have a much more powerful effect on glia than on neurons. There remain, however, the possibilities that initiation or maintenance of these glial Ca^{2+} waves involves neuronal action, which should warn us against overinterpreting this result. What we really need to demonstrate is a molecular site of action for the anticonvulsants, and furthermore that this is located in glia.

Glia also show interesting Ca^{2+} dynamics during propagating waves recorded in vitro. Their intracellular Ca^{2+} rises very slowly, with a delay of around 1 to 5 seconds after the local neuronal activation (Fig. 2). These glial Ca^{2+} kinetics need to be interpreted in the light of the NADH imaging studies mentioned earlier, and future experiments will show whether they also occur in vivo. Given the apparent role for glia in initiating events, it seems quite possible that glial activity might also influence how the epileptiform activity evolves.

These techniques for bulk loading Ca^{2+} dyes are being applied.[20,24,28] One important goal will be to validate the numerous in vitro studies, but there are also many other possibilities.

Summary and Conclusions

We mentioned the possibility of using imaging to follow gene expression in vivo during epileptogenesis. In this case, the screening of involved genes is best done using molecular biological techniques. In other contexts, it is worth stressing that imaging represents an ideal screening tool in its own right. We documented some of the many ways we can use imaging techniques to observe neural function, often relatively noninvasively. The strength of these techniques lies in the possibility of gathering huge amounts of data from many locations in the neural networks simultaneously. Thus, imaging can highlight quickly where the action lies; which cells are active or behaving in unusual ways; which cells are no longer active or have died; and, if changes in gene expression are involved, in which cells and at what times.

We speculate that there are critical components of the network that underlie the majority of epilepsy phenotypes, and that these represent promising therapeutic targets. We suggest that our best chance of identifying these elements will be to use, in tandem with the more classical electrophysiologic and molecular biology techniques, the many imaging techniques that are now being developed.

Acknowledgments

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Chapter 90

Neuropsychology Evaluation â€“ Adults

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Introduction

Neuropsychological impairments are common in many epilepsy syndromes and are related to clinical factors such as seizure frequency and severity, age of seizure onset, as well as the underlying pathologic substrate. It is beyond the scope of this chapter to provide a comprehensive review of all epilepsy syndromes and their patterns of neuropsychological impairment. However, we will highlight several consistent neuropsychological principles.

As described by Hughlings Jackson, there are significant and independent contributions of both static and dynamic factors that affect brain function, and by extension, neuropsychological abilities. Morphologic or structural lesions are associated with relatively nonmodifiable neuropsychological deficits. In contrast, electroencephalographic (EEG) discharges, seizures, and epilepsy treatment are associated with more dynamic brain changes that, to varying degrees, are modifiable and are under direct physician management. Depending on epilepsy type (idiopathic vs. symptomatic), the relative contributions of specific factors will differ.

Disentangling the stable and dynamic cognitive influences in epilepsy often poses a major challenge because the causes of impaired neuropsychological function are not fully independent of each other. Treatment effects, for example, act on and interact with morphology and epilepsy. Although altered brain structure and function may result in epilepsy, epilepsy and its underpinnings may also alter functional cerebral organization. Finally, at the highest level, epilepsy-related cognitive impairment must be evaluated within the patient's developmental context. Certain seizure syndromes show peaks at specific developmental stages, and etiology is associated with age at seizure onset. Cognitive profiles vary depending on age of seizure onset, with differences apparent depending on whether epilepsy develops in the maturing brain versus mature brain versus aging brain. However, age of seizure onset may simply reflect the expression of dysfunctional brain maturation.

Epilepsy is often dichotomized according to whether the EEG abnormalities involve the entire cerebrum (generalized epilepsy) or begin focally (partial epilepsy). Generalized epilepsy includes tonicâ€“clonic seizures, juvenile absence epilepsy, and myoclonic epilepsy. Partial epilepsy includes a variety of seizure types including the so called â€œbenignâ€ partial epilepsy (e.g., benign epilepsy with centrotemporal spikes, or BECTS) as well as symptomatic focal epilepsy (e.g., mesial temporal lobe epilepsy and neocortical epilepsy). In this chapter, we describe disease effects on cognition as a function of epilepsy syndromes, age of onset, and epilepsy course. We also discuss the complex issue of whether poorly controlled seizures are associated with progressive cognitive decline. For ease of discussion, we categorize epilepsy subtypes according to whether they are considered to be idiopathic or symptomatic.

Idiopathic Epilepsy

Idiopathic epilepsy, including both generalized and partial epilepsy expression, is characterized by a genetic predisposition and the absence of readily identifiable brain lesions. Although not completely silent behaviorally or cognitively, idiopathic epilepsy is generally easy to treat and is associated with less severe cognitive impairments than are other seizure types. *Idiopathic generalized epilepsy* (IGE) is characterized by generalized EEG abnormalities involving the entire cerebral cortex, whereas *idiopathic partial epilepsy* (IPE) is associated with regional EEG abnormalities (e.g., centrotemporal EEG in rolandic epilepsy).

As would be predicted from generalized EEG abnormalities, diffuse and generalized cognitive impairments are present, including deficits in attention, psychomotor speed, visuospatial skills, and nonverbal memory. Language and verbal memory, in contrast, appear unaffected.[62,102,107]

The epileptiform discharges and cognition are also closely related. Not only does cognitive impairment vary as a function of seizure activity, but cognition may also induce seizures and seizure discharges.[92] Although this relationship has been described in patients with symptomatic temporal lobe epilepsy (TLE),[50] patients with IGE are particularly likely to show neuropsychological EEG activation. Negative effects of spike-and-wave bursts exist for sensory and executive functions. Therefore, tasks requiring sustained attention are best suited to detect the cognitive effects of EEG changes in IGE.[102] Although cumulative attentional effects may ultimately result in diminished level of function when they occur over long periods, decreased IQ is not a primary feature of the disease, with developmental delay and retardation developing from interference with cognitive functions over a long period of time. Absence epilepsy developing in early childhood is generally associated with poorer outcome than juvenile absence epilepsy.

BECTS is a common epilepsy syndrome (10%â€“15%), beginning between 5 and 9 years of age and extending into adolescence. It has a favorable prognosis, and most patients become seizure-free after puberty. Its neuropsychological prognosis, however, is less benign. During its active phase, neuropsychological deficits may include attention, motor functions, short-term memory, visual and perceptive abilities. Language difficulty relating to the interictal dysfunction of the perisylvian language areas, however, is a major characteristic of BECTS.[102] Learning disabilities are common in BECTS,[143] although they are not progressive in nature. Although children rapidly improve in most areas following seizure remission, minor problems in executive functions and verbal comprehension persist.[80,103] Complete seizure remission is generally needed for a favorable cognitive outcome.

Juvenile myoclonus epilepsy (JME) generally begins between 12 and 18 years of age, and is characterized by neuropsychological and behavioral features associated with

frontal dysexecutive impairment such as reasoning difficulty, poor concept formation, and decreased mental speed and flexibility.[22,64,65,102,130] Of course, frontal lobe dysfunction is not specific for JME. Whether frontal lobe cognitive dysfunction together with personality change (e.g., limited self-control, suggestibility, indifference, rapid mood changes) form a syndrome characteristic of JME merits further study.[65] The presence of more focal impairments in addition to generalized slowing is consistent with the view that IGE should no longer be considered purely a â€œgeneralizedâ€ epilepsy. EEG, histologic, structural and functional imaging studies suggest a specific involvement of frontal lobes, thalamus, and thalamocortical loops in IGE.[1,75,100,118,147]

In conclusion, a wide range of rather mild impairments may be associated with idiopathic generalized or idiopathic partial epilepsy. Mild generalized impairment and learning difficultly have been observed. These are best understood from the close relationship between active epileptic processes interfering with cognitive networks of lower-order functions, on perceptive and executive functions, and on the interference of epilepsy with critical periods of cognitive development (i.e., before, during, or after language acquisition, or at the time before or during frontal executive function development). Frontal/executive functions are the last to fully develop and therefore may represent a common endpoint for the impairments seen in idiopathic epilepsy. Following epilepsy remission, neuropsychological recovery from active epilepsy-driven impairment can be observed. However, some long-term residual deficits may persist, particularly when epilepsy has significantly interfered with cognitive development.

Focal Symptomatic Epilepsy

In contrast to idiopathic epilepsy, the cognitive profiles of symptomatic epilepsy are more strongly related to epilepsy location and etiology. The temporal lobes and temporomesial structures are particularly vulnerable to seizure development, and TLE accounts for approximately 70% of chronic symptomatic epilepsy. Approximately half of TLE patients have hippocampal sclerosis (HS) or hippocampal atrophy, although whether mesial TLE represents a distinct nosological entity or a syndrome is still a matter of debate.[146] Mesial TLE is characterized by impaired declarative memory.[57] Patients with earlier seizure onset tend to have lower IQs, reflecting the interference of seizures (and perhaps their treatment with antiepileptic medications) with normal cognitive and brain development.[54] Accompanying the IQ with earlier seizure onset is a reduction of total brain volume, including both gray and white matter.[54] Memory impairment occurs independent of the age of seizure onset, although the nature of the memory impairment depends on when seizures begin. A more generalized memory impairment occurs with earlier seizure onset, whereas a more focal and material-specific memory impairment that varies according to seizure onset laterality is seen with later seizure onset.[43]

With later seizure development, left temporal/left temporomesial epilepsy is associated with material-specific impairment of verbal learning and memory. Mesial and neocortical structures differentially contribute to verbal memory, with mesial structures subserving consolidation and retrieval, and neocortical structures being more associated with content processing. Thus, impaired delayed recall is more indicative of mesial rather than neocortical temporal lobe damage.[48] Impairment of verbal learning, short-term memory, and naming (i.e., semantic memory) are less specific but also may reflect left inferotemporal or temporolateral lesions.[39,40,42,125,126] Naming impairment is associated with hippocampal volume,[14] and also related to functional activity reflected by spectroscopy.[123] Like memory, the magnitude of naming impairment is strongly associated with seizure onset age.

In contrast to left TLE, right TLE tends affect performance on figural or nonverbal memory tasks.[34] However, this relationship is less consistent than that between left TLE and verbal memory,[6] an effect that has been attributed to nonverbal memory networks being more bilaterally distributed than verbal memory, covert verbalization during task performance, or the type of test and test materials (abstractness, complexity) used. Consequently, using figural memory tests to infer mesial temporal dysfunction will often falsely lateralize seizure onset. However, false lateralizing figural memory impairment in left TLE may also reflect atypical language dominance or sex differences.[43]

Even though the area of seizure onset in focal TLE is limited, neuropsychological impairment often extends beyond the seizure onset zone.[59,89] These â€œfrontalâ€ deficits imply impaired functional connectivity that is disrupted with a temporal lobe focus, and may be considered to reflect â€œnociferous cortexâ€ effects, in which the negative effects associated with ongoing seizure discharge impair brain function at some distance from the active seizure focus.[134] However, magnetic resonance imaging (MRI) volumetrics have demonstrated prominent disruption in ipsilateral hippocampus and neural connectivity (i.e., white matter volume loss) that extends beyond the temporal lobe, affecting both ipsilateral and contralateral hemispheres.[128] TLE patients with secondary generalized seizures are at higher risk of additional general neuropsychological impairment.[70]

Frontal lobe epilepsy (FLE) is seen in approximately 20% of patients with partial onset seizures, and is associated with a less consistent neuropsychological profile than TLE. In contrast to TLE, in which HS is the predominant morphologic feature, frontal lobe epilepsy is associated with a more heterogeneous array of etiologic factors. Moreover, executive functions mediated by the frontal lobe contribute to most other cognitive functions, resulting in diffuse and nonspecific neuropsychological impairments. Patients suffer from attention problems, problems with working memory, mental flexibility, response inhibition, or planning. Tests of motor coordination appear particularly sensitive to frontal lobe epilepsy. At the highest level, a dysexecutive syndrome may comprise problems with response selection, initiation, execution, and inhibition. No consistent lateralized impairment has been associated with focal left versus right FLE.[25,41,129,139]

The neuropsychological characteristics of *parietal lobe epilepsy* and *occipital lobe epilepsy* have rarely been described in a series using adequate sample sizes. Acute parietal or occipital neuropsychological symptoms become evident in seizure semiology, but in chronic epilepsy (most often those patients exhibiting early lesions or malformations), the classic posterior symptoms of aphasia, alexia, agraphia, acalculia, agnosia, and neglect are very uncommon. Primary or secondary perceptive and sensory problems that may be evident at the beginning of epilepsy are often well compensated for behaviorally. Impairments are diffuse, and, as described with seizure semiology and EEG, often mimic frontal or temporal lobe dysfunction.[52,72] Nevertheless, tests of stereognosis or haptic search may be sensitive to parietal lobe epilepsy.[71,117]

Etiology

Partial epilepsy is associated with a variety of etiologies. Lesions include stationary lesions, such as developmental malformations, HS, or atrophy; traumatic brain injury or vascular malformations; as well as potentially progressive defects such as neoplastic and paraneoplastic tumors, CNS infections, and inflammatory and autoimmunologic processes. Independent of

seizure effects, these lesions themselves are associated with cognitive impairments that range from mild impairment in circumscribed domains to severe generalized neuropsychological impairment. However, cognitive impairments in symptomatic epilepsy are not lesion specific, but rather differ according to age at lesion onset, differences in functionality of the affected tissues, differences in the course and dynamics of the underlying disease, and finally differences in lesion lateralization and localization.[7] Although the lesions themselves are generally not associated with ongoing cognitive function, activation of heterotopic gray matter has been demonstrated using functional MRI (fMRI).[66]

A major concern is the cumulative effects of chronic epilepsy on the brain and on cognition. Seizures, and in particular severe seizures, may result in significant damage, although this is more of an individual patient concern than a concern across all patients. For example, multiple reports exist describing amnestic syndromes following either status epilepticus or a series of generalized tonicâ€“clonic seizures. The cumulative effect of less severe seizures on cognition, however, is less clear-cut. In a review of 20 longitudinal studies in children and adults, 12 of 20 reported a relationship between duration of poorly controlled seizures and neuropsychological decline, 5 of 20 described mixed results, and 3 of 20 described no relationship.[82] For those studies reporting an effect, lower IQ with associated increased seizure frequency, greater performance â€œimprovementâ€ in controls than patients, and more important, neuropsychological declines were associated in nonmemory domains.

Cross-sectional studies of chronic uncontrolled TLE suggest a significant IQ decline after three decades.[67] Comparing the age regressions of memory in healthy subjects to those of epilepsy patients puts such a finding into perspective.[45] In chronic uncontrolled TLE, memory decline in a longitudinal design is very slow, and individually proceeding cognitive decline can be suggested. Presumably, this applies for chronic focal epilepsy, but it remains unclear whether specific domains are affected or whether decline is diffuse and nonspecific. Impairment may be seen in patients with symptomatic focal epilepsy even prior to the onset of epilepsy, and cognitive impairment may develop from the interference of lesions/epilepsy with brain maturation and cognitive development. The impact of additional lesions and the interaction of aging with preexisting damage appear much more relevant for individual cognitive change than for the accumulation of seizures alone.[7,43]

Antiepilepsy Drug Effects

Given the many potential influences on cognition for patients with epilepsy, such as age of onset, disease substrate, or seizure frequency and severity, antiepilepsy drugs (AEDs) occupy a unique position because they are under the direct control of the treating physician and his patients. Although the choice of specific AED is guided by seizure type and epilepsy syndrome,[61] within seizure/syndrome categories, AED selection is typically based on clinical experience rather than evidence-based practice. Most major AEDs used to treat partial epilepsy have comparable efficacy,[76] although many recently introduced AEDs are associated with more favorable tolerability profiles that includes less neuropsychological impairment.[73]

Because AEDs decrease membrane excitability, increase postsynaptic inhibition, or alter the synchronization of neural networks, they are often associated with neuropsychological side effects including decreased motor/psychomotor speed and attention.[96] Adverse AED effects are a significant component of treatment effectiveness. The landmark VA Cooperative study reported that standard AEDs including carbamazepine are associated with significant adverse effects that contribute to initial treatment failure in more than 40% of patients,[93] and a separate European trial reported that tiredness was described by more than 50% and sleepiness by more than 35% of patients on phenytoin or carbamazepine monotherapy.[4] Adverse AED effects are strongly associated with poor health reported by patients[30] and with decreased health-related quality of life.[32] After seizure control, the most important aspect of AED treatment is the side effect profile, including problems with cognition, energy level, school performance, childbearing, coordination, and sexual function. Because of side effects, 20% of patients adjusted their AED dosing.[27]

In young adults, neuropsychological AED profiles are generally comparable for the older-generation AEDs carbamazepine, phenytoin, and valproate, with each AED associated with modest psychomotor slowing accompanied by decreased attention and memory.[96] Neuropsychological side effects generally emerge according to a dose-dependent relationship[96]; however, both quality of life[31] and memory may be affected, even when AED blood levels are within standard therapeutic ranges. Central nervous system (CNS) effects of AEDs are reflected by EEG slowing that not only is correlated with short-term neuropsychological decline,[119,120] but is also related to poorer neuropsychological outcome following 1 year of treatment.[28] With the exception of topiramate[87,96,122,135] and possibly zonisamide,[2,10] most newer-generation AEDs have more favorable tolerability and neuropsychological profiles than their predecessors.[86,97,98,99]

Although direct head-to-head comparisons examining the neuropsychological profiles of newer AEDs have not typically included medications thought to have favorable neuropsychological outcomes, some data suggest differences in this regard. For example, in one study, oxcarbazepine was associated with both neuropsychological impairment and EEG slowing in healthy volunteers.[121] Thus, some data suggest that important differences may exist among AEDs, even across newer agents considered to have favorable neuropsychological side effect profiles. Several recent Class I healthy-volunteer studies suggested increased risk of cognitive impairment associated with topiramate[97,121] Because there may be individuals who are at greater risk for developing cognitive impairment, it may be possible to ultimately predict individuals at increased risk for developing treatment-emergent side effects based on pharmacogenetic or pharmacokinetic patient characteristics.

Subjective Report Versus Objective Performance

In addition to poor performance on memory tests and other neuropsychological measures, epilepsy patients often complain of poor memory.[19] Although both subjective and objective memory findings indicate decreased memory, subjective memory ratings and objective memory performance are poorly correlated.[8,29,46,108,142] In studies with sufficient sample sizes, statistically significant relationships between objective and subjective performances have been reported, although these correlations are generally small and account for a small portion of the variance. In contrast, subjective memory correlates much more highly with mood.[19,23,26,108,109] Depressed or anxious patients tend to rate their memory as poor, whereas patients less burdened by poor mood states rate their memory more favorably. Correlations generally account for approximately half of the variance,[5,26] with mood being the single best predictor of subjective memory functioning.[23,33,108]

The association between subjective memory and mood is informative, yet a large portion of the variance remains to be explained. Most studies show no significant relationship between subjective memory and clinical factors such as sex/gender, chronologic age, seizure-onset age, seizure type, seizure frequency, region of seizure onset, and number of AEDs.[23,109] However, memory â€œcomplainersâ€ may have a later age of seizure onset,[19] and a small inverse relationship between age and subjective memory reports has been described.[26,33] There is a tendency for patients on polytherapy to report greater cognitive difficulty than do patients on monotherapy,[33] although this relationship is well-established using formal neuropsychological measures.[96] Although most studies are restricted to TLE patients, those that included both temporal and extratemporal patients document greater reports of memory impairment than in TLE.[19] Although some investigators report no influence of seizure laterality,[5] others have found significant associations between perceived memory and objective verbal memory in left TLE patients, and with objective nonverbal memory in right TLE patients.[12] Although reports exist of a relationship between perceived and objective language performance,[12] others have not observed this relationship.[5]

Ecologic Validity of Objective Measures

Formal neuropsychological measures are established indicators of lateralized or localized cognitive dysfunction.[14] However, the modest correlation between subjective and objective results raises questions regarding ecologic validity of conventional memory tests. Neuropsychological memory tests typically require learning and recall of word lists or abstract designs, whereas â€œeveryday memoryâ€ typically requires incidental memory for complex events in which the individual is personally involved.[49] In two independent studies utilizing memory tests simulating everyday memory demands,[23,49] more ecologically valid tests correlated weakly with subjective ratings, but correlated more highly with conventional test performance. Although a small but significant correlation was found between ecologically valid memory performance and subjective report in patients â€œwithoutâ€ memory impairment,[49] the absence of a significant correlation in the â€œimpairedâ€ group may be related to the more restricted performance range.

The demands of various activities differ considerably, and cognitive deficits may be more apparent in high- versus low-demand situations. In one postoperative series, patients staying at home (â€œlow demandâ€) reported greater subjective complaints than did employed subjects (â€œhigh demandâ€),[35] and this corresponded with objective memory performance as well (i.e., weaker objective memory in the low-demand situations). Although patients were self-selected for group assignment, these data suggest that patients with poorer objective memory were in less demanding situations due to their genuine memory deficits, as well as feeling more impaired.

Tip-of-the-tongue (TOT) phenomena or â€œword finding difficultyâ€ is one of the top three cognitive complaints among epilepsy patients,[20] although the relationship between objective performance using confrontation naming tests[19] or language composite scores[5,108] with patient self-report is low or nil. However, the absence of a stronger relationship may result from language test selection using measures that poorly correlate with word finding difficulty. For example, in a study addressing the ecologic validity of object naming measures, no correlation was found between self-reported word finding difficulty and traditional visual object naming, although a small but significant correlation was noted with auditory description naming, a task developed to better simulate word finding in the context of everyday speech.[39]

Subjective Memory â€œTheoriesâ€

Several studies suggest that laypersons, (i.e., patients, proxies, and normal controls) have a broader definition of â€œmemoryâ€ than do neuropsychologists and neurologists. Specifically, performances on various language tasks, such as word fluency, expressive vocabulary, and naming, correlate significantly with subjective memory ratings.[26,46,104] Thus, when people are asked to rate their memory, they often consider language fluency and word finding difficulty as well as declarative memory processes.

The poor relationship between subjective performance ratings and objective test results raises the question of whether impaired deficit recognition (e.g., anosognosia) exists. A problem in assessing subjective memory in a population with genuine memory deficits is that the task is retrospective and, therefore, a memory task itself.[46,49] The discrepancy between objective and subjective scores is greater in patients with right hemispheric seizure onset, with a greater tendency in these patients to overestimate their genuine memory abilities.[3] This pattern is consistent with the specialized role of the right hemisphere in deficit awareness reported in lesions of other etiologies.

It has been suggested that some patients, unaware of their real memory conditions, exaggerate their memory failures and report this inaccurate self-perception in questionnaires.[109] Although epilepsy patients with and without memory complaints obtain comparable scores across a range of neuropsychological measures, the â€œcomplaintâ€ group scored significantly higher in neuroticism.[142] Thus, both disease-related and personality factors reduce self-awareness, thereby contributing to the discrepancy between subjective complaints and objective performance.

Subjective Change in Postoperative Patients

Whereas pre- (or non-) surgical epilepsy patients tend to â€œover-reportâ€ memory deficits, the prevalence of memory complaints among patients following temporal lobe resection is quite low.[13,124] In fact, postoperative patients tend to report improved memory functioning despite evidence of memory decline on objective measures.[94,95] Accordingly, most studies report little correlation between changes in objective performance and changes in subjective ratings following surgery. Rather, subjective memory ratings in postoperative patients correlate significantly with seizure outcome (i.e., good seizure outcome associated with improved subjective ratings),[58,94,95,124] AED side effects, and, similar to that demonstrated in preoperative patients, with mood[94,124] and neuroticism.[15] Although a higher prevalence of subjective decline might be expected following left anterior temporal lobectomies (ATL) rather than right ATL given the more consistent objective decline following left surgery,[14] subjective complaints do not appear to predict surgical laterality.[8,15,94,95,124] Because of the overall poor correspondence between performance and complaints after surgery, postoperative memory complaints might be considered a marker of depression or other mood disorder.[124] Nonetheless, there is general agreement that, despite these group findings, individual cognitive complaints should be followed up with both formal mood assessment and neuropsychological evaluation.

Practical Implications

The poor correspondence between subjective report and objective performance suggests caution when drawing conclusions from subjective complaints. This is obviously a concern to the treating physician since, in most cases, the presence or absence of memory complaint is based on questioning the patient, rather than on formal memory assessment. Factors to consider include emotional and psychosocial factors, the

potentially broader definition of â€œmemoryâ€ held by patients and their relatives, the patient's level of daily cognitive demands, and seizure onset laterality. For postoperative patients, one should additionally consider seizure outcome and AED burden. Each of these factors carries a potential influence on cognitive self-appraisal; distinguishing among them on an individual basis is critical, because each implicates a different treatment approach.

Wada Testing and Functional Imaging

One of the primary goals in the preoperative evaluation is to identify patients who may be at increased risk for developing significant postoperative neuropsychological impairment. Patients undergoing temporal lobe resection in the language-dominant hemisphere are at higher risk for experiencing postoperative memory decline than are those undergoing nondominant ATL, and knowledge about language dominance and memory representation is important to establish the relative risks to memory associated with temporal lobectomy.

The Wada test is one of the major procedures to establish relative memory risk following ATL, although not all epilepsy surgery centers perform this procedure routinely on all ATL candidates.[83] Wada testing to assess both language and memory function emerged during the 1950s, when structural and functional imaging was almost nonexistent. Although variability in specific protocols exists, the technique generally involves the introduction of amobarbital (or other anesthetic agent) through a transfemoral catheter into the internal carotid artery, which temporarily anesthetizes the distribution of the anterior and middle cerebral arteries. During the period of hemispheric anesthesia, the patient is presented with language and memory acquisition tasks, with memory tested after the drug effects have worn off. Although the memory component of this task was designed to avoid developing a significant postoperative amnesia, this role has largely been supplanted by current functional neuroimaging using MRI, positron emission tomography (PET), and single-photon emission computed tomography (SPECT). Wada memory results, however, are often used to indicate the risk of significant memory decline that may interfere with a patient's overall quality of life.[85]

The Wada test differs from all other approaches to functional assessment, including neuropsychological testing, in that it tests each hemisphere in isolation. By doing so, it helps to disentangle the effects of large-scale distributed brain networks, and it can assess the specific contributions of the anesthetized region and their functional connections to language and memory function. When the hemisphere ipsilateral to a medial temporal lobe focus is anesthetized, the reserve capacity of the contralateral temporal lobe to sustain memory function in isolation is assessed.[16] Multiple reports demonstrate the contribution of Wada memory results to memory outcome prediction.[18,68,74,77,84,116,133] An aphasia confound occurs when testing memory following dominant hemisphere injection and, because of this confound, a selective procedure for anesthetizing the distribution of the posterior cerebral artery may be used,[131] although this approach is associated with a greater risk of stroke and, consequently, is generally not employed routinely.[148] Selective procedures involving other vascular distributions may be performed based on clinical indications.[38,140]

Because the Wada procedure is invasive, fMRI and magnetoencephalography (MEG) are advanced as noninvasive alternatives. Many language fMRI paradigms reliably identify language representation, and the use of fMRI has decreased the frequency of Wada use in some epilepsy centers.[44] MEG is an alternative measure of functional imaging that, unlike fMRI, which relies on indirect measures of neural activity based on blood flow changes, is a direct measure of neuronal function. MEG is also a reliable noninvasive measure of language lateralization.[105,106]

Imaging the medial temporal lobes has proven to be more difficult. However, several reports demonstrate the effectiveness of fMRI related to seizure onset laterality[21,37,69] as well as memory outcome following surgery.[110,113] As the components needed for successful hippocampal activation continue to be understood,[11] it is likely the fMRI will increasingly be used in preoperative epilepsy evaluation, with a corresponding decrease in Wada use.

Postoperative Outcome

Up to 80% of those patients undergoing ATL resection will become seizure-free following surgery,[145] although some patients will experience specific declines in memory, language, or some other aspect of cognitive functioning. A literature has now developed demonstrating how results from presurgical neuropsychological testing, combined with demographic variables and other neurodiagnostic findings, can predict patients who are at greatest risk for developing postoperative decline.

One of the earliest findings from neuropsychological studies is that epilepsy surgery results in very little change in IQ.[44] The view that patients with lower IQ levels, which can suggest greater generalized brain impairment, do not benefit from surgery has been dispelled by research findings comparing seizure outcomes in both low- and high-IQ groups.[36,44] Patients with higher IQ levels and memory performance tend to experience greater cognitive declines following surgery, although they also continue to exhibit a higher level of postoperative functioning than do patients with lower presurgical cognitive performance.[51] These results support the model of *cognitive reserve* that has gained acceptance in the fields of dementia and traumatic brain injury.[114,132]

The majority of epilepsy surgeries are ATLs that involve resection of areas considered important for normal memory processing; consequently, predicting memory outcome has been emphasized. Different rates of memory decline, ranging from 10% to 60%, following ATL have been reported. The prediction of memory decline has been guided by two basic theoretic approaches. The first model is based on Milner's[101] original observation that material-specific memory deficits in verbal and nonverbal memory are associated with ATL of the left (dominant) and right (nondominant) temporal lobes, respectively. The second approach is based on a more recent model, which predicts that the degree of postoperative memory deficit, as well as seizure outcome itself, will be determined by the â€œfunctional adequacyâ€ of the tissue to be resected.[16,74] The type of surgical procedure (e.g., â€œstandardâ€ ATL vs. selective amygdalohippocampectomy) and postoperative seizure status also contribute to postoperative cognitive outcome.[44]

Laterality Effects

Analyses of material-specific memory findings are included in nearly every neuropsychological study of postoperative outcome. The conclusion drawn from recent literature reviews is that strong empirical support exists for the link between surgery on the left temporal lobe and postoperative deficits in verbal memory.[78] There is, however, substantially less support for the proposed relationship between nonverbal memory impairment and surgery on the right temporal lobe.[78,141]

There has been a recent trend moving from group methods of analysis toward predicting the risk of postoperative change in individual patient prediction. To optimize the prediction of individual risk, investigators have been using statistical

processes, such as the reliable change index (RCI) and standardized regression-based (SRB) methods, to control for the reliability of the instruments, practice effects, and regression to the mean. Studies using this methodology have reported that the risk for postoperative decline in verbal memory ranges from 40% to 60% in patients undergoing left ATL, whereas the risk for decline in patients undergoing right ATL ranges from 10% to 30%.[56,91] Significant declines following right ATL are not clearly explained by any simple version of the material-specific memory model. Much less is known about the risk of experiencing a decline in nonverbal memory, a result of methodologic factors and small effect sizes.

Language-dominant ATL has been associated with postoperative naming deficits, although details regarding these deficits are less well known than those associated with memory. Postoperative naming impairment is generally thought to occur in only a minority of patients,[14] although at least one study has found naming declines in 40% of a left ATL sample versus none in those patients undergoing right ATL.[91] The ability to predict postoperative naming deficits through presurgical language mapping using intraoperative or extraoperative methods has been inconsistent. One multicenter study found that the rate of postoperative naming decline was not influenced by the availability of mapping data.[53] Others have found that identification of mapping sites critical for auditory descriptive naming is important for predicting both auditory and visual naming outcome.[40]

There are no consistent findings demonstrating deficits in visual perceptual or spatial functions associated with right ATL. Surgical procedures conducted on patients with frontal lobe epilepsy and other forms of extratemporal epilepsy have been associated with only mild declines in memory, language, or other cognitive functions unless areas of eloquent cortex are involved specifically.[24,47] Laterality effects on cognitive functioning are considered to be less of an issue with pediatric patients than with adults.[7]

Functional Adequacy Model

The functional adequacy model predicts that less postoperative memory decline, as well as a greater likelihood for seizure reduction, will be observed in patients exhibiting lower levels of presurgical functioning in the mesial temporal lobe ipsilateral to seizure onset.[16,74] Functional adequacy is established using both neuropsychological methods as well as measure of structural pathology using preoperative neuroimaging. Most research findings have supported this model, as opposed to the competing â€œfunctional reserveâ€ model that suggests postoperative memory is best predicted by the functional and structural integrity of the contralateral temporal lobe.

Presurgical Neuropsychological Performance

Evidence supporting the functional adequacy model was initially provided by the finding that patients with higher memory performance on presurgical testing were more likely to demonstrate significant memory decline following ATL than those with lower presurgical memory performance.[63,111] These results are not simply the result of statistical â€œregression to the mean,â€ but rather reflect the tendency for the most functional patients at baseline to be more vulnerable to experiencing postoperative memory loss.[17] This is a robust pattern of change following ATL, and it has been observed in many independent series.[55,133,144]

Findings from MRI and Other Studies

Neuropathological studies have consistently demonstrated that memory outcome varies according to the presence of HS ipsilateral to seizure onset.[9,14,60] Not only do individuals with severe unilateral HS exhibit lower levels of preoperative memory, but they are also less likely to exhibit memory decline following surgery.[127] Similar findings have been observed using MRI measures of hippocampal pathology.[137,138] Resection of a relatively nonatrophic left hippocampus generally results in greater memory decline, although memory loss may also occur in some patients with severe presurgical HS.[90] Surgery in patients with bilateral hippocampal pathology, however, does not necessarily cause global amnesia, although greater rates of memory decline are seen in patients with bilateral hippocampal atrophy who undergo dominant-hemisphere ATL.[90] Normal verbal memory in the presence of hippocampal atrophy may also be associated with significant postoperative memory decline.[85] Thus, the functional integrity of the left temporal lobe plays a critical role in predicting memory outcome independent of the presence of structural pathology.[81,85]

Studies using multiple regression methods have demonstrated that prediction of postoperative outcome is best accomplished using a combination of both functional and structural indices.[55,133] The importance of functional adequacy to postoperative change has been demonstrated using both magnetic resonance spectroscopy (MRS) and Wada testing.[74,84] fMRI has been shown to be useful for predicting postoperative naming.[115] Recent presurgical fMRI studies have demonstrated the ability to predict postoperative memory functions.[110,113]

Demographic Predictors

Developmental factors, including age at the time of surgery and the stage of cognitive development at the time of seizure onset, are important factors for predicting postoperative cognitive decline. The risk of cognitive decline following surgery appears to be lower in children younger than age 16 years than in adults.[79] In contrast, older patients may experience greater memory loss, consistent with a profile of accelerated aging.[51] Continuing decline in memory performance may be seen in some individuals 10 years or more following surgery.[112] The postoperative deficit in verbal memory in patients who are seizure free is similar to what is observed over time in nonsurgical patients who are continuing to experience seizures, suggesting normal age-related memory decline.[51]

Age of seizure onset interacts with both functional and structural indices in a manner consistent with the functional adequacy model.[16,88] Those with a younger age of onset will have experienced pathology at an earlier stage of development and will have experienced seizures for a longer period of time. This leads to greater neurologic compromise, which is accompanied by more severe and widespread cognitive impairment. However, earlier seizure onset also permits a redistribution of function to other brain areas, which would lead to less deficit following surgery. In contrast, patients developing epilepsy later in life are not as compromised neurologically, because it does not interfere with cognitive development and maturation, and consequently they do not exhibit the same degree of cognitive dysfunction preoperatively. However, surgery involves resection of more functional brain tissue, which increases the likelihood of developing greater cognitive decline postoperatively. Support for these findings coupling age of onset with function was present in some early studies, but at least one recent study has failed to find a link between severe hippocampal pathology, memory decline, and early onset of seizures.[88]

In general, cognitive deficits become more specific and less reversible with surgery with increasing age. The pattern of findings involving age of onset are generally more consistent for cognitive functions associated with neocortical zones than for those associated with the mesial temporal lobe.[44] For example, more severe naming deficits are observed in older patients. Other studies examining demographic factors have suggested that women, in general, exhibit less severe cognitive decline following surgery than do men.[136]

Summary and Conclusions

Patients with epilepsy frequently have some cognitive and neuropsychological impairment. Cognitive difficulty may be due to the underlying brain disorder, specific epilepsy syndrome, AED effects, psychiatric comorbidity, and ongoing effects of active seizure discharges. Although the neuropsychological impairment is related to the location of the active seizure focus in patients with localization-related epilepsy, often more subtle impairments in executive functions may be present in both focal and generalized epilepsy syndromes, including those commonly referred to as â€œbenign.â€ Because a poor relationship exists between subject performance ratings and formal neuropsychological test results, formal assessment is often necessary to document the presence and extent of cognitive difficulty experienced in individual patients. Cognitive impairments are broadly related to age of seizure onset and seizure duration. Unfortunately, well-established interventions to treat or modulate cognitive difficulty in patients with epilepsy do not exist.

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Chapter 91

Neuropsychological Evaluationâ€"Children

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Introduction

The neuropsychological evaluation of children with epilepsy involves the assessment and interpretation of a broad range of variables that have the potential to alter the natural course of brainâ€"behavior development. These variables include seizure type and frequency, lesion lateralization and localization, type of neuropathology, side effects of anticonvulsants, age of epilepsy onset, and elapsed time since onset. Reliable neuropsychological diagnosis and prognosis of a child or adolescent with epilepsy requires the careful consideration of all of these factors and how they interact to affect future cognitive development and organization within the developing brain. Subsequent neuropsychological deficits can range from relatively specific impairments in one neurocognitive system to severe generalized intellectual disability. A child's ability to compensate for and/or overcome neuropsychological deficits will depend in part on the child's exposure to risk or protective factors within his or her environment, such as quality of educational support, family attitudes toward epilepsy and learning difficulties, socioeconomic status, access to specialist rehabilitative programs, behavioral management strategies, pharmacologic management, and/or surgical management. A combination of these variables interacting with neuropsychological impairments will influence the child's overall quality of life and mental health.

Contemporary pediatric neuropsychology for children with epilepsy plays an important role in both enhancing clinical practice and increasing the knowledge base of developmental cognitive neuroscience. From a clinical standpoint, neuropsychological evaluations in children are carried out to establish cognitive status preoperatively, identify eloquent tissue (subserving language, memory, visuospatial perception, and motor function) that may be at risk during surgical intervention, determine the response of cognitive and/or behavioral systems to neuropharmacologic agents, provide prognostic indicators of cognitive and behavioral outcome to help both clinical management and guide educational support and intervention, monitor postoperative outcome and long-term progress through transitional stages of late childhood and adolescence, and identify children who might be at risk of decline or regression. From a scientific viewpoint, investigations of children with epilepsy using a systems neuroscience approach can advance understanding of the extent and limits of the plasticity and reorganizational capacity of the immature brain, determine the costs of reorganization and the adaptive/maladaptive compensatory responses to brain damage, document the developmental trajectory of functional brain organization in the presence of focal or diffuse pathology, establish brain structure/function relationships, and help identify the neural substrates of cognitive function and dysfunction, with the ultimate goal of translating the basic neuroscience findings to inform clinical diagnosis, prognosis, and management.

Over recent years the neuropsychological study of children with epilepsy has gained considerable momentum due to the rise in neurosurgical procedures conducted at younger developmental ages. Pediatric neurosurgery has increased because of the development of enhanced presurgical investigative techniques (e.g., quantitative methods of structural and functional neuroimaging, electroencephalogram [EEG] telemetry, ictal and interictal single photon emission computed tomography [SPECT], and interictal positron emission tomography [PET] examinations) that help to identify seizure type and focus, site and source of seizures, and type of neuropathology more reliably than before.[5] There have also been improvements in the safety of neurosurgical practice[21] and increasing evidence that early surgery may counteract pronounced restriction or regression of cognitive and psychosocial development due to persisting epilepsy.[23,70]

To reflect the increasing interest in neuropsychological evaluations in relation to pediatric neurosurgery, this chapter will consider many of the developmental issues peculiar to pediatric neuropsychology by focusing on studies of children pre- and post-neurosurgery. Alternative models of the ontogeny of hemispheric specialization are introduced to help understand the potential effects that epilepsy can have on cognitive development early in life. Such models are important for pediatric neuropsychologists to consider when interpreting results of evaluations carried out pre- and post-neurosurgery. The relevance of such models to one of the most common neurosurgical procedures for children with epilepsy, namely hemispherectomy, is discussed based on studies of intellectual function and studies of speech and language. We include data from our series of children who have undergone hemispherectomy to highlight the variables that influence intellectual outcome, in particular the interaction between age at onset of epilepsy and hemispheric side of lesion. The effects on speech and language development in children who have bilateral or unilateral left- and right-sided lesions are outlined, and issues of potential reorganization of speech and language following early left-sided lesions are discussed in relation to recent functional neuroimaging studies that demonstrate the importance of hippocampal involvement in language reorganization. The complexity of understanding brainâ€“behavior development following the onset of epilepsy in childhood will become clear, as will the need for clinical pediatric neuropsychologists to be integrated within multidisciplinary pediatric epilepsy surgery services and work collaboratively alongside developmental cognitive neuroscientists to mutually advance clinical practice and scientific understanding.

The Ontogeny of Hemispheric Specialization

There is often an implicit assumption that brainâ€“behavior relationships identified in adults can be applied to children. For

example, it is well known that the adult human brain is relatively asymmetric in function for some cognitive processes: Acquired lesions to Broca's area and the perisylvian regions of the left hemisphere affect speech and language,[17,77] whereas lesions to the right hemisphere more often affect aspects of visuospatial ability.[64,83] However, the application of such knowledge to the pediatric population is usually made in the absence of supporting empirical data[9] and without an understanding of normal and abnormal patterns of brain maturation and functional specialization during the course of development.

Historically, the evolution of ideas relating to the ontogeny of hemispheric specialization has been dominated by three models. The *equipotentiality* model first proposed by Lenneberg[35] states that the two cerebral hemispheres have equal potential at the start to subserve different aspects of cognitive function but gradually acquire specialization with increasing age and learning experience up to adolescence, when the pattern becomes crystallized and resembles that of adults. The major implication of the *equipotentiality* model is that the earlier the lesion, the more effective is the compensatory processes, and, consequently, the better is the cognitive outcome. In fact, it is now recognized that age at injury per se is not the sole determinant of outcome, and other factors (e.g., severity and extent of damage, locus of injury, etiology of the lesion, elapsed time since the onset of the lesion, presence or absence of epilepsy, unilateral or bilateral pathology) each contributes to the eventual outcome. However, this model can account for the impressive recovery of function (especially for speech and language) that ensues after early unilateral lesions and for the emergence of selective deficits (e.g., aphasic symptoms), signifying a relative decline in plasticity, with increasing age.

The *early-specialization* model posits that early onset of unilateral lesions leads to material-specific deficits that correspond to the side of damage, suggesting that the hemispheric division of labor for the processing of verbal and nonverbal information is present at or shortly after birth (for reviews see Bates et al.[3] and Vargha-Khadem et al.[69]). The early-specialization view was invoked by a number of researchers[10,22,32,80,81,82] to provide a post hoc account for a series of empirical findings on children with unilateral lesions, including hemispherectomy, showing material-specific deficits corresponding to the hemispheric side of damage. A major implication of this model is that brain organization in the young child is modular just as it is in the adult, and that the double dissociation of function that is the hallmark of adult neuropsychology is present from infancy before the emergence of different aspects of cognitive function. Despite its appeal because of continuity with adult models, the early-specialization view does not satisfactorily account for the impressive rescue of articulate and grammatically formulated speech that is frequently seen after extensive left hemisphere pathology of early origin or the absence of chronic dysphasic symptoms after such early insult. A more fundamental problem for the model is the dearth of empirical evidence supporting a clear pattern of hemispheric specialization in cohorts of healthy children at different ages or a double dissociation of function in pediatric patients with early unilateral lesions.[2,3,39,69,72]

In an attempt to reconcile the two extreme views, that of *equipotentiality*, which is compatible with developmental plasticity, versus *early specialization*, which is consistent with modular organization of brain function across the developmental span, Satz et al.[55] proposed a compromise position, referred to by Bates et al.[3] as â€œconstrained plasticityâ€ and by Vargha-Khadem et al.[69] as â€œontogenetic specialization.â€ This model assumes that there is a genetically determined anatomic basis to hemispheric specialization, and that during normal brain development, the functional expression of this genetic predisposition can unfold early in life. The model also assumes, however, that during normal development, there is an interaction between environmentally evoked neural activity that becomes progressively complex and nonredundant and neural plasticity that gradually declines with increasing age. Early brain injury can counteract the genetic predisposition toward specialization and change the normal trajectory of the activity/plasticity interaction. Thus, children who sustain brain damage early in life suffer two setbacks, one relating to the direct consequences of the actual lesion and the other relating to an altered developmental trajectory that is likely to be different from normal. The *ontogenetic specialization* model fits well with theories of brain and cognitive development (e.g., Alexander Luria, Jean Piaget) insofar as it conceives of the interactions between neural activity and plasticity emerging in stages of increasing complexity during childhood and adolescence. Furthermore, it also fits well with research on normal development of intelligence and language functions, in which evidence suggests that (a) whole-brain gray matter volume obtained from magnetic resonance imaging (MRI) is strongly correlated with IQ in older but not younger children,[76] (b) the two cerebral hemispheres are more nearly equal in linguistic processing capacity in infancy[7,8] than they are later in life,[45,59] and (c) the degrees of left lateralized functional MRI (fMRI) activation on a verb generation task[25] and blood oxygenation levelâ€“dependent (BOLD) fMRI signal during sensorimotor and language tasks[56] increase with age. Although the fMRI activation patterns on a variety of language tasks performed by normal children are the same as those in adults,[15,16,79] there are qualitative and quantitative differences suggesting that maturational features in functional neuroanatomy and/or differences in ability are distinct in development.[57,79] Finally, the model is also consistent with increasing recognition that in the aftermath of early unilateral injury, many factors can influence and counteract the normal developmental trajectory toward hemispheric specialization. For example, a small unilateral lesion acquired in the second decade of childhood can leave undisturbed the normal crystallization of hemispheric specialization and yield a selective deficit that is consistent with the early-specialization view. In contrast, an extensive unilateral lesion acquired early in life, before the development of complex cognitive repertoires, can lead to extensive interhemispheric reorganization and relative stunting of cognitive development across all domains, consistent with the equipotentiality model. With advances in quantitative neuroimaging techniques delineating the site and extent of neuropathology and functional imaging paradigms revealing activation patterns associated with specific cognitive tasks, it is now possible to examine structure/function relationships in pediatric patients with epilepsy and translate the findings to aid surgical decision making and subsequent management.

Intellectual Outcome After Hemispherectomy

Hemispherectomyâ€”complete or partial removal or disconnection of one cerebral hemisphereâ€”is one of the commonest forms of pediatric neurosurgery for the relief of epilepsy, constituting up to 30% of neurosurgical procedures,[5] particularly during the first decade of life. When children are assessed for hemispherectomy, one of the central questions concerns the status of cerebral lateralization and the consequences of surgery for intellectual functions and speech and language. Candidates for surgery usually present with a unilateral structural lesion and seizures, the origins of which date to pathologic congenital or perinatal processes or events, such as Sturge-Weber syndrome or hemimegalencephaly, although some children have later acquired disorders such as Rasmussen syndrome that can develop from about 1 year of age through to adolescence.[13]

In 2004, Pulsifer and colleagues reported on the neuropsychological outcome of the largest series (*n* = 71) of

hemispherectomized patients studied to date.[51] Patients were divided into groups depending on the etiologic category (cortical dysplasia; Rasmussen encephalitis; vascular malformations or stroke). Mean IQ scores were almost two standard deviations below normal (i.e., ~70) in the Rasmussen and the vascular malformation/stroke groups but considerably lower (i.e., more than five standard deviations below normal) in the group with cortical dysplasia. These results are broadly consistent with those reported in our series of 33 children who underwent hemispherectomy and were divided into developmental, acquired, and progressive etiologic groups.[11] Results from these two recent studies suggest that both cognitive and seizure outcomes are related to the underlying pathology, with most favorable outcomes occurring in those with acquired and progressive etiologies as compared to developmental etiologies (such as cortical dysplasia, hemimegalencephaly, etc.). Based on the comparison between preoperative versus postoperative IQ scores, the decline and/or arrest of intellectual function occurred well before presentation for surgery, with both studies indicating improvements in long-term follow-up in only a small percentage of cases.[11,51]

Table 1 Details of age at onset of epilepsy in hemispherectomy subgroups and IQ details

Group	*N*	Mean age of onset of seizures in months (SD)	Mean age at test in months (SD)	Mean time to test in months (SD)	Mean full-scale IQ (SD)	Mean verbalâ€“performance discrepancy score (SD)
Left congenital (LC)	9	22 (27)	183 (40)	161 (60)	60 (17)	3.44 (4.47)
Left early (LE)	6	32 (13)	141 (49)	109 (52)	58 (13)	5.5 (4.96)
Left late (LL)	4	103 (46)	176 (59)	73 (66)	59 (10)	18.25 (6.18)
Right congenital (RC)	5	6 (7)	98 (44)	92 (44)	53 (9)	6 (11.72)
Right early (RE)	6	34 (17)	211 (102)	177 (115)	65 (15)	10.33 (16.28)
Right late (RL)	6	90 (21)	188 (34)	97 (23)	73 (10)	13.66 (11.5)

The relationship between etiology and hemispheric side of removal was pursued further in the report by Pulsifer et al. Whereas no differences were found between the means of the left and right hemispherectomized groups within the etiologic category of cortical dysplasia or vascular abnormality on any of the cognitive measures, including intelligence, significant effects of side of removal were indicated in the Rasmussen encephalitis groups.[51] The right hemispherectomy group obtained significantly higher intelligence and language scores than the left hemispherectomy group. The absence of an effect of hemispheric side of removal in the group with cortical dysplasia is consistent with the ontogenetic specialization model, and the notion that in the face of extensive early brain abnormality hemispheric specialization (i.e., nonredundancy of function) is sacrificed to enable the development of cognitive abilities at a basic level.

The question of whether intellectual outcome after hemispherectomy is related not only to etiology and hemispheric side of removal but also to age at onset of pathology deserves attention. In contrast to adult studies,[42,74] previous reports based on large cohorts of pediatric patients with unilateral lesions, with or without epilepsy,[3,18,68,69] failed to reveal a significant difference between verbal and nonverbal intellectual outcome as a function of hemispheric side of lesion. However, in those with late-acquired pathology (i.e., >5 years) a pattern of IQ scores at least qualitatively similar to the one reported in adults has been found (i.e., verbal IQ [VIQ] < performance IQ [PIQ] after late left hemispheric lesions; PIQ < VIQ after late right hemispheric lesions).[69] It is not known whether this age-at-injuryâ€“dependent and side-of-injuryâ€“dependent pattern documented in pediatric patients with unilateral lesions is also found in hemispherectomized patients.

We examined the interaction between age at onset of pathology and surgical side of removal on IQ type in a subset (*N* = 36) of hemispherectomized patients drawn from the series operated at Great Ormond Street Hospital[11] and King's College Hospital.[67,68] Admittedly, our postoperative hemispherectomized cohort is not yet large enough to permit assessment of the effects of three variables (i.e., hemispheric side of removal, age at onset of pathology, and IQ type) in the same analysis. Nevertheless, despite the small groups that this comparison inevitably entails, it is informative to examine the pattern of results in patients who have undergone hemispherectomy compared to patients who have not received surgery but have hemiplegia due to unilateral left- or right-sided lesions and seizures grouped by age at onset of pathology.[58]

Hemispherectomized patients were selected for this study if they could undergo formal intelligence testing and if they had undergone surgery at least 2 years prior to testing. In each case, both verbal and nonverbal IQs were obtained using the age-appropriate Wechsler Scales of Intelligence. The left- and right-hemispherectomized patients were each divided into three groups on the basis of age at onset of pathology (congenital; early, â‰¤5 years; late, >5 years; see Table 1). Therefore we had six subgroups: left congenital (LC), left early (LE), left late (LL), right congenital (RC), right early (RE), and right late (RL). Relevant details regarding the etiology of the seizure disorder leading to hemispherectomy are presented in Table 2. As indicated in Table 1, the full-scale IQs of the six hemispherectomized groups ranged from 53 (RC group) to 73 (RL group). These mean IQ scores are between two to three standard deviations below normal and are consistent with results reported in previous studies.[51,72] The pronounced restriction in overall intellectual ability is the most striking cost of severe intractable epilepsy leading to hemi- spherectomy.

Prior to statistical analysis, the two variables of IQ type were reduced to one by subtracting verbal IQ from nonverbal (performance IQ), thus yielding a discrepancy score. This reduced the number of analyses carried out on a relatively small sample. A discrepancy score above zero indicated a verbal IQ score that was higher than nonverbal IQ, whereas a discrepancy score below zero signified the opposite. FIGURE 1 presents the mean discrepancy scores for each of the six hemispherectomy groups. As indicated, five groups show positive mean discrepancy scores and the LL group shows a strongly negative mean discrepancy score.

Table 2 Etiology of the seizure disorder leading to hemispherectomy

Etiology	â‰¤5 years	5â€“16 years	Total

Cortical dysplasia	3	1	4
Cerebrovascular accident	1	0	1
Cyst	2	0	2
Encephalopathy	1	0	1
Epilepsy of unknown origin	2	0	2
Hemimegalencephaly	1	0	1
Hemistatus	1	0	1
Infarct	3	0	3
Megalencephaly	1	0	1
Mesial temporal sclerosis with cortical dysplasia	1	0	1
Rasmussen encephalitis	6	9	15
Sturge-Weber syndrome	0	1	1
Scar tissue	2	0	2
Vasculitis	1	0	1
Total	25	11	36

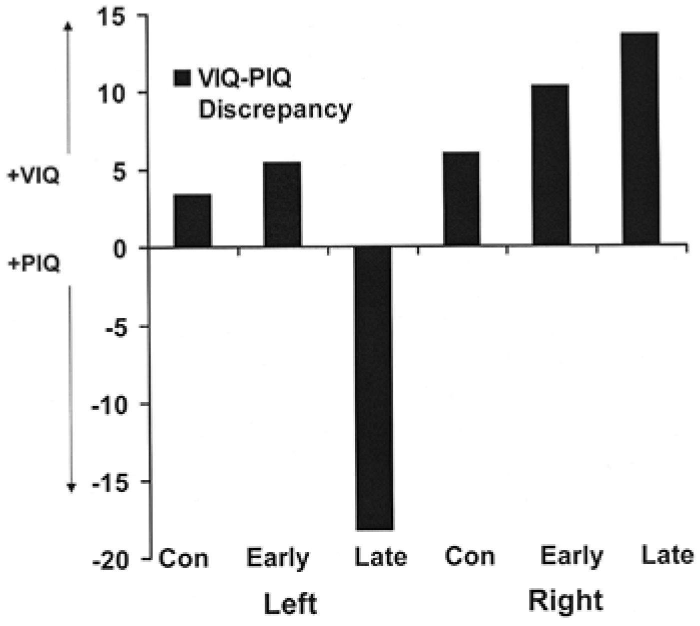

FIGURE 1. Discrepancy scores for verbal minus performance IQ (VIQ and PIQ, respectively) for each of the hemispherectomy subgroups (higher score indicates V > P discrepancy). Con, congenital.

To determine the effects of hemispheric side of removal and age at injury on IQ type, a univariate analysis of variance was performed on the discrepancy scores of the six groups. There was a significant effect of hemispheric side of removal (*F* = 14.88, *p* <.001) and a significant interaction of hemispheric side of removal by age at onset of pathology (*F* = 7.11, *p* <.003). Because these were discrepancy scores, a series of one-sample *t*-tests was performed to test the hypothesis for each subgroup that the discrepancy was significantly different from zero. The mean discrepancy scores of the LC, LE, and RL groups (LC *t* = 2.30, *p* = .05; LE *t* = 2.71, *p* = .04; RL *t* = 2.91, *p* = .03) were significantly above zero, suggesting a relatively stronger verbal IQ compared to nonverbal (performance) IQ in these subgroups. The mean discrepancy scores of the RC and RE groups were actually greater than those of the LC and LE group, but there was considerable variability within the right subgroups (see Table 1). In contrast, the discrepancy score of the left late group was significantly below zero (LL *t* = -5.90, *p* = .01) indicating the reverse relationship. FIGURE 2 presents mean verbal and nonverbal IQ scores of the six groups highlighting the double dissociation of function between IQ type and side of hemispherectomy in relation to age at onset of pathology.

To compare this pattern of results with one obtained from pediatric patients with unilateral lesions and seizures but without neurosurgery, IQ data from the six subgroups (*n* = 52) reported by Vargha-Khadem et al.[69] were selected and are illustrated here. These subgroups are selected on the basis of hemispheric side of damage and age at injury using the same three categories indicated previously for hemispherectomized patients (i.e., congenital; early, â‰¤5 years; late, >5 years) (Table 3). Table 4 presents details of etiologic factors for the groups with acquired hemiplegia and seizures. As indicated in Table 3, the full-scale IQs of the six hemiplegia-with-seizure subgroups ranged from 81 (RE group) to 91 (LL group). These mean IQ scores are within one standard deviation of the normal range and, as such, do not constitute an impairment. The relatively well-preserved level of overall intellectual ability in the hemiplegia-with-seizure groups (Table 3 and Fig. 3) stands in marked contrast to that of the severely deficient level achieved by the hemispherectomized groups (Table 1 and Fig. 2).

As with the hemispherectomy subgroups, IQ discrepancy scores were calculated and are presented in FIGURE 4. Univariate analyses of variance revealed no significant effects of side of lesion (*F* = 3.411, *p* = .071), age at onset of pathology (*F* = 2.19, *p* = .12), or age at onset by side of pathology (*F* = 2.77, *p* = .073). It seems likely, however, that with increased sample size, a pattern similar to the one in the hemispherectomized groups will emerge because the overall profile of the six groups with hemiplegia and seizures is qualitatively similar to that of the hemispherectomized groups (see Fig. 4).

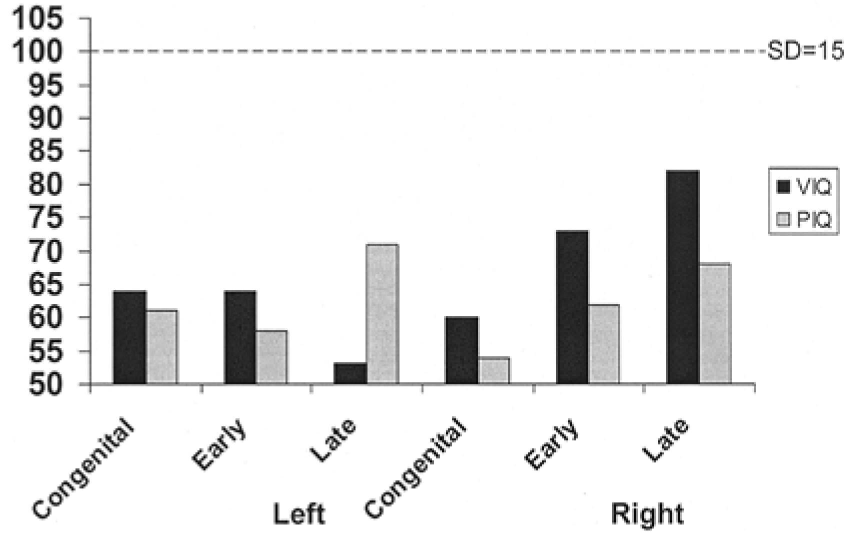

FIGURE 2. Verbal and nonverbal (performance) IQ (VIQ and PIQ, respectively) by age at onset and side of removal in the hemispherectomy group. SD, standard deviation.

Table 3 Details of age at onset of lesion in hemiplegia subgroups and IQ details

Group	*N*	Mean age at injury in months (SD)	Mean age at test in months (SD)	Mean time to test in months (SD)	Mean full-scale IQ (SD)	Mean verbalâ€“performance discrepancy score (SD)
Left congenital (LC)	13	0 (0)	143 (33)	143 (33)	85 (13)	3.28 (6.96)
Left early (LE)	6	32 (10)	148 (61)	116 (60)	90 (10)	0.83 (11.85)
Left late (LL)	5	144 (41)	180 (48)	36 (27)	91 (21)	-16.60 (12.72)

Right congenital (RC)	16	0 (0)	139 (43)	139 (43)	89 (12)	-0.12 (15.24)
Right early (RE)	6	20 (17)	152 (46)	133 (48)	81 (6)	8.33 (20.7)
Right late (RL)	6	108 (44)	147 (34)	39 (33)	90 (13)	2.66 (15.77)

In summary, the data presented here suggest that extensive lesions with seizures leading to hemispherectomy have the profound effect of lowering overall intelligence by more than 2.5 standard deviations below the population mean. Patients in the late left- and right-hemispherectomy subgroups demonstrate an intellectual profile suggestive of a double dissociation of function consistent with the adult pattern. Hemiplegia-inducing lesions with seizures may have a mild effect on reducing overall intelligence (by about one standard deviation below the population mean), irrespective of hemispheric side of lesion and age at onset of seizures. The IQ profile in the hemiplegia with

seizures subgroups, however, suggests that in larger cohorts, children with late onset of epilepsy (5 years and beyond) may demonstrate a similar double dissociation of function to those with late hemispherectomy and to adults with acquired lesions. These findings seem consistent with a model of constrained plasticity[3] or ontogenetic hemispheric specialization,[69] suggesting that the functional expression of the genetically determined process of hemispheric specialization gradually unfolds during early childhood, slowly acquiring the adult form from middle childhood onward.

Speech and Language

As was indicated for intellectual outcome, the level of speech and language competence achieved in the face of early unilateral insult is determined by the combination of a number of variables, most notably etiology and age at onset of pathology and, in the case of acquired lesions, hemispheric side of lesion. The primary focus of neuropsychological assessment for speech and language outcome after hemispherectomy is to guard against the development or exacerbation of any existing speech and language deficits by providing a detailed profile of linguistic abilities against the background of cognitive status, identifying the pattern of lateralization of language, defining the territory of eloquent tissue subserving motor speech functions, predicting the course and timing of any interhemispheric reorganization, and identifying rehabilitation and remediation techniques that may improve recovery and reorganization of speech and language function.

Pathology Affecting the Speech and Language Areas Bilaterally

Bilateral lesions restricted to the perisylvian speech and language areas are exceedingly rare, especially so in children. When such pathology occurs, in the context of either acute injury[34,73] or congenital or acquired pathology with epilepsy (i.e., Worcester-Draught syndrome, bilateral perisylvian/ frontal opercular syndrome, Foix-Chavany-Marie syndrome, Landau-Kleffner syndrome), it marks the limits of the reorganizational capacity of the immature brain to rescue speech and language functions. Children with this type of bilateral damage either fail to develop articulate speech[33,73] or lose the ability to speak and become mute after the onset of the acute injury.[34] The severe and chronic absence of spontaneous and clearly articulated speech is analogous to a severe expressive aphasia and/or dyspraxia of speech and contrasts sharply with the rapid resolution of such symptoms following unilateral lesions sustained in childhood. The persistence of the aphasic symptoms in pediatric patients with epilepsy raises the possibility of bilateral pathology and suggests that a viable neural substrate for the development of speech and language function does not exist within either hemisphere.

Table 4 Etiology of the acquired hemiplegia-with-seizures groups

Etiology	â‰¤5 years	5â€“16 years	Total
Cerebrovascular accident	5	1	6
Hypoxiaâ€“ischemia	2	1	3
Arteriovenous malformation	2	2	4
Tumor	1	0	1
Trauma	1	3	4
Other	1	1	2
Rasmussen encephalitis	0	3	3
Total	12	11	23

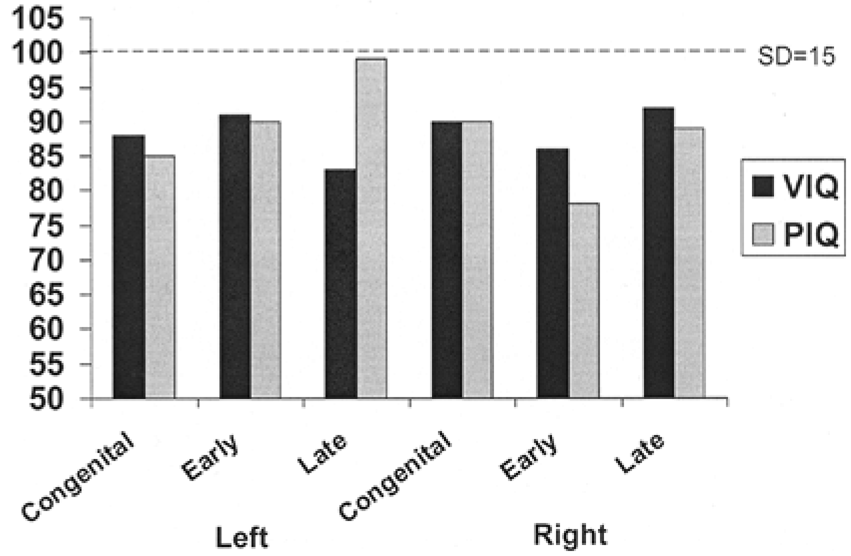

FIGURE 3. Verbal and nonverbal (performance) IQ (VIQ and PIQ, respectively) by age at onset and side of lesion in the hemiplegia group. SD, standard deviation.

Landau[33] described a boy who had cyanotic congenital heart disease. Until the age of 6, he had only developed a limited comprehension but no speech. He was judged to have normal nonverbal intelligence and no hearing impairment. Because his impairment appeared to be an aphasic disorder, at the age of 7, he received speech and language therapy and was reported to develop some useful, albeit limited speech and language.

At the age of 10, the patient died from complications of his cardiac abnormalities. At autopsy, examination of his brain revealed old, bilateral infarctions in the perisylvian regions with retrograde degeneration in the medial geniculate nuclei. The persistent aphasic disorder that failed to resolve with intensive therapy appeared to be the result of bilateral pathology of the perisylvian regions and the thalamocortical pathways.

Similarly, Vargha-Khadem et al.[71] described a young boy who sustained a traumatic birth injury that was reported to be limited to the frontal operculum (including Broca's area) on the left and the inferior precentral motor area on the right. This boy also received speech and language therapy but never developed intelligible speech or sign language.

Bilateral perisylvian polymicrogyria (BPP) is a malformation of cortical development frequently associated with severe dysarthria or anarthria. Patients with BPP have traditionally been considered to have severe learning difficulties. However, Jansen et al.[28] recently conducted a neuropsychological study of 14 adult patients with this diagnosis and demonstrated that only a minority had extremely low intelligence, and that some aspects of their cognitive function correlated with the extent of the cortical disorganization. In this cohort, early age of seizure onset correlated positively with nonverbal intelligence and negatively with the extent of the lesion. Receptive and expressive language skills were found to be equally impaired, but memory abilities and executive functions were relatively well preserved. This study provides further evidence that a malformation of cortical development in the bilateral perisylvian regions can lead to relatively specific aphasic symptoms in both children and adults.

Unilateral lesions also can produce aphasia if epileptiform activity spreads from one hemisphere to the other and thus acts like a functional bilateral lesion. This situation has been seen in pediatric patients with Landau-Kleffner syndrome, Sturge-Weber syndrome, and hemimegalencephaly. Typically, in children with Landau-Kleffner syndrome, speech appears to develop normally until seizure onset, when they become progressively or acutely aphasic as a result of bilateral interference with activity in the perisylvian regions by seizures emanating, in some cases, from the auditory cortex of one temporal lobe.[43,47] That the disorder is partly due to functional interference is demonstrated by the dramatic recovery of speech and language following successful abolition of the epileptiform activity by subpial cortical transection at the primary epileptogenic site.

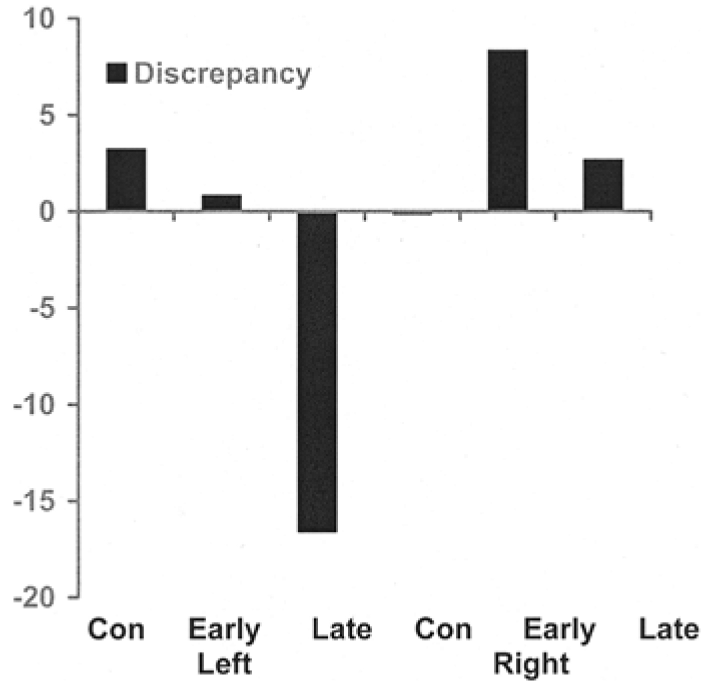

FIGURE 4. Discrepancy scores for verbal (V) minus performance (P) IQ for each of the hemiplegia subgroups (higher score indicates V > P discrepancy). Con, congenital.

Two cases of unilateral pathology resulting from Sturge-Weber syndrome in one and hemimegalencephaly in the other associated with mutism deserve mention. In both cases, mutism was resolved after hemispherectomy and successful abolition of seizures. Fusco and Vigevano[14] described a young girl who had left hemimegalencephaly, which resulted in epileptic discharges that at the age of 3 years spread from the left hemisphere to the frontocentral regions on the right, causing mutism in association with a bilateral frontal operculum syndrome. A few months later, she underwent a left hemispherectomy, which resulted in the abolition of her seizures, and the operculum syndrome resolved, as did her mutism.

Vargha-Khadem et al.[70] described an unusual case (Alex) that challenges the notion of an early critical period for the development of speech and language.[66] Alex had Sturge-Weber syndrome with a pial angioma over the left hemisphere. He did not develop speech as a young child, and at the age of 9.5 years had a mental age and receptive language skills of a 3- to 4-year old. He underwent a left hemispherectomy when he was aged 8.5 years and became seizure free. Shortly after prophylactic anticonvulsant medication was withdrawn, Alex started to speak for the first time in his life at age 9.4 years. Longitudinal examinations of Alex's speech and language functions into the second decade of his life showed that by the age of 15 years he had acquired linguistic abilities of a child aged 10 years. It is significant that Alex generated complex and grammatically formulated sentences, and his articulation was clear with very little evidence of dyspraxia or dysarthria.

The likely explanation of these reversible seizure effects is that the electrographic abnormalities (or their pharmacologic treatment) cause bilateral interference or even bilateral pathology.[70] Therefore the immature brain only has the potential for functional reorganization of speech and language if the thalamocortical systems are preserved and operational in at least one hemisphere.

Interhemispheric Reorganization

The combination of fMRI, neuropsychological assessments, structural MRI, and electrophysiology has made it possible for clinicians to evaluate the status of intra- and interhemispheric organization and reorganization of cognitive and motor function in pediatric patients undergoing epilepsy surgery.[24,26,37,38,41,54,61] The development of these convergent methodologies has reduced the need for some types of invasive investigations to determine lateralization of language and memory functions, such as the Wada test, and has paved the way for longitudinal investigations to track the processes of brain reorganization in the face of early onset epilepsy. In particular, the use of these noninvasive convergent methodologies has helped with (a) delineation of eloquent cortex that needs to be spared during resective surgery, (b) identification of abnormal cortex that is functionally active, and (c) tracking the process of interhemispheric reorganization of function.[38]

Traditionally, interhemispheric shifts in language dominance were thought to result from epileptic lesions encroaching on one or both of the classical language-eloquent regions rather than from lesions located remotely from Broca's and/or Wernicke's areas.[52] Clinical neuropsychologists may have used this evidence alongside handedness, dichotic fused words tests,[30] age at onset of chronic epilepsy, and site of EEG abnormality for predictors of language lateralization. This hypothesis has been recently challenged, however, by functional neuroimaging evidence indicating that in both pediatric and adult cohorts with early onset epilepsy, left- to right-hemisphere shifts in language dominance are more likely to occur in patients who have lesions encroaching the left hippocampus.[29,31,36,75] Hypotheses as to why this might be the case have been reviewed by Weber et al.[75] and include (a) the high degree of interictal epileptiform activity associated with temporal lobe epilepsy,[20,50] which leads to stronger involvement of the nondominant hemisphere in language,[53] (b) the diffuse ipsilateral hemispheric dysfunction that lesions in the hippocampus may cause due to its multiple reciprocal connections,[12,62] and (c) a potential role for the hippocampus in the acquisition of language.[65] It is interesting that neither handedness, age at onset of chronic epilepsy, nor site of EEG abnormality appears to be good predictors of language lateralization,[36] which highlights the need for links between cognitive neuroscience paradigms and techniques such as functional neuroimaging and traditional behavioral testing. Although the shift in language lateralization may be influenced by left hippocampal pathology,[75] the efficacy and speed with which reorganization is achieved may also depend on the frequency, severity, and spread of seizures.[29,75] For example, the catastrophic epilepsy associated with Rasmussen encephalitis (e.g., case PD[27]) may force right hemisphere mediation of linguistic function rapidly compared to seizure activity that is less frequent and less severe (e.g., case MPD[63]). Indeed, the shift in language dominance in the case PD occurred in a matter of weeks. Thus, from the onset of left hemisphere partial motor seizures at age 3.7 up to 4.1 years, each episode was accompanied by complete speech arrest with preservation of consciousness. When PD presented for hemispherectomy at age 4.2 years, however, the frequency of seizures (approximately 200 per day) continued unabated, but now during each episode the child was able to speak in clearly articulated short sentences. Following hemispherectomy, there was no deterioration in speech and language function, and PD continued to develop linguistic abilities in line with predictions based on his intellectual status. Clearly, reorganization of language function from the left to the right hemisphere in PD had been achieved over a period of 3.5 weeks.

Finally, it is usually assumed that when left hemisphere pathology is congenital or perinatal and is of an extent and severity that ultimately requires hemispherectomy, then there has been no interhemispheric reorganization to track.[70] This is because speech and language development will have been completely dependent on the function of the right hemisphere from the start.

Left Hemisphere Pathology

Unlike the situation in adults, unilateral left-sided lesions causing focal epilepsy in children do not appear to produce aphasia if they occur before speech has developed, provided the homologous areas on the right remain functional.[1,52,83] If extensive left hemisphere damage occurs after the onset of speech

but before the age of 4 or 5 years, then aphasic symptoms can result initially, but the symptoms generally resolve prior to hemispherectomy. There is usually postmorbid development of these functions to the extent that, as in patients with congenital or perinatal injury, there is no longer a selective dysphasia.[70] Indeed, language production in these patients may actually exceed their comprehension ability, which tends to fall together with the pathology-induced reductions in their intellectual level.

A mild version of the adult pattern of aphasia typically emerges when extensive left-hemisphere pathology is acquired after the age of 5 years. In such cases, speech arrest, transient mutism, anomia, and/or agrammaticism are seen, and these symptoms often remain chronic.[48,49,63] Basic speech tends to be a resilient function, however, with the patient usually being able to communicate effectively through short phrases and sentences. As indicated earlier (see section on intellectual outcome after hemispherectomy), none of the 15 left-hemispherectomized patients in the congenital and early groups suffered from dysphasic symptoms, despite very low levels of verbal intellectual ability in some patients. Such was not the case with the 4 patients who had onset of left hemisphere seizures after the age of 5 years, each of whom exhibited some degree of dysphasia (e.g., word-finding problems, mispronunciations, phonological errors, etc.) during free speech. Based on these and other data reported in the literature (e.g., Pulsifer et al.[51]), it is evident that the right hemisphere is capable of supporting *basic speech and language* skills from birth.

In a larger study of 31 children who underwent hemispherectomy (11 left, 20 right) with Rasmussen syndrome, Pulsifer et al.[51] reported that the left-hemispherectomy group scored consistently lower than the right-hemispherectomy group in receptive language and expressive language, despite there being no difference in terms of age at seizure onset (average 6.4 years), age at surgery (average 9.7 years), age at follow-up (average 14.7 years), or interval between surgery and postoperative evaluation (average 5.1 years).[51]

In summary, epilepsy-inducing pathology that occurs to the left hemisphere before the age of 5 years and certainly before the onset of speech appears to have little significance for long-term basic fluent speech and language. Difficulties with more complex aspects of language processing have been reported, but it is not clear whether these are significantly greater than the overall lowering of intelligence that frequently appears following any cerebral insult. Presumably, basic language processes are prioritized and spared due to either inter- or intrahemispheric reorganization so that neural substrates outside of the left hemisphere classical language areas support these functions. It is well documented that such compensatory processes also have a cost for nonverbal cognitive functions. Further studies are required of larger groups of children with different ages at onset of epilepsy to elaborate on the decline in available plasticity over the childhood years as brain organization emerges and cognitive processes become crystallized.

Right Hemisphere Pathology

Provided the left hemisphere is intact, right-sided lesions or removal of the hemisphere does not impair long-term speech and language regardless of age at onset of epilepsy or extent of lesion.[1,19,40,46,60,67,78] Right-sided pathology of congenital/ perinatal onset may result in delayed development of speech and language, but there are no *selective* residual dysphasic symptoms. As with pathology leading to removal of the left hemisphere, pathology and subsequent removal on the right at any age has an indirect effect on linguistic function that is related to the lowering of intelligence.[72]

When right-sided pathology is acquired early but after the onset of speech, there may be some initial language disorder such as disorganized speech or restriction of comprehension, presumably due to interhemispheric spread of epileptic activity, but these effects ordinarily resolve following right hemispherectomy and the arrest of epilepsy.

Compared to the investigation of linguistic functions in children, little attention has been paid to nonlinguistic abilities that are usually associated with right hemisphere impairment in adult-onset pathology. There is some evidence that children with congenitally damaged right hemispheres but without seizures present only with lower nonverbal intelligence compared to normal controls.[44] Groups of children with concurrent epilepsy, however, show both verbal and nonverbal intellectual impairment.[44,67] As discussed earlier, this may be due to the seizures interfering with the contralateral hemisphere, and individual variations are masked in large group studies of epilepsy.

Kohn and Dennis[32] reported that visuospatial processing skills might develop in children who have undergone right hemispherectomy up to a maximum of about a 10-year-old level. In a girl who had early right hemispherectomy, Day and Ulatowska[6] reported relevant difficulties with tasks requiring perception or visual-motor coordination. Chiricozzi et al.[4] reported case GT, who had hemiplegia resulting from neonatal ischemic infarction of the right middle cerebral artery. GT developed epilepsy at the age of 4.5 years that was well controlled with anticonvulsants until 10 years of age. GT underwent right hemispherectomy at almost 15 years of age. There was a significant improvement in GT's visuospatial skills following surgery (although they were still below average), suggesting that just as with speech and language, there may be a functional catch-up period that extends well beyond early development. It is not clear, however, whether the ultimate level of visuospatial processing achieved after successful surgical treatment and arrest of epilepsy is consistent with predictions based on intellectual status.

Summary and Conclusions

Neuropsychological evaluation plays a central role in the multidisciplinary investigation and management of children with epilepsy by providing appropriate assessment and advice to optimize the child's cognitive development, educational achievement, and behavioral and mental health function as well as informing decisions in pharmacologic and surgical treatment plans. By combining the advances in functional magnetic resonance imaging, structural MRI, and event-related electrophysiology with neuropsychological assessment, it has become possible for clinicians to evaluate the status of intra- and interhemispheric organization and reorganization of cognitive and motor function in pediatric patients undergoing epilepsy surgery and document the response of the immature brain to injury.

Unlike adults, children with early unilateral left-sided lesions (before the age of 5 years) and seizures do not show persistent deficits in verbal intellect relative to nonverbal intellect and do not demonstrate aphasic features when the left perisylvian regions are injured, provided the right hemisphere remains intact. It appears that fluent speech and language functions at a basic level are prioritized and rescued through a process of intra- or interhemispheric reorganization. Recent evidence suggests that injury to the left hippocampus may play a significant role in speech and language reorganization to the right hemisphere. The efficacy and speed with which reorganization occurs appear to be related to the frequency, severity, and spread of seizures. However, when the early lesion involves catastrophic epilepsy leading to hemispherectomy, the costs for general cognition are striking, with a dramatic lowering of overall intellectual function by between two to five standard deviations below the population mean. If such an epilepsy-inducing lesion occurs after the age of 5 years, as, for example, in Rasmussen encephalitis, there is still a significant lowering of overall intellect, but left-sided pathology has a relatively greater effect on verbal compared to nonverbal intellect, and the reverse occurs in right-sided pathology.

Epilepsy involving bilateral perisylvian regions in childhood can result in mutism or chronic aphasic symptoms similar to those reported in adults following unilateral left Broca's area and perisylvian injury. This also can occur with unilateral lesions in childhood when seizures and perhaps anticonvulsants impede the function of the contralateral hemisphere, this in effect acting like a functional bilateral lesion. Finally, provided the left hemisphere is intact, right-sided lesions or removal of the hemisphere does not impair long-term speech and language regardless of age at onset of epilepsy or extent of lesion. There is some evidence that late right-sided lesions affect aspects of nonverbal processing, although this has not been studied to the same extent as speech and language.

In summary, the findings discussed in this chapter appear consistent with a model of ontogenetic hemispheric specialization, suggesting that the functional expression of the genetically determined process of hemispheric specialization gradually emerges during early childhood, slowly acquiring the adult form from middle childhood onward, with some potential for plasticity and reorganizational capacity early in life, depending on the nature of the brain injury. Contemporary clinical neuropsychological evaluation of children with epilepsy, particularly for children pre- and post-neurosurgery, depends on close collaboration with cognitive neuroscientists so that convergent methodologies are used to help delineate the relationship of pathology, epilepsy, and cognitive development.

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Chapter 92

Options for Long-Term Monitoring

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John S. Ebersole

Introduction

Analysis of the electroencephalogram (EEG) during seizures may be crucial in the management of patients with epilepsy, especially those who are candidates for epilepsy surgery, and essential for the diagnosis of conditions that mimic epilepsy.[4,23] A standard EEG recording, lasting <1 hour, typically does not capture seizures. It may also miss infrequent interictal EEG abnormalities, which themselves contain important diagnostic information.

Long-term monitoring (LTM) permits analysis of infrequent ictal and interictal EEG patterns by recording a patient's EEG continuously for hours, days, or weeks on a storage medium from which selected segments may be subsequently retrieved and analyzed. When it is combined with continuous recording of audio and video signals from a closed-circuit television (CCTV) system, the semiology of the episodes can be examined and correlated with the concurrent EEG patterns. Analysis of seizure semiology is also of great value in the differential diagnosis of epilepsies and the conditions that mimic them.[80,134]

An advantage of LTM, in addition to the increased duration of the recordings, is that it permits EEG analysis during the full sleepâ€"wake cycle. Some patients with epilepsy have almost exclusively nocturnal seizures.[11,31,95,101] The clinical and EEG manifestations in others predominantly occur after[92,95,137] or shortly before[19] they awaken in the morning. Infrequent interictal epileptiform discharges (IEDs) may be activated by sleep, particularly non-rapid eye movement (REM) sleep,[77,86,113] and in some patients may appear only during sleep.[36] However, spikes recorded during slow-wave sleep may have less localizing value than those recorded during REM sleep and wakefulness.[113] Long-term monitoring can also distinguish sleep-related nonepileptic events that resemble epileptic seizures (see Chapter 276).

Applications

Long-term monitoring is used in a variety of clinical settings. The techniques used and the information sought from LTM vary according to the clinical situation in each case.

Seizure Classification and Quantification

Long-term monitoring with CCTV and EEG may facilitate patient management by permitting more accurate classification of seizures and thus more appropriate therapy. For example, complex partial seizures can resemble the absence seizures of primary generalized epilepsy, but they are treated differently. Distinguishing between partial seizures with rapid secondary generalization and primarily generalized seizures also has important therapeutic implications.

Long-term monitoring can be used to distinguish epileptic seizures from intermittent nonepileptic behavioral alterations that resemble epilepsy. Although specific ictal behaviors suggestive of psychogenic seizures have been described,[44] they are absent in many, if not most, patients with psychogenic seizures.[71] It may be impossible to distinguish between psychogenic and epileptic seizures on clinical grounds alone without LTM.

Because epileptiform discharges occur in people who do not have epilepsy,[24,48] including those who have psychogenic seizures,[105] LTM may be required to record seizures and confirm a diagnosis of epilepsy even if a routine EEG shows such epileptiform discharges. Psychogenic and epileptic seizures may coexist. Although some investigators have claimed that this is rare,[72] others report that a substantial percentage[20,65,93,105,132] or even a majority[56,109] of patients with confirmed psychogenic seizures also have, or have had, epileptic seizures. Thus, LTM may be necessary in a patient with known epilepsy if the current episodes are suspected of being nonepileptic. For example, if seizure frequency increases in such a patient despite an unchanged treatment regimen or if new episodes that differ from the previous seizures develop, the nature of the current episodes must be determined. Increased epileptic seizures might require increased doses of antiepileptic drugs (AEDs) or other therapeutic alterations. Increasing the AED dose in a patient with psychogenic seizures does not benefit the patient and may lead to drug toxicity.

Long-term monitoring may be used to quantify seizures such as subtle infantile spasms[43] or frequent brief absences that are not clinically obvious but interfere with a child's school work.[50,69,120] It may also be used to assess the response to AEDs.[97,120] Quantification of seizures and measurement of blood AED levels when the AEDs are being administered by hospital personnel may be of value in cases in which patient compliance with the medication regimen and the validity of information provided about seizure frequency are both questionable.

Identification of Interictal Epileptiform Discharges

Identification of IEDs is useful in the assessment of patients with epilepsy,[29,52,62,111] and it is also important in some patients who have not had seizures (Chapter 73). For example, the presence of IEDs in a child with language regression from a normal baseline but no history of seizures establishes a diagnosis of Landau-Kleffner syndrome.[12]

Interictal epileptiform discharges may be infrequent, and often they do not appear in routine EEG studies of patients who are known to have epilepsy. A single EEG demonstrates IEDs in approximately 30% of adults with partial seizure disorders.[2,112] The yield is higher when the patient is a child[2,22,138] or has a generalized seizure disorder.[121,138]

Sleep and sleep deprivation also increase the yield of IEDs.[22,41,84,115,138] Multiple routine EEG studies are of limited value, and may fail to demonstrate IEDs in as many as 41% of patients with partial epilepsies.[112] Of patients in whom IEDs are detected by routine EEG studies, the first EEG shows them in 45% to 81% of cases.[112,114,121,138] Four EEGs identify 92% to 99% of patients in whom IEDs are ultimately found by routine recordings; each subsequent recording offers a minimal additional yield. Long-term monitoring covering the entire 24-hour day may demonstrate rare IEDs in patients in whom the results of repeated routine EEGs are negative.

Presurgical Evaluation

Long-term monitoring is used to record seizures and localize their origin in patients with medically intractable seizures who are candidates for epilepsy surgery (see Chapter 169). Among epilepsy surgery centers responding to a 1991 survey,[76] 81% always used CCTV-EEG monitoring in the preoperative evaluation of patients with limbic epilepsy, 15% used it sometimes, and only 3% reported that they never used it. Multiple seizures must be recorded[103,128] to ensure that they all arise from the same focus or, if they do not, to quantitate the relative activities of the various seizure foci. Seizures that occur in clusters or flurries are more likely to arise from the same focus and thus carry less localizing information than seizures that are widely separated in time.[51] A patient with partial epilepsy with multiple foci may still be considered a surgical candidate if the vast majority of the seizures come from one resectable site.[117] Because seizures are only rarely captured during routine EEG, LTM is a necessary prelude to surgical treatment in most patients. Long-term monitoring using implanted (subdural and depth) electrodes may be necessary if the data from less invasive (e.g., sphenoidal) and scalp electrodes are not sufficiently localizing. In the 1991 survey, 92% of the epilepsy surgery centers reported that they used invasive recordings in at least some cases, although not necessarily in all patients.[39]

Although unilateral IEDs may have substantial localizing value,[62] examination of IEDs is generally not regarded as sufficient for localization of the seizure focus before surgery. In one study,[136] the lateralization suggested by interictal recordings alone was misleading in 8 of 67 patients with clear unilateral temporal lobe epilepsy. Moreover, many patients with good outcomes after temporal lobectomy have independent bitemporal IEDs on preoperative EEGs.[29,117,123,136] Long-term monitoring shows a unilateral origin of the seizures or a strong lateral predominance in about half of the patients with bitemporal IEDs when only extracranial electrodes are used and in approximately 75% when depth electrodes are used.[54,116] The degree of lateralization of IEDs may have prognostic significance for patients undergoing temporal lobectomy[10,29,45,52,104] even if LTM with depth electrodes shows unilateral seizure onsets.

Intensive Care Unit Monitoring

Long-term monitoring is also used in neurological[53,60,96,130] and neonatal[124] intensive care units (ICUs) to identify deterioration of cerebral function, titrate drug doses for barbiturate coma, detect seizure activity in comatose patients, and confirm that treatment for seizures is successful. If a patient in status epilepticus has been treated with high doses of barbiturates, benzodiazepines, or other sedative or anesthetic drugs, continued obtundation could be a consequence of either medication effects or continued seizure activity. Only the EEG can distinguish between these and guide further treatment.

Seizures cannot be identified clinically in patients who have been pharmacologically paralyzed. When status epilepticus is prolonged, continued electrographic seizure discharges may not produce clinical seizure activity, even in patients who are not paralyzed.[25] Because status epilepticus can cause brain damage even in the absence of overt convulsions and metabolic derangements,[61,66,133] it must to be detected and treated. EEG monitoring demonstrates nonconvulsive seizures, including nonconvulsive status epilepticus, in a substantial percentage of neuro-ICU patients.[61,130]

Technical Aspects

Recording Techniques

During LTM, surface electrodes are securely attached to the patient's head, typically with collodion, to permit prolonged EEG recordings. Electrode impedances should be both low and balanced to minimize noise and maximize the effective common mode rejection ratio of the recording system.[70] Open-hole cup electrodes are used for recordings lasting days to weeks, so that the electrodes can be periodically regelled. The quality of the recordings must be continually assessed so that electrode maintenance can be performed as soon as possible if the data deteriorate.

The patient's head is wrapped to protect the electrodes and to prevent infection when implanted electrodes are used. Strain relief loops to secure electrode lead wires are especially important when implanted electrodes are used. In patients who become confused or combative during or after seizures and who might pull on the lead wires of their implanted electrodes, judicious use of restraints may be necessary to prevent self-injury.

Multichannel EEG data are amplified, undergo initial bandpass filtering, and are recorded on a storage medium, most commonly magnetic tape. Guidelines for amplifier specifications for LTM have been published.[7,37] If the EEG signal is digitized, the analog-to-digital converter must satisfy the Nyquist criterion: The sampling rate for each input channel must be at least twice the highest frequency present in the analog data. Long stretches of cable and wire will pick up electromagnetic and movement artifacts. The higher the amplitude of the EEG signals traversing these wires, the better is the signal-to-noise ratio. Therefore, preamplifiers placed close to the recording electrodes, either on the patient's head (within the head wrapping) or in an electronics package attached to the patient with a strap or belt, are preferable to remote preamplifiers. When the EEG signal is carried from the patient to the recording machinery by cables (cable telemetry), careful attention must be given to patient isolation to prevent electrical hazards.

If radio telemetry is used, the data must be multiplexed; sample values from all the input channels are combined into a single radio signal. Multiplexing is also used for storage media in which a single â€œchannelâ€

contains all the EEG data, as in videotape recording systems; successive data values stored on the tape are derived from consecutive input channels, going from the first to the last channel and then back to the first channel again. The maximum frequency of the data stored for each channel, which must also satisfy the Nyquist criterion, is equal to the storage frequency (samples per second) of the tape divided by the number of channels that are multiplexed together.

The EEG may be recorded either in a referential format, with the same electrode connected to the input 2 of each channel's differential amplifier, or in a bipolar montage. The referential recording permits reformatting of the retrieved EEG data to any desired montage.[67] This requires carefully balanced amplifiers and high-fidelity recording and playback so that the calculated bipolar data will faithfully reproduce the signal that a bipolar analog recording would have provided. A faulty reference electrode can make all of the recorded patient data uninterpretable. Thus, referential recordings are usually confined to a hospital setting (inpatient LTM or daytime intensive monitoring), in which the quality of the data can be assessed frequently and technical problems rapidly fixed. Additional recording channels may be used to record the electrocardiogram, electromyogram, respiratory activity, and other physiologic variables, as well as alarm or marker signals that can be triggered by the patient or hospital staff.

The EEG can be analyzed in real time by a computer program that identifies and marks probable epileptiform patterns (computerized EEG analysis is discussed in Chapter 95) for subsequent analysis. In an inpatient setting, the computer can alert the staff so that the patient's responsiveness, neurologic status, and memory can be tested during a seizure.

The EEG data were formerly stored on magnetic tape, but increases in the speed and capacity of computer disks have made them the preferred storage medium. Data storage in a random-access memory device such as a computer disk also has the advantage that any portion of it can be accessed quickly; with magnetic tape, winding to the desired part of the record can markedly prolong data access times.

When CCTV and EEG data are recorded concurrently, all data should include time markers[57] or other methods that permit them to be correlated or synchronized so that the temporal relationship between EEG changes and behavioral alterations can be examined. Many different kinds of CCTV instrumentation are available.[7,37] Cameras sensitive to low light levels or infrared illumination are useful for monitoring patients at night. Multiple cameras with remote-controlled pan and zoom permit recording of a split-screen image that contains both a close-up of the face and eyes and a view of the patient's entire body and that tracks patients' movements to keep them in view as much as possible.

Types of Long-Term Monitoring: Advantages and Disadvantages

Long-term monitoring procedures can be subdivided according to whether they are performed on an outpatient or inpatient basis and by the specific technology utilized. In outpatient LTM, the patient carries an electronics package and recording device. Initially the EEG was stored on magnetic cassette tape, but advances in semiconductor memory technology now permit ambulatory EEG (AEEG) recordings utilizing solid-state memory arrays. Inpatient LTM involves a hospital admission to a specially equipped monitoring unit in which the patient is monitored continuously for days or weeks. In an intermediate approach, which has been labeled daytime intensive monitoring,[110] the patient undergoes repeated prolonged EEG or CCTV-EEG recordings in the hospital but is not admitted to the hospital and goes home each night. The patient is encouraged to sleep during the recording session; antecedent sleep deprivation may facilitate this. When monitoring is performed in the hospital, either on an inpatient basis or as daytime intensive monitoring, the patient can be connected to the recording equipment with a long cable (an arrangement sometimes referred to as cable telemetry) or the data can be sent by radio or infrared telemetry from a transmitter worn by the patient to a nearby receiver and thence to the recording equipment. During cable telemetry, the same semiconductor memory technology used for AEEG can permit continued EEG recording for a limited time when the cable is disconnected, such as when the patient goes for a procedure in another part of the hospital.

Each of the LTM methods has advantages and disadvantages. For example, considerations of equipment weight and size, recording medium capacity, and battery life place limitations on the number of channels and the duration of recordings that can be obtained during AEEG monitoring, although both have been increased as the technology evolves. The decision about which method to use should include consideration of the particular clinical situation of each individual patient.

Coverage of the Circadian Cycle

Daytime intensive monitoring recordings are longer than standard EEG recordings, but they still cover a relatively small portion of the 24-hour day. Nocturnal seizures and IEDs, as well as those occurring on awakening in the morning, are more likely to be captured during continuous 24-hour recordings, either inpatient or ambulatory. Daytime intensive monitoring may suffice in patients who have frequent daytime events.

Changes in Patient Activity and Environment

One benefit of AEEG monitoring is that patients may be in their usual environments, with their usual patterns of activity, as the EEG is being recorded. Some patients with intractable epilepsies do not have seizures for several days when they are admitted to an epilepsy monitoring unit. This is likely related to the enforced change in daily activities, with decreased physical activity and increased bed rest in a patient who is required to stay in range of the CCTV camera. Less commonly, inpatient monitoring can remove environmental stimuli that trigger seizures. The issue of stress deserves special mention. Although being in an epilepsy monitoring unit itself constitutes a stressful situation for some, hospitalization may remove some of the patient's usual stresses. Patients with epilepsy often report that stress increases their seizure frequency, but studies that quantitatively examined this issue concluded that psychological stress does not increase seizure frequency in most patients, aside from indirect mechanisms such as stress leading to medication noncompliance or sleep deprivation.[90,91]

Closed-Circuit Television Recordings

One advantage of in-hospital LTM is the ready availability of concurrent CCTV monitoring. This is usually not feasible during AEEG monitoring, in which information about the clinical correlates of EEG changes is limited to recorded impressions of the patient and observers. Outpatient monitoring equipment with video recording capability is now available, but the requirement to keep the patient within the field of view of the camera may interfere with normal patterns of activity, limiting one of the benefits of AEEG monitoring. This equipment is most useful during sleep or at other times during the day when the patient remains in a fixed location for an extended period of time. If the camera and the AEEG recording system are separate, careful consideration must be given to time markers and the synchronization/correlation of the EEG and video data.

Number of Channels and Montages

If the number of data recording channels is small, the number of recording electrodes will be limited. This impairs detection of epileptiform abnormalities with restricted topographic distributions, as well as differentiation of brain activity from artifacts by inspection of the fields of the potentials. Extensive coverage of the head is especially important during presurgical evaluation: If a limited number of recording electrodes placed to cover the presumed seizure focus pick up the spread of the seizure discharge, whereas the earliest seizure activity actually begins elsewhere but is not recorded, then the LTM-based localization will be inaccurate.[102]

Early ambulatory cassette recorders had only 3 channels, which severely limited the extent to which the scalp EEG could be sampled. This was subsequently increased to 8 and then to 16 channels. Since then, technological improvements have permitted digital AEEG recordings with as many as 32 channels.[46] Because the quality of the data is not monitored during recording, AEEG LTM should use bipolar rather than referential recording techniques. Retrieved data can be successfully reformatted if carefully designed bipolar recording montages are used.[58]

In-hospital cable or radio telemetry permits recording of 32, 64, 128, or more channels of data simultaneously, facilitating the use of electrodes more closely spaced than the 21 electrode positions of the International

10-20 System.[6] These added electrodes may more accurately localize the source of IEDs and electrographic seizures.[88] A large number of channels is generally needed for recordings from implanted electrodes during presurgical evaluation; such recordings are of necessity done on an inpatient basis.

Maintenance of Data Quality

When LTM is performed in a hospital setting, the EEG data are usually displayed in real time on monitors at the nursing station or EEG laboratory. Recording problems that develop during inpatient monitoring may be rapidly detected and corrected because of the real-time EEG display. In contrast, recording problems may remain undetected and invalidate much of the recorded data during AEEG monitoring.

Presence of Trained Observers

In the hospital, specially trained personnel are present to evaluate patients during seizures. They also may recognize behavioral changes that require analysis at times when the patient has not pressed the alarm switch and online computer analysis has not identified an unusual EEG pattern requiring attention.

Computerized Online Electroencephalogram Analysis

Real-time computer analysis of the EEG is usually performed during LTM in a hospital setting. It was not available during AEEG monitoring in the era of cassette tape recordings, but many digital AEEG monitors now incorporate microprocessors that perform real-time analysis of the EEG.[46]

Use of Invasive Electrodes

Invasive monitoring with depth electrodes or subdural electrode arrays (see Chapters 170 and 171) presents a risk for infection and other complications and requires careful medical supervision. Thus, it is always performed in an inpatient setting. Sphenoidal electrodes are also most often used during inpatient LTM, although successful AEEG monitoring with sphenoidal electrodes has been reported.[28,125] When cortical stimulation for localization of eloquent cortical areas is done extraoperatively before epilepsy surgery,[73,107,127] it is performed in an inpatient LTM setting.

Cost of Long-Term Monitoring

One of the major advantages of outpatient AEEG monitoring is economic. This may become an even stronger factor in the era of managed health care. Technical costs and the charges for interpretation of the LTM data are common to both AEEG and inpatient LTM, but the latter also incurs charges for the hospital room and charges related to the nursing and physician staff.

Yield of Seizures and Interictal Epileptiform Discharges

A few studies have compared the diagnostic yield of inpatient CCTV-EEG monitoring with that of AEEG monitoring or daytime intensive monitoring performed in the same patients. Inpatient LTM with cable telemetry identifies seizures and IEDs in the largest number of patients. For example, in a study in which patients were randomized to outpatient AEEG versus inpatient LTM,[49] seizures were captured in 85% of the inpatient monitoring sessions as compared to 61% of the ambulatory monitoring sessions; this difference did not reach statistical significance, however.

In the appropriate clinical settings, other types of LTM can provide the necessary diagnostic information in many patients, with a yield much higher than that of routine EEG. For example, AEEG LTM demonstrates seizures or IEDs in 1.7 to 2.5 times as many patients as do routine EEGs; the yield of AEEG LTM is 83% to 93% of that of CCTV-EEG monitoring with cable telemetry and is highest for patients with generalized EEG abnormalities.[18,34,35] The superiority of LTM over routine EEG is most pronounced when capturing seizures as opposed to IEDs. For example, in one study of 46 patients, none of whom had seizures during routine EEG with antecedent sleep deprivation, AEEG captured seizures in 7 patents; the yield of IEDs did not differ significantly between the two recording techniques.[75] Daytime intensive monitoring captured seizures in ten times as many patients as did routine EEGs in one study; this yield was 82% of that obtained with continuous EEG monitoring with radio telemetry.[98]

Daytime intensive monitoring may be particularly useful for patients with psychogenic seizures whose attacks can be provoked by suggestion.[14,64,82]

Data Analysis

For most of its history, the EEG has consisted of a paper printout, each page of which was scanned by the interpreter. This is not feasible during LTM, because of both the bulk of the resulting records and the time that would be required to scan through them. Long-term monitoring EEG data are stored electronically, and selected segments are displayed on a computer screen. Digital EEG offers several advantages: Data recorded in a referential format can be reformatted into a variety of bipolar and referential montages, permitting greater accuracy in the analysis of the EEG patterns. The filter and gain settings can be adjusted to obtain a more interpretable display; use of digital filters permits the phase shifts inherent in analog filters to be averted. Additional EEG display formats, such as spectral power displays and plots of spatial coherence, are also possible.

When CCTV-EEG monitoring is performed, video and audio records are analyzed and correlated with the EEG data. Seizures in which the onset of a focal electrographic seizure pattern precedes the onset of the clinical seizure provide more compelling evidence about the location of the seizure focus than do seizures in which the EEG is nonlocalizing at a time when the clinical seizure has already begun. The CCTV recordings can be shown to family members, coworkers, and friends of the patient to confirm that the semiology of the events occurring during LTM is the same as that of the patient's usual seizures.

Selection of Electroencephalogram Segments for Analysis

Visual inspection of all recorded EEG data is not feasible during LTM. Segments retrieved for analysis include those identified by the patient and (in the hospital) by nurses, physicians, and technologists as seizures or auras. Computer analysis of the EEG is used to identify additional segments containing possible seizures or IEDs[47]; it is most efficiently performed in real time, during the LTM. Because data segments not marked by alarm signals or by the computer are discarded without further analysis, computer algorithms are usually set to maximize sensitivity for seizure detection. Selectivity suffers as a consequence; many if not most of the EEG segments marked by the

computer will be found to contain no epileptiform abnormalities. Each retrieved EEG segment should begin before the onset of the clinical event or EEG abnormality that triggered its retrieval, to permit detection of subtle EEG alterations preceding the event and to serve as the baseline for recognizing changes in the EEG.

In the era of AEEG using magnetic cassette tape, the EEG waveforms were played though speakers as sounds to detect seizures; rhythmic seizure discharges sound like tones with a progressive change in pitch. The data were played back at a faster rate (speed ratio of 20:1 to 60:1) to bring the EEG background frequencies into the range of human hearing.[33] Real-time seizure detection during AEEG with digital technology obviates the need for such auditory analysis.

Interictal EEG samples in both the awake and asleep states should also be reviewed in patients undergoing LTM. The real-time computer analysis can be used to select the epochs to be examined to maximize detection of IEDs. Periodic review of interictal EEG samples also provides for repeated assessment of the technical aspects of the recording; faulty electrodes or other problems can be recognized and corrected promptly so that recordings of subsequent seizures will be optimal.

Data Storage and Archiving

All data recorded during LTM cannot be stored permanently because of storage costs and physical space requirements, as well as the cost of magnetic recording media (which can otherwise be erased and reused). However, samples of the patient's typical episodes should be stored in the event that they are subsequently needed for clinical or medicolegal purposes. Hard-copy EEG printouts do not have to be stored if they can be reproduced from electronically stored data.

Ancillary Procedures

In patients for whom the goal of LTM is to record seizures, intervals during which no seizures occur contribute little to the diagnostic workup but do increase the duration of hospitalization, the costs of LTM, and (for patients with implanted electrodes) the risks for infection and other complications. Several ancillary procedures can be used to increase the frequency of seizures, both epileptic and psychogenic, during LTM.

Other ancillary procedures, such as ictal single-photon emission computed tomography (SPECT)[13] (see Chapter 81) and measurement of serum prolactin levels[8] (see Chapter 194), help to characterize the patient's episodes more accurately. Because the SPECT radioisotope must be injected or the prolactin blood sample drawn when the seizure occurs, these tests are practical only during in-hospital LTM.

Antipileptic Drug Taper and Proconvulsant Drugs

Antiepileptic drugs may be tapered or discontinued to increase seizure frequency; in some patients, the taper may be started before admission to the epilepsy monitoring unit. Protective AED blood levels should be reestablished before discharge in patients with epilepsy. Concern has been expressed that AED withdrawal may activate seizure foci different from those producing the patient's usual seizures,[38] leading to misleading findings from monitoring. Subsequent studies have shown that, in most cases, the origins of the seizures do not change: Foci that produce seizures during AED withdrawal also do so at other times. However, partial seizures are more likely to become secondarily generalized, or to become generalized more rapidly, as AEDs are tapered and discontinued.[79,118] When AEDs are withdrawn, the semiology of the seizures should be examined to ensure that those that were captured are the patient's usual seizures. Antiepileptic drug withdrawal is discussed more fully in Chapter 118.

Proconvulsant drugs such as pentylenetetrazol were formerly used to activate seizures, but they have been found to have a substantial risk for activating seizure foci different from those producing the patient's usual seizures, thereby leading to false localization.[135]

Other Methods of Promoting Epileptic Seizures

Sleep deprivation is often used to promote seizures in patients undergoing LTM because it increases seizure frequency in some patients with epilepsy,[108,129] although a recent study of a group of patients with medically refractory partial epilepsy undergoing LTM failed to show an effect of sleep deprivation on seizure frequency.[78] Sleep deprivation also activates IEDs[41]; this effect is most pronounced for patients with relatively few IEDs at baseline.[84]

Other maneuvers that reportedly trigger the patient's seizures may be used during LTM. This is particularly useful in a patient with a stimulus-sensitive or reflex epilepsy. It has been estimated that seizures may be evoked by specific external stimuli in about 5% of people with epilepsy.[106]

Spell Induction for Suspected Psychogenic Seizures

During LTM, placebo procedures, such as intravenously injecting normal saline solution, rubbing an alcohol pad on the patient's neck, or placing a vibrating tuning fork on the patient's body or head, have been used in attempts to elicit psychogenic seizures.[64] The placebo is accompanied by the suggestion that it will bring on a seizure. The suggestion that standard EEG procedures such as photic stimulation and hyperventilation can trigger attacks may also increase the yield of psychological seizures, especially in patients who have had their typical attacks in a medical setting.[82]

Patients with epilepsy may be suggestible, and spell induction can trigger nonepileptic episodes in them as well. It must always be determined whether episodes precipitated by spell induction are the patient's typical seizures. Conversely, lack of a response to a trial of spell induction does not rule out the possibility of psychogenic seizures in the patient. Although it is rare, a true epileptic seizure can occur during spell induction, either coincidentally or as a reflex epilepsy triggered by the procedure used for spell induction (see Chapter 207 for further discussion).[132]

Monitoring of Other Biologic Signals

At least one data channel should be used to record the electrocardiogram, both to detect cardiac arrhythmias and to identify electrocardiographic artifacts in the EEG that might otherwise be misinterpreted as epileptiform discharges. Seizures can cause cardiac arrhythmias, which may even be fatal[59] (see Chapter 189), and primary cardiac arrhythmias can cause convulsive syncope.[74] If both EEG and electrocardiographic changes occur during LTM, their temporal relationship should be examined to determine causality.

In a patient with myoclonic jerks, recording one or more electromyographic channels from the involved muscle or muscles can document the timing of the jerks. The simultaneously recorded EEG can then be examined for antecedent spikes, which would signify cortical myoclonus. If facial or cranial muscles are involved, care must be taken that the muscle and movement artifacts produced in the EEG recordings are not misinterpreted as epileptiform discharges of cerebral origin. Accelerometers can also be used to detect limb movement.[42]

Polygraphic recording (Chapter 77) of multiple physiologic signals, including formal polysomnography with sleep staging, may be performed in conjunction with LTM. This can be especially useful in differentiating parasomnias from nocturnal seizures. Respiratory monitoring is also important during LTM

in patients who become apneic during seizures.[85] Polysomnography typically includes recording of electrooculogram, submental electromyogram, electrocardiogram, respiratory effort, air flow, blood oxygenation, expired carbon dioxide, and body or limb movements, with as few as six channels of EEG.[5] The larger number of EEG channels used for concurrent LTM enhances the detection and localization of epileptiform discharges with restricted topographic distributions.

Yield of Long-Term Monitoring

How does one assess the benefits of LTM? Many studies have attempted to do so, using a variety of approaches and definitions of benefit and yield. Comparisons between various reports are complicated by differences in the patient populations studied, the reasons for referral, the duration of the monitoring, and the monitoring techniques used.

Because one purpose of LTM is to capture seizures, one may ask how often this is accomplished. Although a single large study using ambulatory cassette EEG reported a relatively low yield of 34%,[126] most published studies report higher yields, with 50% to 96% of LTM recordings su- ccessfully capturing seizures, either epileptic or nonepi-leptic.[3,9,16,17,21,26,27,30,32,40,49,55,63,81,83,87,89,93,94,99,110,119,120,127] In one study, in which inpatient CCTV-EEG LTM had a 50% yield, routine EEG had captured seizures in only 2% of the patients.[81] Long-term monitoring is also used to record interictal EEG abnormalities. Interictal epileptiform discharges were identified by LTM in 25% to 40% of patients with normal routine EEGs in two studies.[17,87]

When the purpose of the monitoring is classification of a patients' episodes, LTM can establish a diagnosis in 50% to 95% of cases.[9,15,27,83,93] In 30% to 68% of patients, the findings during LTM may prompt revision of the previous diagnosis.[3,17,26,30,40,63,93,100,122,127] (One additional report[98] gives a much higher figure of 84%, reflecting a large number of patients thought to have a single seizure type in whom multiple seizure types were documented.) It should be noted, however, that in patients in whom LTM does not provide â€œnew information,â€ confirmation of the previous diagnosis might also be of clinical value.

Patients are referred for LTM for a variety of reasons, not just for seizure classification. Several studies have examined how often LTM fulfills its objectives by answering questions posed by the referring physician. This is accomplished in 60% to 88% of LTM recordings.[1,15,16,27,30,110,120,127]

The ultimate test of LTM is the degree to which it influences patient management and leads to improved clinical outcomes. Findings during LTM have been reported to lead to changes in treatment in 45% to 80% of cases.[1,15,17,27,63,68,127] Changes include modifications of the AED regimen and initiation of psychotherapy in patients in whom psychogenic seizures are identified. Most authors also consider epilepsy surgery to be a change in treatment resulting from LTM because surgery would not be performed without LTM. Studies that include many surgical candidates therefore tend to report high rates of treatment modification resulting from

LTM.

An improved outcome may reflect a reduction in the seizure frequency, a reduction in drug toxicity, or other factors that improve the patient's life, such as treatment directed at the causes of psychogenic seizures. Patients found to have nonepileptic events may derive benefits equal to or greater than those diagnosed with epilepsy.[81,131] Long-term monitoring has been reported to lead to improved outcomes in 30% to 74% of patients.[1,15,17,81,98,99,100,122] Reductions in seizure frequency and improvements in quality of life have been shown to persist in most patients during long-term follow-up.[100,122]

Summary and Conclusions

Technological advances have substantially improved both the quality and quantity of EEG data that can be recorded during LTM. During AEEG monitoring, which is relatively inexpensive, data can now be recorded from enough EEG channels to provide full coverage of each hemisphere. In a hospital setting, high-quality data from >100 electrodes can be acquired and correlated with CCTV data. Unassisted analysis of the huge amount of data acquired would be overwhelming, but parallel developments in computerized analysis of EEG data have permitted the online identification of suggestive EEG epochs for further analysis. Closed-circuit television recording also permits a detailed analysis of seizure semiology and confirmation that the episodes captured during LTM are the patient's typical seizures.

During LTM, the patient's EEG can be recorded throughout the 24-hour circadian cycle, increasing the probability of recording seizures and IEDs. Changes in the AED regimen, sleep deprivation, spell induction, and other manipulations can be used to increase the yield of epileptic seizures and nonepileptic events so that the desired diagnostic information can be obtained more rapidly. Recordings with depth electrodes and subdural electrode arrays, necessary for the evaluation of some patients before epilepsy surgery, can be performed only during inpatient LTM. Electrical stimulation for localization of eloquent cortical areas can also be performed in this setting.

Long-term monitoring is a valuable, and at times essential, adjunct to the diagnosis and management of patients with epilepsy.

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Chapter 93

The Epilepsy Monitoring Unit

Gregory K. Bergey

Douglas R. Nordli Jr.

Introduction

Over the last two decades, advances in electroencephalography (EEG) and video-recording technology have fueled a dramatic evolution in the sophistication and number of epilepsy monitoring units (EMUs).[6,32] This chapter focuses on the specialized utility of such units. Other chapters in these volumes deal extensively with interictal EEG (Chapter 73), ictal EEG (Chapter 74), EEG mapping (Chapter 76), computer-assisted data collection and analysis (Chapter 95), the presurgical evaluation (Chapter 169), invasive monitoring (Chapters 170 and 171), and psychogenic seizures (Chapter 207). As a result, while these topics will be mentioned in the context of the EMU, reference should be made to other chapters for more detailed descriptions.

Previous guidelines for video-EEG monitoring have been published,[8] but the most recent ones are those of the International League Against Epilepsy's (ILAE) Commission on Diagnostic Methods Subcommittee on Neurophysiology for long-term monitoring.[33] The ILAE recommendations address monitoring both within and outside (e.g., intensive care unit [ICU]) the EMU (Table 1).

Purpose of the Epilepsy Monitoring Unit: Advantages and Disadvantages

There are two main groups of patients who benefit from inpatient video-EEG monitoring: (a) those in whom the diagnosis is in question or needs to be confirmed and (b) those in whom epilepsy surgery is being considered. Epileptic seizures are episodic brief events, with each ictus typically lasting 2 minutes or less. While the history remains the most important component of the initial evaluation, there are many instances where the clinical details are ambiguous or insufficiently detailed to allow a definitive diagnosis. Patients rarely have seizures during outpatient visits or, with notable exceptions (e.g., unmedicated absence seizures), during routine EEGs. The history may be vague or uncertain because the patient has limited or no memory of the event, there were no observers, or the seizure occurred at night. Multiple types of episodes are sometimes reported, further confounding accurate diagnosis. Interictal EEGs may be normal or show only nonspecific abnormalities. Indeed, even with repeat EEGs about 30% of patients with epilepsy have normal routine EEGs. While a normal EEG does not exclude epilepsy, it also does not assist in making a diagnosis when the question of epilepsy is unresolved. Increased restrictions on administering conscious sedation have made it much more difficult to obtain routine outpatient sleep recordings, which can increase the yield of interictal abnormalities.

The EMU offers the benefits of prolonged recordings with video correlations in a controlled inpatient environment (Table 2). While the recording setup necessarily restricts a patient's activity, this limitation is outweighed by the ability to reduce or withdraw medications if needed, something that is difficult to do safely in the outpatient setting. Simultaneous video recording greatly improves artifact recognition and reduces the likelihood that rhythmic or sharply contoured artifacts are misinterpreted as â€œepileptiform,â€ something that occurs more commonly with ambulatory recordings that do not include video. In addition to analysis of specific events, longer recordings improve assessment of interictal abnormalities. Medication changes can be implemented much more rapidly in the EMU than is possible in the outpatient clinic. In addition, one can more accurately determine the effects of medication. For example, patients who have their antiepileptic drugs (AEDs) discontinued may become aware of cognitive and other side effects that they had not previously recognized as drug related. Inpatient observation also allows trained professionals to interact and assess patients during seizures. This can provide valuable information regarding the precise nature of the ictal symptomatology and localization of the discharge. Also, if the EEG is screened by trained personnel (a frequent but not universal situation), inpatient monitoring may also help in differentiating and characterizing ambiguous EEG patterns. For example, interacting with children during bursts of diffuse rhythmic slow waves or slow spike-wave discharges permits alterations in responsiveness to be determined more accurately. Finally, inpatient monitoring allows alterations in recording methodology to be made â€œon the flyâ€ depending on the EEG findings. This may be particularly helpful in suggesting the use of additional electrodes or the use of polygraphic techniques in selected patients.

Disadvantages of video-EEG monitoring include the need for hospitalization and the inherent limitations on the patient's normal behavior. Antiepileptic drug withdrawal increases the risk of generalized tonicâ€“clonic seizures and status epilepticus. Even with prolonged recording after AEDs have been withdrawn, events that occur infrequently may not be captured for analysis.

Indications for Monitoring in the Epilepsy Monitoring Unit

Diagnosis

Many seizure disorders or epileptic syndromes can be accurately diagnosed from a careful history obtained from the patient and family members who have observed the events. When seizures fail to be controlled with antiepileptic drugs, it is usually an appropriate time to reconsider the diagnosis. If additional history and routine interictal EEGs are not sufficiently helpful, inpatient video-EEG monitoring to capture typical clinical events should be considered to clarify the diagnosis. Such information can be very important as it often leads to changes in therapy.

Table 1 Recommendations Regarding the Use of the Long-term Monitoring Report of the International League Against Epilepsy's Commission on Diagnostic Methods Subcommittee on Neurophysiology

- Detection, characterization, and quantification on video-electroencephalography (EEG) of ictal events, including the appropriate activation procedures to elicit them in individual patients in whom the diagnosis of an underlying epilepsy has already been made, and when the type of seizure or syndrome is not clear
- Documentation of the electroclinical manifestations of habitual seizures including noninvasive and invasive video-EEG long-term monitoring during presurgical evaluations
- Differential diagnosis between epileptic and nonepileptic conditions, characterized by frequently and intermittently occurring behavioral changes including psychogenic nonepileptic events and sleep disorders, particularly those involving paroxysmal movement disorders
- Documentation of diurnal or circadian variation in occurrence of epileptiform paroxysms, in conjunction with pharmacologic interventions and/or of the effect of these interventions on diurnal or circadian behavioral changes
- Documentation of specific patterns in the occurrence of epileptiform paroxysms during sleep and/or of disruption of sleep architecture in so-called â€œcognitive epilepsyâ€ cases in the pediatric population.
- Monitoring in the intensive care unit (ICU) for the effectiveness of treatment of status epilepticus and for the identification of subclinical seizures and subclinical status epilepticus,

conditions that have been shown to be more frequent than usually thought in the ICU

From Velis D, Plouin P, Gotman J, et al. Recommendations regarding the requirements and applications for long-term recordings in epilepsy. *Epilepsia.* 2007;48(2):379â€“384.

Table 2 Epilepsy Monitoring Unit

Benefits

- Offers prolonged recordings with various recording arrays
- Provides video-electroencephalographic correlation of events
- Allows for antiepileptic drug withdrawal in controlled environment
- Assesses patient directly during events
- Assists in differentiation between epileptic and nonepileptic events
- Assists in classification of seizure type
- Helps with presurgical evaluations
- Has less artifact than ambulatory recordings
- Offers better identification of artifacts with video correlation

Disadvantages

- Requires hospitalization
- Limits patient activity
- Carries an increased risk of generalized seizures and status epilepticus
- May not capture infrequent events

Table 3 Seizures That May Be Difficult to Diagnose or Classify

- Absence seizures with automatisms vs. complex partial seizures
- Absence seizures vs. complex partial seizures with motionless stare
- Complex partial seizures without aura
- Frontal lobe complex partial seizures
- Juvenile myoclonic epilepsy and other myoclonic seizures
- Nocturnal seizures
- Seizures in infants and neonates
- Convulsive psychogenic seizures
- Nonconvulsive psychogenic seizures

Examples of seizures and syndromes that can be diagnostically challenging are listed in Table 3. Diagnosing frontal lobe seizures can be particularly difficult, as clinical manifestations often first suggest nonepileptic, especially psychogenic, seizures.[17,36] The nighttime occurrence of many frontal lobe seizures often further confounds the diagnosis as nocturnal paroxysmal events are difficult to characterize fully by history alone. Complex partial seizures are sometimes confused with absence seizures if they manifest as brief behavioral arrests with a paucity of automatisms and a short postictal period. Video-EEG monitoring usually makes this distinction readily apparent. Elderly patients with episodic events can also present diagnostic difficulty as alterations in consciousness can have multiple potential causes in this age group. Furthermore, descriptions of clinical semiology by elderly patients and their spouses are often incomplete or confusing. In one series,[22] video-EEG monitoring provided a definitive diagnosis in over 75% of a group of 94 elderly patients.

Classification

Accurate classification of the epileptic syndrome can be critical to effective management. For example, it is important to recognize that onset of generalized tonicâ€"clonic seizures (GTCSs) in adolescence can be a manifestation of juvenile myoclonic epilepsy (JME)[7] (Chapter 244). Myoclonic jerks are often underreported by teenagers and young adults with JME. Video-EEG monitoring, however, will frequently document the specific different seizure types (GTCS, myo- clonic, absence) that can occur in this syndrome. Diagnosis of JME has important treatment implications. Although seizures are readily controlled in 80% of patients, lifelong therapy is usually required even if the EEG normalizes, as sustained remission is uncommon in JME. Furthermore, failure

to recognize JME can lead to use of AEDs that exacerbate seizures.

Psychogenic Seizures

The possibility of psychogenic seizures (Chapter 207) is an important indication for inpatient video-EEG monitoring. Patients with psychogenic seizures have often been treated unsuccessfully with multiple AEDs, sometimes for years. The EMU environment allows rapid withdrawal of AEDs and detailed analysis of the clinical events, including correlation with sleepâ€"wake states. This can be important as some patients report that their seizures occur during the night. Psychogenic seizures can occur at night, but they do not arise out of sleep. Any event arising out of sleep has a physiologic basis. It may be nonepileptic, but it will not be psychogenic. Video-EEG monitoring assists in making this determination. Arguably, the diagnosis of psychogenic seizures should not be made without video-EEG confirmation, because the implications for treatment are so very important. Frontal lobe neocortical seizures may have few if any recognizable ictal scalp EEG changes at onset. If no video record is available for review, they may therefore be misdiagnosed as psychogenic seizures. Reviewing the clinical manifestations of frontal lobe seizures reveals a stereotyped semiology that supports the diagnosis even if the EEG is not diagnostic. It must also be remembered that 10% to 40% of patients with psychogenic seizures also have epileptic seizures or epileptiform discharges on EEG.[19] Psychogenic seizures often occur early during the EMU stay, in contrast to epileptic seizures.[24] When the diagnosis of psychogenic seizures is established early in the monitoring stay, additional recording, off AEDs, is advantageous to determine if epileptic seizures coexist. Psychogenic seizures and other nonepileptic events are common in most EMUs, typically accounting for 20% to 30% of admissions.[2] Children in particular can have a variety of nonepileptic episodic events.[23] The video component is usually extremely helpful in allowing an accurate diagnosis to be made in children.

Sleep Disorders

Some sleep disorders include episodic events that can be confused with epilepsy.[21] If the EMU admission suggests a sleep disorder, then a formal sleep assessment with polysomnography should be performed (Chapter 276). Polysomnography cannot substitute for video-EEG monitoring, as the typical very limited number of scalp electrodes used for sleep staging is not sufficient in most instances to diagnose seizure disorders, and many false negatives occur. If sleep studies suggest a possible seizure disorder, then an EMU evaluation is necessary to evaluate this effectively.

Epilepsy Surgery

Candidates for epilepsy surgery require EMU evaluations. Multiple seizures must be recorded to localize the area of seizure onset reliably and to determine if seizures arise from more than one site. While interictal recordings provide useful supportive data (e.g., demonstration of a prominent unilateral anterior temporal spike focus), reliance on interictal recordings alone can be misleading; ictal recordings are necessary to make decisions relevant to epilepsy surgery. Withdrawal of AEDs is often required; seizures may not occur until several days after AED dosage has been reduced or stopped. Patients in whom ictal recordings fail to provide definitive localization, or patients with seizures arising in or near eloquent areas, will usually require placement of intracranial electrodes (depth arrays, subdural strips, subdural grids) (Chapters 170 and 171). Patients with intracranial electrodes, particularly those with subdural strips and grids, must be supervised closely to minimize infection, avoid injury, and preserve recording integrity.

Most patients being considered for treatment with the vagus nerve stimulator (VNS) will have had EMU evaluations to assess their suitability for resective surgery. Such monitoring is also important before VNS implantation to determine seizure type and to confirm that the medically refractory seizures are epileptic in origin, not nonepileptic events.

Components of the Epilepsy Monitoring Unit

Hardware and Software

The development of video technology and its adaptation to medical uses have been extremely important for epileptology. Long-term monitoring was first performed using cameras with mirrors to record the patient and the paper EEG record. Video cassette capability was a major technical innovation, as it allowed the EEG and video image to be stored on the same tape for split-screen viewing. Tapes still needed to be changed every 2 to 6 hours if continuous recording was to be maintained. The development of digital video images was a further important step in the evolution of EMUs. Early on, its main limitation was mainly that of storage: A typical day of 30 channels of EEG recording (200-Hz sampling) requires 1 gigabyte (GB) of storage capability. The addition of digital storage of video adds approximately 30 GB of storage per day. At one time this was a major consideration, and temporary storage on hard drives needed to be dumped routinely every 24 hours if continuous recording was to be maintained.

Today, both video and EEG are easily stored digitally and synchronized. EEG activity is typically sampled at 200 to 1000 Hz; higher sampling rates allow for more accurate analysis of higher frequency signals. Sampling should be at the Nyquist frequency, two times the signal frequency, to avoid aliasing and distortion or misrepresentation of the signal. A number of manufacturers provide equipment specifically designed with these capabilities. No longer do video tapes need to be scanned; digital video allows for rapid review and accession of selected time periods. While storage capabilities on computer servers now are in the terabyte range, the amount needed to store EEG is directly proportional to the number of channels and the sampling frequency. Although video storage requirements are still much greater than those for EEG, the capabilities available today allow for many days of continuous recording. Records are typically edited to reduce these requirements. Storage of 7 days of continuous 32-channel EEG (200-Hz sampling) from a single patient would typically require about 7 GB of storage capacity; storage of continuous EEG (without video) from ~100 channels sampled at 1,000 Hz (e.g., intracranial recordings) requires over 100 GB storage. A week of unedited video would require about 200 GB. Therefore, storage of unedited recordings (even EEG alone) requires transfer to external storage devices (e.g., external hard drives). The typical practice in most EMUs is to edit both the EEG and video portions for storage on a single DVD.

The development of infrared low-light cameras has allowed high-resolution black and white video images to be obtained during the night. During the day, color video is obtained routinely using the same camera. The â€œtwilightâ€ period can still be the most challenging. If the camera is still in the color format, resolution of the video image can be severely compromised. This can become an issue if hospital guidelines require a light (e.g., a night light) to be on continuously in EMU patients' rooms, because this may prevent high-resolution nocturnal recordings. If lighting is used in patients' rooms, it should be of very low intensity and located so that it does not prevent the cameras from switching to the infrared mode at night. If this cannot be done, then lights should be extinguished at night.

Current cameras are unobtrusive and typically mounted in small ceiling domes so that camera movement is not apparent to the patient. This is in contrast to early setups, where a large camera hung from the ceiling and the patient was always aware of the panning and refocusing adjustments being made by staff. Attempts at developing cameras that can automatically â€œfollowâ€ patients as they move from the bed to chair or around the room are not yet reliable. Therefore, unless the patient is confined to bed (see Safety in the Monitoring Unit), it is necessary for staff to monitor patient movements and move the camera as needed. Autofocus capability is now routine, but manual zoom is still necessary if a specific region of the body (e.g., face) is of interest during the seizure. Multiple cameras can allow for separate but continuous monitoring of the whole body and face (or selected regions).

Amplifiers are designed to record broadband activity and are located off the head. In addition to the specific recording needs, amplifiers need to be able to record during cortical stimulation when stimuli can produce not only artifact, but also changes in capacitance. The ideal amplifier for EMU use is one where the recording can be restored rapidly to baseline after stimulation.

Early video-EEG by some manufacturers did utilize telemetry, but at present hard-wired recordings offer the best quality. Hard-wired recordings are particularly important with multichannel (often >100 channel) recordings using intracranial arrays. While modern equipment no longer makes it necessary for rooms to be electrically shielded, sources of 50- or 60-Hz (depending on the country) interference may be problematic on occasion and need to be removed. The cables for connection remain a vulnerable component as a source of artifact or basis for failure.

Early EMU video-EEG recording often used modified hardware that increased expense. Now off-the-shelf components can generally be used, allowing for easier upgrades and replacements. Different manufacturers use different software for processing and storing video and EEG data; no standard code exists. Manufacturers differ in their willingness to provide source code. Some provide downloadable software that permits review of recordings. There are also software packages now available that allow for review of EEG data from multiple vendors.

Video-EEG recording requires appropriate patient consent. The consent form typically includes statements that give permission to show videos at conferences and for educational purposes. If videos are to be used for enduring materials, there should be specific language in the consent form explaining this. Digitized EEG recordings used for research or study purposes need to be stored in an approved Health Insurance Portability and Accountability Act (HIPAA)â€“compliant data system, typically with all identifying headers removed.

Epilepsy Monitoring Unit Staffing

Patients may not know when they have experienced a seizure. While spike and seizure detection software and review of periodic epochs can assist in identifying unreported events, there is a definite benefit in having trained personnel observing the patient video monitors in real time. This not only allows for more accurate identification of clinical events, but it also permits assessment of the patient during the seizure and whether the patient is at risk for injury. This is particularly important for patients with intracranial electrodes. Qualified EEG technologists are essential to ensure that the recording arrays are properly placed and maintained. Recognition of artifacts and electrode problems, as well as simple daily maintenance, can often be done by other, less specialized personnel.

The Patient's Room

Because most patients admitted to the EMU are not acutely ill, patient rooms should be designed to be pleasant and comfortable. In-room accommodations should include a bed for a family member or friend. This not only makes a patient's stay more pleasant, but it can also greatly assist in seizure identification and minimizing risk of patient injury. The design of the room and bathroom should, in as far as possible, reduce the number of objects with sharp edges that could injure a falling patient. Unfortunately, carpeted floors compromise infection control and should not be used; padded tile is a suitable alternative. Cable TV and DVD players make a patient's stay much more enjoyable. As already mentioned, development of excellent infrared cameras has made it possible for the patient to sleep in low ambient light without compromising recordings.

Methods for Augmenting Seizure Frequency

Some patients, such as those with frontal lobe seizures or atonic seizures, may have sufficient seizures while on medication that an adequate sample of attacks can be readily obtained during a brief stay without AED withdrawal. This is especially true for young children. Other patients, however, although they have medically intractable epilepsy, might have only several seizures per month. They will typically require reduction of AEDs to obtain an adequate number of seizures for diagnosis, analysis, or presurgical evaluation. In years past, EMU stays of several weeks were not uncommon. Now, for a variety of reasons, which include the expense of monitoring and insurance reimbursement, typical EMU stays are much shorter, often less than a week. The requirement for obtaining an adequate number of seizures for analysis remains, however. If the question is one of diagnosis (e.g., determining if seizures are primary generalized or partial onset), then relatively few seizures may be necessary. Presurgical evaluations typically require a number of seizures, and even more if multifocal onsets are a concern. A comprehensive analysis concluded that recording five stereotyped seizures was presumptive indication of a single seizure focus (confidence interval [CI] 95%).[3] As already mentioned, evaluation of psychogenic seizures should include sufficient monitoring after AEDs have been discontinued to determine if there is a concomitant epileptogenic potential.

Antiepileptic Drug Withdrawal

Withdrawal of AEDs results in increased seizure frequency, but the time course of this effect is unpredictable. In patients with partial seizures, not only does the frequency of partial seizures increase, but also the frequency of secondarily GTCSs increases. This is particularly the case if AEDs need to be withdrawn completely. It is more common than not for patients with intractable partial epilepsy on AEDs to have good control of their GTCSs while continuing to have partial seizures. In the EMU, AED withdrawal may result in recurrence of GTCSs. Sometimes AED reduction without total withdrawal may be adequate to prevent GTCS. In diagnostic and presurgical evaluations, GTCSs are often not needed, but the need to obtain

multiple partial seizures for analysis within a reasonable time period may necessitate total AED withdrawal. With AED reduction may come the appreciation that drugs thought to have little benefit on seizure reduction were actually more efficacious (albeit not controlling the seizures) than previously thought. It may be advantageous to start reducing the dosage of drugs with long half-lives (e.g., phenobarbital, zonisamide) before admission, if this can be done safely, because it takes five half-lives to reach a new steady state.

Seizures may cluster.[12,13] Multiple absence and neocortical partial seizures are usually well tolerated, but recurrent mesial temporal regionâ€"onset seizures or multiple GTCSs in a given day may produce cognitive changes that can take days or even weeks to resolve. AED withdrawal carries the risk of status epilepticus, and benzodiazepines should be used appropriately, especially after several GTCSs, to minimize this risk.

An important question is, are the seizures that occur with AED withdrawal similar to those that occur with treatment? The detailed time-frequency patterns of seizure onset from a given seizure focus are not only consistent from seizure to seizure, but also do not change with AED withdrawal.[14] In addition, analyses from intracranial recordings suggest that although AED withdrawal increases the number of complex partial seizures and GTCSs, the duration of the complex partial seizures does not increase.[1,30] This is consistent with the idea that AEDs reduce seizure frequency and secondary generalization, but do not necessarily influence intrinsic seizure dynamics once the seizures have begun. For the most part, seizures that occur with AED withdrawal are similar in site of origin to those that occur on full AED regimens. However, the possibility that additional foci may become active with AED withdrawal should be considered, particularly if multifocal events only occur late in the monitoring period, after significant AED reduction.

Sleep Deprivation

Sleep deprivation is commonly used to increase the likelihood of seizure occurrence (Chapter 94). Interestingly, however, Malow et al.[20] were unable to demonstrate any significant increase in seizure frequency in EMU patients who were sleep deprived compared to those who were allowed to maintain their normal sleep patterns.

Scalp Recording Arrays: Additional Electrodes

The usual 10 to 20 recording array may be sufficient for determining if events are epileptic or nonepileptic events. However, additional electrodes, especially over the frontal, parasagittal, or anterior temporal regions, may be useful in improving seizure detection and localization. Several reports[15,31] have suggested that sphenoidal electrodes improve detection of mesial-onset temporal lobe seizures by 5% to 10% compared to routine scalp arrays. Others, however, have found that sphenoidal electrodes add little when compared to the yield following addition of anterior cheek electrodes.[4,18] Routine use of sphenoidal electrodes, which involves some discomfort, is not necessary in most patients.

Detecting Seizures

Some patients are aware when their seizure occurs and can reliably use the event marker. Many patients, however, may not recognize the occurrence of some or all of their seizures. The presence of friends or family in the room, and staff watching monitors in the EMU control room, can also increase the reliability of seizure detection. Subclinical seizures may still go undetected. These observations do not take into account the possibility that recording arrays may be suboptimal, or that some types of seizures (e.g., frontal neocortical, some mesial temporal) may have a paucity of scalp findings at seizure initiation.

Spike detection and seizure detection software can be linked either to record marking or alarms, or both.[10,27] When seizure detectors are linked to alarms, it is important to have the alarm threshold sufficiently high so that multiple false alarms do not occur.[25] The ideal seizure detection algorithm should be sensitive and specific, because false detections decrease utilization. The seizure detection algorithm should be tailored to the onset characteristics of seizures in individual patients. This is important because the seizure initiation pattern from a given focus in a given patient is stereotyped from seizure to seizure.[14] While detection is much more easily and reliably applied to intracranial recordings[11] where artifacts are minimized, detection algorithms can be tuned for scalp ictal recordings so as to have relatively few false alarms.[27]

Restarting Treatment

After gathering sufficient information for diagnosis or presurgical evaluation, EMU patients, most of whom have intractable epilepsy, need to be stabilized before discharge. One result of the evaluation may be a recommendation that the AED regimen be changed, and implementation of this can be started at the time of discharge.

Not all AEDs can be initiated rapidly. If carbamazepine has been totally withdrawn, then hepatic autoinduction may be reduced or reversed. This can occur within a week, so reinstitution may need to begin at dosages lower than previous maintenance dosages.[28] If the patient has previously been on lamotrigine for a number of months, reintroduction after EMU withdrawal does not require repeating the initial slow titration. Maintenance doses can be started without increased risk of severe hypersensitivity reactions (e.g., toxic epidermal necrolysis, Stevens Johnson Syndrome). Oral loading with phenytoin or valproate is possible. Bioequivalency studies of parenteral levetiracetam included a single dose of 1,500 mg given orally.[26] This demonstrated that a 1,500-mg oral dose reaches a C_{max} in 45 minutes. Studies of loading patients with oral levetira- cetam after EMU stays have shown this to be a well-tolerated approach.[16] Pregabalin can be started at maintenance doses and will reach a steady state in 30 to 42 hours. Reinitiation of topiramate, oxcarbazepine, zonisamide, and phenobarbital may need to be done more slowly and individualized according to patient tolerance. Patients should usually be advised to reduce their activities for the first few days after discharge to minimize risk of injury.

Safety in the Epilepsy Monitoring Unit

Patients being monitoring in the EMU are often at increased risk for falls, especially as their medications are reduced. Each patient should be assessed for this and treatment individualized. Patients with atonic, tonic, or frequent tonicâ€“clonic seizures should be closely attended when out of bed. When the patient is using the bathroom, the approach requires a compromise between appropriate privacy and the individual patient's seizure pattern. Bed rails should be up and padded when patients are in bed. As a general rule, patients should not be restrained. In rare instances, a vest may be used for defined periods; arms and legs should not be restrained, as this increases the risk of injury during a seizure. In limited and specific situations, protective mittens may reduce or prevent

removal or disruption of electrodes (particularly important with intracranial recordings). Staffing should be sufficient so that the majority of clinical seizures are promptly recognized. Many patients are confused postictally, and this is therefore a time when they may wander, attempt to remove electrodes, and are generally at increased risk of injury.

Vertebral compression fractures[34] and shoulder dislo-cations[5] are uncommon but well-recognized potential sequelae of GTCSs. Bone mineral density loss secondary to enzyme-inducing AEDs or other medications (e.g., corticosteroids) increase the risk of compression fractures. While close attention to preventing falls can reduce the risk of fractures of long bones, vertebral compression fractures and shoulder dislocations are a result of the muscular activity caused by convulsive seizures and cannot be prevented by rail padding or even constant nursing attention.

Summary and Conclusions

The utility of EMUs for evaluating patients whose seizures persist despite adequate medical therapy is well established.[9,33] In most patients, video data add considerably to merely obtaining prolonged EEG recordings.[35] In a recent analysis of 213 admissions, 87.8% of patients received a definitive diagnosis, with epilepsy diagnosed in 73.3% and excluded in 21.6%.[29] The EMU evaluation resulted in a change in treatment in 79% of patients. Patients who had only nonepileptic seizures had been treated a median of 9 years before admission for evaluation. This report underscores the fact that delays in accurate diagnosis may result in many years of inappropriate therapy. Patients who have seizures that fail to respond to AED therapy should be considered for EMU monitoring if the diagnosis is not clearly established, or if presurgical evaluation is a consideration. Advances in monitoring technology have contributed greatly to the increase in presurgical evaluations. The utility and benefits of long-term monitoring can improve accuracy of diagnosis, provide for more specific therapy, and avoid the pitfalls of misdiagnosis.

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Chapter 94

Drug Withdrawal and Other Activating Techniques

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Introduction

Activation in epilepsy refers to the evocation of behavioral or electroencephalographic (EEG) manifestations of epileptic seizures in an established epileptic substrate. In clinical practice, activation is useful if it evokes either behavioral changes or epileptiform EEG abnormalities. In addition, because certain kinds of activation are associated with specific kinds of seizures, successful activation alone can have diagnostic value even in the absence of EEG information. In some instances, identifying an activating stimulus is of therapeutic value to the patient, who can then avoid contact with the stimulus.

Activation is also a valuable tool for investigating human epilepsy. Functional neuroimaging of seizures using positron emission tomography or echoplanar magnetic resonance imaging virtually requires that seizures be activated during the procedure. In the epilepsy monitoring unit, activation can result in tremendous savings in professional and technical resources by facilitating an accurate diagnosis and shortening the length of hospital stay. In that setting, where pseudoseizure is often part of the differential diagnosis, the definition of activation is extended to include the activation of psychogenic nonepileptic seizures (PNES). The following is a review of activation techniques commonly used during long-term epilepsy monitoring.

Pharmacologic Techniques of Activation

Activation by Discontinuation of Antiepileptic Drugs

Studies in the literature concerning antiepileptic drug (AED) withdrawal generally fall into three categories, according to the rate and the purpose of withdrawal: (a) withdrawal during a period of months in patients whose seizures have been well controlled[2]; (b) withdrawal during a number of days to weeks as one AED is switched to another[12]; and (c) abrupt discontinuation to increase the likelihood of recording EEG discharges during long-term monitoring. Because the consequences of AED withdrawal may vary in these different clinical situations, this discussion is limited to rapid AED withdrawal during long-term monitoring.

Activation of Interictal Epileptiform Discharges

Patients with epilepsy often do not have spontaneous interictal epileptiform discharges (IEDs) on their routine EEG recordings. Such discharges are not present on the initial EEG recordings of about 40% of patients with newly diagnosed epilepsy.[52] Approximately 10% of candidates for epilepsy surgery do not have IEDs, even with long-term monitoring.[7] The possibility of suppression of IEDs by AEDs has often been raised.[80] Valproate consistently suppresses generalized spike-wave discharges.[29] Long-term treatment with carbamazepine seems to be associated with less frequent epileptiform discharges.[60] Intravenous phenytoin also can suppress generalized IEDs, but the effect is only transient, lasting for 10 to 20 minutes.[54] A single intramuscular dose of clonazepam has been shown in children to decrease significantly both generalized and focal epileptiform discharges.[8] Selective suppression of some types of epileptiform discharges by AEDs has also been observed. Lamotrigine selectively suppresses long episodes of epileptiform discharges, but not short episodes of discharges.[16] The effect of AEDs on cortical excitability has been studied recently in healthy volunteers by using transcranial magnetic stimulation.[39] The threshold for activating the motor cortex was increased with increasing total and free serum concentrations of carbamazepine and lamotrigine, although acute drug withdrawal decreased the threshold in only a small proportion of patients.

Barbiturate withdrawal in addicted persons who were nonepileptic reportedly has been followed by paroxysmal EEG activities.[86] However, according to currently accepted terminology, many of those reported EEG activities are nonepileptiform. Ludwig and Ajmone Marsan[44] observed that spikes developed after abrupt drug withdrawal in 10 of 13 patients who had had no EEG discharges while taking AEDs. A discrete epileptiform focus developed after drug withdrawal in 57% of all their patients. However, Gotman and Marciani[27] found no correlation between serum AED concentrations and spiking rate after tapering the dose. They showed that spiking activity increased after, and not before, seizure occurrence, and that the increase could last several days. Their findings raised the possibility that increased spike discharges previously attributed to drug withdrawal may have actually been a postictal phenomenon. Their method of computerized detection of spike discharges allowed them to quantitate IEDs continuously during several days. The application of this technology to a kindling model of epilepsy in cats yielded similar findings. Moreover, an earlier study showed that carbamazepine withdrawal in primate models of partial epilepsy failed to intensify spike discharges.[10] Epileptiform discharges that occur after seizure episodes may be more widespread in distribution or contralateral to the focus of seizure onset.[26] Localization of the surgical focus must not rely solely on these discharges.

Activation of Epileptic Seizures

Numerous studies have investigated the effect of discontinuing AEDs on seizure characteristics. The common experience among investigators is that fairly abrupt discontinuation of an AED does increase seizure frequency. However, disagreements exist about the factors most responsible for the increase. Some investigators observed that increases occurred early as AED dosage[50] or concentration declined, rather than when the dose became minimal,[87] and the exacerbation of seizure frequency

was self-limited. It did not always persist toward the end of the tapering process. Hence, the increase in seizures has been attributed to a transient â€œrebound phenomenonâ€ similar to that seen in abstinence syndromes of drug addiction,[18,32] rather than to a loss of therapeutic effect. In a study of patients withdrawing from phenobarbital, Theodore et al.[75] also observed that seizure rates were highest when serum concentrations passed below 15 Âµg/mL, but not when concentrations were very low.

Other studies[5,51] have concluded that loss of therapeutic effect, and not rebound phenomenon, is the basis for increased seizures during AED withdrawal. They found that seizure frequency increased when serum drug concentrations became subtherapeutic and not as they were falling from their baseline values. However, it is difficult to compare these studies critically for the following reasons: (a) drug regimens were not the same between studies, (b) the order or rate of withdrawal was not uniform, (c) serum drug concentrations were not determined using identical schedules, and (d) definitions of withdrawal and baseline periods were either not reported or were dissimilar. Furthermore, the contribution of falling serum levels to seizure exacerbation cannot be completely discounted, because the observation periods in patients undergoing video-EEG monitoring are typically limited.

Despite the difficulty in attributing seizure exacerbation during withdrawal to rebound phenomenon, abrupt discontinuation of barbiturates[18] and benzodiazepines[32] is unequivocally known to produce an abstinence syndrome, with withdrawal seizures occurring even in nonepileptic persons. The seizures develop only within the duration of the abstinence syndrome. They almost always are generalized convulsive episodes without focal onset. Animal studies suggest that these seizures are subcortical in origin.[17] Hence, there is a theoretical possibility of nonlocalizing rebound seizures confounding the identification of the onset of seizures recorded during long-term monitoring. However, rebound seizures have been reported only in a setting of acute withdrawal from prolonged exposure to very high doses of barbiturates and benzodiazepines. Most cases involved short-acting barbiturates (e.g., secobarbital and pentobarbital) that are not used for chronic treatment of epilepsy. In patients with epilepsy who are taking clinically appropriate doses, the long half-life of phenobarbital probably prevents acute abstinence syndrome and rebound seizures from developing. In fact, seizures may not increase until several weeks after phenobarbital is discontinued,[75] whereas rebound seizures in persons addicted to barbiturates occur a few days after medication withdrawal.[18]

Concern has been raised about the possibility that AED withdrawal may precipitate seizures that are new and not typical of habitual or baseline seizures. However, the clinical and EEG onset characteristics of seizures following AED withdrawal are not substantially different from those of baseline seizures.[88] AED withdrawal does not affect seizure onset, although it does increase seizure frequency and duration and the chance of secondary generalization. Therefore, seizures precipitated by AED withdrawal are generally reliable for localization for epilepsy surgery, providing that their onset characteristics are verified to be identical to those of habitual seizures. Nonetheless, previously unrecognized seizure foci may appear after AED withdrawal. Spencer et al.[73] evaluated the video and depth electrode recordings of 71 baseline and 89 withdrawal seizures in 18 patients. During AED withdrawal, four patients had seizures with EEG or clinical features that were not typical of habitual seizures. One of these four patients had a poor surgical outcome despite the fact that the habitual seizures during baseline originated from a single focus. The authors warned that new seizure foci unmasked by drug withdrawal may be sources of recurrent seizures after surgery. In contrast, Engel and Crandall[14] reported a patient who did well after right temporal lobectomy despite clinically different seizures developing from the contralateral side during AED withdrawal.

The potential for withdrawal seizures appearing to be falsely localizing was assessed further by Marciani and Gotman[49] in 14 surgical candidates. The majority had bilateral independent foci on baseline scalp and sphenoidal EEG. Only one patient had a seizure that was unlike habitual seizures, and it arose from an independent focus. This particular seizure may not have resulted from AED withdrawal, because it occurred before the AED dose was substantially reduced. This observation was corroborated later by Marks et al.,[51] who found that most of the notably different seizures in their patients actually occurred outside the withdrawal period.

Nearly half of all patients undergoing AED withdrawal during long-term monitoring experience generalized convulsive seizures.[50] These seizures begin clinically and electrographically as partial seizures that are no different from the patients' habitual seizures.[49] The duration of either partial or secondarily generalized seizures is usually unaffected by AED dose reduction.[70,74] Antiepileptic drug withdrawal does not alter the pattern of ictal discharges at the onset of these seizures, nor does it hasten spread to the contralateral hemisphere.

The preceding evidence indicates that, with rare exceptions, seizures recorded during AED withdrawal are reliable for localization of the ictal focus. Nonetheless, regardless of the status of AED medication and the number of foci detected, recorded seizures should always be verified with the patient and with witnesses to ensure that they are the same as the patient's habitual and disabling seizures. If there is evidence of more than one ictal focus, further inquiry should be made to determine which seizures are primarily responsible for the patient's disability. Constant vigilance is needed so that occult seizure foci are not overlooked. In patients with multiple seizure foci, clusters of seizures precipitated by drug withdrawal may arise from only one focus. Haut et al.[30] initially reported that in patients with bilateral seizure foci, seizures that occur within 8 hours of each other are more likely to arise from the same side than seizures that occur more than 8 hours apart. However, their subsequent study demonstrated that mean interseizure intervals were not significantly different for concordant and discordant seizures.[31] The discovery of multiple ictal foci does not preclude surgery if it can be established that habitual seizures originate from one surgically resectable focus.[14,71] The identification of the predominant focus does not appear to be affected by seizure clustering.[31]

The profile of AED withdrawal seizures derived from the literature is based mainly on collective experience with intractable partial epilepsy. Therefore, the information obtained may not be applicable to patients with primary generalized seizures or other specific epilepsy syndromes. The effect of AED withdrawal on seizure types other than partial seizure disorders needs to be studied.

Potential Complications of Antiepileptic Drug Withdrawal and Methods of Prevention

Withdrawal of AEDs can result in major complications, some of which are life threatening. Of patients undergoing AED withdrawal, about half experience generalized convulsionsâ€"many of whom have never had convulsive seizures before withdrawal. Furthermore, seizures exacerbated by AED withdrawal may lead to seizure clustering in 50% of patients[19,66,87] and to status epilepticus in 3%.[61] The risk factors for seizure clustering are history of seizure clustering at home, mesial temporal sclerosis documented with magnetic resonance imaging, and more than one seizure onset zone.[31] The rate of AED withdrawal and the location of the EEG ictal onset are not risk factors for seizure clustering in the epilepsy monitoring unit.

It should be noted that even isolated seizure episodes can result in falls that cause fractures, joint dislocations, and external or internal soft tissue injuries. The elderly are especially susceptible to compression fractures of the vertebrae.[47] They also may be more vulnerable to the cardiac and respiratory effects of convulsive seizures.

Many of the potential complications of AED withdrawal can be anticipated and prevented if patients are under continuous observation by experienced staff. Patient areas should be designed to minimize the risk for injury from falls or unrestrained postictal behavior. Patients should be accompanied when walking. They should be attended to after every seizure. The time of occurrence and the intensity of each seizure should be noted. When seizures are unacceptably prolonged or increasingly frequent, AED treatment should be considered. Theodore et al.[74] observed that generalized tonicâ€"clonic seizures that stop spontaneously do so within 2 minutes. They advocate the initiation of intravenous AEDs when generalized tonicâ€"clonic seizures last longer than 2 minutes. As a general rule, the authors of this chapter administer an oral dose of AED when two or more generalized tonicâ€"clonic seizures occur within 12 hours. When they occur within 2 hours, either an oral[78,79] or intravenous AED is given at a dose sufficient to achieve the desired serum concentration as promptly and as safely as possible. (As part of the protocol, intravenous access is established and maintained with a heparin lock when the patient is admitted.) The AED used in most instances is preferentially a drug that is being withdrawn. However, if intravenous administration is indicated, phenytoin is generally used, unless immediate cessation of prolonged seizures requires intravenous benzodiazepines. For the treatment of seizure clusters, sublingual lor-azepam in adults[47] or rectal diazepam in children[42] may be used.

To manage life-threatening complications of AED withdrawal, medical staff certified in cardiorespiratory resuscitation must be readily available. The monitoring laboratory must be equipped with instruments and medications for resuscitation. Benzodiazepines and short-acting barbiturates should be withdrawn cautiously, particularly if they are taken at a high dose because of the development of tolerance. Seizures and other symptoms of withdrawal may be particularly severe.[18,72] A state of agitation and dysphoria can follow carbamazepine withdrawal.[11] In our experience, temporary resumption of carbamazepine or the use of an oral benzodiazepine alleviates the symptoms.

If patients must be restricted to bed, complications of prolonged inactivity can be avoided by having them exercise in a recumbent position using a bicycle attached to the bed frame. The risk for major complications generally can be kept below 1% if the above safety measures are used.[47,50]

Procedure for Withdrawing Antiepileptic Drugs for Long-term Monitoring

As mentioned above, the rate and order of AED withdrawal in published studies vary widely. In most instances, the schedule of withdrawal differs according to the clinical judgment of the treating physicians. The approach to AED withdrawal can be individualized to achieve the goal of recording seizures promptly without undue risks for injury. Sometimes, medications can be reduced or discontinued on the day before admission if they unequivocally have had no effect on seizure frequency or if serum concentrations have been clinically negligible. When there is concern about the potential for injury during unattended seizures, at least one concurrent AED can be maintained or drug tapering deferred until after admission.

After admission, all AEDs can be tapered simultaneously by reducing one fourth to one third of the maintenance dose every day. The reason for tapering all AEDs at the same time is that peak activation of seizures can be delayed for weeks when concomitant AEDs are maintained.[5] The only AED that the authors usually discontinue abruptly is valproate. Clinical studies have shown that the pharmacologic effect of valproate persists beyond its complete elimination from the serum.[29,63] Because of the possibility of platelet dysfunction associated with valproate use,[41] it is generally preferable that it be withdrawn before epilepsy surgery is performed.

In some situations, only part of the AED regimen needs to be tapered, or a slower schedule than that mentioned above can be followed. This more cautious approach is warranted when the past history suggests that activation of status epilepticus is highly probable or when the risk for convulsion-related complications is unacceptable. Antiepileptic drugs should not be withdrawn if the patient is already experiencing daily seizures at the time of admission.

Activation with Parenteral Drugs

Before the advent of long-term monitoring, it was not feasible to record adequate amounts of spontaneous ictal and interictal activities for localizing surgical foci. Attempts were made to activate ictal and interictal discharges within a short duration of EEG recording by giving intravenous drugs such as pentylenetetrazol,[60] methohexital,[46] or megimide.[64] However, a retrospective evaluation of 133 patients with depth EEG recordings showed that only 60% of the pharmacologically induced seizures were localized to the same foci as spontaneous seizures. Moreover, resection of the pharmacologically induced seizure foci was associated with a risk for failure twice that associated with resection of spontaneous seizure foci. Thus, pharmacologic activation is not used routinely.

Other Activation Techniques

Sleep Deprivation

According to the literature review by Ellingson et al.,[13] sleep deprivation is effective in activating IEDs in persons with a clinical history of epilepsy. After sleep deprivation, interictal discharges developed in as many as 30% to 70% of those without discharges on the baseline EEG. King et al.[37] evaluated the yields of initial EEG and repeat sleep-deprived EEG in patients with newly diagnosed generalized epilepsy or partial epilepsy. Initial EEG documented IEDs in 68% of generalized epilepsy patients and 44% of partial epilepsy patients. Repeat EEG following sleep deprivation in those with a negative initial EEG detected interictal discharges in 75% of generalized epilepsy patients and 32% of partial epilepsy patients.

The yield of sleep-deprived EEG is higher than the yield of only repeating the EEG.[56,62] Roupakiotis et al.[62] also demonstrated that sleep deprivation is superior to sedation in enhancing detection of interictal discharges. Moreover, activation of discharges is not contingent on the occurrence of sleep during recording. Following sleep deprivation, interictal discharges appear even during awake recordings.[23,38,56,62,68,81] Therefore, sleep deprivation appears to have an inherent, but unexplained, effect on enhancing IEDs.

The benefit of sleep deprivation has also been observed in children,[6] but at least one study cast doubts on the value of sleep-deprived EEG in children. Gilbert et al.[25] reported that the odds of detecting IEDs are not different for sleep-deprived children, partially sleep-deprived children, and nonâ€“sleep-deprived children. However, their study was not blinded and the patients were not randomly assigned to undergo the three degrees of sleep deprivation.

Epilepsy patients commonly report the exacerbation or precipitation of seizures after lack of sleep. A prospective and longitudinal outpatient study of the effect of stressful life events on seizure frequency clearly disclosed sleep deprivation as a significant factor.[55] In another study involving patients who had temporal lobe epilepsy, an increase in seizure frequency correlated with a decrease in the amount of sleep.[57] To reduce the duration of hospital stays, sleep deprivation is widely used to enhance the probability of seizure occurrence during video-EEG monitoring. Hence, when seizures have not occurred in the first few days of monitoring, we deprive patients of sleep about every other night until seizures begin to appear. Because there is no evidence that partial sleep deprivation is ineffective, 2 to 3 hours of nocturnal sleep and daytime naps are generally permitted. However, the value of sleep deprivation in the video-EEG setting had not been assessed formally until Malow et al.[48] conducted a prospective study that showed every other night of sleep deprivation had no enhancing effect on the frequency of complex partial seizures in patients with intractable epilepsy who were undergoing video-EEG monitoring. Also, sleep deprivation did not increase secondarily generalized seizure occurrence. It is not known whether reversing the sleep cycle by nightly sleep deprivation ameliorated with daytime naps would be effective in precipitating seizures. Furthermore, sleep deprivation may have a more consistent effect on the occurrence of primary generalized seizures than on partial seizures.

Hyperventilation

Hyperventilation is known to be the most effective method for activating ictal and interictal EEG abnormalities associated with typical absence seizures. According to Dalby,[9] hyperventilation activates seizures in more than 80% of children with untreated absence seizures. However, it has also been reported to activate almost any type of seizure.[20,53] Miley and Forster[53] found that hyperventilation activated interictal epileptiform activity in 6% of 255 patients with complex partial seizures and activated clinical seizures in 4%. Guaranha et al.[28] found that performing hyperventilation every 3 hours activated focal seizures in 25% of 97 patients. In each case, the activated seizure was similar to the spontaneous seizure. In contrast, Holmes et al.[33] reported that routine outpatient EEG with hyperventilation only activated seizures in 0.5% of 384 patients with partial epilepsy. Various investigators have emphasized the need for hyperventilation to be prolonged and intensive, particularly for activation of partial seizures.[64] However, hyperventilation should be avoided in patients with recent cerebral infarction, increased intracranial pressure, or poorly compensated cardiopulmonary disorders.

Lapses in consciousness during hyperventilation should not be interpreted as an epileptic phenomenon unless they are accompanied by typical epileptiform patterns. Epstein et al.[15] found that among 12 normal children they tested, all demonstrated an impairment of verbal memory, and eight failed to respond to repeated auditory clicks during periods of hyperventilation-induced EEG slowing. None of their subjects had automatisms or abnormal motor activity. In contrast, Lum et al.[46] found that in 22 normal children in whom hyperventilation induced an impairment of consciousness and high-amplitude rhythmic slowing, fidgeting, smiling, and yawning occurred frequently, as well as arrest of activity, staring, and oral and manual automatisms. It is also well known that hyperventilation at any age can trigger psychogenic pseudoseizures and a range of symptoms that include numbness, dizziness, tingling paresthesias, transient blurring of vision, and ringing in the ears.[24] Thus, it appears that episodes mimicking typical absence seizures, including automatisms, can occur during hyperventilation in normal children and that in such cases, only the EEG can reliably distinguish between those with seizure disorders and normal hyperventilation responses. It is also important to be aware that prominent pseudoepileptiform patterns, such as rhythmic midtemporal discharge, may be triggered by hyperventilation.[34]

Photic Stimulation

Photoepileptiform responses (light-induced responses containing epileptiform spikes or spike-and-slow-wave complexes) can be divided into four main topographic categories: (a) generalized; (b) bilateral, posterior dominant; (c) bilateral occipital; and (d) focal unilateral. Approximately 40% of bilateral responses demonstrate consistent asymmetries, particularly at the onset.[4] Rarely, a unilateral EEG seizure may follow a generalized photoepileptiform response in persons with a history of generalized epilepsy.[43] Most bilateral responses have a peak incidence between 6 and 15 years of age and occur frequently in siblings of probands, whether or not the proband has epilepsy. In most cases, therefore, bilateral photoepileptiform responses occur as variable phenotypic expressions of a genetic process that is independent of the genetic determinants of epilepsy. Photosensitivity is greatest between flash frequencies of 9 and 18 Hz, but nearly 50% of sensitive patients respond to frequencies up to 50 Hz, whereas the range of reactivity extends from 1 to >60 Hz.[36] Infrequently, patients may be sensitive to pattern viewing and not to photic stimulation. The most effective pattern is parallel lines. Responsiveness is increased if pattern movement or simultaneous photic stimulation is applied. Roughly one third of patients with stroboscopic light sensitivity demonstrate pattern sensitivity.[89]

Between 70% and 77% of persons with generalized photoepileptiform responses have epilepsy.[83] However, bilateral responses restricted to the occipital lobes are rarely associated with epilepsy. They usually occur in relatives of patients with photosensitive epilepsy.[84] Although it is traditionally taught that photoepileptiform responses that outlast the stimulus are more likely to be associated with epilepsy, recent studies have not confirmed this.[35,67] Similarly, patients who suffer from alcohol withdrawal without having epilepsy were once thought to have a high incidence of photoepileptiform response, but subsequent studies did not find this to be true.[21]

Nearly all persons with photosensitivity have idiopathic generalized epilepsy. When a seizure is elicited by photic stimulation, it is usually a primarily generalized tonicâ€“clonic, absence, or myoclonic seizure.[36] It is uncommon for photosensitivity to occur in partial seizure disorders.[45] A much smaller number of persons have idiopathic epilepsy with focal-onset seizures, particularly benign occipital epilepsy. Juvenile myo-clonic epilepsy is notable among the idiopathic epilepsies for having the highest occurrence of photosensitivity, with reports ranging from 17.4%[65] to 90%.[1] Photic stimulation rarely activates focal or unilateral occipital spikes. When this occurs, there is often a history of a lesion involving the occipital, parietal, or posterior temporal areas. The activation of a more anteriorly located unilateral lesion is extremely rare.[76]

During epilepsy monitoring, particularly for presurgical evaluations, it is important to note that photic stimulation may activate occipital seizures in patients with absence seizures who do not have occipital lobe lesions, in patients with migraine who do not have a history of spontaneous seizures, and in patients with benign partial epilepsy and exaggerated somatosensory-evoked potentials.[59]

Electrical Stimulation of Intracranial Electrodes

Electric stimulation of intracranial electrodes may produce responses that include (a) an afterdischarge, (b) the habitual aura with or without afterdischarge, or (c) a clinical and EEG seizure (see also Chapters 171 and 175). Afterdischarges appear as a rapid series of repetitive spikes that begin at the termination of stimulation, last at least 1 second, and arise from the stimulated electrode but may also involve adjacent electrodes. The afterdischarge is not a reliable localizing sign in depth electrode studies.[3,69] Indeed, the intensity of depth electrode stimulation necessary to induce an afterdischarge may be increased in the epileptogenic hippocampus. The localizing value of afterdischarge in subdural electrode stimulation is unclear. Our experience suggests that a lowered threshold to prolonged afterdischarges is usually concordant with the site of an anatomic lesion and is suggestive of good postoperative outcome in neocortical epilepsy. Otherwise, the value of afterdischarge is limited.

The localizing value of auras or seizures evoked by subdural electrode stimulation is unknown. In studies with depth electrodes, there is some agreement that neither auras nor seizures evoked by stimulating extratemporal sites have reliable localizing value.[3,22] As for the stimulation of temporal lobe structures, the value of electrically induced seizures is also doubtful. They are not reliable for determining the site of seizure onset in patients for whom results of previous, noninvasive EEG studies have been nonlocalizing.[69] Moreover, temporal lobe resections based on electrically induced seizures have a failure rate twice that of resections based on spontaneous seizures.[85]

Role of Activation in Psychogenic Seizures

Psychogenic nonepileptic seizures are the most common kind of nonepileptic attacks encountered at epilepsy centers (see Chapters 207 and 283 for further discussion). Such seizures typically account for 5% to 15% of inpatient admissions for epilepsy monitoring. The diagnosis of PNES is complicated by the common coexistence of epileptic seizures, which in some series occur in more than half of all patients with PNES.[40] Because most patients with PNES are responsive to suggestion, provoking attacks is usually not difficult. This has led to the common practice of using various methods of suggestion to diagnose PNES. The main argument against this practice is that some patients who do not have PNES, particularly those with psychiatric disorders or low intellectual ability, are also suggestible or may consciously fake an attack. Moreover, depending on how the suggestion is given, certain ethical concerns may arise.

There are many compelling reasons for inducing PNES by suggestion. At centers where this form of activation is not used, some patients have no spells after 10 to 12 days of monitoring. Thus, considerable medical resources are consumed without any apparent benefit. Because the recording of habitual spells is crucial in the evaluation of these patients, it is generally a greater disservice to forego a definitive diagnosis than to exercise the power of suggestion. Moreover, because the authors have not encountered and are unaware of any published report of the compromise of the physicianâ€"patient relationship as a result of the use of suggestion to induce spells, they sometimes employ the method of suggestion in cases of suspected PNES if spontaneous attacks have not occurred after several days of monitoring.

In the experience of the authors, the particular maneuver chosen for activation (e.g., injection of saline solution, pressing on the â€œgreater occipital seizure nerveâ€) is not important so long as the physician presents the suggestion in a credible fashion. This means that the patient must be told that the procedure may potentially cause a seizure. The activation procedure should not be performed without simultaneous video-EEG monitoring. Procedures such as the injection of saline solution may actually provoke epileptic seizures in 10% of patients with epilepsy and new nonepileptic spells in 15%.[82] Furthermore, new types of nonepileptic spells may be induced in 8% of patients with proven PNES. Therefore, it is essential that the recording be studied carefully and videotaped events be shown to witnesses of the patient's typical attacks to verify the relevance and significance of the induced seizures. However, it is important to emphasize that the recording of PNES does not rule out the presence of a coexisting epileptic seizure disorder.

Summary and Conclusions

The drive to reduce the cost of medical care has imposed major constraints on the use and methodology of long-term monitoring. Activation procedures are now used routinely to improve the cost effectiveness of long-term monitoring. Although requirements vary according to clinical situations, the general experience among epilepsy programs is that three or more recorded seizures are needed to help formulate a surgical decision.[77] Todorov et al.[77] also demonstrated that the mean duration of monitoring required to record one seizure is 2.9 to 3.7 days; to record three seizures, 4.5 to 5.5 days; and to record five seizures, 6.1 to 7.6 days. Rak[58] reported that at least 5.2 days are needed to establish the diagnosis of seizure, and 5.5 days to localize seizure foci. In an effort to meet these constraints, patient safety should not be overlooked as activation procedures are earnestly employed. It is best to individualize the AED withdrawal schedule and other activation procedures according to the medical condition of the patient and the type of seizures or epilepsy being evaluated. The monitoring staff must be prepared to address the potential limitations and complications of activation procedures. An important general caveat in the use of all activation techniques, particularly activation of pseudoseizures, is that the event elicited may not be related directly to the patient's spontaneous attacks.

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Chapter 95

Computer-Assisted Data Collection and Analysis

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Jean Gotman

Introduction

When evaluating patients with epilepsy, it is often important to obtain a thorough documentation of ictal and interictal electroencephalographic (EEG) patterns, preferably in conjunction with behavioral patterns. This is critical in the differential diagnosis of epilepsy and in the determination of the seizure type so that adequate medical treatment can be administered. An EEG investigation can also provide significant information for the evaluation of candidates for epilepsy surgery. Long-term monitoring sessions are commonly performed during which the EEG and the patient's behavior are observed and recorded continuously. During this time, all spikes and seizures are recorded, observers can interact with the patient during seizures, and EEG and clinical correlations can be performed fully. In some cases, a patient might be monitored during several days or even a few weeks. This might be necessary if a patient's seizures occur sporadically or if a patient suffers from multiple seizure types that need to be properly characterized. Prolonged monitoring might also be required to measure the effect of various antiepileptic drugs (AEDs). Continuous observation and recording of the EEG, typically with 32 to 64 channels, and of behavior during several days or weeks is an immense task. Continuous monitoring is expensive due to the requirements for considerable personnel and equipment during a prolonged period. If sufficient personnel are not available for constant observation, the following questions arise: Should the entire recording be reviewed, which is a very time-consuming task, or should a selective review be performed? If a selective review is performed, how is the selection to be made? Or should the recording be selective, including only the events of interest? Can these tests be performed efficiently and reliably in an outpatient environment?

It has become clear in recent years that computers can be extremely helpful in making the procedure of long-term epilepsy monitoring less tedious and less expensive. They can also assist in the review and analysis of the EEG of epileptic patients, and they can be used for data archiving. Behavioral video recording also can be performed with the assistance of computers. The first part of this chapter considers how computer-based recordings, particularly automatic methods for detection of spikes and seizures, can facilitate long-term epilepsy monitoring in the hospital and at home. The second part discusses the role of computers in EEG review, analysis, and archiving.

Computer-Assisted Long-Term Electroencephalographic Monitoring

In the past, a continuous recording lasting 12 to 24 hours, with the typical 16 channels, could be performed only with a traditional EEG machine and paper or with magnetic tapes running at very low speed. Both media have a limited channel capacity; paper in such a quantity is obviously cumbersome and expensive, and tapes have the disadvantage of being accessible only sequentially. Today, the capacity of computer disks is such that it is simple to perform a continuous 32-channel, 24-hour recording on a standard computer. A computer-based recording allows a flexible review procedure, with random access to any part of the recording and the availability of numerous methods of data manipulation and analysis (see the later section on analysis).

In most 24-hour recordings, 95% to 99% of the recording offers little useful information for the evaluation of an epileptic disorder. Automatic detection methods, despite their imperfections, can facilitate the recording, and thus the review, of valuable information. The recordings of seizures and of interictal spikes are discussed separately. Several reviews of automatic event detection in epilepsy and applications of computer methods to the analysis of the EEG in epilepsy have been published in the last few years.[30,40,41,52,75,122]

Recording Seizures

In the context of epilepsy monitoring, the term *seizure* must be defined. A behavioral seizure can be defined as the clinical manifestation of an epileptic seizure as perceived by the patient, seen by an observer, or recorded on video. The electrographic or EEG seizure can be defined as an abnormal, paroxysmal EEG pattern. In a large fraction of cases, behavioral and electrographic seizures can be observed simultaneously; this is why it has been possible to characterize the EEG changes specific to seizures. There are many cases, however, in which a discrepancy can be observed between behavior and EEG. Two types of discrepancy are possible:

1. A behavioral seizure can be present in the absence of visible EEG changes. If it is assumed that the seizure is indeed epileptic (the means of differentiating epileptic from nonepileptic seizures are not discussed here), then abnormal EEG activity is actually present somewhere in the brain. It is simply not available to the particular method of observation, that is, to the particular arrangement and location of electrodes. The discharge might, for instance, be limited to mesial frontal regions, whereas electrodes might have been placed only on the scalp or only intracerebrally in the temporal lobes. For the purpose of epilepsy monitoring, it must be clear that such a seizure will certainly be missed by observation, review, or computer analysis of the EEG alone.
2. An EEG seizure can be present in the absence of clinical manifestations. This is commonly referred to as a purely electrographic seizure or a subclinical seizure. It was argued in the previous discussion that an absence of EEG discharges can be a pitfall of the method of measurement (a discharge can be present but not be discernible to the electrodes). It similarly can be argued that the absence of a behavioral seizure may be a pitfall of the method of observation: If a patient is lying in bed watching television, unresponsiveness, inability to speak or understand, and minor automatism or loss of muscle tone cannot be observed unless active testing is performed. Even giving correct responses to many questions does not exclude clinical signs; seizures involving only memory have been observed.[100] In other words, the presence of clinical signs is a function of the method of questioningâ€”hence the importance of recording all seizures, with and without overt clinical signs, and of observing them as precisely as possible. The importance of subclinical seizures has been discussed with respect to evaluation for epilepsy surgery.[115] It will be shown later how automatic seizure detection and seizure warning systems can be helpful in this situation.

It is thus obvious that all types of seizures, with or without clinical and EEG manifestations, ideally should be recorded.

Continuous Recording and Review

As indicated earlier, it is possible to perform a continuous recording on a computer disk for a period of 24 hours. This represents a large amount of EEG to be reviewed, but computer review on a high-resolution screen can be quite fast; 32 channels of EEG can be presented 10 to 20 times faster than real time, resulting in a review lasting 1 to 2 hours. However, such a fast review can result in small seizures being missed, particularly when the number of channels goes beyond 12 or 16.[101] The period of 1 to 2 hours just mentioned does not include the time required for the analysis of seizures or other potentially interesting events. Therefore, the full review of a 24-hour recording is quite time consuming and strenuous. Alternative strategies have been developed by many institutions.

These strategies consist mainly in using a partial review with an attempt to select the most relevant sections. The most important sections are, of course, those during which the patient or an observer noted a behavioral seizure. In addition, randomly selected sections are often reviewed as well. As discussed previously, this entails the significant risk that seizures of which the patient is unaware and that are not observed will be almost systematically missed. This might be an acceptable compromise if the patient is under close observation, but it could be quite dangerous otherwise.

Automatic Detection of Seizure Patterns

Some methods of seizure detection are based on behavioral manifestations of seizures; mechanical sensors under a mattress can detect the strong rhythmic movements of generalized tonicâ€“clonic seizures. The limitations of this kind of method are obviousâ€”many seizures do not include such strong movements. This discussion concentrates on seizure detection methods based on EEG analysis. As indicated earlier, some seizures do not have EEG changes, and EEG-based methods cannot be expected to detect them. There are also seizures that have mild or nonspecific changes, such as brief desynchronization, or groups of theta or delta waves.[4] These EEG patterns are only interpreted as being abnormal in the context of a concomitant clinical event. This makes it very difficult for an automated seizure detection system to differentiate these seizure discharges from normal EEG patterns because the computer does not take into account clinical information when analyzing the EEG. There are thus limitations to seizure detection by EEG; fortunately, these limitations are not very significant, because the vast majority of seizures are associated with clear and relatively specific EEG changes.

The problem of seizure detection is inherently difficult because seizure activity can comprise a variety of morphologies; unlike spikes, which have relatively well-defined characteristics, seizures can include patterns such as low-amplitude desynchronization, polyspike activity, rhythmic waves at a wide variety of frequencies and amplitudes, and spikes and waves.[13] In extracranial recordings, seizures are often obscured by electromyographic, movement, and eye blink artifacts. From the point of view of pattern recognition, the problem is therefore complex. We first discuss the methods of detection, and then address the complex issue of establishing these methods in a practical clinical context.

Methods of Seizure Detection

Early methods for seizure detection relied on relatively simple measurements of amplitude. Because an increase in amplitude is fairly common in the ictal EEG, such systems could successfully detect many seizures. Prior et al.[103] described the use of their cerebral function monitor to identify generalized tonicâ€“clonic seizures; these could be recognized on the tracing as a large increase followed by a clear decrease in EEG amplitude (the postictal depression) and by increased electromyographic activity. Such large seizures with major changes could also be identified in monkeys with experimentally induced epilepsy by a characteristic pattern on slow paper tracings (0.25 mm/s).[38] Ives et al.[63] described a method in which 16 channels of EEG were added, bandpass filtered, and subjected to amplitude discrimination. This technique could detect large seizure discharges but was quite insensitive. Babb et al.[8] implemented an electronic circuit for the detection of seizures in recordings from intracerebral electrodes. A seizure was recognized when a rapid succession of large-amplitude spikes, lasting at least 5 seconds, was found.

More sophisticated systems computed several features of the EEG to recognize seizure activity. Murro et al.[93] described a method based on spectral parameters and discriminant analysis. Gotman[37,43] presented a computer method that attempted to recognize a wide variety of seizure morphologies, identifying patterns that might represent seizure activity for later examination by traditional visual inspection. The method was therefore designed to be as sensitive as possible. False detections, as long as they were not extremely frequent, were not detrimental because they could be removed in an ensuing visual review of the detected events. Observation of numerous seizures led to the conclusion that most seizures, at some time during their development, included activity that was paroxysmal compared with the background (the paroxysm could consist of increased amplitude or increased frequency); activity also had to be rhythmic (with frequencies varying from 3 to 20 cycles per second) and relatively sustained in duration (lasting several seconds).

Measurements of these characteristics were obtained by breaking down the EEG into half-waves; for every 2-second epoch, the average amplitude of the half-waves relative to that of the background (indicating whether an epoch was paroxysmal), the average duration of the half-waves (indicating frequency), and the coefficient of variation of half-wave duration (indicating the regularity of duration or the rhythmicity) were measured. The background was constantly updated and included EEG sections before and after the active epoch. Comparing the amplitude, frequency, and rhythmicity measurements of the background to those of the active epoch allowed definition of a decision tree for the detection of seizure activity. It is often forgotten that it is not necessary to detect the onset of a seizure; a detection occurring at any time during the course of the seizure is sufficient because the computer simply marks the time of the detection and the interpreter can page back to determine the exact time of seizure onset. This method of seizure detection has been made available commercially and is

in widespread use throughout the world. It has also been used to monitor experimental animals.[12,88]

Harding[57] presented a method specifically designed for intracerebral recordings based on the detection of a repetitive spiking pattern as well as of possible flattening at seizure onset. This method was implemented online and was subject to an extensive evaluation (see later discussion). Another approach for seizure detection was proposed by Schindler et al.[112] They simulated neuronal cells processing each EEG channel and used leaky integrators to assess increases in amplitude and slope over a certain time.

Artificial neural networks (ANNs) have found broad applications in many areas of pattern recognition, including seizure detection. Jando et al.[64] showed the utility of neural networks for detecting bursts of spike-and-wave in experimental models of epilepsy. Since then, several methods have been presented involving the use of various EEG features as inputs to an ANN.[6,32,116,120] By being presented with a sufficiently large number of training examples comprising seizure and nonseizure data, the ANN can learn to differentiate seizures from normal EEGs. A representative set of features characterizing the EEG needs to be specified in advance (e.g., amplitude, rhythmicity, dominant frequency, and so on), but it is not necessary explicitly to describe the seizure patterns. The ANN automatically determines which combinations of features are characteristic of seizures by adapting its internal structure to reflect the training data. The performance of ANN methods depends on the selection of an appropriate set of features and on the use of a sufficiently large training set containing a wide variety of seizure patterns. It is also necessary to specify a priori the structure of the ANN; large networks can handle complex classification tasks but may risk overfitting the training data and thus be unable to generalize to other types of seizures. It is also very difficult to investigate the operation of a large ANN; the network essentially acts as a black box that outputs classification values depending on the features it receives as inputs. To circumvent this issue, Wilson et al.[124] presented an algorithm based on a general set of rules in which each individual rule was implemented using a small ANN. By using several simple rules, it became easier to analyze the operation of the system.

Recent developments in automatic detection have demonstrated that performance can be improved significantly by incorporating a wide context in detection algorithms. Rather than defining the event only locally (e.g., comparing the characteristics of a 5-second epoch in one channel with the 30 seconds that precede it), it is important to include measurements of the spatial context (activity in other channels) and the temporal context (state of the subjectâ€"awake, stages of sleep, previously recorded events). Qu and Gotman[104] used this philosophy to greatly reduce the false detection rate by allowing the method to remember the patterns that caused frequent false detections in each subject. Klatchko et al.[68] presented a method for spatial and temporal clustering of elementary detections initially made on individual channels and epochs, which resulted in a more global representation of seizures. This reduced the number of false detections by only asserting the occurrence of a seizure if there were a minimum number of elementary detections adjacent in space and time. The system of Khan and Gotman[67] was based on wavelet decomposition to detect seizures in the intracerebral EEG. Wavelet methods allow the analysis of the temporal evolution of the frequencies of a signal; they are thus well suited for the identification of paroxysmal rhythmic activity, which often characterizes seizures. However, intracerebral EEGs also frequently feature rhythmic bursts associated with normal background activity. Therefore, Khan and Gotman's algorithm automatically adapted to the background of each patient by deactivating the detection of paroxysmal activity occurring consistently in the same channels and at the same frequencies. This resulted in an important decrease in the number of false detections (see later discussion).

Methods of Seizure Warning

Seizure detection systems can significantly reduce the load of EEG interpretation during long-term monitoring by requiring only the review of the detected events rather than the entire EEG record. Another purpose of seizure detection could be to warn the medical personnel, patient, or relatives that a seizure is starting, which could be particularly useful if the electrographic onset of the seizure precedes its clinical onset. In the context of long-term monitoring, a seizure warning system would allow close clinical observation early in the seizure and the taking of necessary precautions to avoid injuries that might otherwise occur in sudden unexpected seizures. It could also be useful for increasing the applicability of ictal single-photon emission computed tomography (SPECT) scans.[11] A seizure warning system could also be implemented as an implantable device, and one could even conceive of rapid intervention in the form of electrical stimulation or drug injection to abort the seizure.[80] The seizure monitoring systems described here were designed primarily to mark EEG records at any point during seizures so that the detected events could be reviewed at a later time. In contrast, seizure warning applications are meant to be used in real time and require detections that occur very early in the seizure. Moreover, the false detection rate should be very low because false alarms can be very disruptive in a clinical setting. Promising results were obtained by Qu and Gotman[105,106]; for each patient, a first recorded seizure was used as a template to train the detection system. This approach clearly results in the introduction of a bias in detection performance toward seizures similar to the template. Therefore, this system is highly patient specific and cannot warn of new or different types of seizures. It thus cannot be used for seizure monitoring purposes, but is still useful to assess the occurrence of a particular seizure type. The system was able to generate a warning within an average of 10 seconds of the electrographic seizure onset, with a relatively low false alarm rate. Shoeb et al.[114] designed a system for seizure warning in scalp EEGs. By training the system with wavelet features specific to each patient, they could obtain a high sensitivity and a low rate of false detections.

Although patient-specific systems can be useful, more general methods are more practical in a clinical setting because they do not need to be retrained for each patient. The system of Osorio et al.[98] used a wavelet filter followed by a median filter to detect the onset of seizures in intracerebral recordings. The best performance was achieved when the system was tuned to each patient, but good results were still obtained without this patient-specific adjustment. Saab and Gotman[108] designed a system based on measurements of amplitude and rhythmicity in the wavelet decomposition of scalp EEGs. The wavelet features were then used in a Bayesian classifier to obtain the probability that a seizure had begun. Various criteria were used to automatically reject epochs containing alpha activity, electromyographic artifact, or abnormal signals due to defective electrodes; this allowed the system to ignore these sources of false detections, which are common in scalp EEG recordings. FIGURE 1 shows examples of seizures detected by the warning system. The classifier was trained using a large data set containing a wide variety of seizures; the system is thus sufficiently generic to be useful for seizure monitoring applications. For seizure warning purposes, it is also possible to further reduce the false alarm rate without significantly increasing the detection delay, by manually tuning the system for each patient.

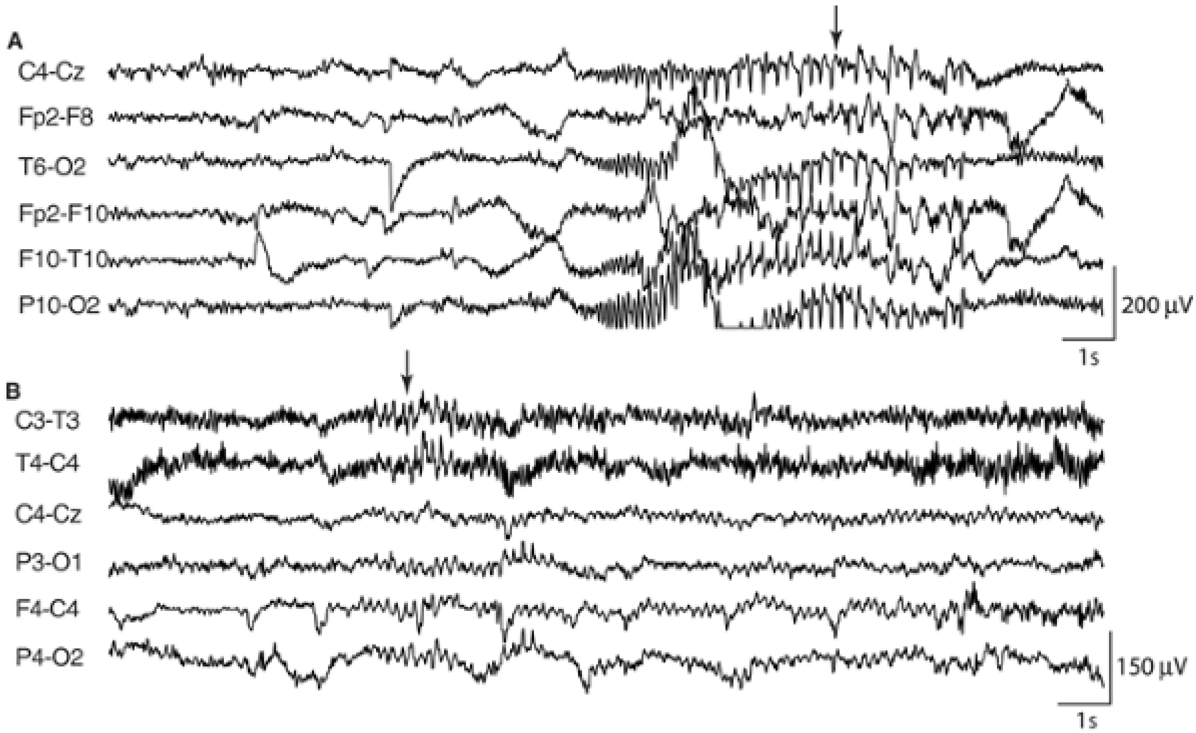

FIGURE 1. Seizures recorded by scalp electrodes that were detected automatically by the seizure warning system of Saab and Gotman.[108] Arrows mark the earliest detections. **A:** Seizure featuring clear rhythmic spikes lasting <8 seconds. **B:** Subtle seizure characterized by somewhat rhythmic discharges of low amplitude.

Whereas the system just described was specific to scalp recordings, a similar methodology was employed by Grewal and Gotman[56] to process intracerebral recordings. They used spectral features in several frequency bands and integrated

measures of spatiotemporal context to detect the onset of seizures. To aid in the detection process, the harmonics of identified rhythmic signals were also examined for the presence of sustained activity. Epochs containing abnormally large amplitude signal or activity at the mains frequency of 60 Hz were automatically rejected, thus reducing the rate of false detections due to artifacts. The system was trained on a wide variety of seizures, resulting in a general detector useful for seizure monitoring, which also provided a tuning mechanism to improve its performance for use as a seizure warning system. Examples of seizures recorded by intracranial electrodes and detected by the method are shown in FIGURE 2.

The seizure warning systems described here aim to detect seizures in real time just as they are starting. On the other hand, recent studies[18,61,79,87,91,95] have indicated that it is sometimes possible to detect changes in the EEG well before the actual onset of clinical and electrographic changes. These results are preliminary, but it might be possible to develop methods for seizure prediction if reliable algorithms can be designed (see Chapter 85).

Detection of Seizures in the Neonate

The detection of seizures in neonates is quite different from that in adults; discharges are often much slower (down to 0.5 Hz), seizure onset can be very gradual, seizures can last several minutes, and waveforms of seizures and of interictal background show a high level of variability. Because of this, several seizure detection systems have been developed specifically for neonates. Liu et al.[84] presented a method based on the autocorrelation function for the detection of rhythmic slow patterns of any morphology. Gotman et al.[47] also developed a system specifically for newborns, based on a combination of various techniques. Spectral analysis was used to detect paroxysmal bursts of rhythmic activity. Spike detection methods were also integrated in the system to detect seizures that consist of irregular spiking patterns. Very slow rhythmic discharges were detected by applying a low-pass filter to the neonatal EEG and then using the seizure detection method of Gotman[43] on the filtered signal. By using a combination of several methods, the system was able to detect a wide variety of patterns occurring during neonatal seizures. Roessgen et al.[107] proposed a different approach to neonatal seizure detection based on a neuronal model of EEG generation. The model takes into account the generation of seizure activity and of background activity. By fitting the model to the EEG data under investigation, it is possible to determine how much of the signal is due to seizure activity. Celka and Colditz[17] presented a method based on singular spectrum analysis, also aimed specifically at seizures in infants. They used the minimum description length (MDL) principle to estimate the signal complexity, which was then used as a detection measure. Their system also implemented an autoregressive moving average (ARMA) model of the EEG as a preprocessing step to separate background activity from seizure activity. Altenburg et al.[7] described a method of detecting neonatal seizures based on interchannel synchronization. They noted that the onset of seizures is often characterized by a sudden increase in synchronization. The method of Hassanpour et al.[58] used time-frequency representations of the signal to detect low-frequency rhythmic activity as well as high-frequency bursts of spikes. Aarabi et al.[1] designed a multistage system for seizure detection in the newborn based on a large number of features. The relevance of each feature was then analyzed, so that only the most appropriate features were selected and used in an artificial neural network to classify seizure and nonseizure EEG.

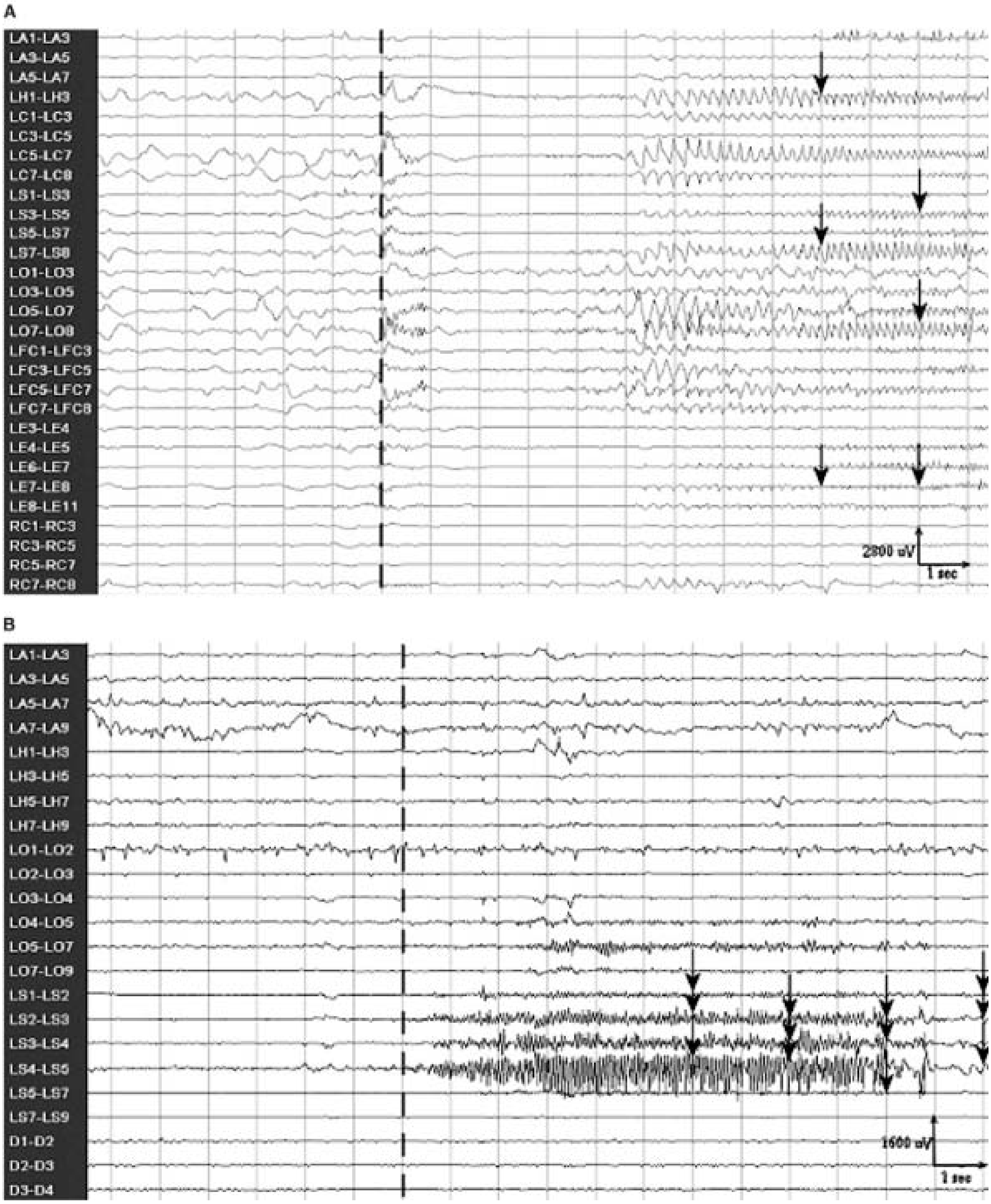
A
LA1-LA3
LA3-LA5
LA5-LA7
LH1-LH3
LC1-LC3
LC3-LC5
LC5-LC7
LC7-LC8
LS1-LS3
LS3-LS5
LS5-LS7
LS7-LS8
LO1-LO3
LO3-LO5
LO5-LO7
LO7-LO8
LFC1-LFC3
LFC3-LFC5
LFC5-LFC7
LFC7-LFC8
LE3-LE4
LE4-LE5
LE6-LE7
LE7-LE8
LE8-LE11
RC1-RC3
RC3-RC5
RC5-RC7
RC7-RC8
2800 uV
1 sec
B
LA1-LA3
LA3-LA5
LA5-LA7
LA7-LA9
LH1-LH3
LH3-LH5
LH5-LH7
LH7-LH9
LO1-LO2
LO2-LO3
LO3-LO4
LO4-LO5
LO5-LO7
LO7-LO9
LS1-LS2
LS2-LS3
LS3-LS4
LS4-LS5
LS5-LS7
LS7-LS9
D1-D2
D2-D3
D3-D4
1600 uV
1 sec

FIGURE 2. Seizures recorded with intracerebral electrodes that were detected automatically by the seizure warning system of Grewal and Gotman.[56] The dashed vertical lines indicate the onset of the seizures. Arrows mark the seizure epochs that were detected by the system. **A:** Seizure featuring typical sustained rhythmic activity, which was detected 9 seconds after the onset. **B:** Seizure characterized by fast rhythmic activity. This seizure was detected only 6 seconds after its onset.

Clinical Validation of Seizure Detection Methods

Evaluating the performance of automatic detection methods is very difficult because results may depend more on the selection

of EEGs included in the evaluation set than on the detection method itself; for instance, a seizure detection method may work well when the patient is resting with eyes closed, perform less well when eye blinks are present, and fail totally if electromyographic and movement artifacts are also included. To give a fair impression of performance, what type of EEG should be included in the evaluation? Several requirements should be met to obtain an accurate validation that corresponds to a realistic clinical setting:

- EEGs used in the validation should be independent of EEGs used in developing the method.
- EEGs should not be preselected, especially with respect to quality. A subjective selection of the EEGs could strongly bias the results. Ideally, the records should be obtained consecutively.
- A large variety of seizure patterns from several patients should be included.
- A large amount of nonseizure data should also be included, to be representative of all conditions that might occur in long-term monitoring.

The performance of the seizure detection methods described earlier will be reviewed. Methods that did not use an extensive amount of independent EEG during their validation will not be considered in detail in this section. This does not mean that these methods do not perform well; in fact, most of them show very promising results. However, their validity in a realistic clinical context has not yet been established.

In evaluating the seizure detection method of Gotman,[43] all efforts were made to avoid bias in data selection. EEGs were recorded from 293 consecutive monitoring sessions totaling 5,303 hours from 49 patients, most of them having medically refractory epilepsy and being considered for surgical treatment. All EEGs were included, independent of EEG patterns and technical quality. Of the 244 seizures in the validation data set, 24% were recorded by the alarm button but were missed by the computer, 35% were detected by the computer and were accompanied by an alarm button press, and 41% were detected by the computer alone. Pauri et al.[101] performed an independent evaluation of the same method and came to very similar conclusions. In a third evaluation, Salinsky[109] concluded that the use of automatic seizure detection made it possible to catch a large number of seizures missed by the patient and observers and to reduce significantly the length of the hospital stay. As in the previous study, approximately 20% of seizures were not detected by the computer but were detected by the patient or an observer.

It is thus clear that one cannot rely exclusively on either human observation (the alarm button) or automatic detection. Using both approaches can considerably increase the yield of long-term monitoring. In addition, the average detection rates given here reflect poorly the reality of individual patients. Some patients had most of their seizures recorded by the alarm button alone, whereas others had most of their seizures detected by the computer without an accompanying press of the alarm button. The computer can be extremely helpful when seizures go unnoticed, such as when they consist of quiet automatisms. All seizures can be detected if a nurse and an EEG technologist observe the patient and the EEG at all times. This procedure is obviously expensive and difficult to achieveâ€"hence the importance of automatic seizure detection methods.

False-positive detection rates were around one to two false detections per hour of monitoring,[43,101] increasing in some patients with intracerebral electrodes to up to four or five false detections per hour. In the majority of cases, the number of false detections is small enough not to be disruptive: False detections merely cause the EEG to be marked unnecessarily and can be removed at the time of review by visual inspection. This selective visual review is clearly preferable to reviewing the entire EEG recording without the benefit of data reduction.

The wavelet-based and context-based method of Khan and Gotman[67] was evaluated on recordings from 10 consecutive patients with intracerebral electrodes, each having 20 hours of recording and at least three seizures. It was compared to the original method of Gotman.[43] Sensitivity was 90% for the original method and 86% for the new method. It thus appears that the original method, even when applied exclusively to intracerebral electrodes, had an excellent performance. The new method had marginally lower sensitivity, but its main advantage was its low rate of false detection of 0.3/hour, compared to 2.4/hour for the original method.

Harding[57] performed a thorough evaluation of his method of seizure detection for intracerebral recordings, also by using large amounts of unselected dataâ€”almost 1,600 hours from 40 patients. He obtained few false negatives and a very acceptable level of false positives. The results are difficult to compare directly with other methods because detection parameters were altered slightly according to the results after the first seizure was recorded. Gabor[31] performed an extensive evaluation of his neural network method using 4,500 hours of scalp EEG from 65 patients. The data were not preselected, so that even low-quality EEGs were included in the analysis. The original method of Gotman[43] was also evaluated using the same data set, resulting in a sensitivity of 74.4% and an average false-detection rate of 3.02/hour. The neural network method yielded an improved performance, with a sensitivity of 90.0% and a false-detection rate of 1.29/hour. Osorio et al.[97] evaluated their method on recordings from 15 patients with intracerebral electrodes. Their results are not presented in the traditional fashion and cannot easily be compared to those of other methods. They indicate that 100% of the 39 seizures were detected, but they only considered seizures for which there was an alarm from the nurse or the patient, and they excluded poor-quality EEGs. Purely electrographic seizures or seizures of which the patient was not aware were not considered. In addition to the 39 detected seizures, their system yielded another 866 detections that were subsequently reviewed; 92% were then reclassified as true detections, including short electrographic bursts, leaving a low rate of false detections. Saab and Gotman[108] tested their seizure warning method on an independent, unselected data set including seizure and nonseizure data from 16 patients totaling 360 hours of scalp EEG. They reported a sensitivity of 77.9%, a false-detection rate of 0.86/hour, and a median detection delay of 9.8 seconds. For use specifically as a seizure warning system, it was possible to tune the system for patients with a large number of false detections. This resulted in a false-detection rate of 0.34/hours, and the sensitivity and median detection delay were almost unchanged at 76.0% and 10 seconds, respectively. Grewal and Gotman[56] tested their intracerebral seizure detection method using an independent testing data set from 19 patients totaling 389 hours of intracerebral EEG. They indicated a sensitivity of 86%, a false-detection rate of 0.47/hour, and a median delay time of 16.2 seconds. They also provided a patient-specific tuning mechanism to reduce the number of false detections for seizure warning purposes. This resulted in a false-detection rate of 0.22/hour, with a sensitivity of 89.4% and a median delay time of 17.1 seconds.

Gotman et al.[46] evaluated their newborn seizure detection method on a large set of data (55 newborns) obtained from three hospitals. Results showed seizure detection rates that were a little lower than those of scalp recordings in adults (around 70%) and false-detection rates of approximately 2/hour. This study illustrated that it can be difficult to extrapolate results from one patient group to another: The performance varied considerably between the data sets of the three hospitals, reflecting the variability of recording conditions, technical quality, and types of pathologic conditions.

Faul et al.[25] performed an independent evaluation of the methods of Liu et al.,[84] Gotman et al.,[47] and Celka and Colditz,[17] using a common data set consisting of EEGs from 13 newborns. Using the default parameters from each algorithm, it was found that the three methods did not perform as well as expected on this particular data set. This again reflects the difficulties in designing a general seizure detector to handle variable conditions. To obtain better results, it might be necessary to adjust the parameters of each method specifically for each hospital. An improved performance was noted when the algorithm parameters were appropriately tuned.

Current seizure detection programs are not perfect and would benefit from significant improvements. It would be extremely difficult, however, to detect all seizures because some seizures have almost no EEG accompaniment, and the discharge morphology is often nonspecific.[4] Nevertheless, computer assistance is almost indispensable for the detection of epileptic events during long-term monitoring. There is no single economical method that ensures the detection of all seizures in every patient: All available help must be used, including staff and patient reporting, and computer detection. In some patients, one method may prove to be more useful than others, but this is not known in advance of the monitoring sessions. Automatic methods of seizure detection can be especially useful in the context of human validation. Moreover, newer methods, relying on a broader contextual analysis of the EEG, can yield a significantly improved performance compared to traditional methods. They can also reliably be used as seizure warning systems, detecting seizures close to their electrographic onset.

Recording Interictal Activity

The interictal activity specific to epilepsy consists of spikes, sharp waves, and bursts of spike-and-wave. Patients with epilepsy also have abnormalities of background, which can be analyzed by computer methods. Paroxysmal interictal activity occurs unpredictably and sometimes infrequently. To obtain a full documentation of the different types of abnormalities, the traditional short recording might not be sufficient. Long-term monitoring might be required, including periods of the different stages of sleep, which most often activates and modifies interictal patterns.[110] The reduction of AED doses, often done during long-term monitoring to precipitate seizures, also results indirectly in increased spiking; it has been shown that spikes are more frequent after seizures.[44,50,53] It is clear that complete review of recordings lasting days and nights is an awkward way to document interictal activity: Automatic detection methods can be very helpful.

Past Methods

The usual approach in early systems for automatic spike detection consisted in (1) selecting EEG sections lasting 1 or 2 minutes, free of artifacts, and including a sufficient number of spikes; (2) devising a method for their detection; and (3) comparing results of automatic detection to what qualified electroencephalographers considered â€œtrueâ€ spikes. Details of the various detection methods have been reviewed extensively.[45] In general terms, these methods relied on one of two approaches: In the first, the EEG is broken down into elementary waves, and the method then attempts to identify waves having morphologic characteristics normally associated with spikes (amplitude, duration, sharpness). In the second, the EEG is analyzed to find statistically improbable events of short duration. With most methods, very acceptable performance was obtained, usually with 80% to 90% of â€œtrueâ€ spikes detected and a low rate of false-positive detection. Many publications ended with statements such as, â€œAs computers become more powerful and less expensive, practical implementation of this method will be simple.â€ Computers did in fact become more powerful and less expensive faster than anybody had expected, but most methods did not reach practical implementation. One major reason is that the detection problem became much more complex when longer sections were analyzed; artifacts and normal transients had to be included, and they caused numerous false detections. In addition, some methods were not readily adaptable to online analysis and were therefore of limited practical utility. For short recordings, human inspection generally performs sufficiently well, so that there is little use for spike detection in these cases. Automatic methods would thus be most useful for prolonged recordings. It should be noted, however, that perfect performance is unlikely ever to be obtained by automatic systems. After all, EEG experts also show a less-than-perfect sensitivity; there is some inherent variability associated with the subjective interpretation of EEG records.[123]

Difficulties of the Problem

The major difficulty of spike recognition methods is their reliance on a very incomplete definition of a spike. The definition quoted by many publications is â€œa sharp transient, easily distinguishable from the background, having a duration of less than 70 msec for a spike and 70 to 200 msec for a sharp waveâ€ (adapted from Chatrian et al.[19]). This definition is extremely incomplete because it lacks features for differentiating transients with the same local morphology that are not spikes, such as eye blinks, vertex sharp waves, isolated alpha or spindle waves, electrode artifacts, and movement artifacts. Such transients are common during prolonged EEG recordings, when automatic spike detection is useful. Because of this, results of standard spike detection methods usually include genuine spikes mixed with false detections caused by nonepileptiform transients.

Which characteristics allow a human interpreter to distinguish an epileptiform sharp wave from an eye blink, even though the waves themselves may have the same morphology and emerge from a similar background? These characteristics most likely relate to the context in which the waves appear; this context likely encompasses a much wider space and time than the background activity surrounding the spike. When interpreting a wave having the morphology of a spike, the human observer takes into account events in other channels (spatial context) and in earlier and later parts of the recording (temporal context), and even non-EEG information, such as the age or clinical state of the subject. Optimism about early detection methods was based on a failure to appreciate how much spike identification relies on context.

It must be noted that these problems do not affect the ability to detect most epileptiform spikes, but they do result in a large number of false-positive detections. For this reason, it is possible to make practical use of an automatic spike detection method, as long as it is conceived as a method for detecting a high proportion of the spikes along with a possibly large number of nonepileptiform transients, rather than as a method to detect only spikes. Such a practical implementation was made with the spike detection algorithms developed at the Montreal Neurological Institute.[40,48] Pietila et al.[102] presented a system including automatic segmentation of the EEG followed by feature extraction. Compared with Gotman's system, this system showed a higher sensitivity but a lower specificity.

Newer Approaches

As in seizure detection systems, artificial neural networks have also become a popular method for spike detection. The process usually requires a large number of sample patterns for training; the ANN then automatically adapts to the discrimination task at hand. This method was used by Gabor and Seyal,[33] who obtained a good performance but evaluated their method on a very small sample.

When designing a neural network method, it is crucial to select an appropriate set of features to use as inputs to the ANN. The relatively short duration of spikes offers the opportunity to use the raw EEG data points as network inputs, thus foregoing the extraction of features. Webber et al.,[121] using a relatively small data set for evaluation, compared the use of the raw EEG to that of preprocessed variables in the ANN and concluded that a better performance was obtained by using the preprocessed parameters. Ozdamar and Kalayci[99] obtained good performance with an ANN trained on raw EEG, but Ko and Chung[69] revisited the data and suggested that the results were erroneous due to inappropriate data preparation.

When using raw EEG instead of preprocessed parameters, the ANN needs to recognize all combinations of the data that can be relevant for the classification task. A very complex ANN will thus be required to obtain a satisfactory performance. It is possible to simplify the problem by using only a small amount of raw EEG as input, as was done by Kurth et al.,[76] who used a data window of only 100 msec. However, the use of such a short window prevents their method from taking into account characteristics such as the slow wave that often follows interictal spikes. The lack of temporal context makes it difficult to prevent false detections caused by transients whose morphologies are locally similar to spikes. Their results are difficult to compare with other methods because they only used a limited data set for validation, and they had separate ANNs trained and tested individually on the same patients. To reduce the complexity of spike detectors using raw EEG as inputs, Acir and Guzelis[2] proposed a multistage approach in which the data are first reduced by identifying nonstationary transients using an autoregressive linear predictor. Only the identified transients are then further examined, by using the raw signal in a support vector machine for classification as spike or nonspike. A sensitivity of 90.3% with 9.5% of false detections was reported after validation with 4.2 hours of EEG from seven patients.

The use of extracted features instead of raw data can result in simpler classifiers for spike detection. Wilson et al.[125] designed several simple rules for spike detection and then used small ANNs to learn each rule. It was then easier to interpret how each small ANN implemented the individual rules. Wilson et al. also used a training set in which EEG data epochs were marked with a probability value rather than a dichotomous classification as a spike or nonspike. This allowed the system to process ambiguous spikes without having to decide on a definitive classification. Hellmann[59] used cross-correlation to identify candidate spikes that resembled a given template, followed by classification using an ANN with various features. The use of a template results in a system that is patient specific and can only identify one type of spike. Nevertheless, this method could be useful if the time of occurrence of known spike morphologies is desired, such as in functional imaging applications. In addition to ANNs, other data mining models can also be used to automatically generate classifiers for spike detection. Valenti et al.[119] implemented C4.5 decision trees and naive Bayesian classifiers with good results, but EEGs from only three patients were used for training and validation.

There has been some interest recently in using wavelet analysis to identify interictal spikes in EEG records.[21,77,111,113] Wavelet features can be useful for describing the time and frequency relationships that exist between the spike and the following slow-wave. These methods are well suited to the characterization of transient signals such as spikes.

Another approach to improving detection performance is to make automatic methods use information from a wider context. This is a simple concept, but it is difficult to implement because the context encompasses a very large amount of information and it must be decided which part of that information is relevant to spike detection. It is this selection process that human interpreters do so well. Glover et al.[35] described a context-based system aimed largely at reducing false spike detections by making use of a wide spatial context; information from all EEG channels, as well as from electromyographic, electrooculographic, and electrocardiographic channels is used to assess whether a transient in a particular channel is likely to be epileptiform.

An approach has been proposed by Gotman and Wang[54,55] in which a wide temporal and spatial context is used to decide on the nature of a sharp event. The method is termed state-dependent spike detection because criteria for spike detection are rendered dependent on the state of the EEG. Five states were defined in which spike detection should be performed differently: (1) active wakefulness, (2) quiet wakefulness, (3) desynchronized EEG, (4) phasic EEG, and (5) slow-wave EEG. In fact, in these different states it is not so much that spike detection has to be done differently as that false detections have to be handled by different means. In active wakefulness, for instance, one must be particularly aware of symmetric frontal sharp waves that may be caused by eye blinks, whereas there is no such concern in the phasic EEG state; in that state, sharp waves maximal at the vertex are a problem (Fig. 3). The method was evaluated in 20 patients, each having close to 2 hours of EEG covering all states; it showed a reduction in false detection of 65% and an increased sensitivity of 35% compared with the original method. Flanagan et al.[27] suggested an improvement to this method by using an equivalent current dipole to model each detection. The goodness of fit and the position of the dipole were then used as features to reject nonspike artifactual transients. It was not necessary to obtain an accurate localization of the spike generator; a simple dipole model provided sufficient information to reject many false detections. Using an independent data set of 20 patients to validate the method, Flanagan et al. reported a 53% decrease in false detections while only removing 4.3% of true spike detections compared to the original method of Gotman and Wang.[54,55]

Whether neural networks or more traditional methods are used, it is unlikely that local wave morphology is sufficient to differentiate epileptiform transients from other transients. Some form of context sensitivity appears to be necessary.

Recording Behavior

The analysis of behavioral manifestations of seizures is obviously a critical element. It can be performed by an observer or by video recording (often by both). It is now possible to record and store a few days of continuous video directly on a computer; the recording can then be reviewed at a later time. Computer networks can greatly facilitate this process by allowing the direct transfer of EEGs and simultaneous video from the recording computer to the review computer. Reviewers can choose to examine only specific sections of the recording, such as those marked by the automatic detection systems described earlier. The entire data set can also be reviewed at an accelerated speed to identify events of interest. For long-term archival purposes, only the sections of interest are usually kept due to limitations in archiving media capacity.

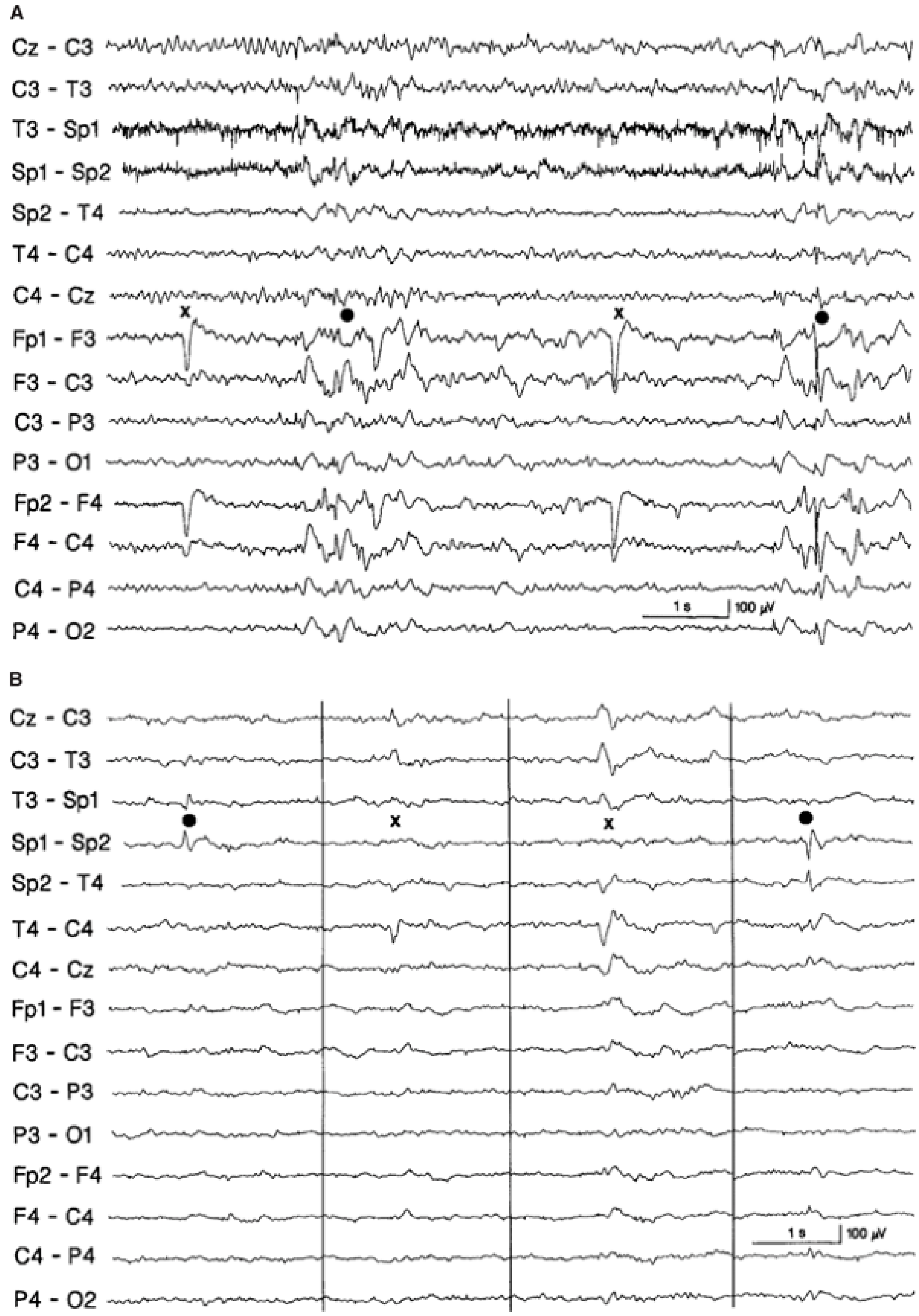

FIGURE 3. Use of spatial and temporal context in spike detection. Nonepileptiform transients are selectively

rejected (rejected events marked with **x**). **A:** During active wakefulness, as determined by automatic state classification, waves having the morphology and distribution of eye blinks are eliminated. **B:** During phasic sleep, sharp waves having a maximum at the vertex are eliminated. (From Gotman J, Wang LY. State dependent spike detection: validation. *Electroencephalogr Clin Neurophysiol.* 1992;83(1):12â€"18, with permission.)

Outpatient Monitoring

Portable devices are available with sufficient memory to allow 24-hour continuous recording of 20 channels of EEG. The recorded data can then be transferred to a standard computer for further analysis and archiving. Data analysis can include all the methods of automatic spike and seizure detection described previously, which can usually process a 24-hour recording in

<1 hour. Outpatient monitoring does not appear to change the spontaneous frequency of the patient's events, as hospitalization sometimes does; the yield of outpatient monitoring is therefore often higher than that of inpatient monitoring. The efficacy of this method was formally evaluated in 344 patients by Morris et al.[92] They concluded that combined pushbutton and automatic detection resulted in useful information being obtained in 74% of patients. Because equipment, methodology, and EEG quality are the same for inpatient and outpatient monitoring, patients can be shifted easily from one environment to the other according to the clinical situation.

Patients need to be selected carefully because outpatient monitoring is not always appropriate. If video is not essential and patients have frequent enough events, then outpatient monitoring is appropriate. When it is necessary to reduce antiepileptic medication to provoke seizure occurrence or when patients have a confusing type of event, then inpatient monitoring with video is recommended.

Display and Analysis After Detection

The benefits derived from computers relate not only to detecting epileptiform events during long-term monitoring, but also to displaying, manipulating, and analyzing the EEG. Some of the possibilities for display and analysis are outlined next.

Computer Review of the Electroencephalogram

A system that presents the EEG on the screen at 10 to 20 times the recording speed is easily implemented on a personal computer. When this is combined with data reduction, it is possible to review the most important information of a 24-hour recording in only a few minutes. This does not include the time required to interpret the EEG, particularly seizures, but rather indicates how long it takes to scan the recording. Seizures can be examined on a high-resolution computer screen displaying a large number of channels; 32 channels are commonly used, and even 128 channels can be viewed simultaneously, greatly facilitating the interpretation of EEGs from multiple intracerebral electrodes or the large subdural arrays sometimes used in presurgical evaluations. Furthermore, simple manipulations, such as changing gains or filters, reformatting the montage, or topographic mapping, can be performed interactively by the person interpreting the EEG at the time this information is required.

Analysis of Seizure Activity

It is possible to go beyond visual interpretation and analyze seizures to extract information of diagnostic or scientific interest. The graphic representation of seizures and quantitative measurements of their features can improve EEG interpretation.[3,5,15,22,45,52] Computerized signal processing tools can also be used to remove artifacts that may obscure ictal activity. For instance, digital filters are commonly used to remove high-frequency electromyographic (EMG) activity that frequently accompanies seizures recorded from the scalp.[49] However, muscle artifacts are known to contain significant power at frequencies below 30 Hz,[96] where seizure activity is also known to occur.[49] There is thus an overlap between the frequency spectra of EEG and EMG. Although aggressive filters could remove the entire EMG artifact, this would also inappropriately attenuate the EEG activity. Moreover, it might become difficult to differentiate between brain activity and the filtered EMG. Therefore, digital filters can only partially eliminate muscle artifact from the EEG.

Recently, methods based on independent component analysis (ICA)[20] have been applied to remove a wide variety of artifacts from the EEG signal. ICA is a blind source separation technique that can be used to decompose linear mixtures of signals. A classical application of ICA occurs in the so-called cocktail party problem, which stipulates that microphones placed at various locations in a crowded room will typically record several voices speaking simultaneously. ICA can then be used to process the recorded signals and extract each individual voice. In general, ICA can extract the sources, or components, contained in recorded mixtures, as long as these sources are statistically independent. This can be accomplished using any of the various algorithms designed for that purpose.[10,16,60]

The EEG signal originates from several independent sources of electrical activityâ€"brain generators, electrical fields due to ocular movements, scalp muscle activity, and so on. These electrical fields are known to propagate to the scalp by volume conduction, so that the signals recorded by scalp electrodes are sums of the activities from each source. EEG signals are thus well suited for processing by ICA. Based solely on the mixtures recorded by each electrode, ICA can automatically extract the original components. In particular, the sources of artifactual activity can be isolated and subtracted from EEG ictal recordings, thus improving the quality of the signal and facilitating seizure interpretation. Urrestarazu et al.[117] successfully applied this method to 10-second EEG segments containing the onset of seizures from patients with focal epilepsy. ICA was applied to these segments, thus automatically decomposing the EEG into several independent sources. The artifactual sources were then visually identified and subtracted from the EEG recordings. Two independent experts reviewed the original and processed EEGs in a random and blind fashion, and they concluded that ICA methods improved the quality of ictal EEG recordings, making it easier to determine the time of onset and topography of the seizures. It was also shown that the improvement in quality was superior to that provided by digital filters alone.

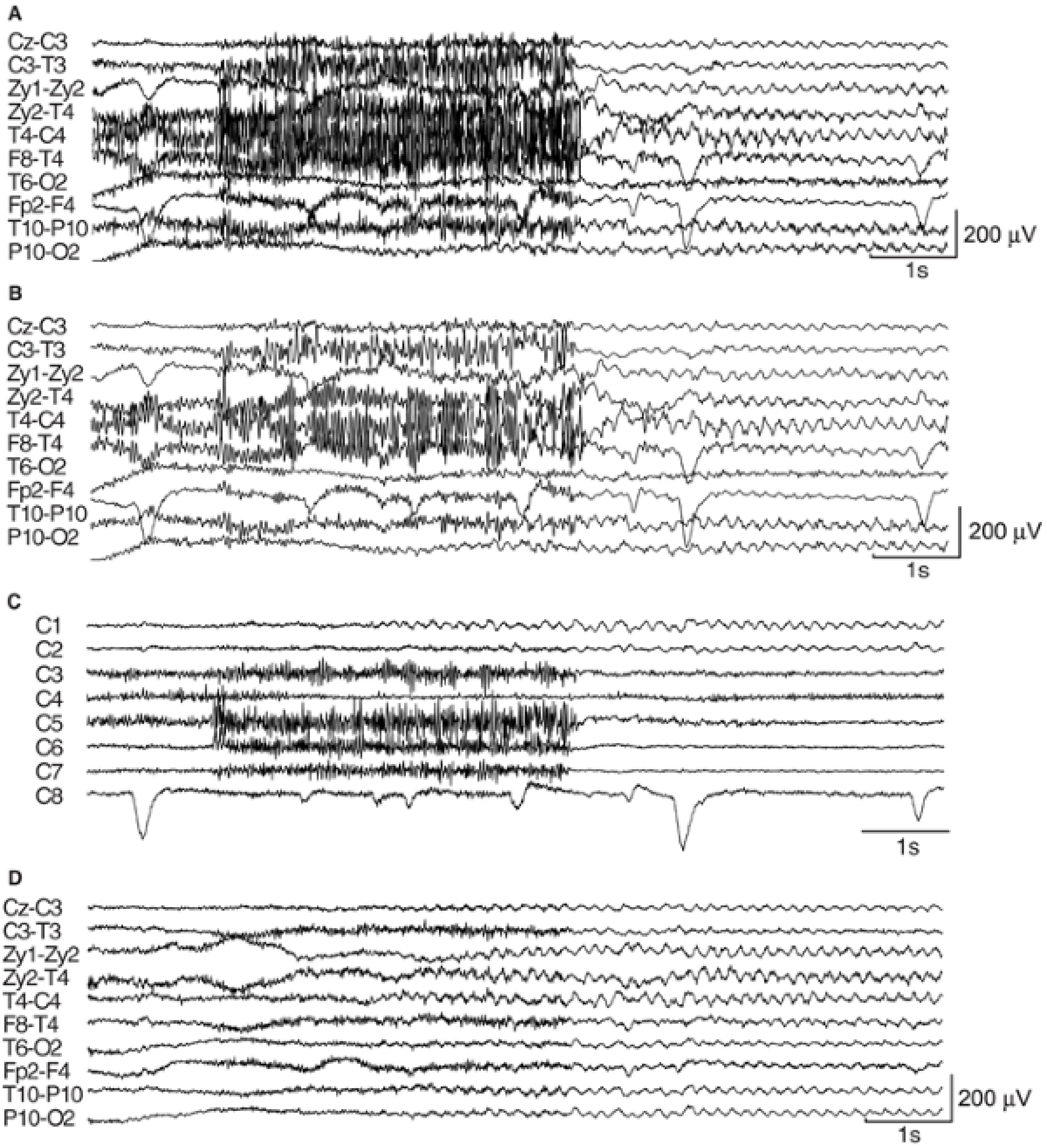

FIGURE 4. Application of independent component analysis (ICA) to automatically remove artifacts from seizure recordings using the system of LeVan et al.[82] **A:** Seizure heavily contaminated by electromyographic artifact, obscuring the onset. Eye blink artifacts are also clearly visible. **B:** Same seizure after the application of a low-pass 30-Hz filter. Muscle artifact is still clearly present at seizure onset. **C:** Time courses of the sources extracted by ICA applied to the seizure in panel A. The figure only shows a subset of the components. Components C1 and C2 correspond to seizure discharges, whereas components C3â€“C7 represent muscle activity. Component C8 corresponds to eye blinks. The amplitudes of the components are normalized because ICA can only extract sources up to a scaling factor. **D:** Electroencephalogram reconstructed after subtraction of automatically selected artifactual components. The eye blink artifacts have been eliminated, along with most of the muscle activity. The ictal discharges at seizure onset are now clearly visible.

There are some difficulties, however, with the application of ICA to remove artifacts from EEG recordings. ICA algorithms extract independent sources in an unpredictable order; this means that the sources must be visually inspected, and those corresponding to artifactual activity must be identified by the operator. This is a tedious process because the ICA decomposition of the EEG results in the extraction of a large number of sources. For example, there will be distinct components corresponding to the generators of epileptic activity and background activity, which might be numerous. In general, the application of ICA can potentially yield as many independent sources as there are recording channels. In a clinical setting, montages using 32 channels or more are common; it would thus be impractical to request that electroencephalographers manually identify the artifacts among the components extracted by ICA.

LeVan et al.[82] proposed a system for automatically classifying the sources extracted by ICA from ictal scalp EEGs. Their system is based on the use of spectral, statistical, and spatial features in a Bayesian classifier to identify artifactual sources extracted by ICA and subtract them from the recording. The system was evaluated using a data set of 23 unselected patients, resulting in the successful recognition of components of brain activity with 87.6% sensitivity while subtracting 70.2% of the artifactual components. A review of the results by an expert concluded that the automatic system could successfully remove a wide variety of artifacts from ictal scalp EEGs and facilitate the interpretation of the seizures without inadvertently subtracting cerebral activity from the recording. FIGURE 4A shows an example of a seizure that was heavily contaminated by EMG and ocular artifacts. The application of a low-pass digital filter

at 30 Hz can reduce the EMG activity (Fig. 4B), but a portion of the artifact still obscures the seizure onset. Application of ICA on the seizure yields several components representing seizure activity and various artifacts (Fig. 4C). After identifying and subtracting the artifactual components using the automatic method, the resulting EEG activity becomes clearer (Fig. 4D). The EMG artifact has been greatly attenuated, and the eye blink artifacts have been eliminated. The onset of the ictal activity is now clearly visible. ICA, combined with the automatic classification of the extracted components, thus can be an effective method for removing artifacts from EEG recordings.

In addition to artifact removal, computer methods can also be used to study seizure propagation. The study of interactions between brain regions during seizures was pioneered by Brazier,[14] who used the coherence function to measure the strength of interaction between seizure discharges in two locations and the phase spectrum to measure time differences of a few milliseconds. Thus, rapid propagation of seizures could be followed. The method was made more reliable by Gotman,[36,38] who included in the measurement a range of frequencies rather than a single frequency. Its validity was established in experimental and human epilepsy in cases in which the location of the focus was known. This method allowed the study of interhemispheric interactions during widespread spike-and-wave activity[36,74] and during temporal lobe seizures.[42,51,83]

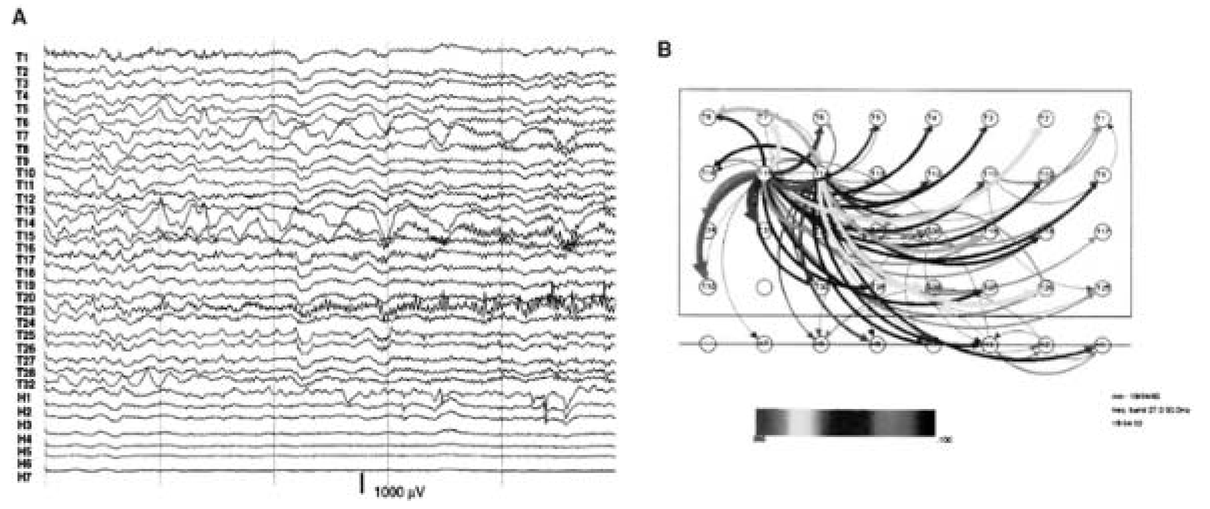

FIGURE 5. A: Intracranial electroencephalogram showing the onset of high-frequency activity in a patient with complex partial seizures. Subdural grid contacts are labeled T1â€“T32, and depth electrode contacts are labeled H1â€“H7. The depth electrode was placed through the grid, with H1 being the deepest contact, in the hippocampal structures. **B:** Plot of the integrated directed transfer function revealing the flow of activity for the 5-second interval illustrated in panel A. Each circle represents one electrode contact. The widths of the arrows are proportional to the value of the integrated directed transfer function for the respective contacts. (From Franaszczuk PJ, Bergey GK. Application of the directed transfer function method to mesial and lateral onset temporal lobe seizures. *Brain Topogr.* 1998;11(1):13â€“21, with permission.)

There are other methods for measuring interactions during seizures. The average amount of mutual information (AAMI) has a theoretical advantage over coherence because coherence can detect only linear (in the mathematical sense) relationships, whereas AAMI can also detect more complex relationships. Average amount of mutual information and other nonlinear methods are described by Lopes da Silva and Mars.[85] Fernandes de Lima et al.[26] compared a linear and a nonlinear regression coefficient in the study of interhemispheric interactions during hippocampal seizures in rats and found that the nonlinear measure was more robust than the linear one and could yield values of interaction when the linear one was at noise level. One important factor is not often discussed when these methods are compared: The size of the recording electrodes probably influences the type of relationship. Discharges recorded from very small electrodes, which can record multiple-unit activity, are more likely to have nonlinear relationships than discharges from macroelectrodes, which record from large populations of neurons. Nonlinear correlation coefficients were also used to investigate cortical and thalamic interactions during absence seizures in rats.[90] Le Van Quyen et al.[78] examined nonlinear interactions during temporal lobe seizures recorded with intracranial electrodes and found an increase in nonlinear interdependence in the early part of the ictal period. Franaszczuk et al.[28,29] presented another type of method, known as the directed transfer function, to study patterns of seizure propagation. This technique can be applied on several channels at once, detecting flows of propagation that cannot be identified visually. FIGURE 5A shows the onset of a seizure recorded in a patient with intracerebral electrodes. The seizure is characterized by high-frequency activity predominantly visible in contacts T14, T15, and T23. The flow of activity revealed by the integrated directed transfer function is illustrated by the arrows in FIGURE 5B. This suggests that the activity originates from contacts T14 and T15, with the largest flow (widest arrows) going from T15 to T23 and from T15 to T32.

Independent component analysis, which was described earlier as a method for separating artifactual sources from EEG sources, also can be useful for the analysis of seizure activity. McKeown et al.[89] applied ICA to spike-and-wave discharges in absence seizures. They found that the spike pattern and the wave pattern were separated into distinct components, with the spikes having a more focal spatial topography. Moreover, there were cases in which multiple components accounted for the wave pattern, with slightly different spatial topographies and a time delay between them. These multiple extracted sources could reflect the propagation of the wave pattern. Nam et al.[94] used ICA to study sources of ictal activity in medial temporal lobe seizures. They noted that the spatial topographies of the ictal sources extracted by ICA were dipolar in nature and could be used to successfully lateralize the seizures. Urrestarazu et al.[118] applied ICA to intracranial recordings of temporal lobe seizures. Among the extracted sources, they sometimes found components with a bilateral distribution even at times when visual inspection suggested that the seizure discharges were unilateral. This phenomenon was more frequent in seizures that subsequently clearly spread to both temporal lobes. The ICA method was thus able to reveal bilateral activity that occurred earlier than originally suspected by visual examination of the EEG.

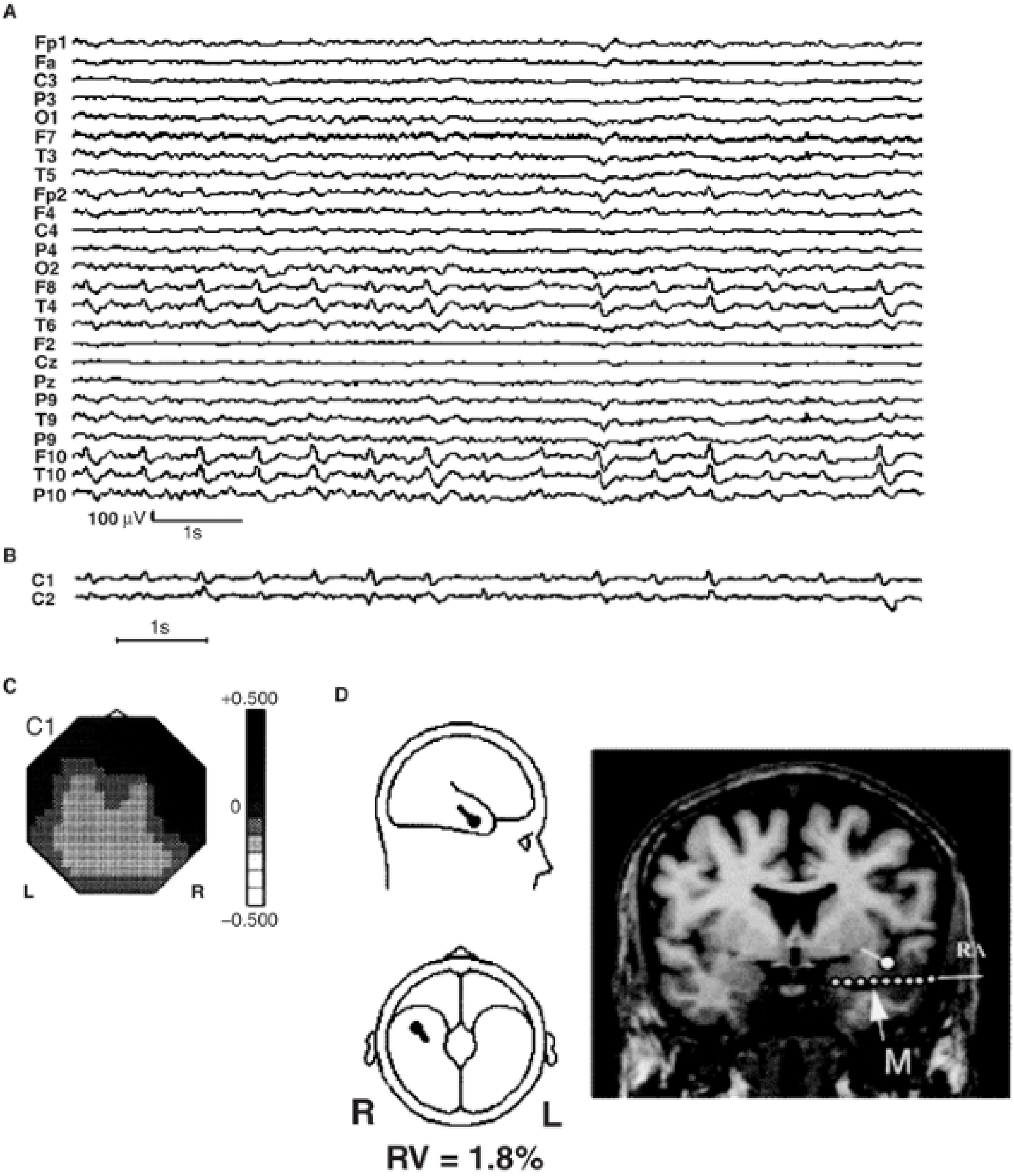

FIGURE 6. Application of independent component analysis (ICA) to the analysis of interictal spikes. **A:** Scalp electroencephalogram record formed by concatenating 15 spikes from one epileptic patient, along with some surrounding background activity. **B:** Two of the sources extracted by ICA include the interictal discharges, whereas the other components, not shown here, correspond to background activity. Component C1 has the clearest epileptic activity. **C:** Spatial map corresponding to component C1. The topography appears dipolar and right-sided. **D:** A single equivalent current dipole can be fitted to the spatial topography of component C1 with a residual variance (RV) of 1.8%. This dipole is then overlaid on a magnetic resonance image along with the locations of the contacts of depth electrode RA, which was part of an intracranial electrode investigation. This investigation revealed a maximal intracranial field M at a distance of 10.8 mm from the equivalent current dipole fitted to component C1. (From Kobayashi K, Merlet I, Gotman J. Separation of spikes from background by independent component analysis with dipole modeling and comparison to

intracranial recording. *Clin Neurophysiol.* 2001;112(3):405â€“413, with permission.)

Analysis of Interictal Activity

Automatic spike detection was described earlier in this chapter mainly in the context of data reduction, but it also offers the benefit of quantification. It is possible to edit interactively on the computer screen the false-spike detections so that only valid detections remain. They can be displayed along with their spatial and temporal distributions. Quantification of spike activity during several days of monitoring has proved to be invaluable in the study of factors that might affect the rate and localization of spikes. It was found that the rate of focal spiking does not change, by either increasing or decreasing, before seizures.[53,66,86] In contrast, there is a large increase in spiking in the days that follow most secondarily generalized seizures and many partial seizures; surprisingly, spiking rates appear unaffected by changes in AED levels.[50,53] These postictal increases in spiking and the absence of decrease in spiking with high AED levels were replicated in the kindling model of epilepsy.[34,39,81] Thus, quantification of spiking rates has established that spiking does not change as was intuitively thought (increasing before seizures and decreasing with high AED levels).

Spikes were also quantified during the different stages of sleep in patients evaluated for epilepsy surgery with noninvasive recordings. Results indicated that spiking is more focal during rapid eye movement (REM) sleep than during slow-wave sleep. The localization obtained from REM sleep spiking correlates better with other tests of localization (e.g., seizure onset, radiologic findings) than the localization obtained during slow-wave sleep or wakefulness.[110]

The question of seizure propagation was discussed previously. The question of whether spike activity propagates between brain regions has also been studied. Emerson et al.[24] used spike-triggered averaging to measure the propagation between temporal and frontopolar regions and concluded that it was possible to see relationships not apparent by visual inspection. Spatiotemporal dipolar modeling has also been used to see whether spikes could be represented by one or several dipoles, in an attempt to localize the source of spike activity.[9,23] The modeling of spike activity with dipole or distributed models is discussed extensively in Chapter 78.

Recently, Kobayashi et al.[72] studied epileptiform discharges by applying ICA on a data matrix formed by concatenating several EEG segments, each containing a spike and some surrounding background activity. The analysis revealed multiple extracted sources corresponding to the discharges, which were clearly separated from the background. The time delays and different spatial topographies of these multiple components could reflect the spatiotemporal evolution of the spikes. The validity of the sources extracted by ICA was later established by comparing the topographies of the spike components with the fields subsequently measured by intracranial electrodes.[73] It was observed that the number of intracranial peaks measured by depth electrodes generally matched the number of spike components extracted by ICA. A single equivalent current dipole was then fitted to the ICA source with the clearest epileptic activity. Despite the use of such a simple model, the distance between the dipole and the intracranial electrode contact with the maximal field was generally small, ranging from 4.7 to 31.9 mm.

An example of this is shown in FIGURE 6. After the application of ICA to the spikes of FIGURE 6A, epileptic activity was found in two of the resulting extracted components (Fig. 6B). The component having the clearest epileptic activity had a spatial topography that was dipolar (Fig. 6C). An equivalent current dipole fitted to that spatial map was 10.8 mm away from the maximal intracerebral field, as determined by a depth electrode investigation (Fig. 6D).

Promising results were also obtained when using the more sophisticated RAP-MUSIC algorithm for source localization; this algorithm was applied to the subspace formed by the epileptic components extracted by ICA.[70,71] ICA was thus used to subtract EEG sources of background activity or artifacts so that only epileptic sources remained. Applying RAP-MUSIC to this processed data set yielded more accurate results than those obtained by using averaged raw spikes. ICA can thus be an effective method for isolating the epileptic activity from the background. Jung et al.[65] analyzed generalized spike-and-wave discharges with ICA. The extracted components corresponding to the epileptic discharges were then modeled using dipole sources in a spherical head model. It was found that the position and orientation of the equivalent dipoles could be used to distinguish between patients with primary or secondary bilateral synchrony. Another recent study used ICA to distinguish between focal and multifocal spikes.[62] Spikes of different origins were generally separated into distinct components; each of these components thus tended to represent one focus of the spike activity.

Summary and Conclusions

Computers can play a variety of roles in assisting the recording and analysis of the EEG of epileptic patients. During long-term monitoring, computer assistance is almost indispensable for the detection of epileptic events. There is no single economical method that ensures the detection of all seizures in every patient; all available help must be used, including staff and patient reporting, and computer detection. In some patients, one method might prove to be more useful than others, but this is not known in advance of the monitoring sessions.

Spike and seizure detection are not simple tasks, as researchers in this area originally thought. The human who reads an EEG uses clues from a wide spatial and temporal context, clues that are difficult to encode in computer programs. Most methods analyze the EEG at a very local level (looking at 10 to 30 seconds of EEG at a time, often one channel at a time). It would therefore be naive to expect a high degree of reliability from such automatic methods. Nevertheless, they can be extremely useful if implemented in the context of human validation. In this case, methods can be designed to yield a sensitivity that is as high as possible, and false detections can be removed manually during a subsequent review of the detected events. On the other hand, automatic warning systems have much more stringent requirements: They must operate in real time, they must detect seizures as early as possible after their onset, and the false-detection rate should be minimized to avoid unnecessary disruptions. Nevertheless, some efficient systems have been designed to satisfy these constraints. Recently, improvements in the performance of detection methods have been achieved by incorporating knowledge of a wider context, such as the state-dependent spike detection method. Further developments in this area will in all likelihood result in much better performance, but it is unlikely that a stage will be reached in which human validation is not required.

Finally, computer analysis of seizures and spikes may provide information that is not readily available from traditional visual examination. This is primarily attributable to the possibility of quantifying the EEG and of making mathematical analyses that can be related to brain function. In particular, the method of independent component analysis is effective at separating the various sources of electrical activity present in the EEG signal. ICA can be used to remove artifactual sources contaminating the EEG signal and to analyze the patterns of propagation of ictal or interictal activity.

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Chapter 96

Overview: General Approaches to Treatment

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Introduction

After making the correct diagnosis of a patient but before writing the prescription for a specific antiepileptic drug (see previous section), the physician must consider a number of additional issues. The full understanding of these issues is reviewed in this section and should permit the best outcome for the patient, regardless of the drug or other therapy that is chosen.

However, before entering into the complexities of treatment strategies, we need to provide a brief reminder about the accuracy of the patient's diagnosis. The correct diagnosis is, after all, the fundament on which all therapy is based. Inadequate or wrong diagnosis is likely to lead to inadequate and potentially harmful treatment. This a difficult area given that epilepsy is not a single disease but a heterogeneous array of syndromes with innumerable causes and a wide range of clinical expressions, the final one of which is the seizure itself. So how are we to make a correct diagnosis of the patient with the disorder? We can only do this by recognizing that multiple levels of diagnosis are present, and these must be identified in each patient.

Levels of Diagnosis

The meaningful levels of diagnosis in patients with epilepsy can conveniently be divided into three basic categories: (a) the etiologic diagnosis, (b) the seizure diagnosis, and, where possible, (c) the epilepsy syndrome diagnosis. The etiologic diagnosis requires identification of the cause of the epileptic seizures. The causes range from obvious structural abnormality of the brain to usually still obscure genetic abnormality. Every patient deserves a search for the etiologic diagnosis—and appropriate specific therapy for this etiology, when possible—even though, in a substantial proportion of patients, the effort will be unsuccessful. In most patients, the correct classification of seizure type(s) and, possibly, epilepsy syndrome permits the correct choice of therapy and, even more specifically, the correct choice of antiepileptic drug. Our ability to establish an accurate diagnosis has been greatly aided not only by a better overall understanding of the disorder, but also by technical advances such as brain imaging (for improved etiologic diagnosis) and intensive electroencephalographic (EEG)/video monitoring (for more precise seizure diagnosis). Although the seizure diagnosis alone can help with the choice of medication, the epilepsy syndrome diagnosis is more important for predicting the prognosis and, potentially, the duration of therapy. Recent improvements have been made in both the seizure classification and the classification of the epilepsies but, as noted in other chapters, considerable refinements are needed for better diagnosis at both of these levels.

Treatment Issues

Once the patient's diagnosis is secure, what are the treatment issues that must be considered to optimize the outcome for the individual? These treatment variables, discussed at length in the following three dozen chapters, have been divided into the following sections: (a) general aspects (indications for treatment, goals of treatment, need for a comprehensive treatment approach, assessment tools, and age considerations), (b) principles of drug treatment, (c) strategies for pharmacotherapy, (d) special therapeutic considerations, and (e) alternative and experimental approaches, although inevitably these areas will have considerable overlap and interaction.

Health-related quality of life (HRQoL) embraces the philosophy that treatment is much more than simply a knee-jerk drug prescription. Indeed, the physician's aim is to ensure that the patient derives the optimal overall value from the recommended therapeutic intervention by including measures of how the patient feels and functions so as to reduce both handicap and disability due to epilepsy and its diagnosis. Rarely does this assessment make inappropriate the primary choice of therapy (e.g., ethosuximide or valproate for absence seizures, or lobectomy for intractable temporal lobe epilepsy), but it does put into context the physician's impact on the whole patient rather than focus only on seizure control. Is the patient with multiple severe handicaps that include epilepsy at greater risk from increasing the antiepileptic drug load than from having a few more seizures every year? Is the patient who had a temporal lobe resection and is now seizure free but is increasingly clinically depressed better off at a time when his family expects him to exhibit greater independence and even to get a job? These highly focused examples are only a small taste of the issues addressed in the chapters on this topic, encouraging all of us to consider total patient care rather than merely seizure control.

The issue of patient autonomy is one of growing importance that needs to be considered and is of relevance to HRQoL. Patients and their caregivers expect adequate and appropriate information about treatments as well as active involvement in therapeutic choices. In many cases, the clinician has ceased to be the major provider of information because this is readily available from other sources that include package inserts and the Internet. He or she still has an important role to play, however, as an interpreter of information for the individual patient. It is axiomatic that the best therapeutic choice is one that is reached jointly by a well-informed patient (with or without caregiver involvement) and clinician. Indeed it can be argued that therapeutic decisions reached by other means are unlikely to be accompanied by adherence.

Principles of Drug Treatment

The section on principles of drug treatment provides a fundamental perspective on how antiepileptic drugs work and how to use them optimally. Those who prescribe drugs must mentally separate the two basic issues of drug action—what the drug does to the body (pharmacodynamics) and what the body does to the drug (pharmacokinetics).

Seizure control and adverse drug effects are both pharmacodynamic measures of a drug's effect on the body, whereas the time needed for drug absorption, distribution, and elimination is a pharmacokinetic measure of the body's effect on the drug. Although a full understanding of both pharmacokinetics and pharmacodynamics is needed to prescribe antiepileptic drugs properly, chapters in this section concentrate on pharmacokinetics, therapeutic drug monitoring (e.g., the use of blood concentration data to improve patients' outcomes), and highly specific pharmacodynamic issues, such as differences in efficacy spectrum and adverse effects profiles between drugs, mechanisms of drug resistance, drug–drug interactions, and teratogenicity. These issues have important consequences for special groups of patients and raise questions concerning the degree to which therapeutic choices should be determined by, for example, gender and age in addition to seizure type and syndrome.

Strategies for Pharmacotherapy

If the previous section is essential for understanding how drugs function, the section on strategies for pharmacotherapy is devoted primarily to application of this knowledge to optimal clinical management. The questions answered here range from “When should one treat?” to “How should treatment be started?” to “How and when should treatment be discontinued?” In addition to these questions are chapters on how to maintain and alter therapy for maximal effectiveness. Although individual drugs are described in detail in the previous section, this section on strategies is the overview that permits the physician to put drug therapy in the best context for patient care.

Special Therapeutic Considerations

Nowhere is the heterogeneity of the epilepsies more evident than in the section on special therapeutic considerations. With emphasis on treatment, this section encompasses many of the vexing issues confronted by the health care provider. Should the first seizure be treated? Should one treat uncomplicated febrile seizures? What is the appropriate first medication for status epilepticus? These are only examples of the difficult questions addressed in this section. Although the section is entitled “Special,” by no means should the reader take this to mean *uncommon*, because some of the conditions considered here are among the most common in routine clinical practice.

Alternative Approaches

Many practitioners have recognized that standard drug therapy or surgical intervention is often suboptimal for the individual patient and that other approaches are worthy of consideration. The section on alternative and experimental approaches is designed to be a rather comprehensive view of therapeutic possibilities other than the usual drugs or standard surgery. These include some treatments that, while developed relatively recently, have already undergone rigorous testing in randomized, controlled trials (e.g., vagal nerve stimulation), treatments that we are just starting to understand although they have been around for almost a century (e.g., the ketogenic diet), and others that have not received much attention from the medical community, such as folk therapies. Although this discussion is small by comparison to the sections on more conventional treatments, interest in these approaches continues to increase for very good reasons—in some patients, some of these approaches are effective when the usual methods fail. No doubt we will be exposed to more experimental alternatives as we search for optimal patient care.

Summary and Conclusions

There are an increasing range of choices of treatments for patients with epilepsy. The best treatment will involve the use of high quality information, its interpretation by the clinician for the individual patient, and the involvement of the patient in the decision making process.

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Chapter 97

Indications for Treatment

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Timothy A. Pedley

Introduction

Epileptic seizures are among the most common symptoms of disturbed brain function. They result from many causes and can have widely varying manifestations. An *epileptic seizure* (a discrete event resulting from transient, hypersynchronous, abnormal neuronal behavior) should be distinguished from *epilepsy* (the condition of recurring epileptic seizures). Seizures are epileptic events and the indispensable characteristic of epilepsy, but not all seizures are manifestations of epilepsy. There are many different types of seizures, each producing a profile of characteristic behavioral changes and electrophysiologic disturbances. Some patients have seizures that are self-limited—that is, they occur only in the course of an acute medical or neurologic illness. Other people have one or two single seizures at some time in their life for which a cause is never determined. Such seizures are not epilepsy. Epilepsy, on the other hand, is a group of chronic disorders, the hallmark of which is recurrent, unprovoked seizures. Many patients with epilepsy have more than one seizure type, and many have other symptoms as well. Sometimes, additional electroencephalographic (EEG), clinical, familial, etiologic, and prognostic data are sufficiently similar among a group of patients with epilepsy that a more specific *epileptic syndrome* can be defined.

Given these considerations, it should not be surprising that the many seizure types and the various forms of epilepsy have different etiologies, different prognoses, and different consequences, each of which may have quite different implications for individual patients. Thus, indications for treatment also vary, and no formula or algorithm can be applied justifiably to all cases.

The nature and severity of the consequences of seizures depend on the type and timing of attacks, the age and condition of the affected individual, the patient's type of employment, the response of the patient's family, societal attitudes, and many other factors. Because the effects of seizure recurrence are so variable, each affected person must be considered uniquely during evaluation of the impact of further seizures in relation to the potential consequences—both beneficial and adverse—of treatment. Ultimately, the decision regarding whether to treat rests with the patient or, in the case of young children, the patient's family. This is as it should be because only the individual affected by seizures, and the family, can determine the extent to which further seizures will interfere with that individual's life. It is therefore the *patient's* perception of the consequences of further seizures that drives the decision to treat or not to treat.

Illustrative Cases

Case 1. Should a 2-year-old girl who has had a single convulsion lasting <2 minutes associated with a fever of 101°F be started on drug treatment? What if the seizure had lasted 20 minutes? What if the child had had a second brief seizure 24 hours after the first? Or another seizure 6 months later?

Case 2. Should a 14-year-old boy be started on drug treatment after a first unprovoked generalized tonic–clonic seizure? Would it make a difference if he were 17 years old and driving?

Case 3. Should antiepileptic drug therapy be recommended to a recently married woman whose husband first noted her early-morning "jumps" and then witnessed a generalized tonic–clonic seizure? Would the advice be different if she were eager to start a family?

Case 4. Should a 3-year-old girl with profound retardation who has been having two staring spells each week for the last several months be started on drug treatment? What if she were having drop attacks instead? Would the physician's advice depend on whether the child was ambulatory? At home or in a long-term care facility?

Case 5. How would a physician advise a factory worker who has had a first nocturnal generalized tonic–clonic seizure? Would the physician's advice be different if the patient expressed concern about failing the plant's required random drug screens and possible job loss after starting drug treatment? Would the physician's recommendations be influenced if the patient used heavy industrial power tools? Or drove a truck? Would the recommendations be the same for a housewife?

Each of these cases emphasizes situations that are unique to a particular patient and illustrates that both the consequences of further seizures and the consequences of treatment can be quite different, depending on individual circumstances. This chapter reviews the factors that physicians should consider in assisting patients and their families to reach informed, reasonable decisions about whether to initiate treatment.

Elements of the Decision-Making Process: Assessing Risks and Benefits

Type of Seizure

It is obvious that different seizure types have different consequences for patients. A generalized tonic–clonic seizure is likely to be far more hazardous and have more psychosocial impact than an absence seizure. A typical simple partial seizure of benign rolandic epilepsy, manifested only by speech arrest, salivation, and facial twitching, may be much less important to an individual than a complex partial seizure with unresponsiveness, prominent automatisms, and postictal confusion. An atonic seizure that causes a child to fall, with risk for injury, can be very debilitating, even though brief. Complex partial seizures that begin with a prolonged aura are usually less

disabling than complex partial seizures that begin with abrupt loss of consciousness. Different epilepsy syndromes, with different seizure types and prognoses, are likely to affect patients in very different ways.

Timing of Seizures

Some persons have only nighttime seizures. Others have seizures only in the morning after awakening. Some women have seizures linked to phases of their menstrual cycles. Other patients have seizures only in certain circumstances (e.g., when deprived of sleep, when under great stress, or after drinking) or with specific triggers (reflex epilepsies). Many patients have seizures that are completely unpredictable. The temporal patterns of seizures clearly influence their impact on patients' lives.

Frequency of Seizures

Only about 30% of persons who have a single, unprovoked, generalized tonic–clonic seizure have a second, regardless of whether they are treated. Many children with benign epilepsy syndromes have only a few seizures. Patients with cryptogenic or symptomatic localization–related epilepsy usually have frequent seizures that may be drug resistant. Individuals with temporal lobe epilepsy typically have many complex partial seizures but relatively infrequent secondarily generalized seizures. Someone with frontal lobe epilepsy, however, may have mainly generalized seizures.

Frequent seizures of whatever type interfere with function, but the responses of individuals, even to daily or weekly seizures, vary widely. Some patients are greatly disabled; they are socially isolated, unemployed, and severely restricted in what they can do. Others with similar seizures are gainfully employed, well adjusted, and productive members of society. Children generally adapt better to a higher rate of seizures than do adults. Thus, although frequency of seizures is closely related to the consequences of epilepsy, the impact varies among individuals, even those with the same rate of seizures, depending on many factors—intrinsic and acquired; personal and societal—that affect a person's support mechanisms and ability to cope and adapt.

Effects of Age on Consequences of Seizures

The consequences of recurrent seizures are age dependent. Infants, whatever the seizure type, are unlikely to be physically injured during a seizure or even be aware, or remember, that a seizure has occurred. Toddlers, although usually in a supervised environment, are more likely to be affected by consequences related to the seizures, but these depend greatly on the type of seizure (e.g., head injury from an atonic seizure). In addition, children begin to feel the effects of overprotection resulting from the family's fear of recurrence. Adolescents, with their desire to conform, sensitivity to embarrassment, and growing desire for independence, are greatly affected by recurrent seizures. Common concerns include loss of control of bodily functions, especially incontinence; not being able to obtain a driver's license or, if they are already driving when seizures begin, loss of the license; social isolation; and conflicts about restrictions—both reasonable and unreasonable—imposed by parents, schools, and sports teams. Adults face restrictions on driving (which may, in some cases, directly affect livelihood); employment (keeping a job or having opportunities for career advancement); and social opportunities, including the ability to develop and maintain significant relationships. Adults are also concerned that they may be unable to meet their responsibilities as parents or providers, and they naturally fear embarrassment.

Environment

The consequences of seizure recurrence at each age may also vary according to whether the patient lives in a city, where medical facilities are generally close by and easily accessible via public transportation, or in a rural environment, where medical services and community resources are limited and often distant, close neighbors are few, and personal automobiles are the only means of transportation.

Consequences of seizures also depend on occupation. For any given seizure type or frequency, the consequences for office workers will likely be different than for persons operating machinery, and individuals who must work in exposed areas face different consequences than those who work in protected environments.

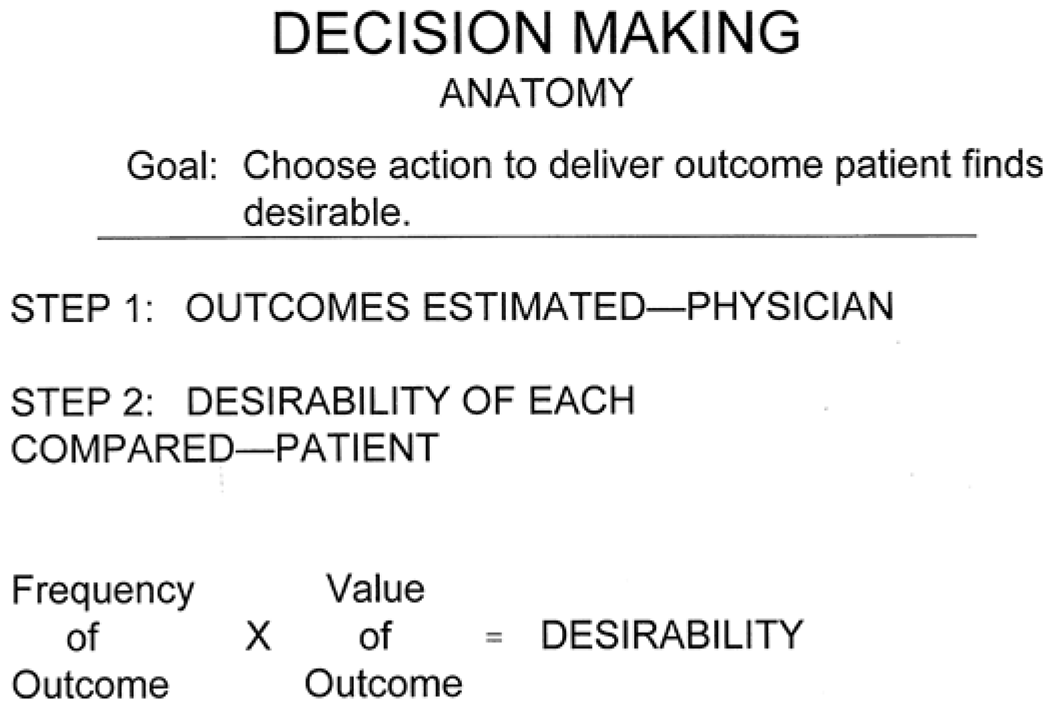
Consequences of Treatment

Consequences of treatment depend on the drug chosen and the number of drugs used. They also depend on whether side effects develop and whether seizures are completely or only partially controlled. All drugs have adverse effects, some more than others, and these range from minor to severe. Neurotoxicity can be subtle, especially in terms of effects on cognition and behavior. Children especially may inadvertently be overtreated, with adverse consequences for learning and psychological development.

Deciding Whether to Treat

The Issue

Although there can be little doubt that drug treatment is indicated and beneficial for most patients with epilepsy, there are certain circumstances in which antiepileptic drugs may reasonably be withheld or deferred or used for only a limited time. The common issues in such cases are those listed in the foregoing section and relate to (a) the probability of seizure recurrence, (b) the likelihood of substantial psychosocial, vocational, or physical consequences with further seizures, and (c) the question of whether the benefit to be derived from treatment substantially outweighs the chance of treatment-related side effects (Fig. 1).



DECISION MAKING
ANATOMY

Goal: Choose action to deliver outcome patient finds desirable.

STEP 1: OUTCOMES ESTIMATED—PHYSICIAN

STEP 2: DESIRABILITY OF EACH COMPARED—PATIENT

Frequency of Outcome X Value of Outcome = DESIRABILITY

FIGURE 1. The key steps in the decision-making process regarding treatment. (Based on data from Eddy DM. Anatomy of a decision. *JAMA* 1990;263:441–443.)

Acute Symptomatic Seizures

Acute symptomatic seizures are those caused or provoked by an acute medical or neurologic illness. Febrile seizures in children are the most common example (see Chapter 57). Other frequently encountered causes include metabolic or toxic encephalopathies (uremia, hypoglycemia and hyperglycemia, hepatic failure, drug withdrawal) and acute brain infections (encephalitis, meningitis). To the extent that there is no underlying permanent brain damage, seizures occurring in these settings are usually self-limited. The primary therapeutic consideration in such patients should be identification and treatment of the underlying disorder. If antiepileptic drugs are used to suppress seizures acutely, they generally do not need to be continued after the patient has recovered from the primary illness. It is important to remember, however, that the presence of a precipitating medical illness does not necessarily exclude the need to search for brain pathology; underlying brain lesions increase the risk for acute symptomatic seizures (as well as epilepsy) in appropriate settings.[7]

The issue of treating acute symptomatic seizures that occur in the setting of stroke, head injury, neurosurgical procedures, and alcohol use is more complicated. Each of these is a significant risk factor for both acute symptomatic seizures and epilepsy.[8] Although antiepileptic drugs are effective in treating seizures acutely, none has yet been shown to delay or reduce the development of later epilepsy. This has been best demonstrated for seizures occurring after a head injury (see Chapter 253). Phenytoin, for example, is highly effective in suppressing seizures in the first week after a head injury, but long-term prophylactic treatment is ineffective in preventing posttraumatic epilepsy.[22] The association between alcohol and seizures is also complicated. Whereas acute alcohol withdrawal can trigger self-limited seizures that do not require treatment, chronic alcoholism is a major risk factor for epilepsy.[14] Thus, over time, many alcoholics may have both acute symptomatic seizures (withdrawal seizures) and recurrent unprovoked seizures (epilepsy).[11,20] Given these considerations, we believe that the approach to patients who have acute symptomatic seizures as well as a substantially increased risk for later epilepsy should be based on the need to suppress active seizures, not on the hope that later epilepsy may be prevented.[17] This approach is supported not only by clinical experience and the results of a limited number of clinical trials, but also by results of animal experiments investigating the mechanisms of action of antiepileptic drugs now available. For the most part, current antiepileptic drugs, although effective as seizure suppressants, do not affect the development of epilepsy (epileptogenesis).[19]

Febrile seizures require special consideration. These are the most common and probably best-studied form of acute symptomatic seizure. They are almost always benign events in the sense that the potential neurologic and medical consequences of even multiple febrile seizures are vanishingly small (see Chapter 57). Furthermore, only about 30% of neurologically normal children with a single febrile seizure have further febrile seizures, and this risk is most clearly related to age.[3,12] Moreover, whereas the risk for later epilepsy is increased modestly in children with febrile seizures, to about six times that of the general population, this varies with the clinical features of the febrile seizures.[1,13,23] There are no data demonstrating that prophylactic treatment alters this risk. Although the possibility of recurrent febrile seizures understandably evokes fear and apprehension in parents, we believe that these concerns are best dealt with by education and reassurance rather than by treatment with antiepileptic drugs. Issues of treatment related to febrile seizures are discussed more fully in Chapter 124.

The Single Unprovoked Seizure

The majority of patients come to medical attention after having had more than one seizure. However, about 30% of patients with unprovoked seizures, virtually always generalized tonic–clonic convulsions, are seen by physicians after only a single attack. It is reasonable to consider whether treatment is indicated in this group of patients (see Chapter 122). The data of Hauser et al.[9] and Shinnar et al.[18] clearly establish low- and high-risk groups for recurrence after a single unprovoked seizure. The risk for epilepsy is greatly increased in the presence of an abnormal EEG, history of brain injury, and family history of epilepsy. Conversely, patients without any of these factors have a much lower risk for further seizures.

Although a large, multicenter, randomized study from Italy[6] demonstrated that antiepileptic drug therapy reduces the risk for relapse following a first unprovoked generalized tonic–clonic seizure, there is little evidence that the ultimate prognosis, especially regarding the development of epilepsy after 2 years or the chance of eventual remission following further seizures, is affected by early antiepileptic drug treatment.

Thus, although data demonstrating the positive effect of therapy on reducing relapse rates, even in patients at low risk for development of epilepsy, are available to justify treatment, we believe that treatment should not be automatic for this group of patients. Treatment decisions following a single unprovoked seizure should still involve a discussion and analysis of the benefits to be gained from treatment versus the potential risks or adverse effects of therapy. For example, in nearly one third of patients treated with antiepileptic drugs, side effects develop that are severe enough to require a change in treatment.[10,21] Furthermore, when there are particular concerns (as in children) about the effects of antiepileptic drugs on brain development, learning, and behavior,[5,16] we tend to avoid or defer treatment, especially if the consequences of further seizures are judged to be insignificant.

Benign Epilepsy Syndromes

Several electroclinical syndromes have been identified that are characterized by seizure onset in childhood; absence of evidence of structural brain pathology, both clinically and on imaging studies; infrequent seizures; and a uniformly good prognosis for complete remission during middle to late adolescence. The most common and best-characterized of these syndromes is benign partial epilepsy of childhood with central-midtemporal sharp waves (see Chapter 236). Other similar syndromes include benign partial epilepsy with occipital spikes-and-waves (see Chapter 237), benign epilepsy with affective symptoms, and benign frontal epilepsy of childhood. When a child with seizures is evaluated and decisions about treatment are made, it is important to determine whether the clinical and EEG criteria fit one of these benign syndromes. Many children have only one or a few seizures, making treatment generally unnecessary. In selected cases, treatment may be viewed as desirable to prevent recurrences and help allay parental concerns. In such cases, drug treatment should be limited to 1 to 2 years. It is a mistake, in our view, to treat until the EEG normalizes, because interictal EEG abnormalities will persist, in the majority of such cases, long after seizures have remitted clinically.

Other Considerations

Is It a Seizure?

Not all paroxysmal events are epileptic seizures, and sometimes the diagnosis remains uncertain even after all relevant clinical and laboratory data have been considered. We generally advocate a period of "watchful waiting" and close follow-up in such circumstances rather than initiate treatment. Using the response to antiepileptic drug therapy as a diagnostic test is usually inadvisable because the placebo effect is high (about 20% to 30% in most clinical trials) and no antiepileptic drug has a therapeutic effect limited to epilepsy. Consider, for example, the widespread use of carbamazepine and valproate in the treatment of psychiatric disorders. In addition, there are unfortunately still adverse psychosocial and other consequences to the individual with epilepsy, and the diagnosis should not be made without reasonable certainty (see Chapter 68).

Factors Affecting Seizure Threshold

It is important to identify any environmental or physiologic factors that can lower an individual's seizure threshold and provoke seizures in certain circumstances (see Chapters 9 and 125). Sleep deprivation and irregular sleep habits are especially common triggers for seizures in some people, but other factors may be important in individual patients. Eliminating these can occasionally obviate the need for antiepileptic drug treatment or allow lower drug doses to be used.

Consideration of the Illustrative Cases

At the beginning of this chapter, several cases were described and questions asked regarding what effect the particular circumstances in each situation might have on treatment recommendations. With full recognition that there are no "right" or "wrong" answers and that treatment decisions are always a matter of judgment based on medical data modified by individual circumstances and patient preferences, we offer the following comments to give an indication of how the issues raised in the vignettes might be approached in the light of the foregoing discussion.

> **Case 1.** Treatment of this child's febrile seizure, whether brief or prolonged, or whether a first seizure or one of several, is not recommended. Attempts should be made to inform the family about febrile seizures, give them literature to take home, and see them regularly for a while to provide continuing reassurance and education. In exceptional circumstances, when parents are unusually panicky and seem to be focusing unduly on preventing a recurrence, phenobarbital sufficient to produce a plasma concentration of 15 µg/mL might be prescribed for 6 months or so, with the drug being stopped if behavioral side effects develop. Diazepam administered rectally[2] or orally[15] at the time of fever is also effective in preventing recurrence of febrile seizures. The risk for recurrence of a first *afebrile* seizure and its consequences in this age group are very similar to those for a febrile seizure. The recommendations in this case, therefore, would be the same.
>
> **Case 2.** Although the chance of a second generalized tonic–clonic seizure is the same in this 14-year-old boy as it was in the 2-year-old girl, the consequences for teenagers are far different. Foremost in most teenagers' minds is the effect another seizure will have on their independence, their ability to obtain a driver's license, and their relations with peers. The impact of another seizure in terms of these issues should be discussed forthrightly with teenagers while parents are out of the room, at least part of the time. Talking to siblings as well as parents is also helpful. In this age group, it is also important to explore the role of alcohol and other drugs, as well as other seizure precipitants (e.g., sleep deprivation). Although our bias in such discussions is against treatment, our ultimate recommendation is strongly influenced by the reaction of teenagers regarding what further seizures will mean to them. To the 14-year-old who will not drive for another 2 years, withholding treatment may be more acceptable than to the 17-year-old whose license is still new and a mark of pride. Physicians should also bear in mind that if drug treatment is recommended, most teenagers prefer to take drugs at home (i.e., once or twice daily), not "in public."

Case 3. This woman most likely has juvenile myoclonic epilepsy (see Chapter 244). It may have been unrecognized until her husband saw the morning "jumps" and then witnessed a generalized tonic–clonic seizure. This syndrome generally persists throughout life, and the probability of further generalized convulsive seizures is high. We would encourage her to start drug therapy, and we consider valproate to be the drug of choice. We also believe that a discussion of pregnancy-related issues and prescription of folic acid are mandatory for any woman of childbearing age, whether she plans a pregnancy in the near future or not. For a woman like this one, who is hoping to start a family soon, the various interactions between seizures and pregnancy should be discussed with her and her husband; it might be recommended that she remain off valproate during conception and for the first few months of pregnancy. Disabling myoclonic jerks can often be treated with small doses of diazepam or clonazepam taken as needed immediately after awakening. In the event of a second convulsive seizure occurring before conception or early in pregnancy, valproate could be started, with the patient followed closely in conjunction with a perinatologist. In new mothers with juvenile myoclonic epilepsy, the effects of unavoidably disrupted sleep and sleep deprivation may make treatment even more necessary.

Case 4. Although she has profound retardation, this child warrants the same thoughtful consideration as the child with seizures who is otherwise normal. The impact of seizures, however, may be quite different. The following questions are always pertinent: "What effect are the seizures having on the child's daily routine and on the ability of the family or others to provide care?" and "How would this child's life be improved in real terms if seizures were controlled?" The answers to these questions depend very much on the type of seizure and also on the child's functional abilities, age, and care setting. Thus, atonic seizures are more disruptive and likely to lead to injury than absence seizures, especially in ambulatory patients. Older (bigger) children are generally more difficult to manage than younger (smaller) ones. Another consideration is the possible deleterious effect drug therapy may have on alertness and behavior. Sometimes, recognized seizures may be only the tip of the iceberg, and EEG recordings demonstrate that the child is having many more seizures that, untreated, are actually contributing to the severity of the encephalopathy. Treatment is virtually always indicated in children with epileptic encephalopathies, but outcome goals need to be defined realistically because complete seizure control is rarely obtained.

Case 5. If careful review of the history confirmed that this was, indeed, a first unprovoked seizure, and if the clinical and EEG data indicated that this person had a low probability of seizure recurrence, we would not recommend drug treatment. However, adults respond differently based on their individual perceptions of the consequences of another seizure (especially on driving and employment) and their view of drug treatment. If this factory worker is less concerned about driving than about an employer's mandatory drug testing policy, a recommendation to defer treatment would probably be acceptable. An important related issue is whether to inform the employer. This is generally the best policy, especially because there is a possibility that if another seizure occurs, it could happen while the patient is at work. However, physicians know, as do their patients, that employers still discriminate. What would happen to this person if results of the drug screen were positive and the employer had not been informed of a medical condition requiring treatment? There are many different combinations of decisions and consequences that can be imagined in this set of circumstances, and it is neither possible nor desirable for the physician to attempt to decide what is best for the patient. In situations like this, patients must make their own decisions and live with the consequences.

The responsibility of physicians is to ensure that patients and their families understand both the medical and psychosocial issues surrounding recurrent seizures, as best they can be defined, and the ramifications of treating or not treating given the various complexities of a particular set of circumstances. In discussions with patients, we have often found it helpful to pose the question, "What is the worst that could happen if…?" These worst-case scenarios help to keep risk-taking behavior in proper perspective. If patients understand and can accept the consequences of "the worst that could happen," then every other alternative is more acceptable.

Summary and Conclusions

Indications for treatment are based on assessing how seizures interfere with a patient's ability to function, quality of life, and health and well-being. Because seizures have diverse manifestations, because epilepsy is a group of conditions, not a homogeneous disorder, and because patients are unique individuals, each with a unique set of circumstances, it is not possible or even appropriate to formulate specific guidelines that specify when or how to treat and that are applicable to all settings. In fact, in many situations there is no single correct answer to the question, "Should this patient be treated?" What is right for one person may be wrong for another. Recommendations regarding treatment must be formulated individually for each patient and based on an interactive decision-making process that considers the consequences—both good and bad—of various courses of action. The physician's obligation is to ensure that patients and their families knowledgeably assess risks and benefits in light of factors that are germane to a given individual, and that the final decision, which must ultimately be the patient's responsibility, is as fully informed as possible.

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Chapter 98

Goals of Therapy

Lawrence J. Hirsch

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Introduction

The goal of all medical therapy is to allow patients to live as normally as possible and to maximize quality of life, especially health-related quality of life. For patients with epilepsy, the desired goal is “no seizures, no side effects,” as emphasized in a National Institutes of Health–sponsored consensus conference in 2000.[12] The availability of a number of newer antiepileptic drugs (AEDs) has helped us to reach this goal, particularly in terms of “no side effects.” Unfortunately, there has not been a comparable benefit in the number of patients who become seizure free.[25]

General Aspects of Treatment

Having epilepsy commonly introduces several consequences that are relatively unique, including restrictions on driving, persistent stigma, and the small but real possibility of sudden death. There are also more subtle issues that affect the quality of a patient's life but can easily be overlooked, even in patients who are seizure free and who seem, on first glance, to be free of adverse effects as well. These include undesired chronic effects of AEDs on cognitive ability, mood, weight (both gain and loss), childbearing, and sexual function. Epilepsy can cause cultural and financial stress, and some AED regimens can be inconvenient and threaten compliance. Such issues are just as important, and can be as complex, in patients with mild epilepsy (or even a first seizure) as they are in those with intractable seizures. For these reasons, it is ideal for all patients who have seizures or epilepsy to be offered an opportunity to consult with an epilepsy specialist.

Successful management of patients with epilepsy requires treatment to be individualized. This can only be achieved if the physician, patient, and family cooperate in a productive partnership. It is useful early on to determine the relative importance the patient attaches to several possible outcomes and then to reevaluate these from time to time during the course of treatment. For a patient who has strong objections to taking medication, it is best to choose the simplest possible regimen with the least risk of side effects. Other reasonable considerations might include, as appropriate, reduction in dose or consideration of AED withdrawal, even if the chance of success is low. Another patient may view the possibility of an additional seizure as sufficiently devastating that he or she will not tolerate even a small risk of recurrence despite the potential benefit of lower doses or discontinuing medication altogether. The reasons may be psychological, professional, social, or practical (e.g., a compelling need to drive).

Although family members who accompany patients can be helpful in providing details and circumstances of ictal events, additional details of the family's history, and information about the patient's infancy and childhood, it is essential for the physician to meet privately with the patient at some point, even if this has not been specifically requested. Privacy encourages most patients to raise questions and express their concerns and also to discuss potentially sensitive issues such as alcohol, drugs, and sex. On rare occasions, patients may express unease about their caregivers, whose motives may not always be in a patient's best interest. For example, a caregiver in a group home might report that a patient's behavior has worsened and become problematic after a sedating medication has been stopped. In reality, the patient might be more alert and interactive but now also requires more attention.

Patients' reports of their seizures are notoriously unreliable. Blum et al.[5] determined seizure awareness prospectively in 31 patients admitted to an epilepsy monitoring unit (EMU). Twenty-three patients had epileptic seizures, but only 26% of them were aware of all of their seizures (regardless of seizure type), and 30% were not aware of any. Similarly, Eisenman et al.[11] found that self-reports of seizure frequency did not correlate with time to first recorded seizure in the EMU. Patients with infrequent seizures, averaging <2.2/month by history, and those who reported frequent seizures, averaging >24.1/month, both averaged 2 to 3 days to record the first seizure. Furthermore, even when patients recall their spells, details regarding impairment of consciousness are unreliable. Regularly obtaining collateral information from spouses, partners, or other close family members can add important information and improve historical accuracy. The foregoing data also suggest that having a low threshold for prolonged electroencephalogram (EEG) monitoring (either ambulatory or inpatient) is frequently necessary to resolve ambiguities or inconsistencies in the history and obtain a more accurate account of the patient's condition.

What do patients care about the most?

Previous work has shown that patients with epilepsy have many health-related quality of life concerns, and these frequently involve issues related to a desire for greater independence (especially in terms of driving, work, and social life), less stigmatization, improved mood and cognition, absence of drug-related adverse effects, and, of course, complete control of seizures.[9,15,39] Although seizure control without AED side effects is an important determinant of quality of life, other factors are also significant. Moreover, many of these may be amenable to educational or therapeutic interventions, resulting in improved quality of life even without a concomitant reduction in seizure frequency or severity.

There is convincing evidence that depression is a common comorbid condition in patients with epilepsy[14] and that the presence or absence of depressive symptoms might outweigh the impact of controlling seizures in determining the patient's perception of well-being[6,21](see also Chapter 205). Depression also influences how patients perceive their seizures. In a survey that assessed self-reported seizure severity and the burden of seizure components, respondents with moderate or severe depression reported significantly worse problems than did those

without depression in terms of overall seizure recovery, overall severity, and overall seizure burden (all $p < .005$). Cognitive, emotional, and physical aspects of seizure recovery were also rated worse among people with severe depression compared to those without depression (all $p < .05$).[7] (See Chapter 199 for an overview of psychiatric issues in epilepsy.)

Several studies have shown that individuals with frequent and more severe seizures have a significantly poorer quality of life than those with infrequent or no seizures.[3,4,20] Adverse events related to AEDs are also detrimental to quality of life. On the basis of a U.S. survey of >1,000 persons with epilepsy, Fisher et al.[13] concluded that “only 68% of respondents were very satisfied with their current seizure medications.” Patients ranked seizure control, fewer side effects, convenient dosing regimens, and cost from most to least important. (See Chapters 100 and 220 for further discussion of quality-of-life and outcome scales.)

Driving

For most people, driving is a surrogate for independence, and freedom to drive is therefore a major contributor to quality of life.[15] Thus, it is not surprising that issues related to driving are among the most difficult routinely encountered in the care of patients, especially those with mild epilepsy. Recommendations must balance a physician's dual obligations—to the patient and also to society. Although advice must conform to applicable statutory requirements, it should, to the extent possible, be tailored to the circumstances of the individual patient.

Fortunately, fatal crashes due to seizures are rare. Between 1995 and 1997, only 0.2% of all driving fatalities in the United States were attributed to seizures in mortality reports. Although patients with epilepsy had a greater rate of fatal crashes than those with other medical conditions, occurrence of fatal seizure-related crashes was 2.6 times *lower* than in the general population.[36]

Many factors can influence a patient's risk for seizure recurrence and, therefore, the risk of seizure-related motor vehicle accidents. Seizure-free interval has been widely adopted by regulatory agencies as a practical measure of driving risk. A consensus statement from the American Academy of Neurology (AAN), the American Epilepsy Society (AES), and the Epilepsy Foundation of America (EFA) advocated a 3-month seizure-free interval, with allowance for modifiers that might extend or shorten the interval[1] (see Chapter 221 for more details). Drazkowski et al.[10] reported that in the state of Arizona, seizure-related crashes did not increase significantly when the seizure-free interval required before driving was allowed was reduced from 12 to 3 months. Krauss et al.[22] found that the following factors were associated with a significantly decreased risk of motor vehicle crashes due to seizures: (a) a seizure-free interval of >6 to 12 months (which is in contrast to the Drazkowski data); (b) the presence of reliable auras (although some patients still had crashes, possibly related to a later finding that some of the “auras” were actually complex partial seizures); (c) no or few prior accidents that were unrelated to seizures; and, unexpectedly, (d) switching or reducing AEDs. Given that 25% of patients with crashes had more than one seizure-related crash, patients with previous crashes due to seizures are likely to be at particularly high risk. Recommendations based on these findings are shown in Table 1.

In general, neither guidelines nor statutory regulations can substitute for clinical judgment. For instance, a patient who has had seizures regularly every 4 or more months for many years may well be seizure free for 3 consecutive months and therefore eligible for licensure in some states. However, such a patient warrants a longer seizure-free interval before driving can be considered acceptably safe.[1,22,23]

Sports, Exercise, Travel, and Alcohol

As with driving, it is hard to make generalizations regarding patients' involvement in sports and other activities. Recommendations have to be individualized, bearing in mind the frequency and type of seizures, presence of a reliable aura, the importance of sports to the patient, and the level of supervision required or available. Although physicians are appropriately concerned about their patients' safety, as are parents of children with epilepsy, it is also important that persons with epilepsy lead as normal lives as possible. Thus, individual decisions need to strike a balance between maximizing safety and minimizing the stigma that inevitably develops as a consequence of “being different” when activities are restricted (see Chapter 216). Nakken[28] reported that over half of 204 patients with epilepsy had never reported having a seizure during exercise. About 10% of the patients, predominantly those with symptomatic localization-related epilepsy, indicated that they often had seizures related to exercise. In general, sports and exercise are safe and healthy for persons with epilepsy, and they can generally be encouraged. Exceptions include such high-risk sports as scuba diving and sky diving, which should be avoided. Swimming must be supervised closely but can be permitted in most patients whose epilepsy is controlled. A “buddy system” works well for many patients. Travel and leisure activities rarely need to be restricted, but it is helpful to advise patients about minimizing sleep deprivation during travel, emphasize the importance of medication compliance, and discuss plans for emergency care while away, should that be necessary (including use of rectal, nasal, buccal, or oral benzodiazepines).

Similarly, many patients consider it important to have a glass of wine at a dinner party or celebration. This poses only a minimal risk if seizures are controlled. How much alcohol is too much should be discussed realistically in terms the patient can understand. In general, patients with epilepsy can tolerate alcohol in small amounts (e.g., one to two drinks per occasion or no more than three to six drinks per week). However, anyone with a history of alcohol or substance abuse, alcohol-related seizures, or noncompliance with AEDs should abstain completely. Adolescents and young adults, who often find it difficult to control the amount of alcohol they consume, should also probably abstain[18] but are not likely to do so. Patients who drink moderately (three to four drinks per occasion) or heavy amounts (four or more drinks per occasion) should be warned that they are at increased risk of having seizures, with the greatest risk occurring 7 to 48 hours after the last drink.[19,30] It follows that driving should be avoided the day or two after significant alcohol use. (See Chapter 268 for further discussion of alcohol and seizures.)

Table 1 Factors associated with reduced odds of seizure-related crashes and possible recommendations for patients with epilepsy who drive

Factor	Possible recommendations for epilepsy patients who drive
Factors associated with reduced odds of crashes	
Long seizure-free intervals	Comply with state or national mandated regulations and required seizure-free restrictions; maximize seizure therapy; consider long (6–12 mo) intervals to minimize risk further
"Reliable" auras[a]	Stop driving during auras; caution patients that auras do not guarantee that they will not crash while driving
Adjusting antiepileptic drugs (AEDs) to reduce seizures	Optimize AED therapy to control seizures; advise limiting driving during AED adjustments
No or few prior non-seizure-related motor vehicle crashes	Note importance of driving safety in general
Additional risk factors[b]	
First seizure while driving	Consider restricting driving for a period if at high risk for seizures (e.g., brain tumor or other structural lesions)
History of previous seizure-related traffic crashes	Caution patients about their increased risk for additional crashes, consider long (≥12 mo) seizure-free periods before driving
Missed AED doses	Reinforce the importance of AED compliance and advise patients not to drive after missing AED doses

[a] Auras "always" precede seizures; consider video/ EEG documentation of retained awareness during auras because patients may not be aware of their impaired consciousness.

[b] Not evident in the case–control analysis but directly linked to crashes.

Source: From Krauss GL, Krumholz A, Carter RC, et al. Risk factors for seizure-related motor vehicle crashes in patients with epilepsy. *Neurology*. 1999;52(7):1324–1329; with permission.

Pregnancy

The vast majority of women with epilepsy can have healthy children and breast-feed if they so desire. A full discussion is provided in Chapter 198.

Sudden Unexplained Death in Epilepsy and Life Expectancy

A review of sudden unexplained death in epilepsy (SUDEP) is provided in Chapter 189, and mortality is discussed in

Chapter 10. Although estimates vary, sudden unexplained death occurs in approximately 1 of 1,000 patients with epilepsy each year; rates are higher in selected subgroups. SUDEP is most common in young adults who have had uncontrolled epilepsy with frequent seizures for many years and are on polytherapy. At present there is no way to prevent SUDEP, although aggressive seizure control and emphasis on compliance are logical recommendations. In a case–control study, Nilsson et al. identified frequent changes in AED regimen as a risk factor for SUDEP.[32] Most SUDEP cases occur during sleep. One retrospective, nonrandomized study found that patients who sleep with someone else in the room or have nocturnal monitoring devices are less likely to be SUDEP victims.[24] It might also be reasonable to avoid AEDs that are known to affect the cardiac conduction system in patients judged to be at increased risk of SUDEP.

There are differences of opinion about if and when SUDEP should be discussed with patients. Although all patients and families should be aware of the dangers of seizures and the importance of medication compliance, we recommend concentrating on discussion of seizure-related injuries and deaths that are clearly preventable, such as those associated with driving, swimming or bathing alone, bicycling on busy roads, working at heights, or other risky behaviors. An extended discussion of SUDEP with every patient does not seem reasonable or warranted, given that SUDEP is not common, and that only a subgroup of epilepsy patients are at relatively high risk. A sense of proportion is required, and the potential of adverse psychological and other effects as a consequence of overemphasizing SUDEP, especially in children and young adults, from increased supervision and limitation of activities should be borne in mind. One approach is to provide all patients with comprehensive information on epilepsy and its consequences, including SUDEP but to discuss it directly only if asked, if patients are noncompliant, if there is a family history of sudden death, or as part of the decision-making process regarding epilepsy surgery. Although there is evidence that successful epilepsy surgery is associated with a lower risk of SUDEP and longer life expectancy,[35,37] some studies have shown little difference between preoperative and postoperative mortality.[31,38] If only seizure-free patients are considered, mortality does appear to be decreased postoperatively.[31,35] It is also possible that differences in survival between operated and nonoperated groups of patients with intractable epilepsy could be due, at least in part, to preoperative biologic differences between cured and noncured patients. For example, autonomic dysfunction appears to be more common in patients who fail surgery,[33] and it has been hypothesized that insular involvement could explain both surgical failure and a predisposition to SUDEP.[34]

Screening for medication side effects

After reviewing the importance of adverse effects of AEDs on health-related quality of life, the Commission on Outcome Measurement of the International League Against Epilepsy (ILAE) recommended the inclusion of reliable and valid screening instruments in clinical trials to assess more accurately subjective adverse effect rates and severity, which would positively affect quality of clinical care.[2] Trials that included systematic recording of adverse effects have consistently shown higher rates compared with spontaneous reporting.[9] For instance, the Veterans Administration Cooperative studies,[26,27] which included a standardized questionnaire for systematic assessment of adverse medication effects, found that such effects contributed to trial exit in 40% to 60% of participants. Gilliam et al.[17] showed that routine use of the Adverse Events Profile (AEP), a simple screening form filled out by patients, was associated with a 2.8-fold increase (95% confidence interval [CI] of 1.7 to 4.8) in AED modifications and significantly reduced adverse effects.

Routine screening for depression is also useful, and several rapid screening questionnaires, such as the Center for

Epidemiologic Studies Depression Scale, exist for this purpose (see Chapters 100 and 205). Gilliam et al.

recently developed the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E), a screening instrument that uses a brief set of symptoms to recognize major depression and differentiate it from common adverse effects of AEDs.[16]

Setting Realistic Goals

For some patients, such as those with Lennox-Gastaut syndrome, becoming free of seizures is not a realistic goal. Once this conclusion has been reached, it is important to minimize ineffective medications in order to maximize interictal cognitive, psychological, and motor function by reducing or eliminating adverse effects. In patients with refractory seizures on polytherapy, AEDs should be decreased or stopped at least as often as they are added or increased. In patients with refractory drop attacks due to seizures, vagus nerve stimulation and corpus callosotomy should be considered when it is clear that further drug changes are unlikely to improve seizure control without side effects. Both of these procedures, although rarely curative, can be effective in reducing seizure-related falls and injuries.[29,37] Callosotomy is probably somewhat more effective, but it also carries a greater risk, although most complications are transient.[29]

Summary and Conclusions

Successful treatment requires therapeutic management plans that are individualized for each patient. The goal is to provide each patient with maximal control of seizures without significant adverse effects. Undesirable effects from AEDs and psychiatric comorbidity, especially depression, profoundly affect quality of life. Systematic screening for these factors will assist in guiding clinical management and optimizing care with minimal additional physician time. For a patient with epilepsy, independence, driving, employment, safety, and social stigma are very real and serious concerns. Although “no seizures, no side effects” should be the primary goal in management, they should not be the only measures of a successful outcome. All aspects of a patient's health-related quality of life should be given due consideration and treated accordingly. In the end, it must be remembered that physicians treat individual persons, not a disease—or, as attributed to Hippocrates, “It is more important to know what sort of person has a disease than to know what sort of disease a person has.”

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Chapter 99

Broader Aspects of Treatment

David C. Taylor

> This human ritual of suppliant and provider of balm is deeply rooted; extending back thousands of years.
>
> —W. Pickering[20]

Introduction

This chapter is about treating people who are sick. The book is concerned with people who have epilepsy, or who appear to have epilepsy, but these remarks also have broader applications in medicine. They do not concern the details of medical, psychological, or surgical treatments of epilepsy. They pose questions and suggest some attitudes about treating people based on the fact that all treatment takes place in some sort of psychological climate and that the better that climate is, the better everybody will feel. Nor is this entirely a plea for "evidence-based medicine"[11] because it is sometimes the evidence that, on reflection, has changed since it was raised.[24]

The general aim is to encourage careful consideration of a range of sense data that are available to therapists for monitoring their therapies. For example, it almost seems to follow necessarily that convulsions (epileptic seizures) should be treated by anticonvulsants or antiepileptic drugs (as they are rather quaintly called). A glimpse at practice tends to confirm this. The logic is similar to the treatment of infections by antibiotics and of depression by antidepressants. That logic, however, soon breaks down. We find we are obliged to consider the duration, scale, type, and origin of the illness and the age, size, resources, and situation of the patient[5,11,25] and any basis the convulsions have in nameable disease. Even then, seizures may continue, and other problems persist. In making a diagnosis for a sick person, naming the illness is not enough. "Diagnosis" requires a larger consideration. It derives from a root word meaning to perceive, to distinguish, to discern, to have knowledge. Diagnosis requires us to know about the sick person. What disease might underlie this illness? What is the situation, the predicament, of this person?[23] Who is this sick person, what life is the patient leading, and what is the patient's agenda, here and now, with me, today?[3,13]

The idea that a sick person with an illness creates a social problem that connects back to the medical problem is usually seen only in the sociological literature.[7,16] The examination of the treatment of epilepsy from such a perspective can be illuminating. There is nothing trivial or metaphorical about epilepsy.[22] Seizures, convulsions, fits, and bad turns all have metaphorical meanings, however, as well as meanings in the language of everyday life, most of them negative. To be diagnosed and treated for epilepsy is something of an ordeal in itself.

Diagnosis and Treatment

Making a diagnosis is an essential prerequisite to being able to help a sick person, but "the diagnosis" is an abstraction. The reality is the treatment that follows, whether reassurance, regimen, manipulation, medication, or surgery. Diagnosis, the knowledge and revelation of the problems that are agreed to exist, may not have been arrived at easily for the patient with epilepsy. The patient may have been pleading the case for his or her sickness to be recognized for a long time before a diagnosis was finally awarded. There could be anger at previous failure and time wasted. That could explain a negative or guarded attitude even toward the team that eventually made the diagnosis. On the other hand, even if the physicians exercised their utmost skill, patience, and technology to achieve the diagnosis, it might not be what the patient wanted because it demands ownership of the sickness with all its perils and stigmata or contradicts the patient's firmly held view of it. “Please doctor,” the father of one patient pleaded, “take away this diagnosis, it will ruin my son's life.” Thus, subsequent treatment might be resisted. Sometimes a diagnosis of epilepsy is ascribed on scant evidence, inadequate information, faulty logic, or with casual indifference. Thus, an illness is foisted on a patient. Occasionally the diagnosis and treatment for epilepsy might suit the patient in some ways, so the patient cleaves to it, and subsequently even a great authority might not succeed in changing the patient's view even though it is wrong and irrational.

These different ways of coming to the diagnosis affect the attitudes of patients and caregivers to the treatment. Treatment confirms the reality of the patient's diagnosis, whether accurate or wanted or not. Some examples of these processes can be given: The infantile spasms were brief and few and not distinctly described, but they were eventually seen by the physician, captured on electroencephalogram (EEG), and investigated to show the tuberous sclerosis of which the previously entirely healthy father proves to be the carrier. He now bears a “responsibility” for his son's condition. The onset of the brief nocturnal disturbances in this young woman was soon diagnosed as epilepsy, but this precluded her from driving and ruined the career that depended on that. The onset of focal motor seizures with some subjective feelings was treated successfully for several years with medication before breakthrough seizures led to investigations that revealed the cerebral tumor. In each case there is a negative side to the “good news” of achieving a diagnosis. Diagnosis and treatments, on one hand, bring relief and hope of cure, but, on the other hand, they convey the reality of what exists, confirm the worst fears, or require the sick person to submit to the ordeal of treatment, which may be a significant burden. At times, the procedures providing the relief of the sickness or the prospect of relief prove to be so hazardous to the patient that the patient feels the need to undermine them. That would be one reason for a therapist to feel frustrated by a patient.

The Treatment Process

Much of the process of medicine is unseen by practitioners, who take for granted the bizarre environment in which they work, which can be terrifying to patients. Diagnosis is achieved through a series of rituals. Some are verbal, such as asking a whole series of unlikely questions (called taking a history); others require apparatus, sometimes of gargantuan dimensions, for which purification and special clothing are required (called routine investigations). The modest EEG by which “they took the electricity from my head, doctor” is nowadays lodged in a bank of computers, TV screens, analog devices, and so on. In such a situation the patient must perform appropriately in order to “qualify” for a diagnosis. Days and days of anxious waiting might be required to capture even a single seizure.[26] Failure to achieve the wanted diagnosis leads to the limbo of unknowing and disqualifies the patient from treatments available to those who do qualify. That is, for them, another kind of failure. An escape with dignity has to be incorporated in our programs of investigation, which are, to patients, not so much diagnostic as a determination of whether they *qualify* for a treatment.

The ordeal of being passaged through our medical temples, at times without a priestly guide, reaches its zenith in neurosurgical treatment. Consider the special rooms, the ritual shaving of the head, the masks and gowns, the apparatus, the lying-in in recovery. What we require of patients generally is that they endure situations that are awesome, interventions that are perilous, and ministrations that are distasteful. The fact that they are tolerated with surprising equanimity for the most part allows us to overlook their impact. The unspoken bargain for the patient is that it is all done in the hope of benefit. It is about a *bargain*. Sometimes it is not a very good bargain.

Most treatment acts breach the ordinary protective taboos about inviolacy of the body. Treatment is intrusive, whether it includes medications being put into the body or rays shone on it or wires attached to it or hands manipulating it or minds analyzing it or holes made in it. The ritualistic aspects of treatment can be elaborated as a way of dealing with these protective taboos. The perpetrators of the intrusions, though granted a limited permit, tend to defend themselves from their violations by a process called "clinical detachment" or "denial" or callousness, depending on one's viewpoint. Within these necessary procedures and wanted effects lies the opportunity for negative effects. These include inciting dependency and amplifying dependency needs, which are necessarily increased at the point of diagnosis and treatment. The danger, once the taboos have been set aside, is that there is scope for degradation. Degradation can follow simply as a psychological outcome of the ordeal of therapy, or it may more explicitly occur as an effect of surgical treatment or, much more regularly, of the medical treatment of epilepsy. The negative effects of treatment are rarely phrased in terms of degradations—"side effects of the drug" or "unwanted outcome of the procedure" are the much-preferred designations. But consider the case of an adolescent girl given a new medication and an appointment in 3 months' time who is unable to deal with the offensive body odor it causes.

The history of medicine reminds us that severe and intractable sickness leads both doctors and patients toward desperate measures in search of a cure. However, the price to be paid by the patient in being rendered obese or bald or plethoric or losing a hemifield of vision or partial loss of verbal memory or experiencing a bout of madness[10,17] has to be balanced against the desired effects of the proposed therapy. That bargain cannot be struck while the negative effects are downplayed with medical euphemisms. It is thus that we forget the lessons of the therapeutics of epilepsy from the past. Korczyn et al.[14] recalled, for example, the monstrous era of colectomy along with purgations and enemas in desperate acts of purification applied to epilepsy. "Evidence" had suggested the presence of a "*Bacillus epilepticus*," a "fact" several times confirmed. That epoch followed on the one in which the sexual parts were surgically assaulted with similar purifying zeal.[21] Now, of course, we are all much more rational, and we hope that this is how we will all appear in retrospect.

There are people who seek therapies because their degrading and self-punitive possibilities meet some of their needs.[18] Such people look for therapists who are likely to satisfy them. In the event of those people also having a chronic illness such as epilepsy, the stage is set for heroics on either side of the treatment bargain.

Outcome

There are many medical and surgical treatments whose outcome is envisaged as a permanent solution. Epileptic seizures, even when considered as just one aspect of the cerebral dysfunction of a person with epilepsy, can be a chronic, even lifelong problem for which there is no "outcome" in the ordinary sense, and the treatment requires close and repeated, endless attention. It is extremely difficult to bear this in mind when we are trying to restore the patient's enthusiasm for yet more tries at new treatments. The aim of each treatment, that is, the *specific* purpose, should be closely considered and noted and referred to at the next appointment. Only in that way can the effect on that aim be reasonably assessed. As things stand, antiepileptic drugs (AEDs) may prove to be rather less specific than has been thought in the control of particular syndromes. It might then be argued that about 50% of patients with epilepsy will respond to any anticonvulsant, and about 50% will not be comfortably controlled by any anticonvulsant.[4]

Over time, the aim of treatment might shift from giving great attention to one aspect of the sickness, say the seizures, to another, for example, the specific learning problem or the behavioral syndrome. These different aims should be made clear to the patient and his or her caregivers. Each treatment offers a prospect of relief, but each treatment also brings the dread of failure or further failure. Even apparent success, such as reducing weekly seizures to annual seizures, may not provide what was hoped for. The wait for the next confirmation that no cure has been effected is simply increased. So is the disappointment unless the patient has understood the palliative nature of the therapy. The restrictions imposed by "being epileptic" may persist. It is recognized that even after a radical cure provided by surgery, the effective outcome may be less than was hoped for. Against the patient's desperate wish for a cure there exists a real concern about losing the identity that was provided as a "sick person" and that is threatened by becoming well for the first time ever, or for the first time in many years.

Thus, ambivalence is all pervasive in the therapeutics of chronic sicknesses. To consider this only in terms of compliance and attribute it to the careless indifference of the patient is an error and a foolish trivialization of the psychology of chronic sickness. All treatments are about striking a deal between the worth of the life that is being lived, as opposed to that which might be lived, and the effort, ordeal, and constraints of the treatment. Many physicians feel obliged to persist with complex therapies despite the fact that they do not achieve their apparent aims. Their unspoken aim may be to guard against fatal accidents or sudden death. It is quite uncertain whether those are realistic.

Conclusions for Action

People who treat other people would do well to consider a series of propositions. They are relevant to every treatment, but they can be (and are) ignored in most treatment encounters because those encounters are trivial and brief. Their outcome is, in any event, only marginally contingent on the therapy. In the treatment of a potentially chronic illness with potentially highly

toxic agents or highly intrusive procedures, these propositions become increasingly important.

How Is the Treatment Offer Made? How Is It Understood?

Is the patient demanding a treatment rather than seeking advice? Can the patient retain some personal control in the therapy? Does the patient understand that all treatments are experimental from the individual viewpoint? Has the patient understood what "palliative" means? Has the patient understood the connection between what he or she complains of (or what is complained of about them) and the treatment? How, for example, will the learning problem (caused, say, by status of minor epilepsy) be addressed by taking certain tablets? Is there any scope for negotiation about this treatment offer? Is there a pause to consider it?

What Does the Treatment Provide, and What Does It Demand?

Is it likely to be worth it? Certain complex regimens may be very convincing and comforting to some people but leave others confused and desolate, not daring to question the procedures, potions, and pills that threaten to overwhelm them. Patients and their families might risk more than they can afford, financially or psychologically, in a demanding treatment sequence.

What Does the Treatment Ambience Provide?

If the treatment is in a hospital or a clinic, do the ambience and the milieu there promote and inspire confidence or do they detract from it or conspire against success? Should patients become aware of plights worse than theirs or more progressed stages of the condition from which they are suffering? Should admission for treatment require that patients associate with more disabled and deteriorated patients? There is a balance to be struck between becoming aware of certain realities (the condition of someone else just after the operation that has just been proposed) and being overwhelmed by them without discussion.

Who Are the Treaters?

The broad gamut of therapists and caregivers encountered by patients might each address some aspect of care. The caregivers are not confined to "the team" that knows the whole patient well. It deserves to be remembered that patients will scout for the opinions that most comfort them and that most conform to their own. Therapists (especially doctors) should be aware of what a small part of the sickness they address and respect the contributions of other therapists.

Consider the Outcome of This Treatment

Whatever it is, the treatment in hand will have its own outcome, and that outcome will be separable from the outcome of the sickness, which might be interminable. Each AED—the first, the next, and so on—will have to have some criterion of success. When cure is not possible or uncertain, how will some lesser degree of success be recognized and explained? How will failure be dealt with and a prophylactic be set up against a disastrous sense of failure? Having treatment hypotheses that are tested over and over is a way of guarding against random prescribing. The same holds for all sorts of managements—social, psychological, or surgical.

Why Are "Alternative Therapies" Attractive?

There are reports of a range of therapies for epilepsy that seem to have in common that they empower the patient to take some personal control of the sickness rather than to be under the control of the therapist or the therapy.[1,19] These include such activities as yoga.[19] Without making any sort of judgment about any of these treatments, it does seem that certain aspects of alternative treatments can be included in a medical treatment package with advantage. They are already evident in the work of some comprehensive multidisciplinary care centers[15] and specific self-management regimes.[6] Some good general principles of care are sustained in many "alternative therapies." First, a personal and individual relationship that is sustained through the therapy creates a good therapeutic bond, whereas chronically sick people tend to see a large number of different doctors. Second, those therapeutic relationships that involve touching, even physical examination, or closeness that comes from sharing the biography and attempting to personalize the relationship help to create a therapeutic effect. Moving from doctor to doctor will undermine this.

Self-selection of the alternative treatment seems to induce credibility, especially when this is allied to personal, emotional, or financial commitment. The notion of offering a real choice of therapies, even when they exist, is not a consistent part of many physicians' repertoires. Antiepileptic drugs are the most expensive part of the treatment of epilepsy,[2] and so they should be used skillfully, thoughtfully, and judiciously.

Summary and Conclusions

Experiencing a treatment is a significant life event. For a chronic illness such as epilepsy the treatment is a large and significant part of a person's life. The psychological dynamics of the treatment process can have negative effects or a positive influence on the sickness and on the quality of life. What, for the therapist, is a routine procedure can be a life-changing ordeal for the patient. Alternative medicine has won many adherents[8] and has aspects that can be used to advantage in routine medical practice. We can make a good start by recognizing that the scale of the sickness can extend beyond the symptom.

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Chapter 100

Quantitative Measures of Assessment

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Introduction

Quality of life refers to an individual's overall well-being and daily functioning. *Health-related quality of life* (*HRQOL*) can be divided into three principal components: (a) physical health (e.g., general health, daily functioning, symptoms such as pain and seizures and side effects of drugs, strength, ability to walk); (b) mental health (e.g., mood, self-esteem, perception of well-being, perceived stigma); and (c) social health (e.g., social activities and relationships). Economic and environmental factors, encompassed by overall quality of life, are not usually included within health-related quality of life. Epilepsy and other disorders have a significant effect on economic and environmental aspects of life, but these areas are beyond the scope of HRQOL.

Quality-of-life issues are most relevant in chronic disorders such as epilepsy, in which mental and social problems extend well outside the usual range of symptoms of disease.[22] Unfortunately, there is often a poor correlation between a doctor's and a patient's assessment of the patient's quality of life, despite the expectation that such perspectives would be very similar. Thus, when used to evaluate the effects of epilepsy and its treatment, HRQOL measures can provide important and complementary information to traditional assessments focusing on seizure control and adverse effects of antiepileptic drugs. Interest in the effects of disease on the patient's HRQOL began in the late 1940s with Karnovsky's rating scale for cancer patients and has grown exponentially during the past decade. Quality-of-life measurement has been increasingly reported in clinical trials, nonexperimental outcome studies, cost-utility analyses, and studies of quality of care.[37,71]

Although the concept of HRQOL is attractive and important, its quantification remains a challenge. Items included in HRQOL scales are often derived mainly from “medical experts,” whereas the patient's opinion of what is important should be given higher priority.[37] Other limitations in HRQOL research include lack of definition of HRQOL or targeted domains, failure to distinguish overall quality of life from HRQOL, and validation. Validation of HRQOL instruments is especially challenging because no gold standards are available. Validation is often based on medical outcomes, which is what HRQOL is intended to avoid.

Assessments of HRQOL may be generic or targeted toward a specific disease or disorder. Generic instruments assess a range of issues of functioning and well-being and can evaluate diverse patient populations. Commonly used generic HRQOL instruments include the RAND 36-Item Health Survey,[42] the Sickness Impact Profile,[12] and the McMaster Health Index Questionnaire.[67] Generic measurements permit comparisons among patients with different diseases, but they often lack sensitivity to change or responsiveness to intervention. For example, if a generic instrument does not assess HRQOL areas relevant to a certain patient group, positive or negative changes in these areas will not be detected when an intervention is made during a longitudinal study.

Disease-specific instruments use information about the ways in which a particular disease affects HRQOL. Such knowledge may be derived from patient interviews, medical and lay literature, expert opinion, or a combination of these sources.[37] Disease-specific instruments assess HRQOL domains that are most relevant to these patients, but they include areas that are less important and omit areas that are more important to patients with other disorders. Disadvantages of disease-specific HRQOL instruments include the time and monetary expenses in their development and the limitations on making comparisons among groups with different disorders. A generic core can be combined with a disease-specific supplement to provide the benefits of both.

Epilepsy: A Chronic Disorder with Special Issues

Epilepsy is often a chronic illness. Chronically ill patients strive not only to minimize their symptoms and survive, but also to lead normal lives despite the problems associated with their illness and its treatment. For most people with epilepsy, the first of these objectives can be realized. However, particularly for those patients with epilepsy that is difficult to control, the restrictions imposed on daily living often make the second objective difficult or impossible to attain.

Special Problems

Outcome measures for epilepsy patients traditionally include seizure frequency, severity, morbidity (e.g., seizure-related trauma), and drug side effects such as sedation, nausea, and tremor. The traditional medical factors—seizures and antiepileptic drugs—are viewed quite differently by patients and physicians. “Occasional” or “mild” seizures and “infrequent” and “tolerable” side effects are often considered as acceptable by physicians. For patients, such seizures and adverse effects can be very troublesome and are not “acceptable.” In many cases, patients have difficulty expressing their feelings to doctors, or doctors may be insensitive to complaints that do not fit their conventional wisdom (e.g., disabling lethargy or confusion associated with subtherapeutic or low therapeutic doses of a “cognitively benign” antiepileptic drug). In either case, the physicians remain unaware of the problems.

People with epilepsy have higher rates of psychosocial problems and psychopathology. Once a person has had two seizures and received the diagnosis of epilepsy, the disorder may cause the greatest HRQOL problems during the seizure-free intervals. The duration of medical therapy is often long, drugs often need to be taken several times a day and can cause side effects that affect a person's daily life, and the psychological and social consequences of epilepsy are often enormous. People with epilepsy may be limited in social, educational, and employment opportunities and modes of transportation—restrictions that may be either real or perceived. There are often parental and societal attitudes that foster low self-esteem and dependence, stigma, discrimination, and restrictions. In considering epilepsy as a chronic burden, one must carefully examine the neglected social, psychological, and behavioral problems as well as physical problems.

Physical Issues

Seizures increase the risk for bruises, lacerations, bone fractures and dislocations, burns, and drowning, as well as unexplained death.[41] Daily drugs reduce the seizure threshold but can cause adverse physical effects (e.g., gingival hyperplasia, sedation, nausea, double vision, tremor, hirsutism) and mental effects (e.g., memory impairment), some of which are subtle but chronic.[54] Quality-of-life measures show impairments in people who have systemic or neurologic adverse effects.[32]

Psychological Consequences

Patients with epilepsy have higher rates of certain behavioral disorders, such as depression and anxiety, and cognitive problems, such as impaired short-term memory and naming. Anxiety about the occurrence of seizures is a common concern, not only because of the suddenness of events, but also because of the possibility of negative sequelae. This loss of control over one's life can underlie many psychological problems. Fear of public exposure or injury can underlie self-imposed social and vocational restrictions. The actual or perceived sense of dependency can be fostered by parents of children with epilepsy and by spouses and families of adult patients. Children with epilepsy had twice as many referrals for mental health services (12%

vs. 23%) as the local population of children.[17]

Because anxiety and depression are the most frequent behavioral problem in adults with epilepsy, HRQOL instruments should be used as screening tools to help clinicians measure a patient's mood status.[26] This is especially important, given that Cramer et al.,[29] in a survey of a community sample of people with epilepsy, found clinical depression to be significantly associated with poorer HRQOL.

Social Consequences

The social label of epilepsy can be paralyzing. Both children and adults with epilepsy may feel and actually become removed from their social group and activities. People with epilepsy may be made to feel "different" by the need to go to the school nurse for medication at lunchtime, being restricted from driving or recreational activities, worries that antiepileptic drugs will be identified during urine tests administered by employers or prospective employers, and fears of rejection by peers if a seizure should occur in public. Epilepsy differs from most other medical and neurologic disorders because of these associated legal restrictions and requirements. Other patients fear dating, marriage (seizures during sex, possible decreased fertility), pregnancy (increased rate of pregnancy complications and birth defects), and parenthood (dangers of a seizure occurring while holding a baby or giving the baby a bath). Employment opportunities are restricted for many people with epilepsy, with unemployment and underemployment prevalent among adults with epilepsy. Employment problems limit financial and health insurance resources.

Multiple etiologies may contribute to the behavioral problems and psychopathology in epilepsy, including social, biologic, and drug-related factors. For example, a social withdrawal syndrome with low rates of employment and marriage may result from a combination of low educational attainment and self-esteem, legislative restrictions, perceived stigma and actual discrimination, and cognitive and behavioral deficits (impaired memory, hyposexuality).[45] Biologic (e.g., cognitive impairment) and drug-related factors (e.g., lethargy, tremor) can further complicate this syndrome. Some of these concerns can be related to incomplete compliance with medication as an aspect of quality of life for individuals.[21]

The selection of which scale to include in a quality-of-life questionnaire is governed by the clinical question being addressed. Measures applied to assessing the effect of treatment in patients with newly diagnosed epilepsy may be different from those assessing therapy for patients with chronic epilepsy or undergoing epilepsy surgery. This approach to individual clinical questions has also incorporated contributions from patients in assessments of their therapy and management. Cramer[23,25] and Leone and colleagues[52] have reviewed the types of measures available and under development for assessment of people with epilepsy.

Early Initiatives in Measuring Psychosocial Outcome in Epilepsy

Recognizing the cognitive and behavioral problems that can accompany epilepsy, many studies have used neuropsychologic testing to define functional brain deficits and the Minnesota Multiphasic Personality Inventory (MMPI) to assess personality issues. More recently, other psychiatric rating scales have been used to assess specific behavioral problems, such as anxiety or depression.

The Washington Psychosocial Seizure Inventory (WPSI)[36] was the first epilepsy-specific psychosocial measure. This 132-item inventory is a self-report measure consisting of eight psychosocial scales (Family Background; Emotional, Interpersonal, and Vocational Adjustment; Financial Status; Adjustment to the Diagnosis of Seizures and Epilepsy; Satisfaction with Medical Management; Overall Psychosocial Functioning) and three validity scales. The WPSI has been widely used in assessing psychosocial outcome among epilepsy patients and in assessing changes in psychosocial functioning before and after a specific intervention, such as epilepsy surgery or a new antiepileptic drug.[35]

The Well-being Scale was developed by Collings.[20] This scale of overall well-being includes six subscales: Self-esteem, Life Fulfillment, Social Difficulty, Physical Symptoms, Worries, and Affect Balance. Testing in 392 patients with active epilepsy showed lower well-being on all scales than in nonepilepsy control groups. The visibility of severe seizures and frequency of seizures were directly related to well-being. Self-image (perception of self) and epilepsy were most predictive of overall well-being. Other important variables included few seizures, mild seizures, recent diagnosis, confidence in the diagnosis, and employment.

The Social Effects scale was developed by Chaplin and colleagues as a postal questionnaire to investigate social aspects of epilepsy in a wide range of epilepsy patients. The Social Effects scale was designed following extensive patient interviews. Initially, 21 areas of concern were identified, but only 14 were included in the final version. Scale reliability, assessed by the test–retest method, was only moderate. Validity was established through a comparison of patient responses and their behavior as observed by medical staff criticism. Further evaluation of the scale is necessary, although the authors have applied the scale successfully in the National General Practice Survey of Epilepsy.[18,19]

Table 1 Epilepsy Surgery Inventory-55

Scale	Number of items
Health Perception	9
Energy/Fatigue	4
Overall Quality of Life	2
Social Functioning	2
Emotional Well-being	5
Cognitive Functioning	5
Physical Functioning	10
Pain	2
Role Limitation	
Emotional	5
Memory	5
Physical	5
Change in Health	1

From Vickrey et al.[75] Permission to use the ESI-55 and scoring manual can be obtained by writing to RAND, 1700 Main Street, P.O. Box 2138, Santa Monica, CA 90407-2138 (Attention: Contracts and Grant Services). Additional information can be obtained from Dr. Vickrey at that address.

Current Measures of Outcome in Adults

Epilepsy Surgery Inventory-55

Vickrey et al.[75] developed a new inventory to assess HRQOL in epilepsy, the Epilepsy Surgery Inventory-55 (ESI-55). Using the RAND 36-Item Health Survey[78] as the generic core, they added 19 items, the majority of which are epilepsy specific. Fifty-four items, shown in Table 1, make up 11 unique scales tapping into distinct dimensions of HRQOL; another item assesses change in health during the preceding year.

The ESI-55 was developed to assess HRQOL outcome after epilepsy surgery. Patients who continued to have seizures after surgery had lower ESI-55 scores (i.e., worse HRQOL) than those who were completely seizure free on all 11 scales ($p < .05$). The ESI-55 was developed to assess HRQOL in a group of postsurgical patients, a small and skewed group of patients with epilepsy. In addition, some aspects of HRQOL were underrepresented in the ESI-55, particularly in regard to social health, for which there is only a two-item Social-Functioning scale.

Liverpool Quality-of-Life Battery

The Liverpool battery began as a way to assess the psychosocial outcomes after a decision to withdraw or not withdraw from antiepileptic drugs.[50] Since then, this group has applied quality-of-life measures to several critical epilepsy issues, including the assessment of a novel antiepileptic drug in patients with refractory epilepsy,[70] quality of life and quality of services for a community-based population, efficacy of a novel antiepileptic drug in children with epilepsy and learning disabilities, and psychosocial outcomes of immediate versus delayed treatment in single seizures and early epilepsy.

Table 2 Liverpool assessment battery

Scale	Number of items
Liverpool Seizure Severity scale	
Perception of Control	8
Ictal/Postictal Effects	12
Nottingham Health Profile[a]	38
SEALS Activities of Daily Living[a]	19

Social Problems Questionnaire[a]	33
Hospital Anxiety and Depression scale	14
Affect Balance scale	10
Profile of Mood States[a]	36
Rosenberg Self-esteem scale	10
Liverpool Mastery scale	8
Stigma scale[b]	3
Life Fulfillment scale[b]	24
Impact of Epilepsy scale[b]	8
Adverse Effects Profile[b]	20

SEALS, Side Effects and Life Satisfaction Inventory.

[a] Deleted from later versions.

[b] Added to later versions. From Baker et al.[10] Additional information can be obtained from Prof. Baker at the Department of Neurosciences, Walton Center for Neurology and Neurosurgery, Lower Lane, Liverpool L9 7LJ, UK.

This group has used a developmental model encompassing measures of physical functioning (Seizure Severity,[9] Seizure Frequency, Activities of Daily Living,[15] Social Functioning, Life Fulfillment,[8] Stigma,[48] Impact of Epilepsy[49]) and of psychological functioning (Affect and Balance scale,[13] Hospital Anxiety and Depression scale,[80] Self-esteem,[65] Mastery scale[61]) as shown in Table 2. Some of these scales were developed to assess the effects of epilepsy and its treatment; others were designed to assess other disorders but were successfully validated in people with epilepsy. Evidence of the psychometric validity has been reported.[8,10,48]

Repertory Grid Assessments

Kendrick and Trimble[51] hypothesized that HRQOL could be improved by increasing actual abilities or decreasing expectations, and that people judge their current quality of life in relation to past experiences and other people. In extensive interviews, patients identified specific issues important to their lives regarding physical functioning, cognition, emotion, social functioning, and financial and work status. A repertory grid technique was used with a Construct Importance scale in which patients identified issues important to themselves and rated the problems during follow-up. Analyses by gender showed that women and men with epilepsy had similar perceptions about their HRQOL.[56] Women were more concerned about friendship and being free of worries and anxiety than men. Men were more concerned than women about controlling their temper and being married. The profiles showed differences between actual (NOW) and desired (LIKE) status. This labor-intensive interview method is not feasible for large populations, but it can be applied in hospital or research settings in which extended interviews are possible, such as during evaluation for epilepsy surgery. The Quality of Life Assessment Schedule (QUOLAS) developed from this method has been modified and streamlined for use by Selai and Trimble[69] and has been used in research settings.[68]

Table 3 The Quality of Life in Epilepsy-89[a] and-31[b] Scales

Scale	Number of items
Health Perceptions	6
Seizure Worry*	5
Physical Function	10
Role Limitation, Physical	5
Role Limitation, Emotional	5
Pain	2
Overall Quality of Life*	2
Emotional Well-being*	5
Energy/Fatigue*	4
Attention/Concentration*	9
Memory	6
Language	5
Medication Effects*	3
Social Function, Work, Driving*	11

Social Support	4
Social Isolation	2
Health Discouragement	2
Sexual Function[c]	1
Change in Health	1
Overall Health[c]	1

[a] The QOLIE-89 contains 17 scales with 87 field-tested questions.

[b] The shorter QOLIE-31 includes items from the seven scales marked with an asterisk. The QOLIE-10 contains one or more questions from each of the seven QOLIE-31 scales.

[c] Two additional items were added after validation studies. U.S. English versions of the QOLIE instruments are available at http://professionals.epilepsy.com/page/qoltools.html. Permission to use the U.S. English versions of the QOLIE-89 and QOLIE-31 and scoring manuals can be obtained by writing to RAND, 1700 Main Street, P.O. Box 2138, Santa Monica, CA 90407-2138 (Attention: Contracts and Grant Services) or from RAND—Health@rand.org. Permission to use the QOLIE-10 can be obtained from Professional Postgraduate Services, 400 Plaza Drive, Secauscus, NJ 07094. Availability of and permission to use translations of the QOLIE-10, -31, -31-P, or -89 or QOLIE-AD-48 should be requested from Joyce.Cramer@Yale.Edu.

Quality of Life in Epilepsy Instruments

The Quality of Life in Epilepsy (QOLIE) Development Group expanded the ESI-55 to create a broad-based instrument for cases of epilepsy encompassing a wider range of severity. The QOLIE test instrument included the RAND 36-Item Health Survey as a generic core, with eight additional multi-item scales. The epilepsy-targeted segment consisted of 48 items derived from patient interviews, literature review, and expert opinion. An open-ended question encouraged patients to report additional items that affected their quality of life. The resulting instruments, shown in Table 3, include the QOLIE-89 (17 scales, 89 items), the QOLIE-31 (7 scales, 31 items), and the QOLIE-10 screening questionnaire (10 items selected from the 7 scales in QOLIE-31). The QOLIE-89 and QOLIE-31 showed good reliability and construct validity. The QOLIE-10 and the QOLIE-31 have been compared by Cramer et al.[27] in a clinical trial of levetiracetam and were found to be highly correlated; both were able to detect change over time and both were able to detect differences among treatments and between groups of responders and non- responders.

Factor analysis of the 17 scales of the QOLIE-89 suggested four dimensions: (a) epilepsy-targeted, (b) cognitive, (c) mental health, and (d) physical health factors. Health care utilization was negatively correlated, whereas education and employment were positively correlated with better QOLIE scores. The mood factor showed high correlation and was a strong predictor of total HRQOL scores, with psychomotor slowing also showing significant relationships.[62] Patients with less severe epilepsy generally had higher HRQOL scores than patients with more severe epilepsy.[33] The epilepsy-targeted factor and the Seizure Worry, Health Discouragement, and Work, Driving, and Social Function scales best discriminated among groups of patients with epilepsy of different levels of severity. Negative correlations were found for all four HRQOL factors and overall scores for neurotoxicity and systemic toxicity. Employment also correlated well with the overall score and cognitive and physical health factors. These findings demonstrate the sensitivity of the instrument to differences among groups based on seizure frequency, demographic characteristics, and adverse effects.

Side Effect and Life Satisfaction Inventory

The Side Effect and Life Satisfaction (SEALS) inventory was initially developed by Brown and Tomlinson[15] as a measure of patient satisfaction with antiepileptic drug (AED) therapy. Originally a 51-item questionnaire, it was modified by Gillham et al.,[38] who reduced it to 38 items, consisting of five subscales (Worry, Temper, Cognition, Dysphoria, and Tiredness). The scale was validated in 307 patients with epilepsy against the Hospital Anxiety and Depression Scale, the Profile of Mood Scale, and the Medical Outcomes Study-Cognitive Functioning.[39] Responsiveness has been assessed in drug trials comparing lamotrigine with phenytoin, carbamazepine, and valproate.[14,16,73]

General Health-Related Quality-of-Life Assessment by the RAND 36-Item Health Survey

Wagner et al.[77] evaluated general HRQOL in 148 people with epilepsy using the RAND 36-Item Health Survey. Scores were compared with the Medical Outcomes Study population matched for social and demographic factors. Epilepsy patients had significantly lower scores in six of eight domains (all but physical functioning and bodily pain). Patients who had at least one seizure during the week before the assessment (31%) had significantly lower scores than patients who were seizure free for >1 year (27%).

Vickrey et al.[76] compared scores for a pictorial item and the eight scales of the RAND 36-Item Health Survey from patients undergoing epilepsy surgery and patients with other medical disorders. After resective surgery, seizure-free patients had generally better scores on all scales, and those with continuing simple partial seizures had HRQOL scores similar to those of patients with hypertension, heart disease, and diabetes. Patients who continued to have complex partial or tonic–clonic seizures after surgery had poorer emotional well-being and overall HRQOL than all other patient groups except those with depression.

Assessments in Adolescents and Children

Instruments for measuring HRQOL must be revised or created to address issues specific to the age group; for example, adolescents with epilepsy have special concerns about the feasibility of driving and dating that differ from those of adults. Therefore, to assess an adolescent's HRQOL, Cramer et al.[30] developed the Quality of Life in Epilepsy Inventory for Adolescents (QOLIE-AD-48). The 48-item questionnaire, which takes about 15 to 20 minutes to complete, provides information about eight different domains (impact of epilepsy, memory and concentration, attitudes toward epilepsy, physical functioning, stigma, social support, school behavior, and health perceptions). Initially tested on 197 adolescents with epilepsy aged 11 to 17 years, the scale was found to have satisfactory reliability and good content and construct validity.

Devinsky et al.[34] used this measure to examine the risk factors for poor HRQOL in 197 adolescents with epilepsy. Based on the QOLIE-AD-48 and data obtained from interviews, medical reports, and health records, they found that older adolescents (age between 11 and 17 years), those with more severe epilepsy and more symptoms of neurotoxicity, and those from lower-socioeconomic-status families were more at risk of reporting poor HRQOL.

Similar results were reported by Heimlich et al.[43] using the Child Attitude Toward Illness Scale. Attitudes toward epilepsy were examined in 197 adolescents, and it was found that adolescent girls had significantly more negative attitudes than adolescent boys, as did older adolescents (age 16 to 17 years) and those with more severe epilepsy.

Baker et al.[11] also found that adolescents with epilepsy in the United Kingdom report higher levels of depression, anhedonia, and social anxiety and a higher number of obsessive symptoms than adolescents without epilepsy. However, this can be mediated by access to appropriate information, seizure frequency and type, social support, and gender.[11,64]

The verbal and intellectual skills of adolescents allow one to assess HRQOL through direct patient reporting. In contrast, assessment of children must often use an interview with the parent or caregiver, and the responses might not reflect what is important to the child. Children with epilepsy often confront issues of self-esteem and dependency. These issues are probably most important in families with overly protective parents. Thus, having parents rate the HRQOL of children with epilepsy can provide a biased perspective.

Sabaz et al.[66] developed a parent-rated HRQOL scale for children of age between 4 and 18 years (the Quality of Life in Childhood Epilepsy questionnaire [QOLCE]). The final Australian version consisted of 76 items with 16 subscales consisting of five domains (physical function, social function, cognition, and emotional and behavioral well-being). The QOLCE has been adapted for use in an American population and evaluated for reliability and validity. The scale has also been used retrospectively to test sensitivity to postoperative outcome in a sample of children who had undergone epilepsy surgery.[66]

Miller et al.,[57] also using parent-rated measures, found diminished HRQOL in 41 children with epilepsy compared to an age-matched control group. Presence of comorbid neurologic impairments such as ataxia, developmental delay, and hemiparesis and number of antiepileptic medications correlated with lowered HRQOL.

A mixture of parent- and child-rated measures was used by van Empelen et al.[74] They assessed HRQOL and self-perceived competence in 21 children and adolescents who had undergone epilepsy surgery 2 years previously. Postoperative improvements were seen in HRQOL, with most improvements falling within the first 6 months.

Studying 127 children (8 to 12 years of age) and their mothers with self-report questionnaires, interviews, and medical records, Austin et al.[2] identified five variables that related to behavior problems: (a) female gender, (b) family stress, (c) family mastery, (d) extended-family social support, and (e) seizure frequency. Comparing children (8 to 12 years of age) with epilepsy versus children with asthma, Austin et al.[3] found more compromises in psychological, social, and school domains in the epilepsy group. The magnitude of differences between the two types of illness and other findings suggests that some other factor is related to poor quality of life in children with epilepsy.

The European DISABKIDS group developed condition-specific modules of the European DISABKIDS HRQOL instrument for children with asthma, juvenile idiopathic arthritis, atopic dermatitis, cerebral palsy, cystic fibrosis, diabetes, and epilepsy for use in seven European countries. These modules, which are to be used alongside a chronic generic module, have been evaluated in 360 children and their families. Further testing of reliability and validity for each country is being carried out.[4]

Heath-Related Quality of Life in the Elderly

Studying the elderly population with epilepsy can also be problematic.[31] There has been little empirical study of quality of life in the elderly,[53] and randomized clinical trials that have been undertaken have failed to use HRQOL measures.[53]

Any quality-of-life measures that have been used have been tested on adults <65 years of age. However, the elderly population differs from both young and middle-aged adults in terms of their epilepsy (etiology, clinical presentation, treatment) and lifestyle.[31]

Baker et al.[6] carried out a large cross-sectional study of epilepsy in the U.K. community. Using the Liverpool QOL battery, it was found that the elderly population diagnosed later in life can suffer from more anxiety and depression and report more negative quality of life than younger adults.

Therefore, given that epilepsy is the third-most-common neurologic condition among those of older age, research and development on quality of life in this group is vital for clinical management and targeting of appropriate psychosocial interventions.

Measures of Heath-Related Quality of Life in Epilepsy Studies

Although several groups have developed approaches to measuring HRQOL for people with epilepsy, few data are available demonstrating their sensitivity to changes in various interventions (e.g., change from two to one antiepileptic drug, change from a sedating to a nonsedating antiepileptic drug).[23] However, the QOLIE-89 has been used to assess improvements in QOL following a 2-year nurse-led structured intervention program. Following group education and extended counseling and teaching, the intervention group demonstrated significant improvements in overall QOL compared to controls.[44]

Furthermore, Privitera and Ficker[63] designed a large, community-based 3-month trial looking at changes in adverse events and HRQOL when switching from immediate-release to extended-release carbamazepine. Adult patients will be asked to complete the Adverse Events Profile (AEP) and the QOLIE-31, whereas adolescents with epilepsy will complete the Hague Seizure Severity Scale and the QOLIE-AD-48. Changes in efficacy of treatment are not expected because only medication formulation will be changed. They hope to detect differences in tolerability and QOL.

Drug Trials

The typical clinical trial of an investigational antiepileptic drug added to a standard antiepileptic drug does not usually produce dramatic clinical changes. Thus, large changes in HRQOL endpoints should not be expected. Most trials are relatively brief (3 to 6 months of blinded follow-up), further reducing the likelihood of finding major changes. Furthermore, Baker et al.[5] concluded that often there is a failure to apply QOL and behavioral measures in a systematic way in randomized, controlled trials. Cramer[25] discussed the importance of carrying out HRQOL measurements in clinical trials and recommended principles for using them in such investigations. Cramer et al.[28] were the first to use the QOLIE-31 as part of a randomized, placebo-controlled, double-blind trial of the efficacy and tolerability of levetiracetam as an adjunctive therapy. Data from 246 patients randomized on levetiracetam 1,000 mg, levetiracetam 3,000 mg, or placebo were analyzed for significant changes in HRQOL at 18-week follow-up. Levetiracetam, especially 3,000 mg, seemed to provide significant positive improvements in HRQOL, particularly for those who were classified as responders (i.e., reduction in seizures of ≥50%). This study highlights the usefulness of the abbreviated QOLIE instrument in interventional studies. However, patients taking long-term open-label medication often have expectations, other changes in therapy, or significant life events that complicate the process of identifying the effect of a drug.

Jacoby et al.[50] used several scales to compare the effect of continuing versus withdrawing medication in patients who were seizure free for 2 years. Patients who relapsed while taking antiepileptic drugs did less well than patients who relapsed after discontinuation of medication, which likely reflects the fear that those relapsing on medications might not remain seizure free or would need to endure higher doses of antiepileptic drugs. These investigators concluded that continuing to take drugs implies persistence of epilepsy, whether or not seizures are controlled. Patients whose drugs were discontinued and who remained seizure free were better able to shed the stigma of the diagnosis.

Surgical Trials

The effect of epilepsy surgery, which can be curative for some patients, is another area beckoning HRQOL assessments. From Horsley's first operation in 1886[46] to cure posttraumatic epilepsy through Penfield's pioneering use of anterior temporal lobectomy in patients without gross lesions,[60] improving HRQOL has been an important implicit motivation for epilepsy surgery. Surgical treatment has often been undertaken to improve the social situation of patients with chronic epilepsy. Recently, the literature has focused on the effects of surgical treatment on other outcome measures relevant to quality of life, such as memory, cognition, and emotional and behavioral adjustment.[58]

Early evaluation of HRQOL before the special attention and stresses of the presurgical evaluation is important to define the patient in a "usual" state. Follow-up assessment should not be attempted too soon after surgery, but might profitably be repeated during several years postoperatively to evaluate changes over time.

Selai et al.[68] assessed the HRQOL of patients pre- and postsurgery using the QOLAS, the ESI-5, and the EQ-5D, which is used in economic analyses. Of the 145 patients evaluated for surgery, 22 underwent the procedure and achieved a 75% seizure reduction. Patients reported significant improvements on two of the three composite scores of the ESI-55 at mean 1-year follow up. They also reported significant improvements in all domains of the QOLAS.

Surgical success does not always equate with psychological or social recovery. Augustine et al.[1] found that most patients who did not work before surgery did not work after successful surgery. Many patients who worked before surgery despite frequent seizures resumed work. Seizure control was only one of many factors related to occupational adjustment.

Changes in HRQOL were also assessed by Cramer after vagal nerve stimulation (VNS).[24] The QOLIE-10 was administered to 136 intractable epilepsy patients before and after 3 months of stimulation. Patients reported improved overall HRQOL and improvements in energy, downheartedness, memory difficulties, work and social limitations, and fear of seizures. However, there were no differences in overall HRQOL or subdomain scores, except for energy level, between those classified as responders and nonresponders to VNS.

Cross-Cultural Adaptation and Translation

There is an increasing interest in conducting multicenter trials in different countries in Europe and the United States. This has meant that measures developed in one country need to undergo translation and retesting for use in another. However, the process is not a simple one. The technical issues are well documented.[40,47] Adaptations require emphasis on making the instrument sensitive to HRQOL concerns of individuals in each culture, with less emphasis on perfecting translation of terms. Various measures have been successfully translated and validated into other languages, including Greek,[59] German,[55] Serbian,[72] and Chinese.[79]

Baker et al.[7] conducted the largest study to date of the effect of epilepsy and treatment on the quality of life of people living in Iran, the Gulf States, and the Near East. The battery of questionnaires was translated forward and backward from English into Greek and Fufha (the official written Arabic language) and given to 3,847 people with epilepsy. Epilepsy was perceived to affect many different aspects of their daily lives and largely confirmed previous findings of the effect of epilepsy on people living in European and other countries.

Summary and Conclusions

Quality-of-life measures are critical for reaching a better understanding of the effect of epilepsy and its treatment. Medical outcomes—seizures and side effects of drugs—define only a small portion of the areas that affect the life of a person who has epilepsy. Furthermore, doctors' and patients' perspectives on how seizures and side effects affect the patient's life can be quite different. Quality-of-life questionnaires can be useful in epilepsy clinical trials and medical practice, allowing patients to express their concerns about a variety of issues affected by the diagnosis, psychosocial impact, seizures, and medication. Thus, the patient's perspective can provide new information about not only the critical psychological and social issues, but also the medical outcomes (seizures, adverse effects of drugs) that are often viewed solely from the physician's perspective.

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Chapter 101

Age-Related Considerations

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Introduction

The goals of therapy for people with epilepsy were discussed in an earlier chapter. They can be seen as being broadly concerned with reducing the impact of the condition on daily functioning and overall quality of life (QoL) by reducing seizure frequency and severity, minimizing the side effects associated with prescribed treatment regimes, and providing the necessary information and support to enable patients to manage their condition successfully. In considering what constitutes appropriate therapy for any individual patient, it is important to recognize that the impact of epilepsy and its treatment will vary across a number of patient characteristics, of which age is an important one. The quality of people's lives overall reflects the level of their functioning within a number of different spheres, and this may be enhanced or reduced by their condition and its treatment. However, the importance attached to optimal functioning within particular spheres varies at different stages of the life cycle, and as a result so does the extent to which the condition and its treatment are seen to impinge on quality of life.

This chapter considers the differential impact on quality of life of epilepsy and treatment for epilepsy at different stages of the life cycle—childhood, adolescence, and the earlier and later years of adulthood. Although the effects of epilepsy and its treatment on the quality of life may differ according to a person's age group, there are nonetheless implications common to all age groups, and these are discussed first.

A chronic illness such as epilepsy is associated with several concomitant problems, regardless of the point in the life cycle at which it develops. Conrad[31] identified among these the problem of managing the uncertainty that accompanies the onset of chronic illness; the impact that chronic illness can have on a person's sense of self; the issue of stigma, which is more problematic in some conditions than others; the impact of chronic illness not only on the patient, but also on the patient's family members; and the problem of managing treatment regimes. These are discussed in greater detail in the following paragraphs:

1. The problem of managing uncertainty in chronic illness. A defining quality of most chronic conditions, including epilepsy, is uncertainty, which relates not only to the interpretation of symptoms and the diagnosis, but also to the projected clinical course. Radley[100] argued that uncertainty is endemic to the situation of people who are chronically ill and “is not limited to one period of time or one situation.” A person with epilepsy can face uncertainty regarding whether and when seizures will recur, the nature of seizures and how they can best be controlled, and whether the illness will ultimately go into remission. The unpredictability of the nature and course of epilepsy can thus be a key factor in the problems it engenders, whatever the age of the person affected.
2. The impact of chronic illness on sense of self. A number of authors have considered the impact that a chronic illness has on a person's self-concept.[21,22,27,140] The restrictions imposed by chronic illness, the inability to fulfill former tasks and roles, the consequent social isolation, and the increased dependency on others combine to make chronic illness what Charmaz[27] described as a fundamental form of suffering because those who become ill have to contend with “a crumbling away of their former self-images, without simultaneous development of equally valued new ones.” This is clearly the case for people with epilepsy,

who may face various statutory and nonstatutory restrictions as a result of their illness, find themselves unable or unwilling to pursue particular activities, either because of their fears of precipitating seizures or as a result of the attitudes of others toward them, and consequently become increasingly socially isolated. The impact on self-concept may be felt equally acutely by the child with epilepsy excluded from sporting activities at school and the elderly person with epilepsy who is no longer regarded as capable of caring for a grandchild.

3. The issue of stigma. It has been argued that all chronic illnesses are stigmatizing to a greater or lesser degree by virtue of their representing a deviation from a state of health,[95] but epilepsy has, historically, been a stigmatizing condition par excellence.[126] For this reason, people with epilepsy often appear to regard their condition as a "new moral weight" that they have to carry,[114] and some see it as having an extremely negative impact on the quality of their lives. A number of authors have shown how the parents of children with epilepsy can act as what Goffman[56] referred to as "stigma coaches," inculcating in their offspring a sense of shame about their condition and counseling them not to disclose it to others.[114,139] Scambler[110] contended that because having epilepsy has more salience for people in some roles and situations than in others (and so, potentially, a greater effect at some periods of the life cycle than at others), the degree to which a person feels stigmatized by epilepsy will vary.
4. Impact of chronic illness on family members. Coping with chronic illness takes a toll not only on the person affected, but also on the patient's family members, so that their quality of life too can be diminished.[4,5,134] Venters[134] listed among the range of familial consequences of chronic illness increased communication difficulties, accentuation of preexisting marital problems, and increased social isolation and disorganization of family routines; although Venters was concerned with a specific condition, cystic fibrosis, it seems likely that these outcomes are common to all chronic conditions, epilepsy included. Confronted with the problem of chronic illness, many families become dysfunctional. Scambler and Hopkins[112]

examined the way epilepsy is accommodated in families and concluded that to survive intact the family must reestablish the equilibrium lost at the onset of chronic illness in one of its members.

5. Managing treatment regimes. Managing a treatment regime is part of the "work" of a chronic illness,[119] and people who are chronically ill often have to become experts in their own treatment, considering the associated costs and benefits and adhering to or adapting their prescribed regimes accordingly. Pinder[97,98] illustrated clearly how people who are chronically ill are constantly involved in maintaining a balance between minimizing the symptoms of their illness and incurring the side effects of medication. The problems of managing a drug regime are nowhere more apparent than in the sociological literature on epilepsy. Schneider and Conrad[114] and Scambler[109] found that adults with epilepsy frequently self-regulated their antiepileptic drugs, missing, raising, or reducing doses at particular times and in particular circumstances. West,[139] considering children with the condition, reported that their parents often decided to contravene the medication rules specified by the child's physician out of anxiety about the effectiveness of antiepileptic drugs and their possible side effects.

Age-Related Impact of Epilepsy

Although all people with epilepsy have to contend to some degree with the problems just outlined, the precise extent to which their impact is felt by any one individual is determined by a number of factors relating to their personal and social situation, of which age is one. This section gives more detailed consideration to the way in which such problems are manifested in childhood, adolescence, adulthood, and older age.

Impact of Epilepsy in Childhood and Adolescence

Epilepsy is the most common chronic neurologic problem of childhood, its incidence being highest in the first decade of life.[60] It is now known that a number of the childhood epilepsies are benign and will either remit or be easily controlled by appropriate treatment, whereas others have a much poorer prognosis and are often accompanied by significant brain dysfunction and developmental delay.[41] The epilepsies of early childhood tend to carry the worst prognosis because they are commonly associated with congenital disorders or birth and perinatal trauma.[99] At least 70% of childhood epilepsies, particularly the benign partial epilepsies, are known to remit at or before adolescence[1]; some, including severe myoclonic epilepsies and the Lennox-Gastaut syndrome, persist through adolescence and into adulthood; a third group, including juvenile absence and juvenile myoclonic epilepsy, begin in adolescence.[39]

Main Quality-of-Life Effects in Childhood

Compared with parallel work in adults, research into the impact of chronic illness on quality of life in children and adolescents has been hampered by a number of difficulties concerning measurement. These relate to the rapid physical, cognitive, and emotional changes that occur through this period,[43] which necessitate the development of scales focusing on narrow age ranges and developmental levels. Although efforts have been made recently to develop appropriate methodologies for obtaining information regarding quality of life from children and adolescents themselves,[28,47] studies of the impact of chronic illness on quality of life in childhood have generally rested on the assessments of parents, for reasons that are self-evident: Very young children are unable to express themselves verbally, and school-age children may have difficulty filling in forms or schedules or may be intimidated when asked questions by an unfamiliar researcher.

Despite such difficulties, an important finding from the work that has been done is that children and adolescents with epilepsy appear to have a relatively more compromised quality of life than children and adolescents with other chronic conditions or their healthy peers.[12,50,90] Identified risk factors for poor quality of life include epilepsy severity, antiepileptic drug (AED) side effects, and lower socioeconomic status.[36] Miller et al.[90] compared quality of life in children with epilepsy and healthy controls, using a generic measure, the Child Health Questionnaire, and showed that the former had more limited life quality in terms of physical function, emotional well-being, self-esteem, parental impact, and family activity; predictors for impaired quality of life were number of AEDs and presence of comorbid neurologic impairments. Räty et al.[101] found that even uncomplicated epilepsy exerted a negative impact, especially in the areas of competence. Both they and others[36,91] reported that patients in late adolescence are at greater risk of compromised quality of life than are those at earlier developmental stages, and as discussed later in this chapter, it appears that such effects sometimes persist into adulthood.

In a recent review of quality-of-life issues affecting children and adolescents with chronic illness,[135] self-esteem and school functioning were identified as being among the most significant. The relevance of both these issues for children with epilepsy is demonstrated in the work of a number of authors. Long and Moore[83] collected information from children with epilepsy about the effects of being “different” from other children and found that they had significantly lower levels of self-esteem than their healthy siblings. Poor self-concept among children with epilepsy has also been reported by Matthews et al.,[87] Hoare,[64] and Austin et al.[12] Matthews and Barabas[86] studied 45 children between the ages of 7 and 12 years, 15 with epilepsy, 15 with diabetes, and 15 in good health. Compared with the rest, the children with epilepsy had poorer esteem in relation to their intellectual and academic functioning and were also more likely to see themselves as unpopular with their peers.

Role of Important Others in Mediating Childhood Quality-of-Life Effects

Matthews and Barabas hypothesized that children's self-concept is threatened by a sense of lack of control, experienced as a result of the unpredictability of their seizures—an element of epilepsy that can, of course, be as much a problem for the families of children with epilepsy as for the children themselves.[7] The “vulnerable child syndrome,”[58] in which the fear and anxiety of both child and parent inhibit normal development, is not an uncommon phenomenon in families with children with a chronic illness such as epilepsy. Overprotectiveness on the part of parents may leave them reluctant to grant the child autonomy, so that his or her sense of competency and self-worth is threatened.[144] Williams et al.[141] documented the role of parental anxiety in compromising the quality of life of children with epilepsy and concluded that targeted interventions and support may be critically important.

Table 1 An ecological framework for understanding the role of family factors in child psychopathology

Proximal factors	Distal factors	Context factors
• Quality of parent–child relationship, e.g., rejection/acceptance, parental attachment • Parenting, e.g., level of parental support and control	• Parent characteristics, e.g., maternal depression, parental beliefs concerning their competence in parenting, ineffective coping strategies • Parental congnitions, e.g., perceptions concerning epilepsy, parental expectations for the child	• Marital conflict • Family adaptation • Family conflict/cohesion • Family stress • Social support

Adapted from Rodenburg et al.[104]

Matthews and Barabas also suggested that children's sense of self is the outcome of the feedback they receive from important others, and that such feedback may be fundamentally different for them than for children without epilepsy. There is evidence for this in the studies of interaction in families of children with epilepsy.[49,57,102] In a recent review, Rodenburg et al.[104] attempted to address the question of whether the families of children with epilepsy differ from others on *distinct* family factors and whether these factors are linked to psychopathology in the affected child. The theoretical framework for their analysis distinguished among proximal, distal, and context factors (Table 1).

Summarizing results from 35 studies involving 1,400 children aged 5 to 25 years, these authors reported that, compared to controls, parents of children with epilepsy appear to be less supportive and competent and more inconsistent and authoritative, with fathers being overnurturing and mothers exhibiting higher levels of emotional overinvolvement. Families of children with epilepsy tend to be more rigid and less close and more stressed and to have fewer social resources and support. With regard to the role of these family factors, maternal warmth and encouragement are shown to reduce psychopathology in children with epilepsy, as are parental support, satisfaction with family relationships, and family social support, whereas maternal criticism, depression and worry about epilepsy, parental overcontrol, perceived limitations and stigma, and family stress and conflict increase it. The authors made some important observations about these findings: Emotional overinvolvement can generate positive, as well as negative, effects for the affected child's adjustment; epilepsy is a stressor for parents as well as their affected child, but parental attitudes can become more positive over time; and lack of knowledge may induce negative parental perceptions of epilepsy but increasing knowledge can decrease parenting problems. They argued that future research should aim to determine the unique contributions made by family factors relative to neurologic and medication factors and to identify strategies to help families cope better with the challenges epilepsy in childhood can present.

Their conclusions are supported by the work of Oostrom et al.[93] who investigated factors associated with cognitive-behavioral function in children with newly diagnosed epilepsy attending mainstream school. Their analysis showed that in "epilepsy-only" children, context-related rather than epilepsy-related factors were important in predicting cognitive and behavioral disadvantages over time; children with persistent deficits were more likely to have shown behavior problems prediagnosis and to come from families with increased dysfunction and where the parents reported discontinuity in parenting style following the onset of epilepsy in their child. Similarly, Fastenau et al.[46] showed that in children with chronic epilepsy, neuropsychologic deficits had a smaller impact on their academic achievement if they were living in supportive and well-organized homes. These authors concluded that interventions that increase family structure, stability, and support can reduce the risk of adverse academic outcomes for such children and, it is hoped, their overall quality of life.

Quality-of-Life Effects for Family Members of Children With Epilepsy

The sometimes considerable effects of chronic illness on other family members, as noted in a number of sociological studies, are evidenced in epilepsy also. Perhaps as a result of parental preoccupation with and overprotectiveness of the affected child, families of children with epilepsy appear often emotionally skewed,[57] so that psychiatric morbidity is increased not only in children with the condition, but also in their siblings.[50,65,66] The effect on their other children was one of the main anxieties expressed by parents in the study by Ward and Bower,[137] who reported that siblings were often upset by the limitations imposed on the family as a whole as a result of the onset of epilepsy, jealous of their parents' preoccupation with the affected child, and resentful at the increased responsibilities assigned to them in helping to care for the child. The negative impact on parents is apparent from the reported higher rates of psychological difficulties[105] and of separation and divorce among the parents of children with epilepsy than in the general population.[115]

Impact of Antiepileptic Drugs on Quality of Life of Children

That the adverse effects of AEDs can reduce the quality of life for children and adolescents with epilepsy is well recognized. Besag[18] noted that although some antiepileptic drugs are notorious for causing gross overactivity and behavioral disturbance in children, others are known to have a marked sedative effect, particularly if used in combination. Aldencamp[2] reviewed findings from more than 300 studies (although not all in children) on the cognitive effects of antiepileptic drugs; these indicate associated impairments in memory, concentration, and mental and motor speed. The adverse effects of AEDS, particularly on cognition,[131] have provided one of the major arguments for their withdrawal in children[25]; it is interesting, however, that Aldencamp et al.[3] studied drug withdrawal in 100 children who were seizure free for at least 1 year and found a significant improvement in their scores on only one of a large battery of cognitive tests. Whether this was because, as the authors suggested, the impact of antiepileptic drugs on cognitive function in children is limited, or because, as Dreifuss[40] argued, it is less likely to be reversible for children than for adults is not clear. Whatever the results of such studies, it is clear from investigating the issue of patient adherence with drug regimes[138] that parents

worry about the adverse effects of antiepileptic drugs on their children and so may decide to discontinue them; one study of the management of childhood epilepsy produced a figure for noncompliance of 60%.[35] With or without parental complicity, nonadherence to medication regimes appears to be a more common feature of adolescence than earlier childhood, a fact that Thornton[129] attributed both to a misunderstanding of the need for medication and an attempt to deny the “predicament” of having epilepsy. Wide fluctuations in blood levels of AEDs among adolescents have been reported by Takaki et al.,[123] indicating that erratic compliance was commonplace.

Reflecting concerns about further undesired effects of antiepileptic drugs on the developing brain, considerable emphasis has been given in studies of quality of life in children with epilepsy to emotional/behavioral issues[10,64,118,128] and the effect of epilepsy on school performance.[67,118,130] Berg et al.[17] assessed longitudinally the influence of epilepsy etiology and syndrome and seizure control for adaptive behavior in children; they concluded that in the majority of cases, it is in the normal range and shows no evidence of decline over time. The exception was for children with what these authors characterized as “epileptic encephalopathies” (including West syndrome and Lennox-Gastaut syndrome), who demonstrate impaired adaptation at the time of diagnosis and continue to experience further decrements. Austin and her colleagues examined academic achievement in children with both recent-onset and chronic epilepsy.[9,89] In a group of children diagnosed 12 months previously, they showed that mean academic achievement was in the average range. The same was true for children with established but low-severity or inactive epilepsy, although not for those with high-severity epilepsy, in whom scores were significantly lower. In both recent-onset children and children with established epilepsy, academic performance was significantly associated with adaptive competency (i.e., working hard, behaving appropriately, and being happy). An unexpected finding from the work reported is that there were no changes in academic achievement over the course of the 4 years during which the latter group were followed, that is, children with high-severity epilepsy did not get any worse in terms of academic achievement, but neither did children whose epilepsy was reduced in severity get any better. These findings highlight the need to ensure that the focus on medical management of epilepsy does not lead to problems with academic performance being overlooked.

The Role of Stigma

To understand fully why children with epilepsy and their families appear to fare worse in terms of quality of life than children with other chronic conditions and their families, it may be helpful to return to another of the common themes highlighted by Conrad,[31] namely, the issue of stigma. As noted earlier, epilepsy has long been a stigmatized condition—in the words of Schneider and Conrad,[113] a “closet illness”—and therefore it may have a particular significance for those in whom it is diagnosed and their relatives.[22] Although lay attitudes toward epilepsy appear to have become increasingly enlightened,[24,73,74] the theories about the nature and causes of epilepsy held by people, including the parents of children with the condition, may have important psychosocial implications. For example, West[139] found that many of the parents in his study held a view of epilepsy that was “predominantly stereotyped” and negative, and so experienced a sense of shame from having children with epilepsy. Thompson[128] commented that such negative attitudes on the part of parents are “easily internalized by the child, with negative consequences for the development of self-identity and self-esteem.”

Bagley[14] reported that teachers too often share in such commonly held stereotypes and prejudices, and as a result they are more likely to consider their epileptic pupils as having academic and behavior problems. The authors of one study reported that children who had seizures at school were significantly more likely to suffer from depressive illness than those whose seizures always occurred outside school hours; they attributed this finding to the rejection such children suffered from their peers as a result of their witnessed seizures.[96] When questioned about their main fears and concerns in relation to their seizures,[8] children with newly diagnosed seizures often said they were worried that their peers might tease or make fun of them. Oostrum et al.[92] reported that both children with epilepsy and their healthy peers attribute more shame to epilepsy than to other disorders. Such fears can be quite realistic, given the findings of Austin et al.[11] that among a general population of adolescents surveyed in the United States, about three fourths agreed that a young person with epilepsy would be more likely to be bullied or picked on, and less than one third would be willing to date someone with epilepsy. These negative attitudes were matched by gaps in U.S. adolescents' knowledge about epilepsy, with only half of them confident that epilepsy is not contagious and only one fourth that it is not a form of mental illness. Thompson[128] cited findings from a survey of schoolteachers' knowledge about epilepsy that showed that as many as 70% considered themselves ill informed about the condition; this has important implications for the quality of life of children with epilepsy because through such ignorance, children can be excluded from particular activities and denied valuable educational opportunities.

The problem of the stigma of epilepsy can be felt particularly acutely by adolescents, whose self-image is fragile and whose concern about the way others see them can be a cause of significant distress. Adolescence is the period during which people with epilepsy first have to confront the legal and statutory restrictions associated with their diagnosis—they may be unable to drive or to pursue certain career options—as well as the informal ones, such as the need to avoid excessive alcohol intake and sleep deprivation. Unable to establish themselves as “normal” in relation to their peer group, adolescents with epilepsy can become socially withdrawn and isolated. The struggle to develop independence, although faced by all adolescents, is thus further complicated for them, and their psychological development, social integration, and future independence may thus be at risk.[39] Kim[77] commented that identity formation can be a particularly difficult task for adolescents with epilepsy who “have not been able to build up competencies in the earlier developmental stages.” The need to consider the particular psychosocial difficulties faced by adolescents with epilepsy in addition to the traditional medical ones has been highlighted,[129] and it can best be served by providing special clinics for this age group.

Impact of Epilepsy on Quality of Life of Younger Adults

Efforts to assess the impact of epilepsy and its treatment on younger adults are somewhat further advanced than those for children, and there is a considerable literature on which to draw. The incidence of epilepsy is at its lowest from ages 20 to 60 years, and seizures are well controlled in the majority of adults in this age group. Despite the fact that the physical aspects of their condition may be of less significance for younger adults, the psychosocial ones may be of greater significance as they face the full weight of the formal legal restrictions on driving and employment that currently apply to people with epilepsy, as well as potential informal stigma and discrimination. Although the social meaning of epilepsy has clearly shifted with time, in the words of Conrad and Schneider,[32] from "badness to sickness," many people continue to regard having *epilepsy* as worse than having *seizures* because of their fear that they might be stigmatized by the label.[109]

The Role of Stigma and Discrimination

The evidence from research on the extent of informal stigma and discrimination in the lay community is somewhat contradictory, as is evidence of the degree to which people with epilepsy perceive it. Information about the attitudes of those without epilepsy toward those with it suggest that, historically, these have been less than favorable[13,59,62,107]; however, recent research suggests that attitudes are improving.[23,24,63,72,73,74] It has been argued that many people with epilepsy are unconvinced by this apparent new enlightenment, believing that their condition is one against which a particular prejudice persists, even when they personally have had no experience of such prejudice.[20,109] Scambler[108] reported that almost all the adults in his study of epilepsy admitted to suffering from what he terms "felt" stigma, even if only sporadically; feelings of stigma were less readily expressed among the subjects studied by Ryan et al.,[106] Chaplin et al.,[26] and Jacoby.[69] However, like Scambler, Jacoby found that felt stigma was significantly more prevalent than was clearly supported by any actual incidences of enacted discrimination, suggesting that people with epilepsy are still aware of the potential stigma of their condition and the ways in which they *could* be marginalized by it. These findings reinforce the need for clinicians who care for people with epilepsy to give greater attention to the "demythologizing and destigmatizing of epilepsy"[111] and to help them to negotiate any statutory restrictions.

Dilorio et al.[37] documented associations of perceived stigma in 320 men and women with epilepsy recruited through three epilepsy centers. Participants ranged in age from 19 to 75 years, the mean age being 43 years. Those reporting higher levels of perceived stigma also reported reduced self-efficacy, more-negative expectations of the outcome of treatment, poorer medication management and adherence, and reduced satisfaction with health care. Factors predicting greatest risk of feeling stigmatized included having a first seizure before age 50 years, not being married or cohabiting, not being in paid employment, and living on a limited income.

Main Quality-of-Life Effects in Adulthood

Thompson[127] pointed out that failure to address the psychosocial problems of epilepsy emerging in childhood and adolescence can result in psychosocial problems in adulthood that are "a greater handicap than the seizures and more intractable to intervention." Two important longitudinal studies provide evidence for her argument.[116,136] The first of these involved 155 individuals in a single Japanese prefecture[136] diagnosed with epilepsy before age 16 years and followed for 20 years. The findings indicate that for the majority of individuals with childhood-onset epilepsy, the long-term medical, educational, and social prognoses are favorable: by the time of follow-up, 148 individuals survived, in whom prevalence of psychiatric complications was low, educational achievement for those of normal intelligence paralleled that of controls, and levels of employment were high. Although the overall rate of marriage was lower, this applied only among the younger age groups. A less optimistic message emerges from the second study, which involved a population-based cohort of 245 individuals in Finland[116] diagnosed as having epilepsy in childhood and then followed prospectively for >30 years. Here, persistent effects were noted when epilepsy continued into adult life, a critical factor being AED medication. For example, those whose epilepsy was in remission and were off medication reported less perceived impact of their condition than did either those in remission but still on AEDs or those with continuing active epilepsy. The role of medication also was evident in relation to objective measures of outcome; for example, few subjects on medication, whether in remission or not, were in employment, and reduced socioeconomic status was noted in these groups, despite the finding that there was no difference in educational achievement.

The conclusion drawn by its authors in the study is that AED medication has a major effect on QOL, regardless of seizure status, and although the cognitive effects may be less marked, adults with epilepsy, like children with epilepsy, have to contend with the unwanted side effects of medication and the possible disruptions they bring to normal day-to-day functioning. Dodrill[38] showed that patients experiencing the cognitive impairments associated with antiepileptic drugs also tended to have more psychosocial problems. Although their reasons may be different, adults can be as likely to not adhere to prescribed drug regimes as adolescents, and it is incumbent on clinicians to consider why this should be so. Many studies of nonadherence have been concerned with documenting its level[52,81,88] and considering ways in which it might be reduced,[33,44,143] but they have paid little attention to understanding the reasons why patients choose not to follow prescribed regimes. The sociological literature makes a valuable contribution to this latter topic, highlighting that for patients, taking medication is only one aspect of managing a chronic illness such as epilepsy, and managing the illness in turn comprises only one of a number of competing daily demands.[42] Stockwell Morris and Schulz[117] commented that whereas clinicians assume that the value of adherence will be self-evident to patients, inasmuch as it will be associated with a positive health outcome, patients determine its value using a variety of criteria and might place greater value on other personal and nonclinical outcomes. This difference between patients' and clinicians' perspectives regarding the place of medication in the management of epilepsy is clearly reflected in the fact that until fairly recently, clinical trials of novel antiepileptic drugs incorporated only purely clinical measures of outcome. However, this is now changing, and the importance of other “quality-of-life” outcome measures is increasingly accepted.

A considerable body of quantitative research has demonstrated that adults with epilepsy have poorer psychosocial functioning than the general population.[80] In particular, they appear to be more socially isolated,[6,78] less likely to marry and have children,[34,82,120] and more likely to be underemployed or unemployed[45,51,60,120] and to be at increased risk for physical[120] and psychological morbidity,[48,60,120] including anxiety,[6,30] depression,[61,103] and poor self-esteem.[29,30,122] There are methodologic problems attached to such findings because many of the studies from which they are derived drew their samples from special epilepsy centers or epilepsy support groups and so tend to overrepresent adults with difficult-to-manage seizures, who may therefore be at increased risk for experiencing psychosocial difficulties. In two recent studies of people with well-controlled epilepsy, the majority of whom were seizure free,[68,70,132] levels of psychosocial distress appeared to be low and subjects emerged as having few problems associated with their condition. The term *epilepsy* represents a variety of disorders with a wide range of severity, and it is not surprising that adults with well-controlled epilepsy, as a group, do better than those with poorly controlled epilepsy.[15,71,79] Nonetheless, those involved in their treatment do a disservice to people with epilepsy if they assume that the relationship between severity of epilepsy and level of psychosocial function is necessarily a linear one. Although seizure frequency emerges clearly as a key factor among potential clinical contributors to reduced quality of life, there is increasing evidence of the

important role of other, nonclinical factors, including medication effects and psychological status.[53,55,75,121,142]

Table 2 Factors that contribute to or detract from quality of life

Factors that contribute	Factors that detract
Family support/relationships	Psychological distress
Social support/relationships	Transport limitations

Religion/spirituality	Stigma/perceived stigma
Leisure activities	Restrictions on freedom
Security	Seizures
Positive self-concept	Cognitive limitations
Employment	Seizure worry
Health	General health
Independence/autonomy	Employment restrictions
Seizure control	Medication effects
Helping others	Heath care problems
	Social isolation
	Poor family relationships

Adapted from Gilliam et al.[54]

Expressed Concerns of Adults with Epilepsy

Recently, qualitative research has provided valuable insights into the domains of QOL that adults with epilepsy perceive as impaired.[19,54] Gilliam et al.[54] identified 24 distinct domains, including driving, independence, social embarrassment, personal safety, medication side effects, and seizure unpredictability. In the study by Bishop and Allen,[19] epilepsy was seen as exerting direct and indirect effects on quality of life at intrapersonal, interpersonal, and extrapersonal levels. This included effects on autonomy and independence, self-concept and mental health, family and social support, and work and productivity. Table 2 shows factors that contribute to and detract from QOL, as identified by those participating in the study.

Understanding the way in which epilepsy affects quality of life (not only in younger adults, but across the life span) is facilitated by considering factors that contribute to and detract from it and the extent to which they balance one another. Explanatory models such as that proposed by Ormel et al.,[94] which proposes that high QOL can be maintained, or at least restored, in individuals facing the onset of a chronic illness such as epilepsy if they can replace QOL losses with equivalent gains, can be helpful for encouraging QOL investigations beyond the purely descriptive.

Impact of Epilepsy and Treatment on Older People

Although it is now known that the incidence and prevalence of epilepsy begin to rise again after the age of 60 years, Tallis[124] commented that epilepsy was long thought to be uncommon and unimportant in this age group, and as a result older people have tended to be excluded from studies both of specific treatment effects and of the broader impact of epilepsy. In reality, epilepsy is the third-most-common neurologic condition of older age, after cardiovascular accident and dementia, and thus represents a significant health problem. Tallis[125] noted that in terms of its impact on older people's quality of life, epilepsy can represent a watershed, with both immediate and less immediate deleterious consequences. In older people, uncertainty over the diagnosis of epilepsy may be prolonged because seizures sometimes are manifested differently in older people and more extensive investigations are required to eliminate the greater number of potential causes for attacks that are suspected of being epileptic in nature; the aftereffects of seizures may be more prolonged, and they may more often lead to injuries, which, because of the aging process, may also be more serious. Tallis cites among the less immediate consequences of epilepsy in older people both social and psychological effects. Older people, like younger ones, suffer a loss of confidence because of the uncertainty of their condition and the unpredictability of its course; in older people, however, this may be accompanied by a much more marked loss of functional independence. Although the majority of older people are no longer in the work force and therefore do not have to contend with problems regarding employment, they may face the loss of other equally valued roles and of the ability to drive, which, because of their increasing physical frailty, may make them more liable to social isolation. They are more likely to live alone and so to have limited social support in coping with their condition, and if they are living with someone else, they may be more likely to be acting as an informal caregiver. Tallis described the social effects of the onset of epilepsy in older age as embodying a process of “marginalization and disempowerment,” which in turn can profoundly undermine the concept of self.

Effect of Antiepileptic Drugs on Quality of Life of Older People

The problems of side effects of antiepileptic drugs may be exacerbated in older people as in children, even though the causes for this differ.[133] Decreases in cognitive functioning associated with the aging processes may be intensified by the effects of antiepileptic drugs, and there may be other, more marked, nonneurologic side effects. Older people are more likely than younger ones to be taking other medications, and so are at increased risk for drug interactions; for the same reason, they may also be less likely to adhere to AED regimes.[76] Jones[76] also points out that recognition of the adverse effects of antiepileptic drugs may be delayed in older people because of prejudice among their doctors, who attribute cognitive impairments more readily to age than to drugs. Given the particular circumstances and physical considerations, Tallis[124] concludes that although the principles of management of epilepsy are the same in older as in younger people, the uncertainties—regarding when to start and stop treatment, which treatment to use and in what dose—are greater.

Quality-of-Life Concerns of Older People

Recently, Martin et al.[85] have documented the concerns older people themselves have about living with epilepsy. Their request to over 300 people over the age 60 living in the US, all of whom were being treated for intractable partial epilepsy, to list their concerns about their condition elicited 28 different areas of concern, the most frequently cited being driving and transportation and medication side effects (each cited by 64%). These were followed by personal safety (cited by 39%), AED costs (by 29%), employment (by 26%), social embarrassment and memory loss (each by 21%). In the United Kingdom (UK), Baker et al.[16] compared the self-reported quality of life of 155 men and women with epilepsy post-retirement age (65 years for men and 60 years for women at the time of the survey) with that of 514 men and women of working age, as part of a large community-based survey. Compared to their younger counterparts, these older people were no more likely to be an-xious or depressed and were less likely to consider that epilepsy impacted significantly on their social relationships and overall health, or to report feeling stigmatized by it. This last difference likely reflects the fact that for older people, discriminatory

attitudes toward epilepsy have less significance than for younger people who may have to confront them in potential employers, and so supports Scambler's[110] suggestion that a person's epilepsy will commonly have more salience for them in some roles and situations than in others. There was, however, evidence of differences among older people themselves, depending on the time at which their epilepsy was diagnosed; with older people diagnosed post-retirement experiencing greater impact on their psychological well-being and overall life quality. Both sets of authors[16,84,85] highlight the need for further empirical exploration of the impact of epilepsy in this age group and a clearer understanding of their preferences and goals for treatment of their condition.

Summary and Conclusions

Examining the impact of chronic conditions such as epilepsy on a person's quality of life has long been the concern of social scientists, who have sought to understand the coping strategies adopted and the process of adjustment to changed life circumstances. Recently, clinicians too have become increasingly interested in disease impact, quantifying it to make more meaningful and comprehensive assessments of the outcomes of particular treatments. Understanding and quantifying the impact of chronic illness and the outcome of treatment are important, given that the aim of health care is to reduce the severity of such impact and its burden to patients, hence improving the quality of their lives. The impact of chronic illness is mediated by a number of factors, of which the age of the affected person is one. In this chapter, an attempt has been made to draw attention to some ways in which illness impact is common across all age groups, and some in which it varies.

In considering the impact of epilepsy, it is important to recognize that the underlying causes of epilepsy may be different in different age groups; its symptoms may be differently manifested; the impact and outcome of treatment may be variable because of physical, developmental, and aging processes; the life circumstances, and therefore the particular aspects of functioning affected, may vary. As a result, affected individuals may have different health care requirements, not only in relation to clinical management, but also in relation to informational needs and need for counseling and support. In conclusion, age-related issues in the quality of life of people with epilepsy should be taken into account, both in the development of measures of the outcome of specific treatment modalities and in the implementation of broader health care interventions.

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Chapter 102

Pharmacokinetics

Emilio Perucca

Introduction

Pharmacokinetics is the study of changes in the concentration of drugs or drug metabolites within the body as a function of time. Its clinical importance stems from the fact that the concentration of the active principle at the site of action is generally the primary determinant of therapeutic and toxic effects. Therefore, pharmacokinetic principles play a critical role in determining the time of onset, magnitude, and duration of drug action.

For some drugs (e.g., carbamazepine), there seems to be a direct relationship between drug concentration in blood and the intensity of pharmacologic effect.[84] In other cases, the relationship between kinetics and effects may be more complex. The duration of action of vigabatrin, for example, may outlast significantly the presence of the drug in the body owing to the fact that the effect is mediated by irreversible inhibition of the enzyme γ-aminobutyric acid (GABA) transaminase.[23] Although in such cases a direct relationship between plasma (or brain) concentration and pharmacologic effect is not anticipated, it is still true that the effects ultimately depend on an adequate amount of drug reaching its site of action in the brain.

Drug kinetics result from a complex interplay among three basic processes: (a) absorption, (b) distribution, and (c) elimination. Characterization of these processes has proved to be invaluable for the rational use of antiepileptic drugs. Therapeutic advances related to an understanding of kinetics include recognition of the need to individualize dose to compensate for interpatient differences in drug disposition, selection of rational dosing schedules and dosing intervals, development of innovative drug formulations, identification of clinically relevant pharmacokinetic interactions, and use of plasma drug level monitoring as a guide to adjustments in dose.[17,69,83]

Absorption

The term *absorption* is used to describe the processes involved in the transfer of the drug from the site of administration to the bloodstream. The most important factors affecting absorption are the route of administration, the physical-chemical properties of the drug, the formulation used, and the pathophysiologic conditions of the patient.

The term *bioavailability* has been introduced to define how much of a drug reaches the systemic circulation after extravascular administration and the rate at which this takes place. Bioavailability primarily depends on the rate and extent of absorption, but it is also influenced by biotransformation or degradation, which may occur before the drug reaches the systemic circulation. For example, a compound may be fully absorbed from the gastrointestinal tract and yet be incompletely bioavailable if a significant fraction of the dose is metabolized during its first passage through the liver (the so-called first-pass effect).

Antiepileptic drugs are normally administered orally, but in particular situations the intravenous, intramuscular, and rectal routes are used alternatively. Other routes are used far less commonly; for midazolam, in particular, a number of studies have suggested that intranasal[47] or buccal[38] administration may result in rapid achievement of serum drug levels sufficient for anticonvulsant activity.

Gastrointestinal Absorption

Several processes must take place before an orally administered drug reaches the systemic circulation. These include (a) disintegration of the pharmaceutical preparation or release from the formulation (in the case of solid dose forms), (b) dissolution into the gastrointestinal fluids, (c) transfer across the gastrointestinal mucosa to the local bloodstream (a process that for some drugs may be affected by the activity of transporter systems located on the intestinal epithelium), and (d) possible presystemic degradation (or biotransformation) in the gastrointestinal tract or in the liver.[66]

Although some drugs can be partially absorbed from the stomach (especially acidic compounds, which are nonionized and lipophilic at low pH values), absorption takes place mostly in the gut and therefore may be slowed when gastric emptying is delayed. In general, absorption is faster after ingestion of syrups or solutions than after intake of solid forms. Formulations produced by different manufacturers may differ in rate or extent of absorption, resulting in potentially important differences in bioavailability. For example, intoxication or loss of seizure control has occurred following the substitution of one formulation for another that was subsequently found to have a different bioavailability. Such problems have been reported with many antiepileptic drugs, including phenytoin,[56] carbamazepine,[21] and primidone.[103] Regulations for the licensing of new formulations, including generics, recently have been tightened in several countries. Therefore, problems resulting from bioinequivalence are less likely to occur when a brand product is substituted with a generic product intended to ensure a comparable absorption profile.[82]

At times, formulations are especially designed to modify advantageously the release of the active principle into gastrointestinal contents. For example, drugs such as carbamazepine and valproic acid, which are absorbed and eliminated rapidly, are also available as sustained-release dose forms; these may be useful for attenuating excessive fluctuations in plasma drug levels and allowing less frequent dosing.[9] Sodium valproate may also be prescribed in the form of enteric-coated tablets, which are designed to avoid disintegration in the stomach and so prevent gastric irritation. Enteric-coated tablets do not behave as sustained-release forms because after dissolution of the coating, absorption proceeds very rapidly. Enteric coating, however, does modify absorption characteristics significantly. In fact, although small particles (<2 mm in diameter) can pass through the pylorus irrespective of the degree of

gastric filling, the motility pattern of fasting is needed for larger particles to leave the stomach.[92] Ingestion of enteric-coated preparations after a meal may result in a long delay (sometimes up to 10 hours or even longer) before the tablet leaves the stomach and reaches the duodenum, where the coating dissolves and absorption occurs rapidly. This phenomenon explains the long latency that may occur before valproic acid is absorbed from enteric-coated tablets taken with or after a meal (Fig. 1).[42]

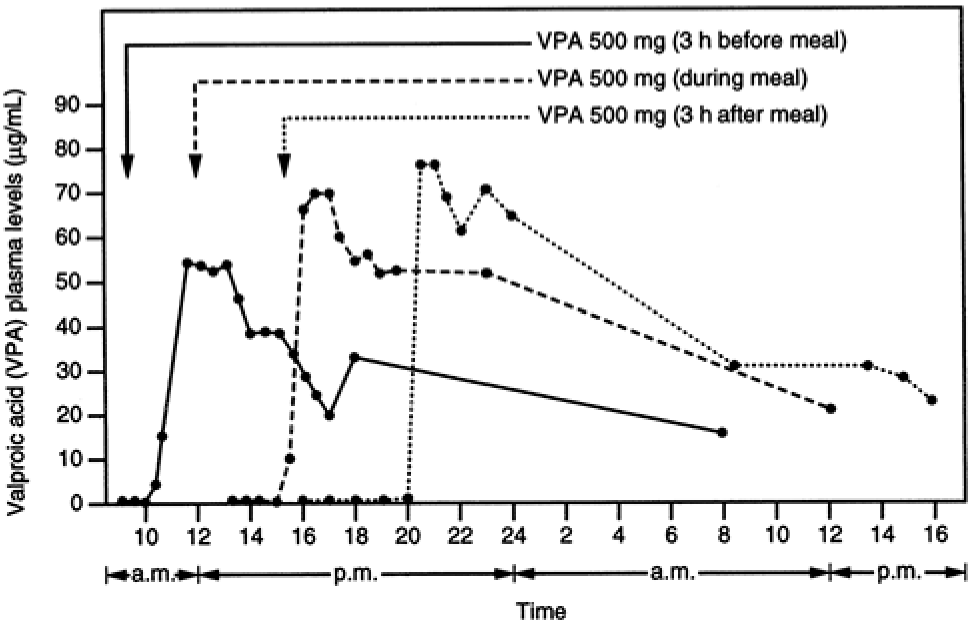

FIGURE 1. Effect of a meal on the absorption of valproic acid (VPA) from enteric-coated tablets in a representative individual. The same dose (one 500-mg tablet) was taken before a meal, during a meal, and 3 hours after a meal. Arrows indicate the time of drug intake. Note the long latency between drug intake and initiation of absorption when the drug was taken during or after a meal. (From Levy RH, Cenraud B, Loiseau P, et al. Meal-dependent absorption of enteric-coated sodium valproate. *Epilepsia*. 1980;21:273–280, with permission.)

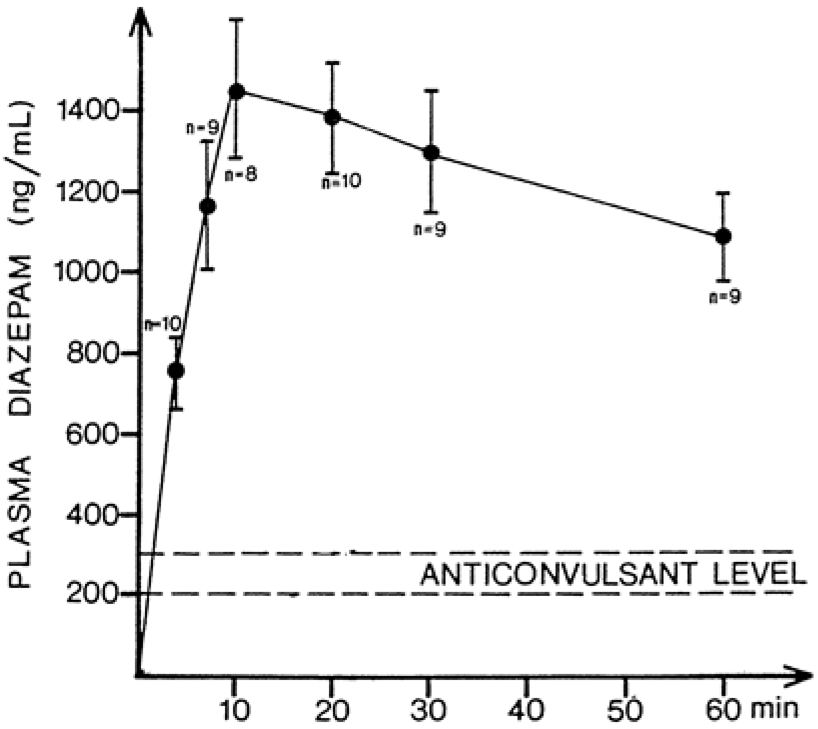

FIGURE 2. Rapid absorption of diazepam from a commercial solution (0.7 mg/µg) after rectal instillation in infants. Anticonvulsant activity is considered to develop when plasma concentration reaches the range of 200 to 300 ng/mL. (Modified from Knudsen FU. Plasma diazepam in infants after rectal administration in solution and by suppository. *Acta Paediatr Scand.* 1977;66:563–567.)

Irrespective of the formulation used, concurrent intake of food may have a profound influence on drug absorption. For some drugs (e.g., azithromycin, albendazole, griseofulvin), the rate and extent of absorption can be enhanced by food intake, whereas for others (e.g., clodronate, etidronate, tetracycline), bioavailability may be reduced drastically when they are taken after a meal.[87] Absorption may also be affected by drug interactions in the gastrointestinal tract, including interactions affecting the activity of transporter systems such as P-glycoprotein (see Chapter 110).

Rectal Absorption

The rectal route may provide a useful alternative when oral administration is not feasible because of, for example, palat-ability problems, nausea and vomiting, or a patient's inability to cooperate during ongoing seizures. For drugs that show a prominent first-pass effect in the liver, rectal administration may enhance bioavailability because only the superior hemorrhoidal vein drains into the portal system.

The efficiency of rectal absorption is influenced primarily by the physical-chemical properties of the drug (lipophilic compounds are usually well absorbed) and by the type of pharmaceutical formulation.[96] Suppositories may be associated with lower rates and extent of absorption, whereas absorption from rectal solutions or rectal capsules can be quite efficient. In the case of diazepam, anticonvulsant concentrations can be achieved within minutes of rectal instillation of the commercial solution (Fig. 2). The rapid absorption of rectally administered diazepam can be exploited when, for example, prolonged seizures must be managed by nonmedical personnel or intermittent prophylaxis is needed against the recurrence of febrile convulsions.[36]

Intramuscular Absorption

The rate of absorption following intramuscular injection is determined by the solubility properties of the drug, the pharmaceutical characteristics of the formulation, and the degree of local blood perfusion. The latter, in turn, varies with site of injection (blood flow and absorption rate are greater in the deltoid region than in the buttock), hemodynamic state (absorption may be inadequate in hypotensive patients), and injection technique (massaging the muscle after the injection, e.g., may hasten absorption).

With some drugs, such as diazepam, intramuscular absorption may be slow and erratic.[32] For this reason, diazepam should not be given intramuscularly for the treatment of status epilepticus. Midazolam, a hydrophilic benzodiazepine, is absorbed from the muscle at a much faster rate than diazepam, and intramuscular midazolam is a viable option for the treatment of acute seizures.[80]

The slow and prolonged absorption of some drugs from muscle should be taken into account when the route of drug administration is temporarily switched from oral to intramuscular to provide therapeutic cover when a patient is transiently unable to take medications orally. For example, if phenytoin needs to be given intramuscularly for a few days, a dose 50% higher than the oral maintenance dose may be needed to compensate for inadequate intramuscular absorption. On resumption of oral therapy, half of the original oral dose should then be given for a period of time equal to the period of intramuscular administration so that toxicity resulting from delayed absorption from muscle stores is prevented.[99] Whenever possible, however, intramuscular administration of phenytoin should be avoided because it may cause local pain and muscle damage. If the patient cannot take phenytoin orally, the intravenous route is a preferable alternative. Another alternative is to switch temporarily to fosphenytoin, which, unlike phenyt-oin, is efficiently absorbed after intramuscular injection (see Chapter 154).

Distribution

After reaching the circulation, a drug undergoes distribution within blood components and body tissues. The rate and extent of penetration into individual tissues depend on a number of factors, such as the physical-chemical properties of the drug, the degree of drug binding to plasma and tissue components, the degree of tissue perfusion (blood flow), the presence of biologic barriers to tissue penetration (e.g., the blood–brain barrier), and the activity of transporter systems that may limit drug access to certain tissues and/or certain cellular or subcellular compartments. Compared with highly water-soluble drugs, lipophilic compounds generally exhibit more extensive tissue penetration, particularly in organs with a high lipid content, such as the brain. Distribution primarily occurs by passive diffusion, although in some cases drug transfer may be regulated by active transport mechanisms.

Table 1 Plasma protein binding of major antiepileptic drugs

Drug	Percentage (%) bound
Carbamazepine	70
Clobazam	90
Clonazepam	85
Diazepam	98
Ethosuximide	0
Felbamate	30
Gabapentin	0
Lamotrigine	55
Levetiracetam	0
Oxcarbazepine[a]	40
Phenobarbital	50
Phenytoin	90

Pregabalin	0
Primidone	30
Tiagabine	96
Topiramate	15
Valproic acid[b]	90
Vigabatrin	0
Zonisamide	45

[a] Binding refers to active metabolite 10-hydroxy-carbazepine.

[b] Binding is concentration dependent.

One estimate of the extent of drug penetration into tissues is provided by the *volume of distribution*. This parameter, which is usually normalized for body weight, can be defined as the virtual volume in which the total amount of drug present in the organism after completion of distribution processes needs to be dissolved to yield a concentration identical to that found in plasma. A volume of distribution of about 1 L/kg indicates that the drug is found in tissues at an average concentration equivalent to that in plasma. A volume of distribution <1 L/kg indicates that the tissue concentration is on average lower than the plasma concentration. Conversely, a volume of distribution in >1 L/kg indicates a high tissue concentration relative to the concentration in plasma. Most antiepileptic drugs have volumes of distribution between 0.6 and 1.2 L/kg, indicating that *on average* their tissue concentration is 60% to 120% of their plasma concentration.[67,68] There are exceptions to this rule, however, the most notable example being valproic acid; the small volume of distribution of this drug (about 0.15 L/kg) indicates its relatively poor tissue penetration.[73] An important concept is that the volume of distribution does not provide any information about drug concentration at specific sites; in fact, any given average tissue concentration may result from drug accumulation at extremely high levels in some organs, with other tissues receiving little or no drug exposure. More specifically, the volume of distribution does not provide any indication about drug concentration in the brain: Some drugs have a high volume of distribution and yet fail to reach the central nervous system because of inability to cross the blood–brain barrier.

Binding to Plasma Proteins

Many drugs are significantly bound to plasma proteins (Table 1). Although the binding is generally of a loose and reversible type, the drug–protein complex is too large to move freely across biologic membranes, and therefore it is only the unbound moiety that creates the diffusion gradient driving drug molecules from the blood into the tissues. Albumin is the most important protein available for the transport of acidic drugs, such as phenytoin and valproic acid, whereas α_1-acid glycoprotein is primarily involved in the transport of basic compounds, such as chlorpromazine and lidocaine. Some drugs (e.g., carbamazepine), bind to a significant extent to both albumin and α_1-acid glycoprotein.[2]

Binding to plasma proteins may have a significant influence on drug kinetics. First, the protein-bound drug represents a reservoir within the bloodstream that tends to increase the concentration in plasma relative to the concentration in tissues. Second, drug binding to proteins may affect the rate of drug elimination. In the case of low-clearance drugs, only the unbound drug can be cleared, and therefore protein binding tends to restrict the efficiency of the elimination process. Conversely, in the case of high-clearance drugs, both the unbound and the protein-bound drug can be cleared; under these circumstances, protein binding enhances elimination by increasing the amount of drug delivered to the eliminating organ.[77,101]

The binding of drugs to plasma proteins may vary considerably among patients because of differences in protein concentrations or the presence of endogenous and exogenous substances competing at protein-binding sites. Because only the unbound drug is in equilibrium with drug molecules at receptor sites, pharmacologic effects usually correlate better with concentration of unbound drug than with total plasma concentration. Therefore, any condition leading to a change in unbound fraction will alter the relationship between plasma drug concentration and therapeutic effect, and this needs to be taken into account when drug levels are interpreted in clinical practice.[74] For example, a reduced binding of phenytoin to plasma proteins is observed in neonates; the elderly; women in late pregnancy; patients with other hypoalbuminemic conditions, hyperbilirubinemia, or uremia; and patients undergoing concomitant treatment with displacing drugs, such as valproic acid.[63] Under these circumstances, total plasma phenytoin levels underrepresent the concentration of unbound, pharmacologically active drug.

Tissue Binding

Some drugs are found in certain tissues at concentrations much higher than concentrations in plasma. To some extent, this may be a consequence of partitioning related to the physical-chemical properties of the drug; a highly lipophilic compound, for example, accumulates in lipidic tissues in a manner roughly proportional to its partition coefficient between oil and water. In some cases, drugs may be “sequestered” in tissues as a result of binding with proteins and other macromolecules. Because the bound drug is not available to interact with receptor sites, the total drug concentration in a given tissue might not provide a reliable estimate of the drug concentration at sites of action within the same tissue.

Tissue Blood Flow and Drug Distribution

After drug administration, distribution phenomena may take a long time to be completed. Initially, distribution tends to be confined primarily to highly perfused organs, such as the heart, liver, kidneys, and brain, which receive a large fraction of cardiac output. Subsequently, the drug redistributes gradually throughout the organism, and distribution can be considered complete only when the plasma-to-tissue concentration ratio has reached equilibrium in all tissues.

A good example of the clinical implications of redistribution phenomena is provided by thiopental, a compound sometimes used in the management of refractory status epilepticus. After a single injection of thiopental, the drug is transferred largely to the brain, where it penetrates rapidly because of its high lipophilicity. Other lipid-rich tissues (e.g., adipose tissue) initially receive little exposure to the drug because their perfusion is low compared with that of the brain. During the subsequent minutes, however, thiopental is redistributed gradually out of the brain into less perfused tissues, which tend to accumulate it at high concentrations.[19] Redistribution is mainly responsible for termination of action after a single dose, and it explains the apparent discrepancy between the short duration of thiopental-induced anesthesia (20–30 minutes) and the relatively long elimination half-life of the drug (about 9 hours). The situation is completely different when thiopental is administered by continuous infusion over several days. Under these circumstances, drug stores in poorly perfused tissues become gradually saturated. When treatment is discontinued, redistribution no longer occurs, and the termination of drug action is then determined by hepatic elimination, which explains the long delay before consciousness is recovered.

Blood–Brain Barrier

The anatomic configuration of the cerebral circulation represents a barrier to the entry of certain drugs into the brain and cerebrospinal fluid. As a general rule, the ability of a compound to diffuse across the blood–brain barrier is directly proportional to its lipid solubility. A number of poorly lipid-soluble drugs, however, may be transported in or out of the brain by selective uptake mechanisms. For example, l-dopa is transported into the central nervous system by a carrier-mediated process, whereas penicillin and salicylic acid are transported out of the brain by a different system of carriers. When carriers are involved, there is possibility of competition by other substrates at the site of transport; some amino acids, for example, compete with l-dopa for entry into the brain, whereas probenecid may block the uptake of penicillin from the cerebrospinal fluid by a similar mechanism.

The kinetics of penetration of antiepileptic drugs across the blood–brain barrier has been investigated in the anesthetized dog.[44] The fastest rates of entry were recorded for clonazepam, *N*-desmethyldiazepam, diazepam, and ethosuximide, whereas valproic acid, phenytoin, phenobarbitone, carbamazepine, and particularly primidone crossed the blood–brain barrier at a much slower rate (Table 2). Ionization did not appear to be a rate-limiting factor in brain penetration because all drugs except for valproic acid are mostly nonionized at physiologic pH. Furthermore, no correlation was found between rate of brain penetration and plasma protein binding, but for most drugs the ratio of cerebrospinal fluid to total plasma concentration at equilibrium was almost equal to the unbound fraction in plasma. Rate of entry into the cerebrospinal fluid correlated with lipid solubility as assessed by the benzene/buffer distribution ratio. Valproic acid showed unique features because it crossed the blood–brain barrier relatively rapidly despite its very low lipid solubility. These data suggest that the brain penetration of valproic acid may be regulated by an active transport process. There is also evidence that valproic acid may be transported out of the cerebrospinal fluid by an active uptake system localized in the choroid plexus, an observation that may explain the very low concentrations of the drug (relative to plasma concentrations) in the brains of patients receiving chronic treatment.[89]

In recent years, the mechanisms affecting access of drugs to the brain have been extensively investigated. Evidence has accumulated that, for many drugs, access to brain is influenced by the expression of efflux transporters, including P-glycoprotein, located in the cerebral capillary endothelial cells and in other cells, for example, astrocytes.[45] These transporters play a key role in reducing the penetration of substrates across barriers where they are expressed, including the blood–brain barrier, the blood cerebrospinal fluid (CSF)–barrier, and the blood–inner ear barrier.[39] Studies have suggested that several anticonvulsants, including phenytoin, phenobarbital, carbamazepine,

lamotrigine, gabapentin, topiramate, and felbamate, are substrates of P-glycoprotein and other transporters, although evidence is not univocal for all drugs.[39] It has also been suggested that overexpression of these transporters may be a cause of drug resistance by limiting access of drugs to their site of action in neurons.[39,86]

Table 2 Rates of penetration of different antiepileptic drugs from plasma into cerebrospinal fluid in anesthetized dogs[a]

Drug	Nonionized[b] (%)	Unbound in plasma (%)	Partition factor[c]	Mean half-time to equilibrium (min)
Carbamazepine	100	28	48	18
Carbamazepine-10, 11-epoxide	100	54	1.2	46

Clonazepam	>99	18	38	3.2
Diazepam	>99	5	84	3.2
Ethosuximide	99	95	0.5	4.6
N-Desmethyldiazepam	>99	4	24	7.2
Phenobarbital	51	55	0.3	16
Phenytoin	89	22	6	17
Primidone	100	80	0.1	43
Valproic acid	0.16	22	0.1	12

[a] Rates expressed as half-times to equilibrium between unbound concentration in plasma and concentrations in cerebrospinal fluid. Each drug was studied in from 2 to 13 animals, except for phenobarbital, which was assessed in one animal.
[b] Percentage of drug nonionized at pH 7.4.
[c] Benzene/buffer (pH 7.4) distribution ratio.
Source: From Loscher W, Frey HH. Kinetics of penetration of common antiepileptic drugs into cerebrospinal fluid. Epilepsia. 1984;25:346–352.

The permeability of the blood–brain barrier is influenced by physiologic and pathologic factors. The increased sensitivity of neonates to some centrally acting drugs may be related, at least in part, to enhanced permeability of the blood–brain barrier during early stages of development. Many diseases can affect the integrity of the barrier. Disruption of the blood–brain barrier, resulting in increased brain exposure to valproic acid, may explain the occurrence of severe valproate encephalopathy within days of supratentorial surgery in some patients.[40]

Selective Drug Delivery to the Brain

The existence of the blood–brain barrier can be exploited by developing chemical systems designed to ensure preferential drug delivery to the brain. The best known of these systems is based on the dihydropyridinepyridinium salt–type redox molecular carrier.[79] In brief, the drug is conjugated with a 1,4-dihydropyridine moiety, resulting in a lipophilic complex that readily penetrates all tissues, including the brain. Thereafter, the complex undergoes quick oxidation to a highly polar quaternary pyridinium salt that is rapidly eliminated from the periphery but remains "locked" in the brain because of the impermeability of the blood–brain barrier. Over time, the active drug is released from the oxidized complex by enzymatic hydrolysis and becomes available to exert its pharmacologic action. The small, polar targeter released by the process of hydrolysis is readily expelled from the brain through an active transport mechanism. Because the system allows selective drug delivery to the brain, peripheral toxic effects can be minimized. Central tolerability may also be improved because of the slow and sustained delivery of the active principle at the site of action.

Experimental delivery systems based on the dihydropyridinepyridinium salt–type redox molecular carrier have been developed for a variety of antiepileptic drugs, including phe-nytoin, valproic acid, and stiripentol. Although at present the practical applicability of these systems is limited by the instability of dihydropyridine moiety in gastric fluids, innovative formulations for clinical use may become available in the future.

Placental Barrier

The use of the term *barrier* to indicate the anatomic structures regulating drug exchanges between mother and fetus is improper. Unlike the blood–brain barrier, generally the placenta does not provide an efficient obstacle to drug penetration. Although lipophilic drugs may enter the fetal circulation more readily than water-soluble compounds, from a practical point of view the fetus can be considered as subject to exposure to all drugs taken by the mother. For gabapentin, drug concentrations have been reported to be almost twice as high in the fetal circulation than in the mother, possibly due to existence of an active transplacental transport.[57]

Distribution Into Breast Milk

The distribution of drugs into breast milk is determined by a number of variables, the most important being the nonionized fraction of the drug in plasma and milk, lipid solubility, and the binding of the drug to plasma and milk proteins.[102] Drug exposure in the breast-fed infant, however, depends not only on the concentration of the drug in milk and the amount of milk ingested, but also on the infant's ability to absorb and clear efficiently the ingested drug.

All anticonvulsants pass into breast milk and the average milk-to-plasma concentration ratio ranges from about 0.7 to 1.4 for gabapentin and levetiracetam to 0.01 to 0.1 for valproic acid, which is hydrophilic and highly protein bound.[30,57,60] As a general rule, the presence of antiepileptic drugs in breast milk is not considered to be a contraindication to breast-feeding, although for some medications, particularly lamotrigine, primidone, phenobarbital, ethosuximide, and, to a lesser extent, carbamazepine and benzodiazepines, intake through breast milk may result in appreciable drug concentrations in the infant and the need to monitor for possible side effects. Because felbamate-induced hematological toxicity may be dose independent, use of this drug during breast-feeding has been discouraged.

Elimination

The most important routes of drug elimination involve direct excretion, mostly into urine, and biotransformation with subsequent excretion of breakdown products in urine and/or bile. The extensive interindividual variability of these processes is largely responsible for the wide differences in plasma drug levels observed in patients receiving the same dose. Therefore, a correct understanding of the factors that may affect drug elimination is crucial for rational prescribing.

Pharmacokinetic Concepts

Drug Clearance

The pharmacokinetic parameter that best describes the efficiency of elimination processes is the *clearance*, defined as the virtual volume of blood (or plasma) from which the drug is entirely removed per unit of time.[101] When a drug is eliminated exclusively by the kidneys in unchanged form, blood clearance equals *renal clearance*. When metabolism contributes to elimination, blood clearance is equal to the sum of renal clearance and *metabolic clearance*. Within any organ involved in drug elimination, the efficiency of the elimination process can be defined according to the formula

$$CL_1 = Q \cdot E \qquad (1)$$

where CL_1 is the contribution of that organ to the total clearance (e.g., in the case of the kidney, CL_1 equals renal clearance), Q is the blood flow through the organ, and E is the extraction ratio (i.e., the fraction of drug passing through the organ that is removed as a result of the elimination process). If a drug is totally removed during a single passage, E is equal to 1 and CL_1 becomes a direct measure of the blood flow through the organ.

From inspection of Equation (1), it is clear that drug clearance is influenced not only by the capacity of the organ to remove the drug efficiently from the bloodstream, but also by the rate of drug delivery to the site of elimination. In this respect, it is useful to differentiate between low- and high-clearance drugs.

In the case of low-clearance drugs, the efficiency of the elimination processes is relatively low, and protein-bound drug cannot be removed by the eliminating organ. The clearance of these drugs is restricted by the degree of binding to plasma proteins; a reduction in plasma protein binding, by increasing the availability of unbound molecules available for removal, will result in a corresponding increase in clearance. Conversely, the clearance of these drugs will not be affected by blood flow because any increase in rate of delivery of the drug to the eliminating organ due to increased blood flow will be offset by the organ's inability to maintain the efficiency of drug removal (i.e., an increase in blood flow will be accompanied by a corresponding decrease in extraction ratio, and clearance will remain unchanged). For these reasons, low-clearance drugs are said to exhibit *restrictive, flow-independent* elimination.[101]

The situation is reversed in the case of high-clearance drugs. These compounds are removed from the circulation so efficiently that protein-bound drug can also be eliminated during a single passage through the organ. The clearance of these drugs is *nonrestrictive* because plasma protein binding does not restrict the removal process but may actually facilitate it by increasing the delivery of the drug to the site of elimination. The clearance of these drugs is also *flow dependent*. In fact, in this case the eliminating organ can cope with an increase in blood flow without losing its extraction capacity, resulting in a direct relationship between blood flow and drug clearance. When the organ responsible for drug removal is the intestine or the liver, a third characteristic of high-clearance drugs is a prominent first-pass effect after oral administration. This is explained by the fact that the efficient elimination (i.e., a high extraction ratio) leads to removal of a significant fraction of the dose before the drug reaches the systemic circulation.

Elimination Half-life

An additional pharmacokinetic parameter used to describe drug elimination is the *terminal half-life* (or, more simply, half-life), which can be defined as the time taken for the plasma concentration to fall by one half during the terminal (postdistributive) elimination phase. The half-life is a useful parameter because it provides a direct measure of the rate of decline of drug concentration in plasma after discontinuation of therapy. In pharmacokinetic terms, however, the half-life is a hybrid parameter, determined not only by the efficiency of the elimination processes (i.e., drug clearance), but also by the volume of distribution. This can be understood easily by considering that after removal of any given amount of drug per unit of time, the percentage of reduction in plasma drug concentration primarily depends on the total drug stores in the body. If body stores are large (i.e., volume of distribution is large), the fall in concentration resulting from the removal will be minor. Conversely, if body stores are small, removal of the same amount of drug will have a much greater impact on plasma concentration.

Based on the foregoing considerations, it is clear that a change in half-life does not always reflect a change in the efficiency of the elimination process (i.e., drug clearance) but may be secondary to an alteration in volume of distribution. For example, the marked prolongation in the half-life of diazepam in the elderly is determined largely, although not exclusively, by an increase in volume of distribution.[35] The differentiation between clearance and half-life has important practical implications. In fact, mean plasma drug concentrations at steady state during long-term dosing are determined exclusively by bioavailability and clearance and are unaffected by half-life. Conversely, the half-life determines the time required to reach steady state (about four to five half-lives) as well as the degree of fluctuation in plasma levels during a dosing interval.

Biotransformation

Most drugs are too lipid soluble to be excreted efficiently by the kidneys, and after being filtered by the renal glomeruli, they are almost completely reabsorbed by diffusion from the tubular epithelium.[77] Elimination of these compounds depends primarily on their conversion to polar and water-soluble metabolites that can be excreted more rapidly in urine. In general, biotransformation products are inactive or less active than the parent drug, although there are numerous examples of metabolites retaining pharmacologic activity and contributing significantly to the production of therapeutic or toxic effects. Among antiepileptic drugs, those converted at least in part to active metabolites include clobazam, diazepam, carbamazepine, primidone, fosphenytoin, and oxcarbazepine (Table 3). Fosphenytoin and oxcarbazepine can be regarded as prodrugs because their effects are mediated virtually entirely by their active metabolites—phenytoin in the case of fosphenytoin, and 10-hydroxycarbazepine in the case of oxcarbazepine.

Almost invariably, the reactions involved in drug meta-bolism are catalyzed by enzyme systems and often exhibit a considerable degree of stereoselectivity. The most important enzyme systems are located in the smooth endoplasmic reticulum (microsomes) of hepatic cells, but significant levels of drug-metabolizing activity can be detected in the microsomes and the cytosol of other tissues, including the gastrointestinal mucosa, kidney, lung, blood, and brain.

The main metabolic pathways involved in drug metabolism include oxidation, reduction, hydrolysis, and conjugation. The first three are collectively known as *phase I reactions*, whereas conjugations are generally referred to as *phase II reactions*. In phase I reactions, functional groups such as —OH, —COOH, and —NH_2 are introduced into the drug molecule. In phase II reactions, functional groups already present in the molecule or introduced in the previous step are conjugated with an endogenous substrate, such as glucuronic acid, acetic acid, or inorganic sulfate, resulting in the generation of water-soluble metabolites that are readily excreted in urine.

Table 3 Main routes of elimination of antiepileptic drugs

Drug	Main route of elimination	Active metabolities
Carbamazepine	Oxidation	10,11-Epoxide[a]
Clobazam	Oxidation	*N*-Desmethylclobazam
Diazepam	Oxidation	*N*-Desmethyldiazepam
Ethosuximide	Oxidation	No
Felbamate	Oxidation[b] + renal excretion	No[a]
Gabapentin	Renal excretion	No
Lamotrigine	Glucuronide conjugation	No[a]
Levetiracetam	Renal excretion + hydrolysis	No
Nitrazepam	Reduction[b]	No
Oxcarbazepine	Reduction	10-Hydroxycarbazepine[a,c,d]

Phenytoin	Oxidation	No[a]
Phenobarbital	Oxidation + renal excretion	No[a]
Pregabalin	Renal excretion	No
Primidone	Renal excretion + oxidation	Phenobarbital[a,c]
Tiagabine	Oxidation	No
Topiramate	Renal excretion + oxidation	No
Valproic acid	Oxidation + conjugation	No[a]
Vigabatrin	Renal excretion	No
Zonisamide	Oxidation + Conjugation[b] + renal excretion	No

[a] Reactive intermediates may contribute to toxic effects.
[b] Other metabolic pathways may be important.
[c] Metabolite is primarily responsible for pharmacologic effects.
[d] Metabolite is eliminated primarily by glucuronide conjugation.

Oxidation

Oxidation is by far the most important among phase I reactions. Although occasionally the enzymes involved may be located outside the endoplasmic reticulum, a large majority of oxidative reactions are catalyzed by a group of closely related microsomal isozymes that utilize a specific cytochrome known as *cytochrome P450* because its complex with carbon monoxide exhibits an absorption peak at 450 nm. In addition to drugs and other xenobiotics, cytochrome P450 isozymes play an important role in the metabolism of endogenous substances such as free fatty acids, leukotrienes, prostaglandins, steroid hormones, and vitamins.[14,77]

Based on the degree of analogy between amino acid sequences in the enzymatic protein, cytochrome P450 (CYP) isozymes can be classified into different families and subfamilies,[54] and preferential substrates for each isozyme have been identified. Because each isozyme system is regulated in a different way by endogenous and exogenous factors, knowledge of the specific enzyme system responsible for the metabolism of a given drug is essential to predict situations associated with clinically significant alterations in the biotransformation of that drug. For example, the metabolism of the antiepileptic drugs mephobarbital (methylphenobarbital) and mephenytoin is catalyzed by an isozyme system that is subject to genetic polymorphism.[58] About 2% to 5% of white patients and 18% to 25% of Japanese and Chinese patients show a genetically determined deficiency of this enzyme and metabolize mephobarbital and mephenytoin at an abnormally slow rate, resulting in increased vulnerability to the toxic effects of these drugs. Because many inhibitors (or inducers) of drug metabolism selectively affect specific CYP isozymes, knowledge of the enzyme system or systems responsible for the metabolism of a given drug can also be used to predict drug interactions (Chapter 110).

A list of major cytochrome P450 isozymes and representative compounds metabolized by each of them is provided in Table 4. Although biotransformation products are usually pharmacologically inert, it is not uncommon for oxidation to result in the formation of active metabolites. At times, drug oxidation generates reactive toxic intermediates that are rapidly detoxified through hydrogenation or conjugation with glutathione or other substrates. When these detoxification processes are not fully efficient, the reactive intermediate can interact with endogenous macromolecules and produce serious toxicity, resulting in immune-mediated drug reactions, hepatic necrosis, mutagenesis, and carcinogenesis.[25] A toxic intermediate, probably the arene oxide, may play an important role in phenytoin teratogenicity, hepatotoxicity, and bone marrow toxicity.[77]

Table 4 Some important cytochrome P450 isozymes and examples of respective substrates

Enzyme	Substrate
CYP1A1	Benzo(*a*)pyrene and other polycyclic hydrocarbons
CYP1A2	Caffeine, theophylline, phenacetin, acetaminophen, imipramine
CYP2A6	Coumarin, losigamone
CYP2C8	Carbamazepine
CYP2C9	Phenytoin, phenobarbital, tolbutamide, *S*-Warfarin
CYP2C10	Tolbutamide
CYP2C19	*S*-Mephenytoin, mephobarbital, nirvanol, phenobarbital, phenytoin, diazepam, *N*-desmethyldiazepam, omeprazole, proguanil
CYP2D6	Amitryptiline, chlomipramine, desipramine, imipramine, nortriptyline, fluoxetine, paroxetine, clozapine, haloperidol, perphenazine, thioridazine, codeine, dextromethorphan, phenformin, alprenolol, metoprolol, debrisoquine, encainide, flecainide, indoramin, propafenone
CYP2E1	Felbamate, phenobarbital, chlorzoxazone, enflurane, halothane, ethanol, acetaminophen
CYP2E2	Benzene, styrene, acrylonitrile, vinyl chloride
CYP3A3/4	Carbamazepine, ethosuximide, felbamate, tiagabine, zonisamide, midazolam, triazolam, nicardipine, nifedipine, nimodipine, nisoldipine, felodipine, cyclosporine, ethinylestradiol, lidocaine, astemizole, terfenadine, lovastatin

Closely related isozymes may participate in the same reaction (e.g., CYP2C8, CYP2C9, and CYP2C10 may all catalyze tolbutamide methyl-hydroxylation).
Source: Modified from Perucca E, Richens A. Biotransformation. In: Levy RH, Dreifuss F, Mattson R, et al., eds. *Antiepileptic Drugs*. New York: Raven Press; 1995:31–50; and Brockmoller J, Roots I. Assessment of liver metabolic function. Clinical implications. *Clin Pharmacokinet*. 1994;27:216–248.

Reduction

Reductive reactions take place predominantly in the hepatic microsomes but also occur to an important extent at other sites. The reduction of certain compounds containing azo and nitro groups, for example, is catalyzed by bacteria found in the gut, not by mammalian enzymes.[53] The most important example of a reductive reaction implicated in the biotransformation of antiepileptic drugs is probably the conversion of oxcarbazepine to the active metabolite 10-hydroxycarbazepine.[49] The conversion of nitrazepam to the corresponding amine and the conversion of chloral hydrate to trichloroethanol provide additional examples of reductive pathways.

Hydrolysis

Hydrolytic reactions take place in many tissues, including blood. Cholinesterases and arylesterases play a role in phase I metabolism of drugs containing ester groups such as succinylcholine and many local anesthetics. Among antiepileptic drugs, hydrolytic enzymes mediate the conversion of fosphenytoin to phenytoin and the conversion of levetiracetam to the inactive metabolite L057.

Epoxide hydrolases represent a separate class of hydrolytic enzymes. An epoxide hydrolase is responsible for the conversion of carbamazepine-10,11-epoxide to its inactive diol derivative. Other hydrolases may be important in the detoxification of reactive epoxide intermediates, and it has been suggested that a relative deficiency of these enzymes may play a role in the pathogenesis of some hypersensitivity reactions to antiepileptic drugs.[78]

Conjugation

In conjugation reactions, a drug or its phase I metabolite is linked covalently with an endogenous molecule or another functional group, resulting in the formation of more polar, water-soluble metabolites suitable for renal excretion.[15] The most common conjugation pathways include acetylation, glucuronidation, glucose conjugation, sulfate conjugation, methylation, cyanide detoxification, glutathione conjugation, and amino acid conjugation. Most of these reactions are catalyzed by families of specific transferases and require high-energy nucleotide intermediates. Some conjugates formed in this way are excreted in the bile and may undergo hydrolysis in the gastrointestinal tract. This results in regeneration of the parent compound, which can then be reabsorbed, giving rise to what is known as the *enterohepatic circulation*.

Like phase I enzymes, conjugative enzymes are subject to modulation by genetic, developmental, and environmental factors. In general, conjugated metabolites are pharmacologically inactive, but there are several exceptions to this rule. Examples of pharmacologically active conjugated metabolites include the 6-glucuronide of morphine and the acetylated derivatives of sulfanilamide, procainamide, and acebutolol.

Most phase I metabolites of antiepileptic drugs are excreted in urine in conjugated form, usually as glucuronides. Lamotri-gine and lorazepam are examples of drugs eliminated primarily by conjugation in the absence of phase I metabolism.

Factors Affecting Drug Metabolism

The large interindividual differences that can be observed in rates of biotransformation are caused by a variety of factors.

Genetic Factors.

Because specific genes code for drug-metabolizing enzymes, it is not surprising that genetic factors play an important role in determining the differences in drug metabolism that are found among species, genders, and individuals. Although the metabolism of all drugs is subject to the influence of genetic factors, the importance of such factors becomes overwhelming in the case of the genetically determined polymorphisms.[20,58,100]

With respect to the cytochrome P450–catalyzed reactions, several important polymorphisms have been described.[20] The CYP2D6 polymorphism, which is transmitted as an autosomal-recessive trait associated with a gene located on chromosome 22, results in a bimodal distribution in the ability to eliminate several drugs metabolized by the CYP2D6 isozyme (Table 4). About 5% of whites (and <1% of Japanese or Chinese individuals) metabolize many of these drugs at a particularly slow rate, with important clinical implications.[58] A second major genetic polymorphism involves the CYP2C19 isozyme responsible for the stereoselective oxidation of the *S*-enantiomer of mephenytoin.[58] In approximately 2% to 5% of whites and about 20% of Chinese and Japanese, an impaired capacity to hydroxylate *S*-mephenytoin and nirvanol, the active metabolite of mephenytoin, results in the accumulation of these compounds at potentially toxic concentrations.[20] This genetically transmitted autosomal-recessive trait affects

not only the metabolism of mephenytoin, but also that of other agents metabolized by the same isozyme, including mephobarbital, hexobarbital, diazepam, *N*-desmethyldiazepam, omeprazole, and proguanil. Defective hydroxylators show an impaired ability to eliminate these drugs, although with some compounds, such as diazepam, the existence of alternative metabolic pathways may limit the extent of drug accumulation.[8] In general, slow hydroxylators also show an increased vulnerability to the toxic effects of drugs metabolized by the isozyme. In the case of drugs such as proguanil, however, which are converted to an active metabolite, an impaired rate of metabolism may result in reduced effectiveness.

Although phenytoin may also be metabolized by CYP2C19, the major enzyme responsible for phenytoin metabolism appears to be CYP2C9, which is also subject to genetic polymorphism. Subjects carrying defective alleles for the *CYP2C9* gene eliminate phenytoin at a slower rate, and the importance of this for endpoints of clinical responsiveness has been demonstrated.[13,20] Evidence for the importance of the *CYP2C9* genotype in affecting phenytoin response was reinforced by a recent pharmacogenomic study that demonstrated a significant association between the presence of the *CYP2C9*3* allele and reduced phenytoin dose requirements in 281 patients with epilepsy.[95]

Genetically determined defects in drug metabolism are not confined to cytochrome P450–catalyzed reactions, and polymorphisms affecting many other drug-metabolizing enzymes have been described.[77] The acetylator phenotype is probably the best-known example of genetic polymorphism affecting phase II metabolism.[97] This polymorphism is related to a defect in *N*-acetyltransferase type 2 activity, which is inherited as an autosomal recessive trait. Approximately 50% of whites (and variable proportions in other ethnic groups) show a reduced capacity to metabolize substrates of the affected enzyme, such as isoniazid, sulfonamides, hydralazine, amrinone, dapsone, prizidilol, and aminoglutethimide. In general, these individuals are at a higher risk for adverse effects, although the reverse may be the case when acetylation results in the formation of potentially toxic metabolites.

An interesting observation is that sometimes genetic polymorphisms in drug metabolism have been associated with changes in susceptibility to a variety of diseases. For example, slow acetylators may show an increased risk for bladder cancer but a lower risk for colorectal cancer. These differences may be related to the role exerted by drug-metabolizing enzymes in the activation or inactivation of certain carcinogens.

Developmental Factors.

The biotransformation of most drugs proceeds at a slower rate in neonates (especially those born prematurely) than in adults.[33,65] The drug-metabolizing capacity of newborns, however, is not limited to the same degree for all drugs, and some metabolic pathways (e.g., glucuronidation) appear to be more affected than others (e.g., sulfate conjugation). Qualitative differences in drug metabolism can also be observed between newborns and adults; for example, newborns may be unable to demethylate theophylline to 3-methylxanthine (the normal metabolic pathway in infants, children, and adults), but they can N-methylate the drug to caffeine, a reaction that does not occur in infants and adults.[11] These findings can be explained by the observation that some forms of enzymes are expressed only in fetal liver and disappear rapidly after birth. The production of drug-metabolizing enzymes can also be affected by exposure to chemicals and drugs during pregnancy; for example, newborns of mothers treated with phenytoin, carbamazepine, or barbiturates during pregnancy may show a surprisingly efficient oxidizing capacity because of the stimulating effect that the same drugs exert on the microsomal enzymes of fetal liver.[65]

Biotransformation rates increase gradually over a period of several weeks to several years to peak rates that are often, although not invariably, higher than those observed in adults. For some drugs, the increased metabolic activity is most evident during the period between 2 to 3 months and 2 to 3 years of age, and after that time the rate of metabolism tends to decline slowly, reaching adult values after puberty. For other drugs, peak metabolic rates occur at a later stage.[65] An increased rate of metabolism in children compared with adults has been described for most antiepileptic drugs, including diazepam, carbamazepine, ethosuximide, phenobarbital, phenytoin, valproic acid, lamotrigine, oxcarbazepine, topiramate, tiagabine, felbamate, and zonisamide.[4,5,70] These findings provide an explanation for the observation that the average dose requirements of most of these drugs (on a milligram-per-kilogram basis) are greater in children than in adults.

Significant alterations in drug metabolism are also observed in the elderly.[26,51] A reduced rate of elimination in elderly patients has been reported for a large number of compounds, including carbamazepine, phenytoin, phenobarbital, valproic acid, oxcarbazepine, lamotrigine, topiramate, felbamate, diazepam, desmethyldiazepam, and clobazam.[7,70,72] In the case of some benzodiazepine drugs, the reduction in metabolic clearance is more pronounced in elderly men than women.[24] Because old age may be associated with reduced drug binding to plasma proteins, the elevated drug concentrations that result from reduced metabolic clearance may not be immediately apparent when total rather than unbound drug concentrations are measured. For example, total plasma concentrations of valproic acid may be similar in the elderly and in the young, but the elderly show an increased concentration of non–protein-bound, pharmacologically active drug.[75] Although the efficiency of glucuronidation pathways may be less susceptible to aging-associated decline, a decrease in clearance in old age is also observed for some agents that are eliminated primarily by conjugation, such as lamotrigine and 10-hydroxycarbaze-pine.[70]

Pregnancy.

Drug biotransformation in pregnancy may be affected by several factors, including hormonal changes, the contribution of the fetoplacental unit to drug metabolism, alterations in binding to plasma proteins, and hemodynamic changes.[43] Although the metabolism of some compounds, notably caffeine and theophylline, is impaired during pregnancy, evidence indicates that the metabolic clearance of most drugs increases during pregnancy, usually reaching a peak in the second or third trimester.[65] The frequently observed decrease in the plasma concentration of carbamazepine, phenytoin, phenobarbital, primidone, valproic acid, and lamotrigine during pregnancy is likely to be related at least in part to faster metabolism, although for some of these drugs, most notably valproic acid and phenytoin, a decrease in plasma protein binding may also play an important role.[60,65,105] The increase in metabolic clearance is especially marked for lamotrigine,[61] and preliminary observations suggest that a marked change may also be observed for 10-hydroxycarbazepine, the active metabolite of oxcarbazepine.[50] Because both lamotrigine and 10-hydroxycarbazepine are primarily cleared by glucuronide conjugation, these observations suggest that the activity of glucuronidation pathways may be particularly susceptible to stimulation by the physiologic changes occurring during pregnancy.

In the case of primidone and phenobarbital, an increase in renal clearance may also contribute to the decrease in plasma drug levels during pregnancy. Of interest, there is evidence that in some pregnant patients, conversion of primidone to phenobarbital may be impaired.[3]

Diet.

Certain constituents of the diet may exert inhibitory or stimulatory effects on the drug-metabolizing enzymes.

One interesting example is the inhibition of CYP3A4, CYP1A2, and other CYP isozymes by ingredients (probably

bioflavonoids) contained in grapefruit juice. Inhibition of cytochrome CYP3A4 results in reduced first-pass metabolism and increased serum concentration of several drugs, including various dihydropyridine calcium antagonists, terfenadine, cyclosporine, and midazolam; for example, concurrent intake of grapefruit juice may increase the peak plasma concentration of felodipine by 56% to 546%.[1] A similar interaction may occur with Seville orange juice, but not with most other types of orange or tangerine juice.[27] Many other dietary components, including some herbal products, influence drug metabolism to a significant extent and may contribute to explain the interindividual variation in the pharmacokinetics of a wide range of drugs.[27]

Enzyme Induction.

The term *enzyme induction* is used to indicate the phenomenon in which certain chemicals stimulate ("induce") the synthesis and/or the activity of drug-metabolizing enzymes in the liver or other organs. This stimulatory action affects predominantly a subset of cytochrome P450 enzymes, although induction of other enzyme systems (e.g., epoxide hydrolase or glucuronyl transferase) has also been documented.[55] The term "induction" is also used more broadly to indicate a stimulatory action of some chemicals on other systems, for example, efflux transporters such as P-glycoprotein.[34] In fact, there is a strong overlap in substrate specificity between CYP3A4/5, a major CYP enzyme, and P-glycoprotein; moreover, inducers and inhibitors of CYP3A4/5 may also induce and inhibit P-glycoprotein and other transporters.[34] Therefore, it is probable that some interactions resulting in decreased blood concentrations of certain substrates are mediated by stimulation of transporter-mediated efflux in the gastrointestinal tract (resulting in reduced oral bioavailability), liver (resulting in enhanced biliary elimination), or kidney (resulting in increased renal excretion) rather than enhanced drug metabolism in the liver and other tissues.

Unlike enzyme inhibition, which may become manifest rapidly after the introduction of the interacting agent, enzyme induction requires several days or weeks to develop fully. Different inducers stimulate specific CYP isozymes or other systems, and therefore they may have different effects on the metabolism of various substrates. The two best-known prototypes of CYP inducers are polycyclic aromatic hydrocarbons and phenobarbital. Polycyclic aromatic hydrocarbons interact with a specific cytosolic receptor, known as the *Ah receptor*, and trigger a sequence of events that results in induction of CYP1A isozymes.[55,104] Because many reactions catalyzed by these isozymes generate carcinogenic intermediates, induction may alter individual susceptibility to the action of environmental procarcinogens. Although polycyclic aromatic hydrocarbons are among the constituents of cigarette smoke, it is likely that other compounds present in smoke contribute to the stimulating effects of smoking on CYP1A activity. Both CYP1A1 and CYP1A2 enzymes are induced by cigarette smoke; in humans, cigarette smoke has been reported to accelerate the oxidation of diazepam, desmethyldiazepam, phenacetin, nicotine, theophylline, propranolol, imipramine, and pentazocine but not the oxidation of meperidine, nortriptyline, ethanol, phenytoin, phenobarbital, and carbamazepine.[31,64] It is interesting that the inducing effect of cigarette smoke is much more prominent at extrahepatic sites, such as the placenta, than in the liver.[59]

Enzyme induction caused by phenobarbital differs from that caused by polycyclic aromatic hydrocarbons.[59,104] Phenobarbital appears to induce hepatic enzymes preferentially to placental enzymes. The most important enzyme system induced by phenobarbital is the CYP3A family, which is responsible for the clearance of the majority of therapeutic CYP-metabolized drugs. Apart from barbiturates, examples of CYP3A inducers include carbamazepine, phenytoin, rifampicin, rifabutin, some glucocorticoids, and St. John's wort. With respect specifically to barbiturates, the spectrum of enzymes stimulated includes not only CYP3A but also CYP1A2, CYP2C9, CYP2C19, and possibly other CYP isoforms, in addition to enzymes involved in glucuronidation and some other conjugation reactions, as well as some efflux transporter systems. Induction of these enzyme systems by barbiturates and/other drugs involve an interaction with specific receptors, such as the constitutive androstane receptor (CAR) and the pregnane X receptor (PXR).[104]

Apart from barbiturates, other antiepileptic drugs that have been shown to act as broad-spectrum inducers of CYP3A and other drug-metabolizing enzymes include phenyt-oin and carbamazepine. Although therapeutic doses of these antiepileptic drugs increase antipyrine clearance (a nonspecific marker of drug-metabolizing capacity) to a similar extent,[76] evidence has been provided that some isozymes induced by carbamazepine and phenytoin may be different from those induced by barbiturates.[85] Topiramate, oxcarbazepine, and felbamate also exhibit some enzyme-inducing activity, but this appears to more restricted than that caused by phenobarbital, phenytoin, and carbamazepine, and is probably limited to fewer CYP3A enzyme isoforms, with special reference to those involved in the metabolism of steroid oral contraceptives and few other drugs.[71] In the case of topiramate, induction of the metabolism of steroid oral contraceptives is seen at doses >200 mg/d and does not occur at doses <200 mg/d, whereas evidence for an interaction at 200 mg/d is equivocal.[10] This observation highlights the important concept that enzyme induction is a dose-dependent phenomenon.[76] Lamotrigine 300 mg/d has also been found to increase the clearance of levonorgestrel, but whether this is due to enzyme induction is unclear.[90] Antiepileptic drugs that are devoid of enzyme-inducing properties at therapeutic doses include benzodiazepines, valproic acid, tiagabine, gabapentin, pregabalin, zonisamide, vigabatrin, and, probably, ethosuximide.

Induction of microsomal enzymes by antiepileptic drugs has important implications.[64,94] In the case of carbamazepine, autoinduction (i.e., induction of its own metabolism) is responsible for the progressive decline of the plasma concentration of the drug a few weeks after initiation of treatment, as well as for the nonlinear relationship between plasma concentration of carbamazepine and dose. The isozymes stimulated by enzyme-inducing antiepileptic drugs also metabolize a large number of endogenous compounds, such as cortisol, testosterone, vitamin D_3, and bilirubin. Induction of the metabolism of vitamins and hormones may play a role in the pathogenesis of anticonvulsant-induced rickets and osteomalacia, folate deficiency, and altered metabolism of steroid and thyroid hormones. Other conditions that might be related to enzyme induction include elevated plasma levels of α_1-acid glycoprotein, sex hormone–binding globulin, γ-glutamyltransferase, and alkaline phosphatase; the precipitation of attacks in patients with acute intermittent porphyria; and an increase in the levels of high-density-lipoprotein (HDL) cholesterol. Finally, induction of the metabolism of concurrently administered drugs is responsible for a large number of interactions (see Chapter 110).

Enzyme Inhibition.

Inhibition of drug-metabolizing enzymes can be caused by endogenous compounds (e.g., certain hormones), food constituents (e.g., grapefruit juice), environmental contaminants, and concurrently administered drugs. The mechanisms involved can include reversible competition by alternative substrates or noncompetitive inhibition caused by irreversible cytochrome P450 inactivation.[55]

Like inducers, inhibitors tend to affect only a limited number of isozymes and therefore can be used as tools to discriminate among the effects of different isozymes. Knowledge of the isozyme metabolizing a given drug also allows drug interactions involving inhibition of that isozyme to be predicted. A detailed discussion of these interactions is given in Chapter 110.

Plasma Protein Binding and Blood Flow.

Plasma protein binding and blood flow influence drug metabolism by determining the availability or the delivery of drug molecules to the site of biotransformation. The relationship between these variables and elimination processes has been considered in the discussion of clearance concepts.

Disease.

Because of the role of the liver in biotransformation, hepatic disease may be associated with significant alterations in drug metabolism. Factors that may affect metabolic elimination in liver disease include a reduction in cell mass, a change in cellular enzyme content or activity, a decrease in plasma protein binding, a decrease in blood perfusion resulting from reduced portal blood flow and extrahepatic and intrahepatic shunting, a reduced exchange across the endothelial lining, and impaired diffusion within Disse spaces.[52] The pharmacokinetic implications vary depending on type and severity of hepatic disease, degree of hypoalbuminemia, age of the patient, and route of administration and intrinsic characteristics of the drug. Oxidative drug metabolism is generally impaired in liver disease (most notably in cirrhosis), whereas conjugation pathways are usually less severely affected.[28]

Disease states affecting organs other than the liver may also affect the rate of drug metabolism,[53] but a detailed discussion of these is beyond the purpose of this chapter.

Renal Excretion

The mechanisms regulating the excretion of drugs or their metabolites in urine include glomerular filtration, active tubular transport, and passive tubular reabsorption.[62] Filtration is determined primarily by the glomerular filtration rate and plasma protein binding, with only unbound drug being able to pass through the glomerular filter.

A number of drugs may be actively transported in the proximal tubules. A major transporter system involves P-glycoprotein and multidrug resistance–associated protein type 2 (MRP2), which are located in the apical brush border membrane and mediate the secretion of amphipathic anions and conjugated metabolites, respectively.[62] Separate transporter systems also exist that are more selective for organic bases such as choline and tetraethylammonium. Other transporters located mainly in the distal tubuli are responsible for active reabsorption of drugs from the tubular lumen back into the circulation. Most of the reabsorption, however, takes place by passive diffusion.

Because of reabsorption of water and electrolytes, a concentration gradient is created within the renal tubules that facilitate extensive backdiffusion of lipophilic drugs into the circulation. Therefore, only water-soluble compounds can be excreted efficiently in urine. In the case of ionic drugs, the degree of passive reabsorption is determined by the proportion of molecules that are in nonionized (lipid-soluble) form. Acidic compounds are excreted more efficiently when urine is alkaline (which results in a higher proportion of ionized molecules), whereas basic drugs are excreted better when urine is acidic. The influence of changes in pH on drug excretion is more profound for those drugs having a pKa within the range of urinary pH (5–8). In some cases, urinary pH can be manipulated deliberately to enhance drug elimination; one example is the use of urine alkalinization to hasten the excretion of phenobarbital in cases of overdose.[48]

Competition for the carrier systems by other drugs or endogenous substrates may lead to inhibition of transport. For example, cimetidine may impair the elimination of many drugs by competitively inhibiting the carrier system responsible for the secretion of organic bases.[91]

In general, urinary excretion is subject to less extensive interindividual variability than is metabolic elimination. A significant impairment in renal elimination is expected whenever the glomerular filtration rate is reduced, as in the newborn, in the presence of acute or chronic renal failure, and in the elderly.[16,70] In some of these conditions, concomitant alterations in active transport mechanisms may contribute to the impairment of elimination processes.

The dose of drugs that are eliminated predominantly unchanged in urine may need to be adjusted in patients with reduced renal function; examples of such drugs include primidone, levetiracetam, gabapentin, pregabalin, and vigabatrin.

Single-Dose Pharmacokinetics

Although pharmacokinetics may be concerned with changes in drug concentrations in any body fluid or tissue, in the clinical setting, kinetic data are usually derived from the most accessible tissue—plasma (or serum) or blood. The rationale for measuring drug concentrations in these fluids is that under most circumstances these are related to the concentration at the site of action. This section provides a simplified description of drug kinetics after single intravenous or oral doses.

Intravenous Administration

The kinetic pattern observed after intravenous injection of a single dose of a drug varies in relation to the distribution and elimination characteristics of the individual compound.[6] In simple terms, drugs can be classified into two categories. The first includes compounds that diffuse almost instantaneously into tissues. In this case, the body can be considered as a single compartment from which the drug is eliminated. The second group of drugs comprises compounds that require some time before distribution can be completed. In this case, the body can be considered as an arrangement of two (or more) compartments, one representing the plasma (or blood) and highly perfused tissues, and the other representing tissues into which the drug distributes more slowly.

One-Compartment Model

When distribution takes place extremely rapidly, drug kinetics can be described according to the one-compartment model (Fig. 3A). In this model, the input is represented by entry of the drug into the circulation (which is virtually instantaneous in the case of a bolus injection), whereas output is dictated by the elimination processes.[6] Unless particular conditions apply (see section Nonlinear Pharmacokinetics), elimination typically follows a first-order process, that is, the amount of drug cleared per unit of time represents a constant fraction of the drug that is present in the body at that time. Under these conditions, the decline in drug concentration over time is described by a monoexponential equation:

$$C = C_0 e^{-kt} \qquad (2)$$

where C is the plasma concentration at time t, C_0 is the concentration at zero time (time of injection), e is the base of the natural logarithms, and k is a rate constant that reflects the efficiency of the elimination process. A semilogarithmic ($\log_{10}$) plot of plasma drug concentrations versus time yields a straight line with an intercept equal to C_0 and a slope equal to $k/2.3$ (Fig. 4A). When $C = ½C_0$, t is by definition equal to the half-life $t_{1/2}$, and Equation (2) can be solved as follows:

$$t_{1/2} = (\ln 2)/k = 0.693/k \qquad (3)$$

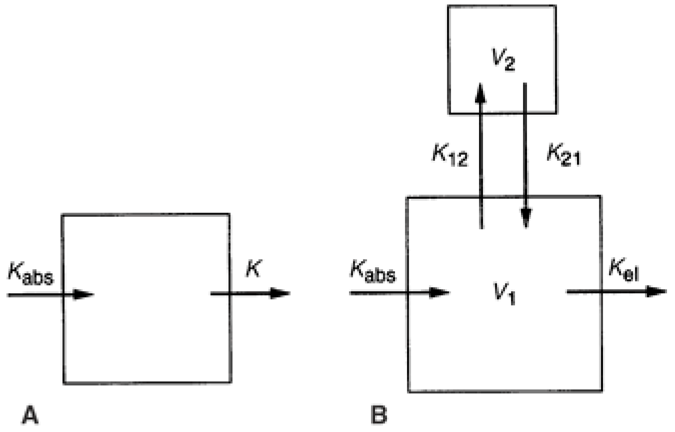

FIGURE 3. Schematic representation of two widely used compartmental models applied to pharmacokinetic analysis. **A:** One-compartment open model. In this model, the body is assimilated to a single compartment. Arrows indicate transfer processes for drug entry and removal. K_{abs} refers to a first-order rate constant of drug absorption, and K refers to a first-order rate constant of drug elimination. Absorption does not apply in the case of instantaneous intravenous injection. **B:** Two-compartment open model. In this model, the bloodstream and tissues undergoing rapid distribution are assimilated to a central compartment (V_1), whereas a peripheral compartment (V_2) is used to represent tissues into which distribution occurs more slowly. Arrows refer to processes of absorption, transfer, and removal. K_{abs} refers to a first-order rate constant of drug absorption, and K_{el} refers to a first-order rate constant of drug elimination; these are assumed to take place in the central compartment. [K_{el} does not correspond to the hybrid rate constant of terminal elimination ß as defined in Equation (8).] K_{12} and K_{21} refer to the transfer rate from the central to the peripheral compartment and vice versa.

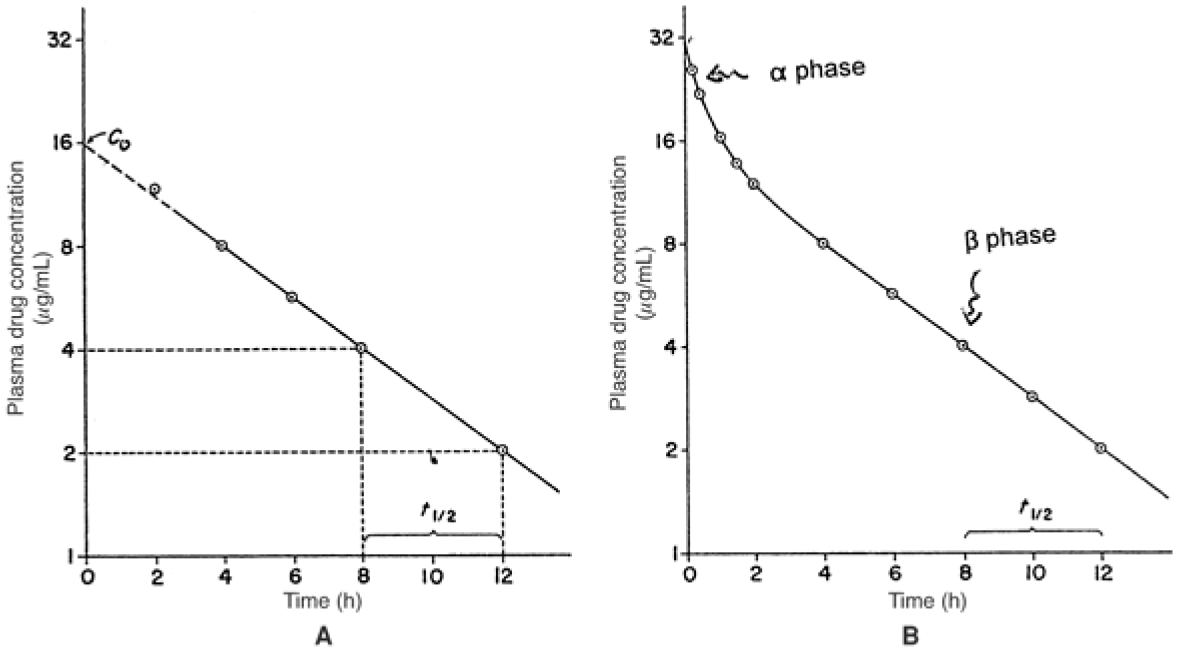

FIGURE 4. Decline in plasma drug concentration following a single intravenous bolus injection. **A:** Concentration declines monoexponentially according to a one-compartment open model. C_0 indicates the concentration at zero time, and $t_{1/2}$ is the half-life of the drug. **B:** Concentration declines biexponentially according to a two-compartment open model. The distributive (α) phase, the elimination phase (β), and the terminal half-life are also shown. (Modified from Buxton ILO. Pharmacokinetics: the dynamics of drug absorption, distribution, action, and elimination. In: Brunton LL, Lazo JS, Parker KL, eds. *Goodman and Gilman's The Pharmacological Basis of Therapeutics.* New York: McGraw-Hill; 2005:1–39, with permission.)

In the one-compartment model, apparent volume of distribution V_d can be calculated as follows:

$$V_d = \text{Dose}/C_0 \qquad (4)$$

which corresponds to the definition of V_d as the virtual volume in which the amount of drug present in the body (which at zero time equals the injected dose) must be dissolved to obtain a concentration equal to that found in plasma (C_0).

The elimination rate *k* is related directly to clearance *CL* and inversely to volume of distribution V_d as follows:

$$k = CL/V_d \qquad (5)$$

Hence, the relationship between clearance and half-life is as follows:

$$CL = 0.693\frac{V_d}{t_{1/2}} \qquad (6)$$

Multicompartment Models

In these models, the drug is administered into a central compartment (which simulates the bloodstream and other tissues into which the drug is distributed almost instantaneously) and diffuses thereafter into peripheral compartments. The latter are intended to represent less-perfused tissues into which the drug is distributed relatively slowly. Drug transfer from the central to the peripheral compartments (and vice versa) is determined by first-order rate constants, and elimination is assumed to take place only from the central compartment. The simplest of these models includes two compartments (Fig. 3B) and is adequate for describing the kinetics of most drugs.

In the two-compartment model, the decline in plasma drug concentration following intravenous administration is initially

rapid, resulting from a combination of two processes: (a) Elimination and (b) distribution into tissues (peripheral compartment). With time, the concentration in the peripheral compartment increases progressively until equilibrium with the central compartment is achieved; at that point, distribution is complete. The decline in plasma concentration then depends exclusively on drug elimination, and it therefore occurs more slowly (Fig. 4B). Although a precise characterization of drug kinetics according to the two-compartment model involves calculation of all rate constants depicted in FIGURE 3B, from a practical point of view the two most informative parameters are the hybrid decay constants α and β, which characterize the distribution phase (α phase) and the terminal or elimination phase (β phase). Determination of these constants allows calculation of the distribution half-life $t_{1/2\alpha}$ and terminal half-life $t_{1/2\beta}$:

$$t_{1/2\alpha} = 0.693/\alpha \qquad (7)$$
$$t_{1/2\beta} = 0.693/\beta \qquad (8)$$

The distribution half-life provides an estimate of the rate at which a drug is distributed into tissues (α phase in Fig. 4B), whereas the terminal half-life reflects the rate of drug elimination. In general, the terminal half-life is a more important parameter because it determines the time to reach steady state (see section Pharmacokinetics During Continuous or Multiple Dosing) and, in most cases, it also indicates the duration of drug action. As discussed in the section on drug distribution, however, there are situations in which the time course of effect is related more to distribution half-life than to terminal half-life.

Model-independent Calculation of Kinetic Parameters

At times, the mathematical models described previously may not be fully adequate for describing the pharmacokinetic pattern observed experimentally, or there may be too few data points to allow a meaningful selection of the most appropriate model. To circumvent these problems, procedures have been developed that allow a model-independent calculation of kinetic parameters. The rationale for this calculation is based on the fact that after intravenous administration, the area under the curve (*AUC*) of plasma concentration versus time from time zero to infinity is related directly to the administered dose and inversely to total plasma clearance. Therefore, this relationship can be used for the calculation of clearance according to:

$$CL = \text{Dose}/AUC \qquad (9)$$

The volume of distribution V_d can be calculated by exploiting its known relationship to clearance and terminal half-life:

$$V_d = CL\frac{t_{1/2}}{0.693} = \frac{\text{Dose} \cdot t_{1/2}}{0.693 \cdot AUC} \qquad (10)$$

Of course, these calculations require reliable characterization of the terminal elimination phase. No pharmacokinetic analysis can provide meaningful information when experimental data are inadequate.

Oral Administration

The kinetic pattern observed after oral administration is similar to that described after intravenous dosing, except that drug entry into the bloodstream occurs more slowly and might be incomplete. Under most circumstances, absorption is a first-order process and can be described in terms of a rate constant k_{abs} that can be incorporated into pharmacokinetic models as an input function representing the rate of drug entry into a single (Fig. 3A) or a central (Fig. 3B) compartment.

During the initial part of the absorption phase, the amount of drug that enters the systemic circulation per unit of time exceeds the amount that leaves the bloodstream as a result of distribution and elimination processes. Under these conditions, the plasma concentration increases gradually. As absorption proceeds, the proportion of drug remaining in the gastrointestinal tract and available for absorption decreases progressively, until a time is reached at which the amount entering the circulation equals the amount that is eliminated. This time corresponds to the peak, or plateau, of plasma drug concentration. After that time, elimination proceeds at a faster rate than absorption, and plasma drug concentration decreases at a rate that eventually equals the terminal elimination rate. Even for drugs with kinetics that are best described by a two-compartment model, a distribution phase during the decline of plasma concentrations may not be detected because of the masking effect of ongoing absorption.

The oral bioavailability (*F*), defined as the fraction of the oral dose that reaches the systemic circulation, can be calculated by comparing the areas under the plasma concentration curves from zero to infinity following oral (AUC_{po}) and intravenous (AUC_{iv}) administration of the same dose:

$$F = \frac{AUC_{po}}{AUC_{iv}} \qquad (11)$$

If different doses are used, a correction factor must be introduced based on the assumption, which is correct in the case of linear kinetics, of a direct relationship between *AUC* and dose. A value for *F* that is <1 indicates incomplete absorption and/or presystemic elimination by first-pass metabolism in the gastrointestinal tract or the liver.

It should be emphasized that the definition of bioavailability given in Equation (11) is overly restrictive. In fact, the term *bioavailability* is generally used to define not only the fraction of the dose that reaches the systemic circulation, but also the *rate* at which absorption occurs. The clinical relevance of this concept is illustrated in FIGURE 5, which depicts plasma drug concentration profiles after administration of the same dose intravenously (Fig. 5A) and orally in two different formulations (Fig. 5B, C). Despite the fact that *AUC* is the same for both oral formulations (indicating no difference in the fraction of the dose reaching the systemic circulation), only formulation B ensures a rate of absorption sufficiently rapid to produce a pharmacologic effect. Formulations B and C can be differentiated pharmacokinetically by also calculating the peak concentration (Cmax) and the time of peak (Tmax).

Pharmacokinetics During Continuous or Multiple Dosing

Continuous Dosing

The most common situation in which continuous dosing is used is in the management of status epilepticus, when drugs may be given by intravenous infusion. If the infusion is given at a constant rate (zero-order input), drug concentration in plasma will increase progressively over time. Because elimination is generally a first-order process, the amount of drug eliminated from the body will increase with increasing plasma concentration up to a point at which the amount eliminated per unit of time will equal the amount administered through the infusion pump. When the rate of drug entry into the system equals the rate of drug removal, the plasma concentration will remain stable at a constant value, and steady-state conditions are said to exist (Fig. 6).

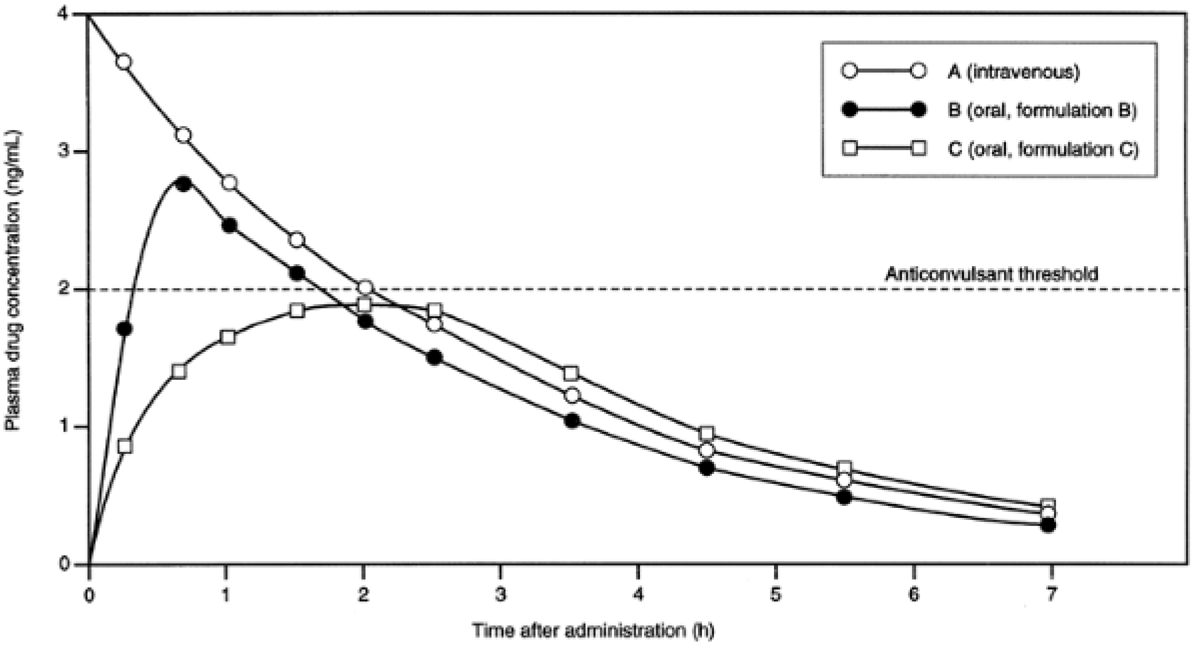

FIGURE 5. Plasma drug concentration profiles following intravenous **(A)** and oral **(B, C)** administration of the same dose. Two different pharmaceutical formulations are represented by B and C. The area under the curve (*AUC*) after intake of formulations B and C is approximately 80% of that observed after intravenous injection, indicating that the bioavailability of the two oral formulations is about 80%. Despite equal values for *AUC*, the two oral formulations differ in absorption rate, and only formulation B allows plasma concentrations to be achieved above the threshold required for anticonvulsant effect.

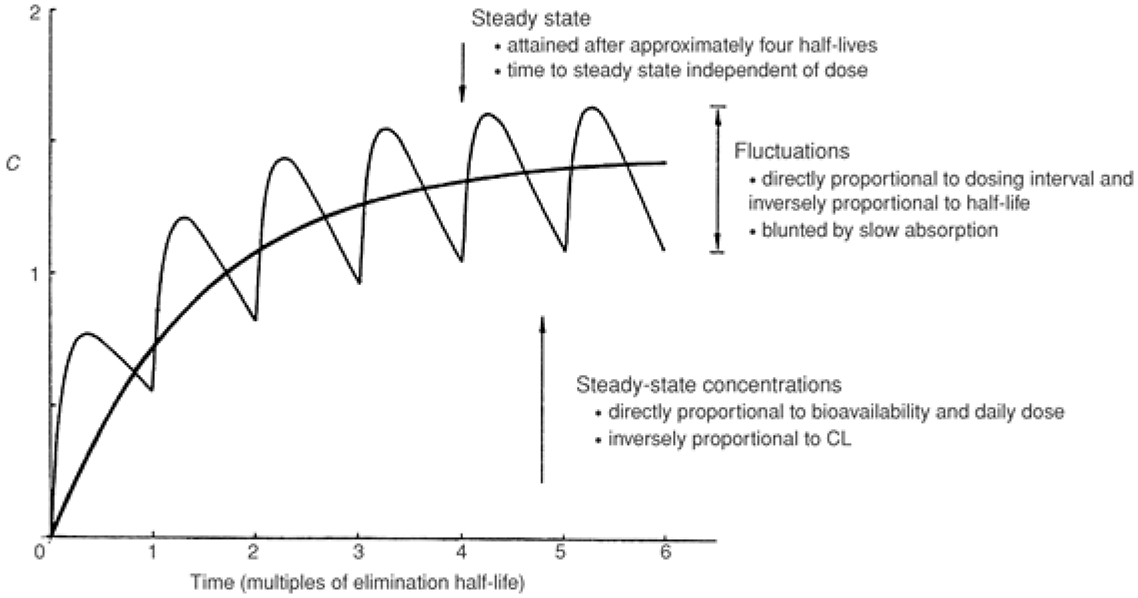

FIGURE 6. Plasma drug concentration (*C*) profiles after initiation of treatment by constant-rate intravenous infusion (*smooth curve*) and by multiple oral doses given at intervals of one half-life (*oscillating curve*). Steady-state conditions are reached after about four to five half-lives. Steady-state

concentration is directly related to bioavailability *F* and dosing rate and is inversely related to clearance *CL*. (Modified from Buxton ILO. Pharmacokinetics: the dynamics of drug absorption, distribution, action, and elimination. In: *Goodman and Gilman's the Pharmacological Basis of Therapeutics*. New York: McGraw-Hill;2005;1–39, with permission.)

The concentration at which steady state is achieved C_{SS} is determined exclusively by intravenous dosing rate and plasma clearance:

$$C_{ss} = \text{Dosing rate}/CL \qquad (12)$$

The drug concentration *C* at any time *t* following initiation of drug infusion is related to C_{SS} as follows:

$$C = C_{ss}(1 - e^{-kt}) \qquad (13)$$

where *k* is the rate constant of the terminal phase, which is related to terminal half-life by the relationship expressed in Equation (3). By substituting in Equation (13) values of *t* that are multiples of the half-life, we can show that after two half-lives, *C* equals 75% of C_{SS}, and that after four and five half-lives, *C* equals 94% and 97%, respectively, of C_{SS}. This underscores the important principle that the time required to reach steady state depends exclusively on terminal half-life. From a practical point of view, steady state can be considered complete when four to five half-lives have elapsed after initiation of treatment.

In the case of drugs that are eliminated slowly (e.g., phenobarbital, with a half-life that may range from 50–150 hours), the time required to reach steady state may be several weeks. When it is desired to obtain steady state in a shorter time (e.g., when phenobarbital is infused intravenously to control neonatal convulsions), an adequate loading dose (mg/kg) may be given initially at an appropriate rate. A rough approximation of the intravenous loading dose may be obtained by multiplying the desired steady-state concentration (mg/L) by the volume of distribution of the drug (L/kg). In practice, however, choice of the loading dose and choice of its optimal rate of administration are dictated primarily by clinical information because in some situations too rapid attainment of high plasma concentrations may lead to serious toxicity.

Multiple Doses

Mean plasma drug concentrations during multiple dosing are roughly equivalent to those achieved during continuous dosing, except that fluctuations will be observed during the dosing interval as a result of the discontinuous mode of administration (Fig. 6). During oral therapy, the mean steady-state plasma concentration C_{SS} is related to administered dose *D*, bioavailability *F*, plasma clearance *CL*, and dosing interval *t* according to the following relationship:

$$\text{Mean } C_{ss} = \frac{FD}{CL \cdot t} \qquad (14)$$

As discussed previously for continuous administration, four to five half-lives must elapse before C_{SS} is reached after initiation of treatment or a change of dose. The degree of fluctuation of drug levels around the mean is determined by absorption rate, dosing interval, and elimination half-life. In the case of reversibly acting drugs with short half-lives, multiple daily doses may be needed to avoid excessive swings in plasma concentration during the dosing interval.

Nonlinear Pharmacokinetics

Most of the pharmacokinetic concepts described previously are valid only when the kinetics is linear, that is, the rate constants describing absorption, distribution, and elimination are first order and do not change over time. When this is the case, steady-state plasma concentrations are linearly related to daily dose (Fig. 7A). When rate constants change with dose or duration of treatment, nonlinear kinetics is said to apply. Nonlinearity is common when drugs are taken in overdose, but occasionally it may occur even at therapeutic dosages with particular drugs. Antiepileptic drugs provide good examples of different mechanisms that may cause nonlinearity.

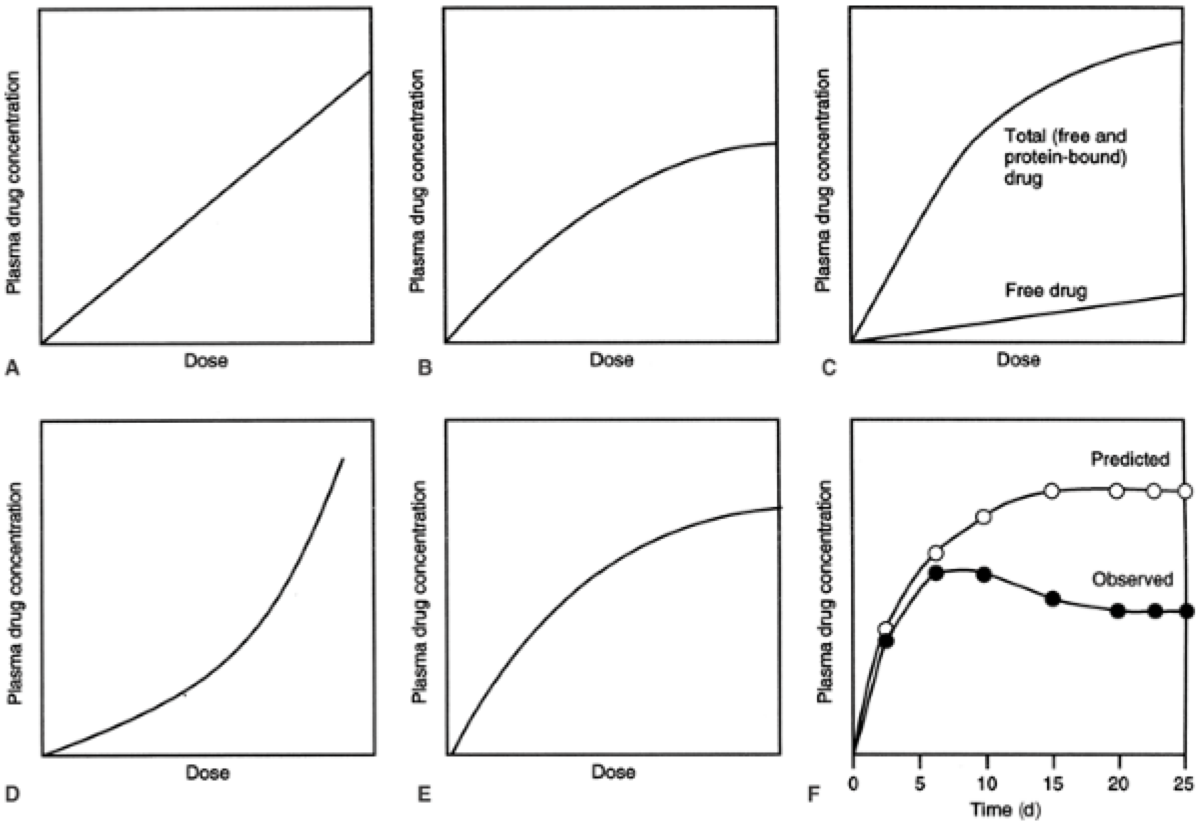

FIGURE 7. A comparison of linear and nonlinear pharmacokinetics. Panels A to E show the relationship between steady-state plasma concentrations and daily dose for drugs exhibiting linear and nonlinear (dose-dependent) pharmacokinetics. Panel F shows an example of time-dependent kinetics. **A:** Linear pharmacokinetics. Plasma concentration is linearly related to dose. **B:** Dose-dependent absorption. Saturation of active transport system in the gut, as documented for gabapentin, causes bioavailability to decrease with increasing dose. **C:** Dose-dependent protein binding. Saturation of plasma protein-binding sites results in increased unbound fraction at higher doses. For drugs exhibiting restrictive elimination, such as valproic acid, this causes an increase in total plasma clearance. However, unbound drug concentration, which is responsible for pharmacologic effect, remains linearly related to dose. **D:** Enzyme saturation. Saturation of the drug-metabolizing enzymes, as seen with phenytoin, causes clearance to decrease with increasing dose. As a result, small dose increments can result in disproportionate increases in drug concentration. **E:** Dose-dependent autoinduction. Enhanced stimulation of its own metabolism causes the clearance of carbamazepine to increase with increasing dose. This results in a flattened dose–concentration relationship. **F:** Time-dependent kinetics. Development of autoinduction of metabolism causes serum carbamazepine concentration to decrease slightly after about 1 week of treatment and to stabilize at a steady-state level lower than predicted from single-dose pharmacokinetic data.

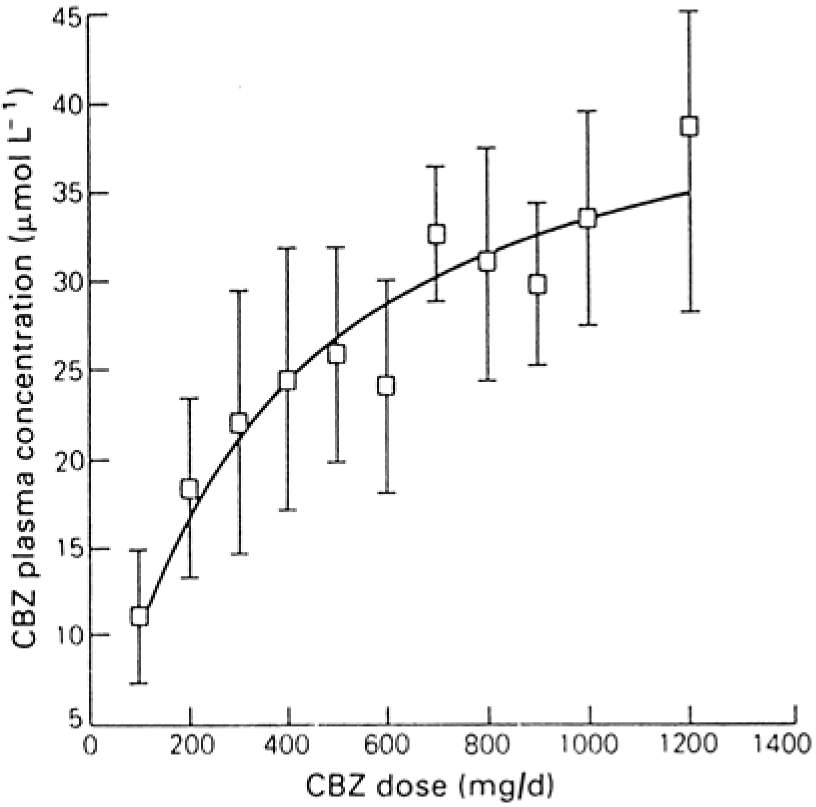

FIGURE 8. Relationship between daily dose and steady-state plasma concentration of carbamazepine in patients with affective disorders. Results are expressed as means ± standard deviation (n = 7–16 at each point). (From Kudriakova TB, Sirota LA, Rozova GI, et al. Autoinduction and steady-state pharmacokinetics of carbamazepine and its major metabolites. *Br J Clin Pharmacol.* 1992;33:611–615, with permission.)

Dose-dependent Kinetics

Kinetics is dose dependent when the rate constants describing the processes of absorption, distribution, or elimination depend on drug concentration.

Dose-dependent Absorption

Some drugs are absorbed by active transport systems that become saturated when a given concentration is exceeded. If this is the case, oral bioavailability may decrease with increasing dose (Fig. 7B). A saturable transport mechanism in the intestinal absorption of gabapentin appears to be responsible for the lack of proportionality between dose and plasma levels of this drug.[93]

Dose-dependent Protein Binding

Plasma protein-binding sites may become saturated within the range of drug concentrations that occur clinically. A situation of this kind is observed with valproic acid; the unbound fraction of this drug in plasma increases with increasing plasma concentration. Because valproic acid shows restrictive, flow-independent elimination, the increase in unbound fraction leads to increased plasma clearance and to a curvilinear relationship between plasma concentration and dose (Fig. 7C).[22] Because of the decrease in plasma protein binding at higher concentrations, however, the curvilinear relationship does not apply to the levels of unbound drug. In fact, unbound valproic acid concentrations are linearly related to dose or, in some cases, may show increments that are even greater than the increment in dose.[12] Under these circumstances, total plasma levels underrepresent the amount of pharmacologically active drug and may lead to incorrect adjustments in dose.[41]

Dose-dependent Metabolism: Enzyme Saturation

The enzymes responsible for the metabolism of a number of drugs may become saturated within the range of doses used clinically. When this is the case, first-order kinetics no longer applies, and the fraction of the drug cleared by the eliminating organ decreases with increasing drug concentration.

In the case of drugs that undergo extensive first-pass metabolism, the high drug concentrations found in the portal blood during the absorption phase may easily saturate the metabolizing enzymes, leading to decreased hepatic extraction and consequently increased oral bioavailability with increasing dose.

Saturation kinetics during the postabsorptive phase is observed more rarely, with phenytoin providing the best example.[81] Because of gradual saturation of the metabolizing enzymes, the rate of elimination of phenytoin decreases progressively with increasing dose and plasma concentrations, resulting in a nonlinear relationship between steady-state plasma level and dose (Fig. 7D). This has clinical significance because small increments in phenytoin dose can easily raise the plasma concentration to toxic levels. Another implication of saturation kinetics is that after discontinuation of treatment, the elimination phase is not log-linear because the rate of elimination increases with decreasing concentrations as the enzymes become desaturated. Under these conditions, a true half-life cannot be calculated, and drug elimination can be described by using the Michaelis-Menten equation:

$$V = \frac{V_{\max} C}{K_m + C} \qquad (15)$$

where V is the rate of metabolism, $V_{\max}$ is the maximum velocity of the metabolic reaction, K_m is the Michaelis constant, and C is the plasma concentration. Various methods have been proposed to predict the adjustment in phenytoin dose required to produce a desired plasma concentration based on rearrangements of Equation (15).[98]

Dose-dependent Metabolism: Enzyme Induction

The ability of carbamazepine to induce its own metabolism is dose dependent, that is, metabolic clearance of carbamazepine increases with increasing dose.[37] This results in a curvilinear relationship between dose and steady-state plasma concentration opposite to that observed in the case of phenytoin (Figs. 7E and 8). Because of the dose-dependent induction of carbamazepine metabolism, the ratio between the concentrations in plasma of the active metabolite carbamazepine-10,11-epoxide and the parent drug increases within certain limits, with increasing dose. This implies that at higher doses, the plasma levels of parent drug may underrepresent the amount of active moieties at the site of action.

Time-dependent Kinetics

The kinetics of certain drugs may change over time as a result of circadian variation in absorption and disposition. In other cases, pharmacokinetic changes may be related to duration of treatment. One example is provided again by carbamazepine (Fig. 7F). Because autoinduction requires some time to develop, the clearance of carbamazepine increases progressively following initiation of treatment, leading to a decrease in plasma concentrations after 1 to 2 weeks of therapy. Eventually, a new steady-steady concentration is reached that is lower than that predicted from single-dose pharmacokinetics.[18]

Population Pharmacokinetics

Because pharmacokinetic properties represent an important determinant of variation in pharmacologic response, it would be useful to obtain an estimate of mean pharmacokinetic parameters in a given population and to quantitate the effects of different variables on the same parameters. The information acquired in this process could then be used to predict the dose required to produce a desired plasma concentration of the drug in an individual patient.

Estimates of population pharmacokinetic parameters can be obtained by different methods.[29] In the *two-stage* method, individual parameters are obtained by intensive sampling in a group of subjects who are considered representative of the population of interest. The mean, standard deviation, and distribution of these parameters can then be calculated and used as estimates for the population values. Refinements of this method by means of iterative approaches and further data processing allow estimation of covariances and correlations between parameters. The *nonlinear mixed effects model* (NONMEM) differs from the two-stage method because it allows use of even a single plasma concentration point per subject.[88] Essentially, the NONMEM model uses individual data points collected at random times from a large number of patients to estimate by means of a computer program the means, standard deviations, and covariances of population parameters. In addition to allowing use of sparse and more easily collected data, this approach usually provides more reliable estimates of population parameters compared with the two-stage approach. A third method of estimation is based on the *nonparametric maximum likelihood* (NPML) approach described by Mallet.[46] This method estimates the entire collection of points and the joint probability density function of the parameters; there is no need to make any traditional (parametric) assumptions about the shape of the distribution assessed. The NPML method permits explicit discovery of previously unsuspected clusters of outliers, such as slow metabolizers of a drug. Refinements of this method have also been described.

Reliable population parameters are essential for the use of Bayesian forecasting in predicting individual dose requirements. In Bayesian forecasting, a computer program uses population pharmacokinetic parameters and their covariances to provide individualized, patient-specific models of drug behavior based on dose and other relevant variables, such as age, gender, body weight, and creatinine clearance. When plasma concentration values for an individual patient are available, the Bayesian approach moves away from the population estimates and uses the data obtained from the patient to refine the estimate of individual pharmacokinetic behavior. Bayesian methods are much more precise than linear regression on logarithms of plasma levels in predicting individual dose requirements.

An extensive discussion of the use of population phar-macokinetics, Bayesian fitting, and pharmacokinetic-phar-macodynamic modeling in dose prediction can be found in the excellent review by Jelliffe et al.[29] These methods can provide valuable information for individualization of dose, but in no case should pharmacokinetic predictions be used without thorough consideration of clinical data and careful assessment of the patient's response.

Summary and Conclusions

The onset and duration of pharmacologic effect is a function of the time course of the concentration of the drug at the site action, which, in turn, is related to the drug concentration in plasma. Therefore, a full understanding of pharmacokinetic principles is essential for a rational use of drugs in clinical practice. Pharmacokinetic parameters that are especially important in therapeutics include (a) bioavailability, which determines the rate and extent at which a drug enters the systemic circulation; (b) volume of distribution, which provides an indication of the amount of drug in the body relative to its concentration in plasma; (c) clearance, a measure of the efficiency of the elimination processes and a major determinant of the plasma drug concentration at steady state; and (d) half-life, which determines the time required to reach steady state and the fluctuation in plasma drug concentrations during a dosing interval. Although under most circumstances pharmacokinetic processes are linear, that is, independent of dose and duration of administration, there are important exceptions to this rule. Examples of drugs whose kinetics may deviate significantly from linearity at therapeutic doses include phenytoin, carbamazepine, valproic acid, and gabapentin. With most drugs, the rates of absorption, distribution, biotransformation, and excretion exhibit wide interindividual differences under the influence of constitutional and environmental factors, such as genetic background, age, associated disease, and exposure to dietary constituents, voluptuary substances, industrial contaminants, and concurrent drug therapy. The resulting variation in pharmacokinetic parameters has important clinical consequences, and it contributes to the requirement to tailor drug doses to individual needs. Although under selected circumstances clinical benefits can be achieved through pharmacokinetic optimization of the dose based on serum drug level monitoring, knowledge of pharmacokinetic characteristics of the prescribed drugs is always essential if dosing schedules are to be implemented correctly, and this is true also for drugs whose dose is individualized on purely clinical grounds.

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Chapter 103

Therapeutic Drug Monitoring

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Introduction

Therapeutic drug monitoring (TDM) can be defined as "the measurement and the clinical use of drug concentrations (levels) in body fluids (usually serum or plasma) to adjust each patient's individual drug dosage and schedule to each patient's individual therapeutic requirement." In practice it is the patient who is treated and not the concentration, so that the dose of a drug is adjusted, using the drug concentration as a guide, to optimize its efficacy, avoid, minimize, or identify toxicity, and detect or confirm poor compliance. It is therefore important to appreciate that TDM begins before a drug concentration is measured and that the measurement itself is only part of the overall process of planning, monitoring, and optimally adjusting the dosage regimen.

Many pharmacologic properties of antiepileptic drugs (AEDs) support suitability for TDM, and during the last 40 years therapeutic monitoring of AEDs has had an undeniable impact on the management of patients with epilepsy.[13] Major contributing factors are our enhanced understanding of AED pharmacokinetics and its relevance to drug therapeutics and the development of robust, reliable, and specific analytical methodologies underpinned by appropriate quality assurance schemes.[102,106] Assay results should be available quickly, preferably within 24 hours of sampling, because the most important use of blood concentrations are for making dosage adjustments and diagnosing toxicity when rapid decisions need to be made. Indeed, on-site, near-patient AED monitoring has been shown to have an immediate impact on clinical decision making and to enhance patient management.[18,49,64]

The criteria for valid TDM are the availability of accurate pharmacokinetic data; a poor correlation between dose and blood concentrations (i.e., substantial pharmacokinetic variability); good correlation between blood concentration and therapeutic effect, toxicity, or both, at least within individuals; a narrow therapeutic index (i.e., the therapeutic dose is close to the dose associated with toxicity); and the availability of simple, accurate, reproducible, and inexpensive analytical assays. However, some AEDs are more suitable candidates for monitoring than others. Phenytoin best fulfills these criteria because its saturable pharmacokinetics makes it very difficult to prescribe the optimum dose without measuring blood levels.

The goal of AED treatment is seizure freedom without side effects. However, even with the introduction of nine new AEDs, a significant number of people with epilepsy are still not achieving this goal. TDM can help to improve seizure control in numerous ways including the following:

- Identification of therapeutic failure due to underdosage.
- Detection of noncompliance with prescribed therapy, which may be responsible for avoidable therapeutic failure.
- Identification of the uncommon situation in which overdosage causes increased seizures.
- Detection of pharmacokinetic interactions that may compromise the adequacy of the therapy.

The following section provides a concise description of the current issues relating to the use of TDM for AEDs.

Principles of Therapeutic Drug Monitoring

Interest in the use of TDM as an aid to optimizing epilepsy treatment stems from the realization that serum AED concentrations may vary severalfold among patients who are prescribed the same dosage.[28] There are multiple reasons for such variability. To start with, the dose prescribed may differ from the dose actually taken, mainly due to variation in the degree of compliance. Even when drugs are taken as directed, serum concentrations may vary dramatically as a result of inter- and intraindividual differences in pharmacokinetics. Although most AEDs are absorbed efficiently from the gastrointestinal tract, the extent of absorption may be variably affected by factors such as age, interactions with foods or other medications, and characteristics of the pharmaceutical formulation used.[22] More important, the metabolic and renal clearance of AEDs is subject to prominent variability, both within and between subjects, under the influence of the genetic background (e.g., variation in genes controlling drug metabolism and drug transport), physiologic factors (e.g., changes in drug-metabolizing-enzyme activity and renal function during development, pregnancy, and aging), drug interactions, and disease states, with special reference to disorders affecting the function of the liver and the kidney.

Because the concentration of AEDs in serum is in equilibrium with the drug concentration at the site(s) of action in the brain, it is not surprising that differences in serum drug concentrations represent an important source of variability in dose requirements. Based on this background, knowledge of serum drug concentrations provides a more direct estimate, compared with prescribed daily dose, of the amount of drug that is available to produce pharmacologic effects. In fact, it is reasonable to assume (and this assumption can be verified in the clinic under many circumstances) that therapeutic and toxic effects correlate better with the concentration of a drug in the serum than with the prescribed daily dose.[21] In other words, under appropriate circumstances, the serum concentration of an AED can be used as a surrogate marker in assessing whether the patient is receiving an adequate amount of the prescribed drug.

Obviously, serum drug concentration measurements are superfluous when tools are available to measure drug effects directly. For example, we do not need to measure the serum concentrations of an antihypertensive drug or an oral anticoagulant because we can measure directly arterial blood pressure or International Normalized Ratio (INR) ratio and individualize dosage directly based on therapeutic response. In the case of AEDs, however, direct measurement of pharmacologic response can be elusive. In a newly diagnosed patient with infrequent seizures, for example, it may take months to determine whether the dosage initially prescribed is sufficient to prevent seizure recurrence. Measuring the serum AED concentration in that patient and comparing it with the concentration range that in previous studies has been found to maximize the probability of seizure control helps in predicting the effectiveness of the administered treatment and in determining whether a dosage adjustment would be appropriate.

Factors Affecting Response to a Given Antiepileptic Drug Concentration

If all patients achieved the best response at the same AED concentration, optimizing treatment would be easy. We would simply need to administer an initial dose, measure the serum drug concentration, and adjust the dose accordingly until the "therapeutic" concentration is achieved. Unfortunately, in real life things are much more complicated because the serum concentration of any given AED required to produce an optimal response varies more than tenfold across individuals and can also change substantially over time within the same individual.[21,75,94] This is due to a combination of factors, all of which may confound the relationship between serum drug concentration and pharmacologic effects, as follows.

Characteristics of the Seizure Disorder

There is evidence that the concentration of an AED required to produce seizure control differs in relation to the type and severity of the seizure disorder. Schmidt and Haenel[89] compared serum AED concentrations associated with complete seizure control in 84 patients stabilized on monotherapy with phenyt-oin, carbamazepine, or phenobarbital. In 26 of the 40 patients (65%) with generalized tonic–clonic seizures only, seizure control was achieved at concentrations of <60 µmol/L (<15 µg/mL) for phenytoin, <108 µmol/L (<25 µg/mL) for phenobarbital, and <25 µmol/L (<6 µg/mL) for carbamazepine. Conversely, only 3 of 32 well-controlled patients (9%) with complex partial seizures achieved remission at these relatively low drug concentrations. The AED concentration associated with seizure control also varied in relation to number of seizures in the first year of epilepsy. The 50 patients who were controlled at concentrations in the low range had suffered a median of 5 seizures (range 1 to 18) in the first year, whereas those who were controlled at higher concentrations had 61 seizures (range 0 to 300) over the same period. Recent studies also suggest that, within a given syndrome, responsiveness to AED treatment also depends on underlying etiology: For example, among patients with localization-related epilepsy, those showing underlying cortical atrophy or cerebrovascular disease may respond more favorably to AEDs than the remainder of the symptomatic group.[54]

Age

Because the distribution of epilepsy syndromes and underlying etiologies vary across age groups, we would expect the optimal concentration of an AED to be influenced by age. Evidence has been provided, in particular, that many elderly patients achieve seizure control at lower serum AED concentrations than younger subjects, although they also tend to develop adverse effects such as impairment of gait and tremor at lower concentrations.[27,39]

Duration of Treatment

For many AEDs, the response to a given drug concentration may change over time, most notably due to gradual development of tolerance to adverse effects. Patients with a prolonged exposure to phenobarbital or benzodiazepines, for example, might tolerate without major untoward effects serum drug concentrations that can cause extreme sedation and even coma in acutely exposed subjects.[14,30] A gradual improvement in central nervous system (CNS) tolerability with slowly rising serum drug concentrations during the initial up-titration phase is also observed with topiramate, tiagabine, pregabalin, and many other AEDs.[73]

Conditions Associated With Altered Drug Binding to Serum Proteins

Although routine methods for measuring AEDs in body fluids do not discriminate between drug molecules that are present in free (unbound) form and those that are bound to plasma proteins, only the free drug is available to move across the endothelium and to equilibrate with the concentration in the interstitial space in the brain. If the free fraction increases, the total drug concentration in serum will underestimate the amount of free, pharmacologically active drug, and under these circumstances therapeutic and toxic effects will be observed at total drug concentrations that are lower than usual.[68] Among AEDs that are commonly monitored, those that are most extensively bound to serum proteins are phenytoin and valproic acid. Impairment in the protein binding of these drugs may be caused by hypoalbuminemia (as observed during pregnancy, old age, liver disease, and many other pathologic conditions), accumulation of endogenous displacing agents (most notably in patients with renal insufficiency), and administration of other medications that compete for plasma protein–binding sites.[2,68] In these conditions, interpretation of serum drug concentration requires special skills: For example, in a patient in late pregnancy, the change in unbound fraction of phenytoin can be predicted by measuring the serum albumin concentration.[75] Techniques are also available for the direct measurement of unbound drug concentrations. These techniques are not used routinely because measuring unbound drug concentrations is more expensive and more cumbersome than measuring total drug concentrations. Moreover, in most situations, the intersubject variability in unbound fraction is relatively small, and measurement of total concentrations is more than adequate for clinical purposes. However, if a major change in unbound fraction is expected (or suspected), measuring unbound drug concentrations might be justified.

Comorbidities

Several diseases, particularly those affecting the liver and the kidney, are associated with changes in the binding of AEDs to serum proteins, and by this mechanism they alter the relationship between total serum concentration of highly protein-bound drugs and clinical effects.[74] Associated disorders may also modify the response observed at any given serum AED concentration at the pharmacodynamic level. For example, it has been elegantly shown that the threshold serum carbamazepine concentration that induces ataxia is significantly lower in patients with magnetic resonance imaging (MRI) evidence of preexisting cerebellar atrophy than in patients without atrophy.[93]

Drug Interactions

As discussed previously, concomitant drugs may affect concentration–response relationships by displacing highly bound AEDs from plasma protein–binding sites. Valproic acid, in particular, causes a marked displacement of protein-bound phenytoin, and in valproic acid–treated patients, therapeutic and toxic effects of phenytoin are observed at total serum phenytoin concentrations lower than usual.[47,68] Concomitant drugs can also affect concentration–response relationships through pharmacodynamic interactions: For example, the tolerability associated with any given concentration of carbamazepine is reduced in the presence of adverse pharmacodynamic interactions caused by oxcarbazepine[1] or lamotrigine.[12]

Confounding Effects of Active Metabolites

At times, effects apparently unrelated to the drug concentration in serum can be explained by the presence of active metabolites. One example is the precipitation of carbamazepine toxicity following addition of valpromide, a valproic acid derivative: The toxic reaction is caused by a prominent increase in the concentration of the active metabolite carbamazepine-10,11-epoxide, whereas serum carbamazepine concentration is unaffected.[77]

The Concept of Therapeutic Range

In the light of the variability discussed earlier, "therapeutic" ranges of serum AED concentrations reported in the literature (Table 1) must be interpreted flexibly. These ranges have merely a probabilistic value, that is, they represent the concentration interval at which the *majority* of patients are expected to show an optimal response. Indeed, some patients may do best at concentrations above and below the range, and there is no justification for modifying dosage in these patients if their seizures are well controlled and no adverse effects have emerged.[38,107]

The validity of therapeutic ranges quoted in the literature depends on the population and methodology that led to their definition. In particular, the pivotal study that led to the widespread acceptance of a 40- to 80-μmol/L (10- to 20-μg/mL) therapeutic range for phenytoin[44] was conducted in a small and preselected population of patients with heterogeneous epileptic disorders who had not responded to phenyt-oin. Thus, it is likely that the study excluded patients who had become seizure free at concentrations <40 μmol/L (10 μg/mL). In fact, in different studies, the proportion of patients achieving complete seizure control at phenytoin concentration <40 μmol/L (10 μg/mL) has been on the order of 22%,[86] 35%,[88] and 73%.[23] Similar observations have been made with other AEDs, leading to the suggestion that the lower limit of the therapeutic range should be disregarded altogether, and that any measurable concentration up to the level at which toxicity is likely to occur should be regarded as potentially therapeutic.[75]

In the light of these considerations, it is clear that therapeutic ranges must be interpreted flexibly, by taking into account all information that is available for the individual patient, and that no dosing changes should be made without careful evaluation of clinical response. Still, knowledge of the probability that a given concentration can be associated with seizure control or toxicity can be useful in specific situations. For example, in a patient with newly diagnosed epilepsy and infrequent seizures who is concerned about potential adverse drug effects and would not be excessively disturbed by the risk of having another seizure, it would make sense to adjust the dosage to achieve a relatively low target concentration. Conversely, a target concentration in the higher range would be appropriate whenever the patient's social, professional, or psychological condition makes it imperative to reduce to the very minimum the risk of seizure recurrence.

The Individual Reference Concentration

The existence of a wide variability in the concentration at which different patients respond justifies an alternative (or complementary) approach to TDM, based on the identification of the so-called *individual reference concentration*.[69] In this approach, treatment is adjusted based on the individual's clinical response (assisted, if appropriate, by monitoring serum concentrations) until a dose is identified that controls optimally the seizures without undue adverse effects. The serum concentration that is associated with that dose represents, for that patient, the *individual reference concentration* and can be helpful during subsequent management in ascertaining potential causes for a change in clinical status or in determining the need for dose adjustment. For example, if the patient will need an additional medication that is likely to increase or decrease the serum concentration of the AED, knowledge of the baseline (reference) AED concentration will allow adjusting the dose of the latter to compensate for the effect of the drug interaction. Likewise, knowledge of the *individual reference concentration* can be invaluable in clarifying the mechanisms responsible for the sudden onset of toxicity or for an unexpected recurrence of previously controlled seizures. An example is provided by a recent study that assessed serum AED concentrations in 52 patients shortly after the occurrence of a breakthrough seizure: In 44% of the cases, the serum concentration measured after the seizure was less than one-half the *individual reference concentration* that had been previously found to be associated with a good response in the same individual.[92] In most cases, this was ascribed to poor compliance. Because the *individual reference concentration* is specific for each patient, it can be used in the absence of information on the serum concentration–response relationships in a population and when such a relationship is very variable across patients. There is, however, an important caveat: At times, concentration–response relationships can change within patients, as when drug responsiveness changes as a function of brain maturation in a child, or when a medication is added that causes displacement of the monitored drug from its serum protein–binding sites.

Assessment of the Impact of Therapeutic Drug Monitoring on Clinical Outcome

Although TDM has been established as a routine aid in the effort to individualize the dosing of AEDs since the 1960s, the impact of using TDM on the outcome of drug treatment of epilepsy has rarely been assessed in a systematic manner. Open uncontrolled studies have demonstrated that the introduction of a TDM service can result in a larger proportion of patients being treated with AED serum concentrations within the recommended ranges.[34,41,49] However, studies on the effect of TDM on outcome in terms of seizure control are scarce. In fact, there are only two published randomized studies comparing the outcome of pharmacologic treatment with or without the use of TDM.[25,35] In the first, 127 chronic epilepsy patients, most on polytherapy, were randomly assigned to treatment with or without the support of TDM.[25] Blood samples for determination of drug concentrations were drawn from all patients, but for one of the two groups the treating physician was not informed about the results. Of the randomized patients, 105 completed the 1-year follow-up. The therapeutic results of the two groups were not significantly different. However, a substantial proportion of patients, similar in both groups, had AED concentrations that fell outside of the therapeutic range. This observation suggests that the physicians responsible for the treatment did not use the information provided by the TDM service, which may have affected the negative outcome of the study. Such interpretation is in line with the observations made in a retrospective analysis of 164 patients with epilepsy.[6] Seizure control one year before the introduction of TDM was compared to results one year after the service was made available. Seizure control was improved only when the physicians, according to the investigators, appropriately used information from the serum concentrations.

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Table 1. Pharmacokinetic parameters of antiepileptic drugs in adults[9,71]

Drug	Oral bioavailability	Time to peak concentration	Time to steady state	Half-life monotherapy	Half-life AED+ enzyme inducers	Serum protein binding	Main route of elimination	Tentative therapeutic range[a]	Conversion factor F µmol/L = F × µg/mL)	Documentation of/ comment on usefulness of serum drug concentration monitoring
	(%)	(h)	(d)	(h)	(h)	(%)		(µmol/L)		
				Older AEDs						
Carbamazepine	~85	4–8[b]	4–7	8–20	5–12	75	Oxidation	15–45	4.23	Useful
Clobazam	~100	1–5	4–7	15–50	<30	85	Oxidation	0.1–1.0	3.32	Limited value
Clonazepam	~100	1–3	5–10	20–60	12–46	82	Oxidation	60–220[c]	3.17	Limited value
Ethosuximide	~100	3–7	5–10	40–60	20–30	0	Oxidation	300–600	7.08	Useful
Phenobarbital	~100	2–8	10–35	50–160	50–160	50	Oxidation, *N*-glucoside conjugation, and renal excretion	50–130	4.31	Useful
Phenytoin	~100	2–8	4–8	7–60[d]	7–60[d]	90	Oxidation	40–80	3.96	Very useful
Primidone	~100	2–5	1–3	4–12	4–12	0	Cleavage of the pyrimidine ring, oxidation to phenobarbital, and renal excretion	30–60	4.58	Monitor serum phenobarbital
Valproic acid	~100	3–6[e]	2–4	11–20	6–12	78–94[d]	Oxidation and glucuronide conjugation	300–600	7.08	Useful
				Newer AEDs						
Felbamate	~100	1–4	3–5	14–22	10–20	30	Oxidation and renal excretion	125–250	4.20	Potentially of value
Gabapentin	Up to 60, decreases with increasing dose	2–3	2	5–7	5–7	0	Renal excretion	70–120	5.83	Potentially of value
Lamotrigine	~100	1–3	3–15	15–30 + VPA 30–90	8–20 + VPA 15–30	55	Glucuronide conjugation	10–60	3.90	Useful
Levetiracetam	~100	1	2	6–8	5–8	0	Renal excretion and hydrolysis	35–120	5.88	Probably of limited value
Oxcarbazepine[f]	Prodrug of MDH	4–6	2–3	8–15	7–12	40	Ketoreduction, then glucuronide conjugation of MHD	50–140	3.96	Serum MHD potentially of value

Table 2 Some general indications for therapeutic drug monitoring

1. After initiation of treatment (to provide a baseline steady-state concentration)
2. After change in drug dose, in particular when nonlinear kinetics applies (to confirm new drug concentration)
3. At therapeutic failure (to confirm or exclude a pharmacokinetic explanation for uncontrolled seizures or adverse effects
4. To identify or control for drug–drug interactions
5. After a change in drug formulation
6. When pharmacokinetic alterations due to physiologic or pathologic changes are anticipated (e.g., pregnancy, hepatic disease, renal disease, gastrointestinal conditions potentially affecting drug absorption)
7. When poor compliance is suspected
8. Routine sampling annually of phenytoin because of saturation kinetics

The second and most recent randomized, controlled trial on the impact of TDM included 180 newly diagnosed, previously untreated patients with epilepsy who were about to start treatment with an older-generation AED.[35] The majority of the included patients were prescribed carbamazepine, and only a small fraction were on phenytoin. Patients were randomized to either treatment with dosage adjusted on clinical grounds alone or treatment with dosage adjusted to achieve serum concentrations within predefined target ranges. Both groups were followed for 24 months. There were no significant differences between the two groups with respect to patients achieving 12-month remission, patients remaining seizure free since initiation of treatment, time to first seizure or to 12-month remission, or frequency of adverse effects. Hence, this study could not demonstrate an effect of routine use of TDM on the clinical outcome of early treatment of epilepsy. In contrast, a small retrospective study from Mumbai, India, indicated that TDM can improve outcome in patients with established "generalized tonic–clonic epilepsy."[79] The proportion of patients with seizure control was higher and the frequency of adverse reactions lower among 25 epilepsy patients who had undergone TDM at least twice a year compared with 25 matched epilepsy patients from the same epilepsy clinic who had not. Unfortunately, there is no information on the type of AEDs prescribed in this study. Although the retrospective design calls for caution in interpretation, the results suggest that TDM can have an impact on outcome in special situations and settings despite the negative findings from randomized studies.

The cost-effectiveness of TDM has recently been assessed in a systematic review.[96] Based on a low level of evidence (level 3), the review concluded that TDM of older-generation AEDs can lead to better control of patients with fewer side effects and be cost-effective. Furthermore, TDM of the new AEDs was considered useful in titrating patients whose epilepsy is difficult to control and in case of questionable compliance and drug–drug interactions.[97]

Thus, there is an obvious need for studies assessing the impact of TDM on the outcome of treatment. Although the two available randomized studies did not provide evidence for the usefulness of routine monitoring of AEDs in general, this does not exclude the value of TDM in special situations.

Table 3 Enzyme-inducing properties of antiepileptic drugs (AEDs)

Non-enzyme-inducing AEDs	Broad-spectrum enzyme-inducing AEDs
Ethosuximide	Carbamaxepine, phenytoin, phenobarbital, primidone
Gabapentin	
Levetiracetam	Narrow-spectrum enzyme-inducing AEDs,[a]
Pregabalin	Felbamate, lamotrigine, oxcarbazepine, topiramate
Tiagabine	
Valproic acid	
Vigabatrin	
Zonisamide	

[a] Felbamate, lamotrigine, topiramate (at doses >200 mg/d), and oxcarbazepine may reduce the serum concentrations of steroid oral contraceptives. Felbamate and oxcarbazepine may reduce the serum concentrations of some other cytochrome P450 substrates; both felbamate and oxcarbazepine may also act as enzyme inhibitors as well as enzyme inducers.

Use of Therapeutic Drug Monitoring in Various Clinical Settings

TDM is of particular value in situations in which clinical effects are difficult to assess and when there is intra- or interindividual variability in drug concentrations that may account for differences in treatment outcome. Examples are discussed in this section; some general indications for TDM are summarized in Table 2.

Settings in Which Clinical Assessment of Effects Is Particularly Difficult

The optimal dose of any AED for a patient with newly diagnosed epilepsy can only be defined clinically after considerable follow-up of the effects of the prescribed treatment. Evidently, most patients would prefer to get the optimal dose from onset rather than having it titrated against toxic effects or continued seizures. Although evidence for the effectiveness of the procedure is lacking, it is therefore advisable to measure the serum concentration of a newly initiated AED once steady-state concentration has been achieved. The value of such concentrations is higher for drugs with reasonably established concentration–effect relationships and is particularly high for a drug such as phenytoin with complicated pharmacokinetics. Although strict adherence to therapeutic ranges is unjustified, the measured concentration could be used for consideration of dose adjustments based on the individual patient's treatment priorities. Even if such an initial steady-state serum concentration does not prompt a dose adjustment, it can be of value as a reference to facilitate interpretation of future drug concentrations associated with toxicity or therapeutic failure.

Some adverse effects of AEDs, not least those affecting cognition, are difficult to identify in certain patient groups with limited abilities to communicate. This includes young children, people with learning disabilities, and elderly patients with dementia. Wide indications for TDM on suspicion of concentration-related adverse effects are therefore justified in these patient groups.

There are also situations in which toxic symptoms and signs might be difficult to distinguish from those of undertreatment. Many AEDs may have a paradoxical seizure-aggravating effect as one manifestation of overdosing.[70] Nonconvulsive status epilepticus, other subtle seizures, and effects of subclinical ictal discharges, on the other hand, can be misinterpreted as a sign of AED toxicity. A drug concentration obtained in situations of seizure aggravation, impaired consciousness, or sedation can help to resolve the issue.

Settings With Alterations in Pharmacokinetics

Pharmacokinetics can change due to physiologic factors, pathologic states, and drug–drug interactions, all of which can potentially result in modified effects. Correctly applied, TDM can identify such alterations and facilitate dose adjustments to maintain efficacy. For example, unless the dosage is adjusted, serum concentrations will change as children grow, partly because of increased body weight, but also due to changes in clearance and other pharmacokinetic parameters.[29] It thus might be justified to monitor AED concentrations at regular intervals in children during their growth, more frequently in children with unstable seizure control, and at longer intervals among those with mild epilepsy.

Age-related alterations in pharmacokinetics occur also at the other end of the age spectrum. Decreased binding to serum proteins, increased volume of distribution, and reduced metabolic and renal capacity can all be seen to a variable degree among the elderly. This complicates prediction of the pharmacokinetics of AEDs in elderly patients[72] and justifies the use of TDM. However, elderly patients seem to obtain seizure control and experience adverse effects at lower serum concentrations than do patients in other age groups,[77] which has to be taken into account in the interpretation of drug concentrations. In addition, an age-related decrease in binding to serum proteins can result in total serum concentrations underestimating the effects of highly bound AEDs, such as valproic acid and phenytoin. Measuring unbound concentrations of these AEDs might thus be preferable in the elderly.

Pregnancy is another physiologic condition that affects the pharmacokinetics of AEDs to an extent that may require dose adjustments.[66,95] The effect of pregnancy on drug disposition varies with different AEDs, and the extent of the effect on a specific AED will also vary among patients.[95] Serum concentrations of most older-generation AEDs tend to decrease during pregnancy.[96] For valproic acid, and to some extent phenytoin, the decline in total concentration is due to a decrease in protein binding, a mechanism that might not imply major changes in the unbound concentration of the drug. A fall in the serum concentrations of other AEDs is mainly related to enhanced metabolism.[95] The most pronounced effects of pregnancy have been reported with lamotrigine, with average concentrations in late pregnancy of only approximately 30% of pre-pregnancy concentrations.[19,56,66,98] Preliminary observations suggest that the serum concentration of the active monohydroxy derivative (MHD) of oxcarbazepine may also decrease markedly during pregnancy.[48] The effect of pregnancy on the pharmacokinetics of other new-generation AEDs has not been adequately explored. In general, because of the possibility of pharmacokinetic changes, monitoring drug concentrations is recommended during pregnancy. Unbound drug concentrations should ideally be measured for highly protein-bound AEDs. The timing and frequency of drug concentration monitoring during pregnancy need to be individualized based on the type of AED used and on patient characteristics. A schedule of once in each trimester is often recommended and is probably sufficient in most cases. More frequent sampling is advisable in patients with complicated epilepsy and in patients under treatment with lamotri-gine. The need for monitoring in the postpartum period depends on the clinical situation and whether dose changes were made during pregnancy.

Pathologic states such as hepatic or renal disease can also affect the pharmacokinetics of AEDs and its predictability.[73] Hepatic disorders can be associated with a reduced capacity to eliminate the many AEDs that undergo extensive metabolism. In addition, binding capacity to serum proteins can be reduced. Serum concentration monitoring is indicated to control for such pharmacokinetic alterations for AEDs that are metabolized or highly bound to serum proteins. Renal failure is also associated with reduced binding of AEDs to plasma proteins. It will also affect the elimination of AEDs that are excreted unchanged through the kidneys. Although the latter correlates with creatinine clearance, measuring serum concentrations of AEDs and, when appropriate, unbound serum drug concentrations is a more direct method for assessing the pharmacokinetic consequences of renal failure.

Pharmacokinetic interactions between AEDs and between AEDs and other drugs are common.[62,63] Interactions involving displacement from plasma proteins will generally not alter the effects of treatment, but they can lead to misinterpretation of the total drug concentrations. Drugs that induce or inhibit the metabolism of an AED, however, can modify the effect of treatment. These interactions are frequent, and the resulting changes in serum AED concentrations are often difficult to predict. Monitoring AED concentrations is therefore recommended whenever a pharmacokinetic interaction can be expected. Ideally, a baseline serum concentration should be obtained before adding the interacting drug and when the effects of combination treatment are stabilized. Because drug interactions are frequent and not always known beforehand, monitoring drug concentrations should be considered whenever addition of a new drug is followed by an unexpected change in clinical state. This will help to distinguish pharmacokinetic from pharmacodynamic interactions, facilitate dosage adjustments, and identify previously unknown interactions.

A change in drug formulation, for example, from brand name to generic or between generics, is another situation in which TDM can be indicated to control for differences in pharmacokinetics. This is particularly important for a drug like phenytoin that has dose-dependent kinetics. Because of these characteristics, any dose adjustment of phenytoin should also be monitored by TDM.

Settings With Unexpected Clinical Response

TDM can be useful in assessing the reasons for an unexpected drug response, clarifying whether this has a pharmacokinetic explanation. A serum concentration should be obtained whenever seizures persist despite a reasonable dose of an appropriate AED. This will help in the recognition of patients who need higher doses because of unusually efficient drug elimination and also those that fail to take the drug as prescribed. A pronounced variation in repeated drug concentrations can indicate noncompliance.[42] Measuring drug concentrations in conjunction with breakthrough seizures has been suggested as another method. Postictal drug concentrations considerably lower than a baseline value for the same patient are likely to imply poor compliance.[92] TDM also facilitates the interpretation of suspected dose/concentration-related adverse effects of AEDs. Trough concentrations obtained before the morning dose should be the routine, but sampling at the time of adverse effects is rational if symptoms are intermittent and suspected to be related to fluctuations in serum concentrations.

Time of Sampling

TDM can be rendered ineffective by random sampling. It is important to ensure that sampling occurs at steady state, which occurs at four to five half-lives after starting treatment or a dose change. For drugs with a short half-life, such as carbamazepine, valproic acid, gabapentin, levetiracetam, pregabalin, tiagabine, vigabatrin, and, in enzyme-induced patients, lamotrigine and topiramate, it is important to standardize the sampling time in relation to dose. Patient noncompliance within a period of three to four half-lives before the blood sample is drawn can

significantly affect the blood level and cause misinterpretation of the result. The ideal blood sampling time for all AEDs is immediately before the next oral dose (trough), but if this is not possible, it is desirable to note the sampling time and the time medication was last ingested. In some cases, two blood samples, for example, one taken at the time of trough and a second taken at the expected time of peak (or in conjunction with the appearance of symptoms suggestive of transient concentration-related toxicity), could be valuable for optimizing the dosing schedule.

If blood sampling is undertaken before steady state, serum concentrations for a given dose will be underestimated. Consequently, if a dose increase is undertaken, this will eventually result in unnecessary toxicity for the patient. In the case of carbamazepine, sampling before autoinduction is complete will result in overestimation of the steady-state concentration. This can result in a dose that is subtherapeutic, and patients may continue to have unnecessary seizures. A meticulous dosage history is therefore required. During overdose, sampling should be undertaken as soon as the patient presents at casualty.

Biologic Matrixes

The matrix of choice for TDM is usually serum or plasma, which can be used interchangeably, although it is preferable to use one or the other consistently. Other biologic matrixes that have been investigated include whole blood, saliva, tears, and hair.

Interest in saliva began in the 1980s when it was suggested that saliva could be used as an alternative to serum. Several recent developments in sample collection and analytical techniques and the growing interest in unbound drug monitoring have provided a renewed interest in saliva monitoring of AEDs.[43] Its value relative to blood sampling can vary in different clinical settings. Collection of saliva is simple and noninvasive; does not require expertise in drawing blood, so that sampling can be undertaken by patients; can be especially useful in patients with disabilities; and is preferred by children and their parents. In addition, for some drugs, measured concentrations reflect the unbound (pharmacologically relevant) concentration in blood. Drawbacks of saliva include the difficulty of measuring concentrations that might be lower than total serum concentrations, the unacceptability of this matrix for some patients, and the possibility of unreliable results due to the presence of drug residues in the mouth or leakage of drug-rich exudate, particularly in patients with gingivitis. There are substantial data suggesting useful correlations between saliva concentrations and free (unbound) serum concentrations for many AEDs.[31,51,52,87] This is not the case for valproic acid, and there is some controversy for phenobarbital.

Analysis of AEDs in scalp hair can provide another useful approach because content has been shown to reflect the mean blood level profile over a prolonged period prior to sampling,[104] and in addition hair sampling is noninvasive (assuming that hair is not at a premium). Because hair acts as a "tape recorder," drug concentration in different hair segments can reflect a history of drug ingestion over a period of months or years (depending on the length of hair), thereby providing data on patient long-term compliance in different periods.[45,103,105]

Analytical techniques

Commercial reagents used in conjunction with a variety of analyzers form the basis for the analysis of the established AEDs (carbamazepine, phenytoin, phenobarbital, primidone, ethosuximide, and valproic acid). For the benzodiazepine drugs (clobazam, clonazepam, and diazepam) and AED metabolites that are pharmacologically active (e.g., carbamazepine-10,11-epoxide and *N*-desmethylclobazam) analysis can only be undertaken by use of chromatographic techniques[85,88] that require specialized equipment and advanced know-how.

Commercial immunoassays are available for topiramate and zonisamide, and those for others, including lamotrigine, are under development.[11] Other new AEDs can only be measured by high-performance liquid chromatography using primarily ultraviolet (UV) detection, but some AEDs require more difficult detection techniques such as fluorescence (e.g., vigabatrin, gabapentin, and pregabalin) and electrochemical (e.g., tiagabine) techniques. Because of the relative ease of use of UV detection, numerous chromatographic techniques have been described for lamotrigine, oxcarbazepine, levetiracetam, felbamate, and zonisamide,[7,26,80] and to increase assay efficiency in terms of both cost and turnaround times, methodologies have been developed whereby these new AEDs are simultaneously measured along with old-generation AEDs.[17,46,57,84]

Various chromatographic fluorescence detection techniques have been described for vigabatrin, gabapentin, and pregabalin, and techniques that involve simultaneous analysis of two or three of these AEDs may be preferable.[81,100] The most difficult AED to analyze is tiagabine, partly because its clinically occurring concentrations in serum are in the nanomolar range (in contrast to micromolar range for all other AEDs) and also because electrochemical detection is more difficult.[32]

Direct Measurement of Unbound Drug Concentrations

The techniques used most commonly involve ultrafiltration of the serum sample to separate a protein-free fluid containing the unbound drug. Important considerations are that unbound concentration values can vary depending on the technique used (e.g., ultrafiltration vs. dialysis) and are temperature dependent (they vary inversely with the temperature at which the separation of unbound drug is accomplished), and therefore results obtained with different techniques are not interchangeable.

Table 4 Pharmacologic factors of importance for the therapeutic drug management of antiepileptic drugs

Mechanism of action	Reversible, except for vigabatrin
Active metabolites	Carbamazepine, clobazam, oxcarbazepine, and primidone
Interindividual variability in pharmacokinetics	Pronounced for clobazam, clonazepam, carbamazepine, felbamate, gabapentin, lamotrigine, phenytoin, tiagabine, topiramate, valproic acid, and zonisamide
	Moderate for ethosuximide, oxcarbazepine, phenobarbital, and primidone
	Slight for levetiracetam, pregabalin, and vigabatrin
Linearity in pharmacokinetics	At therapeutic doses, no major deviations from linearity for clobazam, clonazepam, ethosuximide, felbamate, lamotrigine, oxcarbazepine, phenobarbital, pregabalin, primidone, tiagabine, topiramate, and zonisamide
	Phenytoin shows Michaelis-Menten kinetics; gabapentin, dose-dependent bioavailability; carbamazepine, dose-dependent autoinduction; valproic acid, concentration-dependent plasma protein binding

Relevance and Application of Therapeutic Drug Monitoring in Relation to Individual Antiepileptic Drugs

The value and applicability of TDM are influenced by the pharmacologic properties of the drug to be monitored. The properties of importance for TDM are summarized in Tables 1, 3, and 4 and are referred to in the text for the individual drugs.

Therapeutic ranges of serum concentrations have been proposed for most of the older AEDs, particularly phenytoin, phenobarbital, carbamazepine, ethosuximide, and valproic acid. The usefulness of TDM for clonazepam, clobazam, and primidone is limited because of the poor correlation between their serum concentration and effects and because this relationship can change with time. More work is needed to assess the value of TDM for the newer AEDs, although at least for lamotri-gine and topiramate there is increasing experience that measuring drug concentration can be of considerable help for clinical management.

In the following, both older and newer AEDs are discussed in order of importance in terms of need for and usefulness of TDM.

Older Antiepileptic Drugs

Phenytoin metabolism follows Michaelis-Menten rather than first-order kinetics. The hepatic enzymes responsible for phe-nytoin metabolism become saturated within the clinically occurring serum concentration range, and therefore the time needed to attain steady state increases with increasing serum concentration. Because phenytoin follows nonlinear kinetics, even a slight inhibition of metabolism can lead to a considerable increase in its serum concentration and pharmacologic effect. Its high protein binding with consequent variability in the fraction of unbound, pharmacologically active drug can also be important. The main interactions between phenytoin and other drugs are probably those that lead to an inhibition of phe-nytoin metabolism. Due to the special pharmacokinetic features of phenytoin, use of this drug is difficult without serum concentration monitoring. For most patients the optimal serum concentration is within a range of 40 to 80 µmol/L (10 to 20 µg/mL).[5,8,55,71]

Carbamazepine metabolism can vary considerably, resulting in a poor correlation between dose and serum concentration. The half-life during long-term treatment is considerably shorter than following a single dose, because of autoinduction. The main metabolite of carbamazepine, carbamazepine-10,11-epoxide, contributes to the pharmacologic effect, and its measurement can be useful in special cases (e.g., when the metabolite is suspected to be contributing to toxicity). A number of drugs can influence the pharmacokinetics of carbamazepine. Optimal responses are usually achieved at serum carbamazepine concentrations in the range of 15 to 45 µmol/L (4 to 12 µg/mL).[5,8,55,71]

Phenobarbital metabolism is particularly slow (although the half-life is shorter in children than in adults), and diurnal variations in steady-state drug concentration are therefore small within individuals taking a constant dose. Some drugs, particularly valproic acid, can increase the serum concentration of phenobarbital. The relationship between the serum concentration of phenobarbital and adverse central nervous system effects varies with the development of tolerance. For phenobarbital most patients are optimally treated with serum concentrations between 50 and 130 μmol/L (10 to 30 μg/mL).[4,8,55,71]

Valproic acid disposition is influenced by several factors. Due to interindividual differences in metabolism, there is a poor correlation between the dose and the serum concentration. As with other AEDs, children need higher doses in terms of milligrams per kilogram of body weight than do adults. Enzyme-inducing AEDs lower serum valproic acid concentrations (Table 3). Valproic acid is highly protein bound, and the binding is concentration dependent, especially at serum concentrations in the high range. Most patients are optimally treated with serum valproic acid concentrations between 300 and 600 μmol/L (50 to 100 μg/mL).[4,8,55,71]

Ethosuximide elimination is slow, and its serum concentration is relatively stable even if the drug is given once a day. The half-life in children, however, is considerably shorter than in adults. Due to interindividual differences in ethosuximide pharmacokinetics, it is not possible to predict the serum concentration following a certain dose. In most patients, therapeutic effects are observed at serum concentrations in the range of 300 to 600 μmol/L (40 to 80 μg/mL).[4.55,63,71]

Clonazepam serum concentrations are linearly correlated with dose. The half-life is shorter in children than in adults, and serum concentrations are lowered by concomitant use of enzyme-inducing AEDs. In general, a clear relationship between serum concentration and effect has not been established. In patients treated with therapeutic doses of clonazepam, serum concentrations on the order of 60 to 220 nmol/L (20 to 70 ng/mL) have been reported.[20,40,55]

Clobazam is mainly metabolized to its desmethyl metabolite, which is also pharmacologically active. The metabolite has a much longer half-life than clobazam, and its steady-state serum concentrations are at least eight times higher than those of the parent compound. In general, clinically significant pharmacokinetic interactions between clobazam and other major AEDs are uncommon, although clobazam metabolism is inducible. Because of the active metabolite and development of tolerance to the adverse and, at times, therapeutic effects, no clear correlation exists between serum clobazam concentrations and effect. In patients treated with therapeutic doses of clobazam, serum concentrations on the order of 0.1 to 1.0 μmol/L (30 to 300 ng/mL) for the parent drug and 1 to 10 μmol/L (300 to 3,000 ng/mL for the metabolite desmethylclobazam have been reported.[8,55,83]

Primidone is rapidly metabolized to two active metabolites, phenobarbital and phenyl-ethyl-malonamide (PEMA), and both compounds accumulate during long-term treatment. Primidone probably also has an anticonvulsant effect of its own. There is a great individual variability in the relationship between primidone dose and the concentration of the drug and its metabolites. Because primidone is metabolized to phenobarbital, most often the phenobarbital concentration is used as a guide to therapy. Primidone serum concentrations per se are usually in the range of 30 to 60 μmol/L (5 to 10 μg/mL).[4,90]

Newer Antiepileptic Drugs

Lamotrigine has several pharmacokinetic characteristics that suggest that its use can be optimized by applying TDM. Its serum half-life is shortened by enzyme-inducing AEDs, is considerably prolonged by valproic acid, and is intermediate in patients treated with both enzyme-inducing AEDs and valproic acid. Lamotrigine clearance is higher in children and somewhat reduced in elderly patients. There are large interindividual variations in serum concentrations in patients on monotherapy, and the kinetics is also influenced by interacting AEDs, pregnancy, and oral contraceptives.[5,55,71] In most studies there is an overlap in serum lamotrigine concentrations between responders and nonresponders and also between patients with or without side effects. However, the risk of toxicity increases considerably with concentrations >60 μmol/L (15 μg/mL), although such concentrations seem to be tolerated in many patients. In patients treated with therapeutic doses, serum lamotrigine concentrations on the order of 10 to 60 μmol/L (2.5 to 15 μg/mL) have been reported.[36,37]

Topiramate shows a wide scatter of serum concentrations among patients taking the same dose and wide variation in the relationship between its concentration and therapeutic or toxic effects. Children require a higher dosage in terms of milligrams per kilograms of body weight than do adults to obtain similar serum concentrations. Serum concentrations of topiramate are lowered by enzyme-inducing AEDs.[3,71] In patients treated with therapeutic doses, serum topiramate concentrations on the order of 15 to 60 μmol/L (5 to 20 μg/mL) have been reported, even though most patients will probably have concentrations in the low to mid range with the dose regimens used today.[15,36,37,101,108]

Felbamate disposition is variable. The half-life is shorter in patients on enzyme-inducing AEDs, somewhat prolonged by valproic acid, and longer in renally impaired patients. Clearance is higher in children and lower in the elderly. Monitoring felbamate concentrations can be useful because serum concentrations are not easily predicted from administered doses, especially in patients on polytherapy.[3,33,55,71] In patients treated with therapeutic doses, serum felbamate concentrations on the order of 125 to 250 μmol/L (30 to 60 μg/mL) have been reported.[36,37]

Oxcarbazepine, the 10-keto analog of carbamazepine, is rapidly metabolized to the pharmacologically active MHD (10-hydroxycarbazepine). Elimination is faster in children 2 to 6 years of age than in older children and adults. Conversely, MHD clearance is reduced in the elderly. The metabolism of MHD is enhanced by enzyme-inducing AEDs, which decrease the MHD concentration/dose ratio.[5,55,71] Retrospective analysis of a large number of patients showed a mean serum MHD concentration of 20 μmol/L (5 μg/ml) (range: 12 to 160 μmol/L [3 to 53 μg/mL]), but no detailed correlations with response were presented.[24] In a small study of seizure-free patients the mean MHD concentration was 64 μmol/L (16 μg/mL) (12 to 128 μmol/L [3 to 32 μg/mL]), which was similar to that observed in nonresponders.[99] Somewhat higher concentrations have been reported in children in whom side effects were more frequent at serum concentrations of 140 (35 μg/mL) to 160 μmol/L (40 μg/mL). In patients treated with therapeutic doses of oxcarbazepine, serum concentrations of MDH are on the order of 50 to 140 μmol/L (12 to 35 μg/mL).[36,37]

Zonisamide pharmacokinetics does not appear to show major deviations from linearity at daily doses up to 10 to 15 mg/kg. Its half-life is considerably shortened by enzyme-inducing AEDs, and children require higher doses in terms of milligrams per kilogram body weight than do adults to achieve any given serum concentration. A considerable overlap of serum concentrations between seizure-free patients and non-responders, or between patients with and without adverse effects, has been observed.[53,55,71] No clear relationship between zonisamide serum concentrations and clinical response has been established, but a range of 45 to 180 μmol/L (10 to 38 mg/mL) has been reported in patients treated with therapeutic doses.[36,37]

Levetiracetam excretion is primarily renal. Its half-life is shorter in children and somewhat prolonged in elderly patients. Children seem to need higher doses of levetiracetam in terms of milligrams per kilogram of body weight than do adults to achieve a given drug concentration. Enzyme-inducing AEDs can moderately lower serum levetiracetam concentrations.[16,55,58,71] The role of TDM for levetiracetam has not been established, but there might be useful applications in addition to ascertaining compliance. In patients treated with therapeutic doses, serum levetiracetam concentrations on the order of 35 to 120 μmol/L (8 to 26 μg/mL) have been reported.[36,37]

Gabapentin pharmacokinetics can be very variable, possibly because the absorption mechanism from the gut becomes saturated. The drug is excreted renally, and a decrease in dose may be necessary in elderly patients. Gabapentin has a low drug interaction potential. Cimetidine can reduce the renal clearance, however, and antacids can reduce the absorption of gabapentin.[49,55,71] A wide range of serum concentrations associated with seizure control has been observed. In patients treated with therapeutic doses, serum gabapentin concentrations are on the order of 70 to 120 μmol/L (12 to 20 μg/mL).[36,37]

Tiagabine is extensively metabolized and has a short half-life (5 to 8 hours). Clearance is higher in children than in adults, and its metabolism is inducible. There are large intraindividual and interindividual variations in serum concentration. Due to the short half-life, there are also large tiagabine interdose fluctuations in serum concentration. The high protein binding with consequent variability in the fraction of unbound, pharmacologically active drug might also be important.[55,71] Information on concentration–effect relations with tiagabine is scarce, and difficulties with measuring its low serum concentrations have resulted in poor analytical reliability in some laboratories.[102] In one study, trough concentrations >96 μmol/L (40 μg/mL) were reported to be associated with the greatest reduction in seizure frequency.[86] In patients treated with therapeutic doses, serum tiagabine concentrations are on the order of 50 to 250 nmol/L (20 to 100 μg/mL).[36,37]

Pregabalin is excreted renally in unchanged form, and pharmacokinetic drug–drug interactions involving pregabalin are therefore unlikely. Dose adjustment, however, might be necessary in patients with renal insufficiency.[8] Data on TDM for pregabalin are scarce. Berry and Millington[10] reported on concentration measurements in predose samples from a group of patients escalated up to a maximum of 600 mg daily and found a range of 18 to 52 μmol/L (2.8 to 8.2 μg/mL) at steady state.

Vigabatrin is not metabolized and is mainly excreted unchanged in urine. A dose reduction is required in patients with impaired renal function. The half-life of vigabatrin is very short (6 to 8 hours), and drug–drug interactions are minimal.[55,71] Monitoring the serum concentrations of vigabatrin may not be of great value as a guide to therapy due to its irreversible mechanism of action. Because of long-lasting inhibition of gamma-aminobutyric acid transaminase, the antiepileptic effect of vigabatrin outlasts its presence in serum. However, it might be useful to employ serum vigabatrin concentrations as a check on recent compliance.[36,37]

Summary and Conclusions

The use of TDM, which entails that AED concentrations are always interpreted in conjunction with the clinical status of the patient, can provide important information in making therapeutic decisions (Table 4). Because clinical effects can be more closely related to drug concentrations than to dose, drug concentrations can be used as surrogate for both therapeutic and adverse effects. Interpretation of drug concentrations

requires an understanding of both the pharmacokinetics and pharmacodynamics of the drugs and is made easier if simple dosage regimens are used in conjunction with optimum timing of blood sampling. For highly protein-bound AEDs (e.g., phenytoin and valproic acid), altered plasma protein binding is an important cause of misinterpretation of serum drug concentrations, and in certain clinical settings (e.g., pregnancy and postsurgery) patient management may be best guided by monitoring free (non–protein-bound) concentrations. The indications for monitoring the new AEDs are the same as for older-generation AEDs, although for newer AEDs the optimal ranges of serum concentrations have not been extensively investigated. In any case, for all AEDs the therapeutic range be considered should not as a concentration interval appropriate for all patients, but instead as an expression of the probability of beneficial effects with an acceptable risk of toxicity in a population. Indeed, because the optimal concentration varies among patients, the concept of an *individual reference concentration* is advocated. Furthermore, it is increasingly being recognized that the lower limit of the therapeutic range is of little value because many patients do well with lower serum concentrations.

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Chapter 104

Efficacy of Antiepileptic Drugs

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Introduction

Since 1962, when the Kefauver-Harris Drug Amendments were passed, proof of effectiveness and evidence of reasonable safety have been required to obtain regulatory approval from the Food and Drug Administration (FDA) before a drug can be marketed to the public in the United States. Previously, drugs could be marketed if they were safe and contained what the label indicated, but proof of efficacy was not required. Hence, the antiepileptic drugs that were available before 1962 came to market without scientific studies that established their efficacy in preventing seizures.

The efficacy of an antiepileptic drug is its ability to prevent or interrupt seizures. However, efficacy is only one of several components of a drug's actions that contribute to its clinical usefulness or clinical effectiveness. Whereas the information about efficacy as an isolated variable can be determined readily in experimental animals, actual measures of efficacy generally cannot be obtained in humans because assessment of seizure-suppressing activity is confounded by the occurrence of adverse side effects. As a result, in patients, the term *clinical efficacy* or *clinical effectiveness* is more appropriate even though the term *efficacy* is widely used colloquially.[46] This chapter addresses basic aspects of drug efficacy as well as the clinical effectiveness of antiepileptic drugs in clinical settings.

Basic Measures of Drug Efficacy

Efficacy has two key dimensions: (a) potency and (b) spectrum of activity against different types of seizures. Efficacy is quantified by the term *drug potency*, which refers to the amount of a drug that is needed to produce a defined action. The less of a drug required, the higher is the potency. In measuring antiepileptic action, drug potency can be expressed in several ways. One of the most common ways is to describe the dose of drug that prevents seizures in 50% of experiments, which is abbreviated as ED_{50}. Potency could also be expressed in other ways, such as the minimally effective dose or as the concentration of medication that produces the desired action.

In animal models used for screening antiepileptic drugs, seizures are induced by various techniques such as electroshock or chemoconvulsant administration. These models provide standardized systems in which progressively increasing doses of a drug can be evaluated (Fig. 1). However, due to concerns about drug-induced adverse effects that might occur when very high doses are administered to humans, a comprehensive assessment of efficacy per se cannot be obtained in people. Instead, what is measured and what is most important in patients is *clinical effectiveness*.

Drug toxicity can be quantified in animals using approaches similar to those used to determine efficacy except that the experimental endpoint is a toxic outcome. The rotorod test is a widely used measure of toxicity for antiepileptic drugs in animals. Although this test has little relevance to humans, we mention it here because it has a well-defined outcome and illustrates an idealized measure of drug toxicity. The experimental animal, usually a mouse, is placed on top of a slowly rotating rod. Normal mice can maintain their balance on the rod indefinitely; intoxicated mice fall off the rotating rod, thereby providing a clear experimental endpoint of drug intoxication. By administering progressively larger doses to groups of mice and then testing their ability to stay atop the rotating rod, one can find the dose that produces toxicity in 50% of the mice (TD_{50}). No such clear-cut test exists for evaluating antiepileptic drug toxicity in humans. Furthermore, adverse effects of medications in rodents generally provide little insight into the toxicities that occur in people.

Whereas side effects impose limits on the dose of a drug that can be given, to determine the usefulness of a drug, information is needed about both drug efficacy and drug toxicity. The parameter that combines these measurements is the therapeutic index (TI). The therapeutic index is the ratio of the dose that produces toxicity in half of animals to the dose that is effective in half ($TI = TD_{50} \div ED_{50}$). The larger the therapeutic index, the wider is the margin of safety for the drug and the more likely it is that it will be clinically useful. The wider the therapeutic index, the higher is the percentage of people who are likely to benefit without limiting adverse effects. FIGURE 1 was constructed for a drug with a relatively narrow therapeutic index of 1.5 and results in a clinical dose–response curve on which the best-tolerated dose would benefit only 60% of patients.

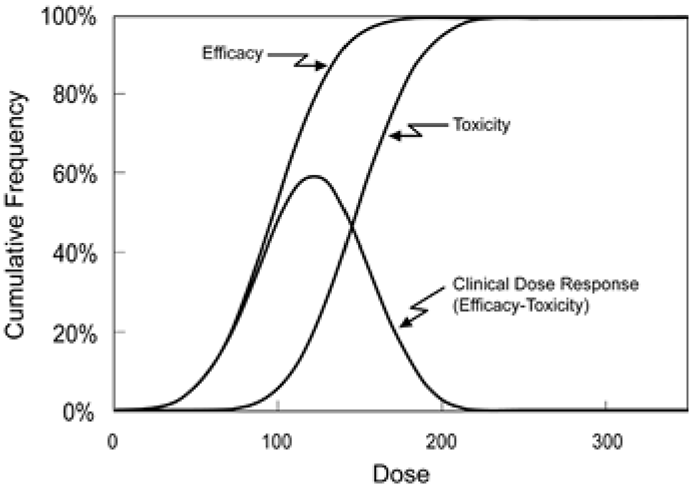

FIGURE 1. Idealized dose–response curves for efficacy and toxicity for a drug with an ED_{50} (dose of drug that prevents seizures in 50% of experiments) of 100 mg and a TD_{50} (dose that produces toxicity in 50% of subjects) of 150 mg, resulting in a therapeutic index of 1.5. The resulting clinical dose–response cure was obtained by subtracting the toxicity curve from the efficacy curve at various doses.

Table 1. Factors that influence antiepileptic drug effectiveness

Patient-related
Age
Gender
Pharmacoresistance factors

Childbearing potential and planning
Concurrent medical illness (comorbidity)
Concomitant medication
Coexisting disabilities
Socioeconomic and financial status
Lifestyle-related behaviors
Epilepsy-related
Etiology
Symptomatic
Idiopathic
Seizure type
Epileptic syndrome (type of epilepsy)
Duration of epilesy
New onset versus chronic
Drug-related
Mechanism of action
Spectrum of activity
Chemical properties and formulations
Molecular size

pKa

Lipid solubility

Dose form

Rate of release of active principle

Pharmacokinetics

Toxicity profile and therapeutic index

Commercial availability

Cost

The therapeutic index indicates the potential clinical effectiveness of a drug in patients. The limit of clinical usefulness of a drug is determined by its tolerability, where the term *tolerability* describes the collective toxicities of a drug that would lead to its being discontinued. In this chapter, the term *clinical effectiveness* is the clinical counterpart of the basic concept of the therapeutic index.

The critical contribution of toxicity to the clinical usefulness of a drug is illustrated by the drugs clonazepam and valproic acid. Among the available antiepileptic drugs, clonazepam is most potent, but it is among the least useful because of its toxicity profile and low tolerability. For practical purposes, clonazepam has an antiepileptic therapeutic index of approximately 1, which is to say that the dose that prevents seizures also causes adverse effects. On the other hand, compared to other antiepileptic drugs, valproic acid has low potency, but it is highly useful because of its even lower toxicity and better tolerability. This results in a larger therapeutic index than that of clonazepam and greater clinical usefulness. Thus, the relationship between efficacy and toxicity—the therapeutic index—is a key determinant of a drug's effectiveness and practical value. Whereas individual people differ in their sensitivity to developing side effects to a given drug, from the perspective of an individual person, the clinical effectiveness of the drug is related to the risk-to-benefit ratio for that individual.[24,46,52]

Besides the efficacy and tolerability of an antiepileptic drug, several other factors help to determine the extent to which a drug is clinically useful (Table 1). These can be categorized as patient related, epilepsy related, and drug related. Epilepsy-related factors dictate the clinical conditions in which a drug might be used. Patient-related factors influence how a drug might be suited for use in various groups of patients. Drug-related factors, such as the pharmacokinetics of the drug, affect the drug's ease of administration and have a major impact on a drug's usefulness. Drug availability and cost put practical limits on drug usefulness as well.

Methods for Establishing Drug Effectiveness

Determining the effectiveness of an antiepileptic drug is a lengthy process that evolves over time. Preclinical studies that are done to satisfy regulatory requirements start with dose-ranging and other pilot studies that provide insight into how to design scientifically sound clinical trials that can document beneficial drug action. A minimum of two clinical trials must be done, but often several more are completed before a drug is approved for public use.

Drug approval requires randomized, controlled trials. These are conducted in groups of volunteer patients with defined clinical features that are selected to minimize subject-to-subject variation and to conform to ethical human studies guidelines. Experimental controls are essential in new drug evaluation because in even the most severe forms of epilepsy, seizure frequencies fluctuate over time, resulting in appreciable placebo effects. For example, cinromide, a drug investigated in the 1970s and 1980s, appeared promising in pilot studies in preventing frequent seizures associated with the Lennox-Gastaut syndrome.[65] A randomized trial, however, disclosed that cinromide's effect was no different than placebo, and hence it was shown to be ineffective.[16]

A wide array of research designs has been used to establish antiepileptic effectiveness in humans (Table 2). Different research designs require different endpoints depending on considerations such as the duration of epilepsy among patients (chronic vs. new onset), seizure frequency, seizure severity, and characteristics of the group selected for study. For both practical and ethical reasons, during the initial phases of new drug evaluation, studies are conducted in patients with severe epilepsy whose seizures have not been controlled with available medications.

Table 2 Trial designs and investigational endpoints used to establish effectiveness of new antiepileptic drugs[20], [21], [46]

Trial designs
Adjunctive (add-on)
Crossover
Parallel groups
Presurgical drug withdrawal
Responder enriched
Conversion to monotherapy
Active control monotherapy
Investigational endpoints
Changes in seizure frequency

Proportion of responders (e.g., 50% responder rate)

Response ratio

Seizure severity

Seizure-free days

Time to *n*th seizures

Duration of therapy (life-table analysis)

Study Designs and Experimental Endpoints

Drug testing starts in patients who have epilepsy with uncontrolled seizures. Whereas these patients have the most to gain by participation in drug trials, the refractory nature of their seizures to medication makes them a challenging group in whom to show effectiveness of a new drug. The most common research design is adjunctive (also called add-on) parallel-group design in which a group of patients with uncontrolled epilepsy are randomly assigned to treatment with the investigational agent or with an inactive placebo. Later in the drug development process, the drug may be evaluated as monotherapy depending on the promise of the drug in terms of its clinical effectiveness and the manufacturer's priorities and resources. As discussed later, despite extensive preclinical testing, information about how to use new drugs in the population at large is patchy and incomplete at the time when drugs are first approved for marketing.[22]

Traditional measures of antiepileptic drug effectiveness in adjunctive studies include percentage seizure reduction from the baseline period, percentage of patients rendered seizure free, and responder rate. Change in seizure frequency is the most widely used outcome measure and is usually expressed as mean or median percentage reduction. This measure compares the seizure frequency during the treatment period to the seizure frequency during the baseline period before the investigational drug is administered. In add-on trials of new drugs, so few patients become seizure free that cessation of seizures is rarely a useful outcome measure.[15]

The responder rate is a widely used outcome when change in seizure frequency is the primary outcome measure.[1,3,45] This is the proportion of subjects whose seizure frequency decreases by various percentages from the baseline period. The proportion that is most often reported is the 50% responder rate. The 50% responder rate is the percentage of patients who experience a 50% or greater reduction in seizure frequency while taking the investigational compound as compared to their baseline seizure frequency. Other levels of response such as the 75% responder rate can be used as well,[8,19,35,48] but the 50% rate appears most often because higher responder rates are uncommon in new antiepileptic drug trials. Representative 50% responder rates during clinical trials of newer antiepileptic drugs introduced since 1992 are in the range of 20% to 50%.

Seizure severity outcomes depend on the use of rating scales or seizure scores. A number of scales have been developed to evaluate seizure severity, adverse drug effects, and overall quality of life, but there is no consensus regarding which scales are most useful. Overall, however, the cessation of seizures has the greatest beneficial impact as measured by quality-of-life scales.[13] On most scales, frequent and generalized convulsive seizures are scored as being more severe than infrequent seizures and nonconvulsive partial or absence seizures.[7,14,46,63] Note that scales for quantifying adverse effects can be better predictors of a person's completing a study than seizure counts. For example, quality-of-life measurements using the Side Effect and

Life Satisfaction (SEALS) Inventory correlated better with study completion than seizure counts in a double-blind comparison of lamotrigine and carbamazepine.[29]

The response ratio has been used infrequently as an investigational endpoint, mainly for gabapentin trials. It is the difference in seizure frequencies during the treatment period minus the frequency during baseline, which is then divided by the sum of the seizure frequencies during both periods.[26,27] The response ratio has no dimensions, and results expressed in this way are intuitively difficult to use.

The outcome of time to the *n*th seizure has also been used in presurgical monotherapy trials.[21,46,51,53,54] This endpoint is versatile, and it offers a measure of protection for patients by limiting the number of seizures that they need to experience before exiting the study and moving on to another treatment. Whereas the time to *n*th seizure outcome is useful in establishing drug effectiveness, it has not been used widely because allowing patients to have seizures while receiving only placebo or a suboptimal therapy, albeit under watchful supervision, introduces risk and raises ethical concerns.

Besides ethical concerns, there are methodologic pitfalls to the time-to-*n*th-seizure endpoint. Whereas time to *n*th seizure can rapidly detect antiepileptic effects in patients with high seizure frequencies, it is not useful for comparing the effectiveness of different drugs. Moreover, applying this endpoint can also be tricky, and if it is not used properly, a beneficial drug action can be missed. For example, if the *n*th-seizure criterion is set at, say, the second or third seizure and if the investigational drug is more effective than expected, the number of seizures that occurs in the study may be insufficient to permit the detection of a difference between treatment groups. This outcome occurred with a monotherapy trial of topiramate in which the time of the second seizure was chosen as the primary outcome variable but the patients had insufficient numbers of seizures during the study.[31] When the study was repeated with the endpoint set to time of the first seizure, the effectiveness of the drug was documented.[4]

Monotherapy Trials

Some drugs that show promise in polytherapy or adjunctive trials are subsequently tested in monotherapy. Whereas add-on study designs actually compare various drug combinations, they do not scientifically establish the effectiveness of drugs used alone in monotherapy. Establishing a drug's effectiveness in monotherapy requires randomized, controlled trials of the drug given alone. Monotherapy can be approached by eliminating other drugs from multidrug regimens or can be evaluated de novo in patients who are untreated.

The optimal design of monotherapy trials is a matter of ongoing discussion. In the United States, the FDA requires that to show efficacy the investigational compound must be superior to a comparator compound. A demonstration of equivalence to an established drug is not sufficient. Even when an active comparator is used (usually a suboptimal dose of an established drug), the investigational agent must demonstrate superiority to establish its effectiveness in monotherapy. Hence monotherapy trials for regulatory purposes in the United States require the administration of either placebo or a suboptimal dose of an established drug. As a result, ethical concerns have been raised when patients are randomized to ineffective doses of drug or placebo and thereby put at risk to the adverse consequences of recurrent seizures.[5] Unlike control patients in add-on trials, who continue to take their baseline medications, control patients in monotherapy trials may have little or no antiepileptic protection during the study.

Evolution of Clinically Relevant Prescribing Information

Although the initial randomized clinical trials provide essential data to justify a new drug's being marketed, information about the effectiveness of new drugs is incomplete when they are introduced to market.[46] This occurs for several reasons. Relatively few people will have taken the medication before it comes to market. Those who took the drug will have had atypically severe epilepsy due to high-frequency seizures with seizures that were previously medication resistant. This situation favors the use of higher doses of medication than might be required by people with milder forms of epilepsy. Similarly, patients with long-standing epilepsy who have taken antiepileptic drugs for long periods of time are likely to tolerate adverse drug effects differently than individuals who are more pharmacologically naive.[30] Finally, the duration of exposure to investigational agents in clinical trials is relatively brief compared to long-term chronic therapy. Due to differences between the way drugs are administered in regulatory trials compared to how drugs are administered in clinical practice, there is a great deal to be learned about dose and administration schedules after a drug comes to market.[46]

As experience accumulates after a drug is marketed, the picture of a drug's clinical effectiveness in the general population evolves and becomes more complete. Gaps in knowledge regarding both the efficacy and tolerability begin to be filled in as more people are treated for longer periods of time. During the early months and years when experience is increasing, information about proper dose is refined and the incidence, severity, and demographics of the drug's tolerability become better known. The process unfolds over a period of years and, in some cases, decades, causing perceptions about the effectiveness of the drug to evolve and leading to refinements in recommendations for administration.

In regulatory trials, patients take predetermined, target doses that are achieved in uniform time periods according to the research protocol. In the clinic, the tried and true approach is to “start low and go slow,” starting with a below-average dose and then slowly escalating it until either seizures are controlled or the person develops intolerable adverse effects signaling that the drug is ineffective. A slow, stepwise escalation of dose has several advantages. It allows individual patients time to develop tolerance to side effects, thereby optimizing the drug's tolerability. It also lets the clinician individualize the dose as necessary due to pharmacokinetic variability and interpersonal variability in responsiveness to the drug's actions. The go slow approach to dose escalation helps to improve seizure control even among people with chronic, severe epilepsy.[34]

The extent to which dosing recommendations change after a drug comes to market can be dramatic. In the case of gabapentin, initially recommended doses of approximately 1,200 mg/d were generally too low as compared to current target doses of 3,600 mg/d. For topiramate, dosing guidelines initially were too high, approximately twice as high as currently recommended starting doses. Early investigations of topiramate evaluated doses of 1,000 mg/d,[58] and when topiramate first went to market, the recommended dose of 400 mg/d was twice as high as the current generally recommended initial target dose of 200 mg/d.[18,57] For lamotrigine, the recommended schedule for implementing therapy was slowed after recognition of the heightened risk of Stevens-Johnson syndrome when the dose was escalated more rapidly. Hence, after a drug comes to market, guidelines for administration nearly always change as experience identifies areas for needed refinements.

Drug tolerability is another area in which knowledge increases because so few people have taken drugs during premarketing drug evaluation.[22,62] Regulatory studies customarily require that the drugs be administered to a few thousand people, typically 2,000 to 5,000. If a drug causes an adverse effect at a frequency of <1 in 5,000, that adverse effect is likely to go undetected in preclinical drug trials. As a rule of thumb, adverse effects usually are not detected until at least three times as many people as the frequency of the side effect have been ex-posed. For example, for a side effect that occurs in 1 per 5,000 patient exposures, 15,000 or more people would need to be exposed to have a 95% probability of at least 1 patient developing such an effect. Furthermore, whether the side effect gets attributed to the medication is influenced by other factors, including its severity and the sensitivity of the surveillance system. Even when adverse effects are severe and dramatic, they can go unrecognized for surprisingly long periods of time. With the drug felbamate, which caused fatal adverse effects in 1:2,500 to 1:5,000 people, approximately 100,000 people were exposed in the first year after the drug went to market before the alarm was sounded. When a side effect such as osteopenia is subtle and slow to develop, extremely long periods of time elapse before the full picture is discerned. It took years before visual changes, endocrinologic disturbances, and reduced bone density were recognized as consequences of treatment with vigabatrin, valproic acid, and phenytoin, respectively.

Ultimately a drug's adverse effect profile—its tolerability—strongly shapes perceptions of its effectiveness and clinical usefulness.

Comparisons of Antiepileptic Drugs

Which drug is best for patients who have a specific seizure type or type of epilepsy? With newer drugs, the question is unresolved. The best way to answer this question is to compare different drugs in the same investigation, so-called head-to-head comparisons. For drugs that were introduced before 1990, the U.S.

Veterans Administration (VA) collaborative studies provided the gold standard for how to approach the question of drug superiority.[42]

The landmark studies sponsored by the VA compared the most commonly prescribed antiepileptic drugs in the 1980s administered in monotherapy by using life-table data analysis. Among all the methods for comparison of antiepileptic drugs, many feel that the duration of continuation of a drug during a trial expressed in a life table is the best measure that combines efficacy and toxicity in order to demonstrate clinical effectiveness.[46] Life-table analysis measures how long patients continue on an investigational agent and reflects the net consequences of beneficial and negative attributes of a drug. Results are expressed as the percentage of patients continuing treatment at periodic time points after the initiation of therapy.[40]

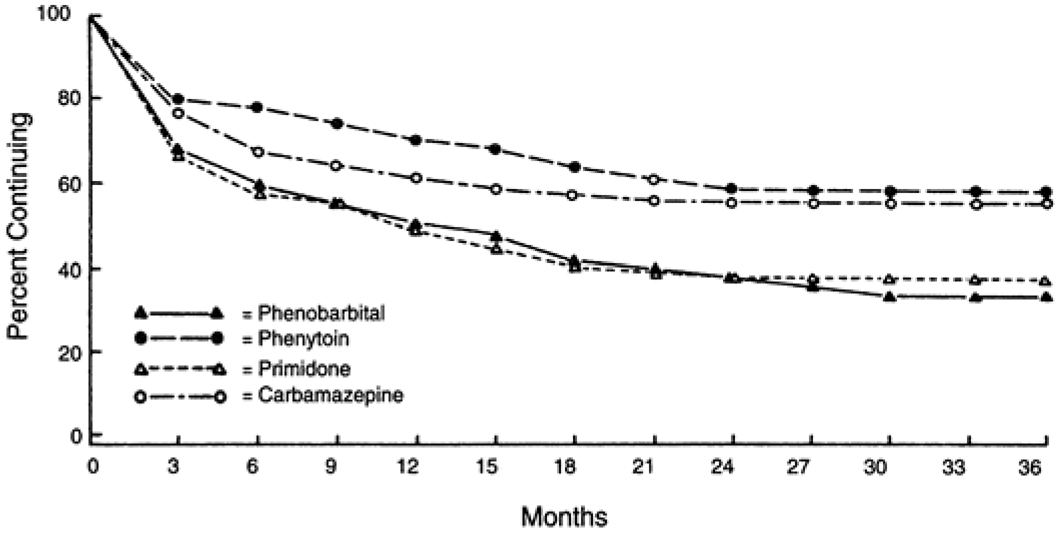

FIGURE 2. Veterans Administration randomized, controlled trial of carbamazepine, phenobarbital, phenytoin, and primidone in previously untreated or undertreated epilepsy. Cumulative percentage of patients with partial seizures that were treated with each drug during 36 months of follow-up. There were 105 patients at 12 months, 67 at 24 months, and 37 at 36 months. (From Mattson RH, Cramer JA, Collins JF, et al. Comparison of carbamazepine, phenobarbital, phenytoin, and primidone in partial and secondarily generalized tonic–clonic seizures. *N Engl J Med*. 1985;313(3):145–151; with permission.)

The first of the VA collaborative studies became available in 1985 (Fig. 2).[42] The investigators enrolled 622 adults, who were randomized to treatment with phenytoin, carbamazepine, phenobarbital, or primidone and then followed for up to 36 months. Although all four drugs prevented generalized tonic–clonic seizures equally well, carbamazepine and phenytoin were best at eradicating partial seizures (FIGURE 2). In this study as in others that followed subsequently, adverse effects that led to discontinuation of therapy were the principal factors that differentiated the four drugs.[61] Phenytoin and carbamazepine had superior tolerability as compared to phenobarbital and primidone, with approximately 60% of patients continuing treatment indefinitely with phenytoin or carbamazepine as compared to only 40% to 50% of subjects continuing with primidone or phenobarbital.[42]

In the second VA collaborative study, a similar approach was used to compare valproate and carbamazepine among patients with partial and secondarily generalized seizures. As in the previous study, the drugs performed equally well in preventing secondarily generalized tonic–clonic seizures, but carbamazepine was superior against partial seizures on four of five outcome variables and had fewer chronic side effects.[41] Thus, valproate was documented to have a broad range of antiepileptic action but was less effective than carbamazepine at preventing partial seizures.

Direct Comparisons of Newer Antiepileptic Drugs

Although there have been comparisons of older versus newer drugs, there are few head-to-head studies comparing antiepileptic drugs introduced since 1992, and none has been as comprehensive as the earlier VA trials. In some head-to-head comparisons of different antiepileptics, no differences were found in either seizure prevention or tolerability. For example, when lamotrigine and gabapentin were administered to patients with new-onset epilepsy, each prevented seizures in >50% of subjects and each was well tolerated.[10] In other comparisons, oxcarbazepine had superior tolerability versus phenytoin in children; carbamazepine was better tolerated than vigabatrin and remacemide.[29] Although comprehensive expert reviews of data from multiple studies have not established any antiepileptic drug as being superior to others, many studies have identified differences in tolerability as indicated by different rates of discontinuation of the medication, patient preference, and results of psychological testing for adverse cognitive effects.

Studies have shown topiramate and tiagabine to have cognitive disadvantages in acute and chronic dosing as compared to lamotrigine, gabapentin, and valproic acid, although in some cases the doses of topiramate were higher than those currently recommended.[25,39] These types of studies also underscore the importance of target doses and dose escalation rates, with lower doses and slower dose escalation being associated with better tolerability. Nonetheless, in a comparison of lamotrigine and topiramate in which each was taken for 12 weeks, 70% of patients preferred lamotrigine.[64] Furthermore, normal volunteers who took 300 mg of lamotrigine and 300 mg of topiramate in a crossover design had superior scores on various cognitive tasks while taking lamotrigine.[44] Similarly, compared to the usual recommended dose of gabapentin of 3,600 mg/d, 400 mg/d of topiramate had a negative impact on cognitive test results.[60] In yet another trial, doses of 400 mg/d of topiramate were associated with worse performance on the Symbol Digit Modalities Test and the Controlled Oral Word Association Test as compared to valproic acid taken at 2,250 mg/d.[43] Similarly, more-negative scores were associated with topiramate 200 to 400 mg/d than with valproate 1,800 mg/d, but the differences were minimized by slow escalation of dose.[2] At lower daily doses of 100 to 200 mg, topiramate has been tolerated better.[2] When compared to carbamazepine 600 mg/d and to valproate 1,250 mg/d, topiramate 100 mg/d was equally effective and had fewest discontinua-tions.[57]

Differences in tolerability of antiepileptics have been found in other investigations. For example, lamotrigine was less likely to be withdrawn than carbamazepine.[28] Different adverse drug effects vary in the extent to which they abate over time due to the development of tolerance. Whereas some adverse effects can be minimized by slow escalation of drug doses, others, such as topiramate-associated paresthesias, are more likely to be persistent.[37]

In 2007, the first monotherapy trial to be published that followed the European regulatory guidelines recommending demonstration of noninferiority of the test product with an acknowledged standard at individually optimized dosages using clinically relevant endpoints compared levetiracetam with controlled-release carbamazepine.[11] Both treatments produced similar seizure freedom rates in adults with newly diagnosed epilepsy at optimal dosing in a setting mimicking clinical practice. This trial has confirmed in a randomized, double-blind setting the uncontrolled observations that most people with newly diagnosed epilepsy respond to their first antiepileptic drug at low dose.[47] The results also support the assertion that optimal doses of antiepileptic drugs identified from randomized adjunctive studies in refractory epilepsy are not applicable to monotherapy trials in a newly diagnosed population.[53]

Indirect Comparisons of Antiepileptic Drugs

Drug trials done for regulatory purposes are poorly suited for direct comparisons of antiepileptic drugs for the reasons noted previously, mainly because the patients in whom drugs are evaluated have severe epilepsy and are not representative of the population at large with epilepsy. In addition, innovations in study designs over the last two decades have facilitated more expedient documentation of antiepileptic efficacy by conducting drug studies in patients with high seizure frequencies such as presurgical patients and children with the Lennox-Gastaut syndrome, but the resulting information has little direct applicability to a majority of patients.[9,17] Nonetheless, in the absence of studies that directly compare various antiepileptic drugs, other approaches have been taken using available information from placebo-controlled trials for comparison using meta-analysis, systematic review, and guideline development in attempting to identify superiority among newer drugs. All of these approaches depend on comprehensive review and interpretation of existing studies by experts in the field.

These approaches start with convening a knowledgeable panel to review all of the evidence, including unpublished studies, grading the evidence as to its scientific rigor and freedom from bias, and then crafting recommendations based on published standards for guideline development. Meta-analysis provides a statistical method for combing results from several studies for purposes of comparing different therapeutic agents.[56] In this approach, a question is posed and then a systematic review of available research is conducted to glean the relevant information regarding a common endpoint such as the 50% responder rate. The studies are evaluated to determine whether they meet quality standards for inclusion, and then the results are expressed in a common format or scale such as the odds ratio or the number needed to treat.[66,67] Most antiepileptics developed since 1992 have been compared using this approach.[50]

Although meta-analytic comparisons have not revealed statistically significant overall superiority, sizeable differences have been noted and consistent trends in differential tolerability have been observed. For example, no statistically significant differences were found in comparisons of 50% responder rates from studies of gabapentin, lamotrigine, tiagabine, topiramate, vigabatrin, and zonisamide in either responder rates or indices of tolerability.[56] In other analyses, the differences point to substantial differences in tolerability. The least tolerable drug was fourfold as likely to be stopped as the best-tolerated drug.[12] For example, in one analysis, the most efficacious drug—topiramate—was twice as effective as the least efficacious—gabapentin—whereas the least tolerable drug—zonisamide—was fourfold as likely to have been discontinued during clinical trials as the most tolerable drug—lamotrigine.[12] Other comparisons of topiramate and lamotrigine versus phenobarbital reveal no differences in seizure control, but adverse effects differentiated the drugs, with phenobarbital faring worst.[36]

Systematic Reviews and Sponsored Guideline Development

Since the 1990s, there have been a number of systematic reviews of various trials of new antiepileptic drugs. The first group to undertake these comparisons was the Cochrane Collaboration (http://www.cochrane.org), which was founded in 1993. Other analyses have been sponsored by the American Academy of Neurology, the American Epilepsy Society, the Child Neurology Society, the National Institute for Clinical Excellence Committee in the United Kingdom, the Scottish Intercollegiate Guidelines Network, and the International League Against Epilepsy.[32] Each of these organizations maintains a website that should be consulted for up-to-date recommendations, reviews, and guidelines (Table 3). A recent search of the Cochrane Database for “epilepsy” resulted in 132 reports, whereas a Cochrane Database search for antiepileptic drugs found 39 citations. In balance, these reviews illustrate the paucity of comparable information in support of claims of overall superiority of any particular agent. Unfortunately, they have not provided a means for discerning the superiority of new agents.[38]

Table 3 Guideline providers and website addresses

American Academy of Neurology (http://www.aan.com)

American Epilepsy Society (http://www.aesnet.org)

Child Neurology Society (http://www.childneurologysociety.org)

Cochrane Collaboration (http://www.cochrane.org)

International League Against Epilepsy (http://www.ilae-epilepsy.org)

National Institute for Clinical Excellence Committee in the United Kingdom (http://www.Nice.org.uk)

Scottish Intercollegiate Guidelines Network (http://www.sign.ac.uk)

All of the newer antiepileptic drugs introduced since the VA-sponsored multicenter studies have been effective in partial and secondarily generalized seizures. Some drugs, such as lamotrigine, have broader spectra of activity against absence seizures as well. As with the older agents, however, the efficacy of the new compounds is curtailed by adverse effects. The new agents include vigabatrin, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, topiramate, tiagabine, and zonisamide. Among these, use of felbamate and vigabatrin has been so diminished by serious toxicity that they will not be mentioned further. Similarly, there is little to say about pregabalin because it was only recently brought to market. Finally, some guidelines do not consider drugs that are unavailable in some countries. These include vigabatrin, felbamate, sulthiame, and clobazam.

These labor-intensive reviews have resulted in guidelines for newer antiepileptic drugs introduced since 1992 in various types of epilepsy.[23,24] The guidelines that have been developed thus far have been less effective at differentiating new drugs than the direct head-to-head comparisons in the VA-sponsored trials. As a result, current guidelines are better able to summarize which drugs are effective than they are to identify a hierarchy of effectiveness. The clinical effectiveness of drugs varies according to patient characteristics, but there is little information that characterizes these differences. There are many reasons for this, but foremost is differential vulnerability of various groups to developing adverse effects. Many different groups can be identified with categories formulated by age, gender, comorbid disorders, and epileptic pathobiology. Among the elderly, drugs such as lamotrigine, gabapentin, and carbamazepine are no different in preventing seizures, but lamotrigine and gabapentin are better tolerated than carbamazepine.[59] In children, systematic reviews generally have not provided a basis for superiority claims. No differences could be documented for ethosuximide, valproate, or lamotrigine among children with absence seizures.[55] Among the drugs lamotrigine, topiramate, and felbamate, which have been shown

to be effective adjuncts in Lennox-Gastaut syndrome, superiority could not be established, but felbamate-associated aplastic anemia and liver failure clearly are the most severe toxicities.[33]

The role of the pathobiology of seizures is rarely evident in influencing drug effectiveness but it is likely to be more important than is commonly appreciated. For example, in one consecutive series of 431 patients treated with topiramate, the presence of a left temporal lobe electroencephalographic (EEG) focus plus simple partial seizures increased risk of topiramate-associated word-finding problems more than fivefold.[49]

Based on the desire to consider more patient-related features in recommendations for drug utilization, an expanded approach has been to categorize patients according to additional features besides seizure type and type of epileptic syndrome.[6] The major additional feature used for the grouping devised by the National Institute for Clinical Excellence Committee in the United Kingdom is the duration of epilepsy, dividing patients into those with newly diagnosed partial seizures versus those with chronic, often refractory partial seizures. This is highly relevant clinically because new-onset seizures are much likelier to respond to any antiepileptic drug than are chronic seizure disorders that have proved resistant to previously administered drugs. Despite this laudable approach to refining the recommendations for drug utilization, the lack of supportive relevant information results in the recommendations from expert panels in the United States and the United Kingdom being quite similar.[6]

Summary and Conclusions

Although efficacy and toxicity of antiepileptic drugs are separable conceptually, in practice they are indivisible and jointly manifest as the therapeutic index or clinical effectiveness. Drug tolerability—the collective impression of a drug's adverse effects—is a major variable that limits the effectiveness of various drugs and distinguishes drugs from each other. The therapeutic index is the indicator of overall clinical usefulness of a drug. The best of the older antiepileptic drugs were clinically effective in only 60% of patients. Based on comparisons between older and newer drugs, newer drugs generally have improved tolerability, but direct head-to-head comparisons among newer drugs are lacking.

Effective doses of antiepileptics vary widely from one person to the next due to individual variability in seizure responsiveness to medication, vulnerability to adverse drug effects, and pharmacokinetics. Unfortunately, for individual patients, these characteristics often are unknown when therapeutic decisions must be made. As a result, doses of properly selected antiepileptics need to be individualized to achieve optimal effectiveness. Due to the inherently high failure rates of antiepileptic drugs, optimal treatment usually requires stepwise dose adjustment and careful follow-up.

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Chapter 105

Dose-Related Side Effects

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Introduction

Most antiepileptic drugs (AEDs) block seizure generation by altering membrane excitability, increasing postsynaptic inhibition, or modifying the synchronization of neuronal networks.[34] At therapeutic doses, this may also cause dysfunction of the central nervous system (CNS) and other organ systems, resulting in adverse effects that may be life threatening in rare cases.[2] Not surprisingly, adverse effects significantly impair health and well being, particularly in patients with refractory epilepsy.[16] Accordingly, the goal of treatment should be seizure freedom with no or a minimum of side effects. The patient should not suffer more from the side effects of treatment than from the epilepsy itself. Fortunately, most side effects of AEDs are predictable, dose dependent, and resolve with dose reduction. Furthermore, a number of unpredictable and idiosyncratic side effects of AEDs are also characterized by a dose–response relationship.[21] As a consequence, one major strategy to minimize dose-dependent side effects is to avoid overtreatment.[33,38] Overtreatment is broadly defined as unnecessary or excessive drug load in the management of epilepsy leading to a suboptimal risk-to-benefit balance.[40] The second major strategy is to recognize patients at increased risk for host-dependent side effects. In this chapter, we give an overview of dose-related side effects of drug treatment for epilepsy. Furthermore, we describe clinical scenarios that often lead to side effects and outline specific strategies to minimize or prevent dose-related side effects of AEDs.

The Scope of Dose-Related Side Effects

The scope of dose-related side effects ranges from rare serious and irreversible adverse events to common reversible side effects.[36] In a survey of >5,000 patients living in Europe, 88% of patients currently treated with AEDs reported at least one side effect, and 44% of respondents said they worried "a lot" or "some" about the possible side effects of their medication.[3] In different studies, the proportion of patients with side effects from AED therapy range from <10% to >70% depending on ascertainment procedures, definitions and measurements of side effects, characteristics of patients, AED dose, and duration of follow-up.[19,30] Important methodologic differences between studies hamper the comparison of side effects among AEDs.[12,19] Although no AED is free of adverse effects, some AEDs have fewer side effects than others, and there are clearly differences in the spectrum of adverse effects produced by specific agents (Table 1). These specific adverse effects influence drug selection in the individual patient. For example, AEDs causing weight gain may not be the best choice for overweight patients. On the other hand, agents that cause weight loss may not be ideal for an anorectic patient trying to gain weight. Finally, it has been suggested that some of the newer AEDs are better tolerated in clinical use than some of the older agents (Table 1).[16] When used appropriately, some of the newer AEDs undoubtedly offer relevant advantages in tolerability, in particular, less sedation and fewer metabolic changes, including fewer drug interactions.[19,38] However, when all newer AEDs were compared in a critical review of 80 randomized, controlled trials reporting adverse events of AEDs, there was no consistent or convincing evidence for better relative safety and tolerability of newer AEDs.[48] For full details of individual side effects and contraindications of each AED, see Summary of Product Characteristics of each AED and respective chapters of this and other books (e.g., Levy et al.[24]).

Irreversible Side Effects

Dose-related side effects may be irreversible and life threatening in some patients. Such cases include severe bradyarrhythmia after rapid intravenous phenytoin, pneumonia with nitrazepam treatment in young children, and respiratory arrest following high-dose intravenous benzodiazepines.[7] In addition, the serious Stevens-Johnson syndrome or the Lyell syndrome may be dose related. The highest incidence of Stevens-Johnson syndrome (1:50 to 1:300) is observed in association with use of lamotrigine in children, particularly when a high starting dose is used or valproate is given as comedication, which increases the serum concentration of lamotrigine by inhibition of its metabolism.[30] The incidence seems to be decreasing following introduction of a slower dose escalation and the wider use of lamotrigine monotherapy.[30] Further examples of irreversible side effects that may be dose related are malformations in the offspring following maternal exposure to AEDs, which is discussed in detail elsewhere in this book. For other irreversible and often severe side effects, a dose relationship is not well documented. This group, as shown in Table 1, includes concentric visual field defects following exposure to vigabatrin and cases of rare phenytoin-associated cerebellar degeneration or Dupuytren contracture and Ledderhose syndrome during chronic treatment with phenobarbital or primidone.[36]

Table 1 Overview of adverse effects of antiepileptic drugs

	CBZ	CLB	ESM	FBM	GBP	LEV	LTG	OXC	PGB	PHB	PHT	TGB	TPM	VPA	VGB	ZNS
								Early-onset adverse events								
Somnolene		++			+	+	+		+	++		++	++		+	++
Dizziness[a]		++	+		+	+	+	++			++	++	++		+	+
Seizure aggravation[a]	+	+			+				+		+	+			++	

Gastrointestinal	+		++	+	(+)	(+)		+						+		+
Liver failure[b]				+										+		
Hypersensitivity[a]	+			+			++	+		+	+		+			
Late-onset adverse events																
Sedation[a]		++	+							++			(+)			
Encephalopathy[a]											+			+	++	
Dyskinesia, tics, parkinsonism	+		+	(+)	+		+			(+)	+	(+)		+	(+)	
Depression[b]			+							+	+	+			+	
Language dysfunction													+			
Behavioral problems[a]					+	+				++	+	+	++		++	+
Psychotic episodes[b]	(+)		++	(+)	+	(+)				(+)	(+)		(+)	(+)	++	
Leucopenia[b]	++		+	+						+	+					
Aplastic anemia[b]	+		+	++						+	+					
Thrombopenia[a]				+										++		
Megaloblastic anemia[a]										+	+					
Pancreatitis[b]					(+)									+		
Nephrolithiasis[b]													(+)			+
Osteoporosis[b]	(+)									+	+			(+)		
Hyponatremia[b]	(+)							+								
Weight gain[a]	+				+				++					+	+	+
Weight loss[a]				+									+			+
Cognition impaired[a]	+	+								++	+		+			+
Teratogenicity[b]														++		

Summary (all +)	9	8	10	8	7	3	5	5	4	14	13	7	10	10	12	9

The incidence of many early adverse events shown here may vary significantly from patient to patient, depending on individual susceptibility, development of tolerance, titration, and drug load. The list summarizes the adverse event potential of a given compound, in the authors' view. In our view, representing evidence class IV, (+) denotes minimally increased risk at effective dose in clinical use, + denotes a risk higher than for AEDs without a + sign, and ++ denotes the highest risk among AEDs. CBZ, carbamazepine; CLB, clobazam; FBM, felbamate; GBP, gabapentin; LEV, levetiracetam, LTG, lamotrigine; OXC, oxcarbazepine: PGB, pregabalin; PHB, phenobarbital; PHT, phenytoin; TGB, tiagabine; TPM, topiramate; VPA, valproate; VGB, vigabatrin; ZNS, zonisamide.

[a] Dose-related side effect.

[b] Dose relationship not proven or controversial.

Source: Modified from refs. 3, 7, 14, 15, 19, 24, 30, 36, 49, and 50.

Reversible Side Effects

A number of CNS side effects such as dizziness, ataxia, or somnolence emerging early in the course of treatment with AEDs are transient despite continued therapy.[24,25,36] The mechanism underlying the resolution of early CNS side effects without dose reduction is the rapid development of functional tolerance to adverse effects within weeks.[28] Functional tolerance to early side effects such as dizziness and gastrointestinal adverse effects was elegantly demonstrated for several first-generation AEDs in a well-controlled comparison of carbamazepine, phenytoin, phenobarbital, and primidone.[28] Although serum concentrations were similar at weeks 1 and 12, the proportion of patients with dizziness and gastrointestinal complaints was much lower at week 12.[28] For newer antiepileptic drugs such as gabapentin, lamotrigine, pregabalin, topiramate, vigabatrin, and zonisamide, resolution of early CNS side effects during continued therapy has also been noted in many patients.[24,25]

The vast majority of persisting side effects occur more often at higher doses and, fortunately, are reversible with dose reduction.[19] Contrary to intuitive belief, hypersensitivity reactions of the skin ranging from mild maculopapular rashes (affecting up to 15% of patients started on lamotrigine, phe-nytoin, and carbamazepine) to severe cutaneous adverse reactions such as Stevens-Johnson syndrome and Lyell syndrome (toxic epidermal necrolysis) occur more often in susceptible individuals with loading doses compared to slow titration. A notable example is skin rash associated with lamotrigine, the incidence of which can be minimized by starting with a low dose and titrating slowly, particularly in patients comedicated with valproate.[49] It is possible that slower titration reduces the risk of allergic reactions by gradual desensitization of the immune system. All antiepileptic drugs have dose-related CNS adverse effects, as noted previously, although some drugs may be more troublesome than others (Table 1). During chronic treatment, the most common side effects involve the CNS and include cerebellar-vestibular and oculomotor symptoms (ataxia, dysarthria, vertigo, tremor, diplopia, blurred vision, various forms of nystagmus, and gaze palsy), extrapyramidal symptoms (dyskinesia, parkinsonism, tics, and myoclonus), drowsiness, fatigue, impairment of cognitive function, and disorders of mood and behavior.[7,50] At high doses, paradoxical seizure aggravation as a manifestation of toxicity (paradoxical intoxication) has been reported with virtually all AEDs, although phenytoin, topiramate, and vigabatrin have been particularly implicated.[32] After massive overdose, virtually all AEDs can cause seizures, even in patients who do not have epilepsy.[32] Seizure aggravation may result, however, from selection of the wrong AED for the patient's seizure/epilepsy type, emphasizing the importance of accurate classification.[32] In addition, deterioration in seizure control may be caused by the development of tolerance to the effect of the drug or be simply related to a spontaneous increase in seizure frequency.[46] Whatever the reason, the treating physician should be aware of paradoxical seizure aggravation to avoid a dangerous vicious circle whereby the dose is increased further in an attempt to bring the epilepsy under control. Finally, seizure worsening after AED withdrawal, especially when abrupt, may also be seen as a reverse dose-related side effect, especially with felbamate and viga-batrin, and can also result in transient increase in seizures or even status epilepticus.[32]

In addition, a number of non-CNS side effects are dose related including gum hyperplasia with phenytoin and frozen shoulder syndrome with phenobarbital.[36] Weight gain has been found to be dose related for AEDs such as gabapentin, pregabalin, valproate, and vigabatrin.[19] For example, pregabalin was associated with weight gain (of at least 7% of initial body weight) in 14% of patients receiving 600 mg/d compared with 7% of those taking 150 mg/d and 2% of patients given placebo.[45] Topiramate weight loss is also dose related, with approximately 10% of patients showing body weight reductions at a dose of 100 to 200 mg/d.[45] Nephrolithiasis may occur with topiramate and zonisamide, and endocrine and metabolic disturbances are seen with a number of AEDs.[45]

Patient Groups With an Increased Risk for Dose-Related Side Effects

Some patients require unusually low doses to achieve optimal therapeutic response due to differences in genetic background, body weight, age, hormonal status, coexisting illness, and interactions with concomitant medications. Failure to take these host-related factors into account may easily lead to overtreatment. For example, the elderly generally require lower AED doses to achieve seizure control, and they may develop adverse effects at doses (and serum drug concentrations) that are usually well tolerated in younger individuals.[19]

For patients with renal impairment, doses of AEDs that are primarily excreted renally, for example, primidone, gabapentin, pregabalin, and levetiracetam, should be reduced. A recent report of increased incidence of gabapentin-induced myoclonus in patients with renal failure highlights the risk of overtreatment in this patient group.[51] Although these patients received gabapentin doses that could be regarded as relatively low in an individual with normal renal function, their use in renally impaired patients probably resulted in excessive accumulation. For patients with serious liver disease, AEDs that are primarily detoxified in the liver, such as barbiturates, phenytoin, suximides, carbamazepine, felbamate, lamotrigine, tiagabine, valproate, and benzodiazepines, may rise to toxic levels and may not be the first choice, or doses may require close monitoring. This reflects, in part, the pharmacokinetic changes and lower serum albumin in elderly adults. Liver volume, blood flow, and metabolism decrease with age.[19] Elderly adults or neurologically impaired patients of all age ranges also may be more susceptible to some dose-related adverse effects, such as dizziness, because of preexisting neurologic problems.

Some types of seizures (but not usually epileptic syndromes) in one age group may be made worse by the same AED that controls them in another age group. For example, vigabatrin reduces myoclonic seizures of infancy (infantile spasms), and yet worsens myoclonic seizures in older patients with other types of epilepsy.[32] Infants and young children, however, are at greater risk for other host-related adverse effects. The occurrence of Stevens-Johnson syndrome was higher in patients taking AEDs who were <18 years of age.[35] Other examples of host-related greater susceptibility for adverse effects are instances in which infants and children have a greater susceptibility to an AED adverse effect.

The influence of genetic variation on drug metabolism has long been recognized. Polymorphisms in the genes that code for drug-metabolizing enzymes, drug transporters, drug receptors, and ion channels can affect an individual's risk of having an adverse reaction.[29] Genetic polymorphism of the cytochrome P450 (CYP) enzymes, which metabolize a range of AEDs, affects their expression and may determine individual susceptibility to drug toxicity. Dosing with "standard" phenytoin regimens without prior knowledge of the genetic profile has been reported to lead to overtreatment and toxicity in isolated cases.[29] As the complexity of genetic influences on treatment responsiveness becomes better understood, pharmacogenetic profiling may become a practical tool for preventing overtreatment in high-risk patients.

In addition, the type and severity of the epilepsy may influence the optimal dose (or serum drug concentration) required. In the Glasgow study,[23] patients with symptomatic or cryptogenic epilepsy were more likely to withdraw from treatment due to side effects compared to those with idiopathic epilepsy, possibly because the latter required lower doses to achieve seizure control. In another study that explored the relationship between serum AED concentrations and clinical response, patients who had tonic–clonic seizures only in their history or a low pretreatment seizure frequency were found to become controlled at much lower AED concentrations compared with those who had partial seizures, multiple seizure types, or a high pretreatment seizure frequency.[42] These observations are important to be able to tailor the initial target maintenance dose to individual needs and avoid overtreatment in patients who are particularly likely to do well at relatively low doses or serum levels. In addition to increased host susceptibility, some treatment strategies may carry a higher risk for side effects than others.

Treatment Scenarios Resulting in an Increased Risk of Dose-Related Side Effects

Although some early CNS side effects improve or even resolve over time without a change in AED dose due to rapid development of tolerance as described previously,[28] dose-related adverse effects are more prominent in the first weeks of treatment. In addition, tolerance and adaptation to dose-related AED adverse effects vary widely among patients for many reasons.[19] Poor adherence to medication regimens may eliminate previously acquired tolerance and transiently worsen the tolerability of treatment. As discussed earlier, idiosyncratic reactions after the start of treatment, such as hypersensitivity reactions and hepatic adverse effects, are most likely to occur within 2 to 8 weeks.[19] Because many adverse effects occur most frequently at the start of treatment, clinicians should be most vigilant during this time.

Patients and their families should be alerted to look for adverse effects during the first weeks of a new AED treatment and should be asked to contact the physician quickly if they have concerns about an adverse effect so that the severity of these complications can be reduced. The patient should be urged to bring to the physician's attention any symptoms that the

patient believes could be side effects (the physician may need to encourage their patients to discuss symptoms related to sexual functioning). Once a patient raises possible side effects, the physician needs to determine whether they are AED related. Some side effects may not be AED related—for example, a contact dermatitis, fatigue secondary to a sleep disorder, and memory dysfunction or erectile dysfunction due to depression—and therefore should not lead to AED dose reduction, which could then lead to increased seizures. In addition, patients should be told not to decrease or stop their medications because of symptoms they believe could be side effects, but rather to contact their doctor and have a discussion (for the same reason as given previously).

When choosing the initial dose or making adjustments, consideration should be given to the dose–response relationship for the individual AED being used. The risk of side effects is particularly high with phenytoin, the pharmacokinetics of which changes from first to zero order across the therapeutic dose range, resulting in a disproportionately large elevation in serum concentration with a small dose increase.[24] Monitoring serum phenytoin levels is important in minimizing side effects with this drug. However, one of the commonest reasons for overtreatment is overreliance on serum drug concentration monitoring. A "therapeutic range" is often interpreted injudiciously to dictate dose adjustment without sensible clinical correlation.[20] Although "therapeutic" or "target" ranges are often quoted for established AEDs in standard textbooks, these should only be used as an aid in dose adjustment, and the clinician must realize that some patients will do well below the lower limit of the range, whereas others tolerate higher levels with benefit and without toxicity.[33] Increasing the dose in well-controlled patients simply because they have a low serum AED concentration will expose them to overtreatment.

Rapid titration, prescribing too-high doses, using too many antiepileptic drugs, and continuing treatment too long, which often cause unnecessary side effects, are discussed in the following paragraphs. In most therapeutic settings, initiation of treatment is best carried out by applying the well-known, but often ignored, "start low, go slow" principle.[43] Slow uptitration minimizes tolerability problems by allowing gradual development of adaptation, or tolerance, to CNS side effects as discussed in the previous section. This is particularly applicable to primidone, benzodiazepines, topiramate, tiagabine, zonisamide, and, to a lesser extent, carbamazepine, phenytoin, oxcarbazepine, and vigabatrin.[31] In a double-blind trial, gradual initiation of topiramate (reaching 400 mg/d in 8 weeks compared to 3 weeks) significantly lowered the incidence of dose-related side effects without delaying therapeutic response.[9] Unfortunately, different titration schedules tend to be poorly investigated in regulatory controlled trials, and optimal dose escalation rates are usually only defined through postmarketing clinical experience.[47] For instance, topiramate and viga-batrin have been found to be often optimally effective at doses that are substantially lower than those tested in early trials,[4] and the neurotoxicity of topiramate may be improved by slow titration.[9] Contrary to intuitive beliefs, the risk of idiosyncratic reactions may also be reduced by slower titration, as reviewed earlier.

Prescribing too-high doses is a well-known and yet still common cause of side effects. This is particularly relevant for AEDs, which have a narrow therapeutic ratio, that is, the dose required to control seizures is usually close to the dose that causes adverse effects.[30] There are at least two common clinical scenarios in which excessively and unnecessarily high dosages may be given. A recent observational study conducted in a large population of patients with newly diagnosed epilepsy in Glasgow provides particularly relevant information in this respect.[23] Among 470 patients who had never previously received AED treatment, 47% became and remained seizure- free on the first AED. Remarkably, around 80% of the seizure-free patients required relatively modest daily doses (600 mg or less of carbamazepine, 1,000 mg or less of sodium valproate, 200 mg or less of lamotrigine), with a sigmoid dose–response relationship.[23] Particularly for carbamazepine, these maintenance doses tend to be lower than those that, in the authors' experience, are initially prescribed by many practitioners, suggesting that overtreatment is not rare among apparently "well-managed" patients.

The second scenario concerns the rationale for excessive dose increments in patients not responding at average doses. There is in fact a paucity of studies that support the rationale for further increasing dose (or serum drug concentrations) beyond a certain limit. In the Glasgow study,[23] only 20% of patients who achieved seizure freedom on the first prescribed AED did so at more than a modest dose, suggesting that a surprisingly modest therapeutic gain can be achieved by increasing doses indiscriminately. In fact, the notion that seizure control increases proportionally with increasing dose is probably inappropriate. For example, in a recent controlled trial in patients with newly diagnosed epilepsy randomized to receive 25 or 200 mg/d to-piramate (or 50 and 500 mg/d in patients weighing 50 kg or more), seizure freedom rates were similar, while paraesthesia as one of the dose-related side effects of topiramate was more frequent (35% vs. 13%, $p < .0001$).[18] There is also evidence that excessively high doses can lead to paradoxical deterioration in seizure control as discussed earlier. These considerations suggest that increasing the dose above a certain level may result in seizure freedom in only relatively few patients, and many more will be overtreated and suffer the associated toxicity.

Finally, using too many antiepileptic drugs is well known to cause side effects. Dose-related CNS side effects, particularly ataxia, somnolence, and dizziness, are often more prominent in patients on multiple AEDs,[26] although it has been suggested that neurotoxicity is better related to total drug load (defined as the sum of defined daily doses for each drug) than to the actual number of AEDs taken.[13] The fact that many patients experience fewer side effects and at times even better seizure control after being converted from polytherapy to monotherapy was first demonstrated in the late 1970s to early 1980s and confirmed in subsequent reports.[41] The negative impact of overtreatment with polytherapy may result from both pharmacokinetic and pharmacodynamic drug interactions. Enzyme inhibition may lead to elevation in the plasma levels of the affected drug, as shown by the effect of valproate on phenobarbital and lamotrigine,[24] resulting in increased toxicity. The combination of valproate and lamotrigine appears to exacerbate the teratogenicity seen with either agent alone, as is discussed in detail elsewhere in this book. Knowledge of the effects of individual AEDs on the metabolizing enzymes of the affected agent will aid in making appropriate dose adjustments and avoiding the negative consequences of these interactions. There is some evidence that adverse pharmacodynamic interactions are more likely to occur when AEDs sharing a similar mechanism of action are combined. For instance, excessive neurotoxic side effects have been noted in patients given a combination of carbamazepine and lamotrigine[8] or carbamazepine and oxcarbazepine, both sodium channel blockers.[5] Recent interim results of the U.K. pregnancy registry, published in abstract form only, suggest that although only 64 cases could be included, the incidence of teratogenicity might be higher in women given a combination of valproate and lamotrigine (11.9%) compared with either drug alone (valproate, 7.2%; lamotrigine, 3%).[6] If this apparently adverse interaction is confirmed, it would be very unfortunate because valproate plus lamotrigine is a particularly useful combination in patients with difficult-to-treat epilepsies, as is discussed elsewhere in this book.

Furthermore, continuation of AED therapy when the risk-to-benefit ratio is in favor of drug withdrawal may be a less common example of overtreatment. At least for the self-remitting epilepsies, such as benign Rolandic epilepsy and childhood absence epilepsy, or rare seizures, AED therapy should not be unnecessarily prolonged after achieving an adequate period of complete seizure control. Another strong predictor for relapse is the duration of seizure freedom before drug withdrawal. It should be noted, however, that risks weigh against discontinuation of AEDs in a number of seizure-free patients.[44] These risks include (a) a seizure recurrence rate between 12% and 66% (mean 34%) and (b) complete and rapid seizure control cannot be guaranteed when AEDs are given for treatment of recurrence. In fact, in one half of the patients, it may take several years to reach control and, in one review, 23% of chronic uncontrolled epilepsy remained uncontrolled in a follow-up of up to 9 years.[44] Relatively little information is available to guide consideration of drug withdrawal after successful epilepsy surgery. According to a review, AED discontinuation is associated with a seizure recurrence in one in three patients rendered seizure-free by epilepsy surgery. Reinstitution of medical treatment after seizure recurrence in patients withdrawn from AED treatment proved effective in most cases. However, 9% of patients developed intractable epilepsy after AED discontinuation despite restarting AEDs. These results will be useful in counseling patients about discontinuing AED treatment after successful epilepsy surgery.[39]

Finally, overdose is a rare but serious cause of side effects of AEDs. With newer AEDs, —doses of up to 48.9 g of gabapentin and, separately, 4 g of lamotrigine—patients developed CNS symptoms including ataxia, confusional state, headache, and sedation but recovered without any sequelae. A patient who ingested between 4 and 5 g of lamotrigine was admitted to hospital in a coma lasting 8 to 12 hours, followed by recovery over the next 2 to 3 days. Another patient who ingested 5.6 g was found unconscious and, following treatment with charcoal, recovered after sleeping for 16 hours. Although no serious clinical consequences were reported in the these cases, in one patient with a lamotrigine overdose of 1.3 g, the electrocardiogram showed QRS width of 110 ms.[11] Vigabatrin overdoses, most commonly at doses between 7.5 and 30 g but up to 65 g, have been reported. Approximately half of these cases involved multiple drug ingestion, none resulting in death (for review see Mattson et al.[28]). Reviews of overdose with older AEDs are available.[36]

Management of Dose-Related Side Effects

The cornerstones of the effective management of a patient with side effects are improved recognition of side effects by systematic assessment and careful reduction of drug load without worsening seizure control. Foremost, prevention of side effects is often easier than correction of an existing side effect.

Table 2 Strategies for preventing side effects of antiepileptic drugs in patients with epilepsy

- Make all efforts to ensure accurate diagnosis and classification, and start treatment only after careful consideration of the risk-to-benefit ratio.
- Select the most appropriate drug for the individual patient based on consideration of the primary strength and weakness of the individual compound. The adverse event potential and specific side effects should influence drug selection in the individual patient.
- Use appropriately lowest dose titration and the lowest maintenance dose based on the epilepsy syndrome and characteristics of the patient.
- Monitor regularly clinical response, with special consideration of adverse drug effects and systematic screening for adverse effects. Increase awareness of toxicity by effective patient information.
- Adjust dose only when there is a clinical indication. Consider the dose–response relationship when making dose increments. If indicated, monitor serum drug concentrations.
- If seizures are uncontrolled and compliance problems are excluded, adjust treatment gradually up to the highest tolerated dose. Return to average dose, however, if the patient dose not benefit from the dose increment. Review diagnosis and classification.
- Most patients refractory to a single drug can do well on an alternative monotherapy. If combination therapy is indicated, consider the possibility of drug interactions and adjust dose accordingly.
- Consider the possibility of paradoxical intoxication whenever an increased drug load is associated with deterioration in seizure control.
- In drug-refractory patients, consider the feasibility of alternative treatments, e.g., epilepsy surgery, ketogenic diet, or neurostimulation.
- Reassess regularly the risk-to-benefit ratio of treatment and consider the possible benefits of reducing drug load.

Source: Modified from refs. 16, 33, 38, and 43.

Prevention

One way to avoid side effects is to carefully consider whether drug treatment is necessary at all. A number of clinical situations exist in which starting drug treatment needs to be individualized in consideration of the individual risk–benefit balance and the patient's preference. A firm diagnosis of an epileptic seizure or epilepsy is crucial to avoid treating nonepileptic seizures such as psychogenic seizure or syncope as outlined elsewhere in this book. Patients with a first epileptic seizure or patients with benign epilepsy syndromes or very rare seizures may neither wish nor need chronic AED treatment. Prophylactic treatment in high-risk patients who did not have a seizure and may never have one (even without treatment) has not been shown to be effective in preventing the development of epilepsy, as outlined elsewhere in this book. Once the decision to start treatment has been made, judicious selection of the most appropriate AED and dose is sensible. General guidelines for prevention of adverse effects of AEDs include a number of recommendations as shown in Table 2.

Identification of Side Effects

Strategies to improve epilepsy care should include systematic monitoring to identify side effects. Despite the apparent importance of medication problems on self-reported health as reviewed previously in this chapter, few investigations have been published on techniques for monitoring adverse effects. Trials that included monitoring of side effects have consistently shown higher rates compared with spontaneous reporting. For example, one benchmark study, which included a standardized questionnaire for systematic assessment of side effects of AEDs, found that such effects contributed to the exit from the trial

in 40% to 60% of participants.[27] This is substantially higher than was found in most studies that used only spontaneous self-reporting.[12] Use of a structured patient interview called the Adverse Event Profile (AEP) provided similar rates of important side effects such as sedation or fatigue with phenyt-oin and carbamazepine in a survey of >5,000 patients from 15 European countries.[3] The utility of the AEP was demonstrated in a randomized trial.[17] The 4-month study showed that care improved with the use of the AEP in an outpatient epilepsy clinic. With more frequent dose reduction in the AEP user group versus the group in which AEP was not available, AED toxicity was reduced and subjective health status improved, notably without seizure worsening.[17] Heightened awareness of side effects, with or without the use of AEP, allows reduction of drug load to lessen medication problems.

Reducing Overtreatment

Although treatment of epilepsy can easily evolve into a situation of overtreatment, reversing the process can be difficult and time consuming. There can be little doubt that decreasing the doses and/or number of AEDs will be associated with a decrease in side effects. This decrease in side effects involves a reduction in their severity, their number, or both. Several studies in the 1980s suggested that a reduction in the number of AEDs reduces the overall occurrence of side effects, in particular the sedative effects and the dose-related neurologic side effects in general.[1,37]

In addition to the dose-related central nervous system side effects of AEDs, there is no doubt that eliminating drugs from the regimen will eliminate the various individual and specific side effects of those drugs that are discontinued, such as excessive weight gain or tremor from valproate, behavioral problems from levetiracetam, or cognitive impairment from topiramate.[10] Additional benefits of reducing overtreatment may include a simplification in the medication regimen, improved compliance, and reduced costs. It is interesting that there was little or no increase in seizure frequency among the patients enrolled in these studies, and a reduction in seizures was actually not uncommon.[1] There are several possible explanations for this observation, including spontaneous fluctuation; removal of paradoxical intoxication and of seizure-aggravating drugs; elimination of enzyme-inducing agents, which may increase the serum concentration and consequently the efficacy of remaining AEDs; and possibly increased compliance with fewer drugs being taken. In addition, the dose of potentially effective drugs may be increased, which was not possible before because of side effects, and this may improve seizure control. However, dose increments may lead to more side effects. This may explain why in some studies there was no difference in tolerability following transfer from two-drug treatment to monotherapy.[37]

The risks include seizure exacerbation due to loss of protection, spontaneous fluctuation in seizure frequency, or withdrawal. At the onset of an increase in seizure frequency that occurs during medication reduction, it is initially virtually impossible to determine which one of these three mechanisms is involved. Loss of seizure protection is a real possibility. In any patient who has been taking several AEDs for a certain period of time, it becomes virtually impossible to determine which one of the drugs, if any, is exerting a protective effect against the seizures. Therefore, any drug that is being reduced or eliminated may actually have been exerting a protective effect whose loss manifests itself as a seizure aggravation. If this is the case, there is usually no change in the intensity or duration of the seizures, and the increase in seizure frequency will tend to persist, in contrast to withdrawal seizures and to seizure increase due to spontaneous fluctuation. In addition, seizure frequency will usually not decrease until the dose of the drug is increased again. A seizure increase due to spontaneous fluctuations may subside spontaneously, and, in an individual patient, it may be impossible to determine whether the exacerbation was due to a spontaneous fluctuation or to a withdrawal phenomenon. The literature provides some evidence suggesting that certain AEDs such as benzodiazepines, carbamazepine, and phenobarbital are more likely to be associated with withdrawal seizures (for review see Zaccara et al.[50]). Reversal of pharmacokinetic interactions may also lead to seizure aggravation or to drug toxicity as well as to some problems with other medication besides AEDs if their dose is not adjusted. When reducing overtreatment, there are three main challenges: (a) to select the drugs that should be eliminated, (b) to choose an appropriate rate of reduction, and (c) to anticipate reversible pharmacokinetic interactions that can have clinically significant consequences. This may seem theoretically relatively simple, but it can be practically more challenging. The answer to the question “Which drug first?” depends on the reason behind the decision to reduce what is perceived as being overtreatment. Accordingly, there will not be a single criterion. If side effects are the main reason, one may first target the drug that is considered to have the worst or strongest adverse effects. It is not always easy to identify that drug, especially when the side effects consist of nonspecific CNS-related symptoms, such as lethargy or mental slowing, which may actually result from cumulative toxicity. In other cases, the adverse effects may be easily attributed to a certain drug, such as excessive weight gain from valproate, excessive weight loss from topiramate, behavioral problems from gabapentin or levetiracetam, or oligohydrosis from zonisamide. Another reason to reduce overtreatment may be the evidence or the suspicion that one of the AEDs may potentially be aggravating the seizures. Obviously, if there is none of these specific reasons to reduce overtreatment, a logical target drug would be the one that is considered to be the least effective. This can sometimes be determined from careful compilation of the drug history and clinical responses. Often, however, it is not possible to determine which of the AEDs the patient is taking is currently effective, if any, especially if the drugs have been prescribed for a relatively long time. Certainly, a drug that was never at any time associated with a seizure reduction is very unlikely to be effective. However, a temporary improvement after the introduction of a given AED is often related by the patients or by the caregivers, in which case one is left with little evidence to go by. Whether tapering and discontinuing a given drug is likely to be associated with withdrawal seizures will only rarely influence the choice of the first drug to be discontinued. Nevertheless, drugs considered to be associated with withdrawal seizures are tapered at a slower rate, and one may choose accordingly to initiate the process relatively early. For slow tapering, the following rates of reduction have been recommended: phenobarbital or primidone, 20% to 25% per month; benzodiazepines, 20% to 25% per month; phe-nytoin, 20% to 25% per week; carbamazepine, 20% to 25% per 2 weeks; valproate, 25% per week; and ethosuximide, 50% per week. For other AEDs, 20% to 25% per 2 weeks may be appropriate.[10] Depending on the severity of the seizure exacerbation, one may chose to increase the dose of the drug back to the previous dose or simply delay the next scheduled dose reduction.

Finally, it is important to anticipate reversible pharmacokinetic interactions. If necessary, the doses of remaining drugs will have to be reduced or increased if it is important to maintain their levels. One should keep in mind that enzymatic inhibition is usually competitive and rapidly reversible. Induction, however, is based on enzyme synthesis and is more slowly reversible. The process of reversal of enzymatic induction may take 3 to 4 weeks to be completed. This reversal of pharmacokinetic interactions does not affect AEDs only. It is

important to remember that enzyme-inducing AEDs may lower the levels of certain anticoagulants, oral contraceptives and other steroids, and cyclosporine. When an enzyme-inducing AED is removed from the drug regimen, it is very important to notify the other specialists, such as the cardiologist, gynecologist, or transplant physician, who are prescribing these drugs, to avoid potentially grave consequences.[10] Overall, there is a lack of published data properly to support recommendations for implementing reduction of overtreatment. This is particularly the case in the pediatric population and for the newer antiepileptic drugs.[10]

Future Approaches

As discussed, most side effects of AEDs respond to dose reduction. To avoid side effects, increasing awareness of medication-induced toxicity and overtreatment and the development of even better-tolerated AEDs will improve the risk-benefit balance of future drug treatment of epilepsy. In addition, advances in pharmacogenetics may help to predict patients with increased risk of adverse effects.[29] Similarly, advances in neuroimaging, such as identification of pretreatment γ-aminobutyric acid (GABA) levels may indicate increased sensitivity to side effects of GABAergic drugs.[22]

Summary and Conclusions

In this chapter, we give an overview on dose-related side effects of drug treatment for epilepsy. Furthermore, we describe clinical scenarios that often lead to side effects and outline specific strategies to minimize or prevent dose-related side effects of AEDs. Most side effects of AEDs respond to dose reduction. To prevent side effects, treatment should be started at very low doses and dose escalation should be slow. Increased awareness of medication-induced toxicity, anticipating inhibitory drug interactions and avoiding overtreatment will reduce the incidence of side effects. The development of even better-tolerated AEDs will improve the risk–benefit balance of future drug treatment of epilepsy. In addition, advances in pharmacogenetics and neuroimaging may help to predict patients with increased risk of adverse effects.

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Chapter 106

Idiosyncratic Adverse Reactions

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Introduction

A perusal of the product information sheets for all antiepileptic drugs (AEDs) reveals a long list of adverse effects. Fortunately, the majority of these adverse effects are mild and predictable from the known pharmacology of the AEDs. These types of adverse reactions are termed type A ("augmented") adverse reactions.[81] They typically tend to be dose dependent, usually improve with reduction in dose, and tend to be identified early during the course of the development of the drug.

AEDs can also cause type B ("bizarre") or idiosyncratic adverse reactions,[81] which are the focus of this chapter. These can be severe and sometimes fatal; they cannot be predicted from the known pharmacology of the drugs. Typically, there is no clear relationship between the occurrence of the reaction and the dose administered to the patient. Nevertheless, for some idiosyncratic adverse reactions, there is evidence of some relationship to dose and/or the speed of titration; for example, the risk of phenytoin-induced rashes seems to be greater if the starting dose is high.[16] Similarly, with lamotrigine, patients started on lower doses and slower titration schedule have a reduced risk of developing rashes.[110]

Idiosyncratic adverse reactions may be acute—occurring soon after the start of therapy—or chronic—occurring after prolonged therapy. They cannot be reproduced in animal models, and the only model in which they can be studied is the human.[71] Idiosyncratic adverse reactions, as the name implies, cannot be predicted and tend to affect a minority of patients taking the drug; the risk factors for individual susceptibility in most cases have not been identified, and genetic factors are thought to be important, although the supportive evidence only exists for a minority of the reactions. Due to their infrequent occurrence, many idiosyncratic adverse reactions are usually not detected during the premarketing phases of drug development and are only identified after licensing when there is high market exposure of the drug. Statistically, this is not surprising given that 30,000 patients have to be exposed to have a 95% probability of detecting 1 case of an adverse reaction occurring at a frequency of 1 in 10,000.[79]

Detection of idiosyncratic adverse reactions therefore largely, although not exclusively, depends on postmarketing surveillance strategies, in particular spontaneous reporting systems such as the MEDWATCH scheme in the United States and the Yellow Card scheme in the United Kingdom. There are limitations of spontaneous reporting systems, however, the most important being the degree of underreporting: Less than 10% of serious adverse reactions are reported.[89] This can lead to a substantial delay in detecting idiosyncratic adverse reactions after the drug is introduced onto the market. In some cases, certain idiosyncratic reactions, although frequent, might not be easily clinically demonstrable, leading to a substantial underreporting. For example, vigabatrin was introduced onto the U.K. market in 1989, but the first reports of visual field constriction appeared 8 years later in 1997,[29] despite the fact that we now know that the prevalence of vigabatrin-induced visual field constriction is between 30% and 40%.[22] In addition, data on adverse reactions submitted to the reporting systems are often incomplete and inadequate, being collected from different sources without expertise or standardization of terms and diagnostic criteria, making their evaluation more difficult.[53]

Idiosyncratic adverse reactions associated with AEDs can take many forms and can affect any body system (Table 1). In this chapter, we do not cover all of the reactions that have been reported with AEDs but focus on certain areas that we feel are perhaps the most important because of their prevalence, severity, or both.

Hypersensitivity Reactions

In this chapter, we use the term hypersensitivity to indicate a presumed allergic drug reaction, most commonly manifested as a maculopapular eruption. In some cases, the associated rash may be more severe, with the development of blisters and involvement of the mucous membranes, as in Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). In other cases, the reaction, with or without rash, may be associated with fever, eosinophilia, arthralgia, and internal organ involvement, a condition known as anticonvulsant hypersensitivity syndrome (AHS), also termed DRESS (drug rash with eosinophilia and systemic symptoms).

Maculopapular eruptions have been reported with most AEDs (Table 2).[5] Fortunately, with most of the drugs, such reactions are relatively mild and infrequent, but they do represent a problem particularly with the aromatic AEDs (phenytoin, carbamazepine, and phenobarbitone) and lamotrigine, in which case they may become more serious with the development of SJS or TEN, or AHS. Maculopapular eruptions are relatively common, occurring in 5% to 15% of patients receiving aromatic AEDs[16,88] and in 10% of patients on lamotrigine.[40] These figures probably represent overestimates, however, because the frequency of rashes is lower with more modern dosing strategies, which start at a low dose and increase the dose slowly.[63] AHS is less common; the risk within the first 60 days of a new prescription for either phenytoin or carbamazepine has been estimated to be 2.3 to 4.5 per 10,000 and 1 to 4.1 per 10,000, respectively.[101] The incidence of SJS and TEN is not known; these conditions are relatively rare, however, with a global population incidence of 1 case per million per year.[18] It is interesting to note that lamotrigine was associated with a higher risk of SJS, particularly in children (1 in 100 incidence), at the time of its introduction.[62]

Table 1 Idiosyncratic adverse reactions reported with antiepileptic drugs

System	Idiosyncratic adverse effect
Cardiac	Arrhythmias, eosinophilic myocarditis
Eyes	Visual field constriction (vigabatrin)
Gastrointestinal	Serum amylase elevation, acute pancreatitis, enterocolitis
Hematologic	Aplastic anemia, pure red cell aplasia Leucopenia, neutropenia, agranulocytosis Thrombocytopenia, platelet dysfunction, von Willebrand disease Macrocytosis, disseminated intravascular coagulation
Immunologic	Selective IgA immunoglobulin A deficiency, immunoglobulin deficiency, systemic lupus erythematosus, pseudo-lymphoma
Kidneys	Interstitial nephritis

Liver	Abnormal liver function tests, microvesicular steatosis, cholestasis, hepatitis, fulminant hepatic failure
Lungs	Pulmonary eosinophilia, acute pneumonitis
Metabolic	Weight gain, insulin resistance, dyslipidemia Folate deficiency, hyperhomocysteinemia Polycystic ovarian syndrome Thyroid dysfunction Osteoporosis, osteomalacia, bone fractures
Skin	Fixed drug eruption, urticaria, maculopapular eruption (and other erythematous generalized eruptions), hypersensitivity syndrome, Stevens-Johnson syndrome, toxic epidermal necrolysis

A wide range of adverse reactions are included here and are termed idiosyncratic; although we may have some knowledge of mechanisms, this list is partial, and in particular cannot explain individual susceptibility.

Table 2 Some Antiepileptic drugs reported to cause hypersensitivity reactions

Antiepileptic drug	Reference
Carbamazepine	96
Ethosuximide	20
Felbamate	13
Gabapentin	87
Lamotrigine	63
Levetiracetam	11
Oxcarbazepine	23

Phenobarbitone	96
Phenytoin	96
Tiagabine	2
Topiramate	93
Valproic acid	45
Vigabatrin	15
Zonisamide	57

This list of antiepileptic drugs causing hypersensitivity is not meant to be exhaustive. It is important to note that some antiepileptic drugs, for example, benzodiazepines, that have been reported to cause reactions that may have an immune basis have not been included. In addition, there have been isolated reports with some of the drugs mentioned here, but this does not necessarily imply causality.

Pathogenesis

Hypersensitivity reactions caused by AEDs have an immune pathogenesis. Initially this was an assumption based on

clinical features (see later discussion) and the rapid recurrence of the reaction on rechallenge.[84] However, more recently, direct evidence indicating that drug-specific T cells are involved in the pathogenesis of hypersensitivity reactions associated with phenytoin,[59] carbamazepine,[59,66] and lamotrigine[67] has been provided. The exact antigens responsible for these reactions, however, remain elusive. Traditionally, it has been assumed that these drugs underwent bioactivation to toxic metabolites such as arene oxides, which then covalently bound to proteins and acted as haptens.[7] According to this hapten hypothesis, the drug–protein conjugate would be recognized as being foreign and an immune response would result. More recently, it has also been suggested that AEDs may be able to stimulate an immune response through direct interaction with the T cell receptors in the absence of any covalent binding or antigen processing.[78] However, such studies have been performed in vitro, and whether the same also occurs in vivo is unclear. It is of interest that it has also been suggested that activation of human herpesvirus 6 (HHV-6) may be responsible for propagating the severity of the hypersensitivity reaction.[69] However, this has largely been shown in Japanese patients, and given the high frequency of background infection with HHV-6 (almost 100% of patients have been exposed to it), it is not clear whether this represents an epiphenomenon or is causal.

Clinical Manifestations

The most common manifestation of a hypersensitivity reaction is a generalized maculopapular eruption (Fig. 1), which typically occurs within the first 3 months of therapy (with a peak in the first 6 weeks). These reactions are usually mild, are not accompanied by systemic symptoms, and resolve on drug discontinuation. Very occasionally, the rash may manifest as an urticarial reaction (FIGURE 1). The rash may be a prelude to the development of full-blown AHS. AHS is manifested by fever (100% of cases), rash (87%), eosinophilia (30%), and atypical lymphocytosis (6%). Internal organ involvement is also common, the liver being the most commonly affected (51%), followed by the hematologic system (23%), kidneys (11%), and lungs (9%).[96] Additional clinical findings may include periorbital or facial edema, exudative tonsillitis, oral ulcers, strawberry tongue, hepatosplenomegaly, flu-like symptoms, myopathy, disseminated intravascular coagulopathy, and pharyngitis.[94]

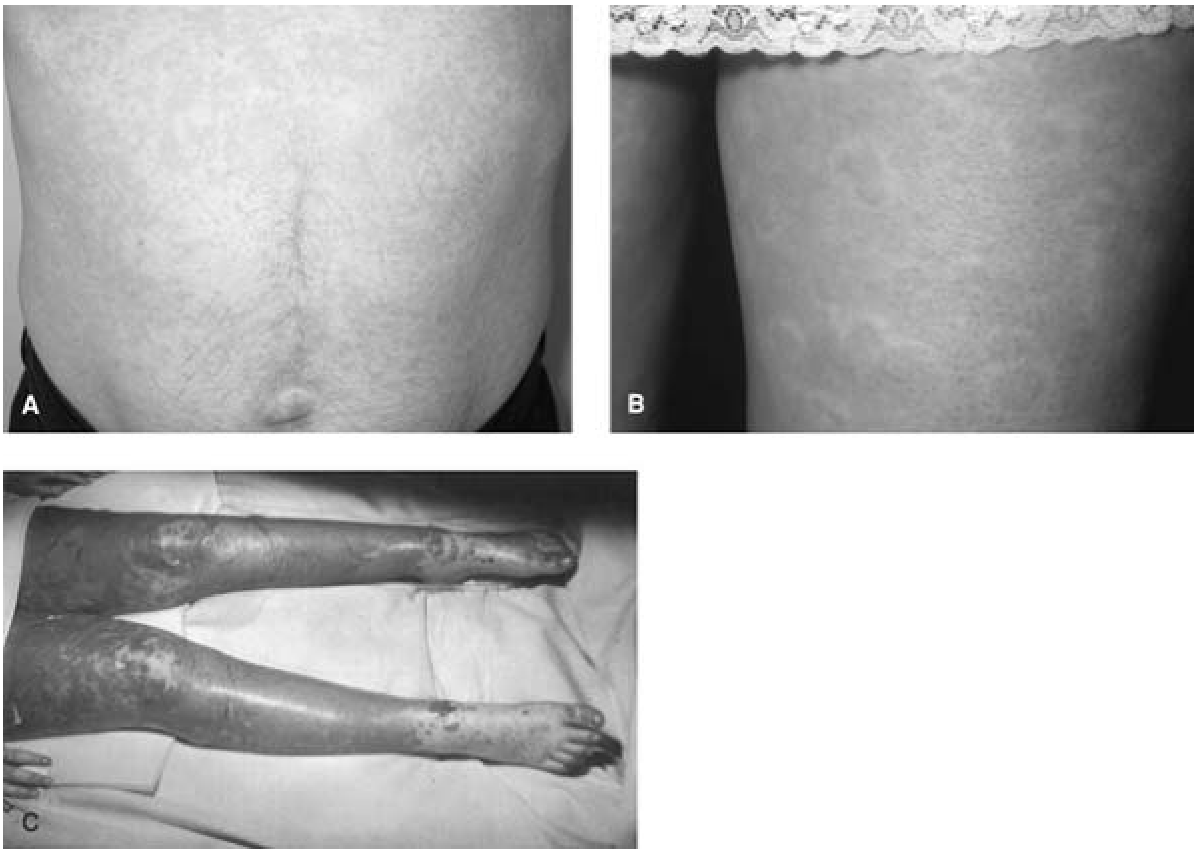

FIGURE 1. Cutaneous manifestations of antiepileptic drug hypersensitivity. **A:** Patient with phenytoin-induced maculopapular eruption. (Figure kindly provided by Dr. Gavin Wong, Liverpool, U.K.). **B.** Patient with carbamazepine-induced urticaria. (Figure kindly provided by Dr. Clodagh King, Liverpool, U.K.). **C.** Patient with carbamazepine-induced toxic epidermal necrolysis. (See the color insert.)

Very occasionally, an erythematous rash may progress to a more severe, blistering condition such as SJS or TEN (FIGURE 1). SJS is characterized by blistering affecting <10% of the body surface area; whereas in TEN, >30% of the body surface area is blistered. Blistering between 10% and 30% is termed the SJS-TEN overlap syndrome.[90] These conditions are characterized by the involvement of at least two mucous membranes, which is uncommon in AHS. Atypical target lesions may also be present in SJS but are absent in AHS. Lymphadenopathy is more common in AHS than in SJS.[39]

Predisposing Factors

The higher incidence of AHS reported in blacks may be a reflection of a higher incidence of epilepsy in this patient group.[94] Chinese seem to have a higher predisposition to develop SJS than whites. Consistent with this, a highly significant association of carbamazepine-induced SJS with *HLA-B*1502* has recently been reported in Han Chinese.[19] This does not seem to be relevant in whites, however, in whom AHS has been associated with major histocompatibility complex (MHC) polymorphisms residing in the ancestral haplotype 8.1.[80]

Management

The key to clinical management is the prompt recognition of the occurrence of the hypersensitivity and withdrawal of the offending drug. With mild maculopapular eruptions, this is often all that is needed, with the reaction improving within a few days. AHS is more severe and may require hospitalization. After withdrawal of the drug, patients may require symptomatic (e.g., antipyretics) and supportive therapy. Corticosteroids are often used, but there is no good randomized, controlled data on their effectiveness.[5] Severe involvement of the internal organs may require treatment by specialists in the field. This is also certainly true of patients with SJS or TEN, in whom treatment in a specialist unit is vital. Nursing care, often in intensive care settings, and adequate topical management reduce associated morbidity and allow a more rapid reepithelialization of skin lesions.[37] Many different therapies have been tried in patients with SJS/TEN, including corticosteroids, intravenous immunoglobulins, and plasmapheresis, but evidence of efficacy is either lacking or contradictory. This issue is beyond the scope of this chapter; see the article by Ghislain and Roujeau[37] for more details. Patients with AHS usually improve over 2 to 3 weeks, but some patients may experience a flare of symptoms a few weeks after the initial improvement. Mortality of AHS, especially if the liver is involved, can be as high as 20%.[94] Patients with SJS/TEN may take several weeks to improve; mortality is high at 5% for SJS and 30% for TEN.[37]

Prevention

Initiation of AED therapy at low doses and slow uptitration seems to be effective in reducing the incidence and severity of hypersensitivity with aromatic AEDs and with lamotrigine.[5] Prompt discontinuation of the offending drug has also been shown to reduce progression to a more severe form of the reaction.[35] There is a theoretical risk that sudden withdrawal of an AED may precipitate status epilepticus; however, this has not been borne out in clinical practice if the patient's treatment is continued with an alternative agent.[39] When the risk of withdrawal seizures is thought to be high, short-term benzodiazepines represent a suitable treatment option. In patients who have had a hypersensitivity reaction with an aromatic AED such as phenytoin, it is prudent to avoid another drug within the same class because of the risk of cross-sensitivity. In vitro, the risk has been estimated to be as high as 80%,[96] but clinically it is probably lower, around 20%.[83] Valproic acid is probably a safe alternative to aromatic AEDs in patients on monotherapy; lamotrigine, despite the fact that it does not demonstrate cross-reactivity with aromatic AEDs, is best avoided because rapid uptitration of the dose is contraindicated. In patients on polytherapy, other drugs such as levetiracetam and gabapentin may also be safe alternatives.

In terms of drug development, prevention of AED hypersensitivity has depended on the development of drugs that do not undergo hepatic metabolism such as levetiracetam, gabapentin, and vigabatrin. Hypersensitivity is not a recognized clinical problem with these drugs, although there have been occasional reports (Table 2). Oxcarbazepine, a keto analog of carbamazepine, is associated with a lower incidence of hypersensitivity, with cross-reactivity being seen in 30% of patients.[48]

Liver Toxicity

Liver injury has been observed with many AEDs; its severity varies and can range from mild asymptomatic elevation of the liver enzymes to acute liver failure, which may require liver transplantation. The hepatotoxicity may be part of the spectrum of AHS, particularly with the aromatic AEDs. However, it can occur in isolation, in which case the pathogenesis may be immune mediated, for example, aromatic anticonvulsants, or due to metabolic idiosyncrasy, for example, with valproic acid.

Aromatic Anticonvulsants

Enzyme induction by these drugs can lead to an increase in γ-glutamyltransferase (γ-GT) and, to a lesser extent, in alkaline phosphatase (ALP). For instance, 64% and 14% of patients on carbamazepine had elevations of γ-GT and ALP, respectively.[99] Phenytoin leads to asymptomatic elevation of γ-GT in almost 100% of recipients.[3] In general, it is not necessary to stop the drug.

Mild elevation of serum transaminases is also commonly seen (22% with carbamazepine[74]), and this sometimes normalizes despite continuation of therapy.[3] The relationship to more severe forms of liver dysfunction is unclear.

Clinically symptomatic hepatic injury is often part of AHS (see prior discussion), although the liver can be affected on its own.[74,96] The exact incidence is unknown; an analysis of all adverse reactions to carbamazepine reported to the Swedish Regulatory Agency showed that liver disorders accounted for 10% of all reactions.[7] The risk was estimated to be 16 cases per 100,000 treatment years. The time to onset of symptomatic hepatotoxicity is about 4 weeks with a range of 1 to 16 weeks.[107] Clinically, liver involvement may be characterized by right upper quadrant abdominal pain and jaundice, which is seen in nearly one half of the patients with hepatitis.[30] Biochemical abnormalities include an elevation of transaminases; however, about 30% of patients with carbamazepine-induced liver injury have a cholestatic pattern. Certainly, cholestasis seems to be more common with carbamazepine than with phenytoin. A prolonged rise in bilirubin levels similar to that seen in primary biliary cirrhosis is observed in patients with vanishing bile duct syndrome secondary to carbamazepine.[31] In patients with hepatocellular necrosis, the rise in bilirubin levels reflects the severity of damage[65] and may be accompanied by changes in clotting parameters. Histologically, granulomatous hepatitis is observed in up to three fourths of patients with carbamazepine-induced liver injury[107] but is less common with phenytoin, which is more commonly characterized by hepatocellular injury accompanied by a prominent inflammatory infiltrate.[64] Prognosis is worse in those with a predominantly hepatocellular pattern than in those with cholestatic injury.[107]

Valproic Acid

Dose-related elevations in hepatic transaminases occur in approximately 40% of patients without attendant symptoms of hepatic dysfunction.[100] These elevations are transient and generally abate with a reduction in dose.[26] Valproic acid also causes weight gain and insulin resistance, which may in some cases lead to the development of a nonalcoholic fatty liver.[55] Occurring less frequently but of greater clinical concern is the potential for fulminant hepatic failure that is irreversible in most cases. Severe hepatic damage initially manifests as nausea, vomiting, abdominal pain, increased seizure frequency, lethargy, and coma.[12,27,28] The onset of symptoms occurs within the first 6 months of therapy in 95% of affected individuals, generally within the first 2 to 3 months. Overall, fatal hepatotoxicity actually occurs in only a small number (<0.01%) of individuals treated with valproic acid, although high-risk groups have been identified (see later discussion). The prothrombin time provides more accurate assessment of residual hepatic function[26] than the elevated high serum transaminase and bilirubin levels. Elevated ammonia levels are also present. The histopathology of valproic acid hepatotoxicity differs substantially from that associated with the aromatic AEDs in that signs of immune involvement and eosinophilia are not present. In fatal cases, the most prominent findings consisted of microvesicular steatosis occurring primarily in periportal zone 1 together with zone 3 necrosis.[110]

The risk of fatal valproic acid hepatotoxicity is highest in children <2 years of age receiving concurrent AED therapy, in whom the incidence was estimated to be approximately 1/500.[27,28] This represents a 16-fold increase in risk relative to children of the same age on valproic acid monotherapy (1/8,000). Patients with inborn errors of metabolism or reduced hepatic mitochondrial activity also appear to be at increased risk for fatal hepatotoxicity associated with valproic acid.[92] Epidemiologic studies have failed to demonstrate a relationship between valproic acid dose and hepatotoxicity.[27,28]

Two general mechanistic hypotheses for valproic acid–associated hepatotoxicity have emerged over the last few years. In each, valproic acid biotransformation appears to be intimately involved in the process leading to hepatotoxicity, although the precise mechanism remains to be elucidated. The immune system is not involved, and this is a form of metabolic idiosyncrasy. The first hypothesis focuses on valproic acid interference with ß-oxidation of endogenous lipids.[9] The second hypothesis focuses on the hepatotoxic unsaturated valproic acid metabolite 4-ene-valproic acid, which is cytotoxic and able to inhibit enzymes in the ω-oxidation pathway.[8]

Felbamate

The risk of hepatic failure due to felbamate was initially estimated to be 1 per 26,000 to 34,000 exposures[76] but has been revised to be approximately 1 per 18,500 to 25,000 exposures.[75] Female individuals seem to be more susceptible, with a time to presentation of 25 to 181 days. Patients may present with nausea, vomiting, and lethargy, with evidence of hepatic dysfunction and eosinophilia. Histology reveals massive to submassive necrosis without significant fibrosis and moderate inflammatory infiltrate.

The mechanism of felbamate hepatotoxicity is unknown but is thought to be due to the formation of a chemically reactive aldehyde carbamate intermediate, which can either undergo detoxification or form the toxic atropaldehyde metabolite.[102] The mechanism by which atropaldehyde causes the liver (and bone marrow) toxicity is unknown. It has been shown that atropaldehyde is cytotoxic and depletes glutathione.[50] In addition, atropaldehyde can bind to glutathione transferases and inhibit their activity, which may in turn enhance its propensity to bind to other cellular proteins and interfere with their function.[25] However, a recent study has also suggested that the reactive metabolite of felbamate is a potent immunogen, suggesting that an immune pathogenesis may also be important.[85] No genetic predisposing factors have been identified.

Management

The essential step in the management of AED-associated hepatotoxicity is the early detection and the recognition that the

drug is responsible for the hepatic injury. Causality is determined as a diagnosis of exclusion by measurement of biochemical, immunologic, and virologic markers to exclude non–drug-induced diseases. In general, for patients that are prescribed a drug with known potential for severe hepatotoxicity, it is a sound practical measure to obtain baseline values for the liver enzymes so that a comparison is readily available. In patients with lower degrees of enzyme elevation (e.g., <3 times the upper limit of normal for transaminases), close monitoring should be instituted. If the drug is suspected and the elevations of hepatic enzymes are progressive or >5 times (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) or >2 times (bilirubin) the upper limit, discontinuation of the offending agent is important. Subsequently, the management of severe hepatic toxicity attributed to AED therapy is essentially supportive. There is little evidence to support the use of steroids in treatment, even when the hepatic injury is thought to be immune mediated.

As mentioned in the discussion of AHS, prevention is important. In the case of valproic acid, the drug should be used with great caution in children <3 years of age and those treated with cytochrome P450-inducing aromatic AEDs and avoided in children with metabolic disorders who are <2 years old. Similarly, extreme caution should be exercised if a family history of fatty acid oxidation defects or urea cycle defects is present. Clearly, any decision to use valproic acid in high-risk groups should be made after careful assessment of the known risks and benefits.

If there has been a hepatic reaction to one aromatic AED, given the possibility of cross-sensitivity, other aromatic AEDs should be avoided. There is no evidence of cross-reactivity between the aromatic AEDs and valproic acid, although it may be prudent to avoid valproic acid in a patient with manifestations of hepatotoxicity. If valproic acid is used, it should be introduced cautiously while liver function is still impaired. Routine monitoring of liver function tests is recommended in product information sheets; however, there is little evidence to support the predictive value of such monitoring.[82] The use of felbamate has been restricted in most countries because of its potential to cause aplastic anemia and hepatotoxicity. However, it may still be useful in certain patients; in such cases, it is important to follow the advice issued by the American Academy of Neurology.[32]

Hematologic Abnormalities

AEDs can induce a number of hematologic adverse reactions, in particular aplastic anemia, agranulocytosis, or thrombocytopenia. The overall rate of blood dyscrasias in a 29,357-patient cohort taking carbamazepine, phenobarbitone, phenytoin, or valproic acid was estimated to be 3 to 4/100,000 prescriptions, with the rate being twice as high in those >60 years of age. The overall rate was 1.2/100,000 prescriptions for neutropenia, 0.9/100,000 for thrombocytopenia, and 0.4/100,000 for hemolytic anemia.[10]

Aplastic Anemia

This is the most severe hematologic abnormality associated with AEDs. Felbamate has the highest potential to cause aplastic anemia; the incidence has been estimated to be 1 per 4,000 to 10,000 exposed patients, compared to an incidence of 2 to 6 per 1 million of the general population.[103] The mechanism is unclear but again is thought to be related to the formation of the toxic atropaldehyde metabolite. Recently, it has been shown that felbamate metabolites can induce apoptosis of hematopoietic cells via redox-sensitive and redox-independent pathways.[46] Patients on carbamazepine have an incidence of aplastic anemia that is five to eight times greater than that in the general population.[43] Aplastic anemia has also been reported very rarely with phenytoin[36] and valproic acid.[1]

Leucopenia and Agranulocytosis

Leucopenia develops in 10% of patients receiving carbamazepine; it is usually transient and of little clinical significance.[43] In some patients, however, carbamazepine can lead to the development of agranulocytosis. A recent population-based study showed that the incidence of community-acquired agranulocytosis was 3.5 per one million patients treated.[47] Carbamazepine was strongly associated with the development of agranulocytosis (odds ratio 115 in an unconditional analysis). Phenytoin was also associated with the development of agranulocytosis with a lower odds ratio (11.6).[47] Patients usually present with fever, oral ulceration, and signs of systemic sepsis. The mechanism is unclear; however, it has been shown that both carbamazepine[33,34] and phenytoin[60,104] undergo bioactivation by neutrophils to toxic metabolites, which may lead to neutrophil depletion either by causing cell death (possibly by apoptosis) or be inducing an immune-mediated reaction.

Thrombocytopenia

Thrombocytopenia has been reported with carbamazepine,[38] phenytoin,[44] lamotrigine,[105] felbamate,[68] tiagabine,[106] primidone,[72] and valproic acid.[24] Most attention has focused on valproic acid. A recent analysis showed that mild thrombocytopenia [platelet count (101–150) × $10^3/\text{mm}^3$] was seen in 9% of patients on valproic acid, whereas moderate thrombocytopenia [(40–1,000) × $10^3/\text{mm}^3$] occurred in 2% of patients. Age (>65 years) and dose (>1 g/d) were identified as risk factors.[21] More-severe falls in platelet count associated with bleeding have also been observed; these may be accompanied by the presence of antiplatelet antibodies.[86] Valproic acid can also induce abnormal platelet function, prolong bleeding time,[95] and lead to the development of acquired von Willebrand disease type I.[1]

The potential problems of hemostasis in patients on valproic acid have led to concern that it may lead to increased blood loss in patients undergoing surgery. Although no increased blood loss has been detected in patients undergoing neurosurgery,[95] patients undergoing orthopedic procedures on valproic acid do seem to have increased blood loss and postoperative blood transfusion requirements[14,17,108] compared with patients not on valproic acid.

Management

As with the other idiosyncratic adverse effects, prompt recognition, withdrawal of the drug, and specialist referral and care are essential. Detection of neutropenia should lead to close follow-up and, if clinically relevant, further investigation. The treatment strategies used in patients with drug-induced hematologic abnormalities are beyond the scope of this chapter, and readers should refer to specialized texts. Although some product information sheets recommend routine monitoring of hematologic parameters, this is not commonly undertaken in clinical practice, largely because the clinical utility has not been defined and monitoring would have to be so frequent as to make it impractical.[82] Frequent clinical assessment, together with

patient education, is therefore important to detect these adverse reactions as early as possible. Patients on valproic acid who are due to undergo surgery do not routinely need to have their valproic acid discontinued. However, patients undergoing major surgery may need assessment of their hemostatic profile, including bleeding time, at least 1 month before their scheduled surgery.[108]

Valproic Acid–Induced Pancreatitis

Valproic acid (VPA) may increase serum amylase concentrations. A review of a database of 3,007 treated patients in 34 clinical trials showed that 2 cases of pancreatitis were probably related to valproic acid, indicating that it is a rare idiosyncratic event unrelated to dose or serum concentration.[77] It can rarely lead to fatalities.[6] Pancreatitis usually presents with progressive epigastric pain, nausea, and vomiting. Symptoms may occur for days, weeks, or months. Younger patients may be at higher risk; a review of 39 patients with pancreatitis showed that most cases (77%) occurred before age 20 years.[6] Twenty-four percent of these patients were on valproic acid monotherapy. Approximately one half of them had been exposed to VPA for <3 months, and in two thirds, pancreatitis appeared during the first year of treatment. In 41% of patients, an associated static encephalopathy was observed (developmental delay, cerebral palsy). Rechallenge is strictly contraindicated because of the risk of recurrence. Any patient on valproic acid who presents with abdominal pain and vomiting should have his or her amylase levels checked. In patients with an elevated amylase in the absence of symptoms, discontinuation of valproic acid is not necessary provided that the other pancreatic enzymes (elastase, lipase, trypsin) are normal.[70] It is important to stress that routine checking of amylase levels in the absence of other clinical signs and symptoms is of little value in predicting pancreatitis.[77]

Vigabatrin-Induced Visual Field Constriction

Vigabatrin was first reported to cause visual field constriction in 1997.[29] The visual field defects occur in approximately 40% of patients.[41,52,54] The prevalence of field defects was 59% using multifocal electroretinography.[61] The mechanism of the retinal damage is unclear, although the visual field defects appear to be the result of peripheral retinal atrophy rather than optic nerve damage. A recent study in rats showed that vigabatrin preferentially accumulates in the retina, and that its toxic effects may be mediated via the γ-aminobutyric acid C receptor, which is highly expressed in the retina.[97] Genetic predisposition has been postulated, but no genetic factors have been identified.[50a]

The evidence suggests that the onset of symptoms varies from 1 month to several years after starting vigabatrin. In virtually all cases, visual field defects have persisted despite discontinuation of vigabatrin, although fortunately there is rarely any further deterioration.[42,51] Male patients appear to be at higher risk of developing retinal toxicity,[49] and cumulative doses > 1,500 g have been found to correlate with the severity of the visual field defects.[58] Patients are usually unaware of the visual field defect, the condition being detected on visual field testing. The typical picture is of bilateral concentric visual field constriction (with some temporal sparing) or of binasal visual field loss. Studies using electroretinograms have shown that vigabatrin affects the inner retina rather than the outer retina. Most of the electroretinographic studies have reported a reduction in *b*-wave amplitude, which may indicate effects on Müller cells, the principal glial cells in the retina, which remove neurotransmitters from the extracellular space after their release from synaptic terminals.[56,91]

Vigabatrin therapy should only be initiated and supervised by an appropriate specialist. Except for the treatment of West syndrome, in which many physicians consider it as a treatment of choice (particularly in infants with spasms associated with tuberous sclerosis),[4,40a] vigabatrin should only be used when all other AEDs have failed.[22] Ophthalmologic consultation and visual field assessment should be undertaken before starting vigabatrin and repeated at 6-monthly intervals during treatment for 3 years, after which screening can be reduced to yearly. Screening should be performed by either Humphrey or Goldmann perimetry. Patients or parents should be counseled about the risk, and patients should be warned to report any new visual symptoms that develop. Those patients with symptoms should be referred for an urgent ophthalmologic opinion with a view to discontinuation of therapy. However, a clinical risk–benefit judgment needs to be made in each case, depending on seizure control and the degree of visual impairment. Patients who have had an excellent antiepileptic response to vigabatrin and demonstrated only mild visual changes may be able to continue therapy safely with close visual monitoring.[73] Vigabatrin should not be used in those patients with preexisting visual field defects, and the dose should not exceed 3 g daily.[4] The use of vigabatrin in young children is further complicated by the fact that conventional perimetry is unsuitable. The use of electroretinography and field-specific visual-evoked potentials may be helpful in the assessment of the pediatric population.[98]

Summary and Conclusions

Idiosyncratic adverse reactions are unpredictable reactions that occur in susceptible individuals and cannot be predicted based on the known mechanisms of action of the offending drug. These reactions are not uncommon following administration of AEDs, and for at least two AEDs (felbamate and vigabatrin) their frequency and severity are sufficiently high as to contraindicate their early use in the treatment algorithm. Typically, there is no clear relationship between the occurrence of the idiosyncratic adverse reactions and the dose administered to the patient; nevertheless, for some reactions, there is evidence of a relationship to dose and/or the speed of titration, as in the case of phenytoin- and lamotrigine-induced skin rashes. The most common idiosyncratic reactions associated by AEDs include cutaneous reactions, which sometimes occur in association with multiorgan involvement (the so-called AHS). Serious idiosyncratic reactions of AEDs also include hepatotoxicity, many hematologic reactions, valproic acid–induced pancreatitis, and vigabatrin-induced visual field defects. Some idiosyncratic reactions involve immune-mediated mechanisms, others have a metabolic basis, and for many the underlying mechanisms are not fully understood. For some reactions, for example, valproic acid–induced liver toxicity, high-risk groups have been identified, and avoidance (or very cautious use) of the offending drug in these groups minimizes their occurrence. Generally, management of idiosyncratic adverse drug reactions requires rapid withdrawal of the causative agent, coupled with supportive measures as appropriate.

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Chapter 107

Long-term Adverse Events

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Introduction

Treatment with an antiepileptic drug (AED) may be prolonged. Recognizing long-term adverse effects of AEDs will have a significant effect on the health of the person with epilepsy. This chapter reviews potential long-term effects of AED therapy.

Cosmetic Effects

AED treatment can result in numerous cosmetic findings including hirsutism, alopecia, changes in hair structure, gingival hyperplasia, and facial feature changes. Valproate use may increase androgen levels, resulting in hirsutism and alopecia in women, whereas phenytoin, carbamazepine, gabapentin, and phenobarbital treatment are associated with hirsutism independent of hyperandrogenism. The hair growth typically occurs on the face and trunk and can last a year or longer after discontinuation. Valproate therapy can also change the texture of hair, producing a kinky hair structure. Gingival hyperplasia is common in phenytoin-treated persons, necessitating good oral hygiene in persons prescribed this AED. Finally, prolonged phenobarbital and phenytoin treatment may result in subtle facial changes characterized by coarsening of facial features. Recognizing these cosmetic changes is important as discontinuation of the AED can result in reversal of findings over time.

Alterations in Body Weight

Many AEDs are associated with changes in weight. Changes in body weight, particularly weight gain, may not only pose substantial health risks, but may lead to reduced adherence to AED therapy. Addressing potential weight change before initiating AED therapy and monitoring weight change during therapy is necessary to understand its effect and impact.

Overall, treatment with valproate appears to be consistently associated with weight gain, both in adult as well as adolescent patients.[55] Weight gain may occur in up to one half of treated patients receiving this medication, and can occur in both men and women. Increases in body weight may be seen relatively early in treatment (within 1 to 2 months), and in one study, did not plateau even after over 6 months of treatment.[5] Although many patients report an increase in appetite, others do not. While the mechanisms underlying weight gain due to valproate are still uncertain, several mechanisms, including reduced energy expenditure due to impaired fatty acid metabolism as well as hyperinsulinemia and insulin resistance, have been proposed.[17,26] The potential development of insulin resistance may be most concerning, as this not only may lead to excessive weight gain, but also may play a role in the development of polycystic ovary syndrome, which has been associated with valproate therapy.[23]

Although the effect appears to be less than valproate-associated weight gain, carbamazepine treatment may also result in weight gain. In a multicenter study comparing carbamazepine and valproate, 32% of patients started on carbamazepine reported weight gain.[35] The reported weight gain was less than with valproate, as only 8% exhibited a gain of >5.5 kg. Increased appetite likely mediates the weight gain and other mechanisms may also be a factor.[22,31]

Weight gain has been noted in association with gabapentin and pregabalin,[58] both newer-generation AEDs that are γ-aminobutyric acid (GABA) analogs and are closely related. Weight gain (10% to 15% increases in body weight) may occur in up to one half of patients treated with gabapentin. Increased appetite is commonly reported in patients receiving this agent.[9] Weight gain associated with pregabalin may be dose related.

In contrast to weight gain seen with several of both older and newer AEDs, weight loss has been reported in patients receiving either felbamate, topiramate (10% to 20% of patients), and, to a lessor extent, zonisamide. In obese patients receiving topiramate, a mean weight loss of approximately 4 kg was seen at 3 months, and 11 kg at 1 year. Reductions in body weight appear to be sustained over time.[4] The mechanisms involved in weight loss are unclear, but patients receiving felbamate or topiramate commonly report substantial reductions in appetite.

Neither lamotrigine nor levetiracetam have been associated with significant changes in body weight, and may therefore be considered to be weight neutral.[16]

Reproductive Health

Effects on reproductive health can occur in childhood, adolescence, and adulthood in women and men with epilepsy. Reproductive dysfunction may be secondary to epilepsy per se, AED treatment, or a combination of both. In females, common symptoms include hyperandrogenism, menstrual disorders with ovulatory failure, polycystic ovary–appearing ovaries or polycystic ovary syndrome (PCOS), and hyperinsulinemia. In males, effects on sperm quality and motility and small testicular size have been described.

AEDs differentially affect steroid hormone levels, depending on how the individual AED affects the cytochrome P450 enzyme system.[41] Treatment with enzyme-inducing AEDs (carbamazepine, phenytoin, and phenobarbital) in women with epilepsy reduces estrone, free testosterone, and androstenedione when compared to a control population without epilepsy. Also, sex hormone–binding globulin (SHBG) is significantly higher in women with epilepsy, further reducing bioavailable sex steroid hormones. In contrast, valproate, an enzyme-inhibiting AED, increases free testosterone in women with epilepsy. Lamotrigine and gabapentin both have no effect on the cytochrome P450 enzyme system and are not associated with changes in sex steroid hormone concentrations. Studies also suggest an independent effect of epilepsy on reproductive hormones. Women with temporolimbic dysfunction had reduced serum estradiol and dehydroepiandrosterone sulfate (DHEAS) levels in one study.[21] Interestingly, these findings were more pronounced in women with left temporal lobe epilepsy.

Women with epilepsy are at increased risk for menstrual cycle abnormalities and anovulation, which may occur in association with PCOS or independent of this endocrinopathy. PCOS is a common endocrinopathy in women. The classification and definition of PCOS have changed as our understanding of the syndrome evolves. A recent consensus group proposed that the syndrome be diagnosed when at least two of the following exist: Oligo-ovulation or anovulation; elevated levels of circulating androgens or clinical manifestations of androgen excess; and polycystic ovaries as defined by ultrasonography.[1] Chronic anovulation most often manifests as oligomenorrhea (less than nine menses per year) and may lead to decreased fertility. Clinical manifestations of androgen excess include hirsutism, androgenic alopecia, and acne. Polycystic ovaries are defined by the number of follicles in the ovary (12 or more) measuring 2 to 9 mm in diameter and/or increased ovarian volume.[1] The syndrome is characterized by obesity, elevated androgen levels (free testosterone), and insulin resistance. Associated health risks of PCOS include impaired glucose tolerance, type II diabetes, hypertension, dyslipidemia, coronary disease, obstructive sleep apnea, and endometrial malignancy.[11] Other reported menstrual cycle disorders include those with abnormal menstrual cycle intervals, oligomenorrhea, polymenorrhea, increased variability of cycle interval, and menometrorrhagia. Increased menstrual cycle disorders have been reported with both temporal lobe epilepsy and idiopathic generalized epilepsy.[19,42]

AEDs, and in particular valproate, may be independently associated with PCOS in women with epilepsy. Hyperandrogenism has been described in reproductive-aged girls and women with epilepsy treated with valproate.[23,38,44,45,64] The findings are significant when compared to control populations that are age and pubertal status matched. Interestingly, this potential effect of valproate has been described in both women with epilepsy and women with bipolar disease.[29,52,53] Of clinical relevance, after discontinuation of valproate, these reproductive abnormalities reverse.[26,42]

Men with epilepsy have reduced fertility, which may be a result of epilepsy and/or AED treatment. Having epilepsy can produce alterations on the hypothalamic-pituitary-gonadal axis as well as effects on sex hormone production and metabolism.[3,39] Testosterone controls both the expression of secondary sex characteristics and production of sperm. Disturbances in testosterone and other male reproductive hormones as well as sperm quality have been described in men with epilepsy.[3,24,27,54,56] Carbamazepine, oxcarbazepine, and valproate are all associated with sperm abnormalities. Testicular volume may also be reduced.[24]

Sexual Dysfunction

Sexual dysfunction, manifested variously as reduced libido, decreased arousal, erectile dysfunction, or anorgasmia, has been reported to occur in 20% to 30% of women and up to 50% of men with epilepsy.[18,39] Both the seizure disorder itself as well as treatment with certain AEDs contribute to this spectrum of adverse effects. Seizures, particularly those arising from the temporal lobe, may alter the release of hypothalamic and pituitary hormones. Epileptic discharges may either stimulate or inhibit the hypothalamus. Treatment with AEDs, particularly the enzyme-inducing drugs including phenytoin, phenobarbital, and carbamazepine, has been associated with decreased sexual function and physiologic arousal in both men and women, as compared to either healthy controls or patients with epilepsy receiving noninducing AEDs.[43] Finally, concomitant psychosocial issues, such as social isolation and low self-esteem, as well as anxiety and comorbid depression can also contribute to dysfunction in both men and women.

Enhanced metabolism of sex hormones as decreased hormone-free fraction has been the most commonly proposed mechanisms involved in both male and female dysfunction. As discussed previously, AEDs that induce the hepatic cytochrome P450 isoenzyme system can increase the metabolism of both gonadal and adrenal hormones. In addition, increased synthesis of SHBG may also be increased in patients receiving enzyme-inducing drugs. Reduced levels of both total and free testosterone, as well as dehydroepiandrosterone and androstenedione, have been reported in patients receiving inducing AEDs. Reductions in bioactive testosterone have been associated with reduced sexual function in both men and women.[20,40] Although prospective studies are warranted to confirm this, it is reasonable to speculate, therefore, that treatment with non–enzyme-inducing AEDs may be less likely to cause these adverse effects.

Bone Health

Fracture rates are increased in patients with epilepsy.[36] Although this increase may in part be secondary to seizure activity, AED effects on bone also contribute. The twofold increased incidence rate among patients with epilepsy compared to controls in a pharmacoepidemiologic based registry highlights this increased risk.[62]

Presently, the most clinically relevant predictor of fracture is reduced bone mineral density (BMD). BMD may be decreased with AED use, particularly enzyme-inducing AEDs. Studies describe higher rates of osteopenia and osteoporosis than expected in persons treated with AEDs.[49] In addition, longitudinal bone loss is evident in men and women treated with enzyme-inducing AEDs, particularly phenytoin.[2,12] Although most of the evidence suggests that enzyme-inducing AEDs result in reduced BMD, valproate use has been associated with decreased BMD in children and adults with epilepsy.[57,59]

In addition to effects on BMD, biochemical indices including calcium, vitamin D metabolites, parathyroid hormone, and markers of bone turnover (formation and resorption) may be affected in association with AED treatment.[47] Many studies find lower calcium, phosphate, and vitamin D metabolite concentrations in persons treated with enzyme-inducing AEDs. Parathyroid hormone levels and markers of bone turnover have been shown to be increased in individuals treated with enzyme-inducing AEDs. These findings are consistent with the theory that enzyme induction results in increased catabolism of vitamin D, leading to a relative hypocalcemia, increased parathyroid hormone, and increased bone turnover to restore calcium concentrations.[13] However, recent studies do not find a correlation of vitamin D with BMD reduction and some find no significant reduction in vitamin D metabolite concentrations in persons treated with enzyme-inducing

AEDs.[48] In addition, evidence of abnormalities in bone health associated with valproate use suggests that other mechanisms may also be influencing the findings.[57,59] The described abnormalities in biochemical indices suggest an effect of AEDs on markers relevant to bone health. However, the mechanisms to explain why these effects occur or if they result in decreased BMD and most importantly fracture are not yet elucidated.

Much of the above discussion has focused on enzyme-inducing AEDs and valproate. Limited information is available on whether newer AEDs such as lamotrigine, topiramate, zonisamide, and levetiracetam affect bone health.

Clinically, all persons should be instructed to take at least the recommended daily allowance of calcium and vitamin D.[10] The recommended daily allowance of calcium depends on age, sex, and reproductive status. It is recommended that all persons obtain at least 400 IU of vitamin, with higher amounts necessary for those treated with enzyme-inducing AEDs. BMD screening with dual energy x-ray absorptiometry (DEXA) is warranted for persons with prolonged AED exposure, especially enzyme-inducing AEDs, and those with other risk factors known to affect bone health or increase one's risk for osteoporosis. Screening of vitamin D status may be useful. If a person has evidence of bone disease, consider changing AED treatment and referring that person for an endocrine bone health evaluation.

Thyroid Function

Thyroid hormones may be affected by AED treatment. Low serum thyroid hormone has been described in association with carbamazepine therapy and has been postulated to be secondary to induction of the hepatic cytochrome P450 enzyme system, leading to an increase in thyroid hormone metabolism.[25,68] Recent studies also suggest that oxcarbazepine treatment results in low serum thyroid hormones in women, men, and children with epilepsy.[28,63] Results are mixed and contradictory in studies evaluating effects of valproate on thyroid function.[25,28,63,65] There are no data available for other AEDs.

Thyroxine and free thyroxine levels are low in persons treated with carbamazepine and oxcarbazepine.[28,63,64,66] Induction of the cytochrome P450 enzyme system may be resulting in some of the findings. However, other mechanisms may also be involved as oxcarbazepine induces the cytochrome P450 enzyme system at high doses. Although thyroxine and free thyroxine are reduced, thyrotropin is normal and all studied persons are clinically euthyroid. In addition, in a cohort of young girls, the reported thyroid hormone changes had no effect on growth and pubertal development and normal serum thyroid hormone concentrations were restored after discontinuation of both carbamazepine and oxcarbazepine.[63]

Studies do not find consistent results of the effect of valproate treatment on thyroid function. Thyroid function has been assessed in adults and children with epilepsy treated with valproate. Although some studies report elevated thyrotropin,[63] others find no abnormalities.[25,65] As reported in girls treated with carbamazepine and oxcarbazepine, there were no effects of valproate on linear growth or pubertal development.[63]

Peripheral Neuropathies

Chronic administration of several AEDs including carbamazepine and phenytoin have been associated with peripheral electrophysiologic abnormalities and, occasionally, clinically significant peripheral neuropathy.[33] In particular, chronic administration of phenytoin has been cited as a cause of peripheral neuropathy involving distal extremity weakness, areflexia, and dysesthesias. Alterations in touch, vibration, and proprioception in the legs and feet have been previously reported. In addition, several reports have described slowing of nerve conduction and electromyographic evidence of distal denervation.[60,61] Sural nerve biopsy in a patient presenting with clinical signs of phenytoin-associated peripheral neuropathy demonstrated demyelination of large myelinated fibers and axonal atrophy.[50]

Although the length of drug exposure sufficient to cause either clinical or electrophysiologic changes is unclear, it appears that long-term exposure (>5 years) as well as exposure to relatively high serum concentrations pose the greatest risk. Conversely, Yoshikawa et al. have reported distal paresthesia and motor weakness occurring in a patient only hours following the administration of phenytoin.[67] Although folate deficiency, which may be common in patients receiving phenytoin, may result in peripheral neuropathy, evidence for this is lacking.[46]

Reduced nerve conduction velocities have also been reported in some studies of patients receiving carbamazepine, but not others.[8,14] Chronic treatment with either carbamazepine or sodium valproate does not appear to result in clinical symptoms of neuropathy.[6]

Cerebellar Atrophy

Cerebellar dysfunction with features of ataxia, incoordination, dysarthria, dysmetria, intention tremor, and nystagmus are well-recognized manifestations of acute phenytoin treatment. Most commonly, these symptoms are associated with elevated phenytoin serum concentrations, and are reversible. Less commonly, irreversible cerebellar dysfunction and atrophy have been observed in patients receiving long-term phenytoin treatment.[15,32,37] Cerebellar atrophy has been demonstrated in several patient series using both computed tomography (CT) and magnetic resonance imaging (MRI) techniques.[30,34] Although the relationship between phenytoin dose and/or concentration and the development of cerebellar degeneration is unclear, the available clinical evidence would suggest that patients with chronic exposure to elevated serum concentrations may be at particular risk.

The mechanisms underlying these changes are unclear. Cerebellar histopathologic changes including loss of Purkinje cells and granule cell damage have been experimentally produced in some animal models of phenytoin exposure, but this finding has not been consistent, possibly due to the confounding effects of seizure- and coma-induced hypoxia seen in some animal experiments.[7] It therefore is reasonable to speculate that repeated episodes of hypoxia resulting from repeated convulsions over time may account for these observations. The implication therefore is that cerebellar degeneration may be more of a consequence of poorly controlled seizures, particularly generalized convulsions, than of long-term exposure to phenytoin. However, in one small case series,[37] McLain et al. noted the occurrence of cerebellar atrophy confirmed by CT that was not associated with repeated, generalized seizures. In this series, patients did appear to have phenytoin serum concentrations that were above the commonly accepted therapeutic range (>20 µg/mL). In addition, cerebellar degeneration has also been observed in patients receiving this agent who did not have seizures.[51]

Summary and Conclusions

Potential adverse effects on cosmetic appearance, body weight, reproductive health, sexual dysfunction, bone health, the thyroid, peripheral neuropathies, and cerebellar volume can occur in association with long-term AED treatment. Recognizing these effects, changing AED therapy if possible, and providing acute treatment or referral for treatment is important in providing optimal care of persons with epilepsy.

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Chapter 108

General Principles: Teratogenicity of Antiepileptic Drugs

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Introduction

Over the past two decades advances in the management of epilepsy and an increased armamentarium of effective antiepilepsy drugs (AEDs) have permitted persons with epilepsy greater freedom and improved quality of life. Women with epilepsy who in past generations were actively discouraged from marriage and childbearing are now marrying at rates equivalent to women without this disorder. This freedom has presented these patients and their physicians with new challenges. Women with epilepsy are unlikely to be able to discontinue medication during pregnancy and as such are at greater risk for complications of pregnancy and adverse pregnancy outcomes. An increased risk of congenital malformations is well recognized as one of these, but mounting evidence suggests that cognitive dysfunction is also seen with increased frequency.

Major efforts have been made to assess the risk of AED use in pregnancy to minimize the risk to both the mother and the child. In the last few years new data have become available on the AED effects on postnatal development. Therefore, although some critical issues remain unsolved, it is important to review the state of knowledge of reproductive and developmental hazards related to AEDs.

An increase in seizure frequency during pregnancy has been reported in approximately 30% of women, which potentiates the risk of maternal complications and perhaps increases the risk of fetal insult (resulting from bradycardia). This information alone precludes discontinuation of antiepileptic medications during pregnancy.

Historical Aspects

The first report of a malformation associated with an AED described a child exposed in utero to mephenytoin, who developed microcephaly, cleft palate, malrotation of the intestine, and a speech defect, and had an IQ of 60.[186] The pregnancy was also complicated by vaginal bleeding.

In 1964 Janz and Fuchs[120] performed a retrospective survey at the University of Heidelberg to evaluate the problem of AED-associated malformations. Their study included 426 pregnancies in 246 mothers with epilepsy. The rates of miscarriages and stillbirths were increased for these patients, but the malformation rate was only 2.2%, not significantly different from that of the general population of West Germany. The authors concluded that AEDs were not associated with an increased risk of malformations.

Pantarotto et al.[208] described a neonate with aplasia of the bone marrow after phenytoin exposure in utero. Centa and Rasore-Quartino [34] reported the first case of congenital heart disease following intrauterine exposure to phenytoin and phenobarbital. Melchior et al. [176] described orofacial clefts with exposure to primidone or phenobarbital.

In a letter in *Lancet* in 1968, S.R. Meadow reported six cases of children with orofacial clefts, four of whom had additional abnormalities of the heart and dysmorphic facial features. All of these children had been exposed to AEDs in utero. He noted that similar abnormalities had been reported following the unsuccessful use of abortifacient folic acid antagonists. Since some AEDs act as folic acid antagonists, he postulated that this might account for AED teratogenicity, and he asked other clinicians to inform him of similar cases. [173]

The first report of malformations associated with a specific AED was published in 1970. [88] Trimethadione was implicated as a teratogen in 8 of 14 pregnancies in which it was taken in the first trimester.

Dr. Meadow's 1968 inquiry concerning AED-associated malformations resulted in the collection of 30 additional cases. This prompted a retrospective survey in which 427 pregnancies in 186 women with epilepsy were studied. This demonstrated for the first time a clear increase in the malformation rates of infants of mothers with epilepsy (IMEs). Speidel and Meadow concluded that (a) congenital malformations are twice as common in IMEs exposed to AEDs; (b) no single abnormality was specific for AED exposure; and (c) a group of these children would have a characteristic pattern of anomalies, which, at its fullest expression, consisted of trigonocephaly, microcephaly, hypertelorism, low-set ears, short neck, transverse palmar creases, and minor skeletal abnormalities.

During the last two decades, a wide variety of congenital malformations have been reported, and every anticonvulsant, whether old or new, has been implicated as a cause. No anticonvulsant drug can be considered absolutely safe in pregnancy, yet most of these drugs do not produce any specific pattern of major malformations. A possible exception to this is the association of sodium valproate with neural tube defects (NTDs). Robert and Guibaud[219] were the first to relate valproate to NTDs. Working in a birth defects registry in the Rhone Alps region of France, they reported NTDs in IMEs exposed to valproic acid in utero. Between August 1979 and August 1982, there were 72 infants with lumbosacral NTDs born in this region. Nine of the 72 (12.5%) had been exposed to valproic acid, although two of the nine also had a family history of NTDs. The mothers of five of these children took valproate monotherapy, one took valproate and phenobarbital, and one took valproate and clonazepam.

Table 1 Incidence of Congenital Malformations in the Offspring of Mothers with Epilepsy Compared to Control Groups

	Offspring of mothers with epilepsy			Offspring of mothers without epilepsy		
		Malformations			Malformations	
Study design	Total outcomes	Number	%	Total outcomes	Number	%
Historical cohorts[3,9,26,27,41,63,71,76,89,121,124,143,162,196,203,220,227,231,240,242,269,275]	12,310	644	5.2	2,431,065	65,064	2.7
Prospective cohorts[37,52,56,68,70,84,105,109,112,115,122,123,138–141,145,178,181,198,205,218,230,237,239,244,247,260,266,278,281]	5,018	327	6.5	655,009	16,212	2.5
Retrospective cohorts[41,110,150,232,267]	800	41	5.1	95,550	2,563	2.7
	18,128	1,012	5.6	3,181,624	83,839	2.6

In an attempt to clarify this observation further, Robert et al. [220] identified 141 pregnancies in women with epilepsy using a combination of questionnaires and electroencephalogram (EEG) registries. This unselected cohort had a malformation rate of 17.7% in the offspring, including four cases of spina bifida. In all cases, there was intrauterine exposure to valproic acid, although only one woman was on valproate monotherapy.

Subsequent analysis of these exposures identified spina bifida aperta as the specific NTD associated with the valproic acid exposure. [158] Methodologic problems make frequency estimates imprecise, because most published data are case reports, case series, or very small cohorts from registries that were not designed to evaluate pregnancy outcomes. The prevalence of spina bifida with valproate exposure is approximately 1% to 2%,[157] and with carbamazepine 0.5%.[103,223] However, a prospective study in the Netherlands found that IMEs exposed to valproate had a 5.4% prevalence rate of spina bifida. Average daily valproate doses were higher in the IMEs with spina bifida (1,640 ± 136 mg/day) than in the unaffected IMEs (941 ± 48 mg/day). Another group of investigators found that valproate doses of 1,000 mg/day or plasma concentrations of 70 μg/mL or less are unlikely to cause malformations.[128] Both groups recommend that valproate dosage be reduced whenever valproate must be used in pregnancy.[128,204]

Overall, data available in the literature suggest that IMEs who have intrauterine exposure to anticonvulsant drugs are twice as likely to develop birth defects as infants not exposed to these drugs. Table 1 shows the incidence of malformations reported by historical cohort and prospective and retrospective controlled studies.

Mechanisms of Antiepileptic Drug Teratogenesis

There are a number of factors that could account for the increased rates of malformations seen in IMEs. These include maternal seizures during pregnancy, a genetic predisposition related to having epilepsy, falls and injuries from seizures, and lower socioeconomic status and its attendant limited access to prenatal care. There are, however, a number of observations that strongly implicate AEDs as the cause of such teratogenicity seen. Comparisons of malformation rates in the offspring of mothers with epilepsy treated with AEDs compared to those without AED treatment consistently reveal higher rates in the children of the treated group (Table 2).

The precise mechanisms by which AEDs cause birth defects are not fully known. Susceptibility to AEDs and the expression of teratologic outcome may be under genetic control, as suggested by the variability in the frequency and pattern of malformations found in humans and in experiments with inbred mouse strains.[30,46,73,159,217,246,265]

One of the earliest hypotheses proposed that the teratogenic effects of AEDs are related to their interference with folate metabolism. The rationale is that, in humans, low maternal levels of folate and vitamin B_1 and high levels of homocysteine are associated with an increased risk of NTDs.[38,137,179,279] These observations, together with the finding that periconceptional folate supplementation significantly reduces the risk of birth defects and, in particular, that of NTDs,[29,36,100] suggest that folic acid antagonists may increase the risk of congenital malformations. Low folate levels have been found consistently in pregnant women treated with AEDs.[102] In addition, the risk of adverse outcome increases with rising AED blood concentrations and decreases with folate levels.[44,45,199]

Details of the relationships between AEDs and NTDs and between AEDs and folic acid are not yet clear, as it is difficult to explain (a) why the use of multivitamin supplements containing folic acid reduces the risk of malformations caused by some folic acid antagonists but not that due to AEDs[100] and (b) why the risk of NTDs is associated with valproate rather than with phenytoin and phenobarbital, two drugs that decrease folate levels the most. Nevertheless, the available experimental data support the idea that folate metabolism is likely to be involved in some particular aspects of valproic acid teratogenesis.[5,60,62,107,129,241,254,255,270]

Bioactivation of AEDs by the embryonic cytochrome P450 (CYP) system to arene oxide reactive intermediates, which are thought to be teratogenic, has been a prevailing hypothesis for many years.[6,20,30,74,75,153,155,169,208,215,225,246] This conclusion was consistent with the particular high risk associated with combinations of carbamazepine, phenobarbital, and valproate reported in humans,[155] and interpreted as being the result of the cumulative effects of inducing AEDs and valproate inhibition of epoxide-hydrolase responsible for epoxide elimination. The use of extended-release forms of carbamazepine and valproate may lower the risk factor as peaks and valleys are eliminated in these preparations. Further studies are needed to assess this concept.

Table 2 Incidence of Congenital Malformations in the Offspring of Mothers with Epilepsy Treated with Antiepileptic Drugs and of Untreated Mothers Compared to Control Groups

	Offspring of treated mothers with epilepsy			Offspring of untreated mothers with epilepsy			Offspring of mothers without epilepsy		
		Malformations			Malformations			Malformations	
Study design	**Total outcomes**	***N***	**%**	**Total outcomes**	***N***	**%**	**Total outcomes**	***N***	**%**
Historical cohorts[3,9,71,121,124,143,162,203,220,227,240,269]	3,137	201	6.4	747	24	3.2	1,192,652	23,727	2.0
Prospective cohorts[37,56,68,70,115,123,138-141,218,239,244,260,266]	2,395	146	6.1	669	21	3.1	367,997	9,644	2.6
Retrospective cohorts[110,150,232,267]	558	23	4.1	109	1	0.9	1,076	13	1.2
	6,090	370	6.1	1,525	46	3.0	1,561,725	33,384	2.1

An argument against the foregoing proposal is that the content of CYP in the embryo is low, making bioactivation of AEDs unlikely. Other information against a bioactivation mechanism for teratogenesis is that the most teratogenic AEDs, such as trimethadione and ethotoin, which cause the same pattern of birth defects as phenytoin, are not metabolized through an

epoxide metabolite.[72,271] Potentiation of phenytoin teratogenesis by drugs inhibiting CYP-mediated metabolism[250] further argues against a role for the CYP system in teratogenic bioactivation of phenytoin.

Another postulated bioactivating pathway is AED co-oxidation to free radical intermediates. After interaction with molecular oxygen, these compounds liberate reactive oxygen species (ROS), which may be teratogenic. Deficiency of free radical scavenging enzymes, responsible for eliminating ROS, has been associated with malformations in the offspring of mothers with epilepsy taking AEDs.[210,272,273] A recent hypothesis proposes that reactive intermediates may be produced by AED-induced embryonic bradycardia/arrhythmia. Such arrhythmias cause periods of interrupted oxygen supply and generation of highly toxic ROS in the embryonic tissues during the reoxygenation/reperfusion phase.[12,39]

Other postulated mechanisms are tissue damage due to fetal hemorrhage, possibly involving vitamin K deficiency,[114] or interference with placental carnitine transport.[277]

Recently, mechanisms involving homeobox (HOX) genes have been proposed as an explanation for AED teratogenicity.[194] Retinoic acid signaling, involved in regulating transcription of genes that are critical to early brain development, may be affected by teratogens.[221] Such effects include alteration of the expression of retinoic acid receptor[87] or valproate inhibition of histone deacetylases,[23,61,91,94,212] a key element in the regulation of many genes playing important roles in cellular proliferation and differentiation.[69,133,170] Phosphodiesterase-mediated inhibition of cyclic adenosine monophosphate,[85] increase of ROS levels,[190] disruption of normal pH within the embryonic milieu,[233] or inhibition of the detoxifying epoxide hydrolase could also be relevant to the teratogenic effect of valproic acid.[116]

In summary, the mechanisms behind developmental toxicity of AEDs are presently far from completely understood, are likely to be multiple, and undoubtedly differ between individual AEDs.

Pathophysiology of Neural Tube Defects

NTDs are uncommon malformations occurring in 6 in 10,000 pregnancies. Spina bifida and anencephaly are the most commonly reported NTDs; they occur in approximately 4,000 pregnancies annually, affecting 2,500 to 3,000 births in the United States each year.[113,187] The types of NTDs associated with AED exposure are primarily myelomeningocele and anencephaly, which result from abnormal neural tube closure between the third and fourth weeks of gestational age.

Previous thinking about NTDs visualized the fusion of the neural tube as one in which the lateral edges met in the middle and fused both rostrally and caudally, similar to a bidirectional zipper. Recent studies have suggested that there are multiple sites for neural tube closure,[90,259] and that different etiologies may result in different types of abnormality. There are four separate sites along the neural tube where neurulation develops. The first is midcervical; the second is at the cranial junction of the prosencephalon and mesencephalon; the third, which fuses in a caudal direction only, is at the site of the future mouth or stomadeum; and the fourth is the region over the rhombencephalon between the second and third regions.[259] The timing of closure differs among the various sites.

The majority of human NTDs can be explained by failure of one or more closure sites. Anencephaly with frontal and parietal defects is due to failure at the second closure site. Holoacrania, which also involves defects of the posterior cranium to the foramen magnum, is due to failure of closure of the second and fourth sites. Lumbar spina bifida results from failure of the first closure site. The development of closure sites is under genetic control but is also affected by environmental factors. In twins, concordance rates are only 56% for anencephaly and 71% for spina bifida. In Great Britain there is a male preponderance of lumbar spina bifida and female preponderance of holoacrania and anencephaly. Even valproic acid appears to have species differential effects being associated with spina bifida in humans and exencephaly in mice.[235] A number of risk factors are associated with neural tube defects.

The strongest association for NTDs (relative risk [RR] 3% to 8%) is a previous pregnancy with NTD.[180] There are strong ethnic/geographic associations with NTDs. Rates per 1,000 are 0.22 for Caucasians, 0.58 for persons of Hispanic descent, and 0.08 for persons of African descent. The incidence of NTDs in Mexico is 3.26 per 1,000; for Mexican-born persons living in California, 1.6 per 1,000; and for U.S.-born persons of Mexican descent, 0.68 per 1,000.[97] Diabetic mothers have 7.9 times the rates of NTDs in their offspring.[17] Deficiencies of glutathione, folate, vitamin C, riboflavin, zinc, cyanocobalamin, and selenium and excessive exposure to vitamin A have been linked to NTDs. Higher rates are seen in children of farmers, cleaning women, and nurses.[28,171] Pre-pregnancy weight also seems to be a factor. The RR for NTDs in women weighing 80 to 89 kg is 1.9, and 4.0 for those weighing over 110 kg. AED exposure may be a necessary but not sufficient risk factor for the development of NTDs. Women with epilepsy, as all women

of childbearing age, should be supplemented with folate. The dose recommended by the Centers for Disease Control and Prevention of 400 µg/day may not be high enough for many women who do not metabolize folate effectively. For those individuals with a history of NTDs, 4 mg of folic acid daily is recommended. Even with folate supplementation, women taking valproate should avail themselves of prenatal diagnostic ultrasound to detect NTDs.

Variables Confounding the Association of Antiepileptic Drugs with Malformations

A primary question in evaluating the relation between maternal epilepsy and congenital malformations is whether the association is further confounded by the genetics of epilepsy itself. Genetic susceptibility to teratogenic effects of AEDs is suggested by family studies.[58,64,86,130,144,160,165,206,211,261,268] Several case-control series reported a higher proportion of relatives with epilepsy in patients with cleft palate or lip[2,57,65,78,136] or NTDs.[156,219] Greenberg et al.[93] found extensive use of phenobarbital among 414 children with cleft palate or lip. However, the statistical significance of the association disappeared after exclusion of cases with a positive history of malformations. Other cohort studies have confirmed familial occurrence of fetal abnormalities.[7,9,32,43,48,63,128,138,174,184,192,193,200,205,243,269] Parental epilepsy was also found to increase birth defects,[49,53,128,136,205] although the majority of such studies reported conflicting findings.[18,110,123,156,200,204,228]

Seizure occurrence during pregnancy does not increase malformation rates according to most[9,56,71,76,110,141,192,218,228,237,240,243,244,281] but not all the authors.[126,158,164,192,203] The issue of whether epilepsy per se increases the risk of congenital malformations was first raised by a large American and Finnish study[237] that reported higher rates of malformations in children of treated mothers and fathers with epilepsy. Later studies confirmed these findings and added that even untreated mothers with epilepsy had a higher risk of having a child with birth defects.[18,79,139,141,163,177,216] Other investigators, however, found no increased risk of congenital malformations among children of fathers with epilepsy.[42,80,157]

A recent meta-analysis concluded that malformation rates among offspring of women with untreated epilepsy were similar to that of nonepileptic controls.[77] However, these results should be interpreted with caution because of differences in ascertaining cases and controls, as well as the small number of studies and cases considered. Data from the U.K. Registry, the largest prospective study available today, indicate that among the 3,607 enrolled pregnancies, the malformation rates for 239 women with epilepsy who had not taken AEDs during pregnancy (3.3%) were similar to those of 2,598 women with monotherapy exposures (3.7%).[185] Data from 31 studies including exposed offspring, nonexposed offspring, and healthy controls confirm that while treatment of pregnant women with AEDs undoubtedly increases the risk of birth defects, the increased risk cannot be entirely ascribed to AEDs (Table 2).

The more common malformations found in the offspring of women with epilepsy are heart defects, cleft lip or palate, hypospadias, and limb defects. There is fairly solid evidence of a specific association between NTDs and valproic acid[10,21,32,101,125,157,204,219,231] and, to a lesser extent, carbamazepine.[10,101,223] The effect of valproic acid appears to be restricted almost entirely to the posterior neural cord.[158,160] Some studies suggest that the risk of congenital heart disease is increased in pregnant women exposed to barbiturates.[8,10,32,56,192] This association emerges also from data of the U.S. Registry,[112] although the authors neglected to point out that 4 of 77 children exposed to phenobarbital were born with congenital heart defects (5.2%). The associations between valproic acid and limb reduction defects[10,222] or hypospadias[10,231] and between barbiturates and cleft palate/lip[10,125,192] need to be confirmed.

Each of the older AEDs has been considered the most teratogenic when compared to other AEDs or no treatment. Several studies reported a higher risk for pregnancies exposed to carbamazepine,[52,123,154,230,231] primidone,[128,192] phenobarbital,[112,154,192,203,266] or phenytoin.[56,71,154,203,227,247] In recent years, considerable attention has been paid to valproic acid teratogenicity. The joint analysis of five European countries[230] and a large retrospective controlled study from The Netherlands[231] found an increased risk of malformations with valproate and carbamazepine monotherapy compared to healthy controls. The Joint Japanese, Canadian, and Italian study reported an increased risk for valproate and primidone monotherapy in comparison to nonexposed pregnancies.[128] A large historical cohort from Finland found higher risks associated with both valproate monotherapy and polytherapy compared to untreated pregnant women.[11] Other studies have found an increased risk for valproate monotherapy compared to carbamazepine,[185,275] lamotrigine,[185] or unspecified other monotherapies.[278] In a large prospective single cohort from Finland,[123] logistical analysis demonstrated that valproic acid, carbamazepine, oxcarbazepine, low serum folate concentrations, and low maternal educational levels were independently associated with an increased risk of malformations. Finally, the Australian Registry, an observational and partly prospective study, also found that any exposure to valproate was associated with an increased rate of malformations compared to a small group of 24 untreated patients.[257]

Data indicating a higher risk for pregnancies exposed to valproic acid compared to other AEDs need to be interpreted in consideration of published data that have failed to find an association between increased risk and exposure to valproic acid.[22,48,127,155,192,203,204,227] The lack of evidence for valproic acid teratogenicity compared to other AEDs can be accounted for by confounding bias characterizing the studies in question. For example, a family history of malformations is a relevant factor considering that the risk for NTDs in the siblings of affected individuals ranges from 3% to 8%.[180] These rates are consistently higher than those found in the general population and even higher than the risk posed by exposure to valproic acid or carbamazepine. Nevertheless, of the aforementioned studies, only the Joint Japanese, Canadian, and Italian study, the Australian Registry, and a large single-center prospective study from Finland[123,128,257] have taken into account familial malformations, other maternal diseases, and seizures during pregnancy, while the prospective U.K. Registry considered family history of malformations.[185] Only three studies considered the type of epilepsy,[128,230,231] four maternal smoking,[123,230,275,278] and all but one[278] maternal age. It is remarkable that none of the studies evaluating family history of malformations[123,128,185] demonstrated differences in the rate of birth defects among valproate and other monotherapies, with the exception of the U.K. Registry, which reported a higher risk for valproate (6.2%) compared to carbamazepine (2.2%).[185] The findings of the U.K. Registry[185] suggest that the risk of malformations attributed to valproic acid is likely to depend on confounding factors. In the U.K. Registry, there was a higher rate of malformations among 715 pregnancies exposed to valproic acid (6.2%) than in the 647 exposed to lamotrigine (3.2%), but the significance was lost after adjustment for confounding factors. Moreover, the authors reported similar risks for pregnancies exposed to lamotrigine at daily doses of 200 mg or higher (5.4%) and to valproic acid at mean doses of 600 to 1,000 mg/day (6.1%).

A majority of studies have found that polytherapy carries a greater risk than monotherapy,[126,128,149,185,236,275] nonexposed pregnancies,[11,47] or healthy controls.[110,123,126,128,149,203,236,275] This association of malformations and polytherapy is further supported by studies comparing malformation rates in two chronologic cohorts. In a multi-institutional Japanese study, the malformation rate in 172 IMEs born between 1978 and 1984 was 13.5% but fell to 6.2% in 145 IMEs born between 1985 and 1989. The decline was attributed to an increase in monotherapy: 16.1% in the first cohort but 63.4% in the second.[127] Similar results were reported by two other studies that compared two consecutive cohorts.[158,200] Other authors have failed to find an increased risk associated with polytherapy.[32,52,66,121,123,124,175,204,244,247,257,266]

The only drug for which many studies have reported a significant dose–effect relationship is valproic acid,[11,59,119,128,172,230,231,257] although three recent publications have failed to find such a difference.[123,228,278] Considering new AEDs, the U.K. Registry has recently reported a significant dose–effect relationship for lamotrigine.[185] Data on carbamazepine have consistently demonstrated similar mean daily doses among cases with or without malformations.[123,126,149,172,185,198,204,205,228,230,231,244,257] Data on the other established AEDs are conflicting. Some authors have concluded that the risk of malformations is greater for higher phenytoin[37,43,96,128,181] and phenobarbital[127] dosages, while others reported no significant association for either phenytoin[64,126,149,192,198,230,240,244,257] or phenobarbital.[66,71,123,126,149,181,230,240,244] Discrepant findings on the teratogenic risk related to AED doses or polytherapy may depend on the confounding effects of the severity of epilepsy or on differences in the teratogenic potential of specific combinations.

Use of Newer Antiepileptic Drugs in Pregnancy

Since 1993, a number of effective new AEDs have been introduced in North America. These include gabapentin, felbamate, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, and zonisamide, all of which are now available in the United States. Their more favorable side effect profiles have made them increasingly popular. There is some tendency to think that since the hazards of the older AEDs are known, the new ones are likely to be more than acceptable substitutes. Unfortunately, there is little information to support their safety. The number of exposed pregnancies that have been reported with these drugs is very low, not large enough to determine if there is, or is not, an increased risk of adverse outcome with fetal exposure. Lamotrigine, levetiracetam, and oxcarbazepine concentrations decline during pregnancy, and this may be true for the other new AEDs as well.[251] The following section summarizes what is currently known.

Gabapentin

Despite its extensive use for a variety of conditions, little has been published about gabapentin's effect on pregnancy outcomes. A large postmarketing surveillance study of 3,100 English patients taking gabapentin identified 11 pregnancies, none of which had malformations.[276] A study that included cases that were collected both retrospectively and prospectively evaluated 44 children born to 39 mothers with epilepsy taking gabapentin. Two of 44, or 4.5%, had major malformations. One child exposed to gabapentin and valproic acid had hypospadias. The other, who had only one kidney, was exposed to gabapentin monotherapy until the 16th week of gestation and then switched to phenobarbital. A single case of minor anomalies, a slight malformation of the left external ear canal and two skin tags at the angle of the jaw, occurred in a child exposed to gabapentin and lamotrigine.[182] One malformation was reported in 31 offspring of mothers exposed to gabapentin monotherapy by the U.K. Registry.[185]

Lamotrigine

A Swedish birth registry study has reviewed 1,398 infants exposed to AEDs: Five malformations occurred among 90 children exposed to lamotrigine monotherapy (5.6%). A recent report from the U.K. Pregnancy Registry found a dose-response effect: Higher rates of malformations were found in infants exposed to lamotrigine doses of >200 mg/day (5.4%) compared to those exposed to lower doses (1.9% at doses of 100 to 200 mg and 1.5% at doses <100 mg).[185] The International Lamotrigine Pregnancy Registry has now identified 1,224 pregnancies reported in women taking lamotrigine in the first trimester. There is a significant difference in malformation rates for lamotrigine used in (a) monotherapy 2.8% (20 of 707 with a 95% confidence interval of 1.8% to 4.9%); (b) polytherapy with valproic acid 11.8% (14 of 119 with a 95% confidence interval of 6.8% to 19.3%); and (c) polytherapy without valproic acid 2.7% (7 of 256 with a 95% confidence interval of 1.2% to 5.8%).[148] No dose-response effect was found in the Lamotrigine Pregnancy Registry.[148]

Lamotrigine crosses the placenta, and at delivery the fetus and mother have similar plasma concentrations. Elimination in infants appears to be slow. Seventy-two hours postpartum, infant plasma levels are 75% that of the mother. Median milk:plasma ratios are 0.61.[201]

Oxcarbazepine

In the first 12 reported cases of pregnancy with oxcarbazepine, there were nine live births and three spontaneous abortions. In a prospective series of 11 pregnancies, there was one child with spina bifida who had been exposed to oxcarbazepine in polytherapy.[80] In the postmarketing period, the manufacturer has been notified of five cases of fetal malformations. One of these was a cardiac defect. There were also three cleft palates and one facial dysmorphism. Three of the five were exposed to AED polytherapy. The largest prospective series reported to date evaluated 42 oxcarbazepine-exposed pregnancies in Buenos Aires. There were no malformations in the 25 monotherapy cases. One child with a ventricular septal defect was exposed to oxcarbazepine and phenobarbital.[214] In a retrospective study from Finland of 133 women with epilepsy, 101 of these were monotherapy exposures and not associated with malformations. In 17 polytherapy exposures, there was one malformation: A ventriculoseptal defect.[117] Oxcarbazepine crosses the placenta with equivalent maternal and fetal cord levels.[189] A recent review of the published world literature on oxcarbazepine exposure in pregnancy suggests that the risk of malformations is similar to that of the general population.[183]

Topiramate

We have little information of the number of pregnancies with topiramate exposure. There is one case report of a child exposed to topiramate monotherapy who developed growth deficiency, hirsutism, a third fontanelle, an upturned nasal tip, and distal digital hypoplasia. During the clinical trials 28 pregnancies were reported with one malformation and two anomalies.[207] Postmarketing surveillance has identified 76 prospectively collected pregnancies. In 57 of these pregnancies there was maternal epilepsy. Twenty-nine were exposed to monotherapy. Eight of the 76 (10.5%) had malformations; seven of eight were exposed to polytherapy.[147] Two malformations were reported in 35 pregnancies exposed to topiramate monotherapy enrolled in the U.K. Registry.[185]

Topiramate crosses the placenta with cord and maternal plasma levels being equivalent at delivery. Milk:plasma concentration ratios average 0.86. Infant elimination appears to be substantial with little measurable drug found in the plasma of breastfed infants 2 to 3 weeks postpartum.[201]

Zonisamide

There have been 26 reported pregnancies with zonisamide exposure. Two of the 26 (7.7%) had congenital malformations. One child was also exposed to phenytoin and the other to both phenytoin and valproic acid.[142]

Zonisamide also freely crosses the placenta with transfer rates of 92%. Though data is available from only two children, milk:plasma ratios are 0.8 and elimination half-life ranges from 61 to 102 hours.[147]

Pregnancy Registries

The need to assess the teratogenic risk of old- and new-generation AEDs has led to the development of pregnancy registries. At the time of this writing, pregnancy registries have been created in the United Kingdom and several other European countries, North America, Australia, and India. The existing registries (EURAP, Australia, and India) agreed with the need to pool "protocols" instead of pooling previously collected information (albeit with very similar designs and methods) in order to achieve properly collected data from larger, heterogeneous populations. The U.K. Epilepsy and Pregnancy Registry, the North American AED Pregnancy Registry (NAREP), and the International Registry of AEDs and Pregnancy (EURAP) are the largest efforts to date. The U.K. and the North American registries originated in 1996 to 1997, and EURAP in 1999. The latest registry originated in several European countries but has since continued to expand to include more centers and countries from Asia, Oceania, and Latin America.

Using somewhat different methodology, each the three registries now include from 3,500 to 5,500 prospective pregnancies. The main differences concern method of recruitment, collection of maternal data, frequency of follow-up, and release of results.

Patients are referred to the U.K. registries by physicians and other health care professionals caring for women with epilepsy and by women themselves. NAREP requires patients themselves to report, while EURAP relies only on physicians. The U.K. and North American registries collect data three times: At enrollment, 7 months of gestation, and 8 weeks after delivery. EURAP participants complete five subforms: One at enrollment, one at the end of each trimester, and the last 14 months after birth. Each subform is submitted in real time to a national coordinator, who checks it for completeness and accuracy before forwarding it to the central registry in Milan. The national coordinators and the central registry are responsible for auditing and solving any inconsistencies or missing data by interacting with reporting physicians.

NAREP discloses malformation rates associated with specific treatments as soon as they are found to differ significantly from the rate in a control group exposed to other unspecified monotherapies. The U.K. registries published the results of a multivariate analysis using category of AED exposure (monotherapy, polytherapy, and no AED exposure), individual AED exposures with more than 25 cases, maternal age at delivery, parity, sex of newborns, periconceptional folic acid intake, and family history of malformations as the independent variables. EURAP is waiting until the number of registered pregnancies will be large enough to perform a multivariate analysis including as independent variables potential risk factors, such as maternal age, type of epilepsy, family history of malformations, exposure to other known teratogens, and maternal educational level.

Several pharmaceutical companies have developed their own registries. The International Lamotrigine Pregnancy Registry collects voluntary prospective reports of lamotrigine exposure during pregnancy.[152] There is a Gabapentin Pregnancy Registry organized by Dr. Georgia Montouris. There is also a registry for vigabatrin, but this drug has not been approved for use in the United States. A pregnancy registry for levetiracetam has also recently been established.

To date, the most productive industry registry has been the Lamotrigine Pregnancy Registry, with 1,224 prospectively registered pregnancies. However, even for this registry lack of comparative data represents a main limitation.

Fetal Antiepileptic Drug Syndromes

Minor anomalies are structural deviations from the norm that do not constitute a threat to health and by definition occur in <4% of the population.[166] Such anomalies frequently occur in normal unexposed infants. Combinations of several anomalies are less common and can form a pattern, or a dysmorphic syndrome, which may indicate a more severe underlying dysfunction.

A variety of syndromes associated with AED exposure in utero have been described. Facial dysmorphisms such as hypertelorism, depressed nasal bridge, low-set ears, micrognathia, and distal digital hypoplasia, sometimes in combination with growth retardation and developmental delay, were first reported in association with exposure to phenytoin.[95] Subsequently, however, similar patterns have been reported with exposure to carbamazepine.[122] Valproate exposure has been claimed to cause a somewhat different dysmorphic syndrome characterized by high forehead, a small and flat nose, long philtrum, and long digits. However, there is a considerable overlap in the various dysmorphisms, and their specificity for a particular drug has been questioned. A more general term, fetal or prenatal anticonvulsant syndrome, has therefore been suggested.[282]

The pathogenesis of these AED-associated dysmorphic syndromes is still somewhat controversial. Some authors have attributed most of the minor anomalies to genetic factors rather than drug exposure.[82] For example, similar dysmorphic features have been described in the pre-anticonvulsant era[13,213] and in children of untreated epileptic mothers.[198] However, a recent study examined only infants born to women not taking AEDs in pregnancy.[109] None of these infants had features of the fetal anticonvulsant syndrome. The long-term outcome and significance of these anomalies are unclear. In the relatively few cases that have been followed into early childhood and reported, the minor anomalies have tended to disappear as the child grew older.[37,134,141,151]

Table 3 Incidence of Major Congenital Malformations by Timing of Assessment

Timing of malformati

	Within the neonatal period		
		Malformations	
Study design	Total outcomes	*N*	%
Historical cohorts[3,9,11,26,27,41,49,63,71,76,89,121,124,143,196,203,220,227,231,240,242,269,275]	14,016	668	4.8
Mainly prospective cohort[4,175,257]	193	10	5.2
Prospective cohorts[24,25,44,54,56,59,68,70,84,92,106,108,111,115,122,123,138,139,140,141,142,146,172,176,181,185,200,228,230,234,236227,228,229,230,231,232,233,234,235,236,237,238,239,244,247,278,281]	7,383	327	4.4
Retrospective cohorts[15,42,88,110,120,150,152,168,177,182,229,232,243,267]	2,141	100	4.7
	23,733	1,105	4,7

Finally, it should be emphasized that minor anomalies are much more difficult to assess objectively than major malformations, and equally difficult to quantify. A few studies have focused on methodologic issues involved in recognizing minor anomalies in children of epileptic mothers. The findings showed that observer and context bias are likely to occur in such studies. [33,98]

Summary and Conclusions

The risk of major congenital anomalies is increased in the offspring of mothers with epilepsy and is largely due to AEDs. However, evaluation of published studies reveals a 10- to 20-fold variation in malformation rates.[14] Consistent differences are also observed for risk associated with AED polytherapy and high doses. [14] The variability of data within the literature reflects methodologic differences. Such differences are usually significant enough to prevent pooling of data for meaningful meta-analyses. [253] The populations studied also vary considerably: Some reports have considered only women exposed to AEDs or only women with epilepsy, whereas others have also included women not taking AEDs or women taking AEDs for reasons other than epilepsy. Different authors have adopted variable exclusion criteria such as maternal malformations, chronic or genetic diseases, twins, and siblings. Differences in the denominators used to calculate birth defects (women, pregnancies, live births only or live births and therapeutic abortions and/or stillbirths and/or spontaneous abortions) also play a major role. Consider, for example, that excluding therapeutic abortions reduces the rate of several malformations present in the general population by about 5%. [67]

Other relevant factors are differences in the timing of outcome assessment and in the teratogenic end-points. Many birth defects are not detectable at birth, while others may disappear after birth. Table 3 shows that the risk of underestimation prevails: The incidence of major structural malformations is increased by about one third when the follow-up ends at birth. In terms of teratogenic end-points, there is a lack of standardized criteria for classifying malformations and of a clear-cut distinction between major malformations, minor anomalies, and postural deformities. In many papers, definitions are not given or malformations are poorly described. The gradient for incidence of malformations at birth between studies considering only severe structural malformations and those including any structural malformation or structural malformations plus minor anomalies is shown in Table 4. As expected, the rates of major and minor anomalies are, on average, twofold higher than those of major congenital malformations only. On the other hand, restricting studies to severe structural malformations only reduces by about one third the incidence of congenital malformations.

Such discrepancies in the literature mirror the variability among study designs and tested populations. Other shortcomings characterize nearly all the studies published to date. [14,16,55,253] For example, most have been based on small samples that fail to reach statistical power; only a few have enrolled more than 500 cases. [11,22,27,121,123,124,128,185,192,230,231,240,275] As a consequence, the majority of old and more recent studies compare the malformation rates of individual AEDs without adjustment for other potential risk factors such as maternal age, ethnicity, social status, other diseases or exposures, and the genetic background. In addition, information on confounders related to epilepsy, such as timing of exposure, severity of epilepsy, duration of epilepsy, and the frequency of and timing of seizures during pregnancy, is also often missing. Finally, randomized trials are lacking for ethical reasons. Therefore, even with rigorous methodology the available evidence is primarily derived from observational studies that are prone to confounding, selection, and measurement bias. [253]

A few observations are firmly established. The first is that maternal epilepsy increases the risk of birth defects by two- to threefold over population rates. The second is that the increased risk is primarily associated with AED treatment, especially polytherapy. A number of congenital anomalies have been observed in cohorts of IMEs, but these cannot be considered major malformations. Their impact on the health of the child is minimal, or they are easily treatable. The most severe malformations are detectable in utero with modern ultrasound techniques. This allows physicians and patients to plan for immediate and early interventions. In the case of valproic acid, there is convincing evidence for an increased risk of neural tube defects in fetuses exposed to the drug. The data for most AEDs, however, are limited to comparing malformation rates of exposed infants to population rates. There are no head-to-head comparison studies, and thus, care must be taken when discussing comparisons between specific AEDs. There is also need for detailed information on the specific frequencies of major structural malformations for second-generation antiepileptic medications. Hopefully, the ongoing prospective registries will clarify these issues, as well as the relative contribution of AEDs and other factors, such as genetic predisposition and maternal epilepsy.

Table 4 Incidence of Congenital Anomalies Detected within the Neonatal Period by Teratogenic End-point

	Teratogenic end-point					
	Severe structural malformations			Any structural malformation		
Study design	Total outcomes	*N*	%	Total outcomes	*N*	%
Historical cohorts[3,11,26,27,41,63,71,89,121,124,143,162,196,203,220,227,231,240,242,247,269,275]	2,391	90	3.8	11,625	578	5.0
Mainly prospective cohorts[4,19,66,175]				193	10	5.2
Prospective cohorts[24,25,54,56,59,68,70,84,108,112,115,123,126_128,136,138,142,145,149,155,167,176,178,185,193,198_200,204,218,228,230,234,236,239,247,263,266,278,281]	1,055	34	3.2	6,328	293	4.6
Retrospective cohorts[15,18,22,88,110,120,121,131,150,152,164,168,182,229,231,232,243,267]				2,141	100	4.7
	3,446	124	3.6	20,287	981	4.8

It should be remembered and emphasized that more than 90% of women with epilepsy will give birth to healthy

children without birth defects or developmental delay, but a more precise estimate of individual risks and the effect of genetic and environmental factors has yet to be determined. Prenatal counseling should be performed when possible, and close monitoring during pregnancy is essential.

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Chapter 109

Neurodevelopmental Effects

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Introduction

The increased risk of major malformations after prenatal exposure to antiepileptic drugs (AEDs) has been established by research extending over three decades (see Chapter 110). The neurodevelopmental effects of in utero exposure to AEDs have not been as extensively investigated as AED-induced somatic abnormalities. This may be because the assessment of functional outcomes is more complicated and time consuming than major malformations that are usually detected at birth and are less affected by confounding factors.

Teratogens interact with genotype to produce both anatomic and behavioral defects. Whether a defect occurs depends on a susceptible genotype and may involve the interaction of multiple-liability genes.[30] The mechanism of anatomic and behavioral teratogenesis may well differ since it appears that the highest risk of anatomic defects is from first-trimester AED exposure, while the highest risk of behavioral defects appears to be from exposure during the third trimester, when neuronal migration and synaptic organization occur.[76]

Animal studies have clearly demonstrated that prenatal AED exposure can produce behavioral as well as anatomic defects. In contrast to somatic malformations in animals, which usually require AED dosages several times above human therapeutic dosages, behavioral impairments can occur at lower dosages and at blood levels similar to human therapeutic levels.[31,42]

The first report of mental deficiency after prenatal AED exposure in children with typical minor anomalies but no major malformation was published in 1975.[18] After that, a number of studies have investigated the relationship between typical minor anomalies and cognitive impairment in AED-exposed children, and several antiepileptic drug syndromes have been proposed. More recent studies have also addressed the question of whether prenatal antiepileptic drug exposure increases the risk of cognitive impairment even in the absence of detectable anatomic teratogenesis.

Animal Data

Behavioral Data for Individual Antiepileptic Drugs

Benzodiazepines

Neonatal benzodiazepine exposure produces widespread apoptotic neuronal cell death in rats (see Mechanism section). Gestational or neonatal exposure to benzodiazepines can affect brain chemistry and behavior.[18] For example, diazepam can affect behavior differentially depending on the stage of development at which the exposure occurs. Midgestation exposure causes transient hyperactivity but no learning or retention deficits on a choice discrimination task. Late prenatal exposure caused no hyperactivity but resulted in poor learning and retention. Early postnatal exposure resulted in lasting hyperactivity as well as learning and retention deficits.[34]

Carbamazepine

Despite the common use of carbamazepine in humans, very few neurobehavioral studies in animals have been published. In utero carbamazepine exposure did not produce hyperexcitability in primates, unlike phenytoin.[70] A preliminary report found that neonatal rats dosed with carbamazepine slightly above the ED50 for anticonvulsant action produced widespread neuronal apoptosis similar to several other AEDs[49] (see Mechanism section).

Phenobarbital

Perinatal phenobarbital exposure in rats reduces brain weight.[21] Phenobarbital causes apoptotic neuronal cell death in neonatal rats (see Mechanism section). Mice exposed prenatally to phenobarbital have neuronal deficits, reduced brain weight, impaired development of reflexes, open-field activity, schedule-controlled behavior, spatial learning, and catecholamine brain levels.[32,57,61,62,103,104] Rats that had seizures induced by kainic acid as neonates exhibited deficits in water maze (a measure of visuospatial memory) and open-field activity when tested subsequently. Rats receiving kainic acid followed by phenobarbital exhibited even greater disturbances in memory, learning, and activity levels.[63] In contrast, this effect was not seen with topiramate, as described below.

Phenytoin

Gestational and neonatal exposure to phenytoin reduces brain weight.[43,83] Phenytoin alters neuronal membranes in the hippocampus.[94] It also alters critical genes and delays neurodevelopment.[8] Dose-dependent apoptotic neuronal cell death occurs in neonatal rats (see Mechanism section). Prenatal phenytoin at subteratogenic dosages (100 to 200 mg/kg) in rats produces impaired spatial learning and motor coordination.[26,64,77,89,90,91,93,97] A dose-effect relationship was noted at maternal levels (10 to 25 μg/mL) overlapping the human therapeutic range. The adverse behavioral effects do not resolve as the rats grow older.[93,94] Prenatal exposure to phe-nytoin in rats results in hyperactivity.[91,97] Similarly, primates who have in utero exposure to phenytoin are hyperactive and hyperexcitable, but those exposed to carbamazepine or stiripentol are not.[70]

Primidone

Gestational primidone can produce behavioral deficits in rats.[71] When tested as adults, the rats that had been exposed in utero to primidone were impaired in their performance of an eight-arm radial maze task and had reduced open-field activity.

Topiramate

Topiramate has been shown to produce adverse cognitive effects in adults. In contrast, the effects of topiramate in neonatal animal models appear to be protective. Topiramate protects against hypoxic-ischemic white matter injury and decreases the subsequent neuromotor deficits when administered posthypoxic insult in neonatal rats.[33] Rats that are treated with to-piramate after a series of 25 neonatal seizures performed significantly better in the water maze than rats treated with saline.[106] These findings are in contrast to the adverse effects of phenobarbital in the same animal model.

Valproate

An in vitro study using rat hippocampus cultures found that valproate interferes with formation of the pyramidal cell layer.[29] In utero valproate can alter neuronal membranes in the hippocampus and cortex of rats.[95] Early postnatal exposure to valproate decreased brain weight in mice.[85] Exposure of neonatal rats to valproate resulted in widespread neuronal apoptosis (see Mechanism section). Adverse neurobehavioral effects in rats have been seen following in utero exposure at doses of 150 to 200 mg/kg,[87,92] although these effects were not as marked as phenytoin in the same animal model.

Antiepileptic Drug Effects on Neurodevelopment: Potential Mechanisms

Folate-related Mechanisms

Folate demands are increased during pregnancy, and women with epilepsy who have lower folate levels are more likely to have abnormal pregnancy outcomes.[20] Several AEDs are known to affect folate metabolism. Phenobarbital, phenytoin, and primidone, but not carbamazepine, deplete folate.[12,13,15,16] Valproate alters folate metabolism.[12]

Ischemia/Hypoxia

Phenytoin can affect cardiac function in fetal rats, and animals exposed in utero to ischemia develop defects that resemble phenytoin-induced defects.[19]

Neuronal Suppression

AEDs suppress neuronal irritability and could reduce neuronal excitation, altering in utero synaptic growth and connectivity and producing long-term behavioral deficits.

Reactive Intermediates

The teratogenesis of AEDs may be mediated by toxic intermediary metabolites rather than the parent compound.[98,99] Oxide intermediates (epoxides) are generated during the metabolism of some AEDs and are highly reactive and can bind nucleic acids. However, the theory of the epoxide mechanism has been questioned because the cytochrome P450 enzymes required for conversion of an AED to an epoxide are not expressed in embryonic tissues.[53] An alternative theory posits that AEDs may be metabolized to free-radical reactive intermediates by prostaglandin H synthetase or lipoxygenases, which are active in the fetus.[98,99] Then, these reactive oxygen species could bind to DNA, protein, or lipids, resulting in teratogenesis.

Antiepileptic Drug–induced Neuronal Apoptosis

The observation that third-trimester gestational ethanol exposure can produce widespread neuronal apoptosis and neurobehavioral deficits led to the hypothesis that the adverse behavioral effects of AED exposure might be due to a similar mechanism.[48] The effect of ethanol is mediated by combined *N*-methyl-D-aspartate (NMDA) glutamate receptor blockade and γ-aminobutyric acid $(\text{GABA})_A$ receptor activation,[48] which are receptor mechanisms affected by some AEDs. Recently, several AEDs have been tested for similar apoptotic effects in a neonatal rat model. Widespread neuronal apoptosis occurs as a result of neonatal exposure to clonazepam, diazepam, phenobarbital, phenytoin, vigabatrin, or valproate.[9,10] The effect appears to be due to reduced expression of neurotrophins and levels of protein kinases, which are important for neuronal growth and survival. Of note, the adverse effects were ameliorated by β estradiol, which has neurotrophic effects.[6,10,39] Similar apoptotic effects were not seen at therapeutic dosages for levetiracetam or topiramate.[39,56,60] Additional studies are needed to examine the effects of other AEDs in this animal model, extend the studies to gestational animal models, and determine if a similar mechanism occurs in humans.

Human Data from Offspring of Mothers with Epilepsy

Syndromes and Minor Anomalies

The fetal hydantoin syndrome (FHS) was first described by Hanson and Smith[42] in five unrelated children whose mothers had epilepsy. Four mothers had taken 100 to 400 mg of phe-nytoin (one monotherapy) and one had been treated with 300 mg of mephenytoin during pregnancy. Four children had also been exposed to barbiturates and one to additional phensuximide. All displayed a characteristic pattern of craniofacial abnormalities (including short nose with low nasal bridge, and hypertelorism) (Fig. 1[65]), hypoplasia of nails and distal phalanges, and postnatal growth deficiency, and four had motor or mental deficiency. In a later cohort study, Hanson et al.[41] estimated that 11% of phenytoin-exposed children showed enough unusual features to be clearly classified as having FHS. Patterns of minor anomalies similar to phenytoin combined with developmental delay have been described in association with prenatal carbamazepine[52] and primidone[66] exposure, but these have never been established as separate syndromes. A different pattern of abnormalities has been described for valproate, as discussed below.

Of the typical FHS features, distal digital hypoplasia (Fig. 2) has been most consistently associated with prenatal phenyt-oin exposure in prospective studies blinded to exposure.[4,55,37] Two studies have used anthropometric methodology. Kelly[54] made a radiologic diagnosis of distal phalangeal hypoplasia based on measurements from hand radiographs in 15 of 47 phenytoin-exposed and one of ten control children. In a controlled population-based study, prenatal phenytoin exposure was observed to have a significant dose-related negative correlation with distal phalangeal length measured from hand radiographs.[36] A radiologic diagnosis of distal phalangeal hypoplasia was made in 8 of 75 (11%) phenytoin-exposed children compared with 1 of 130 children not exposed to phenytoin ($p = 0.003$).[36] In most of these children, distal digital hypoplasia was not obvious on a clinical examination. Growth and intelligence were within the normal range in all.

Controlled prospective and retrospective studies blinded to prenatal AED exposure have consistently shown that the craniofacial minor anomalies considered typical of FHS are increased in children of mothers with epilepsy compared with control children of mothers without epilepsy.[37,46,67,101,105] Most studies observed no increased minor anomalies in

nonexposed children of mothers with epilepsy,[46,101,47] while one study found that some of the facial features such as epicanthus were increased not only in the nonexposed children, but also in the mothers with epilepsy.[37] Although the results on whether these typical anomalies are associated with impaired cognitive development are controversial,[35,45] multiple minor anomalies in general are known to be associated with delayed development[81,86] and should alert the clinician to do a systematic developmental evaluation and follow-up.

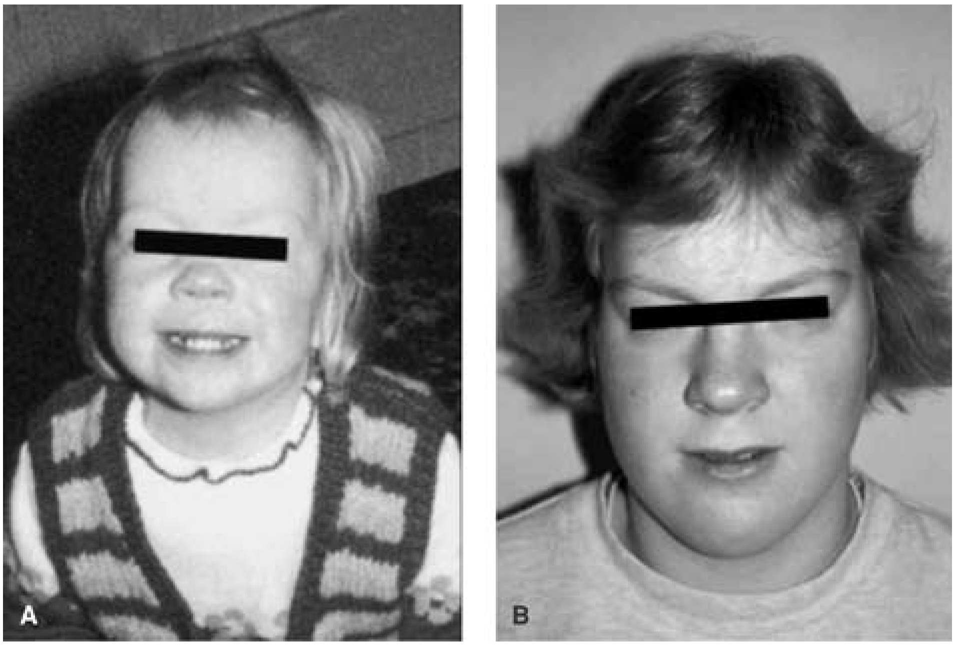

FIGURE 1. A: Child exposed to phenytoin monotherapy, aged 18 months. Note telecanthus; short nose with flat nasal bridge and anteverted nares; long, shallow philtrum; and thin upper lip. **B:** Same child aged 15 years and 3 months. Note that the nose has grown to a more normal appearance. The nasal root

is prominent. The philtrum remains shallow and the upper lip thin. (Reproduced with permission from Moore SJ, Turnpenny P, Quinn A, et al. A clinical study of 57 children with fetal anticonvulsant syndromes. *J Med Genet*. 2000;37[7]:489–497.)

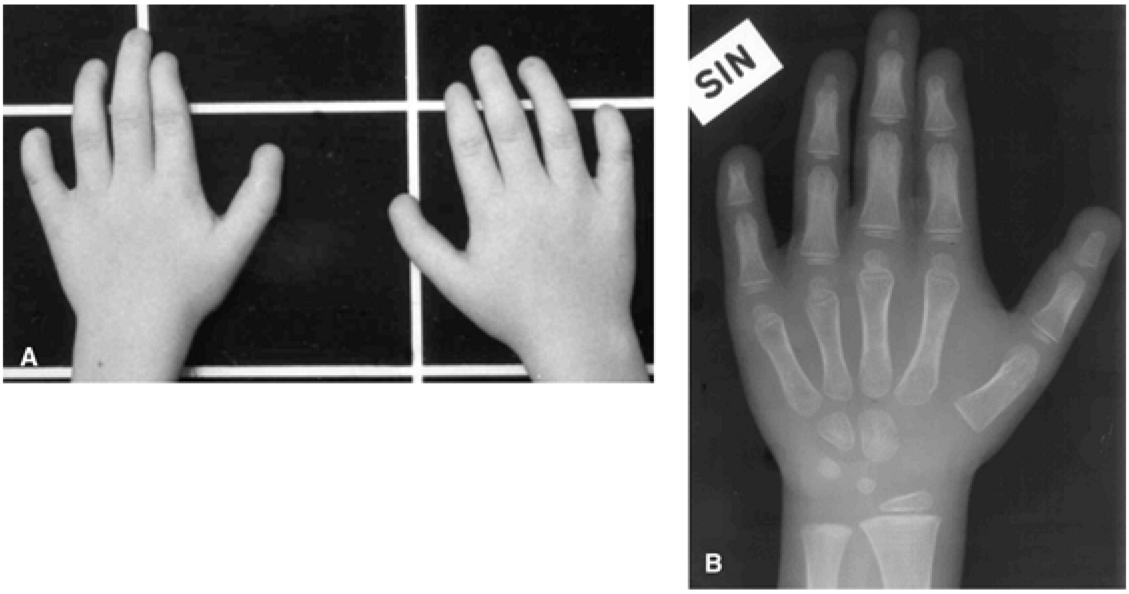

FIGURE 2. A: Severe distal phalangeal hypoplasia in a child with prenatal phenytoin (86 umol/L) and phenobarbital exposure, aged 5 years and 4 months. The child also had mild hypertelorism (not shown). Growth and intelligence were normal. **B:** Left-hand radiograph of the same child at age 5 years and 4 months, showing aplastic distal phalanges in fingers 2 and 5 and hypoplastic distal phalanges in fingers 1, 3, and 4.

The fetal valproate syndrome (FVS) was first described by DiLiberti et al.,[22] later verified by Ardinger et al.[5] in 19 valproate-exposed (eight monotherapy) children of 18 mothers with epilepsy, and reviewed by Clayton-Smith and Donnai.[17] The characteristic craniofacial features include trigonocephaly, bifrontal narrowing with indentation of the outer orbital ridge, medial deficiency of eyebrows, long shallow philtrum with long and thin upper lip, and broad or flat nasal bridge (Fig. 3[59]). Major malformations may also occur: The most common are neural tube defects, congenital heart defects, oral clefts, genital abnormalities, and limb defects. Developmental delay is observed in most children with this pattern of minor anatomic abnormalities; some also have autistic features.[102,73] Pre- and postnatal growth are usually normal.

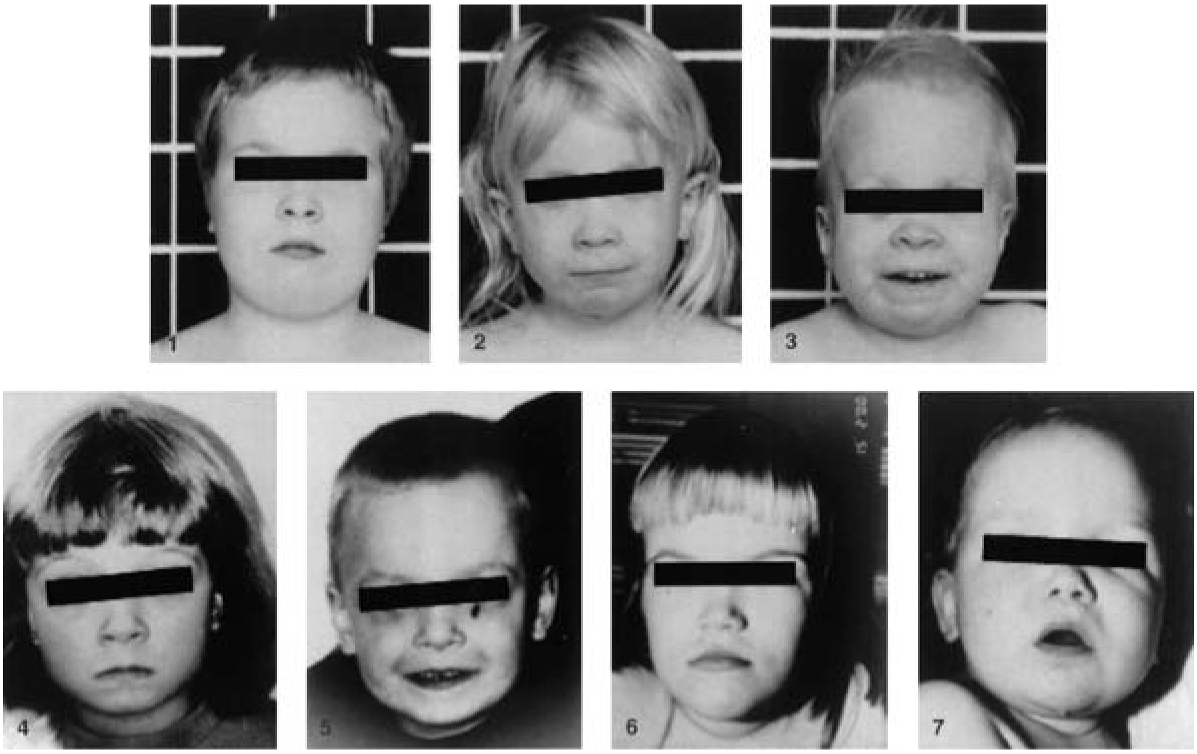

FIGURE 3. Fetal valproate syndrome. Note especially trigonocephaly, medial deficiency of eyebrows, broad nasal root, anteverted nares, shallow philtrum, and long and thin upper lip. Patients 1–3, 4 and 5, and 6 and 7 are siblings. Patient 2 was also exposed to phenytoin and patient 7 to vigabatrin; others were exposed to valproate monotherapy only. (Reproduced with permission from Malm H, Kajantie E, Kivirikko S, et al. Valproate embryopathy in three sets of siblings: further proof of hereditary susceptibility. *Neurology*. 2002;59[4]:630–633.)

The incidences of FHS and FVS are unknown. Based on a prospective population-based study, FHS with mental deficiency appears to be quite rare (<1%), at least in the Finnish population.[35] There is only one prospective study on minor anomalies in valproate-exposed children, observing significantly increased anomalies in valproate-exposed children compared to controls,[51] but there are no prospective data on the incidence on FVS. Case reports describing drug-exposed multiple pregnancies have found different outcomes after similar exposures. Phelan et al.[69] described a dizygotic heteropaternal twin pair exposed to 230 mg of phenytoin during pregnancy, with one twin showing all typical symptoms and signs of FHS, while the other twin was healthy. Bustamante and Stumpff[11] reported trizygotic triplets, exposed to 300 mg of phenytoin and 450 mg of phenobarbital, who showed very different manifestations of FHS. Malm et al.[59] described three families in which all valproate-exposed siblings had FVS, and Kozma[58] reported one family with FVS in two siblings. These observations strongly support the hypothesis that genetic susceptibility significantly enhances the risk of serious adverse outcome after prenatal phenytoin or valproate exposure.

Intelligence

In addition to the rare AED syndromes, there is a recognized risk that prenatal antiepileptic drug exposure may have effects on cognitive development even without signs of anatomic teratogenesis. Studies looking at long-term postnatal development face many challenges. Enrolling children in the study during the mother's pregnancy is mandatory to get reliable prospective exposure data, including maternal drug doses, seizures during pregnancy, and other pregnancy complications. Children must then be followed at least until preschool or early school age. Developmental data acquired from questionnaires or from records not designed for investigational purposes may not be reliable; only standard IQ testing provides data that are comparable across different exposure groups and studies. Before the age of 5 years, cognitive tests have limited predictive power[40] and it is not possible to document milder cognitive deficits than moderate to severe mental deficiency reliably. This results in long study durations with a high risk for loss of follow-up and increasing effect of confounding effects. Maternal education[84] and especially maternal IQ[75] are significant predictors of intelligence in the offspring. Psychosocial and socioeconomic disadvantage associated with epilepsy[50,44] as well as maternal depression[7] may affect postnatal development of children of mothers with epilepsy. Women with epilepsy or a history of epilepsy have lower marriage rates than controls,[79] possibly reflecting a limited choice of partners and resulting in an increased risk of inherited cognitive dysfunction from the paternal side.

Table 1 Intelligence Scores in Children of Mothers with Epilepsy and Control Children from a Population-based Prospective Study

IQ score group	Number of children	Verbal Mean ± SEM	Nonverbal Mean ± SEM	Full-scale Mean ± SEM
Study group all	182	92.8 ± 1.3	100.3 ± 1.2	96.0 ± 1.2
No drug exposure	45	94.3 ± 2.6	98.6 ± 2.9	95.6 ± 2.8
Monotherapy exposure	107	94.4 ± 1.7	101.9 ± 1.4	98.0 ± 1.6
CBZ monotherapy	86	96.2 ± 1.9	103.1 ± 1.5	99.7 ± 1.8
VPA monotherapy	13	83.5 ± 3.8	96.3 ± 4.8	89.7 ± 3.6
Other monotherapy[a]	8	91.1 + 6.4	96.9 + 4.6	93.6 + 5.0
Polytherapy exposure[b]	30	84.9 ± 2.5[c]	97.1 ± 2.9	89.5 ± 2.4
Control group all	141	94.9 ± 1.2	102.4 ± 1.2	97.6 ± 1.4

SEM, standard error of the mean, CBZ, carbamazepine, VPA, valproate.

[a] Six phenytoin, two clonazepam.

[b] Seventeen combinations included valproate.

[c] F = 8.6, $p = 0.004$ versus controls, and F = 5.2, $p = 0.02$ versus study children exposed to monotherapy by covariance analysis, with maternal education and test (WPPSI-R or WISC-R) used as covariates.

Reproduced (slightly modified) with permission from Gaily E, Kantola-Sorsa E, Hiilesmaa V, et al. Normal intelligence in children with prenatal exposure to carbamazepine. *Neurology.* 2004;62(1):28–32.

Possibly the most important confounding factor for prenatal AED effects is maternal epilepsy. Prenatal drug exposure is not random. The choice of treatment prescribed for the mother is determined by maternal epilepsy type or syndrome and the severity of seizures. Several observations suggest that some epilepsy-associated genes may also have an influence on cognitive development. Siblings of children with epilepsy show increased cognitive dysfunction.[25] Cognitive deficits may be present already at onset of idiopathic and cryptogenic epilepsies.[94] Idiopathic partial epilepsies and developmental cognitive disorders (such as dysphasia) overlap.[23] Low socioeconomic status has been found to be a risk factor for epilepsy of unknown etiology.[44] As the risk of cognitive impairment and drugs of choice probably covary in different epilepsy syndromes, the child of a mother with epilepsy may show cognitive impairment that appears to be related to a specific drug but is actually based on genetic traits associated with that particular type of epilepsy. This also makes it impossible to have a perfect control group in cognitive studies. In a control group of children of mothers without epilepsy, not only the prenatal drug exposure, but also the epilepsy factor, is missing. If different drug exposures are compared with each other and with nonexposed children with mothers with a history of epilepsy, we may well be comparing different forms of epilepsy and different genetic risks. To control for the epilepsy factor as

well as possible, carefully determining maternal epilepsy type and etiology as well as obtaining data on maternal intelligence (or at least educational level) are necessary in studies dealing with prenatal AED effects on development.

Carefully conducted prospective clinic-based studies give a good description of what kind of problems may be anticipated in children of mothers with epilepsy and may provide data on the relative risk of different AEDs. The applicability of their results, however, is limited by selection of the study population. Only population-based studies (i.e., studies in which it is possible to reliably estimate what proportion of the population is included in the study) allow a reliable estimation of the magnitude of the risk for cognitive development in children of mothers with epilepsy compared to the general population.

A recent Cochrane review[3] assessed all prospective studies reporting cognitive outcome in children of mothers with epilepsy published from 1966 through 2003. Thirty-one reports based on 18 independent cohorts were included in the review. Eleven studies were considered clinic based and four studies population based (not identified in the review), and the others provided insufficient data on recruitment. Most studies had limited quality and a small number of participants; only seven cohorts included more than 50 AED-exposed children. Attempts to control for confounding factors were described in about half of the studies. Assessment of outcome was blinded in nine studies. Comparison groups varied from study to study, with some studies giving their results only in pooled mono- or polytherapy subgroups and others reporting individual drug exposures (carbamazepine, phenytoin, phenobarbitone). The results were largely conflicting, and the authors concluded that there was very little evidence as to which specific drugs would be more harmful to the prenatally exposed child.

Two controlled, prospective, population-based studies including 50% to 60% of the population[35,78] (both included in the Cochrane review) provided data on intelligence scores at 4[78] and 5[35] years of age in a total of 297 children of mothers with epilepsy. Cognitive assessments were blinded to the prenatal exposures. Two hundred and five children were exposed to phenytoin (81 monotherapy). The most common combination was phenytoin and phenobarbitone. Forty nonexposed children of mothers with epilepsy were also included. Maternal phenytoin levels were measured by Gaily et al.[35]: All except one were well under the upper limit of the reference range. Both studies reported lower IQ values in children of mothers with epilepsy than controls, but no significant associations were observed to any drug exposure or to exposure to maternal seizures.[35]

Hanson et al.[41] extracted data on 104 children exposed to phenytoin (24 monotherapy) from the same data source as Shapiro et al.[78] (i.e., the Collaborative Perinatal Project of the National Institute of Neurological and Communicative Disorders and Stroke[80]). These children were matched for maternal socioeconomic status, maternal age, race, and institution of birth with 100 control children of mothers without epilepsy. Eighty-three children in both groups were tested by Wechsler Intelligence Scale for Children (WISC) at 7 years of age. The mean full-scale score was 92 in the phenytoin-exposed children and 97 in controls ($p < 0.05$). In the absence of other exposure groups and nonexposed children of mothers with epilepsy, it is impossible to know how much of the IQ difference was related to prenatal phenytoin exposure and how much to other epilepsy-related factors.

Two recent population-based studies[100,38] (the former not included in the Cochrane review) reported cognitive outcome in a total of 248 children of mothers with epilepsy with carbamazepine monotherapy as the most common AED exposure. Both studies included approximately 50% of the population of children born to mothers with epilepsy in their catchment areas. The investigator performing the cognitive testing was blinded to exposure. Wide et al.[100] used the Griffiths test at 2 to 8 years and found no difference between 35 carbamazepine-exposed children and 66 control children of mothers without epilepsy. Gaily et al.[38] administered the age-appropriate Wechsler scale at 5 to 11 years. The study included 107 monotherapy exposures (86 carbamazepine), 30 polytherapy exposures (17 including valproate), 45 nonexposed children, and 141 control children of mothers without epilepsy. No impairment was found in the children exposed to carbamazepine compared to nonexposed or controls (Table 1). Verbal IQ was significantly reduced in the polytherapy subgroup. No associations of IQ to maternal epilepsy type or maternal generalized tonic–clonic seizures during pregnancy were observed.

So far prospective data on cognitive outcome in children with prenatal valproate monotherapy exposure are available only for 26 children from two population-based studies.[38,27] In both studies, the mean verbal IQ was 11 to 13 points lower in the valproate monotherapy–exposed group than in children with no AED exposure or exposed to carbamazepine monotherapy. A significant negative correlation between valproate dose of the mother during pregnancy and verbal IQ in the offspring was observed.[38] Although attempts to control for maternal epilepsy type, educational level,[38] and maternal IQ[27] were made, it was impossible to reliably rule out confounding by genetic and environmental factors. Retrospective studies have reported increased educational needs[1] and impaired verbal IQ[2] in children exposed to valproate monotherapy, even when controlled for maternal IQ. The reduction of verbal IQ in the valproate monotherapy group in the retrospective study[2] was in the same order of magnitude (10 points) as in the prospective studies.[38,27] The impairment found in the valproate group has been limited to verbal IQ in all studies except one.[27] The findings highlight the urgent need for prospective studies with sufficient power and careful documentation of maternal epilepsy characteristics to investigate the possible harmful effect of valproate on cognitive development.

Table 2 Incidence of Mental Deficiency in Children of Mothers with Epilepsy, Based on Pooled Data from Three Prospective Population-based Studies[a]

Antiepileptic drug exposure	Number with mental deficiency per total exposed (%)	Comment
Phenytoin monotherapy	0/60	
Carbamazepine monotherapy	2/105 (1.9)	One West syndrome
Valproate monotherapy	3/34 (8.8)	One mother of child with mental

Other monotherapy	0/4	deficiency had subnormal IQ
Polytherapy[b]	1/84 (1.2)	Phenytoin, carbamazepine, and alcohol abuse
No drug exposure	2/64 (3.1)	One Down syndrome
Total	8/351 (2.3)	

[a] The Eriksson et al. study provided population-based data for the valproate monotherapy group only. Included were born in 1975 to 1979 (Gaily E, Kantola-Sorsa E, Granstrom ML. Intelligence of children of epileptic mothers. *J Pediatr*. 1988;113(4):677–684.), 1989 to 1994 (Gaily E, Kantola-Sorsa E, Hiilesmaa V, et al. Normal intelligence in children with prenatal exposure to carbamazepine. *Neurology*. 2004;62(1):28–32), and 1989 to 1997 (Eriksson et al. study).

[b] Twenty-six combinations included valproate.

From Adab N, Jacoby A, Smith D, et al. Additional educational needs in born to mothers with epilepsy. *J Neurol Neurosurg Psychiatry*. 2001;70(1):15-21; Eriksson K, Viinikainen K, Mönkkönen A, et al. Children exposed to valproate in utero - population based evaluation of risks and confounding factors for long-term neurocognitive development. *Epilepsy Res*. 2005;65:189-200; and Jäger-Roman E, Deichl A, Jakob S, et al. Fetal growth, major malformations, and minor anomalies in infants born to women receiving valproic acid. *J Pediatr*. 1986;108(6):997-1004.

Incidence of Mental Deficiency

In the studies reporting intelligence scores, most participating children have performed well within the normal range. As no follow-up data after IQ testing are available from any of the cognitive studies, it is not clear whether the statistically significant group impairments have any clinical significance that would signal an increased risk for learning problems. Mental deficiency, however, has an obvious impact on the child's educational achievement. Prospective population-based data on the incidence on mental deficiency in children of mothers with epilepsy are available from two Finnish studies.[35,38] A third study[27] provided population-based data on valproate monotherapy–exposed children only. The children were tested at age 5 to 13 years. All studies defined mental deficiency as both verbal and nonverbal IQ below 70. Based on the pooled data, the incidence of mental deficiency was 8 of 351 (2.3%) in children of mothers with epilepsy and 3 of 246 (1.2%) in control children of mothers without epilepsy (relative risk [RR] 1.9, 95% confidence interval [CI], 0.5 to 7.0). For comparison, the incidence of mental deficiency in a birth cohort of 12,000 children in Northern Finland was found to be 1.2%.[72] The breakdown of the data to AED exposures and other relevant etiologic information are shown in Table 2. Based on the pooled data, children exposed to valproate monotherapy had a higher risk of mental deficiency (3 of 34, 8.8%) than other children of mothers with epilepsy (5 of 317, 1.6%) (RR 5.6, 95% CI, 1.4 to 22.4).

Human Data from Subjects with No Maternal Epilepsy

Long-term cognitive effects of prenatal phenobarbital exposure was studied by Reinisch et al.[74] based on data from the Danish Perinatal Cohort. This database comprised the offspring of 9,006 deliveries that took place at the largest hospital in Copenhagen between 1959 and 1961. Demographic, socioeconomic, and medical variables (including drug treatment) were recorded prospectively. Phenobarbital exposure was recognized if maternal treatment had lasted for at least 10 days during pregnancy (range 10 days to entire pregnancy). Two separate cohorts of men were later selected from this database with the criteria of phenobarbital exposure and absence of other significant other risk factors (including maternal epilepsy) during pregnancy. Controls were matched for a number of potential confounders, including a maternal complaint score reflecting indication. The study subjects were given either the Wechsler Adult Intelligence Scale (WAIS) (33 subjects, mean age 23 years) or the Danish Military Draft Board Intelligence test (81 subjects, mean age 19 years). Total phenobarbital dosages varied

from 225 to 22,500 mg. Men exposed to phenobarbital showed approximately 0.5 standard deviation (SD) lower scores than expected. The IQ impairment was most marked after exposure in the third trimester, and the effects were increased in those from low socioeconomic status and unwanted pregnancy.

A randomized placebo-controlled blinded study[28] investigated the cognitive late effects of postnatal phenobarbital exposure of toddler-aged children with febrile seizures. Two hundred and seventeen children were randomized to receive either phenobarbital 4 to 5 mg/kg/day or placebo. There was no difference in Bayley scores between the groups at the beginning of the study. At 2 years after the assignment to treatment, the mean IQ was 8.4 points lower in the children assigned to the phenobarbital group compared to placebo ($p < 0.01$). Six months after offset of the medication, there was still a 5.2-point difference in the mean IQ. Sixty-four percent of these children were later examined at the age of 7 years by the Wide Range Achievement Test (WRAT-R) and the Stanford-Binet Intelligence Scale.[82] The children who had been assigned to the phenobarbital group showed significantly impaired performance in WRAT-R reading scores but not on the Stanford-Binet Scale compared to the placebo group. This long-term follow-up study suggests that exposure to phenobarbital during early childhood may have long-term adverse cognitive effects on the skills (especially language) that are actively acquired at that age.

Summary and Conclusions

Neurobehavioral adverse effects have been observed in animal studies after prenatal exposures to benzodiazepines, phenobarbital, phenytoin, primidone, and valproate. Prenatal exposure to carbamazepine in a primate study did not find adverse neurobehavioral effects. Two studies on perinatal topiramate exposure did not find adverse neurobehavioral effects, and to-piramate even appeared protective against ischemia or seizures. Widespread neuronal apoptosis has been found in neonatal rats exposed to benzodiazepines, phenobarbital, phenytoin, valproate, and vigabatrin, but did not occur to therapeutic dosages of levetiracetam or topiramate. Animal data concerning the behavioral effects of in utero AED exposure are, however, incomplete, especially for AED combinations and the newer AEDs. Further, intraspecies differences exist in susceptibility to AED-induced anatomic malformations, and may also exist for behavioral teratogenesis. Although animal data need to be interpreted cautiously and will ultimately require confirmation in humans, investigations in animals can control for a variety of confounding factors and offer insight.

Prenatal exposure to antiepileptic drugs in humans may result in syndromes with mental deficiency and characteristic minor anomalies as the typical features. The incidences of the fetal hydantoin and valproate syndromes are unknown but are probably rare. Case reports from multiple pregnancies and siblings suggest that genetic susceptibility is required for full syndrome expression.

The results of prospective studies investigating IQ at preschool or school age are somewhat controversial. Most studies have observed a mild but statistically significant IQ reduction in children of mothers with epilepsy compared to control children of mothers without epilepsy. There are several important confounding factors, and the contribution of prenatal AED exposure remains unconfirmed. Data from controlled, prospective, population-based studies have provided no evidence that prenatal phenytoin or carbamazepine exposure would impair intelligence. One perinatal cohort study including subjects with no maternal epilepsy and another study including children with febrile convulsions treated in the toddler years suggest that prenatal or early postnatal exposure to phenobarbital may cause permanent mild IQ impairment. The results of retrospective studies suggest that prenatal valproate exposure may reduce verbal IQ, but prospective data on valproate are until now very limited.

The incidence of mental deficiency has been investigated by three population-based studies; the results suggest that the incidence may be slightly increased in children of mothers with epilepsy. Two studies included mainly phenytoin and carbamazepine exposures and established no increased risk in those children. Insufficient data on valproate exposure from two prospective studies raise concern that prenatal valproate may be associated with an increased risk of cognitive impairment, a concern supported by a retrospective study. Further investigation is needed to completely define the cognitive risk of valproate. However, given the increased incidence of major congenital malformations related to in utero valproate exposure,[68] it may be prudent to avoid valproate as a drug of first choice in women of childbearing age. There are no data on cognitive outcome after prenatal exposure to other currently used antiepileptic drugs.

Presently our data on cognitive effects of prenatal exposure to antiepileptic drug are almost limited to IQ only. There is a need in the future to look at other aspects of cognition (e.g., memory and attention) beyond IQ.

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Chapter 110

Drug–Drug Interactions

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Introduction

Within the context of the pharmacologic treatment of epilepsy, the topic of drug interactions has received much attention. Because antiepileptic drugs (AEDs) have narrow therapeutic ranges, treatment is generally individualized, and unpredicted alterations in drug levels might require dose adjustments. Most of the older AEDs are prone to interactions with other AEDs, as well as with other concurrent medications such as anticoagulants, antidiabetic agents, and antidepressants. As a result, the literature associated with AED interactions is extensive. This chapter focuses on recent advances and the integration of pharmacokinetic and pharmacodynamic interactions.

Pharmacodynamic Interactions

The concept of pharmacodynamic interactions between AEDs is quite different from the concept of pharmacokinetic interactions. Whereas pharmacokinetic interactions determine changes in levels of a drug, pharmacodynamic interactions determine changes in pharmacologic effects when another drug is added or discontinued. These pharmacodynamic interactions, therefore, can determine whether it is meaningful for two particular drugs to be prescribed together. In contrast, pharmacokinetic interactions require only dose adjustments; they are unrelated to the qualitative aspects of drug combinations. The amount of information available about pharmacokinetic interactions between AEDs is considerably larger than that available about pharmacodynamic interactions, in part because it is easier to measure drug levels than to quantify various drug actions. In addition, for pharmacodynamic interactions, several pharmacologic actions of drugs can be involved, whereas with pharmacokinetic interactions there is always only one end point, namely, the drug concentration. To analyze pharmacodynamic interactions, it is necessary to understand what the possible interactions can be. Pharmacokinetic interactions can cause a change in drug absorption, metabolism, or elimination or a displacement from serum proteins. Pharmacodynamic interactions are distinguished by whether they are purely additive, supraadditive, or infraadditive. When the interaction is additive, the combined effect of the two drugs administered together for a given pharmacologic effect is equal to the expected sum of the corresponding activity of each drug used alone. For instance, if concentration *x* of drug *A* produces a certain effect, and concentration *y* of drug *B* produces the same effect, one-half of concentration *x* of *A* in the presence of one-half of concentration *y* of *B* will produce the same effect. One-half of *x* and one-half of *y* represent an equivalent "bolus," and this concept forms the basis of the so-called "isobolographic" analysis, an established method for the quantitative assessment of pharmacodynamic interactions.[21] When the interaction is supraadditive, or potentiated, the combined effect of the two drugs is greater than the expected sum of the individual effects of the two drugs. In the foregoing example, less than one-half the concentration of each drug would be required to achieve the same effect. Finally, if the interaction is infraadditive, or antagonistic, the combined effect is less than the expected sum of the individual effects, and, for instance, more than one-half the concentration of each drug would be required to achieve the same effect.

How does this apply to pharmacodynamic interactions between AEDs? AEDs form a heterogeneous group; their common denominator is the ability to prevent the occurrence of seizures. They also all tend to produce toxicity, in particular neurologic toxicity, at certain concentrations. The antiepileptic pharmacodynamic interaction between two drugs is irrelevant in itself. A supraadditive interaction is not necessarily beneficial. The concentration of a single drug could be increased indefinitely if it were not for the occurrence of toxicity. The same upper limit, however, will also apply to two drugs administered simultaneously. Therefore, for a combination of two AEDs to be advantageous, the seizure protection provided by the combination at a certain degree of toxicity (e.g., the threshold for overt toxicity) must be stronger than that with either drug alone at the same level of toxicity. Thus, the antiepileptic and the neurotoxic interactions must differ in favor of the antiepileptic interaction. In clinical reality, this issue is complicated by the fact that side effects of AEDs are not limited to neurotoxicity. In addition, a totally different situation in which a combination of two AEDs can be advantageous can arise when a patient has two different seizure types, each of which responds to a different drug.

Based on these considerations, it is understandable that the information on pharmacodynamic interactions between AEDs is limited. These interactions are difficult to quantify in patients. Even the available data from animal experiments are limited because certain studies considered only the antiepileptic interaction. In many other studies, the analysis was based on doses only. When drug effects are quantified on the basis of drug dose alone, pharmacokinetic interactions can falsify the analysis of pharmacodynamic interactions. For instance, earlier studies based on the analysis of doses in animals suggested an antiepileptic potentiation between phenytoin and phenobarbital.[28,172] This turned out to be a pharmacokinetic artifact due to an acute inhibition of phenytoin elimination in the presence of phenobarbital. Later studies revealed that, in the presence of phenobarbital, single doses of phenytoin produce higher phenytoin brain levels than when phenytoin is administered alone and that the antiepileptic interaction between phenobarbital and phenytoin is purely additive when brain levels are used for the analysis.[20,91]

The results of the first series of experimental studies in which antiepileptic as well as neurotoxic interactions between AEDs were quantified are summarized in Table 1. These studies reveal that the majority of antiepileptic interactions are strictly additive and that antiepileptic potentiation is the exception rather than the rule. In contrast, neurotoxic interactions are divided about equally between those that are infraadditive and those that are additive. These experimental data suggest that only a few combinations among the older AEDs are possibly superior to the corresponding monotherapies. These combinations include valproate with carbamazepine, valproate with ethosuximide, and valproate with phenytoin. Although an infraadditive neurotoxic interaction between phenytoin and phenobarbital was found, the therapeutic index of phenobarbital alone was very low, and the combination still had a lower therapeutic index than did phenytoin alone.[20]

Table 1 Pharmacodynamic interactions between antiepileptic drugs in animal models

	Interaction		
Drug	Antiepileptic	Neurotoxic	Ref.
	A. Older drugs		
PHT + PB	Additive	Infraadditive	20
PHT + CBZ	Additive	Additive	129
CBZ + PB	Additive	Additive	27
VPA + PB	Additive	Additive	21
VPA + ESM	Additive	Infraadditive	22
VPA + CBZ	Additive	Infraadditive	21
VPA + PHT	Supraadditive	Additive	36
VPA + CZP	Supraadditive	Supraadditive	26
ESM + CZP	Supraadditive	Supraadditive	26
CBZ + CBZ-E	Additive	Additive	27
PRM + PB	Supraadditive	Infraadditive	25
PB + PEMA	Supraadditive	Supraadditive	25
	B. Newer drugs		
LTG + TPM	Supraadditive	Infraadditive	115
LTG + VPA	Supraadditive	Infraadditive	115
LTG + CBZ	Infraadditive	Additive	115
LTG + PB	Supraadditive	Supraadditive	115
LTG + PHT	Additive	Additive	115
TGB + GBP	Supraadditive	Additive	116
TPM + FBM	Supraadditive	Infraadditive	113

TPM + OXC	Supraadditive	Additive	113
OXC + FBM	Infraadditive	Additive	113
OXC + LTG	Infraadditive	Supraadditive	113
LTG + FBM	Additive	Infraadditive	114
OXC + GBP	Supraadditive	Additive	114
LEV + TPM	Supraadditive	Infraadditive	111
LEV + CBZ	Supraadditive	Infraadditive	112
LEV + OXC	Supraadditive	Infraadditive	112

CBZ, carbamazepine; CBZ-E, carbamazepine epoxide; CZP, clonazepam; ESM, ethosuximide; FBM, felbamate; GBP, gabapentin; LEV, levetiracetam; LTG, lamotrigine; OXC, oxcarbazepine; PB, phenobarbital; PEMA, phenyo-ethyl-malonamide (primidone metabolite); PHT, phenytoin; PRM, primidone; TGB, tiagabine; TPM, topiramate; VPA, Valproate. *Source:* Modified from Bourgeois BFD, Dodson WE. Antiepileptic and neurotoxic interactions between antiepileptic drugs, In: Pitlick WH, ed. *Antiepileptic Drug Interactions.* New York: Demos; 1988:209–219.

Interactions between low doses of clonazepam and valproate or ethosuximide were all found to be supraadditive for antiepileptic and for neurotoxic effects, but they result in a superior therapeutic index for both valproate and ethosuximide.[22] Using a similar model, Gordon et al.[64] studied the pharmacodynamic interactions between felbamate and older AEDs. They found a potentiation of the antiepileptic activity of felbamate by phenytoin, carbamazepine, valproate, and phenobarbital. In contrast, the neurotoxicity was not potentiated, and the protective index of felbamate was raised by the addition of any one of these four drugs.

Many additional experimental studies of pharmacodynamic interactions have been carried out in recent years, involving mostly the newer AEDs (Table 1).[38] Overall, these studies again reveal that various combinations can have any possible type of association of antiepileptic and neurotoxic interactions. Accordingly, some drug combinations are more promising than others, at least on the basis of this experimental model.

In the end, whether a combination of two AEDs is beneficial for patients needs to be determined by careful clinical assessments. Although pharmacodynamic interactions are more difficult to study in patients than in experimental animals, valuable clinical data have accumulated. One of the first clinical studies addressing in a systematic manner the issue of the beneficial value of an AED combination was reported by Hakkarainen.[70] Among 100 newly diagnosed patients, 33 were refractory to carbamazepine alone and to phenytoin alone. Of those, five (15%) became seizure free on the combination. Rowan et al.[140] demonstrated that absence seizures could be fully controlled by valproate–ethosuximide combination therapy in a few patients who had been refractory to either drug alone. Walker and Koon[169] found that some patients who had not responded to valproate alone and to carbamazepine alone became seizure free on the combination.

A positive synergism between valproate and lamotrigine has also been suggested. Among 347 patients refractory to monotherapy with valproate, carbamazepine, phenytoin, or phenobarbital, the seizure reduction was significantly greater when lamotrigine was added to valproate than when it was added to the other drugs.[24] In a rigorous systematic study of add-on valproate versus add-on lamotrigine, among 13 patients who had not responded to the addition of either one of the two drugs, 4 became seizure free when both drugs were added.[123] When 14 patients whose seizures had not been controlled by monotherapy with carbamazepine and with vigabatrin were given both medications, 5 (36%) became seizure free.[159]

In addition to potentially favorable pharmacodynamic interactions, clinical observations have also revealed that adverse effects of one AED can be potentiated by those of another. An increase in tremor when lamotrigine was prescribed in combination with valproate was observed in two studies.[80,123] An increase in side effects characteristic of carbamazepine was noted in four patients in whom levetiracetam was added to carbamazepine in polytherapy.[156] An exacerbation of carbamazepine toxicity also was noted after the addition of lamotrigine, and this could not be attributed to a pharmacokinetic interaction.[16] Chorea occurred in three patients on phenytoin and lamotri-gine in combination only, and it resolved when one medication was tapered.[175] Finally, it appears that valproate encephalopathy is more likely to occur in the presence of another AED, and it can resolve when either valproate or the other drug is discontinued.[104] More recently, two reports suggested that the addition of topiramate may enhance some side effects of valproate, in particular hyperammonemic encephalopathy.[63,101]

Pharmacokinetic Interactions

Metabolic and Pharmacokinetic Characteristics of Antiepileptic Drugs

Table 2 summarizes the principal metabolic (enzymes with major or minor roles) and pharmacokinetic (route of elimination, half-life and extent of plasma protein binding) characteristics of older (established) and newer AEDs that are relevant to a mechanistic understanding of drug interactions.

Interactions Associated With Older Antiepileptic Drugs

Effects of Established Antiepileptic Drugs on Other Drugs

These interactions result principally from the induction of several metabolic enzymes (cytochrome P450 1A2 [CYP1A2], CYP2C9, CYP2C19, CYP3A4, and glucuronyl transferases) by carbamazepine, phenobarbital, phenytoin, or primidone and the inhibition of a few enzymes by valproic acid.

Table 3 provides a comprehensive listing of drugs affected by the enzyme-inducing effects of carbamazepine, phe-nytoin, and phenobarbital. These include many CYP3A4 substrates, narrow-therapeutic-range drugs such as warfarin, and drugs that are mainly glucuronidated such as lamotrigine. Recent studies show large decreases in serum concentrations for quetiapine (7.5-fold increase in clearance)[66] and tipifarnib (5-fold increase in clearance).[32] CYP2B6 induction by phenyt- oin was observed in a patient taking two CYP2B6 substrates—thiothepa and cyclophosfamide.[41]

Valproic acid behaves as an inhibitor of CYP2C9, CYP2C19, and CYP3A4. It increases the serum levels of phenobarbital, phenytoin, and warfarin. It also inhibits some glucuronyl transferases and elevates the serum levels of lamotrigine[59] and other drugs such as lorazepam,[147] naproxen,[1] and zidovudine.[92] The effects of valproic acid on lorazepam pharmacokinetics were studied in two groups with different uridine glucuronyl transferase (UGT) genotypes—UGT2B15*1/*1 and UGT2B15*2/*2. Results indicated that during the valproic acid–inhibited state, lorazepam clearance was lower in the *2/*2 group, although the percentage changes from baseline did not differ significantly by genotype.[29] Valproic acid produced small increases in area under the serum concentration curve (AUC) and in the peak serum concentration (C_{max}) of the recently approved drug aripiprazole with minimal effects on its active metabolite.[30]). Because valproic acid has the potential to benefit patients suffering from HIV-associated cognitive impairment,[148] its effects were studied in HIV-1–infected patients receiving efavirenz or lopinavir/ritonavir. Valproic acid did not affect efavirenz disposition, but it increased lopinavir concentrations.[44]

Effects of Other Drugs on Established Antiepileptic Drugs

Because established AEDs are substrates of metabolizing enzymes, they are subject to a number of interactions resulting from the inducing or inhibitory effects of coprescribed drugs. These interactions are summarized in Table 4. Inhibitors of CYP3A4, such as ketoconazole, clarithromycin, erythromycin, fluvoxamine, nefazodone, diltiazem, and ritonavir, increase carbamazepine levels. The CYP2C9/2C19-mediated metabolism of phenytoin is inhibited by fluconazole, sulfaphenazole, phenylbutazone, amiodarone, ticlopidine, and more recent drugs such as voriconazole. Other drugs known to reduce the clearance of (S)-warfarin (substrate of CYP2C9) such as zafirlukast are expected to affect phenytoin disposition in a similar fashion. Moreover, concomitant administration of lopinavir/ritonavir and phenytoin results in a two-way drug interaction: phenytoin increased lopinavir clearance via CYP3A4 induction, and lopinavir/ritonavir increased phenytoin clearance via CYP2C9 induction.[98]

There are numerous case reports of decreased or increased valproate valproic acid exposure in the presence of known modulators of transport systems. In the case of carbapenem antibiotics, there is a consistent and marked decrease in valproic acid concentrations often accompanied by breakthrough seizures.[31] The mechanisms of this decrease in valproic acid concentration have not been elucidated.[115]

Interactions Associated with Newer Antiepileptic Drugs

Recently developed AEDs as a group appear to exhibit fewer pharmacokinetic drug interactions. This is the result of a direct attempt to avoid or minimize oxidative metabolism when these drugs were developed (Table 2). Felbamate, lamotrigine, oxcarbazepine and its monohydroxy derivative (MHD), topiramate, and zonisamide are substrates for metabolizing enzymes (CYPs or UGTs), whereas gabapentin, levetiracetam, and vigabatrin are mostly eliminated by renal excretion.

Felbamate

Felbamate undergoes partial hepatic metabolism, with almost 50% of the dose excreted unchanged in the urine of healthy volunteers.

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Table 2 Pharmacokinetics and elimination pathways of antiepileptic drugs in adults

Drug	Half-life (h)	Protein binding (% bound)	Elimination (main route)	Enzyme with major role	Enzymes with minor role	Additional data
Older AEDs						
Carbamazepine	5–26	75	Oxidation to 10,11-epoxide metabolite (65%); glucuronidation (15%)	CYP3A4	CYP1A2, CYP2C8	Epoxide metabolite is active and cleared by epoxide hydrolase
Ethosuximide	40–60		Oxidation (65%)	CYP3A4		
Phenobarbital (primidone: prodrug)	77–128	55	Oxidation to *p*-hydroxy metabolite (20%); *N*-glucosidation; renal excretion	CYP2C9	CYP2C19 CYP2B6	
Phenytoin	7–42	90	Oxidation to 5-(4-hydroxyphenyl)-5-phenylhydantoin (90%)	CYP2C9	CYP2C19	
Valproic acid	9–15	90	Glucuronidation (50%); beta-oxidation (10%–20%)	UGT2B7	UGT1A6, 1A9	Beta-oxidation by mitochondrial oxidases and CYPs
Newer AEDs						
Felbamate	16–22	20–25	Oxidation (15%); renal excretion	CYPs		
Gabapentin	5–7	3	Renal excretion			
Lamotrigine	30	55	Glucuronidation >65%	UGT1A4		
Levetiracetam	6–8	10	Renal excretion; hydrolysis		Hydrolase	Hydrolysis (25%)
Oxcarbazepine (MHD active metabolite)	9 (MHD)	40 (MHD)	Glucuronidation (MHD)		Aldoketoreductase converts oxcarbazepine to MHD	Oxcarbazepine is a produg converted to MHD
Pregabalin	6		Renal excretion (>90%)			
Tiagabine	7–9	98	Oxidation (>30%)	CYP3A4		
Topiramate	18–23	15	Renal excretion; oxidation (15%)		CYP	
S-Yigabatrin	4–7		Renal excretion			

Table 3 Drugs whose serum concentrations are decreased by coadministration of carbamazepine, phenytoin, and phenobarbital

Coadministered agent	Drugs used in epilepsy whose concentration is decreased by the coadministered agent	Other drugs whose concentration is decreased by the coadministered agent
Carbamazepine	Alprazolam	Amitriptylline
	Clobazam	Albendazole
	Conazepam	Citalopram
	Clorazepate	Bromperidol
	Diazepam	Bupropion
	Midazolam	Caffeine
	Ethosuximide	Clozapine
	Felbamate	Cyclosporine
	Lamotrigine	Dexamethasone
	Levetiracetam	Doxepin
	Oxcarbazepine (MHD)	Doxycycline
	Phenobarbital	Etizolam
	Primidone	Felodipine
	Phenytoin	Fentanyl
	Tiagabine	Haloperidol
	Topiramate	Imipramine
	Valproate	Indinavir
	Zonisamide	Itraconazole
		Methylprednisolone
		Mianserin
		Mirtazapine

		Nefazodone
		Nifedipine
		Nimodipine
		Olanzapine
		Omeprazole
		Oral contraceptives
		Praziquantel
		Prednisolone
		Quetiapine
		Risperidone
		Simvastatin
		Trazodone
		Vecuronium
		Vincristine
		Warfarin
		Ziprazidone
Phenytoin	Carbamazepine	Acenocoumarol
	Clobazam	Acetaminophen
	Clonazepam	Albendazole
	Felbamate	Amiodarone
	Lamotrigine	Chloramphenicol
	Levetiracetam	Cyclophosphamide
	Methsuximide	Cyclosporine
	Phenobarbital	Dexamethasone

Primidone	Dicoumarol
Oxazepam	Digoxin
Oxcarbazepine	Dispopyramide
Tiagabine	Doxycycline
Topiramate	Itraconazole
Valproate	Irinotecan
Zonisamide	Lopinavir
	Meperidine
	Methadone
	Methylprednisolone
	Mexiletine
	Mirtazapine
	Misonidazole
	Nisoldipine
	Oral contraceptives
	Oxazepam
	Praziquantel
	Prednisolone
	Prednisone
	Quetiapine
	Quinidine
	Ritonavir
	Sirolimus
	Theophylline

		Thiotepa
		Tirilazad
		Vecuromium
		Voriconazole
		Warfarin
Phenobarbital	Clobazam	Albendazole
(and primidone)	Clonazepam	Cimetidine
	Carbamazepine	Chloramphenicol
	Ethosuximide	Clozapine
	Lamotrigine	Cyclosporine
	Oxcarbazepine	Dexamethazone
	Phenytoin	Disopyramide
	Topiramate	Felodipine
	Valproic acid	Griseofulvine
	Zonisamide	Irinotecan
		Lidocaine
		Losartan
		Meperidine
		Methylprednisolone
		Metronidazole
		Misonidazole
		Nifedipine
		Nimodipine
		Oral Contraceptives

	Paroxetine
	Prednisolone
	Prednisone
	Quinidine
	Tacrolimus
	Teniposide
	Theophylline
	Tirilazad
	Verapamil
	Warfarin

MHD, monohydroxy derivative.

Table 4 Drugs that have been reported to inhibit the metabolism and to increase the serum concentration of carbamazepine, phenytoin, phenobarbital, and valproic acid

Affected drug	Metabolic inhibitor
Carbamazepine	Cimetidine
	Clarithromycin
	Danazol
	Dextropropoxyphene
	Diltiazem
	Erythromycin
	Fluconazole
	Fluoxetine
	Fluvoxamine
	Isoniazid
	Ketoconazole
	Metronidazole
	Nefazodone
	Quetiapine
	Risperidone
	Ritonavir
	Sertraline
	Ticlopidine
	Trazodone
	Troleandomycin
	Verapamil
	Viloxazine

Compounds with enzyme-inducing activity increase felbamate clearance: in two population pharmacokinetic studies, felbamate clearance was 40% higher when felbamate was coadministered with carbamazepine and phenytoin compared to monotherapy; however, phenobarbital treatment did not have any significant effect.[11,84] In a large retrospective evaluation, a prolongation in felbamate half-life from 24 to 32.4 hours was found in patients taking concomitantly gabapentin compared to monotherapy, but this effect is still unexplained.[75]

The disposition of various AEDs can be altered by felbamate. Reductions in carbamazepine levels between 18% and 31% were observed when felbamate was coadministered, with corresponding increases in serum carbamazepine-10,11-epoxide (CBZ-E) levels of 33% to 57%.[4,65,168] Recently, Egnell et al.[52] suggested that induction of CYP3A4 is a possible mechanism for the interaction between felbamate and carbamazepine. Increases in estrogen and progestin clearance have also been associated with felbamate.[141] The only isoform inhibited in vitro by therapeutic concentrations of felbamate was CYP2C19 (K_i = 225 µmol/L).[62] This observation is consistent with clinical findings of increased serum concentrations of phenytoin[62,65,141,143] and might account for the reduced clearance of phenobarbital[130] and the higher levels of norclobazam and clobazam[34] in patients comedicated with felbamate. Felbamate has also been shown to decrease valproic acid clearance by 20% to 50%, presumably via inhibition of the ß-oxidation metabolic pathway.[21,22,23,24,25,34,62,130,143,167]

Lamotrigine

Effects of Other Drugs on the Disposition of Lamotrigine.

Lamotrigine is extensively metabolized by glucuronidation mediated by UGT1A4 and excreted in urine predominantly as the inactive 2*N*-glucuronide conjugate.[155] Comedication with enzyme-inducing AEDs enhances the metabolic clearance of lamotrigine through induction of UGT1A, and higher doses of lamotrigine are needed when the drug is given concurrently with phenytoin, carbamazepine, primidone, and phenobarbital.[7,105,106] Oxcarbazepine and its corresponding monohydroxy metabolite are less potent enzyme inducers than carbamazepine, but they can also decrease serum lamotri-gine concentrations.[105] Methsuximide can also lower lamotri-gine levels, leading to deterioration in seizure control in some cases.[15]

When lamotrigine and felbamate were administered concurrently to 21 healthy individuals, serum concentrations of lamotrigine were similar to those obtained with lamotrigine and placebo,[33] and similar findings were obtained in patients.[57] Levetiracetam did not affect the steady-state serum concentrations of lamotrigine.[58,121] Similarly, treatment with pregabalin, 600 mg/d for 7 days, had no effect on lamotrigine steady-state concentrations.[25] Coadministration of escalating doses of to-piramate in a group of 25 patients resulted in only slight decreases in average lamotrigine levels compared with baseline: lamotrigine levels were decreased 20% to 30% in three of the patients, consistent with the notion that topiramate is a weak enzyme inducer.[14] Steady-state dosing of zonisamide in 20 patients stabilized on lamotrigine monotherapy (150 to 500 mg/d) did not significantly affect lamotrigine $C_{\max}$, AUC, or clearance, but it decreased significantly renal lamotrigine clearance.[95] A 22% increase in lamotrigine clearance has been reported in healthy individuals after administration of retigabine; this interaction was unexpected because retigabine did not show enzyme induction in other interaction studies.[71]

Lamotrigine metabolism is strongly inhibited by valproic acid, resulting in twofold increases in lamotrigine half-life and serum concentrations.[6,80,174] The lamotrigine/valproic acid combination has been associated with an increased risk of toxic epidermal necrolysis.[56] The risk of skin rash seems to

correlate with a high starting dose of lamotrigine and fast dose uptitration when the drug is added to valproic acid. However, Faught et al.[55] analyzed the incidence of rash in patients who had lamotrigine added to their valproic acid treatment regimen and found that the occurrence of rash was not greater than when lamotrigine was added to other drugs, especially when la-motrigine was titrated up very slowly. Other studies confirmed these findings.[173] In combination therapy including valproic acid and AEDs with inducing effects, the inhibitory effect of valproic acid on lamotrigine metabolism appears to be stronger than the inducing effects of phenobarbital or carbamazepine on lamotrigine. However, when valproic acid is combined with phenytoin, the effects of both drugs on lamotrigine disposition seem to compensate each other.[106] Decerce et al.[42] reported that when valproic acid is added to lamotrigine, the greatest impact on the serum level of lamotrigine occurs at dose introduction. In spite of this potentially adverse pharmacokinetic interaction, a favorable pharmacodynamic synergism between valproic acid and lamotrigine was reported by Kanner and Frey.[80] When valproic acid was added to lamotrigine therapy, a significant reduction in the seizure frequency occurred in patients with refractory epilepsy, resulting in seizure-free patients.[80] However, recently two cases of lamotrigine toxicity were reported when the drug was coadministered with valproate; the patients developed downbeat nystagmus, and truncal ataxia occurred in conjunction with toxic lamotrigine serum levels.[5]

Drugs used to treat conditions other than epilepsy have also been reported to affect lamotrigine metabolism. The enzyme-inducing agent rifampicin was found to increase lamotrigine clearance by 97%.[51] Oral contraceptives may also increase lamotrigine clearance, and their intake has been associated with a mean 50% decrease in serum lamotrigine levels.[131,142] In a study with patients using either no hormonal contraception (n = 18), an ethinylestradiol-containing contraceptive (n = 11), or a progestogen-only contraceptive (n = 16), Reimers et al.[131] demonstrated that it is the ethinylestradiol component that interacts with lamotrigine and not the progestogen. A dose adjustment for lamotrigine might be needed in women taking oral contraceptives.[154]

In a parallel, placebo-controlled study in healthy volunteers, coadministration of lamotrigine with olanzapine (5 to 15 mg for 2 weeks) resulted in a small decrease in exposure to lamo-trigine (20% decrease in AUC), suggesting some induction by olanzapine of the glucuronidation pathway of lamotrigine.[153]

Coadministration of acetaminophen enhances the urinary elimination of lamotrigine after single doses of the anticonvulsant (decreases in lamotrigine AUC and serum half-life of 20% and 15%, respectively) when compared to placebo.[43]

There are two reports of patients who experienced an increase in serum lamotrigine concentration following the addition of sertraline; one patient exhibited toxicity when his lamotrigine levels doubled. The authors suggested inhibition of glucuronidation as a possible mechanism for this interaction.[83]

Effects of Lamotrigine on the Disposition of Other Drugs.

During repeated treatment, lamotrigine was shown to induce its own metabolism, resulting in a 25% decrease in its half-life. Consistent with this observation, the addition of lamo- trigine to valproate produced a small (25%) but significant decrease in steady-state serum valproic acid concentration. However, the formation clearances of the hepatotoxic valproic acid metabolites 4-ene- and 2(E),4-diene-valproate were unaffected by lamotrigine administration.[6] Lamotrigine has no significant effect on steady-state concentrations of phenyt-oin, phenobarbital, or primidone.[76,77,100] Increases in serum CBZ-E concentrations and neurotoxicity have been reported following the addition of lamotrigine to a stable drug regimen with carbamazepine.[171] However, this observation was not confirmed in other studies,[16,53,103] suggesting that the interaction with lamotrigine and carbamazepine is pharmacodynamic rather than pharmacokinetic. When pregabalin disposition (600 mg/d for 8 days) was studied in patients taking lamotrigine (100 to 600 mg/d chronically), pregabalin steady-state pharmacokinetic parameters were similar to those found in historical healthy individuals receiving pregabalin alone.[25]

Although an early study suggested that lamotrigine does not increase ethinylestradiol and levonorgestrel clearances,[72] a more recent investigation identified a moderate decrease in serum levonorgestrel levels when lamotrigine (300 mg/d) was given to women taking an oral contraceptive.[154] Although in that study intermenstrual bleeding was reported by 32% of women during coadministration of lamotrigine and the oral contraceptive (and follicle-stimulating hormone [FSH] and luteinizing hormone [LH] concentrations were increased by 4.7-fold and 3.4-fold, respectively), the low serum progesterone concentrations suggested that suppression of ovulation was maintained and that oral contraceptive efficacy was not impaired.[154]

Oxcarbazepine

Oxcarbazepine is a keto analog of carbamazepine that can be considered as a prodrug because it is rapidly converted to its 10-monohydroxy derivative (MHD), which is primarily responsible for the pharmacologic effect. MHD is metabolized by conjugation with glucuronic acid.[54] A small proportion (4%) of MHD is oxidized by the CYP system to the inactive 10,11-dihydroxy derivative. More than 95% of a dose is recovered in the urine as follows: <1% as unchanged oxcarbazepine, 49% as inactive glucuronide conjugates of MHD, and 27% as MHD.[162] No autoinduction of metabolism has been observed with oxcarbazepine.

Although structurally similar to carbamazepine, oxcarbazepine is predominantly metabolized by noninducible ketoreductases. However, coadministration of carbamazepine, phenobarbital, or phenytoin decreases the serum concentrations of MHD, probably by inducing its metabolism.[10,74,110] There is no evidence of a major effect of valproic acid on oxcarbazepine metabolism, and the association with valproic acid should not require any adjustment of oxcarbazepine dose.[10,110]

Several studies evaluated the effects of other drugs on the metabolism and elimination of oxcarbazepine and its major metabolite. In patients comedicated with topiramate, the serum MHD concentration-to-oxcarbazepine dose ratio was not different from that in patients taking oxcarbazepine monotherapy.[10] In the same study this ratio was not altered in patients taking lamotrigine.[10] No significant changes were observed in oxcarbazepine disposition when the drug was concomitantly administered with cimetidine,[86] dextropropoxyphene,[114] erythromycin,[85] verapamil,[88] or viloxazine.[122]

Studies in human liver microsomes showed that oxcarbazepine and its pharmacologically active metabolite MHD have little or no capacity to inhibit the CYP1A, CYP2D, and CYP2E families of isozymes. However, CYP2C19 was significantly inhibited by oxcarbazepine.[165] This inhibition is consistent with the observation of increases in serum phenytoin concentrations up to 40% in patients taking concomitantly oxcarbazepine and phenytoin.[74] Addition of oxcarbazepine to carbamazepine treatment can lead to a small decrease in serum carbamazepine concentration.[110] On the other hand, phenobarbital serum concentrations increased by 14% in patients receiving oxcarbazepine, but this change is not clinically important.[74]

Oxcarbazepine had no effect on the anticoagulant activity of warfarin in ten healthy volunteers.[89] Coadministration of oxcarbazepine to healthy women receiving oral contraceptives has been associated with 47% and 36% decreases in

ethinylestradiol and levonorgestrel AUCs, respectively.[87] When receiving oxcarbazepine with an oral contraceptive, four of six women developed breakthrough bleeding.[99] Repeated coadministration of oxcarbazepine resulted in a 28% decrease in felodipine AUC and a 34% decrease in felodipine $C_{\max}$. The reduction in felodipine bioavailability was much smaller than that observed after coadministration of carbamazepine (i.e., 94%).[176] Oxcarbazepine had no effect on androgen levels in men or on pubertal development in girls with epilepsy.[128] The topiramate concentration-to-dose ratio was not affected by chronic intake of oxcarbazepine.[2]

In its use as a mood stabilizer, oxcarbazepine caused only minimal and no significant changes in the mean serum levels of risperidone, 9-hydroxy-risperidone, and olanzapine, confirming its weak inducing effect on drug-metabolizing enzymes.[137]

When treatment with carbamazepine is changed to treatment with oxcarbazepine, the serum concentrations of various concurrent drugs might increase because of a decrease in he- patic induction. Leinonen et al.[90] described two epileptic patients with major depression and panic disorder whose serum citalopram levels increased and antidepressant response changed following the substitution of oxcarbazepine for carbamazepine. Furthermore, seven patients with schizophrenia or organic psychosis had 50% to 200% increases in serum concentrations of haloperidol, chlorpromazine, and clozapine on switching from carbamazepine to oxcarbazepine.[127,164]

Tiagabine

Extensive metabolism of tiagabine occurs in the liver and is mediated by CYP3A,[18] with possible contributions from CYP1A2, 2D6, 2C9, 2A6, and 2E1. Only 2% of the dose is excreted unchanged in urine, whereas 25% and 63% of the dose is excreted in urine and feces, respectively, primarily as the 5-oxo and glucuronide metabolites.[17]

Concurrent administration of enzyme inducers such as phenytoin, carbamazepine, and phenobarbital reduces considerably tiagabine half-life (which can decrease to 3.8 to 4.9 hours) and accelerates tiagabine clearance (by 50% to 65%).[133,146,158] In contrast, chronic treatment with valproic acid did not have any significant effect on serum tiagabine concentrations in patients.[3,133,146,158] Concomitant administration with ethanol[81] or triazolam[134] did not affect tiagabine pharmacokinetics in healthy volunteers. Similarly, interaction studies with theophylline,[111] digoxin,[157] or warfarin[111] showed that serum tiagabine concentrations were not changed. Coadministration of cimetidine (800 mg/d) to patients taking tiagabine chronically had no effect on tiagabine pharmacokinetics (Gabitril package insert, Abbott Laboratories). When concomitantly administered, erythromycin, a CYP3A inhibitor, did not significantly affect the $C_{\max}$, AUC, or half-life of tiagabine.[163] This lack of effect of erythromycin is unexpected and remains unexplained.

In healthy volunteers, tiagabine treatment did not affect the clearance or the half-life of antipyrine.[69] In addition, the pharmacokinetics of either carbamazepine or phenytoin is not affected by tiagabine.[3,68,69,81,111,134,146,157,163] There was a small decrease in mean valproic acid C_{max} and AUC during concomitant administration of tiagabine, but this change is not clinically relevant.[68]

In healthy volunteers, administration of tiagabine did not alter the steady-state pharmacokinetics or pharmacodynamics of warfarin,[111] digoxin,[157] triazolam,[134] or ethanol.[81]

Mengel et al.[112] studied the effect of low tiagabine doses (8 mg/d for 12 days) on the pharmacokinetics of oral contraceptives in ten healthy women. Tiagabine did not alter the serum concentrations of ethinylestradiol, levonorgestrel, or desogestrel. Similarly, the levels of progesterone, FSH, and LH did not change with tiagabine therapy. The effects of higher doses of tiagabine on the disposition of oral contraceptives have not been reported.

Topiramate

Topiramate is not extensively metabolized, and 55% to 66% of the dose is eliminated unchanged in the urine.[47,79,150] Six metabolites have been identified in humans and result from hydroxylation, hydrolysis, and glucuronidation. These metabolites are inactive, and the isozymes responsible for their formation have not been characterized.

When concomitantly administered with enzyme-inducing AEDs, the proportion of topiramate metabolized by the liver increases, resulting in a shorter half-life and a higher total clearance. Topiramate dose adjustments might be necessary after discontinuation or addition of enzyme-inducing AEDs such as phenytoin, phenobarbital, and carbamazepine.[19,79,144] Recently, the metabolic profile of a topiramate single dose was characterized during induction by carbamazepine (600 mg/d) in 12 healthy individuals. Topiramate remained appreciably excreted unchanged in urine (41%), even though its oral clearance increased twofold. 2,3-*O*-Des-isopropylidene-topiramate (2,3-diol-TPM) was identified as the most prominent urinary metabolite, with recoveries accounting for 3.2% and 7.9% of the topiramate dose under noninduced and induced conditions, respectively. The AUC(metabolite)/AUC(drug) ratio for 2,3-diol-TPM increased threefold after carbamazepine treatment.[23] Concurrent use of topiramate and valproic acid can result in a slight decrease (15%) in topiramate concentrations.[139] Two studies reported no change in topiramate pharmacokinetics in patients given fixed-dose lamotrigine therapy.[2,48]

Topiramate is a weak inducer of CYP enzymes, and, as such, it can decrease ethinylestradiol concentrations at doses >200 mg/d but not at lower doses.[49,138] There is conflicting evidence on whether 200 mg/d of topiramate also reduces ethinylestradiol levels, but any influence of this dose is likely to be small and of dubious clinical significance.[49,138] In a single-dose trial with digoxin, topiramate resulted in a small (13%) increase in digoxin clearance.[97] The effect of multiple dosing with topiramate on the pharmacokinetics of a single dose of haloperidol showed slight increases in haloperidol serum concentrations, although 90% confidence intervals for the ratio of AUC means were within bioequivalence limits.[48]

Topiramate has no major effects on the pharmacokinetics of carbamazepine,[144] primidone, phenobarbital,[46] or valproic acid.[139] Similarly, the serum MHD concentration-to-oxcarbazepine dose ratio was not altered in patients taking topiramate compared to a monotherapy group.[10] Coadministration of escalating doses of topiramate in a group of 25 patients resulted in only slight decreases in average serum lamotrigine levels compared with baseline.[14,47] When phenytoin metabolism is at or near saturation, topiramate can increase phenytoin concentrations by 25%,[60] possibly by inhibiting CYP2C19.[93]

Zonisamide

Zonisamide undergoes acetylation and reduction to form the *N*-acetyl and 2-sulfamoylacetylphenol metabolites, respectively. Of the excreted dose, 35% is recovered unchanged, 15% as *N*-acetyl zonisamide, and 50% as the glucuronide of the 2- sulfamoylacetylphenol metabolite. Reduction of zonisamide is mediated by CYP3A.[116] Recently, Mc Jilton et al.[109] reported that some autoinduction of zonisamide metabolism can occur with chronic dosing.

Concurrent medication with enzyme-inducing AEDs increases the metabolism and clearance of zonisamide and shortens its half-life. In patients taking carbamazepine and phenytoin, zonisamide half-life was 36.4 and 27.1 hours, respectively, indicating a pronounced effect on zonisamide metabolism.[119]

The inducing effects of these drugs on zonisamide metabolism were confirmed by Shinoda et al.,[152] who found that the concomitant administration of zonisamide with phenobarbital, phenytoin, or carbamazepine significantly decreased the ratio of steady-state serum zonisamide concentration to the administered dose (C/D ratio).[152] In that study, clonazepam and valproic acid comedication did not change the zonisamide C/D ratio.

Concurrent administration of cimetidine with zonisamide did not alter zonisamide pharmacokinetics in healthy volunteers.[67] A lack of interaction between ritonavir and zonisamide has been reported in a patient taking the protease inhibitor concomitantly with carbamazepine and zonisamide: Ritonavir administration resulted in a significant elevation in carbamazepine levels, leading to toxicity, without affecting serum zonisamide levels.[82] A single case of decrease in serum zonisamide concentrations after coadministration of risperidone in a patient with schizophrenia was reported.[120] An elevation of serum zonisamide concentration (from a value of 27 to 33 to a value of 61.8 to 64.6 μg/mL) following the addition of lamotrigine was described in two patients receiving stable therapy with zonisamide. One patient also developed signs of zonisamide toxicity after the introduction of lamotrigine.[108]

In vitro studies of the inhibitory effects of zonisamide using human liver microsomes showed that zonisamide does not inhibit CYP1A2 and 2D6 and only weakly inhibits CYP2A6, 2C9, 2C19, and 2E1. The estimated K_i for zonisamide inhibition of CYP3A4 was 1076 μM, 12 times higher than the usual therapeutic serum unbound zonisamide concentration.[126]

The potential effects of zonisamide on carbamazepine pharmacokinetics have not been well characterized, with contradictory literature reports: Some authors found no alterations in carbamazepine or CBZ-E levels by zonisamide,[26,113,149] whereas others reported a rise in carbamazepine concentration,[145] and others reported a fall in CBZ-E/carbamazepine ratio.[152] Recently, the effect of zonisamide, up to 400 mg/d, on the steady-state pharmacokinetics of carbamazepine and CBZ-E was studied in 18 patients with epilepsy.[126] The results indicated no statistically significant differences for mean C_{max}, time to C_{max}, and $AUC_{(0-12\ h)}$ of total and free carbamazepine and CBZ-E measured before and after zonisamide administration. However, CBZ-E renal clearance was significantly (p <.05) reduced. Several studies revealed no significant effects of zonisamide on the serum concentration or protein binding of phenytoin or valproic acid.[26,126,160] However, in a population pharmacokinetic analysis, a statistically significant increase (16%) in serum phenytoin concentration was observed in patients taking zonisamide.[118] This effect was not confirmed in a prospective study designed to measure the effect of the addition of zonisamide (gradually increased to 400 mg/d) on phenytoin pharmacokinetics under steady-state conditions in patients[96]; no significant changes in phenytoin disposition were observed.

Gabapentin, Levetiracetam, Pregabalin, and Vigabatrin

Because gabapentin is not metabolized, interactions via this mechanism are not expected. Indeed, several studies have shown no interaction in either direction with the established AEDs— phenobarbital,[74] carbamazepine,[124] valproate,[124] and phenytoin.[37] A statistically significant but clinically irrelevant decrease (14%) in the oral clearance of gabapentin was reported with concurrent use of cimetidine (Product Information for Neurontin, 1999). A case report indicated that the addition of gabapentin to existing therapy with phenytoin, carbamazepine, and clobazam resulted in increased phenytoin levels from 42 to 177 μM, leading to phenytoin toxicity.[166] An increase in serum phenytoin levels following the addition of gabapentin 900 mg daily was also reported by others.[37] However, adding gabapentin to single-drug therapy with phenytoin did not significantly affect phenytoin levels.[8] Hussein et al.[75] described a pharmacokinetic interaction between gabapentin and felbamate. The study was a large retrospective evaluation in patients taking felbamate alone (n = 40) or felbamate and gabapentin (n = 18); a 50% prolongation of the half-life of felbamate was observed in the patients taking gabapentin.[75] A mechanism for this effect is not evident. In addition, there is no need to adjust the dose of gabapentin when it is coadministered with levetiracetam.[58]

Levetiracetam is eliminated by renal excretion, with 66% of the dose excreted unchanged and 27% as inactive metabolites. The major metabolic pathway of levetiracetam is an enzymatic hydrolysis of the acetamide group, which is not cytochrome P450 dependent, leading to the inactive metabolite UCB-L057 (24% of dose); two other minor metabolites account for <3% of the dose.[170]

Concomitantly administered AEDs do not alter the pharmacokinetic profile of levetiracetam to a clinically important extent. Analysis of serum levetiracetam data obtained during placebo-controlled clinical studies indicated that phenyt- oin, carbamazepine, and phenobarbital can modestly increase levetiracetam clearance by 20% to 30%.[35,107] Lamotrigine and gabapentin do not influence the pharmacokinetics of levetiracetam.[121] In healthy volunteers, multiple-dose coadministration of valproate did not modify the pharmacokinetic or excretion profile of levetiracetam.[27] Likewise, pharmacokinetic parameters of levetiracetam, when it was coadministered with oral contraceptives (Product Information for Keppra), digoxin,[95] or warfarin,[126] were comparable to those of individuals receiving levetiracetam alone.

Levetiracetam and its major metabolite were tested for their effects on different drug-metabolizing enzymes in human liver microsomes. An absence of inhibitory effect of levetiracetam on CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4, CYP2A6, UGTs, and epoxide hydrolase was observed.[117] Levetiracetam did not modify the pharmacokinetic parameters of phenytoin in healthy individuals[27] and in patients.[121] Levetiracetam also had no effect on the serum levels of carbamazepine, valproic acid, phenobarbital, lamotrigine, clobazam. and gabapentin.[40,121,151] In a similar way, prospective studies with digoxin[94] and warfarin[125] indicated that levetiracetam does not affect any of the pharmacokinetic or pharmacodynamic parameters of these drugs. Ethinylestradiol and levonorgestrel pharmacokinetic and pharmacodynamic profiles, assessed during coadministration with levetiracetam for two menstrual cycles, were identical to those observed during coadministration of the contraceptive with placebo.[61]

Pregabalin has been approved recently as adjunctive treatment for partial seizures and for the treatment of neuropathic pain. Single- and multiple-dose studies have shown that >90% of a pregabalin dose is recovered unchanged in urine.[36] This implies that there is no concern for metabolically based drug interactions affecting pregabalin pharmacokinetics, but there is a need for dose adjustment in patients with renal impairment. A recent study was performed in patients receiving carbamazepine, lamotrigine, phenytoin, and valproate with and without 600 mg/d of pregabalin for 7 days.[25] The trough concentrations of these drugs were not affected by pregabalin. Serum pregabalin concentrations in this study were also compared to those of historical controls and no difference was found, implying that these drugs have no effect on the excretion of pregabalin.

Vigabatrin is eliminated essentially unchanged via renal excretion,[13] and two minor urinary metabolites have been detected in humans.[50] Coadministration of valproic acid did not produce significant changes in steady-state serum concentrations of vigabatrin in children with refractory epilepsy.[9] In healthy volunteers, felbamate administration for 8 days had no effect on the AUCs of S(+)-vigabatrin and R(-)-vigabatrin.[129]

Several studies have shown that vigabatrin has no significant effect on the serum concentrations of carbamazepine, phenobarbital, primidone, valproic acid, clonazepam, clobazam, ethosuximide, oxcarbazepine, and felbamate.[39,102,129,132] However, in another study with 66 patients with epilepsy, vigabatrin was added to carbamazepine therapy, and 69.7% of patients exhibited an increase (at least 10%) in serum carbamazepine concentration. A negative correlation between the increase and the initial level of carbamazepine prior to vigabatrin addition was found, which suggested that the lower the initial carbamazepine level, the higher is the increase in concentration after vigabatrin addition.[78] Significant decreases in serum phenytoin levels (up to 30%) have been reported in patients receiving vigabatrin as add-on therapy.[135,136,161] Serum phenytoin levels generally fall after several weeks of combined therapy, and the mechanism of this interaction has not been elucidated.

Bartoli et al.[12] studied the effect of vigabatrin on in vivo indices of hepatic microsomal enzyme activity and the pharmacokinetics of oral contraceptives in healthy individuals. Results indicated a lack of effect on ethinylestradiol and levonorgestrel disposition and also no effect on hepatic microsomal enzyme activity.[12]

Summary and Conclusions

There is evidence for a few pharmacodynamic interactions, some of which are useful, such as the combinations of valproate with carbamazepine, ethosuximide, phenytoin, and lamotri- gine. Others involve an increase in neurotoxicity, such as that observed when lamotrigine is added to carbamazepine. Most clinically relevant interactions of AEDs are pharmacokinetic. Four established AEDs—carbamazepine, phenytoin, phenobarbital, and primidone—are potent inducers of the cytochrome P450 (CYP450) and UDP-glucuronosyltransferase (UGT) isozymes and affect large series of drugs. By comparison, only three of the new AEDs—felbamate, topiramate, and oxcarbazepine—have mild inducing properties, and this is of concern only in the case of oral contraceptives, for which additional precautions or alternative contraception should be taken. A moderate reduction of the serum levels of levonorgestrel, a progestogen component of oral contraceptives, has also been reported with lamotrigine. Among the new AEDs, felbamate, topiramate, and oxcarbazepine can cause CYP2C19 inhibition and may alter the metabolism of phenytoin.

When considered as substrates, a few new AEDs (felbamate, lamotrigine, tiagabine, topiramate, and zonisamide) are affected by established AEDs with enzyme-inducing properties. However, new AEDs are less sensitive to inhibition by other drugs, only lamotrigine being significantly inhibited by valproic acid. Finally, pregabalin, gabapentin, vigabatrin, and levetiracetam do not present any significant pharmacokinetic interactions with other drugs.

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Chapter 111

Drug Treatment in Children

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Introduction

Childhood epilepsy differs from that seen in adults because of age-related seizures, the etiology of seizures in children, the presence of both benign and malignant epilepsy syndromes, and the frequent concomitant presence of neurologic abnormality, mental retardation, or behavioral difficulties.[31] All of these factors have important implications for treatment selection. In addition, children respond differently to antiepileptic drugs (AEDs), with regard to both efficacy and side effects. For those with lesional epilepsy, seeming brain plasticity offers a special opportunity for early surgical intervention. This chapter concentrates primarily on how the medical treatment and evaluation of childhood epilepsy differ from those in adults.

Diagnostic Considerations

Seizures should be treated acutely, and their cause should be determined. If they recur, they should be carefully investigated before chronic therapy is initiated. Febrile seizures or those that occur with minor trauma and those associated with or following sleep deprivation all represent types of seizures that may not go on to be recurrent and, therefore, infrequently need chronic antiepilepsy drug therapy.[30] Neonatal seizures, however, are usually symptomatic of significant or longer-lasting central nervous system (CNS) derangements.[33] Besides the varying etiologies of neonatal seizures requiring extensive evaluation, the semiology of seizures may be quite different from that seen in children of older age and in adults.

In contrast to adults, focal seizures in the very young do not necessarily imply the presence of a focal structural lesion or even a localization-related epilepsy. Indeed, disorders that confer a diffuse susceptibility to seizures, like Dravet syndrome, for example, can express themselves with multifocal seizures. This phenomenon is important to consider because treatment of focal seizures with drugs often used as first choice in adults (carbamazepine, phenytoin, lamotrigine, etc.) can actually exacerbate the seizures, worsen myoclonus, or both. Therefore, although the seizure type is an important consideration in the selection of treatment, the epilepsy syndrome is even more important.

Another important difference between children and adults is the presence of infantile spasms as a fairly unique seizure type. Although this characteristically presents between 6 to 9 months of age, it may occur outside this age range and may be preceded by the presence of focal seizures.[21] Narrow-spectrum agents that are commonly indicated to treat focal seizures may make spasms worse.[28] For these reasons, broader-spectrum agents may be superior for younger children with multifocal seizures, mixed seizure disorders including focal seizures, and focal seizures coexisting with infantile spasms.

In other children with seizures, either no chronic therapy or AED treatment for only a limited time may be needed because of the benign character of a particular epilepsy syndrome.[20] Examples of these benign syndromes include febrile seizures and benign epilepsy with centrotemporal spikes. In the condition of febrile seizures, the workup is simply to ensure that meningitis is not present at the onset. In the case of absence epilepsy, recognition of the syndrome allows one to tailor the evaluation to the physical exam—including hyperventilation—and then to proceed with the electroencephalogram (EEG). Rarely should imaging studies be performed in these children unless there are other significant findings or unless neurologic abnormality is present. In those with classic childhood absence, treatment with a specific drug such as ethosuximide, valproate, or lamo-trigine is given because of the multiple recurrent daily seizures for a limited time because most children need to be treated for only approximately 2 years. In the case of benign epilepsy with centrotemporal spikes, both evaluation and treatment are also tailored by realization of this syndrome. The classic clinical description of nocturnal or early-morning seizures that may have a focal component and EEG that clearly shows the centrotemporal spikes makes the diagnosis. Some authorities question whether these seizures should be treated at all with anticonvulsants, but others would treat for a limited period of time, perhaps 2 years.[10,22] In the case of the encephalopathic epilepsies in children, multiple comorbidities exist, and one must consider not only seizure types and epilepsy syndrome, but also the effect of medications on the child's performance and behavior. Deterioration of function or progression of the epilepsy should always make one suspect a progressive or degenerative condition rather than a static condition. For example, in some children with ceroid lipofuscinosis, early diagnosis of Lennox-Gastaut syndrome may have been made, but as the child continues to lose milestones and the ability to walk or even crawl, it is clearly evident that this is a degenerative process. In addition, at initiation, if the predominant ictal type is myoclonic seizures, the diagnosis of Lennox-Gastaut syndrome should be questioned because its predominant seizure types are axial tonic, atonic, and atypical absence seizures.[1]

The pediatric epilepsies are a conglomeration of a number of conditions or syndromes, each of which must be investigated and treated according to associated hallmark symptoms. Children may manifest a single syndrome or may evolve through different epilepsy syndromes as their seizure characteristics change with maturation.[8,22,31] Understanding this clinical evolution and the required pharmacokinetic changes that occur during childhood sets pediatric epilepsy apart as a true special consideration.

The etiology of childhood epilepsy significantly varies from that seen in adults.[14,31] Whereas lesional epilepsy is much more common in adults and genetic or idiopathic epilepsy is less common, the reverse is true in children. The highest incidence of hereditary or genetic epilepsy has its onset during childhood.

Mid-childhood may be the most common age for these syndromes to occur, with an extension of onset age up to late adolescence. On the other hand, whereas strokes and tumors increasingly are noted as the cause of epilepsy in older adults, they rarely cause epilepsy in younger children. Neoplasia is responsible for only approximately 1% of epilepsy in children. The incidence of vascular disease as an etiology of childhood epilepsy depends on the population being examined. An overall figure of 5% is given by Hauser,[14] but in populations with a greater percentage of black individuals, more children will have epilepsy associated with sickle cell anemia–related strokes. Nevertheless, the proportion will still be far less than that seen in adults, in whom cardiovascular disease appears in much higher proportions of the population. Central nervous system malformations and migrational errors are a cause of epilepsy more commonly recognized in children.

Although far more uncommon, nearly all inherited metabolic disorders responsible for seizures will present in childhood, and the majority are expressed in infancy.

In summary, the evaluation and treatment of epilepsy in children must consider the most likely syndromes and their etiologies to enhance diagnostic and therapeutic efficiency. The diagnosis of epilepsy syndromes and their associated treatments are discussed fully in other portions of this text. Here, we cover some general themes regarding pediatric epilepsy treatment.

Acute Symptomatic Seizures

Acute symptomatic seizures are relatively common in childhood. Epidemiologic studies suggest, for example, that >100,000 children in the United States each year present with febrile seizures.[31] If they are prolonged, these seizures need to be terminated, but there the risk–benefit ratio of subsequent prophylaxis is considered to be so unfavorable that continued treatment outside of the acute period is not recommended in most children.

Idiopathic Localization-Related Epilepsies

Some authors consider these disorders to fall into a spectrum in which the clinical and electrographic presentation is, in part age dependent but also variable in terms of clinical severity and associated comorbidities. For the most part, treatment need not be automatic, and, in fact, it should probably be reserved for those children with persistent seizures that negatively affect the child's quality of life. Expert opinion favors carbamazepine or oxcarbazepine as the drug of first choice.[34] See Table 1. An important subgroup of children may actually worsen with drug treatment, particularly with sodium channel blockers.[28]

Symptomatic Localization-Related Epilepsies

Nearly all medications approved for use by the Food and Drug Administration for therapy of refractory partial seizures in adults are used for the same indication in children, although only a subset have been formally approved for this use. See Table 2.[12,13]

Generalized Idiopathic Epilepsies

These disorders respond well to agents that cover a broad spectrum of seizures (Fig. 1). In addition to the epilepsy syndrome, the types of seizures will influence treatment selection. For example, patients with idiopathic generalized epilepsies with prominent absence seizures will need treatment with an agent that covers absence seizures. Valproate efficacy is established, but adverse events require consideration of other medications, particularly in female adolescents.[34]

Generalized Symptomatic Epilepsies

Agents that cover a broad spectrum of seizure types are commonly used. In addition to the epilepsy syndrome and seizure types, comorbid features are particularly important to consider in this group. These children may be particularly sensitive to the added impairments caused by behavioral disorders, cognitive impairment, cerebral palsy, and learning disabilities. In addition, they may be more vulnerable to adverse events because of limited cerebral reserves and the common need for polytherapy to control their seizures.

Genetically Determined Metabolic Diseases

As mentioned earlier, genetically determined metabolic diseases should be considered when children do not fit into one of the broad groups of epilepsies described previously. They often present early in life, often in etiologically nonspecific ways that make diagnosis challenging. Sometimes, there are useful clues that help to identify the particular disorder. There may be particular physical features, constellation of symptoms, or unique EEG features. In the majority of cases, however, these disorders present as one of the age-related but etiologically nonspecific syndromes that could broadly be considered as epileptogenic encephalopathies. If the metabolic derangement is so severe that the patient presents shortly after disconnection from the maternal–fetal homeostatic mechanisms, then young infants may demonstrate severe disturbances of diffuse cerebral dysfunction on EEG including multifocal sharps, appearance of dysmature features, and extreme discontinuity to the point of burst-suppression patterns. This could appear as early myo-clonic epilepsy as described by Aicardi, early infantile epileptogenic encephalopathy, or Ohtahara syndrome. Prototypic etiologies include nonketotic hyperglycinemia, syndromes with severe lactic acidosis, and urea cycle defects, among other conditions. They may have a variety of primitive seizure types, including multifocal seizures, myoclonus, and tonic postures. If the disturbance becomes manifest later in infancy, then infantile spasms will be a prominent feature with concurrent hypsarrhythmia. Etiologies here include peroxisomal disorders, pyruvate dehydrogenase deficiency, pyruvate carboxylase, and other conditions. Later expressions may show diffuse slowing on the EEG, the appearance of multifocal spikes, and sometimes development of well-organized generalized spike-wave discharges with concurrent generalized seizures, as is the case with myo-clonus epilepsy associated with ragged-red fibers (MERRF), the later expression of glucose transporter type 1 deficiency syndrome (GLUT-1 DS), and the sialodoses, to name a few. These disorders may thus fall into the broad group of symptomatic generalized epilepsies, or epilepsies with both focal and generalized features (see later discussion). Treatment should primarily be aimed at correction of the metabolic defect, wherever possible. When that is not possible, and antiepileptic medication is used, then care should be taken to avoid agents that might potentially exacerbate the underlying condition.

Recognition of metabolic disorders may have several important treatment ramifications. First, some of these disorders have specific treatments, which if administered promptly can result in strikingly good outcomes (Table 3). Examples of this include the B6-responsive epilepsies, central creatine deficiency, pyridoxal phosphate–responsive conditions, and phenylketonuria (PKU) deficiency. Second, these disorders are notoriously

refractory to standard antiepileptic treatment, and identification of the cause can be an important factor guiding the expectations of treatments. Third, there can be severe adverse effects peculiar to certain conditions and treatments (Table 4). Patients with pyruvate carboxylase deficiency, for example, often present with intractable seizures, which might prompt the consideration of alternative treatments. Administration of the ketogenic diet, however, could have lethal consequences, and adrenocorticotropic hormone (ACTH) can worsen spasms in this condition.

Table 1 Comparison of Recommendations for the Treatment of Pediatric Epilepsy

Seizure type or epilepsy syndrome	Pediatric Epilepsy Consensus Survey	ILAE	SIGN	NICE	French study[a]	Approved by U.S. Food and Drug Administration
Partial-onset	OXC, CBZ	A: OXC B: none C: CBZ, PB, PHT, TPM, VPA	PHT, VPA,CBZ, LTG, TPM, OXC, VGB, CLB	CBZ, VPA,LTG, OXC,TPM	OXC, CBZ,LTG (adult men)	PB, PHT, CBZ, OXC, TPM
Benign epilepsy with centrotemporal spikes	OXC, CBZ	A, B: none C: CBZ, VPA	Notspecifically mentioned	CBZ, OXC,LTG, VPA	Not surveyed	None

Childhood absenceepilepsy	ESM	A, B: none C: ESM, CBZ, VPA	VPA, ESM,LTG	VPA, ESM,LTG	VPA,LTG	ESM, VPA
Juvenile myoclonic epilepsy	VPA, LTG	A, B, C: none	VPA, LTG,TPM	VPA, LTG	VPA, LTG	TPM
Lennox-Gastautsyndrome	VPA, TPM, LTG	Not reviewed	Notspecifically mentioned	LTG, VPA,TPM	Not surveyed	FLB, TPM, LTG

CBZ, carbamazepine; CLB, clobazam; ESX, ethosuximide; FBM, felbamate; ILAE, International League Against Epilepsy; LTG, lamotrigine; NICE, National Institute for Health and Clinical Excellence; OXC, oxcarbazepine; PB, phenobarbital; PHT, phenytoin; SIGN, Scottish Intercollegiate Guidelines Network; TPM, topiramate; VGB, vigabatrin; VPA, valproate.

[a] Reproduced from French JA, Kanner J, Bautisa B., et al. Efficacy and tolerability of the new antiepileptic drugs. In: Treatment of new onset epilepsy: report of the Therapeutics and Technology Assessment Subcommittee and Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology*. 2004;62;1252–1260, with permission.

Source: Wheless JW, Clarke DF, Carpenter D. Treatment of pediatric epilepsy: expert opinion. *J Child Neurol.* 2005;20:S1–S56.

Table 2 New antiepileptic drugs for refractory epilepsy. level A or B recommendations

Drug	Partial adult (adjunctive)	Partial (monotherapy)	Primary generalized	Partial 2° generalized	LGS
GBP	Yes	No	No	Yes	No
LTG	Yes	Yes	No	Yes	Yes
TPM	Yes	Yes[a]	Yes (GTC only)	Yes	Yes
TGB	Yes	No	No	No	No
OXC	Yes	Yes	No	Yes	No
LEV	Yes	No	No	No	No
ZNS	Yes	No	No	No	No

GBP, gabapentin; GTC, generalized tonic–clonic; LEV, levetiracetam; LGS, Lennox-Gastaut syndrome; LTG, lamotrigine; OXC, oxcarbazepine; TGB, tiagabine; TPM, topiramate; ZNS, zonisamide.

[a] Not approved by the U.S. Food and Drug Administration.

Source: Reproduced from French JA, Kanner J, Bautisa B, et al. Efficacy and tolerability of the new antiepileptic drugs. I: Treatment of new onset epilepsy: report of the Therapeutics and Technology Assessment Subcommittee and Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology.* 2004;62:1252–1260, with permission.

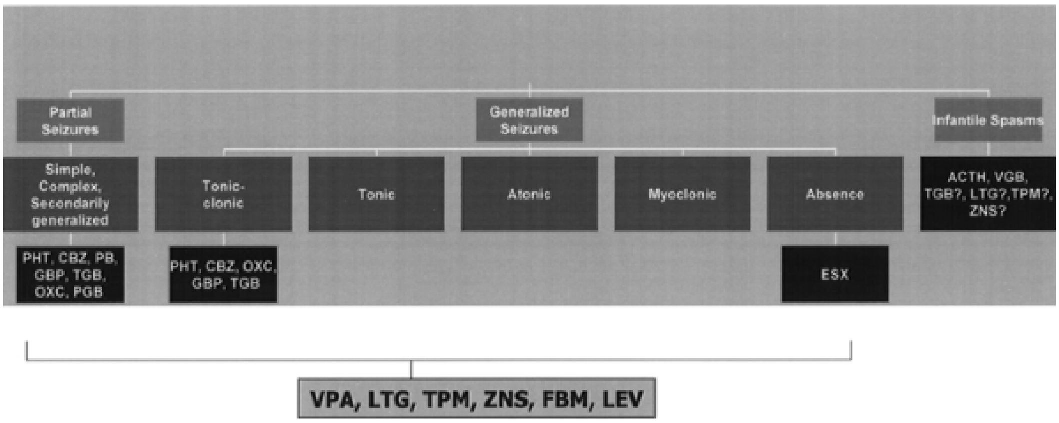
Partial Seizures
Generalized Seizures
Infantile Spasms
Simple, Complex, Secondarily generalized
Tonic-clonic
Tonic
Atonic
Myoclonic
Absence
ACTH, VGB, TGB?, LTG?,TPM?, ZNS?
PHT, CBZ, PB, GBP, TGB, OXC, PGB
PHT, CBZ, OXC, GBP, TGB
ESX
VPA, LTG, TPM, ZNS, FBM, LEV

FIGURE 1. Treatment options. ACTH, adrenocorticotropic hormone; CBZ, carbamazepine; ESX, ethosuximide; FBM, felbamate; GBP, gabapentin; LEV, levetiracetam; LTG, lamotrigine; OXC, oxcarbazepine; PB, phenobarbital; PGB, pregabalin; PHT, phenytoin; TGB, tiagabine; TPM, topiramate; VGB, vigabatrin; ZNS, zonisamide. (From Pellock JM. Epilepsy in patients with multiple disabilities. In: Wyllie E, ed. *The Treatment of Epilepsy: Principles and Practice*, 4th ed. Baltimore: Lippincott Williams & Wilkins; 2006, with permission.)

Metabolic disorders should be suspected when either a specific etiology or a well-recognized idiopathic syndrome is not established. For the most part, these disorders present in an etiologically nonspecific but age-related manner. Multifocal seizures, myoclonic seizures, tonic postures, and spasm are commonly reported in these inherited disorders of metabolism. The EEG features often show slowing of the background with multifocal spikes. In neonates, burst-suppression patterns are often seen. In infancy, hypsarrhythmia is noted, and diffuse spike-wave patterns are seen in the older children.

Table 3 Examples of Metabolic Disorders With Specific Treatments

Disorder	Specific treatment
Pyridoxine-responsive epilepsies	Pyridoxine, pyridoxal phosphate
Central creatine deficiency	Creatine
Phenylketonuria	Dietary restriction
GLUT-1 DS[a]	Ketogenic diet
Pyruvate dehydrogenase deficiency	Ketogenic diet
Some disorders with lactic acidosis	Thiamine Leukovorin

[a] Glucose transporter deficiency syndrome.

Table 4 Conditions That May Worsen With Certain Antiepileptic Medications

Disorder or epilepsy	Condition	Treatments that may worsen
Metabolic derangements	Pyruvate carboxylase deficiency	Ketogenic diet, adrenocorticotropic hormone
	Organic acidurias	Ketogenic diet
	GLUT-1 OS	Phenobarbital
	Conditions with lactic acidosis	Carbonic anhydrase inhibitors (could worsen acidosis)
	Mitochondiral disorders	Valproate

Epilepsies With Both Focal and Generalized Features

These epilepsies may present in the very young with focal seizures and later may develop generalized interictal or ictal features. In striking contrast to adults, focal seizures in the young do not necessarily imply the presence of a focal structural lesion or even localization-related epilepsy. Truly generalized tonic–clonic seizures are rarely observed in infants, and well-synchronized generalized spike-wave discharges are not common until the toddler years. This is similar to the ontogeny

of sleep architecture, in which synchronized diffuse discharges such as synchronized sleep spindles, vertex waves, and K complexes are not present until after age 2 years. Instead, infantile disorders that confer a diffuse susceptibility to seizures, like metabolic disorders or channelopathies, are often expressed with multifocal seizures in the first years of life. Initially, the interictal features are characterized by multifocal spikes, or fragments of generalized epileptiform discharges, that occur with shifting laterality across the hemispheres. Later in life, well-developed generalized spike-wave discharges and generalized seizures may occur. This makes it difficult to classify these epilepsies as either focal or generalized forms of epilepsy because they have both features. Two examples of this phenomenon are the glucose transporter protein deficiency syndrome (GLUT-1 DS, or De Vivo syndrome), which is not an independent epilepsy syndrome but rather a neurologic disorder; and severe myoclonic epilepsy of infancy (Dravet syndrome), which, of course, is a bona fide epilepsy syndrome. In both, focal seizures predominate in the first year of life, but later evolution to generalized seizures (atypical absence) is seen at >2 years of age.[8,22]

These diagnostic considerations can affect drug selection in several ways. First, a treatment other than standard antiepileptic medication may be indicated, as is the case with GLUT-1 DS, in which the ketogenic diet provides an alternative fuel source to the brain. Second, some medications that work well for focal seizures in older children and adults can actually exacerbate these pleomorphic epilepsies in the immature child. In Dravet syndrome, for example, carbamazepine, phenytoin, and lamo-trigine may exacerbate seizures, worsen myoclonus, or both. In GLUT-1 DS, phenobarbital may theoretically cause more neuronal dysfunction and intensify seizures. (Phenobarbital, caffeine, and other substances interfere with glucose transport across the blood–brain barrier.)

Summary of Diagnostic Considerations

Thus, whereas seizure type is an important consideration in the selection of treatment, the epilepsy syndrome, etiology, comorbid features, and possibility of exacerbating seizures are equally important in guiding selection of therapy. The diversity of epilepsy syndromes, the changes in expression as a function of age, and the rich complexity of underlying etiologies make drug selection far from a routine exercise and in fact a continued intellectual challenge for the clinician treating children with epilepsy.

Pharmacokinetics in Relationship to Age

Three relatively distinct pharmacokinetic periods can be seen in children.[7] The first is that represented in newborns. The next is in young children prior to puberty. Then, with puberty, the adolescent pharmacokinetic profile is similar to that seen in adults. General pharmacokinetic concepts will not be discussed in this section (see Chapter 102). Drug utilization patterns in these three childhood stages, however, will be described and compared. Drugs that have linear and nonlinear characteristics in adults show a similar pharmacokinetic pattern in children of any age.

Utilization or clearance rate is age dependent. The age of the child may not only determine the clearance rate, but it also definitely affects how much drug can be bound to protein. The binding of ethosuximide, phenobarbital, and primidone and most of the newer AEDs is low, whereas that of phenytoin, valproate, and tiagabine is high. Newborns and very young infants have reduced drug protein binding because of relative hypoalbuminemia. Higher unbound levels of drugs such as carbamazepine, phenytoin, and valproate are noted; they produce increasing toxicity with what seems to be typical dosing. Disease states can further alter protein binding. Not only the age, but also the entire drug burden affects drug elimination. Antiepileptic drugs induce metabolic pathways. Newborns exposed to drugs in utero usually eliminate antiepileptic drugs at rates comparable to those in adults. Newborns, however, are typically not born to mothers who have needed to receive antiepileptic drugs, and, therefore, they eliminate medications

more slowly than does any other age group. In addition, injury to hepatic or renal systems, as would be seen with hypoxia, may further retard drug elimination in these fragile infants. In term-born infants, postnatal maturation of renal and he-patic systems is rapidly accomplished in the first 6 to 8 weeks of life. More-immature infants who are healthy undergo these maturational changes at about the same rate, whereas others lag behind because of systemic complications. Premature newborns have less capacity than do full-term infants to metabolize drugs such as diazepam and methylxanthines; this is performed through *N*-dealkylation. In the absence of prior drug exposure, the newborn's relative capacity for *N*-dealkylation is approximately 20% of adult values at birth and gradually increases to adult capacity by age 2 years. Cytochrome metabolism is similar but is more rapidly converted to the rapid pattern seen in infants. Therefore, after a loading dose of phenytoin or phenobarbital for the treatment of neonatal seizures, blood levels should be followed before maintenance dose is initiated. Following the initial dose and with maturation over weeks or months, drug clearance may increase two- to fourfold and drug levels may decline by 50% to 70%, so that doses must be increased. Asphyxiation may, however, decrease this capacity.

Changing from intravenous to oral drug administration with phenytoin may lead to slower drug absorption, significantly lowering derived blood levels from the same dose. Slowed absorption causes a reduction in the apparent bioavailability of phenytoin by 20% to 30%. Thus, the total dose may not be as important as following blood levels in neonates and young infants. The appearance of induction, more rapid metabolism (utilization), and decreased absorption may require that large milligram-per-kilogram doses be given to very young infants receiving phenytoin.

Following the neonatal period, two major differences exist between the pharmacokinetics of antiepileptic drugs in children and those in adults. Children have a higher relative clearance than do adults, and children have a greater within-group variability in elimination kinetics. This means that, in general, much larger doses relative to weight will be required to maintain appropriate levels in children as opposed to adults. In addition, because of a decreased apparent half-life, dosing once or twice a day that is appropriate in adults may not be appropriate in children, who require more frequent dosing intervals. Unless extended-release preparations are used, children require twice-daily dosing of phenytoin, three- or four-times-daily dosing of carbamazepine, and three- or four-times-daily dosing of valproate to allow the smoothest pharmacokinetics and to fully protect children at all hours of the day. Extended-release formulations of carbamazepine and valproate should be used whenever possible.[23] The greater within-group of variability in elimination kinetics among children may vary up to 50% of average values for children who are <5 years old. This fact may suggest that drug levels are especially useful in children because of this wide fluctuation.

Drug utilization remains relatively stable through the middle and later years of childhood, and children tend not to outgrow their drug doses. With adolescence, a growth spurt occurs, but it rarely necessitates a dose adjustment because of the dramatic change in relative drug clearance seen at puberty. In general, lowered levels of anticonvulsants are secondary to noncompliance or drug interactions rather than to pharmacokinetic changes.[7] Alterations of AED clearance seen in children are directly related to hepatic mass, relative caloric requirements, and surface area relative to body mass during growth to adult size. Compared to adults, children have a larger surface area relative to body mass, and they are hypermetabolic. With growth, there is increasing body mass. Surface area relative to body mass decreases, and less energy is required.

Adverse Effects of Antiepileptic Drugs

Once the physician and family have made a decision to treat the child that has epilepsy, the need for seizure control must be balanced with expected acute and chronic AED toxicity.[20,35,36] The AED without side effects is not yet available. Successful AED therapy is based on proper diagnosis of the seizure type and epilepsy syndrome and a careful assessment of the pharmacokinetic and pharmacodynamic properties of the chosen treatment. Children have an individual variation in response to each AED and the interactions with other medications they might be receiving. In most children, AEDs will be given in moderate to high doses for many years. In others, relatively low doses will be acceptable and given for only a few years. In all these patients, some adverse effects may occur. Pharmacokinetic effects are those that are measurable and show a clear relationship to drug levels. Pharmacodynamic effects may also occur as adverse reactions but are responses at the target organ without a concomitant measurable change in plasma concentration of medication.

Adverse effects that are also non–dose-dependent may produce drug-induced disease or idiosyncratic reactions acutely or following chronic use. The use of a single AED (monotherapy) and even higher doses and levels of single AEDs is often superior to the use of low or even subtherapeutic levels of multiple agents because of decreased numbers of adverse responses. The advantages of AED monotherapy include less frequently noted and easier management of toxicity and elimination of drug interactions, improved compliance, and reduced costs.[23] In resistant epilepsy, which is estimated to occur in up to 30% to 40% of cases, polytherapy should be considered when monotherapy is unsuccessful. Chapter 121 discusses rational polypharmacy. The adverse effects seen with antiepileptic drugs are discussed in other chapters. This chapter will review only specific issues noted more frequently in children.

Neurotoxicity is the most common acute and chronic adverse effect secondary to treatment with antiepileptic drugs. In adults, this is typically characterized by difficulty concentrating, lethargy, poor coordination, and minor movement disorders such as tremor. Many of these same symptoms are present in children. However, more subtle forms of cognitive and behavioral symptoms can be observed in some children, manifested only as difficulty in school. Observing the behavior and school performance of children with epilepsy is a very important part of monitoring for neurotoxicity of anticonvulsant drugs. Of course, there are many other factors that determine the child's performance in the classroom, but medications may play a significant positive or negative role in the child's ability to concentrate, attend, learn, and perform in this setting.

Especially in children with encephalopathy, sedative drugs may cause problems. Sedative agents such as barbiturates or benzodiazepines may lead to increased seizures because of the sedation or to other behavioral difficulties. Clonazepam and related compounds may increase oral secretions to such an extent that respirations may be comprised, and associated hypotonia may cause marked difficulties for these children, who already have motor difficulties with oral buccolingual incoordination. Medications that typically sedate adults and older children may lead to extreme irritability or hyperactivity in younger children. The well-known hyperirritability and hyperactivity seen in some children when treated with barbiturates may also be produced when benzodiazepines or other “sedative” drug classes are administered.

Systemic complications from medications are also noted. Although hyponatremia is less frequently noted in association with carbamazepine therapy, it has been noted in some children, especially those institutionalized or on set diets with

decreased salt intake. When high-dose phenobarbital is administered to neonates, hypotension may result, such that appropriate cerebral perfusion is not maintained. In the past, very high doses of phenobarbital were used to treat neonatal seizures, but levels >60 μg/mL are no longer recommended. A particular problem in children with disabilities is one of bone abnormalities in children treated with enzyme-inducing antiepileptic drugs who are not exposed to sunlight. Broader attention has concentrated on the bone health of all children treated with AEDs. In children with retardation or those who have frequent trauma, one should pay particular attention to this complication, which may be asymptomatic until increased fractures occur.[17] AED toxicity, therefore, may affect multiple systems and result in hepatic, hematologic, connective tissue, bone, motor, cerebellar, immunologic, cognitive, and behavioral disorders. Several factors predispose to chronic toxicity, including early age of epilepsy onset; long duration of therapy; polytherapy; conditions associated with increased vulnerability, including institutionalization; poor diet; pregnancy; chronic illness or disability; genetic factors; repeated or prolonged acute toxicity; physician lack of awareness; and incorrect diagnosis of epilepsy. Dependent children, especially those with multiple disabilities, share all these risk factors.[25]

Antiepileptic drug idiosyncratic reactions most commonly include hematologic, dermatologic, and hepatic reactions. The mechanisms for these reactions are frequently unknown, but in some situations, particular age groups seem at greater risk. Aplastic anemia, agranulocytosis, and pancytopenia actually seem to be less common in young children than in adults.[27] This is true both for carbamazepine[29] and for the more recent experience with felbamate.[26] Valproate-associated thrombocytopenia is not an idiosyncratic reaction but is rather a dose-dependent adverse reaction. This is seen at all ages.

Dermatologic reactions are the most common adverse effect of any of the idiosyncratic reactions and are more commonly reported in children than in adults. Most, however, represent fleeting symptoms and frequently are not associated with the administered anticonvulsant. The physician thus must differentiate between the reactions that signal a more generalized systemic hypersensitivity response and those that are more innocent. Associated desquamation, mucous membrane ulceration, and painful dermatitis usually herald more intense reactions. The distribution of the rash frequently can differentiate a contact or exposure dermatitis from a generalized hypersensitivity reaction. Medications should be stopped when there is doubt, and skin biopsy can often distinguish benign dermatitis from those with more widespread subcutaneous vasculitis and generalized hypersensitivity reactions. Associated symptoms suggesting other organ involvement should be recognized to diagnose the anticonvulsant hypersensitivity syndrome or drug rash with eosinophilia and systemic symptoms (DRESS)[2] (see Chapter 120). The latter may require systemic steroids or treatment as for burns. In children receiving lamotrigine, rash is increased by rapid dose titration and coadministration of valproate.[19] If rechallenge is performed because of an unclear past history of a possible reaction to an anticonvulsant, the patient's family and physician must be extremely cautious. Nevertheless, far more children have been removed from AEDs because of nonspecific rash or intercurrent disease than have ever experienced a true idiosyncratic dermatologic reaction, but history of prior drug rash to an antiepileptic drug must be taken seriously and may place the child at increased risk for this reaction when a new medication is administered.[15]

Hepatotoxicity associated with anticonvulsant use may be of three broad types. The first type is a drug-related hepatic necrosis, is usually part of a generalized hypersensitivity reaction, and is seen in the first 10 weeks of treatment. The second type presents as acute or subacute hepatic failure leading to stupor and coma, bleeding, and other signs of hepatic disease. Valproate-associated hepatic toxicity of this type occurs most frequently in the first 90 days of therapy. The third type is a chronic hepatic injury that occurs after long-term treatment. Valproate-induced hepatic toxicity seems to have been more commonly identified in young children.[5] This potentially fatal idiosyncratic type of liver failure associated with microvesicular steatosis may be associated with specific, underlying inborn metabolic defects or acquired mitochondrial dysfunction. Valproate hepatic toxicity is most common with AED polytherapy in children <2 years of age who have preexisting encephalopathy or underlying metabolic disease. During polytherapy, omega oxidation through cytochrome P450 is enhanced with the production of a toxic 4-ENE metabolite. This compound, along with other possible toxic metabolites, may be responsible for mitochondrial failure and the pathologic appearance of microvesicular steatosis. Related changes in mitochondrial fatty acid beta oxidation and the production of these metabolites may also be factors in some patients. The role of a relative carnitine deficiency in these patients is unclear, but carnitine administration has proved to be helpful in some cases of severe hepatotoxicity.[11,16] In addition, free radical scavenger deficiencies may play a partial role in valproate hepatotoxicity.[36] It is thus recommended that patients be evaluated for the presence of prior mitochondrial dysfunction or disease states that would put them at higher risk for acquiring valproate-associated hepatotoxicity.[27] Especially in young children, polytherapy is relatively contraindicated whenever possible. The role of carnitine supplementation in preventing valproate hepatotoxicity is unclear.

Monitoring

Because adverse effects may generally be separated into drug-induced diseases and dose-related toxicity, one should monitor with these two categories in mind. In general, the regularly scheduled monitoring of blood levels, hematology, chemistry, and other routine studies is likely to be helpful only if the patient is immediately presymptomatic or shows abnormal signs and symptoms.[27,35] Therefore, the role of this routine laboratory testing for most children is unwarranted (see also Chapter 120). Pretreatment laboratory evaluation prior to AED initiation is almost always indicated as part of the initial evaluation of epilepsy. Specific risk factors may suggest further initial or laboratory studies or monitoring. Examples of these risk factors would be children <2 years of age for whom valproate therapy seems most advantageous or those with prior idiosyncratic drug reactions. In addition, patients debilitated by other disease processes or chronic neurologic dysfunction or institutionalized patients may also have need for more extensive initial and ongoing evaluations. In most patients, chronic monitoring should depend on the clinical state. If a symptom complex develops and suggests possible need for either blood level or systemic blood monitoring, the appropriate evaluations should be performed. In practice, the performance of laboratory tests every few years is probably indicated as a child develops and continues on medication. However, the monthly or bimonthly screening that was done in the past is not being performed and seems wasteful. The best strategy is to alert the patient and parents to a list of significant symptoms that should cause alarm. The patient and referring physician should be aware of these symptoms so that examination of the patient and appropriate laboratory testing should be done when indicated. Frequently, the neurologist will not be contacted for these complaints unless there are difficulties. Blood level monitoring is best performed when answering a specific question such as compliance, toxicity, drug preparation efficacy, autoinduction or interactions, and changes in levels with maturation.[6] Once

the neonatal and early childhood development periods pass, pharmacokinetic patterns stay relatively stable, and dosing requirements change only slightly as children enter puberty and adolescence.

Choice of Drug

The antiepileptic drug of choice should produce complete control of seizures without producing adverse effects. The physician must make a decision to treat with a given drug that is likely to control symptoms in a patient while producing the least amount of toxicity. In children with concomitant diseases, behavioral disorders, or other symptoms, one must select drugs that would be least likely to exacerbate existing symptoms.[20,24] Children with motor disturbances should not receive medications likely to aggravate incoordination. Those already exhibiting tremor will probably do more poorly on medications that produce or intensify tremor. Those children who have eating disorders must have medications considered so that obesity or anorexia is not exacerbated. Because generalized or mixed seizures are more common in some syndromes of pediatric epilepsy in children, those treating pediatric epilepsy will be more likely to use medications such as ethosuximide, valproate, lamotrigine, topiramate, and levetiracetam. Carbamazepine, phenytoin, gabapentin, tiagabine, pregabalin, and vigabatrin should, of course, be given appropriately for partial seizures and convulsions. For many years pediatricians have used phenobarbital exclusively for all types of epilepsy. This practice should be reconsidered because of its ample toxicity and the availability of equally effective AEDs.

Choosing the best AED for chronic treatment of a given patient must depend on seizure type and epilepsy syndrome. Table 2 demonstrates the selection of drugs by expert consensus groups,[34] and FIGURE 1 places AEDs into categories effective by seizure type. Some children with epilepsy, especially those who are encephalopathic, have breakthrough clusters of acute repetitive seizures or have repeat episodes of prolonged seizures or status epilepticus. The home or out-of-hospital treatment of these individuals with rectal diazepam or other benzodiazepine has been quite successful and cost-effective.[3,9,18] This option should be discussed for children with frequent clusters or prolonged seizures. Home therapy with oral benzodiazepines might also be helpful for those able to swallow medications. Continued use of benzodiazepines in children, however, is more frequently associated with increased adverse effects and may lead to increased seizures.

Assessing the Impact of Drug Treatment in Children

In addition to inquiring about medication effectiveness and side effects, an assessment of the impact of epilepsy and its treatment upon the child's ability to function is critical. Quality-of-life instruments specific to children have been developed. In addition, it is particularly useful in the school-aged child to inquire about school placement, performance, and the need for additional resources. This can be done verbally during the interview or as part of a standardized visit questionnaire.

Summary and Conclusions

The complete care of the child with epilepsy requires one to combine consideration of the child's lifestyle with consideration of the disorder. Stopping all seizures is important, but function must be maintained. The initial evaluation must be tailored to include behavioral, cognitive, and functional status. Frequently, the neurologist spends at least as much time in modifying the educational setting for the child as in treating the seizures. Comorbidities of hyperactivity, inattention, mental retardation, spasticity, and their deficits require special attention. Length of therapy is clearly determined by the epilepsy syndrome and the response to medications. In treating the child with epilepsy, one also treats the family. Truly effective treatment of epilepsy includes selection of drug, or surgical procedure along with drug; optimal dosing; indoctrination of the patient and caretakers regarding necessity for timely administration of the agent; eliminating seizure stimuli when these are present; proper social, psychological, and educational support and placement; and, finally, patient monitoring. This monitoring must encompass more than drug toxicity and neurologic status; it must include all aspects of the life of the child with epilepsy.

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Chapter 112

Drug Treatment in Adolescents

Eileen P. G. Vining

Introduction

In general, the incidence of epilepsy tends to decrease slightly in adolescence. It appears to range from 20 to 60 per 100,000 with a prevalence of 1.5% to 2%.[40] Certainly maturation itself, and specifically the effects of sexual maturation and menarche, may play a significant role in the development of seizures during this period of life. Trauma is an important cause of seizures in adolescents, and the idiopathic epilepsies appear to peak in this time frame. Mesial temporal sclerosis, causing temporal lobe epilepsy, frequently is recognized as intractable epilepsy during this period, and some of the rare progressive epilepsies (Unverricht-Lundborg disease, Lafora disease, ceroid lipofuscinosis, and some of the mitochondrial disorders) may also emerge in adolescence. The juvenile idiopathic epilepsies are very distinct entities that require accurate diagnosis and understanding for appropriate and comprehensive therapy. The drugs that are used for these epilepsies (juvenile absence, juvenile myoclonic epilepsy, and epilepsy with grand mal on awakening) are the focus of this chapter, as are issues that are of particular importance to adolescents. Unfortunately, treatment guidelines from the International League Against Epilepsy (ILAE),[19] the American Academy of Neurology (AAN), and the American Epilepsy Society (AES)[13,14] routinely demonstrate how meager the evidence is for our choice of medications, particularly in younger patients. A review of the recent ILAE treatment guidelines indicates that no medication reaches the highest levels of evidence for efficacy in adults with generalized tonic–clonic (GTC) seizures. Carbamazepine (CBZ), lamotrigine (LTG), oxcarbazepine (OXC), phenobarbital (PB), phenytoin (PHT), topiramate (TPM), and valproic acid (VPA) may be considered for initial therapy in adults with GTC. With the exceptions of LTG and OXC, the same statement can be made for children with GTC seizures. Ethosuximide (ESM), LTG, and VPA are possibly efficacious/effective for children with absence seizures. Finally, and of particular importance to this chapter, are the recommendations for juvenile myoclonic epilepsy. At a very low level of evidence (Class IV), clonazepam (CZP), LTG, levetiracetam (LEV), TPM, VPA, and zonisamide (ZNS) may have some efficacy for patients with newly diagnosed juvenile myoclonic epilepsy (JME).[19] The AAN and AES note that TPM is recommended (Class A) for refractory generalized tonic–clonic seizures.[14] In studies of mixed populations with both partial as well as generalized seizures, LTG, TPM, and OXC are effective, and LTG is effective in children with new-onset absence.[13] Given the limitations of evidence-based recommendations, these medications are discussed based on clinical experience and reflect many of the observations made in a recent survey of treatment of pediatric epilepsies.[39] Medications that are particularly useful for the partial epilepsies are appropriately covered in the chapter on adult medications, although the issues that are critical to adolescents are addressed in this chapter.

Medications that are Useful in the Juvenile Generalized Epilepsies

Ethosuximide

Ethosuximide is an extremely effective medication for childhood absence epilepsy (CAE) and may play a role in controlling JAE and sometimes myoclonic seizures. However, since the majority of patients with JAE also have GTC seizures, ethosuximide is usually not considered a good therapy because it does not prevent the GTC events. Occasionally, when other medications are not controlling the absence and/or myoclonic seizures, ethosuximide can be effective when added to other regimens that are controlling the GTC seizures. It can be given once a day, and the side effect profile is acceptable: Gastrointestinal disturbance, headache, rarely rashes, and joint pain.

Valproic Acid, Sodium Valproate

Valproic acid was the first medication that successfully controlled the seizures in the majority of patients with juvenile myoclonic epilepsy.[11] It is effective in controlling myoclonic, absence, and GTC seizures. However, a number of side effects and the availability of alternative medications have diminished its use in the last decade. Weight gain has been recognized as a problem since the early 1980s.[30] When weight gain is going to occur, it usually occurs in the first 10 weeks of use and it persists.[7] It may be more prevalent in those who are heavy to begin with.[30] Many explanations have been postulated, including an increase in serum leptin[37] that would stimulate appetite. VPA may also decrease the binding affinity of albumin for palmitate, leading to an increased availability of long-chain fatty acids. This increases insulin levels and lipogenesis, resulting in decreased lipolysis, and decreases glucose. This then may stimulate appetite via hypothalamic glucoreceptors.[38] VPA has also been associated with hair loss in about 10% to 12% of patients. This may be dose related and is generally mild, and hair tends to grow back well, perhaps with more curl.[22,28] Endocrine issues have cosmetic and general health importance for adolescents. VPA has been associated with hyperandrogenism, especially when started in adolescence,[35] and this may be related to polycystic ovary syndrome, which is reported in as many as 43% of women taking valproic acid.[21] This syndrome can include obesity, menstrual disturbances, hyperandrogenism, and infertility, and may ultimately lead to dyslipedemia, diabetes mellitus, cardiovascular problems, and endometrial carcinoma. Another major concern to women in their childbearing years is a recognized association with neural tube defects and fetal malformations. This risk is typically considered to be 1% to 2%. However, some studies have found rates of adverse pregnancy

outcomes as high as 20%. Of growing concern is the possible association of the medication with an adverse impact on the cognitive development of the children of mothers exposed to the medication.[18,27,44] These problems may be dose related, especially at doses >1,400 mg/d.[36] VPA has also been associated with hepatic dysfunction (even liver failure) and other gastrointestinal problems, as well as hematologic problems. On the positive side, VPA has mood-stabilizing effects and is important in migraine therapy.[12,32]

Lamotrigine

When LTG was introduced in 1994 it was quickly seen to be effective in the generalized seizures of Lennox-Gastaut syndrome and was soon adopted as a therapy in the juvenile generalized epilepsies because of perceived fewer side effects. Both VPA and LTG can be efficacious against absence seizures, although VPA shows a much faster onset of action, at least in part because of its shorter titration schedule.[9] The American Academy of Neurology and the American Epilepsy Society also found evidence of its efficacy in absence epilepsy.[13] Some studies suggested that LTG is as effective as VPA in JME, but most of these studies were retrospective in nature, and there is some evidence that myoclonic seizures may not be as well controlled with LTG as with other medications or combinations of medications; there is also some evidence that it can even worsen myoclonic seizures.[20,31] Although LTG appears to have a generally good risk profile with respect to teratogenesis, further experience is required to understand the complete profile. The major disadvantage in using LTG is the slow titration (8–12 weeks) that is suggested to minimize the risk of developing a rash that might progress to Stevens-Johnson syndrome. This risk appears somewhat greater in children and if it is coadministered with VPA. The risk was virtually abolished when these guidelines were followed.[43] Other side effects that have been reported include dizziness, somnolence, nausea, tics or tremor, and sleep disturbances.

Topiramate

Topiramate has been found effective in controlling refractory generalized epilepsy and has been evaluated in JME, with some suggestion that it might be more effective in controlling the primary generalized seizures but not as effective as other medications in controlling absence or myoclonic seizures.[5,34] It is considered a second-line antiepileptic drug (AED) by the National Institute for Clinical Excellence (NICE-UK) criteria for juvenile absence and JME, but may be a first-line drug in generalized tonic–clonic seizures on awakening.[28a]

Side effects include nephrolithiasis, dizziness, fatigue, ataxia and paresthesias, oligohydrosis, and glaucoma. Weight loss, a potentially beneficial side effect, can be sustained, especially in overweight patients.[3] In addition, cognitive effects have been reported. This includes what is sometimes described as a "fuzziness in thinking" as well as word-finding problems. These effects may be less frequent when the medication is titrated slowly.[6] A major advantage is its concomitant efficacy in treating headache.[42]

Levetiracetam

In a group of patients with idiopathic generalized epilepsy that had failed therapy with at least one other anticonvulsant, LEV was added on or prescribed as monotherapy; 40% became seizure free. The authors noted that some patients with absence seizures did not respond.[25] Many authors have documented its particular efficacy in controlling myoclonic seizures.[26] It is also considered a second-line AED in juvenile absence and JME by the NICE-UK criteria.[28a]

The most common side effects that would be worrisome to adolescents are sleepiness, headache, and behavioral issues. Irritability, agitation, and anxiety are noted, and rarely psychosis. These problems may be ameliorated by slow titration, and particular care should be taken if this medication is used in a patient with an underlying behavioral problem.[4,23,41] A major advantage of the medication is the rapidity with which it can be introduced and its lack of interaction with other important medications.

Zonisamide

Zonisamide is a broad-spectrum anticonvulsant that has been shown to be effective in JME. It was found that 69%, 62%, and 38% of patients were free of GTC, myoclonic, and absence seizures, respectively.[24] It is also considered effective in other disorders in which myoclonus is a significant component. As with TPM, nephrolithiasis, glaucoma, and oligohydrosis are occasionally seen. The most common side effects are lethargy, dizziness, and ataxia. A major advantage is its very long half-life and minimal interaction with other medications.

Adolescent Issues that are Crucial to Therapy

Adolescents are in a critical developmental period, and epilepsy is routinely perceived as a barrier to achieving the independence and lifestyle of a normal teenager.[29] Chronic medication adherence is particularly problematic because it acknowledges and accentuates the restrictions inherent in having a seizure disorder. It further reduces an already damaged self-esteem.[15] Medication regimens must recognize this, and once-daily or, at most, twice-daily schedules are particularly important to this age group so that medication (and the social stigma of going to the nurse's office) does not need to be given at school.

In choosing a medication for an adolescent, efficacy is paramount. Some medications should be avoided because they can exacerbate myoclonic and absence seizures: These include CBZ, gabapentin (GBP), OXC, PHT, tiagabine (TGB), and vigabatrin (VGB).[17] In some individuals LTG can also worsen myoclonic seizures.[16] Because there are no randomized, controlled trials that compare the new antiepileptic drugs with each other or against the traditional antiepileptic drugs, prescribing a medication is often based on consideration of a number of factors that include efficacy, cost, and particularly the side effect profile of the drug. The side effects that are of critical concern to adolescents involve their appearance, their abilities, and to some extent their future. These considerations should be carefully individualized and discussed with the patient.

Teenagers are generally very concerned about how they look. The critical elements in this assessment are weight, skin, and hair. Several medications are known to influence weight. VPA is particularly associated with weight gain, whereas topiramate produces some weight loss in many individuals. Rashes are seen with LTG, and hair loss is seen with VPA.

The functional impact of these medications is also critically important to the adolescent. Teenagers are often tired, typically related to late-night activities (homework, socializing with friends, game playing, watching videos, etc.) and early-morning school schedules. Medications that increase this are typically problematic, and all of the anticonvulsants can produce a feeling of tiredness in some patients. Another area that can cause concern is an adverse impact on coordination. This can seriously affect the young person's athletic prowess or simply interfere with his or her video-game skills. Either can be socially damaging. Some adolescents will be concerned if the medication adversely affects their cognitive abilities, and any changes in academic abilities should be carefully monitored. This could be due to a variety of causes, including depression and anxiety, problems that are frequently seen in young people with epilepsy,[1,2,8] but it may also be due to the medication that is prescribed. Although some of these medications are known to be mood stabilizers (VPA and LTG), others are associated with irritability and other behavioral changes that should be carefully monitored and perhaps, in some vulnerable individuals, avoided (LEV, TPM).

Depending on the age of the adolescent, many other aspects of maturation are of great importance. In particular, this includes driving. Complete seizure control is of concern as this privilege is being pursued. Adolescents must be able to communicate with their treating physician to be sure that therapy is optimized and this full control is achieved. Patients need to feel safe in reporting seizure breakthroughs and reassured that the goal of seizure freedom can be attained. Sexuality is another emerging area of concern for these young people. Contraception is a particularly important area to address. Many of the medications used for the adolescent generalized juvenile epilepsies (VPA, LEV, ZNS) do not interfere with oral contraceptives. Many of the medications that are used for partial epilepsy (CBZ, OXC, PHT, higher doses of TPM, and probably LTG) do require somewhat higher-dose oral contraceptives to achieve successful birth control. Issues pertaining to the risks of teratogenicity need to be explored, when appropriate. Women with epilepsy have a somewhat higher risk of fetal malformations than the overall population, and this is increased considerably with VPA (7%), CBZ (3%), and LTG (3%). The risk for the even newer medications is not yet clear.[10] Young women on anticonvulsant medication should be advised to take folate, although there is no definitive evidence concerning the best dose. Most recommend 1 to 5 mg/d.

Parental Issues that are Important to Therapy

Parents are worried about many of the same things as their children, but the hierarchy of concerns may be somewhat different. They clearly understand the importance of complete seizure control, in terms of both safety and driving. They are more focused on health issues, particularly whether their children need to be monitored for adverse effects on liver and bone marrow. They are more likely to understand the seriousness of severe drug rashes, and they are more likely to use the Internet to search out all the possible adverse events associated with a medication. They will be the ones concerned about how often various parameters need to be monitored. They will need to understand that many of the new medications do not have established and useful therapeutic ranges, and that the physician must prescribe based on dose ranges and the careful monitoring of control versus toxicity. They will not feel relief (as would their child) that their doctors do not advocate frequent blood work to look for toxicities that cannot be foreseen.

Beyond the obvious medical issues, they will be focused on their child's performance, behavior, and school and social life. They will be looking further into the future and will have concerns about whether their child will be able to go to college, how the child will deal with diminished supervision, and whether epilepsy will limit vocational possibilities. Although they are often uncomfortable with issues of sexuality for their children, they need to be aware of the issues. Specifics, however, should be discussed in private with the patient unless he or she gives permission for parents to participate.

Duration of Therapy

In most seizure disorders of childhood and adolescence, physicians will want to consider whether medications can be stopped after a period of complete control. In general, this would be at 2 years of seizure freedom, when the chance of successfully discontinuing medication is about 70%.[33] It is important to approach this topic as early in successful therapy as possible, especially in adolescents, because it will affect the ability to drive. About 80% of those who recur will have declared this by 6 months. This may be an appropriate period of time to counsel young would-be drivers to refrain from driving and to find out whether they will need ongoing medication. Unfortunately, this optimistic prognostication does not pertain to teenagers with the juvenile generalized epilepsies. The majority of these youngsters will need lifelong therapy. Only about 10% will be able to have medication stopped successfully. In the future, genetic studies may help us determine which subset can actually be successfully weaned with minimal risk.

Summary and Conclusions

Unique forms of epilepsy present in adolescence along with those that are more commonly seen throughout various age ranges. In addition, patients in this age range are dealing with a very unique period of life, when they are emerging from the protection and shelter of childhood into the independence of adulthood. It is a stressful period, even in the best of circumstances, for both the young person and his or her family. Epilepsy is a major complication, especially some of the particular epilepsies seen in this age range. The clinician must be able to make a correct diagnosis to provide both the appropriate therapy and counseling regarding the likely impact of the seizure disorder on the adolescent's future. The clinician must be able to negotiate the difficult pathways of working with the patient, who is neither a child nor an adult, and the parents, who still have considerable responsibility and concern (if not control). Prescribing and monitoring medication for these patients requires sensitivity to all of the issues that are critical to the person's rapidly changing life and creativity in finding ways accurately to measure its effects. Successful treatment is likely to have long-ranging effects on whether the adolescent negotiates this difficult transition well and becomes a healthy, productive, and well-adjusted adult.

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Chapter 113

Gender Issues for Drug Treatment

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Introduction

Potential health risks associated with long-term drug treatment raise specific concerns and considerations for the treatment of epilepsy across reproductive ages. The incidence of epilepsy is not significantly different between men and women, and the fundamental principles for managing men and women with epilepsy are very similar. However, gender differences include the effects of menstruation, pregnancy, and menopause on the course and treatment of epilepsy in women, obviously not considerations for men with epilepsy. Women are of particular concern due to the potential impact of antiepileptic drugs (AEDs) on reproductive hormones, contraception, pregnancy, and fetal outcome. However, men and women with epilepsy are both at risk for reduced sexual and reproductive functioning. Epilepsy and its drug treatment have profound implications on quality of life and ability to establish intimate relationships. This chapter discusses the specific gender-related considerations for AED treatment for women and men.

Reproductive Dysfunction

Fertility

The definition of infertility is pregnancy not occurring after 1 year of normal sexual activity for a couple not using contraceptives. Birth rates of live offspring to women and men with epilepsy are decreased compared to the general population[1] and same-sex siblings,[66] suggesting that persons with epilepsy are at risk for infertility. Although these studies adjust for marriage rates, they cannot determine the exact factors accounting for lower birth rates, such as choosing not to bear children in the setting of a chronic illness. One clear biologic factor that may affect fertility is the higher number of anovulatory menstrual cycles per year for women with epilepsy.[48]

Polycystic Ovary Syndrome, Epilepsy, and Valproate Use

Women with epilepsy also have higher rates of polycystic ovary syndrome (PCOS), which is a frequent cause of infertility, than the general population.[4] The current definition of polycystic ovary syndrome is the presence of two of the following three factors: (a) polycystic ovaries, (b) oligo-/anovulation, and/or (c) clinical or biochemical evidence of hyperandrogenism.[25] Other frequently present features of PCOS include an elevated ratio of luteinizing hormone (LH) to follicle-stimulating hormone (FSH) and insulin resistance with or without obesity.[40,56]

The association between PCOS and epilepsy is complex because epilepsy itself may be a cause or precipitant for PCOS. Epilepsy dysregulates hypothalamic activity by propagation of ictal and interictal discharges through the structure, and it therefore disrupts normal LH pulsatility. Several studies have shown altered LH pulsatility in both men and women with epilepsy compared to normal control subjects.[15,27] LH pulsatility is altered in men with epilepsy, although the effects on LH pulsatility differ in the interictal and postictal states.[55] For men in the interictal state, the pulsatile secretion of LH is slower in onset and has higher peak concentrations compared to healthy controls, whereas postictally the pulsatility becomes more irregular.[55]

The alteration of this exquisitely balanced hypothalamic-pituitary-gonadal axis may be further dysregulated via increased gonadotropin-releasing hormone (GNRH) secretion caused by contiguous ictal and interictal physiologic activity. Increased GNRH secretion preferentially increases the LH-to-FSH ratio.[38] Consistent with this postulated effect, elevated LH-to-FSH ratios have been documented in women with epilepsy.[48] LH stimulates ovarian steroidogenesis, and an elevated LH-to-FSH ratio will produce follicles that do not fully mature but, rather, become numerous and cystic. Immature follicles are deficient in aromatase, which is the enzyme that produces estrogen in the ovary by converting it from its precursor testosterone. In this manner, the PCOS ovarian follicle primarily manufactures androgens.

The question of whether valproate can cause, exacerbate, or imitate PCOS remains unclear, but it is clear that valproate is associated with the three primary features of PCOS. Valproate is associated with increased androgens[31,32,45,49,70] and cystic ovaries.[31,32] However, the association between valproate and anovulation has not been consistently found,[32,49,50] but, when present, could contribute to difficulty conceiving. The contribution of valproate to PCOS is confounded by an increased occurrence of PCOS in women with epilepsy in general; a similar rate of PCOS in women with epilepsy taking carbamazepine, valproate, or no AEDs has been reported, around 11% for each group.[4] Valproate itself inhibits aromatase and can block the conversion of testosterone to estrogen and, in this manner, among other mechanisms, contribute to hyperandrogenism.[22,71] Another well-known adverse effect of valproate now clearly emerging as an endocrinopathy is weight gain, which occurs in 40% to 50% of patients.[32] The mechanism of valproate-induced obesity may be due to its association with increased insulin and leptin levels and consequent decreased ghrelin and adiponectin levels.[20]

Because valproate is an effective AED for many persons with epilepsy, the decision to use or continue it despite the risk of endocrine dysfunction is difficult. For women with evidence of reproductive dysfunction, such as anovulation, hyperandrogenism, or PCOS itself, valproate should not be the first choice of AED because it may exacerbate these features. Weight gain with valproate use is also a reason for discontinuation for both men and women, not only for cosmetic reasons, but also due to the health risks associated with obesity.

Sexuality

Decreased levels of free testosterone have been found in a large group of men with epilepsy (*n* = 200) compared to normal controls (*n* = 105).[5] Some nuances were found, however, within the epilepsy group. Decreased testosterone-to-LH ratios were present in the temporal lobe epilepsy group only, whereas this important ratio was normal for patients with idiopathic generalized epilepsy. This ratio is an indicator of testicular function because LH increases in response to low testosterone levels and stimulates testicular testosterone production. Therefore, an increased testosterone-to-LH ratio suggests testicular dysfunction and an inability to respond to LH stimulation. Carbamazepine-treated men in this study had the most altered free testosterone and testosterone-to-LH ratios, consistent with the postulated effect of carbamazepine in increasing the hepatic production of testosterone-hormone binding globulin and inducing aromatase, which metabolizes the conversion of testosterone to estradiol. Valproate, on the other hand, was associated with normal total testosterone and testosterone-to-LH ratios, although the free testosterone level was still significantly decreased.[5]

In an evaluation of 65 men with epilepsy on AEDs, a higher rate of sperm abnormalities, including sperm morphology, motility, and concentration, was found.[33] Of the AEDs evaluated in this report, oxcarbazepine had the least detrimental effect on sperm quality compared to carbamazepine and valproate. The authors stated, therefore, that AED use could be a cause of infertility for men with epilepsy.[33]

In an evaluation of 63 men with localization-related epilepsy, low bioactive testosterone (similar to free testosterone) was found in men not taking AEDs (*n* = 9) and in men taking hepatic enzyme-inducing AEDs (*n* = 36).[28] Enzyme-inducing AEDs were associated with increased sex-hormone–binding globulin as well. Men taking lamotrigine (*n* = 18) showed more normalized bioactive testosterone and better testicular functioning based on the bioactive testosterone-to-LH ratio compared to enzyme-inducing AEDs,[28] indicating that lamotrigine has less detrimental effect on reproductive and sexual functioning than do enzyme-inducing AEDs.

Lamotrigine has been reported to be associated with improved sexual functioning in 141 women and men with epilepsy, including those who were initiated on monotherapy or switched to monotherapy from another AED.[19] Women with epilepsy reported decreased sexual functioning in association with phenytoin use and with low levels of estradiol and dehydroepiandrosterone sulfate, as well as mild depression.[47]

Enzyme-inducing AEDs therefore appear to increase the risk of sexual and reproductive dysfunction in persons with epilepsy, whereas valproate may have less of this negative effect, although it has the risk of other endocrinopathies. Evidence shows lamotrigine to be more neutral with regard to these variables, but epilepsy itself is associated with reproductive disturbances.

Perimenopause and Menopause

Perimenopause is a life epoch when seizures tend to increase, and therefore alterations in epilepsy treatment in response to this increase may be required.[24] At menopause, however, seizures may decrease with the cessation of menses, especially if there had been a catamenial pattern during the reproductive years.[24] An earlier age at menopause has been reported in women with epilepsy, particularly in those with frequent seizures, but no clear relationship to AEDs has been found.[23] However, only a few of the newer-generation AEDs were evaluated in this study.[23]

Hormonal Contraception

General Uses

Treating women with epilepsy of childbearing age should include systematic, ongoing, and accurate counseling concerning optimal choice of contraception. A computerized database study demonstrated that 16.7% of women with epilepsy are prescribed oral contraceptives (OCs) compared to 25% of nonepileptic women at fertile age in an English population.[69] OCs and AEDs can interact in two ways: AEDs can alter the effects of OCs, and OCs can influence the metabolism of AEDs.

Table 1 Interactions Between Antiepileptic Drugs (AEDs) AND ORAL CONTRACEPTIVES (OCs)

AEDs that increase the eliminiation of OCs	AEDs that do not affectthe elimination of OCs
Carbamazepine	Ethosuximide
Felbamate	Gabapentin
Phenobarbital	Lamotrigine
Phenytoin	Levetiracetam
Primidone	Valproate
Oxcarbazepine	Vigabatrin

Topiramate	Tiagabine
	Zonisamide

The Effect of Antiepileptic Drugs on the Pharmacokinetics of Oral Contraceptives

Combined Oral Contraceptives

The potential for pharmacokinetic interactions between AEDs and combined OCs was first suggested in 1972, >10 years after the introduction of the combined OCs.[36] A higher incidence of breakthrough bleeding and contraceptive failure among women with epilepsy has been observed and correlated with the time when the ethinylestradiol fraction of OCs was decreased from 50 to 100 µg to <50 µg to diminish the risk of thromboembolic side effects.[9] Contraceptive failure, therefore, may depend mainly on the concentration of the estrogen fraction.

Currently available combined OC preparations contain much lower estrogen doses, 20 to 35 µg of ethinylestra-diol and <1 mg of progestogen. The major part of the estrogen compound is hydroxylated to inactive metabolites by the hepatic cytochrome P450 (CYP) 3A4 or directly conjugated. AEDs that induce the CYP 3A4 isozyme include carbamazepine,[11] phenobarbital,[2] phenytoin,[11] oxcarbazepine,[18] and topiramate,[59] as shown in Table 1. These AEDs therefore accelerate the hepatic elimination of OCs. A recent study of topiramate with an OC containing 35 µg of ethinyl estradiol demonstrated that topiramate monotherapy at a dose of <200 mg did not significantly affect the clinical efficacy of the OC.[14]

The consequence of this drug interaction is a risk of contraceptive failure and unwanted pregnancy. Therefore, women who are prescribed enzyme-inducing drugs should use

high-dose OCs with the dose of the estrogen compound of at least 50 µg. They should also be advised to use additional barrier methods of contraception, especially in case of intramenstrual bleeding. The extent of enzyme induction is correlated with the dose of the drug but is difficult to quantify because genetic and environmental factors also influence the hepatic isozyme expression.[53,74]

Current data suggest that gabapentin,[16] levetiracetam,[57] losigamone,[13] tiagabine,[44] vigabatrin,[3] and zonisamide[21] do not influence the metabolism of OCs and can be administrated without risk of contraceptive failure. One study demonstrated a modest and probably not clinically relevant decrease of the levonorgestrel compound of the OCs by lamotrigine but no change in the pharmacokinetic parameters of ethinyl estradiol.[68] This is in agreement with the earlier study by Holdich et al.,[30] which found no effect of lamotrigine on the elimination of OCs. A similar finding has been demonstrated with felbamate, which caused a 42% decrease in gestodene first-24-hour area under the curve $AUC_{(0-24)}$ but had no effect on the metabolism of ethinyl estradiol.[60] These studies,[60,68] however, were performed with a moderate dose of reproductive hormones, namely 30 µg ethinyl estradiol, 150 µg levonorgestrel, and 75 µg gestodene. Ovulation might not be suppressed in women who use low-dose OCs (<30 µg ethinyl estradiol and < 75µg progesterone). Midcycle bleeding should therefore always alert the physician and the patient to the risk of contraceptive failure.

Synthetic Progestogens

Data on possible interactions between AEDs and progesterone-only pills, injections, and implants are very sparse. One study demonstrated that the subdermal levonorgestrel implants have a high failure risk in women receiving phenytoin.[26] These contraceptives are therefore generally regarded as less reliable and should not be prescribed in women who are treated with enzyme-inducing drugs. Intrauterine contraceptives do not appear to be affected by AEDs, including those that induce hepatic enzymes.

The Effect of Oral Contraceptives on the Pharmacokinetics of Antiepileptic Drugs

Lamotrigine

OCs can increase the metabolism of glucuronidated drugs by induction of the uridine diphosphate glucuronosyltransferase system.[46,47] Several studies have demonstrated that the elimination of lamotrigine, which is metabolized in the liver primarily by glucuronic acid conjugation, is significantly and substantially (>50%) increased by combined OCs.[58,62,68] The drop in lamotrigine plasma concentration after introduction of OCs is associated with increased seizure frequency or seizure recurrence in most cases.[61]

These pharmacokinetic alterations show considerable interindividual variability due to both genetic factors and whether other AEDs are coadministered. The induced metabolism of lamotrigine can be greatly attenuated and almost blocked by valproate.[73] Because the level of altered elimination is unpredictable for the individual patient, it is recommended that the plasma level of lamotrigine be carefully monitored and doses adjusted before and after introduction or discontinuation of OCs.

The change in lamotrigine metabolism has been attributed to the estrogen rather than the progestin component of the OC.[58] The lack of estrogens affects the pharmacokinetics acutely, and the plasma level of lamotrigine increases in a fairly rapid and linear manner[8,68] already within the "pill-free" week. The hormonal effect shows great interindividual variation, and the concentration at the end of the washout week is up to twofold higher than when coadministrated in the 3-week period before and after.[8] Because of the rapid and significant increase of the plasma level, the authors suggested that uptitration of the lamotrigine dose should not occur in the "pill-free week" to avoid titration-related tolerability problems.

Valproate and Oxcarbazepine

Recent results suggest that similar interactions may exist between combined OCs and valproate. Like lamotrigine, valproate is eliminated mainly by hepatic glucuronidation.[29] The pharmacologically active monohydroxy derivative of oxcarbazepine is also mainly eliminated by glucuronidation.[42] The clinical relevance of this potential effect of OC for the elimination of valproate and oxcarbazepine needs to be further explored.

Pregnancy

General Considerations

The goal of AED treatment in women of childbearing age with epilepsy is to achieve the best possible control of seizures with the minimal adverse effects for both the mother and the offspring. Most AEDs have comparable efficacy when used for the appropriate syndromes, which means that the selection among AEDs with similar efficacy may be done on the basis of their adverse effects. Each AED has its own unique adverse effect profile, which must be carefully considered prior to its selection. Many factors must be taken into account before planning a pregnancy, including the mother's ability to care for an infant, the genetics of her epilepsy, and her current medication regimen. Consideration of these factors serves to open a dialogue with the patient about her fears and worries.

Epilepsy-related difficulties during pregnancy include fluctuating AED plasma levels, an increased risk of seizures, and possible teratogenetic effect of the AEDs. If treatment with AEDs during the pregnancy is necessary, monotherapy at the lowest effective dose needed to control seizures is recommended.

Effects of Epilepsy on Pregnancy

Women treated with AEDs have a two- to threefold higher risk of having a child with an anomaly or malformation than the background population.[35,64] In women with epilepsy who are not treated with AEDS, the risk of teratogenicity is lower.[63] Paternal epilepsy does not influence the risk of teratogenicity.

Several factors may contribute to the poor outcome, including genetic factors, a direct teratogenic effect of the AEDs, or indirect effects via an interference with folic acid metabolism or other genetically determined pathways. The teratogenic risk of individual AEDs and folic acid supplementation are comprehensively covered in Chapter 108. Delivery at a high-risk obstetric unit affiliated with a pediatric department and with experienced neurologists available is recommended.

Effects of Pregnancy on Epilepsy

The pharmacokinetics of AEDs are influenced by the dynamic physiologic changes that occur during pregnancy.[51] These include reduced gastric motility, nausea and vomiting, increased drug distribution, changes in protein binding, and increased renal elimination and altered hepatic enzyme activity. In

addition, there is growing appreciation that many women are not fully compliant with therapy during pregnancy because of concerns about the potential adverse drug effects on the developing fetus.[76]

Pregnancy-induced effects on the plasma levels of AEDs increase the risk of increased seizures or seizure breakthroughs. In the prospective international EURAP study, increased seizure frequency was observed in 17% of 1,718 pregnancies, with the highest risk in patients with localization-related epilepsies and those on polytherapy.[17] Earlier studies disagreed about when in the pregnancy seizure risk is highest. Some, for example, have reported that risk of deteriorating seizure control is highest during the first trimester,[37,65] whereas other studies found that seizure frequency was greatest in the last trimester.[72] The recent EURAP report found no relation to specific trimesters.[17]

The clinical consequences of the drop in plasma levels are controversial; some women do not experience deterioration in seizure control even in the face of decreased plasma levels. Adjustment in dose to prevent or correct a fall in plasma levels has been found necessary in >70% of patients treated with phenytoin, carbamazepine, and barbiturates.[39] With some AEDs, however, that are highly protein bound, such as phenytoin and valproate, the free concentration remains unchanged or even increases during pregnancy because of alteration in protein binding.[72] Furthermore, because teratogenicity is likely related to the drug dose, routinely increasing the dose of AEDs could increase the risk of teratogenicity.

Treatment with lamotrigine poses specific problems during pregnancy because the pharmacokinetics of this drug is especially influenced by gestation.[51,54,75] Seizure frequency increased in 75% of patients on lamotrigine during pregnancy.[12,54] This deterioration was associated with a 40% decrease in the ratio of plasma lamotrigine concentration to dose, which occurred primarily between weeks 20 and 30 of gestation. It has therefore been recommended that careful attention be paid to maintaining stable lamotrigine plasma levels throughout pregnancy to prevent increased seizure frequency.

Recent studies indicate that oxcarbazepine also exhibits major changes in clearance during pregnancy.[7,43] The elimination of the pharmacologically active monohydroxy derivate of oxcarbazepine might be affected by pregnancy because the elimination of the derivate occurs largely by glucuronidation in a way similar to that for lamotrigine. In the prospective EURAP registry study,[17] oxcarbazepine monotherapy was associated with increased seizure frequency.

Little is known about the effect of pregnancy on the pharmacokinetics of other, newer AEDs.

Vitamin K Supplementation

For many years it has been suggested that pregnant women treated with enzyme-inducing AEDs (carbamazepine, phenytoin, and barbiturates) should be given oral supplement of vitamin K in the last month of pregnancy to protect the infant against hemorrhagic disease of the newborn. A recent study, however, has demonstrated that this may not be necessary,[34] and the usefulness of vitamin K at the end of pregnancy remains speculative, although the general tendency is to give the supplement.

Family Planning

The possibility of pregnancy, whether desired or not, must always be considered when prescribing AEDs for women of childbearing age. Comprehensive care of women with epilepsy during the reproductive years should include systematic appropriate and accurate counseling concerning optimal choice of contraceptive method. Ideally, issues related to family planning should be discussed well in advance of any planned pregnancy to allow informed and well-considered choices.

Unfortunately, several surveys have demonstrated that a surprising number of physicians do not have adequate knowledge about specific issues related to family planning in women with epilepsy, and approximately 50% of women with epilepsy taking OCs indicate that they were never given information about a potential interaction between their AEDs and the OCs.[11,41] Shorvon et al.[69] demonstrated that of 2,000 women taking enzyme-inducing AEDs, >50% were taking OCs with an estrogen content <50 µg. A resent survey showed that women with epilepsy of childbearing age do not always recall being given information on contraception and prepregnancy planning, which highlights the need for regular repetitions.[6]

A reevaluation of the diagnosis of epilepsy and need for continued treatment should be central to the counseling process. Women who have been seizure free for 2 to 5 years may be able to withdraw from medication. Any change in the AED treatment and addition of folic acid as a daily supplement should be performed before attempting conception. When a patient treated with lamotrigine is planning to discontinue OC to become pregnant, the plasma concentration of lamotrigine should be closely monitored and the dose reduced to avoid exposing the fetus to unnecessary high drug concentrations.[61]

Factors in Drug Selection in Women of Childbearing Age

The primary goal for the treatment of epilepsy must always be to gain the best possible control of seizures with the least adverse effects. The AED most effective for the specific syndrome and that is the best tolerated should be selected. However, choosing an AED in a woman of childbearing age requires, in addition, specific consideration of the complexities of reproductive health.

Traditional Drugs—Pros and Cons

The older AEDs (carbamazepine, phenobarbital, phenytoin, primidone, sodium valproate) share some less desirable characteristics, such as having complex pharmacokinetics and effects on the activity of hepatic enzyme systems. On the other hand, these older drugs collectively have a broad familiarity, lower cost, known efficacy, and long-term experience.

Carbamazepine, phenobarbital, phenytoin, and primidone induce the hepatic CYP 3A4 isozyme, which accelerates the elimination of endogenous and exogenous sex steroid hormones, including interactions with other drugs, including OCs. Valproate has multiple endocrine effects in both men and women, and it can contribute to anovulation, infertility, and teratogenicity.

Newer Drugs—Pros and Cons

In comparison, several of the newer AEDs appear to have certain advantages. Gabapentin, lamotrigine, levetiracetam, losigamone, pregabalin, tiagabine, vigabatrin, and zonisamide have relative simple pharmacokinetic properties and do not alter plasma levels of steroid sex hormones or interfere with the effectiveness of other drugs, including hormonal contraceptives. Oxcarbazepine and topiramate may selectively affect the efficacy of hormonal contraception. The disadvantages of newer AEDs, however, include limited long-term experience with regard to safety in pregnancy, lack of comparison studies among the drugs, and lack of unequivocal information about teratogenic risk.

Lamotrigine has been recommended as a desirable treatment option for women of fertile age because it is not associated with weight gain, does not disrupt the menstrual cycle, and may have low teratogenic potential. However, after >5 years of clinical use, it became evident that elimination of lamotrigine is affected significantly by sex hormones, which complicate maintaining a stable plasma concentration during pregnancy and while using hormonal contraception.

Another example of delayed recognition of adverse effects is that it took 10 years to recognize the retinal toxicity of vigabatrin. Whether intrauterine exposure to vigabatrin potentially affected the developing retina has not been fully explored.

Summary and Conclusions

The gender issues for drug treatment are based primarily on altered metabolism of AEDs by reproductive hormones or, conversely, changes in the metabolism of reproductive hormones by AEDs. The impact of these interactions is complicated by the effects of epilepsy itself on reproductive health. Valproate likely contributes to, or perhaps mimics, PCOS in women with epilepsy, whereas the enzyme-inducing AEDs have relatively more adverse effects on reproductive parameters for men with epilepsy. The evidence indicates that lamotrigine does not contribute to hormonally related reproductive dysfunction.

Lamotrigine has emerged as an example of how an AED can be affected by exogenous or endogenous hormonal induction of the uridine diphosphate glucuronosyltransferase system, which has important consequences during oral contraceptive use and with pregnancy. Two other AEDs share this pharmacokinetic vulnerability—oxcarbazepine and valproate. There is a need for further information on these interactions.

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Chapter 114

Drug Treatment in the Elderly

Ilo E. Leppik

Angela K. Birnbaum

Introduction

The elderly are the most rapidly growing segment of the population, and demographic trends predict that their number is projected to increase in the United States from an estimated 40 million in 2010 to 71.5 million in 2030.[1] Similar increases are expected throughout the world. The incidence (new cases) of epilepsy is higher in the elderly than in any other age group.[33,34] Because of the rapid growth in their numbers and their propensity to develop epilepsy, elderly persons will represent an increasingly large group of patients needing expert care for this disorder. In the United States, approximately 181,000 persons developed epilepsy in 1995, and approximately 68,000 of these were >65 years of age.[21] Similar high rates have been reported from the Netherlands and Finland.[19,72] Problems faced by the elderly with epilepsy are different and more complex than those faced by younger adults with this disorder. These issues are medical (making the correct diagnosis, selecting the correct medication, working with comorbid illnesses), social, emotional, and economic.

One complicated area is selecting the appropriate antiepileptic drug (AED), which requires the consideration of a number of factors. These include changes in organ function, increased susceptibility to adverse effects, use of other medications known to interact with AEDs, and economic limitations. In addition, the elderly population is heterogeneous, and broad statements about the elderly may not be relevant to each individual patient. Treatment in the elderly carries more risks than in younger persons because they may experience more side effects, have a greater risk for drug interactions, and be less able to afford the costs of medications. In addition to their use in epilepsy, AEDs are prescribed for a variety of other disorders affecting the elderly, including pain and psychiatric disorders. As a cause of adverse reactions among the elderly, AEDs rank fifth among all drug categories.[54] Unfortunately, very little research has been done in this vulnerable population, and only general recommendations can be made at this time.

The Elderly Are Not a Homogenous Population

Like the pediatric population, the elderly (65 years and older) are not a single cohort. Medical issues in persons up to age 18 years cannot be properly interpreted without using the subcategories of newborn, infant, child, and adolescent. Similarly, elderly persons should also be subdivided into appropriate cohorts. A widely used system divides the elderly into the “young-old” (those 65–74 years of age), the “middle-old” or “old” (those 75–84 years of age), and the “old-old” (those 85 years or older). However, because persons develop health issues at different times, further subdivisions have been proposed as shown in Table 1: (a) the elderly healthy (EH) who have epilepsy, (b) the elderly with multiple medical problems (EMMP), and (c) the frail elderly (FE), usually in nursing homes.[48] Thus, one must tailor studies and interventions to nine categories of elderly with epilepsy. In addition, pediatricians must cope with the emotions of adult parents of children, who are often very caring and protective. Similarly, the physician caring for an elderly person with epilepsy must deal with the emotions of adult children of parents. Approaches needed by both groups of physicians have similarities.

In addition, there are major differences between the community-dwelling elderly (independent living) and those residing in nursing homes. Clearly, drug side effects, efficacy, absorption, and other factors may be markedly different between a 93-year-old healthy person living independently and a 68-year-old frail person residing in a nursing home. In addition, issues regarding health care delivery will likely differ between the community-dwelling elderly and the nursing home elderly. Studies should be designed with specific populations in mind, and reports should specify the populations studied.[50]

Diagnosis of Epilepsy in the Elderly

The diagnosis of epilepsy is difficult in the elderly. In the Veterans Administration (VA) study #428, a large portion of patients with epilepsy had been initially misdiagnosed.[68] Other conditions such as cardiac insufficiency, metabolic conditions, convulsive syncope (micturition syncopy, cough syncope), and other conditions must be eliminated before it can be concluded that an event was an epileptic seizure. In the elderly, the most common identifiable cause of epilepsy is stroke, which accounts for 30% to 40% of all cases. Brain tumor, head injury, and Alzheimer's disease are other major causes. However, in a large number of cases, the precise cause cannot be identified and the etiology is cryptogenic. Because most seizures in the elderly are caused by a focal area of damage to the brain, the most common seizure types are localization related. Complex partial seizures are the most common seizure type, accounting for nearly 40% of seizures in the elderly population.[31] Both simple and complex seizures may spread and develop into generalized tonic–clonic seizures. All major AEDs have a U.S. Food and Drug Administration (FDA) indication for use in the types of seizures encountered in the elderly.

Table 1 Categorization of the Elderly with Epilepsy

Young-old, healthy EH	Middle-old, healthy EH	Old-old, healthy EH
Young-old, multiple medical problems	Middle-old, multiple medical problems	Old-old, multiple medical problems
EMMP	EMMP	EMMP
Young-old, frail	Middle-old, frail	Old-old, frail
FE	FE	FE

EH, elderly healthy; EMMP, elderly with multiple medical problems; FE, frail elderly.
Modified from Leppik IE. Introduction to the International Geriatric Epilepsy Symposium (IGES). *Epilepsy Res*. 2006;68(Suppl 1):1–4.

Pharmacoepidemiology of Antiepileptic Drug Use in Elderly

Antiepileptic Drug Use in Community-Dwelling Elderly

The largest study of AED use in community-dwelling elderly in the United States was the VA study coordinated by Berlowitz.[63,64] Of a total of 1,130,155 veterans of age 65 years and older identified from the national data base of 1997 to 1999, 20,558 (1.8%) were identified as having epilepsy by having an ICD-9-CM (International Classification of Diseases, 9th Revision, Clinical Modification) code representative of this condition.

Approximately 80% were receiving one AED and 20% were being treated with two or more. Phenytoin was used as monotherapy by almost 70%, whereas phenobarbital was used as monotherapy by approximately 10%. Another 5% were using phenobarbital in combination, mostly with phenytoin. Carbamazepine was used by just >10%, and newer AEDs (gabapentin and lamotrigine) were used by <10%.[63,64] (Levetiracetam was not available at the time of the survey.) Smaller studies in community-dwelling elderly non-VA patients have found a similar distribution of AED use, with phenytoin by far the most widely used AED in the United States in this population.

Antiepileptic Drug Use in Nursing Homes

As people age, their need for nursing home care increases due to greater frailty and disease. For patients aged 65 years and older, there is a lifetime risk of 43% to 46% of ever becoming a resident in a nursing home (NH).[41,73] At any one time, 4.5% of the elderly U.S. population is residing in a NH.[37] In any research concerning NHs, the distinction must also be made between *residents* and *admissions*. A resident cohort includes all residents in the facility at a specified time, which is usually a cross-sectional sample and consists of a mixture of newly admitted residents and others who have been in the NH for different periods of time. In contrast, an admission cohort includes all people admitted to a facility during a specified time period.[26]

In a study of the residents residing in various nursing homes in the United States during the spring of 1995,[25] the mean age of the 21,551 residents was 83.78 years (SD, 8.13 years). The age group distribution was young-old 15%, middle-old 36%, and old-old 49%. This distribution is similar to the population of 1,557,800 people ≥65 years of age in NHs in the year 2000, based on data from the U.S. Census Bureau.[37] Of the residents in this NH sample, 10.5% had one or more AED orders on the study day, and 9.2% had a seizure indication (epilepsy or seizure disorder) documented in the chart. Phenytoin was used by 6.2% of the residents, followed by carbamazepine (1.8%), phenobarbital (1.7%), clonazepam (1.2%), valproic acid (0.9%), and all other AEDs combined (1.2%); these percentages exceed 10.5% due to AED polytherapy. Approximately 90% of AED use was for an epilepsy/seizure indication. If these results are extrapolated to all 1,557,800 elderly residents in U.S. NHs in 2000,[37] then as many as 163,569 people were likely to have been receiving an AED. Of note, this prevalence is approximately five times that of AED use in the community.[19,32] Age was inversely related to AED use. Of the young-old, 23.7% were prescribed an AED, with 16.4% for seizure indication and 7.3% for other. In the middle-old, 12.2% were prescribed an AED, with 8.3% for seizure and 3.9% for other; whereas the old-old had only 5.8% use, with 3.7% for seizure and 2.1% for other (Fig. 1). This finding was unexpected because of the upward curve in the incidence of epilepsy/seizure disorder with advancing age. Thus, one of the major findings of the study of AED use in U.S. nursing homes is that the young-old are three to four times more likely to be prescribed an AED than the old-old either prior to admission or after admission. Similar results were reported from a study in Italy.[24]

A study of admissions employing a longitudinal design to explore AED use at the time of admission used two study groups: (a) all persons aged ≥65 years admitted between January 1 and March 31, 1999, to one of the 510 Beverly Enterprises NH facilities in 31 U.S. states (*N* = 10,318) and (b) a follow-up cohort (*n* = 9,516) of those in the admissions group who were not using an AED at NH entry.[26] This cohort was followed up for 3 months after their individual admission dates or until NH discharge, whichever occurred first. Approximately 8% (*n* = 802) of the admissions group used one or more AEDs at entry, and among these, greater than half (58%) had an epilepsy/seizure disorder indication. The AEDs used by newly admitted individuals with epilepsy/seizure disorder (*n* = 585) included phenytoin (*n* = 315; 54%), valproic acid (*n* = 57; 10%), carbamazepine (*n* = 52; 9%), and gabapentin (*n* = 27; 5%).

Among residents in the follow-up cohort in the same study (*n* = 9,516) who were not using an AED at admission, 260 (3%) were initiated on an AED within 3 months of admission. Factors associated with the initiation of AEDs during this period included epilepsy/seizure, manic depression (bipolar disease), age group, cognitive performance (Minimum Data Set Cognitive Score [MDS-COGS]), and peripheral vascular disease (PVD). Thus, many persons admitted without a diagnosis of epilepsy are diagnosed as such after entry, and the incidence of newly diagnosed epilepsy in the nursing home far exceeds that in other populations. A crude estimate is 600 in 100,000 per 3 months, or four to six times that reported for elderly community-dwelling elderly. The AEDs used by those in this group with an epilepsy/seizure indication were phenytoin 48%, valproic acid 8%, gabapentin 13%, carbamazepine 12%, and phenobarbital 7%; and the remainder others. There was also an inverse relationship between age group and initiation of an AED. Compared to the young-old, those in the old group (aged 75–84 years) were one third less likely to have an AED initiated ($p < 0.05$), and the oldest-old (aged ≥85 years) were only half as likely ($p < 0.0001$).[26]

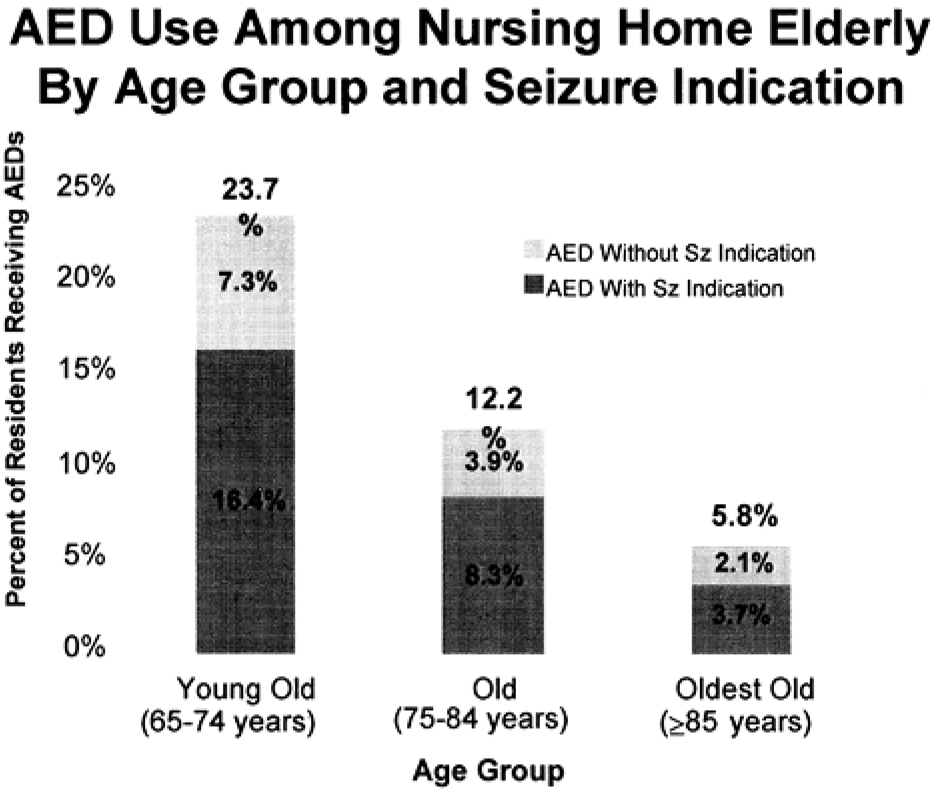

FIGURE 1. The young-old are much more likely to be treated with an antiepileptic drug than are the old-old, the inverse of what is observed in community-dwelling elderly. (Data from Garrard J, Cloyd J, Gross C, et al. Factors associated with antiepileptic drug use among elderly nursing home residents. *J Gerontol A Biol Sci Med Sci*. 2000;55:M384–M392.)

Table 2 Frequency of Use of Comedications With Potential Pharmacokinetic or Pharmacodynamic Interactions With Antiepileptic Drugs in 4,291 Residents of Nursing Homes

Drug category	Use with antiepileptic drugs (%)
Antidepressants	18.9
Antipsychotics	12.7
Benzodiazepams	22.4

Thyroid supplements	14.0
Antacids	8.0
Calcium channel blockers	6.9
Warfarin	5.9
Cimetidine	2.5

Modified from Lackner TE, Cloyd JC, Thomas LW, et al. Antiepileptic drug use in nursing home residents: effect of age, gender, and comedication on patterns of use. *Epilepsia*. 1998;39:1083–1087.

Another issue is that many elderly are using other drugs (Table 2). In addition to AEDs, the average elderly nursing home patient takes six medications concomitantly, greatly increasing the risk for side effects and drug interactions.[44]

Clinical Pharmacology of Antiepileptic Drugs in the Elderly

The theoretical basis for age-related changes in drug pharmacokinetics was described many years ago but has not been widely applied to AEDs. Drug concentration at the site of action determines the magnitude of both desired and toxic responses. The unbound drug concentration in serum is in direct equilibrium with the concentration at the site of action and provides the best correlation with drug response.[79] Total serum drug concentration is useful for monitoring therapy when the drug is not highly protein bound (<75%) or when the ratio of unbound to total drug concentration remains relatively stable. Three of the major AEDs (valproic acid, phenytoin, and carbamazepine) are highly bound, and binding is frequently altered.

The age-related physiologic changes that appear to have the greatest effect on AED pharmacokinetics involve protein binding and the reduction in liver volume and blood flow.[29,69,78,80] Reduced serum albumin and increased α1-acid glycoprotein (AAG) concentrations in the elderly alter protein binding of some drugs.[29,78,79] By age 65 years, many individuals have low normal albumin concentrations or are frankly hypoalbuminemic. Albumin concentration may be further reduced by conditions such as malnutrition, renal insufficiency, and rheumatoid arthritis. The concentration of AAG, a reactant serum protein, increases with age; further elevations occur during pathophysiologic stress such as stroke, heart failure, trauma, infection, myocardial infarction, surgery, and chronic obstructive pulmonary disease.[78] Administration of enzyme-inducing AEDs also increases AAG.[74] When the concentration of AAG rises, the binding of weakly alkaline and neutral drugs such as carbamazepine to AAG can increase, causing higher total serum drug concentrations and decreased unbound drug concentrations. Because of the complexity of confounding variables and the lack of correlation between simple measures of liver function and drug metabolism, the effect of age on hepatic drug metabolism remains largely unknown.[17,18] Genetic determinants of hepatic isozymes may be more important than age in determining a person's clearance.[42]

Renal clearance is the major route of elimination for a number of the newer AEDs. It is well known that an elderly person's renal capacity decreases by approximately 10% per decade, but this also is highly dependent on the general state of health.

Despite the theoretical effects of age-related physiologic changes on drug disposition and the widespread use of AEDs in the elderly, few studies on AED pharmacokinetics in the elderly have been published. The reports generally involve single-dose evaluations in small samples of the young-old (65–74 years). There is a lack of data regarding AED pharmacokinetics in the oldest-old (>85 years), individuals who may be at greatest risk for therapeutic failure and adverse reactions.

Variability of Antiepileptic Drug Levels in Nursing Homes

Studies have shown that in compliant patients, the variability of AED concentrations over time is relatively small. One study

of phenytoin showed that in institutionalized patients, the variability between serial measurements over time was on the order of 10%. In the same study, compliant clinic patients had variability of approximately 20%.[49] Approximately 5% of this can be accounted for by measurement instrument variability, although laboratories not following rigid quality control standards may have a much larger variability. The remainder of the variability arises from day-to-day alterations in absorption or metabolism or differences in AED dose content. The variability for carbamazepine and valproate is on the order of 25%, possibly due to their shorter half-lives and thus increased variability from sampling times.[27] A small study found that phenytoin levels may fluctuate in the nursing home elderly.[55] This was confirmed in an analysis of serial phenytoin levels from nursing home patients across the United States who had no change in dose, no change in formulation, and no additions of other medications.[6] Some residents had a difference of two- to threefold from the lowest to the highest phenytoin concentrations. It is also interesting that some had very little fluctuation and were similar to the younger adults studied, as mentioned earlier. Similar but less severe fluctuations were observed for carbamazepine and valproate. These findings suggest that elderly frail nursing home residents may have great variability in absorption of drugs. Factors that contribute to this must be identified and strategies developed to minimize its effects.

Clinical Trials of Antiepileptic Drugs in the Elderly

All major AEDs have an FDA indication for use for the seizure types most likely to be encountered in the elderly. However, there are few data relating specifically to these drugs in the elderly, and those that are available have been limited to community-dwelling elderly. One post hoc study of the VA cooperative study of carbamazepine and valproate found that elderly patients often had seizure control associated with lower AED levels than seen in younger individuals. However, side effects were also observed at levels lower than those seen in younger persons.[65] A multicenter, double-blind, randomized comparison between lamotrigine and carbamazepine in elderly patients (mean age 77 years) with newly diagnosed epilepsy in the United Kingdom showed that the main difference between the groups was the rate of drop out due to adverse events, with a rate for lamotrigine of 18% compared to a rate of 42% for carbamazepine.[11] The VA Cooperative Study #428, an 18-center, parallel, double-blind trial on the use of gabapentin, lamotrigine, and carbamazepine in patients 60 years or older, found that efficacy did not differ, but the main finding favoring the two newer AEDs was tolerability.[68]

Choosing Antiepileptic Drugs for the Elderly

There are few data regarding the clinical use of AEDs in the elderly. The paucity of information makes it very difficult to recommend specific AEDs with any confidence that the outcomes will be optimal. A drug choice optimal for the EH group may not be appropriate for the EMMP or FE group due to differences in pharmacokinetic or pharmacodynamic properties among these groups. Phenytoin is still the most commonly used AED in both community-dwelling and nursing home elderly in the United States, although expert opinion may disagree with this practice.[64] Before practice can change, evidence must be developed to support opinion. The next section first discusses the most commonly used AEDs, for which there are more data, and then presents an alphabetical review of the newer AEDs. Table 3 summarizes the properties of most AEDs.

Phenytoin

Phenytoin is effective for localization-related epilepsies and has an efficacy profile appropriate for the elderly.

Evidence for this can be gathered from the VA cooperative study, which included some elderly and found that phenytoin was as effective as carbamazepine, phenobarbital, and primidone, but that phenytoin and carbamazepine were better tolerated.[52] Phenytoin has a narrow therapeutic range, is approximately 90% bound to serum albumin, and undergoes saturable metabolism, which has the effect of producing nonlinear changes in serum concentrations with changes in dose or absorption. Clinical studies in elderly patients have shown decreases in phenytoin binding to albumin and increases in the free fraction.[29] The binding of phenytoin to serum proteins correlates with the albumin concentration, which is typically low normal to subnormal in the elderly. One study compared the pharmacokinetics of phenytoin at steady state after oral administration in 34 elderly (60–79 years), 32 middle-aged (40–59 years), and 26 younger adults (20–39 years) with epilepsy. All patients had normal albumin concentrations and liver function and received no other medications, including other AEDs known to alter hepatic metabolism. The maximum rate of metabolism (*V*max) declined with age, and significantly lower values were seen in the elderly group compared to younger adults.[4] Other, smaller studies have also shown that phenytoin metabolism is reduced in the elderly[2,35,45,76]; therefore, smaller maintenance doses of phenytoin may be needed to attain desired unbound serum concentrations. Relatively small changes in dose (≤10%) are recommended when making dosing adjustments. Thus, in the elderly, a daily dose of 3 mg/kg appears to be appropriate, rather than the 5-mg/kg per day used in younger adults.[47] This 3-mg/kg dose is only 160 mg/day for a 52-kg woman and 200 mg/day for a 66-kg man. Several nursing home studies revealed that residents were taking phenytoin (PHT) doses similar to those used in younger adults.[6] In addition, a gender effect was found in this population because women required higher doses than men of PHT to achieve similar serum concentrations.[6] A recent study of age and genotype, however, found that the presence of a mutant cytochrome P450 (CYP) 2C9 or 2C19 isozyme was far more predictive of phenytoin dose than age.[42]

Due to the high protein binding of PHT, unbound PHT concentrations may be a better indicator of efficacy and toxicity than total concentrations. Measurement of unbound phenytoin concentrations is essential for elderly patients who have (a) decreased serum albumin concentration, (b) total phenytoin concentrations that are near the upper boundary of the therapeutic range, (c) total concentrations that decline over time, (d) a low total concentration relative to the daily dose, or (e) total concentrations that do not correlate with clinical response. A range of 5 to 15 m/L total may be more appropriate as a therapeutic range for the elderly.[47]

Table 3 Antiepileptic Drug Pharmacokinetics in the Elderly

Drug	Protein binding (%)	Elimination	Comments
Carbamazepine	75–85	Hepatic, CYP 3A4/5	Protein binding decreases with age Levels are increased by erythromycin, prophoxyphene, and grapefruit juice Decreases levels of calcium channel blockers (dilitiazem, verapamil) Decreases effect of warfarin Decreases tricyclic antidepressant levels
Felbamate	<10	Hepatic	—

Gabapentin	<10	Renal	Elimination correlates with creatinine clearance No drug interactions
Lamotrigine	55	Hepatic glucuronide conjugation	Levels are decreased by inducing agents: carbamazepine, phenytoin, some hormones, and others yet to be determined Levels increased by vaproate
Levetiracetam	<10	Renal	Very water-soluble, intravenous formulation available No drug interactions
Oxcarbazepine	40	Hepatic	Causes hypontremia
Phenobarbital	50	Hepatic, renal	Induces metabolism of many drugs
Phenytoin	80–93	Hepatic, CYP 2C9, CYP 2C19	Protein binding decreases with reduced serum albumin and renal failure Decreases levels of calcium channel blockers (dilitiazem, verapamil) Has a complicated interaction with warfrin Decreases tricyclic antidepressant levels Interacts with diabetes and arthritis medications Decreases effectiveness of cancer chemotherapy
Topiramate	9–17	Hepatic, renal	Inhibits CYP 2C19 and increases serum phenytoin and other drug levels Induces CYP 3A4 isozymes
Valproic acid	87–95	Hepatic, multiple pathways	Protein binding is decreased in the elderly Inhibits glucuronidation and may increase levels of lamotrigine and other drugs Decreases platelet function

CYP, cytochrome P450.

Phenytoin has many drug–drug interactions and should be used cautiously in EMMP patients receiving other medications. Valproic acid, which is also highly protein bound, competes with phenytoin for albumin-binding sites and inhibits phenytoin's metabolism. Carbamazepine induces phenytoin metabolism and necessitates higher phenytoin doses. Phenobarbital is thought to induce phenytoin's metabolism; however, the data are controversial.[13] There is also some indication that SSRI antidepressants may inhibit the cytochrome 2C family of P450 enzymes responsible for metabolizing phenytoin.[59] Fluoxetine and norfluoxetine are more potent inhibitors of this enzyme, followed by sertraline and paroxetine.

The latter two selective serotonin-reuptake inhibitor (SSRI) antidepressants may prove to be a safer choice in the elderly. Coumadin has a very complicated interaction with phenytoin, and often doses of both need to be manipulated.[47]

Phenytoin has some effects on cognitive functioning, especially at higher levels.[75] It is not known whether the elderly will be more sensitive to this problem. In addition, phenytoin may cause imbalance and ataxia. It is likely that EMMP patients, especially those with central nervous system (CNS) disorders, may be more sensitive.[10] In a study of the elderly, among the various lifestyle, demographic, and health factors that contributed to an increased risk, phenytoin was the only drug that was associated with a significant increase in fractures.[8] However, this study could not determine whether this was due to falls from ataxia or seizures or was an effect of bone changes. Phenytoin also is known to be a mild blocker of cardiac conduction and should be used cautiously in persons with conduction defects, especially heart blocks. In spite of its limitations, phenytoin is the least expensive major AED. This and its long record of use may account for it being the most widely used AED.

Carbamazepine

Carbamazepine (CBZ) is effective for localization-related epilepsies and has an efficacy profile appropriate for the elderly. Evidence from two large VA studies showed it to be as effective as phenytoin, phenobarbital, primidone, and valproate but better tolerated than the latter three.[52,53] Two studies of new-onset epilepsy in the elderly found it to be as effective as lamotrigine, but it had a higher incidence of side effects.[11,68]

Apparent clearance of carbamazepine is reported to be 20% to 40% lower in the elderly than in other adults.[2,14,28] A population analysis of patients from ambulatory neurology clinics at three medical centers also showed that the apparent oral clearance of CBZ was 25% lower in patients who were >70 years old.[28] Decreases in clearance result in a prolonged elimination half-life. These changes in carbamazepine pharmacokinetics indicate that lower and less frequent dosing in elderly patients may be appropriate.

Carbamazepine has some significant drug–drug interaction with medications that inhibit the cytochrome P450 enzyme responsible for carbamazepine metabolism, CYP 3A4. Among the inhibitors are erythromycin, fluoxetine, ketoconazole, propoxyphene (Darvon), and cimetidine (Tagamet). At least one food (grapefruit juice) has been identified as interacting with carbamazepine to cause increases in CBZ serum concentrations. EH patients need to be cautioned about these and should be instructed to inform the physician whenever they are beginning a new medication, including over-the-counter medications. Many other drug interactions occur, so that carbamazepine is one AED that needs to be used cautiously in EMMP patients receiving other medications.[47] Carbamazepine can also induce the CYP 3A4 system, reducing the effectiveness of other drugs.

Carbamazepine has some effects on cognitive functioning, especially at higher levels. It is not known whether the elderly will be more sensitive to this problem. In addition, carbamazepine may cause imbalance and ataxia. It is possible that EMMP patients, especially those with CNS disorders, may be more sensitive to these effects.

One of the major concerns with carbamazepine is its effect on sodium levels.[36] Hyponatremia is a well-known phenomenon with carbamazepine use and may cause significant problems in younger adults, especially if there is polydipsia. The hyponatremia associated with carbamazepine is more pronounced as a person becomes older.[20] This may become more problematic if a person is on salt restriction or a diuretic. Because of the mild neutropenia associated with carbamazepine use in younger adults, the effects of this AED on hematopoietic parameters in the elderly will need to be studied. Carbamazepine also is known to affect cardiac rhythms and should be used cautiously, if at all, in persons with rhythm disturbances.

One of the pharmacokinetic problems of carbamazepine is its short half-life and the possible need to take it multiple times a day. In the elderly, however, the half-life may be longer, and slow-release formulations may overcome the need to dose multiple times each day and may also overcome some of the side-effect problems caused by a rapid time to a high peak (short $T_{\max}$ and high $C_{\max}$). Carbamazepine is a moderately priced drug, and should not present a significant cost issue.

Phenobarbital

Phenobarbital is effective for localization-related epilepsies and has an efficacy profile appropriate for the elderly. However, the VA cooperative study demonstrated that phenobarbital and primidone are less well tolerated than carbamazepine or phenytoin.[52] Thus, although phenobarbital is the least expensive of the AEDs, its side-effects profile, which may worsen cognition and depression, make it an undesirable drug for the elderly, especially in the nursing home setting in which declines in cognition are already present.

Valproic Acid

Only a few studies have compared the pharmacokinetics of valproic acid (VPA) in young and old patients.[4,13,62] In a study of steady-state valproate pharmacokinetics in six young adult and six elderly volunteers (66–72 years), the average unbound fraction of valproate was 10.7% in the elderly compared with 6.4% in the younger participants. In the elderly participants, mean unbound concentrations were 57% higher and unbound clearances were 40% lower than in younger adults.[4] Valproic acid, like phenytoin, is associated with reduced protein binding and unbound clearance in the elderly. As a result, the desired clinical response may be achieved with a lower dose than usual. A nationwide elderly nursing home study showed that VPA dose and total VPA concentrations decrease within the elderly age groups.[7] Because the serum elimination half-life is prolonged, the dosing interval can be extended. If the albumin concentration has fallen or the patient's clinical response does not correlate with total drug concentration, measurement of unbound drug should be considered. Because of its effects on mood stabilization, it may be especially appropriate for elderly with a dual diagnosis.

Felbamate

Felbamate is effective for localization-related epilepsies and appears to have a broader spectrum of effectiveness than some of the other AEDs. Elderly subjects had a lower mean clearance (31.2 vs. 25.1 mL/min; 90% confidence interval [CI] -11.4 to -0.9; $p = 0.02$) than adults in a study involving 24 elderly healthy volunteers.[67] It is primarily metabolized by the liver and is known to have a number of drug–drug interactions, both inhibitory and inductive, and therefore may not be a good choice for EMMP patients.

Gabapentin

Gabapentin is effective for localization-related epilepsies and has an efficacy profile appropriate for the elderly. Gabapentin is not metabolized by the liver, but rather it is renally excreted; therefore, there are no drug–drug interactions.[66] Thus, it may be especially useful in EMMP patients. There is a reduction of renal function with advancing age, and so doses may need to be adjusted in both EH and EMMP patients. Levels must be monitored after initiation and doses adjusted accordingly. However, gabapentin does appear to have some sedative side effects, especially at higher levels, and the elderly may be more sensitive to this problem.

Gabapentin has a short half-life, necessitating that it be given multiple times a day. In the elderly, however, the half-life may be longer because of decreased renal elimination. Because gabapentin is effective in treating neuralgic pain, it would be additionally beneficial for someone suffering from both epilepsy and pain.

The VA Cooperative Study #428 study compared carbamazepine with gabapentin and lamotrigine. Efficacies were similar, but withdrawal related to side effects was highest for carbamazepine.[68]

Lamotrigine

Lamotrigine is effective for localization-related epilepsies and has an efficacy profile appropriate for the elderly. However, very few studies regarding lamotrigine in the elderly have been published. Lamotrigine is primarily metabolized by the liver using the glucuronidation pathway, not the P450 system, and this pathway may be less affected by age.[61] Data from a population pharmacokinetic study of 163 epilepsy patients that included 30 patients >65 years, only 10 patients between 70 and 76 years, and no individuals from the old-old age group (≥85 years) showed that age did not affect lamotrigine (LTG) apparent clearance.[40] Based on a study of 150 elderly subjects, the drop-out rate due to adverse events was lower with LTG (18%) than with CBZ (42%). LTG subjects had fewer rashes (LTG 3% vs. CBZ 19%) and fewer complaints of somnolence (LTG 12% vs. CBZ 29%).[11] Lamotrigine clearance is increased by approximately two to three times with coadministration of phenytoin and carbamazepine, whereas lamotrigine clearances decrease twofold when valproic acid is coadministered.[81] The drug interaction studies included very few elderly subjects; therefore, the extent of the changes in clearance with administration of comedications in the elderly is not known. Some caution may need to be observed in EMMP patients on other drugs.

Levetiracetam

Levetiracetam has been approved as adjunctive therapy for partial-onset seizures in adults. It is extremely water-soluble. This allows rapid and complete absorption after oral administration. Levetiracetam is not metabolized by the liver, and thus it is free of nonlinear elimination kinetics, autoinduction kinetics, and drug–drug interactions. Lack of protein binding (<10%) also avoids the problems of displacing highly protein-bound drugs and the monitoring of unbound concentrations. Lack of drug interactions would make it useful for treating elderly epilepsy patients, particularly those patients who have

other illnesses and are taking other medications.[60] The manufacturer reports a decrease of 38% in total body clearance and an increased half-life up to 2.5 hours longer in elderly patients (age 61–88 years), who exhibited creatinine clearances ranging from 30 to 74 mL/min. Doses do need to be adjusted, depending on the renal function of the patient as measured by serum creatinine and levetiracetam concentrations.[23]

One prospective phase 4 study indicates a favorable efficacy profile in the elderly.[56] Levetiracetam also appears to have a favorable safety profile. It was initially studied as a potential agent for treating cognitive disorders in the elderly, and thus a considerable amount of data regarding its tolerability in this age group is available. Analysis of this in a review of 3,252 persons involved in studies of levetiracetam for epilepsy and other conditions demonstrated that it was well tolerated by the elderly.[16]

Oxcarbazepine

Oxcarbazepine is rapidly metabolized by first-pass metabolism to 10-hydroxcarbazepine (10 monohydroxy metabolite or MHD); the 10-OH-carbamazepine metabolite is considered the active compound. MHD is then metabolized further by glucuronidation and excreted by the kidneys.[22] The most extensive elderly oxcarbazepine study involved low doses of oxcarbazepine given to 12 young and 12 elderly healthy male and 12 young and 12 elderly female volunteers. At low doses of oxcarbazepine (300–600 mg/d), a significantly higher maximum concentration, higher area under-the-curve parameters, and a lower elimination rate constant were observed in the elderly volunteers.[77]

Oxcarbazepine can have an effect on the cytochrome P450 system. Oxcarbazepine can induce the metabolism of the P450 3A4 enzyme that is responsible for the metabolism of dihydropyridine calcium antagonists and many other drugs.[43,82] Plasma levels of carbamazepine (a P450 3A4 substrate) can be decreased 15% when it is coadministered with oxcarbazepine.[38] Oxcarbazepine, however, appears to have a more powerful effect on sodium balance than carbamazepine, and this effect increases with age.[20]

Pregabalin

Pregabalin is related to gabapentin but is more potent; doses generally one fifth of those of gabapentin are needed for therapeutic effect. Its absorption also appears to be more predictable because of the lower amounts needed for transport across the intestinal system. Although it may prove to be a favorable AED for the elderly, its cost and lack of experience may limit its use.

Tiagabine

Tiagabine is effective for localization-related epilepsies and has an efficacy profile appropriate for the elderly. It is primarily metabolized by the liver (CYP 3A4). Comedications that affect CYP 3A4 substrates also affect the metabolism of tiagabine, giving it a drug interaction profile similar to that of carbamazepine. A major feature of tiagabine is its potency; the usually effective doses is 20 to 60 mg/d, and the effective concentration is 100 to 300 ng/mL, or as much as 100-fold lower than that of the other AEDs.

Topiramate

Topiramate is effective for localization-related epilepsies and thus has an efficacy profile appropriate for the elderly. Topiramate is approximately 20% bound to serum proteins and is both metabolized by the liver and excreted unchanged in the urine. The enzymes involved in topiramate's metabolism have not been identified; however, the cytochrome P450 system may be involved. Topiramate has not been studied in the elderly, but topiramate clearance may decrease with age, causing higher-than-expected serum concentrations at topiramate doses that are used in younger adults. In addition, topiramate metabolism can be induced in the presence of inducing comedications such as carbamazepine and phenytoin.[70] There is also some indication that topiramate can inhibit CYP2C19 activity,[51] and so levels need to be monitored to ensure that the topiramate dose given does not result in higher-than-expected serum concentrations. Topiramate does have some effects on cognitive functioning, especially at higher levels. It is not known whether the elderly will be more sensitive to this problem.

Drug Interactions With Non–Antiepileptic Drugs

Concomitant medications taken by elderly patients can alter the absorption, distribution, and metabolism of AEDs, thereby increasing the risk of toxicity or therapeutic failure. Comedications are frequently used by patients in nursing homes receiving AEDs (Table 2). No data are available for elderly outpatients. Calcium-containing antacids and sucralfate reduce the absorption of phenytoin.[57] The absorption of phenytoin, carbamazepine, and valproate may be reduced significantly by oral antineoplastic drugs that damage gastrointestinal cells.[9,58] In addition, phenytoin concentrations may be lowered by intravenously administered antineoplastic agents.[58] The use of folic acid for treatment of megaloblastic anemia may decrease serum concentrations of phenytoin, and enteral feedings can also lower serum concentrations in patients receiving orally administered phenytoin.[30]

Many drugs displace AEDs from plasma proteins, an effect that is especially serious when the interacting drug also inhibits the metabolism of the displaced drug; this occurs when valproate interacts with phenytoin.[30] Several drugs used on a short-term basis (including propoxyphene and erythromycin) or as maintenance therapy (such as cimetidine, diltiazem, fluoxetine, and verapamil) significantly inhibit the metabolism of one or more AEDs that are metabolized by the P450 system. Certain agents can induce the P450 system or other enzymes, causing an increase in drug metabolism. The most commonly prescribed inducers of drug metabolism are phenytoin, phenobarbital, carbamazepine, and primidone. Ethanol, when used chronically, also induces drug metabolism.[71] The interaction between antipsychotic drugs and AEDs is complex. Hepatic metabolism of certain antipsychotics such as haloperidol can be increased by carbamazepine, resulting in diminished psychotropic response. Antipsychotic medications, especially chlorpromazine, promazine, trifluoperazine, and perphenazine, can reduce the threshold for seizures. The risk of seizures is directly proportional to the total number of psychotropic medications being taken, their doses, any abrupt increases in doses, and the presence of organized brain pathology.[15] The epileptic patient taking antipsychotic drugs may need a higher dose of antiepileptic mediation to control seizures. In contrast, central nervous system depressants are likely to lower the maximum dose of AEDs that can be administered before toxic symptoms occur.

Dosing

Compliance is a potential challenge in the elderly due to multiple medications, memory problems, and visual problems. In general, twice-daily dosing is preferable. In the long-term care facilities, compliance may be less of an issue than with the

community-dwelling elderly, but reducing staff time spent administering multiple daily doses of medication to many patients may reduce errors and cost.

Summary and Conclusions

The elderly with epilepsy have issues that may alter the approach to their treatment with AEDs. Information obtained from studies of younger adults can sometimes be applicable to the elderly, but in other instances they cannot. The community-dwelling elderly resemble the younger elderly more closely than they do the nursing home elderly. Two major conclusions that deserve special consideration can be reached at this time. The first is that AED levels may fluctuate significantly in the elder nursing home population and dose changes based on a single level may exacerbate the unstable levels. This is particularly true for the older AEDs, but whether the newer or water-soluble AEDs are better needs to be demonstrated. The second is that although age may be an influence on hepatic clearance, earlier studies may have overestimated the degree of this effect and the genetic makeup of the isozymes may have a much greater influence. Of the newer AEDs, gabapentin, lamotrigine, and levetiracetam are the most widely researched and used. As patents expire, their cost may lessen, which may lead to increased use. Much more research is needed, however, to determine the best treatments for the EH, EMMP, and FE cohorts.

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Chapter 115

Mechanisms of Drug Resistance

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Introduction

For most patients with a diagnosis of epilepsy requiring drug treatment, the outlook is favorable. In mature economies, about 70% of patients can expect to become seizure free with antiepileptic drug (AED) treatment.[69] This percentage is an overall figure and may differ for subgroups, and most probably depends on etiology and syndrome.[33,72] Although some patients undoubtedly have complex response patterns that change over time for no obvious reason and defy categorization, some 30% of patients will never have any sustained period of seizure freedom—for example, >12 months—in the history of their epilepsy. Scientific inquiry into the concepts and mechanisms of such resistance to AED treatment has gained significant momentum recently. The resulting body of work constitutes the subject of this chapter.

Epilepsy is a heterogeneous group of conditions. The pathophysiologic derangements in the brain are complex and not fully understood for any single seizure type or epilepsy syndrome. There are only a limited number of ways in which the brain, despite its complexity, can actually manifest its function or dysfunction: Epilepsy and seizures are final common manifestations of a wide range of disruptions in brain structure and function. Of course, many of these disruptions share commonalities at various levels, and advantage is taken of these shared characteristics in labeling, understanding, diagnosing, and treating "epilepsy." Both shared and syndrome-specific characteristics might complicate and hamper these same efforts at managing seizures and epilepsy in humans. As a biologic and clinical phenomenon, resistance to AED treatment is one such shared, complex, multifactorial, and adaptive aspect of epilepsy biology. The study of drug resistance might therefore not only improve rational treatment for patients with drug-resistant epilepsy, with its associated morbidity and mortality, but also cast light on disease pathophysiology, determinants of natural history, and predictors of prognosis.

Recent comprehensive reviews have thoughtfully discussed not only the biologic bases of refractory epilepsy, but also the definition of such epilepsy.[32,72] There may be two patients with the same demography, the same syndrome, and the same underlying imaging and histologic pathology, one of whom responds to the first AED tried and the other who never responds with any prolonged period of seizure freedom despite years of administration of a series of differing AEDs. The effect of AEDs on prognosis in an individual is unknown.[32] AEDs generally have a limited spectrum of potential mechanisms of action, and they may undoubtedly render some individuals seizure free, a state associated with proven benefits. Therefore the question of why some individuals have epilepsy refractory to currently available AEDs is both valid and important.

As an illustration of some of these concepts, it is worthwhile considering epilepsy caused by a particular neurodevelopmental abnormality, periventricular heterotopia (PVH) caused by mutation in the X-linked gene *FLNA*, encoding filamin A. Deleterious mutations in this gene can underlie some cases of familial or sporadic PVH:[21] In some cases, the PVH goes on to cause epilepsy, which may be drug resistant, whereas other patients do not even develop epilepsy.[22] We have a reasonable understanding of the role of filamin in neurodevelopment.[76] We know much about the pathologic anatomy of periventricular nodules themselves, including the disruptions of neurohistologic and immunophenotypic profiles, the abnormal electrical activity that may arise from such nodules, their connectivity with the rest of the brain, and their appearance on imaging. It is clear that even following a single pathologic nucleotide alteration in one gene causing epilepsy as its primary manifestation, a tangled multilayered raft of changes occurs at multiple temporal, spatial, and functional time points, leading eventually in a proportion of cases to drug-resistant epilepsy. Most cases of refractory epilepsy are due to more common pathologies, such as hippocampal sclerosis, but remain in some ways less well understood at root, even though they have been longer studied. It is therefore unsurprising that the biologic bases of AED resistance should be so poorly comprehended.

There are two main hypotheses for the underlying cause of refractory, or drug-resistant, epilepsy: (a) the “target” and (b) the “transport” hypotheses. In essence, the former focuses on pharmacodynamic resistance involving the postulated mechanism of AED action; the latter hinges on pharmacokinetic resistance, positing that overactive transport mechanisms prevent AEDs from reaching their targets in sufficient concentrations in the first place. These hypotheses will be considered in greater detail. Eventually, a number of mechanisms are likely to emerge as important to greater or lesser extents in a range of syndromes. Some other potential mechanisms are also considered.

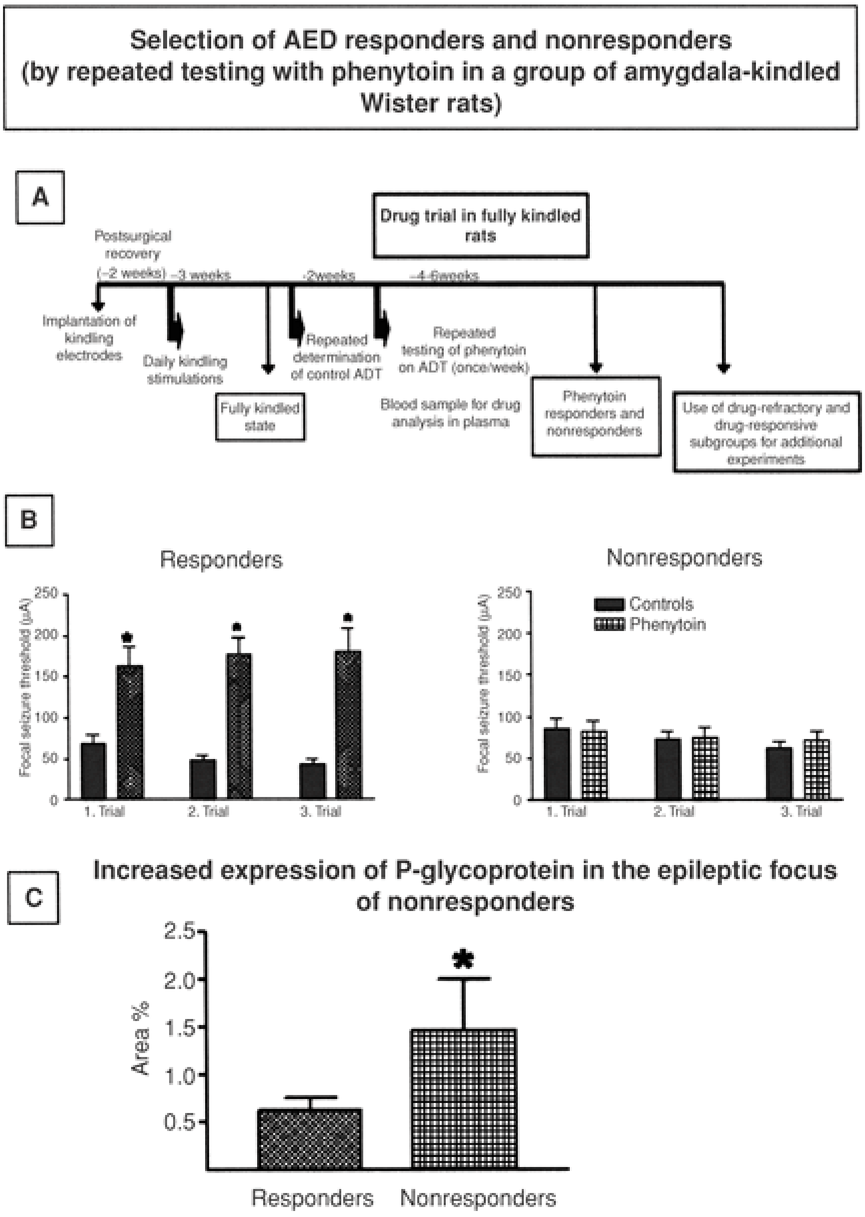

FIGURE 1. Selection of responders and nonresponders to antiepileptic drug (AED) treatment in the kindling model of temporal lobe epilepsy. **A:** The experimental protocol used to select responders and nonresponders from a large group (usually >50) of amygdala-kindled Wistar rats. ADT, afterdischarge threshold. **B:** The results of a typical selection experiment. Responders always react with a significant increase of focal seizure threshold in each trial with administration of phenytoin, whereas nonresponders do not show any anticonvulsant effect of phenytoin at the same doses. Results shown are means and SEM, $^*p < .05$. **C:** The expression of the drug efflux transporter P-glycoprotein (P-gp) in brain capillary endothelial cells that form the blood–brain barrier. Nonresponders exhibit significantly higher expression of P-gp than do responders in the epileptic focus, that is, the kindled amygdala. The expression is shown as area of brain capillary endothelial cells immunohistochemically stained for P-gp. This area was determined by computer-assisted image analysis of brain sections. Data are from Brandt C, Bethmann K, Gastens AM, et al. The multidrug transporter hypothesis of drug resistance in epilepsy: Proof-of-principle in a rat model of temporal lobe epilepsy. Neurobiol Dis. 2006;24(1):202–211.

Animal Models of Drug-Resistant Epilepsy

Animal models of epilepsy allowing selection of pharmacoresistant and pharmacosensitive subgroups of animals constitute a valuable tool for studying mechanisms of intractability and developing more effective treatment strategies.[36,38] Only one model with these characteristics has been extensively explored: The amygdala-kindled Wistar rat, from which phenytoin-resistant and phenytoin-sensitive rats can be selected by repeated testing with phenytoin (Fig. 1).[36,38] Phenytoin-resistant rats are also resistant to various other AEDs, thus offering parallels with the clinical presentation of multidrug-resistant temporal lobe epilepsy. Phenytoin-resistant kindled rats have been used to study mechanisms of drug resistance, described in more detail later. In short, breeding and other studies have indicated that genetic factors and kindling-associated brain alterations are involved in drug resistance in this model.[37] However, one major drawback of this model is that kindled

rats do not exhibit spontaneous recurrent seizures, so that elicited seizures have to be used for drug studies. This is also true for the 6-Hz “psychomotor” seizure model in mice, which has been proposed as a useful model of therapy-resistant limbic seizures.[3]

Some recent studies have indicated that rats with spontaneous recurrent seizures developing after status epilepticus differ in their individual response to AEDs, thus allowing selection of drug-resistant and drug-responsive subgroups.[8,19] This group of models reflects most closely a common form of human drug-resistant epilepsy, the mesial temporal lobe epilepsy (mTLE) syndrome. By using drug-resistant epileptic rats selected from such a post-status epilepticus model of mTLE, it was recently shown that drug-resistant rats differ from drug-responsive rats in (a) expression of multidrug efflux transporters in the brain,[99] (b) expression of drug targets in the brain,[97] and (c) morphologic alterations in the hippocampus.[97] Thus, such post–status epilepticus models, allowing selection of drug responders and nonresponders, are interesting tools for studying mechanisms of drug resistance. As reported recently, they can also be used to study whether overcoming the mechanism(s) counteracts drug resistance.[6]

Apart from selecting subgroups of drug-resistant rats from models of mTLE, another approach is to use models in which all animals appear per se resistant to treatment with certain AEDs.[38] Such models include the 6-Hz “psychomotor” seizure model in mice,[3] the MAM (methylazoxymethanol acetate) model of cortical dysplasia in rats,[82] and certain post–status epilepticus models of TLE.[20] Furthermore, several in vitro brain slice preparations have been proposed to be useful in studying mechanisms of drug resistance.[38,105] As with all models of drug-resistant epilepsy, one major problem in validating these in vitro models is the lack of a positive control, that is, a novel AED with clinical efficacy in the management of refractory epilepsy. As a consequence, it is not known whether novel compounds that are found to be active in models of drug-resistant seizures will be subsequently found to be effective for the management of human refractory epilepsy.[104]

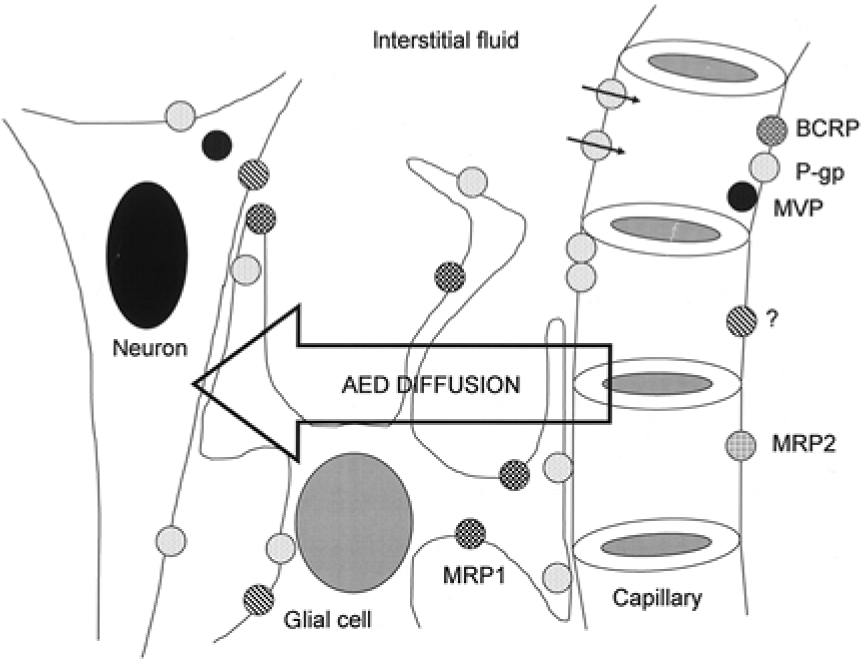

FIGURE 2. Schematic illustrating the transport hypothesis. Most antiepileptic drugs (AEDs) diffuse from the capillary lumen to the interstitial fluid and their targets, usually on the surface of or within neurons. Nonspecific, multidrug transporters (represented by variously filled circles) are present in particular distributions for given transporters. Thus, for example, multidrug-resistance–associated protein 1 (MRP1, *checkered circles*) is overexpressed on glial cells in epileptogenic tissue. The transport hypothesis maintains that AED concentration at the neuron is reduced by the transport activity of various transporters on capillary endothelial cells, glia, and neurons, reducing diffusion of AEDs to their desired site of action and thus reducing their antiepileptic effects. The circle marked with a question mark has been added to emphasize that we do not yet know all the transporters that might be relevant. BCRP, breast cancer resistance protein; MVP, major vault protein; P-gp, P-glycoprotein.

Drug Transport Hypothesis

Background

The "transport" hypothesis embodies the concept that sustained failure of AEDs to stop seizures is due to a subtherapeutic local concentration of AEDs at their site of action caused by the activity of multidrug transporters (Fig. 2). The idea arose by analogy with drug resistance in oncology:[32,47,89] The in vitro dissection of the mechanisms of resistance of cultured tumor

cells to anticancer drugs showed that the activity of the archetypal transport protein, P-glycoprotein (P-gp, where "P" stands for permeability), was important in cell survival. Extensive subsequent studies in cancerous cells both in vivo and in vitro have revealed a spectrum of transport or transport-related molecules with more or less proven roles in the flux or sequestration of anticancer drugs. Tishler et al. in 1995[89] were the first to explore this possible mechanism in drug-resistant human epilepsy, showing both increased expression of P-gp in resected epileptogenic human temporal lobe tissue and reduced accumulation of labeled phenytoin in cultured cells artificially expressing P-gp in comparison to the parent wild-type cells not expressing P-gp.

The field has advanced considerably since. In oncology, the field has somewhat stagnated after initial excitement that modulation of the activity of transporters might offer dramatic new treatment options in refractory cancer; human studies failed to bear out this optimism. Belatedly, oncologists have established that a number of reasons render questionable the negative results obtained in early studies. For example, the presence of transporters mediating resistance was often presumed and not proven in the particular tumors in particular patients; resistance itself was presumed to be present when it may not have been in all cases involved in trials of inhibitors; the inhibitors used were usually preexisting compounds pressed into service but that had poor inhibitor potency or marked interactions with anticancer agents; and when inhibitors were used, absence of surrogate markers of inhibition meant that the degree to which successful inhibition of transporters in tumoral tissue had been achieved in individual patients was not known.[4] Despite these realizations, the area of study has become somewhat discredited (indeed, it is interesting to note that oncology has largely moved to developing specific therapies for specific targets, e.g., herceptin, trasmuzutab[24]). In epilepsy research, although parallels with cancer should not be drawn too far, we would do well to learn from the experience in oncology.[47]

Critically, it is important that work on the transporter hypothesis is pursued rationally. One approach is to consider criteria that need to be satisfied to accept a particular transport mechanism as contributing to resistance in human epilepsy. One set postulated is as follows:[80]

1. Mechanisms must be detectable in epileptogenic brain tissue
2. Mechanisms must have appropriate functionality
3. Mechanisms must actually be active in drug resistance
4. Overcoming the mechanisms should affect drug resistance

Considerable experimental data exist addressing criteria 1 to 3, reviewed below. Criterion 4 will remain the most demanding, complicated particularly by natural redundancy among the many known and unknown transporters, whose presumptive evolutionary purpose includes the protection of cells, organs, and organisms from environmental or endogenous toxins.

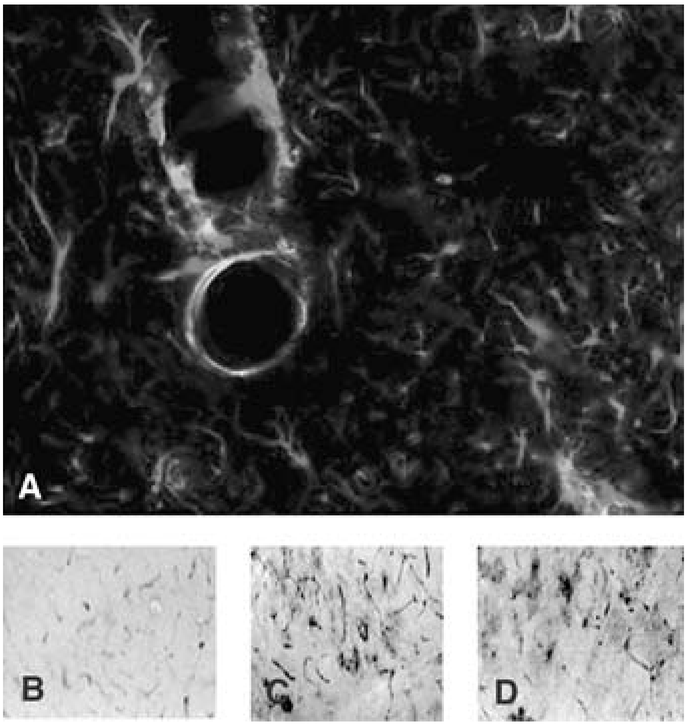

FIGURE 3. Overexpression of P-glycoprotein (P-gp) in an animal model. **A:** Merged image (20×) showing P-gp immunolabeling (*green*) and glial fibrillar acidic protein (GFAP)-positive astrocytes (*red*) in the rat cortex 18 hours after pilocarpine-induced status epilepticus. Colocalization signal (*yellow*) depicts P-gp

expression in astrocytic endfeet adjacent to brain microvessels. **B, C, D:** Representative immunohistochemical micrographs (10×) depicting P-gp immunolabeling in control rat hippocampus **(B)** and 18 hours after pilocarpine-induced status epilepticus. Note that in the control panel only, vessels are lightly labeled, whereas seizures induced P-gp overexpression both in vessels and in astrocytes **(C, D)**. (See the color insert.)

Animal Data: Multidrug Transporter Proteins in Experimental Models of Seizures

Expression Studies

Experimental models of seizures mimicking the neuropathologic features of drug-resistant TLE have been used for studying the molecular mechanisms of intractability.[1,11,14,36,73,83] Suitable models should fulfill at least two criteria: (a) the type of seizures should be similar to those occurring in human epilepsy on both behavioral and electrographic manifestations; (b) standard AEDs should be inactive or weakly active as compared to efficacy in models of primarily generalized seizures that are easily suppressed by AEDs. Although the first aspect has been verified in the case of complex partial seizures,[36] responsiveness of experimentally induced seizures to AEDs has only rarely been addressed (e.g., in models of status epilepticus evolving to spontaneous seizures[83] and in kindled rats[36]).

P-gp is overexpressed in endothelial cells, and ectopically in astrocytes, after induction of sustained limbic seizures in rodents; neuronal expression has been also reported in some instances.[35,75,90,98,106] (Fig. 3). Upregulation of the mRNA of the multiple-drug resistance 1 gene (*mdr1*, which codes for P-gp) was detected in rat brain during both acute seizures[67] and spontaneous seizures[90] caused by status epilepticus. After audiogenic seizures in genetically epilepsy-prone rats, P-gp and *mdr1* mRNA upregulation was specifically detected in brain regions involved in the onset and propagation of epileptic activity.[34] Because limbic seizures were induced in these studies in otherwise normal rodent brain, these experimental findings indicate that epileptic activity per se can increase the expression

of P-gp. These findings are compatible with the observations reported in human TLE tissue (see later discussion).

More recently, Volk and Löscher[99] reported that phenobarbital-resistant epileptic rats exhibit significantly higher endothelial expression of P-gp in limbic brain regions compared to drug-responsive epileptic rats, providing further support for the multidrug transporter hypothesis of drug-resistant epilepsy. Drug-resistant and responsive rats were selected from a post–status epilepticus model of TLE.[99] The severity or duration of status epilepticus or frequency of spontaneous recurrent seizures developing after the status epilepticus did not differ significantly between responders and nonresponders, indicating that drug resistance and overexpression of P-gp may be genetically mediated.

Functional Studies

Rizzi et al.[66] reported that *mdr1* mRNA is overexpressed in mouse hippocampus after the induction of limbic seizures. When phenytoin was systemically administered to these mice, its brain-to-plasma ratio was 30% less than in mice not subjected to seizures, thus indicating reduced drug concentrations in brain. It is still unknown whether the magnitude of changes in brain phenytoin levels is pharmacologically relevant to reduction of the anticonvulsant activity of this drug, and indeed whether the change in *mdr1* mRNA is the unique underlying cause or changes in other, unmeasured entities might also contribute. Potschka et al.[53,54] reported that the efficacy of phenytoin in inhibiting generalized clonic seizures in rats was enhanced by probenecid, the nonspecific inhibitor of a subfamily of multidrug transporters, the multidrug-resistance associated proteins (MRPs), and in MRP2-deficient rats; increased efficacy was associated with ~30% increase in brain-to-plasma concentration ratios of phenytoin. In kindled rats, a widely used model of TLE, significant upregulation of P-gp was reported in brain capillary endothelial cells of limbic brain regions.[100] In these rats, brain-to-plasma concentration ratios of phenytoin in the hippocampus were about 30% lower than those measured in control animals.[57] When kindled rats were divided into phenytoin responders and nonresponders, nonresponders exhibited a significantly higher expression of P-gp in capillary endothelial cells in the epileptogenic focus (i.e., the kindled amygdala) compared to the same region in responders (FIGURE 1).[58]

These findings support a link between the level of expression of *mdr1* mRNA, P-gp protein or MRP2 protein, and the AED-extrusion function of these drug transporters (e.g., increased *mdr1* mRNA/P-gp protein is associated with decreased brain phenytoin levels, whereas decrease in MRP2 protein is associated with increased brain phenytoin levels); in addition, changes in phenytoin brain concentrations of ~30% appear to affect its efficacy in experimental models.

An important aspect to be considered is the subcellular localization of the ATP-binding cassette (ABC) family of drug transporters, of which P-gp is the archetype.[70] Thus, only those proteins localized at the apical membrane of endothelial cells of brain capillaries will be able to decrease whole-brain AED uptake by active extrusion into the blood stream. Examples include P-gp, MRP2, MRP4, and breast cancer resistance protein (BCRP). In contrast, drug transport proteins localized at the basolateral membrane of epithelial cells in the choroid plexus (e.g., MRP1) or in microvasculature (e.g., MRP3 and MRP5) may increase brain uptake of their substrates. Other local changes in the expression of transporters (e.g., in glia) might affect local drug disposition in superimposed local microgradients.

The current hypothesis is, therefore, that P-gp, MRP2, and BCRP localized in microvascular endothelium represent the first barrier for extruding AEDs from the brain. A second barrier may be represented by the presence of P-gp and other transporters in astrocytic endfeet in close apposition with microvasculature. It is notable that parenchymal astrocytes and dysplastic neurons in certain human lesional epileptogenic tissues often express P-gp and MRP1 (see later discussion). The functional consequences of this cell-specific expression are unclear. One speculation is that this multidrug-resistant phenotype in astrocytes and neurons may function as a nonspecific cellular protective mechanism against xenobiotics or toxic compounds that may enter the brain, or be produced in situ, in pathologic conditions. Protective roles for both P-gp[28] and MRPs[63,64] have been proposed.

Table 1 Drug efflux transporters in central nervous system and antiepileptic drug substrate status

Protein	Gene name	Central nervous system expression	Transported antiepileptic drug in humans
ATP- binding cassette (ABC) family			
MDR1, P-gp	ABCB1	Endothelial cells, BBB[a]	Carbamazepine,[b] phenytoin Felbamate, lamotrigine Topiramate, phenobarbital
MRPs			
MRP1	ABCC1	Epithelial cells, choroid plexus	Carbamazepine, phenytoin[c]

MRP2	ABCC2	Endothelial cells,[d] BBB	Phenytoin
MRP3	ABCC3	Endothelial cells,[d] BBB	
MRP5	ABCC5	Endothelial cells,[d] BBB	
BCRP	ABCG2	Endothelial cells,[d] BBB	

Central nervous system expression represents protein localization in normal human brain tissue as assessed by immunohistochemistry or by reverse transcriptase–polymerase chain reaction analysis of mRNA in isolated endothelial cells from brain capillaries as for multidrug-resistance-associated protein 3 (MRP3) and MRP5.[16] The multidrug-resistance (MDR) family of proteins consists of P-glycoprotein (P-gp or MDR1), MDR2, and MDR3 genes in humans and *mdr1a, mdr1b*, and *mdr2* in rodents. MDR1, *mdr1a*, and *mdr1b* DNA confer multidrug resistance. BBB, blood–brain barrier; BCRP, breast cancer resistance protein.

[a] P-gp expression has also been reported in choroid plexus.[60]

[b] One report does not support this evidence.[49]

[c] These results were obtained using probenecid, a broad-spectrum blocker of MRP function. A recent report showed that levetiracetam is not transported by P-gp or MRP1/2.[53]

[d] Endothelial localization of MRP proteins is controversial.[70] Data on antiepileptic drug transport have been obtained in vitro using epithelial cell lines[72,90] or in vivo in rodent brain.[39,52-56,67,79]

Antiepileptic Drugs: Substrates of Multidrug Transport Proteins?

In vitro studies using epithelial cell lines expressing the MDR1 gene provided the first evidence that P-gp can mediate phenytoin efflux from intracellular compartments.[89] Subsequent pharmacologic studies in rodents indicated that both P-gp and MRPs mediate brain efflux of phenytoin, phenobarbital, carbamazepine, oxcarbazepine, lamotrigine, topiramate, and felbamate.[40,41] This evidence was obtained using normal rats given broad-spectrum inhibitors of multidrug transporter function intracerebrally[55] or using genetically modified rodents lacking *mdr1*[67,78] or *mrp2* genes.[53]

In particular, interstitial rat brain concentrations achieved after systemic administration of phenytoin, carbamazepine, felbamate, lamotrigine, phenobarbital, and oxcarbazepine are increased by blocking P-gp or MRP function with the broad-spectrum antagonists verapamil and probenecid.[12,41] The P-gp-mediated transport of phenytoin was further substantiated using PSC833, a more selective blocker of P-gp function.[56] Brain-to-plasma concentration ratios of phenytoin, carbamazepine,[67] and topiramate[78] were found to be higher in mice lacking P-gp because of a deletion of the *mdr1* gene[71] than in wild-type mice. In contrast with previous evidence, one report showed no changes in carbamazepine brain concentration in mice lacking the *mdr1a/b* gene.[48] This discrepancy may be explained by methodologic issues (e.g., measurements of AED in whole brain tissue[48] rather than in specific brain regions[67] or in the extracellular space[55]).

The brain concentration of phenytoin was increased in rats lacking the *mrp2* gene and the encoded protein,[53] whereas the concentrations of carbamazepine, lamotrigine, felbamate, or phenobarbital were not modified, suggesting that, among these AEDs, phenytoin only is transported by MRP2. Thus, under normal physiologic conditions, P-gp and MRPs (e.g., MRP2) appear to mediate brain extrusion of various AEDs (Table 1) because pharmacologic blockade of their function or their absence due to gene deletion results in increased intracerebral levels of those AEDs.

One limitation of these pharmacologic studies is that they are based on the use of P-gp or MRPs blockers with poor selectivity. However, the recent availability of more selective antagonists and the use of rodents with specific multidrug transporter gene deletions may provide adequate tools for strengthening the available evidence. Further experiments will also need to assess the possible upregulation of other transporters in animals lacking a particular transporter: Very likely, there remain transporter proteins yet to be discovered.

Demonstration that multidrug resistance could be prevented or reversed by inhibition of such transporters would be the final step, and the most important one for patients, in considering the multidrug transporter hypothesis of drug resistance in epilepsy. Brandt et al.[6] recently used AED nonresponders that were selected from a post–status epilepticus rat model of TLE. As described earlier, these nonresponders differ from responders in overexpression of P-gp in brain capillary endothelial cells of limbic brain regions such as hippocampus.[99] Combined treatment of phenobarbital-resistant rats with phenobarbital plus the third-generation, highly-selective P-gp inhibitor tariquidar reversed resistance to treatment in dose-dependent fashion, so that most rats became drug-responsive by this treatment.[6] In accord with these findings, using rats that exhibit spontaneous seizures after electrically evoked status epilepticus, van Vliet et al.[91] recently found that a 7-day treatment with therapeutic doses of phenytoin suppressed spontaneous seizure activity but only partially. However, almost complete, but transient, control of seizures by phenytoin was obtained in all rats when this AED was coadministered with tariquidar. P-gp upregulation was confirmed in brains of these chronic epileptic rats along with ~20% reduction in brain phenytoin levels. These findings show that inhibition of P-gp significantly improves the anticonvulsant action of both phenobarbital and phenytoin in these animal models in the short term. More studies are required, however, before therapeutic use of such inhibitors might be considered in humans with refractory epilepsy.

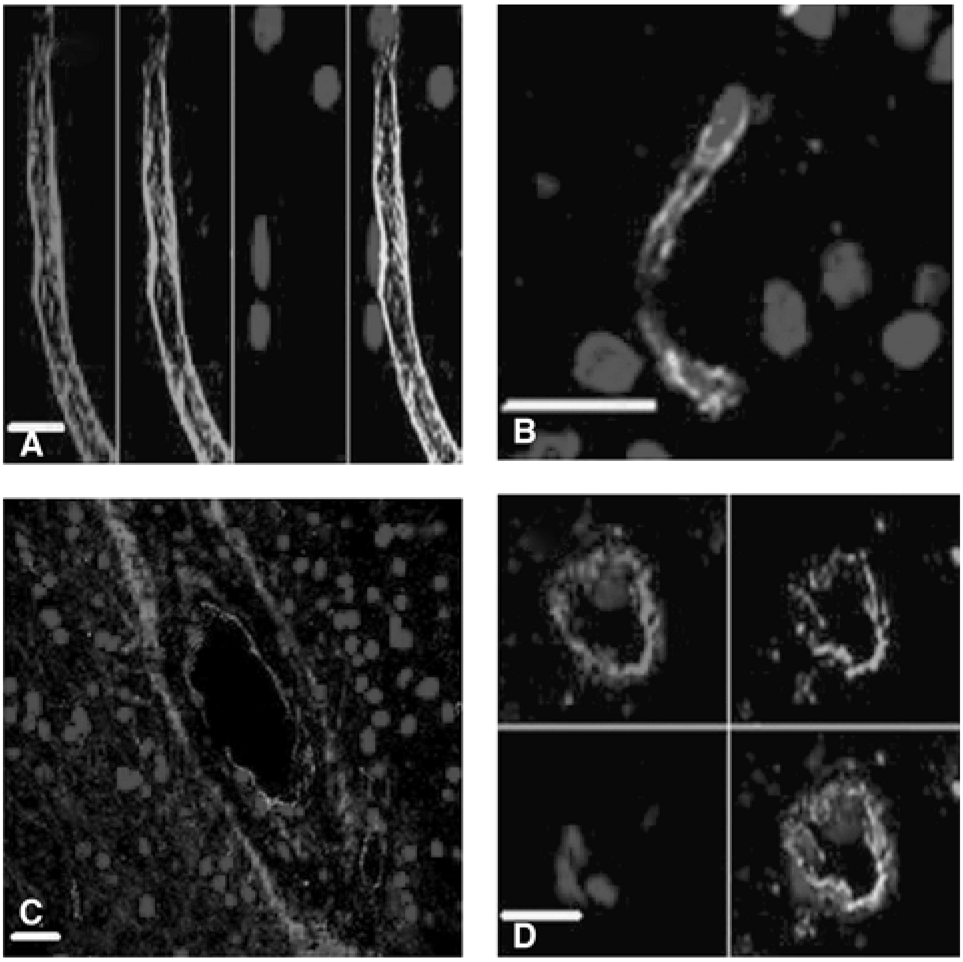

FIGURE 4. Overexpression of multidrug transporters in human epileptogenic brain tissue. Immunohistochemistry using fluorescently labeled antibodies shows colocalization of fluorescence, and thus labeling, for a combination of transporters and presumptively transporter-related proteins in microvasculature in a section of hippocampus resected from a patient with refractory epilepsy due to hippocampal sclerosis. Blue labels cell nuclei. **A:** Red labels P-glycoprotein (P-gp), green labels breast cancer resistance protein (BCRP), and, in the extreme right panel, the two are shown to colocalize by the merged yellow color. **B:** Colocalization, although to a lesser extent, of P-gp (*red*) and major vault protein (*green*). **C:** P-gp (*green*) does not colocalize in these sections with multidrug-resistance–associated protein 1 (MRP1, *red*). **D**: BCRP (*green*) colocalizes with P-gp (*red*). In all sections, the scale bar represents 30 μm. (See the color insert.)

Human Data

In comparison to animal data, information in humans is necessarily more limited. There are considerable data on transporters detectable in human epileptogenic brain tissue; some on their AED transport activity in cultured human cells; some, more controversial, on the role of variation in genes encoding transporters—as surrogate for in vivo activity; and anecdotal information only on overcoming transporters in clinical practice.

P-gp; the related transporter proteins MRP1, MRP2, and BCRP; and the unrelated but resistance-associated major vault protein (MVP) have all been found to be present in normal human brain and also to be ectopically expressed in human epileptogenic pathologies (Fig. 4). Specifically, hippocampal sclerosis, focal cortical dysplasia, dysembryoplastic neuroepithelial tumors, and ganglioglioma have been found to show ectopic expression of combinations of these proteins in certain parenchymal cell subpopulations (for a comprehensive review, see Kwan and Brodie[32]). Discrepancies among studies are likely to be due at least partly to the adoption of different immunohistochemical protocols, a vagary previously confronted in oncology.[5] Nevertheless, it is clear that transporters *could* contribute to human refractory epilepsy because they are at least present and in fact are often coexpressed.

Whether these transporters are capable of transporting AEDs has proved more difficult to establish in humans. Only one recent study has provided in vivo data relating to brain pharmacokinetics of AEDs; it showed an inverse correlation between brain *MDR1* mRNA levels and intraparenchymal concentration of MHD (the active monohydroxy derivative of oxcarbazepine), which has also been shown to be a P-gp substrate in a model system.[12,43] There are no ex vivo data on living human brain tissue nor on any cultured human brain cells for AEDs. Peripheral blood lymphocytes do express P-gp, and at least one study has used these to test whether P-gp in this tissue is capable of transporting carbamazepine (and found that it is not[48]). More such studies are required, incorporating proof that such lymphocytes are satisfactory surrogates for brain transporters. Pharmacogenetics offers an indirect approach to this problem, by determining whether naturally occurring variation in the genes encoding transporters relates to clinical phenotypes. Only variation in one gene (*MDR1*) has been studied in any detail: Although one study showed an association between a particular polymorphism (C3435T) and drug resistance,[77] a replication study failed to support the original report.[87] Others have suggested that a broader haplotype may be relevant.[24] The importance and uncertainty of these findings mandate further work,[79] although it is of interest that it has recently been shown that the 3435T allele affects *MDR1* mRNA stability, at least in liver.[103]

With regard to actual clinical inhibition of transporters in drug-resistant epilepsy, only anecdotal data exist: Two single case reports suggested improvement in refractory epilepsy on addition of verapamil,[25,86] a first-generation, comparatively nonspecific P-gp inhibitor that of course also has additional pharmacokinetic and pharmacodynamic effects.

Altered Target Hypothesis

Development of Hypothesis

Following permeation through the blood–brain barrier, drugs have to bind to one or more target molecules to exert their desired action. The *target hypothesis* of pharmacoresistance contends that molecular changes in drug targets may cause them to be less responsive to AEDs. This reduced sensitivity on a cellular level might then contribute to pharmacoresistance on a clinical level.

Changes in Antiepileptic Drug Targets

A large number of AED targets have been identified in the brain, most of them neurotransmitter receptors and

voltage-gated ion channels. Voltage-gated ion channels are involved in the anticonvulsant effects of drugs such as phenytoin, carbamazepine, valproate, and lamotrigine. Transient and persistent sodium currents respond to all of these AEDs. Calcium channels are also targets for AEDs (i.e., ethosuximide, valproate, phenytoin, or gabapentin), and potassium channels are emerging as potential targets for AEDs (i.e., retigabine). Another large group of drugs, among them benzodiazepines, barbiturates, vigabatrin, and tiagabine, act to enhance the efficacy of synaptic inhibition. It should be noted, however, that the list of targets for established AEDs is almost surely incomplete and will expand as their actions on novel targets are examined.

Altered Antiepileptic Drug Sensitivity of Drug Targets: Data from Models and Human Tissue

Among the known drug targets, a large number display defined changes both in human and experimental epilepsy. Voltage-gated Na^+, Ca^{2+}, and K^+ channels, mixed cationic channels such as those mediating the H-current, as well as neurotransmitter receptors such as the γ-aminobutyric acid (GABA) A receptor, are altered at the molecular level in chronic epilepsy. The many molecular changes cannot be exhaustively enumerated here, but they lead to the next key question: Do drug targets in chronically epileptic brain display decreased sensitivity to AEDs? The first indication that this might be the case was provided in a study demonstrating that a change in the subunit composition of $GABA_A$ receptors in hippocampal dentate granule neurons results in reduced benzodiazepine sensitivity of the receptor complex in the pilocarpine model of epilepsy.[9]

Similar findings have been obtained with respect to voltage-gated Na^+ channels. Generally, the effects of anticonvulsant drugs like carbamazepine or phenytoin on the inward Na^+ current (I_{Na}) are considered to be threefold: (a) a voltage-dependent reduction of I_{Na} amplitude, (b) a shift of the voltage dependence of steady-state inactivation in a hyperpolarizing direction, and (c) a slowing of recovery from inactivation.[2,10,33,61,65] The latter mechanism may be particularly relevant for antiepileptic action because slowing of the recovery from inactivation causes a pronounced frequency-dependent reduction of I_{Na} availability. This mechanism is thought to produce an inhibition of I_{Na} amplitude especially during abnormal high-frequency discharges such as those observed in chronic epilepsy. It is of interest that a complete and long-lasting loss of use-dependent blocking effects of carbamazepine was found in the pilocarpine model of epilepsy in hippocampal dentate granule cells, as well as in epilepsy patients with carbamazepine-resistant temporal lobe epilepsy.[65] A similar loss of efficacy was observed to a lesser extent for phenytoin. Interestingly, this effect was not observed for other AEDs such as lamotrigine or valproic acid.[66] Notably, in tissue obtained from pharmacoresistant patients, no differences regarding valproic acid effects on I_{NaT} were observed.[101,102] Collectively, these results suggest that epileptogenesis causes changes in the pharmacologic properties of I_{NaT} in some but not all cell types. It will be necessary to test the target hypothesis also for other drug targets.

Relationship of Changes in Cellular Antiepileptic Drug Sensitivity to Pharmacoresistance Observed In Vivo

The results just described, although suggestive, leave open the major question of whether loss of AED sensitivity on the level of an ion channel, for example, is associated with pharmacoresistance in intact animals. This question could be ideally answered experimentally by first examining pharmacosensitivity in intact animals and subsequently comparing these in vivo results to the cellular effects of AEDs in the same animals. So far, this approach has only been implemented in a few experiments,[27] which assessed phenytoin-responsive and nonresponsive kindled rats.[39] Such models will prove enormously valuable in probing the molecular underpinnings of altered pharmacosensitivity in groups of animals defined by the AED response.

Investigation of tissue resected from patients with epilepsy during epilepsy surgery permits correlation of clinical responsiveness to AEDs with in vitro data from the same patients. For instance, in patients with epilepsy, the properties of the transient inward Na^+ current (I_{NaT}) seem to differ when patients are separated into two groups—one resistant to carbamazepine and a smaller one responsive to carbamazepine. In the former, use-dependent block of I_{NaT} by carbamazepine was abolished, similar to the findings in experimental epilepsy. In contrast, carbamazepine-responsive patients showed potent use-dependent effects of carbamazepine on I_{NaT}. Thus, the sensitivity to carbamazepine on a cellular level appeared to correlate with the clinical responsiveness to the drug.[65] The same correlation was observed when seizure-like events were induced in human slices by elevation of the extracellular K^+ concentration.[18] Such seizure-like activity was not affected by carbamazepine in vitro at concentrations as high as 100 μM when the corresponding patient was clinically resistant to this drug. In marked contrast, seizure-like activity in tissue from patients who were clinically sensitive to carbamazepine was sensitive to carbamazepine in vitro. These findings are also interesting because in these in vitro experiments, the primary blood–brain barrier is not operative. Thus, the correlation between clinical drug response and in vitro data cannot be explained by changes at the blood–brain barrier and implies that, at least for carbamazepine, there is likely to be a change in a drug target.

These findings seem straightforward; however, there are a number of conceptual issues that remain enigmatic. It should be noted, for instance, that patients who are resistant to carbamazepine very frequently are resistant also to other AEDs.[32] The data, however, indicate that altered sensitivity of Na^+ channels may not account for altered efficacy of other AEDs such as valproic acid or lamotrigine.[66] This finding suggests that resistance to AEDs in epilepsy patients is a complex phenomenon that is likely to involve multiple mechanisms.

Future Directions of Research for the Target Hypothesis

The evidence for a role of target changes in drug resistance is suggestive but does not prove the relevance of this mechanism in a clinical setting. What key pieces of evidence should we consider mandatory to support the target hypothesis? A number of experimental data should be obtained:

- Evidence that an AED influences a target ion channel or receptor at clinically relevant concentrations, preferably both in animal and human systems.
- Evidence that the drug target is altered in such a way that it is less sensitive to an AED in chronic human and experimental epilepsy. Functional and molecular changes should correlate with sensitivity of seizures to AEDs in experimental animals or epilepsy patients.
- Evidence that genetic or pharmacologic manipulation of drug targets in intact animals affects sensitivity of spontaneous seizures to AEDs in chronic models of epilepsy.

In addition, we should attempt to generate the following data in human subjects:

- Association of polymorphisms in drug target genes with clinical pharmacoresistance. This could also include association of polymorphisms with drug target pharmacology measured in vitro in tissues obtained from epilepsy surgery.

What Are the Mechanisms Leading to Altered Target Sensitivity?

So far, the mechanisms under most scrutiny have been changes in the transcription of ion channel subunit genes. It has become evident that seizures cause a highly coordinated change in transcription of certain groups of ion channel subunits both in rat models of epilepsy and in humans with epilepsy. This seizure-induced transcriptional plasticity appears to be differentially regulated in different neuron types. In addition to transcriptional mechanisms, seizure activity may also evoke multiple posttranscriptional modifications of ion channel proteins. These could include altered protein transport and targeting, but also changes in phosphorylation or glycosylation. That the latter changes can in principle influence AED sensitivity of channel proteins was shown by Curia et al.:[15] Increased phosphorylation of sodium channels by protein kinase C affected responsiveness to the AED topiramate. It is quite possible that similar mechanisms may also apply to other ion channel proteins or AEDs.

Both transcriptional and posttranscriptional changes would constitute acquired changes in AED sensitivity. A recent study supports the idea that preexisting genetic factors may also influence target sensitivity. Lucas et al.[42] examined the pharmacology of Na^+ channels containing a mutant β_1 subunit causing the generalized epilepsy with febrile seizures plus (GEFS+) syndrome. The surprising result was that Na^+ channels containing mutant β_1 subunits displayed a dramatic and selective loss of use-dependent block by the AED phenytoin that was very similar to the effects observed in chronic experimental epilepsy for phenytoin and carbamazepine.[65,66]

Individual genetic variation may predispose to some forms of target “alteration” leading to altered sensitivity—including resistance—to AEDs. For example, common variation in gene promoter regions might influence gene transcription responses to stresses, including seizures and drug exposure. Recently, it was shown that a common variation in the sodium channel 1A gene (*SCN1A*), which encodes the alpha subunit of the cerebral neuronal sodium channel, affects the alternative splicing of the gene as well as the maximal prescribed daily doses of drugs targeting this channel.[88]

Rapid Development of Drug Resistance in Status Epilepticus

Resistance to AEDs can also be observed in vitro in some models of recurrent seizure-like events. Such activity can be provoked, for instance, by exposing brain slices to the potassium channel blocker 4-aminopyridine or low extracellular magnesium concentrations. It is of interest that this activity is initially responsive to many AEDs, including valproic acid, carbamazepine, phenytoin, barbiturates, and benzodiazepines. If slices are treated with 4-aminopyridine or low-magnesium-containing solution for prolonged periods (more than approximately 2 hours), however, some of the descriptive features of this seizure-like activity change. More importantly for the purposes of this chapter is the finding that seizure activity is no longer blocked by the very AEDs that were previously effective. Thus, resistance to AEDs in vitro can develop in a matter of hours in the presence of continuous epileptiform activity. This suggests that the underlying mechanisms must be fast and probably do not depend on transcription.

What could these mechanisms be? One important hypothesis is that metabolic dysfunction may be responsible. A number of studies have provided evidence of mitochondrial dysfunction, the onset of which may coincide with the appearance of AED-resistant late activity. This is thought to have two consequences: First, the availability of ATP may be reduced, and second, there may be increased generation of reactive oxygen species (ROS). It is entirely possible that both phenomena could result in target molecule modifications, the onset of which could be rapid. It is interesting to note that mitochondrial function is also profoundly disturbed in chronic experimental and human epilepsy. It might well be that ROS-mediated damage or energy depletion also plays a significant role in chronic epilepsy. In addition, rapid increases in the expression of some multidrug transporter-encoding genes in animal models[67] and widespread increased immunoreactivity for P-gp in a single anecdotal human case[81] have been shown, suggesting another possible contribution to rapid development of resistance.

Other Mechanisms of Resistance to Antiepileptic Drugs

Other, more speculative, mechanisms have been postulated that may also contribute to drug resistance.

Pharmacokinetic/Pharmacodynamic Changes Due to Disease-Related Mechanisms

Intractable epilepsy is often associated with structural brain lesions such as malformations of cortical development, hippocampal sclerosis, and brain tumors,[62,85] suggesting that disease-specific morphologic alterations in the brain (e.g., neuronal cell loss, heterotopia, dysplasia, neovascularization, synaptic reorganization, reactive glia, etc.) may alter neuronal targets and/or reduce their responsiveness to AEDs (see previous paragraphs). These lesions may also cause reduced AED availability at their neuronal targets because of physical or biologic barriers determined by the tissue pathology. For example, AEDs may be sequestered in the perivascular regions because of the presence of edema or entrapped in glial ectopic masses (e.g., tumor or sclerotic tissues), reducing their concentration in the epileptic focus. In addition, vascular malformations or ectopic microcirculation may favor AED delivery to cerebral regions that are not pivotal for effective seizure control.

Cytochrome P450 in the Brain

Metabolic tolerance may occur if one specific AED increases its own metabolism by induction of the cytochrome P450 (CYP) system in the liver,[50,95] but there is no evidence that this phenomenon occurs to any significant extent in human refractory epilepsy. Nevertheless, the expression of CYP species has been detected in neurons and astrocytes in various brain areas.[23,29,45,96] It is of interest that astrocytic CYPs appear to exert significant control over the metabolism of phenytoin.[45] Because reactive astrocytosis and glial cell proliferation occur to a significant extent in drug-resistant epileptogenic tissue, the levels of CYPs in epileptogenic brain regions may play a critical role in enhancing drug degradation in very localized areas.

Nonconventional Interactions of Antiepileptic Drugs With Neuromodulatory Systems

Recurrent seizures and the process of epileptogenesis per se can induce continuing molecular, cellular, and network changes in brain that in turn produce long-term alterations in neuronal and glial cell phenotypes and in the extracellular concentration of neuroactive compounds and molecular adaptations in voltage-gated or metabotropic receptors that often dramatically change the ability of neurons to respond not only to xenobiotics but also to endogenous neuroactive molecules such as classical neurotransmitters or neuromodulators (e.g., neuropeptides, inflammatory mediators).[51]

AEDs act on diverse molecular targets to modify neuronal excitability largely through effects on voltage-gated sodium and calcium channels or by interacting with GABA and glutamate systems.[68] Limited information is available, however, on “nonconventional” effects of AEDs on neuromodulatory systems that are involved in ictogenesis. In this regard, two notable examples exist of interactions between some AEDs and inflammatory mediators or neuropeptides that may play a role in pharmacoresistance.

Antiepileptic Drugs and Inflammation

Concentrations of proinflammatory cytokines and related molecules have been measured in the central nervous system (CNS) and plasma in experimental models of seizures and in patients with epilepsy.[93] It is notable that pronounced inflammatory reactions have been described in the epileptogenic areas in clinical cases of drug-resistant epilepsies.[93] Studies in rodents show that inflammatory reactions in the brain can be proictogenic by enhancing neuronal excitability, lowering the threshold for seizure occurrence and increasing the duration of seizures. Moreover, some nonsteroidal antiinflammatory treatments reduce seizures in experimental models.[93] These findings suggest that the extent and/or the persistence of inflammation in the brain may be involved in mechanisms of hyperexcitability. There is in vitro evidence that some AEDs such as valproate and carbamazepine have antiinflammatory properties because they decrease the lypopolysaccaride-induced activation of nuclear factor (kappa) B (NFkB) and the production of nitric oxide and prostaglandins in rat glial cells or human glioma cells,[26,44] suggesting that the anticonvulsant efficacy of some AEDs may involve also their ability to reduce inflammation in epileptogenic tissue. The therapeutic efficacy of AEDs may therefore be reduced by the extent and/or persistence of inflammation in the brain of pharmacoresistant individuals.

Antiepileptic Drugs and Neuropeptides

A second point of interest concerns the possible functional interactions between AEDs and some neuropeptides endowed with significant anticonvulsant properties such as neuropeptide Y (NPY) and somatostatin.[49,74,92,94] Significant correlations have been reported between CSF levels of phenytoin, valproic acid, and carbamazepine and some neuropeptides, such as somatostatin, NPY, cholecystokinin (CCK), and corticotrophin-releasing factor (CRF), in the interictal or postictal period in patients with complex partial or secondarily generalized seizures. In general, a negative correlation was found between AED levels and these neuropeptides.[16,75] Although no evidence is available on the ability of AEDs to increase directly or indirectly the function of inhibitory neuropeptides, one attractive hypothesis is that defective action of AEDs on specific neuropeptide systems may contribute to the therapeutic failure of these drugs.

Antiepileptic Drugs and Tissue Plasticity

An alternative, not mutually exclusive scenario is that the failure of AED efficacy may depend on the significant changes in neuronal networks, and in the associated glial elements, that occur in drug-resistant epileptogenic tissue. Maladaptive structural and functional alterations in such tissue, including the failure of endogenous inhibitory systems, may decrease the excitability threshold of neurons to such an extent that AEDs alone do not provide sufficient inhibitory control. In this respect, preclinical and clinical research has led to the identification of new nonconventional targets and therapeutic approaches for effective inhibition of seizures, including intraparenchymal brain delivery of therapeutic genes or compounds with long-lasting anticonvulsant properties (for review see Costantin et al.[13] and Noe' and Vezzani[46]). Such strategies could lead to the development of drugs with novel actions, possibly circumventing the mechanisms of pharmacoresistance, which may act in synergy with currently used AEDs.

Summary and Conclusions

The experimental results described in this chapter indicate that functionally relevant alterations can be found in both AED targets and AED transporters. These mechanisms are not mutually exclusive. It is entirely possible that decreased penetration of AEDs into brain tissue in synergy with changes in targets for these drugs together mediate pharmacoresistance. For some AEDs, it could be that drug resistance is predominantly due to one of these two mechanisms. Some lines of evidence, for instance, suggest that carbamazepine is not a substrate of some multidrug transporters,[48] but rather that target sodium channels display a potent loss of sensitivity to carbamazepine.[65] For other AEDs, this may be different. For instance, intraparenchymal phenytoin concentration is potently regulated by multidrug transporters[54,56,67] and epileptic animals lacking a multidrug transporter protein (MRP2) are more sensitive to phenytoin treatment than are wild-type animals.[54] Thus, target mechanisms seem to be less important for phenytoin compared to carbamazepine.[27,66] Although the evidence supporting this view is far from conclusive, it is tempting to speculate that patterns of resistance mechanisms may vary from drug to drug and syndrome to syndrome.

We do not know the chances of either of these schools of thought leading to a definitive explanation of refractoriness. It may be that even if the roles of transport and target alterations are proven, this will not lead to therapeutic benefit. Even if we had an effective drug that counteracts a given derangement, by the time the clinical manifestations have taken place, it is possible that many other changes have occurred, so that even a drug “specific” for the root problem may not work, as illustrated by the example of PVH discussed in the introduction. Increasing data on the many pathophysiologic deviations, often unrelated to the postulated mechanisms of action of current AEDs, seen in some of the more common pathologies causing epilepsy give both reason for reassessment of current concepts and hope for future developments.

Nevertheless, we do have to start somewhere in attempting to tackle the issue of drug resistance. The “target” and “transport” concepts are the best current candidates, especially if we wish to achieve progress in the shorter term in improving the efficacy of available AEDs. Newer methods and strategies may lead, however, to more rapid progress in this field. It is also likely that biologic investigations in this area will at least uncover more of the pathophysiology of disease processes in epilepsy.

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Chapter 116

Compliance

Joyce A. Cramer

Introduction

Issues of compliance with drug regimens are universal across all medical disciplines. The impact of taking none or less than the appropriate amount of an antiepileptic drug can have consequences to the patient and to the health care system. This chapter reviews typical problems and suggests potential ways to enhance compliance to achieve the desired outcome—good seizure control with minimal adverse effects or impact on quality of life.

Background

The high prevalence of inadequate compliance is a major contributor to the cost of medical care in every therapeutic area. The National Council for Patient Information and Education estimates that half of the 1.6 billion prescriptions written in the United States annually are not taken properly. No consequence is so severe that all patients comply. The leading cause of organ rejection in transplant patients is noncompliance with immunosuppressant drugs.[12] Despite the best intentions and understanding of the importance of taking drugs, many epilepsy patients do not take their drugs as prescribed. A postal survey of community-based patients revealed not only that many patients acknowledge having missed doses, but also that patients are aware they had seizures because of missed doses.[4]

Lacking a cure for epilepsy, researchers are developing new drugs to provide better control of seizures. Unfortunately, the availability of a plethora of new and highly effective antiepileptic drugs will not alter a pervasive aspect of human behavior—partial compliance with the prescribed regimen. Few patients are willfully noncompliant, but many are negligent—partial compliers who take fewer (rarely more) doses than prescribed. To improve outcome for patients with few or many seizures, it is necessary to understand when and why patients do not take drugs as prescribed.

The Health Belief Model was developed as a predictor of preventive health behavior.[1] It is based on patient perceptions, similar to the approach in quality-of-life measures. In this model, the patient must be ready to address the issue of compliance, have some motivation (e.g., seizure control), learn how to take drugs, and receive support from family and health care providers. Paradoxically, good seizure control leads to complacency about taking drugs and may ultimately result in a relapse. Although education is an important feature in the model, knowledge does not ensure compliance, as demonstrated by declines in compliance after counseling is discontinued.[11] The number of medical professionals who do not complete their own treatment programs (e.g., antibiotics), leading to a superinfection, or who lapse in complying with their birth control system (e.g., daily oral contraceptive), resulting in an unplanned pregnancy, demonstrates this point. Urquhart[13] noted that "technical knowledge does not compete effectively for priority in a busy schedule."

Compliance Monitoring and Feedback System

A novel approach to understanding patient behavior in taking drugs and providing feedback on compliance is incorporated in the new microelectronic monitoring technology (MEMS'^{250}; AARDEX Ltd., Zug, Switzerland). The system combines monitoring of drug dosing using MEMS bottles and immediate reading of the electronically stored information on a personal computer in the office. Information is provided directly to the patient and medical staff about dosing activities since the last visit.[5]

MEMS units are special caps for medication bottles that have a microprocessor chip embedded in the cap to record the date and time when the bottle cap is opened for dosing. Months of dosing data can be stored in the cap until retrieval during a follow-up visit. Patients are asked to use the electronic caps, with the explanation that the physician would like to understand how the patient takes drugs as part of the treatment plan. The cap mechanism is demonstrated to the patient, with instructions not to open the bottle except when the drug is removed for dosing. When the patient returns for a follow-up appointment, the bottle is placed on a communicator apparatus that reads the electronic information and transmits it to the computer. A base rate of compliance can be estimated using the first month as a control period because the patient does not yet know how the data will be used.

Data are displayed on the screen in the format of a monthly calendar showing the number of times the bottle was opened for dosing each day. A second type of display shows the exact date and time of every bottle opening. Both displays show the actual dosing pattern and any unusual patterns of missed doses on weekends or during morning or evening dosing. Provided with this information and a report of seizure frequency or dose-related adverse effects, the clinical staff can quickly determine whether seizures have occurred after periods of missed doses or toxic effects after periods of extra doses. The issue is whether the drug has failed to control seizures or whether the patient has failed to take adequate amounts of the drug. The immediate electronic report helps the physician to determine whether the dosing regimen needs adjustment or whether the patient needs assistance to remember to take doses. The electronic monitoring system prevents either the patient or the physician from having a misconception about lack of drug efficacy when inadequate doses have been consumed. Display of data is objective and nonjudgmental, providing immediate feedback to the patient about behavior. This is an optimal time for the physician or nurse to ask what strategies the patient is using to remember the doses, focusing on the more commonly forgotten days and times. For example, if a patient tends to skip pills during the weekend or misses more doses in the morning than in the evening, those time periods can be discussed in detail.

In a survey of 55 patients observed for an average of 14 weeks, the overall rate of compliance with dosing regimens was 75% (range: 3% to 100%). Mean compliance rates declined as the number of doses increased (each day, 86%; twice a day, 80%; three times a day, 76%), with a significant decrease to 53% compliance for four-times-a-day dosing.[5,6] In numerous instances, documentation of dosing demonstrates breakthrough seizures occurring only after missed doses. As stated by former Surgeon General Koop, “Drugs don't work in patients who don't take them.”

Who Needs Help with Compliance Planning?

It is not possible to predict which patients will be partially compliant or when doses will be missed.[6] Intelligence, socioeconomic level, personality, age, and education have not correlated well with electronically monitored compliance. Although it is not feasible to use microelectronic monitoring for all patients, those who continue to have seizures or whose seizures occur randomly despite apparently adequate treatment might be candidates for monitoring. Discovery of erratic compliance might be of greater benefit to the patient than frequent changes of dose or drug. Poor compliers might also need to be seen more frequently.[14]

What can Health Care Providers do to Enhance Compliance?

Patients have no trouble taking multiple tablets and capsules at the same time.[5] Polydosing (multiple daily doses) is the problem, not polypharmacy (multiple drugs).

The key elements to enhance compliance that health care providers should keep in mind when prescribing drugs are as follows:

1. Select the fewest possible number of dose times.
2. Schedule when the doses should be taken.
3. Help the patient select a reminder or “cue.”

Selecting a Dose Regimen

The major pharmacokinetic factor to consider when selecting a dose regimen is the duration of action of the drug, based on clearance rates and the effect of interactions with other drugs. Planning a schedule for taking pills that is appropriate for the patient is important. Although numerous reports have demonstrated an improvement in compliance with simpler dose regimens, physicians either forget this fact or consider other pharmacokinetic requirements to be more important than a simple regimen. At times, the initial treatment regimen with multiple small doses is not revised after tolerance develops. Twice-daily dosing for antiepileptic drugs is recommended whenever possible. The twice-daily regimen provides greater tolerance for irregularities in dosing than a once-daily schedule; if the patient misses a single dose, only half the total daily amount is forfeited when the dose is divided. In addition to compliance issues, dividing the total dose into two portions diminishes the risk for adverse effects at peak serum concentrations during absorption.

Because of its complex pharmacokinetic pattern and half-life of <24 hours in many patients (particularly children), phenytoin usually is given twice daily to keep blood levels fairly constant. Many of the newer drugs with a long duration of action are prescribed with a twice-daily dosing schedule. Among older antiepileptic drugs, phenobarbital can be given once daily in *all* patients because of its very long half-life. Four daily doses are so difficult for most patients to achieve (even on a short-term basis) that careful consideration should be given before prescribing this regimen on a long-term basis. Slow-release formulations offer some extension of therapeutic action. These formulations allow for twice-daily dosing with a safety margin for long intervals between doses. Patients commonly take the morning dose between 6 and 7 AM and the evening dose between 11 PM and 12 midnight, leaving a long daytime period during which the drug is not taken.

Scheduling Doses

Coordination of the dosing schedules for the various drugs prescribed for individual patients is important, particularly elderly patients who take multiple drugs. Although a neurologist might prescribe one drug to be taken three times a day, this can create an elaborate schedule for a patient who is already taking several drugs at other times of the day. Instructions for omitting a missed earlier dose or taking it with the bedtime dose should be given by the physician because patients commonly discover a dose omission at bedtime or early the next morning. Clinicians should indicate how to take a divided dose (e.g., 12 hours apart, morning and evening, or morning and bedtime).

Selection of Reminders or "Cues"

Several types of cues can be easily incorporated into a 3-minute session of compliance counseling. The brevity of the counseling is important because physicians typically have little time and need to be concise and direct in their approach to compliance counseling. Development of cues to remind the patient when to take a dose takes careful planning that meshes with individual lifestyles. Three types of cues are suggested for a simple initial program:

1. Clock time. Ask patients if they are usually aware of the time of day using a watch or clock. If they are, suggest that twice-a-day dosing be based on a specific time (e.g., 7 AM and 7 PM).
2. Mealtime. Ask patients if they usually eat meals at a regular time every day. If the answer is yes, suggest that drugs be taken at mealtimes. Explain that a consistent pattern of dosing with or before meals is important because of effects of foods on drug bioavailability.
3. Daily activity. If a patient is neither aware of the time nor eats regular meals, ask what type of daily activities are typical. Ask the patient to establish a specific activity that can be linked to dosing (e.g., combing hair, shaving, removing contact lenses, walking the dog, listening to AM/PM news).

Some patients manage well by using a small *pill box* with a compartment for each day of the week in which a full day's dose can be inserted. This type of packaging was developed for oral contraceptives during the 1960s so that women could see the sequence of daily doses as an aid to remembering whether the current day's pill was taken. However, even such an obvious visual cue can often be missed, as documented by the large number of unexpected pregnancies in women taking oral contraceptive pills. Patients with complex schedules may benefit by use of a *log sheet*, on which they make a check mark after taking each dose, to avoid double dosing or missed doses.

If one cue does not work, another can be tried, or combinations of cues over time. Periodically asking patients about their cues and how well the cues remind them to take drugs not only helps patients to develop a personalized cuing system, but it also makes them aware of the physician's consistent interest in the way they take drugs.

This simple program was found to be effective even with chronically mentally ill patients.[7]

Pitfalls of Erratic Compliance

Therapeutic drug monitoring (measurement of blood levels) is useful primarily in adjusting dose. However, blood levels are a poor surrogate for direct monitoring of compliance because of the relatively short half-life of most antiepileptic drugs. A drug serum concentration in the expected range at a clinic visit should not be assumed to reflect levels throughout the interval since the last visit. It has been shown that compliance declines from an above-average 82% during the 5 days before and after a clinic visit to 67% between visits ($p < .05$).[8] When a patient has a seizure between visits, the physician uses blood levels from the previous and current visits to assess the probable steady-state serum concentration. Without microelectronic monitoring, any omission of doses before the seizure would be unknown. Use of the MEMS system allows both patient and physician to understand that a drug probably works well to control seizures when taken as directed, but that the patient has a low threshold for declining serum concentrations of the drug. If the patient does not remember missing any doses, it is impossible to establish that partial compliance has been responsible for the seizure or that the drug dose might have been increased inappropriately.

In clinical trials, all seizures are considered as a failure of the drug being investigated. Microelectronic monitoring of compliance can be a valuable adjunct to patient reports and can serve as an explanatory variable of differences in outcome. Compliance with multiple antiepileptic drugs was shown to differ from the experimental medication in a short-term clinical trial.[9]

Clinical Monitoring of Compliance

After establishing a simple dosing regimen, explaining when doses should be taken, and helping the patient to select a reminder cue, the message must be reinforced regularly. A brief question can be added to every routine visit: "*How* do you take your medicine?"

Ask *how many* tablets and capsules are taken at each dose, *when* doses are taken, and *which dose* is more difficult to remember. Listening to the patient before ordering a blood level measurement can provide important information about erratic dosing that could confound interpretation of the results. Patients are more likely to comply with the prescribed regimen when they feel accountable. The phenomenon of "white-coat compliance"[10] has been demonstrated by the enhanced rate of compliance before and after scheduled office visits.[8] Regularly asking every patient at every visit about how drugs are taken demonstrates the importance of maintaining the treatment plan.

Summary and Conclusions

Although every person can be considered a potential treatment defaulter, health care providers at all levels can provide simple suggestions and reinforcements to improve compliance, thereby improving treatment outcome. Unfortunately, no single specific strategy works to enhance compliance for all patients. If physicians and other health care providers work in partnership with patients instead of using a didactic approach, they will have a greater influence on compliance.

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Chapter 117

Choice of Antiepileptic Drugs

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Introduction

When the diagnosis of epilepsy has been made and extraneous factors that can provoke seizures are eliminated, then there is usually the decision to treat the patient with an antiepileptic drug (AED). The patient (or parents, when it concerns a child) must be given as complete information as possible about the diagnosis and prognosis and the different treatment alternatives. Without this understanding between the patient and doctor the risk for noncompliance is significant. The goal of treatment is to achieve seizure freedom without side effects, especially those that cause more negative consequences than the seizures themselves and reduce the quality of life.

With the advent of the new era of antiepileptic drugs, heralded by the approval of ten new compounds, all developed in the last two decades, selection of the most optimal therapy is more complex than ever. It often difficult to predict which drug will be the best tolerated and most likely to produce the best seizure control in a given individual. However, it is perhaps possible to narrow the choices among the available drugs to a few optimal selections based on characteristics that are known about each patient when he or she presents. Some patient characteristics can be seen to fall on a continuum, such as that from the newly diagnosed patient, who has a high likelihood of responding to antiepileptic drugs, to the drug-resistant patient, who is unlikely to remit. Another such continuum is that of age, from infancy, through adulthood, and finally advanced age. Different drug choices might be needed at different points on these continua. In addition, within the epilepsy population there are other characteristics that divide patients into subpopulations, including gender, epilepsy syndrome, and comorbidities.

Thus, the choice of AED is based on not only which drug has been shown to be effective for a particular seizure type, but also the patient's age and gender, comorbidities, and whether he or she is newly diagnosed or refractory. Much is known about likelihood of seizure control, drug tolerability, and side effect profile that is specific to each of these characteristics. These characteristics can also inform choices based on potential interactions and even cost. For example, a new AED that is costly but has been shown to be potent as add-on therapy in refractory epilepsy may be warranted in a difficult-to-control patient but not in a patient who is newly diagnosed.

Stages of Disease

Initial Therapy

Studies in patients with newly diagnosed epilepsy have suggested that approximately 40% of patients with newly diagnosed epilepsy will be rendered seizure free on the first therapy tried.[5] Once seizure free, a patient might be unwilling to attempt a change in therapy, even in the presence of side effects. Patient and physician may not choose to risk a medication conversion due to the possibility of destabilization. The stakes become even higher when the patient has returned to previous activities, including driving. The result is that many patients remain on their initial therapy for years, if not a lifetime. For this reason, the choice of initial therapy is a critical juncture in the care of epilepsy.

Efficacy

Although it would be ideal to have efficacy data for all drugs specifically obtained from well-designed trials in the newly diagnosed population, unfortunately there is usually a lag between the time that a new AED is approved and the availability of data on the newly diagnosed. It is unclear whether trials need to be performed prior to using the new drugs in this population. Although it is likely that drugs that work as add-on therapy also work in monotherapy and that drugs that work in refractory patients are also effective in newly diagnosed patients, who are typically considered to be easier to control, it is also reasonable to assume that the pathophysiology underlying refractory epilepsy differs from that of easy-to-control epilepsy, and therefore drugs might be more suitable for one population or the other. For example, vigabatrin was highly efficacious in placebo-controlled add-on trials in refractory patients,[18] whereas it was less effective (but better tolerated) than carbamazepine in a trial of newly diagnosed patients.[8] It does not appear that relative drug efficacy in add-on studies is predictive of better effect in newly diagnosed patients. Despite great hopes, no new AED has been proven to be more efficacious than a "standard" AED in the newly diagnosed population. Trials in newly diagnosed patients have been successfully completed for vigabatrin, lamotrigine, oxcarbazepine, gabapentin, and topiramate, and soon will be for evetiracetam.[1,3,4,5,8,9,11,14,22,31,37]

Safety and Tolerability

The absence of demonstrated efficacy differences between AEDs when tested in newly diagnosed populations puts emphasis on other drug characteristics as a reasonable basis for AED selection in this population. One important issue is drug safety and tolerability. In the presence of an abundance of options, drugs with few or no safety or side effect concerns should be high on the list. The older AEDs, although generally safe, all carry a small risk of potentially life-threatening adverse events such as hepatic failure and aplastic anemia. A number of the newer antiepileptic drugs, although they have not been used for the same duration, or in as many patients as the older drugs, appear to be safer. As experience and duration of follow-up grows, we can hope that this apparent safety will be confirmed. Even now, the newest antiepileptic drug, pregabalin, has reportedly been used in well more than

100,000 unique patients (Pfizer Inc., personal communication). Several older AEDs have also been associated with risk of long-term side effects, such as gum hyperplasia, neuropathy, connective tissue disorders, and osteopenia.[29] Of the newer drugs, vigabatrin has been associated with permanent visual field defects,[25] and topiramate and zonisamide carry a risk of renal nephrolithiasis.[36] So far, no other long-term side effects have been identified for the new AEDs, although it is probably naïve and definitely premature to hypothesize that none exist. It is important to maintain vigilance for such potential effects because they take unexpected forms and may not be identified before hundreds of thousands of patients have been exposed. On the other hand, in the head-to-head comparison trials the new AEDs were almost always as well or better tolerated than the older drugs. Examples are the comparative trials between lamotrigine and carbamazepine[5]; oxcarbazepine and carbamazepine,[14] phenytoin,[3,22] and valproate[11]; topiramate and carbamazepine and valproate[31]; and gabapentin and carbamazepine.[9] Of note, the studies with carbamazepine as a comparator used the immediate-release rather than the currently favored extended-release formulation, and titration rates were not always optimized. Nevertheless, the new drugs probably have better tolerability especially when given in appropriate doses after careful titration. These outcomes might indicate that these drugs should be considered as initial monotherapy in newly diagnosed patients.

Initiation/Dose

Newly diagnosed patients remain at risk for additional seizures until the chosen drug reaches a therapeutic dose. This gives an advantage to drugs that can be initiated at a therapeutic dose or titrated rapidly. Some AEDs, such as lamotrigine, topiramate, and zonisamide, typically require prolonged titration, and this can limit their use in certain patients. Carbamazepine can typically be titrated to an effective dose within 1 to 2 weeks. Other drugs, such as oxcarbazepine, gabapentin, and pregabalin, have been initiated at a therapeutic dose in clinical trials without safety concerns but have been demonstrated to be better tolerated when titrated slowly.[2,16,34] Titration schedules are outlined in Table 1.

Table 1 Initiation schedule for common antiepileptic drugs

Drug	Initiation
Phenytoin	Intravenous/oral load
Carbamazepine	Gradual initiation/1–2 wk
Valproate	Immediate therapeutic dose
Topiramate	Gradual initiation/4–6 wk
Gabapentin	Immediate therapeutic dose
Lamotrigine	Gradual initiation/4–6 wk
Levetiracetam	Immediate therapeutic dose
Zonisamide	Gradual initiation/4–6 wk
Oxcabazepine	Gradual initiation/4–6 wk

It may be difficult to choose a dose to titrate to as initial therapy in a newly diagnosed patient. Table 2 shows the doses that were used in randomized, placebo-controlled trials in newly diagnosed patients. In trials of lamotrigine and oxcarbazepine, variable dosing was permitted in the initial portion of the trial.[4,5,11,14,22] In these cases, it is likely that the average dose used in the trial is a reasonable starting point for newly diagnosed patients. In trials of topiramate and gabapentin, fixed doses were employed. Topiramate 100 mg was better tolerated, and equally as effective, as 200 mg, and gabapentin 900 mg was more effective and better tolerated than 300 or 1,800 mg. However, other doses were not tested.[31]

Table 2 Doses used in randomized, placebo-controlled trials of four new antiepileptic drugs in newly diagnosed patients

Drug	Dose
Gabapentin	Fixed, 300, 900, 1,800 mg[5]

	(900 mg superior)
Lamotrigine	~150 mg[18]
Oxcarbazepine	~1,000 mg (adults)[8,37]
	~18 mg/kg (children)[3]
Topiramate	Fixed, 100 or 200 mg[31]

Hepatic Enzyme Induction

The older AEDs all produce alteration of hepatic metabolism via alteration of the cytochrome P450 system. Most, including phenytoin, carbamazepine, phenobarbital, and primidone, are strong hepatic enzyme inducers. The newer antiepileptic drugs either have no hepatic-inducing properties or are only minimally inducing. This can provide an advantage when a drug will be used over many years, for two reasons. The first is that many intrinsic substances such as vitamins and hormones are subject to induced metabolism. This can produce relative deficiencies. Absence of enzyme induction is a benefit to women during their childbearing years. This will be discussed later. The second issue is that of drug interactions that occur as a result of hepatic induction. Many medications that are eliminated through cytochrome P450 can be subject to induction. Induction produces a shortened half-life, and higher doses are required to maintain effect.[30] This is especially important to consider when initiating a new AED in patients with known concomitant medical conditions and in the elderly, who are likely to be on multiple medications. An example of the potential impact of these interactions can be seen in a study of children with acute lymphoblastic lymphoma. In this study, more deaths occurred in children receiving phenytoin, a classic hepatic inducer. The cause of the higher death rate could be traced to increased metabolism of the standard chemotherapeutic regimen.[32] This is also a concern for younger individuals who might be on other commonly used medications that may require dose adjustments when enzyme-inducing antiepileptic drugs are employed, including statins, oral contraceptives, antidepressants, and antihypertensives.

Evidence for Treatment of Newly Diagnosed Seizures

For partial onset seizures in adults, carbamazepine, phenytoin, and valproate are the drugs that have the best evidence for efficacy.[28] Gabapentin, lamotrigine, oxcarbazepine, and to-piramate are also good choices, but the clinical studies documenting their efficacy in trials up to 1 year are weaker. Oxcarbazepine (OXC), topiramate (TPM), Lamotrigine (LTG), and Gabapentin (GPB) are all new drugs developed after 1980 and registered in the 1990s. More data are needed to determine whether these drugs will be equally effective with, but have fewer side effects than, the older AEDs.

For generalized tonic–clonic seizures the best evidence is for the older drugs as well. However, if the seizure syndrome

causing the tonic–clonic seizures is not known, then treatment with sodium channel blockers such as phenytoin and carbamazepine can unmask other seizure types such as myo-clonias and absence seizures.[20] Ethosuximide has demonstrated efficacy only for typical absence seizures. Lamotri-gine has been compared in a study with valproate for absence seizures,[12] and in this study valproate was slightly but not significantly more effective than lamotrigine at the end of 1 year.

Table 3 Spectrum of activity of new and old antiepileptic drugs

Drug	Partial	Secondary generalized	Tonic-clonic	Absence	Myoclonic
Phenytoin	+	+	+	-	-
Carbamazepine	+	+	+	-	-
Valproate acid	+	+	+	+	+
Phenobarbital	+	+	+	0	?+
Primidone	+	+	+	0	?+
Ethosuximide	0	0	0	+	0
Felbamate	+	+	?+	?+	?+
Gabapentin	+	+	?+	0	?-
Lamotrigine	+	+	+	+	+-
Topiramate	+	+	+	?	?+
Tiagabine	+	+	?	?	?
Zonisamide	+	+	?+	?+	?+
Levetiracetam	+	+	?+	?+	?+
Oxcarbazepine	+	+	+	-	-

Table 3 outlines the current understanding of the spectrum of activity of new and old AEDs.

First Add-On

When patients do not become seizure free on their first or second antiepileptic drug, options for treatment include add-on therapy or sequential monotherapy s bstitution. Substitution can involve the risk of worsening the condition, and sometimes physicians and patients opt to add a second drug. The concept of polytherapy, frowned on in the past, has gained renewed interest with the advent of new drugs with novel mechanisms and fewer drug interactions. Clearly, this is where the newer drugs are at a substantial advantage as compared to older drugs, which were subject to greater risk of side effects when combined, and, due to shared mechanisms such as sodium channel blockade, did not always provide added benefit.[35]

Although combining two drugs with novel mechanisms of action would theoretically provide a better potential for additive benefit, this has not been proven in any clinical study. Most of the new drugs have novel mechanisms, some of which are not elucidated. Even lamotrigine and oxcarbazepine, both of which have putative sodium channel action, may have additional, novel mechanisms and appear to enhance seizure control in patients already receiving other sodium channel blockers.

Drug–drug interactions are important to consider when combining drugs. Interactions can increase the risk of side effects and affect efficacy. The AEDs that have the most risk for interaction are those metabolized in the liver especially through the cytochrome P450 system.[17] The most important drugs with potential interactions are phenobarbital, phenytoin, carbamazepine, primidone, and to some extent topiramate and oxcarbazepine. Even valproate and lamotrigine can interact with each other. The drugs with least interactions, because they are not metabolized in the liver, are gabapentin, levetiracetam, pregabalin, and vigabatrin. These issues are discussed in detail in Chapter 110.

Pharmacodynamic interactions should also be considered. Pharmacodynamic interactions are said to occur when combining drugs causes more than additive toxicity or benefit in the absence of a change in serum concentrations. These can occur for a number of reasons, including similarity of side effects between coadministered drugs exceeding a “threshold” of tolerability (e.g., diplopia or dizziness) or the interaction of two drugs at their site of action in the central nervous system. The first is probably the explanation behind the pharmacodynamic interaction between lamotrigine and carbamazepine, and between carbamazepine and phenytoin. These combinations should probably not be used as a first choice. In some cases a drug combination might provide more benefit than either drug alone. Such a claim, as yet unproven, has been made for the combination of lamotrigine and valproic acid.[6] Some of the newer drugs, such as levetiracetam, gabapentin, and pregabalin, cause fewer pharmacodynamic side effects and seem to be particularly well tolerated as add-on therapy.

Refractory Patients

Refractory patients have been the subjects of study in most clinical trials of new AEDs. Once many drugs have failed, the primary concern is to find a highly efficacious drug. At this point, although side effects, drug interaction profiles, and frequency of dosing are important, they may take a back seat to the goal of seizure freedom. Unfortunately, none of the new AEDs has produced a high percentage of seizure-free patients in controlled trials of this population.[13] Often, seizure-free rates are not even supplied in reports of controlled clinical trials. Fifty percent seizure reduction rates, also called responder rates, are routinely provided. Responder rates have ranged from 15% to 50%.[13] For this reason, treatment of refractory epilepsy often incorporates nondrug strategies such as surgery and the vagus nerve stimulator. Despite less than optimal response even with the new drugs, a proportion of refractory patients are rendered seizure free with AEDs, and efforts at optimizing drug therapy should be continued as long as the patient is willing.

Special Groups

Children

It could be argued that AED selection in children is even more critical than for adults due to the potential for impact on the developing brain and on learning. In addition, children can present with quite different seizure syndromes and seizure types. Most drugs during clinical development are initially tested in adults. Drug trials in children are reserved for a later stage and are therefore less frequent and often involve fewer patients. For example, there are 25 randomized, clinical controlled trials for partial onset seizures in children, but only 3 have enough power to be considered as evidence for which drug should be used as initial therapy. The three trials for new-onset seizures were comparisons between clobazam and carbamazepine,[7] oxcarbazepine and phenytoin,[22] and to-piramate, carbamazepine, and valproate.[31] All of the aforementioned drugs were effective in treating children with partial seizures. Because of its potential to produce changes in bone metabolism and retardation of dental growth, phenytoin should probably be reserved as a second-line therapy. In the absence of pediatric data, physicians will begin to use the new AEDs based upon the data from adult clinical trials. Most likely efficacy will be the same as in adults, but the pharmacokinetics and side effect profiles are different in children, and that is why drugs need to be tested in children as well as adults. Children do not always behave like miniature adults. There can be unique tolerability and safety issues in children. Examples of safety issues include serious rash related to lamotrigine, which is more common in children under the age of 16,[21] and fatal hepatotoxicity related to valproic acid, which has an incidence of 1/37,000 in adults but is progressively more common with decreasing age. For children <2 years of age, the incidence is 1/500.[15] Less serious, but important to be aware of, are hypohydrosis with topiramate and zonisamide[19,26] and behavioral disturbance with gabapentin and phenobarbital.[24,38] It is of interest that phenobarbital tends to be sedating in adults but can cause hyperactivity in children. Similar paradoxical effects of the new AEDs might yet be uncovered. Cognitive disturbance caused by AEDs might be a more serious problem in children when it occurs at a critical learning and development stage.

Because of higher bioavailability in small children, the dose in milligrams per kilogram to reach a given concentration is usually higher. Nonetheless, it is usually prudent to start treatment with a low dose and successively increase it. Children with functional handicaps are more sensitive to AEDs and can develop unacceptable side effects at much lower doses than other patient groups, especially in the form of behavioral abnormalities and cognitive problems. Chapter 111 gives a fuller discussion of drug treatment in children.

Women

When treating women of childbearing potential certain considerations need to be made. Enzyme-inducing drugs such as carbamazepine, phenytoin, lamotrigine, oxcarbazepine, and topiramate (doses >200 mg/d) interact with the contraceptive pill and reduce its effectiveness. Sometimes the effect of the AED is reduced instead, as is the case with lamotrigine. High-dose estrogen contraceptive pills or gestagen preparations are more adequate choices in these patients. It is important for women to discuss appropriate contraception with their gynecologist.

Women on antiepileptic drugs should plan their pregnancies so that the treatment with the AEDs can be adapted if needed. In addition, folic acid should be given in doses of 1 to 5 mg/d. The neurologist should discuss pregnancy with patients who wish to have children and discuss especially the risk for teratogenicity as well as the risks of attempting to withdraw AED treatment prior to the pregnancy. It is the hope that the new AEDs will be less teratogenic than the older AEDs. A number of pregnancy registries are ongoing and should provide further information about the relative risks and benefits of each of the antiepileptic drugs. A prospective pregnancy registry specifically for LTG has provided reassuring data indicating that LTG in monotherapy does not seem to be more teratogenic than CBZ and maybe even less so.[39] This information provides reason for optimism, but it needs to be confirmed from the other ongoing registries. The risk for neural tube defects increases with treatment with valproate and carbamazepine. It is especially recommended that women who are treated with these AEDs take folic acid before the planned pregnancy.[40]

Women with epilepsy receiving AED treatment should be closely followed during pregnancy. It is not unreasonable to treat these pregnancies as high risk, and to refer women to high-risk obstetric care, if available. Monotherapy and the lowest possible dose of AEDs should be the goal of treatment. However, decreasing drugs at the risk of breakthrough seizures is a worse alternative.

So far the consensus is that women with epilepsy should be encouraged to breast-feed because the amount of AED that passes into breast milk is not deemed to hurt the infant. The evidence for this is, however, only at the level of expert opinion.

Chapters 109 and 113 discuss these issues and others related to treatment in women.

The Elderly

The incidence of epilepsy rises over the age of 65 years. Treatment of the older patient with epilepsy has specific challenges. As patients age, they undergo physical and psychosocial changes that affect AED choice.

Late-onset epilepsy tends to respond readily to antiepileptic drugs at low doses. Older individuals tend to have lower thresholds for development of side effects, particularly sedation, cognitive dysfunction, tremor, and gait disturbance. In addition, creatinine and hepatic clearance is reduced in individuals >65 years old. Therefore, lower doses are required for drugs that have full or even partial renal clearance. Other pharmacokinetic changes occur during the aging process as well. There may be an age-related reduction in serum albumin, increasing the free (active) fraction of highly protein-bound drugs such as phenytoin, carbamazepine, and valproic acid. In sum, it is prudent to select drugs with benign side effect profiles and initiate and titrate to lower doses than would be employed in a younger individual. It is optimal to begin at a low dose and slowly increase up to an effective dose, that is, the dose with best effect but few or no side effects. With some drugs, especially the older ones, the dose can be established with help of therapeutic drug monitoring by measuring serum concentration of the AEDs. This helps to prevent toxicity.

Two recent multicenter studies compared new epilepsy drugs to older drugs in the elderly population. In the first, carbamazepine was compared to lamotrigine in individuals with a mean age of 77 years. Efficacy was similar between the two drugs, but lamotrigine was better tolerated and produced fewer dropouts.[4] Only 18% of individuals dropped out in the lamotrigine arm, compared to 42% in the carbamazepine arm. These results were confirmed in a recent Veterans Administration Cooperative multicenter study in elderly patients with the first diagnosis of epilepsy, which compared carbamazepine, lamotrigine, and gabapentin. Again, carbamazepine was the least well tolerated, whereas efficacy was similar for the three drugs. Dropout rates were 27% for carbamazepine, 17% for gabapentin, and 10% for lamotrigine after 12 months.[33]

Older people often have other comorbidities and take medications for other diseases. Thus, interactions can be a problem, and their potential should not be forgotten. Common interactions occur with enzyme-inducing drugs such as phenytoin, phenobarbital, primidone, and carbamazepine. In the elderly, interactions with anticoagulants are of special importance. A good recommendation is to always read about interactions before choosing an AED. A rule of thumb is that when two drugs are metabolized by the same cytochrome isozyme, then there is surely a potential for interaction.[25] Drug treatment in the elderly is further discussed in Chapter 114.

Stopping Treatment

About half of the people with epilepsy have easy-to-control seizures. Many people with epilepsy can achieve long-term remission, and most can reduce or some even stop treatment with AEDs. In children it is possible to try to stop the medication after they have been seizure free for 2 years, whereas for adults the interval of seizure freedom before downtitrating an AED is 3 to 5 years. There are many factors that need to be addressed before recommending downtitration and ultimate cessation of an AED.[10] For one thing, stopping medication is a very individual decision and depends on each person's willingness to accept the possibility of seizure recurrence. This is the decision that should be made with both patient and physician input. For certain syndromes such as juvenile myoclonic epilepsy the risk for recurrence is great so the recommendation for that syndrome is usually to continue medication throughout life. EEG has a marginal importance for making the decision to stop medication. The risk for new seizures after stopping medication is about 35% overall.[10]

Single breakthrough seizures can be an expression of downtitration of a drug and should not cause the physician to necessarily reinstate the drug. Instead, slowing the rate of downtitration is usually the best methodology. In other words, the AED treatment should not be abruptly stopped, but instead it should be slowly decreased. Special care should be taken in downtitration with the older drugs such as clonazepam, phenobarbital, and primidone because these compounds are especially prone to cause withdrawal seizures when reduced. Stopping treatment is addressed further in Chapter 118.

If the treatment does not help

In spite of adequate treatment with AEDs and in spite of adequate compliance on the side of the patients, about 25% to 30% of patients develop refractory epilepsy.[27] If two or three AEDs in both monotherapy or in combination have not had any effect, it is important to refer the patient to a specialized epilepsy clinic for diagnostic reevaluation and for evaluation for potential epilepsy surgery, vagus nerve stimulation, and, for some children, ketogenic diet.

For small children the decision for referral should be made at an earlier date so that the child can obtain maximal treatment to try to prevent mental delay and other catastrophic problems in childhood.

Summary and Conclusions

Choice of antiepileptic drug therapy can have a profound effect on the course of a patient with epilepsy. Selection should be performed carefully and should be based on what is known about the patient coupled with an evidence-based understanding of AED characteristics. Thus, in treating a patient with epilepsy, the physician must weigh many factors in selecting the most appropriate AED and also in deciding when to go on to surgical evaluation and other therapeutic methodologies when the patient is refractory to two or three AEDs.

The National Institute of Clinical Excellence (NICE) guidelines from the United Kingdom are based on extensive cost–benefit analyses for the new AEDs, with the following conclusion:

> Although side-effect profiles of newer and older drugs were different, the Committee considered that the evidence was inadequate to support a conclusion that the newer drugs were generally associated with improved quality of life. The Assessment Group's cost-effectiveness analyses showed a high degree of uncertainty around the costs and benefits of these treatments.[23,28]

It is clear from these statements that more and better data are urgently needed so that the best possible decision-making can be undertaken and optimal quality of life can be achieved for patients with epilepsy.

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Chapter 118

Starting and Stopping Treatment

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Introduction

Although single seizures are common events—as many as 9% of the population have at least one seizure during their lifetime[56] epilepsy develops in only approximately one-third of these people. The decision to start antiepileptic drug (AED) treatment is, therefore, a difficult one. It must be based on the risk–benefit ratio, which depends on the psychosocial circumstances of the patient as well as various characteristics of the seizure disorder, including seizure type(s), epilepsy syndrome, and etiology (see Chapters 96,97,98). In addition, when the issue of starting treatment is raised, questions must be addressed regarding with which drug to use, and for how long (see Chapter 117). Which drug is chosen for treatment depends on the type of epilepsy. The risks of epilepsy and the potential benefits of drug treatment must be compared with the risk of adverse effects from the chosen drug. To improve compliance and avoid the perception of treatment "for life," which is so commonly anticipated by lay people, criteria for terminating treatment must be explained to the patient from the onset of treatment.

Evaluating the Need for Treatment

Many issues must be addressed after a first seizure (Table 1). Perhaps most important is the need to ascertain whether the event in question was indeed epileptic, or a nonepileptic event of physiologic (e.g., hypoglycemic, hypoxic) or psychogenic (e.g., pseudoseizure, "hysterical seizure") origin.

The decision to treat can be divided into three general categories: definitely treat, possibly treat, and probably not treat. These are summarized in Table 2. The clinical research supporting these decisions has been developed in a series of studies of adults and children.[4,5,7,14,16,17,36,54,56,57,73,89,106]

History and Examination

Obtaining a complete history is vital, although often difficult during the first contact. The details surrounding the event are crucial, and past medical history must be reviewed. Provoking factors, such as sleep deprivation, drug use, or hypoglycemia, and specific triggers, such as exercise,[81] hot water immersion,[94] or a history of stress or sexual abuse, must also be evaluated. In adolescence, it is important to determine whether the patient previously had overlooked minor seizures, namely myoclonus in the morning, or simple partial seizures. Some of this information may not be readily forthcoming until a good relationship with the patient has been established. A careful neurologic examination must be performed to determine the presence of Todd paralysis or a more permanent deficit. Screens to detect cardiovascular and metabolic disorders or drug abuse should be done as circumstances dictate.

Seizure Origin

Nonepileptic events must be identified (see Chapter 68). It is particularly important to recognize hyperekplexia and paroxysmal cardiogenic disorders (e.g., rhythm disorders, including prolonged QT syndrome, or pulmonary arterial hypertension), because both are treatable syndromes that may produce sudden unexpected death.[58,77,83,117] Slow waves on electroencephalogram (EEG) are a nonspecific abnormality and may be produced by migraine, breath holding, or syncope. Therefore, the EEG is more reliable in determining the type of epilepsy than in confirming the diagnosis of epilepsy itself.

Occasional seizures raise diagnostic issues. Seizures triggered by fever may range from simple febrile seizures to various kinds of epilepsy that range from benign to catastrophic, such as Dravet syndrome (see Chapter 230). Seizures triggered by photic stimulation, such as video games or television, require long-term treatment with AEDs only if the triggering features cannot be avoided.

If the evaluation leads to the conclusion that the seizure was caused by a transient or treatable disorder, AED treatment is not necessary. If the seizure is determined to be of cerebral origin, and no triggering factor is identified, the next step is to determine the risk for and possible consequences of a second seizure. These may differ considerably between individuals. For example, in some children who have benign partial epilepsy with central-midtemporal spikes, even the small risks associated with treatment may not be warranted, because most patients have only a few seizures before permanent remission occurs, and they cause no danger to the brain[40] (see Chapter 236). On the other hand, for adults working in some occupations, a second seizure could result in harmful consequences. Thus, a specific type of epilepsy should be determined based on seizure type, etiology, family history, and social context, but this may not always be possible when the patient is first seen. An EEG may need to be repeated once or several times, especially during infancy and childhood, and include recordings during sleep.

A number of structural lesions are associated with recurrent seizures, including tumors, cortical dysplasia, and vascular malformations. When these are diagnosed after a single seizure, drug treatment should be started without hesitation.

The recurrence risk for absence and myoclonic seizures is clearly higher than for other types of seizures, and patients referred for treatment usually have already had repeated seizures.

Table 1 Issues to be addressed after a single seizure

Was it a seizure?

Was it really the first seizure?

Are there risk factors for a second seizure?

  Abnormal EEG?

  Abnormal neurologic examination?

  Abnormal structural study?

  Sibling history?

Should the person be allowed to drive?

Should there be limitations on work?

What are the risks of not treating?

What are the risks of treating?

Table 2 When to start treatment with antiepileptic drugs after a single seizure

Definitely

With structural lesion

  Brain tumor, such as meningioma, glioma, neoplasia

  Arteriovenous malformation

  Infection, such as abscess, herpes encephalitis

Without structural lesion

  History of epilepsy in sibling (but not parents)

  EEG with definite epileptic pattern

  History of previous symptomatic seizure (seizure in the context of an illness or a childhood febrile seizure)

  History of previous brain injury, stroke, CNS infection, significant head trauma

  Status epilepticus at onset

Possibly

Unprovoked seizure with none of the above risk factors

Probably not (although short-term therapy may be used)

Alcohol withdrawal

Drug abuse

Seizure in context of acute illness (i.e., high fever triggering simple febrile seizure, dehydration, hypoglycemia)

Postimpact seizure (single seizure immediately after an acute blow to the head)

Specific benign epilepsy syndrome, such as benign epilepsy with centrotemporal spikes

Seizure provoked by excessive sleep deprivation (e.g., college student at examination time)

The indication for an anatomic brain imaging study must be considered, depending of the context (see Chapter 79).

An electroencephalogram (EEG) should generally be obtained as soon as possible after the seizure.

Pseudoseizures may be difficult to diagnose and require prolonged video-EEG monitoring.[19]

Modified from from Leppik IE. *Contemporary Diagnosis and Management of the Patient with Epilepsy*, 2nd ed. Newtown, PA: Handbooks in Health Care; 1996.

Provoked or Unprovoked Seizure

Another step in evaluating the need for treatment is to determine if a seizure was provoked or unprovoked. If a clear provoking factor, such as sleep deprivation or drug abuse, can be identified, the patient should be counseled to avoid the

precipitating stressors. However, a much more common situation is that in which the initial evaluation fails to reveal a specific cause or provoking factor. The risk for subsequent seizures must then be carefully evaluated. Data from clinical studies[11,16,17,51,54,56] in the last decade have identified specific risk factors obtained from a complete evaluation. These factors can help identify persons who are at higher risk for additional seizures.

Recurrence Risk

In children, the risk for seizure recurrence depends on the type of seizure, EEG characteristics, and cause of the seizure. When a first seizure has a remote etiology, the recurrence risk has been estimated to reach 65%. The presence of EEG abnormalities (44%) significantly increases the risk of recurrence.[106]

Type of Seizure

In the absence of a definable etiology, and with normal interictal EEG findings, the risk of recurrence following a first convulsive seizure ranges from 30% to 60% during 3 years; most seizures recur in the year following the first seizure.[11,56] The presence of EEG epileptiform activity increases the risk of recurrence to 60%[86] this rate is no different if spikes are generalized or focal (58% vs. 61%). Ambrosetto et al.[3] and Hamada et al.[49] found that a first seizure with rolandic spikes had a recurrence risk of 85% in the first year, but 71% of the patients had rare seizures (six or fewer). Seizures are usually simple partial. The clinical severity of a seizure usually has no prognostic value in children. For example, a single prolonged seizure with Todd paralysis and vomiting is often the only expression of benign occipital epilepsy, whereas so-called minor seizures often are seen in the most serious childhood epilepsies. The use of EEG in determining recurrence risk for convulsive seizures is valid for children and adolescents with generalized tonic–clonic seizures, but not for infants. Indeed, in patients with severe epilepsy beginning in the first year of life, interictal spikes may be lacking during the first 2 or 3 years of the disease.[25] On the other hand, 3% of school-age children without any history of seizures or cognitive troubles exhibit spike-waves.[18] These spikes tend to resolve spontaneously, and these children do not develop epilepsy. The incidence of spikes without epilepsy is even higher in children who suffer various types of cognitive troubles, including developmental dysphasia,[85] mental retardation,[9] and autism.[53] For all these conditions, any nonepileptic paroxysmal event that requires an EEG could therefore be misleading.

Other Risk Factors

In one study of adults and some teenagers,[56] the recurrence risk of all patients who had no previous history of an insult to the central nervous system (CNS) (idiopathic single seizure) was 10% at 1 year, 24% at 2 years, and 29% at 5 years. This group was evaluated for further risk factors. Family history was important: Among those who had a sibling with seizures, the recurrence rate was 29% at 1 year and 46% at 5 years, compared with 9% at 1 year and 26% at 5 years for those without a sibling having epilepsy. A history of seizures in parents or first-degree relatives in this study was not associated with a risk above that of others with idiopathic single seizures. Another important predictive factor was the EEG. Patients with a pattern of generalized spike-and-wave discharges had a recurrence risk of 15% at 1 year and 58% at 5 years, compared with 9% at 1 year and 26% at 5 years for those with a normal or nonspecific EEG pattern. Another important factor was the history of a previous acute symptomatic seizure; that is, a previous seizure in the context of an illness or a childhood febrile seizure. These persons had a risk of 10% at 1 year and 39% at 5 years. Age, sex, seizure type, abnormal EEG pattern other than

generalized spike-and-wave, and abnormal neurologic examination did not elevate the risk above others in the idiopathic group.[56] Another group in this study was categorized as *remote symptomatic*. These were patients with a history of head trauma, stroke, CNS infection, or static encephalopathy from birth, with mental retardation or cerebral palsy. These patients had a risk for a second seizure of 26% at 1 year, 41% at 2 years, and 48% at 5 years—markedly higher than the corresponding rates of 10%, 24%, and 29% in the idiopathic group. Within the remote symptomatic group, increased risk for recurrence was noted in those with Todd postictal paresis: 41% at 1 year and 75% at 5 years. If a previous symptomatic acute seizure occurred, the risk for a second seizure was 60% at 1 year and 80% at 5 years. If status epilepticus (SE) or multiple seizures occurred at onset, the recurrence rate was 37% at 1 year and 56% at 3 years.[56] Thus, persons with a previous history of CNS insult, a sibling with seizures, prior acute seizure, or an EEG pattern of generalized spike-and-wave discharge have a significantly higher risk of a second seizure than do patients without those risk factors. Most neurologists would treat these patients with AEDs.

Absence of Other Risk Factors

A more difficult decision arises in the case of patients with none of the additional risk factors, for whom the probability of a second seizure is less than 10% in the first year and approximately 20% by the end of 2 years after the single seizure.[56] Is this rate high enough to warrant the risks of treatment? There is no single answer to this question. The decision regarding whether to treat must be based on an evaluation by the patient and physician of the perceived risks and benefits. The risk of treatment with presently available AEDs is generally low. The risk of a second seizure depends on the lifestyle of the patient. In the case of those who need to drive, or for whom a second seizure may pose a significant risk of injury or loss of esteem, treatment may be indicated. There is a great need to emphasize patient choice and involvement in decision making here. The risk for recurrence is greatest in the first 2 years; thus, if treatment is initiated, it probably can be discontinued after the period of highest risk has passed.

Some brain lesions are clearly epileptogenic and occasionally produce severe epilepsy. However, it is often difficult to evaluate whether AED treatment has the ability to prevent epilepsy—particularly severe epilepsy—or the associated motor or cognitive deterioration.[63] Risk factors for epilepsy have been disclosed for both adults and children. In children, the risk for epilepsy following head trauma is increased when a focal cerebral lesion is evident, as indicated by focal neurologic signs, depressed skull fracture, or cerebral contusion on computed tomographic (CT) or magnetic resonance imaging (MRI) scan, and when seizures occur in the initial stage for more than 24 hours[60] (see Chapter 255).

Neurocutaneous Syndromes

The risk for epilepsy varies in different types of neurocutaneous syndromes. In Sturge-Weber syndrome, the first seizure often consists of SE in the first year of life, related to pial angioma, when the cutaneous angioma involves the first root of the trigeminal nerve.[37] Some authors advise prophylactic treatment from the neonatal period to prevent SE.[116] The question of prophylactic treatment arises with the detection of tuberous sclerosis in utero. The highest incidence of onset of epilepsy is in the middle of the first year of life. To date, no data are available to make any scientifically based decision.

Seizure-Related Risks

In terms of treatment, a number of factors must be considered. For an older adolescent or adult, the most important question is that of driving. In most situations, a single seizure is not considered grounds for restricting driving privileges, but the presence of epilepsy, as demonstrated by the occurrence of two or more seizures, subjects patients to numerous restrictions. Thus, some patients, after reviewing the likelihood of recurrence with their physician, elect to begin treatment after a single seizure. These decisions are difficult, and should never be made unilaterally by the physician for the patient. Rather, the patient should be aware of the risks and benefits of the alternative strategies, and the key elements of the decision must be recorded in the chart. In children, there may be less pressure to treat, and the side effect profile of certain AEDs may be less favorable than in adults.[17,106]

Seizure-related risks include sudden unexpected death, direct physical injury, vehicular accidents, brain damage, and psychosocial consequences.

Sudden Unexpected Death

Sudden unexpected death may occur in various situations (see also Chapter 189). Some data suggest that the risk is significant only for remote symptomatic epilepsy.[55] In a community-based study of mortality in children with epilepsy, Harvey et al.[52] found that mortality was not increased in idiopathic epilepsy compared with the general population. However, they found that, in symptomatic epilepsy, the risk of death was 50-fold higher. Gaitatzis et al.[40] concluded that life expectancy was reduced by up to 10 years. Other studies[69,79] suggest that “subtherapeutic” drug levels, mainly in adolescents with rare seizures and poor compliance, may precipitate cardiac arrhythmia or pulmonary edema. Therefore, the risk for death should not be a factor in the decision to start therapy, although the need for good compliance should be emphasized if treatment is initiated.

The risk for suicide is also higher in patients with epilepsy than in the general population, and some AEDs (i.e., phenobarbital) seem to contribute to this increase.[13]

Physical Injury

Falling during a seizure may produce various physical injuries, and patients may drown when alone, either in the bath or when swimming. In adults, the risk depends on the patient's usual activities and seizure type (e.g., if there is an aura, the patient may be able to anticipate and alleviate danger by shutting off the gas flame or water tap, or stopping the car). A survey of a nonselected series of 1,000 adults with epilepsy disclosed five severe head injuries, 22 fractures, and seven burns.[48] In a group of 138 children with epilepsy followed over a 10-year period, six patients sustained physical injuries caused by seizures, none of which produced sequelae.[122] Four of these injuries were the first manifestation of epilepsy.

The incidence of vehicular accidents resulting from epileptic seizures is difficult to estimate. In one population study,[50] the rate slightly exceeded that of the general population. In another series,[42] one-third of patients with epilepsy had seizures when driving, which produced accidents in half the patients. The type of seizure influences the risk for accident; a third of accidents involve seizures with an aura, and two-thirds of accidents involve seizures that lack an aura. Driving regulations vary from country to country.[65] Although a first seizure does not indicate epilepsy, in countries where efficient public transportation is not available, the risk for a second seizure may be considered sufficient reason to start treatment.

Brain Damage

Brain damage and sequelae from very brief seizures are very unusual, and prospective studies[34] have failed to demonstrate any brain damage from short seizures. Damage following SE seems to result mainly from the underlying cause of status.[75] The only exception is prolonged convulsive seizures with fever in infancy, because there is a significant risk of brain damage affecting the mesial temporal structures or the whole hemisphere.[2,101] The overall risk for development of SE in patients with newly diagnosed epilepsy is unknown, but it must be very small.

Psychosocial Factors

It is particularly difficult to evaluate the potential impact of drug treatment on the psychosocial consequences of recurrent seizures. The unpredictability of infrequent seizure recurrence can be extremely difficult for patients. Indeed, seizure control has been shown to be inversely related to self-esteem in adolescents.[57] For younger children, seizures that occur exclusively at home, primarily during sleep, usually have no psychosocial impact.

Cognitive Impact

Growing evidence suggests that continuous or nearly continuous spike activity that persists for months may produce cognitive impairment.[111] The type of cognitive dysfunction depends on age and the area of spike predominance: Speech is involved in Landau-Kleffner syndrome,[61,63] and frontal lobe functions may be affected adversely in epileptic encephalopathy with continuous spike waves in slow sleep (EECSWS).[55] Because overt seizure activity may be absent, the question of the epileptic nature of these conditions has long been disputed.[6] AEDs or steroids treatment clearly improve the cognitive course.[105] However, it may be difficult to distinguish such conditions from congenital cognitive disorders, such as dysphasia, in which the occurrence of spike activity on EEG is common. Whether they contribute to the genesis of cognitive dysfunction remains a matter of discussion.[31,32] The distinction between these two conditions is based on clearly deteriorated cognitive abilities.

Treatment Goals

This topic is also discussed in Chapter 98. Antiseizure therapy aims to prevent symptoms related to seizure recurrence. Treatment is predicated on the assumption that recurrent seizures can be prevented with adequate medication. Some studies show that AEDs may not clearly alter the recurrence rate, but this may be related to poor compliance[17,51,54] after an unprovoked first seizure. Only three major randomized studies have evaluated the efficacy of treatment to prevent recurrent seizures after a single seizure. In one study[89] 397 patients aged 2 to 70 years, who had had a single unprovoked generalized tonic–clonic seizure were randomized to receive treatment with an AED or remain untreated. The treated group had a calculated risk of seizure recurrence at 24 months of 25%, compared with 51% for the untreated persons. Thus, limited clinical studies and intuition would suggest that treatment may prevent some but not all patients from having additional seizures. A prospective randomized study[15] showed carbamazepine to be better than no treatment after a single unprovoked seizure in childhood. In a randomized controlled study of 1,443 patients, comparing immediate versus deferred treatment, there was significant delay of time lag to first and second seizure, and to generalized seizure in the immediate treatment arm, but the incidence of seizure freedom did not differ.[73] Despite excellent compliance, only 52% of children[16] and 38% of adults[74] became seizure-free in the first year of treatment.

The highest risk for recurrence occurs among patients with neurologic deficits and partial epilepsy. The most successfully treated patients are children with age-related idiopathic epilepsies[39] that will probably remit. However, it is most likely that this group is one for whom treatment is the least useful in preventing a chronic neurologic disease.

Antiepilepsy therapy aims at preventing both seizure recurrence and the development of epilepsy, particularly intractable epilepsy, as a chronic disease with cognitive and motor deterioration. Open data are conflicting in indicating whether early treatment may help prevent the development of chronic epilepsy in adults. Reynolds et al.,[91,92] Elwes et al.,[35] and Goodridge and Shorvon[46] have shown that the frequency of convulsive seizures tends to increase with time and that the likelihood of seizure control decreases with time. On the other hand, Hauser et al.,[54] Camfield et al.,[16,17] and Annegers et al.[5] found other factors, such as brain lesions, to be more predictive than early treatment. It is still not clear whether the kindling model or mirror foci have any correspondence in human epilepsy.[45] In West syndrome, early treatment may be antiepileptogenic and may prevent the development of pharmacoresistent epilepsy. A retrospective study of West syndrome caused by Down syndrome showed that early treatment significantly reduces the incidence of chronic epilepsy and major cognitive trouble.[33] This could apply to other childhood epileptic encephalopathies as well.

Pharmacoresistance

In some types of childhood epilepsy therapy, the development of intractability seems to be related partly to inadequate medication. The duration of absence epilepsy has been clearly reduced by changing therapy from barbiturates and phenytoin to valproate and ethosuximide.[24] Open data suggest that, in infantile spasms caused by tuberous sclerosis,[21] the risk for developing intractable generalized epilepsy has been greatly reduced by early treatment with vigabatrin. Although partial seizures persist in half the cases, major cognitive effects are prevented.[59] In infants, the highest risk for severe recurrence involves the early seizures,[2] which may produce hemiconvulsion–hemiplegia syndrome.[1,41] The usefulness of medical therapy cannot, therefore, be addressed in terms of an all-or-nothing result.

Frequent Seizures from Onset

Occasionally, seizures occur several times a day from the onset, particularly in children. Such conditions may be the first manifestations of various epileptic syndromes with a wide range of severity. Some are benign and last only a few days, particularly in newborns and infants.[86,118] Others may later prove difficult to treat, such as Lennox-Gastaut syndrome or myoclonic-astatic epilepsy (see Chapter 234). Although rapid aggravation may be sufficiently alarming to require immediate control of ictal events, it is often useful to determine the type of seizures on video-EEG, which helps to determine the optimal strategy for treatment.

Recurrent Seizures

In rare instances, particularly in children with benign rolandic epilepsy, seizures pose no risk of brain damage or seizure-related physical injury, and have a very moderate psychosocial impact. In such cases, many authors advise against treatment unless seizures become frequent enough to be annoying to the child and to have psychosocial consequences.[3]

Drug-Related Risks

Dose-related Side Effects

Normal dose-related side effects are specific for each given drug and involve 3% to 30% of patients. The highest risk is usually during the first weeks of treatment, especially for rash with carbamazepine or lamotrigine therapy. This is minimized by slow increases in dose[121] but may be challenging when the patient exhibits dozens of seizures daily. The administration of benzodiazepines or of a ketogenic diet[80] may protect the patient against the traumas due to frequent drop attacks during this escalating period.

Idiosyncratic Reactions

Normal idiosyncratic reactions to AEDs are unpredictable, occurring in 1 in 1,000 to 1 in 50,000 patients. They are specific to the drug administered. Although idiosyncratic reactions cannot be prevented, their severity can be reduced if physicians and patients are alert to the initial signs of the side effect. For example, knowing the first clinical signs of hepatic toxicity caused by valproate (vomiting, somnolence, and increased seizures) seems to have reduced the incidence of lethal cases, because the condition may be reversed with quick drug withdrawal.[62] An informational handout helps the patient or caregiver to recognize these symptoms early.

Proper choice of treatment is a crucial point. An inappropriate choice may precipitate new seizures or even new types of seizures.[67,110] Benzodiazepines may provoke tonic seizures[112]; carbamazepine may trigger or exacerbate myoclonic seizures[109] or atypical absences. Vigabatrin may precipitate myoclonic or absence seizures.[68] An experimental model in the newborn rat showed that this aggravation is not reversible.[87]

Withdrawal Seizures

Seizures may occur on withdrawal of AEDs. Although phenobarbital, carbamazepine, clonazepam, and vigabatrin are supposed to have the highest risk of producing withdrawal seizures, one structured study failed to confirm this.[20] This is a particular problem when drugs are changed during the course of epilepsy after a more accurate diagnosis has been obtained.

Choice of Drug

This topic is discussed more fully in Chapter 117. Once the decision to treat has been made, the most critical choice is which drug to prescribe. Factors that must be considered when choosing treatment are type of seizure, epileptic syndrome and etiology, and tolerability and price of the drug. Price is particularly relevant in regards to the newest generation of drugs, which cost three to five times more than second-generation drugs, and over ten times more than first-generation drugs. In most instances, monotherapy is preferred to polytherapy when treatment is initiated, because the benefits of polytherapy are only moderate[100] and clearly outweighed by the risk for toxicity and even a paradoxical increase in seizure frequency.[107] However, in epileptic encephalopathies with many daily seizures, polytherapy may be relevant from onset when any single medication is known to be ineffective and slow increase is requested, such as in myoclonic–astatic epilepsy.[80] The choice of drug must take into account pharmacokinetic characteristics: *absorption*, which is unpredictable for phenytoin and carbamazepine in the neonatal period,[84,90] and *half-life*, which is age-related, dropping abruptly at the end of the first month of life and then increasing progressively to adult values at 10 years of age. These affect the risk of withdrawal, which may be necessary in case of gastrointestinal problems in infants. Phenobarbital may therefore be useful in infancy, when the half-life is short. Phenobarbital can alter cognitive development in infants and children of school age,[38] thus most authors recommend valproate.[117] The short half-life is also relevant to the cognitive side effects of carbamazepine, because the epoxide–carbamazepine ratio is particularly high in infants.[66] Any suspicion of an inborn error of metabolism involving the urea cycle, β-oxidation, or the respiratory chain should prevent the use of valproate in infants unless no other compound is effective.[62,96] Vigabatrin can cause hyperkinesia in mentally retarded children,[27] and gabapentin may produce behavioral abnormalities.

Evidence is growing that, in infancy and childhood, AEDs are most efficacious when given according to specific epilepsy syndromes and etiology.[120] For example, when infantile spasms are caused by tuberous sclerosis, vigabatrin is significantly more effective and better tolerated than steroid treatment,[22] whereas steroids seem to be more effective than vigabatrin for cryptogenic cases[70,115] but with higher relapse risk.[71] Furthermore, in some cases, such as pyridoxine dependency, which produces agitation and multiple seizure types including myoclonus, partial fits, and spasms from the first hours of life,[78] specific treatment is required. However, syndromic diagnosis is often difficult to determine from the first seizures, particularly in the various generalized epilepsies of childhood.[29] In the absence of an accurate syndromic diagnosis, it is important to minimize the risk of worsening a condition through drugs. Thus, the treatment should be based on the seizure type. Results of clinical trials and extensive experience suggest that valproate is best for absence, myoclonic, and other generalized seizures and that carbamazepine is the best drug for seizures of partial onset. However, in infancy and childhood, the possible switch from partial to generalized epilepsy (i.e., to West syndrome or EECSWS; see Chapters 229 and 244) should be considered before carbamazepine is administered.

Partial Seizures

Prospective studies have failed to demonstrate any difference among phenytoin, carbamazepine, phenobarbital, and primidone in controlling secondarily generalized tonic–clonic seizures in adults. However, primidone and phenobarbital produce more troublesome side effects.[74] Carbamazepine was more successful than phenytoin in completely controlling partial seizures (43% vs. 26%).[74] Preliminary studies by Shakir et al.,[102] Wilder et al.,[119] and Turnbull et al.[113] showed no difference between valproic acid and phenytoin in treating partial seizures, but the former was better tolerated and produced fewer problems related to variable pharmacokinetics. Callaghan et al.[14] prospectively randomized patients with newly diagnosed epilepsy to carbamazepine, phenytoin, or valproic acid, and could not demonstrate any difference in terms of seizure frequency. No differences were noted between carbamazepine and valproate in the long-term control of seizures in adults,[93] although there was a trend to earlier control of partial

seizures with carbamazepine. This was interpreted by the authors to be a consequence of the slower escalation of valproate dose relative to carbamazepine.[114]

Primary Generalized Seizures

Primary generalized seizures mainly affect children and adolescents. Valproate seems to be the most valuable first-line drug, because it is effective in absence, myoclonic, and tonic–clonic seizures.[30] According to some authors, childhood absence seizures require treatment with ethosuximide, because the toxicity of valproic acid is higher in children than in adults, and absence seizures are usually the only type of seizure experienced by these patients.[97] The three major risk factors for hepatic fatality are infancy, polypharmacy, and mental retardation, none of which are an issue in childhood absence epilepsy.[26] Recent studies[62] do not report any case of valproate-induced liver failure in patients with childhood absence seizures, and this drug is widely used in Europe as first-line therapy for this population. Juvenile absence seizures are associated with a higher risk for later occurrence of generalized tonic–clonic seizures. Therefore, some authors[76] advise that valproate be used in treating juvenile absence epilepsy, because ethosuximide has been said to occasionally trigger convulsive seizures. However, this remains to be demonstrated.

Isolated tonic–clonic seizures are often the mode of onset of idiopathic generalized epilepsy. Because of the risk of carbamazepine triggering myoclonic seizures, valproate is usually preferred, even if the full-blown syndrome is not present.

Seizure Types that May Be Misleading

It must be emphasized that, in some instances, the type of first seizure may be greatly misleading. In children, atypical absence seizures may be caused by a syndrome of EECSWS, which responds poorly to valproate and may be worsened by lamotrigine[19] and requires treatment with benzodiazepines, ethosuximide, sulthiame, or steroids.[10,72,95] The same syndrome may be precipitated by carbamazepine given for a first seizure of partial benign epilepsy.[103] In infants, severe myoclonic epilepsy often begins with unilateral or partial motor seizures, and may be worsened by carbamazepine. In the first year of life, only patients with proven localization-related epilepsy (based on focal neurologic defect and neuroradiologic data) should be given carbamazepine.

Idiopathic generalized epilepsy with photosensitivity in children or adolescents may produce visual illusions (e.g., micropsia, macropsia), elementary hallucinations, or even partial motor seizures that are often considered to be an indication of partial epilepsy; these patients are erroneously given carbamazepine or phenytoin.[28] For childhood and adult cryptogenic partial epilepsies and for infantile, childhood, and adult symptomatic partial epilepsies, the drug of choice is a sodium channel blocker. Valproate is preferred in other cases, unless a precise syndromic and etiologic diagnosis indicates more specific compounds, such as vigabatrin for infantile spasms, benzodiazepines for EECSWS, ethosuximide for infantile absence seizures, or lamotrigine for Lennox-Gastaut syndrome. In other words, valproate is a wide-spectrum first-line drug, whereas other agents should be reserved for more specific indications.

Initiation of Treatment

Electroencephalogram

Before initiating treatment, an EEG should be performed, and it should include sleep studies. When clinical and EEG characteristics of an idiopathic epilepsy are present, no neuroradiologic investigation is required. In all other cases, and in most infants, radiologic investigation is indicated, usually before any drug treatment is given, because etiology disclosed by the result of radiology may contribute to the choice of drug.

EEG Spikes Without Seizures

In school-age children, spikes may be found on routine EEGs recorded for evaluation of various nonepileptic disorders, including headache and syncope, or following head trauma. Of nonepileptic children of school age, 2% to 3% may exhibit focal spikes or generalized spike-and-wave discharges; the risk for seizures in these children is very low—approximately 10%.[18,82] When seizures do occur in this population, they are usually benign. Therefore, there is no indication in asymptomatic patients to start treatment with AEDs simply because an EEG demonstrates epileptiform activity.

Blood Tests

Routine blood tests (complete blood cell count, liver function tests) should be obtained before treatment is initiated. In infants, clinical and biologic signs of inborn errors of metabolism should be sought. Valproate-associated hepatotoxicity is known to occur in patients with such disorders, but routine blood sampling, measurement of blood levels of AEDs, and repeated EEGs are usually not required for these patients unless clinical signs of toxicity develop.[15]

Adherence

From the beginning of treatment, an effort must be made to promote adherence. Each patient or caregiver should have a good understanding of the disease, the consequences of seizures, and knowledge of the potential side effects of drugs. Preferably, this information should be given to the patient both orally and in writing. Patients should also be urged to keep track of their seizures with a diary. To aid in adherence, an AED should be given once or twice a day, with midday administration avoided. Time of administration does not need to be strict, and the patient should never be awakened to take medication. Patients or caregivers must know that, if a dose is missed, it should be taken as soon as possible after this omission is noticed, provided it is noticed before the time of the next dose. Patients should also be informed about the duration of treatment, or the criteria for terminating treatment. A follow-up visit should be planned 4 to 6 weeks after initiating treatment to assess adherence, tolerability, and efficacy. Treatment may have to be changed or the diagnosis reconsidered at that point.

Termination of Treatment

The decision to stop treatment must be made as carefully as the decision to start. According to Schmidt and Gram,[99] treatment can be withdrawn when adults are seizure-free for 2 to 5 years or longer, and have a normal neurologic examination, normal IQ, and normal EEG. A number of studies have evaluated the recurrence rate of seizures after treatment has been

stopped following remission. In one study,[23] adult patients who had been seizure-free for at least 4 years were given the option of withdrawing from therapy. Of 62 patients who withdrew, 15 (24%) had recurrent seizures; of 157 who declined withdrawal, 10 (6%) had recurrent seizures. In another study,[88] 1,013 patients were prospectively randomized to withdrawal after being seizure-free for more than 2 years. Of those assigned to continuing treatment, 12% had seizures, compared with 41% in the slow withdrawal group. In general, factors leading to successful withdrawal were single seizure type, normal findings on neurologic examination, and normal findings on EEG.[88] One literature review of controlled trials comparing early (less than 2 years seizure freedom) versus late (over 2 years) withdrawal found seven eligible controlled trials for pediatrics but none for adults.[108] Early discontinuation was associated with partial seizures and an abnormal EEG. The pooled relative risk was 1.3 (95% confidence interval [CI], 1.02 to 1.7). In a meta-analysis regarding drug withdrawal in children, Berg and Shinnar[8] found a relapse rate at 1 year of 0.25 (95% CI, 0.21 to 0.30) and at 2 years 0.29 (95% CI, 0.24 to 0.34).

Risk factors statistically related to seizure recurrence in the 70 children of one study were greater than 10 seizures before seizure control, an abnormal EEG in the year before AED discontinuation, presence of focal neurologic signs and/or mental retardation, and presence of a mixed seizure pattern.[44] In one study of 264 children, Shinnar et al.[104] found on multivariate analysis significant factors in the idiopathic group, including age at onset above 12 years, a family history of seizures, the presence of slowing on the EEG prior to medication withdrawal, and a history of atypical febrile seizures, to be correlated to seizure relapse. In the remote symptomatic group, significant predictors of outcome included age at onset older than 12 years, moderate to severe mental retardation (IQ <50), and a history of atypical febrile or absence seizures.

The classical mantra of 2-year seizure-freedom before considering withdrawal has been challenged. Comparing relapse rate after 6 months versus 1 year of seizure freedom in a group of 154 children, Geerts et al.[43] showed that patients treated for 6 months had relatively more relapse (59%) than those treated for 1 year (51%). The issue is again that such studies should not pool different types of epilepsy. Indeed, the consequences of relapse following withdrawal are not the same with idiopathic or symptomatic epilepsy. Even if the relapse rate is high for focal idiopathic epilepsy, the consequences of a relapse are benign.

Reviewing 84 cases of postsurgical drug discontinuation, Schiller et al.[98] found that recurrence was facilitated by normal preoperative MRI, but postoperative EEG and seizure-free duration after surgery were not predictive of seizure outcome after AED withdrawal.

One question is the risk of intractable epilepsy following AED treatment withdrawal. One study followed 40 children who experienced relapse following withdrawal after 2 years of seizure freedom.[12] Half the relapses occurred within the first 6 months of withdrawal. No patient experienced SE. At the end of 5.9 years median follow-up, 40% were seizure-free for over 1 year without medication, 30% were seizure-free for over 1 year with medication, and 30% failed to be seizure-free for over 1 year. Age at onset (if over the age of 5) combined with normal intelligence was predictive of an excellent outcome.

Physicians are often poor judges of the degree of risk that is acceptable to a particular family, and individual families view estimates of seizure recurrence quite differently.[47]

Summary and Conclusions

An accurate clinical description of the seizure is mandatory to determine its epileptic nature and its type. It may be more devastating to omit therapy for treatable nonepileptic events than for epilepsy at the onset. Although interictal EEG must be used cautiously in the diagnosis of epilepsy in children, when combined with a seizure type and age of onset, it may permit a syndromic diagnosis.

A single seizure in adults or children usually does not require treatment unless there is evidence of a brain lesion or major abnormalities on the EEG, particularly generalized spike-and-wave discharges. However, a first nonfebrile seizure between 2 and 5 years may be the first manifestation of epilepsy of myoclonic–astatic type that will require vigorous treatment to prevent the development of SE or epileptic encephalopathy. On the other hand, rolandic spikes in children do not indicate the need for drug treatment unless seizures are frequent and upsetting to the family. If a second seizure would be hazardous to an adult, for reasons related to employment or driving, treatment may be warranted after a first isolated seizure, provided that excellent compliance can be anticipated and the seizure is not related to precipitating factors such as sleep deprivation.

The choice of drug is of the utmost importance and depends on the etiology of the seizures and the type of syndrome or, if the syndrome cannot be determined, the type of seizure. Specific syndromes require specific drugs, although valproate is often most suitable for children because it has a broad spectrum of activity and does not usually exacerbate seizures or lead to cognitive impairment. Children with a second seizure 1 or 2 years after the first may not require treatment. Cognitive deterioration associated with continuous spike-and-wave discharges in slow sleep requires treatment even if the patient has not exhibited an overt seizure.

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Chapter 119

Routine Monitoring for Safety and Tolerability During Chronic Treatment with Antiepileptic Drugs

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Introduction

The goal of epilepsy therapy is to control seizures completely without adverse drug effects. This objective is frequently compromised when complete seizure control cannot be achieved because of secondary drug toxicity.[25,26] Dose-related neurotoxic effects of antiepileptic drugs (AEDs) are bothersome, but with patient education they can be minimized and often tolerated. Part of good patient management is to establish a therapeutic alliance with active patient involvement. Toxic effects of drugs provide one endpoint, independent of blood level monitoring, to allow clinical titration to efficacy. However, idiosyncratic effects of drugs, although rare, may be life-threatening. Some have suggested that monitoring programs be established to detect patients at risk for serious systemic toxicity. For example, DeVries[6] proposed that regularly scheduled monitoring of drug blood levels should be embedded within a program of data collection that includes hematologic assessment, routine serum chemistry studies, and urinalysis. Pharmaceutical companies endorsed this approach by incorporating its elements within standard recommendations for drug use in publications in the United States (*Physicians' Desk Reference*[30]) and Canada (*Compendium of Pharmaceuticals and Specialties*[17]). For many clinicians, such reference sources have defined the medicolegal "standard of practice." In contrast, scientific criteria based on available evidence fail to support routine monitoring; such archival data rarely predict the occurrence of serious drug reactions. Although habits and practice vary both within the United States and in other countries, routine assessment of biochemical and hematologic function should at least be obtained at baseline.[28]

Adverse Effects and Standard of Care

When a drug is selected for use, the physician must review relative risks with the patient, and this discussion must be documented in the patient's record. This process of review and information exchange forms the basis for establishing informal informed consent. Patients must understand the goals of treatment, criteria that will be used to measure success, the process of trial and error in drug selection, and how drugs will be changed, if that becomes necessary. Common dose-related side effects are useful as an aid to management, but they also interfere with treatment. The process is one of negotiation. Patients must also know the nature of side effects, what may have to be tolerated, and how the physician will use side effects in the titration process. Serious, life-threatening, idiosyncratic effects of a selected drug should be reviewed clearly but within the context of rarity. Although patients must participate in an informed way in this therapeutic alliance and understand the need to report promptly should symptoms develop, it is the responsibility of physicians to identify those without advocates or with impaired ability to communicate. For these special patients, a specific monitoring strategy may have to be formulated, something that is not needed by most patients with epilepsy.

Packaging information refers to various side effects. *Frequent* adverse events are those occurring on one or more occasions in at least 1/100 patients; *infrequent* adverse events are those occurring in 1/100 to 1/1,000 patients; *rare* events are those occurring in <1/1,000 patients. Events of major clinical importance are described in the Warnings and Precautions sections.

Efficacy and adverse effects of drugs are important considerations in making treatment decisions, and legal actions from adverse effects have had important consequences on treatment, monitoring, and documentation of patient care.[46] Several classic legal cases involving AEDs have involved determinations of medical negligence in dosing and drug selection and questions about informed consent. The drug regulation process is described further in Chapters 142 and 143 on the roles of the U.S. Food and Drug Administration and European regulatory agencies, respectively.

Standards of care in the United States are derived from expert opinion, source publications, or referreed articles that form the basis for evidence-based medicine. Textbooks of medicine and published practice guidelines are another source for such information. In the United States, both the American Academy of Neurology and the Office of Quality Assurance and Medical Review of the American Medical Association publish treatment guidelines.

In medical malpractice or medical negligence cases, determining the standard of care for a particular treatment is of utmost importance.[46] Standard of care extends not only to treatment, but also to the methods used to obtain informed consent. In litigation, the standard of care is usually established by expert testimony using source publications or articles from refereed publications. One such reference source is the *Physician's Desk Reference* (PDR).[3,30]

As with any area of law in which states are given authority, there can be differences from state to state in the exact manner by which standard of care is determined. These differences are particularly evident with regard to the evidentiary force of the medication package insert and printed information contained in the PDR. States tend to use the PDR and package inserts in one of three ways. Although the differences are not categorical, it is nonetheless useful for educational and discussion purposes to consider them separately. In the first group are states that consider the PDR and package insert as establishing the standard of care [*Haught v. Maceluch*, 681 F.2d 291, reh'ing denied, 685 F.2d 1385 (5th Cir. 1985)].[3] In the second group are states in which the package insert and PDR are considered evidence of standard of care and deviation from the prescribed directions may establish a prima facia case for negligence. In such cases, however, a physician may generally introduce evidence to support his or her basis for using a medication in ways that deviate from the detailed description presented in the PDR and package insert (*Mulder* rule and echo of *Mulder*; see following discussion) [*Thompson v. Carter*, 518 So. 2d 609, 613 (Miss. 1987)]. In *Mulder v. Parke Davis and Co* [181 N.W. 2d 882 (Minn 1970)], the court held that any deviation in drug use from that specified in the PDR requires a physician to explain the reason for that deviation. This requirement is now known as the *Mulder* rule. In light of this, it would seem prudent for the physician who plans to use a drug in ways that vary from recommendations in the PDR or package inserts to record the reasons for doing so and the relevant plan for management in the medical record. In the third group of states, the PDR and package insert as such are given little credence and, in some jurisdictions, are inadmissible without supporting expert testimony. This is known as the “echo” of the *Mulder* rule. [*Spensieri v. Lasky,* 723 N.E. 2d 544 (NY 1999)].[3]

Legal action has also involved issues of informed consent. In *Serigne v. Ivker*, a plaintiff alleged that informed consent had not been obtained because of lack of disclosure of teratogenicity. The court found that the plaintiff had failed to establish a connection between malformations and phenytoin and that informed consent did exist [*Serigne v. Ivker*, 808 So. 2d 783 (La. App. 4 Cir. 2002)]. In the case of *Spano v. Bertocci* [299 A.D. 2d 335, 749 N.Y.S. 2d 275 (N.Y.A.D. 2002)], the plaintiff claimed lack of informed consent based on failure to disclose the teratogenic effects of valproic acid. Trial and appellate courts found that informed consent had been obtained because of the plaintiff's previous knowledge regarding the dangers involved in using valproate during pregnancy.[46]

One landmark decision illustrates the diligence required to provide information for patients with child-bearing potential is well illustrated. In *Harbeson v. Parke-Davis*, claims of failure of informed consent causing wrongful birth and wrongful life were the cause for action when a woman delivered children with fetal hydantoin syndrome. In this case, the court stated that the physicians had a duty to “exercise reasonable care in disclosing ‘grave risks’ of (any) treatment” that they were advocating. Apparently, the physician had failed to do a literature search that would have uncovered the dangers of using phenytoin during pregnancy, and had this been done, it would have allowed the physician to inform the patient [*Harbeson v. Parke-Davis*, 656 P. 2d 483 (1983)].[46]

Serious skin reactions, including Stevens-Johnson syndrome, have also raised issues of informed consent. In *Shinn v. St. James Mercy Hospital*, the plaintiff claimed that disclosure of serious skin reactions to phenytoin had not been provided. In this case, the court stated that it is not necessary to disclose all adverse effects to a patient, but rather only the most common ones. The court also found that given the patient's particular medical circumstance, the patient would not reasonably have declined treatment even if adverse effects had been delineated. [*Shinn v. St. James Mercy Hospital*, 675 F.Supp 94 (W.D.N.Y. 1987)]. Similarly, in *Williams v. Ciba-Geigy Corporation*, the court found that the warnings in the PDR and package insert diminished the “danger-in-fact” of the medication. The court stated “no reasonable trier of fact could conclude that this …medicine is unreasonably dangerous per se” [*Williams v. Ciba-Geigy Corporation*, 686 F. Supp 573 (W.D.La. 1988)].[46]

Documentation is critical. In *Fritz v. Parke Davis & Co.* a patient treated with phenytoin developed hepatic failure. At trial, the court originally found for the plaintiff. On appeal, that decision was reversed. The appellate court stated, “Viewing the record …the skill and care exhibited by defendant's physicians' diagnosis and treatment were marked by devoted diligence and attention and were wholly consistent with the professional skill …employed by other physicians in treating and controlling …the complex disease of epilepsy” [*Fritz v. Parke Davis & Co.*, 152 N.W. 2d 129 (1967)].[46]

Errors in the use of AEDs that amount to negligence have been the basis of litigation. In *Hendricks v. Charity Hospital of New Orleans*, a patient was to receive Dilantin 500 mg/d, but a prescription was written for 500 mg three times a day. Judgment was for the plaintiff. [*Hendricks v. Charity Hospital of New Orleans* 519 So. 2d 163 (La. App. 4th Cir. 1987)]. High plasma levels of Dilantin were associated with a patient's death, and judgment for the plaintiff occurred in this case as well [*Martin v. Life Care Centers of America Inc.* (No. 95-4124-B, 117th Judicial Dist. Ct. Nueces County, TX, April 1998)]. One court found for the plaintiff in a case of failure to diagnosis pancreatitis associated with the use of valproate [*Pester v. Graduate Hospital* (No. 87-05-00357, Court of Common Pleas, Philadelphia, PA Oct 1992)].[46]

Monitoring Blood Levels of Antiepileptic Drugs

There can be no question that therapeutic drug monitoring has been a major advance in helping to determine compliance, compensating for physiologic (age, pregnancy) or disease-related (uremia, hepatic failure) alterations in drug pharmacokinetics, and avoiding undesirable drug interactions (see Chapter 103). In general, however, routine blood level determinations are performed too frequently and often without a specific question in mind. It is important to remember that drug levels must be interpreted in light of a patient's clinical progress. In the clinical setting, therapeutic effectiveness is best judged by two measures: (a) seizure frequency and (b) the appearance of adverse effects. All too often, however, the blood level, rather than the patient, becomes the goal of treatment: therapy must be optimal if a drug's blood concentration is in the "therapeutic range." This oversimplified view can have undesirable consequences. For example, it is not uncommon for low or "therapeutic" blood levels to be cited as evidence against a patient's complaint of side effects. Conversely, drug dose is frequently reduced because of a "toxic" level, even if there has been good seizure control and no indication of adverse reactions. Finally, meaningful interpretation of blood levels requires knowledge about the timing of a blood sample, the dosing schedule, the interval since the last dosing change, and the clinical situation with

regard to complaints about possible side effects and seizure frequency.

Laboratory Monitoring During Chronic Antiepileptic Drug Treatment

Indications for Routine Laboratory Testing

Physicians should perform baseline studies before the initiation of AED treatment (Table 1). There are two main reasons for this. First, they may help to identify previously unsuspected illness. Second, availability of baseline laboratory data in the medical record provides a basis for comparison with subsequent laboratory studies, especially those obtained because of developing symptoms.

Table 1 Blood monitoring in patients with epilepsy

Routine
CBC, differential, platelet count
Serum chemistry: glucose, BUN, electrolytes, calcium, phosphorus, magnesium, creatinine, urate, iron, cholesterol, bilirubin, alkaline phosphatase, AST, ALT, total protein, albumin, globulin
PT, PTT
High-risk patients
Lactate, pyruvate, arterial blood gases
Urinary metabolic screen: organic acids
Ammonia
Carnitine
Specific tests for suspected underlying disease

ALT, alanine aminotransferase; AST, asparate aminotransferase; BUN, blood urea nitrogen; CBC, complete blood cell count; PT, prothrombin time; PTT, partial thromboplastin time.
Source: From Pellock JM, Willmore LJ. A rational guide to routine blood monitoring in patients receiving

antiepileptic drugs. *Neurology.* 1991;41:961–964; with permission.

Two prospective studies have evaluated the efficacy of routine blood and urine screening in patients being treated long term with AEDs. Camfield et al.[4] performed blood and urine testing in 199 children to evaluate liver, blood, and renal function at initiation of therapy and at 1, 3, and 6 months. The screening studies continued to be repeated every 6 months thereafter. There were no serious clinical adverse effects in the patients treated with phenobarbital, phenytoin, carbamazepine, or valproate. In 6% of children, studies were repeated because of abnormal but clinically insignificant results, and in 2 children therapy was stopped unnecessarily. The authors concluded that routine monitoring provided no useful information and sometimes led to unnecessary responses. A second study of 662 adults treated with carbamazepine, phenytoin, phenobarbital, or primidone failed to detect significant abnormalities in laboratory data during 6 months of monitoring.[23] The authors concluded that routine screening was neither cost-effective nor of significant value for asymptomatic patients. In a double-blind, controlled trial, exposure of 480 patients to either carbamazepine or valproate failed to demonstrate the usefulness of routine laboratory monitoring.[22]

After baseline assessment, laboratory tests should be repeated only to answer specific questions. “Routine” blood monitoring is both costly (estimated at >$400 million/yr in North America in 1998) and ineffective in avoiding serious toxicity.[5] The assumption that hepatic failure, aplastic anemia, or other severe drug reactions can be averted by frequent blood tests is not supported by scientific data.[5,28] A case can be made that asymptomatic patients on monotherapy do not require regular blood tests if initial screening laboratory studies were negative. On the other hand, it is important to try to identify patients, at onset of therapy, who are at increased risk for adverse drug reactions. These include patients with known or suspected metabolic or biochemical disorders, a history of previous drug reactions, and medical illnesses affecting hematopoesis or liver and kidney function. Blood monitoring is also indicated in young children receiving polytherapy that includes valproate (see later discussion) and in patients who are unable to communicate symptoms and their health status effectively.

Common Laboratory Findings

Minor elevations in liver aspartate aminotransferase (AST or SGOT) and alanine aminotransferase (ALT or SGPT) occur in about 25% to 30% of patients with epilepsy, and these neither correlate with clinical symptoms nor predict development of hepatitis or liver failure.[22,23,28] Glucose tolerance test (GTT) levels seem to be particularly useless as indicators of clinically significant liver dysfunction in persons with epilepsy.[15] Although routine monitoring of measures of he-patic function have revealed elevated liver enzymes in 5% to 15% of patients treated with carbamazepine, <20 patients with significant hepatic complications were reported in the United States from 1978 to 1989.[38] There were even fewer reports of carbamazepine-induced pancreatitis.

Nearly 20% of patients taking carbamazepine develop a benign leukopenia, as indicated by white blood cell (WBC) counts <4,000/mm.[12,24] A few patients will have WBC counts that drop transiently below 2,500/mm.[12] The risk of developing aplastic anemia is not increased in this group, and such patients do not have increased rates of infections or other possible complications that might be attributed to leukopenia. Leukopenia is less common with oxcarbazepine.[15]

Table 2 Idiosyncratic reactions to antiepileptic drugs

Reaction	CBZ	ETH	FBM	GBP	LEV	LTG	PGB	PB	PHT	TPM	TGB	OXC	ZNS	VPA
Agranulocytosis	X	X	X					X	X					X
Stevens-Johnson syndrome	X	X				X		X	X					X
Aplastic anemia	X	X	X						X					X
Hepatic failure	X		X					X	X					X

Allergic dermatitis	X	X	X	X		X		X	X	X	X	X	X	X
Serum sickness	X	X						X	X					X
Pancreatitis	X								X					X

CBZ, carbamazepine; ETH, ethosuximide; FBM, felbamate; GBP, gabapentin; LEV, levetiracetam; LTG, lamotrigine; OXC, oxcarbazepine; PB, phenobarbital; PGB, pregabalin; PHT, phenytoin; TBG, tiagabine; TPM, topiramate; VPA valproate; ZNS, zanisamide.
Source: Modified from Willmore LJ, Pickens A, Pellock JM. Monitoring for adverse effects of antiepileptic drugs. In: Wyllie E, ed. *The Treatment of Epilepsy*. Philadelphia: Lippincott Williams & Wilkins; 2006:735–745.

Hyponatremia (<135 mEq/L) is less common in patients taking carbamazepine than in those taking oxcarbazepine,[43] in whom the incidence was 2.5% in controlled trials, but was higher in subsequent studies, especially in the elderly.[11] However, only 2.5% of patients have serum sodium values <125 mEq/L, the level at which symptoms usually start to appear. Most patients are asymptomatic.

Life-threatening Syndromes

Although dose-related toxicity is both common and also useful as a target in titration to efficacy, drug-induced diseases are rare. Nearly all the commonly available AEDs are associated with idiosyncratic reactions (Table 2). Severe adverse reactions include aplastic anemia, agranulocytosis, hepatitis, pancreatitis, exfoliative dermatitis, and bullous skin reactions. The frequency of these reactions varies with each drug, the number of concomitant drugs, age and general health of the patient, and the presence of genetic metabolic and immunologic disorders. Monitoring plans should take into account the rarity and unpredictability of life-threatening reactions, most of which have a frequency of <1/50,000 (see later discussion).[37]

Aplastic anemia or agranulocytosis occurs in 2/575,000 patients, with a mortality rate of approximately 1/575,000 treated patients per year.[38] Only 4 of the 65 cases of agranulocytosis or aplastic anemia occurred in children. A similar epidemiologic picture is noted with felbamate-associated aplastic anemia. No blood or urine test clearly defines persons at risk. Young age tends to be protective, whereas previous exposure to AEDs (and perhaps other drugs), hypersensitivity/idiosyncratic reactions, cytopenia, history of autoimmune disorder (especially lupus erythematosis), and <1 year of treatment are risk factors.[26,27]

Patients developing drug-related hypersensitivity syndrome do so early in treatment using aromatic AEDs.[10] Cross-hypersensitivity between phenytoin and carbamazepine is well recognized,[31,32,40] and a history of prior hypersensitivity to other drugs is a risk factor for lamotrigine-associated rash[13] and felbamate-related aplastic anemia.[27] The AED hypersensitivity syndrome includes rash (which may or may not be pruritic), fever, eosinophilia and, sometimes, lymphadenopathy, exfoliative dermatitis, facial edema, and multivisceral involvement including life-threatening hepatic necrosis.[21,36] The DRESS syndrome (drug rash with eosinophilia and systemic symptoms) is caused most often by AEDs and is probably synonymous with anticonvulsant hypersensitivity syndrome.[1,29] Hypersensensitivity reactions are immune-mediated responses in persons susceptible to such effects.[20,21,31] Although treatment remains controversial, everyone agrees that administration of suspected AEDs should be stopped immediately.[10,12,22]

Table 3 Hepatic fatality rates associated with valproate

	1978–1984		1985–1986	
Age (yr)	**Polytherapy**	**Monotherapy**	**Polytherapy**	**Monotherapy**
0–2	1/500	1/7,000	1/800	0

3–10	1/6,500	1/9,000	1/7,000	1/21,000[a]
11–20	1/11,500	0	0	0
21–40	1/16,500	0	0	0
41+	1/38,500	0	0	0
Overall	1/6,500	1/37,000	1/20,000	1/118,000

[a] One fatality occurred in 1985 and was reported in 1988.

Source: From Dreifuss FE, Langer DH, Moline KA, et al. Valproic acid hepatic fatalities. II. US experience since 1984. *Neurology*. 1989;39:201–207; Dreifuss FE, Santilli N, Langer DH, et al. Valproic acid hepatic fatalities: a retrospective review. *Neurology*. 1987;37:379–395; and Pellock JM, Willmore LJ. A rational guide to routine blood monitoring in patients receiving antiepileptic drugs. *Neurology*. 1991;41:961–964, with permission.

Identification of High-risk Patients

Although the mechanisms are not yet fully understood, there is growing evidence that rash and hypersensitivity syndromes are related, at least in some cases, to pharmacogenetic variation in drug biotransformation.[39] This is discussed more fully in Chapter 106. A genetic abnormality in arene oxide metabolism may be present in patients at higher risk for some types of adverse responses, such as hepatitis,[41] but a screening test for such defects is not yet available. In patients in whom exfoliative dermatitis developed alone or as part of systemic hypersensitivity, abnormal blood test results were not found until clinical symptoms developed.[39] At this time, routine monitoring, as commonly practiced, does not allow anticipation of life-threatening effects associated with treatment using carbamazepine, phenytoin, or phenobarbital.[37]

Dreifuss et al.[7,8] emphasized the importance of identifying high-risk patients before instituting treatment with valproate. Most fatalities occurred in the first 6 months of treatment, but hepatotoxicity developed in some patients up to 2 years after valproate was started. In children <2 years of age who were receiving polytherapy, the risk for fatal valproate hepatotoxicity was 1/500 to 1/800. Negative predictors were identified as well. Patients treated with valproate alone were at negligible risk if they were >10 years of age and did not have indications of underlying metabolic or neurologic disorders. Children at intermediate risk were between the ages of 2 and 10 years on monotherapy, as were all patients requiring polytherapy. The risk for fatal valproate hepatotoxicity continued to decline with increasing age, even with polytherapy, after the first decade of life (Table 3).

The majority of patients with fatal valproate-related hepatic failure have had neurologic abnormalities, including mental retardation, encephalopathy, and decline of neurologic function. Two of four patients >21 years of age had degenerative diseases of the nervous system.[7,8] Another report found that 9 of 16 cases of hepatic fatality had neurologic abnormalities.[35] When patients were divided into groups by age at the time of fatal reactions, no statistically significant pattern of vulnerability was revealed. However, in one series, all patients in the 11- to 20-year age group were neurologically abnormal.[8] Specific biochemical disorders associated with valproate hepatotoxicity include urea cycle defects, organic acidurias, multiple carboxylase deficiency, mitochondrial or respiratory chain dysfunction, cytochrome *aa*$_3$ deficiency in muscle, pyruvate carboxylase deficiency, and hepatic pyruvate dehydrogenase complex deficiency in brain.[14,18,34,47] Clinical disorders associated with valproate toxicity include GM$_1$ gangliosidosis type 2, spinocerebellar degeneration, Friedreich ataxia, Lafora body disease, Alpers disease, and myoclonic epilepsy with ragged-red fibers (MERRF) syndrome.[42] Valproate should be avoided in patients with such disorders because of the increased risk of hepatotoxicity.

At this time, high-risk patients must generally be identified by clinical assessment. Medical history, health status at the initiation of AED treatment, and both patient and physician awareness of clinically important symptoms and signs are more likely to suggest the need for further evaluation. Clinical monitoring, although not perfect, is superior to routine laboratory screening.[44,45] A modification of recommendations regarding routine monitoring has been suggested by the Canadian Association for Child Neurology.[5]

Although it has been the practice of most clinicians to order screening studies routinely, the key to treatment monitoring is patient and parent education and counseling. Everyone involved with a patient must be aware of potential complications and the symptoms that might herald the occurrence of a serious adverse event. Furthermore, physicians must be willing to evaluate patients on an urgent basis when changes are reported that suggest the development of significant adverse drug reactions. Such symptoms include bruising, bleeding, rash, abdominal pain, vomiting, jaundice, lethargy, coma, and deterioration in seizure control. Deterioration of seizure control or marked shortening of seizure-free interval is a cause for review of treatment and survey for the presence of adverse drug effects. The development of any of these potentially ominous symptoms is the best indication for deciding whether laboratory evaluation is needed.

Monitoring Strategies for New Drugs

As new drugs are developed and marketed for treating patients with epilepsy, physicians have an obligation to review source documents and devise a strategy for treatment and monitoring. Treatment indications arise from trials involving selected patients. Age ranges are defined, epilepsy syndromes and seizure types are identified, and patients with associated illnesses are generally excluded. Protocols typically expose limited numbers of patients to the protocol drug for a finite period. During such studies, patients undergo intense scrutiny to identify treatment-related symptoms or adverse effects. These restricted study designs and relatively small numbers of patients may fail to uncover drug interactions or recognize serious adverse effects. Reference should be made to individual chapters concerning specific AEDs for a discussion of specific idiosyncratic life-threatening adverse effects.

Because data are limited, initiation of treatment with a newly available drug requires special caution. Although the process of informed consent remains informal, it is more important than ever to give patients as much information as possible. Industry-produced materials may be useful, and physicians should consider providing copies of package inserts supplemented by material they themselves prepare describing how the drug is to be used and any monitoring strategy planned. Although the guiding principle in monitoring patients being treated with established drugs should be to limit use of routine chemical and hematologic studies, based on evidence that such monitoring is ineffective in detecting the occurrence of serious adverse events, the principle may need to be modified with a newly introduced drug, depending on the information available. The following approach may be useful. As with the established drugs, baseline laboratory data should be obtained. Communication is essential, and the patient and/or family must agree to keep the physician informed, and the physician must facilitate such communication. Company inserts and Food and Drug Administration advisories or requirements may specify chemical and hematologic monitoring. Although recommendations may seem excessively conservative, it is best to follow such guidelines until a larger experience has been obtained and postmarketing data become available. This admonition is best illustrated by the experience reported following introduction of felbamate and, more recently, vigabatrin. Only following the initial reports of visual filed deficits associated with vigabatrin administration did formal programs identify the typically asymptomatic visual disturbance that occurs in approximately 40% of children and adults treated chronically.[2] Clinicians should provide patients with symptoms and signs of significance, such as a flu-like illness, abnormal bruising or bleeding, changes in urine color, or any type of skin rash. Emphasis should be on reporting these promptly. Any skin rash occurring during treatment with an AED should be evaluated, carefully and without delay, especially if it occurs within the first 4 to 6 weeks of treatment. The AED should be discontinued at the first sign of rash, unless the rash is clearly not drug related. The vast majority of drug-induced skin rashes are benign and resolve after the drug has been stopped. Only rarely do rashes evolve into full exfoliative reactions including Stevens-Johnson syndrome or toxic epidermal necrolysis. However, when a patient first develops a rash, there are no specific indicators that allow distinction between benign and serious conditions. If there is any indication of mucous membrane involvement, blistering, arthralgias, adenopathy, fever, facial swelling, or exfoliative lesions, the patient should be seen immediately. Rechallenge with an AED after a presumed drug rash is not recommended.[9]

Summary and Conclusions

Recommendations for routine monitoring for safety and tolerability during chronic treatment with antiepileptic drugs must be individualized for patients. Screening laboratory studies should be obtained before initiation of AED treatment as part of the diagnostic evaluation. Data are unavailable regarding the yield of such testing, but baseline studies provide a benchmark and

can identify patients with special risk factors that could influence drug selection. Ongoing blood and urine monitoring in otherwise healthy and asymptomatic patients being treated with AEDs is not necessary. Patients should be advised of specific symptoms possibly associated with toxicity of the prescribed AED, and testing should be done dependent on the appearance of these clinical symptoms. High-risk patients must be identified at the inception of treatment. These patients include those with presumed biochemical disorders, altered systemic health, neurodegenerative disease, or a history of significant adverse drug reaction such as idiosyncratic or hypersensitivity reactions in the past. Monitoring must be designed based on the specifics of the clinical situation. Patients without an advocate or those unable to communicate require a different strategy. Because of communication difficulties or the nonspecific behavior that may be associated with an adverse effect, these patients may well need testing because of a change of their behavior. Although data are unavailable, blood monitoring should be obtained for patients with multiple disabilities who are institutionalized. Monitoring should include basic studies of hematology and chemistry with additional studies as required by the patient's clinical situation. The exact frequency of this clinical monitoring is undetermined. Both clinical monitoring and blood monitoring must be performed. When a patient is being treated with a newly available drug, detailed information must be provided to the patient or the caregiver, just as with established AEDs. Recommended guidelines for blood or other clinical monitoring should be followed until the numbers of patients increase such that data become available to establish whether a given individual falls within a high-risk group. The sharing of information between patient and medical caregivers and communication regarding possible adverse effect are the most important aspects of monitoring for safety and tolerability during chronic treatment with antiepileptic drugs.

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Chapter 120

Rapid Substitution of Antiepileptic Drugs

Blaise F. D. Bourgeois

Introduction

In general, substituting one antiepileptic drug for an other is a relatively slow process that is carried out over several weeks or months. The main reasons for this time frame are the fear of seizure exacerbation resulting from withdrawal of the first drug while the introduced drug is not (or not yet) protective, as well as the fear of side effects associated with rapid introduction of the new drug. However, there are reasons, besides avoidance of unnecessary delays, why it may be desirable to substitute antiepileptic drugs rapidly in some circumstances. One such circumstance is an acute reaction to a drug, such as a severe idiosyncratic adverse effect. In addition, in a patient who is already in the hospital for a seizure exacerbation, it might be desirable to complete a substitution rapidly before discharge and send the patient home on a new drug regimen at therapeutic levels. An additional reason might be the establishment of pharmacoresistance in a potential candidate for epilepsy surgery. The process of establishing pharmacoresistance should be as short as possible for several reasons. First, if the patient's condition is not truly medically intractable, the successful therapeutic step will occur sooner. Second, in a patient who becomes seizure free after surgery, the overall long-term outcome is likely to be better if the surgery is performed earlier. Finally, a patient might already have been referred to a specialized center for epilepsy surgery but not yet meet acceptable criteria of medical intractability, and one additional adequate drug trial needs to be completed as rapidly as pos-sible.

Some clinical experience has been accumulated with the mutual substitutions of several established antiepileptic drugs, mostly in adult patients with focal onset seizures. In many instances, the substitution can be completed within about 5 days. This chapter describes the clinical experience with rapid introduction of carbamazepine, phenytoin, phenobarbital, and primidone, along with the concomitant rapid discontinuation of another drug within this group. Although the rapid replacement of valproate by carbamazepine, phenytoin, phenobarbital, or primidone is easy, the experience with rapid changes from one of these drugs to valproate monotherapy has not been favorable in patients with focal-onset seizures. Less experience has been acquired with the corresponding rapid changes in children, and no systematic observations have been reported about rapid changes involving the newer antiepileptic drugs.

When one antiepileptic drug is replaced by another within a short time, two issues require particular attention: (a) A therapeutic level of the drug to be introduced must be achieved as rapidly as possible and must then be maintained so as to allow rapid discontinuation of the previous drug, and (b) it must be anticipated that any pharmacokinetic interaction between the two drugs will be reversed after discontinuation of one drug. Therefore, rapid drug changes require an understanding of how rapidly a given drug can be introduced, as well as a qualitative and quantitative knowledge of the effect the drug being taken by the patient will have on the pharmacokinetics of the drug to be introduced. These rapid drug changes also require a good level of experience with antiepileptic therapy and appropriate supervision of the patient during the process.

Introduction of Carbamazepine

When carbamazepine is to be introduced rapidly to replace another antiepileptic drug, three points need to be considered: (a) the fact that levels of carbamazepine in the usual therapeutic range are not tolerated during the first days of treatment, (b) the autoinduction of carbamazepine metabolism, and (c) the potential for induction of carbamazepine metabolism by other drugs. For example, if carbamazepine is to be introduced to replace phenytoin, which markedly accelerates the elimination of carbamazepine, the initial dose requirement of carbamazepine will be higher. However, after phenytoin has been discontinued, the dose requirements of carbamazepine decrease within 2 to 4 weeks, and toxic carbamazepine levels will occur if the dose is not reduced. The effects of existing antiepileptic drug regimens on carbamazepine dosage requirements are summarized in Table 1. The processes of heteroinduction and autoinduction of carbamazepine metabolism are all reversible, and the half-life of the induction and deinduction processes is about 4 to 6 days.[8,9] The initial dose for the introduction of carbamazepine is determined on the basis of the preexisting drug regimen.

Patients Taking Phenytoin, Phenobarbital, or Primidone

An initial carbamazepine dose of approximately 25 to 30 mg/kg daily is necessary to achieve carbamazepine levels of about 10 mg/L. However, this dose cannot be administered on the first day because it causes significant neurologic toxicity.[4] The following daily incremental dosage regimen is usually well tolerated: 5 to 7.5 mg/kg on day 1; 10 to 15 mg/kg on day 2; 15 to 22.5 mg/kg on day 3; and 25 to 30 mg/kg each day thereafter. Phenytoin, phenobarbital, or primidone can be discontinued at the time of the introduction of carbamazepine. In my experience, this is generally well tolerated and not associated with significant seizure exacerbation or status epilepticus. However, the abrupt discontinuation of phenytoin, phenobarbital, or primidone is not recommended unless the patient is under close supervision. Discontinuing the previous antiepileptic drug rapidly has the potential advantage of reducing cumulative toxicity during the rapid introduction of carbamazepine. Once phenytoin, phenobarbital, or primidone has been

discontinued, the elimination rate of carbamazepine decreases and the dose has to be readjusted. The dose of carbamazepine should be reduced to 20 mg/kg daily approximately 5 days after the discontinuation of phenytoin, phenobarbital, or primidone, and to 15 mg/kg daily about 3 weeks after these drugs have been discontinued.

Table 1 Dose of carbamazepine required to achieve and average steady-state concentration of 10 mg/L

Drug regimen	Daily dose
Long-term carbamazepine monotherapy	~15 mg/kg
Phenytoin, phenobarbital, or primidone	~20–40 mg/kg
Valproate, benzodiazepine, or no medication	~5 mg/kg[a]

[a] Dose requirements increase during the first month of treatment because of autoinduction of carbamazepine metabolism (see text.)

The validity of this approach has been confirmed in a prospective study in 25 adult patients who were on phenytoin, phenobarbital, or primidone.[6] Following a single-dose pharmacokinetic study of carbamazepine for prediction of the maintenance dose, patients were all switched over to carbamazepine monotherapy successfully within a mean of 6 days. None of the patients experienced an increase in seizure frequency relative to baseline. Twenty of the 25 patients experienced no or only mild adverse effects. Four experienced adverse effects rated as moderate, and only 1 patient with a static encephalopathy experienced severe adverse effects.

Patients Taking Valproate or Another Noninducing Drug

If carbamazepine elimination is not induced, carbamazepine must be started at a low dose. The initial dose should be 3 to 5 mg/kg each day, administered on a twice-daily schedule. The dose can be advanced to 10 mg/kg daily after 5 to 7 days, to 12.5 mg/kg daily after 2 weeks, and to 15 mg/kg daily after 3 weeks. The latter dose is the average carbamazepine dose for long-term monotherapy after full autoinduction of carbamazepine metabolism (Table 1). If the patient is taking valproate, the dose of valproate can be decreased by one third at the time of initiation of carbamazepine and by a second third after 2 to 3 days. The valproate can be discontinued after 5 to 7 days.

Reintroduction of Carbamazepine

When carbamazepine is discontinued temporarily by a patient who is taking carbamazepine alone or in combination with a noninducing drug, a rapid reversibility of the autoinduction of carbamazepine is observed.[9] This process has a half-life of about 4 days only, which means that one-half of the autoinduction of carbamazepine metabolism is lost 4 days after the carbamazepine has been discontinued. Temporary discontinuation of antiepileptic therapy is a common practice during monitoring for epilepsy surgery. If the full previous maintenance dose of carbamazepine is resumed after monitoring, the patient's carbamazepine levels can reach the toxic range within 2 days. If a patient resumes carbamazepine therapy after not taking medication for 5 to 7 days, the following dosage regimen is suggested: 75% of the patient's previous daily maintenance dose of carbamazepine during 10 days, with an increase to the full previous maintenance dose on day 11.

Introduction of Phenytoin

In contrast to carbamazepine levels, phenytoin levels can be brought into the therapeutic range rapidly with little clinical evidence of neurologic toxicity. Therefore, the introduction of phenytoin can be initiated with an oral loading dose, which is then followed by the full maintenance dose. Assuming that a steady-state level of 15 mg/L is desired, one can calculate the loading dose by multiplying the desired concentration by the volume of distribution of phenytoin (approximately 0.75 L/kg). The loading dose is then 11 to 12 mg/kg. The maintenance dose of phenytoin for a desired steady-state level of 15 mg/L can be calculated using the Michaelis-Menten equation and population values for the Michaelis-Menten parameters of phenytoin, $V_{\max}$ and K_m.[2] For an average steady-state level of 15 mg/L, the dose is 5 to 6 mg/kg daily. During the first 24 hours, the patient should receive the loading dose plus the maintenance dose, or about 17 mg/kg, in two or three divided doses. Thereafter, the daily maintenance dose can be prescribed. The antiepileptic drugs to be replaced by phenytoin can be tapered or discontinued when phenytoin is introduced. Phenobarbital and pri-midone can be discontinued at the time of the introduction of phenytoin. The doses of carbamazepine or valproate can be decreased by one third daily until the drug is discontinued.

Introduction of Phenobarbital and Primidone

Phenobarbital

The serum levels of phenobarbital cannot be advanced to the therapeutic range as rapidly as phenytoin levels if significant neurologic toxicity is to be avoided. As with carbamazepine, tolerance to phenobarbital develops within the first few days of exposure. Therefore, loading as described for phenytoin is not possible with phenobarbital or carbamazepine. However, if phenobarbital is introduced by administering only a maintenance dose, a steady-state therapeutic level will be reached after 2 to 3 weeks only, because of the long elimination half-life of phenobarbital. As outlined in the chapter on primidone (see Chapter 156), experimentation with various schedules of phenobarbital titration revealed that the following increases in levels are tolerated with minimal or no sedation by most patients: 5 mg/L after 24 hours, 10 mg/L after 48 hours, 15 mg/L after 72 hours, and 20 mg/L after 96 hours (end of day 4). These levels can be quite accurately achieved by giving 3 mg/kg of phenobarbital orally on day 1 (two doses of 1.5 mg/kg each, 12 hours apart); 3.5 mg/kg on day 2; 4 mg/kg on day 3; and 5 mg/kg on day 4. On day 5, the maintenance dose of phenobarbital can be started. In adults, a maintenance dose of about 2 mg/kg daily results in a steady-state phenobarbital level of approximately 20 mg/L, and a dose of about 3 mg/kg daily results in a level of approximately 30 mg/L. If phenobarbital is introduced to replace phenytoin, the phenytoin can be discontinued during the loading with phenobarbital. If carbamazepine or valproate is being replaced, doses of either can be decreased by one third every 1 to 2 days.

Primidone

Primidone must be introduced slowly; otherwise it produces severe side effects. Based on observations in patients and

experimental animals that phenobarbital produces cross-tolerance to the effects of primidone,[1,3] a schedule was developed that allows rapid advancement to the full maintenance dose of primidone[3,5] (see Chapter 158). The principle is based on giving phenobarbital initially, titrating the serum level as described earlier, and then switching abruptly to the full maintenance dose of primidone. On the fifth day, the patient can be given a full daily maintenance dose of primidone of 12.5 to 20 mg/kg, with no significant new toxicity. Other antiepileptic drugs can be discontinued as described earlier for phenobarbital. In patients taking drugs such as carbamazepine or phenytoin concomitantly, a phenobarbital level of about 30 mg/L will be achieved with an average primidone dose of 10 to 15 mg/kg daily. Kanner et al.[7] confirmed the feasibility of rapid introduction of primidone following prior loading or exposure to phenobarbital in 30 patients. With the foregoing schedule of phenobarbital introduction, or if they were already taking phenobarbital, 2 of 30 patients tolerated the introduction of primidone at 500 mg/day with minimal or no adverse events.

In patients who are taking primidone with a noninducing drug or who are on primidone monotherapy, a phenobarbital level of about 30 mg/L will be reached at a daily dose of approximately 20 mg/kg. Therefore, when carbamazepine or phenytoin is replaced by primidone monotherapy, the dose of primidone might have to be increased 2 to 3 weeks after the discontinuation of phenytoin or carbamazepine to maintain the phenobarbital level. This is caused by deinduction of the enzymatic conversion of primidone to phenobarbital.

Summary and Conclusions

In conclusion, there are certain circumstances under which it may be desirable to substitute antiepileptic drugs within a relatively short time, for example, the need for rapid establishment of pharmacoresistance in a patient undergoing evaluation for epilepsy surgery and the need for rapid substitution in a patient hospitalized with frequent seizures or experiencing an acute reaction to a drug, such as a severe idiosyncratic adverse effect. The main risks of rapid substitution are seizure exacerbation resulting from withdrawal of the one drug while levels of the introduced drug are not yet protective and acute side effects associated with rapid introduction of the new drug. With adequate knowledge of certain pharmacokinetic and pharmacodynamic parameters, however, complete substitutions can be carried out safely within about 5 days. Substitutions between certain pairs of drugs are easier and safer than those between others. Regardless of the antiepileptic drugs involved, rapid drug changes require a good understanding of the potential pharmacokinetic and pharmacodynamic pitfalls, an adequate level of experience with antiepileptic therapy, and appropriate supervision of the patient during the process, preferably in the hospital. Systematic observations on rapid switchover involving any of the newer antiepileptic drugs have not been reported. In addition, some of the newer antiepileptic drugs, such as lamotrigine, just cannot be introduced rapidly. Whenever one drug must be discontinued rapidly but experience with rapid introduction of the chosen replacement drug is lacking, a benzodiazepine can be used temporarily while the new drug is introduced gradually.

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Chapter 121

Adjunctive and Combination Therapy

Blaise F.D. Bourgeois

Frank Gilliam

Introduction

A historical review of the practices of predominant combination therapy versus predominant monotherapy in the medical treatment of epilepsy reveals three sequential currents. After the introduction of phenytoin in 1938, as more antiepileptic drugs (AEDs) became available, it became common practice to prescribe multiple drugs for patients who were not controlled by one. If there was a rationale for this approach, it was mainly based on the assumption that AEDs interact synergistically and can provide more seizure protection together than alone. Even if this was true, the main limitation of this reasoning was that it did not factor in the consequences of combined side effects. Indeed, because of the increasing recognition of the frequent negative impact of polytherapy on the number and intensity of side effects, the concept of monotherapy and sequential monotherapy gained wide acceptance in the late 1970s and early 1980s. The proponents of monotherapy based their recommendations on repeated observations that the severity or number of side effects often diminished following a reduction in the number of AEDs, in most cases without appreciable loss in seizure control.[1,3,10,22,27,28,33] In addition, the beneficial effect of adding a second drug after the failure of a first drug was found to be modest.[27] When patients who had undergone a temporal lobe resection were randomized to ongoing polytherapy or to reduction to carbamazepine monotherapy, both groups experienced the same seizure recurrence rate.[14] However, drug-related side effects were less common in the monotherapy group (10%) than in the polytherapy group (30%). The concept of monotherapy was extended to the practice of "high-dose monotherapy."[15] Two main factors prompted the transition to the third era: (a) The realization that about one third of patients remained refractory even to high-dose monotherapy and (b) the release of many new AEDs after 1993. These newer AEDs have fewer or no pharmacokinetic interactions. Beginning in the 1990s, the concept of "rational polytherapy" was debated and became the object of intense discussion and speculation but of few rigorous clinical studies. The temptation to combine AEDs when single-drug therapy fails to render patients seizure free will endure. Therefore, the advantages and disadvantages of AED combinations must be assessed carefully, and it will always be important to evaluate and identify potentially beneficial specific drug combinations.

Potential Disadvantages of Combination Therapy

Table 1 lists some of the potential disadvantages and advantages of combination therapy. It seems that the disadvantages are more obvious and easier to document, and they will be discussed first.

Increased Number or Intensity of Side Effects

Based on experimental data on pharmacodynamic interactions between AEDs, it appears that the neurologic toxicity of various drug combination is mostly additive, although it can be at times infraadditive or supraadditive (see Chapter 110, Table 1). The consequence of this observation is that two drugs whose concentration is in the usual therapeutic range are more likely to cause dose-related neurologic side effects than either one of the two drugs at the same concentration. This interpretation has been supported by several clinical observations that a reduction in polypharmacy is associated with a reduction in side effects, in particular diminished sedation.[1,3,10,28] Although the drugs involved were often barbiturates that are used less commonly now,[33] subtle toxicity that can occur with any of the other AEDs is more likely to be missed and can include chronic impairment of cognitive function.

Increased side effects during combination therapy can be related not only to cumulative toxicity, but also to the increased statistical probability that the level of at least one drug will be in the toxic range. This might be due also to the fact that patients on combination therapy tend to have more-refractory seizures, and so it is more likely that the dose of their medication will be increased more aggressively. It was found in a prospective study of intelligence in children with epilepsy that the number of children with one or more drug levels in the toxic range increased with the number of drugs prescribed.[7] Toxic levels were recorded in 14% of those taking one drug, whereas they were found in 50% of those taking two drugs and 100% of those taking three or more drugs. Based on a review of the literature, Deckers et al.[9] reassessed the relationship between AED polytherapy and adverse effects; it appears that toxicity during polytherapy is related to the total drug load (i.e., the sum of the relative doses of all AEDs taken by a patient) rather than to the number of drugs. This observation has implications for the concept of rational polytherapy because it implies that a single drug at the maximal tolerated dose can cause more toxicity than two drugs at low doses.

Table 1. Potential advantages and disadvantages of combination therapy

Disadvantages
Increased number or intensity of side effects
Potentiation of dose-related or idiosyncratic side effects
Pharmacokinetic interactions
Difficulty of attributing the response to a given drug
Possible change in the therapeutic range of plasma levels
Cost and complexity of drug regimen
Advantages
Better effectiveness
Milder side effects
Broader spectrum of seizure protection

Cumulative toxicity can also mean that combination therapy will result not only in stronger side effects, but also in more different side effects. Different drugs have different side effects, and combining them will multiply the number of possible side effects, such as thrombocytopenia from valproate, nephrolithiasis from topiramate, and gingival hyperplasia from phenytoin. Conversely, side effects of different drugs might improve when they are combined, such as weight gain or weight loss with valproate and topiramate.

Potentiation of Idiosyncratic or Dose-related Side Effects

The likelihood of some idiosyncratic side effects that are not dose related can be increased by the combined administration of two drugs. The incidence of severe rashes with lamotrigine was found to be higher in the presence of valproate, which is likely to be due to a pharmacokinetic interaction.[4] Treatment with valproate can result in an encephalopathic state, which is usually not associated with toxic drug levels.[17,25] There is a marked slowing of the electroencephalographic (EEG) background activity in the context of significant mental status changes, usually a stuporous state. This condition seems to occur more often when valproate is taken with another AED, and it is fully reversible within a few days on discontinuation of either valproate or the other AED.[17]

It appears that dose-related adverse effects of one drug can also be exacerbated by another AED. When lamotrigine was prescribed in combination with valproate, an increase in tremor was observed in two studies.[13,21] When levetiracetam was added to carbamazepine in polytherapy, an increase in side effects characteristic of carbamazepine was noted in four patients.[29] After the addition of lamotrigine, an exacerbation of carbamazepine toxicity has also been noted, and this could not be attributed to a pharmacokinetic interaction.[5] In three patients, chorea occurred on phenytoin and lamotrigine only when they were combined, and it resolved when one medication was tapered.[35]

Pharmacokinetic Interactions

The pharmacokinetic interactions are reviewed in detail in Chapter 110. Adding as well as removing an AED can alter the dose-to-level relationship of other AEDs and also of other drugs. These changes not only make the medical treatment of a patient more complex, but they also can require more frequent drug level monitoring and dosage readjustments, and they are more likely to result at some point in drug levels that are either too low or too high. Interactions are more likely to be overlooked when a drug causing an interaction is removed than when it is added. In addition, interactions due to an enzyme-inducing drug display their full impact after days to week and are equally slowly reversible, whereas interactions due to an enzyme-inhibiting drug usually occur within hours to days and are rapidly reversible due to the competitive nature of the interaction. Overall, the newer AEDs are less likely to cause interactions, although many of them are susceptible to the effect of enzyme induction by the older drugs. Pharmacokinetic interactions are rarely beneficial, and they are at best not detrimental when they are anticipated or recognized early. An inhibitory interaction, such as the effect of valproate on lamotrigine kinetics, can have the theoretical advantages of decreasing the fluctuation of the levels of lamotrigine by prolonging its elimination half-life and of reducing the dose requirements of lamotrigine for the same average plasma levels. This in itself would rarely be a reason for combining two AEDs. Conversely, enzyme induction will result in a shorter half-life of the affected drug and also in wider fluctuation in plasma levels between doses. Such enhanced fluctuations can increase the risk of a seizure before a dose (lower trough levels) or the risk of toxicity at the time of the peak level. In addition, enzymatic induction can make it difficult to achieve good therapeutic levels of the affected drug, even at very high doses, as has been shown for valproate in children.[12] Finally, the inhibition of lamotrigine metabolism by valproate raises the level-to-dose ratio of lamotrigine. This is considered to be a likely explanation for the higher incidence of rashes associated with lamotrigine in patients taking valproate,[4] and this led to a downward readjustment of the titration rate of lamotrigine dose in these patients.

Difficulty of Attributing a Response to a Given Drug

In clinical practice, when a patient is taking two or more AEDs, it is often difficult to determine which one of the drugs is causing a side effect, unless it is a very specific adverse reaction. This is particularly bothersome when a patient develops a rash and was started within a relatively short time interval on two drugs that are known to have a potential for allergic skin reactions. Idiosyncratic toxic reactions do not always appear soon after the introduction of a drug; therefore, they cannot necessarily be attributed to the last drug added to the patient's regimen. Another common dilemma is to determine, in a patient on two or more drugs, which one is more likely to be contributing to seizure control. Frequent dose changes and short periods of observation can confound these problems.

Possible Change in the Therapeutic Range of Plasma Levels

The therapeutic range provides loose guidelines with regard to the minimal effective concentration and the concentration at which side effects become frequent, and it is a statistical compromise based on previous observations in groups of patients. Given the experimental evidence for additive interactions between AEDs, it is unlikely that the therapeutic range of a drug is the same when it is taken alone as when it is taken in combination with other drugs. When drug levels are within the therapeutic range, polytherapy is more likely to be associated with toxicity. Conversely, it has been suggested that toxicity from valproate[25] and from carbamazepine or phenytoin[15] appears at higher levels when these drugs are taken alone. Therefore, when side effects occur at a certain level of a drug during combination therapy, this does not necessarily imply that a given drug with a therapeutic level is not responsible for the toxicity

or that the side effects will recur at similar levels in monotherapy in the same patient.

Potential Advantages of Combination Therapy

The two main advantages that combination drug therapy can have over single-drug therapy are better overall seizure control and a similar degree of seizure control with fewer or less-pronounced side effects. To fulfill these criteria, a combination of two or more AEDs must either have a better therapeutic index (ratio of seizure protection to toxicity) than either drug alone or a wider spectrum of activity against different seizure types. For example, consider a patient whose partial seizures were not controlled by the maximal tolerated doses of either phenytoin alone or carbamazepine alone, leading to both drugs being prescribed together. If the seizures can be controlled by the combination of phenytoin and carbamazepine at doses tolerated by the patient, a superior therapeutic index for the combination of phenytoin and carbamazepine would have been demonstrated. In another hypothetical case, a patient with both primarily generalized tonic–clonic seizures and myo-clonic seizures in whom clonazepam controlled only the myo-clonic seizures and valproate controlled only the tonic–clonic seizures might do well on both drugs. Although neither drug alone controlled both seizure types, together they might be effective and have a wider antiepileptic spectrum than either one alone. Although the clinical literature provides very few data demonstrating a better therapeutic index for any combination of AEDs, increasing attention is being paid to the theoretical, experimental, and clinical background for the practice of combining AEDs. It is difficult to quantify pharmacodynamic interactions between AEDs in a clinical setting because both seizure protection and neurotoxic side effects of single drugs and of combinations of drugs must be assessed quantitatively in a homogeneous population of patients. Therefore, most of the information on the pharmacodynamic effect of combining AEDs has been obtained from animal experiments (see Chapter 110). Although a supraadditive pharmacodynamic interaction (potentiation or synergism) between two drugs with regard to their protective effect against seizures has often been interpreted as supportive evidence in favor of the combination, this in itself has little meaning unless the neurotoxic effects are also evaluated. If toxicity is also supraadditive to the same or greater extent, the therapeutic index of the combination is equal to or inferior to the therapeutic index of each drug alone. In other words, at the same level of neurotoxicity, the drug combination does not provide more seizure protection than either of the two drugs alone. As shown in Chapter 110, Table 1, there can be many different combinations of antiepileptic and neurotoxic pharmacodynamic interactions between various pairs of AEDs.

Clinical Studies

Only few clinical reports of AED combinations have been based on systematic comparisons between the effects of two drugs administered each in monotherapy and then together. To demonstrate the superiority of a combination, it is not sufficient to compare the effect of adding a second drug with the result of monotherapy with the first drug. It is important to keep in mind that success with add-on therapy should be considered as success of alternative therapy until proven otherwise.

A second drug (carbamazepine, phenytoin, phenobarbital, primidone, valproic acid, clonazepam, or clobazam) was added, if necessary up to the maximal tolerated dose, in 30 adult patients who had failed to respond to the maximal tolerated dose of carbamazepine, phenytoin, phenobarbital, or primidone.[27] In 4 patients (13%), there was a reduction in seizure frequency by 75% or more, but no patient became seizure free, and there was an increase in seizure frequency by more than 100% in 3 patients (10%). When 157 patients who were not controlled on AED monotherapy were randomized to alternative monotherapy or to adjunctive therapy, there was no difference in outcome between the two groups in relation to seizure outcome and to adverse effects.[2]

One clinical study suggested that the combination of valproate and ethosuximide is possibly beneficial in the treatment of absence seizures. Five patients with absence seizures became seizure free when ethosuximide and valproate were combined after they had failed to respond fully to ethosuximide or to valproate alone (or to both).[23] This observation is in agreement with experimental evidence cited in Chapter 110. A frequently quoted study of the combination of carbamazepine and phenytoin was only published as an abstract.[11] One hundred newly diagnosed patients were randomized to monotherapy with carbamazepine or phenytoin. After 1 year, 50 patients were uncontrolled, and they were switched to the other medication. Of those, 17 (34%) became seizure free. The 33 remaining patients, whose seizures had not been controlled by carbamazepine and phenytoin monotherapy, received both medications, and only 5 of them (15%) became seizure free. In a sequential study by Walker and Koon[34] some patients who had failed to respond to valproate alone and to carbamazepine alone became seizure free on the com-bination.

The combination of vigabatrin with lamotrigine was evaluated in 42 patients with intractable epilepsy.[26] The median seizure frequency was reduced by 18% when vigabatrin was added to lamotrigine and by 24% when lamotrigine was added to vigabatrin. However, because patients did not receive both drugs in monotherapy first, the results might just reflect the effect of the second drug added, not of the combination. Tanganelli and Regesta[31] made encouraging observations supporting the combination of vigabatrin and carbamazepine in newly diagnosed patients randomized to monotherapy to either one of the two drugs. The 25 patients whose seizures were not controlled were switched to monotherapy with the other drug, and 11 patients (44%) were controlled by alternative monotherapy. The remaining 14 refractory patients received the two drugs in combination, and 5 (36%) became seizure free.

Evidence suggestive of a synergism between lamotrigine and valproate was found in at least two studies. Lamotrigine was added in 347 patients that were not controlled on monotherapy with valproate, carbamazepine, phenytoin, or phenobarbital.[8] In patients with a 50% or greater seizure reduction, an attempt was made to withdraw the first drug. On the basis of two observations, a synergism between lamotrigine and valproate was suggested: (a) There was a significantly better response after adding lamotrigine to valproate than to carbamazepine or phenytoin ($p < .001$), both for partial seizures ($p < .02$) and for generalized tonic–clonic seizures (not statistically significant), and (b) there was worsening of seizure control after valproate was withdrawn. Pisani et al.[21] carried out a small but very systematic study that added evidence in favor of the potential benefit of the combination of valproate and lamotrigine. Twenty patients with resistant complex partial seizures received valproate as add-on medication. Three of them had a >50% seizure reduction. In the remaining 17 patients, valproate was replaced by lamotrigine added to the same baseline medications. Four of the 17 had a >50% seizure reduction. In the remaining 13 patients, when valproate was reintroduced while

lamotrigine was continued, 4 had a >50% seizure reduction and 4 became seizure free.

Clinical Approach to Selection of Antiepileptic Drug Combinations

At present, there can be no firm guidelines for selecting a combination of two AEDs because there are no definitive clinical studies documenting the superiority of any specific drug combination. In 1995, Meinardi[18] stated that “at present, however, there are too many gaps in our knowledge to make theoretical planning of [combination] drug therapy more promising than an empirical approach." In the absence of unusual circumstances, there is no reason to consider a combination of two AEDs unless at least two sequential monotherapy treatments have failed. When trying to select a meaningful combination of AEDs, one can consider the mechanisms of action, the clinical spectrum of activity, and pharmacokinetic interactions of the drugs. Some have suggested the mechanism of action of AEDs as a criterion for rational combinations, hypothesizing that drugs with different mechanisms of action are more likely be complementary.[16,20] At times, a valuable combination can be found by chance observation in a given patient. A real-life example is the case of a nearly 7-year-old boy with about 30 absence seizures per day and generalized spike-and-waves on the EEG. After about 10 days on ethosuximide, he had about six absence seizures per day but had developed some sudden falls. Valproate was added, and all seizures subsided within days. Two months later, the ethosuximide was tapered and discontinued. Within about 10 days, the absence seizures recurred and then were gradually controlled again when ethosuximide was reintroduced. Clearly, this patient was never seizure free on ethosuximide or valproate alone, only on the combination.

Two drugs can be selected according to their spectrum of efficacy for patients with two or more seizure types that cannot be controlled by one drug alone. The drug likely to be most effective and best tolerated should be selected for each seizure type. The Lennox-Gastaut syndrome is another example of epilepsy with multiple seizure types, and valproate has long been the drug of choice in this syndrome. However, three drugs have now been shown to be effective in double-blind studies—felbamate,[32] lamotrigine,[19] and topiramate.[24] Combinations between these drugs might be more effective in reducing drop attacks as well as atypical absences and tonic seizures than only one drug alone. Conversely, phenytoin and carbamazepine should not be used in any combination because they can exacerbate certain seizures in these patients.[30]

Combinations that should be considered only with caution are those between drugs with similar side effects. Examples are barbiturates and benzodiazepines, or barbiturates and topiramate (sedation, cognitive effects); acetazolamide, topiramate, and zonisamide (nephrolithiasis, acidosis); carbamazepine and oxcarbazepine (hyponatremia); valproate and gabapentin (weight gain); and topiramate, zonisamide, and felbamate (weight loss). In addition, as discussed earlier, combining certain drugs can increase the risk of idiosyncratic reactions. Overall, the need to reduce overtreatment can be as common a clinical situation as the need to find an appropriate duotherapy.[6]

It certainly makes it easier to use two drugs together that have no pharmacokinetic interactions between them. However, it is the physician's responsibility to make appropriate dose adjustments, either as a corrective measure or preferably as a preventive measure, because most pharmacokinetic interactions are known and predictable. Therefore, if a drug combination is of potential benefit to a patient, pharmacokinetic interactions should not be a reason to avoid it.

Finally, a concept of “low-dose polytherapy” could be opposed to the classic concept of “high-dose monotherapy.” All AEDs have in common their antiepileptic effect, but they do not all have the same adverse effects. Accordingly, if a patient had a good seizure response to two drugs in monotherapy but only in the presence of side effects, the two drugs together at lower doses that could be below the clinical threshold for each one's side effects might provide the same seizure control. For example, a child with absence seizures who has thrombocytopenia or tremor at effective doses of valproate and persistent gastrointestinal side effects at effective doses of ethosuximide might have equal seizure control without the side effects while taking the two drugs at lower doses. According to this concept, any two drugs with different side effects but efficacy against the same seizure type could be combined.

Summary and Conclusions

Various clinical problems are associated with antiepileptic drug combinations—pharmacokinetic interactions, cumulative toxicity, a more complicated drug regimen, difficulty in assessing individual drug efficacy and toxicity, and, finally, higher costs. Therefore, two or more antiepileptic drugs should not be prescribed concomitantly unless it can be demonstrated that, compared with either drug used alone in a given patient, that patient derives better seizure protection from the combination with no additional side effects or that the same seizure protection is achieved with fewer side effects. If this is not the case, the patient will be better off on monotherapy with the drug that had previously displayed the best efficacy/toxicity ratio. Rational AED combinations are identified when individual patients do better in terms of seizure control and side effects while taking drugs A and B together (at any dose) than while taking drug A or drug B alone at their respective optimal doses. Under certain circumstances, it could be appropriate to maintain a drug combination even when the foregoing definition is not met. A patient may respond partially to a first drug and experience further improvement after addition of the second drug. In such a case, it is understandable that one might be reluctant to make any change.

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Chapter 122

Treatment of Single and Infrequent Seizures

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Introduction

Epilepsy is a treatable condition characterized by the occurrence of repeated unprovoked seizures. Thus, the patient who presents with an isolated first unprovoked seizure (or cluster of seizures within 24 hours) does not yet qualify for the diagnosis of epilepsy. In the past, it was believed that almost all individuals coming to medical attention for a first seizure would inevitably have additional episodes; such individuals were usually treated with antiepileptic drugs (AEDs).[22,52] In addition, based on studies from tertiary referral centers, there was the perception that epilepsy was a chronic, progressive, unremitting disease.[30,54] Thus, early aggressive treatment with antiepileptic drugs was presumed to be beneficial through suppression or control of the evolving process of the disorder. The results of recent epidemiologic studies and randomized clinical trials have greatly changed our understanding of the nature and natural history of seizures and of epilepsy. For the most part, it is clear that epilepsy is a relatively benign condition with an excellent prognosis for seizure control and, ultimately, discontinuation of AEDs. In light of these changes, the clinical management of a single seizure has to be reconsidered. In this chapter, we will address several issues pertaining to the diagnosis and management of the patient who presents with a single unprovoked seizure, including (a) the diagnosis of epileptic seizures, first unprovoked seizures, and epilepsy; (b) the influence of seizure recurrence and early treatment on the prognosis of epilepsy, based on earlier and present views; (c) the risk of recurrence of a given seizure; (d) the impact of treatment on that risk and on the long-term prognosis of epilepsy; (e) the risk:benefit ratio of pharmacologic treatment; and (f) the sociocultural and legal implications of seizure recurrence compared with the tolerability and acceptance of chronic therapy.

Diagnosis of Epileptic Seizures, First Unprovoked Seizures, and Epilepsy

The diagnosis of epileptic seizures and epilepsy is beyond the scope of this chapter and is being covered elsewhere in this book. Briefly, in any newly presenting patient a series of questions must be addressed: (a) did the individual have an epileptic seizure? (b) Is there an acute cause for the seizure, perhaps one requiring immediate treatment itself? (c) If this is an unprovoked seizure, is it the first ever this person has had or, upon history, is there convincing evidence of previous events?

According to the International League Against Epilepsy and the International Bureau for Epilepsy, an epileptic seizure is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain.[25] Although the occurrence of at least one epileptic seizure as a prerequisite for the diagnosis of epilepsy is still a matter of debate,[6] a first epileptic seizure has an inherent susceptibility to relapse. A first seizure may present as status epilepticus. Status epilepticus is a seizure showing no clinical signs of arresting after a duration encompassing the great majority of seizures of that type in most patients or recurrent seizures without interictal resumption of baseline central nervous system function.[11]

Seizures should also be characterized as *acute symptomatic* or *unprovoked*, with reference to the presence or absence of known precipitants.[19] Seizure definitions are discussed more extensively in Chapter 67. Although acute symptomatic seizures are a risk factor for unprovoked seizures and epilepsy, they may not necessarily recur, provided that the underlying epileptogenic condition is properly diagnosed and treated.

Another aspect of diagnosis that can be particularly difficult in an individual with a history of nonconvulsive ictal events is the determination of whether the event is really the first seizure. Not all forms of epilepsy are equally likely to present with a single seizure.[3] This is frequently an issue in syndromes such as juvenile myoclonic epilepsy, where the patient may come to medical attention for a generalized tonic–clonic seizure but, upon careful questioning, is found to have a history of myo-clonic events that were never recognized as seizures. Similar scenarios are often seen with patients who are found to have a history consistent with complex partial seizures, or absence seizures. Some patients may have had one or more nocturnal episodes that are recognized only in retrospect. Such patients may present with a first seizure requiring medical attention; however, they already have epilepsy.[36] The issue of the diagnosis of the first seizure is further complicated by the high variability of clinical interpretation among neurologists. This variability seems to be reduced only by the use of simple diagnostic criteria and a discussion among the treating physicians.[65]

Changing Views on the Early Prognosis of Epilepsy and the Effects of Early Treatment

Views on the prognosis of epilepsy have changed in the last 40 years. Until the late 1960s it was believed that less than a third of patients with epilepsy would achieve a complete remission from seizures, and the majority (up to 85%) would be likely to have a chronic seizure disorder.[54] Further, it was believed that seizures beget seizures. As Gowers wrote[30]:

> “When one attack has occurred, whether in apparent consequence of an immediate excitant or not, others usually follow without any immediate traceable cause. The effect of a convulsion on the nerve centres is such as to render the occurrence of another more easy, to intensify the predisposition that already exists. Thus, every fit may be said to be, in part, the result of those that have preceded it, the cause of those which follow it.”

In contrast to previous studies, community surveys and prospective studies on referral patients done in the last 30 years have reported that up to 90% of newly diagnosed patients with epilepsy tend to achieve prolonged seizure remission, and about 40% to 60% of these enter remission as soon as treatment is initiated.[39] Likewise, well-conducted, unbiased studies of prognosis following a first unprovoked seizure have also demonstrated that a significant percentage of patients do not have further seizures.[2,31] Although it has been maintained that the better prognoses observed in more recent studies can be attributed to improved treatment,[52] epidemiologic evidence indicates that the poor prognoses observed in earlier studies were largely the result of selection bias: Patients in these studies were from tertiary referral centers where those with poor outcomes are overrepresented.[7] In contrast, recent studies have been conducted on newly diagnosed patients. Given the changes in our understanding of the nature of seizures and epilepsy and the prognosis following a first unprovoked seizure, there are now many considerations that must be made in approaching the management and treatment of the patient who presents with a first unprovoked seizure.

It has been suggested in the past that AEDs should be initiated promptly in newly diagnosed patients under the assumption that epilepsy is an evolving process that, if left untreated, tends to be accompanied by reduced drug response.[52] This assumption was supported by experimental findings in kindled animals.[53] However, the concept that early AED treatment can influence the prognosis of epilepsy is not unanimously accepted. An alternative view is that the outcome of epilepsy is determined largely by the underlying substratum upon which the epilepsy is superimposed and that treatment does not influence the course of the disease.[37,55,61] Epilepsy is a heterogeneous clinical condition and many different forms have been recognized. The outcome to some extent is determined by the type of epilepsy. These contrasting opinions may still greatly affect the decision to treat a patient at the time of his or her first medical contact for unprovoked seizures, which for some individuals may be the first epileptic seizure.

Treatment of a single epileptic seizure is a therapeutic option. Knowledge of the clinical pharmacology of AEDs has led to a more precise outline of the efficacy and tolerability of the available drugs (see Chapter 109). Consequences of recurrence of epileptic seizures must be balanced against the consequences of treatment (Chapters 95 and 108). This chapter will mostly focus on prophylaxis following a single unprovoked seizure. Although a more detailed overview of the epidemiology of isolated seizures has been provided elsewhere in this book (see Chapters 5 and 7), this issue will be summarized briefly here.

Risk of Recurrence of a First Seizure

In patients coming to medical attention with a first unprovoked seizure, the risk of recurrence has been reported to range from 23% to 71%.[4,8] This large range reflects considerable differences among studies with respect to length of follow-up, target population, definition of first seizure, and study design.[7,8] Population-based studies[2,31] provide more homogeneous relapse rates at 1 (36% to 37%) and 2 years (43% to 45%). In a systematic review of 16 reports,[8] the average recurrence risk was 51% (95% confidence interval [CI], 49% to 53%). The risk of recurrence of a first seizure at 2 years ranged from 25% to 52%, with a median of 38%. Numerous prognostic factors have been examined in the literature. These can be divided into three groups: (a) those clearly identifying patients at high and low risk, (b) those clearly considered of no prognostic significance, and (c) those for which available data are insufficient or conflicting.

The two most consistent predictors of recurrence are an abnormal electroencephalogram (EEG) and the presence of an underlying etiology.[8] The EEG is a useful predictor of relapse of a first unprovoked seizure in both children and adults.[8] Children with a cryptogenic first seizure and EEG epileptiform abnormalities have recurrence rates doubling those with nonepileptiform abnormalities. The results are less conclusive in adults, but also suggest that an EEG with epileptiform abnormalities is associated with a significantly increased risk of relapse.[8,57,67] When a first seizure is associated with an underlying neurologic condition or event to which the occurrence of the seizure can be attributed, the risk of recurrence is roughly double that of an idiopathic or cryptogenic first seizure.[8] The 2-year risk of recurrence seems to vary significantly according to the presence of a recognized etiology of the seizure and of an abnormal (not necessarily epileptiform) EEG. The risk is lowest (24%) in patients with idiopathic or cryptogenic seizures and normal EEGs, intermediate (48%) in those with symptomatic seizures or abnormal EEGs, and highest (65%) in those with symptomatic seizures and abnormal EEGs.[8] In three of the four studies that examined the sleep state at the time of the first seizure,[14,38,59,66] the risk of recurrence was doubled in patients who were asleep at the time of the index event compared with those who were awake. In one study,[59] sleep state was a strong predictor of recurrence, even among lowest-risk patients (i.e., those with cryptogenic first seizures and normal EEGs).

Most studies find a small to moderate increase in risk of recurrence associated with a family history of unprovoked seizures. This association appears to be greater among patients with cryptogenic first seizures than among those with a first remote symptomatic seizure. Partial-onset seizures are associated with remote symptomatic etiology and an abnormal EEG. This is particularly the case in patients with remote symptomatic first seizures but less so in those with cryptogenic first seizures. However, in studies controlling for etiology and EEG,[2,14] partial seizures still may be associated with a higher recurrence risk than are generalized-onset seizures.

Some factors were fairly consistently found not to be predictive of recurrence after a first unprovoked seizure. These include gender and status epilepticus. Although the evidence is still limited, the risk of recurrence does not appear to be greater in patients whose first unprovoked seizure was an episode of cryptogenic status epilepticus.[33,60,63] whereas an increased risk of recurrence has been observed in those with a first episode of remote symptomatic status epilepticus.

Factors for which the evidence of seizure recurrence is inconclusive include age and a history of prior provoked seizures. Although developmental factors associated with age play an important role in the occurrence and prognosis of epilepsy, it is not clear whether they play a role in predicting recurrence in patients with a first unprovoked seizure.

Contrary to other reports, two studies[24,66] have found substantial differences in recurrence risk across age groups. In both studies, children and adolescents had higher recurrence risks than did adults. The results for older adults were contradictory in these studies, one reporting a further decrease in risk[66] and the other reporting an increase.[24] Most studies have focused on a history of prior febrile seizures, primarily in patients with cryptogenic first seizures. In studies of children,[14,58] a prior history of febrile seizures does not appear to be associated with the risk of recurrent febrile seizures. In a study primarily of adults,[32] a history of prior provoked seizures (most of which were febrile) was associated with recurrence. Information is insufficient regarding the prognostic significance of neonatal or other prior provoked seizures.

In summary, the overall risk of recurrence after a recognized first unprovoked seizure is about 38% after 2 years. Factors increasing risk of recurrence by 2 years include an antecedent condition associated with an increased risk for epilepsy, an

abnormal EEG (particularly one with epileptiform abnormalities), and, probably, sleep state. In addition, most evidence suggests that family history of epilepsy and partial seizures are associated with a somewhat higher recurrence risk. Either such factors as sex, age at first seizure, status epilepticus, and history of prior provoked seizures were not associated with higher recurrence risk or the available information was inconclusive.

The Impact of Treatment on the Recurrence after a First Seizure and on the Long-term Prognosis of Epilepsy

Observations from clinical trials demonstrate that AEDs are effective in preventing seizures in patients with epilepsy; their role in individuals with a first unprovoked seizure is less defined. Because patients with a recognized etiology and/or an abnormal EEG are considered at higher risk of recurrence, it is conceivable that these subjects are more likely to be treated after the first seizure. However, the proportion of patients treated after the first seizure ranges from 5% to 80% in different published series.[2,12,31,33,38,58] Part of the differences are attributable to the differences in treatment approaches to children and adults. This range can only partly be explained by the different target populations. In fact, the tendency to treat the first seizure may vary across countries, due largely to significant differences in the sociocultural environments (including different legislation and different attitudes of physicians and patients toward treatment).

Several observational studies have assessed the impact of treatment on the risk of further seizures following a first unprovoked seizure.[2,14,33,38] Although some reports documented a striking correlation between the number of seizures prior to initiating treatment and the chance of prolonged seizure remission on follow-up,[18,21,35] with few exceptions,[31,62] these studies reported no significant difference in the risk of recurrence between treated and untreated subjects. However, these findings are most likely confounded by selection bias, as patients considered at higher risk of relapse were most likely to be treated.[62] In addition, some authors[2,12] found recurrences occurring later in treated patients, suggesting that treatment had an effect on the risk of relapse of a first epileptic seizure.

To date, a number of randomized studies have been conducted to assess the effects of treatment of the first unprovoked seizure on the risk of recurrence. In a small Canadian trial[13] of 31 children with a first unprovoked partial or generalized tonic–clonic seizure, patients were randomized to receive carbamazepine or no medication for 1 year or until the time of a second seizure. Overall, 2 of 14 treated and 9 of 17 untreated children had a recurrent afebrile seizure. Four patients discontinued treatment because of adverse reactions, leaving six cases completely seizure free with no unacceptable adverse effects of treatment. Ninety-one patients aged 18 to 50 years with a single generalized tonic–clonic seizure were randomized to treatment (45) or to remain untreated (46) and followed until recurrence or 36 months, whichever first.[27] There were significantly more seizure-free patients in the treated (10) compared to the untreated group (29) ($p < 0.005$). A large multicenter trial (the FIRST study)[24] of 397 children and adults (age range 2 to 70 years of age) was conducted to assess the effectiveness of treatment of the first seizure on the risk of relapse and the long-term prognosis of epilepsy. Patients seen within 7 days after a first witnessed unprovoked tonic–clonic seizure with or without partial onset were randomized to be treated with carbamazepine, phenytoin, phenobarbital, or valproate, or to be left untreated until the time of a second seizure. The mean period of observation was 274 days among patients given immediate treatment and 309 days among patients who did not receive treatment.

Overall, 36 of 204 treated patients and 75 of 193 untreated patients were referred for seizure relapse. The hazard ratio of relapse for untreated patients was 2.8 (95% CI, 1.9 to 4.2). The efficacy of treatment was maintained despite the fact that 41 (20%) of the treated patients discontinued the AED at some point. The results of this study were confirmed by an even larger pragmatic randomized trial (the MESS study) comparing immediate and deferred treatment for early epilepsy and single seizures.[44] Patients aged at least 1 month were randomized if both the clinician and the patient were uncertain whether to proceed with treatment. In this open multicenter trial, 722 patients were randomized to immediate treatment and 721 to deferred treatment. Of these, 404 and 408 had a single seizure at randomization, respectively. Immediate treatment prolonged the time to the first relapse (risk ratio [RR] 1.5; 95% CI, 1.2 to 1.8) and increased the proportion of patients achieving immediate 2-year remission (64% vs. 52%) ($p = 0.023$). These data are consistent with other reports[16,20] and support the assumption that treatment of the first unprovoked epileptic seizure significantly affects the short-term prognosis of a first seizure by reducing the risk of further seizure relapse—regardless of age, presumed etiology of seizures, and EEG abnormalities. However, the FIRST and MESS studies showed that the long-term prognosis of epilepsy (assessed by the chance of achieving 2-year remission after randomization) is virtually unaffected by the treatment of the first seizure[44,47] (Table 1). The long-term outcome of epilepsy was also unchanged by treatment of the first seizures in children enrolled in the small Canadian randomized trial and followed for 15 years.[15] These findings seem confirmed by studies conducted in developing countries, where most—if not all—patients are left untreated or receive drugs only after a prolonged disease course and repeated seizures. In these studies, untreated patients tend to achieve seizure remission in proportions similar to those of patients under treatment,[68] and the start of treatment leads to a proportion of successes and failures similar to that of early treated individuals from the developed countries.[23] In addition, population-based studies in developing countries show high spontaneous remission rates, even without AEDs.[48,50,51]

In summary, treatment of the first unprovoked epileptic seizure seems to reduce the risk of recurrence during the active phase of the disease but does not influence the long-term prognosis of epilepsy. In other words, AEDs exert a symptomatic action but not a curative effect on the course of epilepsy that might be most convincingly related to the underlying epileptic syndrome. It is commonly accepted that the different epileptic syndromes have a different severity and course that might or might not be influenced by AED treatment. A clear demonstration of the symptomatic rather than curative role of AEDs also comes from the results of meta-analyses of studies on their prophylactic use following head trauma,[56] brain tumor,[28] craniotomy,[40] and other clinical conditions.[64] The results of the clinical investigations lend support to the concept that none of the drugs currently in use for the treatment of epilepsy has been clearly shown to be antiepileptogenic in the sense of preventing the establishment of a chronic seizure disorder.[49]

Adverse Effects of Antiepileptic Drugs, Quality of Life, and Patients' Preference

Adverse drug reactions are reported in about a third of ambulatory patients receiving chronic AED therapy, 22% of whom receive monotherapy[17] (see also Chapter 101). Adverse treatment effects may lead to treatment failure in up to 36% of previously untreated or undertreated patients.[45] In the FIRST study,[24] adverse events were reasons for drug withdrawal in 7% of cases (14 of 204). In the MESS study,[44] patients in the immediate treatment group were more likely to report at least one adverse event than those in the deferred group (difference 8.6%; 95% CI, 3.6 to 13.6).

Table 1 Actuarial Cumulative Percentage Achieving 2-Year Remission at Various Time Intervals from Randomization in Patients Receiving Immediate or Deferred Treatment after a First Seizure

	Follow-up				
Study	2 yr	4 yr	5 yr	8 yr	15 yr
FIRST					
Immediate treatment	68	72	NA	NA	
Deferred treatment	60	67	NA	NA	
MESS					
Immediate treatment	69	NA	92	95	
Deferred treatment	61	NA	92	96	
CANADA					
Immediate treatment					80%
Deferred treatment					88%

NA, not available.
Comparative findings from the FIRST study (Musicco M, Beghi E, Solari A, et al., and the First Seizure Trial Group. Treatment of first tonic–clonic seizure does not improve the prognosis of epilepsy. *Neurology.* 1997;49:991–998), the MESS study (Marson A, Jacoby A, Johnson A, et al. Immediate versus deferred antiepileptic drug treatment for early epilepsy and single seizures: a randomised controlled trial. *Lancet.* 2005;365:2007–2013), and the Canadian study (Camfield P, Camfield C, Smith S, et al. Long-term outcome is unchanged by antiepileptic drug treatment after a first seizure: a 15-year follow-up from a randomized trial in childhood. *Epilepsia.* 2002;43:662–663).

The incidence of adverse drug reactions tends to increase with increasing dosage, even when plasma levels are maintained within the so-called therapeutic range.[45,46] The prevalence of any adverse drug effect may be even higher when specific screening procedures are adopted. This is particularly important when behavioral and cognitive functions are being assessed. It is commonly accepted that the currently available AEDs have an adverse influence on mental and behavioral functions, which are increased by higher plasma levels and polypharmacy (see Chapter 114).[29,43]

There are some patients who might have greater susceptibility to the adverse effects of drugs. These include infants (see Chapter 105) and the elderly (see Chapter 106), in whom drug metabolism might be inefficient because of the presence of immature or aging metabolic pathways; pregnant women, who are exposed to the teratogenic effects of AEDs and have an increased liver metabolic capacity and the development of drug-metabolizing capacity in the fetal liver; and patients with hematologic, hepatic, and renal disturbances, in whom drug metabolism may be defective.[42] The risk:benefit ratio of the anticonvulsant drug treatment must be carefully assessed in patients at their first epileptic seizure, as even a modest risk might not be accepted and might affect compliance with the proposed therapeutic regimens (see below).

The impact of treatment of the first seizure on the patient's quality of life and preference is still a controversial issue. In the MESS study,[44] immediate treatment was not followed by a significant change in the scores for anxiety, depression, and mastery. Patients randomized to immediate treatment were then more likely to express a preference for the alternative treatment than were those randomized to deferred treatment.

Other Factors

The decision to treat a first epileptic seizure must be based on factors that are pertinent to the individual patient's situation.[9] A practical factor that might influence the decision to treat a first epileptic seizure is the need for the patient to drive and pertinent licensing regulations regarding patients with seizures.[5] Another factor that may encourage treatment after a first seizure is the local health insurance system. In countries with public health insurance coverage, no pressures are made on the therapeutic decisions by the practicing physicians; however, in countries such as the United States, the risk of recurrence must be minimized to prevent financial complications to the patient. Compliance is also extremely influential in deciding whether to treat a patient after a first seizure. Although it may be difficult to assess compliance in a newly diagnosed patient, it is important to identify poor compliers, as failure to adhere to the proposed treatment regimen is one of the most common causes of treatment failure.[41] In the FIRST trial,[24] poor compliance was among the most likely causes of recurrence in treated patients. In patients with poor compliance, anticonvulsant therapy might be withheld until seizure recurrence, in which case the greater risk for further relapse may change the attitude of the patient toward medication. There are also sociocultural factors for each patient that must be considered when deciding whether the complications of a recurrence outweigh the risk of acute or chronic drug toxicity. These factors must be

carefully evaluated on an individual basis, regardless of any general recommendation.

Starting or Withholding Treatment after a First Seizure

Even in the presence of multiple risk factors for seizure recurrence, the first unprovoked seizure may still remain an isolated episode. In addition, given the high potential for misdiagnosis among epileptic seizures, pseudoseizures, and nonepileptic events, treatment should be generally deferred in most patients with a first seizure. This is also the case for individuals in whom the recurrence of the seizure does not pose significant physical and psychological problems or who might be unduly exposed to the adverse effects of the AEDs (Table 2). Included are children, pregnant women, elderly subjects, and individuals with hematologic, liver, and kidney disorders. In children, for whom the consequences associated with a seizure are generally low because they are usually in a supervised environment and who are particularly susceptible to adverse effects from medications, the decision should usually be not to treat, even if they fall into categories with a high risk of recurrence. Likewise, in women of childbearing age, the recurrence of a first seizure must be balanced with the potential for adverse effects and teratogenic potential of AEDs. The elderly also might be left untreated after a first seizure because they may be less disadvantaged by the consequences of a relapse, their susceptibility to the adverse drug reactions is greater (see above), and the possibility exists that the first seizure is the hallmark of an underlying central nervous system disorder (i.e., progressive, symptomatic seizure). Patients with metabolic disorders will benefit from alternative treatments and may be at greater risk of experiencing drug toxicity. Even in the presence of an apparently unprovoked seizure, the acute manifestation of the disease must be considered.

As about 60% to 70% of recurrences are within 6 months of the first seizure,[2,31,60] patients withholding treatment should consider restriction of dangerous jobs, noncommercial driving, and recreational activities during this period. Commercial and professional drivers with a first unprovoked seizure should be subject to more restrictive rules. Patients at higher risk of recurrence might be considered for treatment after a single unprovoked seizure (Table 3). These include patients with single seizures and EEG epileptiform abnormalities or an associated medical or neurologic condition possibly increasing the risk of further seizures. In adults who depend on driving, the risk–benefit analysis is a matter of personal judgment and must be individualized. Any treatable epileptogenic condition must be identified and given specific therapy. Medical management of first seizures is beyond the scope of this chapter. The treatment of the first unprovoked seizure might be indicated in patients with a documented etiology or an abnormal EEG. Individuals with a first seizure associated with a neurologic deficit present from birth, progressive neurologic disease, or gross structural lesion also might be candidates of immediate treatment. Status epilepticus as the first seizure is a special case that merits careful assessment of the risks and benefits of treatment including prescribing abortive therapy. Those who present with a cryptogenic status as their first unprovoked seizure do not have an increased risk of recurrence.[33,60,63] However, should a recurrence occur, it is likely to be prolonged and the risk of recurrent status is increased.[10,63] However, the treating physician must also balance all the factors that play a role in the outcome of a first seizure, the personal characteristics of the patient, and the advantages and limitations of treatment. In that sense, the social complications (e.g., loss of employment) and the emotional reflections of a relapse should be strongly considered. If treatment is considered, the choice of the AED should be individualized and factors should be considered including teratogenicity, patient's cognitive abilities, drug interactions, physician's familiarity with the drug, and cost. The starting dose should be in the lower range and the maintenance dose should be increased only at the presence of a relapse. In the absence of published guidelines, the duration of treatment should be driven by common sense. In children, there is little justification for continuing treatment beyond 1-year seizure freedom. For adults, at least 1 year of treatment should be recommended and an individual decision is required for drug discontinuation and should consider the medical and social consequences of a recurrence. Where possible, all these data should be communicated to the patient and the relatives or caretakers, who must be as knowledgeable as possible about the issues so that an informed decision can be made.

Table 2 Suggested Treatment Plan in Patients with a First Unprovoked Epileptic Seizure

Favors withholding treatment	Favors considering treatment
Normal EEG	Abnormal (epileptiform) EEG
Cryptogenic/idiopathic etiology	Symptomatic etiology
Blood, liver, kidney disease	Risky occupation
Pregnancy	No disease interfering with drug metabolism Need to drive

EEG, electroencephalogram.

Table 3 Variables Associated with High and Low Risk of Seizure Recurrence after a First Unprovoked Seizure

	Risk of recurrence
Age	+/-
Sex	0
Family history (first-degree relatives)	+
Seizure type (partial)	+/-
Status epilepticus	+/-
Abnormal (epileptiform) EEG	++
Known etiology	++
Sleep state—sleeping	+
History of prior provoked seizures	+
Time elapsed from seizure	+
Abnormal neurologic examination	NA
Todd paresis	+
Drug treatment	-

-, association with low recurrence risk is weak; +/-, association with recurrence risk is conflicting; 0, no association; +, association with high recurrence risk is weak; ++, association with high recurrence risk is strong and/or consistent; EEG, electroencephalogram; NA, data not available.

Treatment of the Patient with Occasional Seizures

In an earlier adult study,[34] the 70% recurrence risk after a second seizure led to the conclusion that treatment with AEDs is appropriate once a second seizure has occurred. In children,[62] the overall recurrence risk of about 70% was higher in those with a remote symptomatic etiology and in those whose second seizure occurred within 6 months of the first. EEG abnormalities and sleep state at the time of the seizure, which helped to distinguish those who had only one seizure from those who experienced a recurrence, were no longer associated with a differential risk of further seizures once a second attack had occurred. Treatment decisions in the child with a second seizure are complex. Many of these children have idiopathic self-limited syndromes such as benign rolandic epilepsy in which the need for treatment has been questioned.[1,26] In addition, only 25% of children who had two seizures experienced 10 or more seizures over a 10-year period.[62] Thus, the decision to treat children with cryptogenic/idiopathic seizures who have a second attack must consider whether a benign self-limited syndrome is present, as well as the frequency of the seizures and the relative risks and benefits of therapy.

More recent studies cast doubt even on the need to treat adults with rare seizures. The MESS study,[44] which randomized subjects to immediate versus deferred therapy, found no differences in outcome between the two groups. Delayed treatment in this study was when the physician and subject agreed to initiate treatment and was not necessarily the second seizure. As noted above, patients randomized to immediate treatment were then more likely to express a preference for the alternative treatment than were those randomized to deferred treatment. As treatment does not influence long-term outcomes, one needs to reassess the risks and benefits of treatment even in adults with two seizures. This is particularly true in young women entering their childbearing years and in patients who live in an urban setting who use public transportation rather than driving.

Summary and Conclusions

In light of the accumulated epidemiologic findings that have changed our understanding of seizures and epilepsy, treatment of a single seizure is no longer automatic. Many factors have to be weighed, including the effect of treatment on seizure recurrence, the effect of treatment on the long-term prognosis of epilepsy, the adverse reactions (including teratogenicity), and the cost of drugs. The diagnosis of the first seizure, the results of an EEG, and the presence or absence of an underlying etiology to which the seizure can be attributed all contribute to the decision of whether to treat. The adverse events of drug treatment, as well as patient lifestyle issues, must also be considered. The decision as to whether or not to treat a first unprovoked seizure must be based on a risk:benefit assessment that weighs the risk of another seizure against the risk of chronic AED therapy. This decision must be individualized and take into account both medical issues and patient and family preference. The Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society have recently developed the following recommendations for children and adolescents[37]: (a) treatment with AED is not indicated for the prevention of the development of epilepsy and (b) treatment with AED may be considered in circumstances where the benefits of reducing the risk of a second seizure outweigh the risk of pharmacologic and psychosocial side effects. In the absence of official guidelines for adults (which are awaited), these recommendations can also be applied to adults.

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Chapter 123

Treatment of Neonatal Seizures

Eli M. Mizrahi

Mark S. Scher

Introduction

The overall goal of treatment of neonatal seizures is to minimize brain injury that may be associated with or caused by recurrent seizures. A critical factor in the therapy of neonatal seizures is accurate diagnosis. This requires precise clinical characterization and classification of neonatal seizures and, when the electroencephalogram (EEG) is available, accurate interpretation of the ictal EEG. These will allow for the determination of the presence or absence of behaviors that can be considered neonatal seizures and, importantly, whether these clinical events can be considered epileptic or nonepileptic in origin. Overall, this provides the basis for the determination of the appropriateness of antiepileptic drug (AED) treatment.

Characterization, classification, and determination of pathophysiology have been discussed in detail in Chapter 56 and are summarized in Table 1. In this chapter, the term *seizures* will be utilized to refer to all clinical seizure types; the terms *epileptic* and *nonepileptic* will be used to specifically address the therapy of these types. The discussion below, for the most part, will be directed toward seizures based on their clinical characteristics. However, some aspects of the discussion will consider electrical seizure activity, either alone or in relation to clinical seizures. In these instances, EEG seizure discharges will be referred to specifically. One practical method of classifying seizures is to consider the clinical events in relationship to electrical seizure activity. Thus, *electroclinical seizures* are those during which both clinical and electrical seizure activity occur simultaneously, *electrical-only seizures* are those without clinical events, and *clinical-only seizures* are those that occur with no associated electrical seizure activity.

Principles of Therapy

The goal of treating neonatal seizures is to prevent long-term central nervous system (CNS) dysfunction, which may be associated with or potential sequelae of seizures. The main objectives in the therapy of neonatal seizures are the treatment of the etiologic factors that may be responsible for the seizures and the cessation of seizures of epileptic origin with either AEDs or etiology-specific therapy. These goals may be achieved in the treatment of some, but not all, infants with seizures. Etiologic factors may not be determined in all cases, and when potential causes are discovered, their precise relationship to the seizures may not be known. Some clinical seizures, because of their nonepileptic physiologic origin, may not require AEDs. Importantly, AED administration in the treatment of some epileptic seizures may not be effective in control of either the clinical or the electroencephalographic seizures. Finally, some electroencephalographic seizures may be difficult to control, despite high doses of multiple AEDs. While it is not definitively determined that either recurring seizures or acute or chronic AEDs have an adverse effect on the developing brain, there is recent evidence suggesting that both seizures and AEDs may have unwanted sequelae.

In addition to the characterization and classification of seizure type, the treatment of neonatal seizures, ideally, is based on the consideration of several interrelated factors. These include identification of the etiology of the seizure, recognition of associated risk factors, determination of pathophysiology of the seizures, assessment of the duration and the severity of the seizures, understanding the natural history of the specific seizure disorder, and assessment of the expected effects that the seizures and the AEDs may have on the developing brain. Unfortunately, information concerning all of these factors may not be complete. Despite limitations imposed by incomplete data, some rational decisions for therapy can be made by understanding these constraints and the information that is known about neonatal seizures.

Phases of Acute Therapy

Three phases of acute therapy for neonates with seizures are initial medical management, etiology-specific therapy, and AED therapy. These phases are typically individualized to each infant.

Initial Medical Management

The usual principles of general medical management, which are important in the care of older children and adults with acute seizures, also apply to neonates with seizures: maintenance of airway, adequate ventilation, and cardiovascular circulation. Neonates with seizures may be critically ill, and the frequency or duration of epileptic seizures may be consistent with the diagnosis of status epilepticus. Changes in respirations, heart rate, and blood pressure may occur (a) in association with clinical seizures, (b) as a consequence of the seizures themselves, (c) as a consequence of the etiologic or risk factors, or (d) in association with vigorous AED therapy. Thus, measures must be taken to ensure adequate ventilatory support and circulatory perfusion of neonates with seizures during initial evaluation and therapy. The anticipation that these potential autonomic changes may occur will increase the likelihood of their successful treatment.

Table 1 Classification of Neonatal Seizures Based on Electroclinical Findings

Clinical seizures with a consistent electrocortical signature (pathophysiology: epileptic)

- Focal clonic
  - Unifocal
  - Multifocal
  - Hemiconvulsive
  - Axial
- Focal tonic
  - Asymmetric truncal posturing
  - Limb posturing
  - Sustained eye deviation
- Myoclonic
  - Generalized
  - Focal
- Spasms
  - Flexor
  - Extensor
  - Mixed extensor/flexor

Clinical seizures without a consistent electrocortical signature (pathophysiology: presumed nonepileptic)

- Myoclonic
  - Generalized
  - Focal
  - Fragmentary
- Generalized tonic
  - Flexor
  - Extensor
  - Mixed extensor/flexor

Motor automatisms
  Oral-buccal-lingual movements
  Ocular signs
  Progression movements
  Complex purposeless movements
Electrical seizures without clinical seizure activity

From Mizrahi EM, Kellaway P. Characterization and classification of neonatal seizures. *Neurology.* 1987;37:1837–1844; and Mizrahi EM, Kellaway P. The response of electroclinical neonatal seizures to antiepileptic drug therapy. *Epilepsia.* 1992;33(Suppl 3):114.

Table 2 Etiology-specific Therapy for Neonatal Seizures of Metabolic Origin

	Acute therapy	**Maintenance therapy**
Glucose, 10% solution	2 mL/kg IV	Up to 8 mg/kg/min IV
Calcium gluconate, 10% solution (9.4 mg of elemental Ca/mL)	2 mL/kg IV over 10 min (18 mg of elemental Ca/kg)	8 mL/kg/day IV[a] (75 mg of elemental Ca/kg/day)
Magnesium sulfate, 50% solution (50 mg of elemental mg/mL)	0.25 mL/kg IM	0.25 mL/kg IM repeated every 12 h until normomagnesemia
Pyridoxine	100 mg IV	

[a] After restoration of normocalcemia, tapering dosage may help in preventing rebound hypocalcemia.

Diagnosis of hypoglycemia, hypocalcemia, and hypomagnesia may vary between laboratories and is dependent on neonate's gestational age (with preterm infants tending to tolerate lower physiologic levels). Administration of metabolic correcting solutions requires careful monitoring of infant's systemic homeostasis, including electrocardiogram monitoring during administration of calcium.[33,34] Table from Mizrahi EM, Kellaway P. *Diagnosis and Management of Neonatal Seizures.* Philadelphia: Lippincott-Raven; 1998:181.

Etiology-specific Therapy

When specific causes of seizures are identified and are potentially treatable, etiology-specific therapy is initiated. The therapy of specific etiologic factors is critical as the seizures may not be responsive to standard AED therapy unless the underlying causes are successfully treated. In some cases, etiology-specific therapy may be the only treatment needed. In other cases, AEDs must be administered because of secondary brain injury caused by the primary process. For example, metabolic etiologies such as hypocalcemia, hypomagnesemia, and hypoglycemia may be corrected, resulting in cessation of seizures and obviating the need for AEDs. On the other hand, these or other etiologies may be associated with additional underlying brain disorders; though therapies must be directed toward central nervous system (CNS) and systemic infections, AEDs may still be required for complete management.

Treatments of metabolic etiologies are listed in Table 2, including therapies for the relatively common conditions of hypocalcemia, hypomagnesemia, and hypoglycemia. For completeness, it also includes the therapy for pyridoxine deficiency. However, while pyridoxine deficiency is often cited as a treatable cause of medically refractory neonatal seizures, it is exceedingly rare and may not warrant the wide consideration it has received as an important cause of neonatal seizures. Other metabolic disorders can masquerade as hypoxic-ischemic encephalopathy with seizures and should be considered in the differential diagnosis, depending on historical, clinical examination, and laboratory findings; glycine encephalopathy, sulfite oxidase deficiency/molybdenum cofactor deficiency, glucose transporter defect deficiency syndrome, mitochondrial disorders, and folinic acid–responsive seizures are a partial listing.[18]

Table 3 Dosages of First-line, Second-line AEDs in the Treatment of Neonatal Seizures

	Dose			
Drug	**Loading**	**Maintenance**	**Average therapeutic range**	**Apparent half-life**
Diazepam	0.25 mg/IV (bolus) 0.5 mg/kg (rectal)	May be repeated one to two times		31–54 h
Lorazepam	0.05 mg/kg (IV) (over 2–5 min)	May be repeated		31–54 h
Phenobarbital	20 mg/kg IV (up to 40 mg)	3-4 mg/kg in two doses	20–40 µg/L	100 h after days 5–7
Phenytoin	20 mg/kg IV (over 30–45 min)	3-4 mg/kg in two to four doses	15–25 µg/L	100 h (40–200)

*Based on Fenichel GM. *Neonatal Neurology.* 3rd ed. New York: Churchill-Livingstone; 1990; Aicardi J. Neonatal seizures. In: *Epilepsy in Children.* 2nd ed. International Review of Child Neurology Series. New York: Raven; 1994:217–252; and Volpe JJ. Neonatal seizures. In: *Neurology of the Newborn.* 4th ed. Philadelphia: WB Saunders; 2001. Table from Mizrahi EM, Kellaway P. *Diagnosis and Management of Neonatal Seizures.* Philadelphia: Lippincott-Raven; 1998:181.

Acute Antiepileptic Drug Therapy

First-line Antiepileptic Drug Therapy

The AEDs traditionally utilized in the acute treatment of neonatal seizures are phenobarbital, phenytoin, and a benzodiazepine (diazepam and, more recently, lorazepam) given intravenously (Table 3). The dosages utilized in the United States are phenobarbital, 20 mg/kg as a loading dose, followed by additional dosages of 10 mg/kg to achieve serum levels between 20 and 40 μg/mL; phenytoin, 20 mg/kg as a loading dose to achieve serum levels between 15 and 20 μg/mL; diazepam, 0.1–0.3 mg/kg in repeated dosages; and lorazepam, 0.05 mg/kg.[4,13,39,40] Acute administration of each of these AEDs may carry some risk of adverse reactions and, therefore, treated infants should be monitored closely. These adverse events may include CNS depression, hypotension, bradycardia, and respiratory depression (phenobarbital, diazepam, lorazepam), and cardiac arrhythmia (phenytoin).

Traditionally, initial dosing has been determined only by body weight of the infant. However, Painter et al.[51] stressed the importance of serum protein characteristics of phenobarbital and phenytoin in initial dosing. The unbound (free) fraction of each of these drugs is pharmacologically active, and the protein-binding characteristics in neonates may vary to an extent that a uniform dosing schedule by weight only may not provide the same efficacy and safety to all infants. Thus, Painter et al. suggested that the use of in vitro binding profiles, calculated for individual neonates at risk for seizures, will allow the establishment of appropriate loading dosages of each drug and will avoid potential toxicity in individual neonates. This technique is not universally available. However, the findings do underscore the potential variability among neonates in the utilization of these drugs.

There is relative consensus of selection of specific AEDs as first- and second-line drugs: Phenobarbital is almost universally accepted as the first-line AED and phenytoin as the second-line AED.[4] However, there is less consensus as to the use of additional AEDs if the initial drugs fail to control the seizures. Most often, a benzodiazepine (diazepam or lorazepam) may be given in these instances.

Despite the wide acceptance of phenobarbital as the first-line AED, there have been few controlled studies of the relative efficacy of various AEDs in the initial treatment of neonatal seizures. Recently, however, Painter et al.[53] compared the effectiveness of acute administration of phenobarbital and phenytoin in seizure control, found no significant difference, and suggested that neither is as efficacious as originally thought.

It is helpful to understand aspects of the pharmacology of phenobarbital and phenytoin in the neonate during their use in treatment of seizures. The availability of active drug given at standard doses may be altered by pathologic conditions in the sick neonates. These principles are discussed in detail elsewhere[12,36,37,50] and summarized here. Phenobarbital is a weak acid and is protein bound. Infants with acidosis may have less active phenobarbital available and those with hypoalbuminemia may have greater unbound or active drug available. Both conditions may be found in sick neonates. Phenobarbital is eliminated by the liver and kidney. Thus, infants with impaired hepatic or renal function, which may occur in infants with hypoxic-ischemic encephalopathy, may have a reduced rate of elimination and, therefore, a potential for toxicity with standard dosing. There is a longer half-life of phenobarbital in preterm compared to term infants, and in term infants the half-life is reduced with chronologic age in the first month of life. Thus, in preterm infants there is a potential for higher serum levels with standard doses and the potential for toxicity. As the infant becomes older there is the potential for identical doses to result in lower serum levels, creating the potential for breakthrough seizures with no other change in the infant's clinical condition. Overall, monitoring trends of serum levels rather than day-to-day fluctuations are more useful in management of phenobarbital therapy.[17,21,52,62]

Important pharmacologic characteristics of phenytoin are described in detail elsewhere[10,16] and summarized here. These features include nonlinear pharmacokinetics, a variable rate of hepatic metabolism, a decrease in elimination rates during the first weeks of life, and a variable bioavailability of the drug with various generic preparations. In addition, there is a redistribution of the AED after the initial dose resulting in a drop in brain concentrations after the first dose. These pharmacologic characteristics indicate that phenytoin use requires individualization of dosing after the initiation of therapy.

Acute Therapy for Refractory Seizures

Because neonatal seizures may be resistant to traditionally utilized AEDs, other medications have been tried with varying success.[26,27,49,50] True efficacy of these agents is difficult to assess because their trials have been conducted either in an uncontrolled manner, on few patients, on infants who have already received and failed with other AEDs, on infants with only clinical seizures with electroencephalographic confirmation, or on infants utilizing oral medication (because of availability of the compound), thereby limiting the assessment of efficacy. In addition, because of the preliminary nature of these trials, little safety data are available. These AEDs have been used as alternative acute drugs or as adjuvant therapy.

The AEDs used as alternative acute therapy—and given intravenously—are midazolam,[31,58] lidocaine,[26,27] and paraldehyde (not available in the United States).[35] One recent study reported success with continuous midazolam infusion in the treatment of otherwise uncontrolled neonatal seizures,[31] although infants experienced treatment-related hypotension that was medically managed. Lidocaine has also been utilized, primarily in Europe, as an AED in neonates. It has been administered intravenously at a rate of 4 mg/kg/hr, which achieves serum levels between 3.4 and 10.5 mg/L. This drug has a narrow therapeutic range; at serum levels between 0.5 and 4 mg/L, lidocaine may act as an anticonvulsant, but at levels of

7.5 mg/L, it may act as a convulsant.[26,27,48,50,55] Boylan et al.[9] reported limited success with lidocaine in refractory neonatal seizures. Another recent investigation[60] reported that during the use of lidocaine (initial loading dose of 2 mg/kg over 10 minutes followed by a continuous infusion of 6 mg/kg/hr), 4.8% of infants experienced a cardiac arrhythmia (all responding to lidocaine discontinuation).

Some AEDs have been used in attempts to control otherwise medically refractory seizures. Agents in both classes have been utilized either intravenously or orally with variable success. Those given intravenously and primarily as alternatives to acute therapy include clonazepam,[3] lidocaine,[9,26,27,60] midazolam,[58] and paraldehyde.[35] Other agents given orally to control medically refractory seizures include carbamazepine,[38] primidone,[56] valproate,[20] vigabatrin,[2] and lamotrigine.[40] The success of this latter group of AEDs is difficult to assess since they have been used in conjunction with other AEDs and well into the course of illness.

These other medications include carbamazepine, primidone, paraldehyde, clonazepam, valproate, vigabatrin, and lidocaine, Carbamazepine has been utilized in dosages of 10 to 16 mg/kg/day to achieve serum levels between 10 and 40 mg/L approximately 6 hours after its oral administration.[38] Primidone, also given orally to neonates with otherwise refractory seizures, has been administered in loading dosages between 15 and 25 mg/kg.[54,56] Paraldehyde, given intravenously, has been utilized with success (200 mg/kg, followed by 15 mg/kg/hr).[23,35] Clonazepam, intravenously in dosages of 0.1 mg/kg, has been given to infants with seizures refractory to phenobarbital.[3] Valproate has been reportedly used to treat neonatal seizures, with serum levels up to 60 mg/L.[20] There are also anecdotal experiences with the use of vigabatrin and lamotrigine in neonates with medically refractory seizures, although few published data of efficacy and safety are available.

Initiation of Therapy

Not all neonatal seizures require acute AED therapy. Some examples include seizures that may be nonepileptic in origin; seizures that may be epileptic in origin but that are adequately treated by etiology-specific therapy; or epileptic seizures that may be considered so brief, infrequent, and short lived as to not warrant AED treatment. Thus, the decision to initiate AED therapy for neonatal seizures should not be automatic after the reporting or recognition of the seizures. Rather, initiation of AED therapy requires the consideration of seizure type, pathophysiology, duration and severity of seizures, natural history of the seizure disorder, and anticipated effects of both the seizures and the selected AEDs on the infant. Though comprehensive data on these factors may not be available, it is essential that these factors be considered at the onset of therapy.

Most often, clinicians consider beginning AED therapy without the benefit of EEG or bedside EEG/video monitoring. Under these circumstances, the clinician must first decide whether the clinical seizures are of epileptic or nonepileptic origin (Table 1) (see Chapter 56). If the seizures are of epileptic origin, they must be assessed for duration and severity.

Antiepileptic Drug Therapy Based on Features of the Clinical Seizure

The clinician may encounter four specific situations in which AED use may be considered based solely on the clinical features of the seizures (Table 1)[43]:

1. **Focal clonic or focal tonic seizures may be prolonged and recurrent**. The clinical features of focal clonic or focal tonic seizures help to designate them as epileptic in origin. Focal clonic seizures are repetitive and rhythmic muscle contractions that cannot be arrested by restraint or repositioning. Similarly, focal tonic seizures, such as sustained posturing of a limb, cannot be altered by these maneuvers. The focal tonic seizures that are characterized by eye deviation can be differentiated from the random eye movements of nonepileptic motor automatisms, as the epileptic tonic eye deviation is sustained and cannot be evoked by stimulation. Once the clinical focal clonic or focal tonic seizures are considered epileptic in origin, duration and severity must be considered. When they are thought to be sustained and prolonged, they are treated vigorously with AEDs.
2. **Focal clonic or focal tonic seizures may be brief and infrequent.** The specific features of these seizures of epileptic origin are the same as those just described, also providing the basis for their designation as epileptic in origin. As such, AEDs may be utilized in attempts to control the seizures. However, because these seizures may be brief, occur infrequently, and have a short natural history with relatively rapid spontaneous resolution, the use of AEDs for these seizures may not be required and is being reconsidered. This re-evaluation is based on the following considerations: epileptic seizures may be reactive, or secondary, to an acute underlying brain disorder; for some infants following the acute injury, seizures may resolve spontaneously as the acute period passes; and, in these instances, the potential adverse effects of AEDs may outweigh the potential risks of these brief and infrequent seizures on the developing brain.[46] Unfortunately, specific criteria for the differentiation of “brief” and “infrequent” seizures from “prolonged” and “recurrent” seizures have not been established. In addition, the issues of whether AEDs or seizures adversely affect the immature brain have not yet been completely resolved.
3. **Generalized tonic posturing and motor automatisms may be responsive to stimulation and may be suppressed by restraint.** Some seizure types may be presumed to be of nonepileptic origin based on their clinical features and their response to stimulation and restraint (see Chapter 56). These include generalized tonic posturing and motor automatisms (including ocular signs, oral-buccal-lingual movements, and movements of progression, and are more traditionally referred to as *subtle seizures*). This determination can be made at the bedside based on the characterization of the events and their response to clinical maneuvers: The spontaneous events can be suppressed by restraint or repositioning of the limbs or trunk, and events similar to spontaneous events can be evoked by tactile stimulation. Traditionally, these clinical events have been treated with AEDs, and in some instances, their frequency and severity have diminished. Whereas this finding has been utilized to support the notion that these events may be epileptic seizures, this effect of AEDs is most likely not the result of specific antiepileptic properties, but rather because some of these drugs are also CNS depressants. Overall, if generalized tonic posturing and motor automatisms demonstrate characteristic clinical features, they can be presumed to be of nonepileptic origin and do not require AED therapy.[41,43] Although the clinical events may be initially quite dramatic, their natural course is one of gradual and spontaneous resolution without AED therapy.
4. **Generalized tonic posturing and motor automatisms may not be responsive to stimulation or may not be suppressed by restraint**. For some infants, the clinical features of spontaneous generalized tonic posturing and motor automatisms may be typical of nonepileptic events, but they may not respond in a characteristic way to the clinical maneuvers of restraint, repositioning, or stimulation. In these instances, the decision to initiate AED treatment is more difficult. Some clinicians may withhold AEDs with the understanding that the clinical features of the spontaneous events are evidence enough of the nonepileptic origin of the events. However, others may initiate AED treatment with the belief that clinical observation and maneuvers alone cannot provide data to indicate underlying pathophysiology.

Antiepileptic Drug Therapy Based on Electroencephalographic or

Electroencephalographic/Video Monitoring

Bedside EEG and EEG/video monitoring are powerful diagnostic tools in the diagnosis of neonatal seizures, and they complement clinical assessment to a considerable degree.[30,42] When these techniques are available and appropriately utilized, additional clinical circumstances may be encountered that determine whether AED therapy should be initiated in the treatment of neonatal seizures.

1. **Clinical seizures may be present in the absence of EEG seizure activity**. These clinical seizure types include generalized tonic posturing and motor automatisms (or some "subtle seizures"). As discussed above, the clinical features of the spontaneous events and the response of the events to clinical maneuvers suggest that they are of nonepileptic origin. The lack of EEG seizure activity at the time of the clinical seizures provides further support for this determination. These clinical events, particularly when they occur in the absence of electrical seizure activity, are not treated with AEDs.
2. **Electroencephalographic seizure activity may occur in the absence of any clinical seizures**. This may occur in neonates who are pharmacologically paralyzed for respiratory care; in neonates with seizure discharges of the depressed brain type (see Chapter 56); or in neonates with epileptic seizures already treated with AEDs. Electrical seizure activity occurring in the absence of any clinical seizure activity is treated with AEDs. However, these electrical seizures may be highly resistant to therapy, despite high dosages of several AEDs, and the degree to which high-dose polypharmacy should be utilized in attempts to abolish EEG seizure activity is controversial (see below).

Response of Seizures to Acute Antiepileptic Drug Therapy

Although AED therapy is initiated to stop epileptic seizures, prevent seizure recurrence, and minimize any adverse consequences of the seizures to the infant, not all of these goals may be easily accomplished. Not all electrical seizure discharges can be eliminated; when some are eliminated, their recurrence can be unpredictable, and it is not clear what, if any, adverse effects seizures may have on the infant.

The response of epileptic seizures to AEDs has been described in investigations utilizing EEG/video monitoring. In an infant not treated with AEDs, clinical epileptic seizures occur in a time-locked relationship to EEG seizure activity. The initial response to AED administration is the cessation of clinical seizures; however, the EEG seizure activity may persist. This initial response to AED treatment has been referred to as decoupling[43,44] or uncoupling[57] of the clinical from the electrical seizure (Figs. 1 and 2). The response of the EEG to additional therapy consisting of increasing dosages or with additional AEDs is variable and not always successful. The electrical seizure activity may prove to be highly resistant to additional AED therapy.

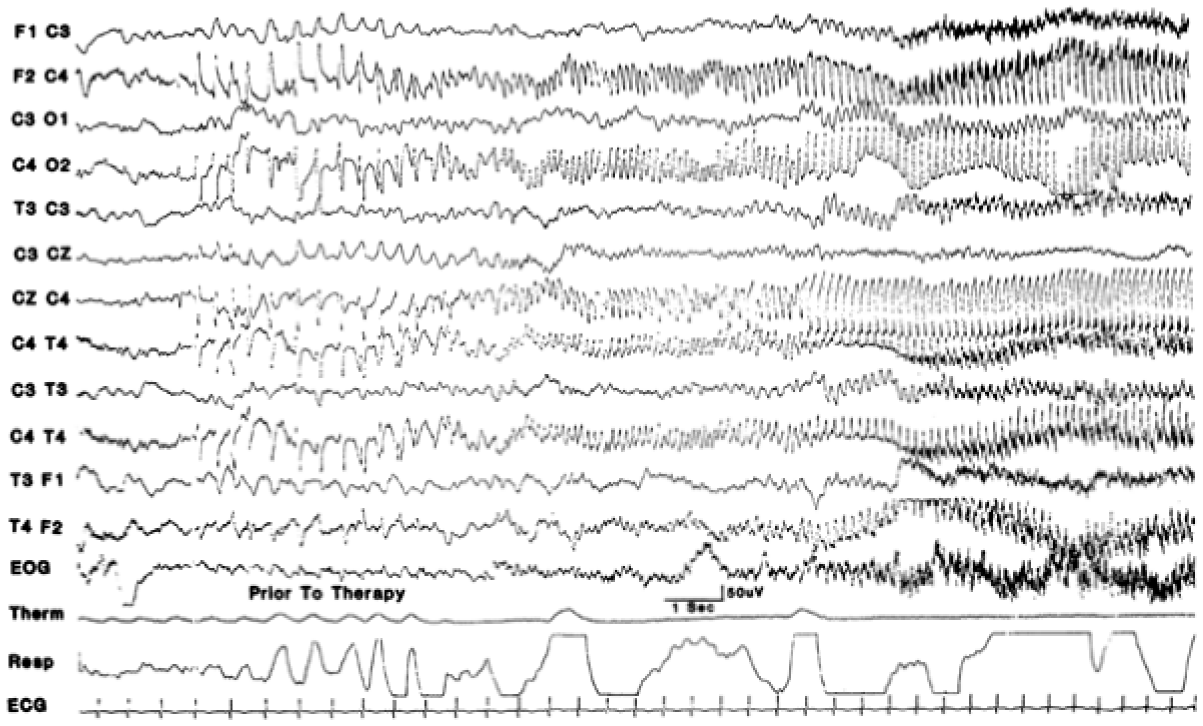
F1 C3
F2 C4
C3 O1
C4 O2
T3 C3
C3 CZ
CZ C4
C4 T4
C3 T3
C4 T4
T3 F1
T4 F2
EOG
Therm
Resp
ECG
Prior To Therapy
1 Sec
50uV

FIGURE 1. Prior to treatment with phenobarbital, this electrical seizure discharge arising from the right central region is associated with focal clonic seizures involving the left arm and leg. (From Mizrahi EM. Consensus and controversy in the clinical management of neonatal seizures. In: Volpe JJ, ed. *Clinics in Perinatology. Vol 16, No 2: Neonatal Neurology*. Philadelphia: WB Saunders; 1989:485–500, with permission.)

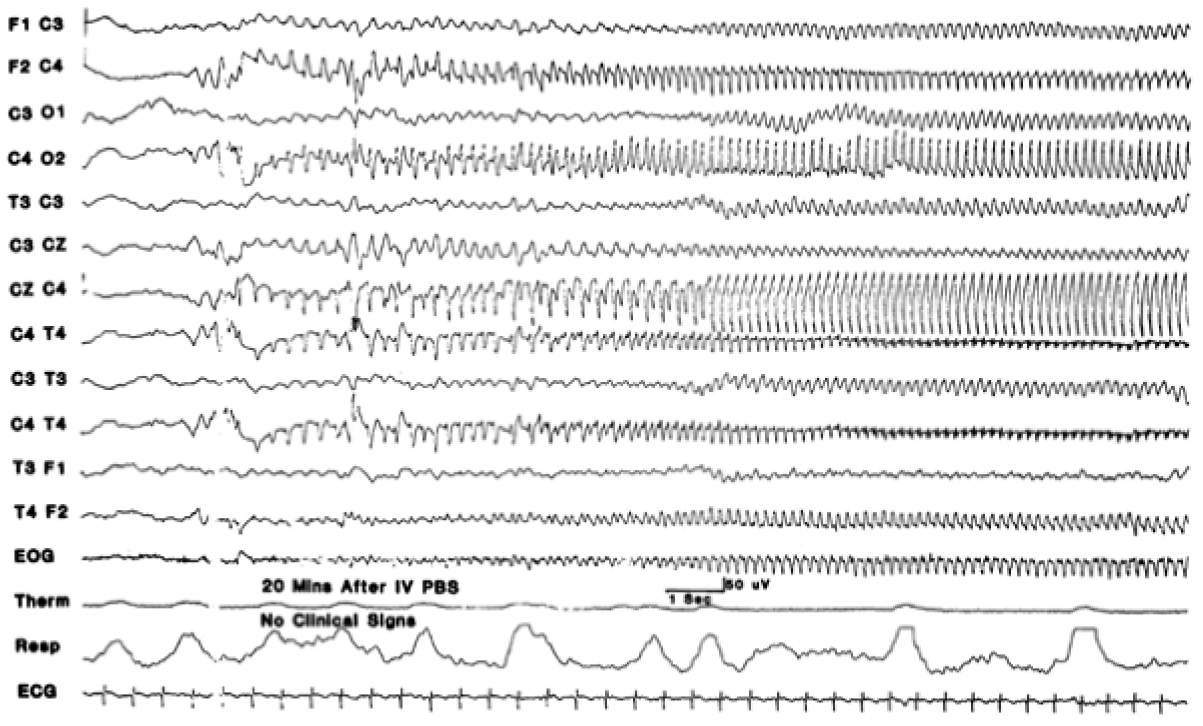
F1 C3
F2 C4
C3 O1
C4 O2
T3 C3
C3 CZ
CZ C4
C4 T4
C3 T3
C4 T4
T3 F1
T4 F2
EOG
Therm
Resp
ECG
20 Mins After IV PBS
No Clinical Signs
1 Sec
50 uV

FIGURE 2. Electroencephalogram from the same infant in FIGURE 1, following initiation of therapy with phenobarbital. The clinical seizure resolved, although the electrical seizure discharge recurs without clinical signs. (From Mizrahi EM. Consensus and controversy in the clinical management of neonatal seizures. In: Volpe JJ, ed. *Clinics in Perinatology. Vol 16, No 2: Neonatal Neurology*. Philadelphia: WB Saunders; 1989:485–500, with permission.)

Whereas the clinical seizures of epileptic origin may be controlled with AED therapy, the electrical seizure activity recorded by EEG that accompanies the clinical seizures may persist.[24] This response to AEDs raises the central question: What is the end-point of AED therapy cessation of clinical seizures or cessation of electrical seizure activity?

Vigorous attempts to eliminate electrical seizure activity may lead to the administration of higher dosages and multiple AEDs. In some instances, this management regime can be successful. However, this strategy may also fail to control EEG seizure activity. Regardless of the degree of success in seizure control, high-dose polypharmacy may be associated with the clinical problems of CNS depression, systemic hypotension, and respiratory depression. Here, the clinician must weigh the potential risks of vigorous AED treatment against the potential benefits and likelihood of success of therapy. In these situations, therapeutic strategies may be devised to strike an even balance. One scheme is to attain high therapeutic levels of phenobarbital and phenytoin, and then utilize individual dosages of a benzodiazepine in attempts to reduce or eliminate electrical seizure discharges. Further AED therapy may not be attempted because of the systemic adverse effects that are frequently encountered.

Chronic Therapy

Maintenance Therapy

Not all neonates require chronic therapy after acute seizures have been controlled; however, specific criteria for selection of neonates for maintenance therapy remain controversial. Once a desired therapeutic effect is obtained in the acute setting, infants are typically placed on regimens of maintenance AEDs. Phenobarbital, alone or with phenytoin (if it had been required to control the clinical seizures acutely), is utilized. The maintenance dosage of each is 3 to 4 mg/kg/day. The principles of monitoring serum AED levels, utilized in older children and adults, apply to neonates: Serum levels are most optimally obtained after five half-lives of the drug to be tested. If drug levels are obtained and found to be in a laboratory-designated *toxic range*, it should be considered in relation to the clinical condition of the infant. The presence of clinical toxicity rather than the isolated finding of elevated serum drug levels should determine alteration of dosages.

Maintenance treatment with either phenobarbital or phe-nytoin may pose some difficulties early in the course of therapy. When maintenance dosages of phenobarbital at 5 mg/kg/day are utilized, there may be drug accumulation within 5 to 10 days.[52] This is related to the relatively slow elimination rate of phenobarbital within the initial 2 weeks of treatment. This is particularly true for asphyxiated infants who may have had concomitant hepatic or renal dysfunction.[17,22,62] Eventually,

however, elimination rates increase with duration of therapy. Thus, maintenance dosage requirements may be relatively lower early in the course of therapy and increase later. Similarly, there may be problems in maintenance therapy with phenyt-oin. Stable serum levels may be difficult to maintain because of phenytoin's nonlinear kinetics and the rapid decrease in elimination rates during the first weeks of life.[10,16] The monitoring of serum AED levels periodically or when the clinical state of the infant changes (e.g., depressed state of alertness or breakthrough seizures) will guide the clinician in drug dosing, despite the relatively unpredictable pharmacokinetics of AEDs in the neonatal period.

Discontinuation of Therapy

Discontinuation of AEDs after a period of clinical seizure control is highly individualized as no specific practice guidelines have been established. An important consideration is the probable natural history of the treated disorder. For example, some seizures may represent a short-lived phenomenon produced in reaction to an acute injury. In this instance, then, the traditional practice of long-term AED therapy will extend treatment beyond what is needed for a relatively short-term clinical disorder. No controlled investigations have resolved this issue, and most clinicians individualize chronic AED therapy. Reported maintenance schedules range from 1 week to 12 months after the last seizure.[8] Although specific clinical and EEG predictors of recurrent seizures following AED withdrawal have not been identified,[11,22] there has been increasing clinical interest in short-term therapy, with AED withdrawal 2 weeks following the infant's last clinical seizure. Whereas EEG may be helpful in the neurologic assessment of infants following neonatal seizures, its use as a predictor of seizure recurrence has not been as valuable. This is, in part, related to the fact that there are no reliable interictal EEG signs of epileptogenesis early in life (e.g., spike-and-wave or sharp-wave transients) that can be present in older children. Therefore, the decision to withdraw AEDs is based primarily on the clinical course of individual infants and the report of the presence or absence of seizures.

Risk Versus Benefit of Antiepileptic Drug Therapy

As with all therapy, the decision to treat neonatal seizures with AEDs is based upon the consideration of relative risks versus relative benefits. Current evidence suggests that the treatment of electrical or electroclinical seizures with AEDs outweighs the relative risks of the use of AEDs themselves on the developing brain. This is particularly true if first-line AEDs at standard doses control the seizures. As increasing doses and AEDs are required, the risk:benefit ratio may change.

Risk of Recurrent Seizures

Primary Risks

For many years it was believed that even though the immature brain was more likely to develop seizures in response to injury than the more mature brain, the immature brain was either more resistant to seizure-induced injury or that any seizure-related alterations were not clinically significant. However, there is no clear consensus as to what, if any, sequelae may be associated with the occurrence of epileptic seizures in the developing brain.[28] Though some investigators suggest that, in animals, there are important changes in the CNS at a cellular or molecular level or involving brain circuitry, these may be transient, or their influence may not be detectable when performance is tested. These issues are the subject of continuing investigations. Various research strategies have been undertaken to further understand this problem with variable results. Overall, emerging evidence suggests that seizures early in life can result in permanent behavior and enhanced epileptogenicity although the mechanisms of some seizure-induced dysfunction have not been clearly delineated.[29,59] A number of mechanisms of seizure-induced injury have been investigated to determine whether seizures cause direct neuronal injury, whether seizures impair brain growth, whether seizures enhance epileptogenesis by altering hippocampal development, and whether seizures alter animal learning and behavior or the development of normal brain pathways.[5,59,61] These are discussed in detail in Chapter 56.

Secondary Risks

In addition, there are few conclusive clinical investigations of the adverse systemic effects of seizures. However, infants with prolonged seizures may experience changes in respiration, heart rate, or blood pressure and may have increased levels of energy utilization. In an infant who may already be medically compromised, these may be unwelcome clinical findings.

Risk of Antiepileptic Therapy

Primary Risks

There is also an equal lack of consensus concerning the possible adverse effects of AEDs on the developing brain. Early experimental data suggest alteration in cell growth and energy substrate utilization.[6,14,15,47]

However, the applicability of these findings to human neonates has been called into question, and the relative risks have been considered small when compared with the overall potential gain.[62] More recently, Ikonomidou et al.[7] assessed the effect of phenytoin, phenobarbital, diazepam, clonazepam, vigabatrin, and valproate on apoptotic neurodegeneration in the developing rat brain in plasma concentrations relevant for seizure control in humans. The basis of their study was the consideration that AEDs work via three mechanisms: limitation of sustained repetitive neuronal firing via blockade of voltage-dependent sodium channels; enhancement of γ-aminobutyric acid (GABA)–mediated inhibition; and blockade of glutamatergic excitatory neurotransmission. However, they hypothesized that these mechanisms that are blocked are also features of an endogenous neuroprotective system in the brain that is crucial for neuronal survival during development. They concluded that AEDs may impair survival-promoting signals and an imbalance between neuroprotective and neurodestructive mechanisms in the brain, which, during a developmental period of ongoing programmed neuronal death, will promote apoptotic neurodegeneration. However, it is unclear if these results can be extrapolated to the human. In addition, recent data from the same group show that another AED, topiramate, lacks the toxicity seen with some of the other drugs mentioned above.[24]

Secondary Risks

There have also been few studies of adverse effects of acute AED therapy. However, vigorous treatment may result in CNS depression, hypotension, bradycardia, and respiratory depression,[25] and may create the potential for secondary CNS hypoxia or ischemia.

Balanced Treatment Regimen

Overall, a regimen that may minimize perceived risks and maximize therapeutic benefit is as follows: (a) initiate acute therapy to eliminate clinical seizures with the first-line AED of phenobarbital; (b) if clinical or EEG seizures persist, increase phenobarbital dosage, add another first-line AED, phenytoin, and, if needed, a benzodiazepine; (c) if clinical seizures are controlled but electrical seizures persist, increase first-line AEDs to obtain high-therapeutic serum levels; (d) after seizure control is attained or is determined to be acceptable based on trials of initial therapy, establish maintenance therapy; (e) withdraw AEDs 2 weeks following the last clinical seizure; and (f) carry out clinical follow-up.

Summary and Conclusions

Treatment and Long-term Outcome

Though it is hoped that successful AED treatment of neonatal seizures will either prevent adverse sequelae or improve long-term outcome of affected neonates, there are few comprehensive studies that provide conclusive data concerning the relationship of cessation of seizures and prognosis. It may be assumed, however, that easily controlled seizures are the result of transient, successfully treated, or benign CNS disorders of neonates. On the other hand, medically refractory neonatal seizures may be the result of more sustained, less treatable, or more severe brain injury. Based on these assumptions, the primary factor that predicts outcome is the underlying cause of the seizures rather than specific characteristics of the epileptic events themselves.

Quality of Life Following Neonatal Seizures

Quality-of-life issues for patients who have experienced seizures have been almost exclusively discussed in relation to older children and adults. However, there are relevant points to be made for the neonate. Discharge from the hospital following the diagnosis and therapy of neonatal seizures is a period of both relief and increased anxiety for parents, other family members, and caregivers of affected infants. Some infants may have multisystem disorders requiring significant medical follow-up; others leave the hospital without any further problems. Despite these differences, discharge planning should include the discussion of seizure recognition; the potential, if any, of seizure recurrence; medication administration; and the course of action if seizures do recur.

Because the long-term outcome for most neonates with seizures is generally good, it is important to stress the fact that individual infants can be expected to have few, if any, problems that could be related to the neonatal seizures (beyond those dictated by the underlying etiology). For those infants with a good prognosis, efforts should be made to help family members look past the neonatal seizures and view their newborns as "healthy" rather than as "ill" children. For those infants whose neurologic outcome will clearly not be normal, clinicians should stress the needs of the potentially multiply handicapped child.

The occurrence of seizures in the newborn could be limiting to infants and children who may eventually be seizure free if parents view them as "at risk." Ample opportunity should be given to families to fully discuss their apprehensions and concerns. The clinician can take the lead in providing a forum for this discussion and, in turn, a basis for the normalization of the lives of infants and children who may have had seizures as neonates.

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Chapter 124

Treatment of Febrile Seizures

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Introduction

From a biologic perspective, febrile seizures are virtually always benign. However, they are frightening for parents and disruptive to family life. Therefore, the primary goal for treatment for febrile seizures should be to provide information and reassurance for parents. Aspects of febrile seizures other than treatment are considered in Chapter 57.

Evidence for the Benign Nature of Febrile Seizures Epilepsy

Epilepsy subsequently develops in only 2% to 4% of children with a first febrile seizure.[1,54,73] When it does, the seizures can be of virtually any type, although the highest association is with generalized rather than partial seizures.[14,61,62] Approximately 15% of children with epilepsy have one or more preceding febrile seizures, regardless of the cause of the epilepsy.[14] This observation suggests that the tendency to have febrile seizures plays an important role in a person's seizure threshold; however, there is no evidence that one or multiple febrile seizures cause epilepsy.[1,54,57] The febrile seizure tendency is likely inherited, possibly as an autosomal dominant trait with variable penetrance (see Chapter 57).

Intractable Complex Partial Seizures (the Mesial Temporal Sclerosis Connection)

For a further discussion of this issue, see Chapter 13. Unquestionably, intractable temporal lobe epilepsy with mesial temporal sclerosis, identified by pathologic studies or magnetic resonance imaging (MRI), has later developed in some children with prolonged febrile seizures.[20,26] These patients are rare,[14] and fortunately febrile status epilepticus is a benign phenomenon in most cases.[48] The cause-and-effect relationship between prolonged febrile seizures and mesial temporal sclerosis in humans is still debated, and the minimum length of febrile seizure that might cause mesial temporal sclerosis is unknown. Some animal experiments suggest that status epilepticus can damage mesial temporal structures in the immature brain,[51,53] but other studies do not.[76] Nevertheless, it seems prudent to stop prolonged febrile seizures promptly. It is important to keep in mind that an estimated 75% of prolonged febrile seizures are the first febrile seizure.[54] Therefore, the effort to eliminate febrile status should not determine the treatment for the vast majority of children with febrile seizures who have an excellent outcome.

Brain Damage

Short febrile seizures do not appear to damage the brain. The National Institute of Neurological Disorders and Stroke (NINDS) Collaborative Perinatal Project included 431 sibling pairs in which only one child had febrile seizures.[24] Testing included the Wechsler Intelligence Scale for Children (WISC) as a measure of overall intelligence and the Wide Range Achievement Test (WRAT) as a measure of academic achievement. No difference was found between children with and without febrile seizures in psychometric test scores at the age of 7 years. Even those 27 children with a febrile seizure lasting 30 minutes or more had a mean full-scale IQ no different from that of their siblings. The only exceptions occurred in sibling pairs in which the child with the febrile seizures was known to be neurologically abnormal before the first febrile seizure.

The British febrile seizure study documented intellectual, behavioral, and achievement function in a national sample of children followed to age 10 years.[74] There was no penalty for having one or more febrile seizures.

In the opinion of these authors, these studies are so robust that the issue of short febrile seizures and brain damage can be put to rest.

Recurrent Febrile Seizures

About 40% of children with a first febrile seizure have at least one recurrence.[1,54] Multiple recurrences are rare, with fewer than 10% having more than three recurrences.[54] There are several statistically valid predictors of recurrent febrile seizures, although for the individual child in a clinical setting, these predictors are often not very powerful.

Age is the most powerful predictor of a febrile seizure recurrence. If a child has a first febrile seizure at an age of <1 year,[54] <15 months,[7] or <18 months,[40] the risk for recurrence is increased severalfold. The risk for recurrence is also increased if the first seizure occurred at a low body temperature or after a short illness, or if there is a close family history of epilepsy.[7] Some authors have noted that atypical features of the first febrile seizure (focal, clustered, or prolonged) may predict recurrence,[57] although the largest studies did not find such a relationship.[1,7] One experienced investigator noted that increased exposure to infectious illness by attendance at a daycare facility increased recurrences.[40]

A typical child with a first febrile seizure who has the highest risk for recurrence (>60%) would be <14 months of age, have a marginally elevated temperature within the first day of being ill, and have a close family relative with febrile seizures. A typical child with a minimal risk for recurrence (<15%) would be >3 years at the first febrile seizure, have a temperature above 39°C at the time of the seizure after an illness of several days, and have no family history of febrile seizures.

If treatment for prevention of recurrent febrile seizures is contemplated, these two extremes of risk should be taken into account. However, the ability to predict recurrence does not mean that preventive treatment is indicated.

Approaches to Treatment

Antipyretic Measures to Prevent Febrile Seizures

Because fever (usually a high fever) is an essential element in the genesis of febrile seizures, it would seem intuitively correct that antipyretics would prevent febrile seizures. Empiric studies suggest the opposite. A meta-analysis concluded that there is no evidence that antipyretic medications reduce the risk of febrile seizure recurrence.[25] A British study found that many children with an initial febrile seizure had received an appropriate dose of antipyretics within an hour or two of a febrile seizure.[65] A Canadian study found no clear benefit in regard to recurrence risk from intensive antipyretic instructions to parents.[17]

A Finnish study randomized children to receive placebo or acetaminophen (10 mg/kg) at the time of illness for 2 years following a febrile seizure.[70] Again, there was no effect on febrile seizure recurrences. Those receiving placebo had recurrent febrile seizures during 8.2% of febrile illnesses, compared with 5.2% for those receiving acetaminophen.

A Dutch study randomized 230 children with at least one risk factor for a recurrent febrile seizure to either receive ibuprofen or placebo during subsequent febrile illnesses. The recurrence risk was identical in treatment and placebo groups.[71]

At present, the only apparent effect of antipyretics on febrile seizure treatment may be to increase “fever phobia."[67] This may be contrasted with the increasing evidence of the beneficial effects of fever during recovery from infections.[66] The compulsive use of antipyretic drugs cannot be recommended, other than to make the child more comfortable. Because sponging the child is ineffective in reducing body temperature and is uncomfortable, it should be abandoned.[55] Despite the strong evidence that antipyretics are ineffective, many health care providers remain attached to their use; more education is needed.[75]

Another obvious approach to reducing febrile seizures would be to reduce the frequency of febrile illness in childhood. Vaccination against common childhood infectious illness is to be supported. Whole-cell pertussis vaccines frequently cause fever, which in turn may provoke a febrile seizure.[34] Acellular pertussis vaccine causes fewer febrile reactions, and now is in widespread use for routine immunization. In Canada and Japan there is good evidence that acellular pertussis vaccine is associated with many fewer febrile seizures.[42,44]

Day care attendance appears to increase the number of febrile illnesses in children in the febrile seizure age range[22] and is associated with first febrile seizures[9] and recurrences.[40] The effect of the size of the day care on rates of febrile illness has not been reported. As the risks associated with a febrile seizure are exceedingly low and the benefits of day care may be large, the issue of febrile seizures should rarely have an effect on the choice of setting for a child's daily care.

Dealing with Febrile Status Epilepticus

Physicians and emergency department personnel should promptly treat any child admitted with an ongoing febrile seizure. Intravenous or rectal liquid diazepam is well studied and demonstrated to be effective.[39] Intranasal midazolam was found equally effective to intravenous diazepam to stop seizures in a randomized study of 47 children presenting to an emergency room with a febrile seizure of at least 10 minutes' duration.[43] From the time of administration, intravenous diazepam had a shorter response time; however, it takes time to achieve intravenous access. The time from arrival in the emergency room to seizure cessation averaged 2 minutes less for the midazolam group. A larger study is needed to confirm these results before intranasal midazolam can be recommended to replace diazepam.[41]

Buccal midazolam was recently shown in a randomized study in the United Kingdom to be statistically more effective and as safe as rectal diazepam in 219 separate febrile or afebrile seizure episodes in 177 children over the age of 6 months.[49] Limitations for the use of intranasal or buccal midazolam are a suboptimal drug formulation (intravenous liquid may not have the optimal pH for this purpose) and absence of licensure for midazolam for this use.

It is likely that other intravenous drugs (lorazepam, phenobarbital, phenytoin) are effective to stop ongoing febrile seizures; however, there are no systematic studies of these agents in febrile status.

Failure to recognize a febrile seizure at home is occasionally a problem. No studies have explored this issue and its possible solution. Anticipatory guidance might be offered to parents during visits for well-baby care if their child is at particular risk for an initial febrile seizure.[9] A child has a high risk for an initial febrile seizure (about 30%) if two or more of the following factors are present: First-degree relative with febrile seizures, second-degree relative with febrile seizures, delayed neonatal discharge, developmental delay, and attendance at day care. Only about 3% to 4% of the overall population of children has this increased risk.[9]

Emergency Room Management and Counseling Families

After a febrile seizure, it would seem prudent to keep the child under medical observation for several hours or longer. Once the child is alert and active and the fever has been adequately diagnosed and treated, the child may be discharged with proper follow-up care arranged. Hospital admission normally does not seem warranted, although no studies have addressed this issue. Families should know that about 15% of children experience another febrile seizure within 24 hours, but it is not possible to predict these recurrences.

Several studies have documented that the majority of parents believe that their child is dying during a first febrile seizure.[5,6] Few studies have addressed the value of strategies to deal with this extraordinary anxiety. Information in the form of audiovisual material and handouts appears to ensure that parents learn the facts about febrile seizures; however, it is the experience of these authors that family routines are still disrupted several weeks after a febrile seizure.[8] The family's management of recurrent febrile seizures seems to be more appropriate following detailed instructions.[36]

Many emergency departments have found written handouts useful. In our opinion, handouts should stress the following points[12,16,68]:

1. Febrile seizures are frightening to watch, but benign. They do not cause brain damage, and the likelihood of epilepsy developing later is small.
2. There is a substantial risk for further febrile seizures during this or subsequent illnesses.
3. Antipyretic medications provide comfort for the child but do not influence the chance of recurrence.
4. If another seizure occurs, stay calm, observe, place the child on the side or stomach; do not force anything between the teeth; and clear the mouth of food or vomitus if necessary. If the seizure does not stop by itself after 5 to 10 minutes, the child should be brought to the nearest medical facility by car or ambulance.

The only serious sequela of most febrile seizures appears to be parental anxiety and subsequent labeling of the child as “vulnerable.” To date, no “treatment” study has addressed this critical question. Nonetheless, two studies have noted that over the next 7 to 10 years children with a first febrile do not consume excessive health care resources, suggesting that parents eventually cope with the emotional upset of a febrile seizure.[28,31]

Drugs to Prevent Recurrent Febrile Seizures

Daily Treatment

Phenobarbital.

There is controversy about the value of daily phenobarbital to prevent recurrent febrile seizures.[47] Some studies have found the drug to be very efficacious provided that compliance is excellent.[17,77] Other studies have noted no effect.[27,32,56] A meta-analysis including all randomized, controlled studies published until the end of 1996 concluded that phenobarbital with a daily oral dose of 3 to 5 mg/kg reduced the risk of recurrence of febrile seizures by 13% (95% confidence interval [CI], 4% to 22%) compared to placebo in follow-up periods ranging from 12 months to 3 years.[59] However, issues of length of treatment, patient characteristics, and compliance have varied across studies making direct comparison difficult.

There is reasonable consensus that phenobarbital has important side effects for many children. Major behavioral changes (catastrophic behavioral disintegration) occur in 5% to 15%.[13,78] One large study noted a modest decrement in IQ in children with febrile seizures treated with daily phenobarbital compared with children receiving placebo[21] and the effect seemed to persist long after the drug was discontinued.[69] Therefore, a price is paid for treatment with phenobarbital, a price that is likely excessive given the benign nature of the disorder. In our opinion, daily phenobarbital should not be a recommended treatment for most children with febrile seizures. Its continued routine use in the United States is of concern.[52]

Phenytoin.

A single randomized trial failed to find phenyt-oin effective to prevent recurrent febrile seizures.[4] Two open trials also found it ineffective.[29,50]

Carbamazepine.

One open study of children with recurrent febrile seizures who had failed with phenobarbital (side effects or efficacy) found daily carbamazepine of little value.[18] A randomized trial comparing carbamazepine with phenobarbital also failed to find it effective.[2]

Valproic Acid.

Several studies have suggested that daily oral valproic acid reduces the rate of recurrent febrile seizures, although there are opposing studies.[19,33,56] The only placebo-controlled, randomized study compared valproate (30 to 40 mg/kg/day), phenobarbital, and placebo to reduce the recurrence risk of febrile seizures during a 21-month follow-up period in 48 children.[45] The risk of recurrence was 30% lower (95% CI 10% to 50%) in the valproate group compared to placebo. However, concerns about reports of fatal hepatitis in this age range[23] or pancreatitis,[15] although rare, make valproate an inadvisable choice.

Intermittent Treatment

To prevent recurrent febrile seizures, a variety of drugs given only at the time of illness have been studied. Intermittent use of drugs has two important limitations. First, one large American study noted that about 30% of children with a febrile seizure are not recognized by parents as being febrile before the convulsion; in these cases, seizures cannot be prevented by intermittent prophylactic drug treatment.[64] Second, the child must be consistently supervised by a small number of trained caregivers if the drug is to be administered promptly and correctly.

Nitrazepam.

One study found nitrazepam to be effective in preventing recurrent febrile seizures when given at the time of illness.[72] Children in the study were considered to be at high risk for recurrence after a first febrile seizure. The study design was "open label" and used historical controls. The authors noted that the drug was well tolerated. The design of this study was not sufficiently rigorous to recommend the use of nitrazepam.

Oral Diazepam.

A French randomized study of oral diazepam at the time of illness after a first febrile seizure found the drug ineffective.[3] The authors felt the result reflected a lack of efficacy of intermittent drug administration rather than of diazepam itself. A larger study found a modest reduction in recurrent febrile seizures with intermittent oral diazepam at doses of 0.33 mg/kg every 8 hours during illness (recurrence rate for treated patients 21% compared with 31% for placebo).[64] Based on the data from this study, we calculated that to prevent one febrile seizure, 14 children would need to be treated.[10] Forty percent of children experienced significant side effects, which included lethargy, ataxia, and irritability. The author's assertion that similar or better results can be obtained in a routine clinical situation seems at odds with a large literature on compliance with complex medical regimes with a low frequency of adverse outcomes.[30,60]

A Finnish study found no benefit from intermittent oral diazepam at doses of 0.2 mg/kg during the 2 years after a first febrile seizure.[70] The drug was given every 8 hours when the child was febrile. Side effects were infrequent with this dose but as noted above, higher doses cause a high rate of significant side effects.[64]

There is no evidence that intermittent oral diazepam alters parental anxiety about febrile seizures. It is possible that the anxiety is increased because of the need to monitor the child's health and temperature frequently and administer for several days a drug that frequently has side effects. This issue requires more study before treatment with oral diazepam should be offered to many children.

Oral Clobazam.

Clobazam is a benzodiazepine that appears to be less sedating than diazepam and is licensed in many countries, although not presently in the United States. An Indian study randomized 39 children with at least one febrile seizure to intermittent clobazam at the time of subsequent fever or placebo.[63] The recurrence risk was markedly reduced in the clobazam group with few side effects except ataxia. An open-label study of intermittent clobazam in 50 children with febrile seizures also found the drug to be very efficacious but 35% had some degree of side effects—vomiting, somnolence, and hyperactivity were most common.[46] It is unclear how oral intermittent clobazam compares with oral intermittent diazepam.

Rectal Diazepam

At the time of illness.

A Danish study found that rectal liquid diazepam given every 12 hours at the time of illness had efficacy similar to that of daily phenobarbital in reducing febrile seizure recurrences.[37] The same criticisms as of intermittent oral diazepam might be directed to rectal administration, except that the reduction in recurrence rate appears to be greater with the rectal than the oral route.

At the time of a recurrent seizure.

Rectal liquid diazepam is rapidly absorbed, with high serum levels achieved within 4 to 5 minutes of administration.[38] In one study,[39] 85% of ongoing febrile seizures stopped promptly after the administration of rectal liquid diazepam. This approach can be used by parents at home to limit the length of febrile seizure recurrences.[11,35]

The child must have only a few caregivers, and families must be warned not to teach others to give the drug. Although this approach keeps drug exposure at a low level and likely prevents prolonged recurrent febrile seizures, it has not been studied with a randomized trial. It will not prevent the majority of prolonged febrile seizures, as most of these occur as the first febrile seizure.[54] In addition, the effect of this approach on parental anxiety is unknown.

Summary and Conclusions

These authors endorse a Practice Parameter from the American Academy of Pediatrics that concluded, "Based on the risks and benefits, neither continuous nor intermittent anti-convulsant therapy is recommended for children with one or more simple febrile seizures. The American Academy of Pediatrics recognizes that recurrent episodes of febrile seizures can create anxiety in some parents and their children and, as such, appropriate education and emotional support should be provided."[58] We would extend the conclusion to all febrile seizures, simple (typical) and complex (atypical).

There does not seem to be any compelling reason to treat children with drugs on a daily or intermittent basis after a first or second febrile seizure. The potential side effects of drugs outweigh their benefits. Exceptions might be made for a child living in an extremely remote area or with poor access to medical care or a marked tendency for prolonged or repetitive febrile seizure episodes.

Most children with multiple recurrent febrile seizures do not require drug treatment. If treatment is to be offered, the use of liquid rectal diazepam to be given at home at the time of an actual seizure is recommended. The benefit is prevention of a prolonged febrile seizure; the approach is appropriate for a well-organized family with only a few individuals caring for the child. Alternatively, intermittent oral diazepam or clobazam at the time of illness might be considered. For success, excellent compliance and a child with only a few caregivers are again essential.

There would appear to be very few indications for daily treatment with antiepileptic drugs. The child with many caregivers and multiple prolonged recurrences might be a candidate. If daily drug treatment is to be used, daily phenobarbital at 4 to 5 mg/kg/day is recommended provided there is careful monitoring for changes in the child's personality or behavior. A last resort would be daily oral valproic acid.

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Chapter 125

Treatment of Provoked Seizures

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Introduction

Provoked seizures are usually contrasted with "spontaneous" seizures. In reality, no seizures are truly spontaneous, as all result from the interaction of any number of intrinsic and external excitatory and inhibitory factors. The dynamic interaction of these factors determines when a seizure occurs. Yet in most cases, our knowledge of these factors is so limited that it is impossible to predict, with any reasonable degree of reliability, when a seizure will or will not occur. Thus, most seizures occur randomly but not spontaneously. In a tertiary care epilepsy center, 62% of patients identified at least one specific precipitant for their seizures.[14] In order of prevalence, those precipitants were stress, sleep deprivation, sleep, fever or illness, and fatigue. In some cases, however, one or (rarely) more consistent factors can be discerned preceding a seizure with a sufficiently short latency that a direct cause-and-effect relationship can be assumed. In certain cases, the seizure follows the provocative factor with such fixed latency and response rate that many have spoken of the "reflex epilepsies." In these cases, the provocative agent is a more or less specific sensory stimulus interacting with established epilepsy. These susceptible subjects almost always have "spontaneous" seizures as well. In other cases, the latency is longer and variable, and the provoking "stimulus" is not always followed by the "response" (seizure). Seizures in catamenial epilepsy and seizures after hyperventilation would be examples. Nevertheless, in either case, the relation is close enough that few would have difficulty in categorizing these seizures as being provoked. On occasion, provocative factors may be of sufficient intensity to bring on seizures in subjects who do not have epilepsy. Fever in young children and sleep deprivation in young adults are the two most frequent examples.

Provoked seizures are indistinguishable, once they have begun, from "spontaneously" occurring seizures. All major types of seizures can be provoked. The electro-clinical manifestations for each type of seizure are the same whether provoked or spontaneous. Thus, it is only the setting in which seizures occur that gives a clue to whether they are provoked or not. One should be suspicious of the presence of provoking factors in any patient who does not respond well to standard treatment or in whom the history suggests that seizures occur in characteristic circumstances, that is, at the same time of day, in the same phases of the diurnal cycle, or in specific psychosocial settings. Although this may also be true for pseudoepileptic seizures, the history usually fails to reveal any "secondary gain," as is so often seen in psychogenic pseudoepileptic seizures.

Provocative factors are both intrinsic and extrinsic. Common intrinsic factors include sleep deprivation,[6] sleep itself, the menstrual cycle, and any number of abnormal systemic toxic–metabolic states. Extrinsic factors include a large array of specific psychophysiologic stimuli (e.g., stroboscopic stimulation) and many less specific states, such as arousal, stress, and mood.

The significance of recognizing provoked seizures is that recognition offers another therapeutic option—that is, attempts to eliminate or avoid the provoking stimulus. Although simple in principle, this is often difficult in practice. Environmental stimuli are ubiquitous. A specific environmental stimulus may be difficult to recognize as the triggering factor. Emotional status is complex and often requires a multifaceted treatment regimen. Many patients require both short-term and long-term efforts to alter habits, behavior, and emotional status. Some patients report the ability to self-control their epilepsy by consciously avoiding high-risk situations and seeking low-risk situations. Further, some patients with aura or warnings can at times abort their habitual seizure.[42] Optimal medical and psychological therapy must be pursued aggressively in those who have coexistent epilepsy, as this is the primary treatment modality.

Isolated or single seizures occurring in nonepileptic subjects are found, on careful inquiry, to have been provoked in the majority of such cases. Identification of the provocative factor must be made with circumspection. Many of these seizures are related to commonly prescribed drugs. It becomes important to appreciate additional factors, such as severity of illness, neurologic status, renal clearance, hepatic elimination, drug dosing and administration route, polypharmacy, and physiochemical and toxicologic properties of the drugs. These factors modify pharmacotherapeutic and toxicologic responses, making their recognition and understanding vital for treatment.

Emotional Factors

Emotional stress is likely the most prevalent provocative circumstance to precipitate seizures in patients with epilepsy. The actual prevalence of this relationship is not known, yet clinical experience and the available clinical studies[28] support its ubiquity and impact. Patients have identified fear, worry, frustration, and anger as common stressors. An immediate temporal relationship is not usually evident—that is, the seizure usually does not occur at the instant the patient senses the anger or other emotion. Nevertheless, the patient is at maximal risk for one or more seizures in close temporal proximity to such states. Patients with complex partial seizures are more susceptible.

It is now appreciated that depression is the most common comorbidity in patients with epilepsy.[20] In patients with treatment-resistant epilepsy, depression reached 54%.[7] There is growing evidence that depressive disorders and epilepsy share an endogenous or biologic association.[20] The linkage of these two disorders and their basic mechanisms is inferred by epidemiologic studies and clinical observations, and supported by animal experimentation. It is apparent that depressive disorders in epilepsy patients may likely create a milieu for seizure provocation and must be appropriately treated.

Certain clinical neurophysiologic analyses are anecdotal yet elucidating.[10] Several different and indirect provocative

processes may occur as a consequence of emotional stress. Willful noncompliance with medication has been demonstrated. Hyperventilation can develop sufficiently to trigger electroencephalographic (EEG) changes and clinical seizures. Sleep deprivation can be a consequence of profound agitation and restlessness. These phenomena, which are associated with emotional stress, do modulate brain excitability. However, it is not clear from such clinical studies whether emotional stress modulates brain excitability through the kind of neuronal mechanisms implied by basic research studies or through other indirect mechanisms.

As emotional stress is ubiquitous and protean, evaluation for its presence should be a part of the initial assessment in every patient with epilepsy. Vigilance for changes in interpersonal relationships, in school or job performance, and in social circumstances should be a routine component of follow-up examinations. Clinical judgment is required to place the significance of this provocative factor in perspective for the individual patient. Failure to pursue this approach and to ameliorate problems often means an increased frequency of seizures regardless of the best attempts at medical therapy.

Treatment includes both medical and nonmedical therapy. Medical therapy may require not only antiepileptic drug treatment, but also use of tranquilizers, antidepressants, or neuroleptics. More specifically, long-term anxiolytics with antiepileptic properties can be helpful; these include clor-azepate and clonazepam. Antidepressants, mood stabilizers, or neuroleptics can be used concurrently with antiepileptic therapy if clinically indicated. However, there is minimal risk for exacerbation of seizures with some of these drugs. Further discussion follows in the section on drug-induced seizures.

More severely ill patients with paranoia, thought disorder, hallucinations, and extreme agitation require treatment with neuroleptics. As with antidepressants, therapeutic precautions apply. High doses of neuroleptics, rapid changes in their levels, and induction of drowsiness may worsen seizures in epileptic patients; some neuroleptics can provoke seizures by direct effect. However, the reduction in agitation, thought disorder, and hallucinations can exert a significant calming effect and restitution of normalcy, which in turn is associated with improved seizure control. Thus, the benefits warrant their use and treatment should not be delayed.

Nonmedical therapy is often the cornerstone in treating patients with emotionally induced seizures. Delineation of the areas of concern is often facilitated by an early consultation with the social worker. Creation of a treatment paradigm for problems in the family or interpersonal relationships or financial difficulties assists in targeting resources and efforts. Psychological methods include individual or group psychotherapy. Therapists who are knowledgeable about epilepsy can promote a more comfortable and effective therapeutic milieu. Other interesting strategies include reward management, self-control exercises,[42] relaxation, desensitization, and biofeedback.[10] Unfortunately, controlled trials that validate the benefits of these therapies are limited.

Fatigue and Sleep Deprivation

Typically, fatigue and sleep deprivation appear in students who study long hours and try to meet early classes, grueling examinations, or a combination of these along with many social exercises. Compulsive workers are also subject to a similar degree of sleep deprivation and fatigue. The addition of alcohol consumption further raises the potential for seizures. It is not uncommon to find this phenomenon of seizure induction by a combination of fatigue, sleep deprivation, and alcohol in nonepileptic patients.[13] Indeed, the revelation of such a circumstance in a particular patient should help dismiss the diagnosis of epilepsy in an otherwise healthy person. The frequency and extent of individual susceptibility to these factors is not known. Experience of the authors suggests that the occurrence of seizures associated with either fatigue or sleep deprivation is not unusual. Fatigue and sleep deprivation are often found to reflect emotional stress rather than isolated provocative stressors. Isolated fatigue may not influence seizures. At least in athletically conditioned epileptic patients, exercise may actually have a beneficial effect on seizure frequency.[9]

Treatment requires the determination of the cause of fatigue and sleep deprivation. Assessment of psychological problems can be revealing. Correction of those problems by counseling precludes the inappropriate addition or change of antiepileptic drugs. Appraisal of sleep deprivation or fatigue often reveals clinical depression or anxiety that warrants therapy with psy-chotropic medications or psychiatric intervention. Medical causes, such as sleep apnea,[6] caffeine abuse, or excessive alcohol use, require specifically directed treatment and counseling.

Alcohol

Alcohol is well recognized as a cause of seizures in nonepileptic patients (see Chapter 268). Basic and clinical concepts about this phenomenon have been considered in detail.[37] Importantly, the constant use of alcohol may represent a predisposition for the evolution of epilepsy in the nonepileptic patient through various mechanisms, including head injury.

Alcohol may be a trigger for seizures in patients with epilepsy. Some patients appear exquisitely sensitive to the effects of alcohol, and seizures occur even with small exposure. Alcohol may provoke seizures in several different ways. The frequent use of alcohol results in induction of liver enzymes, which in turn lowers antiepileptic drug levels. A soporific effect may immediately follow alcohol consumption. Additionally, normal sleep cycles may be disrupted by alcohol. These derangements in wakefulness and sleep have the potential for provoking seizures. Forgetfulness as a consequence of alcohol use may also cause medication noncompliance.

Generally, alcohol is to be avoided. An exact measurement of alcohol consumption by a patient is typically unreliable. Yet in the responsible and stable patient, permission to have an occasional glass of wine or beer is not associated with adverse effects on seizure control. For some patients, it is important to allay feelings of exclusion, which may preclude social integration.

Drug-induced Seizures

Seizures are not a common complication of drug therapy.[29,49] Most drug-induced seizures are self-limited and may be of limited consequence. On the other hand, even status epilepticus may occur as a consequence of drug induction. Failure to recognize that a specific drug is playing a role in causing seizures and continued administration of that drug will result in perpetuation of the seizure problem.

Drug-induced seizures cannot be predicted, but most are associated with excessively high brain concentrations of drugs or their metabolites. Awareness of general and specific circumstances for an individual patient will suggest predisposition. Those factors contributing to drug-induced seizures relate to the drug itself and have to do with the intrinsic epileptogenicity of a specific agent. The route of administration, dosing schedule, and plasma concentration are important. Factors that influence central nervous system levels include lipid solubility, molecular weight, ionization, and transport systems; however, practical knowledge of these drug properties is often missing at the bedside. Changes in protein binding can be inferred using

clinical information regarding serum albumin concentrations, use of multiple drugs that might compete for binding sites, or the presence of azotemia. Patients with impaired renal function (azotemia) and decreased clearance or hepatic dysfunction (decreased protein production) will be exposed to high central nervous system concentrations of drugs that are administered in doses appropriate for healthy patients. The total serum concentrations will be within therapeutic range, but the alterations in drug binding create higher free concentrations. If clinical information is utilized, inferences about brain concentrations can be made at the bedside.

Predisposing factors related to the patient include specific illnesses. Patients who are extremely ill with multiple metabolic problems or multiple organ impairment and those with central nervous system infection are more likely at risk for drug-induced seizures. Additionally, patients with underlying neurologic abnormalities, including tumor, stroke, or degenerative diseases as well as epilepsy, have greater risk. Many of these conditions have in common an impaired blood–brain barrier. Another important point to consider about drug-induced seizures is that whereas such seizures reflect drug toxicity of the brain, drug toxicity may be affecting other organ systems concurrently. If this is suspected, prompt attention to medical management for cardiac, hepatic, or renal effects of drugs is warranted.

Psychotropic and Neuroleptic Drugs

Psychotropic drugs and antidepressant medications[36] may trigger seizures. As discussed earlier, high doses and rapid changes in doses increase risk. Patients with epilepsy who require treatment with these drugs are at increased risk, but they generally do well when doses are moderate and antiepileptic drug serum concentrations are at appropriate therapeutic levels. Patients with epilepsy who require treatment for mood stabilization, as in bipolar affective disorder, can derive dual benefit with either valproate or carbamazepine. Treatment with lithium does not appear to provoke seizures at nontoxic serum concentrations in epileptic patients who are adequately treated with antiepileptic medications. An anticonvulsant effect in some patients with epilepsy is suggested.[40] Risk factors for lithium-induced seizures in patients with epilepsy have been reported as pre-existing EEG abnormality, clinical seizure disorder, acute psychotic symptoms, and decreased renal clearance.

Most antidepressant drugs are well tolerated and can be used safely. It is necessary that the patient have adequate antiepileptic drug levels, appropriate therapeutic drug monitoring, and modest but efficacious doses of the antidepressant. The treating physicians must be aware of drug–drug interactions. There appears to be a selective propensity for antidepressant drug-induced seizures. The drugs more likely to cause seizures include amitriptyline, imipramine, clomipramine, mianserin, maprotiline, and bupropion. Clinical evidence for toxicity otherwise may not be apparent. Serotonin reuptake inhibitors and monoamine oxidase inhibitors are less likely to induce seizures.

Antipsychotic neuroleptics such as clozapine, haloperidol, loxapine, promazine (no longer available), and chlorpromazine increase the risk for seizures in nontoxic doses. This is especially true for the aliphatic phenothiazines.[26] Indeed, intramuscular chlorpromazine administration was used at one time as a provocative test to elicit abnormal EEG activity in persons suspected of epilepsy. The butyrophenones may carry a lower risk for drug-induced seizures. In contrast, the new antipsychotic drug clozapine has been reported to cause seizures in about 2.8% of patients. Addition of an antiepileptic drug is recommended for that patient who has a seizure and requires continued treatment with clozapine. Some antipsychotic drugs may have pharmacokinetic interactions that reduce plasma concentrations of antiepileptic drugs and thus increase the predisposition to seizures of patients with epilepsy.

Antiepileptics Drugs

Antiepileptic drugs sometimes act as proconvulsant compounds. The proconvulsant effect is associated with exceptionally high drug concentrations, as has been described in phenytoin-activated seizures.[23] Further, those antiepileptic drugs that induce sedation may indirectly exacerbate seizures. Specific antagonism of certain seizure types by nontoxic doses of antiepileptic drugs can also be seen. The notion that phe-nytoin can exacerbate absence seizures[25] has been perpetuated in the literature, but supporting evidence is limited.[24] Trimethadione, which is no longer available, exacerbated generalized tonic–clonic seizures.[31] Carbamazepine has been observed to worsen seizure frequency in patients with atypical absence seizures and other generalized seizure types.[41] An EEG with generalized slow (2.5 to 3 Hz) spike-and-wave discharges can predict an increased risk for carbamazepine-induced seizures.

Essentially all antiepileptic drugs, including the most recently available ones, appear to share this propensity for inducing seizures. The literature contains reports on gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, valproate, and vigabatrin. Worsening of the treated seizure type or at times evolution of a new seizure type for that patient can be anticipated. The mechanisms for the worsening include intoxication and a relatively specific drug effect.[35]

Caution is urged when considering case reports, small series, or even clinical trial reports. Nonconvulsive status epilepticus was reported in epileptic[5] and interestingly in nonepileptic patients[50] during treatment with tiagabine and with levetiracetam.[1] Isolated reports of this type are problematic as other investigators[39] upon review of clinical trials have pointed out that there is a fairly high likelihood of spontaneous occurrence of status epilepticus (5% to 10%) in drug-resistant epilepsies over 3 years.

Drugs for Anesthesia

Certain anesthetics may induce seizures. Intravenous administration of lidocaine in elderly patients, who may have congestive heart failure, shock, renal or hepatic failure, and concomitant cimetidine therapy, increases risk for seizures.[15] Paradoxically, lidocaine has also been used to terminate seizures and has been used effectively to treat status epilepticus.[33]

General anesthetics can increase the possibility of seizures, including enflurane, etomidate, and ketamine.[38] Methohexital can induce epileptogenic activity on the EEG yet can have anticonvulsive properties as well.[30] Another short-acting intravenous anesthetic, propofol, has been used for outpatient surgery, anesthesia induction, and sedation in the intensive care unit. Seizures have occurred in epileptic and nonepileptic patients.[27] Like lidocaine, propofol also has been used successfully to treat status epilepticus.

Drugs for Medical Disorders

Certain drugs have been found to cause seizures during treatment for systemic illnesses.[15] These include antibiotics, cardiovascular drugs, chemotherapeutic agents, bronchodilators, antiviral drugs, analgesics, and contrast media. Patients who are treated with these drugs commonly have illnesses associated with impaired organ function, which permits increased penetration of the drugs into the central nervous system. Most patients are quite ill. Specific drugs with increased epileptogenicity should be avoided or used cautiously in predisposed patients.

β-Lactam antibiotics increase central nervous system excitability. High doses of intravenous penicillin may cause seizures.[48] Imipenem is most often administered to patients who are critically ill, and these patients are particularly susceptible to seizures. Associated risk factors include high dose, renal impairment, pre-existing neurologic abnormalities, and, interestingly, *Pseudomonas aeruginosa* infection. Imipenem may induce an EEG picture of confusion and depressed sensorium, which precedes the evolution of myoclonic and generalized tonic–clonic seizures. Withdrawal of the drug results in cessation of seizures, albeit requiring a period of 24 to 72 hours.

Cephalosporins, earlier and recent products, produce seizures[47] if administered in high doses or to patients with renal failure. Laboratory studies in mice indicate that the mechanism of cephalosporin-induced seizures is mediated through the inhibition of $GABA_A$ receptors.[43]

The fluoroquinolone antibiotics can provoke seizures. Once again, the predisposing circumstances include high doses. Administration of these drugs with theophylline or nonsteroidal anti-inflammatory drugs increases risk. This group of antibiotics includes nalidixic acid, norfloxacin, ciprofloxacin, levofloxacin, and enoxacin.

Isoniazid can induce seizures, which are typically multiple. It is recommended that a specific therapy of pyridoxine in 1- to 5-g boluses be given repeatedly every 5 to 20 minutes until the seizures terminate.

Other agents thought to induce seizures include acyclovir, used to treat herpes simplex encephalitis, and zidovudine, foscarnet, and ganciclovir, used to treat HIV infection. Similarly, some vaccinations result in seizures, especially vaccination for pertussis. In each of these situations, the pre-existing central nervous system pathology makes correlation with induction of seizures less than clear.

The alkylating agents chlorambucil and disulfiram and the immunosuppressant agent cyclosporin may induce seizures.

Interferon-α therapy is in wide use for chronic viral hepatitis. Convulsions have been observed in 1% of adults and 4% of pediatric patients. The induced seizures are a latent (2 to 14 months) side effect of this immunologic therapy. While the pathogenic mechanism is unknown, disruption of the blood–brain barrier is an integral component of the epileptogenic process.[34]

Theophylline is well recognized for its ability to provoke seizures. The serum concentration of theophylline and its relationship to seizures is unpredictable.[2] Seizures may not respond well to antiepileptic drugs. Hemodialysis or hemoperfusion offers potential therapeutic modalities in severe overdose.

Reports of seizure induction by cardiovascular drugs are present in the literature. Clinical experience suggests that these drugs must be rare causes of seizures. There are reports of seizures being provoked by standard doses of mexiletine, tocainide, propranolol, alprenolol, metoprolol, oxprenolol, and sotalol, as well as digoxin and disopyramide.

Meperidine can be associated with induction of seizures.[46] After this medication is given repeatedly, its metabolite, normeperidine, accumulates and is responsible for the induction of seizures. Normeperidine concentration is enhanced in cases of impaired renal clearance. Other analgesics such as tramadol taken in large doses and regularly over an extended period (days or weeks) can provoke seizures.

Intravenous contrast media have been associated with seizures,[4,32] slightly, and this risk is increased in patients with metastatic brain cancer. Persons with epilepsy or other structural brain disease may be similarly predisposed.

Drugs of Abuse

Seizures frequently accompany illicit drug use.[8] Cocaine is probably associated with the highest incidence of seizures.[3,22] Phencyclidine, amphetamines, and heroin can also cause seizures. Seizures are not typically associated with the use of marijuana and LSD (lysergic acid diethylamide). Patients taking antiepileptic drugs are probably not protected from the direct toxic effects of these drugs.

Specific Stimuli

The term *reflex epilepsy* has been used in the literature to refer to the occurrence of seizures on a very consistent basis in response to an identifiable stimulus. Other investigators have preferred terms such as *sensory-precipitation epilepsy*, *stimulus-sensitive epilepsy*, and *epilepsy with reflex seizures*. The stimulus is specific for a given individual, and the seizures for that individual are likely to be stereotypical. However, seizures provoked by identifiable stimuli occur in patients with different types of epilepsy and promote different types of seizures. Stimulus-specific seizures have been described as complex partial, simple partial, tonic, absence, astatic, and myoclonic seizures. These provoked seizures are found in 5% to 6% of patients with epilepsy. Reflex epilepsy has been the subject of reviews.[11,51]

It is important to recognize that epilepsy is the primary problem of such patients. The provocation of seizures by specific stimuli is a unique epiphenomenon for these particular patients. Medical treatment of the epilepsy follows standard tenets according to seizure type, EEG and prognosis, and specificity and tolerance of the antiepileptic agent. When the specific stimuli are sought and recognized in an individual patient, efforts to alter patient response or remove the stimuli are undertaken. The efforts at treatment may then include avoidance, conditioning, and other behavioral approaches in addition to medical therapy. Most patients have random epileptic seizures in addition to those that are stimulus sensitive. Patients with stimulus-sensitive seizures also may have symptomatic epilepsy for which additional diagnostic concern and treatment should be given.

Provocation of partial seizures has been ascribed to startle, somatosensory stimulation, proprioception, music, sound or voice, hot-water immersion, eating, and various cognitive activities, such as reading, playing chess, and computation. Primary generalized seizures are related to specific stimuli of light and of thinking and decision making. Light-sensitive seizures may be provoked by different forms of light, including sunlight, sudden bright light, and flickering light. Alternating lines that oscillate out of phase on a television set have also been observed to bring on seizures. Some patients are especially sensitive to patterns and eye closure.

Treatment of light-sensitive seizures is most satisfactory with valproate. Benzodiazepines or ethosuximide has some utility. Avoidance and modification of light and pattern sources are also beneficial. Dark glasses can be helpful. Specifically, glasses that are blue and cross-polarized offer the best protection.[21] Moving back from a television set by a distance of <2.5 meters should be helpful. The proclivity for seizures persists into early adult life. However, there is a notable remission in the third decade,[19] and drugs may eventually be withdrawn.

Forster[12] demonstrated that humans with stimulus-sensitive epilepsy can respond to deconditioning in a Pavlovian paradigm. The primary problem with these techniques is that long-term and continuous conditioning, which is difficult to accomplish, is required.

The basic tenets for treatment of reflex or stimulus-sensitive epilepsies reflect the heterogeneous nature of this particular group of epilepsies. Medical therapy should be directed specifically at the type of epilepsy and epileptic seizures. Additional efforts to remove the provocative stimuli (stimulus avoidance) are sometimes quite successful. Alteration of the stimulus (stimulus modification) may be equally efficacious. Conditioning techniques, including behavioral and physical measures, can also be successful, but they require physician awareness and ingenuity as well as patient cooperation and long-term commitment.

The provocation of epileptic seizures by photic stimulation has taken on a public health posture. In our new society of intense audiovisual stimulation (television, video games, advertisements, special entertainment lighting), there has been a concurrent escalation of seizures triggered by now ubiquitous environmental stimuli that were once considered innocuous. The "pocket monster" (Pokemon) incident[45] in 1997 was associated with nearly 700 people being urgently treated for seizure symptoms after watching a television animated cartoon. The specific series of television frames of this cartoon containing long-wavelength (12-Hz) red frames alternated with blue frames was sufficient to induce seizures in healthy people and people with latent photosensitivity but who had never had seizures. Industry and government preventative guidelines for television broadcasting have focused on changes to ensure appropriate (a) flicker, (b) restriction of alternating high-contrast patterns, and (c) limitation of long-wavelength red.[16] These modifications have been successful in Japan[44] and are likely to be implemented internationally.[11]

Treatment of Provoked Seizures

Persons with Epilepsy

Epilepsy patients who have seizures provoked by photic stimuli are treated as discussed in the above section. The stimulus is removed or modified and AED treatment is administered. Most often valproate is successfully used.

With epilepsy patients whose control is incomplete, a thorough search for seizure-provoking stimuli always must be undertaken. Anxiolytics or selective serotonin reuptake inhibitors are indicated if anxiety or depression is clinically significant. Improvement of mood disorders by these medications can be more beneficial for control than addition of alternative antiepileptic drugs. Improved seizure control may also follow correction of other problems including sleep apnea, fatigue, sleep deprivation, alcohol excess, and use of medications with relative contraindications in epilepsy (e.g., bupropion, theophylline, meperidine, tramadol). For the epilepsy patient it is best to avoid or withdraw medications that have any potential for provoking seizures.

Routine surveillance of medication regimens given by the treating neurologist and also by the primary care physician and other specialists may prevent or discover reasons for seizure exacerbation.

Persons without Epilepsy

Persons without epilepsy who have a first seizure provoked by photic stimulation do not require treatment.[44] These individuals are usually young and 68% remain free from subsequent seizure.[18]

It is possible in many instances to identify agents or circumstances that are sufficient to provoke a seizure in an otherwise healthy individual. Nevertheless, it is impossible to be certain that a first seizure was not the first symptom of undeclared epilepsy. Counseling for avoidance is necessary but medical therapy is not indicated. It is prudent to recommend a period of observation just as one would do after a first unprovoked seizure. It is also prudent to recommend safety precautions for work and at home as well as no driving for at least 3 months. This period is based on the expected time for a majority of unprovoked seizures to recur.[17]

In a healthy person with a suspected provoked seizure, caution is urged when there are extenuating factors such as a nonspecifically abnormal EEG or focal features of the seizure. A 6-month period of observation and restriction after removal and avoidance of the provoking factor(s) is recommended. This is conservative yet indicated. A normal brain imaging study and other normal laboratory studies are favorable findings but do not influence this recommendation. Antiepileptic drug therapy is not warranted unless further seizures occur.

The critically ill patient who develops seizures will require acute antiepileptic drug therapy. All efforts are made to elucidate a cause for seizures. If a provoking substance is found, it should be withdrawn. The choice of antiepileptic drug is dependent on available access, organ viability/involvement, drug compatibility, and, to lesser degrees, seizure type and etiology of seizures. Benzodiazepines can be used acutely but should be converted for maintenance to a longer lived AED with an intravenous formulation. Maintenance therapy should be continued until all medical conditions are rectified. It is best to gradually withdraw this therapy after baseline medical and neurologic status is achieved and there are no further seizures.

Summary and Conclusions

Provoked seizures are those induced seizures for which a definite or putative cause can be identified. In reality, all seizures have provocative elements, although they are not always recognized. Identification and remediation of provocative factors can be therapeutic. Although the intrinsic changes leading to seizures are immensely difficult to determine, extrinsic provocative agents can include readily apparent factors, such as emotional stress, fatigue, alcohol, illicit drugs, television, computer-generated games, and widely utilized and effective drugs. In some patients, the aging process and changes in hepatic and renal function enhance the potential for provocation of seizures by drugs.

Thus, careful clinical assessment of multiple facets of the individual patient's situation provides the cornerstone for prevention and treatment of provoked seizures.

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Chapter 126

Treatment of Status Epilepticus

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Introduction

Status epilepticus (SE) is a medical emergency that requires immediate and vigorous treatment directed at stopping all behavioral and electrical seizure activity. Physiologic changes occur during the course of SE that may result in severe systemic complications and also may damage or kill cerebral neurons. Physiologically, SE is defined as recurrent seizures without complete normalization of neurochemical and physiologic homeostasis in the brain between seizures. This physiologic definition makes clear the rationale for the operational definition of SE as recurrent seizures without full recovery of neurologic function between seizures. In this chapter, we consider goals and general principles in the management of SE and review general measures and specific pharmacotherapy for the successful management of SE.

Goals and General Principles

The goal in the management of SE is simple: To stop seizure activity as quickly as possible. By doing so, neurons are less likely to be damaged, physiologic consequences are less likely to cause organ failure, and patients are more likely to recover fully from the episode of SE. Ideally, SE should be stopped within 30 minutes from the start of the episode. Meldrum[32] and subsequently others[11,12,56] made a distinction between early SE (the first 30 minutes) and late SE (after 30 minutes). They found that physiologic changes occur in late SE that produce systemic complications and put neurons in jeopardy of permanent damage or death (Table 1). Furthermore, the longer SE persists, the more likely that neurons will be damaged by exposure of *N*-methyl-D-aspartate (NMDA) receptors to the excitatory amino acid neurotransmitter glutamate. Activation of NMDA receptors results in an opening of their cation channels to calcium. The marked increase in intercellular calcium that results sets up a cascade of intercellular biochemical events that damages or kills the cell.[17,31] Sustained seizure activity also results in a progressive reduction of γ-aminobutyric acid (GABA)–mediated inhibition.[20] These progressive physiologic and neurochemical changes may provide an explanation for the experimental and clinical observations that the longer the duration of the episode of SE, the more subtle will be the motor manifestations[50,57] and the more refractory the episode will be to pharmacotherapy.[26,50,57]

In most patients with SE, ongoing seizure activity is more likely to cause permanent neurologic damage than systemic factors.[33] Although systemic stress from hypoxia, hyperthermia, and hypotension can augment neuronal injury[33] and must be managed effectively, it is most imperative that early efforts focus on cessation of electrical and behavioral seizure activity. This can be accomplished by initiating treatment as soon as the diagnosis of SE is made and then monitoring the patient's electroencephalogram (EEG) during management. Treatment should never be delayed while awaiting the arrival of the EEG machine. EEG recording may be necessary, however, to confirm successful treatment of the episode. If behavioral seizures stop and the patient is observed progressively to recover consciousness, no EEG recording is needed. If behavioral seizure activity stops but the patient remains in a coma or in an impaired state of consciousness, however, EEG evaluation is essential to determine whether electrical seizure activity has ended. Treiman[49] reviewed the electroclinical aspects of various types of SE. He suggested that a variety of patterns can be considered ictal, including periodic epileptiform discharges, and proposed that all such epileptiform activity be stopped before the patient is considered successfully treated.[49] See Chapter 58 for a more detailed discussion of EEG changes during generalized convulsive SE and for EEG examples of ictal patterns.

General Measures

The management of SE can be divided into general measures and specific pharmacotherapy. General measures include the immediate evaluation and correction of physiologic abnormalities that may occur as a consequence of the episode of SE and concurrent evaluation for potential causes of the event.

Table 1 Physiologic changes in generalized convulsive status epilepticus

Transient or early (0–30 min)	Late (after 30 min)
Arterial hypertension	Arterial hypotension
Cerebral venous pressure (CVP) increased	CVP raised or normal
Arterial pO_2 low or normal	Arterial pO_2 low or normal
Arterial pO_2 high	Arterial pO_2 normal
CV pO_2 (low or high)	CV pO_2 (normal or low)
CV pCO_2 high	CV pCO_2 normal (or high)
Cerebral blood flow (CBF) increased	CBF increased, normal or decreased
Hyperglycemia	Normoglycemia, hypoglycemia
Hyperkalemia	Hyperkalemia
Hemoconcentration	
Lactic acidosis	Hyperpyrexia (secondary)

Source: Modified from Meldrum BS. Neuropathology and pathophysiology. In: Laidlaw J, Richens A, eds. *A Textbook of Epilepsy*. Edinburgh: Churchill-Livingstone; 1976:314–354.

The initial evaluation of any medical emergency, including SE, is focused on stabilization of airway, breathing, and circulation. Often, the most effective way to manage the airway is to terminate the seizures pharmacologically (see later discussion). If it is essential to establish a patent airway, insert an oral airway or an endotracheal tube. If neuromuscular junction blockade is required for intubation, a nondepolarizing agent should usually be chosen unless the patient lacks any risk factors for the development of hyperkalemia with a depolarizing agent. Respiratory effort also must be assessed and supported if insufficient. Arterial blood gas analysis and transcutaneous saturation monitoring are useful to guide airway management and determine whether supplemental oxygen is needed. Blood pressure must be evaluated and supported. Early in SE, blood pressure is usually elevated attendant to the rise in circulating catecholamines. With prolonged SE or administration of intravenous medications (particularly phenytoin, propofol, or barbiturates), however, hypotension may develop. If this occurs, vasopressor agents should be administered. Vasopressors and inotropes are almost invariably needed in prolonged status epilepticus. Once initial emergency evaluation is completed and the patient's airway, respiratory status, and circulatory status are stabilized, blood should be obtained for evaluation of hematologic and biochemical parameters, toxicology screen, and determination of antiseizure drug concentrations. An intravenous line should be placed, preferably in a large vein, and kept open with normal saline. Dextrose-containing solutions should not be used in institutions that use intravenous phenytoin because of the

potential for precipitation. This caveat need not be considered in institutions that have replaced parenteral phenytoin with fosphenytoin.

The patient's blood glucose concentration should be determined by finger stick. If hypoglycemia is detected, the patient should be given an intravenous bolus dose of glucose. The usual dose for hypoglycemia in adults is 50 mL of 50% glucose; the dose for children is 2 mL/kg of 25% glucose. Any adult who could be thiamine deficient (e.g., alcoholics or malnourished individuals) should be given 100 mg of thiamine intravenously before or simultaneously with the glucose in order to avoid Wernicke encephalopathy. Historically, it was common to administer a bolus of glucose to all patients with SE in case the episode had been precipitated by hypoglycemia. However, hyperglycemia may exacerbate neuronal damage caused by cerebral ischemia and SE.[8,18,48] Therefore, the blood glucose should be determined at the bedside and a dose of glucose only given if the concentration is ≤70 mg/dL (3.9 mmol/L).

The next step is to determine the cause of the event. SE may occur in persons with epilepsy (low antiseizure drug concentrations and alcohol are two common causes), as the initial manifestation of epilepsy, or as a consequence of a severe neurologic or systemic insult. The prognosis in the former situations is far better than in the latter.[43] In a patient with epilepsy in whom SE has been precipitated by withdrawal or reduction of maintenance antiseizure drug therapy, the rapid reintroduction of the relevant drug will usually terminate SE (the drug should be given intravenously if possible). In some instances, such as SE caused by metabolic derangements or medication overdose, specific treatments are available to address the underlying precipitant. For example, SE caused by hyponatremia may respond to gradual sodium replacement; SE caused by isoniazid overdose often responds to intravenous (IV) pyridoxine. In infants developing status epilepticus, IV pyridoxine is routinely given. In many cases, however, the immediate cause of SE is not apparent or etiology-specific treatment is not available. Even when there is no specific treatment for the cause of SE, the information is useful because neurologic outcome is largely dependent on the etiology. It is usually wise also to save 50 mL of serum in a patient in whom the cause is not obvious, for later analysis.

Medical complications should be identified and treated. The most common are cerebral complications (venous thrombosis, hemorrhage, infarction), cardiovascular complications (notably hypotension, cardiac arrhythmia, cardiorespiratory failure, pulmonary edema), and systemic complications (hepatic failure, renal failure, pancreatitis, electrolyte disturbance, disseminated intravascular coagulation, rhabdomyolysis, thrombophlebitis, and infections).[44]

Pharmacotherapy (discussed later) is indicated for patients who experience two or more seizures without full recovery of consciousness or who exhibit continuous seizure activity (either behaviorally or electrically) for 5 minutes or longer.[2,27,28,51] Simultaneously, other general measures should be considered. Hyperthermia is common during SE and may markedly exacerbate neuronal damage caused by ongoing electrical seizure activity.[32] Rectal temperature should be monitored during an episode of SE, and fever should be corrected quickly using passive cooling measures.[6] Acidosis from impaired ventilation and lactate release is common during SE and often does not need pharmacologic correction.[45] In the past, some advocated the use of bicarbonate to normalize the pH, but there is no evidence that transient SE-induced acidosis, even with serum pH ≤7.0, results in permanent injury. Generally, once SE is stopped, the serum pH normalizes rapidly. If large amounts of bicarbonate have been administered, however, this may result in iatrogenic metabolic alkalosis once SE is controlled.

The utility of steroids in reducing intracerebral edema during SE has not been proven, nor has the value of monitoring for increased intracranial pressure. Muscle paralysis is rarely indicated in the management of SE (except to facilitate intubation and in certain postoperative situations) and should never be used without ongoing EEG monitoring to detect ongoing seizures.

Table 2 Clinical pharmacologic properties of drugs used as initial therapy in status epilepticus (SE)

	Diazepam	**Lorazepam**	**Phenytoin**	**Phenobarbital**
Intravenous loading dose (mg/kg)				
Adult	0.15–0.25	0.1	20	20
Pediatric	0.1–1.0	0.05–0.5		
Maximum rate of administration (mg/min)	5	2	50	75
Effective serum concentration in SE	200–800 ng/mL	100–200 ng/mL	25–35 µg/mL	20 µg/mL
Time to stop SE (min)	1–3	6–10	10–30	20–30
Effective duration against SE	15–30 min	>24 hr	>24 hr	>24 hr
Elimination half-life (hr)	30	14	24	4–6
Protein binding (%)	97–99	85–93	87–93	45–50
Volume of distribution (L/kg)	1–2	0.7–1.0	0.5–0.8	0.7
Potential side effects				

Depression of consciousness	10–30 min	Several hours	None	Several days
Respiratory depression	1–5 min	Occasional	Occasional	Consider intubation before administration
Hypotension	Occasional	Occasional	Frequent	Occasional
Cardiac arrhythmias	No	No	In patients with heart disease	No

Source: Modified from Treiman DM. Status epilepticus. In: Resor J, Kutt H. eds. *The Medical Treatment of Epilepsy.* New York: Marcel Dekker; 1992:183–193, with permission.

Principles of Drug Treatment

An ideal drug for the treatment of SE would be easy to administer, have immediate and long-lasting antiseizure effects, and would not cause adverse effects on respiratory drive, cardiovascular function, or level of consciousness. Intravenous therapy is always preferred because drugs administered by this route are completely bioavailable and have minimal delay in attaining a therapeutic effect. However, alternate routes of administration (e.g., rectal, buccal, and intranasal routes), have utility when intravenous access is not feasible, particularly in the out-of-hospital setting, and in selected situations for infants and children.[29,30,40] Thus, the choice of treatments for SE is based on efficacy, pharmacokinetic features, toxicity, and relative ease of use. Drugs useful for the termination of SE are most effective when given early in an episode. In one retrospective study, first-line therapy (usually a benzodiazepine followed by phenytoin) was effective in 80% of patients when administered within 30 minutes of the onset of SE. When treatment was delayed by 2 hours or more, however, ≤40% of patients responded.[26] Altered sensitivity of drug targets to antiseizure therapies may contribute to this reduction in pharmacoresponsiveness. In animals, GABA_A receptors from dentate granule cells become progressively less sensitive to diazepam during 45 minutes of continuous pilocarpine-induced seizures. This plasticity in GABA_A-receptor function appears to be drug specific because sensitivity to pentobarbital was preserved over this same time interval.[22] These observations suggest a possible mechanism for reduced pharmacoresponse during prolonged SE in humans, and suggest that future approaches to therapy may need to be tailored to the specific functional state of drug targets as opposed to the “one protocol fits all” approach to SE management that has been used historically.[25]

Pharmacotherapy

Unfortunately, few data directly compare the efficacy of drugs in the management of SE. A number of drugs have been used in the management of SE, including phenytoin; the benzodiazepines diazepam, lorazepam, midazolam, and clonazepam; the barbiturates phenobarbital, amobarbital, pentobarbital, and thiopental; valproate; propofol; paraldehyde; lidocaine; and, in Europe, chlormethiazole. Most evaluations of these drugs have been based on retrospective reviews of their potential efficacy and have reported success rates of 40% to 100% among the patients studied. Table 2 summarizes relevant clinical and pharmacokinetic information regarding the drugs commonly used in the initial treatment of SE.

Initial Therapy

The largest and most informative clinical trial to compare initial therapies for the in-hospital treatment of status epilepticus was the Veterans Administration (VA) Cooperative Trial performed by Treiman et al.[51] This is also the only randomized, double-blind clinical trial in SE to show a statistically significant difference in outcome between active treatments. These investigators compared four initial treatment regimens in 384 patients with overt (clinically evident) SE: (a) diazepam (0.15 mg/kg) followed by phenytoin (18 mg/kg); (b) lorazepam (0.1 mg/kg); (c) phenobarbital (15 mg/kg); and (d) phenytoin (18 mg/kg). Treatment success was defined by cessation of motor and electroencephalographic seizures for a 40-minute time interval beginning 20 minutes after the beginning of drug administration. Treatment was successful in 65% of patients who received lorazepam; 58% of those who received phenobarbital; 56% of those who received diazepam and phenytoin; and 44% of those who received phenytoin alone. Lorazepam was more effective than phenytoin by pairwise comparison ($p = .002$), but other differences were not statistically significant. There were no differences among the four treatments with regard to adverse effects or outcome at 30 days after the event. Patients with SE characterized by coma and ictal discharges on the EEG ("subtle SE") were much less likely to respond to the same treatments (success rates of 8%–24%), and there were no statistically significant differences in primary or secondary outcomes among treatments in this group. Some of the patients with subtle SE had myoclonus after severe anoxia. It seems likely that the prognosis in this group is worse, but the cases were not analyzed separately.

Diazepam has a much shorter duration of antiseizure effect than does lorazepam. Lorazepam is generally preferred as initial therapy of SE for this reason.[36] Diazepam is a highly lipophilic drug that enters the brain rapidly on first pass through the cerebral circulation. However, it also redistributes to other lipoid tissues quickly as well. As a result, brain concentrations of diazepam decline rapidly, and repeat doses are often needed at frequent intervals (e.g., every 15–30 minutes) to prevent seizures from recurring.[37] Lorazepam has a slightly less rapid onset of action but redistributes from brain tissue at a slower rate than does diazepam. This likely explains the longer antiseizure action of lorazepam, even though its plasma half-life (14 hours) is shorter than that of diazepam (30 hours). Midazolam and clonazepam also have been used successfully in the initial treatment of SE.[10,14,47,59] There is no reason, however, to prefer either over lorazepam as initial IV therapy. Buccal or intramuscular midazolam, however, has significant advantages over non-IV administration of other benzodiazepines in view of its unique solubility properties.

As illustrated by the results of the VA Cooperative Trial discussed previously, phenytoin should be administered in conjunction with a benzodiazepine when it is used for the initial treatment of SE. Peak brain concentrations of phenytoin are attained near the time of the end of drug infusion.[58] Phenyt-oin infusions should not exceed a rate of 50 mg/min due to an increased risk of hypotension and cardiac arrhythmias, and sometimes can be given no faster than 25 mg/min. Thus, completion of a phenytoin infusion often takes 20 to 30 minutes or longer, and the maximal clinical effect is correspondingly delayed.

The role of fosphenytoin in the treatment of SE is unclear.[26] Fosphenytoin is a water-soluble prodrug that is converted to phenytoin by phosphatases with a half-life of 15 minutes. Although fosphenytoin can be administered more quickly than phenytoin by the intravenous route (150 mg phenytoin-equivalents of fosphenytoin per minute), the time to attain a therapeutic concentration of unbound phenytoin mirrors that seen with phenytoin given at 50 mg/min.[27] Because fosphenytoin is water soluble, it lacks the propylene glycol diluent used in parenteral phenytoin solution and is administered at a slightly acid pH, in contrast to the highly alkaline pH required to keep phenytoin in solution. Cardiac toxicity has been reported with fosphenytoin,[1] and the relative safety of phenytoin and fosphenytoin given at maximal rates has not been directly compared. Fosphenytoin is much more expensive than parenteral phenytoin, and this is the primary reason for restricted use of the drug by some institutions and formularies.[21]

Because of the potential for phenytoin-induced hypotension and cardiac arrhythmias, blood pressure and electrocardiograms should be monitored in all patients during the administration of either phenytoin or fosphenytoin. Patients with preexisting cardiac disease and the elderly are at higher risk for phenytoin-related cardiovascular complications.[15] If hypotension develops, the rate of infusion can be slowed. If the QT interval on the electrocardiogram widens or if arrhythmias occur, phenytoin administration should be stopped. Extravasation of phenytoin produces severe necrosis of tissues in the vicinity. Intravenous administration has been reported to cause venous damage ("purple glove syndrome").[34]

Among the barbiturates, phenobarbital is the best studied for the initial treatment of SE, although remarkably little information is actually available.[41] Phenobarbital can be administered intravenously at the rate of 50 to 75 mg/min.[27] In many centers, in patients whose seizures continue despite benzodiazepine therapy, phenobarbital is preferred over phenytoin as initial therapy because of its rapidity of action, logistical advantages, and safety.[55] If the patient has already been given a benzodiazepine intravenously, however, the potential for respiratory distress is probably increased. Under such circumstances, respiratory support should be readily available. Phenobarbital may cause hypotension, as do most other anti-SE drugs, and the sedative effects of the drug are prolonged. Phenobarbital has been advocated as a second-line agent for SE, to be used in patients who fail to respond to lorazepam and phenytoin.[27] The likelihood, however, that a second or third agent would succeed after other initial therapies have failed is quite small. Data from the VA Cooperative Trial indicate that the likelihood of any second conventional antiseizure drug stopping SE when the first has failed is no greater than 7%.[7] This is likely to be a consequence of loss of efficacy of these drugs as the duration of SE increases. These data call into question any strategy involving sequences of conventional agents and argue for the earlier use of definitive therapy (e.g., general anesthetic doses of midazolam, propofol, or barbiturates). However, there are no prospective data indicating the outcome of such an approach.

The treatment protocols used vary among countries and centers. Whichever drug or drug sequence is used in the management of SE, however, it is now clear that SE is treated more effectively when a preestablished treatment protocol is used.[20] A number of algorithms have been recommended for the management of SE. FIGURE 1 outlines a protocol that is widely used, especially for the management of generalized convulsive SE.

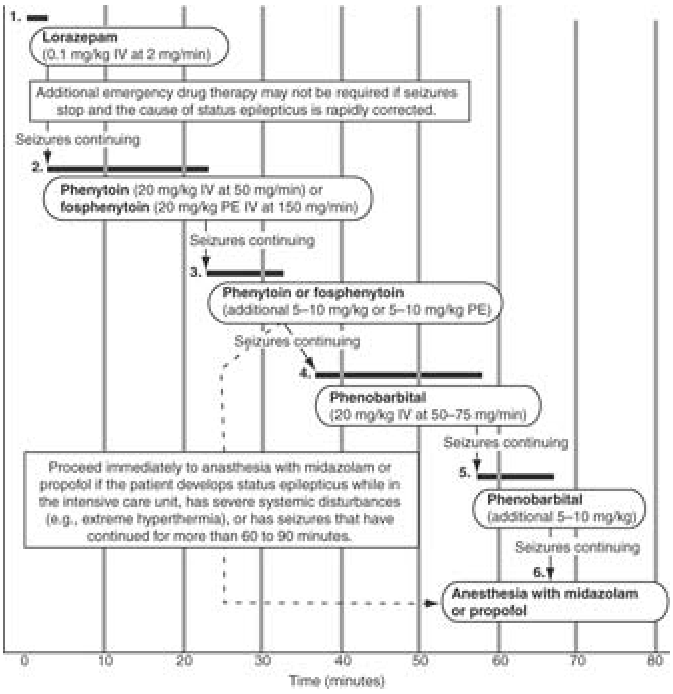
1.
Lorazepam
(0.1 mg/kg IV at 2 mg/min)
Additional emergency drug therapy may not be required if seizures stop and the cause of status epilepticus is rapidly corrected.
Seizures continuing
2.
Phenytoin (20 mg/kg IV at 50 mg/min) or
fosphenytoin (20 mg/kg PE IV at 150 mg/min)
Seizures continuing
3.
Phenytoin or fosphenytoin
(additional 5–10 mg/kg or 5–10 mg/kg PE)
Seizures continuing
4.
Phenobarbital
(20 mg/kg IV at 50–75 mg/min)
Seizures continuing
5.
Phenobarbital
(additional 5–10 mg/kg)
Seizures continuing
6.
Anesthesia with midazolam or propofol
Proceed immediately to anasthesia with midazolam or propofol if the patient develops status epilepticus while in the intensive care unit, has severe systemic disturbances (e.g., extreme hyperthermia), or has seizures that have continued for more than 60 to 90 minutes.
0
10
20
30
40
50
60
70
80
Time (minutes)

FIGURE 1. Drug treatment of status epilepticus. The horizontal bars indicate the approximate duration of drug infusions. IV, intravenous; PE, phenytoin equivalents. (From Lowenstein DH, Alldredge BK. Status epilepticus. *N Engl J Med*. 1998;338:970–976, with permission.)

Initial Therapy of Complex Partial, Simple Partial, and Absence Status Epilepticus

The previous discussion focused on generalized convulsive SE. The management of complex partial SE (Chapter 59), however, is more controversial. In the absence of cardiorespiratory or systemic compromise, most practitioners in Europe would not use an IV protocol for a straightforward case, but usually would rely on oral therapy or at most a single dose of IV lorazepam.[19,44] In the United States, though, more aggressive therapy is often used. Simple partial SE (Chapter 61) is usually treated orally with benzodiazepine or conventional antiseizure drugs. For patients with absence SE (spike-wave stupor), benzodiazepines and valproate (see subsequent discussion) are the drugs of choice (Chapter 60).[52] Drugs such as phenytoin and phenobarbital may exacerbate this form of SE and should not be used.

Valproate

Intravenous valproate sodium shows promise for the treatment of generalized convulsive, complex partial, simple partial, myoclonic, and absence SE.[24,35,42,46,60] No randomized trials of intravenous valproate in SE have been published. Most patients who have received this agent have been refractory to other SE therapies, been allergic to other SE therapies, or had myoclonic or absence seizures as a feature of their SE. Whether valproate should be considered as an initial therapy agent for generalized convulsive SE is not known, but it appeared to be effective in one study.[35] The drug has minimal effect on blood pressure, cardiac rhythm, and respiratory drive.[24] Therefore, valproate can be especially considered in patients with cardiovascular compromise for whom standard initial therapies might pose a

significant risk. The usual dose is 25 to 30 mg/kg, and the drug can be administered undiluted at rates of up to 500 mg/min in adults.[24,53] Although it appears reasonable to target serum valproate concentrations of 100 to 150 mg/L, a clear relationship between concentration and efficacy against SE has not been established. Valproate-related hyperammonemic encephalopathy has been reported after intravenous loading, and this complication should be evaluated (via serum ammonia concentration determination or EEG analysis) in patients who fail to regain consciousness following successful treatment.[38] Patients with urea-cycle disorders should not receive valproate.[9]

Special Considerations in Children

The principles of SE management and choice of drugs in children are similar to those in adults, except that drug doses are adjusted for body weight.[4] Children frequently tolerate higher rates of intravenous drug administration (on a mg/kg/min basis) than do adults. Under some circumstances, alternate routes of benzodiazepine administration (e.g., buccal, intranasal, or rectal) may be necessary either to initiate treatment outside of the hospital or because intravenous access is not feasible. Treatments that have been used successfully for repetitive seizures or premonitory SE in children include diazepam by rectal administration (using intravenous solution or gel formulations)[5,16] and midazolam by buccal or intranasal routes (using the intravenous solution).[23,29,30,40] Paraldehyde, if available, also can be given rectally. The usual dose of paraldehyde is 0.4 ml/kg diluted 1:1 in vegetable oil.[4]

Prehospital Treatment of Status Epilepticus

When SE occurs outside of the hospital, rapid transport to a medical facility is imperative. In past decades, as the emergent need to initiate drug treatment of SE as soon as possible became clear, many emergency medical services (EMS) systems implemented protocols that permitted paramedics to administer intravenous benzodiazepines to patients in SE prior to hospital arrival.[3] Although this approach has intuitive appeal, the safety of this practice had not been demonstrated until recently. Furthermore, the widespread practice in Europe now is to use buccal or intranasal midazolam or rectal diazepam in out-of-hospital situations.[29,30,40] Most paramedics receive little or no training on the recognition of SE, and treatment-related complications may present a significant management challenge in settings that lack the full range of medical equipment and consultants that are routinely available in modern emergency departments.[54] In addition, in dense urban areas, where the time required to transport a patient by ambulance to an emergency department is short, the risks of treatment complications or misapplied therapies could be outweighed by any incremental benefits from earlier drug treatment.

A recent prospective clinical trial in San Francisco addressed these concerns. Adult patients with out-of-hospital SE were randomly assigned to receive intravenous diazepam 5 mg, lorazepam 2 mg, or placebo.[2] Treatments were administered by paramedics, and an identical second injection was available if SE continued between administration of the first injection and arrival at a hospital. Patients were transported by ambulance to local emergency departments, where they received open-label treatment. The primary outcome was cessation of SE by the time of emergency department arrival. The rates of treatment success were higher for lorazepam (59.1%) and diazepam (42.6%) than for placebo (21.1%) ($p = .001$). After adjustment for covariates, the odds ratio for termination of SE by emergency department arrival in the lorazepam group compared with the placebo group was 4.8 (95% confidence interval, 1.9–13.0). The odds ratio was 1.9 (95% confidence interval, 0.8–4.4) in the lorazepam group compared with the diazepam group and 2.3 (95% confidence interval, 1.0–5.9) in the diazepam group as compared with the placebo group. With regard to secondary outcomes, the rates of posttreatment respiratory or cardiovascular complications were 10.6% for the lorazepam group, 10.3% for the diazepam group, and 22.5% for the placebo group ($p = .08$). These results highlight the safety and effectiveness of paramedic-administered benzodiazepines for prehospital SE therapy. Although historically there has been concern regarding the respiratory depressant effects of intravenous benzodiazepines, in fact lower rates of cardiorespiratory complications (primarily, respiratory compromise) were seen among patients who received active treatment as compared with placebo. This difference, however, was not statistically significant, but it suggests that respiratory compromise related to SE itself is at least as important a consideration as that caused by low doses of diazepam and lorazepam. In this study, no treatment-related differences in neurologic outcome at hospital discharge were found.

Although this study validated the practice of prehospital intravenous benzodiazepine therapy for SE in adults, several questions remain: What is the optimal dose of intravenous benzodiazepines for prehospital treatment of SE in adults? Is prehospital intravenous therapy of SE a safe and effective treatment approach for children? Are alternate routes of benzodiazepine administration (e.g., buccal, intranasal, intramuscular, or rectal) preferable to intravenous treatment in terms of rapid termination of SE and ease of use? Is there a role for other, nonbenzodiazepine antiseizure medications in the prehospital management of SE? These are important issues that require further study.

Refractory Status Epilepticus

The term refractory SE describes SE that fails to respond to two or three initial therapies. There have been no prospective studies of the treatment of refractory SE. Therapies in common use include midazolam, propofol, and pentobarbital. When used for refractory SE, these agents are administered in high doses by continuous infusion. Vigilant monitoring of respiratory, cerebral, and cardiovascular function is mandatory, and support measures to maintain blood pressure and adequate ventilation are often required. Thus, these therapies are best suited for application in the intensive care unit.

A review of published studies on midazolam, propofol, and pentobarbital for refractory SE yielded no clear consensus of preferred therapy.[13] Treatment failure was least likely with pentobarbital (3%), but a higher proportion of patients treated with this agent experienced hypotension requiring pressors (77%). Midazolam and propofol were similar with regard to treatment failure (20% and 27%, respectively) and hypotension (30% and 42%, respectively), but breakthrough seizures were more common with midazolam (51% vs. 15% with propofol). Mortality rates were high and not significantly different among the three treatments (midazolam 46%, propofol 52%, and pentobarbital 48%). This review, however, did not use meta-analysis methodology, and in the absence of large-scale trials, a meta-analysis of smaller studies would be valuable.

Topiramate and levetiracetam have been used in refractory SE with benefit in some patients, and the use of ketamine as an anesthetic agent with NMDA-blocking properties also shows promise. Some patients in refractory SE are also given a trial of

high-dose corticosteroid therapy, although the efficacy of this treatment has not been systematically evaluated.

There is controversy regarding the EEG pattern that best represents treatment success in refractory SE. Some investigators titrated drug therapy to EEG background suppression, whereas others targeted seizure suppression regardless of background activity. Based on available evidence, Bleck advocated for seizure suppression on the EEG as the desired goal of treatment.[7] In clinical practice, more than one general anesthetic agent is often used to achieve the desired EEG outcome.[39] An evidence basis for this approach, however, is lacking. The treatment of refractory SE remains a major therapeutic challenge and one in which new approaches are urgently needed and multicenter studies would be helpful.

An important consideration in the management of refractory SE is how long to maintain drug-induced coma and how to reduce the dose of the coma-inducing agent. Here, too, no systemic data are available. Many neurologists maintain full suppression of the EEG for 48 to 72 hours and then begin to reduce the dose of pentobarbital, midazolam, or propofol. Before slowing of the rate of infusion, however, high concentrations of other antiseizure drugs should be ensured. One approach is to load to the patient to achieve a serum concentration of 30 µg/mL of phenytoin and 100 to 150 µg/mL of phenobarbital before reducing the rate of infusion of the intravenous anesthetic. If epileptiform activity returns, the dose of anesthetic agent is increased so that the EEG is fully suppressed again for another 48 to 72 hours or longer, and the process is repeated as many times as necessary. Some patients have recovered after 6 weeks or more of coma.

Summary and Conclusions

SE is a medical emergency that requires immediate and vigorous treatment. Goals of management of SE are to stop seizure activity as quickly as possible, protect neurons from SE-induced damage, and optimize the likelihood of a full recovery. Most neuronal damage is caused by the neurochemical events associated with continuous ictal discharges, but SE-induced neuronal damage can be exacerbated by systemic factors, especially by hyperpyrexia, which should be corrected if present. After establishing an adequate airway, respiratory drive, and circulation, one should obtain blood samples for chemistry, hematology, antiseizure drug levels, and toxicology. An intravenous line then should be established using normal saline, blood sugar should be checked by finger stick (and corrected if true hypoglycemia exists), and then specific pharmacotherapy should be initiated using a predetermined protocol such as the one outlined in this chapter. Children require different doses of antiseizure agents but otherwise should be treated in the same manner as adults in SE. Refractory SE may require high-dose therapy with barbiturates, benzodiazepines, or propofol as a continuous infusion to suppress all epileptiform discharges on the EEG. The patient can then be weaned intermittently to determine whether epileptiform activity on the EEG has ceased.

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Chapter 127

Drug-resistant Epilepsy

Warren T. Blume

Introduction

This chapter discusses some factors that promote antiepileptic drug-resistant epilepsy in 20% to 30% of patients who have seizure disorders.

Accurate and prompt recognition of an epileptic condition that is likely to be intractable to medical and psychological therapy will guide management and the tendering of a prognosis to family and close associates. Unexpected intractability raises the possibility of a focal or diffuse progressive disease, discussed in Chapters 252 and 264.

After an initial section on definitions of intractability, principal aspects pertaining to focal and generalized epilepsies will follow. Interposed between focal and generalized sections, and applying to each, are brief discussions of propagation, genetics, and pharmacoresistance.

Defining Intractability

Paradoxically, defining "intractability" is probably more difficult than discerning which patients have or will have therapy-resistant seizures, as the following considerations illustrate.

Medical Treatment Failure

Persistent seizures despite about two or three appropriately selected and prescribed antiepileptic drugs constitutes medical failure, based upon the sharply declining probability that subsequent drugs will succeed.[2,7,26,31,57] Accurate classification of the seizure disorder through ictal semiology, electroencephalography (EEG) and presumed etiology is prerequisite for antiepileptic drug (AED) selection and sequencing.

Importantly, seizure freedom, only obtained by overt or covert AED toxicity, constitutes intractability. Covert toxicity occurs when polypharmacy is gradually attained or augmented (e.g., with two or more drugs in the "therapeutic range"). Patients, associates, and the treating physician may all be oblivious to this circumstance.

Seizure Occurrence

Minimum seizure frequency is one approach to this component of definition.[26,31] Does one count seizure number or number of seizure days per month or year? Seizure type and circumstance must be considered: A single tonic–clonic seizure in a truck driver will have more impact than rare, brief absences in a school child. The opposite approach is establishing the minimum duration of remission needed to *not* qualify as intractable.[2] With either or both criteria, patients could be classified as always, usually, seldom, or never intractable for each seizure type.

Time Dimension

To avoid hastily labeling as intractable certain patients having seizures with an acute illness or other circumstance, measures reflecting frequency with time have value: (a) minimum time that one is not free of seizures (e.g., 6 months or 12 months), (b) outcome at a specific point in time (e.g., failure to be in 6-month remission 2 years after diagnosis), and (c) minimum seizure frequency at any point in the disorder.[8]

Strict Versus Loose

A strict definition would have high specificity but may miss some patients who should be managed and followed as intractable. A loose definition would unfairly label, depress, and overinvestigate some patients. As the use of this definition will determine the stringency required, the concept of an intractability scale would be useful.[86] For example, a loose definition—or low point on a scale—would be appropriate for referral to an epileptologist, while a strict definition may be required for invasive investigations or surgery.

Children

Principles underlying any definition of intractability may closely resemble those generally applicable, except that age will play a relatively important role. An earlier age of onset correlates with a higher prevalence of intractability.[6,44] However, studies have shown an approximately similar prevalence of intractability in children as in adults, possibly as a higher proportion of benign syndromes that begin in childhood statistically counterbalances the several malignant syndromes of childhood onset (see further).

Intractability may be more difficult to predict in the pediatric age group. Berg et al.[7] found that outcome could not be predicted in almost 40% of children after 2 years of follow-up. Camfield and Camfield[20] found similar predictability in patients with dyscognitive seizures. Additionally, Berg et al.[7] reported ultimate remission in 14% of previously intractable patients. See Farrell et al.[32] for further discussion.

Extraneous Factors

Optimal application of any definition or set of criteria requires reliable data. Thus, an accurate diagnosis is essential, bearing in mind that many intermittent central nervous system events

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represent nonepileptic disorders (e.g., syncope, migraine, pseudoseizures, and diurnal drowsy episodes when sleep deprived). This principle applies to both initial and follow-up information.

Additional causes of misleading data are AEDs inappropriate for a given seizure disorder, the wrong dose of a correct medication, or suboptimal compliance with the prescribed regimen. Premature abandonment of a useful drug may occur because of excessive haste to obtain seizure control or through overoptimistic therapeutic goals for disorders known to be intractable.

Table 1 Some Aspects Auguring Intractability

- **Focal epilepsies**
  - Region
    - Temporal
    - Occipital
    - Primary motor cortex
    - Supplementary sensory motor area
- **Etiology**
  - Mesial temporal sclerosis
  - Cortical dysplasia
  - Hemorrhagic lesions
  - Multifocal epileptogenesis
  - Progressive lesions
- **Generalized epilepsies**
  - Onset in infancy or early childhood

- High initial seizure frequency
- Failure of initial appropriate AED
- EEG
  - Abundant multifocal or bisynchronous spikes
  - Abnormal “background” activity
- Progressive disorders

AED, antiepileptic drug; EEG, electroencephalography.

Stress increases seizure frequency.[37,67] Stress is often associated with depression, which disrupts sleep; this, in turn, lowers a seizure threshold.

Intractable Focal Epilepsies

Several interdependent factors may render a focus of epileptogenesis resistant to AEDs. This section discusses region of ictal onset, etiology, and multifocality of epileptogenesis (Table 1).

Brain Region

Temporal

The mesial temporal lobe is probably the most epileptogenic of brain regions. Hauser and Kurland,[46] in an epidemiologic study, found temporal lobe epilepsy (TLE) more prevalent (1.7 per 1,000) than all other focal epilepsies combined. Ninety percent of temporal lobe seizures begin in the mesial (i.e., limbic) components, as invasive EEG recordings have disclosed.[11,84] Such recordings have shown that temporal lobe seizures most commonly begin regionally within the mesial temporal lobe, involving several components simultaneously. The less common focal onsets arise more often in the hippocampus than in the amygdala.[29,77,83] Paradoxically, kindling, an important experimental model of epileptogenesis, is most easily elicited by stimulation of limbic structures,[38] especially the amygdala.[19]

Occipital

Ebersole and Chatt[28] found layer four of the striate cortex to be highly epileptogenic from effects of discrete penicillin applications to each layer. Similarly, Cain[18] readily produced kindling by electrical stimulation of the deep layers of the occipital cortex, whereas stimulation of superficial layers failed to evoke kindling.

Motor Cortex and Supplementary Sensory Motor Area

The face and hand area of the motor cortex is also a common site of seizure origin.[33,93] A fourth region often involved in intractable seizures is the supplementary sensory motor area.[72,74] Seizures from this region may be intractable because of its abundant efferents to several levels of the motor system.[10,64,92]

Etiology

Focal seizure etiology influences intractability at least as strongly as location. Mesial temporal sclerosis (MTS), cortical dysplasia, and hemorrhagic lesions are examples.

Mesial Temporal Sclerosis

Unfortunately, an unambiguous explanation of MTS epileptogenesis has not emerged from experimental and clinical data as causative, compensatory, and associative factors are intertwined. Although several basic and clinical studies have found data consistent with an increased or maintained γ-aminobutyric acid (GABA) inhibitory system,[17,30] such inhibition has been shown to be fragile[95] or even excitatory in certain circumstances.[3]

Spontaneous epileptic activity occurs in the entorhinal cortex in humans with epilepsy.[5] Collins et al.[23] found that the dentate gyrus only initially restricted propagation of penicillin-evoked seizures in rat entorhinal cortex; as this inhibition was overcome, seizure activity engulfed the hippocampus. Leung and Wu[59] described an increase in excitation of the rat entorhinal cortex–dentate gyrus pathway in kainic acid–treated rats and in CA1 of the hippocampus from CA3 stimulation. Vulnerability of CA3 stratum lucidum interneurons has also been found experimentally,[65] which may lead to an extensive remodeling of mossy fibers in CA3. This may shift the dentate granule–CA3 pathway from feed-forward inhibition to direct excitation, leading to excessive recruitment of CA3 pyramidal cells in epileptic activity.[58] Ratte and Lacaille[78] documented reduction of GABAergic cells in the stratum oriens and alveus in the kainic acid model, increasing the ratio of excitatory to inhibitory synapses in the stratum lacunosum moleculare. Thus, CA1 becomes hyperexcitable despite loss of a large proportion of Schaffer collateral afferents.

Several studies have disclosed enhanced excitation in the epileptogenic mesial temporal region. Leung and Wu[59] described opening of sodium channels with less depolarization producing larger sodium currents. Additionally, an increased pool of releasable glutamate and increased *N*-methyl-D-aspartate (NMDA) receptor activation in MTS has been found.[39,60]

From these physiologic data, it is not surprising that only 11%[81] to 25%[53] of patients with MTS are rendered seizure free by AEDs, whereas a far higher proportion (31%) of TLE patients without MTS are seizure free.[81]

These and other epileptogenic physiologic aberrations are likely further accentuated in multifocal temporal epileptogenesis as Sadler[80] listed disseminated epileptogenesis (e.g., with dual pathology), as a factor leading to temporal lobectomy ineffectiveness.

Cortical Dysplasia

In our anecdotal experience, very frequent, cryptogenic focal seizures in an otherwise neurologically intact patient are often caused by cortical dysplasias (CDs). Studies have described up-regulated NMDA activity in both humans and rats with CD.[4,69,70] Several other investigations have disclosed impaired inhibition with CD.[9,41,79,85,97] This dual physiologic effect on the excitation:inhibition ratio in CD underlies its epileptogenicity: (a) cortical dysplasia is found in 25% of children with intractable focal epilepsy[55] and 15% to 20% of adults so afflicted,[56] and (b) 76% of Semah et al.[81] patients with dysplasia were medically intractable.

Hemorrhagic Lesions

Cavernous angiomas and other micro- or macro-hemorrhagic lesions also possess an epileptogenicity disproportionate to their size and growth and to the general health of the central nervous system. Experimental cortical injection of blood produces iron-filled neurons and macrophages, neuronal loss, and astrogliosis.[43,94] Three sequelae of hemorrhage-induced iron deposition in the brain produce epileptogenesis: (a) subsequent chronic increases in lipid peroxidation, which correlate with epileptiform discharges[82]; (b) impaired glial glutamate transport[27,89]; and (c) a decrease in nitric oxide synthesis from ferric chloride in the cortex, which augments hippocampal epileptogenicity.[40,51]

Multifocality

Multifocal epileptogenesis, as reflected in multifocal interictal EEG spikes, is often intractable: Studies of this EEG phenomenon found daily seizures in 33% to 60% and half had more than one seizure type.[14,71] Multifocal spikes also augment the incidence of secondary bilateral synchrony, a phenomenon also associated with multiple seizure types and with generalized seizures.[13]

Propagation and the Immature Brain

Discussion of some factors facilitating ictal propagation is interposed between the “focal” and “generalized” sections as they apply to each. Rapid propagation may complicate focal seizure semiology, while the distinction between primarily and secondarily generalized seizures may be blurred in some instances.

The "Hyperconnected" Cortex

Epilepsy onset in early childhood increases the likelihood of chronic intractability.[45] Aside from the inherent epileptogenicity of any causative lesion (e.g., tuberous sclerosis), components specific to the immature brain may persist to adulthood because of recurrent seizures. This augments the seizure tendency and its propagation and thus influences its clinical and EEG manifestations. Two examples follow.

The first is immature patterns of innervation. Brain-derived neurotrophin factor is increased in rat neurones whose action potential rate is augmented by seizure activity.[54] This may lead to development of an abnormal neuronal network enhancing epileptogenesis.[35,91] Seizures of the immature brain may lead to a failure of "pruning" or apoptosis, imprinting abnormal connectivity, a situation termed "the hyperconnected cortex."[15,48]

Gap Junctions

Secondly, neuronal gap junction communication (GJC) is particularly abundant in the immature brain, which harbors transient and extensive coupling between groups of neurones.[61,90] Experimental manipulation of GJC has supported its role in the genesis and maintenance of seizures.[75] Epileptic activity in early childhood may abnormally preserve the quantity of GJC, contributing to the network previously described. Such coupling may convert "spiking" neurones of CA1 to bursting cells. If this principle applies to neocortex, it may contribute to ictal propagation, for which intrinsic bursting cells are the principal conduit.[88]

The previously described mechanisms relating to early childhood seizure onset and later intractability are but two among possibly many—discovered and yet undiscovered—that not only enhance the epileptic tendency, but also confound clinical and laboratory analyses of these patients. However, despite the apparently irreducible complexity generated by such factors, most focal seizures of most patients propagate in a consistent manner, obeying the "beaten path" principle of Penfield,[73] confirmed experimentally by Petsche et al.,[76] and in subdurally recorded seizures by Blume et al.[12]

Thalamic Propagation

By circumscribing or undercutting penicillin-induced focal cortical epileptogenic lesions in newborn and pubescent (24 months) Macaca mulatta, Caveness et al.[21] found the direction of seizure propagation to shift from subcortical (presumably thalamic) to contiguous cortical with maturation. Any excessive preservation of subcortical pathways, in a manner similar to the "hyperconnected" cortex, could enhance generalization of a focally originated seizure.

Kindling, Genetics, and Pharmacoresistance

Increasingly appreciated aspects of intractability are genetics and mechanisms of pharmacoresistance.[68] Comprehensive reviews of the genetics of intractable epilepsy by Cossette and Rouleau[25] and of pharmacoresistance by Heinemann et al.[47] and Löscher et al.[63] are also available. These factors apply equally well to focal and generalized seizures and epilepsies.

Kindling has, thus far, been the principal animal model used to study drug resistance or pharmacoresistance. Both the amygdala and the hippocampus have lower afterdischarge (AD) thresholds and are the easiest to kindle. To illustrate the genetic influence in kindling, McIntyre's group succeeded in selectively breeding rats to be either seizure prone (fast kindlers) or seizure resistant (slow kindlers); this supported a concept that human epilepsy consisting of focal seizures with secondary generalization is somewhat influenced genetically. Significantly, although slow kindlers had higher AD thresholds than fast kindlers before kindling, their threshold dropped to equal that of fast kindlers after kindling. This suggests that seizures may convert a seizure-resistant mammal to a seizure-prone one. Thus, Löscher's group found kindling to convert some Wistar rats from phenytoin (and other AEDs) responders to nonresponders. Whether this relates to development of a "multiple drug-resistant gene" from the kindling process has not been determined.

Intractable Generalized Epilepsies

Most generalized epilepsies that resist medical management have the following characteristics: (a) usual onset in infancy or childhood, (b) high seizure frequency and initial failure of an appropriate antiepileptic drug, and (c) abundant multifocal and/or bisynchronous EEG spikes with abnormal "background" EEG activity (Table 1). Cognitive development slows, arrests, or regresses in many such cases.

Lennox-Gastaut syndrome (LGS) occupies a central nosologic position among generalized epilepsy syndromes and is defined as (a) a childhood epileptic encephalopathy with multiple types of seizures, particularly tonic attacks, but also atypical absences and atonic seizures; (b) interictal bilaterally synchronous slow spike-waves on EEG; and (c) runs of bilateral paroxysmal EEG fast activity.[1,36] The medical intractability and the EEG features suggest increased cortical excitability. For example, the slow repetition rate of slow spike-waves suggests an enhanced proportion of the longer $GABA_B$-mediated thalamic inhibitory postsynaptic potentials (IPSPs) that result from increased firing in corticothalamic pathways.[16,52] Bursts of fast rhythmic waves or polyspikes at 10 to 30 Hz, also known as the "epileptic recruiting rhythm," may be associated with tonic or absence seizures. The experimental correlate of this phenomenon appears to be "fast runs," during which most cortical neurons are depolarized.[87] Moreover, a phase of enhanced cortical excitability exists in early development of the mammalian central nervous system corresponding with the usual early onset of intractable epilepsies in humans.[42,66]

In addition to diffuse hemorrhage and multifocal dysplasias whose epileptogenic mechanisms are discussed in a previous section, anoxia and encephalitis may play ictogenic roles. Both non-NMDA and NMDA receptor mechanisms appear to be involved in postanoxia epilepsy.[49,50] A paucity of experimental data relates encephalitis to generalized seizure disorders. Putatively, micro-infarcts and hemorrhages may occur, inducing mechanisms discussed under anoxia and hemorrhage.[96] Astrocytic and microglia proliferation could impair glutamate uptake or alter gap junctions.[96]

Gene Defects

Identification of genetic abnormalities in association with cryptogenic generalized epilepsies may provide additional insights into pathophysiology. An increasing number of gene defects have been found associated with progressive myoclonic epilepsies.[62] Additionally, mutations of sodium channel α subunit type 1 (SCN1A) have been found in intractable childhood epilepsies, including severe myoclonic epilepsy in infancy (Dravet syndrome) and intractable generalized tonic–clonic seizures.[22,24,34]

Summary and Conclusions

This chapter reviews clinical and experimental data relating to medically intractable epilepsy. In the clinical setting, syndrome identification is a first and major step in early recognition or prediction of intractability. The principal syndrome components of seizure localization and etiology are reviewed.

This process allows the physician, the patient and the family to confront the magnitude of the disorder. An overoptimistic patient may prematurely lose faith in the physician and in the medications prescribed. Greater lifestyle modifications will be necessary to optimize medication effectiveness. Any surgical option will be recognized earlier; this allows its evaluation to be initiated while a logical sequence of medications is assessed.

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Chapter 128

Prophylactic Treatment

L. James Willmore

Introduction

Because antiepileptic drugs (AEDs) target brain structures for their effect, they are being used to treat several neurologic conditions other than epilepsy. While control of seizures is the primary therapeutic use for such drugs, as specified in most submissions to governmental regulatory agencies, there is growing interest in AEDs for disease modification or for neuroprotection. *Prophylaxis* is defined as a process of guarding against the development of a specific disease by a treatment or action that affects pathogenesis. In contrast, to *prevent* means to render impossible by an advanced provision, or to keep from happening. A preventive intervention does not imply an effect other than alterations of symptoms, signs, or manifestations of a disease. Prevention may alter some component of a disease, but specificity is not implied, and effect on pathogenesis is not required.

Drugs that control epilepsy or change the intensity of seizures have been used to attempt disease modification. Within years of the introduction of phenytoin, investigators reported various open and uncontrolled trials purporting to show that drug's efficacy as an agent effective for antiepileptogenesis. However, randomized, controlled trials of both phenytoin and valproate failed to show that use of drugs with effects on seizures had any impact whatsoever on chronic epileptogenesis, a marker for brain injury.[68,69,70] In fact, animal studies of the effect of corticosteroids and phenytoin on brain lipid peroxidation initiated by a free radical generating mechanism showed phenytoin associated with unabated brain injury while seizures were controlled.[79] Of interest, high dose corticosteroids in this model caused abatement of both seizures and lipid peroxidation. There is continued interest in disease modification that might accrue should antiepileptic drugs control seizures and somehow protect neural tissue as well.[3] Mechanisms of action of AEDs that are critical to anticonvulsant activity have been considered as having a role in neuroprotection. If this were the case, the therapeutic value of AEDs would include not only control of seizure activity (anticonvulsant), but also the prevention of injury responses, resulting in *disease modification*.[76]

Neuroprotective agents have been sought among various molecular designs, including calcium channel blockers, anti-inflammatory drugs, and various sterol compounds. While animal trials have suggested robust efficacy, clinical studies have failed. Whether the end-point is inappropriate or the nature of the injury to neural tissue of such intensity that a pharmacologic intervention could not possibly succeed has yet to be determined.[50]

Better understanding of the mechanisms of brain injury has had impact on drug design, with introduction of several new antiepileptic drugs for clinical use that have unique actions. Mechanisms of injury in animals and in some human studies have included cerebral infarction, ischemia, status epilepticus, and traumatic brain injury.[66] Common cellular responses to injury include marked increase in the extracellular concentration of glutamate followed by increase in intracellular calcium and cell death.[6] Marked increase in glutamate occurs in humans having seizures as measured with microdialysis.[12] Similar changes occur in animals with status epilepticus.[75] In stroke and hypoxia, failure of high-energy substrates cause failure of transporters with loss of membrane potential and neurotransmitter release.[36] Glutamate binding to specific receptor molecules initiates signaling that is coupled to channels permeable to ions or to G-protein second messenger systems.[10] Inotropic glutamate receptors are categorized by selective responsiveness to *N*-methyl-D-aspartate (NMDA), kainate, or AMPA. Calcium entry into cells by the NMDA receptor complex in the various patterns of brain injury is critical to cell injury,[7] while antagonists are protective.[5,17]

Prevention

One example of preventive treatment is the administration of anticonvulsants to patients with head trauma of such severity that hypertension and hypoxia associated with a convulsive seizure would complicate management. Antiepileptic medications are administered to patients who are thought to be at risk to have tonic–clonic seizures with the intent to prevent the occurrence of convulsive seizures. Patients with absence seizures may be treated with a broad-spectrum antiepileptic drug prior to occurrence of a tonic–clonic seizure, rather than using a syndromic-specific agent such as ethosuximide. Preventive treatment in this narrow context may be successful. However, some patients are given anticonvulsants with an apparent attempt to interfere with the process of epileptogenesis. Examples of this prophylactic use include the routine administration of antiepileptic drugs to patients with head trauma,[54] or to patients undergoing neurosurgical procedures requiring incision of the neocortex.[77] Although prevention of seizures is a worthy goal and may be effective, prophylaxis of epilepsy in the strict sense may not be effective, since no data are available to suggest that antiepileptic drug administration has any impact on the process of epileptogenesis.[70]

Posttraumatic Epilepsy

Trauma dose as estimated by factors correlated with severity of head injury allow a crude prediction of the liability to develop posttraumatic epilepsy (PTE).[14] Classification of head injury based on clinical evidence of trauma dose reveals a correlation with epilepsy risk.[4] Patients with severe head trauma with cortical injury and neurologic sequelae, but with intact dura mater, have an incidence of epilepsy from 7% to 39%.[4] However, if dural penetration occurs in association with neurologic deficits, then the range of epilepsy incidence is 20% to 57%.[4] Application of weighted risk factors

allowing mathematical estimation of liability for development of PTE at the time of injury suggests correlation between severity of injury and subsequent epileptogenesis.[78] Brain volume loss also reflects trauma intensity and provides a correlation with PTE.[59]

Fifty-seven percent of head-injured patients developing PTE will have their first seizure within 1 year of injury.[59] Although specific mechanisms remain unknown, the latency between injury and occurrence of convulsive seizures must represent the process of epileptogenesis. Whether a seizure occurs immediately after injury, within the first week, or beyond the first week may have prognostic significance for development of epilepsy.[25] The occurrence of an immediate seizure, within hours after trauma, and posttraumatic status epilepticus may complicate management of an injured patient by adding hypoxia and hypertension to the primary processes initiated by trauma. Although an immediate seizure may be a nonspecific reaction, such a symptom may herald the presence of an intracranial hematoma.[23] However, if seizures occur within the first week after injury (an early seizure), then an increase in the incidence of late epilepsy has been observed.[26] Other predictors of risk of late epilepsy include 24 hours of posttraumatic amnesia, the presence of a depressed skull fracture, or an intracranial hematoma.[24]

Prophylaxis of Posttraumatic Epilepsy

Because uncontrolled studies suggested that antiepileptic drugs might have a prophylactic effect,[54,82,83] prospective, placebo-controlled assessments were undertaken. Penry et al.[48] administered phenytoin and phenobarbital to head-injured patients in a double-blind fashion, with placebo control. Their report, in abstract format, documented a seizure probability in the treated group of 21% and a probability of 13% in controls. The authors concluded that no significant difference was detected between the treatment and control groups, suggesting that anticonvulsant administration had no effect on the development of posttraumatic epilepsy in the treated patients.

Young et al.[83] reported experience with 179 head-injured patients treated with phenytoin or with placebo for 18 months in a prospective, double-blind fashion. Patients received loading doses of phenytoin or placebo; anticonvulsant blood levels were measured. Eighty-five patients were included in the treated group, while 74 patients were enrolled as placebo control. At the end of the study, seizures had occurred in 12.9% of the treated patients and in 10.8% of the control patients.

Temkin et al.[69] reported their experience with 404 patients treated in a prospective fashion. Patients with severe head trauma were assigned to receive an intravenous loading dose of either phenytoin or placebo. Serum levels were measured at regular intervals, blood levels of drug were maintained in the therapeutic range, and efforts were made to ensure that evaluations were blinded. At 1 year no difference in incidence of PTE was found between the treatment and control groups. However, they did observe that phenyt-oin was effective in prevention of seizures during the acute period immediately after injury. By 2 years PTE had occurred in 27.5% of phenytoin-treated patients and in 21.1% of controls. Valproate had some efficacy in changing the pattern of kindling in animals,[64] but failed as a prophylactic drug in a controlled clinical trial in humans with head trauma.[68,70]

Phenytoin controls seizures for up to 3 weeks after head injury, but no prophylactic effect was observed with regard to development of posttraumatic epilepsy. Although physicians tend to treat those patients with the most severe injuries with preventive intent, the agent that might serve as a prophylactic for a PTE agent remains to be identified.

Absence Epilepsy

Patients with absence epilepsy commonly develop generalized convulsive seizures as an additional manifestation of this epilepsy syndrome. Patients with the best prognosis for control of absence seizures have normal intelligence and a negative family history of epilepsy. These patients may have a 90% chance of remission. In contrast, the overall remission rate for all patients with absence ranges from 37% to 57%. Patients at high risk for the development of concurrent or subsequent generalized tonic–clonic seizures have late onset of absence epilepsy.[57]

Drugs used for treatment of absence epilepsy include ethosuximide, clonazepam, and valproic acid. Ethosuximide has specific efficacy for nonconvulsive seizures, while valproate is effective in controlling both absence and generalized convulsive seizures.[61] Ethosuximide used as initial therapy for this seizure syndrome may leave a patient vulnerable to the occurrence of convulsive seizures. Preventive treatment using a broad-spectrum anticonvulsant such as valproic acid would be appropriate for a patient with late childhood or early adolescent onset of absence seizures. There is no published report addressing the specific efficacy of this course of treatment as preventive for convulsive seizures, particularly with comparison of ethosuximide and valproate. Clinicians should be aware of the possibility of anticipation and prevention in this context by discussing such problems with parents of patients.

Cerebral Infarction

Six to nine percent of patients with stroke may develop the complication of epilepsy.[34] Precise prediction of development of postinfarction seizures may depend on etiology.[39] Not unlike head trauma, a differential liability to develop seizures may depend on acute versus late seizures relative to onset of the infarction.[63] The role of seizures as a so-called precursor to stroke remains controversial.[34] Patients with cerebral infarctions involving the cerebral cortex with persistent paresis have 20% liability to develop seizures.[9] Although the risk of epilepsy following stroke has been recognized, administration of anticonvulsant as a prophylaxis is not a common practice and has not been reported. If medications were to be administered to this group, then specific knowledge of the risks and benefits would be most important before such an action were recommended.

Febrile Seizures

Children from 3 months to 5 years of age may have convulsive seizures associated with fever or febrile illnesses (see Chapter 124). Nonfebrile seizures or epilepsy develop in 2% to 6% of patients with febrile seizures.[45] Risk factors predicting development of epilepsy include the presence of a neurologic abnormality; febrile seizures lasting longer than 15 minutes; a focality to the seizure; recurrent seizures in a single day; onset at <1 year of age, but especially during the first 6 months of life; and an immediate family member with epilepsy. However, identification of risk factors suggests that fever is a precipitant rather than a cause of epilepsy. Most preventive efforts are directed to the high-risk patients. Management of the acute illness may require pharmacologic interruption of a seizure or prevention of a recurrence during the same febrile illness. Rectal diazepam and valproate are effective, but problems with sedation must be anticipated. Although recurrence can be prevented by chronic use of phenobarbital, behavioral problems

and compliance difficulty make this approach impractical.[49] Until the issue of epileptogenesis is resolved, chronic prophylactic antiepileptic drug administration should not be used in patients without risk factors. Decisions regarding prophylactic drug administration in patients with risk factors for recurrence of febrile seizures or for development of epilepsy must be individualized, since data to guide treatment are not available.

The Single Seizure

Information is available regarding the critical factors involved in deciding when to treat a patient with a single seizure (see Chapter 122). The impact of antiepileptic drug therapy on the natural history of the process heralded by a single convulsive seizure is unknown. Sander,[60] in a thoughtful review, addresses issues with regard to prophylaxis within the context of prognosis of epilepsies. Remission of epilepsy, defined as being seizure free for 5 years, was achieved in 76% of patients by 15 years after onset.[1] The Tonbridge study provided similar data; 73% of patients had a period of being seizure free for 2 years.[18] Overall, between 70% and 80% of patients treated with AEDs will achieve remission. The remaining patients have chronic or intractable epilepsy. Data are unavailable to allow a conclusion that AED therapy had a prophylactic effect in preventing chronic epilepsy. However, some observations suggest that the pathologic substrate may be more important than seizure frequency in leading to chronic epilepsy.

Studies of epilepsy prevalence in developing countries provide some suggestions regarding the natural history of untreated epilepsy. A population-based study in Northern Ecuador[52] identified 45% of patients in a 2-year remission. Of the original sample identified, 28% achieved remission regardless of treatment with AEDs. Similar observations were reported for Nigeria,[46] Ethiopia,[67] China,[35] and India.[31] While suggestive, these data must be viewed with caution. Etiology of epilepsy and mortality[44] may influence prevalence rates. Taken together, these data suggest that pathogenesis rather than need for prophylactic drug effects are operant in those patients with chronic epilepsy.

Established Drugs: Neuroprotection

Some AEDs have shown neuroprotective effects in some animal models of injury.[50,51,55] Animal models for study of neuroprotection include induction of status epilepticus in rats by electrical stimulation that is maintained at a controlled rate even in the presence of an anticonvulsant.[19] This model allows measurement of the neuroprotective effect of a particular drug independent of any anticonvulsant activity. Variables can be biochemical, such as measuring the degree of fragmentation of DNA,[29,30] or morphologic, such as the extent of neuronal loss.[66] Phenytoin, phenobarbital, and carbamazepine have all been shown to be neuroprotective to some degree in an ischemic/hypoxic model of neuronal injury.

Recently Available Antiepileptic Drugs

Lamotrigine

Pretreatment with lamotrigine attenuates the elevation of glutamate and aspartate that occurs during reperfusion following experimental ischemia. This attenuation of release of excitatory neurotransmitters by lamotrigine suggests a potential for neuroprotective effectiveness.[8] Some neuroprotective effect was observed during ischemia coupled with hypothermia.[2] Global brain ischemia was evaluated using indices of brain water content measured with magnetic resonance. Lamotrigine failed to prevent development of intracellular water accumulation.[28] However, some evidence for neuroprotective effect in cerebral ischemia was observed with combined administration of the calcium channel blocker flunarizine with lamotrigine.[33] While certain animal models of ischemia fail to demonstrate efficacy for lamotrigine, the drug does appear to have parallel protective efficacy to MK-801 in prevention of excitatory amino acid injury to neurons.[32,80]

Although clinical trials have yet to identify an antiepileptic drug that prevents epileptogenesis,[68,69] many agents are tried in the electrical kindling models to evaluate effect on various parameters. In one study, lamotrigine was found to be effective as an anticonvulsant, but the drug either failed to alter kindling or even facilitated the initial phase of kindling development.[53] Others found that lamotrigine did counteract kindling acquisition, suggesting potential as a neuroprotectant.[65]

Levetiracetam

Levetiracetam does inhibit the pace of kindling in a way similar to antagonists of NMDA receptors.[38] However, when used in focal ischemia, levetiracetam had a 33% protective effect as measured by infarct volume with doses in a range similar to those used in the kindling effect. MK-801 pretreatment, considered the standard in receptor blockage, reached 74% reduction in infarct volume, albeit with hypothermia as a confounding variable.[21,80]

Topiramate

Topiramate has been tested in several animal models of ischemia and limbic status epilepticus. In focal ischemia models, infarct volume was reported to be reduced by 50% to 80% when topiramate was given to rats at 40 mg/kg. This effect exceeded that of MK-801. In similar doses in animals undergoing global ischemia and treated 30 minutes after onset, cells were protected and behavioral skills preserved. Cellular injury was prevented in electrical limbic status epilepticus.[13,56] Protection in animals by topiramate against priming effects of hypoxic seizures and periventricular leukomalacia has been reported.[15,27]

Zonisamide

Zonisamide (ZNS) has been assessed in several models of ischemia, and has been found to have neuroprotective properties in all of them.[22,41,47] In one study, gerbils were subjected to ischemia both before and after administration of ZNS. Damage to the CA1 region of the hippocampus and associated extracellular glutamate accumulation were examined at 7 and 28 days postinjury. ZNS administered prior to the hypoxia resulted in less neuronal damage to the CA1 region and lower levels of glutamate accumulation at 7 days ($p < 0.05$) and at 28 days ($p < 0.01$).[47] In a similar study, rats subjected to 90 minutes of ischemia were treated pre- and postinjury with ZNS, sodium valproate, or carbamazepine at typical anticonvulsant doses. Only ZNS was found to reduce both neurologic deficit and neuronal loss, while carbamazepine demonstrated an effect only at a high dose (60 mg/kg/dose).[41] Neonatal rat pups subjected to ischemia were pretreated with ZNS or placebo by intraperitoneal injection. Mean plasma levels of ZNS were 47.9 μg/mL preischemia and 42.3 μg/mL postischemia. Reduction in the mean volume of both cortical and striatal infarcts was by roughly 90% in the ZNS-treated animals, despite seizure intensity showing no difference between ZNS- and vehicle-treated rats.[22]

While mechanisms for neuroprotection by AEDs in animal models remain unknown, some unique effects of ZNS may be

operant. Zonisamide scavenges free radicals, including both hydroxyl and nitric oxide radicals.[43] This property was initially demonstrated in vitro but was subsequently confirmed in an animal study in which rats were given a cortical injection of ferric chloride, which is known to induce oxidative damage.[29] Rats that were pretreated with ZNS did not show the substantial increase in 8-hydroxy-2′deoxyguanosine (8-OHDG) that was found in the untreated animals, providing indirect evidence that the scavenging of these hydroxyl radicals was responsible for the protective, antioxidant activity of ZNS.[80]

Summary and Conclusions

Specific knowledge about the process of epileptogenesis as initiated by trauma, fever, or genetic factors may contain a specific clue about methods of prophylaxis. However, the principal impediment to pharmacologic interruption of the process of epileptogenesis is lack of knowledge of the mechanism that results in the formation or activation of a seizure focus. The clinical problem of a patient with trauma sufficient to initiate epileptogenesis, and with effects of injury that would be worsened by the occurrence of a convulsive seizure, requires practical intervention for protection during the acute illness. If an anticonvulsant is to be administered to prevent a seizure after a severe head injury, then that medication should be given intravenously, and pharmacologic principles should be followed.

Part of the problem is defining the clinical paradigm and selecting appropriate outcomes to even begin to detect a neuroprotective or prophylactic effect of a drug. Strategies involving antiepileptic drugs that appear to have unique and possibly important mechanisms of action may require multiple drug strategies. While neural injury most assuredly involves initiation at membrane surfaces and receptors, molecular manipulations could be useful. Families of receptors that are not thought of as involving antiepileptic drugs may be critical. Immunophilins regulate the transition pore of mitochondria, stabilize ion channels, act as molecular chaperones, and may well be excellent candidates a neuroprotectants.[20] Caspase inhibitors may have a role in various degenerative diseases.[37,62] Endocannaboids block presynaptic release of glutamate and activate intracellular signaling.[40] Finally, antioxidants have shown potential in various animal models.[16] To-copherol compounds are natural antioxidants that could be of use, particularly if issues of solubility and tissue penetration can be solved.[42,71,81] While amino acid transporter regulation is altered in epileptogenesis,[11,72,74] increasing the expression of glutamate transporters may have the potential to protect neural structures and alter epileptogenesis.[58,73]

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Chapter 129

Ketogenic Diet

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Introduction

The ketogenic diet (KD) is a high-fat, low-carbohydrate, adequate-protein diet that has been used as an alternative therapy for intractable seizures since the early 1920s. At that time, only a few effective antiepileptic drugs (i.e., phenobarbital and bromides) were available to clinicians, and each of these carried significant side effects. In the 1940s and 1950s, when modern antiepileptic drugs such as phenytoin and ethosuximide became available, use of the KD declined rapidly. Nevertheless, there was an occasional resurgence of interest in the KD. In 1971, the medium-chain-triglyceride diet[34] was devised in an attempt to provide more flexibility with respect to carbohydrates, enhanced ketosis, and better palatability. Despite a flurry of new antiepileptic drugs in the 1990s, frustration with the medical intractability of childhood epilepsies has continued, and recently, public awareness of the KD has increased. The KD is now considered a safe and effective alternative therapy for children and adults with refractory epilepsy, with an efficacy that rivals (and perhaps exceeds) the newer antiepileptic drugs (AEDs).[83] More recently, alternative diets for epilepsy treatment, such as the Atkins diet and a low-glycemic-index diet, have been devised that represent modifications of the original KD.

History

Fasting for seizure control was reported as early as the 5th century BC by Hippocrates.[95] References to fasting for seizure control are also found in the Bible (Matthew 17:14-21 and Mark 9:14-29). Jesus, after curing a young boy with convulsions, advised his disciples that such “demons” cannot be purged except by prayer and fasting. Fasting is mentioned again in the medieval writings of John of Gaddesden.[50] There is no further mention of fasting in modern medical literature until 1911, when Guelpa and Marie[30] placed 20 patients on a 4-day fast, noted some improvement in seizure control, and referred to people with epilepsy as *trop alimentés* (“too well fed”).

In 1921, Geyelin[28] reported that the beneficial effect of 3 weeks of fasting continued even after the fast was broken. The work of Geyelin and many others was probably prompted by reports of a young boy whose seizures were treated successfully with prolonged fasting by an osteopathic practitioner, Hugh Conklin. Conklin was a follower of the physical culturalist Bernard Macfadden.[95] Their regimen consisted of 3 to 4 weeks of fasting with only water allowed.[49]

Based on the observations by Geyelin, Wilder[96] theorized that the benefit achieved by fasting might depend on the resultant ketonemia. Utilizing earlier work showing that ketogenesis could be produced by diets very rich in fat and very low in carbohydrate, he proposed a formulation of the KD that is very similar to the one used currently. In 1922, Wilder and Winter[97] showed that ketosis occurred when the ratio of fatty acids to glucose in the diet was >2:1, and they recommended that to maintain ketosis, a ketogenic:antiketogenic (K:AK) ratio of at least 3:1 be used. Peterman,[67,68] working at the Mayo Clinic, revised the diet and determined minimal daily requirements for calories (75% of the Recommended Daily Allowance for a child's height and weight) and protein (1 g/kg body weight).

Studies of KD efficacy for seizure control were published in the 1920s by clinicians at the Mayo Clinic. Peterman reported seizure freedom in 50% of patients[67]; Helmholz and Keith found a third of patients to be seizure free and more than 50% showed "definite improvement" in seizure frequency.[32] These successes led several investigators to study the mechanism of action of fasting and the KD in patients using biochemical analyses.[8,27,48]

Mechanism of Action

Various hypotheses have been put forth over the years to explain KD efficacy, including acidosis, cellular and extracellular dehydration, a direct action of ketone bodies (acetoacetate, *β*-hydroxybutyrate, acetone) on neuronal firing or synaptic function, effects of lipids on neuronal excitability, changes in the source or utilization of energy within the brain, and alterations of mitochondrial metabolism. None of these is a sufficient explanation for the effectiveness of the KD. The challenge has been to understand how an anticonvulsant effect results from a metabolic shift from carbohydrate to fat as an energy source.[21a]

There are multiple sites within relevant biochemical pathways where seizure suppression could be facilitated, and the mechanism by which the KD exerts an anticonvulsant effect likely involves the combination of altered energy homeostasis and regulation of neuronal and synaptic excitability. It is also conceivable that the KD may work in different ways against different seizure types and epileptic syndromes. Both clinical studies and animal experiments have been used to decipher KD mechanisms.[79] Any explanation of mechanism of action must take into account clinical observations and known biochemical alterations resulting from ingestion of the KD (Table 1).

Overview of Brain Energy Metabolism

Since the original formulation of the KD, it has been assumed that fasting and the KD share a common mechanism in alleviating seizures. The first step in understanding how the KD may work as an antiepileptic treatment is to understand how ketosis occurs. Whether the antiepileptic effectiveness of fasting or the high-fat diet is related to the level of ketosis remains a lingering controversy.

Table 1 Animal Models of the Ketogenic Diet: Observations and Clinical Correlates

	Observation in animal models	Clinical correlate
Seizure type	KD is effective in models employing a wide variety of seizure paradigms	KD is effective in many seizure types and epilepsy syndromes
Age range	Younger animals respond better to KD	Children extract and utilize ketones from blood more efficiently than older individuals
Calorie restriction	Increases seizure threshold	Associated with seizure reduction
Diet type	Classic and MCT diets both increase seizure threshold	In patients, classic and MCT KDs are equally efficacious
Ketosis	A threshold level of ketosis is	Ketosis is necessary but not

	necessary but not sufficient to explain antiseizure effect	sufficient
Fat	Better effectiveness with higher ketogenic ratios; uncertain if type of fat is a critical variable	Practical concerns limit the ketogenic ratio; possible role of fat chain length and degree of saturation (e.g., PUFA)
Latency to KD effectiveness	Several days	Seizures may be seen during the pre-KD fast or after a latency of days to weeks
Reversal of protective effect when KD discontinued	Rapid (hours)	Rapid (hours)

KD, ketogenic diet; MCT, medium-chain triglyceride; PUFA, polyunsaturated fatty acid.
From Stafstrom CE. Dietary approaches to epilepsy treatment: old and new options on the menu. *Epilepsy Curr*. 2004;4:215-222.

Ordinarily, the brain is an obligate user of glucose as its energy source. However, when carbohydrates are restricted, as in fasting or the KD, the brain can no longer use glucose exclusively. Metabolism shifts such that the brain preferentially oxidizes ketone bodies derived from fats, instead of carbohydrates, as the primary fuel source.[17,63,77] Dietary fats are ordinarily broken down by *β*-oxidation in the liver into two-carbon acetyl CoA molecules (Fig. 1A), which then enter the tricarboxylic acid (TCA) cycle, producing energy via generation of adenosine triphosphate (ATP). However, under conditions of fasting, starvation, or the high-fat KD, acetyl CoA entry into the TCA cycle is reduced because of low availability of the TCA rate-limiting substrate oxaloacetate and the rate-limiting enzyme *α*-ketoglutarate dehydrogenase (which have been diverted to gluconeogenesis). Instead, acetyl CoA is used to synthesize the four-carbon ketone bodies, *β*-hydroxybutyrate (BHB) and acetoacetate (AcAc), as well as the volatile ketone acetone, which is exhaled with fasting, and the KD produces ketosis (i.e., elevated blood levels of BHB and AcAc). The liver lacks the enzymes necessary to break down ketone bodies, so BHB and AcAc are exported in the circulation to tissues such as muscle and brain.

Therefore, during fasting or high-fat/low-carbohydrate intake, the brain can utilize ketones as the main oxidizable substrate for cerebral metabolism (Fig. 1B).[18,77] Ketones are transported across the blood–brain barrier by facilitated diffusion, using a monocarboxylate transporter[66] induced by fasting. Brain monocarboxylate transporter levels are upregulated by KD treatment.[14,47]

Neurons and glia possess the requisite enzymes to break down BHB and AcAc into acetyl CoA fragments (BHB dehydrogenase and 3-oxoacid-CoA transferase, respectively). Acetyl CoA molecules can in turn enter the TCA cycle and produce energy (Fig. 1B). These enzymes are regulated developmentally, with maximal expression early in life, consistent with the better utilization of ketones at young ages.[14] Although the brain can metabolize ketones if deprived of its usual carbohydrate fuels, cerebral activity may be optimal only if *some* glucose is present. A recent study showed that cortex, brainstem, and primary cultures of cortical astrocytes can express ketogenic enzymes, especially early in development.[13]

Ketones

A reasonable hypothesis is that ketone bodies exert anticonvulsant activity, much like antiepileptic drugs.

Serum ketone concentrations rise markedly in subjects on the diet and urinary ketones are used clinically to indicate ketosis. However, several clinical and experimental studies have shown that the relationship between serum or urinary ketones and seizure control is imprecise.[7,29,33,53] Direct effects of ketones on excitatory and/or inhibitory neurotransmission and on ictal activity in vitro have been disappointingly negative.[78,87] However, in vivo, rats on the KD or a calorie-restricted normal diet exhibited increased paired-pulse inhibition in the hippocampal dentate gyrus and increased resistance to maximal dentate activation (a form of seizure activity).[6] Acetone could also exert an anticonvulsant effect.[51,52,54,59,60,72] In summary, there appears to be a "threshold level" of ketosis that must be achieved and maintained for the KD to be maximally effective.

Alterations in Energy Metabolism and Mitochondrial Function

The alteration in cerebral energetics induced by the KD favors an increase in "energy charge" (i.e., a relative increase in the ATP:ADP ratio resulting from metabolic alterations of the enzymes involved in glycolysis and the TCA cycle[17]). The greater availability of brain energy may reduce cellular excitability by enhancing energy available for cellular processes such as membrane pumps and transporters, which enhance hyperpolarization. The "energy charge" hypothesis is supported by recent studies in fasting humans using ^{31}P spectroscopic imaging, in which ketones are transported from the blood to the brain and are utilized by neurons.[64,65]

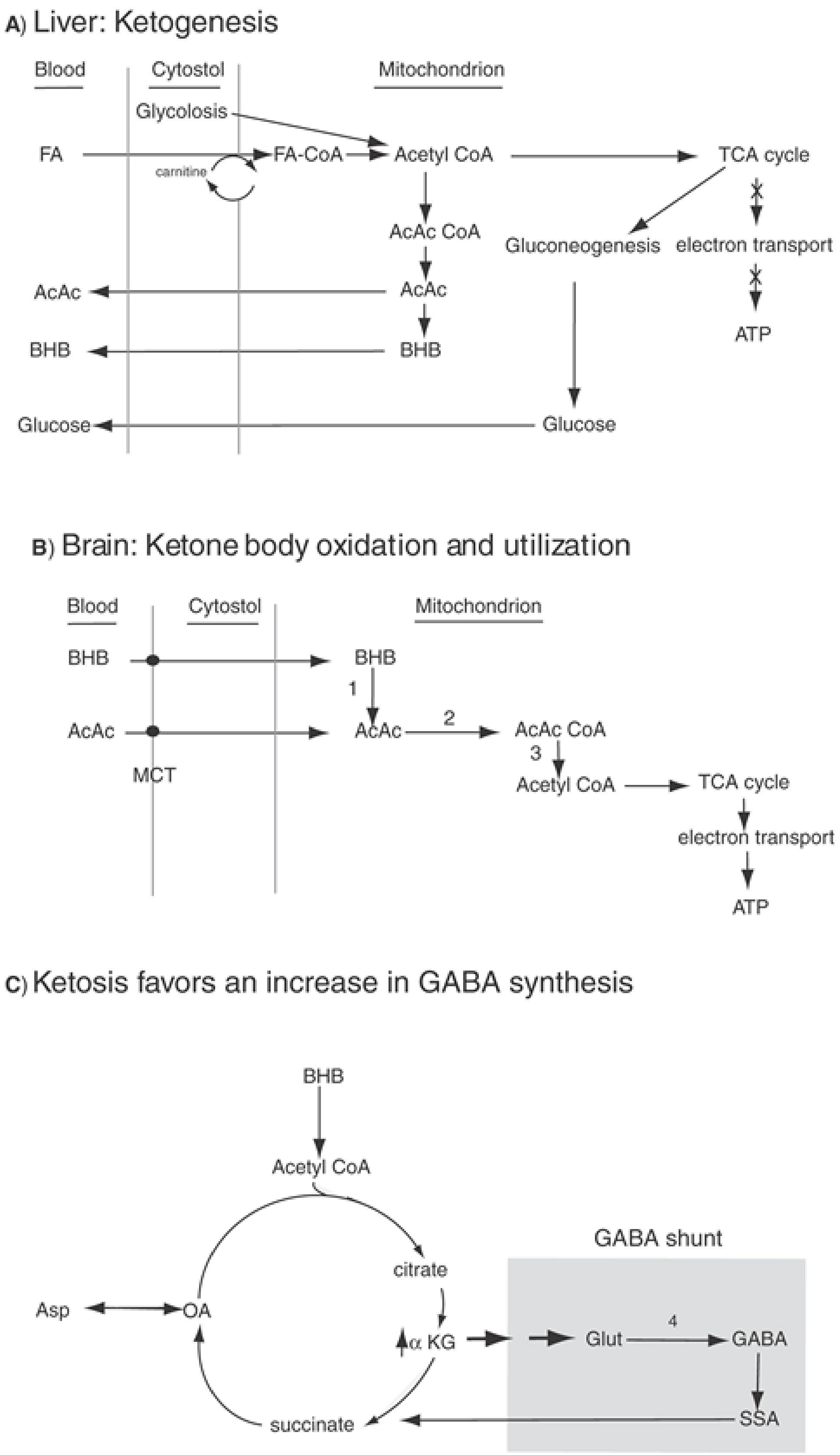
A) Liver: Ketogenesis
Blood
Cytostol
Mitochondrion
Glycolosis
FA
carnitine
FA-CoA
Acetyl CoA
TCA cycle
AcAc CoA
Gluconeogenesis
electron transport
AcAc
AcAc
BHB
BHB
ATP
Glucose
Glucose
B) Brain: Ketone body oxidation and utilization
Blood
Cytostol
Mitochondrion
BHB
BHB
1
AcAc
AcAc
2
AcAc CoA
3
MCT
Acetyl CoA
TCA cycle
electron transport
ATP
C) Ketosis favors an increase in GABA synthesis
BHB
Acetyl CoA
GABA shunt
citrate
Asp
OA
α KG
Glut
4
GABA
SSA
succinate

FIGURE 1. Ketogenesis and ketone body utilization by the liver and brain. **A:** Ketogenesis in the liver. Fatty acids (FAs) from the circulation enter hepatocytes, and then cross the inner mitochondrial membrane by either diffusion (short- and medium-chain FA) or via carnitine transport (long-chain FA). Under conditions of fasting or the ketogenic diet, carbohydrate substrate is lacking, so FAs are metabolized. Since oxaloacetate (a tricarboxylic acid [TCA] cycle intermediate) is diverted to

gluconeogenesis, the TCA is not actively involved in energy generation (*X'd arrows*). Acetyl coenzyme A (CoA) is therefore not funneled into the TCA, but instead is used for ketone body synthesis (acetoacetate [AcAc], *B*-hydroxybutyrate [BHB]). Ketones are exported into the circulation, since the liver lacks the enzymes required to catabolize AcAc and BHB. **B:** In the brain, BHB and AcAc enter neurons via monocarboxylic acid transporters (MCTs). In mitochondria, BHB and AcAc are broken down (by enzymes 1, 2, and 3) into acetyl CoA molecules that can then enter the TCA cycle for energy production. **C:** TCA cycle and γ-aminobutyric acid (GABA) shunt. In ketosis, α-ketoglutarate is increased and GABA synthesis from glutamate (via enzyme 4) is favored.[101] In addition, the GABA shunt, bypassing normal oxidative metabolism, facilitates GABA synthesis. ATP, adenosine triphosphate; AcCoA, acetyl CoA; citr, citrate; succ, succinic acid; OA, oxaloacetate; asp, aspartate; α-KG, α-ketoglutarate; glut, glutamate; SSA, succinic semialdehyde; 1, BHB dehydrogenase; 2, succinyl-CoA transferase; 3, acetoacetyl-CoA thiolase; 4, glutamic acid decarboxylase.

The mechanism by which seizures induce neuronal damage includes mitochondrial dysfunction with the formation of injurious reactive oxygen species (ROS). The KD has recently been shown to increase the expression of brain mitochondrial uncoupling proteins,[84] which act to reduce ROS formation. It was recently demonstrated that BHB and AcAc (in millimolar concentrations) prevented neuronal hyperexcitability induced by exogenous hydrogen peroxide administration in vitro, and that ketones were capable of significantly reducing ROS formation in isolated mitochondria.[38] Additional support for the involvement of the KD in enhancing brain metabolism comes from microarray studies of gene transcription. Of 42 gene transcripts upregulated by the KD, 39 encode mitochondrial proteins.[6a] Taken together, these observations suggest that the KD may protect against seizure activity (and may also be neuroprotective) through antioxidant mechanisms activated by fatty acids and ketones.

Alterations in Neurotransmitters and Synaptic Transmission

The ketogenic diet may enhance the function of γ-aminobutyric acid (GABA), the main inhibitory neurotransmitter of the mammalian brain. GABA is synthesized from glutamate via the action of glutamate decarboxylase (Fig. 1C). In pathways of ketone body metabolism (GABA shunt), glial conversion of glutamate to glutamine (a GABA precursor) is increased by ketosis.[19,100] Enhanced GABA accumulation or function at the receptor level could lead to reduced cortical excitability. At the same time, the rate of glutamate conversion to aspartate, which has an excitatory role, is reduced.[101] In ketosis, α-ketoglutarate, the precursor of glutamate, is increased, thereby enhancing the synthesis of GABA via the “GABA shunt” (Fig. 1C).[19]

Ketones mimic GABA structurally, so they could play a direct inhibitory role on cellular excitability by stimulating GABA receptors or enhancing their action. Ketogenic diet treatment (and calorie restriction) increases the expression of glutamic acid decarboxylase (GAD65 and GAD67) isoforms, providing a mechanism by which GABA synthesis might be increased on the KD.[11] In a study utilizing a variety of seizure induction methods, the most consistent protection with the KD was found when seizures were induced by blocking GABA receptors (i.e., picrotoxin, bicuculline).[4]

Effects of Lipids and Polyunsaturated Fatty Acids

Fatty acids may be important in mediating an anticonvulsant effect. Typically, a KD includes mostly saturated fats of various chain lengths. No attempt is made to specify fat type or chain length in the KD formulation, except for the medium-chain-triglyceride diet, described above.[34] In early clinical studies, there was a correlation between plasma lipids and seizure control in children with epilepsy treated with the diet.[15] Plasma lipid levels peaked as KD-induced seizure control became maximal. In experimental studies, young rats fed a variety of different fat types developed seizure resistance independent of the level of ketosis but dependent upon qualitative differences (i.e., different sources of fats).[16,53] In general, increasing the ketogenic ratio leads to improved KD efficacy.[7,23]

The essential fatty acids, especially the long-chain polyunsaturated fatty acids (PUFAs) of the ω-3 class (as found in certain fish oils), are necessary for the development of neuronal membranes and for subsequent normal behavior and cognition.[43] Fatty acids exert modulatory effects on cellular excitability and receptor-mediated signaling pathways.[82,92,93,99] It is tempting to speculate that PUFAs might be utilized clinically. In human volunteers, a KD enriched with PUFAs resulted in higher levels of circulating BHB than a standard KD.[25] In a case series of nine children on the classic KD, increased serum levels of PUFAs were found and the level of at least one PUFA (i.e., arachidonic acid) correlated with improved seizure control.[21] These findings are of interest because arachidonic acid is known to reduce neuronal excitation.[20] In rats, seizure control correlates with a higher ketogenic ratio, with maximal protection against pentylenetetrazole (PTZ)-induced seizures at a fat-to-carbohydrate plus protein ratio of 6:1.[7] Humans would not tolerate such a high fat content.

Clinical dietary trials of PUFAs were effective in disorders of cardiac excitability.[45] To date, a single human study (not blinded, no control group) has evaluated the efficacy of a PUFA-enriched diet in patients with epilepsy.[74] A supplement consisting of 65% ω-3 PUFAs was given to five institutionalized patients with epilepsy daily for 6 months. Seizure frequency decreased from 1 to 14 seizures per week to 0 to 1 per month with PUFA supplementation. Although intriguing, these findings must be verified in a much larger, well-controlled prospective study.

Calorie Restriction

The original idea for a KD derived from the beneficial effect of fasting on seizures, and this observation has been verified in the modern setting.[24] The health benefits of modest calorie restriction include an increased lifespan, reduced risk of cancer and cardiovascular disease, amelioration of the degenerative effects of aging, and neuroprotection.[12,70] In rats receiving the convulsant kainic acid, there were fewer learning deficits and less histologic damage in rats on a calorie-restricted diet,[9] possibly due to reduced oxidative stress.

Reliable data on calorie restriction in humans with epilepsy are lacking. Children on the KD are typically restricted to 75% of the Recommended Daily Allowance for their ideal weight and height, allowing linear growth but not significant weight gain.[91] In individuals on the KD, blood glucose levels are usually in the lower end of normal, but patients are rarely hypoglycemic.[75] Therefore, a metabolic adaptation occurs in response to the KD to maintain relative euglycemia. The main clinical question, as yet unanswered, is whether calorie restriction reduces seizure burden independent of ketosis.

Recent animal studies have provided evidence that calorie restriction alone can reduce seizures. In epileptic EL mice on a diet restricted to 85% of normal calories, seizure onset is delayed several weeks compared to control EL mice, an effect that is dependent on plasma glucose level.[57,88] In another model, in response to intravenous PTZ, seizure threshold was elevated in calorie-restricted rats.[5] These data suggest that calorie restriction is sufficient to increase seizure threshold and calorie restriction may augment the effects of the KD.

Other Possible Mechanisms and Antiepileptogenesis

Numerous other possibilities are being explored in the search for KD mechanisms, including the roles of fatty acid oxidation,[31] neurotransmitters,[86] neuropeptides,[94] and glia.[35] Of particular interest is whether the KD can exert an antiepileptogenic effect in addition to an anticonvulsant action. There is clinical evidence that the KD results in long-term efficacy, with continued seizure control even after the diet is withdrawn.[23] Experimentally, the KD reduces the occurrence of spontaneous seizures and abnormal sprouting of dentate granule mossy fibers in the kainic acid model.[58] In mice with deletion of the Kv1.1 potassium channel gene, spontaneous seizures and mossy fiber sprouting were also diminished.[73] The KD was also neuroprotective against the damaging effects of kainic acid seizures by inhibition of caspase-3–mediated apoptosis.[61]

The Ketogenic Diet in Practice

There have been multiple variations on the KD since its initial description by Wilder in 1921. These include the classic ketogenic diet, the medium-chain-triglyceride diet, a modified medium-chain-triglyceride diet, and more recently, modified Atkins and low-glycemic-index diets. All of these diets involve some degree of ketosis and restriction of carbohydrates. Ketogenic diets can be adapted for use in diverse cultures and cuisines, including those of Asia and South America.[41]

Selection of appropriate patients is guided by the age of the patient, type of seizure, seizure severity, and response to previous therapies. Initially, the KD was thought to be useful in children with absence seizures, as the alkalosis of hyperventilation and resulting exacerbation of seizures might be compensated with ongoing acidosis. Livingston[55] extended use of the KD to patients with drop (atonic) seizures, and through the years the diet has frequently been prescribed for children with Lennox-Gastaut syndrome. Experience also suggests that it may be useful in infantile spasms[42] and in severe myoclonic epilepsy of infancy (Dravet syndrome).[10]

No randomized clinical studies clearly differentiate which seizure type is more responsive, but there is some evidence that generalized epilepsies may be more responsive than partial epilepsies. Clinicians generally agree that the KD is indicated for intractable childhood epilepsy, glucose transporter type 1 (GLUT1) deficiency, and pyruvate dehydrogenase complex deficiency. The KD can be used effectively over a wide age range (infancy to adulthood).[56,62,76] Absolute contraindications to the use of the KD include pyruvate carboxylase deficiency and porphyria. Relative contraindications include certain mitochondrial cytopathies. Use of the ketogenic diet should be considered when a child's seizures have not been controlled after a trial of two appropriate anticonvulsants, except when specifically contraindicated as noted above. The KD is not a benign therapy, and requires considerable commitment from both the family and the medical community. However, when the burden of seizures and side effects of medication outweigh the potential problems associated with the KD, children should clearly have an opportunityto try it.

The stringency of the KD is explained to the family and/or the patient. Families and patients are encouraged to talk with other patients to learn more about living with the KD. The importance of a multidisciplinary team to manage the KD cannot be emphasized strongly enough.[85]

A decade ago, children were admitted to the hospital for fasting and given only limited water until they became strongly ketotic and lost 10% of their body weight. Seizures are often observed to decrease markedly during the fasting phase.[24] Nevertheless, because of concerns about the stress of this regimen and the pressures of ever-increasing demands for shorter hospital stays, these stringent requirements have eased. Many centers do not use any fasting or hospitalization at diet initiation.[3,37,89,98]

When fasting is used, the child begins fasting after dinner the night before admission. Families are advised to decrease carbohydrates markedly for 2 days before admission. Fasting is then maintained in the hospital, with blood sugar monitoring (Dextrostix) performed every 4 to 6 hours. Unless the patient becomes symptomatic, blood glucose levels as low as 20 to 40 mg/dL are not treated. Fasting is continued until the child becomes strongly ketotic (urine Ketostix large: 4+; 160 mg/mL) or for 48 hours. The KD is then introduced gradually, beginning with a third of the eventual caloric goal on the first day, two thirds of the calories on the second day, and the full number of calories on the third day. Large quantities of fat in ketotic children may lead to vomiting and refusal to eat. Generally, a child who is tolerating the diet on the fourth or fifth day is discharged. The parents are instructed to monitor urinary ketones with Ketostix for the first month. During the brief hospitalization (3 to 7 days), parents and children receive extensive instruction in how to calculate and prepare the KD, including potential sources of glucose and other errors.[23]

Table 2 Basic Diet Calculations

1. Calculate calories needed per day.
   Example: 15 kg (weight of child) × 68 cal/kg/d = 1,000 cal/d
2. Calculate number of dietary units needed per day.
   On the 4:1 diet, each unit is 40 cal (4 g fat = 36 cal; 1 g protein or carbohydrate = 4 cal).
   (1,000 cal/d)/(40 cal/U) = 25 U/d

3. On a 4:1 diet, calculate the number of grams of fat required per day.
   Fat: 25 U/d × 4 g/U = 100 g/d
4. Calculate the remainder of units/calories, allotted to protein and carbohydrate.
   Protein and carbohydrate: 25 U/d × 1 g/U = 25 g/d (combined)
5. Calculate protein requirement.
   Protein: 1 g/kg/d × 15 kg = 15 g/d
6. Calculate remainder, allotted to carbohydrate.
   Carbohydrate: 25 g/d - 15 g/d = 10 g/d
7. Divide these allotments into three meals.

Food	Grams per day	Calories per day	Grams per meal
Fat	100	900	33.3
Protein	15	60	5.0
Carbohydrate	10	40	3.3
TOTAL		1,000	

There is little documented experience in using the diet in adults. Sirven et al.[76] did demonstrate its efficacy in 11 adults. The diet was initiated after 24 hours of fasting at home and another 48 hours of fasting until 4+ ketonuria in the hospital. A 4:1 diet was then initiated beginning with one third of the planned calories and increasing by thirds every two meals until the full diet was achieved.

Calculating the Classic Ketogenic Diet

The KD is calculated for each individual, with each child's food preferences taken into consideration.[102] The calorie count is based on an assessment of the patient's intake according to a dietary history and how close the patient is to ideal body weight. This typically ranges from 60 to 80 cal/kg. Most children are started on the diet with a ratio of ketogenic to antiketogenic foods of 4:1 (a “4:1 diet”). The 4 g of fat plus 1 g of protein and carbohydrate, considered together as a dietary unit, yield 40 calories (36 calories of fat and 4 calories of protein/carbohydrate). The diet allows 1 g of protein per kilogram of body weight daily. Fluid is restricted to 60 to 65 mL/kg/day, generally never more than 1,200 to 1,500 mL/d. A 15-kg child would require about 1,000 calories (68 cal/kg) or 25 dietary units per day. The dietary calculations would be made as in Table 2.

Table 3 Allocating Nutrients for a Basic Meal

1. Follow the calculations in Table 2 .

Food	Calories per meal	Grams per meal
Fat	300	33.3

Protein		20	5.0
Carbohydrate		13	3.3
TOTAL	333		

2. Calculate the amount of heavy cream first. Half of planned carbohydrate in meal is from cream.

0.5 × 3.3 g = 1.7 g carbohydrate as cream

3. Check nutritional tables regarding cream being used. In
100 g of 36% cream are the following:
3.0 g carbohydrate
36 g fat
2 g protein
To provide 1.7 g carbohydrate, give 57 g 36% cream. (100 × 1.7)/3.0 = 57
The 57 g cream also contains 1.1 g protein. (57 × 2)/100 = 1.1

4. Calculate the additional carbohydrate.

Allot 1.7 g carbohydrate as cream, then additional 1.6 g carbohydrate as vegetable B. Using tables, this becomes 23 g vegetable B, which also contains 0.5 g protein.

5. Calculate protein.
Allotment: 5.0 g
As cream: 1.1 g
As vegetable: 0.5 g
Remainder as meat: 3.4 g (5.0 – 1.1 – 0.5)
Using tables again, this allows 15 g of meat. This amount of meat also contains 2.5 g fat.

6. Calculate the remaining amount of fat to be added.
Allotment: 33.3 g
As cream: 57 g of 36% cream = 20.5 g fat (0.36 × 57)
As meat: 2.5 g
Remainder as butter: 10.3 g (33.3 – 20.5 – 2.5)

Once the number of calories per meal has been determined and the number of grams of the various constituents is known, a meal plan can be constructed. There is a hierarchy in this calculation, with fats calculated first, as the fat content is the most important constituent. For example, in a 15-kg child, if 3.3 g of carbohydrate is allowed per meal, then 1.7 g (half of the planned carbohydrate) might be allocated to whipped cream, which often serves as an important fat component. Nutritional tables (or a computer program) are consulted, and as 100 g of 36% cream contains 3.0 g of carbohydrate, 57 g of cream is included in the meal to yield 1.7 g of carbohydrate. The other 1.7 g of carbohydrate is allocated to fruits or vegetables. The remaining protein (meat/fish/poultry, cheese, or egg) that is required is then calculated by subtracting the protein in the cream and vegetable from the total protein allowance. The amount of remaining fat to be eaten is then calculated by subtracting the fat in the cream and protein from the total fat allowance. The cream provides 20.5 g of fat (57 × 0.36), leaving about 12 to 13 g of fat to be added, in the form of mayonnaise, butter, or other high-fat foods (Table 3).

Traditionally, there have been six basic meal plans. Each includes fats, protein, and carbohydrate. They are arranged as follows: (a) meat/fish/poultry, fruit, fat, cream; (b) cheese, fruit, fat, cream; (c) egg, fruit, fat, cream; (d) meat/fish/poultry, vegetables, fat, cream; (e) cheese, vegetables, fat, cream; and (f) egg, vegetables, fat, cream. As is evident from this list, meat, fish, and poultry are considered interchangeable. Other protein sources are cheese and egg. There are two lists of vegetables (A and B). Group B vegetables are higher in carbohydrate, so twice the amount of group A vegetables can be used. Two levels of carbohydrate content are also recognized within the fruit category (10% or 15% fruit). Families are instructed that the entire meal must be eaten in order to maintain the ratio. A sample meal plan for a child is given in Table 4.

Table 4 Outline of Meal

	Food group		
Food	**Fat, g**	**Protein, g**	**Carbohydrate, g**
57 g 36% cream	20.5	1.1	1.7
15 g meat	2.5	3.5	
23 g group B	0.5	1.6	
Vegetable			
10.3 g butter	10.3		
TOTAL	33.3	5.1	3.3

Sample lunch:
Chocolate milk shake (using the 20.5 g cream and allotted liquid as sugar-free chocolate soda)
Steamed broccoli with spicy butter
Julienned chicken sauteed in butter and herbs

The KD can also be calculated as a portable eggnog or a formula for tube feedings. The availability of computerized programs has allowed considerably greater flexibility and accuracy in substituting a wider variety of foods. A nutritionally complete powdered formula (KetoCal, Scientific Hospital Supplies) has also added to the potential convenience of the diet. The KD is deficient in water-soluble vitamins (B and C) and calcium; therefore, a sugarless multivitamin with iron and 600 to 650 mg of oral calcium are prescribed.

Problems during the first month may include hunger, thirst, and toxicity from antiepileptic drugs. The child should neither lose nor gain weight. If either occurs, the calorie content may need to be adjusted. Ice chips, a “free” lettuce leaf once or twice a day as a snack, or vegetables in group A or 10% fruit may be given to increase the quantity of food that can be consumed until the child becomes accustomed to the smaller portions. Thirst can usually be managed by encouraging the child to drink small quantities more frequently. Spices make the meals more palatable, and cutting foods in attractive ways and presenting them in a pleasing manner may make the meals more appetizing. Sometimes using a decorative, smaller plate is helpful. The child should also be involved in choosing food, and if old enough should be involved in meal preparation. The diet can be managed at school with cooperative teachers and students, and the family can travel and dine out by planning carefully in advance.

Drugs need to be monitored as toxicity may occur, especially during fasting. The eventual goal is to decrease or eliminate drugs if seizure control is obtained with the diet. Acetazolamide, which can exacerbate metabolic acidosis, should be discontinued before instituting the KD. Although there has been some concern about the use of various anticonvulsants, including valproic acid, topiramate, and zonisamide, with the ketogenic diet, multiple studies have not demonstrated a significant problem.[1,13a,41a,55a] Sedation may be increased, especially during fasting, in children taking phenobarbital or benzodiazepines.

Clinical Efficacy and Side Effects

The clinical efficacy of the KD has been well documented through the decades. Blinded studies are difficult to perform because of the nature of the therapy, and no blinded studies of efficacy have been done. Even prior to the resurgence of interest in the KD a decade ago, a large number of mostly retrospective studies demonstrated its efficacy. In multiple studies performed over many decades, and despite the availability of many new AEDs, the KD appears to provide excellent seizure control (>90% seizure reduction) in 20% to 30% of patients and improved seizure control (>50% seizure reduction) in 60% to

80% of patients when evaluated at 6 months. The KD does not appear to work in 20% to 40% of patients. Efficacy ultimately depends on a number of factors, including types of seizures, seizure etiology, patient age, compliance with the diet, length of follow-up, and methods used to determine efficacy.

A prospective multicenter study of the classical ketogenic diet, using an intention-to-treat design, showed that 29% of the 51 children who had started the diet had >90% im-provement at 6 months and 53% had >50% improvement.[90] In a larger, similarly designed single-center study, 32% of the 150 children who had started the diet had >90% improvement at 6 months and 51% had >50% improvement.[22] Using these data and nine other studies, a technical review performed for the Blue Cross Blue Shield insurance group in the United States concluded that the KD demonstrated a “significant reduction in seizure frequency” and that “it is unlikely that this degree of benefit can result from a placebo response and/or spontaneous remission.”[46] Furthermore, cognitive improvement is often seen when children are placed on the KD, either as a result of the diet itself or because sedating AEDs can be reduced.[71]

It is difficult to determine the frequency of side effects in children treated with the KD, as few long-term prospective studies have been undertaken. Many of the problems are mild and can be managed with conservative measures. The most common side effects are gastrointestinal in nature, including poor appetite, nausea, vomiting, and especially constipation. Sometimes these problems are associated with excessive ketosis and require alterations in the diet. Constipation is usually managed by increasing fluid intake, maximizing fiber, and using a laxative such as MiraLax (polyethylene glycol). Occasionally an enema is necessary. Renal stones are relatively common and occur in 5% to 7% of children on the diet.[26] These children are typically managed with increased fluids, but sometimes require either lithotripsy or surgical removal. Children with a family history of renal stones should be carefully watched, and occasional screening for hematuria appears appropriate in all patients. There is the possibility that stones can be avoided by monitoring the urine calcium:creatinine ratio. If this ratio is elevated, urine can be alkalinized with Polycitra. A wide variety of other problems have been reported in association with KD use, including sepsis, pancreatitis, hepatitis, cardiomyopathy, prolonged Q-T interval, optic neuropathy, anemia, mineral and vitamin deficiencies, hypocarnitinemia, and osteopenia.[1,2,36,39] Although these adverse effects are rare, they must not be ignored. Parents need to be aware that a wide variety of problems can occur, as when any new medication is started. Typically, if a child becomes ill or his or her function and behavior changes in an adverse manner, these problems must be considered. If an intercurrent infectious illness occurs, the child should be seen by a pediatrician for appropriate laboratory testing.

Long-term concerns regarding growth and bone health are of concern, especially as the diet is being used in younger patients and for longer periods of time.[91] In addition, dyslipidemia has been documented in a prospective study, although its clinical impact in the setting of an otherwise altered metabolic condition is unknown.[44]

Other Forms of Dietary Therapy for Epilepsy

An alternative diet, the medium-chain-triglyceride (MCT) diet, was designed in an effort to increase the palatability of the KD.[34] Huttenlocher et al. noted that the triglycerides of octanoic and decanoic acids are more ketogenic than dietary fats and suggested that 60% of calculated caloric maintenance be given as MCT oil. The oil was mixed with at least twice its volume of skimmed milk and consumed as the beverage for the meal. Instead of 87% of calories as fat, as would be used in the 3:1 classic KD, only 71% of the calories in the 3:1 MCT diet are given as fats, freeing considerably more calories for protein and carbohydrate (10% of calories as protein and 19% as carbohydrates).

A modified MCT diet (the Radcliffe Infirmary diet) was created to eliminate some of the perceived difficulties with the conventional MCT diet (i.e., gastrointestinal distress) while allowing increased flexibility.[75] It allows the recommended daily intake of calories, but gives only 30% of calories as MCT oil and 41% of calories as long-chain saturated fats. It still allows 10% of calories as protein and 19% as carbohydrate.

While the ketogenic and MCT diets are the most widely recognized dietary therapies for epilepsy, other dietary approaches are being developed.[80] A modified Atkins diet recently has been reported to be effective in controlling seizures in a small, uncontrolled case series.[40] This diet does not restrict calories and allows liberal amounts of fats and proteins. However, carbohydrate is restricted to 10 to 20 g/day, which can result in ketosis. In this series of six patients with intractable epilepsy from 7 to 52 years of age, three patients (all below 18 years of age) achieved a seizure reduction of >90% for as along as 20 months, without side effects and with a reduction of their other AEDs. Although the relative roles of calorie restriction versus ketosis in the seizure-protective effect of the Atkins diet have not been elucidated,[81] the Atkins diet represents an easier-to-use and more palatable form of the KD.

Finally, a low-glycemic-index (LGI) diet has recently shown promising efficacy in treating patients with medically refractory epilepsy.[69] Clinical observations suggest that even small amounts of carbohydrate given to patients on the KD will terminate its protective effect and cause seizures.[33] Foods with a low glycemic index cause only modest increases in blood glucose, so such a diet could afford seizure protection yet allow a wider range and amount of carbohydrates than the KD. Of 20 patients initiated on an LGI diet for at least 3 weeks, 10 patients achieved a seizure reduction of >90%, and few side effects were reported. This efficacy rate compares favorably with the KD, and seizure control was reached with less ketonemia than usually seen with the KD.

Summary and Conclusions

The KD has a long history of efficacy in controlling intractable seizures in childhood epilepsy. It appears beneficial in a wide variety of seizure types, although controlled studies evaluating efficacy are lacking. It remains unclear how the KD suppresses seizures. Experimental approaches, including those that allow in vivo evaluation of brain metabolism, are necessary to elucidate the mechanisms involved. It might be possible to design a therapy that is less rigorous and intrusive than the current KD, and promising alternative dietary approaches such as the Atkins diet and LGI diet are emerging. Insights into mechanisms might also lead to a better understanding of seizure pathogenesis, as had been hoped by early investigators such as Lennox.

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Chapter 130

Sex-Hormone Treatment

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Introduction

There is considerable scientific evidence at molecular biologic, neuronal, experimental animal, and clinical levels to indicate that reproductive steroids have neuroactive properties that play a substantive role in the pathophysiology of epilepsy and the pattern of seizure occurrence. Steroids act in the brain by receptor-mediated genomic (long latency), receptor-mediated posttranscriptional (intermediate latency), and direct membrane-mediated (short latency) effects.[40,57,60] Steroid effects may also be valuable in therapeutic interventions using naturally occurring hormones and in the development of hormonally based neuroactive synthetic analogs with potent antiepileptic properties.

Reproductive Hormonal Effects on Epilepsy

Estradiol

Estradiol exerts direct excitatory effects at the neuronal membrane, where it augments *N*-methyl-D-aspartate (NMDA)-mediated glutamate receptor activity.[68,76] This enhances the resting discharge rates of neurons in a number of brain areas, including the hippocampus,[39,68,76] where estradiol increases excitability of the hippocampal CA1 pyramidal neurons and induces repetitive firing in response to Schaffer collateral stimulation.[76]

Estradiol potentiates neuronal excitability by regulating neuronal plasticity. It increases the density of spines and excitatory, NMDA receptor-containing synapses on the apical dendrites of hippocampal CA1 pyramidal neurons via a posttranscriptional mechanism.[78,79] The dendritic spine density on these neurons correlates positively with the levels of circulating estradiol during the estrous cycle of the rat and is decreased by oophorectomy.[78] Estradiol may thus further increase excitatory input to the CA1 neurons.

Estradiol may affect neuronal excitability by cytosolic neuronal estrogen receptor-mediated, genomically dependent mechanisms. Receptors are particularly abundant in the temporolimbic system, especially in the medial and cortical amygdaloid nuclei, and occur in much fewer numbers in the hippocampal pyramidal cell layer and the subiculum.[61,66] Estrogen receptor-containing neurons colocalize with other neurotransmitters, including γ-aminobutyric acid (GABA).[12,56] By regulating the expression of genes affecting the activity, release, and postsynaptic action of different neurotransmitters and neuromodulators, estrogens may act to increase the excitability of neurons, which concentrate estradiol. For instance, estradiol lessens inhibitory neurotransmission by decreasing GABA synthesis in the corticomedial amygdala by reducing the activity of glutamic acid decarboxylase,[75] and enhances brain epileptogenic muscarinic neurotransmission by increasing choline acetyl transferase and acetylcholine.[50]

In adult experimental animals, the thresholds of limbic seizures in female rats fluctuate during the estrus cycle inversely to estradiol levels.[72] Physiologic doses of estradiol activate spike discharges[49,53] and lower the thresholds of seizures induced by electroshock, kindling, pentylenetetrazol, kainic acid, ethyl chloride, and other agents and procedures.[36,49,59,70,77] In fact, topical brain application, as well as intravenous systemic administration, of estradiol in rabbits produces a significant increase in spontaneous electrically recorded paroxysmal spike discharges.[49,53] The increase is seen within a few seconds of application to suggest a direct membrane rather than a genomic effect and is more dramatic in animals with pre-existent cortical lesions.[53] The role of estrogen, however, may be more complex since there is also evidence in some models that estradiol can raise seizure thresholds in the hippocampal region and provide neuroprotection against seizure-induced injury.[73]

Clinically, Logothetis et al.[48] showed that intravenously administered conjugated estrogen clearly activated epileptiform in 11 of 16 women and was associated with clinical seizures in four.

Progesterone

Progesterone and particularly some of its neuroactive metabolites, most notably allopregnanolone, exert direct membrane-mediated inhibitory effects by potentiating $GABA_A$-mediated chloride conductance.[16,57,60] It also potentiates the action of the powerful endogenous inhibitory substance adenosine.[62] Progesterone itself also substantially diminishes nicotinic acetylcholine receptor-mediated conductance, which may be relevant to autosomal dominant nocturnal frontal lobe epilepsy.[6]

Progesterone may act via genomic mechanisms to influence the enzymatic activity controlling the synthesis and release of various neurotransmitters and neuromodulators produced by progesterone receptor-containing neurons.[56] Progesterone binds specific cytosolic receptors not only to produce its own characteristic effects, but also to lower estrogen receptor numbers and thereby antagonize estrogen actions.[37]

Chronic progesterone decreases the number of hippocampal CA1 dendritic spines and excitatory synapses faster than the simple withdrawal of estrogen, counteracting the stimulatory effects of estradiol.[78] Progesterone and allopregnanolone have also been shown to have neuroprotective effects on hippocampal neurons in kainic acid-induced seizure models.[14]

In most adult female animal models, progesterone depresses neuronal firing[67] and lessens spontaneous and induced epileptiform discharges.[46,59,70] It retards kindling and decreases seizure occurrence.

Backstrom et al.[3] found that intravenous infusion of progesterone, sufficient to produce luteal phase serum levels, was

associated with a significant decrease in interictal spike frequency in four of seven women with partial epilepsy.

Neurosteroids

Most of the membrane effect of progesterone is due to the action of its 3α-hydroxylated (i.e., A-ring-reduced) metabolite, 3α-hydroxy-5α-pregnane-20-one or allopregnanolone (AP).[16,60] AP and the 3,5-hydroxylated natural metabolite of the mineralocorticoid deoxycorticosterone, allotetrahydro-deoxycorticosterone (allo-THDOC), are among the most potent of a number of endogenous neuroactive steroids with a direct membrane effect on neuronal excitability.[16,52,60] AP, but not allo-THDOC, is devoid of hormonal effects and may, together with other related neuroactive steroids, be thought of as an endogenous regulator of brain excitability with anxiolytic, sedative-hypnotic, and anticonvulsant properties.[16,52,60] AP and allo-THDOC hyperpolarize hippocampal and other neurons by potentiating $GABA_A$-mediated inhibition.[16,60] At physiologic (nanogram) concentrations, they act as positive allosteric modulators of the $GABA_A$ receptor, interacting with an extrasynaptic steroid-specific site near the synaptic receptor to facilitate chloride channel opening and prolong the inhibitory action of GABA on neurons.[16,51,52,60,80] At higher pharmacologic (micromolar) concentrations, AP also has a direct effect at the synaptic $GABA_A$ receptor to induce chloride currents.[16,60] AP is one of the most potent ligands of $GABA_A$ receptors in the central nervous system, with affinities similar to those of the potent benzodiazepine flunitrazepam, and approximately a thousand times higher than pentobarbital.[16,60] The parent steroid, progesterone, enhances GABA-induced chloride currents only weakly and only in high concentrations.[60,80] Plasma and brain levels of AP parallel those of progesterone in rats. In women, plasma levels of AP correlate with progesterone levels during the menstrual cycle and pregnancy.[60] However, brain activity of progesterone and AP is not dependent solely on ovarian and adrenal production, as they are both synthesized de novo in the brain.[9] Their synthesis is region specific and includes the cortex and the hippocampus.[9] By contrast, allo-THDOC is only synthesized by the adrenal gland and not in the brain.[60]

AP, allo-THDOC, and a number of other endogenous and synthetic pregnane steroids have a potent anticonvulsant effect in bicuculline-, metrazol-, picrotoxin-, pentylenetetrazol-, pilocarpine-, and kainic acid–induced seizures and against status epilepticus, but are ineffective against electroshock and strychnine-induced seizures.[5,16,41,42] The anticonvulsant properties of allopregnanolone resemble those of the benzodiazepine clonazepam.[12,16,42] AP is less potent than clonazepam but may have lower relative toxicity.[41,42] The anticonvulsant effect of AP is greater in female rats in the diestrus-1 part of the ovulatory cycle (equivalent to human midluteal phase when progesterone levels are high) than in estrus (equivalent to ovulation when estrogen levels are high) or in the male.[12,13] Enhanced midluteal efficacy at the $GABA_A$receptor may be related to a progesterone-induced enhanced formation of the δ $GABA_A$ receptor subtype. Rapid withdrawal of progesterone in late diestrus makes the $GABA_A$ receptor insensitive to benzodiazepine, but not AP, perhaps as the result of a decrease in the benzodiazepine-sensitive synaptic $GABA_A$ receptors. This effect can be blocked by inhibiting the formation of the α4 subunit of the $GABA_A$ receptor.[51,69]

By contrast, some of the sulfated neuroactive steroids have excitatory neuronal effects. They include pregnenolone sulfate and dehydroepiandrosterone sulfate (DHEAS), the naturally occurring sulfated esters of the progesterone precursor pregnenolone, and progesterone metabolite DHEA.[60] They increase neuronal firing when directly applied to neurons by negatively modulating the $GABA_A$ receptor[60] and by facilitating glutamate-induced excitation at the NMDA receptor.[38] In animal seizure models, pregnenolone sulfate and DHEAS have a proconvulsant effect.[35] Of note, serum DHEAS levels are substantially reduced by enzyme-inducing antiepileptic drugs such as phenytoin and carbamazepine.[33,45]

Testosterone

The effect of testosterone on experimental seizures appears to be mixed.[40] Testosterone acts on specific neural receptors to promote aggression, competition, potency, and libido. Aromatization to estradiol, a major testosterone metabolite, potentiates glutamate transmission and seizures.[68,76] Reduction to dihydrotestosterone blocks glutamate, specifically NMDA, transmission.[63] Another reduced androgen metabolite, androstanediol, has potent GABAergic, neuroprotective, and antiseizure properties.[15] The net effect of testosterone on neuronal excitability, therefore, may depend on the balance of its conversion to excitatory and inhibitory metabolites, which, in turn, is tissue dependent and varies with the relative local activities of reductase and aromatase enzymes.[68,76] Tissue specificity may be even more complicated. For example, sex- and age-dependent differences in proconvulsant and anticonvulsant actions of sex steroids have been demonstrated between the anterior and posterior regions of the substantia nigra in the rat.[74]

Catamenial Epilepsy

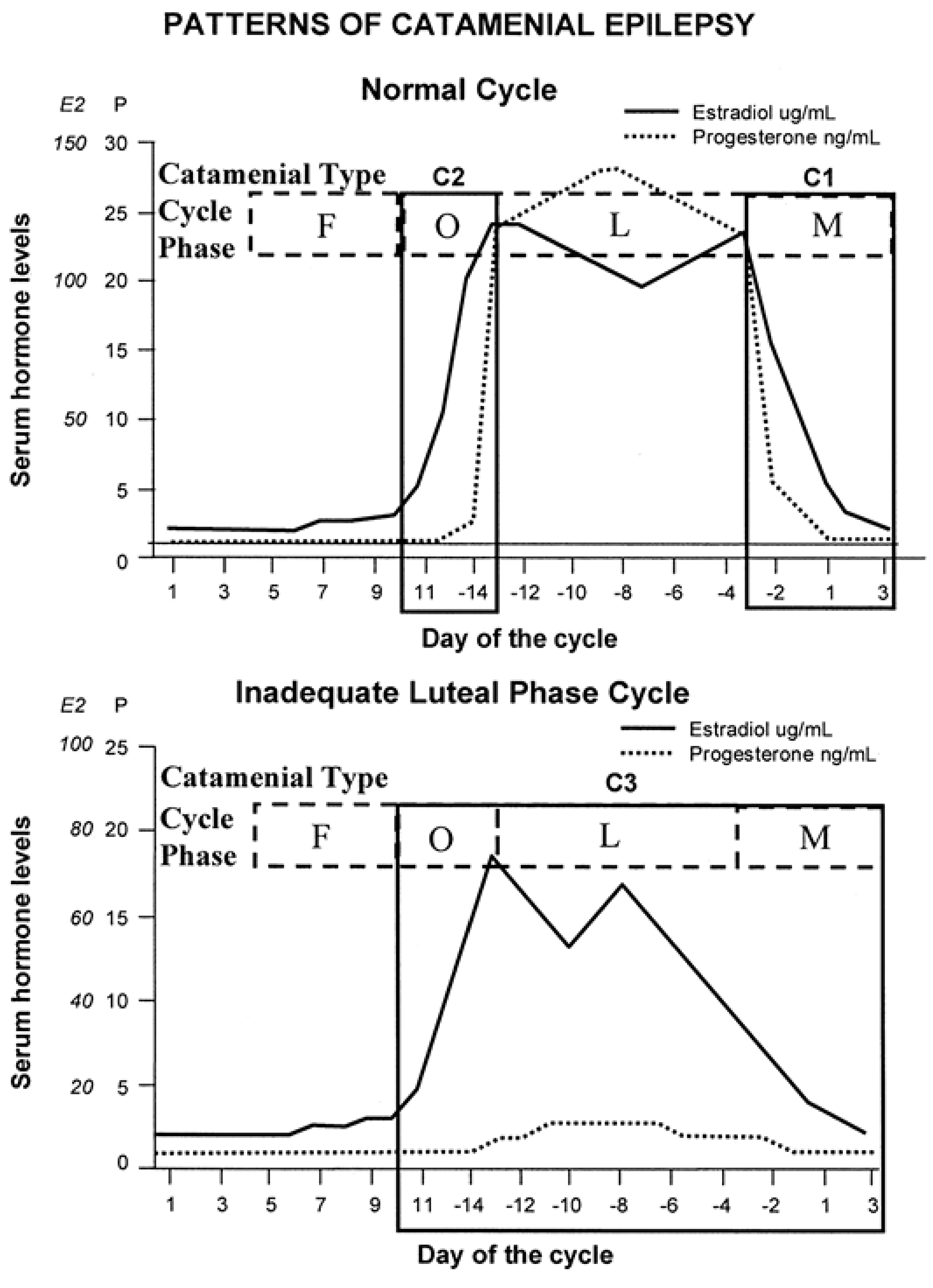

FIGURE 1. Three patterns of catamenial epilepsy: Perimenstrual (C1) and periovulatory (C2) exacerbations during normal ovulatory cycles, and entire second half of the cycle (C3) exacerbation during inadequate luteal-phase cycles where day 1 is the first day of menstrual flow and day 14 is the day of ovulation.

Seizures do not occur randomly in the majority of men and women with epilepsy.[71] They tend to cluster in over 50% of cases.[71] Seizure clusters, in turn, may occur with temporal rhythmicity in a significant proportion of men (29%) and women (35%) with epilepsy.[1] In women, seizures may cluster in relation to the menstrual cycle, commonly known as catamenial epilepsy.[44] This may be attributable to (a) the neuroactive properties of steroid hormones and (b) the cyclic variation in their serum levels.

Physiologic endocrine secretion during the menstrual cycle influences the occurrence of seizures (Fig. 1). In ovulatory cycles, seizure frequency shows a statistically significant positive correlation with the serum estradiol:progesterone ratio.[2] This ratio is highest during the days prior to ovulation and menstruation and is lowest during the early and midluteal phases.[2] The premenstrual exacerbation of seizures has been attributed to the rapid withdrawal of the antiseizure effects of progesterone.[2,52] Midcycle exacerbations may be due to the preovulatory surge of estrogen, unaccompanied by any rise in progesterone until ovulation occurs.[2,44] Seizures are least common during the midluteal phase when progesterone levels are highest,[2,52] except in anovulatory cycles, in which the midcycle surge in estrogen still occurs, albeit not as high as in ovulatory cycles, but unaccompanied by any substantial increase in progesterone levels.[25]

Herzog et al.[25] presented statistical evidence to support the concept of catamenial epilepsy and the existence of at least three distinct patterns of seizure exacerbation in relation to the menstrual cycle (Fig. 1): (a) perimenstrual (C1: days –3 to 3) and (b) periovulatory (C2: days 10 to –13) in normal cycles, and (c) luteal (C3: days 10 to 3) in inadequate luteal phase cycles. In these cycles, day 1 is the first day of menstrual flow and ovulation is presumed to occur 14 days before the subsequent onset of menses (day –14). These three patterns can be demonstrated simply by (a) charting menses and seizures and (b) obtaining a midluteal phase serum progesterone level to distinguish between normal and inadequate luteal-phase cycles (<5 ng/mL).

While the precise definition of catamenial epilepsy remains arbitrary, one may maximize the efficiency of distinguishing between women whose seizure occurrence shows a high versus low degree of hormonal sensitivity by using the points of inflection of the S-shaped distribution curves that define the relationship between the severity of seizure exacerbation and the number of women who have exacerbation.[25] These points are calculated to be in the vicinity of a twofold increase in average daily seizure frequency during the phases of exacerbation relative to the baseline phases for all three types of catamenial exacerbation. We propose the use of these points of inflection values in seizure frequency for the designation of catamenial epilepsy. By this criterion, approximately one third of women with intractable partial epilepsy would qualify for the designation of having catamenial epilepsy.[25,32] Adoption of a standard albeit arbitrary nomenclature may provide greater uniformity to study designs for the investigation of the pathogenesis and treatment of catamenial seizure exacerbation.

Table 1 Investigational Sex Hormone Treatments of Women with Epilepsy

Investigational treatments	Dosage	Potential adverse effects
Progesterone lozenges	Days 14–25: ½–1 lozenge tid Days 26–27: ¼ - ½ lozenge tid Day 28: 1/4 lozenge tid	Sedation, depression, breast tenderness, vaginal bleeding, constipation, exacerbation of asthma, weight gain
Depomedroxyprogesterone	150–250 mg IM q1–3mo	As above plus delay of months to 2 years in recovery of ovulatory cycles during which time seizure numbers may increase sometimes beyond baseline
GnRH analog	Leuprolide:	Menopausal symptoms unless concomitant

	3.75 mg IM q4wk 11.25 mg IM q12wk	estradiol and progesterone supplement is administered
Clomiphene	Days 5–9: 25-50 mg daily	Ovarian overstimulation syndrome (distention of ovaries can be very painful)

GnRH, gonadotrophin-releasing hormone.

Table 2 Adjunctive Cyclic Progestogen Therapy

	Medroxy progesterone (Herzog 1983)	Progesterone suppositories (Herzog 1986)	Progesterone lozenges (Herzog 1995)	Progesterone lozenges (Herzog 3-year follow-up)
Regimen	5-10 mg qd days 15–28 of cycle	100–200 mg tid days 15–28 of cycle	100–200 mg tid days 15–28 of cycle	100–200 mg tid days 15–28 of cycle
Assessment	@ 3 months	@ 3 months	@ 3 months	@ 3 years
Subjects	24	8	25	15 of original 25
Number improved	10 (42%)	6 (75%)	18 (72%)	15 (100%/60% overall)
Seizure frequency	-10%	-68%[a]	-54%[b] CPS -58%[a] SGMS	-62%[b] CPS -74%[a] SGMS

[a] $p < 0.05$.

[b] $p < 0.01$.

CPS, complex partial seizures; SGHS, secondary generalized motor seizures.

Sex-Hormone Treatment of Seizures in Women

Progestogen Therapy

The term *progestogen* refers to the broad class of progestational agents. These include progesterone (i.e., naturally occurring progesterone) and progestins (i.e., synthetic progestational agents). Progestogen treatment (Tables 1 and 2) has taken two forms: (a) cyclic progesterone therapy that supplements progesterone during the luteal phase and withdraws it gradually premenstrually and (b) suppressive therapy in which the goal is to suppress the menstrual cycle, which is generally accomplished using injectable progestins or gonadotropin-releasing hormone analogs.

Cyclic Progesterone Therapy

In contrast to published cyclic oral progestin investigations that did not result in significant reduction of seizure frequency,[10,54] two open-label trials of adjunctive progesterone therapy did result in clinically important and statistically significant reductions in seizure occurrence (Table 2).[18,24] Progesterone therapy benefits some women with catamenial epilepsy.[18,23,24] In one investigation of women who had inadequate luteal-phase cycles with catamenial exacerbation of intractable complex partial seizures, six of eight women experienced improved seizure control with a 68% decline in average monthly seizure frequency over 3 months for the whole group.[18] In a subsequent open trial of adjunctive cyclic progesterone versus the optimal antiseizure medication alone in 25 women (14 with inadequate luteal-phase or anovulatory cycles and 11 with normal cycles and perimenstrual seizure exacerbation), 19 (72%) experienced fewer seizures with an overall average monthly decline of 54% for complex partial and 58% for secondary generalized seizures over 3 months.[24] Progesterone was more efficacious when administered during the entire second half of the cycle, rather than just premenstrually, and then tapered and discontinued gradually over 3 or 4 days at the end of the cycle.[24] Failure to taper gradually premenstrually can result in rebound seizure exacerbation. At 3 years, the average daily seizure frequency per patient showed that the 15 women who remained on cyclic progesterone therapy and their original antiepileptic drugs continued to show improved seizure control in comparison to their own baseline (Table 2: 3-year follow-up).[26] Three women were entirely seizure free. Four had total seizure reductions of 75% to 99%. Eight had reductions of 50% to 74%. Complex partial seizures in these 15 were lower by a statistically significant 62% (baseline: 0.328, 3-year follow-up: 0.125; *p* <0.01); secondary generalized motor seizures, by 74% (baseline: 0.148, 3-year follow-up: 0.038; *p* <0.01). Antiepileptic drug serum levels continued to show no significant change. The three remaining women who continued on progesterone therapy had 10% to 50% improvement at the end of the original investigation at 3 months and were not considered further because they changed antiepileptic drugs.

By way of critique, the weakness of these preliminary progesterone investigations is that they were not placebo controlled or blinded. The favorable 3-year follow-up results are biased by analysis of only 15 of the original 25 subjects. These 15 who remained on the original treatment regimen are more likely to represent those who had the most favorable response. There are reasons, however, to consider that the results of this investigation may represent more than placebo effects: (a) few placebo studies, including our own progestin trial that used a similar methodology and could be used, therefore, as a retrospective control, show favorable response in more than 50% of subjects; (b) few placebo treatments have resulted in >50% seizure reduction; and (c) while placebo effects generally wear off over a few months, substantial and statistically significant improvements in the present investigation persisted after 3 years in the majority of subjects.[28] Another argument against the placebo explanation is that the beneficial effect of progesterone can be eliminated by the concomitant use of a reductase inhibitor[31] that presumably blocks the reduction of progesterone to its potent GABAergic metabolite allopregnanolone. Finally, there is transcranial magnetic stimulation evidence that progesterone may increase inhibition in the brain premenstrually.[29] A prospective multicenter, randomized, double-blind, placebo-controlled investigation of cyclic, adjunctive progesterone therapy in the management of women with catamenially exacerbated, intractable localization-related epilepsy is now under way.[32]

Natural progesterone is available as an extract of yams or soy in lozenge form in variable dosages ranging from 25 to 200 mg and should be administered three times daily because of its brief half-life of about 4 to 6 hours.[18,22,24] The daily regimen to achieve physiologic luteal-range serum levels measured 4 hours after administration ranges from 50 to 200 mg., taken three times daily, with the usual optimal daily dose ranging from 300 to 600 mg.[18,22,24] The maintenance dosage and regimen should be individualized and based on a combination of clinical response and serum progesterone levels between 20 and 40 ng/mL. Progesterone is also available in micronized form in an oral capsule preparation that may also exert similar antiseizure effects, although formal investigations to this effect are lacking. Theoretically, it is possible that first pass through the liver using the oral micronized form may result in the delivery of different concentrations of progesterone and its neuroactive metabolite to the brain.

Adverse effects occur with overdosage and include sedation, emotional depression, and asthenia.[18,22,24] Progesterone use may also occasionally be associated with breast tenderness, weight gain, irregular vaginal bleeding, and sometimes constipation. The vehicle used to dissolve progesterone for suppository use may rarely be responsible for the development of an allergic rash. Discontinuation of the hormone or lowering of the dosage resolves these side effects.[18,22,24]

Drug interactions are an important consideration. Higher progesterone dosages may be required to achieve luteal-range levels in women who take antiseizure medications because carbamazepine, phenytoin, and barbiturates are known to enhance the hepatic metabolism of gonadal and adrenal steroid hormones as well as to increase hormonal binding to serum proteins.[55] Progesterone use has been associated with changes in antiseizure medication levels in some cases, but this effect has been sporadic and not in a predictable direction. Therefore, total and possibly free serum antiseizure medication levels should be checked regularly during concomitant hormonal therapy.

Progestin Therapy

Parenteral depomedroxyprogesterone may lower seizure frequency when it is given in sufficient dosage to induce amenorrhea.[54,81] In one open-label study of 14 women with refractory partial seizures and normal ovulatory cycles, parenteral depomedroxyprogesterone administration in doses large enough to induce amenorrhea (i.e., 120 to 150 mg every 6 to 12 weeks) resulted in a 39% seizure reduction.[54] It was unclear whether the effect was due to direct anticonvulsant activity of medroxyprogesterone or to the hormonal consequences of the induced amenorrhea. One patient who had absence rather than partial seizures did not improve. Side effects included those encountered with natural progesterone. Depot administration, however, is also commonly associated with hot flashes, irregular breakthrough vaginal bleeding, and a lengthy delay of 6 to 12 months in the return of regular ovulatory cycles.[54] Long-term hypoestrogenic effects on cardiovascular and emotional status need to be considered with chronic use. Bone density is generally maintained.

Oral synthetic progestins administered cyclically or continuously have not proven to be an effective therapy for seizures in clinical investigations,[10,54] although individual successes with continuous daily oral use of norethisterone and combination pills have been reported.[18]

Clomiphene Therapy

Clomiphene acts as an estrogen antagonist to increase gonadotropin secretion and induce ovulatory cycles in estrogen-secreting anovulatory women who do not have primary pituitary or ovarian failure.[7] Normalization of reproductive endocrine functions and menstrual cycles among women who have both partial seizures and menstrual disorders with documented inadequate luteal phase has been demonstrated to significantly and sometimes dramatically lessen seizure frequency.[20,47] In one investigation of 12 women, 10 improved and seizure frequency declined by 87%.[20] Clomiphene, however, is a drug with considerable pharmacologic potency and potentially disturbing side effects. Therefore, it should be used only after potential risks and benefits are weighed carefully and treatment with antiseizure medications and progesterone prove inadequate to control seizures. Clomiphene should not be administered in cases of suspected pregnancy or in the absence of adequate birth control measures unless it is used in conjunction with a gynecologist as part of a fertility program. Endometrial carcinoma should be ruled out prior to institution of therapy if abnormal uterine bleeding is present and normal liver function should be assured since clomiphene is excreted in the feces via the enterohepatic circulation.

Clomiphene is available in 50-mg tablets and can be administered in dosages ranging from 25 to 100 mg daily on days 5 to 9 of each cycle. Treatment should be initiated with the lowest dose, and the daily dose may be raised by increments of 25 to 50 mg monthly as required to induce an ovulatory cycle with normal luteal phase. Improved seizure control has been related to normalization of the reproductive endocrine cycle but, as yet, has not been recognized as an approved indication for continued clomiphene use.

In the one published investigation of clomiphene use in a series of 12 women with complex partial seizures, six experienced some side effects ranging from minor breast tenderness and pelvic cramps in three to severe lower abdominal

pain with ultrasound-documented ovarian cysts due to overstimulation of follicular development in two, and one unwanted pregnancy.[20] Women with polycystic ovarian syndrome, which constituted the majority of the epileptic women in this investigation, appeared to be particularly sensitive to the development of overstimulation of follicular development and painful cyst formation.[20] Discontinuation of clomiphene was associated with a return of ovarian size to normal in both cases encountered in this series.[20]

Clomiphene therapy has not significantly altered total or free serum antiseizure medication levels in the few cases that have been studied, but a well-controlled investigation of possible drug interactions remains to be carried out.[20]

Gonadotrophin-releasing Hormone Analog Therapy

Bauer et al.[4] used triptorelin, a synthetic gonadotrophin-releasing hormone (GnRH) analog (3.75 mg) in a controlled release depot form intramuscularly every 4 weeks for an average of 11.8 months in 10 women (aged 20 to 50) with catamenial seizures intractable to high therapeutic doses of carbamazepine, diphenylhydantoin, phenobarbital, and valproic acid in monotherapy or combined. They remained on a stable dose of the anticonvulsant throughout the period of treatment with triptorelin. They reported that three patients became seizure free; four showed a decrease in seizure frequency of up to 50%. In one, the duration of seizures was shortened; two had no therapeutic effect. These results were attained within the first 2 months of starting triptorelin. The study was not a controlled study and longer-term follow-up was not available for some of the patients. Serum luteinizing hormone (LH) and estrogen were measured in one patient before and during the second month of triptorelin treatment, and as expected showed marked inhibition of LH and estrogen production. All the women became amenorrheic. Eight of the ten patients experienced hot flashes, headache, or weight gain.

Haider and Barnett[17] reported on their use of goserelin 3.6 mg subcutaneously every 4 weeks in a 41-year-old woman who had had frequent catamenial status epilepticus despite therapeutic anticonvulsant drug levels, which also did not respond to levonorgestrel/ethinyl estradiol. They reported a decrease in frequency from ten admissions for status epilepticus to three over a similar period.

GnRH analogs basically create a medical oophorectomy. Common side effects are flushing, vaginal dryness, and dyspareunia. Serious long-term risks include osteoporosis and cardiovascular disease. Reid and Gangar[64] suggested the addition of medroxyprogesterone acetate and conjugated estrogens to goserelin to prevent this while still abolishing most of the cyclical fluctuations of ovarian hormones. Finkelstein et al.[11] recently discussed the use of parathyroid hormone to prevent bone loss in women treated with GnRH analogs. Although neither Bauer et al.[4] nor Haider and Barrett[17] reported exacerbation of seizures with GnRH analogs, Herzog[23] found that during the first 3 weeks, when there is an initial stimulation of estrogen before its production is inhibited, some women experienced such a marked exacerbation of their seizures and auras that they could not tolerate further use of GnRH analog.

Sex-Hormone Treatment of Seizures in Men

Sex-hormone treatment trials in men with epilepsy originated in attempts to treat sexual dysfunction rather than seizures. Sexual interest and potency, as assessed by questionnaires in men with localization-related epilepsy and normal controls, suggest that sexual dysfunction occurs in 20% to 25% of men with epilepsy.[19,29,30] It occurs substantially and statistically significantly more often in the setting of hypogonadism.[19,29,30] Hypogonadism in men with epilepsy is unusually common and has been attributed to a number of possible causes. These include (a) psychosocial stress,[30] (b) antiepileptic drugs,[34,43] and (c) epilepsy itself.[19,29,39,58] Each of these is recognized to alter reproductive endocrine secretion. Of note, enzyme-inducing antiepileptic drugs, specifically carbamazepine and phenytoin, have been associated with significantly more sexual dysfunction and lower bioavailable testosterone levels than lamotrigine.[34]

Testosterone Therapy

Testosterone replacement is the most common form of therapy for hypogonadism. In 12 men with localization-related epilepsy who had sexual dysfunction and hypogonadism, intramuscular injections of testosterone enanthate in doses of 200 to 400 mg every 3 or 4 weeks have been associated with normalization of serum-free testosterone levels and moderate improvement in sexual interest and potency scores in all 12 men. Seizure frequency showed no significant change.[26] An ongoing study using biweekly rather than monthly administrations of similar doses of testosterone, however, is showing notably favorable effects not only on sexual function, but also on mood and seizure frequency (Herzog, unpublished). Therefore, the role of testosterone supplement in the management of seizures remains as yet unresolved.

Therapy with Testosterone and Aromatase Inhibitor

Since enzyme-inducing antiepileptic drug use is associated with the rapid conversion of testosterone to estradiol[22,30] that might negatively impact seizure control and androgen production, the use of aromatase inhibitors has been tried.[26] The administration of 300 to 500 mg of testolactone, an aromatase inhibitor, daily and of 400 mg of Depo-Testosterone biweekly to a 52-year-old man with intractable seizures and hypogonadism on carbamazepine improved sexual questionnaire scores and decreased seizure frequency more than the addition of testosterone alone.[26] One study did a retrospective comparison that showed a superior outcome for combined treatment with testosterone and an aromatase inhibitor as compared to testosterone alone not only on sexual function, but also on seizure frequency.

Clomiphene Therapy

Clomiphene dramatically improved sexual interest, potency, and seizure control in a case report of a man with complex partial seizures and hypogonadotropic hypogonadism.[21] Seizures were eliminated during clomiphene use in another case with epilepsy and oligospermia.[8] Clomiphene offered no benefit, however, for a man who had complex partial seizures and hypergonadotropic hypogonadism, that is, gonadal failure.[21] Total and free antiepileptic drug levels were not affected. The mechanism of clomiphene action on seizure activity is conjectural, but may involve the normalization of serum testosterone levels along with increased inhibitory neuroactive steroid concentrations or direct antiestrogenic effects on epileptogenic limbic structures, which have a high density of estradiol receptors.

Summary and Conclusions

Many natural and synthetic reproductive hormones can increase or decrease neuronal excitability. Physiologic, pathologic, and pharmacologic endocrine changes, therefore, can be responsible for the exacerbation of seizures. Hormones, however, may also provide improved seizure control when used in conjunction with antiepileptic drugs or, perhaps rarely, alone. Early investigations suggest that hormonal therapy may be a useful adjunct in the comprehensive management of epilepsy, specifically in the treatment of seizures, reproductive dysfunction, and emotional disorders.[52]

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Chapter 131

Vagus Nerve Stimulation

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Introduction

For patients with medically refractory seizures, the major nonpharmacologic options are limited to epilepsy surgery, the ketogenic diet, and vagus nerve stimulation (VNS). In 1997, the VNS Therapy System (Cyberonics, Inc.) was approved by the Food and Drug Administration (FDA) as adjunctive therapy for adults and adolescents over 12 years of age whose partial-onset seizures were refractory to antiepileptic drugs (AEDs), thereby becoming the first (and only) FDA-approved nonpharmacologic treatment for epilepsy. This chapter reviews the relevant anatomy, possible mechanisms of action, and clinical results in patients with epilepsy.

Relevant Anatomy

The cell bodies of the nodose ganglion relay afferent sensory information that is carried by the vagus nerve to the nucleus of the solitary tract (NTS). From there, one pathway ascends to the forebrain via the parabrachial nucleus, lateral to the locus coeruleus.[98] The parabrachial nucleus transmits sensations of visceral origin to the ventroposterior parvocellular nucleus of the thalamus, which then projects to the insular cortex.[18] The parabrachial nucleus and NTS also project to the amygdala and basal forebrain. c-Fos mapping studies show activation of these nuclei and pathways by VNS,[84] and one intriguing animal study underlines the possible involvement of the locus coeruleus.[52]

Because the right vagus innervates the cardiac atria more than the left vagus nerve and the left vagus nerve provides the predominant innervation of the ventricles,[97] electrical stimulation of the left vagus nerve has generally been used in clinical practice, though right-sided VNS has been reported safe in one case series[73] and is equally effective against seizures as left-sided stimulation in rat models of epilepsy.[53]

Mechanism of Action

Neurophysiologic Studies

Early work showed that repetitive VNS either synchronizes or desynchronizes cortical activity in anesthetized animals, depending on stimulus frequency and current strength, which determines whether myelinated fibers are activated.[20,21,22] Desynchronization of cortical rhythms implied a possible anticonvulsant effect of VNS and prompted further animal experiments in a variety of models,[61,74,104,114,115,116] including a recent report in genetic absence epilepsy rats from Strasbourg that showed no effect of VNS.[23]

Low-intensity trains of VNS (100 µA, 30 Hz, 500 µs, 20 seconds on time) have been found to hyperpolarize pyramidal neurons of rat parietal association cortex.[117] Interestingly, low-intensity stimulation, which predominantly activates myelinated fibers, was more effective in this model in inducing long-lasting inhibitory effects than higher stimulus intensities, which also entrain nonmyelinated vagus fibers. Consistent with these findings, a study of transcranial magnetic stimulation in five patients treated with VNS for epilepsy showed significantly increased cortical inhibition associated with stimulation without any evidence of an effect on cortical excitability.[27] Further, in a limited series of patients whose seizures responded to VNS, Marrosu et al.

found normalization of impaired neuronal inhibition.[71] The same group has more recently shown decreased synchronization of theta frequencies and an increased gamma power spectrum and synchronization in 11 patients treated with VNS.[70] By contrast, Ebus et al. were unable to find a relationship between clinical response to VNS and a reduction of electroencephalographic (EEG) spike discharges after implantation compared to preimplantation.[28]

Neuroimaging Studies

The intracranial effects of VNS have been evaluated with positron emission tomography (PET), single photon emission computed tomography (SPECT), and functional magnetic resonance imaging (fMRI) scanning. The findings on PET studies have variably demonstrated increased blood flow in the ipsilateral anterior thalamus and cingulate cortex[35] or the contralateral thalamus and temporal cortex, and ipsilateral putamen and cerebellum.[50] The group at Emory correlated the extent of bilateral thalamic changes in blood flow and reductions in seizure frequency.[41]

SPECT studies have generally shown decreased regional cerebral blood flow in the medial thalamic regions bilaterally,[93,109] without a relationship between the extent of these changes and clinical outcomes with VNS.[111] An exception is the study of Van Laere et al., which showed a correlation between long-term clinical efficacy and (a) initial stimulation changes in the right amygdala and (b) right hippocampal perfusion changes.[109]

In a series of nonepileptic patients enrolled in a trial of VNS for depression, Bohning et al. assessed VNS-synchronized functional MRI (fMRI) and found changes in bilateral orbitofrontal and parieto-occipital cortices, the left temporal cortex, the hypothalamus, and the left amygdala.[12] The same group has shown that the pulse width of VNS determines the pattern of regional activation, and that a pulse width of 130 microseconds is insufficient for activation of some regions.[78] An fMRI study in four patients treated for epilepsy found that VNS activated the left superior temporal gyrus, inferior frontal gyrus (bilateral), medial portions of the superior frontal gyrus in the region of the supplementary motor cortex (bilateral), and posterior aspect of the middle frontal gyrus (bilateral).[103]

Other fMRI studies reported activations in the thalami (left greater than right) and insular cortices[83] and positive correlations between thalamic activation and clinical response to VNS.[60]

Short-term Efficacy Studies

The first patient with epilepsy was treated with VNS in 1988,[90] followed by two pivotal trials of patients with partial epilepsy, the E03 study[8,37,92,107] and the E05 study.[38] Prior to approval, a compassionate-use trial evaluated VNS in 124 patients with intractable seizures (the E04 study).[56]

The E03 and E05 studies were multicenter, blind, randomized trials that compared two different VNS stimulation protocols for partial-onset seizures: High stimulation (30 Hz, 30 seconds on, 5 minutes off, 500 microseconds pulse width) and low stimulation (1 Hz, 30 seconds on, 90 to 180 minutes off, 130 microseconds pulse width). Enrolled patients were at least 12 years of age, with at least six seizures per month treated with a mean of 2.1 AEDs at study entry.

In both studies, the primary measure of efficacy was the percentage change in seizure frequency during VNS treatment compared to the preimplantation baseline. Changes in seizure frequencies in the high- and low-stimulation groups were then compared in each study. The hypothesis was that the low-stimulation treatment was less effective than the high-stimulation treatment. In the E03 study, the high-stimulation group had a mean reduction in seizure frequency of 24.5%, versus 6.1% for the low-stimulation group ($p = 0.01$). Furthermore, 31% of patients receiving high stimulation had at least 50% reduction in seizures compared to 13% of patients in the low-stimulation group ($p = 0.02$). In the E05 study, the corresponding decreases were 28% and 15% for the high- and low-stimulation groups, respectively ($p = 0.039$), and 11% of patients in the high-stimulation group had at least a >75% reduction of seizures compared to baseline, versus 2% of patients in the low-stimulation group ($p = 0.01$). Thus, both studies showed that high stimulation was more effective than low stimulation.

Long-term Efficacy

Seizure control is maintained in long-term studies of VNS,[26,37,41,42,43,44,45,46,47,48,76,95,108,113] including in catastrophic childhood epilepsy,[67] but these results should be interpreted cautiously since long-term studies are not blinded, and stimulation parameters and AED dosages could be adjusted as clinically indicated. One retrospective study of 269 patients whose AEDs were kept constant for 1 year after VNS implantation found a 45% seizure reduction at 3 months postimplantation compared to preimplantation baseline, and 58% reduction at 12 months postimplantation.[57] On-demand stimulation with the supplied magnet can be an effective adjunct to chronic stimulation for attenuating or interrupting seizures in some patients.[15]

Efficacy in Other Seizure Types and in Children

A number of open case reports and uncontrolled studies of VNS have been published, suggesting possible benefits for patients with medically refractory generalized seizures; in children with intractable seizures, including Lennox-Gastaut syndrome[4,16,32,40,44,65,79,80,82,86,89]; and in developmentally disabled or mentally retarded patients with epilepsy.[36,45] In one adult described in a case report, VNS apparently terminated status epilepticus.[88] Given the limitations of all these studies, randomized, controlled trials are needed to further evaluate VNS in these populations.

Effects on Other Comorbid Conditions

Two studies showed improvement of mood in patients with medically refractory partial-onset seizures[29,39] independent of changes in seizure control. Other studies have also found improvements in mood, as well as reduced tenseness and dysphoria.[1,43,81]

Other studies suggest that VNS may improve daytime alertness and vigilance,[33,94] as well as sleep quality in some patients with reduced daytime sleepiness,[69] though the opposite effect has been described in another study.[42]

Safety and Tolerability of Vagal Nerve Stimulation in Patients with Epilepsy

In the E03 study, side effects that occurred in at least 5% of patients receiving high stimulation were hoarseness (37%), throat pain (11%), coughing (7%), shortness of breath (6%), tingling (6%), and muscle pain (6%), although hoarseness was the only side effect that occurred significantly more often with high stimulation than with low stimulation. In the E05 study, shortness of breath and voice alteration were the only two side effects that occurred significantly more often in the high-stimulation group than in the low-stimulation group. No significant changes in heart rhythm (as measured by Holter monitoring) or pulmonary function were found. No deaths occurred during either study.

Long-term safety and tolerability studies of VNS generally show improved tolerability over time. Among 444 patients who continued VNS after participating in a clinical study, the most commonly reported side effects at the end of the first year postimplantation were voice alteration (29%) and tingling (12%); at the end of 2 years, voice alteration (19%) and cough (6%); and at 3 years, shortness of breath (3%).[77]

Though physiologic studies have generally found no clinically relevant effects of chronic VNS on cardiorespiratory function,[10,31,34] transient asystole lasting up to 20 seconds has been reported in association with the lead test, which is performed during implantation, in approximately 0.1% of cases.[3,5,106] Complete heart block due to atrioventricular nodal block has been documented in one series.[2] There have been no reported serious consequences in any of these reported patients.

A variety of other side effects have been described in case reports or small series.[11,17,48,49,58,63,68,91,96] Children with severe mental and motor retardation on assisted feeding may aspirate if fed during VNS.[66,99] Infections of the subcutaneous pocket that holds the VNS generator, while infrequent, usually require explantation.[87,101]

Patients have been cautioned by Cyberonics not to undergo short-wave diathermy, microwave diathermy, or therapeutic ultrasound diathermy. This warning is based on the theoretic possibility that the generator or lead could heat up and then cause thermal tissue damage, although there are no documented cases of this complication in VNS-treated patients.

After the VNS generator battery is expended, seizure frequency may increase in some patients,[105,112] and others may note decreased or irregular perception of stimulation.[112] Fortunately, the end of battery service can be predicted with the current VNS model, allowing for elective generator replacement before the battery is fully depleted.

The presence of an implanted pacemaker is widely regarded as an absolute contraindication to MRI. In MRI of the heart, considerable heating at the lead tip occurred in animal experiments. Changes of pacing parameters due to MRI could be seen in chronic experiments. Potential risk of tissue damage could not be excluded, even though no reproducible alterations at the histologic level could be found.[64] Dramatic increases in both MRI usage and device-based therapy have resulted in an estimated 50% to 75% probability of a patient being indicated for an MRI over the lifetime of his or her device.

Some recent studies, all of which addressed cardiac pacemakers and defibrillators, have demonstrated “safe procedures” and “no adverse events” in the limited populations, clinical situations, and specific devices and lead orientations tested. While these investigations are useful to help ascertain the hazards for patients with cardiac devices, they do not demonstrate clear freedom from risk.[47]

Since 1996, changes in pacemaker electronics including decreased ferromagnetic content, increased sophistication of the circuitry, and on-board computer capabilities suggest that the absolute contraindication of MRI for pacemaker patients should be reconsidered.[62] An fMRI study at 1.5T showed that enhanced product ion (EPI) scanning could be performed safely in epilepsy patients with an implanted vagal nerve stimulator.[103] From what is currently known, it can be concluded that safety during MRI procedures, especially with 3T, is not established. The future challenge for manufacturers is that all components of active implantable systems should be engineered during the design stage to provide safety in current and evolving MRI environments. Subsequently, device manufacturers need to secure regulatory approval to confirm safety of their devices under multiple clinical and technical variables.

Clinical Use

In clinical use, VNS requires a team of health care providers to implant the device, teach the patient and his or her family about its use, titrate the stimulation parameters to optimum clinical response, and monitor the patient's side effects and the device's battery life. The physician can program the output current (typically 1 mA), signal frequency (typically 30 Hz), signal pulse width (typically 500 microseconds), signal on time (typically 30 seconds), and signal off time (typically 5 minutes). In addition, magnet-activated stimulus parameters—pulse width, output current, and on time—are also programmable.

Besides intermittent stimulation, on-demand stimulation may be brought on by the patient or a companion by placing the supplied magnet on the patient's chest over the generator for several seconds. The stimulator settings employed for on-demand stimulation usually utilize a higher current and pulse width than those used for intermittent stimulation. Some patients have reported that on-demand stimulation interrupts a seizure or reduces its severity if administered at the onset of the seizure, and can be used by patients to attempt to abort an ongoing seizure.

The generator delivers intermittent stimulation until the battery wears out, which is predicted to take 6 to 11 years with the Model 102, depending on stimulation parameters used for an individual patient.

Summary and Conclusions

VNS is effective, safe, and well tolerated in patients with long-standing, refractory partial-onset seizures.[25] There has been no indication of reduction of effectiveness in long-term, open studies. Side effects occur during stimulation in the minority of patients, are usually mild to moderate in severity, and diminish with time or reduction in stimulation intensity. Caution should be exercised when considering VNS for patients with pre-existing sleep apnea,[72] cardiac conduction disorders, and asthma.[63] Surgical complications are infrequent, especially with enhancements in surgical techniques and postoperative care.[19,59,85,110]

Since VNS was approved for epilepsy, clinicians have actively debated its role.[6,9,14,75] Today VNS is generally considered an option for patients with well-documented medically refractory partial-onset seizures, who are either opposed to intracranial surgery, who are not candidates,[54] or whose medically refractory seizures were not substantially improved by prior intracranial epilepsy surgery.[51] Two studies have evaluated the costs of VNS treatment. One study showed an average of $3,000 annual savings in hospital costs per VNS-treated patient, comparing the 18 months preceding implantation with the 18 months after implantation.[7] A prospective study showed that among patients with refractory epilepsy who were nonsurgical candidates, epilepsy-related direct medical costs over 2 years were lower in those who underwent VNS compared to medically treated patients.[13]

While identification of factors that accurately predict the outcome of VNS has been elusive, one retrospective study found that an absence of bilateral interictal epileptiform discharges correlated with seizure freedom during the first year postimplantation,[46] a finding that requires confirmation in a larger, prospective study.

Further controlled studies are also needed to more fully understand the safety, tolerability, and efficacy profile of VNS in children and in patients with generalized seizures, to determine whether any stimulation settings provide more benefit than standard initial settings,[24,55] and to identify patients preoperatively whose seizures are likely to improve with VNS, thereby avoiding the potential surgical complications and costs of implantation in patients who have no clinical response to VNS.[30]

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Chapter 132

Behavioral Therapies

Peter Wolf

> To abolish this disease, one must apply the element which is opposed to it, and not what is favourable and habituated.
>
> *On the Sacred Disease*—Hippocrates

Introduction

Epilepsy is traditionally treated with drugs, and, for pharmacoresistant cases, there may be a possibility of epilepsy surgery. But, although little noticed in textbooks, there is a third line of therapy that can be useful if applied to the appropriate patients: Behavior modification. Behavior modification can be defined as any type of nonpharmacologic intervention aimed at the prevention or abortion of seizures. Like all other epilepsy therapies, the ultimate goal of behavior modification is complete seizure control. To achieve this goal, behavior modification can be used alone or in conjunction with other therapies. It can be used to arrest seizure activity after onset or to prevent seizures altogether.

Arrest of Seizures

History

Treating seizures by some countermeasure that interrupts their development is the oldest of all existing therapies. Probably discovered by patients, arresting seizures was mentioned as an established procedure by Hellenistic physicians such as Aretaeus the Cappadocian and Galen, in the first and second centuries. It was well known to physicians that seizures beginning distally in a limb and spreading to the brain could be interrupted by manipulations such as the application of ligatures. This may have contributed to the concept of sympathetic epilepsy, which was thought to originate in the periphery where a pneumatic substance would spread through the body and to the brain like poison from the bite of a scorpion.[30] The ligature was applied in view of arresting the spread of this substance.

The arrest of seizures through application of ligatures remained in use throughout the history of medicine. Tissot[31] mentions numerous examples and regarded the effectiveness of such procedures as supporting the concept of sympathetic epilepsy. One of the discoveries that seriously shattered this concept was the finding of Odier in 1811[11] that ligature arrested fits due to a cerebral tumor as effectually and more frequently than with any other cause.

Under the influence of Brown-Séquard's experiments, where external stimuli produced convulsions, Jackson[15] suggested in 1870 that a similar relation existed between a peripheral aura sensation preceding the seizure and the internal discharge, the beginning of which was reflected in the outward spasm. However, such a relation could explain only the action of a ligature applied between a first aura sensation and the onset of spasm—not after the onset of the spasm.

Gowers[11] conceived a totally new theory:

> "The arrest must be effected, not in the limb convulsed, but in the centre in which the

> discharge is occurring, of which the local convulsion is the outward manifestation. The strong peripheral impression on the limb above the part convulsed probably raises the resistance in the nerve-cells of the corresponding parts of the brain, and thus arrests the spread of the discharge. The effect of the ligature must first be exerted on the sensory centre, and through this on the motor centre. The two are connected intimately, and their mutual interaction must be constant, so that the condition of the motor centre is no doubt readily influenced through the sensory centre. Hence, a fit may be arrested by the ligature, whether it begins by a sensation or by a motion, i.e., whether the sensory or motor centre leads in the discharge. Additional observation is necessary to determine whether the ligature is more effective in one class of fits than in the other."

The knowledge and discussion of these phenomena were common to the British neurologists of the late 19th century. The Jacksonian seizures of the first patient operated on for epilepsy without evidence of a lesion[13] began with flexor twitching of the thumb, and were arrested by stretching the thumb or applying a ligature. For Horsley, this suggested "the possibility of the so-called muscular sense being represented in the excitomotor area."[13] Ligature and passive stretching of a muscle in spasm are simple countermeasures that have often been reported. In other instances, much more intricate procedures were applied.[15]

Gowers[11] reported a variety of countermeasures (Table 1). Ligature proximal to convulsion, forcible prevention of spasm, and other cutaneous stimulations were often successful in seizures commencing in a limb. Muscular exertion, strong olfactory impression, and strong gustatory sensation were sporadically effective in "attacks which begin by a general or bilateral aura, or by the epigastric sensation" and which can rarely be arrested. However, Gowers pointed out that nitrate of amyl, which had been given in view of vasal dilation, was most successful in cases with a deliberate olfactory aura, perhaps acting through the olfactory nerve.

At the turn of the 19th century, when bromides were the only effective pharmacotherapy available whereas epilepsy surgery mostly dealt with focal motor seizures and carried a rather high mortality risk, treatment by behavioral seizure arrest was an important and sophisticated part of the therapeutics of epilepsy. The advent of new, more potent, and better tolerated antiepileptic drugs starting in 1912 with phenobarbital changed this. Epilepsy came to be considered as a disease for the most part curable with drugs that make the seizures disappear.

In more recent years we have become aware that not all patients respond sufficiently to the available drugs, nor do all patients tolerate all drugs well. New drugs have new side effects and are not effective in all pharmacoresistant patients. Epilepsy surgery for these patients is by no means always possible. Stimulation methods are still experimental or have the drawback of being invasive but only palliative.

Table 1 Arrest of Seizures

Ligature proximal to convulsion
Forcible prevention of spasm
Other cutaneous stimulations (pinch, prick, rub)
Muscular (e.g., quickly walking around the room)
Strong olfactory impression (ammonia, nitrite of amyl)
Strong gustatory sensation (chewing a piece of ginger, swallowing a handful of common salt)

From Gowers WR. *Epilepsy and Other Chronic Convulsive Diseases*. London: Wood; 1881.

Therefore, additional therapeutic options are sometimes most welcome. In addition, quite some patients today hesitate to take drugs, especially on a long-term basis, and ask for treatment alternatives. Often, such patients are prepared to accept responsibility for and contribute to a therapeutic strategy. Ketogenic and other diets are one type of nonpharmacologic conservative intervention and are dealt with in Section V, Part E, Alternative Approaches. Behavioral modification is another.

Modern Accounts

The modern literature about treatment with seizure arrest starts in 1956 with the important case report of Efron[7,8] about a patient whose epilepsy became cured by using an olfactory stimulus to arrest her habitual olfactory aura. No drug treatment was involved. The olfactory stimulus had been the patient's idea, and it took some time to find the most effective smell and the correct timing of the stimulus. The second and even more interesting step in this case report was the conditioning of the olfactory stimulus to a visual stimulus following a request by the patient who, being a professional singer, wanted to avoid the visible procedure of using a sniff bottle in public. She learned to evoke the smell by looking at and, later, thinking of a bracelet that was used as the conditioned stimulus. After some time, the patient began to experience the conditioned smell instead of her habitual aura; eventually this also stopped.

For a long period, no replications of Efron's work were reported, but two authors[22,23] found independently that about 60% of patients with localization-related seizures had personal experiences with countermeasures to arrest ongoing seizure activity. Richard and Reiter[24] estimated that practically all patients had this kind of experience, but this statement is not based on specific investigations.

The applied countermeasures belong to a variety of categories. Specific sensory stimuli, such as a peripheral ligature for focal seizures commencing in a limb or an olfactory stimulus in a seizure with a habitual olfactory hallucination, relate directly to the cortical area involved in the seizure generation and spread. Many patients apply nonspecific arousal and concentration techniques,[24] the action of which can be understood by the well-known antiepileptic effect of exercise[17]; others rely on relaxation procedures. The antiepileptic actions of yoga[41] and of aromatherapy[1] have recently been reviewed.

Anecdotal Observations

Chance observations of patients who are not in medical treatment have led us to assume that successful self-therapy by seizure arrest may not be uncommon among patients who are not undergoing medical treatment. Many of these patients may not even be aware that they are dealing with epileptic phenomena.[36] This possibility should be considered in future epidemiologic field studies of epilepsy because there is no other way of quantifying it.

Table 2 Curative Effect of Aura Interruption: A Hypothesis

1. Detection of an effective countermeasure
2. Systematic well-timed application of countermeasure
3. Successful arrest of all seizures
4. Conditioned reflex interruption
5. Unlearning of seizures by negative feedback

In this five-step process, steps 2 and 3 represent the therapeutic intervention of behavior modification. The therapy becomes potentially curative only if step 4 can be observed, in which seizure arrest becomes an involuntary conditioned response. Step 5 is hypothetic.

Our own experiences with seizure arrest in drug-resistant patients in a specialized epilepsy center by methods building on spontaneous patient experiences and cortical direct-current (DC) biofeedback[6] indicate that, in resistant patients, treatment by systematic seizure arrest is neither less nor more effective than is treatment by a new drug.[36] However, successful behavioral therapy is only possible with well-motivated patients because it requires an unusual amount of effort and compliance. Sometimes, the intervention must be supported by comprehensive psychotherapy.[2] When patients are successful, increased self-esteem and improved self-control are welcome side effects.

We do not propose that patients use trained seizure arrest as a treatment alternative but, rather, as part of a comprehensive therapeutic program that includes pharmacotherapy. In some patients, a tripartite approach combining pharmacotherapy, surgery, and behavioral seizure arrest may be most appropriate.

Theoretical Concepts

Seizure interruption is an intervention suitable only for focal seizures. This is because seizure discharge starts locally from a small neuron population that is continuously producing paroxysmal depolarizations.[18] When these depolarizations spread to partially affected neurons in the vicinity of the focus, a shift may occur from a normal to a paroxysmal mode of discharge. Even normal neuron populations may become involved in the seizure discharge, which then may become generalized.

On the neuronal level, an intermediate state of activation is a prerequisite to the generation of paroxysmal depolarization shifts.[27] Hyperpolarized neurons are inactive and cannot easily be recruited to fire, whereas strongly depolarized neurons already producing action potentials are not available for further activation. A seizure is arrested if all or most neurons that habitually participate in the secondary seizure spread either cannot be recruited or are unavailable.

Curative Effect

If seizures can be successfully treated by arrest, complete relief may result.[8,36] This is surprising because epilepsy therapy usually aims at complete control, including isolated auras, whereas seizure arrest allows isolated auras (i.e., simple

partial seizures) to occur. At best, one would expect this therapeutic achievement to stabilize in the long term. The observation of further improvement seems to indicate that the action is part of the processes of remission that are still little understood.[40] We have suggested a tentative stepwise process (Table 2) that comprises the behavioral therapeutic intervention, observable conditioned responses, and a hypothetic negative feedback mechanism.[36]

Prevention of Seizures

Theoretically, seizure prevention is possible whenever stimuli that precipitate seizures can be defined or conditions that favor the manifestation of seizures can be prevented.

Specific Precipitating Factors

Preventing seizures became possible when specific precipitating factors had been described, that is, with the discovery of what is commonly called *reflex epilepsy*. These factors are discussed in Chapter 257. Forster[10] has devoted extensive investigations to the possibility of treating patients with such disorders by desensitization or extinction of the precipitating stimuli. However, his investigations were little replicated and remained largely isolated. We have reported a partially successful desensitization procedure in a patient with seizures precipitated by touch.[38] In photosensitive epilepsy, the use of protective glasses[3,12,32] and instructions concerning television watching[12,34] have become part of a comprehensive treatment that includes behavioral aspects. In the small group of patients with photosensitive epilepsy, in whom seizures occur exclusively in response to intermittent light stimuli, optic protection may be used as the only line of therapy.[39]

Case 1. Heide W., seen at age 31 years, had, from age 12, a total of six generalized tonic–clonic seizures, all during television watching. She had been treated with carbamazepine for a short time but had discontinued it when she continued to have seizures. The last seizure had occurred when, passing by, she perceived at short distance and from an oblique angle a small-screen television set. The patient was otherwise healthy and active. Her seizures, however, resulted in extreme anxiety in the presence of all electronic displays, and a phobiclike behavior developed. To avoid possible exposure to screens, she rarely left her house. She had never had a spontaneous seizure. Investigation by electroencephalography (EEG) showed that this patient was highly photosensitive. In addition, when she viewed a 38 × 29-cm television screen from a distance of 2.5 meters for 2 minutes, no spike-and-wave activity was noticed. However, viewing the same screen from a distance of 2 meters provoked spike-and-wave activity after a few seconds. Duplex linear polarizing glasses[32] in an angle providing 75% light absorption suppressed the photoparoxysmal response and enabled her to view the screen from a distance of 1.5 meters. The patient adapted to wearing these glasses in all environments that previously caused anxiety. No more problems occurred with television or other intermittent light stimuli, and after a few months the patient felt that she had control of her condition and no longer restricted her activities. She has been followed until the age of 41 and never had another seizure.

In complex reflex epilepsies, such as reading epilepsy[35] and seizures precipitated by praxis[14] or by eating,[42] patients may learn to prevent seizures by finding nonprovocative or less provocative ways of performing the respective activities. For most patients with reading epilepsy, orofacial reflex myocloni (ORM) will precede a convulsive seizure. These can serve as a warning to the patient to stop reading, thereby preventing the seizure.[35]

Nonspecific Precipitating Factors

Preventing seizures by interventions directed toward factors that cause or facilitate seizures is a time-honored therapeutic approach. Those interventions include rigorous early antipyretic treatment in febrile illnesses of children who are prone to febrile convulsions and regulation of the sleep–waking cycle in patients with juvenile myoclonic epilepsy, grand mal on awakening,[16] or other epilepsies sensitive to irregularities of sleep.

The history of this approach is inseparable from that of patients' attempts at psychologically coping with a disease that can strike at any moment. The ability to predict and prevent seizures enables patients to gain a certain amount of control over their lives.[20] Changing an irregular lifestyle or reducing alcohol intake is certainly more helpful than attributing seizures to uncontrollable influences such as menstruation, phases of the moon, or the weather, as some patients are inclined to do.

The provocation of seizures by exogenous stimuli is probably more common in the early phases of epilepsy.[16] Preventing seizures by avoiding precipitating factors is certainly most effective at these times.

Case 2. Bettina K., now aged 30 years, had three generalized tonic–clonic seizures at 19, 20, and 21 years of age. Phenytoin was prescribed. She developed a skin rash after 10 days, stopped the medication, and started homeopathic treatment. She presented at our clinic when, during the following 17 months, she had suffered another three seizures. Initially, no focal signs had been observed, but during the commencement of the last three seizures, a conscious version of eyes and head to the right had occurred. At the onset of one of these, the patient described a right visual hallucination; afterward, she had no recollection of this. One EEG showed generalized spike-and-wave discharges. The magnetic resonance imaging (MRI) was normal except for a moderate widening of the left lateral ventricle, which may account for the focal traits in what otherwise suggested an incipient idiopathic generalized epilepsy. With most seizures occurring shortly after awakening and one seizure occurring during evening leisure, the patient presented the classic biorhythmicity of epilepsy with grand mal on awakening. Typical of this syndrome, almost all seizures had been preceded by irregularities in her sleep–waking rhythm. Because the patient was strictly opposed to drug treatment, a strategy was developed to avoid provocative factors (see Chapter 254). She was fully compliant with this regimen and, in the 7 years of follow-up, has remained completely seizure free.

Psychogenic Precipitants

Perhaps the most common public belief about the causality of epilepsy, as it is broadly reflected in literary accounts of the condition,[37] is that seizures are caused by emotional irritation. Although difficult to assess, this is certainly a possibility, and drug-resistant epilepsies may become treatable when underlying effects such as shame, embarrassment, anxiety, and learned helplessness are therapeutically addressed.[26]

Upsetting events cannot always be avoided, but the therapeutic approach, rather than attempting to avoid the unavoidable, would be to try to define how the arising emotions can be noticed and dealt with in ways that bypass the imminent seizure.

In a behavior analysis preceding treatment of 18 patients, Dahl et al.[5] categorized patients according to whether they were able to predict seizures (by aura sensations, situation association, or both), had at some time been able to counteract seizures, could elicit seizures on demand, could identify situations at low risk for seizure occurrence, reported mainly

positive consequences associated with seizures, and had established healthy social behavior.

These factors occurred with equal frequency in three groups of six patients, each of whom were treated with behavior modification or served as attention controls (a kind of placebo group receiving a psychologist's attention equal to that of the treatment group) or simple controls. Patients in the group receiving behavioral modification were the only ones to experience a decrease in seizure frequency. This program comprised reinforcement of seizure control techniques and healthy behavior as well as relaxation techniques. It also included education of parents and teachers, role-playing, and homework assignments for all persons involved. Fenwick[9] has looked at similar indicators of psychogenesis of epileptic seizures and found them to be unexpectedly common, and inviting behavioral intervention.

In a more psychophysical approach, some authors selected a variety of EEG parameters[28] or the sensorimotor rhythm[19] for EEG biofeedback because they were supposed to exert or be correlated with anticonvulsant action. The results were only partially convincing, but more sophisticated approaches have been developed that aim at individually defining sets of rhythms that require some increase and some down-training. A tailored training program based on these appeared to be a quite successful.[33]

The behavioral and psychophysical views are reconcilable, as shown by Rockstroh et al.[25] in their work on cortical self-regulation by biofeedback of the DC EEG. Our group[6] has used the same method in a more specific way—for seizure arrest in response to an aura. This approach is founded on the observations of negative DC shifts at the onset of seizures.[4] Patients are advised to produce a learned positive DC shift in response to an aura, a strategy comparable to relaxation techniques and opposite to the depolarizing action of seizure arrest by sensory stimuli or arousal. The group has recently tried to develop predictors of success of this treatment based on the initial cortical excitability, the epileptic focus, and personality variables.[29]

Another approach targets biofeedback at the galvanic skin response, and this method was proved effective in a randomized controlled design using sham biofeedback as a control.[21] The proposed mechanism of action is sympathetic arousal.

Behavior Modification Today

At present, there are four main indications for behavioral therapy in epilepsy:

1. Nonsymptomatic first seizures and incipient epilepsies if precipitating factors can be identified. Behavior modification may, in these cases, be applied alone or together with medication. In the latter case, it seems to be the more important agent.
2. Reflex epilepsies, especially the pure forms where no spontaneous seizures occur.
3. Patients who are opposed to taking drugs but seek medical treatment with a request for conservative treatment alternatives. If there is a realistic chance that they will respond to behavioral treatment, they should receive it. Even if the chance of success seems low, patients should not be left to charlatans. Rather, they should be given the best possible medical advice, and some behavioral intervention should be tried. In our experience, several patients after failure of serious attempts at behavioral treatment could accept pharmacotherapy, which they had previously declined, with good compliance. Some patients may decline a dosage increase of their antiepileptic drug and choose behavioral therapy as an adjuvant approach.
4. Patients with drug-refractory epilepsies and poor indications for surgery or patients who refuse further attempts to find successful therapy. In these cases, behavioral modification will typically be part of a complex therapeutic setting.

To provide patients with a full therapeutic program, behavioral therapy should become a more common part of the armamentarium of specialized epilepsy centers. These centers can also best be expected to apply such therapies critically and to evaluate their usefulness and quality. Much more critical research concerning these therapies must be done. Randomization and placebo control of the type used in pharmacotherapy is not possible, and even similar procedures are extremely difficult to design for behavioral interventions. In some of the existing studies,[5,25,29] the introduction of treatment control mechanisms has been attempted with some success. Other studies have combined retrospective and prospective phases and have used patients as their own controls, but the methods of evaluating these therapies should be further developed.

Summary and Conclusions

Before the advent of potent drugs, behavioral modification was an important therapeutic approach to epilepsy. It is receiving renewed interest in response to medical intractability due to inefficacy or intolerance to drugs. The available interventions comprise:

1. Seizure arrest by specific stimuli (simple or complex), nonspecific arousal, relaxation, or DC EEG biofeedback. The probable action of these countermeasures is that they reduce the availability or recruitability of groups of neurons for further seizure spread.
2. Seizure prevention by avoidance, modification, counteraction, or desensitization of nonspecific facilitating factors such as irregular sleep, psychogenic factors, and specific precipitating factors (as in *reflex epilepsies*).

These interventions are often part of a complex therapeutic setting but may occasionally be applied alone. Their main indications are incipient epilepsies, reflex epilepsies, and pharmacoresistant focal seizures. Many patients who are unwilling to take antiepileptic drugs prefer behavioral modification. Behavioral treatment should be part of the therapeutic armamentarium and should become the subject of research in specialized epilepsy centers.

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Chapter 133

Complementary and Alternative Medical Therapies

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Introduction

Despite the introduction of new antiepileptic drugs (AEDs), increasing use of brain surgery, and aggressive worldwide campaigns to improve the diagnosis, treatment, and access to care of patients with epilepsy, nearly one in three patients continues to have seizures despite therapy and others endure side effects from treatment,[9] while the large majority of people with epilepsy around the world have no access to modern treatments.

Whereas AEDs and epilepsy surgery are relatively new in the history of epilepsy treatment (e.g., bromides were introduced in 1857, phenobarbital in 1912, and epilepsy surgery in the 1940s), people with epilepsy have used a variety of therapies for thousands of years. Some of these therapies persist today, especially in regions of the world where access to medical care is poor, and are generally called complementary and alternative medical (CAM) therapies.

The National Center of Complementary and Alternative Medicine (http://nccam.nih.gov/), a National Institutes of Health (NIH) Center, defines CAM therapies as those health care and medical practices that are not currently an integral part of conventional medicine. In this context, “conventional medicine” is generally understood to represent the “Western” system of medical knowledge and practices, as taught in Western medical schools.

CAM therapies emphasize a focused and individualized approach to patients, with respect for the connection between mind and body, the responsibility of patients for their health, the spiritual nature of people, and the need to stimulate the strength and vital energy necessary for the recovery and sustenance of health.[66]

Patients with chronic illnesses, including epilepsy, use CAM therapies for several reasons. They may prefer “natural” treatments to “artificial” or “synthetic” drugs, assuming that “natural” treatments are better and safer. They may believe that alternative health care providers give them more control over their health care decisions. Lastly, they may have ready access to CAM therapies but not Western-style treatments due to geographic, economic, cultural, social, or religious conditions and factors, which is particularly the case in developing countries.

CAM therapies include traditional Chinese medicine, Ayurveda, homeopathy, naturism and acupuncture; mind–body therapies, such as yoga, hypnosis, music therapy, prayer, and therapeutic touch; botanicals and other “natural” substances, including herbs, herbal medicines, and herbal formulas, which in the United States are classified as dietary supplements; special diets; movement and massage therapies, including reflexology, massage, osteopathy, Reiki, and Qigong; and electromagnetic forces.

This chapter reviews several of the more commonly used CAM therapies for epilepsy, regulatory aspects of herbal medicines, safety issues, and opportunities for further research. A discussion of other CAM therapies for patients with epilepsy, such as acupuncture,[94,155] dietary approaches,[92,115] and neurofeedback,[69,90,132,146] is beyond the scope of this chapter. Interested readers are also referred to a book on CAM therapies and epilepsy[29] in which these topics are discussed at length, as well as several other excellent reviews on herbal medicines and epilepsy.[35,101,130,142]

Scope of Use

Developed Countries

In developed countries, CAM therapies are often used for general health maintenance or by patients with chronic conditions that respond poorly or incompletely to conventional treatments, such as back pain, anxiety, depression, headaches, and fibromyalgia.[32,116,145] Despite a lack of evidence for efficacy and safety, surveys suggest that up to one third of patients with epilepsy in the United States and the United Kingdom take herbal medicines and/or dietary supplements, and that the majority of these patients do not discuss this intake with their physicians.[31,107,128] One survey of patients attending an American epilepsy clinic found that ginseng, St. John's wort, melatonin, gingko biloba, garlic, and black cohosh were the most frequently taken herbal medicines and dietary supplements[107]; another found that garlic, gingko, soy, melatonin, and kava were most often taken.[128]

Some of these herbal medicines may be taken for non-seizure-related symptoms (e.g., valerian for difficulty sleeping, St. John's wort for depression, and ginkgo biloba for memory disturbance). Therefore, the herbal medicines and dietary supplements taken by patients with epilepsy may be clues to possible side effects from AEDs or symptoms of possible comorbid disorders.

Developing Countries

Throughout history, CAM practices and therapies have reflected cultural beliefs about epilepsy.[34] In developing countries, people turn to CAM practitioners, often under the influence of their families, either before seeing a Western-style doctor or after the perceived failure of Western medicine.[3,33,36,139] According to a survey conducted in China in 1988, nearly 40% of the respondents would suggest that a friend with epilepsy ask for an herbal medicine doctor or seek acupuncture.[71] It should be understood that traditional local treatments are alternative, or “CAM,” from the Western perspective, not from the local perspective.

Lack of education may favor magical beliefs in the power of CAM therapies.[13,23] For example, in sections of the world

where epilepsy is still believed to have supernatural causes, spiritual healing and CAM therapies are used under the direction of traditional healers and include forehead scarifications, shaving of the entire body using glass, herbal concoctions, roots, baths, infusions, or banishment.[7,12,45,86,91,120]

The situation in Africa is particularly illustrative. Epilepsy is known in African societies by a variety of names, including *ngbitie* (Ivory Coast; meaning the brutal, sudden, or surprising disease); *ibi-foukougni* (Burundi; the snoring disease); *adigbe* (Benin; the falling disease); *tibu sugo* (Mali; the “falling like a rock” disease); *say* (Senegal; convulsion or trance or rabies); and *haoua* (Nigeria; the [strong] black bull). In much of Africa, epilepsy is conceived as a manifestation of supernatural forces, caused by ancestral spirits or attributed to possession by evil spirits, demonic possession, or divine punishment for the commission of sins. It is also thought to be due to witchcraft and “poisoning,” and is often taken to be contagious, especially via breath, blood, sperm, and genital secretions. Consequently, affected persons may seek out traditional healers in addition to practitioners of modern (“Western”) medicine, particularly when it is clear the disorder is chronic.

African traditional healers utilize a variety of techniques for diagnosis, including “complementary exploration” via search with cowries, sand, stones, animal sacrifices, interpretation of dreams, and contact and dialogue with supernatural personages and forces. Recommended treatments usually utilize different elements derived from animals, vegetables, minerals, and liquids, according to the potential benefits as assessed by the practitioner, and may be recommended as amulets or to be inhaled, eaten, drunk, or bathed in. Supernatural forces will be “invited” during special mystical celebrations to either visit the patient if they are protective or to be withdrawn from the patient's body and soul if they are negative. These rituals are often witnessed by the public and accompanied by religious songs and dances. The themes of these evocations generally focus on the patient's family and ancestors. Blood from sacrificed animals may be used to satisfy evil forces or to calm devils.

In many other developing countries around the world, CAM therapies are administered in conjunction with AEDs,[25,74] and authors have stressed the relevance of CAM therapies in the management of epilepsy in those settings.[25,28]

Complementary and Alternative Medicine Therapies Used for Epilepsy

Herbal Medicines and Other Dietary Supplements

Herbal medicines have been used to treat seizures for centuries. Arguably the earliest use of herbal medicines for epilepsy dates back to 6000 BC in India. According to old Chinese medical texts, herbal epilepsy treatments started in China about 3000 BC. In Peru, iconographies on stones dating back to about 3000 BC describe the medicinal use of Saint Peter herb (*Trichocereus peruvianis*). Persian medieval medical texts document the clinical manifestations and herbal treatments of epilepsy.[44] Numerous substances were used to treat seizures over the past 500 years in Europe and in pre-Columbian America.[34] In 1763, Pedro de Horta in Mexico wrote an extensive monograph on epilepsy, including the use of herbal medicines, earning his title as the first American epileptologist.[39] Today, many herbal medicines around the world are anecdotally believed to have anticonvulsant properties in humans, generally with inadequate scientific support.[21,80]

Traditional Chinese Medicine

The use of herbal medicines in China has a long and sophisticated tradition based on a well-developed system of medical principles.[147] Lai and Lai noted that the first known document on epilepsy in China is in The Yellow Emperor's Classic of Internal Medicine, Huang Di Nei Ching, dating from about 770 to 221 BC.[72] Today, traditional Chinese herbal medicine is widely practiced. Similarly, in Japan, over 100 herbal (Kampo) medicines are reimbursed by the national health system and widely prescribed; for example, over 70% of the members of the Kyoto Medical Association who responded to a survey questionnaire on CAM practices routinely prescribe Kampo medicines.[149,150]

Herbal medicines traditionally used to treat convulsive diseases in Asia include *Chai-Hu-Long-Ku-Mu-Li-Tan*, a mixture of extracts from 13 herbal medicines[153]; *Gastrodia elata*[64]; *Uncaria rhynchophylla*[73]; *Menispermum dauricum*[79]; *Shitei-To*, a mixture of extracts from three medicinal herbs, *Shitei* (Kaki Calyx; calyx of Diospyros kaki L. f.), *Shokyo* (Zingiberis Rhizoma; rhizome of Zingiber officinale Roscoe), and *Choji* (Caryophylli flos; flowerbud of Syzygium aromaticum [L.])[87]; a mixture of radish and pepper (which contains the alkaloid piperine)[30]; *Qingyangshen*[46]; *Kanbaku-taiso-to*, a mixture of three herbal drugs, *Glycyrrhizae Radix, Tritici Semen,* and *Zizyphi Fructus*[141]; *Paeoniae Radix*[18]; and *Zheng Tai Instant Powder* (a complex prescription of traditional Chinese medicine used for tonic–clonic seizures).[54]

Published reports suggest that several of these herbs have neuroprotective properties,[51,53,64,65,73] efficacy in animal models of epilepsy[19,30,51,52,53,54,65,87,88,141] and hippocampal slice models,[5] and effects on gene expression.[135,136] Interpretation of these studies is limited, however, by inconsistent descriptions of herbal production and extraction methods as well as the lack of characterization of active ingredients.

Based on the traditional Chinese medicine (TCM) principles of holism and differentiation,[75,81] practitioners recommend individualized prescriptions (formulas/combinations) of herbal medicines and acupuncture to their patients with epilepsy[147] (Fig. 1). Differentiation is the process in TCM whereby different treatable syndromes are diagnosed according to various theories and principles based on symptoms, physical signs, disease history, and other information gathered from other diagnostic methods. As a result, herbal formulas with varying components and acupuncture using different points are commonly recommended to different patients who may have the same seizure type, leading to methodologic issues in conducting clinical research. Accordingly, a comprehensive literature search carried out in March 2005 of published studies using herbal medicines for the treatment of epilepsy in the Far East identified only three randomized controlled trials and five nonrandomized controlled trials, whereas there were six case control studies and 57 observational studies including case reports.[105] Over 135 individual herbal medicines were used singly or in various combinations (formulas) in these investigations (Park, personal communication; Table 1). Rarely was the same herbal formula used in more than one study. Consequently, evidence from controlled trials to support the use of specific Asian herbal medicines either alone or in combination for patients with epilepsy is lacking, and further research is needed.

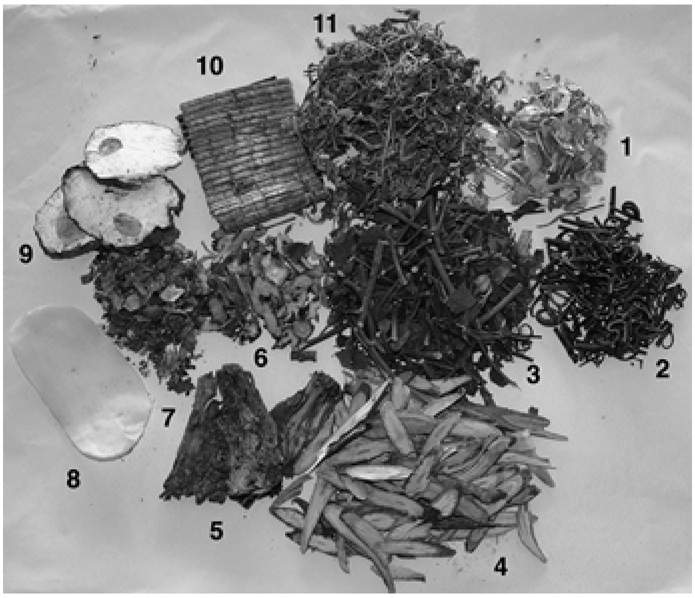

FIGURE 1. An example of an herbal formula, called *Tianma Gouteng Yin*. Concha Haliotidis (*1*), Ramulus Uncariae cum uncis (*2*), Herba Taxilli (*3*), Caulis Polygoni multiflori (*4*), Radix Scutellariae (*5*), Radix Achyranthis bidentatae (*6*), Fructus Gardeniae (*7*), Rhizoma Gastrodiae (*8*), Poria cum ligno hospite (*9*), Cortex Eucommiae (*10*), and Herba Leonuri (*11*). (Reprinted from Sucher NJ. Insights from molecular investigations of traditional Chinese herbal stroke medicines: implications for neuroprotective epilepsy therapy. *Epilepsy Behav*. 2006;8:350–362, with permission.) (See the color insert.)

Table 1 Most Frequently Used Herbs in the Far East for Clinical Studies of Epilepsy

Number of studies	Botanical name	Chinese name
21	*Pinella ternate*	Ban Xia
20	*Arisaemi japonicum*	Tian Nan Xing
17	*Acorus calamus*	Shi Chang Pu
14	*Gastrodia elata*	Tian Ma
13	*Buthus martensii*	Quan Xie
12	*Poria cocos*	Fu Ling

12	*Bombyx bartryticatus*	Jiang Chan
11	*Citrus reticulate*	Chen Pi
11	*Uncaria rhynchophylla*	Gou Teng
10	*Glycyrrhiza glaba*	Gan Cao
10	*Salivae miltiorrhizae*	Dan Shen
7	*Scolopendra subspinipes*	Wu Gong
7	*Bupleurum falcatum*	Chai hu
7	*Succinum*	Hu Po
7	*Paeonia albiflora*	Bai Shao
6	*Panax ginseng*	Ren Shen
6	*Perichaeta communissma*	Di Long
6	*Curcuma longa*	Yu Jin

From Park, personal communication.

Ayurveda

"Ayurveda" means the knowledge of life and is derived from two Sanskrit words: *Ayu*, which means life, and *Veda*, which means to know. Ayurveda is both a medical system and a science of life that is believed to have originated in India 6000 years BC.[59] Ayurveda guides the selection of food and lifestyle so that healthy people stay healthy and those who are sick

improve their health. Specific recommendations are individualized based on ancient texts and are validated by observation, inquiry, and direct examination. Encyclopedic texts written about 1000 BC by Caraka and Susruta are considered the most authentic representatives of the original Ayurveda.[59]

The Ayurvedic literature contains references about several aspects of epilepsylike symptoms, etiology, diagnosis, and treatment. Epilepsy is called "Apasmara." *Apa* means loss or negation and *smara* means memory, cognition, recollection, or consciousness.[82] Epilepsy is classified into four types, all of which are caused by disturbances of the three humors (*doshas*) that are believed to govern the body's physiologic properties: *vayu* or *vata* (air), *pitta* (bile), and *kapha* (phlegm).[59,82] The causes of seizures are thought to be directly related to practices involving diet, lifestyle, emotions, and ingestion of toxins. If toxins in the body are believed to be abundant, they must be eliminated by drastic emesis, enemas, and purgatives.[59]

According to Ayurveda, seizures can be reduced by avoiding looking at shining, fast-moving, or rotating objects; climbing hills or trees; eating candies or oily food; drinking alcoholic beverages; being exposed to coldness or hot temperatures; eating red meat, and masturbating. Further, seizures may be aborted by applying drops of white onion juice into the nose, applying a preparation of water and bitter gourd powder to the nose, inhaling black pepper smoke, or ingesting either fresh or dried tulsi leaves. In addition to these recommendations, Ayurveda includes nutritional guidelines to reduce excessive *dosha*, complemented by herbal supplements once the patient has been cleansed and consoled.[59] Herbal supplements are available for external application, internal use, and topical use in the eyes and nose. The most common ones are Brahmirasayan, Brahmighritham, Ashwagandha, old pure desi ghee, daily fresh juice of brahmi with honey, garlic juice in oil, and powdered root of wild asparagus with milk. Others include *Acacia arabica, Acorus calamus, Bacoppa monnieri, Clitorea turuatea, Celastrus panniculata, Convulvulus pluricaulis, Emblica officinalis, Mukta pishti, Whitania somnifera,* and *Vaca brahmi yoga* (see also reference 17). A growing literature provides an experimental basis to support controlled studies of some of these therapies in patients with epilepsy.[63,70,124,127]

Marijuana

Marijuana, the herbal preparation of *Cannabis sativa*, has been used for thousands of years in Ayurvedic treatments as well as in Unani medicine in the Arabic tradition. There is also evidence of its medical use in Europe dating to the 13th century.

Cannabis contains more than 60 lipophilic cannabinoids. Cannabidiol is the main nonpsychoactive component and Δ^9-tetrahydrocannabinol (THC), identified in 1949 and synthesized in the 1960s, is the primary psychoactive component. Two cannabinoid receptors in the central nervous system are known.[50,152] GABAergic (γ-aminobutyric acid) interneurons in the hippocampus, amygdala, and cerebral cortex express high levels of CB_1 receptors.[57]

Some animal studies suggest that THC may suppress kindling, but others have found a proconvulsant effect.[62,83,144] There are no controlled data to support the use of marijuana in epilepsy.[42]

Melatonin

The dietary supplement melatonin has been reported to be useful for the treatment of sleep disorders (including in children with epilepsy), jet lag, and even glioblastoma.[16,47,49,78,129] Abnormal nocturnal salivary melatonin levels have been found in pediatric patients with epilepsy,[111] though the significance of this finding is uncertain.

Melatonin enhances hippocampal excitability, and nocturnal activation of hippocampal melatonin receptors in rats enhances seizure susceptibility, suggesting a proconvulsant effect.[133] Other animal studies support a possibly beneficial effect of melatonin on seizures.[26,37] Results in humans with epilepsy and neurologic disorders are similarly mixed.[108,126] Given that melatonin is commonly taken by persons with

epilepsy who use CAM therapies,[31,107] additional studies of its efficacy and safety when taken long term by patients with epilepsy are clearly needed.

Psychological Therapies and Mind–Body Techniques

Psychological therapies and mind–body techniques,[41] discussed in detail in Chapter 132, are designed to reduce seizure frequency, avoid AED side effects, and improve quality of life. Examples include behavioral inhibition of symptoms at seizure onset,[6,38] massages[93] (note that certain oils used in aromatherapy have been anecdotally reported to cause seizures[130]), relaxation techniques,[27] creative therapies,[121,140] cognitive-behavior therapy,[38] and systematic desensitization.[11,24,138] Further controlled studies are needed to identify which therapies or techniques are effective and to determine how to select specific therapies for individual patients.[112]

Yoga

Health in the traditional Indian view is the result of perfect harmony between body, mind, and spirit. *Yoga* derives from the Sanskrit word *Yug*, which means “mind control.” There are several forms of yoga: Sahaja yoga, hatha yoga, and transcendental meditation. Yoga practices include exercises with different postures (asanas), special respiratory techniques (pranayama), and mental relaxation and meditation (dhyana).

The aim of yoga is to reach a state of pure consciousness, joy, and relaxation. Yoga and yogic mindfulness meditation have been used for stress reduction[85,96] and therefore have a theoretic role in epilepsy, particularly for patients with stress-induced seizures. However, the last Cochrane review on yoga and epilepsy found no conclusive benefit of yoga as a treatment for epilepsy.[112] Nonetheless, given its favorable safety profile, yoga and other relaxation techniques can potentially be useful in the management of stress in patients whose seizures appear to be associated with stress,[104] and further well-designed studies should be conducted.

Homeopathy

The term *homeopathy* comes from the Greek word *homoios*, which means "similar," and *pathos*, relating to suffering or disease. The basic principles of homeopathy were advanced by Hippocrates and rediscovered by Samuel Hahnemann (1755–1843). Its main tenet is "like should be cured with like"; that is, a homeopathic preparation to treat symptoms in a patient incorporates a drug, often derived from plants or animal products, that causes similar symptoms when given to a healthy volunteer.[143] As proposed by Hahnemann, the active ingredient is serially diluted and then vigorously shaken.[137] Specific preparations are then recommended to a patient based on his or her symptoms or what are believed to be the underlying causes of the symptoms rather than on a specific diagnosis.

Significant doubt has been expressed about the efficacy of homeopathic medicines.[143] Recently, Shang et al. compared placebo-controlled trials of homoeopathy and allopathy and concluded that the clinical effects of homeopathy seen in placebo-controlled trials are compatible with placebo effects.[123] Nevertheless, homeopathic medicines are not infrequently taken by patients with epilepsy,[139] and while the risks appear to be relatively low given the extreme dilution of these preparations, further research to determine their efficacy and safety is needed.

Regulatory Aspects of Herbal Medicines

Reviewing regulations concerning herbal medicines in each country is an insurmountable task, and would quickly become out of date. The situation in the United States is therefore presented as an example and to stimulate discussion in other regions of the world.

Herbal medicines in the United States are regulated by the 1994 Dietary Supplement and Health Education Act (DSHEA), whereas the clinical development, manufacturing, and marketing of prescription drugs must meet the more rigorous requirements of the Federal Food, Drug, and Cosmetic Act. The Food and Drug Administration's (FDA) Office of Nutritional Products, Labeling, and Dietary Supplements is responsible for developing policies and regulations for dietary supplements (http://www.cfsan.fda.gov/~dms/onplds.html; accessed 9/4/2006).

Under the DSHEA, a dietary supplement is defined as a product taken by mouth that contains a dietary ingredient intended to supplement the diet. The dietary ingredients in these products may include vitamins, minerals, herbs or other botanicals, amino acids, and substances such as enzymes, organ tissues, glandulars, and metabolites (http://www.cfsan.fda.gov/~dms/ds-oview.html; accessed 9/4/2006). Manufacturers of herbal products are responsible for the truthfulness of the claims they make on product labels and for controlling the quality of their products and verifying their safety. They cannot claim that their herbal product is effective against a specific disease or medical condition, such as epilepsy, but they may claim it has some effect on a part of the body or its function as long as the claim is accompanied by the following words: "This statement has not been evaluated by the FDA. This product is not intended to diagnose, treat, cure, or prevent any disease."

No U.S. government agency, including the FDA, is required by law to independently review and verify the labeling claims and supporting evidence of herbal products or to independently verify the quality of herbal products and their safety. That is, the FDA is not legally required or authorized to "approve" dietary supplements based on evidence of safety and efficacy. Similarly, no U.S. government agency is required by law to verify that the production of herbal products is consistent with "Good Manufacturing Process" (GMP) standards, as is the case for pharmaceutical products. Therefore, herbal products could potentially be contaminated with microorganisms, pesticides, or toxic metals, as has been documented with some Ayurvedic herbal medicine products sold commercially.[118] Further, they could be adulterated with other herbs or drugs, and the potency and amount per pill/capsule may vary significantly within the same bottle or from batch to batch, or from one branded product to another because of variable manufacturing processes. This situation could occur anywhere in the world. For example, a study conducted in Taiwan found that herbal products from China, Taiwan, and other countries were adulterated with phenobarbital.[55]

In light of the frequent use of herbal medicines and dietary supplements by patients with epilepsy, clinicians should inform patients about the differences in how their particular country's government oversees the production, testing, and labeling of pharmaceuticals as compared to dietary supplements.

Safety Issues

Despite being "natural," herbal therapies are not necessarily safe, intoxication may be fatal, and the long-term safety of most herbal therapies is not known.[56,106] Likewise, the pharmacokinetic interactions between herbal medicines and AEDs, with few exceptions, are not well studied. As reviewed by Conry and Pearl,[21] certain herbal medicines, including St. John's wort,[103] garlic, echinacea, pycnogel, milk thistle, American hellebore, mugwort, and pipsissewa, affect cytochrome P450 enzyme activities and therefore have the potential to alter the serum concentrations of hepatically metabolized AEDs. In addition, a number of herbal products and dietary supplements have been anecdotally reported to precipitate seizures, including in patients with epilepsy.[80,131,142] Examples are anisatin (which is used in Spain and other countries to treat infant colic and is also known as Japanese star anise),[40,60] gingko nuts,[89] essential oils,[131] evening primrose and borage,[130] and the stimulant ephedra (ma huang).[48,67] The extract of star fruit (*Averrhoa carambola*) has been reported to cause seizures in uremic patients[15,97] and its extract is used experimentally to elicit seizures.[14] Similarly, an extract of a Chinese herb used to treat schizophrenia induces a kindling model of pharmacoresistant temporal lobe epilepsy in rats.[148] Therefore, clinicians should take a thorough history regarding herbs and dietary supplements from their patients and ask to see the actual bottles to verify the ingredients. Further, physicians should consult reliable databases for information on herbal medicine safety, as well as possible adverse effects on seizure frequency and AED serum concentrations.

Opportunities for Further Research

Given the need for new AEDs, herbal medicines with a tradition of use for epilepsy and compounds isolated from them, as well as herbal medicines and their constituents that are known experimentally or clinically to have mechanisms of action relevant to epilepsy,[5,8,19,77,84,95,102,151] are particularly attractive targets for research, especially if the herbal medicines are readily available and have low apparent toxicity.[101] Accordingly, a growing number of groups around the world, in addition to the work already cited from Asia, are studying their local or regional herbal medicines as potential anticonvulsants in animal models,[1,4,10,20,100,109,110,157] in vitro assays,[61,113,131] and patients with epilepsy.[2,58,76,125,154] It is anticipated that promising findings from these inquiries will be translated to clinical research when possible.

As an example of the strategies used by workers in this field, the authors and collaborators in Asia are currently engaged in an effort to:

- develop a list of high-priority herbal medicines to be considered for evaluation, based on a number of considerations such as clinical recommendations of senior herbal experts, electronic database searches, review of original text references, existing well-characterized herbal extracts/compounds, and promising results from published clinical studies;
- test crude extracts and selected fractions of these herbal medicines, as well as pure compounds isolated from those fractions, in well-validated animal models of epilepsy; and
- evaluate those fractions and compounds with activity in the animal models using in vitro assays to evaluate mechanisms of action.

The goal of these evaluations is to identify herbal medicines and pure compounds derived from those herbal medicines that are candidates for further preclinical and clinical testing. For example, Huperzine A, a sesquiterpene lycopodium alkaloid isolated from Chinese club moss (*Huperzia serrata*), also known as the Chinese folk medicine *Qian Ceng Ta*, has been traditionally used in China for the treatment of swelling, fever and inflammation, blood disorders, and schizophrenia,[156] and is approved and used in China for the treatment of Alzheimer disease. Huperzine A is a potent, orally active, noncompetitive antagonist of the *N*-methyl-D-aspartate receptor, likely acting at or near the PCP and MK-801 ligand sites, but without psychotomimetic side effects.[43] Huperzine A is active in several animal models of epilepsy; its effects in the 6-Hz model are particularly interesting and appear to offer potential advantages over several classical anticonvulsants as well as the newer agent levetiracetam.[119,151] A phase II clinical study in patients with medically refractory epilepsy is planned.

In addition to potentially identifying new therapies for epilepsy, this approach and others under way around the world may also yield agents that are neuroprotective.[134] Finally, some of the herbal medicines and their derived compounds that are active in the animal models of epilepsy may be found to have novel mechanisms of action that could lead to the development of additional pharmacologic interventions for epilepsy.[79] Natural products have already significantly impacted drug discovery in other fields[22,68]; for example, they have led to the identification of new cell cycle pathway targets for novel chemotherapeutic agents.[98,99]

Summary and Conclusions

CAM therapies are a very heterogeneous system of concepts and therapies with origins in different cultures, religions, and philosophical and healing systems. A significant proportion of people with epilepsy around the world have used one or more types of CAM therapies, often because of lack of access to AEDs and usually without the knowledge of their treating physician, if they see a physician.

Despite the popularity of CAM therapies, there is a paucity of sound evidence at the present time to support their use by patients with epilepsy; further, some herbal medicines may pose a safety risk. As a matter of routine, physicians should ask their patients whether they use these therapies and discuss the risk-to-benefit ratio of CAM therapies with their patients who use or plan to use these treatments.[114,139] In addition, physicians should be familiar enough with these treatments to advise their patients about the use of these treatments, not only in the treatment of epilepsy, but also in the context of their overall health care.

Further research is needed to understand the full scope of use of CAM therapies among people with epilepsy around the world, and particularly with regard to herbal medicines, to explore their mechanisms of action, efficacy, safety, and tolerability.[117,122]

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Chapter 134

New Therapeutic Directions

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Introduction

People with epilepsy, their families, and the clinicians who care for them await the advances that will cure or prevent epilepsy, but all want to know what can be done now (or in the near future) when medications fail or are unrelentingly toxic? This chapter collects a miscellaneous group of therapies that may partially address this question. By selection criteria to be in this chapter, none of the therapies yet is proven as safe and effective. Most, but not all, are available in experimental protocols, none as part of standard therapy.

A general theme of the experimental therapies in this chapter is an attempt to be relatively noninvasive. Surgical procedures should not have to remove more than the minimal amount of brain necessary to stop seizures, or perhaps they should remove no brain at all. Electrical brain stimulation therapies have attempted seizure control without resection. Several targets and strategies have been employed, but most active now are deep brain stimulation in the anterior or centromedian thalamus, subthalamus, or hippocampus, or direct stimulation of a cortical seizure focus. Stimulation can run on a cycle, as with vagus nerve stimulation for epilepsy. Alternatively, stimulation can be made contingent upon recording an electroencephalographic (EEG) pattern indicative of an ongoing (seizure recognition) or impending (seizure prediction) seizure. Noninvasive trans-cranial magnetic stimulation has been tested for seizure control, since transcranial electrical stimulation tends to be painful. Transcranial magnetic stimulation used for diagnostic purposes is discussed elsewhere in this volume.

Focal brain radiation may or may not be less invasive than surgery, but some investigators argue that it is. More important than the avoidance of a craniotomy with Gamma Knife or CyberKnife radiation therapy is the possibility that radiation can spare cells with a sublethal dose but still inhibit seizures.

Why distribute an antiepileptic drug to every region of brain and body when it might only be needed within a restricted region of the central nervous system (CNS)? Why should a kidney stone or severe leukopenia be a risk of therapy for treating the brain? Techniques to distribute medication focally in the brain include intracerebroventricular perfusion, catheter-mediated perfusion in the cortex, drug-eluting polymer wafers, targeted liposomes, seizure-activated prodrugs, and cell transplants that release drugs. The genetic machinery of the neurons and glia in a seizure focus can be altered by gene transplants via viral vectors. Altered genes can produce renewable local neurotransmitters or neuromodulators that serve to inhibit local excitability.

Not every exciting potential new therapy can be covered in one chapter. For example, rapid cooling of a seizure focus[113] has been shown to be effective in blocking seizures in animal systems and in small uncontrolled series of patients. In the following section, investigators working with some of the new technologies will provide a very brief overview of the methods, promise so far, and potential limitations. The hope is that some of these therapies will prove successful, and migrate to the standard care sections of the future editions of this compendium.

Deep Brain Stimulation

Electrical brain stimulation to control intractable epilepsy has been attempted intermittently for several decades, using a variety of neural targets: Cerebellar cortex, deep cerebellar nuclei, caudate nucleus, locus ceruleus, hippocampus, centromedian nucleus of thalamus, anterior nucleus of thalamus, subthalamic nucleus, neocortex, and vagus. Space limitations do not permit review of each stimulation site, but reference may be made to several published recent reviews.[36,40,45,55,65,67,79,82,134] Stimulation of brain tissue to control or partially control medically intractable seizures has several potential advantages over resective surgery. Firstly, stimulation may influence a seizure focus or multiple foci in regions of brain, for which it would not be safe to remove tissue. Secondly, electrical stimulation is an adjustable therapy, with many parameters available for individualization on an empirical basis for each patient. Thirdly, stimulation can be discontinued, as opposed to an irreversible surgery. Nevertheless, clinical experience and at least one randomized study[148] overwhelmingly support resective surgery in circumstances for which a seizure focus safely can be removed. Neural stimulation, therefore, is a candidate for a palliative role, in circumstances for which seizure control is not possible with medications or removal of the seizure focus.

Stimulation of the thalamus for epilepsy originally was proposed by the pioneering neurosurgeon Irving Cooper.[17,18,19,143,144] Only a few studies so far have investigated basic mechanisms of electrical stimulation for seizures. The results of stimulating neural tissue are not predictable from basic physics and electrical field principles. Complications include a complex geometry of nuclei and tracts in the brain; "sign-changing" circuitry, by which inhibitory pathways may be activated or deactivated; exquisite dependence of outcome on parameters of electrical stimulation, such as frequency, intensity, bipolar versus referential application, and intermittent or continuous stimulation; and many other parameters, including some that undoubtedly are not yet recognized. Studies with in vitro slice tissue indicate that both alternating currents[73] and direct-current electrical fields[108] can in some circumstances inhibit epileptiform activity in the model systems. One likely mechanism may be the polarization of neurons with release of extracellular potassium, leading to an induced spreading depression.[8] Inactivation of sodium channels from excess depolarization, thereby blocking action potential formation, may play a role. Direct effects on inhibitory or excitatory systems by stimulation also could reduce excitability in the brain.

Stimulation of the anterior region of the thalamus in rats can raise the threshold for seizures provoked by the acute application of the convulsant drugs pentylenetetrazol[90] and pilocarpine.[44] However, a recent study[69] failed to find benefit, and in fact observed increased seizure frequency, with anterior thalamic stimulation in rats with chronic epilepsy induced by previous doses of kainic acid.

In the 1990s, electrical stimulation to treat epilepsy rarely was the object of serious study, until two events refocused interest on this potential new modality: Success of vagus nerve stimulation for epilepsy[7] and success of deep brain subthalamic stimulation for movement disorders.[4] Two types of brain stimulation currently are in multicenter pivotal clinical trials for treatment of epilepsy: Open-loop stimulation and closed-loop stimulation, which also is referred to as responsive or contingent stimulation. Open-loop stimulation delivers stimuli on a scheduled basis, either intermittently or continuously, but not dependent upon detection of epileptiform activity. Responsive neural stimulation (see elsewhere in this chapter) uses EEG sensors to detect epileptic stimulation and deliver stimuli to the region of the suspected seizure focus or foci. Open-loop electrical stimulation of human diencephalon has been performed in the centromedian thalamus, subthalamus, and anterior thalamic nuclear group.

Centromedian Stimulation

Velasco et al.[146] identified the centromedian nucleus of thalamus as a promising target for electrical stimulation. To date, this target represents the most stimulated site in the brain for epilepsy, but no large, controlled trial has yet been completed of centromedian stimulation to document efficacy. The largest group of patients with centromedian stimulation was published by Velasco et al.[145] A total of 49 patients with a variety of intractable seizures were subjected to bilateral centromedian stimulation at intensities of 2.5 to 5 V, with stimulation frequencies ranging from 60 to 130 Hz. In the study population, centromedian stimulation was effective against generalized tonic–clonic seizures, tonic seizures, and atypical absence seizures, but not against complex partial seizures. A small cross-over trial of centromedian stimulation in seven patients with mixed seizure types[29] showed a trend toward benefit, but not of statistical significance.

Subthalamic Nucleus Stimulation

The subthalamic nucleus is a primary target for electrical stimulation to ameliorate tremor and Parkinson symptoms.[4] Laboratory studies suggest that subthalamic stimulation also can benefit seizures in animal models of epilepsy produced by kindling,[70] genetic absence,[147] fluorothyl,[70] and kainic acid.[79] Nine patients treated with subthalamic stimulation for epilepsy have so far been reported.[5,13,21,79] Six of the nine were said to show more than a 75% improvement in seizure frequency, although each of these reports was uncontrolled.

Anterior Thalamic Stimulation

The anterior thalamic nucleus provides efferents to superior medial frontal and cingulate cortex. In turn, the cingulum white matter projects to the entorhinal cortex, and thereby to the hippocampus. Stimulation of the anterior thalamic nucleus therefore is well placed to influence certain frontal and temporal seizures. Initial work on thalamic stimulation for epilepsy was performed by Cooper, with published results on several dozen patients.[19,143] These studies reported beneficial outcome in several patients, but details and long-term follow-up results were not provided in the publications. Sussman et al.[128] reported in abstract form the benefit of anterior thalamic stimulation at 100 Hz and approximately 5 V in three of five patients tested. Subsequently, pilot studies of anterior nucleus thalamic stimulation were performed on 14 patients from four different study sites.[40,48,58]

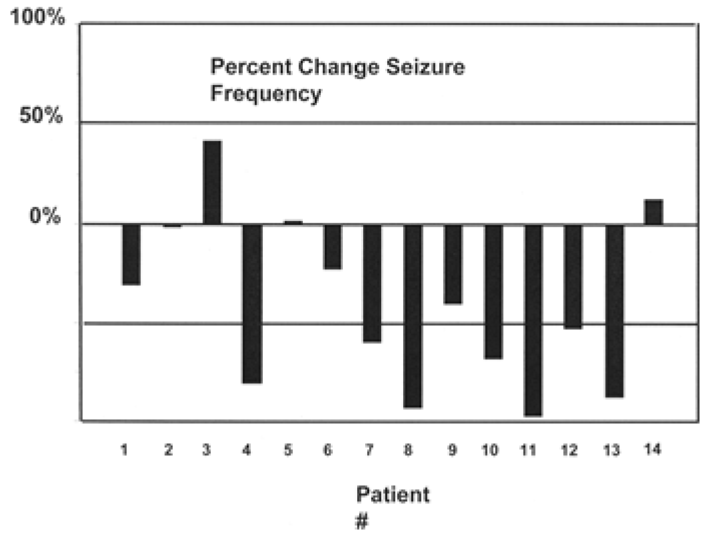

FIGURE 1. Percent change in seizure frequency, measured at a time 7 to 12 months after onset of bilateral anterior thalamic stimulation for 14 patients in the pilot trial of anterior thalamic stimulation. (From Graves NM, Fisher RS. Neurostimulation for epilepsy, including a pilot study of anterior nucleus stimulation. *Clin Neurosurg.* 2005;52:1–8.)

Table 1 Responsive Stimulation after Induced Seizures

	Duration of afterdischarges		
	<2 seconds	**2–5 seconds**	**>5 seconds**
With responsive stimulation	115	22	89
Without responsive stimulation	21	114	340

$p < .001$.

From: Lesser RP, Kim SH, Beyderman L, et al. Brief bursts of pulse stimulation terminate afterdischarges caused by cortical stimulation. *Neurology.* 1999;53(9):2073–2081.

Figure 1 shows the changes in seizure frequency for the patient group before and after stimulation. The mean seizure frequency at 12 months of stimulation was 55% ± 39% of baseline, and 57% of patients exhibited at least a 50% improvement in seizure frequency (responders). Among those believed to have frontal or temporal seizure foci, the responder rate was 67%.[40] Five patients had seizures capable of producing falls; four of these had a marked reduction in such seizures.[58] None of the 14 patients in the pilot trial experienced a serious complication. However, placement of deep brain stimulation electrodes is known to comprise a measurable risk for hemorrhage[9] and infection.[132] One patient implanted at a fifth institution using a similar thalamic stimulation pilot protocol had a hemorrhage leading to contralateral hemiparesis. Hodaie et al. in Toronto[48] have suggested that implantation itself might account for much of the perceived benefit, either by a microlesion effect or placebo effect.

Based on anecdotal and uncontrolled evidence of possible efficacy for anterior thalamic stimulation, a pivotal, multicenter, randomized, and blinded trial has been launched, called SANTE, for Stimulation of the Anterior Nucleus of Thalamus for Epilepsy (see www.epilepsycontrol.com). Eligible patients are those with medically uncontrolled partial or secondarily generalized seizures, not believed amenable to surgical resection. Seizures must be severe enough to interfere seriously with quality of life and must occur at a frequency of at least six per month. The SANTE trial utilizes bilateral implantation of deep brain-stimulating electrodes in the principal portion of the anterior nuclei, connected to a dual-channel Intercept (Medtronic) stimulation module. Stimulation parameters are 145 pulses per second with 90-μsec (approximately 0.1 msec) duration pulses, charge-balanced negative and positive on for 1 minute and off for 5 minutes. Voltage is set to 5 V in the treated group and 0 V in the placebo group. Since the patients, caregivers, or treating medical team cannot perceive the stimulation, this is a true double-blind study. After a 3-month baseline phase, patients receive either 5 V or 0 V stimulation for 3 months, then open-label therapy via a limited number of

parameter sets for 10 additional months. At time of this writing, the study had passed the midstudy “futility analysis” by the unblinded data-monitoring safety board, and the investigators have been given the go-ahead to complete the trial. Final outcome of the trial is not yet known.

Responsive Neurostimulation

Some patients with intractable epilepsy either are not candidates for surgery or do not want to undergo resective or disconnective surgery. For these patients, one option that is currently under investigation is responsive stimulation. Responsive stimulation, as currently available, differs from deep brain stimulation in two major ways: (a) deep brain stimulation involves continuous open-loop therapy delivered into a target region of interest. It is delivered all the time without detection of brain activity in the target or feedback from the target tissue. In contrast, responsive stimulation is closed loop. It is delivered intermittently in response to detected EEG abnormalities. (b) The pulse generator for available deep brain stimulation (DBS) systems is implanted in the chest wall below the clavicle, while the currently available responsive stimulator is implanted entirely within the skull.

The goal of responsive stimulation is to provide brief target stimulation only in response to an EEG-detected “preictal state” or ictal onset. For this approach to work successfully, it requires a precise methodology to detect ictal or preictal EEG activity on the afferent side of the loop and effective stimulation delivery on the efferent side of the closed loop.

The Afferent Loop: Seizure Detection

In order to terminate clinical seizures by responsive stimulation, the seizure must be detected and treated before it spreads to a degree that it cannot be controlled with focal stimulation. This suggests that this therapy will be most effective if stimulation is delivered as early and precisely in the epileptic discharge as possible, usually before the onset of clinical symptoms. Responsive stimulation thus requires sufficiently accurate seizure prediction algorithms (SPAs) for EEGs recorded from intracranial electrodes.

All recent SPAs utilize a “sliding window analysis” in which a window of recorded EEG activity is mathematically analyzed using either linear or nonlinear algorithms. Linear algorithms calculate particular features directly from the EEG, including autocorrelation, spectral band analysis, curve length, accumulated energy, and high-frequency epileptiform oscillation[78,92] nonlinear algorithms. The EEG sliding window is reconstructed in three-dimensional phase space and analyzed using techniques such as the short-term maximum Lyapunov exponent, dynamic similarity, or correlation dimension.[78,92] All of these techniques have been purported to have their advantages in seizure prediction. However, as discussed at the recent Second Annual Seizure Prediction Workshop in April 2006,[77] there is still much work to be done in terms of understanding and applying the basics of seizure dynamics. Future techniques will likely apply multichannel, multialgorithm integrated analysis, utilizing a continuous probability curve rather than binary thresholding. In addition, the relevance of high-frequency epileptiform oscillations prior to seizure onset will need to be determined and incorporated into future SPAs. It is likely that future seizure prediction and detection in an individual patient will utilize more than one SPA, and that the optimal SPA application profile will differ from patient to patient.

The Efferent Arm: Stimulation Delivery

In humans, cortical stimulation has long been known to abort spontaneous or induced epileptiform activity during brain mapping in surgical patients. Penfield and Jasper first applied focal electrical stimulation over 50 years ago to terminate spontaneous seizures detected by electrocorticography (ECoG) at the time of resective surgery. More recently, stimulation has been used to shorten or terminate epileptiform afterdischarge activity in patients implanted with intracranial subdural electrode arrays. During the brain-mapping procedures in these implanted patients, brief electrical stimulations were applied to the cortex, with the stimulus amplitude progressively increased until a clinical alteration or subclinical electrographic afterdischarge resulted. In 17 patients with subdural electrodes who underwent functional mapping, control afterdischarge duration was compared with afterdischarges that received brief bursts of stimulation.[72] A biphasic 50-Hz pulse was presented for 0.3 to 2 seconds at the same stimulus intensity used to generate the afterdischarge. The duration of the afterdischarges was significantly shorter in those patients receiving stimulation (Table 1).

Brief pulse durations (0.5 to 1 second) were more effective in terminating afterdischarges than were stimulations of longer duration. This and other studies suggest that the exact stimulation parameters and timing may be very important in determining whether stimulation will disrupt or further entrain electrographic discharges.

Closing the Loop: Combined Detection and Delivery Systems

Limited animal model and human experience pertains to responsive stimulation. In the genetic absence epilepsy rat of Strasbourg (GAERS) rat, which has a genetic disposition to spontaneous generalized absence seizures, responsive stimulation delivered to the subthalamic nucleus upon detection of spike-and-wave epileptiform activity was effective in suppressing seizures.[147] Interestingly, continuous stimulation had no effect on seizure frequency in this model. Responsive stimulation has also suppressed spontaneous seizures in cats[100] and in rat hippocampal slices.[94]

While still in its infancy, the field of responsive stimulation already has examples of effective clinical application in human epilepsy patients. Osorio et al.[97] at the University of Kansas applied high-frequency electrical stimulation that was delivered either directly to the epileptogenic zone (local closed loop, *n* = four patients) or to the bilateral anterior thalamic nuclei (remote closed loop, *n* = four patients) in response to every other automated seizure detection. The eight patients had a baseline video-EEG monitoring with implanted subdural and depth electrodes that localized epileptic foci and quantified seizure frequency using a linear simple genetic algorithm (SGA). Patients determined to have multifocal onsets were implanted into the bilateral thalami for remote stimulation, while local therapy was delivered to patients with a precisely localized epileptogenic focus. A total of 1,491 stimulations were delivered, 0.2% of which triggered afterdischarges. The mean reduction in seizure rate in the local closed-loop group was 55%; in the three responders the mean decrease was 86%, with two patients rendered seizure free during the local stimulation therapy. In the remote thalamic closed-loop stimulation, the mean seizure reduction rate was 41%, with a 74% reduction in the two responders.

More recently, patients undergoing subdural and depth electrode monitoring for seizure localization and functional mapping were enrolled in a trial testing an externalized version of an implantable responsive neurostimulator (eRNS, NeuroPace, Inc., Mountain View, CA).[64] This device used linear SPAs that could be tuned to patient-specific epileptiform activity to deliver electrical stimulation through up to eight contacts of a combination of subdural and/or depth electrodes implanted at the epileptogenic zone. Of 50 enrolled patients, 40 received responsive stimulation. The experience with four of these patients was subsequently reported. In this trial, electrographic seizures were altered and suppressed in these patients during trials of neurostimulation, with no major side effects. In one patient, stimulation appeared also to improve the baseline EEG.

Implantation of an internalized version of this responsive neurostimulator (RNS) system was subsequently investigated in a multicenter clinical trial assessing feasibility of the device's clinical implantation and implementation. For this trial, enrollment included subjects 18 to 65 years with intractable partial-onset seizures and localized epileptogenic-onset region or regions. Subjects with at least 12 simple partial (SP) sensory or motor, complex partial (CP), or generalized tonic–clonic (GTC) seizures over an 84-day baseline period qualified for implant. The responsive stimulator was connected to up to four contact leads (subdural and/or depth), which were targeted to the seizure focus. This trial's results have been reported in limited fashion. A single center's experience with eight implants resulted in 45% reduction in seizure frequency in seven of eight patients over more than 9 months' follow-up.[30] For the multicenter trial, efficacy was assessed during the most recent 84 days for which a subject could have received therapy. Defining response as at least a 50% reduction in seizures, the responder rate for 56 subjects was 36% for CP, 50% for GTC, and 36% for totally disabling (TD) seizures. The median percentage reduction was CP 28%, GTC 50%, and TD 30%; seizure reduction was significant for CP ($p < 0.005$), GTC ($p < 0.02$), and TD ($p < 0.001$). In 65 implanted subjects, including 17 device replacements, there were no serious unanticipated device-related adverse events. Responsive neurostimulation was well tolerated by the patients.[37]

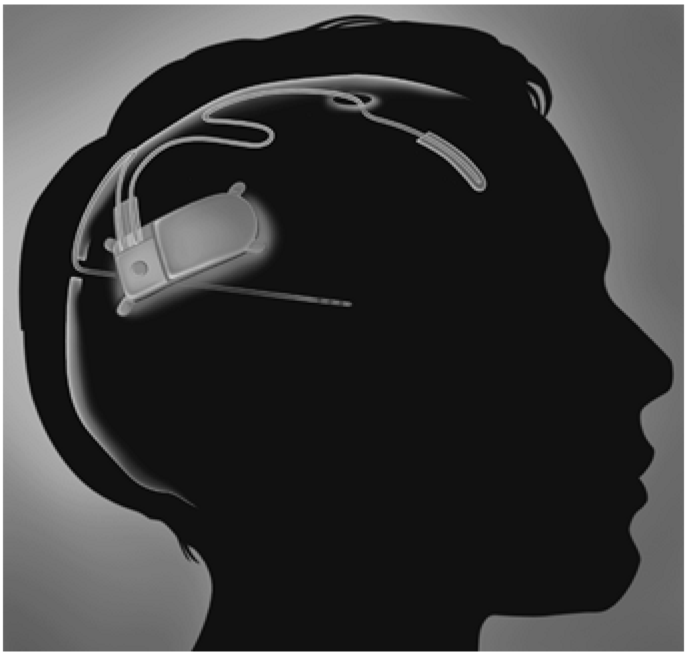

FIGURE 2. Schematic view of the implantable NeuroPace responsive stimulation device (NeuroPace, Inc., Mountain View, CA).

In follow-up to the feasibility trial, a clinical efficacy trial began enrollment in the fall of 2006. In contrast to available implantable deep brain stimulation systems, in which the pulse generator is implanted below the clavicle, the RNS system has two four-contact subdural strip and/or depth electrodes that are attached to a seizure detection and stimulation delivery device that is implanted directly into the skull (Fig. 2). In our center's experience, the most commonly encountered current applications for the RNS trial are dominant mesial temporal seizure onsets in patients with preserved hippocampal function, bitemporal epilepsy with mesial temporal onsets, and seizure onsets arising from a functionally “eloquent” area such as essential language cortex.

Future Directions

Responsive stimulation therapy for epilepsy must be efficacious, well tolerated, and safe in order to offer an alternative to resective surgery or other stimulation modalities in patients resistant to antiepileptic medication. Therapy should be targeted at the epileptogenic region or at seizure propagation pathways and leave other regions of the brain unaffected. It need not interfere with normal brain function, have an acceptable false-positive detection rate, and be stable as a therapy over time. It must also not result in chronic brain damage or the generation of new epileptic foci.

In addition to responsive stimulation, a device with accurate SPA technology will likely be paired in the future with novel treatment strategies such as convection-enhanced local drug delivery[126] or focal cooling[113] to treat epilepsy in closed-loop responsive fashion. Future therapy may be delivered to the epileptic focus, to the epileptogenic region, to propagation pathways, or to deep brain structures. Whether a local responsive treatment can both suppress seizures and inhibit epileptogenesis remains to be determined.

As discussed above, SPA technology will certainly improve and need to be optimized on a case-by-case basis. The ability of responsive stimulation to then terminate detected seizures may depend on a variety of stimulation parameters including exact timing of delivery, current intensity, stimulus duration, the stimulus waveform, pulse frequency, and the delivery of the

stimulation in relation to the morphology of the epileptiform activity. These are all areas requiring further basic and human investigation.

The exact localization of the epileptogenic zone is critical for the future efficacy of responsive therapies. Currently, many mesial temporal and nearly all neocortical responsive stimulation patients require invasive monitoring to determine their seizure onset location or locations. Advances in techniques such as magnetic resonance imaging (MRI)–based localization of interictal and ictal activity have great promise in determining where to apply responsive treatment.

Transcranial Magnetic Stimulation

Transcranial magnetic stimulation (TMS) is a relatively new technique in neurophysiology, with its first description only approximately 20 years ago.[3,62] In contrast to the preexisting transcranial electrical stimulation, TMS provides noninvasive cerebral stimulation that is painless.[89] TMS achieves this by using electromagnetic induction to produce the neurostimulation. The induction is produced by placing a rapidly changing magnetic field adjacent to the scalp. The field is generated by a brief but large electric current through a wire loop and produces an electric current in the subjacent cerebral cortex. This results in synaptic excitation of the neurons within the region of the electric current. Because the magnetic field penetrates the tissue with negligible resistance or attenuation, it is painless. Each magnetic pulse is perceived as a touch or a tap to the scalp.

Technique

TMS has the potential for excellent spatial and temporal resolution. A 0.1-msec stimulation induces a current lasting the same duration and confined to 1 cm^2 of cortex with a maximum depth of about 2 cm.[57,112] When the motor cortex is stimulated, the excitation affects corticocortical neurons predominantly with subsequent activation of corticospinal neurons. The produced movement is a motor-evoked potential (MEP) with measurable conduction time and amplitude. Beyond the stimulation of motor cortex, all cortex that is adjacent to the cranium may be stimulated. Depending on the stimulation parameters, TMS may produce transient dysfunction for purposes of functional mapping or may temporarily alter the intrinsic excitability of the local gray matter. It is this capacity to alter the intrinsic excitability of cerebral tissue that is the foundation of TMS as a potential treatment for epilepsy.

Individual TMS pulses provide a means to measure cortical excitability through several parameters, including intensity thresholds, post-MEP (central) silent periods, and paired-pulse techniques that are similar to those used in basic neurophysiology.[131] These techniques assess different aspects of cortical excitability. Threshold studies apparently represent pyramidal cell membrane excitability as the results are affected by sodium and calcium channel–blocking medications. Central silent period studies likely represent intracortical inhibition and paired-pulse studies are influenced by networks beyond the local cortex. The results of both are dependent on glutamatergic, dopaminergic, and GABAergic (γ-aminobutyric acid) activity.

Single and paired-pulse stimulations do not produce a sustained alteration to the cortical excitability, but such alterations may occur when the stimulation is delivered in trains of pulses. This technique is called repetitive TMS (rTMS). Low-frequency rTMS (LF-rTMS) is defined as pulse trains at or below 1 Hz and high-frequency rTMS (HF-rTMS) as pulse trains above 1 Hz and usually around 20 Hz. The 1-Hz division has practical implications because LF-rTMS is associated with decreases in cortical excitability and HF-rTMS is associated with increases. The occurrence of seizures as an adverse effect of TMS most often occurs during HF-rTMS. Therefore, LF-rTMS is the technique that has been most explored as a treatment for epilepsy. This approach partly depends on abnormal excitability of epileptic cortex, as documented in clinical and animal studies. LF-rTMS delays the development of seizures in pentylenetetrazol-exposed and kindled rats.[1]

Clinical Experience for Epilepsy Therapy

In humans, the reports of rTMS efficacy for seizures have varied considerably with respect to the types of patients included and outcome. Direct electrical stimulation through subdural grid electrodes can decrease both interictal epileptiform discharges and electrographic seizures in patients.[60,116] In a case report of a patient with a focal cortical dysplasia, 100 pulses of LF-rTMS were delivered to the area over the dysplasia twice a week for 4 weeks with a resulting 70% reduction in seizure frequency and a 77% reduction in interictal epileptiform discharges.[88] A report of two patients with epilepsia partialis continua describes each receiving 15 minutes of intermittent HF-rTMS and one becoming seizure free for 2 weeks. Both patients demonstrated a decrease in seizure-related hyperperfusion on single photon emission computed tomography (SPECT).[39]

A series of five patients with intractable focal epilepsy received LF-rTMS over 3 months with modest efficacy.[11] Collective reduction in seizure frequency was 23%, but only one individual within the group demonstrated a significant reduction, which was 43%. The others showed no significant change in mean daily seizure number. In a series of nine patients with various types of focal epilepsy, 1,000 pulses of LF-rTMS were delivered to the vertex daily for 5 days. This produced a seizure frequency reduction >50% for three patients, a 20% to 50% reduction for three patients, a 20% reduction for one patient, and no improvement for the remaining two patients.[133] Those who benefited continued at the reduced frequency for 6 to 8 weeks. A series of seven patients with extratemporal lobe epilepsy received stimulation with 810 pulses of LF-rTMS daily for 5 days.[59] The average frequency of complex partial seizures decreased by 36%, but the decrease in total seizures did not reach statistical significance.

Theodore et al. delivered 30 minutes of LF-rTMS each day for a week to the scalp over the identified epileptic focus in a series of 24 patients.[135] Using a controlled, blinded study design, they observed a 36% reduction in seizure frequency for those patients with neocortical epilepsy and a 12% reduction for those with mesial temporal lobe epilepsy, but the difference was not statistically significant. A similarly designed study with baseline, intervention, and follow-up periods included four patients and observed a seizure frequency reduction >50% in three patients.[115] This study differed from the prior by focusing the stimulation with frameless stereotaxy at a well-defined epileptogenic region, which may explain its more uniform results.

Conclusion

Overall, rTMS has demonstrated promise as a treatment for some forms of epilepsy. The rapid decrement of magnetic field strength with distance suggests that rTMS might be most useful with superficial epileptogenic regions, such as with cortical dysplasias. Further development of rTMS as a treatment will require controlled studies that are designed to determine efficacy and identify patient characteristics that are most associated

with successful treatment. Technical development of rTMS should establish optimal stimulation parameters for affecting seizure frequency by addressing the questions of stimulation intensity, frequency, duration, and targeting. If future clinical investigations identify rTMS methods that produce consistently superior seizure control results, epilepsy care would have the additional benefit of gaining a safe and highly tolerable treatment.

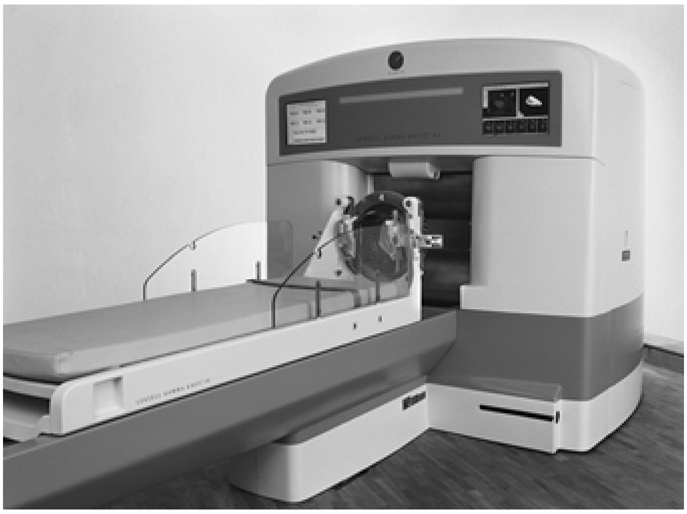

FIGURE 3. A Gamma Knife device. The large housing shields the radioactive cobalt sources. The hemispherical helmet shields the patient from extraneous radiation and contains the collimators that focus gamma radiation to create the surgical lesion. (From Kinoshita M, Ikeda A, Matsumoto R, et al. Electric stimulation on human cortex suppresses fast cortical activity and epileptic spikes. *Epilepsia.* 2004;45[7]:787–791.)

Table 2 Remission of Seizures Following Radiosurgery of Arteriovenous Malformations

Study	Method	Subjects	Total	*N* epilepsy	Remission (%)
Heikkinen et al.[47]	PB	Adults	129	29	16 (55%)
Steiner et al.[127]	GKS	Adults	247	59	41(69%)
Gerszten et al.[35]	GKS	Children	72	15	11 (73%)
Kurita et al.[66]	GKS	Adults	35	35	28 (80%)
Total				138	96 (70%)

PB, proton beam accelerator; GKS, Gamma Knife irradiation.

Gamma Knife Radiosurgery

Gamma Knife radiosurgery (GKS) allows performance of precise radiosurgical lesions deep or adjacent to eloquent cortex or other regions of the nervous system that cannot be accessed easily by conventional surgical approaches. In addition, its ability to target functional lesions noninvasively may be advantageous for select patients. On the other hand, use of GKS requires precise localization of the epileptogenic brain region, which means that its noninvasive advantage becomes somewhat moot in syndromes that require invasive localizing techniques.

Relevant background on Gamma Knife history and methodology can be found in the cited reviews.[33,71] Briefly, the Gamma Knife stereotactically projects multiple gamma radiation sources onto brain lesions (Fig. 3). Whereas the individual sources of radiation are too weak to damage intervening brain tissue, a lesion within the common focus is exposed to high-intensity radiation. It is not known how irradiation produces an antiepileptic effect. Massive necrosis of neuronal tissue does not seem to be a requirement, as the major pathologic findings following irradiation are endothelial damage to small blood vessels and astrocytic reactions.[150] One hypothesis, therefore, is that neuronal damage results from ischemia caused by vascular inflammation.[120] In addition, some neurons (e.g., hippocampal neurons) may show differential susceptibility to irradiation or ischemic injury.[140]

The main use of GKS is in the treatment of tumors[117] or arteriovenous malformations (AVMs)[35,47,66,127] that are inoperable with standard neurosurgical techniques. In patients with tumors, it is difficult to separate the effects of GKS as an antiepileptic procedure from its beneficial effects on the primary lesion. The potential efficacy of GKS in the treatment of symptomatic localization-related epilepsies is most evident in the treatment of AVMs. Steiner et al. reported that 69% of patients with recurring seizures due to an AVM became seizure free after GKS.[127] Nineteen percent successfully discontinued all anticonvulsant medications. Subsequent studies of both proton beam and GKS showed a combined rate of 70% seizure remission following Gamma Knife treatment of AVMs (Table 2).

Table 3 Results of Published Clinical Trials of Gamma Knife Surgery for Mesial Temporal Lobe Epilepsy[a]

Study	*N*	Dose (Gy)	Volume (mL)	F/U (months)	Seizure-free
Régis et al.[103]	7	25	6.25–6.9	24	6 (86%)
Régis et al.[105]	21	24	5.5–9.0	24	13 (62%)
Srikijvilaikul et al.[125]	5	20	6.1–8.7	24	0 (0%)
Cmelak et al.[16]	1	15[b]	NA	12	0 (0%)
McDonald et al.[86]	5	20–24	4.3–5.2	27	NA
Kawai et al.[56]	2	18	6.2–8.7	18	0 (0%)

[a] Treatment dose and volumes are estimated at the 50% isodose limit.

[b] Linear accelerator, dose, and volume at 57% isodose limit.

Steiner et al. noted that seizures remitted independent of radiologic remission of the AVM,[127] a finding that suggests that the focal effects of irradiation, rather than the improvement of the lesion itself, may be antiepileptogenic.

The utility of GKS has also been studied in patients with epilepsy due to lesions such as hypothalamic hamartomas[26,85,101,141,142] or cavernous angiomas[76,102] that are difficult to excise using traditional surgical techniques. Régis et al. conducted a multicenter, retrospective survey of ten patients treated with GKS for hypothalamic hamartomas.[101] Four subjects were seizure free in follow-up durations between 12 and 71 months, although two subjects required two treatments to achieve this success. Two other patients “significantly improved.” No postsurgical morbidity was reported. Preliminary data from a prospective study show that in 27 patients with at least 3 years' follow-up, 37% are seizure free.[106]

There are no published data on the use of GKS for functional neocortical lesions. Because localization of seizure onset in these cases usually requires invasive techniques, the noninvasive nature of GKS loses some advantage.

Mesial temporal lobe epilepsy (MTLE) has received much attention in terms of GKS treatment. Unlike nonlesional neocortical epilepsy, MTLE is commonly diagnosed noninvasively, which makes GKS especially attractive. Furthermore, seizures caused by epileptogenic tumors within the temporal lobe remit in greater rates than seizures associated with extratemporal tumors;[117] the success of GKS in treating space-occupying temporal lesions suggested that temporal lobe epilepsy with

functional, rather than space-occupying, lesions might benefit as well. However, initial attempts in Sweden with Gamma Knife[75] and elsewhere with the use of fractionated radiotherapy and other techniques[2] were not encouraging. The first surgical series employing radiosurgery in a systematic fashion was reported by Talairach,[129] who treated 44 patients between 1959 and 1973 with the use of yttrium.[90] With a mean follow-up of 5.7 years, Talairach reported a 75% rate of seizure freedom for patients with temporal lobe epilepsy.[129]

Régis et al. revived interest in GKS of MTLE when their preliminary studies showed short-term seizure-free rates of >80%.[103,104] These early reports suggested that GKS might offer rates of efficacy that were comparable to standard anterior temporal lobe (ATL) resection. Their prospective multicenter European trial of 21 participants demonstrated a 62% intent-to-treat seizure-free rate at a minimum of 2 years' follow-up.[105] Small case series differ in treatment protocols and results, with most failing to achieve complete remission from seizures.[16,56,86,125] Currently, a U.S. National Institutes of Health (NIH)–sponsored multicenter trial headed by Nicholas Barbaro of the University of California at San Francisco is ongoing.

Published trials are summarized in Table 3. The variability in results of GKS therapy for MTLE underscores the difficulties in clinical research in the determination of basic parameters of anatomic target, dose, and target volume. Anatomic targets in GKS of MTLE are the least variable factor. All studies in Table 3 specify that the 50% isodose volume (the volume encompassing at least 50% of the total radiation) contains regions thought most important in generation of mesial seizures, the amygdala, the head and anterior body of the hippocampus, and the parahippocampal gyrus.[149] Dose (measured in units of radiation absorbed, Gray [Gy]) and lesion volume are more variable among studies. Dose intensity and volume are difficult to extrapolate from animal[14,84] to human protocols. However, comparison of the studies listed in Table 3 suggests that low-dose protocols are less successful than are higher-dose protocols. Dose/volume-response curves extracted from early trials (Fig. 4) suggest a narrow therapeutic window between efficacy and potential toxicity.[103,104]

The ongoing NIH multicenter study will help evaluate the effect of radiation dose volume in that treatment volumes should exceed 5.5 mL, below which GKS was inefficacious, and stay below 7.5 mL, above which postoperative edema appeared too severe. In the current protocol, patients are randomized into 20-Gy or 24-Gy treatment arms. Régis et al. have outlined the typical postoperative course.[103,104,105,107] No significant changes typically occur in seizure frequency or neuroimaging for 9 to 12 months.[103,104,105,107] Nearly all patients experience transient exacerbations in auras or seizures before seizures decrease or remit.[105] The most dramatic drop in seizure rate occurs between 12 and 18 months, coinciding with the development of maximal MRI changes (Fig. 5).[105]

Morbidities of Gamma Knife therapy for MTLE include visual field deficits in 52% of patients, mostly quadrantanopsias, as to be expected after standard ATL resection. One subject had a hemianopia (indicating direct involvement of the optic tract) and another had mixed deficits.[105] Other “transient minor morbidities” consisted of headache, nausea, vomiting, and depression. Headache requires special comment, as it coincides in some subjects with postoperative edema.[105] Steroids, either in response to symptoms or in response to MRI changes, were used in the majority of patients presented in Table 3, but no clear evidence in these studies stand out either for steroid initiation, its effectiveness in treating symptoms, or its effects on eventual seizure remission. In fact, Régis reported that eight subjects were not treated with steroids at any point in the postoperative course.[105]

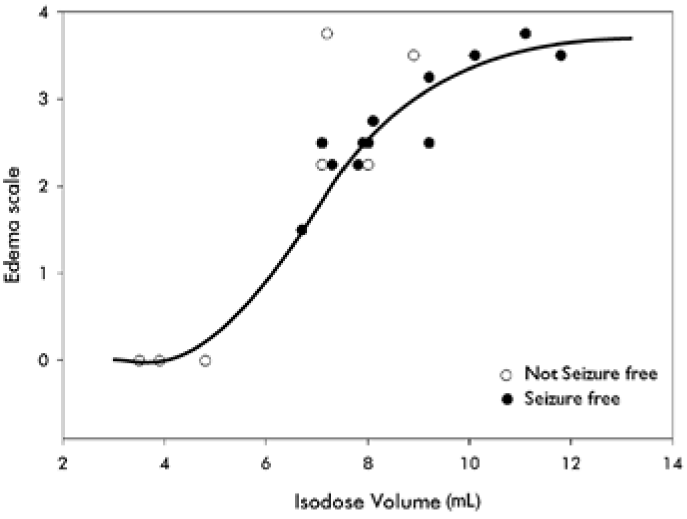

FIGURE 4. Dose-volume response curve of 24-Gy doses of Gamma Knife treatment of mesial temporal lobe epilepsy in early trials (Régis J, Peragui J, Rey M, et al. First selective amygdalohippocampal radiosurgery for 'mesial temporal lobe epilepsy.' *Stereotact Funct Neurosurg.* 1995;64[Suppl 1]:193–201; and Régis J, Bartolomei F, Rey M, et al. Gamma knife surgery for mesial temporal lobe epilepsy. *Epilepsia.* 1999;40:1551–1556). The y-axis indicates the peak severity of transient postradiation changes, mainly edema, that emerge in treated subjects 9 to 15 months postoperatively and slowly resolve. The x-axis indicates the 50% isodose volume of a 24-Gy exposure. (Figure created from data courtesy of J. Régis.)

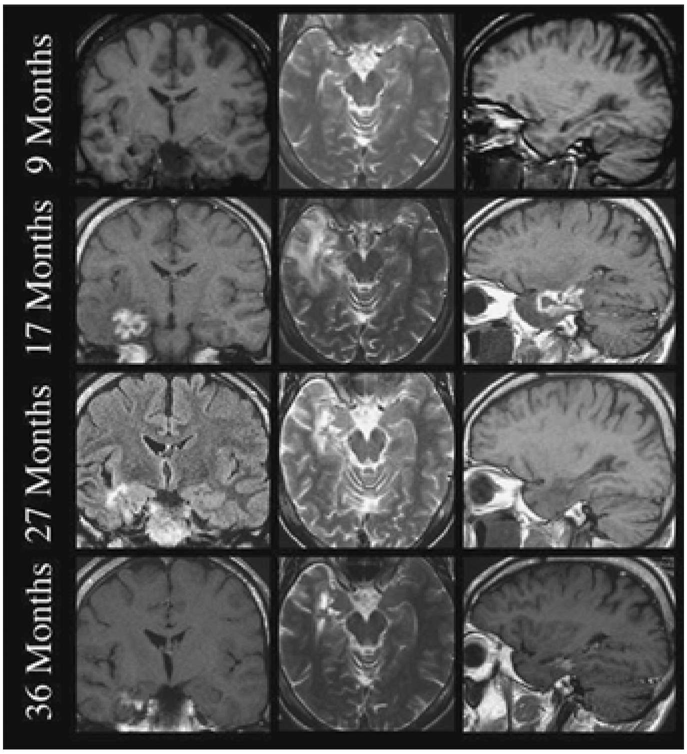

FIGURE 5. Time course of mesial and ipsilateral hemispheric changes following Gamma Knife surgery for mesial temporal lobe epilepsy at 9, 17, 27, and 36 months postoperatively. In this example, no changes are present at 9 months. At 17 months, contrast enhancement surrounded by high T2 signal changes is

evident, along with some minimal mass effect and T1 intensity changes of the temporal lobe. At 27 months and 36 months, changes begin to resolve, leaving a small region of contrast enhancement at the dose center. (From Régis J, Rey M, Bartolomei F, et al. Gamma knife surgery in mesial temporal lobe epilepsy: a prospective multicenter study. *Epilepsia.* 2004;45:504–515.)

One important factor is that the delayed effect of treatment may expose patients to the continued morbidity of ongoing seizures, including sudden death in epilepsy and traumatic injury. Two deaths occurred during the latency period in a case series of five subjects treated with “low-dose” radiation.[125] Future trials of GKS may need to consider supplementary seizure prophylaxis during the period of transient exacerbation of auras and seizures.

Beyond seizure efficacy, studies have begun to evaluate secondary outcome measures such as cognition and quality of life. There are three reports of neuropsychological outcome following GKS for MTLE: The previously noted prospective, multicenter trial[105] and two studies of small series of participants.[86,125] Prospective trial results report no mean neurocognitive changes through a 2-year follow-up period.[105] Similarly, Srikivilaikul et al. reported no group mean changes at 6 months' follow-up, although some individuals showed decline in at least one cognitive domain.[125] McDonald et al. reported on 27-month follow-up in three participants who underwent dominant hemisphere low-dose GKS treatment.[86] No long-term consistent changes in neurocognitive parameters were found, although each patient showed decline in a measure of verbal memory. They concluded that neurocognitive changes following GKS appeared similar to those of standard ATL resection.

In summary, recent trials suggest that certain protocols of GKS for MTLE may offer seizure remission. Further work is needed to clarify whether remission rates or neurocognitive outcomes following GKS are comparable to those following ATL resection. One distinct disadvantage of GKS is the approximate 12-month latency period required while the radiosurgical lesion develops. However, the noninvasive nature of GKS may prove to be an advantage to those who fear craniotomy or those with comorbid medical conditions that may prevent full anesthesia. Another potential advantage, yet to be fully explored in the clinical arena, is the ability to reduce seizures with less than a lethal effect on brain tissue in the seizure focus. Whether this will allow preservation of functions that are at risk from surgical resection remains to be determined.

Focal Delivery of Antiepileptic Drugs

Some of the side effects of antiepileptic drugs derive from actions at the periphery, for example, suppression of blood counts, hepatic or renal toxicity, or rash. Delivery of drug directly to the seizure focus in the brain might improve the therapeutic:toxic ratio of the medication. Direct delivery to the brain also could allow higher doses of drug than would be tolerated by systemic administration. Additional potential benefits include obviating the need for good oral absorption, penetration of the blood–brain barrier, and concern about drug sequestering in fat stores. Several interesting methods have been explored for focal drug delivery to the brain to better control seizures.[28]

One approach is delivery of drug to the cerebrospinal fluid, either via a ventricular catheter or a lumbar intrathecal catheter. The latter is less invasive, but may not distribute drugs to the ventricular system and periventricular brain. A key issue with intracerebroventricular delivery of medication is degree of penetration into brain. Such penetration is very slow when mediated by passive diffusion, but it may be facilitated by convection secondary to pulsatile pressure of cardiorespiratory rhythms.[10] Several studies have evaluated acute administration of antiepileptic drugs into spinal fluid during acutely induced seizures in animal models. Two studies have looked at chronic perfusion via an osmotic pump implanted subcutaneously in rats. One[119] evaluated valproic acid in a kindling model of epilepsy. Another[96] assayed efficacy of gabapentin in the fluorothyl seizure model in the rat. Both studies showed efficacy and reasonable tolerability in the model systems.

Antiepileptic drugs (AEDs) can be delivered via catheters placed over or into a seizure focus. These catheters can continuously perfuse medication, on a programmable schedule (e.g., for patients who might have more seizures during sleep), or in response to seizure detection/prediction algorithms.[126] Trials of focal drug perfusion for epilepsy have not yet been published in a clinical setting, in part because long-term safety and determination of the best medication to use are not fully accomplished. This does, however, remain a promising new approach.

A liposome is a fatty bag of medication.[138] Drug diffuses from the liposome over days to weeks. Targeting mechanisms, consisting of antibodies or receptor-binding agents, can be attached to the liposome so that the liposome adheres to a region of interest. Similar technologies exist for preparation of microsomes from synthetic materials. In neurologic disorders, a key issue is delivering a liposome across the blood–brain barrier. One strategy for doing so is to link it to a transport mechanism, such as for transferrin.[123] Liposomes and microsomes are of proven utility in some cases of infection and neoplasm, but they yet remain to be shown useful for human epilepsy.

Polymer wafers are engineered to release drug from a supporting chemical matrix over a period of months. The strategy has been useful in delivering chemotherapy for malignant brain tumors, as with the Glidel wafer.[12] Tamargo et al. showed that wafers containing phenytoin were active against seizures in a rat cobalt epilepsy model.[130] Whether the time course and efficacy of such wafers will be suitable for human AED therapy remains to be determined.

Medications can circulate systemically in a prodrug inactive state, until activated by a substance released at a seizure focus. One such interesting medication is DP-VPA, which requires action of a phospholipase to cleave a phospholipid moiety from valproic acid.[68] Phospholipase-A2 is elevated at a seizure focus, resulting in locally high concentrations of valproic acid. A small, double-blind clinical trial showed a 30% reduction in seizures during the first 28 days.[111]

Biologic machinery can be harnessed to produce locally renewable supplies of antiepileptic medications, either by cell transplantation or by genetic engineering. These approaches are considered in the subsequent sections.

Transplantation for Partial Epilepsy

Cellular engineering and transplantation have developed to a stage potentially useful for the treatment of neurologic disorders, including epilepsy.[15,38,41,53,63,80,110,121,124] Soon we will be able to use pluripotent stem cells to differentiate into any desired cellular line. Until then, work with other cell lines, such as GABAergic cells derived from neonatal pigs, may serve to test such issues as the ideal location for transplanted cells; the dose or number of cells that are necessary to give a prolonged response; whether GABAergic cells are a reasonable choice or another cellular line is preferred; and whether it is necessary to use immunosuppression on the host. This section broadly reviews the topic of cellular transplantation in the treatment of partial epilepsy in animals and in the one completed “proof of concept” study.

Transplanting cells into a region of epileptic seizure onset represents a novel approach to therapy of seizures. Cellular transplantation techniques might be a reasonable and acceptable alternative to excisional surgery for medically intractable partial epilepsy. In this scenario, the cell line that appears to be most affected by the specific seizure disorder could be grown or harvested, pretreated in such a way as to block a host rejection reaction, implanted through neurosurgical stereotactic means, and allowed to mature. With this model, the transplanted cells sprout and establish synaptic connections in the epileptic brain, allowing for that region to regain self-control over excitability. Such a therapy treats epilepsy, not just seizures, as the manifestations of the disorder.

Several questions come to mind about cellular transplantation for partial epilepsy. Many of these questions were raised during discussions of treatment of Parkinson disease with dopamine-producing cells. What are those concerns? First, what cell line is best suited to treat epilepsy? Cells that primarily produce GABA should be considered. However, dopamine-producing cells, serotonin-producing cells, and others have been tested in animal models for partial epilepsy.[49] Second, what should be the source for these cells? In the Parkinson literature, a number of studies were carried out using aborted fetal tissue.[46] Is this possible for the epilepsy patient? Can we use stem cells? In that case, should they be embryonic,[50] bone marrow,[99] or neuronal in origin? Would they need to be from related or unrelated individuals? What about cells from another species? Xenotransplantation has been used for years, yielding, for example, commonly used porcine heart valves.

Cells used for transplantation must be readily available if this is to be a widely utilized procedure. That, in conjunction with current ethical issues, makes the use of aborted fetal tissue highly unlikely for the near term.

For similar political and ethical reasons, embryonic stem cells are unlikely to be considered candidate sources even though they have many potential advantages. The cells that are transplanted should have a life expectancy similar to the recipient. This is probably not a problem for most human-derived stem cells but may be a limiting factor for xenotransplants, unless one chooses animals with fairly long life spans. The cells will need to be transplanted at a developmental time when they are no longer able to divide (postmitotic) but have not yet sent out extensive branching. Stem cell research has not yet progressed to the point where, when cells are induced to develop along a specific cell line, one can assure the recipient that there is no danger that the cells will continue to divide and reproduce in an uncontrolled fashion. Stem cell research cannot be attempted in humans as a treatment until the issue of uncontrolled reproduction is resolved. Stem cells could be harvested prior to the stage of axonal and dendritic sprouting. In so doing, the cells would be given maximum likelihood to both survive and make appropriate synaptic contact. Xenotransplant cells also can be harvested at a developmental stage when they are postmitotic but have rudimentary processes.

Would the recipient require immune system modulation to allow survival of the transplanted cells?[54] If stem cells come from unknown donors or distant relatives or if xenotransplant cells are used, some type of immunologic modulation will be required to prevent a host-versus-graph rejection reaction. On the other hand, if cells can be harvested from the recipient, grown, and differentiated, they can be given back without the need for immunologic manipulation. Immunomodulation usually utilizes one of two common approaches. In one, the physician pretreats and continues to treat the recipient with an immunosuppressive drug or drugs, for example, cyclosporine. Alternately, the physician treats the donor cells with an incomplete monoclonal antibody directed against the main histocompatibility receptor class I site (MHC-I) on the neuronal membrane. These sites are the main sites that, when activated, will trigger the rejection reaction that will ultimately kill the cell. Young cells and xenotransplant cells stand a better chance for survival than do fetal-derived cells using this technique, because of increasing membrane density of these sites with cell maturation. Studies have shown that ultimate cell survival is about the same with either of these two approaches. Lifelong immunosuppression is not benign, and some immunosuppressants are proconvulsant.

If xenotransplant cells are used, what animal should serve as the source? The considerations are that the source animal should have a reasonable life expectancy compared to humans so that the donated cells may live for the natural life of the human into whom they are transplanted. The source should be plentiful and not create undue social or ethical concerns. Higher primates have some advantages, but they are neither plentiful nor without ethical concerns. The animal should be one that has lived among humans for a long part of our natural history, so that we have been exposed to diseases that are specific to that species and vice versa. One major safety concern is that the exposure of the human recipient population to a new and previously unseen endogenous retrovirus could unleash a major public health threat. Given all these factors, the pig became the species of choice. Mankind has been exposed to pigs and their diseases for centuries. We are aware of and can treat most of the other disorders seen in pigs, and the pig's anatomic and neuronal physiology is very similar to that of humans. Pigs carry a risk of endogenous retrovirus (PERV), but this risk is well known. Humans have been exposed to and in some cases have contracted PERV infections without serious consequences. However, risks from new or previously undiscovered PERVs cannot be quantified. Pigs can be raised under favorable breeding conditions for medical needs.

GABA is present in approximately 60% to 70% of all synapses in the CNS and is the major inhibitory neurotransmitter. GABA-mediated inhibitory pathways are important in the regulation of seizure activity.

Focal-onset epilepsy appears to often be associated with loss of local inhibitory cells. Transplanting GABA-producing

cells to the region of a seizure focus theoretically would provide a biologically active source of inhibition for an indefinite period of time, with little to no systemic side effects. GABAergic cell transplants have been evaluated as antiepileptic therapies in hippocampus, cingulate gyrus, cerebellum, olfactory regions, and septal regions[6] of animal models. Secondary epileptic brain regions also may provide useful targets for transplants.[6,24,81,83]

Fetal porcine cells for transplantation are derived from the lateral ganglionic eminence, an area rich in GABAergic cells.[51] Cells of this lineage previously were reviewed by the Food and Drug Administration (FDA) for the treatment of Huntington disease and of stroke.[114] In animal studies, fetal porcine GABAergic neurons survive following transplantation and continue to express the enzyme required for the synthesis of GABA. The gestational age E 31 to 38 is ideal for harvesting these cells because the cells are postmitotic and have not yet started to send out processes. Studies in animal systems have showed cell survival and migration within certain boundaries.[23] Cells establish synaptic contacts and functional interactions within the local environment.[32] Studies compared cyclosporine treatment and mouse monoclonal antibodies to multiple cloning site 1 (MCS-1). Techniques were developed to determine the level of cell survival and neuronal growth, as well as neuronal integration. In postmortem slides of animal work, stains that recognized porcine repetitive element DNA could easily dissociate the graft and host cells. This technique, while showing survival of the porcine cells within the transplant, did not differentiate between those that were neuronal versus those that were glial elements. Therefore, superimposed upon this stain were porcine glial stains, which identified the glial elements. Neuronal elements themselves could be stained with a specific neurofilament stain. GABAergic origin was documented with an anti–glutamate decarboxylase (GAD) stain. Finally, stains that were specific for new neuronal synapse formation (i.e., synaptobrevin) could clearly differentiate cells that established synaptic contact with existing cells.[27,51] What could not be determined is whether these cells behaved as they would in normal circumstances.

We initiated a “proof of concept” study for porcine GABAergic transplants with individuals who were 18 years of age or older, who had a longstanding history of medical refractory frontal or temporal lobe seizures. The seizure focus onset had to have been localized via invasive EEG testing and found to be surgically treatable. We asked that the exclusion criteria include anyone with a treatable etiology for their seizures, anyone with multifocal-onset seizures, or those who had a history of psychosis associated with GABAergic-enhancing medications. Anyone with a progressive CNS lesion or with a history of status epilepticus within 3 months of the transplant was excluded. Eligible patients had to agree to delay their surgery for a period of 6 months and have the implantation procedure.

Transplants were accomplished using cells from the lateral ganglionic eminence of gestational age 31 to 38 pig fetuses, microscopically dissected and treated with a mouse-derived monoclonal antibody against the MHC-1 sites. This resulted in a suspension with a concentration of 100,000 cells/μL. Approximately 4 μL of this suspension, representing about 500,000 cells, was infused along the line of the electrographically determined epileptogenic zone. A flexible cannula was passed through the depth electrode on one occasion but the tip of the electrode was occluded. Subsequent implants used a cannula guided by stereotactic techniques.

Patients were monitored for adverse events, including PERV exposure, and to obtain preliminary seizure data. At the time of excisional surgery, porcine cell survival and connectivity were evaluated in three subjects, two with mesial frontal lobe foci and one with mesial temporal-onset epilepsy. None of the three suffered any physical or neurologic deterioration during the time of the transplantation. Blood chemistries, hematologic status, and AEDs were monitored regularly. Blood specimens were sent for and then stored for evaluation of PERVs.

Two of the three patients underwent their planned surgical procedure. The patient with mesial temporal-onset seizures was found to have mesial temporal sclerosis. This patient unfortunately died an unobserved death of unknown etiology. No surviving porcine cells were found or identified. The second patient had a mesial frontal removal done at about 9 months following the implantation. He had delayed his surgical removal date because he and his family were convinced that he had fewer seizures and the ones that did occur were milder. He, too, had no visible surviving GABAergic transplanted cells. The third patient maintained a transplant for over 4 years and, for the last 3 years of that time, had no recorded seizures and required no significant medicine changes. Unfortunately, this patient died in association with acute AED withdrawal, when his pharmacy was unable to renew his prescriptions over a long holiday weekend. The family refused postmortem examination.

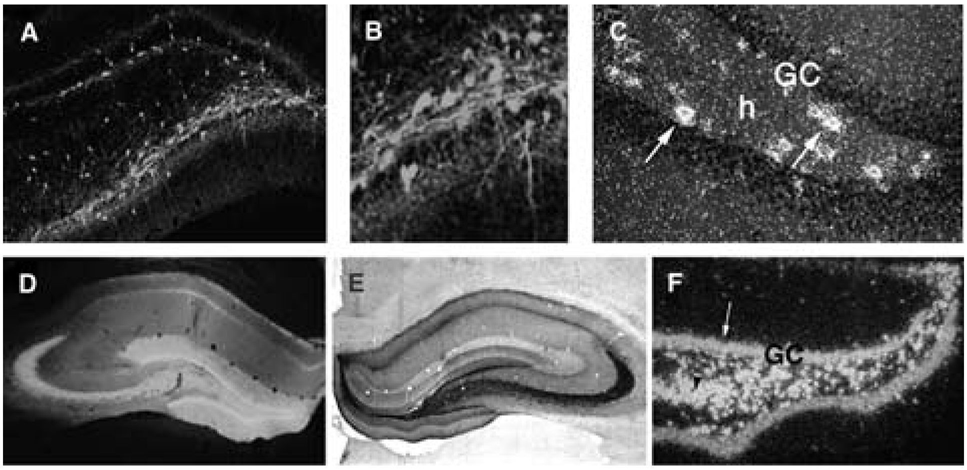

FIGURE 6. Influence of viral serotype on green fluorescent protein (GFP) and neuropeptide Y (NPY) expression in the rat hippocampus. Serotype 2 adeno-associated virus (AAV) induces transgene expression specifically in hilar interneurons with a spread of about 1.5 mm around the injection site. Panels **A** and **B** depict GFP in hilar interneurons and their fibers. Panel **C** depicts NPY mRNA in hilar interneurons (*arrows*). Note that granule cells do not express the transgene. Chimeric serotype 1/2 induces a larger transgene expression including hilar interneurons, mossy fibers, and granule cells with an extension of approximately 2.5 mm around the injection site. Panel **D** illustrates GFP distribution throughout the hippocampus. Panels **E** and **F** show NPY immunoreactivity and its mRNA, respectively. Note that an intense hybridization signal is observed in granule cells (*arrow* in **F**) and CA3 (*arrowhead* in **F**). Transgenes were selectively expressed in neurons since they were under control of neuronal enolase promoter. GC, granule cells; h, hilus. (See the color insert.)

Our "proof of concept" study suggests that it is feasible to identify a subset of potential surgical excisional patients for possible transplantation, although the numbers in the pilot study were small. Mesial frontal seizures without identifiable lesions, a condition that is relatively well known to have a higher than usual surgical failure rate, did seem to respond, whereas mesial temporal sclerosis, a condition where the surgical treatment has excellent outcome results, failed. No adverse effects resulted from the transplants themselves. No new PERV infections emerged. Cell survival and synaptic connectivity in the patients are unknown. The patients with frontal epilepsy had a response similar to that described for implanted latex beads soaked in GABA. Seizure reduction lasted for about 2 weeks, faded, and then reappeared. Speculatively, the delayed response was associated with cell survival and secretion of GABA.

A number of concerns need to be considered prior to further clinical trials. The "proof of concept" study demonstrated that this approach is feasible, but evidence was insufficient to prove that the technique produced the desired effect in the recipient. The study failed to show that these transplanted cells survived or functioned. One of the three cases, however, had a lasting improvement in seizure control, which significantly raises hope. Given the progressive nature of uncontrolled or poorly controlled partial epilepsy, techniques that use xenotransplant cells or stem cells are likely to be tried in the near future. The potential for success appears to be substantial.

Gene Therapy

Gene therapy techniques as a treatment for epilepsy involve the transfer and expression of a gene into the ictogenic brain region or regions, resulting in a long-lasting production of a "therapeutic" molecule endowed of potential antiepileptic action. In principle, patients with intractable seizures of focal onset may benefit from gene therapy approaches that are alternative to resective surgery, offering the possibility to deliver specific "therapeutic" genes directly into the brain area where seizures originate.

The generation of viral vectors transducing neurons, and of other in vivo gene transfer methods, provides attractive strategies for introducing and stably expressing novel genes into the brain.[20,93] Moreover, recent experimental evidence in rodents provided a proof of principle for the applicability of these strategies for inhibiting seizures and rescue neurons from irreversible damage. These two therapeutic outcomes should lead to sparing of function at the level of synaptic transmission, plasticity, behavior, and cognition. Crucial aspects that

contribute to determine the success of a gene therapy approach include the methods of gene delivery, the strategies for improving cell transfection, and the expression of the specific gene, and circumventing possible adverse host tissue reactions to the transgene.

Therapeutic Targets and Delivery Methods

Experimental approaches to gene therapy in rodent models of seizures have characterized several candidate genes that may provide targets to inhibit seizures, including neuropeptides, such as galanin, cholecystokinin, and neuropeptide Y; inhibitory neurotransmitters, such as GABA and adenosine; and *N*-methyl-D-aspartate (NMDA) receptors (for review see reference 95). Neuroprotection from the damaging effects of seizures or prevention of progressive cell loss that may predispose to epileptogenesis also are important aspects that should be considered in the context of a gene therapy approach to epilepsy. Using in vitro and in vivo models of cell death, neuroprotection has been achieved by inducing overexpression of antinecrotic and antiapoptotic genes, neurotrophins, and Glut-1 glucose transporters or using vectors containing a synthetic glucocorticoid-responsive promoter exploiting the high levels of adrenal stress hormones secreted in response to injury.[25,42,87,98] Transgene expression has also provided in some instances recovery from physiologic and behavioral dysfunctions.[25]

Gene transfer can be achieved in vivo using viral vectors, naked DNA, or cation–lipid DNA complexes, or ex vivo using cells previously transfected in vivo with the gene of interest. Viral vectors are generally the most efficient for in vivo transfection since they permit long-term gene expression and can be engineered to preferentially target specific neuronal populations in a controllable manner.[22,52] However, they have size limitations for transgene inclusion in the expression cassette and are potentially immunogenic. Viral vectors such as adeno-associated virus (AAV) vectors, lentivirus, and herpes simplex virus have specific tropism for postmitotic neurons; AAVs have the best safety profile.[91]

Viral Vectors in Experimental Models

Neuropeptides

Attenuation of seizure and neuronal death in rats has been reported following brain application of AAV vectors mediating galanin and NPY expression and secretion.[43,74,109] Haberman et al.[42] engineered a viral vector carrying the secretory signal of the laminar protein fibronectin together with the galanin gene. The secretory signal improved galanin secretion and significantly attenuated in vivo focal seizure sensitivity in rat inferior collicular cortex; moreover, hippocampal hilar cell loss consequent to kainate seizures was prevented. Using a doxycycline-off, regulated AAV vector, this study demonstrated the feasibility of both controllable and long-term (up to 4 weeks) seizure attenuation. Lin et al.[74] adopted an AAV vector in which the galanin gene was driven by a neuron-specific promoter. This study showed long-lasting (up to 2.5 months) functional overexpression of galanin, specifically in hilar interneurons and their terminal projection fields, thus demonstrating that the peptide can be transported along axons even long distance from its site of synthesis. This restricted galanin overexpression resulted in powerful inhibition of seizures induced by intrahippocampal injection of kainic acid.

Richichi et al.[109] induced long-lasting NPY overexpression in the rat hippocampus by local application of AAV vectors with different serotypes. This study showed that enhanced gene transfection can be achieved by varying the capsid genes: Serotype 2 AAV vector increased NPY expression in hilar interneurons only, while the chimeric serotype 1/2 vector caused far more widespread expression including mossy fibers, pyramidal cells, and subiculum (Fig. 6). NPY overexpression resulted in kainate seizures inhibition, blockade of status epilepticus, and delay in kindling epileptogenesis.

N-methyl-D-aspartate Receptors

Haberman et al.[43] cloned an antisense cDNA fragment of the constitutive NMDA receptor subunit (NMDAR1) into an AAV vector, under the control of a cytomegalovirus (CMV) promoter *with or without* a tetracycline (TET)-off cassette. Three weeks after delivery into the inferior colliculus, a well-characterized site of focal seizure genesis, the NMDA-like immunoreactivity was significantly reduced. However, the threshold current for inducing wild-running seizures by electrical stimulation of the collicular cortex was raised only in the rats that received the AAV vector *without the TET-off cassette* since this vector transduced the primary excitatory-output neurons only. A paradoxic increase in focal seizure sensitivity was instead induced by the AAV vector *carrying the TET-off controllable promoter* since this vector primarily depleted NMDA receptors on inhibitory GABA interneurons, thus reducing the GABA-mediated inhibitory drive on excitatory output neurons. Thus, without a detailed knowledge of the transduction pattern in humans, manipulation of neurotransmitter receptors, or inference of ion channels, may lead to a paradoxic increase in seizure sensitivity.

Enzyme Replacement

In humans, a mutation-dependent deficiency of the aspartoacylase (ASPA) gene leads to Canavan disease, and 63% of these patients exhibit epileptic seizures.[139] The ASPA gene is involved in the hydroxylation of *N*-acetyl-L-aspartate (NAA), which has neuroexcitatory properties. This gene was inserted into a defective recombinant adenoviral vector under the control of a chimeric promoter (CAG promoter)[118] and intracerebroventricularly injected in spontaneously epileptic rats, which were obtained from cross-breeding of the tremor rats lacking the ASPA gene. The occurrence of tonic seizures was significantly reduced in these rats; however, this protective effect was lost within 2 weeks after the vector injection, possibly due to the induction of an immune response to this first-generation adenoviral vector. A recent study has shown that delivery of the ASPA gene using AAV vectors in tremor rats persistently attenuated seizures.[61]

Nonviral Delivery Systems

One of the main alternatives to viral vectors for gene transfer into CNS cells is represented by pegylated immunoliposomes carrying the plasmid DNA for expressing the exogenous gene. Using a brain cell–specific promoter and a targeting ligand that binds to a transporting receptor on the blood–brain barrier (i.e., a monoclonal antibody to the transferring receptor), it is possible to limit the expression of the exogenous gene to the brain.[122] The advantage of this delivery system is the possibility of systemic, thus noninvasive, application. However, the persistence, level of expression, and transduction efficiency of the transgene are limited compared to viral vector–mediated gene delivery.

Zhang et al.[151] used lipofectin reagent solution to transfer the CCK gene inserted into a plasmid under the control of SV40 promoter into the ventricles of rats with congenital audiogenic seizures. Seizures were markedly but very transiently decreased, likely because the plasmid was degraded by endogenous cellular nucleases.

Transplantation of Genetically Modified Cells

Cells can be engineered *in vitro* to produce and release a therapeutic molecule after *in vivo* transplantation in specific brain areas. GABA and adenosine have been used as therapeutic targets in cell transplantation approaches because of their well-established inhibitory actions on seizures in various models of epilepsy.

Huber et al.[49] engineered conditionally immortalized fibroblasts to secrete adenosine by inactivating the adenosine-metabolizing enzymes adenosine kinase and adenosine deaminase. These fibroblasts were encapsulated into semipermeable polymers and subsequently grafted into the brain ventricle of electrically kindled rats. Generalized seizures were completely suppressed in rats receiving the adenosine-releasing grafts. An important aspect of this approach was the lack of sedation or ataxia that otherwise was observed after systemic delivery of adenosine or its analogs. However, protection from seizures was limited to the first 12 to 24 days from grafting, apparently due to a decrease in cell viability within the graft. Genetically engineered GABA-producing cells have been obtained from conditionally immortalized mouse cortical neurons and glia[137] by using a plasmid carrying the cDNA for the GABA-synthesizing enzyme glutamate decarboxylase (GAD65), under the control of doxycycline-sensitive minimal human CMV promoter. The rats receiving neuron or glia-derived cell transplants producing GABA in the anterior substantia nigra showed a delayed kindling progression, while acceleration of kindling was observed if these cells were transplanted in the posterior substantia nigra, in analogy with the effects elicited by exogenous application of GABA agonists to the same brain areas. If GABA-producing cells from immortalized cortical neurons were implanted into the piriform cortex, the rats displayed a higher threshold for the induction of generalized seizures after amygdala kindling, but they did not show any alteration in the development of kindling.[34]

The rats that received GABA-producing cells into the substantia nigra 2 weeks after the induction of pilocarpine-induced status epilepticus had significantly fewer spontaneous seizures and suppression of epileptiform spikes. The engineered cells showed evidence of integration with the host, but ongoing cell degeneration was observed within 10 days.[136]

Thus, strategies for the generation of cells with enhanced viability such as introducing survival-enhancing genes (i.e., constitutive active immortalizing oncogenes or apoptosis inhibitors) are warranted to provide long-term anticonvulsive efficacy.

Conclusions

Although the studies in experimental models of seizures and epileptogenesis have shown the potential applicability of gene therapy approaches to epilepsy, an important issue that still remains to be fully addressed is the characterization of the efficacy of gene therapy in chronic epileptic tissue using models of spontaneous and recurrent seizures. Thus, chronic epileptic tissue often is characterized by neuronal loss, synaptic plasticity, and molecular changes that affect the target or targets of the “therapeutic” gene and reduce its effects. Direct gene transfer into human epileptogenic tissue from temporal lobe epilepsy patients has been done in vitro using an AAV vector to transfer and express a reporter gene. Histologic analysis showed expression of the transgene in neurons with no obvious evidence of toxicity.[31] One recent report showed that the incidence and duration of spontaneous seizures were indeed reduced in chronic epileptic rats following hippocampal application of AAV vector overexpressing NPY, and the disease progression appeared to be arrested.[95]

Another important consideration concerns the immune reactions that may be induced by the gene transfer (i.e., production of antibodies against the vector serotypes, promoter silencing, instability of the vector genome, and loss of transduced cells).

A crucial question in the context of clinical applications is the choice of a population of epileptic patients for a clinical trial. One possibility would be to select patients with temporal lobe epilepsy. At some stage before the resective surgery, the vector could be infused into the epileptogenic area and its efficacy could be evaluated before tissue resection.

In conclusion, the inhibitory effects on seizures and epileptogenesis and the evidence for neuroprotection in experimental models by specific transgene overexpression in CNS open the possibility of developing novel therapeutic strategies for the treatment and management of seizures at focal onset, such as temporal lobe epilepsy. In principle, with the rapid advancement in recombinant AAV technology, a clinical-grade vector could be stereotactically delivered directly to the seizure focus in patients. AAV-mediated inhibitory molecule expression someday might provide an alternative to surgical resection.

Summary and Conclusions

Proliferation of interest in and studies of nonpharmacologic therapies for epilepsy serve as testimony to the limits of medication therapies. Some nonpharmacologic therapies, such as epilepsy surgery, the ketogenic diet, and vagus nerve stimulation, are now part of standard care. Others are less accepted. This chapter viewed a diverse collection of alternative therapies for people with medication-refractory seizures.

Deep brain stimulation is a promising technique, but at the time of this writing, efficacy remains unproven. Regions of stimulation include the anterior thalamic nuclei, subthalamic nuclei, hippocampi, and direct stimulation of the seizure focus in cortex or elsewhere. Stimulation can be on a regular cycle, as in the pivotal ongoing trial of SANTE, sponsored by Medtronic. Alternatively, stimulation can be responsive to detected patterns in the continually assayed EEG, as with the responsive neurostimulation trial sponsored by NeuroPace.

Stimulation also can be delivered transcranially, via magnetic pulse, which sets up electric currents in the cortex. Although this approach is attractively noninvasive, the penetration of influence into the brain is limited, and documentation of clinical efficacy is so far mainly anecdotal.

Tissue ablation is possible with radiotherapy, commonly then known as radiosurgery. A linear single-beam approach delivers substantial radiation to points along the pathway. Modern stereotactic radiosurgery utilizes beam-crossing methods, either by lead helmets (Gamma Knife) or computer-driven rotating delivery arms (CyberKnife), to focus the high energy only where desired. In animal models and perhaps in humans, doses of radiation too low to cause tissue necrosis can have antiepileptic efficacy. If borne out by controlled studies, now under way, this would be a truly novel therapy. Skeptics note that adverse reactions from radiation are not evident in some instances for many years.

Focal delivery of AEDs to the brain seems to be a promising approach, mainly in terms of permitting very high local concentrations at a seizure focus, without engendering much distant toxicity. Animal experiments have been favorable in terms of reducing epileptiform spikes and seizures at a cortical or hippocampal seizure focus, but several practical issues are unresolved. How easy is it to localize a seizure focus and infuse it with drug? Can superficially applied drug eventually penetrate enough brain to make a difference? How can the catheters be kept open and working? Which drug should be infused? Will long-term exposure of brain tissue to drug lead to compensatory undesirable “rebound”? Much remains to be done before local infusion can be considered effective and safe.

Liposomal or microsomal delivery of drug is a natural extension of a delivery mechanism that is used now for antibiotics and antineoplastic medications. These delivery vehicles are “bags of drug” with a targeting device, either an antibody or receptor-binding agent. A liposome then homes to a site of interest, sticks, and slowly releases drug. No liposomal products are yet available for epilepsy, because of uncertainty about how to target a seizure focus and how to penetrate the blood–brain barrier. Strategies exist to surmount both of these problems and products may be expected in the future.

Two strategies have the potential of delivering renewable drug or neuromodulators to brain tissue: Cell transplants and gene vectors. Cell transplants tend to be eliminated by the immune system (possible exception in the case of stem cells) unless they are encased in protection. One study of treated porcine GABAergic neurons into the hippocampus of patients has provided proof of concept, but not yet evidence for efficacy.

Gene therapy can use viral vectors to introduce GABA, inhibitory neuropeptides, or antisense signals to excitatory receptors into the CNS. Viral vectors derived from adeno-associated or herpes virus are accumulating a safety record, despite well-publicized initial safety failures. An unsettled issue for clinical application is the efficiency of transfection, that is, how many brain cells incorporate the gene and produce product. What is the duration of production, since frequent brain injections would be impractical? Genes and resulting gene products have been documented in human brain tissue *in vitro*. The next step will be to extend the lessons learned to *in vivo* protocols.

This chapter does not attempt to provide a complete list of upcoming studies of nonpharmacologic therapies for epilepsy. Such an exposition is prohibited by space and by constant emergence of new ideas: Brain cooling, trigeminal nerve stimulation, biofeedback, and many more. If effective and safe, the therapies mentioned in this chapter will move from alternative to complementary.

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Chapter 135

Overview: Antiepileptic Drugs

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Introduction

This section addresses pharmacologic treatment of the epilepsies. Despite the availability of other treatments, including surgery, various devices, and behavioral/homeopathic treatments, antiepileptic drugs (AEDs) continue to be the mainstay of therapy for people with epilepsy. The overwhelming majority of individuals diagnosed with epilepsy will take AEDs for some period of time during the course of their illness, when they are available. Often, this treatment will last for decades and have a major impact on quality of life. There are currently over 20 drugs available for the treatment of epilepsy, and 10 were approved for use within the last 15 years. The availability of a large number of therapeutic options is advantageous for patients, but at the same time, this array increases the complexity of appropriate drug selection and management. The selection of antiepileptic drug is critical to the long-term well-being of the person with epilepsy, and this selection must be made with great care. In the absence of the “ideal” antiepileptic drug, it is optimal to have several reasonable choices in order to cover the great variability in types of epilepsy as well as individual patient characteristics. It is the intent of this section to provide important and useful information that will facilitate the selection of optimal treatment strategies.

Pharmacologic treatment of epilepsy has come a long way in the last century. Before the discovery in the mid-19th century that bromide could be used as a treatment for epilepsy, there was no useful treatment available for the disorder. Of interest, valproic acid existed as a solvent but was not identified as an antiepileptic drug for another 100 years.

Bromide was suggested as an AED in 1857, but for the wrong reasons. When Edward Sieveking presented 52 cases of epilepsy at the Royal Medical and Chirurgical Society in London, one physician, Charles Locock, mentioned that he had used potassium bromide to treat “hysterical” epilepsy, which usually occurred around menstruation (catamenial epilepsy today). It had also been reported that potassium bromide caused impotence in males, and the idea was that bromide would reduce sexual excitement in women and calm down epileptic activity, which, in fact, it did.[7] In 1912 phenobarbital was discovered, and it remains a useful AED today. It is also the major anticonvulsant agent used in veterinary medicine.

The German chemist Adolph von Baeyer synthesized “malonylurea” from a reaction of urea with malonic acid, a chemical found in apples. This became known as “barbituric acid.” Its discovery led to various derivatives, and by 1903 Fischer and von Mering had synthesized a therapeutic barbiturate that induced sleep.

Further development focusing on barbituric acid led to the synthesis of phenobarbital. Hauptmann's clinical studies in 1912 demonstrated both sedative action and anticonvulsant activity.[7] Various alterations in the phenobarbital molecule led to the discovery of benzodiazepines.[10]

The idea that compounds could be tested for anticonvulsant activity now gained a foothold among neurologists and psychiatrists, and this eventually led to more new treatments for epilepsy. After phenobarbital, the next drug to appear was phenytoin. Phenytoin (diphenylhydantoin) was first synthesized in 1908 by a German physician named Heinrich Biltz. He sold his discovery to Parke-Davis, which did not find an immediate use for it. In 1936, H. Houston Merritt and Tracy Putnam discovered phenytoin's usefulness for controlling seizures. Using an animal model of maximal electroshock (MES), Merritt and Putnam found that phenytoin could control seizures without the sedation of phenobarbital, and by 1938 it was marketed as a new antiepileptic drug in the form of Dilantin sodium. Nearly 75 years later, phenyt-oin remains one of the most effective AEDs for partial-onset seizures and is used as a main agent in the treatment of status epilepticus.

After the development of phenytoin, other drugs entered the market, with primidone being introduced in 1952.[11] It was synthesized by making a minor alteration in the phenobarbital molecule. Primidone's efficacy, like that of phenytoin, was established in the MES test developed by Merritt and Putnam. It appeared to have anticonvulsant activity that was independent of phenobarbital and also more effective.

Ethosuximide appeared in 1960, and carbamazepine in 1974. Valproate was accidentally recognized as an AED in the 1960s. As already noted, it had been available as a solvent for other AEDs for some time, but during testing in animal models it was found to be more effective alone than the experimental drugs thought to be of interest. Today, valproic acid is still among the most effective broad-spectrum AEDs available.

In 1969, the National Institutes of Neurological Disorders and Stroke (NINDS) initiated the Anticonvulsant Drug Development (ADD) Program under the leadership of J. Kiffen Penry. In 1975, as a response to the dearth of new compounds being identified for use in epilepsy, the Epilepsy Branch of the NINDS established the Anticonvulsant Screening Project (ASP) in collaboration with investigators at the University of Utah.[12,13] The problem at the time was that the pharmaceutical industry had almost no interest in developing AEDs, and the NINDS believed it had the responsibility of trying to stimulate corporate interest by identifying promising compounds through the drug screening program. The ASP's role was and still is to identify possible drug candidates and evaluate their antiepileptic potential in animal models. Subsequently, the ADD program would (and, to some extent, still does) take these candidate drugs forward into clinical testing. This collaboration was the first attempt to screen organic compounds systematically on a large scale in animal models as a means of discovering and then developing new therapies for epilepsy. To date, the ASP has

screened more than 24,000 compounds. The fact that we have a new generation of antiepileptic drugs available is in large part due to the direct influence and inspiration of the ADD program and the ASP.

There was a long gap between the introduction of valproate and carbamazepine and the next AED that received Food and Drug Administration (FDA) approval. The first of this “second generation” of AEDs was vigabatrin, whose development started in the 1970s in France. It was registered as an AED in 1989 in the United Kingdom. Vigabatrin represented one of the first attempts at mechanism-based drug development. It was designed specifically to increase brain γ-aminobutyric acid (GABA) levels by blocking the enzyme GABA transaminase, based on the underlying hypothesis that increasing the brain's major inhibitory neurotransmitter would control seizures. Progabide actually reached the market before vigabatrin, and it too was a GABA agonist developed based on mechanism. Progabide was marketed in France but never gained popularity because of its perceived weak efficacy. Vigabatrin, however, is still available. Because of serious toxicity causing concentric visual field deficits, it is rarely used now except for treatment of infantile spasms. Tiagabine, a GABA receptor uptake inhibitor, was also designed to increase GABA concentration and is an effective drug for partial-onset seizures. In recent years there has been an explosion in the development of new AEDs Gabapentin, felbamate, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, topiramate, and zonisamide have all reached the market since 1994. None of these has been developed exclusively based on a predetermined hypothesis of mechanism of action, although we have subsequently learned much about the anticonvulsant effects of these drugs.

Perhaps surprisingly, this wealth of newly available AEDs, many associated with novel mechanisms and improved pharmacokinetics, have not demonstrated superior efficacy compared to the older drugs in head-to-head clinical trials of newly diagnosed epilepsy. Rather, these trials have shown efficacy of the old and new AEDs to be equivalent.[1,2,3,4,5,6,14,16] The newer drugs often appear to have advantages related to safety, long-term side effects, and pharmacokinetics, but their benefit is harder to prove. In refractory patients, the newer AEDs reduce seizure frequency by up to 50% when added to pre-existing AEDs, but it is still rare for previously refractory patients to become seizure free.[9]

There are many questions to ponder regarding the future of AED therapy. Are better drugs in the pipeline? Is there a new “blockbuster” on the horizon? If so, where will it come from? Our understanding of the basic mechanisms of epilepsy and epileptogenesis is growing rapidly. Yet it is still unclear how these advances will lead to better drug development and improved seizure control in patients. Is selection based on efficacy in animal models the optimal way to search for new AEDs? Is the search for new mechanisms a methodology that will lead to more potent and safer therapies? Will the solution to drug resistance be better selection of drugs based on individual patient characteristics, or one drug that will benefit all? Perhaps the answer will not be the drug itself, but how it is delivered to its target. There has been great interest recently in addressing transport of AEDs across the blood–brain barrier, as well as in directed delivery of drugs to appropriate targets in the central nervous system.[8,15] Alternatively, targeted therapy that recognizes differences in individual patient response through pharmacogenomics may be an essential component to better therapy.[17] Until these advances are realized, however, optimal care will require a thorough understanding of available drugs, and how they can best be utilized on patient characteristics. The following chapters should prove useful in achieving that goal.

Summary and Conclusions

After a slow 100 year start in antiepileptic drug development, the last two decades of intense focus have substantially increased the number of antiepileptic drugs that are available to clinicians. It will be up to clinicians and clinical researchers to determine how to optimally utilize this resource. It is now more possible than ever to target therapy to individual patient needs and characteristics. Nonetheless new drugs are needed, particularly ones that target refractory patient populations.

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Chapter 136

Cellular Effects of Antiepileptic Drugs

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Introduction

Antiepileptic drugs (AEDs) protect against seizures through interactions with a variety of cellular targets, which include various ion channels, a neurotransmitter transporter, a neurotransmitter metabolic enzyme, and a synaptic vesicle protein. AED actions on these targets can be categorized into four broad groups:

1. Modulation of voltage-dependent ion channels (mainly sodium [Na] but also calcium [Ca] channels)
2. Effects on γ-aminobutyric acid (GABA) systems, including alterations in the cellular disposition of GABA and enhancement of synaptic inhibition mediated by $GABA_A$ receptors
3. Inhibition of synaptic excitation mediated by ionotropic glutamate receptors
4. Modulation of neurotransmitter release, particularly of glutamate, through presynaptic mechanisms.

A critical downstream effect of drugs that target voltage-dependent Na and Ca channels may be to selectively modulate glutamate release while only weakly affecting GABA release.[132] Thus, group 1 and group 4 actions overlap in that they represent mechanisms for the presynaptic regulation of glutamate release. The ultimate effects of the interactions at these diverse targets are to modify the bursting properties of neurons and to reduce synchronization in localized neuronal ensembles. In addition, AEDs inhibit the spread of abnormal firing to distant sites, which is required for the expression of behavioral seizure activity in localization-related epilepsies. Generalized absence seizures, unlike other seizure types, are believed to result from thalamocortical synchronization. Interference with the intrinsic rhythm-generating mechanisms that underlie the synchronized activity in this circuit is necessary to abort these seizures. This chapter discusses the specific actions or combinations of actions that are believed to account for the anticonvulsant activity of marketed AEDs. Each of the AEDs has its own unique pharmacodynamic properties. In some cases, the uniqueness results because the biophysical parameters governing the drug's interaction with its target are distinct. For example, phenytoin and carbamazepine both interact with voltage-gated Na channels, but the kinetic properties of the interaction are subtly different. In other cases, the AEDs act selectively on unique targets. For example, ethosuximide targets T-type Ca channels, vigabatrin targets GABA transaminase, tiagabine targets the GAT-1 GABA transporter, gabapentin and pregabalin target α2-δ proteins, and levetiracetam targets the SV2A synaptic vesicle protein. Finally, in other cases still, AEDs such as phenobarbital, felbamate, and topiramate have mixed actions on various targets; their unique properties as anticonvulsants result from the combination of effects on these targets. These various diverse actions confer on each AED a characteristic and unique clinical profile.[147]

Mechanisms of Action of Established AEDs

Phenytoin and Carbamazepine

Phenytoin and carbamazepine interact with voltage-dependent Na channels at concentrations found free in plasma in patients being treated for epilepsy.[96] Both drugs are highly protective against tonic seizures in animal models (as in the maximal electroshock [MES] test), but do not protect against clonic seizures (as in the pentylenetetrazol [PTZ] test). This profile of activity is typical of AEDs that act as Na channel modulators. Na channels are composed of an α subunit (Na_V1.1–1.9) associated with auxiliary β1-, β2-, or β3-subunits. An α-subunit is sufficient to form the channel and allow functional expression, but the kinetic properties and voltage-dependence of channel gating are modulated by the β-subunits.

Phenytoin and carbamazepine were demonstrated to reduce the frequency of sustained repetitive firing of action potentials.[106,107] The characteristic property of these drugs is that they do not reduce the amplitude or duration of single action potentials but reduce the ability of neurons to fire trains of action potentials at high frequency. The limitation of high-frequency repetitive firing is voltage-dependent, with limitation of firing increasing after depolarization and reducing after hyperpolarization. Once developed, the limitation of firing is prolonged, lasting several hundred milliseconds. The action of the AEDs appear to be due to a shift of Na channels to an inactive state from which recovery is delayed.

On mammalian myelinated nerve fibers, both phenytoin and carbamazepine produced a voltage-dependent block of sodium channels that could be removed by hyperpolarization, a shift of the steady-state sodium channel inactivation curve to more negative voltages, and a reduction in the rate of recovery of sodium channels from inactivation.[155] Sodium channels recovered from complete inactivation in a few milliseconds after a 500-ms depolarization to 25 mV. In the presence of 100 μmol/L phenytoin or carbamazepine, however, recovery was prolonged to 90 or 40 ms, respectively. At 50 μmol/L, phenytoin and carbamazepine each produced a frequency-dependent block. However, the frequency-dependent block produced by carbamazepine was somewhat less pronounced than that produced by phenytoin. Of interest was the finding that phenytoin had a longer time-dependence for frequency-dependent block and for recovery from block than did carbamazepine, which would result in a more pronounced frequency-dependent block for phenytoin than for carbamazepine. Thus, although phenytoin and carbamazepine have qualitatively similar actions on sodium channels, their actions are quantitatively somewhat different. This may explain, at least in part, differences in efficacy for these two drugs in different patients.

In rat hippocampal neurons, phenytoin (200 μmol/L) produced a 20-mV negative shift in the steady-state inactivation

curve for Na channels and produced frequency-dependent block of Na channels.[191] Frequency-dependent block was shown at frequencies as low as 1 Hz, and the block increased to 50% at 10 Hz.[191] It has been suggested that unbinding of phenytoin from the Na channel is driven by channel deactivation, and that phenytoin may not stabilize the "normal" inactivation state.[78] The delay in recovery from apparent inactivation may be due to phenytoin blocking the Na channel by binding to a blocking site on the Na channel that is formed during activation and removed during deactivation and only slowly dissociating from the blocking site after deactivation. The phenytoin block is thus due to the voltage-dependency of deactivation. The slow dissociation, in part, accounts for phenytoin's selective ability to block high-frequency firing: When recovery is slow, the block can accumulate during repetitive activation of the channel. Another important feature of the block of Na channels by phenytoin is its slow onset. Slow binding has two important implications. First, the time course of fast Na currents is not altered in the presence of the drug, and therefore, the kinetic properties of normal action potentials are not perturbed. Second, slow binding means that action potentials evoked by synaptic depolarizations of ordinary duration are not blocked. Even interictal discharges, characterized by depolarizations lasting 50 to 200 ms, are not sufficiently long for drug binding and block of Na channels. Consequently, the frequency of interictal discharges in unaffected by phenytoin. In focal epilepsies, seizure discharges are associated with more sustained depolarizations than those occurring during interictal discharges. Only depolarizations that are as long as those occurring during ictal discharges provide the conditions required for drug binding and block.

Benzodiazepines and Barbiturates

Benzodiazepines and barbiturates enhance GABAergic inhibition at the free serum concentrations found in ambulatory patients[96] by interacting directly with $GABA_A$ receptors. $GABA_A$ receptors are formed by the assembly of multiple subunit subtypes (α1–α6, β1–β3, γ1–γ3, δ, ε, π, θ, and ρ1–ρ3) into a pentamer, although the most common and likely subunit composition has been determined to contain two α-subunits, two β-subunits, and a γ-subunit.[10] The five subunits are arranged in a counterclockwise sequence (as seen from the synaptic cleft) γβαβα.[10] Once assembled, $GABA_A$ receptors form chloride (Cl) ion channels, and the current carried by these channels can be modulated by a number of AEDs, including barbiturates and benzodiazepines.

$GABA_A$ receptors have been shown to be involved in both phasic, inhibitory synaptic transmission and tonic, perisynaptic inhibition[36,98] (see Chapter 23). GABA regulates gating (opening and closing) of the ion channel.[96,186,197] Binding of GABA increases the probability of channel opening, and the open channel can close and rapidly reopen to create bursts of openings.

Barbiturates enhance $GABA_A$ receptor current by binding to an allosteric regulatory site on the receptor, but the specific residues that constitute the allosteric binding site are unknown.[126] Mutagenesis studies have demonstrated that a glycine residue in the first transmembrane domain[21] and a tryptophan residue in the third transmembrane domain[2] of the β-subunit may be involved in barbiturate actions. All $GABA_A$ receptor isoforms containing at least an α- and β-subunit have been shown to be sensitive to barbiturates; in general, only minor differences in sensitivity are noted for different isoforms. However, $GABA_A$ receptors that contain a δ-subunit instead of the more common γ2-subunit and that are believed to be localized perisynaptically, where they mediate tonic inhibition, are more sensitive to barbiturates than are those containing γ2-subunits that are synaptically localized.[1] Single-channel recordings of barbiturate-enhanced single $GABA_A$ receptor currents have directly demonstrated that barbiturates increase mean channel open duration but do not alter receptor conductance or opening frequency.[96,185]

The sensitivity of $GABA_A$ receptors to benzodiazepines requires the presence of a γ-subunit coexpressed with an α1-, α2-, α3-, or α5-$GABA_A$ receptor subtype.[134] Expression of the α4- or α6-subtypes with β1- and γ2-subtypes results in receptors that are insensitive to benzodiazepines.[203] Thus, benzodiazepine sensitivity of $GABA_A$ receptors depends on both γ-subunit and α-subtypes. The single high-affinity binding site for benzodiazepines is located at the α/γ-subunit interface, whereas the two binding sites for GABA are at the α/β-interfaces. These two binding sites are allosterically coupled.[126] Benzodiazepines increase $GABA_A$ receptor current, and single-channel recordings have demonstrated that they increase $GABA_A$ receptor opening frequency without altering mean open time or conductance.[148,189]

Ethosuximide and Trimethadione

Ethosuximide and trimethadione, which are effective in the treatment of generalized absence seizures, have been shown to interact with voltage-dependent T-type Ca channels (Table 1). The multiple Ca channel types[22,122] are designated as L (Ca_V1.1–1.4), P/Q (Ca_V2.1), N (Ca_V2.2), R (Ca_V2.3), and T (Ca_V3.1–3.3), each with different voltage ranges and rates for activation and inactivation. Each channel type is composed of an ion conducting α-subunit (Ca_V1.1–1.4, Ca_V 2.1–2.3) and may include smaller accessory subunits, β- (Ca_V1-4) and α2δ1-4, which are not required for function but do modify gating.[81,22]

Table 1 Molecular targets of antiepileptic drugs

	Molecular target			
Drug	**Na channels**	**Ca channels**	**GABA system**	**Glutamate receptors**
	Predominant Na (and Ca) channel activity			
Phenytoin	I_{NaF} (↓) I_{NaP} (↓)			
Carbamazepine	I_{NaF} (↓)			
Oxcarbazepine	I_{NaF} (↓)			

Lamotrigine	I_{NaF} (↓)	HVA (↓)		
Zonisamide	I_{NaF} (↓)	T-type (↓)		
Predominant Ca channel activity				
Ethosuximide	? I_{NaP} (↓)	T-type (↓)		
GABA systems				
Benzodiazepines			GABA$_A$R (↑)	
Vigabatrin			GABA-T (↓)	
Tiagabine			GABA transporter (↓)	
Mixed				
Valproate	? I_{NaF} (↓) I_{NaP} (↓)	? T-type (↓)	GABA turnover (↑)	
Felbamate	I_{NaF} (↓)	HVA (↓)	GABA$_A$R (↑)	NMDA (↓)
Topiramate	I_{NaF} (↓) I_{NaP} (↓)	HVA (↓)	GABA$_A$R (↑)	KA/AMPA (↓)
Phenobarbital		HVA (↓)	GABA$_A$R (↑)	AMPA (↓)
Novel targets				
Gabapentin	α2δ protein (Ca channel subunit)			
Pregabalin	α2δ protein (Ca channel subunit)			
Levetiracetam	SV2A synaptic vesicle protein			

↑, Indicates increase in activity of target; ↓, indicates decrease in activity of target. *Abbreviations:* AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid; GABA, γ-aminobutyric acid; GABA-T, GABA aminotransferase; GABA$_A$R, GABA$_A$ receptor; HVA, high voltage activated; I_{NaF}, fast Na current; I_{NaP}, persistent Na current; KA, kainate; NMDA, *N*-methyl-D-aspartate.

Adapted from Rogawski MA, Löscher W. The neurobiology of antiepileptic drugs. *Nat Rev Neurosci.* 2004;5:553–564, with permission.[145]

Generalized absence epilepsy is characterized clinically by brief periods of loss of consciousness and electrically by generalized 3-Hz spike-and-wave discharges recorded on the electroencephalogram. Thalamic relay neurons play a critical role in the generation of the abnormal thalamocortical rhythmicity that underlies the 3-Hz spike-and-wave discharge. Whole-cell voltage clamp recordings from acutely dissociated relay neurons from the rat thalamus have demonstrated the presence of low-threshold (T-type) and high-threshold Ca currents.[174] The T-type currents had properties such that channel activation was necessary and sufficient to cause the generation of low-threshold Ca spikes in thalamic relay neurons. Ethosuximide and dimethadione, the active metabolite of trimethadione, both reduced T-type Ca currents of thalamic neurons isolated from guinea pigs and rats[27,28] at clinically relevant concentrations. Phenytoin and carbamazepine, which are ineffective in the control of generalized absence seizures, had minimal effects on T-type current. Dimethadione reduced T-type Ca current by a mechanism similar to that of ethosuximide. Another anticonvulsant succinimide, α-methyl-α-phenylsuccinimide, also reduced T-type currents, whereas a convulsant succinimide, tetramethylsuccinimide, only reduced the T-type current at very high concentrations.[29] These results suggest that anticonvulsant succinimides and dimethadione may have their primary action by reducing the T-type Ca current in thalamic relay neurons. More recent studies have largely confirmed these effects of ethosuximide in additional preparations, although variability in responsiveness occurs.[55,184,183] It has been proposed that certain factors regulating pharmacologic sensitivity, such as the presence of accessory Ca channel subunits, may contribute to the variability. Recent studies with recombinant human T-type Ca channels indicated that the action of ethosuximide is more complex than previously appreciated.[45] There may be two binding sites, one with high-affinity (~0.1 mM) that accounts for ~20% of total channel blockade and a low-affinity site (~10 mM) that accounts for the remainder. Although

ethosuximide did not alter the voltage-dependency of steady-state inactivation or the time course of recovery from inactivation of the T-type Ca current, the drug did inhibit the current in a voltage-dependent manner, with current reduction most prominent at negative membrane potentials and less prominent at more positive membrane potentials.[45] Thus, under conditions in which neurons are normally hyperpolarized (resting membrane potentials varying between –55 and –70 mV), the sensitivity of T-type Ca channels to succinimide block will be enhanced. In particular, these agents would be expected to block T-type Ca currents during slow, GABA-dependent network activity, as is believed to occur during absence seizures.[55]

Valproate

Valproate has many pharmacologic actions, none of which by itself can completely account for its clinical activity in epilepsy and the other conditions for which it is used, including bipolar disorder and migraine headache. It has therefore been proposed that valproate acts through a combination of neurophysiological and neurochemical actions.[88] Among these diverse actions, effects on GABA systems may play a leading role. Although the precise mechanism is obscure, in some specific brain regions thought to be involved in the control of seizure generation and propagation, valproate increases the turnover of GABA and presumably enhances GABAergic function. Indeed, valproate has actions in animal epilepsy models that overlap with drugs that are believed to act on GABA systems. Thus, valproate is especially active in genetic models of absence seizures, such as the genetic absence epilepsy rat from Strasbourg (GAERS).[100] It is also protective against seizu- res induced by methyl 6,7-dimethoxy-4-ethyl-β-carboline-3-carboxylate (DMCM)[129] and in the 6-Hz model, an alternative electroshock model that is sensitive to GABAergic agents.[8,67] Valproate also exhibits protective activity in virtually all other animal AED screening models including the MES and PTZ models, but its potency in any specific model varies depending on the species and route of administration.[88] In view of the activity of valproate in the MES model, which is shared with drugs like phenytoin, carbamazepine, and lamotrigine that are well recognized to modulate voltage-gated Na channels, it has been proposed that valproate might also have an action on Na channels. Indeed, valproate does block sustained high-frequency repetitive firing of neurons in culture.[106] However, detailed voltage clamp experiments of valproate actions on Na currents have not been performed; therefore, it cannot be concluded that valproate has a mechanism of action similar to that of the classical Na-channel AEDs.

Although valproate is effective in the treatment of generalized absence seizures, studies in rat thalamic neurons did not demonstrate any effect on T-type Ca current, but subsequently, the drug was shown to reduce T-type currents in primary afferent neurons.[70] This effect occurred over a concentration range of 100 to 1,000 μmol/L. However, the magnitude of block was modest, with a 16% reduction seen at 1 mmol/L. Whether this modest reduction in T-type Ca current is sufficient to explain the effect of valproate on generalized absence seizures is unclear. Furthermore, the basis for the discrepancy between the results obtained in thalamic neurons and primary afferent neurons remains uncertain. Whether this is a relevant mechanism of action for valproate will have to be determined by future investigation.

Mechanisms OF Action of Newer AEDs

Felbamate

Felbamate is a dicarbamate, which is an analog of the sedative-hypnotic drug meprobamate (2-methyl-2-propyl-1,3-propanediol dicarbamate). Despite its idiosyncratic toxicities, felbamate is a highly effective AED with a broad spectrum of activity, and is one of only three AEDs for which there is evidence, from a controlled clinical trial, of efficacy in the treatment of the Lennox-Gastaut syndrome.[5] Felbamate has been reported to inhibit sustained repetitive action potential firing in cultured neurons, suggesting that it modulates voltage-gated Na channels.[201] Although an effect on recombinant Na channels is observed only at relatively high (1 mM) concentrations,[175] inhibition of Na-channel function could, at least in part, contribute to felbamate's anticonvulsant activity. Felbamate has also been reported to inhibit high voltage–gated Ca channels,[167,168] but the significance of this action for seizure protection is uncertain. Like meprobamate, felbamate potentiates $GABA_A$ receptor currents via an interaction with a site on the $GABA_A$ receptor that is distinct from the benzodiazepine recognition site.[77,137] The threshold concentration for felbamate modulation of $GABA_A$ receptor currents is ~100 μM, and the IC_{50} value for allosteric inhibition of *t*-[^{3}H]butylbicycloorthobenzoate binding to $GABA_A$ receptors in rat brain slices is 250 μM.[77] Because low therapeutic (anticonvulsant) serum concentrations of felbamate are in the range of 100 to 300 μM, the action of felbamate on $GABA_A$ receptors is probably relevant to its anticonvulsant activity. In addition, felbamate at a concentration of 100 μM has been found to block *N*-methyl-D-aspartate (NMDA) receptor-mediated synaptic responses[135] and to inhibit NMDA-receptor currents in cultured neurons (K_d, ~1 mM[137,171]). It has been proposed that felbamate may act as a competitive antagonist at the glycine recognition site of NMDA receptors,[105,193] and studies in animal models seemed to support this concept.[26,200] However, several studies directly examining the interaction between felbamate and the NMDA receptor have shown conclusively that felbamate does not act at the glycine site per se.[73,135,137,171,181] On the basis of whole-cell and single-channel recordings, Subramaniam et al.[171] concluded that felbamate acts both by a channel blocking mechanism and also by distinct effects on channel gating. Details of the effects on gating have been defined by Kuo et al.,[79] who found that low, submillimolar concentrations of felbamate more readily blocked the late sustained phase of NMDA receptor responses but not the initial onset of the response. This phenomenon was ascribed to an acceleration of the decay of responses. It can be speculated that this property would confer selectivity on felbamate to block seizures, because the prolonged pathologic activation that occurs during seizures would be suppressed more strongly than normal (rapid) synaptically generated NMDA responses. In addition, NMDA receptor blockade responses was greater with high concentrations of NMDA, another factor that would allow the drug to selectively block seizure discharges associated with strong activation of NMDA receptors. Kuo et al. further found that felbamate selectively binds with higher affinity to the desensitized state of NMDA receptors (55 μM) than to the resting or activated states (200 and 110 μM, respectively), so that the allosteric blocking action relates to stabilization of the desensitized state.[79]

Felbamate also selectively blocked currents from recombinant NMDA receptors composed of NR2B subunits at lower concentrations (IC_{50}, 0.5 mM) than it blocked currents from NMDA receptors formed from other subunit combinations.[52,73] This selectivity could contribute to the relatively low neurobehavioral toxicity of felbamate in relation to other NMDA receptor antagonists. Unlike the NR2A subunit that is distributed ubiquitously in the central nervous system (CNS), expression of the NR2B subunit in the adult is largely restricted to the forebrain.

Thus, felbamate may selectively target NMDA receptors in forebrain areas critical to seizure generation, with less effect on nonforebrain structures that could mediate side effects. The subunit selectivity could also account for the clinical utility of felbamate in seizure disorders affecting the immature brain, such as Lennox-Gastaut syndrome, because NR2B subunits are more abundant in the developing brain.

Gabapentin and Pregabalin

Gabapentin, the lipophilic 3-cycylohexyl analog of GABA, was originally synthesized in an attempt to develop a brain-penetrant GABA agonist. Pregabalin [*S*(+)-3-(aminomethyl)-5-methylhexanoic acid; *S*(+)-3-isobutyl GABA] is a congener of gabapentin with similar properties. Although both gabapentin and pregabalin are based on a GABA backbone, bulky aliphatic substituents in the molecules preclude binding to the GABA recognition site on $GABA_A$ receptors. The drugs also do not interact with other sites on $GABA_A$ receptors, including the benzodiazepine recognition site.[172] Although there are reports of agonist activity at $GABA_B$ receptors, the preponderance of evidence indicates that $GABA_B$ receptors are not a pharmacologic target.[178] Additional studies have shown that gabapentin does not inhibit GABA uptake or GABA catabolism, although it may enhance GABA turnover.[91] Increases in GABA levels have been reported in humans using noninvasive spectroscopic techniques,[80,131] but neither gabapentin nor pregabalin affect brain GABA levels in the rat,[40] and thus the significance of these alterations in GABA metabolism are uncertain. Nevertheless, there is little doubt that the therapeutic activities of gabapentin and pregabalin do not reside in effects on GABA systems. Indeed, the molecular targets of gabapentin and pregabalin are almost certainly α2δ-proteins, which are believed to be auxiliary subunits of voltage-activated Ca channels. Strong evidence for this concept is the observation that the binding affinities of gabapentin, pregabalin, and related structures to α2δ-subunits correlate in a stereoselective fashion with their anticonvulsant potencies.[12,19] In addition, knockin of a mutation (R217A) in the α2δ-1 subunit in mice, which results in markedly reduced binding of gabapentin and pregabalin, reduces the anticonvulsant activity of pregabalin and eliminates its analgesic activity.[148] Because the anticonvulsant actions of phenytoin and the analgesic actions of morphine are not altered by the same mutation, it is likely that the α2δ-1 protein is a target for the pharmacologic effects of pregabalin. However, since the mutation does not completely eliminate the anticonvulsant activity of pregabalin, it is plausible that effects occur on targets other than α2δ-1. Because gabapentin and pregabalin also bind to α2δ-2, this is a logical second target; but until experiments with mice bearing mutations in both α2δ-1 and α2δ-2 are available, the possibility that the drugs confer anticonvulsant activity through interactions with non-α2δ targets cannot be eliminated.

The α2δ-subunits are highly glycosylated proteins having a molecular mass of ~150 kD (997 to 1150 amino acid residues). Four homologous forms exist, but only subtypes 1 and 2 bind gabapentin and pregabalin with high affinity.[75] Each of the α2δ-subunits are products of a single gene that is posttranslationally cleaved into α2- and δ-peptides, which are then covalently linked by a disulfide bridge. Within the multimeric complex that forms the functional Ca channel, the α2δ-subunit is adjacent to or embedded in the pore forming α1-subunit. The δ-subunit portion of α2δ is in close association with the channel and serves as an anchor for the α2-subunit, which is located largely extracellularly.[204] Mutagenesis experiments have shown that the gabapentin binding site is probably confined to the α2-subunit protein and the external portion of the associated δ component.[18,195] The α2δ-1 and α2δ-2 subunits are believed to form complexes with many voltage-dependent Ca channel types, but it is not yet clear which Ca channels are important for the therapeutic activity of gabapentin and pregabalin, nor is the functional role of the α2δ subunit complex fully understood. However, for some Ca channel types, the α2δ subunit complex has been shown to allosterically enhance current amplitude and also promote channel trafficking to the membrane.

Functional studies of the effects of gabapentin on Ca channel activity have yielded divergent results[178]; however, the general consensus is that gabapentin and pregabalin reduce the release of neurotransmitters from neural tissue, with effects on glutamate release being of particular relevance in epilepsy.[11,38] Thus, in various preparations, gabapentin and pregabalin have been shown to reduce the amplitude of evoked and spontaneous excitatory postsynaptic currents. Surprisingly, however, a reduction also occurs in the frequency of miniature excitatory synaptic currents.[3,128] Because these events do not depend on Ca entry through voltage-sensitive Ca channels, gabapentin and pregabalin do not seem to be acting simply by inhibiting Ca channels in presynaptic terminals. Rather, it has been speculated that binding of the drugs to α2δ-subunits directly influences the release machinery,[147] possibly by affecting physical interactions between presynaptic Ca channels and proteins mediating exocytosis.[165]

Gabapentin and pregabalin are absorbed in the gut and pass across the blood–brain barrier via the system L transporter, which is specialized for the transport of large, neutral amino acids.[170] The fact that these drugs are substrates for this transporter is essential to their anticonvulsant activity because it allows them to gain access to the CNS.[12] However, an interaction with the transporter is not responsible for seizure protection or other pharmacologic activities of the drugs.

Both gabapentin and pregabalin are highly effective in the rat MES test and also are protective against tonic seizures induced by chemoconvulsants, with pregabalin being modestly more potent than gabapentin.[20,178,202] Neither agent is as effective in the mouse, which is unusual, because most AEDs show the reverse species selectivity. Both drugs are effective in protecting against seizures in kindled rats, and are highly potent against audiogenic seizures in genetically susceptible mice. The drugs are only weakly active against chemoconvulsant-induced clonic seizures. They are not protective in models of absence epilepsy, and can even promote absence seizures at high doses.[178] Overall, the preferential activity against tonic seizures, in the MES test and other models, and lack of protective activity against absence seizures, is consistent with the presumed mechanism of action, which is to inhibit synaptic release. This conclusion is based on a comparison with other AEDs with a similar profile in animal seizure models, most notably Na-channel blocking AEDs. Although Na-channel blocking AEDs do not directly alter synaptic responses, as noted earlier, their inhibitory action on Na channels translates into reduced transmitter output at synapses, with a preference for the release of glutamate.

Lamotrigine

Lamotrigine [3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-tria- zine] is a phenyltriazine with weak antifolate activity. Lamotrigine was developed after it was observed that the use of phenobarbital, primidone, and phenytoin resulted in reduced folate levels, and that folates could induce seizures in experimental animals.[136] It was proposed that antifolate activity may be related to the anticonvulsant properties of these AEDs; however, this has not been confirmed in structure-activity studies.[146] Lamotrigine has anticonvulsant activity against tonic seizures in the MES test and also against tonic seizures induced by PTZ, but it is not active in the conventional PTZ test in which clonic seizure activity is the end-point.[110] Lamotrigine is also inactive in rat models of absence epilepsy.[188] Therefore, its profile in animal models is similar to that of Na-channel modulators such as phenytoin and carbamazepine.

Early studies of the mechanism of action of lamotrigine examined its effects on the release of endogenous amino acids from rat cerebral cortex slices in vitro. As is the case for AEDs that act on voltage-dependent Na channels,[87] lamotrigine inhibited the release of glutamate and aspartate evoked by the Na-channel activator veratrine and was less effective in the inhibition of acetylcholine or GABA release.[85] At high concentrations, lamotrigine had no effect on spontaneous or potassium (K)-evoked amino acid release. These studies suggested that lamotrigine acts presynaptically on voltage-gated Na channels to decrease glutamate release. In radioligand studies, the binding of [^{3}H]batrachotoxinin A 20-α-benzoate, a neurotoxin that binds to receptor site 2 on voltage-dependent Na channels, was inhibited by lamotrigine in rat brain synaptosomes.[25] Several electrophysiological studies have investigated the effects of lamotrigine on voltage-dependent Na channels. Lamotrigine blocked sustained repetitive firing in cultured mouse spinal cord neurons in a concentration-dependent manner at concentrations therapeutic in the treatment of human seizures.[25] In cultured rat cortical neurons, lamotrigine reduced burst firing induced by glutamate or K, but not unitary Na action potentials evoked at low frequencies.[86] In cultured hippocampal neurons, lamotrigine reduced Na currents in a voltage-dependent manner, and at depolarized potentials showed a small frequency-dependent inhibition.[115] Lamotrigine increased steady-state inactivation of rat brain type IIA Na channel α-subunit currents expressed in Chinese hamster ovary cells[180] and produced both tonic and frequency-dependent inhibition of voltage-dependent Na channels in clonal N4TG1 mouse neuroblastoma cells, but had no effect on cationic currents induced by stimulation of glutamatergic receptors in embryonic rat hippocampal neurons.[194]

In cultured rat cortical neurons, lamotrigine at high concentrations was able to inhibit peak high-threshold Ca currents and appeared to shift the threshold for inward currents to more depolarized potentials.[86] In clonal rat pituitary GH3 cells, lamotrigine at the same concentration did not inhibit high-threshold Ca currents, caused only slight inhibition of low-threshold Ca currents, reduced rapidly inactivating voltage-dependent K currents, and had no significant effect on Ca-activated K currents.[82] In cultured rat cortical neurons, lamotrigine did not appear to mimic the effect of diazepam when tested on GABA-evoked Cl currents.[86]

These results indicate that the antiepileptic effect of lamotrigine, like that of phenytoin and carbamazepine, is at least in part due to use- and voltage-dependent modulation of fast voltage-dependent Na currents. However, lamotrigine has a

broader clinical spectrum of activity than phenytoin and carbamazepine and is recognized to be protective against generalized absence epilepsy and other generalized epilepsy syndromes, including primary generalized tonic–clonic seizures, juvenile myoclonic epilepsy, and Lennox-Gastaut syndrome.[16,41,133] The basis for the broader spectrum of activity of lamotrigine is unknown, but could relate to actions of the drug on voltage-activated Ca channels.[145] Lamotrigine blocks T-type Ca channels weakly, if at all.[44,49] However, it does inhibit native and recombinant high-voltage–gated Ca channels (N- and P/Q/R-types) at therapeutic concentrations.[49,167,196] Whether this activity on Ca channels accounts for lamotrigine's broader clinical spectrum of activity in comparison with phenytoin and carbamazepine remains to be determined.

Levetiracetam

Levetiracetam [(S)-α-ethyl-2-oxo-pyrrolidine acetamide], the *S*-enantiomer of the ethyl analog of the nootropic agent piracetam, differs from other AEDs in its profile of activity in animal seizure models. Notably, levetiracetam is inactive against both the MES and subcutaneously administered PTZ seizures.[74,89] Nevertheless, the drug does have activity in many acute seizure models. For example, it confers protection against sound-induced clonic seizures and also against clonic seizures induced by pilocarpine and DMCM, but not against seizures induced by other chemoconvulsants such as the $GABA_A$ receptor antagonists bicuculline or picrotoxin or by intracerebroventricular injection of the excitatory amino acid agonists NMDA, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA), or kainate.[74] Levetiracetam also confers protection against kindled seizures,[89] and it can inhibit the development of the seizure-prone state in various kindling models.[47,90] Levetiracetam can also inhibit the developmental expression of tonic convulsions in a genetic epilepsy model.[207] The anticonvulsant activity of levetiracetam is stereoselective (the *R*-enantiomer is very weak or inactive,[47] indicating an interaction with a structurally specific recognition site). In line with the atypical profile of levetiracetam in animal models, the drug also behaves distinctly in brain slice epilepsy models. Unlike conventional AEDs that inhibit high-frequency action potential firing, presumably through effects on Na channels, levetiracetam specifically suppresses synchronized network bursting, indicating an effect on synchronization mechanisms.[120] In this regard, it is noteworthy that levetiracetam has a much larger therapeutic window than do other AEDs (only very large doses ~1,000 mg/kg cause impairment of motor performance), which is consistent with a more specific action on epileptiform activity than that of other AEDs. The various differences between levetiracetam and other AEDs suggest that levetiracetam protects against seizures by a novel mechanism. However, until recently, a reasonable candidate was not at hand. Levetiracetam has been shown to inhibit voltage-activated Ca[119] and K[99] currents at high concentrations. In addition, recognizing that levetiracetam is protective against seizures induced by the benzodiazepine receptor inverse agonist DMCM, it was observed that levetiracetam can reverse DMCM inhibition of $GABA_A$ and glycine receptor responses in cultured neurons.[140] However, none of these actions has been convincingly linked to the anticonvulsant activity of the drug. In 1995, Noyer et al.[123] described a saturable and stereoselective specific binding site for $[^3H]$levetiracetam in brain membranes. The binding site was found to be an integral membrane protein, having an apparent molecular mass of ~90 kDa, which is widely distributed in brain and localized to the synaptic vesicle membrane fraction in neurons. Although the binding site was only of moderate affinity (K_d, 0.8 μM), a series of stereoisomer homologs of levetiracetam demonstrated a rank order of affinity for the $[^3H]$levetiracetam binding site that was highly correlated with their anticonvulsant activity, indicating that the binding was relevant for the anticonvulsant properties of levetiracetam and related structures. Further studies indicated that the binding protein is the ubiquitous synaptic vesicle protein SV2A.[95] Thus, levetiracetam has a target that is distinct from that of other AEDs. SV2A was originally described by Bajjalieh et al.[6] as a 12-transmembrane domain glycoprotein homologous to membrane transporters. However, to date, a transporter activity for the protein has not been established. Rather, SV2A seems to interact with synaptotagmin, which is believed to be the Ca sensor in exocytosis.[153] It is now recognized that SV2A is a member of a small family of homologous proteins that also includes SV2B and SV2C; but only SV2A, the most ubiquitous form, binds levetiracetam. Studies with mice in which the SV2 proteins have been deleted by gene targeting are consistent with a possible role of SV2A in regulating seizure susceptibility, but they have not yet provided answers to the key questions of the function of SV2A and how levetiracetam binding confers seizure protection. In SV2A knockout mice, brain morphology—and indeed the morphology of synapses—is normal.[30,60] However, homozygous SV2A knockout mice experience severe seizures and die between postnatal weeks (P)12 and P23; heterozygous animals are also susceptible to seizures but have nearly normal survival. The SV2 proteins do not appear to be required for synaptic transmission or for the uptake or storage of neurotransmitters, although they may play a subtle role in the release process during repetitive synaptic activation (as occurs during seizure activity) by regulating nerve terminal Ca dynamics.[60] Although there is still much to be learned about the mechanism of levetiracetam, it is now clear that its target is a component of the synaptic release machinery, which supports the unifying concept that the ultimate action of many AEDs, whatever their molecular targets, is to modulate neurotransmitter release. Levetiracetam is the first AED that targets the synaptic release machinery directly. Through this direct mechanism, the drug seems to be able to exert a protective action on seizures with a favorable side-effect profile.

Oxcarbazepine

Oxcarbazepine (10,11-dihydro-10-oxo-carbamazepine) is a dibenzazepine that is structurally similar to carbamazepine, except that is has a keto substitution at the 10 position of the dibenzazepine nucleus. The keto substitution prevents the formation of the 10,11-epoxide, which, in the case of carbamazepine has been hypothesized to contribute to toxicity. Rather, oxcarbazepine is rapidly and nearly completely reduced to 10,11-dihydro-10-hydroxy carbamazepine (licarbazepine; GP 47779; LIC477).[31] Licarbazepine is a racemate, with the *S*(+)-enantiomer (BIA 2-093) about four times as abundant in the urine as the *R*(-)-enantiomer; both enantiomers have approximately equal anticonvulsant activity.[13,154]

Oxcarbazepine and licarbazepine are effective in inhibiting the hind limb extension in rats and mice elicited by MES, but are approximately two to three times less effective against PTZ-induced seizures in mice.[7] In studies using rats at different developmental ages, oxcarbazepine, licarbazepine, and carbamazepine dose-dependently reduced the tonic phase of generalized seizures induced by PTZ and appeared to have identical anticonvulsant profiles in this model.[76] Oxcarbazepine and licarbazepine have relatively poor anticonvulsant efficacy against picrotoxin- and strychnine-induced seizures in mice.[7] Oxcarbazepine was able to completely suppress seizures in rhesus monkeys in a chronic aluminum foci model of partial seizures. At comparable doses, licarbazepine was less effective in suppressing seizures in this model.[61] Oxcarbazepine is effective in the treatment of human partial seizures and generalized tonic–clonic seizures with and without secondary generalization.[33]

In electrophysiologic studies in rat hippocampal slices, oxcarbazepine and licarbazepine enantiomers dose-dependently decreased epileptic-like discharges induced by penicillin.[154] In addition, the compounds reduced sustained high-frequency repetitive firing of voltage-dependent Na action potentials in mouse spinal cord neurons.[194] Oxcarbazepine is slightly more potent than carbamazepine in displacing [^{3}H]batrachotoxinin A 20-α-benzoate from voltage-dependent Na channels in rat cortical synaptosomes and also slightly more potent in inhibiting[22] Na^+ uptake.[13] Together, these observations indicate that the anticonvulsant mechanism of oxcarbazepine is similar to that of carbamazepine, and depends on the modulation of voltage-dependent Na channels.

Tiagabine

Tiagabine [(*R*)-N-(4,4-di(3-methylthien-2-yl)but-3-enyl) nipe-cotic acid hydrochloride] is a nipecotic acid analog with an incorporated lipophilic anchor to facilitate crossing of the blood–brain barrier after oral administration.[84] Like nipecotic acid, tiagabine is a potent and specific competitive inhibitor of the neuronal and astrocytic GABA transporter GAT-1.[17] Tiagabine binds with high affinity to the transporter, thus preventing GABA uptake without itself being transported. By slowing the reuptake of synaptically released GABA, tiagabine increases synaptic GABA levels and prolongs inhibitory post-synaptic potentials.[39,59,150,169,182] The prolongation of inhibitory GABA-mediated synaptic responses by tiagabine may be enhanced with repetitive activation, such as occurs occur during the synchronous discharge of GABAergic interneurons during epileptic activity. This may minimize the behavioral depression that would accompany indiscriminate enhancement of GABA inhibition.

Tiagabine has a unique spectrum of activity in animal seizure models. The drug is highly potent against tonic and also clonic seizures induced by PTZ and DMCM,[32] and is also effective against various types of kindled[113] and reflex seizures.[163] It is only weakly active, if at all, against tonic hind-limb extension in the MES model.[32,118] In addition, tiagabine is effective against status epilepticus (SE) in cobalt-lesioned rats but also produced a hyporeactive state associated with a rhythmic EEG pattern suggesting a generalized convulsant action.[192] In fact, in patients who were not previously recognized as having epilepsy, tiagabine use has rarely been associated with new-onset seizures and SE. Interestingly, tiagabine was also shown to exert an antepileptogenic effect in amygdala kindling[32] and to prevent seizures and neuronal damage in experimental SE.[50]

Topiramate

Topiramate (2,3:4,5-*bis-O*-[1-methylethylidene]-ß-D-fructo-pyranose sulfamate) is a sulfamate derivative of the naturally occurring monosaccharide D-fructose. The drug is active against MES seizures in rats and mice, in amygdala-kindled seizures in rats, and sound-induced seizures in mice.[159] It is ineffective against seizures induced by PTZ, bicuculline, or picrotoxin.[42,159] It therefore has a profile of activity in animal models that is similar to that of Na channel–blocking AEDs[143]; the profile also resembles that of glutamate receptor antagonists.[93] However, the drug has several properties that are atypical for Na channel–blocking AEDs in that it is effective in a rat genetic model of absence epilepsy[117] and can also raise the threshold for clonic seizures induced by intravenous PTZ in mice.[198] Several cellular mechanisms have been proposed to underlie the therapeutic activity of topiramate: (a) activity-dependent attenuation of voltage-dependent Na currents[177,212]; (b) inhibition of high-voltage–activated Ca channels[210]; (c) potentiation of $GABA_A$ receptor-mediated currents[46,68,198,199]; (d) inhibition of AMPA/kainate receptors[43,162,164]; (e) inhibition of types II and IV carbonic anhydrase isoenzymes[37]; and (f) activation of a steady K current.[53] The effects on Na channels occur at relatively low, therapeutically relevant concentrations (25–30 μM). Trough serum concentrations of topiramate associated with antiepileptic activity in clinical trials range from 6 to 35 μM. The biophysical details of the modulation of fast Na currents are similar to that of classical Na-channel blocking anticonvulsants, particularly phenytoin. Thus, the degree of block is enhanced with the long membrane depolarizations as are believed to occur during epileptiform activity. However, the unblock upon membrane hyperpolarization is more rapid than with phenytoin (comparable to carbamazepine and lamotrigine). It has been suggested that the faster recovery is desirable because it would allow ongoing neuronal activity to resume quickly after epileptiform activity is aborted. In addition to effects on fast Na currents, topiramate, like phenytoin, blocks persistent Na currents at low concentrations. Because persistent Na current may contribute to the initiation and maintenance of epileptiform activity,[156] this could represent an important factor in topiramate's anticonvulsant properties. The pharmacologic effect of topiramate on high-voltage–activated Ca current is of uncertain relevance, because the drug was specific for L-type Ca currents[210] and L-type Ca channel blockers are not effective as anticonvulsants.

Effects of topiramate on $GABA_A$ receptors could contribute to the broad spectrum of activity of topiramate, but the evidence is imperfect. Topiramate is not active in those animal models, such as the PTZ test, that are typically sensitive to drugs that positively modulate $GABA_A$ receptors. Nevertheless, the drug does have activity in an absence epilepsy model and on PTZ threshold, consistent with effects on $GABA_A$ receptors.[34] However, the ability of the drug to enhance $GABA_A$ receptor currents within in vitro systems is inconsistent and variable among preparations and does not show ordinary concentration-dependence,[46,53] making the effect difficult to study. The variability could be due in part to subunit selectivity, inasmuch as some $GABA_A$ receptor subunit combinations expressed in *Xenopus* oocytes were potentiated, whereas others were inhibited.[46] The potentiation, when it occurs, is independent of an interaction with the GABA or benzodiazepine recognition sites of the $GABA_A$ receptor, and effects on slow desensitization kinetics are more substantial than on the peak amplitude.[46,199] Modulation of slow $GABA_A$ receptor desensitization could influence seizure susceptibility,[15] but the way in which this might occur with topiramate has yet to be defined. Evidence suggests that topiramate may alter the activity of the various receptors and ion channels with which it interacts by affecting their phosphorylation state.[159] Phosphorylation does influence the kinetic properties of $GABA_A$ receptors,[54] raising the possibility that this mechanism could be relevant to their modulation by topiramate.

As noted, the activity of topiramate in animal models is compatible with effects on glutamate receptors, including NMDA and AMPA/kainate receptors.[143] There is no evidence that to- piramate blocks NMDA receptors.[44] However, in cultured neurons, it does inhibit responses to kainate, an agonist of AMPA and kainate receptors.[44] Recently, topiramate was found to be a more potent and efficacious inhibitor of GluR5 kainate receptor currents in basolateral amygdala principal neurons than of AMPA receptor currents.[48] AMPA receptors are crucial for excitatory synaptic transmission throughout the CNS, and drugs that substantially block AMPA receptors produce dramatic neurobehavioral impairment.[206] Thus, the finding

that topiramate is weak and has low efficacy as an AMPA receptor antagonist corresponds with the clinical observation that the drug is reasonably well tolerated. Kainate receptors represent a new potential anticonvulsant drug target.[145] Blockade of GluR5 kainate receptors is not associated with the side effects associated with blockade of AMPA receptors and, in fact, transgenic mice that lack GluR5 are grossly normal neurologically. The inhibitory action of topiramate on GluR5 kainate receptors develops slowly, suggesting that it acts indirectly. Recently, it has been found that topiramate inhibits phosphorylation of serine 845 of the AMPA receptor GluR1 subunit,[4] suggesting that the effect of the drug on AMPA and perhaps kainate receptors is due to an alteration in the phosphorylation state of the protein. The relevance of the GluR5 kainate receptor–blocking activity of topiramate was confirmed using in vivo experiments in mice with selective glutamate receptor antagonists, in which anticonvulsant doses of topiramate blocked clonic seizures induced by a selective GluR5 kainate receptor agonist but not by an agonist of AMPA receptors.[67] In addition to effects on GluR5 kainate receptors, the drug may also affect the more abundant GluR6-containing kainate receptors.[66]

The action of topiramate on carbonic anhydrase has been assumed not to contribute to its clinical efficacy because cross-tolerance to the anticonvulsant activity of topiramate does not occur with the classical carbonic anhydrase inhibitor acetazolamide in mice.[160] Moreover, topiramate is only a moderate-potency inhibitor of carbonic anhydrase isoenzymes.[121] However, it is noteworthy that acetazolamide, like topiramate, has a preferential activity against MES seizures.[3] Recently, evidence supporting a role for carbonic anhydrase inhibition in the action of topiramate has come from studies of $GABA_A$ receptor–mediated depolarizing responses, which can be elicited by high-frequency stimulation of GABAergic synapses.[53] Such depolarizing GABA currents may promote the generation of seizure discharges. The efflux of intracellular bicarbonate formed by carbonic anhydrase is believed to be a major factor underlying depolarizing GABA currents.[62,166] Topiramate at clinically relevant concentrations strongly inhibited depolarizing GABA currents without affecting hyperpolarizing GABA-mediated inhibitory postsynaptic currents. This effect is assumed to be due to carbonic anhydrase inhibition, because it was mimicked by acetazolamide.

Overall, topiramate's broad spectrum of anticonvulsant activity is likely to result from effects on multiple target sites, including Na channels, kainate receptors, and possibly also $GABA_A$ receptors and carbonic anhydrase isoenzymes. The effects on ion channels are complex and are unlikely to occur through direct effects on channel gating, but are more likely to be mediated indirectly, possibly through inhibition of channel phosphorylation.

Vigabatrin

Vigabatrin (γ-vinyl GABA; 4-amino-hex-5-enoic acid) is a structural analog of GABA that acts as an enzyme-activated (“suicide”) inhibitor of GABA-transaminase (γ-aminobutyrate-α-oxoglutarate aminotransferase; GABA-T), a pyridoxal-5′-phosphate–dependent enzyme localized to mitochondria that is the main degradative enzyme for GABA. The drug initially binds reversibly to the pyridoxal-5′-phosphate cofactor and then binds irreversibly to the enzyme.[35] Because GABA-T inhibition is irreversible, recovery of GABA transaminating activity requires resynthesis of the enzyme. Vigabatrin is a racemic mixture of *S*(+)- and *R*(–)-enantiomers; only the *S*(+)-enantiomer inhibits GABA-T.[83] There is a corresponding stereoselectivity for the anticonvulsant activity of vigabatrin.[108] Administration of vigabatrin leads to large elevations in brain GABA levels in animals[92] and humans.[130] In addition, the drug causes a dose-dependent increase in cerebrospinal GABA in human subjects with epilepsy, without affecting the levels of other neurotransmitters, including monoamines.[139,152] The extent to which vigabatrin increases GABA concentrations differs among brain regions, depending on the density of GABAergic neurons.[24] Although GABA-T is present in both neurons and glia,[23] the increase in brain GABA levels is predominantly due to inhibition of GABA-T in neurons.[149]

The antiepileptic properties of vigabatrin have been attributed to enhanced GABA-mediated inhibition. Paradoxically, however, vigabatrin does not lead to larger $GABA_A$ receptor-mediated synaptic responses, and it has generally been found to inhibit spontaneous and evoked synaptic GABA currents.[58,127,205] In contrast to the effects on synaptic GABA responses, vigabatrin potently increases tonic current resulting from the action of ambient GABA on extrasynaptic $GABA_A$ receptors.[138,205] The increased extracellular GABA levels are attributed to efflux of GABA from neurons via GABA transporters operating in a reverse fashion due to high intracellular GABA. The enhanced activation of extrasynaptic $GABA_A$ receptors produced by the elevated extracellular GABA is believed to produce an anticonvulsant effect through reduced network excitability, although the details of how this occurs remain to be defined. An alternate hypothesis is that vigabatrin prevents the fading of GABA responses during repetitive activation of inhibitory pathways, through reduced function of release-regulating presynaptic $GABA_B$ receptors.[58] Such fading is believed to be an important factor that permits focal epileptiform activity to develop into a full-blown seizure.

Vigabatrin is indicated primarily for the treatment of partial seizures and is also a first-line treatment for infantile spasms. Therefore, its clinical indications differ from other drugs, such as benzodiazepines, that act on GABA systems. No uniform agreement exists on the profile of vigabatrin in animal epilepsy models. The variability in efficacy that has been observed can be attributed in part to differences in dosing and route of administration, because in some studies the drug was administered directly into the brain. The preponderance of evidence indicates that systemically administered vigabatrin is active against seizures induced by chemoconvulsants including strychnine, PTZ, picrotoxin, and isoniazid.[14,33,71,94] It is also effective against sound-induced seizures in mice,[109] epileptic responses in photosensitive baboons,[108] and against amygdala-kindled seizures.[64,161] In fact, as with other drugs that enhance GABAergic function, vigabatrin retards the development of kindled seizures, indicating that it has antiepileptogenic properties, at least in the kindling model.[161] Despite the clinical efficacy against partial seizures, systemically administered vigabatrin has generally been found to be inactive in the MES test.[14] It is also ineffective in genetic absence epilepsy models,[100] which corresponds with it lack of clinical antiabsence activity. Overall, vigabatrin has a unique profile of activity in animals models and in clinical use, which is not surprising because its mechanism of action differs from other marketed AEDs.

Zonisamide

Zonisamide (1,2-benzisoxazole-3-methanesulfonamide) is an AED with a unique chemical structure consisting of an aromatic fused benzene-isoxazole ring structure and a sulfonamide side chain. Zonisamide has a profile of activity in animal seizure models that is similar to that of AEDs that modulate voltage-dependent Na channels, including phenytoin, carbamazepine, and lamotrigine. Like these AEDs, zonisamide is protective in the MES test and inactive against subcutaneous PTZ seizures in both mice and rats[102,179,202]; it is also inactive against seizures induced by bicuculline and picrotoxin. Zonisamide has activity

in various kindling models,[51,63,65,190] and is also effective against tonic–clonic and myoclonic seizures in the Mongolian gerbil, a genetic animal model of reflex epilepsy.[9] In a strain of spontaneously epileptic rats, it suppressed tonic, but not absence-like seizures, and inhibited sound-induced seizures in DBA/2 mice.[117] However, zonisamide did not completely suppress spontaneous seizures in the EL mouse.[116]

Zonisamide prevented spread of epileptiform activity in the cortex of experimental animals, suppressing focal seizure activity induced by direct electrical stimulation of the cat visual cortex and increasing afterdischarge threshold[190]; following unilateral injection of kainic acid into the amygdala of the rat, it reduced the spread of seizures to the contralateral side.[176] Zonisamide also suppressed epileptogenic focal activity induced in the cortex of experimental animals. Zonisamide reduced spiking activity induced by cortical freezing in cat cortex and interictal spikes induced by tungstic acid gel in rat cortex.[56,57]

Multiple mechanisms of action for zonisamide have been proposed. These include (a) modulation of voltage-dependent Na channels, (b) inhibition of T-type voltage-dependent Ca channels, (c) presynaptic inhibition or facilitation of neurotransmitter release, (d) alteration in neurotransmitter turnover and metabolism, and (e) inhibition of carbonic anhydrase. Although some experimental data demonstrate pharmacologic activity relating to all these mechanisms, the effects on voltage-dependent Na channels and T-type Ca channels may be most relevant to the anticonvulsant activity of zonisamide.

The first study of the effects of zonisamide on Na channels was carried out in voltage-clamped *Myxicola* giant axons.[151] Zonisamide had no effect on Na channel activation but produced a shift in the steady-state fast inactivation curve to more negative voltages, and it slowed recovery from both fast and slow inactivation. The effect of zonisamide was only produced with intracellular zonisamide; extracellular zonisamide did not affect Na channel inactivation. The zonisamide effect on fast inactivation occurred at relatively low concentrations (1 to 100 μM) with a half-maximal concentration of 12 μM producing a 20 mV shift in the steady-state inactivation curve. The effect of zonisamide to slow recovery from slow inactivation occurred at even lower concentrations (0.1 to 10 μM). Thus, this early study demonstrated that zonisamide directly affects Na channels at low concentrations.

Recordings from cultured mouse spinal neurons have further indicated that zonisamide modulates voltage-dependent Na channels.[142] Concentrations above 2 μM caused a concentration-dependent limitation of high frequency action potential firing, with half-maximal inhibition at 17 μM. The minimum effective plasma concentration of zonisamide that is protective in the MES test is 10 μg/mL (47 μM), whereas concentrations greater than 70 μg/mL (330 μM) are associated with neurotoxicity.[104] In clinical studies, therapeutic serum concentrations of zonisamide are in the range 20 to 30 μg/mL (94–141 μM).[158] Zonisamide readily crosses the blood–brain barrier, and cerebrospinal fluid concentrations are similar to the free fraction in serum. Because zonisamide is approximately 50% bound to human serum albumin, minimum therapeutic brain concentrations are estimated to be in the range of 50 μM. Thus, the effect of zonisamide to limit the sustained, high-frequency, repetitive firing of action potentials occurred at concentrations that are therapeutically relevant. Although voltage-clamp studies have not been carried out in mammalian neurons, it can be inferred that zonisamide acts on voltage-dependent Na channels in a similar fashion to other Na-channel–modulating AEDs. That is, the drug likely produces use- and voltage-dependent blockade by binding to Na channels in the inactive state and slowing the rate of recovery of these channels from inactivation.

Unlike other Na-channel blocking AEDs, zonisamide also has specific effects on T-type Ca channels that are similar to those of ethosuximide. Thus, in cultured fetal rat cortical neurons, zonisamide produced a concentration-dependent inhibition of T-type Ca current without affecting L-type Ca current.[173] The zonisamide reduction in peak T-type Ca current occurred in a concentration-dependent fashion with zonisamide concentrations in the range of 1 to 500 μM. T-type Ca currents were inhibited 10% to 25% at therapeutic concentrations of 10 to 50 μM, and the maximum inhibition obtained was 60%. Zonisamide also reduced the T-type Ca current recorded from cultured neuroblastoma cells, producing a 38% reduction in current at a concentration of 50 μM and a shift in the inactivation curve to more negative potentials by 20 mV.[72] It seems plausible that the broader clinical spectrum of activity of zonisamide, including its activity in generalized absence seizures,[157] could relate to this action on T-type Ca current.

As is the case for other Na-channel modulating AEDs, the ability of zonisamide to modulate voltage-dependent Na channels is expected to reduce the action potential–evoked release of glutamate through a presynaptic action. In fact, recordings from hippocampal neurons in rat brain slices demonstrated that 20 μM zonisamide suppressed the amplitude of spontaneous action potential–dependent excitatory postsynaptic currents without affecting action potential–independent (miniature) synaptic currents.[144] Thus, these electrophysiologic studies demonstrate that zonisamide is able to block glutamate release through a presynaptic action, and they suggest that this occurs through an interaction with Na channels, and not through downstream components of the vesicular release machinery.

Studies with microdialysis in freely moving rats have indicated that zonisamide has complex actions on the release of various neurotransmitters, and that these effects could be mediated through actions distinct from the interaction with Na channels. The transmitters studied have included GABA, dopamine, serotonin, and acetylcholine. Zonisamide in some cases was found to increase release and in other cases to inhibit it.[69,124,211] The extent to which these effects could contribute to the anticonvulsant activity of zonisamide is not well understood. However, it is interesting that zonisamide can enhance the basal release of GABA.[208] Another observation suggesting that zonisamide could influence GABA systems is that chronic treatment of rats with zonisamide leads to downregulation of the GAT-1 GABA transporter.[187] In addition, there is evidence from radioligand binding suggesting that zonisamide could directly interact with $GABA_A$ receptors. Thus, reports from one research group demonstrated that zonisamide displaced [^{3}H]flunitrazepam and [^{3}H]muscimol binding in rat brain, albeit at relatively high concentrations (100–1,000 μM).[111,112] In addition, [^{3}H]zonisamide was found to bind to a stereospecific binding site in a crude synaptosomal fraction of whole rat brain with a K_d of 90 nM.[112] Clonazepam reduced and GABA increased [^{3}H]zonisamide binding, suggesting that the zonisamide binding site was coupled to benzodiazepine receptors. However, in spinal cord neurons in cell culture, zonisamide did not affect electrophysiologic responses to GABA.[142] Overall, it seems unlikely that effects on GABAergic systems contribute in a major way to the anticonvulsant actions of zonisamide.

In a large number of additional studies, zonisamide has been reported to have various effects on monamine turnover and metabolism (reviewed by Macdonald[98]). Effects on dopamine systems have been particularly well studied, with several reports that zonisamide enhances dopamine turnover at therapeutic concentrations[125] but it is unlikely that these effects contribute to the therapeutic activity of zonisamide in epilepsy.[114]

Zonisamide has a sulfonamide side chain that is a common element of many carbonic anhydrase inhibitors, including acetazolamide, and zonisamide is well recognized to inhibit carbonic anhydrase isoenzymes.[101] At least 15 human carbonic

anhydrase isoenzymes have been described, including forms that are cytoplasmic (I, II, III, and VII), mitochondrial (VA and VB), secreted (VI), and membrane-associated (IV, IX, XII, and XIV). Although zonisamide is a very weak inhibitor of membrane-associated isoenzyme XII, it inhibits isoenzyme IX with high affinity (K_I, 5.1 nM).[121] Given the emerging evidence that carbonic anhydrase regulates GABA signalling,[141] this effect is intriguing. However, a role for carbonic anhydrase inhibition in the anticonvulsant mechanism of zonisamide has been discounted on the basis of structure-activity studies. Thus, both zonisamide and its 7-methyl analog have similar carbonic anhydrase inhibitory activity, but only zonisamide was protective in the mouse MES test.[103] This observation indicates that carbonic anhydrase inhibition is not the sole or major mechanism underlying the anticonvulsant activity of zonisamide; whether it is a contributory factor remains to be determined.

Summary and Conclusions

In summary a key action of zonisamide that likely contributes to its anticonvulsant activity is the modulation of voltage-gated Na channels to limit sustained, high-frequency, repetitive action potential firing. In addition, and in distinction with conventional Na-channel blocking AEDs, zonisamide can inhibit T-type Ca channels. Both effects occur at clinically effective free serum concentrations. By virtue of its action on Na channels, zonisamide inhibits the release of glutamate and other neurotransmitters through a presynaptic action. In addition, zonisamide has complex actions on dopamine, serotonin and acetylcholine metabolism; the relationship of these actions to anticonvulsant activity is obscure. Finally, zonisamide is a potent inhibitor of some carbonic anhydrase isoenzymes, but this action has not yet been linked to its therapeutic activity. The complex cellular actions of zonisamide, including its effects on T-type Ca channels, likely account for its broader clinical spectrum of activity than conventional Na channel blocking AEDs.[209] The multiple mechanisms may extend its range of clinical utility not only to generalized absence seizures, but also to myoclonic seizures (including those in juvenile myoclonic epilepsy), infantile spasms, and the Lennox-Gastaut syndrome.

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Chapter 137

Basic Principles of Medicinal Chemistry

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Raman Sankar

Introduction

Medicinal chemistry is the branch of applied organic chemistry that deals with the design and synthesis of new chemical entities for the symptomatic or curative treatment of human disease states.[30] Medicinal chemistry is a multidisciplinary endeavor. It has as its basis a firm understanding of all branches of chemistry (in particular synthetic organic chemistry), but also embraces many elements of other disciplines that are necessary tools for the practicing medicinal chemist, including pharmacology, pharmacy, physiology, biochemistry, and medicine. The primary objective of medicinal chemistry is to discover new prototype molecules as prospective drugs, and subsequently to optimize any promising drug candidate by improving its beneficial therapeutic effects and minimizing its undesirable side effects. As applied to epilepsy, the role of medicinal chemistry is to discover new drugs to treat seizures with improved efficacy and decreased toxicity.

The medicinal chemistry of anticonvulsants has a long history, and it will probably have a long future. During the past 2,000 years, many compounds have been suggested as potential therapeutic agents for epilepsy. The history of the medicinal chemistry of anticonvulsant drugs can be categorized into three distinct eras: The era of charlatanism (prehistory to 1857), the era of serendipity (1857 to 1980), and the era of rational drug design (1980 to the present). The future of anticonvulsant medicinal chemistry will also hold a number of distinct changes.

The Era of Charlatanism: Ancient Times to 1857

Epilepsy was described by the school of Hippocrates in the book *On the Sacred Disease*, written in 400 BC. Although the role of heredity as well as the relationship between focal head trauma and contralateral seizures was recognized at the time, the overwhelming emphasis on the role of possession by evil spirits and excess accumulation of cold phlegm resulted in therapeutic approaches that focused on occult or magical powers to render a cure. The therapy of that time was dominated by superstition and charlatanism and relied on agents such as gladiator blood, seal penis, mistletoe, and dried human skull extract. Not surprisingly, such cures were of negligible value.

It was not until the “era of serendipity” that truly useful chemical agents to treat seizures first emerged.

The Era of Serendipity: 1857 to 1980

Many important drugs have had their origin in an accident, either in the laboratory or the clinic. The so-called serendipity factor looms large in the history of medicinal chemistry and accounts for several major discoveries, from penicillin as an antibacterial agent to imipramine as an antidepressant. Although this is a humbling realization, the evolution from penicillin to the large number of synthetic *B*-lactams and cephalosporins in use today is a direct result of the application of concepts of drug design. Design concepts that build on a serendipitous lead to generate a large number of synthetic analogs have played a role in the development of several anticonvulsant drugs. One of the authors[30] has stressed the critical importance of serendipity in a historical analysis of antiepileptic drug development, urging investigators to look sideways for the unexpected. From 1857 to 1980, serendipity was the major discoverer of anticonvulsant drugs.

The first application of effective chemotherapy to control seizures was undertaken by Sir Charles Locock, an obstetrician in the mid-19th century. In those days, bromide preparations were known for their sedative and antiaphrodisiac properties, and epilepsy was thought to result from excessive masturbation and hysteria. These factors caused Locock to introduce bromides for the treatment of seizures related to menses and seizures considered to be venereally induced. Although his reasoning was quite erroneous, this inorganic agent was the first effective pharmacotherapeutic agent for epilepsy.

The first synthetic organic medicinal agent to control seizures was phenobarbital, a ureide (a derivative of urea, synthesized by the combination of urea and substituted malonic acid) that was introduced in 1912.[15] The discovery of the anticonvulsant potential of phenobarbital was quite accidental, as the drug had been administered mainly to sedate a ward of noisy epileptic patients during the night. From that point on, the increasing ability of chemists to tinker with the basic ring structure of phenobarbital, combined with new animal models of seizures, became the driving force behind the development of anticonvulsant drugs.

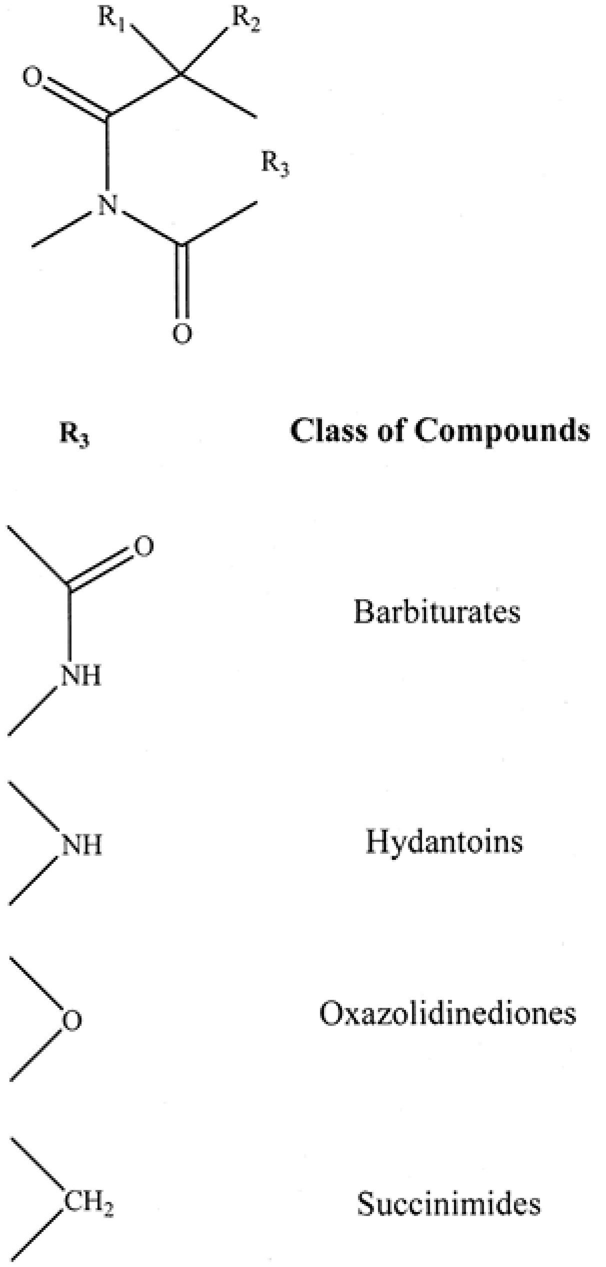


FIGURE 1. Structure common to antiepileptic drugs containing the ureide moiety.

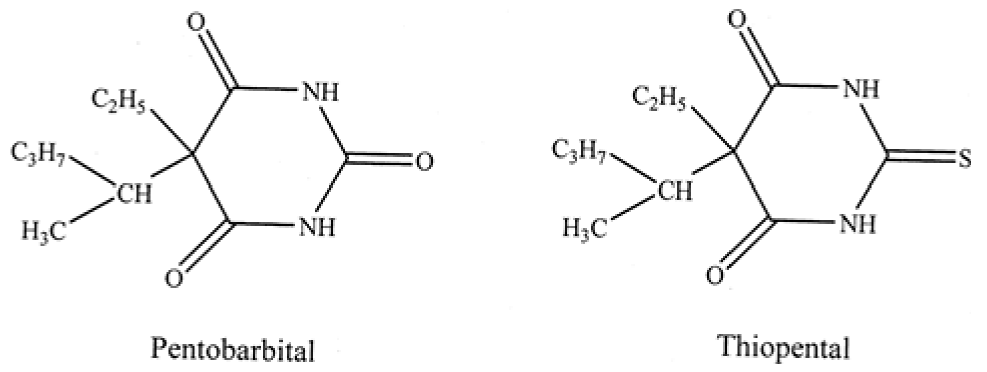


FIGURE 2. Substitution of the urea oxygen on pentobarbital with sulfur to create thiopental results in a compound with increased lipid solubility; this in turn leads to extremely rapid distribution of thiopental into the central nervous system and rapid redistribution to adipose tissue, thus making it a member of the ultra-short series.

The first epochal result of such an approach was the discovery of phenytoin by Merritt and Putnam.[19] The development of the maximal electroshock model by Merritt and Putnam,[20] with its subsequent use as a screening model, was crucial to the availability of phenytoin in 1938. The close structural relationship between phenobarbital (a barbiturate) and phenytoin (a hydantoin) can be discerned from FIGURE 1. The expansion of the barbiturate and hydantoin families came about because the side chains (aryl, alkyl, cycloalkyl) could be varied and *N*-alkyl groups could be introduced to the basic structure of phenobarbital and phenytoin, giving rise to a number of compounds that differed in their onset and duration of action. The subsequent availability of the pentylenetetrazol model gave rise to the development of trimethadione, an oxazolidindione, as a specific agent for absence (then call petit mal) seizures. This compound was originally studied as an analgesic; it was systematic screening using available animal models that resulted in its accidental discovery as an antiabsence drug. The development of the succinimides, especially ethosuximide, yielded effective antiabsence compounds that were also less toxic. The close structural relationship among the barbiturates, hydantoins, oxazolidindiones, and succinimides (families of compounds in the ureide dynasty), all of which possess a cyclic structure, is clearly seen in FIGURE 1. All these compounds resulted from the serendipitous clinical observation of phenobarbital as an anticonvulsant.

A wealth of lessons in medicinal chemistry was learned from the initial studies with ureides. For example, it was noted that the lipid solubility of a given compound within the ureide family could be increased according to the size of the alkyl (cycloalkyl) and aryl side chains, by the introduction of *N*-alkyl groups (which alter the pKa of the compound and hence the extent of ionization), or by replacing an oxygen in the ureide ring with a sulfur (Fig. 2).

The lipid solubility of a compound correlates with the rapidity with which therapeutic levels may be achieved in the brain. Other chemical modifications influenced the rate of drug clearance by affecting plasma protein binding, affinity for the hepatic cytochrome P450/mixed-function oxidase system, and the rate of the oxidative reaction in that matrix. Accordingly, the structural congeners developed via medicinal chemistry gave rise to drugs with distinctive onsets of action as well as duration of action.

The ureides dominated the anticonvulsant drug scene until the arrival of the benzodiazepines, carbamazepine, and valproic acid. All three of these classes of drug were discovered by serendipity. For example, chlordiazepoxide was discovered when it was accidentally synthesized in an attempt to produce antipsychotic tricyclic drugs; its sedative and anxiolytic properties were then observed serendipitously, and only later were the anticonvulsant properties of benzodiazepines realized. Similarly, carbamazepine was designed as a psychotropic tricyclic; its unanticipated anticonvulsant properties were revealed at a later time.

However, the importance of serendipity in drug discovery is most clearly illustrated by the circumstances in which the anticonvulsant activity of valproate was recognized. In 1963, a graduate student in France prepared a series of heterocyclic molecules that were subsequently submitted to a local pharmaceutical company for screening in a variety of biologic assays. Because of the poor solubility of these compounds, they were somewhat randomly dissolved in a series of solvents, of which valproic acid was one. When it was noted that one of the compounds seemed to have anticonvulsant activity, subsequent work revealed that all such activity was located in the serendipitously selected valproic acid solvent.[4,5] Thus, valproate was discovered completely by accident.

As is apparent, the major traditional anticonvulsant drugs (phenobarbital, phenytoin, carbamazepine, valproate, benzodiazepines) were all discovered through serendipitous observations. Because of this element of chance, the medicinal chemistry of these important compounds remains incomplete. For example, modern electrophysiologic studies suggest that phenytoin, carbamazepine, and valproate probably function at the level of the voltage-gated sodium channel; however, the structure of the receptor site, the nature of the drug–receptor interaction, and the portion of the drug molecule interacting with the receptor all remain incompletely elucidated.

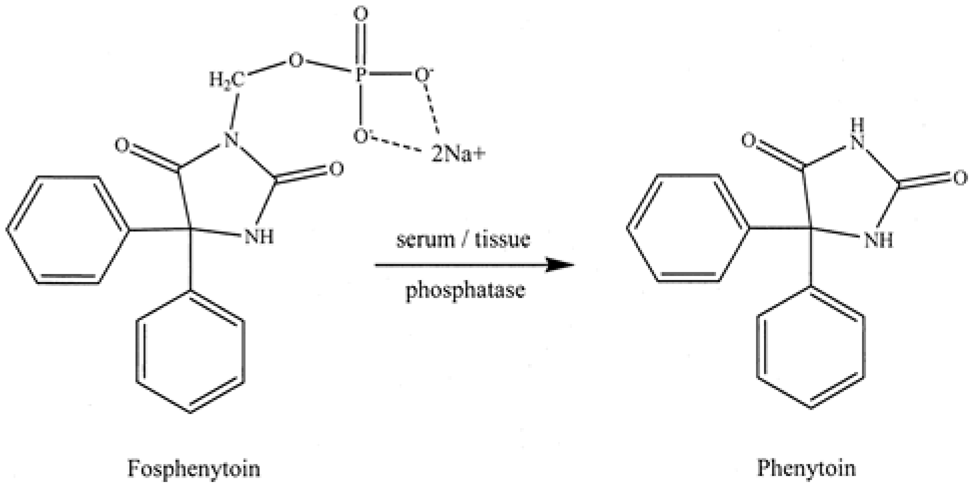


FIGURE 3. Modern antiepileptic drugs.

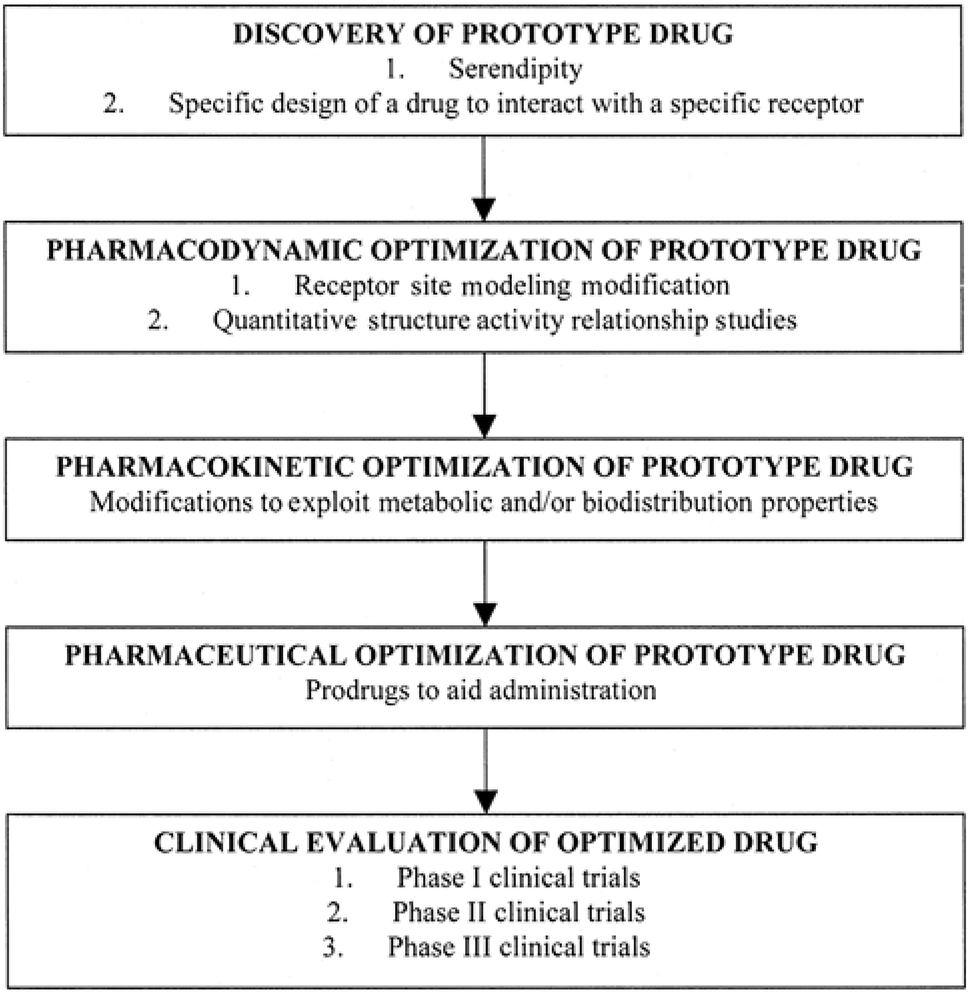

DISCOVERY OF PROTOTYPE DRUG
1. Serendipity
2. Specific design of a drug to interact with a specific receptor
PHARMACODYNAMIC OPTIMIZATION OF PROTOTYPE DRUG
1. Receptor site modeling modification
2. Quantitative structure activity relationship studies
PHARMACOKINETIC OPTIMIZATION OF PROTOTYPE DRUG
Modifications to exploit metabolic and/or biodistribution properties
PHARMACEUTICAL OPTIMIZATION OF PROTOTYPE DRUG
Prodrugs to aid administration
CLINICAL EVALUATION OF OPTIMIZED DRUG
1. Phase I clinical trials
2. Phase II clinical trials
3. Phase III clinical trials

FIGURE 4. Modern antiepileptic drug design and optimization.

Although the discoveries may have been accidental, advances in the medicinal chemistry of anticonvulsant drugs made

accidentally during the era of serendipity paved the way to the present era of rational drug design.

The Era of Rational Drug Design: 1980 to the Present

Over the past 25 years, a number of new chemical entities have been introduced as new agents for the treatment of epilepsy, with many more on the drawing board.[18] Some of these new agents are shown in FIGURE 3. This past quarter-century has been an era of rational drug design.

Strictly defined, rational drug design is a process whereby the three-dimensional structure of some biologic macromolecular receptor involved in the etiology and pathogenesis of a given disease process is determined, thus permitting the intelligent engineering of molecules specifically developed to dock with and alter the function of the receptor macromolecule. Operationally defined, rational drug design is the process of optimizing a prototype drug to yield the best possible clinical candidate. A flow chart describing this process is shown in FIGURE 4.

Rational drug design starts with the identification of a prototype or lead compound. This may be done using several approaches, including random screening and specific design. The

lead compound is then optimized at three distinct levels: Pharmacodynamic, pharmacokinetic, and pharmaceutical. At the pharmaceutical level, the route of administration and the adequacy of solubility and penetration into the organism are determined. The pharmacokinetic level concerns the metabolism of the drug (including first-pass effect through the liver) and its biodistribution to the receptor microenvironment. The pharmacodynamic phase involves the interaction of the drug with its receptor at the molecular level of conceptualization.

Discovering the Prototype Drug

Craig[6] described several methods of “drug discovery” to convey the fact it is usually not restricted to de novo drug design. The general approaches to the identification of prototype compounds include the three described below:

1. Specific design of a drug to interact with a receptor site after the structure of the receptor site has been rigorously determined by x-ray crystallography or other means
2. Preparation of structural analogs of synthetic chemicals with interesting biologic activity
3. Preparation of novel chemicals based on the known structures of naturally occurring, biologically active substances of plant and animal origin

Approach 1: This ultimate ideal in rational drug design involves the isolation, purification, and crystallization of receptor proteins. As many of the relevant antiseizure receptor targets (such as the transmembrane voltage-gated sodium channel) are not amenable to such biochemical manipulations, this approach remains unrealized as far as anticonvulsant drug discovery is concerned. Nevertheless, ion channels remain as an important target for anticonvulsant drug design.[31] Also, recent pioneering work by McKinnon (for which he was awarded the 2003 Nobel Prize in Chemistry) is starting to provide insights into the structure of voltage-gated ion channels.

Approach 2: For years it was believed that folate deficiency was a mechanism of anticonvulsant activity. For instance, many workers suggested that the mechanism of phenytoin might be exerted through this route. Using this as a starting point, attempts were made to design novel anticonvulsant drugs as analogs of compounds with known antifolate activity. Lamotrigine, which was developed as a congener of methotrexate, demonstrated significant anticonvulsant activity. Unfortunately, the success of lamotrigine as an anticonvulsant drug does not occur via a folate mechanism, but rather through a sodium channel blockade—the importance of the serendipity factor persists even in the era of rational drug design.

Approach 3: In rational drug design, discovering a prototype drug usually requires that the underlying biochemistry be understood at some reasonable level of refinement. Seizures occur when an imbalance in the two principal neurotransmitters occurs: L-glutamic acid, an excitatory amino acid neurotransmitter, and γ-aminobutyric acid (GABA), an inhibitory amino acid neurotransmitter. Of these two neurotransmitters, GABA is particularly important in epilepsy. The concentration of GABA is regulated by two pyridoxal-5-phosphate (PLP)-dependent enzymes: L-glutamic acid decarboxylase (GAD, glutamate decarboxylase), which converts glutamate to GABA, and GABA aminotransferase (GABA-T), which catabolizes GABA to succinic semialdehyde. (Although succinic semialdehyde is cytotoxic, it is rapidly and efficiently metabolized to succinic acid by the enzyme succinic semialdehyde dehydrogenase [SSADH].)

Because GABAergic dysfunction seems to play a role in the pathogenesis and etiology of seizures and epilepsy, it seems understandable that GABA or some related analog might be a profitable prototype drug. A wealth of experimental data supports this assertion. For example, when GABA levels fall below a certain threshold level, seizures may occur; likewise, direct injection of GABA into the brains of experimental animals can stop seizure activity. Accordingly, it would seem reasonable that GABA should be an ideal prototype anticonvulsant drug. Nevertheless, when GABA is administered orally, it is devoid of anticonvulsant activity, as it is not bioavailable to the brain; GABA does not cross the blood–brain barrier. Another approach for increasing brain GABA levels would be to discover a compound capable of crossing the blood–brain barrier and inactivating the GABA-T enzyme implicated in the biodegeneration of GABA. Provided the glutamate decarboxylase was not simultaneously inhibited, GABA levels would rise to effective anticonvulsant concentrations. Vigabatrin, a structural analog of GABA, is such a molecule. Vigabatrin is a molecule that functions as a mechanism-based inactivator of GABA-T. Vigabatrin is an unreactive compound that is converted by the normal catalytic mechanism of GABA-T to a reactive intermediate compound that attaches to the GABA-T, thereby inactivating the enzyme.

It is surprising that GABA does not cross the blood–brain barrier, but vigabatrin, which is also a small, charged molecule, is capable of diffusing across the lipophilic blood–brain barrier. There are two reasons for this seeming paradox. First, the attachment of a vinyl substituent increases the lipophilicity of the molecule. Second, the vinyl group is an electron-withdrawing substituent that lowers the pKa of the amino group; this in turn increases the concentration of the uncharged, nonzwitterionic form, which is more lipophilic than the charged, zwitterionic form.

Optimizing the Pharmacodynamic Level

One of the first steps in rational drug design is to optimize a candidate drug at the pharmacodynamic level, that is, at the level of the drug–receptor interaction. In anticonvulsant drug design, the nature and structure of the receptor are not clearly known. For example, although it is known that most current anticonvulsant drugs work at the level of the voltage-gated sodium channel, the structure of this protein remains unsolved. Accordingly, it is necessary to synthesize many analogs (hundreds or thousands!) of a prototype drug in an attempt to discover analogs with improved anticonvulsant activity. The systematic approach employed for this purpose is termed quantitative structure-activity relationship studies.[26]

Quantitative Structure-Activity Relationship Studies

Quantitative structure-activity relationship (QSAR) studies are central to drug optimization. A QSAR study answers the following question: What is it about the structural, physical, and chemical properties of the drug molecule that impart its biologic activity, and how is the biologic activity modified by systemic variations of molecular structure?[13] The phenobarbital molecule may be considered an example.

There are many ways of approaching a QSAR study of barbiturates. Bikker et al.[2] have published a theoretic quantum pharmacologic QSAR study of barbiturates. These authors identified 48 barbiturates with varying anticonvulsant activities, which had been assessed using comparable biologic assays. Each barbiturate, regardless of its activity, was analyzed according to a series of descriptors. These descriptors were divided into four groups: Geometric, electronic, topologic,

and physiochemical. Geometric descriptors (e.g., bond lengths, bond angles, interatomic distances) reflect the shape and size properties of the molecules.[21] Electronic descriptors (e.g., atomic charges, molecular dipole) encode the electron distribution properties within the drug. Topologic descriptors are numeric representations of molecular branching and complexity.[16] Physiochemical descriptors (e.g., log P, the octanol-water partition coefficient) reflect the capacity of the drug to traverse biologic membranes and barriers.[14] These groups of descriptors are calculated, using classic mechanics and quantum mechanics, for each drug molecule. Statistical algorithms are then employed to discern the minimal number of descriptors capable of distinguishing activity from inactivity. As a corollary, it is possible to gain insights into the nature of the drug receptor site. This study clearly demonstrated that there are different portions of the phenobarbital molecule necessary for activity against maximal electroshock seizures and against pentylenetetrazol-induced seizures. The portion of the molecule responsible for its bioactivity is its *bioactive face* or *pharmacophore* (the three-dimensional arrangement of atoms necessary for biologic activity).

Once the QSAR studies permit the structure of the pharmacophore to be deduced, it is possible to optimize the drug by refining its structure.

Optimizing the Pharmacokinetic Level

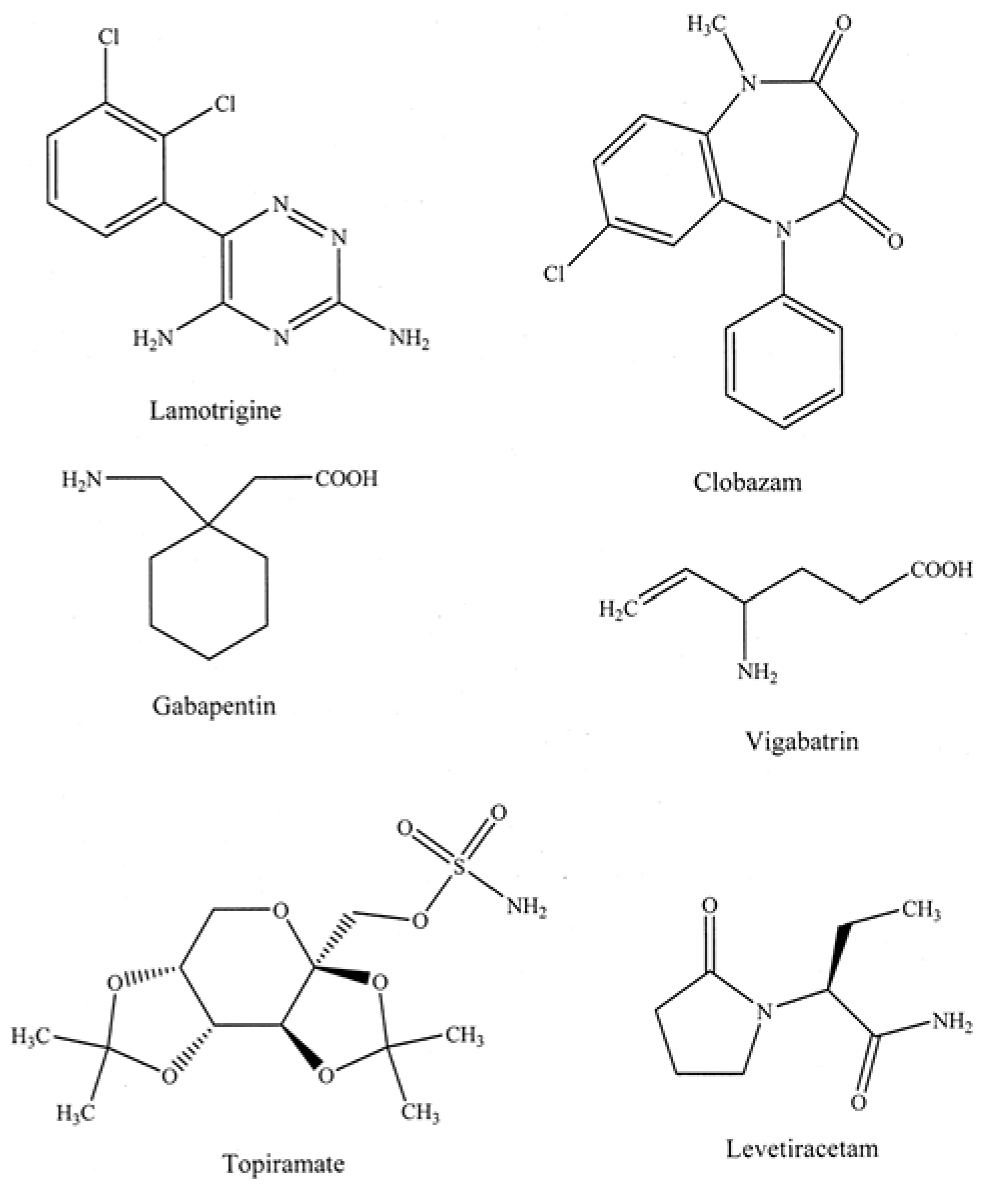
Metabolic Masking: Carbamazepine Versus Oxcarbazepine

The oxidation of the 10,11-double bond of the seven-membered azepine ring in carbamazepine (CBZ) to form epoxy-CBA is quantitatively the most important pathway in the biotransformation of CBZ.[9] Although the anticonvulsant efficacy and neurotoxicity of this epoxide metabolite are comparable with those of the parent drug,[3] it has long been implicated as a significant contributor to the clinical toxicity of therapy with CBZ. This is because epoxy-CBZ is inactivated by conversion to the *trans*-diol by an epoxide hydrolase that is less inducible by repeated doses of CBZ than the P450 isoforms that produce the epoxy-CBZ.[7] Oxcarbazepine (OCBZ), the 10-keto derivative of CBZ, was developed to overcome this problem. This compound is rapidly converted to a monohydroxyl derivative, 10-hydroxy-CBZ, which is responsible for the anticonvulsant effect. In this sense, oxcarbazepine is a bioprecursor and is activated by an enzymatic reduction to the active metabolite. Oxcarbazepine compares with CBZ in efficacy and appears to produce fewer adverse effects. Allergic reactions may also be less frequent with OCBZ and CBZ, as covalent interaction of the epoxide with cellular macromolecules may be responsible for the generation of haptens that produce immunologic responses.

Optimizing the Pharmaceutical Level

Bioprecursors Versus Prodrugs: Fosphenytoin

It is possible to create a temporary linkage between an active drug and a carrier moiety to modify strongly the lipophilicity or water solubility of a drug. The carrier group may be readily hydrolyzed on administration by chemical or enzymatic processes for rapid release of the active moiety (parent drug molecule). An example of this approach is seen in the design of fosphenytoin. Phenytoin, even as the sodium salt, has very limited water solubility. The intravenous preparation has a pH of approximately 12 and employs a vehicle that includes 40% propylene glycol and 10% ethanol, making it a highly irritating solution. The limited solubility also precludes the possibility of using the solution intramuscularly. Fosphenytoin is the disodium phosphate ester of 3-hydroxymethyl-5,5-diphenylhydantoin (Fig. 5). It has significantly better solubility than phenytoin sodium, and the intravenous preparation has a pH of 8.8 (approximately 1,000-fold less alkaline than a solution of sodium phenytoin). This compound may be used with ease intravenously with far less irritation than that caused by phenytoin sodium. It may also be used safely as an intramuscular injection. The ester is rapidly converted by serum alkaline phosphatase to free phenytoin, and the C_{max} and T_{max} of free phenytoin achieved by infusion at 100 mg/min are comparable with those attained by a 50-mg/min infusion of phenytoin sodium; the incidence of pain and burning immediately after infusion are dramatically reduced.[10]



Lamotrigine

Clobazam

Gabapentin

Vigabatrin

Topiramate

Levetiracetam

FIGURE 5. Hydrolytic conversion of fosphenytoin to phenytoin. The disodium phosphate moiety provides for a more water-soluble, less alkaline, and less irritating product.

The Future of Anticonvulsant Medicinal Chemistry

The future of anticonvulsant medicinal chemistry holds significant promise.

Anticonvulsant Discovery by High Throughput Screening

Modern drug discovery through screening is emerging as an ever-improving technologic tour de force.[30] If a reliable bioassay is available, it is possible to screen thousands or even millions of compounds in this bioassay. The crystal structures of key protein receptors involved in the disease process do not have to be known; indeed, the proteins do not even have to be identified. If the bioassay is fast and efficient, and if the library of compounds being screened is diverse and comprehensive, then in principle it should be possible to identify a lead compound. However, the key to success lies in the “diversity of the library of compounds” (i.e., a combinatorial chemistry library) and in the efficiency of the screening bioassay (i.e., high throughput screening methods).

The first key to success in drug discovery by screening is the availability of a large and structurally diverse library of compounds. If the library contains a million compounds that are all analogs of each other, then it may be large, but it is probably not sufficiently diverse. The library should have the full range of chemical functionalities displayed in all possible combinations in three-dimensional space. Creating such a library is not a trivial task.

Combinatorial chemistry is both the philosophical and the practical method with which to create such structurally diverse compound libraries. Combinatorial chemistry is defined as that branch of synthetic organic chemistry that enables the concomitant synthesis of large numbers of chemical variants in such a manner as to permit their evaluation, isolation, and identification. Historically, the first major libraries were oligomers of naturally occurring monomers. A good example would be a library of all possible tripeptides. Using the 20 naturally occurring amino acids, it is possible to produce 8,000 different tripeptides. Such peptide libraries are easy to synthesize, and, since amino acid side chains possess a wide variety of different functional groups, it is possible to achieve a good measure of structural diversity. However, in general, peptides are not drugs and a peptide lead would have to be modified into a druglike molecule.

A step beyond the naturally occurring oligomeric libraries is to create libraries from nonnaturally occurring monomeric building blocks. The medicinal chemistry literature contains a fair number of examples of such libraries. Although these libraries overcome the limitations of naturally occurring oligo- meric libraries, most drugs are not polymers. To address this problem, new libraries are emerging in which the central moiety is a small organic molecule, not a polymer. The diversity library is then constructed by attaching many different substituents to this central moiety. Through these various techniques, large and structurally diverse libraries of compounds are becoming available.

The second key to success in drug discovery by screening is the availability of a high throughput bioassay with which to screen the large, chemically diverse library of molecules in a time-efficient manner. If a 200,000 compound library is available, the biologic evaluation assay must be rapid and reliable. If the assay were capable of testing five compounds per day, it would take 110 years to evaluate the entire library. Clearly, this is not the time for elaborate in vivo testing. Fast, efficient in vitro assays are required. The ability to inhibit an enzyme is a good example of a potentially useful assay for high throughput screening. This issue is crucial in anticonvulsant drug discovery. Most models of seizures are slow, tedious animal models (maximal electroshock, pentylenetetrazole models), which are not amenable to high throughput screening (HTPS). If future anticonvulsant drug discovery is to employ HTPS, then efficient bioassays relevant to epilepsy must be identified.

A variety of high throughput assays have been developed and perfected over the past 10 to 20 years. These include the following three basic types of assay:

1. Microplate activity assays (assay is in solution in a well; the result of the assay, such as enzyme inhibition, is linked to an experiment observable to enable identification of bioactivity)
2. Gel diffusion assays
3. Affinity selection assays

Of these, microplate assays are probably the most widely used. Screening combinatorial libraries on microplates containing 96 or 384 (or more) wells is time and cost efficient. Using robotic techniques, it is possible to perform more than 100,000 bioassays per week in a microplate system (permitting the above-described 200,000 compound library to be screened in 2 weeks, rather than over a century).

In addition to selecting an appropriate assay, it is also necessary to have a pooling strategy. It is more efficient to test many compounds per well on the microplate, rather than one compound per well. If one could test 100 compounds per well, then the standard 96-well plate would enable almost 10,000 compounds to be evaluated in one experiment.

The evolution of methods for combinatorial syntheses and high throughput screening will be necessary to address the explosion of druggable targets soon to be identified by the genomics and proteomics revolutions. Genomics and proteomics represent the future of lead compound identification for drugs in general and perhaps anticonvulsants in particular.

Genomics is the study of genes and their functions. On June 26, 2000—the dawning of the present century—a historic milestone in genomic science was attained when researchers involved with the Human Genome Project jointly announced that they had sequenced 97% to 99% of the human genome. The human genome consists of 23 pairs of chromosomes with 3 billion base pair codes for approximately 24,000 to 30,000 functional genes.

Determining gene structure and function through genomics definitely does illuminate the path for linking specific genes to specific disorders, such as epilepsy. Although genomics did deliver phenomenal masses of raw information, the pathway to using genomics for anticonvulsant drug discovery is not immediately apparent. Such an endeavor will require postgenomics technologies. Taking genomics one step further for the purpose of anticonvulsant drug discovery will require linking specific proteins to those specific genes. Clearly, there exists a vast gap between genomics and drug discovery. Bridging this gap will ultimately be a daunting task that lies within the domain of proteomics.

Proteomics is a protein-based science that seeks to provide new, fundamental information about proteins on a genome-wide scale. Proteomics seeks to elucidate the structure and function profiles of all proteins encoded within a specific genome; this collection of proteins is termed the proteome. The proteomes of multicellular organisms present an immense challenge in that more than 75% of the predicted proteins have no apparent cellular function. Furthermore, although the human proteome has more than 100,000 proteins, only a fraction of these proteins are expressed in any individual cell type. If epilepsy is to be linked to specific proteins, it is imperative that ways be developed to deduce which individual protein is expressed in which individual cell.

Since protein and mRNA concentrations tend to be correlated, DNA microarray technology is a powerful technique with which to monitor the relative abundance of a specific mRNA in an individual cell and to correlate this with a specific protein. In addition to these microarray technologies, many other technologies will be required if proteomics is to deliver the drugs promised by genomics. For example, drug design requires much more than merely knowing the primary amino acid sequence of a protein—it requires a precise knowledge of the protein's three-dimensional structure, down to the level of the Angström. To date, science has no technology that enables one to use the information coded in a protein's primary amino acid sequence to deduce the overall tertiary structure of the protein. This is the protein folding problem. The need to solve this problem has given rise to the subdiscipline of structural proteomics, a technology that is based upon the principle that structure underlies function and that endeavors provide three-dimensional structural information for all proteins.

Despite these advances, the pathway to the awaiting plethora of anticonvulsant drugs is still far from perfect. In general, anticonvulsant drugs are small organic molecules. Obtaining these drug molecules will require yet another step in the “from genomics to proteomics to disease” cascade. Just as proteomics is a crucial bridge uniting genomics to disease, so too will an equally crucial bridge be needed to unite proteomics with therapeutics. The bioinformatics/cheminformatics spectrum may be that bridge.

Bioinformatics/cheminformatics constitute an *in silico* science that endeavors to predict the phenomenology of cellular physiology and pharmacology at a molecular level using computational methods. Using databases of compounds and other theoretic molecular design techniques, bioinformatics and cheminformatics will attempt to identify novel molecules to alter the function of various proteins defined by the genome-based proteome. Bioinformatics/cheminformatics will apply knowledge-discovery and pattern-recognition algorithms to the genome-wide and proteome-wide experimental data, thereby facilitating anticonvulsant drug design. If structural proteomics has identified the functional portion of an important protein, cheminformatics will search large databases of druglike molecules to identify one that has the right shape and properties to dock with the protein.

Adopting New Methodologies of Drug Design

The ways in which drugs are designed and synthesized are changing. In the future, anticonvulsant drugs will be designed in part using *quantum pharmacology* calculations, also called *molecular modeling studies* or *computer-assisted molecular design (CAMD)*. Indeed, CAMD is emerging as a biotechnology of the future. CAMD calculations are performed using molecular mechanics, molecular dynamics, and semiempirical molecular orbital and *ab initio* quantum mechanics calculations. Molecular mechanics calculations employ a classic mechanical approach, in which an empiric force field equation describes the shape of a molecule as a function of energy. Molecular mechanics conceptualizes atoms as distensible spheres, focusing on the position of nuclei and not considering electrons explicitly. Quantum mechanics, on the other hand, treats electrons explicitly, using the nonempiric Schroedinger equation in preference to a force field equation. Regardless of the mathematical method employed, all these techniques permit energy to be calculated for some shape (conformation) of the molecule. These methods are then used to optimize the shape of the drug molecule, the shape of the receptor protein, and the nature of the interaction between the drug and its receptor.

Designing Rational Polypharmacy in a Single Drug

Existing methods for CAMD attempt to optimize the drug molecule to a receptor with which it may interact. Emerging understanding of the patterns of abnormal neuronal excitability that underlie many models of the epilepsies suggests that multiple neurotransmitters and subtypes of their receptors are involved. For instance, strong evidence from both in vitro and in vivo studies of the glutamatergic system suggests that both *N*-methyl-D-aspartate (NMDA) and non-NMDA mechanisms have important roles to play in several models; epileptiform activity may be abolished by drugs that act at nonglutamatergic sites (modulators of GABA activity). The possibility then exists that a drug that has suitable low-affinity interactions at multiple receptors may provide considerable efficacy with low neurologic toxicity.[23]

Topiramate is an example of a drug that has at least three interesting interactions built into one molecule: (a) use-dependent blockade of voltage-dependent sodium channels; (b) blockade of sodium currents mediated by activation of non-NMDA α-amino-3-hydroxy-5-methyl-4-isoxazoleproprionic acid (AMPA) receptors;[24] and (c) enhancement of GABA-mediated chloride currents. In addition, topiramate also exhibits weak carbonic anhydrose antagonism; the contribution of this activity to the overall anticonvulsant activity of topiramate may not be significant.

The conventional view in drug design has been that reduction of side effects is best achieved by high selectivity and

potency. On the other hand, it seems logical that in the case of anticonvulsant drug molecules that modulate excitability mechanisms critical to normal brain function, agents with high potency and efficacy may carry the liability of unacceptable toxicity. The strategy of searching for drugs that exert low-efficacy effects on more than one receptor seems to be a worthwhile one. It should be kept in mind that both felbamate and topiramate are products of extensive screening. From the point of view of CAMD, once optimal structural features for specific drug interactions have been defined, further algorithms may become important in looking into the possibility of building multiple pharmacophores and the requisite conformational freedom to facilitate multiple interactions in a single molecule.

Designing “Curative” Antiepileptogenic Drugs

The drugs currently available for treating epilepsy are little more than symptomatic agents, suppressing the symptoms of epilepsy (i.e., seizures) while failing to contend meaningfully with the fundamental pathologic process that initially causes (and continues to cause) the underlying susceptibility to seizures. Furthermore, the current drugs for the symptomatic suppression of seizures are effective in <65% of patients. The direction to be pursued in the development of these new agents is not apparent. With an existing drug selection populated by a diversity of old agents (e.g., phenytoin, carbamazepine) and newer agents (e.g., vigabatrin, lamotrigine), the interests of the patient population will not be served best by simply more of the same. Central to the rational design of truly novel new compounds will be the evolution of concepts concerning the etiology and pathogenesis of epilepsy. The new agents developed to interact with target receptors based on these concepts must have the capacity to influence the natural history of epilepsy in a curative sense, not merely mask the symptoms.

An important first conceptual step in target selection for future curative drug design will be differentiating between the notions of ictogenesis and epileptogenesis.[29] A seizure (Latin, *ictus*) is a single, discrete clinical event caused by an excessive electrical discharge from a collection of neurons. A seizure is merely a symptom of epilepsy. Epilepsy, on the other hand, is a dynamic and frequently progressive process characterized by an underlying sequence of pathologic transformations whereby normal brain is altered, becoming susceptible to recurrent seizures. Ictogenesis (the initiation and propagation of a seizure in time and space) is a rapid and definitive electrical/chemical event occurring within seconds or minutes. Epileptogenesis (the gradual process whereby normal brain is transformed into a state susceptible to spontaneous, episodic, time-limited, recurrent seizures through the initiation and maturation of an epileptogenic focus) is a slow biochemical/histologic process occurring insidiously through a period of months to years. Obviously, the chemistries of ictogenesis and epileptogenesis have unique differences, and not surprisingly, therapeutics targeting these two processes may also have definite differences. For the purposes of rational drug design, both processes must be explicitly understood at the molecular level.

Ictogenesis is a fast, short-term event. Heuristically, ictogenesis can be divided into the rapidly sequential phases of initiation and elaboration; elaboration arises from the extension of the seizure in time and space. Ictogenesis involves excessive brain electrical discharges propagated by a cascade of chemical events initiated by the sequential opening of Na^+ channels and subsequent involvement of K^+ channels and the Na^+/K^+ATPase pump. The electrical activity passes from neuron to neuron via the CA^{2+} channel-mediated release of neurotransmitters. Logically, diverse approaches exist for the rational design of anti-ictogenic (anticonvulsant, antiseizure) drugs, including agents that (a) block voltage-gated ion channels, (b) antagonize excitatory neurotransmitters, and (c) mimic inhibitory neurotransmitters. The obvious central role of the transmembrane voltage-gated Na^+channel protein in ictogenesis has resulted in the majority of currently available anticonvulsant drugs (e.g., phenytoin, carbamazepine, lamotrigine) being targeted against this receptor site.

Epileptogenesis, unlike ictogenesis, is a gradual, two-phase process showing dynamic changes over the course of time. Phase 1 is the initiation of the epileptogenic focus/predisposition, and phase 2 is the maturation of the epileptogenic focus/predisposition. Phase 1 epileptogenesis denotes the events that take place before the occurrence of the first seizure. There may be a considerable delay of months to years between the occurrence of the brain injury (e.g., stroke, trauma) and the onset of spontaneous, recurrent seizures; during this latent period, epileptogenesis is taking place, culminating in active epilepsy characterized by recurrent seizures. Phase 2 epileptogenesis denotes the events that take place after the first seizure has occurred. This also is a long, protracted process, in which seizures may become more frequent, more severe, more refractory to treatment, or phenomenologically different in their clinical manifestations. As the design of antiepileptogenic drugs is central to the discovery of truly curative agents, understanding the pathogenesis of epilepsy at the molecular level is crucial.

The cascade of histologic and biochemical events that characterize epileptogenesis differs from those of ictogenesis. At the histologic level, epileptogenesis involves cellular alterations that, in the clinically important partial epilepsies, are usually at the level of the limbic system. Morphologically, epileptogenesis is accompanied by neuronal loss in a variety of limbic structures, including the entorhinal cortex, the endopyriform nucleus, and the CA3 and CA1 pyramidal cell fields and granule cell layer of the dentate gyrus in the hippocampal formation. At the biochemical level, studies of partial seizures originating in limbic structures indicate that epileptogenesis involves abnormalities of synaptic chemistry. From these morphologic, physiologic, and biochemical studies, two theories of epileptogenesis have emerged: (a) the mossy fiber sprouting hypothesis and (b) the dormant basket cell hypothesis. The mossy fiber sprouting hypothesis, which has emerged from work by Sutula et al.,[27] postulates an upregulation of excitatory coupling between neurons. This excitatory upregulation is mediated by NMDA glutamatergic receptors, which are activated in chronic epileptic brain under circumstances that would not lead to activation in normal brain. In contrast, the dormant basket cell hypothesis suggests a downregulation of inhibitory coupling between neurons. This hypothesis postulates that the connections that normally drive GABA-releasing inhibitory interneurons are disturbed, thereby rendering them functionally disconnected or dormant. Studies by Sloviter[25] and Bekenstein and Lothman[1] support this hypothesis. The mossy fiber sprouting hypothesis invokes augmentation of glutamatergic excitation, whereas the dormant basket cell hypothesis invokes diminution of GABAergic inhibition. Although either abnormality could in isolation predispose an individual to epileptiform paroxysms, the fundamental disturbance that yields epileptogenesis seems to represent a combined, concurrent imbalance of both excitation (too much) and inhibition (too little).

Although glutamatergic and GABAergic processes are leading candidates for the mechanisms of epileptogenesis, there are other molecular pretenders to the throne. For example, recent studies have shown that in animal models of limbic seizures and of the experimental form of epileptogenesis known as *kindling* (in which repetitive, subconvulsive, subcortical electrical stimulation evokes progressively prolonged electroencephalographic and behavioral responses that culminate in

generalized seizures), expression of nerve growth factor (NGF) protein is enhanced in the dentate gyrus;[8,12] moreover, the intracerebroventricular administration of antibodies to NGF delays the onset of kindled seizures.[11,28] Nerve growth factor is also required for hippocampal sprouting in response to a proconvulsive head injury. A synthetic peptide designed to interfere with the binding of NGF to receptors has been shown to retard seizure development and inhibit mossy fiber sprouting.[22] These various observations suggest that neurotrophic peptides like NGF play a facilitating role in hippocampal synaptic reorganization, thereby contributing to the evolution of the epileptogenic state. Clearly, the future design of much needed antiepileptogenic agents must identify the full range of target molecules, extending from the small (NMDA antagonists, GABA agonists) to the large (NGF antagonists).

Summary and Conclusions

Future rationally designed drugs for epilepsy must extend beyond the scope of simple ictogenesis and should encompass the greater mandate of epileptogenesis. Just as staphylococcal meningitis is treated with penicillin in preference to aspirin, so too must epilepsy be treated more than simply symptomatically. Achieving this goal will require changes in antiepileptic drug design and testing; it is hoped that the final result will be a truly curative agent for epilepsy—an agent that will revolutionize the therapeutic expectations of this large and significant patient population.

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Chapter 138

Molecular Targets for Novel Antiepileptic Drugs

Brian S. Meldrum

Introduction

The majority of antiepileptic drugs (AEDs) introduced since 1938 have been identified as anticonvulsants by means of screening tests using in vivo models of seizures. The most widely applied models have been electrically or chemically induced seizures in normal animals. The maximal electroshock (MES) test in mice and rats and the "threshold" pentylenetetrazol (PTZ) test in mice have been rigorously standardized since 1978.[52] This has had several predictable consequences. Drugs functionally similar to phenytoin appear to be preferentially identified by the MES test. Thus, most AEDs introduced since 1978 suppress sustained rapid repetitive firing in cultured neurons, apparently by prolonging inactivation of voltage-dependent sodium channels (e.g., lamotrigine, zonisamide, topiramate, felbamate, and oxcarbazepine).

The other most widely used anticonvulsant screen is the "threshold" pentylenetetrazol test, which is used to identify drugs potentially active against absence seizures[52] (see Chapter 139). This is particularly sensitive to benzodiazepines and some other agents acting via the γ-aminobutyric acid $(GABA)_A$/benzodiazepine receptor and to drugs acting on T-type calcium channels.

Thus, a key criticism of the traditional anticonvulsant screens is that they tended to identify drugs with the same mechanism of action as existing drugs because they have been validated in terms of their capacity to select existing AEDs. This applies both in a precise mechanistic sense (i.e., in terms of their molecular targets) but also in the broad sense that most currently used drugs are direct-acting agents with a close temporal correlation between plasma or brain levels and action at the target molecule and antiepileptic effect (with only vigabatrin, gabapentin, and valproate as partial exceptions). Thus, our current acute models may miss compounds that have indirect actions with potential delays in antiepileptic effect, as is possible for compounds acting via metabotropic receptors, protein kinases, neurotrophins, or changes in gene expression.

A further problem is that the epileptic brain differs from the normal brain. Elements thought to play a critical role in acute ictogenesis (i.e., events initiating a spontaneous seizure) include the transmembrane movement of ions (Na^+, K^+, Ca^{2+}, Cl^-) and the release, postsynaptic action, and reuptake of excitatory and inhibitory neurotransmitters. The assumption that these processes are abnormal in the epileptic brain is supported by substantial data obtained in kindled animals[71] and tentative data from patients with epilepsy.[3,4,6,64] It follows that drugs modifying acute ictogenesis need to be studied in the epileptic brain, not in the normal brain. The genuinely epileptic model that has been most extensively used for screening is sound-induced seizures in DBA/2 or Fring's mice. These are highly sensitive screens that identify a wide range of AEDs; they also identify some agents acting on monoaminergic systems that are relatively effective in reflex epilepsies but are not notably effective against other epileptic syndromes.[16]

Electrically kindled seizures would appear to be highly appropriate for pharmacologic studies because of their multiple abnormalities in ion channel and neurotransmitter receptor function.[71] They are perhaps one of the better models of complex partial seizures, including the drug-resistant cases.[58] However, the time-consuming nature of this model means that it is used not as a primary screen, but at a late stage in the evaluation of compounds identified by other anticonvulsant screens. A simplified procedure not involving electrode implantation (corneal kindled seizures) has been used as a tertiary screen[14,51] (see also Chapter 139).

There are also genetically determined models of absence seizures in mice and rats that are responsive to antiabsence drugs and could be used to screen novel agents. These include the GAERS (genetic absence epilepsy rat Strasbourg) and several single gene mouse mutants (e.g., lethargic, stargazer, totterer).[11]

In contrast to the approach of in vivo screening of novel compounds with seizure models or epilepsy models is the mechanism-based approach, in which a molecular target is first defined and compounds are synthesized to optimize the action at this target and tested on a variety of in vitro systems before in vivo evaluation. This approach is totally dependent on our understanding of the causes of epilepsy and the mechanisms of chronic and acute ictogenesis. If attention is focused on mechanisms of action of existing drugs, this approach will have defects similar to in vivo screening. It is clearly important to focus attention on mechanisms of ictogenesis that have not yet been exploited therapeutically.

The following account attempts to describe some of the potential targets for novel therapies, putting them in the context of what is known about the mechanism of action of existing drugs and some novel agents currently in preclinical development whose clinical value is presently unknown.

The molecular targets for AEDs have recently been reviewed by Meldrum and Rogawski.[69]

Drugs Acting on Ion Channels

Table 1 Genetic Mutations Involving Voltage-gated and Ligand-gated Ion Channels and Epileptic Syndromes

Gene	Gene product (Channel)	Epilepsy syndromes
SCN1A	*α* subunit of Nav1.1	GEFS+ (type 2), SMEI, ICEGTCS
SCN2A	*α* subunit of Nav1.2	GEFS+ (type 2), BFNIS
SCN1B	*β* subunit of Nav1.1 to 1.4	GEFS+ (type 1)
CACNA1A	*α*1 subunit of Cav2.1 P/Q type	EAT2 + E, AEA
EFHC1	Coassembles with Cav2.3 R type	JME
CACNA1H	*α*1 subunit of Cav3.2 T type	CAE
CACNB4	*β*4 subunit of P/Q and other channels	IGE + EA
KCNA1	*α* subunit of Kv1.1	EAT1, MK, PS
LGI1	Coassembles with Kv1.1, 1.4, and Kv*β*1	ADTLE
KCNAB2	*β* subunit (Kvβ2) combines with *α* subunit of Kv1.1 and Kv1.4	Epilepsy

KCNMA1	*α* subunit of Kca1.1 (BK)	GEPD
KCNQ2	*α* subunit of Kv7.2	BFNC
KCNQ3	*α* subunit of Kv7.3	BFNC
KCNJ3	*α* subunit of Kir3.1 (Girk1)	Absence
CLCN2	CLC2 Cl$^-$ VG channel	JME, CAE, JAE, EGMA
CHRNB2	*β*2 subunit nicotinic ACh receptor	ADNFLE
CHRNA4	*α*4 subunit of nicotinic Ach receptor	ADNFLE
GABRA1	*α*1 subunit, GABA$_A$ receptor	JME
GABRBD	*β* subunit GABA$_A$ receptor *β*3 subunit GABA$_A$ receptor	JME Angelman syndrome
GABRG2	γ subunit GABA$_A$ receptor	GEFS+, CAE, SME1
GABRD	*δ* subunit GABA$_A$ receptor	GEFS+

ATLE, autosomal dominant temporal lobe epilepsy; AEA, absence epilepsy with ataxia; BFNC, benign familial neonatal convulsions; BFNIS, benign familial neonatal-infantile seizures; CAE, childhood absence epilepsy; EAT1, MK, PS, episodic ataxia type 1 with myokymia; EAT2 + E, episodic ataxia type 2 with epilepsy; EGMA, epilepsy with grand mal seizures on awakening; GEFS+, generalized epilepsy with febrile seizures plus syndrome; GEPD, generalized epilepsy with paroxysmal dyskinesia; ICEGTCS, intractable childhood epilepsy with generalized tonic–clonic seizures, IGE + EA, idiopathic generalized epilepsy with episodic ataxia (Escayg et al. 2000); JAE, juvenile absence epilepsy; JME, juvenile myoclonic epilepsy; SMEI, severe myoclonic epilepsy of infancy.

Voltage-gated or ligand-gated ion channels in the neuronal membrane generate the electrical currents associated with the normal and abnormal functioning of the nervous system. The abnormal pattern of neuronal firing associated with epileptic seizures thus depends on abnormal functioning of these ion channels. They are thus the primary target for AEDs. This is confirmed by our present understanding of the mechanism of action of the established AEDs (see Chapter 136 and references 69 and 84). It is also broadly confirmed if we look at genetically determined syndromes of epilepsy, either those occurring spontaneously in man and rodents or those induced by genetic manipulations in mice.[2,35,99] These studies (Table 1) clearly identify the voltage-gated Na$^+$, Ca^{++}, and K$^+$ ion channels as playing a critical role in causing idiopathic generalized seizures (and possibly some partial seizures in the case of K$^+$). They do suggest that the VG K$^+$ channels are of equivalent significance to the Na$^+$ and Ca^{++} channels. They also identify the GABA$_A$ receptors as crucial contributors to generalized epilepsies.

Voltage-Gated Sodium Channels+

The majority of AEDs introduced since 1938 have properties that suggest they act on voltage-dependent sodium channels (Table 2). As suggested above, this emphasis on Na^+ channel inactivation may be a consequence of the screening procedures employed.

Advances in the molecular biology of voltage-dependent Na^+ channels now permit a precise definition of potential target sites for anticonvulsant drug action.[24,55]

The principal element of a voltage-dependent Na^+ channel is the *a* subunit (260 kDa), which has four domains, each with six transmembrane helices, four of which form the voltage sensor and two (S5 and S6 connected by the P-loop that confers the ion-selectivity) forming the "pore domain." The α subunit is assembled with subsidiary β1 to β4 subunits. Different cells express different *a* subunits; in the brain, I, II, IIA, and NaCh6 *a* subunits are found. Following an action potential, there is a transient process of inactivation during which the Na^+ channel is unresponsive to voltage. This inactivation has fast and slow components that have been shown by site-directed mutagenesis to have distinct structural correlates. The loop linking domains III and IV act as a mechanical gate—"hinged lid"—producing fast inactivation. It can be rendered inoperative by proteolysis or site-directed mutagenesis.

Site-directed mutagenesis was also used to establish that three amino acids in the sixth transmembrane segment in domain 4 play a critical role in the binding of local anesthetics, phenytoin, and carbamazepine.[12,82] Recently it has been shown that binding of lamotrigine and some related compounds is dependent on the same three amino acid residues in IV6 and also two in III6.[12,82,119]

Table 2 Voltage-gated Sodium Channels: Genes, Currents and AED Actions

Gene	Channel current	AED action
SCN1A	Na_V 1.1 transient I_{Na} persistent I_{Na}	Phenytoin, carbamazepine, and lamotrigine prolong inactivation of transient I_{Na}
SCN2A	Na_V 1.2 transient I_{Na} persistent I_{Na}	Phenytoin, carbamazepine, and lamotrigine prolong inactivation of transient I_{Na}
SCN8A	Na_V 1.6 transient I_{Na} persistent I_{Na}	Phenytoin, topiramate, and valproate decrease persistent I_{Na}

AED, antiepileptic drug.

Table 3 Voltage-gated Calcium Channels: Genes, Channels, and AED Actions

Gene	Channel current	AEDs decreasing current

CACN A1S	Ca_V 1.1 L-type HVA	(Barbiturates, felbamate)
CACN A1C	Ca_V 1.2 L-type HVA	(Dihydropyridines block)
CACN A1D	Ca_V 1.3 L-type HVA	
CACN A1F	Ca_V 1.4 L-type HVA	
CACN A1A	Ca_V 2.1 P/Q type HVA	Lamotrigine (gabapentin)
CACN A1B	Ca_V 2.2 N-type HVA	Lamotrigine (gabapentin)
CACN A1E	Ca_V 2.3 R-type HVA	Topiramate (gabapentin)
CACN A1G	Ca_V 3.1 T-type LVA	Ethosuximide, zonisamide (modest reduction in I_{Ca})
CACN A1H	Ca_V 3.2 T-type LVA	
CACN A1I	Ca_V 3.3 T-type LVA	
ACNA 2D1	α2δ1 subunit in Cav X.X	Gabapentin, pregabalin
CACN A2D2	α2δ2 subunit in CavX.X	Gabapentin, pregabalin

AED, antiepileptic drug.

Thus, there are specific sites within the α subunit that provide targets for AEDs, prolonging inactivation of voltage-sensitive Na^+ channels. The four different α subunits expressed in the brain also may be seen as distinct targets.

There is a further function of Na^+ channels that is a target for AEDs. They provide persistent, noninactivating Na^+ currents that contribute to certain patterns of burst firing.[103] Phenytoin diminishes these currents,[15] as do topiramate and valproate.

Thus, Na^+ channels provide a multiplicity of targets. Acting on two families of sodium channels may be advantageous for anticonvulsant efficacy. There are homologies of sequence and morphology between voltage-sensitive Na^+, Ca^{2+}, and K^+channels, and some known Ca^{2+} channel blockers also act on Na^+ channels (e.g., flunarizine). Thus, designing compounds that block both classes of ion channel may lead to improved AED efficacy.

Voltage-gated Calcium Channels

These Ca^{2+} channels were originally classified in terms of biophysical measurements across neuronal membranes, determining voltage activation threshold, conductance per channel, and inactivation kinetics, giving T-, N-, and L-type Ca^{2+} channels. Other channels (P/Q, N, and R) were later identified (Table 3).[13,105] The role of voltage-gated calcium channels in immunoglobin (IG) E has recently been reviewed.[43,50]

As explained in Chapter 136, there is an apparent link between action against 2- to 3-Hz absence attacks and a partial suppression of Ca^{2+} T-channel conductance.[22] The T-type calcium current makes a specific contribution to oscillatory responses in thalamic neurons, and these oscillations play a critical role in 2- to 3-Hz discharges in the cortex and thalamus.[122] Thus, the suppression of absence attacks by ethosuximide and dimethadione has been attributed to the reduction in T Ca^{2+} currents they produce, although a variety of other effects on ion channels may also be involved. High concentrations of valproate reduce T currents in primary afferent neurons.[46] Zonisamide also reduces T Ca^{2+} currents. Perhaps T-type Ca^{2+} channels are best regarded as an auxiliary or supplementary target to broaden the spectrum of activity of a compound intended to affect more than one molecular mechanism.

The greatest interest in terms of targets for novel drugs are the high-voltage-activated channels designated as P/Q, N, and R type (Cav 2.1 to 2.3), because of their presynaptic role controlling release of neurotransmitters. N-type channels appear to be important for synaptic release of monoamines and some peptides.[109] The P/Q-type Ca^{2+} channels are important for the release of monoamines, glutamate, and GABA.[37] There is evidence suggesting that some established and novel AEDs act on presynaptic Ca^{2+} channels.[30,53,98,111] Thus, P/Q-, N-, and R-type calcium channels appear to be key targets for the development of novel AEDs. It should be remembered, however, that mutations leading to impaired function of P/Q-type channels produce ataxia and absence seizures in man and mouse.

Table 4 Potassium Channels: Genes, Channels, and AED Actions

Gene	Channel current	AED action
KCNA1	K 1.1 delayed rectifier (A-type)	
KCNQ2	K 7.2 M-type	Retigabine
KCNQ3	K 7.3 M-type	
KCNQ5	K 7.5 M-type	
KCNJ3	Kir 3.1 Girk1	
KCNJ6	Kir 3.2 Girk2	
KCNJ10	Kir 4.1	
KCNJ11	Kir 6.2	
KCNMA1	K_{Ca} 1.1 BK or slo1	

AED, antiepileptic drug.

Voltage-gated and Other Potassium Channels

Potassium selective ion channels were originally differentiated in biophysical studies and are found in all mammalian cells. Today they are classified partially on the basis of their functional properties and partially on the basis of their evolutionary origin and molecular morphology[120,121] (see Tables 1 and 4). The 75 or more distinct α subunits identified in genetic studies provide four main families: Voltage gated (Kv1 to Kv10); calcium activated (Kca2.1 to 2.3, Kca1.1); inwardly rectifying (kir); and the two-pore K^+ channels that provide the "leak" currents (K_{2P}). The voltage-gated and calcium-activated K^+ channels are part of the S4 superfamily and have an *a* subunit with a core formed by six putative transmembrane helices. The S1 to S4 segment provides the voltage sensor domain homologous with that of the Na^+ and Ca^{++}ion channels. A linker helix connects this to the S5 and S6 segments, which, with their P-loop, form the ion-selective channel.[21,56,57] Opening K^+ channels has the effect of hyperpolarizing neurons or reversing depolarizing actions. At least two different calcium-activated K^+ channels underlie afterhyperpolarizations.[89] One, SK_{Ca}, with a fast time course, is mediated by small conductance channels; the other has a slow time course and is modulated by numerous G-protein–coupled neurotransmitters. Studies of dentate granule cells isolated from patients with temporal lobe epilepsy show a prominent delayed rectifier outward current (I_K) whose steady-state voltage dependence differs according to whether the specimen shows Ammon horn sclerosis or not.[3]

Many compounds that act as potassium channel blockers are convulsant, for example, 4-aminopyridine and various scorpion and sea anemone toxins such as dendrotoxin I and pandinus toxin.[44,108] In in vitro systems, 4-aminopyridine–induced discharges are commonly used as a model for analyzing seizure activity. Several drugs thought to act as potassium channel openers such as chromakalim, minoxidil, diazoxide, and pinacidil show antiepileptic effects when injected intracerebroventricularly in rodent models of epilepsy.[32,80] The most definitive data concern a drug retigabine, developed as a GABA modulator but shown in 2000 to activate Kv7.2 and Kv7.3 channels responsible for the M-type current on soma and dendrites and the slow K^+ current (I_{ks}) on axons.[88,115] Mutations involving the genes encoding these channels (KCNQ2/KCNQ3) are responsible for benign familial neonatal convulsions.[19,96] Retigabine shifts the voltage dependence of the M current to hyperpolarized potentials, speeds the rate of activation, and slows inactivation. It has a similar effect on Kv7.4 and Kv7.5, which are also expressed in the brain, but is inactive on Kv7.1, the cardiac homolog. Experiments with chimeric channels and point mutations[90,118] have shown that the pore domain is the site of action of retigabine and that its action is dependent on a tryptophan residue on S5 found in KCNQ2 to 5 but not in KCNQ1. Further compounds have been identified with a similar channel-opening effect and activity in rodent models of epilepsy.[117] Thus, the potassium channels responsible for the M current are clearly identified as a target for AEDs. Genetic and pharmacologic data suggest that the voltage-gated K channels responsible for the A-type K^+ currents, which play an important role in controlling the excitatory threshold in synaptic terminals, are also an important potential target for novel AEDs,[21,69] but drugs potentiating these currents have yet to be identified. The calcium-activated channels and the inwardly rectifying and leak currents may also be targets, but evidence is less clear.

Many reports describe effects of established AEDs (such as phenytoin, carbamazepine, lamotrigine, and levetiracetam) on various K^+ currents,[69] but the significance of these for antiepileptic effect remains uncertain.

Carbonic Anhydrase Inhibition

A possible mechanism for the antiepileptic action of carbonic anhydrase inhibition involves GABA-mediated inhibitory potentials.[97] $GABA_A$receptors open ion channels that are permeable to HCO_3 as well as to Cl. HCO_3 moves outward, producing a depolarizing effect that is normally smaller than the hyperpolarizing action of the inward flux of Cl. With strong $GABA_A$ receptor activation, the Cl gradient in dendrites collapses sooner than does the HCO_3 gradient (which is preserved by the inward flux of CO_2 and carbonic anhydrase activity). GABA thus develops a depolarizing effect that can be blocked or diminished by carbonic anhydrase inhibitors. The conversion of GABA's effect to depolarization may contribute to several epileptic manifestations, and carbonic anhydrase inhibitors may be beneficial.

Table 5 AEDs and Related Compounds Potentiating GABA-Mediated Inhibition

Drug	Molecular target	Functional effect	Action in GTCS and TLE	Action in absence
Vigabatrin	GABA-transaminase	Increases extracellular	Benefit	Exacerbates

		[GABA], enhances tonic inhibition		
Tiagabine	GAT-1 (forebrain neuro- and glial GABA transport)	Prolongs IPSPs, potentiates tonic inhibition	Benefit	Exacerbates
THIP (gaboxodol)	$GABA_A$ receptor (agonist site)	Agonist-opens Cl^- channels		Exacerbates
Phenobarbitone	$GABA_A$ receptor (barbiturate site)	Directly opens Cl^- channels Potentiates GABA action at phasic and tonic receptors	Benefit	No benefit
Diazepam Clobazam Clonazepam	$GABA_A$ receptor (BZD site)	Potentiate GABA at phasic receptors containing α1, α2, α3, and α5 subunits, and γ1 or γ2	Benefit	Suppresses
Ganaxolone Alphaxalone	$GABA_A$ receptor (neurosteroid site)	Potentiates GABA action at tonic $GABA_A$ receptors		
Chlormethiazole	$GABA_A$ receptor (chlormethiazole site)	Direct action at $GABA_A$ Potentiates GABA action		
Topiramate	$GABA_A$ receptor (topiramate site)	Potentiates GABA action	Benefit	Suppresses
Felbamate	$GABA_A$ receptor (felbamate site)	Potentiates GABA action at phasic receptors	Benefit	Weak action
Loreclezole	$GABA_A$ receptor (loreclezole site)	Direct action plus potentiates GABA		

AED, antiepileptic drug; GABA, γ-aminobutyric acid; GTCS, generalized tonic-clonic seizure; TLE, temporal lobe epilepsy.

Drugs Enhancing GABA-mediated Inhibition

In the 1970s, evidence that barbiturates and benzodiazepines potentiate GABA-mediated inhibition by acting on $GABA_A$ receptors accumulated. In addition, it became clear that any impairment of GABA-mediated inhibition was associated with a lowered seizure threshold or spontaneous seizures. There was tentative evidence that GABAergic neurons or GABAergic

functions were lost in situations favoring epileptic discharges. Beginning around 1975, enhancing GABA-mediated inhibition became the preferred rational approach to AED design.[66] It is now clear that GABA provides two forms of inhibition via $GABA_A$ receptors (phasic and tonic involving synaptic and extrasynaptic receptors)[28] and two forms of inhibition via $GABA_B$ receptors (see below).

Potential means of enhancing GABA-mediated inhibition are listed in Table 5.

Inhibition of GABA Uptake

GABA uptake after synaptic release is provided by specific carriers in neuronal and glial membranes that are coupled to Na^+/Cl^-.[83] Four genes and transporter proteins have been identified in mammalian brain. Their nomenclature differs in mice, rats, and humans. The distribution of these four transporters varies markedly, with GAT-1 being predominant in the rat forebrain and hippocampus.

Nipecotic acid and guvacine were initially identified as GABA uptake inhibitors, and subsequent compounds were designed to incorporate their molecular features. Early compounds encountered difficulties relating to brain penetration and to neurologic and cognitive side effects. These problems have been largely overcome by tiagabine, which has been shown to be effective in drug-refractory cases of complex partial epilepsy.[70] Tiagabine and several related compounds are apparently specific for GAT-1.[9] Tiagabine increases the extracellular concentration of GABA in the hippocampus. It prolongs the postsynaptic inhibitory effect of synaptically released GABA.[100] It also enhances tonic (extrasynaptic) inhibition. In prolonged seizure activity, synaptically available GABA may become depleted, and blockade of glial GABA uptake may be more effective for suppressing discharges than blockade of neuronal uptake.[77] It is possible that other GABA transporters (GAT-2, GAT-3) expressed more strongly in the brainstem represent a target for agents acting on primary generalized seizures. Synergistic antiepileptic effects have been demonstrated for the combination of GAT-1 and GAT-2/GAT-3 inhibition.[114]

Inhibition of GABA-Transaminase

GABA-transaminase inhibition blocks the further metabolism of GABA to succinic semialdehyde and increases brain GABA content as well as seizure threshold. Irreversible or catalytic inhibitors of GABA-transaminase have the advantage of a more sustained effect. Total inhibition of GABA-transaminase is highly toxic. Vigabatrin is the first novel AED developed on a rational mechanistic basis (i.e., irreversible inhibition of GABA-transaminase).[54] Brain and cerebrospinal fluid (CSF) GABA are increased in man. This leads to some desensitization of phasic $GABA_A$ receptors, but increased tonic inhibition. The high incidence of visual field defects in patients receiving vigabatrin has led to doubts about the safety of GABA-transaminase inhibition.

Potentiation of GABA at $GABA^A$ Receptors: Benzodiazepines

Potentiation of the Cl conductance change induced by GABA has long been recognized as a principal anticonvulsant mechanism for 1,4-benzodiazepines such as diazepam and clonazepam and 1,5-benzodiazepines such as clobazam (see Chapter 136). The $GABA_A$/benzodiazepine receptor is formed from five peptide subunits selected from 19 isoforms that belong to various subfamilies (α1 to 6; β1 to 4; γ1 to 4; δ; ε; θ; π; ρ1 to 2).[95]

The subunit composition of $GABA_A$/BZ receptors varies in different parts of the brain and in different cell lines.[60,116] Native $GABA_A$/BZ receptors conform to about ten patterns in terms of subunit composition.[60] In the rat brain receptors containing α1, β2, and γ2 subunits are the most abundant and widely expressed. The subunit composition critically influences the pharmacology of the $GABA_A$receptor.[42,87] In particular, for different benzodiazepines and related compounds acting at the same site, the strength and nature of their effect depends on the α and γ subunit components.[59,87] Benzodiazepine responsiveness is dependent on the presence of an α subunit chosen from *a*1, *a*2, *a*3, *a*5 (possessing a histidine residue at 101), and a *γ* subunit (from *γ*1 to *γ*3). The α subunit also largely determines the neurologic side effects of the benzodiazepines. The anxiolytic effect is mediated by receptors containing *a*2 and *a*3 subunits. In rodents, sedative and myorelaxant effects are mediated by receptors with *a*1 subunits. GABA receptors mediating tonic responses have *δ* rather than *γ* subunits and are not potentiated by benzodiazepines.

It may be important to use human isoforms to make recombinant receptors for studies of this kind. A ß-carboline derivative, abecarnil, with a highly selective pattern of action at recombinant receptors that sharply differentiates between receptors with different α subunits[81] shows high antiepileptic potency in rodents and primates with reflex epilepsy with an exceptionally good therapeutic ratio.[106] This superior therapeutic index is not found in humans, suggesting that the regional and functional differentiation of $GABA_A$ receptors in rodents and nonhuman primates is not replicated in humans. Considerable attention is now being devoted to the development of compounds acting on the BZ receptor site that may have a better side effect profile than existing drugs.

Potentiation of GABA: Neurosteroids

An antiepileptic effect of adrenal steroids was known[23] long before it was shown to be mediated by an action on $GABA_A$ receptors.[49] Neurosteroids include endogenous metabolites of deoxycorticosterone and progesterone, which may contribute to mood changes in the menstrual cycle and to catamenial epilepsy. Various synthetic steroids, such as the anaesthetic alphaxalone and the experimental compound ganaxolone, act at this site to potentiate tonic inhibition. Ganaxolone is a 3ß-methyl-substituted analog of 3α-hydroxy-5-α-pregnan-20-one that shows a broad spectrum of anticonvulsant activity in preclinical tests and has entered clinical trials.[85]

Potentiation of GABA: Other Compounds

There are a large number of sites (at least 12)[42] at which a very wide range of synthetic and natural products can act to enhance the action of GABA at $GABA_A$ receptors, either directly or by potentiating GABA. These include the sites at which alcohol, loreclezole, chlormethiazole, felbamate, and topiramate act.[36,110] There is clearly still scope for the identification of agents acting on the $GABA_A$ receptor with a subtype selectivity that confers superior therapeutic benefits.

$GABA_B$ Receptors

$GABA_B$ receptors act presynaptically to decrease GABA release by decreasing Ca^{2+} entry but act postsynaptically to provide a slow afterhyperpolarization by increasing K^+ conductance. $GABA_B$ receptors are overexpressed in lethargic mice,[41] and enhanced activity at the $GABA_B$ receptors contributes to the spike-and-wave activity in this absence model. In the thalamus, $GABA_B$ receptors occur pre- and postsynaptically and contribute to excitatory, inhibitory, and oscillatory membrane responses.[26] Selective $GABA_B$ agonists, such as baclofen, have long been known to induce spike-and-wave discharges in animal models.[68] $GABA_B$ antagonists, such as CGP 35348, suppress spike-and-wave discharges in genetic and chemical models of absence attacks. Thus, the $GABA_B$ receptor is a target for AEDs with a selective action against 2- to 3-Hz discharges.

Spectrum of Anticonvulsant Activity of GABA-related Antiepileptic Drugs

Drugs potentiating GABA have a characteristic preclinical and clinical spectrum of anticonvulsant action, except that benzodiazepines and some related compounds are anomalous.

All GABA-potentiating agents are active against threshold PTZ seizures; they are mostly weak against MES seizures. (When they do show activity, it may be due to additional mechanisms of action, i.e., Na^+ channel inactivation by diazepam.) Clinical trials show that GABA-potentiating drugs are nevertheless effective in complex partial seizures, a result not predicted on the basis of the MES tests. Their effects in 2- to 3-Hz absence attacks are divergent—pure GABA agonists and compounds increasing extracellular GABA concentration are not therapeutic and may facilitate spike-and-wave discharges. Benzodiazepines are, however, therapeutic. This difference is not fully explained; the role of $GABA_B$ receptors in the corticothalamic discharges of absence epilepsy may be part of the explanation,[61] but pure $GABA_A$ agonists such as muscimol and 4,5,6,7-

tetrahydroisonazolo[5,4-c]pyridrin-3-ol (THIP) can facilitate cortical spike-and-wave discharges.[122]

Drugs Diminishing Excitatory Transmission

Around 1980 it became widely accepted that glutamate is the principal excitatory neurotransmitter in the brain.[112] There is still uncertainty about the role of aspartate and various sulphinic and sulphonic analogs of glutamate and aspartate. Also at that time it was proposed that glutamate acted postsynaptically on three classes of ion channel–linked receptors, named after their preferred agonists: *N*-methyl-D-aspartate (NMDA), *a*-amino-3-hydroxy-5-methylisonozole-4-proprionitic acid (AMPA), and kainate. Subsequently, molecular biologic studies confirmed the existence of these three families of receptors, each receptor complex being composed of subunits with a high degree of homology[27,39,65] (Table 6). The properties of each receptor are determined not only by the particular subunits, but also by splice variants, RNA editing, and phosphorylation.

Table 6 Glutamate Inotropic Receptors as AED Targets

Receptor subunit	Agonists	Antagonists: competitive	Open channel blockers	Antagonist AEDs
GluR1(A)	AMPA ACPA Kainate	NBQX GYKI 52466 Talampanel		Phenobarbital Topiramate
GluR2 (B)	AMPA	NBQX GYKI 52466		
GluR3 (C)	AMPA			
GluR4 (D)	AMPA			
GluR5	Kainate, domoate	UBP 296		
	SYM2081	UBP 310		
	(S)ATPA	NS 3763		
	LY339434	LY382884		
GluR6	Kainate SYM2081			
GluR7	Kainate			
KA1	Kainate			

KA2	Kainate			
NR1	Glycine, D-serine	Kynurenic acid, licostinel GV150526	Phencyclidine Ketamine Dizocilpine (MK801) CNS1102 (Aptiganel) Memantine	Felbamate
NR2A	NMDA, glutamate			
NR2B	NMDA, glutamate	Ifenprodil Troxoprodil		
NR2C	NMDA, glutamate			
NR2D	NMDA, glutamate			
NR3A	NMDA			
NR3B	NMDA			

AED, antiepileptic drug.

Glutamate/NMDA Antagonists

NMDA receptor ion channels are permeable to Na^+, K^+, and Ca^{2+} and are subject to a voltage-dependent block by magnesium, which means that they only become operative when the cell is partially depolarized (e.g., by AMPA receptor activation). For activation, NMDA receptors require occupation of both a site recognizing glutamate or aspartate and a site recognizing glycine or D-serine. Thus, NMDA receptors can be blocked by competitive antagonists acting either at the glutamate or the glycine recognition site. The properties of NMDA receptor channels are altered in hippocampal neurons from kindled rats.[48]

In 1982 it was shown that selective NMDA receptor antagonists were potent anticonvulsants in reflex epilepsies and in chemically induced seizures[25] (Table 6). Similar activity is shown by glutamate competitive and glycine-site competitive antagonists.[67] Noncompetitive open-channel blockers such as phencyclidine and dizocilpine (MK-801) are also potent anticonvulsants but have a poor therapeutic index, producing enhanced motor activity and stereotypies at anticonvulsant doses.[17] Lower-affinity channel blockers such as memantine appear less toxic.[75]

The competitive antagonist 3-(2-carboxypiperazin-4-yl)propenyl-1-phosphonic acid (D-CPPene) has a potent and prolonged anticonvulsant activity in animal models.[76] In a preliminary trial as an add-on treatment in refractory complex partial seizures, however, it failed to show efficacy but augmented neurologic and cognitive side effects.[101] Early clinical trials of the noncompetitive NMDA antagonists dizocilpine and dextromethorphan also failed to give evidence of therapeutic action.

There remains scope for the development of (a) low-affinity, noncompetitive antagonists, (b) subtype-selective glutamate competitive antagonists, and (c) glycine site antagonists.[47,75] It is also possible that other allosteric sites on the NMDA receptor, such as the redox site, are potential targets for AED development.

Glutamate/AMPA Antagonists

AMPA receptors are responsible for the fast depolarizing actions of glutamate and make the major contribution to fast excitatory transmission in the central nervous system (CNS). In spike discharges and paroxysmal depolarizing shifts in in vitro models of epileptic activity, the AMPA receptors are responsible for the early component of the discharge, with NMDA receptors commonly contributing to later elements. The first AMPA receptor antagonists to be developed were the quinoxalinediones.[40] One of these, 1,2,3,4-tetrahydro-6-nitro-2,3-diono-benzo[f]quinoscaline-7-sulfonamide (NBQX), is systemically active and is anticonvulsant in reflex epilepsy models, MES, and some chemical seizures.[18,102] Subsequently, anticonvulsant activity was reported for some structurally related AMPA antagonists (e.g., YM 900) and for some novel structures (e.g., LY 293558 and the isatin oxamines).[112] A further class of AMPA antagonists is provided by the 2,3-benzodiazepines, GYKI 52466, GYKI 53455, and GYKI 53733 (Talampanel), which are noncompetitive allosteric inhibitors of AMPA receptors. They also are anticonvulsant in reflex epilepsies and in some other models.[18] Talampanel is in phase III clinical trials in humans.[85]

Table 7 Metabotropic Receptors (Glutamate, GABA$_B$, A1, M2) as Potential AED Targets

Gene	Receptor	Site	Agonists (*effect*)	Antagonists (*effect*)
	mGluR1	Postsynaptic, perisynaptic	DHPG *(convulsant)*	LY 367385, LY 456236, AIDA (*anticonvulsant)*
	mGluR5	Postsynaptic, perisynaptic	CHPG, DHPG *(convulsant)*	MPEP, SIB-1893 *(anticonvulsant [CHPG])*
	mGluR2	Presynaptic	LY 354740 *(anticonvulsant)*	Ethylglutamate *(convulsant)*
	mgluR3	Presynaptic (axonal)	LY354740	Ethylglutamate
	mGluR4	Presynaptic	ACPT-1,(RS)PPG	MAP-4, MSOP. MPPG (*convulsant)*
	mGluR7	Presynaptic	AMN082	MAP-4,MSOP, MPPG
	mGluR8	Presynaptic	ACPT1,(RS)PPG (S)3,4-DCPG	MAP-4,MSOP,MPPG

GABAB1	Presynaptic, postsynaptic	Baclofen, APPA (*augment SWD)*	Phaclofen, Saclofen *(reduce SWD)*
GABAB2	Presynaptic, postsynaptic	CGP7930	
Adenosine A1	Presynaptic	N(6)-cyclopentyladenosine	8SPT, DPCPX
mACh R,M2	Presynaptic	Carbachol	Atropine

AMPA receptors are assembled from four peptide subunits (known either as GluR1, 2, 3, and 4 or as GluRA, B, C, and D), which are differentially expressed in particular cell types.[33]

Receptors containing the GluR2 subunit have a low Ca^{2+} permeability and show a linear or outwardly rectifying current voltage relationship, whereas receptors lacking this subunit show a significant Ca^{2+} permeability and are inwardly rectifying. This effect of the GluR2 subunit is linked to a process of messenger RNA editing, whereby a glutamine is converted to an arginine through the site-selective action of an adenosine deaminase acting on the codon. In genetically engineered mice in which this editing process is partially impaired, the calcium fluxes induced by AMPA are modestly enhanced.[10] Such mice show a wide variety of seizures early in life. This suggests that agents that selectively block AMPA receptors not containing GluR2 (and therefore showing Ca^{2+} permeability) might be good antiepileptics.

The availability of selective kainate receptor antagonists has recently improved,[7] including the development of some agents with selectivity for GluR5 versus GluR6/7 subunits.[65a] Among AMPA antagonists, NBQX also acts as an antagonist at GluR5 and GluR6, GYKI 52466 acts at neither, and LY 293558 antagonizes GluR5 but not GluR6.[8] The significance of this differential effect for antiepileptic activity is not known, but it may be relevant for specific syndromes involving altered glutamatergic receptor function.

Glutamate Transporters

Five glutamate transporters in neuronal and astrocytic membranes mediate high-affinity uptake of glutamate and aspartate. The transporters control extracellular levels of glutamate and its activity at nonsynaptic NMDA receptors and presynaptic metabotropic receptors. GLT-1 (EAAT2) expressed in astrocytes is the predominant transporter in the adult mammalian brain. Seizures are seen in GLT-1 knockout mice and following its inhibition. Compounds that enhance the function or expression of GLT-1 have been identified.[29,86,93] Thus, glutamate transporters are significant targets for novel AEDs.

Drugs Acting on Metabotropic Receptors

Metabotropic receptors are found in the plasma membranes of neurons and glia and respond to their ligands by generating second messengers rather than opening ion channels, although they have important actions on calcium and potassium conductances.[20,78] They are coupled through G proteins to enzyme systems in two broad categories, either modifying activity of adenylate cyclase or guanylate cyclase (changing the availability of cyclic adenosine monophosphate [cAMP] or cyclic guanosine monophosphate [cGMP]) or acting on phospholipase C or D, producing diacylglycerol, inositol triphosphate, or free fatty acids as second messengers, with important effects on protein kinases. Thus, there are significant effects on the phosphorylation of membrane receptors, transporters, and other enzymes, modifying their function over short or long periods.

Thus, metabotropic receptors can produce transient or sustained changes in neuronal excitability and are potentially important targets for novel AEDs.

Some of the metabotropic receptors for glutamate, acetylcholine, GABA, and adenosine are listed in Table 7. This table shows that some of these receptors are found presynaptically at which site they modify the synaptic release of glutamate and/or GABA.

Recent studies have drawn attention to the possible role of glutamate metabotropic receptors in acute and chronic epileptogenesis. Group I reponses, as judged by phosphoinositide hydrolysis induced by quisqualate, AMPA, or glutamate, are potentiated in the amygdala or hippocampus of the kindled rat.[1,45]

The variety and selectivity of pharmacologic agents acting on glutamate metabotropic receptors has been progressively augmented[91] and now includes many allosterically acting drugs with high subtype selectivity.[62,94] Extensive studies in rodent models of epilepsy show a consistent pattern of effects.[72] Group I mGluR agonists such as 1S,3R-aminocyclopentane-1,3-dicarboxylic acid (1S,3R ACPD) and

3,5-dihydroxy-phenylglycine (3,5-DHPG) are powerful convulsants when given intracerebroventricularly.[34]

Group I antagonists, such as LY 367385 ((+)2-methyl-4-carboxyphenylglycine) and AIDA ((R,S)-1-aminoindan-1,5-dicarboxylic acid) given intracerebroventricularly, or MPEP and SIB1893 (mGluR5 allosteric antagonists, given intraperitoneally) are anticonvulsant in several types of rodent seizure models. Group II (LY 354740, LY379268) and group III agonists (ACPT-1, (R,S)PPG) are also anticonvulsant.

mGluRs are important potential targets for novel AEDs. Now that the human receptors have been cloned and expressed in cell systems, they provide an excellent means for identifying selective agonists and antagonists for each receptor subtype. The availability of positive and negative allosteric modulators with high subtype selectivity allows precise targeting of specific systems. Such compounds need to be tested in a wide range of seizure models because the antiepileptic effects might be very syndrome specific. They also need to be tested over a wide range of doses and time courses.

Acetylcholine acting on muscarinic receptors, GABA acting on $GABA_B$ receptors, and adenosine acting on A1 receptors can produce presynaptic effects modifying neurotransmitter release, with varying specificity for excitatory or inhibitory synapses. They may show complex interactions with other presynaptic receptor systems.

Novel Approaches

Growing understanding of the molecular biology of acute and chronic ictogenesis suggests many possible novel molecular targets for antiepileptic drugs. These include novel ion channels such as the HCN channel responsible for the I_h.

HCN Channels

Hyperpolarization-activated cyclic nucleotide-gated cation channels play an important role in determining excitability in the hippocampus and neocortex, and their expression and function is modified during epileptogenesis in several models.[79] The HCN channels may thus be significant targets.

Connexins

Gap junctions between glia and between neurons have been shown to play a significant role in the synchronization of epileptic discharges in in vitro and in vivo models.[73] Thus, the connexins (such as Cx43 in astrocytes and Cx36 and Cx45 in neurons) provide potential molecular targets.

Protein Kinases

There are more than a thousand protein kinases expressed in the brain. They change the excitability and function of neurons and glia over short or long periods by phosphorylating receptor molecules, ion channels, transporter molecules, and enzymes. Protein kinases may play a crucial role in epileptogenesis in several different syndromes. A CAM-kinase II knockout mouse shows limbic seizures. The extremely diverse effects of topiramate on synaptic function (including effects on AMPA/kainate receptors, GABA receptors, and Na^+ and Ca^{++} channels) may be explained by a primary effect on phosphorylation sites.[53,92] Modifying kinase activity by pharmacologic or molecular genetic means is likely to prove a fruitful approach to blocking or reversing epileptogenesis.

Neurotrophin Receptors

Seizures induce changes in the expression of neurotrophins, such as nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and neurotrophin 3 (NT3).[5,31] Neurotrophins increase synaptic efficacy and are thought to play a role in epileptogenesis.[104] The kindling process is slowed by intracerebroventricular infusion of antibodies to NGF.[107] Compounds acting on neurotrophin receptors (trkA, trkB, trkC) also may affect epilepsy or seizure expression. Conditional deletion of TrkB in the mouse forebrain severely impairs the kindling process.[38] Therapeutic approaches could involve pharmacologic agents acting on the neurotrophin receptors or on downstream events. Acute and chronic manipulations of the neurotrophin systems often have opposite effects on epileptogenesis due to regulatory mechanisms, so there is uncertainty about the correct strategy. It is also possible that genetically modified cell lines could be transplanted intracere-brally.[63]

Altering Gene Expression

Gene expression can be modified by growth factors, cytokines, and other factors that may be important in epileptogenesis; most importantly, neuronal activity itself modifies gene expression. Changes in cAMP and intracytoplasmic or nuclear [Ca^{2+}] act through cAMP response elements (CREs) and transcription factors such as CRE binding protein (CREB) whose effect is modified by phosphorylation. Seizure activity produces notable changes in [Ca^{2+}], and this is probably the factor leading to the expression of immediate early genes (such as those encoding the fos and jun families of proteins, which are important in transcriptional activation) in many brain regions shortly after seizure activity.

Established AEDs can alter gene expression. Valproate is a potent histone deacetylase inhibitor and through this mechanism has very diverse effects on gene expression.[44a] These have been well documented but their role in epileptogenesis or possible antiepileptogenesis has yet to be elucidated.

Manipulation of gene expression is likely to emerge as a major approach to suppressing or reversing epileptogenesis.

Single Versus Multiple Mechanisms

Mechanism-based approaches to the design of AEDs naturally tend to focus on a single mechanism of action, successfully so in the cases of vigabatrin and tiagabine. The serendipitous AEDs such as valproate, felbamate, and topiramate apparently have a multiplicity of mechanisms of action. There are many reasons why a multiplicity of action may be favorable. Obviously the spectrum of clinical activity may be enhanced. There also may be additive or synergistic effects of the different mechanisms. The therapeutic ratio may be improved, and the risk of developing tolerance may be diminished. A multiplicity of actions may be achieved in two principal ways. First, one pharmacophore may correspond to two target molecules. This may be the case in terms of several homologous targets, that is, different sodium channels (voltage dependent and persistent), different ion channels (such as voltage dependent sodium and calcium channels), or different glutamate receptors (inotropic and metabotropic). Examples of drugs combining these targets are already known and undoubtedly could be improved upon. Second, one molecule can contain more than one pharmacophore. Techniques of combinatorial chemistry that have

recently been brought to a high level can be used to exploit this possibility.

A whole range of such drugs could be designed to match either the range of clinical seizures experienced by a particular patient or to match the particular altered molecular function in the patient.

Summary and Conclusions

The future search for AEDs should concentrate on identifying drugs with novel mechanisms of action on acute or chronic ictogenesis. Further understanding of these processes is required before such a mechanism-based program can be fully effective. Screening tests are required that identify delayed or long-term effects on acute ictogenesis and effects on chronic epileptogenesis. Important potential targets for suppression of acute ictogenesis include potassium channels, presynaptic calcium channels, metabotropic receptors, and various proteins involved in presynaptic accumulation and release of neurotransmitters. More tentative targets include HCN channels and connexins. Selection of subtype-specific drugs (using recombinantly expressed channels or receptors) acting on sodium, potassium, and calcium channels; $GABA_A$/BZ receptors; AMPA; and NMDA receptors may allow better separation of antiepileptic effects from unwanted actions.

Chronic epileptogenesis involves a wide variety of changes in gene expression involving ion channels, receptors, and transporters. Drugs acting on protein kinases and on neurotrophic systems may be of particular importance. Improved understanding of the nature of chronic epileptogenesis will facilitate its prevention or reversal.

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Chapter 139

Screening of New Compounds and the Role of the Pharmaceutical Industry

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Introduction

The search for new antiepileptic drugs (AEDs) requires the appropriate choice of a number of models for the identification of new therapeutic agents for the treatment of epileptic seizures. The animal models used in the search of new anticonvulsant drugs are varied and have been the subject of several recent reviews.[50,88,97,102,104,107,111,201]

Different approaches can be used in the discovery of new therapeutic agents for the treatment of seizure disorders. The model choice can be specific for a seizure type, such as complex partial,[44,104] absence,[24,163,194] and status epilepticus (SE).[94,196] It can be based on a mechanism of action, such as decreased neural excitability[33] or enhanced inhibition.[103] Alternatively, a seizure model in which the compound blocks the final expression of the experimental seizure can be used; for example, a "mechanism-independent" model such as the maximal electroshock seizure (MES).[179,181]

Several restrictions and conditions are inherent in the choice of model for identifying a new drug. It would be ideal and more efficient if the model were capable of screening large numbers of compounds without requiring large amounts of any one compound. Neither should the complexity and technical expertise required for the development and implementation of such a model be difficult.

Validation is a criticism often raised about new mechanistic seizure models. In the validation process, the new model must be evaluated against current, clinically effective therapeutic agents. The question then arises as to whether a model that is capable of identifying clinically effective compounds whose mechanisms are known will be able to identify unique compounds.

A second question that often arises is whether a given model reflects the pathophysiologic processes and symptomologies of the epilepsies. Currently, a number of model systems are highly predictive of efficacy against generalized tonic–clonic seizures (e.g., the MES test), generalized absence or spike-and-wave seizures (e.g., the genetically absence epileptic rat of Strasbourgh, the Lh/Lh mouse, γ-hydroxybutyrate induced spike-wave seizures), and partial seizures (e.g., the kindled rat).

No single approach can be used to identify an effective compound for the treatment of epileptic seizures. Furthermore, no ideal animal model would effectively identify a drug active against all forms of seizures, regardless of its mechanism of action. Therefore, new approaches must be undertaken for the discovery of new therapeutic agents.

In this era of molecular biology, when targets have become important in drug development, target validation using in vivo animal models is appropriate. As unique structural compounds are identified using basic screening procedures, they should be immediately evaluated in molecular target screening procedures. The reverse of this process should also occur.

When lead compounds are identified, additional information must be obtained before the development process begins. These include the establishment of a compound's pharmacologic and toxicologic profile and in vitro studies designed to ascertain proposed mechanisms of action. Other parameters such as absorption, distribution, excretion, metabolism, and drug–drug interactions must also be characterized.

Loscher et al. have published seven critical reviews dealing with the role of technical, biologic, and pharmacologic factors in the laboratory evaluation of anticonvulsant drugs. These seminal reviews should be read before undertaking the task of evaluating new chemical entities for their potential in the treatment of seizures. The reviews discuss in detail the influence of administration vehicles on seizure threshold[107]; the nuances of the various MES seizure models[97] and pentylenetetrazol (PTZ) seizure tests[102]; and the calculation and utility of protective indices[106]; the consequences of seasonal influences on amygdala kindling,[204] MES, PTZ,[99] and mouse models of generalized seizures.[100]

The objective of the initial part of this chapter is to discuss the historical background of the discovery and utilization of seizure models, then describe those models and methods that have direct applicability to the discovery of new anticonvulsant drugs and their mechanisms of action.

Historical Perspective

Prior to the discovery and development of phenytoin, anticonvulsant compounds such as phenobarbital and bromides were used for the treatment of seizures in patients without any preclinical experimental information. Although methods for producing seizures were known, Merritt and Putnam[130] first used a systematic approach in evaluating the potential of a series of compounds as antiseizure agents (see White for review and references[199]).

They studied the ability of a series of chemicals to raise convulsive threshold by using graded electrical stimulation in cats. They knew that phenobarbital was a clinically effective compound in treating seizures, whereas other barbiturates were comparatively ineffective or toxic (e.g., produced narcosis). A number of Parke Davis compounds were submitted for evaluation. Six were analogs of phenobarbital. A few were hydantoins, one of which was 5,5 diphenylhydantoin (diphenylhydantoin, phenytoin).

Several significant observations were made. They found that diphenylhydantoin, acetophenone, and several phenones and ketone derivatives had an anticonvulsant effect equivalent to that of phenobarbital, but without producing sedation.

The majority of compounds evaluated by this procedure were inactive.

They also found that carbon dioxide raised seizure threshold when hypercapnia was observed. For example, it was impossible to produce convulsions with 40 milliamperes of current. When animals were allowed to breathe air for a few moments, the seizure threshold returned to normal. This result predicted the use of carbonic anhydrase inhibitors in treating seizures.

During the 1940s and 1950s, new compounds were synthesized, and structure-activity relationships (SARs) were investigated for anticonvulsant and hypnotic activity.[3,8] This approach, using methodology similar to that of Merritt and Putnam, gave rise to mesantoin, nirvanol, trimethadione, methylphenylsuccinimide, and phenacemide. Because these compounds are known to be chemically similar to phenyt-oin, their therapeutic potential was not unexpected. Vida summarized the anticonvulsant activity of a large number of compounds.[195]

During the mid 1940s to early 1950s, a number of papers appeared describing the properties of electrically induced seizures and the effect of chemical agents on them. Two basic mechanisms were proposed to explain how anticonvulsant drugs prevented seizures: by raising seizure threshold or by preventing seizure spread. Once the seizure threshold was exceeded by more than 20%, the pattern and duration of the seizure was relatively constant and independent of the intensity or duration of the stimulus.[187]

No matter whether a seizure was chemically or electrically induced, the drug effect on seizure pattern would be modified in an identical manner. Therefore, agents that inhibit seizure spread would attenuate the extensor tonic component of the seizure, independent of how the maximal seizure is produced. Toman and Goodman[186] summarized the “state-of-the-art” methodology for identifying new therapeutic agents. They concluded that a single test could adequately define the anticonvulsant properties of a drug.

Chen and Ensor[20] determined the anticonvulsant activity of nine known drugs by testing in both an electrical and chemical model. They then compared the results with the known clinical utility of these same drugs. The two methods ranked the potency of the drugs in a similar manner. This was done to see if similar qualitative and quantitative data could be obtained by using two methodologies. By 1951, phenytoin had opened a new era for the treatment of generalized tonic–clonic seizures.

The discovery of trimethadione and paramethadione for the "petit mal triad" soon followed. An animal model for evaluating therapeutic agents for the treatment of partial seizures was lacking. Toman et al.[185] described a "psychomotor" test in which mice are subjected to low-frequency stimulation to produce seizures resembling those seen in humans. A rectangular pulse of 6 Hz, 1 msec. pulse width, and a current of 32 mA is delivered for 3 seconds via electrodes placed on the cornea. The mice display an abnormal behavior for 25 seconds, which can best be described as "stunned." They remain motionless and do not respond to painful stimuli. These types of in vivo screening models are still used for the identification of new therapeutic agents for the treatment of seizures.

Animal Models for Drug Discovery

Genetic Models

Because of their seizure predisposition, genetic animal models of epileptic seizures have been used to identify and profile potential anticonvulsant compounds. These models are thought to mimic the clinical situation more closely than traditional electrically or chemically induced seizures in experimental animals.[1,105] The genetic models include the photosensitive baboon (*Papio papio*)[127,128]; several strains of audiogenic seizure mice, such as the DBA/2,[16] SJL/J,[54] Frings, and O'Grady[25]; genetically epileptic prone rats, GEPR-3 and GEPR-9[35,93]; Mongolian gerbil (*Meriones unguiculatus*)[101,113,116]; chickens[74]; tottering mice (tg/tg strain)[64]; and dogs.[112]

Audiogenetic Mice

Audiogenic seizure–susceptible mice exhibit wild running followed by generalized tonic seizures when exposed to high-intensity sound. The intensity of sound usually is in the range of 90 to 120 dB with frequencies between 11 and 16 kHz. Seizure susceptibility in some stains is enhanced if the mice are exposed to high-intensity sound following a priming stimulus.[25] Strain difference in seizure susceptibility occurs with age, usually reaching a maximum level between 2 and 4 weeks of life.[154] These seizure-prone mice have been used to identify a number of different types of central nervous system (CNS)-active agents.

The Frings mice maintain their susceptibility to sound stimulation over their entire adult life. Swinyard described similar activity in both Frings and O'Grady strains of mice for phenytoin, phenobarbital, and trimethadione.[180] Unfortunately, non-anticonvulsant drugs will also attenuate sound-induced seizures. Ataraxic agents, muscle relaxants, chlorpromazine, and reserpine will attenuate the sound-induced seizures of Frings mice in nontoxic doses.[140]

Several experimental compounds were evaluated for anticonvulsant activity using the Frings strain of audiogenic seizure–susceptible mice. MDL 27,266 was found to have similar values in the Frings and DBA/2 strains, with ED50s of 5.0 and 5.1 mg/kg, respectively.[200] Valrocemide (TV-1901), a valproic acid analog, was found to be more potent than valproic acid when administered intraperitoneally to Frings mice.[69]

The most commonly used strain of audiogenic seizure mice is the DBA/2. Chapman et al.[16] reviewed the literature for the use of DBA/2 mice in evaluating the pharmacologic activity of known anticonvulsant drugs. All of the commonly used anticonvulsant drugs, such as benzodiazepines, γ-aminobutyric acid (GABA) agonists, GABA-transaminase inhibitors, GABA-uptake inhibitors, competitive[33,136] and noncompetitive excitatory amino acid antagonists,[17,18,19] and calcium entry blockers,[40] were active in suppressing sound-induced seizures in DBA/2 mice.

Several currently marketed anticonvulsants have been profiled for anticonvulsant activity in the DBA/2 strain. Pregabalin's anticonvulsant activity was profiled in a number of animal models. Its anticonvulsant ED50 in DBA/2 mice was 2.7 mg/kg following oral administration.[193] Felbamate produced dose-dependent effects for suppression of sound-induced tonic, clonic, and wild-running phases using ED50s of 23.1, 48.4, and 114.6 mg/kg, respectively.[39] Retigabine was found to be active in many of the rodent models. The ED50 in the DBA/2 is 2.3 mg/kg following intraperitoneal administration.[147]

El Mouse

The El mouse is an electroencephalographically authentic animal model of epilepsy.[155,176,177] Seizures are induced by vestibular stimulation and become spontaneous after the mice experience several (10–15) induced seizures. The seizures appear to originate in the hippocampus or deep temporal lobe structures and are characterized by excessive salivation and automatism of the head and limbs. Paroxysmal electroencephalographic discharges are seen in the temporal lobe. King and LaMotte[87] published a comprehensive review of the El mouse as a model

of focal epilepsy. These seizures can be inhibited by phenytoin at 40 mg/kg twice daily for 3 days.[119]

Fueta et al. studied the antiepileptic action induced by a combination of vigabatrin and tiagabine in the El mouse.[52,53] They used brain slices from the El and the control ddY mouse and found that no synergistic effects took place. An α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) antagonist, YM928, in doses of 5 mg/kg or 10 mg/kg, administered intraperitoneally, significantly increased the number of stimulations required to elicit generalized seizures.[207] The novel anticonvulsant compound BW534U87, which is active in several electrically and chemically induced seizure models, is also active in preventing the focal seizures in the El mouse. The anticonvulsant activity is partially reversed with a selective adenosine A1 receptor antagonist.[166] Competitive *N*-methyl-D-aspartate (NMDA) antagonists have been shown to inhibit NMDA whole-cell currents in mouse spinal neurons as well as to block seizures in a dose-dependent manner in the El mouse.[34]

Several of the clinically effective anticonvulsant drugs, including ethosuximide, inhibited seizures induced by the intravenous administration of pentylenetetrazol.[174] The results were compared to those obtained by original sensory-induced seizures. The authors felt that PTZ-induced seizures were a more precise measure of anticonvulsant activity in the El mouse.

Tottering (tg/tg) and Quaking Mouse

The tottering mouse exhibits bilaterally synchronous spike-and-wave (6–7 Hz) discharges[132,133] that are sensitive to drugs used to treat absence seizures in humans.[64] The discharges are accompanied by movement arrest, fixed stare, twitching of the vibrissae, and myoclonic jerks of the head and jaw. Behaviorally, this genetic strain appears to exhibit both simple partial seizures with motor symptoms and absence seizures. Microscopically, there appears to be cellular loss and vesiculations of the cytoplasmic membranous structures in the cerebellum. The quaking mouse, like the tottering mouse, has an autosomal recessive genetic disorder that produces tonic–clonic seizures.

The homozygous mice exhibit tonic–clonic seizures when lifted by the tail and slowly rotated 180 degrees; approximately 85% of the control mice handled in this manner exhibit seizures. Drugs used to treat human absence seizures, such as ethosuximide, are ineffective in this seizure model, whereas drugs for the treatment of generalized tonic–clonic seizures and partial seizures are effective.[184]

The clinically effective anti-absence drugs diazepam, phenobarbital, and ethosuximide were effective against the absence-like seizures in the tottering mouse.[64] In contrast, phenytoin did not significantly reduce the incidence of the absence seizures in doses up to 60 mg/kg. The CNS-stimulant caffeine, in doses of 5 to 15 mg/kg, significantly decreased absence-like seizures 4 hours following intraperitoneal administration.[90]

The quaking mouse, like the tottering mouse, has an autosomal recessive genetic disorder that produces tonic–clonic seizures. The homozygous mice exhibit tonic–clonic seizures when lifted by the tail and slowly rotating them 180 degrees. Carbamazepine and phenytoin were effective in controlling the seizure, whereas ethosuximide and diazepam were ineffective. Valproate completely controlled the seizure when a dose of 400 mg/kg was administered.[184] Tonic–clonic convulsions in this genetic species were attenuated by both competitive and noncompetitive NMDA antagonists when administered by the intracerebroventricular route of administration.[131]

Unfortunately, most genetic models of spontaneous seizures are presently impractical as a means of identifying potential candidates in primary screens due to the limited availability of test animals and/or irregular seizure frequency.[110]

Audiogenetic Rats

Two separate and distinct colonies of genetically epilepsy-prone rats, GEPR-9 and GEPR-3, have been bred and are used to identify anticonvulsant drugs.[35] The two colonies differ in the convulsion intensity following a sound stimulus. The GEPR-9 rats exhibit a seizure pattern similar to the DBA/2 mice, characterized by a terminal complete tonic phase. The seizure pattern of the GEPR-3 consists of an initial running phase followed by clonic seizures. Changes in sound pressure and frequency are important factors to be considered when establishing this model in a laboratory.[183]

Several neurochemical deficits occur in the GEPR that may have human correlates. Both noradrenergic (NE) and serotonergic deficits appear to be important in the seizure disposition of the GEPR. Browning et al. found that a NE deficit greatly enhances the incidence of tonic convulsions and supports the hypothesis that an increase in excitatory neurotransmitters in the GEPR inferior colliculus may act to initiate audiogenic seizures, whereas the NE deficit may allow expression of the tonic components of the seizure seen in some GEPR.[12]

The GEPR-9 is extremely sensitive to electrically induced seizures.[13] The threshold current (mA) needed to produce tonic seizures in the GEPR-9 is one-fourth that of the GEPR-3 or normal rat. In fact, forelimb or facial clonus could not be elicited in the GEPR-9 at any current. A complete description of the ontogenetic development, neurochemistry, and seizure disposition of the GEPR has been summarized by Jobe et al.[71]

All the established AEDs attenuate the sound-induced seizures in the GEPR. In 1997, Consroe and Wolkin[26] compared the anticonvulsant profile of phenytoin, cannabidiol, delta 9 tetrahydrocannabinol, and cannabinol to clinically effective anticonvulsants in both the MES test and GEPR rats. They found that cannabidiol was relatively more potent than phenytoin. In general, phenytoin and carbamazepine, on a mg/kg basis, are more potent in blocking the tonic phase in the GEPR-9 than in attenuating the clonic seizure in the GEPR-3. Phenobarbital and ethosuximide are, however, equally potent in both strains of rats.[35]

Valproate is more potent in the GEPR-3 than the GEPR-9. Antidepressants such as imipramine and amitriptyline act both as anticonvulsants and proconvulsants in these models. This dichotomy can be explained by the fact that antidepressants and antiarrhythmics lower the seizure threshold while at the same time preventing seizure spread.

NMDA receptor antagonists significantly decreased AGS severity in the GEPR-9 rat. Systemic administration of the competitive NMDA antagonists 3-[(±)-2-carboxy-piperazin-4-yl]-propyl-1-phosphonate (CPP) and 2-amino-7-phosphonoheptanoic acid and the noncompetitive antagonist dizocilpine (MK-801) were effectively anticonvulsant in the GEPR-9 rat.[38]

The selective neuronal GABA uptake inhibitor NNC-771 has been found to protect against both the clonic and tonic seizure phases at doses of 0.23 mg/kg following intraperitoneal administration.[175] Bilateral injections of tiagabine, a GABA uptake inhibitor, into the inferior colliculus of GEPR-9 rats significantly reduced seizure severity.[48] These results suggest that GABA is an important inhibitor of acoustical transmission in this brain structure.

Epileptic Fowl

Seizure susceptibility in domestic fowl (*Gallus gallus*) is due to a homozygous autosomal recessive trait.[29] Spontaneous seizures occur at the time of hatching and continue to occur throughout the bird's life. Seizures can be induced by photic stimulation using an optimal frequency of 14 flashes per second.[30] Heterozygotes do not respond to the stimulus. The seizures are characterized by an upward and backward tonic extension of the head and neck, followed by loss of leg muscle control. A final phase consists of violent wing flapping with clonic leg movements. The interictal electroencephalogram (EEG) is characterized by high-voltage, slow-wave activity.

Seizure incidence and severity was evaluated following the administration of several of the clinically effective anticonvulsant drugs. Phenobarbital, primidone, phenytoin, and valproic acid reduced seizure susceptibility at plasma concentrations approximating those considered within the therapeutic range for controlling generalized and focal seizures in humans.[36,73,74,75,76,77] Ethosuximide was the only ineffective anticonvulsant in this model.[36]

Several experimental GABA mimetic compounds, GABA-selective transport inhibitors, and tetrahydrocannabinol were also active in attenuating the induced seizures.[73,153,206] Pedder et al.[137] demonstrated that both competitive (CPP and APH) and noncompetitive NMDA antagonists (MK-801) delayed the onset of seizures in a dose-dependent manner. An antiparasitic agent, ivermectin, attenuated photic stimulation-induced seizures in a dose-dependent manner.[31]

Hyperthermia can cause seizures in epileptic chicks but not in the adult epileptic chickens.[78] Phenobarbital and valproic acid attenuated the seizure activity, whereas phenytoin did not.[72]

Light-sensitive Epileptic Baboon

Killam et al.[86] found 60 of 100 baboons (*Papio papio*) exhibited paroxysmal responses to the first exposure of flashing light. Intermittent light stimulation (25 Hz) produces a characteristic EEG and motor paroxysmal response. In some animals, self-sustained epileptiform discharges appeared prior to the motor seizures.[85] Myoclonus of the eyelids, face and neck, trunk, and limbs characterized the motor seizures. The effect and duration of drugs can be evaluated in a dose-response relationship by scoring the severity of the seizure pattern. The administration of a subconvulsant dose of allylglycine (200 mg/kg intravenously) 2 to 9 hours prior to the photic stimulation produces a stable level of sustained generalized myoclonic responsiveness.[128]

A number of clinically effective and experimental anticonvulsants have been evaluated in this model of epilepsy. Benzodiazepines and phenobarbital are extremely effective in attenuating the light-induced epileptiform seizures.[85,128,138] GABAergic compounds produce mixed responses. Valproate partially attenuated seizures at high, clinically therapeutic plasma concentrations,[125] whereas muscimol and 4, 5, 6, 7 tetrahydroxyisoxazolo (4, 5, c) pyridine 3-ol (THIP) are proconvulsant.[124,138] Vigabatrin completely blocked the generalized myoclonus for several hours.[126] Phenytoin, carbamazepine, and ethosuximide are relatively ineffective in attenuating the myoclonic seizures.[127,172]

Other experimental compounds have been evaluated using this seizure model. These include beta-carboline abecarnil[192]; MDL 27266, an NMDA antagonist[200]; memantine, an NMDA channel-blocking antagonist[129]; and progabide, a GABA agonist.[15]

Electrically Induced Seizures

Maximal Seizure Pattern Test

Electrically induced seizures are perhaps the most frequently used model system for the identification of anticonvulsant activity. The type and intensity of the seizure is related to the intensity of the stimulus current and site of stimulation.[139] The electrical stimulus can be delivered via the cornea or ear clips. As the current is increased, the behavioral characteristics become more severe. The lowest effective current produces a "stunned response." Higher currents produce "twitching of the vibrissae" and facial clonus. The behavioral responses continue to proceed to forelimb clonus and rearing. Finally, a current is reached that produces tonic flexion-extension of the fore- and hind-limbs.

The change in threshold current to produce tonic hind-limb extension in 50% (CC50) of the rodents can be used as a primary screen for anticonvulsant activity. Loscher et al.[97] demonstrated that ethosuximide was the only anticonvulsant that did not raise the threshold for tonic seizures. Phenytoin and carbamazepine tripled the current required to produce a tonic hind-limb seizure. Diazepam, valproic acid, and primidone were far less active in raising the CC50. It is therefore not surprising that these less potent drugs are relatively poor in preventing seizure spread in the supramaximal seizure pattern (MES) test.

It is also important to characterize a compound's effect on raising seizure threshold. In the early studies, a large number of animals were required to determine the CD50 for a given population. Loscher then described a direct cortical ramp-stimulation model to determine the changes in CD50 in rats following administration of known anticonvulsant drugs. This methodology allows for repeated determination of seizure threshold at short-time intervals in individual rats without inducing postictal threshold changes.[91] The changes in current needed to produce hind-limb extension using this method for carbamazepine, phenytoin, and valproate were similar to the earlier methods using a large population of animals. Thus, this approach offers distinct savings in animal costs and requires less compound.

When groups of mice are used to establish changes in seizure threshold, a "staircase" procedure can be used to define the population threshold.[49] The stimulus intensity of the next animal is determined by the response of the animal just tested. The stimulus intensity is increased to the next higher increment if the previous animal failed to exhibit a seizure or the next lower increment if the animal exhibits a seizure.[178] Using this information, the investigator can then calculate the current necessary to produce a seizure in 50% of the population; that is, the CC50.

The MES test is used to identify drugs that prevent seizure spread, and it is often employed as a primary screen for anticonvulsant activity. Phenytoin and carbamazepine are extremely active in this animal model. The electrical current for the supramaximal MES test in the CF1 mouse is 50 mA at 60 Hz for 0.2 seconds. This is delivered via corneal electrodes,[179,188] and is four to five times greater than the threshold current needed to produce a tonic hind-limb extension seizure.

The choice of mouse strain is extremely important in the MES test. When evaluating the strain, the CD97 is usually determined first, then the final current for the test can be estimated. For the supramaximal test, a current that is three to five times that of the CC97 is typically used. Because death doesn't usually occur in the CF1 male mouse following the tonic phase of the seizure,[189] this strain has been historically employed by the NINDS-sponsored ADD Program at the University of Utah.[202] In contrast, approximately 10% of young rats and a higher percentage of older rats may fail to display a tonic extension at a supramaximal stimulation (e.g., 150 mA, 0.2 sec.).

In most cases, electroshock stimulation is delivered through corneal electrodes, although other stimulation sites can be used. For example, transauricular stimulation in rats also produces a similar seizure pattern.[11] There are, however, differences in some seizure parameters. Transauricular stimulation is more effective in eliciting tonic convulsions, whereas facial and forelimb clonus is lost. The threshold for clonus is lower when transcorneal electrodes are used.

Direct electrical stimulation to various brain structures produces the identical behavioral responses seen following corneal stimulation. The studies of Esplin et al.[45,46] demonstrated that direct electrical stimulation of the spinal cord produces a seizure pattern similar to that seen following corneal stimulation. These observations suggest that the spinal cord serves as a conduction pathway for impulses generated from higher brain levels. Phenytoin had a minor effect on the tonic-extensor phase of the spinal cord–induced seizure. The anticonvulsant activity of phenytoin therefore must be due to its action on higher brain centers. Conversely, phenytoin, phenobarbital, and ethosuximide block the tonic hind-limb extension component of seizures induced by stimulation of the mesencephalic reticular formation of rats.[21]

Febrile Seizures

Febrile seizures are commonly observed in children; depending on their severity, the patient may be treated prophylactically with phenobarbital. Unfortunately, phenobarbital has been associated with negative effects on learning and behavior. Several animal models have been developed and validated for the purpose of identifying nonsedating anticonvulsants for the treatment of febrile seizures. Holtzman et al. developed a microwave-hyperthermia model that raises core temperature of 2- to 10-day-old rats and results in convulsions similar to febrile convulsions in human infants.[67] In 1983, Hjeresen et al., using similar microwave technology, used 13- to 17-day-old rats to produce seizures. This heating procedure impaired neither brain growth nor performance during behavioral testing. There appears to be a decrease in seizure susceptibility with age in the rat pups following microwave hyperthermia.[66]

Similar studies were conducted using chicks that display a genetic epileptic seizure phenotype. Epileptic seizures are produced by elevating their body temperature using microwave diathermy.[72] These hyperthermic seizures differ from those seen in photo-stimulated, epileptic-prone chickens. Hyperthermia does not produce seizures in adult epileptic chickens. Seizures in hyperthermia-induced epileptic chicks are attenuated by phenobarbital, whereas valproic acid and phenytoin have no effect.[72]

Hyperthermia can be produced in weanling rats (21 days old) by immersion in a 45°C water bath for a maximum of 4 minutes (four exposures over a 2-week period). The rat's seizures increase in severity and progress to a stage 5 generalized seizures.[135] This method was used to characterize the anticonvulsant activity of several drugs: clonazepam, MK801, valproic acid, remacemide, and phenobarbital. Remacemide and phenobarbital were inactive. Valproate actively decreased seizure severity and modestly attenuated seizure duration. It also reduced the number of animals experiencing seizures on test day one. Clonazepam effectively lowered seizure score and reduced the number of animals experiencing seizures during three of the four testing periods. MK801, at the dose used, caused behavioral side effects while reducing the maximum seizure grade.

Baram et al. were interested in the long-term outcome of febrile seizures in infants and young children.[2] They developed a methodology to produce hyperthermic-induced seizures using the infant rat. The seizures were induced by a regulated stream of mildly heated air over 1- to 11-day-old rats; the presence of seizures was confirmed by behavioral and EEG analysis. Stereotypical seizure activity was observed in 94% of the heat-treated rat pups, with 11% mortality. Depth recording from the amygdala and hippocampus clearly showed epileptic activity. Thus, this model allows for long-term studies of the mechanisms and outcome of febrile seizures.

In their initial studies, hyperthermic seizures—but not hyperthermia alone—resulted in numerous argyrophilic neurons in discrete regions of the limbic system. Within 24 hours of seizures, a significant proportion of neurons in the central nucleus of the amygdala and in the hippocampal CA3 and CA1 pyramidal cell layer were affected. However, by 4 weeks after the hyperthermic insult, no significant neuronal damage was evident in these regions.[191]

Chemically Induced Seizures

The use of chemicals to induce seizures began over a century ago and is still used in epilepsy research and drug discovery today.[37,173] Camphor, picrotoxin, and strychnine were used before the turn of the 20th century. The most commonly used chemoconvulsant, PTZ, was introduced in 1926.[65]

In addition to PTZ, other commonly used chemoconvulsants include bicuculline, picrotoxin, γ-hydroxybutyrate, NMDA, AMPA, kainate, and quisqualate. Other ictal- or seizure-producing compounds mentioned in the literature, but less frequently used in drug discovery, include pilocarpine, homocysteine/cobalt, flurothyl, 3-mercaptoproprionic acid, allylglycine, β-carboline, penicillin, zinc, alumina, and tetanus toxin.[37]

Results obtained in these tests should be interpreted with some caution. For example, the finding that an experimental drug blocks the tonic seizures caused by theophylline does not prove that it works through a purinergic mechanism. Most compounds that prevent seizure spread, such as phenytoin and carbamazepine, are effective in blocking the tonic maximal seizure caused by theophylline, but do not attenuate the clonic seizure associated with theophylline.

Pentylenetetrazol

PTZ (Metrazol, leptazol) was one of the first and remains the most commonly used chemoconvulsants to identify anticonvulsant activity. Unfortunately, it cannot be used to differentiate drugs effective in “grand mal” or “petit mal” epilepsy when tonic seizures are used as the endpoint.[47]

Loscher et al.[102] systematically evaluated the role of technical, biologic, and pharmacologic factors that can influence PTX-induced seizures. PTZ, when infused intravenously, is an excellent convulsant for detecting changes in seizure threshold.[61,134] Some of the clinically effective anticonvulsants are effective in delaying the onset of clonic seizures. Santucci et al. measured the onset and characteristics of the EEG paroxysms initiated by a slow intravenous infusion of pentylenetet- razol in gallamine-immobilized, artificially ventilated rats.[152] Compounds with “anti-petit mal” activity are effective in this model, whereas drugs primarily effective against tonic extension seizures (e.g., phenytoin and carbamazepine) are not. Similar results were observed in anesthetized rats.[84] Pollack and Shen[141] used this method to quantify the anticonvulsant activity of valproate in rats.

When PTZ is administered subcutaneously in doses that only produce myoclonic jerks followed by clonic seizures, phenytoin, primidone, and carbamazepine are not able to completely attenuate the clonic seizure.

The strain of mouse must be carefully considered for this test. It is extremely difficult to obtain only clonic seizures in 97% of the randomly bred mice without producing generalized seizures characterized by wild running and then tonic extension. The CF1 mouse is different in this respect. A dose can be determined that produces clonic seizures in 97% of the mice without observing tonic limb extension. When PTZ is administered intravenously, it can be used as a primary screen to assess the effect of anticonvulsant drugs on seizure threshold.

Some experimental anticonvulsant compounds appear to be both anticonvulsant and proconvulsant when administered in higher doses. These compounds prevent seizure spread induced by the MES test in both mice and rats, but are ineffective

in blocking clonic seizures induced by chemoconvulsants. The timed intravenous PTZ test is used to evaluate the proconvulsant potential of new compounds. PTZ is infused into the tail vein of mice. The time to the appearance of the first focal seizure (first twitch) and the clonic seizure is measured. Proconvulsant compounds require less PTZ (mg/kg) to produce these endpoints. At high (e.g., behaviorally toxic) doses, phenytoin and carbamazepine decrease the amount of convulsant needed to produce these end-points even though they are both able to block the tonic hind-limb seizure induced by this chemical stimulant. Mexiletine (an antiarrhythmic) and lidocaine have been shown to inhibit seizure spread, but lower seizure threshold in this test.

Repeated administration of PTZ to mice can produce a kindling effect.[83] The kindling effect was directly proportional to the dose or the intensity of the kindling stimulus and a dosing interval of 3 days. Two anticonvulsants, ethosuximide and cannabidiol, blocked the development of kindling to the PTZ-induced minimal convulsions.

Flurothyl

Flurothyl (Indoklon), a fluorinated derivative of ethylic ether, produces seizures in both humans and animals following its inhalation or parenteral administration. Seizures are characterized by clonic movements of the fore limbs with loss of posture followed by tonic flexion and extension of the hind limbs. The entire episode lasts about 40 seconds in mice. Similar behavioral responses are seen in both normal[190] and seizure-prone rats.[51] Simon et al. evaluated the effects of 18 drugs used for the treatment of a variety of different seizure types in preventing the flurothyl initiated clonic–tonic seizures and death in mice.[157] All the drugs studied were effective in attenuating the tonic seizures. Compounds that prevent seizure spread, such as phenytoin and carbamazepine, were ineffective in preventing the clonic seizures.

Felbamate (300 mg/kg) prolonged the latencies to flurothyl-induced seizures.[22] A synthetic epalon, ganaxolone, when administered to postnatal (9, 15, 30, and 60 days old) Sprague–Dawley rats, preferentially attenuated the tonic–clonic seizures over clonic seizures.[95] The anticonvulsant activity of gabapentin was evaluated in immature rats that received kainic acid on postnatal day 35. Cilio et al. found that gabapentin raised flurothyl-induced seizure threshold in all age groups tested.[23]

Compounds that are not known as clinically effective anticonvulsants will attenuate flurothyl-induced seizures. Some imipramine-like and antiparkinson drugs block the tonic seizures at near toxic doses. Parenterally active synthetic analogs of the endogenous morphinomimetic pentapeptide Met5-enkephalin raise the seizure threshold of flurothyl- induced seizures.[28] A highly selective κ-opioid agonist, U50488, was shown to attenuate electrically induced seizures but did not raise the threshold of flurothyl-induced convulsions.[190]

Gamma-hydroxybutyric Acid and Generalized Absence Seizures

Gamma-hydroxybutyric acid (GHB) is a GABA metabolite that occurs naturally in the mammalian brain.[148] When it, or its pro-drug form γ-butrylactone, is administered to rats,[117] cats,[165,203] and monkeys,[159] the EEG displays slowing with occasional spikes and bursts of poly spiking interspersed with periods of electrical silence. The spike-and-wave characteristics of the EEG following GHB treatment are similar to that seen in absence seizures. Cortez and Snead[27] have recently presented an excellent review of this animal seizure model. Clinically effective anticonvulsant drugs for the treatment of generalized absence seizures have validated this model.

Ethosuximide, at plasma levels of 140 μg/mL, greatly redu-ced the incidence of spiking, whereas phenytoin worsened the condition.[160] In additional experiments with anticonvulsant drugs, Snead[161] demonstrated that intravenous clonazepam and ethosuximide abolished the intravenously administered GHB-induced changes; however, diazepam marginally improved the spike-and-wave response, and phenobarbital was without effect. The CNS stimulant dextroamphetamine and the specific opioid antagonists naloxone and naltrexone also attenuated or blocked the GHB-induced spike-and-wave discharges. These observations suggest that the GHB-induced EEG changes have either a dopaminergic or adrenergic component.[162,164] Seizures observed in the GHB model of absence seizures are analogous to those seen in the PTZ model and the genetic spontaneous spike-and-wave Wistar rat. These seizures can be blocked by T-type Ca^{2+} channel blockers, benzodiazepines, and $GABA_B$ drugs, and potentiated by phenobarbital, tiagabine, vigabatrin, and other nonselective GABA agonists.[163]

Focal Seizures: Kindling

A review of several acquired focal models of seizures and epilepsy has been published.[96] Many of these models are used to gain a greater understanding of how seizures originate and propagate over time. Various kinds of kindling models that produce acquired focal seizures have been used to identify potential therapeutic agents for the treatment of partial seizures. Recently, kindled seizure models have been used to identify drugs for the treatment of therapy-resistant epilepsy.[96]

Kindling is a model of epilepsy produced by repeated administration of an initially subconvulsive electrical stimulus. This results in an increase in seizure activity, culminating in a generalized seizure. The kindled phenomenon is possible in several species, usually cats, mice, and rats. The kindled model of epilepsy has been extensively reviewed by McNamara,[121,122,123] Loscher and Schmidt,[110] Racine,[145] and McIntyre.[120] The electrographic and behavioral components of kindled seizures are thought to be similar to human partial seizures, since the focal component of the kindled seizure can progress into a generalized seizure. In this model, quantification of a drug's effect on both the focal and generalized seizure is possible by using a graded response.[145]

Electrical stimulation of several limbic sites of the brain (e.g., entorhinal cortex, amygdala, and hippocampus) can produce kindling. The most common way to produce the kindled state is stimulation of a specific area of the amygdala via implanted electrodes. A fixed current is applied until an afterdischarge is produced at the site of stimulation. Repeated daily stimulation produces behavioral responses that can be classified or graded. In the early stages of kindling, animals develop focal clonic seizures that progress to rearing with loss of balance. At this point, the EEG has the characteristic of a generalized seizure.

The majority of studies evaluating drug effects in kindled rats use the model in which electrodes are implanted into the amygdala. The advantage to this model is the ability to observe changes in the afterdischarge duration as well as changes in behavioral response following drug administration. Data on the effects of clinically effective anticonvulsants in this model have been published over the last 30 years. Phenytoin and carbamazepine are not extremely effective in attenuating focal seizures, lowering the Racine scale from control grade 5 to grade 3 or 4. On the other hand, valproic acid is effective in blocking focal seizures. From the clinical standpoint, both phenytoin and carbamazepine appear to be more effective in treating a patient's partial seizures than does valproate. This

dichotomy in the relationship between effectiveness in the kindled rat seizure model and clinical response may be due to the differences in sensitivity to drugs within the rat population.

Several experimental drugs or drugs recently approved by the U.S. Food and Drug Administration (FDA) for the treatment of epileptic seizures in patients were studied in amygdala-kindled rats. Two NMDA receptor antagonists, CGX-1007 and CI-1041, were shown to attenuate the secondarily generalized seizure and not affect the focal kindled seizure.[7] The water-soluble AMPA receptor antagonist YM872 blocked fully kindled seizures in rats[62]; however, this effect may be at doses that produce ataxia and sedation. A broad-spectrum anticonvulsant analog of valproic acid, ABT-769, was shown to have similar activity to valproic acid in the amygdala-kindled rat.[55] Both compounds decrease afterdischarge duration and attenuate both the generalized and focal seizure component.

Loscher and Rundfeldt[108] studied the anticonvulsant activity of phenytoin in a large number of amygdala-kindled rats. They found that about 60% of the rats showed a variable response to phenytoin when they used focal seizure threshold as the end-point of the drug's anticonvulsant effect. The difference in response in phenytoin-treated kindled rats was restricted to kindled seizures. The threshold remained the same for generalized tonic electroconvulsions (determined via transauricular electrodes) in phenytoin responders and nonresponders of the kindled groups. The difference in response between groups was not due to differences in phenytoin's pharmacokinetic parameters.

Corneal stimulation is an alternative method to produce the kindled state. Corneal kindling can be done in both mice and rats. The major advantage of using mice as the experimental animal is that of cost. The efficacy of kindling depends on several stimulus parameters, including duration, intensity, and interval of the 60-Hz corneal electrode stimulation.[151] In general, mice are stimulated once daily for 2 seconds at 3 mA, whereas rats are stimulated twice daily for 4 seconds at 8 mA, as described by Walz et al.,[205] White et al.,[200] and Matagne.[118] Electrical stimulations are continued until a Racine stage 5 generalized seizure is obtained. Typically, ten consecutive stage 5 seizures (rearing and falling with clonus) are observed before drug testing is done.

Several experimental compounds were evaluated for their ability to prevent the generalized and focal seizures induced by corneal kindling. The neurosteroid ganaxolone was shown to be a potent anticonvulsant against fully kindled stage 5 seizures induced by corneal kindling in rats (ED50 of 4.5 mg/kg intraperitoneally), producing these effects at doses well below those that resulted in ataxia (TD50 of 14.2 mg/kg intraperitoneally).[14] An anticholinergic compound, F-721, was shown to both inhibit amygdala-kindled and corneal-kindled generalized seizures as well as decrease the afterdischarge duration by 83%.[182] A novel NMDA receptor antagonist that is selective for NR2B subunit, Cl-1041, blocked the fully expressed secondarily generalized seizure in a dose-dependent manner. Complete attenuation of the kindled seizure was only achieved at toxic doses.[7]

The use of corneally kindled mice also appears to be suitable as a primary screen for anticonvulsant activity.[118] Large numbers of mice can be rapidly kindled for drug screening studies. The pharmacodynamic characterization of responses from several drug studies gave reproducible results. The anticonvulsant activity in corneally kindled mice is similar to that observed in amygdala-kindled rats. Potschka and Loscher[144] compared the behavioral and pharmacologic differences in corneal kindling versus conventional kindling in mice. A clear progression of kindling development is seen in rats that is not seen in mice. Also, lethality in mice was a problem. Phenytoin nonresponders, seen frequently in kindled rats, were not observed in kindled mice.

Stimulation of other brain areas, such as hippocampus or cortex, also produce kindled seizures. Kamei et al.[79] compared the effects of several AEDs on seizures kindled in the neocortex, hippocampus, and amygdala of rats. They also studied the development of seizures (epileptogenesis) in these three brain areas. Amygdala-kindled rats developed generalized seizures more rapidly than did hippocampus- and neocortex-kindled rats. Although neocortex-kindled rats developed a kindled seizure similar to limbic-kindled seizures, more days of stimulation were required to produce the same effect.

Lothman et al.[114] described an alternate method for producing the fully kindled state in rats: the rapidly recurring hippocampal seizure (RRHS) model. The RRHS model stimulates the hippocampus of rats with 10-second trains of suprathreshold tetanic electrical stimuli every few minutes. Seizure intensity was quantified using the duration of afterdischarge and the accompanying behavioral responses. Severe limbic seizures were elicited on the first day following the initial repeated stimulation of the hippocampus. Seizures intensified on the second day and remained stable thereafter.

The RRHS model was used to screen and characterize several AEDs.[115] Behavioral seizures, electrographic seizures, afterdischarge thresholds, afterdischarge duration, and neurotoxicity were measured before and after intraperitoneal drug administration. Carbamazepine, phenobarbital, primidone, valproate, and diazepam suppressed the behavioral seizures in a dose-dependent manner. Phenytoin consistently had no effect on afterdischarge duration, and none of the drugs tested affected the afterdischarge threshold. Ethosuximide was totally without effect. The overall response patterns of the anticonvulsant drugs tested in the RRHS were similar to those seen in the amygdala-kindled rat model, although the mechanisms producing the phenomena may not be the same.

Levetiracetam, a newly clinically approved drug for the treatment of seizures, was evaluated in a model of rapid kindling with recurrent hippocampal seizures. Rats were given a dose of 54 mg/kg intraperitoneally and were stimulated 1 hour later. The seizure score fell from control stage 5 to an average of 1.67. The afterdischarge duration decreased from 57 to 21 seconds.[41]

Pharmacoresistant Animal Models

Introduction

Since 1993, several new AEDs have been brought to the world market for the management of partial epilepsy. With the exception of levetiracetam, the majority of these new AEDs were identified and developed as a result of their ability to block acute evoked seizures in rodent models of epilepsy. As discussed earlier, the mainstay of most AED discovery programs has been the MES test, the subcutaneous PTZ (scPTZ) test, and the kindled rat (also see the work by White et al.[201]). Unfortunately, despite their clinical predictiveness, there still remains a significant unmet need for the patient with "pharmacoresistant" epilepsy. To this end, the identification and characterization of one or more model systems that would predict efficacy in the pharmacoresistant patient population would be a valuable asset for any AED discovery program. Unfortunately, a model will only become clinically validated at the time that a drug is found to markedly reduce the incidence of therapy-resistant epilepsy in patients with epilepsy. In addition to being useful for therapy development, the ability to segregate animals on the basis of their responsiveness or lack of sensitivity to a given AED would be useful for attempting to understand the

molecular mechanisms underlying pharmacoresistance. In addition to understanding the mechanism of pharmacoresistance, an animal model of therapy resistance would be an asset for those studies designed to assess whether it is possible to reverse drug resistance, or potentially to predict which patient will remit and become pharmacoresistant. Given that most of these questions are extremely difficult to address directly in patients, it is important to continue the efforts to validate the established and newer models as they become available.

At present, a number of potentially interesting model systems of therapy resistance are available. The remainder of this section reviews the salient features of those models that have emerged in recent years that may ultimately prove valuable for both basic research and therapy discovery.

Defining Pharmacoresistance

In 2001 and 2002, two Workshops on Animal Models, jointly sponsored by the National Institutes of Health (NIH), National Institute of Neurological Disorders and Stroke (NINDS), and the American Epilepsy Society (AES), were convened to discuss the currently employed process whereby an investigational AED is evaluated.[170,171] These workshops evolved from a landmark White House–initiated conference, "Curing Epilepsy: Focus on the Future," which was sponsored by the NINDS in collaboration with the AES, Citizens United for Research in Epilepsy, Epilepsy Foundation, and the National Association of Epilepsy Centers. The participants of these workshops agreed that any proposed model of "pharmacoresistant" epilepsy should meet certain criteria. For example, "pharmacoresistance in animal models, based on human experience, can be minimally defined as persistent seizure activity that does not respond to monotherapy at tolerable doses with at least two current AEDs. An important need for the therapy-screening process is to find animal models that do not respond, or respond poorly to currently available AEDs" (see Stables, et al.[170]). Thus, the "demonstrated resistance" to two or more of the first-line AEDs employed in the treatment of partial epilepsy was considered pivotal. Furthermore, it was recommended that any model for therapy-resistant epilepsy should demonstrate parallels to human forms of pharmacoresistant epilepsy. Ideally, it would be hoped that any proposed model would lead to the identification of "a new therapy that will later be found to be effective in humans resistant to existing AEDs."

Models of Pharmacoresistant Epilepsy

In recent years, several in vivo model systems have been described that display a phenotype consistent with pharmacoresistant epilepsy (see Loscher[96] for review). These include the phenytoin-resistant kindled rat,[109,150] the lamotrigine-resistant kindled rat,[143,167,168,169] the 6-Hz psychomotor seizure model of partial epilepsy[4]; the post-SE models of temporal lobe epilepsy (TLE)[9,56,59,60,94]; and the methylazoxymethanol acetate (MAM) in utero model of nodular heterotopia.[158] See Loscher[96] for review and references. All these models are being utilized with increasing frequency in the search for novel AEDs, in an effort to differentiate them from the existing AEDs. The remainder of this section focuses on the above-mentioned in vivo models as they are currently being employed for therapy discovery. This is not to imply that other approaches utilizing in vitro systems are of any less value. For a discussion of this approach, the reader is referred to Dichter and Pollard[42] and Heinemann et al.[63] for review and references.

Antiepileptic Drug-resistant Kindled Rats

Phenytoin-resistant Kindled Rats

Over the last 20 years and more, the kindling model of partial epilepsy has been utilized with increasing frequency in the AED development process. The kindling model, unlike the MES and PTZ tests, is a model of focal epilepsy and one that displays a pharmacologic profile consistent with human partial epilepsy. Kindling refers to the process in which a progressive increase occurs in electrographic and behavioral seizure activity in response to repeated stimulation of a limbic brain region, such as the amygdala or hippocampus, with an initially subconvulsive current.[57] The kindling process is associated with a progressive increase in seizure severity and duration, a decrease in focal seizure threshold, and neuronal degeneration in limbic brain regions that resemble human TLE.

Löscher et al. have conducted extensive pharmacologic evaluations in the kindled rat model over the years and were among the first to demonstrate that kindled seizures were less sensitive to anticonvulsant treatment than were MES-induced generalized tonic extension seizures.[98,104] In subsequent investigations in the amygdala-kindled Wistar rat, Rundfeldt et al. found that the individual response of a fully kindled rat to a challenge dose of phenytoin differed markedly.[149] In their initial studies, they observed two population of rats: those that consistently responded to a challenge dose of phenytoin, and those that never responded to the same dose of phenytoin. This observation became the cornerstone of numerous studies designed to evaluate the effectiveness of "established" and "investigational" AEDs in phenytoin responders and nonresponders. Historical data collected over the years from more than 200 rats has demonstrated that approximately 16% of the animals display a consistent anticonvulsant response to a challenge dose of phenytoin; 23% display a variable response to the same challenge dose; and the remainder (61%) displays no response to phenytoin (see Löscher[96] for review and references). Based on this rather stable response, Löscher has suggested that these three groups of kindled rats model three different clinical populations: those patients who achieve complete seizure control; those who display a reduced seizure frequency in response to pharmacotherapy but never become seizure-free; and those who would be considered drug-refractory.

With the exception of levetiracetam, all the AEDs that have been tested in this model have been found to be less efficacious in the phenytoin nonresponder kindled rats. This observation is consistent with the clinical situation in which patients who are refractory to one AED are very likely to be refractory to other AEDs.[92,146] The finding that the efficacy of levetiracetam is maintained in the phenytoin-resistant rat would suggest that it might offer some potential advantage in the patient who has failed multiple AEDs. Unfortunately, not every patient who is refractory to one or more AEDs becomes seizure-free when treated with levetiracetam. As such, there still remains a significant unmet need for this patient population.

As with any chronic animal model, the phenytoin-resistant kindled rat model is very time- and labor-intensive. In addition to the surgical implantation of electrodes and the subsequent kindling protocol, there is the postkindling selection process wherein rats are repeatedly tested with a challenge dose of phenytoin to identify the responder and nonresponder population for the pharmacologic studies. One particular advantage of the phenytoin-resistant kindled rat is that it allows for comparative studies in both the responsive and nonresponsive population of rats from the same strain. In addition, the kindled rat, unlike the spontaneous seizure models (discussed later), does not require continuous video-EEG monitoring because the seizures are evoked.

The Lamotrigine-resistant Kindled Rat Model

The lamotrigine-resistant kindled rat model of partial epilepsy was first described in 2000.[143] Unlike the phenytoin-resistant kindled rat, resistance to lamotrigine can be induced by treating rats with lamotrigine during the kindling acquisition phase. Thus, as shown by Postma et al.,[143] exposure to a low dose (5 mg/kg) of lamotrigine during kindling development leads to reduced efficacy of lamotrigine when administered to the fully kindled rat. A similar phenomenon was reported earlier for carbamazepine.[198] Based on these observations, Srivastava et al.[169] assessed whether this phenomenon would generalize to the PTZ kindling model. Indeed, when lamotrigine (5 mg/kg) was administered to Sprague-Dawley rats prior to each PTZ challenge dose during the kindling acquisition phase, fully kindled rats were found to be resistant to a subsequent challenge with a higher dose of lamotrigine. Perhaps more important is the observation that lamotrigine-refractory rats are also resistant to carbamazepine, phenytoin, and topiramate, but not to valproate or the investigational $KCNQ_2$ activator retigabine.[167,168,169]

Although less well characterized, the lamotrigine-resistant kindled rat may offer a practical advantage over the phenytoin-resistant rat in that it is not necessary to embark on an extensive prescreening protocol to identify those animals that are pharmacoresistant. In this regard, it might serve as an early model of drug-resistant epilepsy to identify novel AEDs for further evaluation in more extensive model systems, including the phenytoin-resistant kindled rat.

The Low-frequency (6 Hz) Electroshock Seizure Model

In many respects, the 6-Hz seizure model offers many of the same advantages of another acute electroshock seizure model: the MES test. As with the MES test, the 6-Hz seizure is an acute, electrically evoked seizure using standard corneal electroshock; it is a high throughput method, and requires minimal technical expertise. The only real difference is the frequency (6 Hz vs. 50 Hz) and duration (3 sec vs. 0.2 sec). As it turns out, these two stimulus parameters produce a seizure that is characterized by immobility, forelimb clonus, Straub tail, and facial automatisms that are thought to more closely model human limbic seizures.[4,5,10] When compared to either the MES or PTZ seizure, the 6-Hz seizure displays a pattern of neuronal activation, as measured by c-Fos staining, that is primarily localized to the amygdala and piriform cortex. At high current intensities (i.e., 44 mA), the dentate gyrus is recruited and displays prominent c-Fos staining.

When it was first introduced, the 6 Hz-model was thought to represent a useful model for identifying therapeutic agents for the treatment of “psychomotor seizures.” Unfortunately, at the time of its initial characterization, it failed to predict the clinical utility of two widely employed AEDs: phenytoin and thiantoin. Because it did not offer any particular advantage over the other models in place at the time, it was abandoned shortly after its introduction.[10]

Some 50 years later, Barton et al.,[10] at the University of Utah, resurrected the 6-Hz model as a potential screen for drugs effective against therapy-resistant epilepsy. Interestingly, the pharmacologic profile of the 6-Hz model is somewhat dependent on the intensity of the stimulation. For example, at a convulsive current (CC) sufficient to induce a prototypical seizure in 97% of the population tested (i.e., the CC_{97}), all AEDs evaluated (phenytoin, lamotrigine, ethosuximide, levetiracetam, and valproate) were effective in blocking the acute seizure. As the current intensity is increased to a level that is 1.5 times the CC_{97}, several AEDs lose their ability to protect against a 6-Hz seizure. At a current equivalent to two times the CC_{97}, only valproate and levetiracetam retained their ability to block 6-Hz seizures; albeit with a marked decrease in the potency of both drugs at two times the CC_{97}.[4] The finding that levetiracetam was found to be active at a specific stimulus intensity, whereas other anticonvulsants display little to no efficacy illustrates the use of the 6-Hz model as a screen for novel anticonvulsant compounds. This is a particularly important observation when one considers that levetiracetam was inactive in the acute seizure models, such as the MES and PTZ seizure tests.[58,89] Thus, the incorporation of a simple acute screen that would minimize the chances of “missing” a unique drug like levetiracetam should be an important consideration when setting up an anticonvulsant testing protocol to evaluate investigational AEDs. To this point, the 6-Hz seizure model has been incorporated into the testing protocol of the Anticonvulsant Drug Development Program at the University of Utah to examine those drugs that test negative in both the MES and PTZ seizure tests.

As a result of renewed interest in the 6-Hz model as a potential model of pharmacoresistant epilepsy, several new investigational drugs have been tested in this model.[5,6,68,69,70,80,81,82,96,156] Whether this approach will ultimately lead to the identification of a more efficacious AED for the treatment of refractory partial epilepsy remains to be determined. However, the finding that this model offers a means to differentiate the anticonvulsant profile of promising investigational AEDs is of interest in that it is a fast and simplistic model that can be used to quickly identify those drugs for further differentiation in more chronic, labor-intensive models, such as the kindled rat or post–status spontaneous seizure models (see later discussion).

In a manner similar to the earlier c-Fos studies, Duncan and Kohn[43] have shown that a 6-Hz seizure (32 mA, 3 sec duration) produces a robust increase in ^{14}C-2-deoxyglucose (2-DG) uptake in cerebral cortices, lateral amygdala, and caudate-putamen, but not the hippocampal areas. Interestingly, the investigational AED lacosamide (20 mg/kg, intraperitoneally), when administered 30 minutes prior to stimulation, completely antagonized the seizure-induced metabolic activation but did not affect basal 2-DG uptake.[43] These results demonstrate that lacosamide is able to block seizure-induced neural activation without suppressing normal brain metabolic activity.[43]

Post-status Epilepticus Models of Temporal Lobe Epilepsy

Post-SE models of refractory epilepsy are beginning to emerge as important tools in the differentiation of investigational AEDs. These models of pharmacoresistant epilepsy differ significantly from the AED-resistant kindled rat and the 6-Hz seizure model in that seizures are spontaneously evolving and not evoked. This adds another level of complexity to any pharmacologic evaluation. For example, issues of how to administer drug to an animal for a prolonged period of time become overshadowed by the challenge associated with detecting and evaluating efficacy using chronic video-EEG recording to quantitate seizure frequency and severity as outcome measures.

The development and characterization of this model system for pharmacologic testing has, in a large part, been due to a focused effort of the epilepsy community to identify clinically relevant models of pharmacoresistant epilepsy.[170] Because drug trials in rats with spontaneous seizures take on another level of complexity and are extremely laborious and time-consuming, there have only been a few pharmacologic studies conducted to date.[9,59,60] In many respects, the post-status models described thus far fulfill one very important characteristic of the ideal model system: They model spontaneous recurrent seizures (SRS) following a species-appropriate latent period.[170,171]

In one of the first studies conducted using this model, Leite and Cavalheiro[94] found that high doses of phenobarbital (100 mg/kg), carbamazepine (120 mg/kg), phenytoin (100 mg/kg), and valproic acid (600 mg/kg), were highly effective in blocking SRS in the pilocarpine post-status model when administered over a 14-day period. In contrast, high-dose ethosuximide (400 mg/kg) was ineffective in this model. These investigators suggested that SRS following pilocarpine-induced SE could be a useful model for the identification of more efficacious drugs for difficult-to-treat complex partial seizures. In contrast to clinical experience, almost all the rats that received phenobarbital, phenytoin, carbamazepine, and valproate were protected against spontaneous seizures in their experiment. Whether this finding is the result of excessively high blood and brain levels of these AEDs is not known because levels were not determined in this study.

In an effort to control for some of the variables associated with chronic drug administration to rats, Glien et al.[56] has employed the use of implanted mini–osmotic pumps to deliver an AED (or vehicle) over a prolonged period of time. In one such study, Wistar rats were subjected to pilocarpine-induced SE, and SRSs were recorded in the months following status. At the point of study initiation, a group of eight rats with frequent SRSs were implanted subcutaneously with a saline-filled osmotic minipump for 2 weeks (predrug control period). They then were implanted subcutaneously with a levetiracetam-filled minipump for another 2 weeks (drug period). For the last 2 weeks of the study, rats were implanted subcutaneously with a saline-filled minipump (postdrug control period). For this study, the concentration of levetiracetam in the pump was sufficient to achieve blood levels consistent with those obtained in patients with TLE. Seizures were recorded by video monitoring for the 6-week duration of the study. The pre- and post-drug seizure frequency of the epileptic rats in this study was 21 and 25 seizures, respectively. During the levetiracetam arm of this study, the average seizure frequency was reduced to eight during the 2-week drug-treatment period. Interestingly, as with most randomized clinical studies, marked variability in the response rate was observed despite the fact that blood levels of levetiracetam were virtually identical in all rats. For example, three of eight rats were considered responders, achieving complete or almost complete seizure control, whereas three others were considered nonresponders; because of substantial predrug and postdrug control seizure frequency variability, two of the eight could not be included in either group. This study with levetiracetam shows that the testing of drugs in epileptic rats can yield interesting results that are likely to be more clinically relevant than results obtained from acute evoked-seizure models.

Results from another study evaluating the chronic effect of phenobarbital on SRSs in an electrical model of post-SE–induced epilepsy (i.e., sustained electrical stimulation of the basolateral amygdala of Sprague-Dawley rats) has demonstrated that it is possible to select drug responders and nonresponders from yet another model.[9] In this study with 11 rats, seizure frequency was monitored for 2 weeks before dosing with phenobarbital was initiated. The dose and dosing protocol for phenobarbital administration was based on pilot experiments designed to achieve blood levels within a therapeutic range of 10 to 40 μg/ml. This protocol was maintained for 2 weeks, then the seizure frequency was monitored for an additional 2 weeks in the absence of any drug treatment. Analysis of blood levels demonstrated that therapeutic levels were maintained in all rats for the duration of the active drug treatment period. Six of the eleven rats with SRSs became seizure-free in this experiment, one rat displayed a >90% reduction in seizure frequency, and three of the 11 rats showed an increase in seizure frequency during drug treatment; one of the 11 showed only a moderate (<50%) reduction in seizure frequency.[9]

In yet another example of how post-SE rats can be utilized for pharmacologic evaluation, Dudek et al. have employed a repeated-measures, cross-over treatment protocol to evaluate the efficacy of topiramate and the investigational AED RWJ 333369 in a post-kainate status model.[59,60] In these studies, RWJ 333369 was found to dose-dependently decrease the relative seizure frequency of SRSs at nontoxic doses. Furthermore, efficacy correlated very well with measured plasma concentrations.[59] When compared to results from an identical study conducted with topiramate, RWJ 333369 displayed a greater level of efficacy, and a greater percentage of rats displayed complete seizure freedom (seven out of eight rats vs. one out of eight rats, respectively). Collectively, these data support the concept that a repeated-measures, cross-over protocol is an effective method for testing AEDs in animals with post-status SRS. Furthermore, this approach may be useful for the development of adjunct therapies.

These examples demonstrate that it is possible to establish a model in which the pharmacology of the preclinical model mimics the human condition (e.g., the presence of responders and nonresponders). By testing new drugs in animals that are found to be nonresponsive to existing therapies, we may be able to better predict efficacy in a particular patient population and thereby enrich our chances of identifying the truly novel therapy. This approach, albeit costly and labor intensive, should be considered when attempting to differentiate a new drug from those that are either on the market or currently undergoing clinical trials.

The Methylazoxymethanol Acetate in utero Model of Nodular Heterotopia

Seizures associated with cortical dysplasia are often found to be resistant to the commonly employed AEDs.[32,208] Despite the fact that a number of animal models of cortical dysplasia are available, only one has been subjected to a systematic pharmacologic evaluation. In 2002, Smyth et al.[158] described the results of their study to investigate the effects of a limited number of AEDs in Sprague-Dawley rats exposed to methylazoxymethanol acetate (MAM) in utero. In utero exposure of the fetus to MAM causes nodular heterotopia with hyperexcitable dysplastic brain regions. In contrast to age-matched control rats, valproate did not increase the latency to kainate-induced seizures in those animals exposed in utero to MAM.[158] Furthermore, 4-aminopyridine–induced epileptiform bursting in acute hippocampal slices from MAM-exposed rats was resistant to treatment with phenobarbital, carbamazepine, valproate, ethosuximide, and lamotrigine. In contrast, 4-aminopyridine–induced bursting in slices from control rats was suppressed by these AEDs. The results from this limited study suggest that MAM-exposed rats have a reduced sensitivity to commonly prescribed AEDs, thereby mimicking the clinical response in patients with dysplasia-associated epilepsy. Given the unique nature of this model, there is a clear need for further evaluation of its validity to the human condition.

Summary

All these models are being utilized with increasing frequency in the search for novel AEDs in an effort to differentiate them from existing AEDs. It is too early to say whether any of these models, if implemented into the routine evaluation of investigational AEDs, will lead to the identification of the next-generation AED. The results from these various models have demonstrated that it is possible to “differentiate” compounds on the basis of their efficacy in one or more of these models.

Furthermore, the use of these models has led to the development of novel drug-testing protocols in animals that more closely resemble human clinical protocols. Equally important is that each of these models provides a biologic system in which to evaluate the mechanisms underlying pharmacoresistant epilepsy and to test novel approaches designed to overcome or reverse therapy resistance, and to perhaps identify appropriate surrogate markers of pharmacoresistance. Through a greater understanding of these factors, one can envision the day when we will be able to identify the patient at risk for developing therapy-resistant epilepsy and institute a prophylactic therapy that prevents the emergence of pharmacoresistance.

Role of the Pharmaceutical Industry

Introduction: A Brief History of AED Discovery and Development

The pharmaceutical industry has played a pivotal role in the discovery and development of new AEDs (technically antiseizure drugs) since at least the 1930s, when Parke-Davis sent a series of compounds to Merritt and Putnam for screening using electroshock seizures in cats.[130] The discovery of phenytoin by these investigators was not only a remarkable discovery for patients, but documented, for the first time, that drugs could be evaluated in the laboratory for their efficacy. The event also probably represents the first successful industry–academia collaboration in AED discovery. In the next few years, a whole series of compounds followed, based on the hydantoin cyclic ureide structure—drugs such as Tridione and ethosuximide for absence seizures, as well as additional hydantoins and barbiturates. Ethosuximide was marketed in the United States in 1960, and marked the end of the exploitation of this particular molecular series. A long dry spell then occurred in the United States, with only diazepam marketed as an adjunctive therapy. Meanwhile, in Europe, both carbamazepine and valproate were moving onto the market. It was 1979 before valproate was available in the United States. Again, a void occurred in development until the early 1990s, when a veritable profusion of drugs appeared; for the first time, these were marketed early in the United States, as compared to other countries.

The Roles of the Industry in AED Discovery and Development

To consider the unique roles of the pharmaceutical industry in the process of getting effective new drugs to the patient, one must define the various processes needed to take a primitive but promising molecule and make it into a drug. This section covers each of the following six topics: (a) discovery, (b) chemical and pharmaceutical development, (c) drug safety, (d) drug metabolism, (e) drug regulatory processes, and (f) clinical development. Typically, each large drug company has departments (often of considerable size) in each of these somewhat oversimplified categories.[142] Each of the topics will conclude with discussions of potential collaboration between academia, government, and the industry.[197]

These six processes of drug discovery and development *are not entirely sequential*. This concept is worthy of considerable emphasis. Clearly, a drug must be discovered before it is tested in drug safety models or in humans. But pharmaceutical development begins very early and may eventually result in a follow-on drug after the first clinical launch. Likewise, drug metabolism begins early with animal studies and extends well into the clinical program—it may not end until late clinical phases utilizing studies such as population pharmacokinetics. Therefore, even though these categories are presented here in linear fashion, concurrent work by each group, especially after discovery, is the rule rather than the exception.

Discovery

The invention of a new molecule, either discovered in a disease model or rationally designed for a disease process, is the very first step in the process of making a new drug. The odds against such a molecule actually becoming a drug are exceedingly poor—perhaps one in 10,000 at this early stage (Fig. 1). Although high-throughput screening has been challenging rational chemical design, in fact both techniques are used in today's world of drug discovery. The next key ingredient, especially in large companies, is a cadre of medicinal chemists; these experts can take a promising molecule and make all kinds of improvements to it. Such improvements range from increased potency in the disease model all the way to simple but extremely important issues such as solubility and bioavailability. Patentability is also exceedingly important for drugs that are expected to be major financial contributors to a large company.

After the initial compounds are sorted out, a lead compound is usually put forth as the best candidate from all the various aspects. Consideration is always given to whether a new compound is potentially a better drug than one already available. For AEDs, a relatively new and sometimes disturbing consideration is whether the drug may also be effective in other indications, notably pain and/or bipolar disorder. These latter markets are often more lucrative—a drug that has promise only for epilepsy may fall out of the company's portfolio and thereby fail in the competition for the resources needed for further development.

At this stage, the potential for academic collaboration with industry is enormous. All sorts of possibilities can occur. An academic investigator who has discovered a promising molecule has many options available. These range from selling the molecule outright (or with royalty arrangements) to another small or large company, all the way to creating a new startup company (usually with venture capital support) to further the work on the molecule and make it (hopefully) more valuable in the marketplace. Universities have created business development offices just to handle such transactions, and the federal government has designed programs to assure that both the government and the federal inventor share in any eventual profits attained. Transfer usually includes not just one molecule, but, in addition, a whole series of patentable analogs. Clearly, the object of the latter is to protect the financial position of the deal.

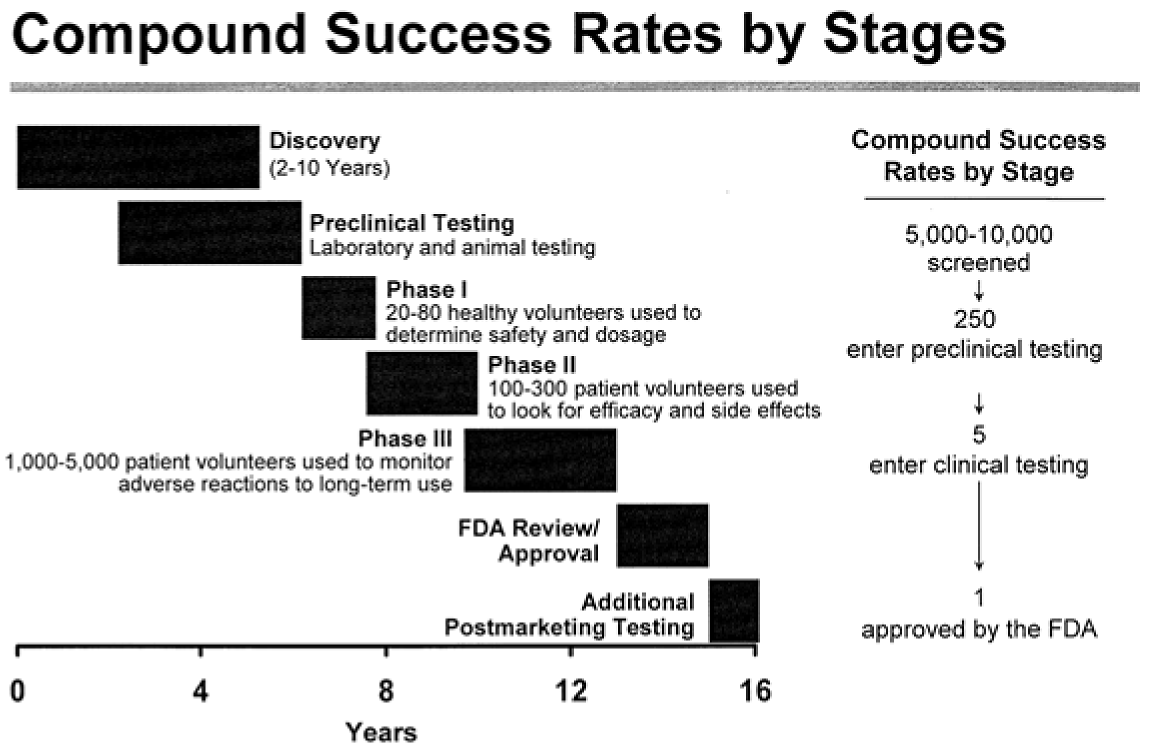

FIGURE 1. Compound success rate by stage. As can be seen, only 250 compounds of 5,000 to 10,000 screened enter preclinical testing, and only five of these enter the clinic. Only one of these five is approved for marketing. Although this figure emphasizes approval by the U.S. Food and Drug Administration, all large companies now emphasize worldwide registration, and most attempt, insofar as possible, simultaneous approvals worldwide. (From Pharmaceutical Research and Manufacturers of America. *1999 Industry profile.* Washington, DC: Pharmaceutical Research and Manufacturers of America, with permission.)

Pharmaceutical Development

When a scientist discovers a new drug, it is usually only available in small quantities through the original synthesis. But the further the drug is advanced in the development process, the more bulk compound is needed for further testing, not only by the original scientist, but by drug safety and metabolism study groups and, eventually, for clinical investigation. One of the early tasks, therefore, of the pharmaceutical department is to design more efficient syntheses to produce the drug in larger quantities. Eventually, the drug will have to be made under very careful, reproducible laboratory conditions with strict limits on impurities. Adherence to Good Manufacturing Practice (GMP) conditions is a huge (but exceedingly important) burden on drug manufacturers.

But having enough pure drug is only the beginning for this department, which is also responsible for the formulation of the drug, that is, the creation of a dosage form—such as a capsule or a pill—that is successful in the marketplace. A drug

taken orally, for example, must be bioavailable, meaning that the drug must reach the intended target in the body. Usually this means passing through the wall of the intestine, passing through the portal system of the liver, and reaching the systemic blood. Incredibly promising drugs can (and do) fail in pharmaceutics and are left behind. On the other hand, a wide and increasingly sophisticated variety of techniques are available to increase bioavailability for stubborn compounds.

Further discussion of pediatric formulations, parenteral formulations, extended-release formulations, and the like is beyond the scope of this chapter, but these formulations are also the responsibility of the pharmaceutical development department.

Except for highly specialized departments in academia and government, collaboration in this area is not very common. Making new formulations, for example, is not considered cutting-edge science by most academic investigators. Also, the process can be surprisingly expensive and labor-intensive. On occasion, one observes a new formulation which is made by an academic team, but the vast majority of this kind of work—which is highly regulated by the FDA—is left to the industry.

Drug Safety

When the FDA evaluates a drug, it must be "safe and effective for the intended use." Safety of the drug is as important as effectiveness, and safety testing is an integral part of the development of a new drug. Typically, a large pharmaceutical company has a drug safety department and a series of laboratories for a very wide range of testing, beginning with in vitro studies and, assuming that the drug continues to be safe, ending in animal testing. Although animal testing is mandatory, increasing sophistication of various non-animal studies has allowed an increasing number of studies to be performed without the use of live animals. Currently, every effort is made to limit the number of animals used to those that are absolutely necessary to support safe development in humans.[197] Further, only a limited number of studies (successfully performed, of course) are needed to begin human testing. A drug may fail in early human testing, in which case extensive animal testing will never be performed with that drug. The longest animal studies, typically the carcinogenicity studies, are not even started until the drug has been through a series of human studies, usually including a proof of concept for efficacy in humans.

A number of specific areas must be studied. These include both acute and chronic studies, and involve not only carcinogenicity as mentioned, but also, among others, reproductive and developmental toxicity, genotoxicity, cardiovascular toxicity, immunotoxicity, and neurotoxicity. The aim is rarely to find a compound that is completely safe, but one in which the adverse effects are minimal and manageable by the patient and the physician. Obviously there is a much greater tolerance for adverse effects in drugs for life-threatening diseases (such as cancer) than for more benign conditions (such as allergic rhinitis).

Some early in vitro tests can be carried out by academic laboratories, but drug safety testing is left to the industry for several reasons. First, although the testing is often very sophisticated, it is rarely exciting science, and academicians (and science funding agencies) have little interest in the process. Second, the process is highly regimented and controlled, requiring very detailed record keeping. The process must meet the standards of Good Laboratory Practices (GLP) and all studies must be available for inspection by the FDA or other regulatory agency. Failure to meet the proper standards may mean failure of approval of the drug, regardless of its therapeutic potential. Because of the rigor of the testing and its (usually) lack of scientific excitement, collaboration is uncommon.

Drug Metabolism

The drug metabolism department of a large pharmaceutical company becomes involved very early in the process of drug development, and usually stays involved up to the time of drug registration or beyond. The department is responsible for determining what happens to the drug in animals and in humans. The acronym ADME describes much of what the team does for oral medications—they study *a*bsorption, *d*istribution, *m*etabolism, and *e*xcretion.[197] The department is also responsible for the development and implementation of the assays for the drug (and its metabolites) in animal and human blood. The initial work in animals is used to predict what will happen in humans. If, for example, an active metabolite is suspected and discovered in animals, this may have an impact on how the drug will be studied in humans. Many other functions of this department impact the program—these include pharmacokinetics, analysis of dosage forms, drug distribution in the body, toxicokinetics, and the like.

Some departments of pharmaceutics in academia have developed sophisticated programs for determining certain drug ADME characteristics, and collaboration is possible. Again, if the academic laboratories wish to participate, GLP practices will be necessary for anything other than preliminary investigations. In many cases, the pharmaceutical companies will out-license some of the drug metabolism work to contract research organizations (CROs), some of which specialize in this kind of work and are very proficient at performing it. Large pharmaceutical companies prefer to do much of this work themselves (or closely supervise a CRO) for the simple reason that they do not wish to lose control over this critical part of drug development. This is especially true when one considers that drug metabolism departments are not nearly as expensive, say, as clinical departments.

Regulatory Affairs

The regulatory affairs department handles the proper paperwork flow, especially between the company and the responsible government agencies—such as the FDA. The area is not suitable for much collaboration, although its importance to the company can hardly be overemphasized. Regulatory affairs is so complex for large companies that subgroups develop expertise in certain areas or in certain parts of the world.

Clinical Research

After the discovery department has chosen the best compound from its series, the chemical and pharmaceutical sciences department has made and formulated enough pure compound, the drug safety department has done at least the early toxicologic studies, and the drug metabolism department has a sensitive assay in plasma, the regulatory affairs department can submit a document, usually with a clinical protocol created by the clinical research department, to the FDA or other health authorities to begin clinical investigations.[197]

Clinical research is classically divided into three phases (Fig. 1). Although it has become popular not to use this categorization in some companies, it is the most elementary way of thinking of drug development. Phase I trials are typically performed in young human volunteers to test the safety of the drug. Phase II trials are typically performed in a limited number of patients to see if the drug has efficacy for the disease in question—sometimes called *proof of principle*. Phase III trials serve to cement the proof of efficacy in a larger number of patients and to expose enough patients such that most (but not all, unfortunately) adverse effects can be well described. Overall, a typical program will expose 1,500 to 2,000 subjects in the clinical trial period over several years, although this number may vary widely depending on the disease under investigation.

A Phase I trial is a highly specialized program usually undertaken by the clinical pharmacology department within clinical research. The overall plan is to expose humans to a drug for the first time in a highly controlled setting, beginning with very small single doses and eventually giving larger doses for 10 to 14 days. Although this seems simple on the surface, proper safety measures will cause such a program to consume 8 to 12 months before enough data are available to move to Phase II. Collaboration with academia or government is not typical in most cases, because highly specialized inpatient units, either within the company or in a CRO, can perform these studies with maximum efficiency and safety. A prominent exception occurs in Phase I when the decision is made to use patients instead of volunteers. Under these circumstances, a combination of a source of patients allied with an inpatient facility is ideal, and either academia or government agencies (such as the NIH) can perform the studies in collaboration with the pharmaceutical company. Academic centers with specialized clinical research units are often ideal for such studies. Good Clinical Practices apply to all phases of clinical research.

Collaboration with patient caregivers is critical to Phase II trials. The collaboration is not always with academia, because some academic medical centers tend to be very bureaucratic and ponderously slow in making decisions and getting the research accomplished. Because speed of development is one of the most important financial factors for a company, other sources of patients, such as those gleaned from private practice, have been recruited.

In any case, the pharmaceutical company cannot perform Phase II trials without a source of patients, and therefore the company must collaborate with others. Using physicians in various institutions to collect a specialized population of patients is a natural trend, and negotiations are usually undertaken to the benefit of the physician, the company, and the patients; the latter will have an opportunity to try a new medicine that may be of considerable benefit to them. Phase II studies are intense. Safety of the first few patients to receive the drug is paramount. The optimal dose to be used in the patients is usually not well understood, and part of the Phase II effort is to attempt to narrow the range of doses that will be effective but produce few adverse effects. It should be noted that, aside from diseases exclusive to children, most studies are performed in adults before children are exposed. Women, on the contrary, are now entered early into the clinical trial process.

The collaboration in Phase II trials requires that the company and its partners adhere to Good Clinical Practices (GCP). This means, for example, adherence to a specific protocol (which may be jointly developed with the physician caregiver), very careful documentation of all data collection, and adherence to rules set forth for institutional review boards and for privacy. Phase II trials, especially if late in the program, are typically well-controlled for bias; this means protocols using randomization, control groups, blinding, and the like as part of the studies. Many good academic centers have teams who fully understand this process, are greatly experienced with these kinds of challenges, and produce excellent data as a result.

The collaborative needs of the industry during Phase III trials are similar to those in Phase II, except that the process is now on a large scale. The ideal drug dose may not be fully known, but a range is usually available from Phase II such that only a few dose groups must be studied. The adverse effects are better characterized, so that newly participating physicians know more of what to expect. Again, the studies are likely to be controlled, requiring local knowledge of how to perform complex studies and keep meticulous records. All aspects of GCP, of course, apply to Phase III.

After a drug is approved, companies very often continue studies in patients for a variety of reasons. Studies in children may be needed. A new dosage form may need to be investigated.

Studies in other countries may be needed for country-specific approvals. These are just a few of the reasons for Phase IV studies, all of which require collaboration with physician caregivers who are willing to become physician investigators.

Summary and Conclusions

Drug discovery and development is a very complex, expensive, time-consuming process (Fig. 1). Pharmaceutical companies are very sophisticated in this process, but need collaboration, especially during discovery and clinical research. The collaborative opportunities for academia are many, and are especially reflected in the rapid growth of clinical trial participation by physician-investigators in these and other institutions.

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Chapter 140

Clinical Trials of Antiepileptic Drugs in Adults and Children

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Introduction

The modern age of drug testing was ushered in in 1962 by the passage of the Kefauver-Harris amendments to the Federal Food, Drug, and Cosmetic Act.[25] This act required for the first time that a drug be proven effective prior to marketing and sale. In most countries, extensive efficacy and toxicity testing is required before a new antiepileptic drug is approved for general use, supervised in the United States by the Food and Drug Administration (FDA) (Chapter 142) and in Europe by the European Agency for the Evaluation of Medicinal Products (EMEA) (Chapter 143). This information is obtained by performing clinical trials. These trials are of great significance for two reasons. The first is that if trials fail to demonstrate efficacy to the satisfaction of registration boards, a potentially useful drug may not emerge on the market. The second is that at the time that a drug is approved for clinical use, all that is known about its efficacy and toxicity derives from information obtained through clinical trials. Improper trial design or inadequate analysis of results may lead to misinformation and misuse of the drug. It is of vital importance that these trials be performed in a logical and comprehensive manner. This chapter will explore aspects of antiepileptic drug trials, including design issues, different types of trials, ethical issues, special populations, and analysis of results.

Phases of Testing in Humans

After a drug has undergone extensive in vitro experiments and testing in animal models of seizures and epilepsies and there is preclinical evidence of efficacy and safety, an investigational new drug application will be obtained from regulatory agencies indicating that the drug is ready to be tested in humans. Before efficacy can be assessed, the drug must be evaluated in volunteers (phase I testing). Phase I testing is performed for evaluation of safety, pharmacokinetics, and human metabolism. Initially, single rising doses will be administered to healthy volunteers in order to determine the dose at which toxicity will emerge, and to make preliminary assessments of pharmacokinetics; these studies expose approximately 20 subjects. Single-dose studies will be followed by more chronic administration studies. Again, toxicity and pharmacokinetics are assessed, including determination of drug half-life, clearance, volume of distribution, time to maximum serum concentration, and presence or absence of nonlinear pharmacokinetics. Metabolites and means of elimination are identified.[13] An important determination from these studies is maximum tolerated dose. Phase I may also include studies of special populations who may be at particular risk from a given drug. For example, a drug with renal metabolism may be tested in patients with renal failure.

Obtaining quality information during phase I is critical for proceeding to phase II trials. The first testing of epilepsy patients will usually occur during phase II, which includes initial efficacy and safety testing in the population of interest, and usually also includes the first large multicenter safety and efficacy trials. The earliest trials are usually what is called “proof of principle.”[64,65] These trials are performed to get a first impression of whether the drug will be antiepileptic in humans. Based on this trial, a “go–no-go” decision may be made by the company testing the drug. In other words, the company will decide whether an investment in larger, more expensive testing is warranted. One example of a common proof-of-principle trial is a study in photosensitive epilepsy patients. Photosensitivity studies are ideal as an early trial, as they can usually be performed with a range of single doses. The fact that an investigational drug can be shown to reduce or eliminate the photoepileptiform response can be taken as an indication that it has passed the blood–brain barrier and may have an antiseizure effect, demonstrated on the surrogate marker of the photoparoxysmal response. Efficacy in this model is also often taken as an indication that the drug may have activity against a broad spectrum of seizure types.[11,64] Early trials may also include a maximum tolerated dose (MTD) study in epilepsy patients, as tolerated doses are known to differ significantly between normal volunteers and patients. Early trial results may also give a first indication of potential pharmacokinetic as well as pharmacodynamic interactions.[65] Several large phase II trials have failed because the dose has been poorly chosen.

Phase III testing includes continuation of safety and efficacy testing as well as trials for specific indications, or in special circumstances. Monotherapy studies and studies in patients with distinct epilepsy syndromes such as the Lennox-Gastaut syndrome might be included in phase III testing plans. When the drug is approved, trials frequently continue during phase IV or postmarketing studies with the aim to define the drug's optimal use in a general clinical practice population and to broaden the well-documented safety database. Other pivotal phase III trials for extended indications such as pediatric use, primary generalized seizure types, or a monotherapy indication may be pursued either before or after initial approval. Postmarketing surveillance is also done, looking for rare adverse events, pregnancy outcomes, and other information that might not be obtainable in preapproval data.

Efficacy Trials

As noted above, efficacy trials are usually performed as part of phases II and III. These pivotal trials are designed to definitively determine whether a drug has antiepileptic potential in humans. Trial design and implementation is driven by several independent and potentially conflicting needs. These include the need of a pharmaceutical company to find out whether a compound is worth developing, in the least expensive way possible; the need of the company to demonstrate efficacy and safety to registering agencies (e.g., the FDA and EMEA); and, lastly, the need of physicians to know the potential utility of a new drug in the treatment of patients with epilepsy. It is frustrating to clinicians that the last need, which they may see as the most vital, may have the least influence on trial design. Unfortunately, if the first two needs aren't met, the drug may never come to market. Only after the drug is registered may there be the "luxury" of determining its clinical properties.

The fact that many efficacy trials are registration driven explains why trial design is very different in different countries. In Europe, active-control monotherapy trials are considered acceptable, and crossover designs have been more common in the past. Both these design elements are seen as problematic by the FDA, and are rarely or never used in the United States. As development programs have become global programs aiming at one dossier used for filings around the world, study designs are fairly standardized nowadays.

Trial Design

Need for Blinding and Control Groups

Efficacy trials must compare two treatment groups in a blinded fashion. It is not typical to use a population as its own control, comparing a baseline pretreatment epoch with an epoch after treatment has been initiated, because of placebo effect. In other words, patients who have an expectation that they may improve will demonstrate improvement with or without new treatment.

Physicians may have difficulty accepting the reality of the placebo effect in intractable epilepsy patients, who have been switched from treatment to treatment without benefit, yet time and again patients in the placebo arm of multicenter epilepsy studies will demonstrate a substantial seizure reduction. The degree of placebo effect will vary from study to study for unclear reasons. In recent studies, 0% to 36.5% of patients in the placebo arm of blinded trials showed a 50% or greater seizure reduction over a standard 3-month exposure period.[14] The degree of a placebo effect also varies between regions and individual centers within one large multicenter trial.

Active Versus Placebo Comparisons

For some purposes it is considered acceptable or even desirable to choose two active treatment arms as blinded comparison groups. Some of the best early examples of this type of trial were two VA cooperative studies,[46,47] which randomly assigned patients with newly diagnosed seizures to different antiepileptic drug therapies. This allowed direct comparison of these drugs in terms of both efficacy and safety. A large number of active control comparison trials have been performed in the last decade, comparing standard drugs such as carbamazepine and phenytoin to the newer drugs.[10,12,15,17,18,39,41,55,68] This type of trial may be extremely informative for clinical purposes. In Europe, they have contributed to the registration of a number of new antiepileptic drugs (AEDs) as monotherapy. In the United States, however, the FDA does not accept active controlled trials as proof of monotherapy efficacy.[43] These active-control trials, including the VA cooperative studies, were able to demonstrate equivalence between drugs. In order for the FDA to accept a trial as proof of efficacy, superiority of the new drug must be demonstrated.

Adjunctive Versus Monotherapy Trials

There are inherent disadvantages to adjunctive, or add-on, trials in which active treatments or placebo is added to the patient's baseline antiepileptic drugs. It is more difficult to prove efficacy in a patient who is already partially treated. Side effects may be magnified by combining drugs, and pharmacokinetic interactions may alter baseline or experimental drug levels. Despite these drawbacks, most efficacy trials use an adjunctive therapy design because of the ethical issues raised by monotherapy parallel trials involving placebo in patients with epilepsy. New trial designs were developed in the 1990s that attempted to circumvent ethical issues and permit monotherapy studies. The two most popular designs were described by Pledger and Kramer.[53] The first, which involves randomization to drug or placebo in inpatients who have had their background antiepileptic drugs withdrawn for presurgical evaluation, has been deemed too short to be used for registration purposes and not relevant for extrapolation to a general clinical population, and is now used primarily for a proof-of-principle trial.[13,28,63] A second design is performed in outpatients.[8,29,38,53,60,62] Patients are randomized to treatment with an experimental drug or placebo, after which baseline therapy is withdrawn over 2 to 8 weeks. A modified, or “ethical," placebo is utilized rather than a true placebo to reduce the likelihood of status epilepticus or secondary generalization. This can consist of a minimally effective dose of either the same investigational drug or of any other therapy presumed to be less effective than the test drug. A starting dose of valproic acid (15 mg/kg) has been employed in a number of trials for this purpose. Outcome is assessed in terms of “failures" and “completers." Failure is determined on the basis of escape criteria, such as doubling of seizure frequency, occurrence of generalized tonic–clonic seizures, or increase in seizure severity. If more patients receiving the experimental drug at a therapeutic dose in monotherapy can complete the trial, without fulfilling escape criteria, than patients receiving modified placebo in monotherapy, the treatment is considered effective in monotherapy. This trial design has been successfully used to obtain a monotherapy indication from the FDA for oxcarbazepine and lamotrigine (withdrawal to monotherapy in refractory patients). A drawback of this design is that antiseizure effects are evaluated in an AED withdrawal situation only.

Two other monotherapy designs have been employed to gain FDA monotherapy approval. These have been performed in patients with newly diagnosed epilepsy. One study compared oxcarbazepine to placebo in patients having frequent seizures (average 5.5 per month) at baseline.[59] The end-point was time to third seizure. Another study compared 50 mg of topiramate to 400 mg in newly diagnosed adolescents and adults with partial-onset seizures.[1] Outcome measures included time to first seizure as well as seizure-free rate at 6 months and 1 year. Although all these monotherapy trials led to registration of at least one AED as monotherapy, the trials continue to raise ethical as well as pragmatic issues. For this reason, efforts are under way to devise new methods to perform monotherapy trials.[30,34]

Parallel Versus Crossover Designs

In parallel trials, patients are randomly assigned to one of two treatment groups for a period of time. Their seizure frequency during the treatment period is compared to a pretreatment baseline. Seizure outcome is compared between the two groups. In a crossover design, patients are also randomly assigned to two treatment groups, but after a period of time each group is crossed over to the other treatment, usually after a washout period. Outcome as compared to baseline is determined for each treatment. There are some advantages to a crossover design. Far fewer patients are required to perform the trial, provided

that the subjects complete all required crossover periods, including the washouts. Also, if two active treatments are used, this trial design is more like clinical practice, in which patients are usually crossed from one treatment to another. Each patient will receive both treatments, allowing more direct comparison of efficacy and tolerability. The disadvantages of a crossover trial include a much longer duration, risk of patients dropping early, and, more importantly, a potential unblinding of the trial. This is of the utmost concern in a trial that compares placebo to active drug. Patients may be able to discern a difference in side effects when switching from placebo to drug, or vice versa. There may be carryover effects of a drug, which would impact the initial portion of the second treatment phase. For these reasons, the FDA and the EMEA do not favor such trials.

Patient Issues

Overall trial makeup is influenced as much by the population chosen for the trial as by the trial design. Trial populations may differ in terms of epilepsy syndrome, as well as disease severity.

Epilepsy Syndrome Selection

The majority of phase II and phase III AED trials are performed in patients with partial epilepsy, specifically with complex partial seizures. These patients comprise the majority of adults with uncontrolled seizures, and the pharmaceutical companies need an indication from registering bodies to treat partial seizures, for market share. With rare exceptions, a drug that is unable to treat such patients would not be profitable to develop. Recently, there has been discussion regarding bringing drugs forward for niche indications or for orphan diseases such as Lennox-Gastaut syndrome. Nonetheless, to date no new AEDs have been approved without a partial seizure indication.

When a partial seizure indication has been obtained, further studies may be performed to assess efficacy in other syndromes. Studies in different syndromes offer their own potential obstacles and may impact trial design. One example can be seen in the Lennox-Gastaut population. Initially, it was felt that seizures in these patients were easily recognizable, and that placebo effect would not be an issue in this severely impaired population. Therefore, open trials were undertaken in patients treated with cinromide, a drug that was in development. The results were very promising, demonstrating a >50% response. However, when the study was repeated with a placebo control, it was found that the entire treatment effect could be attributed to a placebo response.[23] It was felt that this reflected not only a bias in parental observation, but also a difficulty in differentiating between seizures and abnormal behaviors, common in this population. As a result, subsequent trials incorporated video-electroencephalographic (V-EEG) monitoring to train parents on differentiating seizures. In addition, the primary outcome variable was reduction in motor (tonic, atonic, and generalized tonic–clonic) seizures, which are the most recognizable. This led to a successful trial design, and ultimately to approval of three of the new AEDs (felbamate, lamotrigine, and topiramate) for use in the Lennox-Gastaut syndrome.[26,49,61] This and other examples of potential populations, study limitations, and ways of circumventing them are given in Table 1.

Seizure Severity

Another patient characteristic that may impact AED trials is disease severity. It cannot be taken for granted that a drug that has been proven to be highly effective in intractable, severely affected patients will also be the most ideal drug for new-onset patients. It is feasible that some drugs may work preferentially in refractory patients, due to specific pathophysiologic alterations that are found in these patients. One possible example of this relates to the antiepileptic drug vigabatrin. This drug exhibits retinal toxicity in selected populations and is not available in the United States, but is approved in Europe. In placebo-controlled add-on trials in refractory patients, this drug appeared to be more potent than almost any other available antiepileptic drug.[31] However, when tested in a head-to-head fashion against carbamazepine, it was not as effective.[16]

Once a drug has been proven safe, trials in new-onset patients are frequently performed. These trials have usually been performed as active-control comparisons, in which an investigational agent is compared to a standard agent, with the exception of oxcarbazepine, which was tested against placebo.[59] Both placebo control and active control may have drawbacks to confirm the efficacy of AEDs in newly diagnosed patients. Placebo-controlled trials are short by necessity, and only prove that a drug is better than "nothing." On the other hand, if the population for an active-control equivalence trial is chosen poorly, if the trial is not designed properly, or if the sample size is not sufficient to have the power to show a difference when one exists, then equivalence may be demonstrated between two drugs for which there actually exists a clinically meaningful difference in efficacy or safety.[34]

Women of Childbearing Age

Women of childbearing potential also bear further consideration. In earlier epilepsy trials, women were only included in studies if they were postmenopausal or had undergone surgical sterilization. Recently, there has been pressure to include more women in trials at an earlier point in development.[42] In order to do this, it is necessary to expose women of childbearing potential to drugs that do not have established efficacy and safety. Most protocols lay out strict guidelines for contraception that is considered acceptable during a trial based on potential hormonal interaction data. Occasionally, contraception will fail and a pregnancy will ensue. It is often the policy at present to discontinue the investigational drug immediately in such a situation. This may not always be the safest course for the mother or fetus, particularly if the individual had a very significant seizure reduction from that drug. Postmarketing pregnancy registries by sponsor companies and academic consortia have been set up to better investigate the comparative teratogenicity of AEDs.

Children

Clinical testing of antiepileptic drugs considers children separately because of the age-related changes in both brain and overall physiologic and biochemical status that occur during childhood along with the age dependency of certain seizure types and epileptic syndromes. Most studies on AEDs have considered "children" to be those younger than 12 years of age, and have included those aged 12 years and over in trials designed primarily for adults. The population of patients younger than 12 years is often subdivided into neonates (<1 month postnatal age); infants (1 month up to 2 years), and children (from 2 years up to 12 years). The children group can be further subdivided into preschool (2 to 5 years) and school age (5 to 12 years). This last division is not arbitrary; there are differences in the type of epilepsies likely to present before and after 5 years[57] and there are different methods and scales used to monitor behavioral and cognitive side effects between these two age groups.

Table 1 Epilepsy Syndromes and Potential Obstacles They Present

Epilepsy syndrome	Potential obstacle	Solution
Partial seizures	Simple partial seizures may be subjective and difficult to count	Count only observable simple partial or complex partial seizures
Primary generalized epilepsy (absence, myoclonic and tonic–clonic seizures)	Seizures usually well controlled on currently marketed medications Absence seizures may not be clinically apparent	Perform add-on study in refractory patients, using minor seizures such as myoclonus as end-point Perform inpatient monitoring, measuring spike-wave on EEG for

		absence
Lennox-Gastaut syndrome	Too many seizures to count accurately; in severely retarded subjects, abnormal behaviors may not be distinguishable from seizures	Use videotape to train parents to distinguish seizures from behaviors Use tonic–atonic seizure frequency as an independent outcome variable (less frequent and easily countable)
Neonatal seizures	Difficult to count clinically Difficult to do add-on, but placebo control raises ethical issues	Use video-EEG to count events Perform short placebo-controlled trials
Status epilepticus	Difficult to obtain informed consent Convulsive and nonconvulsive status have different prognoses	Obtain waiver of consent Carefully define clinical status syndromes, and randomize to different groups

EEG, electroencephalogram.

Trials targeted at resistant partial seizures in adults can be relevant to the same type of disorder in childhood. However, the spectrum of childhood treatment-resistant epilepsies is different than those in adulthood, and it should not be assumed that AEDs effective in adults will be appropriate for the resistant epilepsies special to childhood. In the infant, early myoclonic encephalopathy and early infantile epileptic encephalopathy[51] respond only rarely to established AEDs. West syndrome, severe myoclonic epilepsy in infants, myo-clonic astatic epilepsy, and Lennox-Gastaut syndrome, although responsive to some of the more recently introduced AEDs, remain difficult to treat in at least half of affected children. Epilepsies with cognitive symptomatology, such as acquired epileptic aphasia (Landau Kleffner syndrome) and epilepsy with continuous spikes and waves during slow sleep, are rare, with difficult-to-quantify clinical features making these patients challenging subjects for AED trials. Although these syndromes are relatively rare in adults, epilepsies with features of Lennox-Gastaut and West syndromes may persist beyond childhood. Children with these epilepsies deserve to have closely monitored trials designed to specifically address their needs.

The patterns of seizures and the designations of epileptic syndromes may evolve throughout childhood; these transformations are probably related to maturational features in the brain. For most circumstances, it is not known whether this, of necessity, means that the newly acquired state is likely to be more or less responsive to AEDs. However, the researcher must appreciate that alterations in seizure type during a trial can be due to evolution of the epilepsy, rather than the AED. For example, about one third of patients with an initial presentation of early infantile epileptic encephalopathy (EIEE, with suppression burst on the EEG) can progress to West syndrome (with hypsarrhythmia on EEG) and later appear to have Lennox-Gastaut syndrome (with diffuse slow spike-wave on EEG). Alternatively, some infants with initial EIEE later have focal spikes, having, in some cases, had hypsarrhythmia as an intervening stage.[50] Children with West syndrome often have resistant partial seizures later. Another transformation that would be problematic for the AED trialist occurs with severe myoclonic epilepsy in infants. Predominantly clonic, often lateralized, seizures occur in the first year of life, followed by myoclonic jerks and partial seizures during the second year, accompanied by the development on the EEG of generalized spike and polyspike waves, photosensitivity, and focal abnormalities.[24] Even in noncatastrophic epilepsies transformation can occur. For example, although childhood absence epilepsy is not accompanied by other seizure types in 60% of cases, generalized tonic–clonic seizures or progression to juvenile myoclonic epilepsy may occur in others.

The majority of inborn errors of metabolism of which seizures, particularly myoclonic seizures, are symptomatic present in childhood, particularly in infancy. Consideration of whether such an underlying condition could be present but unrecognized must always be an important feature of the assessment of suitability for AED trials. Alternatively, knowledge of the specific biochemical defect and the mode of action of the new AED might allow prediction of success or eliminate the likelihood of precipitation of adverse biochemical states. Maximal understanding of the biochemistry and pharmacology of new AEDs is essential before they are used for childhood seizures.

Drug Issues

In order to design and successfully implement a clinical trial with a given drug, a significant amount should be known about that drug's unique characteristics. Every trial design will not work for every drug, and innovative alterations may be necessary in a standard design, due to specific drug properties. Failure to fully explore drug–drug interactions early on can lead to problems in a phase II trial. For example, in an early phase II trial, felbamate was used as adjunctive therapy in patients taking carbamazepine as a baseline drug.[70] This trial failed to demonstrate efficacy against placebo, in part because felbamate caused a reduction in carbamazepine levels, possibly leading to seizure exacerbations. Felbamate is also known to increase phenytoin levels by 20%. When felbamate was tested in a Lennox-Gastaut protocol, all patients had to have phenyt-oin doses reduced by 20% prior to the baseline period.[26] If this had not been done, the increased phenytoin levels in the treated group could have lead to toxicity, and the study could have been unblinded. Similarly, since valproic acid doubles the half-life of lamotrigine, patients on valproic acid were excluded from blinded trials with that drug.[6,40,45,48] Pharmacodynamic interactions may also confound a trial. In the only adjunctive trial of oxcarbazepine in adults with partial seizures, the dropout rate in the high-dose group was >70% in the absence of pharmacokinetic interactions,[5] despite this dose having been very tolerable in a monotherapy trial.[9] It is felt that the high dropout rate was due to pharmacodynamic disturbances when oxcarbazepine was added to other AEDs, coupled with a relatively rapid titration. Knowledge about the tolerability of rapidly titrating an AED may be important for other reasons. Inpatient monotherapy trials require rapid titration of study drug, as the treatment period is usually 2 weeks or less. Drugs that need a slow titration would not be suitable for this type of trial.

Selecting the appropriate dose range is essential for running a successful trial. In most circumstances, a dose approaching the maximally tolerated dose should be selected. If too high a dose is chosen, there will be excessive patient dropouts from toxicity. If, on the other hand, too low a dose is selected, efficacy may not be demonstrated. Overall perceptions about a drug may be predicated on the dose chosen for phase II studies. For example, initial adjunctive studies with topiramate (see Chapter 159) were performed at or near the maximally tolerated dose. This produced the appearance of a very potent drug, with a high side effect profile. In contrast, trials with lamotri-gine (Chapter 150) and gabapentin (Chapter 149) were performed at lower doses, resulting in an appearance of only moderate potency but good tolerability. If different doses had been selected, the results may have looked quite different.

The pharmacokinetic differences between children and adults cannot be ignored during drug evaluation. Most drugs administered orally are absorbed by passive diffusion in the small intestine. Multiple age-related factors affect the rate and extent of oral medication absorption, including gastric pH (reaches adult values by 2 to 3 years), gastric acid secretion (adult values by 3 months), gastric emptying (adult values by 6 to 8 months), and intestinal motility (variable in neonates, unknown when it reaches adult values). Oral absorption of phenobarbital and phenytoin are reduced in neonates compared to older children. Similar problems exist with intramuscular absorption in neonates; at this age the rectal route is probably the most reliable, provided a suitable formulation can be obtained. In contrast, in infants and children, drugs given orally or intramuscularly are absorbed more rapidly than in adults.

Age-dependent distribution factors (e.g., changing body composition, variable degree of protein/tissue binding) combine with physiochemical properties of the drug to determine a drug's distribution characteristics.

Body composition changes markedly from newborn to adult. For example, a newborn's brain mass and skeletal muscle mass is 12% and 25% of its total body weight compared to 2% and 40% in adults, respectively. Acidic drugs are less well bound to plasma proteins in neonates and infants than in older children. Weak bases are also less well bound in neonates, but binding may be increased in infants and children.

In the absence of exposure to enzyme-inducing drugs in utero, metabolic degradation of AEDs is very slow during the first 2 weeks. A rapid increase in metabolic rate occurs for the next 2 years, after which the rate gradually declines to adult levels. Renal excretion of drugs is very slow in the neonate, but is comparable to that of the adult by age 6 to 8 months. The highest relative capacities to excrete AED are found in infants aged 1 to 13 months.

Some drug-specific pharmacokinetic phenomena, such as whether a drug undergoes linear or nonlinear metabolism, is constant across all ages. Information obtained in adults on this type of AED property is relevant to all ages. Compared to adults, children tend to receive more short courses of other types of drugs (e.g., antibiotics); it is important that interactions, and particularly effects on pharmacokinetics of a trial AED, are explored and recognized. Febrile illnesses, which may affect drug elimination, are common in young children. Should fever occur during an AED trial, its presence should be noted, both as a possible adverse reaction and as a potential influence on pharmacokinetic parameters.

Analysis of Results: Standard Measures

The standard measure used in analysis of AED trials is seizure frequency. Typically, different seizure types are counted separately. For example, for a trial evaluating patients with partial seizures, simple partial, complex partial, and secondarily generalized seizures would be analyzed separately.

Choosing an Outcome Variable

In every trial, a primary outcome variable must be chosen in advance. This is to prevent an ineffective drug from appearing effective because there was a chance reduction in seizure frequency for one seizure type out of many. Typically, reduction in complex partial seizures is chosen as the primary outcome variable. It is much more difficult to demonstrate reduction in simple partial seizures, because they are more variable and subjective, and in secondly generalized seizures, because only a fraction of enrolled patients will have this seizure type.

Handling Seizure Data

There are intrinsic problems inherent in analyzing seizure data. One can get a good understanding from an example given by Gordon Pledger.[54] Two patients are enrolled in a trial. One has a baseline seizure rate of 50 per month, the other 100 per month. Both patients have a reduction of 50 per month. Whereas one has a 50% reduction in seizure frequency, the other has a 100% reduction. Has the drug been equally effective in both patients? In another example, how do two patients compare when one who has gone from three to two seizures per month, and the other has gone from 30 to two per month? Seizure data are nonparametric. One way of handling this problem is to normalize the data prior to applying a statistical treatment. Another is to use an analysis that is suitable for nonparametric data. Since there are so many ways to handle the data, a statistical treatment must be chosen in advance. Unfortunately, not all of the statistical treatments are intuitively comprehensible to a clinician who is trying to review the data. For example, the multicenter gabapentin trials were analyzed using response ratio.[35,36] This consists of the difference between the treatment and baseline seizure rates divided by the sum of the two rates; for clinicians, this ratio has no obvious clinical meaning. The other problem with the vast array of methods of analysis is that results from different trials are not easily compared.

Intent to Treat

All drug study outcomes are evaluated by “intent to treat” analysis. This means that all randomized patients are entered in the analysis, even if they drop out early on. Using the last-observation-carried-forward (LOCF) approach, the last obtained seizure frequency count will be used as outcome, even if the patients did not complete the exposure required by the protocol. The impact of dropouts on a trial may vary based on the chosen outcome variable as well as the trial design. Dropouts are often "censored" from the results at the time of dropout. This is why in a trial of oxcarbazepine in which over half the patients dropped out of the 2,400-mg arm, the

50% responder rate could still be 50%.[5] On the other hand, in some circumstances, dropouts will reduce the likelihood of a significant outcome. For this reason, investigators must make a determined effort to enroll only patients who are likely to complete the trial.

Other Analysis Problems

Many patients with epilepsy have seizures in clusters. This can cause problems in analysis in situations when seizures are so frequent during a cluster that they seem to blend together. It may be impossible for an observer to separate or count the seizures. This problem is particularly troublesome in Lennox-Gastaut trials. Enrolling patients who do not have epilepsy at all would cause serious problems in data analysis. To prevent this, some trials require electrographic evidence of epilepsy in the form of an interictal abnormality, although this is becoming less frequent due to the problems it causes in recruitment. The presence of such an abnormality may also be helpful in correctly classifying patients.

Noncompliance is another serious potential problem. A drug cannot be effective if the subject is not ingesting it. Because of intent-to-treat analysis, even patients in whom there is evidence of noncompliance will be included in analysis. Patients with known noncompliance must be excluded as subjects, and compliance must be monitored during the trial by pill counting or other means.

Nonstandard Outcome Measures

Seizure frequency may be a crude measure of antiepileptic drug effect. Unquestionably, patients may receive substantial benefit from a drug without any change in seizure frequency. Recently there has been renewed interest in exploring novel outcome measures.

One such outcome measure is seizure severity. After receiving a new drug, a patient might experience a significant reduction in falling and injury with seizures, or postictal period may shorten, without any reduction in seizure frequency. Several seizure severity scales have been developed to objectively assess changes in seizure severity.[2,3,4,19,20] The scales may incorporate information obtained by questionnaire from both patients and observers. One such scale has been used successfully to evaluate outcome in a trial of lamotrigine.[67] At the present time these data are considered purely elective and cannot be used in isolation for drug approval.

Quality-of-life scales are another way of assessing outcome from clinical trials. These scales attempt to combine efficacy, tolerability, and safety in an overall measure. Information is again obtained from questionnaires filled out by patients and significant others. The most frequently used scale is the QOLIE (quality of life in epilepsy). More information about these scales can be obtained in Chapter 100. Although these scales are certainly valuable, they have been criticized because they cannot distinguish the various factors that may go into "feeling better." For example, if a drug had antidepressant properties, patients' quality-of-life scores might improve substantially, and yet the drug may have no antiepileptic effect whatsoever.

Another method that has been used to assess overall outcome is time on the drug. If patients or their physicians are dissatisfied with either efficacy or tolerability of a drug, they are likely to implement a change to another agent. In an early VA cooperative study, four antiepileptic drugs were compared in new-onset patients.[47] Although there was no significant difference in efficacy, patients discontinued phenobarbital and pri-midone earlier than phenytoin and carbamazepine, due to side effects. Many of the newer AEDs have also demonstrated longer time on a drug when compared to older AEDs in active-control equivalence trials, and this has always directly related to better tolerability.[10,12,17,18,21,39,58,68] However, in some of these trials, some efficacy outcome measures, such as time to first seizure, have gone in the opposite direction to tolerability outcomes, making interpretation of time-on-drug outcomes difficult.[32] Complicating matters, interpretation of drug tolerability outcomes may be confounded by titration rates, selection of doses, and use of suboptimal formulations such as immediate-release carbamazepine (used in earlier trials vs. controlled-released carbamazepine formulations used in most recent studies).

Safety Trials

Safety of an investigational AED can be assessed in several ways. Phase II trials are designed to assess both safety and efficacy. In addition, some trials may be performed solely for safety evaluation. These are usually part of phase III.

Safety Testing during Phase II Efficacy Trials

Large multicenter placebo-controlled trials provide the first information about drug safety and toxicity. Even in a placebo-controlled trial, toxicity directly related to an investigational drug is difficult to determine. Most of these trials are add-on. Pharmacodynamic interactions with baseline AEDs will tend to amplify apparent toxicity from the new drug. In a study by Schmidt, toxicity developed in 90% of patients who were converted from monotherapy to polytherapy with standard agents.[66] Monotherapy studies almost always demonstrate lower adverse event profiles than adjunctive studies with the same drug. It is very important to compare side effects in the placebo and drug-treated groups. Also, since this list of side effects usually includes 20 to 30 items, by chance some may have a statistically higher occurrence in the treatment group. Several trials must be performed before a clear picture of toxicity develops.

Many development plans include studies comparing multiple doses. If such information is not available, it may be very difficult to determine which side effects are dose related and which are idiosyncratic, although investigators who have participated in the study may have a sense of this from their clinical experience.

Placebo-controlled studies usually have a 3-month treatment duration and are performed in 60 to 120 patients per dose arm studied. These trials cannot assess long-term toxicity, nor will they be likely to uncover rare idiosyncratic toxicities, such as blood dyscrasias and liver failure. For this reason, studies are necessary using more chronic treatment in a large number of subjects. Part of this information will derive from subjects who choose to remain on a drug after a placebo-controlled trial is completed. To obtain broader information, a drug development plan will frequently include a safety trial, in which a large number of patients are treated for 1 to 2 years. These trials are difficult to interpret, because there is no control group. Certain adverse events, such as sudden death and psychosis, are more common in patients with epilepsy than in the population at large. The true incidence may not be known, particularly for the intractable population that are candidates for investigational drug trials. In recent years, several adverse events have been uncovered either in long-term open label studies or even when the drug has been used after approval. Significant examples include visual field defects associated with vigabatrin, glaucoma associated with topiramate, hypohidrosis associated

with both topiramate and zonisamide, and renal calculi associated with topiramate and zonisamide.[27,44,56,71]

Safety Issues in Children

The pediatric epilepsy population presents special safety concerns including potential effects of the investigational AED on brain growth and development, cognitive development, and physical development. Normal development of the brain and, in particular, of the neocortex has been reviewed by Evrard et al.[31] The chemical factors underlying the various anatomic and physiologic stages of brain maturation remain ill understood. The neuroepithelium is derived from the dorsal midline ectoderm. Segmentation is induced by the notochord. Neuronal and glial elements are generated by the neuronal tube. During the first half of gestation, after neurulation, there is neuronal multiplication, followed by neuronal migration and, later, regional development of the cerebral vesicles. Toward term, growth and arborization of the neurons is followed by the development of synapses, myelination, and gliogenesis. In early childhood, considerable plasticity of development is present, with remodeling of synaptic connections and loss of those apparently redundant. At this stage, persistence of transmission through unwanted pathways, such as may occur in seizures, is clearly undesirable, yet it is equally important that an AED not inhibit normal synaptogenesis.

Neuronal migration and its disorders are now recognized to be of major importance in the pathogenesis of epilepsy.[52] Anatomic events are well described: Neuroblasts in the periventricular germinal matrix migrate to the neocortex in close attachment to specific glial cells with which they interact in a dynamic manner through cell adhesion molecules, but the underlying biochemical events remain speculative. Thus, the brain of the young child is undergoing considerable anatomic and physiologic change. This is particularly so in preterm and term neonates, and to a marginally lesser extent in the infant. By the nature of their activities, AEDs are developed for their abilities to reduce neuronal excitation. Such damping of cerebral activity might, in theory, lead to failure of development of appropriate synaptic connections, to poor perpetuation of their connections, or to early or excessive loss of synapses. It is expected that major effects on the immature brain would be identified in preclinical trials in animal models. Nevertheless, awareness of potential problems in relation to brain growth and neurologic and cognitive development is important in AED trials, especially when previously untried agents are prescribed for immature infants who, by virtue of the presence of seizures, already have abnormal brain function. Serial assessments of head circumference and neurodevelopmental status are essential in pediatric AED trials.

Some established AEDs are associated with unacceptable weight gain in childhood. It is important to closely monitor new AEDs for this effect. Established AEDs can cause alterations in blood levels of hormones, but these do not appear to be of clinical importance for height growth.[69] Nevertheless, effects on height and timing of puberty need to be considered when using a trial AED.

During childhood, the liver, kidneys, and other organs are growing and theoretically could be more vulnerable to adverse effects of AEDs; their growth also may indicate a greater capacity for recovery. To date, in the absence of specific inborn errors of metabolism, nonneurologic organs are no more likely to suffer damage in childhood than in adulthood.

It is important to ensure that every pediatric subject in a drug trial has been thoroughly evaluated (prior to study entry) for an underlying metabolic or other chronic medical disorder that could worsen as a result of participation. The greatest risks lie with the severely handicapped and the very young (whose seizures may be the first signs of an underlying disorder). In general, a child with epilepsy who is otherwise healthy (e.g., normal growth and development, no history of chronic medical problems) is unlikely to have a significant underlying metabolic disorder. However, caution for all neonates, infants, and young children is appropriate both prior to entry into the trial and as they progress through the study.

Prior to commencing a trial AED, tests of renal and hepatic function, a full blood count, an electrocardiograph, and microscopy of the urine are essential. Certain biochemical tests, such as alkaline phosphatase, have different normal values in children, and these must be acknowledged. Only in exceptional circumstances is it acceptable to use a trial drug when the biochemical status is other than completely normal.

Ethical Issues

Many antiepileptic drug trials involve investigational drugs. Particularly in early stages of testing, the risks of treatment with these agents may not be known. Even in later stages of testing, in trials involving standard drugs, a rigid protocol may impose inconveniences and risks to subjects, when compared with standard clinical care. Yet, these trials are vital in the process of drug development and approval. Any patient who enrolls in an antiepileptic drug trial must be made aware of the potential risks and benefits of participation, by means of informed consent. In this respect the Helsinki-Charter and its amendments look after the patient's best interest, and its implementation is locally supervised by institutional review boards (IRBs).

It is always difficult to determine what risks are appropriate for patients to be subjected to. Most patients enter trials with investigational drugs because they have failed all standard drugs and continue to have seizures that impair their quality of life. They may also be influenced by the promise of free medical care or free drugs, which are offered by pharmaceutical companies. Because of this, it is frequently the most severely afflicted patients who are enrolled in trials. This may affect trial outcome, as these patients may be the most difficult to treat. Whereas it may be more beneficial for drug development to enroll less severely affected patients, physicians may be constrained by the ethics of doing so. Each physician must make his or her own decisions on who they feel comfortable enrolling. The further a drug is in development, the more comfortable a physician may feel in enrolling patients who have less intractable epilepsy.

In most AED trials, the patient's treating physician is an investigator in the study. This raises potential conflict of interest. The physician is usually paid commensurate with the number of patients enrolled. There may be circumstances in which two trials are running concurrently, one of which is more lucrative than the other. That same physician is the one who will explain options for treatment. A physician in this situation must guard against painting an overly rosy picture of an investigational drug. This is more true now than ever, as more new drugs are approved and drug study subjects become more difficult to find.

Ethical Issues in Children

The multiple ethical issues involved in research involving children are examined in detail by Grodin and Glantz.[38] Some ethical issues that deserve particular mention include the need for parental written consent and, if possible, child consent or assent; the importance of considering the patient's epilepsy

syndrome on trial suitability; the investigator's large responsibility to properly classify the patient's seizure type and epilepsy syndrome; and lastly, where possible, the need to take action to reduce patient pain during the trial.

Persons below the age of 18 (or, in some societies, 16) are considered not to be competent to make their own decisions about treatment. For most children, the parent or legal guardian is considered an allowable surrogate in the matter of consent to medical treatment. This presumption is made on the basis that such a surrogate will have the child's best interests at heart. In addition, since parents are inevitably involved in the consequences of treatment choices, they have a right to stand by their own values in relation to the child's upbringing, and they are entitled to promote circumstances in which the family may function as an intimate unit.[38] The child's consent to such parental involvement must be assumed, but this makes it particularly incumbent on the investigator to ensure that parental comprehension of the risk–benefit ratio is maximized. Written information and written consent are essential. Clearly, in children able to understand the implications of a drug trial, information should be given to the individual involved and that individual's written consent or assent obtained.

For many children with epilepsy, a specific syndrome can be identified. Where this is possible, a reasonably accurate prognosis can be given. The threshold for using a trial AED should be higher for those epilepsies that are likely to remit than where severe, frequent seizures are expected to persist despite optimal use of established AEDs. Thus, only if it is believed that side effects would be fewer should a trial drug be used early in its investigation for childhood absence epilepsy or benign partial epilepsy with centrotemporal spikes. On the other hand, it is justifiable to consider the early use of trial therapy in situations such as the Lennox Gastaut syndrome and seizures secondary to inoperable structural lesions.

The clinician investigator's prime aim always must be the child's well-being.[38] The clinician investigator carries a heavy responsibility to ensure that his or her knowledge of epilepsies is sufficiently sophisticated to allow proper categorization of childhood seizures and identification of syndromes. Otherwise, children may unnecessarily be exposed to a drug that is not expected to help them.

All monitoring procedures should be conducted with as little discomfort as possible. For example, the use of anesthetic cream can minimize the pain associated with venipuncture. Neurophysiologic measurements, if indicated, should be taken, if at all possible, without the use of needle electrodes.

Applicability of Trial Data to Clinical Practice

The goal of regulatory authorities is to obtain rigorous scientific evidence that a new AED is safe and effective. The goal of clinicians is to obtain the kind of clinically relevant information about a new AED that will lead to appropriate selection of treatment for their patients, including information about how to use a drug to its maximal advantage, and data that can determine accurate risk assessment. Several areas where these two may differ have already been discussed above. For example, regulatory trials are usually short in duration, and may not supply sufficient information regarding long-term side effects of medication. This may impact the ability of the clinician to make an accurate risk–benefit assessment. Antiepileptic drugs may not necessarily undergo rigorous testing in certain epilepsy syndromes, particularly in children, that are of great interest to clinicians. Therefore, clinicians may be left to extrapolate data from the trials that have been done. Also, many randomized controlled trials of drugs in development are performed in patients with the most severe epilepsy. It is unclear whether the results can or should be generalized to the remainder of patients with epilepsy, who, by and large, do not have intractable disease. It may also be difficult to determine whether the patient with less severe epilepsy will be willing to remain on a medication with some side effects, which may seem less concerning to the patients with severe refractory epilepsy.

Efficacy Versus Effectiveness

The concept of efficacy versus effectiveness becomes even more important in an age when evidence-based medicine has become a guiding principle in clinical care. The concept of evidence-based medicine is that if clinical trial data are available, that data should be used to make treatment decisions. However, it is important to remember that clinical trials usually focus on *efficacy* rather than *effectiveness*. Efficacy can be defined as the ability to reach an end-point in the context of a clinical trial. Effectiveness is defined as the value of an antiepileptic drug in the environment of use or, in other words, its ability to benefit patients in clinical practice. Although efficacy and effectiveness are linked, they are not always the same. For example, in clinical practice, duration of titration may be guided by patient response. If the patient begins to complain of side effects, titration rates can be slowed or concomitant antiepileptic drugs can be reduced. This is usually not possible in the setting of a clinical trial, where trial methodology has to be predetermined. This may lead to an appearance of poor tolerability in a trial compared to clinical practice. Further, in a clinical trial all patients are titrated to a predetermined dose, often irrespective of tolerability. This too may impact trial outcome. Trial doses and titration rates must often be selected before ideal conditions of use have been determined. Many examples of this can be seen. As already noted above, a 2,400-mg dose was included as one arm in an adjunctive oxcarbazepine trial. This led to dropout of over 50% of patients.[5] In a trial of topiramate as monotherapy in newly diagnosed patients with partial seizures, patients were randomized to either 50 mg or 400 mg. The low dose led to failure due to seizure recurrence, whereas the high dose led to a high dropout rate. The conclusion was that 400 mg was an effective dose. While this may be true, the trial could not assess whether this was the optimal dose, since only two doses were tested. More tolerable doses such as 100 and 200 mg were not included in the trial.[1] Conversely, the highest dose of gabapentin tested in randomized placebo-controlled trials was 1,800 mg.[33] Since no higher doses were included in this study, it is impossible to determine whether 1,800 mg was the highest optimal dose. Many such examples could be given. Clearly, in essence clinical trials may represent a “proof of principle” that a specific treatment is effective in a specific condition. However, trials may not definitively outline optimal use. There is clear need for more pragmatic trials that will provide more guidance.

Summary and Conclusions

The pathway to antiepileptic drug approval is relatively clear-cut. Trial methodology is well established for add-on efficacy and tolerability studies in patients with treatment-resistent partial seizures. These studies lead to market approval in the U.S. and Europe, but leave many important clinical questions unanswered. In addition, trial designs for monotherapy studies, studies in children, and in syndromes outside of partial epilepsy are not well characterized, and progress is needed. Also, there is a need for better early (proof of principle) studies that will identify potentially successful versus unsuccessful drugs at an earlier stage.

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Chapter 141

Pharmacogenetics and Pharmacogenomics

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Introduction

Although pharmacologic treatment successfully controls seizures for a majority of patients with epilepsy, current treatment options are far from satisfactory for many patients. Recent progress emerging from the genome project and related activities suggests that it may finally be possible to systematically search for genetic differences among patients that influence how they respond to treatment. Here we review the potential of pharmacogenetics to improve the treatment of epilepsy and address some of the barriers to progress.

Limitations of Current Epilepsy Treatment

Perhaps the most important weakness of current treatment options is that they fail to control seizures for a substantial minority of patients. Nearly one-third of patients do not achieve adequate seizure control upon treatment with any of the currently available antiepileptic drugs (AEDs).[63] Furthermore, those who fail even one drug trial have a poor prognosis: Only 11% of patients who withdraw from their first AED due to inefficacy will ever go on to achieve seizure freedom.[17,40,41] The end result is a significant number of patients who are forced to (a) live with recurrent seizures or (b) resort to invasive surgery, which is not available to all refractory patients, is not guaranteed to eradicate seizures, and can have devastating consequences in some cases.

Although nine new AEDs have been approved during the last 15 years, these have made only a modest impact on the proportion of patients who respond well to treatment. There are currently more than 15 pharmacologic agents now available for clinical use, but approximately 30% of epilepsy patients remain refractory to treatment.[5,63] The chances of achieving seizure freedom with new AEDs has not been significantly improved, although levetiracetam (Keppra) is reported to reduce seizures in 40% of refractory patients, with 6% to 13% achieving seizure freedom.[8,39,68]

The other key limitation is that AEDs can cause both serious and life-threatening adverse reactions, as well as less serious reactions that may nonetheless have important effects on patient quality of life. It has been estimated that 17% of emergency room visits due to adverse drug reactions (ADRs),[58] and 10% of ADRs leading to hospitalization[87] are caused by AEDs. ADRs were cited as the cause of discontinuation in nearly 40% of decisions to terminate treatment with a particular medication[40] and, although patients exposed to high doses of AEDs are more likely to develop ADRs, side effects are not necessarily dose related and also can occur during the course of efficacious drug trials.

The newer AEDs, although offering little improvement for refractory cases, do tend to be tolerated better by patients. Withdrawal rates due to adverse reactions are significantly lower for the newer AEDs.[41] However, older ADRs have not been eradicated and some new ADRs have been introduced, such as the behavioral and cognitive ADRs associated with levetiracetam and topiramate respectively. Tolerability remains a major limitation in epilepsy treatment.

In addition to these key aspects, there are secondary challenges in the use of AEDs, notably the trial-and-error process usually required to identify appropriate doses or drug combinations for individuals. Patients require dramatically different doses to control seizures (Fig. 1), however efficacious dose is impossible to predict. Current routine, nonemergency methods of dosing stipulate, “start low, go slow.” A patient is slowly titrated upward until he becomes seizure-free or he experiences dose-related ADRs; at this point, use of a new drug is often considered. This can take months for those who require uncharacteristically high doses of a medication, or years for those who fail one or more trials and must repeat the process—during which time patients continue to suffer seizures.

Pharmacogenetics as a Probe into Biological Processes

In our view, the improvement of seizure control and the minimization of side effects are the primary motivations for pharmacogenetics studies in epilepsy, and projects should be prioritized on this basis. It is also worth noting, however, that pharmacogenetics may open a window into biologic process that are poorly understood in humans and otherwise not amenable to study.

Levetiracetam and Human Behavior

The approval of levetiracetam has brought seizure relief to some previously refractory patients. It is generally well tolerated, but has been known to cause behavioral abnormalities. Behavioral ADRs have been cited as the most common reason for withdrawal from levetiracetam treatment, and between 5.9% and 30.7% of patients report experiencing behavioral changes.[35,86] Levetiracetam-induced behavioral abnormalities can manifest as irritability, aggression, depression, or psychosis. The identification of gene variants relevant to these ADRs therefore could identify pathways relevant to human behavior, and perhaps more specifically relevant to neuropsychiatric conditions such as schizophreniform psychosis.

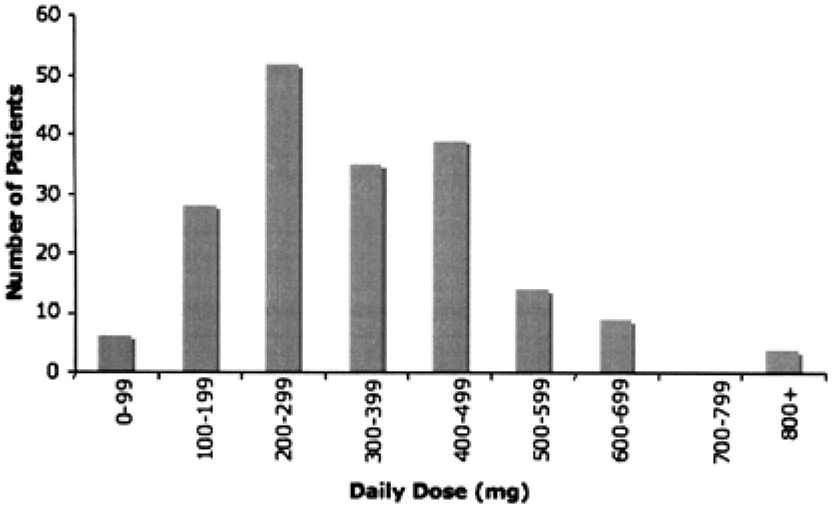

FIGURE 1. Distribution of maintenance dose of lamotrigine. Maintenance dose among patients from the same clinic is highly variable. All patients were treated with Lamo-trigine at the National Hospital for Neurology and Neurosurgery, Queen Square, London. Additional (maximum) dose distributions can be found in Tate et al.[76]

Topiramate and Human Cognition

Topiramate is a new AED commonly used as adjunctive and monotherapy. The most common reason for discontinuation of topiramate therapy is cognitive side effects, which can manifest as mental slowing, language difficulties, and confusion.

Nearly one-half of patients exposed to topiramate report cognitive ADRs (unpublished data), and 27% of patients who discontinue topiramate treatment cite cognitive adverse events as the cause of cessation.[77] Although topiramate is most commonly used as add-on therapy, and the incidence of ADRs is increased with polytherapy, healthy volunteers challenged with topiramate alone also experience cognitive difficulties, as determined by neuropsychological tests.[47,49] Although many AEDs have negative cognitive side effects, topiramate's profile is distinctive. For example, verbal fluency is more affected by topiramate than by other AEDs[24] and appears to affect only a subset of susceptible patients.[51] If genetic differences that mediate to-piramate sensitivity exist among people, their identification may inform clinicians about the underlying brain systems involved in verbal fluency tasks.

Epilepsy Pharmacogenetics: What is Needed?

Genetic Methods

It is possible (although still not certain) that systematic pharmacogenetic research can identify gene variants that will considerably improve the use of AEDs. Here we describe the key elements of contemporary pharmacogenetics research.

Candidate Gene Approach

Until recently, it was not feasible to consider in a single study more than a handful of genes; even then, the genetic information considered for each gene was very limited. Very recently, however, it became feasible to carry out large-scale candidate gene studies in which the genetic variation in hundreds of genes is systematically analyzed. Moreover, whereas whole-genome association studies remain costly, reasonable coverage of most polymorphisms in the full human genome is available in standardized sets of polymorphisms, such as those supplied by Illumina.

In pharmacogenetics, a particularly strong case can be made for candidate gene approaches because the likely modes drug action are usually known or suspected, at least partially. Therefore drug targets make obvious candidate genes and clearly deserve careful evaluation. Consistent with this notion, recent work on the targets of warfarin and phenytoin/carbamazepine identified polymorphisms associated with dosing.[14,76] Moreover, nearly 80% of genetic variants identified by pharmacogenetics reside in the three major categories for pharmacogenetic candidates: Drug targets, drug metabolizing enzymes, and drug transporters (although this reflects in part the bias of where researchers have chosen to look; for a review of this subject see the work by Goldstein, Tate, and Sisodiya[28] and their unpublished update.

For epilepsy pharmacogenetics, a set of high-priority candidate genes are readily identified on the basis of both pharmacokinetics and major modes of action.

Pharmacokinetic candidates

- Drug-metabolizing enzymes (DMEs). The most studied genes to date in pharmacogenetics are those encoding DMEs. For most AEDs, the key enzymes that metabolize the parent compound and active (or toxic) metabolites are well known (Table 1), and many of them have well described functional variants. It is already clear that these variants have some impact on patient response to AEDs: For example, CYP2C9 variation affects phenytoin dosing (see discussion in next section). It does not appear likely, however, that DME variation will prove of substantial clinical relevance in epilepsy.
- Transporters. Drug transporters may influence AEDs at a variety of points. They can influence uptake in the gut, the amount of metabolism in the liver and, perhaps most important, the properties of the blood–brain barrier. In the latter case, the effect of transporters may either be general or affected by seizures. As a class of proteins, however, drug transporters are not well studied. It is not clearly known what transporters move which drugs at therapeutically relevant concentrations, and few examples of functional variation have been characterized, making it unclear what role transporters play in pharmacogenetics.

- However, drug transporters are known to be overexpressed in resection tissue from refractory epilepsy patients.[7,18,72,78] The apparent upregulation of transporter expression at the seizure focus indicates a potential causative role for transporters in refractory epilepsy.

Table 1 Drug-Metabolizing Enzymes of Commonly Used AEDs

AED	Major DMEs	Minor DMEs
Carbamazepine	CYP3A4 epoxide hydrolase	CYP2C8 GST
Ethosuximide	CYP3A4	CYP2B
	CYP3A5	CYP2C isoenzymes CYP2E
	100% Renal clearance	
Gabapentin		
	Renal clearance	
Levetiracetam		
Lamotrigine	UGT1A4	
	Renal clearance	
Pregabalin		
Phenytoin	CYP2C9	CYP2C19
Topiramate	Renal clearance	CYPs (specific enzymes unknown)
Valproate	B-oxidization	CYP2C9 CYP2A6

Table 2 Known and Suspected Mechanisms of Action of Commonly

Used AEDs

Drug	Major drug target	Other suspected actions
CBZ	Sodium (Na) channel α-subunit	Inhibition of voltage-gated calcium (Ca^{2+}) channels and potentiation of potassium (K^+) channels Antagonism of adenosine receptors Inhibition of glutamate release Increase of extracellular serotonin and dopamine transmission Decrease of basal and stimulated cAMP levels[3]
ETX	T-type calcium channels	Inhibition of Na^+/K^+ ATPase[27]
GBP	Ca channel α2δ-subunits 1 and 2	Inhibition of GABA transaminase[43] and GABA reuptake[21] Decreased free content of glutamine/glutamate and reduced glutamate release[19,50]
LEV	Synaptic vesicle protein 2A	N-type Ca^{2+} channels[46] Inhibition of intracellular Ca^{2+} release[4]
LTG	Na channel α-subunit	Suppressed presynaptic Ca^{2+} influx[10] Vesicular release, independent of Na^+ and Ca^{2+} currents[13] Enhanced/inhibited hyperpolarizing K current[32] Downregulation of cortical 5-HT1A receptors[82]
PGB	Ca channel α2δ-subunit	
PHY	Na channel α-subunit	Inhibition of Ca^{2+} channels[66,80] Inhibition of Ca^{2+} calmodulin-mediated protein phosphorylations[15,16]
TPM	Voltage-gated Na channels L-type Ca channels AMPA/Kainate receptors $GABA_A$ receptor Carbonic anhydrase	
VPA	Glutamic acid decarboxylase GABA transaminase Succinic semialdehyde dehydrogenase Voltage-gated Na channels	

CBZ, carbamazepine; ETX, ethosuximide; GBP, gabapentin; LEV, levetiracetam; LTG, lamotrigine; PGB, pregabalin; PHY, phenytoin; TPM, topiramate; VPA, valproate.

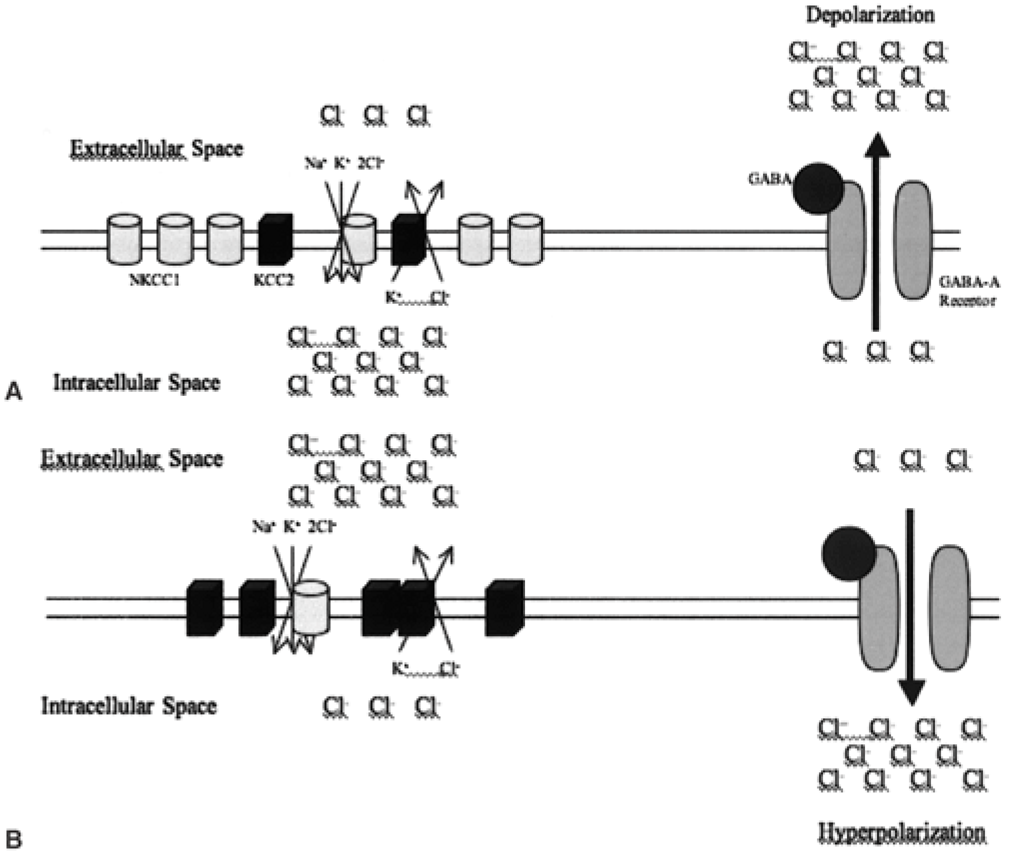
Depolarization
Cl⁻ Cl⁻ Cl⁻ Cl⁻ Cl⁻ Cl⁻ Cl⁻ Cl⁻ Cl⁻ Cl⁻ Cl⁻
Cl⁻ Cl⁻ Cl⁻
Extracellular Space
Na⁺ K⁺ 2Cl⁻
GABA
NKCC1
KCC2
K⁺ Cl⁻
GABA-A Receptor
Cl⁻ Cl⁻ Cl⁻
Intracellular Space
A
Extracellular Space
Na⁺ K⁺ 2Cl⁻
K⁺ Cl⁻
Intracellular Space
Hyperpolarization
B

FIGURE 2. Chloride transporter expression and GABAergic neurotransmission. **A:** In fetal neurons, NKCC1 is the predominantly expressed chloride transporter, resulting in a high intracellular concentration of Cl⁻ ions and depolarization upon GABAergic opening of chloride channels. In fetal tissue, GABA is excitatory. **B:** In mature neurons, KCC2 is the predominant chloride transporter, resulting in a high extracellular concentration of Cl⁻ and hyperpolarization upon GABAergic opening of chloride channels. In adult tissue, GABA is inhibitory.

Pharmacodynamic candidates

- Drug targets. The major modes of action for most AEDs are known, although in some cases the most important among several candidate modes of action remains unclear (Table 2). The major modes of action fall into one of three broad categories: Modulation of voltage-gated ion channel function, enhancement of γ-aminobutyric acid (GABA)-mediated inhibition, and attenuation of excitatory (glutamate-mediated) transmission.[42] In addition to

the precise target itself, it should also be appreciated that molecules downstream of the drug targets upon which an AED acts may contain variation that influences response. Thus, pharmacogenetic studies of GABA-acting drugs should appropriately consider chloride ion homeostasis broadly and consider relevant genes. The importance of this perspective is clearly illustrated by chloride ion transporters.

- Chloride ion homeostasis is primarily regulated by a balance of oppositely acting chloride transporters: NKCC1 (also known as SLC12A2), which transports chloride ions into the neuron and KCC2 (also known as SCL12A5), which extrudes chloride ions from the neuron. In adult neurons, KCC2 is the dominantly expressed transporter, resulting in a high extracellular concentration of chloride ions. In fetal neurons, the balance is reversed, such that NKCC1 is dominantly expressed, and there is a high intracellular chloride ion concentration.[54,61] The change in expression results in GABA having an inhibitory effect in mature neurons and an excitatory effect in fetal neurons (Fig. 2). This is known to have pharmacologic implications, because GABA-acting drugs can exacerbate seizure activity in infantile seizures.[25] In addition, expression levels of these chloride channels are altered in seizure-affected brain tissue.[52,67] From a pharmacogenetic standpoint, genetic alteration of chloride transporter protein expression or function most certainly has the potential to affect patient response to GABA-acting drugs.

Direct and Indirect Genetic Methods

Association studies to identify gene variants that influence a particular phenotype can be divided into direct and indirect approaches. In the direct approach, all variants that are good candidates for being functional are identified and checked for association with response. In the indirect approach, a set of genetic markers is identified that is sufficient to represent common variation in the region of interest through haplotype tagging, relying on linkage disequilibrium (LD) among polymorphisms.

To date, pharmacogenetics has followed essentially a direct approach. Many of the important DMEs have been resequenced, and all variants that looked to be potentially functional have been studied. In this way, it is possible, for example, to carry out an association study for phenytoin simply by relating the two low-activity variants of its major metabolizing enzyme, CYP2C9, and patient response.

Beyond DMEs, however, knowledge of functional variation in genes is very limited. One could resequence exons, but this could still miss important regulatory variation. These reasons argue for a tagging-based approach.

Tagging, however, will never perfectly capture all genetic variation and, in particular, it is known that variants with low minor allele frequency may not be well represented.[1,88] For this reason, we strongly favor a hybrid approach that combines elements of direct and indirect association. This model utilizes bioinformatic criteria to identify variants that are more likely to cause functional consequences than a randomly chosen polymorphism (putatively functional single-nucleotide polymorphisms [SNPs]). In our own work we have used the following criteria:

- SNPs that cause amino acid changes are predicted to cause functional differences (i.e., mRNA stability) or lie within splice junctions[36]
- SNPs in promoter regions[79]
- SNPs that occur in regions that are known to be highly conserved across species[9,70]

Today tagging SNPs (tSNPs) are usually selected on the basis of the genotype data provided by the HapMap project. This project has genotyped over 1 million polymorphisms in 269 DNA samples from four ethnic backgrounds (central European, Han Chinese, Japanese, and Yoruban Africans).[2] Critically, the project preferentially typed variants that are more likely to be functional. For this reason, the majority of SNPs selected on the basis of the above criteria have been typed in HapMap. It is therefore considerably more efficient to take into account the possible functional variants that are to be typed when selecting tSNPs. As an example, we applied this hybrid approach to 450 candidate genes for response to AEDs (Fig. 3). We found that, on average, 10 SNPs are required to tag a gene. It is estimated that humans have 10 million polymorphisms,[12] and there are currently over 9 million SNPs dbSNP (with some redundancy).[48] Thus, it is possible to screen most polymorphisms within a set of candidate genes.

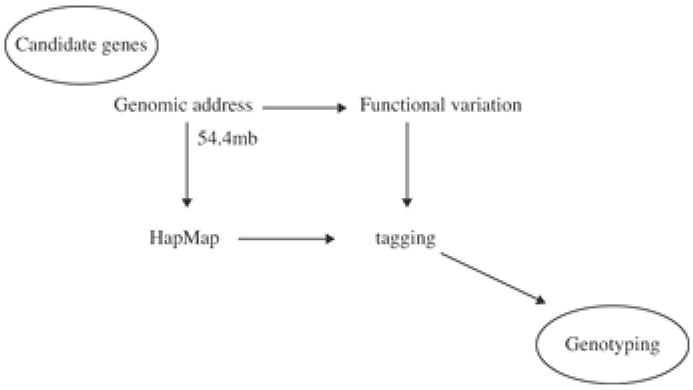

FIGURE 3. Scheme of tag selection using hybrid tagging approach. Using the genomic sequence of all candidate genes, putatively functional variants are identified according to (a) potential coding/splicing function, (b) location in promoter region, and (c) location in regions of high evolutionary conservation. In addition, the genes are tagged using available HapMap data and force, including as tags HapMap SNPs that appear in the functional set. A final set of tags is produced that is predicted to represent all common variants up to a specified threshold.

High Throughput Genotyping

The comprehensive approach just described results in an average of about 10 tSNPs per gene. This means that approximately 5,000 SNPs for 500 genes would be reasonable to cover the most attractive candidate genes in epilepsy pharmacogenetics, a number that was previously cost-prohibitive. The genotyping costs for a high-throughput platform such as Illumina are now about US$0.03 to US$0.04 per sample per genotype, meaning that sample sizes in the thousands can now be analyzed in the context of project grant support.

Analyses

Several issues must be addressed when undertaking large-scale case-control studies. Of particular importance is population stratification, which has been known to cause false-positive associations, especially when allele frequencies differ across populations. Study groups, therefore, must be assessed for ethnicity using ancestry-informative markers. Results and replication attempts can also be confounded by genetic heterogeneity, where a different gene/allele contributes to disease based on population/ethnic differences. Most important, though, is power. To maintain power, especially when testing many genes/polymorphisms for the same phenotype, large numbers of cases and ethnically matched controls must be used.

In addition to these classical pitfalls of genetic association studies, there are novel challenges that currently have no solution. Particular to pharmacogenetics is the unmonitored exploration of complex phenotypic space. There are many ways to consider response phenotypes and, as discussed earlier, no consensus exists on how it should be done.

Also, phenotype depends on a number of factors, none of which relies solely on one gene or allele. Common disease and response phenotypes occur as a result of interactions between genes and environment, and genes and other genes. Analyses can match cases and controls to try to control for as much of the phenotypic variation as possible, however gene–gene interactions cannot be controlled for and neither does there exist a way to identify them.

Clinical Cohorts

In both disease genetics studies and treatment response studies, many of the key challenges are not on the genetic side, but rather on the clinical side. It is very difficult and time-consuming to build well-phenotyped clinical cohorts, and it is often not clear how phenotypes should be defined. These challenges are acute in epilepsy, where clinical diagnosis is inexact, and response phenotypes are often arbitrary.

Retrospective and Prospective Cohorts

Retrospective cohorts are valuable resources because they are immediately accessible; however, they also come with several limitations: Phenotypic data from retrospective cohorts are collected from a clinical perspective and can overlook certain points of interest for genetic studies (for example, serum levels are not always recorded in routine clinical practice but are important when studying dose from a pharmacogenetic standpoint). Additionally, retrieving response information from patient records can be difficult and time-consuming, and the phenotypes necessary for pharmacogenetic study must be tailored to the available clinical data, which can compromise its validity and accuracy.

Prospective cohorts can solve many of these problems. Phenotypic data are ascertained by the clinician with the specific aims of the genetic study in mind to ensure that the appropriate phenotypes are specific and consistent. Patient recruitment can also be tailored to the aims of the study. However, prospective cohorts take time to build, and doing so is a costly endeavor. For these reasons, few pharmacogenetic studies in epilepsy utilize prospective cohorts, and therefore these studies reflect the limitations that retrospective cohorts necessarily entail.

Drug Response Phenotypes

Efficacy phenotypes.

“Refractory,” as it is currently used is a qualitative clinical term applied to patients who have failed a specified number of syndrome-appropriate drug trials. However, this definition implies nothing about the biologic cause of drug failure, and does not necessarily specify the trialed drugs. However, patients who fail only sodium (Na) channel–acting drugs are not biologically equivalent to patients who fail all drugs regardless of drug mechanism. Furthermore, it can only be said that a patient is resistant to Drug A if Drug A has failed. Therefore, simply classifying a patient as “refractory” is an inadequate phenotype. Instead, refractory patients should be subgrouped according to the drug(s) or drug class(es) to which they are resistant.

“Responder” likewise is not an objectively measured phenotype. The responder phenotype can be confused with spontaneous seizure remission, and patients with infrequent seizures prior to drug treatment are frequently too hastily qualified as responders. Additionally, a patient who achieves seizure freedom after failing the first two AEDs is not necessarily biologically equivalent to a patient who responds to the first drug trial.

Many factors must be considered. For example, a patient who becomes seizure-free from a starting point of one seizure per year clearly has a different response phenotype from a patient who becomes seizure-free from a starting point of hundreds of seizures per year. In epilepsy pharmacogenetics, currently no guidelines exist that specify how to take into account seizure frequency before and after initiation of treatment, and over what time frame, to arrive at a biologically (and clinically) meaningful definition of response.

Adverse events phenotypes.

Serious adverse events are probably of most interest for pharmacogenetic study. However, these are rare and are unlikely to be captured in sufficient numbers for study by assembled cohorts. Additionally, many mild adverse events can go unreported. For example, many patients, while exposed to topiramate, never complain of any cognitive side effects. It has been observed, however, that upon withdrawal of the drug, patients experience measurable cognitive improvement, indicating that these adverse events are easily overlooked and often underestimated.[38]

Also, adverse events can be difficult to quantify. The behavioral effects of levetiracetam, for example, can be reported as irritability or feelings of aggression, effects that cannot be measured, thus making phenotype classification heavily reliant upon the description of the patient.

Dosing phenotypes.

During the course of treatment, patients are exposed to many doses during the titration period, and dose remains subject to change throughout the course of treatment. There is currently no way to integrate a patient's dosing history into a single maintenance dose. Moreover, at a biologic level, clearly a number of different definable phenotypes relate to the dosing decisions made by a clinician. For example, the maintenance dose on polytherapy may be influenced by drug–drug interactions or the induction of relevant DMEs by concomitant medications in addition to any pharmacodynamic variants, whereas under monotherapy, variants relevant to drug interactions and enzyme induction may be less important.

Similarly, increases in dose may be constrained in some patients by tolerability, whereas other patients do not increase dose due to the achievement of effective seizure control.

These points alone make clear that dose, however defined, is likely to be a “heterogeneous trait,” to use the analogous terminology from the study of common disease. This sort of heterogeneity has made dose a surprisingly controversial phenotype in the epilepsy community, especially given the clear example from other therapeutic areas (e.g., warfarin).

We should therefore make clear that, from the perspective of both complex trait genetics and pharmacogenetics, dosing is quite a standard choice as a phenotype. Many things will influence it, and there are various subphenotypes masquerading underneath any specific “dosing” phenotype (e.g., maximum dose, maintenance dose defined one way or another, etc.). But two clear and related motivations exist for investigating dose as a phenotype in pharmacogenetic studies. First, although genetics will never explain all the variation among patients in what dose clinician ultimately settle on, in may well explain some of that variation. It is therefore possible that gene variants that predict dose requirements will eventually have clinical utility. How do you find such variants? You use dose as a phenotype, of course, in a complex trait study of the genetic determinants of dose. Second, dose as a phenotype may be an effective phenotype for identifying gene variants that influence how patients respond to AEDs, which may be variants that are well worth knowing about, regardless of whether they offer clinically useful predictions. The SCN1A intronic polymorphism was identified in exactly this way[76] and, if it turns out to be a real functional polymorphism that affects splicing, as appears very likely, it illustrates the value of dose as a phenotype.

Pharmacogenetic Studies to Date

Past pharmacogenetic associations in epilepsy have been limited by the technical issues discussed earlier and therefore have focused mainly on pharmacokinetics and have been limited to one or a few candidate genes.

CYP2C9 and Phenytoin Dosing

CYP2C9 is the major metabolizing enzyme for phenytoin and has two common variants, CYP2C9*2 and CYP2C9*3, with reduced enzymatic activity[59,74] making it an obvious candidate for dosing studies. The *3 allele was first associated to the phenytoin poor-metabolizer phenotype in a study of 12 individuals,[37] and several independent studies have since confirmed that CYP2C9 allelic variants are associated with a maximum tolerated dose of phenytoin.[45,76,81] An additional study found that slow-metabolizing alleles are a risk factor for phenytoin-induced cutaneous ADRs (cADRs; rash).[44] These findings are among the first in epilepsy pharmacogenetics; however, they fail to account for the majority of dose variation in patients, thus suggesting that an additional, more important factor is responsible for dose. Indeed, more recent studies have found a pharmacodynamic factor that is more important than CYP2C9 in determining phenytoin dose.[76]

ABCB1 and Drug Transport

ABCB1 (also known as multidrug resistance protein 1 [MDR1], P-glycoprotein) has been shown to have a weak affinity for AEDs.[56,57,64] It shows overexpression in resected human epileptiform brain tissue,[18,72,78] and has characterized functional variation: A synonymous substitution in exon 26 that causes decreased transporter expression[29,30] due to its effects on mRNA stability.[84] This suggests that it may play an important role in drug-resistant epilepsy due to increased reduced concentrations of AEDs at their target site, the brain.

Pharmacogenetic studies have shown this variant[69] and haplotypes containing this variant[33,89] to be associated with drug-resistant epilepsy. It should be emphasized, though, that the only true attempt to replicate the initial study found no association.[75]

Recently, the transport of AEDs at clinically relevant concentrations by ABCB1 has come into question,[7,85] suggesting that these associations are false positives or that the exon 26 variant is in high linkage disequilibrium with an as yet unidentified causal variant.[73]

Although these pharmacokinetic pharmacogenetic associations have proved (a) to be without clinical application or (b) to be potentially false, more recent work in pharmacogenetics have identified pharmacodynamic variants that appear to be replicable and to have great potential for future clinical applicability.

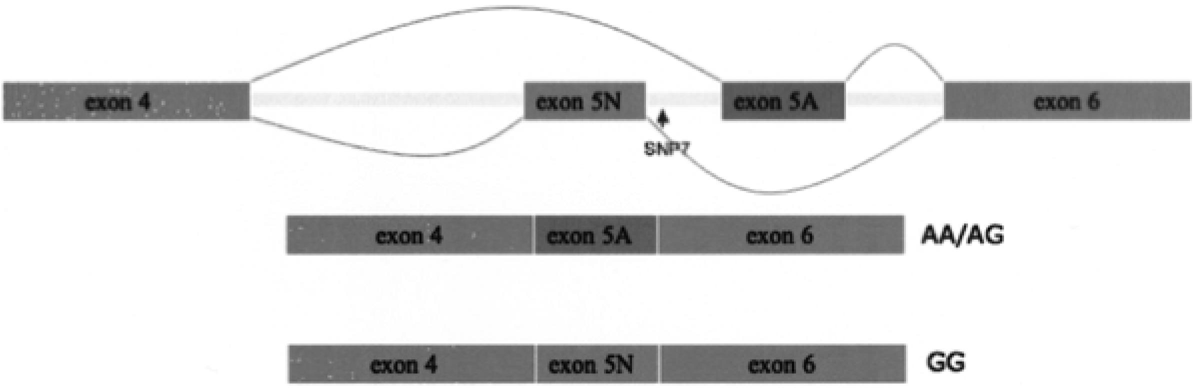

FIGURE 4. SCN1A splicing. The proportion of the two splice variants is genotype-dependent. The major allele (**A**) disrupts a splicing sequence for exon 5N, whereas the GG genotype restores the site and allows for efficient splicing of the exon. Patients with the GG genotype have higher proportions of the 5N exon in resected brain tissue. This genotype also associates with lower maximum doses of phenytoin and carbamazepine, perhaps attributable to higher proportions of a more drug-sensitive exon being expressed in Na channels. Differential sensitivity of the 5A and 5N exons has yet to be assessed.

HLA and SJS/TEN in Carbamazepine-exposed Patients

Many different classes of drugs are known to cause severe cutaneous adverse reactions manifesting in the form of Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN). These conditions are rare but are acutely life threatening, with a mortality rate as high as 40%[62]; they have been recorded as idiosyncratic reactions upon exposure to

the aromatic AEDs, mainly carbamazepine, lamotrigine, and phenytoin.

cADRs have been hypothesized to result from the inability to metabolize drug compounds or certain active metabolites, however no genetic defects altering the structure of AED DMEs have been associated with cADRs. Instead, immune reactions are likely to be responsible for severe cADRs, and evidence suggests that major histocompatibility complex (MHC)-dependent presentation of a drug or its metabolites activates T cells and causes a severe immune response and cell death.[53,65] Furthermore, carbamazepine and/or its metabolites may be capable of binding peptides that are presented to the MHC and are recognized by T cells, which elicits the severe reaction,[31,55] thus suggesting that HLA is a strong candidate region for these severe cADRs.

It was recently reported that the *1502 allele of the MHC B gene (HLA-B) is strongly associated with carbamazepine-induced SJS/TEN.[11] In this small study, this allele was present in 100% of SJS cases, but only 3%

of carbamazepine-exposed controls.

An expansion of this study to include larger numbers of patients confirmed these findings. Of 60 SJS/TEN cases, 59 patients had the *1502 allele. The remaining patient had an additional HLA-B minor allele, HLA-B*1558, present at low frequency in the study population and absent from carbamazepine-exposed tolerant controls.[34]

The strong association of the HLA-B*1502 variant suggests a potential for the clinical applicability of the SJS/TEN marker, although replication and prospective evaluation must precede large-scale clinical application.[34]

SCN1A and Dosing

As previously mentioned, different patients require highly variable doses of the drugs phenytoin and carbamazepine to control seizures. Tate et al.[76] used a candidate gene approach to identify gene variants that might affect the dose of phenytoin and carbamazepine, namely CYP2C9, ABCB1, and SCN1A. SCN1A is the major target of both phenytoin and carbamazepine,[20,42,71] and also harbors rare mutations that are responsible for some Mendelian forms of epilepsy.[22,23,60,83] CYP2C9 and ABCB1 both have known functional variation (see earlier sections), but no functional variants were known to exist in the SCN1A gene, so a haplotype tagging strategy was employed to represent common variation. A significant association was found with one of the tagging SNPs and the maximum dose of both drugs.

The Function of “Tag 7”

Upon association of genotype at Tag 7 with a maximum dose of phenytoin and carbamazepine, the SNP was assessed for functional implications that might explain how it affects dose. This SNP, SCN1A IVS5–91 G>A (rs3812718), lies in a donor splice site of an alternatively spliced exon. This alternative exon, 5N, is the predominant form of exon 5 in fetal Na channels, whereas 5A predominates in the adult form of Na channels. The major allele disrupts the splice sequence for 5N, whereas the minor allele (G) restores an intact splicing sequence (Fig. 4). The hypothesis, then, is that the polymorphism affects dosing requirements by changing the relative amounts of 5A and 5N forms of the α-subunit, and these forms are differentially sensitive to AEDs, although this is unconfirmed.

5N and 5A in the Epileptic Brain

To further investigate this hypothesis, Tate et al.[76] compared the relative proportions of 5A and 5N in resected tissue from patients who had undergone surgery for refractory temporal lobe epilepsy. Results showed that, among epilepsy patients, those with the GG genotype have a significantly higher proportion of 5N in temporal lobe tissue than do the wild-type (AA) and heterozygous (AG) genotypes. Surprisingly, there were no significant differences between genotype and proportion of 5N in the seizure focus: The hippocampus. This is possibly due to a high level of neuronal loss in the hippocampus; also, the lack of correlation between the G >A polymorphism and 5N proportions may reflect the relative paucity of neurons compared with other cell types. Future investigations will necessarily assess the proportions of 5N in individually identified neurons from the seizure focus.

In addition, comparisons of patient resection tissue with control brain tissue from a PD brain bank revealed that, regardless of genotype, the proportion of the 5N form of the α-subunit is significantly higher in patients than in controls. This is true for multiple Na channel subunits, including those encoded by the genes *SCN1A* and *SCN8A* (Fig. 5). The upregulation of the fetal form of the α-subunit in multiple Na channel genes is likewise seen in animal models following seizure induction,[6,26] indicating that 5N upregulation is the result, rather than the cause, of seizure activity.

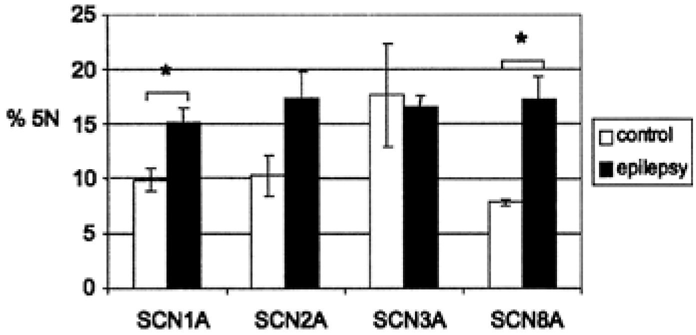

FIGURE 5. Upregulation of 5N in multiple Na channel genes. The proportion of 5N transcripts is significantly upregulated in two of four Na channel genes in resected seizure tissue when compared with postmortem control tissue.

Implications of 5N in Epilepsy

Prior to this pharmacogenetic work in SCN1A, the upregulation of the fetal form of the α-subunit had never been observed in human epileptic brain tissue. Although the exact cause and effect of this phenomenon remain unknown, the observation that patients with the GG genotype (and consequently higher proportions of 5N) require lower doses of AEDs, and that 5N-containing forms of the α-subunit are upregulated in these patients' brains suggests that this form of the exon may be somehow protective. The molecular characterization of a cause and effect relationship between seizures and 5N upregulation could will provide insight into the pathophysiology of epilepsy and perhaps suggest new molecular targets for the development of new AEDs.

Summary and Conclusions

The potential of epilepsy pharmacogenetics may be well illustrated by the examples of carbamazepine, phenytoin, and warfarin dosing. In these studies, one of the most obvious possible places to look for gene variants that influence response, the target of the gene, was very carefully studied. In both cases, intronic polymorphisms were discovered that associate with dosing decisions. If these are true associations, they suggest the possibility that pharmacodynamic variants that influence response to treatment might be common.

As studies that are sufficiently large to identify multiple effects are finally getting under way, the next several years will prove hugely informative. In our view, it is likely that, for certain genetic diagnostics, it may be necessary to consider multiple polymorphisms. Thus, although neither the SCN1A or CYP2C9 variants appear to explain enough variation in dosing decisions to be clinically important (although the role of SCN1A remains to be carefully studied in control settings), it may be the case that a number of such polymorphisms in combination will provide better dosing predictions.

It seems to us unlikely that treatment will be impacted over that time frame, but we should at least have an idea of how important genetic variation is in patient response. If many new variants are identified, it will warrant the establishment of translational research facilities that are sufficient to work out how to apply the genetic findings to improve care.

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Chapter 142

The Role of the Food and Drug Administration

Russell Katz

The views expressed in this article are those of the author and do not reflect an official position of the Food and Drug Administration.

Introduction

Legal authority for the regulation of drug and biologic products moving in interstate commerce in the United States and for granting approval to market drug and biologic products rests with the Food and Drug Administration (FDA), an agency of the Public Health Service in the Department of Health and Human Services. Practically speaking, this means that an investigator who wishes to administer an unapproved drug product to a human being must do so under an Investigational New Drug (IND) application that has been submitted to the FDA. Although any qualified individual may submit such an application (and a large number of such applications are submitted by individual investigators), this chapter is largely concerned with issues of drug development faced by commercial sponsors intending to bring a drug product to market. The relevant laws and regulations governing research with investigational drugs, as well as standards for marketing of new drugs, have been described in detail elsewhere.[1,2,3]

Although many of the issues encountered in the development and evaluation of antiepileptic drugs also pertain to drugs of other classes, epilepsy does present a number of relatively unique problems for the regulatory agency, as well as for the sponsor. These problems range from the general, such as the choice of the appropriate clinical trial designs, to the specific, including such fundamental aspects of trial conduct as the appropriate collection of the basic data on which an adequate interpretation of the study depends. Most of these issues and problems have arisen in the context of the three most recent New Drug Applications (NDAs) acted on by the FDA.

Clinical Trials

Add-on Trials

The most fundamental question that needs to be addressed is the appropriate design for the adequate and well-controlled clinical investigations required by law in determining the effectiveness of a treatment. By far the most commonly employed clinical trial design currently being utilized by sponsors is the so-called add-on design, in which patients not adequately controlled by optimal therapy with currently available treatments are randomized to have the investigational therapy added on to their current treatment regimen, or to have placebo added on to their current treatment regimen. This trial design has great appeal for two reasons: First, ethical concerns regarding the use of placebo do not arise, because those patients who receive placebo continue to receive their standard treatment. Second, the trial is designed to demonstrate the superiority of the investigational treatment over the placebo treatment; in other words, the trial is designed to demonstrate a difference between treatments. Studies designed to demonstrate an equivalence between treatments (e.g., a study comparing the effects of an investigational antiepileptic drug with a standard antiepileptic drug) ordinarily cannot be interpreted unambiguously.[4,5]

The standard add-on trial is not without problems, some of them structural, and therefore not fixable, and some related to study conduct, which can be handled. In the first place, this type of study can be relied on to offer conclusions about the new treatment only in combination with other antiepileptic drugs; that is, it is incapable, by design, of addressing the question of whether the treatment in question is effective when given alone, as monotherapy. It is possible that a therapy, because of pharmacodynamic interactions, is effective only in the presence of other antiepileptic drugs, but not by itself. Some consider a demonstration of effectiveness only in add-on trials to be an inadequate basis for the approval of a proposed new treatment for epilepsy; however, as of this writing, it is clear that the FDA is willing to permit marketing solely on the basis of data from add-on trials.

Add-on trials pose other difficulties. Beyond any potential pharmacodynamic interactions, most investigational antiepileptic drugs have pharmacokinetic interactions, often complex, with standard antiepileptic drugs. Unless the plasma levels of the (unbound) standard treatments are tightly controlled in a clinical trial, any apparent effect (beneficial or negative) of the new treatment may simply be the result of an alteration in the plasma level of one or more of the concomitant antiepileptic drugs. Unfortunately, sponsors ordinarily do not adequately characterize or quantify the possible kinetic interactions between their treatment and individual standard antiepileptic drugs, let alone the highly complex interactions that may occur when a new treatment is added to a regimen consisting of several concomitant antiepileptic drugs, before these same combinations are used in definitive clinical trials. Then, once the trials begin, plasma levels of the standard antiepileptic drugs are often not monitored with sufficient frequency or rigor to provide assurance that they are indeed constant. Given these conditions, it is often impossible to address this crucial question with adequate data.

Although the add-on design does permit internally consistent conclusions about the effectiveness of the treatment (albeit only in combination with other treatments), it is often misinterpreted. The demonstration of the superiority of the new treatment does not imply, as some suggest, that the new treatment is superior to the standard treatments used as concomitant therapy. In reality, add-on trials permit only the conclusion that the new treatment, when added on to standard treatments, is superior to placebo when added on to standard treatments. This is an important distinction. Even if patients achieve better control with the add-on treatment than they had with the standard before the study, this trial design cannot be

interpreted as demonstrating superiority over any of the drugs in the regimen, or to any of the standard drugs with which the patients may have previously failed therapy. For superiority to be proved, the new treatment would need to be compared directly with a standard treatment (either in a monotherapy or add-on setting) and be shown to be superior to it. It is generally acknowledged that the demonstration of such a difference would ordinarily require studies including so many patients as to make them essentially impossible from a practical point of view.

An additional problem with add-on studies relates to the use of specific concomitant antiepileptic drugs and the ability of the study to support adequate directions for use in approved labeling. Specifically, if sufficient numbers of patients are not receiving a particular standard antiepileptic drug, it may not be possible to draw adequate conclusions about the effectiveness of the new treatment in combination with that particular standard.

Novel Trial Design

Although trials of antiepileptic drugs have often used a crossover design (especially in Europe), the FDA's experience with this design has been disappointing, and most trials that have resulted in NDA approvals have employed the more acceptable parallel design.

Recently, trials with other novel designs, including monotherapy trials, trials utilizing outcome measures not directly related to seizure frequency, and trials with fixed plasma level designs, have been performed; these have been discussed by others.[6,7,8]

Because seizures occur (more or less) frequently and unpredictably, seizure counts, the primary data for these studies, must be recorded by the patient or a responsible caregiver. This is ordinarily accomplished with the use of a detailed diary, in which the number of events, type and time of seizures, and other details are recorded. A particular problem arises, however, when these events occur in rapid succession, or a single event is sufficiently prolonged, so that accurate mensuration is impossible. These events, often idiosyncratically identified as seizure clusters or seizure flurries (or even status epilepticus), pose a thorny problem in the interpretation of a trial that depends on accurate counting of events. Lack of prospective definition of these episodes makes accurate assessment almost impossible, and arbitrary assignment of a particular number of seizures to such an episode, as has been done, is unsatisfactory. A satisfactory method of dealing with these episodes (which appear to occur not infrequently in the setting of large controlled trials) has not yet been established, and this continues to be an unsolved problem in the analysis of clinical trials.

Evaluation of Clinical Data

An issue of great importance in the evaluation of antiepileptic drugs concerns the specific data necessary to support a specific indication. Specifically, in the three most recent cases (felbamate, gabapentin, and lamotrigine), the Advisory Committee (a group of outside experts empaneled to assist the FDA) recommended that these drugs not be granted a general claim as antiepileptic drugs, but rather recommended that they be indicated as adjunctive therapy (or monotherapy if the data supported it) for the treatment of specific seizure types, usually refractory partial seizures. In addition, the Committee made a clear distinction between partial seizures with and without generalization. Specifically, for a sponsor to be granted a claim for the treatment of partial seizures with generalization, an *independent*, statistically significant decrease in secondarily generalized seizures in the treatment group compared with the control group is required. Should sponsors wish to gain a claim for this specific seizure type, they are advised to enroll sufficient numbers of patients with this seizure type to be able to demonstrate a genuine drug effect on this type of seizure.

Drugs for Status Epilepticus

Essentially all antiepileptic drugs currently under development in this country are proposed as treatments for patients with chronic epilepsy. However, there is some interest in developing treatments for status epilepticus. Status epilepticus poses a particularly difficult problem for the sponsor interested in developing a treatment for this serious condition, as well as for the regulatory agency. Because status epilepticus is considered a potentially life-threatening emergency, sponsors and investigators are naturally reluctant to treat these patients with a presumably inactive control (i.e., placebo). However, as has been seen, studies designed to demonstrate equivalence between two active treatments cannot ordinarily be interpreted, because to do so requires a precise and accurate knowledge of the natural history of the untreated condition. In the case of status epilepticus, this natural history (e.g., how long a particular event will last) is not precisely known. Therefore, it poses a great challenge to design a trial with the capacity to demonstrate a difference between an acceptable control and an investigational treatment. The FDA has explored this issue and has promoted the view that because no standard treatment regimen for status is universally accepted, investigators should be willing to enter into a trial in which varying treatment modalities and regimens could be compared. When acute serious conditions like status are treated, early rescue with standard treatments can be incorporated into the design. For example, two doses of a treatment can be compared, with a rescue treatment given after an appropriate (brief) period of observation. The rate of administered rescue therapy between the two treatment groups could be an important outcome measure. Conducting these studies, however, is always more difficult when an attempt is made to rigorously study a drug that is already approved for another indication but is considered standard treatment for status.

Issues Concerning Children

A particularly problematic area in the development of antiepileptic drugs involves children. Traditionally, drug studies in children have been performed relatively late in the development of a particular treatment, with children usually being enrolled only when there is reasonably good evidence of the safety and effectiveness of the treatment in adults. A recent workshop on the development of drugs to treat children with epilepsy sponsored by the Epilepsy Branch of the National Institutes of Health recommended, however, that such studies be undertaken much earlier in the process, reflecting the community's view that much more should be known about the effects of new drugs in children at the time of their approval, especially as all new drugs to treat patients with epilepsy are used in children, regardless of the populations studied before approval.

A problem still remains, however, in the (most common) case in which a drug is approved for adults with a particular seizure type and a sponsor desires approval for the same seizure type in children. The question then arises regarding what sort of additional evidence of effectiveness, if any, is required. In the case of the three antiepileptic drugs previously mentioned,

the Advisory Committee explicitly insisted that additional controlled trials be performed in children with partial seizures to support a pediatric claim, despite the fact that controlled trials had demonstrated the effectiveness of these drugs in partial seizures in adults. This vote reflected the Committee's view that events (partial seizures) that appeared the same in children and adults need not necessarily result from the same pathogenetic mechanisms in these two populations, and that it could not be assumed that the treatment applied would necessarily have identical effects in both populations. (It should be noted that at the previously mentioned National Institutes of Health workshop, participants voted overwhelmingly to recommend that if a drug is shown to be effective against a particular seizure type in adults, it should be considered effective against the same seizure type in children.)

Summary and Conclusions

This chapter has attempted to discuss just a few of the complex regulatory and scientific issues that need to be considered by the pharmaceutical industry and the FDA during the process of bringing safe and effective antiepileptic drugs to the marketplace as expeditiously as possible.

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Chapter 143

The Role of European Regulatory Agencies

Michel Baulac

Eric Abadie

Introduction

Since 1989, eleven new antiepileptic drugs (AEDs) have been approved in the EU countries for epileptic disorders as indication. The regulatory work also included the evaluation of new dosages and routes of administration, as well as new indications when a drug initially approved for a given seizure type or epileptic condition was subsequently approved for additional seizure types or populations. In parallel, the EU pharmaceutical legislative framework was progressively implemented. The European Agency for the Evaluation of Medicinal Products (EMEA) was established in 1995 to coordinate and harmonize the processing of EU licence applications. The Committee for Human Medicinal Products (CHMP) is the advisory committee to the EMEA for medicines for human use, and comprises two delegates from each EU member state.

The national competent authorities or drug agencies from the member states are the scientific pillars of the EMEA. The EMEA's guidance and recommendations are conveyed through an ensemble of guidelines. The EMEA position concerning AEDs is included in a specific scientific note for guidance, but it also derives from the experience acquired through the scientific advice provided and the EU procedures that involved recent applications for registration of new AEDs.

Overview of the Licensing Process in EU Countries

There are three routes by which a drug may be granted a product licence in the European Union. The centralized procedure, by which the company is authorized to release the drug in the market in any EU country, and the mutual recognition procedure, and a decentralized procedure. Some details of these procedures are shown in FIGURE 1. The national procedures, which involve the regulatory agencies in each individual member state, are critical in the mutual recognition system. The latter procedures also continue to be used when a drug initially approved through a national procedure, mostly before 1995, is subsequently considered for extension of its indications within the same country.

Once a product receives a marketing authorization from the EMEA, the company can approach individual governments to have it introduced in the relevant national markets. However, a company may decide not to launch in a particular country for commercial reasons. It is at this stage that other factors come into play, including the evaluation of the drug's added value by the national health systems and pricing negotiations, which can significantly delay the actual marketing process.

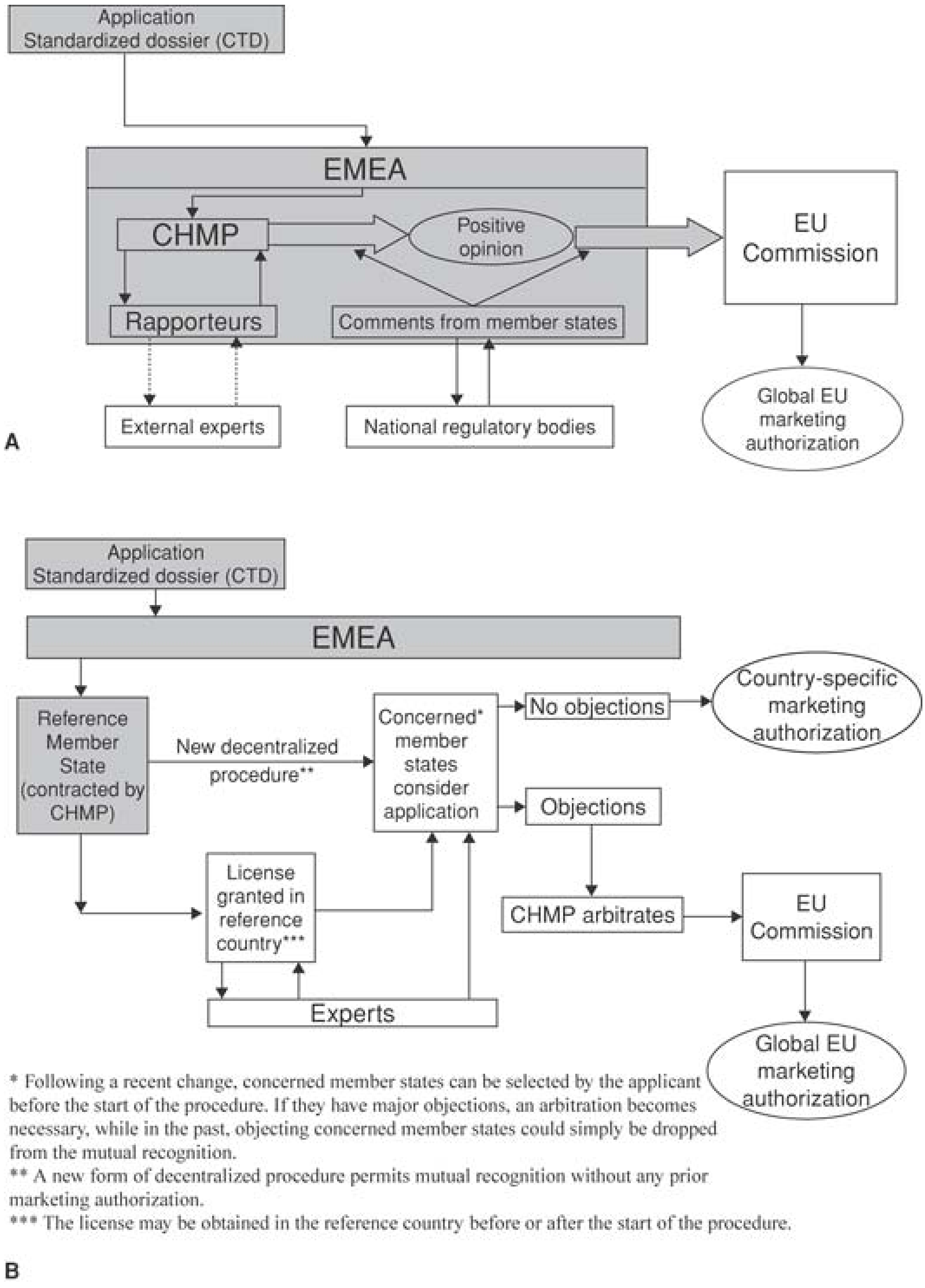
The AEDs recently marketed in EU countries have followed different routes. Vigabatrin, lamotrigine, gabapentin, felbamate, and topiramate were marketed through national procedures, which were initiated before 1995. Every variation or extension of their indications continues to be dealt with by the individual national regulatory bodies, which explains some variability across EU countries regarding the wording of the indication, the dosage recommendations, or the age range, especially in the pediatric indications. Tiagabine, in 1996, was the first AED whose license application followed an EU procedure—the mutual recognition procedure. The EU approval of oxcarbazepine was also obtained through mutual recognition in 2000, given the fact that some EU countries had already individually approved this drug in the early 1990s. Levetiracetam

(2000), pregabalin (2004), and zonisamide (2005) gained their EU approval through the centralized procedure. In addition, rufinamide was approved in 2006 for the adjunctive treatment of the Lennox-Gastaut syndrome seizures through Orphan Drug application.

EMEA Guidance and Recommendations

Within the framework of the pharmaceutical legislation, EMEA guidelines do not have legal force in that the definitive legal requirements are those outlined in the relevant EU legislative framework as well as appropriate national rules. However, guidelines are to be considered as a harmonized EU position and, when followed by relevant parties such as the applicants, companies, and regulators, will facilitate assessment, approval, and control of medicinal products in the European Union. Nevertheless, alternative approaches may be taken, provided that these are appropriately justified.

Scientific guidelines (or notes for guidance), including those related to quality, efficacy, and safety, are based on the most up-to-date scientific knowledge. A guideline is normally developed in accordance with the following steps:[15] (a) selection of topic and inclusion in the relevant work program(s); (b) appointment of a rapporteur and (if necessary) a corapporteur; (c) development of a concept paper and release for consultation; (d) preparation of the initial draft guideline; (e) release for consultation of the draft guideline and collection of comments; and (f) preparation of the final version, adoption for publication, and implementation.


Application
Standardized dossier (CTD)
EMEA
CHMP
Positive opinion
EU Commission
Rapporteurs
Comments from member states
External experts
National regulatory bodies
Global EU marketing authorization
A
Application
Standardized dossier (CTD)
EMEA
Reference Member State (contracted by CHMP)
New decentralized procedure**
Concerned* member states consider application
No objections
Country-specific marketing authorization
Objections
License granted in reference country***
CHMP arbitrates
EU Commission
Experts
Global EU marketing authorization
B

* Following a recent change, concerned member states can be selected by the applicant before the start of the procedure. If they have major objections, an arbitration becomes necessary, while in the past, objecting concerned member states could simply be dropped from the mutual recognition.

** A new form of decentralized procedure permits mutual recognition without any prior marketing authorization.

*** The license may be obtained in the reference country before or after the start of the procedure.

FIGURE 1. A: The centralized procedure for the EU approval of medicinal products for human use. The pharmaceutical company files an application including the Common Technical Document (CTD) to the European Agency for the Evaluation of Medicinal Products (EMEA), which is then passed to the Committee for Human Medicinal Products (CHMP). Two CHMP members, known as the "rapporteur" and "corapporteur," are selected to consider the application, and they can involve the external experts of their choice. Their assessments form the basis for the final approval by the CHMP. Following assessment, the CHMP gives an "opinion" on the application, which, in turn, is considered by the EU Commission, which is the licensing authority. The CHMP works according to a strict timetable laid down

in EU law. An "opinion" (positive or negative) has to be issued within 210 days (average 180) of receipt of the application. In the case of a positive opinion, the recommendation by the CHMP is transformed into a decision by the EU Commission. **B:** The EU decentralized system, or mutual recognition procedure, for the EU approval of medicinal products for human use: Under this system, the CHMP does not take part in the decision-making process unless there is disagreement between member states. The company asks one member state, which must have already approved the product, to act as Reference Member State. Then, the other member states for which licensing is requested ("Concerned Member States") have 90 days to "mutually recognize" the marketing authorization already granted in the Reference Member State. When other countries raise major objections, the matter is referred to the CHMP for arbitration. Selection of the member states that are "concerned" by the indication reduces disagreements. A new decentralized procedure is now applicable, bypassing the step of a preexisting marketing authorization in the Reference Member State.

The need for a new guideline may be made evident by frequently encountered problems with established products or by questions brought forward within the framework of scientific advice. A need for a guideline may also arise due to the development of new technologies, new practices, or new therapeutic areas. Inputs for developing or revising guidelines may also be received from interested parties (e.g., industry, health professional groups, scientific societies, patients' associations, etc.). Guidelines can also be initiated and drafted by the International Conference on Harmonization (ICH).

The rapporteur for the development of a guideline is a member of the CHMP Efficacy Working Party who works on the

draft with experts of his or her choice. After release for consultation, comments are expected from EU/EEA/EFTA countries, other regulatory authorities (e.g., the U.S. Food and Drug Administration, Health Canada), industry associations, scientific and academic societies, patients' groups, and health care professionals. Unless otherwise indicated, guidelines come into operation 6 months after their adoption. The current EMEA guideline on AEDs[11] was drafted from April 1998 to September 1999, commented on from October 1999 to April 2000, and adopted in November 2000, and it came into operation in May 2001.

Specific EMEA Guidance on Antiepileptic Drugs

The specific EMEA position concerning the development of AEDs is described in the current note for guidance,[11] but it also derives from the experience acquired through scientific advice and EU procedures that involved AEDs. Key aspects are reviewed in the sections below.

Global Development Plan for a New Drug

The clinical development of a new AED follows a stepwise approach. The preclinical data, including data on pharmacologic actions, toxicology, pharmacokinetics, and interaction profile, should be known before starting studies in humans. Initial human safety and pharmacokinetic data are usually obtained in healthy volunteers. For ethical reasons, the patient population selected for the initial clinical trials is usually represented by subjects with epilepsy who have continuing seizures in spite of several attempts to control the disorder with appropriate AEDs, used in combination and at optimized dosages. Therefore, the first application usually concerns the add-on indication in refractory partial seizures in adults, based on results of randomized, parallel-group, double-blind, adjunctive-therapy, placebo-controlled trials. A sufficient number of adolescents (over 12 years of age) should be recruited in the confirmatory studies. It is useful at this stage to submit a global development plan, showing which extensions are envisioned. In particular, the preclinical profile or some clinical exploratory studies (e.g., a double-blind cross-over study after an open enrichment phase) may suggest that the test drug has a potential for usefulness in other seizure types (e.g., seizure types associated with generalized epilepsies) or other syndromes. Once evidence for a beneficial effect has emerged from studies in adults, it is recommended to implement pediatric studies as planned in the clinical development plan and before registration of the product in adults (see guidelines on investigation of medicinal products in the pediatric population[6]). It may also be useful for the applicant to define at an early stage plans regarding the monotherapy indication, and which patient populations will be investigated for this purpose. A policy regarding elderly patients is also of importance. The development of parenteral formulations is encouraged. Besides bioequivalence and safety data, the demonstration of efficacy in status epilepticus may be an important objective with such formulations, although very little regulatory experience has been acquired in this particular domain.

Approach by Seizure Type and Epileptic Syndrome

Patients included in the clinical trials should be classified according to the International Classification of Seizures and, when possible, the International Classification of Epilepsies and Epileptic Syndromes. It is recommended to evaluate the whole spectrum of effectiveness of the test drug, not only according to the type of seizures (e.g., partial vs. generalized seizures), but also to the type of seizures associated with a specific epileptic syndrome. It is acknowledged that patients with partial epilepsies usually represent the initial target, since they are the most prevalent and a substantial percentage of them are not well controlled. Efficacy, however, should be evaluated for all the seizure types present in this condition, including simple, complex partial, and secondarily generalized tonic–clonic (GTC) seizures. A pooled analysis across several studies, optimally prespecified, may permit assessment of efficacy in the less frequent seizure types.

The other syndromes should be explored separately, which is the case for idiopathic generalized epilepsies and symptomatic/cryptogenic generalized epilepsies, including some syndromes specific for infancy and childhood (e.g., West syndrome or infantile spasms, Lennox-Gastaut syndrome, Doose syndrome, Dravet syndrome). Addressing these syndromes will require evaluating the efficacy of an agent separately on the different seizure types present in the given condition (e.g., spasms, GTC seizures, absences, and myoclonic, tonic, or atonic seizures). The impact upon the other clinical features of the disease, such as cognitive outcome, should also be addressed. The global antiepileptic efficacy of an agent in a specific epileptic syndrome can only be claimed when efficacy has been shown for all seizure types associated with that syndrome.

In newly diagnosed patients, who often have a low number of seizures, it may be difficult to identify the seizure type or the syndromic context at the time of inclusion. Some apparently primarily GTC seizures may in fact be secondary to unrecognized partial seizures, particularly in patients with nocturnal seizures. Other GTC seizures may occur in an unrecognized context of idiopathic generalized epilepsy, in the absence of typical electroencephalographic (EEG) traits or other seizure types. The choice of including or excluding undetermined GTC seizures should be made in relation to the expected efficacy spectrum of the test drug, and of the comparator in case of active control trials. Some of these undetermined seizures may be classified later on in the trial, and it might be important to see whether response for these reclassified seizures or syndromes are compatible with the efficacy spectrum of the test product and of the comparator.

Development of Antiepileptic Drugs in Children

Pediatric studies should be conducted as early as the development of the test product allows, in order to avoid an excessive delay in obtaining a marketing authorization for children compared to the marketing authorization for adults. The pediatric needs in epilepsy were assessed by the CHMP Pediatric Expert Group,[2] which identified the general need for studies of AEDs in refractory epilepsies. Existing data are generally insufficient in two particular domains: (a) pharmacokinetic, efficacy, and safety data of the newer AEDs in refractory epilepsies in young children, particularly under the age of 3 to 4 years, and (b) long-term safety including effects on cognitive function and brain maturation.

A recurrent regulatory issue is the need for evidence of efficacy in children when demonstration of efficacy has been already obtained in adults. To authorize an indication in refractory partial epilepsy, for instance, is it necessary to replicate a randomized controlled trial in children when efficacy in partial epilepsy has already been demonstrated in adults, or would pharmacokinetic and safety data be sufficient? The current CHMP position is that demonstration of efficacy in children

remains necessary in most of the cases, because there are examples of negative add-on studies in children contrasting with positive results obtained in similar epileptic conditions in adults. Specific seizure types seen in only childhood (e.g., infantile spasms) or specific seizure types within an epileptic syndrome seen in childhood (e.g., Doose syndrome, Lennox-Gastaut syndrome, and continuous spike wave in sleep syndromes) need specific investigations. These syndromes may qualify for classification as orphan disorders and benefit from incentives for orphan indications.

From the safety viewpoint, approximately 100 children treated with the study drug should be followed for at least 1 year. Moreover, short-term and long-term studies should be designed to detect possible impact on learning, intelligence, growth, endocrine functions, and puberty. Some of these studies may require continuation in the postmarketing period.

Development of Antiepileptic Drugs in the Elderly

The prevalence of newly diagnosed epilepsy increases substantially after 65 years of age. Elderly patients who may have suffered from epilepsy for years or may have developed epilepsy recently should be considered differently. Efficacy and safety of AEDs in newly diagnosed elderly patients may be different from those seen in younger adults for the following reasons: (a) different epilepsy etiologies; (b) age-related differences in pharmacokinetics; (c) an increased risk of adverse effects associated with standard dosages, especially with respect to impact on cognitive functions, vigilance, and the cardiovascular system; and (d) pharmacokinetic and/or pharmacodynamic interactions with other drugs frequently used in the elderly. Based on this background, it is important to determine whether the pharmacokinetic behavior of the drug is different in elderly subjects as compared to younger adults. Moreover, a reasonable number of geriatric patients should be included in the phase III database. The clinical impact of the test product, especially on cognitive function and on alertness, should be evaluated. Potential drug interactions of the test drug should also be assessed, especially with other products frequently used in this age group. Depending on the data, specific efficacy and safety trials in this population may be needed.

The Add-on Indication

The add-on indication may be granted on the basis of positive results in the pivotal add-on trials. These trials should utilize a multicenter, double-blind, placebo-controlled, randomized, parallel-group design. Several studies with a similar design are generally needed to confirm efficacy and safety in a sufficient number of patients, and to explore the dose range. Head-to-head comparative add-on studies with new AEDs would also be of interest.

Since efficacy end-points are usually based on changes in seizure frequency, seizures must be recognizable by either patients or relatives, and a policy should be defined when seizures occur in clusters. The spontaneous fluctuations of the epileptic disorder must be taken into account; for example, patients whose baseline seizure frequency differs substantially from their usual seizure frequency should not be included, in order to minimize the regression to the mean phenomenon.

Great attention should be paid to the exploration of the dose range, and any maximal predefined dose should be justified. The dose range should be explored with several dose arms in order to establish the minimum clinically effective dose, as well as the maximum effective or maximum tolerated doses, and to characterize the dose-response relationship. A too-short titration period may lead to high dropout rates for adverse reactions early in the trial, and may prevent adequate exploration of the upper part of the dose range. The maximum tolerated dose should be defined with consideration of the percentage of patients who withdrew due to adverse events. An excessive withdrawal rate may compromise the effectiveness of this maximum dose.

The maintenance treatment period in add-on trials should be at least 12 weeks in order to establish that efficacy is not short lasting. Determination of the plasma levels of the test product may be useful in correlating plasma concentration values to efficacy and occurrence of adverse events. The interaction potential should be taken into account in both directions (e.g., interaction of the concomitant treatment vs. the test product and of the test product vs. preexisting AED treatment). The therapeutic dosages may be different in the presence of enzyme inhibitors or inducers. If the test product inhibits the metabolism of a concomitant AED, and thus increases its plasma concentration, proof of efficacy of the test product will require that the plasma concentrations of the concomitant drug(s) have been maintained within certain limits.

At the end of the maintenance period, further assessments should be performed to generate three orders of information: (a) data on the long-term effects of the test product, both in terms of safety and absence of tolerance, with 1-year duration of assessment being considered the minimum; (b) data on the consequences of the withdrawal of the test product, particularly with respect to potential rebound phenomena; and (c) data on conversion to monotherapy with the test product.[5]

The assessment of efficacy is essentially based on the change in seizure frequency during the double-blind treatment period. One valuable primary variable is the percentage change in seizure frequency, or some parameterization of it. The other variable dichotomizes the data into responders/nonresponders, where responders are patients who obtained at least a certain percentage of seizure frequency reduction versus baseline (a 50% reduction is generally the cutoff used, but a more ambitious cutoff such as a 75% reduction might also be used). It is recommended to provide information for both these variables, irrespective of whichever is defined as the primary one. Other variables such as seizure severity, number of days with or without seizures, and scales measuring quality of life have been less frequently employed. Efficacy variables should allow full investigation of the distribution of changes in seizure frequency during treatment. In particular, potential exacerbation of seizures should be assessed.

The percentage of seizure-free patients is considered an important outcome parameter, even if these percentages are usually very low in refractory populations. A clinically meaningful assessment of seizure freedom should be done over the entire double-blind treatment period, 3 months for instance.[8] Careful explanation of how responder rates (including seizure-free rates) are calculated is also necessary for a meaningful interpretation of the results: For example, seizure-free rates may refer to completers who were seizure free during the entire treatment period, or may be calculated by using the last-observation-carried-forward analysis and therefore include patients who discontinued the trial prematurely.

Some difficulties have been encountered when interpreting add-on studies, for example, when the parallel groups turn out to be dissimilar in terms of baseline seizure frequency, when a given seizure type was underrepresented, or when unexpectedly high placebo responses were observed. In some instances, a particular dose arm that was assessed with insufficient statistical power in an individual trial may turn out to be very important for the demonstration of the dose-response relationship, or for the determination of the therapeutic dose range. When

several studies are available, meta-analyses have been used in such circumstances to obtain some supportive information.

Assessment of long-term efficacy, which in follow-up studies is made difficult by the open-label design and by changes in concomitant AEDs, should take into account the progressive enrichment of the population remaining in the study.

The Monotherapy Indication

There is consensus among clinicians and regulators that when an AED has been approved for adjunctive therapy, the extension of the indication to monotherapy should be based on specific regulatory trials conducted in monotherapy settings. Obtaining a monotherapy license for new AEDs has become increasingly difficult, mainly due to methodologic difficulties with these trials, different viewpoints from the scientific and regulatory communities, and well-founded ethical concerns regarding the use of suboptimally treated control groups in some trial designs.

Presurgical designs generate information that generally can only be considered as proof of concept or as supportive data. Withdrawal or conversion to monotherapy studies[5] usually consists of an initial period of add-on treatment followed by gradual withdrawal of the concomitant AED(s), leading to a maintenance phase in which the test drug is administered alone in the regimen. The control group is usually given a low, suboptimal (pseudoplacebo) dose of the test drug or of another AED, which raises serious ethical concerns despite use of escape criteria designed to minimize the risks associated with possible seizure deterioration. The primary efficacy variable in this paradigm is retention time in the trial after withdrawal of concomitant AED treatment. Retention is often very short and does not allow assessment of long-term seizure control, which should be the clinical objective in patients under monotherapy treatment. The dose(s) tested, moreover, may be different from those needed in less severe patients. This design, however, presents definite advantages, because it has demonstrated assay sensitivity in differentiating test drugs from pseudoplacebo, thereby providing unequivocal proof of efficacy in a monotherapy setting. The suggestion was recently made that if the data from the pseudoplacebo arms in all the studies conducted to date were pooled, perhaps through a meta-analysis, the pooled data set could be used as historical control data, thereby eliminating the need for a concurrent placebo or pseudoplacebo arm in future studies.[9] This proposal could be evaluated by the CHMP and its Efficacy Working Party; however, according to the current CHMP guideline and recent regulatory procedures, withdrawal to monotherapy data can only be considered as supportive in the monotherapy dossier. When provided within the context of an adjunctive therapy application, positive data obtained in a withdrawal to monotherapy study may also be regarded as useful safety information about the risk incurred by patients who might discontinue by themselves concomitant medication after addition of the new drug. The overall understanding, in any case, is that trials performed in patients with chronic refractory epilepsy cannot be directly extrapolated to other populations, particularly recently diagnosed patients, because of differences in disease characteristics and drug responsiveness. One possible way of circumventing this problem is to conduct dose-controlled studies in which a low dose of the test product is compared with a high dose of the same product in patients with newly diagnosed epilepsy. Although these studies have been employed for the demonstration of the efficacy of a new AED in monotherapy, the use of low (suboptimal) doses remains an ethical concern, even when escape criteria are incorporated to protect the patient against the risks of an ineffective treatment. Moreover, these trials may not allow a sufficiently long duration of double-blind assessment, and the high and the low dosages selected may not be clinically optimal, resulting in inadequate evaluation of the risk–benefit balance of the test product.

Trials conducted in newly or recently diagnosed patients are more representative of the population of patients treated with monotherapy. The use of placebo or pseudoplacebo as a control treatment is generally considered unethical in this population. Double-blind active control trials are therefore required to assess response to monotherapy in these patients; follow-up duration should permit assessment of long-term efficacy and tolerability, with seizure freedom being the primary objective in this group of patients. Accordingly, the recommendation is that the study should assess as a primary efficacy variable the proportion of patients remaining seizure free for at least 6 months (excluding the dose-escalating period). The trial should also have a minimum of 1-year duration in order to assess safety and maintenance of efficacy. Retention time on treatment, which is a combined measure of efficacy and tolerability, should also be determined because it enables assessment of the global effectiveness of the drug. Any exit criteria used to assess lack of efficacy (e.g., second or nth seizure) should be justified.

Existing active-control trials, which were designed to demonstrate superiority of a test product over an established comparator (usually carbamazepine), have failed to do so.[13] Therefore, demonstration of noninferiority is regarded as a more realistic working hypothesis for these trial designs; the clinical objective would then be the demonstration of a similar risk–benefit balance of the test product as compared to an acknowledged, optimally used standard AED. Optimal use of the comparator implies that the comparator should have an adequate spectrum of efficacy against the seizure types exhibited by the population considered for the study and that its dosage should be titrated properly and adjusted flexibly, allowing for dosage decreases in case of tolerability problems, and dosage escalations (up to a predefined maximum) in case of seizure recurrence.

Noninferiority trials, to be valid, must meet several requirements.[14] There must be evidence, either direct or indirect, that the comparator is showing its usual level of efficacy. The trial should be strictly comparable to earlier similar trials with the same comparator, and these similarly designed trials should have been consistently able to identify a difference in efficacy between the comparator and a less active treatment, which defines assay sensitivity. Such historical evidence of sensitivity to drug effects is weak for AED trials in newly diagnosed patients, although a few trials demonstrated superiority of an active control over the test product. For these reasons, active-control trials in newly diagnosed patients have been criticized on the ground that they involve a risk of not distinguishing between equivalent effectiveness and equivalent ineffectiveness.

Demonstration of noninferiority is also based on predefinition of a noninferiority margin, which represents the lowest efficacy limit that may be considered as a clinically acceptable difference versus the comparator. This margin should be determined based on statistical reasoning, clinical judgment, and past experience with placebo-controlled trials. In order to demonstrate efficacy, this margin cannot be greater than the smallest effect size that the active control would be reliably expected to have compared with placebo.[14] The notion that an established treatment, carbamazepine, for example, consistently shows superiority to placebo, and by which margin, may be regarded as insufficiently documented in newly diagnosed epilepsy.[3]

While acknowledging these difficulties, the CHMP is open to adopt a pragmatic attitude and to discuss designs of noninferiority active-control trials during scientific advice. A noninferiority margin can be determined from historical studies with the same comparator, taking into account the variability in

efficacy results. The noninferiority margin should be expressed as an absolute value as well as a relative value. The EMEA note for guidance does not indicate any specific noninferiority margin for seizure freedom or retention rates, in order to keep the possibility of adapting to the state of the knowledge and to the specificities of individual trials.

Particular attention should be given to the characteristics of the newly diagnosed patients. In particular, the number of prerandomization seizures is a factor that may influence the outcome. This was suggested by studies where patients with less than three seizures during the last 3 months prior to initiation of treatment had better efficacy outcomes than those with more than three seizures.[1,10] Any selection of the population concerning the number of prerandomization seizures should be justified. For the same reasons, designs that select patients who had a single seizure, and in whom using a placebo control would not be unethical, may not be representative enough of the general population with newly diagnosed epilepsy.

Most of the newer AEDs that are licensed for monotherapy use in EU countries, including lamotrigine, gabapentin, and topiramate, have been approved for this indication through national procedures in individual member states. The only EU procedure, the mutual recognition procedure, was conducted for oxcarbazepine in 2000, before implementation of the current guideline. The oxcarbazepine monotherapy dossier included four active-control studies in newly diagnosed patients[13] using phenytoin, sodium valproate, or an immediate-release form of carbamazepine as comparators, including a total of 780 patients. These studies did not permit identification of any differences between oxcarbazepine and the comparators in terms of efficacy, but they were not designed to demonstrate noninferiority. In addition, supportive efficacy data for oxcarbazepine were obtained in refractory patients with withdrawal to monotherapy trial designs.

Safety

The EMEA guideline includes general principles regarding the identification of adverse effects, whether they belong to the systemic, neurologic, or psychiatric domain. The safety database may include information gained in other therapeutic indications for which the drug is developed (e.g., neuropathic pain or migraine). Special efforts should be made to assess potential adverse effects that are characteristic of the class of the product being investigated, depending on its pharmacodynamic properties, mechanism(s) of action, and the receptor sites involved. For example, AEDs sharing the property of inhibiting carbonic anhydrase have some common adverse effects.[4]

Possible exacerbation of seizures should also be investigated. There is an increased awareness that AEDs can sometimes aggravate epileptic disorders, and this possibility should be taken into account in the design of clinical trials. Aggravation may consist of increased seizure frequency, often for specific seizure types (e.g., absence or myoclonic seizures), or appearance of new seizure types. Efforts should be made to identify the mechanisms involved (e.g., inappropriate choice of the drug for the patient's seizure types or syndrome, modifications of concomitant therapy per protocol requirements or due to drug interactions, spontaneous fluctuation of the condition, AED intoxication with or without overdosage, and paradoxic reactions whereby an AED appears to exacerbate a type of seizure against which it is usually effective). For instance, episodes of nonconvulsive status epilepticus, sometimes associated with signs of toxic encephalopathy, have been reported in refractory patients with partial epilepsy receiving adjunctive treatment with tiagabine.[12]

The Article 31 of directive 2001/83 of the European Commission permits the referral to the CHMP of any safety concern affecting the interests of the EU population. This procedure was followed for vigabatrin after the discovery of the risk for visual field constriction, and led to changes in the indication and warnings in the summary of the product characteristics.

Incentive Programs for Rare Diseases and Orphan Medicinal Products

Several epileptic diseases or syndromes meet the criteria for rare disease designation by the EMEA. Examples include severe myoclonic epilepsy in infancy, Lennox-Gastaut syndrome, West syndrome, and progressive myoclonic epilepsies. A dedicated committee (Committee for Orphan Medicinal Products [COMP]) reviews applications for these designated conditions and recommends their approvals. Incentives are available to foster the development of new therapies for rare diseases. Rufinamide was approved through this legislation for the adjunctive treatment of the Lennox-Gastaut syndrome seizures. Stiripentol has also been registered for the adjunctive treatment of seizures in the Dravet Syndrome (Severe Myoclonic Epilepsy in Infancy). There is a requirement, however, for additional data showing the efficacy of stiripentol associated with maximum doses of clobazam and valproate.

Collaboration with Other Organizations

In a move designed to improve the coordination of regulatory approval procedures, the U.S. Food and Drug Administration and the EMEA have started a pilot program, allowing companies to seek parallel scientific advice from both agencies simultaneously for the testing of their products. With respect to collaboration with other countries, including non-EU European countries, the revised EU pharmaceutical legislation has introduced a new provision that allows the CHMP to give opinions, in cooperation with the World Health Organization (WHO), on products that are intended for use outside the European Union. At present, these recent programs are intended for breakthrough medicines for life-threatening diseases, but they might open the door for larger-scale regulatory collaboration in other domains, including AED development and approval.

Summary and Conclusions

The EMEA coordinates and harmonizes the processing of EU license applications. The CHMP is the advisory committee to the EMEA for human medicinal products and comprises two delegates from each EU member state. The scientific expertise relies on the individual national drug agencies from the member states. The EMEA guidance and recommendations are conveyed through an ensemble of guidelines. The specific EMEA position concerning the development and approval of AEDs is described in a specific scientific guideline, but it also takes into account the experience acquired subsequently through the scientific advice and EU procedures that involved recent AEDs.

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Chapter 144

Adrenocorticotropic Hormone and Steroids

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Introduction

Since the 1950s, adrenocorticotropic hormone (ACTH) and corticosteroids have been used to treat a variety of seizure types and epileptic syndromes. In most instances, these agents have been utilized after trials of standard antiepileptic drugs proved them to be ineffective. However, with the exception of infantile spasms, the therapeutic benefit of ACTH and corticosteroids in the treatment of disorders, such as Lennox-Gastaut syndrome, Landau-Kleffner syndrome, Rasmussen syndrome, and others, remains to be substantiated. In this chapter, the role of ACTH and prednisone in the treatment of various epileptic disorders is reviewed, and possible mechanisms by which the agents exert their antiepileptic effects are discussed.

Structure and Chemistry

Adrenocorticotropic Hormone

ACTH is a polypeptide containing 39 amino acids, the first 24 of which are required for full biologic activity. The sequence of these 24 amino acids is the same in humans and many animals, and for commercial use, ACTH is extracted from the pituitary glands of certain mammals.[109] Synthetic preparations are also available commercially (typically $ACTH_{1-24}$), and both forms have been used in the treatment of seizure disorders.

Prednisone

Prednisone is a synthetic glucocorticoid with significant anti-inflammatory and immunosuppressant effects, and only minimal mineralocorticoid properties. It is a white, odorless, crystalline powder that is formulated with several inactive ingredients for commercial use.[109] The structural formula of prednisone is shown in FIGURE 1.

Basic Mechanisms of Action

The mechanisms by which ACTH and corticosteroids produce their antiepileptic effects are not known. Certain observations during the hormonal treatment of patients with infantile spasms, to the effect that only short (less than 2 weeks) courses of therapy are required in most patients to produce permanent control of seizures, suggest that the mechanism by which ACTH and corticosteroids produce seizure control, at least in the case of infantile spasms, is unlike that of traditional antiepileptic agents. One basic question has yet to be answered: Is the effect of ACTH simply related to its ability to stimulate the release of steroids from the adrenal cortex, or does ACTH work directly on the brain to produce its antiepileptic effect? Certain evidence suggests that the latter case may be true. There are several reports that ACTH may be effective in treating patients with infantile spasms whose adrenal function is suppressed.[20,29,167] Also, the fact that some patients with infantile spasms who fail to respond to corticosteroids respond to ACTH and vice versa, lends support to this hypothesis.[60,64] Unfortunately, the treatment of infantile spasms with ACTH fragments, which are devoid of adrenocortical stimulatory effects, has been unsuccessful.[127,166]

Some of the potential mechanisms by which ACTH and corticosteroids may produce their antiepileptic effects are summarized below.

- *ACTH and corticosteroids regulate brain growth and metabolism.* Glucocorticoids and ACTH have been reported to accelerate the growth of neuroblasts in culture.[129,135] ACTH accelerates myelination[125] and stimulates RNA and DNA synthesis,[3] and both ACTH and steroids induce various enzymes of the central nervous system (CNS). For example, corticosteroids stimulate the sodium-potassium exchanger (or Na^+/K^+ATPase) in the developing cerebral cortex of the kitten.[68] Recent studies using highly sensitive gene expression profiling techniques (including DNA microarrays) have, for example, identified over 200 corticosteroid-responsive genes in the rat hippocampus alone, and these have included genes known to be involved in cell adhesion, growth promotion, axogenesis, synaptogenesis, and signal transduction.[165] Animal studies have demonstrated that corticosteroids upregulate basic fibroblast growth factor (bFGF)-2 gene expression in various brain regions. This neuropeptide has been shown to have widespread neurotrophic effects (on neurons, astrocytes, and oligodendrocytes) that regulate differentiation and function of the CNS, and it also appears to have neuroprotective activity that may facilitate recovery from injury.[114] In a human study, ACTH treatment of patients with infantile spasms was associated with increased levels of ß-nerve growth factor (NGF) in patients who had a good response to therapy,[141] suggesting that steroid modulation of NGF gene activity may be one factor underlying the efficacy of hormonal therapy. ACTH therapy for infantile spasms has also been shown to result in significant increases of serum and cerebrospinal fluid (CSF) lactate and pyruvate levels, with the most pronounced changes observed in patients who responded favorably to therapy,[113] suggesting that ACTH-induced alteration of pyruvate metabolism may contribute to its therapeutic effect. Because of these diverse effects of ACTH and corticosteroid therapy on CNS development and metabolic function, hormonal modulation of such physiologic events at a critical stage of brain maturation is one of the most commonly proposed hypotheses concerning the mechanism of action of these agents in infantile spasms.[135]

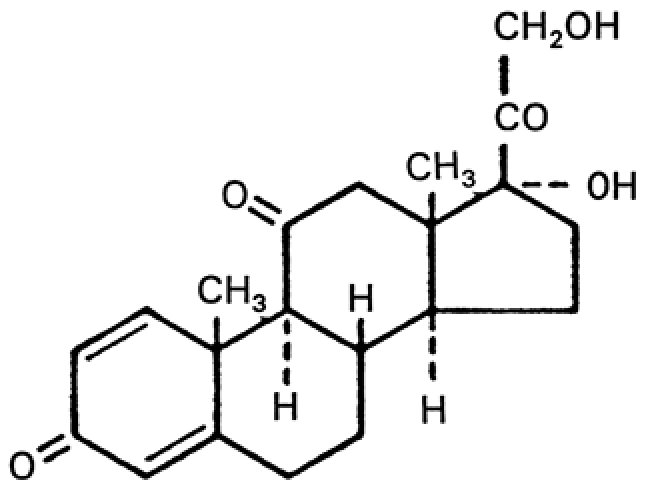

FIGURE 1. Structural formula of prednisone.

- *ACTH and corticosteroids have direct anticonvulsant effects.* In animal models, ACTH has both pro- and anticonvulsant effects. In young rats, ACTH has been shown to have a proconvulsant effect, reducing the threshold for minimal clonic electroshock seizures. However, in adult rats, ACTH increases the threshold for electroshock seizures, and moderate to high doses of ACTH delay seizure kindling.[129] Corticosteroids have been shown to reduce hippocampal excitability in vitro.[163]

- *ACTH and corticosteroids modulate various neurotransmitter systems.* ACTH and related peptides have been reported to increase or decrease γ-aminobutyric acid (GABA) and dopamine D_2 receptor sites, reduce serotonin 5-HT_2 sites in cortex, and increase ß-adrenergic receptor binding in cortex.[27,130] The reported effects of ACTH on the metabolism of neurotransmitters have been variable. In developing animals, ACTH treatment did not alter whole-brain levels of 5-hydroxytoptamine, 5-hydroxyindolacetic acid, dopamine, dihydroxyphenylacetic acid, homovanillic acid, or glutamic acid decarboxylase,[72] whereas in adult rats, the effects of ACTH treatment on the levels of dopamine, norepinephrine, acetylcholine, serotonin, and GABA have ranged from no effect to increased turnover to increased synthesis.[130] Corticosteroids have been shown to increase the activity of GABA[79] and to block 5-hydroxytryptophan–induced myoclonus in animals.[81]

Dysfunction of certain neurotransmitter systems, most commonly the serotonergic and adrenergic, has been suggested as the pathophysiologic mechanism underlying infantile spasms.[56] However, investigations of the levels of CSF metabolites of these and other neurotransmitters in patients with infantile spasms have been inconclusive, as have studies of the effects of hormonal therapy on neurotransmitter metabolite levels.[56,130] Also, attempts at treating patients with infantile spasms using antiserotonergic and antiadrenergic drugs have not been highly successful.[58,59]

Thus, although ACTH and corticosteroids are known to modulate various neurotransmitter systems, the significance of these neuromodulatory influences in relation to the antiepileptic effects of these agents remains unknown.

- *ACTH and corticosteroids suppress the immune system.* It has been a longstanding hypothesis that an immunologic defect might be the mechanism underlying infantile spasms.[56] Several immunologic abnormalities have been reported in patients with infantile spasms, including antibodies to brain tissue in sera,[115,133] increased numbers of activated B cells and subsets of T cells in sera,[66] and an increased frequency of the human leukocyte antigen (HLA).[54,65,159] However, a definite link between the immune system and infantile spasms has not been established.
- *A dysfunction of the hypothalamic-pituitary-adrenal axis exists*. Several studies have identified reduced CSF levels of ACTH[6,7,28,117,118] and cortisol[6] in infantile spasms patients. Considering the known effectiveness of ACTH and corticosteroids in this disorder, these findings suggest a possible role for the hypothalamo-pituitary-adrenal axis in the pathogenesis of infantile spasms. Baram and her colleagues[4,7,10] have hypothesized that the basic abnormality underlying infantile spasms is stress-induced production of corticotropin-releasing hormone (CRH) early in life. The presence of elevated CRH levels produces permanent excitatory changes in brainstem circuits, which become the region from which spasms originate. The efficacy of ACTH and corticosteroids is thought to be related to their ability to downregulate CRH synthesis. However, although CRH has been shown to produce seizures in developing animals, the seizures and interictal electroencephalogram (EEG) features of these animals are not typical of those associated with infantile spasms.[7] Furthermore, elevated CSF levels of CRH have not been found in infantile spasms patients,[7] and treatment of infantile spasms patients with α-helical CRH, a competitive antagonist of CRH, has not proven beneficial.[5] Therefore, the applicability of this model to infantile spasms is doubtful.

Pharmacologic Fundamentals

Adrenocorticotropic Hormone

Although ACTH is available as a lyophilized white amorphous solid that may be reconstituted with sterile water for injection, repository ACTH injection (ACTH in a solution with partially hydrolyzed gelatin) is usually used in the treatment of patients with seizures. Following intramuscular administration of repository ACTH, the drug is absorbed during a period of 8 to 16 hours. In healthy adults, subcutaneous administration of 80 U of repository ACTH produced peak plasma concentrations of 17-hydroxycorticosteroids in 3 to 12 hours, and baseline concentrations were attained in 10 to 25 hours.[109] In most normal adults, maximal adrenal stimulation is attained after infusing 1 to 6 U of ACTH intravenously during a period of 8 hours. More cortisol is secreted with a fixed dose of ACTH if the drug is slowly given intravenously or if ACTH is given intramuscularly as the repository injection.[109] The study of Hrachovy et al.[63] on the effects of ACTH on serum cortisol levels in patients with infantile spasms showed no difference in maximal serum cortisol levels attained between patients receiving 20 U/day of repository ACTH and those receiving 30 or 40 U/day.

In the blood, ACTH is transported with Cohn protein fractions II and III. The precise distribution of the drug is not known, but it is rapidly removed from the plasma by many tissues.[109] Although the precise metabolic fate of ACTH is not known, circulating ACTH may be enzymatically cleaved at the 16-17 lysine–arginine bond by the plasmin-plasminogen system.[109] The half-life of ACTH in plasma is about 15 minutes.[50]

Prednisone

Prednisone is well absorbed following oral administration, and peak serum concentrations are seen 1 to 2 hours following oral administration.[22] Prednisone is 70% protein-bound,[14] and prednisolone, the primary metabolite of prednisone, is nonlinearly bound to transcortin and albumin.[33] The volume of distribution of prednisone is approximately 1 L/kg.[42] After oral dosing with either prednisone or prednisolone, the plasma concentration-time profiles are superimposable. A first-pass exposure to liver enzymes after oral administration of prednisone facilitates the establishment of an equilibrium between prednisone and prednisolone before they reach the systemic circulation.[33] The serum half-life of prednisone following a single oral dose of the drug is 2.6 to 3 hours.[22,31] The biologic half-life (duration of action) is between 12 to 36 hours.[50]

Adverse Effects

Dose-Related Effects

Although the side effects of hormonal therapy in epileptic patients have not been studied systematically, complications of treatment depend on the size of the dose and duration of treatment. Most of the data concerning side effects of ACTH and corticosteroid therapy in epileptic patients have been collected from patients with infantile spasms.

Hypertension

Hypertension develops in 4% to 33% of patients with infan-tile spasms who are treated with ACTH or corticoster-oids.[36,61,64,137] Evidence suggests that hypertension occurs more commonly in patients treated with higher doses.[61,137] Hypertension, if it develops following initiation of hormonal therapy, can be treated by reduction of dose, salt restriction, or use of antihypertensive medications.

Immunosuppression

A variety of infections have been reported to occur in patients treated with ACTH and corticosteroids, including pneumonia, septicemia, urinary tract infections, gastroenteritis, ear infections, candidiasis, and encephalitis.[17,21,43,61,91,96,99,137,139,146] Pneumonia is one of the most commonly occurring infections and may result in death. Thus, the preexistence or development of a respiratory tract or other infection is sufficient reason to delay or discontinue hormonal therapy.

Electrolyte Abnormalities

Hypokalemia may occur rarely in patients with infantile spasms receiving hormonal therapy.[43,61,95,99,139,140] This side effect is usually seen in patients receiving higher doses and longer durations of hormonal treatment.[61,99] Electrolyte disturbances have also been reported to occur more commonly in patients receiving synthetic ACTH.[19]

Hypertrophic Cardiomyopathy

Echocardiographic studies have shown that evidence of myocardial hypertrophy develops in 72% to 90% of patients with infantile spasms who are treated with ACTH.[2,9,88,95,132,136,158] These echocardiographic changes are reversible within months after discontinuation of ACTH therapy. It has been suggested that this myocardial change may be secondary to arterial hypertension, hyperinsulinism, and a direct effect of ACTH on myocardial cells or thickening of the myocardium, which is due to increased interstitial edema caused by increased sodium and water content.[88,95]

Brain Abnormalities

Studies using computed tomography (CT) and magnetic reson-ance imaging (MRI) have revealed that brain “shrinkage” may develop in patients with infantile spasms who are treated with ACTH and corticosteroids.[12,39,46,51,53,71,84,86,94,101,102,105,122,145,148,172] This phenomenon reportedly reverses on discontinuance of therapy; however, in several studies[39,71,106,122] the shrinkage was not reversible in 12% to 44% of patients. A variety of explanations have been suggested for these CT changes occurring during hormonal therapy including communicating hydrocephalus, loss of water, inhibition of brain growth, and alterations in the blood–brain barrier.[36,39] Intracranial hemorrhage, probably secondary to arterial hypertension, has been rarely reported in patients with infantile spasms treated with hormonal therapy.[137] Subdural effusion or subdural hematoma also occurs rarely.[46,70,71,122,145]

Eye Abnormalities

Long-term steroid therapy may be associated with the development of posterior capsular cataracts. This side effect was not observed by Hrachovy et al.[60,61,62,63,64] in patients with infantile spasms treated with ACTH or prednisone; some of these patients were given formal ophthalmologic examinations, including slit lamp examinations before, during, and following hormonal therapy. Elevated intraocular pressure was reported in a small number of patients with infantile spasms treated with high-dose corticosteroid therapy.[35] The elevated intraocular pressure was controlled with antiglaucoma medication.

Gastrointestinal Disturbances

Gastrointestinal ulceration and hemorrhages may occur in patients receiving ACTH and corticosteroids.[116] This problem has been reported rarely in patients treated with hormonal therapy.[25,38,116]

Genitourinary Disturbances

Nephrocalcinosis has been reported in small numbers of patients with infantile spasms receiving ACTH and cortico-steroids. This adverse effect has been found at autopsy[140] and using imaging studies.[131]

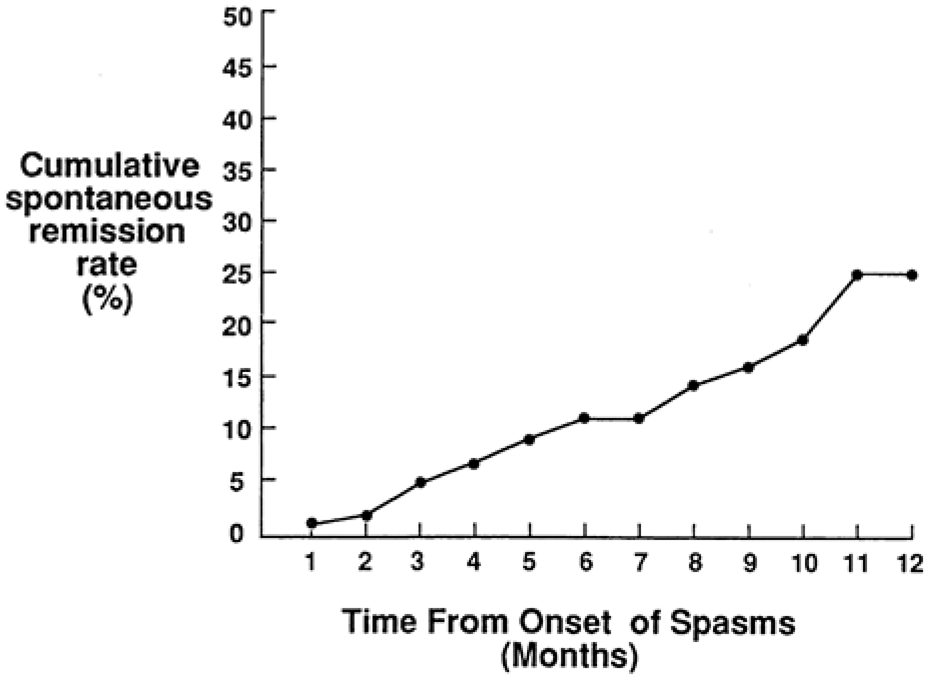

FIGURE 2. Spontaneous remission rate during the first year after onset of infantile spasms in patients who did not receive hormonal therapy (*n* = 44). From Hrachovy RA, Glaze DG, Frost JD Jr. A retrospective study of spontaneous remission and long-term outcome in patients with infantile spasms. *Epilepsia.* 1991;32:212–214, with permission.

Osteoporosis

On rare occasions, osteoporosis has been reported to occur in patients with infantile spasms treated with ACTH and corticosteroids.[99,137,140] This rare side effect would be expected to occur only in those patients receiving long-term hormonal therapy.

Weight Gain and Cushingoid Features

Many patients receiving ACTH or corticosteroids exhibit weight gain of variable degree and Cushingoid features. These changes are most pronounced in patients receiving higher doses.[16,18,21,25,61,95,96,99,137,153,154]

Irritability and Behavioral Changes

Irritability and other behavioral changes (e.g., sleep disturbance) have been reported to develop in 33% to 85% of patients with infantile spasms treated with ACTH or corticosteroids.[16,18,25,45,61,99,137,153,154,164]

Skin Disturbances

Hirsutism and acne may develop in patients treated with ACTH and corticosteroids.[99,137,154] These effects rapidly disappear following discontinuation of therapy.

Drug Interactions

Drugs that induce hepatic enzymes, such as phenobarbital or phenytoin, may increase the clearance of corticosteroids. Therefore, increases in corticosteroid dose may be required to achieve the desired response. However, it is not known if the concurrent use of drugs such as phenytoin or phenobarbital diminishes the "anticonvulsant" effect of prednisone in seizure disorders.

Clinical Indications and Contraindications

ACTH and corticosteroids are indicated as first-line therapy of infantile spasms. Their therapeutic role in Lennox-Gastaut syndrome, Landau-Kleffner syndrome, Rasmussen syndrome, and other myoclonic seizures is undetermined.

With the exception of known hypersensitivity to the drugs, the only other definite contraindication to the use of ACTH and corticosteroids in epileptic patients is systemic infection.

How to Use the Drug

Dosage Formulations and Strengths

Adrenocorticotropic Hormone

Repository ACTH injection (the most commonly used form of ACTH in epileptic patients) is available in strengths of 40 U/mL (U.S. Pharmacopeia) or 80 U/mL (USP). One USP unit of ACTH is equivalent to 1 milligram of the international standard.

Prednisone

Prednisone is available in tablet form in strengths of 1, 2.5, 5, 10, 20, and 50 mg.

Treatment Regimens for Specific Disorders

The studies reporting the effectiveness of ACTH and cortico-steroids in the treatment of seizures and epileptic syndromes have been plagued with many methodologic problems, making it difficult to evaluate and substantiate the therapeutic benefit of these hormones in the treatment of such disorders. Some of these methodologic shortcomings are reviewed, after which the treatment of specific disorders with ACTH and prednisone is discussed.

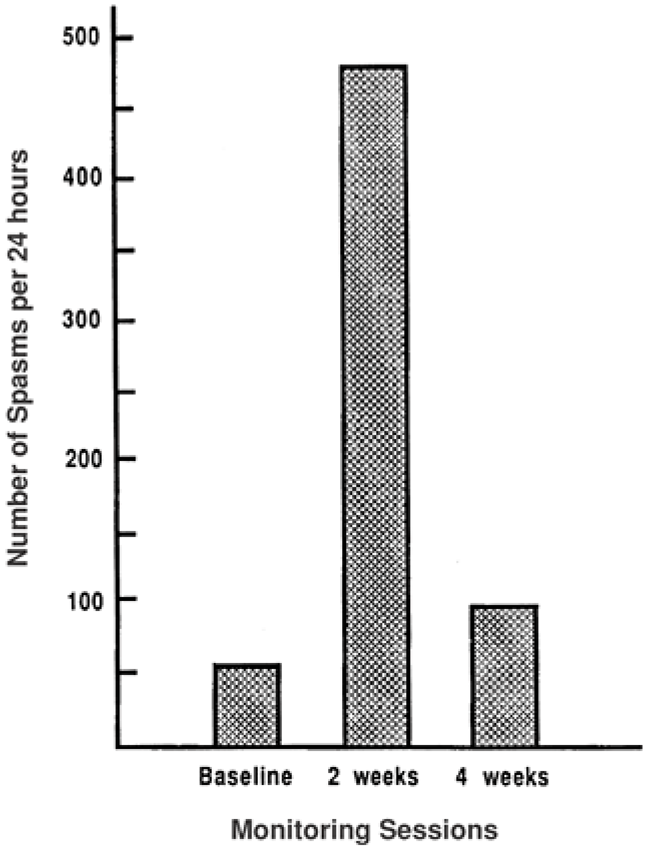

FIGURE 3. Variation in spasm frequency in a patient monitored at 2-week intervals.

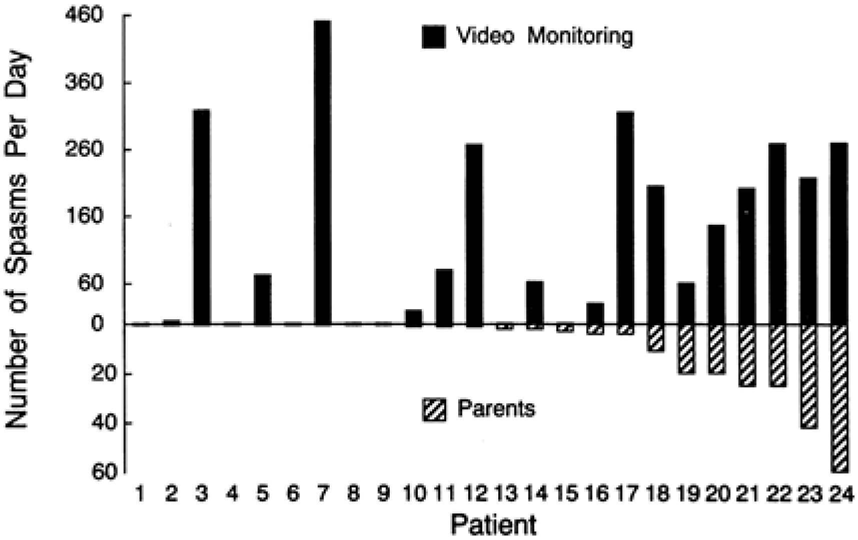

FIGURE 4. Spasm frequency after institution of ACTH or prednisone therapy: comparison of parents' estimates with 24-hour polygraphic/video monitoring.

- The natural history of many disorders that have been treated with ACTH and corticosteroids is poorly understood. For example, patients with infantile spasms or with the Landau-Kleffner syndrome may experience spontaneous remissions at various times following onset of the disorders. A retrospective study of infantile spasms[67] revealed a relatively linear rate of spontaneous remission, with 25% of patients experiencing spontaneous cessation of spasms within 12 months of onset (Fig. 2). Furthermore, in such disorders as infantile spasms,

Lennox-Gastaut syndrome, Landau-Kleffner syndrome, and various myoclonic epilepsies, seizure frequency varies tremendously over weeks and months. The variability of seizure frequency over time for a patient with infantile spasms[55] is demonstrated in FIGURE 3. Obviously, it is not possible to control for these two factors totally in any study of anticonvulsant efficacy in the disorders mentioned; however, they must always be considered in interpreting the results of any study reporting the effectiveness of ACTH, corticosteroids, or other agents in the treatment of these disorders.

- Very few well-controlled, blinded studies have evaluated the anticonvulsant efficacy of ACTH and corticosteroids, and these have been restricted to the disorder of infantile spasms (see the following paragraphs). Most studies either have been retrospective or have consisted of anecdotal reports.[36]
- The doses of ACTH and corticosteroids given, and the duration of treatment, have varied markedly. For example, doses of ACTH used to treat infantile spasms have ranged from <1 U/day to 180 U/day, and treatment duration has ranged from 1 week to more than 12 months.[36,92] Similar variations in doses of ACTH and corticosteroids and duration of treatment exist in studies of other seizure disorders.
- The study population is not always clearly defined. For example, some studies do not clearly separate patients with Lennox-Gastaut syndrome from those with other myoclonic epilepsies or infantile spasms.[1,36,92,154]
- Some investigators have treated epileptic patients with either ACTH or corticosteroids alone, whereas others have used both drugs in tandem, usually ACTH followed by corticosteroids.[36,77,80,92,96,99,119]
- The methods for determining response to ACTH and corticosteroid therapy have usually not been objective, or the means of determining response has not been stated.[36] Most studies reporting the effectiveness of ACTH and corticosteroids in various seizure disorders have relied primarily on the subjective observations of parents or other caretakers to determine therapeutic benefit. It has been documented by means of video electroencephalographic (V-EEG) monitoring that parents of infants with infantile spasms usually grossly underestimate the number of spasms their child is experiencing[55,57] (Fig. 4). Parents of children experiencing absence, myoclonic, atonic, and tonic seizures have similar difficulties in accurately determining seizure frequency.
- Appropriate criteria for determining response to therapy are not standardized and are often unspecified. For example, in the disorder of infantile spasms, some investigators have used total cessation of spasms as the definition of therapeutic response,[60,61,62,63,64] whereas others have used various graded-response paradigms.[36,92] Objective criteria for determining response in other disorders (e.g., Lennox-Gastaut syndrome) also remain to be established. Should response in the Lennox-Gastaut syndrome be defined in terms of seizure frequency only, or should drug effects on interictal epileptiform activity also be included? Until such objective criteria are established, the role of hormonal therapy, as well of as that of other agents used to treat these disorders, will remain controversial.

Infantile Spasms

Since the report in 1958 by Sorel and Dusaucy-Bauloye[157] that treatment of infantile spasms with ACTH results in the cessation of spasms and disappearance of the hypsarrhythmic EEG pattern, many reports have appeared concerning the treatment of this disorder using ACTH and corticosteroids. An in-depth review of this topic can be found in a recently published book by Frost and Hrachovy.[36] The therapeutic response to these agents can be divided into two categories—acute effects and long-term effects.

Acute effects.

During the past five decades, three basic opinions concerning the acute effects of ACTH and corticosteroids on spasm frequency and the hypsarrhythmic EEG pattern have evolved. Some individuals consider ACTH and corticosteroids to be equipotential, whereas others consider ACTH to be superior.[8,80,90,92,99,100,153,154,155,167] Still others believe that higher doses and longer durations of ACTH therapy[8,15,18,44,80,87,94,96,99,152,153,154] are superior to lower doses and shorter durations of therapy.[43,47,49,69,73,74,85,89,104,112,120,121,134,145,160,161,167,170,172] The most dramatic results have appeared in the reports by Snead et al.[153,154] and Kivity et al.,[80] in which 92% to 100% of patients treated with high-dose ACTH experienced cessation of spasms and disappearance of the hypsarrhythmic pattern. These results obtained with high-dose ACTH therapy far surpassed any previously reported. Unfortunately, most previous studies have suffered from many of the methodologic problems listed earlier, most importantly the lack of controlled, blinded trials and the lack of an objective means of assessing response.

Starting in the late 1970s, a series of controlled trials of ACTH and corticosteroids in the treatment of infantile spasms was performed by Hrachovy et al. in small numbers of patients. Serial, long-term polygraphic/video monitoring studies were utilized to determine objectively the acute response to therapy. In all studies, response was defined as cessation of spasms and disappearance of the hypsarrhythmic EEG pattern. The initial studies were aimed at comparing the relative efficacies of low-dose ACTH (20 to 30 U/day for 2 to 6 weeks) and prednisone (2 mg/kg/day for 2 to 6 weeks).[60,62,63,64] The results of these studies are as follows: (a) There was no significant difference in response to low-dose ACTH and prednisone; (b) patients who failed to respond to ACTH could respond to prednisone and vice versa; (c) approximately 60% of patients responded to low-dose ACTH, prednisone therapy, or both; (d) response to hormonal therapy usually occurred within 1 to 2 weeks of initiation of therapy in most patients, an observation reported by others;[36] (e) once a response was documented, hormonal therapy could be immediately discontinued, and the response maintained; (f) if a relapse occurred, a second course of ACTH or prednisone therapy was usually effective; (g) treatment lag and etiology were not useful predictors of response to hormonal therapy—patients with long treatment lags responded just as well as those with short ones, and symptomatic patients responded just as well as cryptogenic patients; (h) disappearance of the hypsarrhythmic EEG pattern could occur after ACTH or prednisone therapy, even though spasms continued; and (i) the side-effect profiles of low-dose ACTH and prednisone were similar.

Following completion of the studies of low-dose ACTH and prednisone therapy, a single-blind study of high-dose ACTH versus low-dose ACTH therapy in patients with infantile spasms was performed.[61] Patients receiving high-dose ACTH therapy were treated as follows: 150 U/m^2/day for 3 weeks, then 80 U/m^2/day for 2 weeks, then 80 U/m^2 every other day for 3 weeks, then 50 U/m^2/day for 1 week, with the dose tapered to none during a final 3-week period. Patients assigned to low-dose ACTH therapy received 20 to 30 U/day for 2 to 6 weeks. The results of this study were as follows: (a) No significant difference in response rates was noted between patients assigned to high-dose or low-dose ACTH therapy— 58% of patients treated with low-dose ACTH responded, versus 50% of those treated with high-dose ACTH; (b) no significant difference was noted in the number of normal EEG findings in patients who responded to high-dose versus low-dose ACTH therapy; (c) no significant difference was noted in the relapse rate between the two groups; and (d) the side effects seen in both treatment groups were similar, with the exception of hypertension, which occurred more frequently in the high-dose group.

In 1996, Baram et al.[8] reported the results of a controlled, blinded trial of high-dose ACTH (beginning dose 150 u/m^2/day) versus prednisone (2 mg/kg/day) utilizing V-EEG monitoring to determine response objectively. Of the patients treated with high-dose ACTH, 13 of 15 (87%) responded in comparison to 4 of 14 (29%) patients treated with prednisone.

Unfortunately, not only are the results of these controlled studies conflicting, but the numbers of patients in these studies are too small to reach meaningful conclusions. Thus, although ACTH and corticosteroids have been used to treat patients with infantile spasms for half a century, there remain major disagreements and conflicting views about the use of these agents. In 2004, committees of the American Academy of Neurology and the Child Neurology Society[103] published a practice parameter for the medical treatment of infantile spasms. These committees rigorously reviewed the scientific merit of the various agents used in the treatment of infantile spasms. As concerns the treatment of infantile spasms with ACTH and corticosteroids, the committee concluded that ACTH is probably effective in the short-term treatment of infantile spasms, but there was insufficient evidence to suggest an optimal dosage or duration of treatment with ACTH. Also, the committee determined that insufficient evidence existed that corticosteroids are effective in the treatment of infantile spasms.

The reported relapse rates for low-dose ACTH have ranged from 21% to 100%;[43,47,61,74,104,112,156,170] those for high-dose ACTH have ranged from 13% to 59%;[8,18,61,87,153,154] and those for prednisone have ranged from 9% to 100%.[21,74,82,126,154] However, the relapse rate in most studies is in the range of 25% to 33%.[36]

Many investigators have reported that treatment lag is not a useful predictor of acute response to therapy.[32,52,61,62,63,64,87,124,167,173] However, several authors[69,90,99,119,143,147,160] have observed better response rates in patients with short treatment lags (usually less than 1 month). Also, some investigators have reported that symptomatic patients responded as well as cryptogenic patients.[32,52,62,63,64,87,120,124,167,173] On the other hand, some authors have reported a better response in cryptogenic patients.[69,96,99,119,138,143,147,160]

Long-term effects.

The results of studies assessing long-term outcome in patients with infantile spasms following ACTH and corticosteroid therapy are just as varied as those regarding the acute effects of hormonal therapy. About 9% to 13% of patients with infantile spasms treated with lower doses and shorter durations of hormonal therapy have been reported to have normal development.[75,76,90,108,124,168,169] However, some investigators have found no difference in long-term outcomes in treated versus untreated patients.[34,36,75,90,92] Others have reported better outcomes in patients given higher doses and longer durations of ACTH therapy.[80,99,151] These studies are plagued by many of the problems described earlier. Primarily, most studies concerned with long-term outcome have been retrospective. Furthermore, the classification of patients (cryptogenic vs. symptomatic) has been highly variable from study to study, and many studies have not used such diagnostic tests as CT or MRI to aid in classifying a patient as symptomatic or cryptogenic.[36] A major problem inherent to all studies of

this disorder is the inability to predict long-term outcome accurately in most patients with infantile spasms at time of onset. Without such knowledge, it is extremely difficult to assess the effects of hormonal therapy.

Very few prospective studies evaluating long-term outcome in infantile spasms have been performed. One such study by Glaze et al.[40] that included patients treated with low-dose ACTH (20 to 30 U/day for 2 to 6 weeks) or prednisone (2 mg/kg/day for 2 to 6 weeks) revealed the following: (a) Only 5% of patients had a normal outcome; (b) severe or very severe impairment was observed in 67% of the patients; (c) no significant difference was noted between responders and nonresponders with respect to long-term outcome; (d) no significant difference was noted in long-term outcome between responders to ACTH and responders to prednisone; (e) no significant difference was noted in long-term outcome between patients treated within 5 weeks after onset of spasms and those treated more than 5 weeks after onset—early treatment of cryptogenic patients did not ensure a normal long-term outcome even if the patients responded to therapy; (f) cryptogenic patients had significantly better outcomes (40% were normal) than did symptomatic patients (5% were normal)—this is one consistent finding among all studies of long-term outcome in this disorder; (g) factors could not be identified that would allow prediction of which patients would have good outcomes and which would not, even in the cryptogenic group; and (h) other seizure types developed in roughly half the patients. However, no other seizures developed in cryptogenic patients who responded to hormonal therapy. In a subsequent prospective study in a small number of patients that compared high-dose ACTH (150 U/m^2/day) with lower doses of ACTH (20–30 U/day), there was no significant difference in developmental outcome between the two groups at an average follow-up period of 10 years.[13]

Considering the lack of controlled, prospective studies examining the effect of ACTH and corticosteroids on long-term outcome, it is not surprising that the committees of the American Academy of Neurology and the Child Neurology (see earlier) concluded in 2004 that the data were insufficient to make any recommendations regarding the use of ACTH or corticosteroids to improve long-term outcome in infantile spasms patients. Also, they concluded that the data were insufficient to indicate that early initiation of treatment with these agents would improve long-term outcome. Similar conclusions were reached by Frost and Hrachovy[36] in their review of the subject.

Recommended treatment regimen for infantile spasms.

A variety of therapeutic agents have been reported to be effective in the treatment of infantile spasms. If an agent is effective, the response usually occurs within the first few weeks of initiation of treatment. Thus, the key factor in treating these patients is to avoid unnecessarily prolonged treatment with ineffective agents. If one modality does not produce a response in a short time, it is withdrawn and a new trial is initiated using a new agent.[36] If hormonal therapy is chosen, either ACTH or corticosteroids may be used. If ACTH is used, a lower dose is recommended, because the current evidence does not indicate that higher doses of the drug produce better response rates, and adverse effects are more common with higher doses (see earlier discussion). Before institution of hormonal therapy, clinical evaluation (including CT, MRI, or both) should be performed, and a baseline EEG, including a sleep tracing, should be obtained. If ACTH is chosen, the initial dose is 20 U/day. After 2 weeks of ACTH therapy at 20 U/day, the EEG is repeated. If the patient shows a response (defined as total cessation of spasms and disappearance of the hypsarrhythmic pattern), ACTH is tapered and discontinued during a 1-week period. If the patient has not responded after 2 weeks of ACTH therapy, the dose is increased to 30 U/day, and treatment is continued at this dose for an additional 4 weeks, after which it is tapered and discontinued during a 1-week period. The EEG is repeated at this point. Patients who have responded to ACTH are followed in a routine clinical manner. If a relapse occurs later, a course of ACTH is repeated at the dose at which the initial response occurred. If a patient does not respond to ACTH and has not been treated with prednisone, prednisone can be given after ACTH has been discontinued for 1 week. If prednisone is administered, it should be given at a dose of 2 mg/kg/day. The follow-up is similar to that of patients receiving ACTH. If a patient shows a response after 2 weeks of therapy, prednisone is tapered and discontinued during a 1-week period, and the patient is followed routinely. If the patient has not responded after 2 weeks of prednisone therapy, the drug is continued at a dose of 2 mg/kg/day for an additional 4 weeks, after which it is tapered during a 1-week period and discontinued. Patients who have responded to prednisone are followed in a routine manner. If a relapse occurs, a course of prednisone is repeated. If the patient does not respond to prednisone and has not been treated with ACTH, ACTH is begun after prednisone therapy has been discontinued for 1 week.

Throughout the entire course of ACTH or prednisone therapy, the patient's blood pressure should be monitored closely, and serum electrolytes should be checked weekly. The patient also should be observed closely for signs of infection.

Synthetic ACTH and ACTH fragments.

Different formulations of ACTH are used throughout the world to treat infantile spasms patients. In the United States and some other countries, most physicians use natural ACTH, which is injected intramuscularly in gel (repository) form. In Japan and many other countries, synthetic preparations (typically $ACTH_{1-24}$) are used. There appears to be no difference in the therapeutic efficacy between the naturally occurring ACTH preparation and the various synthetic ACTH compounds.[36] Treatment of infantile spasms using certain fragments, $ACTH_{4-10}$ and $ACTH_{4-9}$, which are devoid of stimulating effects on the adrenal cortex, has been unsuccessful.[127,166]

Lennox-Gastaut Syndrome

ACTH and corticosteroids have been reported to be effective in a significant number of patients with the Lennox-Gastaut syndrome.[1,24,90,93,123,142,149,171] Doses of ACTH of up to 100 U/day and prednisone of up to 4 mg/kg/day were used in these studies. Duration of treatment has ranged from 10 days to many months. Although response rates of 40% to 60% have been reported, it is not clear which seizure types seen in Lennox-Gastaut patients are most responsive to ACTH or corticosteroid therapy, or how the EEG is affected by hormonal therapy. Also, it has been reported that the effects of hormonal therapy are transient and that relapses are common.[1] The marked variability in seizure frequency over time and the difficulty in assessing seizure frequency in patients with Lennox-Gastaut syndrome, as well as the lack of objective criteria for evaluating response, make the determination of antiepileptic efficacy in such patients extremely difficult.

Finally, if ACTH and corticosteroids are beneficial in stopping seizures and improving the EEG patterns of patients with Lennox-Gastaut syndrome, it is difficult to explain why the EEG and clinical features of Lennox-Gastaut syndrome develop in some patients with infantile spasms while they are being treated with ACTH or corticosteroids (R. A. Hrachovy, unpublished observations).

At present, the role of ACTH and corticosteroids in the treatment of Lennox-Gastaut syndrome remains uncertain. Current evidence indicates that hormonal therapy does not significantly alter the course of these patients.

Landau-Kleffner Syndrome

A handful of studies concerning the treatment of Landau-Kleffner syndrome with ACTH and corticosteroids have been published.[11,78,97,98,107,110,123,144,150,162] The reported efficacy is highly variable, ranging from no effect to reduction of seizure frequency and improvement in neuropsychologic function and language. The information on dosage in these studies is limited. In those studies in which the doses of prednisone were indicated, the initial daily dose ranged from 25 to 60 mg/day. The doses of ACTH used have not been provided.

Early treatment, initially high doses of steroids, and long duration of therapy (many months) have been identified as important factors leading to response and decreased rates of relapse.[97,107] However, the relatively few number of patients treated, the lack of controlled trials, and the markedly fluctuating course of patients with Landau-Kleffner syndrome make it difficult to determine if the clinical and EEG improvements reported are in fact attributable to steroid therapy. Further studies are needed to determine if ACTH and corticosteroids are effective in treating this disorder, and what treatment regimen is most effective.

Rasmussen Syndrome

Initial anecdotal reports of hormonal therapy in patients with Rasmussen syndrome were negative.[41,128] However, recent studies have been more encouraging. Dulac et al.[26] reported that all seven patients with epilepsia partialis continua secondary to Rasmussen syndrome initially responded after 1 to 18 months of high-dose corticosteroid therapy, consisting of 3 to 18 boluses of methylprednisolone (400 mg/m^2) during the first year and oral prednisone for 2 to 26 months. Only one of the seven patients achieved a “stable response” during the 2-year follow-up. The remainder had transient exacerbations of decreasing intensity (five patients); the final patient with epilepsia partialis continua showed increasing deficit. Hart et al.[48] reported that 10 of 17 patients (59%) with Rasmussen syndrome who were treated with steroids showed some reduction (25%–75%) in seizure frequency in the “short term.” Doses of prednisone used varied across patients. ACTH was used in one patient, but the dose was not provided. Some of the patients treated with steroids also received immunoglobulins. Only two patients showed prolonged benefit after steroid withdrawal. These authors attributed the somewhat better results reported by Dulac et al.[26] to the differences in the steroid regimen used. They also suggested that in “optimal doses,” steroids may modify the endpoint of the disease, and that the quality of life at that point may be superior to that after hemispherectomy.

At present, the real benefit (short-term and long-term) of steroid therapy for Rasmussen syndrome has not been established. The difficulties in performing blinded studies of therapy in this disorder are summarized by Hart et al.[48] Because the incidence of Rasmussen syndrome is very low, these authors recommend the establishment of a central registry and the use of standardized protocols in the assessment of the medical treatment of this disorder. The general recommendation for the treatment of Rasmussen syndrome by these investigators is an initial course of intravenous immunoglobulins. If no improvement is seen after 1 month of immunoglobulin therapy, a combination of intravenous methylprednisolone given at variable intervals during 3 years and oral prednisone for 1 to 2 years should be tried.

Specific recommendations concerning the treatment of Rasmussen syndrome with hormonal therapy cannot be made until further studies are completed.

Other Disorders

Isolated reports document the use of ACTH and cortico-steroids as being beneficial in patients with various other types of seizures, including absence,[37,83,111,154] generalized tonic–clonic,[23,83] myoclonic,[37,154] partial,[154] and status epile-pticus.[30,111] The information provided in these reports is insufficient to recommend the treatment of these seizure types with ACTH or corticosteroids.

Discontinuing the Drug

The information concerning when and how to discontinue ACTH and corticosteroids in the treatment of infantile spasms was presented earlier. Response criteria and optional duration of treatment for Lennox-Gastaut syndrome, Rasmussen syndrome, and Landau-Kleffner syndrome have not been established.

Summary and Conclusions

In summary, although ACTH and corticosteroids have been shown to be effective in the treatment of infantile spasms, their role in the treatment of other seizure disorders has yet to be determined. Side effects associated with hormonal therapy can range from mild and transitory to fatal; consequently, patients must be closely monitored. The mechanism by which ACTH and corticosteroids exert their antiepileptic effect remains to be elucidated.

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Chapter 145

Benzodiazepines

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Introduction

The benzodiazepines represent a clinically relevant class of compounds that possess a broad range of properties, including anticonvulsant efficacy. In 1965, diazepam was the first benzodiazepine used to treat status epilepticus (SE) in humans and, since then, several other benzodiazepines have entered the market.[29] Currently, benzodiazepines such as diazepam or lorazepam are drugs of first choice for emergency treatment of acute seizures, series of seizures, and initial treatment of SE.[56] More recently, buccal midazolam has been evaluated for emergency use in acute seizures, mainly in children.[44] In addition, a number of other benzodiazepines such as clobazam, clonazepam, clorazepate, and nitrazepam are in clinical use in various parts of the world, mostly as add-on medication for refractory epilepsy. However, sedation and hypersalivation at doses that are comparable to those that protect against seizures, and, importantly, loss of efficacy during prolonged treatment, have limited their usefulness. Earlier reviews are available.[29,57] This chapter outlines the chemistry, pharmacology (including clinical pharmacokinetics), efficacy, adverse effects, and clinical use of several benzodiazepines—clorazepate, clobazam, clonazepam, diazepam, lorazepam, midazolam, and nitrazepam—used in the treatment of epilepsy.

Chemical Structure, Formulations and Methods for Determination in Body Fluids

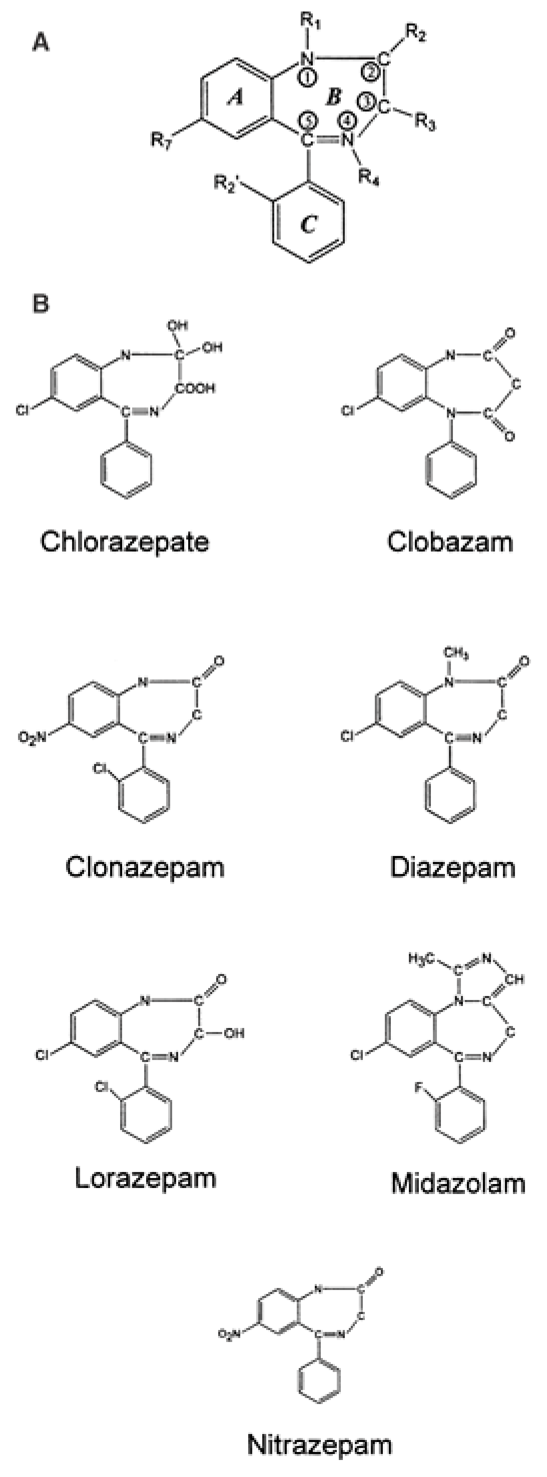
The term *benzodiazepine* refers to that central portion of the chemical structure comprising a benzene ring attached to a seven-membered diazepine ring (Fig. 1A). The majority of clinically important benzodiazepines contain a third ring (5-aryl substituent) and have nitrogen substitutions at the 1 and 4 positions of the diazepine ring (Fig. 1B); these are generally referred to as 1,4-benzodiazepines. Altering the positions of the two nitrogen atoms in the heterocyclic ring can confer similar anticonvulsant properties. An example is clobazam, a 1,5-benzodiazepine.[2,29] Both midazolam, a short-acting benzodiazepine, and flumazenil, an equally short-lived benzodiazepine competitive antagonist, have imidazole rings attached at position 1 of the diazepine ring, in contrast to other anticonvulsant benzodiazepines, which have hydrogen or an alkyl group in that position.[2]

Formulations

In many countries—with the notable exception of the United States—clobazam is available for oral administration as tablets but not available for intravenous or intramuscular injection. Clonazepam can be administered as tablets and drops and as an intravenous formulation. Clorazepate can be prescribed as tablets and slow-release capsules and, in some countries, as an intravenous and intramuscular formulation. Diazepam is administered by oral, intravenous, intramuscular, and rectal routes and is available as oral solution, tablets, a sustained-release capsule, a rectal suppository, a rectal solution, a rectal gel, and a parenteral formulation. Intramuscular injection of diazepam produces variable serum levels and is not a recommended route of administration.[57] Lorazepam is widely available as oral and sublingual tablets and as an intravenous and intramuscular formulation. Midazolam is in use as a tablet, syrup, and a parenteral formulation for buccal, oral, intranasal, and rectal routes. Nitrazepam is administered by oral, rectal, and intravenous and intramuscular routes.[2]

Methods for Determination of Benzodiazepines in Body Fluids

Assay methods are available for the determination of serum levels of various benzodiazepines, including gas and liquid chromatographic procedures.[2,29] However, as will be pointed out, their usefulness for guiding the treatment of epilepsy is limited, mainly because the dosage is usually titrated against immediate therapeutic effects, and the correlation of serum concentration to effect during chronic treatment is hampered by the development of tolerance to therapeutic and adverse effects of benzodiazepines.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Chlorazepate
Clobazam
Clonazepam
Diazepam
Lorazepam
Midazolam
Nitrazepam

FIGURE 1. A: The generic chemical structure of benzodiazepines. **B:** The chemical structure of common anticonvulsant benzodiazepines. Note that clobazam is a 1,5-benzodiazepine.

Pharmacology

Activity in Experimental Models of Seizures/Epilepsy

Benzodiazepines effectively block seizures induced by pentylenetetrazol, a potent noncompetitive antagonist at γ-aminobutyric acid $(GABA)_A$ receptors. Activity in this animal seizure model has been considered very predictive of drugs with potential clinical utility against myoclonic and absence seizures.[39] Benzodiazepines also block seizures induced by maximal electroshock model, which is used to screen possible antiepileptic drugs (AEDs) for the treatment of partial seizures with or without secondary generalization. In addition, the benzodiazepines have been shown to be effective in models of partial seizures induced by cortical lesions induced by a variety of agents, including alumina cream, cobalt, penicillin, and strychnine.[39] Finally, loss of efficacy during prolonged treatment with benzodiazepines has been shown in a number of experimental models of partial epilepsy, including amygdala kindling.[37]

Mechanisms of Action

The primary target of benzodiazepines is a postsynaptic receptor for the neutral amino acid GABA, the major inhibitory neurotransmitter in the central nervous system (CNS). GABA is released from presynaptic neurons and binds to at least two classes of receptors, $GABA_A$ and $GABA_B$ receptors, which are found on almost all cortical neurons.[40] It is well established that benzodiazepines have primary actions as anticonvulsants by interacting with $GABA_A$ receptors at the benzodiazepine binding site and allosterically modifying the GABA receptor currents to enhance inhibition.[40] Binding to the benzodiazepine recognition site results in enhancement of $GABA_A$ receptor current by increasing the frequency of the $GABA_A$ receptor opening without significantly affecting the mean open time or conductance of the channel.[40] This is in contrast to barbiturates, which increase the mean open time and burst duration of $GABA_A$ receptor channel openings without affecting frequency of channel opening.[40,51] It is important to recognize that benzodiazepines, unlike barbiturates, cannot directly activate the $GABA_A$ receptor in the absence of GABA, the endogenous ligand, even at very high concentrations.[40] However, advances in understanding the molecular biology of GABA receptors demonstrate that the GABA receptor is made up of many different subunits (α, β, γ, δ, ρ) with different subtypes in many combinations; it is undergoing continual characterization.[40] $GABA_A$ receptors containing the α_1 subunit are an important target for protection of seizures by benzodiazepines.[51] The effects of benzodiazepines on tonic $GABA_A$ receptor currents, which originate from GABA acting on extrasynaptic receptors, may be important for their action.[51] The antiabsence activity of benzodiazepines probably results from their ability to interfere with hypersynchronous activity in the thalamocortical circuitry that is believed to underlie the 3-Hz spike-and-wave activity that is characteristic of generalized absence seizures.[51] More specifically, benzodiazepines are thought to reduce the inhibitory output of the reticular neurons by effects on benzodiazepine-sensitive α_3-containing $GABA_A$ receptors and therefore prevent absence seizure activity.[51]

It is of clinical interest that the multiple GABA receptor isoforms described here have a differential sensitivity to benzodiazepine receptor ligands that may have different clinical actions. In the future, it may be possible to develop benzodiazepine receptor ligands that have selective anticonvulsant actions without undesirable side effects. One such side effect is the development of tolerance to effect during prolonged treatment. Although the exact mechanism of tolerance is not clear, it has been suggested to include a reduction in the allosteric interactions between the $GABA_A$ receptors at the benzodiazepine recognition site and changes in the subunit pattern.[49] Because tolerance to adverse effects such as sedation sets in within days, whereas tolerance to efficacy takes weeks to months to fully develop, the mechanisms for tolerance to side effects and efficacy may differ. However, some of the clinical effects of benzodiazepines in experimental animals cannot be explained simply by their potentiation of GABA-activated currents,[29] and benzodiazepines may act on targets other than the GABA$_A$ receptor. Through unknown mechanisms, benzodiazepines may produce elevations of GABA levels in the cerebrospinal fluid.[38] At high concentrations, especially those that may be achieved in the treatment of SE, benzodiazepines may have significant effects on inhibiting currents carried by voltage-gated sodium and, to a lesser extent, calcium channels.[40]

Table 1 Clinical pharmacokinetics of benzodiazepines

AED	T_{max} (h)	V (L/Kg)	Fraction bound (%)	Half-life (h)	Clearance (m/min/kg)
Clobazam	1.3-1.7	0.87-1.83	82-90	16.6–48.6, DMC 36–46	0.36-0.63
Clonazepam	1-4	2.1±0.6	86	17–56	94-125
Clorazepate	PO: 0.5-2, IM: 2.7–11	0.7-2.2	96-98	40–130	0.18-0.27
Diazepam	PO: 30–90 min, IM: 30–60 min Rectal gel: 10-30 min	0.95-2.0	96-99 DMD 97	28-54	15-35
Lorazepam	PO: 2.4 ±0.3 SL: 2.3±0.7 IM: 1.2 ±0.3	0.85-1.5	93.2±1.8	7–26	0.91-1.76
Midazolam	PO: 0.5–0.97 IM: 0.24–0.51	0.7-1.7	96	1.36–4	6.4-11.1
Nitrazepam	1.35–2.47	2.5-2.9	85-88	21–40	1.51-1.91

(DMC, desmethylclobazam; DMD, desmethyldiazepam; IM, intramuscular; PO, oral, SL, sublingual; T_{max} time of peak concentration; V, volume of distribution; mean ± standard deviation. Modified from Anderson GD, Miller JW. Benzodiazepines. Chemistry, Biotransformation and Pharmacokinetics. In: Levy R, Mattson R, Meldrum B, Perucca E, eds. *Antiepileptic Drugs*, 5th ed. Philadelphia: Lippincott Williams & Wilkins;2002:187-205, with permission.)

Clinical Pharmacokinetics

Absorption

In general, the benzodiazepines are absorbed rapidly, with peak concentrations after oral use ranging from 0.5 to 4 hours. The absorption of orally administered benzodiazepines is 80% or more.[2]

Although clorazepate is soluble and well absorbed orally, the acidic gastric environment is bypassed during intravenous administration, resulting in less production of the active metabolite desmethyldiazepam. Thus, intravenous administration is not useful in the treatment of SE.[2]

Within tens of seconds after intravenous administration, the anticonvulsant effect of diazepam can be seen on an

electroencephalogram (EEG) as suppression of epileptiform discharges in humans.[57] On a cautionary note, intravenous diazepam solution may precipitate when mixed with saline solution, and it may also adsorb to polyvinyl tubing.[29,56] If left diluted in an intravenous fluid bag for 24 hours, diazepam is reported to lose 95% of its intrinsic activity;[29] thus, fresh solutions should be made within 6 hours of use. Rectal delivery of diazepam results in higher and earlier peak blood concentrations compared with either oral or intramuscular routes.

Lorazepam can be administered orally, sublingually, and intravenously. It is rapidly distributed into the brain, and peak levels are attained within 5 minutes.[2] Human studies demonstrate sedative effects and EEG sleep spindles within 0.5 to 4 minutes of infusion of doses ranging between 2 and 5 mg.[29] The ability to administer lorazepam sublingually is attractive when intravenous access is not readily available.[24] Sublingual use of lorazepam is easier to administer, maintains privacy, and is seen as more dignified than rectal application of diazepam. Some physicians recommend it instead of rectal diazepam for prevention of seizure recurrence. Sublingual lorazepam was successful in controlling serial seizures in ten children.[69]

Plasma Protein Binding and Distribution

The various benzodiazepines are fairly highly protein-bound, although it is the free (unbound) benzodiazepine that is active (Table 1). The benzodiazepines as a group are lipophilic and have a high volume of distribution. In obese patients, the volume of distribution is larger.[29] Some studies show a larger volume of distribution of benzodiazepines in female patients compared with that in male patients, which is thought to be a reflection of the proportion of adipose tissue.[29] Brain levels of diazepam are nearly double that of serum concentrations, and appear to be highest in brainstem and white matter compared with gray matter.[29] Protein binding is reduced in neonates and patients with hepatic disease. The mean apparent volume of distribution is approximately 1.1 L/kg (range, 0.8 to 2.6 L/kg), and is generally higher in young children.[29] Renal or hepatic disease results in a decreased plasma clearance of desmethyldiazepam. Diazepam distributes rapidly throughout lipid tissues and quickly crosses the blood–brain barrier (BBB).[29] Within minutes, however, brain concentrations decline swiftly as diazepam is redistributed to other fatty tissues, resulting in a short distribution half-life ($t\alpha$, approximately 1 hour).[29,57] After a single bolus injection, the concentration of free (active) diazepam in the brain may fall below therapeutic levels within half an hour.[57]

Metabolism

All the anticonvulsant benzodiazepines, except for lorazepam and clonazepam, are metabolized by hepatic microsomal enzymes to pharmacologically active demethylated and hydroxylated compounds[26,29] (Fig. 2). These metabolites are subsequently glucuronidated to inactive, more water-soluble compounds that are readily excreted in the urine. The active metabolites are often very important; for example, clorazepate is essentially a prodrug for its active metabolite, desmethyldiazepam. Clobazam has up to 14 metabolites, but the main active metabolite is desmethylclobazam, also called norclobazam. Desmethylclobazam has comparable affinity for the brain benzodiazepine receptor and also has antiepileptic activity.[57] After long-term administration, at steady state the serum concentration of desmethylclobazam in most studies is eight to 20 times higher than that of clobazam.[29] Clobazam and its metabolite desmethylclobazam both have anticonvulsant properties, but desmethylclobazam is only one-fifth as potent as the parent compound.[29] Because the ratio of plasma levels of the metabolite desmethylclobazam to those of the parent drug is about 10:1, and because the metabolite also has a longer half-life, the anticonvulsant property may be more attributable to desmethylclobazam than to clobazam.

Clonazepam undergoes nitroreduction to 7-aminoclona-zepam, followed by acetylation to 7-acetamidoclonazepam, but neither metabolite appears to have clinically important pharmacologic activity.[25] A major metabolic pathway for clonazepam involves acetylation. Rapid acetylators are more likely than slow acetylators to require higher doses.

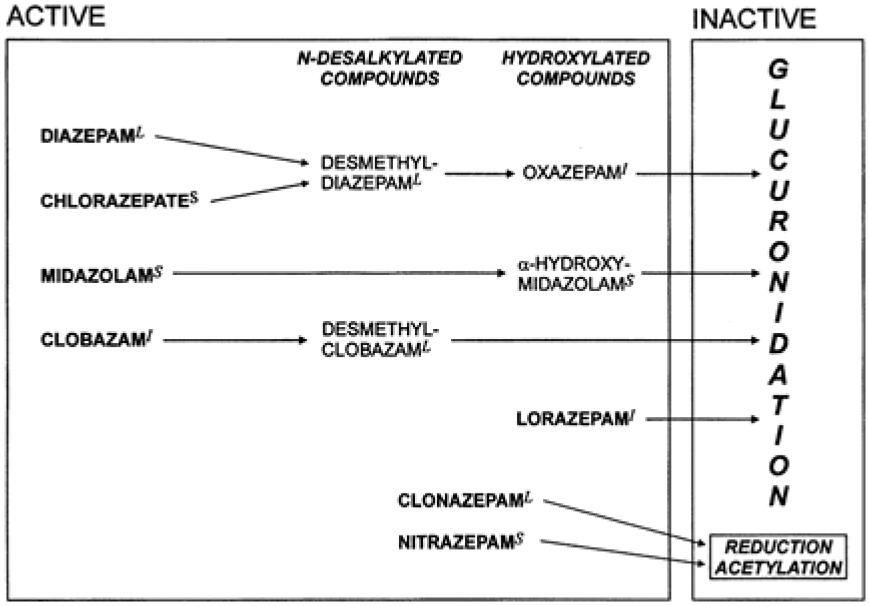

FIGURE 2. The metabolism and biotransformation of anticonvulsant benzodiazepines.

Clorazepate is a prodrug and exerts its effects through its active metabolite, desmethyldiazepam. Clorazepate undergoes complete transformation (100%) to desmethyldiazepam.[29] Desmethyldiazepam is also the main metabolite of diazepam

(see section on diazepam for a description of its characteristics). Clorazepate has intrinsic anticonvulsant activity, but this is small compared with that of desmethyldiazepam. Clorazepate is decarboxylated to desmethyldiazepam mainly in the stomach and bloodstream. The decarboxylation rate of clorazepate to desmethyldiazepam in the stomach is pH-dependent, with a lower pH resulting in a faster rate of conversion. There is a relatively instantaneous breakdown of clorazepate to desmethyldiazepam at a pH of 4 (90% at 10 minutes and 97% at 1 hour).[29] Desmethyldiazepam rapidly crosses the BBB. Desmethyldiazepam is hydroxylated to oxazepam, which is conjugated fairly rapidly and excreted; thus, desmethyldiazepam has no active metabolites.

Diazepam is biotransformed by hepatic microsomal enzymes in two principal steps: initial demethylation to desmethyldiazepam, followed by hydroxylation to oxazepam (see Fig. 2). Oxazepam is then conjugated to glucuronide, producing an inactive metabolite that is largely excreted in the urine.

Desmethyldiazepam, which is also an active metabolite of clorazepate (see section on clorazepate), has one-third the anticonvulsant potency of its parent compound, diazepam.[21] Biotransformation is also age-dependent, with limited demethylation and hydroxylation beginning as early as the 13th week of gestation, and enzymatic capacity increases steadily to maturity during the first few years of life.

Lorazepam is rapidly converted by hepatic metabolism to a glucuronide through conjugation at the 3-hydroxyl portion of the seven-membered diazepine ring.[28] More than 75% of the drug is converted to the glucuronide and excreted in the urine. The glucuronide is an inactive metabolite and does not have any toxic or antiepileptic effects. Two minor metabolites have no significant toxic or antiepileptic activity.[28] Hepatic failure results in the accumulation and reduced clearance of the parent drug, lorazepam, resulting in prolongation of the elimination half-life of lorazepam by 50%.[28] Renal failure does not affect clearance of the parent drug; however, it causes accumulation and reduced clearance of the glucuronide metabolite, but no additional toxicity.[28,29]

Midazolam metabolism occurs by oxidation of the imidazole ring, mostly to 1-hydroxymidazolam, which has about 10% of the biologic activity of midazolam and an elimination half-life of 1 hour.[2]

The major metabolic pathway of nitrazepam involves hepatic nitroreduction, with 7-aminonitrazepam and 7-acetami-nonitrazepam being the principal metabolites. The metabolites are inactive and are excreted renally. Only about 1% of the unchanged nitrazepam shows up in the urine.[29] Glucuronidation is less affected by aging or hepatic disease than demethylation or hydroxylation. Thus, lorazepam and midazolam would be preferable among benzodiazepines for elderly patients or individuals with cirrhosis. Nevertheless, caution must always be exercised in prescribing drugs to older patients, who have a generally diminished volume of distribution and decreased metabolism.[22]

Elimination

Clonazepam and clobazam and its metabolite desmethylclobazam are slowly eliminated, with a half-life of 20 to 56 hours (see Table 1). Because of its long half-life, alternate-day administration of clonazepam or clobazam is possible and has been suggested to reduce tolerance without sacrificing seizure control. Because of the long half-life of desmethyldiazepam, clorazepate can be given once a day, but divided doses decrease the likelihood of toxicity and allow for more stable steady-state levels than once-a-day dosing.[66] Clearance of unbound desmethyldiazepam was reduced in renal failure, although the free fraction was increased and the elimination half-life (tß) was shortened compared with those of healthy controls, highlighting the complex nature of drug pharmacokinetics in certain disease states.[29] Severe liver disease seems to prolong the half-life of desmethyldiazepam.

The tß of diazepam ranges from 1 to 2 days in healthy volunteers and is age-dependent—shorter in infants and children, and prolonged in premature infants and the elderly.[57] Desmethyldiazepam has a much longer tß than diazepam, because its formation depends on the continued redistribution of diazepam from peripheral to central compartments, and back again to the periphery. Thus, the tß for desmethyldiazepam is longer with administration of diazepam than of clorazepate, a prodrug completely converted to desmethyldiazepam. This results in a greater accumulation of desmethyldiazepam than diazepam in both plasma and cerebrospinal fluid during long-term treatment.[29]

For clinical use, the duration of effect of various benzodiazepines is an important variable. The “long-acting” agents, such as clobazam, clorazepate, and lorazepam, have half-lives longer than 24 hours and produce active metabolites;

the “intermediate-acting” benzodiazepines, such as nitrazepam and clonazepam, have half-lives shorter than 24 hours and do not produce active metabolites; there are also “short-acting” agents, such as midazolam.[26] Two factors must be taken into consideration regarding duration of effect: distribution half-life (tα) and tß. During acute administration, as in the treatment of SE, the rates of absorption and distribution are important, whereas during long-term therapy, in which distribution is complete, the tß is more critical, because it largely determines steady-state serum levels of a drug. This principle is best illustrated by the clinical use of diazepam and lorazepam. Oral diazepam has a short tα (approximately 1 hour) but a long tß (approximately 40 hours); furthermore, the major active metabolite, desmethyldiazepam, prolongs the tß to 100 hours or more. The net result after a single dose, because of rapid distribution, is a short duration of action. After repeated doses, diazepam and its metabolites potentially accumulate in the body. Oral lorazepam, on the other hand, has a longer tα (1.5 hours) than diazepam but a shorter tß (14 hours), and it produces no active metabolites.[23] Thus, compared with diazepam, a single dose of lorazepam leads to a longer lasting clinical effect, and repeated doses of lorazepam are less likely to produce very high levels throughout the body.

Relationship Between Plasma Concentration and Effects (Including Value of Therapeutic Drug Monitoring)

Levels of each benzodiazepine can be obtained, but therapeutic levels for most drugs are not clearly defined, because wide ranges are possible, and these have not been well defined according to seizure type and age. The development of tachyphylaxis during acute administration of repeated doses and the onset of tolerance during prolonged treatment result in a relatively poor correlation between plasma levels and efficacy and side effects, limiting the usefulness of therapeutic drug monitoring. Furthermore, the means to obtain benzodiazepine levels rapidly is not always readily available.

Efficacy

Emergency Treatment

Clonazepam is still used widely in the treatment of various forms of SE (Table 2). Its indications are the same as for diazepam, and its effectiveness is similar.[60] It can be given intravenously or as oral and rectal solution. A few drops of the solution are swallowed as a last resort by some patients anxious to control incipient seizures at home or when out of the house. *Diazepam* was the first benzodiazepine used to treat generalized convulsive SE, and for many years it has been the initial drug of choice in arresting SE.[29,57] Diazepam is most widely used in the treatment of SE, both convulsive and nonconvulsive. Early reports soon after the introduction of diazepam into clinical use provided spectacular results in a large majority of patients with severe epilepsy.[29,57] However, the reported efficacy of diazepam in arresting different forms of SE varies widely across many studies (75%–93%). Diazepam appears to be more effective against partial seizures (simple or complex) than generalized seizures.[29,57] In contrast, SE arising in the context of certain childhood encephalopathic epilepsies responds less favorably to diazepam.[60] The presence of structural brain lesions, an increased susceptibility to seizures, or both in children may account in part for this age-related difference.[60] Although a single intravenous bolus of 10 to 20 mg (in adults), given at a rate of 2 to 5 mg/min, can stop various types of SE in more than 80% of patients within 5 to 10 minutes, the relapse rate is high (>50%) among initial responders.[57,60] This finding, not unexpected given the pharmacokinetics of diazepam, led to the development of protocols for continuous intravenous infusion, with recommended target serum levels of between 200 and 800 ng/L.[17] The rapid development of tolerance, lack of consistent efficacy, uncertainty of long-term complications, and requirement for intensive monitoring render this approach less than desirable.[60] At present, with safer alternatives available, continuous intravenous infusion of diazepam as a treatment for SE has largely fallen out of favor.

The short duration of effect of diazepam prompted studies of the combined use of diazepam and phenytoin (15 to 20 mg/kg), which has a slower onset but a longer-lasting effect, to maintain seizure control and prevent relapse of SE.[60] Of note, diazepam and phenytoin cannot be infused through the same intravenous line, because crystallization may occur, although this may not happen with fosphenytoin, a water-soluble prodrug of phenytoin.[29] Intravenous diazepam, rather than magnesium sulfate, may be the preferred anticonvulsant agent to treat initial preeclamptic seizures.[19] Rectal administration of diazepam gel (0.5–1.0 mg/kg; maximum, 20 mg) has been shown to be effective and safe in stopping serial seizures, both in children and adults. Between 55% and 71% of patients remained seizure-free for 12 hours after administration of rectal gel, which was statistically significantly different from 23% to 29% reported for placebo.[12,13,18] Sedation is the most common side effect, occurring in approximately one-quarter of patients, and the risk of respiratory depression is lower than with intravenous use of diazepam.[48] One further advantage of rectal diazepam is that treatment can be administered by caretakers in a nonmedical setting. Rectal diazepam has also been studied as prophylaxis of febrile seizures (FS), with conflicting reports of its efficacy.[57]

Table 2 Clinical use of benzodiazepines

Drug	Clinical use	Main advantages	Main disadvantages
Clobazam	Second-line adjunctive therapy for refractory partial and generalized seizures, intermittent therapy, nonconvulsive SE	Highly effective, may be better tolerated than other benzodiazepines; rapid onset of action	Tolerance in 30%-50%, withdrawal problems
Clonazepam	Second-line adjunctive therapy in partial and generalized seizures (especially absence and myoclonic seizures), Lennox-Gastaut syndrome, and the premonitory stage and early status epilepticus, second-line for established status	Useful second-line adjunctive drug	Strong sedation, hypersalivation in some patients, tolerance
Diazepam	First-line treatment for the premonitory and early stage of SE (intravenous, bolus or rectal solution). Second-line for established status (intravenous infusion), nonconvulsive SE. Prophylaxis of FS. Home treatment of acute repetitive seizures (rectal solution or gel)	Highly effective, rapid onset of action, several methods of administration	Sedation, tolerance, withdrawal problems
Lorazepam	First-line treatment for the early stage of SE (intravenous bolus)	Longer duration of action than diazepam, can be repeated often, rate of injection not critical	Sedation, frequent and rapid development of tolerance and tachyphylaxis
Midazolam	Second-line treatment for the early stage of SE (IM, intravenous bolus, rectal solution)	Effective, rapid onset of action, can be given intramuscularly	Collapse of respiratory pathways, sedation
Nitrazepam	Second- to third-line adjunctive therapy in partial and generalized seizures (especially myoclonic	Last resort for severe childhood epilepsies	Severe sedation and muscular hypotonia in some patients

seizures, infantile spasms)

(Modified from Schmidt D. Benzodiazepines: Diazepam. In: Levy RH, Mattson RH, Meldrum BS, eds. *Antiepileptic Drugs,* 4th ed. New York: Raven Press;1995:705-724.) Preference may vary, and the list of clinical use is not exhaustive (see text).

Clinical studies of *lorazepam* in SE since the mid-1970s have long confirmed that its anticonvulsant effect is rapid and prolonged. The Epilepsy Foundation of America Working Group on SE, which summarized the data comparing the four major drugs used to stop SE, reported an average range of 6 to 10 minutes to stop status with lorazepam.[20] In 1983, Leppik et al.[36] compared lorazepam with diazepam and found that the median time for lorazepam to stop clinical SE was 3 minutes (range, 0–15 minutes). As initial treatment, 4 mg of lorazepam was effective in 78% of patients, versus 58% with 10 mg of diazepam. The difference in efficacy, however, between the two drugs was not statistically significant. More patients required a second dose of diazepam, but not a second dose of lorazepam. Appleton et al.[3] studied 102 children and found that lorazepam was superior to diazepam in children with acute convulsions of SE. A single dose of lorazepam was effective in terminating seizures in 76% of cases, versus 51% for diazepam. The recurrence rate of seizures or status was significantly lower in the lorazepam group.[3] In a comparison of 2 mg intravenous lorazepam, 5 mg intravenous diazepam, and placebo for the out-of-hospital treatment of SE, both drugs were safe and more effective than placebo when administered by paramedics in adults with prolonged or repetitive generalized convulsive seizures.[1] An identical second injection was given if needed. SE had been terminated in more patients treated with lorazepam (59%) or diazepam (42%) than patients given placebo (21%). The odds ratio for termination of SE at arrival was 1.9 (95%; confidence interval, 0.8 to 4.4) in the lorazepam group as compared to the diazepam group. The rates of respiratory or circulatory complications after the study treatment had been administered were 10.6% for the lorazepam group, 10.3% for the diazepam group, and 22.5% for the placebo group. The authors concluded that lorazepam was likely to be a better therapy than diazepam for paramedic treatment of out-of-hospital SE in adults. The lower recurrence

rate of SE with lorazepam versus diazepam is thought to be the consequence of its longer tα within the brain, and the more extensive redistribution of diazepam within lipid stores.[15,60] The effective duration of diazepam is only 15 to 30 minutes, versus 12 to 24 hours for lorazepam.[20] Thus, despite the slower penetration of lorazepam across the blood–brain barrier (BBB) compared with diazepam (6–10 minutes vs. 3–6 minutes), lorazepam may be preferable for its longer duration of action.[29]

The effectiveness of intravenous lorazepam versus intravenous phenytoin has also been studied. Treiman et al.[63] reported the results of a randomized open study of lorazepam versus phenytoin, and found that lorazepam stopped status significantly faster than phenytoin. Further, lorazepam was effective as a single initial agent in 79% of patients, whereas phenytoin was effective in only 56%. There was a slightly higher recurrence rate in patients treated with lorazepam than in those treated with phenytoin, which has led Treiman et al. to recommend adjunctive treatment with phenytoin within 24 hours of starting lorazepam treatment.[63] How rapidly a drug controls status may be as critical as its efficacy in stopping status. The time required to stop status is a major determinant in the morbidity and mortality of status.[60] Therefore, the rapidity with which lorazepam stops status gives it a profound theoretical and clinical advantage over phenytoin (see Table 3 for recommended dosages).

The use of high-dose lorazepam has been reported in a limited number of patients with refractory SE. Labar et al.[32] reported that in nine patients with refractory SE, lorazepam in doses of up to 0.3 to 9 mg/h as a continuous infusion was used effectively without causing significant arterial hypotension.[32] They speculate that lorazepam may be an alternative to high-dose barbiturates, which can cause significant hypotension. Lorazepam in a dose of 0.1 mg/kg has been suggested as the drug of first choice for terminating SE.[42]

Table 3 Dosing recommendations

Drug	Dosing recommendations
Clobazam	Oral: Children: 0.87 mg/kg (SD, ±0.6), Adults: 30.8 mg (SD, ±16.7), Mostly: 10–20 mg/day
Clonazepam	Oral: Starting dose: 0.25 mg, increase to 0.5, up to 4.0 mg. Children: 1–3 mg/day; IV: 1 mg bolus injection over 1 min in adults, and 250–500 µg in children. IM injection of as low as 0.02 mg/kg in children[44]
Clorazepate	Starting dose of 0.3 mg/kg/day increasing no faster than once a week to avoid sedative effects. Chronic dose between 0.4 and 3 mg/kg/day. Because of more rapid metabolism, children are dosed at the higher end of this range and average adult doses are 0.5–1 mg/kg/day.
Diazepam	IV: Out of hospital: single IV bolus of 10–20 mg (in adults), given at a rate of 2–5 mg/min, 0.25–0.5 mg/kg in children at a rate of 1–5 mg/min. ICU: 20 mg, 2 mg/kg/day infusion. Children: 0.2–0.3 mg/kg/day, maximum: 20 mg. Rectal: diazepam gel: 0.5–1.0 mg/kg; maximum 20 mg in adults and children.[24], [25], [26], [27] Adults: 10–20 mg; children: age 2–5: 0.5 mg/kg; age 6–10: 0.3 mg/kg; 12 years and older: 0.2 mg/kg (given over 2–5 min).
Lorazepam	IV bolus of 0.07–0.1 mg/kg, usually 4 mg, in adults, repeated after 10 minutes if necessary; in children a bolus of 0.1 mg/kg is recommended. The rate of injection not more than 1 mg/min. IV infusion with a loading dose of 0.2 mg/kg and an infusion rate of 0.08 to 0.39 mg/kg per hour.[60] Sublingual: 0.05 mg/kg-0.15 mg/kg in children.[13]
Midazolam	IV bolus of 0.1–0.3 mg/kg, at a rate not exceeding 2 mg/min, which can also be repeated once. Continuous IV infusion: loading dose of 0.2 mg/kg and an infusion rate of 0.08–0.39 mg/kg/hour; IM: 5–10 mg adults, 0.15–0.3 mg/kg children, can be repeated once. Buccal: instillation of 10 mg can be given by catheter and syringe in children and adults. Intranasal: 0.2–0.3 mg/kg in a 5 mg/mL ampoule dripped directly into the nostrils, over 3 min in children, over 5 min in adults.
Nitrazepam	Oral: adults: <0.5 mg/kg/day; children: up to 1 mg/kg/day. Usually 1.25–10 mg/day.

(Modified from references 12, 13, 16, 18, 29, 31, 44, 57, 67, and 69, with permission.)

Sublingual lorazepam was successful in controlling serial seizures in ten children.[69] The effective dose is from about 0.05 mg/kg to 0.15 mg/kg.[69] Side effects were minimal and consisted of drowsiness, unsteadiness, nausea, and hyperactivity.

Sublingual lorazepam appears to be an easy and effective way to treat serial seizures at home.[69]

Midazolam, as an intravenous bolus, intramuscular, intranasal or rectal solution, has been used as an alternative to diazepam or lorazepam during management of prolonged seizures, of early SE, and the premonitory stage of SE. It is more water soluble than diazepam and is rapidly and completely absorbed after intramuscular, nasal, and buccal administration.[29] Treatment of refractory generalized SE with continuous infusion of midazolam has been described in clinical observations of adults and children.[45,46] However, loss of initial efficacy was reported in many patients with refractory nonconvulsive SE receiving prolonged intravenous infusion of midazolam.[14] Midazolam, when administered as an intravenous bolus and subsequent continuous infusion, has controlled EEG-confirmed neonatal seizures with no response to phenobarbital.[11] In a small study of patients with refractory SE, midazolam, administered with an intravenous bolus and followed by an infusion, and intravenous propofol did not differ in clinical and EEG seizure control.[50] As pointed out above, midazolam solution is rapidly absorbed after buccal and nasal instillation. Buccal midazolam was at least as effective as rectal diazepam in the acute treatment of prolonged seizures lasting more than 5 minutes.[59] The authors suggested that buccal administration is more socially acceptable and convenient, particularly for treatment of long seizures that occur outside the hospital setting.[59] Midazolam nasal spray appears to be as effective as diazepam rectal solution in the acute treatment of seizure exacerbations.[65] Furthermore, most patients and caregivers preferred the nasal spray because of the ease of administration and social acceptability, including protection of privacy.[42,65] Intranasal midazolam has been shown to be useful in a small study of first-aid treatment of acute seizures in pediatric community settings.[27] Intranasal midazolam was compared with intravenous diazepam in children with SE in a hospital setting.[41] Although intranasal midazolam was safe and as effective as diazepam, seizure control was more rapidly achieved with diazepam.[41] In a small randomized study of children with FS, intranasal midazolam controlled seizures later than diazepam administered intravenously.[35] However, for obvious ethical reasons, no placebo control group was available; thus spontaneous remission of FS may have occurred in both arms of treatment, at least in some patients. Intranasal midazolam can be used when intravenous administration is inconvenient or not possible.

Chronic Treatment

Clobazam has been shown in a large Canadian randomized controlled trial to be an effective anticonvulsant for monotherapy of previously untreated children with partial-onset seizures, with a similar efficacy compared to phenytoin or carbamazepine. Phenytoin and carbamazepine induced more biologic side effects, such as rash, whereas clobazam induced slightly more behavioral side effects.[7,10] Tolerance to effect, according to the authors' definition, developed in 7.5% of patients receiving clobazam, 4.2% with carbamazepine, and 6.7% with phenytoin.[10] As shown in randomized trials, clobazam is also efficacious when used as add-on treatment for refractory partial epilepsy in children and adults,[30,58] and intermittent clobazam therapy may be useful for treatment of FS.[52] The Canadian Clobazam Cooperative Group performed the largest single study, comprising 877 epileptic patients,

both children and adults, with all types of seizures—atypical absence, myoclonic seizures, Lennox-Gastaut syndrome, and generalized tonic–clonic seizures.[9] More than half the patients became seizure-free or had a greater than 50% reduction in seizure frequency.[9]

Clonazepam add-on treatment has shown efficacy in a number of small randomized trials performed during the 1970s and 1980s against many types of seizures, including both partial and generalized seizures in all age groups, both as add-on treatment[29] or as monotherapy for previously untreated patients with absence seizures or partial seizures.[29] Clonazepam is an efficacious AED for adjunctive therapy of generalized absence and myoclonic seizures and also for partial seizures. However, due to sedation, tolerance, problems during withdrawal, and hypersalivation, it is increasingly used as a second- or third-line adjunctive drug only when better-tolerated adjunctive AEDs have not been helpful. It has been evaluated in single-arm studies in partial and generalized epilepsy, and the effects have generally been modest. It has been used in benign rolandic epilepsy and also in epilepsia partialis continua. In the generalized epilepsies, its effectiveness is similar to that of ethosuximide for absence seizures,[55] and it can be useful in myoclonic seizures, such as in juvenile myoclonic epilepsy and Lennox-Gastaut syndrome.[54] When given as a single intramuscular injection of as low as 0.02 mg/kg body weight in children, clonazepam reduced epileptiform activity in the EEG and reduced partial and generalized seizures.[16] This interesting finding suggests that lower than previously considered dosages of clonazepam may be effective. Clonazepam is also useful for bridge therapy while AEDs are changed or withdrawn.[53]

Sharing the fate of oral diazepam, *clorazepate*, a prodrug that is converted to the active AED desmethyldiazepam, is only rarely used for the treatment of epilepsy.[29] Early clinical studies of clorazepate therapy in epilepsy from the 1980s suggested that it may be useful as add-on treatment for absence, atonic, myoclonic, and partial seizures.[29]

Oral *diazepam* is rarely used, and not recommended for chronic treatment of epilepsy, as reviewed by Schmidt.[57] Controlled trials during the 1970s showed that diazepam is less effective than phenytoin or phenobarbital for treatment of generalized tonic-clonic seizures and about as effective as pheneturide, a now obsolete agent, in control of partial seizures.[57] A single 20-mg dose of oral diazepam significantly reduced the incidence of serial seizures at plasma concentrations of 273 ± 190 (SD) ng/m.[57] Oral intermittent diazepam given for prophylaxis of recurrent FS showed no difference to placebo (reviewed in Schmidt[57]). After excluding many protocol violators, however, analyzing children actually receiving diazepam showed an 82% and statistically significant reduction in the risk of FS with diazepam.[57] The poor efficacy of long-term oral diazepam treatment in epilepsy may be related to the development of tolerance and the difficulty to maintain effective serum concentrations.

Midazolam has not been evaluated in trials of chronic oral treatment for epilepsy.

Nitrazepam is largely confined to second- or third-line treatment of severe childhood epilepsies, mainly West syndrome (see Table 1). Although quite effective, it is rarely used because of severe, and in some patients intolerable, drowsiness, ataxia, hypersecretion, and hypersalivation (due to nitrazepam-induced hypotonia of muscles used for swallowing saliva), and aspiration pneumonia in some patients.[5] Nitrazepam has largely been superseded in the treatment of infantile spasms (West syndrome) by vigabatrin, valproate, steroids, or adrenocorticotropic hormone (ACTH). Furthermore, intravenous nitrazepam has precipitated tonic SE in a patient with Lennox-Gastaut syndrome.[62]

Adverse Effects

Dose-Related, Nonidiosyncratic Adverse Effects

Benzodiazepines are relatively safe drugs despite potential adverse effects. Very large doses, whether taken accidentally or intentionally, are rarely fatal unless other sedative drugs or ethanol are taken concomitantly. Mechanistically, this is supported by pharmacologic studies demonstrating that benzodiazepines cannot directly activate the γ-aminobutyric acid $(GABA)_A$ receptor, even at very high concentrations, without the presence of the endogenous ligand GABA or other allosteric modulators capable of direct activation, such as barbiturates.[61]

The principal clinical concern when administering benzodiazepines acutely, as in SE, is respiratory and cardiovascular depression, as well as sialorrhea and inability to handle oral secretions.[29] These side effects may worsen with concomitant administration of other CNS depressants, such as phenobarbital. The combination of a benzodiazepine and phenobarbital should be used cautiously because of the potential for respiratory depression, hypotension, and sedation. Status protocols usually require intubation when these agents are used together.

In rare instances, intravenous administration of benzodiazepines may induce generalized tonic SE in patients with the Lennox-Gastaut syndrome.[8] Intravenous injections of diazepam can cause thrombophlebitis, but this may be primarily a consequence of precipitation following rapid injection, or it may result from the concurrent administration of diazepam and phenytoin through the same intravenous line, causing crystallization.

During long-term therapy, it is well known that benzodiazepines cause dose-related CNS depression, hypotonia, ataxia, incoordination, dizziness, dysarthria, nystagmus, blurred vision, diplopia, and behavioral abnormalities such as hyperactivity, restlessness, short attention span, irritability, disruptiveness, and aggressiveness.[29] Benzodiazepines can also cause drooling and incoordination of swallowing.[68]

Clobazam, a 1,5-benzodiazepine, is thought to have fewer side effects than other benzodiazepines at equipotent doses.[29] Interestingly, levels of the metabolite desmethylclobazam but not of clobazam correlated with side effects.[29]

Increased frequency of seizures and the emergence of different types of seizures have been suggested to follow clonazepam therapy.[4,55] However, natural fluctuation of seizure frequency may have been responsible, at least in part, for the observed increase of seizure frequency.

Diazepam may precipitate generalized tonic or tonic–clonic seizures and may cause conversion of absence status to tonic SE.[57]

Prolonged sedation due to accumulation of conjugated metabolites of midazolam has been described in nonepileptic patients with renal failure.[6] This may explain why in some patients with renal failure sedation persists while serum concentrations of midazolam and its unconjugated metabolite have fallen to ineffective levels.[6]

Idiosyncratic Reactions

Idiosyncratic reactions of the skin or other organ systems (for example, aplastic anemia) have not been reported. For this reason, patients with severe hypersensitivity reactions to several AEDs who need further treatment, but cannot tolerate

continued exposure to those drugs, will benefit from switching treatment to benzodiazepines.

Second Generation Effects (Including Teratogenicity and Other Effects on the Offspring)

It is not clear that benzodiazepines alone have significant teratogenic potential; many of the women from the reported cases were treated for psychiatric disease, epilepsy, and diabetes, and some were on polypharmacy with other known teratogens. Nevertheless, benzodiazepines may possibly augment the teratogenic potential of other drugs,[34] and there may be neurobehavioral problems in some children stemming from long-term benzodiazepine use during pregnancy.[43] Perhaps the best described teratogenic abnormality after exposure to agents such as diazepam and chlordiazepoxide during the first trimester of pregnancy is facial clefts and, to a lesser extent, cardiac or musculoskeletal malformations.[33] There is one letter reporting severe congenital malformation in a mother exposed to clorazepate in the first trimester of pregnancy.[47] All the anticonvulsant benzodiazepines are excreted into breast milk, but the levels are low and generally do not pose a significant hazard to the newborn.[29]

Tolerance to Therapeutic and Adverse Effects

Tolerance with partial or complete loss of efficacy during prolonged treatment limits the usefulness of benzodiazepines as AEDs. On average, tolerance to effect usually develops within the first several months in as many as one in three to one in two epilepsy patients treated with either clobazam or clonazepam for epilepsy.[29,56] Cross-tolerance to benzodiazepines may occur with long-term administration, rendering use of alternative benzodiazepines less effective.[29] Tolerance to sedative effects occurs more rapidly, usually within the first weeks of treatment. Potential explanations for how tolerance develops have been discussed in the section on mechanism of action. Tolerance usually forces clinicians either to withdraw a drug, risk further sedation, or exceed labeled dose ranges with increasing doses. Dose increments overcome tolerance in some patients, at least for a while. Because tolerance is reversible when the drug is discontinued, intermittent treatment and drug holidays have been suggested for patients who have developed tolerance.[9] However, the available anecdotal evidence suggests that such maneuvers are useful in only a minority of patients.[9]

Benzodiazepines can also produce physical drug dependence, not to be confused with drug tolerance or addiction, which can lead to withdrawal symptoms.[29] Tremulousness, agitation, insomnia, autonomic symptoms (tachycardia), depression, disorientation, and seizures (including status), can occur after abrupt cessation of benzodiazepines in patients with epilepsy.[29] Withdrawal symptoms are more frequently seen in patients receiving short-acting, high-potency benzodiazepines than in those receiving long-acting compounds such as clobazam or clonazepam.[29]

Tachyphylaxis, or reduced efficacy with repeated doses, has been reported for lorazepam[67] and for rectal diazepam.[48] Tachyphylaxis may also be a function of the duration of status, and the fact that recurrent episodes of status may represent subclinical status, which is more refractory to medical treatment. The longer the duration of status, the less effective benzodiazepines are in controlling it.[64] This may possibly be a consequence of the upregulation of GABA receptors and a relative increase in GABA levels after prolonged status.[64]

Drug Interactions

The benzodiazepines appear to be relatively inert in terms of drug interactions. They do not have enzyme-inducing effects.[22,23] In epileptic patients treated with enzyme inducers such as carbamazepine, phenytoin, and phenobarbital, the clearance of desmethyldiazepam is much larger than in normal controls.[67] Many cytochrome P450 enzyme-inducing drugs can decrease serum concentrations of diazepam and its metabolites. Alternatively, microsomal enzyme inhibitors, such as valproate, isoniazid, cimetidine, and diltiazem, can elevate serum diazepam levels.[29] The benzodiazepines are generally highly protein-bound, but they do not significantly affect and are not affected by the protein binding of other drugs, although there are exceptions. Protein binding of diazepam appears to be displaced by valproate, which results in increased free levels of diazepam.[29] When benzodiazepines are used with other AEDs that have readily measurable and reliable levels, measuring drug levels may be helpful in patient management. Antacids affect the absorption of clorazepate and desmethyldiazepam; they slow absorption and lower levels of desmethyldiazepam, although there was no significant difference of absorption as measured by the area under the plasma level-time curves.[29]

Role in Epilepsy Treatment

Indications

The benzodiazepines lorazepam and diazepam, along with intravenous phenytoin and phenobarbital, play a major role in the treatment of SE. Lorazepam is considered the drug of first choice for terminating SE.[42] Their intravenous route of administration, combined with their quick onset of action, makes them suitable as the initial treatment of status. Continuous intravenous infusion of lorazepam or midazolam for seizure control may become more commonplace in the intensive care setting.[31,46] Refractory SE has also been treated with midazolam; in patients with normal renal and hepatic function, midazolam has a much shorter half-life than lorazepam, and it can be easily administered by continuous intravenous infusion.[31] The rectal use of diazepam gel is an important effective and safe on-site treatment to stop series or clusters of seizures.

In contrast, results of the use of oral benzodiazepines in the long-term treatment of epilepsy have been less spectacular. Nevertheless, these drugs have an important role, because they appear to have some efficacy in many types of seizures and epilepsy syndromes. Benzodiazepines are usually administered on a long-term basis as adjunctive drugs. For example, benzodiazepines are often the first- or second-choice drug for myoclonic seizures along with valproic acid. Their long-term use is limited by tolerance, but intermittent administration, such as the use of diazepam to prevent serial or cluster seizures in adults and children, may bypass tolerance, at least in some patients.[29]

Dosing Recommendations

Dosing recommendations including titration issues, differences for adults and children, and the impact of comedication are summarized in Table 3.

Precautions

Benzodiazepines should be used with caution in renally and hepatically impaired patients because impaired renal excretion and hepatic metabolism may lead to excess accumulation. In addition, parenteral benzodiazepines should be used with caution in patients with compromised respiratory function, and in patients on comedication with sedating agents such as phenobarbital. In the elderly, in whom benzodiazepine clearance is reduced, the dosage should be decreased to minimize ataxia and sedation.

Contraindications

Benzodiazepines are contraindicated in uncommon cases with a known hypersensitivity to benzodiazepines.

Summary and Conclusions

Benzodiazepines play an important and varied role in the treatment of epilepsy. Diazepam and lorazepam are the most frequently used drugs in the initial treatment of SE. Lorazepam is the intravenous drug of first choice for terminating SE. Additionally, midazolam and lorazepam are being used increasingly as continuous intravenous drips in cases of refractory SE. Buccal and intranasal midazolam and rectal diazepam are useful in treating clusters of seizures or prolonged seizures at home, thus reducing the need for emergency room visits.

Benzodiazepines, although extremely potent anticonvulsant drugs, are most effective when used as acute or emergency treatment; they have disadvantages that limit their use as chronic therapy, the most notable of these being tolerance and sedation. Nonetheless, benzodiazepines have a wide spectrum of activity and have a useful niche as adjunctive medications in selected patients with both partial and primary generalized seizures. They are especially suitable for intermittent use in patients who have clusters of seizures, because this may circumvent the problem of tolerance, at least in some patients. Because this class of drugs can be administered effectively by many different routes, they are extremely versatile and useful agents in a variety of clinical settings.

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Chapter 146

Carbamazepine

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Introduction

Carbamazepine (5*H*-dibenz[*b,f*]azepin-5-carboxamide) is one of the most widely prescribed antiepileptic drugs for the treatment of partial and generalized tonic–clonic seizures in the United States and Europe. Since 1993, nine new antiepileptic medications have been approved by the U.S. Food and Drug Administration [felbatol (Felbamate), gabapentin (Neurontin), lamotrigine (Lamictal), topiramate (Topamax), tiagabine (Gabitril), oxcarbazepine (Trileptal), levetiracetam (Keppra), zonisamide (Zonegran), and pregabalin (Lyrica). In general, these “second-generation” antiepileptic medications have better pharmacokinetic and tolerability profiles than the “first-generation” antiepileptic medications such as carbamazepine.[41] Lacking, however, is any demonstration of superior efficacy. In addition, the newer agents can be significantly more expensive, and there is no clear evidence that they are more cost effective.[136] Likely because of its wide availability, relative inexpensiveness, and proven clinical efficacy, carbamazepine continues to be widely used for epilepsy.

Chemical Structure, Formulation, and Monitoring

Chemical Structure and Synthesis

The development of carbamazepine, like that of many anti-epileptic drugs, came about indirectly. According to the reports of Galbraith[43] and Schmutz,[118] C. J. Geigy, Ltd., sought to develop a psychoactive drug in the 1950s following the introduction of the neuroleptic chlorpromazine by Rhone Poulenc. Researchers at Geigy who were seeking to develop a similarly acting tricyclic drug substituted a CH–CH for the sulfur in the chlorpromazine molecule. This change produced imipramine (Tofranil), which, unlike chlorpromazine, demonstrated antidepressant properties when tested in psychiatric patients (Fig. 1). In further efforts to find a neuroleptic, studies were made of other tricyclic carbamoyl compounds of an imino-stilbene that had been synthesized earlier in the Geigy labs by Morel.[43,118] Structural changes in the molecule included the substitution at the 5 position of carboxamide for the basic side chain present in imipramine. One of these compounds (G26301) revealed even more potent anticonvulsant activity, especially in the maximal electroshock test. Early studies in animals and clinical trials confirmed its value as an antiepileptic drug. In 1957, Shindler and Lattner[43,118] replaced the CH_2–CH_2 with a CH=CH bridge (Fig. 1) to produce carbamazepine.

Formulations

Carbamazepine is available in scored 100- and 200-mg tablets; the former are chewable and particularly useful in treating children. A suspension is also available for patients who have problems swallowing tablets or require treatment though nasogastric tubing. This liquid formulation yields peak levels about 2 hours after ingestion; peak levels are lower and occur later with the tablets.[20,91,108] A slow-release formulation is available in Europe, and two for twice-daily administration are available in the United States.[6,46,126,128] Use of the slow-release formulation allows avoidance of the peak and trough levels sometimes encountered when the standard tablets are used. This is important, particularly when carbamazepine is coadministered with enzyme-inducing drugs, such as phenobarbital and phenytoin.[6,58,70,126,128] A recent prospective, open-label study demonstrated improved tolerability of the extended-release formulation as compared to the immediate-release formulation.[38]

Unfortunately, a parenteral formulation is not available because of the poor lipid solubility of carbamazepine. A soluble preparation based on a complexation of carbamazepine in cyclodextrins appears to be promising, but it has not been fully developed.[37]

Methods for Determination in Body Fluids

Immunoassay is the most common technique used for the determination of carbamazepine concentration in the blood. In general, this technique does not measure the metabolites of carbamazepine, some of which are biologically relevant.[92] Liquid chromatographic assays have the advantage of allowing quantification of carbamazepine and its principal metabolite, carbamazepine-10,11-epoxide. Determination of free carbamazepine concentration has no additional advantage over determination of total plasma concentration.[92] Carbamazepine levels in saliva have been shown to correlate predictably with plasma levels, but this technique has not been accepted into common clinical practice.[19,27,68]

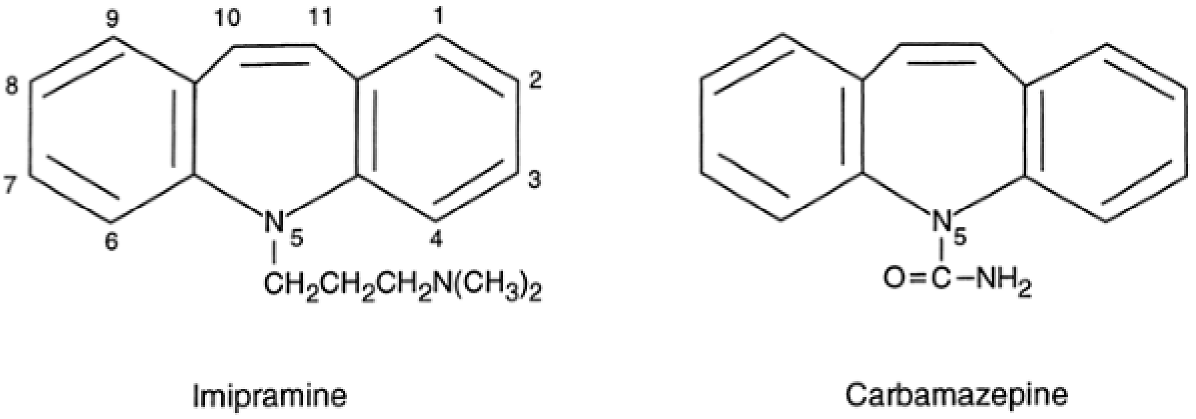

FIGURE 1. Structural formulas of imipramine and carbamazepine.

Pharmacology

Activity in Experimental Models of Seizures/Epilepsy

The original detailed pharmacologic studies of Theobald and Kuntz[127] in animal models revealed potent efficacy against seizures induced by maximal electroshock, with much less effect in preventing experimental seizures induced by pentylenetetrazol. Studies in hippocampal slice preparations revealed a reduction of burst firing in a calcium-free environment, implying a direct membrane, rather than a neurotransmitter-mediated action.[55,71,85] These actions closely paralleled those of phenytoin. The promise of this new drug led to further development. Predictions of efficacy against epileptic seizures were borne out in early clinical trials of adults and children.[8,10,106] Blom[8] also reported that carbamazepine was effective in the treatment of trigeminal neuralgia. These early trials noted that, unlike older available antiepileptic drugs, carbamazepine often conferred a positive “psychotropic” effect as well.[32] This was attributed, at least in part, to its structural similarity to the antidepressant imipramine.

Many open and controlled trials during the last four decades have established carbamazepine as a drug of first choice, based on its potent efficacy and overall good tolerability for the treatment of partial and tonic–clonic seizures.[7,70] Europeans acquired considerable experience with the drug as a treatment for epilepsy in the 1960s. The use of carbamazepine to treat trigeminal neuralgia was approved by the U.S. Food and Drug

Administration in 1968, but approval for its use in the treatment of epilepsy was delayed until 1974 because of reports of aplastic anemia. Although the initial reports of studies in children were favorable,[106] carbamazepine was not approved for treatment of children in the United States for more than another 20 years.

Mechanism of Action

Confirmation of the neural membrane effect came from the very important studies by McLean and MacDonald,[85] which indicated an effect at the sodium channel. They found that carbamazepine, like phenytoin, markedly reduced sustained high-frequency repetitive neuronal firing at clinically relevant concentrations. The effect was voltage and use dependent. This combination of characteristics led these and other investigators to conclude that the drug acted at the sodium channel in the "inactive state."[71] This mechanism explained why seizures with high-frequency discharge would be suppressed, whereas normal neuronal firing at lower rates would be unaffected by the drug, an observation quite in keeping with clinical effects at the usual dose.

Many other possible mechanisms have been investigated, including a synaptic action on excitatory amino acid receptors, but the evidence is not persuasive that carbamazepine is active at these sites at clinically relevant concentrations. Similarly, effects on γ-aminobutyric acid (GABA), adenosine, acetylcholine, and monoamine systems have been postulated, but without convincing evidence. On the other hand, it can be inferred that carbamazepine must have other effects on the central nervous system in addition to its action on the sodium channel because the drug has somewhat different adverse effects than phenytoin and, unlike phenytoin, possesses efficacy in the treatment of endogenous depression[70] and seizures associated with alcohol withdrawal.[39]

Clinical Pharmacokinetics

Absorption

Carbamazepine is a member of the family of iminostilbenes—tricyclic structures that are extremely insoluble in water. The partition coefficient of carbamazepine is 58 in the octanol/aqueous system.[37] Absorption is relatively complete in human studies, although some evidence indicates that infrequent large doses are less bioavailable than are more frequently administered smaller quantities.[6,91,108] Samples of both generic carbamazepine and Tegretol brand have clinically relevant decreased bioavailability when kept in a humid environment.[4] The drug should be stored in a closed container in a cool, dark, dry place.[20] The bioavailability can vary considerably from lot to lot of both different generic formulations as well as the innovator product (Tegretol).[88,91] Because of this variable absorption, patients should continue to use the same product rather than change between different generic preparations or the brand name Tegretol.

Absorption also may change perioperatively, perhaps because slowed gastrointestinal activity during bed rest at the time of surgery for epilepsy or other conditions may be associated with a transient drop in blood levels and loss of seizure control, which is then followed by toxic peak levels caused by a large reabsorption occurring after activity is resumed.[124] Perioperative metabolic changes with decreased clearance also probably account for delayed transient increases in blood concentrations postoperatively. Hiremath et al. found that postoperative carbamazepine blood levels directly correlated with preoperative carbamazepine blood levels, total intraoperative fentanyl dose, and body weight. A preoperative carbamazepine level >9 was a significant risk factor for the development of symptoms of clinical toxicity following surgery.[53] Carbamazepine dose reduction in the immediate postoperative period should be considered for some patients. Monitoring carbamazepine blood levels is also useful at this time.[74]

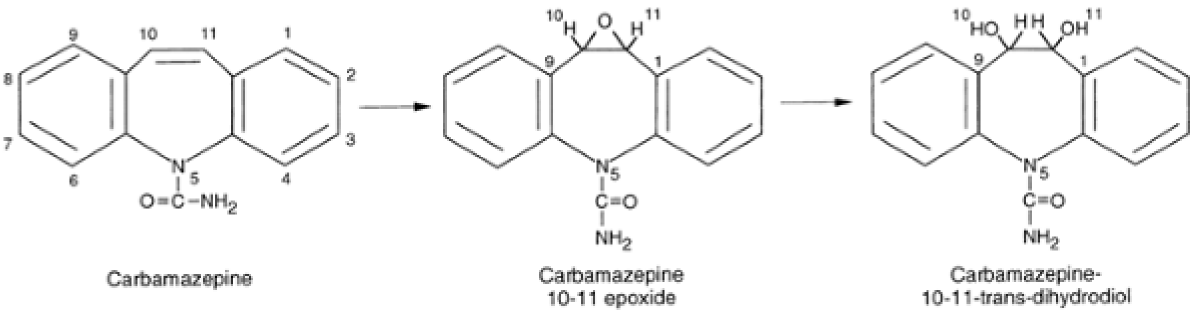
Carbamazepine
Carbamazepine 10-11 epoxide
Carbamazepine-10-11-trans-dihydrodiol

FIGURE 2. Biotransformation of carbamazepine.

Plasma Protein Binding and Distribution

Carbamazepine is approximately 75% protein bound, primarily to albumin. A smaller quantity is bound to α-acid glycoprotein. The free fraction may change in medical conditions that lower serum level of albumin, such as renal and hepatic disease, which may also alter the binding properties of α-acid

glycoprotein. Certain highly bound compounds, such as valproate, may displace carbamazepine and increase its free fraction. Carbamazepine is extensively distributed to body tissue and has a volume of distribution of approximately 1.5 mL/kg.[91] Following an initial dose, concentrations are highest in tissues with increased blood flow, such as cerebral cortex. During long-term administration using divided doses, brain concentration is more evenly distributed. Using intracerebral extracellular microdialysis in patients with epilepsy, Scheyer et al. determined that brain concentrations closely parallel concentrations of free carbamazepine in blood in both time and quantity.[116] Entry of the metabolite carbamazepine-10,11-epoxide is more gradual, but concentrations also parallel free blood levels. The less rapid entry of the epoxide most likely reflects its lower lipid solubility.

Metabolism and Elimination

Clearance is almost entirely by hepatic metabolism. Carbamazepine is primarily oxidized by the cytochrome P450 system (CYP 3A4 isoform) to carbamazepine-10,11-epoxide. The intermediate metabolite is further hydrolyzed by microsomal epoxide hydrolase to carbamazepine-10,11-*trans*-dihydrodiol (Fig. 2).[5,37,63,66,91] The diol and the conjugated product are eliminated by the kidneys.[63,91]

Carbamazepine clearance can be quite variable for several reasons. On initial administration in a single dose to volunteers, the half-life of carbamazepine is 24 to 36 hours or longer, but autoinduction during continuous administration as monotherapy approximately doubles the clearance.[37,89,115] Autoinduction leads to a new steady state within a few weeks and to a half-life of about 12 to 15 hours in adults.[5,36,63,66,89,114,115] Carbamazepine clearance can also be influenced by its interaction with other drugs (see later discussion).

Role of Therapeutic Drug Monitoring

The boundaries of carbamazepine's therapeutic range vary by institution, but in general it is considered to be from 4 to 12 μg/mL. Dosing, however, should be titrated according to clinical response. Some patients with carbamazepine levels in the "therapeutic range" may have symptoms of toxicity because of elevated levels of carbamazepine-10,11-epoxide.[92]

The pharmacokinetic complexities of carbamazepine, especially when it is coadministered with other drugs, require awareness of factors that may inhibit or enhance its clearance as well as its pharmacologically active intermediate metabolite carbamazepine-10,11-epoxide.[63,66] When an inducing or inhibiting drug is coadministered, the physician must be alert to clinical changes, and periodic monitoring of blood levels of carbamazepine is helpful. Induction may occur within a week and deinduction within a matter of days.[114] If carbamazepine treatment is initiated in patients receiving oral contraceptives, antipsychotics, antiviral therapy for HIV, statins, warfarin, or cyclosporine, clearance of these drugs can be increased, with loss of efficacy and serious consequences.[29,66,84,97] Inhibition of carbamazepine clearance by drugs such as erythromycin or propoxyphene may lead to increased levels and neurotoxic adverse effects within a few days. If the carbamazepine dose is lowered to compensate for the changes, reinstitution of higher doses will be needed when the interacting drug is discontinued. Levels of carbamazepine-10,11-epoxide may increase to a clinically relevant range in patients receiving carbamazepine and valproate, especially if phenobarbital or phenytoin is coadministered.[63,66,74] It may be advisable to use a consistent formulation, whether generic carbamazepine or Tegretol, to minimize effects due to variable bioavailability. Periodic blood level monitoring is advisable when clinical problems arise or changes are made in coadministered drugs. All of these changes in pharmacokinetics need to be anticipated to ensure optimal control and minimal adverse effects. Measurement of complete blood cell counts and serum liver chemistries, as well as other laboratory monitoring and history and examination, especially during the first weeks and months of therapy, may help to detect medical problems.[34,74,99]

Efficacy

Screening tests in animals had indicated high potency in the maximal electroshock model, which commonly predicts efficacy for partial and tonic–clonic seizures. Relative lack of efficacy in the pentylenetetrazol model suggested that usefulness in generalized seizures of absence or myoclonic type would be limited. In keeping with these studies, early clinical reports[8,10,106] indicated efficacy both as add-on and monotherapy in open trials. Many other open, uncontrolled trials were reported during the next decade both in adults[95] and children,[45] confirming efficacy for partial and generalized tonic–clonic seizures.

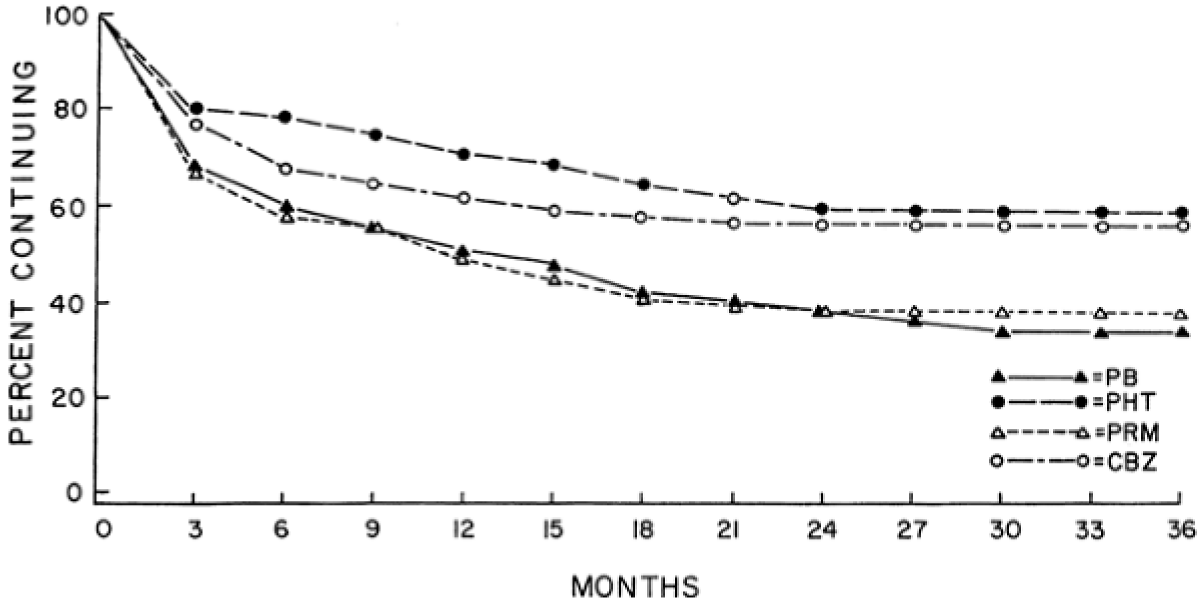

FIGURE 3. Retention (successful treatment) of 622 patients with partial seizures randomized to carbamazepine (CBZ)[80], phenobarbital (PB), phenytoin (PHT), or primidone (PRM). *p* <.05 CBZ/PHT versus PB/PRM.

Table 1 Patients with complex partial seizures who were seizure free for 12 months

	Number	Percentage
Carbamazepine[a]	14	67
Phenobarbital	3	21
Phenytoin	12	43
Primidone	7	33

[a] $p \leq .04$ for carbamazepine versus phenobarbital or primidone.
Source: From the VA Cooperative Study No. 118, unpublished data.

Use in Adults

Carbamazepine has been most widely studied for use in adults, and it has been compared to both the older and newer antiepileptic medications. In the 1970s, double-blind, controlled trials of carbamazepine as add-on therapy[17,64,110,120,130] provided evidence that it was comparable in efficacy to phe-nytoin, primidone, or phenobarbital. Kosteljanetz et al.[64] confirmed these results using carbamazepine and phenytoin as monotherapy; no differences were found, but the study lasted only 10 weeks and numbers were small. Ramsay et al.[105] also

found carbamazepine and phenytoin to be comparably effective for partial and tonic–clonic seizures in a double-blind, randomized parallel study of monotherapy in 70 patients followed for 6 months. Many subsequent studies have confirmed these results. The largest long-term double-blind, active control comparative studies of monotherapy were conducted by the Veterans Administration (VA) Cooperative Study Groups No. 118 and No. 264. In an initial trial, 622 adult patients with partial and secondarily generalized tonic–clonic seizures were randomized to treatment, and carbamazepine was found to be equally as effective as phenobarbital, phenytoin, or primidone in controlling secondarily generalized tonic–clonic seizures in adults (Fig. 3).[80] Although the results for many outcome measures of efficacy in the treatment of predominantly partial seizures (seizure frequency, rate, score, and time to first seizure)[22] were equal, carbamazepine proved to be more effective than the barbiturates in providing complete control of all partial seizures, both simple and complex, at every follow-up visit for a mean duration of 3 years. This difference was statistically significant ($p < .05$) at the 12-month visit for patients with complex partial seizures (Table 1).

No difference in efficacy was observed between carbamazepine and phenytoin. In this study, phenytoin was not shown to be significantly more effective than the barbiturates. The only trial showing a difference in efficacy between carbamazepine and phenytoin was reported by Callaghan et al.[15] They reported that generalized seizures were controlled completely in 73% of 37 patients treated with phenytoin and in 39% of 28 patients given carbamazepine ($p < .01$). The reason for the superior efficacy for phenytoin is unclear. Because all other trials have found equivalence between the two drugs, their finding may be a chance outcome. A meta-analysis was performed comparing the efficacy of carbamazepine and phenytoin monotherapy for children and adults with partial onset or generalized onset tonic–clonic seizures.[131] Individual patient data were only available for analysis from 3 of the 10 studies that met their inclusion criteria for the meta-analysis,[30,50,80] but nearly 60% of the individual patient data were from VA Cooperative Study Group No. 118. Not surprisingly, the meta-analysis results were congruent with this VA study: No difference was determined for efficacy between carbamazepine and phenytoin (measured in terms of 6- and 12-month seizure remission, time to first seizure) nor in time to withdrawal of treatment.

A meta-analysis was performed by the same group to examine the efficacy of carbamazepine versus phenobarbital,[132] and again, of the four trials included in the analysis,[30,50,80,102] the bulk of individual patient data were from the VA Cooperative Study Group No. 118. For all seizure types, time to 12-month remission and first seizure favored carbamazepine, but the results were not statistically significant because the confidence interval crossed 1. Time to withdrawal of therapy clearly favored carbamazepine, however, and was statistically significant. In subset analysis of individuals with partial seizures, phenobarbital was superior for time to first seizure. This was not a robust finding because both agents were equivalent for time to 12-month remission.

Table 2 Measures of the efficacy of carbamazepine versus valproate at 12 months in patients with complex partial seizures

	Carbamazepine (no. patients)	Valproate (no. patients)	*p* Value
Seizure-rating score[a]	4.0 (71)	4.2 (75)	.79
Complex partial (n^+ 206) seizure count[a]	2.7 (60)	7.6 (65)	.05
Monthly seizure rate	0.9 (96)	2.2 (105)	.01
Seizure control (% of patients)[a]	34 (62)	29 (65)	.57
Seizure-rating score[b]	2.0 (57)	6.2 (61)	.04

[a] Seizures occurring in the first month were excluded.

[b] The higher the score, the worse is the seizure control.

Source: From Mattson RH, Cramer JA, Collins JF, and the VA Epilepsy Cooperative Study No. 264 Group. A comparison of valproate with carbamazepine for the treatment of partial seizures and secondarily generalized tonic–clonic seizures in adults. *N Engl J Med.* 1992;327:765–771, with permission.

Carbamazepine is comparable in efficacy to valproate for treatment of both generalized and partial seizur-es.[15,31,50,57,69,104,109] Many trials, however, have been limited by nonblinded design, short follow-up, or relatively small numbers of patients.[76,79,122] In a second VA Cooperative Study, 480 adult patients were randomized to carbamazepine or valproate. Efficacy measures again included seizure count, seizure rate, seizure score, time to first seizure, and percentage of patients who remained seizure free. Although statistically significant differences were not detected for those with *predominantly* tonic–clonic seizures, the trend favored carbamazepine. In fact, a later retrospective analysis of patients with *only* tonic–clonic seizures revealed carbamazepine to be significantly ($p < .05$) more effective than valproate in providing complete control at 12-month follow-up.[79] For treatment of *predominantly* complex partial seizures, carbamazepine was significantly more effective than valproate in four of the five outcome measures but not for 100% seizure control (Table 2).[82]

In contrast to these reported differences in efficacy, several large long-term studies conducted in the United Kingdom and a more recent trial comparing topiramate, carbamazepine, and valproate monotherapy did not find that carbamazepine had superior efficacy. The study by Heller et al. of adults used as primary measure the percentage adult of patients entering long-term remission, a point not assessed in the VA studies.[50] In the "Epiteg" trial, Richens et al.[109] found that the percentage of patients entering long-term remission was similar for carbamazepine and valproate. Carbamazepine, however, had a more successful outcome in regard to time to first seizure at 1 year of follow-up. Richens et al. concluded that the apparently better outcome for carbamazepine was attributable to suboptimal dosing of valproate early in the study, and that higher doses later in the course of the treatment resulted in comparable remission rates. Another factor that might explain the different outcomes between the VA studies and those from the United Kingdom include different outcome measures.[22] Only time to first seizure and complete seizure control were used in all studies. In addition, the populations were different. Patients in the UK studies had new-onset epilepsy, whereas approximately half of the patients in the VA trials had been previously treated. Patients with a history of previous treatment or undergoing long-term treatment represent a more difficult population for achieving control,[83] and modest differences in efficacy may become apparent only with inclusion of more difficult cases of epilepsy. Finally, and of equal importance, differences may have been found in the VA studies because the very large number of patients in the complex partial seizure group (more than twice the number in any other study) provided the power to detect statistically significant differences. A meta-analysis comparing carbamazepine versus valproate was performed that included individual patient data from the four original studies cited earlier[30,50,82,109] and an additional small pediatric study.[133] Only one study was double-blinded.[82] There were no overall differences in time to withdrawal of treatment, time to first seizure, or time to 12-month remission of seizures, but in subgroup analysis of patients with partial-onset seizures, carbamazepine was superior to valproate for time to first seizure and time to 12-month remission of seizures. Valproate was not, as one would expect, superior to carbamazepine for generalized-onset tonic–clonic seizures; however, the subgroup with this seizure type was small. There were also concerns that patients with partial-onset seizures may have been misclassified as generalized-onset seizures because the age of onset for this group was suspiciously late for this syndrome. In addition, outcomes for only generalized-onset tonic–clonic seizures were examined, but one would expect a greater effect of valproate for absence or myoclonic seizures. A more recent double-blind comparison of topiramate, carbamazepine, and valproate monotherapy in newly diagnosed epilepsy found no differences in efficacy in the subset with partial epilepsy.[104]

Table 3 Carbamazepine versus oxcarbazepine monotherapy for newly diagnosed, previously untreated epilepsy

	Carbamazepine	Oxcarbazepine	*p* Value
Mean final daily dose (mg)	684 (300–1400)	1040 (300–1800)	
Mean serum concentration (μmol/L)	29.6 (±9.0)	57.0 (±20.0)[a]	

>50% Seizure reduction (% of patients)[b]	81.4	80.2	n.s.
Seizure freedom (% of patients)[b]	60	52	.3
Incidence of side effects (% of patients)	74	68	n.s.
Severe side effects requiring withdrawal (% of patients)	26	14	.04

[a] 10,11-dihydro-10-hydroxy-CBZ.

[b] 48-week maintenance phase.

Source: From Dam M, Ekberg R, Loyming Y, et al. A double-blind study comparing oxcarbazepine and carbamazepine in patients with newly diagnosed, previously untreated epilepsy. *Epilepsy Res.* 1989;110:209–215, with permission.

Table 4 Measures of the efficacy and tolerability of carbamazepine versus vigabitrin in patients with newly diagnosed, previously untreated epilepsy

	Hazard ratio[a]	**95% Confidence interval**	***p* Value**
Time to withdrawal of therapy, absence of therapeutic effect, or adverse event	0.83	0.57–1.20	n.s.
Time to withdrawal of therapy, absence of therapeutic effect[b]	2.37	1.09–5.18	.0298
Time to withdrawal of therapy, adverse event[b]	0.63	0.43–0.94	Not provided
Remission at 12 mo[b]	1.15	0.88–1.51	n.s.
Time to achieve 6-mo remission[b,c]	1.18	0.89–1.55	.57
Time to first seizure[d]	1.57	1.23–2.02	.0003

[a] Hazard ratio >1 indicates that an event is more likely on vigabitrin than carbamazepine.

[b] Adjusted for covariates.

[c] After maintenance dose reached.

[d] After randomization.

Source: From Chadwick, D. Safety and efficacy of vigabatrin and carbamazepine in newly diagnosed epilepsy: a multicentre randomised double-blind study. Vigabatrin European Monotherapy Study Group. *Lancet.* 1999;354:13–19, with permission.

Brodie et al.[12] compared carbamazepine with lamotrigine in a population of patients with new-onset epilepsy and failed to reveal differences in seizure control. Because this was a more treatment-responsive (new-onset) patient population and because the number of patients with complex partial seizures was not large, small differences in efficacy may have escaped detection. A randomized, open-label, multicenter trial of la-motrigine versus carbamazepine for patients with partial and/or generalized seizures also did not find a statistically significant difference in efficacy, but there was a trend that the higher dose of lamotrigine (200 mg) was more effective than carbamazepine (600 mg).[107] Time to withdrawal was used as a composite measure of safety and efficacy, and there was no difference of this measure between the two groups. However, more patients on carbamazepine withdrew due to adverse events.[107] A more recent open-label multicenter trial compared lamotrigine and carbamazepine for patients aged 2 years or older with newly diagnosed partial epilepsy. As with the two earlier trials, no statistically significant difference in efficacy was found, but overall lamotrigine was better tolerated.[93] A meta-analysis compared carbamazepine and lamotrigine as monotherapy for partial onset or generalized onset tonic–clonic seizures in adults and children. Individual patient data from 1,384 patients were collected from five studies[11,12,93,107] (one of which[12] consisted of two studies with similar protocols). As would be expected from the trials analyzed, lamotrigine was significantly better than carbamazepine in regard to time to treatment withdrawal. Carbamazepine was superior to lamotrigine in regard to the efficacy measures of time to first seizure postrandomization (hazard ratio [HR] 1.14; 95% confidence interval [CI] 0.92–1.43) and seizure freedom at 6 months (HR 0.92; 95% CI 0.81–1.04), but as unity was crossed, these results were not statistically significant. Longer-term outcomes could not be determined by this meta-analysis.[44]

A controlled comparative trial of carbamazepine with oxcarbazepine also revealed equivalent efficacy.[25] No significant difference was seen for seizure freedom during the 48-week maintenance phase or the number of individuals having at least 50% seizure frequency reduction. Although the incidence of side effects was equivalent, more individuals in the carbamazepine arm were forced to exit the trial due to “severe side effects.” Allergic side effects were the most common reason for withdrawal of trial medication (Table 3). Additional randomized, controlled studies comparing carbamazepine and oxcarbazepine have not been performed.

An initial unblinded trial in Finland reported by Kalvainen et al.[60] indicated that carbamazepine was somewhat more successful in control of partial seizures than vigabatrin, although the latter had fewer important adverse effects. A larger multicenter, randomized, double-blind study in 459 patients with newly diagnosed, previously untreated partial epilepsy confirmed that carbamazepine was superior to vigabatrin in both time to first seizure after the first 6 weeks of randomization and seizure freedom at 1 year (58% vs. 38%). No difference, however, was seen in the primary outcome of withdrawal due to lack of efficacy or adverse events (Table 4).[18]

A multicenter, randomized, double-blind study of patients with newly diagnosed, previously untreated epilepsy indicated that carbamazepine had superior efficacy to the investigational agent remacemide for all outcome measures (time to first seizure after dose titration and time to second, third, and fourth seizure after randomization).[13]

Table 5 Carbamazepine versus lamotrigine in elderly patients with newly diagnosed epilepsy

	Carbamazepine	Lamotrigine	*p* Value
Median daily dose (mg)	400 (200–800)	100 (75–300)	
Median serum concentration (mg/mL)	6.9	2.3	
Seizure freedom (% of patients)[a]	21	39	.027
Maintained treatment (% of patients)	42.6	71	<.001

[a] Last 16 weeks of treatment.

Source: From Brodie MJ, Overstall PW, Giorgi L. Multicentre, double-blind, randomised comparison between lamotrigine and carbamazepine in elderly patients with newly diagnosed epilepsy. The UK Lamotrigine Elderly Study Group. *Epilepsy Res.* 1999;37(1):81–87, with permission.

Table 6 Patients with new-onset geriatric epilepsy completing the trial (52 weeks)

	Number	Percentage
Carbamazepine	70	35.5
Gabapentin[a]	95	49
Lamotrigine[b]	111	55.8

[a] $p \leq .008$ for gabapentin vs. carbamazepine.

[b] $p \leq .0001$ for lamotrigine vs. carbamazepine.

Source: From the VA Cooperative Study No. 428, and Rowan AJ, Ramsay RE, Collins JF, et al. New onset geriatric epilepsy: a randomized study of gabapentin, lamotrigine, and carbamazepine. *Neurology*, 2005;64(11):1868–1873, with permission.

Use in Children

Results of efficacy studies in children very closely parallel those reported for adult populations.[34,45,70,98,106,125,133,137] Partial seizures associated with benign rolandic or symptomatic epilepsy as well as secondarily generalized tonic–clonic seizures all respond well to carbamazepine therapy.[9,34,45,70] A randomized, double-blind comparative study of two fixed doses of to-piramate and carbamazepine or valproate was performed in children ages 6 years and older. No difference was seen for time

to exit, time to first seizure, or seizure freedom at 6 months. Carbamazepine had equivalent efficacy to topiramate for the partial seizure subset.[135] A Canadian double-blind comparative study of clobazam for treated or previously untreated children with partial or generalized onset seizures found no overall difference in retention at 12 months. Efficacy data were not presented for the partial seizure subset alone.[16] A small open-label comparative trial of carbamazepine and vigabatrin in children found no difference in efficacy but suggested that the latter was better tolerated.[137]

Use in the Elderly

Two double-blind, randomized monotherapy trials compared carbamazepine to lamotrigine or lamotrigine and gabapentin in the elderly with newly diagnosed epilepsy.[11,112] Because of the late age of onset of epilepsy, the majority of individuals in these trials can be assumed to have partial epilepsy. The UK Lamotrigine Elderly Study Group found no difference in time to first seizure between carbamazepine and lamotrigine, but significantly more patients on lamotrigine versus carbamazepine were seizure free during the last 16 weeks of treatment (Table 5).[11] This finding may be a reflection of the short duration of the trial. The duration of follow-up extended to 1 year in the more recent VA Cooperative Study 428. No difference among carbamazepine, gabapentin, and lamotrigine was seen for the efficacy outcome measures of time to first seizure, seizure freedom at 12 months, and seizure free retention at 12 months. Withdrawal of therapy due to adverse events was higher for carbamazepine than for the other drugs in both studies (Table 6). Overall, these studies suggest that carbamazepine and lamotri-gine have equivalent efficacy in the elderly with new-onset untreated epilepsy, but that lamotrigine should be considered for initial monotherapy given its better tolerability profile in this age group. Both studies used the immediate-release formulation of carbamazepine, and it is unknown whether the extended-release formulation of carbamazepine would have fared better in regard to tolerability in these studies. The study also used an “intent to treat” analysis in seizure control such that withdrawals due to adverse effects were also considered seizure control failures. Analysis of results from evaluable data prior to withdrawal indicated a trend to best control by carbamazepine followed by lamotrigine and least efficacy for gabapentin.

Limits of Use

In contrast to partial and generalized tonic–clonic seizures, absence, myoclonic, and atonic seizures do not improve with carbamazepine therapy and may even be aggravated in some patients.[47,48,101,119,123] Carbamazepine, like most standard antiepileptic drugs, has not proved very useful in the management of symptomatic generalized epilepsy syndromes such as Lennox-Gastaut syndrome or West syndrome. Carbamazepine's insolubility and consequent lack of a parenteral formulation make it less useful in treating neonates and infants.

Table 7 Incidence and prevalence of adverse effects with use of carbamazepine

Effect	Percentage of patients[a] (*n* = 231)	Percentage at 12-month visit[b] (*n* = 130)

Sedation	42	8
Weight gain	32	9
(Large weight gain)[c]	8	3
Nystagmus	30	6
Gastrointestinal symptoms	29	6
Gait problems	25	4
Change in affect or mood	24	4
Tremor	22	5
Cognitive disturbance	18	3
Rash	11	1
Diplopia	10	0
Impotence	7	2

[a] Percentage of patients in whom each type of adverse effect occurred at any time during the trial (mean follow-up, 36 mo).

[b] Percentage of patients in whom each type of adverse effect was noted at the 12-mo visit.

[c] >12 lb.

Source: From Mattson RH, Cramer JA, Collins JF, and the VA Epilepsy Cooperative Study No. 264 Group. A comparison of valproate with carbamazepine for the treatment of partial seizures and secondarily generalized tonic–clonic seizures in adults. *N Engl J Med.* 1992;327:765–771, with permission.

Adverse Effects

Carbamazepine is a well-tolerated antiepileptic drug, and for this reason it has won a place as a drug of choice for the treatment of partial and secondarily generalized tonic–clonic seizures, especially within the European medical community.[70] The reported frequency of adverse effects is variable, in part because of methods of assessment. Active questioning and direct examination of patients will elicit more presumed drug-related effects than passive self-report.[78,80,82] In the VA Multicenter Studies, adverse effects were measured at every visit. Both patients and families were specifically asked about, and patients were examined for, each possible adverse effect. If the complaint (e.g., tiredness) could only be attributed to the drug, it was recorded as a drug-related adverse effect. Consequently, this method errs on the side of overrecording adverse effects. Table 7 shows the adverse effects recorded in 236 patients randomized to carbamazepine in the comparative trial with valproate.[82] The problems are quite similar to those encountered with other standard antiepileptic drugs. Tremor and weight gain were significantly less common than with

valproate. In the initial VA Cooperative Study No. 118, patients taking carbamazepine had less impotence than those taking barbiturates and fewer cosmetic adverse effects than those taking phenytoin.[80] It is interesting that a retrospective analysis disclosed that carbamazepine-treated patients had significantly greater weight gain than those on phenobarbital, phenytoin, or primidone (unpublished data). Of importance is the low prevalence of adverse effects at the 12-month visit, confirming excellent long-term tolerability. The types and frequencies of adverse effects in 155 patients randomized to carbamazepine in the first VA Cooperative Study were very similar.[80]

Dose-related, Nonidiosyncratic Reactions

The systemic adverse effect that most commonly occurs during initiation of therapy is nausea or gastrointestinal discomfort, which abates in most patients as pharmacodynamic tolerance develops and autoinduction lowers blood and brain concentrations (Table 7).

Neurotoxic adverse effects are primarily dose related and reversible. During initiation of therapy, dizziness, diplopia or blurred vision, sedation, and headache are most comm-on.[17,34,52,54,80,81,82,105,110] Slow, gradual increase in dose at startup minimizes these effects. With long-term administration, these symptoms usually subside, unless maximal dose is given because of difficulty in obtaining seizure control (Table 7). When coadministered with an enzyme-inducing drug, such as phenobarbital or phenytoin, peak levels of carbamazepine commonly occur several hours after intake and persist for approximately 1 hour.[37,58] Shorter intervals between doses or use of a sustained-release formulation may minimize this pattern.[70] Following accidental or purposeful carbamazepine overdose, dizziness, incoordination, ataxia, mydriasis, ophthalmoplegia, dyskinesia, stupor, coma, and respiratory arrest can occur. Although overdose is potentially life threatening, the prognosis is favorable with optimal medical support.[134] As might be expected because of the close chemical relation to tricyclic antidepressants, cardiac arrhythmias can occur.[54,82,134] Occasionally, movement disorders are seen, including dystonia, choreoathetosis, and tics.[54,134] These may be associated with overdose but also appear to be idiosyncratic and occur in patients with usually well-tolerated blood concentrations.[54] Although most reports of adverse effects have been in blinded, controlled studies conducted on adults, extensive clinical experience also indicates carbamazepine has an adverse effect profile in children.[34,52,54,98,125]

Adverse neuropsychological effects of carbamazepine are generally minimal, especially when compared with those of the barbiturates. Studies by Trimble[129] as well as initial reports from Troupin et al.[130] indicated that carbamazepine produced fewer cognitive effects than phenobarbital or phenytoin. In a later reanalysis, Dodrill and Troupin[33] concluded that the differences between carbamazepine and phenytoin in their original study were attributable to unusually high doses and blood levels of phenytoin, which affected speed and coordination of motor tasks. In the first VA Cooperative Study No. 118, extensive testing was carried out on repeated visits using a battery of neuropsychological tests. There were no statistically significant differences among carbamazepine, phenobarbital, phenytoin, or primidone during long-term administration when doses and blood levels of drugs were within the target range. In the analysis of data from this study, however, Smith et al. reported that patients taking carbamazepine most often had the lowest (most favorable) score on most tests in the battery.[121] In the second VA Multicenter Cooperative Study No. 264, carbamazepine and valproate were compared using a battery of behavioral tests before treatment and again after 6 months of therapy. No worsening of test performance was found for patients on either drug, nor were differences found between the two drugs.[103] No improvement (practice effect) was observed, however, in contrast to results in a control group. Similarly, in a study comparing carbamazepine with vigabatrin in nonblinded long-term monotherapy trials, Kalvainen et al.[60] found that patients taking vigabatrin as well as a control group improved in neuropsychological test performance on repeated administration, whereas those treated with carbamazepine failed to show this presumed practice effect. Meador et al.[86,87] compared carbamazepine, phenytoin, and phenobarbital in patients and normal controls. They found no significant differences between carbamazepine and phenytoin but did observe some greater compromises in subjects given phenobarbital. The lack of significant cognitive adverse effects was confirmed in children taking carbamazepine by Aldenkamp et al.[1] Withdrawal of carbamazepine and other antiepileptic drugs had little effect on cognitive tests. In a review of available trials, they also concluded that there were no differences in cognitive test results between patients taking carbamazepine or phenytoin but pointed out that no study was fully adequate.[2] Overall, the evidence suggests that in the usual doses of 10 to 15 mg/kg and with blood concentrations of 4 to 12 mg/mL, carbamazepine is well tolerated and causes minimal adverse effects on cognition, affect, and behavior.

Idiosyncratic Reactions

Serious systemic effects are uncommon. Approximately 10% of patients experience a hypersensitivity rash during the first weeks or months of treatment.[12,18,57,80,82,109] This effect was observed in the two double-blinded monotherapy multicenter studies in adult epilepsy patients conducted by the VA.[80,82] Rash occurred in 9% of 155 patients randomized to carbamazepine in the first study and in 11% of 240 in the second trial. These figures agree very closely with those

recorded in the “Epiteg” trial in the United Kingdom[109] and in a double-blind study comparing carbamazepine and lamo-trigine.[12] The frequency of rash does not differ significantly from that observed with administration of other standard antiepileptic drugs, with the exception of valproate.[80] Fewer than 1% of patients taking valproate had a sensitivity rash.[82] In approximately half of the patients experiencing a hypersensitivity reaction, lowering the dose or temporarily stopping the drug results in disappearance and may allow continuation or reinstitution of carbamazepine therapy, especially if the reaction is mild. More severe reactions may include uncomfortable pruritus and, infrequently, fever, malaise, and generalized aches and pains. Involvement of mucous membranes and other systemic manifestations indicate a serious medical problem, such as Stevens-Johnson syndrome or Lyell syndrome, requiring prompt and total discontinuation of the drug. Other interventions, including antihistamines, steroids, and hospitalization,[40,54] may be required. Fatal eosinophilic myocarditis has also been reported as a manifestation of hypersensitivity.[113]

The other major life-threatening complication associated with carbamazepine use is aplastic anemia or agranulocytosis. This adverse effect delayed approval of carbamazepine in the United States by the Food and Drug Administration for some years. Long-term surveillance of serious idiosyncratic toxicity suggests an incidence of aplastic anemia of approximately 1 case in 200,000 exposures to carbamazepine.[20,98,99] It is unclear why the risk seemed to be considerably higher during the original trials. The initial cases were reported in patients being treated for trigeminal neuralgia, suggesting that elderly patients are at greater risk. It is unlikely that regular monitoring of the complete blood cell count and platelet count allows early detection and discontinuation of drug before the toxic burden becomes irreversible.[34,99] In view of the rarity of aplastic anemia, it can be readily calculated that routine monitoring to identify rare cases costs millions of dollars. Confounding the issue of monitoring for aplastic anemia is the leukopenia that occurs frequently during initiation of drug therapy.[25,99] Indeed, in the original VA Multicenter Antiepileptic Drug Trial, 30% of patients had leukocyte counts <5,000 cells/mm^3 during the first 6 months of follow-up.[80] Although this was more common with carbamazepine than with phe-nytoin, phenobarbital, or primidone, the differences did not reach statistical significance. More important, neutropenia of a clinically significant degree (<1,000 cells/mm^3) was observed in only one blood sample from one patient treated with carbamazepine. The cell count fell to 896 cells/mm^3; on repeated determination (without changing drug dose), the value had risen and remained at <1,000 cells/mm^3, so long-term treatment was continued. Although leukopenia is rarely clinically significant, a gradually decreasing white blood cell count engenders fear of the rare but potentially catastrophic aplastic anemia and at times may lead to discontinuing of carbamazepine unnecessarily.[34,70]

Other serious adverse effects include hepatitis, which is usually seen in association with a generalized hypersensitivity reaction,[3,40,121] and systemic lupus erythematosus.[3,54] Cardiac conduction disturbances have also been reported[62,82] and may require discontinuing therapy, especially in elderly patients with cardiac disease. A more common systemic effect with long-term carbamazepine administration is hyponatremia. Conflicting evidence concerning the mechanism suggests both a direct renal tubular effect and inappropriate release of antidiuretic hormone.[59] The hyponatremia is usually not clinically significant, but if it is coupled with hemodilution or insufficient salt intake, encephalopathy and worsening of seizures may result.[82,100] Hyponatremia may be more frequent and severe in patients treated with oxcarbazepine than with carbamazepine, especially the elderly.[35] The mild anticholinergic properties of carbamazepine infrequently aggravate glaucoma or urinary retention.

Second-generation Effects

Teratogenic effects have been reported in offspring of mothers taking any of the standard antiepileptic drugs.[28] (For detailed review, see Chapter 108.) Initially, carbamazepine was thought to be safer than phenobarbital, phenytoin, or valproate, but later reports[28,54,67] suggested an increased risk for major malformations, including spina bifida.[111] Although carbamazepine use was associated with an increased frequency of spina bifida relative to phenobarbital and phenytoin, the number of cases was very small.[111] The risk for malformations was especially high when carbamazepine was coadministered with phenobarbital or valproate. Lindhout et al.[67] suspected that this effect was perhaps secondary to increased concentrations of carbamazepine-10,11-epoxide or other epoxide intermediates. In the more recent U.K. Epilepsy and Pregnancy Register, 3,607 pregnant women with epilepsy were followed prospectively. The malformation rate was significantly lower for carbamazepine monotherapy (2.2%; 95% CI 1.4%–3.4%) than valproate monotherapy (6.2%; 95% CI 4.6%–8.2%). The malformation rate was also slightly lower for carbamazepine than for lamotrigine monotherapy (3.2%; 95% CI 2.1%–4.9%) or even women who took no antiepileptic medication during pregnancy (3.5%; 95% CI 1.8%–6.8%). Polytherapy increased the risk of malformation, especially when the regimen included valproate.[90] Overall, the evidence does not suggest that any standard antiepileptic drug is preferable to the others in pregnancy, and selection should be based on epilepsy syndrome, seizure control, and tolerability.[28] Ideally, monotherapy with the lowest effective dose should be used (see Chapters 108 and 198).

Drug Interactions

An increase in clearance is characteristically seen when carbamazepine is coadministered with other enzyme-inducing drugs, such as phenobarbital, phenytoin, and oxcarbazepine.[5,66,96] This results in a half-life as short as 6 hours, and frequent dosing may be required to avoid clinically undesirable peak and trough effects.[56] Conversely, biotransformation can be inhibited by coadministration of a number of drugs, including the macrolide antibiotics (erythromycin and others), cimetidine, calcium channel blockers (verapamil and others), danazol (a synthetic estrogen), dextropropoxyphene, and several imidazoles.[20,24,66,97] Some of these are generally given for short periods, but if they are administered on a long-term basis, determination of carbamazepine blood levels is indicated and changes in dose may be required. The epoxide hydrolase can also be inhibited, most notably by valproate, an antiepileptic drug commonly used together with carbamazepine when monotherapy is adequate to control seizures. The coadministration of an enzyme-inducing compound, such as felbamate, phenobarbital, or phenytoin, with carbamazepine induces its conversion to the 10,11-epoxide.[63,96] If the patient is also treated with valproate, inhibition of the epoxide hydrolase can lead to clinically meaningful concentrations of the pharmacodynamically active metabolite.[5,36,63,66,74,77]

Interactions are frequent when carbamazepine is given in combination with other drugs, and these can significantly increase or decrease the clearance of carbamazepine and its active intermediate metabolite carbamazepine-10,11-epoxide, as indicated earlier. In addition to the effect of other compounds on carbamazepine clearance, the inducing properties of carbamazepine can increase the clearance of other antiepileptic drugs, including ethosuximide, felbamate, lamotrigine, oxcarbazepine and its active metabolite tiagabine, topiramate, and valproic acid,[96] and produce a competitive inhibitory effect on phenytoin. This sometimes results in modest elevations in phenytoin serum concentrations.[14,66] The inductive effects on valproate clearance appear to be somewhat less than on phenytoin.[77] Carbamazepine increases the clearance of sex hormones given as oral contraceptives, occasionally resulting in unplanned pregnancies.[66,84] Carbamazepine can also increase the clearance of other important drugs metabolized by the CYP3A4 pathway, including antiarrhythmics, antiviral therapies for HIV, antineoplastics, statins, and oral anticoagulants such as warfarin.[97] Both the autoinductive and deinductive effects begin within days, and deinduction occurs rapidly.[66,77,114]

Changes in protein binding are usually too modest to have clinical significance,[66] although valproate may physically displace carbamazepine and increase its potential for causing peak dose-related adverse effects, especially when seizure control is difficult and high doses are used.[73,74,77]

Role in Epilepsy Treatment

Indications

Carbamazepine and other major established drugs, such as phenytoin, are equally effective in the treatment of many seizure types, but the response to treatment may differ among individual patients. Many comparative crossover studies of carbamazepine and phenytoin have shown that carbamazepine may be effective and tolerable when phenytoin fails and vice versa.[15,49,64,130] The newer antiepileptic medications have not been shown to have superior efficacy as monotherapy for new-onset epilepsy to the older agents like carbamazepine or phenytoin.[65] However, when selecting an antiepileptic medication for monotherapy, efficacy is only one of the variables that should be taken into account. Consideration should also be given to other comorbidities such as migraine, psychiatric disease, or obesity. Other factors to be considered are hormonal milieu and risk of endocrine-related conditions such as osteoporosis; risk of teratogenicity; and metabolism of concurrently prescribed medications. Factors external to the patient's health status such as the medication's availability, cost, and coverage by third-party payers should also be considered.[41,42] Compliance is also more likely with a simpler dosing schedule, and when carbamazepine is selected, if possible, an extended-release formulation should be used. When poor control of seizures requires coadministration of two or more antiepileptic drugs, carbamazepine is effective. Indeed, in the original controlled clinical trials, carbamazepine was added on to other established antiepileptic drugs.[17,64,120,130] Because comparative trials have not been performed, there is no evidence to suggest that the newer antiepileptic drugs are more effective for refractory epilepsy than carbamazepine or phenytoin.

In summary, even when the newer antiepileptic medications are taken into account, the preponderance of evidence indicates that carbamazepine is unsurpassed in efficacy for the treatment of partial and secondarily generalized seizures and by some measures is more effective than traditional antiepileptic medications such as barbiturates or valproate as well as gabapentin and vigabatrin among new antiepileptic drugs in the treatment of partial seizures.[10,18,80,82,112] In a recent survey of expert opinion, carbamazepine and oxcarbazepine were rated as the initial treatment of choice for symptomatic localization-related epilepsy, and in contrast to a prior survey, phenytoin was no longer rated as a first-line therapy.[61]

Dosing Recommendations

In cases of new-onset epilepsy, the treatment should be initiated gradually because carbamazepine often produces dizziness, gastrointestinal upset, sedation, and visual disturbances if full daily maintenance doses are used. For most outpatients, carbamazepine is best started with an initial test dose of 100 mg, followed by further increments as tolerated. Should no adverse effects appear with 100 mg on the first day, administration twice daily can be attempted and repeated for another day, followed by an increase to three 100-mg doses approximately equally divided throughout the day. In most patients, an increase to 200 mg twice daily is appropriate and possible during the first week. This slow and gradual escalation minimizes side effects. The relatively low doses still provide adequate blood levels because of the initially slow clearance.[37,114,115] Autoinduction steadily reduces blood levels relative to the dose and, together with pharmacodynamic tolerance, allows dose increases to 200 mg three times daily by the end of the first or during the second week. The presence of uncomfortable dose-related side effects during initiation of therapy (see earlier discussion) should lead to withholding the subsequent dose until symptoms have cleared. If subsequent reintroduction of the previous dose continues to produce side effects, the dose should be lowered. For most adults (60–80 kg in weight), doses of 600 to 800 mg (10 mg/kg) are reasonable first targets for long-term therapy.[82] If seizures are not controlled, one dose should be increased gradually in 100- or 200-mg increments until control is obtained or unacceptable adverse effects appear. In the latter case, a slight reduction is indicated until the symptoms abate or decrease to a tolerable level. If at this point control is unacceptable, it may be necessary to coadminister carbamazepine with another antiepileptic drug or substitute it with another. Clinical response dictates dose, but monitoring of antiepileptic drug levels during initiation of therapy helps to achieve a target concentration that can reasonably be expected to provide control. This is valuable in view of carbamazepine autoinduction.

This recommended dosing regimen depends to some degree on the severity of the epilepsy and how difficult it is to achieve control. For patients with new-onset epilepsy associated with tonic–clonic seizures, modest doses given twice daily may be quite satisfactory.[82] This regimen facilitates compliance and provides relatively smooth blood concentrations.[23] On the other hand, when carbamazepine is coadministered with phenytoin or phenobarbital, its clearance is significantly enhanced and the half-life may decrease to 6 to 8 hours.[37,66] To optimize absorption and minimize peak and trough effects, especially when the dose needs to be close to maximally tolerated quantities, more frequent daily administration is recommended to maximize control without producing peak toxic effects.[58,70] Use of sustained-release formulations of carbamazepine given twice daily minimizes the fluctuations and should prove optimal for these patients.[88,128]

Clinical use in children is similar to that in adults. Doses need to be reduced according to size. On the other hand, clearance in preadolescent children is increased, and they may require a 50% increase in dose to achieve blood concentrations comparable with those of adults.[34,37]

Precautions

Among women using oral contraceptive pills, caution is advisable because of the increased risk for contraceptive failure resulting from the increased clearance of female sex hormo-nes.[54,66,84] In fertile women, especially if they are planning pre-gnancy, some concern arises about the risk for congenital

malformations, including especially spina bifida.[67,111] All standard antiepileptic drugs carry some teratogenic risk, however, although the association with spina bifida and neural tube closure appears to be greatest for valproate. In general, when these antiepileptic drugs, including carbamazepine, are used at the lowest effective dose as monotherapy, teratogenic risks are relatively low, and drug selection is based more appropriately on the best agent for treatment of the mother's specific epilepsy and seizure type.[28] Carbamazepine is present in breast milk, but its effect on infants has not been studied. Use of carbamazepine in elderly patients is somewhat more complicated. These patients often take multiple other drugs, and carbamazepine may induce metabolism of compounds such as warfarin (Coumadin) and cyclosporine.[29] Interactions may have potentially serious consequences.[66,77] Carbamazepine-associated hyponatremia and cardiac dysrhythmias, as well as the absence of a parenteral formulation, also make carbamazepine a less-than-optimal drug for this population.[75,76] As in all cases of drug selection, however, a decision should be reached based on a review of the needs and risks of each individual patient rather than on the basis of age alone.[76] Precautions should also be taken in patients with history of adverse hematologic reaction or hypersensitivity to other medications (especially anticonvulsants), glaucoma, liver or kidney dysfunction, or history of atypical absence seizures.[20]

Contraindications

Carbamazepine is contraindicated for patients who have had prior hypersensitivity reactions to carbamazepine or tricyclic compounds. Concomitant monoamine oxidase inhibitor and carbamazepine therapy can result in seizure exacerbation and hyperpyrexia.[20] It is recommended that monoamine oxidase inhibitors be discontinued at least 14 days prior to initiating therapy with carbamazepine. Carbamazepine should also not be used in patients with prior bone marrow depression.[20]

Summary and Conclusions

Carbamazepine is one of the most frequently prescribed first-line drugs for the treatment of partial and generalized tonic–clonic seizures; it is effective in both adults and children. In contrast, carbamazepine is ineffective against absence, myoclonic, and atonic seizures, and it may even aggravate them. Carbamazepine is as potent as phenytoin but has fewer cosmetic side effects. Compared to valproate, tremor and weight gain are much less common. Most patients do not experience significant cognitive adverse effects. About 10% of patients develop a hypersensitivity rash during the first weeks of treatment, but if the reaction is mild, reducing the dose or temporarily stopping the drug may allow carbamazepine therapy to continue. Aplastic anemia, originally a feared idiosyncratic reaction, is rare: There is about 1 case in 200,000 exposures. Routine blood tests are not useful in preventing irreversible aplastic anemia. In contrast, benign leukopenia occurs in up to 30% of patients taking carbamazepine, but this does not appear to increase the risk of aplastic anemia. Elderly patients are especially vulnerable to the consequences of hyponatremia and effects on cardiac conduction.

Treatment should be initiated at a low dose (e.g., 100 mg/d) and then increased gradually in the absence of side effects. Clearance is initially slow, but autoinduction shortens the drug's half-life substantially and steadily reduces blood levels relative to dose within the first 3 to 4 weeks of therapy. For most adults, long-term treatment requires at least 10 mg/kg daily. Children clear carbamazepine more rapidly and thus may require doses up to 50% higher than adults to achieve comparable blood levels.

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Chapter 147

Ethosuximide

Edward B. Bromfield

Introduction

Among several succinimides synthesized as modifications of the hydantoin-barbiturate heterocyclic ring, only one, ethosuximide, is still in widespread use; another, methsuximide, has a broader spectrum of action but is used less often (see Chapter 163). Ethosuximide has been available since 1958, and remains a first-line drug for the treatment of absence and related seizures.

Chemical Structure, Formulations, and Methods for Determination in Body Fluids

The similarity of ethosuximide, 2-ethyl-2-methylsuccinimide (Fig. 1), to other traditional antiepileptic drugs (AEDs) with a five- or six-membered heterocyclic ring structure is apparent, with a nitrogen atom located between two carbonyl groups. Unlike most, however, it is highly water-soluble. It has one asymmetric carbon and is used in its racemic form.[22] It is a crystalline powder or a waxy solid, sold as a liquid-filled capsule (250 mg) or as syrup (250 mg/5 mL). High-performance liquid chromatography can be used to measure plasma levels.[28]

Pharmacology

Activity in Experimental Models of Seizures/Epilepsy

Ethosuximide's efficacy against absence seizures is consistent with its potency in several chemical convulsant models, particularly pentylenetetrazol, as opposed to the maximal electroshock model.[14] It is also successful in other models believed to mimic absence seizures, including systemic penicillin, intravenous γ-hydroxybutyrate, intraventricular leucine-enkephalin, and spontaneous seizures in selected genetically epilepsy-prone rodents (Strasbourg), and as well experimental seizures induced by fluorothyl, enflurane, barbiturate withdrawal, and cortical estrogen or cobalt.[14,19,21,25] On the other hand, ethosuximide is relatively ineffective against seizures induced by bicuculline, strychnine, aminophylline, kainic acid, and *N*-methyl-D-aspartate, as well as cortical aluminum or amygdaloid kindling.[14,21,25]

Activity in Other ModelszHH

Low-threshold, “transient” (T-type) calcium (Ca) channels on thalamic neurons seem to play a critical role in the thalamocortical interactions that underlie the 3-Hz spike-and-wave pattern characteristic of absence seizures.[14,19] Ethosuximide blocks the low-threshold Ca current mediated by these channels in a voltage-dependent manner, such that the degree of current blockade increases at more hyperpolarized conditions.[8,14,25] That this mechanism is adequate to decrease abnormal thalamocortical excitability without affecting normal, tonic thalamic cell activity has been demonstrated in a computer simulation.[17] Dimethadione, another specific antiabsence drug, also blocks these currents at therapeutically relevant concentrations, whereas carbamazepine and phenytoin do not,[8,19] and valproate does so to a much lesser degree.[19] Ethosuximide also has other potentially important ionic effects, such as partial blockade of noninactivating sodium (Na) currents and Ca-dependent potassium (K) channels.[14,16]

Mechanisms of Action

Although the main effect of Ca-current blockade appears to be a decrease in thalamocortical excitation, ethosuximide may also interfere with rhythmic inhibitory activity,[11,14] which appears to be important in generating absence seizures.[2] Effects on neurotransmitter synthesis, metabolism, or action do not seem to underlie these effects, but the effects on T-type Ca channels discussed earlier could be responsible.[8,14]

Clinical Pharmacokinetics

Absorption

Absorption after oral administration is essentially complete, and peaks 3 to 5 hours after ingestion of the capsule;[22] absorption occurs slightly more quickly in acute than in long-term administration, and with the syrup as opposed to the capsule formulation. No significant first-pass metabolism occurs.

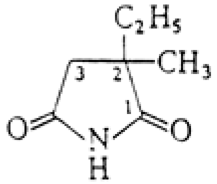
Plasma Protein Binding and Distribution

Because of ethosuximide's high water solubility, its volume of distribution is high, estimated at 0.7 L/kg.[22] Concentrations in adipose tissue are about one-third of those in plasma.[22] Ethosuximide rapidly crosses the blood–brain barrier, and equilibration between plasma and cerebrospinal fluid occurs in 20 to 30 minutes; this is three to four times as rapid as for valproate, phenobarbital, phenytoin, or carbamazepine.[22] Concentration is uniform within the brain. Because ethosuximide is not significantly protein-bound, cerebrospinal, salivary, and lacrimal concentrations are similar to those of plasma. Breast milk has only slightly lower concentrations, with a milk-to-plasma ratio of 0.8 to 0.9.[15,22]

Metabolism and Excretion

During long-term administration, approximately 20% of the dose is excreted renally unchanged, with the remainder

hepatically metabolized to inactive compounds via the cytochrome P450/mixed-function oxidase system, principally CYP3A.[1,22] These reactions include mainly hydroxylation of the ethyl side chain in either the 1- or 2- position (see Fig. 1), with metabolites conjugated predominantly with glucuronic acid and then excreted in the urine. Elimination of ethosuximide follows first-order kinetics.[22] In adults, serum half-life is approximately 40 to 60 hours, with substantial variation between individuals; in children and newborns, half-life is slightly shorter, 30 to 40 hours.[15,22] Levels during pregnancy may fall, but not as much as those of some other drugs.[15,22] Although autoinduction of metabolism has been demonstrated in rats, this process probably does not occur in humans.[22]



ETHOSUXIMIDE

FIGURE 1. Chemical structure of ethosuximide.

There is little data on ethosuximide concentrations in hepatic or renal disease, but increases would be expected. Ethosuximide is dialyzable, with an estimate of a 50% decrease in levels over a 6-hour dialysis session.[22]

Relationship Between Plasma Concentrations and Effects

Given ethosuximide's relatively long half-life, it takes 7 to 12 days of administration to reach steady-state plasma levels, and little variation is noted between peaks and troughs, even with once-daily administration,[22] although it is usually administered twice a day. Average daily doses are 15 to 40 mg/kg to achieve the usual therapeutic range of 40 to 100 µg/mL. Although the dose-level relationship is generally linear within the usual dose range, there is evidence of saturation kinetics in some patients.[22] Among 33 patients with complete control of absence seizures, 91% had levels of at least 40 µg/mL.[29]

Efficacy

Ethosuximide remains a drug of first choice for typical absence seizures, and there is evidence of efficacy against atypical absence and myoclonic seizures, particularly epileptic negative myoclonus. In several series of patients with typical absence seizures, with or without concomitant tonic–clonic seizures, approximately half the patients experienced complete or nearly complete (>90%) control of absences, and 95% had at least a 50% decrease.[4,29] This proportion is similar to that obtained with valproate.[26,29] Absence status epilepticus, or "spike-wave stupor" (Chapter 60), in its purest form occurs in either patients with childhood- or adolescent-onset idiopathic generalized epilepsy, and often responds to ethosuximide for long-term prevention of recurrence, although benzodiazepines and other shorter-acting drugs are usually used for acute treatment.[10] Based on anecdotal evidence, adjunctive use of ethosuximide has also been proposed for myoclonic seizures, as in juvenile myoclonic epilepsy and Lennox-Gastaut syndrome, and perhaps photosensitive epilepsy.[29]

Epileptic negative myoclonus is the only focal seizure type for which ethosuximide is typically effective. Although rare, it can occur in a variety of idiopathic and cryptogenic epileptic syndromes, and is characterized by interruption of ongoing electromyographic (EMG) activity contralateral to a lateralized electroencephalographic (EEG) spike-and-wave discharge[29] (see Chapter 50).

Adverse Effects

Dose-related Effects

Dose-related adverse effects involve mainly the gastrointestinal and nervous systems. In early studies, published mainly during the 1960s, 26% to 46% of patients experienced adverse effects.[12] Gastrointestinal effects include nausea, abdominal discomfort, vomiting, anorexia, and diarrhea. These usually appear early and may resolve spontaneously or with dose reduction. Administering the same total daily dose but in more frequent, smaller doses, especially with food, can also be effective; this is the main reason for the standard twice-a-day schedule, given that the half-life is sufficiently long to allow q.d. use otherwise. The other main dose-related effects involve the nervous system, including especially drowsiness, as well as dizziness and fatigue.[9,12,21] Insomnia, hiccups, and ataxia may also occur. Headache and behavioral disturbances, including nervousness, irritability, depression, hallucinations, psychosis, and cognitive impairment, may have idiosyncratic as well as dose-related components. It is notable, however, that improvements in cognitive performance with the use of ethosuximide have also been reported in individuals both with and without epilepsy.[4,9,12]

Idiosyncratic Reactions

Among the idiosyncratic adverse effects of ethosuximide are serious skin rash, including erythema multiforme and Stevens-Johnson syndrome, as well as connective tissue syndromes resembling systemic lupus erythematosus or scleroderma.[9,12] Antinuclear antibodies usually accompany the lupus-like syndrome, but may be asymptomatic.[9] As in other drug-induced lupus-like conditions, renal involvement is extremely rare. Bone marrow toxicity, including granulocytopenia, thrombocytopenia, or pancytopenia, has rarely been noted,[9,12] with eight cases reported over the first 36 years of use, but six of these eight were on other AEDs.[12] As with other drugs, clinical screening by patient education and direct questioning about symptoms is more important than "routine" blood counts.[12,20] The latter may, however, reveal a dose-related, reversible granulocytopenia.[9] There are extremely rare reports of hepatic failure and autoimmune thyroiditis.[9]

Rare instances of dramatic behavioral and psychiatric impairments, including psychosis and impaired consciousness, may be not the direct result of the drug, but rather of its therapeutic effects on the abnormal EEG pattern and associated seizures, a phenomenon known as "forced normalization."[9,31] This has been reported in children with typical absence seizures and no history of psychiatric illness.[12]

Extrapyramidal movement disorders have also been reported, perhaps as a cumulative effect related to dose and duration of use. These include acute dystonic reactions that are responsive to antihistamines, similar to those seen with neuroleptics, as well as bradykinesia, parkinsonism, dyskinesias, and akathisia.[9,12]

Second-Generation Effects

Because ethosuximide is most commonly used in children, and rarely if ever used alone in adults, little information exists about teratogenic effects.[9,29] Rodent studies suggest that these effects are less than with other common AEDs,[9,12] perhaps because no epoxide metabolite has been identified. However, because ethosuximide is not significantly protein-bound, the fetus is exposed to higher levels than with the more highly bound AEDs.[12,15,29] Ethosuximide, as mentioned, is present in breast milk, and adverse behavioral effects on the nursing infant have been reported by some but not all observers.[15,29] Breast-feeding infants have approximately 30% to 50% of the serum ethosuximide concentrations of their mothers.[15]

Drug Interactions

The hepatic metabolism of ethosuximide underlies its pharmacokinetic interactions with other AEDs. Although there is a suggestion that ethosuximide may inhibit P450 enzyme metabolism, this effect is inconsistent and probably minor.[22] Furthermore, the lack of protein binding precludes interactions via displacement from binding sites. There is a potentially important effect of enzyme-inducing drugs on the metabolism of ethosuximide. Concurrent administration of phenytoin, carbamazepine, or phenobarbital may result in falls in ethosuximide serum levels on the order of 15% to 25%, with clearance of a single dose increasing by about 65%.[22] Valproic acid, commonly combined with ethosuximide, inhibits some P450 isoforms and may elevate ethosuximide levels slightly,[9,18,22] although there are rare reports of decreases in ethosuximide after the addition of valproate, as well as of no change.[22] With regard to drugs other than those prescribed for epilepsy, enzyme inducers such as rifampin increase clearance, and inhibitors such as isoniazid may inhibit its metabolism.[22]

Role in epilepsy treatment

Indications

Ethosuximide is a first-line drug for typical absence seizures in the syndrome of childhood absence epilepsy, and it can be used as monotherapy if generalized tonic–clonic seizures are not present. Although valproic acid is equally effective,[7,26] hepatotoxicity is a concern, especially in younger children, arguably making ethosuximide the drug of choice. In older children, in whom new-onset generalized tonic–clonic seizures are more common—approximately 40% above age 7[29]—valproate monotherapy may be preferable. If generalized tonic-clonic seizures have already occurred, ethosuximide must be combined with another drug effective against these, or monotherapy with valproate or one of the newer broad-spectrum drugs, such as lamotrigine, topiramate, zonisamide, and levetiracetam, must be instituted. Of these, only lamotrigine has received significant study, but reviews have found insufficient data to compare its effectiveness with that of the older drugs.[23] In the minority of patients whose absence seizures are not well controlled on either ethosuximide or valproate, the alternative drug or a combination of the two may be efficacious;[7,29] Bourgeois[3] has found in an experimental model that the therapeutic effects of this combination are additive, whereas toxic effects are less than additive, resulting in a favorable therapeutic ratio. Ethosuximide may also be combined with benzodiazepines or acetazolamide, as well as with the newer drugs mentioned earlier, in cases of refractory absence.

Ethosuximide is also useful in the control and prevention of absence status epilepticus,[13,24,29] particularly when this is associated with a known history of primary generalized epilepsy, as noted earlier. When absence status presents de novo in adults, it can represent “secondary bilateral synchrony” from an occult focus[30] and, in this instance, it would not be expected to respond to ethosuximide, although clinical data are sparse. In combination with clonazepam, ethosuximide has also been somewhat effective in the childhood syndrome of continuous spike-and-waves during slow-wave sleep.[32]

Atypical absence seizures, as seen in symptomatic generalized epilepsies, may respond to ethosuximide alone,[29] but because of the high incidence of additional seizure types, other drugs, particularly valproate, are almost always required. Evidence for the effectiveness of ethosuximide in other primarily generalized seizures, such as myoclonic, tonic, or atonic seizures, is limited, but it may have an adjunctive role.[27,29] On the other hand, ethosuximide is clearly indicated for the rare partial seizure type of epileptic negative myoclonus.[29]

Dosing Recommendations

Ethosuximide is manufactured in two forms, a 250-mg capsule and a syrup containing 250 mg/5 mL. Although its long half-life could allow once-daily dosing, most patients do better with two or three doses, particularly after meals, to minimize gastrointestinal side effects.[29] In younger children, a full target dose of 15 to 20 mg/kg can be given, with steady state reached in 1 to 2 weeks. In older children and adults, Sherwin[29] recommends starting at 250 mg/d and increasing the daily dose by 250 mg every 3 to 4 days until a daily dose of 15 to 20 mg/kg is reached, dose-related side effects occur, or seizures are controlled. In the elderly, whose metabolism may be slower and whose sensitivity to side effects greater, increments of 125 to 250 mg/d can be added at weekly intervals, aiming for a slightly lower target range of 10 to 20 mg/kg/d. Depending on clinical response, daily doses as high as 40 mg/kg/d in children, or 2,000 mg/d or 30 mg/kg in adults, can be used.[29] As mentioned, the usual therapeutic range is 40 to 100 µg/mL (300 to 700 µmol/L),[5,29] although levels up to 150 µg/mL may be needed, particularly in cases of absence status. In growing children, intermittent dose increases will be needed to maintain levels. Because patients may be unaware of having these seizures, and because even clinically inapparent generalized spike-and-wave complexes may impair function,[6] routine or prolonged EEG studies may provide useful information about drug efficacy.[26]

Precautions

During titration, patients should be monitored for adverse effects, especially those affecting the gastrointestinal or central nervous systems (CNS). Regarding a possible risk of marrow suppression, intermittent measurement of complete blood counts is reasonable, although it is not clear that any regular interval is indicated.[20] Counseling regarding symptoms of granulocytopenia or thrombocytopenia, such as fever, sore throat, and bleeding, is more important.

As with any AED, ethosuximide should be discontinued and another appropriate drug substituted if unacceptable side effects occur at doses that do not control seizures. If seizures are controlled, consideration for drug withdrawal is appropriate after 2 years without seizures, particularly if EEG with hyperventilation shows no spike-and-wave activity. It is

prudent also to repeat the EEG approximately 1 month after the drug has been withdrawn.[29] Because of its long half-life and the usually minor clinical impact of the absence seizures for which ethosuximide is given, abrupt discontinuation is probably safe, but gradual reduction during several weeks is preferable unless the drug is being withdrawn because of severe adverse effects.

Contraindications

The only absolute contraindication to ethosuximide is a severe prior allergic reaction to the drug or to other succinimides. Relative contraindications are a history of psychiatric illness, blood dyscrasias, or systemic lupus erythematosus. It must be used with caution in patients with renal or hepatic disease. Ethosuximide is not indicated for patients with partial or generalized tonic–clonic seizures unless absence seizures are also present.

Summary and Conclusions

Ethosuximide is a first-choice drug for the treatment of typical absence and related seizures. Mechanistically, it reduces rhythmic activity in the thalamocortical system, possibly by blockade of the low-threshold, voltage-dependent Ca current mediated by T-type Ca channels on thalamic neurons. Although generally well tolerated, it has the potential for dose-related adverse gastrointestinal and CNS effects, and can have idiosyncratic neuropsychiatric, dermatologic, and, rarely, bone marrow effects. There is a fairly well established therapeutic range of plasma levels, which can be achieved with once daily or more frequent dosing. Even in an era of newer, broad-spectrum drugs, ethosuximide will likely retain its place as a selective antiabsence drug.

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Chapter 148

Felbamate

William H. Theodore

Introduction

Felbamate (2-phenyl-1, 3-propanediol dicarbamate) (FBM), structurally unrelated to any other antiepileptic drug (AED) in current clinical use, is particularly interesting because its pharmacologic activity in animal models suggests a spectrum broader than that of most other AEDs, indicating the potential for clinical efficacy in patients with generalized as well as localization-related epilepsies.[68] Moreover, it is one of the few nonsedating agents available. Unfortunately, it is associated with a high risk for hematologic and hepatic toxicity.

Chemical structure

FBM is related structurally to the antianxiety drug meprobamate (Fig. 1A). Its molecular weight is 238.24, and the factor to convert from micrograms (µg) per milliliter to micromoles (mmol) per liter is 4.2. It is relatively insoluble in water or ethanol, but it penetrates the central nervous system readily.[11,59]

FluoroFBM (FFBM, 2-phenyl-2-fluoro-1, 3 propanediol dicarbamate), currently in preclinical development, is an analog designed to have clinical efficacy similar to FBM without the serious adverse effects of the latter.[4] FFBM has a fluorine substituted for hydrogen in the 2-position of the propanediol moiety (Fig. 1B). This substitution appears to prevent the production of the reactive toxic metabolite of FBM, atropaldehyde (ATPAL, or 2-phenylpropenal). If FFBM does prove to have similar efficacy and dose-related toxicity, but no severe systemic side effects, it may become an extremely useful AED; there are still only a few without cognitive side effects.

Methods for Determination in Body Fluids

High-performance liquid chromatography (HPLC) with spectrophotometric detection is the standard method for FBM measurement; multiple AEDs can be measured simultaneously.[9] Gas-liquid chromatography and HPLC provide comparable results.[23] Capillary electrophoresis has been proposed as a more rapid alternative.[72] Interlaboratory variation does not depend on the method used; it may be greater for AEDs like FBM that are measured less frequently, and laboratory participation in an external quality control program is essential.[89]

Pharmacology

Activity in Experimental Models of Seizures/Epilepsy

FBM is active in maximal electroshock, pentylenetetrazole, bicuculline, and picrotoxin seizure models in experimental animals, suggesting a broad spectrum of activity.[58] Its protective index (TD_{50}/ED_{50}) in the rat maximal electroshock model is 63 (compared with 100 for phenytoin), and in the pentylenetetrazole model it is 12 (vs. 1.6 for valproic acid).[59] No pharmacodynamic evidence of tolerance to FBM was found in 15-day studies in rats and mice.[76] FBM increased the threshold for focal seizures and reduced seizure severity, duration, and afterdischarge duration at doses that produce no adverse behavioral effects in amygdala-kindled rats.[92] FBM is not protective against bupropion-induced seizures.[84] FBM in doses of 100 to 500 mmol had no effect on soman-induced burst frequency, but decreased duration.[26]

Both FBM and its congener fluoroFBM are effective in the perforant path stimulation model of status epilepticus, even in late stages, and may have some antiepileptogenic effects.[49,50] Some studies have suggested pharmacodynamic synergism between lamotrigine and FBM in activity against maximal electroshock, 4-aminopyridine, and pentylenetetrazole-induced seizures.[12,48] Interestingly, lamotrigine but not levetiracetam showed additive toxicity to FBM in mice.[46,47]

Mechanisms of Action

In cultured hippocampal neurons, FBM has an unusual pattern of activity, blocking currents evoked by *N*-methyl-D-aspartate (NMDA) but facilitating γ-aminobutyric acid (GABA)ergic responses.[64,82,90] The pattern of interaction with $GABA_A$ receptors suggests relatively weak, barbiturate-like, modulatory (rather than direct agonist) activity.[64] Strychnine (0.25–0.5 mg/kg) and picrotoxin (3 mg/kg) impaired the protective activity of FBM against maximal electroshock (MES), suggesting that GABAergic inhibition and strychnine-insensitive glycine receptor–mediated events may contribute to anticonvulsant activity.[75]

Proposed mechanisms and sites for the NMDA receptor interaction include competitive antagonism at the glycine site, open channel blocking or, most likely, noncompetitive allosteric channel effect.[51] FBM does not appear to affect inhibitory glycine receptor currents in hippocampal neurons.[35] These features may explain both the AED spectrum of FBM and its stimulant-like side effects at clinical doses. FBM has neuroprotectant effects that could be mediated by NMDA receptor interaction.[52] Several pharmacologic features of FBM may account for its clinical properties. At therapeutic concentrations (50–300 mmol) FBM may bind to resting NMDA channels in the absence of glutamatergic ligands and decrease subsequent NMDA currents by stabilization of desensitized channels, thus inhibiting seizure discharges but having less effect on normal activity.[44] NMDA subunit specificity, with selectivity for NR1a/NR2B subunits, could have a similar effect.[27,40]

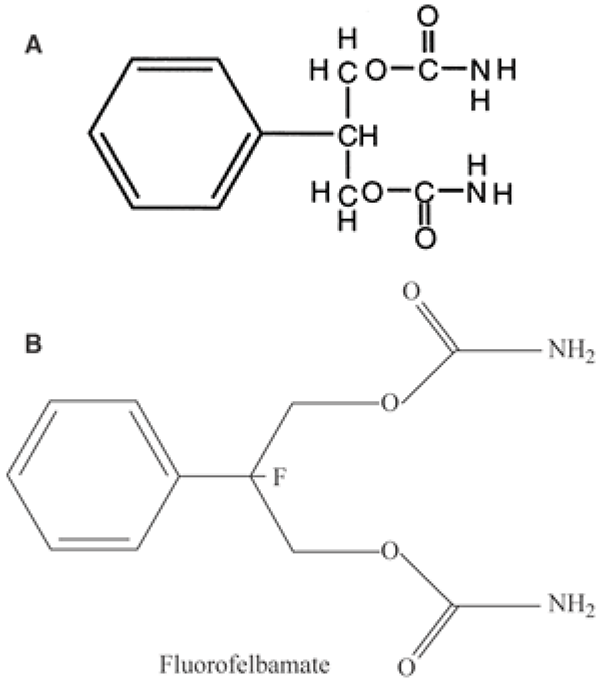

FIGURE 1. A: Structure of FBM. Although it resembles meprobamate, it has no anxiolytic effects. **B:** Structure of fluorofelbamate.

Some studies suggest that sodium (Na) channel blockade may contribute to antiseizure activity. FBM inhibited voltage-dependent Na^+ currents when α-subunits from rat and human brain were expressed in *Xenopus* oocytes, but only when

perfused on the intracellular side of the membrane.[77] FBM also blocked sustained repetitive firing in mouse spinal cord neurons.[90]

Activity in Other Models

In rats, FBM (100 and 300 mg/kg) attenuated overall naloxone-precipitated opiate withdrawal severity in a dose-related manner and reduced occurrences of chews, teeth chatters, and penile grooming, possibly due to glycine antagonist activity.[42] A similar mechanism may account for FBM's efficacy against D2 (haloperidol) but not D1 receptor–mediated akinesia, a pattern similar to other NMDA receptor complex glycine site antagonists.[43]

Toxicity Models

Early studies had shown only relatively nonspecific effects, such as decreased body weight and food consumption in mice, rats, and dogs, and increased liver weight without associated histopathological changes.[54] An increased incidence of hepatic cell adenoma and of interstitial cell tumors of the testes in rats also occurred.[53]

Recognition of FBM's idiosyncratic toxicity has triggered a search for possible mechanisms. Most studies have suggested that reactive intermediates, such as atropaldehyde (2-phenyl-propenal) an unsaturated aldehyde, may be the most important metabolites for hepatic and hematological toxicity.[14,33,34] 2-Phenylpropenal irreversibly inhibits GSTM1-1, the form of glutathione-S-transferase in liver.[15,16]

Glutathione might protect against reactive intermediate formation, although some toxicity mechanisms may be redox-independent.[29,60] Interestingly, the level of uridine diphosphoglucuronosyltransferase activity had no effect on the metabolic pathway in rats.[14] In human liver preparations, FFBM does not form reactive intermediates.[4]

Clinical pharmacokinetics

Formulations

FBM is available in 400- and 600-mg scored tablets, and in a suspension containing 600 mg/5 mL. Because there is no difference in bioavailability, the formulations should be interchangeable.

Absorption

FBM is about 90% absorbed after oral administration.[91] Bioavailability is similar for the suspension and both the chewable and standard tablets, and it is not affected by food.[58] Peak plasma concentration is reached 2 to 6 hours after dosing.[27,91]

Plasma Protein Binding and Distribution

Plasma concentration, area under the curve (AUC), and maximal concentration (C_{max}) increase linearly with dose.[58] The apparent volume of distribution, about 0.8 L/kg, is the same after a single dose or continued administration. FBM is relatively lipid-soluble and readily crosses the blood–brain barrier.[11] P-glycoprotein but not ABCC2/MRP2-mediated efflux may limit FBM brain access in rats.[61,62] FBM is 20% to 25% reversibly bound to plasma protein, mainly albumin. FBM does not show preferential accumulation in any peripheral organ or specific brain region. Pharmacokinetic parameters are stable during continued administration.[11]

Metabolism and Elimination

FBM is metabolized by the cytochrome P450 system, which probably accounts for its interactions with other

AEDs.[59] The terminal elimination half-life ranges from 13 to 23 hours. About 40% to 50% of the absorbed dose appears unchanged in the urine. Metabolites include *p*-hydroxyphenyl FBM, 2-hydroxy FBM, monocarbamate derivatives, and polar compounds (including conjugates), none of which has significant antiepileptic activity; these make up about 15% of plasma radioactivity when labeled FBM is given.[58] Children may metabolize the drug more quickly than adults. Beagle pups had decreased bioavailability but unchanged absorption and volume of distribution compared with adult beagles, suggesting faster elimination.[1] In humans, clearance is 40% higher in children than adults, and half-life approximately is 15 hours.[5,7] However, there do not seem to be any sex-related differences. FBM blood levels are stable during long-term treatment, with no evidence for autoinduction of metabolism.[17,68]

Elderly patients have lower clearance, longer half-life, as well as higher mean AUC and C_{max} values.[65] FBM clearance was decreased, and half-life, C_{max} and AUC values increased in subjects with renal dysfunction, in significant correlation with creatinine clearance.[21]

Drug Interactions

When FBM is used, drug interactions may be an important factor. FBM reduces blood carbamazepine levels by about 20%, whereas levels of the active metabolite, carbamazepine epoxide, are increased by 25% to 50%.[2,19,22,82,86]

Several investigators[22,45,85,91] have reported that FBM increases phenytoin, valproic acid, and phenobarbital levels. The doses of these drugs may need to be reduced by 10% to 30%

to maintain constant levels when FBM is given concurrently, although the effect varies from patient to patient. For phenytoin, the effect on blood levels may be related to increasing FBM doses.[71] FBM increases conversion of clobazam to its active metabolite N-desmethyl-clobazam (N-CLB), apparently to a greater degree than does phenytoin or carbamazepine.[10] Because the metabolite appears to be more potent than the parent drug, this effect could increase both efficacy and toxicity. FBM does not appear to have a clinically significant interaction with clonazepam, lamotrigine, or vigabatrin.[79,87]

In monotherapy, the FBM plasma concentration versus dose relationship was linear up to 6,000 mg/day.[70] Carbamazepine and phenytoin increase FBM clearance by about 30%, and consequently lower blood levels of FBM. On monotherapy at 3,600 mg/day, plasma concentrations of FBM ranged from 60 to 90 mg/L, whereas patients on hepatic enzyme-inducing drugs had levels of 30 to 70 mg/L. In patients receiving hepatic enzyme inducers and FBM at a maximum daily dose of 3,000 mg, FBM levels were in the range of 30 to 40 mg/L, compared with 70 to 80 mg/L in patients on FBM monotherapy at 3,600 mg/day.[17,45,68,80] Valproic acid decreased FBM clearance by about 15%[58] in some studies, particularly in children.[37] Protein binding of other AEDs does not seem to be affected by FBM.[19,58] FBM levels are not affected by erythromycin.[69] In a study reporting reduced AUC for the gestodene but not the ethinyl estradiol component of an oral contraceptive, one subject had intermenstrual bleeding but none had evidence for ovulation.[67]

Relationship Between Plasma Concentration and Effects: Value of Therapeutic Drug Monitoring

There are few data on the relation of plasma levels of FBM to clinical response. Children in the Lennox-Gastaut syndrome trial tended to have fewer seizures at plasma levels of 45 than of 18 mg/L.[18] Although the data are not directly comparable, the response in adult trials may have been better in the range of 60 to 80 mg/L than of 30 to 40 mg/L.[5,17,45,68,80] Some investigators have suggested a lower therapeutic range of about 30 to 60 mg/L (125 to 250 mmol/L).[32] Because FBM clearance is increased by carbamazepine and phenytoin, higher doses may be necessary to achieve comparable plasma levels when these drugs are given at the same time.

Adverse Effects

Dose-Related Effects

The median lethal dose (LD_{50}) could not be established in rats, because the animals did not succumb after ingestion of 3 g of FBM, the maximum dose that could be administered.[59] FBM was well tolerated in clinical trials; only about 7% of patients stopped treatment prematurely because of adverse events. In clinical trials, adverse effects that occurred significantly more often with FBM than placebo included nausea and vomiting, diplopia, blurred vision, headache, and ataxia.[30,31] However, these effects were more common in add-on than monotherapy trials, and they often disappeared when the other drugs, particularly phenytoin, were stopped.

In adults on monotherapy, insomnia and weight loss tend to be the most frequently reported side effects, followed by gastrointestinal distress and headache. Weight loss is reported in up to 75% of patients in clinical trials, averaging about 3 kilograms.[3] It tended to be lower in children.

Stimulant-like effects are prominent.[39] Some patients may experience psychiatric deterioration, particularly an anxiety-dysphoria syndrome associated with insomnia; but up to 50% may report modest improvement in mood. Children, in contrast, may experience sleepiness (perhaps analogous to the paradoxic effect of amphetamine-like drugs). FBM does not appear to have anxiolytic effects or attenuate the adverse psychological consequences of AED withdrawal.[39] Baseline insomnia and anxiety may be markers for poorer psychiatric responses to FBM. Isolated cases of tremor, involuntary movements, and psychosis have been reported, which may or may not have been caused by FBM.[28,38,41]

There have been several reports of crystalluria associated with FBM overdoses, leading to acute renal failure in at least one case when peak plasma levels were 200 μg/mL.[55,63] Acute urolithiasis occurred in a patient taking 3,000 mg/day with trough levels ranging from 52 to 170 μm/mL.[74]

Patients tend either to like FBM very much, feeling increased energy and well-being along with better seizure control, or to tolerate it poorly. FBM side effects such as anorexia, dyspepsia, headache, insomnia, or anxiety usually do not remit on continued treatment. Some patients not only lose weight, but develop a “washed out” appearance, rather like a ring-wraith in Tolkien.

Idiosyncratic

No evidence is noted of clinically significant hepatic or hematologic change in clinical trials, although mild elevation of serum liver enzymes and other abnormal clinical laboratory values occasionally were noted.[30,31,58] Rashes and hypersensitivity reactions, sometimes including fever and lymphadenopathy, occurred in 3% to 4% of patients; toxic epidermal necrolysis has been reported.[83] The number of patients studied, about 1,600, would have been too small to detect the incidence of hematologic and hepatic toxicity that has begun to be reported with wider clinical use of FBM.

Hematologic abnormalities, including fatal aplastic anemia, are more frequent in patients taking FBM than would be expected by chance. In an analysis of 31 cases, 23 met formal diagnostic criteria, excluding patients with other causes such as systemic lupus erythematosus.[36] Using an estimate of 110,000 patients exposed, the risk was estimated to range from 2 to 209 per million per year, depending on whether cases were included only when no other contributing cause was present, such as another AED, or all cases; the most “probable” estimate was 127 per million. The incidence seems higher in women. Patients had been taking FBM for up to a year before symptoms began.

At least 18 cases of liver failure (with eight deaths) ranged in age from 3 to 56 years; six were children. Exposure had ranged from 14 to 265 days; some of the patients had a rash as well as liver toxicity. All the patients were taking other AEDs.

Teratogenic Effects

Results of teratology studies in rats and rabbits have been negative, but no human data are available.

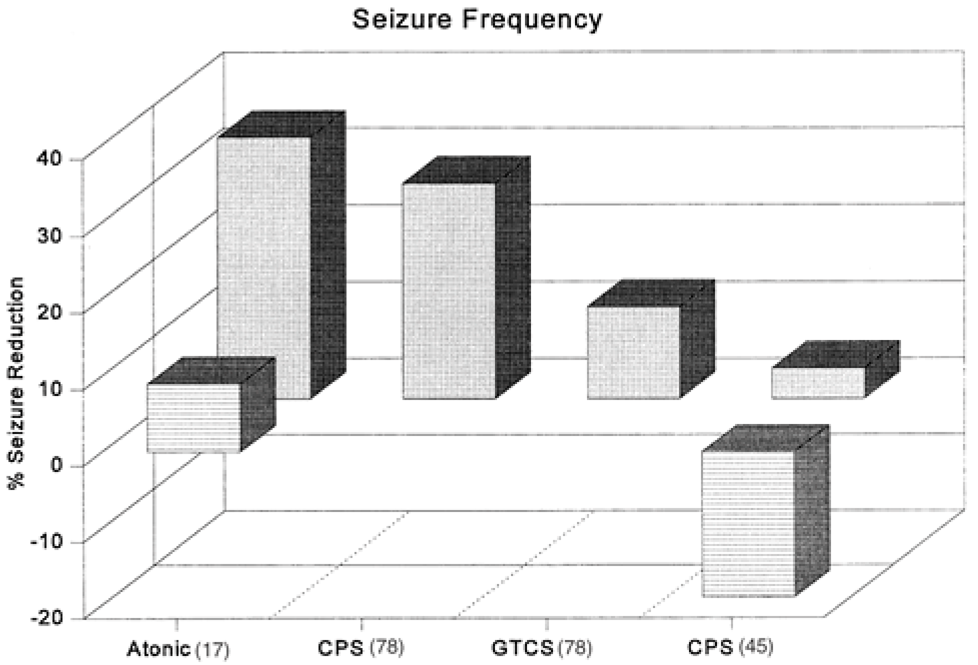

FIGURE 2. Percentage reduction of seizures in patients treated with FBM compared with placebo in double-blinded add-on trials of patients with complex partial (*CPS*), secondarily generalized tonic-clonic (*GTCS*), and atonic seizures. One study[78] compared FBM with placebo during the blinded phase, whereas the other two compared both treatments with baseline. Leppik et al. found the difference in effect in their study was mainly a consequence of increased seizures on placebo.[45] Numbers in parentheses are reference numbers.

Effects Related to Drug Interactions

Drug interactions may play an important role in the frequency of side effects experienced by patients on FBM. Increased levels of phenytoin and valproic acid may contribute to nausea and vomiting, diplopia, blurred vision, and ataxia. Even though carbamazepine levels fall, levels of the pharmacologically active metabolite, carbamazepine epoxide, may increase. This compound could also contribute to side effects, because its protein binding is lower than that of carbamazepine itself, and it may penetrate the brain more readily.

However, it is possible that some of the therapeutic effects of FBM in add-on trials could also be related to drug interactions, particularly increased levels of phenytoin and valproic acid. One study suggested that the fall in carbamazepine levels might lead to reduced seizure control, despite increased levels of carbamazepine epoxide.[80] It may be valuable to measure epoxide as well as carbamazepine levels when patients are taking both FBM and carbamazepine. Considerable variation exists between individuals in the effect of FBM on other AEDs. Rather than automatically adjusting other drug doses, it is important to measure their levels. Because FBM does not have an appreciable effect on the protein binding of other drugs, it is not necessary to measure free AED levels.

Efficacy

Localization-Related Epilepsies

A series of published clinical trials showed that FBM is effective against simple partial, complex partial, and generalized tonic–clonic seizures in patients with localization-related epilepsy. These trials were carried out in patients with intractable seizures that had failed to respond to a number of other AEDs. Many were candidates for surgery. Two cross-over add-on studies showed a reduction of about 15% to 30% in seizure frequency, comparing FBM with placebo periods, at doses of 2,300 to 3,600 mg/day and plasma levels of 30 to 40 mg/L[45,80] (Fig. 2). One of these used a three-period design to obviate carry-over effects. Two trials used the AED withdrawal for a surgical monitoring scenario to conduct monotherapy studies. In one, 8 of 19 patients randomized to placebo, as compared with 13 of 21 receiving FBM, completed 18 days of monotherapy.[78] Two FBM patients dropped out because of seizures, and six dropped out because side effects, including anxiety, difficulty sleeping, abdominal discomfort, acute psychosis, and orobuccal dyskinesias. Ten placebo patients met the criteria for premature discontinuation owing to seizures, and one had an episode of panic. Overall, patients on FBM alone had a seizure rate only 25% that of patients on placebo alone. In the other trial, a nonsignificant trend occurred for patients on FBM to have fewer seizures over 10 days.[13]

Three studies used an endpoint of "survival" rather than seizure frequency. In an add-on trial after surgical monitoring, a fourth seizure was less likely to occur in 28 days in patients on FBM than in those on placebo[5] (Fig. 3). Two studies compared FBM at 3,600 mg/day with low-dose valproic acid (15 mg/kg/day) during 112 days.[17,68] Other AEDs were tapered by day 28. Of the patients on FBM, 18% to 40%, compared with 78% to 91% on valproic acid, dropped out because of increased seizure frequency or severity (Fig. 3). A reduction in seizure frequency of 50% or greater compared with baseline was noted in 29% of patients on FBM, compared with 11% of those on low-dose valproic acid.[30]

In an open-label study of 36 patients who had not responded to other AEDs, and a mean follow-up of 10 months (range 2–27), 5% of patients given FBM were seizure-free, 11% had seizure reduction of more than 75%, and 23% had seizure reduction between 50% and 75%.[6]

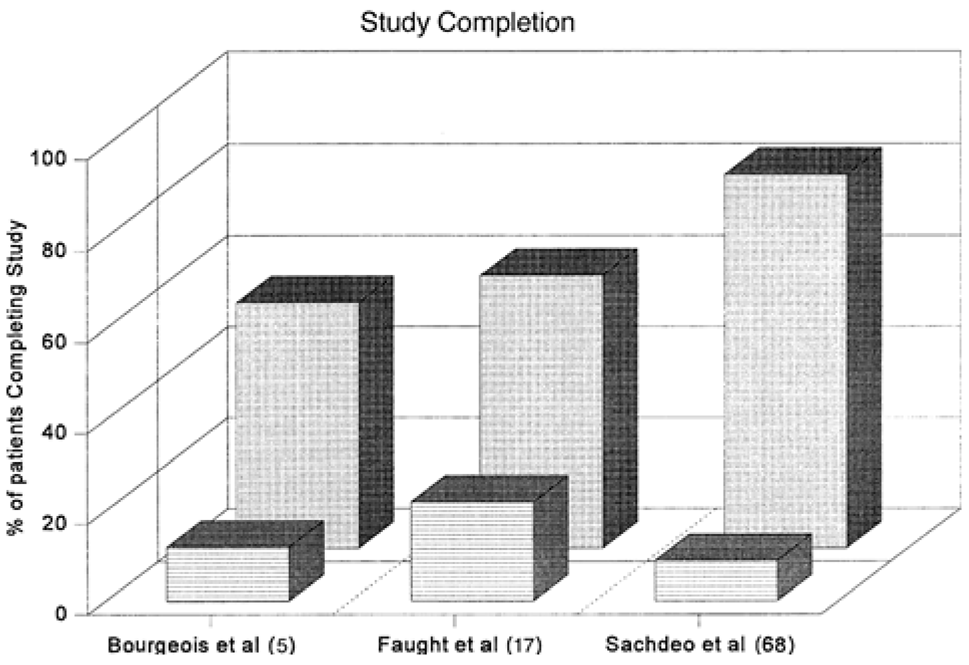

FIGURE 3. Percentage of patients taking FBM compared with placebo[5] or low doses of valproic acid[17,68] who reached a defined endpoint of seizure frequency or severity. Patients on FBM were more likely to complete the trial in each study. Numbers in parentheses are reference numbers.

Generalized Epilepsies

FBM is effective in patients with the Lennox-Gastaut syndrome.[18] Overall seizure counts by the parents or guardians of patients on FBM at a dose of 45 mg/kg (3,600 mg/day maximum; mean blood level, 43.8 mg/L) were 19% lower compared with baseline; they were only 7% lower in patients on placebo ($p = 0.01$). Atonic seizure frequency was reduced 34% by FBM but only 9% by placebo ($p = 0.002$). The effect of FBM may have been greater at 45 mg/kg per day than at 15 mg/kg per day. Subsequent data analysis[31] showed that 47% of patients had a reduction of at least 50% in total seizures, and of 57% in atonic seizures. In this study, phenytoin and valproic acid levels varied up to 22%. In another study, patients had 40% fewer drop attacks ($p < 0.03$) and 60% fewer total seizures ($p < 0.02$) on VPA and FBM compared with VPA alone. However, VPA levels rose by 12.7% when FBM was added ($p < 0.01$). In this study, multivariate analysis suggested that FBM's therapeutic

effect on drop attacks is caused in part by increased VPA levels, but the combination may be synergistic for the effect on total seizure number.[73]

Preliminary reports in small groups of patients have suggested that FBM may be effective in other generalized seizure syndromes and seizure types, such as absence or juvenile myoclonic epilepsy, when other drugs have failed.[79] Although the results are consistent with the effect found in Lennox-Gastaut syndrome, they have not yet been confirmed by controlled studies.

FBM may be more or less useful than other new drugs for any given patient. It is very difficult to compare efficacy data across clinical trials, or to judge the relative effectiveness of AEDs. Even within a single trial, the effect of the design may vary with seizure type. FBM appeared to be more effective against complex partial seizures than generalized tonic–clonic seizures[80] (see Fig. 2). However, the difference may have been a consequence of the better baseline control of the latter achieved by carbamazepine in this add-on study.

Most clinical trials have a relatively short duration, particularly compared with the course of seizure disorders. During long open-label follow-up periods, there is a tendency for patients gradually to discontinue most experimental drugs.[79] A high frequency of seizures on standard AEDs is a criterion for trial entry, and surgery is an alluring alternative. Although it proved difficult to taper baseline AEDs during open-label follow-up after FBM add-on studies, efficacy does appear to be maintained during long-term treatment with FBM in patients with Lennox-Gastaut syndrome as well as localization-related epilepsy.[30,31,85]

Because FBM appears to be less sedating than other AEDs, it may be useful for patients who find this side effect particularly debilitating.

Activity in Other Indications

Relatively little interest has been expressed in using FBM for other conditions. Several patients with trigeminal neuralgia and hemifacial spasm were said to have a favorable response.[7,56]

Role in epilepsy treatment

Indications

At this point, there are relatively few indications for FBM. Given the large number of new AEDs now available for patients with localization-related epilepsy, and the increasing attention to surgical therapy, few patients will be appropriate for FBM. Some children with Lennox-Gastaut syndrome and similar syndromes may benefit from FBM, because current therapy generally is disappointing, and none of the new AEDs has made a dramatic impact. FBM would have the advantage of minimal cognitive toxicity as well.[8,25] Some investigators have suggested that FBM could be used in patients with infantile spasms unresponsive to other therapy; here, other alternatives such as corticosteroid therapy or vigabatrin have severe toxicity as well.[57]

FBM appears to be effective for treatment of partial seizures in dogs.[66]

Dosing Recommendations

Starting Doses

Although rapid escalation of therapy has been performed in clinical trials, a slow titration schedule may lead to fewer initial adverse effects, particularly gastrointestinal disturbance, insomnia, and anxiety. The drug seems to be better tolerated when it is taken with meals and the doses are spread out as much as possible. FBM can be started at 400 mg three times a day, with increases of 400 to 600 mg/day every 1 to 2 weeks. Some patients, particularly the elderly, may need lower starting doses and slower increases. For children, an initial dose of 15 mg/kg per day with weekly increases to 45 mg/kg per day seems reasonable.

FBM decreases clearance of phenytoin and valproic acid. To maintain steady-state plasma levels of these drugs, it may be necessary to reduce their doses when FBM is started. However, this should be done cautiously to avoid seizure exacerbation, because it may take several weeks to reach therapeutic doses of FBM.

Maximal Dose

The highest dose of FBM used in adult clinical trials has been 3,600 mg/day, but some patients have received 5,000 to 6,000 mg/day. The maximal dose tried in the Lennox-Gastaut trial was 45 mg/kg or 3,600 mg/day. Clinical experience will be required to determine the true upper limit of the dose. In some patients, because of gastrointestinal discomfort, the maximally tolerated dose is in the range of 2,400 to 3,000 mg/day. Children usually are more rapid metabolizers than adults, and therefore need relatively more drug (on a mg/kg basis) to maintain effective blood levels. The pharmacology of FBM has not been studied in elderly patients, but metabolism is likely to be reduced. Moreover, the elderly are usually more sensitive to the central nervous system side effects of AEDs. The starting dose, and subsequent increases, should probably be reduced by about one-third.

Stopping the Drug

Because of the risk for aplastic anemia or liver disease, FBM should be stopped when it is not effective. On the other hand, because it is likely to be used when all other agents have failed, patients may be able to tolerate side effects that are not life-threatening. Insomnia, gastrointestinal distress, and weight loss may be less discomforting to some patients than the side effects of other drugs, particularly if seizures are controlled.

There is little evidence for acute exacerbation of seizures during FBM withdrawal, which has been carried out rapidly in clinical trials. One study reported increased seizure activity during FBM withdrawal, but the effect persisted for 3 months, suggesting the effect was not a transient exacerbation but simply due to removal of an effective AED; moreover, levels of phenytoin and carbamazepine fell after withdrawal.[88] Patients who were placed on gabapentin had smaller seizure increases.

The drug should certainly be stopped abruptly if there is evidence of hematologic or liver disease. When reports of these complications began to appear, the FBM doses of many asymptomatic patients were tapered during 1 to 2 weeks without a sudden increase in seizures, although many patients experienced a long-term rise in seizure frequency despite higher doses or addition of other drugs.

Precautions and Contraindications

It may be prudent to avoid combining FBM with other drugs that can cause hepatic or hematologic dysfunction, such as valproic acid or carbamazepine. Aplastic anemia may be more likely to develop in women than in men. FBM should not be given to patients with a history of blood dyscrasias or autoimmune disorders. Patients with a history of psychiatric disorders may be more likely to experience acute anxiety or even psychosis on FBM. FBM was less well tolerated in elderly subjects compared with young subjects, with higher rates of adverse events and dropouts at the higher dose level.[65]

The manufacturer advises that patients on FBM have blood counts and liver function tests every 1 to 2 weeks. It is probably reasonable to continue this schedule for 3 to 4 months, followed by monthly testing. Unfortunately, even this high degree of caution may not detect incipient toxicity. Aplastic anemia and hepatic failure may not be reversible even if detected early. Moreover, symptoms may develop after the drug has been stopped. Platelets and white blood cells have a short life span, but red cells live 120 days, so peripheral evidence of marrow injury may have a delayed appearance. Mild elevations of hepatic enzymes are found often in patients taking AEDs, and may not be an indication of "toxicity."

It may be possible to identify patients with reduced erythrocyte glutathione peroxidase, superoxide dismutase (SOD), and glutathione reductase activities compared with age-matched controls, who would be particularly at risk for aplastic anemia,[20] or to quantify production of 2-phenylpropena; patients with high levels might be at greater risk as well.[81]

Like many other AEDs, FBM appears to increase ALA synthase activity, and might provoke attacks of acute intermittent porphyria.[24]

Summary and conclusions

FBM has a broad antiepileptic spectrum. Children with the Lennox-Gastaut syndrome and related secondarily generalized epileptic syndromes, for whom few therapeutic options exist, may benefit most from FBM therapy. It can also be tried in patients with refractory partial and secondarily generalized seizures that have not responded to other drugs. For some patients, who can attain seizure control with other drugs only at the cost of unacceptable central nervous system depressant side effects and who are not candidates for surgery, the risk for systemic toxicity associated with FBM may be acceptable. FBM should be used only when seizures have not been controlled by other drugs. Results of clinical laboratory tests should be monitored closely and the drug stopped if any abnormalities are detected. When deciding to start a patient on FBM, it is important to assess the risk–benefit ratio very carefully.

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Chapter 149

Gabapentin

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Introduction

Gabapentin is a novel antiepileptic drug (AED) related in structure to the neurotransmitter γ-aminobutyric acid (GABA) (Fig. 1). It was synthesized as a GABA-mimetic agent that could freely cross the blood–brain barrier (BBB). Despite its structural relationship to GABA and its recognized antiepileptic properties, it is doubtful that therapeutic activity results from any form of direct GABAergic effects.

Mechanism of Action

Gabapentin has been shown to prevent seizures in several animal models (Table 1) and in clinical studies. It has a mechanism of action that appears to be different from other AEDs; this topic has been recently reviewed by Sills.[35]

In vitro, gabapentin does not interact with neuronal sodium channels or L-type calcium (Ca) channels.[39] Gabapentin is inactive at concentrations up to 100 μmol in standardized tests for interaction at $GABA_A$, $GABA_B$, benzodiazepine, glutamate, *N*-methyl-D-aspartate (NMDA), quisqualate, kainate, glycine, MK-801, and strychnine-insensitive glycine receptors. In addition, many other neurotransmitter receptors have been screened, including A_1 and A_3 adenosine receptors; α_1, α_2, and ß-adrenergic receptors; D_1 and D_2 dopamine receptors; $histamine_1$ receptors; S_1 and S_2 serotonic receptors; M_1, M_2, and nicotinic acetylcholine receptors; μ-, δ-, κ-, and σ-opiate receptors; leukotriene B_4, D_4, and thromboxane A_2 receptors; phorbol ester dibutyrate receptors; and binding sites on Ca channels labeled by nifedipine and diltiazem and on sodium channels labeled by batrachotoxinin.[39] These negative results support the idea of a novel mechanism of antiepileptic action for gabapentin.

Although gabapentin does penetrate the BBB effectively,[47] and has antiepileptic properties in vivo,[39] it does not interact with $GABA_A$ receptors, nor is it converted to GABA or a GABA agonist. Early evidence did not suggest that gabapentin is an inhibitor of GABA uptake nor of degradation by GABA transaminase at relevant concentrations. However, it can increase GABA accumulation in rat brain, by increasing GABA synthesis[41] and preventing metabolism.[20] In human brain slices[16] and in the intact brain, as measured by magnetic resonance (MR) spectroscopy,[32] it may indeed have modest effects in increasing brain concentrations. It may also have some effects on the GAT-1 GABA transporter system.[51] The degree to which this may contribute to its antiepileptic effects remains uncertain.

It may also possess some baclofen-like effects at the presynaptic $GABA_B$ receptor. It can reduce potassium-evoked Ca influx via voltage-gated channels in a pituitary cell line expressing functional subunits of the receptor, an effect reversed by other selective $GABA_B$ antagonists.[8,30] This may enable gabapentin to selectively reduce excitatory neurotransmitter release with relative sparing on inhibitory neurotransmission. This is despite any evidence that gabapentin can interact with the $GABA_B$ receptor.[39]

Specific binding of gabapentin is highest in the superficial layers of neocortex and dendritic layers of hippocampus, with low levels of binding in the white matter and brainstem.[19] This binding site, which doesn't bind any other conventional AED, has now been identified as the $\alpha_2\delta$ subunit of the voltage-gated Ca channel.[18,49] It appears that two of four isoforms of this subunit are capable of binding gabapentin and its structural analogs.[40] There is now a general consensus that this is the site of action responsible for the great majority of gabapentin's pharmacologic antiseizure activity. It does not appear to act as an inhibitor of any conventional subtype of voltage-gated Ca channel, but rather acts as a selective blocker of channels that contain the $\alpha_2\delta$-1 subunit.[11]

Pharmacologic Fundamentals

Gabapentin is absorbed via the L-amino acid transport system in the proximal small intestine. Absorption is rapid, with maximum plasma concentrations occurring 2 to 3 hours after oral administration.[46] Gabapentin appears to move across the gut and into the blood by a saturable transport mechanism competitively inhibited by L-leucine[36] (the amino acid transporter known as system L). Experiments with the system L transporter in cultured Chinese hamster ovary tumor cells also support the notion that gabapentin competes with L-leucine, L-valine, and L-phenylalanine and is itself a substrate for transport by system L. This may explain why gabapentin penetrates into the brain: The amino acid structure of gabapentin and the very high hydrophilicity of the compound would otherwise reduce its access across biologic membranes. The time of peak antiepileptic action with gabapentin is delayed about 2 hours after intravenous administration, past the time of peak drug concentration in either the blood plasma or the brain interstitial space.[50] Structure activity studies indicate that activity in seizure models correlate with affinity for this transporter system,[37,38] although it remains doubtful that the transporter has anything other than an indirect relationship to gabapentin's ultimate antiseizure activity.

Absorption is dose dependent due to saturation of the L-amino acid transport system. The bioavailability of gabapentin decreases from 0.54 ± 0.11% at a dosing rate of 400 mg three times daily, to 0.35 ± 0.07% at a dosing rate of 1,200 mg three times daily. The bioavailability of gabapentin is not affected by food.

Gabapentin is not bound to plasma proteins to any significant degree. Gabapentin is transported from plasma across the BBB to the brain via the L-amino acid transport system. Gabapentin concentration in a single specimen of human brain was 80% of plasma concentration, confirming animal distribution studies.[31]

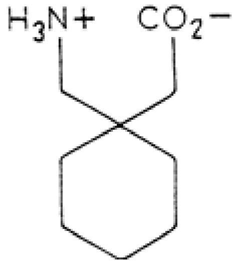


FIGURE 1. Structure of gabapentin.

Table 1 Activity of gabapentin in animal models of seizures

Species	Convulsant agent	Dose route	ED^{50} (mg/kg)
Mouse	Tonic extensor seizure (maximal electroshock)	IP	78
Rat	Tonic extensor seizure (maximal electroshock)	PO	9.1
Rat	Tonic extensor seizure (maximal electroshock)	IV	2.1
Rat	Behavioral seizure score (hippoc, kindled rats)	IP	30[a]
Mouse	Threshold clonic seizure (pentylenetetrazole)	IP	47
Mouse	Threshold clonic seizure (bicuculline)	IP	>500
Mouse	Threshold clonic seizure (picrotoxin)	IP	>500
Mouse	Threshold clonic seizure (strychnine)	IP	>500
Mouse	Tonic extensor seizure (thiosemicarbazide)	IV	6.3
Mouse	Tonic extensor seizure (isoniazide)	PO	20
Mouse	Tonic extensor seizure (*N*-methyl-D-aspartate)	IP	>240[b]
Rat	Tonic extensor seizure (kainate)	IP	>300
DBA/2J mouse	Tonic extensor seizure (audiogenic)	PO	2.5
Wistar rat	Absence seizure (EEG) (genetic predisposition)	IP	Not effective (25–100 mg/kg)

Gerbil	Tonic extensor seizure (genetic predisposition)	PO	15
Gerbil	Clonic forelimb seizure (genetic predisposition)	PO	19
Baboon	Photogenic myoclonus (genetic predisposition)	IV	Not effective (1.0 to 240 mg/kg)

All results are from unpublished studies.

[a] Lowest effective dose.

[b] At this dose, seizures were significantly delayed but not prevented.

Gabapentin is not metabolized.[46] It is excreted unchanged in urine, with a renal clearance approximately equal to total clearance (120–130 mL/min) and an elimination half-life of 5 to 7 hours. The clearance and elimination half-life of gabapentin are not altered by increased dosing rates or by chronic administration.[44] The clearance of gabapentin is decreased in the presence of renal disease, requiring a decrease in dosing rate for persons having a creatinine clearance rate of less than 60 mL/min. This mechanism probably is responsible for the observed age-related decrease of gabapentin clearance in later life. Pharmacokinetic studies in children show an increased clearance in children under the age of 5 years.

A series of studies have been completed to detect possible interactions between gabapentin and other drugs. These have been conducted either in patients receiving antiepileptic monotherapy or in healthy subjects. An interaction between gabapentin and one of the established AEDs would influence the design and interpretation of phase II and III efficacy studies, and early evaluation of this possibility was important. Interactions in both directions have been sought: that is, an effect of gabapentin on the kinetics of the established drugs and vice versa. In addition, selected potential interactions have been examined with the following compounds:

- An aluminum/magnesium hydroxide antacid, because these preparations reduce the absorption of some drugs
- Cimetidine, which is a known inhibitor of the oxidative, drug-metabolizing system in the liver
- Probenecid, which can inhibit renal tubular secretion of acidic drugs
- The components of the combined oral contraceptive pill, the metabolism of which is enhanced by enzyme-inducing AEDs

No detectable interaction occurs between gabapentin and the four AEDs tested (carbamazepine, phenytoin, phenobarbital, valproate).[33] This would be expected of a drug such as gabapentin, which is renally eliminated and does not induce hepatic microsomal enzymes.

The aluminum/magnesium antacid Maalox TC (Rhone-Poulenc Rorer) caused a slight reduction in the absorption of gabapentin, but no more than 20%, which is probably not of clinical significance.[13] Cimetidine decreased glomerular filtration and caused a 12% decrease in the renal clearance of gabapentin; but again this is unlikely to be of clinical importance. Probenecid, however, did not affect renal clearance, indicating that gabapentin does not undergo renal tubular secretion by the pathway blocked by probenecid. Finally, no effect of gabapentin was seen on the kinetics of single doses of norethynodrel and ethinylestradiol, which is predictive of a lack of interference with oral contraception.

Gabapentin readily passes into breast milk. Milk-to-maternal plasma concentration ratios of gabapentin are close to 1. However, it appears that plasma concentrations of gabapentin attained in infants being breast-fed by mothers taking gabapentin are probably not clinically significant.[42] Umbilical cord–to-maternal plasma concentration ratios suggest gabapentin is accumulated in the fetus.

Table 2 Summary of the ten adverse events occurring most frequently in patients receiving gabapentin

	Controlled studies		
	Placebo (*n* = 307) No. (%)	**Gabapentin (*n* = 485) No. (%)**	**All studies Gabapentin (*n* = 1,160) No. (%)**
Patients with more than one adverse event	174 (56.7)	369 (76.1)	944 (81.4)
Adverse events			
Somnolence	30 (9.8)	98 (20.2)	283 (24.4)
Dizziness	24 (7.8)	87 (17.9)	235 (20.3)
Ataxia	16 (5.2)	64 (13.2)	202 (17.4)
Fatigue	15 (4.9)	54 (11.1)	171 (14.7)
Nystagmus	15 (4.9)	45 (9.3)	174 (15.0)
Headache	28 (9.1)	42 (8.7)	176 (15.2)
Tremor	12 (3.9)	35 (7.2)	174 (15.0)
Diplopia	6 (2.0)	31 (6.4)	124 (10.7)
Nausea and/or vomiting	23 (7.5)	29 (6.0)	108 (9.3)
Rhinitis	12 (3.0)	22 (4.5)	101 (8.7)

Gabapentin's pharmacokinetic profile has many of the features of the ideal AED, and implies that it should be a simple drug to use in clinical practice, in contrast to some of the currently available preparations.

Adverse Effects

Within epilepsy regulatory studies using short-term, add-on gabapentin therapy, an increased frequency was noted of the types of adverse events that commonly occur with the use of currently marketed AEDs, particularly those symptoms related to the central nervous system (CNS), most particularly dizziness, ataxia, fatigue, and somnolence[22] (Table 2). These adverse events usually were transient, occurred early in gabapentin therapy, and diminished with time. Gabapentin has not been associated with liver injury, serious allergic reactions, or changes in the hematopoietic system. Clinical laboratory abnormalities have not been shown to change in association with gabapentin treatment.[12] These data from placebo-controlled add-on studies in epilepsy are now augmented by data from studies of neurogenic pain, in which the drug would be more likely to be given as monotherapy. The pattern of newly emerging adverse events was very similar in these trials.[5]

Insufficient data are available to demonstrate that gabapentin is safe during human pregnancy, although the malformation rates associated with its use appear low.[27,29] It showed no evidence of mutagenicity in vitro or in vivo. Its effects on pregnancies in mice, rats, and rabbits appear minimal. It may cause delayed ossification given at dosages of one to four times the maximum recommended human dosage, and there is also evidence of an increased incidence of hydroureter and hydronephrosis in rats. However, the incidence of other malformations was not increased.

It is still too early to make any statements about the potential chronic toxic effects of gabapentin. However, the longer-term, open, follow-up studies with the drug do not suggest any development of new adverse effects, and the absence of any significant effects on biochemical and hematologic parameters in the shorter term also appears reassuring.

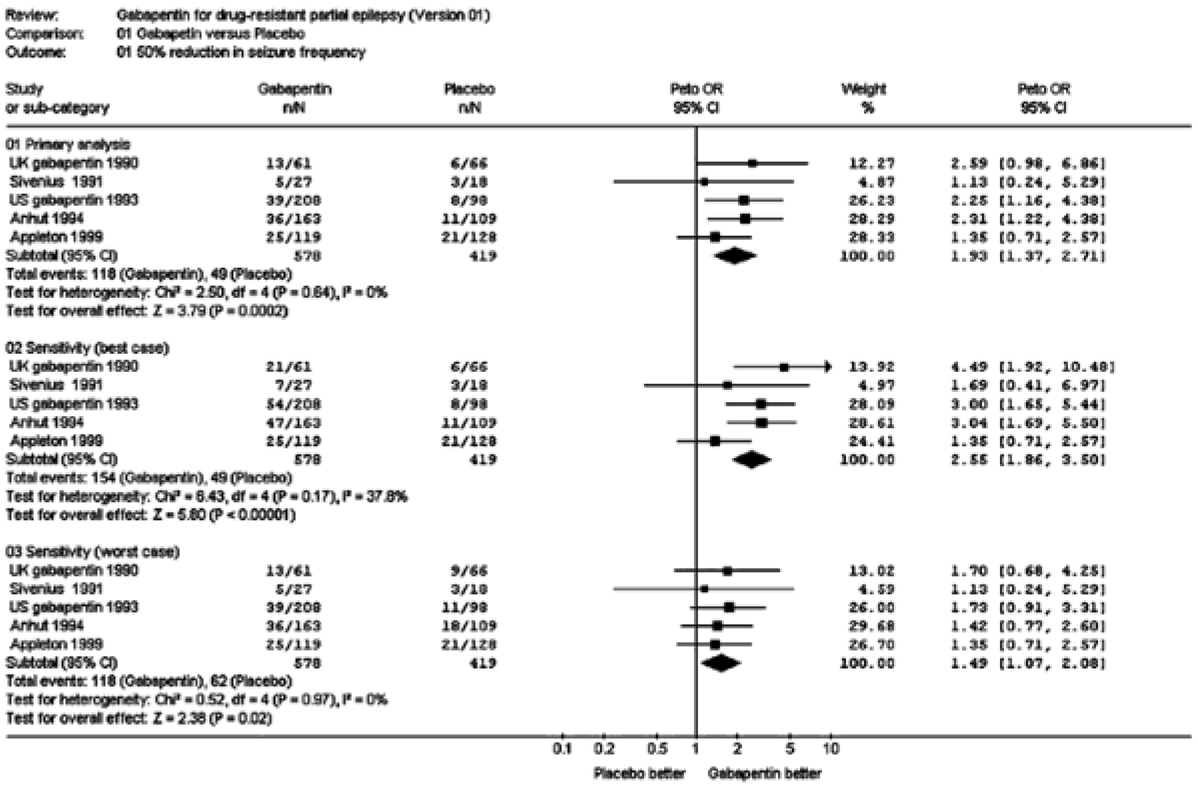
One area that has caused some concern arose from the longer-term animal toxicologic studies. Toxicology data from 2-year bioassay studies conducted in rats and mice showed an increase in benign acinar cell tumors of the pancreas in male Wistar rats only. The tumors did not alter lifespan and were not seen in female rats or mice of either sex. In the study, designed to evaluate carcinogenicity, male and female rats were given gabapentin at 250 mg/kg, 1,000 mg/kg, or 2,000 mg/kg daily for 2 years. Mean plasma concentrations at these dosages were 84.6 μg/mL, 51.2 μg/mL, and 84.6 μg/mL, respectively. For reference, plasma concentrations from current clinical studies commonly range from 2 μg/mL up to peak concentrations of 15 μg/mL. The U.S. Food and Drug Administration reviewed this matter and concluded that it probably does not represent a significant clinical risk.

Role of the Drug

Adjunctive Therapy for Partial Seizures

The indications for gabapentin are best defined in randomized, placebo-controlled, add-on studies in partial epilepsies. Five studies, undertaken for regulatory purposes, shared a common parallel group design: four in adults and one in children.[3] These have been subject to a systematic review.[24]

Two of the trials[2,45] tested two doses of gabapentin and hence had three treatment groups (including the placebo group). These five studies recruited a total of 750 adults and 247 children. In the adult studies, patients were randomized to one of the following doses: 600, 900, 1,200, and 1,800 mg gabapentin per day. In Appleton's 1999 study, children received between 600 and 1,800 mg per day depending on weight.[3] A total of 61 patients were excluded from the reported analyses, 38 of whom did not complete the treatment phase and nine who had inadequate seizure data recorded. After a 12-week baseline assessment with standard AEDs, patients with partial seizures refractory to standard AEDs were randomly assigned to receive either placebo or gabapentin in addition to standard AEDs. Patients who completed double-blind treatment could continue gabapentin treatment as part of an open-label trial. All patients had partial (simple, complex, or secondarily generalized) seizures refractory to marketed AEDs.



Review: Gabapentin for drug-resistant partial epilepsy (Version 01)
Comparison: 01 Gabapetin versus Placebo
Outcome: 01 50% reduction in seizure frequency

Study or sub-category	Gabapentin n/N	Placebo n/N	Peto OR 95% CI	Weight %	Peto OR 95% CI
01 Primary analysis					
UK gabapentin 1990	13/61	6/66		12.27	2.59 [0.98, 6.86]
Sivenius 1991	5/27	3/18		4.87	1.13 [0.24, 5.29]
US gabapentin 1993	39/208	8/98		26.23	2.25 [1.16, 4.38]
Anhut 1994	36/163	11/109		28.29	2.31 [1.22, 4.38]
Appleton 1999	25/119	21/128		28.33	1.35 [0.71, 2.57]
Subtotal (95% CI)	578	419		100.00	1.93 [1.37, 2.71]
Total events: 118 (Gabapentin), 49 (Placebo)					
Test for heterogeneity: $\text{Chi}^2 = 2.50$, df = 4 (P = 0.64), $I^2 = 0\%$					
Test for overall effect: Z = 3.79 (P = 0.0002)					
02 Sensitivity (best case)					
UK gabapentin 1990	21/61	6/66		13.92	4.49 [1.92, 10.48]
Sivenius 1991	7/27	3/18		4.97	1.69 [0.41, 6.97]
US gabapentin 1993	54/208	8/98		28.09	3.00 [1.65, 5.44]
Anhut 1994	47/163	11/109		28.61	3.04 [1.69, 5.50]
Appleton 1999	25/119	21/128		24.41	1.35 [0.71, 2.57]
Subtotal (95% CI)	578	419		100.00	2.55 [1.86, 3.50]
Total events: 154 (Gabapentin), 49 (Placebo)					
Test for heterogeneity: $\text{Chi}^2 = 6.43$, df = 4 (P = 0.17), $I^2 = 37.8\%$					
Test for overall effect: Z = 5.80 (P < 0.00001)					
03 Sensitivity (worst case)					
UK gabapentin 1990	13/61	9/66		13.02	1.70 [0.68, 4.25]
Sivenius 1991	5/27	3/18		4.59	1.13 [0.24, 5.29]
US gabapentin 1993	39/208	11/98		26.00	1.73 [0.91, 3.31]
Anhut 1994	36/163	18/109		29.68	1.42 [0.77, 2.60]
Appleton 1999	25/119	21/128		26.70	1.35 [0.71, 2.57]
Subtotal (95% CI)	578	419		100.00	1.49 [1.07, 2.08]
Total events: 118 (Gabapentin), 62 (Placebo)					
Test for heterogeneity: $\text{Chi}^2 = 0.52$, df = 4 (P = 0.97), $I^2 = 0\%$					
Test for overall effect: Z = 2.38 (P = 0.02)					

FIGURE 2. Systematic review and meta-analysis of placebo-controlled studies of gabapentin in the treatment of partial epilepsy.[23]

The primary efficacy criterion was reduction in the frequency of partial seizures from baseline to treatment levels. Seizure frequency was defined as the number of seizures per 28 days of observation. The primary efficacy parameters

reported in the trials were response ratio (RR) and percentage change in frequency of seizure relative to the baseline.

The RR compares baseline seizure frequency (B) with treatment seizure frequency (T), as follows: RR = (T - B)/(T + B). The RR avoids the skewing associated with percentage change and, because RR is normally distributed around zero, it allows parametric statistics to be used in the interpretation of the data. Values for RR range between -1 and +1. The Cochrane systematic review computed more conventional odds ratios (OR) for a 50% reduction in seizure frequency between gabapentin and placebo. The overall OR (95% CIs) for 50% responders across all doses in all studies is 1.93 (1.37 – 2.71) (see Fig. 2), indicating a statistical superiority of gabapentin over placebo. There was a linear dose-response across all doses, with a log odds increase by 0.215 (SEM, 0.052) for a 300-mg increase in daily dose, which is roughly a 25% increase in odds of response for a 300-mg increase in dose. There was no evidence of plateauing of this dose–response relationship at the highest doses tested in these RCTs.

In addition to the double-blind studies, a total of 774 patients participated in five long-term, open-label studies of gabapentin as adjunctive therapy for partial seizures.[12] Patients were the same or were similar to those in the above double-blind studies. The majority of patients were receiving two concurrent AEDs. These results indicated no evidence that the efficacy of gabapentin is not maintained over time for these patient populations.

The above studies used gabapentin dosing rates of 2,400 mg/day or less. Further open-label studies of gabapentin at dosing rates up to 4,800 mg/day as adjunctive therapy for partial seizures also reported good long-term retention of efficacy with good tolerability.[6,28]

Gabapentin has been compared as add-on therapy to other AEDs in two RCTs. One study compared gabapentin and vigabatrin in 102 patients as a first add-on treatment. The study was stopped because of concern about the potential retinal toxicity of vigabatrin before any meaningful results were available.[21] Gabapentin was compared to lamotrigine in a randomized, but open-label, study of adults with learning disability. Similar numbers of patients achieved a 50% reduction in seizure frequency (50% and 48%, respectively) with maximal doses of 3,600 mg/day and 400 mg/day. The study did not recruit sufficient numbers of patients to detect clinically important differences.

No other direct comparisons between gabapentin and other standard or newer AEDs as add-on treatments for partial seizures are available. Information is available from indirect comparisons from systematic review and meta-analysis of similarly structured, placebo-controlled add-on studies of new AEDs.[26] These data indicate that gabapentin at the relatively low doses used in placebo-controlled regulatory studies is well tolerated (as judged by odds-ratios for withdrawal from studies) relative to other drugs, such as lamotrigine, tiagabine, levetiracetam, topiramate, vigabatrin, oxcarbazepine, and zonisamide, but shows a trend toward lesser efficacy (from odds-ratios for 50% reduction in seizure frequency). This view receives some support from a large postmarketing surveillance cohort in the United Kingdom, which showed that time to treatment failure was shorter for gabapentin than for lamotrigine or vigabatrin.[1]

Monotherapy for Partial Seizures

An outpatient RCT of 275 patients with refractory complex partial and/or tonic–clonic seizures was performed in which patients were converted to monotherapy with 600, 1,200, or 2,400 mg/day of gabapentin.[9] Only 20% of patients completed the study, which provided no evidence of a dose–response relationship, most likely due to assay insensitivity in this type of design. A further monotherapy inpatient study using the presurgical paradigm did show a statistical difference between doses of 300 mg and 3,600 mg/day over a period of 8 days,[7] although extrapolation of this result to everyday clinical practice would be hazardous.

In an outpatient study of 271 patients with newly diagnosed partial epilepsy, 205 received gabapentin monotherapy at dosages of 300, 900, or 1,800 mg/day (blinded allocation) or carbamazepine 600 mg/day.[15] The outcome was retention in the trial, with exit allowed when patients experienced three partial seizures, one secondary generalized tonic–clonic seizure, or adverse events. The two higher doses of gabapentin were superior to 300 mg/day, with retention using 1,800 mg/day being similar to the outcomes in the group treated with 600 mg/day of carbamazepine.

Gabapentin has also been compared to other active AEDs in RCTs. In a 24-week parallel group study, 599 patients with newly diagnosed partial seizures were given gabapentin (daily dose up to 3,600 mg/day) or lamotrigine (daily dose up to 300 mg/day) with the primary outcome being the retention time in the trial. Similar numbers of patients completed the study (71% of gabapentin subjects, 67% of lamotrigine subjects), with similar numbers remaining seizure-free. Both drugs were well tolerated, but the study lacked sufficient power to determine whether the drugs were truly equivalent.[10] The same two drugs in doses of 1,500 mg/day and 150 mg/day, respectively, were compared with carbamazepine (600 mg/day) in a RCT in an elderly population of newly diagnosed epilepsy.[34] The primary outcome was retention over 12 months. Significantly more early terminations occurred with carbamazepine (65%), but there were no differences in the seizure-free rates at 12 months.

A much larger study of over 1,400 patients has compared gabapentin as a variable dose monotherapy to carbamazepine, lamotrigine, oxcarbazepine, and topiramate in a pragmatic randomized study.[25] Although well tolerated, gabapentin was inferior to the other drugs for efficacy and overall effectiveness, confirming the inferences drawn from other studies.

Generalized Seizures

The place of gabapentin in the treatment of generalized epilepsy syndromes is poorly defined. One placebo-controlled, add-on, parallel group RCT has been performed in refractory generalized epilepsies. This failed to show statistically significant effects for 1,200 mg/day of gabapentin, although there was a trend toward reduction in generalized tonic–clonic seizures.[14] There was no evidence of any adverse or beneficial effects on absence seizures from a cross-over, add-on study comparing gabapentin with placebo.[43] There are, however, some case reports of exacerbation of absence and myoclonus by gabapentin.[4,48] The balance of evidence would therefore argue against the use of gabapentin in patients with generalized seizures.

How to Use the Drug

Gabapentin is available in 100-, 300-, 400-, 600-, and 800-mg capsules. In adults, titration to a minimally effective dosage of 900 to 1,200 mg/day can be undertaken quickly in most patients.[17] The initial dosing rate is 300 mg/day. The dosing rate usually can be increased by 300 mg at 1-day intervals (i.e., 3 days to attain a dosing rate of 900 mg/day). An occasional patient develops CNS side effects with this starting regimen. Such patients usually develop tolerance to the drug with a slowed initiation protocol (e.g., 300 mg/day increases every 4–7 days). In view of the relatively short elimination half-life, the drug should be administered three times daily.

For children 3 to 12 years of age, the starting dose should range from 10 to 15 mg/kg per day in three divided doses, The effective dose of gabapentin in patients 5 years of age and older is 25 to 35 mg/kg per day, given in three divided doses. The effective dose in pediatric patients 3 and 4 years of age is 40 mg/kg per day, given in three divided doses. Doses up to 50 mg/kg per day have been well-tolerated in long-term clinical studies.

In the elderly and in those with renal impairment, the total dose of the drug given may need to be reduced in proportion to any impairment in creatinine clearance, given that the drug is largely eliminated by this route. Instructions for dosing in renally impaired patients are contained in the package insert.

Currently, the maximal dose is poorly defined. Early randomized clinical trials in partial epilepsy suggested increasing effectiveness at dosages of up to 1,800 mg/day, and such dosages are well tolerated. Evidence from ongoing studies indicates dosages of up to 3,600 or 4,800 mg/day are well tolerated and may be more effective than lesser dosages in some patients.

There seem to be relatively few indications for routine blood level monitoring with this drug. Its own pharmacokinetics are simple, and there seems to be no evidence of drug–drug interactions. Certainly no satisfactory studies define either a minimally effective serum level or a maximally tolerated serum level, although blood levels in the range of 2 to 20 μg/mL have been advocated. The only possible indications for blood-level monitoring may relate to testing compliance or to the possible rate-limiting absorption of the drug at higher doses. Thus, in patients tolerating the dose of the drug at high doses, but showing suboptimal therapeutic benefits, there may be temptations to increase the administered dosage above 3 g/day. In these circumstances, it would seem wise to monitor blood levels to show that further increases in dosage do indeed result in an increase in blood levels.

Discontinuing the Drug

Gabapentin should be discontinued in the absence of significant therapeutic benefit at the maximum tolerated dose, the maximum absorbed dose, or when unacceptable side effects occur. The dose can usually be reduced in decrements of 300 or 400 mg every 3 to 4 days.

Summary and Conclusions

Gabapentin has been shown to be effective in the management of partial epilepsies in randomized clinical trials exploring dosages of up to 1,800 mg/day. Such dosages seem to be exceptionally well tolerated, and additional benefits may be derived from higher doses. The drug has simple pharmacokinetics and little or no potential for drug–drug interaction. Its main use will continue to be as a second-line treatment in refractory populations of patients.

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Chapter 150

Lamotrigine

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Introduction

Lamotrigine, a phenyltriazine derivative, has been available globally as an antiepileptic drug (AED) for more than 15 years. The drug was initially synthesized as one of a sequence of folic acid antagonists following the suggestion that antifolate drugs may have antiepileptic properties. Although this theory was subsequently discredited, lamotrigine was discovered to have multiple mechanisms of action that may account for its broad spectrum of activity.[62] Following regulatory studies during the 1980s and 1990s, lamotrigine became available as an adjunctive agent for the treatment of partial and primary and secondary generalized seizures in adults. More recently, it has been used in children, in patients with the Lennox-Gastaut syndrome (LGS), and as monotherapy in newly diagnosed epilepsy.[121]

Chemical structure, formulations, and methods for determination in body fluids

Lamotrigine (3,5-diamino-6-[2,3-dichlorophenyl]-1,2,4-tria-zine) (Fig. 1) is synthesized by reacting thionyl chloride with 2,3-dichlorobenzoic acid to make an acid chloride derivative, which is converted to the corresponding ketonitrile in the presence of cuprous cyanide.[34] When the ketonitrile is condensed with aminoguanidine under strongly acidic conditions, the resulting amidinohydrazone compound is cyclized in basic conditions to produce lamotrigine. The drug is poorly soluble in water and ethanol, and has a molecular weight of 256.09 and a pKa of 5.5.

Lamotrigine is available as Lamictal (GlaxoSmithKline) in 25-, 50-, 100-, and 200-mg tablets, and as dispersible chewable tablets in 2-, 5-, 25-, and 100-mg doses.[66] No difference has been shown in bioequivalency between the two formulations. A number of generic preparations are available. The drug can be measured in serum or plasma by high-performance liquid chromatography[27,39] and by immunofluorometric assay.[102]

Pharmacology

Seizure Models

The anticonvulsant activity of lamotrigine has been demonstrated in models of different seizure types. Positive results have been obtained with maximal electroshock (MES) and pentylenetetrazole-induced tonic seizures, which are thought to be models of partial and generalized tonic–clonic seizures.[82,120] The drug abolished hind limb extension in the MES model at an oral mean effective dose (ED_{50}) of 2.6 mg/kg in the mouse and 1.9 mg/kg in the rat.[81] The ED_{50} was smaller and the therapeutic index and duration of action greater than those of phenyt-oin, carbamazepine, sodium valproate and diazepam. Similar ED_{50} values were obtained in maximal seizure tests with pic-rotoxin and bicuculline but, like phenytoin and in contrast to ethosuximide and valproate, lamotrigine had no effect on leptazol threshold[64] or on clonus latency after leptazol,[81] suggesting lack of efficacy against absence seizures. The drug was ineffective in the genetic absence epilepsy rat from Strasbourg, although it did not aggravate spike-and-wave discharges, unlike some other antiepileptic drugs.[33]

Lamotrigine yielded positive results in the lethargic mouse model of absence epilepsy.[57] As with valproate and ethosuximide, lamotrigine inhibited visually evoked afterdischarges in the rat, which may also be interpreted to suggest efficacy against absence seizures.[65] Lamo-trigine delayed the development of electrical kindling and modified seizures, but failed to prevent subclinical afterdischarges during the kindling process in the rat.[89]

Mechanisms of Action

Lamotrigine acts by use- and voltage-dependent blockade of neuronal voltage-activated sodium (Na^+) channels[124] in a similar way to carbamazepine and phenytoin.[67]

Waldmeier et al. found that lamotrigine attenuated veratrine-induced glutamate, γ-aminobutyric acid (GABA), and dopamine release in rat brain slices, but much less potently inhibited electrical stimulation–induced GABA and dopamine release.[118] The drug also inhibited electrical stimulation–induced release of serotonin, acetylcholine and, to a lesser extent, noradrenaline. Leach et al. reported that lamotrigine inhibited veratrine-induced glutamate and aspartate release, but less potently inhibited GABA and acetylcholine release.[68]

Lamotrigine also has effects on other ion channels.[117,119] In rodents, the drug modulated transient potassium outward currents in CA1 pyramidal cells,[52] and inhibited cortical and striatal voltage-activated calcium currents.[111] Some studies have suggested that lamotrigine may have selective neuroprotective effects. Hippocampal neuronal loss and optic nerve axonopathy were reduced by the drug in rats.[31] Lamotrigine was also neuroprotective in gerbil[107] and pig[29] models of global ischaemia.

Clinical pharmacokinetics

Lamotrigine is rapidly absorbed after oral administration. The peak plasma concentration is achieved in 1 to 3 hours, and increases linearly with dosage (Table 1).[28] Bioavailability is almost 100%. The weight-normalized volume of distribution after intravenous administration and the weight-normalized apparent volume of distribution after oral administration vary between 0.9 to 1.5 L/kg.[28] Protein binding is approximately 55%.[43] Salivary concentrations appear to be similar to free plasma concentrations.[114]

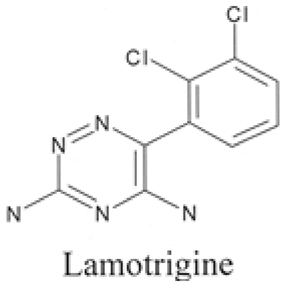

FIGURE 1. Structure of lamotrigine

Table 1 Pharmacokinetic properties of lamotrigine

Parameter	Mean ± SD
C_{max} (mg/L)	1.6 ± 1.3 (120 mg dose)
t_{max} (hours)	2.8 ± 1.3
F (%)	98 ± 5
Plasma protein binding (%)	55
F_e (%)	70
Vd/F (L/kg)	1.2 ± 0.1
CL/F (L/h)	2.5 ± 0.6
$T_{1/2β}$ (h)	24 ± 6

C_{max}, peak plasma concentration; t_{max}, time to c_{max}; F, absolute bioavailability; F_e, fractional urinary excretion; Vd/F, apparent volume of distribution; CL/F, apparent oral clearance; $T_{1/2β}$, plasma elimination half life.

Lamotrigine undergoes linear pharmacokinetics, with an elimination half-life varying between 24 and 35 hours.[28]

The drug is metabolized primarily by hepatic glucuronidation catalyzed by a number of different isoforms of UDP-glucuronosyltransferase converting lamotrigine to *N*-2- and *N*-5-glucuronides (80% and 10%, respectively) and other minor *N*-oxide metabolites.[28] The metabolites are almost entirely excreted in the urine, with 94% of radiolabeled lamotrigine being recovered in this way and 2% being found in the faeces.[35] There is conflicting evidence as to whether the drug induces its own metabolism.[58] As would be expected, the drug passes freely into breast milk.[90]

Lamotrigine's clearance is reduced in patients with unconjugated hyperbilirubinemia (Gilbert syndrome[96]) and in severe hepatic cirrhosis,[74] but not in end-stage renal failure.[42] There is little difference in lamotrigine pharmacokinetics in the elderly compared with younger adults.[58] In children, oral clearance and volume of distribution are greater, but half life is similar to corresponding values in adults.[25] Limited data available for different races suggests that clearance may be lower in Asians.[34]

Concentration–Effect Relationships

A variety of reports have been published regarding the relationship between lamotrigine dose and circulating plasma concentration. Of six large scale clinical trials, only two demonstrated a significant relationship between plasma concentration and efficacy.[70,104] Loiseau et al. found lamotrigine concentrations ranged from 0.3 to 4.9 mg/L on 150 to 300 mg/day.[70] Schapel et al. documented concentrations ranging from 0.66 to 4.65 mg/L in patients taking 150 or 300 mg daily.[104] Of the four studies that found no clinically statistical relationship,[60,80,99,110] Jawad et al. reported that 75 to 400 mg lamotrigine produced trough plasma concentrations of between 1.5 and 2.5 mg/L.[60] Using 200 to 400 mg lamotrigine daily, Smith et al. achieved mean plasma levels of 2.2 to 2.4 mg/L.[110] Messenheimer et al. achieved mean steady-state concentrations of 1.6 mg/L on 200 mg/day and 2.9 mg/L on 400 mg/day.[80] Concentrations of 3.8 mg/L on 200 mg and 2.06 mg/L on 100 mg were reported by Reunanen et al. when la-motrigine was used as monotherapy.[99]

Kilpatrick et al.[63] found widely varying lamotrigine doses in patients who were seizure-free (median dose 200 mg, range 25–850 mg; median concentration 3.8 mg/L, range 1.4–8.7 mg/L) and in those reporting side effects (median dose 300 mg, range 100–900 mg; median concentration 4.0 mg/L, range 0.4–18.5 mg/L). These results are partly at odds with those from Hirsch et al.,[55] who reported a significant relationship between increasing lamotrigine concentrations and toxicity. With concentrations of less than 0.5 mg/L, 7% of patients reported side-effects; with 5 to 10 mg/L, 14%; with 15 to 20 mg/L, 34%; and with greater than 20 mg/L, 59%. Increasing efficacy occurred with concentrations up to and exceeding 20 mg/L. A target range of 1.5 to 10 mg/L was recommended. Another study retrospectively examined the relationship between plasma lamo-trigine concentrations and dosage and concluded that a therapeutic range of 3 to 14 mg/L was realistic, although hardly precise.[85]

Chong and Dupuis argued that, although the majority of studies did not demonstrate a clear relationship between lamotrigine concentration and pharmacologic response, many of these were methodologically flawed.[26] They concluded that clinical end-points rather than plasma concentrations remain the most important guide for lamotrigine therapy. Certain special populations exist, however, in which obtaining a circulating concentration may be useful. These include patients in whom poor drug adherence is suspected and those with renal or hepatic failure.[55] Because lamotrigine concentrations are decreased markedly during pregnancy,[93,94] and dose adjustments are frequently needed under these circumstances to control seizures,[115] therapeutic drug monitoring has benefit in pregnant women with poor seizure control or symptoms of drug toxicity. The ethinylestradiol component of oral contraceptives can reduce circulating lamotrigine concentration by up to 50%.[98,101] Women taking the combined oral contraceptive pill could, therefore, also be candidates for lamotrigine measurement.

Clinical efficacy

The clinical effects of lamotrigine have been investigated in a wide range of seizure and epilepsy types in children and adults, in previously untreated patients, as well as in those with refractory epilepsy.

Partial Seizures and Localization-Related Syndromes

A series of randomized, double-blind, placebo-controlled studies have assessed the effectiveness of lamotrigine as add-on therapy in patients with refractory partial epilepsy. Three studies in adults[77,80,104] and one in children[36] met the Class I criteria in the American Academy of Neurology assessment of new AEDs.[46] In the largest, 191 patients taking enzyme-inducing AEDs were randomized to placebo, or lamotrigine 300 mg/day or 500 mg/day.[75] The responder rate (that proportion of patients with at least 50% seizure reduction from baseline) was 18% on placebo, 20% on lamotrigine 300 mg/day, and 34% on lamotrigine 500 mg/day. In a second study, 88 adult patients taking enzyme-inducing drugs were randomized in a cross-over design to placebo or lamotrigine 400 mg/day.[80] The

responder rate with lamotrigine was 20% compared with 0% with placebo. The third study included only 41 patients on enzyme-inducers and or valproic acid randomized in a cross-over design to placebo or lamotrigine 300 mg/day (150 mg/day if on valproic acid).[104] The responder rate on lamotrigine was 22%, and 0% on placebo.

In a meta-analysis, Ramaratnam et al.[97] included eight additional randomized trials—two cross-over and six parallel studies.[10,14,60,70,99,103,106,110] A total of 1,243 patients (1,044 adults and 199 children) were included in this analysis of la-motrigine add-on for drug-resistant partial epilepsy. The overall odds ratio versus placebo for 50% or greater reduction in seizure frequency was 2.71 (95% confidence interval [CI] 1.87–3.91), demonstrating the efficacy of lamotrigine in this patient population. The odds ratio for treatment withdrawal in the same meta-analysis was 1.12 (95%; CI,0.78–1.61), indicating that patients were not more likely to discontinue lamotrigine than placebo.[97] One of these studies evaluated lamotrigine as add-on treatment in children with refractory partial epilepsy.[36] In this double-blind parallel group study, 199 children aged 2 to 16 years were randomized to placebo or lamotrigine (2.7–12.9 mg/kg/day). The responder rate was 45% with lamotrigine and 25% with placebo, whereas the discontinuation rates were similar in the two groups, 5% and 6%, respectively.

One randomized double-blind study assessed lamotrigine as monotherapy in adults and adolescents with refractory partial epilepsy.[50] Overall, 156 patients with different baseline medications were randomized to receive lamotrigine 500 mg/day or a low dose of valproic acid (1,000 mg/day). Baseline medication was gradually withdrawn, aiming at monotherapy with lamotrigine or valproic acid. More patients on lamotrigine (56%) compared to valproic acid (20%) were successfully maintained on monotherapy. Although this regulatory trial demonstrated the effect of lamotrigine as monotherapy in refractory partial epilepsy, it is difficult to translate the results into clinical practice.

Lamotrigine has also been assessed as monotherapy in new-onset partial epilepsy in adults. Three randomized double-blind parallel group studies met American Academy of Neurology Class I criteria.[45] The first study[18] randomized adult patients with partial seizures (*n* = 146) or primary generalized tonic–clonic seizures (*n* = 122) to lamotrigine (initial target dose 150 mg/day) or carbamazepine (initial target dose 600 mg/day). Of patients with partial seizures, 22% on lamotrigine and 31% on carbamazepine remained seizure-free during the last 40 weeks of treatment, compared to 35% and 37%, respectively, during the last 24 weeks. Retention was presented for partial and generalized seizure patients together. More lamotrigine (65%) than carbamazepine (51%) recipients completed the study. This difference was due to fewer withdrawals because of adverse events on lamotrigine.

Steiner et al.[112] randomized 90 patients with partial and 91 with primary generalized tonic–clonic seizures to lamotrigine (modal dose 150 mg/day) or phenytoin (modal dose 300 mg/day). Of those with partial seizures only randomized to lamotrigine, 16% remained on treatment and were seizure-free during the last 40 weeks of the study, compared with 22% on carbamazepine. Corresponding figures for the last 24 weeks were 41% and 48%, respectively. These differences were not statistically significant, nor was there a significant difference between the drugs in time to discontinuation from the trial.

In a third study, 150 elderly (65 years and older) patients with newly diagnosed epilepsy were randomized in a 2:1 ratio to lamotrigine (median dose 100 mg/day) or carbamazepine (median dose 400 mg/day).[17] Although a proportion was classified as having idiopathic generalized epilepsy, the vast majority of patients had partial seizures. Significantly more patients continued on treatment with lamotrigine than on carbamazepine, 71% versus 42%. This was largely explained by a higher dropout rate due to adverse events on carbamazepine (42%) compared with lamotrigine (18%).

Lamotrigine has been assessed in an additional comparative study of new-onset partial epilepsy in older people.[100] In this double-blind, parallel group study, 593 patients aged 60 years or older were randomized to gabapentin (target dose 1,500 mg/day), lamotrigine (target dose 150 mg/day), or carbamazepine (standard tablets, target dose 600 mg/day). Although epilepsy was of new onset, 43% of the patients were already taking AEDs, which were tapered to zero during titration of the study medication. The primary outcome measure was retention in the trial for 12 months. Early termination, largely due to adverse events, was significantly more common with carbamazepine (65%) than with lamotrigine (44%) or gabapentin (51%). Seizure-free rates at 12 months were similar across treatment groups.

Lamotrigine has also been compared with gabapentin in adults with newly diagnosed partial or primary generalized tonic–clonic seizures.[16] In this double-blind, parallel group study, 309 patients were randomized to gabapentin (flexible dosage from 1,200 to 3,600 mg/day) or lamotrigine (100 to 300 mg/day). There was no difference in the primary end-point, time to exit, or in the proportion of patients completing the 24-week maintenance phase—72% on gabapentin and 67% on lamotrigine. Of those completing, 76% taking gabapentin or lamotrigine remained seizure free during the last 12 weeks of the trial.

Two additional open randomized studies compared the efficacy of lamotrigine and carbamazepine in newly diagnosed partial epilepsy[88] or partial and/or generalized tonic–clonic seizures,[99] both supporting the view that the two drugs are equally effective, although lamotrigine may be better tolerated. It should, however, be noted that the controlled-release formulation of carbamazepine has not been used in any of the comparative trials, and that the statistical power to detect differences in efficacy has been low.

The only sizeable data from randomized trials on children with newly diagnosed partial epilepsy come from the open comparison with carbamazepine.[88] This study included 233 patients aged 2 to 12 years, of whom 158 were randomized to lamotrigine (2–15 mg/kg/day) and 75 to carbamazepine (5–40 mg/kg/day). Of those with data for at least 18 weeks, 66% on lamotrigine were seizure-free for the last 16 weeks, which was not statistically different from the 75% on carbamazepine.

Generalized Tonic–Clonic Seizures

Two of the Class I studies of lamotrigine in newly diagnosed epilepsy included subgroups of adult patients with primary generalized tonic–clonic seizures.[18,112] In the study by Brodie et al.,[18] 37% of the 60 patients randomized to lamotrigine remained seizure free during the last 40 weeks, compared with 35% among the 62 assigned to carbamazepine. The corresponding numbers for the last 24 weeks were 47% for both treatment groups. In the study by Steiner et al.,[112] 42 patients with primary generalized tonic–clonic seizures were randomized to lamotrigine and 49 to carbamazepine. Of those taking lamotrigine, 30% were seizure-free and remaining on treatment during the last 40 weeks, compared with 32% on phenytoin. Corresponding figures for the last 24 weeks were 44% and 34%, respectively, which did not significantly differ.

Lamotrigine has also recently been assessed as add–on treatment in patients with refractory primary generalized tonic-clonic seizures.[13] In this double-blind, parallel group study, 121 patients aged 2 to 55 years (23 were 2–12 years of age) were randomized to adjunctive treatment with lamotrigine or placebo. The median percent reduction in frequency of generalized tonic–clonic seizures from baseline (primary efficacy endpoint)

was 67% with lamotrigine and 33% with placebo. The study included 33 patients who had myoclonic in addition to tonic–clonic seizures. Although not designed to assess effects on seizure types other than tonic–clonic, there was no evidence of deterioration in other seizure types with lamotrigine.

Idiopathic Generalized Epilepsy Syndromes

One double-blind study assessed the short-term effects of la-motrigine in children with newly diagnosed typical absence seizures.[44] It enrolled 45 patients into an open-label dose escalation phase of lamotrigine. Responders (*n* = 28) entered a 4-week double-blind, placebo-controlled comparison in which they were randomized either to continue lamotrigine or be weaned onto placebo. The proportion of patients remaining seizure free during the double-blind treatment phase was greater for lamotrigine (62%) compared to placebo (21%). There are no randomized trials of lamotrigine in juvenile myoclonic epilepsy (JME). Some case series and open uncontrolled studies indicate that the drug may be effective and that some patients can be switched successfully from valproic acid to lamotrigine.[20,48,84] There are, however, also reports of exacerbations in myoclonic seizures with lamotrigine.[30]

Lennox-Gastaut Syndrome

Adjunctive lamotrigine has been shown to significantly reduce the frequency of major seizures in a double-blind, placebo-controlled study of children with LGS.[87] In this parallel group study, 169 patients were randomized to treatment with lamo-trigine or placebo. The median frequency of all major seizures changed from 16.4 during baseline to 9.9 per week during lamotrigine treatment, and from 13.5 to 14.2 in the placebo group. Among patients receiving lamotrigine, 33% demonstrated at least a 50% reduction on seizures compared to 16% in the placebo group. Lamotrigine was assessed as add-on in 20 children with LGS and 10 with other therapy-resistant generalized epilepsy syndromes.[38] The 17 responding during open-phase treatment with lamotrigine went into a randomized, double-blind, placebo-controlled, cross-over study, 60% of whom demonstrated at least 50% reduction in seizure frequency.

Indications Other Than Epilepsy

Lamotrigine has been investigated as a mood stabilizer in bipolar disorders. Lamotrigine 50 mg/day or 200 mg/day was significantly more effective than placebo in improving depressive symptoms in a short-term, randomized, double-blind, controlled study of bipolar depression.[21] Lamotrigine, 50 to 400 mg/day, was also more effective than placebo in a 26-week, randomized, controlled study in the prophylaxis of rapid-cycling bipolar disorders.[22] A small cross-over study compared lamotrigine, gabapentin, and placebo in rapid-cycling bipolar patients resistant to other mood stabilizers.[47] Lamotrigine, but not gabapentin, was superior to placebo in this study. A larger randomized, double-blind, parallel group study compared lamotrigine (100–400 mg/day), lithium, and placebo in the long-term treatment of patients with bipolar I disorder with recent manic or hypomanic episodes.[15] In this study, lamotri-gine was particularly effective in the prevention of depressive episodes.

At a dose of 400 mg/day, lamotrigine was superior to placebo as add-on treatment in patients with refractory trigeminal neuralgia,[126] but randomized monotherapy studies are lacking. The effects of lamotrigine have also been studied in other pain syndromes. Although a randomized, placebo-controlled, double-blind study failed to show an effect of la-motrigine, 200 mg/day, in a mixed population of neuropathic pain syndromes[77] the same dosage was superior to placebo in the treatment of post-stroke pain in another randomized controlled trial.[116] Lamotrigine, 300 mg/day, also significantly reduced pain scores in a placebo-controlled, double-blind study of neuropathic pain in HIV patients.[109] The only double-blind, placebo-controlled study in the prophylaxis of migraine failed to demonstrate efficacy with 200 mg lamotrigine daily.[113]

Adverse effects

Dose-Related, Nonidiosyncratic Adverse Effects

The most common dose-related adverse effects affect the central nervous system. Headache, asthenia, nausea, sleepiness/somnolence/drowsiness, and dizziness are the most frequently reported symptoms in monotherapy trials of lamotrigine.[18,99,112] However, drowsiness was less common in patients on lamotrigine monotherapy (100–300 mg daily) than among those on carbamazepine (300–1,400 mg daily, non–controlled release tablets)[18,99] or on phenytoin (300–600 mg daily).[112] Fewer patients on lamotrigine (15%) than on carbamazepine (27%) withdrew because of adverse effects in the randomized comparative monotherapy study.[112] A similar difference was reported in an open study comparing fixed dosages of lamotrigine (100 or 200 mg/day) and carbamazepine (600 mg/day). The withdrawal rate due to adverse events was 4.3% to 4.5% with lamotrigine, and 10.3% for patients on carbamazepine,[99] whereas there was no difference between lamotrigine and phenytoin in discontinuation because of adverse events in a double-blind randomized trial.[112] A double-blind comparison between lamotrigine and carbamazepine in 150 elderly patients with new-onset epilepsy also reported a lower dropout rate due to adverse events with lamotrigine compared with carbamazepine, 18% versus 42%.[17]

In another comparative study of new-onset epilepsy in senior citizens, 12.1% taking lamotrigine terminated the study due to adverse events compared with 21.6% on gabapentin and 31% on carbamazepine.[17] It should be noted that standard carbamazepine tablets rather than controlled-release formulations were used in all these comparative trials. Nevertheless, the results indicate that lamotrigine is comparatively well tolerated in these patient populations. A systematic Cochrane review of lamotrigine as add-on for drug-resistant partial epilepsy included three parallel and eight cross-over, randomized, add-on trials.[97] In this meta-analysis, ataxia, dizziness, diplopia, and nausea were more likely to occur with lamotrigine compared to placebo, whereas odds ratios for fatigue and somnolence included unity.

Cross-sectional and short-term studies indicate that there are no major adverse effects of lamotrigine on endocrine function, body weight, or bone mineralization.[12,59,91]

Idiosyncratic Reactions

Skin rash has been the most concerning adverse effect of la-motrigine leading to withdrawal in 6.1% of adult patients in the early monotherapy trials,[78] which, however, should be compared to withdrawal rates due to rash of 8.9% for carbamazepine and 5.3% for phenytoin in the same trials. In a review of all clinical trials including 3,348 adult patients

and 1,096 children (<16 years of age) exposed to lamotrigine, the incidence of rash was 10.7% among adults and 12.6% in children.[79] Rashes were generally mild, often morbilliform in appearance, with onset usually within the first 2 to 3 weeks. However, serious skin reactions, such as anticonvulsant hypersensitivity syndrome, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), can occur.[6,53] Rash has been the single most frequently reported serious adverse event in both add-on and monotherapy trials of lamotrigine.[79] In the randomized trials, 3.5% of adults and 4.7% of children discontinued lamotrigine because of rash. Possible SJS or hospitalization for rash occurred in 0.3% of adults and 1.0% of children.[53]

The risk of SJS and TEN in relation to exposure to AEDs has recently been assessed using the German Registry for Serious Cutaneous Reactions.[83] Fifteen cases of SJS or TEN among lamotrigine users were reported during the period 1998 to 2001, all but one occurring within the first 63 days of starting treatment. The incidence per 10,000 person-years of use, based on sales data of defined daily doses in Germany, was 1.8 for lamotrigine compared to 0.5 for carbamazepine, 1.3 for phenobarbital, 1.2 for phenytoin, and 0.1 for valproic acid.[83] However, when an attempt was made to estimate the risk of SJS/TEN in new users of AEDs, the assumed incidence was 3.8 per 10,000 for lamotrigine, 1.5 for carbamazepine, 8.2 for phenobarbital, 6.9 for phenytoin, and 0.5 for valproic acid.[83]

The risk of severe rash appears to be higher in the pediatric population than among adults.[79] Comedication with valproic acid, high starting doses, and rapid dose-escalations have been identified as additional risk factors.[6,53,78] The highest incidence (19.5%) of all types of rash occurred when lamotrigine was combined with valproic acid in the absence of other AEDs, whereas the lowest incidence (6.7%) occurred in combination with enzyme-inducers. Severe rash associated with hospitalization was also more common when lamotrigine was combined with valproic acid.[78] Previous allergy to another antiepileptic drug, particularly carbamazepine, has been found to predict the risk of rash with lamotrigine.[9]

Other serious idiosyncratic adverse effects of lamotrigine are rare but have included a few cases of multiorgan failure with disseminated intravascular coagulation.[24,72,73,105]

At least 12 cases of serious liver toxicity induced by la-motrigine have been reported, five of which resulted in death.[73] A British prescription-event monitoring study of 11,316 patients, however, confirmed that such serious adverse events are rare. Only two cases of disseminated intravascular coagulation, four cases of neutropenia, and three cases of thrombocytopenia were identified.[71]

A potential association between the use of lamotrigine and the occurrence of sudden unexplained death in epilepsy (SUDEP) was discussed during the clinical development of the drug. However, the SUDEP rate in epilepsy patients exposed to lamotrigine in clinical trials was not found to be higher than expected in patients with severe epilepsy.[69] A postmarketing surveillance study reported similar SUDEP rates for those exposed to lamotrigine and gabapentin.[123]

Additional Safety Issues

Among the newer-generation drugs, lamotrigine has by far the most extensive documentation with respect to use in pregnancy and teratogenic outcome. The manufacturer, GlaxoSmithKline, set up an international lamotrigine pregnancy registry in 1992. The outcome of prospective pregnancies with first-trimester exposure to lamotrigine was recently summarized.[32] There were 12 outcomes with major malformations among 414 pregnancies with lamotrigine monotherapy, yielding a malformation rate of 2.9% (95% CI, 1.6%–5.1%). Among 88 first-trimester exposures to lamotrigine in combination with valproic acid, 11 outcomes were noted with major birth defects (12.5%; 95%; CI,6.7%–21.7%), an apparently higher rate than in association with lamotrigine in other combinations (*n* = 182, 2.7%, 95%; CI,1.0%–6.6%).

The UK Epilepsy and Pregnancy Register[86] reported a rate of major congenital malformations of 3.2% (95%; CI,2.1%–4.9%) among 647 prospective pregnancies with lamotri-gine monotherapy, similar to the 2.2% (95%; CI,1.4%–3.4%, *n* = 900) with carbamazepine, whereas the malformation rate associated with valproic acid monotherapy in the same study was 6.2% (95%; CI,4.6%–8.2%, *n* = 715). A positive dose-response relationship was noted with lamotrigine, as with valproic acid and carbamazepine, with a malformation rate of 5.4% (95%; CI,3.3–8.7%) for daily lamotrigine doses exceeding 200 mg. The malformation rate for pregnancies exposed to lamotrigine in combination with valproic acid was 9.6% (95%; CI,5.7–15.7%, *n* = 141).

In the North American pregnancy registry, 15 of 564 infants born to women taking lamotrigine in the first trimester had major malformations, 2.7% (95% CI 1.5%–4.3%), the relative risk (RR) compared with background rate was 1.7 (95% CI 1.0–2.7). Five of those exposed to lamotrigine had oral clefts, considerably higher than expected from the background rate, RR 32.8 (95% CI 10.6–101.3).[56]

Seizure Aggravation

Although lamotrigine is effective in the treatment of idiopathic generalized epilepsies (IGEs), reports of seizure aggravation also exist. Lamotrigine has been shown to worsen seizures in severe myoclonic epilepsy.[54] It has also been associated with exacerbation, de novo myoclonus, and myo-clonic status in patients with IGEs including JME, juvenile absence epilepsy, and IGE with isolated generalized tonic–clonic seizures.[11,23,30]

Drug interactions

Pharmacokinetic Interactions

Enzyme-inducing AEDs, such as phenobarbital, primidone, phenytoin, and carbamazepine enhance lamotrigine clearance and lead to reduced steady-state concentrations and shortened half-life, sometimes resulting in the need for dose adjustments.[2,5]

Oxcarbazepine, methsuximide, and possibly topiramate can also induce the metabolism of lamotrigine.[8,76,122] Among non-AEDs, rifampicin reduces lamotrigine concentrations.[37] Likewise, oral contraceptives induce lamotrigine metabolism, reducing steady-state concentrations by 40% to 65%.[101,108] This effect appears to be associated with the ethinylestradiol component, whereas progesterone-only contraceptives do not seem to affect lamotrigine plasma concentrations.[98] The de-induction of lamotrigine metabolism is fairly rapid. As a consequence, lamotrigine plasma concentrations become twofold higher during the pill-free week with use of sequential oral contraceptives.[108]

Table 2 Lamotrigine dosing and titration schedules

	As add-on therapy Concomitant antiepileptic drugs	
Adults	**Valproate**	**Others**
Weeks 1 and 2	12.5 mg daily[a]	50 mg daily
Weeks 3 and 4	25 mg daily	50 mg twice daily
Maintenance	50–100 mg[b] twice daily	100–200 mg[b] twice daily
Children	**Valproate**	**Others**

Weeks 1 and 2	0.15 mg/kg	0.6 mg/kg
Weeks 3 and 4	0.3 mg/kg	1.2 mg/kg
Increments	0.3 mg/kg	1.2 mg/kg
Maintenance	1-5 mg/kg[b]	5–15 mg/kg[b]
As monotherapy	**Adults**	**Children**
Weeks 1 and 2	25 mg daily	0.5 mg/kg
Weeks 3 and 4	25 mg twice daily	1 mg/kg
Maintenance	50–100 mg[b] twice daily	2–8 mg/kg[b]

[a] 25 mg every other day is more common in the United States.

[b] Higher doses can be tried if seizures persist and the patient's tolerance is good.

Valproic acid is a potent inhibitor of UGT1A4 and thus of lamotrigine metabolism,[1,125] which can result in a 200% increase in circulating concentration.[108] Maximal inhibition of lamotrigine metabolism can occur with valproate doses of 500 mg/day and above.[49] The antidepressant sertraline is another inhibitor, producing a substantial increase in lamotrigine concentrations.[61]

Pharmacodynamic Interactions

Patients treated with lamotrigine in combination with carbamazepine or oxcarbazepine seem to be at a higher risk of developing clinical signs of central nervous system toxicity, such as diplopia and dizziness.[4,7] This is more common in patients with high serum concentrations of carbamazepine, and can be resolved by reduction in the carbamazepine dosage.[7] Independent studies suggest that lamotrigine in combination with valproate may be particularly effective in preventing seizures.[19,95] The pharmacokinetic interaction between the drugs is not sufficient to explain this synergistic effect, which can only be understood through a pharmacodynamic interaction.[95]

Role in Epilepsy treatment

Indications

Lamotrigine has a broad range of efficacy against partial-onset and primary generalized seizures and seizures associated with the LGS. The drug is licensed as adjunctive therapy for these indications in adults and in children over 2 years old and as monotherapy in adults and in children aged 12 years and over. It may also be useful in epilepsies with myoclonic seizures and typical absences.[3] The combination of lamotrigine and valproic acid appears particularly effective for partial and tonic–clonic seizures.[19,95] This effect has also been observed in patients with absence and myoclonic seizures.[40,41,92]

Dosing Recommendations

Recommended dosing schedules for lamotrigine are outlined in Table 2.[51] With adjunctive therapy, the titration rate depends on comedication, and the aim of the low starting dose and slow titration schedule is to minimize the risk of rash. Lamotrigine is usually prescribed twice daily in patients taking hepatic enzyme–inducing AEDs, but a single daily dose can be taken by patients on monotherapy or treated with valproic acid. Most patients receiving monotherapy respond to doses of 100 to 300 mg/day. Higher doses of 400 to 800 mg/day may be required in refractory epilepsy or when the patient is also taking an enzyme-inducing AED. An equivalent dose in valproic acid–treated patients would be 150 to 200 mg/day.

Precautions

Lamotrigine is usually well-tolerated, with rash in 3% of patients started on the drug as monotherapy being the most serious side-effect. Evidence suggests that a low starting dose and slow titration schedule help to minimize this problem, particularly in patients also taking valproic acid. For some patients taking carbamazepine or oxcarbazepine, the addition of lamotrigine can produce headache, dizziness, ataxia, and diplopia. In severe hepatic impairment (Child-Pugh grade C), initial and maintenance doses of lamotrigine should be reduced by 75%. Caution should also be exercised when treating patients with Gilbert syndrome. Although single-dose studies in people with end-stage renal failure showed no significant alteration of plasma lamotrigine concentrations, it might be expected that toxicity could occur due to accumulation of glucuronide metabolites. It is, therefore, prudent to exercise care if using lamotrigine in this population.

Contraindications

Lamotrigine can worsen severe myoclonic epilepsy and should be avoided in patients with this condition. Increasing evidence suggests that the drug can also exacerbate some other myo-clonic syndromes.

Summary and conclusions

Lamotrigine is a broad-spectrum AED that is widely used as an adjunctive agent and as monotherapy in adults and children. Its anticonvulsant activity has been demonstrated in several seizure models. The drug has been shown to operate via a variety of cellular mechanisms, including blockade of voltage-gated Na^+ channels. Lamotrigine undergoes linear pharmacokinetics and is metabolized mainly via hepatic glucuronidation. Controversy still exists over whether the drug is suited to routine therapeutic drug monitoring, although levels can be useful in pregnant women and in those starting or coming off the oral contraceptive pill. Lamotrigine is effective against most seizure types, although it may make certain types of myoclonic epilepsy worse. Adverse effects include nausea, headache, and ataxia, with rash being the most serious common problem. SJS and TEN have been reported, especially in children. Drug interactions are few, but combining lamotrigine with sodium valproate can be particularly efficacious, although at an increased risk of producing skin rash. Detrimental pharmacodynamic interactions can occur between lamotrigine and carbamazepine and oxcarbazepine. The licensing of lamotrigine in recent years for the treatment of bipolar I disorder serves to underline its therapeutic range.

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Chapter 151

Levetiracetam

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Jennifer Cavitt

Introduction

Levetiracetam, an antiepileptic drug (AED) with an interesting development history, has become widely used in the treatment of several types of epilepsy. Initial performance in standard animal screening models proved disappointing,[34] but the drug's success in clinical trials in humans have led some to question whether standard screening models should be reevaluated. Levetiracetam's newly discovered mechanism of action is unique among AEDs, and has led to development of new compounds with binding at the SV2A site.[45] For clinicians, levetiracetam has proved attractive because of its lack of hepatic metabolism, minimal drug interactions, activity against several seizure types, and ability to start an effective dose on day one.

Pharmacology

Levetiracetam—(S)-alpha-ethyl-2-oxo-pyrrolidine acetamide-—is a novel AED, chemically related to the nootropic agent, piracetam (Fig. 1).[44]

Standard animal models for screening and testing of AEDs indicate that levetiracetam may work differently than other AEDs. Klitgaard showed that levetiracetam did not stop seizures following acute maximal electrical shock (MES) and maximal pentylenetetrazol (PTZ) in rodents.[34] However, these investigators showed that levetiracetam did protect against generalized seizures in rodents that had been kindled (i.e., animals who developed seizures due to chronic, submaximal stimulation with electrical shock or PTZ administration). Additionally, levetiracetam was ineffective in various maximal chemoconvulsive tests, except for protection against secondarily generalized activity from partial seizures induced by pilocarpine in mice and pilocarpine and kainic acid in rats. The antiseizure activity of levetiracetam persisted with chronic administration of methyl-6,7–dimthoxy-4–ethyl-beta-carboline-3–carboxylate, and it did not lower the seizure threshold of an inverse benzodiazepine receptor agonist. This pattern of activity differs greatly from that of other AEDs. An evaluation of levetiracetam's major metabolite, (S)-alpha-ethyl-2–oxo-1–pyrrolidine acetic acid, using the same tests showed it to be inactive. There was a wide safety margin in normal and amygdala-kindled rats using the Rotorod impairment test.

Löscher et al. corroborated the findings of Klitgaard on the antiepileptogenic effects of levetiracetam in the kindling model of temporal lobe epilepsy.[43] Only two of the older AEDs, valproate and phenobarbital, demonstrate mild antiepileptogenic properties in similar animal models for kindled seizures. The dose required to produce this effect is much greater, and the strength of the effect is much less for valproate and phenobarbital, compared with levetiracetam.

At the time of initial studies and U.S. Food and Drug Administration (FDA) approval, the mechanism of action of levetiracetam was unknown. Now, several lines of evidence indicate that levetiracetam exerts its antiepileptic action through binding at the synaptic vesicle SV2A receptor.[45] Brain membranes and purified synaptic vesicles from mice lacking SV2A do not bind a tritiated levetiracetam derivative, indicating that SV2A is necessary for levetiracetam binding. Levetiracetam and related compounds bind to SV2A expressed in fibroblasts, indicating that SV2A is sufficient for levetiracetam binding. No binding was observed to the related isoforms SV2B and SV2C. A high degree of correlation occurs between binding affinities of a series of levetiracetam derivatives to SV2A in fibroblasts and to the levetiracetam-binding site in brain. Finally, a strong correlation exists between the affinity of a compound for SV2A and its ability to protect against seizures in an audiogenic mouse animal model of epilepsy. There appears to be some consensus that levetiracetam does not exert its antiepileptic activity through modulation or γ-aminobutyric acid (GABA) transmission or direct effect on sodium or calcium channels.[57,63] These new and intriguing findings on levetiracetam's mechanism have the potential to open a new avenue of investigation into proteins involved in vesicle exocytosis, and into SV2 in particular, as targets for the development of new AED therapies.

A study of levetiracetam's efficacy in an experimental model of self-sustaining status epilepticus (SE) induced in rats by electrical stimulation revealed that intravenous pretreatment with levetiracetam reduced or prevented the development of self-sustaining seizures, and levetiracetam treatment during self-sustaining seizures decreased or aborted seizures.[47] This study also found that levetiracetam significantly enhanced the anticonvulsant effects of diazepam, even at subtherapeutic doses.

Clinical Pharmacokinetics

Levetiracetam pharmacokinetics have been evaluated in pediatric, adult, and elderly patients, as well as in patients with renal and hepatic failure. Its rapid absorption, excellent bioavailability, minimal protein binding, lack of hepatic metabolism, and linear pharmacokinetics, make levetiracetam dosing straightforward.

Absorption

Following oral administration of 250 mg to 5,000 mg, the absolute bioavailability of levetiracetam is 95% to 100%.[52] Peak plasma concentrations of approximately 31 μg/mL are achieved within 1 hour of a 1,000-mg oral dose. Repeated doses of 1,000 mg twice daily yield steady-state peak concentrations of approximately 43 μg/mL within 2 days. Peak concentrations and area under the plasma concentration-time curve (AUC) were linear for doses ranging from 500 to 5,000 mg in healthy volunteers. Food and antacids (calcium carbonate and aluminum hydroxide) slowed the rate of absorption, but did not decrease the extent of absorption. Additionally, there was no change in bioavailability with administration of a single 500-mg tablet compared with administration of two 250-mg capsules.

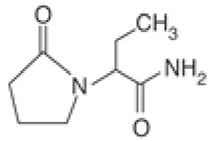

FIGURE 1. Levetiracetam's chemical structure (2-(2-oxopyrrolidin-1-yl)butanamide).

Table 1 Levetiracetam dosage adjustments in renal insufficiency (manufacturer's recommendations)

Group	Creatinine clearance (mL/min)	Dosage (mg)	Frequency
Normal	>80	500 to 1,500	Every 12 hours
Mild	50–80	500 to 1,000	Every 12 hours
Moderate	30–50	250 to 750	Every 12 hours
Severe	<30	250 to 500	Every 12 hours
ESRD patients using dialysis	—	500 to 1,000	[a]Every 24 hours

Following dialysis, a 250 to 500 mg supplemental dose is recommended.

Plasma Protein Binding and Distribution

Levetiracetam appears to be distributed to intracellular and extracellular fluid with a volume of distribution of 0.5 to 0.7 L/kg.[33] Less than 10% is bound to plasma proteins. Animal studies indicate that levetiracetam readily crosses the blood–brain barrier and appears to be evenly distributed throughout the brain.[19]

Metabolism and Elimination

Within 24 hours of an oral dose of levetiracetam, 93% of the drug has been excreted, 66% as unchanged drug in the urine and 27% as inactive metabolites.[52] One major inactive metabolite, L057, accounts for 24% of the dose, and is formed in blood by hydrolysis of an acetamide group. This deamination process does not involve either the cytochrome P450 or UDP-glucuronyl transferase isozyme (UGT) systems. Two other minor metabolites account for 3% of the dose, and their metabolic pathway has not been determined.

The renal clearance of levetiracetam is 40 mL/min/1.73 m^2 or 0.6 mL/min/kg and clearance of the major metabolite is 4.2 mL/min/kg.[33] Levetiracetam apparently undergoes glomerular filtration with some tubular reabsorption, whereas L057 is actively secreted in renal tubules in addition to tubular reabsorption. Concomitant administration of probenecid increased concentrations of L057, but not levetiracetam. Because L057 is inactive, this change in elimination should not result in changes in response to levetiracetam. In normal adult volunteers, the elimination half-life of levetiracetam is 6 to 8 hours and is unchanged by doses up to 5,000 mg, route of administration, or frequency of administration. Steady-state concentrations are reached within 48 hours.[52]

Pediatric and Elderly Populations

In children with epilepsy who are 6 to 12 years old, the elimination half-life of levetiracetam is approximately 6 hours, and apparent total body clearance is 30% to 40% lower than adults.[52] The peak concentrations and AUC adjusted for a dose of 1 mg/kg were also 30% to 40% higher than in adults. The fraction excreted unchanged in the urine was similar to that of adults, but the percent of L057 in the urine was lower in children. These values indicate that children may require doses that are 1.3 to 1.4 times a weight-normalized adult dose. For elderly patients, the elimination half-life is prolonged at 10 to 11 hours.[31]

Renal and Hepatic Impairment

The renal clearance of levetiracetam correlates directly with creatinine clearance, as does its primary metabolite.[52] Patients with mild to moderate renal impairment (creatinine clearance of 20–89 mL/min/1.73 m^2) had the total body clearance of levetiracetam decreased by 35% to 60%. Total body clearance was reduced by 68% in a patient with a creatinine clearance of <19 mL/min/1.73 m^2. As expected, the steady-state peak concentration, half-life, and AUC increased with declining renal function. During hemodialysis, the elimination half-life for levetiracetam is approximately 25 hours for the interdialytic period and 3.1 hours for the intradialytic period. Approximately 50% of levetiracetam is removed during dialysis. Based upon these data, the manufacturer recommends dosage adjustments for varying degrees of renal function (Table 1).[33]

In subjects with mild (Child-Pugh A) to moderate (Child-Pugh B) hepatic impairment, the pharmacokinetics of levetiracetam were unchanged. In patients with severe hepatic impairment (Child-Pugh C), total body clearance was 50% that of normal subjects, but decreased renal clearance accounted for most of the decrease. No dose adjustment is needed for patients with hepatic impairment.[33]

Race and Gender

Levetiracetam C_{max} and AUC were 20% higher in women (n = 11) compared with men (n = 12), however clearances adjusted for body weight were comparable. Formal pharmacokinetic studies of the effects of race have not been conducted. Cross-study comparisons involving whites (n = 12) and Asians (n = 12) show that the pharmacokinetics of levetiracetam were comparable between the two races. Because levetiracetam is primarily renally excreted and there are no important racial differences in creatinine clearance, pharmacokinetic differences due to race are not expected.[31]

Value of Plasma Concentrations

Plasma concentrations of levetiracetam were obtained in controlled trials. No study has demonstrated a relationship between plasma concentration and efficacy or adverse effects independent of dose. Levetiracetam does not undergo hepatic metabolism, is not protein bound, and lacks drug interactions with most other medications; thus routine monitoring of plasma concentrations does not appear indicated.

Intravenous Formulation

The equivalence of levetiracetam injection and the oral formulation was demonstrated in a bioavailability study of 17 healthy volunteers.[32] In this study, levetiracetam 1,500 mg was diluted in 100 mL 0.9% sterile saline solution and was infused over 15 minutes. The selected infusion rate provided plasma concentrations of levetiracetam at the end of the infusion period similar to those achieved at T_{max} after an equivalent oral dose. It is demonstrated that levetiracetam 1,500 mg intravenous infusion is equivalent to three 500-mg oral tablets of levetiracetam. The time-independent pharmacokinetic profile of levetiracetam was demonstrated following a 1,500 mg intravenous infusion for 4 days with twice-daily dosing. The $AUC_{(0-12)}$ at steady-state was equivalent to AUC_{inf} following an equivalent single dose. Equivalent doses of intravenous levetiracetam and oral levetiracetam result in equivalent C_{max}, C_{min}, and total systemic exposure to levetiracetam when the intravenous levetiracetam is administered as a 15-minute infusion.

Efficacy

Efficacy as Adjunctive Treatment in Partial Seizures

Levetiracetam is effective adjunctive treatment for medication-resistant partial seizures with or without secondary generalization. Several randomized, placebo-controlled trials have established that levetiracetam doses of 1,000 to 3,000 mg/day significantly reduce mean seizure frequency rates and produce significantly greater numbers of 50% responders when compared with placebo.

Shorvon et al.[56] studied 324 patients, aged 16 to 65 years, with medication-resistant partial seizures and found that add-on levetiracetam significantly reduced seizure frequency compared with placebo, and 50% responder rates were significantly greater in levetiracetam groups compared with placebo. The median percentage reduction in seizure frequency was 17.7% and 26.5% for levetiracetam doses 1,000 mg/day and 2,000 mg/day, respectively, compared with 6.1% for placebo. In addition, a 50% reduction of 50% or greater in seizure frequency was seen in 22.8% of patients on levetiracetam 1,000 mg/day and 31.6% of patients on levetiracetam 2,000 mg/day, compared with 10.4% of patients taking placebo. However, no significant difference was found between levetiracetam doses of 1,000 mg/day and 2,000 mg/day. Betts et al.[12] also failed to find greater efficacy with a higher dose of levetiracetam. In fact, in a study of 119 patients, aged 16 to 70 years, with medication-resistant epilepsy that included partial seizures with and without secondary generalization, as well as primary generalized tonic–clonic seizures, 2,000 mg/day add-on levetiracetam produced a significantly greater 50% responder rate (48.1%, $p < 0.05$) compared with placebo (16.1%). However, the 50% responder rate for patients on 4,000 mg/day levetiracetam (28.6%) was remarkably not significantly better than placebo, although no significant differences were found in seizure reduction by seizure type between the treatment groups.

In contrast, two other randomized, controlled trials did find a dose–response relationship for levetiracetam in medication-resistant partial seizures. In 324 patients, aged 16 to 65 years, studied by Boon et al.,[13] both 1,000 mg/day and 2,000 mg/day doses of add-on levetiracetam significantly reduced mean seizure frequency and increased 50% and 75% responder rates compared with placebo. Specifically, 26.2% of patients on levetiracetam 1,000 mg/day and 34.3% of patients on levetiracetam 2,000 mg/day had a ≥50% reduction in seizure frequency, compared with 12.2% of those on placebo. Furthermore, the 50% responder rate with levetiracetam 2,000 mg/day was significantly greater than that with levetiracetam 1,000 mg/day ($p = 0.018$). Of patients receiving 1,000 or 2,000 mg/day levetiracetam, 13.7% and 20% of patients, respectively, had ≥75% reduction in seizure frequency, compared with 4% in the placebo group.

Similarly, Cereghino et al.[15] found that both 1,000 mg/day and 3,000 mg/day add-on levetiracetam doses significantly reduced mean seizure frequency compared with placebo (32.5% and 37.1%, respectively, vs. 6.8% for placebo, $p < 0.001$) and significantly increased 50% responder rates compared with placebo in 294 patients aged 16 to 70 years. Of those taking 1,000 mg/day or 3,000 mg/day levetiracetam, 33% and 39.8%, respectively, had a ≥50% reduction in seizure frequency, compared with 10.8% of patients taking placebo. Moreover, a significantly greater number of patients in the 3,000 mg/day levetiracetam group (eight of 98 or 8.2%, $p = 0.01$), but not the 1,000 mg/day levetiracetam group (three of 94 or 3.2%) were seizure-free, compared with placebo (0 of 93).

Another randomized, controlled trial by Ben-Menachem et al.[10] evaluated in 286 patients, aged 16 to 70 years, with medication-resistant partial seizures the efficacy of add-on levetiracetam 3,000 mg/day versus placebo. The investigators found that median seizure frequency, median percentage seizure reduction, and 50% responder rates were all significantly better in the levetiracetam group (1.06 seizures/week, 39.9%, and 42.1%, respectively) compared with the placebo group (1.75 seizures/week, 7.2%, 16.7%, respectively).

Ben-Menachem et al.[9] also examined long-term efficacy of levetiracetam using data from 1,422 patients treated with levetiracetam in multiple studies. The investigators found that median percentage seizure frequency reduction did not decrease over time within cohorts of 6 to 54 months of levetiracetam exposure, suggesting that tolerance was not observed. In addition, 50% and 75% responder rates were similar (38.6% and 20.1%, respectively) for the whole treatment period of up to 54 months as those seen in randomized, controlled trials, indicating that short-term efficacy is sustained over a longer observation period as well.

French and Arrigo[21] evaluated the rapid onset of action of levetiracetam in a pooled analysis of data from three randomized, double-blind, placebo-controlled trials of 883 patients, aged 16 to 70 years, with refractory partial seizures started on levetiracetam 1,000 or 333 mg/day versus placebo. The proportions of seizure-free patients in each group were analyzed for 3 days before and after starting levetiracetam or placebo. In the 1,000 mg/day levetiracetam group, the increase in the proportion of seizure-free patients over the day prior to treatment initiation was 15% for the first day of treatment, 17% for the second day of treatment, and 17%

for the third day of treatment. All these differences were found to be statistically significant ($p < 0.001$). In the 333 mg/day levetiracetam group, the increase in the proportion of seizure-free patients over the day prior to treatment initiation was 7% for the first day of treatment, 9% for the second day of treatment, and 9% for the third day of treatment, but none of these differences was statistically significant. No major changes were observed in the proportion of seizure-free patients following initiation of placebo, with increases of 1%, 2%, and 1%, respectively, for days one, two, and three following treatment initiation, and these changes were also not statistically significant. Thus, rapid onset of action was noted when starting levetiracetam 1,000 mg/day.

A follow-up study[22] examined the proportion of seizure-free days each week for the 3-month period following treatment

initiation for those same 883 patients to determine whether a change in efficacy occurs during the duration of the trial. A significantly greater mean proportion of seizure-free days was observed beginning with the first week after treatment initiation in the levetiracetam group compared with placebo. Moreover, a significantly greater mean proportion of seizure-free days was also seen for each week of the 3-month period, suggesting sustained efficacy of levetiracetam. Interestingly, the difference in mean proportion of seizure-free days between the levetiracetam and placebo groups was most pronounced in the first week after treatment initiation (0.81 for levetiracetam vs. 0.69 for placebo). However, the efficacy was stable for the following weeks in the 3-month period.

Krakow et al.[35] analyzed the long-term continuation rate and efficacy of levetiracetam in 1,422 patients with medication-resistant epilepsy treated with adjunctive levetiracetam in several double-blind, placebo-controlled trials and open-label studies during the developmental program of the drug in Europe and the United States. Patients ranged in age from 5 to 78 years, but the majority of patients (95.2%) were 16 to 65 years old. The vast majority (93%) had localization-related epilepsy. Of 1,422 patients exposed to levetiracetam, 562 were still treated at the cut-off date. Kaplan-Meier survival analysis estimated continuation rates of 60%, 37%, and 32%, respectively at 1, 3, and 5 years. Adverse events led to treatment withdrawal in 225 of 1,422 patients (15.8%), and lack of efficacy led to withdrawal in 261 patients (18.4%). In 374 of 1,422 patients (26.3%), levetiracetam was discontinued due to reasons inherent in clinical trials, such as protocol violations, withdrawal of consent, study completed without starting open follow-up, lost to follow-up, and the like. Cox regression revealed four factors that significantly affected levetiracetam continuation: high maximum dose, low starting dose, presence of generalized seizures, and smaller number of AEDs at baseline. In 1,325 patients for whom seizure frequency data were available for both baseline and treatment periods, 512 (39.6%) had a ≥50% reduction in seizure frequency, 266 (20%) had a ≥75% reduction in seizure frequency, 183 (13%) were seizure-free for at least 6 months, 109 (8%) were seizure-free for at least 1 year, and 65 (4.5%) were seizure free from the first day of exposure.

Efficacy as Monotherapy in Partial Seizures

A large prospective trial demonstrated the effectiveness of levetiracetam as monotherapy. Ben-Menachem et al.[8] studied the efficacy of 1,000 to 3,000 mg/day levetiracetam monotherapy versus 400 to 1,200 mg/day controlled-release carbamazepine monotherapy in 472 patients with newly diagnosed, localization-related epilepsy followed for at least 12 months in a randomized, double-blind, head-to-head trial. Six-month seizure freedom rates were similar in the levetiracetam (73.0%) and carbamazepine (72.8%) groups. Twelve-month seizure-freedom rates were 56.6% in the levetiracetam group and 58.5% in the carbamazepine group. Significantly fewer patients taking levetiracetam (16.1%) discontinued therapy or had a dose change due to an adverse event compared with carbamazepine (23.0%).

In the randomized, controlled add-on trial described earlier, Ben-Menachem et al.[10] evaluated in 286 patients with refractory partial seizures—first the efficacy of add-on levetiracetam 3,000 mg/day versus placebo, then open-label conversion to monotherapy (levetiracetam 3,000 mg/day vs. placebo) for those study patients who qualified by virtue of a good response during the add-on phase. Although only 86 of 286 patients were eligible for the monotherapy phase, significantly more patients receiving levetiracetam completed the study compared with placebo.

In several small, retrospective studies Alsaadi et al.[3,4,5,6] examined the efficacy of levetiracetam monotherapy, both as a first-line treatment and as conversion to monotherapy. A chart review identified 46 patients with partial seizures who received levetiracetam monotherapy either as first-line treatment (n = 11) or as add-on therapy (n = 35) with subsequent conversion to monotherapy.[4] This review included some patients' data reported in an earlier study.[6] Of the 46 patients, three were lost to follow-up, five discontinued levetiracetam due to lack of efficacy, and three discontinued levetiracetam due to adverse effects. Thirty-five patients continued on levetiracetam monotherapy for 1 year, and 19 (54%) were at least 6 months' seizure-free at 1-year follow-up. Thirty-two of 35 patients (91%) had >50% reduction in seizure frequency at 1 year. A similar small, retrospective study evaluated the efficacy of levetiracetam monotherapy in 14 elderly patients, ages 62 to 92 years.[3] Five began levetiracetam as first-line therapy, and nine converted to levetiracetam monotherapy after failing initial AED trials. Thirteen (93%) continued levetiracetam for at least 6 months, and eight patients (62%) became seizure-free. Twelve of the 14 elderly patients (86%) had a >50% reduction in seizure frequency.

Efficacy in Generalized Seizures

Levetiracetam is approved in many countries for use in patients with partial-onset seizures. Although most randomized, double-blind, controlled clinical trials have focused on patients with partial-onset epilepsy, preliminary evidence suggests levetiracetam may be effective in primary generalized seizure types as well. Animal studies in genetic models of epilepsy[26,34,42] and open-label or single-blind trials in humans indicate levetiracetam may reduce the frequency of generalized-onset seizures, but few randomized, controlled trials have been conducted.

In a randomized, double-blind, placebo-controlled trial, Verdu et al.[60] studied the effect of adjunctive levetiracetam 3,000 mg/day in 122 patients, aged 12 to 65 years, with idiopathic generalized epilepsy with myoclonic seizures taking one concomitant AED. Of patients taking levetiracetam, 58.3% had a ≥50% reduction in days with myoclonic seizures, compared with 23.3% of patients taking placebo (p = 0.0002). In addition, thirteen patients on levetiracetam became seizure-free, compared with two seizure-free patients taking placebo.

In an open-label study of 55 patients, aged 16 to 67 years, with medication-resistant idiopathic generalized epilepsy treated with levetiracetam 500 to 4,000 mg/day, Krauss et al.[37] found that a majority of patients (76.4%) had a ≥50% reduction in seizure frequency, and 40% became seizure-free. The greatest 50% responder rate (23 of 26, 88.4%) was seen in patients with juvenile myoclonic epilepsy (JME). Fourteen of 18 patients with epilepsy with tonic–clonic seizures (77.8%) had a ≥50% reduction in seizure frequency, whereas five of 11 patients with absence epilepsy (45.5%) were 50% responders.

Labate et al.,[38] on the other hand, evaluated open-label levetiracetam monotherapy (n = 8) or adjunctive therapy (n = 27) for 12 months in 35 patients with different types of idiopathic and symptomatic generalized epilepsies, including JME, severe myoclonic epilepsy of infancy, Lennox-Gastaut syndrome, myoclonic-astatic epilepsy, myoclonic absences, benign myoclonic epilepsy in infancy, and undetermined generalized epilepsy syndromes, all with prominent myoclonic seizures. Levetiracetam doses ranged from 1,000 to 3,000 mg daily, with a mean dosage of 2,000 to 3,000 mg daily. All patients receiving levetiracetam monotherapy had JME. Twenty-nine of 35 patients (83%) had a ≥50% reduction in seizure frequency, including six of eight patients (75%) on levetiracetam monotherapy and 23 of 27 patients (85%) on levetiracetam add-on therapy. Fifteen of 35 patients (43%) were seizure-free, including five of eight patients with JME (62.5%). In four of 35 patients (11.4%), seizure frequency was unchanged and, in two of 35 patients (5.7%), seizure frequency increased. However, the greatest response was seen in patients with JME, lack of change or increase in seizure frequency was seen more often in patients with refractory generalized epilepsy, such as severe myoclonic epilepsy of infancy and Lennox-Gastaut syndrome.

Abou-Khalil et al.[1] studied individualized doses of levetiracetam 1,000 to 3,000 mg/day in an open-label study that included 37 patients, aged 16 to 70 years, with medication-resistant generalized epilepsy. Twelve of the 37 had the diagnosis JME, and four others had a combination of myoclonic and absence seizures with or without generalized seizures, suggesting the diagnosis of JME, even though the syndrome diagnosis was not specifically stated. One patient had juvenile absence epilepsy, and three patients had isolated generalized tonic-clonic seizures. Four had Lennox-Gastaut syndrome, four had unspecified symptomatic generalized epilepsy, and eight had generalized epilepsy that was not further specified. Nineteen of 37 (51.4%) patients had a ≥50% seizure reduction. This included three of seven patients (42.9%) on levetiracetam ≤1,000 mg/day, five of nine patients (55.6%) on 1,001 to 2,000 mg/day, ten of 20 patients (50%) on 2,001 to 3,000 mg/day, and one of one (100%) on 3,001 to 4,000 mg/day.

Another open-label study by Mohanraj et al.[49] of levetiracetam therapy in 156 patients, aged 16 to 78 years, with medication-resistant epilepsy of any type included 20 patients with idiopathic generalized epilepsy. Thirteen of those 20 (65%) had a ≥50% reduction in seizure frequency, including eight patients (40%) who became seizure free. JME was the most common type of idiopathic generalized epilepsy in this study (n = 11), and five (45%) of these patients became seizure free.

In addition, several small studies and case reports have suggested that levetiracetam reduces epileptiform activity on electroencephalogram (EEG) as well. An open-label, uncontrolled study of twelve patients with photosensitive epilepsy[30] examined levetiracetam's effect on photoparoxysmal response on EEG. Nine of twelve patients (75%) had a clear suppression or abolition of photoparoxysmal response after a single dose of levetiracetam. A dose-dependent response was seen, with complete abolition occurring only at 750- to 1000-mg doses. Although it was not one of the study objectives, two of the patients with myoclonic jerks noted a reduction in their myoclonus. One of these patients remained on levetiracetam for 3 years, with complete control of myoclonus and persistent suppression of photoparoxysmal response.

Gallagher et al.[23] quantitatively analyzed spike-and-wave density and spike-and-wave complex duration in ten patients with idiopathic generalized epilepsy treated with levetiracetam during continuous video-EEG monitoring. In three patients, entire EEG records were not available. Based on the available record, two patients had frequent spike-and-wave complexes before levetiracetam initiation and none after. The third patient had no response to levetiracetam. Of the seven patients for whom entire EEG records were available, all had a significant reduction in spike-and-wave density during levetiracetam treatment compared with periods without levetiracetam. Finally, a single case report[14] demonstrated an increase in generalized spike-and-wave discharges following discontinuation of levetiracetam, subsequent reduction of generalized spike-and-wave following reinstitution of levetiracetam, and corresponding changes in clinical absence in a patient monitored with continuous video-EEG. Four to 56 generalized spike-and-wave bursts per hour were noted at baseline, and this increased to 406 to 914 per hour following levetiracetam discontinuation. These bursts lasted ≥2 seconds and were associated with clinical absence. Subsequent reduction to 135 bursts of generalized spike-and-wave discharges per hour occurred 3 hours after reinstitution of levetiracetam.

Efficacy in Pediatric Epilepsy

Although levetiracetam has not been studied as extensively in pediatric epilepsy populations, one randomized, double-blind, placebo-controlled trial demonstrated efficacy in patients aged 4 to 16 years with refractory partial seizures,[24] leading to FDA approval of levetiracetam as adjunctive treatment for epilepsy in patients ≥4 years of age. This study evaluated 198 patients, aged 4 to 16 years, with refractory partial seizures with or without secondary generalization treated with levetiracetam 20 to 60 mg/kg per day versus placebo. A ≥50% reduction in seizure frequency was seen in 45 of 101 patients taking levetiracetam (44.6%), but in only 19 of 97 patients taking placebo (19.6%, p = 0.0002). In addition, 20 of 101 patients on levetiracetam (19.8%) had a ≥75% reduction in seizure frequency, compared with five of 97 patients taking placebo (5.1%), which was also statistically significant. Overall, the percentage seizure frequency reduction for levetiracetam over placebo was 26.8% (p = 0.0002).

Grosso et al.[28] conducted a prospective, open-label study to evaluate the efficacy of add-on levetiracetam 10 to 60 mg/kg per day in 110 children under 16 years of age with refractory epilepsy that was localization-related (n = 53), generalized (n = 45), or unclassifiable (n = 12). Forty-three of 110 children (39%) had a ≥50% reduction in seizure frequency, and ten children (9%) became seizure free. Twelve children (11%) had an increase in seizure frequency. Of those patients with a ≥50% reduction in seizure frequency, 58% had localization-related epilepsy. Among the patients with localization-related epilepsy with the highest responder rates were those with cryptogenic partial seizures.

Lagae et al.[39] examined the efficacy of open-label, add-on levetiracetam (12–62 mg/kg/day) in 67 children, aged 6 months to 16 years, with refractory partial, generalized, or mixed seizure types. At the same time, they evaluated open-label levetiracetam monotherapy in ten children, 4 to 16 years of age, six of whom had generalized seizures (two with childhood absences, two with myoclonic seizures, and two with tonic–clonic seizures), and four of whom had partial seizures. In the add-on trial, 33 of 67 patients (49%) had a ≥50% reduction in seizures, and three children became seizure-free. In the monotherapy trial, nine of ten patients had a ≥50% reduction in seizure frequency, and two children became seizure-free. Of note, 10 of 67 children (15%) in the add-on trial had an increase in seizure frequency, with a median increase of 50% (range 18%–420%). No differences in response were observed by seizure type or epilepsy syndrome. However, 85% of patients in the study population were mentally retarded.

Wheless et al.[61] evaluated the efficacy of open-label levetiracetam in 39 children, younger than 16 years of age, with refractory partial-onset and/or generalized seizures, all but one of whom received levetiracetam as add-on therapy. Twenty-five patients of 39 patients (64.1%) had a ≥50% reduction in seizure frequency, and three of these patients (7.7%) were seizure-free on a mean maintenance levetiracetam dose of 53.3 mg/kg per day. In a smaller, open-label study, Glauser et al.[25] found that twelve of 23 children (52%), aged 6 to 12 years, with medication-resistant partial-onset seizures, who were treated with 20 to 40 mg/kg per day levetiracetam, had a ≥50% reduction in seizure frequency. Finally, Lagae et. al.[40] studied the efficacy of add-on levetiracetam (17–60 mg/kg/day) in 21 children aged 11 months to 14 years, who had various refractory childhood epilepsy syndromes and mild or severe mental retardation. Ten children (47.6%) had a ≥50% reduction in seizure frequency, but none of the epilepsy syndromes showed

a significantly better outcome. In addition, no significant differences were found in the responses of generalized, partial, and mixed epilepsy syndromes. However, in comparing response by seizure type, among the generalized seizures, the best response was seen for myoclonic seizures, with seven of 11 patients (64%) having a ≥50% reduction in seizure frequency; only in the myoclonic group was seizure frequency reduction statistically significant.

Efficacy in the Elderly

The incidence of epilepsy increases sharply after 60 years of age, and the physiologic changes that occur with aging, as well as the presence of comorbid medical conditions, present unique challenges in treating epilepsy in elderly patients. In particular, decreased rates of hepatic and renal metabolism and decreased serum albumin concentrations affect the metabolism and serum concentrations of many AEDs, leading to increased risk for toxicity with certain AEDs. The presence of comorbid medical conditions in elderly patients often requires long-term treatment with other medications, many of which may interact with AEDs on the basis of induction or inhibition of hepatic cytochrome P450 enzyme systems or through competitive protein-binding. Finally, elderly patients often are more sensitive to the cognitive adverse effects that are seen more frequently with older AEDs.[11]

Despite the high prevalence of epilepsy in the elderly, few studies examine the efficacy of AEDs in this population. Ferrendelli et al.[20] evaluated an elderly subset of 78 patients ≥65 years of age in a large (n = 1,030), open-label study examining the efficacy of levetiracetam in patients with refractory partial seizures. Maximum levetiracetam dose for most patients (41 of 78, 52.6%) was 1,000 mg/day, but for 16 patients (20.5%), it was 2,000 mg/day, and for 15 patients (19.2%), it was 3,000 mg/day. Overall, a ≥50% reduction in seizure frequency was seen in 76.9% of patients, whereas a ≥75% reduction was seen in 56.9% of patients, and 40% of patients were seizure free. Fifteen patients (19.2%) discontinued levetiracetam due to adverse events, including one for lack of efficacy and 14 for adverse effects. Somnolence and dizziness were the most common adverse effects noted in this elderly subgroup, as well as in the overall study population, and somnolence was seen more commonly in elderly patients taking two or more concomitant AEDs.

Alsaadi et al.[3] evaluated in a small, retrospective study the efficacy of levetiracetam monotherapy in 14 elderly patients, aged 62 to 92 years. Five began levetiracetam as first-line therapy, and nine converted to levetiracetam monotherapy after failing initial AED trials. Thirteen (93%) continued levetiracetam for at least 6 months, and eight patients (62%) became seizure free. Twelve of the 14 elderly patients (86%) had a >50% reduction in seizure frequency. The total dose ranged from 500 to 3,000 mg/day (mean 1,839.2 mg/day). Levetiracetam was well-tolerated in this small series of elderly patients, and in no patients was levetiracetam discontinued due to adverse effects.

Alore et. al.[2] examined the pattern of levetiracetam use in 39 hospitalized patients ≥65 years of age in a retrospective database review. Over half (54%) received levetiracetam during admission to a neurosurgery or trauma service, and intracranial hemorrhage was the most common cause of seizure. Most of these patients (80%) received levetiracetam as first-line monotherapy. Patients with stroke comprised the second-largest group (38%) of patients receiving levetiracetam, and a majority of these patients also received levetiracetam as first-line therapy. The average number of discharge medications was 9.4. A similar retrospective review examined the pattern of levetiracetam use compared with other AEDs in all patients admitted to a neuroscience intensive care unit.[48] Of 358 patients treated with AEDs, 124 received levetiracetam. In this population, intracranial hemorrhage and trauma were the most common diagnoses. Older patients and those with previous medical complications from AEDs or underlying disease were noted to be preferentially treated with levetiracetam.

Although data regarding the use of levetiracetam in older patients is quite limited, clinicians treating the elderly sometimes choose levetiracetam over standard AEDs, based on its favorable adverse effects profile, its lack of drug–drug interactions, minimal protein-binding, and lack of hepatic metabolism. Levetiracetam is renally excreted, and the rate of excretion correlates with creatinine clearance. Oral clearance of levetiracetam may be decreased in the elderly by 20% to 40%.[53] Thus, in prescribing levetiracetam for elderly patients, lower starting doses should be used for those with decreased creatinine clearance, a common finding in older patients. Osteoporosis often affects elderly patients, and this condition may be exacerbated by standard AEDs, especially the enzyme-inducing drugs. As levetiracetam neither induces nor inhibits hepatic enzymes, there is reason to expect that it would have less negative effect on bone health, but long-term data supporting this contention have not yet been published.

Efficacy in Status Epilepticus

Status epilepticus is a neurologic emergency defined as continuous or repeated seizure activity occurring for 30 minutes or more, without return to baseline between repeated seizures. Urgent treatment with benzodiazepines typically is followed by another AED given intravenously. Fos-phenytoin, phenytoin, phenobarbital, and valproic acid have all been shown to be effective in the acute treatment of SE. However, SE remains a clinical challenge, particularly in cases of refractory SE, which carries a mortality rate of 32%.[59] Although few published studies have examined the use of levetiracetam in the setting of SE, the development of an intravenous formulation of levetiracetam may increase levetiracetam use in the hospital setting, including cases of refractory SE.

Case series in humans have suggested that levetiracetam may be effective in treating SE. Rosetti and Bromfield[55] reported 13 cases of SE in which levetiracetam was administered enterally and compared these cases to age- and sex-matched controls from their SE database. Daily doses of 1,000 mg to 6,000 mg were used in combination with benzodiazepines (in all but one case) and other AEDs. In four patients (31%), levetiracetam was administered de novo. Three of the thirteen patients (23%) were identified as probable responders, and another patient (8%) reportedly responded but subsequently died. Responders were defined as patients in whom SE resolved within 3 days of start or increase of levetiracetam, without recurrence. Four patients (31%) were nonresponders, and five (38%) had an undetermined response. No significant difference in efficacy of SE treatment was seen between the levetiracetam group and the control group. The authors conclude that levetiracetam may be a valuable alternative treatment of SE.

Patel et. al.[51] reported their experience using oral levetiracetam in six patients, aged 16 to 91 years, to successfully treat SE refractory to two or more initial AEDs. Levetiracetam doses of 500 to 3,000 mg/day produced seizure control within 12 to 96 hours in patients with various types of refractory SE, including convulsive, focal, and nonconvulsive SE. Etiologies of SE also varied in this series, including ischemic and hemorrhagic infarcts, CNS vasculitis, posttraumatic epilepsy, static encephalopathy, and noncompliance.

Although preliminary evidence from animal studies and these few case series suggests potential efficacy of levetiracetam in refractory SE, other studies have suggested a

paradoxical effect of levetiracetam in some patients, including new occurrence of SE following initiation of levetiracetam. Nakken et al.[50] prospectively examined adjunctive levetiracetam treatment in 78 adults and 44 children with intractable epilepsy in an uncontrolled clinical study. Although a >50% reduction in seizure frequency occurred in 40% of adults and 20% of children, including ten patients who became seizure free, the authors observed in 14 adults (18%) and 19 children (43%) a >25% increase in seizure frequency, including the development of SE in three adults and four children. This paradoxical effect occurred more frequently in mentally retarded patients during the first 2 months of treatment on relatively high doses (>30 mg/kg), although two children developed SE after 5 and 7 months, respectively. Withdrawal of the drug led to reduction in seizures. The numbers of different epilepsy types in each group were insufficient to determine a differential effect of levetiracetam in different epilepsy syndromes.

Atefy and Tettenborn[7] also reported two adult patients who developed nonconvulsive SE while on levetiracetam. Neither patient had a history of SE or mental retardation. Both patients had complex partial seizures, and both patients were treated with levetiracetam at only 2,000 mg/day. One patient had recurrent nonconvulsive SE after the levetiracetam dose was lowered to 500 mg/day and lamotrigine was added. Neither patient had recurrent SE after discontinuation of levetiracetam.

Thus, in light of the scant and somewhat contradictory information regarding levetiracetam and SE, its role in treatment of SE has yet to be clearly defined. Further study with randomized, controlled trials is needed to determine whether levetiracetam is effective in the treatment of SE or refractory SE, as well as what the potential adverse effects may be. Given the limited number of AEDs available in intravenous formulation, the limited efficacy of those drugs in refractory cases of SE, and the lack of drug–drug interactions with levetiracetam, the development of intravenous levetiracetam may increase the use of levetiracetam on inpatient neurology wards and intensive care units and lead to further examination of its potential efficacy.

Efficacy in Nonepilepsy Indications

Many of the standard and new AEDs have demonstrated efficacy in nonepilepsy indications such as headache, pain, or a variety of psychiatric disorders.[54] Levetiracetam has not shown efficacy in other nonepilepsy indications at this time.

Adverse Effects

In randomized controlled trials, levetiracetam was generally well tolerated. The most common adverse effects reported from clinical trials include somnolence, asthenia, infection (colds), and dizziness. The most common causes of discontinuation due to adverse effects were somnolence, dizziness, and asthenia. No serious hypersensitivity or Stevens-Johnson–type reactions were noted. Postmarketing experience includes case reports of leukopenia, neutropenia, pancytopenia, and thrombocytopenia, although evidence sufficient to establish causation is lacking. Betts et al.[12] noted in a randomized, controlled trial of levetiracetam 2,000 mg/day or 4,000 mg/day versus placebo that somnolence occurred more frequently in patients receiving 4,000 mg/day than in those receiving 2,000 mg/day or placebo, suggesting somnolence is a dose-related effect. Both somnolence and asthenia were noted to increase with escalating levetiracetam doses of 1,000, 2,000, 3,000, and 4,000 mg daily in another study by Grant et al.,[27] further supporting the dose-dependent nature of these adverse effects.

In a Cochrane meta-analysis, Chaisewikul et al.[16] found that only dizziness (OR 2.36, 99% CI 1.21–4.61) and infection (OR 1.82, 99% CI 1.05–3.14) were significantly more likely to occur with levetiracetam than with placebo. Furthermore, Marson et al.[46] performed a meta-analysis of levetiracetam treatment withdrawal across four randomized, controlled trials, and they found that relative risk for treatment withdrawal was 1.21 (95% CI 0.88–1.66), indicating levetiracetam was not significantly more likely to be withdrawn than placebo.

Behavioral and mood disturbances have been connected to levetiracetam therapy. In controlled trials, 13.3% of patients receiving levetiracetam experienced behavioral symptoms, such as aggression, agitation, anger, anxiety, apathy, depression, and emotional lability, compared with 6.2% of patients receiving placebo. Such adverse effects prompted discontinuation or dose reduction of levetiracetam in 2.5%. Furthermore, 0.5% of patients on levetiracetam attempted suicide, compared with no patients in the placebo groups. However, postmarketing experience suggests that behavioral side effects may be more common than initial studies indicate.

A case-control study by White et al.[62] examined the incidence of and risk factors for severe behavioral side effects of levetiracetam. In 553 patients studied, 38 (6.9%) discontinued levetiracetam due to behavioral abnormalities, including depression, irritability, aggression, and psychosis with hallucinations. In this study population, behavioral adverse effects were the most common reason for levetiracetam discontinuation. Three patients with depression were suicidal, ten patients were found to be a danger to themselves or others, and seven patients were aggressive toward others. No mortality or permanent psychiatric deficit was associated with levetiracetam, however. Such adverse effects led to levetiracetam discontinuation on average 3 months after initiation, but as late as 10 months after initiation. Patients who had severe behavioral side effects were significantly more likely to have symptomatic generalized epilepsy, a history of psychiatric disease, and a faster rate of levetiracetam titration to maximum dose. In addition, these patients had significantly lower maximum levetiracetam doses compared with controls, suggesting that such adverse effects do not necessarily reflect dose-related toxicity, but rather an idiosyncratic reaction.

Cramer et al.[18] analyzed the frequency of behavioral adverse effects with levetiracetam in placebo-controlled trials of patients with epilepsy compared with trials of patients with cognitive disorders or anxiety disorders. In an analysis of 3,252 patients exposed to levetiracetam during placebo-controlled trials, behavioral side effects were significantly more common among epilepsy patients than among patients with cognitive or anxiety disorders treated for similar time periods. This may indicate an underlying increased susceptibility of epilepsy patients to behavioral adverse effects with levetiracetam.

Anecdotal reports of improvement of behavioral adverse effects associated with levetiracetam following vitamin B_6 (pyridoxine) supplementation led Chez et al. to perform a retrospective chart review of 21 children started on levetiracetam who were observed for behavioral side effects and started on vitamin B_6 if behavioral side effects occurred.[17] Twelve of sixteen patients started on vitamin B_6 (50–400 mg/day, 118 mg/day average dose) for behavioral adverse effects with levetiracetam were noted to improve. Two patients did not improve, and two patients' charts had insufficient information to determine effectiveness. Although the 75% response rate appears promising, results from this small, retrospective study must be interpreted with caution, and a controlled trial is indicated.

Pregnancy and Lactation

Levetiracetam is categorized by the FDA as pregnancy category C.[31] In animal studies, levetiracetam exposure during pregnancy at doses similar to or greater than human therapeutic doses produced minor fetal skeletal abnormalities, growth

retardation, behavioral alterations in offspring, and increased fetal mortality. One small case series of three women taking levetiracetam monotherapy during pregnancy reported no major or minor malformations or cognitive problems in infants followed for 1 year.[41] Another case series of 11 women on levetiracetam as monotherapy (n = 2) or in combination with other AEDs reported no fetal malformations in nine live births.[58] One spontaneous abortion occurred, in which no fetal malformations were detected. Another pregnancy was voluntarily terminated. Although no malformations were noted, two of the nine live-born infants had a birth weight below the tenth percentile, and one had a birth weight below the 23rd percentile. The data from these small series are insufficient to draw conclusions regarding the teratogenic effects of levetiracetam. However, the Keppra Pregnancy Registry, the European Registry of Antiepileptic Drugs and Pregnancy, and the Antiepileptic Drug Registry are collecting information about the effects of levetiracetam use during pregnancy.

Levetiracetam is excreted in breast milk. Kramer[36] reported a case of a breast-feeding woman taking phenytoin and valproic acid, who had levetiracetam added to her regimen. When the infant became hypotonic and had increasing difficulties feeding, levetiracetam levels in breast milk (99uM) were found to be three times higher than those in maternal serum. In contrast, a small study (n = 8) by Johannessen et al.[29] of breast-feeding women on 1,500 to 3,500 mg levetiracetam daily measured umbilical cord levetiracetam levels at birth, milk levetiracetam levels during lactation, and infant serum levetiracetam levels during breast-feeding. Similar levetiracetam concentrations were found in umbilical cord and maternal serum at birth. After delivery, similar levetiracetam concentrations were also found in maternal serum and breast milk 3 to 5 days after delivery and with sampling 2 weeks to 10 months after delivery. However, the breast-fed infants had very low serum levetiracetam levels (<10–15 uM) at 3 to 5 days after delivery and with continued breast-feeding, no adverse effects were noted in the infants. Nevertheless, this study was limited by its small sample size, and the potential risks to the infant of adverse effects due to levetiracetam must be weighed against the benefits of breast-feeding. If a mother elects to breast-feed, the infant should be observed closely for signs and symptoms of toxicity.

Role in Epilepsy Treatment

Indications

Levetiracetam is indicated as adjunctive treatment of partial-onset seizures in all countries where it is approved for use. A single, randomized, controlled noninferiority trial comparing it to carbamazepine supports its use as monotherapy in newly diagnosed partial epilepsy. Randomized controlled trials supporting its use in generalized-onset seizures or in SE have not been reported.

Dosing Recommendations

Onset of action is unknown, but peak plasma concentrations occur approximately 1 hour after an oral dose, with 100% bioavailability. Prescribing information in the United States recommends that adults receive an initial dose of 500 mg twice daily, increased by 1,000 mg/d every 2 weeks until good clinical response or a maximum of 3,000 mg/day (divided b.i.d.) is achieved.[31] Many clinicians start patients at 500 mg/day. There are no known drug interactions that affect dosing. The minimal effective dose in clinical trials is 1,000 mg/day; the maximum dose reported in randomized, placebo-controlled trials was 4,000 mg/day.[27] No published data are available regarding the value of a loading dose, but clinical trials started with 1,000 mg/day, which is the reported minimally effective dose. One study demonstrated onset of antiepileptic action on the first day of levetiracetam treatment.[21]

For pediatric patients, aged 4 to <16 years, treatment should be initiated with a daily dose of 20 mg/kg in two divided doses (10 mg/kg b.i.d.). The daily dose should be increased every 2 weeks by increments of 20 mg/kg to the recommended daily dose of 60 mg/kg (30 mg/kg b.i.d.). If a patient cannot tolerate a daily dose of 60 mg/kg, the daily dose may be reduced. In the clinical trial, the mean daily dose was 52 mg/kg. Patients with body weight >20 kg should be dosed with oral solution. Patients with body weight >20 kg can be dosed with either tablets or oral solution. Only whole tablets should be administered.[31]

Intravenous Formulation

When switching from oral levetiracetam, the initial total daily intravenous dosage of levetiracetam should be equivalent to the total daily dosage and frequency of oral levetiracetam and should be administered as a 15-minute intravenous infusion following dilution in 100 mL of a compatible diluent. At the end of the intravenous treatment period, the patient may be switched to levetiracetam oral administration at the equivalent daily dosage and frequency of the intravenous.

Precautions

For levetiracetam, the main precautions relate to somnolence, behavioral disturbances, and rare instances of hematologic dysfunction, as described earlier in the Adverse Effects sections.

Contraindications

This product should not be administered to patients who have previously exhibited hypersensitivity to levetiracetam or any of the inactive ingredients in Keppra tablets or oral solution.

Summary and Conclusions

Levetiracetam is an effective and well-tolerated AED. Mechanism of action is through a novel effect on the synaptic vesicle receptor SV2A, an effect that has already led to development of compounds in testing with similar mechanism of action. Levetiracetam has demonstrated efficacy as an adjunctive treatment for partial-onset seizures in adults and children, and as monotherapy in adults with newly diagnosed partial-onset seizures. The drug is well-tolerated, with the most common adverse effects being somnolence, dizziness, and asthenia. Less common but important adverse effects include psychiatric and behavioral abnormalities in adults and children. Levetiracetam has a favorable pharmacokinetic and drug interaction profile, with no hepatic metabolism, an absence of clinically significant drug interactions, and no appreciable protein binding. Future areas of investigation include levetiracetam's role in generalized epilepsies and SE.

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Chapter 152

Oxcarbazepine

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Introduction

Although oxcarbazepine (OXC) has been available for many years in Europe, it was only approved by the Food and Drug Administration (FDA) for use in the United States in early 2000. Since its launch its use for partial epilepsy has increased, and it is currently considered by experts as a first-line medication for all partial-onset seizures.[32]

Chemical Structure and Methods for Determination in Body Fluids

OXC (10,11-dihydro-10-oxo-5H-dibenz[b,f]azepine-5-carb-oxamide; Trileptal, Timox, Tolep) is a derivative of carbamazepine, from which it differs by a ketone group at position 10. OXC is a white to faintly orange crystalline powder. It is slightly soluble in chloroform, dichloromethane, acetone, and methanol and practically insoluble in ethanol, ether, and water. Its molecular weight is 252.3. Its main metabolite, mono-10-hydroxy derivative (MHD), is a neutral lipophilic compound with a molecular weight of 254.3. Chemically, MHD is a racemic compound composed of *R*(–) and *S*(+)-MHD.

OXC and MHD levels can be determined in biologic matrices by high-performance liquid chromatography (HPLC) and gas chromatography.[23,36] HPLC is the most common procedure, and specialized methods continue to be developed for use in routine therapeutic drug monitoring,[19] in pharmacokinetic studies requiring the analysis of metabolites,[13] and in the separation of the MHD enantiomers.[58] Currently, no immunoassays for the determination of OXC or MHD are commercially available.

Pharmacology and Mechanisms of Action

In animal models, OXC and MHD are active against tonic extension seizures induced by maximal electroshock and against focal seizures in monkeys with chronic aluminum foci; they have little or no activity against clonic seizures induced by phenothiazine, picrotoxin, and strychnine. This anticonvulsant profile is similar to that of carbamazepine.[60] The main mechanism of action of OXC and MHD is assumed to be the use-dependent inactivation of voltage-gated brain sodium channels.[38,51] Limited experimental data suggest that some of their anticonvulsant effects are mediated through action at the potassium channels and at the high-threshold, voltage-gated type N- and/or P- and/or R-type Ca^{2+} channels,[38,51,60] actions that may differentiate OXC from carbamazepine.[49]

Clinical Pharmacokinetics

The clinical pharmacokinetics of OXC have been recently reviewed.[23,36] Plasma concentrations of OXC in chronically treated patients are very low with respect to MHD, and MHD is assumed to be the clinically relevant compound. Most pharmacokinetic and disposition studies focus on the racemic MHD, and only limited data are available for the separate enantiomers.

Absorption

After oral administration OXC is rapidly absorbed from the gastrointestinal tract, with a bioavailability >90%; peak concentration (C_{max}) of OXC and MHD occurs within 1 to 3 hours and 4 to 6 hours, respectively.[23,36]

The effect of food on the pharmacokinetics of OXC, at least with the currently marketed pharmaceutical preparation, is minimal, and without therapeutic relevance.[23,36]

Plasma Protein Binding and Distribution

The reported apparent volume of distribution (V_d) of MHD ranges from 0.3 L/kg (estimated from urine data) to 0.7 to 0.8 L/kg.[36]

Approximately 40% of the total MHD is bound to plasma proteins, mainly albumin. Data are consistent for healthy volunteers and patients with different pathologies. The binding seems to be independent of serum concentration within the therapeutically relevant range. Protein binding of OXC is slightly higher, at about 60%.[36]

The erythrocytes/plasma concentration ratio in various studies ranged from 0.88 to 1.34,[31] to 0.9 to 1.75,[27] to 1.4 to 1.9,[55] suggesting some accumulation in erythrocytes.

Published data on brain and cerebrospinal fluid (CSF) concentrations of MHD and OXC are scanty. May et al.,[36] citing their own unpublished data and data on three patients reported by Christensen et al.,[17] indicated that MHD CSF concentrations are 50% to 60% of total plasma concentrations. Similarly, citing their own unpublished data in 13 patients undergoing surgery for epilepsy, May et al.[36] reported slightly lower (by about 14 ± 6%) MHD concentrations in the neocortex as compared to serum. In a recent paper, Marchi et al.[35] studied nine patients undergoing brain surgery for epilepsy and found that brain and plasma concentrations of MHD did not correlate (brain-to-plasma ratio ranging from 1% to 103%), whereas in eight patients, the MHD brain-to-plasma ratios were correlated to the level of expression of the multidrug transporter MDR1 mRNA, measured in resected epileptic hippocampal or cortical tissues. The same paper showed that MHD is also a substrate for the multidrug transporter protein P-gp. Clinckers et al.[18] indicated that OXC is a substrate for multidrug transporters at the blood–brain barrier.

OXC and MHD can be transferred significantly through the placenta in humans, with comparable concentration in the maternal and umbilical cord serum. Concentrations of OXC and MHD in breast milk are about 50% of the corresponding plasma concentrations.[23,36]

Metabolism

After administration, OXC undergoes presystemic metabolic 10-keto reduction to MHD mediated by cytosol arylketone reductases. MHD is then cleared by uridine diphosphate glucuronyl-transferase (UGT)-mediated glucuronide conjugation and, to a lesser extent, by cytochrome P450 (CYP)-mediated oxidation to 10,11-trans-di-hydroxy metabolite (dihydroxy derivative [DHD]), an inactive metabolite also derived from carbamazepine.

The reduction of OXC to MHD is stereoselective, with the formation of (S)-(+)-MHD and (R)-(–)-MHD. After oral administration of OXC to healthy volunteers, the plasma concentration-time curves (AUC) of the (S)- and (R)-enantiomers were in the ratio of about 4:1.[10,23,36] As the two enantiomers seem to have similar anticonvulsant properties,[51] this pharmacokinetic imbalance probably lacks clinical relevance.

Elimination

OXC exhibits first-order linear kinetics during long-term administration. MHD plasma concentrations vary linearly with the OXC dose within patients, although marked interindividual variability was observed.

Elimination half-lives of 1 to 5 hours for OXC and of 7 to 20 hours (mean values) for racemic MHD were reported in studies of healthy volunteers after single or repeated doses of OXC. The half-life can be shorter in pediatric patients and in patients treated with enzyme-inducing antiepileptic drugs (AEDs).[36]

After single-dose administration in healthy volunteers, some authors described a monoexponential decay of MHD, whereas others observed a biphasic MHD concentration-time curve, suggesting that the metabolism of OXC is a saturable process, and that enterohepatic recirculation of OXC might occur. The possibility that OXC reduction is a saturable process at higher dosages is also suggested by a clinical case of attempted suicide with a large dose of OXC (about 30 g), where higher ratios of OXC to MHD concentrations were found.[57]

Reported values of renal clearance (CL_R) of MHD in healthy volunteers (young adults) ranged from 12 to 14 mL/min to about 58 mL/min.[36] Methodologic differences between the various studies probably contribute to the wide variability observed. Renal clearance did not differ between the (R)- and the (S)-enantiomers.[10]

Pharmacokinetics in Special Populations

Most available data on OXC and MHD kinetics in children are published as abstracts only. Children younger than 5 to 6 years show higher renal clearance, lower dose-normalized AUC of MHD, and a shorter MHD half-life than adults and older children.[23,36] Consequently, an increased dose in mg/kg body weight may be needed in children to achieve plasma levels similar to those of adults.

In elderly subjects aged 60 to 82 years, the dose-normalized AUC of MHD was higher than in young adults (18 to 32 years) and related to creatinine clearance, suggesting that the differences in pharmacokinetics are due to impaired MHD renal clearance with age. Consistently, a modest effect of age on MHD concentrations was observed in patients.[23,36]

Bulau et al.[14] reported similar plasma concentrations of OXC and MHD in a newborn girl and in the treated mother. Concentrations of both compounds in the newborn declined rapidly over days in spite of the availability of both compounds via breast milk.

Therapeutic Drug Monitoring

No clearcut relationship between plasma concentrations and clinical effects has been demonstrated for OXC or MHD. Therapeutic drug monitoring of MHD can be useful in titrating patients whose epilepsy is difficult to control and in cases of questionable compliance and drug–drug interactions, or to confirm concentration-related drug toxicity. As for many other AEDs, however, a precise optimal interval of MHD plasma concentrations has not been defined in prospective controlled studies, but derived from clinical trial data and clinical experience. The most often reported values range from 12.5 to 15.0 µg/mL to 30 to 35 µg/mL.[30]

Efficacy

Partial-Onset Seizures

OXC is approved in the European Union and the United States for initial monotherapy, conversion to monotherapy, and adjunctive therapy in children and adults suffering from partial-onset seizures. Its efficacy was established in a number of multicenter, double-blind, randomized clinical trials in varying patient populations with localization-related epilepsy, ranging in severity from the newly diagnosed to the medically refractory patients being evaluated for epilepsy surgery.

Active-Control Comparative Monotherapy Trials in Newly Diagnosed Epilepsy

The efficacy of OXC was evaluated in four comparative, double-blind, parallel-group trials conducted in adults[11,16,20] and children[29] with newly diagnosed epilepsy. The trial design was similar across all four trials. Patients who had experienced a minimum of two seizures in the preceding 6 months were randomized to treatment with OXC versus phenytoin,[11,29] valproate,[16] or carbamazepine.[20] The trials consisted of an 8-week titration phase followed by a 48-week maintenance phase. OXC was initiated at 300 mg/day on a tid schedule (150 mg/day in the trial conducted in children and adolescents) and gradually titrated biweekly based on the clinical response during the 8-week titration phase. The primary efficacy variable was the percentage of patients who remained seizure free throughout the 48-week maintenance phase. Secondary outcome variables included the percentage of patients who exited due to adverse events and treatment retention.

There were no significant differences in the primary efficacy variable between OXC and the comparator drugs in any of the trials (Table 1). The median daily doses of OXC during the maintenance phase of the three adult trials were 1,053 mg, 1,028 mg, and 1,040 mg (mean dose). The corresponding values for phenytoin, valproate, and carbamazepine were 313 mg, 1,146 mg, and 684 mg (mean dose), respectively. For the trial conducted in children and adolescents, the median daily doses of OXC and phenytoin were 18.8 mg/kg and 5.8 mg/kg, respectively. OXC was, however, better tolerated than phenytoin or carbamazepine based on significantly lower exit rates due to adverse events (Table 1). There was no significant difference in exit rates due to adverse events between OXC and valproate.

Although those trials are frequently alleged to demonstrate equivalent efficacy of OXC to that of the standard AEDs, it is important to note that these studies were not powered as equivalence or noninferiority trials. The controversies surrounding the interpretative difficulties of equivalency trials were recently discussed.[7]

Table 1 Active-control Comparative Trials of Oxcarbazepine in Patients with Newly Diagnosed Epilepsy

	Patients (No.)	Daily dosage (mg)	Seizure free	Exit rate	Exit rate due to AE
OXC vs. PHT (5–18 yr)[29]	OXC (97) PHT (96) Total (193)	OXC (300–1,350) PHT (100–400)	OXC 61% PHT 60%	OXC 24% PHT 34%	OXC 2%[a] PHT 14%
OXC vs. VPA (15–65 yr)[16]	OXC (128) VPA (121) Total (249)	OXC (600–2,400) VPA (600–2,700)	OXC 56.6% VPA 53.8%	OXC 52% VPA 41%	OXC 15% VPA 10%
OXC vs. PHT (16–65 yr)[11]	OXC (143) PHT (144) Total (287)	OXC (600–2,100) PHT (100–650)	OXC 59.3% PHT 58.0%	OXC 56% PHT 61%	OXC 5%[a] PHT 16%
OXC vs. CBZ (14–63 yr)[20]	OXC (94) CBZ (100) Total (194)	OXC (300–1,800) CBZ (300–1,400)	OXC 52% CBZ 60%	OXC 16% CBZ 27%	OXC 14%[a] CBZ 25%

AE, adverse events; CBZ, carbamazepine; OXC, oxcarbazepine; PHT, phenytoin; VPA, valproate.

[a] $p < 0.05$.

Monotherapy Trials in Patients with Refractory Focal Epilepsy

The definitive evidence of OXC efficacy as monotherapy was established in randomized, double-blind, placebo-controlled, and dose-response multicenter clinical trials.[8,44,48] In a 10-day trial, inpatients admitted for presurgical epilepsy monitoring were randomized to treatment with OXC at 2,400 mg/day versus placebo.[48] This trial incorporated specific exit criteria to maximize patient safety. Time to exit and completer rates were significantly in favor of the OXC-treated patients. This study demonstrated that OXC administered as monotherapy possesses short-term anticonvulsant properties.

The extended efficacy of OXC as monotherapy was demonstrated in two outpatient trials, conducted in patients with medically refractory localization-related epilepsy.[8,44] In the first trial patients experiencing two to 40 seizures per month while maintained on one or two baseline AEDs were randomized to OXC at 2,400 mg/day or 300 mg/day administered on a twice-daily schedule.[8] In this trial, patients randomized to the high daily OXC dose had a significantly longer time to exit, based on individualized exit criteria related to baseline seizure frequency. In addition, 42% of patients randomized to the OXC 2,400-mg/day group experienced a 50% or better improvement in their monthly seizure frequency compared to baseline and 12% remained seizure free throughout the 126-day double-blind treatment phase. This study established the efficacy of OXC as monotherapy, and demonstrated that conversion to OXC as monotherapy can result in significant improvement in seizure frequency in a proportion of patients with medically refractory partial epilepsy.[8]

The second trial was an enrichment design clinical dose-response study,[44] which also showed significantly better efficacy with high-dose compared to low-dose OXC.

Adjunctive Therapy Trial in Refractory Patients with Focal Epilepsy

The efficacy and tolerability of adjunctive therapy with OXC was evaluated in two large, multicenter, double-blind, placebo- and dose-controlled clinical trials.[5,26] In the adult trial, 694 patients with medically refractory partial epilepsy and experiencing at least four partial-onset seizures per month while maintained on one to three AEDs were randomized to add-on treatment with placebo, OXC 600 mg/day, OXC 1,200 mg/day, or OXC 2,400 mg/day.[5] There was a statistically significant reduction in seizure frequency at all three OXC doses compared to placebo. In addition, there was a dose-response relationship with mean reductions in seizure frequency of 8%, 26%, 40%, and 50%, for patients randomized to placebo, OXC 600 mg/day, OXC 1,200 mg/day, and OXC 2,400 mg/day, respectively.[5] The premature discontinuation rates because of significant adverse events were also dose related with 12%, 36%, and 67% exiting from OXC 600 mg/day, OXC 1,200 mg/day, and OXC 2,400 mg/day, respectively, compared to 9% for placebo. Although this study clearly demonstrated the efficacy of adjunctive therapy with OXC in adult patients with medically refractory partial epilepsy, it also showed that OXC can be associated with side effects in a substantial proportion of patients treated with high doses as adjunctive therapy.

In the pediatric trial, 267 children (3 to 17 years) experiencing at least eight partial-onset seizures during a 56-day baseline period while maintained on constant doses of one to two AEDs were randomized to placebo or OXC titrated to 30 to 46 mg/kg per day.[26] Adjunctive treatment with OXC resulted in significant improvement in seizure frequency with median reductions of 9% and 35% for the placebo and OXC groups, respectively. In this trial, OXC was better tolerated than the adult trial, with a 10% premature discontinuation rate due to adverse events.

Other Seizure Types

Although OXC was not evaluated in randomized clinical trials in patients with generalized epilepsies, there are anecdotal data that it might exacerbate seizures in juvenile myoclonic epilepsy[25] and in children with benign epilepsy of childhood with centrotemporal spikes.[15]

Adverse Events

Neurologic

In the pivotal and open-label long-term trials, OXC adverse events were most commonly related to the central nervous system (CNS) and included dizziness, headache, and fatigue.[8,44,48,52] Less frequently reported neurologic events were insomnia, ataxia, diplopia, tremor, somnolence, and visual dysfunction.[9,44] These side effects were dose related and more frequent when OXC was used as part of a polytherapy regimen.[8,9]

Gastrointestinal

Gastrointestinal adverse events included nausea, vomiting, dyspepsia, and diarrhea.[8,9,44,48] These adverse events were mild to moderate in severity and typically occurred during the early phase of treatment.[8,44,52] Although OXC can cause elevation of liver function tests, it is not associated with significant hepatic toxicity.

Metabolic

Significant hyponatremia (defined as serum sodium below 125 mmol/L) was noted in 2.5% of the 1,524 patients who participated in the controlled epilepsy trials.[56] More recent data suggest that the incidence of significant hyponatremia is higher.[22] The frequency of mild hyponatremia (sodium level below 135 mmol/L) is higher and estimated at 20% to 30%[22,52] compared to 13.5% in carbamazepine-treated patients.[22] Mild hyponatremia is usually asymptomatic, and rarely results in morbidity or drug discontinuation.[24,42,43,49,52]

Hyponatremia is uncommon in children[12] and has higher incidence with increasing age and with the concomitant use of sodium-depleting drugs.[22,33,46]

The mechanism for OXC-induced hyponatremia is not due to the syndrome of inappropriate secretion of antidiuretic hormone and is possibly related to a direct effect of OXC on the renal collecting tubules or an enhancement of the effect of circulating antidiuretic hormone.[45]

Hyponatremia is managed through water restriction, reduction of the dose of OXC, and, if necessary, discontinuation of the medication.[53]

Other Side Effects

Skin rash occurred less frequently with OXC compared to carbamazepine. The frequencies of cutaneous reactions among 2,436 patients on OXC and 277 patients taking carbamazepine were 3% and 7%, respectively.[50]

More severe cutaneous reactions were also reported. Two cases of exfoliative dermatitis occurred with OXC treatment.[6] More recently, a labeling update issued by the FDA warned that serious dermatologic reactions occurred in adults and children on OXC, including Stevens-Johnson syndrome and toxic epidermal necrolysis. The reporting rate of those serious cutaneous reactions exceeded the background incidence rate estimates by a factor of three- to 10-fold. In a study that evaluated the risk of cross-sensitivity between OXC and carbamazepine, it was found that 27% of 51 patients with a rash on carbamazepine developed an allergic cutaneous reaction to OXC. In the majority of those cases, the rash on OXC appeared during the first month of treatment.[21]

Teratogenicity

A recent study of seven prenatal exposures to OXC monotherapy reported no major malformations.[40] In another cohort from Finland, one urogenital malformation was identified among 99 babies with prenatal exposure to OXC monotherapy.[4] Lastly, in 55 prenatal exposures to OXC (20 polytherapy and 35 monotherapy), only one cardiac congenital malformation in a patient receiving a combination of OXC and phenobarbital was identified.[39]

Drug Interactions

When OXC is substituted for an inducing drug in polytherapy, the clinical status of the patient and the plasma concentrations of other AEDs should be closely monitored, as partial or total enzyme deinduction may increase plasma concentrations of the other drug(s).[2]

In general, OXC treatment has a modest enzyme-inducing effect, more evident at high doses and related to the action on specific isoforms of CYP enzymes.[2] Indeed, in vitro studies showed that OXC and MHD induce only CYP3A4 and 5 isoforms. On the other hand, Lakehal et al.[34] showed in human liver microsomes that MHD is a competitive inhibitor of CYP2C19, an enzyme involved, for example, in the metabolism of phenytoin. OXC and MHD showed a modest inducing effect on UGT enzymes in vitro.[23,36]

Effects of Oxcarbazepine on Antiepileptic Drugs

In patients treated in polytherapy with OXC, carbamazepine concentrations can be reduced by about 15% on average, whereas the concentrations of phenytoin and phenobarbital may be increased to the same extent.[2,47] Particularly in patients treated with phenytoin at high doses and in the presence of high concentrations of MHD, the increase in phenytoin levels may be clinically relevant (up to +40%).[2]

A recent well-designed study in 47 healthy subjects[54] found no significant effect of OXC cotreatment on lamotrigine AUC or C_{max} at steady state. In patients cotreated with OXC, however, May et al.[37] reported a reduced lamotrigine level-to-dose ratio (–33%) with respect to lamotrigine monotherapy, and Weintraub et al.[59] reported that the clearance of lamotrigine was increased by approximately one third, an effect considered to be of possible clinical relevance. A similar trend was observed by Sallas et al.[47] in children with MHD concentrations in the range of 12 to 25 µg/mL, whereas only a nonsignificant reduction of the MHD concentration–to–OXC dose ratio (about –10%) was reported by Armijo et al.[3] in children and adults.

Effects of Oxcarbazepine on Other Drugs

In healthy volunteers, OXC did not significantly modify the action of warfarin as measured by prothrombin time (mean Quick values 36.6% at baseline, 38.1% after OXC), whereas it reduced the absolute bioavailability of the calcium antagonist felodipine from about 15% to about 10%. However, no patient data are available for either drug.[2]

OXC treatment reduces the bioavailability of the estrogen and Prostagen components of oral contraceptives, probably through induction of CYP3A-mediated metabolism. Thus, the same precautions exercised with enzyme-inducing AEDs also apply to OXC.[2]

In psychiatric patients OXC treatment did not modify the concentration of risperidone (and its active metabolite 9-hydroxy- risperidone) or olanzapine.[41]

Effects of Antiepileptic Drugs on Oxcarbazepine

Inducing AEDs like phenobarbital, phenytoin, and carbamazepine was found to decrease MHD AUC in adults and

children.[2,47] In most cases these changes of OXC and MHD are modest, but the interaction may become clinically relevant in some patients.

Theis et al.[54] reported that MHD kinetics was not significantly affected by lamotrigine treatment in healthy volunteers. However, Guenault et al.[28] reported a twofold higher ratio of MHD concentration to OXC dose in a small group of patients treated with lamotrigine cotherapy with respect to OXC monotherapy.

Gabapentin, felbamate, and benzodiazepines like clonazepam, diazepam, and possibly clobazam have no clinically relevant interactions with OXC. Similarly, valproic acid may decrease MHD plasma binding, but the interaction is probably clinically irrelevant and the association with valproic acid should not require any adjustment of OXC dosages.[2,47]

Effects of Other Drugs on Oxcarbazepine

Cimetidine and erythromycin (studied in healthy volunteers) and dextropropoxyphene (studied in patients) had no major influence on the pharmacokinetics of OXC and MHD. Verapamil (240 mg/day for 1 week) decreased the MHD AUC by 20% compared with baseline in healthy volunteers stabilized on OXC 900 mg/day, an effect that remains to be explained. A 10-day add-on treatment with viloxazine in six epileptic patients receiving chronic OXC monotherapy (1,500 ± 465 mg/day), increased MHD concentrations by 11% and decreased DHD concentrations by 31%, an effect considered by the authors not to be of clinical relevance.[2]

Clinical Use

The concordant results of a large number of well-controlled clinical trials have clearly established OXC as an efficacious and safe drug for the treatment of partial-onset seizures. Its advantages over phenytoin and carbamazepine include better tolerability and a more favorable pharmacokinetic profile. The package insert recommends a starting dose of 300 mg twice daily with weekly a increment of 300 to 600 mg until an efficacious dose is reached. Clinical experience, however, has shown that this titration schedule, derived from that used in the pivotal randomized clinical trials, is frequently associated with adverse events, predominantly somnolence, dizziness, fatigue, and gastrointestinal disturbances. This is particularly true for elderly patients and for patients with newly diagnosed epilepsy naive to antiepileptic drug treatment. It is therefore important to individualize the starting dose and the titration schedule based on seizure frequency and severity. In certain situations it is appropriate to initiate treatment at 150 mg twice daily with weekly increments of 300 mg until a target dose is reached. In certain cases, administering the total daily dose of OXC during the titration phase on a three-times-a-day schedule can improve tolerability. For the newly diagnosed patients with localization-related epilepsy, the active-control clinical trials have uniformly found that the median effective dose of OXC was around 1,000 mg/day. Breakthrough seizures in the compliant patient are managed by a 300-mg increment in the daily OXC dose.

For patients with localization-related epilepsy poorly controlled on another antiepileptic drug, conversion to OXC as monotherapy can be attempted acutely or gradually. Some have advocated a so-called "overnight switch" in which the baseline antiepileptic drug is stopped acutely and treatment with OXC at its full target dose is initiated.[1,21] This has been particularly advocated for patients converted from carbamazepine monotherapy, for whom the target dose of OXC has been recommended to be 1.2 to 1.5 times the daily dose of carbamazepine. Other reports have advocated a more gradual crossover with a gradual increment of OXC and a gradual taper of the baseline AED over 3 to 4 weeks.[21]

When used as part of a polytherapy regimen, the addition of OXC can result in a substantial improvement in seizure frequency, but can be associated with significant adverse events, especially at daily doses above 900 to 1,200 mg. When higher daily doses of OXC are deemed to be necessary, it usually requires a concomitant reduction in the dose of the baseline AED.

In addition to the CNS and gastrointestinal adverse events, OXC can be associated with lowering of the serum sodium level. Although this is usually of inconsequential clinical relevance, the hyponatremia can, on occasion, be severe enough and lead to obtundation, gastrointestinal disturbances, and worsening of seizure frequency. Although this can occur in any patient, those at particular risk include the elderly and those being treated with natriuretic drugs. It is therefore advisable to check the serum sodium level prior to initiating OXC and to have a follow-up sodium level determination during the first 2 to 3 months of therapy.[53]

Summary and Conclusions

OXC is believed to exert its anticonvulsant effect through use-dependent inactivation of voltage-gated brain sodium channels. Overall, it has a favorable pharmacokinetic profile and minimal drug-drug interactions when used with other hepatically metabolized drugs.

OXC is an effective first line AED for localization related epilepsy, and appears to be better tolerated than phenytoin and carbamazepine. It can be associated with dose-related CNS and gastrointestinal adverse events, and can lead to lowering of the serum sodium level especially in the elderly and with the concomitant use of natriuretic drugs.

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Chapter 153

Phenobarbital and Other Barbiturates

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Introduction

The antiepileptic effect of phenobarbital (phenobarbitone) was described by Alfred Hauptmann as long ago as 1912,[29] a little more than half a century after Locock, in 1857, had recognized what proved to be the first effective antiepileptic agent, potassium bromide. Phenobarbital has been in continuous use as an antiepileptic agent for nearly a century. In recent years, its popularity in developed countries has declined, although it and its congener primidone still account for some 14% of all antiepileptic drug (AED) use in Britain.[52] It is more widely used in less affluent societies and, on a global scale, remains one of the most important AEDs. Phenobarbital possesses a broad spectrum of antiepileptic activity and an effectiveness similar to that of many other marketed AEDs. It is safe, cheap, and available in convenient oral and parenteral dosage forms. These advantages have led some investigators to call for renewed scientific study to enhance its proper use in the modern therapeutic era.[42]

Attempts have been made to modify the phenobarbital molecule to derive agents with greater efficacy and lesser toxicity. Primidone (desoxyphenobarbital) has gained a place as an established antiepileptic agent in its own right (see Chapter 158). However, at least part of its pharmacologic action is effected via phenobarbital, to which it is metabolized in the body. The *N*-methyl analog of phenobarbital, mephobarbital (*N*-methylphenobarbitone), was introduced into therapeutics by Blum in 1932.[8] In some places, it was preferred to phenobarbital although its use appears to be declining. Phenobarbital and mephobarbital analogs that lack an aromatic ring on the 5-carbon atom of the barbiturate ring (barbital and metharbital) also possess antiepileptic properties. However, few data concerning them are available, and they now appear to be little used. Eterobarb (1,3-dimethoxymethylphenobarbital) underwent some modern scientific studies, but thereafter it did not seem to achieve any widespread clinical use. Only phenobarbital, and to an extent mephobarbital, will be discussed further.

Chemistry, Formulations, Assay

Chemistry

Phenobarbital (5-ethyl-5-phenylbarbituric acid) is a white crystalline material with a pKa of 7.2. Mephobarbital (5-ethyl-1-methyl-5-phenylbarbituric acid) is chiral at the carbon atom at the 5-position of the barbiturate ring by virtue of the methyl group substituent on the 1-position of the barbituric acid molecule. It is supplied commercially as a racemate. The racemic material is more lipophilic than phenobarbital and has a pKa value of 7.8.

Figure 1 shows the formulas and metabolic pathways for phenobarbital (5-ethyl-5-phenylbarbituric acid), *r*-(-)-mephobarbital, and *s*-(+)-mephobarbital.

Formulations

Phenobarbital has been marketed either as the acid or the sodium salt in 15-, 30-, 50-, 60-, and 100-mg tablets. However, not all strengths may be available in all countries. Oral solutions of various strengths containing sodium phenobarbital can be prepared. Parenteral solutions of the drug usually contain 100 or 200 mg of the sodium salt.

Mephobarbital has been marketed as 30-, 32-, 50-, 60-, 100-, and 200-mg tablets.

Assay

Phenobarbital in biologic fluids has been measured by ultraviolet spectrophotometry, gas and liquid chromatography, and various immunoassay methods. Mephobarbital is usually measured by gas or liquid chromatography, although methyl derivative formation for gas chromatography results in any phenobarbital that is present after biotransformation being measured as mephobarbital.

Pharmacology

Mephobarbital is biotransformed to phenobarbital, and it is believed that most of the anticonvulsant action of mephobarbital depends on this metabolic product. However, there is some indirect evidence that intact *R,S*-mephobarbital probably has an antiepileptic effect[14] whose mechanism is not established. Only the mechanism of action of phenobarbital is considered further in this chapter.

Seizure Models

Inconsistent reports are available of phenobarbital's effects on epileptic activity in experimental seizure foci in animals.[23] The drug appears to limit the spread of activity from such foci, probably by interfering with synaptic neurotransmission.[25] Consistent with its clinical effect against generalized tonic–clonic seizures, phenobarbital is effective in the maximal electroshock model. It is also active against pentylenetetrazol-induced seizures, although it has no effect against human absence seizures.[81]

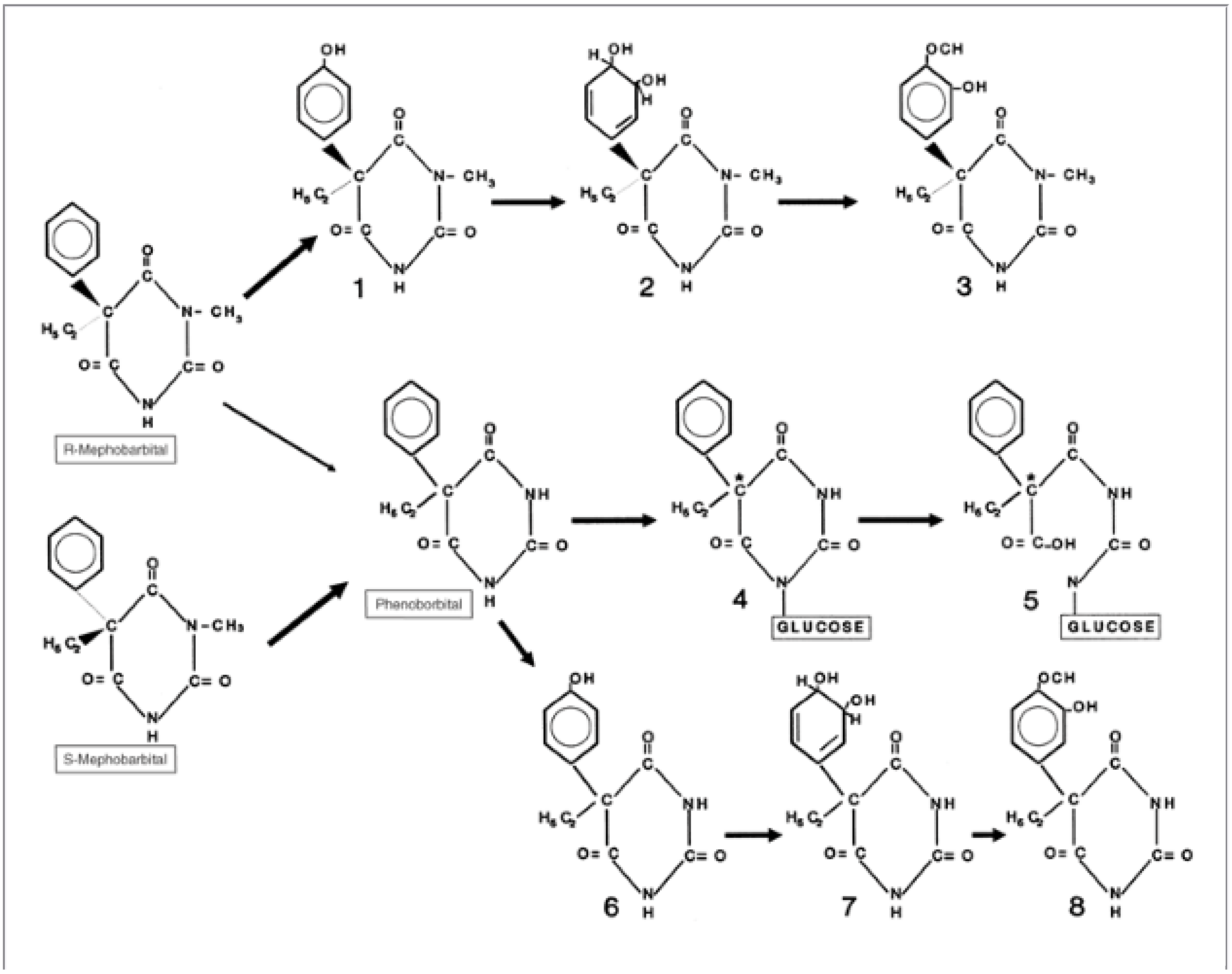

FIGURE 1. Chemical formulas and known metabolic pathways for mephobarbital and phenobarbital. *1*, *p*-Hydroxy derivative of *R*-mephobarbital. *2*, Diol derivative of *R*-mephobarbital. *3*, *O*-Methyl catechol derivative of *R*-mephobarbital. *4*, Phenobarbitone-*N*-glucoside (the asymmetric carbon atom is marked with an *asterisk*, but the structures of the separate enantiomers are not drawn). *5*, Barbiturate ring-opened derivatives of phenobarbitone-*N*-glucoside. *6*, *p*-Hydroxy derivative of phenobarbital. *7*, Diol derivative of phenobarbital. *8*, *O*-Methyl catechol derivative of phenobarbital. Many of the metabolites containing a hydroxyl group are excreted in part as glucuronides.

Mechanism of Action

Although a number phenobarbital's biochemical actions have been described, such as inhibition of mitochondrial electron transport, some are significant only at drug concentrations

appreciably higher than those at which an antiepileptic effect occurs in clinical use. It is thought that phenobarbital acts as an anticonvulsant mainly by prolonging the opening of the postsynaptic cell membrane chloride (Cl^-) channel, a component of the γ-aminobutyric acid (GABA)-A receptor.[5] The resultant increase in Cl^- flux tends to hyperpolarize the postsynaptic neuronal cell membrane, thus impeding the transmission of epileptic activity. At concentrations higher than the usual human therapeutic ones, it may also affect voltage-dependent sodium (Na^+) channels to diminish rapid neuronal firing.[47]

Clinical Pharmacology

Absorption

Phenobarbital is virtually fully bioavailable after oral administration[54] and appears to be absorbed fairly rapidly. Eadie et al.[21] calculated the mean absorption half-time as 1.37 hours. It has sometimes been stated that the drug is slowly absorbed, but this assertion appears to be based on the finding that the peak plasma concentration did not occur until some 6 to 18 hours after intake.[46] However, the time of maximal concentration (T_{max}) of a drug occurs when its elimination rate equals its absorption rate. The slow elimination of phenobarbital could have accounted for its late T_{max}. More recent studies suggest a T_{max} of 0.5 to 4 hours after oral administration, compared with 2 to 8 hours after intramuscular injection.[54,80] Generally little difference is noted in T_{max} or bioavailability between the oral and intramuscular routes of administration.[78]

The oral dose of mephobarbital on a molar basis must be approximately twice that of phenobarbital to achieve the same steady-state plasma concentration of the latter. Because of this, it has sometimes been assumed that mephobarbital has only a 50% oral bioavailability. However, Hooper et al.[33] showed in two subjects that oral *R,S*-mephobarbital was 75% bioavailable, and in further work showed that the oral clearance of *R*-mephobarbital (approximately 0.5 L/kg per hour) was high enough to suggest that this enantiomer of the drug probably underwent significant presystemic elimination,[34] at least in extensive metabolizers of the enantiomer. Therefore, the reduced oral bioavailability of *R,S*-mephobarbital is probably due to appreciable presystemic metabolism rather than incomplete

absorption. The absorption half-time for *R,S*-mephobarbital was 0.48 and 0.38 hours in two subjects,[33] and the mean T_{max} for *R*-mephobarbital was 2.29 ± SD 1.03 hours and that for *S*-mephobarbital was 3.50 ± SD 1.52 hours.[21] However, the absorption parameters of *R,S*-mephobarbital and its individual enantiomers are less relevant clinically than the time (around 4 or 5 days) when peak plasma concentrations of derived phenobarbital occur after a dose of mephobarbital.

Distribution

The value of the apparent volume of distribution of phenobarbital in humans (approximately 0.5 to 0.7 L/kg) suggests that the drug is distributed throughout body water, with little selective regional or tissue concentration. Some 50% to 60% of the phenobarbital in plasma is protein-bound. Concentrations of phenobarbital in the cerebrospinal fluid correlate with its unbound serum levels.[46] In vivo studies in rats have shown that phenobarbital is a substrate of the efflux drug transporter P-glycoprotein, which is expressed at cerebral capillary endothelium. The clinical relevance of this remains to be determined, but growing evidence suggests that, by extruding AEDs from their intended site of action in the brain, overexpression of P-glycoprotein could potentially play an important role in the pathogenesis of pharmacoresistance in epilepsy.[43]

Compared with phenobarbital, *R,S*-mephobarbital has a higher apparent volume of distribution (mean, 132 L in adults).[20] This value correlates with the greater lipophilicity of the drug, suggesting that it may achieve higher simultaneous concentrations in tissues than in plasma. Craig and Shideman[14] found brain concentrations of *R,S*-mephobarbital were about eight times its simultaneous blood concentrations in rats. The mean apparent volume of distribution of *R*- and *S*-mephobarbital was 5.32 ± SD 3.33 L/kg and 1.73 ± SD 0.31 L/kg, respectively,[44] but the value for the former may have been overestimated. Approximately 67% of *R*-mephobarbital and 59% of *S*-mephobarbital in plasma are protein bound.[44]

Metabolism

Figure 1 depicts a metabolic schema for both barbiturate derivatives.

Phenobarbital

At steady state, a mean of 25% to 27% of a phenobarbital dose is excreted unmetabolized in urine.[7,82] Because the pKa of phenobarbital (7.2) is slightly above the usual pH of urine, any increase in the alkalinity of urine is likely to increase the ionized fraction of the drug in urine and the amount of intact phenobarbital excreted.

The majority of a phenobarbital dose is eliminated by hepatic metabolism via hydroxylation and glucosidation, with wide interindividual variability in the contributions from these routes. Hydroxylation is attributed to the cytochrome P450 (CYP) enzyme system, yielding a phenolic derivative (*p*-hydroxyphenobarbital), most of which is then conjugated, mainly with glucuronic acid, before being excreted in urine. This phenolic metabolite is thought not to be biologically active. It accounted for 16 ± SD 10% of the drug dose in the steady-state metabolic balance study of Bernus et al.[7] There is uncertainty over the precise CYP isoenzymes involved, but they would appear to include CYP2C9, with minor contributions from CYP2C19 and CYP2E1.[1] Reports on the influence of genetic polymorphism of CYP2C19 on the clearance of phenobarbital are conflicting.[28,49] Whether variation of the CYP2C9 gene affects the overall metabolism of phenobarbital has not been reported.

The urinary excretion of unmetabolized phenobarbital and its phenolic metabolite (conjugated and nonconjugated) accounts for approximately 40% of a drug dose.[7,82] In addition, phenobarbital undergoes *N*-glucosidation,[56,71] yielding *R*- and *S*-enantiomers of the glucoside. Bernus et al.[7] found that, under steady-state conditions, 14 ± SD 11% and up to 4% of a phenobarbital dose were excreted as the *S*- and *R*-enantiomers of the glucoside, respectively. Paibir et al.,[56] working with human liver microsomes, found a *S:R* glucoside ratio of 6.75 ± SD 1.34:1.0. Even when *N*-glucoside formation is taken into consideration, a considerable discrepancy still exists between a phenobarbital intake and the measured output of the drug's identified urinary excretion products. However, the *N*-glucosides of phenobarbital are pH-labile and begin to decompose once the environmental pH exceeds 5, forming barbiturate ring-opened derivatives.[77] The subsequent fate of these ring-opened compounds is unknown. In vitro, at 37°C and a pH of 7.4, *S*-phenobarbital-*N*-glucoside has a half-life of about 15 hours.[7] It is therefore possible that the phenobarbital-*N*-glucosides may undergo significant breakdown to as yet untraced derivatives while still present in the blood and tissues of the body, and also in urine while in the bladder. Hence *N*-glucosidation may possibly be the main elimination pathway for phenobarbital in humans.

Mephobarbital

Less than 3% of a mephobarbital dose is excreted in urine unmetabolized.[20] The biotransformation of the *R*- and *S*-enantiomers of the drug is relatively stereoselective. The *R*-enantiomer is metabolized by CYP2C19 to yield phenolic derivatives;[40] which are then transformed to glucuronides. The key role of CYP2C19 is evidenced by the much slower elimination of mephobarbital by subjects with the slow metabolizing alleles of the enzyme.[39] Excretion of 4-hydroxyphenobarbital (*p*-hydroxyphenobarbital) glucuronide, predominantly as the *R*-enantiomer, accounts for some 35% of an oral dose of the racemic drug.[33] It is likely that some of this 4-hydroxyphenobarbital is further metabolized to dihydrodiol and *O*-methyl catechol derivatives. A small amount of *R*-mephobarbital is oxidatively dealkylated to produce phenobarbital. [R]-mephobarbital may accumulate in plasma in poor metabolizers of the drug,[34] although the extent of the biologic activity of this enantiomer is not known. In contrast, *S*-mephobarbital does not undergo aromatic hydroxylation, but is oxidatively dealkylated to yield phenobarbital, some of which is then further metabolized, as described earlier. Some 8% to 25% of a dose of *R,S*-mephobarbital appears in urine as phenobarbital,[20] and phenobarbital formed from mephobarbital seems to account for most, if not all, of the drug's biologic activity under steady-state conditions. It is not known whether *N*-glucosides are formed from either mephobarbital enantiomer.

Elimination

Phenobarbital is a low-clearance drug. Its total plasma clearance is about 0.004 L/kg per hour in adults, and declines in old age (0.0032 L/kg per hour in those over 65 years, as compared with 0.0041 L/kg per hour in adults aged 20–50 years [51]), but is up to 0.012 L/kg per hour in young children. Consequently phenobarbital has a relatively long half-life (3 to 5 days in adults and 1.5 days in children) that decreases with repeated administration of the drug,[78] consistent with autoinduction of metabolism. Lim and Hooper,[44] in six volunteers, all probably extensive metabolizers, showed that the clearance of *S*-mephobarbital was relatively low (0.017 ± SD 0.001 L/kg per hour) with an average half-life of 69.8 ± SD 14.8 hours. The oral clearance of *R*-mephobarbital was much higher (about

0.47 ± SD 0.18 L/kg per hour) and its half-life comparatively short (mean value, 7.5 ± SD 1.7 hours). Some evidence suggests that the clearance of *R,S*-mephobarbital is higher in the presence of enzyme-inducing agents.[20] Details of the effects of age and sex on the disposition of the individual enantiomers of mephobarbital have been published.[34]

Because of its long elimination half-life, steady-state conditions may not be achieved until 2 to 3 weeks after a change in the dosage of phenobarbital. Although steady-state conditions would be reached earlier than this for *S*-mephobarbital when *R,S*-mephobarbital is used, the more clinically important consideration in mephobarbital use is the time when steady-state conditions also apply for the phenobarbital formed from the parent drug.

Concentration–Effect Relationships

Plasma phenobarbital concentrations may be used as a guide to dosing. Because of the long half-life of phenobarbital, under steady-state conditions, its plasma concentrations show very little fluctuation during interdose intervals of as long as 24 hours. Hence, steady-state predose measurement of the drug's plasma concentration rarely offers advantages over measurements carried out at random stages during the dosage interval.

It has been proposed that plasma phenobarbital concentrations of 15 mg/L or higher would seem necessary to control seizures of a type likely to respond to the drug.[22] However, target plasma phenobarbital concentrations recommended in the literature and employed in randomized clinical trials have ranged from 10 to 45 mg/L.[9,19,30,50] There is also wide variation in the dosage required for seizure control as well as in that tolerated between individual patients due to various factors. For instance, evidence suggests that higher plasma concentrations might be needed to control partial than generalized tonic–clonic seizures.[66] In general, plasma phenobarbital levels above 35 to 40 mg/L are increasingly likely to be associated with sedation.

No information is available concerning plasma levels of the individual enantiomers of mephobarbital. Steady-state plasma levels of racemic mephobarbital (probably mainly levels of the *S*-enantiomer) average 10% to 14% of the simultaneous plasma phenobarbital levels; in practice, the latter provide an adequate guide to treatment with mephobarbital.

Efficacy

In the past, phenobarbital was widely employed as a sedative and tranquilizer. In many countries, it is used almost exclusively for the treatment of epilepsy. It is effective against partial seizures (whether or not they become secondarily generalized), tonic–clonic seizures associated with generalized epilepsies, and in some varieties of myoclonic seizures. It is not effective against absence seizures.

Meta-analysis of randomized controlled trials showed that phenobarbital had similar efficacy to phenytoin and carbamazepine for the treatment of partial and generalized tonic–clonic seizures, but was more likely to be withdrawn because of a greater incidence of adverse effects.[72,74] Controlled and uncontrolled studies conducted in developing countries where the drug is widely used suggest that phenobarbital is effective and well tolerated.[42]

Adverse Effects

Because phenobarbital begins to appear within a few hours following the administration of mephobarbital, it is not known whether either of the enantiomers of the latter has adverse effects in its own right. Therefore, the effects of both drugs will be considered together.

Dose-Related Effects

Phenobarbital can produce a range of dose-related neurotoxic effects, including sedation, behavioral problems, impaired cognition, and depressed mood and affect. Some tolerance to sedation may develop, particularly if the drug is introduced gradually and in progressive stages. It is not known whether humans develop true pharmacologic tolerance to the drug. Most of the data on the neurotoxicity of phenobarbital is derived from pediatric populations. Before the presence of sedation becomes apparent, it may have already slowed the patient's cognitive processes and possibly caused difficulty in thinking and learning. This may result in educational difficulties when the drug is used on a long-term basis in children.[70] Secondary behavioral disturbances may follow these difficulties, in part determined by the subject's underlying personality traits. Some patients taking the drug may become irritable, short-tempered, and aggressive, whereas others become morose and depressed, particularly if the dose has been titrated up too rapidly. At higher doses, sedation and mental slowing become more obvious; at high enough doses, depression of consciousness occurs. Paradoxically, young children sometimes react to increasing phenobarbital dosage by becoming hyperexcitable,[63] although this does not seem to occur if the same patients are again treated with the drug when they have become adults.

Although phenobarbital has produced marked cognitive and behavioral toxicity in studies performed in developed countries, it has been reported to be relatively well tolerated when used in the developing world.[57] Possible explanation for this discrepancy in tolerability might include the use of lower dosage in the latter, bias in open-label studies, medicosocial factors, and genetic influence.[42]

Long-continued phenobarbital intake may be associated with dose-related acceleration in vitamin D catabolism via induction of CYP enzyme activity, leading to decreased calcium absorption, secondary hyperparathyroidism, and osteomalacia, resulting in a higher tendency to bone fractures.[76] Regular measurement of bone density, and calcium and vitamin D supplements, should be offered to those patients at high risk, such as elderly, nonambulatory patients. Phenobarbital may also cause folate depletion, which may ultimately result in macrocytic anemia if left untreated.[17] Other recorded but uncommon, possibly dose-related, adverse effects of protracted phenobarbital intake include thickening of the heel pad,[65] Dupuytren contracture,[16] and a peculiar thickening of the facial features and the occurrence of a "shoulder–hand" syndrome.[18]

Idiosyncratic Reactions

Phenobarbital use has been associated with a number of rare, presumably idiosyncratic, unwanted effects. These include skin rashes that range in severity from a fine punctate erythema through large erythematous macules to exfoliative dermatitis,[48] agranulocytosis, aplastic anemia, hepatitis, and jaundice. There is a 40%

to 60% risk of cross-sensitivity to rash with other aromatic AEDs (carbamazepine and phenytoin).[3]

Second-Generation Effects

Reports of an association between phenobarbital intake during pregnancy and fetal malformations first emerged over 30 years ago,[69] but the increased risk did not reach statistical significance in a number of these older studies. Because it is difficult to obtain control data on the malformation rates in adequately

sized populations of pregnant women with equally severe but untreated epilepsy, it is hard to determine whether and to what degree any increased malformation rate in phenobarbital-exposed pregnancies is a consequence of the AED therapy or of the epilepsy for which it was prescribed. In a retrospective study, Shapiro et al.[67] found no increase in the fetal malformation rate in nonepileptic Finnish women who took phenobarbital as a sedative during pregnancy. There are reports that the risk is enhanced if phenobarbital is used during pregnancy in combination with phenytoin[45] or with ethosuximide.[64] An early prospective study suggested that the incidence (4 out of 79; 5.1%) of malformations in offsprings exposed to phenobarbital monotherapy in utero is similar to those exposed to other established AEDs.[38] Preliminary results from the U.S. Antiepileptic Drug Registry, which included similar numbers of prospective pregnancies with in utero exposure to phenobarbital, suggested a fetal malformation rate of 6.5% (5 out of 77) compared with a presumed background rate of 1.62%.[31] In this preliminary analysis, the malformation rate associated with phenobarbital exposure was not statistically significantly greater than that associated with other AEDs (23 out of 796; 2.9%), but the identity of these drugs was not given in the report and the sample size for analysis was relatively small. Analyses with larger number of pregnancies from this and other ongoing prospective pregnancy registries are awaited before definite conclusion regarding the teratogenicity of phenobarbital can be drawn.

Phenobarbital intake during pregnancy can be associated with coagulation defects in the newborn due to vitamin K deficiency as a result of CYP enzyme induction.[53] As with other enzyme-inducing AEDs, prenatal vitamin K_1 supplementation of 10 mg per day from the 36th week of gestation until delivery is recommended.[2] If prenatal vitamin K has not been administered, the vitamin may be given intravenously to the neonate at birth. Infants born to mothers who were treated with phenobarbital during pregnancy may be hypotonic and irritable during their first 3 postnatal days, possibly due to drug withdrawal.[24] Short-term (median 3.4 days) exposure to phenobarbital immediately before birth did not seem to affect the intelligence, achievement, and behavior of children when assessed at the age of 7 years,[73] but a retrospective study suggested that longer exposure could lead to lower verbal intelligence in adulthood.[62]

Drug Interactions

Pharmacodynamic interactions can occur between phenobarbital and other drugs with sedative properties and between phenobarbital and other AEDs. Whether combinations of phenobarbital with other AEDs could result in synergistic (supra-additive) effects in seizure control has not been well studied.[11] Phenobarbital has a strong propensity for pharmacokinetic interactions with other drugs. There is no published material concerning interactions with mephobarbital.

Effects of Phenobarbital on Other Drugs

Phenobarbital is a potent and nonspecific inducer of various microsomal enzymes including those of the CYP system,[13] such as isoforms CYP 1A2, 2B6, 2C9, 2C19, and 3A4,5,7, resulting in enhanced clearance of a large number of endogenous substances and drugs that undergo hepatic biotransformation. These endogenous substances include bile salts, cholesterol, lipids, bilirubin, cortisol, folate, renin, unconjugated estriol, testosterone, and vitamins D and E. Table 1 lists some of the drugs whose clearances are increased (and plasma concentrations reduced) by phenobarbital. As the knowledge regarding the CYP isoforms responsible for the metabolism of various drugs accumulates, the number of alleged interactions with phenobarbital continues to expand. Many of the more important interactions have been recently reviewed,[59] and regularly updated information is available in Internet databases (e.g., http://medicine.iupui.edu/flockhart/table.htm). It has been suggested that impaired absorption from the alimentary tract may be relevant in the cases of the interactions between phenobarbital and cyclosporin, cimetidine, or griseofulvin.[58]

Phenobarbital also induces certain uridine glucuronyl transferase isoforms (e.g., UGT 1A9[68]), and by this means may increase the clearance, and decrease the plasma concentrations, of lamotrigine. Phenobarbital induces formation of epoxide hydrolase, responsible for further metabolism of the biologically active 10,11-epoxide metabolite of carbamazepine. It also induces the formation of γ-glutamyl transpeptidase[75] and produces increased plasma concentrations of sex hormone–binding globulin.[35]

Effects of Other Drugs and Therapies on Phenobarbital

Phenytoin and carbamazepine intakes may raise plasma levels of phenobarbital,[27] although this interaction may not be consistent.[22,59] The intake of methsuximide and phenylacetyl-urea may also raise plasma phenobarbital concentrations. Valproate causes considerable increases in plasma phenobarbital concentrations,[10] because of impairment of the body's capacity to form phenobarbital-*N*-glucoside.[6] A range of other drugs can alter the plasma concentration of phenobarbital (Table 2).

Making the urine alkaline (e.g., by administration of ammonium chloride) increases the excretion of phenobarbital and thus lowers its plasma concentrations.[61] Intake of activated charcoal impairs the absorption of phenobarbital from the alimentary tract.[55] The administration of multiple doses of activated charcoal has been found to be more effective than urinary alkalinization in enhancing phenobarbital elimination.[26] In cases of severe overdose, elimination of phenobarbital can be expedited by charcoal hemoperfusion or conventional hemodialysis.[36]

Table 1 Selected Pharmacokinetic Interactions Between Phenobarbital and Other Drugs

Phenobarbital reduces plasma level of drugs			Drugs that increase plasma level of phenobarbital
Antiepileptic drugs	**Non-antiepileptic drugs**		**Antiepileptic drugs**
Carbamazepine* Ethosuximide Felbamate Lamotrigine Methsuximide Oxcarbazepine** Phenytoin† Remacemide Tiagabine Topiramate Valproate Zonisamide	Acetaminophen (paracetamol) Amlodipine Atorvastatin Bishydroxycoumarin Buspirone Chloramphenicol Chlorpromazine Cimetidine Cisapride Clobazam Cyclosporin Cyclophosphamide Diazepam Dicophane Dicoumarol Diltiazem Dipyrone Doxycycline	Griseofulvin Haloperidol Lignocaine Meperidine (pethidine) Mesoridazine Methadone Nimodipine Nortriptyline Ondansetron Oral contraceptives Phenylbutazole Salbutamol Simvastatin Tacrolimus Tamoxifen Theophylline Thioridazine	Carbamazepine Phenytoin Valproate **NON-ANTIEPILEPTIC DRUGS** Acetazolamide Frusemide Methylphenidate Propoxyphene **DRUGS LOWER PLASMA LEVEL OF PHENOBARBITAL** Chloramphenicol Dicumarol Folate Phenylbutazole Pyridoxine

Ethinylestradiol	Vincristine
Felodipine	Warfarin
	Zolpidem
	(folate)

*And its 10,11-epoxide metabolite

**And its biologically active 10-hydroxy metabolite

†Plasma levels sometimes raised

Table 2 Average Daily Doses of Phenobarbital and Mephobarbital

Reference	Age group, yrs	Phenobarbital mg/kg	Mephobarbital mg/kg
Eadie et al., 1977[22]	<4	3.1	5
	4–14	2.3	5
	15–40	1.75	4
	>40	0.9	1.8
Messina et al., 2005[51]*	20–50	1.51	—
	65–90	1.19	—

The doses expected to achieve steady-state plasma concentrations of phenobarbital of 15 mg/L in persons of different ages reported in 2 different studies. Note wide inter-individual variation (see text).

*No statistically significant age-related decline in dosage within individual age groups was observed in this study.

Role in Epilepsy Treatment

Indications

In most clinical situations, phenobarbital and mephobarbital can be considered interchangeable, provided allowance is made for the need to use between 1.7 and 2.0 mg of mephobarbital for each 1 mg of phenobarbital to compensate for the consequences of the rapid elimination of *R*-mephobarbital, except in slow metabolizers. However, there has been an argument for preferring mephobarbital to phenobarbital. Within the range of plasma concentrations of phenobarbital usually encountered therapeutically, steady-state plasma concentrations of phenobarbital in the individual subject increase in direct proportion to the dose of *R,S*-mephobarbital. In contrast, when phenobarbital itself is prescribed, its steady-state plasma levels tend to increase more with each increment in dose than would be expected from the plasma level-to-dose ratio when the increase is made.[22] Thus, steady-state plasma concentrations of phenobarbital in the individual patient behave in a more predictable way when a mephobarbital dose is increased than when a phenobarbital dose is increased. Hence, less chance exists of producing unexpected overdosage effects if mephobarbital is used. This may have contributed to the word-of-mouth reputation that mephobarbital acquired of being less likely than phenobarbital to produce sedation in patients.

Phenobarbital is employed to treat the following:

- Neonatal seizures, for which phenobarbital and phenytoin are the agents usually recommended. This is partly because both are marketed in preparations suitable for parenteral use, the administration route often required in neonates.
- As a second- or third-line option for generalized tonic–clonic seizures and myoclonic seizures when valproate and possibly other AEDs have failed or are contraindicated. Phenobarbital and mephobarbital possess reasonable efficacy against these seizure types but with, in most subjects, less desirable toxicity profiles, particularly in relation to the effect of sedation. However, Jha et al.[37] considered that phenobarbital was ineffective in juvenile myoclonic epilepsy.
- Partial seizures with or without secondary generalization in adults, although phenobarbital is often regarded as second- or third-line treatment in developed countries due to its neurotoxicity.
- As second-line therapy for convulsive status epilepticus when intravenous benzodiazepines (e.g., lorazepam, diazepam) have failed. In this situation, phenobarbital can be considered an alternative to phenytoin (or its prodrug fosphenytoin), because it is more convenient to administer parenterally than phenytoin itself and, in higher doses, it can be effective when other therapies fail.[15] The drug may produce temporary sedation when given in a sufficient parenteral dose, but this usually is not an unacceptable price to pay to achieve control of a life-threatening situation such as status epilepticus. Respiratory depression is another concern, but it is not common.

- Febrile convulsions, although it is nowadays generally believed that prophylactic therapy is rarely indicated.[4]

Because of its relatively long elimination half-life, phenobarbital may also be preferred to other agents for patients who are prone to short periods of noncompliance (e.g., binge drinkers).

Dosing Recommendations

Initiating Dosage

Because of the long half-life of phenobarbital, phenobarbital and mephobarbital may be taken once daily, conveniently at bedtime. Systematic data is lacking as to whether a target dose or a target serum concentration should be aimed for when initiating the drugs. The approach undertaken is, therefore, often dictated by the personal preference and practice of the individual treating physician, as well as the availability of therapeutic drug monitoring service. With either approach, titration should not be dogmatic but should be tailored to individual response in terms of efficacy and tolerability.

Dosages correlating with different plasma concentrations of phenobarbital and mephobarbital have been derived from routine therapeutic drug-monitoring databases. Although linear population regression lines for steady-state plasma drug levels and dosage could be drawn, there was wide scattering of individual data points, suggesting wide interindividual variation in the dose required to achieve a specific plasma concentration.[22] Table 2 sets out the average doses of phenobarbital and mephobarbital needed to achieve an initial target plasma phenobarbital concentration of 15 mg/L for different age groups based on population data from two such studies.[22,23,51] The nonuniformity in study populations and data presentation has made it difficult to compare results and has probably led to discrepancies in findings. These data should best serve as reference values that highlight the interindividual variability in dose-serum concentration relationship, and strengthen the argument for an individualized approach in dose titration. In particular, although it is generally agreed that the dose of phenobarbital required to achieve a specific plasma concentration declines with old age (65 years or above),[51] the degree to which this reduction occurs has not been consistently demonstrated, and whether any age-dependent effect on dosing can be observed in younger adults is unclear.

The optimal way to titrate the drugs to therapeutic dosages has not been properly studied. Phenobarbital can be tolerated even when taken in full therapeutic dosage at initiation,[60] although some clinicians prefer to introduce these drugs gradually due to fear of causing sedation and behavioral disturbance. Increasing the drug dosage slowly in stages may minimize or avoid these problems, but the onset of seizure control can then be a little more delayed. This should be explained to patients before treatment begins. Using this step-wise approach, titration to the target plasma concentration may take 6 to 12 weeks. A quarter to a third of the daily dose expected to achieve an initial target plasma concentration of, say 15 mg/L, might be prescribed for the first 2 or 3 weeks. After that, the dose might be doubled if no untoward effects occur. A further increment in dose would be made 2 or 3 weeks after that, and perhaps a final increment another 2 or 3 weeks later. With such a titration schedule, drug doses will be increased only when there has been time for near steady-state conditions to apply at the previous dose. The actual schedule adopted should be individualized based on the clinical response. Dosage should not be increased if mild but tolerable adverse effects appear and too little time has passed since the last dose increment for the state of seizure control to be known. However, if seizures continue and even mild adverse effects have appeared, there may be little sense in persisting with the drug unless no potentially satisfactory alternative is available.

Large-scale observational studies performed in developing countries have consistently demonstrated that phenobarbital can be successfully initiated and maintained based on clinical response without the aid of therapeutic drug monitoring.[42] For example, in a recent study conducted in China with 2,455 patients commenced on phenobarbital, only 1% withdrew from treatment due to adverse events.[79] A reasonable initiating phenobarbital dose for adults could be 60 mg per day and for children 1.5 to 3 mg/kg per day. Some patients may respond to this initiating dose level. This is particularly the case for newly diagnosed patients, many of whom will respond to moderate dose of the first AED.[41] Dosage can be adjusted subsequently according to clinical response. In these pragmatic studies, the most common maintenance doses were 120 to 180 mg per day for adults and 3 to 5 mg/kg per day for children, although higher doses, up to 240 mg per day and 8 mg/kg per day, respectively, might be required and tolerated by some patients.

Maintenance

Once the initial target plasma phenobarbital level or target dosage has been achieved, or the patient's seizures are known to be suppressed, and the drug is tolerated comfortably, it is reasonable to make no further change in dose until the patient's clinical response to the treatment has time to become clear. Obtaining a measurement of the plasma phenobarbital concentration when the patient's seizures appear fully controlled may serve to indicate the provisional therapeutic concentration for that particular patient and serve to as a reference value for interpretation of future clinical situations. When adjusting the dose, it should be remembered that steady-state plasma phenobarbital concentration may rise disproportionately more than the size of the dose increment of phenobarbital, but in proportion to that of mephobarbital.[22]

Using a staged, progressive introduction of barbiturate AEDs, patients may tolerate plasma phenobarbital concentrations of 40 mg/L or even higher, although by levels of 50 mg/L most patients experience some degree of mental dullness. The phenobarbital dose corresponding to these toxic plasma drug concentrations might be 240 to 300 mg per day, and that of mephobarbital 600 to 800 mg per day. If seizures cannot be controlled at maximally tolerated dose, a different AED should be prescribed, whether or not phenobarbital (or mephobarbital) is continued at reduced dose or is discontinued.

If for any reason the patient becomes unable to take phenobarbital or mephobarbital orally, phenobarbital may be given by daily intramuscular injection or intravenous infusion. The parenteral dose is the same as the clinically satisfactory oral dose of phenobarbital, or half the oral dose of mephobarbital.

Discontinuation of Therapy

Therapy with phenobarbital or its *N*-methyl analog is discontinued when (a) unacceptable adverse effects have developed, (b) the therapy has provided unsatisfactory seizure control, (c) the therapy has been associated with seizure control long enough for a trial withdrawal of the drug to appear indicated, or (d) the patient elects to cease treatment for any reason.

Because phenobarbital has a relatively long half-life, even if intake of the drug is ceased abruptly the antiepileptic effect

should decline progressively during the next 1 or 2 weeks, thus making withdrawal seizures perhaps less likely than when other AEDs are discontinued suddenly. However, progressive gradual withdrawal of the drug is still advisable. In the U.K. Medical Research Council Antiepileptic Drug Withdrawal Study, there was no evidence that gradual withdrawal of phenobarbital was more often associated with exacerbation of seizures, as compared with other established agents.[12] Most clinicians prefer to withdraw barbiturates in stages over a period of several weeks or months, unless there is a good medical reason for ridding the body of the drug more quickly, for example, because of a serious idiosyncratic adverse effect. Thus, the dose might be reduced by 25% of its initial value each month for 4 months, or by 33% each month for 3 months.

Precautions

Phenobarbital and mephobarbital should be used with caution in persons with medically important disorders that are being treated with drugs whose clearances are likely to be altered by the administration of a drug metabolism–inducing agent such as phenobarbital. An example is persons receiving oral anticoagulant therapy. Phenobarbital should also be used cautiously in persons with hepatic and renal insufficiency and in the elderly. In both of these populations lower-than-usual doses may be required.

Contraindications

Phenobarbital (or mephobarbital) is contraindicated in persons with histories of previous hypersensitivity reactions to the agent, and in individuals with porphyria. The drugs should preferably be avoided in patients allergic to other aromatic AEDs (carbamazepine and phenytoin) since there is a 40% to 60% risk of cross-sensitivity.[3]

Summary and Conclusions

Phenobarbital and its congeners are effective, relatively broad-spectrum antiepileptic agents that can be conveniently administered parenterally as well as orally. They are the cheapest AEDs available. To some extent, these advantages are offset by the tendency of the drugs to cause sedation and behavioral disturbance, although these unwanted effects may be sometimes caused by excessive doses or too rapid increases in doses that ignore the elimination characteristics of phenobarbital.

Phenobarbital is long out of patent, and there seems to have been less interest in studying its optimal clinical use compared with most other AEDs. It remains an important antiepileptic agent, but one that has been allowed to acquire a rather undeserved reputation for adverse effects without its merits receiving equal attention. There is a possibility that phenobarbital may be allowed to fade from use, at least in affluent societies, not so much because of its limitations but because its virtues are not adequately recognized. On a global scale, phenobarbital is the most prescribed AED. Modern, comprehensive, prospective evaluation programs to optimize its use are warranted.[42]

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Chapter 154

Phenytoin, Fosphenytoin, and Other Hydantoins

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Introduction

The hydantoins are derivatives of a common five-membered heterocyclic ring that differ according to their unique combinations of alkyl and phenyl substitutions at three positions on the ring (Table 1). Phenytoin (PHT) is the most commonly prescribed hydantoin, and fosphenytoin is a phosphate ester prodrug of PHT used for parenteral administration of PHT. Ethotoin and mephenytoin are prescribed less frequently than PHT but may be useful in specific situations.

Phenytoin

Chemistry

The structural formula of PHT (5,5-diphenylhydantoin) is shown in Table 1. PHT has a molecular weight of 252.26 and is a weak acid with a pK_a of 8.3 to 9.2 under different experimental conditions.[70] Because of its high pK_a, PHT is relatively insoluble in water at acid or physiologic pH but is quite soluble in water at alkaline pH. These relationships have important clinical consequences, discussed below. The sodium salt of PHT has a molecular weight of 274.25 and contains the equivalent of 91.98% PHT acid.[70]

Multiple reliable methods for determining the concentration of PHT in biologic fluids have been reported. These employ gas–liquid chromatography, high-performance liquid chromatography, and immunoassay techniques.[87]

Pharmacology

PHT has multiple effects on cell function, which presumably explain its therapeutic and toxic effects. Three of these functions seem particularly important. First, PHT causes use-dependent inhibition of sodium channels necessary for the "firing" of action potentials. Sodium channels exist in resting, open, and inactive states. Each time sodium channels open during the passage of an action potential, some sodium channels become inactivated for a period of time before reverting to the resting state. When enough sodium channels become inactivated, the cell can no longer propagate an action potential. By stabilizing the inactivated form of the sodium channel, PHT hastens the process of use-dependent inhibition of action potentials. This phenomenon at least partially accounts for PHT's ability to control ictal excitability. Second, the ability of PHT to regulate calmodulin and second messenger systems may account for some of its widespread effects on cellular function. Third, PHT has the ability to regulate voltage-dependent neurotransmitter release at the synapse, which may be related in part to its action on calcium or sodium ions. The mechanisms of action of PHT have recently been reviewed in detail elsewhere[53] (see Chapter 137).

Clinical Pharmacokinetics

Absorption by Oral Route: General Considerations

As a weak acid with a pK_a of approximately 9.0, PHT is <1% ionized and has a water solubility of 14 μg/mL[70,189] at a pH of 1 to 2. At a pH of 7.5, PHT is 3% ionized and has a water solubility of 100 μg/mL. Thus, only a small amount of PHT is absorbed in the stomach, and most PHT absorption takes place in the small intestine where its solubility is approximately 100 μg/mL.[189]

PHT's low solubility has several important consequences. Not all of an oral dose of PHT is absorbed, and some is lost in the feces. There also are apparently considerable differences in the amount of PHT absorbed by different people, especially when the capsule form is used. Some otherwise normal people require large doses of PHT to reach average drug plasma concentrations, and these people sometimes are accused incorrectly of being noncompliant. Altered PHT absorption is also influenced by certain physiologic states. Pregnancy may be associated with reduced gastrointestinal absorption of PHT.[156] Neonates absorb oral PHT incompletely and erratically.[16,140] A final consequence of the marginal intestinal solubility of PHT is that any substance that interferes with the dissolution of PHT or adsorbs PHT in intestinal fluids (e.g., nasogastric feedings, antacids, certain foods, and certain other drugs) will inhibit PHT's absorption.[7,189]

Peak plasma concentration of PHT is usually reached 4 to 8 hours after an oral dose, although the peak may be reached as early as 3 hours or as late as 12 hours.[187,189]

Differences in Oral Bioavailability among Formulations

There are three types of oral preparations of PHT: Prompt, sustained (extended) release, and liquid suspension. Prompt products are absorbed rapidly in the small intestine, result in an early peak plasma PHT concentration, and must be administered at least twice daily. Sustained-release products such as Dilantin Kapseals and Phenytek are the most commonly prescribed PHT products in the United States, deliver peak plasma concentration values 4 to 8 hours after administration, and may be administered once daily to adults. The liquid suspension is rapidly absorbed, has greater bioavailability than many capsule preparations, and also must be administered at least twice daily.[146]

Table 1 Hydantoins

Substituents			
R₁	**R₂**	**R₃**	**Name**
H	C_6H_5[a]	C_6H_5	Phenytoin
$CH_2OPO_3Na_2$	C_6H_5	C_6H_5	Fosphenytoin
CH_3	C_6H_5	C_2H_5	Mephenytoin
C_2H_5	C_6H_5	C_2H_5	Ethotoin

[a] Phenyl ring.

Prompt and sustained-release preparations differ sufficiently in pharmacokinetic properties that they cannot be interchanged. Most generic PHT products marketed in the United States are prompt preparations and cannot be substituted for sustained-release preparations. It should be noted that some preparations (e.g., Dilantin suspension or Dilantin Infatab chewable tablets) contain PHT acid, while others (e.g., Dilantin Kapseals and Phenytek) contain the sodium salt. Because there is approximately an 8% increase in drug content with the free acid form over that of the sodium salt, dosage adjustments may be necessary when switching from a product formulated with the acid to a product formulated with the sodium salt or vice versa.

Generic substitution of prompt preparations for sustained-release preparations is furthermore problematic because of three risk factors for inequivalence among generic forms of a drug: (a) poor water solubility, (b) nonlinear pharmacokinetics, and (c) narrow therapeutic range of plasma concentration.[133,134] PHT possesses all three risk factors, so it is not surprising that comparisons of generic PHT products have yielded conflicting results, with more studies reporting inequivalence than equivalence.[39,45,57,127,144,145,146,149,169,192] Two generic sustained-release PHT products were introduced in the United States and later withdrawn because of concerns that they may not be equivalent to brand-name Dilantin.[15,64,169] Switching between preparations that are not equivalent may result in decreased drug plasma concentration (increased seizures) or increased drug plasma concentration (increased toxicity).[20] Based on this information, an American Academy of Neurology position statement recommends that patients be managed with one form of PHT preparation supplied by one manufacturer.[133,134]

The oral suspension form of PHT is useful for patients who have difficulty swallowing capsules, especially children. The oral suspension also is useful in patients who do not absorb PHT capsules well.

Absorption by Intramuscular Route

Dissolving PHT in a small volume of liquid for parenteral administration requires a solution pH of 12. When this preparation is injected intramuscularly (i.e., into a medium with a pH of about 7.4), the water solubility of the drug decreases substantially, PHT crystals precipitate in the muscle,[20] and the drug is absorbed very slowly.[20,88]

Peak plasma PHT concentrations occur approximately 24 hours after a single intramuscular injection and are considerably less than the peak concentration produced by the same dose given by intravenous infusion.[88] PHT should not be given via the intramuscular route in emergency situations (e.g., status epilepticus) because of the slowness of absorption and the relatively low peak plasma concentrations produced by that route.

Use of the intramuscular route for administration of maintenance doses of PHT remains controversial. Eventually, almost all of an intramuscular injection of PHT is absorbed, and regimens for administration of maintenance doses of intramuscular PHT have been reported. However, peak plasma PHT concentrations after an intramuscular injection are variable.[88] Furthermore, the plasma concentration may fall below therapeutic levels shortly after a switch to the intramuscular route from the oral or intravenous route and may ascend into the toxic range because of accumulation after switching back from the intramuscular to the oral route.[88] In most situations, maintenance doses of PHT should not be given by the intramuscular route because of the slowness and variability of absorption and because of the danger of over- and undermedication when switching to and from other routes of administration.

Fosphenytoin is a water-soluble phosphate ester prodrug of PHT that eliminates many of the problems of sodium PHT for injection. Fosphenytoin is described below.

Plasma Protein Binding and Distribution

Plasma Protein Binding.

PHT is 69% to 96% protein bound in adults.[81,110] In the absence of associated disease or displacing agents, the average extent of plasma protein binding is about 90%. Binding is lower in neonates[59,145] and in the elderly.[81]

Distribution into Tissues and Other Body Fluids.

The concentration of PHT in brain parenchyma and cerebrospinal fluid (CSF) reaches peak values 15 to 60 minutes after intravenous injection in humans.[189] However, the brain parenchyma concentration of PHT remains greater than the plasma concentration of free PHT once steady-state plasma concentrations are reached.

The concentrations of PHT in CSF, saliva, semen, and bile are essentially identical to the concentrations of free (non–protein-bound) PHT in plasma.[189]

PHT freely crosses the placenta.[189] It enters breast milk, with a milk:plasma PHT concentration ratio of about 0.2.[189]

Metabolism and Elimination

PHT is excreted in the urine and feces mainly as its metabolites, none of which has significant antiepileptic activity. Less than 5% is excreted in urine in an unmetabolized form.[28,189] The major route of biotransformation is *para*-hydroxylation of a phenyl ring by the liver cytochrome P450 system (primarily isoforms CYP2C9 and CYP2C19) to form 5-(*p*-hydroxyphenyl)-5-phenylhydantoin (*p*-HPPH).[6,28] Over 60% of a PHT dose is excreted in urine as *p*-HPPH, the majority of which is conjugated with glucuronic acid.[28,189] Minor metabolites include a dihydrodiol derivative; *meta*-HPPH (mHPPH); diphenylhydantoic acid; 5,5-bis(4-hydroxyphenyl) hydantoin; 5-(3,4-dihydroxyphenyl)-5-phenylhydantoin; and 5-(3-methoxy-4-hydroxyphenyl)-5-phenylhydantoin.[28,189]

PHT is a prochiral compound. Introduction of a hydroxyl group in one of the phenyl rings leads to the creation of a chiral center and results in the formation of enantiomeric phenolic metabolites. The *p*-HPPH from human urine consists of a 10:1 mixture of levo- and dextrorotatory isomers.[28,173] The amount of *m*-HPPH in human urine is too low to permit isolation and measurement of optical rotation. The majority of dihydrodiol in human urine is in the *S* configuration with varying *S:R* ratios.[2,111,113,114,152] The *S:R* ratio is due to an approximately 40 times greater stereoselectivity of CYP2C9 for the *S* isomer and CYP2C19's lack of stereoselectivity for either isomer.[6]

Occurrence of Nonlinear (Michaelis-Menten) Pharmacokinetics.

Nonlinear pharmacokinetic properties have major effects on PHT's clinical usage. The rate of change of plasma concentration (*C*) of a drug metabolized by an enzyme system can be expressed by the Michaelis-Menten equation:

$$\frac{dC}{dt} = \frac{V_{max} \times C}{K_m + C} \qquad (1)$$

where *t* is time, V_{max} is the maximum velocity of the enzyme system, and K_m is the Michaelis constant of the enzyme system (plasma concentration at which half of the maximum velocity of the enzyme system is attained). The mean steady-state plasma concentration (C_{ss}) of the drug can be expressed as:

$$C_{ss} = \frac{R \times K_m}{V_{max} - R} \qquad (2)$$

where *R* is the dosing rate. When *C* is similar to or greater than K_m, dC/dt will vary in a nonlinear fashion with *C;* when *R* is equal to or greater than $0.1 \times V_{max}$, C_{ss} will vary in a nonlinear fashion with *R*. These observations are the basis of nonlinear pharmacokinetics.

Based on 55 reported determinations, the mean apparent value for PHT's K_m in adults is 6.3 μg/mL and the range is 1.5 to 30.7 μg/mL. The mean apparent value for PHT's V_{max} in adults is 0.45 μg/mL/hr with a range of 0.14 to 1.36 μg/mL/hr based on 54 reported determinations.[3,27,60,66,68,69,79,121,155] These values appear to be determined principally by arene oxidase enzyme system K_m and V_{max} values. The other minor pathways of PHT metabolism potentially could have modifying effects on the apparent values of K_m and V_{max} for PHT.[108] However, attempts to demonstrate an effect of these other pathways on PHT pharmacokinetic parameters in humans have been negative.[28,35]

The apparent K_m values computed for humans are based on total (protein-bound and non-protein-bound) PHT plasma concentration. Because only non-protein-bound PHT can be acted on by the metabolizing enzyme system and the non-protein-bound fraction for PHT is approximately 10% in humans,[210] the K_m of the enzyme responsible for *para*-hydroxylation of PHT actually should be approximately 0.6 μg/mL. This prediction has been verified in rat liver microsomes.[193]

Eadie et al.[60] performed the first comprehensive comparison of PHT K_m and V_{max} values in children and adults. The K_m values from 21 adults (mean 5.8 μg/mL) and 15 children (mean 5.3 μg/mL) were not significantly different. The V_{max} values from 21 adults (mean 0.48 μg/mL/hr, assuming a PHT volume of distribution of 0.7 L/kg) were significantly (p <0.025) less than the V_{max} values from 15 children (mean 0.74 μg/mL/hr assuming a PHT volume of distribution of 0.7 L/kg). Suzuki et al.[67a,183] later confirmed these observations regarding K_m and V_{max} in children. These observations predict that the clearance [$V_{max}/(K_m + C)$] of PHT should be greater in children than in adults. This prediction is confirmed by the observations that the elimination half-life of PHT is shorter in children than in adults and that the average dosing rate of PHT (in milligrams per kilogram per day) required to achieve a given plasma concentration is greater in children than in adults.[20,56,90]

The V_{max} for PHT increases significantly during pregnan-cy.[54] This explains part of the observed decrease in PHT steady-state plasma concentration during pregnancy (Equation 2).

PHT will exhibit nonlinear pharmacokinetic properties in the majority of patients because the usual therapeutic plasma concentration values (10 to 20 μg/mL) exceed the usual K_m (6.3 μg/mL), and the usual dosing rate (0.15 to 0.45 μg/mL/hr) is greater than 0.1 times the usual value of V_{max} (0.45 μg/mL/hr). The consequences of nonlinear pharmacokinetics are discussed in the following sections.

Relationship between Plasma Concentration, Clearance, and Half-life.

According to the Michaelis-Menten equation, drug clearance is equal to $V_{max}/(K_m + C)$. Drug elimination half-life is equal to 0.693 × volume of distribution/clearance. Thus, PHT clearance will vary inversely with plasma concentration, and PHT elimination half-life will vary directly with plasma concentration (Fig. 1).[25,26,35] Browne et al.[27,35] described and validated a method for calculating PHT elimination half-life at any given PHT plasma concentration if the patient's K_m and V_{max} values for PHT are known. The results (plasma concentration and calculated elimination half-life) for a group of six adult men on PHT monotherapy were 1 μg/mL, 12.8 hours; 10 μg/mL, 25.8 hours; 20 μg/mL, 40.2 hours; and 40 μg/mL, 69.1 hours. Based upon these results, PHT's commonly believed elimination half-life of 24 hours applies principally to plasma concentration values in the low therapeutic range (10 μg/mL) and the elimination half-life often is longer at higher plasma concentrations (also see Fig. 1). The range of elimination half-life values at a PHT plasma concentration of 40 μg/mL was 37.1 to 96.8 hours. Because of PHT's long and variable elimination half-life values at toxic plasma concentration values, one cannot predict the time required for PHT plasma concentration to fall from a toxic value to a therapeutic value in a given individual. In such circumstances, one must withhold PHT and obtain daily plasma concentration determination values until the plasma concentration has fallen back into the therapeutic range.

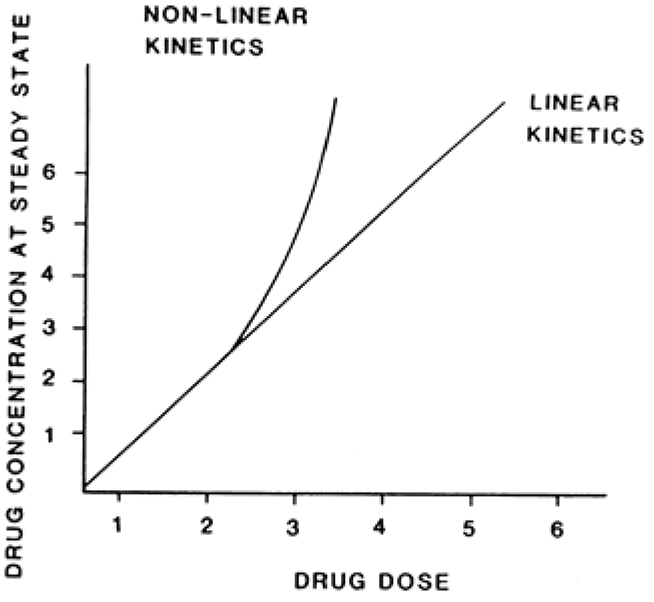

FIGURE 1. Relationship between dosing rate and steady-state plasma concentration for drugs with linear pharmacokinetics and for drugs with nonlinear Michaelis-Menten pharmacokinetics.

Relationship between Steady-State Plasma Phenytoin Concentration and Dosage.

For drugs with Michaelis-Menten pharmacokinetics similar to PHT's, steady-state plasma concentration increases to a greater extent than dosing rate when dosing rate is increased, and plasma concentration decreases to a greater extent than dosing rate when dosing rate is decreased (Equation 2) (see Fig. 2).[32,56,204] Thus, the steady-state plasma concentration of a drug with these Michaelis-Menten pharmacokinetics at one dosing rate does not directly predict the steady-state plasma concentration of the drug at another dosing rate.

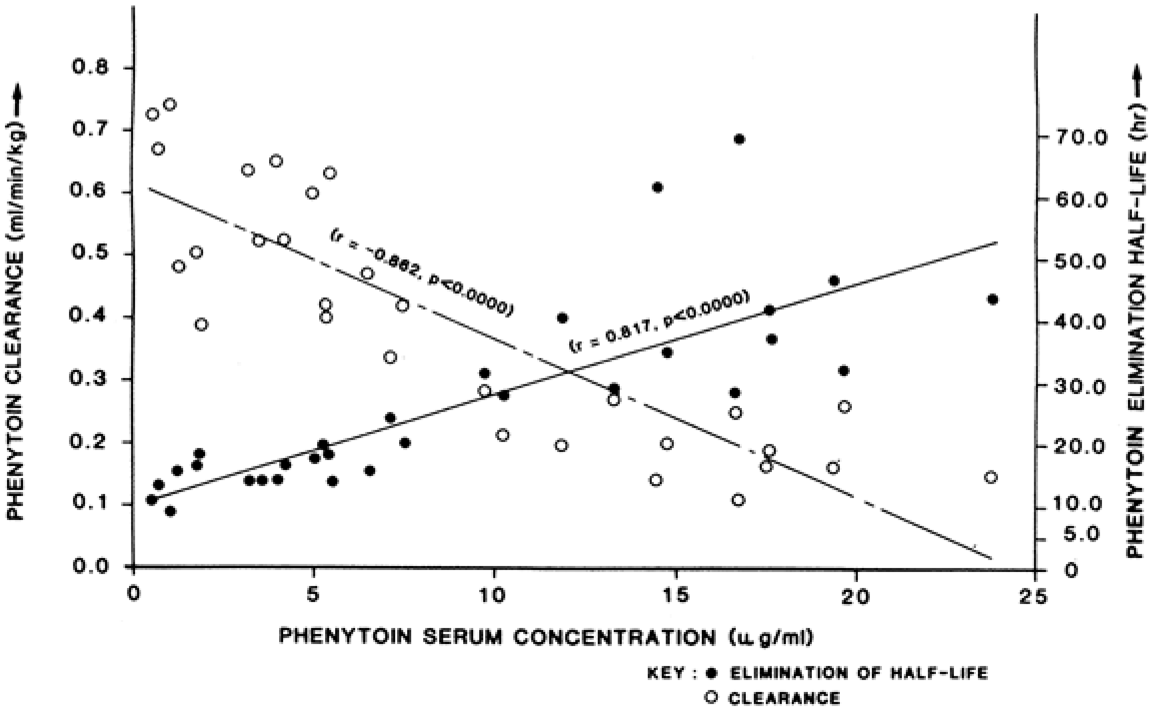

FIGURE 2. Phenytoin clearance and elimination half-life values determined by stable-isotope tracer techniques at 30 different serum concentration values in 18 adult men on PHT monotherapy. (From Browne TR, LeDuc B. Phenytoin: chemistry and biotransformation. In: Levy RH, Mattson RH, Meldrum BS, eds. *Antiepileptic Drugs*. 4th ed. New York: Raven Press; 1995:283–300, with permission.)

If the clinician attempts to increase or decrease PHT steady-state plasma concentration by simple linear extrapolation from a known plasma concentration versus dosing rate point, the result is often an unexpectedly high or low plasma concentration when the new steady-state value is attained (Fig. 2). Numerous mathematic and tabular methods have been published that claim to be able to predict the PHT dosing rate necessary to produce a given steady-state plasma concentration from a single steady-state plasma concentration versus dose point, and these methods have been critically reviewed elsewhere.[23,32,131,138,139] A useful rule of thumb in titrating PHT dosage upward in adults is to increase dosing rate in increments of 100 mg/day at monthly (see below) intervals until a steady-state PHT plasma concentration of 5 to 10 μg/mL (a value approximately equal to K_m) is attained; later increases should not exceed 50 mg/day at monthly intervals.

Nonlinear pharmacokinetics complicates the issue of generic equivalence of PHT products. The weighted mean value for absolute bioavailability of brand-name sustained-release PHT (Dilantin Kapseals, 100 mg, Parke-Davis) was 86% in three studies.[20] Less than complete absorption of brand-name PHT is at least in part a consequence of the use of a sustained-release preparation (see above). Different generic preparations of PHT have the potential to differ in bioavailability from the brand-name preparation by 14% or more. Because of PHT's nonlinear pharmacokinetics, a 14% difference in bioavailability is expected to result in a >14% increase or decrease in steady-state plasma concentration. For example, the bioavailability of a single dose of Mylan extended-release PHT given with a high-fat meal was found to be 13% lower than the bioavailability of Dilantin Kapseals taken under similar conditions.[206] Pharmacokinetic simulations based on these data showed that substituting the Mylan product for Dilantin in patients with baseline plasma PHT concentrations within or above the optimal range would be expected to result in a median 37% decrease in PHT concentrations, whereas substituting Dilantin for Mylan would be expected to produce a median 102% increase in PHT concentrations. A national epidemic of PHT intoxication occurred in Australia when a more bioavailable formulation was substituted for an older formulation.[154,199] Ludden et al.[108] and Browne et al.[36] have reviewed the effect of nonlinear pharmacokinetics on bioavailability studies in more detail.

Effect of Nonlinear Pharmacokinetics on Time to Reach Steady-State Plasma Concentrations.

According to the principles described above, as PHT plasma concentration rises, PHT clearance decreases and elimination half-life decreases (see Table 2 for typical values for these changes in a group of six patients started on PHT monotherapy). This results in a further rise in PHT plasma concentration and a further decrease in PHT clearance. This self-propagating cycle can require a long period of time to go to completion. The time (t) required to attain a given plasma concentration can be computed by the equation:

$$t = \frac{V_d\,(C_{s,t} - C_{s,0})}{(R - V_{max})} - \frac{V_d K_m V_{max}}{(R - V_{max})^2} ln\, \frac{(R - V_{max})\,C_{s,t} + RK_m}{(R - V_{max})\,C_{s,0} + RK_m} \qquad (3)$$

where V_d is volume of distribution, $C_{s,t}$ is plasma concentration at time t, and $C_{s,0}$ is plasma concentration at time 0.[204] Assuming average values for K_m and V_{max}, it is possible to compute an accumulation half-life ($t_{1/2A}$) for PHT as follows:

$$t_{1/2A} = 0.270 \times C_{ss} \qquad (4)$$

where $_{1/2A}$ has units of days and C_{ss} has units of micrograms per milliliter.[94] Equations 3 and 4 predict, and empirical data confirm, the following: (a) time to reach steady-state plasma

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concentration will vary nonlinearly with dosing rate; (b) time to reach steady-state plasma concentration will vary linearly with plasma concentration; and (c) the time required to attain new steady-state plasma concentration values after starting PHT therapy or increasing or decreasing PHT dosing rate may be as long as 28 days (Fig. 3).[26,32,94,204] Therefore, in some individuals, particularly when the plasma concentration of the drug is in the high range, a PHT plasma concentration value measured <28 days after a change in PHT dosing rate may not be an accurate indication of the ultimate new steady-state

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plasma concentration that will result from the change in dosing rate.

Table 2 Phenytoin pharmacokinetic values for six patients at three times during monotherapy determined with 150-mg tracer doses of stable-isotope-labeled phenytoin[a]

	Week 0[b]	**Week 4[c]**	**Week 12[d]**	**Significance[e] (*p*)**
Mean total (labeled and unlabeled)				
PHT plasma concentration (μg/ml)	1.2 ± 3.5[f]	5.4 ± 2.4	10.0 ± 6.1	<0.01
Clearance (ml/min per kg)[g]	0.587 ± 0.149	0.456 ± 0.147	0.387 ± 0.187	<0.05
Elimination half-life (hr)[g]	13.2 ± 3.6	18.4 ± 5.0	25.9 ± 9.7	<0.01

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[a] From Brown et al., ref. 20, with permission.

[b] Week 0, value from single-dose (150 mg) study performed before monotherapy.

[c] Week 4, value after 4 weeks on monotherapy (300 mg/day).

[d] Week 12, value after 12 weeks on monotherapy (300–500 mg/day).

[e] Difference among values for weeks 0, 4, and 12 by analysis of variance for one group with repeated measures.

[f] Mean ± standard deviation, here and throughout table.

[g] Value for tracer dose of phenytoin.

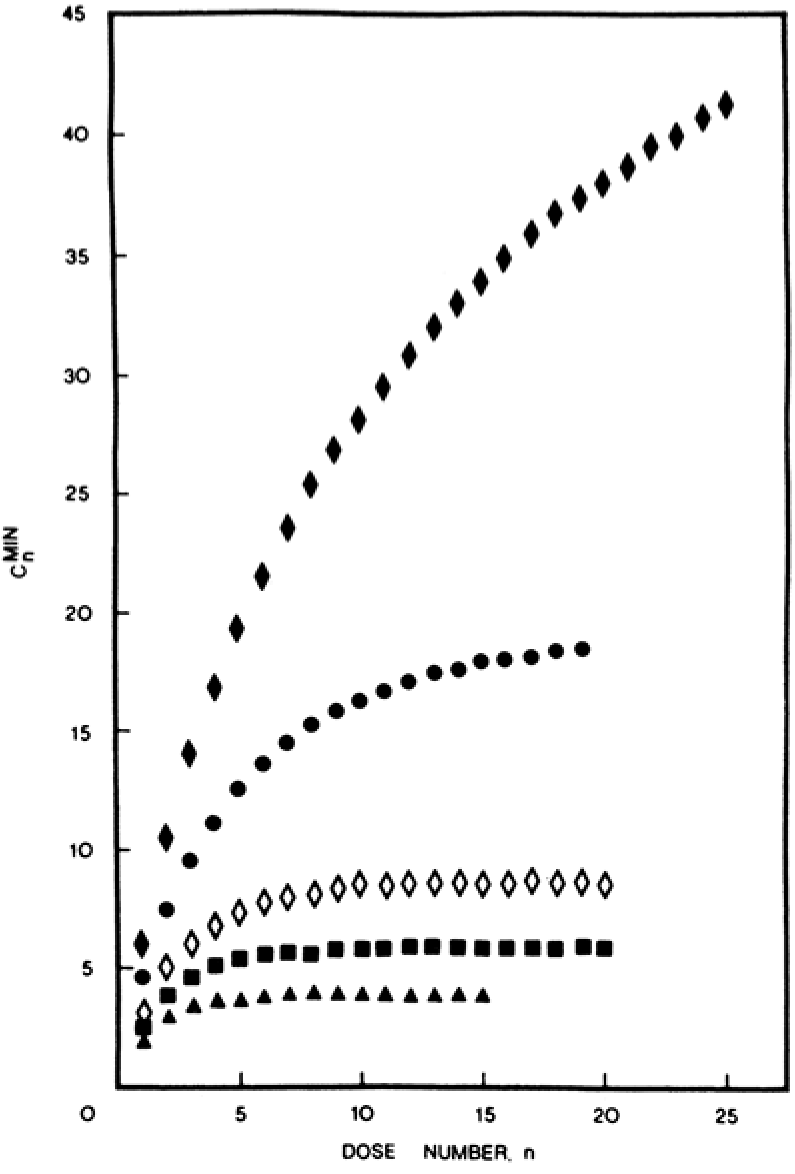

FIGURE 3. Plot of minimum serum concentration after the *n*th dose, C_{min}, versus dose number *n*. Symbols and dosing rates (g/day) are: [black four-pointed star], 0.50; •, 0.40; ♦, 0.30; ▪, 0.25; and ▲, 0.20. (From Wagner JG. Time to reach steady state and prediction of steady state concentration for drugs obeying Michaelis Menten elimination kinetics. *J Pharmacokinet Biopharmaceut*. 1978;6:209–225,

with permission.)

Factors Affecting Plasma Phenytoin Concentration Versus Dose Relationship: Age.

Neonates eliminate PHT more slowly than adults or children (see below). Young children metabolize PHT more rapidly than older children and adults, requiring higher milligram-per-kilogram doses of PHT to achieve a given plasma concentration and sometimes not maintaining therapeutic plasma concentrations with once-daily administration.[20,56] Plasma-unbound PHT concentrations for a given daily dose tend to be higher in the elderly than in young adults, probably because of a decreased metabolic rate, even though total plasma PHT concentrations may not differ to a major extent between young adults and elderly subjects.[5,6a,62] Elderly individuals may also show a wide (two- to threefold) intraindividual variability in plasma PHT concentrations despite unchanged daily doses, possibly due to day-to-day variability in absorption efficiency.[11]

Factors Affecting Plasma Phenytoin Concentration Versus Dose Relationship: Pregnancy.

Decreasing total PHT plasma concentrations are usually noted throughout preg-nancy.[102,147,186,187] However, the plasma concentration of free (unbound), pharmacologically active PHT falls much less than total PHT plasma concentration during pregnancy.[186,187] Monitoring of free PHT plasma concentration may be advan-tageous during pregnancy.

Factors Affecting Plasma Phenytoin Concentration Versus Dose Relationship: Hepatic Insufficiency.

The oxidative metabolism of PHT and many other drugs is slowed in patients with hepatic disease.[148] In addition, protein binding may be reduced by any of three occurrences: (a) hypoalbuminemia, (b) displacement by bilirubin or other substances, and (c) changes in the configuration of albumin. The overall result is usually an increase in the total plasma drug concentration, the free (unbound) drug concentration, or both.

Unfortunately, there is no formula for predicting the proper dose of an antiepileptic drug in a patient with hepatic dysfunction based on plasma albumin concentration or liver function tests. One must adjust drug dosage on the basis of clinical response and frequent determinations of the drug plasma concentration.

Factors Affecting Plasma Phenytoin Concentration Versus Dose Relationship: Renal Insufficiency.

Uremic patients receiving PHT have lower total plasma PHT concentrations, higher plasma *p*-HPPH concentrations, and shorter PHT elimination half-lives than nonuremic patients receiving the same dosage of PHT.[72,98,123] In renal insufficiency, the hepatic biotransformation processes continue and may accelerate, but renal excretion of metabolites is slowed. The high plasma concentration of *p*-HPPH is presumably a result of impaired renal excretion of the metabolite. The short elimination half-life is presumably caused by increased accessibility of PHT to hepatic biotransformation enzymes as a result of decreased protein binding from low plasma albumin concentration, displacement of PHT from protein-binding sites by *p*-HPPH and endogenous metabolites, and structural alterations of plasma proteins.[137] The low total plasma PHT concentration reflects primarily enhanced drug clearance as a result of increased accessibility of PHT to he-patic biotransformation enzymes. Because of the reduced PHT binding to plasma proteins and increased unbound fraction, total plasma PHT concentration in patients with uremia underestimates the concentration of free, pharmacologically active drug. Therefore, therapeutic and toxic effects occur in these patients at lower than usual total plasma PHT concentrations. In individuals with uremia, PHT therapy should be preferably monitored by measuring free (unbound) plasma PHT concentration.

Hemodialysis has little effect on the plasma concentration of PHT.[105]

Efficacy

Tonic–Clonic and Partial Seizures

The older literature on the effectiveness of PHT for tonic–clonic and complex partial seizures has been reviewed by Coatsworth.[46] More recently, a series of trials has compared PHT with other older antiepileptic drugs (carbamazepine, phenobarbital, primidone, and valproic acid) as initial therapy in neonates, in children, and in adults with tonic–clonic and partial seizures.[41,78,117,119,141,145,157,166,184,194,195,196,207] The results of these studies may be summarized as follows: (a) no drug was more effective than PHT in a randomized, prospective double-blind study; (b) PHT and carbamazepine were very similar in efficacy and toxicity; and (c) phenobarbital and primidone generally had more adverse effects than PHT or carbamazepine and, in some studies, were less effective when treating patients with partial seizures. There is also evidence-based data showing that PHT, oxcarbazepine, and lamotrigine have similar efficacy for the initial therapy of partial seizures.[10,71,130,181] Although there have been no direct comparisons of PHT with topiramate and gabapentin, a recent trial suggested that topiramate may have inferior tolerability, and gabapentin inferior efficacy, compared with carbamazepine in patients with newly diagnosed partial seizures.[114b] Among newer generations antiepileptic drugs (AEDs), only oxcarbazepine and topiramate are approved by the Food and Drug Administration (FDA) for this indication.

In most of the above studies, tonic–clonic seizures were mostly secondarily generalized seizures in patients with focal epilepsy. However, PHT is also effective for primarily generalized tonic–clonic seizures.[158,207] Although PHT is effective as prophylaxis against acute symptomatic seizures that may occur soon after traumatic brain injury, it does not decrease the risk of later developing remote symptomatic seizures or epilepsy.[44]

Status Epilepticus

PHT is an important therapy for status epilepticus manifesting with tonic–clonic or partial seizures. A randomized, double-blind trial of four treatments for status epilepticus found lorazepam to be more effective than PHT for seizure control at 1 hour, but it was equally effective to a combination of diazepam and PHT or phenobarbital alone.[188] PHT was inferior to valproic acid for terminating convulsive status epilepticus in a randomized comparison trial of intravenous formulations with each medication given without benzodiazepines and with efficacy measured at the end of the infusion.[129] However, valproic acid does not have FDA approval for this use.

Other Epileptic Disorders

Older studies, without adequate controls, yielded conflicting results in the value of PHT in treating alcohol withdrawal seizures.[1] However, two modern and well-controlled studies strongly indicate that PHT has no value in treating or preventing alcohol withdrawal seizures.[1,161]

Animal models predict that PHT should not be effective for controlling absence seizures, and clinical experience has shown this prediction to be correct.[205,207]

Other Indications

PHT controls trigeminal neuralgia in a smaller percentage of patients than carbamazepine, but the combined use of PHT and carbamazepine for trigeminal neuralgia is sometimes more effective than carbamazepine alone. PHT has been suggested as a therapy for a wide variety of organic and functional diseases of the nervous and cardiovascular systems, as well as for a variety of other conditions.[13]

Adverse Effects

Dose-related Central Nervous System Adverse Effects

The usual dose-dependent adverse effects of PHT include nystagmus, ataxia, and drowsiness.[38,49] Nystagmus is usually horizontal but can include vertical movements at high drug plasma concentrations. The ataxia involves station and gait more than fine motor movements. There is an approximate correlation of signs of PHT intoxication with drug plasma concentration. In the majority of patients, nystagmus appears with drug plasma concentrations of about 20 μg/mL, ataxia with levels of about 30 μg/mL and drowsiness with levels of >40 μg/mL.[90] However, there is considerable variation among patients in the plasma PHT concentration at which a symptom occurs, and not all patients experience all symptoms. At high plasma concentrations (usually >40 μg/mL), a reversible external ophthalmoplegia may occur.[180] Patients also may experience an excited delirium rather than sedation with therapeutic and toxic PHT plasma concentrations.[49]

Perhaps the most important questions about PHT toxicity are concerned with what, if any, effects the drug has on cognitive function and behavior at typical therapeutic plasma concentrations. The cognitive effects of PHT have been studied extensively. Early studies were flawed by the fact that PHT slows motor speed, causing slowing of timed tests that is not related to slowed cognition. Recent studies indicate that (a) PHT has modest or little effect on cognition, (b) PHT and carbamazepine have similar and modest effects on cognition, and (c) barbiturates may have greater effects on cognition.[38,47,55,117,124,176,203]

A reversible syndrome of "PHT encephalopathy" has been described as a complication of chronic PHT therapy, usually with PHT plasma concentrations in the toxic range.[49,163] The syndrome is characterized by mental changes, increased slowing and increased paroxysmal activity on electroencephalograms (EEG), increased seizure frequency, and a change in seizure pattern involving development of more tonic components. The mental changes may include drowsiness, progressive decline in higher intellectual function, depression, or euphoria. Focal neurologic signs such as hemiparesis and hemisensory defects may occur. Ataxia and nystagmus may be present or absent, and the CSF protein value may be elevated. This encephalopathy is more common in children, and pre-existing brain damage may be a risk factor for it.[165] All these features generally disappear when PHT is discontinued.

Movement disorders (usually choreoathetosis and orofacial dyskinesia; rarely asterixis, ballismus, hyperkinesia, external ophthalmoplegia, periodic alternating nystagmus, or downbeat nystagmus) have been reported to be caused by PHT.[49,160,180] These disorders usually occur with toxic PHT plasma concentrations but may occur with plasma concentrations in a typically therapeutic range for a smaller minority of patients.[49]

Murphy et al.[131] reported 85 cases of PHT intoxication following unintentional overdose (PHT plasma concentration 30.3 to 95.0 μg/mL, median 46.5 μg/mL). The most frequent symptoms were nystagmus (95%), ataxia (80%), lethargy (22%), and seizures (19%). No patient had cardiac abnormalities attributable to PHT intoxication. Outcome was generally good, but three patients had serious complications (hip fracture, infections).

Dose-related Gastrointestinal Adverse Effects

PHT can cause nausea, vomiting, or constipation. Administration with or immediately after meals can reduce gastrointestinal discomfort.

Dose-related Cardiovascular Adverse Effects

Intravenous administration of PHT may cause hypotension, atrioventricular conduction block, and other dysrhythmias. These effects are related to dose and rate of administration, and conventional practice is to limit the rate of intravenous PHT infusion to 50 mg/min or less. Blood pressure and electrocardiographic (ECG) monitoring are recommended when PHT is administered intravenously, particularly at the higher dosages and infusion rates that are used for loading or for the treatment of status epilepticus. Some patients develop the cardiovascular side effects of the intravenous infusion even at the recommended maximum rate of 50 mg/min.

Chronic Adverse Effects

Effects on the Nervous System.

A loss of cerebellar Purkinje cells has been reported in association with PHT therapy.[49,163] However, loss of

Purkinje cells is a common finding in patients with epilepsy, whether or not they take antiepileptic drugs. Dam[49] reviewed the human and animal data on the effects of PHT on Purkinje cells and concluded that PHT in therapeutic doses does not lead to changes in the density or substructure of Purkinje cells. Reynolds[163] concluded that although much of the data on this topic are controversial, there are several convincing clinical reports of chronic cerebellar dysfunction following acute PHT intoxication. Since Reynolds' review, additional reports of cerebellar atrophy following PHT intoxication have emerged[38,116] as well as reports of PHT-related cerebellar degeneration in patients without seizures.[135,159] Conversely, Murphy et al.[131] found no evidence of permanent cerebellar dysfunction in 85 cases of severe PHT intoxication. Thus, permanent cerebellar dysfunction may be a rare complication of PHT intoxication and may be related to the duration of acute PHT toxicity or to pre-existing pathologic damage in the cerebellum from seizures, other drugs, or other causes.[163,164]

Chronic PHT administration may lead in some, but not all, patients to a bilateral peripheral neuropathy characterized by decreased reflexes, decreased nerve conduction velocities (especially motor), and sensory deficits.[49,100,163,175,178] Most patients are asymptomatic, although a minority of patients complain of weakness or dysesthesia. The occurrence of this complication correlates with the duration of PHT therapy. The neuropathy does not seem to be related to folate level, vitamin B_{12} level, hemoglobin, blood cell counts, or blood sugar. Administration of folic acid or withdrawal of PHT does not seem to improve the neuropathy.

Cosmetic Adverse Effects.

Gingival hyperplasia occurs in approximately 20% of adult patients on PHT,[117] and the incidence may be higher in children.[163] It usually becomes apparent within 2 to 3 months after commencing PHT therapy and reaches a maximum in 9 to 12 months.[163] Gingival hyperplasia can be reduced by good oral hygiene. Periodic gingivectomy can remove the excess tissue and improve cosmetic appearance. Discontinuing PHT will result in regression of the gingival changes in 3 to 6 months.[163] When severe, gingival hyperplasia may negatively impact dental health, so it is not always a purely cosmetic effect.

Enlargement of the lips and nose, coarsening of the facial features, hirsutism, chloasma-like pigmentation, and acne all have been reported to occur in patients on chronic PHT therapy.[163] Except for hirsutism, which is well documented, the evidence for a cause-and-effect relationship between PHT and these conditions is questionable. The evidence consists of retrospective, nonblinded studies of patients, many of whom took other drugs and had moderate to severe mental retardation, often with institutionalization. Thus, the effects of other drugs, genetics, and environment were not controlled.

Endocrine and Metabolic Adverse Effects.

PHT initially causes an increase in circulating adrenocorticotropic hormone (ACTH) and cortisol, but levels of these hormones subsequently decline to below-normal concentrations.[163] Chronic PHT administration enhances hydroxylation of cortisol and increases urinary excretion of 6-*β*-hydroxycortisol.[163]

PHT depresses the release of antidiuretic hormone and oxytocin.[163] PHT also can displace thyroxine (T_4) and triiodothyronine (T_3) from thyroxine-binding globulin,[49,163,214] which can result in decreased serum T_4 and T_3 to maintain normal free T_4 and free T_3 concentrations and a euthyroid state.[182] Therapeutic plasma concentrations of PHT decrease the insulin secretory response of the pancreas to glucose.[163] This can result in hyperglycemia.[49,163]

Biochemical abnormalities suggesting metabolic bone disease are common in patients on chronic PHT. These include elevated plasma alkaline phosphatase and reduced plasma calcium and plasma 2-hydroxycholecalciferol.[38,163] Bone biopsy studies of patients on chronic PHT therapy reveal decreased bone density in approximately half of patients.[8,151] These findings may be secondary to decreased intestinal absorption of calcium, increased hepatic metabolism of vitamin D, or altered parathyroid hormone function.[38] Although laboratory abnormalities are common, clinically significant osteomalacia is uncommon in patients taking PHT.[38,163] Testosterone and estradiol metabolism are enhanced by PHT.[38] Chronic PHT therapy may be associated with elevated plasma concentrations of sex hormone–binding globulin in men and women.[48] The significance of these findings is uncertain.

PHT may precipitate porphyric attacks in patients with acute intermittent porphyria.

Hematologic Adverse Effects.

Aplastic anemia, leukopenia, thrombocytopenia, erythroid aplasia, and pancytopenia have all been associated with PHT therapy.[73,150] These side effects are very rare, usually occur during the first few months of therapy, are unrelated to dosage, and are often associated with other evidence of hypersensitivity phenomena.[150] Mild leukopenia (total white blood count 3,000 to 5,000/mm^3) is common with chronic administration of many antiepileptic drugs, including PHT.[117] This does not usually require discontinuing the drug until the count for segmented forms falls below 1,500/mm^3.

Macrocytosis is found in 0% to 36% of patients on chronic PHT therapy.[163] Subnormal serum folate levels are found in 27% to 91% of patients on chronic PHT therapy, and subnormal CSF folate levels are found in 0% to 45% of such patients.[38,163] The mechanism of producing low serum folate levels is not known for certain; possible mechanisms have been reviewed.[38] Despite the high incidence of macrocytosis and folate deficiency in patients on PHT, only 0.15% to 0.75% of patients develop megaloblastic anemia.[158] Subnormal serum vitamin B_{12} levels are found in 0% to 11% of patients on chronic PHT therapy, probably because of malabsorption of vitamin B_{12} as a secondary effect of low serum folate levels.[158]

The clinical importance of these findings is controversial. Megaloblastic anemia that is reversible with folate can occur with PHT, and there is highly controversial evidence that folate deficiency may lead to psychiatric disturbances in patients on PHT that are reversible with folate.[158] These considerations favor routine detection and treatment of folate deficiency in patients on PHT. However, animal research indicates that folate antagonizes the antiepileptic effect of PHT, and there is conflicting clinical evidence that administration of folate may increase seizure frequency in patients taking PHT.[163] Folate levels are an expensive laboratory test. Indications for folate treatment, the dose and duration of therapy, and the question of whether to give vitamin B_{12} as well as folate all remain to be clarified. The prophylactic use of folic acid to reduce the risk of birth defects in women of childbearing potential is discussed in Chapters 110 and 114.

Idiosyncratic Reactions (Including Immune-mediated Adverse Effects)

Table 3 signs and symptoms in 38 cases of phenytoin hypersensitivity reaction[a]

Sign or symptom	Percentage of patients
Rash	
Morbilliform or licheniform	66
Erythema multiforme	18
Stevens-Johnson syndrome	13

Total	74
Fever	13
Abnormal liver function tests	29
Lymphoid hyperplasia	24
Eosinophilia	21
Blood dyscrasias	
Leukopenia	16
Thrombocytopenia	5
Anemia	16
Increased atypical lymphocytes	3
Total	31
Serum sickness	5
Albuminuria	5
Renal failure	3

[a] From Haruda, ref. 67, with permission.

A variety of signs and symptoms in various combinations may occur as a result of PHT hypersensitivity reactions (see Table 3). The majority of such reactions occur during the first 3 months of PHT therapy.[75,118] One exception to this is the “purple glove syndrome,” which is a triad of edema, pain, and discoloration in the limb distal to the infusion site of intravenous PHT that typically occurs within a day of receiving PHT. The reaction occurs in about 2% to 6% of patients and usually resolves with conservative treatment; however, surgical treatment sometimes is necessary.[40,136]

Rashes, which are most common in children (especially when large starting doses are used) and young adults, usually occur within the first 10 days of PHT therapy and may be accompanied by fever, leukopenia, or lymphadenopathy.[49] The incidence of rash in adults starting PHT is approximately 10%.[117,118] These symptoms disappear when the drug is discontinued and reappear with readministration of PHT.[49]

More serious dermatologic disorders that can be rare side effects of PHT include erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis.[49] The relative risk of PHT causing Stevens-Johnson syndrome or toxic epidermal necrolysis has been estimated to be about 290 (95% confidence interval, 9 to 9,239).[104]

A "serum sickness"-like illness with rash, fever, arthralgias, and atypical lymphocytes may occur with PHT administration.[49] In addition to discontinuing PHT, cortico-steroids may be helpful in treating this disorder.[49]

Hepatitis (hepatic necrosis, inflammation, cholangitis) is a rare but serious complication that usually occurs during the first 6 weeks of PHT therapy.[49,143] It usually occurs in association with other symptoms of hypersensitivity such as rash (100%), fever (90%), lymphadenopathy (75%), or blood dyscrasias.[49,143]

Systemic lupus erythematosus (SLE) has been reported in association with PHT therapy.[49] In some cases, SLE appears to result from PHT administration, but in other cases, pre-existing

SLE probably caused a seizure disorder that caused PHT to be prescribed.[49]

Although lymphadenopathy is not uncommon with PHT therapy, the question of whether PHT can cause malignant lymphomas remains controversial.[150,173] Cases with features such as lymphadenopathy, fever, eosinophilia, hepatomegaly, splenomegaly, and certain malignant-appearing features on lymph node biopsy that remitted when PHT was stopped have been reported.[49,150] A smaller number of cases of persistent malignant lymphoma after PHT was discontinued has been reported.[49,150] It is difficult to know whether such symptoms are caused by PHT, other drugs, or the spontaneous appearance of malignant lymphoma. Nevertheless, it is prudent to discontinue PHT in a patient with lymphadenopathy.

PHT may suppress both humoral and cellular immune mechanisms.[179] Production of immunoglobulin A (IgA) is reduced.[38] Antinuclear antibodies and lymphocytotoxins of the IgM class have been found in patients taking PHT.[138]

Idiosyncratic reactions involving primarily the bone marrow may also occur, and have been listed in the section on hematologic adverse effects.

One case of fatal allergic interstitial nephritis in association with PHT therapy has been reported.[123] PHT has been reported to precipitate autoimmune myasthenia gravis in patients not known to have the disease and to exacerbate the disease in patients known to have it.[66,178]

Teratogenicity

The absolute and relative (compared to other therapeutic options) teratogenicity of PHT is an extremely complex topic. The following general observations apply.[38,51,52,115] First, there may be an increased risk of malformations (cleft lip and palate, cardiac defects, cranial anomalies, limb anomalies, hypospadias, intestinal atresia, and possibly mental retardation) in infants born to mothers with epilepsy taking no medication. This, however, has not been established conclusively, and was not found to occur in a large population-based case-control study.[80] Second, these malformations, which were formerly termed "fetal hydantoin syndrome," are more common in mothers taking most antiepileptic drugs. Third, the risk is especially high in mothers taking two or more drugs in combination. Fourth, there is significant additional risk, especially for neural tube defects, in infants born to mothers taking valproic acid.[211] Genetics, severity of epilepsy, nutritional status (including folic acid intake), and drugs all may play a role in determining risk of malformation.[38,51,52] Available evidence does not support the notion that prenatal exposure to PHT involves a greater teratogenicity risk compared with exposure to other established antiepileptic drugs.[146a] For more information on existing data and the management of epilepsy in women of childbearing potential and during pregnancy, the reader is referred to recent reviews[51,52,146a] and to Chapters 110 and 114 in this book.

Drug Interactions

Effects of Other Drugs on the Pharmacokinetics of Phenytoin

A comprehensive description of drug–drug interactions affecting PHT pharmacokinetics can be found in recent reviews,[114a,144a,144b,146b] and only the most relevant examples will be discussed in this section.

Administration of PHT with some antacids[144b] or with certain nasogastric or enteral feedings[7,210a] can result in impaired PHT absorption and a marked fall in plasma PHT concentration, with the attendant risk of loss of seizure control.[147b]

Highly protein-bound drugs can displace PHT from plasma protein-binding sites. Unless additional mechanisms are involved, these interactions are not clinically significant because the displaced drug redistributes rapidly into a large volume of distribution and is eliminated through a compensatory increase in drug clearance: The overall result is a fall in total PHT concentration, but the concentration of free, pharmacologically active PHT is unchanged.[144a] Clinicians need to be aware of the interaction when interpreting plasma PHT concentration in these patients, especially because the presence of a displacing drug may produce both therapeutic and toxic effects of PHT at low total plasma PHT concentrations. Therefore, a decrease in total plasma PHT concentration caused by these interactions should not lead to an automatic increase in PHT dosage. Valproic acid is the drug most commonly responsible for displacing PHT from plasma protein-binding sites, and it may also inhibit PHT metabolism. When valproic acid is added on to the therapeutic regimen of patients stabilized on PHT, total plasma PHT concentrations usually decrease, whereas free PHT concentrations remain unchanged or even may increase.[120,210a]

Most drug interactions causing a change in PHT pharmacokinetics involve interference with PHT metabolism.[91,144b,148] The metabolism of PHT can be accelerated or slowed by drugs that induce or inhibit CYP2C9 and CYP2C19.[33,91,95,99,148] As described by Kutt,[91] marked changes in plasma PHT concentration occur commonly with only a few drugs and less commonly with other drugs in unusually susceptible individuals. Most interacting combinations can be used if clinically indicated with careful clinical and laboratory monitoring to guide dosage adjustments as necessary. Interactions that involve an acceleration in PHT metabolism and a decrease in plasma PHT concentration include rifampicin and folic acid.[144b] Vigabatrin,[29] cisplatin, and other antineoplastic drugs[201a] also may lower plasma PHT concentrations, but the mechanism underlying these interactions is unclear. Drugs that have been reported to inhibit PHT metabolism and to increase plasma PHT levels, at least in some patients, include felbamate, oxcarbazepine, valproic acid, carbamazepine, clobazam, topiramate, methsuximide, sulthiame, stiripentol, fluoxetine, fluvoxamine, imipramine, sertraline, trazodone, viloxazine, chloramphenicol, fluconazole, isoniazid, miconazole, sulfaphenazole, some antineoplastic drugs (doxifluridine, fluorouracil, tamoxifen, tegafur), allopurinol, amiodarone, azapropazone, cimetidine, chlorpheniramine, dextropropoxyphene, diltiazem, disulfiram, omeprazole, phenylbutazone, sulfinpyrazone, tacrolimus, ticlopidine, and tolbutamide. In the case of highly protein-bound drugs that displace PHT from plasma protein-binding sites (e.g., valproic acid, tolbutamide, phenylbutazone), the increase in plasma PHT concentration may be limited to the free, unbound fraction, and may not be apparent when only total PHT concentrations are monitored.[21,91,114a,114b,146b,208]

Effects of Phenytoin on the Pharmacokinetics of Other Drugs

PHT is a potent inducer of microsomal drug-metabolizing enzymes and by this mechanism it accelerates the metabolism of a large number of concurrently administered drugs, thereby decreasing their plasma concentrations.[114a,114b,146b] Antiepileptic drugs whose plasma concentration is decreased by PHT include carbamazepine, lamotrigine, topiramate, tiagabine, zonisamide, felbamate, and many benzodiazepine drugs.[101,146b,215] PHT also lowers the plasma concentration of valproic acid[122] and increases the production of the “4-en” valproic acid metabolite, thought to be responsible for hepatic toxicity.[100] Other drugs whose plasma concentration may be lowered by PHT include oral contraceptive steroids, dexamethasone and other glucocorticoids, nisoldipine, felodipine and most

other dihydropyridine calcium antagonists, cyclosporin A, certain antineoplastic agents, meperidine, methadone, acetaminophen, theophylline, chloramphenicol, itraconazole, indinavir, doxycycline, praziquantel, folic acid, digitoxin, bishydroxycoumarin, warfarin (for which an initial decline in the plasma concentration may be followed by an increase in plasma warfarin concentration and increased anticoagulant response), metyrapone, 25-hydroxycholecalciferol, and thyroxine.[91] Many of the above interactions are clinically important and may result in loss of pharmacologic effect of the affected drug. Coadministration of PHT has been reported to raise the plasma concentration of phenobarbital derived from primidone and N-desmethylmethsuximide derived from methsuximide.[21,91,95]

Indications

Oral Treatment

PHT is indicated for the treatment of partial seizures, with or without secondary generalization, and for the treatment of primarily generalized tonic–clonic seizures. Because PHT may potentially aggravate other generalized seizure types such as absence and myoclonic seizures,[147a] it is not the best choice to treat primarily generalized tonic–clonic seizures in syndromes associated with other generalized seizure types. As discussed in more detail in Chapter 118, the choice of an AED is dictated not only by its efficacy spectrum, but also by other considerations such as adverse effects, drug interaction potential, cost, and individual characteristics of the patients. The use of PHT varies considerably across countries and across different clinical settings. While many physicians consider PHT as a valuable treatment option for initial treatment, others prefer to utilize PHT as a second-line agent due to concerns with its dose-dependent pharmacokinetics, cosmetic side effects (particularly in young women), and potential for drug interactions (particularly in the elderly).

Intravenous Treatment

PHT is an important therapy for tonic–clonic and partial status epilepticus. Its best use for status epilepticus is in combination with a benzodiazepine, which should be given first because of the benzodiazepine's faster onset of antiseizure effect.[125] A more detailed discussion of the role of PHT in the treatment of status epilepticus is provided in Chapter 127.

Dosing Recommendations

Initiation of Treatment and Dose Adjustment

The usual initial dosage in adults is 300 mg/day, and the usual initial dosage in children is 5 mg/kg/day. Because of the very slow metabolism of PHT in premature and term infants, the usual doses of PHT can produce toxic plasma concentrations in these infants.[106] It is often impossible to predict the proper dosage of PHT in such patients, and the dosage must be adjusted by frequent monitoring of PHT plasma concentration.

Clinical response should be monitored carefully after initiating treatment. In patients with unusually slow rates of PHT metabolism, the usual starting dosage may result in excessively high plasma PHT concentrations and occurrence of adverse effects. More commonly, the usual daily dose of 300 mg/day may not produce good seizure control, and the dosage must then be raised until seizure control is obtained or toxicity precludes further increases. In raising the dosage of PHT, one is faced with two conflicting considerations. In some patients, a small increase in PHT dosage will result in an unexpectedly great increase in plasma concentration and drug toxicity owing to the phenomenon of concentration-dependent metabolism. This result argues for increasing the dosage in small increments. Other patients absorb PHT poorly and require large increases in dosage to achieve therapeutic drug plasma concentrations. This would argue for increasing dosage in large increments. One workable compromise is to increase PHT dosage in 100 mg/day increments until a plasma concentration of 10 μg/mL is reached. After that, further increments of 50 mg/day or 30 mg/day can be added. Only one increment should be added every 4 weeks or longer because it may take that much time to reach a steady-state plasma concentration and to discern the full therapeutic and toxic effects of the dosage regimen. Monitoring plasma PHT concentration is invaluable during the process of dose individualization, or whenever there is an unexpected change in clinical response (Chapter 104).

As noted above, some patients who do not absorb PHT capsules well will absorb the oral suspension form much better. If a patient is taking a dose of 500 mg/day and does not have a therapeutic plasma concentration and noncompliance has been excluded, it may be helpful to switch from the capsule form to the oral suspension form. This often results in therapeutic (and sometimes toxic) plasma concentrations. PHT oral suspension must be shaken well before each dose to prevent the drug from settling in the bottom of the bottle, resulting in undermedication when the suspension is taken from the top of the bottle and overmedication when it is taken from the bottom of the bottle.

Divided Dose Versus Single Daily Dose

Several groups have shown that once-daily administration of extended-release PHT will maintain therapeutic plasma concentrations in the majority of adults, although there can be a twofold difference between maximum and minimum PHT plasma concentrations because for some patients, particularly when the plasma PHT concentration is in the low range, the elimination half-life can be <24 hours.[20,28,90,187] Because once-daily administration is the most convenient dosage schedule for many patients, it probably encourages increased compliance. However, there are four groups of patients who should receive PHT in two divided doses. The first group is patients of any age taking immediate-release PHT. The second group is adults who have side effects associated with peak plasma concentrations after once-daily administration. The third group includes patients of any age with poorly controlled seizures. Dividing the dose of PHT will result in a smaller fall in PHT plasma concentration at times of minimum drug serum concentration. The fourth group is children, because children metabolize PHT more rapidly than adults and cannot always maintain a therapeutic plasma concentration with once-daily administration.[20,56,106] Even with their more rapid rate of elimination of PHT, children can maintain therapeutic plasma concentrations with twice-daily administration.[56]

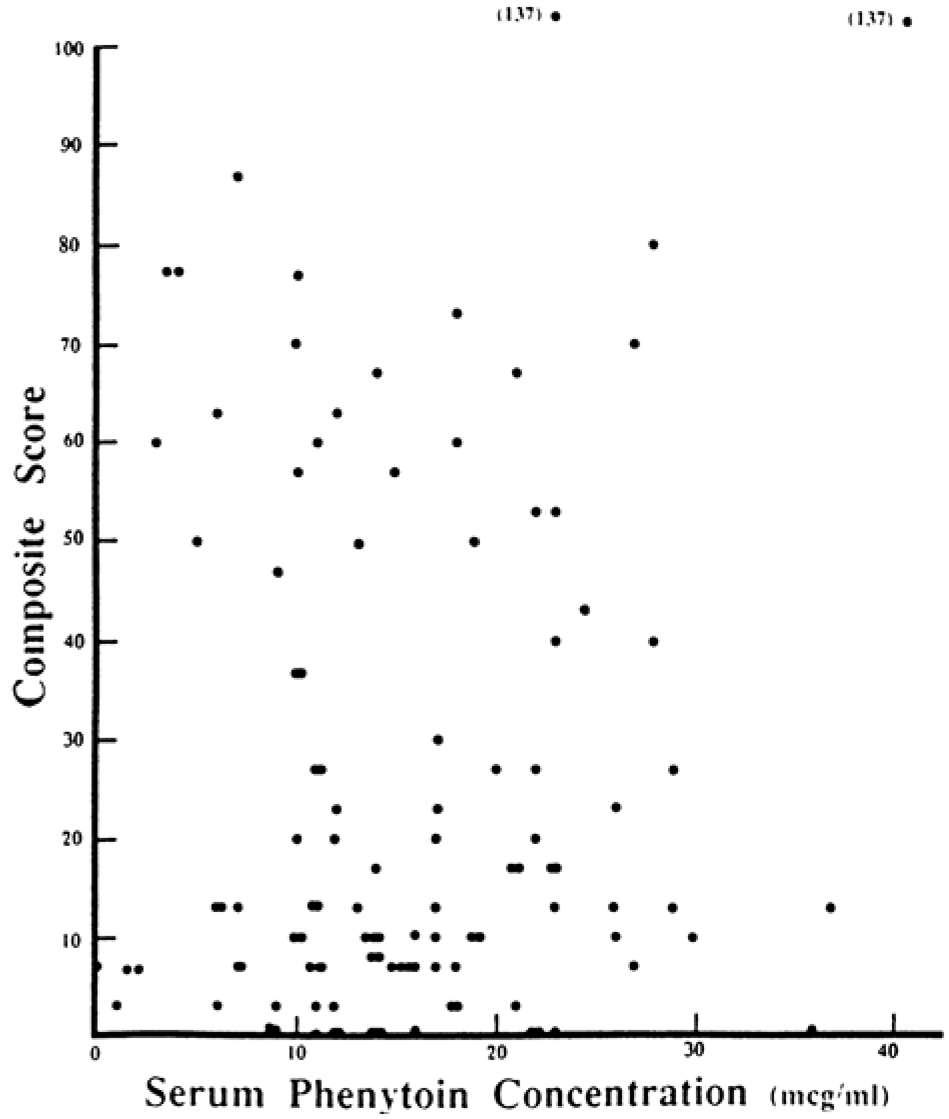

FIGURE 4. Plot of plasma phenytoin concentration versus composite score for overall response (efficacy and toxicity) to drug (0, no seizures and no side effects; 1–20, good response; 21–49, acceptable but less than optimal response; 50+, unacceptable seizure frequency or toxicity). (From Schumacher GE, Barr JT, Browne TR, et al., and the Veterans Administration Epilepsy Cooperative Study Group. Test performance characteristics of the serum phenytoin concentration [SPC]: the relationship between SPC and patient response. *Ther Drug Monit*. 1991;13:318–324, with permission.)

Administration of PHT in three or four divided doses is almost never necessary and should be avoided. Patients often omit doses of drugs that must be taken at school or work, and three- or four-dose daily regimens often lead to increased noncompliance.[20]

The largest dose of PHT is usually given at bedtime. This reduces drowsiness, ataxia, and other side effects that can be associated with peak PHT plasma concentrations.

Loading Dose

It can take several weeks to reach a steady-state plasma PHT concentration when therapy is initiated with the usual maintenance doses. If it is necessary to achieve a plasma concentration in the therapeutic range rapidly, a loading dose can be given. Therapeutic plasma concentrations can be achieved very quickly with an intravenous loading dose in emergency situations. The intravenous loading dose of PHT is 15 to 20 mg/kg (see Chapter 127). Specific information on intravenous dosing recommendations for the treatment of status epilepticus is provided in Chapter 127.

Administration of an oral loading dose of PHT is less rapid but less dangerous than intravenous loading. In adults, administration of 400 mg followed after 4 hours with 300 mg followed after 4 hours with a final 300-mg dose will result in therapeutic PHT plasma concentrations 14 to 20 hours after the first dose and steady-state plasma concentrations 36 to 40 hours after the first dose.[198] More rapid administration of oral PHT in alert patients may result in gastrointestinal upset, drowsiness, and “spacey” feelings.

In children, oral loading with PHT can be accomplished by administering four doses of 5 to 6 mg/kg at 8-hour intervals. With this regimen, plasma concentrations of 10 μg/mL or more are reached 16 to 38 hours after the first dose.

Administration of a loading dose of PHT via the intramuscular route is not possible using injectable sodium phenytoin (see above). However, a loading dose of PHT can be administered via the intramuscular route using fosphenytoin (see below).

Plasma Phenytoin Concentration as an Aid to Dose Adjustment

The average dosage (in milligrams per kilogram) required to achieve a given plasma PHT concentration is greater in children than in adults.[20,90] However, the plasma concentration produced by a given dose of PHT varies so much that it is impossible to predict a given patient's drug plasma concentration from the dosage.[90] Laboratory tests are the only assured method of determining a patient's drug plasma concentration.

The commonly provided target range provided by clinical laboratories for PHT plasma concentration is usually 10 to 20 μg/mL. The lower limit of 10 μg/mL is determined by the observation that the majority of patients with PHT plasma concentrations <10 μg/mL do not achieve good seizure control.[20,90] The upper limit of 20 μg/mL is determined by the observation that the majority of patients will show signs or symptoms of PHT intoxication with plasma concentrations above this value.[20,90] However, the range of 10 to 20 μg/mL is only a guideline or set of reference points. In a study of optimally managed patients, Schumacher et al.[171] found that approximately 25% of patients on PHT monotherapy had plasma concentrations in each of four groups: 5 to 10 μg/mL, 10 to 15 μg/mL, 15 to 20 μg/mL, and 20 to 25 μg/mL (Fig. 4). Other reports also confirm that some patients do best with PHT plasma concentrations above or below the provided range.[77,109] The use of plasma concentration monitoring as

a guide to dosage adjustment is discussed in more detail in Chapter 104.

Precautions

PHT should be used cautiously in patients with generalized epilepsies, due to the potential of precipitating or aggravating seizure types against which the drug is ineffective, particularly absence and myoclonic seizures. The use of PHT in patients with liver impairment also requires caution because of the increased likelihood of dose-related adverse effects. Observation for rash, especially after initiation of treatment, is warranted because of the possibility of a serious dermatologic reaction such as Stevens-Johnson syndrome or toxic epidermal necrolysis.

Contraindications

PHT is contraindicated in patients with known hypersensitivity to hydantoin drugs. Other contraindications include progressive myoclonic epilepsy of the Unverricht-Lundborg type[146a] and acute intermittent porphyria.

Because of its effect on ventricular automaticity, the intravenous use of phenytoin is contraindicated in sinus bradycardia, sinoatrial block, second- and third-degree atrioventricular block, and patients with Adams-Stokes syndrome.

Fosphenytoin

Chemistry

Fosphenytoin (disodium phosphate ester of phenytoin; ACC-9653; CI 982; Cerebyx) (Table 1) is a phosphate-ester prodrug of PHT developed as a replacement for standard injectable sodium PHT.[28] After absorption, PHT is cleaved from the prodrug by phosphatase enzymes. Fosphenytoin has a molecular weight of 406.3. Thus, 1.5 mg of fosphenytoin releases 1.0 mg of phenytoin. To simplify discussion, all fosphenytoin doses in this paper have been converted to “PHT equivalent doses” (fosphenytoin dose divided by 1.5). Unlike PHT, fosphenytoin is freely soluble in aqueous solutions (including standard intravenous solutions). The water solubility of fosphenytoin at 37°C is 7.5×10^4 μg/mL (vs. 20.5 μg/mL for PHT).[34] Because it is much more water soluble than PHT, fosphenytoin is formulated as a simple aqueous solution in trimethamine (Tris) buffer at pH 8.8.[142] In contrast, injectable sodium PHT is formulated with 40% propylene glycol and 10% ethanol in water adjusted to pH 12 with sodium hydroxide. The propylene glycol and high pH can cause local toxicity at injection sites (see below).

Pharmacology

The pharmacologic activity of fosphenytoin on the nervous system is via PHT released from fosphenytoin. The mechanism of action of PHT is discussed above.

Clinical Pharmacokinetics

Absorption

The extent of absorption (absolute bioavailability) of fosphenytoin has been determined by measurements of the ratios of the area under the plasma concentration versus time curve (AUC) for PHT derived from fosphenytoin versus the AUC values for standard injectable sodium PHT administered by the intravenous route. A ratio of 1.0 indicates complete bioavailability. In single-dose studies in drug-free volunteers by the intravenous[24,85] and intramuscular[24] routes and in single-dose intravenous studies in patients with therapeutic PHT plasma concentrations,[34] the AUC ratios obtained were close to 1.0. Bioavailability studies of drugs with nonlinear pharmacokinetics (such as PHT) present special difficulties, which have recently been reviewed.[28,34,36] Unlike intravenous administration, which has peak serum fosphenytoin concentration at the end of the infusion, the peak serum concentration of intramuscularly administered fosphenytoin occurs approximately 30 minutes after the injection. For both intravenous and intramuscular administration, the time of peak fosphenytoin serum concentration is not as clinically meaningful as the time of peak PHT serum concentration, which results from enzymatic conversion. When fosphenytoin is given intravenously, peak total (free + bound) PHT concentrations occur 30 to 60 minutes after starting the infusion, whereas peak free PHT concentrations occur at 15 to 30 minutes.[65a] The difference in time to peak between total and free PHT is due to the fact that fosphenytoin displaces PHT from its plasma protein-binding sites in a concentration-dependent manner.[65a] The peak in plasma PHT concentration after intramuscular injection of fosphenytoin occurs at about 1.5 to 4 hours, and it is significantly lower compared with the peak concentration produced by intravenous fosphenytoin or PHT.

Plasma Protein Binding and Distribution

Fosphenytoin is a very polar, water-soluble molecule with a volume of distribution of 0.04 to 0.13 L/kg, and it remains largely in the plasma compartment, distributing more widely after its cleavage into PHT and the phosphate moiety.[13,34,65a,99,103]

Fosphenytoin binds competitively to the same plasma protein-binding sites as PHT.[62,63,84] Thus, in the presence of fosphenytoin, the free PHT plasma concentration (for PHT derived from fosphenytoin or from previous administration) is higher than expected. The free PHT fraction increases with increasing fosphenytoin plasma concentration and with increasing fosphenytoin infusion rate (especially rates >50 mg/min). Prior administration of diazepam has no effect on the protein binding of fosphenytoin.[84]

Metabolism and Elimination

PHT is cleaved from fosphenytoin by phosphatase enzymes present in liver, red blood cells, and other tissues.[142] The half-life for conversion of fosphenytoin to PHT is approximately 8 to 15 minutes with modest interindividual variability.[3,14,19,24,28,34,63,68,103,142] The conversion half-life of fosphenytoin appears to be independent of plasma concentration of fosphenytoin or PHT.[19,24,34,63,103] The clearance of fosphenytoin is approximately 200 mL/min at lower dosing and infusion rates and increases to approximately 400 mL/min at higher dosing and infusion rates, presumably because of changes in distribution (see above).[19,24,34,63,103] The conversion half-life of fosphenytoin to PHT is shorter in patients with hepatic or renal disease, possibly because of differences in protein binding.[4]

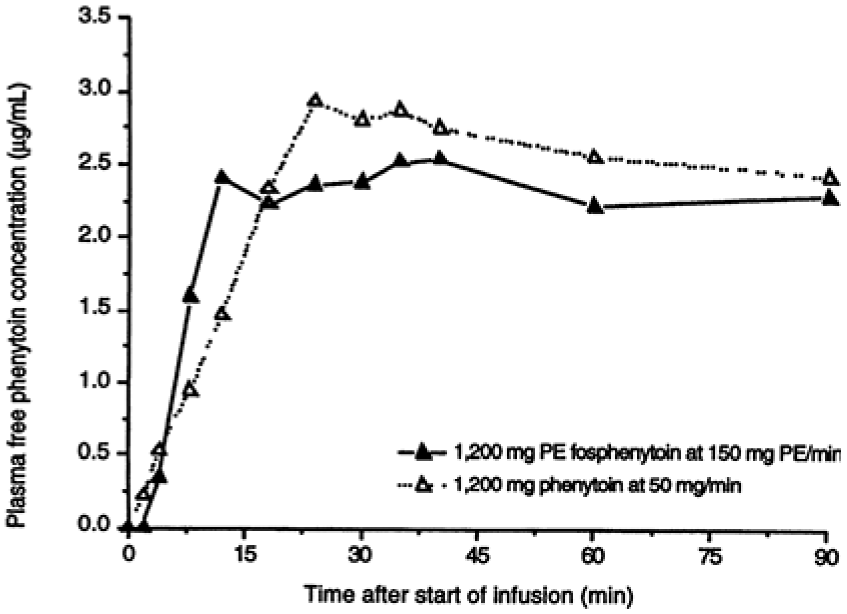

FIGURE 5. Mean free plasma phenytoin (PHT) concentration following administration of 1,200-mg doses of PHT and fosphenytoin (in PHT equivalents) to 12 healthy subjects. (From Browne TR, Kugler AR, Eldon MA. Pharmacology and pharmacokinetics of fosphe-nytoin. *Neurology*. 1996;46(Suppl 1):S3–S7. with permission.)

Direct renal excretion of fosphenytoin is small (0% to 4% of dose) and clinically insignificant.[34,142] PHT derived from fosphenytoin is eliminated in the same way as PHT administered as such.[19,24,34,103]

Efficacy

Being a prodrug of PHT, fosphenytoin has an efficacy profile equivalent to that of PHT.

Adverse Effects

Animal[93,177,197,199,200,205] and human[50,60,62,63,86,87,103,209] studies show convincingly that fosphenytoin causes fewer local adverse effects (burning and pain) when given by the intramuscular route (20% incidence, usually mild) or the intravenous route (<5% incidence, usually mild) compared with standard injectable sodium PHT. This is presumably a result of differences in the physicochemical characteristics of the formulations (see above).

Animal and human work indicates that most of the toxicity associated with fosphenytoin is attributable to enzymatically derived PHT.[19,43,50,62,63,74,97,103,168,177] The most common side effects reported for fosphenytoin in large clinical trials are nystagmus, headache, ataxia, and somnolence.[50,97] Pruritus or paresthesias of the groin, back, lower abdomen, head, or neck rarely occur during PHT infusions, but have been reported in 0% to 30% of volunteers or patients in various studies of parenteral fosphenytoin.[19,103,142] Pruritus and paresthesias usually occur during intravenous administration of higher doses and at higher dosing rates and rapidly resolve without sequelae.[19,103,142]

The maximum rate of infusion of standard sodium PHT for injection is determined by cardiac depression (hypotension, atrioventricular block). This rate is usually stated to be 50 mg/min, although there are no definitive published data to establish it. Similarly, the maximum rate of infusion of fosphenytoin is determined by cardiac depression, presumably from PHT derived from fosphenytoin. It has been found that infusion of fosphenytoin at a rate of 150 mg PHT equivalents/min produces free PHT plasma concentrations similar to those produced by standard injectable sodium PHT infused at 50 mg/min (Fig. 5). The incidence of cardiac depression with fosphenytoin infused at 150 PHT equivalents/min is similar to or less than the incidence with sodium phenytoin infused at 50 mg/min, possibly because of elimination of propylene glycol from the fosphenytoin preparation.[22]

Role in Epilepsy Treatment

Indications

Fosphenytoin is a valuable alternative to parenteral PHT. Its main indications are the treatment of status epilepticus and as parenteral replacement therapy for oral PHT in patients temporarily unable to take PHT orally.

Dosing Recommendations

Intravenous Treatment of Status Epilepticus.

The half-life for conversion of fosphenytoin to PHT is 8 to 15 minutes, potentially slowing its effectiveness in treating status epilepticus. However, this observation is offset by two other observations. First, fosphenytoin can be infused safely at a rate of 150 mg/min of PHT equivalents, whereas the maximum safe infusion rate for PHT is 50 mg/min. Second, the free fraction of plasma PHT is increased in the presence of fosphenytoin, especially at high fosphenytoin infusion rates. Volunteers and patients receiving fosphenytoin infusions at 150 mg/min have free PHT plasma concentrations equivalent (in time and extent) to those produced by standard injectable sodium PHT infused at 50 mg/min (Fig. 5).[28,62,63] As expected, the dosing rates of these two drugs produce similar systemic toxicity, but there is less local toxicity with the fosphenytoin preparation.[28,62,63]

The administration of fosphenytoin for status epilepticus is recommended in the FDA-approved prescribing information to be 15 to 20 mg PHT equivalents/kg intravenously at a rate of 100 to 150 mg PHT equivalents/min. A reduction of the infusion rate by 25% to 50% has been suggested when infusing fosphenytoin in patients with renal or hepatic disease, hypoalbuminemia, and the elderly.[65a] In all patients, continuous monitoring of electrocardiogram, blood pressure, and respiratory function is recommended during the infusion and for 20 minutes after the infusion has completed, although the risk of autonomic complications is less than that from intravenous PHT. Because of the delay related to the conversion of fosphenytoin to PHT, a benzodiazepine or other more immediate-acting antiseizure medication is recommended to be given concomitantly with fosphenytoin.

Intramuscular Loading Dose.

An intramuscular loading dose of fosphenytoin equivalent to 9 to 12 mg/kg of PHT will produce a maximum PHT plasma concentration of approximately 12 μg/mL 4 hours after injection.[50] These parameters are acceptable for management or prophylaxis of chronic epilepsy but not for status epilepticus. Intramuscular loading doses of fosphenytoin often need to be divided into two injection sites because of the associated large fluid volume.

Intramuscular Maintenance Dose.

After administering a loading dose of PHT (or in patients on chronic PHT therapy with therapeutic PHT plasma concentration values), therapeutic PHT plasma concentrations can be maintained with equimolar (equal to usual oral PHT dosing rate) doses of intramuscular fosphenytoin for at least 14 days.[50,58,209] When switching patients from oral PHT to equimolar doses of intramuscular fosphenytoin, however, plasma PHT levels may increase significantly, due to greater bioavailability of intramuscular fosphenytoin compared with oral PHT.[65a] Therefore, regular monitoring of PHT levels is recommended in these patients. Numerous studies report less local toxicity at injection sites with fosphenytoin than with PHT.[50,58,209]

Role of Plasma Level Monitoring.

Determinations of fosphenytoin plasma concentration are of little clinical value because fosphenytoin largely remains in the plasma compartment and is rapidly converted to PHT. However, methods for determination of fosphenytoin plasma concentration have been developed for research purposes.[68,103,168] For clinical purposes, fosphenytoin therapy can be monitored by measuring plasma PHT concentrations.

Ethotoin

Chemistry

Ethotoin (3-ethyl-5-phenylhydantoin; Table 1) is a white crystalline compound with a molecular weight of 204.22.[89] Ethotoin contains a chiral center at the 5 position of the hydantoin ring. The specific rotation of the *R* (-) enantiomer is 88 degrees. Ethotoin is insoluble in water but is soluble is most organic solvents. Published methods of detection include gas chromatography, mass spectrometry, and high-performance liquid chromatography (HPLC).[89]

Pharmacology

The addition of an ethyl group in position 3 and the deletion of one phenyl group from position 5 in the hydantoin ring (Table 1) result in a compound that is both less potent against maximal electroshock seizures in animals and less toxic than PHT.[89,128] Ethotoin has some activity against pentylenetetrazol seizures in animals but has proved to have little effect on absence seizures in patients.[46,89,128] The mechanisms of action of ethotoin have not been studied but may be similar to those of PHT.

Clinical Pharmacokinetics

Peak plasma concentrations of ethotoin occur 2 to 4 hours after oral doses.[89,190] Ethotoin is 46% protein bound.[190] The elimination half-life of small, single doses of the drug is 3 to 12 hours, and the drug has no active metabolites.[82,89,190] The absorption and elimination of the two isomers of ethotoin are similar.[82] Therefore, the package insert states that ethotoin must be given in four or more divided doses to minimize fluctuations between peak and trough plasma concentrations.

The major metabolic pathway of ethotoin is ring hydroxylation, similar to PHT.[89] Also similar to PHT, ethotoin appears to have nonlinear pharmacokinetic properties.[82,126,213] Because drugs with nonlinear pharmacokinetic properties have longer elimination half-lives at steady-state plasma concentrations than at the low plasma concentrations of single-dose studies, it may be possible to administer ethotoin three times daily.[30] The details of ethotoin metabolism have been reviewed recently elsewhere.[89]

Efficacy

There are no controlled trials of ethotoin. Uncontrolled studies indicate that ethotoin has some efficacy against tonic–clonic and complex partial seizures but probably does not control such seizures as efficiently as PHT.[46,128,172] The lack of efficacy of ethotoin may be related in part to the large doses necessary to obtain seizure control and to the necessity to administer the drug in four to six divided doses daily. The drug has little or no efficacy against simple partial and absence seizures.[46,128]

Adverse Effects

Side effects occur less frequently than with PHT and include rash (2%), anorexia and vomiting (3%), drowsiness, nystagmus, and occasionally lymphadenopathy.[128] Ataxia occurred only with large doses.[128] Gingival hyperplasia has not been reported.[128] Congenital malformations similar to those associated with PHT have been reported in association with ethotoin.[65]

Role in Epilepsy Treatment

Indications

Ethotoin is approved by the FDA for the treatment of tonic–clonic and complex partial seizures. However, due to the lack of sound evidence for efficacy from controlled trials, ethotoin is very rarely used in the current treatment of epilepsy. Uncontrolled reports have suggested that ethotoin may be used for the treatment of patients with (a) tonic–clonic seizure disorders and hypersensitivity to more potent agents[128]; (b) refractory partial or generalized seizures[12,126]; and (c) good therapeutic effect but cosmetic side effects with PHT. However, due to the availability of many alternative agents with better documented efficacy and safety, switch to ethotoin therapy rarely is justified.

Dosing Recommendations

In adults, the initial dose should be 1,000 mg/day or less. Dosage is then gradually increased for several days until the optimal dosage is reached. Most adults require 2,000 to 3,000 mg daily. Doses of <2,000 mg/day seldom are effective.

In children, the initial dose should be 750 mg/day or less. The usual maintenance dose is 500 to 1,000 mg/day, although daily doses of up to 3,000 mg are sometimes necessary.

Ethotoin usually is administered in four to six divided doses daily because of its short elimination half-life in single-dose studies. The drug should be taken after meals, and the doses should be divided as evenly as possible. The optimal range of ethotoin plasma concentration is estimated at 15 to 50 μg/mL.[42,96,191] Because of the concentration-dependent pharmacokinetics, it may be possible to administer ethotoin three times per day once steady-state plasma concentration has been reached.[30]

Mephenytoin

Chemistry

Mephenytoin is a white crystalline substance with a molecular weight of 218.25 (Table 1). Because of the asymmetric carbon atom at position 5 of the hydantoin ring, mephenytoin is produced as a racemic mixture. The chemical details of the isomers of mephenytoin have been reviewed elsewhere.[89] Mephenytoin, Nirvanol (active metabolite), and other mephenytoin metabolites can be quantified by HPLC,[89] and other methods exist to quantify the enantiomers of these molecules.[89]

Pharmacology

N-methylation at position 3 in the hydantoin ring and substitution of an ethyl for one phenyl group at position 5 provide a broader spectrum of action in animal screening tests for antiepileptic activity than PHT. Mephenytoin has some protective effect against pentylenetetrazol seizures, whereas PHT does not.[89,128] However, these structural changes in mephenyt-oin also result in greater neurotoxicity and smaller potency and protective index against maximal electroshock seizures than seen with PHT.[89,128] The basic mechanisms of action of mephenytoin have not been studied but may be similar to those of PHT.

Clinical Pharmacokinetics

Peak plasma concentrations of mephenytoin occur 45 to 120 minutes after an oral dose.[89,190] Mephenytoin is partly hydroxylated, and partly demethylated to the active metabolite Nirvanol (5-ethyl-5-phenylhydantoin).[89,185,190] Nirvanol is partly eliminated by renal excretion and partly by *p*-hydroxylation and glucuronide formation.[89,209a] A number of other minor metabolic pathways of mephenytoin have been reported.[89] The protein binding of mephenytoin is 39%, and that of Nirvanol is 29%.[190]

There is a marked enantioselectivity in the metabolism of mephenytoin. While the S-enantiomer is rapidly hydroxylated by CYP2C19 and eliminated with a half-life of about 1 hour, the R-enantiomer has a half-life of about 70 hours and is slowly demethylated to R-Nirvanol, which, in turn, is eliminated very slowly (half-life of 150 to 200 hours), mostly by renal excretion, and accumulates in plasma at concentrations much higher than those of the parent drug.[89,190,191] Subjects with genetically determined CYP2C19 deficiency (about 4% of Caucasians and 20% of Japanese) do not hydroxylate S-mephenytoin efficiently and, as a result, both enantiomers are converted to Nirvanol. S-Nirvanol derived from S-mephenytoin in these subjects is also cleared more slowly, and also accumulates at high concentrations.[89,204a,209a] Because of the high levels of S-mephenytoin and Nirvanol in poor CYP2C19 metabolizers, these subjects are at increased risk for concentration-dependent toxicity. Because of the long elimination half-life of Nirvanol, mephenytoin needs to be given only once or twice a day, and many weeks may be required to reach steady-state plasma concentrations.[191,209a]

Efficacy

There have been no controlled clinical trials of mephenyt-oin. Uncontrolled trials reported that a majority of patients with tonic–clonic or simple partial seizures will experience a considerable reduction in seizure frequency with mephenyt-oin, whereas only a minority of patients with complex partial seizures respond favorably.[46,89,128] Absence seizures do not seem to be affected.[46,128]

Adverse Effects

Compared with PHT, mephenytoin causes less ataxia, less gingival hyperplasia, and less nausea and vomiting.[128] These advantages are offset by a greater incidence of drowsiness, serious dermatitis, agranulocytosis, aplastic anemia, and hepatitis.[128] The incidence of fatalities and serious side effects appears to be greater with mephenytoin than with PHT.[128,191] The package insert should be consulted for instructions on monitoring for adverse affects.

Drug Interactions

The drug interactions of mephenytoin are numerous and complex.[190,191] Autoinduction of metabolism of mephenyt-oin and Nirvanol occurs, leading to a downward drift of plasma concentration of both drugs with chronic administration. Also, mutual induction of metabolism occurs when mephenytoin is coadministered with carbamazepine or barbiturates. At low plasma concentrations of mephenyt-oin, Nirvanol, and PHT, there is mutual induction of biotransformation (with a fall in drug plasma concentrations), whereas at high plasma concentration, there is mutual inhibition of biotransformation (with an increase in drug plasma concentrations).

Role in Epilepsy Treatment

Indications

Mephenytoin is approved by the FDA for treatment of tonic–clonic, simple partial, and complex partial seizures. Because of the availability of safer, newer drugs, mephenytoin is used very rarely in the current treatment of epilepsy.

Dosing Recommendations

The initial dosage is 50 to 100 mg/day during the first week. The daily dosage is then increased by 50 or 100 mg at weekly intervals until seizure control is obtained or toxicity precludes further increases. Increases in dosage should not be made more often than once a week. Because of the toxicity of mephenytoin, one should attempt to control seizures with the smallest possible dose. The average daily dose required is 200 to 600 mg in adults and 100 to 400 mg in children.

Total combined mephenytoin plus Nirvanol plasma concentration must be determined for therapeutic drug monitoring. Total concentrations of 1.5 to 40 μg/mL have been reported for patients having a good response.[172,190,191]

Summary and Conclusions

PHT is a well-established option for the initial treatment of partial and generalized tonic–clonic seizures. It possesses proven efficacy and, in its extended-release formulation, may be administered once daily for many adults. Prescribers of PHT should be familiar with its nonlinear pharmacokinetic properties, its potential drug interactions, and its several formulations. PHT is an important therapy for status epilepticus, and fosphenytoin is a parenterally administered PHT prodrug that offers some advantages in terms of local tolerability and safety over injectable formulations of PHT. Ethotoin has been reported to be of benefit in treating complex partial and tonic–clonic seizures, but there are no controlled trials supporting this claim and its usage is limited by labeling indicating administration four to six times per day. Mephenytoin has also been reported to be effective for the treatment of partial and tonic–clonic seizures, based on results of uncontrolled trials. However, its use is limited by a number of side effects including

drowsiness, dermatitis agranulocytosis, aplastic anemia, and hepatitis.

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Chapter 155

Pregabalin

Gregory K. Bergey

Introduction

Pregabalin is the most recent antiepileptic drug (AED) introduced in the United States; it received approval as adjunctive therapy for partial seizures in 2005. Pregabalin has also been approved for treatment of neuropathic pain associated with diabetic neuropathy[55,57] and postherpetic neuralgia.[22,59] Several controlled trials have been done with pregabalin in generalized anxiety disorder (GAD), and approval for GAD exists in other countries, but not in the United States.[44,45,48,49,52] Pregabalin is a congener of gabapentin (Chapter 149), an AED approved in 1994.[60] Although pregabalin and gabapentin share certain features, important distinctions also exist. Because these two compounds are chemically related, and there is considerable experience with gabapentin, this chapter will specifically include a discussion of the similarities and differences between the two drugs, where they are known. Although comments regarding efficacy will be limited to the epilepsy studies, discussion of adverse reactions will, where appropriate, include the pain and anxiety studies, because these provide additional information from controlled studies.

Chemical Structure, Formulations, And Methods For Determination In Body Fluids

Pregabalin (Lyrica) is S-3-(aminomethyl)-5-methylhexanoic acid, a compound with a molecular weight of 159.23.[3] It is freely soluble in water. Although a structural analog of γ-aminobutyric acid (GABA) (Fig. 1), the additional side chain alters the distance between the GABA subunit terminals, with the net result that it is not a GABA mimetic. Gabapentin has a ring structure whereas pregabalin is a branched structure. Pregabalin development was the result of screening gabapentin analogs to develop an agent with greater antiepileptic efficacy, first by studies of inhibition of [3 H] gabapentin binding and then by animal studies.[8] The S-isomer binds to the α-2-δ receptor, the same receptor involved in gabapentin-specific binding.[12] Although freely soluble in water, at present approved formulations are only capsules. Development of liquid formulations are in progress, and the potential for a parenteral formulation exists. Therapeutic levels have not yet been established, but pregabalin can be assayed in plasma and other fluids using high-performance liquid chromatography.[10]

Pharmacology

Mechanism of Action

Like gabapentin, pregabalin binds to the α-2-δ subunit of voltage-gated calcium (P/Q) channels, and allosterically modulates calcium (Ca) influx, reducing it by up to 40%—with the greatest reduction occurring in states in which high neuronal activity is present.[63] There are four subtypes of the α-2-δ subunit; pregabalin binds to subtypes 1 and 2 only. This modulation has been shown to reduce the presynaptic release of neurotransmitters, including noradrenaline,[20,21] substance P,[26] and the excitatory amino acid glutamate.[19,42] These effects require binding of pregabalin at the α-2-δ subunit. Although the α-2-δ type 1 knockout is a lethal mutant, studies have been performed using the R217 A knock-in mice with α-2-δ type 1 receptors that have preserved function but markedly reduced binding of pregabalin,[12,63] especially in the neocortex, hippocampus, basolateral amygdala, and spinal cord. In these mice, pregabalin has no benefit on pain, and has reduced anxiolytic and antiepileptic effects.[28,63] These studies supplement the binding studies by showing that binding of pregabalin to the α-2-δ receptor is necessary for maximal therapeutic effects. In addition, in cultured hippocampal neurons, some evidence suggests that the effects of pregabalin on synaptic vesicular release are greatest before and early in the course of a train of electrical stimuli.[42] In neuromuscular preparations, pregabalin reduced nerve-evoked muscle contractions by 16%.[38] When pregabalin cannot bind to the α-2-δ receptors, as in mutant R217 A mice, it has no effect. There has been no demonstrated effect of pregabalin on L-type Ca channels in muscle. α-2-δ Type 1 and 2 receptors are present outside the central nervous system (CNS) (e. g., in spleen, liver, lung) but at much lower concentrations.[61]

Despite the structural similarity of pregabalin to the inhibitory amino acid GABA, the addition of the side chain changes the configuration of the GABA subunit, with the net result that no binding to pre- or postsynaptic GABA (A or B) receptors occurs.[51,62] Pregabalin does not have any GABA mimetic properties, and there is no effect on GABA or chloride flux. In addition, brain GABA levels are not significantly altered by pregabalin,[24] and there is no effect on GABA uptake or degradation. Studies to date have not revealed significant effects of pregabalin on other known antiepileptic mechanisms (e.g., voltage-dependent sodium conductances), nor is there evidence that pregabalin affects the postsynaptic responses of any neurotransmitters. Therefore, at present, pregabalin appears to have a specific binding site that modulates and reduces the presynaptic release of neurotransmitter through a mechanism of action that does not depend on any GABAergic actions.

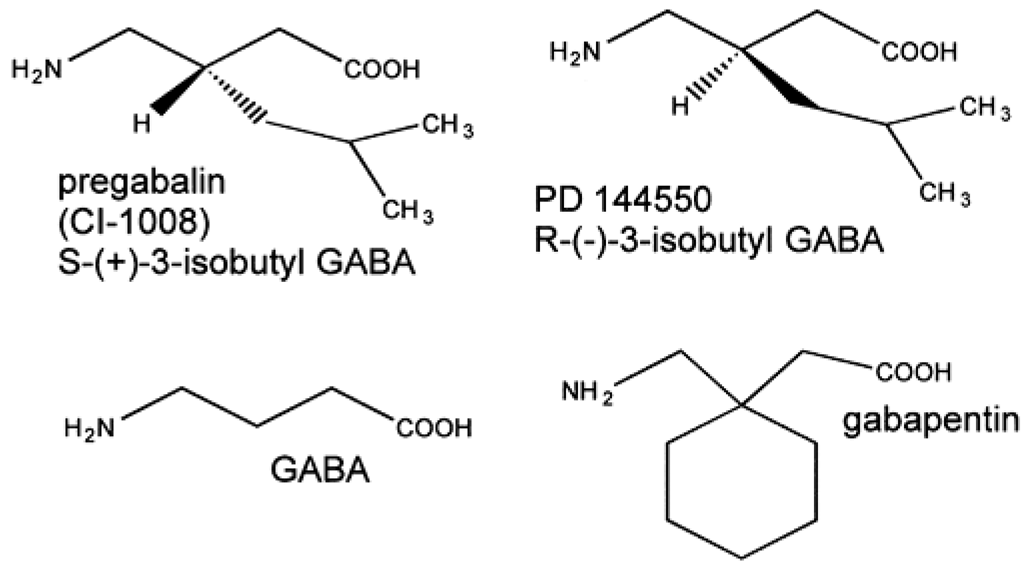

FIGURE 1. Chemical structures of gabapentin and pregabalin (3-isobutyl GABA) and the inhibitory neurotransmitter GABA.

Activity in Experimental Models of Epilepsy

The efficacy of pregabalin has been investigated in various animal models of epilepsy.[63,64] Pregabalin potently inhibits tonic extensor seizures in the electroshock model (ED50 = 1.8 mg/kg, administered orally), and it also prevents tonic extensor seizures in the DBA/2 audiogenic mouse model (ED50 = 2.7 mg/kg, administered orally). The time course of action of pregabalin reflects the time course of radiolabeled drug in the CNS. In a kindled rat model of partial seizures, pregabalin prevented the more fully evolved stage 4 and 5 behavioral seizures (lowest effective dose 10 mg/kg, intraperitoneally) and also reduced the duration of the electrographic discharges. All these are models of partial epilepsy or models that predict AED efficacy in partial epilepsy (maximum electroshock; MES).

At much higher doses (ED50 = 31 mg/kg, orally), pregabalin prevented seizures in the pentylenetetrazole (PTZ) model of epilepsy in mice. However, pregabalin did not prevent spontaneous absence-like seizures in the genetic absence epilepsy rats from Strasbourg (GAERS) and, in fact, seizures actually increased.[64] At one time, it was thought that AED efficacy in the PTZ model predicted anti-absence efficacy, but more recently[35,36] this has not been thought to be as reliable as the various genetic models for testing anti-absence efficacy of AEDs. Pregabalin does not appear to have significant anti-absence efficacy.

In one study[4] using the lithium pilocarpine model of status epilepticus in rats, early treatment with pregabalin delayed the appearance of later epilepsy and reduced neuronal damage in the piriform cortex and entorhinal cortex but not the hippocampus. At present, however, insufficient evidence is available to conclude that pregabalin is neuroprotective or antiepileptogenic; additional studies are needed.

Clinical Pharmakokinetics

Absorption

When fasting, oral bioavailability of pregabalin is excellent with >90% absorbed within 1 to 1.5 hours.[14] Absorption is linear for both single doses up to 300 mg and multiple doses up to 900 mg/day (Fig. 2). This is an important difference and advantage of pregabalin compared with gabapentin, which is absorbed slowly, reaching peak doses in 3 to 4 hours. Although both compounds are transported across the gut and blood–brain barrier by an L-amino acid transport system, pregabalin has linear kinetics across and even above the clinical dosing range. This is quite different from the case with gabapentin, where even a 900 mg daily dose, given as 300 mg three times a day, has only 60% bioavailability, and a 3,600 mg daily dose has only 33% bioavailability when given as 1,200 mg three times a day.[14] In comparing these two compounds, dose ranges of gabapentin from 900 mg to 3,600 mg per day and of 150 mg to 600 mg per day of pregabalin are commonly used, recognizing that these doses exceed the maximum approved dose for gabapentin in the United States (1,800 mg/day). Although the rate of pregabalin absorption is decreased slightly with food, the total amount absorbed is not affected.

Plasma Protein Binding and Distribution

Like gabapentin, pregabalin has negligible protein binding. The volume of distribution is approximately 0.5 L/kg.[3]

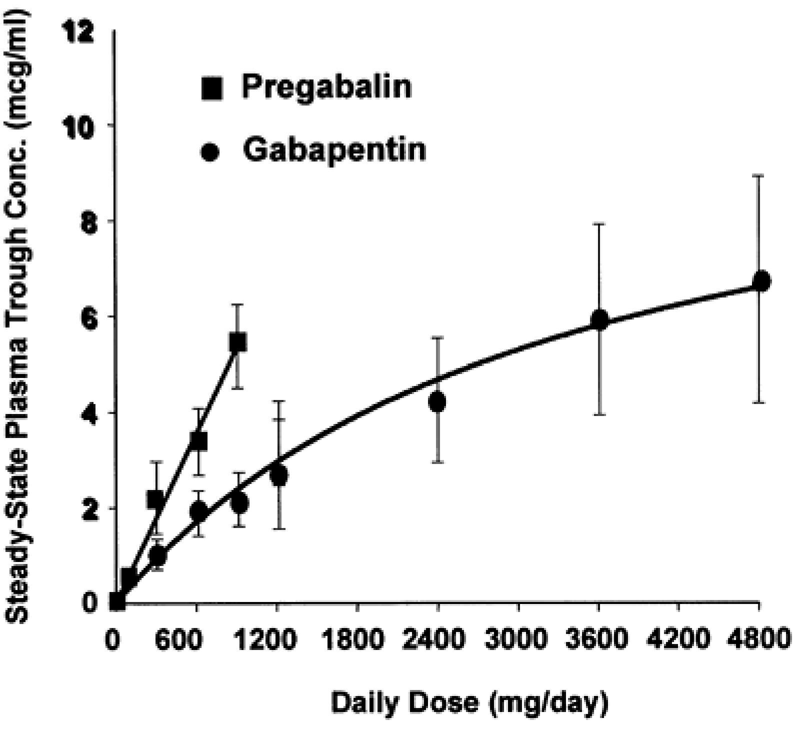

FIGURE 2. Comparison of gabapentin and pregabalin pharmacokinetics. (Bockbrader H MR, Spiegel K, Barrett J, et al. The Pharmaco-kinetic and pharmacodynamic properties of pregabalin and gabapentin in epilepsy. Differences and similarities. *Elepepsia.* 2005;46(Suppl 8):261. used with permission.)

Metabolism

Pregabalin is not metabolized significantly; more than 90% is excreted unchanged in the urine. Pregabalin is not metabolized in the liver to any extent, nor does it induce or inhibit any of the P450 isoenzymes.[3,9] The major metabolite, an *N*-methylated derivative, accounts for <1% of the dose.

Elimination

Elimination of pregabalin is primarily renal; the drug has a mean elimination half-life of 6.3 hours. Pregabalin clearance is proportional to creatinine clearance (CLcr), and patients with renal insufficiency (CLcr <60 mL/min) will need appropriate dose reductions. A 50% reduction in dose is recommended

for patients with a CLCr between 30 and 60 mL/min.[54] Because of pregabalin's low protein binding, it will be removed by hemodialysis, and postdialysis adjustments may need to be made. Elderly patients with reduced CLcr will have proportionately reduced pregabalin clearance.

Relationships Between Plasma Concentration and Effects (Including the Value of Therapeutic Drug Monitoring)

Therapeutic levels for pregabalin have not been established, and there are no recommendations for monitoring of plasma levels. Because of the 6-hour half-life, steady-state levels are achieved rapidly after initiation or dose adjustment, in about 30 hours (five half-lives). Arroyo et al.[6] found that steady-state doses of 150 mg/day produced mean plasma pregabalin levels of 1.27 µg/mL (range 0.29–2.84 µg/mL), and doses of 600 mg/day produced mean plasma pregabalin levels of 4.88 µg/mL (range 0.87–14.2 µg/mL).[34] The dose range study of French et al. had similar findings.[32] Beydoun et al.[11] reported that 600 mg, given three times a day, produced mean plasma pregabalin levels of 5.82 µg/mL (range 0.38–18.2 µg/mL); twice-daily dosing produced mean plasma pregabalin levels of 6.84 µg/mL (range 0.32–14.80 µg/mL). Although twice-daily dosing resulted in higher peak levels and lower daytime trough levels than the three-times-daily regimen, morning trough levels were similar in both groups. Efficacy in reducing seizures correlated with these mean levels. Because of pregabalin's rapid elimination, it would be expected that broad fluctuations in serum levels would occur even at steady state, and this is reflected in the broad ranges of plasma levels obtained for a given dose. This characteristic reduces the utility of random pregabalin sampling except to document compliance. It is possible that morning trough levels of pregabalin might be useful, but the range of such levels has not been established. It is not known how the pharmacokinetic profile of pregabalin in the serum relates to the pharmacodynamic profile in the CNS. The fact that efficacy with twice-daily dosing is not significantly different from three-times-daily dosing suggests the possibility of a pharmacodynamic effect distinct from plasma pharmacokinetics, but this has not been studied.

Efficacy

Pregabalin's efficacy in reducing seizures has been studied in three double-blind controlled pivotal trials involving a total of 1,052 patients with intractable partial epilepsy.[6,11,32] Although the criteria for entry into these trials were similar to other new AED trials—three seizures per month and failure with one AED—patients enrolled in the pivotal trials had frequent seizures and highly refractory epilepsy, with an average duration of epilepsy of 24 to 25 years, a mean monthly seizure frequency of 22, and a median monthly seizure frequency of 10. Approximately half the patients randomized to pregabalin were already taking two AEDs, and another quarter were on three AEDs, meaning that, during the actual trial, 75% of patients receiving active compound were taking three or four AEDs, including pregabalin. As predicted by pregabalin's lack of known interactions with any AEDs, no significant effects on concomitant AEDs were observed.

One study[32] was a dose-ranging study using from 50 mg/day to 600 mg/day given twice daily. A second study[6] compared placebo with 150 mg/day and 600 mg/day of pregabalin given three times a day, and a third study[11] directly compared 200 mg three times a day with 300 mg twice daily. The primary outcome variable in the first two studies was reduction of seizure frequency measured by the RRatio. The RRatio is defined as $[(T - B) / (T + B)] \times 100$, where B is the patient's 28-day baseline seizure frequency, and T is the patient's 28-day seizure frequency during treatment. Although statistically rigorous, the RRatio yields numbers ranging from –100 to +100, with a value of –100 equivalent to no seizures and –33 equivalent to a 50% reduction in seizures. The RRatio was statistically significant for pregabalin doses of 150 mg/day and above. Doses of 50 mg/day did not produce significant reductions in seizures. Because these numbers are difficult to equate with clinical situations, most of the discussion here will focus on the more clinically relevant measures: seizure frequency and responder rates (here defined as a 50% reduction in seizures).

Converting the RRatio data to seizure frequency and responder rate yields similar results, although in one instance, the 150 mg/day dose in the Arroyo et al. study, the *p* value was not quite significant ($p < 0.08$). However, the number of seizures at this dose was significantly reduced. Indeed, the seizure numbers paralleled the illustrated responder rates. At the highest total daily dose, 600 mg per day with twice-daily or three-times-daily dosing, results were remarkably consistent from trial to trial, with responder rates of 43% and 51%, respectively. Although caution is warranted about extrapolating from one series of clinical trials to another, these responder rates at 600 mg/day of pregabalin compare favorably with the best results obtained with other new AEDs in similar patient populations characterized by highly refractory partial seizures.[30]

Although seizure control is the goal of treatment, becoming seizure-free with any new AED is extremely rare in such patients, and therefore one should be cautious about conclusions claiming seizure freedom based on short clinical trials. Brodie[15] reports this short-term seizure free data in his recent review. Seizure-free rates ranged from 3% to 17% at all effective dose ranges (150 mg–600 mg/day) during the last 28 days of the trial. At the highest dose (600 mg/day, given in a divided dose three times a day), 11% of patients achieved seizure freedom during this interval.

No significant differences were noted between twice-daily and three-times-daily dosing, either in the trial using direct comparison between 200 mg three times a day and 300 mg twice daily,[11] or comparing across trials. FIGURE 3 illustrates the responder rates for these trials, specifically 43% versus 49% in the twice- versus three-times-daily direct comparison. The reduction in seizure number was 44% for 300 mg twice daily and 51% for 200 mg three times a day (p = not significant [NS]). Based on these studies, pregabalin received approval for twice-daily or three-times-daily dosing. The lack of significance between the two dosing regimens may reflect pharmacodynamic effects at the CNS receptor that are different from the plasma half-life of 6 to 7 hours. One commentary[25] speculated that the study was not sufficiently powered to detect a difference (something acknowledged by the authors of the original paper), and that showing that there is no difference is not the same as proving equivalence. This remains a possibility, although the number of patients in this study was similar ($n = 313$ entering) to the other two studies. Many more patients would probably be needed to demonstrate any difference, if indeed such a difference exists.

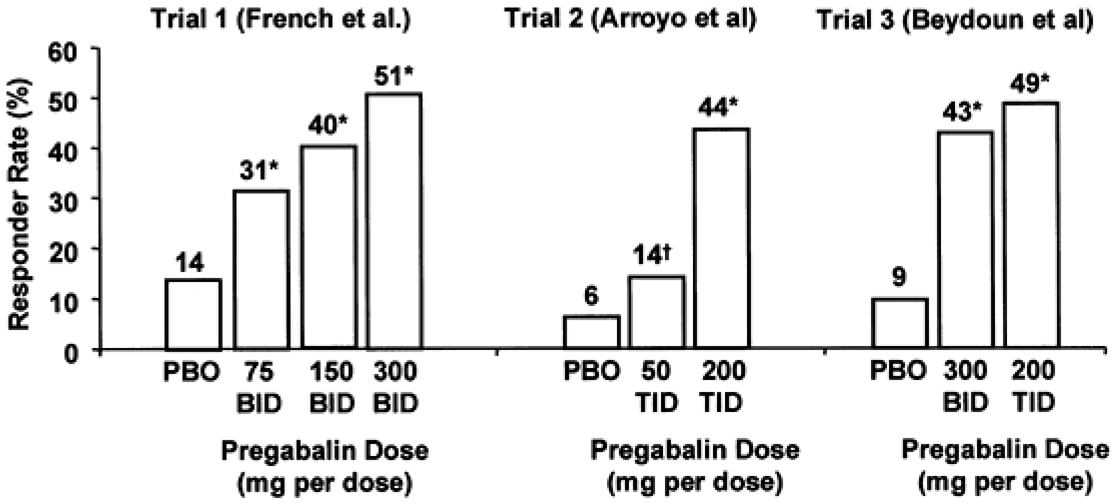

FIGURE 3. Responder rates (patients with >50% reduction in seizures compared to baseline) for the three pivotal epilepsy trials. PBO, placebo, $*p \leq 0.01$, † $p \leq 0.08$. As noted, the pregabalin amount is per dose (e. g., 300 mg twice daily = 600 mg daily).

To address whether certain subgroups (e.g., those with less frequent seizures or more readily reduced seizures) were more likely to respond to pregabalin, analyses were performed examining patient groups by number of concomitant AEDs and average number of seizures. There was no significant difference in response whether patients were taking one, two, or three other AEDs. There was no difference in response based on seizure frequency (stratified from <5 seizures/month to >23 seizures/month). There is no evidence, therefore, that pregabalin responders were patients with less severe or less refractory epilepsy. Having said this, there may be subgroups who respond better than others. A model of exposure–response

analysis of pregabalin response in the three pivotal trials revealed that 25% of patients did not have a significant decrease in seizure frequency, whereas 75% had a dose-related decrease.[43] In the 75% who had significant seizure reduction, less than 200 mg/day was expected to reduce seizures by 50%. The characteristics of patients who might be more likely to experience a reduction in seizure frequency with pregabalin therapy have not been determined.

In another well-controlled, double-blind study comparing a fixed dose of pregabalin (600 mg/day using twice daily dosing) with flexible dosing, the fixed-dose arm achieved highly significant reductions in RRatio and seizure number.[23] The fixed-dose arm achieved a 49.3% seizure reduction, and 45.3% of patients had a >50% reduction in seizures, very similar to the three pivotal trials. In the flexible arm (average daily dose at conclusion of study was 508 mg/day), seizure reduction was 35.4%. This study provides further evidence for efficacy using a twice-daily dosing regimen.

The 600 mg/day dose appears to have been an appropriately selected upper range. Subjects have taken up to 900 mg/day on a regular basis, but a higher incidence of side effects was observed. There are no studies of efficacy at these higher doses.

In contrast to the pregabalin trials, the three pivotal trials that led to approval of gabapentin as adjunctive therapy for partial seizures had responder rates of 22% to 28% at the highest doses for each trial.[1,2,5] The highest dose utilized was 1,800 mg/day in divided doses. Although higher doses may well have resulted in greater efficacy, this has not been demonstrated in double-blind trials. The nonlinear absorption of gabapentin resulting from the rate-limiting L-amino acid transport becomes much more significant at higher gabapentin doses. A dose of 3,600 mg/day of gabapentin (a commonly used dose in clinical practice, although outside of the U. S. Food and Drug Administration [FDA]-approved dose range), given as a divided dose three times a day, has only 33% bioavailability.[14] These pharmacokinetic characteristics of absorption make it less likely that higher doses of gabapentin would have produced responder rates comparable to those of pregabalin, although direct controlled trials comparing the efficacy of pregabalin to gabapentin have not been done.

Adverse Effects

The parallel pivotal controlled trials of pregabalin in epilepsy, pain, and anxiety resulted in a larger cohort of patients to assess adverse events than if only epilepsy studies were performed. However, it should be recognized that these patient populations may differ significantly. For example, patients with diabetes will typically be older and have more significant medical comorbidities than will epilepsy patients. Postherpetic neuralgia is also much more common in the elderly.

In any assessment of adverse events, it is important to separate safety-related side effects from other complications. Gabapentin is an extremely safe medication. The American Academy of Neurology (AAN) review of new AEDs in 2004 concluded that gabapentin was one of only two AEDs with no associated serious adverse effects.[31] Pregabalin had not yet been approved at the time, and whether pregabalin will enjoy an equivalent safety record is now being determined. Because pregabalin has been approved for both pain and epilepsy in the United States and, additionally, for anxiety in the European Union, many more patient exposures have occurred than would have occurred in the same time for epilepsy alone. To date, over three million patient exposures to pregabalin have occurred, and no safety-related side effects have been attributed to the drug.

Dose-Related, Nonidiosyncratic Adverse Effects

Most dose-related adverse events with pregabalin involve nonspecific CNS side effects, many of which occur at the time the drug is started and either abate with time or can be reduced in severity with more gradual titration. Table 1 lists the most common adverse events reported in the controlled clinical trials for epilepsy. Nonspecific CNS side effects (dizziness, somnolence, ataxia, and blurred vision) were most common, and resulted in 15% of participants taking pregabalin withdrawing from the trials, compared with 6% of those taking placebo.

Some of these side effects may reflect initiation side effects related to the fixed-dose nature of the trial design, which was different from the gradual titration typical of clinical practice. In the pregabalin flexible-dose study,[23] 33% of the fixed-dose group (600 mg/day) withdrew due to an adverse event, compared to 12% of the flexible-dose group and 7% of the placebo group. The two most common treatment-emergent side effects were dizziness and ataxia. Dizziness was reported in 43% of the fixed-dose group and resulted in a 14% withdrawal rate, compared with 24% of the flexible-dose group and 5% discontinuations. Ataxia occurred in 21% and 9% of the fixed-dose and flexible-dose groups, respectively, resulting in 13% and 3% discontinuations, respectively.

Table 1 Discontinuation Rates Due to Adverse Effects (AEs) in Pregabalin Epilepsy Studies

	Percentage of patients		
	Incidence of AEs*	Discontinuation* (treatment group)	Discontinuation* (placebo group)
Dizziness	32	6	<1
Somnolence	22	3	0

Ataxia	15	3	<1
Weight gain	14	<1	0
Blurred vision	10	2	0
Diplopia	9	2	1
Tremor	8	2	0
Thinking abnormal	8	2	0
Increased appetite	5	<1	0
Peripheral edema	5	<1	0
Amnesia	5	<1	0
Speech disorder	5	1	0

*Excludes 50 mg/day dosage.

Lyrica® (pregabalin) capsules CV [package insert]. New York, NY: Pfizer Inc; 2005; Data on file, Pfizer Inc.

Further support that most nonspecific CNS side effects with pregabalin are initiation-related is provided by an analysis of the duration of adverse events in patients participating in the double-blind trials.[7] By week 2, the incidence of dizziness dropped to 2.7% for all doses, and for weeks 2 to 12, it was 1.6% in the groups taking 300 mg twice daily compared to 27.7% reporting dizziness in the first week in this group. Similar changes were seen in reports of sleepiness and ataxia. The lower incidence of side effects was not due just to patient withdrawal; the intensity of adverse effects did not affect their duration.

Weight Gain

In the double-blind pivotal trials for epilepsy, weight gain (defined as ≥7% of baseline) occurred in from 5% (150 mg/day) to 16% (600 mg/day) for the various dose groups (10.4%) overall. This was slightly higher than that seen in the trials for diabetic neuropathic pain or postherpetic neuralgia, in which only 6% and 7% of those patients taking 600 mg/day of pregabalin gained weight. Weight gain, however, resulted in withdrawal from the studies in <1% of participants. The average weight change in all patients in the controlled trials for epilepsy was 2.1 kg.[15] In a postmarketing survey from a single center of 40 patients taking an average of 2.7 concomitant AEDs, 56% reported some weight gain, with the mean weight gain being 4.6 pounds and the median weight gain, 4.6 pounds.[53] In this short-term study of several months' follow-up, 22% of patients reported weight loss (average 4.6%). In the pivotal trials for epilepsy, 2.9% of patients taking gabapentin had weight gain but, as mentioned earlier, these trials had 1,800 mg as a maximum dose.

Idiosyncratic Reactions

Hypersensitivity reactions associated with pregabalin administration are uncommon; less than 1% of the patients in the three pivotal trials had rashes, and similar low incidences were reported in the neuropathic pain and anxiety trials. No severe hypersensitivity reactions (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis) have been reported.

Teratogenicity

The data on pregabalin in human pregnancy are insufficient at this time to establish the safety of pregabalin in pregnancy. It is classified as pregnancy category C (no human data). Animal data have not shown any malformations at plasma levels up to two times that achieved in humans taking 600 mg/day. Decreased ossification, body weight, and organogenesis in animals was demonstrated at plasma exposures 5 to 16 times levels seen in humans at the maximum recommended dose (600 mg/day).[3]

Based on human studies with gabapentin[47] and animal studies with pregabalin,[3] it is anticipated that pregabalin will be excreted in human breast milk. In one small study of six breast-fed infants, plasma concentrations of gabapentin were 12% of the mothers' plasma levels, and no adverse effects were seen.[47] Pregabalin excretion and concentrations in breast milk would be expected to be similar to gabapentin. General guidelines for breast-feeding for mothers with epilepsy recommend breast-feeding while on AEDs unless this produces sedation in the infant. Even with the limited available human data from pregabalin, it is reasonable to recommend breast-feeding for women taking pregabalin who desire to breast-feed, because the multiple benefits of breast-feeding to the child are well known.

Carcinogenicity

Hemangiosarcomas were seen in a dose-dependent relationship in two strains of mice treated with 200 to 1,000 mg/kg per day of pregabalin for 2 years; the lowest dose produced plasma levels comparable with 600 mg/day in humans.[3] No similar tumors have been found in other animal tests, and none has been reported in humans, either in pre- or postmarketing studies and surveillance.

Table 2 Pregabalin and Gabapentin: Comparative Characteristics

Differences between pregabalin vs. gabapentin	Pivotal trials demonstrate higher responder rates with pregabalin*
	Efficacy demonstrated with b.i.d. dosing regimen of pregabalin
	More rapid absorption of pregabalin (peak conc in 1–1.5 hrs vs. 3–4 hr)
	Increased oral bioavailability for pregabalin (≤90% at all doses)

	Linear absorption for entire dose range of pregabalin
	Possibly higher incidence of weight gain with pregabalin
Similarities of pregabalin and gabapentin	Similar spectrum of action: partial seizures and secondarily GTCSs
	Binds to α-2-δ subunit of the voltage-gated calcium channel
	Similar mechanism of action, modulation of neurotransmitter release
	No effects on hepatic enzymes
	No known significant interactions with other drugs
	Not affected by other drugs
	Total absorption not significantly affected by food
	Negligible metabolism
	Negligible binding to plasma proteins
	Renally excreted
	Low incidence (≤1%) of allergic or hypersensitivity reactions
	Side-effect profile similar for most reported adverse events
	Favorable cognitive profile
	No safety-related issues to date

*Note: Direct comparative trials between pregabalin and gabapentin have not been performed.

Controlled Substance Classification

Pregabalin is a controlled substance (Schedule V).[3] This classification resulted from the trials required for generalized anxiety. In 15 patients who were recreational drug users, there were reports of a single 450-mg dose of pregabalin producing pleasant drug effects comparable to a single 30-mg dose of diazepam. In all the controlled clinical trials (pain, epilepsy, anxiety), overall, 4% of patients reported euphoria (vs. 1% with placebo), but interestingly <1% of patients in the epilepsy and postherpetic neuralgia trials reported euphoria, and only 2% of patients in the diabetic peripheral neuropathy trials reported euphoria. There were some reports as well that discontinuing pregabalin resulted in transient insomnia, nausea, or headache. Although gradual discontinuation is desirable when possible, there is no danger (other than increased seizure frequency) from rapid discontinuation. No dependency on pregabalin has been reported, and pregabalin is not active at sites known to produce addictive behavior. Therefore, the controlled classification is a caution, but should not restrict clinical use for most patients.

Overdosage

Data are limited regarding overdosage with pregabalin; no serious side effects have been reported. It should be expected that more pregabalin will be absorbed than a corresponding amount of gabapentin because of the nonlinear kinetics of gabapentin. Although no data exists on hemodialysis with overdose, pregabalin, because of its low protein binding, is readily hemodialyzed should the perceived need arise.

Drug Interactions

Because pregabalin has negligible protein binding and no significant hepatic enzyme induction, no significant drug interactions have been reported. Specific studies have not demonstrated significant interactions with other AEDs (carbamazepine, gabapentin, lamotrigine, phenytoin, valproate), oral contraceptives, lorazepam, or oxycodone.[3,13,16] Conversely, pregabalin has not been demonstrated to have effects on other coadministered drugs such as diuretics, hypoglycemics (glyburide, insulin, metformin), and AEDs (carbamazepine, lamotrigine, phenobarbital, phenytoin, topiramate, valproate).

Role in Epilepsy Treatment

Indications

The current FDA-approved indications reflect the double-blind pivotal trials performed and submitted for approval. Pregabalin is approved as adjunctive therapy for partial seizures. This includes simple and complex partial seizures. The policy of the FDA to include generalized tonic–clonic seizures in the indication has been amended in recent trials of new AEDs because the number of secondarily generalized tonic–clonic seizures (GTCSs) is not a primary or secondary outcome variable. It is, however, appropriate and within indications to use pregabalin for both partial and secondarily GTCSs, because GTCSs are a type of partial seizure (i.e., partial onset). Therefore, the lack of mention of GTCSs in the indications does not imply any lack of efficacy for these secondary seizures. In actual practice, the secondarily GTCS of patients with partial seizures are often more readily controlled than are the partial seizures. In the report by Brodie,[15] there was no significant difference in RRatio by seizure type between simple partial, complex partial, and generalized tonic–clonic (presumed secondarily generalized) seizures, and all seizure types had similar dose–response characteristics.

Monotherapy trials of pregabalin are currently being planned. The FDA requires specific monotherapy trials to receive this indication.[33] Although this requirement for specific monotherapy trials is not unreasonable, the demand that monotherapy trials employ a superiority trials design, using either placebo or active control treatment arms, makes these trials extremely difficult to do. While acknowledging that the superiority trial design is more statistically rigorous, such trial designs may violate the Helsinki agreement for human trial design and may be unethical to do. Such trial designs are not required for monotherapy approval of AEDs in the European Union, where noninferiority trials in new-onset epilepsy are sufficient. The FDA also does not typically require such superiority trials in cardiology, oncology, and many other disease states. Alteratives to superiority trials, such as historical controls, which would eliminate the need for placebo or active control arms are being proposed.[29]

Pregabalin's spectrum of action is similar to that of gabapentin. It is not expected that pregabalin will be effective for myoclonic or absence seizures. New-onset focal or multifocal myoclonus has been reported in patients taking pregabalin, particularly at higher doses (e. g., 600 mg/day).[37] These effects resolved or improved with reduction in dosage. Whether pregabalin exacerbates primary generalized myoclonic seizures or absence epilepsy has not been determined.

Dosing Recommendations

Pregabalin was the first AED with which the FDA implemented the policy of requiring determination of the least effective dose. This provides important information to supplement the demonstration of efficacy at various doses. One of the pivotal trials was a dose-ranging trial. The least effective dose for significant seizure reduction was 150 mg/day; therapy can be initiated at this dose and titrated upward as needed and tolerated. Treatment can begin as either 75 mg twice daily or 50 mg three times a day in adults. Steady state is achieved within 1 to 2 days. Periodic increases can be made after steady state has been reached, as appropriate. If adverse events are significant, introduction and titration can be adjusted, recognizing that many of the side effects observed are initiation-related and transient. The 600 mg/day dose approved is a reasonable upper range if needed. Although doses of 900 mg/day have been administered, there is no evidence for improved efficacy at these doses, and side effects are increased.

Pregabalin is available in 25-, 50-, 75-, 100-, 150-, 200-, 225-, and 300-mg capsules. These various dose strengths can facilitate titration and reduce pill number in patients on stable dose regimens. Because the pricing in the United States is similar per pill regardless of strength, considerable economies can be achieved by using the largest pill strength.

Pregabalin is readily soluble, and liquid formulations are in development.

Effects on Mood

The comorbidity of epilepsy and mood disorders is well established, and many studies have emphasized the coexistence of depression and epilepsy. From 20% to 50% of patients with epilepsy may have coexisting depression.[39] Recently, it has been acknowledged that coexisting anxiety disorders may also be common. One study in children found that anxiety was the most common mood disturbance, occurring in 33% of children with epilepsy, compared with 6% of controls.[17] Another study found a prevalence of anxiety in 48% of patients with partial epilepsy, with 23% reporting (using the Hospital Anxiety and Depression Scale and QOLIE-10) moderate to severe anxiety, compared with 38% of patients reporting depression (18% moderate to severe).[18]

A number of AEDs have psychotropic effects.[46] Although it is beyond the scope of this chapter to discuss pregabalin's effects on mood in detail, comorbidities in patients with epilepsy can influence the selection of AED therapy. Several positive placebo-controlled trials have all demonstrated significant benefits of pregabalin on GAD when compared to placebo and comparable efficacy to comparative drugs.[27,44,45,48,49,50,56] Pregabalin has approval for the treatment of GAD in Europe; approval has not yet been granted in the United States. Symptoms from abrupt cessation were similar in rates and intensity to serotonin specific reuptake inhibitors and less common than those seen with benzodiazepines.

Cognitive Function

Gabapentin has been demonstrated to have a favorable cognitive profile in several well-controlled studies in healthy subjects and patients with epilepsy.[41] To date, there have been relatively few well-designed studies with pregabalin. Because of the high degree of polypharmacy in the patients participating in the pregabalin pivotal trials, attributing adverse effects on cognition to pregabalin is problematic. Nonetheless, 8% of patients reported “thinking abnormal” in these studies. A recent small, well-designed (double-blind, placebo-controlled, crossover) study in 24 healthy volunteers indicated that pregabalin did not differ from placebo on most measures, producing only minor, transient impairment on a few of the cognitive and psychomotor measures.[34] This was in contrast to the positive control alprazolam, which produced significant changes in all objective measures. A recent preliminary report evaluating cognitive function in elderly patients (*n* = 89, mean age 70.4) being treated with pregabalin for anxiety demonstrated a significant improvement in mood and no measurable effect on cognitive function.[34] Additional studies are needed, but pregabalin appears to have a favorable cognitive profile. Gabapentin had many advantages that made it one of the preferred AEDs for use in the elderly.[40,58] Pregabalin appears to share these advantages based on the known pharmacokinetic profile and available data on side effects.

Precautions and Contraindications

Precautions regarding pregabalin relate mainly to the adverse events detailed earlier. No safety related issues have been raised to date. Patients with a known hypersensitivity to pregabalin should not take pregabalin. It is not known whether any cross-reactivity occurs between hypersensitivity for pregabalin and gabapentin. They have distinct chemical structures, and each has a low incidence of hypersensitivity reactions. Like all antiepileptic medications, pregabalin should be withdrawn gradually over days or weeks unless a serious associated adverse event requires more prompt cessation.

Summary and Conclusions

Pregabalin is the most recently approved AED. Although related to gabapentin, with which it shares a number of characteristics (see Table 2), pregabalin was the result of a screening program to identify compounds with a similar mechanism of action but with greater potency. The double-blind studies to date, in highly refractory patient populations, have demonstrated consistent levels of response. Although comparative clinical trials comparing pregabalin with other AEDs are lacking, responder rates with pregabalin at the highest doses tested in the clinical trials are as good as any seen with second-generation AEDs in similar populations. This is in contrast to the more modest responder rates seen in the gabapentin trials. Pregabalin's linear pharmacokinetics contrast sharply with the highly nonlinear profile for gabapentin and represent an important advantage.

Although pregabalin's spectrum of efficacy is likely to remain focused on partial seizures with or without secondary generalization, it is likely to be useful as monotherapy and in children. Trials are currently being planned to assess these uses. The lack of drug interactions make pregabalin an attractive agent for patients requiring AED polypharmacy or comedications for medical illnesses. Although pregabalin's lack of hepatic enzyme induction would suggest that it should not be a major potentiator of osteoporosis, this issues should be looked at specifically. Pregnancy data are limited at this time. The use of pregabalin for pain has significantly increased the number of patient exposures, and no significant safety-related adverse events have been demonstrated. Pregabalin's side-effect profile is predominantly one of nonspecific CNS effects, and these often abate during the initiation period. Weight gain occurs in a minority of patients; it may be somewhat more common than that seen with gabapentin. Formal cognitive studies with neuropsychological testing remain to be done, but early reports suggest that pregabalin will have a favorable cognitive profile, particularly when tested as monotherapy. Its potential usefulness as an anxiolytic agent makes it an attractive choice when anxiety or depression coexists with epilepsy. Pregabalin should also be an AED useful in the treatment of epilepsy in the elderly, an important group of patients with a high incidence of new-onset epilepsy.

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Chapter 156

Primidone

Blaise F. D. Bourgeois

Introduction

Primidone has been in clinical use since 1952. Based on its chemical structure, primidone is not strictly a barbiturate. Therapeutically, however, it is appropriate to consider primi-done a barbiturate, because its clinical effect can be attributed in part to the phenobarbital produced by hepatic biotransformation. It has never been clearly established whether primidone is a phenobarbital prodrug, or whether treatment with primidone can be clinically distinguished from treatment with phenobarbital. Primidone does have independent antiepileptic activity in experimental models. If some of the therapeutic effect in humans can also be attributed to primidone, long-term therapy with primidone can be regarded as an obligatory combination therapy. In addition, independent antiepileptic activity has been demonstrated experimentally for the other main metabolite of primidone, phenylethylmalonamide (PEMA). These unique qualitative aspects of primidone biotransformation must be integrated into any discussion of its pharmacokinetics, pharmacodynamics, and clinical use.

Chemical Structure

Primidone was first synthesized in 1952.[8] Chemically, primi-done differs from phenobarbital only by the lack of the carbonyl group in position 2 of the pyrimidine ring, and it is therefore a desoxyphenobarbital (Fig. 1). The exact chemical composition is 5-ethyldihydro-5phenyl-4,6(1*H*,5*H*)-pyrimidinedione. It is very poorly soluble in water, somewhat soluble in ethanol, and virtually insoluble in organic solvents. Primidone can be synthesized by reduction of phenobarbital, desulfuration of thiophenobarbital, or ring closure of phenylethylmalonamide.[1,10] The molecular weight of primidone is 218.25, and the factor to convert from milligrams to micromoles is 4.59. Thus, a concentration of 1 mg/L is equivalent to 4.59 μmol/L (Table 1). Because the pyrimidine ring of primidone contains only two carbonyl groups, and not the three carbonyl groups that characterize barbituric acid, primidone is not a barbiturate in the strict sense. However, it is appropriate to list the clinical use of primidone among the barbiturate therapies because of the biotransformation to phenobarbital, which accumulates to therapeutic levels during long-term administration of primidone to patients.

Pharmacology

The basic pharmacologic mechanism of action of primidone itself has received relatively little attention. One reason is that it remained uncertain for some time whether primidone itself actually has independent antiepileptic activity. In addition, primi-done is never present alone during long-term therapy, and at least one active metabolite, phenobarbital, is present after repeated administration in humans as well as in experimental animals. As discussed later, a second active metabolite, PEMA, may be involved in the overall pharmacodynamic effect of primidone. All the evidence regarding the individual pharmacodynamic properties of primidone, phenobarbital, and PEMA is derived from experiments in animals in which seizures were provoked. Because the metabolites begin to accumulate a few hours after administration of the first dose, a possible long-term protection by primidone alone against seizures occurring spontaneously cannot be assessed in humans. Independent anticonvulsant activity of primidone was first demonstrated in dogs; the animals were found to be protected against induced seizures at a lower concentration of phenobarbital when primi-done was also present.[22] Subsequently, it was shown that rats were protected against induced seizures after a single dose of primidone before the active metabolites were detectable[4]; similar protection was achieved in mice when the biotransformation of primidone was delayed by the preadministration of a metabolic blocker.[14,32] In terms of potency against seizures induced by maximal electroshock, primidone and phenobarbital are quite similar. Against seizures induced chemically by pentylenetetrazol or bicuculline, phenobarbital is effective but primidone is totally ineffective.[14] This suggests that the experimental anticonvulsant spectra of primidone and phenobarbital differ and that the two compounds may be two different antiepileptic drugs (AEDs) with different mechanisms of action. The experimental anticonvulsant spectrum of primidone is similar to that of carbamazepine and phenytoin. Primidone and phenobarbital differ pharmacodynamically not only on the basis of their anticonvulsant spectrum, but also on the basis of their protective or therapeutic index. In terms of brain concentrations in mice, primidone was found to be 2.5 times less neurotoxic than phenobarbital, with a correspondingly higher therapeutic index.[14] When phenobarbital and primidone were administered together in single-dose experiments in mice,[15] their anticonvulsant activity was found to be supra-additive (potentiated), and their neurotoxic effect was found to be infra-additive. The best therapeutic index was achieved using a combination of the two drugs at a brain concentration ratio of 1:1. The results of interactions between primidone and phenobarbital obtained in mice were confirmed by experiments in amygdala-kindled rats. After single doses, the anticonvulsant effect of phenobarbital was potentiated by primidone, whereas side effects of phenobarbital, such as ataxia and muscle relaxation, were not increased by combined treatment with primidone.[35]

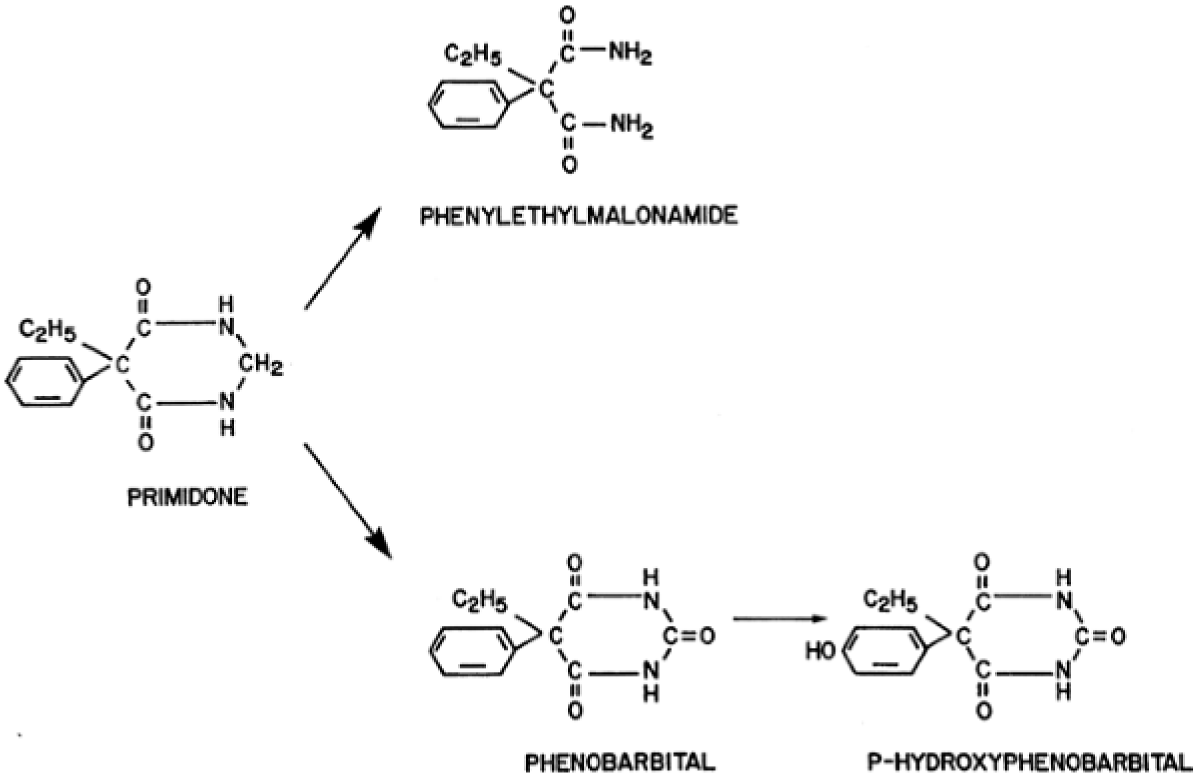

FIGURE 1. The two main pathways of primidone metabolism.

Table 1 Conversion

Primidone

Conversion factor:

CF = 1,000/mol wt = 1,000/218.3 = 4.58

Conversion:

(μg/mL) × 4.58 = μmol/L

(μmol/L)/4.58 = μg/mL

PEMA

Conversion factor:

CF = 1,000/mol wt = 1,000/206.2 = 4.85

Conversion:

(μg/mL) × 4.85 = μmol/L

(μmol/L)/4.85 = μg/mL

After direct administration, PEMA was found to have a relatively weak independent anticonvulsant activity in rats[5] as well as in mice.[14,32] When neurologic toxicity and protection against maximal electroshock-induced seizures were quantified in mice in terms of brain concentration,[14] PEMA was found to be 16 times less potent than phenobarbital in terms of seizure protection, and eight times less potent than phenobarbital in terms of neurotoxicity. However, PEMA potentiated both the neurotoxic effect[15] and the anticonvulsant effect[5,14] of phenobarbital. However, a quantitative analysis of these experimental results, together with the blood levels measured in patients on long-term therapy with primidone, suggests that PEMA

probably contributes little or not at all to the antiepileptic effect or clinical toxicity in patients.

Primidone's basic anticonvulsant pharmacologic mechanism of action has been studied in mouse neurons in cell culture.[36] Primidone was compared with phenobarbital for its effect on amino acid responses and on sustained, high-frequency firing. In contrast to phenobarbital, primidone had no effect on postsynaptic γ-aminobutyric acid (GABA) and glutamate responses at concentrations up to 50 μg/mL. However, both primidone and phenobarbital limited sustained, high-frequency, repetitive firing at relatively high concentrations (>50 μg/mL). Primidone and phenobarbital together limited sustained, high-frequency, repetitive firing at clinically relevant concentrations of 12 μg/mL for primidone and 20 μg/mL for phenobarbital. The authors concluded that primidone and phenobarbital may act synergistically to reduce sustained, high-frequency, repetitive firing.[36] These in vitro findings are all in good agreement with the observations made in whole animals.

Clinical Pharmacokinetics

Absorption

Only oral preparations of primidone are available, and these include tablets and syrup. The extremely low solubility of pri-midone precludes its parenteral administration. Pharmacokinetic parameters of phenobarbital, the main active metabolite of primidone, are not reviewed here. The time to peak serum concentration of primidone after oral ingestion of tablets was found to be 2.7 hours[24] and 3.2 hours[23] in adult patients with epilepsy. In children, the peak blood concentration after a single oral dose was reached after 4 to 6 hours, and 72% to 123% of the total dose (average, 92%) was recovered in the urine as unchanged primidone and as metabolites.[31] This suggests that the oral bioavailability of primidone is fairly complete. The concomitant administration of acetazolamide reduced the oral bioavailability of primidone.[54] One report has suggested that the bioavailability of a generic preparation is lower than that of the brand product.[57]

Distribution and Protein Binding

Reported values for the volume of distribution of primidone vary: 0.54 L/kg (after acute administration)[38] and 0.86 L/kg.[43] In a study involving direct oral administration of PEMA, a volume of distribution of 0.69 L/kg was found for this metabolite of primidone.[44] The protein binding of both primidone and PEMA in human plasma was found to be less than 10%.[5,23,44]

Primidone brain concentrations were lower than the simultaneous plasma concentrations, both in mice[14,32] and in rats.[4] In humans, variable brain-to-blood concentration ratios of pri-midone have been reported. An average brain-to-plasma concentration ratio of 87% was measured in a group of patients undergoing surgery for intractable epilepsy.[28] In a different group of six patients, also undergoing epilepsy surgery, brain concentrations of primidone ranged between 0 and 2.2 μg/g, whereas the average plasma concentration was 6.3 μg/mL.[32] Reported values for the cerebrospinal fluid-to-plasma ratio of primidone in humans range from 0.8 to 1.13.[23,28,39,51] These values are similar to saliva-to-plasma concentration ratios for primidone,[39,51] and they reflect the low affinity of primidone for plasma proteins. The brain penetration of PEMA seems to be good. In mice, brain concentrations of PEMA were found to be 93%[32] and 77%[14] of the simultaneous plasma levels.

Metabolism

More than for any currently used AED, an understanding of the qualitative and quantitative aspects of primidone metabolism is a prerequisite for the rational clinical use of this drug. This is because, after repeated administration, clinically significant accumulation of at least one active metabolite, phenobarbital, and possibly of a second, PEMA, occurs (Fig. 1). Phenobarbital is further metabolized to *p*-hydroxyphenobarbital, an inactive metabolite. It would be desirable for optimal clinical use of primidone to know the relative antiepileptic potency and toxicity, as well as the expected ratios of blood levels, of primidone and its two active metabolites. The ratios of blood levels have been well studied, but, as outlined earlier, information on the pharmacodynamic aspects is limited mostly to data in animals; corresponding data are virtually impossible to obtain in humans. Following the introduction of primidone, PEMA was the first metabolite to be identified. It was found initially in rats[7] and then in every species studied thereafter. A few years later, phenobarbital and *p*-hydroxyphenobarbital were identified,[17] and this identification was soon followed by the first descriptions of clinical intoxications that were considered to be caused by the derived phenobarbital.[45] Although other metabolites of primidone have been identified, they have no practical significance because of their low concentrations and lack of pharmacologic activity. The quantitative aspects of the biotransformation of primidone to phenobarbital and PEMA have been the object of several clinical studies. The fraction of primidone that is metabolized to phenobarbital was estimated by comparing the ratios of serum phenobarbital levels to the maintenance dose of either phenobarbital or primidone given as long-term therapy in the same patients. One such analysis suggested that 24.5% of the ingested primidone is converted to phenobarbital,[41] based on the observation that the dose of primidone (in milligrams per kilogram per day) required to maintain a certain phenobarbital level was approximately four times higher than the dose of phenobarbital necessary to maintain the same level. The results of another study indicated that the primidone requirements for a given phenobarbital level are about five times higher than the corresponding phenobarbital dose.[6] The extent of the biotransformation of primidone and the ratios of the blood levels of primidone and its metabolites are so sensitive to interactions with other AEDs that they are best discussed under that heading.

Elimination

The elimination half-life of primidone is quite variable, and this is a consequence of the different degrees of enzymatic induction that depend on whether a patient is on monotherapy with primidone or is taking other AEDs known to be enzymatic inducers. The elimination half-life of primidone was calculated to be 10 to 15 hours in adults on long-term primidone monotherap.[9,18,58] In contrast, in adults taking other AEDs in addition to primidone, values for the half-life ranged between 6.5 and 8.3 hours.[18,23,24,58] In 12 children, of whom four took primidone alone and eight also took phenytoin, estimates of the half-life of primidone ranged from 4.5 to 11 hours, with a mean of 8.7 hours.[31] The ability of newborns to metabolize primidone to phenobarbital or to PEMA appears to be very limited,[46] and in neonates the half-life of primidone was calculated as 23 hours, on average, with a range of 8 to 80 hours.[40] It is not possible to calculate accurately the elimination half-life of PEMA in patients who are on long-term therapy with primi-done, because production of PEMA by the liver takes place as long as primidone remains in the body. In a study based on direct oral ingestion of PEMA by adults, the average half-life of PEMA was 15.7 hours.[44] The pharmacokinetics of phenobarbital are discussed in Chapter 153.

Adverse Effects

As with the antiepileptic effect, it is difficult to separate long-term side effects of primidone therapy from those of phenobarbital therapy. Although depression may be more common with primidone than with other AEDs,[34] it is difficult to determine whether depression is more common than with phenobarbital. Because phenobarbital is always present during long-term therapy with primidone, it is not possible to attribute side effects clearly to one or the other, and it can be said that primidone shares all the side effects of phenobarbital. Consequently, it is also impossible to establish a therapeutic range for primidone with any degree of certainty. The primidone-to-phenobarbital concentration ratio can be quite variable, and at a primidone level of 15 mg/L, the patient is more likely to experience side effects if the concomitant phenobarbital level is 50 mg/L than if it is 20 mg/L. In children, monotherapy with primidone was found to be tolerated as well as, if not better than, monotherapy with phenobarbital, phenytoin, or carbamazepine.[27] Overall, however, there is no qualitative difference between the dose-related, long-term side effects of primidone therapy and those of comparable phenobarbital therapy. The same applies also to idiosyncratic side effects and potential teratogenicity. No specific teratogenic pattern has been associated with primidone therapy, as opposed to phenobarbital therapy. Birth defects described in the offspring of women who took primidone during pregnancy include ventriculoseptal defects, microcephaly, and poor somatic development.[3,47]

Table 2 Serum Level Ratios[a]

		Ratios of serum levels to PRM dose[b]			Ratios of serum levels[b]	
	N	PRM	PB	PEMA	PB:PRM	PEMA:PRM

Monotherapy	10	0.78 ± 0.25	1.47 ± 0.53	0.64 ± 0.39	1.65 ± 0.74	0.70 ± 0.36
Comedication[c]	53	0.40 ± 0.15	2.40 ± 0.98	0.75 ± 0.42	5.83 ± 2.62	1.71 ± 0.75

Ratios of serum level of PRM, PB, and PEMA to PRM dose, and ratios of serum levels of PRM, PB, and PEMA at steady state. PRM, primidone; PB, phenobarbital; PEMA, phenylethylmalonamide.

[a] All blood samples were drawn before the morning dose in hospitalized patients.
[b] Mean ± SD;PRM dose in mg/kg/d, serum levels in mg/L.
[c] Comedication consisted of phenytoin, carbamazepine, or both.
From Bourgeois BFD. Primidone. In: Resor SR, Kutt H, eds. *The Medical Treatment of Epilepsy*. New York: Marcel Dekker; 1992:371–378, with permission.

One aspect of side effects that clearly distinguishes primi-done from phenobarbital is acute initial toxicity. Even after a low initial dose of primidone, some patients can experience transient side effects so debilitating that they may be reluctant to take another dose of primidone. These side effects usually include drowsiness, dizziness, ataxia, nausea, and vomiting.[37] This acute toxicity can be shown to occur before phenobarbital or PEMA is detected in the blood, and it must therefore be caused by primidone itself. Because much larger doses of primi-done are tolerated by the same patients later during long-term therapy, tolerance to primidone must develop. This tolerance probably develops quite rapidly, in a matter of hours to days. The ratio between a clinical toxicity score and serum primidone levels was determined in a group of patients receiving their first dose of primidone.[33] This ratio was shown to begin to decrease significantly as early as 6 hours after the ingestion of primi-done. Cross-tolerance to primidone following phenobarbital exposure could be demonstrated unequivocally in experimental animals. To achieve the same degree of seizure protection and the same level of neurotoxicity, higher brain concentrations

of primidone were necessary in mice that had received phenobarbital daily for 2 weeks than in mice not previously exposed to any drug.[11]

Clinical evidence also is available that phenobarbital produces a cross-tolerance to acute primidone toxicity, because patients on long-term phenobarbital therapy are less likely to experience the same degree of toxicity when first exposed to primidone.[25,33] Bourgeois et al.[16] took advantage of this pharmacodynamic interaction to develop a protocol for rapid introduction of primidone, using a gradual phenobarbital loading protocol over 4 days, followed by the introduction of primidone at full maintenance dose on day 5. More recently, Kanner et al.[30] confirmed the feasibility of the rapid introduction of primidone following prior loading or exposure to phenobarbital. Under this protocol, two of 30 patients tolerated the introduction of primidone at 500 mg per day with minimal or no adverse events.

Drug Interactions

Primidone is the cause as well as the object of numerous pharmacokinetic interactions. The biotransformation of primidone to phenobarbital and PEMA can be both markedly induced and markedly inhibited by other drugs, and this results in pronounced interindividual variability not only in the relative concentrations of the three compounds, but also in the ratio between primidone dose and the blood levels. The effect of induction was studied extensively in a group of adult patients with epilepsy who received an intravenous injection of ^{14}C-labeled primidone, followed by urinary assay of primidone and its metabolites for 5 days.[58] Group 1 consisted of patients taking no other AED, and group 2 consisted of patients on combination therapy. The total urinary recovery was similar in the two groups, 75.5% and 77.4%. However, 64% of the dose was excreted as unchanged primidone in group 1, and only 39.6% in group 2. The difference was even more pronounced for PEMA recovery, which represented 6.6% of the primidone dose in group 1 and 27.9% in group 2. The corresponding numbers were 2.1% and 3.3% for phenobarbital, and 3% and 6.5% for unidentified metabolites. In addition to being more sensitive to induction, the conversion of primidone to PEMA appears also to be more rapid, because PEMA can be detected in the blood within a few hours after a first dose of primidone, as opposed to phenobarbital, which may not be detectable for 24 hours.[9,23,24] Similar data were obtained from 24-hour urine collections in 12 children on long-term primidone therapy.[31] The total urinary recovery was 92%, on average: 42.3% as unchanged primidone, 45.2% as PEMA, and 4.9% as phenobarbital and *p*-hydroxyphenobarbital. Of these 12 children, four were taking primidone monotherapy and eight were on combination therapy.

The most pronounced acceleration of the enzymatic biotransformation of primidone appears to be caused by phenyt-oin, which is a known potent enzymatic inducer.[2,18,21,48] This causes a decrease in the primidone-to-phenobarbital serum concentration ratio. Carbamazepine also accelerates the conversion of primidone, but to a lesser extent.[2,18] Rarely, carbamazepine may even inhibit the conversion of primidone to phenobarbital, causing a rise in the primidone-to-phenobarbital serum concentration ratio.[13] The effect of comedication with phenytoin, carbamazepine, or both on the concentration-to-dose ratios and on the ratios between the concentrations of primidone, phenobarbital, and PEMA are summarized in Table 2. Morning trough levels of primidone in relation to the daily dose of primidone are reduced by about 50% in the presence of phenytoin or carbamazepine in comparison with primidone monotherapy. This is a consequence of accelerated biotransformation, and phenobarbital levels are accordingly raised (by a factor of 1.6) in relation to the maintenance dose of primidone. The practical application is that dosage requirements of primidone to achieve a given phenobarbital level are about 1.6 times lower in patients taking phenytoin or carbamazepine than in patients taking primidone alone. This is the opposite of what is usually seen with enzymatic induction, when the drug dose must be increased to maintain the same drug level. In the case of primidone, phenobarbital is the product, not the substrate, of the induced enzymatic step, yet its concentration is usually the one relevant for the clinical effect. Thus, adding an inducing drug to a pre-existing primidone monotherapy may actually raise phenobarbital levels into the toxic range. It can also be seen in Table 2 that the morning trough serum concentration ratio of phenobarbital to primidone is more than three times higher in the presence of phenytoin or carbamazepine. The practical meaning of these numbers is that, in a patient with a primidone level of 10 mg/L, the simultaneous average phenobarbital level would be 16.5 mg/L if the patient is on primidone monotherapy, but the average phenobarbital level would be 58.3 mg/L if the patient is also taking phenytoin or carbamazepine. Different effects of valproate on primidone kinetics have been described. In one study, transient elevations of primi-done levels were observed after the addition of valproate[56]; phenobarbital levels were not included in this analysis. Other authors[20] found no consistent changes in the levels of primidone or phenobarbital after the addition of valproate to pri-midone therapy.

Inversely, the antituberculosis drug isoniazid was shown to inhibit the conversion of primidone to phenobarbital markedly and thereby produce high levels of primidone in relation to phenobarbital levels.[53] The same effect has been described with nicotinamide.[13] Primidone therapy can also be the cause of drug interactions and thus influence the levels of other drugs. There is no information on the potential of primidone itself to inhibit or induce the biotransformation of other drugs. However, because of the derived phenobarbital, primidone treatment causes the same interactions as those described in conjunction with phenobarbital treatment, mainly induction of the biotransformation of many other drugs.

Role in Epilepsy Treatment

Indications

Primidone has been used in the treatment of epilepsy since 1952,[7] but its neurologic side effects have prevented it from becoming a drug of first choice for any seizure type. Because it is metabolized to phenobarbital during long-term therapy, it has been virtually impossible to determine with any certainty whether primidone is merely a phenobarbital prodrug, or whether treatment with primidone differs clinically from treatment with phenobarbital. In view of the demonstrated independent antiepileptic activity of primidone in animal models, it is likely that primidone is potentially antiepileptic in humans. If this is the case, long-term treatment with primidone represents an obligatory combination therapy involving pharmacodynamic interactions between primidone, phenobarbital, and possibly PEMA.

Primidone is used generally for the same indications as phenobarbital, but because primidone is not available in a parenteral formulation, it is not used in the acute treatment of status epilepticus. Several studies have addressed the issue of the comparative antiepileptic efficacy of primidone and phenobarbital. In most studies, primidone could not be shown to be more or less effective than phenobarbital.[26,41,55] In a cross-over study, the efficacies of primidone and phenobarbital were compared sequentially in the same patients.[42] Similar phenobarbital levels were maintained during both therapies, and primidone treatment was found to be slightly more effective against generalized tonic–clonic seizures than phenobarbital treatment. Primidone is as effective as any other drug against generalized tonic–clonic seizures. Primidone was used as a drug of choice in the treatment of juvenile myoclonic epilepsy.[19,29] Because of its greater efficacy and overall better tolerability, valproate has generally replaced primidone for this indication. The degree of seizure control achieved by primidone in partial and secondarily generalized seizures is similar to that achieved by phenytoin or carbamazepine.[49,55] The most comprehensive and systematic controlled comparisons among carbamazepine, phenytoin, phenobarbital, and primidone in the treatment of partial and secondarily generalized seizures was the study by Mattson et al.[37] Virtually no difference was noted in efficacy among the four drugs, but treatment with primidone was associated with the highest rate of failures, mainly as a consequence of a higher incidence of side effects during the early phase of treatment. In this study, the percentage of failures was lowest with carbamazepine and phenytoin.

Primidone is rarely indicated as treatment for any type of seizures besides partial and secondarily generalized seizures. In particular, it has little or no role in the generalized epilepsies encountered in childhood, such as absence epilepsy and the Lennox-Gastaut syndrome. Although it has been shown to be potentially useful in the treatment of neonatal seizures,[46,50] primidone is almost never used for this indication. Primidone is contraindicated in any patient who has previously had an allergic reaction or a severe idiosyncratic reaction to primidone or phenobarbital. It is also contraindicated in patients with hepatic porphyria.

How to Use Primidone

Only oral formulations of primidone are available, and these include 250-mg and 50-mg tablets as well as a syrup containing 50 mg/mL. Because of the potentially severe acute toxic reaction after the first exposure to primidone, it is more important than with any other antiepileptic drug to start primidone therapy at a low dose. Most patients can tolerate a first dose of 125 mg (one-half tablet) at bedtime, but some cannot even tolerate this dose, in which case the second dose must be reduced to one-quarter tablet (62.5 mg). The dose can be increased again as tolerated at intervals of 3 days, up to a final daily maintenance dose of 10 to 20 mg/kg. A schedule that allows rapid advancement to the full maintenance dose of primidone was developed[16] on the basis of observations in patients and in experimental animals that phenobarbital produces cross-tolerance to the effects of primidone.[11] The principle is based on giving phenobarbital initially, titrating the serum level as rapidly as tolerated up to 20 mg/L, and then switching abruptly to the full maintenance dose of primidone. Experimentation with various schedules of phenobarbital titration revealed that the following increases in levels are tolerated with minimal or no sedation by most patients: 5 mg/L after 24 hours, 10 mg/L after 48 hours, 15 mg/L after 72 hours, and 20 mg/L after 96 hours (end of day 4). These levels can be quite accurately achieved by giving 3 mg/kg of phenobarbital orally on the first day (two doses of 1.5 mg/kg each, 12 hours apart), 3.5 mg/kg on the second day, 4 mg/kg on the third day, and 5 mg/kg on the fourth day. On the fifth day, the patient can be switched abruptly to a full daily maintenance dose of primidone of 12.5 to 20 mg/kg, with no significant new toxicity.

As can be derived from Table 2, primidone monotherapy at a daily dose of 20 mg/kg will result, on average, in phenobarbital levels of 30 mg/L. The steady-state levels of phenobarbital will be reached only after 2 to 3 weeks on a constant dose of primi-done. In patients comedicated with drugs like carbamazepine or phenytoin, the same phenobarbital level of 30 mg/L will be achieved with an average daily dose of primidone of 10 to 15 mg/kg. As with most AEDs, average dose requirements may be higher in children and lower in the elderly.

Because of the relatively short half-life of primidone, it is usually recommended to divide the daily dose into three doses, although the necessity to do so has never been documented. If the dose of primidone is adjusted on the basis of blood levels, it is probably preferable to base a decision on phenobarbital levels rather than on primidone levels because, as stated earlier, at the usual concentration ratios occurring in patients, further dosage increases are more likely to be limited by the phenobarbital levels. A therapeutic range of about 3 to 12 mg/L has been suggested for primidone,[52] but monitoring these levels has very limited clinical value. Because PEMA, at the levels observed in patients, probably does not contribute significantly to the pharmacologic effect of primidone therapy, there seems to be no reason to monitor PEMA levels during primidone therapy.

Primidone should be used preferably alone or in combination with a noninducing drug like lamotrigine, levetirace-tam, gabapentin, or a benzodiazepine. As discussed earlier, inducing drugs such as carbamazepine and phenytoin shift the primidone-to-phenobarbital ratio so much in favor of phenobarbital that the situation becomes practically equivalent to prescribing phenobarbital instead of primidone. For the same reason, prescribing primidone and phenobarbital simultaneously in the same patient makes no sense. Valproate may also increase phenobarbital levels, on the basis of its demonstrated inhibition of phenobarbital elimination. Animal experiments suggest that the maximal benefit from primidone therapy is obtained at a primidone-to-phenobarbital concentration ratio of about 1:1. This ratio is rarely seen in patients,

even on primidone monotherapy, and never in patients comedicated with carbamazepine, phenytoin, or phenobarbital. Attempts have been made to raise the primidone level in relation to the phenobarbital level so as to increase the pharmacologic contribution of primidone. This shift in ratio could be achieved by adding nicotinamide to primidone.[13] However, the doses of nicotinamide necessary to obtain this change in concentration ratio may cause gastrointestinal side effects and hepatotoxicity.

Discontinuing Primidone

Although abrupt discontinuation of an AED is clearly associated with an increased risk for seizure recurrence and even status epilepticus, the rate at which a given drug should be tapered has never been adequately documented. However, withdrawal of barbiturates and benzodiazepines seems to be associated with a higher overall risk for withdrawal seizures. Unless there is a specific reason to proceed faster, it is appropriate to taper primidone in a linear fashion over the course of 3 to 6 months, with dosage reductions at monthly intervals.

Summary and Conclusions

In conclusion, primidone is a drug that is still widely used in the treatment of epilepsy, and it is an intriguing drug because of the unique quantitative and qualitative aspects of its metabolism. Primidone is both a drug in itself and a phenobarbital prodrug. Its clinical indications and its side effects do not differ much from those of phenobarbital. The clinical use of primidone represents an obligatory combination between a drug with a short elimination half-life and a drug with a long elimination half-life. If primidone is prescribed under the assumption that it differs from phenobarbital, the primidone-to-phenobarbital serum concentration ratio should be maintained as high as possible. Drugs causing enzymatic induction, such as phenytoin and carbamazepine, invariably lower the primidone-to-phenobarbital concentration ratio. The lower the primidone-to-phenobarbital concentration ratio, the more unlikely it becomes that primidone therapy differs from phenobarbital therapy. Therefore, it makes little clinical sense to prescribe primidone in combination with such drugs, and it makes even less sense to prescribe primidone in conjunction with phenobarbital.

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Chapter 157

Rufinamide

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Introduction

Rufinamide is a broad-spectrum antiepileptic drug (AED) with documented ability to block sodium (Na) channels.[24,34] Following discovery of antiepileptic activity in animal models, it has been undergoing Phase II and III clinical trials. Rufinamide has demonstrated efficacy against partial seizures in adults and generalized seizures in patients with the Lennox-Gastaut syndrome (LGS).[5,10,14] Clinical trials have reported a good tolerability profile. Rufinamide is currently under evaluation by the European Medicines Agency and the United States Food and Drug Administration (FDA).

Chemistry

Rufinamide (1–(2,6-difluorophenyl)methyl-IH-I,2,3triazole-4–carboxamide) (Fig. 1) is a triazole derivative structurally dissimilar to currently marketed AEDs.[2,17] Rufinamide is a lipophilic compound with a partition coefficient (logP = 0.88) and solubility in water and in gastric and intestinal fluids of 40 to 70 mg/L.[9] There are no currently marketed formulations of this compound. In clinical trials, film-coated tablets have been used.[9]

Plasma concentrations for rufinamide and its inactive carboxylic acid major metabolite (Fig. 1) are determined using high-performance liquid chromatography (HPLC).[27] The limit of quantification of this validated HPLC assay is 25 ng/mL for rufinamide in plasma, 2.5 µg/mL for rufinamide in urine, and 5 µg/mL for rufinamide's carboxylic acid major metabolite in urine.[27]

Pharmacology

Activity in Experimental Models of Seizures/Epilepsy

Rufinamide exhibits broad-spectrum anticonvulsant properties at nontoxic doses.[34] In animal models, rufinamide's protective index (PI = TD_{50}/ED_{50}) was superior to AEDs such as phenobarbital, phenytoin, ethosuximide, and valproic acid.[2,34]

The maximal electroshock (MES) test can identify AEDs with potential efficacy against partial seizures and generalized tonic–clonic seizures.[20,22,26] Rufinamide given orally was protective against MES-induced tonic–clonic seizures in both mice and rats with an ED_{50} of 23.9 mg/kg and 6.1 mg/kg, respectively. Rufinamide's anticonvulsant potency in the MES test was comparable to standard AEDs (Table 1).[9] In rats and mice, tolerance was not noted over 5 days.[34]

The subcutaneous pentylenetetrazole (PTZ) test can identify AEDs with potential efficacy against clonic or absence seizures.[20,22,26] Rufinamide's efficacy in the subcutaneous PTZ test was species and route dependent. In mice, rufinamide suppressed PTZ-induced seizures with an ED_{50} of 45.8 mg/kg.[34] Although orally administered rufinamide's ED_{50} is less potent than phenobarbital's ED_{50} (12.6 mg/kg), it is lower than the ED_{50} values for ethosuximide, valproic acid, and phenytoin[9] (Table 2). Intraperitoneal rufinamide suppressed PTZ-induced clonus with an ED_{50} of 54.5mg/kg in mice.[34] In rats, oral rufinamide was inactive against subcutaneous-induced PTZ seizure[9] (Table 2).

Intraperitoneal rufinamide blocked clonic seizures induced by subcutaneous bicuculline and picrotoxin in mice with ED_{50} values of 50.5 mg/kg and 76.3 mg/kg, respectively.[34] Similar to its results in the PTZ test, rufinamide was less potent than phenobarbital but more potent than ethosuximide and valproic acid (phenytoin is inactive in this test).[9] For seizures induced by intraperitoneal picrotoxin, rufinamide had lower potency (ED_{50} of about 300 mg/kg). Rufinamide's lowest potency was seen in mice in the glycine-related subcutaneous or intraperitoneal strychnine test, where the maximum protection rate of 37.5% occurred at a dose of 125 mg/kg.[9,29] Overall, rufinamide's tolerability (determined by either the chimney test in rats or the Rotorod test [6 rpm] at time of peak neurotoxic effect in mice) was similar to or exceeded that of any established AED except phenytoin administered orally to rats.[34]

Once-daily threshold electrical stimulation of the amygdala in animals induces epileptic electroencephalogram (EEG) afterdischarges and results in the kindling phenomenon.[15,16,20,28] In rats treated daily with oral rufinamide (20 mg/kg and 60 mg/kg) an increase in afterdischarge duration occurred, but no change in convulsive behavior was seen compared with controls.[29] Carbamazepine and phenytoin produce similar effects.[23,30] In cats, oral rufinamide (100 mg/kg and 300 mg/kg) delayed kindling development and suppressed afterdischarges in fully kindled animals. Carbamazepine (40 mg/kg) and valproic acid (180 mg/kg) produced similar effects.[9] Rufinamide antagonized kindling but did not provoke motor disturbances.[9]

Electrically induced hippocampal and cortical afterdischarges are also used to investigate the effects of AEDs against seizures originating from a focus. In cats, intraperitoneal rufinamide (300 mg/kg) reduced hippocampal and cortical afterdischarge duration by more than 50%.[9] Rhesus monkeys with aluminum hydroxide implants in the motor cortex provide an animal model of chronically recurring partial seizures with or without secondary generalization. Subchronic treatment with oral rufinamide (30–50 mg/kg daily for 15 days) reduced seizure frequency by 75% to 100% without a significant change in mean seizure duration.[9]

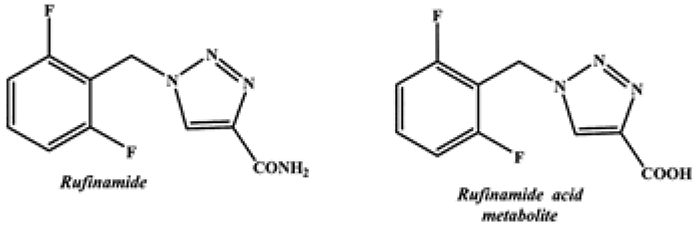

FIGURE 1. Chemical structure of rufinamide and its major acid metabolite.

Table 1 Rufinamide and other orally administered AEDs. ED_{50} for the MES test in rodents (performed at NIH and Novartis pharmaceuticals)[9],[29]

	Mouse: ED_{50} in mg/kg		Rat: ED_{50} in mg/kg	
Compound	**NIH**	**Novartis**	**NIH**	**Novartis**
Rufinamide	23.9	19.2	6.1	8.0
Carbamazepine	n.r.	13.7	n.r.	8.0
Phenytoin	9.0	11.0	29.8	26.0
Lamotrigine	n.r.	6.1	n.r.	4.7
Topiramate	n.r.	35.7	n.r.	17.3
Phenobarbital	20.1	16.5	9.1	5.5
Valproic acid	664	220	489	450
Ethosuximide	Ø 2,000	>1,000	Ø 1,200	>600

Pretreatment period: variable (NIH), 1 hour (Novartis); n.r., not reported; Ø, no effect at indicated dose; >, less than 50% protection at indicated dose.

Mechanism of Action

Rufinamide's full mechanism of action is not yet known in detail. Some of its anticonvulsant effect is thought to result, in part, from blocking Na channels.[24] In rat cortical neurons, over a wide range of concentrations, rufinamide caused rest- and use-dependent block of Na currents coupled with slowed recovery from inactivation.[24] The rufinamide concentration that limited firing in 50% of neurons was 3.8 μmol /L (range 2–10 μmol/L).[24]

Rufinamide does not significantly interact with neurotransmitter systems, including γ-aminobutyric acid (GABA), adenosine, monoaminergic and cholinergic binding sites, *N*-methyl-D-aspartate (NMDA), and other excitatory amino acid binding sites.[17,29]

Clinical Pharmacokinetics

Absorption

During Phase I clinical trials, single- and multiple-dose studies were performed in healthy subjects to assess the pharmacokinetic profile of rufinamide. Based on urinary recovery of radioactivity following oral administration of C^{14}-labelled drug (600 mg as capsules) with food, the bioavailability of low doses of rufinamide was estimated to be approximately 85%.[9] Peak plasma concentration (C_{max}) of rufinamide was reached 5 to 6 hours after dosing.[2,3,7] The intersubject variability in the mean area under curve (AUC) and

C_{max} values of rufinamide were less than 26% for both tablets and suspension. Contribution of the intrasubject variability to the overall variability was small (20%).[2,7] The tablet formulation was bioequivalent to the suspension in terms of rate and extent of absorption. Rufinamide exhibited dose-limited absorption; doses higher than 400 mg for both fasted and fed healthy subjects demonstrated less than proportional increase in peak concentrations (C_{max}) and plasma AUC.[9] Similar to the single-dose healthy volunteer studies, multiple-dose studies found a less than dose proportional increase in steady-state rufinamide plasma levels, due to dose-limited absorption.[9]

After intake in the fasting state, rufinamide has an oral bioavailability of approximately 60%; however, food increases rufinamide's extent of absorption and plasma exposure (AUC).[3,15] In a 1998 Phase I study using an older formulation, food increased the extent of absorption or plasma exposure AUC by 44% and the C_{max} by 100%.[6] The time to reach C_{max} (t_{max}) was 8 hours in fasted conditions and 6 hours in those fed after breakfast.[6] However, unpublished data using a newer formulation of rufinamide indicates food increases rufinamide's extent of absorption or plasma exposure AUC by 34% and the C_{max} by 56%.[9] The increase in rufinamide's AUC when administered concomitantly with food might be due to a change in gastrointestinal absorption and dissolution of the parent drug. The low water solubility and high lipophilicity (as indicated by its relatively large partition coefficient; logP = 0.88) supports the hypothesis of an increased solubility in the presence of food due to a larger volume of liquid and stimulated biliary secretion.[5]

Plasma Protein Binding and Distribution

Rufinamide's protein binding is low (34%).[2,17] Binding is predominantly to albumin. Rufinamide is evenly distributed between erythrocytes and plasma, and its apparent volume of distribution (V/F) is similar to the total body water (50–80 L).[3,9]

Metabolism and Elimination

Rufinamide is extensively metabolized, and the metabolites are mainly excreted in the urine. Only a small fraction of the dose is eliminated unchanged in the urine (2%) and feces (2%).[2,17] Rufinamide's major metabolic pathway is hydrolysis of the carboxamide group to form the acid metabolite previously called CGP 47292.[2,17] Minor additional metabolites have been detected and appear to be acyl-glucuronides of the acid metabolite.[9] This hydrolytic metabolism does not appear to involve the hepatic microsomal cytochrome P450 isozyme system.[9]

Rufinamide metabolites are predominantly renally excre-ted.[17] A single-dose study in three fed healthy male volunteers using 600 mg of [^{14}C] rufinamide administered as microcrystalline solid in capsules found 80% of the total plasma radioactivity was rufinamide, and 16% its acid derivative.[9] Rufinamide oral clearance (CL/F) is dose-dependent and, at a median dose level, ranges between 2.7 L/hour (children) and 6.6 L/hour (adults). The half-life of rufinamide ranges from 6 to 10 hours.[2,17]

Pharmacokinetics in Epilepsy Patients

Rufinamide's pharmacokinetics in patients with epilepsy was studied in a trial involving 647 adults (ages 15 to 65 years), taking one to three concomitant AEDs, with treatment-resistant partial seizures (with or without secondary generalization). Patients were randomized equally to either rufinamide 200 mg/day, rufinamide 400 mg/day, rufinamide 800 mg/day, rufinamide 1,600 mg/day, or placebo. Rufinamide was given twice daily (b.i.d.) in all trials except the monotherapy trials, where it was given three times a day (t.i.d.). Plasma rufinamide levels increased approximately dose-proportionally with doses of 800 mg/day or less, but when doses were more than 800 mg/day, a less than proportional increase in rufinamide plasma levels was observed.[10]

Rufinamide did not demonstrate linear pharmacokinetics in a study of ascending doses in 16 pediatric patients with inadequately controlled seizures receiving one to two other concomitant AEDs.[1] In this study, rufinamide was administered orally (b.i.d. dosing) over 14 days at a starting dosage of approximately 10 mg/kg per day (days 1–7) and then increased to 30 mg/kg per day (days 8–14). A 12-hour pharmacokinetic profile was obtained on days 7 and 14. A threefold increase in rufinamide dose provided only a 2- to 2.5-fold increase in the AUC_{0-12h}, C_{maxss}, and minimum concentrations (C_{minss}) at steady state.[1] There were no differences between any 2 of the 3 pediatric subgroups (under 6 years, 7–12 years, and 13 to under 18 years) for AUC_{0-12h}, C_{maxss}, and C_{minss}.[1]

In a trial of 65 patients with LGS, rufinamide's CL/F increased linearly with increased body surface area, independent of patient age, sex, or race.[8] Using a patient of median body surface area and taking a median dose level for the relevant age group, the typical values of rufinamide's CL/F in adults was 6.6 L/hour, adolescents 4.5 L/hour, and children 2.7 L/hour. The median body sizes used for this calculation were 24.0, 40.5, and 66.2 kg, respectively, for the three groups. Clearance was not affected by kidney function.[8] Rufinamide's bioavailability decreased with increasing doses.[8]

Gender did not appear to have a significant influence on rufinamide pharmacokinetics.[9] Age (4–65 years) was tested as a covariate in population pharmacokinetic studies and in two studies (one pediatric, one elderly). Age itself was not a significant covariate after taking into account body size.

Table 2 Rufinamide and other orally administered AEDs. ED_{50} for the s.c PTZ test in rodents (performed at NIH)[9]

Compound	Mouse: ED_{50} in mg/kg	Rat: ED_{50} in mg/kg
Rufinamide	45.8	Ø–1000
Phenytoin	Ø–300	Ø–800
Phenobarbital	12.6	11.6
Valproic acid	388	179
Ethosuximide	192	54.0

Pretreatment period: variable; Ø, no effect at indicated dose.

Efficacy

Overview of Clinical Efficacy Trials in Humans

Following a proof-of-principle study in adults with partial or primary generalized tonic–clonic seizures,[25] rufinamide had been studied in randomized controlled trials of adults with treatment-resistant partial onset seizures either as adjunctive therapy[5,10] or monotherapy,[21,32] children with treatment-resistant partial onset seizures,[12] adults with treatment-resistant generalized tonic–clonic seizures,[4] and children with LGS.[13,14] Adjunctive rufinamide therapy was more efficacious than placebo adjunctive therapy in adults with treatment-resistant partial onset seizures and children with LGS.

Proof-of-Principle Study

A small, double-blind, placebo-controlled, randomized, parallel-group, weekly rising dose (400–1,600 mg/day) study was performed as the first proof-of-principle clinical trial examining the efficacy and tolerability of rufinamide therapy. Fifty patients with therapy-resistant partial or primary generalized tonic–clonic seizures were equally randomized to rufinamide and placebo treatment groups; rufinamide doses were increased weekly (to 400, 800, 1,200, and 1,600 mg/day over the course of the 4-week study). In the evaluable population, the rufinamide group had a larger median percentage change in seizure frequency compared with the placebo group (41% reduction, $n = 23$ vs. 52% increase, $n = 21$, $p = 0.0397$). The 50% responder rate (i.e., patients experiencing ≥50% reduction in seizure frequency per 28 days from Baseline Phase) was higher in the rufinamide group compared with the placebo group (39% vs. 16%, $p = 0.096$); this trend was seen despite the small sample size. Based on this proof-of-principle study, further studies were conducted to better delineate rufinamide's anticonvulsant efficacy.[25]

Adults with Partial Onset Seizures: Adjunctive Therapy

The results of a double-blind, randomized, placebo-controlled, parallel-group study examining the efficacy of rufinamide versus placebo in adults with inadequately controlled partial seizures had been reported in abstract.[10] Adults (ages 15–65 years) on one to three concomitant AEDs with nine or more partial seizures (with or without secondary generalization) during a 3-month baseline were eligible for a 3-month double-blind treatment phase. Patients were randomized equally to either rufinamide 200 mg/day, rufinamide 400 mg/day, rufinamide 800 mg/day, rufinamide 1,600 mg/day, or placebo. Among the 737 enrolled patients, 647 were randomized at the end of the baseline period. Rufinamide demonstrated a linear trend for dose response for seizure frequency per 28 days in the double-blind period ($p = 0.003$) and for treatment responders ($p = 0.0035$). Compared with the placebo group, the median seizure frequency ratio was significantly reduced in patients treated with rufinamide 400 mg/day (11%, $p = 0.0274$), rufinamide 800 mg/day (16%, $p = 0.0123$), and rufinamide 1,600 mg/day (17%, $p = 0.0163$). The seizure frequency ratio for each patient was the number of seizures that occurred during the double-blind phase divided by the number of seizures that occurred during the baseline phase. This was expressed per 28-day intervals. The authors concluded that rufinamide's efficacy was demonstrated in a dose-dependent manner.[10]

Another multicenter, double-blind, placebo-controlled, randomized, parallel-group study that assessed the efficacy of adjunctive rufinamide therapy in adult patients with inadequately controlled partial seizures was reported in an abstract form.[5] Adults (ages 16 and older) on one or two concomitant AEDs with six or more partial seizures during a 56-day baseline were eligible for a 91-day double-blind treatment phase. Eligible patients were then randomized to rufinamide adjunctive therapy (3,200 mg/day) or placebo adjunctive therapy. The titration period was 14 days, and the maintenance period was 77 days. The 313 randomized patients were evenly divided between the two treatment arms (rufinamide, $n = 156$; placebo, $n = 157$). The median reduction in partial seizures per 28 days relative to baseline was better in the rufinamide group compared with the placebo group (rufinamide 20.4% reduction; placebo 1.6% median increase, $p = 0.0158$). The percentage of treatment responders (patients with ≥50% reduction in partial seizure frequency) was higher in the rufinamide group compared with the placebo group (28.2% vs. 18.6%, $p = 0.0381$). The study concluded that rufinamide adjunctive therapy (3,200 mg/day) was generally effective for adult patients with inadequately controlled partial seizures.[5]

Children with Partial Onset Seizures: Adjunctive Therapy

Based on the efficacy of rufinamide in adults with partial seizures, a randomized, double-blind, placebo-controlled, adjunctive therapy trial was conducted to assess the efficacy and safety of rufinamide as adjunctive therapy in pediatric patients with inadequately controlled partial seizures taking stable dosages of one or two other AEDs. The results have been reported in abstract form.[12] Following a 56-day baseline phase, 268 patients (4–16 years) were randomized to either rufinamide or placebo adjunctive therapy. Study drug dosages were titrated to 45 mg/kg per day over 14 days, followed by a 77-day maintenance period. There was no difference in the mean reduction in partial seizure frequency per 28 days between the adjunctive rufinamide patients and the placebo patients (7.0% vs. 12.8% respectively, $p = 0.621$). There was no difference in the percentage of treatment responders (defined as patients with ≥50% reduction in partial seizure frequency) between the adjunctive rufinamide group and the placebo group (27.2% vs. 18.3%, respectively, $p = 0.060$). This study did not demonstrate the efficacy of adjunctive rufinamide therapy for pediatric partial seizures.[12]

Adults with Partial Onset Seizures: Monotherapy

Two studies investigated the efficacy of rufinamide as monotherapy in patients with treatment-resistant partial seizures.[21,32] One study employed a double-blind, placebo-controlled, parallel-group, monotherapy design in adolescent (≥12 years) and adult patients with treatment-resistant partial seizures who had completed an inpatient evaluation for epilepsy surgery.[21] Following a 48-hour baseline phase, patients were randomized to double-blind monotherapy of either rufinamide or placebo for 10 days. During the double-blind phase, the rufinamide doses were initiated at 2,400 mg/day on day 1, then increased to 3,200 mg/day on day 2, and maintained at that dose for the remainder of the 10 days. Patients exited in the double-blind phase if they met any of four defined sets of types and numbers of seizures. A total of 104 patients were evenly randomized to rufinamide ($n = 52$) or placebo ($n = 52$). During the double-blind phase, the group's mean daily rufinamide dose was 2,970.7 mg/day. The rufinamide-treated patients had a greater median number of days to meet one or more exit criteria versus placebo-treated patients (4.8 vs. 2.4 respectively, $p = 0.0499$). The rufinamide group had significantly greater median times to first, second, and third partial seizures than did the placebo group ($p < 0.0348$). This study demonstrated that rufinamide was more effective than placebo as monotherapy for the short-term treatment of refractory partial seizures.[21]

A second monotherapy study examined the efficacy of high- versus low-dose rufinamide monotherapy in patients with treatment-resistant partial seizures using a double-blind, randomized, parallel-group study design.[32] Eligible patients with treatment-resistant partial seizures on one or two AEDs were randomized to either a low rufinamide dose (300 mg/day, $n = 70$) or a high rufinamide dose (3,200 mg/day, $n = 72$) for 112 days. During the first 42 days of the double-blind phase, rufinamide was titrated upward and concomitant AEDs were simultaneously tapered. Patients either exited the study by meeting criteria based on severity and frequency of seizures or completed the entire 112 days of therapy. A total of 142 patients (12 years and older) were randomized: 70 to rufinamide 300 mg/day and 72 to rufinamide 3,200 mg/day. There was no significant difference between the groups for the primary outcome variable: the percentage of patients meeting one exit criterion (high-dose 66.7% vs. low-dose 72.5%, $p = 0.4402$). The median time to meeting one exit criterion was not different between the two groups (high-dose, 56 days vs. low-dose, 32 days, $p = 0.0968$). Overall, the efficacy analysis did not show a significant difference between the high- and low-dose groups for the efficacy outcome variables.[32]

Adults with Primary Generalized Tonic–Clonic Seizures

A multicenter, double-blind, placebo-controlled study examined the efficacy of adjunctive rufinamide therapy (800 mg/day) for patients with treatment-resistant primary generalized tonic–clonic (GTC) seizures.[4] A 56–day baseline phase was followed by a 140–day double-blind phase. Eligible patients were 4 years and older, with treatment-resistant primary GTC seizures, taking one or two concomitant AEDs, and they had at least three GTC seizures during the 56–day baseline phase (at least one seizure during each of two consecutive 28-day baseline periods). During baseline, the median number of GTC seizures per 28 days during baseline was 3.5 (range, 1.5–84). Following the baseline period, 153 patients (mean age 29.3 years, range, 4–63 years) were randomized to either rufinamide ($n = 78$) or placebo ($n = 75$). There was no difference in the median percent change from baseline in GTC seizure frequency per 28 days between the rufinamide and placebo groups (36.4% vs. 25.6%, respectively; $p = 0.633$). The responder rate (the percentage of patients who had ≥50% reduction in GTC seizure frequency relative to baseline) was not different between the two groups ($p = 0.3162$).

Lennox-Gastaut Syndrome

The efficacy of adjunctive rufinamide therapy for treatment-resistant LGS was examined in a multicenter, double-blind, placebo-controlled, randomized, parallel-group study.[13,14] The study began with a 28-day baseline phase followed by an 84-day double-blind phase (14-day titration phase followed by a 70-day maintenance phase). Patients were eligible if they were between 4 and 30 years, had 90 seizures in the month prior to the baseline phase, and were taking one to three concomitant AEDs. The rufinamide target dose was 45 mg/kg per day. A total of 138 patients, mean age of 14.1 years (range, 4–37 years),

was randomized to either rufinamide (*n* = 74) or placebo (*n* = 64). The median dose in both groups was 1,800 mg/day (42–45 mg/kg/day). In the rufinamide group, the median percent reduction in total seizure frequency per 28 days relative to the baseline phase was significantly higher than in the placebo group (32.7% vs. 11.7%, $p = 0.0015$). The median percent reduction in tonic–atonic seizure frequency per 28 days relative to the baseline phase was significantly higher in the rufinamide group compared to the placebo group (42.5% vs. 1.4%, $p < 0.0001$). The tonic–atonic seizure responder rate was significantly higher in the rufinamide group compared with the placebo group (42.5% vs. 16.7%, $p = 0.0020$) (Fig. 2). An improvement in seizure severity was observed in 53.4% of the rufinamide group compared with 30.6% of the placebo group ($p = 0.0041$). The authors concluded that rufinamide was efficacious as an adjunctive therapy for the treatment of resistant seizures in patients with LGS.

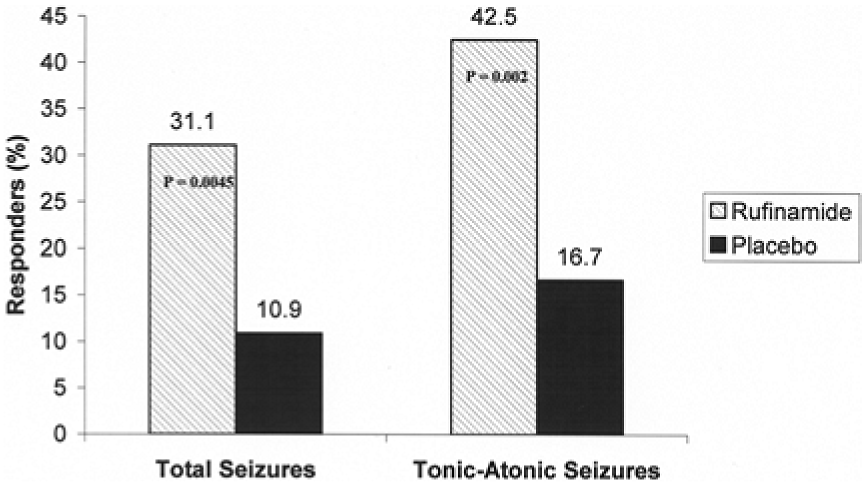

FIGURE 2. Percentage of Lennox-Gastaut patients with ≥50% reduction in tonic–atonic and total seizure frequency (per 28 days during the double-blind phase relative to baseline).

Adverse Events

Dose-Related, Nonidiosyncratic Adverse Effects

In animal studies, rufinamide's safety ratio (defined as the toxic dose in 3% of animals/effective dose in 97% of animals, the TD_3/ED_{97}) was 3 to 900 times greater than for other AEDs.[2]

In humans, the short- and long-term safety of rufinamide in patients with epilepsy was evaluated in a pooled analysis of the adverse event reports from clinical studies.[19] Safety data from all patients with epilepsy who received one or more doses of study drug in any of 12 double-blind, placebo-controlled studies or 12 controlled or open-label studies of rufinamide for short- and long-term therapy were included. The analysis of adverse events used the *Medical Dictionary for Regulatory Activities,* and results were presented by system organ class. The results were reported in abstract form and only common adverse events that occurred in 10% or more of patients were identified. In addition, the analysis examined the time to onset of the common adverse events in only the double-blind, placebo-controlled studies.[19]

Table 3 Adverse events in placebo controlled rufinamide trials

	Rufinamide (*n* = 1,240)	Placebo (*n* = 635)
Headache	22.9	18.9
Dizziness	15.5	9.4
Fatigue	13.6	9.0
Somnolence	11.8	9.1
Nausea	11.4	7.6

Short-term safety data from 1,240 rufinamide-treated patients and 635 placebo patients (mean ages, 31.7 and 28.6 years, respectively) were analyzed. The median duration of exposure of rufinamide (2.8 months) and placebo (3.0 months) was similar. The group's mean rufinamide dose was 1,373 mg/day. The most frequently reported short-term adverse events are shown in Table 3.[19] The time to onset of these short-term adverse events was comparable between the groups. The most commonly reported serious adverse events were epilepsy-related, such as convulsions. Overall, serious adverse events were noted in 6.3% of rufinamide-treated patients compared with 3.9% of placebo-treated patients. Treatment discontinuations due to adverse events were higher among rufinamide-treated patients compared with placebo-treated patients (8.1% vs. 4.3%).[19]

The long-term safety of rufinamide was assessed in 1,978 patients (mean age, 31.3 years) who took rufinamide in controlled or open studies of less than 1 month to more than 4 years in duration. Almost half the patients (47%) had taken rufinamide for 12 months or longer. In this long-term exposure group, the mean rufinamide dose was 1,700 mg/day, with a maximum dose of 7,200 mg/day. The most common organ systems involved were the nervous (64.7%) and gastrointestinal systems (42.3%).[19] The most frequently reported adverse events seen in patients receiving long-term rufinamide therapy were headache (29.5%), dizziness (22.5%), and fatigue (17.7%). Adverse events led to rufinamide discontinuation in 13.1% of the patients.[19] The most common serious adverse events were convulsion, status epilepticus (SE), and pneumonia; overall, 13.2% of patients reported serious adverse events. As the median rufinamide dose increased, the rates of adverse events generally increased. The authors concluded that overall, rufinamide was well tolerated, the commonly occurring short-term adverse events had an early onset with rapid resolution, and long-term rufinamide use was safe and well tolerated.[19]

In the placebo-controlled adjunctive rufinamide pediatric partial seizure trial, the most commonly reported adverse events were headache (rufinamide, 19.1% vs. placebo, 9.8%), somnolence (14.7% vs. 8.3%), vomiting (13.2% vs. 6.1%), and upper respiratory tract infection (6.6% vs. 11.4%). All adverse events classified were mild to moderate in severity. Ten rufinamide-treated patients (7.4%) and four placebo-treated patients (3.0%) prematurely discontinued the study due to adverse events. Ten rufinamide-treated (7.4%) and nine placebo-treated (6.8%) patients had nonfatal serious adverse events.[12]

In the controlled trial involving LGS patients, the most common adverse events experienced included somnolence (24.3% rufinamide, 12.5% placebo), vomiting (21.6% rufinamide, 6.3% placebo), pyrexia (13.5%

rufinamide, 17.2% placebo), and diarrhea (5.4% rufinamide, 10.9% placebo). Cognitive/psychiatric adverse events of interest, such as psychomotor hyperactivity and lethargy, occurred in a lower percentage of patients in the rufinamide group (17.6%) than the placebo group (23.4%).[13,14]

To date, rufinamide is not associated with consistent clinically significant changes in vital signs, physical examinations, electrocardiogram (ECG) recordings, or laboratory tests.[1,4,5,12,13,14,21,32,33] No deaths have been reported in the volunteer-treated population.[9] Twenty-eight deaths have been reported in patients who received either rufinamide or placebo to date.[9] All deaths occurred in patients with epilepsy. For all treated patients with epilepsy, the rate of deaths was 0.71 per 100 patient-years of exposure to rufinamide. The rates were 0.69 per 100 patient-years of exposure to rufinamide and 2.67 per 100 patient-years of exposure to placebo for all patients with epilepsy who received study drug in double-blind studies. None of the deaths was considered to be causally related to rufinamide therapy by either the investigator or the Novartis Medical Monitor.[9] The rate of sudden death was 0 per 100 patient-years for rufinamide and 2.67 per 100 patient-years for placebo.

Idiosyncratic Reactions

The incidence of skin rash is not higher in rufinamide-treated patients compared with placebo (3.1% vs. 3.3%). None of the 1,978 patients included in the clinical database experienced erythema multiforme, Stevens-Johnson syndrome, or toxic epidermal necrolysis. However, a total of five patients in the clinical database might have suffered an AED hypersensitivity syndrome (fever, rash, and any evidence of internal organ involvement). In all cases, the reaction appeared during the first 4 weeks of treatment. All patients were children. None of them had mucosal involvement or blistering of the skin. All patients quickly recovered after discontinuation of rufinamide.

Status Epilepticus

Estimates of the incidence of treatment-emergent SE among patients treated with rufinamide are difficult because standard definitions were not employed. In controlled trials, 11 of 1,240 (0.9%) patients had episodes that could be described as SE in the rufinamide-treated patients compared with none in the placebo-treated patients.

Teratogenicity

To date, no reports of newborn malformations have been associated with maternal rufinamide use. Thirteen pregnancies occurred during the clinical studies (database includes 979 females treated with rufinamide). Six of the 13 pregnancies were known to have resulted in the birth of six healthy babies. One pregnancy was ended by a spontaneous abortion, and three by elective abortions. No information was provided to the sponsor about the outcome of the remaining three pregnancies. However, the overall patient exposure is too low to make any definitive conclusions. Rufinamide is likely to be excreted in breast milk.

Drug Interactions

In vitro testing using human liver microsomes demonstrated that rufinamide did not act as a competitive or mechanism-based inhibitor of the following human P450 enzymes: CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2El, CYP3A4/5, or CYP4A9/11.[17,18] These results indicate that rufinamide should not be expected to inhibit the pharmacokinetics or biotransformation of coadministered drugs metabolized primarily by CYP isozymes.[17]

In patients taking AED polytherapy, rufinamide does not cause clinically significant effects on the pharmacokinetics of concomitant AEDs.[11] A pooled analysis of rufinamide effect on the pharmacokinetics of carbamazepine, lamotrigine, phenobarbital, phenytoin, topiramate, and valproate was performed using five rufinamide multicenter, double-blind, placebo-controlled, randomized, parallel-group studies. The results have been reported in abstract form.[11] These studies involved pediatric and adult epilepsy patients treated with one to three AEDs.[11] The population pharmacokinetic analysis used nonlinear mixed-effect modeling (NONMEM). Six separate populations were analyzed based on the concomitant AEDs: carbamazepine (*n* = 903, median age 32.3 years, range 3.9–68.8 years); lamotrigine (n = 200, median age 22.7 years, range 4.7–68.5 years); phenobarbital (n = 149, median age 34.5 years, range 4.3–62.6 years); phenytoin (n = 299, median age 34.4 years, range 4.5–72.3 years); topiramate (n = 69, median age 15.6 years, range 4.1–53.7 years), and valproic acid (n = 488, median age 27.2 years, range 4.3–68.6 years). Rufinamide did not change the CL/F of topiramate and valproic acid but did increase to a minor extent the CL/F of carbamazepine and lamotrigine, while decreasing to a minor extent the oral clearance of phenobarbital and phenytoin (as a function of rufinamide plasma concentration). Rufinamide-induced changes in AED oral clearance were similar among age groups; rufinamide adjunctive therapy is predicted from the modeling to lead to a less than 18% change in the pre-rufinamide AED CL/F at a rufinamide concentration of 15 ug/mL (i.e., a typical steady-state rufinamide concentration in a patient taking either 45 mg/kg per day in children or 3,200 mg/day in adults). The changes in concurrent AEDs' oral clearance would result in changes of steady-state AED concentrations of less than 21%.[11]

Rufinamide's pharmacokinetics does not appear to be affected by carbamazepine, clobazam, oxcarbazepine, or vigabatrin.[17] Valproic acid decreases rufinamide's CL/F by approximately 22%; phenytoin and barbiturates increase rufinamide's CL/F by approximately 25%.[9,17]

The effect of rufinamide on low-dose oral contraceptives was examined in a single-center, open-label, multiple-dose 56-day study.[31] Overall, 18 healthy female volunteers took Ortho-Novum 1/35 for at least two cycles prior to randomization and throughout the entire study. Rufinamide 1,600 mg/day was given on days 22 through 35. Coadministration of rufinamide and Ortho-Novum 1/35 resulted in a mean decrease in the ethinyl estradiol $AUC_{0\text{-}24}$ of 22% and norethindrone $AUC_{0\text{-}24}$ by 14% on day 34, as compared with baseline levels taken on day 7. The clinical significance of this decrease is unknown since this study did not measure any markers of ovulation.[17,31]

Role in Epilepsy Treatment

Indications

Rufinamide is not yet approved for prescription use. In controlled clinical trials, it has demonstrated efficacy against partial seizures in adults and in patients with LGS.[5,10,14]

Dosing Recommendations

In clinical trials, the best rufinamide efficacy results have been seen with doses of 3,200 mg/day in adults and 45 mg/kg per day in children. In adults, treatment should be initiated with a daily dose of 400 to 800 mg/day, as twice-daily dosing. Additional dosing increments may be given (400–800 mg/day every 2 days in two equally divided doses) to a maximum recommended daily dose of 3,200 mg. Doses greater than 3,200 mg/day have been used in open-label studies for periods of 48 months and longer. In general, no clinical trial evidence indicates that doses greater than 3,200 mg/day confer additional benefit. Dose titration should be guided by clinical outcome. In children, treatment should be initiated at a daily dose of approximately 10 mg/kg per day administered in two equally divided doses. The dose should be increased by approximately 10 mg/kg increments every other day to a maximum of 45 mg/kg per day or 3,200 mg/day, whichever is less, administered in two equally divided doses. Some patients have responded at lower doses, whereas others have needed higher dosages (up to 4,800 mg/day in adults). A more complete understanding of the optimal dosing for rufinamide must wait for a larger patient experience (e.g., through large-scale postmarketing clinical trials).

Precautions

In addition to hypersensitivity reactions and the incidence of SE mentioned earlier, rufinamide should be withdrawn gradually to minimize the risk of precipitating seizures, seizure exacerbation, or SE. If abrupt discontinuation of the drug is medically necessary, the transition to another AED should be made under close medical supervision. In clinical trials, rufinamide discontinuation was achieved by reducing the dose by approximately 25% every 2 days.

Contraindications

Rufinamide is contraindicated in patients with a known hypersensitivity to rufinamide, triazole derivatives, or to any excipients used in the formulation.

Summary and Conclusions

Both in animal models and in human clinical trials, rufinamide appears to have efficacy against a broad spectrum of seizure types. Efficacy is well documented as adjunctive therapy against partial-onset seizures in adults and generalized seizures in patients with LGS. Although overall patient exposure is still relatively low, its dose-dependent adverse event profile is encouraging, and there appears to be a low risk of idiosyncratic reactions. Rufinamide undergoes dose-dependent absorption, is eliminated with a half-life of 6 to 10 hours, and it shows a limited potential for drug interactions. It is not yet approved for prescription use.

Based on its characteristics and clinical trial results, rufinamide shows promise as a valuable addition to the currently approved assortment of AEDs.

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Chapter 158

Tiagabine

Reetta Kälviäinen

Introduction

Tiagabine (Gabitril) (Fig. 1) is a selective γ-aminobutyric acid (GABA) reuptake inhibitor (SGRI), which increases synaptic GABA availability via inhibition of the GAT-1 GABA transporter on presynaptic neurons and glial cells.[10] It is structurally related to nipecotic acid, but has an improved ability to cross the blood–brain barrier. Tiagabine has been approved for add-on therapy in patients with refractory partial seizures with or without secondary generalization in approximately 30 countries.

Mechanism of Action

Potentiation of GABA is regarded as one of the most important mechanisms of action for novel antiepileptic agents. GABA uptake inhibitors represent a new class of antiepileptic drugs (AEDs), of which tiagabine was the first to be introduced into clinical practice. Tiagabine prevents GABA uptake by inhibiting selectively the GAT-1 GABA transporter, with little or no activity on GAT-2, GAT-3, or BGT-1, which are the GABA transporters responsible for the uptake of the neurotransmitter into neurons and glial cells after synaptic release.[10,60] Tiagabine's affinity for inhibiting glial GABA uptake is 2.5-fold greater than that for neuronal uptake.[11] Tiagabine is not a substrate for the GABA uptake carrier and is therefore unlikely to act as a false transmitter at GABAergic neurons.[11] Blockade of GABA uptake temporarily sustains levels of endogenously released GABA in the synapse.[60] This is the only known mechanism of tiagabine action.

Although both tiagabine and vigabatrin act by enhancing GABA neurotransmission in the central nervous system (CNS), preclinical data show that vigabatrin and tiagabine have different pharmacologic profiles and different mechanisms of action at the cellular level.[55] Tiagabine prolongs the duration, but not the magnitude, of the peak inhibitory postsynaptic current, consistent with temporarily sustained levels of endogenously released GABA in the synapse.[49] By contrast, vigabatrin inhibits presynaptic GABA degradation by selective, enzyme-activated irreversible blockade of the mitochondrial enzyme GABA transaminase, and thus it induces a persistent fivefold increase in whole brain GABA concentration, and also high concentrations in the retina.[56] Tiagabine does not induce the widespread increase in total brain GABA concentrations that accompanies GABA-T inhibition. Moreover, viga-batrin seems to accumulate in the retina, whereas tiagabine does not.[56]

Experimental Studies

The anticonvulsant action of tiagabine has been studied in animal models of epilepsy induced by electrical, chemical, and sensory stimuli, and in genetic models of epilepsy. When administered intraperitoneally to amygdala-kindled rats, tiagabine attenuates the expression of secondarily generalized seizures and completely blocks the expression of partial seizures.[20] Tiagabine also suppresses amygdala kindling–induced epileptogenesis in a dose-dependent manner in the rat.[21]

Intraperitoneal tiagabine was shown to be an active anticonvulsant in experimental studies by protecting against audiogenic and methyl-6,7-dimethoxy-4-ethyl-β-carboline-3-carboxylate- and pentylenetetrazol (PTZ)-induced tonic or clonic seizures in mice and PTZ-induced tonic or clonic seizures in rats.[46] However, tiagabine did not protect against maximal electroshock-induced tonic seizures in mice or rats.[20,46] Tiagabine did not prevent tonic or clonic seizures induced by the potassium channel antagonists dendrotoxin or 4-aminopyridine in mice.[16,64]

In common with GABA agonists, tiagabine may enhance the occurrence of spike-and-wave discharges in animal models of nonconvulsive epilepsy. In WAG/Rij rats, a genetic model of generalized nonconvulsive absence epilepsy, spike-and-wave discharges were increased by tiagabine 3 and 10 mg/kg administered intraperitoneally, but not by a 1 mg/kg dose.[15] Walton et al.[63] reported that tiagabine was effective in treating status epilepticus (SE) in cobalt-lesioned rats. At doses ≥5 mg/kg intraperitoneally, it produced rhythmic high-voltage discharges. At even higher doses, a similar pattern could be produced in normal rats as well. Exacerbation of absence seizures has been found also in rats with genetic absence epilepsy (GAERS) and in the lethargic mouse model.[29]

Tiagabine reduced both seizure-induced damage to pyramidal cells in the hippocampus and impairment of spatial memory associated with hippocampal damage in the perforant pathway stimulation model of SE in the rat.[28] Neuronal cell death was also reduced by tiagabine in the hippocampus of gerbils subjected to cerebral ischaemia[30] and in the rat cerebral ischaemia model of delayed pyramidal cell death.[31]

Pharmacokinetics

Tiagabine is rapidly and nearly completely absorbed after oral administration, with peak concentrations seen within 30 to 90 minutes of dosing.[27] Food delays the time to peak concentration from a mean of 0.9 to a mean of 2.6 hours, but does not change the total quantity absorbed. Because tiagabine has a short elimination half-life, the smoother absorption produced by concomitant intake of food helps in reducing excessive fluctuations in plasma drug levels during the dosing interval and, for this reason, it is recommended that the drug be taken at meal times, preferably at the end of the meal.

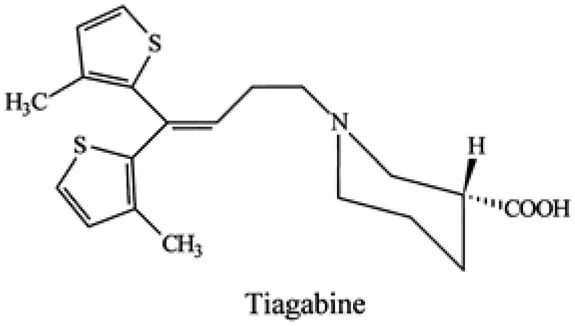

FIGURE 1. Chemical structure of tiagabine.

Table 1 Efficacy of tiagabine as add-on therapy in partial epilepsy

	Responder rate (>50% seizure reduction) for all partial seizures

Reference	Number of patients	Daily dose mg/day	Tiagabine	Placebo
Richens et al., 1995	42	33	52%	24%[b]
Crawford et al., 1993	36	46	40%	14%[a]
Uthman et al., 1998	297	16	10%	4%
		32	20%	4%[b]
		56	31%	4%[c]
Sachdeo et al, 1997	318	32 (16 mg b.i.d.)	28%	8%[c]
		32 (8 mg q.i.d.)	23%	8%[b]
Kälviäinen et al. 1998	154	30	10%	5%
Ben-Menachem 1995	951	16–56	23%	9%

[a]$p < 0.05$, [b]$p < 0.01$, [c]$p < 0.01$
Data from five double-blind, placebo-controlled trials and from an integrated analysis of these studies.

Protein binding is high at 96%, but tiagabine does not displace highly protein-bound drugs such as phenytoin and valproic acid from their binding sites. The volume of distribution is approximately 1 L/kg. Tiagabine is widely metabolized in humans, mainly by isoform CYP3A4 of the cytochrome P450 family. Less than 1% is excreted unchanged in the urine, and no active metabolites have been identified.[45]

Tiagabine pharmacokinetics are linear at doses up to 80 mg/day.[58] There is no evidence that tiagabine either causes induction or inhibition of cytochrome P450 enzymes.[27] Consequently, tiagabine has shown no action on hepatic metabolism, which would be expected to alter the pharmacokinetics of cimetidine, carbamazepine, digoxin, erythromycin, oral contraceptives, phenytoin, theophylline, valproate, and warfarin.[12] However, enzyme-inducing AEDs such as carbamazepine, phenytoin, phenobarbital, or primidone increase the hepatic clearance of tiagabine when given in combination.[32] The plasma half-life, which is normally 5 to 9 hours,[27] is reduced to 2 to 3 hours in combination with enzyme-inducing drugs.

Clinical Efficacy

Evidence from Randomized Controlled Trials

Tiagabine has proven effective as add-on therapy in patients with refractory partial seizures with or without secondary generalization. The primary clinical evidence for this efficacy is based on five controlled add-on trials in adults with epilepsy unsatisfactorily controlled with current AEDs (Table 1).

The first phase II multicenter trials were two small, placebo-controlled cross-over studies. In an initial titration period lasting up to 8 weeks, patients started with a tiagabine dose of 8 mg/day, and the dose was titrated either to reduce seizures sufficiently or to produce unacceptable adverse events. Patients then entered a 4-week fixed-dose period on the dose attained in titration. The maximal dose allowed in the first study was 52 mg/day.[48] Patients were eligible to enter the double-blind cross-over phase if their seizure frequency had been reduced by at least 25% during the fixed-dose period. In this two-period crossover study, patients were randomized to placebo/tiagabine or their previously determined dose of tiagabine/placebo, remaining on each of these two regimens for 7 weeks. The 7-week treatment periods were separated by a 3-week washout period. The median daily dose of tiagabine in the double-blind phase was 32 mg/day. Of the total of 42 patients who contributed data for both periods of the crossover phase, 26% of those with complex partial seizures and 63% with secondarily generalized tonic–clonic seizures ($n = 27$) experienced a reduction of at least 50% in seizure frequency during the tiagabine period compared with the placebo period. The median seizure rate during the tiagabine treatment period was significantly lower than during the placebo treatment period for complex partial seizures ($p = 0.05$) and secondarily generalized tonic–clonic seizures ($p = 0.009$).

The second phase II study used the same design but allowed a maximal dose of 64 mg/day.[18] The intent-to-treat group comprised 36 patients who received a mean total daily dose of 46 mg in the tiagabine treatment periods. Tiagabine was significantly better than placebo in reducing all partial seizures ($p = 0.002$), complex partial seizures ($p < 0.001$), and partial seizures with secondary generalization ($p = 0.030$). A total of 46% of patients with complex partial seizures had at least a 50% reduction in weekly seizure rates.

Altogether 769 patients took part in the three multicenter, parallel-group, double-blind add-on studies in which tiagabine was compared with placebo—a dose-response study, a dose-frequency study, and a three-times-a-day (t.i. d.) dosing study.[35,50,62] The dose-ranging multicenter study in the United States had a fixed-dose, placebo-controlled parallel-group design ($n = 297$)[62]. During a 4-week period, tiagabine-treated patients were given increasing doses until the dose level to which they had been randomized was reached (16, 32, or 56 mg/day, divided in four equal doses). The patients then remained on a fixed dose for 12 weeks of double-blind treatment. Median decreases in 4-week complex partial seizure frequency for 32 mg (–2.2) and 56 mg (–2.8) tiagabine groups were significantly greater than for the placebo (–0.7) group ($P = 0.03$ and $P < 0.03$, respectively); 20% and 29% of patients in the 32- and 56-mg groups had a 50% or greater reduction in the frequency of complex partial seizures compared with 4% in the placebo group ($P = 0.002$ and $P < 0.001$, respectively).

The dose-frequency study was also a randomized, double-blind, placebo-controlled U.S. multicenter study with a parallel-group, add-on design ($n = 318$).[50] The study lasted for 24 weeks and consisted of an 8-week baseline, a 12-week double-blind treatment phase, and a 4-week termination period. During the first month of treatment, doses were increased weekly to 32 mg/day. The treatment groups were placebo, 16 mg tiagabine twice a day (b.i.d.) and 8 mg tiagabine four times a day. The median changes in 4-week complex partial seizure rates were –1.6 ($p = 0.055$) for the 16 mg twice-a-day group and –1.2 ($p < 0.05$) for the 8 mg four-times-a-day group, versus –0.2 for placebo. Statistically significant differences between placebo and two tiagabine groups occurred in the proportion of patients experiencing >50% rate reduction for complex partial, simple partial, and all partial seizure rates.

The thrice-daily dosing study was a Northern-European multicenter parallel-group study that compared a dose of 30 mg/day tiagabine with placebo as add-on therapy ($n = 154$).[35] The study included 12-week baseline, an 18-week double-blind treatment phase, and a 4-week termination period. The median change from baseline in complex partial seizure rates was –1.3 for patients on tiagabine, whereas placebo patients had a median increase of 0.1 in complex partial seizure rates (p <0.05). Tiagabine was significantly more effective than placebo in patients with simple partial seizures with respect to the proportion of patients achieving a seizure reduction of at least 50% (21% vs. 6%; p <0.05).

The meta-analysis across all these three trials for 50% responders showed an odds ratio of 3.03 (95%; CI 2.01–4.58) in favor of tiagabine.[44] The summary odds ratios for each dose indicate increasing efficacy with increasing doses, with no suggestion that the effect of the drug had reached a plateau at the doses examined in these studies. A 16-mg dose has a fairly small effect of 2.40 (95%; CI 0.65–8.87). There is a substantial increase with doses of 30 or 32 mg to odds ratio of 3.17 (95%; CI 2.03–4.96) and a smaller additional gain for a dose level 56 mg, odds ratio 7.95 (95%; CI 3.09–20.49).

A multicenter, open-label, randomized, parallel-group study compared the efficacy, tolerability, and safety of twice- and thrice-daily dosing of tiagabine as an adjunctive therapy for the treatment of refractory patients with partial seizures.[8] A total of 347 patients were randomized and treated (175 t.i.d and 172 b.i.d.). Each group was administered the same daily dose of tiagabine incremented stepwise during a 12-week fixed-schedule titration period to a target 40 mg/day. The patients were followed for a further 12-week flexible continuation phase. The proportion of 50% responders was similar for both groups (44% for b.i.d. and 48% for t.i.d.) during last 8 weeks of treatment. The long-term efficacy and safety of twice-daily dosing was verified by another similar study by Arroya et al.[4]

A multicenter trial has also been performed to determine whether the combination of AEDs with different mechanisms of action may be superior to the combination of AEDs with similar mechanism of action. In this study, patients on carbamazepine or phenytoin monotherapy with inadequately controlled complex partial seizures were randomized to add-on tiagabine or phenytoin (if previously on carbamazepine) or add-on tiagabine or carbamazepine (if previously on phenyt-oin) and titrated to an optimal dose in a double-blind trial.[9] In this trial, tiagabine (n = 170) showed similar efficacy to traditional AEDs (carbamazepine or phenytoin) (n = 175) adjunctive therapy for complex partial seizures at low average doses of 24 to 28 mg/day. The study also suggested that tiagabine may be better tolerated when added to phenytoin or carbamazepine than when carbamazepine or phenytoin are added to each other.

Evidence from Other Studies

Data are available from six long-term open-label trials. More than half of the 2,248 patients have been treated with tiagabine for more than 1 year. For each type of partial seizure, 30% to 40% of the patients obtained considerable treatment effect, which was maintained after 12 months of treatment.[5] Daily dosages in the long-term studies were between 24 and 60 mg in the majority of patients, and mean and median doses were 45 mg/day for most studies. However; up to 15% of patients received a dose of between 80 and 120 mg/day after their first year of treatment.[42]

Pragmatic trials use larger patient numbers and a longer follow-up than do the trials required for drug registration and they more closely mimic routine clinical practice. Three such pragmatic studies have been conducted using add-on tiagabine in patients with refractory partial epilepsy and using the newly recommended titration schedule in a total of 1,151 patients, aged 3 to 93 years, who were followed for up to 6 months.[6,19,51] Tiagabine was given three times a day, at an initial dose of 5 mg per day and, following the new schedule, with increases of 5 mg per week. The average dose was 30 mg (range 5–90) per day. Rates for 50% responder varied from 41% to 61%, and 8% to 22% of patients became seizure-free.

Efficacy as Monotherapy

The efficacy of tiagabine during monotherapy in patients with chronic partial epilepsy not satisfactorily controlled by other drugs has been studied in a double-blind, parallel-group study in 198 patients with refractory epilepsy, comparing 6 mg per day tiagabine with 36 mg per day after gradual withdrawal of other AEDs over 29 weeks.[52] Altogether 33% of the patients on the low dose completed the study, compared with 47% taking the higher dose. For both dose groups, the median complex partial seizure rates decreased significantly during treatment compared with baseline (p <0.05). However, a higher proportion of patients in the 36 mg/day group experienced a reduction in complex partial seizures of at least 50% compared with the 6 mg/day group

(31% vs. 18%, $p < 0.05$). In addition to showing a dose–response relationship, this study suggested that even as low a dose as 6 mg/day of tiagabine may be effective when used as monotherapy or with noninducing AEDs.

The second study was a double-blind, randomized comparison of a slow and fast switch to tiagabine monotherapy from another monotherapy, followed by an open-label evaluation of the safety and efficacy of tiagabine as monotherapy for chronic partial epilepsy.[37] If the patients did not tolerate the double-blind titration scheme for tiagabine, even slower open-label up-titration of tiagabine could be used. Thirty-four (85%) of the 40 patients were successfully switched to tiagabine monotherapy in either the double-blind or open-label drug switching schemes. According to this trial, it seems that the open-label up-titration using 5 mg/day with weekly increments of 5 mg/day should be recommended in clinical practice. Monotherapy in newly diagnosed partial epilepsy has been studied comparing the efficacy and safety of tiagabine versus carbamazepine as monotherapy in a double-blind, randomized, parallel-group trial ($n = 290$).[13] During the 6-week titration period, patients were titrated from tiagabine 5 mg/day or carbamazepine 200 mg/day to tiagabine 10 or 15 mg/day or carbamazepine 400 or 600 mg/day in a step-wise fashion. During the 44-week assessment period, dosage could be adjusted within the ranges for carbamazepine 10 to 20 mg/day for tiagabine or 400 to 800 mg/day. All doses were administered twice daily. The study has so far only been published in abstract form, showing a significant difference between the study groups with regard to

the end-point “time to meeting the exit criterion” ($p < 0.05$). An exit criterion was either SE or the occurrence of the second seizure at maximum tolerated or maximum allowed dose level. In the tiagabine group 41% (60 of 146) and in the carbamazepine group 53% (77 of 144) completed the assessment period either seizure-free or with a single seizure ($p < 0.05$). It has been suggested that failure of tiagabine monotherapy to show efficacy comparable to carbamazepine in this trial might have been related to the relatively low maximum dose of tiagabine that was used.

Efficacy in Pediatric Patients

Use of tiagabine in children has been studied as adjunctive therapy in over 200 pediatric patients. A European study was carried out at two centers in Denmark and one center in France.[61] This 4-month, single-blind study evaluated the tolerability, safety, and preliminary efficacy of ascending doses (0.25–15 mg/kg/day) of tiagabine add-on therapy in 52 children over 2 years of age with different syndromes of refractory epilepsy. Tiagabine appeared to reduce seizures more in localization-related epilepsy syndromes than generalized epilepsy syndromes. Seventeen of the 23 patients with localization-related epilepsy syndromes entered the fourth dosing period. The 17 patients had a median reduction of seizure rate in the fourth month of treatment of 33% compared with baseline. In comparison, 13 of 22 children with seven different generalized epilepsy syndromes entered the fourth dosing period with a median change of seizure rate of 0%. Among generalized seizures, tonic seizures and atypical absences responded best, with median percentage reductions in the weekly seizure rate of 77% and 63%. The overall maximum daily tiagabine dose level received and tolerated (mean ± S.D.) was 0.65 ± 0.37 mg/kg.

In the United States, the long-term use of tiagabine has been studied also in an open-label extension study in 152 children, aged 2 to 11 years, from antecedent double-blind studies.[17] Of the 140 evaluable patients, 10 were seizure-free with tiagabine add-on therapy, and 13 achieved seizure-freedom with tiagabine monotherapy for periods ranging from 9 to 109 weeks. The shortest seizure-free or monotherapy durations represented patients with recent enrollment dates at the time of report. Dose range was from 4 to 66 mg/day, and average dose was 23.5 mg/day. In a recent preliminary open trial in infantile spasms, six of 12 infants had at least 50% seizure reduction at dosages of 0.5 to 3.1 mg/kg per day.[39]

Table 2 Treatment-emergent CNS-related adverse effects

Adverse event	Placebo	Tiagabine

	(*n* = 275), n(%)	**(*n* = 494), n(%)**
Dizziness	41 (15)	131 (27)[b]
Asthenia	39 (14)	99 (20)[a]
Nervousness	8 (3)	50 (10)[b]
Tremor	9 (3)	46 (9)[a]
Difficulty with concentration/attention	6 (2)	30 (6)[a]
Depression	2 (<1)	17 (3)[a]
Language problems	0 (0)	8 (2)[a]

[a]$p < 0.05$; [b]$p < 0.01$
Significantly higher treatment-emergent CNS-related adverse events reported by ≤1% of tiagabine-treated patients during the experiment period in the three placebo-controlled, parallel-group, add-on epilepsy studies by Leppik et al.[42]

Clinical Safety

From short-term trials compared with placebo, it was clear that some CNS-related adverse effects are particularly common with tiagabine treatment (Table 2). Dizziness is most frequent. This is a feeling of light-headedness or unsteadiness, and develops usually within 1 or 2 hours of taking a tiagabine dose. It is associated with the peak concentration of the drug. Also more common with tiagabine than with placebo were asthenia (lack of energy), nervousness, tremor, concentration difficulties, depressive mood, and language problems (difficulty in finding words or initiation of speech). The increased risk of CNS-related adverse events compared to placebo occurred during the titration period only. There was no difference in side effects during the fixed-dose period.[42] This experience suggests that tiagabine should be titrated slowly. It is recommended, on the bases of these studies, that initial dosages of tiagabine can be given twice a day, but a change to three times daily dosing is recommended with dosages above 30 mg/day. Tiagabine should always be taken with food to avoid rapid rises in plasma concentrations. Individually, four times daily dosing may also be helpful at least with higher doses. Somnolence or drowsiness were not seen more frequently in tiagabine patients than in patient receiving placebo.

No idiosyncratic reactions have as yet been linked to the use of tiagabine.[41] No systematic abnormalities have been noted in hematology values or common chemistry values; therefore, no specific guidelines are available for routine monitoring of laboratory values during tiagabine treatment.[42] The relationship of adverse events has correlated more strongly with dose than with the plasma concentration of tiagabine.[42] Therefore, it is most important to up-titrate the dosage according to the tolerability of the individual patient, and there is no need to follow-up routinely on the plasma concentration.

Because of its action on GABAergic mechanisms, the question has been raised as to whether tiagabine, like vigabat-rin, can result in visual field abnormalities. To date, however, no evidence suggests that the increased risk of concentric visual field defect is a class effect of GABAergic drugs. A cross-sectional study compared vigabatrin add-on patients with tiagabine add-on patients and controls and found that, unlike vigabatrin, tiagabine treatment seemed to be associated with normal electroretinography and visual fields.[33] The first ophthalmologic study of 15 patients using tiagabine as monotherapy (mean daily dosage 21 mg, range 5–60 mg; mean duration of therapy 38 months, range 23–55 months) did not show any evidence of a relationship between visual field constriction and tiagabine treatment.[47] A larger cross-sectional study was set up in newly diagnosed patients with partial epilepsy receiving tiagabine, carbamazepine, or lamotrigine as initial monotherapies.[36] Neurologic and ophthalmologic tests, including Goldmann and Humphrey perimetries, were performed. A neuro-ophthalmologic expert blindly reviewed all visual charts. Seventy-three patients were included and completed the study. The population eligible for analysis included 68 patients, of whom 32 were treated with tiagabine (median duration, 25 months), 24 with carbamazepine (21 months), and 12 with lamotrigine (15 months). No clinically relevant abnormalities in visual fields resembling those known with vigabatrin were detected, particularly in patients treated initially with tiagabine monotherapy. These findings support the evidence that tiagabine is not associated with retinal toxicity. The results of a small study (*n* = 20) of newly diagnosed patients with partial epilepsy suggest that tiagabine does not have

an effect on visual contrast sensitivity but may interfere with color perception, a phenomenon common to many of AEDs.[59]

There has also been concern that tiagabine may be associated with an increased incidence of psychosis, particularly with rapid titration. Evaluation of psychosis-related adverse effects showed no excess risk of this disorder attributable to tiagabine beyond what would be expected from the population with difficult-to-control partial seizures. The incidence of psychosis was 0.8% in the tiagabine-treated patients and 0.4% in the placebo-treated patients in the three parallel group add-on trials.[42] However, the addition of tiagabine in clinical trials was associated significantly more often with depression than was the use of placebo (5% vs. 2%).[42] Because of this concern, if a history of behavioral problems or depression is present, treatment with tiagabine should be initiated at a low initial dose under close supervision, because there may be an increased risk of recurrence of these symptoms during treatment with tiagabine.

The cognitive effects of tiagabine add-on therapy and monotherapy have been widely evaluated. In the largest short-term double-blind study, 162 adults completed a multicenter, dose–response study with random assignment to placebo or 16, 32, or 56 mg/day tiagabine.[23] Results on 19 measures of cognitive abilities and 18 measures of adjustment and mood showed only findings attributable to chance. Long-term cognitive results have been presented in a double-blind, placebo-controlled, parallel-group add-on study with an open-label extension study with 18- to 24-month follow-up.[34] The neuropsychological and electroencephalogram (EEG) evaluation did not indicate any adverse effects of tiagabine during the double-blind phase at low doses or the long-term open-phase at higher doses up to 80 mg /day. One study compared the cognitive effects of add-on tiagabine therapy to add-on topiramate therapy and found that topiramate, but not tiagabine appeared to be associated with persistent cognitive side-effects.[25] Dose-related impacts of tiagabine on cognition and mood were studied in a conversion-to-monotherapy study comparing doses of 6 mg/day and 36 mg/day of tiagabine as monotherapy in previously uncontrolled epilepsy patients.[22] The study showed modest improvements in cognitive abilities and adjustment compared to the more traditional AEDs given at baseline. In patients with inadequately treated chronic partial seizures, an evaluation of the effects of tiagabine monotherapy on cognition and mood was performed.[2] The results from the 18 patients who successfully converted to 1-year tiagabine monotherapy[2] or even longer[3] treatment suggest that tiagabine does not have an adverse effect on cognition or mood. A pooled analysis of two studies in newly diagnosed patients with partial seizures showed that, after 52 weeks of tiagabine (20–30 mg/day) monotherapy (*n* = 42), there were no detrimental effects on cognition; and the results was similar to the results with carbamazepine monotherapy (400 and 800 mg/day) (*n* = 42 and *n* = 1, respectively).

Several cases of nonconvulsive SE have been reported, with disappearance of the status after withdrawal of the drug or reduction in dosage.[38] In double-blind, placebo-controlled trials on patients with partial epilepsy, however, the incidence of spike-and-wave SE, or any kind of SE, was 3% (8 of 275 patients) on placebo and 4%

(22 of 494 patients) on tiagabine, the difference being not statistically significant.[54] Further study of individual cases suggested that most of the subjects with apparently tiagabine-associated nonconvulsive status had pre-existing spike-and-wave patterns and, that, in some cases, the condition was related to drug-induced encephalopathy rather than SE. However, it might be wise not to use tiagabine in patients with unclassified epilepsy or patients with generalized epilepsy, especially those with a history of absence or myoclonic seizures, with a history of spike-and-wave discharges on EEG, or nonconvulsive SE.[53] Tiagabine has not been shown to be effective in these patients, and other evidence suggests that those AEDs that increase GABAergic transmission may exacerbate or induce absences or myoclonus.[43] In patients with a history of spike-and-wave discharges, cognitive or neuropsychiatric disturbances can be associated with exacerbation of the EEG abnormalities. In 2005, the U.S. Food and Drug Administration (FDA) announced that a Bolded Warning will be added to the labeling for tiagabine to warn prescribers of the risk of seizures in patients without epilepsy being treated with this drug. The FDA had become aware of reports of the occurrence of seizures in more than 30 patients prescribed tiagabine for conditions other than epilepsy.[24] Most of these uses were in patients with psychiatric illnesses. In addition to the occurrence of isolated seizures, FDA has received several reports of SE in patients without epilepsy. The use of tiagabine in psychiatric disorders, sleep disorders, and drug dependence has been studied in several small trials,[7] but the safety and efficacy of tiagabine have not yet been systematically evaluated for indications other than epilepsy and, therefore, its off-label use should be discouraged.[24]

Role in epilepsy treatment

Tiagabine is recommended as add-on treatment of adults and children over 12 years with partial seizures, with or without secondary generalization, that cannot be satisfactorily controlled with other AEDs. In the preclinical and clinical studies, the tiagabine dose was expressed in terms of milligrams (mg) of hydrochloride. A conversion factor of 0.91 has been used to calculate the dose as tiagabine free base, which is available as 2.5-, 5-, 10-, and 15-mg tablets, except in the United States, Canada, and Mexico, where 2-, 4-, 12-, 16-, and 20-mg tablets of tiagabine hydrochloride are used. The current labeling with tiagabine free base states that the initial dosage is 7.5 to 15 mg/day, followed by weekly increments of 5 to 15 mg /day. In the United States, Canada, and Mexico, labeling is already modified toward a lower initial dose of 4 mg/day tiagabine hydrochloride, followed by weekly increments of 4 to 8 mg/day.

Phase IV trial and clinical experience to date would suggest starting tiagabine with 4 or 5 mg/day and gradually increasing the dosage by weekly increments of 4 or 5 mg /day, to minimize CNS-related side effects. Initial dosages can be given twice a day, but a change to three-times-daily dosing is recommended with dosages above 30 to 32 mg/day. Tiagabine should always be taken with food, and preferably at the end of meals, to avoid rapid rises in plasma concentrations. Individual dosing four times daily may also be helpful, at least with higher doses.

Population pharmacokinetic analyses indicate that tiaga-bine clearance is 60% greater in patients taking enzyme-inducing AEDs. The usual initial target maintenance dosage in patients taking enzyme-inducing drugs is 30 to 32 mg/day and, in patients not taking enzyme-inducing drugs, 15 to 16 mg/day.[53] The usually recommended range of maintenance dosage in patients taking enzyme-inducing drugs is up to 50 to 56 mg/day and, in patients not taking enzyme-inducing drugs, up to 30 to 32 mg/day. However, high daily doses of at least 70 to 80 mg are well tolerated for some individual patients. Patients taking a combination of inducing and noninducing drugs (e.g., carbamazepine and valproate) should be considered to be enzyme-induced. No AED should be suddenly withdrawn, and although there are no clinical data, it seems sensible to withdraw tiagabine gradually over at least 2 to 3 weeks.[53]

The pharmacokinetics of tiagabine in elderly patients are similar to those observed in younger patients, hence there should be no need for dosage modification.[57] The pharmacokinetics of tiagabine has not been investigated in adequate and

well-controlled clinical trials in patients younger than 12 years. The apparent clearance and volume of distribution of tiagabine per unit body surface area or per kilogram were fairly similar in 25 children (aged 3 to 10 years) and in adults taking enzyme-inducing AEDs. In children who were taking a noninducing AED, the clearance of tiagabine based on body weight and body surface area was 2- and 1.5- fold higher, respectively, than in noninduced adults with epilepsy, thus suggesting that dosage requirements (on a mg/kg basis) may be higher in children.[26] In the pediatric study, the maximal tolerated doses for children over 2 years old on inducing AEDs were only slightly higher than in children on noninducing AEDs, but the difference was not significant (0.73 ± 0.44 mg/kg vs. 0.61 ± 0.32 mg/kg).[61]

The pharmacokinetics of tiagabine is unaffected in patients with renal impairment or in subjects with renal failure requiring hemodialysis.[14] Patients with mild or moderate liver function impairment have been shown to have higher and more prolonged plasma concentrations of both total and unbound tiagabine after administration, compared with normal subjects. The patients with hepatic impairment also had more neurologic side effects. Tiagabine should therefore be given with caution to patients with epilepsy who have impaired hepatic function. Patients with impaired liver function may require reduced initial and maintenance doses of tiagabine and/or longer dosing intervals, compared with patients having normal hepatic function. The patients should be monitored closely because of the potential for an increased incidence of neurologic side effects.[40] Tiagabine should not be used in patients with severely impaired liver function.

Summary and Conclusions

Tiagabine, a selective GABA-uptake inhibitor, is effective against all partial seizures and has a relatively favorable safety profile. The frequency of idiosyncratic drug-related reactions, including cutaneous reactions, is low with tiagabine. Moreover, tiagabine has a favorable cognitive profile. The characteristic concentric visual field defect seen with vigabatrin treatment has not been observed in two tiagabine monotherapy trials. Thus, tiagabine is recommended for use as an add-on treatment in partial epilepsy, for example after failure with the first-line sodium-channel–blocking AEDs or if the first-line AED has caused idiosyncratic reactions. Tiagabine is suitable also for patients for whom it is particularly important that the AED does not cause any deterioration in cognitive performance. If a history of behavioral problems or depression is present, treatment with tiagabine should be initiated at a low initial dose under close supervision, because there may be an increased risk of recurrence of these symptoms during treatment with tiagabine. Tiagabine should not be used in patients with unclassified epilepsy or patients with generalized epilepsy, especially those with a history of absence or myoclonic seizures, or with a history of spike-and-wave discharges on the EEG or nonconvulsive SE.

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Chapter 159

Topiramate

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Tracy A. Glauser

Introduction

Topiramate (TPM) is a broad-spectrum antiepileptic drug with multiple mechanisms of action. It was originally synthesized as part of a search for fructose-related compounds with hypoglycemic activity.[63] It was not developed for that purpose, but was discovered to have antiepileptic activity in animal models in the 1980s. Phase II clinical trials began in 1988 and it was approved for prescription use in the United States in 1996. It is available in over 80 countries.

Chemistry

Topiramate(2,3:4,5-bis-*O*-(1-methylethylidene)-ß-D-fructop- yranose sulfamate) is a monosaccharide derived from D-fructose, and is not structurally related to other antiepilepsy drugs (Fig. 1). It exists as a white crystalline powder, has a molecular weight of 339.37 and empirical formula of $C_{12}H_{21}NO_8S$, and is soluble in water and organic solvents at physiologic pH.[54]

Pharmacology

Activity in Experimental Models of Seizures/Epilepsy

TPM is effective in the rodent maximal electroshock model, inhibiting tonic hind-limb extension;[101] this indicates an action against seizure spread. It raises seizure thresholds lowered by pentylenetetrazole and bicuculline, but this effect is less robust.[100] TPM is effective in the amygdalar kindling model[71,114] and in genetic models including DBA/2J mice, spontaneously epileptic rats,[72] genetic absence epilepsy rats, and Wistar rats with audiogenic convulsions.[87]

Mechanisms of Action

TPM has at least five putative mechanisms for its antiseizure effects, but their relative importance is unknown. The first action described was sodium channel modulation,[19] which occurs at therapeutic concentrations and correlates with inhibition of sustained repetitive firing in a voltage- and use-dependent manner.[64] It also has a modulatory action against glutamate-mediated excitatory neurotransmission, acting primarily on the kainate receptor type.[99] It antagonizes the action of kainate receptors of the GluR5 subtype in cultured rat amygdalar neurons, apparently postsynaptically.[42] Furthermore, unlike carbamazepine, it protects against seizures in mice induced by the convulsant substance ATPA, a GluR5 kainate receptor agonist.[49] Although TPM also antagonizes the action of the *a*-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) subtype of glutamate receptor, this effect is less striking than that seen with carbamazepine. TPM has no effect on the *N*-methyl-D-aspartate (NMDA)-mediated glutamate receptor type, unlike felbamate.[19] Modulation of calcium currents may occur via the glutamate receptor effects,[83] but direct effects on L-type voltage-sensitive calcium currents have also been described.[120]

In addition to these antiexcitatory mechanisms, TPM may enhance inhibition by promoting *γ*-aminobutyric acid

(GABA) activity. TPM, like benzodiazepines, increases the frequency of opening of $GABA_A$-mediated chloride channels, but does not bind to the benzodiazepine receptor site on the postsynaptic membrane.[116,117] It appears to increase GABA content in human brain as measured by magnetic resonance spectroscopy in vivo,[55,82] but how this may occur is uncertain. TPM may further enhance inhibition by increasing potassium channel conductance, as observed in rat neurons.[47] Finally, TPM is a carbonic anhydrase inhibitor, but this effect is much weaker than that of acetazolamide and may contribute little to its efficacy.[21]

Activity in Other Models

Neuroprotective effects against neuronal injury from hypoxia[53] and status epilepticus[77] have been demonstrated in animal models.

Clinical Pharmacokinetics

Absorption

Across all age groups, TPM has linear pharmacokinetics. In adults, after administration of single, oral doses ranging from 100 to 1,200 mg, TPM was rapidly absorbed from the gastrointestinal tract.[23] Estimated bioavailability is approximately 80%.[75,113] TPM's absorption is not significantly affected by food.[23]

Plasma Protein Binding and Distribution

Topiramate is not highly bound to plasma proteins (9% to 17%).[81] The volume of distribution in healthy adult volunteers was 0.6 to 0.8 L/kg, consistent with a distribution into total body water.[26] Ninety percent of the maximal plasma concentration (C_{max}) was achieved within 2 hours (range 1.4 to 4.3 hours) after oral administration.[23] Mean values for C_{max} and area under the concentration-time curve (AUC), reflections of drug absorption and clearance, increased linearly with respect to dose in adults.[48] Steady state is achieved in about 4 days when renal function is normal.[113]

Metabolism and Elimination

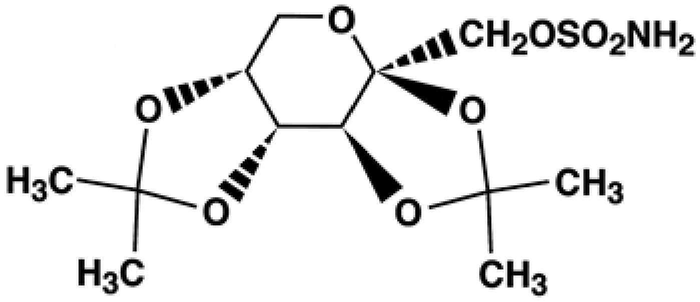

FIGURE 1. Structure of topiramate.

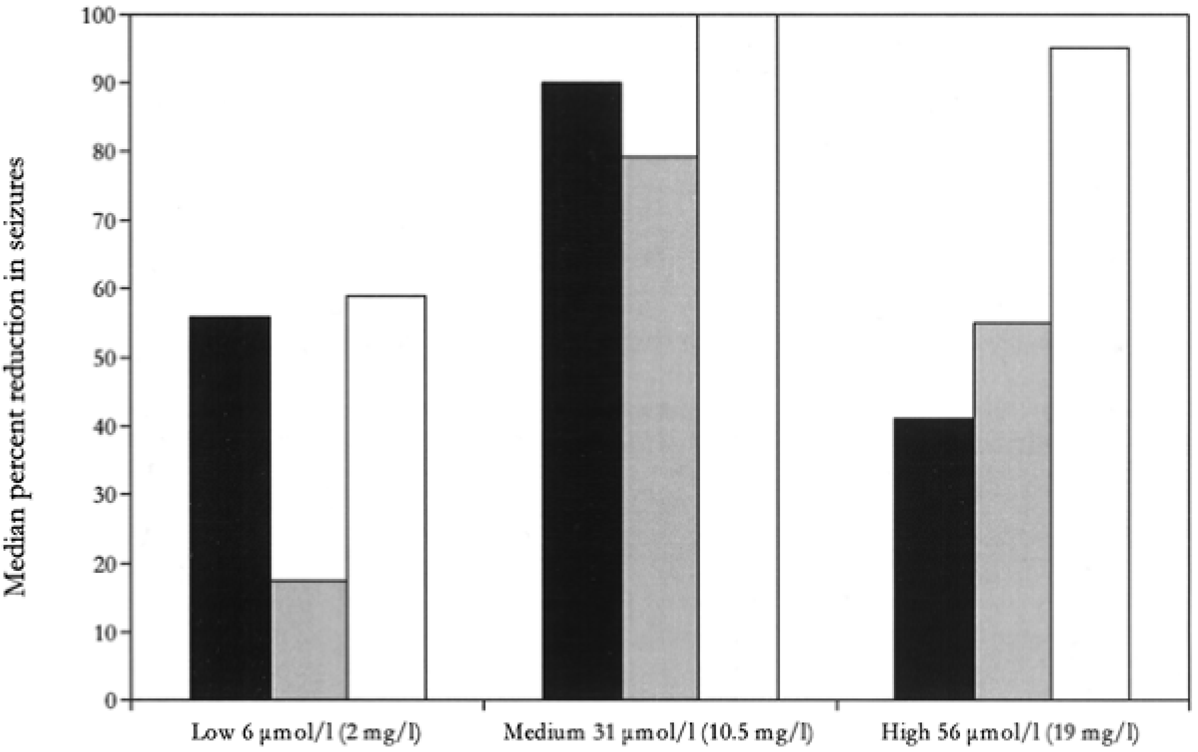

FIGURE 2. The relationship of serum level to median percent seizure reduction for three ranges of topiramate levels: *Black,* simple partial; *gray,* complex partial; *white,* secondarily generalized tonic–clonic. (Reproduced with permission from Christensen J, Andreasen F, Poulsen JH, et al. Randomized, concentration-controlled trial of topiramate in refractory focal epilepsy. *Neurology.* 2003;61(9):1210–1218.)

In monotherapy, TPM is not extensively metabolized.[48] Six trace metabolites of TPM, formed by hydroxylation,

hydrolysis, and glucuronidation, have been identified;[118] none exhibits significant antiepileptic activity.[48,118] In adults, the elimination half-life ($t_{1/2}$) values for TPM when used as monotherapy range from 19 to 25 hours.[95]

Renal excretion is a major route of TPM elimination.[118] In adults, estimates are that at least 51% of the dose is excreted by the kidney within the dose range of 200 to 1,200 mg.[23] The renal clearance of TPM is much lower than its glomerular filtration rate,[23] suggesting that it may undergo tubular reabsorption. A twofold increase in AUC and $t_{1/2}$ occurs with renal failure (creatinine clearance <30 mL/min/1.73 m^2),[35] implying that patients with renal impairment may require reduced dosages. During hemodialysis, TPM is cleared from plasma roughly nine times faster than in patients with normal renal function, implying that patients may need additional doses after hemodialysis.[34] Although moderate/severe liver impairment increased TPM's half-life and lowered its oral clearance, there was not a clinically significant increase in plasma TPM concentration following a single 100-mg oral dose in adults.[24]

TPM pharmacokinetics in children and adolescents was determined from a single-center, open-label outpatient trial of 18 patients with epilepsy.[89] Patients aged 4 to 17 years received oral adjunctive TPM therapy up to a target dose of 9 mg/kg/day. Plasma clearance was not affected by TPM dose. Compared to adults, clearance values were 54% greater in children when TPM was administered in the presence of enzyme-inducing drugs and 44% greater in the absence of enzyme-inducing drugs.[89]

Two studies have examined TPM pharmacokinetics in young children. In a study of five children (2 to 2.5 years old), mean plasma clearance was slightly higher than that reported for children and adolescents and higher in infants on concomitant enzyme-inducing antiepileptic drugs (AEDs) than in those on non-enzyme-inducing concomitant AEDs.[38] A more recent study of 22 children (6 months to 4 years) found TPM oral clearance significantly higher in infants and young children on concomitant enzyme-inducing AEDs (85.4 ± 34.0 mL/hr/kg) compared with those taking valproic acid (VPA; 49.6 ± 13.6 mL/hr/kg) or non-enzyme-inducing AEDs (46.5 ± 12.8 mL/hr/kg).[68]

Plasma Concentrations

TPM plasma concentrations can be obtained through most large clinical laboratories. A randomized, concentration-controlled trial of topiramate in adults with treatment-resistant partial epilepsy demonstrated that optimal treatment response is most likely to occur at plasma concentrations ranging of about 10.5 µg/mL (Fig. 2). Another study found that for older children (6 to 12 years) on TPM monotherapy, serum concentrations ranged from 1.5 to 20.4 µg/mL, while children aged 5 and younger had higher TPM serum concentrations (3.2 to 28.8 µg/mL).[98]

Efficacy in Adults and Children

Partial-onset Seizures in Adults: Adjunctive Therapy

Results from eight multicenter, randomized, placebo-controlled trials of TPM as adjunctive therapy for refractory partial-onset seizures in adults have documented efficacy at all dosages of 200 mg/day or more.[10,29,41,43,84,102,106,119] In early trials, the minimum effective daily dose was found to be 200 mg/day,[29] with 400 mg/day being the most effective dose in intent-to-treat analyses.[8,29] Doses from 600 to 1,000 mg/day conferred no additional benefit but increased the rate of adverse effects.[8,29,84] Later clinical trials featured a slower titration rate[41,43] or lower target dose.[43,119] Good results from these later studies have led to recommendations for an adjunctive-therapy initial target dose for adults of 200 to 400 mg/day, achieved by weekly 25- to 50-mg/day upward dose titration. Nearly all patients in these studies had TPM added to enzyme-inducing drugs; in their absence, lower doses of TPM may result in similar serum levels.

Partial-onset Seizures in Children: Adjunctive Therapy

A multicenter, double-blind, randomized, placebo-controlled trial demonstrated the efficacy of adjunctive TPM in children between 1 and 16 years with refractory partial-onset seizures with or without secondary generalization.[27] An 8-week baseline was followed by a 16-week double-blind treatment phase (8-week titration period followed by an 8-week stabilization period) with a weight-based target dose of 6 mg/kg/day. Forty-one TPM-treated and 45 placebo-treated children aged 2 to 16 years completed treatment. For partial-onset seizures, the median percent reduction from baseline in the average monthly seizure rate in the TPM-treated group was 33% compared to 11% in the placebo group ($p = 0.034$).[27]

Partial and Generalized-onset Seizures: Monotherapy

Four monotherapy trials have been conducted.[32,33,34,35] In the first, adult outpatients with refractory partial-onset seizures were converted gradually from one or two standard drugs to either 100 mg/day or 1,000 mg/day TPM.[94] Stopping rules for patient safety were used, such as a doubling of the baseline seizure frequency. Success, defined as conversion without invoking a stopping rule, was more common with the high dose, and 13% of the high-dose patients but no low-dose patients became seizure free.

Two randomized, controlled multicenter trials with a similar design explored lower TPM dosages in recently diagnosed epilepsy in children and adults.[5,33] As in most new-onset trials, patients with both partial-onset seizures and generalized-onset tonic-clonic seizures were included. In the first trial, 252 patients 3 years of age or older with epilepsy for <3 years took either a low dose (25 mg/day if weight <50 kg, 50 mg/day if weight >50 kg) or a high dose (200 mg if weight <50 kg, 500 mg if weight >50 kg).[33] Patients were either on no medication at baseline (56%) or on one drug, which was withdrawn within 6 weeks. Although the primary end-point, time to second seizure, was not statistically significant between these doses, when the time to first seizure was added as a covariate, the high dose proved superior ($p = 0.01$). Fifty-four percent of high-dose and 39% of low-dose patients were seizure free during the 6-month trial ($p = 0.02$). In the second multinational study, patients 6 years of age or older with untreated epilepsy for <3 months took either 50 mg/day or 400 mg/day.[5] The primary end-point, time to first seizure, favored the high dose. Seizure-free rates at 12 months were 76% and 59% for the high and low doses, respectively ($p = 0.001$).[5]

Lower doses, 100 and 200 mg/day, were used in a fourth study of new-onset seizures.[85] For each patient, physicians were given their choice of either valproate 1,200 mg/day or carbamazepine 600 mg/day as the active control agent. Patients were then randomized to TPM 100 mg/day, TPM 200 mg/day, or the control drug. Seizure control was statistically equal among all patient groups. As expected, physicians usually chose valproate for suspected generalized-onset seizures and carbamazepine for suspected partial-onset seizures, but in both groups the TPM efficacy was equal to that of the control agent. Because 100 mg/day TPM proved just as effective as 200 mg/day, the authors suggested 100 mg/day as an initial target dose for patients with new-onset seizures. In the subset of pediatric partial-onset seizure patients, the time to first seizure was similar for patients in the TPM, carbamazepine, or valproate arms, as were the proportions of seizure-free patients during the last 6 months of treatment.[115]

Generalized Tonic–Clonic Seizures of Nonfocal Origin

The efficacy of TPM for children and adults with uncontrolled generalized tonic–clonic (GTC) seizures of nonfocal origin was examined in a double-blind, placebo-controlled, multicenter study.[14] Patients had to be at least 4 years old, have had at least three GTC seizures during an 8-week baseline phase, have EEG findings consistent with generalized epilepsy, and be taking no more than two standard AEDs. Patients were randomized to either TPM or placebo adjunctive treatment, titrated to target dosages of 6 mg/kg/day over 8 weeks, and maintained at that dose for 12 weeks.

Eighty patients (3 to 59 years) were randomized to either TPM or placebo adjunctive therapy. The median baseline average monthly rate of GTC seizures was 5.0 in the TPM group and 4.5 in the placebo group. The mean TPM dosage during the stabilization period was 5.0 mg/kg/day. At the end of the 20-week double-blind phase, the median percent reduction from baseline in the average monthly GTC seizure rate was 57% for the TPM group compared with 9% for the placebo group ($p = 0.019$). A larger percentage of the TPM-treated patients experienced a ≥50% reduction in GTC seizures compared with the placebo-treated controls (56% vs. 20%; $p = 0.001$).

Lennox-Gastaut Syndrome

A multicenter, double-blind, placebo-controlled trial established TPM's efficacy as adjunctive therapy in patients with Lennox-Gastaut syndrome.[93] Patients had to have active drop attacks (either tonic or atonic seizures), a history of or active atypical absence seizures, and a prior EEG showing a slow spike-and-wave pattern, and be taking one to two concomitant AEDs. After a 4-week baseline, they were randomized to either TPM or placebo adjunctive therapy. TPM dosage was increased at weekly intervals over 3 weeks to 6 mg/kg/day and then maintained at that dose for 8 weeks.

Ninety-eight patients, aged 2 to 42 years (mean age 11), were randomized. The median monthly drop attack frequency during the baseline period was 90 in the TPM group and 98 in the placebo group; the median monthly frequency of all seizure types was 267 in the TPM group and 244 in the placebo group. The median average TPM dosage during the stabilization period was 5.8 mg/kg/day.[93]

Patients in the TPM group had a greater median percent reduction from baseline in drop attacks (15%) compared to the placebo group (–5%; $p = 0.041$). TPM-treated patients were nearly twice as likely to show an improvement in seizure severity as compared with controls (52% vs. 28%; $p = 0.040$) based on parental global evaluations.[93]

Infantile Spasms (West Syndrome)

At least eight open-label trials have examined efficacy in infantile spasms.[3,36,40,46,68,108,111,112] A pilot study of 11 patients with infantile spasms documented by 24-hour video-EEG utilized an initial dose of 25 mg TPM, followed by a "rapid-dose" titration schedule of 25-mg increments every 2 to 3 days over a 4-week period until either a maximal tolerated dose was reached, spasms were controlled, or a maximal dose of 24 mg/kg/day was achieved. Five patients (45%) became spasm free with absence of infantile spasms and hypsarrhythmia proven by repeat 24-hour video-EEG.[36] Seven of the 11 patients (64%) were able to achieve TPM monotherapy, while the others were able to reduce their intake of concomitant AEDs.[36]

In a retrospective study of TPM in patients with intractable epilepsy, four of seven infants with West syndrome became seizure free with TPM therapy.[108] Another study reported the efficacy of TPM in 13 infants with West syndrome as part of a multicenter study of 224 unselected patients with a variety of epilepsy types. Seven of the 13 (54%) West syndrome infants had a >50% reduction of their seizures and two (15%) became seizure free. Nine of the patients used TPM as initial monotherapy with doses up to 16 mg/kg/day.[46] An open-label, multicenter chart review study of 28 infants treated with TPM included eight infants with West syndrome. Almost all (seven of eight, 88%) of the patients with infantile spasms improved with TPM therapy and three patients were treated with TPM monotherapy.[112] An open, prospective, pragmatic study of TPM in 59 infants with epilepsy included 19 patients with West syndrome. Four of the six patients with cryptogenic West syndrome became seizure free after a median follow-up of 14 months. Among 13 patients with symptomatic West syndrome, four patients were classified as responders but only 1 of 13 (8%) became seizure free.[40] In contrast, one study of 18 patients with spasms (14 infantile, four late onset) found six responders but none seizure free.[68] A prospective open-label trial of TPM in 47 children (6 to 60 months old) with refractory epilepsy included nine patients with infantile spasms. Two of the nine patients became seizure free and another two experienced a >50% reduction in seizure frequency.[3] A retrospective review of TPM use in 13 children younger than 2 years old reported four infants with infantile spasms; following initiation of TPM therapy two became spasm free, one had a >75% reduction in spasms, and the other had no response to TPM.[111]

Severe Myoclonic Epilepsy of Infancy (Dravet Syndrome)

Four studies have examined TPM's efficacy for children with severe myoclonic epilepsy in infancy (SMEI).[18,40,68,78] One prospective multicenter open label add-on study in 18 patients (2 to 21 years, mean 9 years) with SMEI used a starting TPM dose of 0.5 to 1 mg/kg/day, with 2-week increments of 1 to 3 mg/kg/day up to a maximum of 12 mg/kg/day. Three patients (16.7%) became seizure free and ten patients (55.5%) had a >50% reduction in seizures (mean 11.9 months with range of 2 to 24 months). No patient experienced seizure worsening.[18] A second SMEI trial examined effectiveness in 18 patients with SMEI using a starting dose of 1 mg/kg/day, increasing every 1 to 2 weeks with a maximum dose of 6 to 8 mg/kg/day. Three patients (16.7%) became seizure free, and ten (55.6%) had a >50% reduction in seizure frequency (mean 10.5 months with range of 6 to 18 months).[78] A smaller study found that three of five SMEI patients responded to TPM therapy.[68] An open, prospective, pragmatic study of TPM in 59 infants with epilepsy included six patients with SMEI. Only two of the six SMEI patients responded and none became seizure free.[40]

Other Epilepsy Syndromes

There are small studies suggesting that TPM is effective for juvenile myoclonic epilepsy,[13,105] absence epilepsy,[20] Doose syndrome,[68] and progressive myoclonic epilepsies.[6]

Long-term and Open-label Treatment

Among 214 adults with refractory partial-onset seizures who elected to take TPM after completion of blinded, controlled trials, 64% continued for another 30 months. Of the one third converted to monotherapy, 28 (13% of the 214) were seizure free for at least the last 3 months.[91] In an analysis of 131 adults and children who had completed studies of refractory primary generalized tonic–clonic seizures, 63% had a 50% decrease in seizure frequency during a mean follow-up period of 387 days and 16% were seizure free for the past 6 months.[69]

For the 83 children with partial-onset seizures, with or without secondary generalization, who continued long-term open-label TPM therapy after the double-blind trial phase, the mean TPM dosage was 9 mg/kg/day.

Seizure frequency over the last 3 months of therapy was reduced by ≥50% in 57% of children; 14% of children were seizure free for ≥6 months at the last visit.[88] In the open-label extension phase of the Lennox-Gastaut trial, 97 patients received a mean TPM dose of 11 mg/kg/day for a mean duration of 539 days (range, 44 to 1,225 days); at the last clinic visit, drop attacks were reduced by ≥50% in 55% of patients; 15% of patients had no drop attacks for ≥6 months.[37]

However, these trials were response conditional, enrolling only successful completers of randomized trials. Prospective open-label series may be more predictive of results in clinical practice. Among 292 adults with refractory seizures treated with adjunctive TPM and followed for a mean of 2.2 years (84 to 804 days), mean reductions of >50% in both partial and generalized-onset seizures were observed, and 10% were seizure free for at least 6 months.[1] Discontinuations were more often due to adverse effects (32%) than to lack of efficacy (19%), a pattern typical for TPM treatment.[1,15,58,107] In a 6-month Canadian multicenter study of 209 adults given TPM as adjunctive therapy, patients experienced a 41% median seizure frequency reduction during the final 8 weeks, with 10% becoming seizure free and with improvements in quality-of-life measurements.[7] Long-term retention rates of 30% to 50% for 3 to 4 years have been reported from three large open-label series,[39,41,43] suggesting that a satisfactory effect is sustained for many patients.

Most patients in open-label series were considered refractory; insufficient data are available on the long-term outcome of new-onset epilepsy patients treated with TPM as the first drug.

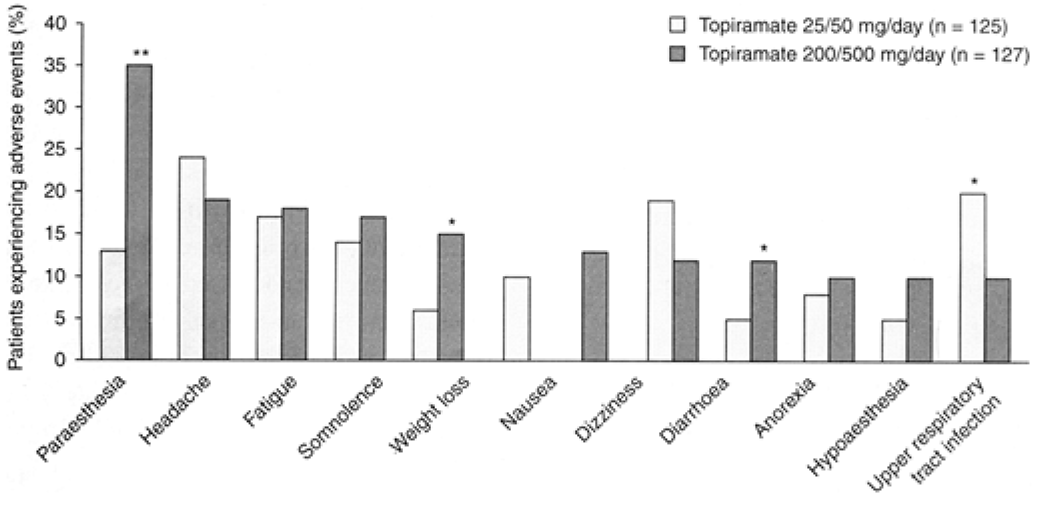

FIGURE 3. Adverse effects at low doses (25/50 mg/day) and high doses (400/500 mg/day) in monotherapy. (Reproduced with permission from Waugh J, Goa KL. Topiramate as monotherapy in newly diagnosed epilepsy. *CNS Drugs*. 2003;17(13):985–992.)

Adverse Effects

During short-term controlled clinical trials of adjunctive therapy, 11% to 28% of patients had TPM discontinued because of adverse effects.[86] Monotherapy is better tolerated (Fig. 3). Cognitive problems, paresthesias, anorexia, and decreases in serum bicarbonate are dose related. Effects seen mostly during dose initiation and unrelated to final dose include dizziness, somnolence, fatigue, and ataxia.[61,103] Gastrointestinal symptoms, renal stones, and psychiatric effects are dose related in some reports. FIGURE 3 relates dose to adverse effects in a monotherapy study. Serious adverse effects are rare.

Dose-related Adverse Effects

Cognitive Effects

The most salient adverse effects, and the ones most likely to limit therapy, are effects on cognition.[15,107] Cognitive effects are in part qualitatively different from those typically seen with other antiepilepsy drugs, tending to affect language function in particular.[62,65,109] In the early, high-dose, rapid-titration, adjunctive-therapy clinical trials, cognitive effects were prominent.[86,103] "Thinking abnormal" was reported in 13% to 33% and "concentration impaired" in 15% to 25%; these effects were dose dependent. In contrast, only 5% of patients in a 200-mg target dose adjunctive therapy trial with slow upward titration of 25 to 50 mg/week experienced "concentration/attention difficulty."[43] Two studies compared the effect of adding either TPM or valproate to carbamazepine using a cautious dosing strategy.[4,66] In the first, patients taking TPM did worse on two tests of verbal memory, but not on eight other cognitive tests,[4] and differences diminished with continuing therapy. Short-term verbal memory was the only one of 17 variables worse among the TPM group in the second study.[66] Among patients with new-onset seizures treated with monotherapy carbamazepine 600 mg/day, valproate 1,250 mg/day, or TPM 100 or 200 mg/day, no cognitive side effect exceeded 8% in any group, though valproate was slightly better tolerated.[85]

Generic terms in standard adverse-event dictionaries do not accurately convey the nature of TPM cognitive effects. Expressive language function may be impaired as well as verbal memory,[109] and a general slowing of cognitive processing may occur.[40,86] These effects often appear without sedation or mood change. There may be a mild dysnomia,[70] or just hesitation in verbal replies. Word fluency declines were seen in normal volunteers[62,67] and in patients with epilepsy.[109] Improvements in verbal fluency, working memory, and other frontal lobe–associated functions were seen in 19 patients withdrawn from TPM as polytherapy.[52] Word-finding difficulty may be more likely in patients with dominant-hemisphere seizure foci or pathology.[70]

Monotherapy reduces the probability of cognitive effects[5,33,94] (Fig. 3). In one trial, effects on concentration/attention occurred in 7% and on memory in 4% of patients assigned to 50 mg/day, and in 8% for each effect in patients assigned 400 mg/day.[5] The total incidence of at least one cognitive effect was 19% for the 50-mg/day group and 26% for the 400-mg/day group, but dose reduction was necessary in only 2% and 7%, respectively.[80]

Cognitive effects are not universally present; many patients are completely unaffected even at higher dosages: Group differences are strongly influenced by a subset of patients who are severely affected.[47,66] Patients with intellectual disabilities[51,104] and the elderly[44] do not appear to be more susceptible. Besides slowing titration rate and limiting dose, another effective strategy is concomitant medication reduction.[74] Physicians should question patients and families carefully about changes in cognitive functions after TPM initiation and after dose increases.

Effects Related to Carbonic Anhydrase Inhibition

Paresthesias, metabolic acidosis, and renal stones are associated with the inhibition of carbonic anhydrase isozymes II and IV.[21] Paresthesias are much more common in monotherapy, probably because of higher serum levels.[33,94] In migraine clinical trials, 35% of subjects had paresthesias at 50 mg/day and 49% at 200 mg/day.[110] Tingling or numbness involves hands and feet, or sometimes the whole body. Patients should be reassured that it is harmless and usually transient.

TPM often lowers serum bicarbonate levels. The manufacturer states that this is a dose-dependent effect, with 32% of adults taking 400 mg/day having levels below 20 mEq/L;[110] however, a lesser effect, an average decrease of 5.1 mEq/L (26.8 to 21.7), was reported in one study.[32] This effect is more prevalent in children.[110] Serum pH is ordinarily compensated and patients are asymptomatic. A clinically significant non–anion gap hyperchloremic acidosis could occur in some circumstances, including ketosis, renal or respiratory insufficiency, or status epilepticus. Serum bicarbonate should be measured at baseline, at the target dose, and after large dose increases.

Weight Loss and Anorexia

Many patients taking topiramate lose weight, probably because of anorexia, but the extent and duration is variable. The average decrease in body weight is 4.6%, usually plateauing by 18 months of therapy,[86,92] but obese patients tend to lose more.[9] Weight loss is usually beneficial, though it sometimes limits therapy in thin people and those who cannot voluntarily increase caloric intake. In TPM placebo-controlled trials involving children, weight loss occurred in 9% of the TPM group versus 1% of the placebo group.[79]

Overdose

Overdoses produce drowsiness and lethargy, but serious toxic effects are rare.[59] Gastrointestinal decontamination reduces severity.[61] One fatal case was reported: An adult found dead in bed had taken an unknown amount; a postmortem serum blood level was 170 μg/mL.[56] At autopsy pulmonary and cerebral edema were present. Because TPM protein binding is low, 15%,[97] hemodialysis should remove it effectively, if clinically necessary.

Adverse Effects Not Definitely Related to Dose

Somnolence

Sleepiness during short-term clinical trials affected 15% to 35% of subjects,[29,41,84,106] but it is usually transient and does not limit therapy.[107]

Fatigue

Fatigue, or asthenia, is a common effect of many antiepilepsy drugs.[28] Among adults in adjunctive TPM clinical trials, fatigue was noted in 13% assigned to placebo, 15% in those assigned to 200 to 400 mg/day, and 30% in those assigned to 600 to 1,000 mg/day.[110] Fatigue was seen in 16% of children taking adjunctive TPM and 5% taking placebo.[110] An incidence of about 16% was unrelated to dose during monotherapy trials of 25 to 500 mg/day.[113]

Effects on Mood

Depression was reported in 15% of participants in the first five controlled trials of adjunctive TPM, no more than with placebo.[103] In an open-label series, 11.9% of patients were described as having depression, hyperirritability, or aggressiveness.[15] In another survey 5% had depression and 5.7% irritability or aggressive behavior; these effects were more likely in patients with psychiatric histories.[50]

Idiosyncratic Reactions

Rare and potentially dangerous adverse events of topiramate include hyperchloremic, non–anion gap metabolic acidosis;[39] acute myopia and secondary angle closure glaucoma;[30] oligohidrosis and hyperthermia;[11] and hyperammonemia with or without encephalopathy.[16,57,60]

Teratogenicity

In teratology studies, TPM caused right-sided ectrodactyly (congenital absence of all or part of a digit), micromelia, and amelia in rats; increased embryo/fetal mortality in rabbits; and fetal malformations (primarily craniofacial defects) in mice.[76] These effects of TPM are similar to those reported with acetazolamide and other carbonic anhydrase inhibitors.[73,104]

Topiramate is rated by the U.S. Food and Drug Administration as Pregnancy Category C.[76] The Category C label means (a) animal reproduction studies have shown an adverse effect on the fetus, (b) there are no adequate and well-controlled studies in humans, and (c) the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks.[2]

Drug Interactions

TPM is not an enzyme inducer and protein binding is low. Therefore, it has minimal effects on other drugs, although its metabolism is enhanced by enzyme-inducing agents. TPM is eliminated mainly by the kidneys, but these drugs increase the proportion metabolized by the liver from 20% to 50%.[31]

Effects of Topiramate on Other Antiepilepsy Drugs

In vitro, TPM has no effect on most cytochrome P450 isozymes,[12,110] and no effects on concomitant drug levels were detected in add-on clinical trials.[29,84] However, in one study, in three subjects with baseline phenytoin levels of 15 μg/mL or higher, phenytoin levels rose 30% to 50% when TPM 400 to 800 mg/day was added,[66] probably by inhibiting CYP2C19, the secondary enzyme for phenytoin metabolism.[95]

Effects on other antiepilepsy drugs are negligible.[12,96,110] Carbamazepine[96] and lamotrigine[22] levels are unaffected. TPM has little net influence on valproate clearance, but shifts the proportions of several valproate metabolic pathways,[65,69] the clinical significance of which is uncertain. An increase in a potentially toxic metabolite, 4-ene-valproate, has been proposed as a factor in the rare cases of hyperammonemic encephalopathy observed with combination TPM-valproate therapy.[45]

Effects of Topiramate on Oral Contraceptives

TPM at doses of 200 mg/day or more reduced serum levels of ethinyl estradiol derived from an oral contraceptive by 30%,[90] but in another series of women, TPM doses of 50, 100, and 200 mg/day had no significant effect.[25] This effect is less than that of carbamazepine, phenytoin, and phenobarbital, and unlike these agents, TPM does not lower progestin levels.[25] Nevertheless, women taking over 200 mg/day of TPM should take precautions. The absence of breakthrough bleeding is not a reliable sign of secure birth control, but its occurrence may suggest a need for a higher estrogen dose or a second method.

Effects of Topiramate on Other Drugs

In the presence of TPM, lithium, amitriptyline, and risperidone clearances increase and levels decrease slightly.[12] Metformin AUC increased by 25% in healthy volunteers given TPM.[110] When TPM is used as migraine prophylaxis, it has no pharmacokinetic effects upon concomitant propranolol, sumatriptan, or dihydroergotamine.[12]

Effects of Other Drugs on Topiramate

Both phenytoin and carbamazepine double the clearance of TPM[95,96] and thus reduce serum levels by about 50%. If these drugs are withdrawn, the TPM level will rise. Barbiturates may have a similar effect but have not been studied.

Role in Epilepsy Treatment

Indications

In the United States, TPM is indicated as adjunctive therapy for adults and children ages 2 to 16 years with partial-onset seizures or primary generalized tonic-clonic seizures and in patients 2 years of age and older with seizures associated with Lennox-Gastaut syndrome.[110] It is also indicated for the prophylaxis of migraine headache in adults.[110]

Dosing Recommendations

Topiramate is available in oral preparations either as a tablet (25-mg, 50-mg, 100-mg, and 200-mg strengths) or as a sprinkle capsule (15 mg and 25 mg).[76] There is no intravenous preparation commercially available.

Based on its clinical trials, TPM has been shown to be effective in a wide variety of seizure types (partial-onset seizures, generalized tonic–clonic seizures of nonfocal origin, drop attacks). Attention to the initial dose of TPM, subsequent titration rates, and the maintenance target dose are important to maximize tolerability and subsequently maximize effectiveness. In adults, initial TPM dosing ranges from 25 to 50 mg/day with subsequent weekly or every-2-week increments of 25 to 50 mg/day. For initial monotherapy, target doses as low as 100 mg/day may be effective. In an open-label naturalistic TPM monotherapy clinical trial involving 441 adults at 127 centers throughout Europe and the Middle East, the median final topiramate dose was 125 mg/day (range 25 to 700 mg/day).[44] As adjunctive therapy, TPM target doses range from 200 to 400 mg/day.

In children, initial TPM dosing ranges from 0.5 to 1 mg/kg/day with subsequent weekly increments of 0.5 to 1 mg/kg/day. In an open-label naturalistic TPM monotherapy clinical trial involving 114 children (<12 years old) at 127 centers throughout Europe and the Middle East, the median final topiramate dose was 3.3 mg/kg/day (range 1.3 to 13.0 mg/kg/day).[44] As adjunctive therapy, TPM target doses range from 6 to 9 mg/kg/day. Infants and some children may require significantly higher initial and target doses. Some infants and children benefit from TPM doses up to 50 mg/kg/day—particularly in the presence of a concomitant enzyme-inducing AED such as carbamazepine.

As with all AEDs, TPM should be titrated until there is a clear response (either seizure control without intolerable adverse events or persisting seizures with intolerable side effects). In patients showing some seizure reduction without intolerable adverse events, the dose of TPM can be further increased. If adverse experiences do occur, titration can be slowed; on the other hand, titration can be more rapid if the suppression of seizures is urgently needed. A small subset of patients (1% to 3%) appears unable to tolerate even the lowest doses of TPM.

Precautions

The manufacturer recommends measurement of baseline and periodic bicarbonate levels.[110] It is reasonable to do this at baseline, at the target dose, after large dose increases, and in circumstances predisposing to metabolic acidosis. Clinical judgment should guide whether dose reduction or alkali treatment is needed; minor decreases in bicarbonate require no action. No other routine laboratory testing is recommended.

Patients should be advised to seek medical care at once if blurred vision or severe unilateral eye pain occurs. The possibility of cognitive effects, renal stones and hyperthermia may be discussed at the time of TPM initiation.

Contraindications

The only absolute contraindication is hypersensitivity to components of the compound.

Summary and Conclusions

Topiramate, perhaps because of multiple modes of action on the central nervous system, is effective against many seizure types. Efficacy is best documented as monotherapy and adjunctive therapy against partial-onset seizures and generalized-onset tonic–clonic seizures, and against component seizure types of Lennox-Gastaut syndrome. Because of this broad spectrum, TPM is a reasonable therapeutic choice for new-onset seizures. It is particularly attractive for patients who may benefit from its antimigraine or anorectic qualities.

Pharmacokinetic characteristics are favorable, with good absorption, low protein binding, mostly renal elimination, few drug interactions, and a linear relationship between dose and serum level. Cognitive side effects occur in about one fourth of patients and may limit therapy. Renal stones occur in 0.5% to 1.5%. Rare side effects include reversible angle-closure glaucoma, oligohidrosis with hyperthermia, and hyperammonemia with or without encephalopathy.

For new-onset epilepsy in adults, 100 mg/day may suffice. With concomitant enzyme-inducing drugs, the target dose range is 200 to 400 mg/day. Some patients will benefit from, and tolerate, higher dosages. A slow titration rate of 25 to 50 mg/day at weekly intervals for adults, and of 1 mg/kg/day per week for children, will improve tolerability.

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Chapter 160

Valproate

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Introduction

Valproic acid was first synthesized in 1882 as an organic solvent in research laboratories.[59] Its anticonvulsant effects were discovered serendipitously in 1962, when it was used as a lipophilic vehicle for dissolving water-insoluble khellin derivatives. A significant anticonvulsant effect against pentylenetetrazol-induced seizures was observed in the vehicle control.[94] The first clinical trials of valproic acid were reported in 1964.[24] It was initially marketed in France in 1967, and later approved by the U.S. Food and Drug Administration (FDA) as a treatment for epilepsy in 1978. Since then, valproic acid has established itself as one of the major antiepileptic drugs (AEDs) with efficacy against multiple seizure types.

Chemical Structure and Formulations

Valproic acid is a simple, branched-chain carboxylic acid with a structure unlike other AEDs[77] (Fig. 1). It is a colorless liquid with a pKa value of 4.56 and a molecular weight of 144.21.[76] Because it is highly ionized at a pH of 7.4, valproic acid is less lipophilic than the standard AEDs.[78] This results in a low volume of distribution, because only the nonionized, lipid-soluble part of a drug distributes from blood to tissues via passive diffusion. Therefore, the rapid penetration of valproic acid into the brain cannot result from its chemical properties and is thought to be mediated by active transport mechanisms across the blood–brain barrier.[77]

Valproate (VPA) is available in multiple forms. Sodium valproate is the sodium salt and dissociates rapidly in the body to valproic acid. Divalproex sodium is a stable coordination compound, comprised of sodium valproate and valproic acid in a 1:1 molar relationship, which dissociates in the gastrointestinal tract into valproic acid.

The extended release divalproex (Divalproex ER) is a newer formulation (Fig. 2) consisting of a hydrophilic polymer matrix, controlled-release tablet system, which allows for the slow release of the drug in the stomach, small intestine, and large intestine over an 18- to 24-hour period.[2] This extended-release product is intended for once-a-day oral administration.

Pharmacology

Activity in Experimental Models and Mechanisms of Action

Experimentally, VPA has an anticonvulsant effect on almost all animal models of seizures including different types of generalized and partial seizures.[77] The cellular mechanisms of action of VPA include primarily potentiation of γ-aminobutyric acid (GABA)ergic mechanisms and, less importantly, blockades of voltage-dependent sodium (Na) channels and glutamatergic mechanisms.[77]

VPA increases cerebrospinal fluid (CSF)[79] and whole-brain GABA levels.[52,100] This increase in GABA level may be due to an inhibitory effect on GABA degradation or an enhancement of GABA synthesis.[77] Another potentially important mechanism is direct potentiation of the neuronal responses to GABA.[82,105] VPA suppresses glutamate responses and *N*-methyl-D-aspartate (NMDA)-evoked transient depolarization in rat neocortex.[148] This attenuation of NMDA receptor–mediated excitation may be an essential mode of action for the anticonvulsant effect of VPA. VPA was also shown to diminish the high-frequency repetitive firing of action potentials of cultured central neurons.[77] It was suggested that the most likely explanation for this effect is through use-dependent reduction of the inward Na current.[91] Although this mechanism is somewhat similar to that of carbamazepine and phenytoin, the reduction in sustained repetitive firing in the case of VPA might be due to enhancement of potassium (K) channels involved in action potential repolarization.[46,95]

VPA was shown to block low-threshold T-type calcium (Ca) channels in peripheral ganglion neurons but not in thalamic neurons.[32,71]

VPA also appears to affect basal ganglia circuits, which are important in cortical hyperexcitability and seizure spread. For example, VPA increases the excitatory threshold for the caudate-thalamocortical systems[97] possibly through increased activity in the substantia nigra pars reticulata.[65]

Clinical Pharmacokinetics

Absorption, Protein Binding, and Distribution

Valproic acid bioavailability after oral administration ranges from 70% to 100% in humans.[77] The bioavailability of divalproex ER is approximately 8% to 20% less than divalproex. Proportional dosing with 8% to 20% higher daily doses of divalproex ER compared with divalproex was shown to produce equivalent serum VPA levels in healthy volunteers and patients with epilepsy.[41,129]

Following oral administration, peak plasma VPA concentrations (C_{max}) are achieved within 2 hours (T_{max}) for valproic acid and sodium VPA, and within 3 to 8 hours for divalproex and divalproex ER.[70]

Valproic acid is highly protein bound (~90%), and this binding is saturable at therapeutic levels. For example, when the total VPA serum level increases from 50 to 150 µg/mL, the serum level of the free fraction of VPA increases from 3.5 to 45 µg/mL.[33] The apparent volume of distribution of VPA is 0.13 to 0.19 L/kg, with the central nervous system (CNS) concentration averaging 20% of the serum concentration.[77]

Metabolism and Elimination

VPA is primarily metabolized by three primary pathways in the liver to a number of metabolites, some of which are

biologically active.[70] Less than 5% of the parent compound is excreted unchanged in the urine. The primary pathway is through mitochondrial β-oxidation to three metabolites: 2-en-VPA, 3-OH-VPA, and 3-oxo-VPA. The 2-en-VPA is biologically active, with a long half-life.[140] The second pathway is via the cytochrome P450 system to toxic intermediary metabolites known as 4-en-VPA and 2,4-en-VPA. The concomitant use of hepatic enzyme inducers activates this pathway and increases the toxic metabolites of VPA. The third pathway consists of glucuronidation of VPA to a number of inactive compounds.

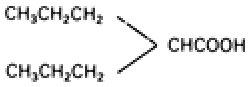

FIGURE 1. Chemical formula of valproate.

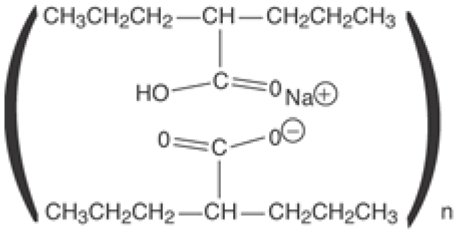

FIGURE 2. Chemical formula of extended-release divalproex.

When administered as monotherapy to adults, the elimination half-life of VPA averages 13 to 16 hours.[55,108] In the presence of hepatic enzyme inducers, its half-life is decreased to 9 hours.[109] Children metabolize VPA faster, which results in an average half-life of 11 to 12 hours.[28]

Efficacy

Absence Seizures

Typical absence seizures can occur in a number of epilepsy syndromes, including childhood absence (pyknolepsy), juvenile absence, juvenile myoclonic, and myoclonic absence epilepsies. VPA is considered to be a first-line agent for the treatment of absence seizures despite a paucity of data derived from well-designed clinical trials. Three small studies compared the efficacy of VPA and ethosuximide for children and adolescents with absence seizures.[23,87,123] Two were open-label, parallel group trials that randomized patients with newly,[23] or recently diagnosed[87] simple absence seizures to VPA or ethosuximide monotherapy. The third was a randomized double-blind conditional cross-over study that randomized 45 children and adolescents with newly diagnosed or refractory absence seizures to monotherapy or add-on treatment with VPA or ethosuximide.[123] All trials found a comparable efficacy between the two AEDs, with seizure-free rates ranging between 40% and 86%.[111] However, none of those trials was powered to detect equivalence. The most common side effects reported in those studies consisted of nausea, vomiting, drowsiness, thrombocytopenia, and leukopenia.

A more recent open-label trial compared VPA with lamotrigine in 38 children newly diagnosed with childhood or juvenile absence seizures.[30] The dose of VPA was initiated at 10 mg/kg per day and, if needed, increased by 5 mg/kg per day every 3 days up to a maximum dose of 30 mg/kg per day. Lamotrigine was started at 0.5 mg/kg per day for 2 weeks, titrated to 1 mg/kg per day for 2 weeks with increments, if needed, of 1 mg/kg per day every 5 days up to a maximum dose of 12 mg/kg per day. The percent of seizure-free patients at 1 month were 52.6% and 5.3% in the VPA and lamotrigine groups, respectively ($p = 0.004$). At 3 months, those percentages were 63.1% and 36.8%, respectively, a difference that did not reach statistical significance. After 12 months of treatment, the percentages of seizure-free patients were 68.4% and 52.6% in the VPA and lamotrigine groups, respectively. Adverse events occurred in 10.6% of children treated with VPA and 31.8% of those treated with lamotrigine. This study showed that both VPA and lamotrigine can be efficacious against absence seizures, but that VPA's efficacy is much faster, partly due to its shorter titration schedule.[30] It is, however, important to note that this trial was not powered to detect equivalence, and that the lack of a significant difference in efficacy between the two drugs could be due to the small sample size.

Juvenile Myoclonic Epilepsy

VPA is often considered the drug of choice in juvenile myoclonic epilepsy, an epilepsy syndrome characterized by myoclonus, generalized tonic–clonic seizures, with or without absence seizures. This is mostly based on clinical experience, because the evidence derived from clinical trials is scant and anectodal.[35,54,107]

Partial-Onset Seizures and Generalized Tonic–Clonic Seizures

The fact that VPA possesses anticonvulsant properties as monotherapy and add-on therapy against partial-onset seizures was unequivocally demonstrated in double-blind, parallel group, multicenter superiority trials.[13,142] The monotherapy study was a concentration-dependent trial that randomized 143 patients with medically refractory partial-onset seizures to high (80–150 μg/mL) or low (25–50 μg/mL) plasma VPA groups. The efficacy results were significantly in favor of the high plasma VPA, with a 30% median reduction in complex partial seizure frequency compared to baseline, versus a 19% increase for patients randomized to the low plasma VPA group.[13] Adverse events that occurred significantly more frequently in the high plasma VPA group included tremors, thrombocytopenia, alopecia, asthenia, diarrhea, vomiting, and anorexia.[13]

The adjunctive trial randomized 144 patients experiencing at least eight complex partial seizures over an 8-week period while maintained on carbamazepine or phenytoin monotherapy to add-on treatment with VPA or placebo.[142] Add-on treatment with VPA resulted in a median reduction of 7.9 complex partial seizures per 8 weeks compared with 2.5 in the placebo group ($p = 0.001$). In addition, the 50% responder rates were 38% and 19%, in the add-on VPA group and placebo group, respectively ($p = 0.011$).

The comparative trials that evaluated the relative efficacy and effectiveness of VPA versus other standard or newer AEDs have yielded conflicting results, especially with regard to efficacy against partial seizures. A number of open-label, active-control trials compared the relative efficacy of VPA, carbamazepine, phenytoin, and phenobarbital in adults and children with newly diagnosed epilepsy.[22,36,58,80,115,117,133,136] Most trials only enrolled patients with newly diagnosed epilepsy, including those with partial-onset and generalized tonic–clonic seizures,[22,36,57,117,133,136] whereas one trial only enrolled patients with primarily generalized tonic–clonic seizures.[115] All trials reported similar efficacy between VPA and the other AEDs on the outcome variables that included time to first

seizure, percent of seizure-free patients, and time to seizure remission. Those results were similar when data from patients with partial-onset seizures and primarily generalized tonic–clonic seizures were separately analyzed.

The only double-blind comparative trial was an active-control study that compared VPA to carbamazepine in

480 patients with partial-onset seizures.[88] Patients were stratified into two groups, one consisting of those with predominantly secondarily generalized seizures and the other of those with predominantly complex partial seizures. For patients with predominantly secondarily generalized tonic–clonic seizures, no significant efficacy differences were noted between VPA and carbamazepine. On the other hand, the efficacy of carbamazepine was reported to be significantly better than VPA for patients with predominantly complex partial seizures, based on multiple outcome measures, including time to first seizure and a composite score of seizure severity.[88] However, the percentages of patients who remained seizure-free at 1 year were comparable between the two groups. A number of factors were suggested to explain the discrepancy of results between this trial and the open-label comparative trials, including that the majority of patients in the VA cooperative trial were males, and that only approximately 50% of the participants were newly diagnosed with epilepsy.[116] However, a meta-analysis of trials comparing carbamazepine and VPA found that, for partial-onset seizures, carbamazepine was significantly superior for time to 12 months of seizure remission and time to first seizure.[86] A separate meta-analysis failed to find significant difference in efficacy between VPA and phenytoin for partial seizures or primarily generalized tonic–clonic seizures.[132]

Two comparative trials evaluated VPA with one of the newer AEDs. In a double-blind, parallel-group trial, 249 patients with newly diagnosed epilepsy, aged 15 to 65 years and experiencing partial-onset seizures or generalized tonic–clonic seizures, were randomized to treatment with VPA or oxcarbazepine.[26] The study consisted of an 8-week titration followed by a 48–week maintenance period. The results showed no significant efficacy difference between the two groups, with 53.8% and 56.6% of patients randomized to VPA and oxcarbazepine, respectively, remaining seizure-free throughout the 48–week maintenance period. The numbers of premature discontinuations due to adverse events were also comparable between the two groups.[26]

A more recent active-control, double-blind trial compared the efficacy of topiramate with the investigator's choice of carbamazepine or VPA as initial treatment for patients with newly diagnosed epilepsy.[113] The investigators were asked to select carbamazepine (600 mg/day) or VPA (1,250 mg/day) based on the clinical presentation. Within each group, patients were randomized in a double-blind fashion to treatment with one of the two standard AEDs versus topiramate administered at 100 mg/day or 200 mg/day. Patients continued double-blind treatment until exiting the study or until 6 months after the last patient was randomized. Of the 78 patients randomized to VPA, 42% were considered to have partial-onset seizures, 63% primarily generalized tonic or clonic or tonic–clonic seizures, and 1% could not be classified. In that subgroup, 145 patients were randomized to topiramate (100 mg/day or 200 mg/day), with 41% considered to have partial-onset seizures, 65% primarily generalized tonic or clonic or tonic–clonic seizures, and 2% could not be classified. The results indicated no significant difference in time to exit, adverse events, or inadequate effect between the VPA and topiramate groups.[113]

Infantile Spasms

Two uncontrolled, open-label, prospective studies suggested the efficacy of VPA against infantile spasms[45,126] at daily doses ranging from 25 to 100 mg/kg per day. Cessation of spasms occurred in 72% to 73% of children within 2 weeks to 3 months after initiation of therapy, with a 23% relapse rate reported in one of the studies.[126] Consequent to the high doses used, approximately one-third of the children developed thrombocytopenia.[126] Long-term outcome of children with infantile spasms was evaluated in two retrospective studies, with conflicting results.[61,103] One study, which compared treatment with adrenocorticotropic hormone (ACTH), pyridoxine, and VPA reported that none of the VPA-treated patients had a normal IQ, but that all were seizure-free.[104] In the other study, which compared ACTH to VPA, only 26% of children were seizure-free, with no significant difference between the two groups.[61]

The data on VPA in infantile spasm are largely anecdotal and insufficient to recommend VPA as initial treatment of infantile spasms[83] but may be considered in patients with spasms that are refractory to ACTH and vigabatrin.

Febrile Seizures

A number of studies evaluated the efficacy of continuous treatment with VPA in the prevention of recurrent febrile seizures (FS).[73,84,101,138,141] In an open-label, randomized trial of 58 children who experienced their second simple febrile seizure, the recurrence rate did not differ between the VPA-treated group and the no-treatment group.[141] The other trials comparing the relative efficacy of VPA to that of phenobarbital and placebo or no treatment found that VPA was significantly better than no treatment or placebo in preventing further FS, and that its efficacy did not significantly differ from that of phenobarbital.[73,84,101,138] For example, 73 children with their first generalized febrile seizure were randomized in a single-blind, placebo-controlled clinical trial to treatment with VPA, phenobarbital, or placebo.[84] The recurrence rates were 4%, 19%, and 35% in the VPA, phenobarbital, and placebo groups, respectively. Similar results were reported in another, double-blind, placebo-controlled trial conducted in children enrolled after their first simple febrile seizure.[101]

Those data provide evidence that continuous treatment with VPA significantly reduces the likelihood of further FS and that its efficacy in that regard is overall at least comparable to that of phenobarbital. However, the Practice Parameter developed by the American Academy of Pediatrics does not recommend the use of daily anticonvulsant treatment, because it does not influence the long-term outcome in children with simple FS.[7] In addition, the risk of serious hepatotoxicity is greatest in the age group in which FS usually present, and studies of valproic acid in FS were insufficiently powered to detect a risk of serious hepatotoxicity.

Status Epilepticus

Following the availability of the intravenous formulation of VPA, there was an interest to evaluate its potential usefulness in the management of patients with status epilepticus (SE). Its theoretical safety advantages compared to phenytoin, the benzodiazepines, and the barbiturates is that it can be administered at a physiologic pH and has not been found to be associated with hypotension, sedation, or respiratory depression.[99,112]

Efficacy data in children and adults are mostly anecdotal and based on case reports or small open-label series.[25,60,134] In the great majority of cases, VPA was administered to patients with refractory convulsive or nonconvulsive SE who had failed previous treatment with benzodiazepines, phenytoin, and barbiturates. In children, the loading dose was 20 to 30 mg/kg over 1 hour, followed by maintenance doses of up to 60 mg/kg per day with an attempt to achieve plasma VPA concentrations between 60 and 100 μg/mL.[25,60] In the largest series to date, 41 children with refractory SE received a VPA loading dose of 20 to 40 mg/kg administered over 1 to 5 minutes, followed by a maintenance rate of 5 mg/kg per hour.[134] Using this protocol, SE was successfully aborted clinically and electroencephalographically in 78% of children. The majority of those recovered following the administration of the loading dose, which resulted in mean plasma VPA concentrations of 121 μg/mL. No adverse events were reported with the use of this protocol.[134]

The data in adults are overall similar and using more aggressive loading doses as clinical experience grew. For example, in the initial published study, a loading dose of 400 mg was administered followed by a maintenance dose of 100 to 300 mg/hour.[112] In later case series, the loading dose of VPA was increased up to 25 mg/kg and administered at 20 to 50 mg/minute.[99] As would be expected in patients with refractory status, some patients improved while others did not following the administration of intravenous VPA. One study is of particular importance,[51] because intravenous VPA was used as the initial treatment in 23 adult patients with SE (15 with nonconvulsive and eight with convulsive SE). The initial protocol, which consisted of a 12-mg/kg loading dose followed by a maintenance dose of 0.5 mg/kg per hour, was only used for the first four patients, because it resulted in a mean post-loading serum VPA level of only 52.5 μg/mL. The amended regimen, consisting of a loading dose of 15 mg/kg followed by a 1-mg/kg per hour maintenance dose was used in the remaining 19 patients and resulted in a mean post-loading serum VPA level of 68.5 μg/mL.[51] In that study, it was reported that the status was aborted clinically and electroencephalographically within 20 minutes of initiation of VPA treatment in 19 patients (83%), and that both patients with convulsive and nonconvulsive status responded equally well. No adverse events were reported using this treatment regimen.[51]

There is little data on the use of intravenous VPA for other types of SE. In a case report, a 15-year-old girl who presented in myoclonic SE reportedly recovered after receiving 500 mg of intravenous VPA administered over 30 minutes.[127] Her VPA plasma level was 28 μg/mL when she recovered clinically.

The data so far suggest that intravenous VPA is a promising option for the treatment of SE in children and adults. There is still insufficient data to recommend this drug as initial treatment, but it can certainly be considered in patients with refractory status who failed treatment with phenytoin (or fosphenytoin), benzodiazepines, and/or barbiturates. The optimum loading and maintenance doses have not yet been established, but a loading dose of 20 to 40 mg/kg administered over a few minutes, followed by a maintenance dose of 5 mg/kg per hour appears to be safe and efficacious in children. In adults, a loading dose of at least 15 mg/kg followed by a maintenance dose of at least 1 mg/kg per hour should be used.

Adverse Effects

Neurologic

A postural tremor can occur following treatment with VPA. This side effect is dose- and serum level-dependent and usually improves following a dose reduction or treatment with propranolol.[13,69] Sleepiness, lethargy, and confusion can occur with VPA treatment, but are rare and typically occur with serum VPA levels above 100 μg/mL.[19] VPA has also been associated with reversible parkinsonism, thought to be unrelated to dopaminergic neuronal loss.[11,43,122]

Another neurologic side effect related to VPA is a reversible encephalopathy characterized by acute mental status changes that can progress to coma. This condition is associated with generalized δ-wave slowing on electroencephalograph (EEG), is unrelated to hyperammonemia, and usually improves within 2 to 3 days of stopping VPA.[85,119] VPA-induced hyperammonemic encephalopathy is characterized by an acute deterioration of mental status with confusion and lethargy, focal findings on neurologic examination, and increased seizure frequency that can progress to stupor and coma.[137] EEG changes consist of generalized slowing associated with an increase in the frequency of epileptiform discharges. The ammonia level is elevated without concomitant evidence of liver failure. No association between VPA dose, elevation of ammonia level, and severity of the encephalopathy was found.[137] VPA-induced hyperammonemic encephalopathy quickly resolves following discontinuation of VPA.[137]

Gastrointestinal

VPA frequently causes nausea, vomiting, diarrhea, and anorexia.[13] These symptoms typically occur during the initiation of treatment and were found to be less frequent and less severe with the enteric-coated formulation.[19]

Elevated liver enzyme activity is common with the use of VPA, and it has been suggested that raised liver enzymes up to three times the upper limit of normal do not require a change in treatment in asymptomatic patients with no other abnormal liver function tests.[48] Benign elevation of liver enzymes should be differentiated from fulminant hepatotoxicity, a relatively rare and serious idiosyncratic adverse event characterized by decreased alertness, jaundice, vomiting, hemorrhage, increased seizures, anorexia, and edema as the most common presenting signs.[21,39,40] The major risk factors associated with this idiosyncratic reaction were young age, polytherapy, developmental delay, and coincident metabolic disorders.[21] Children under 2 years of age receiving VPA polytherapy had a 1:600 risk of liver failure. The risk was extremely low in adults and cognitively normal individuals. The much higher incidence of hepatotoxicity in children with metabolic disorders, particularly Alpers disease, other mitochondrial disorders, and urea cycle disorders, may reflect the fact that these diseases often manifest with both seizures and liver failure. Dreifuss reported that five pairs of siblings with inherited metabolic disorders died of hepatic failure and had histopathologic findings consistent with VPA hepatotoxicity but were discordant for VPA exposure.[21] Nonfatal and fatal pancreatitis can rarely occur in adults and children on VPA.[15,53]

Weight gain is a common side effect in patients receiving VPA.[31,38,42,44,66,102,130] In a recent randomized, double-blind comparative study of VPA versus lamotrigine, patients treated with VPA at 20 mg/kg per day experienced a mean weight increase of 12.8 ± 9.3 lb after 8 months of treatment.[16] In this study and previous studies,[102,130] there were no predictive factors for weight gain, such as age, gender, pretreatment body weight, or VPA dosage.

Reproductive

In 1993, a possible association between the use of VPA and occurrence of reproductive endocrine disturbances in women with epilepsy was reported.[67] This was followed by other studies from the same group reporting a high frequency of polycystic ovaries, hyperandrogenism, high serum insulin levels, and menstrual irregularities related to treatment with VPA, raising the possibility of an association between VPA and polycystic ovaries syndrome.[66,68] More recently, the effect of epilepsy syndrome (localization-related epilepsy vs. idiopathic generalized epilepsy) and type of AED (carbamazepine, phenytoin, phenobarbital, VPA, lamotrigine, or gabapentin) on ovulatory function was evaluated in 94 women with epilepsy and 23 controls.[96] No significant associations were found between the type of AED used and anovulatory cycles, nor between the type of AED and presence of polycystic ovaries. However, it was reported that women with idiopathic generalized epilepsy who were taking or who had taken VPA within the previous 3 years were at the highest risk for anovulatory cycles. Of importance is that none of the women in this study satisfied the National Institutes of Health criteria for the polycystic ovaries syndrome.[96] Other studies failed to detect an association between reproductive abnormalities and the intake of VPA. For example, a prospective study on 93 women with chronic focal epilepsy failed to detect an association between VPA and polycystic ovaries syndrome.[12] In contrast to other studies, menstrual disorders were found to be more common among women taking AEDs (33%) other than VPA (24%).[12] Similar results were reported in two other studies.[14,81]

The issue of a possible association between VPA and reproductive abnormalities, polycystic ovaries, or polycystic ovaries syndrome was recently reviewed critically.[93] It was concluded that women with epilepsy are at risk for developing reproductive endocrine disorders, but that there is not yet definite evidence that polycystic ovaries syndrome is more frequent in these patients nor that VPA may be the cause of endocrine problems. It is likely that both the epileptic disorder and the antiepileptic treatment play different roles in the development of such disturbances.[95] (For further discussion, see Chapters 196 and 198.)

Hematologic

VPA can lead to various hematologic adverse events including dysfunction of the coagulation system, thrombocytopenia, abnormal platelet function, hypofibrinogenemia, von Willebrand disease, and, rarely, a decrease of vitamin K–dependent factors.[3,49,110,131] Occasional fatal bone marrow failure, myelodysplasia, and a clinical picture resembling acute promyelocytic leukemia have been reported with VPA use.[3] A significant relationship was found between platelet counts and impaired platelet function on the one hand and VPA dose and VPA plasma concentrations on the other.[13,49] These hematologic dysfunctions usually occur with serum VPA levels greater than 100 μg/mL and may improve with dosage reduction.[3]

Other Side Effects

VPA was found to cause osteopenia and osteoporosis by direct bone resorption, a mechanism different from that of enzyme inducers, such as phenytoin, carbamazepine, and the barbiturates, which cause hypovitaminosis D and secondary bone loss.[18,124]

Teratogenicity

Maternal exposure to VPA has been associated with a variety of major malformations, including neural tube defect (NTD), and with developmental delay (see Chapter 108). A fetal AED syndrome has been associated with several drugs, particularly phenytoin and VPA. Characteristic features of the VPA syndrome consist of arched eyebrows, short nose, thin upper lip, and broad nasal bridge.[37] Other traits include cleft lip and palate, radial ray defects, congenital heart defects, and genitourinary problems. In addition, prenatal VPA exposure has been associated with bilateral congenital blepharoptosis and optic chiasm hypoplasia.[50,92] A prospective study in North America reported that the prevalence of major malformations was 10.7% in infants born to mothers receiving VPA compared with 2.9% in infants born to mothers receiving other AEDs, and 1.62% in infants born to nonepileptic mothers not receiving any AEDs.[145] Thus, the relative risk of having a major malformation after exposure to VPA when compared with mothers not exposed to AEDs was 7.3. Similarly, a prospective study in Australia reported that the prevalence of major malformations was 16% in infants born to mothers receiving VPA in the first trimester compared with 2.4% in infants born to mothers receiving other AEDs in the first trimester and 3.1% in infants born to epileptic mothers not receiving any AEDs.[135] This study emphasized the effect of higher dosages on teratogenicity. The prevalence of malformations was 30.2% with VPA doses of greater than 1,100 mg and 3.2% with doses of less than 1,100 mg/day.

The association between VPA and NTDs was first reported in 1982.[118] Since then, a number of risk factors for the development of NTD were identified. They include a previous pregnancy with a NTD, ethnic and geographic predisposition, excessive exposure to vitamin A, a higher prepregnancy weight, and deficiencies of glutathione, folate, vitamin C, riboflavin, zinc, cyanocobalamin, and selenium.[139] It is even suggested that VPA may be a necessary but not sufficient risk factor for the development of NTDs.[146]

An analysis of five prospective studies found that VPA was associated with spina bifida in 3.8% of at-risk pregnancies.[121] This association was dose-dependent, so that spina bifida did not occur with VPA doses of less than a 1,000 mg/day (0 out of 54 pregnancies), whereas it occurred in 6.7% of exposed women on daily VPA doses of 1 to 1.5 g (2 out of 30 pregnancies). This percentage increased to 37.5% when the dose of VPA exceeded 1.5 g/day (three out of eight pregnancies). A similar dose-related increase in major congenital defects was reported in another study.[89]

In addition to the teratogenic risk, recent evidence suggests that children exposed to VPA in utero are at an increased risk of developmental delay.[4,104] (For further discussion, see Chapter 109.) For example, a recent study found a significantly decreased verbal IQ in children exposed to polytherapy with VPA, but no effect from exposure to carbamazepine.[47] Another study showed that children exposed to VPA monotherapy in utero had significantly lower verbal IQ (VIQ) scores compared with children exposed to carbamazepine or phenytoin monotherapy, with suggestions of a dose-related effect. Risk factors for drop in VIQ were the occurrence of five or more tonic–clonic seizures during pregnancy and low maternal IQ.[5] However, a recent review identified a number of methodologic shortcomings with those studies and concluded that the currently available data are insufficient to draw any definite conclusions.[6]

Drug Interactions

Effects of Valproate on Other Drugs

The hepatic metabolism of drugs occurs via the cytochrome P450 (C450) and uridine diphosphate glucuronosyltransferase (UGT) enzymes. C450 is a family of multiple enzymes that include three major families (CYP1, CYP2, CYP3). The seven isoenzymes primarily involved in the hepatic metabolism of most drugs are CYP1A2, CYP2A6, CYP2C8/9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4. The last is the most abundant isoenzyme, has the broadest substrate specificity, and is involved in the metabolism of more than 50% of all drugs.[144]

VPA is a broad-spectrum inhibitor of hepatic metabolism, including inhibition of CYP2C9, uridine glucuronyl transferase (UGT), and epoxide hydrolase.[8,64] VPA primarily inhibits drugs metabolized by the CYP2C9 subfamily

(phenobarbital and phenytoin).[125] VPA significantly increases lamotrigine plasma concentrations, presumably by competitively inhibiting the glucuronidation of lamotrigine.[147] It also inhibits the epoxide hydrolase enzyme, which catalyzes the metabolism of carbamazepine 10,11-epoxide.[90,114] Therefore, when VPA and carbamazepine are concomitantly administered, the serum concentrations of the carbamazepine 10,11-epoxide increases with or without an increase in the total carbamazepine concentration, which could result in side effects.

VPA is highly protein-bound to albumin, and can displace other highly protein-bound drugs (phenytoin, carbamazepine, diazepam) from their binding sites, increasing the free plasma levels of those drugs.[125] For example, the effect of VPA on phenytoin is a combination of displacement from protein-binding sites and enzyme inhibition. These interactions can result in a disruption of the relationship between free and total plasma phenytoin concentrations. Total phenytoin concentrations can increase, decrease, or not change when VPA is added. However, the free phenytoin fraction will usually increase. Ideally, free phenytoin concentrations should be monitored in a patient receiving both VPA and phenytoin.[56,72,75]

Concerning medications other than antiepileptics, VPA does not affect the cyclosporine level[57] nor does it interact with the metabolism of oral contraceptives.[34] However, it increases the plasma level of lorazepam[9] and zidovudine,[74] by inhibiting the glucuronide conjugation of these drugs. In addition, VPA increases concentrations of amitriptyline and its major metabolite, nortriptyline, by approximately 20%.[143]

Effects of Other Drugs on Valproate

VPA is metabolized through the liver, predominantly by UGT-catalyzed glucuronide conjugation and ß-oxidation (VPA is a substrate for CYP2C9 and CYP2C19).[8] The concentration of VPA is decreased in the presence of CYP2- and UGT-inducing drugs such as phenytoin, carbamazepine, and phenobarbital.[8] Felbamate significantly inhibits VPA metabolism by inhibiting the ß-oxidation pathway.[62] Lamotrigine is a weak inducer of UGT and causes a decrease in VPA plasma concentrations.[10] Topiramate causes a modest decrease in VPA plasma concentrations by inducing its ß-oxidation.[8] Ethosuximide was found to reduce VPA concentrations by approximately one-third,[120] whereas tiagabine resulted in a slight reduction in VPA plasma concentrations.[20]

Acetylsalicylic acid displaces VPA from albumin, leading to higher unbound levels,[106] and inhibits the beta-oxidation of VPA, resulting in increased microsomal metabolism and 4-en-VPA.[1] Carbapenems inhibit the hydrolysis of VPA-glucuronide to VPA; this causes a decrease in plasma concentration of VPA and results in seizure exacerbation in patients treated with VPA and carbapenems.[27,29,98]

Role in Epilepsy Treatment

VPA is considered to be a broad-spectrum AED, effective against all seizure types. It is generally considered a first-line agent (or drug of choice) for absence, myoclonic, and primarily generalized tonic–clonic seizures. In addition, it is often used as monotherapy or part of a polytherapy regimen for patients with symptomatic generalized epilepsies. For patients with newly diagnosed, localization-related epilepsy, clinicians do not usually consider VPA to be the drug of choice. It is, however, frequently used as an alternative monotherapy agent or as part of a polytherapy regimen for patients with refractory seizures of partial onset.

VPA is available in oral formulations of various strengths and as a parenteral formulation. To minimize adverse events, it is best to start the drug at a low daily dose with a gradual titration to efficacy. For adults, and especially the elderly, a starting dose of 250 mg twice daily is usually better tolerated than the 10 to 15 mg/kg starting dose recommended in the package insert. The dose can subsequently be increased by increments of 250 mg/day on a weekly basis. For patients with newly diagnosed epilepsy, the usual effective daily dose is between 750 and 1,500 mg. Patients with localization related epilepsies will usually require higher daily doses and higher trough serum levels to achieve seizure control, compared with those with idiopathic generalized epilepsies. For children, a starting dose of 15 mg/kg per day is recommended, with weekly increases of 5 to 10 mg/kg per day. The usual maintenance dose ranges between 15 and 30 mg/kg per day. Patients experiencing adverse events on the delayed release formulation,[2] or those wishing to be treated with a once-daily regimen, can be switched to the extended-release formulation.[2] This is based on a few studies that suggested that divalproex ER is better tolerated by some patients compared with the delayed-release formulation.[128] If such a switch is conducted, the total daily dose of divalproex ER should be 10% to 20% higher that that of divalproex DR to ensure similar steady-state serum levels. The intravenous formulation of VPA is useful for patients unable to take medications orally or for initiation of therapy before discharge from the epilepsy monitoring unit.[17] As previously mentioned, the role of intravenous VPA for the treatment of SE is promising, but more studies are needed to better delineate its potential role in this condition.

The most common early side effects of VPA involve the gastrointestinal tract. Dose-related side effects include tremor and thrombocytopenia. Although the tremor usually responds to treatment with ß-blockers,[69] it is best to try to reduce the dose if the tremor is bothering the patient. Hair loss sometimes responds to treatment with zinc and selenium supplementation.[63] Some patients develop substantial weight gain on VPA, which can be treatment limiting.

Patients treated with VPA, especially at high doses, should have their platelet counts monitored. Liver function tests should be monitored in very young children, especially those who are mentally retarded and with symptomatic generalized epilepsy. Amylase and ammonia levels should be checked based on the clinical picture. Because patients on long-term treatment with VPA are at risk to develop osteopenia or osteoporosis,[124] it would be useful to have a baseline bone densitometry performed with follow-up studies every few years. Treatment with calcium and vitamin D supplementation should be considered in all patients, whereas bisphosphonates should be reserved for patients who develop osteopenia/osteoporosis.

There are some concerns about the use of VPA in women of childbearing age, because of its potential association with polycystic ovary syndrome and risk of teratogenicity. Although alternative agents can easily be considered for the localization-related epilepsies, VPA can be the most efficacious AED in the generalized epilepsies and the only AED associated with seizure control. For those patients, VPA should be considered the drug of choice, and the minimal effective dose of VPA with folate supplementation (0.4–5 mg/day) should be used. Pregnant women on VPA should undergo a serum α-fetoprotein level and a level II ultrasound at 14 to 18 weeks of gestation to evaluate for the possibility of NTDs.

Summary and Conclusions

VPA possesses multiple mechanisms of action, has a broad spectrum against all seizure types, and an adverse event profile that differs from other AEDs. It is available in oral formulations of various strengths and as a parenteral formulation. VPA is an

inhibitor of hepatic metabolism and therefore can increase the serum level of other drugs, including some AEDs, notably lamotrigine. Although the use of VPA in pregnancy is associated with NTDs, it still may be the best option for treating some specific epilepsy syndromes.

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Chapter 161

Vigabatrin

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Introduction

Vigabatrin is a novel antiepileptic drug (AED). It differs from most other agents in that it was designed to have a specific effect on brain chemistry and was subsequently proved to produce that effect. Thus, it is still one of the few AEDs whose mechanism of action is presumably completely known. The mechanism consists of irreversible inhibition of γ-aminobutyric acid (GABA)-transaminase, the enzyme that degrades the inhibitory neurotransmitter GABA in the central nervous system (CNS). A great deal of information has been obtained about this unique compound from clinical trials and also from the large number of patients receiving vigabatrin as a registered drug in nearly 50 countries worldwide. It is not, however, available in the United States because of its tendency to cause irreversible visual field defects (VFDs). The possibility exists, nevertheless, that vigabatrin will one day be available in the United States for use in children with infantile spasms. This chapter reviews the current preclinical data, efficacy, safety, and clinical use of vigabatrin.

Chemical Characteristics, Formulations, and Methods for Determination in Body Fluids

Chemical Characteristics

Vigabatrin (4-amino-5-hexenoic acid, γ-vinyl GABA, GVG) is a structural analog of GABA with a vinyl appendage (Fig. 1). It is a rationally designed, enzyme-activated, irreversible selective inhibitor of GABA-transaminase.[38,76] Vigabatrin is highly water-soluble, only slightly soluble in ethanol and methanol, and insoluble in hexane and toluene. It is a white to off-white crystalline solid with a melting point of 171° to 177°C. The molecular weight is 129.16, and the conversion factor (CF) is 7.75 (mg/L × CF = μmol/L).

Vigabatrin is a racemic mixture of *R*-(-) and *S*-(+)-enantiomers in equal proportions and exhibits no optical activity. The pharmacologic activity and toxic effects of vigabatrin are associated only with the *S*-(+)-enantiomer; the *R*-(-)-enantiomer is entirely inactive.[40,87] The duration of effect is determined by the half-life of the enzyme rather than by that of *S*-(+)-vigabatrin because GABA-transaminase has a much longer half-life than *S*-(+)-vigabatrin itself.[8,50]

Formulations

The only available forms of vigabatrin are oral formulations (500-mg tablets and 500-mg sachets). Sachet contents may be placed in a beverage (e.g., water, fruit juice, or milk) immediately before oral administration.

Methods of Determination in Body Fluids

Vigabatrin is a highly water-soluble amino acid and can be measured using standard automatic amino acid analysis, high-performance liquid chromatography (HPLC), or gas chromatography-mass spectrometry.

HPLC is the most commonly used method of analysis for vigabatrin in body fluids. A reversed-phase HPLC assay was developed by Smithers et al.[101] Tsanaclis et al.[111] described a single-step protein precipitation with subsequent precolumn derivatization with *o*-phthaldialdehyde and direct injection into a Microsorb C18 column. The isocratic HPLC method developed subsequently by Chollet et al.[20] is more rapid than previous methods. Since only the *S*-(+)-enantiomer is pharmacologically active, it is generally preferable to utilize assays that differentiate between enantiomers, such as that described by Vermeij and Edelbroek.[113]

Pharmacology

Activity in Experimental Models of Seizures/Epilepsy

Vigabatrin has been tested in numerous seizure models and has been shown to be effective in some, but not all. It is inactive in models such as maximal electroshock (MES), bicuculline (GABA antagonist), and pentylenetetrazol unless injected directly into the midbrain of rats.[31] However, after an intravenous injection of vigabatrin, seizure protection was observed against bicuculline-induced myoclonic activity,[54] strychnine-induced tonic seizures,[98] isoniazid-induced generalized seizures,[98] audiogenic seizures in the mouse,[96] light-induced seizures in the baboon,[71] and amygdala-kindled seizures in the rat.[76,103]

Stereotaxic injections of small amounts of vigabatrin into certain areas of rat brain gave seizure protection in relation to the locally increased GABA levels.[31] Seizure protection in the MES model was most prominent with local GABA increases in the midbrain tegmentum, including the substantia nigra and the midbrain reticular formation. Injections of vigabatrin into the thalamus, hippocampus, and cortex did not protect against seizures in this model. The duration of seizure protection was as long as 72 hours after a single injection to the substantia nigra. Only by the fifth day did the rats respond normally to MES. This finding supports the observation that the rate of recovery of GABA-transaminase is 5 days,[50] and suggests that the anticonvulsant effect is a consequence of the local increase in GABA levels rather than of a direct effect of vigabatrin itself.

Mechanisms of action

Studies in Animals

The pharmacokinetics in the CNS and effects on GABA, GABA-transaminase, glutamate decarboxylase, and other neurotransmitters and amino acids in animals demonstrate the specific effects of vigabatrin in the brain. In one of the first experiments studying the effects of vigabatrin, 1,500 mg/kg of the compound were injected intraperitoneally in mice. The brain content of GABA, GABA-transaminase, and glutamate decarboxylase was measured over time. By 4 hours, a fivefold increase of whole-brain GABA was noted.[50] At the same time, a sharp decline occurred in GABA-transaminase activity, with a recovery to 60% of baseline after 5 days. Glutamate decarboxylase was also affected, with a 30% reduction of activity. However, this decrease was seen only at very high doses (1,500 mg/kg), and the probable cause is considered to be feedback following the rise in GABA concentration.

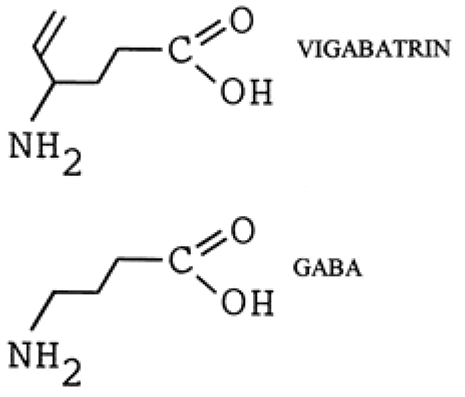

FIGURE 1. Chemical structure of vigabatrin.

In addition to GABA, vigabatrin also influences other amino acids and transmitters, at least at high doses.[82] An increase in brain ß-alanine (an alternative substrate for GABA-transaminase), as well as homocarnosine and hypotaurine, was demonstrated, whereas glutamine and threonine levels decreased.

Studies in Humans

Observing effects on GABA and other neurotransmitters in the cerebrospinal fluid (CSF) has been an important method to study the effects of vigabatrin on GABA and other neurotransmitters and amino acids in the human brain. The first study to investigate the relationship between vigabatrin and GABA in the CSF was carried out by Grove et al.[38] Patients with various neurologic conditions were given 0.5, 1, 2, or 6 g daily for 3 days. Free and total GABA, ß-alanine, homocarnosine, and vigabatrin increased in a dose-responsive manner, except at a dose of 0.5 g/day, with which no changes in the parameters studied were recorded. Schechter et al.[96] studied ten patients given 0.5 g vigabatrin twice daily for 2 weeks followed by 1 g twice daily for 2 weeks and then placebo for 2 weeks. When parameters were measured at the end of the treatment period, there were no changes from baseline in homovanillic acid (HVA; the metabolite of dopamine) and 5-hydroxyindolacetic acid (5-HIAA; the metabolite of serotonin), but dose-related increases were seen in free and total GABA, and in homocarnosine. At the end of the placebo period, the levels of GABA and homocarnosine had declined to baseline levels.

No changes in CSF levels of acetylcholine, somatostatin, ß-endorphins, prolactin, cyclic adenosine monophosphate, or cyclic guanosine monophosphate were observed during long-term treatment.[84,99] No consistent changes have been found in amino acids, HVA, or 5-HIAA with long-term treatment of vigabatrin at 50 mg/kg up to 3.5 years either in tissue or CSF.[7,99] In a single-dose study, however, HVA and 5-HIAA concentrations increased initially up to 100%, but they returned to the baseline level or slightly below baseline level after 1 month of treatment.[8]

At a dose of 50 mg/kg, vigabatrin causes a 200% to 300% increase in GABA in the CSF and brain tissues.[6] A reduction of vigabatrin dose from 3 g/day to 1.5 g/day caused a proportional reduction of GABA concentrations in the CSF.[99] Dose and percentage increase in CSF GABA concentrations show a good linear relationship, but the relationship between dose and efficacy appears more complex and depends on the nature of the epilepsy. Nuclear magnetic resonance spectroscopy in patients treated with vigabatrin have confirmed the observations seen using CSF GABA analysis.[69]

The effects of vigabatrin are also seen in blood GABA and platelet GABA-transaminase levels. Administration of vigabatrin causes a marked reduction in platelet GABA-transaminase at therapeutic doses of 2 to 3 g/day. It appears that a dose of 2 g/day maximally inhibits platelet GABA-transaminase, with mean enzyme inhibition at approximately 70%.[89] The concentration of plasma vigabatrin is almost tenfold that seen in the CSF and, because platelets cannot regenerate GABA transaminase, the effect of vigabatrin on this test system is also influenced by platelet regeneration.

There is no clear-cut correlation between blood concentration of vigabatrin and efficacy.[57]

Clinical PHARMACOKINETICS

Absorption

The only available forms of vigabatrin are oral. There are no intravenous or rectal formulations, so the absolute bioavailability of the drug has not been determined in humans. Studies in animals, however, indicate that the areas under the plasma concentration versus time curves (AUCs) are similar when intravenous, intraperitoneal, subcutaneous, intramuscular, and oral doses are administered.[50,101]

All pharmacokinetic studies[39,40,92] in humans have demonstrated that absorption is rapid, with the peak concentration reached in the first 2 hours after doses of between 0.5 and 3 g. Absorption half-life ranges from 0.18 to 0.59 hours. In a single-dose kinetic study that used an enantioselective assay,[40] peak plasma concentrations for both enantiomers were reached between 0.5 and 2 hours after a 1,500-mg dose.

The bioavailability of vigabatrin in tablet form and in solution has been studied in healthy volunteers.[45] Although there was a slightly lower, delayed peak concentration for the tablet, the pharmacokinetic profiles were very similar. Thus, it can be concluded that the vigabatrin tablet is bioequivalent to the oral solution. Approximately 60% to 80% of the drug can be recovered unchanged in the 0- to 24-hour urine. This indicates that bioavailability is at least 60% to 80%.

The effect of food on the bioavailability of vigabatrin in tablet form has been studied.[30,45] The AUC for fasted and fed volunteers was not significantly different. This indicates that food does not have an effect on the extent of absorption. The half-life was 7.15 hours, and renal clearance was 95.0 mL/min for the fasted group, and 9.15 hours and 99.9 mL/min for the fed group. Therefore, the time of administration and what and when a person eats should not influence the clinical response to vigabatrin.

Plasma Protein Binding and Distribution

Plasma Protein Binding, Volume of Distribution, and Penetration into the Cerebrospinal Fluid

Vigabatrin does not bind at all to plasma proteins.[89] The distribution of vigabatrin in the body is very wide. This is not surprising, because vigabatrin is not protein-bound and is a highly water-soluble compound. The apparent volume of distribution is 0.8 L/kg (total body water is 0.6 L/kg) in volunteers, with the half-life of distribution at 1 to 2 hours.

Vigabatrin levels in CSF have been analyzed in patients with epilepsy. The concentration of vigabatrin in the CSF was approximately 10% of that in the blood.[8] In this study, patients taking concomitant AEDs were given 50 mg/kg as a single dose. CSF and blood samples were taken for up to 5 days after dosing. The highest concentrations of vigabatrin were found in CSF after the first sample. By 24 hours, only a trace was detectable in the CSF, and no vigabatrin was found at 72 hours or thereafter. The peak concentration in the blood was reached by 1 hour and decreased thereafter, with only trace amounts detectable at 72 hours. After a 3-year follow-up at doses of 50 mg/kg per day, the levels of vigabatrin in CSF were not significantly increased when compared with the 6-month levels.[7]

Distribution in Placenta

Passage of *S*-(+)-vigabatrin and *R*-(-)-vigabatrin across the human placenta in vitro was studied by Challier et al.[16] The transfer from maternal to fetal blood across the placenta was low and comparable with that of other acidic α-amino acids. Clearance for both of the enantiomers was about 27% that of phenazone.

Distribution in Special Populations

To determine whether vigabatrin has a different distribution profile in the elderly, 1.5 g vigabatrin was given as an oral dose to healthy volunteers between the ages of 60 and 75. Steady-state volume of distribution was not markedly different from that in the younger volunteers.[39] However, in volunteers between the ages of 76 and 97 years, a decrease of the apparent volume of distribution occurred.

In renally impaired patients, the volume of distribution was about one-half to one-third that in healthy volunteers.[39] Because most of the renally impaired volunteers were elderly (mean age, 86.4 years), the reduced muscle mass probably contributed to the reduced volume of distribution.

Metabolism

Vigabatrin is not significantly metabolized in humans. Up to 82% of the oral dose is excreted unchanged in the urine (data on file, Sanofi-Aventis, Paris, France).

Elimination

Half-Life and Clearance

The elimination half-life is 5 to 8 hours, and the total clearance is about 1.7 to 1.9 mL/min per kilogram, with renal clearance accounting for 70% of the total apparent oral clearance. Elimination is not influenced by dose or duration of treatment.[37] Again, it should be stressed that the biologic half-life—that is, the half-life for inhibition of GABA-transaminase—is measured in the order of days, not hours.

Elimination parameters have also been assessed separately for the two vigabatrin enantiomers. The pharmacokinetics of the *S*-(+)-enantiomer is independent of that of the *R*-(–)-enantiomer. After dosing with pure *S*-(+)-vigabatrin, the mean terminal half-life was 386 minutes. The half-life for the *R*-(–)-enantiomer was 485 minutes, and 447 minutes for the *S*-(+)-enantiomer in the racemate.[40] The AUC was 39.2 µmol/mL per minute for the *R*-(–)-enantiomer and 30.1 µmol/mL per minute for the *S*-(+)-enantiomer. The AUC for the pure *S*-(+)-vigabatrin was 30.6 µmol/mL per minute. An explanation to account for the lower AUC value for the *S*-(+)-enantiomer is that some of the *S*-(+)-enantiomer is bound irreversibly to the enzyme GABA-transaminase and is unavailable for analytical measurement. The *R*-(–)-enantiomer is inactive and therefore does not bind to the enzyme. No chiral inversion exists in humans.

Elimination in Children

In a preliminary study, children and, particularly, infants showed a lower AUC than historical adult controls, but renal clearance was comparable.[87] This might indicate that infants and children may have a lower bioavailability (which could explain why infants may need higher doses of vigabatrin to achieve seizure control), although more studies are required to characterize differences in vigabatrin pharmacokinetics between adults and children.

Elimination in the Elderly and the Renally Impaired

In elderly patients, both renal and total body clearance are slower. Terminal half-life showed an inverse relationship to renal function.[39] The elimination of vigabatrin is slower in elderly patients because of their reduced renal function. A direct correlation exists between renal clearance of vigabatrin and creatinine clearance. Renally impaired patients have higher plasma concentrations of vigabatrin, and the half-life is longer. The half-life in renally impaired patients with reduced creatinine clearance is approximately twice that of normal healthy volunteers. Analysis of AUC-to-body weight ratio versus creatinine clearance shows a nonlinear increase in the ratio of AUC to body weight as creatinine clearance falls below 60 mL/min.[39]

Efficacy

Adjunctive Therapy in Adults

Partial Seizures

The largest number of controlled clinical trials of vigabatrin have been performed in adults with previously intractable seizures taking the drug as add-on therapy. Table 1 outlines the designs of the six single-center, double-blinded European trials. Although most of the trials enrolled patients with other seizure types, the majority of patients had partial seizures. All trials demonstrated a statistically significant superiority of vigabatrin over placebo. In all but one, an overall mean or median seizure reduction of 40% or greater was obtained when patients were on vigabatrin in comparison with placebo. In a somewhat different type of trial design,[88] 33 patients were placed on open-label vigabatrin. Only those achieving a seizure reduction greater than 50% were studied further in a double-blinded phase and randomized to placebo or continued vigabatrin. Patients randomized to vigabatrin maintained a mean 54.7% seizure reduction, whereas patients randomized to placebo had a relatively rapid return of seizures.

Table 1 Summary of the double-blind placebo-controlled add-on trials of vigabatrin for refractory (mainly partial onset) seizures

Authors and date (Ref.)	Trial design	Length of trial	Number of patients	Completers	Seizure type	Responder rate (50% seizure reduction)
Rimmer and Richens 1984[90]	Crossover	9 weeks	24	21	Mainly partial seizures	Not given. Mean of 6.2 seizures/week for placebo vs. 3.5 seizures/week for vigabatrin (3 g)
Gram et al. 1985[34]	Crossover	12 weeks each arm	21	18	Complex partial seizures	Eight patients (vigabatrin dose: 3 g)
Loiseau et al. 1986[59]	Crossover	10 weeks each arm	23	19	17 partial seizures; two primary generalized seizures	11 patients (vigabatrin dose: 3 g)
Remy et al. 1986[86]	Crossover	12 weeks	23	17	Partial, primary generalized, and secondarily generalized	Mean 37% decrease in seizure frequency (vigabatrin dose: 3 g)

					tonic-clonic seizures	
Tartara et al. 1986[106]	Crossover	7 weeks each arm	23	20	17 partial seizures; six mixed seizure types	12 patients (vigabatrin dose: 2 or 3 g depending on body weight)
Tassinari et al. 1987[108]	Crossover	12 weeks each arm	31	30	15 complex partial seizures; 15 mixed seizure types	10 patients (vigabatrin dose: 2 or 3 g depending on body weight)
French et al. 1996[28]	Parallel-group	12 weeks	182	170	Complex partial seizures	19% placebo 43% vigabatrin 3 g
Dean et al. 1999[23]	Parallel-group	12 weeks	174	149	Complex partial seizures	7% placebo 24% at 1 g 51% at 3g 54% at 6 g
Bruni et al. 2000[12]	Parallel-group	36 weeks	111	90	Complex partial and/or partial secondarily generalized seizures	26% placebo 48% vigabatrin (vigabatrin dose: 2–4 g)

The European trials were performed primarily on patients with partial seizures, but patients with other seizure types were also included. A meta-analysis was performed to examine results among the 98 patients with partial epilepsy. In 46%, seizure reduction was greater than 50% after vigabatrin treatment in comparison with placebo, whereas in 11%, seizures worsened.[34,59,86,90,106,108]

Unlike the European trials, the two U.S. double-blind trials were of parallel rather than crossover design, and both were multicenter trials.[10,23,28] They enrolled exclusively patients with complex partial seizures, with or without secondary generalization. Details of these trials are outlined in Table 1. Both trials demonstrated a statistically significant reduction in seizures when vigabatrin was compared to placebo.

In the Canadian double-blind trial,[12] 111 patients with refractory partial seizures were given either placebo or vigabatrin at doses of 2 to 4 g per day. Magnetic resonance imaging (MRI) and evoked potentials and neuropsychological testing were done at regular intervals for a 36-week period. In the vigabatrin group, 48% of patients achieved a 50% or more seizure reduction compared with 26% on placebo. However, seizure-free rates were not presented, only seizure-free days. Vigabatrin was well tolerated, and no changes were noted in the MRI or visual evoked potential (VEP) in this short-term study.

The response to vigabatrin in partial epilepsy may depend on patient characteristics. Patients with localization-related epilepsy, one seizure type, and a low seizure frequency appear to have a greater chance of improvement.[108] All the European and U.S. trials enrolled patients with secondarily generalized tonic–clonic seizures. Many of these trials were able to demonstrate a trend of improvement in the secondarily generalized seizures but, in most, the percentage of patients with this seizure type was too small for improvement to reach statistical significance.[11,28]

Long-Term Efficacy

Several AEDs, most notably the benzodiazepines, may be highly effective initially, but effectiveness may wane. Theoretically, increased GABA levels in the CNS for a prolonged period could bring homeostatic mechanisms into play to reduce GABA levels, or postsynaptic receptors could become desensitized as excess GABA floods the synapse. Because of the unique mechanism of action of vigabatrin, it is very important to assess long-term efficacy. Studies have demonstrated that GABA levels in spinal fluid remain elevated during years of long-term use of vigabatrin.[6,7] Several studies of long-term efficacy have been performed. One way of evaluating long-term efficacy is by assessing how many patients remain on treatment through time. Presumably, patients for whom the treatment loses efficacy will abandon treatment to search for other drugs. In several long-term studies, 39% to 72% of patients remained on vigabatrin for more than 3 years. Among the patients electing to continue treatment, the majority had maintained their initial positive response and, in this particular subset, there was no evidence of loss of efficacy.[11,21,73,85,100,107]

Monotherapy in Adults

In a Finnish trial, 100 patients with new-onset epilepsy of all types were randomly assigned to receive carbamazepine or vigabatrin.[51] Treatment was more likely to fail because of lack of efficacy in the vigabatrin group and because of adverse events in the carbamazepine group. Thirty-two percent of the vigabatrin patients were seizure-free, in comparison with 52% of the carbamazepine patients. None of the vigabatrin patients and 24% of the carbamazepine patients discontinued treatment because of adverse events. Rash was the most common reason for carbamazepine discontinuation. The lower seizure-free rate seen with vigabatrin may in part have been a consequence of the heterogeneous patient population enrolled, which included many patients with generalized epilepsy.

The definitive study on the efficacy of vigabatrin in new-onset seizures is from the United Kingdom.[15] A total of 459 patients were enrolled in this study and randomized to either carbamazepine or vigabatrin for new-onset seizures. The patients were followed for 1 year. The results demonstrated that, although vigabatrin was better tolerated, patients on vigabatrin had more psychiatric symptoms than those on carbamazepine (25% vs. 15%), and weight gain was also more common on vigabatrin than on carbamazepine (11% vs. 5%). The carbamazepine group had more rashes (10% vs. 3%). As for efficacy, carbamazepine was more effective at time to first seizure but not at 6 months, at which point the number of remissions did not differ statistically between the groups. This study concluded that “vigabatrin seems less effective but better tolerated than carbamazepine, which is the first-choice drug for the treatment of partial epilepsies. Vigabatrin cannot therefore be recommended as a first-line drug for monotherapy in this group of patients.”

Children

Partial Seizures

Children with partial seizures have a response to vigabatrin similar to that of adults, with up to 50% reduction in seizure frequency in adjunctive therapy studies.[2,18,35,62,78]

An attempt to compare vigabatrin to carbamazepine in newly diagnosed partial seizures in children led to the conclusion that the two drugs had comparable efficacy and similar proportion of side effects.[102] However, this study only included 28 children per group, was open-label, and apparently not randomized, and therefore no firm conclusions can be drawn about the comparative effectiveness of vigabatrin and carbamazepine monotherapy in children.

Other Seizure Types (Excluding Spasms)

Fewer data are available about seizure types other than complex partial. In an analysis of published adjunctive-therapy trials, the majority (71%) of patients with generalized epilepsy syndromes did not respond to vigabatrin.[72] There have been varied reports of worsening after vigabatrin administration in patients with Lennox-Gastaut syndrome and myoclonic epilepsy,[40,50] whereas others report significant improvement.[27,44] Rarely, myoclonic jerks or absence seizures may develop when none have been seen previously.[22,119]

Infantile Spasms

Several trials have assessed vigabatrin for the treatment of infantile spasms, and all have shown an impressive response.[2,17] Overall, the majority of children with infantile spasms improve substantially with the addition of 100 to 150 mg/kg of vigabatrin daily, even when spasms have been previously resistant to drug therapy. Based on these results, vigabatrin has been proposed as an alternative first-line therapy to adrenocorticotropic hormone (ACTH) or steroids, the reference therapy in infantile spasms.[3]

Table 2 Incidence of the most frequent (>5%) adverse events (AE) reported in a randomized double-blind monotherapy trial of vigabatrin versus carbamazepine in adults with newly diagnosed partial epilepsy

Adverse event (AE)	Carbamazepine group (*n* = 229,195 with at least one AE; %)	Vigabatrin group (*n* = 228,191 with at least one AE; %)
Central nervous system	63	62
Amnesia	7	7
Drowsiness	28	21
Fatigue	22	20
Headache	21	21
Psychiatry	15	25
Agitation	6	7
Depression	3	7

Insomnia	2	7
Skin	23	14
Rash	10	3
Other	13	12
Other events		
Asthenia	7	2
Weight increase	5	11
Dizziness	13	13

(From Chadwick D. Safety and efficacy of vigabatrin and carbamazepine in newly diagnosed epilepsy: A multicenter randomized double-blind study. Vigabatrin European Monotherapy Study Group. *Lancet*. 1999;354(9172):13–91, with permission.) The study was conducted before the discovery of visual field defects.

Vigabatrin has been shown to be effective in the treatment of spasms in double-blind trials that compared it to placebo[4] or compared low (less than 40 mg/kg per day) to high (100 to 150 mg/kg per day) doses.[26] Efficacy is greater in patients starting before the age of 3 months (>90%) than in those starting later.[1] Overall, more than a third of children can be expected to have complete resolution of spasms, and more than 50% to have a reduction greater than 50%.[17] The response is favorable in symptomatic as well as cryptogenic etiologies, but the actual rate of total suppression of spasms depends on etiology. It is reached in 90% of infants with tuberous sclerosis[19] and focal cortical dysplasia,[61] whereas patients with spasms due to perinatal hypoxic–ischemic injury better respond to hormonal treatment (ACTH) than to vigabatrin.[114] Only 54% in patients with a variety of other conditions than tuberous sclerosis completely cease to have spasms with vigabatrin, a proportion significantly inferior to that observed with hormonal treatment at 14 days of randomized therapy.[64] However, the absence of spasms later on, at 12 to 14 months of age, is similar on vigabatrin and hormonal treatment,[64] and the rate of relapses is higher with ACTH.[114] In cryptogenic cases, the success rate may reach 100% when adding ACTH in patients not responding to vigabatrin monotherapy.[36,53] There seems to be a particular group of patients with psychomotor delay prior to the first spasms and no MRI abnormalities who also require the combination of vigabatrin and hormonal treatment to come under control and a duration of treatment of more than 3 months to prevent relapse.[115]

Long-term outcome is favorable in terms of maintaining spasm reduction, but less favorable in terms of overall development. The children who become spasm-free tend to remain so in long-term follow-up (up to 3 years). This is particularly true of patients with tuberous sclerosis. However, other seizure types, such as partial seizures, may emerge, and progressive cerebral deterioration may continue despite control of spasms.[67]

Treatment strategy in infantile spasms mainly depends on drug availability in different countries. In most countries, vigabatrin is considered the drug of choice as first-line monotherapy, although evidence is still insufficient for consensus,[65] the major remaining question being for how long treatment should be continued. In Down syndrome, 6-month control of spasms using vigabatrin was followed by no relapse after the cessation of treatment.[77] However, in tuberous sclerosis and cortical dysplasia, the risk is definitely high until the age of 5 years (personal data), and spasms following relapse tend to be highly pharmacoresistant.[14]

Adverse Effects

Dose-Related, Nonidiosyncratic Reactions

Most Common Adverse Effects Observed in Early Clinical Trials

Most data on the adverse effects of vigabatrin are based on add-on studies in patients with previously uncontrolled seizures taking between one to four other AEDs concomitantly. Table 2 shows the most significant side effects (except for VFDs) from the U.K. monotherapy trial comparing carbamazepine and vigabatrin.[15] Sedation and fatigue were the most commonly reported side effects. Weight gain can also be a not-uncommon troublesome effect, particularly during long-term use.

Visual Field Defects

Vigabatrin was deemed a drug with few side effects and rather safe. Microvacuoles, which were evident in animal models using rats and dogs, have not been detected in humans despite repeated MRI studies and pathologic analyses of brains retrieved during autopsy or epilepsy surgery.[14,47] Animals had also shown retinal changes, and so patients in clinical trials were investigated using VEPs, visual evaluation according to Donders, and funduscopy. No investigator or treating physician looked specifically at visual field problems associated with vigabatrin (or with any other drug for that matter). In 1997, Eke et al.[25] published the first paper indicating that some patients had VFDs that adversely affected their daily living activities. This was an important finding, and all patients on vigabatrin were encouraged to have their visual fields tested more rigorously. The particular VFD induced by VGB is recognized as a defect involving peripheral vision, with a pattern of typically bilateral, concentric (most often profound nasally) constriction of the visual field, the severity of which varies from mild to severe, although it remains asymptomatic in the large majority of cases.[117]

The prevalence of VFDs attributable to vigabatrin discloses a huge disparity (from 14%–92%) mainly arising from the sampling bias of relatively small cohorts and from the diversity of the perimetric techniques used to assess the visual fields. Static perimetry (Humphrey) should be preferred to kinetic perimetry (Goldman) when available. The validity of visual electrophysiologic techniques (such as electroretinography, electro-oculography, or VEPs, which do not require patient collaboration, contrary to perimetry) to diagnose vigabatrin-induced VFDs is not yet fully established.[43] Because of difficulties in assessing the visual field by perimetry below a developmental age of 9 years, a specific method based on visual-evoked potentials is under development in children 3 years of age and older.[42]

From published studies, it would seem that at least 30% of adult patients who have taken vigabatrin have VFDs.[52] The prevalence of VFDs may be lower in children,[112] and no child treated for infantile spasms in infancy has as yet been shown to develop symptomatic VFDs. Three risk factors for vigabatrin-induced VFDs have emerged: male gender, increased duration of treatment, and cumulative dose of vigabatrin given.[66,112] Data gathered so far suggest that the cumulative incidence increases rapidly during the first 2 years of treatment and within the first 2 kg of vigabatrin intake, and stabilizes at 3 years and after a total vigabatrin dose of 3 kg.[52] Patients with VFDs who are withdrawn from vigabatrin do not show improvement in the visual defects but do not progress either.[79] Based on this identified toxicity, recommendations are now given to monitor the visual field before treatment and every 4 to 6 months on vigabatrin and to reconsider the benefit-risk ratio if any VFD attributable to vigabatrin is discovered.

The etiology for the VFDs is not known. One study in rats[24] showed that damage affected initially the cone inner and outer segments, possibly because vigabatrin causes a high concentration of GABA in the retinal area. However, a study by Izumi et al.[46] in rats showed that an increase in GABA did not cause retinotoxicity with damage to the cones. Vigabatrin caused retinotoxicity, but only when the animals were exposed to light and not to darkness. This suggests that retinal toxicity is related to vigabatrin itself and not to GABA.

Vigabatrin, because of this serious irreversible side effect, should not be used as a first-line drug, except in catastrophic epilepsies of childhood such as infantile spasms. If used, then the time on treatment should be limited and the dose given be as low as possible.

Psychiatric Adverse Effects

In clinical trials, about 2.2% to 7.3% of patients withdrew because of psychiatric side effects. Depression, confusion, and other behavioral abnormalities accounted for about 5% of the reported adverse events. In children, hyperkinesia and agitation were reported in some patients, most often in those treated with high doses.[2] Most side effects were dose-related and could be reversed when the drug was stopped or the dose reduced.

Depression seems to be an established adverse effect of vigabatrin, and the same applies to psychosis. The question of whether vigabatrin can elicit psychosis was first raised by Sander et al.,[93,94] who reported that 14 of 210 patients experienced severe psychiatric reactions in connection with vigabatrin treatment. Subsequently, other case reports have been published in the literature with warnings that vigabatrin can cause psychosis. The two U.S. multicenter, placebo-controlled double-blinded studies[23,28] included a careful analysis of psychiatric side effects. The studies did not, however, include patients with severe brain damage or severe psychiatric disorders because it was assumed that development of clinically important psychiatric adverse events would result in patient drop-out. From the combined results of the two studies, 0.7% of patients in the placebo group (n = 135), 2.2% in the 1-g treatment group (n = 45), 6.6% in the 3-g treatment group (n = 135), and 7.3% in the 6-g treatment group (n = 41) dropped out because of a psychiatric adverse event. These and similar results from other studies support the contention that severe psychiatric adverse events do appear in about 5% of patients treated with vigabatrin. A large postmarketing surveillance study of vigabatrin from the Drug Safety Research Unit at the University of Southampton that included more than 6,000 patients, however, reported only 88 cases (0.64%) that could be associated with psychotic reactions, such as hallucinations, paranoia, or delusions (data on file at Sanofi-Aventis, Paris, France). This is not greater than the number of severe psychiatric adverse events seen during treatment with other AEDs,[68,118] which is not surprising, because psychiatric problems are common in patients with intractable epilepsy, especially those with partial seizures.[105]

To minimize the problem of psychiatric adverse events, patients who have a history of severe psychiatric disturbances, who have very severe brain damage, or who respond to vigabatrin with a dramatic reduction in seizures should be watched carefully. Patients with a dramatic reduction of seizures can experience “forced normalization,” which has been described to cause psychosis.[55] Vigabatrin should be titrated upward slowly, except in small children, and should never be withdrawn rapidly, because rapid withdrawal can elicit an increase of seizures and lead to postictal psychosis.

Intramyelinic Edema

During toxicology studies, vigabatrin doses as low as 30 mg/kg were found to cause intramyelinic vacuolation or edema in specific areas of rodent and dog brains, primarily the hippocampus, cerebellum, visual pathways, and columns of the fornix.[33] These microvacuoles were reversible when the drug was stopped. Monkeys treated with 300 mg/kg daily for 16 months did not have more microvacuoles at autopsy than did controls.[32] Delayed conduction times using somatosensory and VEPs were found to correlate with the onset of vacuolation in dogs as detected by MRI.[104,116]

Because the microvacuoles could be detected with MRI investigations, and their existence monitored by testing for increased conduction times using evoked potentials, it has been considered important to follow with both MRI and studies of evoked potentials those patients who participated in the initial studies and who have been treated for long periods. According to Sanofi-Aventis, MRI and evoked potentials have been

used to follow more than 500 patients, with no indication that microvacuolation occurs in humans. Some of the patients have been followed for more than 8 years without changes in evoked potentials being detected.[10,41,56,107,110]

Neuropathologic studies have been carried out on patients who died or had epilepsy surgery during vigabatrin treatment. Sixty case reports have been published comprising 10 postmortem and 50 surgical samples. Treatment periods were up to 108 months. These cases were reviewed in a blinded fashion, with other samples from patients not treated with vigabatrin used as a basis for comparison. None of the material examined has shown evidence to suggest that vacuolation occurs in humans.[14]

Idiosyncratic Reactions

Immune-mediated hypersensitivity reactions such as skin rashes or other allergic reactions are observed rarely with vigabatrin.

Second-Generation Effects

In animals, no teratogenic effects have been reported, except for an increased incidence of cleft palate in rabbits receiving high doses (data on file at Sanofi-Aventis, Paris, France). Because vigabatrin has been primarily used as add-on therapy in patients taking other AEDs with known teratogenic effects, it is very hard to determine the relationship of vigabatrin alone to any malformations that may appear. As with all AEDs, there is a class warning against the use of vigabatrin in pregnancy because of inadequate evidence regarding teratogenic effects. The same caution should therefore be taken as with the older AEDs. Published information about pregnancy and vigabatrin comprises 48 pregnancies. All patients were taking at least one other AED. Twenty-three continued to use vigabatrin throughout pregnancy, and the offspring were normal. Twelve patients used vigabatrin during the first trimester only and had normal offspring. Five spontaneous abortions occurred between 7 and 14 weeks, as well as four reports of major abnormalities: an absent diaphragm, a death because of intracerebral hemorrhage, a case of Siamese twins in which an abortion was carried out at 17 weeks, and a case of spina bifida. Four minor abnormalities were reported: one undescended testicle, one hip dysplasia, one hypospadia, and a possible club foot.[75] These 48 pregnancies may not represent a random sample of all the pregnant patients taking vigabatrin, because pregnancies resulting in adverse outcomes are more likely to be reported. Now, since vigabatrin use is restricted, very few pregnancies are reported with vigabatrin.

Drug Interactions

Vigabatrin does not appear to interact significantly with most other AEDs or other compounds. However, in two early placebo-controlled clinical trials to determine the efficacy and safety of vigabatrin in patients with partial epilepsy taking other AEDs simultaneously, phenytoin concentrations fell by about 20%.[10,90] Phenobarbitone and primidone were also significantly lower in the first study. The reason for this is not apparent, although several studies attempted to elucidate the nature of the reduction of phenytoin.[91] No changes have been found in protein binding or in the absorption, metabolism, or clearance of phenytoin.[89] No evidence suggests that any loss of efficacy occurs because of the lowered concentrations of phenytoin in occasional patients. Jedrzejczak et al.[49] reported an increase in serum carbamazepine levels of at least 10% in 70% of patients started on adjunctive therapy with vigabatrin. This observation contrasts with results of clinical trials, which did not detect any major changes in serum carbamazepine concentrations during vigabatrin treatment.

Role in EPILEPSY TREATMENT

Indications

Vigabatrin can be used as a first-line treatment for infantile spasms. It may also be used for patients with partial onset seizures who have been refractory to several other AEDs. Before starting treatment, the patient or his parents or guardians must be made aware of the risk of irreversible VFDs and about the need to monitor the visual fields at regular intervals to detect if any damage has occurred.

Dosing Recommendations

Optimal Maintenance Dosage

The most commonly used effective dose range in adults is between 2 and 4 g/day. This dose range was established from the results of several dose-titration studies[10,11,95] in which many patients experienced increasing benefit as doses were titrated upward. When, in a clinical trial, vigabatrin doses were reduced from 3 to 1.5 g/day in a blinded fashion, the majority of patients experienced deterioration in seizure control, although seizure frequency did not return to baseline.[99] Some evidence suggests that the optimal vigabatrin dose varies with the individual. Some patients may deteriorate when the dose is raised from 2 to 3 g, whereas others may improve.[70,76] In the large U.S. multicenter studies,[23,28] efficacy at 1, 3, and 6 g of vigabatrin was compared. Statistically significant seizure reduction could not be demonstrated with 1 g. Efficacy was equivalent and statistically significant with 3 and 6 g, but side effects increased substantially at the higher doses.

In infants with infantile spasms—the primary indication—optimal dosages range from 100 to 150 mg/kg daily. Due to the risk of retinal toxicity, the optimal regimen should be the minimal dose and the minimal duration necessary to obtain therapeutic benefit. Doses of at least 100 mg/kg per day have proved to produce the best response in most patients;[26] in fact, Asian patients constantly relapsed at doses under 60 mg/kg per day,[109] and there was a need to increase dose from 50 to 100 mg/kg per day in 59% of European patients.[1] How long to treat remains a major question, considering the risk of relapse of spasms and subsequent development of intractable seizures.[13] In Down syndrome, a short vigabatrin course proved sufficient.[17] In cryptogenic cases, 6 months seems to be reasonable. For tuberous sclerosis, the risk of a severe and intractable relapse seems to persist until the age of 5 years.

Dosing Interval

Dosing once or twice daily is recommended. Theoretically, the ability of vigabatrin to inhibit GABA-transaminase irreversibly should produce an effective CNS half-life of several days. Yet seizure control seems to deteriorate when vigabatrin is administered at intervals of greater than 24 hours.[9]

Dose Titration

Although there is no pharmacokinetic reason to titrate vigabatrin slowly, there is concern that rapid dose titration may

increase the likelihood of side effects, especially sedation, depression, confusion, and, rarely, psychosis. At present, the recommendation in adults is to initiate therapy with 0.5 to 1 g and titrate upward by similar amounts every 1 to 2 weeks depending on clinical urgency. In the treatment of infantile spasms, rapid titration to 100 mg/kg per day (in less than 5 days) proved to be well tolerated[4] and efficacy was obtained in less than 2 weeks,[19,26] two important advantages if one considers the rapid deterioration of psychomotor status associated with infantile spasms.

The tablet dissolves completely in water and is tasteless. Therefore, in infants and other patients who cannot swallow tablets, these (or the contents of the sachet) can be quickly dissolved in almost any fluid.

Withdrawal

Crossover efficacy studies, in which half of the patients were switched from active drug to placebo, provide information about the effect of abrupt withdrawal of vigabatrin. In four such studies,[18,59,90,108] possible withdrawal seizures were seen. Tassinari et al.[108] reported 4 of 16 patients with nearly continuous seizures after withdrawal. Therefore, vigabatrin treatment should not be interrupted abruptly.

Precautions and Contraindications

Careful consideration of the risk to benefit ratio is needed in view of the risk of VFDs, and monitoring of visual fields (or alternative electrophysiologic measures, as discussed earlier) is required before and during vigabatrin treatment.

Patients with a history of depression, psychosis, or behavioral disturbances may be at greater risk to develop psychiatric effects. If vigabatrin is considered necessary in these patients, slower dose titration and careful monitoring of response is required.

Elderly patients have been found to develop adverse CNS effects at lower dosages compared with younger adults. If vigabatrin is used in elderly persons, the initial doses should be lower and titrated more slowly. Similar precautions apply to patients with impaired renal function.

Vigabatrin may induce aggravation of seizures, particularly absence and myoclonic seizures in patients with generalized epilepsies.[60]

Summary and Conclusions

Vigabatrin is a selective, irreversible inhibitor of GABA-transaminase, the enzyme that degrades the inhibitory neurotransmitter GABA. It thereby increases GABA levels in the CNS in a dose-related manner. Vigabatrin is an amino acid that is not metabolized, nor is it protein-bound. It is excreted unchanged in the urine. Efficacy for refractory partial seizures and infantile spasms has been confirmed from a large number of clinical trials, but the discovery of irreversible toxicity on the retina has deeply modified the indications and limited the use of this very effective drug. Infantile spasms, a highly refractory and deleterious epileptic encephalopathy, is now the primary indication of vigabatrin, whereas its use in refractory partial epilepsy is limited to adjunctive therapy, when all other appropriate drug combinations have proved inadequate or have not been tolerated, and with mandatory visual field testing before the start of treatment and at regular intervals during treatment.

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Chapter 162

Zonisamide

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Introduction

After a long hiatus in the development of novel drugs for treating epilepsy, the early 1990s saw several new antiepileptic drugs (AEDs) developed and approved for use in patients with epilepsy. This progress in the treatment of epilepsy may have occurred because we understand more about the mechanisms of action of existing AEDs as well as the underlying pathophysiology of epileptic seizures. However, despite the advances made, a large number of patients with various types of seizures still remain refractory to treatment using existing AEDs.

One of the new drugs to join the global therapy list of AEDs during the 1990s is zonisamide (ZNS) (Fig. 1), a broad-spectrum AED that was developed in Japan by Dainippon Pharmaceutical Co. Ltd. Zonisamide was originally synthesized in 1972 by Uno et al.[58,59] as one of a series of 1,2-benzisoxazole derivatives. In the course of routine tests with these derivatives, some of the sulfonamide analogs, most notably ZNS, showed anticonvulsant activity in maximal electroshock (MES) experiments. In animal models, ZNS also demonstrated strong anticonvulsant activity and, based on its structure–activity relationship, was selected as a candidate for development.[55]

Structure and Chemistry

Zonisamide (1,2-benzisoxazole-3-methanesulfonamide) (Fig. 1) is chemically similar to indole. Zonisamide is synthesized from 1,2-benzisoxazole-3-acetic acid, which is prepared by the Posner reaction between 4-hydroxycoumarin and hydroxylamine.[58,59] The intermediate compound, 1,2-benzisoxazole-3-methanesulfonic acid sodium, was synthesized by a chlorosulfonic acid–dioxane complex method. The molecular formula of ZNS is $C_8H_8N_2O_3S$, its molecular weight is 212.23, and its melting point is 164°C to 168°C. Zonisamide consists of nonhygroscopic white to pale yellow crystals or crystalline powder, and it has a slightly bitter taste. It is freely soluble in acetone, sparingly soluble in methanol, and slightly soluble in 95% ethanol. Solubility in water depends on pH and increases sharply at a pH of 8. The infrared spectrum shows absorption bands indicating an amino group at 3,320 and 3,160 cm^{-1} and a sulfonyl group at 1,330 and 1,145 cm^{-1}. The nuclear magnetic resonance spectrum shows signals corresponding to methylene protons, amino protons, and aromatic protons.[59] The ultraviolet spectrum in a methanol solution shows absorption maxima at 239, 245, and 284 nm. The N-O bond of ZNS was cleaved by hydrogenation to give 1-(2-hydroxybenzoyl) methanesulfonamide and its imide, the former being identical to one of the metabolites. At present, plasma and urine concentrations of ZNS can be measured using high-performance liquid chromatography (HPLC),[20,35] gas chromatography,[35] and enzyme immunoassay[21] without disturbance of the other AEDs and their metabolites.

Basic Mechanisms of Action

ZNS was tested in many animal models to investigate its antiepileptic properties. When administered orally, ZNS protected mice, rats, rabbits, and dogs from induced maximal seizures.[30] The plasma concentrations that suppressed the tonic extensor components of MES were approximately 10 mg/L in all of the animals examined[30,31] and caused neurologic side effects at concentrations over 70 mg/L, demonstrating a wider therapeutic range than phenytoin (PHT) or carbamazepine (CBZ).[31] In contrast to the latter two drugs, the anti-MES effect of ZNS remained unchanged after repeated oral administration in rats, indicating no development of metabolic or pharmacodynamic tolerance to its anti-MES effect.[32] On the other hand, ZNS had no effect on minimal seizures induced by subcutaneous administration of pentylenetetrazol in mice.[30] In spontaneously epileptic rats, ZNS inhibited tonic seizures without affecting absence-like seizures.[38] These results suggest that ZNS, like PHT and CBZ, exerts anticonvulsant effects by inhibiting the spread of seizures and has a wider therapeutic plasma concentration range than the latter two drugs.

The antiepileptic action of ZNS was found to result from inhibition of seizure propagation in behavioral studies, and this was confirmed in electroencephalographic (EEG) studies on animal models of epilepsy.[18,60] Specifically, ZNS restricted the spread of focal seizures evoked by electrical stimulation of the visual cortex in cats and prevented the propagation of seizures from the cortex to subcortical structures evoked by cortical freezing in cats and by electrical stimulation in visual cortex–kindled cats. One paper reported that ZNS prevented spreading from the amygdala to the hippocampus and cortex of seizures induced by intra-amygdaloid application of kainic acid in rats.[54] Other EEG studies confirmed that ZNS has another mode of antiepileptic action, that is, suppression of the epileptogenic focus activity. ZNS, like sodium valproate (VPA), decreased the amplitude and frequency of spikes induced by cortical freezing in cats and abolished interictal spikes induced by cortical application of tungstic acid gel in rats, whereas PHT, CBZ, and phenobarbital did not,[13,18,19] suggesting that ZNS suppresses epileptogenic focus activity.

In kindled models, ZNS suppressed clinical convulsions and afterdischarges in cortex- and hippocampus-kindled rats[23] and amygdala-kindled rats[10] and cats.[22] Zonisamide also suppressed photically evoked myoclonus in lateral geniculate–kindled cats.[61] In addition to its effectiveness in kindled animal models, ZNS has demonstrated its antiepileptic effects in other animal models of epilepsy.[1,17]

The mechanism of action of ZNS has been clarified in several cell lines. One of the first reports showed that ZNS selectively increased the time constant for recovery from steady-state slow sodium (Na^+) inactivation in voltage-clamped *Myxicola* giant axon.[47] In another report by Rock et al.,[46] ZNS, like PHT, blocked the sustained repetitive firing of the intracellular action potential without affecting the initial firing of cultured mouse embryo spinal cord neurons, suggesting an

effect of ZNS on Na^+ current inactivation kinetics. Furthermore, Suzuki et al.[53] reported that ZNS dose-dependently reduced voltage-dependent transient inward currents (T-type calcium [Ca^{2+}] currents) in cultured neurons of the rat embryo cerebral cortex. This reduction by ZNS of T-type Ca^{2+} currents was confirmed in cultured human neuroblastoma cells.[25] These results suggest that ZNS suppresses neuronal hypersynchronization through the blockage of Na^+ and Ca^{2+} channels.

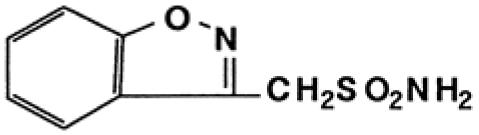

FIGURE 1. Chemical structure of zonisamide.

Pharmacologic Fundamentals

In animals and humans, ZNS was rapidly and virtually completely absorbed, evenly distributed in the whole tissues including the brain, and rather slowly eliminated. The metabolism of ZNS was extensive, and its excretion route was through urine.

Absorption and Routes of Administration

When [^{14}C]ZNS was administered orally in rats, dogs, and monkeys, radioactivity in plasma reached maximum levels within 3 hours.[35] In healthy volunteers administered single oral doses of 200, 400, and 800 mg ZNS, mean plasma concentrations reached peaks of 2.3 to 3, 5.2 to 5.5, and 12.5 mg/L, respectively, within 2 to 5 hours.[20,35] The linear pharmacokinetic properties of ZNS were observed in rats and in adult and pediatric patients. When ZNS was administered once a day for 2 days in volunteers, mean peak plasma concentration was 5.1 mg/L after 200 mg daily and 13 mg/L after 400 mg daily. Extrapolation of pharmacokinetic data obtained from single-dose administration indicates that plasma concentration of ZNS reaches steady state after 10 days of daily administration of a 200-mg dose.[20]

ZNS was markedly concentrated in erythrocytes, as are other sulfonamides. In healthy volunteers administered a 200-mg oral dose, the mean concentration of ZNS in erythrocytes was approximately four to nine times higher and maintained longer than in plasma.[20,35] However, uptake of ZNS by erythrocytes was both linear and saturated[20]—ZNS bound to erythrocytes rapidly at low concentrations, and therapeutic concentrations of ZNS in erythrocytes and whole blood exerted a nonlinear relationship with the dose administered.[41] Thus, it is recommended that the plasma or serum concentration of ZNS be measured for therapeutic monitoring. Erythrocytes contain a large amount of carbonic anhydrase. Thus, it is possible that ZNS, like acetazolamide, inhibits the enzyme. However, the inhibition by ZNS of human carbonic anhydrase II, an essential enzyme involved in the antiepileptic effect of acetazolamide, was 180 times less potent than that by acetazolamide.[29]

Distribution and Protein Binding

Distribution of [^{14}C]ZNS was rather uniform. The levels of radioactivity in most tissues, including brain, were similar to plasma levels, with slightly higher levels in the liver and kidney, and decreased in parallel with the plasma levels in rats.[34,35] In pregnant rats, levels of radioactivity in the fetus and placenta were similar to maternal plasma levels.[6] Tissue levels in sucklings were virtually the same as in young adult rats.[33] When [^{14}C]ZNS was administered intravenously, high uptake was observed in the rat cortex and midbrain.[37] In a single-oral-dose study in epileptic patients, the apparent volume of distribution decreased from 1.8 L/kg after a 200-mg dose to 1.2 L/kg after an 800-mg dose, reflecting the nonlinear binding characteristics of ZNS in erythrocytes.[20]

Protein binding of ZNS was 30% to >50% in rat plasma and serum[24,35] and >50% to 60% in human sera.[35,41] In human serum, approximately >50% of ZNS bound to protein in vitro at 21.3 mg/L; binding was not significantly affected by the presence of therapeutic levels of PHT, phenobarbital, and sulthiame.[35]

Metabolism

The metabolism of ZNS was rather extensive, measured by evaluating metabolites in animal urine.[36,52,66] Direct acetyl or glucuronyl conjugation occurred. Hydroxylation occurred and was followed by oxidation of the methylene carbon of the sulfamoylmethyl group, finally resulting in loss of the sulfamoyl group. N–O bond cleavage of the isoxazole ring produced two ring-cleft metabolites. Hydroxylation also occurred in the benzene ring. The latter three pathways were followed by conjugation with sulfuric acid or glucuronic acid. Analysis of urine samples in healthy volunteers revealed that ZNS was metabolized by acetylation, and cleavage of the isoxazole ring was followed by conjugation with glucuronic acid.[20,35] The P450 CYP3A species is the major isoenzyme involved in its metabolism to the primary metabolite.[39] Metabolites of ZNS, with the exception of acetyl-ZNS, were pharmacologically ineffective.

Elimination

Plasma elimination half-lives of orally administered ZNS were 8, 15, and 23 hours in rats, dogs, and monkeys, respectively,[35] and 50 to 68 hours in healthy volunteers administered single oral doses of 200 to 800 mg.[20] In healthy volunteers administered 200 mg and 400 mg, the excretion rates of ZNS and glucuronyl conjugate in urine were 29% to 48% and 12% to 19%.[35] The total combined excretion recovered in β-glucuronidase-treated urine was 48% to 60%, suggesting that urine is the major route of excretion in humans.[20] When [^{14}C]ZNS was administered orally to rats and dogs, radioactivity rates in urine were 87% and 97%, supporting the results obtained in humans. Within 48 hours after oral administration of [^{14}C]ZNS in biliary fistula–implanted rats, biliary excretion of radioactivity was 22%.[35]

Adverse Effects

Dose-Related Effects

The incidence rates of adverse events in U.S. and European placebo-controlled studies were 92% and 59% in the ZNS group and 58% and 28% in the placebo group (Table 1).[48,62] Adverse events in both the U.S. and European studies were somnolence, ataxia, anorexia, confusion, and abnormal thinking, and the incidence rate was significantly higher in the ZNS group than in the placebo group. Discontinuation rates because of adverse events in the U.S. studies were 14% in the ZNS group and 1% in the placebo group. In the European studies, the discontinuation rate because of adverse events was

3% in the ZNS group; there were no discontinued cases in the placebo group.

Table 1 Incidence rate of adverse events with zonisamide in multicenter clinical trials

		Incidence of adverse events	
Study (Ref.)	Number of patients	ZNS (%)	Control (%)
Placebo-controlled (U.S.) (56)	152 adults	92	58 (placebo)
Placebo-controlled (Europe) (42)	139 adults	59	28 (placebo)
Active-controlled (Japan) (51)	123 adults	52	57 (CBZ)
Open-labeled (U.S.) (26)	169 adults	81	
Open-labeled (Japan) (45)	538 adults	58	

Open-labeled (Japan) (45)	257 children	44

The incidence rate of adverse events in the active-control study on ZNS and CBZ in Japan was 52% in the ZNS group and 57% in the CBZ group (Table 1),[51] with no statistical significance between the two groups. The incidence rates of somnolence, slowing of mental activity, decreased spontaneity, and skin rash or itching were almost the same in the two groups, whereas anorexia was observed more frequently in the ZNS group (12% vs. 0%, $p = 0.02$), and ataxia was observed more frequently in the CBZ group (35% vs. 9%, $p < 0.01$). The rates of discontinuation for adverse events were 12% in the ZNS group and 16% in the CBZ group. The overall safety ratings of ZNS and CBZ evaluated according to adverse events and laboratory test deviations were 83% and 66% (cumulative of "safe" and "almost safe"), suggesting that ZNS is safer than CBZ ($p = 0.08$).

The incidence rate of adverse events in the open-labeled, multicenter studies in the United States was 81% (Table 1),[26] and the withdrawal rate because of adverse events was 13%. On the other hand, the incidence rates in Japanese studies were 58% in adults and 44% in children.[45] Of 1,008 patients in Phase II and Phase III open trials in Japan, the overall incidence rate of adverse events was 51%, and the dropout rate for adverse events was 18%.[49] The most frequent adverse events in these patients in order of frequency were drowsiness (24%), ataxia (13%), loss of appetite (11%), gastrointestinal symptoms (7%), loss of or decrease in spontaneity (6%), and slowing of mental activity (5%). In 55 patients on ZNS monotherapy, drowsiness (9%), loss of appetite (7%), gastrointestinal symptoms (7%), loss of or decrease in spontaneity (6%), headache (6%), skin rash or itching (6%), and loss of weight (6%) were observed.

In postmarketing surveillance in Japan, anhidrosis accompanied by increased body temperature was reported in pediatric patients in the summertime, especially during extremely hot periods.[7,14] In the United States, a postmarketing study has reported an estimated incidence of one case per 5,490 patient-years, with most cases occurring in children.[28]

In two U.S. studies and one European study, 13 (11 in the United States and two in Europe) of 505 patients developed nephrolithiasis. Ten of these 13 patients had positive histories of renal calculi, urinary tract surgery, and similar disorders.[50] On the other hand, only two cases out of 1,008 patients in Japanese Phase II and III open studies developed kidney stones; both patients had family histories of renal calculi, and the stones passed spontaneously. Furthermore, in postmarketing surveys conducted over 6 years following launch in Japan, only three cases with renal calculi were reported out of 5,418 patients surveyed. In six cases out of the 13 patients mentioned above[50] in whom ZNS administration was ongoing or temporarily discontinued, 24-hour urine collections were obtained; these revealed a decrease in urine citrate concentration, which can be an inhibitory factor for the formation of calcium stones, and a marginal increase in urine pH.[67] Similarly, the 24-hour urine collections of ten epileptic patients in Japan taken 1 month before and after the start of ZNS administration showed no change in urinary calcium levels, and only a decrease in urinary citrate concentration was observed.[50] In short, although differences were observed in the number of incidences of renal stones in the United States and Europe versus Japan, decreases in urinary citrate concentration were consistent, as was the composition of the stones (calcium oxalate, calcium phosphate).[5]

The only adverse event differing significantly from placebo was weight loss, although somnolence, anorexia, and ataxia were slightly more common with zonisamide treatment.[3] The odds ratio (OR) for treatment withdrawal was 1.74 (95%; confidence interval [CI], 1.03 to 2.95). Side effects found to be significant with OR ratios associated with zonisamide were ataxia 3.94 (1.23 to 12.57); somnolence 2.11 (1.11 to 3.98); agitation 3.52 (1.26 to 9.68); agitation and irritability 2.43 (1.04 to 5.66); and anorexia 2.98 (1.38 to 6.42).

Not all side effects are negative. Weight loss has been observed in studies of zonisamide.[5] To more fully evaluate the efficacy of zonisamide for weight loss in obese adults, a 16-week randomized, double-blind, placebo-controlled trial was conducted. Fifty-five (92%) women and five (8%) men (mean [SE] body mass index, 36.3 [0.5]; mean age, 37.0 [1.0] years) were randomly assigned to receive zonisamide or placebo. Zonisamide therapy was started at 100 mg/d orally, with gradual increase to 400 mg/d and further increase to 600 mg/d for some patients. The zonisamide group lost more body weight than the placebo group (mean [SE], 5.9 [0.8] kg [6.0% loss] vs. 0.9 [0.4] kg [1.0% loss]; $t = 5.5$; $P < .001$) during the 16-week period.[8]

Idiosyncratic

Hypersensitivity reactions such as eruptions were observed in 6% of cases in Japanese clinical trials.[49] Postmarketing studies in Japan reported the following adverse events: Stevens-Johnson syndrome, Lyell syndrome, agranulocytosis, and acute renal failure.[16]

Teratogenicity

In monkeys, spontaneous abortion was observed at the maximal human daily dose (10 mg/kg), and in mice, rats, and dogs, teratogenic effects were observed at 50, 20, and 3 times the human maximal daily dose.[56,57]

To date, the following events have also been reported: imminent abortion in one patient treated concurrently with phenobarbital (PB), abortion (abnormal development of cranium and abnormal cerebral and cerebellar growth) in one patient treated concurrently with PHT, and atrial septal defect in one patient treated concurrently with PHT and VPA.[16] Therefore, treatment is recommended for women who are pregnant or suspected to be pregnant only if the therapeutic benefits outweigh the potential risks.

Drug Interactions

Protein binding of ZNS is unaffected by PHT, PB, or CBZ, and the converse is also true. Zonisamide did not affect the extent of protein binding of VPA or PHT in patients.[50] The elimination half-life of ZNS is decreased to 36 hours with CBZ and to 27 hours with PHT.[43] The mean ratio of plasma levels to daily dose (L/D ratio) was 3.8 in 65 epileptic patients with monotherapy and slightly lower at 3.0 in 781 patients with at least one concomitant AED.[15] A significant decrease in ZNS plasma concentration was observed in concurrent therapy with CBZ or VPA.[64] One exceptional case of PHT toxicity caused by add-on therapy with ZNS was reported.[40] Therefore, concurrent treatment with PHT, CBZ, and VPA may decrease plasma concentration of ZNS, just as reduced or discontinued dosage of these concomitant AEDs may cause blood levels of ZNS to be elevated.

Clinical Indications

Indications

The efficacy of ZNS was evaluated in two placebo-controlled double-blind studies in the United States and Europe.[48,62] In these studies, 152 American and 139 European adult patients with complex partial seizures refractory to other conventional AEDs were enrolled and placed on add-on therapy for 12 weeks with ZNS or placebo while being treated with other AEDs. The results of these two studies were very similar. The median percentage change in seizure frequency in the ZNS group was a decrease of 28% to 30% in both U.S. and European studies, which was significantly different from the placebo group in both studies ($p < 0.01$). Furthermore, the percentage of patients with >50% or more reduction in seizure frequency in the ZNS group was 29% to 30% in the U.S. and European studies and again significantly different from the placebo group in both studies ($p < 0.05$). The percentage of patients in the ZNS group who were judged “improved” by physicians was 62% in the two studies (placebo versus ZNS, $p < 0.01$).

In addition, two randomized controlled studies were performed in Japan to evaluate and compare the efficacy of ZNS using CBZ and VPA as active control drugs.[42,51] In the study using CBZ, 123 adult patients with complex partial seizures refractory to up to three other conventional AEDs were enrolled and randomly treated with ZNS or CBZ for 16 weeks. Although the safety rating in the ZNS group was superior to that in the CBZ group, there was no statistical significance to the efficacy of either drug. The average seizure frequency, expressed as number of simple or complex partial seizures every 4 weeks, decreased from 13 to four in the CBZ group and from 15 to three in the ZNS group, and that of secondarily generalized tonic–clonic seizures decreased from two to 0.7 and from two to 0.6. The percentages of patients with >50% or more reduction in seizure frequency were 71% in the CBZ group and 82% in the ZNS group, and the overall improvement rates were 65%

and 66% in those groups.

In the study using VPA, 32 pediatric patients (>15 years old) with convulsive or nonconvulsive generalized seizures (more than four seizures/month), who were refractory to up to three other conventional AEDs, were enrolled and treated with either VPA or ZNS for 8 weeks. The median percentage changes in seizure frequency of generalized tonic–clonic seizures were decreases of 67% and 81% from baseline, the percentages of patients with >50% seizure reduction were 53% and 77%, and the overall improvement rate was 44% and >50% in the VPA and ZNS groups.

In Phase II and III open studies in Japan, a total of 55 patients (23 children and 32 adults) were treated with ZNS monotherapy.[63] The percentage of patients with >50% reduction in seizure frequency was 75% (41 patients) for partial seizures and 25% (14 patients) for generalized seizures.

A search of the Cochrane Epilepsy Group trial register reviewed three trials (499 participants). The overall OR (95%; CI) for >50% or more reduction in seizure frequency compared to placebo was 2.72 (95%; CI, 1.74 to 4.25) for the full treatment period of 12 weeks including varied rates of titration to 400 mg/day.[3] The OR for treatment withdrawal was 1.74 (95%; CI, 1.03 to 2.95). Side effects found to be significant with OR ratios associated with zonisamide were: ataxia 3.94 (1.23 to 12.57); somnolence 2.11 (1.11 to 3.98); agitation 3.52 (1.26 to 9.68); agitation and irritability 2.43 (1.04 to 5.66); and anorexia 2.98 (1.38 to 6.42).

Since the Cochrane report, two other major studies have been published. A randomized, double-blind, placebo-controlled trial enrolling 203 patients conducted at 20 U.S. sites to assess ZNS efficacy found 400 mg/day ZNS reduced the median frequency of all seizures by 40.5% from baseline, compared with a 9% reduction ($p = 0.0009$) with placebo treatment. A >50% or greater seizure reduction was observed in 42% of patients. A dosage of 100 mg/day produced a 20.5% reduction in median seizure frequency ($p = 0.038$ compared with placebo), and a dosage of 200 mg/day produced a 24.7% reduction in median seizure frequency ($p = 0.004$ compared with placebo), indicating a dose-response relationship.[5] The only adverse event differing significantly from placebo was weight loss, although somnolence, anorexia, and ataxia were slightly more common with ZNS treatment.

A study specifically designed to identify a dose-response relationship was conducted as a double-blind, placebo-controlled study of adjunctive ZNS in 351 patients with refractory partial seizures receiving a stable regimen of one to three AEDs. Patients were randomized to placebo or ZNS, 100 mg, 300 mg, or 500 mg/day (2:1:1:2) after a 12-week baseline. Dose titration was undertaken over a 6-week titration phase, which was followed by an 18-week fixed-dose assessment phase. Compared with placebo, a dose of ZNS 500 mg/day resulted in a significantly greater decrease in CP seizure frequency from baseline (51.2% vs. 16.3%; $p < 0.0001$) and a significantly higher proportion of CP responders (52.3% vs. 21.3%; $p < 0.001$). Both ZNS 500 mg/day and 300 mg/day were statistically superior to placebo. For all seizures, a significant dose-response relation was observed ($p < 0.0001$).[2]

Twenty-five previously untreated patients with cryptogenic localization-related epilepsy were treated with ZNS at 8 mg/kg per day once daily for more than 12 months in an open-labeled long-term study, in which 68% of patients showed complete seizure control. In three patients who experienced seizure recurrence, trough plasma ZNS levels were 15 μg/mL, and in three patients who complained of continuous drowsiness and whose peak levels were 40 μg/mL, dosage was reduced.[6]

In a ZNS open monotherapy (2–10 mg/kg/day) study in which 32 patients with partial epilepsy (21 cryptogenic and 11 symptomatic) and 15 patients with generalized epilepsy (11 idiopathic, one cryptogenic, and three symptomatic) were enrolled, seizures in 66% of these patients disappeared, and the percentage of patients with >50% or more reduction in seizure frequency was 17%.[11]

In another ZNS open monotherapy (6 mg/kg per day) study in which 65 pediatric patients with partial and generalized seizures refractory to other AEDs were enrolled, the percentage of patients with >50% reduction in seizure frequency was 91% in both cryptogenic and symptomatic localization-related and generalized epilepsies (localization-related, 42 patients; generalized, 11), suggesting that ZNS monotherapy is just as effective on partial seizures as on generalized seizures.[64]

Seizure frequency was remarkably reduced by ZNS in two patients with the Unverricht-Lundborg (Baltic) type of progressive myoclonus epilepsy, and the seizures were well controlled.[12] Seizures in a patient with progressive myoclonus epilepsy ragged-red fibers (MERRF) disappeared with ZNS monotherapy (200 mg/day), and seizure frequencies in two patients with progressive myoclonus epilepsy in infancy were remarkably reduced.[63]

In four patients with severe myoclonic epilepsy in infancy (Dravet type) and ten patients with Lennox-Gastaut syndrome, add-on therapy with ZNS reduced seizure frequency by >50%, and seizures disappeared in three of the ten patients with Lennox-Gastaut syndrome.[65]

Recently, there have been remarkable cases of improvement in patients on ZNS monotherapy or add-on therapy. Seizures were significantly reduced or disappeared in five patients with infantile spasms (West syndrome), four patients with Lennox-Gastaut syndrome, and 14 patients with other symptomatic generalized epilepsies. Atypical absence seizures disappeared in a patient with Landau-Kleffner syndrome with ZNS add-on therapy.[64]

In Japan and South Korea, ZNS monotherapy or add-on therapy is approved in adults and children with the following types of seizures:

- Partial seizures: simple partial seizures, complex partial seizures, and partial seizures evolving into secondarily generalized tonic–clonic seizures.
- Generalized seizures: tonic–clonic seizures, tonic seizures, and atypical absence seizures.
- Mixed seizures: compound/combination of the above seizures.

Contraindications

ZNS is contraindicated in patients who are known to be hypersensitive to sulfonamides or ZNS.

How to Use the Drug

Dosage Formulations and Strengths

In Japan, ZNS is available in tablet and powder form. One tablet contains 100 mg ZNS, and 1 g of ZNS powder contains 200 mg of ZNS (20%). In the United States and Europe, ZNS is available in 25-, 50-, and 100-mg two-piece hard gelatin capsules.

Starting Doses

In adults, the recommended initial dose is 100 to 200 mg daily, in one or two divided doses.

In children older than 1 year, ZNS is administered at the initial daily dose of 2 to 4 mg/kg in one, two, or three divided doses. Dosage and safety have not been established in infants younger than 1 year of age.

Although 328 elderly patients over 65 years of age were observed in postmarketing surveys in Japan,[16] no systematic studies have been performed in elderly patients. In general, treatment should be started in these patients at the lowest dose of the therapeutic dose range. Reduced hepatic, renal, and cardiac functions as well as concurrent drugs should be taken into consideration in selecting the initial dose.

Maintenance Doses, Dosing Frequency, and Maximum Dose

Because the elimination half-life is as long as 60 hours, and 7 to 10 days is required to reach a steady-state plasma concentration, doses should be titrated gradually at 1- to 2-week intervals while efficacy and tolerability are carefully monitored. Abrupt dose increases may cause psychological symptoms and gastrointestinal symptoms such as anorexia.

Maintenance doses of ZNS in adults and children are 200 to 400 mg/day and 4 to 8 mg/kg per day, respectively.

The small difference between peak and trough of plasma concentration during treatment makes once-daily administration of ZNS possible.

The maximum dose is 600 mg/day for adult patients and 12 mg/kg per day for pediatric patients.

Monitoring of blood levels of ZNS should be performed to control administration of the appropriate dosage. Therapeutic ranges of blood levels have been reported to be 20 to 30 mg/L or 10 to 50 mg/L; however, there are no established data.[64] Further studies are required to determine the optimal range of blood levels for ZNS.

Add-on therapy with other AEDs such as PHT, CBZ, and VPA, and reducing or discontinuing the dosage of concomitant AEDs, may cause blood levels of ZNS to become reduced or elevated, respectively. Careful monitoring of blood levels of ZNS in these patients is recommended.

Discontinuing the Drug

ZNS therapy should be discontinued immediately if clinical seizures are aggravated. Because Stevens-Johnson syndrome, Lyell syndrome, agranulocytosis, and acute renal failure may occur during ZNS treatment, administration should be discontinued if signs indicating these syndromes develop. Administration should also be discontinued if hypersensitivity reactions such as eruption or overt psychiatric disorders occur.

To minimize the possibility of increased seizure frequency, an abrupt discontinuation of dosage should be avoided. Dosage should be tapered off gradually and with caution.

Summary and Conclusions

ZNS has a broad antiepileptic spectrum and is effective against partial seizures (simple or complex partial seizures and secondarily generalized tonic–clonic seizures), generalized seizures (tonic–clonic, tonic, and atypical absence seizures), and compound and combination seizures in adults and children on monotherapy and add-on therapy. However, its efficacy against typical absence seizures and massive myoclonic seizures is still unclear. Against some types of progressive myoclonus epilepsies, ZNS has shown efficacy, but against juvenile myoclonic epilepsy, the effect of ZNS is unclear and further studies are needed.

Randomized controlled studies were conducted comparing ZNS with CBZ and valproate in Japan and with placebo in the United States, and results for ZNS were promising. However, to assess the benefits of ZNS thoroughly in relation to other AEDs, further randomized controlled studies comparing ZNS with PHT are necessary.

Adverse reactions related with ZNS are mainly drowsiness, loss of appetite, gastrointestinal symptoms, decreased

spontaneity, and loss of weight. Serious adverse events that may be life-threatening have not been reported.

Incidence rates of renal stone during ZNS treatment were 2.6% (13 of 505 cases) in U.S. and European studies and 0.2% (two of 1,008) and 0.1% (three of 5,418) in clinical trials in Japan and the 6-year postmarketing surveillance, respectively. Analysis of the renal stones revealed the same calcium oxalate and calcium phosphate composition in the United States, Europe, and Japan, as well as decreased concentrations of citrates, or inhibitory factors of calcium stone generation, in the urine of these patients. The difference in incidence rate of renal stones in the United States, Europe, and Japan may therefore be explained by the interaction of the decreased levels of the inhibitory factor with patient lifestyle and/or genetic factors.[4,9] Although a long-term study on the incidence of renal stones during ZNS treatment is needed, it is also worth investigating if oral administration of citrates to epileptic patients with decreased citrate concentrations in urine and a medical history of calcium renal stones could help prevent generation of renal stones.

The initial human experience with ZNS began with clinical trials almost 25 years ago. It was approved for use in Japan over 15 years ago, and in the United States more than 5 years ago. It has been recently approved in Europe. Clinical studies and postmarketing experience has shown it to be a useful addition to the list of drugs used for the treatment of epilepsy.[27]

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Chapter 163

Trimethadione, Paraldehyde, Phenacemide, Bromides, Sulthiame, Acetazolamide, and Methsuximide

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Introduction

Trimethadione, paraldehyde, phenacemide, bromides, sulthiame, acetazolamide, and methsuximide are antiepileptic drugs (AEDs) that are rarely used today, because for most patients they are generally less effective or more toxic than alternative drugs. Each of these, however, may still occasionally be useful in carefully selected patients or special situations. Only paraldehyde and acetazolamide are available in the United States.

Trimethadione

Trimethadione is not marketed in the United States.

Structure and Chemistry

Trimethadione (3,5,5-trimethyl-2,4-oxazolidinedione; Tridione; TMO) is an oxazolidine-dione with a ring structure similar to that of other classes of antiepileptic drugs (Fig. 1). Several other oxazolidinediones also possess antiepileptic properties. Dimethadione (DMO) is of interest because it is the major, and perhaps the only, metabolite of TMO. Both TMO and DMO are white crystalline powders with molecular weights of 143.15 and 129.12, respectively. Trimethadione is readily soluble in aqueous and organic solvents.

Basic Mechanism of Action

A number of pharmacologic agents, including pentylenetetrazol, γ-hydroxybutyrate, and penicillin, induce seizures in rodents with clinical and EEG manifestations that are very similar to those of human absence seizures.[203] Such models are reproducible and easy to standardize, and they are useful in predicting the antiabsence activity of a drug in humans. Ethosuximide and DMO block the seizure manifestations of this group of agents.

T-type calcium channels (TCCs) are present in high densities in thalamic neurons and contribute importantly to the regenerative bursts that drive normal and pathologic thalamocortical rhythms.[45,46,47,48] Ethosuximide and DMO at therapeutic concentrations reduce TCCs when applied to thalamic neurons, whereas phenytoin and carbamazepine do not.[45,48] Reduction of TCCs is probably the mechanism of antiabsence activity for DMO.[15,45,175] Dimethadione may decrease the number of available TCCs or reduce individual TCC calcium conductance.[45]

Pharmacologic Fundamentals

Absorption and Routes of Administration

Trimethadione is rapidly absorbed by the oral route. Peak plasma TMO concentrations occur 30 to 60 minutes after oral administration.[246]

Distribution and Protein Binding

Neither TMO nor DMO binds to plasma proteins.[24,246] Trimethadione is distributed to the total body water in humans[24,246] and, in animals, has highest concentrations in brain, kidney, muscle, and liver.[247] Animal work indicates that DMO is rapidly distributed to, but not bound by, the various body tissues and has a volume of distribution somewhere between extracellular water and total body water volume.[247]

Metabolism, Including Active Metabolites, and Excretion

Trimethadione is quantitatively demethylated to DMO by he-patic cytochrome P450 enzymes (probably isoforms CYP3A4, CYP2C9, and CYP2E1).[34,76,166,216,249] Dimethadione is the only important metabolic product of TMO[247] and does not undergo further metabolic change. Of an administered dose of TMO, 96% to 99% is excreted in the urine as DMO (trimethadione and DMO have approximately equal antiepileptic properties).[24,75,245] Because TMO is rapidly metabolized to DMO, which is slowly excreted by the kidneys, DMO is the major antiepileptic drug present in the plasma of patients on chronic oral TMO therapy. The ratio of TMO to DMO in the plasma during chronic oral TMO therapy is approximately 1:20.[24,25]

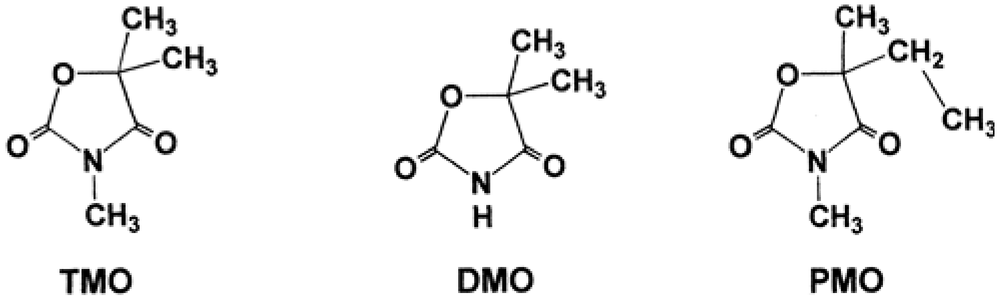


FIGURE 1. Structural formulas of trimethadione (TMO), dimethadione (DMO), and paramethadione (PMO).

Clinical Pharmacokinetics

The elimination half-life of TMO is approximately 12 to 16 hours in the young and 24 hours in the elderly.[24,25,76,215] The resulting DMO is excreted very slowly, with an elimination half-life of approximately 10 days or more.[25,35,76,115] The very slow elimination of DMO has three clinical consequences. First, the time for buildup to a steady-state DMO level is 30 days or more, and therefore, it takes many days before the full therapeutic (and toxic) effects of a given dose of TMO are realized.[38,89,246] Second, cessation of TMO therapy does not result in an immediate drop in DMO plasma concentration or in an immediate increase in seizure frequency.[89] Third, DMO

plasma concentrations vary very little during the day, whereas plasma concentrations of TMO (which is more rapidly cleared) vary by 30% between peak and trough values on a three- or four-dose daily regimen.[25]

Several studies have indicated that 700 μg/mL is the lower limit of the therapeutic range for plasma DMO level.[23,25,38,115] The majority of patients with absence seizures who have DMO levels above 700 μg/mL have good control of seizures, whereas most patients with DMO levels below 700 μg/mL do not.[25]

Adverse Effects

Dose-related Effects

Hemeralopia (day blindness) is a phenomenon in which visual acuity is normal in low illumination but decreases when illumination is normal or brighter than normal. This is thought to be a retinal phenomenon in which the neuronal elements of cones (but not photochemical elements) are affected.[202] There are no external or ophthalmoscopic changes.[134] Detailed study reveals that TMO greatly prolongs the time of visual acuity adaptation when illumination changes from low to high or from high to low.[202] In most patients, visual acuity becomes normal after adaptation is complete.[202] Hemeralopia occurs in 30% of patients taking TMO[133,236] and disappears 1 to 10 weeks after TMO is discontinued.[78,133]

Drowsiness occurs in 3% to 6% of patients on TMO[133,236] but often subsides as tolerance to the drug develops.[78] Behavioral disturbances occur in 4% to 8% of patients on TMO.[133,236] Other central nervous system (CNS) side effects may include malaise, insomnia, vertigo, headache, paresthesias, and hiccups.[25,78,133,236] Increased frequency of tonic–clonic seizures has been reported by some workers[82] and denied by others.[54,177] Nausea, vomiting, abdominal pain, or gastric distress occurs in 7% to 8% of patients on TMO.[133,236]

Idiosyncratic Effects

Hematologic side effects are the most frequent and troublesome serious side effects of TMO.[78,236] Three classes of adverse hematologic responses to TMO have been identified: Modified normal response, controlled neutropenia, and pancytopenia.[78] More than 3,000 neutrophils per cubic millimeter constitutes a modified normal response, whereas less than this number is called a controlled neutropenia. The incidence of controlled neutropenia in association with TMO therapy is about 20%.[51,236] Unfortunately, the peripheral blood count is not an accurate reflection of changes in the bone marrow, and agranulocytosis may be established in the bone marrow well before the peripheral count is altered.[57] There have been at least 19 reported cases of pancytopenia in association with TMO therapy, and 13 ended fatally.[236] The earliest change in the peripheral blood is a decrease in megakaryocytes, followed by a reduction in the number of platelets; this in turn is followed by a prolonged clot retraction time.[57] Frequent examination of peripheral blood, including megakaryocytes and platelets, and measurements of clot retraction time are essential in patients taking TMO.

A possible relationship between TMO and lymphadenopathy or tumors of blood-forming organs has been discussed by Gallagher.[78] Firm proof of such a relationship has not been established.[78]

Dermatologic side effects include rash, erythema multiforme, and exfoliative dermatitis (including one fatal case)[79,236] and occur in 9% to 14% of patients taking TMO.[133,236] These disorders usually occur early in the course of TMO therapy and may be more frequent in children under the age of 10 years.[133] The more severe dermatologic reactions are rare and are generally nonfatal.[78]

At least nine cases of nephrotic syndrome (albuminuria, decreased plasma albumin, hypercholesterolemia) in association with TMO therapy have been reported.[78,236] Two of these cases ended fatally.[236]

Myasthenic syndrome, hepatitis, lupus erythematosus, hiccups, anorexia, hair loss, changes in blood pressure, photophobia, and diplopia have been reported to accompany TMO therapy.[26,61,78,119,173]

Teratogenicity

There are numerous reports of fetal malformations in association with TMO therapy.[26,86,164,216] A large collaborative study reported malformations in 18 of 61 children born to mothers who had taken TMO during the first trimester.[165] In some children, a characteristic set of findings has been termed the “fetal trimethadione syndrome.”[26,86] Malformed or low-set ears, cleft lip and palate, delayed mental development, speech impairment, urogenital malformations, V-shaped eyebrows, irregular teeth, skeletal malformations, and cardiac defects are the common features.[26,86] Less common features of the fetal trimethadione syndrome include intrauterine growth retardation, short stature, microcephaly, ocular anomalies, and simian creases.[86] In addition, the spontaneous abortion rate is high.[26] The mechanism of TMO teratogenicity may be oxidative macromolecular damage.[237] Although the mother was taking other drugs in most of these cases, the evidence suggesting TMO teratogenesis is so strong that TMO should be given during pregnancy only if the potential benefits are great enough to outweigh the considerable potential risks.

Drug Interactions

Although TMO and DMO have been in clinical use for many years, reports of interactions with other drugs are scarce.[248] The following animal data may have some clinical relevance: (a) TMO and methobarbital interfere with demethylation of each other by liver microsomes; (b) DMO inhibits demethylation of TMO and methobarbital; (c) drugs causing a distortion of acid–base balance (e.g., NH_4Cl, acetazolamide, and $NaHCO_3$) can affect the distribution and excretion of DMO (a weak acid); and (d) TMO does not induce liver enzymes.

The Role of the Drug

Trimethadione is no longer manufactured in the United States. Chewable tablets (150 mg) are manufactured in Europe (Slovakofarma AS).

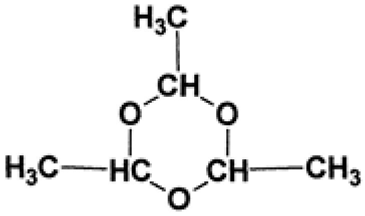


FIGURE 2. Structural formula of paraldhyde.

Trimethadione has been used to treat absence seizures that are refractory to less toxic drugs (i.e., ethosuximide, valproic acid, clonazepam, acetazolamide, and lamotrigine). Millichap and Aymat[159] reviewed 431 reported cases of absence seizures treated with TMO. Absence seizures were reduced in frequency by 75% or more in 56% of cases and were completely controlled in 18% of cases. Coatsworth's review[44] showed similar results. The drug thus possesses considerable antiabsence activity. A trial of TMO may be indicated when absence seizures are not controlled with less toxic drugs and when the potential benefits of TMO outweigh the potential risks (see above). Trimethadione is also sometimes effective for treating the refractory atypical absence, myoclonic, and atonic seizures of the Lennox-Gastaut syndrome.[52,56,134] TMO is also used as a cytochrome P450 2E1 probe for hepatic disease.[166,217]

How to Use the Drug

The usual starting daily dose is 0.9 g in adults and 0.3 g in children in three or four divided doses. Because of the long elimination half-life of DMO, adequate plasma concentrations should be maintained with doses given once daily, although such a regimen has not been systematically studied to determine the plasma concentrations and side effects of once-daily administration. The dosage of TMO may be increased at weekly intervals by 150 mg/day in children and 300 mg/day in adults. Maintenance dosage should be the smallest amount of drug required to maintain adequate seizure control. An oral solution form is available for children.

Paraldehyde

Structure and Chemistry

Paraldehyde (2,4,5-trimethyl-1,3,5-trioxane; PARALDEHYDE) is a cyclic polymer of acetaldehyde (Fig. 2). It is a colorless liquid with a strong aromatic odor and a burning, disagreeable taste. It is miscible with oils and has a molecular weight of 132.16.

Basic Mechanism of Action

The mechanism of action of paraldehyde is unknown.

Pharmacologic Fundamentals

Absorption and Routes of Administration

The times to peak plasma concentration of paraldehyde by various routes are as follows: IV route, immediately after infusion[79]; IM route, 20 to 60 minutes[1]; oral route (in water), 30 minutes[3]; oral route (in oil), 2 to 4 hours[79]; rectal route (in oil), 2 to 4 hours.[8,79] Clinical effects are usually evident long before maximum plasma concentration.[8,79,193,224]

Distribution

Paraldehyde is rapidly distributed to the brain. Following an IV injection, drowsiness ensues within 2 to 5 seconds, and anesthesia occurs within <2 minutes.[8,79,193] The steady-state volume of distribution of paraldehyde is 890 mL/kg.[8] Paraldehyde readily crosses the placental barrier and may cause delayed respirations in neonates.[79]

Metabolism and Excretion

Seventy to eighty percent of paraldehyde is metabolized by the liver, 20% to 30% is exhaled by the lungs, and a very small amount is excreted unchanged by the kidney.[14] In patients with liver disease, the rate of elimination of paraldehyde and the percentage of paraldehyde eliminated by the liver decrease, and the percentage of paraldehyde eliminated by the lungs increases.

Paraldehyde is depolymerized to acetaldehyde by the liver, and acetaldehyde is then oxidized to acetic acid, which is ultimately metabolized to carbon dioxide and water. Formation of acetaldehyde from paraldehyde has been demonstrated using mouse liver cytochrome P450 enzymes.[258,259]

Elimination Half-Life

The elimination half-life of paraldehyde in adults and children is 3.4 to 9.8 (mean 6.1 to 7.4) hours.[6,224] In two studies performed in neonates, the elimination half-life of paraldehyde was 10.2 ± 1.0 and 18.1 ± 5.5 hours.[79,83,90] The plasma disposition kinetics of paraldehyde fit an open two-compartment model after intravenous injection.[8] The elimination half-life of paraldehyde is prolonged in patients who have received phenobarbital before paraldehyde.[79]

Adverse Effects

Since paraldehyde was introduced in 1882, there have been at least 95 reports of death associated with its use.[14,103] These reports have led to widespread disrepute and infrequent use of paraldehyde. However, many (probably most) of these deaths were from one of the following factors: (a) suicidal overdosage, (b) use of decomposed drug, (c) use of doses larger than those currently recommended, and (d) use of improperly diluted paraldehyde. The incidence of death and serious side effects with U.S. Pharmacopeia (USP)-quality paraldehyde at recommended doses and following recommended administration procedures is unknown but probably is less than is generally supposed.

Overdosage

Overdosage with paraldehyde produces coma, right heart failure, and pulmonary edema and hemorrhages.[34,53]

Side Effects

By Any Route

Paraldehyde administered by any route may cause disagreeable breath odor (from exhaled paraldehyde), right heart failure, pulmonary edema and hemorrhage (especially if the drug is used in excessive dosage), rash, irritability, toxic hepatitis, or toxic nephritis.[14,34,201] Chronic use of paraldehyde may produce a metabolic acidosis.[103] Chronic paraldehyde use may

produce tolerance or physical dependence with a withdrawal syndrome similar to that seen with alcohol withdrawal.[107]

Intravenous Route

Three series[18,79,193] (totaling 181 patients) in which IV paraldehyde was used as an anesthetic agent report no serious complications, although many patients experienced coughing, choking, pharyngeal irritation, tachycardia, or pain at the site of infusion. On the other hand, there are case reports of IV paraldehyde suddenly producing apnea, coughing, cyanosis, hypotension, and clinical and radiographic signs of pulmonary edema.[201] All the above studies involved injection of undiluted or 10% solution of paraldehyde and thus failed to properly dilute paraldehyde so that it would remain soluble after IV injection (see below). Gessner[82] postulates that the above-cited pulmonary–cardiac complications were the result of pulmonary embolism of precipitated droplets of pure paraldehyde in the bloodstream as a result of improper dilution and cites two studies[8] in which properly diluted paraldehyde (4% to 8% solution) was administered IV without complications. Note that intra-arterial injection of paraldehyde may cause vascular injury[96,234] and that direct injection of undiluted paraldehyde into an umbilical artery catheter may cause vascular injury and injury to tissues by microembolization.[90,97]

Oral and Rectal Routes

Paraldehyde can cause irritation and corrosion of the mouth and stomach when given orally and of the rectum and large intestine when given rectally.[1] Rectal administration of decomposed paraldehyde has resulted in perforation of the large intestine.[1] The drug should be diluted properly before administration by these routes (see below).

Intramuscular Route

Permanent, severe sciatic nerve damage may result if paraldehyde is injected too close to the nerve.[70,103] Skin sloughing and sterile abscesses have also been caused by IM paraldehyde.[103]

Decomposed Paraldehyde

Decomposed paraldehyde may contain very high concentrations of acetic acid. Acetic acid is a highly toxic substance, and paraldehyde containing acetic acid appears to be considerably more toxic than USP-quality paraldehyde.[1,5,103]

Role of the Drug

Status Epilepticus

Evidence for the efficacy of paraldehyde in status epilepticus consists of uncontrolled trials[2,29,98,154,241,244] and testimo-nials.[29,55,238] One open-label study found that intramuscular paraldehyde controlled seizures lasting more than 5 minutes in children within 10 minutes of administration in 49% of patients.[2] These reports contain few details but suggest that paraldehyde can probably control status epilepticus in most adults and children; may control status epilepticus when other agents fail; and may be more effective for tonic–clonic status epilepticus than for partial status epilepticus. On the whole, paraldehyde is disappearing from hospital pharmacies as better and easier-to-store antiepileptic drugs have become widely available in the United States. However, paraldehyde is still used to treat status epilepticus in developing countries.[2] Comparison of the reported evidence leads to the conclusion that for almost all patients, IV lorazepam or diazepam is preferable to IV paraldehyde when immediate control of seizures is necessary, and that for most patients a loading dose of phenytoin or phenobarbital followed by maintenance doses is preferable to continued paraldehyde.[32,113] In patients with tonic–clonic status epilepticus refractory to first-line drugs (e.g., lorazepam, diazepam, phenytoin, and phenobarbital), anesthetic coma (if available) is probably more effective and safer than paraldehyde. There are three special situations in which paraldehyde may still find limited used for status epilepticus: (a) when the initial therapy must be given IM; (b) when the patient is allergic to safer agents; and (c) when phenytoin, phenobarbital, lorazepam, and diazepam fail, and anesthetic coma cannot be practically managed (no intensive care unit [ICU], no ventilator).

Paraldehyde may be the drug of choice for status epilepticus when drugs can be administered only by the IM route (e.g., no physician immediately available, suitable vein cannot be found, resuscitation equipment not available). Paraldehyde absorption by the IM route produces near-peak plasma concentrations in 15 to 20 minutes. Lorazepam, diazepam, phe-nytoin, and phenobarbital require significantly longer times for absorption by the IM route and do not produce therapeutic plasma concentrations within 15 to 20 minutes when given in the usual doses IM.[105,110,127,210,232,240]

Patients with no history of seizures except during alcohol withdrawal and patients with true seizure disorders and therapeutic plasma concentrations of antiepileptic drugs who have seizures only when withdrawing from alcohol are most often treated with benzodiazepines. Paraldehyde is an effective alternative to benzodiazepines, but paraldehyde probably has more side effects.[29,203] The preponderance of experimental and clinical evidence suggests that phenytoin is not effective for alcohol withdrawal seizures (see Chapter 268), and barbiturates are not generally used for treating alcohol withdrawal symptoms in the United States because of concern about habituation.

When status epilepticus continues after full loading doses of phenytoin and phenobarbital have been administered, paraldehyde is sometimes effective in stopping seizures.[29,238] However, the greater certainty of seizure control and greater safety of anesthetic coma makes it the treatment of choice, if available, for refractory status epilepticus.

Alcohol Withdrawal Syndrome and Delirium Tremens

There is abundant evidence that paraldehyde is effective as a primary therapy for alcohol withdrawal syndrome and for delirium tremens.[29,82,105,161] However, benzodiazepines are generally preferred because of greater safety and ease of use.

Other Indications

Paraldehyde has been reported to be effective for neonatal seizures,[126] including those due to hypoxic-ischemic encephalopathy.[10]

How to Use the Drug

Formulation

The water solubility of paraldehyde is greatest (12.8%) at 12°C and decreases as the temperature rises above, or falls below, this point. At 37°C, the water solubility of paraldehyde is 7.8%. Lack of awareness of these critical facts has led to the practice of injecting paraldehyde intravenously in its pure form or as a 10% solution. In either case, the solubility of paraldehyde at 37°C would be exceeded, and droplets of pure paraldehyde may form in the bloodstream, which can result in pulmonary emboli (see above).

Paraldehyde has a slight tendency to depolymerize back to acetaldehyde. In the presence of air, acetaldehyde oxidizes to acetic acid, which then acts as a catalyst for further depolymerization of paraldehyde to acetaldehyde. Improper storage of paraldehyde has resulted in some samples containing 40% to 98% acetic acid,[103] and as little as 7 mL of such decomposed paraldehyde has proved fatal.[6] A survey of 42 paraldehyde samples collected from hospital wards in 1957 revealed that only 11% met USP standards.[103]

In 1965, USP specifications were altered to state that paraldehyde must be preserved "in well-fitted, tight, light-resistant containers not exceeding 30 ml and that the unused contents of any container that has been opened more than 24 hr be discarded." Such procedures should reduce (but may not completely eliminate) the hazards of decomposed paraldehyde.

Treatment of Status Epilepticus

The dosage of paraldehyde for treatment of status epilepticus is 0.1 to 0.15 mL/kg. This dose may be repeated every 2 to 4 hours if necessary. Before any paraldehyde is administered, it should be checked for purity and conformity with USP standards for storage.[29] The minimum therapeutic plasma concentration of paraldehyde for control of status epilepticus is approximately 300 ng/mL.[98]

The safety of paraldehyde by the IV route is controversial. When immediate control of seizures with an IV medication is indicated, one should probably use another drug (e.g., lorazepam or diazepam) whose safety by the IV route is much greater. If IV paraldehyde must be given, it needs to be diluted to a 4% solution and infused slowly.

Paraldehyde decomposes many plastics, including poly-styrene and styrene–acrylonitrile copolymer, and also rubber.[29,69,81,116,194,199,239] Glass syringes usually are recomm-ended.[118]

Absorption by way of the oral route is slower than by the IM route.[29] There is also a risk of aspiration of paraldehyde, which is highly noxious to the lungs. The oral route is best avoided in patients with status epilepticus.

The ease of administration of paraldehyde by way of the rectal route probably accounts for its frequent administration this way. However, rectal absorption is considerably slower than that by the IM or oral route, making the rectal route particularly undesirable for treating status epilepticus.[75] Furthermore, the slow rectal absorption of paraldehyde can result in administration of large doses to obtain a plasma concentration high enough to control seizures. When the large rectal reservoir of paraldehyde is eventually absorbed, toxic plasma concentrations of paraldehyde may result.[31] If rectal paraldehyde is administered, it should be diluted 2:1 in oil (olive or cottonseed) or diluted in 200 mL of 0.9% sodium chloride.

Phenacemide

Phenacemide is not marketed in the United States.

Structure and Chemistry

Phenacemide (phenylacetylurea, phenacetylcarbamide, Phe-nurone, PAC) is a straight-chain analog of 5-phenylhydantoin (Fig. 3).

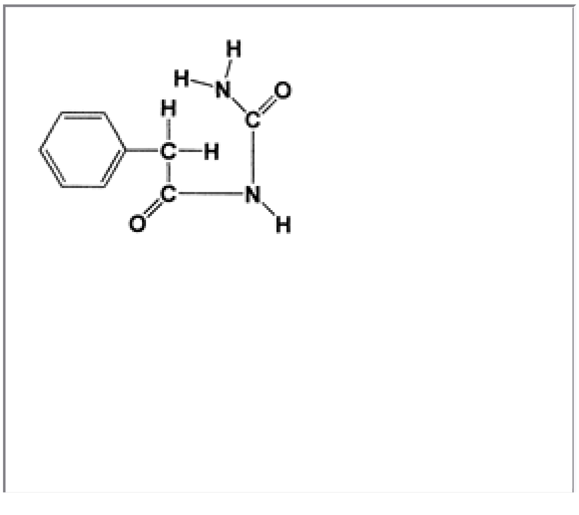


FIGURE 3. Structural formula of phenacemide.

Table 1 Toxicity of Phenacemide*

Side effect	Percentage of patients
Psychic changes	
All patients	15–20
Patients with pre-existing psychiatric problems	27
Patients without pre-existing psychiatric problems	5
Gastrointestinal symptoms	8–13
Rash	1–8
Headache	2–6
Drowsiness	4–5
Abnormal urinary findings	1–3
Hepatitis	0.6–2
Blood dyscrasia	0–2

*Based on data from Davidson DT, Lennox WG. Phenacetylurea (Phenurone) in epilepsy. *Dis Nerv Syst*. 1950;11:167–173; Gibbs FA, Evert GM, Richards RK. Phenurone in epilepsy. *Dis Nerv Syst*. 1949;10:47–49; Livingston S, Pauli LL. Phenacemide in the treatment of epilepsy: results of treatment of 411 patients and review of literature. *N Engl J Med*. 1957;256:588–591; and Tyler MW, King EQ. Phenacemide in the treatment of epilepsy. *JAMA*. 1951;147:17–21.

Basic Mechanism of Action

In experimental models of epilepsy, phenacemide elevates the seizure threshold for minimal electroshock, maximal electroshock, and pentylenetetrazol seizures.[158,212] In fact, phenacemide has higher protective indexes against minimal electroshock seizures (a model of complex partial seizures) and maximal electroshock seizures (a model of tonic–clonic seizures) than either phenytoin or phenobarbital.[212] The mechanism of action of phenacemide is probably similar to that of phenytoin because of the similar structural and three-dimensional conformation of phenacemide and phenytoin.[36,249]

Pharmacologic Fundamentals

Phenacemide is well absorbed from the intestine, with peak plasma concentrations occurring 3 to 5 hours after a single oral dose.[229] The extent of protein binding is unknown. Phenacemide is metabolized by means of hepatic microsomal enzymes by *para*-hydroxylation of the phenyl group followed by conjugation to a glucuronic acid.[193,229] Ring closure to form hydantoin does not occur.[31] The metabolite and its glucuronide are excreted through the kidneys, with little or no unchanged phenacemide found in the urine.[31] The elimination half-life of phenacemide is 5 to 12 hours.[31,192] The effective plasma concentration ranges from 16 to 75 μg/mL.[229]

Adverse Effects

The frequencies of the most common side effects of phenacemide are summarized in Table 1.

Dose-related Effects

Anorexia, nausea, vomiting, weight loss, and abdominal pain occur in 8% to 13% of patients on phenacemide.[89,140,227] In about 3% of such cases, the drug must be discontinued.[142] Headache or a feeling of "fullness in the head" occurs in 2% to 6% of patients on phenacemide.[49,89,140,227] The headache appears during the first few days of phenacemide therapy and is often severe. Drowsiness occurs in up to 5% of patients.[227]

Idiosyncratic Effects

Destructiveness, belligerence, marked irritability, restlessness, and depression are the most commonly observed behavioral changes.[89,140,227] Suicidal tendencies, paranoia, and acute psychotic states have also been reported.[227] Behavioral symptoms occur most commonly during the first 4 to 6 weeks of phenacemide treatment and disappear within a few weeks of stopping the drug.[134,227] Behavioral or psychiatric changes necessitate discontinuing phenacemide in about 10% of patients.[227] On the other hand, in some patients with pre-existing personality disorders, improvement has been noted after starting treatment with phenacemide.[49,140] In patients who have a history of psychiatric disorders, hospitalization during the first week of phenacemide therapy may be advisable. Patients and family should be alerted to report changes in behavior such as decreased interest in surroundings, depression, or aggressiveness.

Rashes of the maculopapular, scarlatiniform, or acneiform type may occur.[40,134,140] Rashes are most common during the first 3 weeks of phenacemide therapy and may be accompanied by fever.[49,134] The rashes are not dose related and disappear within a week of stopping the drug.[49]

Transient proteinuria without serious renal damage occurs in up to 3% of patients during the first week of paraldehyde treatment.[89] Acetonuria and glycosuria may also occur.[227] Nephritis and a fatal case of hepatorenal syndrome have also been reported.[227]

Hepatitis, which is often reversible, occurs in 0.6% to 2% of patients on phenacemide.[49,89,140,227] At least ten deaths from phenacemide-related hepatic toxicity have been reported.[97,140] The histologic picture in these cases was one of zonal (chiefly centrolobular) to submassive toxic necrosis.[97] If the patient survives, postnecrotic cirrhosis may develop.[97] Phenacemide should be avoided in patients with a history of hepatic disease. Liver function studies should be performed in all patients before and during phenacemide therapy.

Leukopenia, leukocytosis, thrombocytopenia, agranulocytosis, and aplastic anemia occur in 0% to 2% of patients on phenacemide,[49,89,140,227] and two fatal cases of aplastic anemia have been reported.[140] Complete blood counts should be obtained before starting phenacemide and at regular intervals during treatment.

Other side effects of phenacemide include insomnia, fatigue, fever, dizziness, paresthesias, muscle pain, palpitations, pruritus, and insensitivity to pain.[49,89,227]

Teratogenicity

The teratogenic potential of phenacemide in humans is unknown. However, because of its structural similarity to phenyt-oin and its high incidence of side effects, it is reasonable to suspect that phenacemide would likely produce teratogenic effects similar to those of phenytoin. Phenacemide should not be given during pregnancy unless the potential benefits outweigh the potential risks.

The Role of the Drug

Phenacemide is no longer manufactured in the United States. We could find no other international manufacturer.

Complex Partial Seizures

The major use for phenacemide has been in treatment of complex partial seizures (CPSs) that are refractory to less toxic drugs. Although phenacemide is moderately effective as a primary drug for CPSs,[140,227] it should never be used as the drug of first choice for any seizure type because of its high incidence of serious side effects (see above). Several studies have shown that phenacemide completely controls or markedly decreases CPSs in 30% to 60% of patients refractory to phenytoin and barbiturates.[49,89,140,227]

Phenacemide should not be administered to a patient with CPSs until it has been documented that maximum tolerated doses of first-line drugs (e.g., phenytoin, carbamazepine, oxcarbazepine, topiramate) and less toxic "backup" drugs (e.g., gabapentin, lamotrigine, levetiracetam) will not control seizures.

Tonic–Clonic and Simple Partial Seizures

Phenacemide has not proved particularly effective against either tonic–clonic or simple partial seizures, either as a primary or adjunctive agent.[44,140,227] However, a minority of patients with tonic–clonic seizures refractory to hydantoins and barbiturates have had a good response to phenacemide.[49,89,140,227]

Absence Seizures

Phenacemide is effective against absence seizures in only a minority of patients.[44,49,89,140,227] Given the abundance of less toxic antiabsence drugs that are available, there is no indication for phenacemide for this disorder.

How to Use the Drug

For adults, the usual starting dose of phenacemide is 1,500 mg/day in three divided doses. If seizures are not controlled, the daily dosage may be increased by 500 mg at weekly intervals. The usual daily maintenance dose in adults is 2,000 to 3,000 mg, although some patients have required as much as 5,000 mg/day. In children 5 to 10 years of age, the dosage of phenacemide is approximately one-half the adult dosage, administered in three divided doses. Because of its many side effects, maintenance dosage should be the smallest amount that provides adequate seizure control.

Phenacemide may be administered alone or in conjunction with other antiepileptic drugs. However, extreme caution must be exercised if the other antiepileptic drugs cause similar toxic effects. When phenacemide is to replace other antiepileptic drugs, the latter should be withdrawn gradually as the dosage of phenacemide is increased to maintain seizure control.

Bromides

Bromides are no longer marketed in the United States.

Bromides were the first effective antiepileptic drug treatment and thus a major turning point in the history of neurology. Potassium bromide was first prepared by Ballard in 1826 and first used for the treatment of scrofula by Pourché in 1828.[13] Potassium bromide was included in the London Pharmacopoeia in 1836 but subsequently excluded from the 1851 edition.[205] In the 1850s, its sedative properties were recognized, and the drug became used for psychiatric purposes.

In 1850, Huette called attention to the development of impotence and depression of the libido in a young man treated with bromide.[13] This effect quickly reversed after discontinuation of treatment. It was this observation that led Sir Charles Locock, an obstetrician to Queen Victoria, to use bromides in women with “hysterical” epilepsy. At the time, onanism and

excessive sexual excitement were regarded as well-established causes of epilepsy, thus making bromides a logical choice for the treatment of seizures believed to be associated with such factors.[151] In 1857, Locock presented his experience with 14 or 15 women with “hysterical” epilepsy during the discussion of a paper presented by Edward Sieveking at the Royal Medical and Chirurgical Society of London.[143] Locock's patients had seizures mainly around the menstrual period, and they improved significantly when potassium bromide was administered. At the time, this was interpreted as a confirmation of the theories of onanism, nymphomania, and other forms of excessive sexual excitation in the genesis of epilepsy. Shortly after, C. Bland Radcliffe and Sir Samuel Wilks, based on Locock's observations, extended the use of bromides to other cases of epilepsy not necessarily related to “ovarian irritation.”[77] In the ensuing years, use of bromides became massive, and by the mid-1870s, 2.5 tons of bromides were dispensed yearly at the National Hospital Queen Square.[221] Bromides continued to be the only effective medication for epilepsy until 1912, when phenobarbital was introduced.

Structure and Chemistry

Bromide is a simple inorganic anion that behaves in ways very similar to chloride. It is an essential micronutrient and can be found naturally in food, especially vegetables, or as a residue of certain chemicals such as pesticides. It is used by the thyroid gland in the biosynthesis of thyroxine and triiodothyronine. It is normally found in plasma in very small concentration, and a daily intake of 4 mg/kg is considered safe for humans.[231]

Mechanism of Action

It has been shown that both chloride and bromides cross the nerve cell membrane in response to inhibitory neurotransmitters.[63,65] Furthermore, the hydrated bromide ion has a smaller diameter than chloride and penetrates neuronal membranes more rapidly.[87] It is presumed that bromide enters neurons through the chloride channels. Intracellular accumulation of the negatively charged bromide ions hyperpolarizes the neuronal membrane, making it more difficult to generate action potentials. Bromide, like γ-aminobutyric acid (GABA), inhibits the basal and potassium-stimulated release of acetylcholine in the superior cervical ganglion, and this effect is additive with that of baclofen, a GABA receptor agonist.[151] In rat models, the addition of bromide resulted in an increased binding of [^{3}H]flunitrazepam to the benzodiazepine receptor.[173] It is likely that this effect on the GABA receptor complex is related to the action of bromide on the GABA ionophore (chloride channel). This conclusion is supported by the selective antagonism by bromide of picrotoxin- and pentylenetetrazol-induced seizures in animal models.[12] In this way, the action of GABA, which results in opening of the chloride channel and subsequent hyperpolarization of the neuronal membrane, is potentiated by the presence of bromide.[214] A more recent in vitro study confirmed the ability of bromine to increase GABAergic inhibition and suggested an effect of bromine on membrane excitability.[155]

Pharmacologic Fundamentals

Absorption and Distribution

All inorganic salts of bromide are highly water soluble and thus rapidly and completely absorbed from the intestinal tract. The bioavailability has been estimated at 96% ± 6% with a range of 75% to 118%.[230] Bromide is passively absorbed from the small intestine at a slightly faster rate than chloride.[204] The absorption of bromide is saturable, but only at very large doses.[230] The distribution of bromide is mostly into extracellular water space, similar to that of chloride. For this reason, oral bromide can be used in the calculation of the extracellular space.[230]

Bromide and chloride displace each other because body tissues do not distinguish between the two ions. With increasing bromide levels, the concentration of chloride is gradually decreased, because chloride is more rapidly eliminated by the kidney. When very large doses of bromide are given, as much as 40% to 45% of the total chloride in the body can be replaced.[59] Bromide is not bound to plasma proteins. The volume of distribution of bromide has been estimated at 408 ± 17 mL/kg (range 353 to 484 mL/kg).[230] Other studies have found slightly lower volumes of distribution.[255] Bromide is present in all extracellular fluids at concentrations similar to plasma with some exceptions: The concentration of bromide in saliva and gastric juice is higher than that of plasma by a ratio of 1.5.[255] The bromide secreted in saliva and gastric juice is completely reabsorbed at the small intestine, so that no bromides are usually found in feces. On the other hand, the concentration of bromide in the cerebrospinal fluid is lower than that in plasma.[249]

Bromides appear to be removed from the cerebrospinal fluid by bulk flow via the arachnoid villi and by active transport across the choroid plexus.[255] The latter process appears to be the most important and probably accounts for the lower concentrations of bromide in the cerebrospinal fluid.[255] Bromide freely crosses the placenta, with maternal plasma concentrations being slightly higher than fetal concentrations.[223]

Elimination and Pharmacokinetics

The half-life of bromides has been estimated at 11.9 ± 1.4 days.[230] Bromide is eliminated almost exclusively by the kidney as a result of glomerular filtration and tubular reabsorption. In a study of normal volunteers, the clearance rate of bromide was estimated to be 26 ± 1.7 mL/kg/day.[230] Chloride and bromide compete for tubular reabsorption. Thus, a high chloride load will increase bromide clearance and shorten its half-life.[130] A low concentration of chloride, as a result of a salt-deficient diet for example, may actually prolong the elimination of bromide. Given the very slow elimination rate of bromide, steady-state concentrations are not reached until about 40 to 50 days after starting chronic treatment.

Adverse Effects

Acute Intoxication

Acute bromide poisoning is rare today because of the shrinking use of bromides. Ingestion of a large dose usually results in gastric irritation and prominent vomiting, thus limiting its absorption.[136] At high doses, bromides are nephrotoxic and ototoxic.[136] Death can occur from acute renal failure.[24] Histologic examination shows acute tubular necrosis in the proximal convoluted tubules along with interstitial edema, followed by tubular dilation, cellular necrosis, and finally interstitial fibrosis and sclerosis.[92] The excretion of N-acetyl-*B*-glucosaminidase and *B*-galactosidase, lysosomal enzymes that are a sensitive and reliable method for detecting renal tubular dysfunction, was increased in patients with epilepsy taking a combination of valproate and potassium bromide.[168] Even though the significance of these changes is still unknown, patients receiving antiepileptic drugs show a slight increase in the amounts of these enzymes in the urine.[168] Patients taking a combination of valproate and bromides showed the highest urinary levels of N-acetyl-*B*-glucosaminidase.[168]

Chronic Toxicity

Chronic toxicity from bromides has long been recognized in the medical literature and is known as bromism or bromide toxicosis. This condition is now rare but still occurs occasionally.[114] Clinical symptoms develop insidiously given the very prolonged half-life of bromides (about 12 days). Elderly persons are most susceptible, especially in the presence of decreased renal function, systemic illness, dehydration, or concomitant encephalopathy.[17,59] Early signs of bromism include drowsiness, asthenia, dizziness, headache, irritability, and emotional instability. Memory loss and lack of concentration are frequent and can be confused with Alzheimer disease or other dementias. More severe intoxication can result in dysarthria, hallucinations, disorientation, delirium, or even stupor.[17] Loss of papillary reflexes, hyperreflexia, or loss of deep tendon reflexes have been reported as well.[59,226] Skin rash occurs in 25% to 30% of cases and appears to be more common in younger patients.[226] It is usually an acneiform eruption that affects the face and trunk but may become generalized. More rarely, the rash may be nodular or bullous. When mild, bromide intoxication can be treated simply by eliminating the drug or reducing the dosage. Excretion of bromide can be accelerated by administration of chloride in the form of sodium chloride (saline injection) or ammonium chloride. Peritoneal or hemodialysis is an effective method for promoting clearance of bromide in cases of acute intoxication.[136] Neonatal bromism has been described in children born to mothers on bromide therapy, and it is characterized by hypotonia and depression of consciousness.[147,178] Significant concentrations of bromides are also found in human milk.[5] For this reason, use of bromides should be avoided during pregnancy or breastfeeding.

Patients on bromide therapy show enhancement of cerebral blood vessels on computerized axial tomography as a result of the similar radiodensity of the bromide and the iodide halides.[172] Another common finding in patients receiving bromides is an apparent increase in chloride levels when automated electrolyte analyzers are used. This methodology does not distinguish between the chloride and bromide halides, leading to an artifactual or "pseudohyperchloremia."[164,191,257] Woody et al. have shown that there is a linear correlation between the increase in the values of "chloride" and the resulting calculated anion gap with the bromide serum concentrations.[257] In this way, an indirect determination of bromide levels can be obtained by using the widely available automated electrolyte analyzers. Steele and Woody have found enhanced neutrophil function in children on chronic bromide therapy.[207]

Drug Interactions

Bromide is not metabolized, has no liver-inducing properties, and does not bind to plasma proteins. As a result, no significant pharmacokinetic interactions with other antiepileptic drugs would be expected. Bromide has been shown not to interact with topiramate.[153] Bromides, however, appear to have a pharmacodynamic effect enhancing the action of other CNS depressant drugs, especially benzodiazepines.[255] Bromide levels are higher in patients receiving lithium salts.[39,238]

The Role of the Drug

Pharmaceutical preparations of bromide are no longer manufactured in the United States. However, pharmaceutical bromide preparations are available in several countries, including Japan.[120]

Following the introduction of phenobarbital in 1912 and phenytoin in 1938, the use of bromides dropped dramatically. Since then, the drug earned a reputation, unjustly according to several authors, of having a very narrow therapeutic index and being less effective than newer antiepileptic drugs.[117,141,256] Sporadic reports about the efficacy of bromides support the claim that this compound still has a limited but definite role in the management of epileptic seizures.[16,60,68,169,207,215,218,256] The majority of these studies, however, are mostly retrospective, unblinded, and uncontrolled.

Bromides seem to be most effective in treating generalized tonic–clonic seizures, somewhat effective in partial seizures, and generally ineffective in absence, myoclonic, and tonic seizures. Several authors have actually reported that bromides exacerbate tonic and myoclonic seizures.[22,68,198,203,218] Because bromides do not induce hepatic enzyme systems, they have been useful in the treatment of epilepsy associated with porphyria.[203]

Unlike most other antiepileptic drugs, bromide has a long elimination half-life in animals (e.g., 1.6 weeks in cats). Bromide is still used to treat epilepsy in cats and dogs.[27,180,225]

How to Use the Drug

Bromide is typically available as a potassium salt or as triple bromides, consisting of a combination of equal amounts of potassium, sodium, and ammonium bromide. It has been generally used as an elixir at concentrations of 1,200 mg of bromide salt per 5 mL, but tablets are also available. Recommended doses in children range from 30 to 80 mg/kg/day, with doses as high as 170 mg/kg having been used by some investigators without significant toxicity.[68,208] The starting dose is usually 10 mg/kg/day in two or three divided doses. Given its very prolonged half-life, monitoring plasma bromide concentration is of great importance in order to prevent toxicity. Under normal circumstances, steady state is reached in 40 to 50 days. The therapeutic concentration of bromide is approximately 75 to 125 mg/dL, with levels over 150 mg/dL being potentially toxic.[59] In a recent series, Steinhoff et al. reported mean bromide concentrations of 253 mg/dL (range 156 to 367 mg/dL) and proposed a therapeutic range of 200 to 300 mg/dL.[208] The authors noted that clinical toxicity was observed frequently with levels over 300 mg/dL.[207] In their series, however, the incidence of patients experiencing side effects was 53%, slightly higher than in other reports. Most other authors have recommended more conservative doses and a lower therapeutic range.[59,68,169,218] Certainly, with levels over 200 mg/dL, patients should be monitored very closely.

It should be noted that most of the preceding information comes from pediatric patients, who are have better tolerance to the neurotoxicity of bromides than adults and especially elderly patients. More conservative doses and closer monitoring are necessary in the elderly.

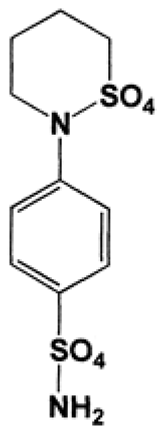


FIGURE 4. Structural formula of sulthiame.

Sulthiame

Structure and Chemistry

Sulthiame (tetrahydro-2-*p*-sulfamoylphenyl-2 H-1,2-thiazine-1,1-dioxide; Ospolot, Conadil, Elisal) is a sulfonamide derivative first synthesized in 1960 by Helferich and Kleb[104] (Fig. 4). It was introduced as an anticonvulsant in the early 1960s in Europe and Australia but never marketed in the United States because of lack of convincing evidence of its antiepileptic effect.[96] Sulthiame is chemically related to sulfanilamide and acetazol-amide. It is a carbonic anhydrase inhibitor but has no antibacterial activity and very weak diuretic properties.[243] Sulthiame is a white solid with a molecular weight of 290 and a melting point between 183°C and 187°C.[62] It is soluble in alkaline solutions but poorly soluble in water, ethanol, or acid solutions.

Mechanism of Action

There is evidence for two mechanisms of action of sulthiame: Inhibition of carbonic anhydrase and blocking sodium channels. In animal models, sulthiame has shown efficacy against maximal electroshock and pentylenetetrazol seizures; it has no effect against strychnine-induced seizures.[243] There has been speculation that the mechanism of action may be similar to that of acetazolamide, given its similar but weaker inhibitory effect on carbonic anhydrase.[132,134,244] The inhibitory effect of sulthiame on the enzyme is about one-sixteenth the potency of acetazolamide.[244] The degree of anticonvulsant action of different carbonic anhydrase inhibitors parallels the degree of enzyme inhibition.[219] Tanimukai et al. found a differential effect of sulthiame on brain and erythrocytic carbonic anhydrase, with sulthiame being significantly more potent on the brain enzyme.[219] It has also been shown that sulthiame reduces voltage-gated sodium currents.[146]

Pharmacologic Fundamentals

Sulthiame is rapidly and completely absorbed from the gastrointestinal tract. In humans, over 90% of an oral dose is absorbed, with peak plasma concentrations observed within 1 to 5 hours.[58,99] The drug penetrates body tissues readily, and concentrations of sulthiame in brain and plasma have been similar in animal studies. However, in certain tissues such as red blood cells, sulthiame was slightly more concentrated. Although there is no direct evidence that sulthiame binds to plasma protein, Hooper et al. have found that sulthiame displaced phenytoin from plasma albumin to some extent.[107] A significant proportion of sulthiame, ranging from 17% to 69%, is eliminated unchanged in the urine.[58] An additional 25% to 50% of the dose undergoes hepatic metabolism and is eliminated as an inactive hydroxylated derivative.[58]

May et al. estimated the half-life of sulthiame in 11 patients with epilepsy after withdrawal of the drug.[152] The elimination of sulthiame was satisfactorily explained by a first-order or linear kinetics model.[152] The mean half-life was 8.65 ± 3.1 hours, with a range of 4.7 to 15.4 hours.[152] In this study, children under the age of 14 years showed shorter half-lives and higher daily fluctuations in plasma concentration, indicating a higher clearance of sulthiame. The relationship between sulthiame plasma concentrations and daily dosage has been ambiguous.[64,152] Feely et al. found a poor correlation ($r = 0.54$) in ten patients studied.[70] At doses between 4 and 12 mg/kg/day, levels usually ranged between 1.5 and 20 μg/mL, although extremes of 0 and 45 μg/mL were observed.[70] Other studies have found a better correlation.[64,152] In a study of 86 patients with epilepsy, sulthiame dose and plasma concentration were highly correlated ($r = 0.82$).[152] Children had lower sulthiame plasma concentrations compared to adults, although dose per body weight was comparable. In addition, patients comedicated with carbamazepine had lower sulthiame concentrations than those receiving valproate, an observation probably due to the liver enzyme–inducing properties of carbamazepine.[152]

The relationship between sulthiame plasma concentrations and seizure control remains poorly understood.[21,37,96,152] There are no studies that show a clear relationship between sulthiame plasma levels and efficacy.[152] Green et al.[96] commented that the lack of correlation between seizure frequency and plasma levels was disappointing. In this study, plasma concentration in most patients ranged from 10 to 50 μg/mL, but levels as high as 74 μg/mL were observed.[96] Callaghan et al., in a smaller series, also failed to show any significant correlation.[37] Egli et al. proposed a therapeutic range between 6 and 10 μg/mL but pointed out that good responses were also observed in individual patients with considerably lower levels.[64] Doose, who studied a series of patients with rolandic epilepsy, suggested a therapeutic range between 1.5 and 2.5 μg/mL.

Adverse Effects

Side effects are common with sulthiame. Hyperpnea is present to some extent in almost every patient.[142] The hyperpnea in itself is usually well tolerated, but it frequently may present as an exertional dyspnea with a decrease in respiratory reserve. When severe, it can be frightening to the patient and often a reason to discontinue the drug. Sulthiame stimulates pulmonary ventilation and leads to a compensated respiratory alkalosis.[244] At doses between 1,600 and 3,000 mg, sulthiame is associated with a decrease in plasma bicarbonate, along with a decrease in the PCO_2 and a corresponding increase in the PO_2; blood pH remains unchanged.[244] The hyperpnea often improves with reduction of the dose.[62] Paresthesias, often persistent, are another common complaint in patients taking sulthiame and are similar to those observed with acetazolamide.[62] They frequently affect the distal extremities or have a perioral distribution. The paresthesias appear to be dose related and often improve with a reduction in dose.[62] Gastrointestinal complaints are common including anorexia, nausea, or weight loss.[131,138]

Other reported side effects include headache, asthenia, somnolence, ataxia, hypersalivation, and dizziness. Occasionally, mental changes such as hallucinations, psychosis, and catatonia have been observed.[4,80,93,96,137,163,179] In some early studies, status epilepticus was reported as a relatively frequent complication, but more recent series have not supported this finding.[96] There is one report of acute renal failure associated with the use of sulthiame.[11] Deposits of calcium phosphate crystals in the renal papillae have been found at autopsy in one third of dogs on chronic sulthiame intake.[142] A single case of Stevens-Johnson syndrome associated with the use of sulthiame in combination with phenobarbital has been reported.[213] Rare cases of peripheral neuropathy developing during sulthiame therapy have been observed.[71] Acute overdose with sulthiame has usually been followed by a rapid recovery, but at least one fatal case has been reported.[3,209] There is virtually no information concerning the sulthiame's teratogenicity.

Drug Interactions

Sulthiame is a potent inhibitor of phenytoin metabolism, resulting in a consistent and often considerable elevation of phe-nytoin concentrations.[101] Sulthiame appears to inhibit the hydroxylation of phenytoin, leading to prolonged elimination half-life and a decrease in the 24-hour urinary excretion of 5-(*p*-hydroxyphenyl)-5-phenylhydantoin (HPPH).[101,109] For reasons not well understood, this interaction may sometimes be delayed for 10 to 20 days.[101,177] Morselli et al.[162] found that when sulthiame was given to rats already receiving phe-nytoin, the brain concentrations of phenytoin were significantly higher in relation to the plasma concentrations (the phenyt-oin plasma/brain ratio fell from 1.6 to 0.9). Houghton and Richens[108] noted that 40% of patients admitted to their center receiving phenytoin in combination with sulthiame showed toxic levels of phenytoin. This important drug interaction may be partly responsible for the high incidence of side effects noted in the early studies, when sulthiame was frequently used in combination with phenytoin. Sulthiame may also elevate the plasma levels of phenobarbital and primidone, but this interaction appears to be of much less clinical significance.[171,177] It is possible that the effect in the inhibition of phenobarbital metabolism may be partially compensated by an increase in its urinary excretion because sulthiame increases 24-hour diuresis and the alkalinity of the urine.[171] Antiepileptic drugs with liver enzyme–inducing properties decrease the elimination half-life of sulthiame and result in lower plasma concentrations at a given dose.[152] Sulthiame does not lower topiramate plasma concentration.[153] Little is known about the interactions of other drugs with sulthiame.

The Role of the Drug

Early studies of sulthiame focused on partial seizures, especially complex partial seizures. Studies from the 1960s, when the drug was more widely used, showed that sulthiame was often effective as an adjunct for treating complex partial, generalized tonic–clonic, and myoclonic seizures.[28,111,123,125,131,142,148,160] Almost all of these early studies used sulthiame in combination with other antiepileptic drugs and seldom measured plasma concentrations. The study designs were generally inadequate to provide definitive evidence of efficacy by our current standards. When the interaction of sulthiame with phenytoin, and possibly other antiepileptic drugs, was recognized in 1968, results from the early studies were regarded with skepticism, and the efficacy of sulthiame as a primary antiepileptic drug was severely questioned.

In 1974, Green et al. published the results of a controlled clinical trial comparing sulthiame and phenytoin as monotherapy in 67 patients with partial seizures.[96] Patients were randomized to two consecutive 6-month treatment periods with sulthiame or phenytoin in a double-blind fashion. Doses of sulthiame ranged from 400 to 3,600 mg/day (mean 1,993 ± 648 mg/day), and plasma concentrations from 10 to 74 μg/mL (mean 28.9 ± 14.9 μg/mL). Only 21 patients completed the study. Of these, ten had fewer seizures on sulthiame, nine had fewer seizures on phenytoin, and two were seizure free with either drug. However, six of the ten patients on sulthiame and both seizure-free patients elected to continue treatment with phenytoin, mostly because of side effects. As a result, of 67 patients entering the study, only four preferred sulthiame. Analysis of patients who were dropped from the study showed that 21 left while taking phenytoin and 25 while taking sulthiame. However, in the phenytoin group, only seven left because of increased seizure frequency versus 17 in the sulthiame group, a statistically significant difference ($p < 0.05$). Toxicity was also significantly higher in patients receiving sulthiame. The authors' conclusion was that sulthiame had very little value as a primary antiepileptic drug. After this study was published, use of sulthiame dropped dramatically, and the drug was never marketed in the United States.

Several more recent studies of sulthiame have focused on its use in benign epilepsy with centrotemporal spikes (BECTS). The Sulthiame Study Group performed a randomized, double-blind, 6-month study of sulthiame monotherapy versus placebo for treatment of BECTS.[200] The primary outcome variable was treatment failure events (TFE) per group. TFEs consisted of first seizure after a 7-day run-in period, intolerable adverse events, development of another epileptic syndrome, or termination of trial by parents or patient. Twenty-five of 31 sulthiame-treated patients (81%) and 10 of 35 placebo-treated patients (29%) completed the trial without any TFEs ($p = 0.00002$). A number of uncontrolled studies also report favorable efficacy and tolerability of sulthiame for BECTS.[19,128]

The Sulthiame Study Group also found that the electroencephalogram (EEG) normalized in 21 of 31 patients on sulthiame and 5 of 35 patients on placebo ($p < 0.0001$).[13] Uncontrolled studies of the effects of sulthiame on the EEG in patients with BECTS have reported similar results.[19,66,128]

Debus et al.[54] performed a randomized, double-blind study of 37 infants with newly diagnosed infantile spasms (all on pyridoxine) who were randomly assigned to sulthiame or placebo. Complete cessation of infantile spasms and resolution of hypsarrhythmia on EEG were the criteria for being classified as a responder. Thirty percent of patients on sulthiame were responders, while none of the patients on placebo were responders ($p < 0.025$).

Uncontrolled trials of sulthiame for infantile spasms have also reported favorable results.[53] Limited evidence suggests that sulthiame may have efficacy against juvenile myoclonic epilepsy[135] but not absence seizures.[96]

Sulthiame is not approved by the Food and Drug Administration (FDA) in the United States, but it is available in Europe. It has only a limited role in the management of epilepsy. However, randomized, double-blind, placebo-controlled studies have demonstrated efficacy of sulthiame for BECTS and infantile spasms.

How to Use the Drug

Sulthiame is generally available in 50- and 200-mg tablets. Treatment should be initiated slowly and at low doses in order to minimize side effects. Maintenance doses of 5 to 10 mg/kg/day appear reasonable in children, whereas in adults recommended doses usually fall between 400 and 2,000 mg/day. Much higher doses have been used with relatively good tolerance.[96] Because of its short half-life and the marked daily fluctuation of its plasma concentrations, the drug should be administered at least twice, preferably three times, a day.[152] The clinical value of monitoring sulthiame plasma concentrations appears at present to be very limited.[177] A therapeutic range of 6 to 10 μg/mL has been proposed, but good results have been observed at concentrations ranging from 1.5 to 50 μg/mL.[96,110]

Acetazolamide

Structure and Chemistry

Acetazolamide (5-acetamido-1,3,4,-thiadiazole-2yl-sulfona-mide, Diamox) is an unsubstituted sulfonamide that was synthesized in 1950 by Roblin and Clapp.[194] Its use in the treatment of epilepsy was first reported by Bergstron et al. in 1952,[20] and its efficacy in the treatment of different seizure types was studied by Ansell and Clarke,[7] Forsythe et al.,[73] Golla and Sessions,[88] Lombroso et al.,[144] Millichap,[156] and Rating.[184] Acetazolamide has a molecular weight of 222 g. Its chemical structure is shown in FIGURE 5.

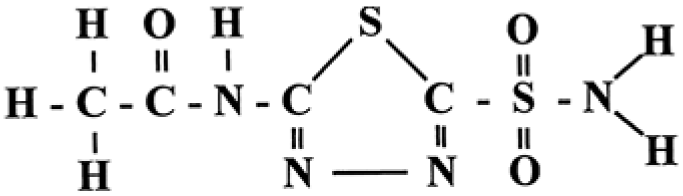


FIGURE 5. Structural formula of acetazolamide.

Basic Mechanism of Action

The enzyme carbonic anhydrase catalyzes the conversion of carbon dioxide and water to bicarbonate, which is important in maintaining acid–base balance. Inhibition of the enzyme

is the only known and documented mechanism of action for acetazolamide and is believed to mediate the activity of the drug.[9,94,95,157,187] More than 99% of the brain carbonic anhydrase activity can be inhibited by acetazolamide, which results in the accumulation of CO_2.[250,251] The anticonvulsant effect of CO_2 can be potentiated by acetazolamide,[252,253] and aceta-zolamide probably acts by causing an accumulation of CO_2 in the brain.

Pharmacologic Fundamentals

Absorption and Routes

Acetazolamide is a weak acid (pKa of 7.4) and remains in the nonionized form in acidic pH of the stomach (pH ~2.0). The nonionized form has little water solubility, and only small amounts are absorbed in the stomach. The increasingly higher pH and larger absorptive surface area in the duodenum and upper jejunum make it the preferential site of absorption of acetazolamide. Peak plasma levels occur 2 to 4 hours after oral administration. Whereas oral doses of 500 to 750 mg (5 to 10 mg/kg) are completely absorbed,[149] absorption of higher doses is less predictable, which results in variable plasma levels.[150] The time-release formulation yields peak plasma levels at 3.5 hours and is maintained for 10 hours.

Distribution and Protein Binding

Acetazolamide is 85% to 95% protein bound,[149,150,254] and the affinity for the protein carrier is concentration dependent. The free fraction increases as the plasma level rises. The highest tissue concentration of acetazolamide is found in erythrocytes, kidney, and stomach, which contains high levels of carbonic anhydrase. The high volume of distribution of 1.8 L/kg is consistent with high tissue binding even in the early distribution phase.

Metabolism

The compound is not metabolized; it is eliminated unchanged in the urine, 20% through glomerular filtration and 80% through tubular secretion.[149,150] The renal elimination of acetazolamide is pH dependent and can be enhanced by alkalinizing the urine. A small quantity of acetazolamide is also excreted in bile and reabsorbed from the small bowel.

Clinical Pharmacokinetics

At physiologic pH, approximately 50% of the acetazolamide free in the serum is present in the un-ionized state, which diffuses into different body compartments. After a single dose, the plasma level time plot reveals two phases. The first phase lasts about 100 minutes and represents the rapid movement of the unbound drug into tissue compartments. Once in a tissue compartment, the drug binds to carbonic anhydrase enzyme and forms a stable inactive complex. The second, slower phase of the plasma decay curve represents the slow dissociation of drug–enzyme complex and subsequent renal excretion. The plasma half-life of the second phase is 2 to 4 days, with steady state achieved after 1 week or more of dosing. Effective blood levels may be maintained for 4 to 5 days after stopping the drug. The pharmacodynamic effect may exceed the pharmacokinetic profile, because upon entry into tissues acetazolamide forms a stable complex with carbonic anhydrase, which blocks the action of the enzyme. In elderly patients, elimination is altered by reduced glomerular filtration and by reduced protein binding. The two effects offset each other, and elimination in the elderly may be similar to that seen in children and younger adults.[42]

Acetazolamide decreases the bulk flow of cerebrospinal fluid (CSF). This reduces drug elimination from the brain by CSF bulk flow resulting in an increase in brain concentration of coadministered drugs. For example, a patient on phenobarbital may experience increased drowsiness.

Adverse Effects

Dose-related Effects

Acetazolamide is generally very well tolerated. Most side effects occur at initiation of treatment and are most likely to include lethargy, dizziness, nausea, numbness, and paresthesias, which usually affect the distal part of the limbs, and less often the face. Side effects may worsen as the dose is increased. Shortness of breath has been reported but is not associated with clinically evident cardiac or pulmonary dysfunction. Reduced exercise tolerance was described in a study involving healthy volunteers.[206] Metabolic acidosis, fatigue, depression, decreased libido, and decreased appetite have also been noted occasionally.[67,189,250] An increased risk of metabolic acidosis is found in patients treated concurrently with silicates[121]; it is also more frequent in elderly patients.[211]

An interesting side effect is the occurrence of dysgeusia, or altered taste.[91,102,255] Although not usually reported spontaneously, this symptom may occur in up to 90% of patients. Acetazolamide eliminates the tingling sensation from carbonated drinks as a result of inhibition of carbonic anhydrase located in the taste buds.

Renal stones have been associated with drugs that inhibit carbonic anhydrase. The reported frequency has varied from 1 of 277 patients[145] up to 43% of patients treated for epilepsy, glaucoma, and periodic paralysis.[121,189,220]

Idiosyncratic Effects

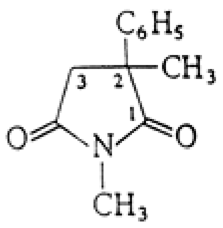
The most serious adverse effect associated with acetazolamide is aplastic anemia, which occurs predominantly in older patients (mean age 71).[123] The prodromal symptoms in patients developing aplastic anemia were usually nonspecific: Lethargy, anorexia, and fatigue, followed by bleeding or signs of infection.[123] Other idiosyncratic reactions encountered less frequently include renal failure, thrombocytopenic purpura, and agranulocytosis.[74,123,174,186,196,228]

Teratogenicity

An increased incidence of congenital abnormalities has been found in animal studies. In humans, there are isolated reports of malformations associated with the use of acetazolamide during pregnancy, including microcephaly, congenital heart defects, and congenital glaucoma. However, the overall risk of malformations from acetazolamide has not been established. Thus, use in pregnancy cannot be recommended unless the therapeutic benefit to the mother clearly outweighs the potential risk to the fetus.

The Role of the Drug

Acetazolamide is an antiepileptic drug with a broad spectrum of efficacy. Efficacy has been reported in the treatment of partial,[41,73,145,170] primary generalized tonic–clonic,[7,41,156,189] absence,[7,88,106,145,195] and myoclonic seizures.[190] Inhibition of carbonic anhydrase is the only mechanism that has been identified as the basis for the drug's antiepileptic effect. A stable acetazolamide–carbonic anhydrase enzyme complex is formed with a pharmacodynamic effect exceeding 24 hours. Once-a-day dosing is therefore realistic with acetazolamide. The main factor limiting wide use is development of tolerance, which results in diminishing efficacy over time.[7,112,144,145,156] As a result, acetazolamide is often prescribed for intermittent use. It is thus well suited to the treatment of catamenial seizures.[7,72,85,167,182,185,190,195]



METHSUXIMIDE

FIGURE 6. Structural formula for methsuximide.

How to Use the Drug

Effective plasma levels range from 8 to 14 μg/mL and 1 to 22 μg/mL.[170] The usual daily dose of acetazolamide is 10 to 20 mg/kg given two to three times daily.[129,197] When acetazolamide is used as adjunct therapy, the starting dose should be 250 mg/day to minimize sedation; the dose should then be increased as tolerated. The effective dosage varies considerably, but few patients benefit from doses above 20 mg/kg[170] or 750 mg/day.[145] Resor and Resor[189] found that patients with juvenile myoclonic epilepsy responded to acetazolamide monotherapy in doses ranging from 500 mg/day (6.7 mg/kg) to 1,750 mg/day (27 mg/kg), with an average dose of only 893 mg/day (14 mg/kg). Doses above 15 mg/kg are not usually effective and lead to a significant increase in side effects. Looking at cumulative seizure control, Oles et al.[170] found that most patients responding to acetazolamide had done so with doses of 9 mg/kg or less. Children should require higher doses than adults because of higher renal clearance. However, most reports have recommended doses of 500 to 750 mg/day (10 to 15 mg/kg/day) in children.[73,145,156]

When acetazolamide is first begun, it should be taken in the morning because it has a diuretic effect that continues for the first 3 to 5 days of treatment. As the diuretic effect abates, evening doses can be used without difficulty. Elderly patients may require adjusted doses.

Methsuximide

Structure

Methsuximide (*N*,2-dimethyl-2-phenylsuccinimide; Fig. 6) differs from ethosuximide in having a phenyl group at the 2-carbon position and a methyl group at the 5 position. Its structure is consistent with the generalization that short alkyl chains at the 2, 3, and 5 positions of the succinimide ring are associated with activity in the pentylenetetrazol model, whereas phenyl substitutes at the 2 and 3 positions confer activity in the maximal electroshock model.[30,43,176,229]

Basic Mechanism of Action

Methsuximide's mechanisms of action are unknown. Its efficacy against absence seizures may be due to an action similar to that of ethosuximide in which low-threshold calcium currents in thalamic neurons are blocked.[43,45,46,47,124,142] The drug's effectiveness in the maximal electroshock model and in partial seizures is likely mediated by changes in sodium conductance, as with phenytoin, or other ionic or neurotransmitter effects.[229]

Pharmacologic Fundamentals

Methsuximide and ethosuximide (Chapter 147) are similar in both structure and function.

Adverse Effects

Adverse effects occur in 35% of persons taking meth-suximide.[20] Dose-related side effects principally involve the gastrointestinal tract and central nervous system. Gastrointestinal effects include anorexia, nausea, hiccups, and abdominal pain. Central nervous system side effects include drowsiness, confusion, photophobia, headache, irritability, dizziness, and ataxia.[30,177,183,222,229,242] Delayed coma after overdose may reflect time required to convert the drug to its *N*-desmethyl metabolite.[30,229] Idiosyncratic reactions are rare and include rash, behavioral changes, and extrapyramidal reactions.[30,181,235] Hepatic failure has not been reported.[30] There have been rare cases of transient leucopenia, and a single case of pancytopenia was reported but the association with methsuximide was questionable.[30,229] There has been one case of reversible osteomalacia.[181] Few data are available regarding teratogenicity. However, methsuximide's metabolism by arene oxidase implies an epoxide metabolite, which may contribute to the teratogenic effects of several drugs in susceptible individuals.[259,260]

Methsuximide overdosage is characterized by stupor, coma, respiratory depression, central neurogenic hyperventilation, increased or decreased reflexes, myoclonus, and second-degree heart block. Favorable results were reported in a single case in which charcoal hemoperfusion was used.

Patients taking methsuximide in combination with phenyt-oin or phenobarbital have higher plasma concentrations of *N*-desmethylmethsuximide than patients taking methsuximide alone. The plasma concentrations of phenytoin and phenobarbital are increased appreciably when methsuximide is added. These interactions probably occur as a result of competition for the common enzyme involved in their metabolism, CYP2C9/10. A significant fall in carbamazepine level may occur with addition of methsuximide. This is probably due to induction of CYP2C9, the enzyme that metabolizes carbamazepine.[30]

Role of the Drug

In one study that looked at initial treatment of absence seizures with methsuximide, complete control was not achieved in any patient.[140] In studies in which methsuximide was used as adjunctive therapy for treatment of absence seizures, 0% to 31% of patients had complete seizure control, and 13% to 66% of patients had 50% or greater reduction in seizure fre-quency.[30,139] In comparison to methsuximide, ethosuximide (Chapter 147) has the following advantages: Higher frequency of seizure control, fewer side effects, and fewer drug interactions. Methsuximide is indicated for absence seizures only when less toxic drugs fail to produce adequate control.

When methsuximide is used as adjunctive therapy in treating complex partial seizures, the majority of patients who have failed trials of phenytoin, phenobarbital, and carbamazepine will not have a 50% or greater reduction in seizure frequency.[30] Patients having a good initial response to methsuximide often lose the response after 4 to 7 months.[33,242]

How to Use the Drug

The usual adult starting dose is 300 mg/day, which is increased using increments of 150 or 300 mg/day every 1 to 2 weeks; the longer interval is favored by Browne[30] and others because of the long half-life of methsuximide's active metabolite, particularly at higher levels. Although this long half-life could allow once-daily dosing, as with ethosuximide, side effects are less if it is given in two or three divided doses. In children or the elderly, a lower starting dose of 150 mg/day is preferable. The target dosage is 10 mg/kg, with a maximum of 900 to 1,200 mg in adults. Several investigators[30,33,181,229,235] suggest a therapeutic range of 10 to 40 mg/L for the measured active metabolite, *N*-desmethylmethsuximide. Presently, methsuximide is available in the United States only as Celontin 300-mg tablets.

Discontinuing the Drug

As with other antiepileptic drugs, indications for drug withdrawal include unacceptable adverse effects, ineffectiveness at maximal tolerated dose, or successful long-term seizure control. In the case of an allergic reaction, methsuximide can be withdrawn abruptly, especially if other drugs are maintained; otherwise, gradual withdrawal is advisable.

Summary and Conclusions

Trimethadione is sometimes useful in treating absence seizures and Lennox-Gastaut syndrome in patients refractory to less toxic agents. Paramethadione has been withdrawn from the U.S. market. Paraldehyde is effective in treatment of status epilepticus and alcohol withdrawal seizures but is seldom used because safer drugs are available for these indications. Phenacemide is an effective but toxic drug for partial seizures that should be considered only after less toxic drugs have failed and surgical therapy has been excluded. Modest success has been reported in treating refractory tonic–clonic seizures with bromide. Bromide is one of the few antiepileptic agents that can be taken safely by persons with porphyria. Methsuximide is a second-line drug for partial seizures. In an era of new alternatives for the treatment of epilepsy, the usage of the drugs discussed in this chapter will almost certainly continue to decline.

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Chapter 164

Investigational Drugs: Brivaracetam, Carisbamate, Eslicarbazepine Fluorofelbamate, Gamaxolone, Isovaleramide, Lacosamide (Harkoseride; SPM927), Losigamine, Retigabine, Safinamide, Seletracetam, Stiripentol, Talampanel, and Valrocemide

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Introduction

During the 16 years between 1989 and 2005, a number of new antiepileptic drugs (AEDs) entered the market for the add-on treatment of partial seizures as their initially approved indication. The availability of these AEDs has contributed to the management of epilepsy, either as adjunctive therapy or as monotherapy. In addition to providing more choices for the physician and his/her patients, many of these drugs have led to improved seizure control and have been shown to possess a more favorable tolerability and pharmacokinetic profile than some of the older "first-generation" AEDs. Unfortunately, for the patient with refractory epilepsy, there still remains a substantial need for more efficacious therapies. Thus, none of the AEDs currently available can claim to be capable of providing complete seizure control in a sizeable proportion of patients with refractory partial epilepsy. In addition, only small advances in the therapy of certain seizure types and epilepsy syndromes have been made. Therefore, there is still significant room for improvement.

Despite the advancements in our understanding of the pathophysiology and molecular genetics of various epilepsies, little progress has been made in the development of a therapy that targets the presumed molecular basis of a given seizure type. To this end, several of the drugs in development today evolved from a nonmechanistic approach and the use of a battery of animal seizure and epilepsy models to define their in vivo anticonvulsant profile. This is not to imply that target-driven discovery is not employed in the discovery of investigational AEDs. As reviewed here, a number of the drugs in development have emerged from very focused programs designed around a "validated" molecular target.

Many of the drugs reviewed in this chapter will likely emerge from clinical studies over the next 2 to 5 years, and at least some of these new agents will offer some level of improvement to the multitude of patients whose seizures are not fully controlled with existing anticonvulsants. Whether any of these drugs will lead to complete seizure freedom in a major proportion of refractory patients or emerge ultimately as first-line agents for the treatment of one or more types of epilepsy has yet to be determined.

Brivaracetam (UCB 34714) and Seletracetam (UCB 44212)

Structure and Chemistry

Brivaracetam, (2S)-2-[(4R)-2-oxo-4-propylpyrolidinyl]bu-tanamide, and seletracetam, (2S)-2-[(4S)-4-(2,2,difluorovinyl)-2-oxopyrrolidin-1-yl] butanamide, are two very potent levetiracetam analogs in clinical development by UCB Pharma (Fig. 1).

Pharmacology

The development of brivaracetam and seletracetam stems from the recognition that the action of levetiracetam is related to its ability to bind with a novel site identified as synaptic vesicle protein 2A (SV2A).[95] The demonstration that the efficacy of levetiracetam and a series of analogs is correlated with their SV2A binding affinity stimulated a drug-discovery program at UCB to identify compounds with higher affinity for SV2A than levetiracetam. Seletracetam and brivaracetam emerged from this effort, wherein approximately 12,000 compounds were initially screened against SV2A.[64] These two analogs were chosen from 900 that were selected for in vivo evaluation in the audiogenic seizure-susceptible mouse, and from 30 that were subsequently selected for more extensive evaluation in the kindling model.

Seletracetam appears to be a more potent analog that shares a similar anticonvulsant profile with levetiracetam. For example, seletracetam is not active in the traditional maximal electroshock (MES) or pentylenetetrazole (PTZ) seizure models but is more potent than levetiracetam in the corneal-kindled mouse (10-fold) and the genetic absence epilepsy rat from Strasbourg (GAERS) model of spike-and-wave epilepsy (25-fold). In addition to increased potency, seletracetam also appears to possess an even higher protective index (i.e., the ratio of a drug's median toxic dose to its median effective dose) in animal models than does levetiracetam.[104]

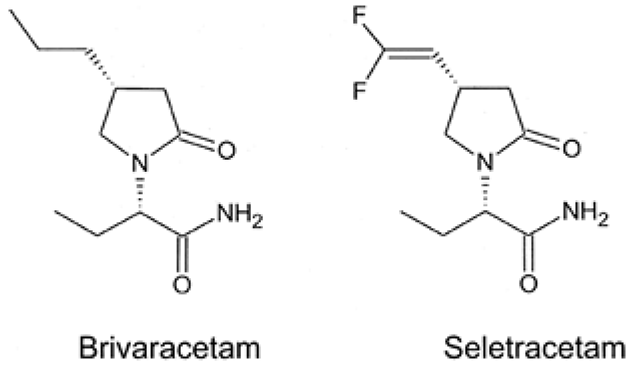


FIGURE 1. Structure of brivaracetam and seletracetam.

Brivaracetam differs from both levetiracetam and seletracetam in that it appears to possess a slightly broader activity spectrum in animal seizure models, and it is active in the MES and PTZ seizure tests. These effects of brivaracetam are thought to be related to its modest inhibition of sodium (Na) channels.[129,175] Brivaracetam also appears to be more effective than levetiracetam in its ability to suppress both the behavioral seizure and electrographic afterdischarge in the amygdala-kindled rat model of partial epilepsy. In addition to its more potent action against the fully expressed kindled seizure, brivaracetam also appears to be more potent and more effective than levetiracetam in preventing the acquisition of corneal kindling.[103]

At the cellular level, brivaracetam does not directly display any direct effects on γ-aminobutyric acid (GABA)-, glycine-, kainic acid-, or α-amino-3-hydroxy 5 methyl isoxazole 4 propionate (AMPA)-gated currents.[128] It has been found to exert a small inhibitory effect on the amplitude of the plateau phase of *N*-methyl-D-aspartate (NMDA)-evoked currents.[127] Seletracetam also appears to be a potent inhibitor of high-voltage activated (HVA) calcium (Ca^{2+}) currents.[121] Results from combination studies conducted with seletracetam, ω-conotoxin GVIA and ω-conotoxin MVIIC suggest that this effect of seletracetam is mediated by both N- and Q-type HVA channels. In addition, seletracetam has also been found to reverse the inhibitory effect of zinc and ß-carboline inhibition of glycine-gated currents.[127] In contrast to brivaracetam, seletracetam is inactive at voltage-gated Na^+ channels.[175]

Low concentrations of brivaracetam (1–10 μM) suppress high potassium (K), low calcium (Ca)-induced epileptiform bursting in hippocampal slices.[100] Levetiracetam has been shown to exert a similar action but requires substantially higher (i.e., 32 μM) concentrations. Brivaracetam (3.2 μM) differs from levetiracetam in that it is also capable of reducing spontaneous bursting; whereas levetiracetam is inactive at concentrations up to 32 μM. The ability of brivaracetam to inhibit spontaneous bursting may be related to its inhibitory effect on voltage-activated Na^+ currents.[176]

Brivaracetam has also been found to be effective at nontoxic doses in two models of neuropathic pain, including chronic constriction injury and streptozocin-induced diabetes.[76] Similarly, brivaracetam was found to be very efficacious in the harmaline-induced tremor model.[36]

Pharmacokinetics

To date, published clinical information is available only for brivaracetam. After single doses up to 1,400 mg and multiple doses up to 800 mg/day in healthy volunteers, brivaracetam is rapidly absorbed from the gastrointestinal tract, with a median time of peak concentration at 1 hour.[99] Plasma drug levels increase proportionally with dose.[131] Concomitant intake of food does not affect extent of exposure, but the rate of absorption is lower and peak concentrations are reduced by about 30%.

The half-life of brivaracetam in healthy volunteers is in the range of 6 to 11 hours (average 7.7 hours).[99] Only a minor fraction of the apparent oral clearance (CL/F) of brivaracetam is accounted for by renal clearance of unchanged drug.[131] Identified urinary metabolites include 2-(2-oxo-4-propylpyrrolidin-1yl)butyric acid and 2-(2-oxo-4-propylpyr-rolidin-1yl)-4-hydroxybutanamide.[99]

Efficacy and Adverse Effects

In a Phase II study in 19 photosensitive epilepsy patients, single oral doses of brivaracetam ranging from 10 to 80 mg were effective in reducing the photoparoxysmal electroencephalographic response, which was abolished in 78% of patients.[63a,99] The 80 mg dose was most effective in terms of time to reach the maximal response and duration of response. Median time to maximal response for all doses was 0.5 hours and median duration of effect was about 28 hours after 10, 20, or 40 mg, and 59.5 hours after 80 mg.

In healthy volunteers given single doses up to 800 mg/day and multiple doses up to 800 mg/day, adverse events were usually dose-related and included dizziness, somnolence, headache, nausea, and euphoric mood.[99] In the photosensitivity study, the adverse effect profile was similar to that reported in healthy volunteers.

Eslicarbazepine Acetate (S-Licarbazepine Acetate, BIA 2-093)

Structure and Chemistry

Eslicarbazepine acetate (S-licarbazepine acetate, BIA 2-093), *S*-(-)-10-acetoxy-10,11-dihydro-5H-dibenzo/b,f/azepine-5-car-boxamide, is structurally related to carbamazepine and oxcarbazepine in that it shares the dibenzazepine nucleus[53] (Fig. 2). In this respect, eslicarbazepine acetate was designed by BIAL, Portugal, to be a potentially improved alternative to carbamazepine and oxcarbazepine. However, as shown in FIGURE 2, it is important to note that oxcarbazepine is metabolized to (*S*)-licarbazepine (eslicarbazepine) and (*R*)-licarbazepine in a 4:1 ratio. Thus, the only difference between oxcarbazepine and eslicarbazine acetate is that eslicarbazepine acetate is only metabolized to the (*S*)-enantiomer with minor chiral conversion to the (*R*)-enantiomer, whereas oxcarbazepine is converted to both the (*S*)- and (*R*)-enantiomers.[a] Given that there is no evidence to suggest that the (*R*)-enantiomer is more toxic than the (*S*)-enantiomer or that it interferes with the efficacy of the (*S*)-enantiomer, it is not likely that eslicarbazepine acetate will provide any major advantage over oxcarbazepine. In fact, in the MES test, the less potent (*R*)-enantiomer displays an equivalent, if not more favorable protective index (i.e., the ratio of the median toxic dose in the rotorod test to the median MES efficacious dose) than the (*S*)-enantiomer.[15]

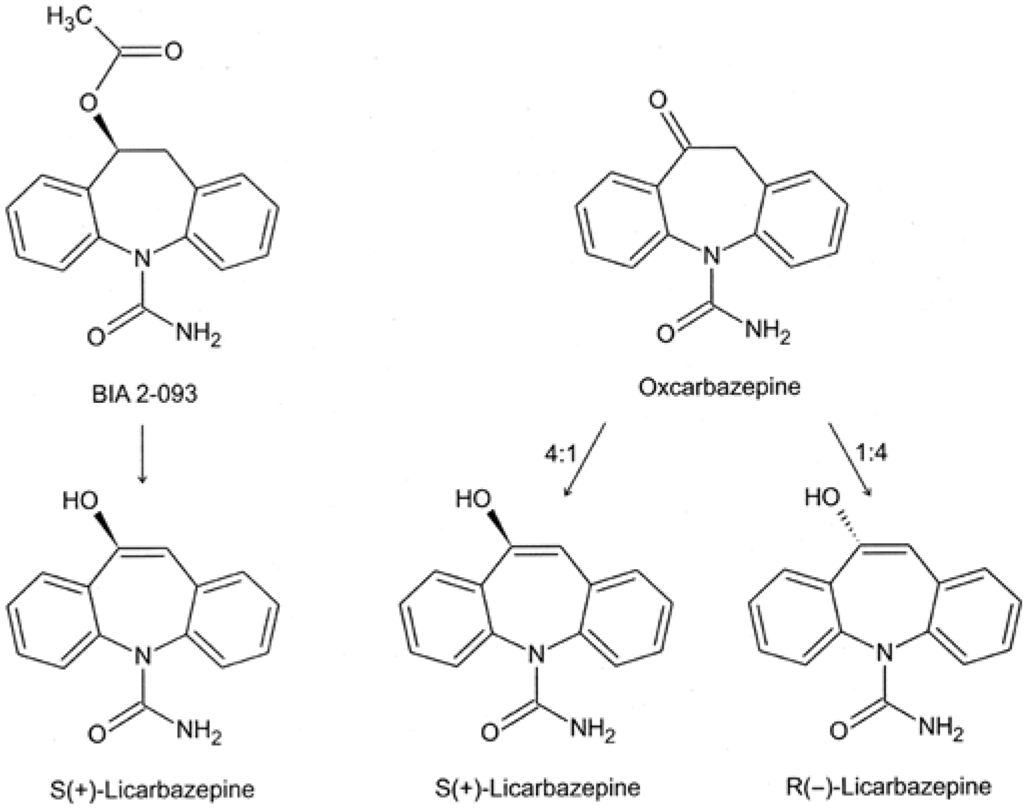


FIGURE 2. Structure of eslicarbazepine acetate (BIA 2-093) and ox-carbazepine. Eslicarbazepine is rap-idly metabolized to its active meta bolite *S*(+)-licarbazepine. Oxcarbazepine is also converted to its mono-hydroxy derivatives *S*(+)-licar-bazepine and *R*(-)-licarbazepine in a 4:1 ratio. (Modified from Rogawski MA. Diverse mechanisms of antiep-ileptic drugs in the development pipeline. Epilepsy Res. 2006;69(3):273–294, with permission.)

Pharmacology

Eslicarbazepine acetate behaves very much like carbamazepine and oxcarbazepine in animal seizure and epilepsy models.

It is effective against tonic extension seizures induced by MES and focal seizures in the amygdala-kindled rat model of partial epilepsy.[15] Like carbamazepine and oxcarbazepine, eslicarbazepine is mostly inactive against clonic seizures induced by PTZ. This activity profile would predict efficacy in humans against generalized tonic–clonic seizures and partial seizures, respectively.[168] In these models, eslicarbazepine acetate is equipotent to carbamazepine and more potent than oxcarbazepine.

Mechanistically, eslicarbazepine displays a voltage-depen-dent block of voltage-dependent Na currents.[21] In a manner similar to other voltage-sensitive Na channel blockers, eslicarbazepine inhibits Na-dependent neurotransmitter release at concentrations similar to those observed for carba-mazepine and oxcarbazepine.[6,116]

Pharmacokinetics

After oral administration of single and multiple doses, unchanged eslicarbazepine acetate is generally undetectable (<10 ng/mL) in plasma.[4,5] Eslicarbazepine acetate is rapidly and extensively converted to (*S*)-licarbazepine, whose chemical structure corresponds to the *S*-enantiomer of 10-hydroxy-carbazepine, the active mono-hydroxy-metabolite of oxcarbazepine.[4,5,15,53] Chiral conversion of (*S*)-licarbazepine to (*R*)-licarbazepine is minor, and only about 5% of circulating licarbazepine is in the *R*-form[2,18]; by contrast, after administration of oxcarbazepine, the ratio between (*R*)- and (*S*)-licarbazepine in blood is on the order of 20% to 25%.[164]

Peak plasma concentrations of licarbazepine occur 0.75 to 4 hours after single oral doses of eslicarbazepine acetate ranging between 20 and 1,200 mg.[4] The bioavailability of licarbazepine, measured in terms of area under the curve (AUC), is about 16% greater than that observed after an equivalent molar dose of oxcarbazepine.[18] The pharmacokinetic profile of licarbazepine is not affected by coadministration of eslicarbazepine acetate with food.[98] Bioequivalence between a suspension and a tablet form has been demonstrated.[49]

During multiple doses ranging from 200 mg twice a day to 2,400 mg once daily, peak licarbazepine concentrations are usually observed 2 to 3 hours after each dose intake, and steady-state concentrations are reached within 4 to 5 days of once or twice daily administration.[5,162] The extent of systemic exposure to licarbazepine increases in an approximately dose-proportional manner after both single and multiple doses.

The half-life of licarbazepine has been estimated to be in the range of 8 to 17 hours after single doses and 9 to 13 hours after multiple dosing,[2,4,5] although an “effective” half-life of 17 to 24 hours has been inferred from the time taken to reach steady-state.[2,5] Licarbazepine is excreted in urine in free and conjugated form, with about 20% and 40% of the dose being recovered within 12 and 24 hours post-dose respectively.[3,4,5] Oxcarbazepine has been detected as a minor metabolite.[4]

In a study that compared the plasma levels of (*R*)- and (*S*)-licarbazepine after single (600 mg) and multiple doses (600 mg once daily for 8 days) in 12 young (mean age 30 years, range 18–38) and 12 elderly (mean age 70 years, range 65–80) healthy volunteers, no pharmacokinetic differences were identified between the two age groups.[2]

Drug Interactions

Because licarbazepine clearance in patients taking oxcarbazepine is known to be moderately increased by coadministration of enzyme-inducing AEDs,[106] it is reasonable to assume that a similar interaction may apply to licarbazepine derived from eslicarbazepine acetate.

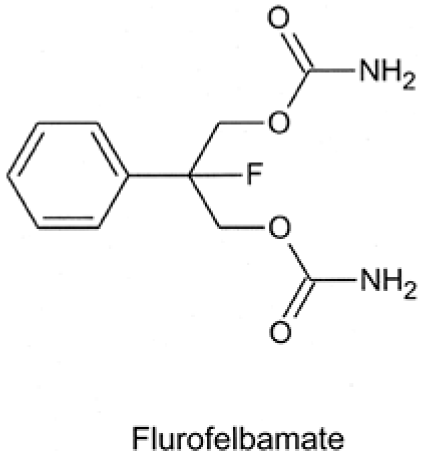


FIGURE 3. Structure of fluorofelbamate.

In healthy subjects, eslicarbazepine acetate at a dosage of 1,200 mg/day did not affect the pharmacokinetics of digoxin to a clinically significant extent.[97] Whether eslicarbazepine acetate shares with oxcarbazepine the ability to stimulate the metabolism of steroid oral contraceptives and other substrates has not been reported.

Clinical Efficacy

A multicenter double-blind, parallel-group, adjunctive-therapy study compared once daily and twice daily eslicarbazepine acetate (at escalating doses of 400, 800, and 1,200 mg/day, each for 4-week periods) with placebo in 143 patients with refractory partial seizures.[18,96] The proportion of responders (defined as patients showing at least 50% seizure reduction) during the 800- and 1,200-mg/day periods were significantly higher in the once-daily group than in the placebo group, and there were no statistically significant differences in responder rates between the once- and twice-daily group.

Adverse Effects

In healthy volunteers, single and multiple doses of eslicarbazepine acetate up to 1,200 mg and 1,200 mg/day, respectively were tolerated well.[3,5] In the adjunctive therapy trial, tolerability was rated as good or very good in 90% of patients in the once-daily group, 80% in the twice-daily group, and 83% in the placebo group.[18]

Fluorofelbamate

Structure and Chemistry

Fluorofelbamate (2-phenyl-2-fluoro-1,3 propanediol dicarbamate) is a felbamate analog designed to have the clinical efficacy of felbamate without its serious adverse effects (i.e., aplastic anemia and hepatic toxicity). Structurally, fluorofelbamate differs from felbamate in that it possesses a fluorine atom instead of a hydrogen at the 2-position of the propanediol moiety (Fig. 3). This substitution is thought to result in a more stable molecule and to prevent the production of atropaldehyde (ATPAL, or 2-phenylpropenal), the proposed toxic reactive metabolite of felbamate.[154] Fluorofelbamate is being developed by MedPointe Healthcare, Inc.

Pharmacology

Fluorofelbamate, like felbamate, is active against a variety of electrically and chemically induced seizures in animal models.[18] In addition to blocking tonic extension in the MES test, it also blocks clonic seizures induced by picrotoxin, and sound-induced seizures in the Frings mouse. Fluorofelbamate (100 and 200 mg/kg) is also quite effective in reducing the cumulative seizure duration in the perforant path model of self-sustaining status epilepticus (SE) when administered early. Slightly higher doses (i.e., 200 and 300 mg/kg) attenuated seizures in the self-sustaining status model when administered late and at a time when the status was refractory to treatment with conventional anticonvulsants.[107]

In addition to is anticonvulsant activity, fluorofelbamate has been reported to be neuroprotective in several models. For example, it decreases neuronal damage in an in vitro chemical model of ischemia (i.e., NaCN), protects against hypoxic CA1 hippocampal neuronal damage in an in vitro slice model, decreases the infarct volume in an in vivo rat pup model of hypoxia, and reduces CA1 damage associated with transient global ischemia in gerbils.[18,166]

Limited in vitro data are available regarding the mechanism of action of fluorofelbamate. Based on the electrophysiologic studies thus far reported, it would appear that fluorofelbamate is not a potent modulator of either inhibitory- or excitatory-mediated neurotransmission. It has been reported to produce a modest inhibition of kainate- and NMDA-mediated currents in mouse cortical neurons and to exert a modest inhibition of voltage-dependent Na currents in NIE-115 neuroblastoma cells.[18,129] It is not clear whether these modest effects are sufficient to account for its seemingly broad anticonvulsant and neuroprotective profile in animal models.

Pharmacokinetics

Based on evidence suggesting that a reactive metabolite, ATPAL, may be responsible for the toxicities observed during therapy with felbamate, Parker et al.[117] tested the hypothesis that fluorofelbamate would not be metabolized to ATPAL. They compared the metabolism by in vitro human liver postmitochondrial suspensions (S9) of selected felbamate and postulated fluorofelbamate metabolites and concluded that fluorofelbamate is not metabolized in vitro by S9 to ATPAL.

In pharmacokinetic studies in rats and dogs, exposure increased proportionally with dose. In dogs, peak plasma concentrations were reached in 2 to 6 hours, and the terminal half-life was estimated at 6 to 9 hours.[18] No studies in humans have been reported to establish fluorofelbamate pharmacokinetics, interaction potential, efficacy, or adverse-effect profiles.

Ganaxolone (CCD 1042)

Structure and Chemistry

Ganaxolone, 3α-hydroxy-3β-methyl-5 α-pregnan-20-one, is the 3β-methyl analog of the endogenous steroid allopregnanolone and is a potent positive modulator of $GABA_A$ receptors. It is currently under development by Marinus Pharmaceuticals (Fig. 4).

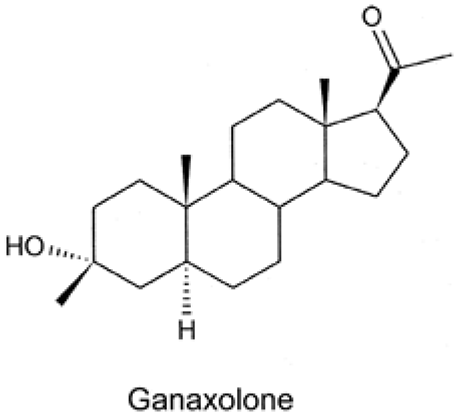


FIGURE 4. Structure of ganaxolone.

Pharmacology

In seizure and epilepsy models, ganaxolone is effective against clonic seizures induced by PTZ and bicuculline.[25] At nontoxic doses, ganaxolone is less active against tonic extension seizures induced by MES. It is also active against seizures induced by aminophylline, τ-butyl-bicyclo-phosphorothionate, and fluorothyl (see Perucca and Kupferberg[120a], for review and references). Ganaxolone has also shown activity in the 6-Hz model of pharmacoresistent partial epilepsy,[61] is active in acute SE models,[70] and demonstrated efficacy against partial seizures in the corneal- and amygdala-kindled rat models.[25,126] In contrast to the benzodiazepines, the anticonvulsant activity of ganaxolone in animal models is not diminished with chronic treatment.

Ganaxolone is a potent positive modulator of $GABA_A$-evoked currents. It is active at $GABA_A$ receptors containing most αsubunits, including α1, α2, α3, α4, and α6. Unlike the benzodiazepines, the activity of most neurosteroids at the $GABA_A$ receptor is not dependent on the presence of a γ2 subunit.[25] Interestingly, GABA receptors containing a δ-subunit are particularly sensitive to modulation by neurosteroids.[129,169] Because of their presynaptic and extrasynaptic localization,[43,113] δ-subunits containing $GABA_A$ receptors are ideally suited to mediate tonic currents and may represent an important molecular target for ganaxolone and other potential neurosteroids.[129]

Pharmacokinetics

Seven different studies in normal volunteers were performed examining the pharmacokinetics of ganaxolone after single (50 to 1,500 mg) and multiple dose regimens (≤300 b.i.d. for 10 days or 500 mg once daily for 2 weeks).[110] Because ganaxolone is highly insoluble in aqueous media, it has been formulated as a solution complexed with ß-cyclodextrin or 2-hydroxypropyl-ß-cyclodextrin to enhance bioavailability.

After oral dosing, ganaxolone is absorbed rapidly, and peak plasma levels are generally attained within 3 hours. Absorption is followed by a biphasic elimination phase, with a rapid decline in plasma concentration over the first 12 hours and a subsequent slower decline characterized by a terminal half-life of 37 to 70 hours.[110] Plasma concentrations after multiple doses are similar in shape to those observed after single doses, with a sharp decrease in plasma levels over the first 12 hours. Accumulation is limited, as indicated by a lack of increasing trough levels during repeated dosing. The pharmacokinetics of ganaxolone appear to be linear, with mean peak plasma levels at steady state ranging from 32 ng/mL at 50 mg once daily to 376 ng/mL at 500 mg once daily.

Drug Interactions

In children aged 7 months to 7 years with infantile spasms, no consistent changes in the serum levels of concomitant AEDs with administration of ganaxolone were observed.[66]

Clinical Efficacy

A double-blind, randomized, placebo-controlled trial to examine the safety, tolerability, and antiepileptic activity of ganaxolone after withdrawal from other AEDs during presurgical evaluations was performed in 52 patients who were randomized to receive ganaxolone (24 patients) or placebo (28 patients) for up to 8 days.[78] Ganaxolone was administered at a dose of 1,500 mg/day on day 1 and 1,875 mg/day on days 2 to 8. Dosing occurred three times per day. The primary endpoint was time to withdrawal from the trial. Intent-to-treat survival analyses revealed a trend toward efficacy with ganaxolone ($p = 0.0795$, log rank test). Kaplan-Meier curves depicted a clear separation between treatment groups, with 50% of the ganaxolone-treated patients completing the entire study, compared with 25% of patients treated with placebo. Covariate analyses revealed a significant treatment effect on survival time in men ($p = 0.03$). Post-hoc analyses focusing on patients who completed the entire study revealed a significant difference ($p = 0.04$) between treatment groups. A clear relationship between trough serum concentrations and efficacy was not evident.

A multicenter, open-label, add-on trial investigated the safety and efficacy of ganaxolone in 20 children (age 7 months to 7 years) with refractory infantile spasms, or with continuous seizures after a prior history of infantile spasms.[66] The dose of ganaxolone was increased to 36 mg/kg per day (or to the maximally tolerated dose) over 4 weeks, then maintained for 8 weeks before tapering off. The frequency of spasms was reduced by at least 50% in 33% of the subjects with spasms, with an additional 33% experiencing some improvement (25%–50% reduction in spasms frequency). In these subjects with highly variable sampling times, a ganaxolone concentration-response curve could not be established.

Adverse Effects

In normal volunteers, ganaxolone was well tolerated after single doses (≤1,500 mg) and multiple doses (≤300 mg b.i.d. for 10 days).[110] No serious or life-threatening adverse events attributed to the drug were observed. The majority of adverse events were mild (82%) to moderate (14%) and were limited to headache, dizziness, somnolence, gastrointestinal disturbances, and malaise. There was no apparent effect on electrocardiogram (ECG) or vital signs.

In the presurgical study of Laxer et al.,[78] 47 adverse events were reported in the ganaxolone group and 38 in the placebo group. Central nervous system (CNS) adverse effects occurred in both groups, with dizziness being the most common complaint. Two serious adverse events occurred; one patient receiving ganaxolone experienced agitation and depression on the first day of treatment, and one patient receiving placebo experienced postictal psychosis.

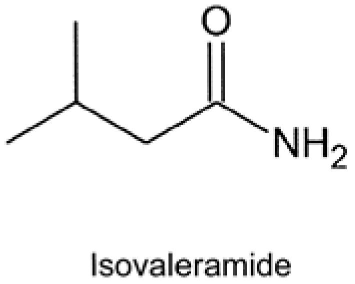


FIGURE 5. Structure of isovaleramide.

In the infantile spasms study, the most common adverse events thought to be possibly, probably, or definitely related to ganaxolone were somnolence, diarrhea, nervousness, and vomiting.[66] In another open-label pediatric study in 15 children aged 5 to 15 years treated with doses up to 12 mg/kg three times a day, adverse events included somnolence, sleep disturbances, nervousness, constipation, change in seizure types and, in one case, disturbed behavior and cognition.[79]

Isovaleramide (NPS 1776)

Structure and Chemistry

Isovaleramide (NPS 1776), 3-methylbutanamide, is a low-molecular-weight, branched-chain amide that displays a broad-spectrum of activity in animal models (Fig. 5). It is being developed by NPS Pharmaceuticals.

Pharmacology

In animal seizure and epilepsy models, NPS 1776 possesses an anticonvulsant profile similar to that of valproate (VPA). It is orally active against tonic extension seizures in the MES test and clonic seizures induced by PTZ, bicuculline, and picrotoxin. Furthermore, it is effective in reducing the behavioral seizure score in both the corneal- and amygdala-kindled rat models of partial epilepsy, and it reduces the afterdischarge duration in the amygdala-kindled rat. Daily dosing with NPS 1776 has also been found to delay the acquisition of kindling in the amygdala-kindled rat, thereby suggesting that this compound, like VPA, may exhibit antiepileptogenic effects. NPS 1776 is also effective in two genetic seizure models (i.e., the Frings audiogenic seizure susceptible mouse and the Wistar rat). In the Wistar rat, NPS 1776 was found to reduce the spontaneous electrographic spike-and-wave discharges. In a chronic dosing study in the Frings audiogenic seizure-susceptible mouse, no sign of tolerance was observed following daily dosing with NPS 1776 for 28 days. Overall, the preclinical anticonvulsant profile of NPS 1776 suggests that it will have broad-spectrum efficacy against partial and generalized seizures.[16,18,167] In addition to its anticonvulsant action, NPS 1776 has been found to possess antispastic, analgesic, and anxiolytic activity.[18]

To date, the mechanism of action of NPS 1776 has not been elucidated. It is inactive in in vitro binding and uptake assays against a number of receptor- and voltage-active ion channels at a concentration of 1,000 μM, suggesting that it does not exert an action through a direct interaction at the sites studied.[18]

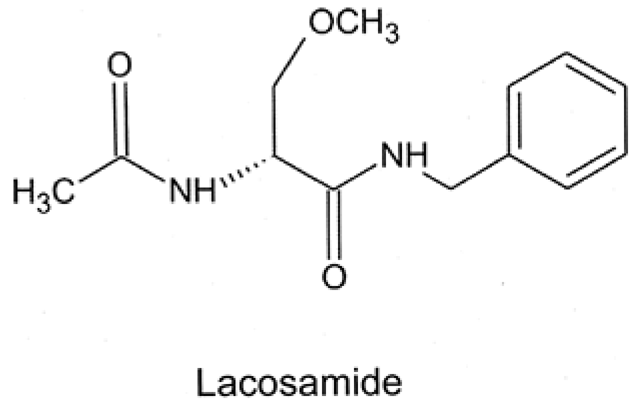


FIGURE 6. Structure of lacosamide.

Pharmacokinetics

After single and multiple doses up to 1,600 mg and 2,400 mg/day, respectively in healthy volunteers, isovaleramide is rapidly absorbed from the gastrointestinal tract.[18] The increase in systemic exposure with increasing dose is slightly more than dose-proportional after single doses, but no major deviations from linearity were observed after multiple dosing.

Isovaleramide is negligibly bound to plasma proteins and is rapidly eliminated with a half-life of 2 to 4 hours. Less than 4% of an orally administered dose is excreted unchanged in urine, and elimination is primarily metabolic. A sustained-release formulation is under development.[18]

Drug Interactions

In vitro, isovaleramide does not inhibit any of the major CYP isoenzymes.[18]

Efficacy and Tolerability

Isovaleramide has shown excellent tolerability in Phase I studies in healthy volunteers. Clinical studies have been initiated to assess its potential value in the treatment of epilepsy and in the acute treatment of migraine, but no results have been reported to date.[18]

Lacosamide (Harkoseride, SPM 927)

Structure and Chemistry

Lacosamide, also formerly known as harkoseride and SPM927, is the *R*-enantiomer of 2-acetamido-*N*-benzyl-3-methoxy-propionamide. It is currently under development by Schwarz BioSciences for the treatment of partial epilepsy and neuropathic pain (Fig. 6).

Pharmacology

Lacosamide displays broad-spectrum anticonvulsant activity in rodent models of generalized and partial epilepsy.[18,148] It is effective against audiogenic seizures in Frings mice and is a potent blocker of MES-induced tonic extension seizures in mice and rats. Lacosamide is less effective against clonic seizures induced by PTZ, but it is quite potent against limbic seizures in the 6-Hz psychomotor seizure model of pharmacoresistant epilepsy.[40] Lacosamide is also very effective in blocking both the behavioral seizure and afterdischarge duration in the hippocampal-kindled rat model of partial epilepsy. Last, lacosamide is effective in reducing the cumulative seizure duration in the perforant path model of self-sustaining SE. In addition to its effects in seizure and epilepsy models, lacosamide has demonstrated

an ability to attenuate the acquisition of amygdala kindling and displays in vitro and in vivo neuroprotective properties. For example, lacosamide has been shown to delay the development of amygdala kindling at doses of 10 and 30 mg/kg.[23] Furthermore, it decreased the infarct volume in the rat middle cerebral artery occlusion (MCAO) model of ischemia when administered 15 minutes before MCAO and for 4 hours postinfusion.[122] In contrast, lacosamide was ineffective in preventing brain damage or functional deficits in a rat model of traumatic brain injury.[122] In organotypic rat hippocampal slice cultures, lacosamide produced a concentration-dependent block of glutamate- and oxygen-glucose deprivation–induced apoptosis. These latter effects might suggest that lacosamide possesses a disease-modifying effect; however, additional studies are required to fully evaluate this potential attribute.

Lacosamide is effective in various animal models of chronic pain.[149] For example, it is active in the formalin, carrageenan model, and the adjuvant-induced arthritis models of chronic pain. The results from these studies support the ongoing clinical investigations in the treatment of pain associated with diabetic neuropathy.

From a mechanistic perspective, more can be said about what lacosamide does not do at the cellular level than what it does do. To date, little is known about the molecular mechanism underlying its broad-spectrum anticonvulsant profile.[129] Lacosamide does not directly interact with GABAergic or glutamatergic neurotransmission. It does not block sustained repetitive firing or voltage-dependent Na currents. Furthermore, it does not enhance K currents or attenuate Ca currents. Lacosamide does appear to block slow but not fast depolarization-induced action potential firing in cultured cortical neurons. Like carbamazepine, lacosamide is effective in the 4-amino-pyridine (4-AP) model of epileptiform bursting, and its activity in this model, unlike that of carbamazepine, is completely reversible.[80] The results obtained to date suggest that lacosamide has a potentially unique mechanism of action relative to a majority of the available AEDs.

Pharmacokinetics

Lacosamide is efficiently absorbed from the gastrointestinal tract, with peak plasma concentrations being achieved within 1 to 5 hours of dosing.[18,75] Oral bioavailability is virtually complete, as documented by the observation that plasma lacosamide levels after the administration of the same dose using either oral tablets or 30- or 60-minute intravenous infusions meet criteria for bioequivalence.[75,132] Concomitant intake of food has no effect on the rate or extent of lacosamide absorption,[27] and plasma concentrations are linearly related to dose over the 100- to 800-mg dose range.[132]

Lacosamide is negligibly (<10%) bound to plasma proteins.[18] The half-life is on the order of 12 to 16 hours, and elimination occurs partly by renal excretion in unchanged form and partly by biotransformation. About 40% of an orally administered dose is recovered unchanged in urine, and another 30% is recovered in the form of the inactive *O*-dimethyl-metabolite SPM 12809.[18,75,140] In a study designed to assess the potential role of CYP2C19 on lacosamide disposition, plasma lacosamide levels after oral and intravenous administration were similar in eight extensive metabolizers and three poor metabolizers for CYP2C19. However, the plasma levels of the *O*-demethyl-metabolite were markedly reduced in the poor metabolizers, suggesting that CYP2C19 contributes to lacosamide demethylation.[74]

After normalization for dose and differences in body weight, plasma lacosamide concentrations do not differ significantly between males and females. In a multiple-dose study, plasma lacosamide concentrations at steady-state in 23 elderly subjects (≥65 years, age range not stated) were about 10% to 35% higher than those observed in a similar cohort of subjects aged 18 to 45 years.[140]

Drug Interactions

In studies conducted in healthy volunteers, lacosamide pharmacokinetics were not affected by coadministration of carbamazepine 400 mg/day or valproic acid 600 mg/day.[74]

In vitro, lacosamide shows no potential to inhibit CYP1A2, CYP2A6, CYP2C9, CYP2D6, CY2E1, and CYP3A4 in human hepatocytes.[74] In studies with human recombinant CYPs, lacosamide inhibits CYP2C19, but the median inhibitory concentration (0.45 mg/mL) is greater than the anticipated human therapeutic plasma levels. Lacosamide does not induce CYP1A2 and CYP3A4 activity in human hepatocytes.

In healthy volunteers, lacosamide (400 mg/day) has been found not to affect the pharmacokinetics of carbamazepine, valproic acid, metformin, digoxin, ethinylestradiol, and levo-norgestrel. Likewise, clinical trials in patients receiving adjunctive treatment with lacosamide at dosages up to 600 mg/day did not identify any change in serum levels of carbamazepine, carbamazepine-10,11-epoxide, phenytoin, valproic acid, lamotrigine, mono-hydroxy-carbazepine, topiramate, zonisamide, levetiracetam, and gabapentin.[18,59,74]

Clinical Efficacy

Studies in Epilepsy

A multicenter, double-blind, randomized, parallel-group, placebo-controlled trial assessed lacosamide (200, 400, and 600 mg/day in two divided doses) as adjunctive therapy in 418 patients with refractory partial-onset seizures.[14,59] Lacosamide was titrated to target dose in 100 mg/day increments at 1-week intervals, followed by a 12-week maintenance phase. In the full analysis (ITT) data set, median reduction in seizure frequency (maintenance vs. baseline) was 10% on placebo, 26% at 200 mg/day, 39% at 400 mg/day, and 40% at 600 mg/day. Responder rates (proportion of patients with at least 50% seizure reduction) was 22% on placebo and 33%, 41%, and 38% at 200, 400, and 600 mg/day, respectively. Response rates at the 400- and 600-mg dose were statistically superior to placebo. The proportion of patients completing the maintenance period without major protocol deviations was 78%, 74%, and 60% in the 200, 400, and 600 mg/day groups, respectively, compared with 88% in the placebo group.[59] Follow-up observations in patients who continued open-label lacosamide after completion of the double-blind phase suggest that efficacy is maintained during long-term treatment.[35]

Studies in Neuropathic Pain

Lacosamide has been investigated in two multicenter, double-blind, randomized, parallel-group, placebo-controlled trials in patients with neuropathic pain attributed to distal diabetic neuropathy. One trial explored dosages of 200, 400, and 600 mg/day in a total of 370 patients,[170] while the second trial assessed 400 and 600 mg/day in 357 patients.[174] The study design involved gradual titration to the target dose and a 12-week maintenance period. In both studies, the best response was in the 400 mg/day dose groups. In one of the trials, the reduction in pain score in the 400-mg group was statistically significant compared with placebo,[170] while in the other the difference compared with placebo during the last 4 weeks of treatment failed to reach statistical significance.[174] Administration of a

600 mg/day dose did not appear to confer additional benefit in reducing pain scores, and was less tolerated.

Adverse Effects

In the adjunctive-therapy placebo-controlled trial in patients with partial onset seizures, the most commonly observed adverse events were dizziness, headache, fatigue, ataxia, gastrointestinal disturbances (nausea, vomiting), and visual disturbances (blurred vision, diplopia, and nystagmus), most of which were dose-related.[14] The most common of all events was dizziness, which was reported by 24%, 26%, and 55% of patients at 200, 400, and 600 mg/day, respectively, compared with 10% on placebo. The proportion of patients withdrawing due to adverse events was 5% on placebo, 11% at 200 mg/day, 19% at 400 mg/day, and 30% at 600 mg/day. Remarkably, there were little differences in proportion of patients reporting somnolence between the placebo and any lacosamide dose group.

A formulation of lacosamide for intravenous use is being developed to allow replacement therapy for patients temporarily unable to continue oral therapy. In healthy volunteers, adverse events after infusion of 200 mg lacosamide over periods of 15, 30, and 60 minutes were similar to those observed after intake of a 200-mg tablet.[75] Likewise, adverse events associated with 30- to 60-minute infusions (up to 300 mg b.i.d. for two days) given as replacement treatment in patients with epilepsy stabilized on oral lacosamide were comparable to those observed after oral dosing.[18,132]

Studies in Neuropathic Pain

In the first trial conducted in patients with neuropathic pain, the proportion of patients discontinuing treatment due to adverse events was 8.6%, 23.1%, and 39.8% in the placebo, 200, 400, and 600 mg/day groups, respectively.[170] In the second trial, discontinuation rates were 11.3% and 23.3% at 400 and 600 mg/day, respectively, compared with 5.4% on placebo.[174] In both trials, lacosamide was generally well tolerated, with similar rates of adverse events in the placebo and active treatment groups at doses up to 400 mg/day. In the 600 mg/day group, the incidence of dizziness (29.0% in the first study and 19.5% in the second study) was considerably higher than in the other groups.

Losigamone

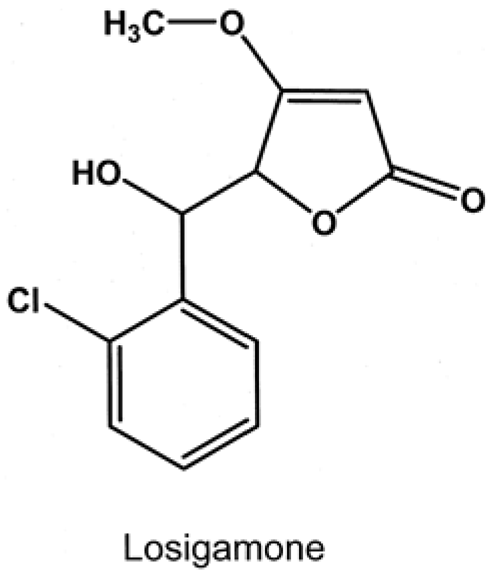


FIGURE 7. Structure of losigamone.

Structure and Chemistry

Losigamone, threo ±5(*S,R*)-5-[(2-chlorophenyl)hydroxyl-methyl)]-4-methoxy(5H)-furanone, is a racemic mixture that was synthesized at the Willmar Schwabe Company in Karlsruhe, Germany (Fig. 7).

Pharmacology

In most pharmacologic studies conducted to date, the *S*(+)-enantiomer of losigamone is more potent than the *R*(-)-enantiomer.[173] In animals, losigamone is active in blocking tonic hind limb extension induced by a number of stimuli including MES, PTZ, bicuculline, nicotine, and 4-aminopyridine but not strychnine or picrotoxin.[146] It is also effective against clonic seizures induced by PTZ, bicuculline, and picrotoxin.[146] In addition, losigamone has been shown to inhibit audiogenic seizures in rats and gerbils and to attenuate behavioral seizures in the PTZ-kindled mouse.[120]

Like many of the AEDs, the precise mechanism of action of losigamone has yet to be established. In the in vitro hippocampal slice preparation, losigamone has been demonstrated to reduce the frequency and amplitude of picrotoxin-, low Ca^{2+}/low magnesium (Mg^{2+}), and low Ca^{2+}/low Mg^{2+}/high K^+-induced seizure-like events in a concentration-dependent manner.[68,69,81,146] At higher concentrations, losigamone has been found to decrease the late recurrent epileptiform discharges in area CA1 and CA3 of the hippocampus and the ictiform events in the entorhinal cortex that develop following prolonged exposure to low-Mg^{2+} containing buffer.[173] Losigamone has also been shown to decrease depolarization-induced repetitive spike firing and stimulus-induced excitatory postsynaptic potentials in the entorhinal cortex slice preparation[141] and 4-aminopyridine-induced epileptiform activity in rat hippocampal slice preparation.[172] Losigamone does not appear to modify either fast or slow inhibitory postsynaptic potentials.[141]

At the cellular and molecular level, it is not clear how losigamone is exerting its effects in the in vitro slice studies that have been conducted to date. Losigamone has been shown to enhance GABA-mediated chloride (Cl) flux in vitro. For example, in the absence of exogenously applied GABA, losigamone increased Cl flux in cultured spinal cord neurons. In addition, it has been shown to enhance GABA-evoked Cl flux. These two effects of losigamone were both blocked by the Cl channel blocker picrotoxin and the $GABA_A$ receptor antagonist bicuculline. Interestingly, results from radio-ligand binding studies suggest that losigamone is not directly interacting with either the benzodiazepine or GABA receptor binding site (see Stein[70] for review and references). In addition, losigamone has been reported to decrease depolarizations induced by the glutamate agonist NMDA, but not those induced by AMPA.[144] In a separate study, *S*(+) losigamone, but not *R*(-) losigamone has been found to decrease both K- and veratridine-evoked glutamate and aspartate release from cortical slices.[60] Collectively, the results of these two latter studies suggest that losigamone may be exerting some of its anticonvulsant effects by modulating glutamate release.

Losigamone has been reported to decrease spontaneous synaptic activity in cultured hippocampal neurons and sustained repetitive firing evoked by somatic current injection.[39] In contrast to classical Na channel blockers, losigamone does not affect the fast transient Na current but instead inhibits the

persistent Na current in hippocampal neurons.[51] This is particularly interesting given that the persistent Na current has been implicated in the fine control of neuronal excitability. For example, it has been suggested that the persistent Na current can contribute to subthreshold oscillations that can determine the behavior of neuronal networks in a number of brain structures, including the neocortex and entorhinal cortex.[159] Through its action on the persistent Na current, losigamone may be acting to "fine tune" neuronal excitability, thereby reducing hyperexcitability without the adverse effects associated with those drugs that inhibit fast Na channels (see Errington et al.[41a] for further discussion and references).

Pharmacokinetics

After single oral doses up to 700 mg and multiple doses up to 600 mg three times a day, losigamone displays linear pharmacokinetics.[19,120] The compound is rapidly absorbed from the gastrointestinal tract, is approximately 50% bound to plasma proteins, and is eliminated primarily by oxidation and conjugation.[118,156,165] CYP2A6 appears to be a major enzyme involved in losigamone metabolism.[67,156]

The mean CL/F of losigamone racemate after single oral doses in healthy volunteers is on the order of 300 to 400 mL/min. There are, however, important pharmacokinetic differences between enantiomers, due to stereoselectivity in drug metabolism: In particular, CL/F values of the (*R*–)-enantiomer are more than 10-fold greater than those of the *S*(+)-enantiomer, and the *R*(-)-enantiomer also shows more extensive first-pass metabolism after oral dosing.[118,120,156] The half-lives of the *R*(-)- and *S*(+)-enantiomer are on the order of 2.2 and 4.8 hours respectively.

Drug Interactions

In studies using nonenantioselective assays, losigamone CL/F values in patients taking enzyme-inducing AEDs such as carbamazepine and phenytoin have been on the order of 500 to 600 mL/minute, which are higher than those observed in healthy volunteers. Patients taking enzyme-inducing AEDs also show relatively shorter losigamone half-lives (about 3.8 hours) and steady-state plasma losigamone levels which are about one-third lower than in patients not taking enzyme inducers.[71] Valproic acid and lamotrigine do not affect losigamone pharmacokinetics to an important extent.[37,72]

Losigamone does not appear to have enzyme-inducing properties[19]; does not affect the serum concentration of phenyt-oin, carbamazepine, carbamazepine-10,11-epoxide, and lam-otrigine[71,120,137]; and does not influence significantly the pharmacokinetics of a combined steroid oral contraceptive.[38] Losigamone may, however, reduce slightly the serum concentration of valproic acid.[72,73]

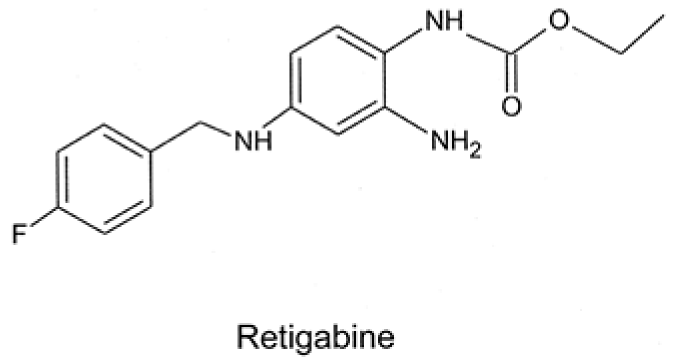


FIGURE 8. Structure of retigabine.

Clinical Efficacy

A first double-blind, multicenter, placebo-controlled study explored the potential efficacy of losigamone (500 mg t.i.d) in 203 patients with partial seizures.[11] Median percent reduction in seizure frequency was 15% in the losigamone group compared with 7% in the placebo group ($p = 0.004$); however, there were no statistically significant differences in the proportion of patients achieving at least 50% seizure reduction (losigamone, 22% vs. placebo, 15%). In a second trial using a similar design, 264 patients with refractory partial seizures were randomized to receive adjunctive treatment with placebo, losigamone 400 mg three times a day, or losigamone 500 mg three times a day for 12 weeks.[12] Median reduction in partial seizure frequency was 3% for placebo, 20% for losigamone 1,200 mg/day, and 25% for losigamone 1,500 mg/day, with the difference in both active treatment groups being significant ($p < 0.01$) in comparison with placebo. Responder rates were 12% for placebo versus 17% and 29% for the 1,200 mg/day and 1,500 mg/day groups respectively, the difference being significant ($p = 0.004$) for the higher dose group. The authors concluded “that it might be promising to study higher dosages in the future and that the potential of the drug has not yet been entirely explored.” In addition to the adjunctive therapy studies summarized here, some evidence for losigamone efficacy against partial seizures has been provided in a short presurgical monotherapy trial.[145]

Adverse Effects

In the first double-blind trial, adverse events were reported in 60% of patients in the losigamone group compared with 38% on placebo.[11] In the second trial, corresponding proportions were 59% on placebo, 66% on losigamone 1,200 mg/day, and 76% on losigamone 1,500 mg/day.[12] Adverse effects most commonly reported with losigamone include dizziness, sedation, fatigue, visual disturbances, vertigo, ataxia, and anorexia. The majority of these typically occur in less than 15% of patients, and the suggestion has been made that they might be reduced by slow dose titration.[12] An increase in serum cholesterol, γ-glutamyltransferase, and other liver enzymes has been described, but the clinical significance of these findings is uncertain.[12,120]

Retigabine (D23129)

Structure and Chemistry

Retigabine, *N*-[2-amino-4-(-4-fluorobenzylamino)-phenyl]car-bamic acid ethyl ester, is a structurally novel AED in devel-opment by Valeant Pharmaceuticals, Costa Mesa, CA (Fig. 8).

Pharmacology

Retigabine is truly a broad-spectrum AED in animal models.[133] It is effective against electrical (MES), chemical (PTZ, picrotoxin, penicillin, kainate, intracerebroventricular administered NMDA), and genetic (genetically epilepsy-prone rats and audiogenic seizure–susceptible mice) seizures (see Perucca and Kupferberg[120a] for review and references). Similarly, retigabine is effective in blocking the fully expressed behavioral seizure

and decreasing the duration of electrographic afterdischarge in the fully kindled rat.[155]

Retigabine has been found to prevent the acquisition of kindling in the amygdala-kindled rat and to enhance learning performance in a model of cerebral ischemia.[18] It is also effective in two models of neuropathic pain, suggesting that it may find utility for this additional indication.

From a mechanistic perspective, retigabine is quite novel. In the late 1990s, retigabine was found to be a "potassium channel opener" in cultured neurons.[134] Subsequent, the compound was found to specifically interact with a particular K current—the M-current, which is carried by the K-channel, voltage-gated, KQT-like subfamily (KCNQ) (see Bialer et al.[18] and Rogawski[129] for review and references). The M-current is a slowly activating current which, when activated, enhances membrane stabilization.[136] Retigabine is thought to reduce excitability by shifting the activation of the KCNQ current to more hyperpolarized potentials and to slow the deactivation and increase the activation phase.[151,152] This effect is of particular interest in that mutations in *KCNQ*$_{2/3}$ genes have been associated with benign familial convulsions (BFNC), an autosomal dominant epilepsy of childhood.[20,143] By enhancing M-currents, retigabine decreases neuronal excitability by inhibiting spike-frequency adaptation.[115]

In addition to enhancing M-currents, retigabine has also been found to increase GABA-mediated currents at concentrations that are only slightly higher than those that enhance M-currents.[114,135] Retigabine increases GABA-mediated currents through a nonbenzodiazepine-mediated action because its effect is not blocked by the benzodiazepine receptor antagonist flumazenil.[135]

Given the broad-spectrum anticonvulsant profile of retigabine, it is conceivable that both mechanisms contribute to its efficacy in in vitro and in vivo seizure and epilepsy models.

Pharmacokinetics

After oral intake of immediate-release formulations, the absolute bioavailability of retigabine is about 60%.[56] Retigabine pharmacokinetics are characterized by rapid absorption, moderate CL/F (0.6–0.7 L/kg), high apparent volume of distribution (6.2 L/kg), moderate plasma protein binding (about 80%), and a half-life of 5 to 9 hours.[46] In healthy subjects, the pharmacokinetics of retigabine are linear and dose proportional for doses of 100 to 700 mg, and steady-state pharmacokinetics after twice daily administration are in agreement with single-dose pharmacokinetics.[46] Food does not alter significantly the pharmacokinetics of retigabine.[17] In black subjects, retigabine CL/F and volume of distribution were 25% and 30% lower, respectively, after normalizing by body weight, leading to higher exposure in this population.[46] In a study exploring the influence of gender and age on retigabine CL/F, there were no substantial sex-related differences in the disposition of retigabine, but there was a relevant decrease in CL/F, resulting in higher exposure, in elderly patients, believed by the authors to be related at least in part to decline of renal function with age.[55] In patients with epilepsy, dose linearity of retigabine could be demonstrated up to 1,200 mg/day.[17]

Retigabine is cleared by nonoxidative metabolism and, to a lesser extent, by renal excretion in unchanged form.[17] Plasma profiling and spectroscopic analysis of two isolated urinary metabolites obtained after single oral dosing of 600 mg retigabine in healthy volunteers indicated that both acetylation and glucuronidation are major metabolic pathways in humans.[54] Two distinct inactive *N*-glucuronides have been identified as the primary metabolites.[108] Another metabolite, the *N*-acetyl derivative (AWD21-360), which is rapidly formed and cleared at the same rate as retigabine, is pharmacologically active,[17] and is found in serum at concentrations comparable to those of the parent drug.[56]

Of ten recombinant human uridin-glucuronosyl transferases (UGTs) evaluated, only 1A1, 1A3, 1A4, and 1A9 catalyzed the *N*-glucuronidation of retigabine. UGT 1A4 is considered the major isoenzyme responsible for the metabolism of retigabine in the liver and other organs.[57] It has been suggested that cleavage of the retigabine glucuronides in the gastrointestinal tract may lead to significant enterohepatic cycling.[57]

Drug Interactions

Retigabine does not appear to alter to any important extent the plasma levels of carbamazepine, phenytoin, valproic acid, phenobarbital, and topiramate.[45,48] In turn, retigabine pharmacokinetics are not altered by valproic acid or topiramate, whereas a moderate (about 30%) increase in retigabine CL/F is observed in patients receiving concomitant treatment with carbamazepine or phenytoin. This indicates that patients treated with carbamazepine and phenytoin may require higher dosages of retigabine to achieve a given retigabine concentration.[18]

Because both retigabine and lamotrigine undergo glucuronidation, a pharmacokinetic interaction study was performed.[56] Retigabine and lamotrigine exhibited a modest pharmacokinetic interaction on one another. A slight decline (13%) in retigabine CL/F after administration of a very low dose of lamotrigine (25 mg/day for 8 days) was believed to result from competition for renal elimination rather than competition for glucuronidation. An increase in lamotrigine CL/F by 22% due to retigabine (600 mg/day) was unexpected, because retigabine did not show enzyme induction in various other drug–drug interaction studies.[56]

Retigabine has been reported not to affect the pharmacokinetics of an oral contraceptive containing ethinylestradiol and levonorgestrel.[47]

Efficacy

Sachdeo et al.[138] performed an open-label dose-finding study of retigabine titrating 60 patients with epilepsy to a maximum dose of 1,200 mg/day in either a two or three times a day regimen. Median seizure rate was reduced by 21%, and 44% of patients had at least 50% reduction in seizure frequency.

Porter et al.[124] reported the results of a randomized controlled trial of retigabine in which 399 patients were randomized to daily doses of 600 mg, 900 mg, 1,200 mg, or placebo. Median monthly partial seizures decreased by 13% for placebo, 23% for 600 mg retigabine, 29% for 900 mg retigabine, and 35% for 1,200 mg retigabine. The 900 and 1,200 mg doses were significantly superior to placebo, and the 1,200 mg dose was significantly superior to 600 mg. Responder rates were 16% for placebo, 23% for 600 mg, 32% for 900 mg, and 33% for 1,200 mg; both the 900 mg and 1,200 mg doses were statistically superior to placebo.

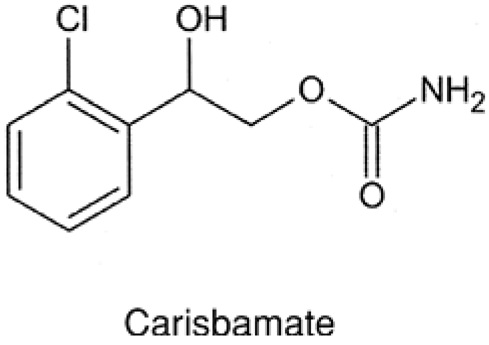


FIGURE 9. Structure of carisbamate.

Adverse Effects

In the open-label dose finding study, the most common adverse effects were dizziness, asthenia, somnolence, nausea, speech disorder, and tremor.[138] Dizziness and somnolence were the most common adverse effects that were dose limiting. Several different titration schedules were compared for 73 patients receiving retigabine in a randomized double-blind study.[1] A schedule of 150 mg increases every 7 days was associated with fewer discontinuations than increases every 2 or 4 days. The

most common adverse events were somnolence, speech disorder, ataxia, dizziness, and asthenia.

In the four-arm randomized controlled trial, the most common adverse events were somnolence, dizziness, confusion, speech disorder, vertigo, tremor, amnesia, abnormal thinking, convulsions, ataxia, abnormal gait, paresthesia, incoordination, and nervousness.[124] Most discontinuations associated with CNS-related symptoms occurred in the 1,200-mg retigabine group, suggesting that these adverse events may be dose related.

No clinically significant changes in laboratory parameters, ECG, Holter recordings, or vital signs were observed in any of the three large scale studies.[1,124,138]

Carisbamate

Structure and Chemistry

Carisbamate, 2-carbamoyloxy-1-2-chlorophenyl-ethanol, is a monocarbamate in clinical development by Johnson & Johnson Pharmaceutical Research & Development, Raritan, NJ (Fig. 9).

Pharmacology

Carisbamate is active in acute rodent seizure models including the MES, PTZ, bicuculline, and picrotoxin tests.[129] In addition, carisbamate is effective in the kindled rat model of partial epilepsy and the GAERS model of spike-and-wave seizures.[112] Carisbamate is effective against recurrent spontaneous seizures in the kainate post-SE model.[52] When tested several weeks post kainate treatment, carisbamate was found to be more efficacious than topiramate in this model, in that it rendered a larger fraction of rats seizure-free at a lower dose.

In addition to its acute anticonvulsant effects, carisbamate when administered at 1 and 8 hours, followed by twice daily dosing for 6 days after the onset of lithium-pilocarpine–induced SE, was reported to confer a neuroprotective and antiepileptogenic effect.[50] These results suggest that carisbamate may be disease-modifying in addition to being an anticonvulsant.

At present, nothing definitive can be said about the molecular actions of carisbamate that contribute to its broad-spectrum anticonvulsant profile and neuroprotective action.

Pharmacokinetics

The pharmacokinetics of carisbamate were evaluated after single doses (100 to 1,500 mg) and multiple doses (100–750 mg b.i.d.) in a total of 123 healthy volunteers. Carisbamate exhibited linear pharmacokinetics and was rapidly absorbed, with a peak concentration at 1.3 to 2.7 hours. The primary route of elimination appears to be metabolic,[171] with glucuronide conjugation being an important pathway.[30,31] The mean elimination half-life of carisbamate is in the range of 11.5 to 13.9 hours, mean CL/F values are in the range of 2.9 to 3.8 L/h,[30,31,171] and apparent volume of distribution after oral dosing (Vd/F) is on the order of 52 to 66 litres.[171]

Drug Interactions

Three separate studies were performed to evaluate the interaction between carisbamate and valproic acid, lamotri-gine, and carbamazepine.[30,31] Each of these studies enrolled 24 healthy volunteers. Carbamazepine treatment (600 mg/day) increased carisbamate CL/F by about 40%, and reduced its half-life from 10.4 to 7.4 hours on average.[30,31] Neither valproic acid (500 mg b.i.d) nor lamotrigine (50 mg b.i.d.) had substantial effects on the pharmacokinetics of carisbamate.[30,31] The pharmacokinetics of carbamazepine were not affected by carisbamate (500 mg b.i.d.).[30,31] Concomitant carisbamate (500 mg b.i.d) reduced valproic acid and lamotrigine exposure by approximately 20%, which was not considered to be of clinical significance.[30,31]

Efficacy

A small proof-of-principle study was undertaken in 13 patients with photosensitive epilepsy[63]. Ten of 13 showed some response to carisbamate at doses of 500, 750, and 1,000 mg based on photosensitivity score; three of the ten showed complete suppression of EEG photosensitivity. Reduction in photosensitivity was greatest after the 1,000 mg/day dose.

Adverse Effects

In the single-dose pharmacokinetic study in healthy subjects,[171] the most common adverse events were euphoria, hypoesthesia, dizziness, and paresthesia. These were rated mild to moderate in severity. The frequency of adverse events was greater in subjects receiving 1,000 mg and 1,500 mg than in those subjects receiving lower doses or placebo. In the multiple-dose pharmacokinetic study at doses up to 750 mg twice a day,[171] the most frequent adverse effects were somnolence, insomnia, euphoria, abnormal thinking, headache, hypoesthesia, dizziness, asthenia, malaise (*n* = 5), and paresthesia (*n* = 4). Eight subjects, including three receiving placebo, withdrew from the study because of adverse events.

In three different drug interaction studies with a total of 72 subjects, the most common adverse events were dizziness, headache, somnolence, fatigue, headache, paresthesia, hypoesthesia, somnolence, impaired concentration, and nausea.[30,31]

In the study conducted in 13 patients with photosensitive epilepsy, dizziness, nausea, and abnormal thinking were seen more commonly in those receiving carisbamate than placebo (Kasteleijn-Nolst-Trenite personal communication to M. Privitera). Adverse events were more common at doses of 750 mg and 1,000 mg compared to 500 mg or 250 mg.

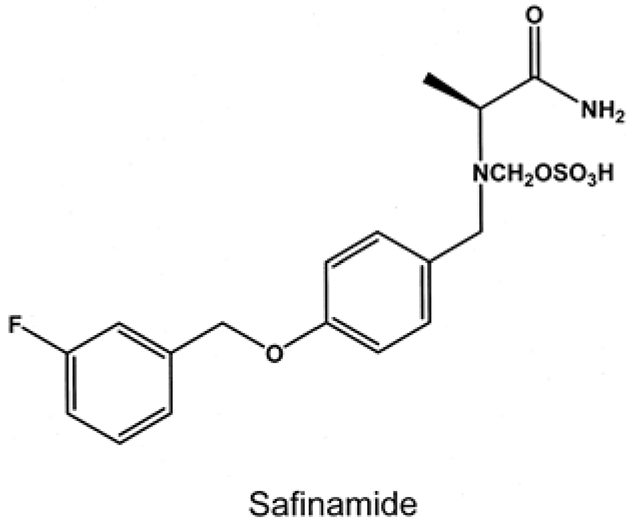


FIGURE 10. Structure of safinamide.

Safinamide (NW 1015, FCE 26743 PNU 151774)

Structure and Chemistry

Safinamide, (*S*)-(+)-2-4-[(3-fluorobenzyloxy) benzyl amino]propanamide methanesulfonate, is an alaninamide derivative

in development by Newron in Italy for treatment of epilepsy and Parkinson disease (Fig. 10).

Pharmacology

In animal seizure and epilepsy models, safinamide possesses a broad-spectrum anticonvulsant profile[18]. It prevents tonic extension-induced seizures by MES stimulation and strychnine. In addition, it is active against clonic seizures induced by bicuculline and picrotoxin. Safinamide is also effective in blocking seizures induced by the glutamate agonists NMDA and kainate. Safinamide blocks behavioral and electrographic seizures in the amygdala-kindled rat and behavioral paroxysms associated with afterdischarge-generating stimuli to the amygdala in a monkey model of partial epilepsy.[42] In addition to its ability to block kainate-induced SE, safinamide is also effective in decreasing kainate-induced neuronal cell loss. Furthermore, safinamide has been found to be neuroprotective in the gerbil model of cerebral ischemia. Based on its anticonvulsant profile, safinamide is expected to be effective in human partial and generalized seizures. Its demonstrated neuroprotective effects also suggest that it might be disease modifying in epilepsy and other degenerative disorders.

Safinamide acts by binding to the batrachotoxin recognition site of the Na channel, and it is a potent blocker of voltage-gated Na currents.[139] In addition, safinamide is a negative modulator of Ca channels and possesses a modest affinity for the σ-1 receptor. Functionally, one or more of these actions could account for its ability to prevent veratridine- and KCl-induced glutamate and aspartate release. Last, safinamide is a potent inhibitor of rat and human monoamine oxidase (MAO)-B, and this activity is thought to contribute to both its neuroprotective effects and to its potential utility for the treatment of Parkinson disease[18].

Pharmacokinetics

Safinamide is rapidly absorbed from the gastrointestinal tract, with peak plasma concentrations being achieved within about 2 hours after a single dose.[18] Concomitant intake of food reduces the rate of absorption, but peak concentrations and AUC are unaffected compared with the fasting state.[102] Both in healthy volunteers and in patients with epilepsy and Parkinson disease, plasma safinamide levels increase proportionally with the administered dose over the explored dose range of 50 to 300 mg/day.[102] Steady state is reached by day 5 of administration, and peak plasma levels during multiple dosing occur between 5 and 6 hours after intake.

Safinamide is about 90% bound to plasma proteins. In healthy volunteers and in patients not receiving enzyme inducers, the half-life is about 22 hours.[102] Clearance occurs primarily by metabolism. Approximately 70% of an orally administered dose can be accounted for by an inactive phase I metabolite, which is excreted in urine in conjugated form.[18]

Drug Interactions

The half-life of safinamide in patients comedicated with enzyme-inducing AEDs is shortened to about 16 hours, suggesting that safinamide metabolism is at least in part mediated by inducible enzymes.

In vitro, safinamide does not affect the activity of various CYP isoenzymes involved in the metabolism of other AEDs.[18,150] Preliminary observations in patients with epilepsy receiving safinamide doses up to 300 mg/day have not identified changes in the plasma concentration of concomitantly administered carbamazepine, lamotrigine, phenobarbital, or valproic acid.[18]

Because tyramine shows MAO-B inhibiting activity, studies have been performed to test potential interactions with the effects of intravenous and oral tyramine. No clinically significant interactions have been detected in these studies.[18,26]

Clinical Efficacy

In a study that assessed the response to transcranial magnetic stimulation in healthy volunteers as a surrogate marker for potential anticonvulsant activity, safinamide was found to reduce the motor evoked potential at doses of 1 and 2 mg/kg.[17] In an exploratory adjunctive-therapy trial in 43 patients with refractory epilepsy, 16 of 39 evaluable patients showed a greater than 50% decrease in seizure frequency on safinamide (at dosages up to 300 mg/day) compared with an initial prospective baseline.[18] Randomized controlled trials of safinamide in epilepsy have not been reported to date.

Safinamide is also being developed for the treatment of Parkinson disease, because of its potent MAO-B inhibiting activity.[8] In healthy volunteers, dose-dependent, progressive platelet MAO-B inhibition has been observed at single doses starting from 0.025 mg/kg, with virtually complete inhibition at 0.6 mg/kg.[102] In a multinational Phase II trial in patients with Parkinson disease, a median safinamide dose of 70 mg/day (range 40–90 mg/day) was associated with improved motor scores.[147]

Adverse Effects

In all studies conducted to date in patients with epilepsy and Parkinson disease, safinamide was generally well tolerated. The most commonly reported adverse events observed in adjunctive-therapy studies in epilepsy patients were dizziness, headache, vertigo, nausea, and blurred vision.[18]

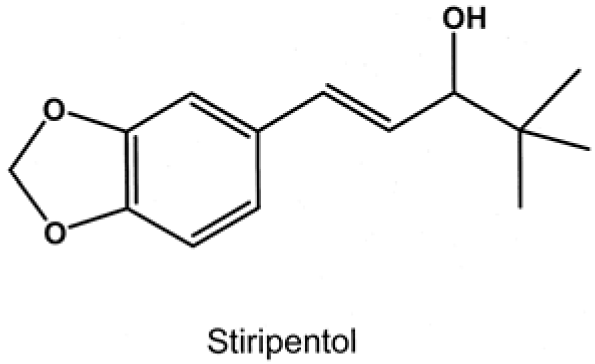


FIGURE 11. Structure of stiripentol.

Stiripentol

Structure and Chemistry

Stiripentol, 4,4-dimethyl-1-[(3,4 methylenedioxy)phenyl]-1-penten-3-ol, is an allyl alcohol that exists in two enantiomeric

forms (Fig. 11). Stiripentol has been under clinical investigation for about 30 years, and has been made available by Biocodex for compassionate use under a special program in France and Canada for over 10 years.[32] In 2001, stiripentol was granted orphan drug status in the European Union as a potential treatment for severe myoclonic epilepsy of infancy and has been approved recently by the European Medicines Agency (EMEA) for the treatment of this condition, adjunctively to valproic acid and clobazam. In clinical trials, assessment of its potential antiepileptic efficacy has been complicated by pharmacokinetic interactions, which result in marked changes in serum levels of concomitantly administered AEDs.

Pharmacology

Stiripentol is effective against a wide range of models that include tonic extension seizures induced by MES, clonic seizures induced by PTZ and bicuculline,[91,123] and spike-and-wave discharges in genetically susceptible Wistar rats.[109] It is also effective in suppressing interictal electroencephalographic discharges in the alumina gel rhesus monkey model of focal epilepsy.[90]

Despite the long-term use of this drug, very little can be said about the molecular mechanisms underlying its anticonvulsant action. The suggestion has been made that the efficacy of stiripentol could be related to positive modulation of GABAergic inhibitory neurotransmission. For example, stiripentol has been found to inhibit GABA-transaminase and β-hydroxybutyrate dehydrogenase activity, and to affect the uptake of glycine and GABA (for review and references see Loiseau and Duche[91]).

Pharmacokinetics

Despite evidence that stiripentol enantiomers differ in pharmacologic activity[142] and that the pharmacokinetics of the drug in rodents is stereoselective with preferential accumulation of the less active *S*-enantiomer,[10] published pharmacokinetic studies of stiripentol in humans appear to have been conducted utilizing nonenantioselective assays.

Following single oral doses ranging from 300 to 1,200 mg in powder form in healthy volunteers, stiripentol is rapidly absorbed, with peak plasma concentrations being attained mostly within 2 hours.[87] Stiripentol administered as a solution was found to possess a bioavailability of only 21% ± 9% compared to the powder form, possibly due to precipitation of the drug in the aqueous environment of the gastrointestinal tract.[87]

Stiripentol distributes extensively into tissues and is avidly (99%) bound to plasma proteins.[91] After single oral doses in healthy subjects, the elimination is multiphasic, with a mean residence time of 4 hours and a CL/F of 1.3 to 1.8 L/h/kg.[83] Single-dose pharmacokinetics are not predictive of pharmacokinetics at steady-state, because a several-fold decrease in CL/F is observed during multiple dosing.[83] Repeat administration studies at dosages up to 1,800 mg/day in healthy subjects and up to 2,400 mg/day in epileptic patients clearly demonstrated that stiripentol follows Michaelis-Menten kinetics, and that steady-state serum concentrations increase nonlinearly with increasing dosage.[83,86,87,91] In patients receiving stiripentol as adjunctive therapy, dosage increments from 600 to 1,200 mg/day resulted in a 253% increase in concentration, and a further dosage increment from 1,200 to 2,400 mg/day resulted in a 397% increase in drug concentration, which corresponds to an approximately fivefold decrease in CL/F (from 1.7 to 0.35 L/h/kg) when switching from the lowest to the highest dose.[87,91]

The occurrence of Michaelis-Menten kinetics is probably due to saturation of the enzymes responsible for stiripentol metabolism. At least five different pathways and 13 metabolites have been identified, with renally excreted metabolites accounting for 73% of the dose and about 13% to 24% of the dose being recovered unchanged in the feces.[111] The major pathway appears to involve oxidative cleavage of the methylene dioxy ring to yield catechol metabolites. Other pathways include conjugation with glucuronic acid, hydroxylation of the *t*-butyl group, *O*-methylation of catechol derivatives, and conversion of the allylic alcohol side chain to the isomeric 3-pentanone structure.[91,111]

Evidence suggests that stiripentol metabolism is stimulated by concomitant administration of enzyme-inducing AEDs. At a dosage of 1,200 mg/day, stiripentol CL/F in patients comedicated with carbamazepine, phenytoin, or barbiturates is about three times as high as that observed in healthy subjects, although the degree of interindividual variability is considerable.[86,87,91] Despite the fact that in recent years stiripentol has been used mainly in the treatment of pediatric patients, information on its pharmacokinetics in infants and children is very limited. Observations by Farwell et al.[44] suggest that stiripentol CL/F is lower in children than in adults receiving equivalent dosages.

Drug Interactions

Stiripentol inhibits a variety of CYP enzymes in vitro, including CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4.[105,157] Inhibition of the metabolism is responsible for a significant elevation in serum levels of concurrently administered AEDs,[91] including phenytoin,[44,87,91,105] carbamazepine,[28,65,85,88,94,105] clobazam and its active metabolite norclobazam,[33] phe-nobarbital,[91,93] primidone,[13,91] and valproic acid.[84,85,89] Many of these interactions are clinically significant. For example, the increase in carbamazepine concentration after starting stiripentol may be more than twofold, and a reduction in carbamazepine dosage is usually required to minimize the risk of toxicity.[44,65,82,158] Because stiripentol inhibits the conversion of carbamazepine to carbamazepine 10,11-epoxide,[28] the serum concentrations of the latter decrease considerably in patients receiving carbamazepine in combination with stiripentol.[65,88] Another major interaction occurs with clobazam. Dose-normalized clobazam concentrations increase about twofold after adding stiripentol, whereas the increase in the concentration of the active metabolite norclobazam is about threefold.[33] The magnitude of the increase in valproic acid levels in patients comedicated with stiripentol is of a considerably lesser magnitude compared with the increase reported for carbamazepine and clobazam.[33,89] The degree of interaction with phenytoin, phenobarbital, and primidone has been incompletely characterized, but preliminary observations suggest that, at least for phenytoin and phenobarbital, dose adjustments are required to minimize the risk of toxicity.[91]

As discussed earlier, enzyme-inducing AEDs increase stiripentol elimination and decrease serum stiripentol concentration at steady state.[86,87] Potential effects of valproic acid on stiripentol pharmacokinetics do not appear to have been investigated.

Clinical Efficacy

Most studies conducted with stiripentol to date have been open-label uncontrolled trials in which stiripentol was given as adjunctive therapy in adults and children with refractory epilepsies. Maintenance dosages have been in the range of 1,200 to 3,000 mg/day in adults, and 20 to 90 mg/kg in children. Many of these trials reported a decrease in seizure frequency, including partial seizures,[93,101,125] refractory absence seizures,[44,91,94,119] and possibly other seizure types.[91] Unfortunately, these results are difficult to interpret due to lack of a control group and, in many patients, an increase in the serum concentrations of underlying AEDs. In some studies, attempts to discontinue concomitant medications resulted in prominent deterioration of seizure control, suggesting that stiripentol has little or no antiepileptic efficacy when administered as monotherapy in these patients.[91,101] A double-blind, placebo-controlled trial of stiripentol (2,000 mg/day) added on to carbamazepine (whose dosage was reduced in the stiripentol group to compensate for the effect of interaction) in 201 patients with partial epilepsy has only been reported in summary form, and results were stated to be “non conclusive because of too low a dose of stiripentol … and an insufficient reduction in carbamazepine dosage, resulting in increased plasma levels” of carbamazepine.[91,92]

In an open trial, a particularly marked reduction in seizure frequency was observed when stiripentol was added on to clobazam in 20 children with severe myoclonic epilepsy in infancy (SMEI).[119] This led to a randomized, double-blind, parallel-group adjunctive trial in which stiripentol (50 mg/kg) or placebo was evaluated over a 2-month period in a total of 41 patients (mean age 9.4 years, range 3–21 years) with SMEI. All the patients were on a combination of valproate and clobazam.[33] In seven patients, progabide was also part of the underlying regimen. Of 21 patients treated with stiripentol, 15 (71%) were responders (defined as a >50% reduction in the frequency of clonic or tonic–clonic seizures during the second treatment month vs. baseline), compared with one (5%) of the 20 patients who received placebo. Nine stiripentol-treated patients were free of clonic and tonic–clonic seizures during the assessment month, compared with none on placebo. Percent change in seizure frequency was also greater on stiripentol (-69% vs. + 6% on placebo, $p < 0.0001$). Although the results of this trial clearly show a much better outcome in the stiripentol group, the findings may not be regarded as a conclusive demonstration of the drug's efficacy. In fact, to minimize intolerance due to drug interactions, valproate and clobazam dosages were kept within a predefined ceiling at baseline, implying that some patients may have received suboptimal dosages of these comedications. More importantly, despite a reduction in clobazam dosage in some patients, the concentration of clobazam and norclobazam increased markedly during stiripentol administration. For example, in the double-blind period serum concentration were 50% (clobazam) and twofold (norclobazam) higher in the stiripentol group than in the placebo group. Therefore, it cannot be excluded that the improvement in outcome was related at least in part to increased serum levels of comedication, rather than to an effect of stiripentol itself.[160] The authors, however, argued that the magnitude of the response was greater than expected from the elevation in clobazam and norclobazam levels.

An additional limitation of the double-blind SMEI trial is that patients were assessed under controlled conditions over a very short period. At the end of the double-blind phase, all patients went on to receive open-label stiripentol with a median follow-up of 24 months, and the authors reported a putatively favorable response in 21 of the 37 who could be meaningfully assessed. The drug was discontinued in four patients due to lack of response and in three patients because of adverse events, and two other patients died suddenly for reasons unrelated to the drug. The authors commented that "in comparison with the initial response … during the double-blind period, efficacy was maintained at last visit in 50% of the cases." A broader assessment of long-term outcome data in a total of 83 SMEI patients, including 37 from the double-blind trial described above and 46 from another trial[153] concluded that about 20% have a major benefit (fewer seizures) when stiripentol is added to inadequately effective valproate-clobazam combination therapy, and the best effects seem to be seen in the youngest patients.[9] The impact of stiripentol on psychomotor development, a major concern in this population, is unknown.

Adverse Effects

The most common adverse effects observed in patients given stiripentol include drowsiness, tremor, ataxia, hyperexcitability, insomnia, nausea, anorexia, weight loss, and occasional vomiting.[9,161] Hematologic abnormalities, including neutropenia and thrombocytopenia, have also been described.[33,161] Although some adverse effects can be ascribed to toxicity from other AEDs (whose serum levels increased following administration of stiripentol), and these abate after reduction in dosage of comedication, other effects, particularly nausea, vomiting, anorexia, and weight loss, probably reflect a direct effect of stiripentol.[119] In the double-blind trial in SMEI, CNS adverse events, particularly drowsiness, hyperexcitability, and aggressiveness, were reported in 91% of patients on stiripentol, compared with 25% of those on placebo.[33] Digestive system adverse events were reported in 67% of the stiripentol patients and 35% of the placebo patients. No patient, however, withdrew from the study because of adverse events, and many adverse events resolved after a reduction in dosage of comedication.

Talampanel (GYKI 53773; LY 300164)

Structure and Chemistry

Talampanel, currently developed by Teva, Israel, is the active (*R*)-enantiomer of the *N*-acetylated derivative of the 2,3-benzodiazepine GYKI 52466 (Fig. 12).

Pharmacology

Talampanel is effective against tonic seizures induced by MES and clonic seizures induced by PTZ.[7,17,163] Talampanel is also effective in blocking the expression of focal seizures in mouse and rat kindling models.[7,17,18,163] In combination with other AEDs, talampanel was found to potentiate their anticonvulsant action.[34] In one study, a low dose of talampanel (2 mg/kg) when administered with subtherapeutic doses of valproic acid (25–75 mg/kg) reduced the severity and duration of kindled seizures without negatively affecting long-term memory or motor coordination.[22]

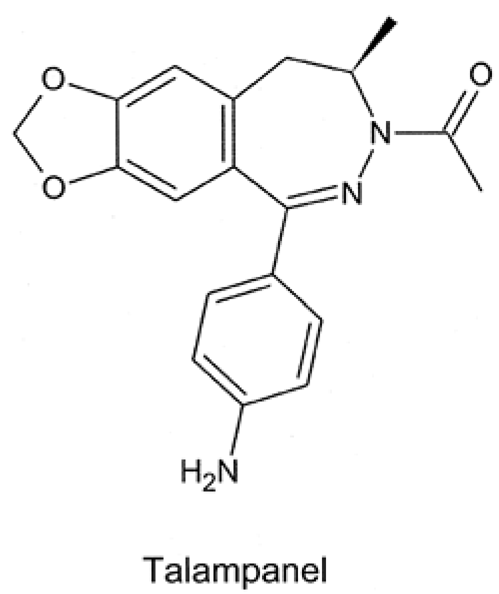


FIGURE 12. Structure of talampanel.

Talampanel is a noncompetitive antagonist of glutamate-mediated excitation evoked through the AMPA receptor.

AMPA receptors play a key role in mediating seizure spread and are implicated in seizure-induced neuronal damage. As such, AMPA receptors represent rational targets for AED discovery, and effective drugs that penetrate the blood–brain barrier at nontoxic doses may be useful for both the symptomatic treatment of epilepsy and the prevention of damage associated with chronic epilepsy and acute SE.[129,130] AMPA antagonists, unlike NMDA antagonists, do not block the induction of long-term potentiation and are thus thought to be devoid of the potential for inducing disturbances in long-term memory.[62] Through its noncompetitive interaction with the AMPA receptor, talampanel may offer some advantage over competitive AMPA receptor antagonists because its effect cannot be overcome by an excess of the endogenous ligand, such as glutamate. This is particularly important given that extracellular glutamate levels rise prior to the onset of electrographic seizure activity[41] and during excessive neuronal discharge associated with SE and other brain insults such as trauma and hypoxia-ischemia.

Pharmacokinetics

In studies conducted in healthy volunteers, talampanel is absorbed rapidly from the gastrointestinal tract, with peak plasma concentrations being observed within 3 hours after dosing.[18] Intake with a meal has no major influence on pharmacokinetic parameters. Between 67% and 88% of plasma talampanel is bound to plasma proteins, and its mean half-life after multiple dosing is on the order of 6 to 7 hours.[18] Half-life values of about 4 hours are observed after single doses of 30 to 35 mg, with longer values (about 7 hours) after 75 mg doses,[24] indicating nonlinear pharmacokinetics.

Langan et al.[77] assessed talampanel pharmacokinetics after single and multiple doses in patients taking enzyme-inducing AEDs. In these patients, plasma talampanel concentrations showed considerable interindividual variability and were on average less than one-half those seen in healthy volunteers. Mean talampanel half-life values after single doses were 3.0 hours compared to 4.2 hours in healthy volunteers, whereas mean CL/F values were 81.4 L/h compared to 26.2 L/h in healthy volunteers. After administration of multiple doses (mostly 50 mg t.i.d.) in the same patients, the half-life of talampanel increased to 5.6 hours and CL/F decreased to 39.5 L/h. The nonlinear pharmacokinetics of talampanel imply that plasma talampanel levels at steady-state increase more than proportionally with increasing dosage.

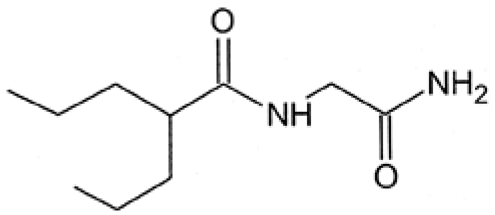
In humans, talampanel is converted to a variety of metabolites, including the 4′-*N*-acetyl, the 7-*O*-methyl catechol, and *O*- or *N*-glucuronidated compounds.[18] The *N*-acetyl metabolite has been reported to be inactive in vitro, but to be about one-third as active as talampanel in some in vivo studies, possibly because it can be deacetylated to talampanel.[18] In humans, acetylation by *N*-acetyl transferase NAT2 represents only about one-fourth of the total elimination even in homozygous fast acetylators, and therefore the impact of acetylator status on talampanel disposition is modest.[24,77] In patients taking talampanel, the plasma concentrations of the *N*-acetyl metabolite seem to be very low.[24,77]

Drug Interactions

As discussed, enzyme-inducing AEDs such as carbamazepine stimulate talampanel metabolism and decrease its plasma concentration at steady-state. In a randomized controlled trial of 49 patients[29] talampanel target doses were adjusted based on concomitant medication. Despite adjusting target doses, talampanel plasma concentrations were 66 ng/mL in patients receiving two hepatic enzyme-inducing drugs, 155 ng/mL in patients receiving one hepatic enzyme-inducing drug, and 372 ng/mL in patients receiving no enzyme-inducing AEDs. Thus, talampanel has a complex drug interaction profile that may make it difficult to predict its plasma concentrations when used as an adjunctive therapy.

Despite the fact that talampanel may inhibit CYP3A4 activity in vitro,[18] there is no clear evidence that talampanel affects to an important extent the pharmacokinetics of other AEDs. In a cross-over trial, six of 32 patients who were given talampanel in addition to carbamazepine required a reduction in carbamazepine dosage to maintain the serum carbamazepine concentration within 30% of baseline.[29] In another study, however, serum carbamazepine concentrations in 12 patients were not affected by talampanel.[77] Preliminary observations in a few patients also did not identify any effect of talampanel on the plasma concentrations of clobazam, clonazepam, topiramate, lamotrigine, primidone, and vigabatrin.[77] In the same study, the suggestion was made that talampanel and valproic acid may inhibit each other's metabolism. In fact, in one patient receiving talampanel and valproic acid (but not receiving carbamazepine), plasma talampanel concentrations and half-life were higher than previously recorded in healthy subjects. In addition, three of the four patients treated with valproic acid experienced significant increases in plasma valproic acid concentrations when talampanel was added on. In a more recent study in 10 healthy subjects, however, administration of valproic acid (500 mg/day for 5 days consisting of a total of 10 doses starting on the evening of day 2, with single 25 mg doses of talampanel administered on day 1 and 6) did not affect significantly the pharmacokinetic parameters of either talampanel or its *N*-acetyl metabolite. Administration of talampanel (25 mg) in this study caused a slight increase in trough total and free valproic acid concentrations (day 7 vs. day 6), which was not significant for total valproic acid, and marginally significant ($p < 0.05$) for free valproic acid.[18]

A lovastatin interaction study found no changes in plasma levels of lovastatin, a CYP3A4 substrate, after 10 days of talampanel dosing of 60 mg three times daily.[17]



Valrocemide

FIGURE 13. Structure of valrocemide.

Efficacy

Chappell et al.[29] performed a double-blind, placebo-controlled, randomized, add-on crossover trial of talampanel in 49 patients

with refractory partial seizures. Patients were titrated to the maximum tolerated dose, but there were three different target doses, determined by the patient's concomitant AEDs. Patients receiving enzyme-inducing AEDs had a target of 75 mg three times a day; those not receiving an enzyme-inducing drug or receiving an enzyme-inducing drug plus valproic acid had a target of 60 mg three times a day; those receiving valproic acid without an enzyme-inducing drug were targeted to 25 mg three times a day. While receiving talampanel, patients experienced a statistically significant median seizure reduction of 21%.

A pilot placebo-controlled study of talampanel (up to 50 mg t.i.d.) in 50 patients with amyotrophic lateral sclerosis (ALS) showed a trend towards a slower clinical deterioration in the talampanel group, but the difference versus placebo failed to reach statistical significance.[16,17]

Adverse Effects

In the pharmacokinetic study in patients conducted by Langan et al[77] no serious adverse events were reported; the most frequently reported adverse events were dizziness, ataxia, drowsiness, and headache.[78] Most patients taking enzyme-inducing AEDs did not tolerate the target dose of 75 mg three times a day, and required a dose reduction to 50 mg three times a day. The patient who was taking valproic acid without enzyme inducers was targeted to receive 35 mg three times a day, but his dosage had to be reduced to 10 mg three times a day. It was suggested that talampanel adverse effects occur at lower doses in patients taking AEDs than in healthy subjects, presumably due to the additive CNS effects of comedication.

In the randomized crossover trial, the most common adverse effects were dizziness (52%), ataxia (26%), headache (13%), and somnolence (13%), although headache and somnolence were seen almost equally in the placebo group.[29] Dizziness was reported to be mild to moderate, transient, and associated with peak plasma concentrations.

Valrocemide (TV-1901)

Structure and Chemistry

Valrocemide, *N*-valproylglycinamide, is currently under development by Shire (Fig. 13).

Pharmacology

Valrocemide is a broad-spectrum valproic acid-like anticonvulsant that was in early clinical development by Teva Pharmaceutical until 2004. Like valproic acid, valrocemide is active in many animal seizure and epilepsy models but, unlike valproic acid, it is not embryotoxic in rats and rabbits. This is likely due to the fact that the main metabolic pathway for valrocemide is enzymatic amide hydrolysis, which yields *N*-valproyl glycine.[18,58] In animal models, valrocemide is active against tonic extension seizures induced by MES, sound-induced seizures in the Frings audiogenic seizure-susceptible mouse, and focal seizures in the hippocampal-kindled rat. Valrocemide is also active in the 6-Hz model of pharmacoresistent limbic seizures. Consistent with its broad-spectrum anticonvulsant profile, valrocemide is also active against spike-and-wave seizures in the lethargic mouse and clonic seizures induced by the chemoconvulsants PTZ, bicuculline, and picrotoxin.

In addition to blocking seizure spread, valrocemide is thought to exert its anticonvulsant effect through an effect on seizure threshold. From results obtained in the intravenous PTZ seizure threshold test, valrocemide increased the dose of PTZ required to evoke a first twitch and clonus. Unfortunately, the precise molecular mechanism underlying all the anticonvulsant actions of valrocemide is not known.

In addition to its anticonvulsant effects, valrocemide has been found to reduce both the peripheral horizontal and vertical activity in the rat amphetamine-induced hyperactivity model of mania.[18] In addition, valrocemide has been found to decrease rearing in a manner similar to that observed with lithium. Thus, valrocemide, much like valproic acid, is a broad-spectrum neuromodulator that is likely to have effects against multiple CNS disorders including epilepsy and bipolar disorder.

Pharmacokinetics

Valrocemide is well absorbed after oral administration, with a linear relationship between serum concentration and dose after single doses up to 4,000 mg and multiple doses up to 1,000 mg three times a day.[17]

Valrocemide CL/F in healthy volunteers has been estimated at about 4 to 6 L/h, and the half-life is in the range of 6.4 to 9.4 hours after both single and multiple doses.[16,17]

The major metabolic route involves conversion to the inactive derivative *N*-valproyl-glycine, whose urinary recovery accounts for 40% of the administered valrocemide dose. Together, renal clearance of unchanged valrocemide and formation clearance of *N*-valproyl-glycine account for 57% to 75% of CL/F. Valproic acid has been detected as a minor metabolite and, based on pharmacokinetic parameters in healthy volunteers, it has been estimated that about 4% to 6% of a valrocemide dose is converted to valproic acid.[16,17]

Drug Interactions

Patients receiving concomitant mostly enzyme-inducing AEDs exhibit higher CL/F values (mean 8.2 L/h) and shorter half-lives (mean 4.7 hours) than do healthy volunteers, suggesting that valrocemide metabolism is mediated by inducible enzymes.[16]

Studies with human liver microsomes showed that, at clinically relevant concentrations, valrocemide and *N*-valproyl-glycine are devoid of inhibiting activity on a variety of CYP enzymes, including CP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E2, and CYP3A4, and epoxide hydrolase.[16]

Efficacy and Tolerability

In an adjunctive-therapy 13-week exploratory study in 22 patients with epilepsy, valrocemide has been up-titrated to the highest tolerated dosage or up to a maximum of 2,000 mg twice a day. Fourteen patients tolerated 2,000 mg twice a day, and there were no serious adverse events. The most common adverse events affected the CNS or the gastrointestinal tract. Although valrocemide was associated with a significant improvement in seizure frequency compared with baseline, the lack of a control group prompts caution in the interpretation of the results.

Summary and Conclusions

A number of investigational drugs currently are in development for the treatment of partial epilepsy. Their anticonvulsant activity was identified through the use of a battery of well-established animal and seizure models. Given the validity of the models employed, it is highly likely that most if not all of these investigational drugs will be found effective in patients with epilepsy. Because several of the drugs currently winding down the road to regulatory approval process possess a broad anticonvulsant profile, it will be of interest to see whether they will possess a similarly broad spectrum of activity in patients with multiple seizure types. In addition, an important question that remains to be answered is whether one or more of these drugs will lead to a marked improvement in seizure-free rates in patients with epilepsy refractory to current treatments.

Many of the drugs in the pipeline share a similar mechanistic profile with the marketed AEDs. On the contrary, the molecular mechanism of a few AEDs in development has yet to be defined. The inability to define a particular mechanism to a given drug suggests that it is unique relative to the other AEDs, and the hope would be that this would translate into improved efficacy over the established AEDs. It is important to note that several of the drugs in the pipeline have been found to prevent neuronal damage secondary to an acute brain insult. It is possible that this action may one day lead to the development of a "disease-modifying" therapy that slows, halts, or prevents the development of epilepsy in the susceptible individual. Such a therapy would be a major leap forward for the patient with newly diagnosed epilepsy, or even the person at risk for developing epilepsy. The challenges associated with the development of a disease-modifying therapeutic agent are immense, but worthy of pursuit.

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Chapter 165

Immunoglobulin and Immunomodulatory Therapy

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Introduction

The use of immunoglobulin in intractable epilepsy is one of its oldest applications in medicine, starting from the empirical observation of its beneficial effect on seizures.

The immune system and its associated inflammatory reactions have been implicated, by numerous experimental and clinical findings, in the pathogenesis of several forms of epil-epsy. The relationship between epilepsy, the immune system, and the inflammatory cascade is, however, exceedingly complex and possibly bidirectional.

The wide range of immune abnormalities observed in patients with epilepsy and the reported efficacy on seizure control of different immunomodulatory and/or anti-inflammatory treatments suggest the existence of different subtypes of epileptic syndromes associated with variable abnormalities of the immune system.

In this view, intravenous immunoglobulin (IVIg), with its broad immunomodulatory mechanism of action, could be effective in different forms of immune-dysregulated intractable epilepsies.

IVIg may also share nonimmunologic mechanisms of action: Its possible anticonvulsant properties and the ability of IVIg to interfere with the final common pathway of seizures at a cellular level, with a significant increase in seizure threshold, have been suggested by human epilepsy data and have been demonstrated in different experimental epilepsy models.

Although IVIg may represent a valuable resource in some drug-refractory epilepsies, and its effectiveness has important pathogenetic implications, controlled studies with the systematic monitoring of immunologic markers are needed to define more precise indications and to optimize the administration protocols.

The Central Nervous System and the Immune System

The central nervous system (CNS) is considered an immuno-privileged site because of the presence of the blood–brain barrier (BBB), its ability to accept grafts, the absence of classical lymphatic drainage, and the reduced traffic of monocytes and lymphocytes; it is, however, also considered an immunologically specialized site, because immune and inflammatory reactions do occur in the CNS, originating in the CNS itself (innate immunity), or are imported by competent immune cells from the peripheral tissues (acquired immunity).[75,92] The transition between innate and acquired immunity is mediated by a large variety of inflammatory mediators (e.g., cytokines, Toll-like receptors) not detectable or barely detectable under physiologic conditions.[3] Although such mediators are classically produced by cells of the immune system in response to infection or other pathologic stimuli, they are also produced by brain parenchymal cells such as microglia, astrocytes, and neurons, and by cells of the BBB and choroid plexus.[53,80]

It is worthwhile to note that an immune response in the CNS may be also triggered by endogenous ligands. Signals from damaged cells or arising from molecules entering the brain through a damaged BBB may initiate an immunologic response followed by an inflammatory reaction. A large spectrum of injuries, such as ischemia, trauma, and seizures, may initiate such a pathological process.[4,49]

The patterns of induction of inflammatory molecules and their time course of activation/persistence in brain tissue are related to the nature of the CNS injury and may be relevant in planning the treatment of epilepsy by immunomodulation.

Immunologic Alterations in the Epilepsies

Alterations of the immune system described in patients with different forms of epilepsy are numerous. Both humoral (predominantly IgA and IgG2 deficiencies)[29,33] or cellular[30,45,89] immunity may be impaired in these patients.

Conflicting reports have been published on serum immunoglobulin concentrations in patients with epilepsy. In a recent study serum IgA, IgG, and IgM concentrations were determined in a large cohort of epileptic patients and compared to a reference population.[76] The patients with epilepsy had lower serum IgA concentrations compared with controls. Low serum IgA levels were also found in patients taking phenytoin or who had previously been treated with that drug. No differences in serum IgG and IgM concentrations were observed between patients and control subjects.

Several recent reports have shown an increase in the markers of inflammation in serum, cerebrospinal fluid (CSF), and brain resident cells following seizures. Tonic–clonic seizures, for example, may induce a proinflammatory increase of cytokines such as interleukin (IL)-6, but may also reduce the IL-1RA/IL-1α ratio[46,68,71,72] in plasma and CSF. Experimental studies suggest that IL-1β prolongs seizure duration and, at the same time, promotes neuronal damage, whereas its effect is blocked by IL-1RA.[91] Increased levels of IL-1β and other cytokines have been observed in the experimental model of glycerol-induced seizures,[26] as well as in patients with either partial or generalized epilepsy.[64] These observations and the association of polymorphisms in the IL-1 gene complex with temporal lobe epilepsy and hippocampal sclerosis[50] and other forms of drug-refractory, localization-related epilepsies,[70] together with an increase in the expression of proinflammatory molecules in neurons and glia in brain tissue obtained from patients surgically treated for drug-resistant epilepsies,[9,23,58,77,83] are consistent with previous data suggesting a modulatory effect of cytokines and other proinflammatory molecules on neurotransmission and seizures.

Anti-brain antibodies[61,73] or autoantibodies[11,42] have also been related to different forms of epileptic syndromes and to more complex neurologic syndromes with prominent epilepsy, such as Rasmussen chronic encephalitis (RE).

Other evidence, although indirect, of the possible role played by the immune system in epilepsy includes the immunologic abnormalities induced by antiepileptic drugs (AEDs) such as phenytoin and carbamazepine,[34,65] and the anticonvulsant efficacy of immunosuppressive drugs such as adrenocorticotropic hormone (ACTH) and corticosteroids on the intractable seizures of West's Syndrome (WS).

The inflammatory response is strictly regulated genetically: Different prevalences of human leukocyte antigen (HLA) class II haplotypes in epileptic patients, compared with the general population, have been described.[44] The analysis of IL-1β, IL-1α, and IL-1RA gene polymorphisms[69] in a cohort of drug-resistant epilepsy patients versus healthy controls suggested an association between cytokine gene haplotypes and development of intractable focal seizures, but this observation was not confirmed by other authors.[17,41]

Clinical studies underscored the role of stress hormones in epilepsy. Increased ACTH and cortisol levels have been reported in human epilepsies and in status epilepticus (SE).[18,35,36] Activation of the ACTH/glucocorticoids axis in response to antecedent injury or stress has been suggested in the pathogenesis of WS.[8]

Dysfunction of the BBB has been demonstrated both in epilepsy experimental models[101] and in human epilepsy.[22] In most cases, however, routine examination does not provide evidence of BBB disruption with normal CSF.[87,99]

Increased BBB permeability induced by seizures, inflammation, or both has several clinical implications, which include the entry of compounds with immunogenic or inflammatory potentials,[66] the upregulation in the expression of multidrug transport proteins limiting AED access to the brain,[52] and facilitation of the entry of those compounds with therapeutic potential with limited or no access to the CNS, such as immunoglobulins.

The Use of Immunomodulatory Treatments in Human Epilepsies

From a clinical point of view, although the role of the immune system in the pathophysiology of human epilepsies is still only partially understood, the possibility of treating different forms of epilepsies by immunomodulatory agents is supported by extensive evidence.

IVIg, corticotropin, corticosteroids, plasma exchange, immuno-adsorption with protein A, and interferon (IFN)-α have been applied with some success in several epileptic syndromes: The antiepileptic effect of these agents may be at least partially mediated by their immunomodulatory and anti-inflammatory effects.

The concept that immunomodulatory and anti-inflamm-atory treatments may have a beneficial effect on epileptic seizures in human epilepsy has been first suggested after the empirical observation of Pechadre et al.[67] as early as 1977; the authors observed a decrease in the frequency and severity of seizures in children with epilepsy treated with intramuscular immunoglobulin for recurrent upper respiratory tract infections. Following this observation, the old allergic theory of epilepsy[24,97] was revised, and a new immunologic approach to epilepsy was proposed. Studies on the relationship between the immune and nervous systems flourished,[78] as did attempts to treat epileptic seizures with immunoglobulin. The anticonvulsant efficacy of immunomodulatory drugs with anti-inflammatory actions has been well documented. In particular, ACTH and steroids are very effective in severe childhood epileptic encephalopathies.[27,37,39,79,84] The antiepileptic mechanisms of these drugs have not been completely elucidated: Seizure inhibition may involve, at least in part, the ability of steroids to modulate various neurotransmitters, including γ-aminobutyric acid (GABA).[51,74] Their immunosuppressant and anti-inflammatory activities may play a major role in epilepsies with an immune component, such as RE.

The Use of IVIG in Epileptology

The use of IVIg in intractable epilepsy is one of its oldest applications in medicine.[93] This application followed its use for substitution in immunodeficiency states,[16] but preceded the work of Imbach et al.[48] on idiopathic thrombocytopenic purpura in childhood and the subsequent use of this treatment in numerous non-neurologic and neurologic diseases.

IVIg Preparation

Commercial IVIg is human polyclonal IgG prepared from the pooled plasma of as many as 10,000 or more donors. For this reason, there are concerns about the quality and safety of the IVIg preparations. Although it is considered unlikely that IVIg preparations may cause infections, good manufacturing practice is of utmost importance.

IVIg in the Central Nervous System

In neurologic disorders, the access of IVIg to the nervous system is limited by the blood–nerve, blood–brain, and blood–cerebrospinal fluid barriers. Because IgG is virtually absent in the brain parenchyma, the chances of IgG entering the CNS after intravenous infusion of IVIg are low, unless some degree of barrier damage exists. The effectiveness of IVIg therapy has been related to the concentration of IgG in the CNS, as demonstrated for other neurologic disorders such as encephalitis. Investigations of the CSF in patients with intractable epilepsy before and after IVIg treatment aimed to clarify the role of this treatment in epilepsy. Van Engelen et al.[88] examined the CSF of 15 patients with cryptogenic WS and Lennox-Gastaut syndrome (LGS): None of these patients had CSF abnormalities, and all had an apparently normal blood–CSF barrier permeability. After IVIg therapy, the total serum and CSF IgG concentrations increased by 76% and 44%, respectively, demonstrating a normal transfer of IgG from blood to the CSF. Because no restrictive barrier exists between the CSF and the extracellular fluid of the brain,[96] IgG may probably reach certain parts of the brain, at least within short diffusion distances, thus favorably altering neuronal excitability in areas of the brain and brainstem adjacent to the CSF. On the other hand, IgG may reach relevant sites in epileptic patients in whom the BBB may have been focally destroyed by seizure activity, as demonstrated in an experimental model.

IVIg Mechanisms of Action

Although the role of the immune system in epilepsy is not completely clarified, the mechanism of action of IVIg in epilepsy is considered mainly immunologic.

The suggested, but not proven, mechanisms of action of IVIg therapy have been related, among others, to the compensation of possible IgG2 deficiencies, suppression of infections,[21] neutralization of pathogenic autoantibodies by anti-idiotypic interactions,[25] and interference with cytokine production.

Nonimmunologic mechanisms of action have been also suggested, based either on human epilepsy data or on animal experimental data. One evidence for a nonimmunologic action of IVIg is related to the time course of the response to treatment of patients with different forms of epilepsy; an immediate response suggests a direct neuromodulating effect. The possible anticonvulsant properties and the ability of IVIg to interfere with the final common pathway of seizures at a cellular level have been investigated in different experimental epilepsy models. By significantly increasing seizure threshold, an anticonvulsant effect of IVIg has been demonstrated in subsets of animals in a model of kindled cats[43] and in a direct cortical stimulation model of epilepsy.

Efficacy of IVIg in the Epilepsies

The evaluation of the efficacy of IVIg treatment in epilepsy is difficult due to the heterogeneity of the available studies, with high variability in the study designs, patients' selection, treatment modalities, and outcome parameters. A publication bias must be also considered because the results of small series of nonresponders may have not been published.

Furthermore, with few exceptions,[80] most of the studies on intractable epilepsy were not double-blind and placebo-controlled, because of the obvious limitations related to the route of IVIg administration and to the problems related to a cross-over study design.

Data from noncontrolled studies suggest that IVIg may work differently in different subgroups of epileptic patients; the search for markers predictive of response is therefore important in this context.

IVIg in West Syndrome and Lennox-Gastaut Syndrome

LGS and WS are epileptic encephalopathies, characterized by severely refractory polymorphic seizures and often catastrophic effects on cognitive development. The evidence for an immune-mediated pathogenesis is mostly based on the observation of positive responses to immunomodulatory agents.

Corticotropin and corticosteroids are often more effective than AEDs in controlling seizures, thus suggesting a role for inflammation in the pathophysiology of these syndromes.

IVIg has been applied both in WS and LGS, with some encouraging results. A cumulative meta-analysis is not possible because the studies are heterogeneous and not controlled. On the other hand, if we consider the available noncontrolled studies and small case series, most authors have reported good positive response rates. In WS, seizure-free status after IVIg treatment was achieved in 40% to 60% of patients, whereas the same outcome was reached using ACTH in 20% to 70% of patients.[2] In LGS, total absence of seizures was achieved using IVIg in 10% to 44% of patients. The use of ACTH in LGS is less standardized (the reported rates of seizure-free patients ranged from 50% to 60%[1]) and because of a high rate of relapse (from 70% to 90%) during the ACTH taper, limited to phases of particularly active epilepsy. For the similar positive response rates and for the lack of potentially fatal side effects, the use of IVIg in these forms of intractable epilepsy may be considered a good alternative to ACTH.

IVIg in Landau-Kleffner Syndrome

Landau-Kleffner syndrome (LKS) is a rare, probably etiologically heterogeneous, pediatric neurologic disorder, characterized by progressive loss of language skills, behavioral problems, and, in many patients, epilepsy. It has been associated with neurocysticercosis, *Haemophilus influenzae* type B meningitis, temporal lobe tumors, demyelinating lesions, and cerebral arteritis. Several lines of evidence point to an autoimmune etiology in LKS. An autoimmune response to central and peripheral myelin has been reported by Nevsimalova et al.[62] Serum IgG antibodies to endothelial cells were found in 45% of 11 patients with an LKS variant, compared with 2% of 29 healthy children and 22 controls with non-neurologic disorders.[20]

The immunopathogenic hypothesis has also been suggested by other authors[32,54,60] following the observation of a dramatic improvement of language function and EEG abnormalities after treatment with corticosteroids and/or repeat IVIg infusions. Interestingly, in one of these cases, the pretreatment CSF IgG index was increased, suggestive of intrathecal IgG production, and this was reversed to normal after the first IVIg treatment. On the other hand, other therapeutic attempts involving AEDs and steroids have had only limited success to stop disease progression or to reverse the language deficit. Although the results with IVIg were encouraging, with long-term remission, the studies are single-case reports that do not allow one to draw definitive conclusions about the efficacy of this treatment in LKS.[32,54,60]

IVIg in Rasmussen Encephalitis

Rasmussen's encephalitis (RE) is a rare condition that typically appears during childhood and is characterized by progressive unilateral brain dysfunction, intractable partial epilepsy, epilepsia partialis continua (EPC), and inflammatory histopathology. Its etiology is unknown, but persistent chronic viral infection and a local autoimmune response have been hypothesized. Nonviral autoimmune mechanisms were first suggested by pathologic evidence of cerebral vasculitis with immune complex deposition in a child with typical RE, associated with CSF oligoclonal bands and high antinuclear antibody titres.[5] This mechanism was more strongly supported by the work of Rogers et al.: They first reported the presence antibodies directed against the neuronal glutamate receptor subunit 3 (GluR3) in RE patients, and induced seizures and inflammatory histopathologic changes, similar to those observed in RE, in rabbits immunized with GluR3.[81] Many other authors have successively confirmed Rogers' findings. Subsequent studies have provided (partly contradictory) evidence for potential mechanisms of action of anti-GluR3 in RE.

Direct evidence of the pathogenicity of GluR3 antibodies via receptor activation was demonstrated using both rabbit-derived GluR3 antibodies and serum obtained from patients with active RE. These results could not be reproduced by other groups. Instead, a complement activation by GluR3 antibodies was suggested. Levite et al. showed that GluR3 immunization of mice elicits both a humoral and a cellular autoimmune response.[56] Oligoclonal local T-cell and B-cell responses[10,57] have been found in the lesions of RE patients. Bien et al.[14] documented the in situ presence of a predominantly $CD3^+/CD8^+$ lymphocytic infiltrate in brain specimens of RE patients, suggesting that cytotoxic T cells contribute to neuronal damage in RE. Although these reports suggest the existence of an autoimmune response at the basis of RE, some observations argue against this hypothesis, and in particular the evidence that GluR3 antibodies are neither always present in the serum of RE patients nor specific for RE.[13,59,98] Bernasconi et al.[13] demonstrated the presence of GluR3 antibodies in 82% of RE patients, but also in 64% of patients with partial epilepsy.

The hypothesized immunologic basis for RE prompted clinicians to try new immunomodulatory and anti-inflammatory treatments and, although the available experience is limited, it offered further circumstantial evidence for RE as an autoimmune condition.

Table 1 Immunomodulation in RE treatment

Papers	Type of treatments	Outcome

	(number of patients)	
Rogers et al., *Science* 1994[81]	Plasma exchange (*n* = 1)	Seizure reduction and neurologic improvement; reduction of GluR3 antibodies
Chinchilla et al., *J Neurol Neurosurg Psychiatry* 1994[19]	High-dose corticosteroids (*n* = 8)	Seizure reduction and neurologic improvement in seven patients
Hart et al., *Neurology* 1994[40]	High-dose corticosteroids (*n* = 17) IVIg (*n* = 9)	Seizure reduction and neurologic improvement in 10 patients Seizure reduction in eight patients
Antozzi et al., *Neurology* 1998[6]	Immuno-adsorption with protein A (*n* = 1)	Seizure reduction and neurologic improvement; reduction of GluR3 antibodies
Leach et al., *Neurology* 1999[55]	IVIg (*n* = 2)	Seizure reduction in both patients
Villani et al., *Neurology* 2001[95]	IVIg (*n* = 1)	75% seizure reduction, disappearance of EPC, improvement of neurologic deficits
Granata et al., *Neurology* 2003[38]	IVIg (*n* = 10 childhood-onset; *n* = 1 adult-onset) High-dose corticosteroids (*n* = 14) Plasma exchange (*n* = 5) Immuno-adsorption with protein A (*n* = 3)	50% seizure reduction and slight neurologic improvement in two children. In the adult patient (see Villani et al., 2001), the positive effect was transient, although prolonged. Transient seizure reduction and neurologic improvement in six patients Blocked SE in one patient Seizure reduction and neurologic improvement in one patient
C.G. Bien et al., *Neurology* 2004	Tacrolimus, N=7 (children and adults)	In comparison to a historical untreated control cohort, tacrolimus treated patients had a significantly better motor outcome and less tissue loss on brain MRI. There was, however, no difference in seizure frequency between the two groups.
Villani et al.,	IVIg (*n* = 6)	Transient seizure reduction and neurologic

		improvement in three patients
Epilepsia 2005[94]	Immuno-adsorption with protein A ($n = 4$)	Transient seizure reduction, improvement (two of four patients) and stabilization (two of four patients) of neurologic deficits
	High-dose corticosteroids ($n = 7$)	Useful in SE
	Chronic corticosteroids ($n = 9$)	Uncertain effects, but deterioration at withdrawal

C.G. Bien, U. Gleissner, R. Sassen. G. Widman, H. Urbach, and C.E. Elger. An open study of tacrolimus therapy in Rasmussen encephalitis. Neurology 2004;62:2106–2109.

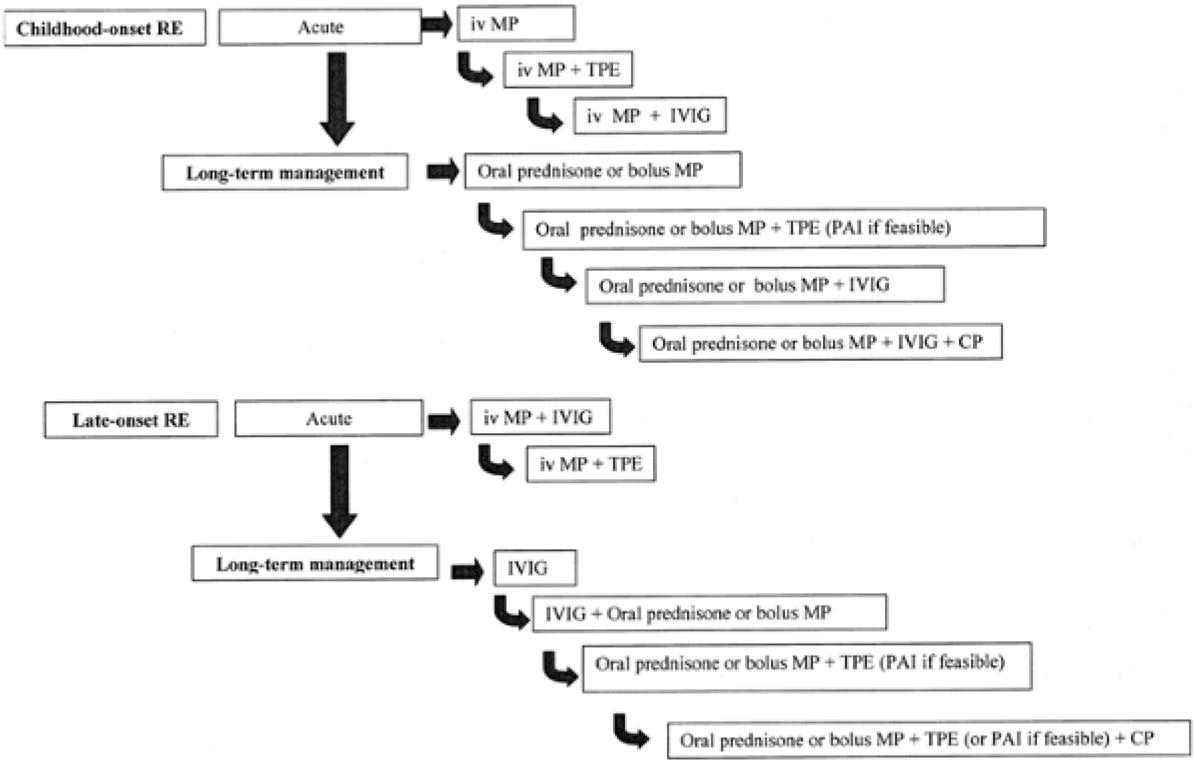
Childhood-onset RE
Acute
iv MP
iv MP + TPE
iv MP + IVIG
Long-term management
Oral prednisone or bolus MP
Oral prednisone or bolus MP + TPE (PAI if feasible)
Oral prednisone or bolus MP + IVIG
Oral prednisone or bolus MP + IVIG + CP
Late-onset RE
Acute
iv MP + IVIG
iv MP + TPE
Long-term management
IVIG
IVIG + Oral prednisone or bolus MP
Oral prednisone or bolus MP + TPE (PAI if feasible)
Oral prednisone or bolus MP + TPE (or PAI if feasible) + CP

FIGURE 1. Proposed flow-chart for administration of immunomodulatory treatments in childhood and late-onset Rasmussen encephalitis (RE). MP, methylprednisolone; TPE, therapeutic plasma exchange; IVG, IN immunoglobulin; PAI, protein A immunoadsorption; CP, cyclophosphamide. (From Granata T, Fusco L, Gobbi G, et al. Experience with immunomodulatory treatments in Rasmussen's encephalitis. *Neurology* 2003;61:1807–1810.)[37]

A number of medical treatments have been proposed, including high-dose corticosteroids, IVIg, plasma exchange, and immuno-adsorption with protein A (Table 1), particularly in the early disease stages, when patients still present mild neurologic deficits and surgery may not be the best choice (it may result in hemianopia, hemiparesis, and also aphasia when the dominant hemisphere is affected).[38]

The use of IVIg has produced encouraging results in the treatment of patients with the adult-onset variant of RE.[55,95] The less encouraging response to IVIg in the more typical childhood form of RE, along with the slow progression of adult-onset RE, may suggest different disease mechanisms in these two variants.[38] The extreme rarity of this pathology does not allow the efficacy of this treatment to be assessed in controlled trials.

Clearly, multicenter studies are necessary to investigate the indications for and timing of immunomodulatory interventions in RE. Immunomodulation may delay surgery, particularly in patients with late-onset (adolescent or adult) RE.[15,55,95] Based on these and other data[15,40,55,95] a nonsurgical approach to the treatment of RE for childhood and late-onset RE variants (Fig. 1) has been recently proposed.[38] This therapeutic scheme presents a graduated approach to the acute phases of the disease (i.e., SE and worsening of EPC) and for long-term immunomodulation in patients ineligible for surgery, and underscores the role of IVIg in this rare pathology as recommended by a European consensus proposal for the immuno-threatment of RE.[14a]

Summary and Conclusions

IVIg may exert beneficial effects in different form of epileptic syndromes, ranging from the frequently catastrophic childhood epileptic encephalopathies, such as WS and LGS, to RE, where its efficacy, maximal in the adult-onset variant, may be transient but nevertheless useful in delaying more invasive therapeutic approaches.

The favorable effect, generally attributed to an immunologic mechanism, supports the immunogenetic hypothesis for these epilepsies. Possible nonimmunologic mechanisms, involving a direct effect on membrane excitability, should also be taken into account. Although IVIg treatment may represent a valuable approach in some drug-refractory epilepsies, and its effectiveness has important pathogenetic implications, controlled studies, utilizing the systematic monitoring of immunologic markers, are needed to define its indications and to optimize the administration protocols.

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Chapter 166

Overview: Surgical Therapy

Jerome Engel Jr.

Heinz Gregor Wieser

Dennis D. Spencer

Introduction

Surgical treatment for epilepsy has a long and distinguished history.[11,15,33] Trephination was practiced since prehistoric times in many parts of the world, and cauterization, a popular therapy in the European Middle Ages, persisted into the late 19th century. The modern era of epilepsy surgery was inaugurated when surgeons began to operate on “invisible” lesions based on principles of functional cerebral localization developed largely by John Hughlings Jackson.[32] Macewen, in 1879,[24] and Horsley, in 1886,[19] were the pioneers of this approach. The advent of electroencephalography (EEG) in the first half of the 20th century made it possible for Bailey and Gibbs[3] and the Montreal group led by Penfield and Jasper[20,27] to perform epilepsy surgery, predominantly anterior temporal lobectomy, based on electrophysiologic evidence alone. Much of the early neuroscience research that characterized and mapped human cortical function was derived from the work that Penfield and Jasper performed during surgery for epilepsy.[27] Nevertheless, surgical treatment was offered to only a few patients. Although this therapeutic modality has gained increasing acceptance in recent years, it remains underutilized today.

Whereas surgical intervention during the early years was constrained by the limited localizing capabilities of available diagnostic tools, initially consisting of seizure semiology and direct observation of defects in the skull and cortex, and later including EEG, pneumoencephalography, and cerebral angiography, the factors that continue to restrict epilepsy surgery today are more sociopolitical. With recent tremendous advances in our ability to accurately delineate structural and functional epileptogenic brain regions and to safely and effectively remove them, there has been a resurgence of interest in epilepsy surgery, and the number of patients undergoing surgical treatment for medically refractory epileptic seizures doubled or tripled worldwide between 1985 and 1990.[16] It has been estimated for the United States that there may be over 100,000 potential surgical candidates, with 5,000 to 10,000 added annually,[18] but only about 2,000 surgical procedures to treat epilepsy were performed in the United States in 1990. The number has not changed appreciably since then, despite a randomized controlled trial of surgery for temporal lobe epilepsy,[36] and a Practice Parameter published by the American Academy of Neurology recommending surgery for this condition.[17] This underutilization is typical of other industrialized countries as well and can be attributed in part to (a) the reluctance of third-party payers to provide support for expensive presurgical evaluation, a problem that is currently being addressed by efforts to streamline the diagnostic process where possible, and to conduct studies that demonstrate the cost-effectiveness of surgical intervention over the long run; and (b) inadequate dissemination of information concerning advances in epilepsy surgery to primary care physicians, who too often are not identifying potential candidates and referring them to epilepsy surgery centers in a timely fashion. Furthermore, when patients are referred for epilepsy surgery, it is after an average of 22 years of seizures, often too late for meaningful rehabilitation.[4,14]

Underutilization of surgical treatment for epilepsy is steadily being reversed, and surgical intervention is playing an increasingly important role in the epileptologist's therapeutic armamentarium, as evidenced by the escalating number of conferences, books, and monographs on this subject in recent years.[2,5,6,7,8,9,10,22,23,26,28,29,31,35,37,38,39,40] This is a direct result of new developments in structural and functional neuroimaging; improvements in other areas of diagnosis, particularly involving EEG and long-term monitoring; and refinements in surgical technique. However, the growth of surgical treatment is also due to a better understanding of the pathophysiology of those epileptic disorders that are amenable to this therapy, which to a large extent has derived directly from basic research conducted on the human brain in epilepsy surgery centers. Consequently, many different surgical procedures are available to treat specific individual epileptic disorders, and a variety of presurgical evaluation protocols can be applied depending on the suspected underlying epileptogenic disturbance and proposed surgical intervention. Therefore, surgical approaches are no longer dependent on the particular experience or biases of the surgical team in each center, nor are they constantly changing, with each new patient seen as a unique problem. Rather, a number of universally accepted strategies have been developed based on data derived from many epilepsy centers worldwide and validated by their results, which can be applied to categories of patients in a well-organized fashion according to predetermined criteria. Furthermore, based on years of cumulative data, reasonably reliable prognoses can be made before the recommendation of surgery, and specific surgically remediable syndromes can be easily identified for which medical prognosis is so poor and surgical prognosis so good that early surgical intervention can be deemed the treatment of choice.[13]

The chapters in this part review the current concepts of surgical treatment for epilepsy for nonsurgical physicians. The first three (Chapters 167,168,169) address identification of surgical candidates by primary care physicians, the general approaches to surgical treatment, and the basic principles of presurgical evaluation and surgical intervention. The vast majority of surgical candidates can be evaluated today using routine noninvasive electrophysiologic, neuroimaging, and neuropsychological investigative techniques, each of which is described in more detail in Section IV. With proper application of these approaches, surgical treatment for approximately one-quarter to one-half of patients with medically intractable epileptic seizures, or 5% to 10% of all patients with epilepsy, could be achieved noninvasively in a safe and cost-effective manner.

There remains a smaller number of patients with medically refractory seizures who could also benefit from surgical treatment but who require more expensive invasive presurgical evaluation. The next several chapters (Chapters 170,171,172,173,174,175) are devoted to these diagnostic techniques, including both chronic and intraoperative intracranial recordings used to localize the epileptogenic region and intracranial recording and stimulation techniques used to delineate essential primary cortex that must not be damaged during the surgical procedure. These approaches are unique to epilepsy surgery programs. In addition, Chapter 173 discusses intra-arterial amobarbital procedures, which are semi-invasive tests that yield information about lateralization of language and memory that is important whether or not invasive testing is required.

The next group of chapters (Chapters 176,177,178,179,180,181,182) presents the specific therapeutic surgical procedures performed as a treatment for epilepsy. Although these chapters provide considerable technical detail, they are not designed for neurosurgeons, but rather to help neurologists and other potential referring physicians understand the rationale for these various approaches and the indications for their application. Therapeutic surgical interventions include procedures designed to resect epileptogenic brain regions, procedures that disconnect epileptogenic areas, and procedures that selectively remove discrete lesions. In addition, reoperation is discussed. Experimental invasive procedures such as deep brain stimulation are presented in Chapter 134.

The next two chapters are concerned with surgical results. Outcome assessment (Chapter 183) is essential to evaluate the efficacy of presurgical evaluation protocols and specific surgical procedures and provides critical information necessary for validating advances in the field. Recent emphasis has rightly moved away from seizure outcome per se and toward more global quantitative measures of quality of life. In view of the shrinking resources for health care, increasing importance is also being placed on determining which surgical approaches for epilepsy are most cost-effective. Whether surgical intervention succeeds in reversing disability, so that the patient becomes not only seizure-free but independent and capable of leading a satisfying and productive life, depends in part on early surgical intervention, but also on effective postoperative rehabilitation (Chapter 184).

The final chapter in this section addresses special pediatric considerations that are not adequately covered in the preceding chapters. Surgical treatment is becoming an increasingly important therapeutic approach for infants and children with epilepsy (Chapter 185).

Surgical treatment for epilepsy is an evolving discipline, and continuing progress, much of which is currently unforeseen, will undoubtedly occur during the lifetime of this textbook. Future directions can be divided into three parts: (a) technological advances that improve the safety, accuracy, and cost-effectiveness of epilepsy surgery; (b) application of surgical treatment in countries with limited resources, as a direct result of cost reduction; and (c) expanded use of the unique opportunities provided in an epilepsy surgery setting to conduct invasive research on the human epileptic brain.

Technological improvements will undoubtedly involve continuing advances in both structural and functional neuroimaging; more streamlined approaches to EEG monitoring; the development of noninvasive techniques for three-dimensional localization of interictal and ictal epileptiform abnormalities, such as magnetoencephalography and functional magnetic resonance imaging (fMRI); and the widespread use of advanced computer technology to coregister multidisciplinary data. New developments in these areas are expected to expand the population of medically refractory patients who can be considered surgical candidates and to result in even better surgical outcomes, but these advances will also make it possible for an increasing number of patients to undergo surgical treatment without the added expense and risk of invasive intracranial presurgical procedures. Improvement in cost-effectiveness, particularly if early surgical intervention is encouraged to maximize surgical outcome, will make surgical treatment more acceptable to third-party payers and enhance its availability. It will also contribute to the application of surgical treatment in countries with limited resources.

The burden of world epilepsy is overwhelmingly borne by developing countries, where it is estimated that upwards of 90% of people with epilepsy live.[21] Although the treatment gap in these areas of the world refers to the fact that considerably more than half of these people receive no medical therapy at all for their recurrent epileptic seizures, improving access to treatment should include surgical intervention where appropriate, as well as pharmacotherapy. As identification of patients with surgically remediable syndromes becomes easier with the application of relatively inexpensive noninvasive EEG and MRI approaches, and with the demonstration that 80% of those with surgically remediable syndromes can become seizure-free and lead relatively normal lives after early surgical intervention, surgery should become the most cost-effective approach for such patients, particularly in countries with limited resources. The establishment of at least one epilepsy surgery facility in larger developing countries, and regional centers in areas where countries are too small to support their own epilepsy surgery program, could provide service for large populations of patients. Screening patients with MRI could then make it possible to identify the best candidates as early in the course of their disorder as possible, so that presurgical evaluation and surgical intervention would proceed in a relatively inexpensive manner. Indeed, this process is already underway.[38]

It is important not to forget that much of our current understanding of the basic mechanisms of human epilepsy now derive from studies conducted on brain tissue obtained through epilepsy surgery, or by direct in vivo investigations of the human epileptic brain during the course of invasive presurgical evaluations. Expansion of the number of epilepsy surgery centers around the world has not only made surgical treatment available to an increasing number of patients, but also greatly facilitated access of basic neuroscientists to these unique research opportunities. The growth of invasive research on the epileptic human brain could tremendously enhance our future understanding of the fundamental disturbances underlying the various forms of pharmacoresistant epilepsy that are currently treated surgically. This understanding, in turn, could alter our approaches to surgical intervention, which might be more specifically directed at the structural or functional epileptogenic disturbance, resulting in procedures that are more effective and less likely to induce unwanted side effects. In addition, anatomic, chemical, physiologic, and molecular biologic research on the human epileptic brain is essential for developing new concepts for nonsurgical approaches to control disabling epileptic seizures and to prevent the occurrence of epileptic disorders.

Summary and Conclusions

Modern surgical treatment for medically refractory epilepsy has been available for well over 100 years;

however, recent technological advances in clinical neurophysiology and neuroimaging, as well as an improved understanding of the anatomic substrates and pathophysiology of a number of symptomatic epileptic conditions, have greatly enhanced the safety and efficacy of surgical intervention and markedly increased the number of patients who might be considered surgical candidates. Although this may be as many as half of all patients with epileptic seizures that cannot be controlled by pharmacotherapy, only a very small percentage of these are actually identified and referred for surgical treatment today. Surgically

remediable syndromes can now be easily diagnosed noninvasively in most cases, and 60% to 80% of patients with these disorders can expect to become seizure-free postoperatively. Many patients with more complicated epileptic conditions can also benefit from surgery, although invasive studies might be required, and prognosis may be somewhat poorer. Early surgery provides the best opportunity for complete psychosocial rehabilitation. The major purpose of this section, therefore, is to provide practicing physicians with information about surgical treatment for epilepsy that will help them to identify potential surgical candidates and refer them to epilepsy surgery centers as early in the course of their disorder as possible. The ultimate aims are to offer surgical therapy to the greatest number of patients who might benefit from this intervention, to maximize the opportunities for complete surgical cure, and to prevent the development of adverse psychiatric and social consequences of recurrent disabling epileptic seizures.

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Chapter 167

Indications and Criteria for Surgical Intervention

Michael S. Duchowny

A. Simon Harvey

Michael R. Sperling

Peter D. Williamson

Introduction

The estimated lifetime cumulative incidence and prevalence of epilepsy are 3% and 0.5% respectively, with approximately 60% of patients manifesting partial seizures.[47,48] Although most patients with new-onset epilepsy have few seizures or are well-controlled, an estimated 5% to 10% of patients become sufficiently medically intractable to consider surgical therapy.[47,86] Data from a Danish registry of unselected patients with partial epilepsy suggest a cumulative incidence for intractable epilepsy of 135 per 100,000.[62] Intractable epilepsy is a major risk for personal injury, quality of life, and in some cases, mortality. Furthermore, recurrent seizures have a significant socioeconomic cost to the individual and society.

In recent decades, there has been increasing interest in the surgical treatment of patients with intractable seizures. At the second Palm Desert conference on epilepsy surgery, the number of procedures performed at major epilepsy surgery centers between 1986 and 1990 was more than twice that reported before 1985.[34] This remarkable increase has been fuelled by a combination of technological advances in neuroimaging and electroencephalography, new appreciation of the devastating personal and socioeconomic effects of recurrent seizures, delineation of surgically remediable epilepsy syndromes, and recognition of the long-term benefits of early surgical intervention.

Temporal lobe resections make up approximately two-thirds of all procedures currently performed at epilepsy surgery centers, reflecting the predominance of adult patients with intractable temporal lobe epilepsy (TLE). In pediatric epilepsy surgery centers, a greater proportion of patients undergo extratemporal, multilobar, and hemispheric resections.[54,85,126]

It is currently estimated that as many as 5,000 new patients annually in the United States might benefit from epilepsy surgery,[86] yet less than one-third receive treatment at the major centers.[34] Underutilization of epilepsy surgery is also apparent in other countries.[79,97] The education of primary care physicians to refer patients with surgically remediable epilepsies, instruction of health insurers and government health agencies regarding reimbursement for epilepsy surgery, and refinement of epilepsy surgical protocols should increase the number of patients with intractable epilepsy who may benefit from epilepsy surgery.

Who Is a Candidate for Epilepsy Surgery?

A simple statement can be made that epilepsy surgery may be considered by anyone whose seizures recur despite use of appropriate antiepileptic drugs (AEDs). For properly selected patients, surgery offers a relatively safe and effective means of either abolishing seizures, diminishing their severity, or reducing seizure frequency. Because most of the benefits conferred by surgery accrue when seizures are completely stopped, palliative surgery is a viable option only if it would improve quality of life or lessen the risk of injury or death. Surgery may seem a rather drastic measure for intermittent symptoms that may not prevent someone from living a happy and fulfilling life. However, uncontrolled epilepsy has numerous adverse medical and psychosocial consequences, some of which appear only after years or decades of illness. Surgery is performed precisely because it is effective, and its risks are generally less than the aggregate long-term risks of uncontrolled seizures.

What kinds of seizures and types of epilepsy provoke the consideration of epilepsy surgery? The most common types of seizures that lead people to consider surgery are those that cause alteration of consciousness or awareness or injury. These seizures have the greatest potential to cause injury and impair quality of life. Hence, complex partial and secondarily generalized tonic–clonic seizures are common indications for surgery because of their adverse psychosocial and medical repercussions. Loss of awareness prevents legal operation of a motor vehicle, forces people to rely upon others for transportation (which limits independence), reduces employment opportunities, diminishes educational choices, and imposes psychological burdens. Common activities, such as using pubic transportation, are fraught in ways that people who do not suffer from seizures cannot imagine. In addition, when seizures might cause someone to precipitously fall with resultant injury (e.g., tonic–clonic, atonic, tonic, and some simple partial seizures), activity is further limited. In addition, some seizures, although they might not cause injury or loss of awareness, might be so unpleasant or psychologically disruptive that surgery could still be an option. For example, seizures that either produce intense nausea and vomiting or cause socially unacceptable behavior might warrant surgical therapy. Lastly, some postictal behaviors, such as recurrent postictal psychosis and prolonged postictal confusion or lethargy, may cause more difficulty than the seizures themselves and prompt a patient to consider surgery. In general, the individual who suffers from the seizures is the only one who can state with certainty whether residual symptoms are inadequately controlled or not, although it is the physician's responsibility to assess medical risks.

How often should seizures occur to consider surgery? There is no objectively determined seizure frequency required to consider surgery. Although most people who have surgery have seizures at least once every month or so, others have had fewer seizures and decided that surgery was worthwhile. Having just one or two seizures per year prohibits the legal operation of a motor vehicle and can lead to serious medical and psychosocial consequences. In our experience, some patients with as few as two or three seizures per year have had surgery and viewed it as worthwhile; careful preoperative counseling

should always be performed so that patients will have realistic expectations.

The time at which seizures occur might also influence the decision to have surgery. Seizures that occur at predict-able times pose fewer problems than seizures that appear randomly. For example, the person who has seizures occurring only while asleep (nocturnal seizures) may drive an automobile and live a relatively unrestricted life. However, these seizures might still be psychologically disturbing, disrupt sleep, and pose medical risk so that surgical consideration is legitimate.

Last, the type of epilepsy syndrome must influence the decision to consider surgery. Some types of epilepsy are known to disappear with the passage of time, so that it would be overly aggressively to perform surgery for them. Other types of epilepsy are associated with a progressive downhill course, (e.g., progressive myoclonic epilepsy, seizure associated with malignant tumors) so that surgery will certainly not afford long-term benefit and probably should not be done. Other types of drug-resistant epilepsy (e.g., medial TLE) often favorably respond to surgical treatment, and surgery might be considered early in the course of treatment.

Rationale for Surgical Intervention

In addition to the physical harm posed by epileptic seizures, accumulating evidence suggests that chronic epilepsy results in deterioration of brain function and structure. It is recognized that many patients with epilepsy, particularly patients with seizures of temporal lobe origin, suffer a progressive decline in learning and memory.[51] The loss of verbal memory skills has particularly devastating consequences on quality of life and may lead to a significant decline in socioeconomic status. It is not altogether clear to what degree seizures, their underlying pathologic substrate, or the cumulative effects of drug treatment contribute to decline, but a longer duration of epilepsy appears to be a critical factor in cognitive decline. Helmstaedter et al.[50] performed a longitudinal neurocognitive study of 147 surgically treated and 102 medically treated adults with TLE. They found that a higher proportion of the medically treated group suffered a significant decline in memory skills between 2 and 10 years after baseline evaluation. Seizure-free patients had the best outcome, with superior recovery of both memory and nonmemory functions. Cross-sectional studies have further shown that a duration of TLE greater than two decades is associated with the greatest deterioration of cognitive ability and is independent of patient age and age at seizure onset.[61] Additional evidence suggests that frequent interictal discharges and short nonconvulsive seizures can cumulatively impair cognition and educational achievement.[2]

In parallel with studies of cognition, serial neuroimaging studies in patients with refractory seizures reveal evidence of progressive degeneration at anatomic loci remote from seizure origin. Recurrent temporal lobe seizures are associated with decreased hippocampal volume 3.5 years after seizure onset if recurrent seizures are present,[41] whereas progressive volume reduction occurs in the amygdala and entorhinal cortex ipsilateral to the atrophic hippocampus.[14] Voxel-based morphometry of unilateral TLE reveals abnormalities in the thalamus, cerebellum, and extratemporal neocortex as well as temporal and extratemporal white matter.[80] These findings collectively reveal that chronic TLE is associated with widespread secondary changes that affect multiple brain regions and the connectivity between cerebral hemispheres.

Criteria for Surgical Candidacy

Medical Intractability

The decision to refer patients for epilepsy surgery rests on the perceptions of the patient and physician that medical treatment is failing. These perceptions are based on the belief that the physician has exercised “due diligence”—she has administered optimal medications at high serum therapeutic concentrations. However, there are few established guidelines to assist the physician's choice of medications, dosing interval, duration of treatment, monitoring of serum concentration, and withdrawal of therapy. Thus, medical treatment of seizures is still largely individualized, with no unique point in time when intractability is established.

Certain risk factors dictate a low probability of seizure remission. The likelihood of persistent seizures is increased by additional factors such that patients with multiple risk factors have the poorest outcome.[21] High seizure frequency in the form of daily or weekly episodes constitutes a major risk factor for medical intractability, whereas seizure clustering increases the risk still further.[1] Early seizure onset, particularly in infancy, predicts seizure persistence,[77] and infantile hemiconvulsive status epilepticus (SE) is specifically linked to the development of TLE.[20,42,45] Motor convulsions in a nonconvulsive disorder are a risk factor independent of the number of lifetime episodes.[90] Patients with organic brain damage are less likely to undergo spontaneous seizure remission.[1,56] Thus, abnormal neurologic status by physical examination or neuroimaging criteria is associated with both a greater risk of developing epilepsy and a reduced likelihood of remission. As a rule, the more severe the brain damage, the greater the likelihood of seizure persistence.[113]

Deficient medical management may, in some cases, simulate medical intractability. Patient noncompliance or intermittent compliance may masquerade as “pseudointractable” seizures. Physician failure to administer a first-line or appropriate adjunctive antiepileptic medication, or more commonly failure to attain high therapeutic serum concentrations, is not infrequently discovered in patients referred for surgical evaluation.[43] Nonepileptic disorders and psychogenic seizures must be exposed at the outset, but approximately 10% of epileptic patients also manifest coexistent psychogenic seizures.[23] The range of conditions resembling epilepsy in early childhood is particularly broad.[104] Mistaking complex partial seizures for absence epilepsy, or failing to identify precipitating factors, such as sleep deprivation, leads to suboptimal therapy. Neurodegenerative disorders and inborn errors of metabolism are a rare but important cause of seizures that do not respond to medications, and inborn errors of metabolism may go unrecognized in patients with structural brain abnormalities. Indolent gliomas occasionally manifest as refractory epilepsy but are usually detectable with serial neuroimaging.

Seizure frequency and duration of epilepsy should not be the sole determinants of medical intractability, because infrequent seizures or short duration of epilepsy may still pose significant risks for the patient and impair quality of life. For example, yearly seizures may make it impossible for a patient to drive or perform certain occupations. Similarly, infrequent but severe seizures or recurrent bouts of SE pose a significant medical risk. Occasionally, patients with a relatively brief seizure history present with extremely frequent or disabling seizures, such as in epilepsia partialis continua or certain infantile syndromes. Medical intractability must therefore be assessed in the context of the patient's quality of life and likelihood of seizure remission.

Recent studies suggest that patients at risk for intractable epilepsy can be identified with a surprising degree of accuracy early in the course of their epilepsy. This would suggest that patients can and should be placed on a "watch list" by their treating health care providers. Epilepsy patients who have already experienced multiple seizures before seeking treatment, and who have an inadequate response to initial attempts to control seizures using AEDs are likely to have refractory epilepsy.[71] In children, for example, after adjusting for epilepsy syndrome, the occurrence of high seizure frequency, focal electroencephalographic (EEG) slowing, and acute symptomatic or neonatal SE are associated with a higher risk of intractability, whereas seizure onset between 5 and 9 years was associated with a lower risk.[10] In contrast, lack of early remission in patients who are not medically refractory is not associated with a poor outcome.[9]

Identification of a Surgically Remediable Syndrome

A significant proportion of epilepsy surgery candidates manifest seizures in the context of specific epilepsy syndromes. Candidates for excisional procedures usually have localization-related epilepsy syndromes, whereas candidates for commisural surgery typically have generalized epilepsy syndromes. Patients with surgically amenable epilepsy syndromes fall within the cryptogenic and symptomatic etiologic groups, because idiopathic epilepsy syndromes are genetically determined and are therefore unlikely to be influenced by surgical intervention. Many epilepsy syndromes are well characterized and have defined prognoses, simplifying the selection process; thus, idiopathic partial and generalized epilepsies are not surgically amenable, whereas surgery might be considered the treatment of choice for some specific epilepsy syndromes such as mesial TLE; neocortical epilepsy caused by discrete, easily resectable lesions; chronic epilepsy associated with Sturge-Weber syndrome; tuberous sclerosis; focal cortical dysplasia; hemimegalencephaly; and Rasmussen syndrome.

The Landau-Kleffner syndrome of acquired epileptic aphasia is a rare disorder characterized by regression of language in early childhood, prominent EEG abnormalities, and often seizures. In some children with impaired language who fail medical treatment, multiple subpial transection of perisylvian cortex on one side may be of benefit.[53]

The syndrome of gelastic epilepsy and hypothalamic hamartoma is another rare epilepsy syndrome for which cortical resection and anterior callosotomy are ineffective in alleviating seizures.[17] Recently, seizure remission has been achieved by hamartoma resection,[88,116] confirming seizure origin in the hypothalamic lesion. These observations suggest that other cases of intractable epilepsy syndromes associated with subcortical lesions such as subcortical heterotopias may also be surgically amenable.

Surgical treatment is advocated for some patients with infantile spasms. Infants who fail to respond to treatment with conventional anticonvulsants and corticosteroids, and who demonstrate predominantly unilateral abnormalities on EEG, positron emission tomography (PET), and magnetic resonance imaging (MRI) may be suitable for lobar or multilobar cortical resection.[22,105] Early resective surgery is also indicated in infants with catastrophic presentations of partial seizures.[28]

Loss of Quality of Life

Chronic epilepsy is associated with considerable comorbidity and deterioration in overall quality of life. Decline in social, behavioral, and intellectual domains is a prime motivating factor in seeking surgical intervention. This is especially true for children, who are at higher risk for behavioral and cognitive disturbances as well as the emergence of depression in adolescence.[29,30,86] Children with medically resistant seizures who are intellectually disadvantaged show an even greater compromise in their quality of life, irrespective of their intellectual ability level.[101]

The benefits of surgical intervention have recently been demonstrated for adults with TLE. Aydemir et al.[4] found that successful surgery improved social activities and resulted in greater independence. Similarly, Lowe et al.[78] found that long-term seizure-freedom after temporal lobectomy uniformly improved quality of life.

Earlier definitive surgical intervention would be expected to set the stage for improved self-esteem, greater social opportunity, and career advancement. Two separate studies have confirmed this hypothesis. Van Empelen et al.[118] performed a longitudinal follow-up of 21 children and found that, 2 years after surgery, children began to perceive themselves as being socially more competent and having greater self-worth. Adolescents began to improve sooner after surgery; at 2 years, they demonstrated improvement in the domains of athletic competence and romance. Sabaz et al.[102] also found improved quality of life in a prospective study of families of 35 children with medically resistant epilepsy undergoing epilepsy surgery, but significant gains occurred primarily in patients who became seizure-free.

Role of Early Intervention

The evidence for neuronal injury and subsequent epileptic and cognitive deterioration in chronic epilepsy has been discussed. The detrimental effects of recurrent seizures pose special risks to the developing brain of infants and young children. Uncontrolled seizures also jeopardize the chances for an independent lifestyle, and children with intractable epilepsy are likely to be excluded from normal schools and from social and vocational opportunities.[74,75,76] Thus, uncontrolled chronic epilepsy has the potential for irreversible cognitive, behavioral, and psychosocial problems in later life. For this reason, syndrome characterization, medical intractability and likely prognosis should be established early in patients with uncontrolled seizures, allowing the consideration of early surgical intervention. Additional consideration takes into account the neural plasticity data from lesioning studies,[65,66,67] which suggest that functional recovery from cerebral resection is superior if surgery is performed earlier in postnatal life.

Goals of Surgery

The goal of any treatment for epilepsy is to permit the patient to live as normal a life as possible. Maximizing normal function and minimizing adverse effects is part of the overall goal of therapy, whether medical or surgical. Treatment must therefore restore a sense of well-being and alleviate the psychosocial disability, medical morbidity, mortality, and risk for associated seizures. Refractory-seizure patients often have cognitive, linguistic, motor, sensory, psychiatric, and social impairments,[3,38,39,60,64,111] and treatment must also address these problems. A comprehensive rehabilitative plan is an important component in an epilepsy surgery program.

Two broad categories of surgical therapy for epilepsy, curative and palliative, define the relative success of surgical intervention. Curative surgery eradicates seizures and the need for medication, whereas palliative surgery lessens seizure severity or frequency or prevents the occurrence of some seizure types.

These outcome measures are similar to the goals of surgery in other conditions (e.g., for cancer surgery, complete tumor removal vs. debulking).

Curative surgery should eliminate the psychosocial disability associated with seizures and therefore remains the best hope for achieving a “normal” life, including improved schooling, greater personal independence, enhanced employment opportunities and attainment of a driver's license. Studies have shown that return to a normal lifestyle after surgery rarely occurs in patients who do not achieve seizure freedom.[110] However, curative surgery may also create unanticipated psychosocial problems due to newly acquired independence or upward vocational mobility.[15]

In some patients, only one of several seizure types is cured by surgery, but this may be a worthwhile outcome. For example, patients with mixed seizure disorders usually benefit from elimination or marked reduction in the frequency of tonic or atonic seizures, due to the reduction in medical risk and attendant injuries (e.g., fractures, lacerations). Similarly, patients with TLE may benefit from abolition of complex partial seizures and tolerate occasional auras without loss of consciousness. Palliation requires a clear a priori definition of the surgical objectives, so that an intelligent appraisal of results can follow surgery.

Whenever surgery for epilepsy is contemplated, the risks and benefits must be carefully weighed. The risks of epilepsy surgery are acceptably low in the modern era, with overall mortality being less than 0.5% and morbidity 5%. Surgical complications include cerebral infarction, intracranial hemorrhage, intracranial infection, and direct cranial nerve or cerebral injury, possibly resulting in temporary or permanent neurologic deficits. Morbidity and mortality vary according to the patient's age and type of surgery; risks appear to be slightly higher in children compared with adults, and in hemispherectomy and corpus callosotomy compared to anterior temporal lobectomy and extratemporal resections.[116,117]

The risks of surgery must also be compared with the risks of continued medical treatment. At present, little data address the relative risks of medical versus surgical treatment. Risks associated with ongoing epilepsy and their medical treatments include death, injury, SE, possible detrimental effects of seizures, and adverse effects of medication. People with epilepsy have increased mortality rates compared with the general population,[73] and a preliminary report suggests that this risk might be reduced by epilepsy surgery.[119] A large prospective controlled study of patients with persistent seizures revealed that achieving complete seizure control after epilepsy surgery reduces mortality to a level that is indistinguishable from the general population, whereas seizure persistence is continues to be associated with high mortality rates.[108] Thus, given the reduced risk of death after successful epilepsy surgery, the long-term risks of medical therapy exceed the risks of epilepsy surgery in suitable candidates.

The issue of epileptic and intellectual deterioration in chronic epilepsy is controversial, but experimental and clinical studies provide evidence that seizures can produce cognitive impairment[16,55,98] and produce cellular changes.[5,81] Studies suggest the hippocampus is particularly vulnerable, especially in early childhood.[20,45,103]

Types of Surgical Treatment

Surgical procedures to treat epilepsy include lesionectomy, lobectomy, corticectomy, multiple subpial transection, corpus callosotomy, and various combinations of these procedures. For hemispheric epilepsy syndromes, various forms of hemispheric resection and disconnection are utilized. The specific type of surgery employed for a patient depends on the predominant seizure type, the location of the seizure focus, the presence of a demonstrable lesion, and the patient's cognitive and neurologic status. The timing of surgery must take into account the natural history of the epilepsy syndrome, the patient's developmental status and, in children, issues related to cerebral plasticity.

Mesial Temporal Lobe Epilepsy

Disorders of the mesial temporal lobe often give rise to seizures that ultimately become refractory to medical treatment, constituting the most common surgically remediable epilepsy syndrome. Although mesial temporal lobe epilepsy (MTLE) can be caused by tumors, vascular malformations, developmental anomalies, and other discrete epileptogenic lesions that are potentially resectable, within this condition the most common syndrome is MTLE with hippocampal sclerosis.[40,125] There is often a history of febrile seizures or other neurologic insults in early childhood,[20,45] and complex partial seizures typically begin in the first or second decade. The syndrome is additionally characterized by anterior or midtemporal spikes on EEG and hippocampal atrophy and signal abnormality on MRI.[13,57] Additionally, patients may have temporal lobe hypometabolism on PET,[31,33] temporal lobe hypoperfusion on single photon-emission computed tomography (SPECT),[71,100] and specific memory disturbances on neuropsychological testing and intracarotid amobarbital testing. Longitudinal studies of patients with complex partial seizures suggest that less than 20% undergo spontaneous remission of seizures,[44,69,77] and that a significant proportion of patients with refractory seizures experience cognitive, interpersonal, and psychiatric problems.[74,75,76] Thus, all patients with medically intractable TLE should be given consideration for surgery, early in the course of their epilepsy.

Prior to high-resolution MR and functional neuroimaging, surgical candidates frequently required invasive EEG monitoring with temporal lobe depth or strip electrodes. More recently, preoperative investigations have been limited to scalp EEG monitoring, MRI, neuropsychological testing and, at some centers, PET or SPECT.[32,109,112] Chronic subdural or depth EEG monitoring, or both, are presently advocated for patients without MRI evidence of hippocampal pathology. When language-dominant lateral or posterior neocortical temporal seizures are suspected, extraoperative functional mapping of language is recommended.

For patients with unilateral or predominantly unilateral seizures, most centers perform a standard anterior temporal lobectomy in which the amygdala, anterior hippocampus, and anterior temporal neocortex are resected.[36] Intraoperative electrocorticography and cortical stimulation are used at some centers to tailor the lateral temporal resection according to the extent of EEG abnormality and the location of the language cortex.[27,115] Selective amygdalo-hippocampectomy, sparing the lateral temporal neocortex, is performed at some centers,[106,128] while other centers perform only lateral neocortical resections, sparing amygdala and hippocampus.[70] The aim of modified temporal resections is to reduce postoperative cognitive deficits; however, the indications for these procedures are not standardized and, as a result, surgical decisions are largely based on local institutional philosophy and the results of preoperative MRI and neuropsychological testing.

Lesional Neocortical Epilepsy

Partial epilepsy associated with a discrete neocortical lesion such as a tumor, vascular malformation, or focal cortical dysplasia constitutes another surgically remediable

epilepsy syndrome.[17,91,93] In this setting, the potential exists to cure the patient's seizures with minimal electrophysiologic investigation and localized resection. However, surrounding cortex may harbor occult pathology and be epileptogenic, necessitating more thorough electrophysiologic investigation and wider resection.[11,12] For lesions that do not involve critical cortex, the surgeon can perform a generous resection that includes the lesion and surrounding cortex. When lesions are close to or directly involve language, cognitive, motor, or sensory cortex, excisional surgery may be contraindicated or may only be feasible with stereotactically guided lesionectomy,[18] corticectomy or lesionectomy guided by EEG localization and functional mapping,[12] or resection combined with multiple subpial transection.[82] Patients with large lesions, such as large areas of pachygyria, may still benefit from epilepsy surgery but only by extensive resection of the lesion and surrounding epileptogenic cortex. For patients with multiple lesions, such as patients with tuberous sclerosis or patients with multiple cavernous angiomas, successful surgery is still possible if seizures can be localized to a single lesion or group of lesions.[6,35]

An important surgical consideration is that developmental lesions in proximity to critical cortex do not necessarily displace or transfer function to the opposite hemisphere.[24,25] Complete resection of the lesion appears crucial for seizure-freedom in lesional epilepsy surgery.[37,92] Advances in MRI and functional MRI should facilitate the selection and preoperative investigation of patients with lesional epilepsy.

“Nonlesional” Neocortical Epilepsy

Patients with “nonlesional” partial epilepsy are the most challenging group of surgical candidates and are typically evaluated at specialist centers. Many have extratemporal epileptogenic regions and present with a wide spectrum of simple partial, complex partial, or secondarily generalized seizure types. When the seizure semiology suggests a well-localized site of onset, the scalp EEG shows localized discharges, and the patient's neurologic examination and cognitive profile do not suggest extensive cerebral dysfunction, surgery is a reasonable consideration. By contrast, surgery is often unrewarding in patients with poorly localized electroclinical findings or evidence of pervasive cerebral dysfunction.

A detailed description of the patient's aura and careful attention to the ictal behavioral sequence on video monitoring may suggest the lobe and side of seizure onset. Interictal and ictal EEG monitoring with special electrodes or extra closely spaced electrodes may further localize the field of electrographic abnormality or reveal discharges from basal or interhemispheric cortex that may not be obvious from the routine EEG.[83] Ictal SPECT is particularly useful in nonlesional extratemporal epilepsies, often revealing discrete neocortical regions of activation not appreciated by EEG monitoring or MRI.[46,52] Interictal SPECT and PET are usually unrewarding in aiding localization of “nonlesional” extratemporal epilepsies. Once a putative epileptogenic region is identified, repeat MRI using thin coronal slices and optimized pulse sequences through the suspected region may identify a previously occult lesion.

In patients with no demonstrable cortical lesion, intracranial EEG recording of seizures using subdural or depth electrodes or a combination of both is often necessary to plan the resection.[26,127] Occasional patients with a discrete epileptogenic region may benefit from localized corticectomy, but many patients require large resections due to either poorly demarcated areas of epileptogenicity or evidence of widespread epileptic dysfunction. Alternatively, some centers perform a generous lobectomy or multilobar resection in patients with nonlesional extratemporal epilepsy, based on noninvasive preoperative data and intraoperative electrocorticography. Seizure outcome in this difficult group of patients again depends on the ability to resect the epileptogenic region.[60]

Hemispheric Epilepsy Syndromes

Several neurocutaneous disorders, cerebral malformation syndromes, and acquired cerebral pathologies are manifest by intractable seizures of hemispheric origin. Specific examples include Sturge-Weber syndrome, hemimegalencephaly, Rasmussen syndrome, and infantile hemiplegia with unilateral cerebral atrophy or porencephaly. In the developmental and early acquired syndromes, seizures often begin in early infancy and are associated with developmental slowing, arrest, or regression. In this group, early surgical intervention not only offers relief from seizures but also permits attainment of the child's full developmental potential. Early hemispherectomy for patients with Rasmussen syndrome is advocated by some centers.[121]

Hemispherectomy is generally indicated in patients with widespread unilateral EEG abnormalities, diffuse unilateral structural abnormality, and clinical evidence of hemiparesis and hemianopia. In young patients, hemispherectomy may be performed in the absence of all these features in hopes of greater seizure-freedom and more complete transfer of function to the other hemisphere. Detailed preoperative EEG monitoring and functional neuroimaging are usually unnecessary to lateralize seizures but may help to exclude contralateral seizure onset and confirm the functional integrity of the contralateral hemisphere.

Various surgical techniques are employed to treat hemispheric epilepsy syndromes, and these include anatomic hemispherectomy, functional hemispherectomy, hemispherectomy, and hemidecortication. The choice of technique depends in part on the patient's age, the type of lesion, the size of the hemisphere and lateral ventricle, and the surgeon's expertise.

Secondary Generalized Epilepsies

The symptomatic/cryptogenic generalized epilepsies, such as the Lennox-Gastaut syndrome, bilateral cerebral dysfunction, and bilateral seizure onset, usually preclude focal cortical resection. Atonic, tonic, and tonic–clonic seizures may, in some patients, respond to corpus callosotomy, the rationale being interruption of the rapid secondary bilateral synchrony that underlies these seizures types.[89,107] The indications for corpus callosotomy are not standardized, but patients with “drop attacks” usually respond best. Recurrent episodes of convulsive SE are also eliminated in most cases.[98] The influence of intelligence, EEG abnormalities, and MRI abnormalities on outcome is variable.

Preoperative investigations are usually limited to EEG monitoring and MRI to exclude focal onset of seizures and therefore possible benefit from focal cortical resection. Neuroimaging studies often reveal lateralizing abnormalities, but may also reveal lesser but potentially significant problems in the good hemisphere. Both ictal and interictal EEG may be uninformative and, in some cases, actually misleading by indicating greater abnormalities over the good hemisphere.[122] Documenting seizure types may add useful lateralizing information even in the absence of EEG confirmation.

Debate exists as to the superiority of anterior versus total corpus callosotomy with respect to seizure control and postoperative neuropsychological status. Corpus callosotomy is occasionally performed in patients with nonlocalizable partial epilepsies in whom secondary generalization and falling

occur. Timing of surgery is not an issue in patients with infantile hemiplegia, but may be more problematic in disorders such as Rasmussen syndrome, in which children are generally normal at the outset and then slowly deteriorate. If there is concern for neurologic functions in hemispherectomy candidates, corpus callosum section should be considered. Corpus callosotomy has been offered as an alternative to hemispherectomy in infantile hemiplegia syndromes and remains a viable option.[124]

Contraindications to Surgery

Absolute contraindications to epilepsy surgery include underlying degenerative or metabolic disorders or supervening medical illness. Progressive neurologic disease must therefore be diagnosed at the outset, because these disorders are unlikely to benefit from surgical therapy.

Benign epilepsy syndromes for which seizure remission is anticipated at a later date constitute another absolute contraindication to epilepsy surgery. Benign rolandic epilepsy and benign focal epilepsy of childhood with occipital spikes are the most common idiopathic partial epilepsies, and present with characteristic clinical and EEG features.[49,94] However, some patients with atypical rolandic or occipital seizures may be difficult to differentiate from patients with occult lesional epilepsies.

Relative contraindications to surgery include medication noncompliance, interictal psychosis, and severely dysfunctional family dynamics. Mental retardation is a potential surgical contraindication, but has little practical importance for resective procedures, and is a not a factor in determining candidacy for corpus callosotomy. Medication noncompliance is considered by some to be a contraindication to surgery, because noncompliance compromises the establishment of medical intractability and predicts postoperative noncompliance. Persistent interictal thought disturbance in a patient with intractable epilepsy is a controversial surgical contraindication, because psychotic patients still fare better if their seizures can be controlled.[114] Although mental retardation indicates pervasive cerebral dysfunction, retarded patients also benefit from the elimination of recurrent seizures and medication. Finally, families that are psychodynamically dysfunctional rarely tolerate the intensive or prolonged hospitalizations required for epilepsy surgery and may also be unable to rationally evaluate its attendant risks or work with the epilepsy surgery team members.

Cost-Effectiveness as a Criterion for Surgery

Economic considerations are important when considering epilepsy treatments. Patients who are resistant to medical therapy suffer most from the detrimental economic and social impacts of the condition. Whereas the most refractory patients comprise only a small proportion of those with epilepsy, they account for a large share of the total costs imposed by epilepsy. One study estimated that the 15% of patients who are most refractory account for at least 50% of the total costs of the illness.[8] Another found that cost correlated with the severity of the illness, and that intractable patients cost eight times more that those with controlled epilepsy.[60] The added expense comes from both medical (direct) costs and nonmedical (indirect) costs. Medical expenses include the cost of physician visits, emergency room visits, hospitalizations, medications, diagnostic laboratory testing. These are much higher in patients with recurrent seizures than in controlled patients. Indirect expenses, which account for up to 75% of total costs, include lost productivity from unemployment, underemployment, or lost work time; excess mortality; transfer payments (e.g., disability pension); and lost work by relatives or friends to care for the ill person.[8,59]

Murray et al.[84] estimated the lifetime cost analyses of refractory epilepsy in the United States in the mid 1900s, which were estimated to comprise 29% of adult cases. Indirect costs included lost wages due to unemployment and underemployment and lost caretaker earnings. Transfer payments and mortality costs were excluded. Prevalence analysis found direct costs of $912,553,518 and indirect costs of $2,992,629,945, with a total annual cost of nearly $4 billion (USD) ($11,745/person). Indirect costs accounted for 77% of the total.

In another analysis, Begley et al.[8] estimated the 1995 costs of epilepsy in the United States at $12.5 billion. The direct costs included were direct medical costs. Lost wages and mortality were included in indirect costs. For incident cases, those with intractable epilepsy represented 25% of all cases, but accounted for 79% of estimated costs; indirect costs accounted for 88% of the total expense. For prevalence cases, patients with intractable epilepsy comprised 43% of all cases, but accounted for 80% of estimated costs; indirect costs accounted for 84% of the total cost.

The foregoing analyses all show that refractory patients are far more expensive than well-controlled patients, and one could infer that successful treatment of refractory patients—that is, making them seizure-free—would reduce costs in the long run. Several analyses have been performed to assess the cost-utility or cost-effectiveness of epilepsy surgery.[68,71,95,96] Similar conclusions have been drawn from all analyses, that epilepsy surgery is cost-effective. King et al. calculated that the cumulative discounted benefit from temporal lobectomy was 1.1 quality adjusted life years (QALYs), equivalent to 1.1 extra years in good health. They found that surgical evaluation and treatment had an average marginal cost of $29,800 per patient, yielding a cost-utility ratio of $27,200 per QALY. Langiftt et al.[71] determined that surgery conferred an improvement of 1.61 QALY, for a cost of $15,581 per QALY for surgery.

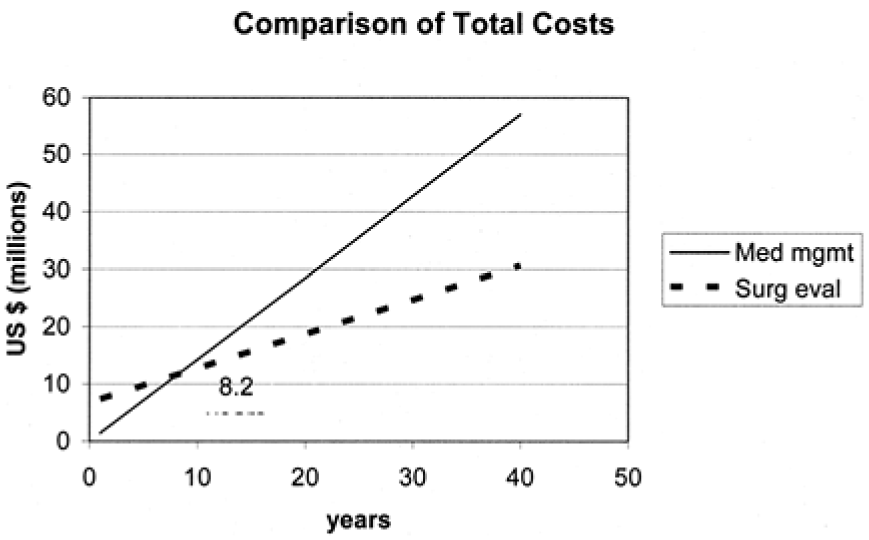

FIGURE 1. Medical management (*solid line*) has a higher per annum cost than surgical treatment. Although cheaper in the early years, the cumulative effect is that net costs over many decades are considerably higher than for surgical treatment (*dashed line*). (From Platt M, Sperling, MR. A comparison of surgical and medical costs for refractory epilepsy. *Epilepsia*. 2002;43(Suppl 4):25–31, with permission.)

Several studies have compared the costs of medical and surgical therapy. Wiebe et al.[123] modeled long-term direct medical costs in two cohorts each containing 100 patients: One treated medically, and the other evaluated for surgery. For a 35-year period, they estimated that the cost for treating the medical group were $10,741,425, whereas the cost for treating the surgical group was $8,117,911. Sensitivity analyses did not change the findings. This study did not estimate nonmedical direct costs nor indirect costs, and therefore the dollar amounts reflect only a portion of the overall costs in medical and surgical therapy. Platt and Sperling[96] performed an analysis comparing medical and surgical costs in an American cohort, and concluded that surgical treatment of TLE is cheaper than medical therapy, although this clearly requires a long-term societal perspective. When all indirect costs are combined with direct costs (Fig. 1), the total costs for the surgical group were less than the medical group 8.2 years after assignment, approximately 45% less time than if only direct costs are used in the calculations. The disparity in costs increased further with the passage of time. More recently, Picot et al.[95] evaluated a French cohort and had remarkably similar findings—that cost-effectiveness is demonstrated between 7 and 8 years after surgery. Whereas surgery has much higher costs in the first year, due to the expense of testing and hospitalization, the long-term benefit is substantial since patients who favorably respond to surgical treatment have much reduced costs in the long run.

Summary and Conclusions

The different medical and psychosocial backgrounds of the patients, the variety of investigational modalities available to the physician, and the number of potential surgical procedures detract from the precision of the selection process. Nevertheless, efforts are underway to delineate selection criteria and preoperative protocols for the surgical treatment of the more common surgically remediable epilepsy syndromes. If it can be demonstrated conclusively that recurrent seizures are harmful to the developing or fully developed brain, it is likely that surgery will be considered at an earlier point in the treatment time-line. Early surgical intervention in appropriately screened patients is likely to benefit long-term neurobehavioral status, in addition to controlling seizures, and thus improve overall quality of life and costs to the patient and community.

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Chapter 168

Surgically Remediable Syndromes

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Introduction

The safety and efficacy of surgical treatment for epilepsy have improved greatly in recent years as a result of major advances in diagnostic technology, particularly long-term electroencephalographic (EEG) monitoring and neuroimaging, as well as refinements in surgical procedures.[21,24,32,56] The vast majority of patients can undergo surgical intervention without the need for chronic invasive recordings, which contributes greatly to a decrease in morbidity, mortality, and cost, and more accurate localization of the epileptogenic region has resulted in better surgical results, leaving 80% to 90% seizure-free in some series of carefully selected patients. These developments have led to an important conceptual advance in epilepsy surgery: The view that surgical intervention need not always be considered a therapy of last resort but, rather, an early treatment of choice for certain well-defined surgically remediable syndromes.[23,24,29] Surgically remediable epilepsy syndromes are disorders for which (a) the pathophysiology is understood; (b) the natural history is reasonably well known to be medically refractory or even progressive once the major first-line antiepileptic drugs (AEDs) fail; (c) presurgical evaluation can be accomplished noninvasively; and (d) surgery offers an excellent chance that disabling seizures will be completely eliminated.

The prototype of a surgically remediable syndrome is mesial temporal lobe epilepsy (MTLE), the form of temporal lobe epilepsy (TLE) that is often, but not always, associated with hippocampal sclerosis (HS).[91,92] Neocortical epilepsies caused by well-circumscribed solitary lesions[13] and a variety of unilateral but relatively diffuse hemispheric disorders in infants and young children[78] are also in this category.

Arguments for Early Intervention

Uncontrolled epileptic seizures can severely impair activities of daily living. In MTLE, complex partial seizures are usually prominent in adolescence and early adulthood, when they disrupt schooling and the acquisition of the social and vocational skills necessary to lead a normal, productive, and satisfying life. Frequent seizures in infants and young children can have an even more disastrous effect on psychomotor development. The avoidance of irreversible psychosocial consequences of epilepsy, therefore, is a strong argument for early intervention in surgically remediable epilepsies. There is, however, additional evidence for direct deleterious effects of certain seizure types on the brain.[84] The progressive nature of epilepsy, although controversial, has been well demonstrated by phenomena such as kindling[38] and secondary epileptogenesis,[59] seen in experimental animal models. If similar processes exist in human epilepsy, they could result in a worsening of epileptic seizures, manifested as more frequent or more severe seizures, more medically refractory seizures, or perhaps even surgically refractory seizures. Enduring disruption of normal cerebral function and the appearance of interictal behavioral disturbances could also result from these progressive changes or appear as a side effect of those natural, protective seizure-suppressing mechanisms that develop to maintain the interictal state.[26]

What is the evidence that progressive processes exist in the surgically remediable epileptic syndromes? In MTLE, seizures usually do not become medically refractory until many years after onset of the habitual events,[8] and interictal behavioral disturbances are reported to be common in this disorder.[25,92] Furthermore, some evidence suggests that surgery is less likely to produce complete freedom from seizures when performed late in the course of the disorder.[27] In lesional neocortical epilepsy (LNE), late surgical intervention also decreases prognosis for elimination of all ictal events.[60] In both these disorders, cognitive function improves following surgical treatment, particularly the material-specific memory function of the temporal lobe contralateral to an anterior temporal lobectomy.[70] Reversal of developmental delay by surgery for diffuse hemispheric epileptogenic disturbances in infants and young children[79] is particularly remarkable because children with these disorders who continue to have seizures almost invariably develop mental retardation and often require institutional care. These observations strongly support the view that at least some types of epileptic seizures can themselves induce progressive cerebral dysfunction and provide a strong case for early surgical intervention.[25]

Because complete freedom from seizures early in the course of the disorder can prevent the development of disabling psychosocial consequences of epilepsy as well as interictal behavioral disturbances that might result directly from seizures, early surgical intervention for the surgically remediable syndromes offers the best opportunity for achieving a normal postoperative quality of life (88). Also, because the cost of presurgical evaluation and of the surgery itself is the same whether performed early or late, and early intervention is most likely to eliminate future medical expenses and result in an independent, tax-paying individual, this approach is certainly more cost-effective.

To practice early intervention, however, it is necessary to redefine the concept of medical intractability, and this requires further study. At present, for adolescents and adults, failure of two or perhaps three of the most appropriate AEDs as monotherapy at maximum tolerable doses seems to be an adequate definition, whereas the use of second-line medications and multiple-drug combinations would unnecessarily delay a potentially definitive therapy. The need for rapidly establishing surgical candidacy may be even more urgent for infants and young children with very frequent seizures and developmental delay. Specific ages at which a timely decision might be particularly critical are (a) 5 to 7 years, when the plastic properties of the developing brain begin to decrease sufficiently to cause concern that hemispherectomy or multilobar resection will cause additional neurologic disability, particularly for language; and (b) early adolescence, when continuing seizures have a negative effect on social development and academic achievement.

Recognition that a patient might have a surgically remediable epilepsy syndrome as soon as possible after the onset of seizures and expedient trials of the most effective AEDs to establish medical intractability in a timely manner provide the best opportunity for early surgical intervention and optimum postoperative results. To achieve this goal, it is necessary for primary care physicians and practicing neurologists in the community to know how to identify these patients so that crucial years are not lost pursuing ineffective pharmacotherapy. The remainder of this chapter is devoted to the best-defined surgically remediable epilepsy syndromes.

Specific Syndromes

Syndromes to be Excluded from Early Surgical Intervention

It is important to note at the outset that many epilepsy disorders that are not surgically remediable syndromes can be easily identified early in their course. Obviously, patients with benign idiopathic epilepsies are not candidates for surgical treatment; most of these disorders are characterized by generalized seizures that are easily controlled by medication. An old argument against early surgical treatment for TLE in children, however, was that temporal lobe seizures often disappear in adolescence. Now that the syndrome of benign childhood epilepsy with centrotemporal spikes and related disorders can be readily distinguished from TLE,[50,51] it is believed that most patients previously thought to recover spontaneously from TLE[52,53,54] actually had idiopathic localization-related epilepsy. Because the clinical and EEG presentation is so characteristic, and the seizures are so responsive to medication, children with idiopathic localization-related epilepsy that will resolve spontaneously are easily excluded from a presurgical population. At the other extreme are patients with clearly intractable seizures who do not meet the criteria for having a benign idiopathic syndrome, but who have either no abnormalities on structural or functional neuroimaging or diffuse bilateral lesions.

These patients may well ultimately become surgical candidates; however, if the epileptogenic region can be defined only electrographically, the surgical results are not as good as for patients with surgically remediable syndromes, and the need for invasive monitoring greatly increases the risk and cost of presurgical evaluation.[87] It is reasonable, therefore, to pursue additional AEDs alone and in combination for much longer periods before such patients are referred for surgical treatment.

Mesial Temporal Lobe Epilepsy

Most patients considered candidates for surgical treatment today have localization-related symptomatic epilepsies, with seizures resulting from an epileptogenic lesion that is limited to one hemisphere and is potentially resectable. Lesions in the limbic system, particularly those involving mesial temporal structures, give rise to complex partial seizures with a relatively characteristic semiology as a result of preferential propagation patterns that are reasonably well understood. Because anterior temporal resections are the most commonly performed surgical treatment for epilepsy, a considerable amount of basic research has been done on mesial temporal tissues taken from patients with medically refractory complex partial seizures, and a common pathophysiologic substrate has been described for many. This consists of HS,[7] the most common lesion found in patients with epilepsy.[75] Most workers now recognize a syndrome of MTLE with HS (MTLE-HS) that has characteristic clinical features, often gives rise to medically refractory complex partial seizures, and responds well to surgical intervention (Table 1).[23,91,92] Sixty percent to 80% of patients with this disorder can expect to become free of disabling seizures following anterior temporal lobectomy.[31,32,90]

HS is characterized by a specific pattern of cell loss and neuronal reorganization that is presumed to underlie the epileptogenicity.[6] Although structural changes are concentrated in the hippocampus, amygdala, and adjacent limbic cortex, functional disturbances are much more extensive. Hypometabolism on positron emission tomography (PET) usually involves the entire temporal lobe and frequently includes the ipsilateral thalamus and, less often, other ipsilateral cortical and subcortical structures,[30,40] and contralateral mesial temporal abnormalities are evidenced by the common appearance of contralateral interictal EEG spikes[31] and material-specific memory disturbances.[69] It is unclear to what extent these abnormalities reflect mechanisms that contribute to epileptogenicity and to what extent they reflect disruption of normal function caused by propagation of epileptic activity. Although merely resecting the anterior and mesial portions of the temporal lobe, and in some cases only the amygdala and hippocampus, can abolish disabling seizures, auras tend to persist in this group of patients, supporting a view that the epileptogenic region is widespread.[91]

The fact that habitual seizures in MTLE-HS most commonly begin within the first decade of life and are usually responsive to medication for several years, with events characteristically becoming refractory to medication in adolescence,[8] suggests some progressive nature of the epileptogenic process. The commonly encountered family history and presence of microdysplasias in this disorder suggest a familial and/or congenital predisposition to the development of HS, given a specific cerebral insult early in life.[91] The frequent occurrence of prolonged febrile convulsions can be seen as evidence of a preexisting epileptic diathesis but also could serve as a HS-inducing insult. Other early insults are common in this disorder,[57] and it is conceivable that, in some children, seemingly innocuous events, such as common childhood viruses, are sufficient to set the epileptogenic process in motion. The resultant characteristic cell loss and neuronal reorganization are accompanied by the development of a propensity to generate spontaneous epileptic seizures. This presumably takes many years, accounting for the latent period between the initial insult and the onset of habitual ictal events.[37] It would be unreasonable to assume, however, that this epileptogenic process would suddenly cease at this point; rather, it is more logical to suggest that these underlying aberrant neuronal changes continue to some extent and account for a worsening of the epileptic condition and the eventual appearance of medically refractory seizures.[28] Similar progressive changes might also account for the even later appearance of interictal behavioral disturbances.[26] For this reason, and because 60% to 80% of patients can expect to become seizure-free following appropriate anterior mesial temporal lobe resection, early surgical intervention as soon as monotherapy with the two or three preferred AEDs has failed would offer the best opportunity for relief of seizures, complete psychosocial rehabilitation, and a normal, productive lifestyle.[23,24,25,32]

Table 1 The Syndrome of Mesial Temporal Lobe Epilepsy with Hippocampal Sclerosis (MTLE-HS)[a]

History

Increased incidence of complicated febrile convulsions

Increased incidence of a family history of epilepsy

Onset in latter half of first decade of life

Auras common and occur in isolation

Secondarily generalized seizures occur infrequently

Seizures often remit for several years until adolescence or early adulthood

Seizures often become medically intractable

Interictal behavioral disturbances can occur (most commonly depression)

Clinical seizure

Aura is usually present: most common is epigastric rising, often other autonomic or psychic symptoms, with emotion (e.g., fear), can be olfactory or gustatory sensation (several seconds)

Complex partial seizure: often begins with arrest and stare, oroalimentary automatisms and complex automatisms common; posturing of one upper extremity can occur contralateral to the ictal discharge (1 to 2 min)

Postictal phase: usually includes disorientation, recent memory deficit, amnesia for the event, and dysphasia if seizures begin in the language-dominant hemisphere (several minutes)

Neurologic examination

Usually normal

Can have recent memory deficit

EEG

Unilateral or bilateral independent anterior temporal spikes, maximum amplitude in basal electrodes

Can have intermittent or continuous rhythmic slowing in one mesial temporal area

Extracranially recorded ictal activity appears only with complex partial symptoms, usually initial or delayed focal onset pattern of 5- to 7 per second rhythmic activity, maximum amplitude in one basal temporal derivation

Depth electrode recorded ictal onset most often high-amplitude rhythmic spikes or sharp waves, less commonly low-voltage fast or suppression

Propagation to contralateral side is slow (>5 sec, but may be minutes) or does not occur at all

Focal functional deficits

Usually temporal lobe hypometabolism on interictal FDG-PET, often involves ipsilateral thalamus and basal ganglia

Usually temporal lobe hypoperfusion on interictal SPECT and characteristic pattern of hyper- and hypoperfusion on ictal SPECT

Usually material-specific memory disturbances on neuropsychological testing and amnesia with contralateral intracarotid sodium amobarbital injection

Mesial temporal EEG slowing and attenuation of normal rhythms can be seen with scalp/sphenoidal electrodes but more common with depth electrodes; exacerbated by intravenous pentobarbital test

Structural imaging

Usually has small hippocampus on one side on MRI

Usually has increased hippocampal T2 signal on one side on MRI

Can have small temporal lobe on one side

Can have enlarged temporal horn on one side

Can have reduced NAA on MRS

Pathophysiology

Hippocampal sclerosis (>30% cell loss with specific patterns)

Sprouting of dentate granule cell mossy fibers

Selective loss of certain hilar neurons (somatostatin- and NPY-containing cells)

Gliosis

Dentate laminar dispersion

Hamartomas and heterotopias can occur as "dual pathology"

Microdysgenesis common

Seizures usually originate in sclerotic hippocampus, but much larger area appears to be included in the epileptogenic region

Features that place diagnosis in doubt

History of severe head trauma, encephalitis, or other specific causal events after the age of 5

Focal motor or specific sensory symptoms at seizure onset or postictally

Interictal focal neurologic deficits other than memory disturbance

Marked cognitive impairment on neuropsychological testing

Bilaterally synchronous, generalized, or extratemporal focal EEG spikes

Diffuse or extratemporal focal EEG slowing
Cerebral lesion other than hippocampal sclerosis on MRI

Modified from Engel J Jr. Update on surgical treatment of the epilepsies. *Neurology.* 1993;43:1612–1617, with permission.

MTLE-HS can usually be suspected early in the course of this disorder from the typical history and characteristic simple and complex partial seizures (see Table 1). Referral to an epilepsy surgery program should be made once habitual seizures become disabling and are resistant to at least two appropriate AEDs at maximum tolerable doses. At most

epilepsy surgery centers, demonstration with long-term EEG video monitoring that the habitual seizures originate electrographically from one mesial temporal area and either magnetic resonance imaging (MRI) evidence that the hippocampus on that side is damaged or PET evidence that the temporal lobe on that side is hypometabolic is sufficient to recommend surgery, provided there are no conflicting findings such as atypical initial seizure semiology, other suspicious lesions on MRI, or evidence of a nonconcordant localized functional deficit. Surgical treatment for MTLE-HS, as well as MTLE due to most other causes, is particularly cost-effective because the presurgical evaluation can almost always be performed noninvasively, and the chances of restoring the patient to a completely normal lifestyle are high, making this an ideal surgically remediable syndrome.

Lesional Focal Epilepsies

The pathologic finding underlying the epileptogenic zone in approximately 30% of patients undergoing epilepsy surgery is a *substrate-directed* abnormality, such as a tumor or vascular malformation.[13] Identification of the epileptogenic lesions by MRI is imperative in patients with pharmacoresistant seizures because of the demonstrated beneficial effect of surgical treatment.[11,12] MRI has increased the identification of structural alterations in patients being considered for surgical treatment of intractable focal epilepsy.[12,74] Surgically remediable epilepsy syndromes associated with substrate-directed focal epilepsy includes patients with MTLE related to HS (see previous section) and lesional epilepsy syndromes.[13,90] Selected patients with lesional focal epilepsy may be highly favorable candidates for surgical treatment. The surgical pathologies in patients with lesional focal epilepsy include primary brain neoplasm, vascular anomaly, and a malformation of cortical development (MCD).[13] The common tumors identified at the time of surgical excision of the epileptogenic cortex include low-grade gliomas, gangliogliomas, dysembryoplastic neuroepitheliomas (DNETs), and mixed glial neoplasms.[11,12,62,82] The cavernous hemangioma with remote hemorrhage is the most frequently resected vascular anomaly in patients with medically refractory focal epilepsy.[13] Focal cortical dysplasia is an increasingly important etiology of lesional focal epilepsy because of the increased diagnostic yield of structural neuroimaging techniques and the performance of epilepsy surgery in younger patients.[63,81] The outcome of epilepsy surgery depends on the pathology and location of the epileptogenic lesion.[13] Approximately 80% of patients with a low-grade glial neoplasm, ganglioglioma, DNET, or cavernous hemangioma are rendered seizure-free following surgical treatment. Resection of a focal MCD in individuals with lesional focal epilepsy is less effective in reducing seizure tendency.[14,63,81] Patients with MTLE are more favorable candidates to achieve a seizure remission than are those individuals with neocortical (mainly frontal lobe) focal seizures.[62,90,91]

The electroclinical presentation and response to AED therapy in patients with lesions in medial temporal structures are indistinguishable from those with focal seizures caused by HS.[34,93] Patients with lesional epileptic syndromes, however, may not have all the clinical features of MTLE shown in Table 1, although this remains to be clearly demonstrated. The ictal semiology of patients with lateral temporal or extratemporal neocortical lesions can also be similar to that of individuals with HS if there is propagation of seizure activity to the amygdala and hippocampus. In these patients, the initial ictal symptom or aura may provide a clue as to the neocortical onset of the seizures. Complex partial seizures associated with a visual aura suggest an occipital lobe onset, and those with an auditory or vertiginous aura suggest a lateral temporal onset.[1] Not uncommonly, however, the ictal semiology in patients with lateral temporal lesions reflects spread into the amygdala or hippocampus, which does not allow differentiation from MTLE related to HS. Neocortical epileptogenic lesions that do not produce a spread of ictal discharges into the mesial temporal structures give rise to partial seizures with clinical features different from MTLE. Neocortical focal seizures more commonly are associated with secondarily generalized tonic–clonic seizure activity.

Importantly, the neuroimaging findings alone should not be used to determine operative candidacy and surgical planning.[12,74] Certain lesions, such as focal cortical dysplasia, may fail to be identified by MRI or may be multifocal, which does not allow determination of the site of seizure onset.[13,63] Imaging alterations consistent with venous angiomas and small-vessel cerebral infarction are less likely to be epileptogenic. A consensus exists at present that a comprehensive epilepsy presurgical evaluation should be performed in patients with a suspected substrate-directed focal epilepsy associated with pharmacoresistant seizures to establish a relationship between the MRI-identified lesion and the epileptogenic zone.[35] Long-term EEG monitoring is considered necessary because of the possibility that the lesion can be remote from the ictal onset zone.[13] Subtraction ictal single photon emission computed tomography (SPECT) coregistered with MRI (SISCOM) has been shown to be useful in the operative strategy of patients with substrate-directed focal epilepsy and in planning the placement of intracranial EEG electrodes for identification of the ictal onset zone.[12,63] The rationale for chronic intracranial EEG recordings in patients with lesional epileptic syndromes is predominantly to determine the location of essential cerebral cortex that should not be damaged during surgery.[13,35] The most effective operative strategy in patients with lesional epilepsy includes a total lesionectomy with cortical margins.[35] Lesions involving essential cortex can be safely resected using extraoperative or intraoperative cortical functional mapping.[64] Lesionectomy alone based on stereotactically derived operative techniques can render some patients seizure-free, although removal of cortical margins increases the chances of a beneficial seizure outcome.[13,15,35] Postoperative MRI should be performed to confirm the extent of lesion excision. Residual or recurrent structural abnormalities can be associated with focal seizure activity and prompt a consideration for surgical reoperation.[82]

Diffuse Hemispheric Epilepsies

Some epileptic disorders, such as Rasmussen encephalitis, Sturge-Weber syndrome, and hemimegalencephaly, are associated with epileptogenic structural disturbances that tend to be limited to one hemisphere. These give rise to severe medically refractory epileptic seizures that are typically unilateral. However, the seizures can appear to be bilateral although they are caused by an abnormality in a single hemisphere. The structural pathology is usually associated with a contralateral hemiparesis and, in such cases, the removal of the entire epileptogenic hemisphere causes little or no additional neurologic deficit and offers an excellent chance of seizure remission.[3,78]

In 1950, Krynauw reported 12 children in whom he performed hemispherectomy to treat medically intractable epilepsy.[48] The initial reports were very encouraging because the children had markedly improved seizure control and, as a bonus, had improved behavior and cognition. Over the next decade, more that 50 hemispherectomies were performed with similar results. However, in 1966, the first report of a serious long-term complication was published, indicating that 7 to 11 years after hemispherectomy, some children developed recurrent intracranial bleeds with fatal consequences.[65] Some centers found that this occurred in as many as 30% of the

patients.[94] The enthusiasm for hemispherectomy waned until improved surgical techniques were developed. This complication is no longer a significant problem, and hemispherectomy is now one of the most successful surgical procedures used in the treatment of intractable epilepsy.[67] The procedure is typically performed in patients with Rasmussen encephalitis, Sturge-Weber syndrome, infantile hemiplegic epilepsy, or severe developmental defects such as hemicortical dysplasia or hemimegalencephaly. These disorders are reviewed briefly, as they relate to surgical therapy.

Rasmussen encephalitis was first reported in 1958.[68] It is a sporadic disease of unknown cause. Most patients are entirely normal until the onset of seizures, generally around 5 years of age. They typically begin with focal seizures that become increasingly frequent and medically intractable, culminating in nearly continuous seizures (epilepsia partialis continua). The majority develop progressive hemiparesis and moderate dementia if seizures are not controlled. Rarely, progressive hemiplegia can precede the onset of seizures or can be the only indication of Rasmussen encephalitis.[46] Hemispherectomy is currently considered the treatment of choice. However, there have been reports indicating the presence of antibodies to the brain receptor GluR3 in some Rasmussen encephalitis patients,[72] but GluR3 antibodies do not occur in all patients.[89] Autoantibodies to *N*-methyl-D-aspartate (NMDA)-type GluRepsilon2 have also been reported.[85] Because of the implication that autoimmunity to specific receptors may underlie Rasmussen encephalitis, plasmapheresis and/or high-dose intravenous immunoglobulin (IVIG) therapy have been touted as possible therapies, but no convincing evidence suggests that such therapy is successful in the long-term.[33] Immunomodulatory therapy can slow disease progression for a time and can be considered in patients with late-onset disease in the dominant hemisphere or in patients with bilateral involvement.[39] In most cases, resective surgery should be considered as soon as the diagnosis is confirmed and some degree of hemiparesis has developed. Although most patients will require hemispherectomy, an occasional patient can benefit by a more localized cortical resection. In other patients, the disease is more diffuse throughout the hemisphere, but significant hemiparesis has not developed, and the question of timing of hemispherectomy arises. If the patient is old enough to begin to lose plasticity for language, has involvement of the language-dominant hemisphere, and the diagnosis has been confirmed (usually by biopsy), it may be necessary to perform the hemispherectomy, thus causing a new hemiparesis but preserving maximum potential for language recovery.

Sturge-Weber syndrome is characterized by angiomatosis of the leptomeninges over the posterior area of the hemisphere, resulting in progressive injury to the subjacent cortex. Thus, most patients have gyriform calcification of the ipsilateral occipital/parietal cerebral cortex (usually after 2 years of age), contralateral seizures and hemiplegia, mental retardation plus associated ipsilateral facial angiomatosis, and glaucoma. If patients have severe, uncontrolled epilepsy in the first year of life, cortical resection is indicated. Although hemispherectomy is often required, if the cortical involvement is limited to the occipital/parietal areas, then a more limited resection can be possible, thereby preserving motor function. Early surgery can prevent progression with consequent damage to frontal structures and can also result in improved cognitive outcome in those patients with early-onset seizures that are medically intractable.[4] In one study, poor developmental outcome correlated best with high seizure intensity in the early period rather than with age of onset or degree of hemiparesis.[47] Some authors suggest that surgery should be performed as soon as the diagnosis is confirmed, but others suggest that surgery should be reserved for patients with intractable seizures. Because many patients with Sturge-Weber syndrome will do well developmentally if seizures can be controlled with anticonvulsant drugs, surgery may create an unnecessary neurologic deficit. Surgery should be reserved for patients who have demonstrated medical intractability.

Although infantile hemiplegic epilepsy is not a recognized syndrome, the term describes a group of children noted to have hemiparesis early in life, and who develop intractable focal and secondarily generalized seizures. Many of these patients have encephaloclastic lesions such as porencephalic cyst, often in the distribution of the middle cerebral artery, suggesting an early-onset stroke. Some patients have developmental disorders such as hemimegalencephaly or schizencephaly, while others have the hemiconvulsion, hemiplegia, and epilepsy (HHE) syndrome characterized by acute-onset focal seizures followed by the appearance of hemiplegia and intractable epilepsy. Whatever the cause, severe hemiparesis associated with medically intractable seizures should trigger consideration of hemispherectomy. Many children also have involvement of the visual system, with partial or complete hemianopsia. It has been noted that in such cases, using the term "hemispherectomy" to describe the surgery is not entirely accurate; "tidying up what Mother Nature has done" more accurately reflects the character of the surgery.

The decision to perform hemispherectomy or hemispherotomy is relatively straightforward in some patients (e.g., severe hemiplegia with frequent and intractable partial seizures); in others, it can be quite difficult (e.g., infantile spasms with only generalized electrographic seizures). The epilepsy syndromes that are amenable to hemispherectomy usually are associated with severe, very frequent seizures, failure to acquire normal cognitive abilities if the seizures begin very early in life (e.g., Sturge–Weber syndrome), or loss of intellect if a later onset of seizures occurs (e.g., Rasmussen encephalitis). Because hemispherectomy always results in hemiparesis with loss of fine motor control of the affected hand, the hoped-for improvement in seizure control, cognition, and language must be balanced against any surgically induced loss of motor function. In cases with established moderate or severe hemiparesis, there is little motor ability to be lost, so the decision to perform surgery is relatively easy. However, in patients with a progressive disorder such as Rasmussen encephalitis, the decision can be more difficult. As a general rule, the patient should have, as a minimum, some loss of hand function before hemispherectomy is considered. But the decision process can be further compounded by potential loss of language skills if the dominant hemisphere is involved and the child has acquired language. In patients less than 6 or 7 years of age, the side of language dominance is not critical because "plasticity" will allow for development of language in the remaining hemisphere. After that age, the plasticity gradually decreases. It is not clear at what age language could not be recovered, but patients as old as 11 years have had left hemispherectomy with recovery of substantial language ability.[33] When the patient has involvement of the dominant hemisphere, surgery should not be unnecessarily delayed once it is clear that hemispherectomy is the treatment of choice, even though the surgery may result in significant loss of motor function.

Secondary Generalized Epilepsies in Infants and Small Children

Symptomatic generalized epilepsies have, in the past, been considered to be the result of diffuse, bilateral brain disturbances, and thus, the patients were not candidates for treatment by cortical resection. It is now clear that some children have generalized seizures as the result of localized cortical abnormalities. Initial studies indicated that patients with infantile spasms were the primary candidates for this approach. However, recent

reports indicate that some young children with catastrophic childhood epilepsies other that infantile spasms are also surgical candidates. Because the attention has been directed to infantile spasms, many other children with other seizure types and significant developmental failure were not referred until much later in their course. In a recent report, the developmental outcome was better in the patients with infantile spasms who had been referred for surgery early compared with patients who had similar pathology but did not have infantile spasms, because the latter patients were referred later in their course.[44]

The concept that generalized seizures could result from a localized brain abnormality is not entirely new. Indeed, there have been a few published cases of patients with focal brain abnormalities in whom a surgical procedure resulted in cessation of infantile spasms. For example, infantile spasms ceased after surgical resection of a right temporal astrocytoma in one case,[58] by resection of a choroid plexus papilloma in another,[9] and by fenestration of porencephalic cysts in four cases.[66] Since these reports, it has become clear that many patients with generalized seizures have a localized cortical disturbance that is amenable to surgical intervention.[17,18,77,78,79,80] Other workers have now made similar observations. Uthman et al.[86] reported that an 18-month-old child with infantile spasms was successfully treated by surgical resection of a porencephalic cyst. Similarly, Carrazana et al.[10] reported that six children with identified localized cortical disturbances associated with infantile spasms had good response to surgery. The cortical disturbance has been called the *zone of cortical abnormality* (ZCA) by the University of California Los Angeles (UCLA) group to distinguish it from the concept of the epileptogenic region. This distinction is necessary because the seizures may be generalized in onset, despite being caused by a localized cortical abnormality and, as such, identification of the electrographic area of seizure onset may not be relevant.

Recent reports indicate that another generalized seizure disorder associated with developmental decline is amenable to effective surgical intervention. Hypothalamic hamartoma has long been recognized as a cause of gelastic seizures. Most patients start having seizures early in life and suffer moderate developmental consequences. Anticonvulsant medications are rarely helpful and surgical interventions via the subfrontal or temporal approach have had high morbidity and poor seizure control. Improvements in surgical techniques and approach have markedly improved both seizure control and developmental outcome.[51a,75,95a]

The identification of appropriate candidates for the evaluation for epilepsy surgery can be more difficult among patients with infantile spasms or other generalized seizure disorders than among those suffering from partial seizures. The “gold standard” for most epilepsy surgery candidates is the identification of the area of seizure onset. Because patients with infantile spasms typically have generalized seizures, this approach cannot be used. However, almost all patients with infantile spasms who ultimately had cortical resection to control seizures had evidence of focal cortical abnormalities prior to the formal surgical evaluation. Many patients with infantile spasms caused by a ZCA had focal seizures and/or focal cortical abnormalities detected by EEG, x-ray, computed tomography (CT), or MRI.

It has long been recognized that other seizure types can be associated with infantile spasms, including focal seizures.[43,45,55,95] Carrazana et al.[10] reported 16 children in whom consistent focal seizures preceded the onset of infantile spasms, and Donat and Wright[20] reported 11 patients with focal seizures that occurred simultaneously with infantile spasms. Indeed, even the characteristic hypsarrhythmia pattern can be asymmetric or unilateral.[42] Careful observation can reveal focal disturbances more frequently than had been previously appreciated; Riikonen[71] observed focal abnormalities in 110 of 149 cases. Focal abnormalities can be easier to detect in the early EEGs. Once the hypsarrhythmia is established, it is easy to miss relatively subtle EEG abnormalities, such as focal slowing or decreased β activity. In addition, the relationship between infantile spasms and focal seizures can become less apparent with time. Carrazana et al.[10] noted that the relationship between focal seizures and infantile spasms was lost in 11 of 12 patients followed for more than 6 months. Thus, early identification of localized EEG abnormalities may be critical.

Structural defects detected by CT or MRI are less common but may be more obvious than the EEG abnormalities.[83] Alvarez et al.[2] reported three children with porencephaly who developed infantile spasms. They proposed that the porencephaly was the cause of the infantile spasms. Cusmai et al.[19] found CT evidence of focal abnormalities in 17 of 174 cases. Sankar et al.[73] reported that MRI is able to detect very subtle focal gray matter disorders by developmental changes in the subjacent white matter. Chugani et al.[16,18] first reported that PET could detect cortical disturbances, in some cases even when the MRI and CT are normal. However, advances in MRI imaging have greatly improved our ability to identify subtle focal cortical dysplasias that were not able to be detected in the past. PET scan remains an important adjunct in many cases. Magnetoencephalography (MEG) is also playing a role in some difficult cases.[67a] It is especially useful in patients with tuberous sclerosis who have numerous cortical tubers but only one or two that are responsible for the seizures.

Because the goal of the evaluation is to identify the ZCA, it would seem likely that patients who are surgical candidates have evidence of the presence of a ZCA prior to the formal surgical evaluation. Indeed, many patients do demonstrate clear evidence of a localized brain disturbance. The characteristics of patients with infantile spasms who may be considered for surgical evaluation are noted in Table 2.

At the conclusion of surgical evaluation, children are recommended for surgery if there is a confluence of historical, EEG, closed-circuit television (CCTV)/EEG, CT, MRI, PET, and/or MEG data indicating the presence of a ZCA (a single lobe, contiguous multilobes, or one hemisphere). No single abnormal test is sufficient to lead to surgery. Surgical resection of the ZCA results in complete or near-complete control of the seizures, including generalized seizures, in about 75% of cases. More important, perhaps, is the observation that the developmental outcome can be improved.[5,44] The improvement is related to age at surgery (earlier being better for development) and to severity of developmental delay at the time of surgery. Not surprisingly, children who had better development at the time of surgery had the best developmental outcomes.

Table 2 Profile of Patients with Infantile Spasms Who May Be Considered Candidates for Evaluation for Epilepsy Surgery

1. The seizures are medically intractable
    - As a minimum, the child should have failed adrenocorticotropic hormone (ACTH) or prednisone, plus one or two other anticonvulsant medications; early evidence suggests that vigabatrin can be particularly effective in this group of patients and should be administered prior to surgical consideration if possible (it is not approved in the United States as of this writing)
2. Evidence of localized brain abnormality
    - The most useful is a localized abnormality on neuroimaging (cortical disturbances are best seen with MRI or PET, but CT and SPECT can also be very helpful); and/or
    - There are focal seizures that precede, follow, or occur simultaneously with the infantile spasms; and/or
    - The interictal EEG shows evidence of localized cortical disturbance such as:
        - Unihemispheric or localized delta activity
        - Unihemispheric or localized decreased or absent beta activity
        - Localized interictal epileptiform discharges including hemihypsarrhythmia
        - Unilateral sleep spindles
    - The ictal EEG is localized;[76] generalized seizures such as infantile spasms can be preceded or followed by consisently localized epileptic activity; and/or
    - There is an abnormal neurologic examination with localized features

Other Situations in Which Surgical Treatment Can Be Considered

Surgical treatment can be very effective in patients who do not have obvious surgically remediable syndromes. All patients with symptomatic epilepsy who have disabling, medically refractory seizures should be considered *potential* surgical candidates; however, if they do not have one of the recognized surgically remediable syndromes, it is quite likely that chronic intracranial recordings will be necessary to delineate the epileptogenic region for surgical resection, and chances for complete cure may be relatively small. Consequently, surgical intervention is often not as cost-effective as it is for the surgically remediable syndromes, and trials of second-line AEDs, as well as polypharmacy, may be justified before surgical referral is considered. This includes patients with diffuse or bilateral

structural lesions in whom only one small part of the structural abnormality might be epileptogenic, as is sometimes the case with schizencephaly,[49] or in patients who have ictal EEG onsets that are poorly defined or appear to be coming independently from both hemispheres. Corpus callosotomy remains a surgical option for patients with disabling drop attacks that do not respond to AEDs or vagal nerve stimulation.[36] Multiple subpial transection is an alternative surgical approach that spares cortical function when the epileptogenic region involves essential cortical areas, as is the case, for example, in Landau-Kleffner syndrome.[61]

When electroclinical data indicate that focal seizures are of neocortical origin, but no structural lesion can be identified, surgical treatment is based on electrographic delineation of the boundaries of the epileptogenic region, and results are often poor.[87] In these patients, seizures could be caused by (a) structural lesions similar to those that produce LNE but are too small to be identified; (b) pathologic processes similar to those that occur with HS, which can not be detected by available histochemical techniques; or (c) an entirely different, and as yet unknown, epileptogenic pathologic process. It is likely that more than one explanation for this condition exists. The relatively poor results encountered under these circumstances could be related to failure to delineate accurately the epileptogenic region and adequately remove it or to the possibility that the underlying disturbance is actually very widespread. If the latter is the case, the associated functional disruption would appear to be subtle compared to that observed with MTLE because a large region of hypometabolism is rarely encountered with interictal PET in nonlesional neocortical epilepsy, as opposed to its common association with MTLE.[41]

Summary and Conclusions

Early surgical intervention for medically refractory epilepsy provides the best opportunity for complete freedom from seizures and avoidance of irreversible psychosocial consequences of disabling illness. As a result of recent advances in presurgical diagnosis, as well as improvements in the safety and efficacy of surgical treatment for epilepsy, an excellent postoperative outcome can be confidently predicted in appropriately identified surgical candidates. For this reason, surgical intervention is no longer considered a last resort but rather an early treatment of choice for certain well-defined surgically remediable syndromes for which (a) the pathophysiology is understood; (b) the natural history is reasonably well known to be medically refractory or even progressive; (c) presurgical evaluation requires only noninvasive studies; and (d) surgery offers a 60% or greater chance of abolishing disabling seizures. Examples of surgically remediable syndromes include MTLE-HS; focal epilepsy caused by discrete structural lesions that can be resected without introducing additional neurologic deficit; and catastrophic unilateral or secondary generalized epilepsies of infants and young children that result from disturbances confined to one hemisphere, such as hemimegalencephaly, Sturge-Weber syndrome, Rasmussen encephalitis, and relatively large but unilateral developmental abnormalities such as cortical dysplasias and porencephalic cysts. These conditions can be treated with anteromesial temporal lobectomy, localized cortical resection, hemispherectomy, hemispherotomy, or multilobar resection. The best results with respect to subsequent seizures, psychosocial readjustment, and quality of life are obtained when surgery is performed as soon as it can be established that high-dose first-line AEDs as monotherapy have failed.

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Chapter 169

Presurgical Evaluation: General Principles and Methods

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Introduction

Epilepsy surgery is considered when seizures are incompletely controlled by medication and it is apparent that further medical therapy will be futile. Surgery is typically offered to patients who have uncontrolled seizures that are disabling, cause loss of awareness, pose risk of injury, impair quality of life, or are psychologically disruptive. When the question of surgery arises in such cases, a presurgical evaluation should be performed. The evaluation is carried out by multidisciplinary teams composed of epilepsy specialists in neurology, neurosurgery, neurophysiology, neuroradiology, psychiatry, and neuropsychology, with additional input from professionals in social work and nursing. This chapter reviews the basic objectives, methods, and principles of the presurgical evaluation. A brief overview of the testing generally included in presurgical evaluations is provided, with full details about each method referred to in subsequent chapters.

Timing of Referral for Presurgical Evaluation

The goal of any treatment for patients with epilepsy is “no seizures, no side effects,” as advocated at the National Institutes of Health (NIH)-sponsored meeting Curing Epilepsy: Focus on the Future; A White House-Initiated Conference on Epilepsy (CURE).[48,94] For most patients, even a rare seizure can be an unacceptable level of control because of restrictions on driving and the impact on social and vocational status.[96,103] While the CURE group acknowledged that complete seizure control cannot be achieved in all patients, it recognized that complete absence of seizures made such a difference in a person's quality of life that this objective should be as close to the standard of care as possible.

Physician experts in epilepsy care recommend that patients with refractory epilepsy, defined as failure of two to three appropriate antiepileptic drugs (AEDs) or disabling medication side effects, should be referred to a comprehensive epilepsy center for a further evaluation that includes surgery as one of the therapeutic options.[5,13,26] The purpose of the referral is to verify that patients have a correct epilepsy diagnosis (i.e., exclude nonepileptic seizures and improper seizure classification that may affect treatment recommendations) and to consider all potential further therapies, such as surgery, that might be employed in an attempt to stop seizures. Of course, not every patient referred to an epilepsy center will have surgery.[9] Changes in medical management can often substantially improve seizure control or even eliminate seizures so that patients can be returned to their community physicians. Likewise, additional nonsurgical therapies, such as the ketogenic diet and vagus nerve stimulator (VNS), can be considered at the time of a presurgical evaluation.[37,39,99]

There is now irrefutable evidence that uncontrolled seizures are associated with progressive anatomic and functional changes, neurologic compromise,[52,67,88,97] and higher than expected mortality rates.[74,78,90] Although there still continues to be some debate as to the definition of therapy resistant,[8,10,68] these considerations have led to the recommendation that therapy-resistant patients should be referred to an epilepsy center for presurgical evaluation once they have failed initial AED therapy.[12,14,33,35] This recommendation is especially important for infants and young children, who are at greatest risk of epilepsy-induced encephalopathy.[29,53,54] It has even been advised that children with uncontrolled seizures or infantile spasms under age 2 years should be referred to a specialty center regardless of magnetic resonance imaging (MRI) findings.[26] MRI-demonstrated lesions should also be referred to an epilepsy center for presurgical evaluation, regardless of seizure control, as these substrates may eventually lead to therapy-resistant seizures, or the lesion itself may prove to be progressive.[28,85] In addition, intractable focal epilepsy can result from low-incidence etiologies that require the special experience of a comprehensive epilepsy center. Examples of these pathologies include adolescents and adults with focal cortical dysplasia and hippocampal sclerosis, and children with hemimegalencephaly,[82] Rasmussen syndrome,[11] Sturge-Weber Syndrome,[31] tuberous sclerosis complex,[31] Landau-Kleffner syndrome,[73] hypothalamic hamartomas,[45,66] and polymicrogyria.[3] The upper limit at which surgery should be considered is not certain. We have had successful experience with surgery for patients in their 60s who are otherwise in good health.

Goals and Types of Surgical Considerations

The goal of a presurgical evaluation is to characterize a patient's epilepsy thoroughly and completely. In doing so, the multidisciplinary epilepsy team determines what type of seizures and epilepsy syndrome the patient has and the likelihood that it can be treated successfully with surgery. At the completion of the process, the team should be able to provide the patient and his or her family with a comprehensive assessment of the risks and benefits of different treatments and the risks that may be associated with the natural history of the epilepsy syndrome. If surgery is an option, a detailed description of the proposed surgical procedure, surgical risks that may be encountered, and long-term seizure control that can be anticipated from medical therapy alone should be provided. This information must be

communicated effectively to patients and their families so they can make informed decisions about subsequent management. The epilepsy team cannot tell the patient what to do, but it can provide sufficient information and education, in a manner that patients can understand, so that they and their families are informed about all the options and can make decisions about their care. It should also be noted that there are no age restrictions in considering patients as possible candidates for epilepsy surgery.[43,69]

The types of surgical procedures can be divided into two general categories.[69] *Resective* operations are those where the intent of the surgery is to remove the epileptogenic brain area. The goal of resective surgery is to eliminate seizures completely and, hopefully, improve cognitive and psychosocial outcomes (see Chapter 167). Most resective procedures involve removal of cerebral cortex, and they can be subclassified as focal (lesion and surrounding cortex, Chapters 176, 177, and 179), lobar or multilobar (Chapter 178), or hemispheric (hemispherectomy, Chapter 178). Resections can also involve removal of subcortical lesions, like hypothalamic hamartomas[35,36] (Chapter 250). Also included under this category are procedures like radiosurgery, where focused x-ray beams destroy defined epileptogenic regions of the brain, and multiple subpial transections (MSTs; Chapter 182), which are thought to disconnect epileptogenic zones selectively from the rest of the cortex.[72] With *palliative* procedures, the intent of therapy is to stop the most disabling seizures and/or reduce seizure frequency, but not necessarily eliminate all seizures. The most common palliative operations are corpus callosotomy[40,65,77] (Chapter 180) and VNS[7,37] (Chapter 131). Most callosotomies involve sectioning of the anterior two thirds to four fifths of the callosum, although a complete callosotomy is occasionally done in individuals with a major unilateral deficit or after failure of initial anterior resection.

Localized Cortical Resections and Cerebral Hemispherectomy

The ideal candidate for resective surgery is a patient with therapy-resistant epilepsy due to a clearly demarcated localized brain abnormality (symptomatic epilepsy) where removal of the pathologic lesion has a high probability of producing seizure control with acceptable or no side effects.[33,34] The precise identification and localization of the responsible epileptogenic brain region is the goal of the presurgical evaluation.[44] Thus, the evaluation aims to (a) identify discrete structural abnormalities using modern neuroimaging and, inferentially, from associated functional deficits; (b) provide convincing evidence that seizures arise at or near the structural lesion; and (c) establish whether eloquent brain regions that support speech and motor-sensory functions are at risk. If these objectives are satisfied, then there is a high likelihood of a good postoperative seizure control. However, these aims may be modified in some patients with well-defined seizure syndromes or in individuals at risk for seizure-induced cognitive deficits. For example, patients with MRI-demonstrated unilateral hippocampal sclerosis may have multiple areas of interictal or ictal abnormalities on electroencephalography (EEG) but still respond well to anterior lobe resection. Similarly, infants and children with symptomatic epilepsy may present with what appears clinically and electrographically to be generalized epilepsy, but they nonetheless sometimes respond well to surgical removal of an identified cortical abnormality such as cortical dysplasia.[23,24] Perhaps the ultimate localized cortical resection is cerebral hemispherectomy, an operation that has evolved considerably over the years.[25,30] The basic objective in evaluating patients for hemispherectomy is similar to that in focal resection, namely, to identify an area of brain that can be removed safely to eliminate seizures. The presurgical evaluation in patients who are candidates for hemispherectomy aims to establish the following: (a) a unilateral structural abnormality; (b) widely distributed abnormal excitability in that hemisphere; and, in older children and adults, (c) significant impairment of motor and sensory function (and perhaps language) in that hemisphere.

Palliative Surgery

Corpus callosotomy and VNS can be useful when the realistic therapeutic goal is to reduce the burden of epilepsy without stopping all seizures. As a consequence, the clinical approach to such patients and the surgical risk–benefit ratio are different than for patients being considered for resective surgery. When epileptogenic areas of the brain are widespread and involve both hemispheres, localized cortical resection is not usually a viable option. However, interruption of the interhemispheric connections via corpus callosotomy or stimulation of the vagus nerve (VNS) can often palliate seizures in such patients. This is especially true for patients that suffer injuries from generalized tonic, atonic, and tonic–clonic seizures. Corpus callosotomy and VNS may also benefit patients with complex partial seizures who are not candidates for focal resection.[6,83] For palliative procedures, the evaluation should determine if there is (a) evidence of generalized epilepsy or nonlocalizable partial epilepsy with abnormal generalized or multifocal discharges on the EEG, (b) lack of suitability for a resective procedure, and (c) presence of tonic, atonic, tonic–clonic, or therapy-resistant complex partial seizures. Neuroimaging is less critical in planning palliative operations unless it strongly suggests a discrete lesion, in which case consideration should be given to a focal resection.[93]

The Conceptual Approach to Defining Epileptogenesis

The overriding principle of the presurgical evaluation is to define abnormalities of structure and function that can be attributed to abnormal cortical areas and EEG-determined pathologic excitability, and then remove those cortical areas in which all relevant data are concordant. Historically, our concepts of what constitutes the cortical region(s) that should be removed to control seizures have been determined by the evolving tools available for clinical use.[34] Over time, a series of terms that embody these concepts have been developed.[32,81] They are recapitulated and described here based on the current state of our understanding and their application to the evaluation process. In general, the greater the degree of overlap among the different tests, the higher the likelihood of accurately defining the epileptogenic zone and achieving a good postsurgical result.

Epileptogenic Zone

Identifying the epileptogenic zone is the fundamental goal of the presurgical evaluation. The epileptogenic zone is defined as that area of cortex that is indispensable for the generation of clinical seizures and that, if removed in its entirety, would abolish seizures. Clinicians use various diagnostic tools to try to define this zone, including analysis of seizure semiology, interictal and ictal EEG recordings, and neuroimaging (MRI, ictal single photon emission computed tomography [SPECT], ^{18}F-fluorodeoxyglucose positron emission tomography [FDG-PET]). However, each of these methods defines cortical zones

that are associated with different aspects of epileptic symptomatology. At the present time, there is no direct way to define the epileptogenic zone definitively. Rather, inferences about the boundaries of the epileptogenic zone are inferred from the composite picture that is pieced together through an understanding of the sensitivities and specificities of each of the diagnostic methods described below.

Irritative Zone

This is the cortical area that is capable of generating interictal EEG discharges.[86] The interictal spike is usually closely related to the brain area that generates seizures but it is not identical to it. Interictal spikes often appear beyond the region that needs to be removed for seizure control; can be more limited in spatial extent than the epileptogenic zone; or may be entirely absent over a discrete structural or functional lesion.[76] Moreover, the location and extent of the irritative zone depends on the EEG method employed. For example, because of the disparate volumes of cortex sampled by scalp, intracranial electrodes, and magnetoencephalography (MEG)/magnetic source imaging (MSI), the irritative zone is defined somewhat differently by each.[4,79] The duration of EEG recording; whether sleep is recorded and, if so, what stages are included; seizure frequency; and timing of the EEG in relation to monthly hormonal cycles can all influence localization of the irritative zone.

Ictal Onset Zone

This is the cortical area from which seizures arise as recorded by EEG or MEG/MSI. It also is not congruous with the epileptogenic zone, which is often a larger region of cortex. While the ictal onset zone provides an approximate indication of the brain region involved in seizure generation, resection of the ictal onset zone alone may not result in elimination of seizures. As with the irritative zone, the ictal onset zone is typically defined by scalp and intracranial EEG.[87] MEG/MSI, however, is increasingly used to determine the area of ictal onset.[58,104] The delineation of the ictal onset zone is methodology dependent, in that extracranial EEG often provides a somewhat different picture than intracranial EEG, which in turn may differ from results obtained by MEG/MSI. Moreover, whether intracranial EEG is recorded by depth or strip electrodes can also influence the identification of the ictal onset zone because of bias introduced by the amount of spatial sampling of the EEG, the frequencies measured, and the size and number of electrodes used.

Although it seems logical that removal of the cortical tissue in which seizures start would abolish them, even careful extirpation of a precisely defined area of seizure onset offers no assurances that seizures will stop. The potential ictal onset zone is a manifestation of a complex nonlinear system with predilections for certain topographic regions.[61,71] Resection of just the observed area of ictal onset without addressing the underlying histopathologic substrate may simply enable a new cortical region to become the preferred zone of seizure origin. Because of these variables, the spatial extent of the irritative zone is not as precisely delineated as might be hoped.

Epileptogenic Lesion

The epileptogenic lesion is the structurally abnormal area of brain that presumably causes the epilepsy; it is best identified using high-resolution MRI.[18,19,80,101] Although complete excision of a structural lesion usually ensures a good postoperative result, it does not guarantee success.[64] Sometimes the structural lesion is incidental and unrelated to the epilepsy. Thus, it is important to confirm the epileptogenicity of a lesion using EEG before presuming it is the cause of the seizures.[18] Alternatively, the visible structural lesion may comprise only a portion of the histopathologic abnormality. For example, developmental tumors, cavernous angiomas, or subtle cortical dysplasia (Palmini type I)[75,84] may be accompanied by a tandem sclerotic hippocampus located distant from the tumor (dual pathology), or microscopic disease may occupy cortical areas more extensively than indicated by the macroscopic lesion.[98] It is also important to note that a portion of the epileptogenic zone may contain anatomically normal but functionally abnormal tissue that must be excised for seizure relief.[19]

Functional Deficit Zone

This is the area of cortex that produces interictal dysfunction, such as abnormalities found on neurologic examination, deficits discovered with cognitive testing, regions of impaired perfusion or metabolism defined by nuclear medicine scanning (e.g., PET, SPECT), or a focal nonepileptiform EEG abnormality, among others.[70,100] Determining this zone is useful because it is presumed that such functional deficits are related to an underlying structural abnormality or physiologic derangement of the brain. This information provides confirmatory evidence to support the identity of the ictal onset zone and epileptogenic lesion. The scope of the functional deficit zone depends greatly on the tests used. Some measures may overestimate the size of the epileptogenic zone, whereas others may underestimate it. For example, FDG-PET scans often reveal extensive temporal, nontemporal, and subcortical abnormalities in patients with mesial temporal lobe epilepsy who respond to an anteromesial temporal resection. Nonetheless, information gained by testing for a functional deficit is an important component of the presurgical evaluation as it helps physicians and patients understand the extent of abnormalities that exist before surgery and that may not be improved after surgery.

Symptomatogenic Zone

The symptomatogenic zone is the area of cortex that, when activated by a seizure, produces the initial symptoms and signs of a seizure.[81] Because it is impossible to tell whether the first ictal symptoms arise from the ictal onset zone or from propagation of the seizure to more distant cortex, and because seizures often arise in "silent" cortex, early features of the seizure are only moderately reliable as an indication of localization. Production of clinical symptoms and signs by secondary spread are probably more common. They can still be helpful if propagation routes are known. For example, an aura consisting of a rising epigastric sensation is moderately specific for a mesial temporal lobe seizure, although it actually may arise elsewhere. Likewise, forced head version, unilateral ictal dystonia, postictal aphasia, postictal nose wiping, unilateral eye blinking, and ictal vomiting are other ictal manifestations that have localizing value.

Overview of Presurgical Methods

As already noted, different methods and tests are used to define the epileptogenic zone, and no single presurgical test provides definitive information on which surgery can be based. Rather, data from multiple tests are integrated to form a hypothesis regarding the likely location and extent of the epileptogenic zone. Some tests are benign and pose little or no risk. Others can cause discomfort or risk of injury. With the remarkable technologic advancements that have occurred over the past two decades, most patients now proceed to surgery without an invasive presurgical evaluation, and the future should see a further increase in the proportion of these patients where the presurgical evaluation is nearly risk free.

Table 1 Tests Used in Evaluation of Patients

- Noninvasive tests
  - Tests of structure
    - MRI including DTI
  - Tests of excitability
    - Interictal and ictal video-EEG
    - Ictal SPECT and PET

- Interictal and ictal MEG/MSI
- Ictal functional MRI

- Tests of functional deficit
  - Interictal EEG
  - Interictal PET
  - Interictal SPECT
  - Wada test
  - Neuropsychological testing
  - Interictal MEG
  - Interictal functional MRI
  - Magnetic resonance spectroscopy
- Tests of cortical function
  - Wada test
  - Functional MRI
  - Magnetic stimulation
  - PET
  - MEG

Invasive tests

- Tests of excitability

- Intraoperative ECoG
  - Chronic interictal and ictal semi-invasive and intracranial EEG
- Tests of functional deficit
  - Interictal EEG
- Tests of cortical function
  - Intraoperative electrical stimulation
  - Extraoperative electrical stimulation

DTI, diffusion tensor imaging; ECoG, electrocorticography; EEG, electroencephalography; MEG/MSI, magnetoencephalography/ magnetic source imaging; MRI, magnetic resonance imaging; PET, positron emission tomography; SPECT, single photon emission computed tomography.

Tests can be broadly categorized as noninvasive or invasive (Table 1). Certain noninvasive tests, like EEG (Chapters 73 and 74) and MRI (Chapter 79), are routinely used in the presurgical evaluation of all patients. Other noninvasive tests, like ictal SPECT (Chapter 81), FDG-PET (Chapter 80) and neuropsychological examinations (Chapters 90 and 91), supplement EEG and MRI and are used on an as-needed basis. Invasive testing, which refers to EEG recordings made from implanted intracranial electrodes, are reserved for patients in whom the results of noninvasive testing are inconclusive or conflicting, or who need careful delineation of specific areas of cortical function before a resection can be offered. The degree to which different noninvasive tests are used, the access to different technologies, and the experience of the epilepsy team vary somewhat from one epilepsy center to the next, and these considerations usually play a role in whether invasive EEG monitoring is recommended.[105]

It must be emphasized that the most important part of the presurgical evaluation takes place before any tests are performed. The neurologic history provides the critical elements, and all subsequent testing must be considered in light of the patient's history. Knowledge of the patient's early development, a history of any neurologic injury or febrile convulsions, need for special education, the age when seizures started, the tempo at which the epilepsy developed, the existence of a latent period, the types of seizures experienced and whether they generalize, seizure duration, the time of day that seizures occur, their relation to monthly hormonal cycles, characteristics of the aura and its evolution, features of the postictal period, response to medications, and family history is critical to determining if surgery will be feasible and what the chances of success are. The neurologic examination can also provide useful information. Consider the following example. A child had a history of a prolonged febrile convulsion at age 1, development of afebrile seizures at age 8, and a latent period without seizures from ages 12 to 16, followed by the development of uncontrolled epilepsy. Seizures were characterized by an initial rising epigastric aura leading to diurnal complex partial seizures with postictal speech difficulty. There were no secondarily generalized seizures. The patient had difficulty learning new material, and neurologic examination showed a diminished right nasolabial fold. This information alone points to an almost certain diagnosis of mesial temporal lobe epilepsy, probably of left-sided origin. For this patient, further testing is useful but will likely only validate the clinical diagnosis. Furthermore, this clinical information implies that the postoperative prognosis is excellent, although additional testing will help confirm that opinion. Thus, while there is no question that technology has made surgery available to a larger number of patients and improved outcome, it must supplement, not supplant, clinical judgment. Experienced epileptologists and neurosurgeons should recognize those features of the neurologic history and examination that are key to making correct diagnostic and treatment decisions.

Noninvasive Tests

Electroencephalography

Despite its clinical introduction more than 70 years ago, EEG remains an essential tool in evaluating patients for epilepsy surgery[57,76] (Chapter 73). When combined with the history and neurologic examination, the interictal EEG often suggests the diagnosis of the epilepsy syndrome and whether it can be treated surgically. For example, observing generalized slow spike-and-wave activity or widespread multifocal spikes in a patient with significant developmental delay raises the possibility of Lennox-Gastaut syndrome, where corpus callosotomy and VNS are more likely to be used if any operative procedure is indicated. Persistent interictal frontal lobe spikes are usually correlated with frontal lobe epilepsy, as anterior temporal lobe spikes are with temporal lobe epilepsy.[49,50,91,92] However, the limitations of interictal EEG are well known, and it is hoped that more sophisticated EEG techniques being developed will be of even greater help in epilepsy diagnosis.[36,106] Likewise, the presence of nonepileptiform abnormalities, such as a focal interictal slow-wave disturbance, also helps in identifying functionally abnormal areas of the brain and assist in understanding clinical phenomenology and planning surgery.

The ictal scalp EEG remains the definitive method of establishing the diagnosis of epilepsy (Chapter 74). Epileptic seizures have now been sufficiently characterized by video-EEG monitoring that different ictal EEG patterns have diagnostic value in helping classify the type of epilepsy. Moreover, the ictal scalp EEG often accurately suggests the site of seizure origin, although it sometimes lacks sensitivity and specificity.[62] An ictal EEG may be obtained with continuous monitoring performed either on an outpatient or an inpatient basis. However, inpatient monitoring offers more flexibility and substantial technical advantages, especially for managing antiepileptic medications and obtaining video studies of behavior (Chapter 93).

Analysis of ictal behavior has an important role in the presurgical evaluation. In epilepsy monitoring units, video monitoring is routinely used to record behavior. It accurately documents ictal semiology, and this is helpful in confirming the origin of the seizures.[81] In addition, focal postictal deficits, such as aphasia, provide valuable localizing information.

Structural Brain Imaging

Advances in structural brain imaging have revolutionized our concepts of surgically treatable epilepsy syndromes and reduced the need for intracranial EEG recordings.[42] Because identification of a structural abnormality is one of the key objectives of the presurgical evaluation, neuroimaging, especially using high-resolution MRI with newer techniques like diffusion tensor imaging (DTI), has become irreplaceable (Chapter 79). The routine availability of high-resolution MRI has substantially increased identification of tumors and cortical malformations as well as cortical dysplasia and atrophic lesions such as hippocampal atrophy.[1,2,20,21,47,82] Additionally, some preoperative MRI findings, such as hippocampal atrophy, have been correlated with seizure relief and cognitive status after surgery.

Functional Neuroimaging

Several techniques provide additional physiologic information, thereby helping to define the functional deficit zone or area of ictal onset. PET scans using FDG and other ligands show localized defects in the brain's metabolism[55,56,70,100] that often correspond to the epileptogenic zone (Chapter 80). PET has particular value in infants and children with neocortical epilepsy, as EEG and MRI may not fully reveal the spatial extent or even the presence of a localized epileptogenic zone in such cases.[24] SPECT shows characteristic changes in perfusion in the interictal state, during seizures, and postictally that help identify sites for resection.[46,59] Its highest yield appears to be in the ictal or immediate postictal states, and ictal subtraction SPECT can provide important localizing information (Chapter 81). Functional MRI can also show localized perfusion abnormalities in focal epilepsy (Chapter 83). Magnetic resonance spectroscopy and MEG/MSI are other tools that are capable of demonstrating localized or lateralized deficits in focal epilepsy, and they are assuming a larger role in defining zones of interictal functional deficit[38,95] (Chapter 82). Because the presurgical evaluation obtains different types of information that can be used collectively to make a surgical decision, neuroimaging has acquired great importance as a result of its versatility.

Neuropsychological Testing

Neuropsychological evaluation provides information about the patient's baseline cognitive, linguistic, and other higher cortical functions[41,60] (Chapter 90). The localizing value of neuropsychological testing is more variable in patients with intractable epilepsy beginning in early childhood, as cortical functions may have reorganized or developed in atypical ways. Consequently, neuropsychological testing in children with epilepsy requires special expertise and flexibility, as usual and traditional rules regarding localization of brain function may not apply (Chapter 91).

Psychiatric Evaluation

The patient's psychiatric status has a bearing on outcome, and therefore most patients ideally should have a psychiatric evaluation before surgery, preferably by a psychiatrist experienced with the particular emotional and psychiatric symptoms and conditions in this patient population (see Chapter 209). As a practical matter, appropriate preoperative diagnosis can avert, or at least anticipate, possible psychiatric decompensation around the time of surgery. While major psychiatric disorders used to be considered a contraindication for epilepsy surgery, more flexibility is now the rule as centers have gained substantial experience in managing psychiatric disorders.[16,17] Some have argued that epilepsy surgery may have the additional benefit in children of reducing or preventing the likelihood of future behavioral and psychiatric problems.[26]

Wada Test

The intracarotid amobarbital procedure (Wada test) is used to assess hemispheric dominance for language and evaluate the contribution of each hemisphere to supporting long-term memory (Chapter 173). In separately anesthetizing each hemisphere with an intracarotid amobarbital injection, this test is not entirely risk free, although the chance of a permanent serious complication is low. As a localizing tool, the test is used mainly in temporal lobe epilepsy patients to compare recognition memory in each hemisphere and determine the risk of postoperative global amnesia. It also helps define the functional deficit zone and assists in predicting seizure relief after surgery.[63,92]

Functional Magnetic Resonance Imaging and Magnetoencephalography

Newer noninvasive techniques are increasingly being applied to map cortical function in relation to epileptogenic cortex. Functional MRI (fMRI) provides discrete localization of motor, sensory, visual, and cognitive functions (Chapter 83). MEG/MSI can help identify cortex capable of initiating seizures and also map sensory and language cortex (Chapter 78).

Invasive Tests

Intracranial EEG recordings are obtained in circumstances when resective surgery is being considered and noninvasive tests have failed to define the presumed epileptogenic zone unambiguously. Intracranial EEG affords the opportunity to record the beginning of a seizure without the limitations of scalp EEG. Currently, it is used in about one third of patients undergoing resective epilepsy surgery.[9] To obtain intracranial EEG requires surgically placing electrodes within or over the brain (Chapter 171). Although it is reasonably safe, the operation carries a small risk of complications.[15] Also, the principle of offering surgery based on concordant data of different types (e.g., structural, epileptiform, and nonepileptiform functional) from the noninvasive surgical evaluation is modified when intracranial EEG is performed. With intracranial EEG, the decision to offer surgery rests primarily on the ictal EEG findings. If seizure onset is well localized, resective surgery is recommended. If it is poorly localized or multifocal seizure onsets are detected, then resective surgery is often not advised.

It must be recognized, however, that the value of intracranial EEG is limited.[51] Removal of the ictal onset zone determined by intracranial EEG, no matter how well defined, does not always result in abolition of seizures. To optimize the chance of finding a resectable ictal onset zone, the surgical team must have a well-framed hypothesis regarding its possible location that guides the placement of intracranial electrodes. Here, the noninvasive evaluation plays a key role in establishing a few reasonable possibilities. Answers are then sought to the following questions: Is there a single ictal onset zone, and where is it located? What is its extent? Is it near a structural lesion or functional area of the brain? What is the function of the cortex in that region, and will its removal lead to a permanent deficit?

Intracranial Electrodes

These are discussed in detail in Chapter 171, and only comments need be made here. The main types of electrodes used are intracerebral or depth electrodes, subdural electrodes, and epidural electrodes. Depth electrodes are placed within the substance of the brain and find their greatest use in recording from buried cortex such as hippocampus. Subdural and epidural electrodes are best suited to record from the neocortical surface of the brain, whether over the convexity, in the interhemispheric fissures, or from basal surfaces. Depth and subdural electrodes may be used in combination, depending on the questions posed, to allow the surgical team to map the ictal onset zone and trace the route of ictal spread. These electrodes are used for chronic EEG recording lasting from several days to several weeks. The main purpose of chronic monitoring is to record seizures, characterizing the ictal onset zone and patterns of seizure propagation.

Intraoperative electrocorticography (ECoG) can be performed in the interictal state during surgery to further define the area to be resected, either as an independent procedure or to supplement chronic intracranial recording (Chapter 172). The major limitation of this ECoG is that of time, because it is restricted to the operation.

Semi-invasive Electrodes

These include foramen ovale electrodes and epidural pegs (Chapter 170). Insertion of these electrodes is somewhat less painful than that of intracranial electrodes, although the complication rate of foramen ovale electrodes may be similar to that of more invasive types. These electrodes provide more localizing EEG information than scalp electrodes, because they are closer to the source generators. However, they have not achieved wide popularity, and their ultimate fate in the presurgical evaluation remains to be determined.

Functional Mapping Using Intracranial Electrodes

If the region to be resected appears to contain or be near eloquent cortex whose resection would result in an unacceptable neurologic deficit, electrical stimulation can be used to map the function of that cortex and its relation to the ictal onset zone. Surgery can then be carried out sparing critical tissue, or at least with the knowledge that a particular deficit will likely occur. Intracranial electrical mapping is less important in mesial temporal lobe epilepsy or in operations on “silent” areas such as the frontal pole, but it is critical in posterior frontal, anterior parietal, mesial occipital, and posterior temporal resections, especially those involving the dominant hemisphere. It has limited utility in small children, where it may be necessary to remove large portions of brain (e.g., hemispherectomy) in order to obtain seizure control. Electrical stimulation can be done with chronically implanted electrodes (Chapter 175) or acutely in the operating room at the time of resection (Chapter 174). Typically, chronically implanted subdural grids are used for extraoperative functional mapping, but other electrode types can be used on occasion.

Synthesis and Patient Counseling

At the completion of the presurgical evaluation, the surgical team should be able to provide the patient and family with reasonable estimates of the chance of becoming seizure free following surgery.[22] Particular features in the MRI, Wada test, PET scan, and other tests influence the prognosis. For example, a patient with MRI-demonstrated unilateral hippocampal atrophy has a 75% to 80% chance of becoming seizure free after anterior temporal lobe resection, whereas a patient with symmetric hippocampi has perhaps only a 50% chance of becoming seizure free.[49,89,102] Despite all the modern presurgical tests, prediction for individual patients after epilepsy neurosurgery still has its uncertainities, and patients and their families must be aware of the potential risks and benefits of different therapeutic options (see Chapter 183). In the final analysis, it must be remembered that patients seek surgery to improve the adverse psychosocial consequences of epilepsy as much as, or more, than the medical repercussions, and this need must be addressed.[27]

Before undertaking a presurgical evaluation, the patient should be informed about the risks of the tests. Some tests are basically risk free, such as MRI, neuropsychological testing, ictal SPECT, FDG-PET, and scalp EEG. However, invasive and semi-invasive EEG recording, the Wada test, and intracranial mapping all carry some risk, albeit low, and must be justified by the need for the information they provide. A general statement can be made, however, that the riskier evaluation procedures such as intracranial EEG recording are warranted in appropriate cases. Evaluation with intracranial electrodes has allowed hundreds of patients to have surgery who otherwise would not have been offered an operation. A large percentage of those patients have benefited from their operations, with reduction in their long-term medical risk from epilepsy and psychosocial improvement.

Summary and Conclusions

The decision to evaluate a patient for epilepsy surgery has potentially significant long-term medical and emotional consequences. The aim of the evaluation is to determine if a patient is a candidate for surgery, establish the type of operation that should be performed, and assess its potential benefits and risks. The evaluation should seek to obtain multiple lines of evidence, both structural and physiologic, that can be used to formulate the best surgical option. Improved methods of defining the epileptogenic zone are still needed, and as these are developed, our understanding of epilepsy and seizure-related phenomena will be enhanced.

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Chapter 170

Foramen Ovale and Peg Electrodes

Heinz Gregor Wieser

Introduction

The foramen ovale (FO) electrode recording technique was developed in Zürich in 1983.[26] Its goal was to make less invasive and simplify the neurophysiologic part of the presurgical evaluation protocol for candidates for selective amygdalohippocampectomy (AHE). Before 1983, stereoelectroencephalography (SEEG) had been used for the majority of patients being evaluated there for epilepsy surgery.[21,23] The accumulated SEEG experience revealed that the mesial temporal lobe (TL) structures, in particular the hippocampus, the parahippocampal gyrus, and the amygdala, play important roles as seizure-generating structures in most patients with temporal lobe epilepsy (TLE). As a consequence of these findings, in 1975, the so-called *transsylvian AHE*[33] was developed and has since become the operative approach of first choice for surgical treatment of mesial TLE (MTLE) in Zürich as well as in many other centers.

Peg electrodes were developed at the Cleveland Clinic in 1988.[2,3] They are usually used as sentinel electrodes, often in combination with other invasive techniques, for obtaining epidural ictal recordings.

Data obtained from Engel's survey carried out before the 1992 Palm Desert conference showed that, at that time, 15 centers (15%) used FO electrodes and four centers used epidural pegs. FO electrodes had been used only in 5% of all reported patients operated on from 1986 to 1990 (*n* = 7,664), but in 21% of 662 reported AHE patients.[7] Since then, FO electrodes seem to be used increasingly in more centers,[1,6,12,15,18,34] whereas peg electrodes are presently used by only two epilepsy surgery centers.

FO and peg electrode recording techniques have been labeled an intermediately invasive or semiinvasive approach.

Indications

Peg electrodes allow artifact-free recording of the electrocorticogram in relatively small but widely separated regions of the cortical convexity. They were designed to determine surgical suitability in patients in whom the clinical, electrographic, and neuroimaging information did not localize the epileptogenic zone well; that is, they were used in circumstances in which exact placement of a subdural grid array was uncertain from the clinical, neuroimaging, and scalp electroencephalogram (EEG) data. Often they were inserted as sentinel electrodes contralateral to subdural grid placement, to confirm that ictal discharges were not beginning contralaterally. Depending on the particular clinical circumstances, peg electrodes may be used with other electrodes including FO electrodes, depth electrodes, and subdural grid arrays.

FO electrodes record from the mesial aspects of the TL. Compared with intracerebral depth electrodes, subdural grid electrodes, and most probably also subdural strip electrodes, FO electrodes are less invasive, but nevertheless the possibility of complications is inherent in the FO electrode technique. Therefore, its use should be restricted to presurgical evaluation of possible candidates for epilepsy surgery. Moreover, it is obvious that its main indication is for patients with TLE, in particular for patients suffering from the syndrome of MTLE.[25] Today FO electrodes are mainly used in patients with suspected MTLE with ambiguous seizure onset lateralization or with other noncongruent findings. Bilateral hippocampal sclerosis (HS) and/or bilateral independent interictal spiking are the second most often encountered reasons to insert FO electrodes. HS is the neuropathologic substrate most often found in MTLE. Vossler et al.[22] found that marked hippocampal atrophy (HA) and high-grade HS are associated with initial ictal discharges (IID) restricted to the hippocampal formation, whereas low-grade HS and absence of HA are associated with slower (2–4 per second) scalp IID frequencies and with lobar or regional seizure onsets not restricted to medial structures. Therefore, FO electrodes are particularly useful in patients without marked HS and when AHE is intended. However, in such constellations, the combination with subdural strip or grid electrodes is often necessary.

Table 1 Types of FO electrodes and combinations with other invasive recording technique (*n* = 264)

		Bilateral	**Unilateral**		**Number of electrode contacts**				
	Total	R+L	R	L	1	3	4	8	10
Patients	264	253	6	5	34[+]	1	138	7	84
FO with thermoelement	14	6	5	3					
		FO Electrodes combined with other intracranial electrodes							
		+**SEEG**	+**Strip**	+**Strip** + **Grid**	+**Grid**				
Patients	49	14	32	2	1				
%	18.6	5.3	12.1	0.7	0.4				

R= right hand side; L= left hand side.

[+] First FO EEG was recorded from a patient with trigeminal neuralgia.

44 DIXI Electrodes (DIXI microtechniques, France), the remaining were designed in our own laboratory.

Thermoelement for research purpose (Landolt et al., 1995).

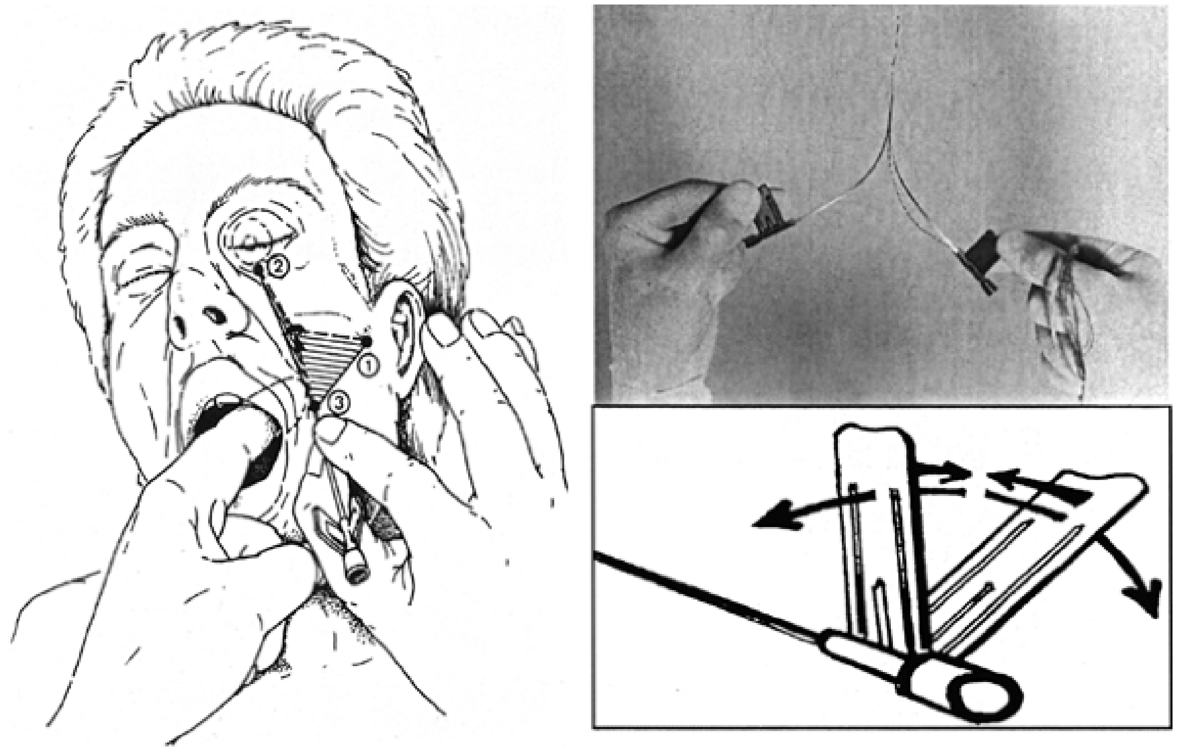

FIGURE 1. *Left:* Insertion technique of foramen ovale electrodes according to the technique of Kirschner (1932) using the landmarks of Härtel (1914). *1* is a point 5 cm anterior to external auditory meatus. *2* is the medial pupillary point. *3* is the electrode entry side, 3 cm lateral to oral commissure. The index finger is in the pterygoid fossa. The needle is inserted as described in the text, and then the special splittable cannula is withdrawn and broken.

Techniques

Foramen Ovale Electrode Design, Insertion, Removal, and Recording

In recent years, several types of FO electrodes have become commercially available. Until June 1999, the FO electrodes used in Zürich were site-made.[28] In brief, these FO electrodes consisted of Teflon-insulated, helically wound silver or platinum wires (diameter 0.1143 mm [0.0045 inches]) ending in four, eight, or ten poles. They were mounted on a “surgical” (highly corrosion-resistant) stainless steel wire 0.1 mm in diameter. This carrier, isolated with a special varnish, had adequate mechanical properties. It was flexible enough and had a special end to avoid penetration of the arachnoidal-pial layer. Each pole consisted of 90 parallel windings and was 2 or 4 mm long. The distance between two contacts was 2 to 5 mm, depending on the type of electrode (Table 1). The external diameter of the FO electrode types was such that it passed through a special split Table 18-gauge cannula (produced and marketed by Medialimed SA, CH-1604 Puidoux, Switzerland). This splittable cannula is still in use (Fig. 1). It has an external diameter of 1.23 mm and an internal diameter of 0.93 mm and permits the multipin connector to be mounted and soldered, and the stabilizing insulator poured in well before implantation. The site-made electrode impedance ranged from less than 200 ohms to a maximum tolerated 700 ohms, respectively, whereas the DC offset potential was less than 2 mV. These electrodes could be armed with other specific recording devices.

Temperature-sensitive devices have been used in 14 patients[14] (see Table 1), and special ictal and interictal DC recording with monopolar silver FO electrodes were carried out in five patients (Fig. 6).[20]

Insertion

Insertion of the FO electrode can be done under local anesthesia. Currently, however, the procedure is done in Zürich under general anesthesia. With the stylet inside it, the special cannula is inserted 3 cm lateral to the oral commissure and directed along the intersection of two orthogonal planes: (a) the plane defined by the insertion point, a point on the lower eyelid corresponding to the medial border of the pupil, and the tip of the electrode directed toward the foramen ovale; and (b) a plane defined by the insertion point, a point 5 cm anterior to the external meatus acusticus, and the tip of the electrode directed toward the FO (Fig. 1).

The patient usually responds to the passage of the needle through the FO with a wince and a brief contraction of the masseter muscle. After withdrawal of the stylet, some cerebrospinal fluid usually leaks, and the electrode can then be carefully positioned under radioscopic control. In most instances, the tip of the electrode slips without any resistance into the caudal end of the ambient cistern (Fig. 2, see Fig. 7). After the splittable cannula has been withdrawn and broken off, the freed electrode is fixed to the skin by a special clamp. Gauze and adhesive tape cover the electrode where it penetrates the skin. Antibiotic protection is given throughout the recording period and is continued for 3 days after the removal of the electrode.

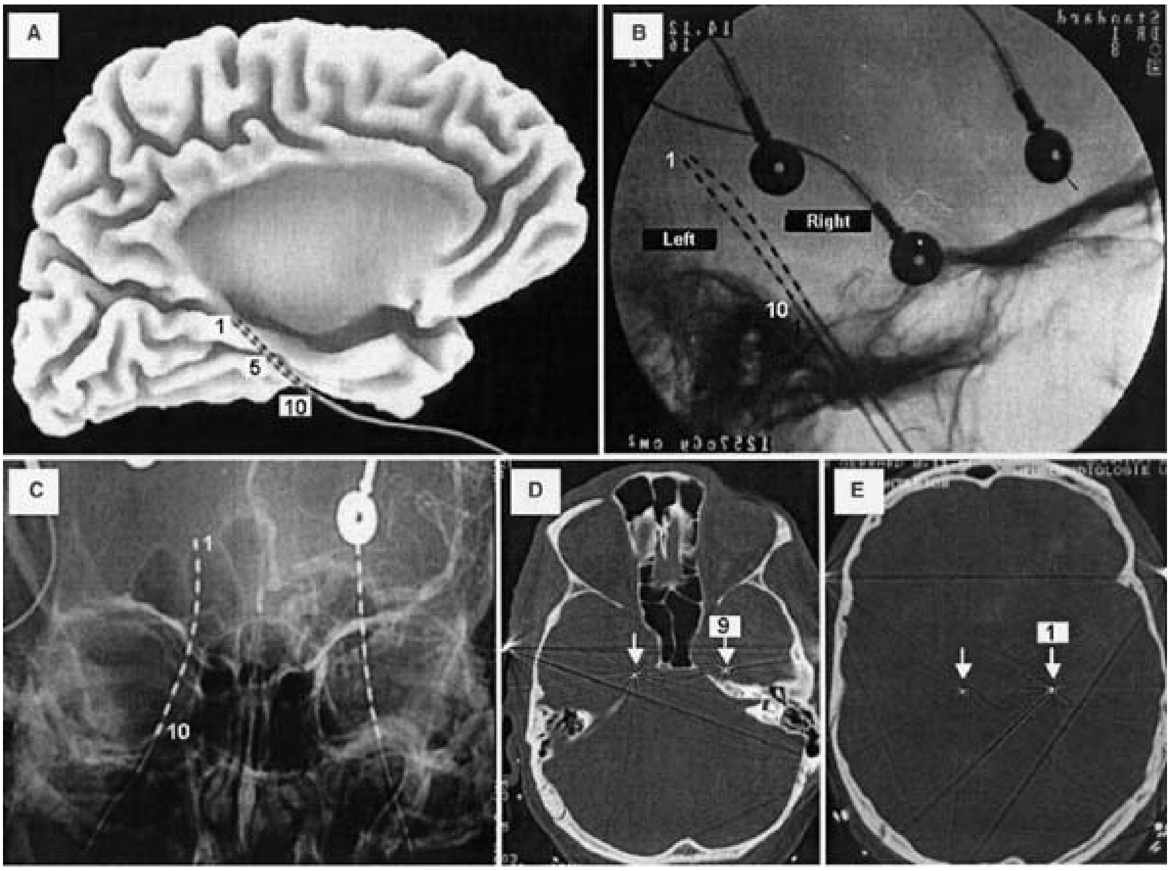

FIGURE 2. Schematic illustration of implanted 10-contact foramen ovale electrodes (**A**), as depicted by lateral (**B**) and AP x-ray (**C**) and CT imaging (**D, E**). Electrode contacts are numbered 1 to 10. **A** is used with permission of Dr. Dominik Zumsteg.

Removal

For the removal of the FO electrode, anesthesia is not necessary. During the withdrawal of the electrode a brief painful sensation in the ipsilateral teeth is relatively common. Therefore, the patients should be informed about this possibility before the explantation.

Montage, Recording, and Analysis

Sophisticated DC recording with FO electrodes has been done hard-wired with 32 channels in the laboratory, but seizure monitoring in AC mode is now realized by 64 or more channels with the patient on the ward. For routine monitoring, an uninterrupted bipolar montage connecting the ten contacts of both FO electrodes is recommended, as shown in FIGURE 3. The other channels are used for simultaneous scalp EEG and other intracranial EEG records, as well as polygraphy, if indicated.

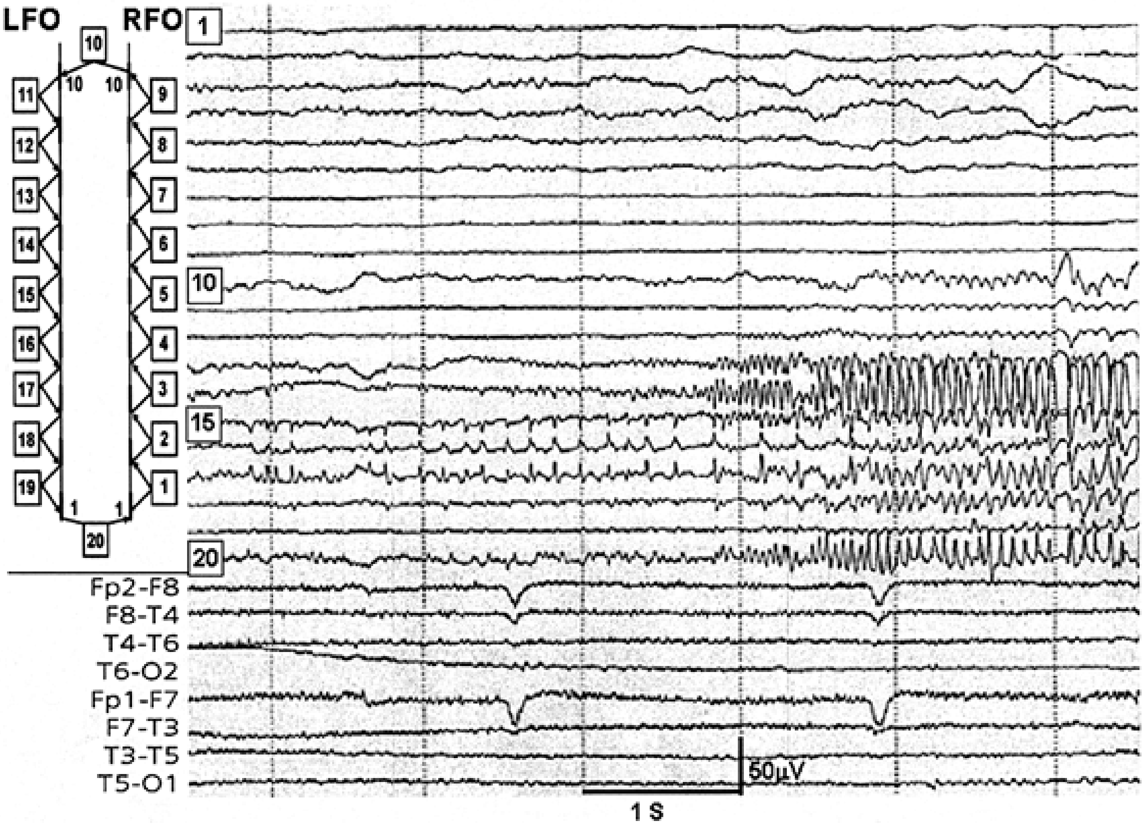

FIGURE 3. Example of a 10-contact foramen ovale (FO) electrode recorded seizure onset at contact 5 of the left FO electrode (phase reversal between channels 15 and 16) with repetitive 7/sec sharp waves and evolving rhythmic more wide-spread spike discharges of 19/sec. Note that the scalp-EEG channels do not show the seizure onset. At the *left* the montage for recording from 10-contact FO electrodes is shown. For routine long-term seizure monitoring, we prefer the depicted closed chain with 20 channels (number in boxes).

Patient Data of the Zürich FO Electrodes Series

With two exceptions (the first FO electrode patient had no epileptic seizures, but trigeminal neuralgia, and one patient had aggressive outbursts thought to reflect limbic seizures), all patients who underwent FO electrode implantation in Zürich had medically refractory complex partial seizures with or without secondary generalization. In most of these patients, before FO electrode implantation, there was rather strong suspicion of mesiobasal limbic seizure onset, as evidenced from the seizure semiology, interictal and ictal scalp EEG, neuropsychological examinations, and structural (computed tomography [CT], magnetic resonance imaging [MRI]) and/or functional (single positron emission computed tomography [SPECT] and positron emission tomography [PET]) imaging. These patients were evaluated with the aim of demonstrating a unilateral mesiobasal limbic seizure onset with a degree of confidence sufficient for surgical intervention. In recent years, FO electrodes were only used in patients with less clear evidence for mesiobasal TL seizure onset; that is, in patients with some contradictory findings pointing to lateral TL or extra-TL seizure onset, and in patients in whom lateralization was a problem (bilateral MTLE). At the beginning of the use of FO electrodes in Zürich, the majority of these patients were evaluated

simultaneously with FO and stereotactic depth electrodes. In recent years, FO electrodes were often combined with strip and sometimes with grid electrodes. In a small proportion of our FO electrode patients, mesiobasal limbic seizure onset was rather unlikely. These patients underwent long-term monitoring with FO electrodes to rule out mesiobasal limbic seizure onset definitively (in which case they would no longer have been candidates for surgical treatment) or to prove a possible secondary pacemaker role of one mesiobasal TL (in which case a so-called *palliative AHE* would be considered a treatment option).

In Zürich, during the period from 1970 to 1983, a total of 94 patients underwent SEEG exploration, and this resulted in a total of 69 operations (73%). From 1984 until today, FO electrodes were used in a total of 264 patients, in 18.6% FO electrodes were combined with other invasive recording techniques. Table 1 lists details in this respect.

The analysis of the therapeutic actions after presurgical evaluation in the last consecutive 100 patients with FO electrodes in Zürich (May 1995 to November 2005) reveals that 73 patients had AHE and eight had resection in TL and/or adjacent areas, other than AHE. Two patients underwent reoperation in TL, five patients underwent temporal lobectomy outside our center, two patients received a vagal nerve stimulator, and 10 patients had no surgery. Sixty-six of these last 100 patients had presurgical evaluation with FO electrodes alone. In 34 patients, FO electrodes were used in combination with other intracranial electrodes: FO *and* strip (n = 29); FO *and* grid (n = 2); FO *and* grid *and* strips (n = 2); FO *and* SEEG (n = 1).

It is interesting to have a look at the Zürich AHE series, which started in 1975. This series now contains a total of 517 AHE patients. Two-hundred seventy-six (53.4%) had intracranial EEG monitoring, 32 (6.0%) had SEEG only, 198 (38.3%) had FO electrodes only, 46 (8.9%) had combined intracranial electrodes (SEEG and FO, FO and strips/grids). The remaining 241 (46.6%) had AHE without intracranial recordings. Table 2 shows the obvious trend for less invasive presurgical evaluation in candidates for AHE: In recent years, the percentage of AHE without intracranial presurgical evaluation amounted to 69.6%.

Table 2 Amygdalohippocampectomies performed in Zürich and type of presurgical EEG evaluation tabulated for four time periods (*n* = 517)

	1975–1985		1986–1992		1993–1999		2000–Nov 2005		Total	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
Number of AHE	103		151		115		148		517	
AHE with SEEG alone	31	30.1	1	0.6	0		0		32	6.0
AHE with combined intracranial electrodes (SEEG + FO; FO + strips/grids)	7	6.8	3	2	32	27.8	4	2.7	46	8.9
AHE with FO alone	3	2.9	84	55.6	70	60.9	41	27.7	198	38.3
AHE with noninvasive EEG	62	60.2	63	41.7	13	11.3	103	69.6	241	46.3

Despite the overall less-invasive presurgical evaluation, the seizure outcome at 1 year after AHE improved steadily over time. In the 1975 to 1992 period Engel Classes I to IV were 69%, 9%, 13%, 9%, respectively (*n* = 254); in the period 1993 to 1999, the respective numbers are 75%, 10%, 13%, 2% (*n* = 115); in the period 2000 to 2001, the preliminary outcome assessment for 50 AHE patients revealed 89%, 11%, 0%, 0%.[30]

In this context, it is important to remember that, since 1978, CT emerged as an imaging technology; since 1985, MRI; since 1987, SPECT and 31P-MRS; since 1988, PET; and since 1993, proton magnetic resonance spectroscopy (1H-MRS) at the Zürich center.

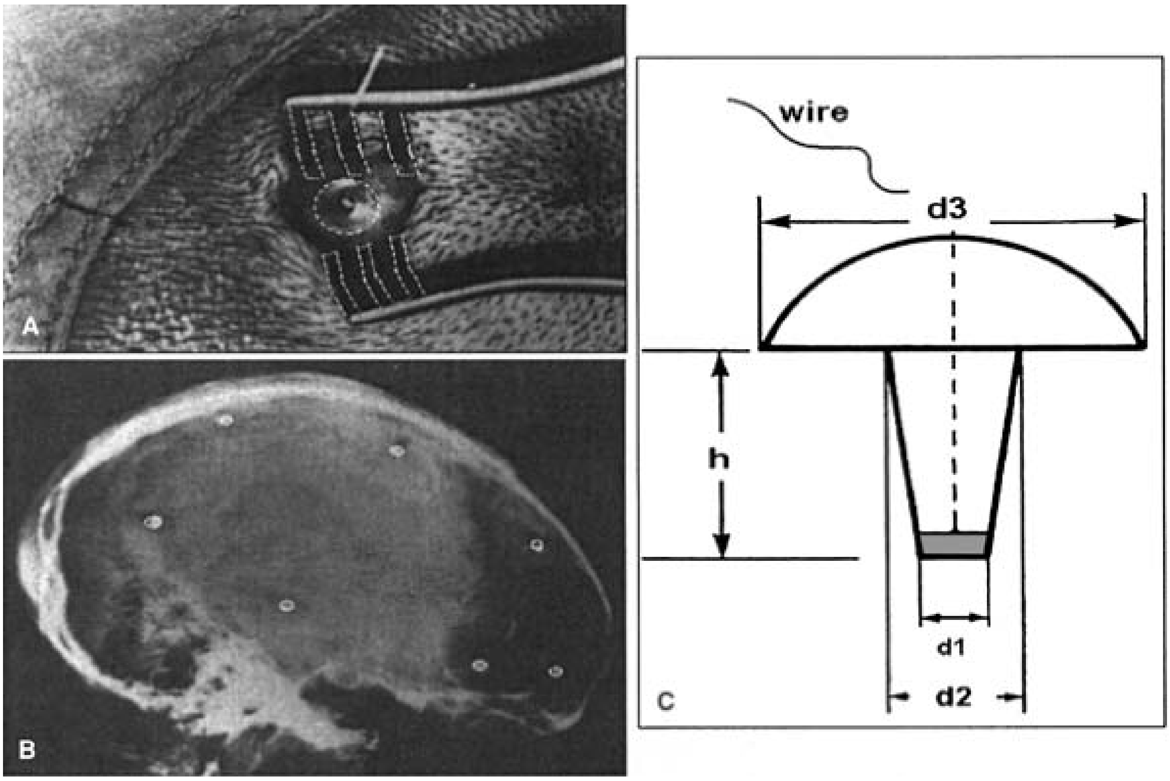

FIGURE 4. Epidural peg electrodes. **A**: The electrode consists of a stainless steel or platinum disc embedded into a mushroom-shaped silastic housing. The stalk has a gradual taper from a maximum diameter (d2) of 4.7 mm to a tip diameter (d1) of 4.5 mm. Stalk heights (h) range from 3 to 19 mm in 2-mm increments to match skull thickness. The cap has a diameter of 12.7 mm (d3) and a height of 2.5 mm (MDX4-4210, Dow Corning Corp. Midland, MI). The peg is implanted via 1.5 cm scalp incision and burr-holes (**B**). **C**: Lateral skull radiograph with epidural peg electrodes. (Modified from Wieser HG, Quesney LF, Morris HH III. Foramen ovale and peg electrodes. In: J. Engel Jr., ed. *Surgical Treatment of the Epilepsies*, 2nd ed. New York: Raven Press; 1993:331–339, with permission; original sources from Awad IA, Assirati JA Jr, Burgess R, et al. A new class of electrodes of “intermediate invasiveness”: preliminary experience with epidural pegs and foramen ovale electrodes in the mapping of seizure foci. *Neurologic Res*. 1991;13:117–183; and Barnett GH, Burgess RC, Awad IA, et al. Epidural peg electrodes for the presurgical evaluation of intractable epilepsy. *Neurosurgery.* 1990;27:113–115.)

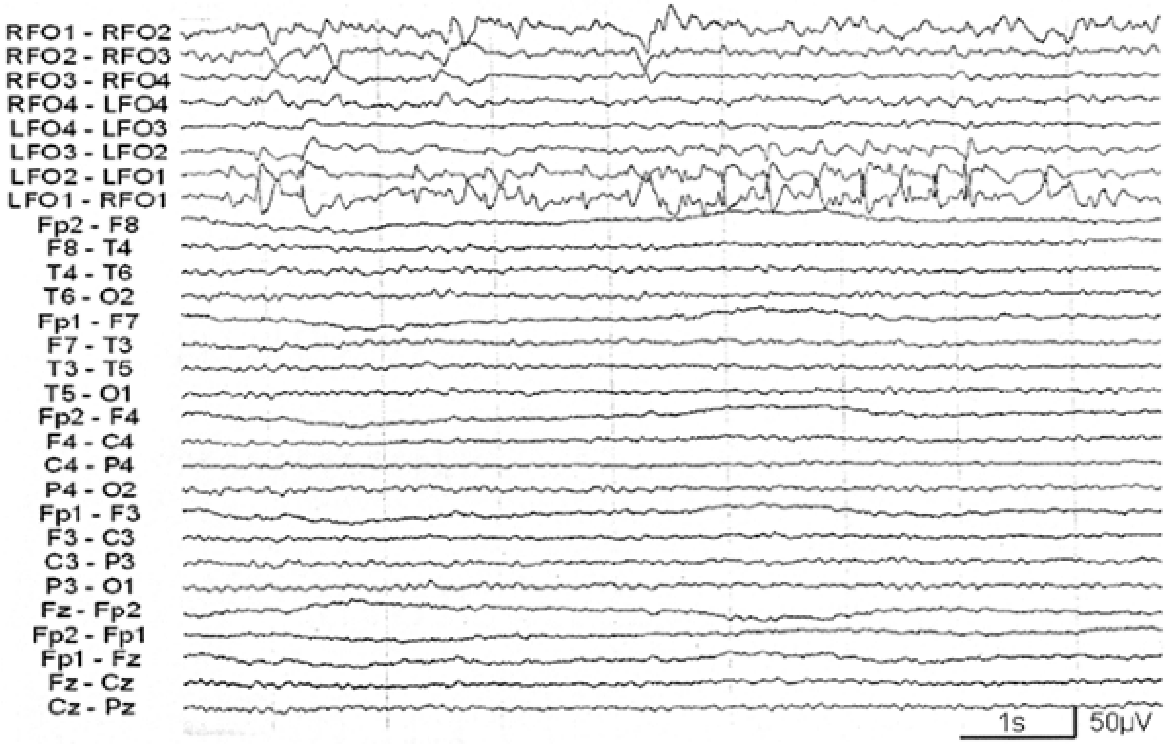

FIGURE 5. The four-contact foramen ovale (FO) electrode recorded infraclinical left posterior mesial TL seizure discharge (LFO1) not detected in the scalp EEG.

Epidural Peg Electrodes Design

Epidural peg electrodes (Fig. 4) are mushroom-shaped composites of Silastic plastic with a “cap” diameter of 12.7 mm, a

slightly tapered stalk, and a tip consisting of a 4.5 mm disc electrode made of either platinum or stainless steel. The electrodes are made with different stalk lengths to adapt to different skull thicknesses. A 1- to 1.5-cm scalp incision is made to expose the skull at the predetermined electrode positions. A twist drill with a “stop” is used to create a 4.5-mm burr hole; the electrodes are then inserted by hand into the hole. The 38-gauge Teflon-coated steel wire from the electrode is threaded through a surgical needle and exits the scalp approximately 2 cm distant to the electrode itself. The scalp over the electrode is then sutured. The Bethel Epilepsy Center has reported on a slightly smaller version of the original epidural peg electrode.[10]

Comparison of FO Electrodes with Sphenoidal Electrodes and Other Noninvasive Recording Techniques from the Temporal Lobe

The value of the sphenoidal electrodes is controversially discussed.[4,5,11] From his extensive review of the studies comparing sphenoidal electrodes with other basal electrodes, and with scalp electrodes, both interictal and ictal, Schomer[16] came to the conclusion that “it is not clear that the sphenoidal electrode offers a substantial benefit over other “basal” electrodes, such as the minisphenoidal electrodes, the T1/T2 electrode, the zygomatic, or the anterior temporal electrode." If, however, the standard sphenoidal electrode is placed with “great care just inferior to the foramen ovale, it may be able to differentiate laterality of temporal lobe seizure onset better than the more superficial “basal” electrodes."[11]

Advantages of Foramen Ovale Electrodes

FO electrodes provide a definite advantage over scalp EEG and over sphenoidal electrodes. In several instances in which the Zürich group used sphenoidal and FO electrodes simultaneously, they found FO electrodes to be superior in detecting epileptiform activity from the mesial aspect of the TL. In several patients, specially constructed FO electrodes were implanted, which had equally spaced intracranial and extracranial contacts (see Fig. 7); the distribution of the peak amplitudes for various epileptiform graph elements, recorded referentially against Cz, were measured. From this study,[24] it became clear that most spikes could not be reliably detected in the extracranial electrodes, because of a very steep voltage gradient. Zumsteg et al.[35] averaged FO electrode and scalp EEG spikes for representative interictal epileptiform discharges (IED) and studied the cortical activation during the ascending phase of the FO electrode–recorded spike using statistical low resolution electromagnetic tomography (LORETA) solutions. In 11 of 15 studied patients, 19 of 30 (63%) IED patterns showed a very restricted activation of ipsilateral mesial temporal lobe that could be detected in the scalp EEG, but only after averaging. A widespread neocortical activation involving frontal and temporo-posterior structures, which could be reliably detected in the scalp-EEG without averaging, occurred in five of 15 patients (representing 6 of 30 [20%] IED patterns). Very restricted mesial temporal spike that could not be detected in the scalp EEG despite averaging occurred in four of the 15 patients (representing five of 30 [16.7%] of IED patterns). Epileptiform discharges originating in the posterior hippocampal formation are usually not detectable in the scalp EEG. The epileptiform activity, depicted in FIGURE 5, originates at the posterior contact of the left four-contact FO electrode and is neither seen in the simultaneously recorded scalp EEG nor in the anterior contacts of the FO electrode. Because the anterior contact of FO electrode is situated close to the foramen ovale, it may well be comparable to an optimally placed sphenoidal electrode.

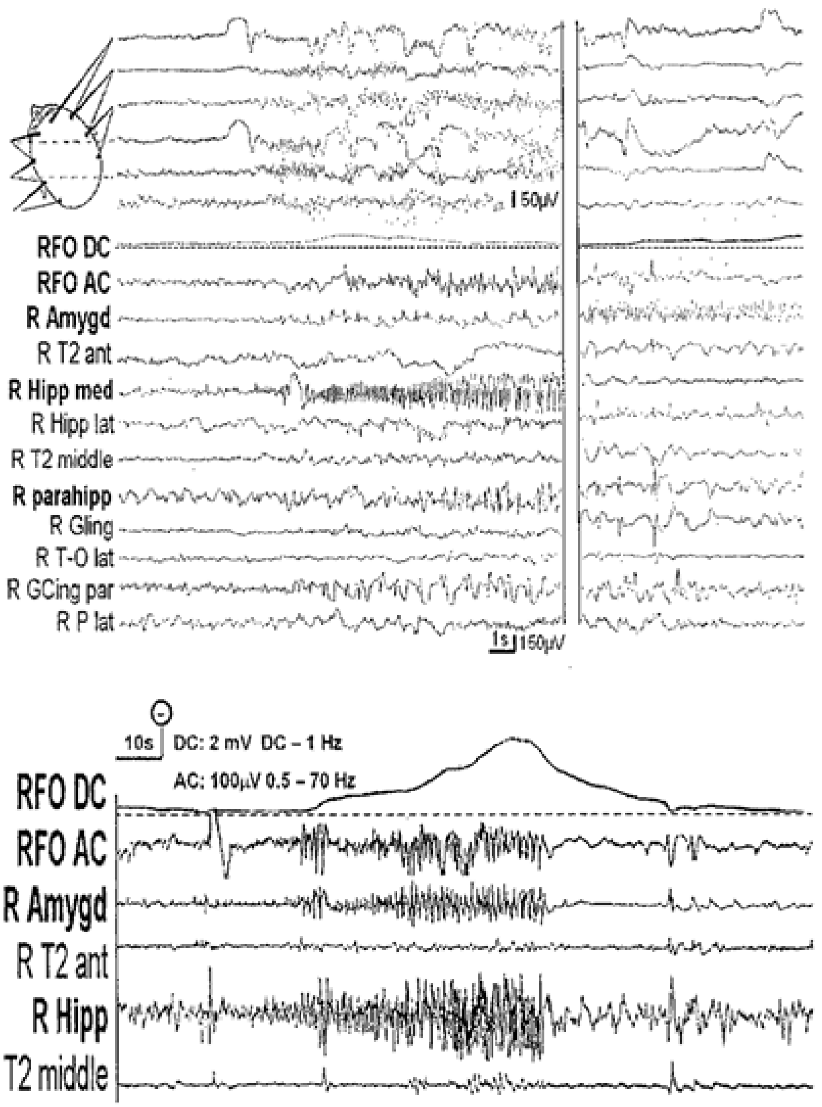

FIGURE 6. *Upper part*: Stereoelectroencephalographically recorded right hippocampal (R Hipp) seizure discharge onset (*left*) with moderate spread to ipsilateral amygdala (R Amygd), right parahippocampal gyrus (R parahipp) and posterior cingulate gyrus (R G Cing par). Note that the right foramen ovale electrode (RFO) recording in AC mode reliably depicts this discharge, which is accompanied by a negative DC shift in the FO DC recording (RFO DC). The amygdala discharge *(right)*, however, is accompanied by attenuation without clear spikes. *Lower part*: The seizure discharge in right amygdala and right hippocampus is very well depicted by the right foramen ovale electrode recording in AC mode (RFO AC) and accompanied by a marked negative shift in the DC recording.

Compared to stereotactic depth electrodes, FO electrodes reliably pick up epileptiform activity generated or involving the hippocampal formation. This is illustrated in FIGURE 6. Song et al.[19] reported on eight patients who had intraventricular recordings with an electrode endoscopically placed along the

lateral margin of the hippocampus. Seven of these patients also had subdural grid or strip electrodes, and four had FO electrodes. One complication occurred (thalamic contusion) and, in another patient, the tip of the electrode was misplaced into the frontal horn of the lateral ventricle instead the temporal horn. The authors illustrate two seizure onsets from two patients. In both, the intraventricularly recorded hippocampal discharge is well depicted by the FO electrodes. The depicted discharge pattern looks very similar in both recording techniques, but exhibits a phase reversal between the intraventricular and the FO electrodes.

Pure amygdala discharges, however, may escape detection in the scalp and FO electrodes, as illustrated in the upper right part of FIGURE 6 and in FIGURE 7.

An advantage of FO electrodes is that they explore the mesial temporal lobes symmetrically and thus allow studying the seizure spread to the opposite hemisphere (Figs. 8 and 9). Because of their good spatio-temporal resolution, multicontact FO electrodes also allow the study of various types of seizure patterns and interictal epileptiform discharges (Figs. 9 and 10). Finally they are very helpful for monitoring the time course of amobarbital-induced slow δ-wave activity and/or other mesial TL EEG changes in selective TL amobarbital tests with inactivation of the territory of the anterior choroidal artery. It has been shown[29] that an appropriate intracranial EEG recorded from depth electrodes or FO electrodes in combination with a scalp EEG is indispensable for a reliable interpretation of the amobarbital effects of selective tests. The increase of δ-wave activity is judged as the most typical amobarbital-induced EEG effect. Other amobarbital-induced EEG patterns are the isoelectric line, the burst suppression pattern, and the high- and low-voltage β-activity. In the Zürich selective TL amobarbital series (106 patients), the δ-increase, the “activation phenomenon,” and spike reduction were observed. The activation phenomenon and the spike reduction were only reliably detected using intracranial EEG recording techniques. As expected, δ-wave increase at the site of amobarbital action was the most commonly observed EEG pattern, and was present in 75%.

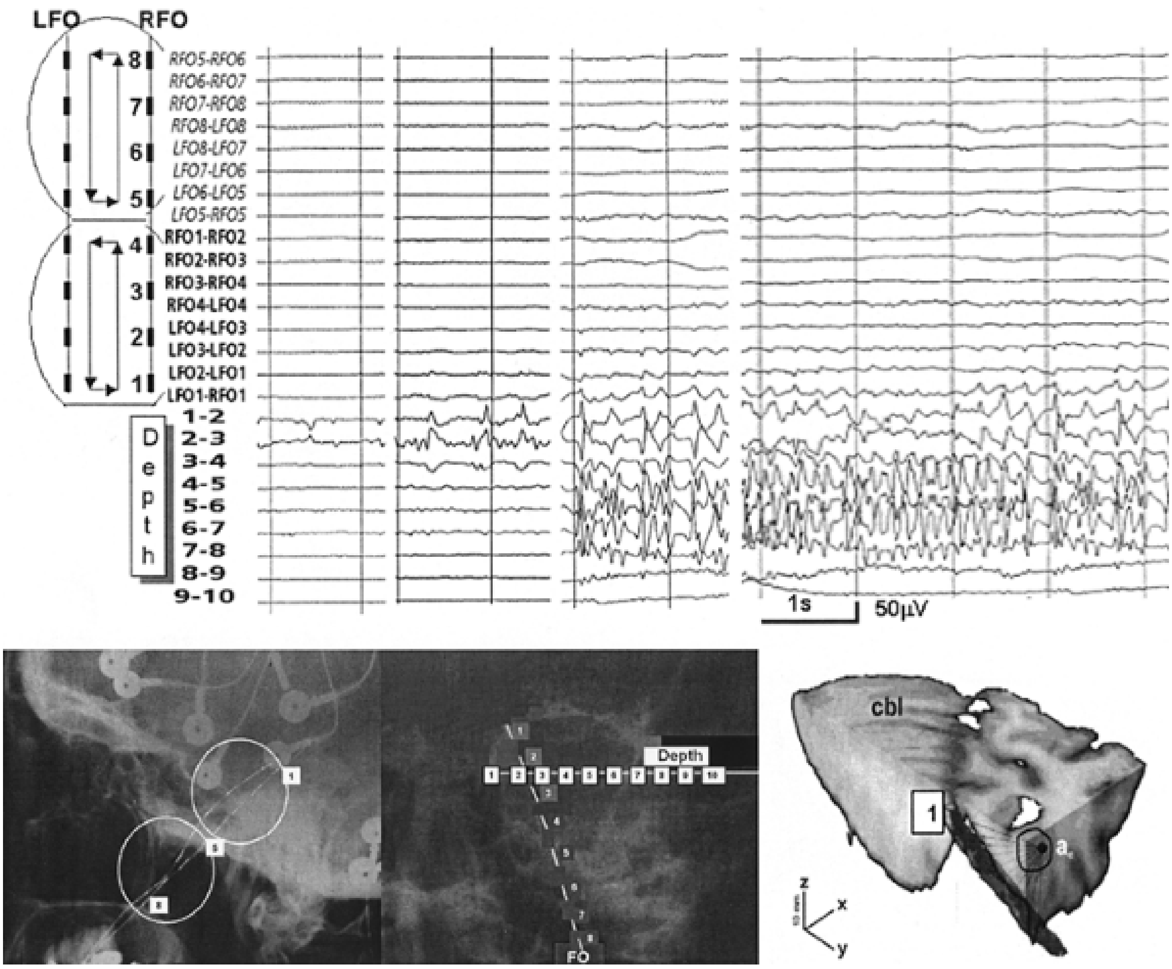

FIGURE 7. *Top:* Four sections of an amygdala seizure, recorded with specially constructed eight-contact foramen ovale (FO) electrodes, which have contacts 1 to 4 intracranially situated, and contacts 5 to 8 extracranially situated (see radiograph, *bottom, left*) and a stereotactically implanted multicontact depth electrode orthogonal insertion, with its tip (contact depth 1) in the left amygdala (*bottom, middle part*). At the *bottom, right*, the 3-D reconstructed topographic relationship of a FO electrode to the amygdala is shown. A minimal distance of 15.9 mm of the nearest contact to the center of the amygdala (a_c) was measured. *cbl, cerebellum.* The deepest contact 1 (rectangulated) is at the end of the ambient cistern. The depicted seizure discharge was accompanied by abdominal pain. Note that (a) the amygdala seizure onset is not reliably picked up in the FO electrode contacts, and (b) the extracranially located contacts of the FO electrode—with contact 5 representing an optimally placed sphenoidal electrode—do not even show the late discharge which, however, is well reflected by repetitive sharp waves in the intracranial left FO electrode recording (contact 2, *LFO2*). Recordings from intracranially placed FO electrode contacts are indicated in bold. Parts of this figure are modified from Eschle D, Siegel AM, Wieser HG. Amygdala seizure onset characterized by severe abdominal pain. *Mayo Clin Proc.* 2002;77:1358–1360 (*upper part*); and Wieser HG, Schwarz U. Topography of foramen ovale electrodes by 3D image reconstruction. *Clin Neurophysiol.* 2001;112:2053–2056 (*bottom, right*).[31]

In a comprehensive study,[29] in which the amobarbital-induced memory performance was correlated with the amobarbital-induced EEG changes, a significant correlation between the dosage and the duration of the EEG changes ($p < 0.05$) was found, but there was no significant correlation between the dosage and the EEG pattern. Moreover, the appearance of an “activation phenomenon”; that is, the evocation or increase of spikes (or other epileptiform graph elements) predisposed to a marked decrease of the memory performance not only for material specific for the side of injection, but also for material specific for the contralateral, noninjected hemisphere.

Combined FO electrode and scalp EEG monitoring during selective TL amobarbital tests is therefore very important for correct interpretation of the test results.

Limitations

FO electrodes have definite limitations: The nature of the FO electrode recording technique implies that only restricted questions can be answered by this technique, namely: (a) Do the seizures originate at the mesiobasal TL structures? If yes, (b) are they constantly lateralized? In addition, (c) information is obtained as to whether the seizure origin is more anterior or posterior. However, if the seizures do not originate at one mesiobasal TL, the patient is by definition no longer a suitable candidate for curative selective AHE, and it must then be decided whether further evaluation is indicated with a view toward more extensive TL or even extratemporal surgery.

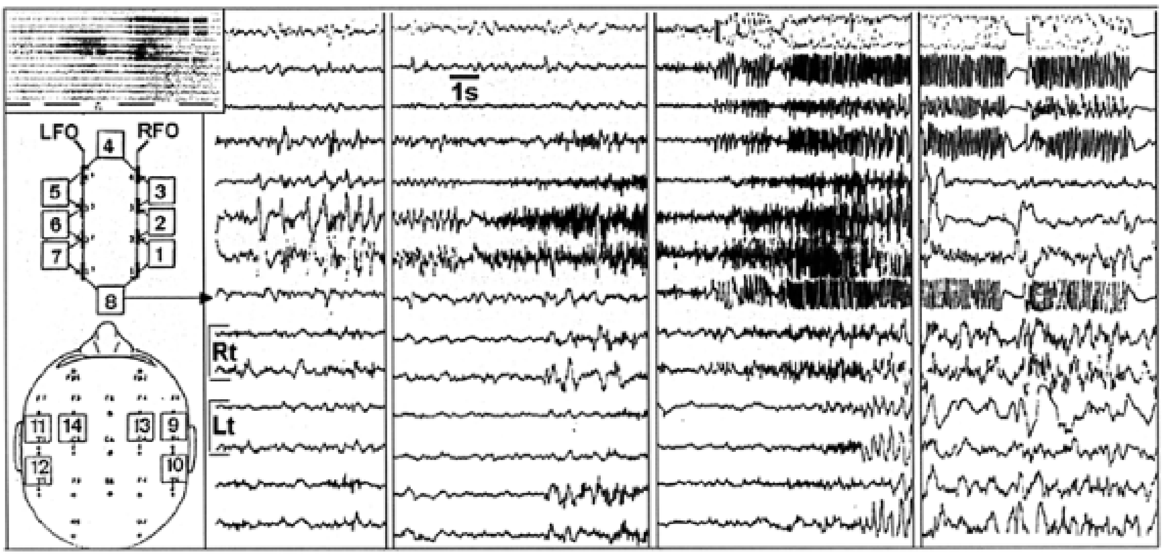

FIGURE 8. Illustration of a prototypic four-contact foramen ovale (FO) electrode-recorded MTLE seizure with left mesiotemporal onset (phase reversal at contact 2′ of left FO electrode (LFO) (i.e., between channels 6 and 7). *Section 1 (left)* shows repetitive 1/sec sharp waves resembling the "hypersynchronous seizure onset pattern"; *section 2,* the high-frequency spike discharge; *section 3,* the subsequent spread to the right mesial temporal lobe (i.e., the bilateral mesial temporal discharges); *section 4 (right),* the cessation of the left temporal discharge in the anterior FO electrode contacts but with some ongoing discharge in the deepest contact 1 (channel 7), and the end of the seizure. Channels 1 through 8 record from the FO electrodes (closed chain montage), channels 9 through 14 are selected bipolar scalp EEG recordings, as indicated in the scheme with numbers in rectangular boxes. Bars in the insert indicate sections 1 through 4.

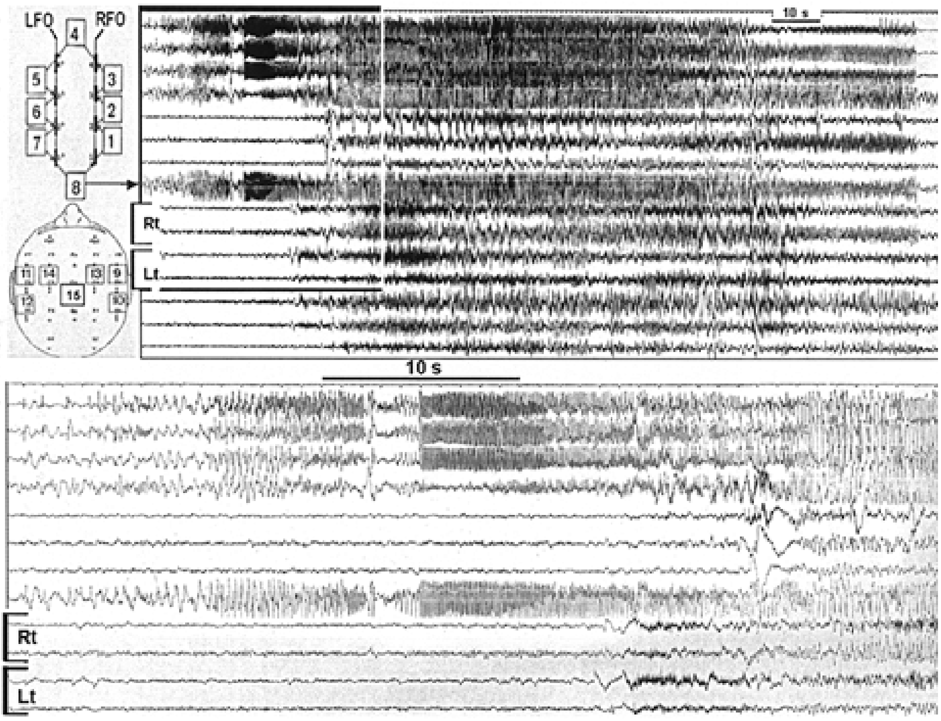

FIGURE 9. Combined four-contact foramen ovale (FO) and scalp recordings of a seizure with right mesial temporal lobe onset lasting 2.7 minutes and with spread to the left mesial temporal lobe (*upper part*). The *lower part* depicts the beginning of the seizure (marked) with better time resolution. Note the dynamics of the discharge with the intermediate 2.5 seconds long paroxysmal pattern shift (lower part) and that the selected scalp EEG channels from the right temporal (Rt) and left temporal (Lt) do not reliably pick up the seizure onset, but show the late seizure discharge.

Evidently a risk exists of falsely localizing an apparent seizure origin in the mesiobasal TL and missing the true origin outside these structures when the FO electrode technique is used. The best way to minimize this risk is to carefully study the clinical features accompanying the seizures by recording the occurrence of the subjective auras and/or the objective signal symptoms and correlating these with the simultaneously

recorded EEG. In addition, as already mentioned, FO electrodes can be combined with other recording techniques, such as subdural strips.

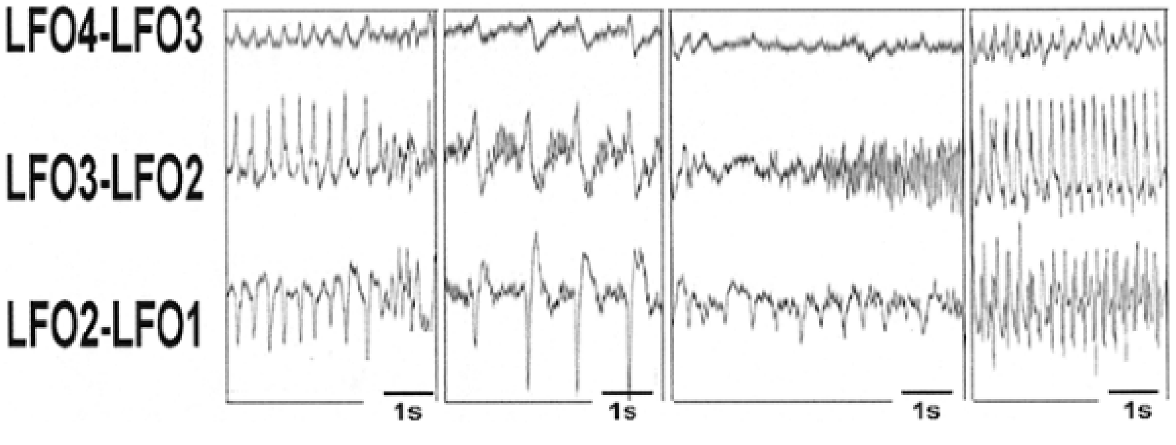

FIGURE 10. Four sections of a left foramen ovale (LFO) electrode recorded seizure with typical discharge patterns. *From left to right:* Electropositive "hypersynchronous" recruiting rhythm at contact 2 (LFO2); "afterdischarge-like" polyspike-slow complexes; critical decrement and high-frequency low-amplitude ("tonic") discharge pattern with crescendo-like increase of the amplitude at LFO3; and 4/sec rhythmic discharge. (Modified from Wieser HG. Stereoelectroencephalography and Foramen Ovale Electrode Recording. In: Niedermeyer E, Lopes da Silva F, eds. *Electroencephalography: Basic Principles, Clinical Applications, and Related Fields,* 4th ed. Baltimore: Williams & Wilkins; 1999:725–740, with permission.)

The most reliable seizure onset patterns recorded with the FO electrodes are the high-frequency, low-amplitude discharge pattern and the so-called hypersynchronous seizure onset pattern.[27] In the absence of these patterns, the localization of the seizure focus should be questioned. A well-localized decrement at the FO electrodes was the most frequently observed initial seizure pattern in the Zürich FO

electrode series. When followed within 3 to 5 seconds by a high-frequency discharge at the same localization, it was also a reliable pattern. From analysis of simultaneous recordings from depth electrodes inserted directly into limbic structures, such as the amygdala, anterior and posterior hippocampus, and parahippocampal, as well as the fronto-orbital and cingulate gyri, and from FO electrodes, it became evident that a well-localized initial flattening of the EEG record from the FO electrode was nearly always associated with a high-frequency, low-amplitude discharge observed in the stereotactic depth recordings from the hippocampal formation and/or amygdala.

The FO electrodes usually pick up mesial TL epileptogenic activity very reliably.

Only in the very rare cases of prolonged discharges totally confined to the amygdala and not affecting the hippocampal formation may the FO electrode miss the discharge. This is because the amygdala behaves as a closed electrical field. In the SEEG series, however, amygdala seizures accounted for only about 3% of all psychomotor seizures.

The limited placement of peg electrodes represents their main limitation. The use of the epidural peg electrodes at the Cleveland Clinic has declined significantly over the past years. In part, the changes reflect surgical preference, but to a large extent they reflect improvements in noninvasive evaluations, including (a) high-resolution MRI scans, (b) volumetric analysis of the hippocampus, and (c) digital EEG allowing reformatting and filtering of data. It has also become apparent that, in the evaluation of a patient with a focal epilepsy whose studies include no focal MRI abnormalities and no localizing EEG abnormalities, epidural peg electrodes are unlikely to demonstrate a clear epileptogenic focus. In other words, they are not very helpful in a "fishing expedition."

Complications

The risks of insertion of FO electrodes and peg electrodes are considerably less than those for depth and subdural strip and grid electrodes.

In 1987, we had one serious complication in the Zürich FO series: A subarachnoid hemorrhage that led to a transient upper pontine syndrome. MRI-documented subarachnoid hemorrhages without any neurologic deficits occurred in two other patients. Meningitis occurred in two patients and was treated by intravenous antibiotics without sequelae. Placement of FO electrodes may be associated with transient morbidity, especially facial pain. Temporary facial pain has occurred in 19% of our patients. Two patients reported mild transient temporomandibular joint dysfunction. Recurrence of labial herpes was seen in 5%. A transient hypo- or dysesthesia, localized in one corner of the mouth, was reported in 9% of the cases. No other side effects or complications, and, in particular, no persisting trigeminal impairments occurred in Zürich.

One patient pulled out one FO electrode in a postictal confusional state; one patient injured one electrode during shaving. Since the information gathered was not sufficient, both electrodes had to be reimplanted.

At the Palm Desert Epilepsy Surgery Conference, it was reported that a few other severe complications had occurred at other centers.[17]

Complications of Epidural Peg Electrodes

By the end of 1993, approximately 77 patients had over 500 epidural peg electrode insertions and studies at the Cleveland Clinic; at the Bethel Epilepsy Center, 36 patients underwent evaluation using approximately 420 epidural peg electrodes. No major complications were seen in these patients. In one Cleveland patient, a single cortical contusion was discovered on CT scan.

Culturing the peg electrodes at time of removal yielded a bacterial colonization rate of approximately 22% in the Cleveland Clinic series; no patient had a clinical infection attributable to these electrodes. The lack of clinical infection was in part a result of prompt treatment with appropriate antibiotics if the electrode cultures proved positive.

Costs

The cost of FO electrodes and their insertion are considerably less than that of other invasive electrode techniques. Although general anesthesia is usually preferred, insertion of FO electrodes can be done under local anesthesia and does not require a sophisticated neurosurgical theater or a neuroradiological examination under stereotactic conditions. Usually no intensive care unit is necessary, and patients with FO electrodes alone can be evaluated outside very specialized units. Likewise, the cost of insertion of peg electrodes is less than that of grid electrodes. However, the major expenses derive from the long-term monitoring, and they are similar whether the electrodes are semi-invasive or invasive.[7]

Future Directions

Whereas FO electrodes may be viewed as a major step in making TL surgery less invasive, the usefulness of peg electrodes remains limited. It is our guess that FO electrodes will be increasingly used in nonlesional TLE patients being evaluated as candidates for mesial temporal lobe resections, and the use of peg electrodes might decline further. Arguments for this prediction are that, in TLE, very effective standardized surgical procedures are available and the main goal of the preoperative evaluation in patients is to answer the question of whether a patient is a suitable candidate for one of these standardized surgical procedures. In MRI-negative extratemporal epilepsies, however, exact localization and determination of the extent of the epileptogenic area still remain a very demanding and difficult task requiring a tailored approach with invasive intracranial techniques in almost all cases.

Summary and Conclusions

On the basis of the Zürich experience, with strict indications, the semiinvasive technique of FO electrode recording is suitable for the evaluation of potential candidates for AHE. Because AHE has virtually abolished larger TL resections in Zürich, a considerable proportion of patients considered for surgical treatment of TLE are candidates for bilateral FO electrode evaluation. The aim of the FO electrode insertion is to record and study the patient's spontaneously occurring habitual seizures.

Epidural peg electrodes are a useful and safe addition to the surgical epileptologist's toolbox. However, they should be seen as being complementary to other invasive electrodes and not as replacement for them.

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Chapter 171

Intracranial Electrodes

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Introduction

Reports and experience worldwide have shown that resection of the epileptogenic area of brain in uncontrolled epilepsy patients with stereotyped partial seizures can cure the epilepsy, or at least prevent recurrent seizures.[30,57,81] The corollary of this statement is that if the surgery fails, the area removed was incorrect or incompletely resected or was only one of several cerebral regions responsible for seizures. Accordingly, accurate definition of the location and limits of this epileptogenic area has become a major preoccupation among epileptologists.

The first need is to define *epileptogenic area,* a term synonymous with epileptogenic region or epileptogenic zone. This is defined as the area of brain necessary to generate seizure activity,[31] resection of which (or inactivation or complete disconnection of which) will result in cessation of seizures. We seek to differentiate this epileptogenic zone from the irritative zone (of interictal spiking), the ictal onset zone (where the electroencephalogram [EEG] shows spontaneous seizures to arise), the symptomatogenic zone (activation of which produces initial ictal symptoms or signs), the zone of functional deficit (with evidence of reduced or abnormal metabolism, blood flow, and cognitive ability), and the epileptogenic lesion (demonstrated by structural imaging).[74] Although those areas usually overlap, they do not precisely coincide with the epileptogenic zone and, at times, appear to diverge. We might eventually develop techniques that allow visualization of the epileptogenic zone in other ways, but currently the demonstration of electrographic seizure onset offers the most logical means of verifying its approximate location,[36] except in childhood catastrophic epilepsy, in which the ictal onset zone is typically reported to be generalized even if the causative, epileptogenic zone is localized.[72] (An exception to this is the occasional case of childhood catastrophic epilepsy in which intracranial recording has demonstrated intrinsic epileptogenicity of a lesion, such as hypothalamic hamartoma.)[48] Because the latter cases are not likely to be studied with intracranial electrodes, this chapter concentrates almost exclusively on the evaluation of partial seizure disorders.

The electrographic delineation of the epileptogenic zone can be supported by delineation of the irritative zone, the symptomatogenic zone, the area of focal functional deficit, and the epileptogenic lesion such that the complementary nature of the respective studies allows one to infer the limits of the epileptogenic zone from less precise electrographic information, a scenario most often found when an epileptogenic lesion is roughly colocalized with a surface EEG recording abnormality.[32,33,83] In other situations, however, particularly in the absence of compelling data to characterize the epileptogenic lesion, irritative zone, and zone of functional deficit, the ability of the surface EEG to determine the ictal onset zone is suboptimal. For the purpose of designing an effective resective procedure for uncontrolled epilepsy, intracranial electrodes are then used to localize ictal onset as well as interictal spike distribution; this information is then used with the other data to infer the location of the epileptogenic area.

Intracranial EEG recording fills a specific need only in the context of a specific question. Extensive knowledge of seizure patterns, surface EEG expression of the ictal onset and irritative zones, and functional and structural abnormalities accompanying the epilepsy is necessary to properly design an intracranial EEG study. The nature of the procedure requires that its risk be sufficiently balanced by the possibility of useful gain in the localization, definition, and understanding of the uncontrolled epilepsy. In addition, the appropriate intracranial techniques must be used to answer the questions posed.

Intracranial EEG is indicated in the setting of uncontrolled epilepsy considered for resective surgical treatment when (a) there is likely to be a single region of seizure onset; (b) localization of this region is insufficiently precise or impossible based on the combination of ictal clinical manifestations, noninvasive EEG, and tests of focal functional deficit and structural abnormalities; and (c) the spectrum of findings in the individual allows a hypothesis about the suspected region or regions of seizure onset to be further investigated.

These considerations are important because intracranial recording has significant limitations, costs, and risks.[91] Implanted electrodes necessarily record from a limited volume of cortex. They must therefore be placed appropriately to address the questions at hand. Furthermore, because chronic implantation carries the known risks of hemorrhage and infection and the unknown risks of cognitive effects and epileptogenic potential, it is desirable to restrict the number of implanted electrodes to as few as possible. This must be done without compromising the ability to detect the zone of seizure onset with sufficient precision to use in the determination of the epileptogenic area for subsequent surgery.

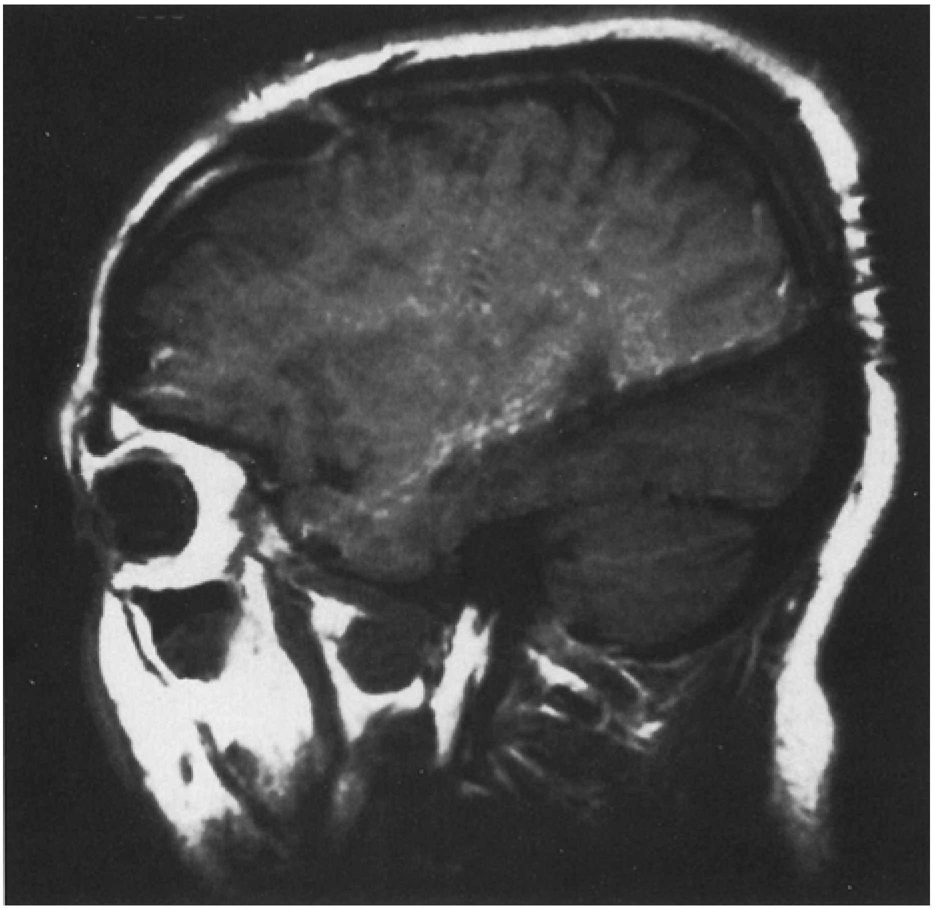

FIGURE 1. Sagittal magnetic resonance imaging (MRI) view of temporal lobe depth electrodes inserted by a posterior approach, illustrating multiple contacts.

Technological advances have altered the use of intracranial recording over the past decade in several ways.

High-quality neuroimaging, with qualitative and quantitative magnetic resonance imaging (MRI) at the forefront, has improved our detection of macrostructural abnormalities in epilepsy, including certain gliomas, developmental abnormalities (cortical dysplasia, hamartomas), and restricted atrophic lesions such as hippocampal atrophy. As accumulated experience has supported significant correlations between excision of these lesions and seizure relief, finding evidence for a structural lesion has assumed increasing importance in the localization of the epileptogenic zone for epilepsy surgery.[16,20,83,89] Now, the presence of certain "lesions" more often allows the less precise scalp EEG localization of the ictal onset zone to suffice because the additional information required to infer the localization of the epileptogenic area is provided by the MRI. Although scalp EEG localization to the region of the structural abnormality is still considered imperative to prove that the lesion is epileptogenic,

localization by interictal surface EEG without discordant information from ictal surface recording has become acceptable for this purpose at most centers. The opinion that only imaging might be sufficient to define a cortical region of epileptogenesis has been voiced, but some patients are known to have coincidental structural lesions irrelevant to the electrically abnormal area.[34,84] In Yale's recent experience, patients with discordant MRI and overall EEG localization represent approximately 10% of those with hippocampal atrophy, tumors, or developmental lesions.[34] About half of these patients have had surgery based on ictal onset localization, with cure of seizures. This means that, although the MRI is highly sensitive in localizing epileptogenic structural lesions in uncontrolled epilepsy patients and these lesions are often where uncontrolled seizures begin, the structural abnormality does not necessarily indicate the epileptogenic zone.

The increasing sophistication of imaging has also been responsible for generating a new population of patients for intracranial study who may not have been considered candidates before. These are patients with bilateral hippocampal atrophy or with so-called "dual pathology" such as a tumor or cortical developmental abnormality with hippocampal atrophy. In these situations, experts agree that intracranial recording is essential to determine which potentially epileptogenic lesion is indeed responsible for the uncontrolled seizure disorder.[34] In one recent study, patients with bilateral hippocampal atrophy were found to be good candidates for cure of seizures after temporal lobe resection, with the side of resection based on intracranial ictal onset EEG localization and not on the severity of the atrophy.[51] An MRI demonstration of dual pathology is also not always synonymous with dual epileptogenesis, although it might be.

Intracranial EEG has been in use since the 1950s. It was initially applied infrequently, mainly in patients with poorly localized surface EEG or evidence for bitemporal EEG abnormalities, who comprise 10% to 15% of surgical candidates. In the late 1960s and 1970s, some centers used intracranial EEG in all surgical candidates before resecting tissue for seizure control. This practice generated considerable historical and practical information but is no longer necessary. Now, some form of intracranial EEG investigation is performed on approximately 15% to 45% of adult patients at most centers that do epilepsy surgery. The proportion of patients considered for intracranial investigation depends on the referral population. In the pediatric population, both the need for and the practicality of intracranial recording diminish with decreasing age. Although invasive recordings can be done in infants,[127] they are rarely necessary.[23]

Intracranial EEG is obtained with depth electrodes (Figs. 1 and 2), subdural strip electrodes (Figs. 3,4,5), subdural grid electrodes (Fig. 6), and/or epidural electrodes. They are multicontact, usually flexible electrodes that require an operative procedure for insertion in preselected locations based on prior evaluation. All of them can be used for chronic or acute recording over 1 to 4 weeks (rarely up to 8 weeks) for the purpose of localizing the epileptogenic zone by recording multiple spontaneous ictal events. They differ predominantly in the parts of brain that can be recorded. Only depth electrodes penetrate brain tissue directly. They are therefore best suited for recording from deep, buried structures such as amygdala and hippocampus (Figs. 1 and 2), planum temporalis, and insula. These electrodes are also well suited for recording from sulcal cortex, as well as near lesions in deep cerebral locations. Subdural electrodes are best suited for recording from the cortical surface, including dorsal, basal, and interhemispheric regions, and provide a method for safe, extensive cortical sampling. Subdural strip electrodes and depth electrodes can be inserted to record from multiple lobes and areas in both hemispheres. Subdural grid electrodes are restricted in insertion to previously defined zones.

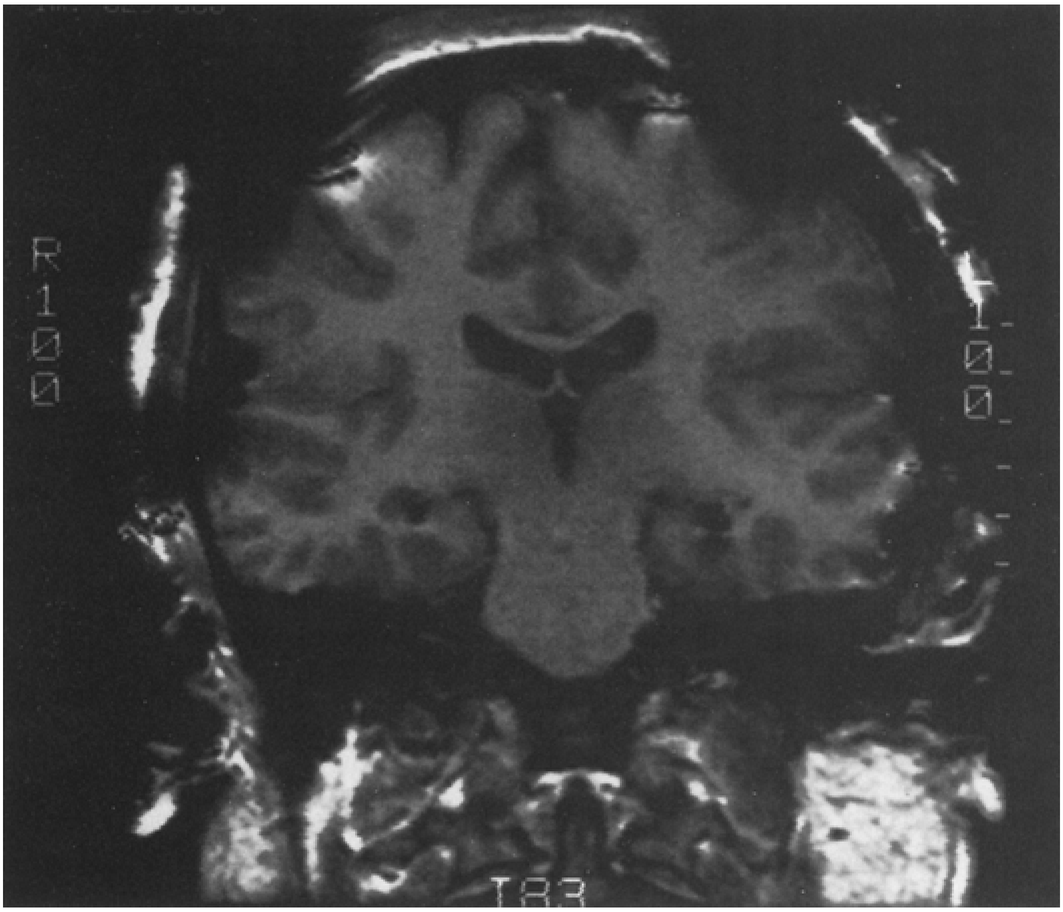

FIGURE 2. Coronal magnetic resonance imaging (MRI) view of temporal lobe depth electrodes inserted by a posterior approach, illustrating the location of the depth electrodes in hippocampus bilaterally.

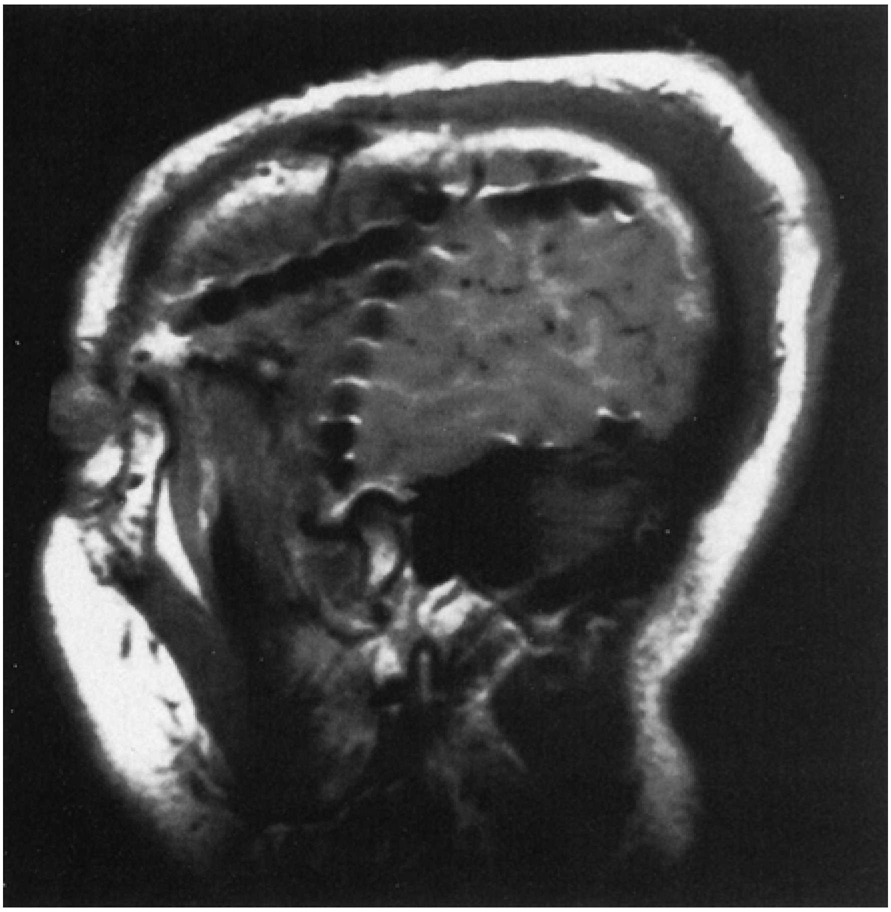

FIGURE 3. Sagittal magnetic resonance imaging (MRI) view of multiple subdural strips placed through a single burr hole; individual contacts can be identified.

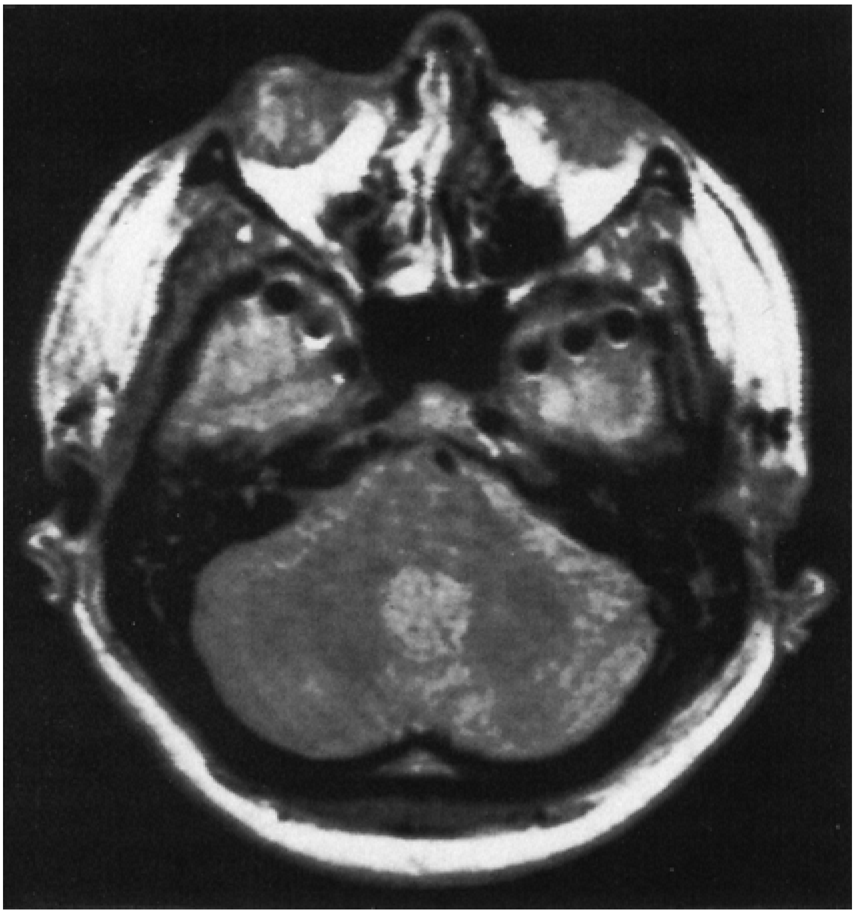

FIGURE 4. Basal view showing inferior medial placement of bilateral temporal subdural strips.

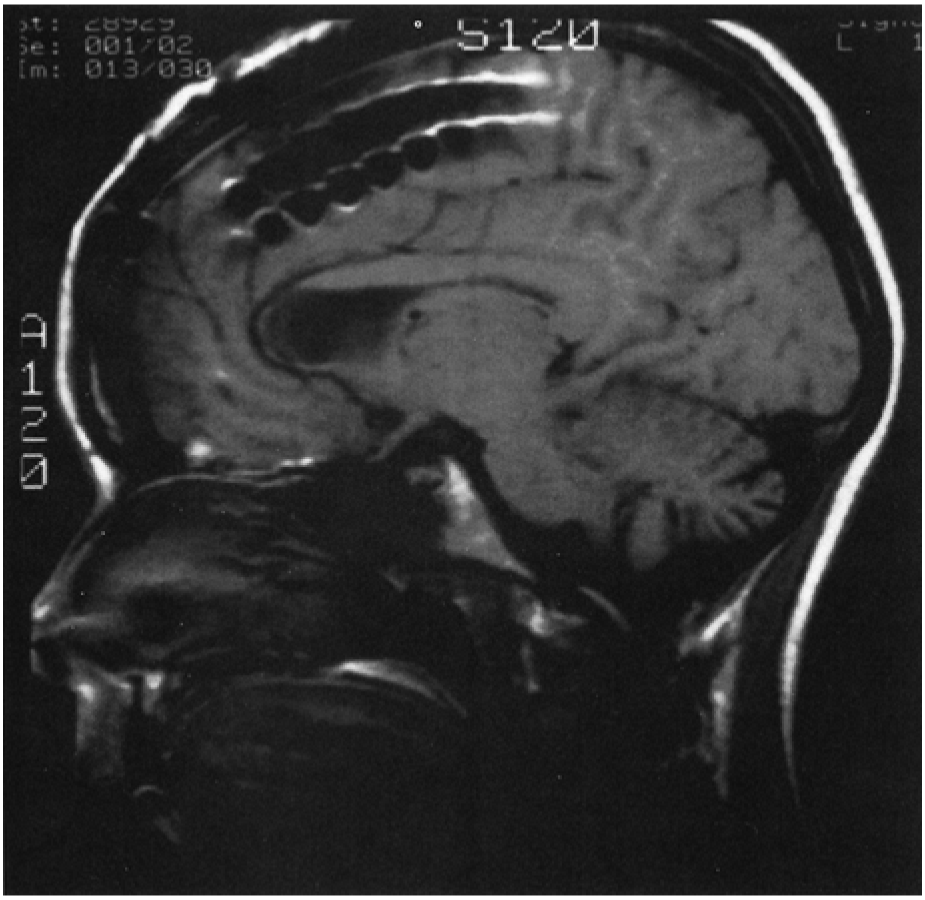
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FIGURE 5. Midline sagittal magnetic resonance imaging (MRI) view of interhemispheric placement of subdural strips.

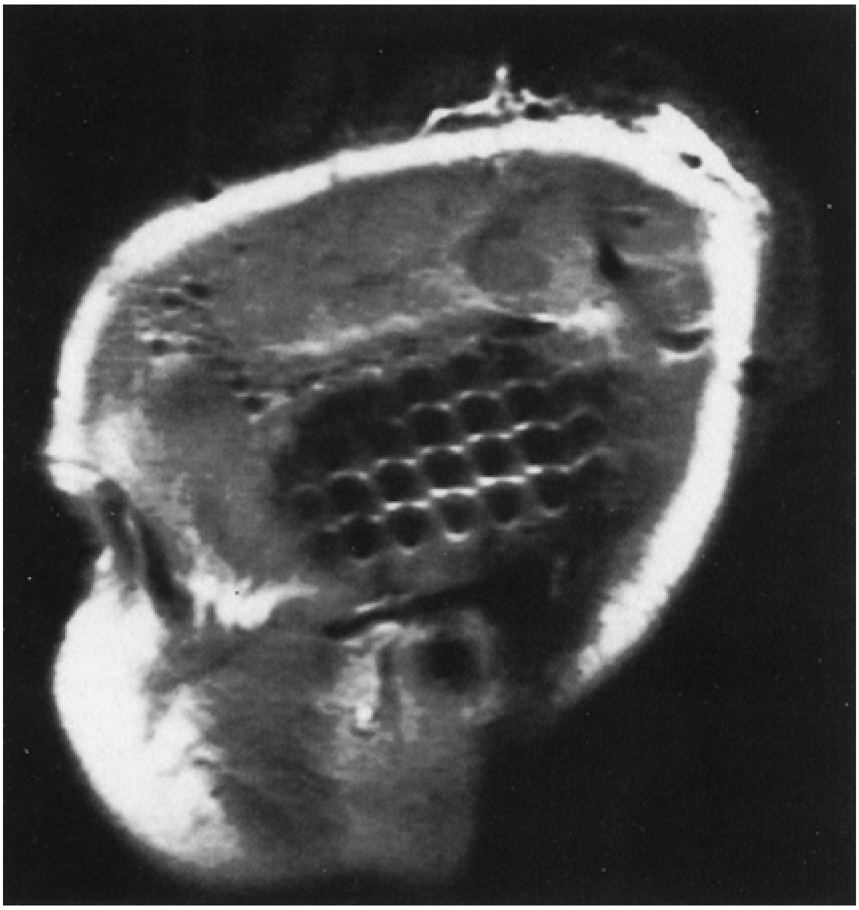

FIGURE 6. Sagittal magnetic resonance imaging (MRI) view of subdural grid placed to record from temporal neocortex.

The electrodes differ in the method of insertion, and with these differences come predictable differences in safety profiles. Depth electrodes are inserted with stereotactic MRI or computed tomographic (CT) guidance such that the trajectory, termination point, and location of each contact can be accurately predetermined.[62,87,91] These electrodes are usually inserted bilaterally, and accurate symmetric placements can be routinely achieved, not an insignificant accomplishment when comparison of the homotopic areas for onset and propagation of seizure activity is paramount in interpretation (see Depth Electrodes, Interpretation further on in this chapter). The strategy for selection of target locations of depth electrode placement differs somewhat in North American and certain European centers. The differences are partly a result of the more frequent combination of depth with additional implanted (subdural) electrodes in North America, thus allowing a more restricted use of depth electrodes for only some of the regions to be studied. The approach at some European centers developed from the stereo-electroencephalography method of Talairach and Bancaud, and aims to simultaneously and three dimensionally display all areas potentially involved in the onset, propagation, and clinical manifestations of the ictus, using only depth electrodes.[11,12,25,47,64,103,104] Both are based on hypotheses developed from noninvasive study. The European approach may incorporate more regions of suspected propagation and evolution, a consideration that influences the surgical approach of those centers. Subdural strip electrodes are inserted with the least precision because they are passed through burr holes and "slid" in the subdural space to the desired target (Figs. 3,4,5). Adhesions caused by prior surgery, infection, or injury often deflect the desired placement, and thus strict precision and homotopic sampling are rarely achieved. Depth and subdural electrodes can be removed at the bedside. Subdural grid electrodes require craniotomy for insertion and removal and can be placed accurately. Subdural grid electrodes are usually placed only when a reasonably well-defined epileptogenic zone is known, and they serve to aid in precisely defining the limits of resection. They provide optimal cortical coverage for functional mapping with stimulation if seizures begin near language, motor, or sensory cortex.

Increasingly, the intracranial EEG methods are combined to achieve optimal sampling of all suspicious areas for seizure onset. They can all be used at any age, although the range of indications tends to be more restricted in young children, especially infants. The specific indications, construction, insertion, interpretation, limitations, risks, cost, and accuracy of each of these methods are the subjects of the remainder of this chapter.

Indications for Intracranial Electrodes

Intracranial electrodes are indicated when it is reasonable to believe that a therapeutic resective procedure could be performed but the noninvasively obtained data are inadequate and more information is needed. Intracranial electrodes are then used to precisely identify the location of the ictal onset zone and can also delineate functionally important tissue that should be spared at the time of resection. Some protocols, particularly in certain European centers, also strive to delineate other regions of initial or early involvement that can be incorporated in designing the resection. Exact criteria for what constitutes sufficient concordant or discordant data vary somewhat from one epilepsy center to another.

Specific indications for intracranial electrodes in the evaluation of patients with refractory epilepsy include the following:

1. Insufficient concordance of noninvasively obtained data such that there remains uncertainty regarding the localization of the epileptogenic zone. Circumstances

   leading to intracranial electrode use include the following:

   a. An MRI showing an atrophic, developmental, or space-occupying lesion with nonlocalized interictal and ictal EEG.
   b. A normal or nonlocalized MRI with insufficient evidence of localized functional deficit and localized abnormality of excitability in a single region.
2. Discordance of noninvasively obtained data, so that the existence of a single epileptogenic zone must be proven and better localized.
3. Occupation by the epileptogenic lesion of territory within or immediately adjacent to vital cortex (e.g., motor strip, language areas) so that invasive functional mapping must be performed before resection in conjunction with precise localization of the epileptogenic zone.

Although there are no set criteria that can be systematically used to decide whether intracranial recordings should be performed, these statements give broad guidelines. Factors such as the presence of a lesion and the type of epilepsy (temporal versus extratemporal) influence to various degrees the need for invasive recordings. In the great majority of cryptogenic cases, for instance, the use of intracerebral recordings remains essential.[65] In temporal lobe epilepsy, although diagnosis of mesial temporal lobe seizures and the side of ictal onset is now possible in the majority of patients using noninvasive investigation, additional long-term monitoring with intracranial electrodes is appropriate when the side of mesial temporal ictal onset is unclear, if neocortical or extratemporal ictal onset is considered possible, or when electroclinical arguments suggest that the epileptogenic zone extends outside the boundaries of a more traditional approach to the mesial temporal lobe resection. The delineation of extratemporal epileptogenic networks is much more difficult than that of temporal lobe regions of seizure origin, so that many more patients with extratemporal epilepsy undergo invasive EEG recordings: There are no clear extratemporal epilepsy “syndromes,” there is no equivalent of hippocampal sclerosis on MRI, scalp EEG is often mislocalizing and even mislateralizing, and there are no standardized resection techniques.

Certain electrode types are more suited to some locations than others and are therefore indicated under different circumstances. Because depth electrodes penetrate the substance of the brain, they are indicated when EEG recording is needed from buried cortex (e.g., hippocampus, amygdala, or basal or interhemispheric cortex inaccessible to subdural electrodes). In practice, depth electrodes are often used to record from the mesial temporal lobes when mesial temporal lobe epilepsy is suspected. They are also useful for recording from other deep cortical structures that can be involved (insula, planum temporalis). They are also essential for targeting deep regions of suspected seizure onset, for example, one or several heterotopic regions of gray matter.[2,76,105] Subdural electrodes overlie the surface of the brain and are most suited for bilateral neocortical EEG recording, often in combination with depth electrodes. Subdural grids are ideal for functional mapping of cortex, though regional preoperative localization is needed to select the (restricted) sites for placement. In practice, subdural strips are also often used additionally with grids for better sampling of other lobes ipsilaterally or contralaterally.

Depth Electrodes

Construction

Most commercially available depth electrodes are multicontact with platinum contacts. In the past, nichrome alloy and stainless steel were also used.[87,91] These kinds of electrode contacts are all considered safe for postplacement MRI documentation of electrode contact positions with respect to anatomic landmarks,[129] although high-resolution CT is often used for this purpose, with later MRI coregistration to improve localization in relation to anatomic definition. These multicontact electrodes carry 4 to 12 contacts along their length, usually spaced 5 to 10 mm apart at variable or constant intervals. Others have up to 18 contacts with 1.5 mm spacing. Exact locations of contacts along the shaft can be varied to start and terminate at predetermined locations. The electrodes are commercially available from several vendors. They are flexible and are inserted with a rigid introducer that lies alongside or within the electrode. Rigid electrodes are also used.

Insertion

Insertion of depth electrodes is now routinely done by standard stereotactic methodology utilizing a Todd Wells, BRW, or Lexell frame[63,79]; more recently, frameless stereotactic methodology has been used. Electrodes enter through burr holes with usual targets of medial temporal and medial frontal regions (Figs. 1 and 2); deep, extratemporal locations are also targeted. The total number of electrodes varies but rarely exceeds 15, the total depending on the hypotheses generated and the array of electrodes selected to adequately address those. Electrodes can be inserted parasagittally or orthogonally such that, for example, they traverse the occipital lobe and occipitotemporal junction or lateral temporal lobe en route to medial temporal regions. Because the electrodes sample multiple locations, additional areas of preferred sampling can also determine which approach is used; some centers use either parasagittal or orthogonal placements, depending on the individual situation, but most have a preference for one or the other approach based on prior experience. Some centers use a computer-driven robot for electrode implantation,[15] particularly when nonorthogonal implantation is preferred either because of anatomic constraints or particular targets (insula, gyrus rectus). Neither approach is reported to be associated with a higher risk of complications. Lateral (orthogonal) placement is more common.

Recording

Commercial digital recording equipment allows referential recording and reformatting with desired electrode combinations, filter settings, and bipolar and referential display montages. This provides considerable flexibility. Most commercial equipment now allows sampling at 200 to 800 Hz; recent work in patterns of seizure onset suggests a potential benefit of using higher sampling rates. The multiple contacts, especially with combined procedures, usually require at least 64 channels of simultaneous EEG recording to display and interpret the information adequately, and often twice that number or more are optimal.

Electroencephalographic recording is done in parallel with continuous audiovisual correlation. The main goal is localization of the region of ictal onset recorded during spontaneous seizures. It is critical to scrutinize all electrode contacts carefully in relation to one another and in relation to the time of synchronized clinical seizure activity.

Seizures are precipitated by controlled withdrawal of antiepileptic medications during continuous recording. Current literature suggests that carbamazepine, phenytoin, valproate, or lamotrigine withdrawal does not produce false localization or atypical seizures[59,90,94,111]; the other, newer antiepileptic drugs have not been assessed in this regard. Barbiturate and benzodiazepine withdrawal should be avoided

because they can produce unreliable and/or false locali-zation.[116] Usually, spontaneous seizures are recorded within 7 to 10 days despite the patient's inactivity; seizures that occur earlier or later during the session do not have different profiles or accuracy for confident localization of the epileptogenic zone. Most centers prefer at least three seizures for analysis, and some require up to ten for the study to be considered complete. No rules can be developed, however, because seizures vary in their frequency, intensity, similarity to the usual clinical events, and similarity to one another. To this is added a variable number of subclinical seizures, recording mishaps, immediate postictal seizure onsets, immediate postoperative seizure onsets, insufficient clinical examinations, and other confounding variables that make the protocol and the interpretation as much an art as it is a science.

Although the recording of spontaneous seizures remains the best way to assess the extent of the epileptogenic zone, some centers, mostly in Europe, use electrical stimulation, particularly when ictal discharges are poorly defined, multifocal, or widely extended from the onset of the seizure. Observation of a complete and habitual seizure sequence after such stimulation is the goal, to provide insight into the spatial organization of the epileptogenic zone and other structures. The activation of regions removed from the specific site of electrical stimulation, however, that are unsampled by the electrodes represents a difficult, potentially confounding aspect of interpretation. Chemical stimulation is generally avoided because of its potential to precipitate nonhabitual seizures.[12]

Risks

The risk of intracerebral hemorrhage after depth electrode study ranges from 1% to 4%.[110] The use of intraoperative angiography, visualization of the cortical surface, and MR guidance might have reduced the hemorrhage rate, but insufficient information is available to conclude this definitively. Intracerebral hemorrhage is the most serious complication of intracranial electrode study and is reported only after use of depth electrodes, with several deaths as a result. Infection also occurs, but fatalities and long-term morbidity are rare.

Whether rigid electrodes have more potential for damage to normal cortical tissue than flexible ones is not established. One study reviewed the MRI appearance of 210 stainless steel depth electrode tracks 1 to 64 months after electrode removal.[63] Of 57 patients studied, 33 had rigid electrodes and 24 had flexible ones, all inserted in paramedial locations from occipital or frontal entry points targeted to medial temporal and frontal locations. Punctate 1- to 2-mm hyperintensities along the electrode track were the most common abnormality, found in 41% of cases. Four tracks (2%) showed punctate signal voids consistent with microhemorrhage, and one patient had a macroscopic occipital lobe hemorrhage. The authors did not note any difference between rigid and flexible electrodes with respect to these findings. Another comparison study of complications from depth and subdural electrodes found consistent moderate to severe multifocal inflammatory reactions to subdural electrodes and only mild to moderate reaction to depth electrodes. Although depth electrodes were on occasion associated with clinically unsuspected hematoma formation, microhemorrhage was much more common under subdural electrodes. Smooth, blunt construction with adequate insulation between contacts is essential.

There seems to be no substantive long-term risk of depth electrodes to otherwise normal cortical tissue.[3,102] They do not appear to cause epilepsy. Centers routinely employing a bilateral depth electrode study before surgery for epilepsy have similar short- and long-term success rates for seizure control to those that do not. Long-term relapse after apparent seizure cure occurs occasionally whether or not depth electrodes were part of the preoperative evaluation. Occasionally, the depth electrodes themselves (or the procedure under general anesthesia) seem to “cure” the epilepsy, an observation made on <0.5% of patients at several centers.[91] These considerations suggest that depth electrodes are indeed not epileptogenic. With respect to clinically significant damage to the function of underlying tissue, in the absence of other complications or subsequent surgery, the literature does not document any negative functional effects of depth electrode investigation.[87,91]

Interpretation

Background

Background activity in depth electrodes conforms to expected rhythms on scalp EEG. Interpreters must remember, however, that because of the loss of frequency filtering from scalp and skull, and because recording is from a smaller volume of tissue, the waveforms are sharper and higher frequencies are noted, and some normal activity takes on an unusual appearance if not an unusual location. For example, high-amplitude potentials in motor cortex can mimic spikes. Occipital alpha activity, central mu rhythm, frontal beta predominance, lambda waves, and sleep spindles are seen as on surface EEG. Asymmetric activity, especially slowing, has the same significance as on scalp recording. Asymmetric or localized flattening of the recording as well as slowing can suggest progressive hemorrhage, fluid collection, or infection. However, a focal depression of activity might be seen with electrodes in white matter. In addition, some slow activity can occur in the first 48 hours after implantation and resolves spontaneously.

Interictal Activity

Interictal spikes are more widespread in intracranial EEG recording than in scalp EEG recording.[79.91,114] Although interictal spiking rates often are higher in the area where seizures begin, for example, in medial temporal lobe epilepsy, this relationship does not always hold. Furthermore, multifocal extratemporal interictal spikes in both temporal and extratemporal epilepsy with a single ictal onset zone are common. Accordingly, most experts agree that interictal spikes recorded with depth electrodes (or any intracranial electrodes)

are less important for localization of the epileptogenic region than ictal onset.[66] However, although only some of the interictal spikes recorded intracranially are associated with the epileptogenic area, *some* interictal spikes are generated there, and the ability to reliably distinguish those, perhaps because they are associated with particular background changes or have unique morphology, could advance localization. Accordingly, interictal paroxysmal abnormalities are always scrutinized because they can provide additional confirmation of localization, and eventually may prove of even more important localizing value in certain settings. This seems to be true, for example, in focal cortical dysplasia of Taylor, in which the interictal spikes can be a good marker of the extent of dysplastic cortex that needs removal to abolish the seizures.[22,106]

Gotman and Koffler[37] reported an increase in spikes postictally; other authors confirmed this observation.[49] It can be well demonstrated with intracranial recording. Gotman and Marciani did not localize the postictal spikes to the region of seizure onset,[38] but Katz and Spencer[49] felt that certain populations of postictal spikes do emanate from the area of epileptogenesis. This issue requires resolution in larger numbers of temporal and extratemporal epilepsies recorded with surface and intracranial electrodes. Certainly, many interictal spikes recorded with depth electrodes (or any intracranial electrodes) cannot be seen with any noninvasive technique, and further work to investigate their significance is needed to assess what determines their expression on surface EEG as well.

Based on earlier work in epileptic rat hippocampus, recent investigators using microelectrodes examined higher sampling rates and recorded high-frequency oscillations termed “ripples” (96 ± 14 Hz) and “fast ripples” (250 to 500 Hz) in hippocampus and entorhinal cortex of patients with mesial temporal lobe epilepsy. Whereas ripples were considered physiologic oscillations, fast ripples were predominant in the areas of seizure onset, suggesting that they might reflect pathologic hypersynchrony in epileptogenic tissue.[101] High-frequency oscillations were also described (60 to 100 Hz) in neocortical areas, and they sometimes appeared in anticipation of seizure onset.[123] Investigation of this potentially important pattern is ongoing.

Ictal Activity

Onset.

Although the goal of intracranial recording is widely accepted to be localization of the ictal onset zone, the criteria for interpretation of ictal onset in intracranial EEG have been slow to evolve.[50] A variety of EEG patterns and frequencies occur at the start of seizures, but certain patterns predominate in particular locations. Spencer and Spencer[92] found that medial temporal lobe seizure onset, often termed hippocampal seizure onset, tends to vary in exact location and morphology, appearing in hippocampus or entorhinal cortex in different seizures, in patients with mesial temporal sclerosis. The medial temporal lobe (hippocampal/entorhinal) onset pattern is distinguished by a 10- to 16-Hz rhythm. Medial temporal lobe seizure onset can also present as a characteristic pattern of slow (1 to 2 Hz), periodic spike activity in the same location as the 10- to 16-Hz onset rhythm but before it begins (Fig. 7).[107] This periodic pattern can last from 5 to >100 seconds. This periodic pattern is seen almost exclusively in the hippocampus and is inversely related to CA1 cell loss, one marker of mesial temporal sclerosis.[86] Sperling also observed a peculiar high-amplitude triangular wave pattern at the onset of seizures arising in amygdala.[98]

Ictal onset patterns appear to be more reproducible and consistent in location from seizure to seizure in neocortical epilepsy.[85] Neocortical seizure onset is characterized by a combination of often superimposed slower (4- to 10-Hz) and faster frequencies at seizure onset (Fig. 8).[39,50,85] Although Spencer et al. reported that the fast frequencies were in the vicinity of 40 to 50 Hz, other studies suggest that the frequency of recorded neocortical seizure onset can approach 200 Hz.[4,35,39,50,85,113] Isolated low- or high-frequency seizure onset recorded from neocortex or medial temporal structures, however, might represent a propagation pattern rather than actual ictal onset.

In any cerebral location, apparent rhythmic activity or frank ictal discharges differing from background can develop focally but not propagate or produce symptoms. This so-called subclinical seizure activity has been correlated with an excellent outcome after surgery,[100] specifically surgery in the area of the subclinical seizure discharge.[108] It may have a somewhat different morphology or location than the clinical ictal discharge or appear identical to the early parts of clinical seizures. The recording of such subclinical discharges does not substitute for the recording of the full clinically typical seizures on which localization is based for purposes of resection.[10]

Propagation Patterns.

Successive involvement of cerebral regions in the rhythmic patterns characteristic of seizure discharges has often been called propagation, although no physiologic mechanism is implied for the term used in this context. Propagation time from one hippocampus to the other has been studied by several authors, all of whom found that long (>20 sec) interhippocampal propagation time correlated with excellent outcome after medial temporal lobe resection, implying that it signified a true epileptogenic zone in the medial temporal region (Figs. 7 and 9).[53,54,88] Spencer et al.[88] found that interhippocampal propagation time correlated inversely and significantly with CA4 cell counts. Because CA4 is the origin of the main interhippocampal commissural connection, cell loss there might indeed prolong the process of seizure propagation. Fewer than 25% of medial temporal lobe onset seizures propagate first to the contralateral hippocampus; most initially propagate to ipsilateral temporal neocortex or frontal lobe, and both of these patterns are fairly common (Figs. 7 and 9).[1,50,96,97,98,99] The spread pattern can vary depending on the exact region of medial temporal origin; Chabardes et al.[21] found that temporal/polar seizures propagated to superior temporal gyrus/periopercular cortex, whereas other mesial temporal seizures propagated to basal and lateral temporal cortex. Parietal and occipital lobe seizures can show variable propagation by infra-Sylvian or supra-Sylvian routes, with subsequent temporal or frontal electroclinical evolution.[119,122] Seizure propagation recorded with intracranial electrodes follows known pathways but can be modified by damage to these pathways or their origins. Thus, frontal lobe seizures often show very rapid propagation to the contralateral frontal lobe, often too rapid to allow determination by visual EEG inspection of which frontal lobe triggered the seizure.[91,120,121] It is these situations that stand to benefit most from computerized EEG analysis.

Termination.

Termination patterns of seizures recorded intracranially have been neglected in research and the literature. There are three typical patterns: (a) sudden cessation of seizure activity diffusely or focally; (b) gradual decrease in frequency and increase in amplitude, usually focally; and (c) decreased frequency of a burst-suppression-like pattern, usually diffusely. The focal pattern of termination is the most common, with seizures often ending earlier in the temporal lobes than in the frontal lobes. Termination in the temporal lobe of onset recently has been correlated with cure of seizures after resection of that temporal lobe.[93] Seizure duration has not been correlated with hippocampal cell counts, suggesting that cell loss and contribution of existing pathways are not as important as other mechanisms in the termination of spontaneous human seizures.

Anticipation.

Various linear and nonlinear quantitative EEG approaches to depth electrode recorded signals have been used to identify changes in the EEG that precede and herald the oncoming seizure but cannot be appreciated by visual interpretation. Such methods fall in the purview of seizure prediction but might also be viewed as more sensitive approaches to seizure detection or detection at an earlier stage. Early investigators applied nonlinear dynamical approaches: Le Van Quyen and colleagues found that a measure of phase synchronization could define a pre-ictal state in mesial temporal lobe epilepsy; Litt and colleagues used a measure of signal energy to predict seizures; and Martinerie and colleagues applied a measure called correlation density.[52,55,56,60] Although one approach might not fit all seizures and patients, the collected work and evidence supports the conclusion that detectable changes based on quantitative EEG analysis are likely to appear 10 to 30 minutes before visually identified seizure onset. Developments in this field depend on continued analyses of intracranial EEGs and are likely to expand our approaches to, and knowledge of, the process of seizure generation.

Advantages and Limitations

The obvious advantage of depth electrode recording, an advantage shared with other intracranial recording over scalp EEG, is its ability to demonstrate an early electrical signal that precedes clinical seizure onset and is devoid of signal artifact. Depth electrodes are ideally suited for studying medial temporal lobe onset seizures. Depth electrodes demonstrate hippocampal/entorhinal seizure onset before medial temporal subdural strips, and both show this activity considerably before scalp EEG.[97,99] Access to buried cortex makes depth EEG the only method capable of detecting the earliest electrographic changes from seizures arising in these regions. Depth electrodes are also unique in the accuracy with which they can be placed as a result of stereotactic methodology. The major limitation of depth electrodes is limited spatial sampling. One cannot be certain that the earliest activity truly comes from the area where it was recorded.

P.1799
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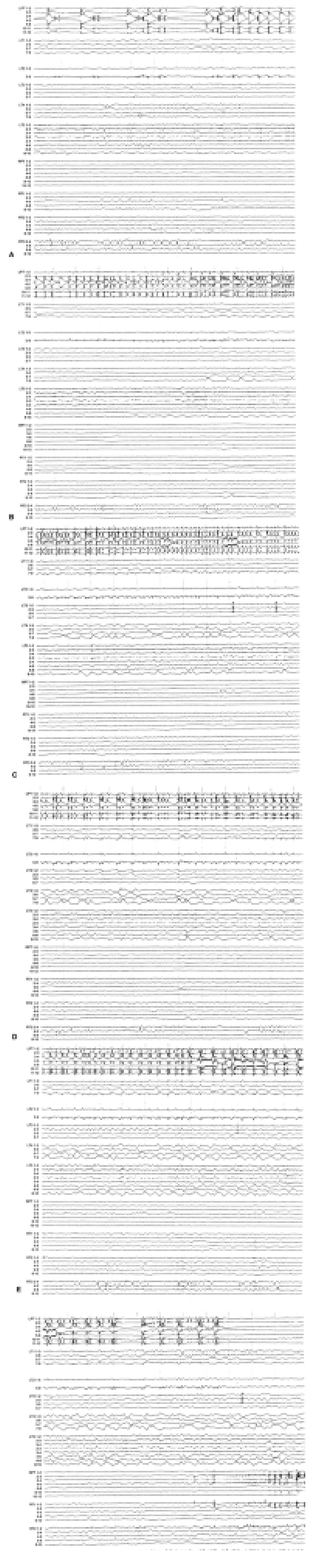
A
B
C
D
E

FIGURE 7. Continuous segments of electroencephalogram recorded with depth electrodes in hippocampi (LPT, left; RPT, right) and multiple subdural strips over temporal neocortex bilaterally, including anterior (LT1, LT2, RT1), middle (LT3, LT4, RT2), and posterior (LT5, RT5) locations. **A:** Before onset of spontaneous seizure, showing the slow periodic spike pattern characteristic of medial temporal lobe seizures associated with CA1 cell loss, in the left hippocampal depth electrode (LPT); note absence of abnormality in medial contacts of left anterior temporal strips (1 to 3 on LT1, LT2, LT3). **B:** The periodic pattern in LPT is accompanied by the lower-voltage, 10- to 15-Hz discharge characteristic of medial temporal seizures. **C:** The rhythmic left hippocampal activity slows, and left medial temporal neocortical rhythmic activity is reflected in subdural strips LT1, LT2, and LT3. The more posterior temporal neocortex is also involved (see LT4 and LT5) in segments **D** and **E**. Only a full minute after seizure onset (**F**) does the right hippocampus (RPT) become involved. This is the prolonged delay characteristic of interhippocampal propagation in medial temporal lobe epilepsy. Each division, 1 s; electrode positions are numbered distal (1) to proximal.

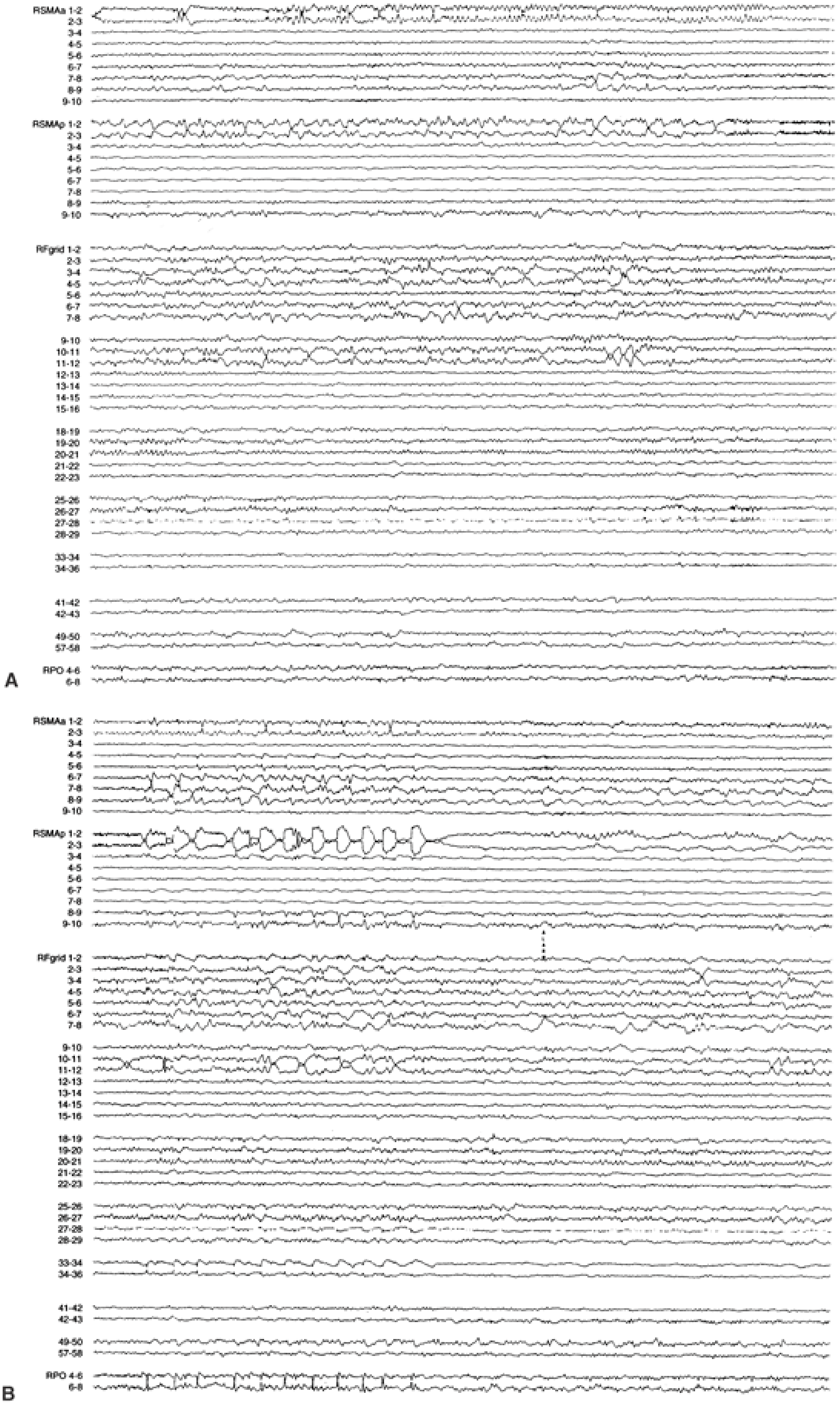
RSMAa 1-2
2-3
3-4
4-5
5-6
6-7
7-8
8-9
9-10
RSMAp 1-2
2-3
3-4
4-5
5-6
6-7
7-8
8-9
9-10
RFgrid 1-2
2-3
3-4
4-5
5-6
6-7
7-8
9-10
10-11
11-12
12-13
13-14
14-15
15-16
18-19
19-20
20-21
21-22
22-23
25-26
26-27
27-28
28-29
33-34
34-36
41-42
42-43
49-50
57-58
RPO 4-6
6-8
A
B

FIGURE 8. Continuous intracranial electroencephalogram segments recorded from medial frontal subdural strips (and others) in the patient of FIGURE 5. Seizure onset is seen as combined very high-frequency and slower discharge focally in the right supplementary motor area (RSMAp 1–2, 2–3). Each division, 1 s. RF grid, right frontal grid; RPO, right parietooccipital strip; RSMAa, RSMAp, right supplementary motor anterior and posterior strips, respectively.

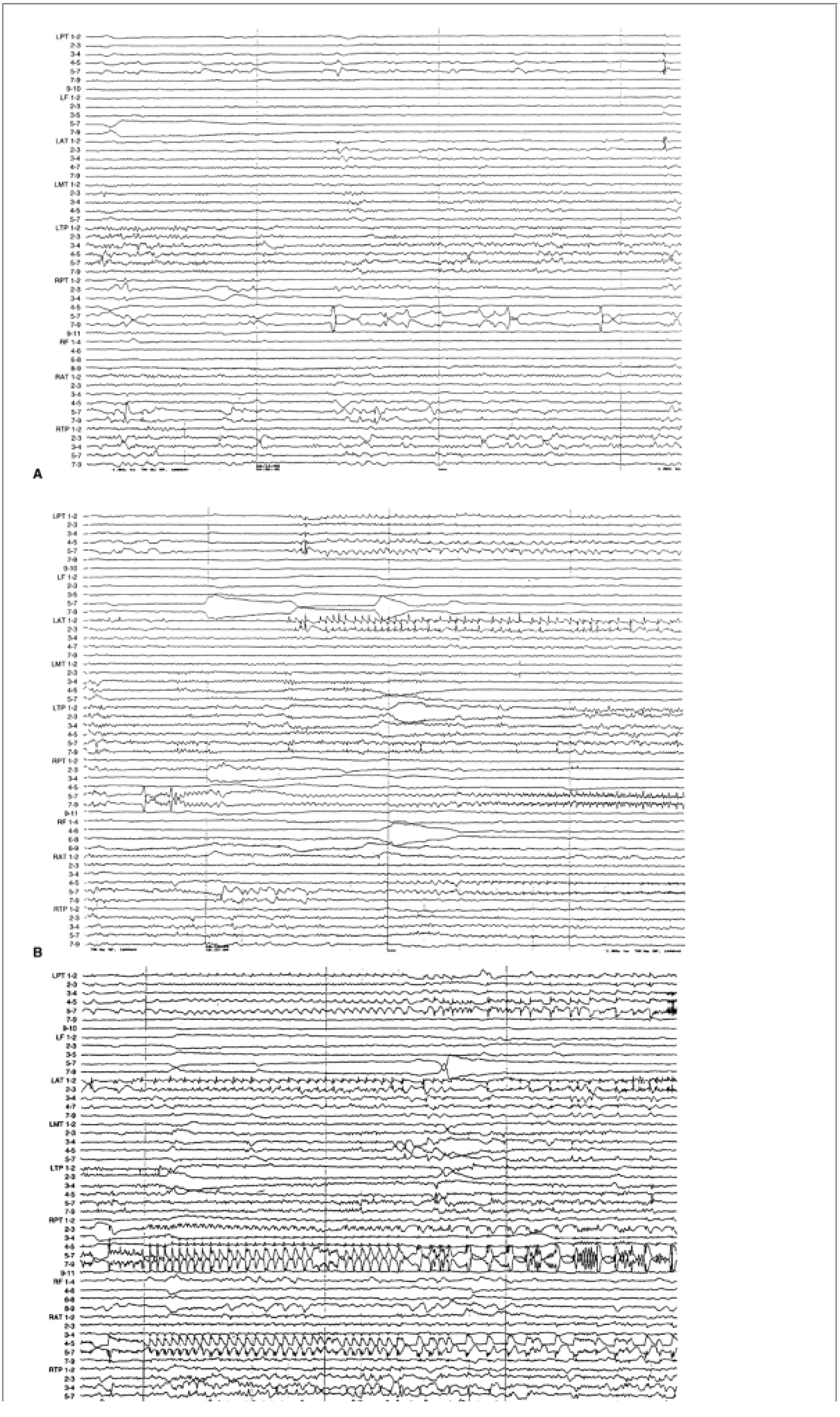
LPT 1-2
2-3
3-4
4-5
5-7
7-9
9-10
LF 1-2
2-3
3-5
5-7
7-9
LAT 1-2
2-3
3-4
4-7
7-9
LMT 1-2
2-3
3-4
4-5
5-7
LTP 1-2
2-3
3-4
4-5
5-7
7-9
RPT 1-2
2-3
3-4
4-5
5-7
7-9
9-11
RF 1-4
4-6
6-8
8-9
RAT 1-2
2-3
3-4
4-5
5-7
7-9
RTP 1-2
2-3
3-4
5-7
7-9
A
B

FIGURE 9. Continuous electroencephalogram segments of spontaneous seizure recorded from left and right hippocampal depth electrodes (LPT, RPT) and multiple subdural strips over frontal (LF, RF), anterior temporal (LAT, RAT), midtemporal (LMT), and temporoparietal (LTP, RTP) neocortical areas. Onset in the right hippocampus (RPT 7) with 8-Hz activity is followed rapidly by rhythmic activity in the left hippocampus (LPT, LAT). Such short propagation times to the contralateral medial temporal region raise doubt about true hippocampal onset; absence of the periodic pattern and very slow onset are also atypical (compare Fig. 7). This patient failed to achieve seizure control after temporal lobectomy.

Yield and Accuracy

Most centers select patients for depth electrode study carefully enough that they report 60% to 85% yield of focal seizure onset detection in this population.[80,82,91] The yield obviously depends on the population studied and the acumen with which the study sites are selected. In 1980 and again in 1990, in reviewing the literature and personal experience, Spencer found an equivalent proportion of all depth-EEG-studied patients to be localized.[82] Depth EEG produced a change in management of 50% of patients studied. The yield has been fairly constant despite advances in patient evaluation that have changed the population of patients who have depth electrode studies. We do not have information on patients studied after 1990 to examine whether MRI, by reducing the need for depth electrode study among the large group of lesional and hippocampal atrophy patients, has reduced the overall yield of depth electrode localization; experience suggests that this might be true, at least at some centers. A recent retrospective study of depth electrode investigations in 211 patients, however, suggests that the yield for localization might be steady (it was 87% in this report, highly comparable to results in earlier decades).[25] The yield of these studies of course depends on the sites selected for electrode placement, the specific kinds or combinations of electrodes used, and the referral population of the center.

The concept of yield is really of no value, however, without scrutiny of its accuracy. The reported surgical success and seizure cure after patient selection for operation with depth electrodes approximates the success without them in older studies.[80,82] This does not imply that such studies are unnecessary, but, rather, it probably reflects the fact that they permit more complicated patients to benefit from surgery who would have been rejected according to noninvasive protocols. This might also be because the patients studied with depth electrodes were often suspected of having medial temporal lobe epilepsy and confirmed as such, and this group of patients has a known high surgical success rate. The experience at some centers suggests, however, that seizure outcome after resections based on depth electrode localization might not be as high as for patients selected by noninvasive EEG criteria. Similar to the previous comments on the yield, the outcome of resection based on these results depends on many factors that differ among centers and patient populations. It is even more difficult to assess the accuracy of depth electrodes compared to other intracranial electrode studies because depth electrode studies are done in a special group of patients, among them those suspected of having medial temporal lobe epilepsy, whereas grids and strips are typically employed in more difficult, neocortical cases. Depth electrodes (and other intracranial methods) have also been responsible for the diagnosis of unlocalized or multifocal epilepsy in 10% to 20% of patients thought to have a reasonable possibility of localization based on noninvasive electrical, functional, and structural studies.[80,82] These patients

are then excluded as surgical candidates by the intracranial EEG results. Although it is conceivable that poor electrode positioning, inappropriate electrode site selection, or inadequate interpretation obscured focal onset and deprived some of these individuals from potentially successful surgical treatment, this is rather unlikely: In one study, surgical success was poor when the depth EEG was not localized and the resection site had to be determined based on other data.[80] The accumulated evidence suggests that depth EEG has been and continues to be an accurate method with reasonable yield for localization of the epileptogenic zone in an otherwise untreatable population, and that these figures are not changing dramatically.

Cost

Forty-five thousand dollars is not an overestimate of the cost of a depth electrode study, considering the hospitalization, operating room, and technical and professional fees involved. This cannot be justified if simpler means enable similar treatment at comparably high success rates. For the otherwise untreatable, unlocalizable patient, however, this cost pales in comparison to the cost of a lifetime of unemployment, disability, and medical expenses. Even if only one fourth of depth electrode studies produce productive lives from totally dependent ones, the net gain to society and the individuals involved is substantial.

Subdural Electrode Strips

Construction

Subdural electrode strips are flexible strips of Silastic or Teflon into which are embedded platinum, stainless steel, or silver contact disks spaced 5 to 10 mm apart.[124,126] The arrangement can include bisurface electrodes; up to ten contacts can be arranged in one or two rows. These electrode devices are often MRI compatible, and many varieties are commercially available.

Insertion

Through burr holes, subdural strip electrodes are manually manipulated to the desired target areas in the subdural space. These commonly include medial inferior temporal and interhemispheric regions of frontal, parietal, and occipital cortices and any other lateral neocortical surface location (Figs. 3,4,5).[5] The operation is usually done under general anesthesia. Up to six, but usually two or three, electrodes are inserted through one burr hole with different planned trajectories, and some surgeons use an expanded "trough" to accommodate implantation of more strips (Fig. 3). Subdural strip electrodes can be inserted bilaterally, with an attempt at roughly homotopic placement, or asymmetrically, depending on clinical need. With appropriate experience, medial inferior temporal lobe structures including the entorhinal cortex can be adequately sampled with subdural strips (Fig. 4). Accurate placement, however, can be difficult because of adhesions or bridging veins, especially in basal and medial regions, and multiple strips might be needed to fully sample medial temporal locations from anterior to posterior.

With the advent of MRI-compatible electrodes, precise anatomic correlation of electrode locations is possible after implantation. The appearance of subdural strips on MRI in several planes as they curve around, however, as well as the use of multiple strips and arrangements can create a challenge in assigning which electrode contacts of which strip are represented at each cortical location. Meticulous attention to detailed reconstruction is necessary to assure valid interpretation.

Subdural strip electrodes can be removed without significant discomfort in the patient's room at the conclusion of the recording session. Even study extending up to 8 weeks does not create sufficient inflammatory reaction to prevent removal, although sometimes more prolonged recording is associated with the (rare) need to reopen the operative site.

Recording

The comments on depth electrode recording procedures with respect to medication withdrawal, appropriate activation procedures, the duration of the study, the number of necessary seizures, and the importance of electroclinical correlation apply equally well to subdural strip recordings and are not reiterated here. Because digital recording and reformatting with appropriate gain and filter settings is commonplace, cautions and recommendations on recording parameters are less cogent than for analog recordings. Every attempt should be made to record from all contacts simultaneously. In studies involving ten strips or more, 128 channels offer such a distinct advantage that this recording capacity is an almost necessary option for the equipment.

Risks

No mortality and relatively infrequent (predominantly infectious) morbidity (1% to 2%) are reported after subdural electrode study, and these risks are lower in experienced hands.[73,125] Although hemorrhagic complications are known, mainly from tearing of bridging veins in medial temporal and interhemispheric regions, they are rare. When multiple nearly adjacent strips are used such that the array approximates a subdural grid, cerebral edema is a conceivable complication but is unusual. Epileptogenic potential and damage to functional cerebral tissue are not a consideration here in the absence of bleeding because the brain is not penetrated.

Interpretation

The comments regarding depth electrode interpretation also apply to subdural strips. Strip recordings give increased sensitivity to interictal spikes compared to scalp EEG.[26,58,71] Seizure onset within the hippocampus is detected earlier in depth electrodes than in subdural strips, however, even when the latter are placed very medially (Fig. 7).[97,99] The characteristic periodic spike pattern of hippocampal seizure onset is less often appreciated in medial temporal subdural strip recording, and the 10- to 16-Hz onset is rare. When seizure onset is recorded from subdural strips in medial temporal locations, it more often is characterized by faster (>16 Hz) activity. Weinand et al.[112] found that medial temporal seizure onset recorded with subdural strips in patients who became seizure free after medial temporal resection usually took the form of "fast spike trains" but could be characterized as low-voltage fast activity.[112] Neocortical seizure onset characteristically shows adjacent or colocalized slow (4- to 7-Hz) rhythm in addition to the faster frequency.[85,87,91] As already mentioned, seizure onset can be characterized by faster frequencies, and some such onset patterns can be invisible to certain equipment sampling rates. Neocortical locations of onset are detected more readily by these subdural strip arrays.

As with depth electrode recording, subdural strip electrodes can demonstrate variability of the seizure onset pattern in medial temporal structures, and more consistent morphology is observed in seizures that begin in neocortical regions.[87,91,112] Prolonged time to interhemispheric seizure propagation and onset of electrical activity frequently preceding clinical signs are also characteristics shared by the depth and subdural electrode studies of medial temporal lobe epilepsy.[112] Blume and Kaibara[19] described the "start–stop–start" phenomenon in subdural-strip-recorded seizures; it is characterized by a short-lived, localized rhythmic ictal discharge, a period of 1 to 10 sec of normalization, and resumption of ictal discharge, usually but not always in the same location, which is then followed by clinical seizure activity.[19] The initial "start" location was correlated with the location of onset in seizures in the same patient that did not show this phenomenon. The pattern was interpreted as aberrant seizure evolution, not origin; interpretation of subdural ictal onset should take these observations into account.

Some early reports documented false lateralization of medial temporal lobe epilepsy with subdural electrodes[99]; usually, with adequate medial extent of strip termination, localization of the side of medial temporal lobe seizure onset is accurate, but their reduced sensitivity prevents detection of many subclinical seizures in the hippocampus[97] and occasionally results in nonlocalizing subdural studies when depth studies are localizing.

Advantages and Limitations

An advantage of subdural strips is the ability to perform cortical mapping of functional activity by stimulation through these electrodes. This role is better filled by subdural grids (their main advantage; see later discussion) but has been successfully accomplished with subdural strips as well, particularly when adequate numbers of contacts cover the cortex in question. Stimulation at up to 15 mA can also invoke afterdischarge or clinical seizure activity, although these stimulated seizures might not serve to accurately localize the epileptogenic zone. Subdural strip electrodes have low morbidity, which remains an advantage.

The main limitations of subdural strips are their inaccurate and unpredictable placement by virtue of the insertion technique, a limitation that is only partly overcome by the skill and experience of the surgeon. Despite less sensitivity for study of medial temporal lobe structures, they provide better representation of neocortical areas.

Yield and Accuracy

The yield of subdural strips has been reportedly high, as has surgical success based on this localization,[82] but determining the specific yield of strips in current practice is complicated by the increasing use of simultaneous depth and subdural electrode recording. The best distillation of available evidence indicates an acceptably high and accurate yield of subdural strips for localization of the epileptogenic zone based on seizure outcome after resection, with an excellent risk-to-benefit ratio, limited only by the selection of implantation and recording sites. As in the case of depth electrodes, it might be true that surgical success is lower in patients localized in this way (or with other intracranial methods), but formal studies do not support this conclusion.

Costs

Subdural electrode recording has similar costs to depth electrode recording because it requires the same intraoperative placement, chronic audiovisual/EEG monitoring, medication withdrawal, electroclinical correlation, and recording of multiple spontaneous seizures. With even lower risk and acceptable yield, societal expense is thus more than justified.

Subdural Grids

Construction

Subdural grids are simply expanded subdural strips. They are sheets of inert material, usually Silastic or Teflon, into which are embedded multiple platinum, silver, or stainless steel electrode disks with variable contact spacing (usually 1 cm) to create grids that record from the large areas of cortex over which they are placed. The grid can be 4 × 5 or 8 × 8 cm or any other selection; irregular shapes are also possible, as are combinations of grids to cover predetermined cortical regions; these are fashioned intraoperatively. Grids are commercially available and MRI compatible such that verification of locations with respect to lesions and cortical surface anatomy is easily and accurately accomplished.[87]

Insertion

Because of their size, subdural grid electrodes require a craniotomy for insertion and removal (Fig. 6). Accordingly, placement is accurate. The bone flap can be replaced or left off for the duration of the study; the latter has the potential advantage of avoiding some of the complications of cerebral edema that can occur with extensive cortical grid coverage. This is a particular safety concern with children, in whose heads a given size of grid takes up proportionately more space than in an adult head. One or more grids can be inserted over a hemisphere. Subdural strips can be inserted in conjunction with grids, usually to sample interhemispheric or medial temporal regions simultaneously. Because of technical considerations, grid insertion is usually unilateral, although they can be used bilaterally. In those circumstances, smaller grids are used contralateral to the area of predominant interest.

Recording

As with all intracranial methods, localizing seizure onset with clinical correlation is the main goal of subdural grid recording, with the added possibility of functional mapping. Continuous recording during antiepileptic drug withdrawal to record a number of spontaneous seizures (usually at least three) is pursued as with other intracranial recording techniques. Recording parameters are generally equipment driven, and because reformatting of montages to bipolar or referential forms with variable filters is possible, the relative advantages or disadvantages of specific settings are not pertinent. Display of spontaneous seizure onset with different filters and gains can optimize one's ability to detect both the slow and fast components of the activity characteristic of spontaneous neocortical seizure onset. Recording sessions with subdural grids tend to be lengthier than those with other intracranial EEG methods. There might be several reasons for this observation. Functional mapping is time consuming and is often postponed until spontaneous seizures have been recorded, at which time medications are resumed. There is no evidence that this practice inhibits one's ability to stimulate functional cortex because of adhesions or reactive changes around the inserted electrodes. In addition, large electrode arrays situated in the subdural space can lessen the rate of spontaneous seizure occurrence. Neither the operational mechanism nor the predictable occurrence of this phenomenon has been systematically investigated, but it seems to be a repeated observation.

Risks

The risks of a subdural grid study are weighted toward infection and cerebral edema; these occur in up to 4% of patients who undergo subdural grid study, sometimes with significant prolongation of hospital stay and morbidity. Very rarely mortality or intracranial hemorrhage has been associated with grid recording. More extensive cortical coverage is associated with an increased risk of cerebral edema.

Interpretation

Background and interictal interpretation suffer from the restricted cerebral sampling obtained with grid studies, with the resultant inability to compare homotopic signals in various regions, assess the presence or absence of the expected normal rhythms in unsampled locations, or evaluate propagation patterns and timing.[87] Because of this, absolute background rhythm assessment is less useful than changes that occur during the recording session. Progressive slowing or attenuation is a significant predictor of metabolic or structural interference and can appear before other evidence of such intervening complications. Interictal spike distribution can be extensive, covering large portions of the grid, or can be restricted. Complete absence of interictal spiking or its relative paucity is not known to be a negative prognostic factor for ictal onset localization.

Ictal onset recorded in subdural grids can be quite focal, starting in one or two contacts, or can be widespread in nonadjacent contacts. The more focal the onset changes, the higher is the degree of confidence in the ictal localization. The characteristic pattern of neocortical seizure onset—a high-frequency discharge with adjacent simultaneous, or immediately superimposed, slow theta rhythm—is seen in subdural grid or strip recordings or depth electrodes. Eventually, all grid contacts become involved in high-frequency seizure activity, and this successive involvement and the manner in which it evolves are more rapid and less useful, with our current knowledge, than the propagation patterns across lobes or hemispheres. It is important to interpret subdural grid recordings (and all intracranial EEG recordings) with clinical correlation to ensure that electrical changes precede or are at least simultaneous with clinical involvement, for the diagnosis of ictal onset location.

Advantages and Limitations

Subdural grids are better suited than any other intracranial recording method for mapping of functional cortex near a suspected epileptogenic zone before resection. The density of contacts and the accuracy of placement are unsurpassed. Multiple subdural strips cannot control the locations of contacts with the same precision to achieve the desired array for ideal mapping.

The extensive regionalized array of contacts so ideal for mapping restricts placement of other electrodes when subdural grids are used. This limitation is the main disadvantage. In addition, physiologic effects of large subdural grids can affect the quality or character of recorded signals. The Yale group found poor yield (see later discussion), delayed electrical seizure onset, a remarkably high incidence of initial electrical change at the edge of the grid, and occasional difficulty in recording spontaneous ictal events at all. Whether these difficulties reflect insufficient sampling is questionable because grids often overlie structural lesions whose proximity to seizure onset is undeniably demonstrated by the commonly observed success in seizure cure after the lesion is removed. The "blanketing" of cortex by the subdural grid might alter the pathophysiology and the criteria by which we should interpret these EEGs, but the current state of knowledge affords no means of knowing when this might occur or how to proceed.

Yield and Accuracy

Use of subdural grids for localization of the epileptogenic zone has not been proven accurate or reliable.[109] The application of grids to localization stems from their utility for functional cortical mapping combined with a logical extension of the ability of subdural strips to provide useful localizing information about the ictal onset zone. Subdural grid recording might not be as useful as subdural strips or depth electrode study for electrical confirmation or demonstration of the ictal onset zone (Fig. 10).

“Accuracy” has a different meaning in this context; it is difficult to judge because grids are placed over areas already suspected of being epileptogenic on the basis of other localizing studies; often a structural lesion is present. Because the location of a (single) lesion on structural imaging procedures in uncontrolled epilepsy patients is often highly correlated with the region of epileptogenesis, the selection bias rather than the grid recording might be responsible for the accuracy of localization as judged by seizure cessation after lesion removal. Masuoka and Spencer[61] studied 25 patients who underwent 26 separate subdural grid studies employing chronic recording with 20 to 64 contacts. Computerized and visual analyses of digitized electrical data recorded during spontaneous seizures with electroclinical correlation were used to identify the location of the ictal onset zone. Adequate location of seizure onset was possible in only 4 of the 26 studies, and the remainder of the patients showed spontaneous seizures to be accompanied by diffuse or regional electrographic seizure onset in most or all grid contacts, lack of EEG change, or clinical onset preceding electrographic alterations in the grid recording (Fig. 10). Fourteen of the 25 patients had structural lesions, and the grid was placed over the lesions. Two of those patients had subdural EEG localization to the lesion site, and the other 12 were not localized. Six of the 12 unlocalized lesional patients have been seizure free for >2 years after resection of the lesion. These observations suggest that subdural grid recording infrequently localizes seizure onset in the absence of other localizing information and should not be promoted for that purpose alone.

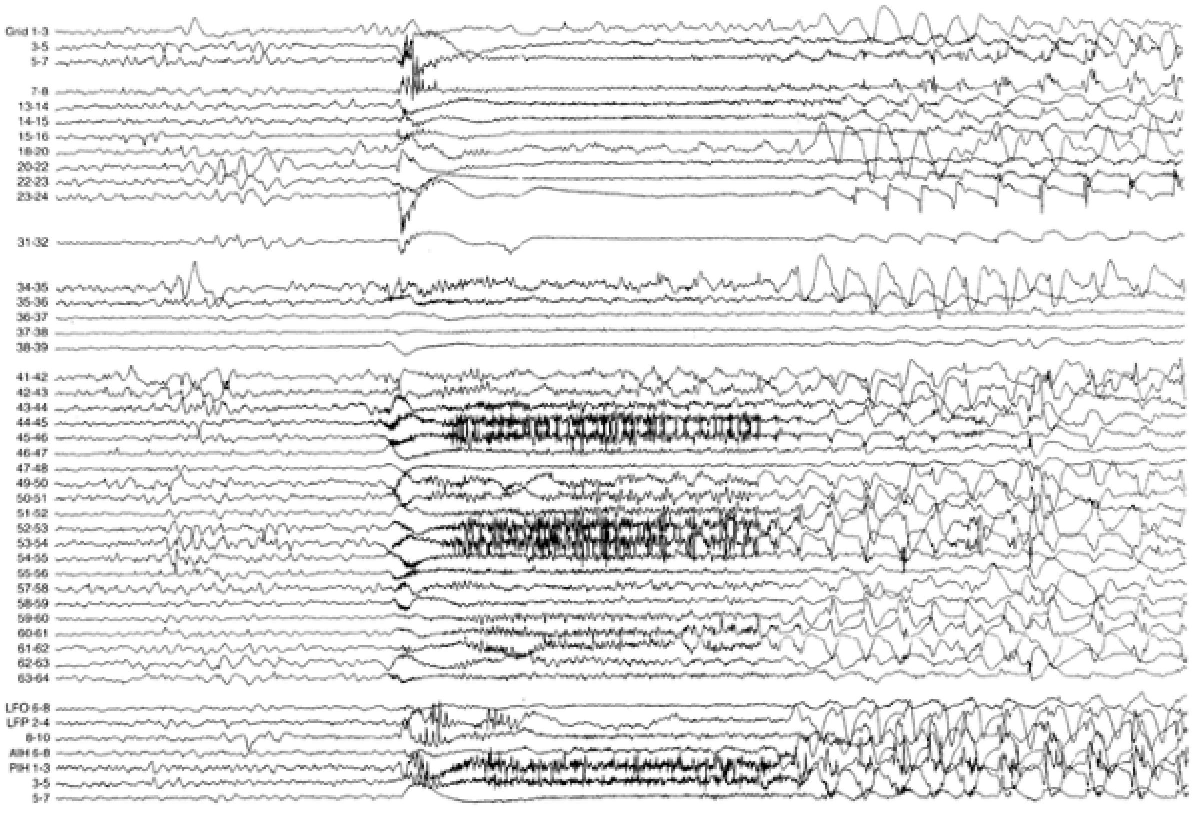

FIGURE 10. Spontaneous seizure recorded with subdural grid. Diffuse high-frequency discharge without clear localization is often a problem of subdural grid recording; there is a suggestion of slightly earlier onset in grid contact 43.

Awad et al.[9] reported 47 patients with chronic grid recording in association with lesions on neuroimaging in whom an epileptogenic “focus” was defined as the zone of maximal interictal activity “from which the patient's seizures arose.” The patients were classified into three groups: (a) seizure “foci” in the region of the lesion, (b) seizure "foci" extending beyond the lesion, and (c) one or more "foci" of ictal onset remote from the lesion. Resection was performed to include the lesion and the "focus" when possible. Although the ability of grids in this study to localize the epileptogenic zone is hard to determine because interictal activity was mainly used to denote the "focus," these authors also found that only 11 of the 47 patients had "foci" exclusively in the lesion location and that complete resection of the lesion but not of the "focus" was associated with seizure control. Such data support the contention that localization of the epileptogenic zone by subdural grid recordings is a tenuous concept without proven support. Jennum et al.[45] reported that tailored resection using grids and intraoperative electrocorticography to guide resection produced best results if the "ictal field" was included in the resection.

Costs

The cost of subdural grid recording is similar to that of other intracranial recording methods but can be higher if recording lasts longer (see earlier discussion). Chronic extraoperative mapping represents an additional cost, but mapping would otherwise be necessary intraoperatively. Removal of subdural grids, however, must be done in the operating room at additional cost and risk.

Combined Studies

Frequent mention has been made of combined intracranial recording methods, usually depth electrodes and subdural strips. This combination has already become the standard for adequate intracranial EEG in many situations. Risks are additive, but cost and time are equivalent, and additional sampling theoretically allows improved accuracy of localization.[91,97] Combined studies have also allowed clinical investigation of patterns of seizure evolution, onset, propagation, and termination with correlative studies providing insights into the pathophysiology of human epilepsy that have themselves produced useful modifications of the methods used to study epilepsy. Thus, findings that have depended on the simultaneous use of depth electrodes and medial temporal subdural strip electrodes include the demonstration of frequent subclinical seizure activity in hippocampus proper, not seen in nearby medial temporal subdural strips[99,100] (Fig. 7); the interaction between entorhinal cortex and hippocampus demonstrated by depth electrode/subdural strip combinations[92]; and the initial propagation of medial temporal lobe seizures to temporal neocortex, frontal lobe, or contralateral hippocampus with its implications for anatomic alterations and for a functional hippocampal commissure in humans[96] (Figs. 7 and 9). European approaches using only depth electrodes can provide similar information in many cases if an ample number of electrodes are implanted with careful tailoring of placement by using information from multiple superficial as well as deep recording contacts.

Subdural grids can be part of combined procedures. Subdural grids and strips are often used in combination, and grid and depth electrode combinations are used less often.[14] The practical difficulty of placing grids at craniotomy, with the stereotactic apparatus required for depth electrode placement, means that usually if depth electrodes are to be combined with subdural grids, they are placed freehand with much less precision, negating one of their main advantages; frameless stereotaxic insertion can avoid this problem.

Special Considerations in Infants and Young Children

Indications

As mentioned already, invasive monitoring is indicated much less frequently in young (e.g., <5 years old) pediatric surgical candidates than in adults or older children. This is because there is a much higher relative incidence of epilepsies caused by discrete lesions (congenital or perinatally acquired) that are identifiable and localizable by structural and functional imaging in the very young population. Of course, surgical candidacy assumes that evidence from clinical signs, seizure semiology, and noninvasive electrophysiology are topographically convergent or at least noncontradictory. Other authors provide a more complete discussion of some of the uniquely pediatric concepts of preoperative evaluation (see Chapter 185).[29,69,70,72,78] This section focuses more on certain technical and clinical considerations in the performance of these recordings.

In very young children, invasive monitoring is indicated in the fairly small minority of cases of intractable localization-related epilepsy in which doubt remains about the causal relationship between an evident structural lesion and the patient's habitual seizures. Examples might include a case of dual or multiple pathology in which one of the lesions is suspected to be the epileptogenic culprit but this cannot be deduced with sufficient certainty to justify resection (e.g., in tuberous sclerosis[8]) or a single lesion in which the electroclinical aspects of the seizures are insufficiently localizing or even lateralizing and the epileptogenicity of the lesion is uncertain. These concepts are similar to those that apply in adults.

It should be emphasized that collective experience with intracranial recordings in this age group is relatively limited. Most of the literature concerning invasive recordings in "childhood" involves adolescents and older children; very few centers have applied these techniques to infants or even "young" children (<5 years old).[43,127] Patterns of usage among these centers vary considerably and probably relate in great part to the availability and type of functional neuroimaging. For example, interictal positron emission tomography (PET) scanning provides better spatial resolution and specificity for the epileptogenic zone than interictal single photon emission computed tomography (SPECT),[17,23,24] so that centers with PET tend to use intracranial recordings less frequently than those without it. Much remains to be learned about indications, safety, and efficacy in this age group. There has been little experience with invasive recordings in infants with catastrophic generalized seizures secondary to a "zone of cortical abnormality," which is usually localized by the convergence of noninvasive indicators plus intraoperative electrocorticography.[29,72,78] Recently, Asano and colleagues reported findings from subdural recordings in infants and children with epileptic spasms.[6,7] The following discussion pertains to young children with intractable *partial* seizures.

If a suspected epileptogenic lesion is near functionally important cortex and an invasive study is indicated, additional useful information can be obtained from functional mapping through cortical stimulation, keeping in mind developmental factors that affect the optimization of stimulus parameters.[40,41] Although extraoperative cortical stimulation can be performed in infants, less information is obtainable than in adults because of the limited repertoire of clinical responses and the inability of the patient to cooperate or to report subjective sensations. In addition, these patients have an apparently increased incidence of eliciting afterdischarges at stimulation intensities substantially below the current level required for eliciting functional responses. Because localization of the primary sensorimotor strip can be accomplished intraoperatively by means of evoked potentials, it seems that functional mapping would rarely, if ever, be a determining reason to perform intracranial monitoring in an infant.

The type of invasive monitoring most appropriate for young children also differs significantly from that in adults. Whereas depth electrodes are used very often in adult epilepsy surgery centers, they are seldom indicated in young children for several reasons. First, from a purely technical point of view, the infant skull is too thin to anchor rigid depth electrodes, and there is little experience in the stereotactic placement of flexible depth electrodes in infants.[46] Second, the clinical contexts in which depth electrodes are often indicated in adults—mesial temporal lobe epilepsy of unclear lateralization or limbic epilepsy of unclear localization or lateralization—are quite uncommon in young children. Although infants do have temporal lobe seizures,[27,28,128] the etiology is hardly ever hippocampal sclerosis, but rather is some kind of neocortical congenital tumor, hamartoma, or malformation, for which localization and lateralization are typically straightforward. Third, as a corollary, because one of the main structures for which depth electrodes are superior to subdural strips—the hippocampus—is rarely the main diagnostic issue, there seem to be few situations in which depth electrodes would provide critical information that subdural strips or grids would not.

Therefore, the remainder of this section focuses on subdural electrodes. The use of depth electrodes in older children with limbic epilepsy is not essentially different from their use in adults.

Surgical Aspects

Because of the small head size, far fewer subdural electrodes can be placed in young children than in older ones and adults. On the other hand, for the same reason, a relatively greater proportion of neocortex can be sampled by a given number of electrodes. In the context of encephaloclastic lesions such as porencephalic cysts, there might be adequate intracranial room for the electrode arrays, but they might also be more difficult to keep anchored in the desired place for the duration of a monitoring session.

The greatest risks specific to this age group are anesthetic rather than surgical. Such procedures should be limited to institutions with expertise in pediatric anesthesia and intensive care. Small children easily become hypothermic in the typically cold operating rooms. Their fluid and electrolyte balance is more precarious, and apparently small amounts of blood loss can deceptively correspond to a significant proportion of total blood volume. Blood vessel walls are thinner, and bridging veins are more easily torn through excess traction or friction against the edge of a strip during insertion (particularly interhemispheric). In infants with still-unfused sutures, the risks of cerebral edema and increased intracranial pressure are lessened, although not eliminated, by the flexibility of the skull.

Nursing Aspects

Perhaps the most important differences about invasive pediatric monitoring are in the area of nursing. For children who are mature enough to communicate, preoperative preparation by means of explanations, acting out procedures with dolls, visiting the intensive care unit, and so on is important both for humanitarian reasons and for obtaining optimal recordings through maximal cooperation. A dedicated Clinical Nurse Specialist or Child Life Specialist is an element of the pediatric epilepsy team whose importance cannot be overemphasized.[29]

Unlike adolescents and adults, who are generally highly motivated to be rid of their epilepsy, younger children have less impulse control, and their cooperation cannot be relied on at all times despite their degree of motivation. For this reason, patient safety requires that monitoring be conducted with one-to-one nursing care, and preferably with a parent or closely related adult in attendance as much of the time as possible. Monitoring can take place either in a relatively private zone of a pediatric intensive care unit using portable recording equipment or in an epilepsy monitoring unit that is adequately equipped and staffed for young patients. Creativity and patience are necessary for keeping a cranially tethered child occupied throughout waking hours and as happy as possible under the circumstances. Pain control is an aspect of care that often receives insufficient attention, especially with infants or developmentally delayed children whose discomfort cannot be verbalized but manifests itself only as irritability. Extra analgesia rather than mere sedation might be called for.

Timely recognition of postoperative complications such as cerebral edema, expanding hematoma, or infection requires personnel skilled in pediatric intensive care. The early clinical signs can be subtle and evolve more insidiously than in adults, who can report subjective symptoms more reliably and whose neurologic examinations include a greater variety of potentially localizing signs. Early signs of increased intracranial pressure, for example, might be nothing more specific than increased fussiness, easily attributable to boredom and frustration, or lethargy, easily attributable to postoperative state or sedative medications.

Fortunately, the duration of intracranial recording sessions is typically much shorter in young children than in older patients because the former typically have much more frequent seizures and because cortical stimulation, if performed at all, is less elaborate. A typical duration of monitoring is a few days to a week, in contrast to adults, in whom it typically lasts one to several weeks.

Interpretive Aspects

The challenges and caveats in determining the zone of ictal onset already discussed apply at all ages—difficulties related to incomplete spatial sampling, regional or diffuse “onsets” that probably represent spread patterns from some unsampled site, and “onsets” at the edge of a grid, which also could represent spread from an adjacent unsampled area.[44] Very rapid spread tends to be less of a problem, however, because of the immaturity of myelination of intercortical connections.

The repertoire of ictal patterns is much richer and more variable than in older patients. Although the classic low-voltage fast discharge that slows, grows, and converts into rhythmic spiking is common, repetitive spiking or merely slowly repetitive stereotyped waveforms from the onset can also be seen. Sometimes it is difficult to discern ictal onsets from background activity: A focal discharge might be obvious after having undergone considerable evolution, but it seems to emerge imperceptibly out of the background, and its moment of onset is impossible to pinpoint within the order of seconds, tens of seconds, or, rarely, even minutes.

In their considerable experience with subdural recordings in children, Jayakar et al.[42] described an ictal phenomenon that they consider a significant indicator of the epileptogenic zone—the intraictal activation of a secondary focus. This is a discrete ictal discharge that seems to arise de novo in a disparate location during the course of evolution of the primary discharge and persists beyond the termination of the primary discharge. Inclusion of these secondary foci in the resection resulted in improved seizure outcomes.

Palmini et al.[68] described a pattern believed to be characteristic of cortical dysplasia, consisting of trains of continuous or nearly continuous spiking at varying frequencies, which the authors described as "ictal" or "ictal-like," although at times a more classically evolving ictal pattern emerges out of the same location, perhaps suggesting an interictal nature of the spikes.

Apart from this apparently specific pattern, the more usual kind of sporadic, often multifocal, interictal spikes are even less localizing for the epileptogenic zone in children than in adults and should not be relied on as the sole or even main criterion for determining the margin of resection.

Comparative Assessments

Depth Versus Subdural Strip Electrodes

As noted, this combination has become standard, with good reason: Multiple studies showed that complementary information and improved ability to interpret actual localization of the ictal onset zone result without increased risk. Complementary information from interictal recording has also been documented,[71] although its utility in planning extent of resection is questionable. From analyses of these combined studies, there is little question that depth electrodes are more sensitive to epileptogenic disturbances in hippocampal and medial temporal lobe locations; subclinical seizure discharges, pre-ictal spikes, and early seizure activation are regularly seen in these depth electrode contacts, although simultaneous subdural strips extending medially in the temporal lobe do not show them.[97,99] On the other hand, subdural strips typically detect the seizure discharge before scalp recording and before clinical seizure activity and can provide satisfactory data most of the time. Rare instances of false contralateral temporal lobe localization by subdural strips have been documented.[99] In extratemporal locations, no strict comparison studies have been reported, probably because most placement protocols in suspected neocortical epilepsy use subdural strips or grids but no depth electrodes. It should be possible to compare the relative yield of depth and subdural electrodes in medial occipital, parietal, and frontal areas, but this has not been reported. In our experience, either one can detect the earliest manifestation of the seizure, even in nonlesional extratemporal epilepsy, but the yield is lower than in temporal lobe epilepsy, probably as much due to sampling locations as to any superiority of one technique or the other.

Depth or Subdural Strips Versus Grids

As emphasized earlier, because grids record from a restricted, predetermined area, their role is not strictly comparable to that of subdural strips and depth electrodes. For localization of ictal onset, even if the region is suspected, we still have the impression that the broader although sparser spatial sampling afforded with depth electrodes and subdural strips conveys a significant advantage in addition to differences in the physiology of the recording procedure itself.

Depth or Subdural Strip Versus Scalp Electrodes

Intracranial electrodes detect an artifact-free epileptic signal much earlier than scalp electrodes. Any single depth or subdural study is sufficient to prove their markedly superior sensitivity to scalp electrodes. Depending on the referral population, scalp ictal EEGs provide minimal or insufficient localization of the ictal onset zone in 50% of patients; however, 75% of depth or subdural studies provide ictal onset localization in that unlocalized group.[82] Furthermore, although localization might be apparent on surface ictal EEG, it can be unreliable and usually occurs after clinical seizure activity has begun.[95] Although the lateralization of temporal lobe ictal discharge is still usually appropriate, temporal versus extratemporal localization must be confirmed by other means, usually structural or functional abnormalities. When ictal onset localization is obtained by scalp EEG in frontal lobe locations, it tends to be widely distributed, and subdural EEG provides much more precision.[75]

Depth or Subdural Electrodes Versus Pegs

Minimal information is available with respect to the comparison of depth or subdural electrodes and epidural pegs, a novel form of EEG recording first reported by Barnett et al. in 1990.[13] Pegs are mushroom-shaped individual electrodes inserted in the skull to sample the epidural EEG, providing a signal with less muscle artifact than scalp recordings and avoiding the confusing aspects of surface recording in the setting of skull defects. This potential improvement over scalp EEG has not been formally tested but appears to be logical. The limited sampling of only dorsolateral cortical locations by this method prevents such electrodes from providing access to signals from the deep or medial locations that depth and subdural electrodes can sample. It is unlikely that peg electrodes provide resolution of temporal lobe abnormalities superior to that from sphenoidal electrodes, but they might be another approach to semi-invasive examination of extratemporal electrical activity associated with the ictus. They are most profitably used to sample EEGs from several lobes and confirm lack of activity in those regions not thought to be part of the epileptogenic zone.

Depth or Subdural Electrodes Versus Foramen Ovale Electrodes

In 1985, Wieser et al. described the use of an electrode inserted through the foramen ovale (subsequently modified to include four contacts) for chronic ictal recording. It is inserted freehand under local anesthesia.[117] Although it is semi-invasive, the technique is considered simpler than depth or subdural electrode study and has relatively low morbidity and no reported mortality. Its morbidity, however, might not be lower than that of depth or subdural electrodes. The most frequent serious complications are brain stem syndromes and subarachnoid hemorrhage. The electrodes allegedly record from mesial basal aspects of the temporal lobe. Accordingly, they are used in patients considered for medial temporal lobe resective procedures as an alternative to chronic intracranial recording. Comparisons with depth electrodes, subdural strips, and scalp electrodes in dogs with hippocampal foci suggest that ictal discharge and interictal spikes from the hippocampus are accurately reflected but restricted abnormalities and early seizure discharges, especially from the anterior hippocampus and amygdala, are not well demonstrated.[118] Although no difference was seen in postoperative seizure control between patients selected for amygdalohippocampal resection by foramen ovale electrodes or depth electrodes, patients studied by foramen ovale electrodes were a selected sample without complicated profiles.[115] One comparison of patients with foramen ovale and depth electrodes and subdural strips noted occasional false lateralization of seizure onset with foramen ovale recording, suggesting the need for caution in interpretation.[18]

Chronic Depth or Subdural Electrodes Versus Electrocorticography

Electrocorticography refers to acute intraoperative direct cortical recording. This is performed with a subdurally placed multicontact electrode grid similar to that used for chronic grid recording, multiple subdural strips, or a series of wick or ball electrodes suspended from a frame. No direct comparison of acute and chronic subdural recording has been reported, but because the manner of recording is so similar to that with subdural grids, many of the previous comments with respect to depth or subdural electrodes versus grids apply. The major disadvantage of electrocorticography is its duration, limited to brief intraoperative periods and often complicated by anesthetic effects. A review of results of electrocorticography and correlations with postoperative outcome and other EEG methods is beyond the scope of this chapter, but the usual absence of ictal recording is a major disadvantage of that technique compared to chronic ictal EEG recording methods. The ubiquity of interictal spike activity on intracranial EEG and its inconsistent correlation with ictal onset location indicate that limited interictal recording is likely to be of minimal benefit in localization of the epileptogenic zone for the purpose of resection. Successful prediction of postoperative seizure control in this context is likely to be an epiphenomenon related to selection of the site for electrocorticography (usually based on a structural lesion) rather than to the utility of the electrocorticogram itself. Electrocorticography might play a greater role in the operative planning in children with "catastrophic generalized" epilepsy, in which nonepileptiform abnormalities of the interictal recording are the focus of attention.[67,70,77,78]

Grid Versus Scalp

Although grids reduce artifact, the restricted spatial sampling they provide is a major disadvantage compared to the scalp EEG. The scalp EEG, however, reflects ictal activity long after propagation and involvement of multiple sites and well after clinical activity has occurred. No formal comparison of ictal grid versus ictal scalp EEG has been published.

Synthesis

General Indications

Intracranial EEG recording, regardless of the specific technique, is used when precise localization of the epileptogenic zone (the area necessary and sufficient to cause spontaneous seizures) is required to plan surgical resection for treatment of medically uncontrolled seizures and/or when precise localization of functional cortex is required in planning safe resective procedures for epilepsy with or without a lesion. Because it carries a 1% to 4% risk of significant morbidity and possible mortality, it can be considered appropriate only when sufficient conclusions about localization cannot be obtained by less invasive methods. Furthermore, because restricted sampling of cortical regions is desirable, the clinical situation must allow a reasonable a priori hypothesis as to which areas need study.

Distinctions Among Techniques

Whether depth, subdural strip, or subdural grid recordings are used for this localization depends on the specific questions being asked and the areas involved. Depth electrodes and subdural strips are preferable for bilateral cortical recording that can be analyzed with regard to onset, delay, propagation, and termination patterns. Subdural grid recordings, like electrocorticography in the operating room, are limited to circumscribed regions that are also studied for functional localization. Each technique has advantages in specific situations, and selection must consider technical limitations as well. Current practice almost always dictates combined types of intracranial electrodes for maximal advantage in one recording session, an approach that is not known to increase morbidity.

Techniques for Specific Situations

On the basis of worldwide published experience, technical details, the evolution of other localizing and diagnostic techniques, and the kinds of questions that are most often approached with intracranial study, the following recommendations are proposed to address specific topographic epilepsy syndromes. One must bear in mind, however, the unique problem presented by each individual patient.

Temporal Lobe Epilepsies

Whether lateralizing medial temporal lobe seizure onset, distinguishing between medial and lateral temporal lobe seizure onset, or differentiating temporal lobe from orbital frontal, medial parietal, or medial occipital seizure onset, the approach must account for what is known about the intracranial EEG patterns of medial temporal lobe epilepsy. Recording from anterior, middle, and posterior hippocampus bilaterally with orthogonally or parasagittally placed depth electrodes, combined with bilateral anterior, middle, and posterior temporal neocortical recording from orthogonal depth electrodes or multiple subdural strips, should be considered a minimum to adequately assess subclinical seizure discharges in hippocampus, pre-ictal spikes, propagation patterns, propagation time to contralateral hippocampus, and the EEG morphologic characteristics that allow accurate diagnosis of medial temporal lobe epilepsy and its distinction from neocortical regions of seizure onset. In any event, because increasing evidence suggests that the distinction between medial and lateral temporal discharges is an oversimplification and that medial temporal lobe epileptogenic zones can incorporate a participatory network that extends beyond these traditional confines, spatial sampling needs to be generous to allow information that permits adequate definition of the region for resection. When the laterality of temporal lobe onset is not questioned but the intratemporal location is a concern, the depth and subdural strategy might be exchanged for a temporal grid with medial subdural strip placement, especially in the dominant hemisphere, when language mapping needs to be performed.

Because medial frontal, parietal, or occipital lobe seizures can begin silently and propagate to medial temporal lobe structures, masquerading as temporal lobe seizures on scalp EEG, temporal lobe studies are ideally complemented by additional depth or subdural electrodes placed bilaterally in medial parietal, occipital, and/or frontal regions of concern. Additional data from functional imaging, functional testing, historical data, or structural abnormalities on MRI can suggest the need for this and other, additional intracranial sampling. Subdural strips are well suited for studying most interhemispheric locations as well as other extratemporal neocortical regions, and rarely are depth electrodes necessary except to complement the subdural strips when deeper regions appear to require study because of abnormal structure. Simultaneous recording with scalp or peg electrodes can provide important information that places the restricted information from intracranial electrodes into broad perspective.

Frontal Lobe Epilepsies

Successful localization is poor without imaging and behavioral clues in frontal regions because frontal lobe seizure semiology is so diverse and sampling of this large structure is always so limited. Because contralateral propagation occurs with startling rapidity, lateralization is often very difficult even if frontal lobe ictal onset localization can be obtained. In addition, the level of experience and the kinds of guidelines for interpretation that are available for temporal lobe epilepsy are not available for frontal lobe seizures, nor is any specific frontal lobe location considered the most common area of seizure onset. Clinical clues can direct study to primary motor area, supplementary sensorimotor area, dorsolateral, orbital, or polar frontal regions. Seizures with limbic characteristics suggest cingulate or orbitofrontal origin.

For most patients thought to have frontal lobe seizure onset, study is usually done with multiple subdural strips bilaterally but concentrated on one side, primarily in motor or supplementary motor versus lateral or polar regions, as suggested by clinical seizure characteristics. When structural and functional assessment clearly places seizure onset in one frontal lobe region, grids can be used. When prior evaluation suggests cingulate or orbital frontal complex partial lobe seizures, depth electrodes might be an alternative. They are usually placed bilaterally, especially because lateralization of the seizure characteristics can be difficult in nonmotor frontal areas. The area of any structural lesion thought to be important for epileptogenesis should be included in the design of the electrode array. Both depth and subdural electrode sampling can be fruitful in these locations. The experience in Europe suggests that use of multiple depth electrodes to target regions of frontal lobe and their connections can also be effective, based on carefully formulated hypotheses. Thus, for example, to study suspected orbitofrontal seizure origin, oblique electrodes sampling gyrus rectus, orbital cortex, and frontal pole and electrodes recording activity in lateral frontobasal cortex, anterior cingulate, and anterior temporal lobe are used.

Parietal and Occipital Lobe Epilepsies

The comments about frontal lobe localization apply equally to parietal and occipital seizure onset. Imaging clues or primary sensory or occipital symptomatology can help to guide the study, but even with those, rapidity of contralateral or rostral propagation, seizure onset in silent regions, and lack of interpretative standards contribute to the commonly observed difficulty in localization of ictal onset areas in these lobes. Although depth electrodes alone can be used for these studies, a large number will be needed for sufficient sampling, for the aforementioned reasons. Occipital lobe seizures can propagate variably to frontal and to medial temporal lobe areas bilaterally and independently and be mistaken for temporal lobe epilepsy or multifocal epilepsy, which will be undetected without extensive bilateral study. Thus, a combination of subdural strips and depth electrodes is commonly used, bilaterally because of rapid propagation and because some of the pathologic entities causing seizures in these locations (e.g., cortical dysplasia) tend to have bilateral epileptic manifestations. Seizures might appear in the general vicinity of a lesion but not the exact location; this is characteristic of occipital lobe epilepsy.

Screening Studies

A patient with uncontrolled and stereotyped complex partial seizures might have minimal localization by scalp EEG, normal MRI, nonlocalizing auras and seizure semiology, and no significant historical features to allow an educated guess with respect to localization of seizure onset. The patient deserves surgical treatment if possible, but intracranial study demands that specific questions be addressed. In these situations, the question can be reshaped in a broader sense: Can we define a single cerebral region for further intracranial study? Sometimes this is possible by sampling medial and lateral temporal lobes and frontal, parietal, and occipital neocortex with subdural strips and depth electrodes; analysis of seizure onset and propagation patterns can be used to design a second intracranial study with more focused questions and electrodes that eventually enable a resective procedure. The yield of this approach, however, to define even an area for further invasive study is lower than when more information is available to guide the selection of the

intracranial electrode array in the first place, so it is considered an option only in very few and special situations.

Lesional Patients

Implicit in the foregoing discussion was the targeting of neocortical and deep tissue in the vicinity of MRI-identified structural lesions in patients with uncontrolled epilepsy. In many lesional patients (for these purposes usually including tumors and hippocampal atrophy), the frequent concordance of scalp EEG with the lesion location allows the additional information from functional studies to suffice for excision without the need for intracranial EEG. In certain other lesions (some cortical dysplasias and atrophic regions), particularly when the process might be multifocal, and in all patients with “dual pathology” of a lesion and hippocampal atrophy (combined cortical dysplasia and hippocampal atrophy, tumor and hippocampal atrophy, or bilateral hippocampal atrophy), intracranial EEG is nearly always needed to differentiate among several areas of possible epileptogenesis. A combination of subdural strips and depth electrodes allows safe and representative sampling of the hippocampus and the vicinity of the lesions; depth EEG study as in the stereo EEG approaches in Europe can also suffice with sufficient electrode coverage. Grid recordings are reserved for patients in whom a single lesion consistent with scalp EEG localization is close to functional cortex.

Summary and Conclusions

We have watched neuroimaging revolutionize the diagnosis of epileptic disorders, allowing more precision in diagnosis, classification, and treatment. This is especially applicable to the surgical treatment of epilepsy. Probably half as many patients require intracranial EEG as did only a decade ago, and of those who do, success in localization is improved by structural and functional clues to the regions of abnormal brain. Will advances in functional and structural imaging eventually reduce or eliminate the need for intracranial EEG? This is doubtful because more sensitive imaging reveals multiple lesions more often, and these demand intensive electrical study to distinguish the ones with epileptogenic potential. The marriage of new technologies opens the door for increased understanding of brain physiology in epilepsy while enabling improved diagnosis and treatment; it might in fact herald the need for more intracranial studies than are currently done.

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Chapter 172

Intraoperative Electrocorticography

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Introduction

The method of recording electrical potentials directly from the cerebral cortex (electrocorticography [EcoG]) or from the cerebral cortex and subjacent structures was pioneered in humans by Berger, who detected these activities with electrodes placed over the dural surface in patients with skull defects[15] and with a needle inserted through the cortex and underlying white matter of a patient with a distant brain tumor.[16] Subsequent work continued to be aimed at validating the cortical origin of scalp-recorded electroencephalogram (EEG) rhythms and demonstrating alterations of electrocerebral activity caused by brain tumors,[2,42,98,116] but direct brain recordings soon became established primarily as aids in the surgical treatment of medically refractory partial epilepsy.[7,44,54,55,57,63,78,114] The initial role of intraoperative ECoG in defining sites of ictal origin has been supplanted in recent decades by advances in continuous EEG-video monitoring (both noninvasive and invasive) and by developments in neuroimaging. The role of intraoperative ECoG has evolved primarily as a tool for better understanding the likely boundaries of the epileptogenic zone and as guide to determining the extent of surgical resection. Despite the changing role of ECoG, the technique and interpretation of direct brain recordings during surgery has changed little during the last six decades. This review summarizes traditional technical and interpretive principles of intraoperative ECoG and highlights evolving concepts of this method. The original work of Jasper[55] and the comprehensive reviews of Bates,[13] Ajmone-Marsan and O'Connor,[8] and Gloor[46] are sources of additional information.

Indications

In patients afflicted by chronic, medically intractable partial seizures, the ECoG is performed during surgery (Fig. 1) following preoperative studies that have identified an epileptogenic region in the hemisphere targeted for surgery. Intraoperative ECoG is intended to (a) identify the limits of the epileptogenic zone, (b) guide the extent of resection, and (c) assess its completeness.

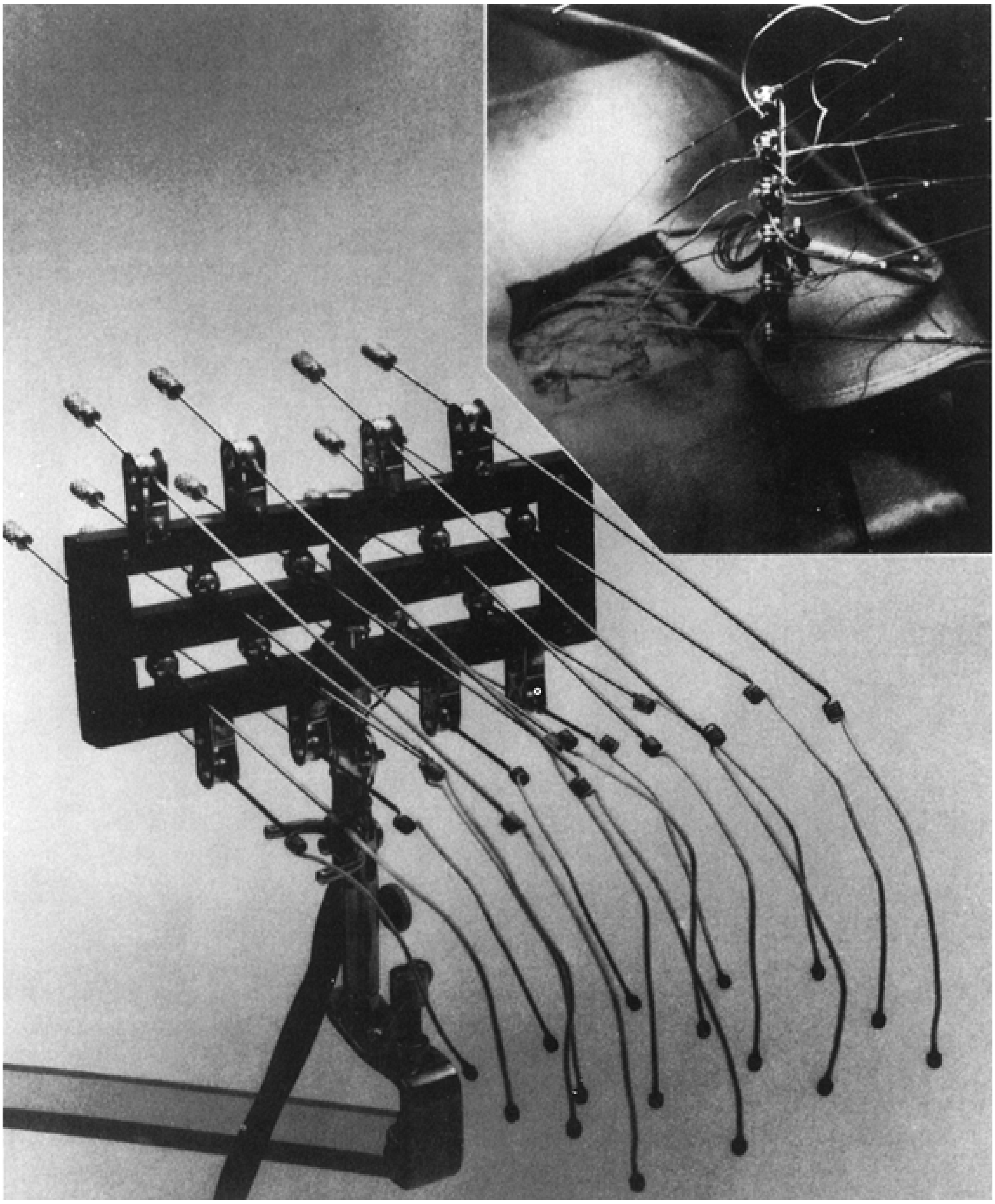

FIGURE 1. Sixteen-electrode ECoG set used at the University of Miami and at NINCDS, modified from an original design of the Montreal Neurological Institute. **Inset:** Set in place, with holder clamped to the bone edge of the craniotomy and electrodes in contact with the exposed cortex. (From Ajmone-Marsan C. Chronic intracranial recording and electrocorticography. In: Daly DD, Pedley TA, eds. *Current Practice of Clinical Electroencephalography*, 2nd ed. New York: Raven Press, 1990;535–560, with permission.)

Identification of the Epileptogenic Zone

Determination of the site of the epileptogenic zone by intraoperative ECoG relies on several factors, including demonstrating an area of brain that (a) displays interictal epileptiform discharges, (b) shows susceptibility to repetitive electrical stimulation, and (c) gives rise to the initial, or all, manifestations of the patient's habitual seizures when electrically stimulated. In fact, however, it is rare that, seizure onset can be determined only by ECoG.

The Interictal Spiking Area

Because intraoperative ECoGs are of relatively short duration, electrographic seizures are rarely recorded except in some particular conditions,[11,46] and spontaneous epileptic activity consists almost exclusively of interictal discharges, that is, spikes, sharp waves, and their variants. For the sake of brevity, these are referred to in this chapter as "spikes." Because of this limitation, the utility of the ECoG during epilepsy surgery depends on the following assumptions: (a) that intraoperatively recorded interictal spikes are reliable markers of the epileptogenic process and (b) that they provide dependable information on the site and extent of epileptogenic tissue to be removed to successfully control the patient's attacks. The following observations suggest that both of these assumptions have limited validity:

1. It is impossible to distinguish with assurance in ECoG recordings primary epileptiform discharges arising from a given brain location from secondary discharges propagated from a distant epileptogenic site.[27,55,59]
2. The extent of the intraoperatively determined interictal spiking area can be increased or diminished by a number of anesthetic, analgesic, and other medications commonly administered during surgery and by the intrusion of drowsiness or non–rapid eye movement (REM) sleep in the waking ECoG.[66,96]
3. In many patients with medically intractable partial seizures, multiple interictal spiking areas are demonstrated by EcoG.[48,72,105,109,110] This finding precludes attempts to delineate a single interictal spiking zone with distinct boundaries.

Localized Electrical Stimulation of the Brain

Because the topographic extent of interictal ECoG discharges provides limited assistance in defining the boundaries of the surgically relevant epileptogenic zone, attempts have been made to identify this area by localized repetitive electrical stimulation of the brain. When of sufficient intensity, this excitation elicits an "afterdischarge," that is, a seizure discharge that typically begins at the stimulated site and subsequently either remains restricted to this location or spreads to adjacent or wider cortical regions as well as to subcortical structures (Fig. 2). Afterdischarges vary widely in duration from <1 sec to as much as 90 sec or longer and are frequently followed by postictal depression, which is in turn succeeded by slow activity of variable duration, often most obvious at the site of stimulation.[55,114] Localized stimulation of the brain of patients with chronic, intractable partial seizures was originally undertaken with the hope that (a) human epileptogenic tissue might display increased susceptibility to this stimulus in the form of afterdischarges of lower threshold, longer duration, or both, relative to nonepileptogenic tissue, and (b) the afterdischarge so elicited would be accompanied by clinical changes reproducing the initial, or all, manifestations of the patient's habitual seizures. However, intraoperative as well as extraoperative studies have demonstrated that afterdischarge thresholds and durations vary among cortical areas[55,114] and even within the same area from day to day[114] and from one stimulation to the next.[3] Their thresholds were elevated shortly after a prolonged afterdischarge[114] and were altered by structural changes in the area stimulated, although conflicting results were obtained by stimulating normal and sclerotic human hippocampi.[17,26] In addition, afterdischarges could be especially prominent and long-lasting at locations not demonstrating interictal spikes,[46] were not consistently related to the site of spontaneous ictal onset,[17] and sometimes occurred solely, or persisted longer, at sites distant from those stimulated.[55]

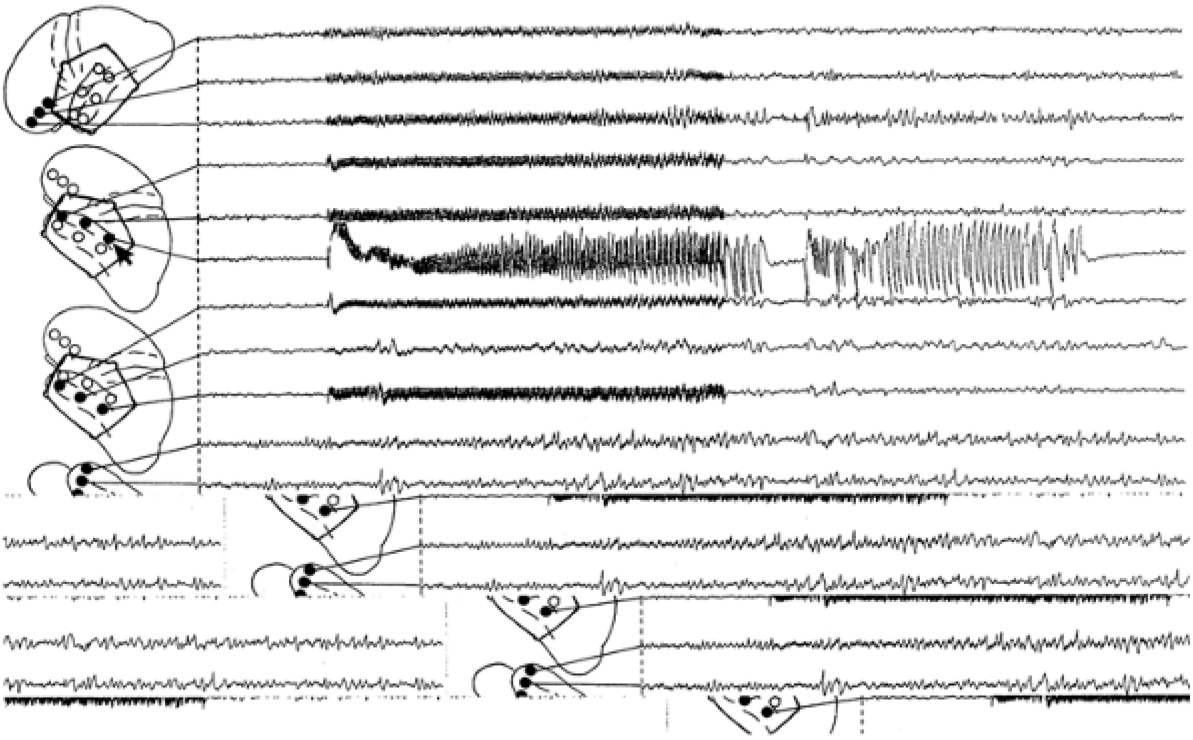

FIGURE 2. Brief, localized afterdischarge (channel 6) unaccompanied by clinical changes is elicited by electrical stimulation of the posterior portion of the left superior temporal gyrus (rectangular diphasic pulses, 0.3 msec, 60 Hz, 4 mA, 6.5 sec) in a patient with temporal lobe seizures arising from the medial and anterolateral temporal cortices.

Penfield and his associates[37,46,83,94] among others made extensive use of localized electrical stimulation of the brain to reproduce in waking patients undergoing surgery the initial, or all, manifestations of their habitual partial seizures. The ability of this technique to localize the epileptogenic zone depended on the validity of the assumptions that (a) the initial manifestations of partial seizures, that is, the "auras," indicated the site of the brain from which the seizures developed and (b) the reproduction of these manifestations by electrical stimulation of a restricted area of the brain confirmed this localization. Conflicting opinions were expressed on the localizing significance of the aura,[5,82,105,114] and attempts to reproduce it intraoperatively or extraoperatively by electrical stimulation of cortical

and subcortical structures provided evidence that, in many instances, the aura did not reflect an ictal discharge arising at the site stimulated but resulted from spread of seizure activity at a distance from this location.[12,34,114,120] The results of one study[40] indicated that the electrically elicited initial manifestations of the patient's habitual seizures, whether occurring in the presence of a localized afterdischarge or at the very onset of a spreading afterdischarge, lacked lateralizing or specific localizing value and at best suggested the most likely lobar origin of the patient's spontaneous attacks. Clinical manifestations appearing during the course of a spreading afterdischarge were likely related to the involvement of brain areas other than that stimulated.

The available information indicates that the topography of intraoperative interictal spiking, the afterdischarge threshold and duration, and the reproduction of the clinical manifestations of the patient's seizures by localized electrical stimulation of the brain do not consistently identify the epileptogenic zone.

Functional Mapping

Additional assistance in determining the boundaries of "tailored" resections of epileptogenic tissue is offered by the identification in waking patients of motor and sensory cortices and the delineation of regions involved in speech and memory functions, which are achieved by localized electrical stimulation of the brain at intensities mostly subliminal for afterdischarge (see Chapter 174, Intraoperative Functional Mapping).

Technique

Electrodes and Instrumentation

ECoG electrodes[8,13] must be capable of detecting the electrical activities of the cortex exposed by craniotomy and of adjacent as well as more remote areas of the lateral, inferior, and medial surfaces and, at times, subcortical areas of the hemisphere undergoing surgery. Most commonly, electrode-holder assemblies (Fig. 1) are used that typically incorporate 16 insulated silver wires. The distal ends of these wires terminate with a carbon ball[32] or a silver/silver chloride ball covered with cotton soaked in physiologic saline solution, which makes contact with the exposed cortex. Their proximal ends are connected by coiled springs to thin stainless steel rods, which are mounted on the universal ball joints of a holder clamped to the bone edge of the craniotomy. Wires from these joints lead to the inputs of the recording system. An alternative technique uses variously shaped assemblies of 4 to 64 or more small platinum, silver, or stainless steel disk electrodes embedded 10 to 15 mm apart in soft, flexible, clear, silicone plastic (Silastic) sheets.[121] These strips or grids can be laid over the exposed cortex or introduced from the edges of the craniotomy over or under adjacent lateral, inferior, and medial cortical regions.

A common practice is to use holder-supported electrodes to record from the exposed cortex and Silastic-embedded electrodes to explore more remote cortical areas simultaneously.[109] During temporal lobe surgery, single or multicontact needle electrodes are often inserted freehand transcortically into the regions of the amygdala and hippocampus that are inaccessible

by noninvasive means.[34,46,48,59,63,86,104] An alternative approach to hippocampal, but not amygdalar, recording requires making either an incision in the lateral temporal cortex or an anterolateral temporal lobe resection to expose the hippocampus through the opened lateral ventricle and allow placement of individual electrodes[59,60,75] or a multicontact Silastic strip[86,110] over its ventricular surface. Various reference leads can be used for intraoperative brain recordings, including two interconnected electrodes on both sides of the neck[109,110] or an alligator clip attached to a muscle near the edge of the craniotomy. Grounding of the patient usually is provided by a metal clamp attached to the post of the electrode holder or to the bone edge of the craniotomy. The ECoG electrode sets require cleaning and appropriate sterilization after each surgery to prevent transmission of agents highly resistant to decontamination,[73] whereas commercial Silastic-embedded and intracerebral electrodes generally are disposable.

In most centers, the ECoG is recorded digitally with a 16- or 21-channel electroencephalograph ideally located in a gallery adjacent to, but separate from, the operating room.[54] A large glass window enables the clinical neurophysiologist to view the operating field, and an intercom system provides verbal communication between the neurophysiologist and the neurosurgeon. Photographs of the operating field can be taken through a tilted mirror. A recording system bandpass of 0.5 to 70 Hz (-3 dB) ensures appreciation of both epileptiform discharges and background activities. Further limiting the low-frequency response of the instrument is neither necessary nor justified except during electrical stimulation. In the course of this procedure, a low-frequency cutoff of 1.6 Hz or even 5.0 Hz helps to diminish the duration of amplifier blocking following discontinuation of the stimulus. Because activities recorded directly from the cortical surface are about 2 to 60 times larger than those detected on the scalp,[1] instrumental sensitivities of 10 to 50 μV/mm are most commonly used for ECoG recordings. Modifications of the traditional instrumentation and physical arrangement for ECoG are suggested later in this chapter.

Recording and Electrical Stimulation

Preresection ECoGs survey, in a systematic order, cortical regions within and outside the area of exposure. In patients undergoing temporal lobectomy, recordings must include exploration of infratemporal and orbital frontal cortices, the hippocampus, and the amygdala; ECoGs omitting the assessment of these structures are both inadequate and potentially misleading.[109,110] Postresection ECoGs examine the cortices surrounding the ablation as well as more distant structures. Following temporal lobectomy, these typically include the remnants of the hippocampus and parahippocampal gyrus, the insula, and neighboring extratemporal cortices. Total duration of preresection and postresection ECoGs, including monitoring of the effects of electrical stimulation but excluding functional mapping, is generally about 1 to 2 hours and sometimes longer. Both before and after resection, ECoGs can be obtained either bipolarly or referentially, but recording referentially expedites the interpretation and improves its accuracy.

Protocols followed in most centers for intraoperative electrical stimulation designed to elicit afterdischarges (Fig. 2), reproduce clinical manifestations of the patient's habitual attacks, or both entail delivery of 0.5- to 2-msec diphasic pulses applied at 50 to 60 Hz over 1 to 5 seconds between two ball electrodes that terminate a pencil-shaped probe held by the surgeon.[8] The stimulus can also be delivered between adjacent Silastic-enclosed electrodes. Individual stimulus trains are separated by at least 15 seconds,[3] but longer intervals up to several minutes are necessary following a prolonged afterdischarge producing temporary refractoriness.[3] Different stimulus parameters can be used for intraoperative functional mapping (Chapter 174).

Activation and Effects of Anesthesia

When no or rare interictal spikes are detected in the preresection ECoG, "activation" techniques can be used to elicit or enhance them. These procedures commonly consist of the intravenous administration of a general anesthetic such as thiopental sodium,[18,34] methohexital,[11,39] etomidate,[43] or propofol.[52] In the appropriate dose, these agents often cause the appearance or increase the rate of interictal spiking. However, the area displaying spikes, if any were present before the injection, frequently expands to wider cortical regions, and focal discharges can appear in noncontiguous, previously silent areas outside the anticipated margins of the resection. Thus, some results of the activation used with these agents, if not critically appraised, can encourage excessively wide surgical excisions. However, in a proportion of cases, the activation is restricted to a limited cortical area shortly after the injection, becomes again confined to this region as the action of the drug declines, or both (Fig. 3).[10] In these instances, it is possible that the site displaying the earliest and the last drug-induced activation represents the patient's epileptogenic area, although proof of the correctness of this inference is lacking. Over the last several years newer agents, specifically the short-acting opioids alfentanil[71,91] and remifentanil,[117] have been introduced for activation purposes during ECoG and may show greater promise for reliably identifying the epileptogenic zone, specifically in cases of temporal lobe epilepsy. Alfentenil has been reported to result in marked increases in spikes in hippocampus and parahippocampal regions and, to a lesser extent, in basal and lateral temporal cortex.[91] Electrographic seizures triggered by this agent have also been shown to be concordant with spontaneously recorded clinical seizures.[91] On the other hand, remifentanil can increase spikes in epileptogenic zone while suppressing discharges in the surrounding "normal" brain.[117] Nevertheless, in the absence of unequivocal criteria reliably differentiating between drug-induced spiking indicative of an epileptogenic area to be removed and spurious drug effects that can be safely neglected, the results of activation procedures should be interpreted with caution.

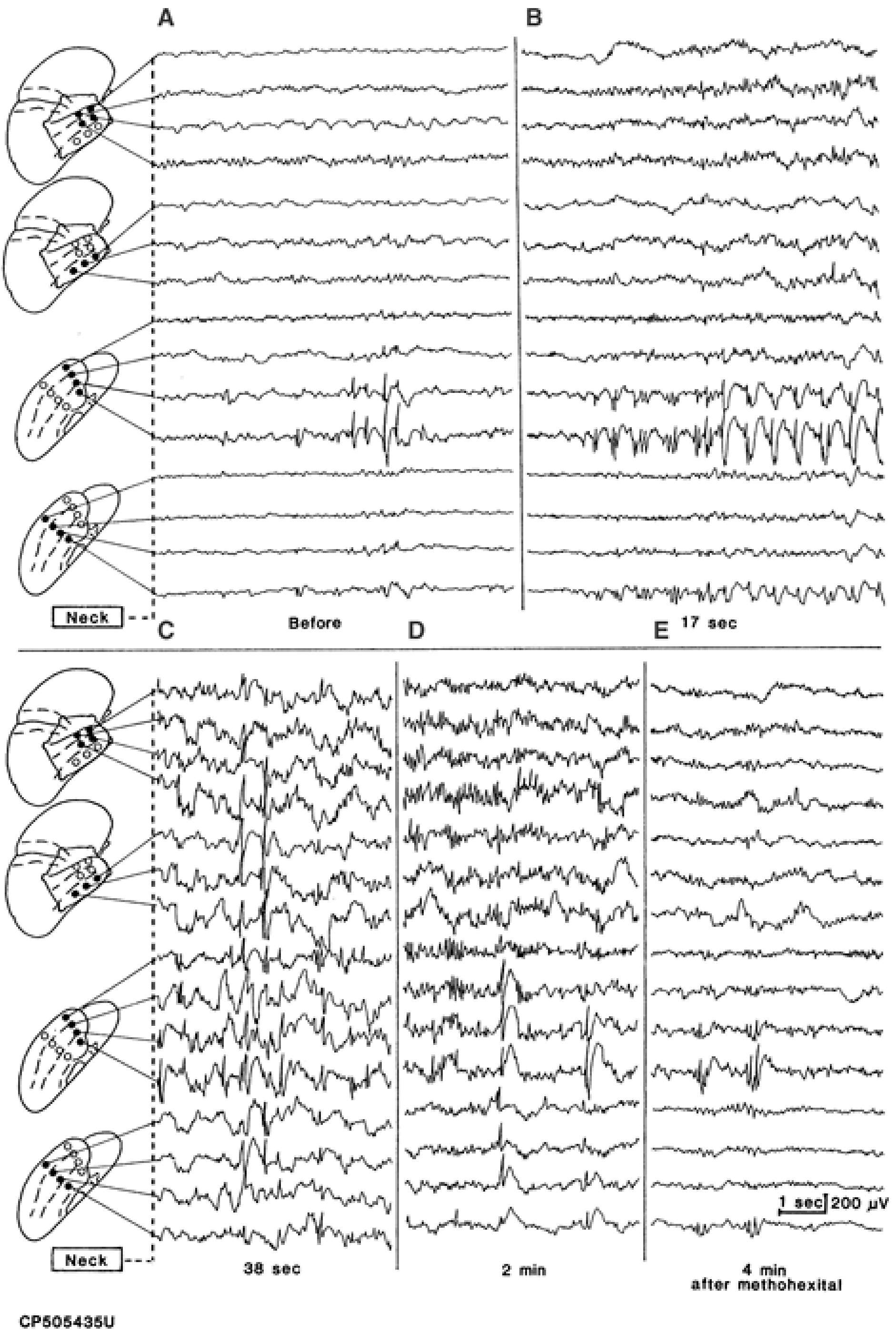

FIGURE 3. Twenty-three-year-old man with seizures characterized by feeling of weightlessness followed by loss of awareness and complex automatisms. Scalp EEGs showed sharp waves over the right anterior temporal and inferior frontal areas with some spread to adjacent regions. Before activation, intraoperative preresection ECoG shows right anterior inferomesial spike-and-slow-wave activity maximal over the uncus/anterior parahippocampal gyrus (**A**). After rapid intravenous injection of 100 mg of methohexital, the recording successively demonstrates repetitive spike-and-slow-wave activity in the same location as in **A** and beta activity in all areas surveyed (**B**); spikes and delta waves occurring diffusely or multifocally within the cortices explored (**C**); spiking confined to anterior infratemporal surface as well as decreased delta and increased beta activities (**D**); multiple spike-and-slow-wave activity restricted to the areas involved before activation, and further diminution of beta and delta

potentials (**E**). Patient fell asleep, and no ictal manifestations accompanied these ECoG changes. The hippocampus was slightly sclerotic with minor anterior herniation.

General anesthetics can influence epileptiform activity not only when rapidly injected intravenously to activate the EcoG, but also when used in relatively stable concentrations to produce general anesthesia.[66] However, even when anesthetics do suppress spikes, the intraoperative ECoG may still reliably reflect the awake interictal spiking pattern, provided that the spike frequency is >1 spike/min.[10] The opioid analgesics commonly administered during epilepsy surgery, whether performed under local or general anesthesia, can influence interictal spiking and offer no clear advantages over fentanyl.[20,45,66] On the other hand, neither propofol[102] nor nitrous oxide[51] is described as interfering with the awake ECoG. Large-dose propofol used as the sole anesthetic does not appear to trigger electrographic seizures in epilepsy patients.[25] These effects should be taken into consideration in choosing the anesthetic and analgesic agents to be used during epilepsy surgery.

Propofol is a particularly popular agent for conscious sedation during epilepsy surgery.[68] It produces a dose-dependent suppression of the EEG similar to barbiturates, and despite the role it might play in treating status epilepticus, it does not usually completely suppress spikes. It can enhance epileptiform discharges in some patients, and can produce burst suppression and electrical silence at high doses. Because of rapid metabolism, propofol can be used to induce sleep during the early portions of the craniotomy. Subsequent awake testing and ECoG are then possible because of rapid elimination of the drug.[68]

Interpretation

Relationships Between Scalp Electroencephalogram and Electrocorticography Recordings

The intraoperative ECoG has peculiarities that distinguish it from the scalp EEG. In the absence of gross structural pathology, the same normal rhythms that characterize scalp recordings can be detected from the cortical surface. However, these potentials usually are much larger in amplitude and more sharply demarcated on the cortex than on the scalp.[8,46,55] In addition, because in the transmission of cortical potentials to the scalp, higher-frequency activity is attenuated to a greater extent than that of slower frequencies,[84] most rhythms tend to have a much sharper appearance in ECoG than in scalp recordings, and, in general, the ECoG contains more prominent and abundant beta potentials than the scalp EEG.[8] The presence of very sharp-appearing alpha and mu rhythms, variably reactive to eye opening and to contralateral limb movement,[58] sometimes makes it difficult for even experienced interpreters to distinguish individual components of these rhythms from spike discharges.

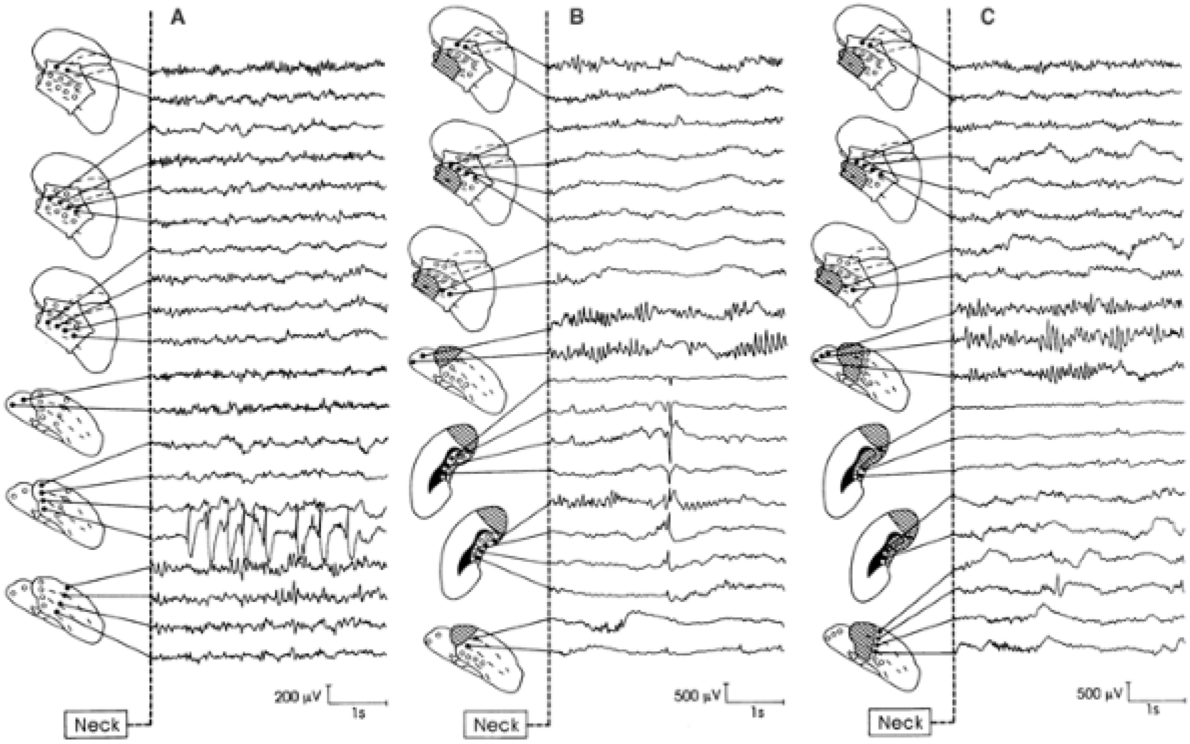

FIGURE 4. Thirty-three-year-old man with episodes of strange feeling, automatisms of hands, loss of awareness, and occasional tonic–clonic generalization. Scalp EEGs demonstrated spikes over the left mid- and posterior temporal regions. In the preresection ECoG, bursts of 2- to 3-Hz spike-and-slow-wave activity were detected over the uncus/anterior parahippocampal gyrus (**A**). After anterolateral resection, spikes occurred simultaneously over the hippocampus and the parahippocampal gyrus, with a major component that was positive on the former and negative on the latter (**B**). Following final ablation including 2.5 cm of hippocampus and parahippocampal gyrus, infrequent spikes and sharp waves occurred posteriorly to the inferomedial margin of the excision (**C**). Three years after surgery, patient was seizure-free.

Among the abnormal patterns recorded in the ECoG, interictal discharges, that is, spikes, sharp waves, and their variants, have features resembling those that characterize them in scalp recordings. However, cortically recorded spikes often attain amplitudes as large as 0.5 to 1 mV and can have durations as brief as 10 to 20 msec.[8] Special difficulties can be posed by the interpretation of areas of low-amplitude activity that can be caused by equipotentiality of electrodes linked in bipolar derivations, the shunting effect of pooling of saline solution, or structural pathology in the underlying cortex.[8] Similarly, in the absence of visually apparent structural alterations, it can be difficult to determine whether areas of arrhythmic delta activity apparent in preresection recordings are caused by surgical trauma, such as that related to division of adhesions, or by preexisting pathology.[6] In contrast, the finding in postresection ECoGs of similar alterations at and close to the margins of the resection can be more confidently attributed to the trauma of the excision.[8] Generally, artifacts caused by improper electrode contact, the electrocardiogram, pulsating blood vessels, or respiratory movements are easily identified, as are those related to surgical manipulations, including the spraying of saline solution and the use of electrocautery equipment.

ECoGs require instant, unhesitant interpretation that can have major consequences for the conduct of surgery, and they must be interpreted by an experienced clinical neuro-physiologist.[6]

Electrocorticography in Temporal Lobectomies

Patients with long-standing, medically intractable temporal lobe seizures most commonly demonstrate in their intraoperative preresection ECoGs interictal spikes whose distribution varies in a continuum from individual, relatively restricted, to widespread, often multiple areas of the temporal lobe (Fig. 4) and can variably extend into neighboring cortical regions, especially, but not exclusively, the frontal cortex[31,34,59,63,90,105,115] (Fig. 5). In a quantitative study,[109] 81% of spikes recorded before resection involved the infratemporal surface, 18% the lateral temporal, and 1% the orbital frontal regions. In this group of patients as a whole, interictal epileptogenicity decreased from inferomedial to lateral and from anterior to posterior portions of the temporal lobe, attaining a maximum over the uncus and the anterior portion of the parahippocampal gyrus. In keeping with observations by others,[18,86] following anterolateral temporal lobectomy sparing the hippocampal complex and providing access to the ventricular surface of the hippocampus, all patients in this study displayed interictal spikes over the hippocampus and the parahippocampal gyrus with temporal and polarity relationships suggesting that they were generated within either or both structures[110] (Fig. 4B).

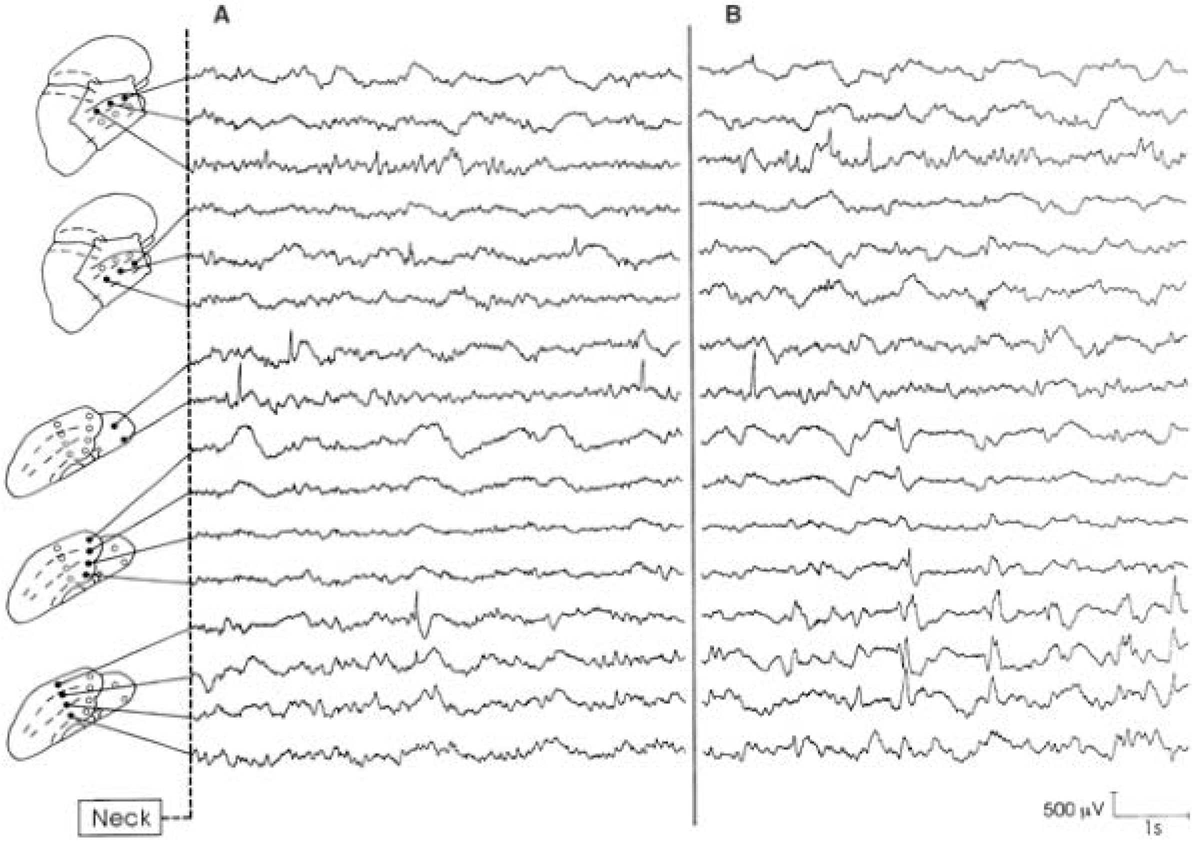

FIGURE 5. Thirty-one-year-old woman with episodes of dizziness, déja vu, automatisms of the upper extremities, loss of awareness, and occasional generalized tonic–clonic seizures. In preoperative scalp EEGs, sharp waves occurred over the inferior frontal and anterior and midtemporal regions. Interictal and seizure discharges detected in long-term subdural recordings arose from the infratemporal surface of the right temporal lobe. Intraoperative preresection ECoGs demonstrated spikes and sharp waves involving the right temporal and orbital-frontal cortices multifocally, as in this figure. (From Tsai M-L, Chatrian G-E, Pauri F, et al. Electrocorticography in patients with medically intractable temporal lobe seizures: I. Quantification of epileptiform discharges prior to resective surgery. *Electroencephalogr Clin Neurophysiol.* 1993;87:10–24, with permission.)

Although epileptiform activity is frequently detected and predominates in some patients, in extrahippocampal locations, spikes involving the hippocampal complex are the most common finding in the intraoperative ECoGs of patients undergoing temporal lobe resections. This is in harmony with the notion, long established by acute and chronic depth recordings, that the vast majority of temporal lobe seizures develop from the hippocampus, the amygdala, or both.[9,12,23,29,64,87,98,104,111,120] However, there is evidence that the demonstration of interictal hippocampal spikes in intraoperative ECoGs does not per se differentiate between mesial and neocortical temporal lobe epilepsies[18,75,110] and that no relationship exists between lateral or inferomesial and anterior or posterior temporal locations of the sole or primary ECoG spiking area and the type and location of pathology within or outside the mesial temporal region.[72]

Over the last six decades, numerous authors have variously expressed the belief that in patients suffering from chronic, medically intractable temporal (as well as extratemporal) epilepsies, the topography of intraoperative preresection spiking provided guidance in deciding the extent of excision of epileptogenic tissue.[7,14,38,48,59,83,92,105] Other investigators have disagreed with this view, and some have even advocated and successfully performed anatomically standardized temporal lobectomies without ECoG control.[28,36,103,106] Several observations[31,72] demonstrated lack of relationships between the presence of preresection spikes outside the ordinary limits of temporal lobectomy and seizure outcome. However, by far the strongest argument against the need to excise all or most of the preresection spiking area has been provided by the therapeutic success of amygdalohippocampectomy, which removes only a small portion of the region displaying spikes in individuals afflicted by mesial temporal lobe epilepsy.[72] The evidence suggests that the limits of the interictal spiking area in the preresection ECoG do not offer reliable clues regarding the amount of epileptogenic tissue to be excised to ensure the success of resective surgery in patients with medically intractable temporal lobe epilepsy, whether of mesial or neocortical origin.

The proportion of patients demonstrating spikes in their ECoGs after temporal lobectomy varies widely in different reports, from 22% to 85%,[7,31,38,110] although postresection spiking areas generally are significantly less numerous and less extensive and attain smaller maximal voltages than they did before resection[110] (Fig. 4C).

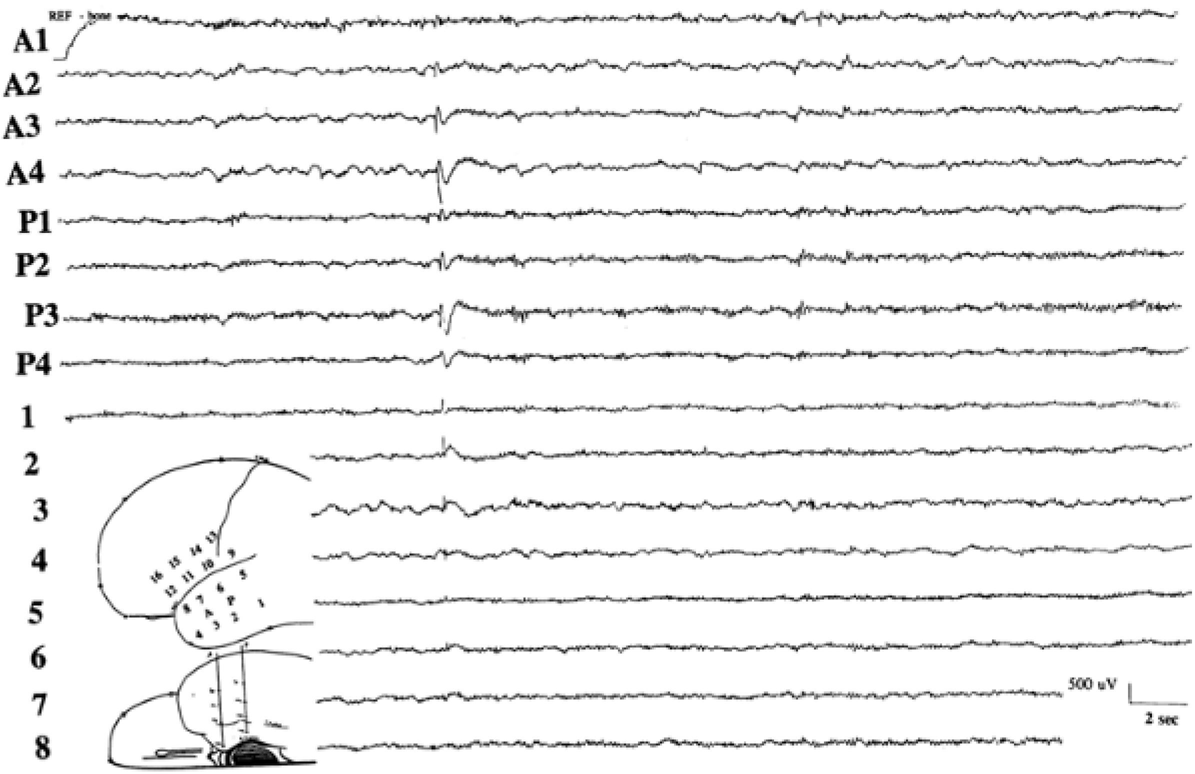

FIGURE 6. Thirty-six-year-old man with temporal lobe seizures. The EEGs demonstrated left temporal

interictal spikes, and MRI showed left amygdalar and hippocampal atrophy. Intraoperative preresection ECoG displays infrequent spikes involving most prominently the left inferior temporal gyrus, the amygdala, and the hippocampus, apparently simultaneously. A1–A4 and P1–P4, progressively deeper contacts along anterior and posterior depth electrodes inserted manually through the midtemporal gyrus and aimed at the amygdala and the anterior hippocampus, respectively. (From Cendes F, Dubeau F, Olivier A, et al. Increased neocortical spiking and surgical outcome after selective amygdalo-hippocampectomy. *Epilepsy Res.* 1993;16:195–206, with permission.)

The concept that the postresection ECoG can contain information predictive of postoperative seizure outcome has also been the subject of controversy for decades. Numerous authors affirmed the existence of a relationship between presence or absence of ECoG spiking after resections and poor or satisfactory postoperative seizure control, implicitly or explicitly advocating resection of as much spiking tissue as is compatible with avoidance of neurologic deficits,[4,6,8,14,46,55,56,57,59,65,101,105,112] whereas no such association was found in other series.[7,18,21,31,33,35,48,72,93,99,108] A more recent concept has evolved according to which in “tailored” temporal resections intraoperative hippocampal ECoG can be used to predict the extent of hippocampal resections.[61,68,74] In one study[74] of 140 consecutive patients who underwent an intraoperative tailored strategy for mesial temporal lobe epilepsy based on ECoG-guided hippocampal resection, no correlation was found between size of resection and outcome in the group as a whole or when stratified by pathologic subtype (mesial temporal sclerosis [MTS] vs. non-MTS). Individuals with large resections (>2.5 cm) were not more likely to have better outcomes than those with smaller resections, and the presence of postresection hippocampal spikes portended significantly worse outcomes in both MTS and non-MTS patients. These studies suggest that hippocampal ECoG can be used to maximize the probability of seizure-free outcome while

simultaneously possibly sparing functionally important hippocampus. There are also reports that ECoG can be very useful in guiding the extent of subcortical ectopic gray matter resection in cases of medial temporal epilepsy with this concomitant pathology.[76]

Electrocorticography in Amygdalohippocampectomy

The ECoG changes incident to selective amygdalohippocampectomy (sAHE) differ from those following temporal lobectomy. In patients with mesial temporal epilepsy whose preresection intraoperative ECoGs demonstrate variable amounts of interictal spiking, either confined to mesial temporal structures or also involving the lateral temporal surface (Fig. 6), sAHE is followed by a marked increase in frequency and a distinctive change in pattern of the epileptiform discharges most evident over the anterior temporal cortex (Fig. 7).[22,72,79] Increased spiking following this surgery is probably related to acute disconnection of preserved neocortical from excised mesial temporal structures and shows no significant relationship to the amount of epileptiform activity in postoperative scalp EEGs or to the degree of seizure control.[22] These observations strongly argue against the validity and general applicability of the concept that undiminished or increased epileptiform activity in the postresection ECoG presages unsuccessful seizure outcome following sAHE. On the other hand, a recent series of consecutive patients who underwent sAHE suggests that the preresection distribution of spikes on ECoG might predict outcome. Patients with spikes restricted to basal-mesial temporal lobe may be more likely to be seizure free than those with spikes on lateral temporal cortex as well.[24]

Electrocorticography in Extratemporal Resections

The intraoperative ECoG of patients afflicted by chronic, medically intractable neocortical epilepsies of extratemporal origin offers variable assistance in determining the location of the epileptogenic process and estimating the boundaries of the surgically relevant epileptogenic zone. Because of anatomic and functional peculiarities, the interictal spiking detected in the ECoG of patients with frontal lobe epilepsies varies in a continuum from localized to regional, multilobar, or even bilateral frontal or widespread distributions, with no clear relationship to the amount of epileptogenic tissue the removal of which would yield successful seizure control[89] (Fig. 8). Epilepsies arising in centroparietal cortices are also frequently associated with widespread epileptiform activity in intraoperative EcoGs,[88] and occipital epilepsies often generate discharges that spread variably to adjacent posterior temporal and parietal regions.[95] The distinctive tendency of epileptiform activity to be broadly distributed in the ECoGs of patients with uncontrollable extratemporal epilepsies is emphasized by observations indicating that interictal spikes extend outside subsequently resected tissue in as many as 75% of patients who underwent frontal lobectomy and in 91% of individuals treated by corticectomies in various locations, as opposed to 40% of patients in whom temporal lobectomies or amygdalohippocampectomies were carried out.[18,72]

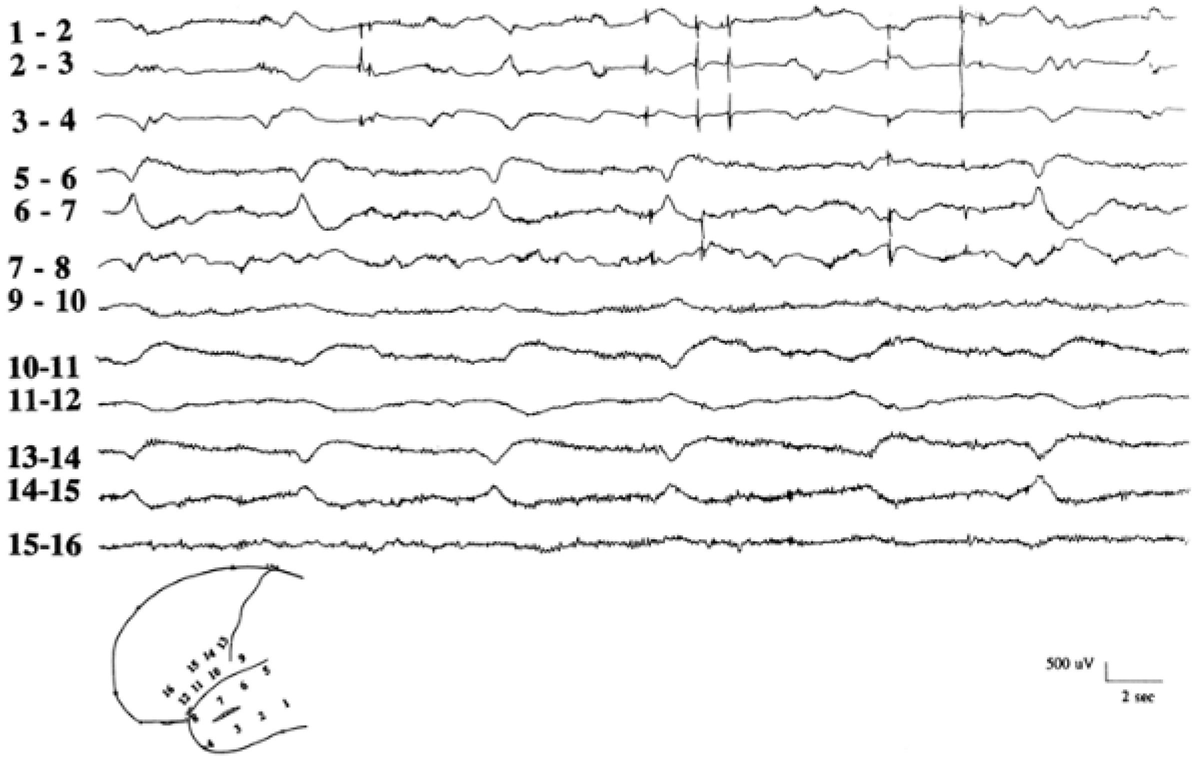

FIGURE 7. Same patient as in FIGURE 6. The ECoG after transcortical amygdalohippocampectomy shows frequent spikes over lateral temporal and suprasylvian cortices, with intervening periods of voltage depression and slow waves. (From Cendes F, Dubeau F, Olivier A, et al. Increased neocortical spiking and surgical outcome after selective amygdalo-hippocampectomy. *Epilepsy Res.* 1993;16:195–206, with permission.)

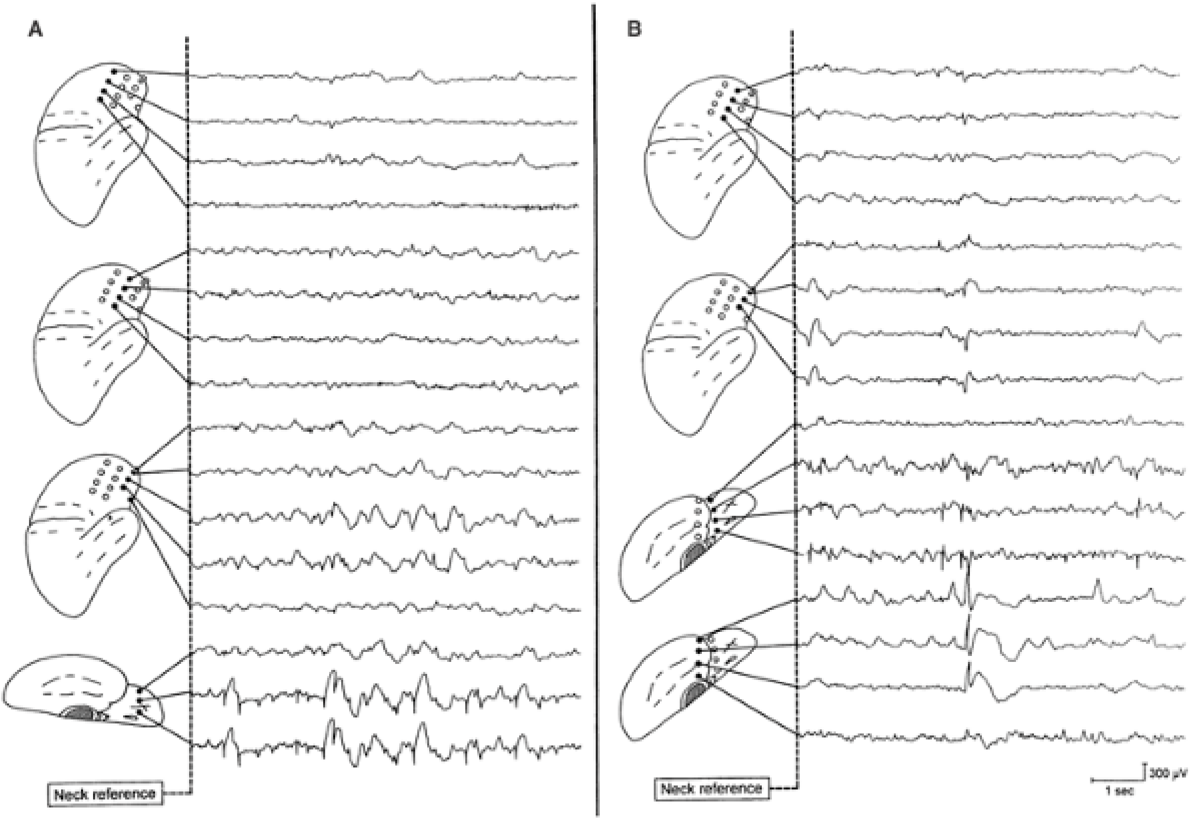

FIGURE 8. Thirty-one-year-old man with seizures characterized by body numbness and tingling, queasy feeling in stomach, frightened expression and vocalizations, gross body movements and flailing movements of arms and legs, and infrequent minor automatisms, followed by prompt recovery of responsiveness and denial of having lost consciousness. Occasionally, seizures were followed by tonic–clonic generalization. Scalp EEGs demonstrated frequent bilaterally synchronous spike-and-slow-wave activity maximal over the right frontopolar region and rare right temporal discharges. In long-term subdural strip recordings, interictal discharges involved and seizures developed from the right frontal lobe, multifocally or diffusely, both frontal lobes, or the right infratemporal surface. Intraoperative ECoG depicted here showed frequent spikes and sharp waves over the right orbital frontal and inferior frontal cortices, with complex polarity and temporal relationships, and spike-and-slow-wave activity and sharp waves over the right infratemporal surface. Two years after surgery, patient was seizure-free.

Although the precise boundaries of the surgically relevant epileptogenic area cannot be determined by ECoG, there is evidence that in frontal lobe epilepsy, ECoG findings do have prognostic significance. In both nonlesional and lesional frontal resections, when preresection spikes are restricted in distribution to no more than two gyri and postresection spikes are absent, a favorable outcome can be anticipated.[118,119] Removal of ECoG-identified, dispensable epileptogenic cortex on the margins of highly epileptogenic neoplastic, developmental, malformative, or cicatricial lesion in any location yields better seizure control than lesionectomy alone.[19,85,97,107] Cortical resection guided by ECoG in cases of porencephaly can result in effective seizure control while preserving motor and visual function.[53] Studies also indicate that the ECoG demonstration of frequent or continuous discharges over neuroimaging- or histologically identified cortical dysplasias characterizes highly and intrinsically epileptogenic cortex the ablation of which successfully controls the patient's seizures in an appreciable proportion of cases[50,81] (Fig. 9). In contrast, direct cortical recordings contribute some information that can be helpful but is not essential in the resection of large hemispheric lesions by hemispherectomy, hemidecortication, or multilobar removals.[113]

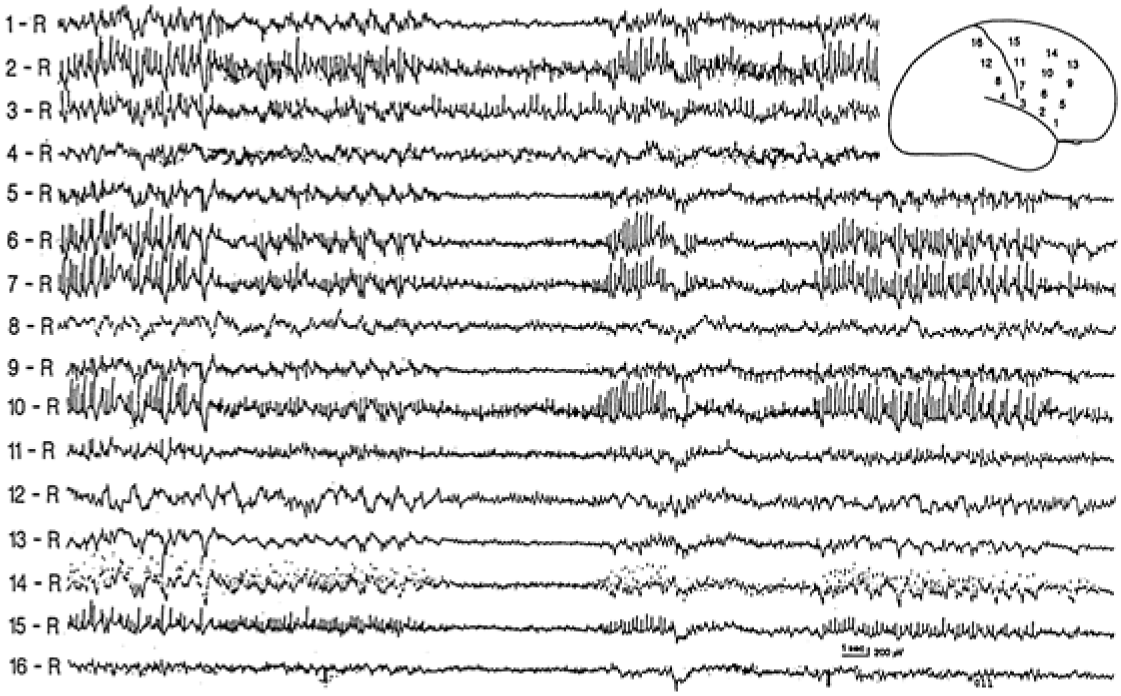

FIGURE 9. Seven-year-old girl with quasi-continuous spikes and sharp waves over the right frontocentral region in her scalp EEG and a right frontocentral dysplastic lesion demonstrated by MRI. Her intraoperative ECoG shows bursts of spikes of variable amplitude and duration detected diffusely from the right frontocentral cortex, as in this figure. (From Palmini A, Gambardella A, Andermann F, et al. Intrinsic epileptogenicity of human dysplastic cortex as suggested by corticography and surgical results. *Ann Neurol.* 1995;37:476–487, with permission.)

Electrocorticography in Cortical Disconnection Surgeries

The utility of the ECoG in cortical disconnection surgeries, including multiple subpial resection and corpus callosotomy, is not clearly established. Morrell et al.[77] reported that following multiple subpial transections performed to relieve intractable partial seizures caused by epileptogenic processes encroaching on nonresectable cortical regions, the ECoG from the transected area generally demonstrated immediate depression of all activities followed by recovery of background rhythms but not of epileptiform discharges. In contrast, in a preliminary study, Binnie et al.[18] reported that ECoG spike rates following this surgical procedure varied from complete abolition to 200% increase without demonstrable relations to either seizure outcome or completeness of transection.

Binnie et al.[18] used ECoG recordings to determine the effects of successive stages of callosotomy on the bilateral synchrony of epileptiform discharges detected before the procedure. Although a better clinical outcome was observed among patients in whom the bilateral synchrony of epileptiform activity was disrupted by callosal section, they questioned the validity of this result because of possible biased preresection findings in their small series. A recent report of children with Lennox-Gastaut syndrome who underwent anterior callosotomy disclosed that blockage of bisynchronous discharges in ECoG during callosotomy was not correlated with a prognosis that differed significantly from cases in which blockage did occur.[69] Thus, there is no adequate evidence that ECoGs are more reliable than surface EEGs in monitoring the immediate effects and prognosticating the results of corpus callosotomy.

Advantages and limitations of Intraoperative electrocorticography

Advantages

1. Intraoperative ECoG allows entirely flexible placement of recording and stimulating electrodes within the surgical exposure and on accessible adjacent cortices.
2. Intraoperative ECoGs detect large numbers of interictal discharges that are not apparent in EEGs, whether recorded with conventional scalp electrodes only or combined with auxiliary scalp or facial leads and nasopharyngeal, sphenoidal, or foramen ovale electrodes.
3. ECoGs offer the opportunity to perform direct electrical stimulation of the brain to elicit afterdischarges, possibly reproduce clinical manifestations of the patient's habitual seizures, and delineate functionally eloquent cortical areas.
4. When performed with the appropriate technique, ECoGs are free of many of the artifacts that hinder recordings not taken directly from the brain.
5. New electrode placements can be devised at each stage of the procedure to answer the questions raised by findings of the previous stage.
6. Recordings can be taken before and after each stage of resection to determine the presence or absence and features of postresection spikes.
7. ECoG findings, particularly when combined with the results of functional mapping (Chapter 174), can offer guidance in determining the extent of resection.

Limitations

1. Intraoperative ECoG requires previous lateralization and at least broad localization (“regionalization”) of the epileptogenic process.
2. With some notable exceptions, no spontaneous ictal activity is recorded intraoperatively.

3. Interictal spiking might be absent entirely, or the full extent of the interictal spiking area might not be observed in the course of a relatively brief ECoG. This can lead to performance of surgery without ECoG monitoring and use of activating procedures the results of which can raise interpretive problems.
4. It is not possible to survey during surgery the lateral and inferior temporal lobe surfaces simultaneously with the amygdala and hippocampus without violating the integrity of these structures. In addition, medial and inferior hemispheric surfaces are not accessible through standard craniotomies designed for temporal lobe resections.
5. The background activity and ECoG spiking rate and distribution are variably influenced by general and local anesthetics, opioid analgesics and other drugs, surgical trauma, and state of the patient (wakefulness, drowsiness, or sleep). These factors can raise difficulties in interpretation.
6. Waking intraoperative ECoGs might not be suitable for uncooperative adults and children.
7. The method requires additional equipment, personnel, and expenditure of time.

Complications

Prolongation of surgery and cortical exposure by about 90 minutes could conceivably result in some increase in morbidity, but this has not been demonstrated and quantified. The occurrence of a fully developed partial seizure with prolonged confusional state is likely to cause delay or abandonment of further ECoG and cognitive testing. In addition, the possible precipitation by electrical stimulation of a generalized tonic–clonic seizure possibly carries risks because of the development of acute edema and herniation of the brain through the open craniotomy. However, we found no information in the literature on the frequency of these complications.

Future Directions

The availability of computer-based digital recording systems and networking technologies offers the opportunity to modify the traditional instrumentation and promote new approaches to the analysis of the intraoperative ECoG. By using an instrumental setup such as that suggested in FIGURE 10, one can survey as many as 64 to 128 brain sites simultaneously. These recordings are displayed on high-resolution monitors at multiple locations, including the operating room gallery, the operating theater, and the EEG suite. A closed-circuit color television system can provide both the clinical neurophysiologist and the operating room staff with a detailed view of the surgical field at the same locations, and an intercom system can allow communication between the clinical neurophysiologist and the neurosurgeon while a microphone records the patient's verbalizations. The synchronized ECoG, surgical field images, and verbal communications are stored on appropriate media for later retrieval. The digitized, referentially recorded ECoG can be formatted on- or off-line in any desired referential, bipolar, or mixed montage. Such a system would offer the clinical neurophysiologist the option of conducting the whole or part of the ECoG procedure from a location remote from the operating theater whenever desired. However, more important would be the acquired capability to supplement the visual appraisal of the ECoG with a variety of computer analyses. These could be designed to aid not only in the recognition and quantification of epileptiform discharges, but also in the assessment of their topographic and morphologic features and patterns of propagation and in the differentiation between primary and secondary

areas of epileptogenesis.[46,67,70] These analyses can increase the localizing power of the ECoG and improve the accuracy of estimation of the epileptogenic zone. We also view as desirable the inclusion in the recording system of stimulus artifact reduction capabilities making it possible to record the ECoG during stimulation, and the development of digital recording systems with sampling rates allowing the recording and storage of ECoG signals with a broader bandpass, such as DC to 300 Hz.[41] This last feature would facilitate the study of events having faster[41] or slower[49] frequencies than those recorded with current instrumentation.

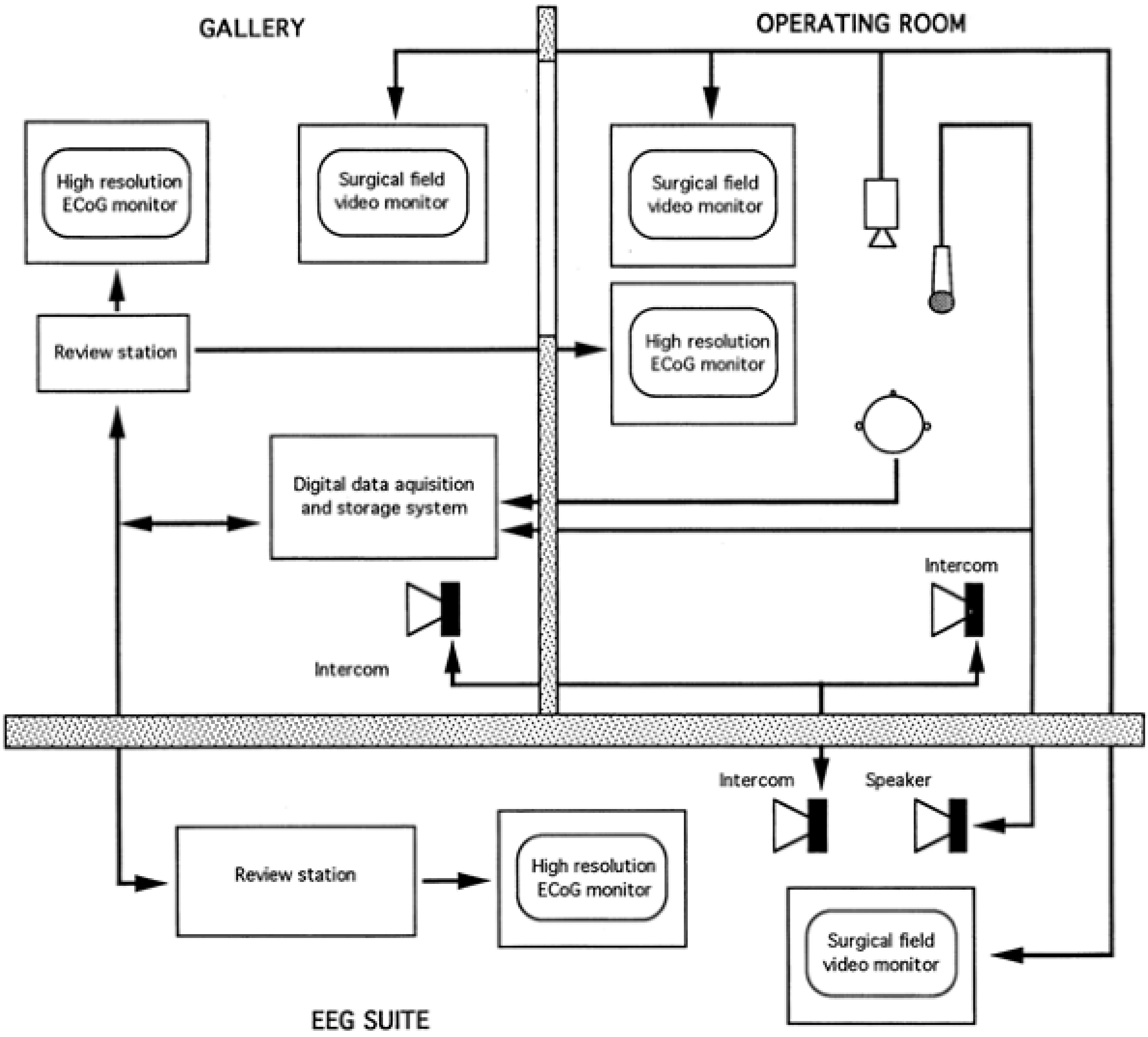
GALLERY
OPERATING ROOM
High resolution ECoG monitor
Surgical field video monitor
Surgical field video monitor
Review station
High resolution ECoG monitor
Digital data aquisition and storage system
Intercom
Intercom
Intercom
Speaker
Review station
High resolution ECoG monitor
Surgical field video monitor
EEG SUITE

FIGURE 10. Diagram of suggested physical arrangement and computer-based instrumentation for ECoG recording and analysis.

An especially promising development is that the rapidly improving resolution of magnetic resonance imaging increasingly offers the opportunity to visualize the structural location of functional abnormalities of the brain by generating three-dimensional anatomic maps on which different functional images, such as those from functional MRI, PET, SPECT, magnetoencephalography, EEG, evoked potentials, and ECoG, can be superimposed. Frameless stereotactic systems interactively guided in the operating room by multimodal neuroimages, including the ECoG, are already in operation in several centers.[30,80] Their use is hoped to improve the precision of epilepsy surgery and provide novel insights into normal brain function and its aberrations in epilepsy.

Summary and Conclusions

No individual feature of the preoperative ECoG, as we presently assess it, is clearly indicative of the site of origin and pathophysiologic mechanisms of the patient's seizures, the site and nature of pathology, when any is demonstrable, or the extent of the epileptogenic zone Nevertheless, the method plays a major role in tailored temporal resections, which are based on the practice of excising only those regions of resectable hippocampus shown to demonstrate ECoG-identified interictally spiking tissue. In contrast, ECoGs serve no practical purpose in anatomically standardized temporal lobectomies. The method may be potentially misleading in selective amygdalohippocampectomies, which are typically followed intraoperatively by a marked increase of interictal spiking unrelated to seizure outcome, although preresection ECoG in these cases may relate to outcome. In frontal lobe and other extratemporal epilepsies without preoperatively identifiable structural pathology, the ECoG is of limited assistance in localizing the epileptogenic zone, although preresection spike distribution and post-resection spike presence or absence may have prognostic significance.

In the presence of a neuroimaging-demonstrated localized lesion, the utility of the method depends on factors that include

the nature and extent of pathology and the surgical approach chosen, among others. Removal of gross structural lesions and of extrinsic, dispensable epileptogenic tissue and excision of highly intrinsically epileptogenic, dysplastic cortex depend in large measure on clues provided intraoperatively by the ECoG. In contrast, the utility of this method is questionable in the resection of large hemispheric lesions by hemispherectomy, hemidecortication, or multilobar removals and is not clearly helpful in cortical disconnection surgeries such as multiple subpial transection and corpus callosotomy.

Changes in ECoG instrumentation, mostly based on available technology, are suggested. A major potential advantage of these modifications is the ability to apply powerful methods of computer analysis to the ECoGs with the hope of increasing the localizing power of this technique. In addition, especially promising is the recent introduction of image-guided neurosurgical systems that make it possible to determine interactively in the operative room the location of electrodes used to record the ECoG and other functional images relative to the underlying CT- and MRI-determined three-dimensional anatomy of the patient's brain.

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Chapter 173

Intraarterial Amobarbital Procedures

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Introduction

Successive hemianesthesia of the two cerebral hemispheres elicited by injection of an anesthetic agent into the internal carotid artery has been practiced for >40 years. The technique is highly specialized and highly specific: It is performed in some patients who will undergo elective brain surgery. A simple rationale underlies this procedure: Temporary anesthetization of one hemisphere should allow the awake hemisphere to be tested alone, and the results of those tests should allow prediction of certain possible sequelae of the proposed surgery. It is an essential part of neuropsychological evaluation in most epilepsy centers and is carried out for two different purposes: (a) to determine cerebral dominance for language and (b) to evaluate memory function in each hemisphere independently.

This procedure was originally introduced in North America in the late 1950s by Juhn Wada,[118] and hence the frequently used nickname, “Wada test,” despite the now-formal appellation “intracarotid amobarbital procedure” or IAP. The basic procedure has undergone very little change over the years, with a few exceptions. One exception is the brain region targeted for anesthesia: Some centers use more selective procedures that target the medial temporal lobe (anterior choroidal artery) or language areas. Another exception is the use of other anesthetic agents in recent years; these are discussed later in a section about techniques. For simplicity, throughout most of this chapter we refer to these anesthetic procedures collectively as IAPs.

Indications

In some institutions, all surgical candidates receive an IAP as part of the presurgical workup. In others, only certain patients undergo this procedure. When only selected patients receive an IAP, it might be performed because cerebral dominance is uncertain, or it might be indicated for further assessment of memory. Whether the test is being performed for evaluation of language or of memory, the actual procedure is the same.

Language

An IAP to assess cerebral dominance is performed when there is reason to suspect an atypical cerebral organization for language, because this might interfere with the planned surgical intervention. Left-handed individuals, those with a strong family history of left-handedness, and people with evidence of early damage in or near speech areas of the left hemisphere fall into this category. Patients whose anatomical and functional (cognitive) lateralization is discordant are also candidates for an IAP because in such cases the mismatch can reflect right-hemisphere speech dominance. Dichotic-listening tasks are sometimes used as a screening test for atypical speech representation. In those tasks, competing verbal stimuli are delivered simultaneously to the two ears, with the expectation that the stimuli will be perceived best by the ear opposite the speaking hemisphere.[113,129] If there is little or no difference between the ears, or if best performance is observed from the left ear (right hemisphere) in the presence of normal hearing, then an IAP to determine cerebral speech dominance may be performed.

Memory

Patients are selected to undergo an IAP for memory evaluation based either on the presence of significant deficits on verbal and nonverbal memory tests uncovered during a basic neuropsychological assessment or on electroencephalogram (EEG), anatomic magnetic resonance imaging (MRI), or other evidence suggesting bitemporal damage. An IAP might also be performed in cases of mismatch between EEG and anatomic MRI findings such that an EEG focus is observed in one temporal lobe and a significantly small hippocampus is found on the opposite side.

Techniques

The basic technique involves injection of an anesthetic agent, usually sodium amobarbital, into one cerebral hemisphere, usually through the internal carotid artery. This anesthetizes the injected hemisphere and allows one to test the abilities of the awake hemisphere in isolation. With this agent and this technique, the effect is short and is usually dissipated after about 6 to 8 minutes,[10,102] depending on the dose[21,70] and individual differences[31] (a procedure with different timing is discussed later under "alternative drugs and techniques"). During the effect, simple speech and memory tests are administered. The tests are kept simple because the effect is short, patients must perform them with a single hemisphere, and the basic clinical questions asked by this procedure can be answered adequately with simple tasks.

Neuropsychologists usually administer the cognitive tests. An angiogram is obtained before the IAP to make sure that there is no serious vascular anomaly and to predict the distribution of the drug; this is done by a radiologist, who also performs the injection. The effect of the drug on the brain is monitored by EEG[92,107]; in some institutions this is done online during the test, and in others the EEG is recorded on a computer for playback and blind interpretation by an electroencephalographer afterward.[2,10,26] The patient's recovery from the hemiplegia that is induced by amobarbital injection is also monitored to estimate return of function, although this estimate is less satisfactory[10,17] (but see Bookheimer et al.[9]).

Testing Paradigms

Before injection, basic speech and memory tests are performed to establish a baseline. On injection, more speech and memory tests are administered while only one hemisphere is functional. The same speech tests as used in baseline testing are performed after injection, but new memory material is shown. Memory for the new material is tested later, after the drug is no longer active and the injected hemisphere has returned to baseline functioning.

IAP speech tests sample different aspects of language, including serial or automatic speech (counting, reciting days of the week), naming, repetition, spelling, reading, and auditory comprehension (see, e.g., Fedio et al.[21] and Ravdin et al.[102]). Cerebral dominance should not be assessed with a single task because dissociations among types of speech functions are sometimes observed.[11,103,110] Tasks should be rotated throughout the crucial period of hemianesthesia so that all can be sampled.

Superimposed on the basic methodology of memory testing during the IAP are the many variations used by different institutions. The number of items introduced after injection to test the formation of new memories varies from only a few, such as five,[46] to continuous presentation for as long as the hemianesthesia is present.[67,100,101] The timing of memory item presentation can also vary.[72] Some centers[15,16] test memory using a mixture of materials that includes words, pictures, phrases, and commands, whereas others use all words or all pictures or all real objects. Real objects have the advantage of being perceived more easily by either hemisphere.[52] In most but not all centers the final interpretation of memory results is based on the patient's ability to recognize later the new material that had been shown during hemianesthesia, but free recall is taken into account in some institutions.[104] Despite this lack of uniformity in details of IAP memory-test methods, the essence of the procedure does not differ, and results from one institution can usually be interpreted by another.

Selective Studies

Although most centers carry out a "standard" intracarotid amobarbital test, some perform special procedures for selective temporary inactivation of temporal and extratemporal structures. The development of selective temporal lobe (TL) amobarbital tests was motivated by skepticism about the ability of "standard" IAP to predict postoperative memory performance in patients who would receive a TL resection,[69] especially a restricted resection such as selective amygdalohippocampectomy.[125] The main reasons for the skepticism were that the hippocampal formation may not be sufficiently anesthetized with the IAP[42] (but see refs. 26, 79, and 80) and that inactivation of large parts of one hemisphere does not allow examination of the functional role of the specific structures of interest. Furthermore, the sudden anesthesia of one hemisphere can produce an initial period of confusion, inattention, and disorientation, as well as aphasia if the speech-dominant hemisphere is involved. These side effects interfere with memory testing.

For anesthesia of medial TL structures, at least three selective procedures were developed—two anterior procedures and a posterior one. One *anterior* procedure[120,121,122,123,124] consists of a temporary balloon occlusion of the internal carotid artery distal to the origin of the anterior choroidal artery (acha), with subsequent injection of amobarbital into the territories of the acha, the posterior communicating artery, and the opthalmic artery. The second anterior procedure is a selective catheterization of, and injection of amobarbital into, the acha. Whether the selective inactivation of medial temporal-lobe structures by injection into the anterior choroidal artery has the advantages that are claimed for it should be verified by further studies.

The *posterior* TL amobarbital test[42,43,94,120,123] consists of selective catheterization and subsequent injection of amobarbital into the P2 segment of the posterior cerebral artery.

In the hands of an expert interventional neuroradiologist with appropriate sophisticated catheter techniques, *extratemporal* brain regions can be selectively approached and temporarily inactivated by amobarbital. Because of the inherent risks of such procedures, they are rarely performed. The need for extratemporal amobarbital testing arises if the function of the brain region under consideration involves potential essential cortex, such as classic speech or motor areas, or if the alternative approach of intraoperative functional mapping with the patient awake is not possible. Between October 1986 and December 2005 the Zürich group carried out selective amobarbital tests in 106 patients, only 6 of whom received an extratemporal procedure. One of these was a selective inactivation of Broca's region in a patient slated for resection of a tumor invading the left frontal operculum, 1 was a regional left frontal inactivation in a patient with a left anterior frontal epileptogenic lesion, 1 was a sequential Broca and Wernicke inactivation, 1 was a left posterior insula and Wernicke inactivation, and the remaining 2 underwent inactivation of selected branches of the middle cerebral artery.

Selective procedures are carried out far less frequently than the "standard" IAP; in a survey of epilepsy centers it was determined (among 68 respondents) that only 4% of all amobarbital procedures performed annually were selective.[101] Although no newer survey has been conducted, a PubMed search yielded only 13 articles about selective amobarbital procedures in the period from 1996 to 2006. This represents 5% of the approximately 250 articles that were published about the IAP in that same time period. Furthermore, judging by those publications, most selective procedures are being performed in Europe. The largest series of selective tests has been performed by the Zürich group; for details of their results, including angiographic, clinical, electroencephalographic, positron emission tomography (PET), and single photon emission computed tomography (SPECT) findings and memory performance, see Wieser et al.[123]

Alternative Drugs and Techniques

Owing to repeated shortages of amobarbital, within but especially outside of the United States, some centers have switched to other drugs. The most frequent alternative has been methohexital,[3,13,41] but propofol has also been used.[6,108,115] Clinicians who use methohexital are pleased with it as an alternative to amobarbital. It has an important limitation, however, in that it is so short-acting that it usually has to be reinjected within a test, leading to waxing and waning of the effect at least twice within critical testing time. This lack of control over the level of anesthesia is a problem for presentation of new memory items and consequently for interpretation of memory results. Propofol, which is used in the same way as amobarbital with a single injection and subsequent waning of the effect, is also problematic because it must be injected in a lipid carrier. It is a newer alternative, and has been used in only a few patients except for one series of 12[115]; the articles about propofol have also reported overall satisfaction with it. A third alternative, etomidate, has been used successfully in >42 patients (84 tests), and in this case the alternative also includes an important change in the procedure: In the etomidate Speech and Memory test (*e*SAM), the level of anesthesia is maintained with an infusion following the initial bolus injection.[52] This allows all critical speech and memory tests to be administered

during full hemianesthesia, eliminating the time pressure during test presentation, and consequently eliminating the incidence of uninterpretable memory tests that occur in the IAP owing to presentation of items when the drug is no longer active. The limitation for *e*SAM is that in about 45% of the first 26 tests performed, a side effect was observed that consisted of a shiver-like tremor. This was very mild or almost imperceptible in more than half of those incidents and was seldom noticed or remembered by the patients.

There were no serious adverse effects reported for any of these three alternatives to amobarbital.

Another agent is also used for a different but related purpose: Lidocaine has been used together with amobarbital for patients with cerebral arteriovenous malformations (AVM) who undergo superselective intraarterial injections and behavioral testing (language, memory, motor) before receiving embolization to treat the AVM.[23,98] According to Fitzsimmons et al.,[23] the reason for including lidocaine in those procedures is that amobarbital selectively inhibits gray matter structures, whereas lidocaine inhibits white matter tracts as well. They found that using both agents provided a fuller picture in predicting possible deficits following embolization of AVMs.

Interpretation

Speech and memory results from an IAP (or similar anesthetic procedure) can be interpreted only if the test is valid. Slow waves in the EEG and contralateral hemiplegia provide information that the drug is active, a necessary prerequisite to a valid test,[50] but it is also necessary to know that the test is indeed assessing what it aims to test. It is not valid if the patient is not attentive[40] or is not actively participating. Therefore many centers also monitor level of consciousness during the IAP.[76,82]

Given a valid test, interpretation of *speech* results is most often clear and simple. The results are unambiguous when a patient is aphasic while the drug is active after injection in one side and continues talking without significant errors after injection into the opposite side. This is the most common pattern. However, in cases of bilateral speech representation a range of different patterns can be observed. These include (a) disruption of all speech functions tested after injection in one hemisphere with minor but significant disruption after injection in the other; (b) dissociation of type of disruption (e.g., naming in one hemisphere and comprehension in the other); (c) equal and significant disruption in both hemispheres; and (d) no obvious disruption in either hemisphere. Interpretation of bilateral speech differs among institutions,[103] and as a consequence reports of the incidence of this type of atypical language organization varies widely.[101,109]

Underlying the interpretation of the *memory* application of the IAP is a basic assumption that the patient will have to rely on the awake hemisphere to remember material shown while the drug is active, and that the material will not be remembered if the awake, or noninjected, hemisphere is damaged.

The important test for memory is when the hemisphere of the planned surgery is injected because in that case one is testing the memory function of the hemisphere that will be left intact. It is expected that in that situation the test should predict how well the patient's memory will function after resection from a temporal lobe. In addition, ideally memory should be impaired when the hemisphere of planned surgery is tested (injection into the healthy hemisphere) because that result provides confirmation on dysfunction in memory structures that are to be resected.

A second assumption underlying IAP memory tests is that they are addressing the adequacy of hippocampal function specifically.[84] Therefore, in some centers a limited resection that spares hippocampus is performed in patients who fail amobarbital memory tests after injection into the hemisphere of a planned temporal lobe excision. In some other centers, surgery is denied altogether to such patients, whereas in still others operation with encroachment on the hippocampus has been offered. Thus, failing an IAP memory test can have important consequences for a patient's surgical management, but the consequences differ among centers.

Failure of an IAP memory test is also defined differently in different centers. Indeed, the way that the IAP memory-test results are interpreted is changing, and the concept of simply passing or failing is becoming infrequent. In many centers the test is used in a more general sense to predict postoperative memory performance, without specific reference to "failure" or to amnesia (see, e.g., Kneebone et al.[58]). It is also used as additional evidence in determining the side of epileptic focus when injection opposite the supposed focus results in substantially poorer memory performance than when injection was made on the side of suspected focus.[20,93,128]

Implications

One reason for carrying out an IAP is to screen for a risk of potential severe memory loss after resection from a temporal lobe, but it is very difficult to prove whether this test actually does predict amnesia. If patients who have failed amobarbital memory tests are denied surgery, or if they do undergo surgery but the hippocampus is spared, one cannot know whether they would have become amnesic if an extensive removal of hippocampus had been performed.

Some evidence does exist, however. There are two known cases of postoperative amnestic syndrome in patients who had been designated by IAP to be a risk and who still underwent resection from a temporal lobe.[68,99] Furthermore, in a survey of 71 epilepsy centers concerning IAP issues, an additional four such amnesic cases were reported,[101] and a later publication reported an additional patient who became globally amnesic for an extended period of time but who gradually recovered to a state of deficient memory but not amnesia.[28] Many other patients who have undergone temporal lobectomy after "failing" the memory test have not developed amnesia.[17,19,71]

Evidence that the IAP memory test does address hippocampal function can also be found. Sass et al.[106] counted hippocampal cells in resected temporal-lobe tissue and showed that patients with severe cell loss had shown deficient memory during the relevant amobarbital test when injection had been made opposite that damaged temporal lobe. Similarly, studies examining amobarbital memory performance as a function of hippocampal atrophy, as measured on magnetic resonance imaging (MRI), show significant memory failures after injection opposite the hemisphere harboring hippocampal atrophy and good memory after injection opposite a normal hippocampus.[51,75]

The foregoing results suggest that we are indeed testing hippocampal function with amobarbital memory tests. We infer further that doing so indeed allows us to predict postoperative memory loss, although this remains difficult or impossible to prove. Studies of later memory performance in patients who have passed versus those who have failed IAP memory tests suggest that the IAP is predictive.[19,48] Those studies show postoperative losses and long-term memory deficits in patients who had been determined to be at risk for serious global memory impairments. However, the patients in those studies were not amnesic. As we have just seen, postsurgical amnesia does occur, but rarely.

In many centers the IAP is used in a more general sense to predict postoperative memory performance without reference to global amnesia. Such prediction is based partly on the confirmation of side of epileptic focus when injection opposite it results in memory failure.[97,128] In addition, g*ood* memory after injection opposite a temporal lobe targeted for surgery shows that that temporal lobe, and presumably that hippocampus, functions well and may be intact. Resection from a healthy hippocampus can result in a more marked postoperative memory loss than resection from a damaged one.[36,74,116] Thus IAP memory performance in both tests, ipsilateral and contralateral to proposed surgery, should be taken into account in decisions regarding hippocampal excision.

The question of seizure control is closely linked to questions of sparing hippocampus. Because at-risk patients who undergo surgery show poor memory but are not amnesic, and because most of them experience a significant postoperative reduction in their seizures,[89] they gain as well as lose from surgery. Thus, surgical decisions concerning hippocampal excision weigh the negative effect of possible memory dysfunction against the positive effect of seizure control, but this issue is complex and must add the presurgical efficiency of the patient's memory and hippocampus into the equation. Furthermore, memory efficiency itself can contribute to predicting outcome: IAP results that clearly lateralize dysfunction with a difference score comparing performance of the two hemispheres have been shown to be successful predictors of seizure control.[73,111]

Application to Children

Language

The intracarotid amobarbital procedure has been used with patients as young as 3 years of age, although it is usually used with children of school age or older. As is the case for adult patients, centers in North America differ in the selection of pediatric patients for the IAP, with all surgical candidates undergoing the procedure in some programs and only certain children receiving it in others. Confidence in the use of the procedure in children is evidenced by its acceptance as the "gold standard" for establishing the validity of other methods for language localization and lateralization in the pediatric age range.[5,7,12,22,37,38,53,56]

There is also general consistency in the procedures involved in testing for language.[25,105] Many of the protocols are adapted from those used with adults. There is reliance to a large degree on counting at the time of injection, followed by tests of naming of pictures or objects; reading is also widely assessed, although in young children or children with mental retardation, single letters or digits can be used instead of words. In some protocols, serial speech tasks such as spelling or reciting the days of the week or the alphabet can be used, and some include questions that vary in complexity, requiring gestures, yes/no responses, or more complicated answers. The language testing included in the protocol must be individualized to the child, which may require considerable pretest preparation. Chronological age, mental age, and delay in language development all factor into the choice of procedures and test items. Thus, there may be more variability across subjects in the items used than is typically the case with test protocols used with adults.

A major divergence from the procedures used with adults is seen in the preparation of the child for the amobarbital test. It is recognized that the setting and procedures are unfamiliar to children and therefore can be extremely stressful. To inform the child about the procedures, and thus to elicit maximum cooperation, a "dress rehearsal" is often performed. This practice might involve taking the child to the neuroradiology suite, providing information about who will be present during the test, and having someone familiar to the child, such as a nurse or child care worker, present in the rehearsal as well as during the catheterization and test.[47,114] Some children become fearful and anxious because of the unfamiliarity and stress involved in the catheterization. It has been reported, however, that the use of propofol (Diprivan), a short-acting sedative–hypnotic agent, during the catheterization succeeds in avoiding these problems and permits the test to be completed with quite young children.[8,37,77] With proper preparation, the test is feasible, even with young and intellectually delayed children.[44]

A review of the small number of studies conducted on language lateralization with the IAP revealed somewhat disparate estimates of left hemisphere language representation in children selected for epilepsy surgery. Several studies have demonstrated that approximately two thirds of their samples had speech represented exclusively on the left,[32,105,114] whereas others reported that 85% to 88% of their samples had left hemisphere speech.[37,119,126] Thus, the data show an approximate bimodal distribution in the estimates of language representation in the left hemisphere in children with epilepsy. The discrepancy in the estimates might reflect differences in testing procedures or criteria for classifying unilateral versus bilateral speech representation or actual differences in the patient populations studied at different surgical centers. For example, it appears that there was a higher percentage of younger children in the patient series that had the lower estimates of left language dominance than in those series with the higher estimates.

Memory

In children, the assessment of memory during the intracarotid amobarbital test is not always as successful as the assessment of speech.[30,47] The difficulty in arriving at a valid and reliable indicator of memory status can result from the fast-paced and stressful conditions, the inability of young children to comprehend the requirements of the task, or the failure of children to attend sufficiently well to the test items to ensure proper registration of the materials.[32,114] Szabo and Wyllie[114] also raised the possibility that children have less effective memory strategies than do adults, and these strategies are therefore more sensitive to disruption by the amobarbital than is the case for adults.

A number of patient characteristics have been examined for their contribution to the success of testing memory using the IAP and to the outcome of such testing. Sex of the child, dose of amobarbital, and order of hemispheres injected do not appear to influence the results of memory testing.[119,126] One of the major factors in determining whether the test yields any useful information may be age. Williams and Rausch[126] obtained the most reliable results in children >13 years of age but found that age interacted with language dominance; thus, younger children with epileptogenic regions in the nondominant hemisphere also performed the test well. Hempel et al.[32] found that memory testing was possible among 8- to 11-year-olds but met with considerably less success in children under <7 years of age. Obtundation and agitation, preventing successful memory testing, were found more frequently among younger children.[30] The effect of age may also interact with IQ; it has been reported that children who were brighter and older were more likely to have valid tests than younger children with low IQ.[47,119] Williams and Rausch[126] and Hempel et al.[32] found that IQ alone does not appear to bear on the outcome of memory testing, but others have described poorer performance in children with low IQ.[30,114]

Szabo and Wyllie[114] and Westerveld et al.[119] found that greater success on memory testing is associated with injection ipsilateral to the epileptogenic region, but, in fact, performance may be related not only to the site of epileptogenicity but also to whether speech is represented in that hemisphere.[30] Williams and Rausch[126] showed that memory performance was more likely to be impaired after injection of the language-dominant hemisphere (when the epileptogenic region was also within that hemisphere), although this effect again appeared to interact with age, being more pronounced in children <13 years old.

One difficulty in determining the predictive value of memory testing in children is the existence of wide differences across centers in the nature of the protocols and in the criteria used for determining whether a test has been passed or failed. In this respect, the issues are very similar to those encountered in the literature with adult patients.[18] For example, cutoff scores used for determining a pass range from 33% to 67% correct by either recall or recognition.[32,114,126] Szabo and Wyllie[114] found much lower overall retention scores in children than in adults, even with a modified pediatric memory protocol, and suggested that a lower passing score may be appropriate for children. Their finding was not confirmed by Westerveld et al.,[119] who showed that children <13 years of age did not obtain scores different from those of adolescents or those expected of adults. Patient characteristics other than age may have produced the differences in the former study. The materials used in the test may also be of importance. Real objects as stimuli during the IAP memory test are superior to mixed stimuli (a combination of verbal and nonverbal stimuli such as photographs, line drawings, printed words, geometric designs, arithmetic problems, and objects) for predicting side of seizure onset.[65] This differential sensitivity was most pronounced among younger children.

In comparison with the adult literature, the field is in a fledgling state with respect to using the IAP to predict laterality of seizure focus or the possibility of memory decline after surgery. Several studies have been conducted on the validity of the procedure with respect to identification of lateralized pathology identified with seizures. When the memory data are used in this way, the scores for the two hemispheres are compared to determine which is less efficient in the performance of the test. Westerveld et al.[119] demonstrated that the resulting laterality scores correctly predicted side of surgery in 91% of a group of children and adolescents with seizure foci in the temporal lobes. Szabo and Wyllie[114] found that, among children who failed memory testing after one injection and passed the other, the failed injection was always contralateral to the hemisphere with the predominant epileptogenic focus. In a much larger sample of children from a multicenter study, Lee et al.[63] found that asymmetries predicted side of seizure onset using group data, but prediction was less robust on an individual case level, particularly among children with left temporal-lobe epilepsy. In this group, prediction was better among children with older age of seizure onset. The memory asymmetry score correctly classified laterality of seizure onset in 69% of all cases (left and right hemispheres, temporal and extratemporal foci), a classification rate lower than is typically observed in adults, suggesting that IAP memory asymmetries should be interpreted cautiously for this purpose. It is interesting that another multicenter study showed that the memory asymmetry scores were predictive of seizure outcomes; 75% of children with asymmetries consistent with the seizure focus became seizure free after surgery, in contrast with 56% whose memory score asymmetries were inconsistent with the laterality of the seizure focus.[64]

The use of the IAP in children to predict memory decline after surgery has been addressed in only one study. Lee et al.[66] found that asymmetry scores were not related to change in performance on visual/figural memory tasks or to recall of a word list; however, more children with asymmetry scores showed improvement on story recall after surgery compared with those without memory asymmetries. This finding needs to be treated cautiously due to a small sample, but it suggests that further research should be done. Prediction of the possibility of memory change after surgery is clinically important for children, in whom new learning and school performance are of utmost significance.

Comparison to Other Approaches

Methodologic limitations to the predictive ability of IAP memory testing have led to the development of other techniques to determine the risk for postoperative global amnesia. One of these is electrical stimulation of the hippocampal region with memory testing.[29,124] However, this technique is only applicable in those few patients who require hippocampal depth electrode implantation for adequate identification of the seizure onset zone. The same limitation holds true for limbic TL evoked potentials.[27,81] Although noninvasive techniques like SPECT, PET, hippocampal MR-volumetry, MR-spectroscopy, and neuropsychologic testing have proven very useful in the prediction of the side of seizure onset, it has not been adequately tested or validated whether they can predict postsurgical amnesia or degree of postoperative material-specific memory loss.[14,39,61,62,81,112]

Functional MRI (fMRI) and, to a lesser extent, PET activation studies are also being developed as techniques that may serve this purpose. Several studies suggest that fMRI[1,45,59] and PET[33,34,35] have a good potential for taking on this role. These methods need to be validated in a larger number of patients with more variable pathology and should be compared with the IAP. The best prediction of memory outcome may require different tasks or batteries of tasks during fMRI with dominant and nondominant TLE patients. Thus the use of fMRI to predict postoperative memory outcome may eventually provide a satisfactory alternative to the IAP as part of the routine presurgical evaluation, but at this point it remains a future possibility.

Testing cerebral dominance with a number of other methodologies—prominent among them fMRI, PET, transmagnetic stimulation (TMS),[57] and magnetoencephalography (MEG)—has been attempted for a longer time and has reached a higher degree of success. In a study by Woermann et al.,[127] determination of language dominance using fMRI was compared with results of the IAP in 100 patients with different localization-related epilepsies. Those authors found 91% concordance between the two tests. The overall rate of false categorization by fMRI was 9%, ranging from 3% in left-sided temporal-lobe epilepsy to 25% in left-sided extratemporal epilepsy. Language mapping using MEG has also been compared with IAP. A study of 100 patients by Papanicolaou et al.[91] showed 87% concordance between MEG and IAP and a high sensitivity for MEG of 98%. However, selectivity was 83%, reflecting the tendency for MEG, as for fMRI,[117] to find some language on the nondominant side in cases in which IAP does not. A relative weakness of MEG is that most work has been on receptive language and thus posterior language areas (e.g., see Lee et al.[60]); more work is needed on expressive language to identify anterior language areas.

We conclude that language mapping with fMRI or MEG might reduce the necessity of performing an IAP to assess hemispheric dominance for language, especially in TLE and especially in straightforward cases in which language is all on the left or all on the right. In cases of discrepant findings, such as those reported for IAP and fMRI by Kho et al.,[54] disagreements might be solved by electrocortical stimulation mapping in the awake patient.[54,90] Finally, should fMRI become the standard for evaluation of language dominance, it is highly likely that there will still be certain patients for whom an IAP will be necessary. For example, some patients will not be testable by fMRI because they are too claustrophobic or too obese to go into the scanner, and some patients will have an uninterpretable or an unreliable result after being scanned successfully.

Thermal inactivation, or cooling, of brain[4] is another method for studying reversible brain dysfunction. Various groups examined the effects of localized brain cooling in epileptic patients, mainly with a view toward the alteration of EEG activity and the effects on local spiking, whereas Flanigin et al. in Georgia used intraoperative thermal inactivation of the hippocampus in 33 patients to predict amnesia following temporal lobectomy.[24] Although they reported that their technique of hippocampal cooling with memory testing can be useful in selected cases, even at their center hippocampal cooling is no longer performed. Intraoperative functional mapping, especially speech mapping in the awake patient, is another approach used to tailor surgical resections according to the individual functional organization of the brain.[86,87,88]

Advantages

Intraarterial anesthetic procedures yield a nearly instantaneous result because an IAP can be interpreted immediately on completion of the second injection (both hemispheres tested). Conclusions about cerebral dominance can usually be made without ambiguity, and although memory results are less frequently unambiguous, solid conclusions about memory function can also be made in most cases. The brief reversible lesion provided by IAP gives a valuable preview to postoperative function that cannot be obtained by other means, including the techniques of intraoperative cooling and electrical stimulation, which affect very limited regions of brain compared to the gross hemispheric IAP effect. Because of its wide-ranging effect, one should expect the IAP to predict the maximum possible deficits that might result from surgery.

Limitations

The possible advantage of the IAP that it is likely to predict maximum possible deficits can be viewed also as a limitation because IAP memory testing might be an overly sensitive procedure that results in an excess of false-positive results[69,85] (but see McGlone and MacDonald[78]). In addition, the IAP yields a certain number of uninterpretable tests, especially for memory, because the sudden loss of function in one hemisphere sometimes results in confusion and obtundation that persists until too late to carry out valid behavioral testing. This latter problem does not exist in a new variant on the IAP (the etomidate Speech and Memory test discussed earlier) and to some extent in the selective amobarbital procedures. Furthermore, since about 1998 it has become evident that amobarbital injection sometimes has no effect or a reduced effect. Although the first hypothesis regarding the reason for this was that there had been a change in the drug itself, a source was found by Bookheimer et al.,[9] who showed that the anesthetization failures were occurring in patients who were taking antiepileptic drugs (AEDs) with carbonic anhydrase–inhibiting properties, in particular topiramate and zonisamide. The most frequent occurrence was in association with topiramate, and one patient showed reduced anesthetization when the IAP was performed 5 weeks after discontinuation of that drug. The authors therefore recommended that patients be tapered off these specific AEDs for at least 8 weeks prior to IAP. Given that it has been shown that patients who undergo IAP while taking topiramate show greater memory deficits than those who are not taking it,[55] discontinuing that AED before attempting an IAP is an important concern.

That there is no universally accepted and standardized IAP memory-test procedure may be considered a limitation, given that techniques of injection and scoring criteria differ among centers.[101,109] In addition, the fact that IAP lateralizes language but does not localize speech areas within a hemisphere is a limitation, and when one needs to know how the epileptogenic zone overlaps with language areas, language-mapping techniques have an advantage over IAP. Finally, the fact that the IAP is invasive must be taken into account, especially if alternative, noninvasive procedures become available.

Complications

In the hands of skilled specialists in experienced centers the complications of IAP and selective amobarbital tests are relatively low. However, by nature they carry an inherent risk. This risk must be weighed against the anticipated beneficial gains. Transfemoral carotid angiography is associated with complications that include thromboembolism and stroke (0.5%–1%), allergic contrast medium reactions (1/40,000), and local complications of femoral puncture.[96] In Rausch et al.'s survey of 68 epilepsy centers, the morbidity rates for the standard IAP were reported to range from 0% to 5%, with the majority of centers (61%) having experienced no complications.[101] Accidental injection of hypertonic saline during an IAP was associated with mortality in one case, and another mortality was associated with the angiography itself.[96] Because selective amobarbital procedures are relatively infrequent, less information is available about complications from those procedures. Petersen et al.[95] reported complications in 3 patients in a series of 59 who had undergone the posterior cerebral artery procedure, and, based on this relatively high rate, they and others have discontinued its use.[49] In Zürich, the center with the largest series of selective amobarbital tests, no complications have occurred (H.-G.Wieser, unpublished data, 2005).

Cost

In the context of the total cost of epilepsy surgery, the cost of an amobarbital test is minor. If the procedure is scheduled to be performed while implanted intracranial electrodes or attached scalp electrodes are already in place, there are no additional costs for an extra hospitalization or for EEG monitoring done during the IAP. Angiographic techniques that use several special catheters and the availability of a sophisticated angiography system can add to the costs. The main cost factor, however, is the availability of a well-trained team consisting of a neuroradiologist experienced in angiographic catheter procedures, neuropsychologists, an electroencephalographer or an EEG technician. and a nurse. A comprehensively monitored amobarbital study might therefore amount to $1,000 to $1,300 U.S. according to a detailed cost estimate published in 2004[83] or to as much as $1,500 to $2,000 U.S. according to calculations based on costs for 43 epilepsy surgery cases in Zürich, where selective procedures are used. IAP costs usually represent <5% of the total cost of a presurgical evaluation, however, and <3% of the total cost of a surgical case. Moreover, when the procedure is performed only in patients considered to be at risk, an IAP might not contribute more than 0.4% of the total cost incurred by an epilepsy surgery center.

Summary and Conclusions

The IAP is used to determine cerebral dominance for language before operation in patients who will undergo brain surgery. It is also used as a screening device to predict, and thus, it is hoped, to prevent, severe postoperative memory losses in patients who will undergo a unilateral resection from a temporal lobe. In addition, comparing the IAP memory results from the two hemispheres can indicate the dysfunctional side, providing confirmatory evidence (or not) for conclusions about the site of seizure focus.

The literature on the use of the IAP with children indicates that it provides valid information on language lateralization and will continue to be a valuable tool in identifying the variables that determine reorganization of function. Its usefulness in assessment of memory is less well established, with best results obtained in older and brighter children.

Although the IAP and its variants are invasive, complications are rare, and these procedures provide quick and reliable information about cerebral dominance for language and useful information about memory function. Despite the growth of other techniques such as PET, MEG, and functional MRI, the IAP—including the selective procedures in some centers and variations such as the *e*SAM—continues to play an important role in decisions about a patient's surgical management.

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Chapter 174

Intraoperative Functional Mapping

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Introduction

This chapter describes established intraoperative methods for identifying functionally important cortex during resective epilepsy surgery. Several other chapters are complementary. A promising new technique for intraoperative functional localization, optical imaging of the "intrinsic signal," is discussed in Chapter 86. Like extraoperative methods for functional localization discussed in Chapter 175, the established intraoperative methods rely on electrical stimulation mapping. Although the technical details of stimulation mapping differ in the different settings, several controversial issues concern both methods. How reliable is stimulation mapping in identifying areas that must be spared in a resection to avoid a functional deficit? When is stimulation mapping required for planning a cortical resection? Compared to intraoperative methods, extraoperative methods expose the patient to additional risks (including an extra craniotomy) and require a substantial additional investment of health care resources.[23] An additional area of controversy, then, is when the additional risk and cost of the extraoperative method are justified.

Application of an electric current to the cortical surface has a variety of effects, exciting both neurons and *en passage* fibers and also blocking their function, effects that can produce excitation and inhibition locally or at a distance.[37] Thus, the effects of stimulation cannot be easily predicted physiologically but rather must be determined empirically. In the quiet patient, responses are readily evoked from primary motor and somatosensory cortex (localized movements or dysesthesias), somewhat more rarely from primary visual cortex (localized phosphenes), and quite infrequently from primary auditory cortex. There are usually no responses from stimulation of other cortical areas at currents below the threshold for afterdischarges, although in patients with temporal lobe epilepsy, larger currents associated with afterdischarge will occasionally evoke the interpretive and experiential responses studied by Penfield et al.[8,20,34] However, if the patient engages in an ongoing measure of language, stimulation of some dominant hemisphere cortical areas outside primary cortices will disrupt language performance. Presumably the predominant effect of stimulation at those sites is a disruption of function, probably by depolarization blockade. This is the technique of intraoperative stimulation mapping of language developed initially by Penfield and Roberts.[35]

The choice of language measure to use with stimulation mapping is somewhat controversial. Penfield used object naming. This also has the advantage as a screening measure for language function that all aphasic syndromes include deficits in naming. This is the language measure most often used by the author.[31] However, reading has also been used as a screening test, particularly with extraoperative stimulation.[18]

The reliability of stimulation as a technique for identifying functionally important areas depends on how localized the effects are and how reliably those effects predict the effect of resecting that cortex. Intraoperative imaging of the changes in the "intrinsic signal" indicating where the stimulating current is altering neurons has shown that with bipolar cortical surface stimulation below the threshold for afterdischarge, as used by the author, the changes are confined to tissue between the electrodes in both man[11] and animals.[10] Behaviorally, both sensory-motor and language effects of intraoperative stimulation are usually localized on a scale of millimeters to a few centimeters. Threshold sensory-motor effects with intraoperative cortical stimulation are usually confined to a few millimeters on each side of the central sulcus, showing the classical homuncular pattern of localization. Sensory-motor changes with extraoperative stimulation are often evoked from a wider area.[17] Sites where intraoperative stimulation repeatedly evokes naming errors are often confined to several separate cortical sites, each 1 to 2 cm^2 in extent, often with sharp boundaries (Fig. 1).[31] Extraoperative stimulation mapping of language has often shown changes from somewhat wider areas.[16,32]

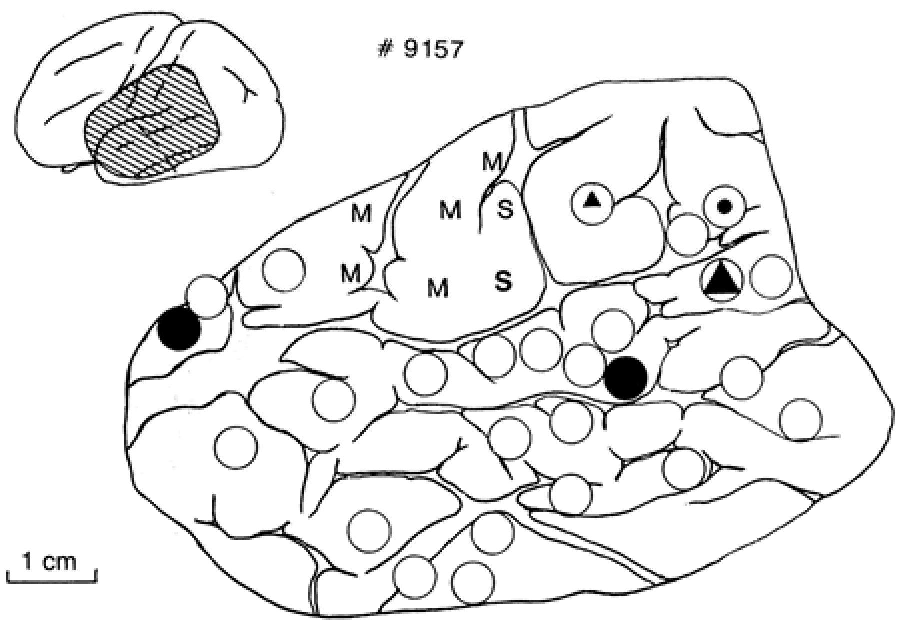

FIGURE 1. Location of areas essential for language in an individual, based on intraoperative electrical stimulation mapping during naming in two languages. *Circles* are sites of stimulation. *Filled circles* are sites of repeated errors in naming in English, this patient's primary language. *Small circle* is site with a single error out of three stimulations during English naming. No errors in naming the same pictures in Spanish were made at these sites. *Large triangle* is site with repeated errors in naming the same objects in Spanish. *Small triangle* is site with a single error out of three stimulations during Spanish naming. No errors in English naming were made at these sites. The patient was a teacher of English to Spanish-speaking students. He was fluent in both languages. Note that sites essential for each language occupy only a small portion of the classical language areas and that essential areas for the two languages are separate. (From Ojemann GA. Different approaches to resective surgery: standard and tailored. In: Theodore W, ed. *Surgical Treatment of Epilepsy*. Amsterdam: Elsvier; 1992:169–174, with permission.)

Evidence from several studies has shown that perisylvian sites identified as important to naming by intraoperative stimulation mapping can predict the language effects of a resection. In resections for epilepsy, Ojemann and Dodrill[27] found that when anterior temporal resections came within 2 cm along a continuous gyrus of a site where stimulation evoked repeated object-naming errors, testing with a sensitive aphasia battery 1 month after operation showed subtle language changes that were not present when the resection had not come within 2 cm and that were not related to the size of the resection, the degree of seizure control, or the patient's preoperative verbal abilities. In temporal lobe tumor resections, Haglund et al.[9] found that when the resection came within 5 mm of a site showing repeated naming errors with intraoperative stimulation, about one third of patients had a permanent postoperative clinically evident aphasia, whereas when these sites were 15 mm or more from the margin of the resection, no patient had even a temporary clinically evident aphasia. Very large resections in classical language cortex have not been followed by postoperative aphasias when stimulation mapping demonstrated all essential sites for naming elsewhere.[31]

Thus, stimulation and lesions seem to identify the same cortical sites as essential to language. Interestingly, surface cortical stimulation predicts effects of resections that include both surface and buried cortex, suggesting that essential language areas are rarely if ever located only in buried cortex.

On the other hand, stimulation in the dominant hemisphere outside of the perisylvian area evokes repeated changes in language measures in areas where resection does not lead to a permanent language deficit. These include the supplementary motor area in the superior frontal lobe,[7,24,35] where resection of sites with repeated naming or reading errors often results in a dramatic initial deficit (patients may be mute), but with rapid resolution, so that there is little or no permanent language change.[39] Similarly, repeated language errors have been evoked by stimulation of basal temporal cortex,[18] but resection of this area rarely is associated with a persisting language deficit.

Indications

The location of eloquent areas is mainly a concern in planning cortical resections in central portions of the hemisphere and, in the language-dominant hemisphere, posterior frontal and posterior temporal-inferior parietal areas. Although language is usually lateralized to the left hemisphere, statistically independent of handedness,[48] when there is any question about unusual language lateralization, this should be established preoperatively with the intracarotid amobarbital perfusion test.[46] Eloquent areas can be identified either anatomically or functionally. However, the anatomic landmarks that identify rolandic cortex, vertically oriented gyri with a “U” shape at the sylvian fissure, are often hard to discern through the intact pia and may be displaced by tumors. Common anatomic landmarks for avoiding language areas in the dominant hemisphere are anterior to the pterion for frontal resections and, for temporal resections, the line of rolandic cortex or the vein of Labbe or 4 to 4.5 cm from the temporal tip, sparing superior gyrus.

Electrical stimulation mapping often localizes language to several quite focal perisylvian areas in an individual patient, but these sites are in somewhat different places in different patients (Fig. 2).[31] This variability in exact location of language areas is such that only the most posterior portion of inferior frontal gyrus, immediately in front of face motor cortex, is essential for language in a large proportion of patients. Elsewhere, including any portion of the entire Wernicke area, essential language areas are present in not much more than a third of patients. This substantial variability is one of the strongest arguments for mapping function in each patient rather than depending on anatomic landmarks derived from population studies. Use of anatomic landmarks rather than individual stimulation mapping to localize language unnecessarily restricts resections for many patients while not avoiding essential language areas in a few patients.[31] Thus, stimulation mapping is of value in safely maximizing resections in posterior frontal and posterior temporal lobes, whether the resection is for epilepsy or for a structural lesion including tumors and vascular malformations.[2]

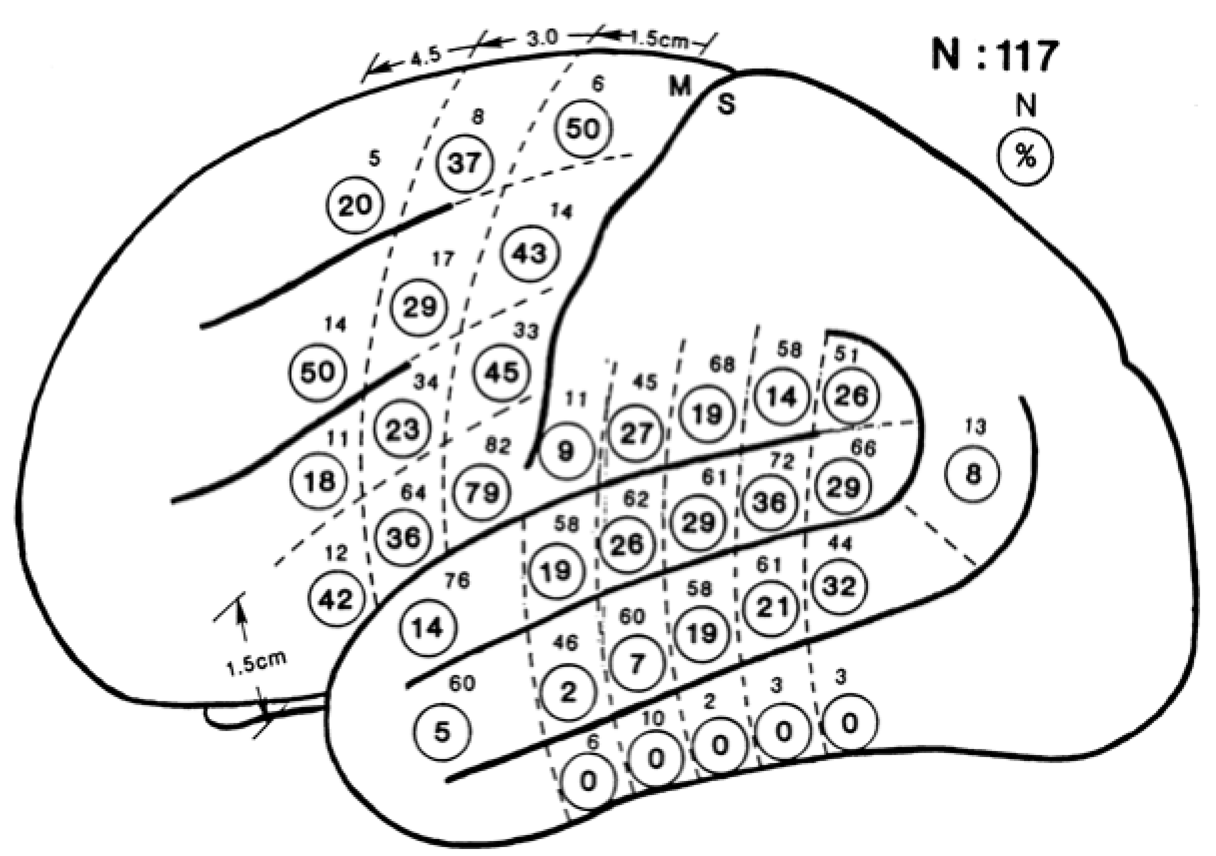

FIGURE 2. Variability in language localization in left hemispheres of 117 patients, all left dominant for language based on intraoperative electrical stimulation mapping. Maps of individual patients were aligned to common anatomic landmarks, and the cortex was divided into the arbitrary zones indicated by the *dashed lines.* The upper number in each zone is the number of patients with samples of stimulation effects on naming errors during stimulation. Substantial variability in location of essential language areas between individuals is evident. (From Ojemann GA, Dodrill C. Verbal memory deficits after left temporal lobectomy for epilepsy. *J Neurosurg.* 1985;62:101–107, with permission.)

Whether location of language areas is important to planning anterior temporal resections for epilepsy in the dominant hemisphere is controversial.[32] Stimulation mapping has occasionally identified sites related to language within 3 cm of the temporal tip, even in middle temporal gyrus. There are no randomized studies to resolve this issue, but a report of consecutive series of anterior temporal lobectomies with or without identification of language areas suggested that there was a slightly greater risk of a postoperative language deficit in the series done without identification of language areas, although the difference was small.[1,13]

Technique[1]

Motor cortex can be identified under either general or local anesthesia with intraoperative stimulation mapping, although motor mapping under general anesthesia requires a technique in which the patient is not paralyzed, and the resulting motor map is usually rather crude, with responses only at large currents; the extensive area devoted to tongue movement usually cannot be identified. An alternative method for intraoperative identification of rolandic cortex under general anesthesia is recording of somatosensory-evoked potentials (SSEPs).[47] However, with this technique, too, identification of face and tongue representation is difficult, and the author finds SSEP recording more time consuming than stimulation mapping. Detailed intraoperative mapping of rolandic cortex and intraoperative mapping of language require that the patient be awake, under local anesthesia, for that portion of the operation. Having the patient awake for part of the operation also allows recording of the electrocorticogram (ECoG) without alterations induced by general anesthetic agents. Thus, we discuss the technique of awake craniotomy with modern intravenous propofol anesthesia, followed by the technique of intraoperative stimulation mapping.

The advent of propofol intravenous anesthesia has made "awake" craniotomy much easier for both the patient and surgeon.[42] About the only demand now made on the patient is that he or she be able to hold still for 1 to 2 hours while awake. Thus, the technique can easily be used in children aged 12 or older and most adolescents and adults. It can also be safely used in the presence of an intracranial mass, although the brain will

be slightly "tighter" than is usually observed with modern endotracheal anesthesia, and it may be necessary to be slightly more aggressive with the use of intravenous osmotic agents in that setting compared to general anesthesia.

We now use only the lateral position with propofol. With that position we have not had difficulties maintaining an airway; those problems have occurred in patients in the supine position. The patient is positioned while awake, with particular attention to his or her comfort. The head rests on a foam "doughnut"; skeletal fixation is not used. Propofol anesthesia is then induced intravenously. Once the patient is asleep, a local anesthetic field block is placed, using a mixture of equal volumes of 0.5% lidocaine and 0.25% bupivacaine (Marcaine), both with 1:200,000 epinephrine. Propofol is not a particularly good analgesic, so the "asleep" patient will often show more reaction to the placement of this block than will an awake patient. Thus, we use the same technique, making the first injections slowly through a 30-gauge needle at sites near the major scalp nerves. Use of small amounts of intravenous fentanyl is of value in reducing responses to placement of the block. If the incision is to extend to the root of the zygoma, the insertions of the temporalis muscle are also infiltrated. The scalp incision and craniotomy then proceed in the usual manner. Once the dura is exposed, dural pain sensation is blocked by intradural injection of small quantities of the local anesthetic on each side of the middle meningeal artery, using the 30-gauge needle. A clamp is placed on the skull at the edge of the craniotomy, not only to provide a place to attach ECoG recording equipment, but also to provide a handle to control the head if the patient becomes restless.

At this point, all pain-sensitive structures have been blocked with local anesthetics, and the noisy bone removal has been completed, with the patient asleep. The lateral surface of the brain, of course, is insensitive to pain or touch. We usually awaken the patient before opening the dura, unless that opening is expected to be very tedious, for example, when extensive pial–dural adhesions are anticipated. Patients are usually able to converse within 7 to 12 minutes of stopping the propofol. At that time, they are reminded that they are in the operating room and should not move their head without first asking. The longest period before awakening in our experience has been 30 minutes. The patient usually awakens abruptly without a period of confusion, a major advantage of propofol. Propofol is also not a particularly good antiepileptic agent. We have very occasionally observed clinical signs of spontaneous seizures in severe epileptics asleep with propofol. Short-acting benzodiazepines or barbiturates may be needed to control those seizures but will interfere with subsequent recording and stimulation.

Several technical factors are important to successful stimulation mapping: (a) mapping is difficult beyond the edges of the craniotomy. The exposure should therefore be generous, to include likely locations of functionally important areas. (b) Sites where language is located must be identified, for only then does the absence of language changes indicate cortex that can be resected with a low risk of aphasia. This also requires that the exposure include areas that are likely sites for language. (c) The stimulating current must be sufficiently large to alter function in cortex but not so large as to evoke a seizure. (d) The patient must make few errors on the language measure in

the absence of stimulation. Only a few samples of stimulation effect at any one site can be obtained. If there are many errors in the absence of stimulation, errors during stimulation may be random events and not related to stimulation effects at that site. The author regularly obtains three samples of stimulation effect at each site. For errors on all samples to have less than a 5% probability of being random events, the error rate in the absence of stimulation must not exceed 40%. Thus, stimulation mapping is of limited value in severely aphasic patients. Patients with mild aphasias may not be able to name with a low enough "control" error rate but may be able to read single words or can be continuously engaged in conversation during stimulation, although neither technique seems to be as satisfactory as naming for localizing language.

The only parameters of stimulation varied in the author's technique are the current level and train duration. All stimulations use 60-Hz trains of biphasic pulses, each phase 1 msec in duration, delivered from a constant-current stimulator across 1-mm stainless steel bipolar ball electrodes 5 mm apart. Most other contemporary stimulation techniques use somewhat shorter pulses, often 0.3 msec for each phase, and some use 30-Hz frequency but are otherwise similar. Levels of electrical charge that produce histologic changes in tissue have been extensively studied in animals (see reference 32 for review). Histologic examination of stimulation sites in resected human cortex does not show any changes in the author's patients (unpublished data). Moreover, patient performance in the absence of stimulation does not deteriorate after repeated stimulations. These findings both indicate that stimulation at the indicated parameters does not permanently alter cortex.

After the patient is awakened and the dura opened, ECoG recording is undertaken. At the completion of this recording, the afterdischarge threshold is established for the area of cortex to be sampled with language mapping. A small current, commonly 2 mA between pulse peaks, is applied for 4 seconds to cortex adjacent to an ECoG electrode; in the case of temporal exposures, thresholds are first determined for more posterior electrodes. This stimulation is repeated at increasing currents until afterdischarges are evoked, the patient reports a response, or an arbitrary upper limit on current is reached, usually 10 mA between pulse peaks for direct cortical stimulation. The current is then reduced 2 mA below that afterdischarge threshold, and the threshold at the next most anterior electrode is determined. After all electrodes are sampled, a process that requires 5 to 10 minutes, a current is selected for mapping that is at the lowest threshold. The main reason for establishing the afterdischarge threshold is to avoid evoking a seizure. A brief train of afterdischarge after a stimulus train is usually not a problem, but afterdischarge thresholds are occasionally <2 mA. Using larger currents in such patients is likely to evoke a seizure. However, using that small a current in other patients with higher thresholds may not alter cortical function and so may not provide a reliable mapping.

Sensory-motor cortex is then identified. The author uses stimulus trains beginning at 2 mA and asks the patient for any evoked sensory responses while an assistant looks for any overt movements. Current is increased in 1-mA intervals until responses are obtained. The site of each positive response is identified with a sterile numbered ticket. Electromyographic responses to single pulses have also been used to identify motor areas. Following identification of rolandic cortex, sterile numbered tickets are placed across the remaining cortex that is to be sampled during naming. The patient then begins the naming task. The author uses slide pictures of common objects to elicit naming, showing slides at 4-second intervals on a back-projecting slide projector. Stimulation is applied to one of the sites identified by a ticket at the appearance of the second or third slide. An assistant records the patient's responses and the number of the site stimulated. Another site is stimulated two or three slides later, until all sites have been sampled once. The process is then repeated in a different order two more times, so that stimulation effects on naming have been determined three times for each site. Sites with repeated naming errors are considered essential for language. With this technique, stimulation effects on naming can be determined for 20 sites in 20 minutes. Stimulation mapping with other language measures follows this same general plan, although the relation of applying the current to the behavioral measures may vary, especially in assessing memory. Our specialized and rather time-consuming protocol for assessing cortical stimulation effects on the input, storage, or retrieval phases of recent verbal memory has been published.[27]

Comparison to Other Approaches

For some patients, extraoperative methods are the only option for stimulation mapping. These include patients requiring language mapping who cannot cooperate with an awake craniotomy, such as young children, or when recording of seizure onsets is needed to plan the resection, as when there are widespread or multifocal interictal spikes on scalp electroencephalogram (EEG), and particularly if these overlap eloquent areas. Then it is often of value to establish the relationship between the site of seizure onset and the eloquent areas. However, use of chronic electrode techniques exposes the patient to two operations, one to place the electrodes and one to remove them and undertake any indicated resection. Both the risk, particularly that of infection, and the total investment of health care resources are increased when larger arrays of chronic electrodes are used, as is required for detailed mapping. Extraoperative stimulation mapping involves an additional investment of 1.5-fold or more over the amount required for a resection including electrocorticography, intraoperative stimulation mapping, and postoperative care.[23] In addition, although there is more time for extraoperative stimulation mapping, the anatomic resolution of that technique seems to be less than that with intraoperative stimulation because of both uncertainties about the relationship of the electrodes to the cortical surface with the extraoperative technique and the inflexibility of the electrode array, preventing mapping beyond its edges.

If chronic electrodes are to be used in patients who could alternatively be managed with awake craniotomies, an improved outcome must be present to justify these increased risks and costs. That is *not* the case for adolescents and adults who require only mapping (as in lesions near eloquent areas) or who do not require intracranial ictal recording (as with patients with epilepsy and a focus clearly established by noninvasive preoperative evaluation). In the author's view, these patients are best managed with awake craniotomy.

Functional Magnetic Resonance Imaging and Electrical Stimulation Mapping

Preoperative functional magnetic resonance imaging (fMRI) mapping of language is an emerging approach that may augment and in some cases substitute for cortical stimulation mapping (Chapter 83). Numerous studies at the group level (i.e., representing averaged language maps across a cohort of volunteers or patients) have proven effective in identifying the organization of language functions in the brain and in elucidating the nature of this organization. In patients with epilepsy, such studies have been few in number and most have emphasized

hemispheric laterality. Rarely, however, is hemispheric dominance the critical question in subjects undergoing electrocorticography; rather, the goal here is to locate eloquent areas *within* the hemisphere. Few studies to date have attempted to demonstrate the accuracy of fMRI in localizing critical language areas within the hemisphere in comparison to the “gold standard” of electrocorticography, at the single-subject level. If fMRI is ever to substitute for cortical stimulation, a very high degree of reliability within subjects must be demonstrated, particularly in those with anomalous language laterality. Patients with epilepsy are more likely to have atypical language organization; thus, to be useful, fMRI studies will have to include sufficient numbers of language-reorganized subjects, with electrical stimulation mapping confirmation, in order to prove its worth as an alternative to direct cortical stimulation. Furthermore, the studies must be reliable for each individual, confirmed with appropriate sensitivity and specificity measures. An additional complication with developing fMRI for intrahemispheric language mapping is that different techniques, including image acquisition parameters (field strength, pulse sequences), activation tasks chosen, and analysis approaches, can yield strikingly different results. Thus, a validated fMRI approach in one center may not support the utility of fMRI in another center that uses different experimental paradigms or technical procedures. To date, only a few studies have attempted to meet high standards of fMRI sensitivity and specificity profiles using electrical stimulation mapping as a validation tool.

One study examining fMRI in arteriovenous malformations reported sensitivity and specificity of a standardized fMRI approach with electrical stimulation mapping validation. Pouratian et al.[36] used three activation tasks, deriving “conjunction maps” showing brain regions activated across tasks with an expressive component (object naming and reading comprehension with naming) and a comprehension component (reading comprehension and auditory comprehension). Conjunction maps show regions of the brain that are significantly activated for each task included in the analysis (a logical “AND” operation rather than an average). Optimal results for frontal regions were found using expression maps, while temporal and parietal regions correlated best with comprehension maps. Activation maps for each subject were projected onto MRI-derived brain surfaces, which were in turn registered to intraoperative photographs of brains labeled with tags following electrocorticography. For each subject, the authors calculated the distance between the external boundary of the fMRI activation and a radius around the center of the electrical stimulation mapping tag. Both positive and negative areas were compared with radii of 2.5, 5, and 10 mm. In 17 patients, the sensitivity of finding frontal and temporal or parietal regions with expression and comprehension maps, respectively, were 100% (frontal-expression) and 90% (temporal/parietal-comprehension) at a 5-mm diameter; given a 10-mm radius, sensitivity of both regions was 100%. fMRI was less specific, however, with 66% frontal-expression specificity and 81% temporal/parietal-comprehension specificity at a 0.5-mm radius. This result is characteristic of fMRI, which effectively measures all brain regions involved in, though not necessarily essential to, task performance. The margin of error—0.5 to 1 cm—is relatively large and likely reflects the additive errors across the various transformations, including functional to structural MRI misregistration, errors in matching fMRI to intraoperative photographs, distortions due to the local magnetic fields in MRI, and displacement of the brain during surgery, to name a few. One report indicates that intraoperative brain displacement may vary by more than a centimeter relative to the skull,[14] though much of this error may be accounted for by adjusting the simple offset from skull to brain surface. While more sophisticated nonlinear image registration techniques can reduce these errors, such as those using extensive manual tracing of cerebral sulci,[45] these are very time consuming and require special training, perhaps impractical for a clinical setting. Nonetheless, by sacrificing specificity, fMRI appeared to be extremely sensitive in revealing significant language areas that correlated with electrostimulation mapping results in the Pouratian et al.[36] series of arteriovenous malformation (AVM) patients.

While the majority of fMRI electrical stimulation mapping comparison studies have focused on AVM or tumor cases, a few have included a large percentage of patients with epilepsy. For instance, Yetkin et al.[49] compared electrocorticography with preoperative fMRI using a range of functions from finger, lip, and tongue movements to counting and word generation in 28 patients with lesions near motor cortex; of these 22 had epilepsy and 13 of the subjects were mapped for language using a word generation task (12 left, one right hemisphere). Of these patients, only one had activation further than 10 mm from the lesion; however, results for smaller diameters were not specified for the language regions. Sensitivity was 100% given a 20-mm diameter, and 87% within 10 mm overall across all tasks (including motor tasks). It should be noted, however, that the slice thickness (10 mm) would be considered unacceptably large by today's standards, and the 2-cm distance required for 100% sensitivity is probably too large for surgical decision making in the absence of correlated electrical stimulation mapping measures (specificity was not reported in this study). Another limitation of this study was the absence of patients with temporal lesions; Pouratian et al.[36] found posterior language regions less reliably identified by fMRI than the frontal regions targeted by Yetkin et al.[49] A more recent study of 13 patients with epilepsy used four different language tasks during fMRI in comparison with electrical stimulation mapping[41]; 11 patients successfully completed electrical stimulation mapping, which identified language cortex in eight of these patients. fMRI sensitivity was 100% in seven of eight patients and 38% in the remaining patient, while specificity was 51%. Overall, the level of predictive validity given these sensitivity and specificity figures of fMRI was too poor to be considered useful (51%). Nonetheless, the authors argue that fMRI may have accelerated the electrical stimulation mapping procedure by guiding the surgery toward likely candidate regions. The small number of subjects, especially those with anomalous language organization by electrical stimulation mapping (*n* = 1), limit the generalizability of these results to a broader sample of patients with epilepsy. Larger series comparing fMRI with electrical stimulation mapping have been conducted on tumor cases in the motor system,[15] but without sensitivity and specificity measures.

In the largest fMRI electrical stimulation mapping series to date, Duffau et al.[5] combined clinical information from both procedures and reported on the long-term outcome of 103 surgical patients receiving both procedures; they found 94% had no deficits (motor or language 3 months postoperatively (10% had actually improved). However, without randomized trials it remains unclear whether the addition of fMRI changed the clinical outcome. In summary, though fMRI is increasingly performed in presurgical patients and has become more widely available to treatment centers, there remains far too little data to consider fMRI as an alternative to direct cortical stimulation in most cases.

Aside from the dearth of data supporting the exclusive use of fMRI for surgical planning, fMRI has an additional disadvantage in epilepsy cases in that one cannot determine the relationship between defined eloquent cortex and abnormal electrical activity determined intraoperatively. Nonetheless, there are several instances in which fMRI may have a clear advantage. One is when subject cooperation during an awake procedure is simply impossible, such as in many children and in patients with excessive apprehension of the procedure. Another is in those patients for whom stimulation at low thresholds

produces significant afterdischarges, particularly when they evolve into seizures during electrocorticography. In cases where functional tissue may be buried deep within a sulcus, electrical stimulation mapping may not show disruption on the brain surface, leading to false-negative results and potential patient harm. One such case was reported recently[40] where fMRI demonstrated an area of activity buried deeply beneath the surface, which electrical stimulation mapping found negative on traditional surface stimulation; however, when the lesion (a tumor) was resected leaving the fMRI-identified area exposed, stimulation produced significant language disruption. fMRI frequently reveals areas of activation that do not reach the brain surface[36]; no studies to date have examined these regions with regard to electrical stimulation mapping, and their significance and frequency are unknown.

Ultimately, fMRI may prove most useful as an adjunct to, rather than a replacement for, electrical stimulation mapping. Rutten et al.[41] argue that a high-quality fMRI may be useful in focusing in on likely language areas, potentially reducing the length of the stimulation procedure. Methods and applications of fMRI for surgical planning and in seizure focus localization are discussed in detail in Chapter 83 of this volume.

Future Directions

Stimulation mapping has been a useful technique for investigation of human cortical organization, particularly for language and memory.[22] Some of those findings also have implications for planning resections very close to eloquent areas. Patterns of localization of perisylvian sites essential for naming differed between men and women, with a subset of women tending to have fewer temporal-parietal naming sites, including a small group who seemed to have only frontal sites.[31] Patients who were verbally brighter tended to have naming sites in middle temporal gyrus; those with poorer verbal skills had sites in superior temporal gyrus. Highly localized perisylvian essential sites for naming have been identified in children as young as age 4.[31]

When perisylvian stimulation effects on different language measures are examined intraoperatively, the general rule seems to be that slightly different cortical areas are essential for different language dimensions. Different sites seem to be essential for naming the same objects in two different languages,[3,21,33,38] including sign and oral languages.[12,19] Different sites are often essential for naming or reading[21,25] and for naming or reading compared to recent verbal memory,[27] generating verbs from nouns, and different semantic categories.[30] In a few special settings, it may be useful to map localization of some of these other functions (e.g., in a patient heavily dependent on a second language or on reading skill). Avoiding cortical sites related by stimulation to recent verbal memory has been shown to be of value in decreasing the likelihood of a postoperative memory deficit in epilepsy patients who “fail” intracarotid amobarbital assessment of memory function.[27,28]

In this context of frequent separation of sites where intraoperative stimulation affects different dimensions of language, the finding of several different dimensions altered at a common site takes on added significance. A particularly striking combination of effects was observed in an intraoperative investigation of the effects of stimulating the same site during identification of phonemes and mimicry of orofacial speech gestures, singly or in sequence.[21,29] Single orofacial speech gestures were altered by stimulation at posterior frontal sites, whereas sequences were altered by stimulation in superior temporal and inferior parietal gyri. Thus, “motor speech” representation extends well beyond the frontal lobe in the perisylvian cortex. At 85% of these same sites, stimulation at the time a phoneme was presented interfered with later identification (in the absence of stimulation), suggesting that stimulation at the site altered some mechanism common to language perception and production. Several possible common mechanisms have been suggested.[17,21,44] Based on the sites where stimulation altered these two functions, as well as effects at these and other sites on naming, reading, and recent verbal memory, a model of the organization of language in perisylvian cortex has been proposed that differs from the classical one derived from lesion aphasiology.[21,22]

In addition, stimulation mapping has been used to investigate localization of visuospatial functions in the nondominant hemisphere, including the identification of sites in posterior middle temporal gyrus that were related to identification of facial emotional expressions.[6] However, to date, nondominant hemisphere stimulation mapping has not been used to plan resections.

Summary and Conclusions

Human cortex has localized areas that are crucial for different functions, including language and motor systems. These areas are often quite localized in any individual, sometimes to locations not predicted on purely anatomic localization criteria. These locations also vary between subjects. Intraoperative electrical stimulation mapping provides a technique for identification of these crucial areas in an individual patient, so that any resection can be planned to spare them, reducing the chances of postoperative functional deficits. Compared to extraoperative techniques for stimulation mapping, the intraoperative method provides somewhat greater localization, less risk, and considerably less resource utilization. Thus, for patients who could be managed with either technique, the intraoperative approach is preferable. Intraoperative identification of crucial language sites requires an awake patient, under local anesthesia. With the use of intravenous propofol anesthesia for craniotomy and placement of local anesthetic blocks, most adolescents and adults can cooperate with intraoperative language mapping. Language mapping also involves careful selection of stimulation current levels to avoid evoking seizures while using a current large enough to alter cortical function. Recent investigations suggest that separate cortical areas may be crucial for many different dimensions of language, including different languages, different linguistic and semantic functions, and recent verbal memory. These studies suggest that under some circumstances, intraoperative mapping of multiple language dimensions may be advisable to reduce the risk of functional deficits after cortical resections.

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Chapter 175

Extraoperative Functional Mapping

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Introduction

Focal cortical resections are now frequently performed in patients with partial seizures or hemispheric tumors. During resection, it is important to spare "essential" cortical regions whose removal would lead to an unacceptable neurologic deficit. Essential areas generally can be spared by limiting the resections to certain anatomic landmarks. For example, a left anterior temporal lobectomy restricted to approximately 4 to 5 cm from the temporal tip will usually spare language cortex.[10,22] There is considerable variability, however, in both the location and the extent of essential cortex in different subjects. The anatomic approach thus does not allow the maximal removal of abnormal tissue, nor does it provide complete security that eloquent cortex is not resected.[24,44]

Electrical stimulation has been used for greater than half a century to accurately map essential cortex intraoperatively. With development of the subdural electrode technology, extraoperative functional mapping became an option, especially in patients in whom invasive ictal recordings are necessary for planning resection. Responses to electrical stimulation have also been used by some epileptologists to confirm the location of epileptogenic tissue. This chapter reviews the role and technique of extraoperative mapping in patients undergoing cortical resections.

Effects of Electrical Stimulation

Electrical stimulation can produce a variety of effects. It may evoke "positive" responses such as localized movements from the primary or supplementary motor cortex, dysesthesia from the somatosensory cortex, phosphenes from visual cortex, or, rarely, "buzzing" from auditory cortex. Formed visual responses may be elicited from secondary visual cortex. Alternatively, stimulation may block function, presumably by sustained depolarization or activation of inhibitory systems. This effect cannot be appreciated in a quiet, resting patient and can only be demonstrated by having the patient engage in specific tasks during the stimulation. For example, stimulation of specific regions of the cortex can interrupt higher cortical functions such as those involved in receptive or expressive language. In areas such as the primary or supplementary motor cortex, both "positive" responses in the form of motor movements and "negative" responses such as arrest of movement or speech can be demonstrated.

In addition to clinical responses, stimulation also can provoke sustained electrographic afterdischarges, which generally last from seconds to minutes after cessation of the stimulus. Because afterdischarges are known to propagate to remote regions, functional localization is often felt to be more reliable when clinical responses are elicited without provoking afterdischarges. It is also generally assumed that the observed clinical response arises from cortex below the stimulated electrode or from the region between two closely spaced bipolar electrodes, an assumption that is supported by evidence from experimental models, although remote effects may occasionally occur.[35,42]

The thresholds for evoking both clinical responses and afterdischarges are usually higher in children than in adults.[2,26,35] This difference is particularly striking in the first 2 years of life. Young children also differ from adults in that they rarely demonstrate clinical responses in the absence of an electrical afterdischarge.[11,26] As illustrated in FIGURE 1, clinical response threshold usually exceeds the afterdischarge threshold in children younger than age 4 to 6 years, although this trend may occasionally be seen in older children and adults as well. This finding has important practical implications because the lack of a clinical response during an afterdischarge does not guarantee the absence of underlying eloquent cortex.[26]

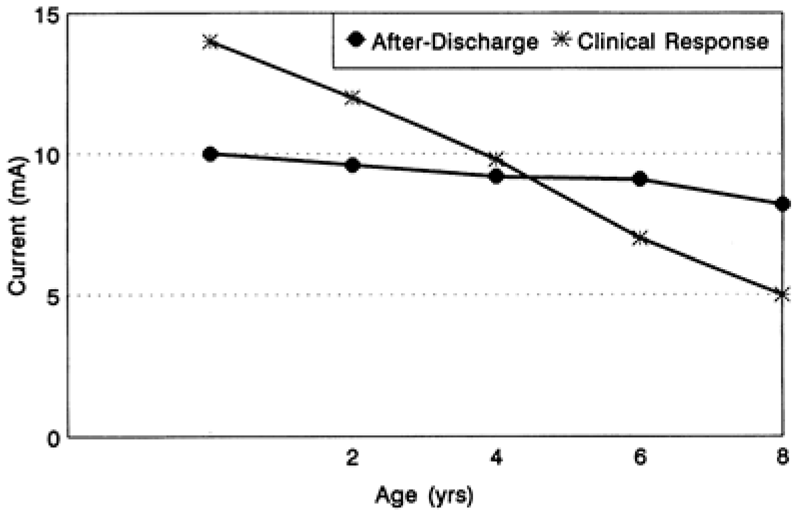

FIGURE 1. Graphic representation of the mean thresholds (mA) for clinical responses and afterdischarges obtained during functional mapping in 20 children (160 electrodes). Note that clinical responses in the very young are obtained only above afterdischarge thresholds.

Indications

Functional mapping is used primarily to define essential cortex during surgeries for epilepsy or removal of structural lesions such as tumors or arteriovenous malformations (AVMs). Once eloquent cortex is precisely defined, the surgical resection can be accomplished to within 0.5 to 1.0 cm from it. In specific cases such as the one illustrated in FIGURE 2, one can assess the risk–benefit relationship and decide to resect a part of the motor cortex involved in the epileptogenic process. Functional mapping thus allows the removal of the most tumoral or epileptogenic tissue possible without incurring significant postoperative deficits.

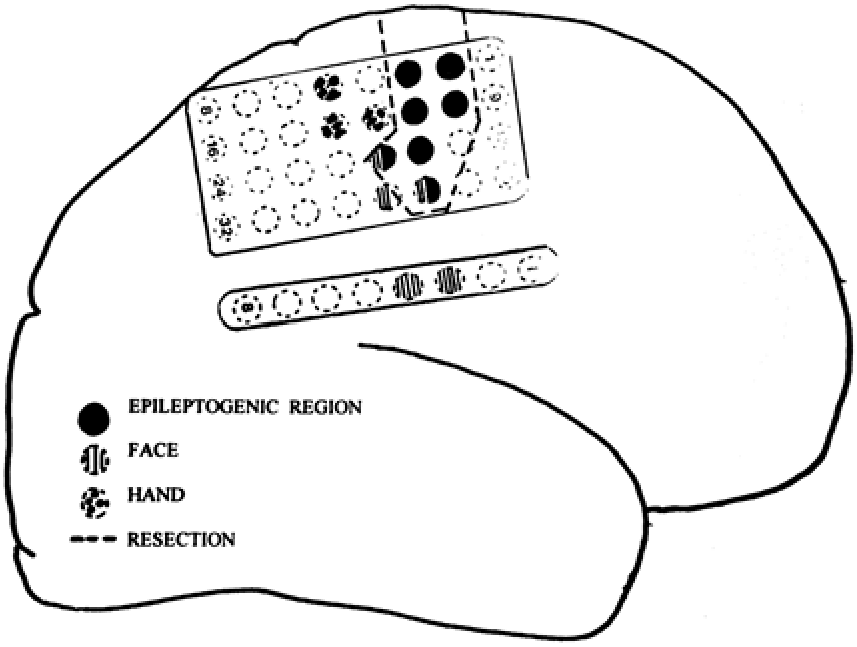

FIGURE 2. Functional mapping of the motor cortex revealed a rather extensive face area. Resection included a part of the face region that was significantly involved in the epileptogenic region defined by ictal onset and prominent interictal spiking. There were no significant postoperative deficits.

Identification of Normal Cortical Function

Mapping is most frequently indicated to define critical cortical regions subserving primary sensorimotor and language functions, which are often very localized in a patient but show considerable intersubject variability. This variability may be even more pronounced in patients in whom underlying lesions such as tumors cause considerable displacement of critical cortex. It is not unusual to find functional responses occurring over wide regions in a patchy distribution (Fig. 3), especially when a mass lesion is present. The thresholds for eliciting responses may also vary surrounding the tumor sites.

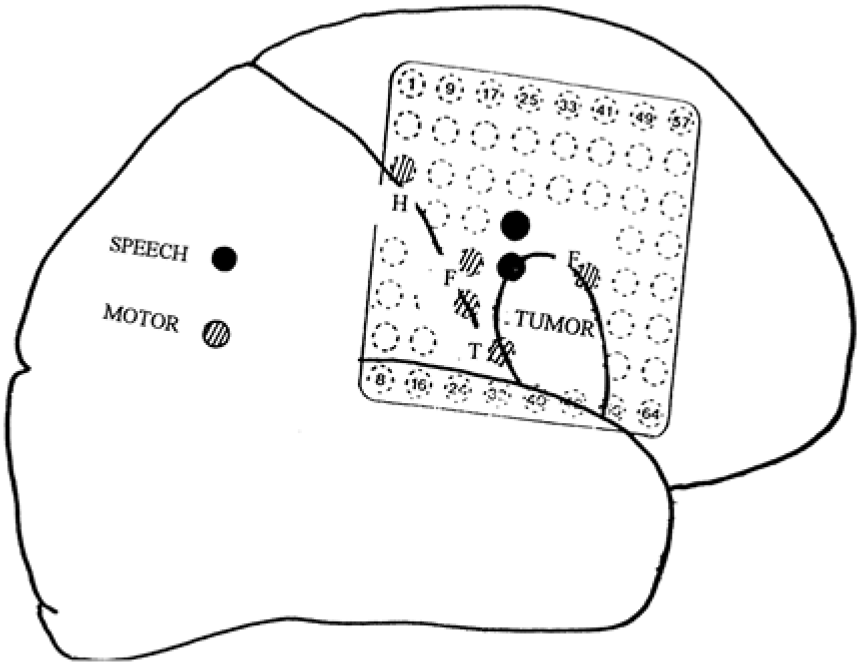

FIGURE 3. Functional mapping in a right-handed patient with a frontal lobe tumor. Language cortex is pushed upward, and motor area for the face (F) is splayed over both the anterior and posterior aspects of the tumor.

Language Cortex

Cortical stimulation of specific areas will block comprehension or other language-related activities such as spoken speech and writing abilities. Although language is most frequently represented in the left hemisphere, right hemispheric language dominance can occur even in patients who are motorically right handed (Fig. 3). The majority of patients will demonstrate language cortex over both frontal and temporoparietal sites. However, in a few patients, essential language cortex is found only over the frontal or temporoparietal regions but not over both.[46]

Localized regions of language cortex can be identified in children even as young as 2 1/2 years old (unpublished observation). Ojemann et al.[46] reported both frontal and temporal language sites in children 4 to 10 years of age, including sites within 3 cm of the temporal tip. These findings indicate that a high degree of language localization occurs very early in childhood and suggest that mapping may have a role in planning resections even while the brain is still plastic.

Frontal Lobe.

In general, the frontal language area is anterior to but contiguous with the bulk of the motor and sensory area, although considerable overlap between these regions can occur.[34,44] It is most frequently located at the posterior aspect of the inferior frontal gyrus or middle frontal gyri or both. However, language functions may occasionally be disrupted on stimulation of inferior frontal regions as far anterior as the pterion or even posterior to the rolandic sulcus. Writing capability is generally represented at sites overlapping those representing verbal speech, but in some patients they may be separate and involve the posterior part of the middle frontal gyrus.[34,37]

Temporal Lobe.

Stimulation of the posterior aspects of the superior or middle temporal gyrus in the dominant hemisphere can interrupt reading, naming, comprehension, and other language-related functions.[36,44] Either single functions or groups of functions may be affected at single sites. Critical language cortex is usually located >4 cm from the temporal tip, although more-anterior locations are occasionally observed.

Stimulation in the adjacent temporo-parieto-occipital junction can affect nonverbal capabilities. For example, Morris et al.[41] demonstrated all of the features of Gerstmann's syndrome in this region, including right–left confusion and finger agnosia. Hart et al.[21] reported an area where stimulation selectively interfered with the representation of size. These observations appear to support the idea that many types of information may be organized in a categoric fashion by the brain.

In addition to the temporo-parieto-occipital junction, language function may also be subserved by the temporal base.[8,39] A variety of language functions can be altered at sites throughout the dominant temporal base, but unlike the convexity sites, resection of basal sites generally does not lead to significant permanent deficit.

Stimulation of some sites in the left lateral temporal cortex reportedly disrupts pathways involved in recent verbal memory. These sites cannot be consistently demonstrated in all patients, even after detailed testing extraoperatively, and the role of mapping memory cortex is yet to be fully defined.

Sensorimotor Cortex

Motor or sensory responses can be elicited by stimulating not only the primary sensorimotor cortex but also adjacent regions, which are not as critical and are termed the supplementary sensorimotor areas.

Primary Sensorimotor Cortex.

The primary motor and sensory homunculi do not necessarily conform to specific gyri on either side of the rolandic sulcus. Although the motor cortex is in general located anterior to sensory cortex, there is often an overlap, with some electrodes revealing both motor and sensory responses. Motor responses are usually elicited from a thin, strip-like region that varies in width between 1 and 2 cm. Wider motor representation of >3 cm also can be demonstrated, especially during extraoperative stimulation.[53] Such wide representation may be attributable to atypical gyral orientation or technical factors such as current spread.

Motor responses in children show a developmental trend and become increasingly complex and well defined with age.[2,11] Although hand and face regions can be defined, movements of an individual finger or the tongue are rare below age 2 years and become reliably elicited only after age 4 to 6 years. One could speculate that these findings may somehow reflect immaturity of cortical systems subserving fine finger movements or oroglossal coordination necessary for speech.

Stimulation of the lower rolandic region in children <1 to 2 years of age elicits bilateral rather than unilateral responses from the lower half of the face, suggesting that lower as well as upper facial muscles are likely to be innervated bilaterally in fetal and early postnatal life. Maturation would therefore lead to a loss of ipsilateral lower representation, probably through synaptic or axonal elimination. Such a hypothesis is consistent with the observation that the lower face is completely spared in prenatally acquired hemiplegia but is invariably involved when insults are acquired postnatally.[32] On occasion, there can be ipsilateral as well as contralateral responses in adults as well, especially when stimulation is used to inhibit movement.

Supplementary Sensorimotor Area.

The supplementary sensorimotor area (SSMA) occupies mainly the superior frontal gyrus within the interhemispheric fissure, anterior to the primary motor cortex with variable extension onto the premotor convexity.[38] Regions over the paracentral lobule, the precuneus, and even the adjacent cingulate gyrus, however, may reveal similar responses (Fig. 4). Stimulation of the SSMA can elicit unilateral or bilateral movements from both upper and lower extremities and the face. Stimulation at specific sites may interrupt ongoing motor activities, for example, those that produce alternating movements in the extremities or speech or writing. In general, the face and upper extremities are represented anteriorly and the feet toward the paracentral lobule.[14,38]

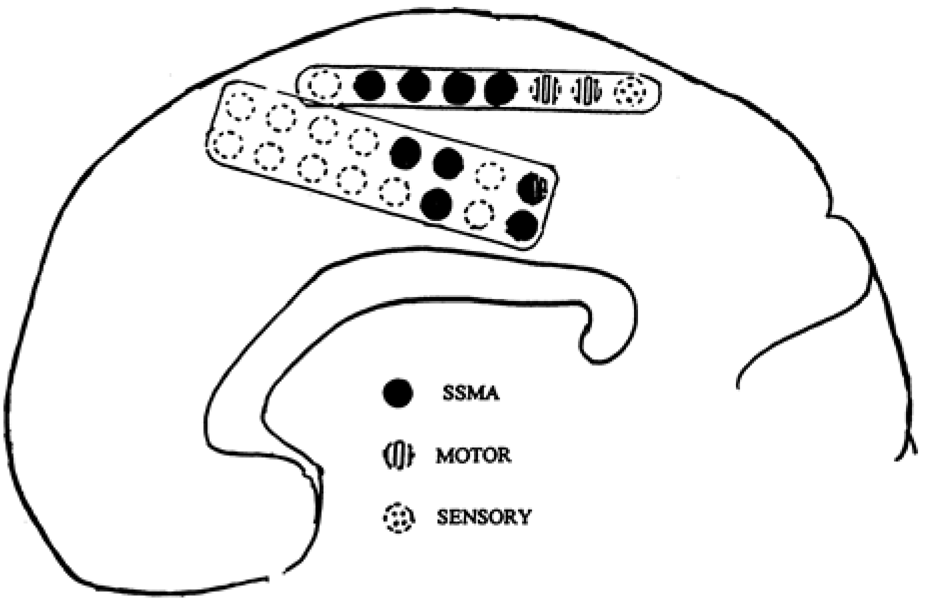

FIGURE 4. Functional map of the right interhemispheric cortex. The supplementary sensorimotor area (SSMA) is located anterior to but encroaches on primary motor and sensory regions.

The SSMA is presumably involved in the planning and initiation of motor movements. Resection of this region on one side usually produces only transient alteration of movement or speech. From a practical standpoint, it is therefore important to differentiate the SSMA from the primary motor leg area located just posterior to it. Besides eliciting ipsilateral limb movements, SSMA response thresholds can be higher than those in the primary motor cortex. Time-locked responses to single-pulse stimuli reportedly occur only from the primary cortex and may help to further differentiate it from premotor areas.

Premotor Cortex.

Stimulation of the frontal premotor convexity produces head and eye movements. This region is usually very discrete and located anterior and contiguous to the primary face and hand cortex. Head version is almost always contralateral to the hemisphere stimulated. The eyes may be deviated tonically or exhibit saccadic movements.

Visual Cortex

Like other sensory areas, the visual cortex is also represented as primary and secondary regions. The primary visual or striate cortex is located around the calcarine sulcus on the mesial aspect of the occipital lobes. The macula is represented at the pole, whereas the peripheral retina is represented along the calcarine fissure, forming concentric circles away from the pole. In general, the upper halves of the retina are represented superior, and the lower halves inferior, to the calcarine fissure. The secondary or association visual cortex is located around the primary cortex and occupies the base and posterior convexity of the occipital lobe.

Stimulation of primary visual cortex over the occipital pole or in the region of the calcarine cortex produces phosphenes

or flashes in the corresponding visual fields. Association visual areas are generally associated with formed visual responses.

Other Critical Functions

Many functions can be defined by stimulating specific regions in either hemisphere, but few have been systematically studied. "Buzzing" can be elicited from primary auditory cortex, whereas more complex auditory experiences occur from auditory association areas located over the posterior perisylvian region. Stimulation at sites in the right middle temporal gyrus may affect ability to label facial expression.[15]

Identification of Dysfunctional or Displaced Cortex

Epileptogenic Cortex

In patients being assessed for seizure surgery, functional mapping serves the additional role of defining dysfunctional cortex. Several features of the stimulus response may be of relevance in defining the epileptogenic region. The most widely studied is the threshold for eliciting afterdischarges. Unfortunately, afterdischarge thresholds vary considerably and can be either below or above those of the surrounding normal cortex. Thresholds may also change from one trial to the next.

In some patients, stimulation may elicit extremely prolonged afterdischarges lasting up to several hours. Occasionally, prolonged afterdischarges are provoked not at the stimulated electrodes but at remote sites. Although these findings suggest that the underlying cortex is hyperexcitable, the various patterns and features of the provoked afterdischarge generally fail to reveal a consistent correlation to the epileptogenic region.[7]

Stimulation may also elicit auras or activate clinical seizures and assist in defining the spontaneous ictal focus. Bernier et al.[6] found that the side from which seizures were provoked generally corresponded to the side of spontaneous seizures, both for temporal and extratemporal seizure foci. However, in our experience, seizures are often provoked on stimulating regions remote from the spontaneous ictal focus and are thus less reliable for defining the exact location of the seizure focus within the same hemisphere. The reliability of defining the ictal focus sometimes is increased if the provoked seizure shows the same clinical semiology as the patient's habitual seizures.

Displaced or Atypical Representation

When lesions involve the dominant hemisphere early in life, while the brain is still plastic, language reorganization is often complex and tends to vary with the nature of the underlying pathology. Language tends to move away from destructive lesions, and when damage of the dominant hemisphere is widespread, there can be an almost complete transfer to the opposite hemisphere. In patients with epileptogenic lesions, however, language cortex is often observed to overlap and scatter around the epileptogenic cortex rather than shift to remote sites.[8,11] Even some right-handed patients may reveal language cortex surrounding a focal epileptogenic lesion over the right hemisphere. These findings indicate that most epileptogenic lesions do not cause relocation of critical language cortex and stress the importance of accurate functional mapping.

Children with developmental pathology may also reveal atypical distribution of motor cortex in which there may be inversion or duplicate representation of some body parts.[11] For example, we have observed a child with double shoulder regions above and below the hand and finger areas, the lower atypical shoulder region being the site of ictal onset (Fig. 5). Aberrant and secondary motor representation of the face has been demonstrated in the infrasylvian region over the middle temporal gyrus[27,29]; in the case reported by Jayakar et al.,[27] ipsilateral facial contractions were elicited by stimulating an area of left temporal cortical dysplasia. Resection of such aberrant duplicated representation sites generally does not result in clinical deficits.

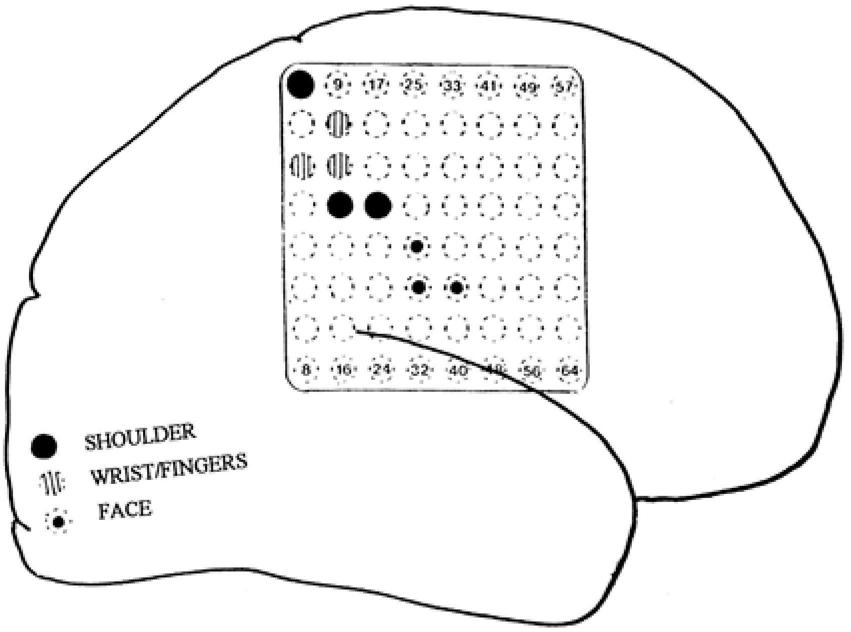
9
17
25
33
41
49
57
8
16
24
32
40
48
56
64
SHOULDER
WRIST/FINGERS
FACE

FIGURE 5. Functional mapping in a child with cortical dysplasia. Note the “atypical” double representation for the shoulder; the lower of the two is also the seizure focus.

Although it could be argued that these findings merely represent extreme variations of the normal, the developmental nature of pathology in these patients leads one to speculate that disturbed neuronal migration and other factors operating during fetal life may be responsible for the anomaly. This hypothesis would be in keeping with experimental observations that prenatally acquired lesions can produce both anomalous sulci and functional reorganization of cortex.[18,19]

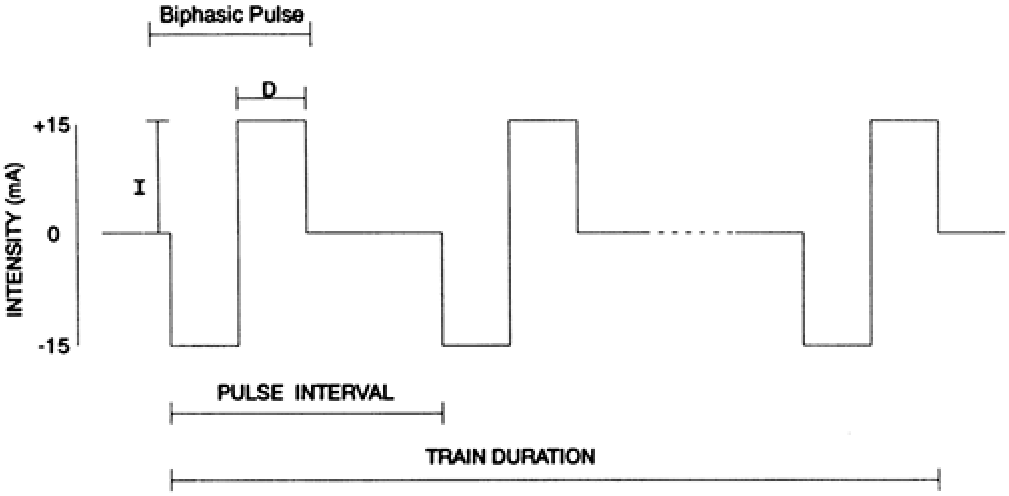
Biphasic Pulse
D
+15
I
0
-15
INTENSITY (mA)
PULSE INTERVAL
TRAIN DURATION

FIGURE 6. Graphic illustration of stimulus parameters using a rectangular biphasic pulse.

Technique

Electrodes

The subdural electrodes used in standard clinical settings usually are thin metal disks with exposure ranging from 2.3 to 4.0 mm in diameter and electrode centers typically spaced 0.5 to

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1 cm apart. The size and configuration of subdural electrodes can be tailored to the area of interest. Strips of four to eight electrodes can be used for sampling basal or mesial structures and allow the option of insertion via a burr hole. Larger rectangular arrays ranging from two by four, to two by eight, to eight by eight are suited for monitoring the hemispheric convexity, and these arrays can be tailored to fit the configuration of the cortex found in the operating room. A combination of grids and strips can be used for adequate cortical coverage. Arrays of somewhat different configurations have also been used; for example, in interhemispheric regions, a curvilinear array can be placed mesially over the corpus callosum to record from supplementary motor or cingulate cortex.

Electrodes available for extraoperative mapping are composed of either platinum–iridium or stainless steel. Platinum is less prone to ionic deposition than stainless steel when current is passed and is thus, in theory, safer than the latter. However, the risk of injury related to ionic diffusion becomes significant only when stimulation is carried out continually over several weeks.[1] Because stimulation in the clinical setting occurs only in brief sessions daily for at most a few days, the practical differences between the two metals in terms of safety should be relatively minor. Platinum electrodes, by virtue of being less ferromagnetic than stainless steel, are also presumably more suitable for magnetic resonance imaging (MRI) scans, which help to document the relationships of electrodes to the underlying cortex.[31]

Stimulation Parameters

Cortical mapping is generally performed by delivering biphasic pulse stimuli at a rate of 50/s in trains lasting 3 to 8 seconds (Fig. 6). Faster rates of 100 to 300 pulses/s and slower rates of 5 to10 pulses/s have been used for transcranial elicitation of motor responses, but their efficacy and safety for direct cortical stimulation are yet to be established.

Pulses also can vary with respect to intensity, duration, the charge and energy applied, and the corresponding densities. The smaller the diameter of the electrodes used, the higher are the charge and energy densities.

The limits of stimulus strength used clinically are guided primarily by safety considerations. Stimulation-induced tissue injury can occur by several mechanisms, which include accumulation of ions (polarization), hydrolysis of water, and heat generation.[1,50,54] Use of a biphasic stimulus pulse minimizes effects of polarization but does not protect against other mechanisms of tissue injury. It is thus critical to try to use the minimal stimulus strengths necessary to elicit a response.[25]

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In the clinical setting, stimulus intensity is maintained between 1 mA and a maximum of 15 to 17.5 mA. Gordon et al.[20] reviewed the charge densities from a variety of techniques and concluded that intraoperative testing with hemispheric ball electrodes would result in charge densities from 159 to 796 mC/cm^2 per phase for peak currents of 2 to 5 mA. By comparison, the estimated charge densities for the grid electrodes in clinical use were 52 to 57 mC/cm^2 per phase for peak currents of 13.6 to 15 mA.

These charge densities are larger than the “safe” limit derived from animal studies, which was approximately 40 mC/cm^2 per phase.[1] However, animal studies typically have used continuous stimulation over more prolonged periods of time.[3,4,50] In humans, mapping is performed by stimulating intermittently for relatively brief periods, and the total length of stimulation time at any given site is far less than was utilized in the animal studies. In addition, humans have a thicker pia–arachnoid and a larger volume of subarachnoid cerebrospinal fluid, so that greater current shunting should occur in humans than in animals.

Gordon et al.[20] studied the microscopic characteristics of cortical tissue samples that had undergone a large number of subdural electrode stimulation trials and found no evidence that electrical stimulation had caused cortical changes. Gervin[17] reported on a patient who had received occipital cortical stimulation via subdural electrodes for a period of 10 years for the purposes of artificial vision production. There were no reported pathologic changes when the electrodes were removed.

Yet another safety consideration relates to the possibility of kindling the brain because of recurrent electrical stimulation. However, there is no evidence that stimulation thresholds progressively decrease on repeated trials, as might be expected were a kindling phenomenon present. Furthermore, kindling of the neocortex is difficult, especially in higher primates.

Testing Parameters

Cortical mapping is generally performed by delivering biphasic pulse stimuli at a rate of 50/s to adjacent pairs of electrodes. Responses at individual electrode sites can be confirmed by monopolar stimulation using a reference electrode located over a remote noncritical site—a procedure that reduces the likelihood of false detections. Stimulation is begun at a low intensity, generally 1 mA, and increased in 0.5- to 1.0-mA increments until a functional change occurs, afterdischarges are elicited, or the ceiling on the stimulation device is reached. Maximum intensity is that of the stimulator utilized, for example, 15 mA for the Grass S88 stimulator and 17.5 mA for the Grass S12 stimulator. Pulse durations are maintained constant at 0.3 msec. Stimulation is continued for 3 to 5 seconds, but longer-duration trains may be required to test more complex functions such as language and praxis.

When afterdischarges occur, one can test again at the same or slightly lower intensity and in many cases avoid the occurrence of additional afterdischarges. It often is possible, using this method, to gradually increase the intensity of stimulation to a current setting much higher than that at which afterdischarges originally occurred, without continued afterdischarges, so that functional changes can be documented. In patients who have unusually large numbers of afterdischarges, small doses of benzodiazepines, generally lorazepam or diazepam, may be needed at the time of stimulation testing. To avoid the occurrence of afterdischarges or seizures, at each testing session the stimulation threshold should be reassessed by beginning at a low stimulation intensity and gradually increasing.

Special considerations are pertinent to stimulation in children.[26] Stimulation paradigms that work well for adults do not necessarily work in children,[51] probably because immature cortex and nonmyelinated nerve fibers require different pulse characteristics to be activated. Immature neural tissues typically have longer chronaxies with their strength–duration curves shifted to the right and thus require stimuli with longer pulse duration to elicit responses. A stimulation paradigm based on stepwise increments of both stimulus intensity and pulse duration converges to the tissue chronaxie and is usually effective for mapping children.[26] This paradigm also keeps the energy and charge requirements to a minimum,[16] a feature that is especially welcome because there are no firm guidelines for electrical safety in this setting. During stimulation, the patient can be subjected to specific tasks designed to test language and memory functions or identify supplementary motor areas.[36,43,45,46,49] In general, the testing paradigms are modified according to age and neurodevelopmental status of the patient. The tasks used most commonly for defining language cortex include naming of common objects and colors, reading of age-appropriate materials, spontaneous speech, and basic mathematics skills. Auditory or visual cues can be administered separately to test receptive or expressive functions. The patient can be asked to respond either verbally or through writing or gestures. Intraoperative testing can be accomplished by showing materials to the patient under the surgical drapes, or even via small computer monitors or television screens. More complex standardized testing of specific functions such as word frequency, grammatic form, or semantics can also be performed.[33,45] Bilingual subjects need to be tested in both languages.

Comparison to Other Approaches

Intraoperative Versus Extraoperative Mapping

Intraoperative functional mapping can be an option when intracranial ictal recording is not needed to plan resection. Motor and sensory homunculi can be easily defined intraoperatively in awake, cooperative adults who describe their subjective sensations. However, in patients under general anesthesia, responses are crude and are usually obtained only at high stimulus strengths. It thus becomes difficult to obtain a fine spatial definition of motor cortex. The effects of anesthesia are even more profound in young children, and motor mapping may occasionally fail despite the use of maximum stimulus strengths (unpublished observation). In some children higher current intensities of 18 to 30 mA may be needed, but their safety is yet to be documented.

There is a general consensus that extraoperative language mapping is indicated in patients who cannot be expected to cooperate during surgery under local anesthesia. Extraoperative mapping is thus clearly the only means to define language cortex in children. There are differing opinions regarding the relative value of intraoperative and extraoperative language testing.[47] Some authors believe that language can be adequately mapped using local and ultrashort anesthetic agents and argue that the cost and risks of extraoperative mapping cannot be justified in these patients. Most authors believe, however, that, given the time restriction, language cannot be mapped with adequate precision in the intraoperative setting. It is not possible to determine thresholds at each tested site, and stimulation may occur at intensities that are not optimal for producing minimal functional alterations. Furthermore, they believe that the much greater time spent in the operating room for intraoperative mapping offsets much of the cost benefits. Extraoperative functional testing occurs during a time when extraoperative localization of epileptogenic cortex is occurring in any case.

There are some technical differences in the two methods of mapping. The electrodes used for intraoperative stimulation are generally much smaller than those employed extraoperatively.[13,43,44,46,48] The smaller electrodes have the advantage that they allow one precisely to define the functions in very small areas of cortex. In addition, they are placed by hand, with direct visualization of the cortex. However, smaller size could potentially be a disadvantage if one wants to screen functional capacities of larger neuronal networks. The smaller electrodes also lead to higher charge densities, but safety is less likely to be an issue because intraoperative testing lasts for only short periods.

Subdural electrodes bear a fixed relationship to one another, and so some electrodes might be over vessels or otherwise suboptimally placed in the extraoperative setting. In comparison, one can ensure adequate electrode contact with the brain during intraoperative mapping. Intraoperative mapping has the added advantage of monitoring critical function during the course of surgical resection. Periodic stimulation of cortex or the exposed white matter pathways enhances the security of motor or language integrity; the latter can be tested only with the patient awake.[5,12,28] Many centers now use a combination of extraoperative and intraoperative mapping techniques.

Somatosensory-evoked-response Topography

The sensory cortex can alternatively be defined by mapping the topography of the somatosensory-evoked responses from the cortex. Typically, the evoked response reveals a phase reversal in the region of the central sulcus. In some patients, however, the phase reversal may be difficult to define or may be 1 to 2 cm anterior or posterior to the central sulcus and thus could potentially mislead the localization of motor cortex. Furthermore, this technique does not help to delineate the anterior extent of the motor cortex and thus serves mainly as an adjunct to stimulation mapping.

Future Directions

Although cortical stimulation has been a very successful technique for mapping eloquent functions, there are complementary electrophysiologic methods that are likely to be helpful in the future, such as event-related potential or gamma frequency recordings and frequency analysis–based techniques.[9,23,30,40,52]

Magnetoencephalography and functional imaging using positron emission tomography, functional MR, or optical techniques also promise to be valuable tools for demonstrating eloquent cortex. These newer methods of functional assessment define the network involved in a particular task and not necessarily the critical sites alone. By contrast, electrical stimulation produces a transient reversible lesion and may thus more accurately identify the tissue that is critical for the function being tested, a factor of importance when considering the potential effects of surgical resection.

Finally, the use of three-dimensional imaging modalities should make it possible to determine more precisely the location of the electrodes and define their relationship to the underlying cortex. This will make it easier to establish anatomic–physiologic correlations during electrical stimulation and thus help us to understand better the overall organization of cortical functions in humans.

Summary and Conclusions

Electrical stimulation provides a safe and effective method for functionally mapping critical cortex. Although testing of various functions can be carried out intraoperatively, extraoperative mapping allows a more detailed analysis that can be reliably reproduced on sequential trials and is particularly suited to mapping in children.

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Chapter 176

Anterior Temporal Resection

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Introduction

Temporal lobectomy is the most common surgical procedure performed for medically refractory symptomatic epilepsy. This operation has evolved with our understanding of the pathophysiology of medial temporal epileptogenesis. The neurosurgical approaches presented in this chapter reflect this evolution and, undoubtedly, will continue to change as we refine our knowledge of the responsible epileptogenic substrates in the temporal lobe and other lobar regions. In fact, defining the symptomatic epilepsies by substrate adds the needed specific pathologic diagnosis to the traditional lobar localization classification to further characterize the various diseases that are expressed as temporal lobe epilepsy (TLE).[73] Temporal lobectomy continues to play an important role not only in the treatment of epilepsy, but also as a bridge between laboratory and clinical research because the resected tissue is assumed to be epileptogenic and a variety of neurobiologic tools can be used to examine this hypothesis. The modern neurosurgical rationale for the more selective medial temporal resections depends on our contemporary knowledge of temporal lobe function and the pathophysiology of the epileptogenic substrates. This has continued to evolve over time as our knowledge about patient selection and outcomes has expanded and accumulated.

Historical Perspective

Bouchet and Cazauvieilh, in 1825, described grossly visible and palpable abnormalities of hippocampal autopsy specimens obtained from nine patients with “alienation epilepsy.”[7] This was the first evidence linking the most common form of partial epilepsy to a pathologic substrate. In another autopsy study, Sommer, in 1880, described gliosis and pyramidal cell loss within the hippocampus of epileptic patients and hypothesized that this finding was responsible for their epilepsy.[71] In 1872, Hughlings Jackson suggested that hyperexcitable brain adjacent to temporal lobe lesions was responsible for epilepsy, and in 1888 he pointed out the association of the “dreamy state” and the classic auras of taste, smell, and epigastric sensations with temporal lobe lesions.[30] Therefore, well over 100 years ago, a variety of temporal lobe epileptogenic substrates were recognized.

Surgical resection provided the link between medial temporal pathology and seizures by permitting the correlation of seizure control and electrophysiologic evidence of epileptogenicity with the resected tissue's histopathology. The first operations were pioneered by Horsley[18] in 1886, who performed surgery for epilepsy by excising visible cortical scars. Bailey and Gibbs, in 1951, popularized the resection of the temporal lobe using electrographic data, limiting their resection to the lateral temporal cortex.[5] Penfield[20] also adopted intraoperative electrocorticography (ECoG) to determine the extent of his temporal lobectomy, but, with Baldwin, he noted an increase in successful outcome with more complete resection of the medial structures (amygdala and anterior hippocampus).[60]

Early Role of Pathology

Surgical experience continued to verify the significance of the medial abnormalities. Earle et al.,[12] in 1953, described diffuse atrophic changes in the inferior medial portion of the temporal lobe in the majority of their patients with epilepsy who underwent temporal lobectomy. Margerison and Corsellis[43] found hippocampal sclerosis (neuron loss and gliosis) in patients diagnosed with TLE. Morris, in 1956, described intraoperative abnormal electrographic discharges originating from the amygdala and anterior hippocampus and pointed out that pathologic changes were most noticeable in these structures.[48] He proposed that the "standard temporal lobectomy" should include 6.5 cm of the lateral cortex, the uncus, the amygdala, and 2 to 4 cm of the anterior hippocampus. This was similar to Walker's description of the standard temporal lobectomy.[97] Falconer then described detailed pathology in the en bloc temporal lobe resections he performed. The atrophy and gliosis he found included and extended beyond the hippocampus, leading him to call the abnormality mesial temporal sclerosis (MTS).[15] He noted that patients exhibited a better prognosis if either MTS or a lesion was discovered within the specimen.[16,17] Falconer also directed his resection to the lateral temporal neocortex, but the emphasis on medial pathology served to help model most technical modifications that followed.

Impact of Early Electrophysiology Studies

Stereotactic depth recordings, introduced by Bancaud and Talairach,[6,88] further altered patient selection. This technique of using acute interictal recordings with depth electrodes provided better intracranial electrophysiologic localization of some partial epilepsies. Crandall also used depth electrodes, but extended the use to chronic recordings of both medial and lateral temporal lobe during seizure events. He also adopted a standardized en bloc resection, which preserved the tissue anatomically, and this was, therefore, well suited for the correlation of ictal electrophysiology with tissue histopathology.[9,38] These intracranial studies demonstrated the frequent hippocampal origin of ictal events in TLE, stimulating further surgical interest in medial resection and setting the stage for more selective surgical intervention and more sophisticated tissue studies.[75,101]

Impact of Neuroimaging

During the decade between 1975 and 1985, computerized tomography (CT) revolutionized neurology's and neurosurgery's diagnostic acumen, particularly regarding intracranial hemorrhage, stroke, and some brain tumors. The impact on the surgery of medically refractory epilepsy was limited, but a great deal of progress was made by coupling video electroencephalographic (EEG) monitoring and intracranial electrode technology. Positron emission tomography (PET) began to confirm unilateral temporal lobe metabolic dysfunction in a majority of patients who were concordantly localized to the same medial temporal lobe.[14] In the late 1980s, magnetic resonance imaging (MRI) confirmed that the neuronal loss and gliosis that had been demonstrated pathologically for decades could be visualized as hippocampal atrophy and signal change. This stimulated a number of clinical investigations that correlated these MRI changes with both quantitative hippocampal cell counts and qualitative visualization and surgical outcome. Because these were retrospective studies, it is not surprising that there is a strong correlation of hippocampal pathology and MRI hippocampal atrophy discovered in patients coming to partial temporal lobe resection. In most studies, an imaging abnormality was a major criterion for selection of surgical candidates. On the other hand, even in series in which both MRI and invasive monitoring were used to select patients with presumed TLE, a high incidence of hippocampal neuronal loss and gliosis was identified in the resected tissue and was highly correlated with preoperative MRI quantitative atrophy and hippocampal signal change.[35,36,81]

A meta-analysis of the literature was performed to determine whether any one imaging method was more sensitive to the detection of TLE and how these methods correlated with each other.[80] The techniques available for analysis included MRI, single-photon emission computed tomography (SPECT), and PET. Both MRI and PET were highly intercorrelative and quite sensitive and specific to mesial temporal sclerosis the most common substrate of medial temporal lobe epilepsy (MTLE), but they did not delineate other forms of pathology that might be more subtle and more regional, such as cortical dysgenesis. There is evidence that the extent of resection of areas identified as hypometabolic by PET is related to short-term outcome.[94] Thus, imaging, invasive electrophysiology, and light microscopic pathologic studies directed the surgeon's attention to the medial temporal structures as the primary generator or amplifier in TLE. What has become increasingly clear is that the medial temporal structures participate in a much larger, complex network. The individual variations in both the location and extent of damage of this network lead to the clinical phenomena that we associate with temporal lobe epilepsy. Magnetic resonance spectroscopic imaging has also corroborated evidence based on anatomic MRI that frequently there are *bilateral* medial temporal abnormalities.[58] These abnormalities may actually improve following resection of the lobe responsible for seizure generation.[92] It is likely that variations in both of these network-related findings contribute to variations in outcomes as well.

Frequency of Use

Temporal lobe resection in some form continues to be the most commonly performed operation for the medically intractable symptomatic epilepsies. Almost all temporal lobectomies performed before the late 1970s involved a generous lateral temporal neocortical resection, which was either standard or determined by intraoperative ECOG spikes and limited by essential cortex such as language and visual fields. The volume of medial hippocampus, parahippocampus, and amygdala removed was extremely variable and surgeon dependent.

In the late 1970s, based on invasive electrophysiology and pathology, Spencer modified the standard resection for those patients with medial temporal ictal onset, such that all of the medial structures (amygdala, hippocampus, and parahippocampus) were removed via a limited temporal pole resection.[75] At the same time, Wieser and Yasargil independently devised the more restricted amygdalohippocampectomy for presumptive medial basal epilepsy with or without an associated amygdalohippocampal mass (usually tumor).[100] Although some centers still perform generous lateral resections often based on ECOG, modifications of these more selective medial approaches have been used increasingly over the last decade. The increased use of selective medial resection has been based on the aforementioned convergence of medial electropathophysiology and on additional literature demonstrating more failures of temporal lobe resection when the medial structures are incompletely resected.[51,56,63]

Recently, a number of centers have looked at the seizure and neuropsychological outcomes of patients that have undergone transsylvian selective amygdalohippocampectomy.[57] These results seem to indicate that seizure control is equivalent to that with resections that involve limited resection of the lateral structures.[57] The neuropsychological results show either equivalence[41] or some trends toward decreased morbidity for functions involving the temporal lobe but increased morbidity for frontal lobe functions, especially when associated with subarachnoid hemorrhage from the sylvian dissection.[25]

Indications

Principal Candidates

The following discussion is concerned with patients undergoing evaluation for surgical candidacy for treatment of *intractable epilepsy*. Typically, patients with new-onset seizures and significant MRI findings are treated with paradigms that address their underlying pathology first but may be considered for epilepsy surgery should their epilepsy prove to be intractable despite optimal treatment of their underlying pathology.

Patients With Pathogenesis Acquired Younger Than the Age of 4 to 5 Years

Three groups of MRI-analyzed substrates are commonly recognized as epileptogenic and when found in the temporal lobe are presumed to be responsible for the ictal events and the typical behavior of TLE. The first is classical MTLE associated with the pathology of MTS (neuronal cell loss, gliosis, and synaptic reorganization). The other imaged substrates are responsible for lesion-related TLE (LRTLE) and are not restricted to the temporal lobe but may interact uniquely with this portion of the limbic system and require special attention, particularly when they are situated medially. These are primarily vascular cavernous angiomas (CAs), arteriovenous malformations (AVMs), focal developmental abnormalities (DAs), and low-grade neoplasms. The last group, cryptogenic TLE (CTLE), has no imaged lesion or atrophy, and the temporal lobe is identified as the presumed epileptogenic source based primarily on electrophysiology.

MTLE represents 60% to 70% of all localization-related epilepsies and constitutes a syndrome because it has been defined by a common etiology (early injury, particularly febrile seizure at age <4 years), diagnostic evaluation, unilateral ictal EEG and MRI hippocampal atrophy, resistance to medical therapy, and responsiveness to selective resection. The pathogenesis of this syndrome represents a special substrate (MTS), even if the etiology and maintenance of epileptogenicity are not fully understood.

The patients with LRTLE do not have a significant history of early injury, are older when their seizures begin, most frequently have unilateral temporal scalp EEG ictal onset, and, with the exception of some DAs, respond well to resection of the mass and a surrounding margin of tissue.[77] It is not clear whether any of the medial temporal lobe structures other than the immediate surround need to be included in the resection for seizure control. The resected hippocampi of this group generally have the characteristics of relatively normal tissue, with only some neuronal loss and no reorganization.[33] A variable percentage of hippocampi associated with lesions may demonstrate atrophy on MRI. This does not necessarily indicate that the atrophic hippocampus is nonfunctional and epileptogenic and should be removed.[21] Although this dual pathology has been increasingly characterized by hippocampal atrophy with neocortical DAs (mostly neuronal dysgenesis), the concurrence of a mass and hippocampal atrophy has stirred a debate regarding whether the hippocampus has been only passively injured or is epileptogenic and needs to be removed for best seizure control.[37] There are insufficient data to answer this question, but it is particularly relevant when dominant, temporal lobe–specific, short-term memory is normal or only mildly impaired and a medial dominant mass has been targeted for resection. Is the atrophic hippocampus or its more normal adjacent parahippocampus capable of normal function, and is there a risk of cognitive deficits if it is included in the resection?[66] The LRTLE group shares this feature of a usually preserved hippocampus with patients in the CTLE group. Patients with CTLE have presumptive electrophysiologic localization but do not have the consistent history of developmental injury or medial temporal lobe atrophy visualized on MRI.

Patients With Pathogenesis Acquired Older Than the Age of 4 or 5 Years

Trauma and infection after the age of 4 or 5 years may cause isolated injury and consequent excitability in one temporal lobe, but frequently there is more diffuse neocortical involvement requiring invasive electrophysiology for localization.

Thus, patients who have medically intractable complex partial seizures with regional temporal lobe scalp EEG localization may be candidates for some form of temporal lobe resection. The form this resection takes, however, varies considerably with a given substrate. Patients with CTLE or TLE acquired after age 4 or 5 years should be evaluated for resection based on invasive recordings, and such resection should exclude the reorganized essential brain, such as those areas governing language and verbal memory.

Evaluation Criteria

Selecting patients with TLE for the appropriate operation begins by first using MRI to classify them into the three anatomic substrate categories noted earlier: (a) hippocampal atrophy (MTLE with presumed MTS), (b) lesions (LRTLE), and (c) normal anatomy (CTLE). Noninvasive tests are then applied to search for either concordance to an anatomic abnormality or a well-delineated temporal lobe EEG localization when the MRI is normal. For example, in a patient with a history of febrile seizures or early injury at age <4 years and unilateral hippocampal atrophy, a selective medial temporal resection might be indicated if the MTLE syndrome was confirmed by video-EEG–recorded appropriate ictal pattern, temporal lobe–specific short-term memory deficit, and unilateral hypometabolic PET scan when available. Finally, although the method and interpretation vary considerably, the intracarotid Amytal procedure (IAP) will usually demonstrate a more specific memory deficit in the suspicious temporal lobe.

A patient with a temporal lobe lesion also requires EEG concordance. Neuropsychological, PET, and IAP testing can range considerably from normal to various degrees of abnormality. These latter three tests are not well categorized regarding usefulness in deciding about a resection or its volume. Nonetheless, the concordance of scalp EEG and anatomic substrate directs the surgeon to a specific region. The variability of other tests can result from lesion location, extent and age of an injury or lesion, and the central nervous system response to the same. The IAP's major role has been to assure the physician that memory is adequate in the temporal lobe opposite to the one to be surgically addressed. Outcome studies with substantial numbers of patients are needed to clarify how cognitive testing, IAP, PET, and ictal and interictal SPECT can be used in modifying decisions based on the major criteria of MRI substrate and EEG localization.

In cases in the third category (CTLE), in which hippocampal atrophy or T2 signal change does not clearly predict MTS and the MRI appears normal, all EEG criteria must be typical of MTLE and the PET scan likewise positive for selective medial temporal resection to be performed in some centers. Patients in this group with a normal MRI often undergo chronic invasive electrophysiologic recording of seizures. Almost all centers agree that some form of invasive recording must be used if the preoperative evaluation criteria are discordant with one another; particularly when any imaging abnormality (MRI, PET, or SPECT) conflicts with the EEG. The temporal lobe resection region will then be tailored to the invasive ictal findings.

Chronic invasive electrophysiologic monitoring shows that the majority of ictal events observed in TLE originate in the medial temporal lobe, often within the hippocampus.[78,79,82,83] Electrographic ictal localization with invasive studies, such as depth and subdural electrodes, is accepted as the most accurate method for identifying the region of seizure onset.[14,23,79] Use of interictal spikes was advocated historically and is still advocated by some to define the cortical resection.[55] However, the location of interictal spikes has only been weakly correlated with the site of ictal onset or any pathology within the resected tissue.[23,72]

Considering that interictal spikes may represent synaptically mediated events propagated from distant abnormal sites, this finding is not unexpected.[103] Epileptiform spiking can be nonspecific because it has been described in nonepileptic individuals.[8] Ictal electrophysiologic data remain the standard for resective procedures for TLE. The disconnection of afferent and efferent networks also helps to explain how varied temporal lobectomy approaches across the spectrum from standardized to tailored resections can have similar outcome efficacy.

Discordant electrophysiology and imaging also may be seen in patients with LRTLE and may lead to invasive recordings to clarify ictal onset. When an MRI lesion is present, the necessity for invasive EEG is substrate dependent. It is infrequently necessary when the lesion is a neoplasm, circumscribed DA, or CA, unless there is ictal scalp onset clearly from another lobe or the opposite hemisphere. Other MRI lesions may not be associated so robustly with just perilesional epileptogenicity because a microscopic substrate may extend beyond the imaged abnormality. These patients with LRTLE require invasive recording to define the necessary and sufficient temporal lobe volume that must be removed. Common lesions in this category are most of the DAs, such as cortical dysplasia and gyration defects, and the indeterminate substrates, including traumatic and infectious gliosis and neuronal loss. Separate consideration for invasive monitoring may be necessary to stimulate and localize certain essential cortical regions such as language and sensorimotor areas when awake craniotomies are not possible, such as in children or adults with limited ability to undergo awake procedures.[23]

Goals of Surgery

In MTLE that meets evaluation criteria, neuropathologic, neuroanatomic, and neurophysiologic[10,33,102] findings all identify abnormalities in the medial temporal structures, particularly the hippocampus. Therefore, an extensive medial resection removes the majority of this epileptogenic substrate. Accumulated evidence suggests that the medial structures should be resected extensively in this syndrome. Depth electrodes placed parallel and through the long axis of the hippocampus have shown that electrical abnormalities are usually found throughout the body of the hippocampus, and less often is there a distinct segment of the hippocampus that initiates the seizure. In approximately 20% of patients with unilateral TLE studied with depth electrodes, abnormal electrical foci in the posterior portions of the hippocampus were not routinely resected by traditional standard lobectomies.[78,83] MRI most frequently shows atrophy of the entire hippocampus.[44] And although investigators have described a decreasing gradient of neuronal cell loss from anterior to posterior hippocampus, pathology is generally seen throughout.[4] The need to include the posterior portions of the hippocampus in the medial resection was addressed by designing a more radical hippocampus and parahippocampectomy that preserved the lateral temporal cortex—the anterior medial temporal resection (AMTR). Finally, Wyler et al. reported a prospective, randomized study of patients undergoing surgery for MTLE, with ictal onset verified in each case by subdural recordings.[105] They compared the AMTR to a more limited medial resection in this group. Complete seizure control was seen in 69% of the AMTR patients and in only 38% of the patients with a partial hippocampectomy. Other surgical options are also reviewed in what follows, representing variations of opinion of the extent of medial resection necessary and sufficient for success, and representing different approaches to minimizing the functional disruption of overlying cortex. They all share the common goal of medial temporal resection, specifically of the hippocampus.

Surgical Approaches

Reliance on Presurgical Evaluation Emphasizing the Substrate

Medial Temporal Lobe Epilepsy

Most temporal lobectomies today are subtotal temporal resections for MTLE where MTS is the presumed pathology based on MRI showing unilateral atrophy and/or increased T2 signal change in one hippocampus. Dysfunction of this temporal lobe, particularly the medial region, is expected in this syndrome and corroborated by specific cognitive deficits, particularly temporal lobe–specific memory loss and PET hypometabolism. Temporal lobe ictal onset recorded by scalp electrodes may be sufficient to assume relatively isolated medial temporal lobe epileptogenesis when imaging and cognitive deficits are concordant. Invasive medial electrical onset using depth electrodes and/or subdural strips may otherwise be required. With either of these approaches, that is, concordant noninvasive studies or invasive recordings, the medial temporal lobe has become increasingly the targeted region of resection. Resection strategies in this syndrome still include intraoperative ECoG in some centers, but most involve removing a preoperatively determined volume of temporal lobe, emphasizing substantial parts of the hippocampus, parahippocampus, and amygdala and preserving the lateral temporal neocortex.

Anterior Medial Temporal Resection.

The extent of lateral temporal resection in the AMTR developed at Yale is limited to the temporal pole to provide access for a generous resection of the medial structures (Fig. 1).[72,74,75] Because cognitive function is not at risk in the majority of patients with MTLE, this complete removal of amygdala, hippocampus, and parahippocampus is logical because maximal efficacy is assured with one definitive safe surgical procedure.

This method's advantages are similar to those of the other approaches described later. They all preclude intraoperative ECoG, and the limited anterior temporal resection makes language mapping unnecessary in the dominant hemisphere. Operations can then be performed under general anesthesia. With this approach, visual field cuts often can be avoided or, if present, not exceed a partial contralateral superior quadrantanopia.

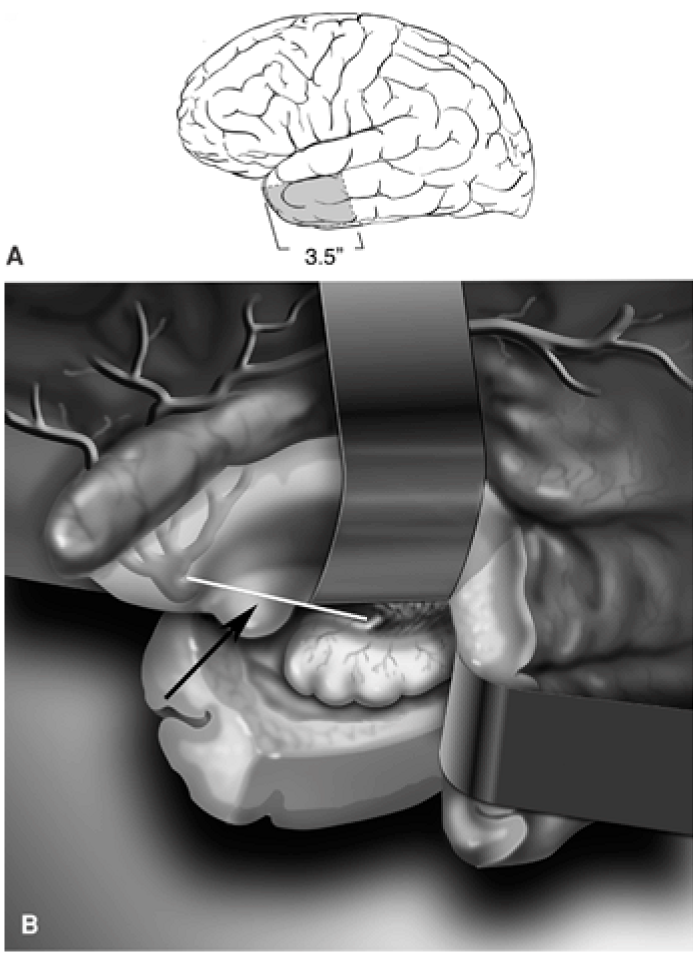

FIGURE 1. Anteromedial temporal resection. **A:** The lateral resection is invariant from dominant to nondominant side and consists of the anterior 2.5 to 3 cm of the middle and inferior temporal gyri. **B:** Diagram illustrating retractor placement and exposure of the medial temporal lobe structures as viewed from anterior to posterior. Arrow points to a line connecting the "knee" of the middle cerebral artery in the sylvian fissure to the velum terminale or anterior choroidal point in the temporal horn of the lateral ventricle. This line is used as a guideline to the extent of the resection of the amygdala.

Standardized AMTR permits assessment of intact tissue from the en bloc removal and allows evaluation of surgical outcome without the confounding variations inherent to varied tailored resections. Standardized procedures permit studies of induced changes in neuropsychological and psychosocial function, validation of presurgical criteria, and correlation of the pathology in the resected tissue with new assessment criteria and modalities.

Transsylvian Amygdalohippocampectomy.

Wieser and Yasargil reported a series of patients who underwent selective unilateral amygdala-hippocampectomy for drug-resistant TLE.[100,101] Their operation was very selective, including only the amygdala, uncus, and hippocampus posteriorly to the level of the superior colliculus. With their transsylvian approach, lateral temporal cortex was not resected. Detailed neuropsychological testing was not reported for these patients, but the investigators thought in general that there were fewer functional deficits than in a comparable group that they treated with larger temporal lobectomies.

The transsylvian approach is technically demanding.[101] In addition to limitations associated with the very restrictive exposure, there is a risk of morbidity related to dissection through the sylvian fissure. This involves possible damage to the sylvian veins, branches of the middle cerebral arteries, the anterior choroidal artery, and the branches of the posterior cerebral artery.[34] The vessels need not be damaged, because vasospasm alone can result in hemiparesis or hemianopsia. Both vasospasm and blood flow are significantly different in patients undergoing transsylvian versus transcortical approaches.[67]

Transcortical Transventricular Amygdalohippocampectomy.

Niemeyer, in 1958, presented a small series of histologic abnormalities mostly within the hippocampus of temporal lobes removed by standard temporal lobectomy[52,100] and provided the rationale for the procedure he went on to describe. He developed a transventricular amygdalectomy and a 3-cm hippocampectomy performed through a 2-cm middle temporal gyrus incision. The disadvantages of this technique include its limited field of exposure and its preclusion of en bloc excisions. A variation of this approach is used by Olivier at the Montreal Neurological Institute for selective resections.

Subtemporal Amygdalohippocampectomy.

The subtemporal approach is also technically complex because it entails zygomatic process removal for exposure of the inferior middle fossa. For rare cases of tumor or cavernoma in the dominant hemisphere, this can be considered, but alternative approaches, notably awake temporal lobectomy with functional mapping, is usually preferred.[107]

Stereotactic Frame, and Frameless Amygdalohippocampectomy.

Open stereotactic selective amygdalohippo-campec-tomy[34] is also described as a method for minimizing neocortical resection. Although the technique was developed for removal of neoplastic lesions, it has been used in selective resections of the amygdala–hippocampal complex in patients with TLE.[32] The lateral transcortical temporal approach uses a stereotactic, computer-based, image-directed system. According to its advocates, this method offers selective resection with very limited superficial cortical resection, avoiding the functional cortex and not exposing important vascular elements. A large series using this technique is not available for comparing efficacy of seizure control and neurologic outcome.

There are also isolated reports of closed stereotactic ablations of medial structures in the literature.[50,85,89] However, they are limited to relatively small areas of anatomy and usually have poor results. No formal modern series comparable with open craniotomies is available.

Lesional Temporal Lobe Epilepsy: Developmental Abnormalities, Neoplasms, and Vascular Anomalies

A complete preoperative evaluation is just as critical when an MRI lesion in the temporal lobe is discovered in a patient with chronic epilepsy.

To direct surgical attention to the lesion, the scalp EEG should be concordant, and video-EEG is recommended to confirm appropriate temporal ictal onset and verify the behavior of a complex partial seizure. In general, discrete MRI lesions of all three substrates—developmental, neoplasms, and vascular anomalies—can then be approached and the operation designed to remove the pathology and its surround until one is assured that only normal cytoarchitectural brain remains. Lesions in the lateral dominant temporal lobe require either intra- or extraoperative language mapping. More controversial is the handling of medial lesions adjacent to the amygdala and hippocampus, sometimes called the parahippocampus complex.

Three surgical solutions to this problem are possible. First, only the lesion may be removed; second, the lesion and some portion of the medial structures may be removed to assure a margin of resection; and, finally, a formal AMTR may be performed in addition to removal of the lesion. The larger, more complete resection may sound more attractive; however, often cognitive testing shows normal specific short-term memory. A medial resection in the nondominant hemisphere may be functionally inconsequential; however, the same resection in a normally functioning dominant hemisphere may drop verbal memory scores by more than two standard deviations and significantly affect the patient's learning ability and quality of life.

Some still advocate a medial resection in these circumstances when the hippocampus is atrophic on MRI, feeling that this represents the dual pathology of lesion plus MTS. However, hippocampal atrophy may be seen accompanying a variety of lesions at variable distance from the medial temporal lobe where lesion resection alone has been sufficient to stop seizures. As a corollary, dominant temporal lobe–specific memory may be normal in the setting of hippocampal atrophy, and resection of that hippocampus may still be harmful. There are clearly not enough data in this regard to solidly support one or another approach. Therefore, it may be most prudent to approach this problem with a conservative resection when faced with normal cognitive examination results. This issue again emphasizes the importance of the preoperative evaluation in the surgical decision.

Another controversial problem regarding MRI lesions is the DA and gliosis of trauma. Although there are no outcome data to support this approach, it is not unreasonable to handle discrete DAs (hamartomas) like neoplasms and vascular anomalies. On the other hand, when MRI depicts a more diffuse DA, such as pachygyria or schizencephaly, and the gliosis of trauma, invasive recording is recommended to define what broader epileptogenic region is most likely. A resection based on these ictal recordings is again tempered by the cognitive evaluation, particularly in the dominant temporal lobe.

Cryptogenic Temporal Lobe Epilepsy: No Image Substrate

This group constitutes the most difficult management problem. They most frequently do not have the history or cognitive findings of MTLE, although the scalp electrophysiology and seizure semiology may demonstrate probable temporal lobe ictal onset. These patients require one and sometimes two chronic invasive recording sessions to define the resection volume. They may undergo an initial bilateral depth or subdural analysis to define the suspicious temporal lobe, and then they may require a more regional grid-and-strip study to define a more focal volume and its relationship to structures essential brain.

These resections are all totally electrophysiologically guided by a combination of ictal and interictal activity. In some instances, the seizure source is determined to be outside the temporal lobe such as the occipital or temporooccipital region and projected into the temporal lobe. Nonetheless, good surgical outcome is less well assured in this group, and the resected tissue is either normal or, increasingly, the DA of neuronal microdysgenesis is appreciated. This is clearly a group of patients that needs further intense scrutiny before they can be appropriately classified and treated.

Alternatives to Resection

For some patients, neuropsychological morbidity or patient preference leads to considerations for alternatives to resection to ameliorate seizure activity. For patients in whom the morbidity or resection is too high, for instance, in patients with well-preserved verbal or visual-spatial memory ipsilateral to the intended resection or demonstrated poor memory contralateral to resection by IAP, nondestructive means of altering the pathologic network can be entertained. Either programmatic[90] or

responsive electrical stimulation[47] directly to the hippocampus or parahippocampus has shown limited success in early studies. Other groups are attempting multiple subpial transections of the hippocampus, but superior neuropsychological outcomes and seizure efficacy have yet to be substantiated.[70] For patients wishing to avoid open surgery for health or other considerations, several groups have attempted stereotactic radiosurgery, again, with limited[65] to no success.[86]

Outcome and Predictors of Success

Success

Comparing success rates among different surgical techniques or among different epilepsy centers is difficult because a uniform criterion of success has not been established. Typically, outcome of surgery for TLE is reported with respect to seizure frequency, usually independent of whether patients remain on anticonvulsant medications.[64] Efforts recently have been made to include quality-of-life indicators such as social and personal factors in outcome classification schemes because social, familial, psychiatric, and employment issues are recognized as equally important in describing the overall outcome and success when treating this functional disease. Outcome can be considered quite individualized. For example, a rare seizure in one individual may represent a dramatic improvement in this patient's life, whereas in another patient even one rare seizure could have a serious negative effect. Because reports of various centers often depend on the variables that reflect the center's surgical philosophy, outcome for a particular procedure may be directly related to the patient selection process. Therefore, direct comparisons between published series cannot be readily made.

The binary classification scheme of being either seizure free or not seizure free offers the most valuable information because it is the seizure-free category that has the most potential impact on a patient's life. Neuropsychological improvement and the quality of life show the most improvement when the patient is seizure free[27,39,93,96]; however, subjects do report a meaningful positive change in health-related quality of life with either Engel grade I or II outcomes.[95]

One-year outcome statistics show that with AMTR, 78% of the patients with MTLE have complete seizure control. As a comparison, patients with temporal lobe tumors with TLE had an 85% seizure-free outcome.[74,77] In the short term, patients experience benefits in quality of life regardless of seizure outcome, but by 1 year the two groups significantly diverge.[84] At 2.5 to 5 years, patients who undergo surgery report better quality of life than matched nonsurgical controls.[45] Patients' outcome groups do not remain static over time; even at 10 years, patients who initially have enjoyed seizure freedom may relapse.[106]

Surgical Failures and Their Pathoetiology

In the majority of surgical failures, seizures recur within the first year after surgery, often as early as in the first weeks and months after surgery.[13,40,87] Seizure recurrence increases progressively with the length of follow-up; however, being seizure free 1 year after surgery is an excellent predictor of continued seizure-free outcome.[40] Engel reported that 79% of patients seizure free at 1 year remained seizure free at 5 years, and 63% remained so at 10 years.[13] In a large multicenter evaluation of outcomes, similar numbers were found: 83% of patients at 1 year, 72% at 5 years, and 56% at 10 years, although about half of these patients experience one or fewer seizures a year.[106] Realizing that the original insult that these patients suffer can sometimes be linked to a remote childhood event, such as febrile seizures, that does not manifest itself until adulthood, one can hypothesize that a slow “neurodegenerative” process might be responsible for some of these late failures.

There are several reasons for surgical failure. Epileptogenic scarring at the resection edge is uncommon and perhaps just theoretical; proving this is difficult. However, there may be a predisposition to epileptogenicity in these patients, either genetic or acquired. Therefore, these patients are more prone for either recurrence or for developing new extra-resection epileptogenic areas.[1] A satisfactory resection of one epileptogenic region may still result in failure when another site such as the opposite medial temporal area begins or continues to cause seizures.[2,42] This probably is the etiology for many recurrences observed after years of seizure-free status. Outcome studies have correlated poor outcome with the duration of preoperative illness and the presence of normal pathology of the resected specimen.[106] An error in localizing the epileptogenic area during the preoperative evaluation will direct the wrong surgical removal and could be another cause of failure and thus lead to the findings of normal pathology. Localization error in presumed TLE cases may occur when seizure onset in the lateral temporal neocortex or in an extratemporal location was not recognized. This represents a failure of patient selection rather than a surgical technical failure. Often, repeat evaluation shows that both temporal lobes harbor dependent or independent epileptogenic potential. Finally, the association of lengthy preoperative illness with poor outcome raises the question of whether the phenomenon of secondary epileptogenesis within the network responsible for the patient's original seizures may play a role.

The most important reason for technical surgical failure is probably insufficient excision of epileptogenic tissue or, in the setting of a lesion, incomplete resection of the epileptogenic surround. This accounts for the majority of patients with recurrent refractory epilepsy. In patients with TLE, Olivier et al. recognized the role of retained mesial structures in patients with failed temporal lobectomy.[56] Wyler et al. also reported on a large series of reoperations, also concluding that primarily insufficient resection of medial structures at the first operation was the etiology for failure.[104] Awad et al. reported similar results. The majority of their cases had persistent epileptogenicity related to inadequate resection, retained mesiotemporal structures, or retained epileptogenic structural lesions. Other cases had more remote areas of epileptogenicity or diffuse epileptogenicity in the residual temporal lobe.[2,3]

Surgical failures should be managed aggressively. They require repeat evaluation with anatomic and metabolic imaging and video-EEG monitoring and careful review of their surgical pathologic profile (substrate classification).[73] The AMTR surgical approach results in a uniform aggressive hippocampal removal during the first operation. Therefore, failures of this resection are usually due to an epileptogenic contralateral medial temporal lobe or extensive ipsilateral regional disease, often of developmental origin in either the temporal or extratemporal cortex. Simply removing more lateral temporal lobe often is not successful in converting these failures to successes. In the setting of tumors, seizure recurrence often precedes radiographic tumor recurrence by about 6 months.[77]

In failed amygdalohippocampectomy patients, Wieser and Yasargil reoperated using a standard anterior temporal lobectomy with a 50% success rate.[99] Short- and medium-term seizure control has been accomplished in most of the reported cases of reoperation.[42,56,104] Nearly half the reported patients in another series[3] remained seizure free for periods of up to 72 months, and another one third showed worthwhile improvement in seizure frequency despite severe intractable seizures before reoperation.[2]

Neuropsychological and Neurologic Sequelae

With resective surgery involving the hippocampus and lateral temporal lobe, one would expect possible sequelae of visual field defects, deterioration in memory function, and fluent dysphasia. The visual field defect in a patient who has an anterior temporal lobectomy is usually a superior quadrantanopia contralateral to the surgery.[91] The visual loss becomes more hemianopic as the lateral incision is extended more posteriorly.[19,31] The posterior location of the optic radiation fibers is variable among individual patients, and, as a rule, patients will acquire more than an upper quadrant visual field cut. By limiting the lateral cortical resection to only that sufficient to allow entry into the temporal ventricular horn (3–3.5 cm from the temporal tip), typically one observes only a partial superior quadrantanopia or often no field defect at all. A homonymous hemianopsia has never resulted.

Dysnomia and other fluent speech errors elicited by stimulation are found in variable locations on the lateral temporal cortex of the dominant hemisphere.[54] Resecting these positive stimulation areas is thought to result in some degree of permanent fluent dysphasia. Preserving one gyrus between the cortical incision and the most anteriorly located site of the speech error most often avoids a permanent speech deficit. With stimulation in awake patients, only one occasion of fluent speech was represented in the Yale series more anteriorly than 4.5 cm on the middle temporal gyrus and 3 cm on the superior temporal gyrus, as measured from the anterior temporal tip.[54,75] This is well beyond the posterior resection margin. Wyler studied language function in patients with medial temporal epilepsy who underwent anterior temporal lobe resection modeled after the AMTR description.[29] He found that AMTR of the dominant hemisphere can be accomplished without intra- or extraoperative language mapping with no measurable compromise of language function.[29] He also demonstrated that patients rendered seizure free by any surgical procedure demonstrated significant gains in several language areas, whereas patients who continued to experience even some seizures showed no improvements in language function.[26]

Historically, the hippocampal model of human memory was elaborated by Scoville, Penfield, and Milner, who observed that bilateral hippocampal ablation produced permanent complete amnesia.[46] They also found that the dominant hippocampus served verbal memory function, whereas the nondominant hippocampus served nonverbal (i.e., visual-spatial) memory function, and that the extent of unilateral hippocampal ablation seemed to relate to the severity of the memory deficit.[46,62] This is contrary to the Yale group's findings that patients who underwent extensive unilateral hippocampectomy did not demonstrate either amnesia for specific material or memory impairment greater than that occurring with traditional partial hippocampectomy.[75] This is probably a result of selection because AMTR is not typically indicated in patients demonstrating intact material-specific memory on the presumed affected side. Typical patients with MTLE have had an early injury to the medial structures that are not generally functional.

This also may support the concept that temporal lobe memory mechanisms are not exclusively confined to medial temporal structures.[75,101] Ojemann reviewed the occurrence of verbal memory deficits after dominant hemisphere temporal lobectomies and found that they correlate with the extent of lateral, but not medial, resection.[55] All of these findings suggest that it is the lateral cortex rather than medial structures that must be preserved to avoid memory deficits in this particular epileptic population but not in the group that retains modality-specific memory.[69,76]

It is known that seizure activity and many anticonvulsants depress cognitive functions,[11,68] and following surgical control of seizures, selected cognitive functions improve. The improvements are due to the elimination of ictal disturbances and from reduction in medications. The most likely improvements to occur are those related to general measures of cognition such as IQ and learning or to selective functions associated with brain regions outside the resected area.[28,49,53,64,98] Therefore, there is growing evidence that a limited anterior temporal resection in either hemisphere does not produce significant long-term adverse neurologic or neuropsychological sequelae, and the result of a seizure-free status may even improve the patient's neuropsychological baseline.

Surgical Complications

Complications are not frequent. There are general complications of neurosurgical procedures that are common to all intracranial operations, and there are specific neurologic complications associated with AMTR. General complications include acute postoperative hemorrhage, retraction injury, wound infection, and the usual perioperative sequelae such as anesthetic and medication intolerance, deep vein thrombosis and infections of the bladder, lung, and intravascular lines.

Transient Deficits

Complications associated with AMTR and other temporal lobectomy procedures for TLE are considered separate from the transient deficits that are seen. Penfield described "neuro-paralytic edema," which contributed to the transient deficits he observed.[59] Whether it is retraction injury or functional damage from temporary ischemic conditions, if functional cortex is involved, then transient neurologic dysfunction will result. Such deficits include memory impairment, decreased spontaneous speech, and anomias. Transient diplopia, ptosis, and pupillary dilation result from manipulation of the third and fourth cranial nerves just under the arachnoid of the perimesencephalic cisterns and the tentorial edge. These transient deficits invariably clear within several days but sometimes may last longer.[96]

Permanent Deficits

Anything less than a contralateral upper quadrant defect should not be considered a complication. In 1961, Penfield et al. presented eight patients who developed a postoperative hemiplegia,[61] which Penfield called "manipulation hemiplegia." He believed this to be a consequence of traction on the middle cerebral artery perforators, resulting in vasospasm and infarction of their vascular territory.[24,61] In >300 temporal lobe procedures, Girvin had only 1 postoperative hemiplegia that was due to infarction within the internal capsule.[22] This was attributed to injury of the anterior choroidal artery. Early in the Yale experience, a patient was encountered who experienced a dense contralateral hemiparesis but who, fortunately, subsequently recovered. MRI showed that this was clearly a result of coagulating the choroid plexus lying on the hippocampal body with inadvertent coagulation of a branch of the anterior choroidal artery. Anterior choroidal artery injury probably accounts for the majority of manipulation hemiplegia cases. The choroid in the choroidal fissure should be gently retracted and never coagulated.

Summary and Conclusions

Evaluation of the MRI and study of the resected hippocampus show that there are different forms of TLE characterized by history and image, as well as by the degree of neuronal cell loss, gliosis, and neuronal reorganization within the hippocampus. LRTLE is associated with a structural mass, usually a low-grade tumor or cavernoma. In general, the hippocampus is removed

in these patients only if a margin is required for complete tumor extirpation. Conservative hippocampal resection in these patients is always the rule in the dominant temporal lobe with intact short-term verbal memory. AMTR was designed for the treatment of MTLE that involves the medial structures, and by offering en bloc resection of these structures, this operation is ideal for clinical studies in which the anatomically intact pathologic substrate is required.

Patients who undergo AMTR require careful preoperative evaluation and, if selected properly, have had excellent seizure control, small visual field defects, and fewer and shorter-lived speech deficits. Neuropsychological testing shows no additional deficits resulting from modified temporal lobectomy compared with the deficits seen after the standard operation. Most patients have had less impairment in visual-spatial perception than was common with the more standard lobectomy. Because of these encouraging results, some form of limited medial resection has gained popularity as a standard operation for MTLE.[75]

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Chapter 177

Neocortical Resections

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Introduction

The histories of extratemporal epilepsy, epilepsy surgery, and neurosurgery are intimately related. The intractability of posttraumatic epilepsy led to the early use of trephination as a treatment modality. In the eighteenth century, Percivall Pott, a British neurosurgeon, established that the brain rather than the skull was responsible for the seizures. Posttraumatic scars were often focal and offered guidance for early neurosurgeons into the functional anatomy of the brain. The era of modern neurosurgery was ushered in by Sir Victor Horsley,[46] who introduced asepsis, anesthesia, and the new science of cerebral localization. He also described the technique of subpial cortical dissection and resection, a standard technique used by epilepsy surgeons today.

The seizure outcome after surgical management of patients with temporal lobe epilepsy is excellent in most of the recently reported series,[73] and a recent randomized, controlled trial comparing surgical to medical treatment showed a significantly better outcome in the surgical group.[136] However, the results of surgery in extratemporal epilepsy are less encouraging. Many factors seem to account for this difference: Whereas mesial temporal sclerosis constitutes the majority of temporal lobe epilepsies, extratemporal epilepsy is a more heterogeneous group and lacks a common pathologic substrate. Furthermore, the difficulty in interpreting the semiology, the uncertainty of the localizing value of the different studies performed, and the vicinity of eloquent areas to the epileptogenic focus in many of these cases appear to decrease the chances of obtaining an excellent outcome.

In spite of the difficulties previously mentioned, recent radiologic and neurosurgical advances undoubtedly revolutionized this field: Modern anatomic and functional imaging are able to detect more-discrete lesions, and neurosurgical techniques help to optimize resections while minimizing morbidity.

Historical Perspectives

Impact of Neuroimaging

The advent of magnetic resonance imaging (MRI) and its ever-improving sensitivity in detecting cerebral abnormalities had its greatest impact on the surgical management of neocortical epilepsy. With the improvement in the anatomic details provided, more-subtle variations are being observed and a larger number of patients are being diagnosed as harboring neoplastic or developmental lesions. Nevertheless, even with these advances, MRI was unrevealing in 39% of histologically verified focal cortical dysplasia in a recent study,[22] and it has been estimated that ~25% of cases with refractory epilepsies have normal MRI.[67,120]

Overall, MRI is more sensitive in detecting tumors than neuronal migration disorders,[47] and in general, the detection of abnormalities by MRI is known to be associated with good surgical outcome.[47,69,147]

New MRI techniques such as diffusion-weighted MRI[29,80] and quantitative MRI[11] appear to be promising and may further help to localize the epileptic focus.

Impact of Pathology and Electrophysiology

Whereas most temporal lobe epilepsy (TLE) is characterized by hippocampal pathology,[12,61,62] neocortical epilepsy lacks a common pathologic substrate. A wide range of structural anomalies has been associated with chronic partial neocortical epilepsy. These anomalies can be classified into five large categories: (a) malformative, (b) tumoral, (c) ischemic, (d) traumatic, and (e) infectious. In a small number of patients, the nonspecific substrate of gliosis is found. Most of these lesions are not believed to be epileptogenic per se; rather, the epileptogenicity is due to excitability of the surrounding cortex. Numerous mechanisms have been implicated.[104,105] These include neurochemical changes, pressure effect, and ischemia. In the congenital malformative diseases, intrinsic epileptogenicity has been established with recording of continuous ictal epileptogenic discharges on electrocorticography.[86] Dual or multiple pathologic substrates are increasingly detected owing to advances in imaging techniques and careful pathologic studies from large surgical series. The occurrence of hippocampal volume loss in association with pathologies outside of the archipallium are examples of distant but coexistent disease.[17,66,72,101] Furthermore, the coexistence of dysplastic and neoplastic disease has been established in developmental tumors, for example, gangliogliomas and dysembryoplastic neuroepithelial tumors (DNETs).[50] This has important consequences for the surgical strategies, which are generally designed to resect all identified pathology for best results. In fact, the identification and resection of all focal pathology is considered a predictor of good outcome following neocortical resection.

Indications

Principal Candidates

The indications for surgery are discussed in the chapters referring to the surgically remediable syndromes (see Chapters 167,168,169). Briefly summarized, three major groups are identified.

The first group consists of lesional, nondevelopmental pathology causing partial epilepsy. A majority of these patients continue to have intractable epilepsy despite antiepileptic drugs

(AEDs). A favorable outcome following resective surgery is expected, often with lesionectomy alone. The second group consists of developmental abnormalities causing partial epilepsy and is characterized by a more diffuse pathology and difficulty in precisely localizing the ictal onset zone (Table 1). Patients in this category are considered for surgical treatment only following failure of AEDs. The third group has partial epilepsy without evidence of a lesion on MRI or metabolic imaging. This is the most difficult subgroup of patients who have less favorable results following resective surgery. These patients should be investigated in an experienced epilepsy surgery center.

Table 1 Developmental abnormalities associated with epilepsy

Abnormalities of gyration	Megaloencephaly
Agria	Heterotopias
Macrogyria, focal, diffuse	Tuberous sclerosis

Polymicroggyria, focal, diffuse	Focal cortical dysplasia, microdysgenesis
Polymicrogyria, or macrogyria with cleft	Cortical dysgenesis associated with neoplasia

Evaluation Criteria

The goal of the evaluation criteria is to identify the epileptogenic zone, or the area of abnormal brain tissue responsible for genesis of the seizures, and its relationship to essentially normal brain. In this respect, the stages or steps in the presurgical evaluation are essentially similar to the evaluation of temporal lobe epilepsy. These steps include neuroimaging, interictal and ictal recordings with video-electroencephalography (EEG), neuropsychological testing, and the Wada test for speech lateralization. The value of the sodium Amytal test for memory localization in neocortical epilepsy is unclear[57] because in a significant number of patients a decreased memory reserve is noted without evidence of limbic disease.

Careful anatomic imaging is essential and should be performed early in the presurgical evaluation so as to guide the electrophysiology evaluation and correlate it with the lesional pathology using magnetic resonance imaging protocols. The specific sequences are evolving and at present include (a) a coronal, high-resolution volumetric acquisition (e.g., three-dimensional [3D] spoiled gradient-echo [SPGR]) in the coronal plane to produce 2-mm contiguous slices of the entire brain (flip angle 10/TR 11/TE 4.4/TI 300/250 mm Fov/192 × 256 matrix); (b) a conventional double-echo T2-weighted sequence in the coronal or axial plane (TR 2000/TE 20, 80/230 mm Fov/192 × 256/5 mm slice/2 mm gap); and (c) a two-dimensional fast fluid-attenuated inversion recovery (FLAIR) sequence in the coronal or axial plane (TR 2000/TE 80/TI 2400/230 mm Fov/192 × 256/5 mm slice/2 mm gap). The combination of the conventional pulse sequences is used to characterize a structural abnormality using morphology, signal intensity characteristics, and, if appropriate, the degree of enhancement with gadolinium. The fast FLAIR sequence has been particularly useful in localizing structural abnormalities of the neocortex and archicortex because it is essentially a heavily T2-weighted sequence with dark cerebrospinal fluid (CSF). This contrast results in increased conspicuousness of peripheral cortical lesions or subtle underlying white matter abnormalities that may be identifiable on the conventional pulse sequences only in retrospect. The volumetric acquisition is then used to further characterize morphology, accurately localize the lesion within the brain, and precisely define its 3D spatial relationships relative to adjacent normal brain. The 3D study is also specifically designed so that the data can be reformatted along any orthogonal or oblique plane without significantly compromising image quality or subjected to alternative postprocessing algorithms (surface reconstruction, volumetric analysis). This has been proven to be especially helpful in the identification of subtle neocortical developmental anomalies[121] (e.g., small focus of polymicrogyria or more subtle cortical disorganization) (Fig. 1) or very mild volume loss in the archicortex. Hippocampal volumetric data are obtained when a dual pathology is suspected.[17]

The role of positron emission tomography (PET) scanning in neocortical epilepsy is controversial.[1,128] In patients in whom a lesion is identified on MR, the PET scanning role is superfluous because the relationship between the ictal onset zone and the hypometabolic zone, when identified, has not yet been determined. Interictal PET has been carried out mainly with fluorodeoxyglucose and flumazenil. In temporal lobe epilepsy it demonstrates hypometabolism in 60% to 90% of patients; however it is less sensitive in extratemporal epilepsy (45%–60%).[42,118] Flumazenil-PET may have a higher sensitivity than fluorodeoxyglucose-PET in delineating the epileptogenic zone in extratemporal cases,[75] but these findings need further study for confirmation.

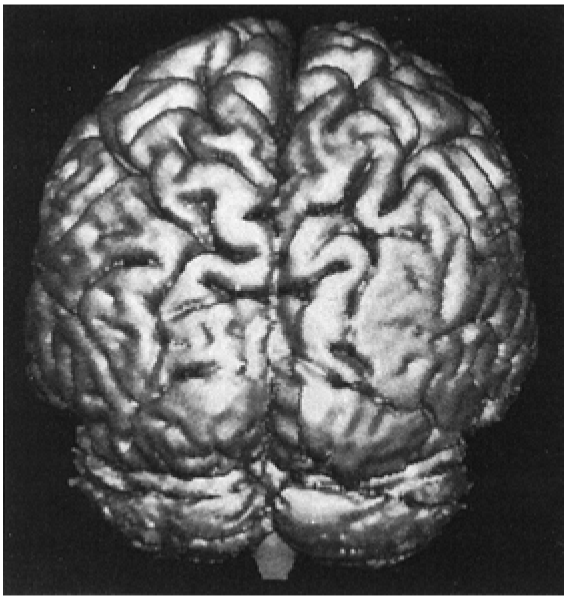

FIGURE 1. Posterior hemispheric three-dimensional volumetric re-cord rendering: A cortical dysplastic area is noted posterior parietal. This abnormality was not seen on standard magnetic resonance imaging studies.

Single photon emission computed tomography (SPECT) scanning performed interictally, and particularly ictally, can be of help in the localization of neocortical epilepsy. Ictal SPECT is complicated by the need to deliver the radiopharmaceutical early in the ictal phase and poor resolution leading to variable interpretation. The SPECT information should be used judiciously and carefully correlated with the electroclinical syndrome. Recent studies tried to establish its sensitivity and specificity. The following results were obtained when SPECT was compared to intracranial EEG recordings (considered as gold standard): Interictal SPECT was consistent with intracranial EEG localization in 33% of patients and was normal in 52% of patients in whom seizures were localized by intracranial EEG. On the other hand, ictal SPECT was consistent with the intracranial localization in 74% of patients and was normal in 7% of cases in which seizures were localized by intracranial EEG. The presence or absence of a structural lesion did not appear to affect the reliability of ictal SPECT in this study.[126]

SISCOM (subtraction SPECT coregistered to MRI) refers to the subtraction of ictal and interictal SPECT scans with subsequent coregistration to MRI. This technique is clearly superior to conventional visual analysis and appears to be a better predictor of surgical outcome.[78,111]

Several centers have reported the use of proton MR spectroscopy in nonlesional epilepsy.[76,77] The high-resolution metabolic imaging is combined with precise delineation of anatomic structures. Decreased *N*-acetylaspartate (NAA) and increased choline are seen interictally. Postictally, a focal increase in lactate[36] appears to correlate with the ictal onset zone.

Goals of Surgery in the Ideal Candidate

The goal of the surgery is to render the patient seizure free without disturbances in cognitive function and off or with decreased antiepileptic medications. This goal can be reasonably achieved in patients with localized pathology and concordant with the electroclinical syndrome. In the less-than-ideal candidate, when a seizure-free outcome is less likely, surgery is undertaken when there are significant chances of seizure improvement and psychosocial gain.

Surgical Approaches

Reliance on the Presurgical Evaluation

History, Neurologic, and Cognitive Examination

In establishing the electroclinical syndrome, the history and physical examination are paramount, and family and friends can provide important information. The familial and prenatal histories yield clues to genetic susceptibility or early insults. Information concerning the natural evolution of the seizure pattern is gathered, particularly the presence of an aura, as well as findings of the various seizure types and response to medication for each type. The semiology of the ictal phenomenon can yield important clues to locate the generator. In some patients, subtle neurologic deficits are noted, which helps in the localization process. The cognitive deficits should be interpreted in relation to dominance established by the Wada test.[133] It is essential to establish the lateralization of speech in neocortical epilepsy because there is a high incidence of unusual speech lateralization in this patient population, particularly with an early age of seizure onset.

Scalp and Invasive Electroencephalography

Scalp EEG with interictal and ictal recordings are essential in the localization process of focal epilepsy. The distribution of interictal discharges correlates better with the extent and location of the epileptogenic zone than ictal recordings. Because in neocortical epilepsy the epileptogenic zone is larger than in temporal lobe epilepsy, the interictal discharges tend to be widely distributed. In addition, the availability of several pathways of propagation results in a poor localization of the ictal discharges. False localization–lateralization occurs in 28% of occipital and 16% of parietal lobe epilepsies. Generalized ictal onsets are noted in mesial frontal and occipital lobe epilepsies. Lateral frontal and parietal lobe seizures frequently have a localized onset.

To further define the ictal onset area, several classes of invasive electrodes have been introduced.[70] These consist of electrodes of intermediate invasiveness such as epidural pegs, foramen ovale, and more invasive electrodes such as depth, subdural grid, and strip electrodes. Each type offers specific advantages and disadvantages, and these are reviewed in Chapters 170 and 171. Recently, with the introduction of advanced MR techniques, there has been less reliance on invasive electrodes in the preoperative workup.

Functional Mapping

When the lesion or the epileptogenic zone involves or is adjacent to eloquent cortex, functional mapping should be performed so that a safe and complete resection is possible. Mapping is usually performed when resections are contemplated in the central area, dominant inferior frontal cortex, dominant temporal lobe posterior to the precentral sulcus, and the dominant parietal lobe and occipital lobe. A variety of mapping methods is available (see Chapters 173,174,175), and newer, noninvasive methodologies are being assessed, for example, functional MR techniques[10,24,63,79] and magnetoencephalography.

Awake Craniotomy

This technique has been facilitated with the introduction of propofol anesthesia[71] (refer to Chapter 174 for complete description of the method). Patient cooperation and an anesthesiologist familiar with the technique are essential.[4] This technique provides continuous feedback while the patient is maintained awake during resections adjacent to language areas. An awake craniotomy is difficult to perform in children, who, therefore, may require an implanted grid and extraoperative language mapping.[2]

Acute Mapping Using General Anesthesia and Intubation

Cortical stimulation can be performed in the primary motor cortex with judicious use of short-acting muscular blockade agents, low concentrations of inhalation agents, and the substitution or addition of propofol, with adequate responses. This may be supplemented by somatosensory-evoked potentials to map the postcentral gyrus.[143]

Chronic Mapping Using Subdural Electrodes

This method offers several advantages because it allows repeated stimulation under variable intensities and with full patient cooperation. Cortical areas that are difficult to stimulate acutely, such as the dominant posterior basal temporal lobe and occipital and medial frontal lobe, can be carefully investigated using this method. The area to be stimulated and potentially resected can be thoroughly discussed with the patient preoperatively. There are several disadvantages to this technique. The functional areas seem to be wider than on acute studies,[41] which would indicate that this may be due to the larger grid electrode size, the method of stimulation, and simultaneous responses from adjacent gyri and current spread. The cost of this investigation is high. Infections are a rare but serious complication.

Functional Magnetic Resonance Imaging

Functional MRI (fMRI) allows noninvasive functional mapping. The combination of echo-planar imaging (EPI), which is a fast magnetic resonance imaging technique, with the blood oxygenation level–dependent (BOLD) method allowed functional brain imaging. fMRI studies have used successfully in

identification of the primary motor and sensory cortex.[40,54,97] Cortical simulation and fMRI activation were found to lie within 3 to 5 mm of each other.[35] On the other hand, fMRI of language processing has focused on language lateralization and, to a lesser extent, on localization. Numerous studies showed excellent agreement of the fMRI lateralization with the intracarotid amobarbital test or electrocorticography.[28,44] The value of speech localization by fMRI remains unclear.[14,32]

Reliance on Preoperative Substrate

Developmental Substrate

Malformations of cortical development are frequently associated with intractable epilepsy. From 8% to 12% of patients with partial epilepsy are found to have cortical dysplasia. It is expected that, with the improvement in MRI technology, this incidence will increase as a significant number of patients with negative MRI show cortical dysplasia on surgical specimen. Recently reported surgical series show that cortical dysplasia is the leading etiology in patients subjected to epilepsy surgery.[34,134,142,147]

The term focal cortical dysplasia was initially used by Taylor et al. in 1971.[125] Subsequently this term has been used for a wide range of abnormalities. There is a general agreement that classifications based on pathologic findings are the most useful. These have adopted a three- or four-tier classification with minor, moderate, and severe disruption of cortical structure. The Taylor type represents the most extensive disruption.

The mild dysplasia, classified also as type 1a or architectural dysplasia, consists of cortical dyslamination with or without poorly differentiated cells and occurs mostly in the temporal lobe in association with hippocampal sclerosis. MRI is frequently negative or shows focal hypoplasia and gray–white matter blurring. The moderate dysplasia, or type 1b or cytoarchitectural dysplasia, consists of disruption of cortical layering with giant neurons. MRI, when positive, shows focal hypoplasia but no significant signal alterations. PET and SPECT are important imaging methodologies in the localization of the epileptogenic zone.

The Taylor-type dysplasia, or types 2a and 2b, is characterized by the absence of cortical layering and the presence of giant dysmorphic neurons with or without balloon cells. MRI often detects these lesions as focal thickening of the cortex and blurring of the gray–white matter junction. A funnel-shaped increased signal intensity on T2 with its summit reaching the ventricle is characteristic of the Taylor-type dysplasia with balloon cells.

In general, postoperative seizure control is less favorable than with other lesions, such as tumors or vascular lesions. A seizure freedom rate ranging between 35% and 55% was reported in many series.[45,85,95,144] A number of studies suggest an influence of the histopathology on the seizure outcome, with the presence of milder histologic abnormalities being a predictor of a better outcome.[31] Nevertheless, the presence of balloon cells (even though a sign of a more severe abnormality) was also associated with a favorable outcome.[21,124,132]

Tumors

Brain tumors are found in 15% to 30% of patients undergoing surgical resection for neocortical epilepsy.[34,134,142,147] These tumors can be classified into two main categories: (a) glial (mainly astrocytomas, oligodendrogliomas, and oligoastrocytomas) and (b) neuronoglial (mainly gangliogliomas and dysembryoplastic neuroepithelial tumors [DNETs]). In the published experience at Cleveland Clinic Foundation over a 17-year period,[34] 133 patients underwent extratemporal resections for epilepsy: tumors were found in 27.8% of cases; of these, 27% were low-grade astrocytomas, 18.9% gangliogliomas, 16.2% DNETs, 16.2% glioneuronal hamartomas, 10.8% oligodendrogliomas, 8.1% anaplastic astrocytomas, and 2.7% mixed oligoastrocytomas.

Seizures are more frequently associated with low-grade than with high-grade tumors, and their occurrence appears to be a favorable prognostic factor.[9] The pathogenesis underlying these seizures remains poorly understood; multiple mechanisms have been proposed: Traditional explanations included impaired vascularization and ischemic changes in the surrounding cortex[90] and local peritumoral ischemia induced by the mass effect.[39] More recent studies invoke peritumoral disturbance of compounds that alter the membrane potential of neurons,[9] mainly amino acid neurotransmitters (gamma-aminobutyric acid [GABA], taurine, aspartate, and glutamate)[38,55,115,116] and magnesium[6] and iron ions.[119] Furthermore, the pH, which modulates neuronal excitability, is significantly more alkaline in the peritumoral cortex.[68,81]

On the other hand, glioneuronal tumors (gangliogliomas and DNETs) may have intrinsic epileptogenic activity. The histopathologic hallmark of these tumors is a combination of neuronal and glial cell elements.[140] The neuronal component of the tumor itself may contribute to epileptic activity.[13]

Compared to other lesions, tumors were found to have a higher rate of seizure control after surgery.[130] Several authors have reported a seizure-free rate ranging between 66% and 82%.[15,37,147] Laoprasert et al.[64] reported a better seizure outcome with total compared to partial resection (89% seizure-free with total vs. 63% with partial resection).

Given their developmental nature, neuronoglial tumors are frequently associated with cortical dysplasia.[96] This could explain the persistent seizures following some lesionectomies. The role of electrocorticography has not been established because the interictal discharges are frequently diffuse or not prominent at all. In dealing with this pathology, wide resection of the gyrus involved is recommended rather than a pure lesionectomy. If seizures persist, an invasive electrode study is indicated.

Gliotic Substrates

Trauma.

Hippocrates first reported seizures as a complication of head injury. Subsequent landmarks in understanding the pathophysiology of epilepsy and cerebral localization resulted from the careful studies of meningocerebral scars by pioneers of epilepsy surgery.[88,89] Recent data show that posttraumatic epilepsy can complicate 25% to 30% of cases of severe head injury and 5% to 10% of cases of mild to moderate injury.[51] It is a common cause of epilepsy, accounting for approximately 4% of focal epilepsy in the general population, and it is the leading cause of epilepsy with onset in young adults (15–24 years of age).[3]

Two types of head injury are distinguished—penetrating and nonpenetrating. A variety of pathologic changes are noted following blunt or nonpenetrating injury to the brain. These include axonal damage, intracerebral hematomas, ischemic parenchymal changes, and contusion frequently involving the orbitofrontal cortex and the basal and anterior temporal lobes. The incidence of seizures following blunt injury is variable.[18,19] Due to the diffuse nature of closed-head injury, localization of the epileptogenic cortex is frequently difficult. Dual pathologies can occur with the presence of orbitofrontal and associated mesial temporal epilepsy.[72] Patients are considered for surgery when there is a good correlation between the electroclinical syndrome and pathologic changes on MRI. Wide cortical resections are recommended to ensure a good surgical outcome. Invasive electrodes should be used when focal resections are contemplated or dual pathologies are suspected.

Missile injuries to the brain are frequently complicated by seizures.[18,19] Focal and diffuse pathologic changes are noted. The focal damage results in the classically described meningocerebral scar. The management of meningocerebral scars has been described in the classical papers of Penfield. Seizure outcome following cortical resection is excellent if the pathologic changes are focal and correlate well with the semiology and electrophysiology of the seizures.

Strokes

The surgical treatment of intractable epilepsy following ischemic vascular events has not received much attention,[52,58] likely because the incidence of strokes is highest in the elderly, who would not qualify for surgical management. In this pathology, it is paramount to consider the pathophysiologic mechanism leading to ischemia. The epileptogenic zone can overlap the ischemic area or can occur at some distance from it. As an illustrative case, a 16-year-old, right-handed girl suffered from transposition of the great vessels, which was repaired at the age of 2 years. Postoperatively, she suffered a cardiac arrest and was resuscitated. Subsequently, she developed seizures characterized by an aura of a scary feeling and complex visual phenomenon. The MRI showed a watershed, right parietal infarct. Interictal and ictal data were suggestive of a posterior temporoparietal epileptogenic zone. The visual field examination was normal. Subdural electrodes were placed over the parietooccipital area and basal temporal lobe. Typical seizures were recorded with a right amygdala and anterior parahippocampal onset. No seizures were noted from the vicinity of the ischemic area. She underwent an anteromedial temporal resection and has been seizure free for 2 years.

Vascular Malformations

Vascular malformations are increasingly being detected in patients with localization-related epilepsy. These usually fall into three categories: (a) cavernous angiomas, (b) arteriovenous malformations (AVMs), and (c) venous angiomas. The surgical management of intractable epilepsy associated with these lesions is controversial, and different pathophysiologic mechanisms leading to epileptogenicity are likely in each.

Cavernous angiomas can be considered as one of the more focal models of epilepsy in humans. Seizures are their most common presenting symptom, observed in 38% to 100% of cases in different reported series,[26,53,56,103] and they probably result from the toxic effects of iron deposition in the form of hemosiderin.[119,135] Although the pathophysiologic mechanism appears to be very focal, several series have recorded suboptimal seizure outcome following lesionectomies. This could be due to incomplete resection of the hemosiderin-impregnated area or the existence of dual pathology, specifically when located in the mesial temporal lobe. An accepted management strategy is to resect the surrounding damaged cortex until normal cortex is identified. In primary cortex or speech areas, surgery can be performed under local anesthesia.

The role of radiosurgery remains questionable and its results regarding seizure control are inferior to those of surgery: Regis et al.[102] reported a seizure-free rate of 53%, and Shih et al.,[117] in a comparative study between craniotomy and radiosurgery, found better results with craniotomy (79% seizure free with craniotomy vs. 25% with radiosurgery). Furthermore, many authors reported no effect of radiosurgery on the bleeding risk associated with cavernous malformations.[49,114]

In the case of AVMs, several mechanisms for the pathogenesis of epilepsy have been advanced, including previous hemorrhage resulting in gliosis or hemosiderin, perilesional neurochemical changes, and focal cerebral ischemia due to a steal phenomenon.[59,141,145] A number of earlier studies showed a poor seizure outcome following surgery, with some even reporting an increase in seizure frequency.[25,33,74,87] More recent series, however, documented postoperative seizures in <40% of patients with a history of preoperative seizures and <10% in those without a history preoperative seizures.[94,146] A recently published large series[129] found that there was >50% reduction in seizure frequency from the preoperative incidence. Furthermore, 75% and 83% of patients were seizure-free postoperatively in two recent surgical series.[30,94] On the other hand, seizure-free rates ranging between 51% and 80% are reported in recent series of gamma knife radiosurgery,[51,60,112] the antiepileptic effect of radiosurgery being unknown.

Venous angiomas are rarely associated with epilepsy. They are at times discovered during the surgical workup and are frequently unrelated to the seizures. Resection of these lesions can yield to hemorrhagic infarcts; thus, surgical excision is not recommended.

Technique

Cortical Resections

Defining the Boundaries of the Epileptogenic Zone

Resection of the epileptogenic cortex is an established treatment modality for neocortical intractable epilepsy. If the epileptogenic zone is circumscribed, focal cortical resection is recommended. When the ictal area is wide, a lobectomy might be considered. The resection strategy should take into consideration the peculiar gyral and sulcal organization of the brain and its arterial supply and venous drainage. Frequently, anatomic considerations have a significant effect on the geometry of the resected area. The subpial dissection is a preferred technique. Penfield noted long ago the absence of a meningocerebral scar and distal ischemic insult when this technique was used. When a focal cortical resection is performed, the subcortical white matter pathways should be preserved.

Role of Pre- and Postresection Electrocorticography

Despite the very early introduction of this technique as an effort to improve outcome following surgical treatment, the value of intraoperative electrocorticography (ECoG) is questionable. Interictal discharges are variable in location, intraoperative time constraints lead to sampling errors, and resective strategy is more influenced by ictal recordings from invasive electrodes. In the absence of invasive ictal recordings, the geometry of the epileptogenic zone is inferred from the converging evidence of the nature, location, and symptomatology of the structural abnormality and its concordance with the scalp electrophysiology. In some cases, the surgeon may apply a two-staged procedure using a minimalist approach at the first stage, reserving a more aggressive resection if the first procedure fails to produce a desired effect.

Frontal Lobe Resections

The frontal lobe encompasses one third of the cerebral cortex volume, yet, despite its large size and its high epileptogenicity, the frequency of surgically treated frontal lobe epilepsy is small as compared with temporal lobe epilepsy. This varies between 18%[65,83] and 5.5% in large reported series.

The manifestations of frontal lobe epilepsy are protean[8,137] and can be divided into three major groups[109]: (a) supplementary motor type, (b) complex partial seizures, and (c) focal motor seizures. Five electroclinical syndromes[27,65] are distinguished: (a) frontopolar, (b) orbitofrontal, (c) dorsolateral,

(d) supplementary motor area, and (e) cingulate. The localization of an ictal onset area is difficult in frontal lobe epilepsy and is facilitated when a lesion is present on imaging.[65] In nonlesional cases, chronic recordings are recommended using subdural electrodes.

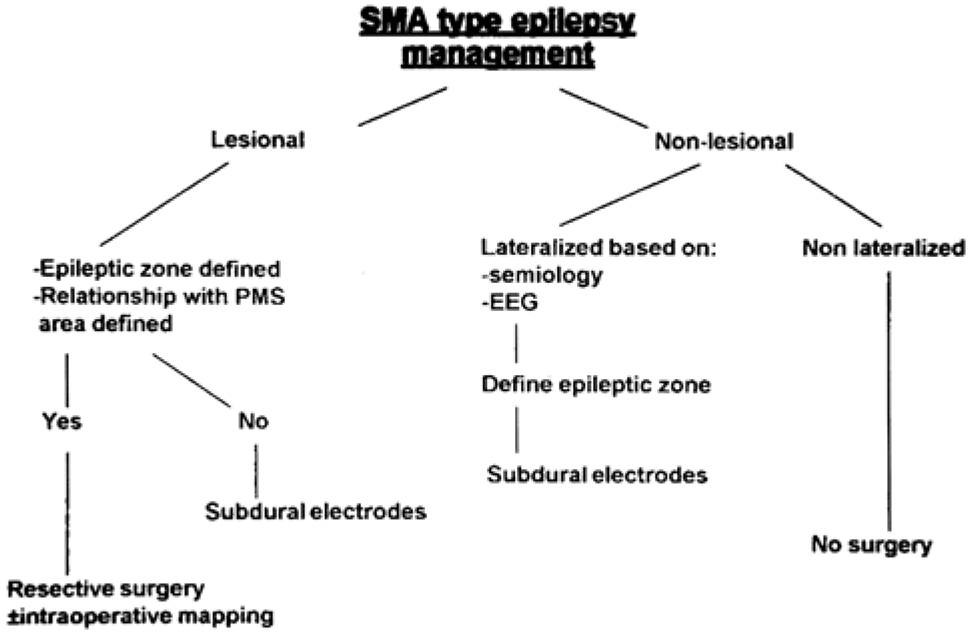

FIGURE 2. Management of epilepsy of the supplementary motor area (SMA) type. EEG, electroencephalogram.

Frontal Lobectomy

When the epileptogenic zone is diffuse, a complete frontal lobectomy anterior to the precentral sulcus can be performed under general anesthesia. The patient is positioned supine, with the head slightly rotated to the contralateral side. A large, C-shaped skin incision is fashioned, followed by a large craniotomy extending to the midline. The location of the central sulcus is determined using somatosensory-evoked potentials or cortical stimulation.[82,84] The resection initially is carried one gyrus anterior to the precentral sulcus. This is subsequently removed in a subpial fashion, taking care not to undercut the white matter tracts coursing from the precentral gyrus; the ascending venous system draining the central area is spared. On the dominant hemisphere, the Broca area should be identified and preserved.[82,83,93] This is best performed under local anesthesia or with the use of a subdural grid. The complications of a complete frontal lobectomy are rare. Hemiplegia occurs in 0.5% of reported cases. There are no significant neurophysiologic deficits.

In the Montreal Neurological Institute series reported in 1975,[99] 55% of patients benefited from a frontal lobe resection, with 23% becoming completely seizure free. In a more recent series,[65] 68% became seizure free following frontal lobe resection. In this series, chronic EEG recordings were found to be helpful in planning surgery but had limited sensitivity and specificity.

Supplementary Motor Area

The supplementary motor area (SMA), as defined by Penfield and Welch,[92,93] is located in the mesial superior frontal cortex anterior to the primary motor cortex of the lower extremity and superior to the cingulate gyrus. Functional studies have shown that this area is activated during initiation of movement and vocalization. Stimulation of this area leads to a fencing posture with bilateral motor movement. Unilateral responses are rare. Resection of this area leads to transient contralateral weakness and apraxia. The SMA is extensively and somatotopically connected through the corpus callosum; this results in quick spread of the ictal discharges to the contralateral side, making lateralization of the ictal onset zone difficult.[130] An algorithm for investigation of SMA-type seizures is shown in FIGURE 2. When the ictal onset area is not clearly defined, bilateral subdural electrodes are placed within the interhemispheric fissure. These are also used to delineate the primary motor cortex. There is considerable anatomic variation in the precentral sulcus and its relationship with the marginal ramus. On long-term follow-up, no gross motor deficits are noted with this resection.

Orbitofrontal Resections

The orbitofrontal area is limited laterally by the orbitofrontal sulcus, medially by the olfactory sulcus, anteriorly and superiorly by the frontomarginal sulcus, and posteriorly by the anterior perforated area. The orbitofrontal cortex is extensively connected with the anterior and mesial temporal lobe, cingulum, and opercular area. For this reason, orbitofrontal seizures are frequently misdiagnosed as anterior temporal.[126] Adequate sampling of these structures using invasive electrodes is recommended. On the nondominant side, extensive resection of the orbitofrontal cortex can be performed. The intersection of the optic nerve and olfactory nerve is used as the posterior limit of the resection. On the dominant side, mapping of the Broca area should be performed.

Resections in the Primary Motor and Sensory Cortex

Central-type epilepsies are rare, and their surgical management remains a challenge because of the risk of a permanent neurologic deficit. However, we recently reported our series of 24 patients operated at the American University of Beirut between 1997 and 2003, in which we showed that selective resection in the primary sensorimotor cortex (PSMC) can be performed,

and the neurologic deficit observed in the immediate postoperative status is transient.[20]

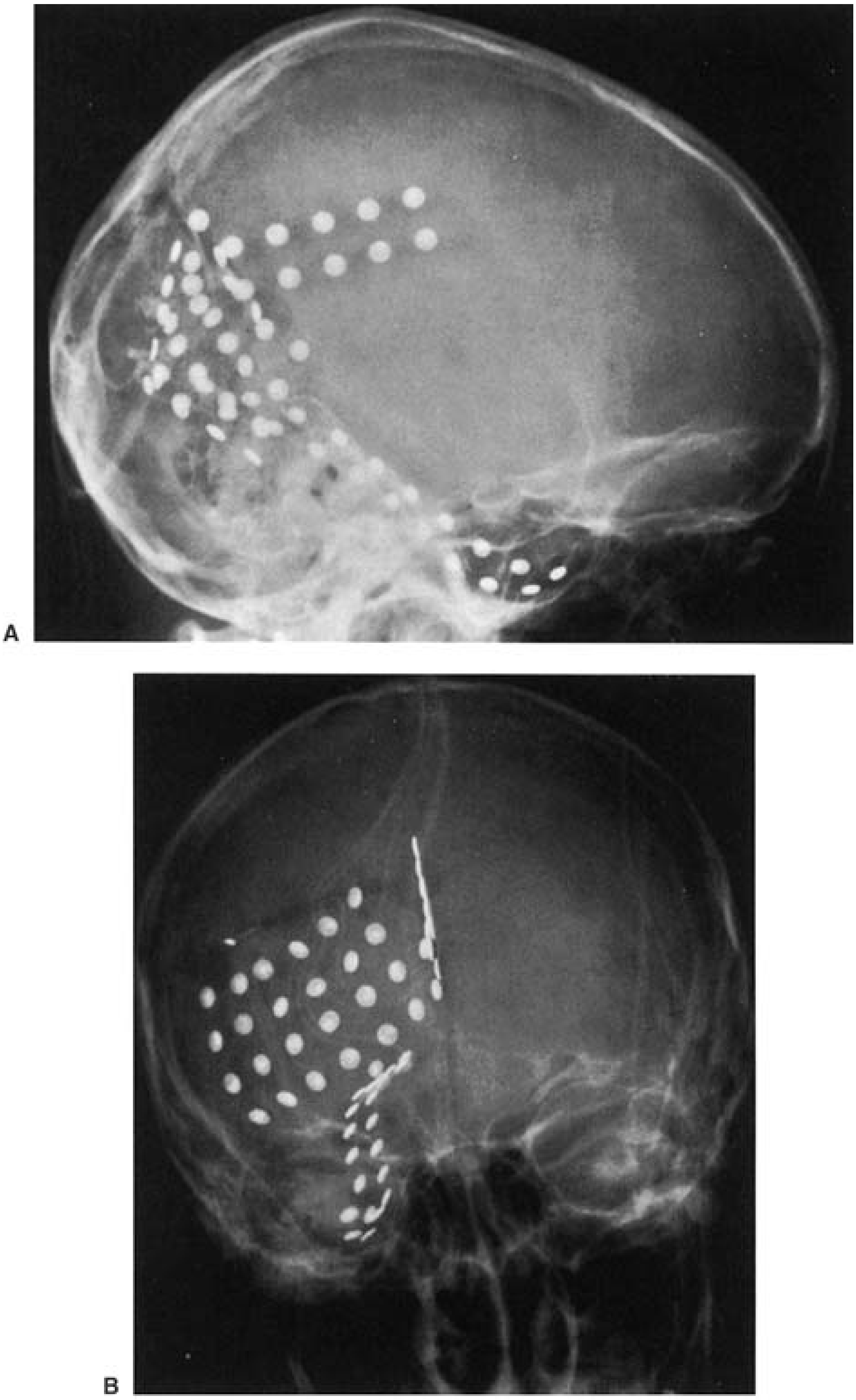

FIGURE 3. Subdural electrode coverage in occipital lobe epilepsy.

Following selective motor resections, severe motor deficit occurred in the immediate postoperative period, gradual improvement started 1 month postoperatively on average, and substantial improvement was found at 6 months of follow-up. Long-term sequelae included impaired fine hand movements after motor hand area resection, and no recovery of toe movements after motor leg area resection.

Following sensory resections, severe sensory deficit occurred in the immediate postoperative period but progressively improved over 2 to 3 months. Long-term sequelae included impaired position sense after sensory hand area resection.

The average period of follow-up was 4.6 years, and 18 of 24 patients remained seizure free at last follow-up.

Functional recovery following injury to the PSMC has been studied in experimental animal studies[105] and in humans following strokes (mainly using fMRI[48] and PET[112]). The main proposed mechanisms for recovery involve reorganization within the PSMC,[48,105] recruitment of nonprimary motor areas,[105,112] and possibly recruitment of the contralateral PSMC.[16,73]

Parietal Lobe Resections

Seizures originating in the parietal lobe account for up to 6% of reported series. A large proportion of patients exhibit an aura, most commonly somatosensory.[108] Pain, vertiginous sensations, aphasia, or disturbance of body image suggest parietal origin. The ictal manifestations are varied and reflect the quick spread to the frontal lobe in superior parietal epilepsies and to the temporal lobe in inferior parietal cases.[136] Interictal and ictal scalp EEG recordings were not reliable markers for parietal lobe epilepsy. In two recent series, lesions were noted on imaging in all cases, and surgical resections yielded an excellent result. Salanova et al. recently reported the Montreal Neurological Institute (MNI) experience of 79 patients with nontumoral parietal lobe epilepsy. Of these, 45.5% were seizure free, 19% had rare seizures, and 21.5% had worthwhile improvement. Persistent dysphasia was noted in 2 patients, a Gerstmann syndrome in 1, and contralateral weakness in 3.

Occipital Lobe Epilepsy

Occipital lobe seizures are rare, representing 1% of the MNI series.[107] Early clinical manifestations of elementary visual hallucinations, ictal amaurosis, eye movement sensations, and blinking are highly suggestive of an occipital origin.[138] In infracalcarine cases, quick spread to the temporal lobe can produce symptomatology typical of mesial temporal lobe epilepsy. Various spread patterns have been described and can make diagnosis difficult. The presence of a superior quadranopsia or posterior temporal interictal and ictal discharges should suggest occipital lobe epilepsy. An imaging abnormality is found in a large proportion of cases.[138] In patients with hemianopsia, resective surgery carries little risk. On the dominant hemisphere, the speech-related cortex should be identified and spared. The management of patients with intact vision is challenging. When a circumscribed lesion is found, lesionectomy can yield satisfactory results. In nonlesional cases, the ictal onset area should be precisely localized using invasive electrodes. These are used in addition to mapping of the calcarine cortex and speech-related cortex. With this strategy, visual deficits can be minimized (Fig. 3). Resections of the dominant basal temporal lobe should be carefully planned because this can yield an alexia without agraphia deficit.

Good results have been reported in 65% to 80% of patients with occipital lobe epilepsy in recent series. In the MNI series of 37 patients, 46% became seizure free, 21% had rare seizures, and 10% had a worthwhile improvement.

Summary and Conclusions

The management of neocortical epilepsy relies on the identification of a pathologic substrate, which will guide the electrophysiologic evaluation. Circumscribed cortical resections are performed when the pathologic substrate is focal and concurs with an electroclinical syndrome. When the pathologic substrate is diffuse or nonconcordant, electrophysiologic invasive electrodes should be used to determine the volume of resection. The outcome following neocortical resections has significantly improved with the introduction of high-resolution MRI. However, it is still not optimal. Advances in metabolic imaging could yield a more precise definition of the epileptogenic cortex.

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Chapter 178

Multilobar Resections and Hemispherectomy

Devin K. Binder

Johannes Schramm

Introduction

Multilobar resection and hemispherectomy are surgical options available for the treatment of medically intractable seizures arising from a diffuse area of epileptogenicity that remains unilateral but extends beyond one lobe. The nature and extent of the underlying pathologic process, the patient's neurologic status, and the results of preoperative neurophysiologic and neuroimaging studies together determine which surgical procedure should be recommended.

For clarity, hemispherectomy and multilobar resections are presented separately in this chapter.

Hemispherectomy

Historical Perspectives

The term hemispherectomy refers to a variety of operations that functionally isolate the cerebral cortex of one hemisphere from the rest of the nervous system. In 1928, Dandy[24] and L'Hermite[59] originally described hemispherectomy for diffuse infiltrative glioma, but in the next decade few other reports of hemispherectomy for tumor were published.[40] Ten years later, McKenzie performed the first hemispherectomy for epilepsy.[69] In 1950, Krynauw reported on hemispherectomies in 12 children with infantile hemiplegia and intractable epilepsy.[58] In this report, he noted excellent seizure control as well as marked and long-lasting behavioral improvement.

Because of the success of the operation for improving seizure control and behavior, hemispherectomy became widely used in the treatment of seizures associated with infantile hemiplegia. In addition, it came into use for the treatment of other unihemispheric syndromes associated with intractable epilepsy, such as Sturge-Weber disease, Rasmussen encephalitis, and cerebral infarct. By 1961, White reviewed 267 cases from many neurosurgical centers.[113] However, enthusiasm for hemispherectomy waned in the 1960s as more effective anticonvulsants became available and as significant long-term complications became apparent. Many patients developed delayed neurologic and intellectual deterioration postoperatively, and ultimately it became clear that hemorrhage, superficial cerebral hemosiderosis (SCH), and resultant mass effect and hydrocephalus were responsible, and even caused significant mortality.[33,42,74,83]

Over the next two decades, modifications to anatomic hemispherectomy were proposed, aimed at eliminating the late complications of SCH and hydrocephalus. The Oxford-Adams modification involved occlusion of the foramen of Monro with a muscle plug and stripping down the dura to reduce the subdural space.[1,7] Peacock et al. routinely implanted a shunt system into the subdural cavity.[78] Rasmussen developed a new technique termed *functional hemispherectomy* that involved a large central resection, temporal lobectomy, callosotomy, and fronto- and parieto-occipital disconnection.[82] This procedure improved seizure control while maintaining a low incidence of SCH. Other approaches removed only the cortex, termed *hemidecortication* or *hemicorticectomy.*[48,52,115]

Over the past 10 to 15 years, there have been further development and modification of functional hemispherectomy techniques, including hemispheric deafferentation,[89,90] peri-insular hemispherotomy,[107] dorsal transcortical subinsular central hemispherotomy,[26,109] Shimizu and Maehara's variation,[94] and the transsylvian keyhole functional hemispherectomy[88,91] (Table 1). All of these procedures are aimed at less resection and more disconnection, increasing the safety of the procedure and reducing postoperative complications. The improved safety of these modifications and the improvements in neuroimaging and neurophysiologic monitoring have made hemispherectomy a more attractive option for patients with intractable unihemispheric epilepsy.

Role of Pathology

Typical pathologies leading to diffuse unihemispheric disease and intractable epilepsy include neonatal injury, vascular insults, hemimegalencephaly, hemispheric cortical dysplasia and other neuronal migration disorders, Sturge-Weber syndrome, and Rasmussen encephalitis.[34,100] One group of patients has experienced the acute onset of a massive insult resulting in a fixed neurologic deficit. These include those with infantile hemiplegia resulting either from posttraumatic brain injury or vascular insults.[12,58] A second group of patients has malformations of cortical development (MCD), which vary in severity from focal cortical dysplasias to hemispheric cortical dysplasia and hemimegalencephaly.[16,53,102,108,110] In these patients, neurologic manifestations are often delayed or progressive. Another group of patients has Sturge-Weber syndrome (encephalotrigeminal angiomatosis).[32,45,72] Characterized by a facial port wine stain (*nevus flammeus*) and pial angiomatosis, patients develop intractable epilepsy associated with impaired cognitive development and hemiparesis. A final group has acquired progressive neurologic deterioration with intractable epilepsy. The prototype for this is Rasmussen encephalitis. In 1958, Rasmussen et al. first described this chronic childhood encephalitis that leads to intractable epilepsy and neurocognitive deficits.[84] In this disease, the presentation may be delayed but the disease course, once established, is inexorably progressive.

Table 1 Hemispherectomy Techniques

Anatomic hemispherectomy	With basal ganglia removed Without basal ganglia removed En bloc Fragmented
Modification to anatomic hemispherectomy	Oxford-Adams modification “Shunted” hemispherectomy (Peacock)
Procedures preserving white matter	Hemidecortication Hemicorticectomy
Functional hemispherectomy	Classic (Rasmussen) technique Technical variations Hemispheric deafferentation Peri-insular hemispherotomy (Villemure) Japanese modification (Shimuzu/Maehara) Transvertex hemispherotomy (Delalande) Lateral hemispherotomy (Mathern) Transsylvian keyhole (Schramm)

Role of Functional Localization

Because no portion of the hemisphere is to be spared functionally, preoperative or functional localization has no specific role. However, as discussed below, the presence or absence of residual language, motor, and visual function in the affected hemisphere will affect risks of surgery.

Impact of Electrophysiologic Studies

The primary goal of electrophysiologic studies is to lateralize the disease to the radiographically and clinically abnormal hemisphere. Typically, a detailed investigation with both ictal and interictal recordings is performed. Most often, interictal surface electroencephalograms (EEG) show a clearly asymmetric tracing with abnormal slowing, low background voltage, and multifocal independent sharp waves and spikes over the affected hemisphere.[96] In specific disorders, there may be characteristic EEG abnormalities; for example, in hemimegalencephaly, the EEG may demonstrate hemihypsarrhythmia.[75,99]

The other important goal is to determine whether there are abnormalities in the "good" hemisphere. Bilateral independent epileptogenic foci are associated with a poor prognosis for seizure control.[14,96,118] In a study of 12 patients, Carmant et al. demonstrated that a good outcome from hemispherectomy was associated with interictal EEG suppression over the abnormal hemisphere, absence of contralateral slowing, absence of generalized discharges, and absence of bilateral independent spiking.[14] In a study of 28 patients, Doring et al. found that 75% had bilateral EEG abnormalities preoperatively, which was more common in patients with MCD than with acquired lesions.[29] Notably, 77% of patients with acquired lesions became seizure free, compared with only 47% of patients with MCD. Thus, the presence of bilateral EEG abnormalities alone does not preclude consideration for hemispherectomy.

In general, the EEG will lateralize well with structural imaging abnormalities. For hemispherectomy, accurate lateralization and not intrahemispheric localization is most important. In cases without radiographic lateralization, of course, both surface EEG and, when necessary, invasive EEG monitoring play a critical role in both lateralization and localization.

Impact of Neuroimaging

Structural neuroimaging plays an integral role in the preoperative evaluation of the hemispherectomy candidate. The advent of computed tomography (CT) imaging in the 1970s permitted direct visualization of the "good" and "abnormal" hemispheres. While CT can still provide important information (e.g., calcification in Sturge-Weber syndrome), magnetic resonance imaging (MRI) has become the study of choice, as it provides excellent visualization of structural abnormalities in the cerebral cortex and subcortical white matter. It also provides a high-resolution assessment of the "good" hemisphere.

Structural imaging may reveal the severity of disease in vascular or posttraumatic hemispheric injury, from atrophy to porencephalic cysts. Atrophy, characterized by loss of gray and white matter and the presence of an enlarged ventricle, is encountered in most conditions and may be of varying degree, depending on the severity or chronicity of the underlying disease process. In Sturge-Weber syndrome, CT and plain films may show "tram-track" hemispheric calcification, and gadolinium-enhanced MRI demonstrates pial angiomatosis.[67,68] In hemimegalencephaly, structural imaging shows marked enlargement of the affected hemisphere with abnormal thickening of the cortical mantle.[35,50,116] High-resolution structural MRI showing both large and subtle cortical abnormalities has also revolutionized the diagnosis of MCD.[4,63] Early MRI may be useful in the diagnosis of Rasmussen encephalitis,[17,61] but definitive diagnosis requires the appropriate clinical picture together with biopsy demonstrating perivascular lymphocytic cuffing and gliosis.[8,9,36,43,84]

Functional imaging may also be incorporated into the evaluation of the hemispherectomy candidate. For example, positron emission tomography (^{15}O-PET) can be useful to follow disease progression, either with hemimegalencephaly,[85] Sturge-Weber syndrome,[19,60,79] or Rasmussen encephalitis.[17,61] Diffuse unilateral interictal hypometabolism of the affected hemisphere is most commonly found. Single photon emission computed tomography (SPECT) scanning, which provides information regarding cerebral blood flow, may show hypoperfusion in the affected hemisphere.[15,17,18] In one study of seven patients undergoing hemispherectomy, the six patients with unilateral preoperative SPECT findings all had a favorable outcome regardless of the surface EEG.[15] Functional studies are most important in cases without lateralizing findings on structural imaging studies.

Frequency of Use

Hemispherectomy is primarily a pediatric operation, as perinatal, congenital, and early developmental pathologies account for the majority of conditions leading to intractable unihemispheric epilepsy. In 1993, of 47 surveyed epilepsy surgery centers, 29 were performing hemispherectomies; hemidecortication was advocated in three, the anatomic technique in four, and functional hemispherectomy in 22.[97] In an extensive multicenter study of 333 hemispherectomies from 11 centers published by Holthausen et al. in 1994, distribution of etiologies was as follows: 31% hemispheric dysplasia, 25% Rasmussen encephalitis, 14% vascular, 13% hemiatrophy, 8% Sturge-Weber, and 8% other.[47] Surgical techniques included functional hemispherectomy (33%), “Adams modification” (18%), hemidecortication (18%), hemispherotomy (17%), and anatomic hemispherectomy (13%). With the introduction of modern functional hemispherectomy techniques with reduced risk and postoperative complications,[88] and as patients are offered the benefit of the operation earlier in life, it is expected that the number of centers and hemispherectomy cases will increase.

Indications

The indications for hemispherectomy include damage to one hemisphere accompanied by medically intractable epilepsy and accompanying neurologic deficits. As described above, etiologies include extensive hemispheric dysplasia, hemimegalencephaly, Sturge-Weber disease, Rasmussen encephalitis, and perinatal infarction. One group of patients presents with a maximal hemispheric deficit, with contralateral hemiplegia and hemianopsia, usually due to a fixed perinatal insult. The other group presents with intractable epilepsy associated with progressive neurologic deterioration, most often due to a pathology that will evolve ultimately into a maximal hemispheric deficit (e.g., Rasmussen encephalitis).

Hemispherectomy is contraindicated if preoperative evaluation fails to demonstrate that ictal activity arises from the affected hemisphere. Usually, the history of medically intractable epilepsy often with lateralizing semiology is combined with evidence of extensive hemispheric involvement on high-quality MRI and further lateralization and localization with inpatient video-EEG seizure monitoring. Furthermore, hemispherectomy is not employed if less extensive surgical therapy (callosotomy or focal or multilobar resection) may potentially be effective.

Evaluation Criteria

Evaluation of whether and when to recommend hemispherectomy relies on seizure characteristics, neurologic examination, language evaluation, EEG and imaging findings, and the natural history of the associated pathologic process.

Seizure Characteristics

Hemispherectomy candidates may have a variety of seizure types and severity, including drop attacks, focal motor seizures, complex partial seizures, epilepsia partialis continua, and generalized seizures. The seizures are frequent and severe enough to be incapacitating in daily activities; typically, patients will have 10 to 200 seizures per day. In around 80% of patients, a partial motor seizure pattern appears to predominate as a clinical manifestation. Epilepsia partialis continua is characteristic of chronic encephalitis, whereas infantile spasms appear related to a variety of etiologies.

The seizures must truly be medically intractable for a patient to be considered for hemispherectomy. Therapeutic trials of different antiepileptic drugs (AEDs), alone or in combination, should be attempted by a neurologist expert in AED management strategies. However, continued unsuccessful trials of many different

AEDs must be balanced against the potential benefits of early surgery in individual cases.

Neurologic Examination

In addition to intractable epilepsy, these patients typically present with other findings of unilateral hemispheric damage, including impairment of cortical sensory modalities, hemianopsia, hemiplegia, and spasticity. Often they are able to walk and movement of the arm is often more impaired than that of the leg. Fine motor control (pincer grasp) is often absent, but gross motor control (e.g., handgrip) may be preserved. In these cases, no new motor deficit is created by hemispherectomy; occasionally, there may be immediate postoperative hypotonia and loss of voluntary movements that may last a few days to a few weeks. Postoperative completion of hemianopsia is unavoidable and should be part of informed consent, but is not considered an absolute contraindication to hemi-spherectomy.

Language Evaluation

Preoperative language function depends on whether the dominant hemisphere is affected and the severity of disease progression. The younger the age of injury, the more likely language transfer to the healthy hemisphere will occur. Thus, the potential for postoperative language deficits depends on the timing of transfer of language function, and incomplete transfer of language function is a relative contraindication to hemispherectomy. Older children with dominant hemisphere disease and some language function should undergo assessment of lateralization of language (e.g., with the intracarotid amobarbital [Wada] test). The "worst-case scenario" is late appearance of progressive disease (e.g., Rasmussen encephalitis) in the dominant hemisphere; these patients may have severe language deficits following dominant hemispherectomy.

Electroencephalography and Imaging Findings

As described above, there is usually a concordance between EEG abnormalities and a structurally abnormal hemisphere as seen on preoperative imaging studies. In a significant number of cases, however, EEG abnormalities may be recorded from the good hemisphere, either secondary to or independent of the abnormalities of the diseased hemisphere.[47] Bilateral abnormal EEG findings do not represent an absolute contraindication to hemispherectomy, as they may reflect secondary epileptogenesis and disappear after surgery. An explanation for the presence of independent epileptic activity recorded from the good hemisphere should be taken into account during the decision-making process for hemispherectomy.

Etiology, Natural History, and Timing of Surgery

Three aspects of the etiology and natural history of the condition may affect timing of surgery: Whether the condition is congenital or acquired, whether it is strictly unilateral or possibly bilateral, and whether it is static or progressive. Congenital pathologies such as large porencephaly resulting from in utero or perinatal insult or the Sturge-Weber syndrome, which are usually strictly unilateral, have a better prognosis with surgery than a congenital lesion such as hemimegalencephaly or hemispheric dysplasia, which may be associated with some degree of contralateral involvement. Acquired unilateral pathology, such as Rasmussen encephalitis, has a better prognosis than infectious processes, which usually have bilateral involvement.

Timing of surgery is determined by the severity of epilepsy, the age of the patient, the natural history of the disease, and the adequacy of therapeutic trials of anticonvulsant medications. Hemispherectomy before the second or third year of life carries no risk of increasing deficit and is therefore ideal in those cases that present early for diagnosis and evaluation. In later-onset cases (e.g., Rasmussen encephalitis in older children), timing is controversial; while complete transfer of language and motor function to the healthy hemisphere is less likely to occur in older children, nevertheless, the intractable seizures can produce neuropsychological deterioration and may prompt earlier surgery. Evidence is accumulating that seizures themselves as opposed to the pathologic substrate may significantly delay cognitive and psychosocial development.[49,64,87] In certain conditions (e.g., inborn brain malformations) leading to catastrophic infantile epilepsy, very early surgery may be optimal; in our experience, hemispherectomy can be performed safely at 4 months of age.

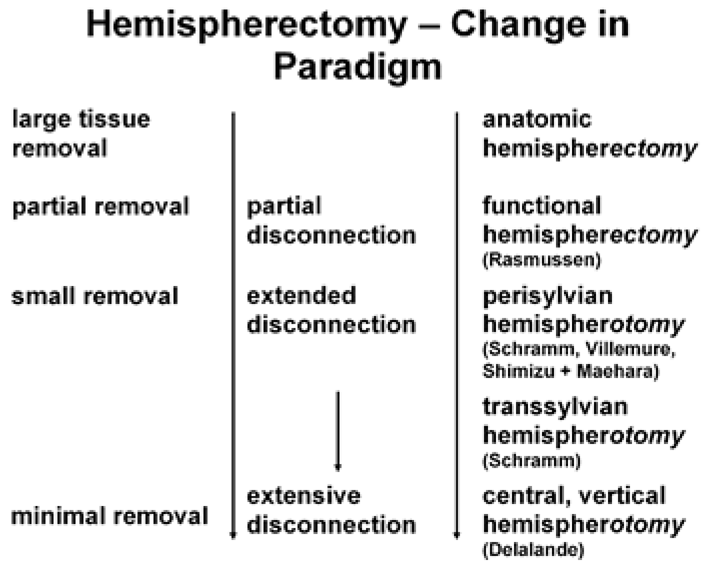
Hemispherectomy – Change in Paradigm
large tissue removal
partial removal
small removal
minimal removal
partial disconnection
extended disconnection
extensive disconnection
anatomic hemispherectomy
functional hemispherectomy (Rasmussen)
perisylvian hemispherotomy (Schramm, Villemure, Shimizu + Maehara)
transsylvian hemispherotomy (Schramm)
central, vertical hemispherotomy (Delalande)

FIGURE 1. Hemispherectomy techniques. Over time, there has been a change in paradigm to more minimal resections combined with more extensive disconnection.

Goals of Surgery

The primary goal of hemispherectomy is to achieve seizure control via complete disconnection of the epileptogenic abnormal

hemisphere from the “good” hemisphere. In anatomic hemispherectomies, this was accomplished by extirpation of the affected hemisphere. In functional hemispherectomies, the emphasis is on complete disconnection rather than resection, although some tissue is resected in each of the current variations of functional hemispherectomy.

The second major goal is to improve psychosocial and cognitive development. Adequate seizure control can be expected to lead to better psychosocial and cognitive development and improved quality of life.[30,49,58]

Surgical Approaches **(Table 1*,* Fig. 1)**

The classic *anatomic hemispherectomy* involved a large T-shaped skin incision along the midline down to the temporal base; hemicraniotomy; occlusion of the anterior and middle cerebral artery and parasagittal veins; interhemispheric callosotomy and frontobasal disconnection; disconnection of insular cortex and temporal stem; and removal of the hemisphere en bloc or in lobes. Total anatomic hemispherectomy was associated with severe intraoperative hemorrhage, hypotension, early and late hydrocephalus, and SCH.[25,33,42,44,74,83,88,104] Development of hydrocephalus necessitated shunting in ~50% of patients. SCH typically developed after 8 to 15 years and led to progressive neurologic deterioration, increased intracranial pressure, and death in many cases.[33,42,74,83]

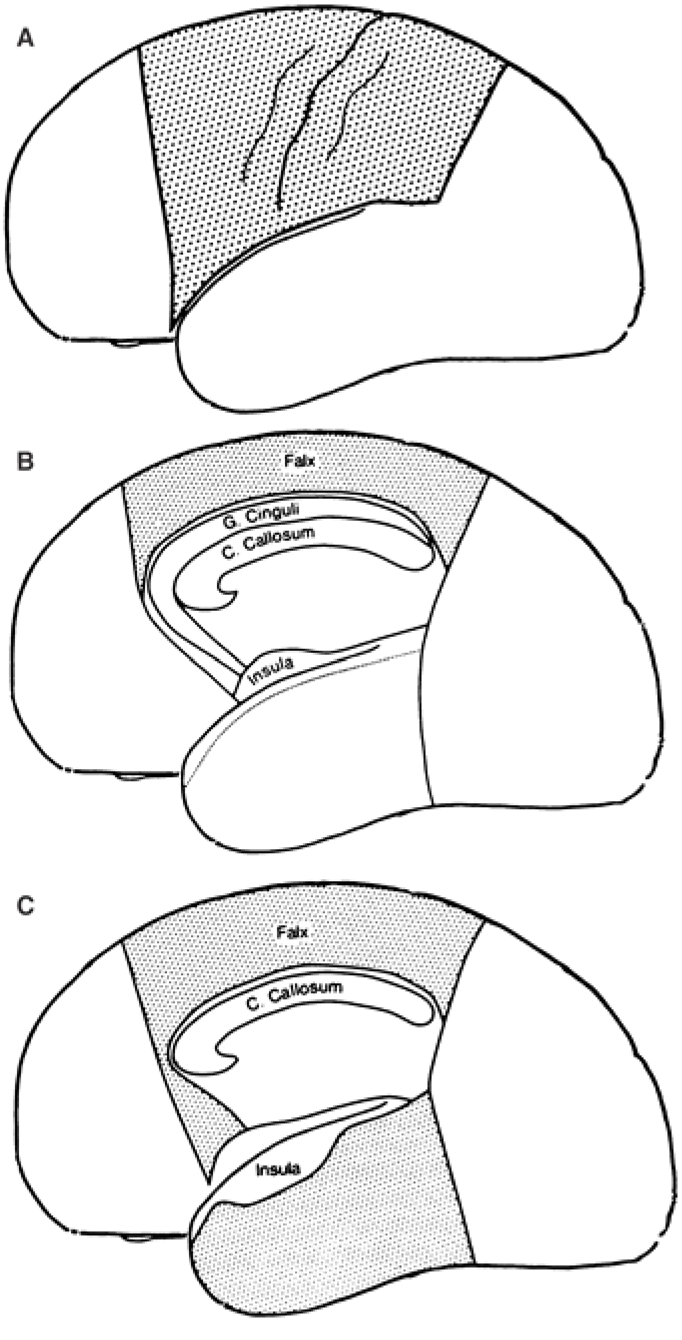

FIGURE 2. The Rasmussen functional hemispherectomy. Diagrammatic representation of left functional hemispherectomy. **A:** Excision of central suprasylvian region, lateral aspect. **B:** Medial aspect. **C:** Removal of cingulate and subcallosal gyri, frontal and parieto-occipital disconnection, and temporal lobectomy. (Reproduced from Rasmussen T. Commentary: extratemporal cortical excisions and hemispherectomy. In: Engel J, ed. *Surgical Treatment of the Epilepsies.* New York: Raven Press; 1987:417–424, with permission.)

The *Oxford-Adams modification* was an attempt to avoid the complications of SCH and hydrocephalus by reducing the subdural space and insulating the subdural cavity from the ventricular system. In this technique, the classic anatomic hemispherectomy is supplemented by occlusion of the foramen of Monro with a muscle plug and occlusion of the subdural space by folding down the convexity dura onto the tentorium, falx, and floor of the middle fossa, thus creating a large extradural space.[1,7] The *shunted hemispherectomy* used by

Peacock at UCLA supplemented the classic anatomic hemispherectomy with routine subdural drainage for 5 days postoperatively to evacuate the debris resulting from the operation followed by placement of a shunt in all cases.[78]

Hemidecortication or *hemicorticectomy* was developed based on the principle that only the ictogenic cortex needs to be removed. This procedure, developed by Ignelzi and Bucy in 1968,[48] involves a large craniotomy; removal of all cortical gray matter while the white matter is left intact, without callosotomy; and no opening into the lateral ventricle except at the temporal tip required to remove the hippocampus. Several modifications of hemidecortication have been proposed.[44,52,115]

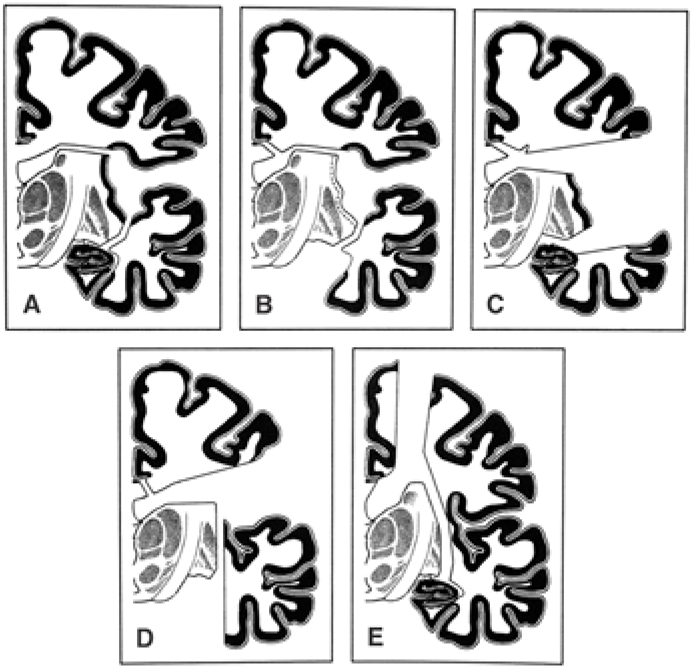

FIGURE 3. Modified functional hemispherectomy techniques. **A:** Transsylvian transsulcal keyhole approach to ventricle (Schramm J, Kral T, Clusmann H. Transsylvian keyhole functional hemispherectomy. *Neurosurgery.* 2001;49[4]:891–900). **B:** Second part in transsylvian keyhole approach: Temporomesial resection, mesial disconnection, and insular cortex removal. **C:** Peri-insular window technique (Villemure JG, Mascott CR. Peri-insular hemispherotomy: surgical principles and anatomy. *Neurosurgery.* 1995;37[5]:975–981; Villemure JG, Vernet O, Delalande O. Hemispheric disconnection: callosotomy and hemispherotomy. *Adv Tech Stand Neurosurg.* 2000;26:25–78). **D:** Variant of peri-insular window technique (Shimizu H, Maehara T. Modification of peri-insular hemispherotomy and surgical results. *Neurosurgery.* 2000;47[2]:367–372). **E:** Dorsal transcortical subinsular hemispherotomy (Delalande O, Pinard JM, Basevant C, et al. Hemispherotomy: a new procedure for central disconnection [Abstract]. *Epilepsia.* 1992;33[Suppl 3]:99–100 [abst]; Villemure JG, Vernet O, Delalande O. Hemispheric disconnection: callosotomy and hemispherotomy. *Adv Tech Stand Neurosurg.* 2000;26:25–78). (Reproduced from Schramm J. Hemispherectomy techniques. *Neurosurg Clin N Am.* 2002;13[1]:113–134, with permission.)

In response to the problems associated with classic anatomic hemispherectomy, Rasmussen introduced the *functional hemispherectomy*, which involved a slightly smaller craniotomy, temporal lobectomy, large central hemispheric resection, callosotomy, and fronto- and parieto-occipital disconnection[82] (Fig. 2). This procedure improved seizure control while maintaining a low incidence of SCH.

Over the past 10 to 15 years, there have been further development and modification of functional hemispherectomy techniques, including hemispheric deafferentation,[38,89,90] peri-insular hemispherotomy,[107] transcortical subinsular hemi-spherotomy,[26,109] the Japanese peri-insular modification,[94] and the transsylvian keyhole functional hemipherectomy[88,91] (Fig. 3). While in the literature these are sometimes called "hemispherotomies," there is a degree of brain resection in each case in addition to the disconnection from the contralateral hemisphere and long tracts, and consequently it is logical to refer to all these procedures as "functional hemispherectomies." All of these procedures have the common anatomic goal of complete hemispheric disconnection[70,111] and involve smaller brain resections with disconnections and callosotomy that are essentially variations of the Rasmussen functional hemispherectomy. The goal of these procedures is to maintain efficacy while increasing safety and reducing postoperative complications.

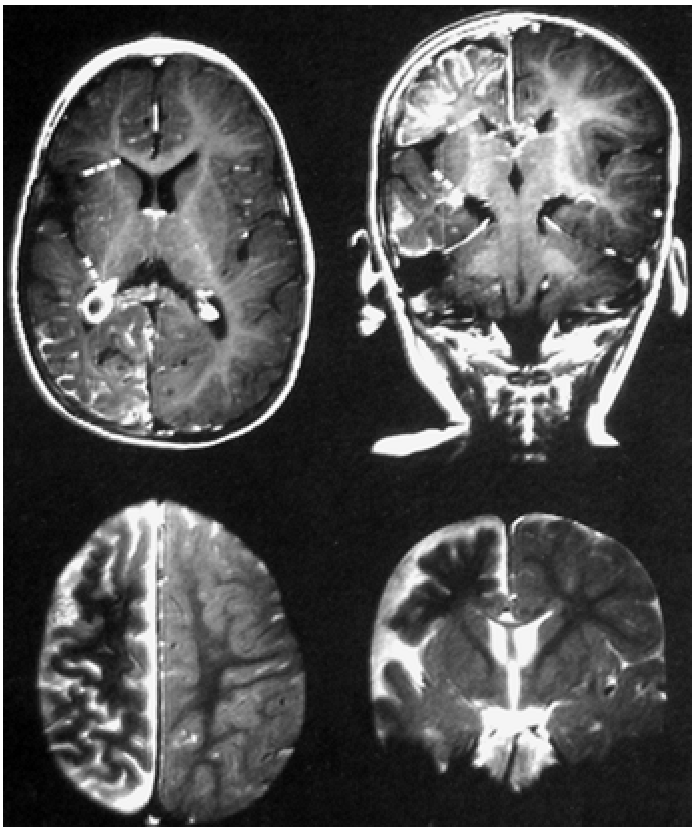

FIGURE 4. Sturge-Weber disease in a 16-month-old male. Axial **(left)** and coronal **(right)** magnetic resonance images with contrast **(upper)** show the pathologic vascularization and the enlarged insular cistern and atrophy of single gyri and the whole hemisphere. White lines indicate the short distances between circular sulcus and ventricle. This case was done with the transsylvian keyhole functional hemispherectomy technique. (Reproduced from Schramm J. Hemispherectomy techniques. *Neurosurg Clin N Am.* 2002;13[1]:113–134, with permission.)

For example, the transsylvian-transventricular keyhole functional hemispherectomy developed at our center[88,91] entails four main features: (a) linear incision and small craniotomy; (b) a transsylvian exposure and resection of the mesial temporal structures (uncoamygdalohippocampectomy); (c) transventricular callosotomy; and (d) transsylvian frontobasal disconnection and transsylvian-transventricular occipitoparietal mesial disconnection (Fig. 4). It is ideal for atrophic hemispheres with enlarged ventricles and is especially suitable for cases of perinatal infarction and cystic encephalomalacia. A key important advantage over the "classic" Rasmussen functional hemispherectomy is in the smaller exposure, shorter operative time, and lower blood loss.[91] However, it is not ideal for hemimegalencephaly, in which there is an enlarged and dysplastic hemisphere. Instead, for hemimegalencephaly, a hemispherectomy technique with sufficient exposure and tissue resection is preferred to allow space for postoperative swelling (Fig. 5).[21,28,41]

One specific question that arises in these functional hemispherectomy modifications is whether insular cortex should be removed. The concern is that residual insular cortex may be a generator of persistent postoperative seizures. Villemure et al. report using intraoperative electrocorticography from the insular cortex following hemispherectomy and proceed to remove the structure if abnormal spiking is recorded.[105,106,112] This question has also been addressed by other investigators.[2,37] However, in a large multicenter study and in a recently reported series, the presence of residual insular cortex was not statistically associated with poor seizure control.[41,47] Perhaps the most prudent approach is to always opt for removal of insular cortex during the initial surgery to exclude this possible cause of persistent seizures.[88,92]

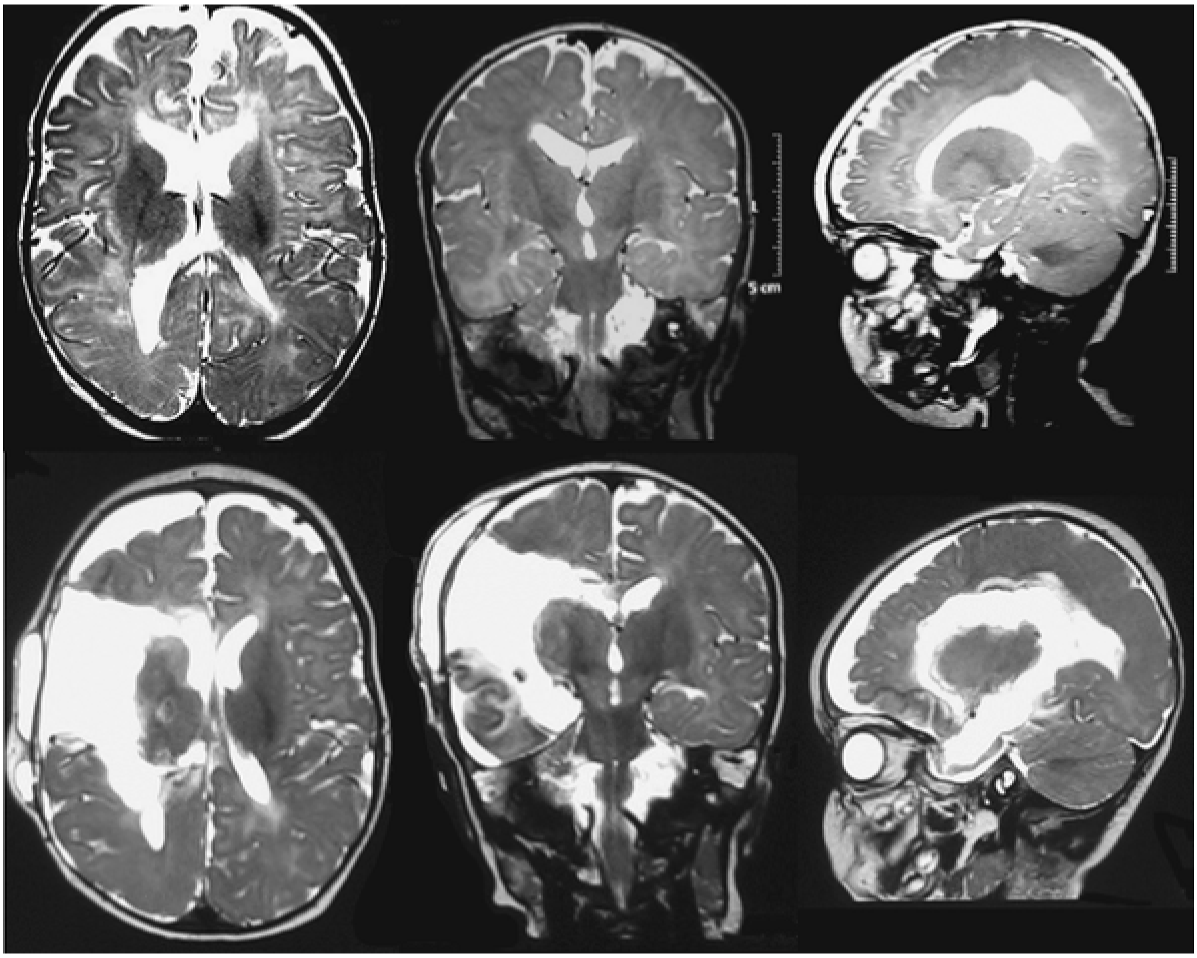

FIGURE 5. Right-sided hemimegalencephaly in a 7-month-old male. Preoperative T2-weighted magnetic resonance images **(top)** demonstrate an enlarged right hemisphere with impaired sulcation, especially posteriorly. Corresponding axial, coronal, and sagittal postoperative images **(bottom)** demonstrate functional hemispheric disconnection. This case was done with a perisylvian window technique.

Results and Complications

Potential operative and postoperative complications include hemorrhage, infection, hydrocephalus, SCH, and cerebral

edema.[103,104] In early series, these problems led to unacceptably high perioperative mortality (6% to 8%). Modern series are associated with lower mortality: In the recent multicenter series reported by Holthausen et al. mortality was 1.5%.[47] The original Montreal series of anatomic hemispherectomy had a 52% hydrocephalus rate and a 30% SCH rate.[33,114] Fortunately, there have been few reports of SCH since the 1970s,[51] and the hydrocephalus rate is much lower in modern procedures. The Oxford-Adams modification was associated with a reduced rate of hydrocephalus (<10%).[100,105] However, modern hemispherectomy approaches are still associated with an appreciable rate of hydrocephalus requiring shunting: 10 of 53 patients with the Delalande technique,[109] 5 of 32 cases with Shimizu and Maehara's technique,[94] 5 of 63 cases with Villemure's perisylvian window technique,[109] and 2 of 49 cases with Schramm's transsylvian keyhole technique.[10,91]

Important perioperative advantages of newer techniques include reduction in operative time and blood loss. In Schramm's series, operative time (mean 6.3 hours) and transfusion requirement (100% of patients) was higher for the classic Rasmussen technique than for the transsylvian keyhole hemispherectomy (3.6 hours and 15%, respectively).[91] In a recently published UCLA study, lateral hemispherotomy was associated with lower operative blood loss and intensive care unit (ICU) stay compared with anatomic and Rasmussen functional hemispherectomy.[21] In addition, operative blood loss and other perioperative complications differed by pathologic subgroup, highest in hemimegalencephaly cases.[21]

All of the modern hemispherectomy techniques have as their primary goal the elimination of seizures via total hemispheric disconnection. Approximately 70% of patients will be seizure free following surgery, with anticonvulsant requirement either eliminated or simplified. Comparisons of seizure outcome between series are limited by lack of standardized outcome measures in some studies. Most useful is the extensive review of 333 patients from 11 centers reported by Holthausen et al.[47] In that study, overall 70.4% of patients became seizure free (Engel class I). Interestingly, there appeared to be significant differences between operative techniques, with better results from modern functional hemispherectomy techniques (85.7% class I) compared with the Rasmussen technique (66.1% class I) or the hemidecortication techniques (60.7% class I).[47] In Schramm's series of 49 patients, with a median follow-up of 52 months (range 12 to 146 months), 44 patients were seizure free (Engel class I, 90%), three patients experienced seizure reduction of more than 75% (Engel class III, 6%), and two patients had no seizure relief (Engel class IV, 4%).[10] In the Holthausen et al. series, there was also a difference in outcome by pathology, with the best results in Sturge-Weber syndrome (Engel class I, 82.1%) and the worst with dysplastic lesions (Engel class I, 56.6%). No significant relationship was found between seizure outcome and preoperative EEG, seizure characteristics, or age at surgery.

Clearly, longer follow-up is necessary in all modern series,[27,39,41,49,56,78,91,98,109,110,117] both with respect to late development of complications and whether the seizure

control is persistent. For example, in a large recently reported series from UCLA, 78.6% of patients were seizure free at 6 months, 76.3% at 1 year, 70.4% at 2 years, but only 58.0% at 5 years.[49] In addition, longitudinal studies of these patient populations will be critical to determine long-term postoperative cognitive,[5,7,27,80] language,[11,22,23,87,101] and developmental[3,13,25,49,65,100] outcomes.

Multilobar Resections

Indications and Role of Pathology

Multilobar resections are indicated for the control of pharmacologically refractory seizures in the presence of epileptogenic zones that affect more than one lobe of the brain in patients with some preserved neurologic function.[73,81] As for hemispherectomy, multilobar resections are considered with pathologies that lead to unihemispheric disease and intractable epilepsy, including neonatal injury, vascular insults, tumors, gliosis, hemispheric cortical dysplasia and other neuronal migration disorders, and Sturge-Weber syndrome.[34] The extent of the pathologic process responsible for the seizures or the wish to spare some function guides the extent of the resection and the decision between multilobar resection and hemispherectomy. Seizures related to large porencephalic cysts resulting from prenatal vascular occlusion of either the anterior or posterior main branch of the middle cerebral artery may be successfully treated by bilobar or trilobar resection. A significant percentage of patients with Sturge-Weber syndrome do not have complete hemispheric involvement, and if the sensorimotor cortex is not involved, a lobar or multilobar resection can be performed. Extensive dysplastic lesions may also be associated with multilobar epileptogenicity. In general, if the degree of cortical dysplasia is less than that seen in hemimegalencephaly and the patient has no evidence of a hemiplegia, multilobar resection can be considered instead of hemispherectomy. In contrast, in Rasmussen encephalitis, epileptogenicity may appear partial at the onset but the disease is known to be progressive and ultimately involve the whole hemisphere; in this disease, early multilobar resection is unlikely to provide permanent seizure control.

Role of Functional Localization

In multilobar resections, surgery aims at excising the epileptogenic zone as completely as possible while sparing function and avoiding the creation of a new deficit or the exacerbation of an existing one. Preoperative or intraoperative functional localization may be obtained to map out the anatomic region responsible for speech as well as sensorimotor cortical areas. Functional mapping before resection is obtained either through depth electrodes or subdural grids for localization of epileptogenic sites and motor, sensory, or speech areas. Intraoperative mapping by cortical electrical stimulation or the use of sensory-evoked potentials may help to indicate the exact location of motor and sensory functional areas, so that damage to them during resection can be avoided and the extent of removal of the epileptogenic zone optimized. The widespread extent of brain pathology in these patients (e.g., large atrophic lesions or extensive dysplasia) may distort the normal anatomy and therefore functional mapping may be helpful.

Impact of Electrophysiologic Studies

Electrophysiologic investigations follow the usual approach of interictal surface EEG recordings, including sleep recordings, drug tapering, and long-term video-EEG monitoring of ictal and interictal states. Typical findings with multilobar epileptogenic regions are widespread interictal abnormalities with independent multifocal features. It may be difficult to determine the exact lobar zone of seizure onset. As usual, electrophysiologic findings must be correlated with seizure semiology and imaging findings.

In some patients, there is also a role for invasive intracranial monitoring (9% in our series in Bonn). Placement of depth electrodes, subdural strips, or grids can help to delineate the predominant epileptogenic zone[73] and also to map functional areas. However, Rasmussen observed that in these patients even the full battery of recording techniques frequently failed to demonstrate a focal seizure onset in the damaged hemisphere.[81] In cases in which the imaging studies demonstrate a widespread lesion corresponding anatomically to diffuse electrophysiologic abnormalities, there is probably no need for invasive recording, and it can be assumed that the epileptogenic zone corresponds with the zone of anatomic abnormality. In some cases (34% of the Bonn series), after an intermediate degree of resection and/or disconnection, intraoperative electrocorticography may help to determine the final extent of resection, sparing certain areas if no spikes can be recorded there following the nearby resection.

Impact of Neuroimaging

Imaging studies are important to localize the hemispheric pathology. However, it is important to keep in mind that the epileptogenic zone may extend outside the range of the obvious anatomic lesion. CT is useful, especially in processes of atrophy, showing enlarged sulci and ventricles. MRI is superior in defining the anatomy and adds higher resolution in delineating the gyral pattern and in demonstrating parenchymal lesions or signal abnormalities. Recent improvements in MRI have led to much greater recognition and delineation of varieties of cortical dysplasia.[4]

If the pathology on imaging is focal and the epileptic activity widespread, metabolic imaging studies may help in the localization of the epileptogenic zone. For example, Chugani et al. demonstrated the value of PET when combined with intraoperative electrocorticography in defining the boundaries for multilobar resections.[20] Hypometabolism on interictal fluorodeoxyglucose-positron emission tomography (FDG-PET) was found in the parieto-occipitotemporal cortices of patients who eventually underwent multilobar resections with successful control of their seizures.[18]

Frequency of Use

Multilobar resections constitute a small proportion of epilepsy surgery procedures. In the Bonn series of 2,000 epilepsy procedures, there were 32 multilobar resections (1.6%). However, the increased diagnosis of hemispheric or subhemispheric pathologies (such as multilobar cortical dysplasia) with modern MRI techniques may lead to identification of more patients who would benefit from multilobar resections, especially in those with preserved functions that are not good candidates for hemispherectomy.

Evaluation Criteria

The most important decision with this group of patients is whether to perform a hemispherectomy or a multilobar resection. The presence of only a minimal or moderate hemiparesis, the presence of useful vision in the contralateral

visual field, or the preservation of speech functions in the damaged hemisphere often precludes consideration of hemispherectomy despite the presence of extensive damage and widespread epileptogenicity in the involved hemisphere.[81] In particular, patients with nonprogressive disorders (e.g., atrophy, gliosis, dysplasia) with good contralateral extremity function (e.g., fine finger movements and foot tapping) are potential candidates for multilobar resections instead of hemispherectomy. However, if a hemiplegia is present with loss of digital dexterity, the EEG shows diffuse abnormalities throughout the affected hemisphere, and the MRI reveals widespread hemispheric pathology, hemispherectomy is indicated. If the history is suggestive of Rasmussen encephalitis, and surgery has been decided upon, it is wisest to perform a hemispherectomy as the primary procedure, because any lesser procedure is unlikely to control seizures and the inevitable subsequent surgery is rendered more difficult. In young children with infantile spasms, the clinical appearance of the seizures and the hypsarrhythmic pattern on EEG would suggest a generalized seizure disorder, rendering the patient unsuitable for surgery.

During the preoperative evaluation for multilobar resections, attempts are made to tailor the surgical excision for maximal benefit. To eradicate the epileptogenic tissue, the epileptogenic zone must be defined. Clues are obtained from analysis of the patient's history, which helps determine the possible etiologic factors. These may be congenital (dysplastic) or acquired (infection, head injury), static (vascular), or progressive (Rasmussen encephalitis). The clinical seizure pattern often helps to indicate laterality and localization of onset. Noninvasive and invasive electrophysiologic studies further pinpoint the epileptogenic zone. These observations should be closely correlated with findings from anatomic (CT and MRI) and functional (PET, ictal SPECT) imaging investigations.

In cases in which the imaging abnormalities are minor, invasive monitoring may be indicated or a multistage surgical approach may be considered. In staged multilobar resections, the obvious focal, lobar, or multilobar epileptogenic zone may first be excised, with the plan to proceed to further excision at a later date if seizures are not satisfactorily controlled. Recently, this “multistage” approach has been successfully applied by the NYU group.[6,86] Olivier as well has taken the approach of proceeding in successive stages, limiting the initial resection to the most active or most damaged lobe and proceeding, 1 or 2 years later, with resection of another area if the seizures persist.[73]

When an obvious anatomic abnormality is demonstrated by imaging that correlates with the clinical and electrophysiologic definition of the epileptogenic zone, there is no need for invasive monitoring. Examples include porencephaly reflecting atrophy of more than one lobe; extensive but subhemispheric Sturge-Weber syndrome; and hemi-hemimegalencephaly.

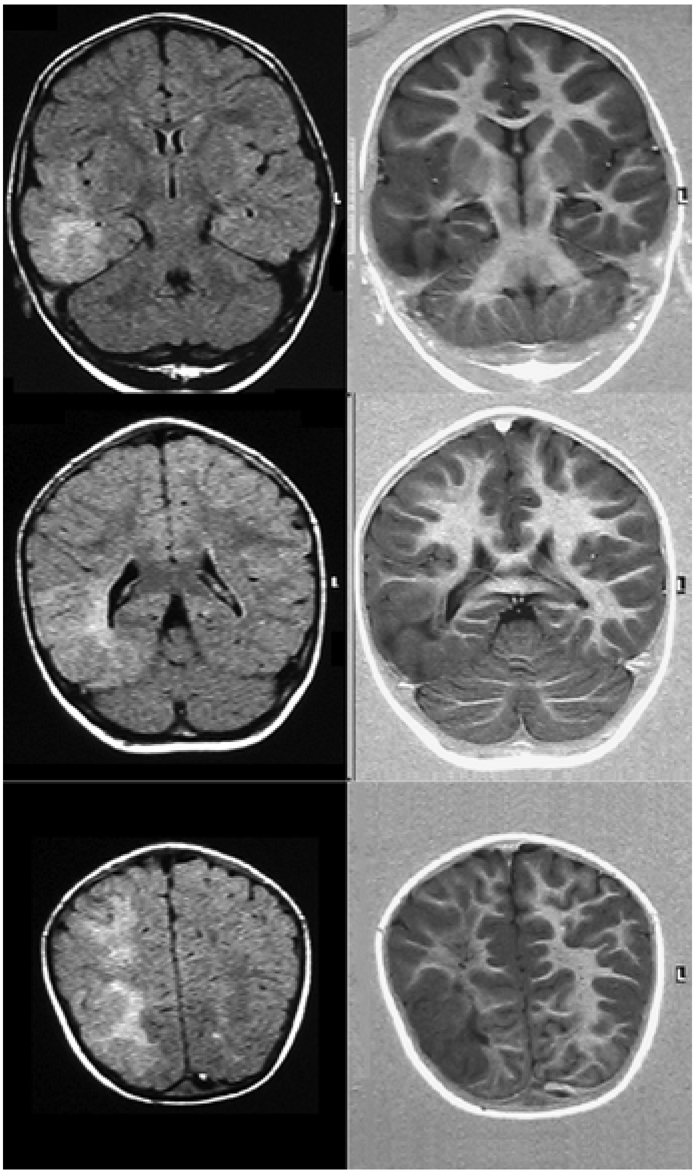

FIGURE 6. Multilobar resection for hemispheric cortical dysplasia in a 4-year-old male who presented with intractable seizures. Fluid-attenuated inversion recovery **(left)** and spoiled gradient-echo **(right)** magnetic resonance images demonstrate a right temporal-parietal-occipital lesion consistent with hemispheric cortical dysplasia at three different coronal levels. An extended right temporal-parietal-occipital lesionectomy was done with electrocorticography. Pathology demonstrated focal cortical dysplasia type IIb.

Goals of Surgery

Multilobar resection aims at achieving complete cessation of seizures or significant improvement in seizure frequency without producing neurologic deficits. Most widespread lesions responsible for seizure disorders are static and thus do not require surgery to alter their natural course. Atrophic, porencephalic, and dysplastic lesions are not by definition progressive disorders. However, these static lesions may indirectly interfere with brain function through mechanisms of secondary epileptogenesis.[71] On the basis of these mechanisms, another goal of multilobar resections may be to prevent further brain damage. It is thus important to identify candidates, localize the lesion, and then proceed to surgery early in the evolution of the seizures. Good seizure control in these patients is accompanied by improved psychological performance and social integration, which are often listed as secondary benefits.[64] The ultimate goal of the surgery should be to improve psychosocial functioning and thereby promote a better quality of life.

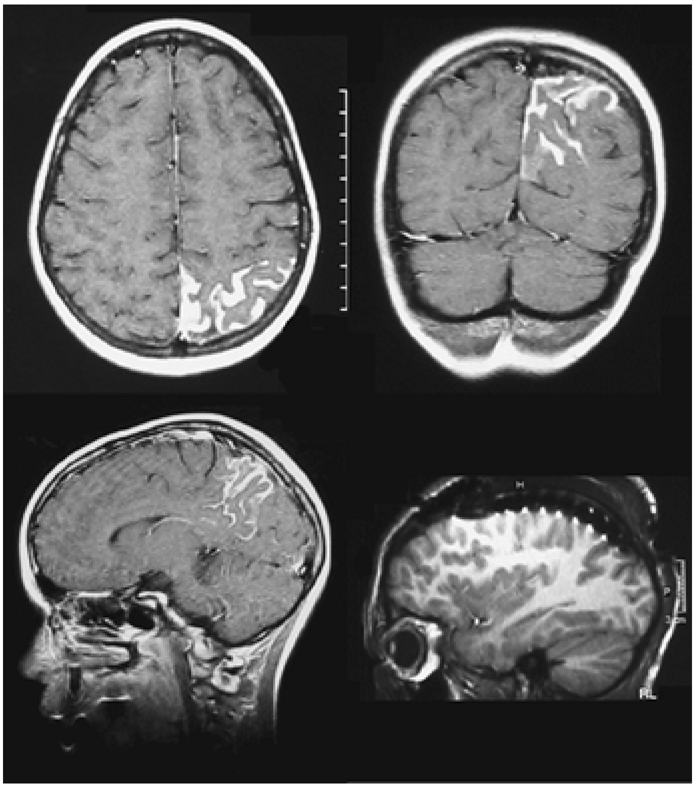

FIGURE 7. Multilobar resection for Sturge-Weber disease in a 10-year-old female. Axial **(top left),** coronal **(top right),** and sagittal **(bottom left)** magnetic resonance images demonstrate a left parieto-occipital lesion consistent with vascular malformation. Invasive diagnostic monitoring was performed with grid and strip electrodes **(bottom right)**. Subsequently, a left parieto-occipital extended lesionectomy with multiple subpial transections was performed. Pathology demonstrated Sturge-Weber disease.

Surgical Approaches

Multilobar resections may involve the frontotemporal, frontoparietal, parieto-occipitotemporal, or parieto-occipital lobes (Figs. 6 and 7). The techniques utilized vary from extensive corticectomy, lobar excision, or lobe disconnection to a combination of these. The corticectomy technique involves excision by aspiration of the cortical gray matter felt to correspond to the epileptogenic zone. Lobar excision consists of the anatomic removal of gray and white matter corresponding to the epileptogenic zone, the brain structural abnormalities responsible for the seizures, or both. Disconnection of a lobe

or its isolation from the rest of the brain has been utilized by some authors, thereby avoiding removal of the lobe (frontal or parieto-occipital) but eliminating, by disconnection, the epileptic manifestation. Removal of the epileptogenic tissue by en bloc resection appears to be the preferred technique in multilobar resections. Rasmussen stressed two important technical aspects of the resection strategy: (a) subpial removal along sulci to leave the removal cavity lined by untraumatized pial-covered gyri and (b) avoidance of movement of the underlying white matter during the cortical excision to minimize risk of injury.[81]

Unlike the case of hemispherectomy, intraoperative attention to preservation of function is essential. When a less than maximal hemiparesis is present, the arm and leg area of the sensorimotor gyri should be preserved. If a useful visual field is present, the posterior parietotemporal and occipital regions should also be preserved. During surgery, somatosensory-evoked potentials and motor-evoked potentials can be used to delineate the sensorimotor cortex, which can then be left intact. Preoperative investigations localizing the epileptogenic area should be available in the operating room, so that the intraoperative findings can be correlated with those obtained preoperatively. Some surgeons have also used intraoperative electrocorticography to further define the margins of the multilobar resection.

Results and Complications

There have been relatively few studies of outcome in children undergoing extratemporal and multilobar epilepsy surgery.[31,46,54,57,62,77,95,117] One problem is that this is a very heterogeneous group of patients, both in clinical and pathologic characteristics. In general, seizure-free outcome in patients with multilobar resections is poorer than those with unilobar resections or hemispherectomy,[57,62,77,117] which is not surprising since most unilobar resections are temporal lobectomies, and hemispherectomy provides a complete disconnection of the affected hemisphere. Outcome for hemispheric cortical dysplasia is clearly related to the extent of resection of the dysplastic tissue.[31,46,54,76,77] For the subset of patients with malformations of cortical development in particular, approximately 50% of patients become seizure free postoperatively.[31,57] One recent study indicates that the presence of acute postoperative seizures is an independent predictor of poor postoperative seizure outcome at 2 years.[66]

Complications are not usually separately reported for multilobar resections. Clearly, neurologic outcome depends on preoperative neurologic status as well as location and extent of multilobar resection. Patients undergoing multilobar resections as a repeat resection for initially failed epilepsy surgery have increased potential for neurologic deficits after the second operation.[93] Long-term follow-up of cognitive outcomes, as for hemispherectomy, will be an important component of future research.[55]

Summary and Conclusions

In multilobar resections and hemispherectomy, intractable seizures are secondary to widespread, usually unilateral, hemispheric damage resulting from multiple possible etiologies—some static, others progressive. Surgery has to be extensive and should aim at eliminating the influence of the abnormal tissue responsible for epileptogenicity. Seizure characteristics, neurologic status, EEG and imaging findings, and judgment regarding medical intractability all guide the decision regarding timing of surgery and the most appropriate surgical procedure. In the presence of some degree of preserved neurologic function, multilobar resection should aim at eliminating the epileptogenic zone without creating new deficits. In similar pathologies in which the underlying condition has created a complete hemispheric syndrome, the need to preserve function does not limit the surgery and hemispherectomy can be considered. Hemispherectomy under these circumstances is most likely to bring about complete seizure control. With the use of modern functional hemispherectomy techniques, operative morbidity and mortality can be minimized, and seizure control is usually good. The improved safety of these modifications together with improvements in neuroimaging and neurophysiologic monitoring has made hemispherectomy a more attractive option for patients with intractable unihemispheric epilepsy.

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Chapter 179

Lesionectomy: Management of Substrate-directed Epilepsies

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Introduction

Nearly one third of patients with newly diagnosed epilepsy on long-term follow-up will have their seizures unsatisfactorily controlled by treatment with antiepileptic drugs.[125] A majority of these patients with difficult-to-control seizures have focal epilepsies.[20] Nearly half of the patients with medically refractory focal epilepsies are potential candidates for epilepsy surgery.[44] The remarkable advances in neuroimaging technologies during the past two or three decades has allowed detection of a variety of brain lesions responsible for refractory focal epilepsies such as hippocampal sclerosis, malformations of cortical development, neoplasms, vascular malformations, and focal gliotic lesions that are amenable to surgical treatment. Table 1 summarizes the frequently encountered surgically remediable lesional epilepsy syndromes. The understanding that a majority of patients with substrate-directed intracranial lesion–associated chronic focal epilepsies can be selected for surgery based on a noninvasive presurgical evaluation has resulted in recent years in both an increase in the number of epilepsy surgeries being performed in developed countries and in the creation of epilepsy surgery programs in developing countries. A recent survey revealed that in 26 of 142 (18.3%) economically disadvantaged nations, at least one center regularly conducted epilepsy surgery, compared to 18 of 24 (75%) developed countries.[149]

In this chapter, we willc review the etiologies and pathogenesis of refractory lesional epilepsies and discuss the surgically remediable lesional syndromes including the presurgical evaluation strategies, surgical management, and postsurgery outcomes. The syndrome of mesial temporal lobe epilepsy with hippocampal sclerosis, which is the prototype of medically refractory lesional human epilepsy syndromes, is discussed in Chapter 247. Therefore, we will confine our discussion to the remaining lesional epilepsy syndromes listed in Table 1.

Historical Perspectives

Lesionectomy was introduced as one of the earliest surgical treatments for patients with partial or localization-related epilepsy. The modern era of epilepsy surgery began on May 25, 1886, when Victor Horsley operated, at the National Hospital for Paralysed and Epileptic at Queen Square in London, on a 22-year-old male referred to him by John Hughlings Jackson with focal motor seizures due to a focal cortical scar left behind by a depressed skull fracture he sustained 15 years before.[65] A month later, on June 22, 1886, Horsley operated on a second patient of Jackson's, a 22-year-old male who for 2 years suffered from recurrent focal motor seizures with onset in the left thumb and forefinger progressing on to involve the rest of the left upper extremity and left half of the body, the so-called jacksonian seizures.[65] At exploratory operation, Horsley found a tumor at the site of brain predicted by Jackson based on the seizure semiology that turned out to be a tuberculoma. This second operation is truly the first substrate-directed surgical treatment of epilepsy, not only because it was guided by the meticulous analysis of the seizure semiology, but also because it involved resection of the lesion and the surrounding brain tissue responsible for the seizures.

The introduction of electroencephalography (EEG) by Hans Berger in the 1930s permitted identification of epileptiform discharges.[12] Herbert Jasper, in collaboration with Wilder Penfield, effectively utilized EEG in the neurosurgical treatment of focal epilepsies at the Montreal Neurological Institute, not only in preoperative localization of the epileptogenic focus, but also during surgery to tailor the extent of resection—intraoperative electrocorticography.[69] The development of inpatient video-EEG recordings and digitalization of the EEG data in the 1980s and 1990s permitted precise electroclinical correlation of focal seizures.[22]

Although the introduction of computed tomography (CT) in the 1970s facilitated detection of some overt lesions,[53] the most important advance in the surgical treatment of focal epilepsies is the introduction of magnetic resonance imaging (MRI) in the 1980s.[83] A high-resolution MRI has become the integral part of presurgical evaluation of focal epilepsies, as it is the only investigation that can distinguish between substrate-related and substrate-unrelated epilepsies. Several studies, both in temporal and extratemporal epilepsies, have shown that an MRI-identified lesion is a strong predictor of favorable seizure outcome following surgery.[23,93] Newer MRI techniques like MR spectroscopy, MR volumetry, MR T2 relaxometry, and diffusion-weighted MRI have further improved the yield of detection of the epileptogenic focus.[41] A wide array of additional investigations such as positron emission tomography (PET), single photon emission tomography (SPECT), functional MRI (fMRI), MR tractography, and magnetoencephalography (MEG) and the coregistration of data from multiple sources have helped not only in detecting areas of altered electrical activity, blood flow, and metabolism, but also in defining the relationship of the lesion to adjacent cortical areas and white matter tracts with critical neurologic function.[43,87,113,136]

Table 1 Surgically Remediable Lesional Epilepsy Syndromes

- Hippocampal sclerosis
- Neoplastic lesions
  - Neuronal and glial neoplasms
    - Ganglioglioma
    - Dysembryoplastic neuroepithelial tumor
  - Glial neoplasms
    - Pilocytic astrocytoma
    - Low-grade astrocytomas
    - Pleomorphic xanthoastrocytoma

        - Oligodendroglioma
        - Oligoastrocytoma
- Developmental lesions
    - Malformations of cortical development
        - Focal malformations of cortical development
        - Periventricular heterotopia
        - Polymicrogyria and schizencephaly
    - Tuberous sclerosis complex
    - Hypothalamic hamartoma
- Vascular lesions
    - Arteriovenous malformations
    - Cavernous angioma
- Chronic inflammatory focal lesions
    - Tuberculoma
    - Cysticercosis
- Focal encephalomalacias
- Large hemispheric lesions
    - Rasmussen encephalitis
    - Hemimegalencephaly/hemi-hemimegalencephaly

Hemiconvulsion-hemiplegia-epilepsy syndrome

Sturge-Weber syndrome

New surgical techniques such as microneurosurgery and image-guided surgery have made lesionectomy safer and more effective.[30] The role of radiosurgical techniques in selected substrate-related focal epilepsies such as those due to vascular malformations[129] and hypothalamic hamartomas[117] are currently undergoing evaluation.

Pathophysiology of Substrate-directed Epilepsies

The underlying pathophysiologic mechanisms of lesion-related epilepsies are multifactorial and poorly understood. While focal malformations of cortical development[17,108] and hypothalamic hamartomas[72] are intrinsically epileptogenic, in brain tumors and focal gliotic lesions, it is often the alterations in the perilesional cerebral cortex that incite epileptogenesis. Occasionally, long-standing lesions within or adjacent to the temporal lobe can result in hippocampal sclerosis. In these patients with dual pathology, either the primary lesion or the secondary hippocampal sclerosis or both may initiate epileptic seizures.[25,27,46,49]

Several histologic changes have been observed in the brain tissue immediately surrounding a brain tumor, but it remains unclear how these factors relate to epileptogenesis.[127] Comparison of peritumoral cortex from patients with and without seizures have demonstrated significant differences in the number and organization of the synapses with an increase of excitatory synapses[94] and a decrease of inhibitory synapses.[59] Wolf et al.[151] investigated perilesional changes in pharmacoresistent tumoral epilepsies by using the immunoreactivity of the γ-aminobutyric acid $(\mathrm{GABA})_A$ receptor, NR1-*N*-methyl-D-aspartate (NMDA) receptor subunits, and glutamate decarboxylase activity and concluded that not only alterations of concentrations of neurotransmitters in peritumoral cortex occur, but also that these changes involve heterogeneously the number of receptors and the concentration of enzymes that synthesize and degrade neurotransmitters. Additionally, the multidrug resistance (MDR) protein-1 and the MDR-associated proteins may play a role in contributing to pharmacoresistance.[88,135] Recently, the CC genotype at the C3435 T polymorphism of the MDR-1 gene was shown to be associated with resistance to antiepileptic drugs.[131]

Glioneural tumors like ganglioglioma and dysembryoplastic neuroepithelia tumor are frequently associated with dysplasia in the adjacent cortex. In a recent study, in 20 of 24 (83%) surgically treated cases of dysembryoplastic neuroepithelial tumor (DNET), associated cortical dysplasia was found on pathologic examination.[141] To achieve favorable postoperative seizure outcome, presurgical evaluation and surgical treatment in these lesions should be aimed at defining and radically resecting the pathologic areas, both the tumor and associated dysplasia. Similarly, in an analysis of the seizure outcome of a group of patients with refractory focal epilepsies associated with cavernous malformations, complete removal of surrounding hemosiderin-stained brain tissue along with the vascular lesion was shown to result in a better seizure outcome when compared to removal of the lesion alone.[9]

Substrate-directed Epilepsy Syndromes

Tumoral Epilepsies

Brain neoplasms comprise 10% to 30% of the pathologic substrate in surgically treated patients with medically refractory focal epilepsies.[21,138,150] The histopathologic profile of tumor-related chronic epilepsy is quite different from the usual pattern of primary brain neoplasms. Although low-grade tumors such as ganglioglioma and DNET account for only a very small proportion of primary brain neoplasms, they are more frequently associated with tumoral refractory epilepsies.[74,91,98,109]

Ganglioglioma

The recent World Health Organization classification on brain tumors defines ganglioglioma as a neoplasm composed of neoplastic neural and neoplastic glial cells (Fig. 1).[75] Ganglioglioma may occur in any part of the neuraxis, but the most frequent site is the temporal lobe. Ganglioglioma is a common cause of tumor-related refractory epilepsies and in some series account for nearly half of the tumoral substrates,[54,91,98,109] though in others it is lower.[18,50] In one series of 38 patients with ganglioglioma (28 temporal and 10 extratemporal), the mean age at surgery and mean duration of epilepsy prior to surgery was 19.3 years and 9.7 years, respectively.[99] In another series of 23 patients with surgically treated ganglioglioma, the median age at surgery was 20 years and the median duration of epilepsy prior to surgery was 9 years.[116]

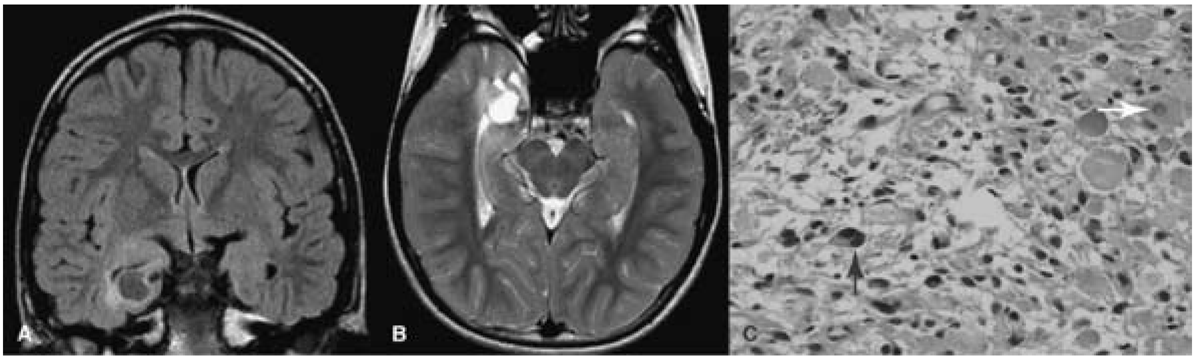

FIGURE 1. Imaging and histopathologic data of an 11-year-old boy with complex partial seizures since age 1½ years. **A:** Coronal fluid attenuated inversion recovery magnetic resonance imaging sequence shows a cystic space-occupying lesion involving the right hippocampus and parahippocampal gyrus with surrounding areas of hyperintensity. **B:** T2-weighted spin echo sequence shows extension of the lesion to the amygdala and head of hippocampus. **C:** Photomicrograph shows admixture of neoplastic neurons (*white arrow*) and astrocytes (*black arrow*) characteristic of ganglioglioma (hematoxylin and eosin ×200). The patient was seizure free for 18 months following anterior temporal lobectomy with amygdalohippocampectomy.

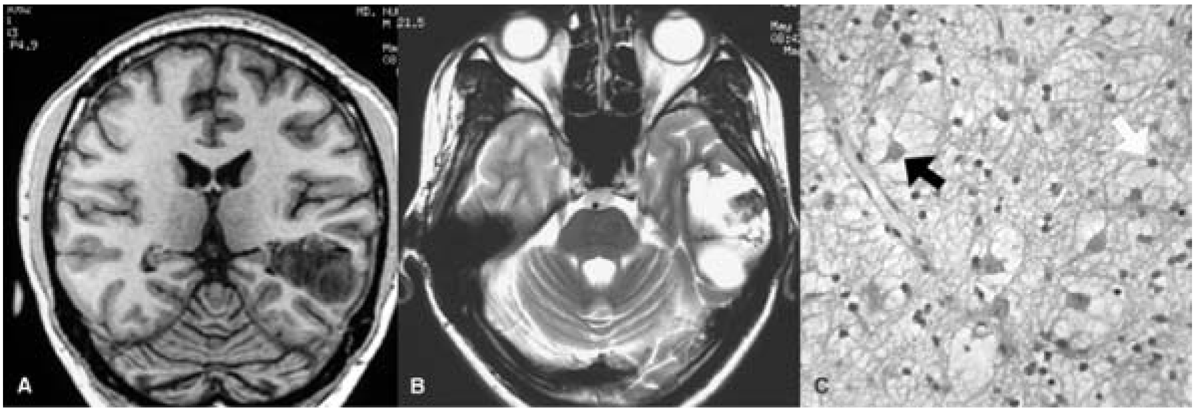

FIGURE 2. Imaging pathologic correlation in a 20-year-old male with complex partial seizures with behavioral arrest, oral and bilateral upper automatisms, head and eye deviation to the right, and frequent secondary generalization. A multicystic mass lesion involves the left inferior temporal gyrus with remodeling of the overlying skull, which is hypointense on T1 coronal sequence **(A)** and hyperintense on axial T2 sequence **(B)** with hypointensity within suggestive of calcification. **C:** Photomicrograph shows microcystic spaces with floating neurons (*black arrow*) and oligodendrocyte-like cells (*white arrow*), characteristic of a dysembryoplastic neuroepithelial tumor (hematoxylin and eosin ×200). Patient was seizure free for the last year following lesionectomy.

The typical CT appearance of gangliogliomas is a well-circumscribed hypodense or isodense lesion, with focal calcification in one third of tumors and enhancement in nearly half.[52] With MRI, they appear as a heterogenous mass, hypointense on T1-weighted and hyperintense on T2-weighted sequences (Fig. 1). Cystic changes and slight enhancement are frequently observed.[52]

Dysembryoplastic Neuroepithelial Tumor

The DNET accounts for 10% to 20% of chronic tumoral epilepsy syndromes.[35,91,109] Its typical pathologic features include disorganized arrangement of neural and glial elements

without significant cytological atypia[35] (Fig. 2). The frequent association of DNET with cortical dysplasia is being increasingly recognized.[114,141] From these features, DNET might be regarded even as an atypical hamartomatous lesion.[35] The histologic diagnosis of DNET may be challenging in the absence of a sizeable specimen preserving the peculiar disarray of the neural and glial elements. In a group of 39 patients with DNET, age at onset of seizures ranged from 1 to 19 years (mean 9 years), and the duration of epilepsy prior to surgery averaged 9 years (range 2 to 18 years).[35] In a recent Japanese series of 20 patients, the mean age at seizure onset was 16.8 years (range 1 to 38 years) and the mean age at surgery was 24 years (range 4 to 46 years).[141]

The CT demonstrates a well-circumscribed hypodense lesion, but may be normal in 10% of cases.[52] The MR appearance of DNET may be indistinguishable from that of ganglioglioma, astrocytoma, and oligodendroglioma. Absence of calcification, the cortical location and associated gyral thickening, and frequent cystic changes may be helpful in differentiation[52] (Fig. 2).

Low-grade Glial Neoplasms

Pilocytic astrocytoma, low-grade gliomas, pleomorphic xanthoastrocytoma, and oligodendroglioma comprise a substantial part of the pathologic substrates of tumoral chronic epilepsies.[18,50,91,109] Seizures occur in 70% of those with astrocytomas and in 92% of those with oligodendrogliomas.[16,138] Nearly 75% of glial neoplastic lesions associated with chronic epilepsy involve the temporal lobe.[16,98,138] Fried et al.[50] have

proposed that limbic and neocortical gliomas associated with chronic seizures constitute a unique group of glial tumors that involve the gray matter, arise in a young host, and exhibit stable biologic behavior over many years. Yet the possibility of malignant transformation cannot be ruled out. This is an added consideration in the treatment of these lesions, as their total re-moval addresses the issues of both seizure and tumor control.

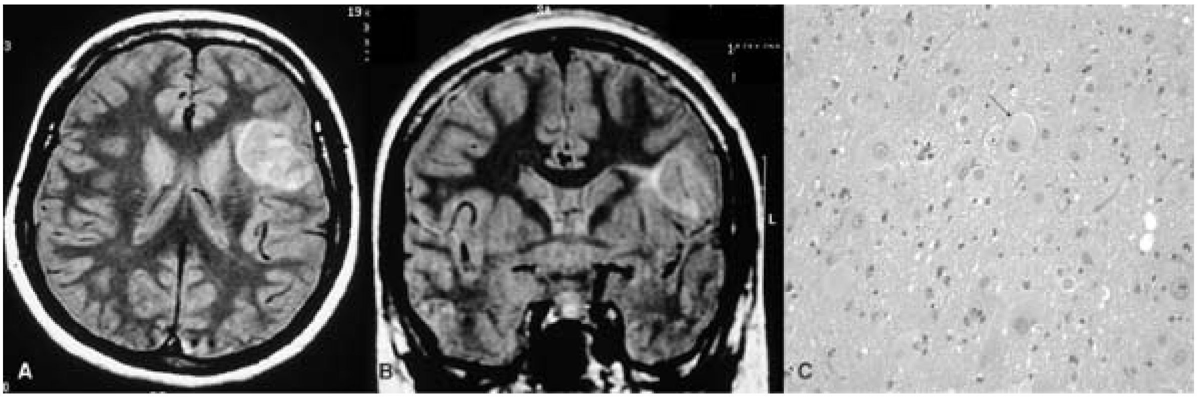

FIGURE 3. The data of a 19-year-old female with frequent complex partial seizures characterized by cephalic sensation, bilateral upper limb clonic jerks, and falls. **A:** Axial proton density (PD) magnetic resonance imaging sequence shows thickened left inferior frontal gyrus forming a globular hyperintense lesion. **B:** Coronal PD sequence depicts a radial band extending transmantally up to the frontal horn of left lateral ventricle. **C:** Photomicrograph shows dysplastic neurons with variation in size and shape and balloon cells (*arrow*). There were no postoperative neurologic deficits and no disabling seizures for the last 4 years following lesion resection under awake craniotomy and cortical stimulation and mapping.

Malformations of Cortical Development

Malformations of cortical development are second only to hippocampal sclerosis as a frequent pathologic substrate detected in 20% to 40% of pediatric and adult surgically treated patients with pharmacoresistent epilepsies.[115,152] Developmental malformations are fully discussed in Chapter 259. The main pathologic hallmark of malformations of cortical development is the presence of columnar and laminar disorganization that can be intermixed with various cellular abnormalities that include dysmorphic neurons, giant neurons, and balloon cells.[115] The classification scheme of Barkovich et al.[7] is centered on three processes of cerebral development: Neuronal proliferation and eventual apoptosis of selected cells; neuronal migration; and cortical organization. In relation to resective surgery, the following malformations of cortical development are relevant: Focal cortical dysplasia or more appropriately focal malformations of cortical development, periventricular heterotopia, polymicrogyria, and schizencephaly.[100,134] In addition, malformations of cortical development associated with DNET and tuberous sclerosis significantly contribute to the pathogenesis of refractory focal epilepsies.

Focal Malformations of Cortical Development

The focal malformations of cortical development are important substrates for focal motor status epilepticus or epilepsia partialis continua. Preoperative detection of focal malformations of cortical development depends on high-resolution MRI. The following MRI features suggest focal malformations of cortical development: Local cortical thickening, blurring of gray–white matter interphase, increased signal in the underlying white matter, and sometimes a wedge-shaped tail extending radially to the ventricle ("transmantle dysplasia") (Fig. 3).[6] Distinction from tuberous sclerosis–associated lesions may not be possible and may not even be rationale.[10,92] Focal malformations of cortical development are most frequently encountered in the frontal or temporal lobes, though may occur anywhere.

Periventricular Heterotopia

This is a form of focal malformations of cortical development in which neurons generated in the periventricular region have failed to migrate, resulting in nodules abutting the ventricular ependymal lining. Isointensity of periventricular nodules with normal gray matter on all sequences of MRI helps to distinguish periventricular nodular heterotopia from the subependymal nodules of tuberous sclerosis.[5] The pathophysiologic basis of epilepsy in periventricular nodular heterotopia may be related to their intrinsic epileptogenicity and connection to other nodules and to the cortex.[80]

Polymicrogyria and Schizencephaly

Polymicrogyria is the presence of an excess number of abnormal small gyri resulting in an irregular cortical surface. Polymicrogyria is not invariably associated with epilepsy. Patients may present with developmental delay, learning disabilities, or congenital hemiparesis.[134] The mechanism of epileptogenesis in polymicrogyria is unknown; surrounding cortex is implicated in epileptogenesis. Perhaps because of this reason, surgical resection of the microgyric area alone seldom results in favorable seizure outcome. Schizencephaly is currently grouped with polymicrogyria, which is defined by the presence of transcortical cleft, open or closed, lined by gray matter, and often with microgyria along the cleft borders.[7] Schizencephaly may be associated with a wide range of other malformations involving the septum, optic nerve, and hippocampus.[61]

Tuberous Sclerosis Complex

Tuberous sclerosis complex is an autosomal dominantly inherited multisystem genetic disorder characterized by variable phenotypic expression, resulting from mutations in one of two genes, TSC1 on chromosome 9q34 encoding hamartin, and TSC2 on chromosome 16p13 encoding tuberin.[33] The brain lesions in tuberous sclerosis complex are due to disordered

neurogenesis and neuronal migration, resulting in very different neurologic phenotypes including seizures, mental retardation, learning disabilities, and autism. Pathologically, tubers are characterized by disorganized cortical laminations, aberrant dendritic and axonal projections and arborizations, astrocytic proliferation, dysplastic neurons, and giant cells.[32] Giant cells are the pathognomonic histologic feature of tuberous sclerosis complex.[33]

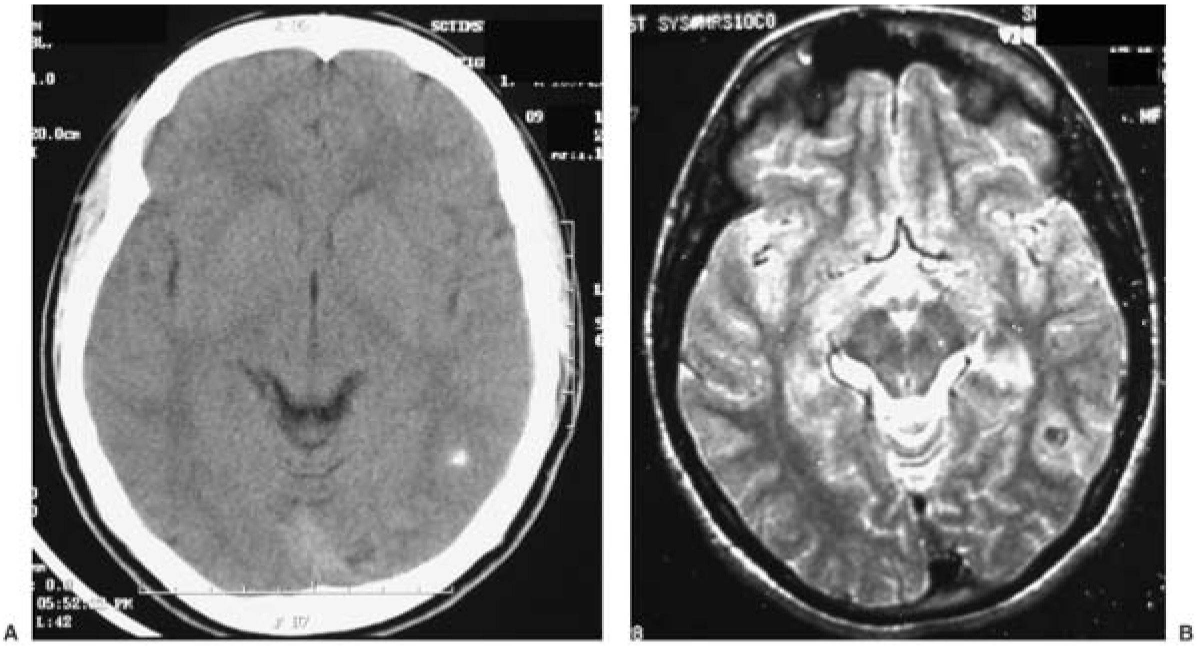

FIGURE 4. A 17-year-old male referred to the Comprehensive Epilepsy Program of the Sree Chitra Tirunal

Institute for Medical Sciences and Technology, Trivandrum, India, from an endemic area for cysticercosis in southern India for refractory complex partial seizures since the age of 14 years. **A:** Noncontrast axial computed tomography shows a calcified lesion in the left posterior temporal region. **B:** T2 axial magnetic resonance imaging sequence shows hypointense calcification with surrounding hyperintensity representing gliosis. The patient was seizure free for nearly 2 years following lesionectomy.

Epilepsy is the most common presenting symptom of tuberous sclerosis complex. The seizures are focal or multifocal in origin and are often resistant to antiepileptic drugs.[105] Immunohistochemical evidence and electrophysiologic evidence have indicated that the neurons within cortical tubers are intrinsically epileptogenic.[33] Surgical management of epilepsy is challenging in patients with tuberous sclerosis complex because the epileptogenic tubers are often multiple, bilateral, and extratemporal, overlapping with eloquent cortex.[57,68,82]

Hypothalamic Hamartomas

With improved detection of the lesion by MRI, the wide clinical spectrum of epilepsy syndromes associated with hypothalamic hamartoma is being increasingly understood. In addition to gelastic seizures, hypothalamic hamartoma can manifest with partial seizures of temporal or frontal semiology and with a catastrophic pediatric epileptic encephalopathy with polymorphic seizures, intellectual deterioration, and marked behavioral disturbances.[8,72,139] The seizures in individuals with hypothalamic hamartoma are often refractory to antiepileptic drugs, but in most cases are reversed by surgical excision,[48,103] radiofrequency thermocoagulation, or Gamma Knife surgery (Chapter 250).[117]

Vascular Malformations

Seizures occur in about one third of patients with arteriovenous malformations and the response to antiepileptic drug therapy is variable.[64] Among those with medically refractory focal seizures, nearly three fourths of patients benefit either from lesion resection[111] or from radiosurgery.[129] Seizures represent the most common symptomatic presentation of supratentorial cerebral cavernous malformations.[31,73] In a comparative analysis of the seizure propensity of patients harboring arteriovenous and cavernous malformations, Awad et al.[4] found a prevalence of 50% to 70% in cavernomas and 20% to 40% in arteriovenous malformations. Recurrent microhemorrhages and the resultant hemosiderin deposition may contribute to the epileptogenic potential of cavernomas.[9]

Cerebral Cysticercosis

Neurocysticercosis currently represents a major public health problem in developing countries of Latin America, Asia, and Africa, as well as in industrialized nations with a high immigration rate from endemic areas.[37,133] As the number of immigrants entering the United States from Latin America has increased, so has the incidence of neurocysticercosis. More than 1,000 new cases are being diagnosed in the United States annually, and large neurocysticercosis case series have been reported from California, Texas, Oregon, Chicago, and New York.[38,119,128,137,144] Seizures are the most common neurologic symptoms associated with neurocysticercosis, occurring in up to 70% of symptomatic patients. Neurocysticercosis might lead to chronic epilepsy either due to calcified lesions or by triggering epileptogenesis at distant sites (Fig. 4). In a recent study, out of 512 patients evaluated for intractable epilepsy in an endemic area in Brazil, isolated cysticercosis was found as the cause only in eight patients (1.6%). However, the authors observed calcified cysticercus lesions more frequently in patients with hippocampal sclerosis, raising suspicions of dual pathology.[146]

Focal Encephalomalacia

Encephalomalacia resulting from destructive brain injury accounted for as much as 17% of all focal structural lesions in a recent large MRI series of patients with refractory focal epilepsies.[85] Encephalomalacia can result from perinatal insults, head injuries, or previous surgical procedures. Similar to patients with other types of structural lesions, patients with encephalomalacia may benefit from resection of the lesion and the adjacent electrophysiologically abnormal brain tissue.[71] Accompanying porencephalic cyst may necessitate modification of the surgical procedure.[58]

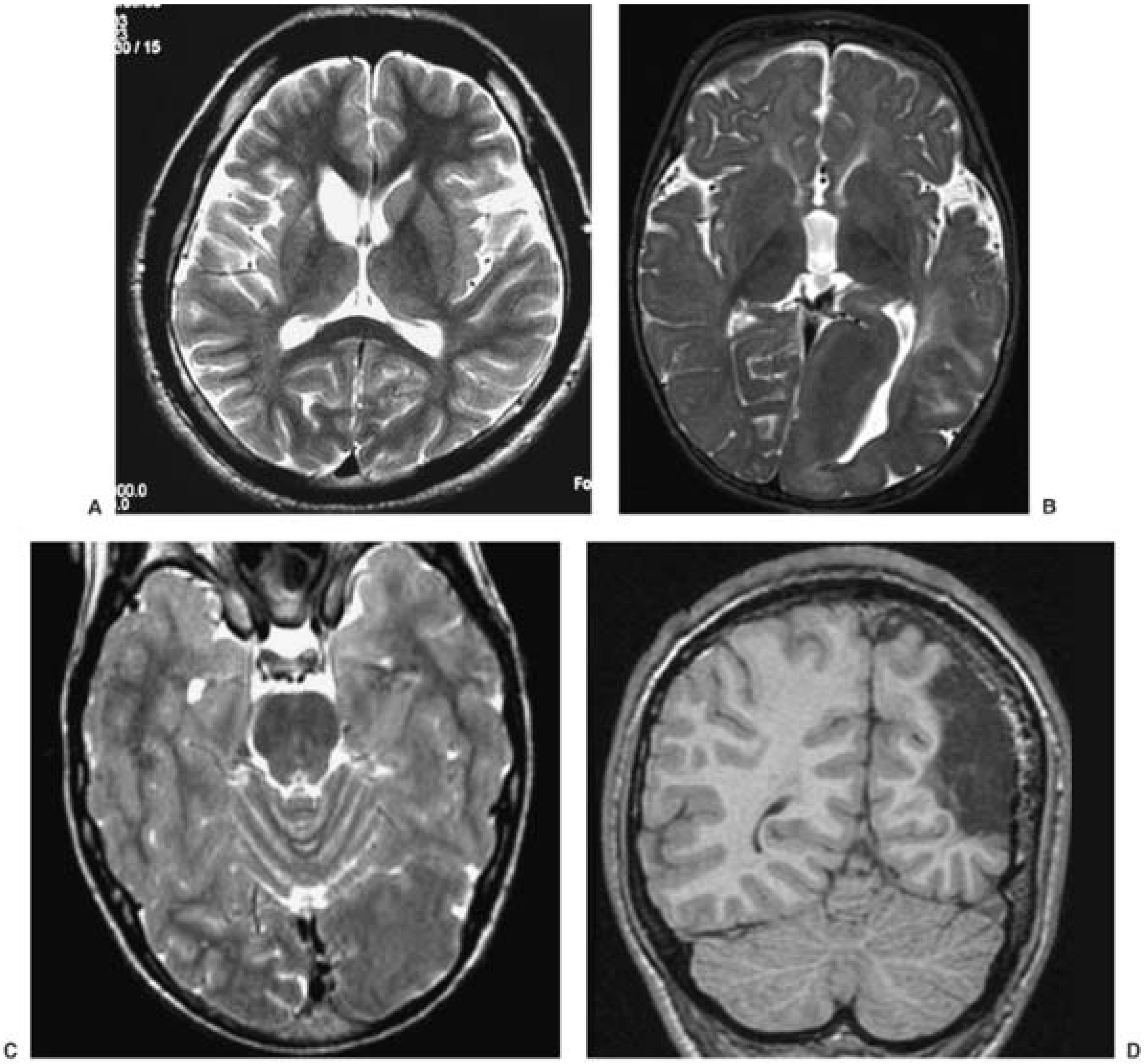

FIGURE 5. Major hemispheric lesional substrates from patients who had undergone hemispherectomy or multilobar resections. **A:** Right hemispheric predominant perisylvian and right caudate head atrophy characteristic of Rasmussen encephalitis. **B:** Left hemimegalencephaly. **C:** Left posterior quadratic dysplasia. **D:** Profound left hemispheric atrophy in hemiconvulsion-hemiplegia-epilepsy syndrome.

Multilobar and Widespread Hemispheric Lesions

Patients with major lesions involving one hemisphere such as Rasmussen encephalitis, Sturge-Weber syndrome, hemimegalencephaly, and hemiconvulsion-hemiplegia-epilepsy (HHE) syndrome are potential candidates for hemispherectomy or multilobar resections.[55,79] These are only briefly discussed here and are presented in more details in other chapters.

Rasmussen Encephalitis

Rasmussen encephalitis is a chronic inflammatory disease of uncertain etiology, usually affecting one cerebral hemisphere (Chapter 243).[15] The disease evolves from an initial prodromal phase with infrequent focal seizures to epilepsia partials continua and progressive hemiparesis lasting several months or years, and subsequently passes into a residual stage with marked decrease in the frequency and distribution of focal seizures.[14,56] The MRI after transient focal swelling and hyperintensity involving the cortex, especially over the insular and preinsular regions, shows progressive atrophy of the involved hemisphere.[14,15] Disproportionate atrophy of the head of the caudate nucleus of the involved side is a characteristic MRI appearance of Rasmussen encephalitis (Fig. 5A). The pathologic changes are multifocal in distribution within the hemisphere, characterized by a variable combination of neuronal damage, astrogliosis, and lymphocyte infiltration.[110] Although in some patients the progression may be arrested by immunotherapy with corticosteroids, intravenous immunoglobulin, or plasma exchange, a majority would require hemispherectomy to control their severely disabling epilepsia partialis continua and secondary generalized seizures.[14,145] An occasional patient presenting in the residual stage of the disease with epilepsia partials continua of a restricted distribution may benefit from focal cortical resection.[102]

Sturge-Weber Syndrome

Sturge-Weber syndrome is a rare, sporadic neurocutaneous syndrome characterized by unilateral facial nevi, leptomeningeal angiomatosis, and congenital glaucoma.[39,143] Epilepsy occurs in 75% to 90% of the cases and is often refractory to medical treatment. Although controversies still exist regarding the advantages of early (prophylactic) versus later surgical interventions, excision of the angiomatous cortex or hemispherectomy in those with extensive unihemispheric involvement should be considered once the seizures become refractory to antiepileptic drugs and disabling.[78]

Hemimegalencephaly

Hemimegalencephaly is a malformation of cortical development arising from an abnormal proliferation of anomalous neuronal and glial cells leading to hypertrophy of the whole affected cerebral hemisphere (Fig. 5B). Hemimegalencephaly can occur alone or may be associated with neurocutaneous disorders, such as neurofibromatosis, epidermal nevus syndrome, hypomelanosis of Ito, and Klippel-Trenaunay-Weber syndrome.[40] Severe drug-resistant epilepsy is a dominant clinical picture of hemimegalencephaly, and hemispherectomy is the most effective treatment to control seizures.[55,79] Posterior quadrantic dysplasia (hemi-hemimegalencephaly) involves the occipital, parietal, and posterior temporal lobes (Fig. 5C).[34]

Hemiconvulsion-Hemiplegia-Epilepsy Syndrome

HHE syndrome is characterized by prolonged unilateral convulsions during fever in children under 4 years of age, who subsequently develop a permanent hemiparesis.[124] Focal seizures, poorly responsive to antiepileptic drugs, ensue later. An extensive atrophy of the involved hemisphere is evident on neuroimaging (Fig. 5D). In developing countries, HHE syndrome still forms a significant proportion of patients selected for hemispherectomy.[36]

Indications for Surgery

Because of the widespread availability and increasing use of MRI, today patients presenting with epileptic seizures are likely to be imaged quite early for a structural lesion than in the years past. The identified lesion may require resective surgery either because of the epileptic seizures that are refractory to antiepileptic drugs, for pathologic verification of the lesion before additional treatments such as radiotherapy or chemotherapy can be administered, or because of the risks other than seizures associated with the lesion, such as potential for malignant transformation from a suspected benign neoplasm or hemorrhage from a vascular malformation. All patients with medically refractory epilepsies and an MRI-identified lesion should be referred for presurgical evaluation. Several years of polytherapy with antiepileptic drugs is not required to define medical refractoriness. Although a period of 2 years of observation on adequate antiepileptic drug therapy is advocated prior to consideration for epilepsy surgery, infrequent seizures that are potentially injurious and socially disabling, even of 1 year or shorter duration, may necessitate referral for surgery. In patients harboring a suspected low-grade neoplasm, whose seizures are well controlled with antiepileptic drug therapy, it remains controversial whether resection of the tumor either improves long-term survival or the control of epilepsy. The controversies surrounding the management of low-grade intracranial neoplasms[20] are beyond the scope of this chapter, but it has been proposed that low-grade astrocytomas associated with chronic seizures in a young host represent a distinct clinicopathologic entity with a unique biologic behavior.[50]

Presurgical Evaluation

Basic Principles

The objective of epilepsy surgery is to make the patient seizure free without producing any unacceptable neurologic sequelae (Chapters 167,168,169). Finding an intracranial lesion in a patient with recurrent focal seizures does not necessarily mean

that the lesion is responsible for the seizures. It is necessary not only to confirm the relationship between the lesion and the seizures, but also to delineate the relationship of the lesion to adjacent functional networks. The relationship between the lesion and seizures is much more complex than what may be envisaged. First, in a majority of patients, the seizure-generating focus may be contiguous with but may extend beyond the lesion itself. Second, in patients with malformations of cortical development, the MRI-identified lesion may be “the tip of the iceberg,” and there may be additional MRI occult areas contributing to epileptogenesis. Third, in patients with multiple lesions, such as in tuberous sclerosis complex, it is necessary to identify which of the lesions is primarily responsible for the patient's habitual seizures. Fourth, the lesion may have resulted in a second epileptogenic focus, such as hippocampal sclerosis (dual pathology), which may be responsible for perpetuation of seizures. Last, the lesion occasionally may be incidental and bear no causal relationship to epileptogenesis. For example, in a recent study from an endemic area for neurocysticercosis, although a significant proportion of patients with medically refractory epilepsies had calcified brain cysticercus lesions, a majority of them had additional lesions like hippocampal sclerosis classically associated with refractory epilepsies.[146]

Failure of epilepsy surgery to control the seizures means that the epileptogenic zone has not been adequately resected. The *epileptogenic zone* by definition is the area of brain that is necessary and sufficient for initiating seizures, whose resection or disconnection is necessary for abolition of seizures.[89] Since the epileptogenic zone is a theoretical concept and there is currently no way of defining it prior to surgery, information

is obtained during the presurgical evaluation about identifiable zones as listed in Table 2 and are utilized to reliably predict the epileptogenic zone.[45] As the lesional zone is already evident at referral in patients with substrate-related epilepsies, the objective of presurgical evaluation is aimed at identifying other zones and establishing their relationship to the lesion.

Table 2 Definition of Abnormal Brain Areas Involved in Focal Epileptogenesis

Area	Definition	Mode of definition
Epileptogenic lesion	Structural brain abnormality that is the direct cause of seizures	Structural imaging, tissue pathology

Irritative (spiking) zone	Area that generates interictal spikes	EEG and MEG
Ictal onset zone	Area of cortex that generates seizures	EEG and MEG
Symptomatogenic zone	Area that produces the initial clinical symptomatology	History, observation during video-EEG monitoring
Functional deficit zone	Cortical area with functional abnormalities	Neurologic examination, neuropsychological testing, EEG, MEG, PET, SPECT
Epileptogenic zone	Area of brain that is necessary for generating seizures and whose removal or disconnection abolishes seizures	Theoretical concept

EEG, electroencephalography; MEG, magnetoencephalography; PET, positron emission tomography; SPECT, single photon emission tomography.
Modified from Liégeois F, Cross JH, Gadian DG, et al. Role of fMRI in the decision-making process: epilepsy surgery for children. *J Magn Reson Imaging.* 2006;23:933–940.

Patients with medically refractory lesional epilepsies belong to different categories depending on the degree of complexity involved in presurgical evaluation. The decision making for epilepsy surgery requires a multidisciplinary approach in which the epileptologist, neurosurgeon, neuroradiologist, and neuropsychologist work in conjunction to understand the integrated picture of epileptogenesis. Understanding when not to operate because of the need for further evaluation is as important as knowing which patients may benefit from surgery with the investigative facilities available in a particular epilepsy surgery center.

Generally, the presurgical evaluation follows the steps listed in FIGURE 6. Information obtained by noninvasive means such as history, neurologic examination, MRI, and scalp and video-scalp EEG monitoring are discussed in the patient management conference to decide about surgical candidacy or the need for further investigation. To minimize the requirement of intracranial EEG monitoring, multiple noninvasive investigative strategies such as PET, ictal SPECT, MEG, fMRI, and peri-ictal diffusion-weighted MRI are currently available that can provide information to localize the epileptogenic zone.[41,76] Furthermore, information obtained from these sources can be combined with MRI, as in subtraction ictal SPECT coregistered to MRI (SISCOM)[136] and MEG coregistered to MRI (magnetic source imaging)[43,77] to provide structural and functional data correlation. The relative sensitivity of these new technologies in predicting the localization of the epileptogenic zone and therefore their relative role in presurgical evaluation are uncertain. The local availability and expertise in a particular technique dictates the preferential usage of one technology over the other by individual epilepsy surgery centers. For example, despite lacking these new technologies, in the last decade, several epilepsy centers in economically disadvantaged countries have successfully implemented epilepsy surgery programs and have produced results comparable to those from industrialized countries by selecting for surgery patients in whom the epileptogenic zone can be localized by using locally available, relatively inexpensive, and noninvasive strategies.[140] The availability of newer technologies has helped in selecting more and more patients for surgery, in whom the initial evaluation data have remained inconclusive.

History and Examination

A thorough neurologic examination may detect subtle motor or sensory neurologic signs or visual field defects that may assist in clinically lateralizing the functional deficit zone. Emotional facial weakness (mimic facial paresis) may occur in nearly two thirds of patients contralateral to a temporal lobe lesion.[26,67] Age at onset of seizures and duration of epilepsy prior to seeking medical attention are seldom helpful in predicting the nature of the lesion.

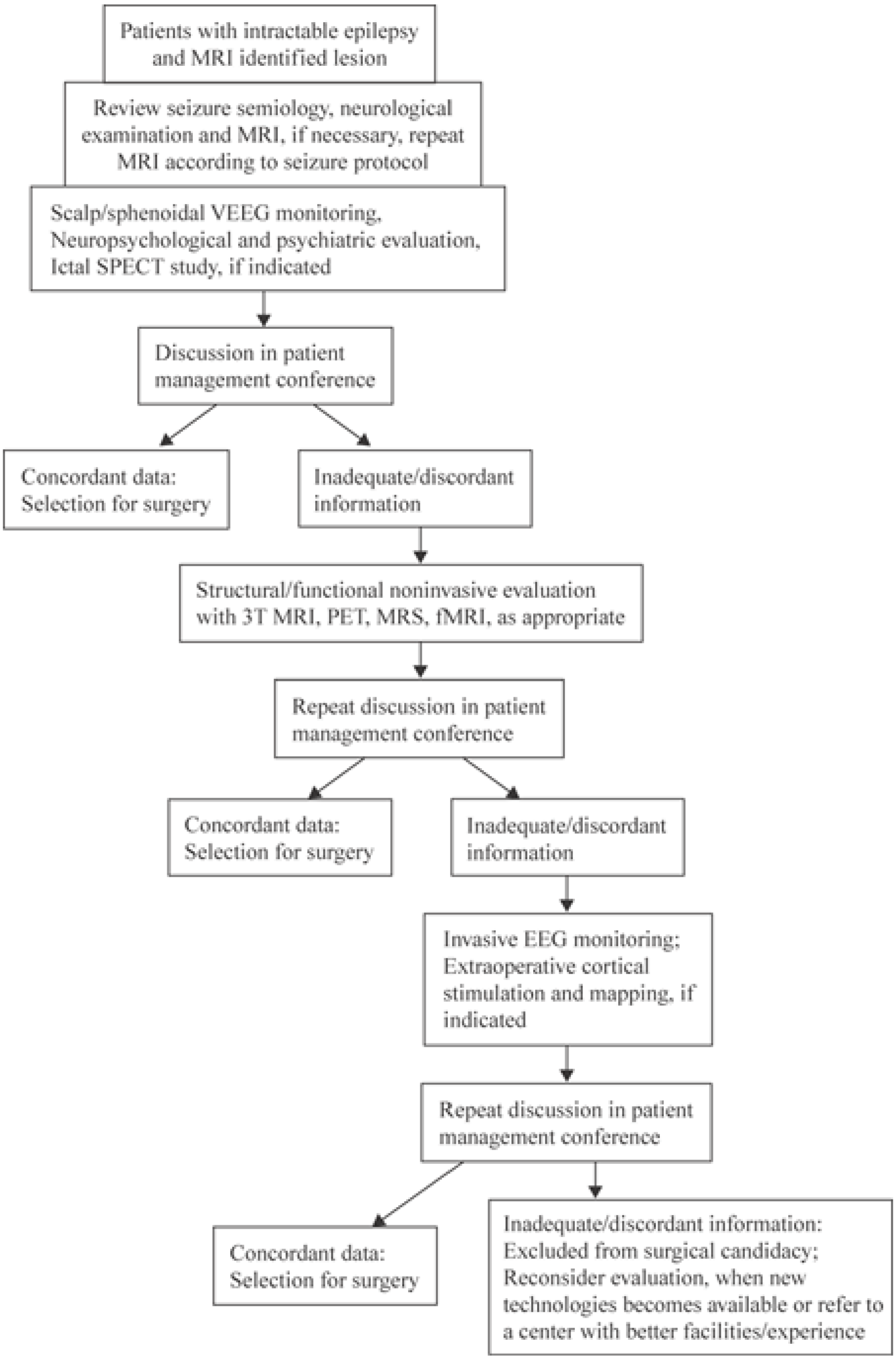
Patients with intractable epilepsy and MRI identified lesion
Review seizure semiology, neurological examination and MRI, if necessary, repeat MRI according to seizure protocol
Scalp/sphenoidal VEEG monitoring, Neuropsychological and psychiatric evaluation, Ictal SPECT study, if indicated
Discussion in patient management conference
Concordant data: Selection for surgery
Inadequate/discordant information
Structural/functional noninvasive evaluation with 3T MRI, PET, MRS, fMRI, as appropriate
Repeat discussion in patient management conference
Concordant data: Selection for surgery
Inadequate/discordant information
Invasive EEG monitoring; Extraoperative cortical stimulation and mapping, if indicated
Repeat discussion in patient management conference
Concordant data: Selection for surgery
Inadequate/discordant information: Excluded from surgical candidacy; Reconsider evaluation, when new technologies becomes available or refer to a center with better facilities/experience

FIGURE 6. Steps in the presurgical evaluation of a patient with substrate-directed refractory epilepsy syndrome.

Clinical Seizure Characteristics

Lesional epilepsy may be associated with simple partial, complex partial, or secondarily generalized tonic–clonic seizures. There is an established association between gelastic seizures and hypothalamic hamartomas; however, children with these lesions can also present with complex partial seizures simulating temporal lobe seizures, and with polymorphic seizures, intellect deterioration, and behavioral problems simulating Lennox-Gastaut syndrome.[8,139] In a patient presenting with chronic epilepsia partialis continua, the differential diagnosis includes Rasmussen encephalitis and focal malformations of cortical development; associated progressive hemiparesis points to the former. The most frequent seizure type associated with tumoral epilepsy is complex partial seizures. The semiology of auras may have localizing value.[51] While the majority of the patients with temporal, frontal, and occipital lesions present with complex partial seizures conforming to the semiologic features well known to be associated with their respective location, seizures originating in the parietal lobe can mimic temporal, occipital, or frontal seizures.[24,122] A simple partial seizure as a manifestation of a lesional syndrome, either alone or with complex partial seizures or secondarily generalized seizures, was found to be nearly always associated with a neoplasm by some investigators.[16,138]

Structural Imaging

MRI is the structural imaging of choice in patients with refractory focal epilepsies. When reviewing the MRI, in addition to identifying the lesion, close attention should be paid to not only the lesion, but also its relationship to neurologic function in adjacent areas and any secondary changes such as hippocampal sclerosis associated with the lesion. The MRI done outside a comprehensive epilepsy program may not provide all of this required information and often needs to be repeated according to dedicated MRI imaging protocols as performed at the epilepsy surgery centers. Von Oertzen et al.[147] compared the sensitivity of identifying focal lesions between standard MRI reported by "nonexpert radiologists," standard MRI evaluated by "expert radiologists," and epilepsy-dedicated MRI read by "expert radiologists" among 123 consecutive patients undergoing epilepsy surgery evaluation. While the sensitivity of "nonexpert" reports of standard MRI for focal lesions was 39% and "expert" reports of standard MRI 50%, the yield of epilepsy-dedicated MRI was 91%.[147] Neoplastic, vascular, and inflammatory mass lesions are almost always evident in routine sequences of MRI. The diagnostic yield of MRI is variable in patients with malformations of cortical development. With improvements in MRI techniques such as 3.0 Tesla MRI, the use of special sequences such as fluid attenuated inversion recovery, and diffusion tensor imaging, it is now possible to better define malformations of cortical development and its relationship to white matter tracts.[41,62] CT is much more sensitive than MRI in detecting calcifications within lesions such as ganglioglioma, oligodendroglioma, neurocysticercosis, and vascular malformation.

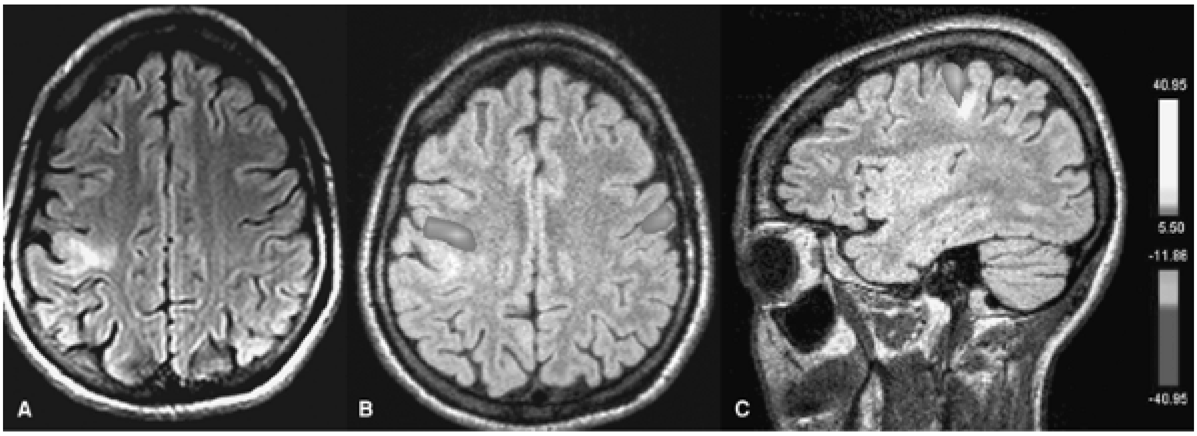

FIGURE 7. A 25-year-old female with daily refractory focal seizures characterized by paresthesia and tonic posturing of left upper extremity, occasionally progressing on to the left lower extremity since the age of 10 years. **A:** Axial fluid attenuated inversion recovery magnetic resonance imaging (MRI) sequence shows a focal cortical malformation in the right sensorimotor cortex. Inline blood oxygenation level–dependent functional MRI axial **(B)** and sagittal **(C)** during left finger tapping versus rest show right motor activation very close and within the lesion. Surgery was deferred in view of the high likelihood of postoperative left upper extremity weakness.

Video-electroencephalographic Monitoring

Although digitalization has enhanced clarification of the EEG by allowing reformatting of the recorded data by changing montage and filter settings, the yield of scalp EEG in substrate-related epilepsy syndromes in general is unsatisfactory. In a comparative analysis of the distribution of scalp-recorded interictal epileptiform abnormalities in temporal lobe epilepsy due to hippocampal sclerosis versus temporal lobe tumors, Hamer et al.[60] observed more widespread distribution of interictal epileptiform abnormalities in tumor patients compared to the restricted spiking zone at the anterior temporal region in patients with hippocampal sclerosis. In patients with frontal, parietal, and occipital epilepsies, scalp EEG may provide misleading information in one third to one half of patients.[126] In view of the poor predictive value of the interictal and ictal EEG abnormalities in patients with tumoral focal epilepsies, the need for long-term video-EEG monitoring in such patients has been questioned.[99] Ictal monitoring, however, is the only method to document the patient's habitual seizures and to exclude associated nonepileptic behavioral events. Moreover, video-EEG monitoring is mandatory for timing the ictal SPECT injection. The information gathered from surface video-EEG recording can be improved by additional electrode placements as indicated by relevant clinical and EEG data, such as sphenoidal electrodes in detecting temporal activity and supraorbital electrodes in detecting orbital-frontal activity.[70,126]

Noninvasive Functional Mapping

2-[^{18}F] Fluoro-2-deoxy-D-glucose PET (FDG-PET), ictal SPECT, and MEG are currently established functional imaging tests that can provide information toward localization of the epileptogenic zone.[76] The data from these tests can be coregistered to high-resolution MRI to offer epilepsy-related structural and functional disturbances with a degree of confidence, comparable to that obtained with intracranial monitoring. Recently, the use of fMRI correlated with interictal discharges to delineate epileptogenic networks has been investigated.[123] In addition, fMRI and MEG are being increasingly used to map functional cortical areas and provide information about whether the lesion itself is functionally active (as in malformations of cortical development) and whether any functional reorganization has occurred (Fig. 7). The fMRI in recent years has significantly contributed to the decision-making process about surgical candidacy and to surgical planning.[3,87] However, additional studies are needed to compare these newer mapping techniques with electrical stimulation map-ping.

Invasive Monitoring

A small proportion of patients whose noninvasive presurgical evaluation data are inconclusive would require invasive EEG monitoring by placing strip or grid electrodes over the surface of the brain or depth electrodes intracerebrally. Such monitoring is much less common in lesional epilepsy compared to nonlesional epilepsy. Still, it provides an opportunity for gathering ictal and interictal data as well as performance of detailed electrical stimulation mapping of the nearby cortical functional zone. Invasive monitoring should always be hypothesis driven. The noninvasive presurgical evaluation data should be subjected to a detailed discussion in the patient management conference to generate a hypothesis about the probable localization and extent of the epileptogenic zone and its resectability without acceptable neurologic sequelae before making decision about the feasibility of invasive monitoring and the monitoring strategy (Fig. 5). Although MRI-detected structural substrate may guide the electrode placement, more often the epileptogenic zone may extend well beyond the MRI-identified lesion location and extent.

Surgical Strategies

Lesionectomy

Strict lesionectomy entails resection of the MRI-apparent lesion. Modern neurosurgical techniques now use navigational frameless stereotactic tools enabling resection of the imaged lesion. The particular MRI sequence best delineating the lesion should be used. For instance, fluid-attenuated inversion recovery (FLAIR) imaging may be useful in delineating the full extent of many low-grade glial tumors, which commonly do not enhance with MR contrast agents. Strict lesionectomy does not involve the use of electrophysiologic tools such as intraoperative electrocorticography to guide resection, and the resection is anatomically guided. See Chapter 179 for a more complete discussion.

Extended Lesionectomy

The most common resection strategy involves excision of the lesion with a “margin” around the lesion.[20] The margins may be structural, such as removal of all hemosiderin-laden tissue around a cavernous angioma or tumor margins around a low-grade glioma that may exceed the boundaries of the MR-apparent image. The seizure outcome has been shown to be better after resection of vascular malformations, when the hemosiderin-stained brain tissue is included within the resection.[9]

The use of intraoperative electrocorticography (ECoG) to guide extended lesionectomy has been controversial. The role of ECoG in tailoring resection in tumoral focal epilepsies is uncertain. Some studies have found better seizure outcome in patients who underwent resection of the neoplasm under electrocorticographic guidance,[13,112] while others have achie-ved the same results without assistance of electrocorticogra-phy.[106,116] Mikuni et al.[95] recently analyzed the outcome of 25 patients with refractory epilepsy associated with benign neoplasm. Removal of the tumor and additional irritative zone as demonstrated by electrocorticography was associated with seizure-free outcome in over 90% of patients. Especially in patients with DNET, because of the frequent association with malformations of cortical development, extended resection guided by electrocorticography may achieve better postoperative seizure control.[141] There are reports that better seizure outcome in cases with focal malformations of cortical development is achieved when resection of both the MRI-identified lesion and the cortical areas displaying continuous rhythmic spiking (ictal-like pattern) can be performed.[107]

Extended lesionectomy is subject to functional considerations delineated by functional mapping, usually electrical stimulation mapping, which can be performed intraoperatively when the lesion is in the vicinity of functionally critical cortex, such as language or rolandic cortices. fMRI has been increasingly applied as an aid for surgical planning in this setting. Delineation of cerebral white matter using MR tractography and integrating this information with intraoperative neuronavigation may be helpful in resecting lesions adjacent to fibers of these cortices.[30,63] This strategy may be especially useful in malformations of cortical development, which often extend deeply through the white matter to the periventricular region (transmantle dysplasia).[6,28]

In cases where extended lesionectomy is limited by adjacent functional cortex, multiple subpial transactions[97] can be used as an adjunct to the resection of the lesion.[11] In this setting, lesionectomy plus multiple subpial transactions has been shown to provide good seizure control with less neurologic morbidity.[66,101]

Dual Pathology and Secondary Epileptogenesis

Two concepts form the basis for significantly wider resections beyond lesionectomy in cases of lesional epilepsy: Secondary epileptogenesis and dual pathology. According to the model of secondary epileptogenesis, irreversible lesions develop in patients who experience frequent seizures over a long period of time. Such a lesion may develop as a second, independent epileptogenic zone.[96] In theory, then, resection of the primary lesion in these patients may not be sufficient to control seizures. In a report by Awad et al.,[4] 18 of 47 patients with intractable seizures and lesions had an epileptogenic region (defined by intracranial EEG) that was not contiguous with the lesion. It is not clear to what extent the resection of the epileptogenic zone contributed to seizure control. However, when complete resection of the lesion was achieved in these patients, the extent of the epileptogenic region resected did not affect outcome.

The concept of dual pathology implies additional or concomitant pathology beyond the primary pathology (i.e., the lesion). This concept is often invoked to explain involvement of the hippocampus in cases of structural lesions outside the hippocampus. There is evidence that epilepsy patients with mass lesions in the temporal lobe have some degree of cell loss in the hippocampus. The extent of cell loss is related to several variables, including the type of lesion, the distance of the lesion from the hippocampus, the age at seizure onset, and the occurrence of a prolonged first seizure.[49,84] Patients with gliomas or cavernous hemangiomas, patients with lesions distant from the hippocampus, and patients with a late age of seizure onset are less likely to have hippocampal cell loss. On the other hand, patients with arteriovenous malformations or heterotopias, patients with lesions close to the hippocampus, and patients with early onset of seizures are likely to exhibit significant cell loss in the hippocampus.

High-resolution MRI has been shown to detect extrahippocampal lesions plus hippocampal atrophy in about 5% to 20% of patients referred for refractory focal epilepsies.[85] Some structural substrates, such as malformations of cortical development and porencephalic cysts, are more likely to be associated with hippocampal atrophy, independent of the distance of the lesion from the hippocampal formation.[27] In an analysis of 41 surgical interventions in patients with dual pathology, lesionectomy plus mesial temporal resection resulted in complete freedom from seizures in 73% patients, while only 20% who had mesial temporal resection alone and 12.5% who had lesionectomy alone were seizure free.[85] Therefore, whenever possible, in patients with dual pathology, removal of both the lesion and the atrophic hippocampus should be considered as a surgical option.[25,85] However, the decision to remove the mesial temporal structures including the hippocampus in a patient with an extrahippocampal lesion is very complex and depends on multiple considerations, including not only the type of the lesion, but also the neuropsychological profile of the patient and the potential for cognitive sequelae, specifically memory dysfunction, following resection of the hippocampus. For instance, for a patient with epilepsy and a small cavernous angioma in dominant middle temporal gyrus, who has good verbal memory function, a resection of the lesion with the mesial temporal lobe structures may entail significant morbidity in mnemonic function.

Special Cases

The variety of lesions associated with epilepsy include special cases requiring varying surgical strategies. Two strikingly different examples include hypothalamic hamartoma, a highly focal lesion outside the traditional cortical boundaries, and wide hemispheric lesions such as Rasmussen encephalitis requiring hemispheric resection and disconnection procedures. The discussion of hemispherectomy and hemispherotomy is beyond the scope of this review and is discussed in Chapter 178.

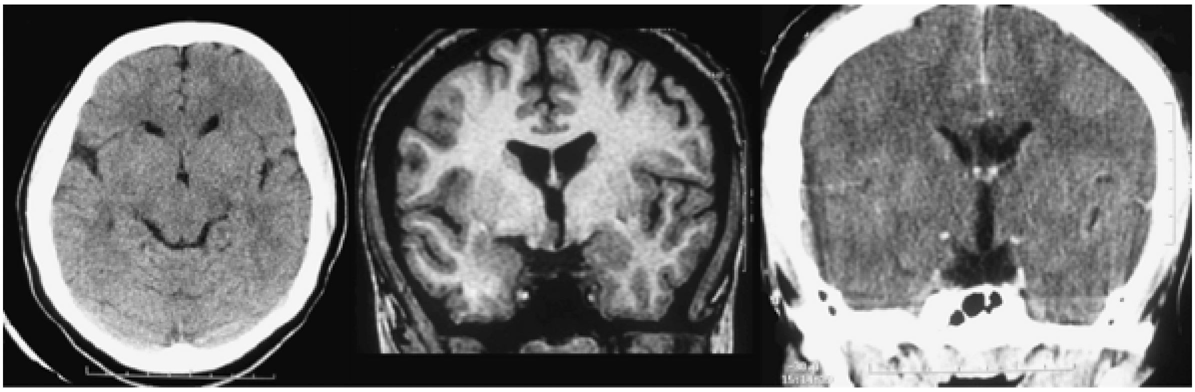

FIGURE 8. A 16-year-old girl with seizures since the tenth day of birth characterized by behavioral arrest, oral and upper limb extremity automatisms, ictal speech and incessant cry or laughter for 2 minutes, and urinary incontinence occurring approximately ten times per day. Electroencephalography (EEG) revealed bitemporal epileptiform discharges, and video-EEG monitoring could not localize seizure onset. The patient underwent hypothalamic hamartoma resection by the transcallosal anterior forniceal approach at the Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum, India, in November 2003, and has been seizure free since then except for a few auras of fear. Axial and coronal magnetic resonance imaging sequences show the lesion abutting the right lateral wall of the third ventricle; postoperative computed tomography shows complete lesion resection.

Hypothalamic Hamartoma

The surgical management of hypothalamic hamartoma has generally met with limited success and a high complication rate. In 2001, Rosenfeld et al.[120] described the use of a transcallosal, anterior forniceal approach for microsurgical resection of hypothalamic hamartoma in patients with refractory epilepsy with good results. Alternate surgical approaches such as lateral pterional and midline frontal through the lamina terminalis and endoscopic treatment through foramen of Monro; radiofrequency ablation; and Gamma Knife surgery are currently available to treat hypothalamic hamartoma.[8,117] The specific approach should be tailored according to the surgical anatomy of the lesion and the experience of the surgeon. While small lesions may be amenable to Gamma Knife, larger lesions will require surgical excision or disconnection. The transcallosal approach is best suited for intraventricular lesions, while the pterional approach is useful for interpeduncular lesions (Fig. 8).[8,103,117]

Postoperative Outcome

The beneficial effects of epilepsy surgery in patients with MRI-identified lesions in general are far superior to those with normal or nonspecific MRI findings.[24,93]

Tumoral Substrates

Over three fourths of patients become seizure free following resection of neoplastic lesions associated with refractory focal epilepsies.[42,50] In a recent analysis of 207 patients with tumor-associated chronic epilepsies such as ganglioglioma, DNET, pleomorphic xanthoastrocytoma, and pilocytic astrocytoma, during a median follow-up of 8 years, 82% of patients were seizure free,[91] remarkably consistent with earlier series.[50] Even among patients with astrocytomas, tumor recurrence at 10-year follow-up was only 25% and the 10-year survival was 90%.[91] While patients with ganglioglioma and low-grade gliomas do uniformly well,[54,109,116] because of its frequent association with peritumoral malformations of cortical development, DNET carries a less favorable outcome.[141] In a retrospective analysis of 18 patients who underwent removal of DNET, during a median follow-up of 10 years, two thirds of the patients were seizure free.[29] Although patients with temporal lobe lesions or patients with dual pathology have a better seizure outcome with resection of the mesial temporal structures, the decision to remove the latter is a complex one and should only be undertaken in carefully selected cases, taking into consideration the type of lesion (e.g., DNET and cortical dysplasia) and the neuropsychological evaluation. Neuropsychiatric considerations may sometime be relevant. For instance, an increased occurrence of psychosis with predominant depressive and paranoid features following surgical treatment for temporal lobe ganglioglioma has been observed.[2,142]

Malformations of Cortical Development

The postoperative seizure outcome of patients with malformations of cortical development has improved in recent years because of better definition of the lesion due to advances in structural and functional imaging, careful selection of ideal surgical candidates, and more radical resection of the lesion guided by electrocorticography and functional mapping.[90] A significant proportion of patients with malformations of cortical development still require invasive EEG monitoring to localize the ictal onset zone. In a recent series of 41 patients (22 adults and 19 children) with MRI-defined malformations of cortical development, after a minimum follow-up of 1 year, 63.4% of patients were seizure free.[1] Better seizure outcome was observed following temporal resection. In another study involving 53 patients with histopathologically confirmed malformations of cortical development (24 temporal and 29 extratemporal), after a mean

follow-up of 50 months, 38 (72%) patients were seizure free.[81] The patients with widespread cortical dysplasia who required multilobar resection had the poorest outcome. In a multicenter series, out of 21 patients with focal cortical dysplasia of Taylor type with adult-onset seizures, after surgery, 16 (76%) were rendered seizure free.[132]

Vascular Malformations

Nearly three fourths of patients with refractory seizures who underwent resection of arteriovenous malformations had significant reduction in seizures.[111] Schäuble et al.[129] analyzed the seizure outcome of 65 patients with cerebral arteriovenous malformations who underwent radiosurgery. During the median follow-up of 4 years, 51% were seizure free and 78% had an excellent outcome (either seizure free or auras only). Noto et al.[104] recently compared the outcome of 15 patients with cavernous angiomas who were continued on medical treatment without surgery to 16 patients who were treated surgically. During the mean follow-up period of 5.3 years, the seizure-free outcome was significantly higher in the surgical group than the medical group (80% vs. 19%). In addition, the number of antiepileptic drugs required was also significantly less in the surgical group. Considering the epileptogenic effect of the hemosiderin-stained brain tissue immediately surrounding the cavernoma, resection only of the cavernoma may not be sufficient for optimal seizure control. In an analysis of 31 patients with refractory epilepsy, patients in whom hemosiderin-stained brain tissue had been removed completely had a better chance of seizure outcome compared to those in whom only the cavernoma was resected.[9] However, in another study involving 163 patients with cavernous angiomas who underwent “pure” lesionectomy without removal of hemosiderin-stained gliotic parenchyma, 68.7% were seizure free.[47] If feasible, attempts should be made to remove the hemosiderin-stained tissue in addition to the cavernoma to optimize postoperative seizure outcome.

Hypothalamic Hamartoma

The previous dismal outlook for children with severe seizures and encephalopathy with hypothalamic hamartoma has now changed. Following transcallosal removal, more than three fourths of patients reportedly become essentially free of all seizures.[48,103,121] Gelastic seizures respond immediately, while other seizure types may take a few weeks or months to run down. In children with epileptic encephalopathy, cognitive decline stops and marked improvement in behavior has been reported.[8] Both transventricular resection and Gamma Knife surgery are associated with similar success rates and less morbidity.[8,117]

Tuberous Sclerosis

Most of the studies that have evaluated the postsurgical outcome of patients with tuberous sclerosis have concluded that good seizure outcome correlated with focal seizures and concordant imaging and EEG findings.[33,68,118,148] Resection of epileptogenic tuber(s) can result in seizure freedom in nearly three fourths patients.[33] In a recent analysis of 25 consecutive children (13 had invasive monitoring), at 6-month or more follow-up, 84% were practically seizure free.[148] Even children with multifocal seizures who required initial bilateral intracranial electrode study achieved excellent seizure outcome. Reduction in seizures and medication is associated with improvement in quality of life in nearly 95% of the operated children.[118] There is a concern that the nonresected tubers could become epileptogenic and could result in seizure recurrence during follow-up. However, in a recent study, only a quarter of patients who achieved an initial excellent outcome had recurrence of seizures when followed for more than 5 years.[68]

Summary and Conclusions

Patients with substrate-related epilepsies with suboptimal seizure control should be identified early and referred for presurgical evaluation before irreversible deterioration in their quality of life ensues due to long-standing disabling seizures and chronic antiepileptic drug–related side effects. In addition, the consideration of the natural history of the lesion and its potential risk to the host regardless of the seizures should always be considered. Although most of the tumors associated with chronic seizures have an indolent biologic course, the potential for malignant transformation should not be overlooked. The potential for spontaneous bleeding of a vascular lesion should also be considered. The best treatment should be based on both lesional and epileptogenic considerations. Success of epilepsy surgery depends on accurate preoperative localization of the epileptogenic zone and its complete resection. Patients with medically refractory lesional epilepsies belong to different categories depending on the degree of complexity involved in presurgical evaluation to define their epileptogenic zone. While some patients, such as those with tumoral epilepsy syndrome, can be selected for surgery by simple noninvasive presurgical evaluation strategy, others with malformations of cortical development and those with multiple lesions often require complex and invasive means to define their epileptogenic zone. Recent advances in structural and functional imaging have obviated the need for invasive monitoring in the majority. These advances along with improvement in surgical techniques have made lesionectomy safer and more effective. The role of radiosurgical techniques in the treatment of selected substrate-related epilepsy syndromes such as those associated with vascular malformations and hypothalamic hamartomas are currently undergoing evaluation.

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Chapter 180

Corpus Callosotomy

David W. Roberts

Introduction

A number of newer procedures—most notably, multiple subpial transection, vagal nerve stimulation, and deep brain stimulation—have become available in the treatment of seizure disorders, and these have legitimate roles either as alternatives to resective procedures or as strategies when a resective procedure is not an option. [15,35,49,89,139] The role of the corpus callosotomy in this setting warrants reevaluation.

Surgical division of the corpus callosum for the treatment of certain medically intractable seizure disorders, at one time about the only alternative to resective surgery, was first undertaken >60 years ago on the basis of two lines of evidence. The first was the observation of Van Wagenen that epileptic patients who subsequently suffered strokes or tumors involving the corpus callosum often had concurrent improvement in their seizure disorders.[128] The second was a growing experimental literature demonstrating, most notably in the work of Erickson in monkeys, [25] that the corpus callosum was the major route of seizure propagation from epileptogenic focus to generalization. [25,52,53,70,71] Van Wagenen went on to perform callosal section in a small number of patients with some success,[128] and similar clinical experiences were reported by Bogen and coworkers[11,12,13] and Luessenhop.[64,65] It was not until the series of Wilson and coworkers[136] that a sustained clinical experience developed, and over the last three decades, there has been widespread adoption of the surgical procedure.

Removing an epileptogenic region with the goal of surgical cure has always been preferred, but in those patients with generalized seizures in whom a discrete epileptogenic region could not be identified or resected, surgical disruption of secondary generalization was logical. Consequently, the earliest patients for this surgery were those who were not candidates for resective surgery but who demonstrated secondary generalization.

It was quickly appreciated that of the types of seizures most likely to be helped—drop attacks (variously classified as atonic and akinetic seizures)—are among the most responsive, often being eliminated altogether; tonic and tonic–clonic generalized seizures also have been shown in multiple series to be similarly affected.[3,4,7,10,14,17,18,20,26,29,31,33,34,35,41,43,45,46,47,48,50,51,55,56,57,59,66,67,68,69,72,73,76,77,78,79,80,81,82,83,87,88,90,93,94,95,96,97,98,99,102,103,104,106,108,111,112,114,115,116,117,118,119,122,123,124,125,130,131,132,133,134,135, Whereas corpus callosotomy had been performed in fewer patients than had most other epilepsy operations, and in many respects the procedure was not as well understood as other surgeries, it was reasonable that many patients underwent callosal section largely on the basis of their seizure semiology.

From a historical perspective, the role of pathology, as well as that of electrophysiologic studies, has been secondary. A spectrum of disease has been encompassed in clinical series. Williamson [131]) looked at surgical outcomes in terms of clinical diagnoses and classified patients into groups of infantile hemiplegia, forme-fruste infantile hemiplegia, Rasmussen syndrome, Lennox-Gastaut syndrome, frontal lobe epilepsy, and other secondarily generalized epileptics. Slightly better outcomes were found in the first two groups, but there was sufficient improvement in all categories to justify surgical intervention.

The electrophysiologic role has been an indirect one, by demonstrating the absence of a resectable epileptic region. In addition, however, electroencephalogram (EEG) findings in patients selected for callosotomy have been analyzed by a number of investigators. [44,54,58,62,74,84,92] Correlating EEG with surgical results, Geoffroy et al.,[41] Spencer et al.,[124] and Matsuzaka et al.[75] all reported better results in patients with lateralized EEG abnormalities. The majority of patients have evidence of bilaterally synchronous epileptiform activity, and this does not necessarily represent a bad prognostic sign. The significance of bilateral, independent foci is undetermined.

The impact of neuroimaging on the callosotomy experience has been limited. Lateralized structural lesions have been believed to be associated with a better surgical outcome, [124,136] but in the selection process their presence or absence has always been secondary to clinical and electrophysiologic information. As imaging technologies continue to evolve with increasing sensitivity and specificity, they are directing such aspects of the seizure evaluation as intracranial recording electrode placement. This increased sophistication of seizure investigation affects both patient selection and perhaps the surgery itself.

From the isolated clinical experiences of Van Wagenen,[128] Bogen and coworkers,[11,12,13] Luessenhop,[64,65] and Wilson and coworkers,[132,133,134,135,136] callosum section has seen a cautious but marked increase in application over the last several decades. Less than a dozen centers were performing callosal section in 1982 when the first Dartmouth workshop on the corpus callosum was held; nearly every surgical epilepsy center performs this surgery today. A survey of epilepsy centers in 1986 found 197 patients who had undergone corpus callosum section [23]; a follow-up survey 5 years later reported 563 patients so treated.[24]

Indications

The principal candidates for callosal section are those medically intractable epileptic patients in whom a resectable seizure focus cannot be identified and whose generalized seizures are believed likely to be ameliorated by disruption of seizure propagation. Patients in whom seizure semiology, electrophysiologic studies, neuroimaging, and neuropsychologic testing have shown localized disease amenable to resection are excluded. The remaining candidate pool is heterogeneous, including patients with infantile hemiplegia, forme-fruste infantile hemiplegia, Rasmussen syndrome, Lennox-Gastaut syndrome, frontal lobe epilepsy, and other secondarily generalized epilepsies.

Selection criteria at our institution, in addition to the principal exclusion of resectable disease, include (a) medical intractability of at least 2 and usually 4 years' duration, with exhaustive anticonvulsant regimens and documented adequate serum anticonvulsant levels, (b) generalized seizures, usually but not necessarily major motor or akinetic in type, and

(c) potential functional benefit if improvement in the seizure disorder is achieved. We have not automatically excluded patients from surgery because of retardation, age, mixed hemisphere dominance,[69,108] lack of demonstrable partial seizure onset, or bilaterally independent EEG abnormalities, although the likelihood of success may be less in certain instances.

The goal of surgery with callosal section is distinguished from that of other epilepsy surgeries in usually being palliation rather than cure. Although a seizure-free patient is always hoped for, such an outcome is achieved in only 5% to 10% of patients.[23,24] More likely, callosal section will achieve a significant reduction and perhaps elimination of certain seizure types, such as drop attacks or secondarily generalized seizures, but often with persistence of attenuated partial seizure activity. The positive impact of such an outcome on these patients is often dramatic and greatly appreciated.

Surgical Approaches

The greatest variable in callosal surgery is that of extent of section. Early clinical series often included division of the corpus callosum, the underlying hippocampal commissure, and additional structures, including the anterior commissure and, in some instances, one fornix. [11,13,64,65,128,132,134,135] Nearly all series today restrict division to the corpus callosum and, in posterior or complete callosal section, the hippocampal commissure that is immediately apposed to the ventral aspect of the posterior portion of the callosum. There remains variation, however, with regard to which part or how much of the structure is divided. Seizure outcome appears to have some correlation with extent of section, [104,122] and because neuropsychologic consequences of callosal section are encountered primarily with complete section,[126,129] most centers today usually divide the anterior three fourths and spare the splenium at initial surgery. Completion of the section can then be performed in those patients who fail to obtain an adequate response to such surgery. Exceptions to this approach are division of a smaller, select portion of the callosum, division of the posterior half as an initial procedure, and division of the entire callosum in one operation. The presurgical evaluation and preoperative substrate may influence the consideration of these alternatives.

The history, neurologic exam, and cognitive evaluation are useful in suggesting diffuse or bilateral disease for which commissurotomy may be an appropriate strategy; these factors contribute in the consideration of the risk-benefit ratio for partial or complete section. The sensory dissociation whereby visual, auditory, or tactile information received by the nondominant hemisphere may not be accessible to the speech-dominant hemisphere is of diminished consequence in the severely impaired individual, and in such a setting complete section may be a reasonable surgical approach. This is especially true if drop attacks, which usually respond to anterior section, are not the predominant seizure pattern. If presurgical evaluation, including electrophysiologic studies, demonstrates predominantly parietal-occipital disease, it may be appropriate to consider posterior partial section as the first stage.

The preoperative epileptogenic substrate is important for reasons similar to those for the preoperative evaluation. A more discrete pathology may direct one toward an appropriate partial section, [119] and diffuse disease may render any partial section futile. The correlation between extent of disease and successful section, however, is insufficient to place great reliance on these factors. Lateralized pathology does have a modest but worthwhile role in determining the side of the interhemispheric approach; this is usually on the nondominant right side, but in the setting of an atrophic left-hemisphere or right-hemisphere language dominance, surgery from the left side of the falx may be indicated.

Surgery is usually performed under general anesthesia, and intraoperative electroencephalographic recording, when performed, has been primarily for investigative purposes. Tailoring of the length of resection based on intraoperative EEG information has been advocated by at least one center, [73] but given the reality of often insufficient abnormal interictal EEG findings intraoperatively, as well as the observation that subsequent seizure propagation may occur across remaining, adjacent callosal fibers, most have not adopted this practice. The patient is placed supine on the operating table, with the head unturned and secured in three-point pin fixation. For the anterior division, the neck is kept in neutral position; for the posterior division, flexion of approximately 20° facilitates exposure. Spencer has favored placing the patient's head such that the hemisphere to be retracted is dependent, thereby allowing gravity to help provide the exposure (Spencer D. D., personal communication, 1986).[29,68] This has the appeal of minimizing any retracting force placed interhemispherically, although other surgeons have not considered this retraction significant enough to warrant the perhaps less comfortable and differently oriented horizontal positioning.

Linear incisions and 2-inch trephinations[100,133] have been easy and reliable in our series, but the actual type and extent of craniotomy is relatively unimportant. A 9-cm transverse incision with one third of its length across the midline and placed 2 cm in front of the coronal suture is used for the anterior procedure. A similar incision and trephination at the level of the parietal eminence is used for the posterior procedure. The placement of the craniotomy across the sagittal sinus requires caution but facilitates exposure down the interhemispheric fissure with minimal retraction.

Localization of parasagittal draining veins by angiography prior to transcallosal procedures has been advocated, but this has not been a routine step in our series. It has always been possible to work on either or both sides of such a vein using microsurgical technique without requiring its sacrifice. Nevertheless, Apuzzo et al.'s observation that in 42 of 100 angiographic studies, significant veins were noted to enter the sagittal sinus within 2 cm of the coronal suture, with 70% of these posterior to that suture, is of interest. [5] Such angiographic information may be available in those patients who have previously undergone Amytal testing or in whom magnetic resonance angiography (MRA) techniques have delineated parasagittal venous structures.

Dural opening follows standard practice, with a curvilinear incision and reflection on the sagittal sinus. Dissection is begun down the interhemispheric fissure under loupe magnification, and retraction is aided by the earlier administration of mannitol (1 g/kg). Pressed Gelfoam (Upjohn, Kalamazoo, MI) is used to protect the exposed cortex, and a Greenberg self-retaining retractor is placed prior to employment of the operating microscope. Gentle retraction is accomplished with a single retractor blade on the ipsilateral hemisphere, and, when occasionally needed, an additional blade retracts the inferior aspect of the falx or contralateral cingulate gyrus.

The exposure can be rendered difficult by adhesions between the hemispheres, which is especially common in the setting of previous infection or trauma. With patient microsurgical technique, these are usually surmountable, although approaching the callosum more posteriorly and using the deeper extension of the falx can help in this situation. The corpus callosum is distinguished from the more superficial cingulate gyrus by its glistening white appearance, and exposure along the length of callosum to be divided is obtained prior to entering the commissure. The pericallosal arteries are easily identified overlying the callosum, and care is taken to avoid their injury. Actual sectioning of callosal fibers is usually carried out between these arteries, although division lateral to these vessels can be performed if this is more convenient.

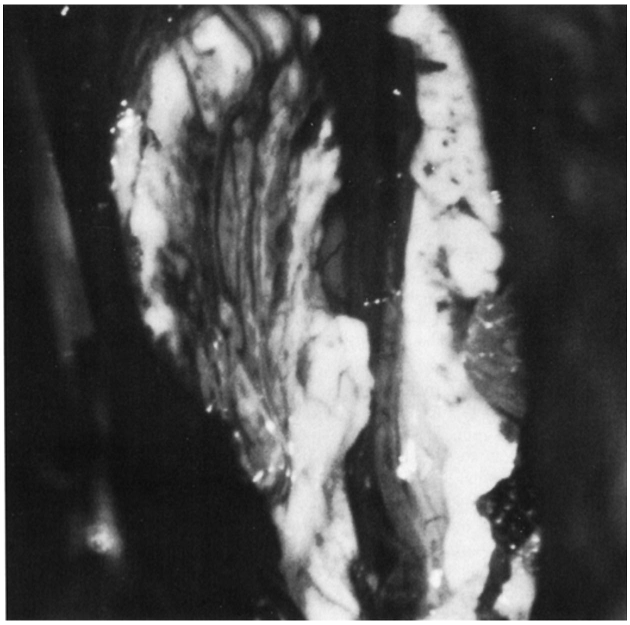

FIGURE 1. Division of the genu, whose cut surfaces appear glistening white, reveals the underlying paired anterior cerebral arteries, which course anteriorly, superiorly, and then posteriorly around the commissure. (From Roberts DW. Corpus callosum section. In: Spencer SS, Spencer DD, eds. *Surgery for Epilepsy*. Boston: Blackwell Scientific; 1991:168–178, with permission.)

The operating microscope with its superb magnification and illumination has proven invaluable during the final exposure and actual sectioning (Fig. 1). Bipolar cautery is used for coagulation of small vessels supplying only the callosum itself. The actual division of callosal fibers is carried out with a microseptal or microsuction tip. The ultrasonic aspirator may prove to be of greater utility in this step as it becomes more refined and thinner.

The bluish appearance of the underlying ventricular ependymal surface is described in early reports of callosal section that recommend using this landmark as the limit of division. [134] The alternative of identifying the midline, however, offers numerous advantages that have become increasingly evident over the course of our series. These include unequivocal assurance of completeness of fiber division, elimination of possible lateral deviation (especially in the frontal region), decreased likelihood of entering the lateral ventricle, and less operative time. A blunt microinstrument is gently swept from side to side as the callosum is nearly traversed, and this will usually expose the midline cleft between lateral ventricles. Once this cleft has been identified, the remainder of the section is easily accomplished.

Localization of the midline during the anterior division is easiest at the posteriormost portion of the genu or the anterior portion of the body. The actual direction of subsequent section is not particularly important. Division around the genu and down the rostrum is performed extraventricularly as far as possible. The rostrum at this point is nearly paper thin, and any remaining fibers are insignificant. No attempt is made blindly to divide the anterior commissure.

The posterior extent of the division is readily performed following the midline cleft (Fig. 2). If an attempt is being made to achieve success with a partial division, it is reasonable to carry the division through approximately the anterior three fourths. A number of methods have been employed to ensure accomplishment of the desired length of section. These include physical measurement of the exposed callosum to be sectioned, identification of structural features (such as the thinning of commissure generally seen in the posterior body or the appearance of the fornices), intraoperative radiographs,[8] and, more recently, the image guidance of frameless stereotactic navigational systems. When assurance of section and hemostasis is complete, a metal clip attached to a small piece of Gelfoam is placed at the posterior extent of the divided callosum; at subsequent surgery, such a marker has often been greatly appreciated when gliosis may obscure the extent of previous resection. It has not created an undesirable, excessive magnetic resonance imaging (MRI) artifact.

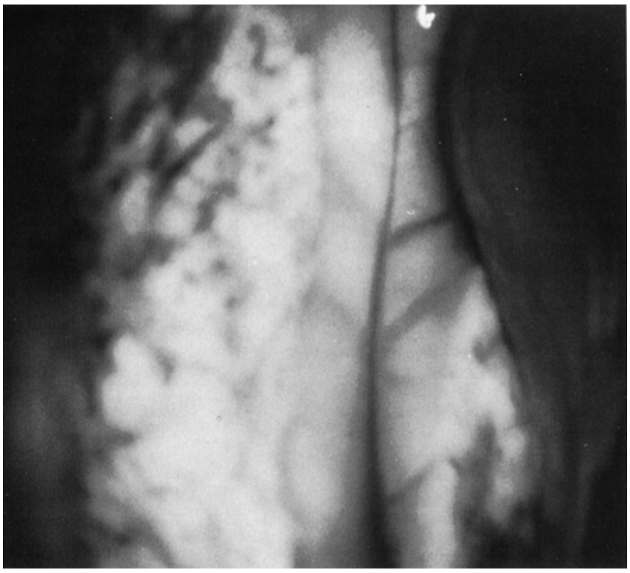

FIGURE 2. Continuing callosal section posterior to the genu is greatly facilitated by following the midline cleft formed by the ependyma of the lateral ventricles. (From Roberts DW. Corpus callosum section. In: Spencer SS, Spencer DD, eds. *Surgery for Epilepsy*. Boston: Blackwell Scientific, 1991:168–178; with permission.)

Section of the posterior corpus callosum, either as a second or initial procedure, is accomplished in a similar manner. The more extensive falx cerebri greatly facilitates this exposure. The fibers of the splenium are divided with similar instrumentation, and under magnification the completeness of the

section is certain. The underlying arachnoid, beneath which lie the pineal and quadrigeminal cistern, is preserved. The posterior hippocampal commissure may be difficult to distinguish from the overlying callosal fibers, but this is of no practical significance because it is divided as well. If an anterior section has already been performed, the previously placed clip is retrieved. If the posterior section is the initial commissurotomy procedure, a clip is left as a marker at the anteriormost extent of the section.

Closure follows standard surgical practice. The dura is closed over Gelfilm (Upjohn, Kalamazoo, MI) using 4-0 Vicryl (Ethicon, Inc., Johnson & Johnson, Somerville, NJ) after confirmation of hemostasis. The bone flap is secured with a bone-plating system; the galea aponeurosis is reapproximated using 3-0 Vicryl; and the skin is closed with either 4-0 Prolene (Ethicon, Inc., Johnson & Johnson, Somerville, NJ) or staples. The patient is observed in the neurosurgical observation unit overnight and transferred to the neurosurgical ward the following morning. Mobilization begins immediately, and the patient is typically discharged 4 to 5 days following surgery; in anterior section alone or in children, hospitalization may be shorter. Anticonvulsant medication is generally left unaltered until at least subsequent follow-up. A decision regarding completion of the callosotomy is made a minimum of 2 months after the first procedure.

Alternative techniques have been occasionally proposed. Stereotactic lesioning, radiosurgery,[85] and endoscopic strategies[127] can certainly be used, but experience with these techniques for this specific purpose is very limited. Any such technique must be ensured to not inadvertently spare commissural fibers, because suboptimal seizure outcomes have been attributed to such sparing during open procedures. Such techniques must also match the low morbidity and mortality of today's microsurgical procedure.

Image-guided surgical techniques (neuronavigation) have been incorporated into the majority of neurosurgical operating room environments. They are routinely used in microsurgery, particularly in epilepsy, and, as alluded to earlier, can be a useful aid in callosal section as well. With respect to intraoperative MRI, computed tomography (CT) or other updated imaging, the role for these more resource-intensive techniques has not been demonstrated for this procedure. Intraoperative brain shift or deformation is less an issue in either such a central location or in a nonresective procedure.

Complications of corpus callosotomy can be considered as surgical or functional in nature.[86] Frontal lobe swelling or infarction with resultant hemiparesis or plegia can result from excessive retraction or sacrifice of bridging veins, and hydrocephalus requiring shunting has been seen with larger surgeries in which there may have been soiling of the ventricular system with surgical debris and blood.[134,136] Current microsurgical technique, with reduced retraction and extraventricular callosal sectioning, has greatly reduced the incidence of these sequelae. The risk of infection at this time is similar to that of standard neurosurgical procedures.

A syndrome of usually transient mutism or decreased spontaneity of speech, with or without mild hemiparesis, has sometimes been noted following anterior callosal section and is

presumed to result from either medial frontal retraction or perhaps disconnection.[91,105,133] When it does occur, it almost always resolves within days and is rarely problematic. Posterior section, on the other hand, disrupts interhemispheric transfer of visual, tactile, and auditory information and is responsible for the long-term disconnection syndromes associated with this operation.[36,37,38,39,126] Objects presented solely to the hemisphere that is not dominant for language may not be verbally reported by the patient, but because isolation of such stimuli to one hemisphere usually requires a fairly constrained, laboratory environment (e.g., tachistoscopic hemifield visual presentation), it is unusual for this to cause disability. Most patients, as well as many early investigators, have been unaware of the deficit.

Complete callosal section can be associated with independent and sometimes conflicting behaviors generated by the two hemispheres.[119] Anecdotal reports of uncooperative or antagonistic action of the two hands while the person is getting dressed or repeated hesitation about whether or not to enter a room are certainly true, but over time such behaviors generally abate.

Of greater concern has been the deficit that can arise when an interhemispheric compensatory mechanism that has developed after an earlier hemispheric insult is disrupted by callosal surgery. Mixed dominance, in which language resides in the hemisphere ipsilateral to the dominant hand, may predispose to postoperative language difficulty,[107] but this has not been a consistent finding. By a similar mechanism, a preexistent hemiparesis might worsen following commissurotomy. Fortunately, such deficits are relatively uncommon. The nature of an occasionally observed postoperative memory disturbance remains incompletely understood.[126,138]

Summary and Conclusions

For certain patients who have failed medical management, who are not eligible for resective seizure surgery, and who have either preferred not to undergo vagal nerve stimulation or failed to respond to that procedure, commissurotomy may successfully reduce seizure frequency and severity. Atonic seizures (drop attacks) and secondarily generalized major motor seizures are most likely to be improved, but other seizure types may also respond.

Division of the corpus callosum alone achieves the aforementioned success. Complete callosotomy may not be required in all patients, and anterior three-fourths section, followed by completion of the section if needed, remains a reasonable approach in most patients. As a microsurgical procedure, extraventricular division of the corpus callosum can be safely and assuredly performed. Although there are always numerous variations in surgical technique, the procedure of corpus callosum section is probably less variable than that of most other, longer-established surgical interventions for the treatment of epilepsy.

The behavioral sequelae of commissurotomy have received extraordinary attention in the past for their neuropsychologic interest,[1,2,6,9,14,16,19,21,22,27,28,30,36,37,38,39,40,42,60,61,63,105,107,108,109,110,113,126,129,138] but it is uncommon to encounter permanent disabilities. For the great majority of patients, the benefits resulting from the procedure outweigh any such effects.

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Chapter 181

Reoperation for Medically Refractory Epilepsy

Robert R. Goodman

Introduction

Medically refractory epilepsy (MRE) has been widely recognized as a medical problem that significantly impairs quality of life[3] and significantly decreases life expectancy.[8] The surgical treatment of epilepsy was developed more than 50 years ago[2] and has expanded greatly since the early 1980s.[4] Epilepsy surgery generally involves a resective surgery with the goal of rendering a patient free of disabling seizures.[4] Surgical candidates are generally patients who have undergone an extensive evaluation and are thought to have seizures originating from a single brain region. In the majority of patients, this "seizure focus" is felt to be confined to one of the temporal lobes. Resective surgery is pursued if it is thought that there will either be no noticeable neurologic deficit or that any deficit will be "acceptable" (i.e., some verbal function and/or verbal memory impairment with dominant temporal resections). Many medical centers[4] and a multicenter National Institutes of Health (NIH)-sponsored study[22] have reported a high percentage of patients to be seizure free following resective surgery. It is presumed that this result indicates that all (i.e., in patients ultimately able to discontinue antiepileptic medication) or an adequate amount (i.e., in patients rendered seizure free with well-tolerated antiepileptic medication) of epileptogenic tissue has been resected. Many patients continue to have rare seizures or a much lower frequency or severity of seizures and have a difficult-to-assess degree of improvement or benefit.[5] A significant percentage of patients continue to have medically refractory seizures that are frequent enough and/or of a severity that prompts consideration for a reoperation with the goal of accomplishing the original surgical goal. This was reported by Penfield and Jasper in the 1950s[14] and subsequently further explored by Rasmussen, operating on patients from Penfield's series.[15] A number of more recent reports[1,6,7,10,12,16,17,18,19,20,23] have provided much more knowledge regarding the subject of reoperation for MRE. A significant percentage of patients were reported to be seizure free following reoperation, often indicating that the full extent of the epileptogenic tissue had not been appreciated at the initial surgery or (in a minority of patients) that the "seizure focus" had been misidentified. Patients without improvement after a reoperation have often been felt to harbor multiple or widespread epileptogenic brain areas and it is often concluded that these patients are not able to be rendered seizure free by resective surgery. The analysis of patients who failed to achieve the desired result with a first, or subsequent, resective surgery may be one of the keys to improving resective surgery for MRE, both by improving our ability to select patients who can be rendered seizure free by resective surgery and by improving our understanding of the tissue that must be resected to achieve this goal. For the purposes of this chapter, reoperation will refer to a resective surgery intended to achieve the elimination of seizures in a patient who has previously undergone a similar surgery. It is often helpful to subdivide patients having resective surgery for MRE into three subgroups: Medial temporal lobe resection, resection of a structural/pathologic lesion with associated epileptogenic cortex, and resection of a neocortical nonlesional epileptogenic region. Reoperations can be similarly categorized. In this chapter, the published experience of a number of epilepsy centers with such reoperations will be considered by, wherever possible, subdividing the reoperations into these same three subgroups. This may be the most useful way to gain from the reported experience and to use this knowledge in approaching patients undergoing either an initial or a repeat resective surgery for MRE. Glial neoplasms are being excluded from the structural lesion subgroup, because these lesions often progress over time and should be considered a distinct entity with regard to the management of associated medically refractory seizures. This subject is not addressed in this chapter. Reoperation sometimes is a hemispherectomy. This surgery does not have the same goal as the initial surgery (i.e., focal resection with preservation of hemispheric function) and falls outside of the scope of reoperation defined above. Callosotomy is a distinct type of epilepsy surgery that typically aims to eliminate a specific seizure type and will not be addressed here. Palliative surgery following resective surgery, having the goal of reducing seizure frequency and/or severity (not seizure elimination), such as vagal nerve stimulation, similarly will not be considered reoperation. Also, such surgery as an initial operation will not be considered a “first” operation for MRE.

Incomplete Medial Temporal Resection

Many of the reports of reoperation for epilepsy have included patients whose reoperation involved resection of medial temporal structures, often the posterior hippocampus. The series reported by Rasmussen in 1975[15] included 129 nontumor patients who had a reoperation between 1928 and 1971. Of the 115 patients with at least a 2-year follow-up (2 to 39 years), 29 (25%) were seizure free and 31 (27%) were categorized as having significant improvement of seizure frequency. It is probable that the majority (possibly all) of the benefited patients had an extension of their original temporal resection and that this included an extension of the medial temporal resection, although the publication does not provide enough detail to confirm this. By 1984, Spencer et al.[21] had reported that depth electrode evaluations indicated that about 20% of hippocampal seizures had a posterior onset and they described a surgical technique to accomplish a complete hippocampal resection. The importance of this recommendation for complete hippocampal resection is supported by subsequent experience. A large percentage of patients who have been reported to be seizure free after reoperation have had a posterior hippocampal resection at the second surgery. The abstract by Olivier et al. in 1988[13] reported that 20 of 425 anterior temporal resections for epilepsy were

reoperations. Of these, 13 (65%) had not had any hippocampal resection at the initial surgery and seven (35%) had only an anterior/partial resection. The seizure outcome for this group was six (30%) seizure free, three (15%) with a marked reduction, and seven (35%) with worthwhile improvement. Another series reported in 1989[23] included 28 nontumor patients who had a second focal resection for medically refractory epilepsy. Although not specifically stated, it seems that in 16 of these patients the second surgery was an extension of the temporal lobe resection that included additional hippocampus and that 10 of the 16 (62.5%) were reported seizure free at follow-up (duration not reported). It is important to note that one patient had a permanent hemiparesis after reoperation. Three other patients in this series were seizure free after reoperation (frontal lobe structural lesions) and will be discussed later. Subsequently, Wyler et al.[24] reported on a study to compare seizure outcome with anterior versus complete hippocampectomy that showed a significantly greater seizure-free outcome with the complete resection.

The Cleveland Clinic in 1991[1] reported on 15 reoperated patients from an overall series of 154 resections for medically refractory seizures. Ten of these patients had their initial operation at their center. The 15 patients were selected from 23 patients who were felt to have “truly intractable seizures” following a resective surgery. In this group, seizure recurrences occurred within 7 months of surgery and reoperation occurred 3 months to 12 years after the first surgery (mean = 38 months). Eleven of the 14 focal resection patients (one patient had a functional hemispherectomy as the second surgery) had invasive electrode investigation before the second resection. Seven of these 14 were seizure free at the last follow-up (range of 8 to 82 months), but four of the 12 had <12 months and only one had >15 months follow-up (82 months). Reoperation in 6 of the 14 involved resection of residual medial temporal structures in patients without structural lesions, and these accounted for three of the seven seizure-free patients and two of the four patients with a >90% seizure frequency reduction. The other eight patients are discussed later. The series had no mortality or serious morbidity.

The Montreal Neurological Institute reported an experience with reoperation on the temporal lobe (for refractory epilepsy) in 1994.[7] This included 40 of the approximately 260 temporal lobe surgeries performed by the senior author (A. O.) over a 9-year period. The senior author performed the first surgery in 31 of the 40 (nine had been done at other institutions). The original surgery was based primarily on scalp/sphenoidal interictal and ictal evaluation, with 6 of the 40 having depth electrode evaluations due to inadequate lateralization or localization. Recurrent seizures were similar to preoperative seizures and occurred within 6 months in 60% and by 2 years in 90% of the patients. The mean time to reoperation was 5.5 years. Reoperation was based on scalp electroencephalogram (EEG) in 36 patients (31 with temporal and five with mostly temporal, but multifocal, onsets) and depth electrodes in four patients (three with multifocal and one with temporal onsets). At follow-up (range 2 to 11 years; mean of 4.8 years), 21 patients were seizure free and four had rare seizures (one to two per year). All of these patients had resection of residual medial temporal tissue, with some having resection of neocortex as well. Three of the other 15 patients were rendered seizure free by a third operation, one by resection of a missed cavernous malformation, one by resection of additional neocortex, and one by resection of further mesial tissue. Lack of seizure improvement was associated with multifocal EEG abnormalities and seizure recurrence within 1 month of the first surgery. There was no significant permanent neurologic morbidity in the series.

Experience with reoperation at the University of Washington was reported in 1999.[10] This involved 21 patients who had their reoperation between 1991 and 1996 and represented <5% of the epilepsy surgeries performed over that period at that center. At follow-up (1 to 5 years, mean of 3 years), nine (43%) were seizure free and two (9%) had a >95% seizure reduction. There was no surgical morbidity. Only 17 of the patients had focal resections, with two having multiple subpial transections of motor cortex and two (children) having hemispherectomies. The results of the various types of surgery were not reported. Thus, it is not possible to determine how many patients were rendered seizure free by resection of medial temporal structures or residual structural lesions. Eleven of the 17 focal resections were of temporal tissue only, and seven of these included resection of mesial structures. Also, two patients had calcified lesions in the temporal lobe and one had an intraventricular calcified lesion (the pathologies of the series included one ganglioglioma, one cortical dysplasia, and 19 with gliosis). Resections were described as tailored and 11 of the patients had intracranial electrode evaluations. It is possible that all seizure-free outcomes occurred in patients who had either a resection of medial temporal structures or a structural lesion. The study did find two factors that significantly correlated with outcome: (a) that four of the patients had a central nervous system (CNS) infection before the onset of epilepsy and that none of these patients became seizure free, and (b) that the seven patients with a focal magnetic resonance imaging (MRI) abnormality concordant with the ictal EEG onsets before and after the first surgery had a better seizure outcome than the other 14 patients.

In 2000, a group of patients with persistent or recurrent seizures after temporal lobe resection for MRE at the Kings College Hospital of London was analyzed,[9] in an attempt to identify the apparent cause for failure to achieve seizure freedom and to possibly identify appropriate candidates for reoperation. This study has limited usefulness for the assessment of the role of, or optimal approach for, reoperation, but does seem to provide some insight into the population of patients who have been subjected to reoperation. From a series of 282 consecutive temporal lobe resections for MRE between 1976 and 1995, 56 patients (20%) were known to postoperatively have at least one seizure per month and 44 of these patients were assessed in detail. Of these 44 patients, 20 were diagnosed with mesial temporal sclerosis (MTS), ten with a structural/mass lesion (dysembryoplastic neuroepithelial tumor [DNET], discussed below), and 14 with nonspecific pathology (discussed below). Of the 20 patients with MTS, the postoperative electroclinical diagnosis was of ipsilateral temporal seizures in 12 patients (although one was felt to have independent ipsilateral frontal seizures and two were felt to have contralateral seizures), ipsilateral nonlocalized seizures in one patient, ipsilateral frontal seizures in one patient, generalized seizures in one patient, and contralateral temporal seizures in five patients. None of the patients had evidence of contralateral seizure onsets preoperatively. Five patients had residual hippocampus, but only two were felt to have seizures from this area. One also had a new major seizure type with apparent contralateral frontal onset and one had a reoperation for resection of the residual hippocampus and was seizure free at last follow-up (6 months after surgery). Reoperation was not performed in any other of these patients, although 11 were felt to have strictly ipsilateral neocortical onset seizures.

A more recent study, from the Yale University Epilepsy Center,[18] contrasted itself from prior studies by including only patients who had had their initial surgery at their own center (and thus had undergone a thorough and fairly uniform preoperative evaluation), had a preoperative MRI, and had a minimum 1-year follow-up after reoperation. Importantly, no patient had partially retained medial temporal structures, since any patient who had a medial temporal resection had had a complete one. This series reported on a total of 27 patients, 17 of whom had two successive resective surgeries with the goal of seizure elimination, while the others had a palliative surgery (corpus callosotomy or vagal nerve stimulator) as either the first or second operation. Of the 17 patients, five had glial tumors (oligodendrogliomas) and one became seizure free with a functional hemispherectomy as the reoperation (for a presumed hemispheric syndrome that had been suspected before the initial surgery), leaving 11 patients without a glial tumor or hemispheric syndrome who had two resective surgeries. Interestingly, all 11 of these patients had a focal MRI abnormality prior to their initial operation. One of these was a patient with temporal neocortical changes and hippocampal atrophy who had only a neocortical resection, without preliminary invasive electrode evaluation. A subsequent medial temporal resection rendered this patient seizure free. The three patients with a medial temporal resection for presumed MTS at their initial surgery had invasive electrode evaluation beforehand, due to a discordant evaluation. Ten of the 11 patients, accumulated over 11 years at an active epilepsy surgery program, had resections involving structural lesions or neocortex, with only one becoming seizure free (see later sections). No mortality or significant morbidity was reported.

A recent publication reviewed the Mayo Clinic experience with reoperation.[20] This represented 64 of 1,486 operations (4.4%) from 1985 to 2000, with 18 of the 64 not having had their first operation at Mayo Clinic. Fifty-one of the 64 had an MRI before the first surgery. No patient had a malignant tumor, but 18 had low-grade tumors and two had tuberous sclerosis lesions. Information is not provided that would allow a breakdown of results based on reoperation for mesial temporal structure resection without lesionectomy versus structural lesionectomy versus neocortical resection alone. Temporal surgeries were performed in 44 of the patients, with 16 involving lesionectomies. Resection of mesial temporal structures was involved in 31 of these patients, but it is not clear how many of these also had a structural lesion. Fourteen of these 31 were rendered seizure free. Twenty-eight of the temporal surgeries did not involve a structural lesion and eight were rendered seizure free. It is not stated, but from the available data it is possible that all of these included resection of mesial temporal structures. Of the 20 nontemporal resections, 17 involved lesionectomies (six became seizure free) and three were nonlesional (one becoming seizure free). With regard to EEG, surgeries were largely guided by scalp ictal findings, with intraoperative corticography in a large percentage (56% at the first and 77% at the second surgery) and rare invasive ictal data (three patients at the first and six patients at the second surgery). Seizures recurred within 1 year of surgery in 56 patients, but 2 to 11 years after surgery in the other eight patients. Following reoperation (three surgeries in nine patients and four in two patients), with a follow-up of at least 1 year, 25 (39%) of the 64 patients were seizure free and six (9%) had rare seizures postoperatively. Predictors of seizure freedom, using a logistic regression model, included seizure onset after 15 years old, seizure duration ≤5 years, and focal spikes on scalp EEG. Also, reoperations that included resection of residual medial temporal structures were more commonly associated with seizure freedom than the other reoperations. Interestingly, prognostic factors for a first surgery did not predict seizure outcome with reoperation and seizure freedom was similar for the temporal and extratemporal reoperations. The morbidity in this series was very low, with one permanent mild hemiparesis, two wound infections, and one subdural hematoma. Five patients had a new quadrantic visual field deficit and four had an increase of a prior field deficit (the extent was not reported).

A recent publication reviewed the experience of a single neurosurgeon, at Indiana University, with reoperation after failed surgery for temporal lobe epilepsy.[16] Initial surgery involved 262 patients operated on from 1984 to 2002. All patients had an MRI, with volumetric MRIs since 1994, but the findings were not described. Most patients had ictal single photon emission tomography (SPECT) and 2-[^{18}F] fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) scans were done since 1993. Intracranial electrodes were used in 24 patients, 18 with bilateral temporal grids/strips and six with bilateral temporal depth electrodes. Unilateral onsets were recorded in 259 patients, bitemporal onsets with over 80% from one side were recorded in two patients, and one patient (with a cavernous malformation) had no seizures recorded. Electrocorticography (EGoG)-guided en bloc temporal resections or lesionectomies including the presumed epileptogenic zone were performed. Complications were rare, with one mild hemiparesis, one transient hemiparesis, and one homonymous hemianopsia. There was no mortality. With follow-up of 1 to 18 years, 65% were seizure free, 19% had rare seizures, and 16% (41 patients) were Engel class III or IV. Compared to the seizure-free patients, the class III and IV patients were significantly less likely to have a history of febrile seizures or to have abnormal MRI, and more likely to have a history of head injury and to have had an invasive electrode evaluation. Among the 41 patients with significant persisting seizures were 9 of the 24 patients who had undergone an invasive electrode evaluation preoperatively. Thirty of these 41 patients had postoperative MRI, with 28 having residual posterior medial temporal structures (two also had posterior temporal lesions) and two having posterior temporal lesions. The 41 were considered for reoperation. Twelve were not recommended for reoperation: Six who had invasive electrode evaluation preoperatively, five who had frequent bilateral temporal interictal epileptiform discharges (IEDs), and one who had frequent right frontotemporal IEDs and was felt to have an extensive epileptogenic zone. Twenty-nine of the patients were recommended for reoperation and 21 elected to proceed. All 21 patients had resection of residual posterior medial temporal tissue, under general anesthesia and with electrocorticography, with two also having resection of a posterior temporal glioma. ECoG guided additional posterior basal temporal resection in five patients. At follow-up (1 to 16 years), 12 patients (57%) were seizure free (one with a glioma) and five (24%) had rare seizures. Of the four patients with significant persisting seizures, one had a posterior temporal glioma. There was no surgical mortality or significant morbidity. Importantly, during long-term follow-up the mortality rate (excluding one patient who died due to cancer) was 1.1% for seizure-free patients (none of those seizure free after reoperation) and 15% for patients with persisting seizures (including two following reoperation). These results suggest that if the initial surgery had included a complete resection of the medial temporal structures, then the rate of seizure freedom might have been increased from 65% to 69% and for rare seizures from 19% to 21%.

A recent report summarized the Montreal Neurological Institute experience with surgery for temporal lobe epilepsy in 109 children (up to 19 years old) from 1985 to 2000.[12] Invasive electrode evaluation was performed in six of these patients. Ten patients had gliomas. Resections were tailored by ECoG. Twenty-three patients had a reoperation, with 14 (61%) becoming seizure free (including all three with resection of residual medial temporal structures) and three (13%) having a >90% seizure reduction. Reoperations included 15 patients with neocortical resections and five with recurrent gliomas. The seizure outcomes for these subgroups were not detailed. Overall, reoperation increased the good seizure control rate from 71% to 86% of patients. In the entire experience, there was no surgical mortality or permanent neurologic deficit.

A recent case report[6] emphasizes the importance of complete mesial temporal resection for patients with hippocampal sclerosis. The report involved a 30-year-old patient with recurrent seizures after two temporal lobe resections. Residual hippocampus was seen on MRI and invasive recording

identified seizure onsets from this tissue. Resection yielded long-term seizure freedom.

To summarize the published experience reviewed in this section, of the 249 reoperations that included resection of medial temporal structures (the vast majority having had a partial resection at the first operation), without a structural lesion, 94 (38%) were reported seizure free. The reported surgical morbidity was very low. This suggests that when an initial surgery for MRE is to include a mesial temporal resection, a complete resection of the medial temporal structures is preferable to a partial resection. Such an approach will of course eliminate the consideration for a reoperation to complete the resection of medial temporal structures for patients with persistent or recurrent seizures after a first resective surgery for MRE.

Reoperation for Structural Lesions

Medically refractory seizures associated with a structural or “MRI visible” lesion represent a distinct subgroup of patients with regard to initial operation and reoperation with the goal of achieving seizure freedom by a focal resection. Reported experience strongly suggests that complete lesion resection is the single most important factor for these patients with regard to achieving the desired outcome. As noted above, glial neoplasms complicate the analysis of reoperation for MRE, since they often are not static, and an attempt will be made to exclude them from consideration here. The lesions being considered primarily include malformations of cortical development, dysembryoplastic neuroepithelial tumors, cavernous malformations, and other vascular malformations. Some reports of reoperation for MRE have not distinguished glial neoplasms from other structural lesions, and these will be included in this section.

In the Wyler series,[23] three of six frontal resections were reported to be seizure free. Two of these were extensions of cortical dysplasia resections in pediatric patients (the details of the third were not clear). Also, four temporal resections had had frontal resection at the first operation and had no seizure improvement, suggesting that they had a widespread or multifocal epileptogenic zone.

In the Awad series,[1] 4 of the 14 resection patients had an excision of a residual structural lesion (three vascular malformations and one hamartoma) and these accounted for three of their seven seizure-free patients. The Montreal Neurological Institute series reported in 1994 (see above) included two patients rendered seizure free by resection of cavernous malformations that had not been resected at the first surgery.

As noted above, the University of Washington series reported in 1999[10] apparently included only one resection of a structural lesion (a patient with a ganglioglioma), although two patients were noted to have calcified temporal masses on MRI. The seizure outcome was not reported. One patient had hemispheric dysplasia (presumably one of the children who had a hemispherectomy).

The failed patients analyzed by the Kings College Hospital of London[9] included ten patients with temporal DNETs and three patients with temporal resections despite the presence of known extratemporal structural lesions. Postoperative electroclinical diagnosis in the ten temporal tumor patients included four with temporal seizures, three with frontal seizures (two with incomplete resections), and three with a generalized or multifocal seizure disorder. Of the four with temporal seizures, two had residual lesion on MRI and one had a reoperation for resection and was seizure free at last follow-up (4 months after surgery). None of the other patients had a reoperation. The three patients with extratemporal structural lesions included two occipital lesions and one hypothalamic hamartoma, and none had a reoperation.

In the Spencer series,[18] 6 of the 11 relevant reoperations involved MRI-visible structural lesions (two DNETs, one cavernous malformation, one angioma, two focal cortical dysplasias). Although not explicitly stated, it seems likely that most (possibly all) of these patients had an invasive electrode evaluation for the second resection. One of the DNET patients was rendered seizure free by intentional resection of the foot primary motor area, with an expected residual deficit. Two of the other five patients were reported to have a >75% reduction of seizure frequency (the angioma was found to have an unsuspected developmental abnormality in the resected tissue). Interestingly, without detailed explanation, the authors reported that the cavernous malformation was incompletely resected. The focal cortical dysplasia patients were postulated to have widespread epileptogenic tissue that limits the reliability of even widespread invasive electrode evaluations, even when localized onsets are felt to be well defined. The DNET patient who did not have significant seizure reduction was felt to have widespread undetected focal cortical dysplasia. The authors discouraged reoperation for failed surgery in patients with developmental abnormalities.

In the Mayo Clinic series,[20] 33 of the 64 patients had structural lesions at the initial surgery, although the lesion was “missed” in three of them. These three were seizure free after lesionectomy at reoperation. Of the nine who had partial lesionectomies at the initial surgery, reoperation for further lesionectomy yielded seizure freedom in five (56%) and rare seizures in two (22%). “Complete” lesionectomy was reported for the initial surgery for 21 of the 33 patients and, although not explicitly stated, reoperation was presumably guided by non-MRI data (EEG, ECoG, interictal PET, ictal SPECT, etc.). The 30 pathologies reported included nine low-grade glial tumors, three gangliogliomas, three pilocytic astrocytomas, three nonspecified lesions, two tuberous sclerosis lesions, six focal cortical dysplasias, and four “gliosis.” As a group, seizure outcome for the 33 reoperations was quite good, with 16 (48%) seizure free, five (15%) having rare seizures, and five (15%) with significant reduction of seizure frequency. In contrast to many other reports, completeness of lesionectomy was not significantly related to seizure outcome. Apparently, this was due to the high percentage of “lesion” patients who had successful reoperation despite a “complete lesionectomy” at their first surgery. An interesting observation in this patient series was that in all 33 patients the recurrent seizures after the first surgery were unchanged in semiology, while this was generally not true for the nonlesion patients (see below).

As noted in the prior section, the series from Indiana University[16] included two patients reoperated with posterior temporal gliomas. One of the two was seizure free after reoperation.

To summarize the published experience reviewed in this section, a total of 13 patients were reported seizure free after reoperation on a residual nonglioma structural lesion. It is difficult to determine the total number of patients that were operated on in this category to yield these seizure-free patients, but it seems that the rate of achieving seizure freedom was well over 50%. Two more patients were reported to have rare seizures after resection of a residual lesion and one patient was reported to have a 75% seizure reduction after a subtotal lesion resection. Interestingly, the series reported by Siegel et al.[20] included 21 patients who had a neocortical resection after having had a complete lesionectomy, with eight patients rendered seizure free and three patients having only rare seizures. These reports suggest that for patients with refractory seizures associated with a structural lesion, completeness of lesion resection appears to be important for seizure control in many, but there is a significant subgroup that requires resection of nonlesional neocortex to be rendered seizure free.

Nonlesional Neocortical Resections

In the Awad series,[1] 4 of the 14 resection patients had a neocortical resection and did not have structural lesions. One of these patients was seizure free at follow-up (only 9 months), having had an extensive lateral/inferior temporal resection after originally having primarily a medial temporal resection. Two of the four were reported to have a >90% seizure frequency reduction, including one patient who seemed to develop a new seizure type (frontal) after being seizure free for 7 months following a temporal resection. In the Montreal Neurological Institute series,[7] 28 of the 40 patients were either seizure free or had rare seizures. One of the 28 had only a temporal neocortical resection at the reoperation.

The Montreal Neurological Institute experience with reoperation after a prior frontal lobe resection for epilepsy was reported in 1994.[17] The initial surgery did not involve a primary motor/sensory resection, a tumor, or a multilobar resection. Of the 284 patients operated on between 1929 and 1980, 39 (14%) had a reoperation, with 26 being frontal lobe (three included supplementary motor area [SMA] and five included the leg, arm, or face motor area) and 13 being frontotemporal resections. Reoperation decision was based on seizure semiology and scalp interictal and ictal EEG findings, except for two patients who had bilateral depth electrode evaluations. Surgery was performed with the patient awake for ECoG-guided resection. At reoperation, 26 of the 39 patients had cortical stimulation, with 12 having habitual seizures elicited (seizure outcome was not separately reported for these patients). With the first operations, 257 patients had follow-up of 2 to 49 years, with 26% seizure free and 30% with worthwhile improvement ("occasional" seizures or no more than two per year). With the reoperation, follow-up (4 to 46 years) was available in 35 patients, with seven (20%) seizure free and 11 (31%) with worthwhile improvement. In the seven seizure-free patients, six had spikes eliminated or markedly reduced on postexcision ECoG. Patients who were seizure free or who only had occasional seizures had either SMA, frontal pole, or inferior frontal gyrus resections. Three of the 39 patients had a permanent neurologic deficit (mild facial weakness, mild hemiparesis, or leg paresis).

Miami Children's Hospital reported one of the few experiences with reoperation for epilepsy in the pediatric age group.[19] Of the 20 patients reported, 12 had a delayed operation involving a focal neocortical resection. Most of these patients had cortical dysplasia, but the report does not give adequate detail to determine which patients had resections at least in part guided by an MRI-visible abnormality. Most of the 12 (possibly all, but details were not included) had extraoperative evaluation with subdural electrode arrays before resection. Four patients had an extension of the original resection, with three (with ectopic neurons or cortical dysplasia) rendered seizure free and one (with posttraumatic encephalomalacia) having a >90% reduction of seizures. Four had a resection in a remote lobe, with two becoming seizure free and two without improvement. Four patients had multilobar resections at reoperation, with two becoming seizure free (one with cortical dysplasia and one with hippocampal sclerosis). All three unexpected neurologic deficits occurred in this latter group, including one with aphasia and hemiparesis and one with deterioration from an intraventricular hemorrhage 2 days after surgery.

As noted above, the University of Washington series reported in 1999[10] did not provide enough information to know if any neocortical (nonstructural lesion) resection provided a seizure-free outcome.

The failed patients analyzed by the Kings College Hospital of London[9] included 11 patients who had a neocortical temporal resection without a known structural lesion. Postoperatively, two were found to have nonepileptic seizures, one to have contralateral temporal seizures, one to have uncertain origin seizures, one to have ipsilateral central seizures, one to have ipsilateral frontal seizures, and one to have ipsilateral hemispheric origin seizures. The remaining four patients were diagnosed with ipsilateral temporal seizures, with three felt to be of neocortical origin and one from residual hippocampus (not reoperated due to a failed IAP). None of these patients had a reoperation.

In the Spencer series,[18] 4 of the 11 relevant reoperations involved temporal neocortical resections based on invasive electrode evaluations. None were rendered seizure free, while two were reported to have at least a 75% seizure frequency reduction. The authors postulated that the invasive recording of well-defined onsets was misleading in these patients and failed to reveal their probable widespread epileptogenic tissue.

In the Mayo Clinic series,[20] 31 of the 64 reoperations were in “nonlesional' patients. It appears from the reported data that only 3 of the 31 were nontemporal neocortical resections. One of these three patients was seizure free postoperatively. As stated previously, of the 28 temporal surgeries, eight patients became seizure free, but the number of these that did not include resection of mesial temporal structures is not reported.

A recent report provided evidence that an *a*-[11 C]methyl-l-tryptophan (AMT)-PET scan could be of value in pursuing reoperation for neocortical epilepsy.[11] They reported on seven patients who had a reoperation after an AMT-PET scan identified a localized area of increased uptake that correlated with the ictal scalp EEG focus. Six of these patients were “nonlesional,” having dysplasia or gliosis, with five of these six having a subdural electrode evaluation before resection. One patient had DNET and thus would be classified in the structural lesion category, and was seizure free with at least a 1-year follow-up. Of the other six patients, four were seizure free and two had a >75% seizure frequency reduction. This report mentioned another ten patients who had a reoperation without a localizing AMT-PET scan, but did not provide the surgical outcome for that group. Interestingly, the authors reported that the AMT-PET scans were more likely to be positive within 2 to 3 years of the initial surgery. It remains unclear to what degree the AMT-PET scan findings improved or altered the surgical approach to these previously operated patients, since the reoperated patients with positive scans also had a localizing scalp ictal EEG.

To summarize the published experience reviewed in this section, of the reports that provide adequate information, of 64 patients who had a reoperation to excise nonlesional neocortical tissue, 19 were reported seizure free at follow-up. Clearly this is a very heterogeneous group of patients with varied surgical approaches. In any case, the reported experience provides evidence that reoperation for these patients can be successful in a significant percentage of patients. The overall morbidity reported was quite low, although somewhat greater than for initial surgeries (especially in the pediatric series).

Summary and Conclusions

The reported experience with reoperation for patients with medically refractory epilepsy is quite varied, but it does indicate that patients who continue to have refractory seizures after a resective surgery do have a significant chance of being rendered seizure free with a reoperation. The rate of seizure freedom appears to be significantly less than with the initial operation and the risk of significant morbidity is higher (although the risk remains quite low). The reported experience does not permit a conclusion about the best surgical strategy to employ, since significant success has been reported with very different approaches (including tailoring resections with intraoperative ECoG and identifying epileptogenic cortex with ictal recordings using intracranial electrodes). Understanding the nature of the patient's original operation (including both the preoperative evaluation and the surgical procedure performed) appears to play an important role in determining the appropriateness of pursuing a reoperation that involves a further resection. The experience at one of the premiere epilepsy surgery centers[18] has suggested that a patient with recurrent seizures after surgery at the center is very unlikely to benefit from another resective procedure. However, as noted above, the reported experience with reoperation at that center was rather limited and may not be adequate to extend this conclusion to other centers. Postoperative changes (i.e., “scarring”) present technical challenges with reoperation that are probably largely responsible for the increased morbidity. These include adherence of the dura to significant cortical veins and scarring of medial temporal structures to significant arteries, cranial nerves, and brainstem structures that raise the probability of causing infarctions. Prior scalp incisions and craniotomies complicate surgical planning. These considerations make the decision to pursue resective surgery more complicated for reoperation than for the initial surgery. These patients warrant consideration for “palliative” surgical options. These include multiple subpial transactions, vagal nerve stimulation, and implantable brain stimulation devices. The latter devices, including deep brain stimulation and responsive neurostimulation, are currently being subjected to clinical trials. These alternatives are discussed in other chapters. In the near future, it may be appropriate to pursue studies that will systematically compare reoperation for resection to alternative surgical approaches.

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Chapter 182

Multiple Subpial Transections and Other Interventions

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Introduction

Disconnection and ablation are long-standing techniques in the surgical treatment of epilepsy. They are based on the rationale that epilepsy afflicts the brain by setting up and using abnormal pathways within the brain, and that therefore, if such pathways are interrupted or destroyed, then the abnormal pathways and activity will cease to influence the brain and thereby reduce or remove the clinical manifestations of epilepsy. These ideas, however, were not based on pure speculation but initially on observations from electroencephalographic (EEG) recordings in experimental models. The development of epilepsy surgery both in North America and in Europe was much accelerated after the Second World War, and in particular the growth of stereotactic techniques applied to the clinical problems resulted in the use of stereotactic lesions in various cerebral structures to try to control epilepsy. A more detailed account follows later, but there were two main groups of targets. One group was the thalamic nuclei because of the perceived relationship between the thalamus and cortex; the other group was the temporal lobe structures, especially the hippocampus and amygdala, when it was recognized that they were part of the limbic circuit and concerned with temporal lobe epilepsy. There had been a search by the early workers for models in EEG work in animals, which would suggest that interventions that changed the EEG features would control clinical seizures. The work of Erickson and others demonstrating that the corpus callosum played a major part in the generalization of seizures from an epileptogenic focus was part of the rationale for the next major procedure, callosotomy.[7] The present status of callosotomy is dealt with elsewhere in this volume. There were other operations of historical interest involving disconnection, as, for example, the temporal lobotomy described by Turner.[49]

By and large the field remained with callosal section and its variations until the description of multiple subpial transection by Morrell and Hanbery in 1969.[23] This was based on extensive experimental work over many years on secondary epileptogenesis. A detail of this work was the demonstration that epileptic discharges travel tangentially in the cortex, and that a minimal population of neurones was necessary to maintain the momentum of an epileptic discharge. As a result, Morrell and Hanbery hypothesized that if the connections within and from epileptic cortex were divided horizontally, then the propagation of the epileptic discharge would be prevented and the clinical manifestations of seizures abolished. As a result, and based on the animal work, a surgical intervention was devised using special instruments to divide the short tangential fibers within the cortex.

The final stage in the development of disconnection and lesioning takes a physiologic twist: The discovery by Benabid et al. that high-frequency stimulation is effectively lesioning the adjacent tissue, with the advantage that it can be reversed.[1]

Multiple Subpial Transection

Rationale

Morrell himself pointed out that multiple subpial transection (MST) was a technique that attacked the epileptogenic lesion at its source by compromising the capacity of the cortex to develop the synchrony necessary for epileptogenesis. He advanced three types of experimental evidence to support this idea. The first was the idea that a minimal volume of transversely arranged contiguous tissue was necessary for the initiation and propagation of an epileptic discharge. The second was the observation from many different sources that the vertically orientated column is the key to cortical organization and that a consequence of this is that normal cortical function is based on these radially orientated columns and their afferent and efferent connections, largely in the same plane. This was broadly confirmed by some work carried out in Sperry's laboratory in the 1950s, which showed that if the cortex was interrupted vertically by section and the insertion of mica plates, the normal function of that cortex was retained. Although not neglecting the subtle contributions of these tangential connections to normal cortical function, Morrell realized that the majority of cortical function would be available if the tangential fibers were interrupted. It was clear that the vertical cut had to involve the whole depth of the cortical ribbon, and from laboratory experiments he concluded that the distance between the cuts should be a maximum of 5 mm. The area of cortex to be transected (i.e., both the location and the actual area) was determined by defining the epileptogenic zone. This was performed mainly as a neurophysiologic exercise. As a check on the efficacy of the procedure, elimination of the abnormal discharges, which was not always possible, was taken as the end-point of the procedure.

Indications for Multiple Subpial Transection

Although MST can be used alone or in combination with cortical resection, the selection criteria remain the same. The selection criteria, based on the rationale for MST, are an identified area of epileptogenic cortex whose resection is precluded by potential loss of function. This translates into a number of clinical scenarios, some of which are listed in Table 1.

Table 1 Indications for Multiple Subpial Transaction

Epilepsia partialis continua
Focal motor seizures
Focal sensory seizures—somatosensory or visual
Transection in association with resection, where the epileptogenic zone includes an eloquent cortical area, especially the primary motor and sensory areas and speech cortex
Landau-Kleffner syndrome
Other indications that are more contentious

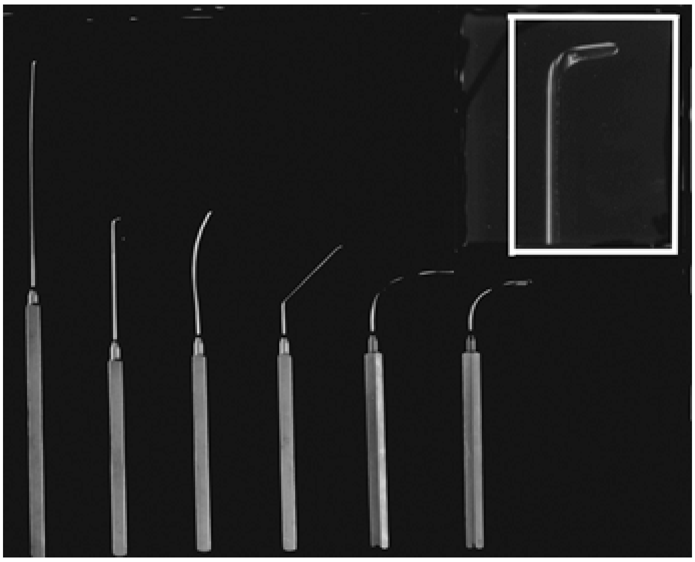


FIGURE 1. The six special hooks used for transection. The inset shows the tip of one of these hooks; the tip is the same in each of them.

Technique

A clear strategy for the use of MST is needed prior to surgery. In addition to the usual clinical details and investigations involved in a presurgical assessment program, it is necessary to identify the epileptogenic zone. This will frequently depend on the use of intracranial electrodes, often grid electrodes, since the accurate identification of epileptogenic cortex will be required to determine the extent and location of the craniotomy. In operations for Landau-Kleffner syndrome, it is almost always necessary to open the sylvian fissure. Although the record of MST suggests that functional complications such as hemiparesis and dysphasia are low, where circumstances are appropriate it may be prudent to perform the procedure under local anaesthesia. It is clearly necessary to use electrocorticography in these cases in order to determine the end-point of the procedure.

Technical aspects of the procedure are fairly straightforward. A set of specially designed instruments is used (Fig. 1). Each consists of a heavy steel wire flattened at one end to a thickness of 0.3 mm and turned up at an angle of 105 degrees with respect to the rest of the wire. The upturned portion is exactly 4 mm long (the thickness of most areas of cortical gray matter in humans). The other end of the wire is fused to a handle that is flattened at the sides so as to be exactly aligned with the flattened surface of the upturned end of the wire. The latter feature is important because the instrument must be maintained in a strictly vertical orientation with respect to the gyral surface (even when the tip is not visible to the surgeon) to avoid damage to the vertically arranged neural elements. The “springiness” of the wire is also critical, as the tip must be drawn along the undersurface of the pia, slightly elevating it but not producing a pial tear.

The gyri containing epileptogenic activity are delineated by the presence of epileptiform potentials on intraoperative electrocorticography (ECoG). A small hole is made in the pia, using the tip of a Beevor knife, or with a No. 20 needle, at a site situated as close to the lateral margin of the sulcus as it is possible to reach, access often being limited by the presence of large blood vessels. The instrument is introduced through this pial opening and then swept forward, dipping in an arc-like fashion underneath the gyrus (Fig. 2). The thin but blunt blade is maintained in a strictly vertical orientation to avoid undercutting the cortex. The tip is maneuvered so that it impinges, as low as possible, on the subpial surface of the vertical portion of the gyrus opposite the point of insertion. It is then drawn up this surface until it reaches the visible part of the gyrus opposite the point of insertion. From here, the tip is visible beneath the pia, which it just elevates but does not penetrate. The blade is then gently drawn straight back across the gyrus in the same plane as its forward movement, with the tip always kept visible through the pia until the gyrus is transected. Care is taken not to snag with the blade of the hook any cortical vessels, especially from the opposite sulcus, and this is largely a matter of feeling the movement of the tip of the blade. Finally, the hook is inserted vertically downward at the point of insertion to approximately 4 mm, with the tip against the vertical wall of the sulcus and withdrawn to the surface. The next transection is made parallel to the first and 5 mm away (Fig. 2). A small piece of card cut to an appropriate size and held between the jaws of a hemostat can be used to judge the position of the next transection. Transections are repeated as often as necessary to include the entire area of electrical abnormality, and they may encompass several gyri. The capillary bleeding associated with each traverse of the instrument results in a fine red line. The bleeding does not seem to cause damage, and the line is a useful landmark against which to gauge the location of the next transection. This is continued over the selected area until the abnormal discharges have been minimized on ECoG; it is not always possible to abolish them completely, although this has been achieved in the case illustrated in FIGURE 3. The operative appearance of the transected cortex is shown in FIGURE 4, and in FIGURE 5 there is a photomicrograph of transection from a patient who subsequently underwent hemispherectomy.

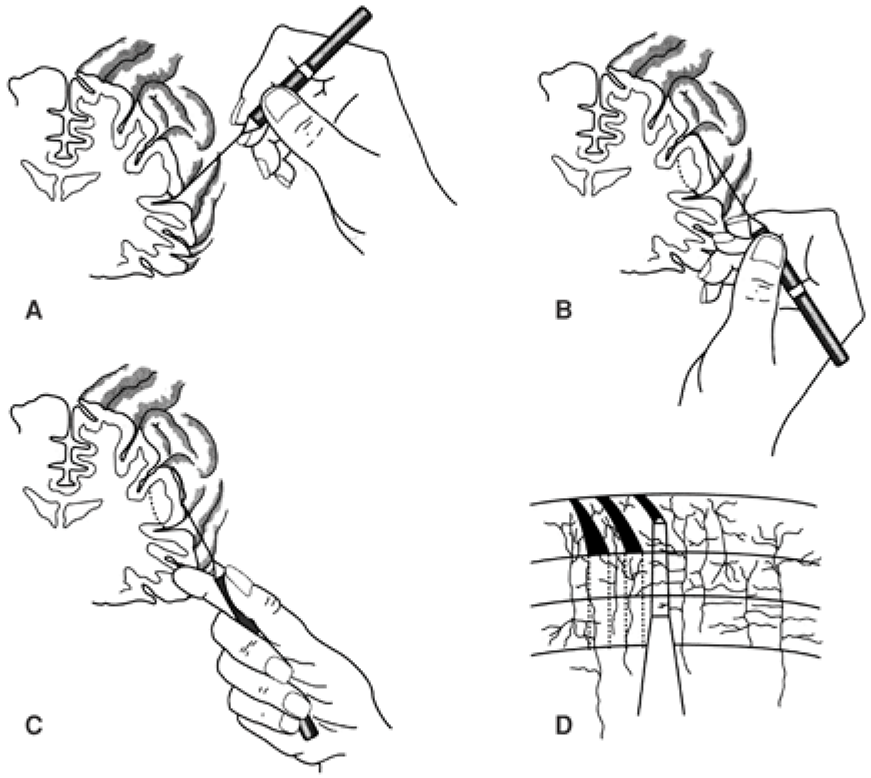
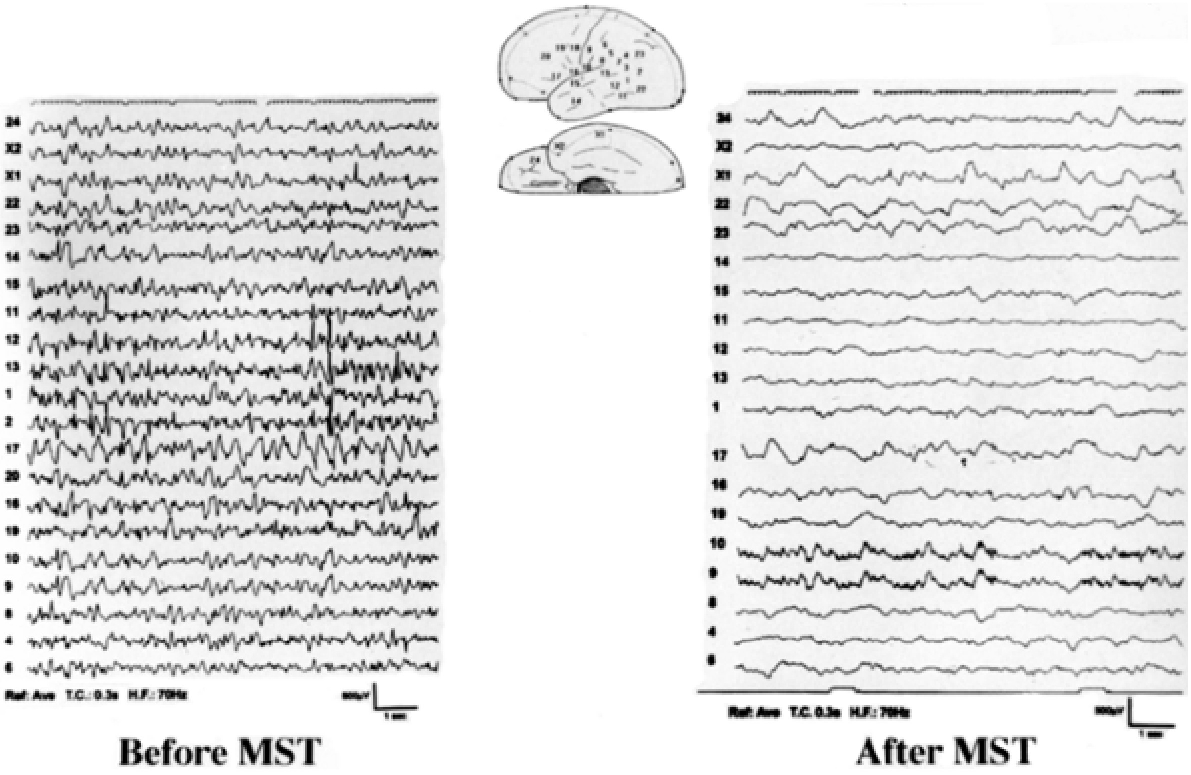


FIGURE 2. Technique of multiple subpial transaction. The hook is introduced at **(A)** and the transection is made by moving the hook appropriately **(B,C)** before being removed. **D:** The serial transections of a gyrus are shown.



Before MST

After MST

FIGURE 3. Electrocorticography recordings before and after transection. There are very obvious spikes in channels 11, 12, 13, 1 and 2. These channels in particular, and the record as a whole, are free of spikes after the transection. MST, multiple subpial transection.

There are technical limitations to the use of MST. Although the handles of the complete set of six instruments are designed to get into awkward areas, a minimal space is required in which to record and work. Furthermore, retraction to gain access may itself risk complications, and finally the distribution of venous drainage, especially in the posterior part of the hemisphere, may limit retraction. The buried part of the insular cortex can be exposed with careful microsurgical technique, and this is mandatory when using the technique for the treatment of Landau-Kleffner syndrome. Access to the orbital part of the frontal cortex is likely to be difficult, as is the primary visual area on the medial surface of the occipital lobe. However, in many of these areas access depends on the individual arrangements of vessels in any particular patient. As may be surmised, although the trauma is minimal, the technique is traumatic and therefore, after transecting large areas, some swelling might be expected. In the absence of clinically significant problems, the use of postoperative steroids is not mandatory.

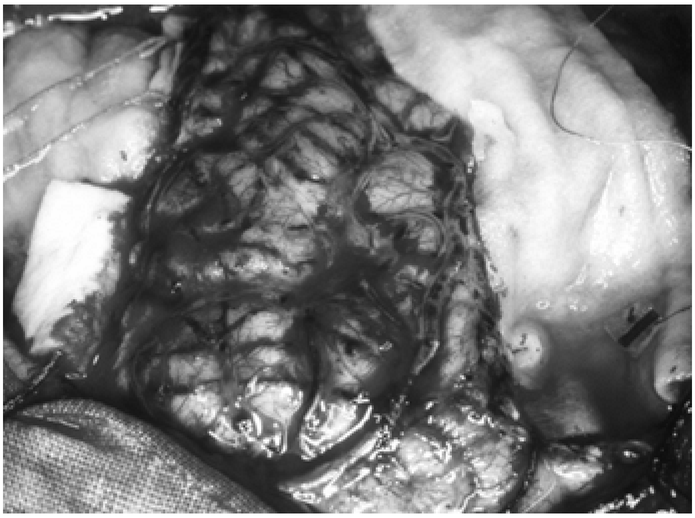


FIGURE 4. Appearance of the cortex in a patient with Rasmussen's disease who has undergone a frontal resection and multiple subpial transection of the adjacent cortex.

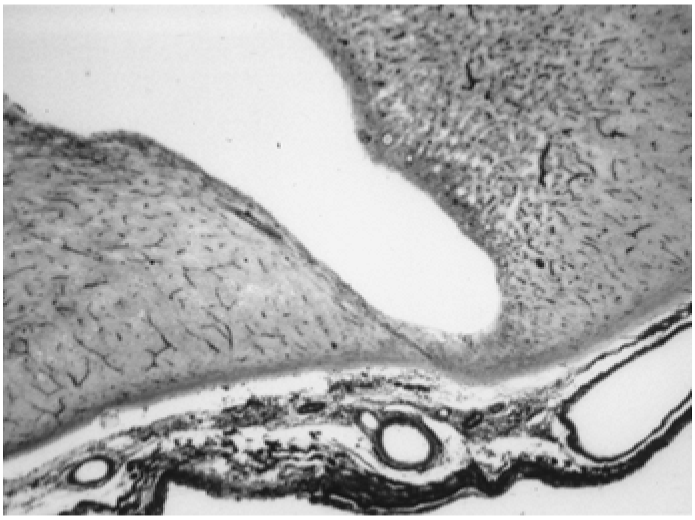


FIGURE 5. Photomicrograph of a patient who underwent hemispherectomy after multiple subpial transaction. The cut extends to the pial surface without breaching it or disturbing the pial vessels.

Outcome from Multiple Subpial Transection

A number of considerations apply to the assessment of the outcome from MST. These include whether the technique is used alone or in combination with a resection, the effect on seizure control using accepted outcome scales, and the frequency of complications, especially in relation to the normal function of the treated cortex. With the exception of some reports from China and the meta-analysis of Spencer et al.,[47] the number of patients described in series in the literature is <100. The methodology of this meta-analysis varies in two other respects from the other papers. The patients are grouped into those with >95% improvement in seizure control, so that it is not possible to discover how many patients were seizure free. It also deals with the response of individual seizure types to the intervention. In this respect the authors make two important observations. The first is that the procedure is more effective in partial seizures than generalized seizures and that this is the expected result from the physiologic basis of MST. They also noted that in their material the superiority of resection combined with MST over MST alone applied only to generalized seizures. Finally, they also reported that partial seizures sometimes increased in frequency after MST. The literature includes reports of patients varying in numbers from 10 to 200, and is invariably divided into those patients in whom the technique has been combined with resection and those in whom it was used alone. In general, and possibly at variance with the meta-analysis, complete seizure freedom is only seen where MST is combined with resection. In relevant series, seizure-free rates between 31% and 56% are reported.[2,5,13] Mulligan et al. reported that none of their 12 patients became seizure free, and although it was not statistically significant, it appeared that resection with MST was more effective.[25]

Similar outcomes are described in children. In a report of 158 pediatric cases, Shimuzu and Maehara used MST in 25 (15.8%) and reported an Engel class I or II outcome in ten of these cases.[45] Hader et al., in a series of children with focal cortical dysplasia (FCD), noted that when combined with incomplete resection MST did not improve the control of seizures, whereas complete resection of the lesion outside of an eloquent area gave the best results, with 87% of patients in Engel class I or II compared with 50% of patients who were treated with incomplete resection and MST.[11] Otsubo et al. reported the use of MST in seven children with malignant rolandic-sylvian epilepsy. In six children interictal scalp EEG spikes were seen over the frontocentrotemporal regions bilaterally and unilaterally in one. Magnetoencephalography (MEG) showed bilateral spike sources in the perisylvian region in two patients and in the perirolandic fissure in five, two of which were bilateral. Three patients required bilateral subdural strips to lateralize seizures before electrocorticography. ECoG showed an ictal onset zone around the rolandic region in four cases and the rolandic-sylvian regions in three cases. After cortical excision and multiple subpial transection, three were seizure free and four had seizures rarely with a mean follow-up of 30 months. Histology showed definite evidence of neuronal migration disorders in three cases and gliosis in two.[29]

There are a number of reports of MST being used alone. The largest series of 20 patients was described by Schramm et al. Although a good outcome, judged either by Engel's scale or by an alternative outcome scale, was seen in 45% and 50% of patients, respectively, only two patients (10%) were seizure free. A better outcome was seen when there was no magnetic resonance imaging (MRI) lesion and a worse one when the area of MST was greater.[42] Wyler's group described six patients in whom sensory motor cortex was transected. In four of these patients the MRI was normal. Where samples were taken the cortex showed gliosis. One patient was rendered seizure free and two of the remaining patients had a >90% decrease in their seizures.[50] Rougier et al. also reported seven patients with pure MST, and three patients had a >75% decrease in their seizure frequency with follow-up periods between 1 and 4 years.[41] Shimizu et al. described the use of MST in the exposed hippocampus, using abolition of seizure discharges as the end-point. They did not report the result with reference to seizure control but noted that postoperatively, verbal memory was preserved. In the absence of other details it is difficult to evaluate this report.[44] The two reports from Chinese groups do not distinguish between various combinations of treatment and therefore their seizure-free rates of 64% and 47.5% are difficult to interpret.[18,19]

The use of MST in Rasmussen's disease was first mentioned by Morrell in his original paper, where he noted that it would abolish seizures originating from the motor area but would not prevent the progression of the disease and therefore the appearance of seizures from other cortical areas. He made a useful summary in his contribution to Andermann's update on Rasmussen syndrome in 1991. There he gives a number of illustrative cases, but also summarizes their experience at the time of seven patients with pathologically verified Rasmussen's disease. In four of the seven the target seizures were eliminated but in three others they were not, including elimination of ECoG-monitored spikes in two cases.[24] In a personal communication Michael Smith noted the use of MST in delaying definitive hemispherectomy in older patients with dominant hemisphere involvement with functional language and hand use. The patients in whom MST failed were those where the epileptic abnormality was at the depth of the sulcus and unaffected by MST on the cortical surface. All of these patients developed an epileptic disturbance outside the transected cortex over time.

We have used the procedure in five cases, obtaining improved seizure control in four over follow-up periods between 18 months and 7 years. However, in one case it was combined with an extensive frontal resection. Two of the remaining three patients progressed and after 6 months in one case and 21 months in the other, they were subjected to hemispherectomy with class I outcome in both cases. The remaining patient obtained sufficient seizure control, Engel class 1C after 6 years, with MST alone. Hufnagel et al. noted one patient with no benefit.[13] There are no other recent reports; the meta-analysis does not describe such patients separately.

There are two reports on the use of MST in patients with refractory status epilepticus; on both occasions the intervention halted the status.[6,20] The major rationale for MST is the avoidance of complications when it is applied to eloquent areas of cortex, including those that have language and cognitive functions. The bulk of the evidence is in agreement with the conclusions of the meta-analysis that such complications do occur and that they are more often transient than permanent and equally associated with MST alone and MST when combined with resection. In the various series quoted above, the transient complications occur in 30% to 70% but permanent complications in 10% or less. The meta-analysis does not report the transient deficits, but permanent deficits were seen in 23% of patients treated with MST and resection, whereas in pure MST the permanent complications were 19% but did not include aphasia or psychiatric problems.[47]

The effects and mechanism of MST have been described in a number of papers. Sugiyama et al., who also investigated the physiologic properties of this model, described the appearances of the resected cortex in rabbits. Histology showed very little damage with transection of the horizontal fibers. By studying afterdischarges they showed that cortical hyperactivity was reduced but also that propagation of afterdischarges by kindling was also inhibited.[48] Another study, carried out acutely in the course of temporal lobectomy, showed that in most instances, midlevel horizontal fibers were damaged. However, one third of the specimens showed additional deep injury that would sever afferent and efferent axons.[14] Shimizu et al., investigating a child with simple partial seizures involving the left arm and cortical dysgenesis, found hyperexcitability of the relevant motor cortex using transcranial magnetic stimulation (TMS), which was modified by MST, improving the various abnormal responses. The patient showed a fair motor recovery and good seizure control after the procedure. Theoretically, MST depends on normal cortical organization to produce its effect, whereas in cortical dysgenesis the cortical organization is abnormal in terms of both structure and function. Shimizu et al. speculated that in this particular case MST might have improved abnormal synchronization in excitatory pyramidal neurones by cutting their recurrent axon branches and basal dendrites rather than the axons of inhibitory interneurones.[46] There are other anecdotal reports of the functional effects of MST. Leonhardt et al. investigated the effect of MST on positron emission tomography (PET) activation in a 30-year-old woman with MST where the right frontoparietal cortex was transected. Motor activation to a finger-to-thumb opposition task was preserved and additional areas of bilateral prefrontal and contralateral parietal activation were seen when compared with healthy controls.[16] Moo et al. examined the recovery of functional MRI (fMRI) activation in a patient who had undergone MST of the right sensorimotor cortex. Immediately after the procedure there was some transient loss of dexterity of the left hand. Seven weeks later dexterity returned to normal and left-hand finger tapping corresponded with multiple bilateral foci of fMRI activation. At 16 weeks, fMRI activation returned to pretransection levels. These data were interpreted to indicate that cortical injury due to MST resulted in the temporary recruitment of distant cortical sites, which presumably subserved normal motor function during recovery.[22]

MST has also been used in patients with multifocal epilepsy and in some patients with problems that may not be construed as primarily epileptic, such as autistic regression syndrome. Publications on these themes have been restricted to two groups. The first is Devinsky et al. in New York and the other is Patil et al. in Omaha. Both groups have used a similar strategy: Investigating the patients, often with intracranial electrodes, to establish the number and location of the epileptogenic zones. In two publications Devinsky et al. described a group of patients with multiple epileptic foci, either in both cerebral hemispheres or in several lobes in the same hemisphere. They described 13 patients who required MST together with resections. Only 6 of the 13 patients had no lesion on MRI. Wherever possible, resections were carried out and MST was used in eloquent areas. The only patients who achieved a grade I outcome were those in whom a discrete lesion was resected and the foci involved only two lobes.[5] In a second report the same group examined 36 patients diagnosed with autistic regression syndrome or autism. All the patients were evaluated with video-electroencephalography. Within this group they identified 15 patients with clinical seizures, 11 from the 19 patients with autistic regression syndrome and 4 of 12 with autism. Seven of these 15 patients were resistant to therapy. MST was carried out in the left neocortex in the temporal, parietal, and frontal regions, often including regions within the classic perisylvian language areas. One patient also had a left temporal lobectomy. In all seven patients, seizure control on EEG improved after operation. Language, social, and overall behavior improved to a moderate degree, although in most improvements were temporary.[27] Patil et al. have also used this technique in multifocal epilepsies. In two publications in 1997 they described patients with multifocal epilepsy. In one paper 19 patients are reported, all of whom had multiple seizure foci identified, and in all 19 MST was performed at the identified sites. Seven of these patients had additional topectomies and nine had amygdalohippocampectomies. Histology was available for five specimens from these resections; four showed gliosis and in the remaining one there were heterotopic neurones. Nine patients (47%) are either free of seizures or have only rare seizures; eight patients (41%) have >90% reduction in seizure frequency.[35] In the second paper, from a group of 31 patients 15 are reported who required further resection of dominant seizure foci, which are defined as discrete foci that did not respond to MST. Nine of the 15 patients are free of seizures, three have rare seizures, two have >90% reduction in seizure frequency, and one has >70% reduction in seizure frequency.[33]

A further publication in 2004 summarized the Patil group's experience with 61 patients. Follow-up ranged between 15 and 90 months with a mean follow-up of 41.5 months. Fifty patients had complex partial seizures, three had Lennox-Gastaut syndrome, four had myotonic seizures, two had infantile spasm, and two had myoclonic seizures. MST was the principal procedure, which was supplemented in 17 patients with minimal cortical resection when intraoperative EEG indicated that an area had failed to respond to MST. In five patients an additional epileptogenic focus in the amygdalohippocampus complex was treated with stereotactic amygdalohippocampectomy. The eloquent cortex was treated in 51 patients. Two lobes were treated in five patients, three in five patients, four in ten patients, five in two patients, six in 38 patients, and eight in one patient. Seizure outcome, based on Engel's modified classification, was as follows: 52.45% were class I, 8.2% were class II, 24.59% were class III, 4.9% were class IV, and 9.83% were class V. There was no statistical difference between those who were operated on in the first half of the series and those who were operated on in the second half of the series ($p = 0.1636$). There was no statistical difference between those who had MST

alone and those who had MST plus minimal cortical resection ($p = 0.1698$). There was no permanent neurologic complication in this series.[34]

The possibility of using MST in the treatment of autism and in particular in a subset of patients with autistic regression syndrome, some of whom also have clinical epilepsy, arises out of the experience with multiple foci and with Landau-Kleffner syndrome. There are clear differences between the two populations as pointed out by Palac et al. in their article on this topic. They noted three points. First, there is no conclusive evidence that epileptic activity plays a major pathogenic role in autistic regression; second, the abolition of the epileptic activity does not result in a worthwhile improvement of the autistic symptomatology; and lastly, the epileptogenic areas in autistic regression are multifocal and not all accessible for surgical intervention.[30]

The application of MST to Landau-Kleffner syndrome is dealt with in detail in Chapter 242. It is one of the most successful uses of MST, provided the indications are strictly observed. The patients must have the correct syndrome, and in both the Rush series and our series on Denmark Hill, the unsuccessful cases have been those with a wrong diagnosis. It is also worth recalling that the primary focus is not always in the left hemisphere, that MEG may be helpful in lateralization, and that intracranial recording may occasionally be necessary to prove the lateralization. A few patients may relapse within weeks or months of the initial operation as evidenced by seizures, failure or slowing of language recovery, and recurrence of continuous spike-and-wave activity during slow sleep (CSWS) EEG patterns. In our experience on Denmark Hill, another MST will usually produce a further improvement and in no case have we had to operate a third time. The indications for surgery are genuine Landau-Kleffner syndrome with CSWS, severe speech difficulty or mutism for more than 1 year, and in our view permanent reliance on steroids to maintain improvement. Because the disruption is functional, we believe that there is a window of opportunity in which the procedure is most effective. Otherwise, surgery is relatively free of complications and brings about improvement in language and behavior, which, as Frank Morrell himself predicted, will not necessarily return completely to normal. Recovery will be at least as good as the natural history of the disease, but achieved sooner and with less disruption to the patient and his or her family.

Stereotactic Lesioning

Stereotactic lesioning was popular and prolific in the 1950s and 1960s. The results were difficult to assess for a number of reasons. Presurgical assessment was less rigid, it was rare to be able to verify the site and size of the lesion, and follow-up data were poor, being short and inaccurate. By the mid-1970s there was considerable literature replete with methodologic inconsistencies, some of which can only be perceived retrospectively, and the situation has been sensibly summarized by Ojemann and Ward.[28] In addition to a number of miscellaneous targets such as the internal medullary lamina, fields of Forel, and the hypothalamus, there have been two principal areas of interest. The first was the thalamic nuclei, based on a proposed relationship between these areas and the cortex, as suggested by bilateral secondary synchrony and 3/sec spike-and-wave. On this basis lesions were made in the ventroanterior, ventrolateral, and centromedian nuclei of the thalamus. The second area of major interest was the amygdala and hippocampus, as these areas became recognized as important structures in the genesis of seizures. In particular, the work of Narabayashi in targeting these structures in patients with aggressive behavioral disorders suggested that the main benefit from these procedures was relief of epilepsy.[26] Reports of lesions in these structures, both unilateral and bilateral, are numerous and the details are summarized by Ojemann and Ward.[28] The principal criticisms of this work, namely, poor selection criteria, no verification of the lesion site, and poor follow-up data, consign the results to history. Most of these procedures have been abandoned in their original form, although there is increasing interest in functional lesioning in these structures as represented by high-frequency stimulation. Exceptions in recent times include the application of stereotactic radiosurgery to produce lesions in the mesial temporal structures and to treat hypothalamic hamartomata.[37,38] Radiosurgery, using stereotactically implanted interstitial radiosurgery with I_{125}, in four cases of hypothalamic hamartoma has also been described,[43] However, there is some more recent work using stereotactically placed radiofrequency lesions in the amygdala and hippocampus. Parrent and Blume in 1999 described 22 operations in 19 patients using two different techniques. In one group the lesions were discrete and in the other group they were confluent. The success rate was 20% in the first group and 60% in the second. All lesions spared the parahippocampal gyrus, and in their discussion they admitted that exclusion of the entorhinal cortex may have contributed to the poor results compared with microsurgical procedures.[31] A report from Tianjin in China describes 23 patients who had radiofrequency lesions made unilaterally in the amygdala and hippocampus. With follow-up periods of 8 to 32 months, they obtained seizure freedom in 43.48% of these patients.[51] Radiofrequency lesions have also been used in the treatment of hypothalamic hamartoma. Most case reports are of single cases,[9,10,32] but Kuzniecky and Guthrie have reported more than one case[15] and our unpublished experience of two cases has shown significant and persisting improvement in seizure control (Fig. 6).

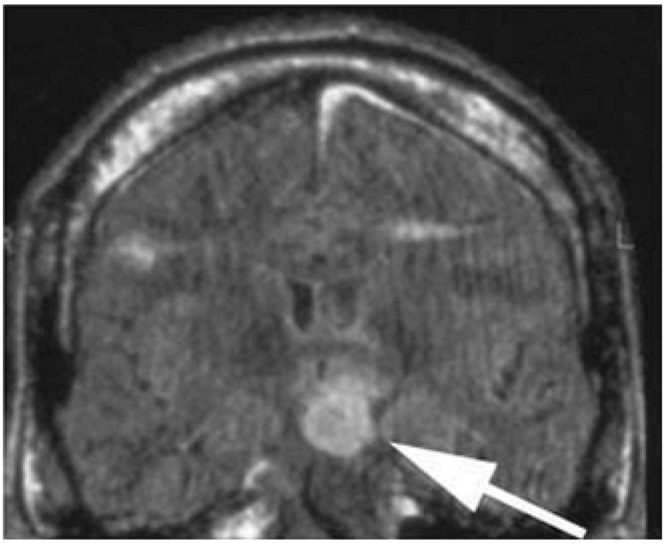


FIGURE 6. Coronal magnetic resonance imaging scan of a patient with a hypothalamic hamartoma. The hamartoma had been treated with stereotactically guided radiofrequency ablation a few days before.

Disconnections apart from Division, Partial or Complete, of the Corpus Callosum

In practical terms, disconnection, aside from multiple subpial transection, has been used in recent times almost exclusively in the treatment of hypothalamic hamartoma. These lesions, whose part in severe epilepsy has only recently been realized, are difficult to access surgically. The most relevant approach at present is the transcallosal approach developed by Rosenfeld and his team in Melbourne. Although the complications are low, it involves a complex major intracranial procedure. Therefore, other approaches have been sought, including the disconnection technique described by Delalande and Fohlen in France and the use of neuroendoscopic techniques to minimize operative trauma and duration.

Between 1997 and 2002, Delalande's group treated 17 patients with refractory epilepsy due to hypothalamic hamartoma. Sixteen of these 17 patients were treated by disconnection. Sixteen patients had gelastic seizures, 14 had partial seizures, and three had generalized tonic–clonic seizures. The mean seizure frequency was 21 per day. Four patients had a borderline intelligence quotient and the others were mentally retarded. MRI in each patient showed the hamartoma as a stable homogeneous interpeduncular mass implanted either on the mamillary tubercle or on the wall of the third ventricle with variable extension to the bottom. Sixteen patients underwent disconnection through open surgery in 14 procedures and/or endoscopy in nine procedures. Among the 17 patients, eight patients became seizure free, one patient had only brief gelastic seizures, and eight patients were dramatically improved with a mean follow-up of 18.6 months (8 days to 43 months). Surgery was safe in all but two patients: The first patient had transient hemiplegia and third cranial nerve paresis, and the other developed hemiplegia due to ischemia of the middle cerebral artery territory. Quality of life and behavior and school performance were greatly improved in most patients. Endoscopic disconnection seems to be a very safe way to treat hamartomas in intraventricular locations.[4] Choi et al. reported a successful outcome in four patients where endoscopic disconnection was used. There were two patients who became seizure free; one third lost seizures that could be attributed to the hamartoma. Three of the four patients suffered a transient disconnection syndrome.[3]

Other Strategies

Cooling the epileptic focus has been suggested as a means of suppressing the epileptic discharge. Of course, it must be possible to identify the focus, which itself must be small and discrete to allow this method to work. There is convincing animal and human experimental work in acute situations. Recently a practical device has been described, and the practical aspects of applying this to drug-resistant focal epilepsy is discussed in a paper by Rothman et al.[40]

Gene therapy as a treatment for intractable focal epilepsy is still largely theoretical. A number of investigators have shown that various factors including release of adenosine and overexpression of neuropeptides and of galanin can all suppress seizures in animal models.[12,17,39] It has also been shown that adeno-associated virus vectors could be used to transfer genes into brain slices from temporal lobectomy specimens.[8] Peltekian et al. have pointed out the problems and uncertainty of adenovirus-mediated gene transfer, which are explored in detail in a recent review by McCown.[21,36]

Summary and Conclusions

This chapter has concentrated on multiple subpial transection, and others chapters of this book discuss in detail a number of other surgical interventions including callosotomy, vagus nerve stimulation, and deep brain stimulation. All of these interventions share a common feature, which is that they are functional interventions, different in character from the resective interventions, which rely, in large part, on the coincidence of the epileptogenic zone and structural pathology. There are also outcome implications in that the proportion of patients rendered and remaining seizure free as a consequence of the surgical intervention is greater with resective surgery. The use of MST and alternative procedures, both those covered in this chapter and elsewhere, is therefore dependent on the proper use of a presurgical assessment program. Within this structure there will be some patients unsuitable for resection in which these procedures are used as alternates or in addition to these resective procedures.

MST can be used in those situations where resective surgery is inappropriate or cannot cover the whole problem. In relation to these situations and in combination with resection, MST has resulted in sustained freedom from seizures in up to 50% of patients. When MST is used alone, the results originally reported by Morrell of 48% patients being seizure free have not been replicated. In this situation it appears to render only 10% or less seizure free. MST in Landau-Kleffner syndrome seems to give excellent results. The use of MST in multifocal epilepsy remains controversial, in part because this is a complex problem that few epilepsy surgery programs choose to address. The other interventions described in this chapter are of limited but sometimes useful application.

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Chapter 183

Outcome Measures

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Introduction

During the nearly 10 years that have elapsed since the first edition of this book, there have been several new studies and reports that have advanced our understanding of the outcomes of epilepsy surgery. Large retrospective, single-center studies and one large prospective, multicenter study have been reported, and the first randomized trial of epilepsy surgery was successfully completed. The methodologic standards for operationalizing and studying the various outcomes considered important to epilepsy surgery have improved and seem to be converging toward consensus. Increasingly, there is an emphasis on the long-term outcomes that, in the early literature, had been largely ignored.

The following discussion summarizes the current state of outcome assessment and provides a brief summary of the current understanding based on the strongest, most methodologically rigorous studies. The outcomes to be covered are seizures, mortality, neurocognitive deficits, psychiatric disorders, health-related quality of life, utility measures, and employment. Although consensus is developing for measurement of these outcomes, the measurements themselves are of relatively little value if they are not done in the context of an appropriately designed and analyzed study.

Study Design: Some Basic Concepts and Principles

The Hypothesis

At the heart of any good study is one or more clearly articulated study questions. These questions are then operationalized into testable hypotheses. The term "testable" in part refers directly to the process of subjecting the data to statistical tests appropriate to their form. Thus, one plans a study based on the final form the results will take.

The Design

The value of a study's results also heavily depends on the quality of the study design (to ensure validity of results) and the size of the study sample (related to statistical power and stability of findings). There are a few common approaches used in studying epilepsy surgery.[5,12]

Retrospective Cohort Based on Chart Review

Such studies are easy and convenient to do. They can help to generate hypotheses and provide descriptive data or novel information useful in designing a rigorous prospective study. All else being equal, a retrospective chart review is the weakest design. It requires depending on information not recorded for research purposes, in general, and with the investigator's specific research questions in particular. Consequently, data are often inappropriate to the question being asked, incomplete, or just missing entirely. Follow-up—something absolutely front and center for an outcomes study—is of uneven intensity and completeness across patients, often as a function of outcome. This alone can invalidate a study's findings.

Retrospective chart review studies can be strengthened by (a) performing consistent and well-documented follow-up through the charts and (b) limiting the study to information that is reliably and routinely recorded in the medical records. An important advantage of a well-conducted retrospective study is that long-term data can be obtained without the need for actually waiting many years. It is an appropriate first approach to a question not previously addressed and should be followed with more definitive studies if warranted. In some cases, a cohort can be assembled retrospectively, and then continued follow-up can be conducted prospectively as in a recent study from Australia.[62,63]

Prospective Studies

In contrast to relying on chart review, in a well-done prospective study, one can ensure that patients are appropriately identified and enrolled; that baseline evaluations are made and their results recorded in a consistent, meaningful, and analyzable format; that outcome measures are assessed in a standardized manner; and that follow-up is consistent for all patients. There are at least three ways in which one might do a prospective study. We note that the first, a randomized trial, can never be done retrospectively; however, the other two approaches often are.

Randomized Clinical Trial.

For comparing the outcomes of two treatments, a randomized trial is the single best design. Although excellent for a basic test of treatment efficacy, randomized trials have several important limitations: (a) For practical or ethical reasons, the eligibility criteria are often very restrictive, making the results of limited generalizability outside of the highly selected trial population, (b) patients are typically less willing to participate in randomized clinical trials (RCTs) than in observational studies, especially in studies of highly invasive interventions; and (c) randomized trials are generally not powered to detect infrequent adverse events, which often only surface in large follow-up studies. All of these factors impose limits, sometimes severe, on the generalizability and scope of the trial's results.

A recent randomized trial of epilepsy surgery done in Canada overcame the first two of these concerns.[99] This was possible because there is a 1-year waiting period for surgery in Canada. Willing candidates were randomized either to immediate surgery (the waiting period was waived) or to the normal wait that they would have had were they not in the trial. Generalizability was not of concern either because the eligibility criteria captured typical temporal lobe epilepsy patients presenting for surgical evaluation.

Table 1 Summary of considerations in designing a clinical research study of outcomes

Study considerations	Comments
Clear testable hypotheses	Formulated in terms of specific statistical tests and comparisons
Study design	Appropriateness depends on level of knowledge and degree to which information will represent a contribution to extant knowledge; well-powered, prospective study designs are preferred

Sample-size considerations	Must be planned in advance; larger samples provide better statistical power and allow detection of smaller but still meaningful effects
Standardized outcome measures	Should reflect real outcomes of interest; when they are available, accepted, well-vetted measures should be used (e.g., for neuropsychological, psychiatric, and quality of life)
Standardized follow-up protocol	Explicit predetermined plans for periodic contact with patients to collect data, carried out consistently across study participants; use of clinic visits alone is often suboptimal
Consistent approach to measuring and collecting all other relevant data	Ideally, the investigator has some control over this information prospectively; if dependent on clinical records, do some preliminary exploration in advance and determine what reliably can be recorded from these sources; have a standardized procedure for collecting and recording information

For an intervention such as surgery, another significant limitation is that the outcomes of greatest interest today are those that take years, even decades, to realize. In fact, after 1 year, most of the patients in the Canadian trial who were randomized to the usual delay before surgery went on to have surgery.

Nonrandomized Control Group.

Although it is appealing, a nonrandomized study is much more difficult to execute well. The comparison of treated to untreated patients will almost always be confounded by fundamental differences between the two groups. Well-designed and carefully analyzed studies can provide results of comparable quality to that of randomized trials[11,26]; however, this requires knowing what the differences are and being able to measure them adequately. In the end, there is often a lingering doubt about the accuracy if not the outright validity of findings from nonrandomized studies.

Surgical Cohort (Series).

Most surgical outcome studies are limited to a surgical cohort or case series. Although inappropriate for assessing the efficacy of surgery, it is reasonable to use this type of study for identification of pre- and early postoperative predictors of outcome. Such a design is also appropriate for studying the relationship between seizure control and other outcomes (e.g., employment, depression, health-related quality of life, etc.) after surgery. For example, “does someone who stops having seizures after surgery experience improvements in his employment status?”

There are several other considerations that cut across all study designs:

1. Sample size and statistical power. Statistical power refers to the ability of a study to detect a difference if one exists. It is a product of several factors, including sample size and the size of the effect to be detected.[25] All other things being equal, the larger the effect to be detected, the better is the statistical power. Likewise, the larger the sample size for a given effect, the greater is the statistical power. Any study should be planned with an adequate sample size to detect meaningful effects. This process is made quite easy today by the availability of software that help to determine the necessary sample size under a

variety of conditions and assumptions.[32]

2. A deliberate, standardized, and meaningful assessment of outcomes. Measures that reflect outcomes of real interest and that can be reliably assessed should be used. Use of published well-validated and accepted instruments, where they exist, to measure various outcomes is strongly encouraged. The use of idiosyncratic, unvetted instruments for factors and concepts for which well-developed methods already exist adds little to the literature.
3. Rigorous protocol for data collection. Whether the study is a randomized trial or not, all data should be collected according to a carefully designed rigorous protocol constructed to ensure accurate, complete, timely, unbiased collection of all data in the same manner for all study participants.

The basic considerations for study design are summarized in Table 1.

Seizure Outcome

In the earlier literature, seizure outcomes were assessed in a variety of idiosyncratic ways[94] at varying points after surgery. A recent guideline emphasized the importance of complete seizure freedom and of assessing seizure outcome each year.[100] The use of various outcome categories, although popular, leads to imprecision and difficulty in comparison and interpretation of results. With the widespread availability of fairly standard statistical techniques (as a class known as survival methods[31]) investigators are increasingly using remission (complete seizure freedom) and subsequent relapse and studying the determinants and patterns of these outcomes over prolonged (many year) periods of follow-up.[62,63,71,76,102] Thus, at least for resective surgery, the preferred and most consistently applied approach to studying seizure outcomes is to study remission and relapse over time since surgery. Other methods may still be preferred in drug trials or for studying the outcomes of palliative procedures (e.g., callosotomy or vagus nerve stimulation).

Only relatively recently was a randomized trial of temporal lobectomy successfully completed.[99] Once and for all, this study demonstrated the efficacy of surgery with respect to seizure control. One year after surgery (or randomization) 58% of surgical versus only 8% of nonsurgical patients ($p < .001$) were completely seizure free. Large-scale observational studies, some retrospective, some prospective, have also appeared. In addition to demonstrating the high rate of seizure freedom following epilepsy surgery, they have provided insight into the course of the long-term seizure outcomes after surgery. These have turned out to be complex.[34,63,80,101,102] In particular, patients who become immediately seizure free after surgery may not always remain so. Relapse rates can be high (25%–30%). To the extent to which it has been studied, it is found that many patients who relapse after a remission regain remission fairly

quickly. In fact, some relapses may occur in association with discontinuation of antiepileptic drugs (AEDs), although at least two large studies failed to find a strong if any effect on relapse associated with AED withdrawal.[14,63]

Prediction of which patients deemed appropriate for surgery will be the most likely to become seizure free remains challenging. Many small reports pepper the literature with various findings, few of which are ever replicated. For an extensive review of the literature on this subject see McIntosh et al.[64] For temporal lobe epilepsy, the recent large-scale studies confirm the presence of unilateral mesial temporal sclerosis as the most important and consistently demonstrated predictor of a good seizure outcome. A history of generalized tonic–clonic seizures also seems to predict a poorer chance of remission. Apart from these factors, presurgical prediction of seizure outcome after temporal lobectomy has not advanced much. Current findings must be interpreted, however, in the context of the fact that patients are already highly selected. Recent reports do not provide any firm basis for recommendations that could improve current selection procedures and criteria.

Information about outcomes after extratemporal resection is much scarcer. In general, extratemporal surgery tends to be associated with a lower chance of complete remission after surgery.[89] Studies often report better outcomes if there is a discrete, resectable lesion and if electroencephalographic (EEG), clinical, and imaging findings are congruent. A recent meta-analysis exemplifies the difficulties in summarizing and pooling results from studies with differing methodologies, patients, and procedures and emphasizes the importance of adopting standard research methods. In this study, highly heterogeneous results precluded conclusions about the predictive value of congruence of EEG and magnetic resonance imagining (MRI), extent of surgical resection, and presence of interictal discharges. On the other hand, an abnormal MRI, history of febrile seizures, mesial temporal sclerosis or resectable tumors, and absence intracranial monitoring augured seizure freedom.[91]

Mortality

Mortality, especially unexpected death, is higher in people with epilepsy than in the population at large.[39,56,84] Among adults with epilepsy, it is highest in those with intractable seizures.[90,97] Assessing death is generally not difficult in a study with rigorous follow-up methods in place. Determining cause of death can be more complicated, especially if one is interested in determining whether a death was a sudden unexpected death associated with epilepsy (SUDEP),[90] and most especially when relying on death certificate data, a commonly used source of information.[10]

In separate studies, moderately to substantially lower mortality rates have been reported after surgery in patients who became seizure free compared with those who did not.[65,82,84] Ryvlin provided a critique of the methodologic difficulties of assessing the impact of surgery on mortality risk.[72] In particular, he suggested that the same factors that might render patients inappropriate for surgery or at highest risk of not becoming seizure free might also be associated with cardiac arrhythmias, thus independently placing them at increased risk of SUDEP. An RCT would address these concerns by balancing risk factors in medical and surgical groups. In the only surgical RCT, one patient died in the medical group and none in the surgical group at 1 year.[99] In children, there is agreement that SUDEP is rare, mortality is higher only in those with symptomatic epilepsy, and it is often related to the underlying neurologic condition.[13,19,21]

Cognitive Outcomes

Specific cognitive functions (e.g., memory and sensory and motor functions) may be impaired before or after epilepsy surgery as a result of the surgery itself. Assessment of such impairments involves several considerations including adequacy of pre- and postsurgical assessments, rigorous study design, and appropriate methods for determining whether a real and meaningful change has occurred. In the neuropsychological outcome literature for surgery, weaknesses in basic methodologic considerations (discussed earlier) are common. These include small sample sizes, retrospective designs, loss to follow-up, and inadequate controls.

Methodologic Issues in Assessing Cognitive Change

There are additional concerns that are more specific to assessing real and meaningful changes in cognitive function.

1. A difference of means. Early studies reported cognitive outcome as group mean change scores from pre- to postsurgery. When group mean scores improved, this was taken as evidence for beneficial effects of surgery on cognition. Even without biases introduced by selective loss to follow-up, group mean changes do not always reflect changes at the individual level. Furthermore, not all changes are clinically relevant.
2. Practice effects. When testing study participants repeatedly over time, the study design and particularly the analysis must account for the fact that all cognitive tests are subject to practice effects and test–retest variability. Regression to the mean for unusually high or low initial test scores can be expected. Therefore, a change score can simply reflect the change expected due to these statistical characteristics and not necessarily a true change in cognitive function.
3. Reliable change. Concerns about practice effects have led a number of authors to develop methods of determining how much a cognitive test score must change for it to be considered likely to reflect true change. Reliable change indices (RCIs) or standardized, regression-based (SRB) change scores are two methods for determining the incidence and direction of true cognitive changes. A RCI provides a confidence interval around a retest score that reflects the variability that is to be expected on the basis of test–retest variability and practice. An SRB score is a standardized score (i.e., z-score) that reflects these

factors along with regression to the mean. RCI and SRB scores are typically calculated from samples of clinically stable, medically managed patients tested on two separate occasions. For a given test, an individual change score outside the RCI/SRB-defined range is said to represent a “statistically reliable” change. Table 2 shows neuropsychological instruments used in two recent, large, multicenter studies of epilepsy surgery with references to the source of RCI/SRB data[43,59,73] and estimated administration time for each test.

Table 2 Neuropsychological tests that have been be used in assessing the cognitive effects of surgery

Cognitive domain	Test and source of RCI/SRB	Administration time (min)
General intelligence	WAIS-R,[a,b] WAIS-III[c]	90[20]
Motor function	Grooved Pegboard[b]	10[10]
	Grip Strength[d]	5[20]
Auditory attention	WAIS-R Digit Span,[a] WAIS-III Digit Span[c]	5[e]
Visual attention	Trail Making Test Part A[a]	5[20]
Confrontation naming	Boston Naming Test[b]	15[20]
Verbal fluency	Controlled Oral Word Association Test (COWAT)[a,b]	5–10[85]
Visuospatial analysis	WAIS-R Block Design,[a] WAIS-III Block Design[c]	15[e]
	Hooper Visual Organization Test[a]	10[20]
Verbal memory	Rey Auditory Verbal Learning Test (RAVLT)[b]	30[58]
	California Verbal Learning Test (CVLT)[a]	30[20]

	WMS-R Logical Prose,[a,b] WMS-III Logical Prose[c]	15[e]
Nonverbal memory	Brief Visuospatial Memory Test–Revised (BVMT-R)[d]	15[85]
	Rey-Osterreith Complex Figure[d]	15[20]
Executive function	Trail Making Test Part B[a]	5[20]

RCI, reliable change indices; SRB, standardized, regression-based change scores.
[a] RCI/SRB found in Hermann et al.[43]
[b] RCI/SRB found in Sawrie et al.[73]
[c] RCI/SRB found in Martin et al.[59]
[d] RCI/SRB not available. [e] Author's estimate (J. T. L.).

4. Meaningful change. A change in a test score that is "statistically reliable" may not always represent a change that is clinically meaningful or even noticed by the patient. Patients who show a reliable decline on objective verbal memory tests are more likely to report a subjective change.[57,58] On the other hand, correlations between objective memory performances and subjective assessments have generally been weak and confounded by emotional factors.[61,74,92] It has been suggested that these weak relationships reflect the inclusion of large numbers of unchanged patients in these analyses. Because their judgments are more prone to other biases, they obscure the stronger relationship between objective and subjective measures in those who have truly experienced changes.[57] There is very limited information about the relationship between changes on neuropsychological tests and changes in functional status (e.g., employment or ability to carry out complex activities of daily living).

The Neuropsychological Assessment

A range of tests can be used in neuropsychological assessment of the epilepsy surgery candidate.[50] In principle, assessment should provide a robust estimate of cognitive domains that are affected by surgery. Test selection therefore depends in large part on the area and side of surgery. A typical assessment battery contains a measure of overall intellectual function—typically a Wechsler IQ test, which can be administered in its entirety or in an abbreviated form, using subtests sensitive to changes in affected cognitive domains. Batteries should employ redundant measures of affected domains to increase sensitivity to surgical effects because cognitive failures in epilepsy often are intermittent (e.g., word-finding problems). Measures of verbal learning and verbal retrieval are overrepresented in the tests listed in Table 2 because these domains are particularly affected by temporal lobe dysfunction. On the other hand, assessment of patients with frontal lobe epilepsy should be weighted toward "executive" functions such as working memory, concept formation and response initiation, inhibition, and shift.

Neurocognitive Changes After Surgery

Most of the available information has come from patients who have undergone mesial temporal lobectomies with partial or complete hippocampectomy. Estimates of the incidence of change from studies prior to the development of RCI methods are unreliable, for reasons stated earlier. In studies that have used RCI or SRB methods, improvements in cognitive scores are relatively uncommon at the group and individual levels. Specifically, most studies reported that <15% of patients improved on a measure of verbal memory.[23,42,60,74] Reliable decline in verbal memory occurred in 21% to 58% of patients after dominant temporal resections and in 2% to 34% of patients after nondominant temporal resections in these studies. Reliable declines on tests of nonverbal memory were reported in 2% to 34% of cases. Variability in incidence of change across studies probably reflects differences in patient selection, tests employed, and how reliable change was defined.

Psychiatric Disorders

For studying psychiatric conditions, perhaps most important and least realized is the need to do an independent, standardized assessment of psychiatric conditions. Reliance on medical records has been shown to be very insensitive to psychopathology because many individuals are never adequately if at all diagnosed.[22,33]

Table 3 Instruments frequently used for psychiatric assessments in research studies

	Type of measure	Adminstration and time	Comments
ASEBA[1,2,3]	Checklist for current/recent behavioral problems, not diagnostic	Self, 15–20 min	Multiple forms available for proxy and self-report at different ages, population norms
BAI, BDI[8,9]	Checklists for current anxiety or depression, not diagnostic	Self, ~5 min each	For BDI, good sensitivity and specificity when compared to diagnostic instrument
CES-D[67]	Checklist for current depression	Self, ~5 min	—
CIDI[70]	Complete psychiatric interview	Administered by trained interviewer, 15 min–1 hr	For adults
DIS,[69] DIS-C[77]	Complete psychiatric interview	Administered by trained interviewer, 15 min–1 hr	Adult and child versions are comparable

ASEBA, Achenbach System of Empirically-Based Assessment; BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; CIDI, Composite International Diagnostic Interview; CES-D, Center for

Epidemiologic Studies Short Depression Scale; DIS, Diagnostic Interview Schedule; DISC, Diagnostic Interview Schedule for Children.

There are several high-quality instruments available for measuring psychiatric disorders (Table 3). Note that they do not all measure the same concept, or if they do measure the same concept, it is in ways that are not strictly comparable.

Symptom Checklists Versus Diagnostic Interview

Symptom checklists such as the Beck Depression and Anxiety Inventories (BDI and BAI, respectively)[7,8,9] and the Center for Epidemiologic Studies Short Depression Scale (CES-D)[67] provide rapid assessments of the respondent's current or recent state. They are self-administered and only take a few minutes each to complete. The item responses can simply be summed to provide a continuous measure. Cut-offs are provided by the tests' developers to identify respondents with mild, moderate, and severe depression. A recent comparison of these checklists for measuring depression versus a diagnostic instrument indicated a very high degree of both sensitivity and specificity.[49]

A popular group of instruments used for children in studies of epilepsy is the Achenbach System of Empirically-Based Assessment (ASEBA). The Child Behavior Checklist (CBCL) is perhaps the best known of the instruments in this group, and several versions of this instrument are available.[1,2,3] For children of age 6 to 18 years, there are parent-completed and teacher-completed forms. A youth self-report version is available for children of age 11 to 18 years. A young adult self-report module was recently replaced with another for adults of age 18 to 59 years. Proxy respondent (parent, caretaker, spouse, or other) versions are available for the same age range. These instruments are worded in the present tense, and respondents are asked to respond based on their experiences over the last 6 months.

The Achenbach instruments provide a series of narrowly defined scales as well as broader scales for overall, internalizing, and externalizing behavior problems. Cut-offs for clinically significant behavioral problems are also provided. Some of the scales are "*Diagnostic and Statistical Manual* (DSM) oriented," that is, they tap into the concept of, for example, depression, but are not meant to be used as diagnostic instrument. For research purposes, however, these instruments provide numerous advantages. Results for each scale are reported as t-scores age and sex-normed to a population sample. A dichotomous assessment of clinically significant or not is also provided for each scale. In addition, the ASEBA instruments are self-administered and generally only take about 15 to 25 minutes to complete. At least in children with epilepsy, they have become a common means for assessing behavioral problems.[4,66] Because of the consistency in content across forms designed for different age ranges and because of the standardization procedures used, it is possible to follow someone from childhood into early adulthood. This should only be done using the same informant. A youth self-report can be compared to an adult self-report. A parent report on a child, however, should not be compared to a later self-report by that same individual. In fact, multiple proxy reports on a given individual should probably use the same proxy (e.g., the mother for all or the father for all). The ASEBA instruments for adults are relatively new and consequently have not been used as extensively as the instruments for children. This approach provides a well-validated means of quantifying current behavioral traits and is highly practical for research purposes.

Diagnostic Instruments

Instruments such as the Composite International Diagnostic Interview (CIDI),[70] the Diagnostic Interview Schedule (DIS),[69] and the Diagnostic Interview Schedule for Children (DISC)[77] are designed to cover a wide range of psychiatric disorders but are also designed in modular format so that selected parts of them can be given. Such instruments are designed to provide diagnoses according to DSM criteria. The diagnoses are not just for current state but for lifetime as well. The approximate timing of the initial diagnostic episode of a disorder can also be obtained from these instruments so that age at onset can be estimated. These instruments are administered by a trained lay interviewer. The training courses for these instruments can be costly and can take up to several days to complete. These instruments can also take >1 hour to administer, depending on whether the respondent endorses key questions pertinent to specific diagnoses. The DIS for adults and DISC for children are designed so as to be as comparable as possible, facilitating their use in a study group of mixed ages or for follow-up of younger study participants into adulthood. The Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS) is another popular instrument for use in children and has been used specifically in children with epilepsy.[52]

Although diagnostic instruments such as these seem ideal and provide information not obtained from a simpler checklist approach, they are much more cumbersome and expensive to use. It might be difficult to obtain cooperation of study participants with repeated use of such instruments. A very careful assessment of the precise research question and the purpose for asking the question is required before deciding which psychiatric instruments to use.

Psychiatric Outcomes of Surgery

Psychiatric disorders are an important component of understanding epilepsy, its consequences, and its outcomes. Epilepsy is intrinsically associated with a variety of other neurologic and cognitive disorders. Increasingly, depression, suicidal tendencies, and internalizing behavioral disorders have all been shown to be associated with the risk of developing epilepsy, that is, they are present before the onset of seizures.[44,45,46,66] Community surveys of prevalence in epilepsy patients find even high rates of these disorders, and depression has been reported to be present in up to half of patients with intractable epilepsy seen in specialty centers.[75]

The effect of surgery on psychiatric disorders and symptoms is slowly becoming better understood. Earlier reports based on relatively small samples of patients (<100) found improvements in levels of depression and anxiety after surgery. Improvements were seen largely in patients who became seizure free.[17,27] These and other studies have reported paradoxical increases or de novo cases of a variety of psychiatric disorders as well.[16,17,27] Recently, a large, prospective, multicenter study reported on psychiatric outcomes 2 years after surgery.[28] This study demonstrated substantial pre- to postsurgical declines in levels of depression and anxiety. As with previous studies, some patients with presurgically low depression and anxiety levels had developed these conditions when assessed 2 years after surgery. There was a significant but not absolute association between lower depression and anxiety levels and complete postsurgical seizure freedom.

Health-Related Quality of Life

Health-related quality of life (HRQOL) is defined as patients' perceptions of their physical, mental, and social health. Inclusion of HRQOL represents a relatively recent addition to the assessment of therapies.[6,47,93] Advantages of including HRQOL as an outcome measure include (a) detection of impacts of treatment that might be unanticipated and (b) assessment of patients' perceptions of their functioning and well-being; these can provide a summary measure of both the positive and negative impacts of a treatment.

Operationalizing Health-related Quality of Life

HRQOL cannot be directly measured, and there is no gold standard. Instruments for measuring HRQOL typically include a series of questions that are combined into an index or scale. Wherever possible, these instruments are obtained by self-report, either self-administered or interviewer administered. There are two kinds of HRQOL instruments: (a) profile instruments and (b) utility instruments. Both typically yield continuous scores. Utility measures have characteristics that make them appropriate for use in economic analyses of health care.

Selected Issues in Studying Health-related Quality of Life

Two issues in developing and using HRQOL profile and utility instruments are (a) generic versus disease-targeted approaches and (b) ability to detect change, or responsiveness.

Generic Versus Disease-specific Approaches

Generic HRQOL instruments are relevant to and can be used with anyone regardless of health status. A number of generic HRQOL instruments are available and have been used in epilepsy. Generic instruments are particularly useful for making comparisons among people with a variety of conditions or with healthy controls.[96] In contrast, disease-targeted instruments are tailored to a particular disease, although they can include "generic" HRQOL domains that are not specific to that disease. Several profile instruments of HRQOL for epilepsy have been developed over the last decade and applied in a growing body of research.[29,35]

Responsiveness

Ability to detect meaningful changes in actual HRQOL is critical for outcome measures for any longitudinal clinical study and is often the least well-studied property of any kind of outcome measure. Disease-targeted instruments may, in theory, be better able to detect change than generic instruments.[15] In general, instruments that assess a reasonably broad and diverse range of domains are better able to reflect the full impact of a disorder such as epilepsy.[54]

Profile Instruments

Examples of generic and epilepsy-targeted profile instruments of HRQOL are shown in Table 4. The most commonly used HRQOL instrument that has been developed for use in epilepsy contains both generic and disease-specific components.[29]

Results with Profile Instruments

The Canadian randomized trial clearly demonstrated significant and substantial improvements in health-related quality of life in the patients randomized to immediate surgery versus the usual 1-year delay starting immediately after surgery and persisting for the full year.[99] The Multicenter Study of Epilepsy (MSES), a prospective cohort study of surgical patients, has also documented a substantial improvement in HRQOL scores in patients who become completely seizure free after surgery. Most improvements occur within the first year but some continue to accrue at 2 years. After 2 years, no further improvements were seen.[81] Changes in HRQOL appeared to parallel seizure remission, and patients who never experienced a minimum of 1 year seizure free, despite some initial gains, ultimately experienced no meaningful change in HRQOL compared to presurgical levels.

Table 4 Selected generic and epilepsy-specific health-related quality-of-life Instruments

Instrument and reference	Content	Age	Administration time and comments
Impact of Epilepsy Scale[48]	Assesses eight areas, yielding a single score	Adults	Self-administered, 5 min
Epilepsy Concerns Index[35]	Epilepsy specific, derived from surveys of adults with epilepsy	Adults	Self-administered, 20 items

Child Health Questionnaire[53]	Generic measure with multiple domains including physical and mental health and impact on family	Children, 6–16 yr	There are separate child and parent report versions; each takes 15–20 min
SF-36[41]	Generic measure with physical and mental health aggregate scores and individual scales	Adult, >16 yr	Self- or interviewer administered; ~10 min; national age- and gender-adjusted norms available
Epilepsy Surgery Index (ESI)-55[95]	Epilepsy-specific with generic (SF-36) core; three composite scores in physical health, mental health, and role functioning; 11 individual scale scores	Adults	Self- or interviewer administered; 15 min
QOLIE-89[29]	Epilepsy specific with generic (SF-36) core; developed out of the ESI-55; has an overall score and four aggregate scores in domains of physical health, mental health, cognitive distress, and epilepsy-targeted health; also yields 17 individual scale scores	Adults	Self- or interviewer administered; 11 translations available; administration time ~25–30 min

QOLIE-89, Quality of life in Epilepsy Inventory-89.
Also see http://www.proqolid.org.

Utility Instruments

Utility instruments measure HRQOL in cost-utility analyses (CUAs) of health care.[36] Utility instruments have two characteristics that most HRQOL profiles do not have. First, they are “preference based” (i.e., they reflect the relative preference, or value, that society expresses for different health outcomes) because the goal of a CUA is to assess how efficiently societies trade valuable resources (e.g., time and material resources, represented by money) to obtain something else of value (i.e., better and longer-lasting HRQOL). Second, utility measures capture the full range of HRQOL on a 0 to 1 scale, where 0 represents death and 1 represents perfect health. Changes on a measure scaled in this way can be directly combined and compared with changes in mortality, using a single index of treatment effectiveness, typically expressed as quality-adjusted life-years (QALYs). For example, an intervention that improves HRQOL over a 20-year period from a value of 0.5 to 0.75 produces 5 QALYs (i.e., [0.75 - 0.50] × 20 = 5). In a CUA, this effect is valued the same as increasing normal, healthy life expectancy by 5 years (i.e., 1.0 × 5 = 5).

Multiattribute utility scales (MAUS) are utility instruments that convert HRQOL profiles to utility scores, based on extensive normative data from community-based samples. A number of MAUS have been developed.[18,30,38,40,51,78,79] Most are generic because they are costly to develop and most CUAs aim to compare efficiency of resource use across different diseases. However, like the HRQOL profiles on which they are based, generic MAUS may be less responsive to change than are disease-targeted instruments.

MAUS have only recently been applied to studies of epilepsypatients.[55,86,87,98] In one study, more severe seizures were associated with lower scores on four MAUS instruments, but instruments varied considerably in their responsiveness to a seizure-free outcome after epilepsy surgery.[5] SF6D, a MAUS based on the SF-36, had the strongest overall evidence for validity and responsiveness, in part due to its focus on psychosocial aspects of HRQOL that are affected by seizures. The Quality of Life in Epilepsy Inventory-89 (QOLIE-89) was more valid and responsive than any MAUS, reflecting its disease-targeted focus and finer-grained measurement scale.

Employment

Many individuals with uncontrolled epilepsy are either under- or unemployed. To the extent that this situation is a result of the seizures, successful epilepsy surgery should, in theory, lead to an improvement in employment. Improvement in employment status could result in financial independence, reduced disability costs, and enhanced quality of life for the individual and greater productivity for society. Long-term documentation of employment outcome, however, has been minimal and problematic due to variability in duration of follow-up when assessed retrospectively and differences in categorization of employed, unemployed, and underemployed, a particularly elusive construct. A standardized and meaningful approach to studying this issue is much needed.

Despite methodologic (measurement) concerns, there are indications from some although not all studies that have examined employment that there are small gains in employment after surgery.[24,37,68,83,99] The Canadian trial found modest and ultimately nonsignificant gains after 1 year.[99] Studies with longer-term follow-up suggest that the gains may require several years to occur, and it is not entirely clear that all of these studies have measured the most important aspects of employment relevant to surgical patients.

Summary and Conclusions

The assessment of surgical outcomes has become more sophisticated and somewhat more standardized. Reasonable and high-quality approaches to study design as well as appropriately sophisticated approaches to measurement and analysis of outcomes are becoming increasingly accepted. The tables in this chapter provide a representative although by no means exhaustive selection of recommended instruments. This may have the beneficial effect of improving the cohesiveness of the literature by eliminating variation due to inadequate methodology and ensuring that investigators gather comparable if not identical information, thus allowing meaningful comparison and pooling of data from several studies. The methodologic bar has been set higher than in the past. For future studies to contribute to existing knowledge, they will need to be large, prospective, well designed, and adequately powered.

As it currently stands, it is amply clear that medial temporal lobe resection provides a significant chance of complete seizure remission. It is also clear that seizure outcomes are not entirely stable over prolonged periods of time. This is an area in need of further investigation. Improvements in seizure outcomes after surgery are linked to improvements in depression and anxiety, health-related quality of life, and employment. All of these factors are intertwined. Surgery also poses some calculable risk in the form of selective neurocognitive impairments, although gains may also be seen.

There are many questions that require continued consideration. Perhaps the two most vexing regard (a) the further refinement of the surgical evaluation and selection protocol to better target surgery to those most likely to experience maximum gains and to steer those unlikely to benefit toward other options and (b) a better understanding of the long-term course after surgery, including the reasons for seizure relapse after a significant period of being seizure free.

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Chapter 184

Pre-/Postoperative Rehabilitation

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Introduction

Although evidence regarding the medical benefits of epilepsy surgery continues to increase,[11,13] the psychosocial benefits of the operation remain less well studied. Dasheiff et al.[9] suggest that the findings concerning the quality of life and functional capacities of patients undergoing resection are not uniformly good. It is important to realize, however, that changes in psychosocial status do not generally occur routinely without some targeted intervention.[6] This is particularly so when substantial neuropsychological impairments, behavioral difficulties, psychiatric problems, and limited cognitive functioning are involved. The patient's situation is further complicated if a difficult seizure disability has been experienced for years with some of the above-mentioned related difficulties. This chapter considers the types and intensity of psychosocial assessment and intervention that are required for psychosocial functioning to be maximized postoperatively.

Psychosocial Outcome in Epilepsy Surgery

Review of the Literature

Dodrill et al.[13] reviewed 17 studies on the psychosocial impact of epilepsy surgery. This review was limited to studies presenting actual data regarding changes in six major areas of functioning, including interpersonal relationships, vocational adjustment, capacity for independent living, impact of seizures on everyday functioning, personal adjustment, and overall psychosocial functioning. It is of interest that psychosocial changes are most commonly evaluated by professional ratings; in only a few instances were standardized tests to assess psychosocial adjustment utilized. Positive changes, however, were found both in the studies that used ratings and in those that used inventories.

Findings from these studies suggest that improvement in interpersonal relationships was noted about two thirds of the time. Changes in vocational functioning were examined more specifically than any other area, and it was noted that employment status generally improved. These positive vocational changes, however, tended to be reported only for patients who were seizure free or nearly seizure free. Individuals with major psychiatric or cognitive problems or who were chronically unemployed seldom made the transition to full-time employment. The criteria in these studies were not often stringent, did not always relate to paid employment, and sometimes included ratings of such items as positive employability and productive work activity in the home. In one investigation, 43 of 60 patients gained partial or full economic self-sufficiency who had had neither before surgery.[20]

The perceived impact of surgery has not been frequently reported in the literature, but in those studies in which it has been addressed, the typical patient has experienced a significant decrease in seizures. Impact on personal adjustment is more difficult to assess; part of the problem is that it has been examined in only a few studies with varying periods of follow-up and has been evaluated from various perspectives (e.g., sexual functioning, personal initiative, and self-image). A final perspective from the review by Dodrill et al. is on changes relative to an index of overall adjustment. Most patients seem to improve psychosexually in these studies, approximately 50% according to an overall index of adjustment. In a decided majority of cases, psychosocial improvement was linked to seizure relief.

More recent studies, not included in the review of Dodrill et al., have also examined aspects of psychosocial functioning. A study by the Montreal group[37] clearly shows positive changes in psychosocial functioning on the Washington Psychosocial Seizure Inventory at 1 year for 15 patients who gained complete relief from seizures; no appreciable positive changes occurred in 15 patients who did not gain complete relief, and on six of eight scales they actually showed a modest increase in problem scores. The importance of seizure relief relative to psychosocial gains is therefore underscored. This is especially the case if there are no accompanying interventions that might maximize the benefits of limited seizure relief.

At the Japanese National Epilepsy Center, Mihara et al.[35] developed a quality-of-life questionnaire with forms designed separately for surgical patients and their families. The questionnaire assessed the following quality-of-life domains: Seizures, role activities, social relationships, leisure activities, emotional well-being, physical well-being, financial status, and memory problems. All patients were followed for up to 2 years after surgery. Patients and their families rated overall quality of life as having markedly improved following surgery. However, the domains of financial status, role activities, and social and family relationships improved relatively little. These areas, including financial status, which subsumed vocational functioning, appear to be more resistant to change. The study underscores the importance of early intervention in order to have an impact on needs and life satisfaction. It is of interest that individual concerns, such as emotional well-being, tend to be affected by the operation, whereas others that are more environmentally determined (e.g., financial functioning or social relationships) are more resistant to change. This type of finding emphasizes the need for targeted psychosocial or rehabilitation intervention of an “ecologic” nature—assisting individuals to deal with the external world through systematic and interactional changes.

Spencer et al.[39] undertook a more sequenced review of quality of life (Quality of Life in Epilepsy [QOLIE]-89) and depression and anxiety (Beck Inventories) at 3, 12, and 24 months from surgery with a large multisite study involving 355 patients. At 3 months, all patients seemed to show significant improvement on quality of life (QOL) and decreased depression and anxiety. Over time, however, only the seizure-free group showed significantly better QOL with reduced anxiety and depression, evincing a nonsignificant trend in the seizure-free versus the continuing seizure group. These authors concluded that 2 years may be an insufficient follow-up period to determine not only seizure outcome, but also concomitant QOL and psychiatric outcomes.

Gilliam et al.[18] compared the psychosocial status of 125 patients who had received an anterior temporal lobectomy for epilepsy 1 year postsurgery to a group of 71 patients awaiting the operation. Patients who had undergone the operation showed significantly less concern on living with epilepsy on 16 of 20 items of the Epilepsy Foundation of America (EFA) Concerns Index and 8 of 11 scales of the Epilepsy Surgery Inventory (ESI)-55 assessing quality of life. It is of interest that on the regression analysis, mood status, employment, driving, and antiepileptic drug cessation were all predictive of better quality of life, while IQ and seizure-free status were not. The authors cautioned that the controls were still receiving intensive attention and that future prospective, controlled studies are needed involving both surgical and psychosocial intervention. Another study by Aydemir et al.[1] involving a postsurgery versus a presurgery group comparison indicated that QOL was significantly better at a mean of 27 months postsurgery. Continuing seizures, comorbidity, and continuance of antiepileptic medication all negatively impacted QOL.

Findings related to employment outcome following temporal lobe resection deserve special attention. In several studies,[16,17] it appeared that on the whole unemployment rates did not change after temporal lobe resection, although underemployment may be decreased. A study by Guldvog et al.[23] revealed the same findings. Williams et al.,[46] however, reported that overall employment increased after epilepsy surgery from 42% to 62%. These findings may be confounded, however, by the inclusion of students and homemakers in the employed outcome category. There is a consistent trend throughout this literature, however, of individuals with better seizure outcomes correspondingly adapting more easily to the employment market.

Sperling et al.[40] evaluated employment following temporal lobe resection in 86 patients 3.5 to 8 years after surgery. Seventy-three patients qualified for the workforce before and after surgery. Unemployment rates declined after surgery from 25% to 11%. Underemployment was also reduced. Seizure-free status was related to improved employability (e.g., seizure-free patients did better than individuals with only some seizure-free years). Age at surgery also influenced vocational outcome, with older patients (above age 40) doing more poorly than young adults. It is also of note that employment gains came slowly, with some patients taking up to 6 years to obtain work. Individuals who were students at the time of surgery, however, tended to do quite well in regard to employment. This is one of the more detailed analyses of employment outcome that has been attempted. Although a few homemakers were included in the employed categories, the numbers would not significantly affect findings.

A more recent study by Jones et al.[24] followed 61 patients who had anterior temporal lobectomies versus 23 patients not undergoing the surgery and serving as a medical comparison group. Mean follow-up was approximately 6 years from the surgery. The surgical group had almost double the employment rate (69% vs. 39%) of the medical comparison group. Of more importance was the fact that the surgical group was experiencing gains in amount of hours worked and financial independence when compared to the nonsurgical group, which seemed to be “losing ground.” There is, however, some doubt concerning the comparability of neuropsychological abilities between study and control groups, as controls were mostly persons for whom surgery was not possible.

A number of other studies focus on psychiatric outcomes. To date, findings appear to be relatively consistent, in that some type of postoperative psychosis develops in <10% of cases,[30] but depression and anxiety occur more often. Both of these disorders appear to be chiefly transient in nature. Fenwick[15] described depression as occurring in as many as 25% of operated patients and being more transient in nature than anxiety disorders, which tend to persist.[26] It would make sense, however, that anxiety could be persistent, particularly if individuals are adjusting to a new seizure-free status and concomitant responsibilities for employment, independent living, and social activity. Williams et al.[46] indicated that there appears be a correlation between some symptoms of emotional distress on the Minnesota Multiphasic Personality Inventory (MMPI) (elevated False and hypomania scales) and improved vocational outcome. They hypothesized that these elevated scales indicate frustration that may be channeled into later positive psychosocial outcomes.

In terms of predicting depression, Derry et al.[12] indicated that the Washington Psychosocial Seizure Inventory (WPSI) Emotional Adjustment Scale was a better predictor of postoperative adjustment than the Center for Epidemiological Studies Depression and other WPSI scales. Glosser et al.[19] indicated that the onset of new psychiatric problems in the months directly following epilepsy surgery may be as high as 31%. At 6 months postsurgery, the severity of these concerns is much lower than preoperation. The Glosser group described patient reaction as a complex symptom entity, involving mixed features of anxiety, depression, and irritability that cycle around the operation.

Most patients continue to be satisfied with the impact of surgical intervention on their psychosocial functioning—approximately 75%, according to Guldvog.[22] Some individuals report satisfaction even if they remain unemployed. Persons undergoing surgery before the age of 30 or as students tend to have significantly better outcomes, particularly vocationally. Patients with poorer cognitive functioning, impairing neuropsychological deficits—specifically of memory—and severe preoperative or postoperative psychiatric conditions can do less well. Koch-Stoecker[28] indicated a strong relationship between freedom from seizure involvement and lack of an axis I or axis II disorder (89%), while only 43% of those with a consistent axis I or axis II disorder reached seizure-free status. As pointed out by Mihara et al.,[35] changes that are more environmentally determined, which would include both employment and family interactions, may be more difficult or resistant to change. Work by Derry et al.[10] suggests the value of assessing the relationship between learned resourcefulness and internal locus of control relative to psychosocial outcome. These authors found that patients who tend to make internally oriented attributions to seizure control (i.e., a significant attribution to personal behaviors) enjoyed more a positive adjustment to their environment.

As reviewed by Dasheiff et al.,[9] the quality of life and functional capacities of patients is not uniformly good after epilepsy surgery. Batzel and Fraser[3] suggested that some of the difficulties relate to the ratings on life satisfaction scales, which because of scale stability require that interventions yield enormous impact to show useful outcome ("a whopper effect"), and also to basic difficulties entailed in using scale ratings. These become particularly problematic when patients and controls rate themselves as high in satisfaction through naiveté, cognitive impairment, or other psychiatric difficulties, or rate themselves as inordinately low because of transient, organically mediated moods. Studies from the Epilepsy Centers at the University of Washington and Bethel are discussed below. These studies have placed significant emphasis on the area of employment.

Another factor influencing postoperative outcome might be preoperative expectations. Several studies have addressed this

point. Thorbecke[43] asked for expected changes in several social domains. The greatest expectations were present for elimination of seizures followed by improved mobility, employment opportunities, sports, leisure time activities, more social contacts, and the hope to find a partner. In fact, the perception of difficulties in any social domain correlated consistently and highly with the strength of the expectation of change after surgery. Wheelock[44] and Wheelock et al.[45] asked patients and significant others for expected life changes following epilepsy surgery. Having more friends, being less dependent, others worrying less about the patient, improved marital/family relationships, ability to drive, ability to work, and ability to do more things on his or her own were mentioned most often. Taylor et al.[41] asked 69 patients for expected life changes who already had decided to get surgery, and who were able to depict their postoperative aims with respect to their cognitive and psychiatric status. The mean number of statements was 3 (range 1 to 5). Improved work situation, driving, independence, socializing, and relief of taking medication/relief of side effects were the five most often mentioned aims. Surprisingly, there was little expressed interest in improving cognitive functioning.

An interesting question addressed in these studies is what types of expectations have the best chances to be fulfilled. Wheelock et al.[45] presented the finding that those patients whose expectations were postoperatively fulfilled were more satisfied. This was associated with better psychosocial functioning. Wilson et al.[50] asked the patients preoperatively about their expectations with respect to surgery and postoperatively to rate the success. According to the authors, the successful subgroup primarily reported expectations that led to a practical or clearly identifiable result, such as seizure ablation, driving, employment, and the initiation of new activities. In contrast, the not successful subgroup reported less practical expectations (difference for expectations to become employed <.05) but more expectations of psychosocial nature and the expectation that the operation would generally enhance their QOL. In Wheelock's and Thorbecke's studies[43,45], it was the opportunity to do these practical things now that was delineated as postoperative changes.

In all three studies,[43,44,45,50] no differences with age or gender were reported and persons who had not become completely seizure free reported fewer changes. Wheelock et al.[44] and in a similar way Wilson et al.[50] showed that the expectations of those whose seizures were not completely eliminated but were improved were only slightly or moderately fulfilled. It is evident that these findings should have practical consequences for pre- and postoperative counseling, especially for a better adaptation of those improved but not completely seizure free.

Studies from Bethel, Germany, and the University of Washington

In March 1997, a specialized rehabilitation unit for people with epilepsy was launched within the Bethel Epilepsy Center in order to ameliorate the psychological, social, and vocational consequences of the patients' epilepsies. This program is mainly funded by the state pension insurance, and is run on an inpatient basis with a capacity of 17 places. Enrolled are mainly patients in danger of losing their work or their working capacity, as well as those with a recently diagnosed epilepsy or with a first seizure for whom the question of suitability for their job and the need for retraining is raised. A further group is patients after surgical treatment of their epilepsy with early relapses or with neuropsychological or psychiatric complications or a high risk for such complications. Interventions mainly include modification of the antiepileptic drug regimen; psychotherapy to improve adaptation to epilepsy; patient education about epilepsy; neuropsychological assessment, counseling, and training; sport/recreational activities; assessment and training of vocational abilities in occupational therapy and in real work environments; assessment of the risks inherent in the patients' seizures for driving, sports, everyday activities, and certain types of employment; and extensive counseling of patients and relatives. The interventions are carried out by a multidisciplinary team.[38]

In an ongoing study, a group of 103 patients having temporal lobe resection (TLR) having had surgery after opening of the short-term inpatient rehabilitation unit (STRU) was compared with a group of 103 patients having had surgery before its opening. There were no differences in respect to seizure outcome, side of operation, gender, IQ, and frequency of personality and psychiatric disturbances. The patients operated on after the opening of the STRU were 4 years older than the patients from the early group (p <.05). Of the patients operated on after opening of the STRU, 65 postoperatively were enrolled in the program of the STRU, staying there about 3 weeks. Outcome of the 103 patients with respect to employment was compared between the 103 patients operated on before opening of the STRU and the 115 patients operated on after the opening. “Employed” was defined as “employed in the general labor market, homemakers,” “unemployed” but available in the labor force, on early disability, or “sheltered employment.” Unemployment in both groups preoperatively was 34% 2 years after surgery; without specific rehabilitation intervention, unemployment had risen to 34%, whereas it had fallen to 24% in the intervention group.

At the University of Washington Epilepsy Center,[3] differences were assessed in psychosocial functioning utilizing an interviewer-administered protocol, the Washington Structural Psychosocial Review (WSPR), and the Washington Psychosocial Seizure Inventory (WPSI). The study sample included 108 adult patients who had had surgery 5 or 10 years earlier and 83 unoperated controls who had similarly been assessed at 5 and 10 years and were matched by age and education to the surgical group. (Because there were no statistical differences between the 5- and 10-year surgical and control groups, the data were combined.)

On the WSPR protocol, five areas were assessed: Interpersonal skills, emotional adjustment, vocational functioning, adjustment to seizures, quality of life, and an overall adjustment score. Controlling for interaction effects, surgical patients improved significantly more than the controls only on adjustment to seizures (p <.001) and overall adjustment (p <.01). It appears that both the surgery and control groups perceived themselves as improving at follow-up, and only somewhat more so with substantial seizure relief. Batzel and Fraser[3] concluded that this finding suggests that there may be some type of “halo effect” to the interview, which may be compounded by a patient's neuropsychologic impairment, social naiveté, and other factors.

On the self-report psychometric measure, the WPSI, again controlling for interaction effects, the surgical patients improved more than the controls in four areas: Emotional adjustment, vocational adjustment, adjustment to seizures, and overall psychosocial functioning (p <.001). Improvement on the inventory was clearly related to better relief from seizures within the surgery group. Findings appear to be more consistent on this expanded psychometric inventory than in the structured WSPR interview, with its briefer rating format and fewer domains of functioning. It should be noted that changes are not reported in areas more environmentally determined (e.g., interpersonal functioning, family background, and financial status).

One of the more interesting aspects of the findings from the University of Washington research series is related to employment functioning. Discrete aspects of job functioning were compared between surgery patients and controls during the 2 years preceding surgery and the 2 years preceding follow-up.

Student functioning was examined separately; persons staying at home and individuals receiving workers' compensation or disability subsidies were excluded from the study. Surgery patients gained in mean number of weeks worked during the second 2-year span (51 weeks after surgery vs. 40 before surgery), whereas the controls actually lost ground (39 weeks before surgery vs. 28 after surgery; significant at p <.01).

The surgery patients also did better than controls in earnings and ratings of job performance. The salary gain was particularly impressive; surgery patients were earning $7.09 hourly at follow-up, a gain of $2.88 from before surgery, whereas controls were earning only $5.19 (significant at p <.01). There was also a consistent trend for patients whose seizures decreased to do better than those whose seizures did not decrease, with the latter faring about the same as the controls or a little worse on job performance. As reported earlier,[3] the student surgery group did considerably better at follow-up than the student control group, with 18 of 20 (90%) surgical patients working part to full time at follow-up versus 7 of 15 (47%) of the controls (p <.001). This study makes a strong case for the vocational and financial benefits of epilepsy surgery, which obviously affects a number of psychosocial domains.

Conclusion

As indicated by Dodrill et al.,[13] improvement is often selectively found in one or more areas of psychosocial functioning after epilepsy surgery but is certainly not universal in nature. Significant relief from seizures obviously can be associated with significant improvement in various domains of functioning. For patients with a significant neuropsychological, behavioral, or psychiatric disability, there is a general limit or occasional decrement in psychosocial improvement. This group does not routinely experience psychosocial improvement. These patients may specifically require targeted counseling and vocational or other types of intervention preoperatively to realize significant gains or at least adjust better to their outcome status. To date, research has focused on assessment of psychosocial outcome, and controlled studies have related preoperative status to outcome or the benefits of targeted intervention. More detailed analysis of preoperative and postoperative status, as in the studies by Fraser et al.,[17] Sperling et al.,[40] and Jones et al.,[24] provides a better understanding of what is happening and the impact of important variables, such as time from surgery.

Psychosocial Adjustment Modeling around Epilepsy Surgery

Recent studies and perspectives are moving the field toward a more uniform and holistic understanding around the surgery event and a better understanding of points for intervention. Derry and Wiebe[11] provide the perspective that preoperative positive psychosocial adjustment, good perceived quality of life, low neuroticism, a tendency toward learned resourcefulness, and available social support all increase the possibility of positive postsurgical outcomes. Poorer prognosis relative to psychosocial outcome related to marked psychological distress, anxiety, and neuroticism; a helpless attitude toward medical self-management; strong unrealistic expectations; and a poor relationship with the patient's physician. A second domain, as illustrated by Wilson et al., relevant to psychosocial outcome is preoperative expectations.[50] Wilson et al.[47,48] added the construct of the "burden of normality" or the demand on medically improved patients to discard the sick role. McLachlan et al.[33] and Wilson et al.[47] added the perspective of lag time in the adjustment process in dealing with this burden and other aspects of psychosocial adjustment. Wilson et al.[47] emphasized that it is important to track the burden of normality demands across different domains of psychosocial functioning to include the psychological, behavioral, affective, and sociologic during 2 years postsurgery and ideally more.

Psychosocial Intervention and Goal Planning

Presurgical Expectations of Patient and Family

As discussed, there can be some very unrealistic preoperative expectations on the part of both the patient and family members. This is particularly true for individuals with lower cognitive levels, neuropsychological impairment, and various types of psychiatric disturbances. Minimally, counseling interventions may be necessary to shape these expectations and build a better bridge to goal realization. More probably, however, activities will be needed that help identify the steps involved in realizing goals made attainable by an improved seizure status. Such activities might include preparations for a change in functional status, such as informational interviews with employers, an actual job tryout, visits to technical schools, entrance into training programs, and training in independent living skills (e.g., managing a budget, using public transportation, cooking). An earlier article[17] presents one case from the Bethel Epilepsy Center, in which preoperative monitoring was delayed until a patient actually began training in independent living skills, counseling, relaxation exercises, and consideration of vocational options. This patient naively believed that an operation would "fix everything," and involvement in more purposeful and targeted activity was required by the medical team before further medical intervention was considered. As indicated by Dasheiff et al.,[9] patients too often have unrealistic expectations about epilepsy surgery and its outcome. It is often viewed as a method of turning one's life around without having to invest any more effort into the process other than having surgery. As also indicated by Dasheiff et al., individuals who show the greatest degree of psychosocial improvement (unless they are very young at the time of surgery) have been functioning at a higher level of independence before surgery, so that it is important to promote more independent activity as soon as possible.

Work by Langfitt et al.[29] indicated that a family's predominantly positive affect (e.g., affection, appropriate concern, indications of connectedness, etc.) presurgery was significantly related to postsurgery adjustment on the part of the patient. This group recommended further research on treatments that can improve positive family affect in the patient's environment and support of autonomous behavior on the part of the patient. Wilson et al.[50] also suggested that having both patient and family focus on practical expectations (e.g., driving or making vocational gains) as a function of the operation is a better intervention focus than less tangible psychological or social goals (e.g., self-change or new relationships).

Importance of the Assessment Planning Function

Assessment is generally very carefully done, taking into account the medical variables related to surgery and other significant variables, including duration of disease and age at onset. If a functional change is to occur, it is very important that neuropsychological, psychiatric, and social functioning status also be carefully assessed. Another type of assessment described in a prior study[17] includes the actual setting of psychosocial

goals using goal attainment scaling as developed by Kiresuk and Sherman[25] for community mental health programs. In this prior article, specific scales developed for each goal constituted a graded series of possible intervention outcomes. Five-point scales are assigned numerical values: –2 for the least favorable outcome and +2 for the most favorable, with a midpoint at 0. These ratings could be established, for example, in relation to a specific vocational goal. Thorbecke[43] used a similar scaling procedure to rate expected levels of functioning in different domains of life on expectation “ladders” with rating rungs numbered from 1 to 10. It is obvious that the more precise the proposed goal and level of expectation, the more probable it is that expectations can be shaped as necessary and goals—or at least more realistic goals—can be achieved. This type of effort would typically be coordinated by a unit social worker, counseling psychologist, or perhaps a nursing coordinator. In the United States today, this type of assessment, goal planning, and scaling of achievements are seldom performed. If a treatment team is interested in effecting significant psychosocial outcomes and quality of life changes with some expediency, it must be performed. Otherwise, the patient may either experience few changes; or, if he or she does achieve them, do so in a more protracted manner, particularly in areas that are more environmentally determined; or could actually lose functional ground, particularly if the operation is not successful.

Steps in Goal Identification

Presurgical Cognitive, Psychiatric, and Social Assessment

Intellectual and neuropsychological assessment is a standard part of the surgical consideration process. With regard to psychiatric or emotional functioning, a psychiatric interview or assessment on the MMPI I or II is also a standard part of the screening process. Because the identification of psychiatric or character issues can have a significant impact on functional outcome, particularly depression or longstanding personality disorders, additional structured psychiatric interviews such as the SCID-II or computerized psychosocial report instruments such as the WPSI are also often used. The Millon Clinical Multiaxial Inventory (MCMI I to III) can be very helpful in identifying personality disorders and longstanding behavioral propensities that relate to axis I diagnoses, such as depression, and can at times benefit from intensive intervention. Personality disorders often go unidentified in the assessment process. Psychiatric conditions are not necessarily a contraindication for surgery, but such individuals may need more monitoring; they can generally benefit from surgical intervention.[27,28] If assessment is minimal in this area, it can be difficult to delineate psychiatric and psychosocial issues carefully, and consequently conditions that may be unlikely to change despite changes in seizure status. Additional methods can be very helpful in planning. A series of studies by Derry et al.[10,12] suggest that assessment of personal responsibility for seizure occurrences and learned resourcefulness may be key variables in predicting psychosocial functioning and predictive of the need for intervention with certain patients. These authors utilized a modification of a questionnaire by Affleck et al.[2] to assess the influence of personal behavior on the occurrence of myocardial infarction. They also utilized a self-control schedule developed by Rosenbaum et al.[36] to assess an individual's level of learned resourcefulness. These measures appear to be very promising in predicting postsurgical psychosocial functioning. Both variables of learned resourcefulness and acceptance of some personal responsibility for seizure occurrences were very predictive of postoperative psychosocial functioning. With severity of illness controlled for, attribution of seizures to stress factors and low level of learned resourcefulness were predictive of postoperative unemployment and receipt of disability benefits. Patients with low levels of learned resourcefulness and high levels of seizure attribution to external stressors might obviously require more intervention than those patients accepting more responsibility for seizure occurrence and having higher levels of learned resourcefulness. Derry et al.[12] also considered measurement of perception of social support as relevant to postoperative adjustment.

Steps in Presurgical Planning

The clinical interview, cognitive and neuropsychological testing, and utilization of psychiatric and psychosocial self-report measures can be very helpful in identifying concerns. Individuals who are cognitively and psychiatrically compromised and also perceive themselves as less in control of their seizure status or have low levels of learned resourcefulness may be particularly in need of intervention. As discussed, planning steps can be based on a goal attainment scaling procedure developed by Kiresuk and Sherman,[25] in which goals across different domains of psychosocial functioning are clearly established and scaled relative to outcome desirability. The method of Thorbecke[43] of scaling levels of expected postoperative outcome relative to functioning in diverse domains of life (e.g., school functioning, social activities, relationship with significant others) on the “1 to 10” rungs of a domain ladder provides a very graphic and simplistic format in which the patient can write expectations that can then be discussed in detail. Necessary steps to reach these goals can subsequently be outlined, which often would be required irrespective of any positive changes in seizure status. Bladin[5] described a very comprehensive interview process to explore patient and family issues most germane to adjustment, including the burden of normality.

Approaches to Rehabilitation

Psychosocial Team

To achieve a favorable outcome with regard to psychosocial status, in addition to the neurosurgeon, neurologist, neuropsychologist, and nursing staff, several psychosocial team members are generally necessary. These may include a vocational rehabilitation counselor to assist in educational and vocational planning, a job site coach or mentor, an occupational therapist for training in independent living skills, a rehabilitation psychologist as a primary therapist for the patient and family members, an educational consultant or tutor, and occasionally an assistive technologist or rehabilitation engineer, who can recommend changes in work site procedures, physical modifications to a setting, or assistive equipment (e.g., dictating machines, palm-top computers, electronic toggle switches that cut off power) that will enable individuals to compensate for cognitive limitations and sometimes alleviate physical safety issues. In any case, referral to state or national departments of vocational rehabilitation or developmental disabilities can be very helpful in securing the services of personnel and funding that are critical to making functional gains in the community. These personnel and services are not available at most epilepsy surgery centers.

Type and Timing of Interventions

Presurgical Interventions

As soon as an individual is identified as a surgical candidate in need of intervention, it should be initiated. This obviously

begins with a comprehensive assessment and proceeds to the identification of optimal psychosocial goals and steps required to reach those goals. Individuals with better independent living skills and vocational and educational functioning before surgery will do better after surgery; any incremental gains that can be established in these and other psychosocial areas before surgery are ideal. Education is an obvious area of intervention for all patients undergoing the surgery. Such education should not be related simply to surgical and presurgical procedures but should also involve some discussion of the transitory emotional stages (e.g., anxiety or depression) and headaches, double vision, and other problems that often affect patients temporarily after surgery. The patient must be made to understand by some key member of the allied health team, ideally a social worker or psychologist, that psychosocial changes do not occur magically as a function of the operation, and that planning for functional changes needs to occur presurgically as soon as possible. As an example, one patient was able to complete a full 6-month course in bookkeeping before surgery. Another voluntarily began a job tryout at a science museum, which evolved into a well-paid job in the wood shop following surgery and an ideal gain in seizure control. The education of family members and significant others can be just as important to the patient's psychosocial gains. They often need to begin to change expectations and gradually reduce their level of support so that the patient begins to break away from a "dependent and lower resourcefulness" status before surgery; this is particularly important within families that have not supported the patient's autonomy.

Postsurgical Interventions

Intervention after the operation again often begins with education. Some centers have groups to which the extended family can come to learn more about the postsurgical adjustment process, and more specifically about their loved one's cognitive, emotional, and physical functioning and seizure status. They can also be further oriented or reoriented to realistic expectations for the patient and appropriate modes of interaction with the patient. At the Bethel Center, formal postoperative workshops of this type have been scheduled.

Cognitive, Psychiatric, and Psychosocial Interventions

Interventions related to optimal postsurgical psychosocial functioning, as discussed above, should begin as soon as possible. Goal setting very obviously needs to take into account the individual's general intelligence level and any specific neuro-psychological deficits. This can be problematic when certain interventions are being proposed by external state vocational rehabilitation counselors or school personnel, who may not have a complete appreciation of the individual's difficulties with memory, level of language, capacity for problem solving, or other neuropsychological concerns. Much can actually be accomplished through a team meeting of all involved allied health and service parties; this can be done via speaker phone or other form of telecommunication if the patient lives at some distance from the center and it is difficult to have all members physically present. In one case at the University of Washington Epilepsy Center, a child's school speech and language pathologist, school psychologist, and teacher were all sent for individualized instruction with members of the allied health team. Future communication will be accomplished by conference calls. Knowledge of the individual patient's cognitive strengths and areas of weakness is crucial, and this basic understanding is often lacking or partially lacking.

If patients have difficulty in a specific area of cognitive functioning (e.g., receptive speech, visual-spatial memory, speed of information processing), changes in procedures, physical modifications to an activity site, or assistive equipment at the workplace can be very beneficial. The input of the neuropsychologist can be very helpful in regard to procedural changes. The arrangement of physical modifications or assistive equipment required because of a cognitive problem is often discussed and negotiated by a neuropsychologist and a rehabilitation engineer (assistive technologist) or speech and language pathologist. Most interventions in this area relate to procedural changes (e.g., an individual performing a job from late afternoon to early evening because of attention deficits in a chaotic work setting) or low-cost assistive equipment (e.g., an electronic timer on a watch as a reminder to take medication or a palm-top computer to store important dates, car maintenance schedules, and other organizational aspects of daily living).

Interventions related to emotional functioning generally consist of efforts to ameliorate anxiety or depression, sometimes through antidepressant and antianxiety agents. Verbal psychotherapy that includes supportive interpersonal counseling, utilization of cognitive behavioral strategy, encouragement of moderate programs of physical exercise, building social support, scheduling of social events within budget, and other psychotherapeutic interventions are common. Psychotherapy for individuals with dependent personality propensities can be particularly significant. This intervention can involve Socratic questioning regarding goal identification and steps needed to reach goals, reinforcement of gains, and a general effort to empower the patient and family members to choose and implement steps toward improved psychosocial functioning in the home, at work or school, and within the community.

With regard to social deficits, action steps must be taken presurgically to enable the patient to reach expected changes or precise psychosocial goals. If there are deficits in independent living, this issue can often be remedied through training by an occupational therapist or an assigned trainer from a developmental disabilities agency, or through formal training in budgeting, shopping, or cooking provided by local epilepsy associations. In sum, psychosocial functional changes do not occur spontaneously, and specific steps must be taken to ensure that an individual is functionally capable of living independently, particularly if there is a dramatic reduction in seizure activity.

Remediation of employment or educational deficits can often be accomplished through referral to a local vocational rehabilitation agency within the United States. This agency will assist in providing funding for a vocational evaluation, community-based assessment, and structured job tryout; develop a formal on-the-job training program or job coaching program; or simply assist the patient in obtaining direct placement. In some cases, technical or formal academic education may be recommended, depending on the individual's cognitive capacities, age, and personal desires. Germany and several other countries have specialized work training centers for individuals with epilepsy.

Whenever possible, a representative of the school system should be included in the planning process if the patient is a youngster or an adolescent. In the United States, specific required transition steps may be built into the individual education plan (IEP), for which the school system is responsible. These plans are often more effective if a vocational rehabilitation counselor, social worker, or neuropsychologist affiliated with an epilepsy center provides direct input. For a number of youths, there needs to be a very delicate balance between mainstream and special educational experiences and the development of independent living skills and work-related abilities. Some students within the United States who are eligible for generic developmental disabilities services are kept in school until the age of 21, supposedly as a service to the family. This is often done simply because of lack of direction or considered options on the part of school personnel, parents, and

other concerned parties. For youngsters with improved seizure status and residual cognitive disabilities, development of school-to-work plans, vocational and technical training, and interpersonal skills training programs need to be fostered as soon as possible. Activities such as observing people at work, instruction in work-related interpersonal skills, trips to job sites at an appropriate cognitive level for a youngster, and vocational skill development often need to begin during the freshman year of high school. For youngsters with improved seizure status but residual associated disabilities postoperatively, a routine school-to-work transition is often not to be anticipated.

Youngsters with severe epilepsy and accompanying cognitive limitations can be socially isolated to a considerable degree. Assessment by therapeutic recreational specialists can be very helpful to identify leisure time activities and hobbies in which such children can develop competency and that they can use as a social medium. Their peers who are not disabled often develop social skills while engaging in such leisure time activities, and youngsters with severe epilepsy who are anticipating surgery need similar experiences. Work at the University of Washington Epilepsy Center[7] indicates that groups for teenagers are very well attended, as these children seldom have contact with other teenagers because of the problem of frequent, unanticipated seizures. This type of contact can help them to become less self-absorbed and more interested in directed and positive life activities. It can be particularly helpful if formal psychotherapeutic group experiences are mixed with social trips and activities within the community. Adults can similarly profit from this type of leisure time assessment services. On a one-to-one basis, a social worker or counselor can arrange participation in local programs, such as a YMCA physical conditioning program or an age-appropriate social group. When possible, involving several individuals who are to undergo surgical intervention in a specific group can be helpful. Community mobility is often a problem for individuals with severe seizures. Some of these issues can be remedied by training in use of the bus system and any specialty transportation that may be available in the community. Involvement in social groups can also be helpful because transportation options are often available for all group members, or the significant others of group members can alternate in providing transportation.

McCullough et al.[34] have described a multidisciplinary follow-up program for 40 patients who underwent temporal lobe resection at the UCLA neuropsychiatric hospital. In addition to a number of medical and cognitive concerns, several psychosocial concerns needed to be addressed and referrals made. Difficulties at school or work, family readjustment concerns, transitory depression, and changes in attitudes and expectations were common. Through standard monthly contact by an assigned member of the multidisciplinary team, many of these concerns could be triaged effectively and referral made as necessary. Interdisciplinary staffing was also helpful in resolving concerns with appropriate interventions. It would seem that this type of follow-up approach, which can involve simple reassurance and triage, not only fosters and maintains effective psychosocial functioning, but also reduces demands on the medical system and reinforces medication compliance and other aspects of the medical regimen.

Bladin[5] discusses the use of the comprehensive Austin Comprehensive Epilepsy Program (CEP) interview at intake, but more importantly at follow-up periods of 1, 3, 6, 12, and 24 months postsurgery. The interview explores in-depth both patient and family concerns, and that the interview's focus differs over the follow-up period reflects the evolution of the adjustment process. Wilson et al.[48] indicated that a 2-year follow-up period could be minimal. Work by Wilson et al.[49] suggests that psychosocial outcome trajectories can be identified by temporal markers and that patients evidencing markers for negative psychosocial outcome might be better identified for intervention. Cost-effective models of phone follow-up at scheduled intervals can also be borrowed from other disability groups (e.g., the problem identification and triage approach as applied in the field of traumatic brain injury by Bell et al.[4]). Currently, there is a lack of standardized approach to pre- and postsurgical assessment and intervention throughout the industrialized world, while the epilepsy operation itself is becoming relatively common.

Assessing Effect of Surgery with Regard to Rehabilitation and Psychosocial Functioning

Psychometric Measures

(See also earlier section on Psychosocial Outcome in Epilepsy Surgery.) Cramer[8] has reviewed a number of the new psychometric instruments for assessing quality of life, including the QOLIE-89, QOLIE-31, and QOLIE-10. These have been developed as measures of overall patient functioning, with those quality-of-life instruments that comprise a larger number of items and the ESI-55 measuring a number of domains of functioning. These tools provide a means for comparing the effect of different surgical outcomes on diverse areas of functioning, including psychosocial, cognitive, and physical health status. To some degree, they can be helpful for assessing the psychosocial impact of an intervention, as can the WPSI. For purposes of planning rehabilitation and fostering psychosocial gain, however, more specific instruments relating to goal attainment and level of expectation within specific domains of functioning are probably more appropriate, as are other comprehensive interview methods as previously discussed.

Community-based Measures of Effectiveness of Rehabilitation

Although it is at present not done at most centers, it will be necessary to utilize discrete measures of community-based functioning to evaluate more precisely the impact of surgery on psychosocial outcome. Clarification of outcome will be based on scaling of goal attainment or other direct measures of community functioning, such as discrete measures of independent living competencies, number of credit hours taken in school (mainstream vs. special education), grade point average, number of weeks worked full time or part time, hourly wage, promotions, and other indications of upward job mobility. Currently, assessment of functioning in these areas is not routinely done because it is time-consuming and costly, and because of a community re-entry time curve, these discrete measures may not reveal changes for some time postoperatively.

Synthesizing Psychometric and Community-based Measures of Functioning

As underscored by Fabian[14] and Batzel and Fraser,[3] accurate assessment of the psychosocial impact of surgery will eventually require an approach that includes follow-up interview, quality-of-life and WPSI self-report measures, and discrete measures of functioning within the community. Thorbecke[42] pointed out that it must be differentiated between quality-of-life measures, which are subjective in nature and strongly determined by emotional well-being,[31] and more objective measures of life functioning. In this context of reasoning the Bethel group developed the PESOS (Performance, Sociodemographic aspects, Subjective evaluation/estimation) questionnaire. The PESOS questionnaire comprises demographic and clinical data, items on performance in daily activities, and quality-of-life scales.[32] Use of multiple types of measures allows better assessment of different domains of functioning and a more comprehensive view of postsurgical psychosocial outcome.

Future Directions

Postoperative Lifestyle

In years to come, there will be an increasing emphasis on the postoperative lifestyle of the patient. The study by McCullough et al.[34] indicates a number of postoperative issues that deserve attention and intervention, such as independent tapering of drugs by the patient, sexual concerns, sleep disruption, pain, and limited jaw motion. These patients may be "trying on" new life activities and behaviors, and at times the overly confident or naive push their capabilities and place themselves at risk for additional difficulties. It would appear that monthly monitoring by an assigned team member might dramatically curtail injurious or negative behavior while reinforcing positive, goal-related steps. This postoperative period, associated with a number of physical or emotional complications of the desire and expectations for life gains, is a difficult time. For a number of patients, particularly those with poor social support, it can be a particularly confounding experience. This period of time requires more team attention and an emphasis on intervention follow-through.

Social Support

In addition to monitoring by an assigned team member, promotion of social support activities can be very helpful for postoperative patients. Linking patients presurgically with successful postoperative patients can be both inspiring and comforting. Receiving instruction regarding to the diverse aspects of the operation in a group setting can also be very comforting. Promoting preoperative and postoperative development of small groups that include patients' significant others can have a very positive effect but should be monitored to some degree based on patient homogeneity. Individuals with a number of associated impairments, particularly postoperatively, are simply not going to do as well psychosocially as successful peers, and group experiences may be rather difficult within the context of others who are doing well and making significant life gains. Phone networks can be helpful for individuals who are coming into a center from rural areas and have no contact with others who have experienced surgery and, in some cases, no contact with others who have the disability. Parents who are attempting to change expectations and set new realistic goals for a son or daughter could benefit from contact with other parents and the significant others of those undergoing similar experiences.

Dealing with Postoperative Complications

There are a number of postoperative issues that occur infrequently but present decided concerns for individuals who experience them. These can include visual field problems, double vision, memory decrements, word-finding problems, and other, usually subtle, neuropsychological concerns. In some cases, these problems are transitory in nature. When visual problems are not temporary, referral to a neuro-optometrist or neuro-ophthalmologist can be helpful. In some cases, those with visual problems can profit from training in scanning and visual perception techniques,[21] but longer-term concerns can require considerable time for adjustment.

Memory problems can be overcome through training in association techniques and categorization of information that needs to be remembered, as well as the use of electronic calendars, palm-top computers, notebooks, and diverse electronic cueing devices. Some patients who make the effort and are well organized can perform as well or actually better than peers. Individuals with language problems, particularly word finding, can be coached to "stall" or have a question repeated until they can respond appropriately. For individuals with more complicated cognitive problems, such as paresthesias, psychotherapy can aid in adjustment. It must be emphasized that complications occur in a minority of cases, but unforeseen complications do occur.

New Research Directions

As mentioned earlier, future research should focus on more detailed analysis of preoperative and postoperative psychosocial functioning using a multimethod approach that includes structured interview quality-of-life inventories and discrete measures of community functioning. A multimethod approach would thus include the perception of patients and their significant others of the psychosocial impact of the surgery. The inclusion of more discrete measures of community functioning (e.g., weeks worked on a full-time or part-time competitive basis) provide more of a "tire meets the road" view of outcome. Detailed, multimethod preoperative and postoperative assessment, including new measures such as learned resourcefulness, burden of normality, and causal attribution of seizures, will make possible more precise identification of those most in need of preoperative and postoperative intervention, leading in turn to better characterization of those who require interventions, even among the group that are currently anticipated to have problems (i.e., those with associated disabilities, who are older, and have a longer seizure history). Eventually, it is hoped that preoperative and postoperative evaluation of interventions will be done more frequently.

Summary and Conclusions

This chapter has reviewed the literature on psychosocial outcomes following epilepsy surgery and predictors of postoperative functioning. A perspective has been offered on both the preoperative psychosocial assessment process and the importance of refining the expectations of patients and their significant others to establish realistic postoperative goals. It has also been emphasized that psychosocial or rehabilitative intervention must begin before surgery and that psychosocial functional changes will not take place incidentally, except perhaps in the case of those who are relatively young at the time of surgery. It is also critical that more detailed, multimethod analysis of psychosocial functioning be conducted preoperatively and postoperatively as progress is made toward more targeted intervention to improve postoperative functioning. Much remains to be done to improve the psychosocial functioning of a patient who is being rendered physically functional through the benefits of epilepsy surgery. Progress in overcoming rehabilitation challenges is made difficult by limited personnel, limited funding, geographic distances, and to some degree limited emphasis on the part of the medical community. It is hoped that this attitude will change in the future, with greater emphasis placed on evaluating psychosocial interventions before and after the operation, as opposed to assessing quality-of-life changes as a function of the medical intervention.

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Chapter 185

Special Considerations for Pediatric Epilepsy Surgery

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Introduction

The surgical treatment of pharmacoresistant partial seizures in children has come into its own as a primary therapeutic option. Several factors have contributed to this important trend. First, an increasing body of information concerning the natural evolution of many clearly defined pediatric epilepsy syndromes suggests that early definitive surgical intervention is the most effective and perhaps the only way to completely eliminate seizures. Second, chronic epilepsy is now understood to be a progressive disorder with deleterious consequences for cognition, behavior, and socialization. Finally, evidence is now emerging that surgically induced seizure freedom may have positive and lasting benefits on the quality of a child's life and improve overall family functioning. This chapter reviews key elements of the evaluation of pediatric patients for epilepsy surgery, special aspects of the surgical procedures, and the outcome of epilepsy surgery.

Preoperative Evaluation

Ictal Semiology

The presurgical evaluation of children with medically resistant seizures must accurately assess the nuances of ictal semiology in the developing brain. The manifestations of partial seizures in very young patients often differ considerably from those in adolescents and adults. For example, complicated behavioral disturbances, auras, and other sensory alterations are decidedly unusual in young children.[57] Automatisms in the infant are typically primitive, consisting of simple sucking or chewing movements or simple gestures.[10] There is also an enhanced tendency for partial seizures to secondarily generalize in infants and toddlers, not uncommonly almost immediately after seizure onset. In contrast, complex partial seizures with pure loss of awareness are less common in children and rare in infants. Similarly, formed hallucinations and illusions are uncommon, suggesting that limbic-cortical networks have not fully matured.[52]

Video/electroencephalographic (EEG) analysis of seizure patterns in children reveals that certain ictal seizure manifestations consistently lateralize seizure onset throughout childhood, whereas others have lateralizing value only at the end of the first decade.[34] Unilateral tonic or clonic seizures, Todd paralysis, nystagmus, and postictal nose wiping lateralized seizure onset in children of all ages. In contrast, unilateral manual automatism, dystonic posturing, version, postictal dysphasia, and postictal facial wiping occur more frequently in older children. Thus, older children have a greater tendency to manifest lateralizing seizure semiologies, which suggests that the evolution of seizure manifestations in childhood occurs in step with increasing brain maturation.

Infants constitute a particularly challenging population to evaluate for surgery because their ictal manifestations may be subtle or nonlateralizing. Attempts to classify seizures in infants according to International League Against Epilepsy (ILAE) criteria are often difficult.[85] Automatisms are typically brief and simplified in appearance. Head version, a classical lateralizing finding in adults with partial epilepsy, may be less forceful and sustained and less likely to have true lateralizing value.[1] Whereas focal motor seizures are reliably contralateral to the hemisphere of seizure onset, hypomotor patterns are common in childhood and more likely to be accompanied by generalized EEG discharges.[45] Hypomotor seizures associated with regional EEG onsets are usually of longer duration and begin in the temporal or parietal lobes.[62] Epileptic spasms are particularly frequent in infants with intractable epilepsy. They are more often observed in the context of generalized syndromes but may also accompany localization-related epilepsy syndromes.[24]

Electroencephalogram

The EEG evaluation continues to be the cornerstone of the pediatric evaluation for epilepsy surgery. The identification of a discrete focus of seizure origin greatly simplifies surgical planning and increases the likelihood of seizure freedom. In a study of the value of preoperative scalp EEG in 47 children who had focal resections for intractable epilepsy, Vossler et al.[97] found that children with a single interictal focus (or a single focus with rare discordant discharges) or who demonstrated unilateral well-localized or lateralized seizure onsets in serial routine scalp EEG recordings obtained high rates of seizure relief. Localized EEG findings are especially useful when they converge to the same anatomic location represented in other diagnostic modalities such as anatomic or functional imaging.

Pediatric long-term monitoring units use recording equipment similar to that in adult units. Higher overall activity level in children, however, requires certain modifications in the recording protocol. More frequent periods of physical activity may be necessary to ensure completion of the monitoring. Frequent assessment of electrode contact and integrity of the recording system will prevent excessive movement artifact. For infants and toddlers, replacing the metal side rails of the hospital crib with a sheet of clear Plexiglas assists in viewing video-recorded seizures.

Satisfactory localization of the primary epileptogenic zone is more often achieved in adults who are more likely to have temporal lobe epilepsy and hippocampal sclerosis (HS) as the underlying pathologic substrate. The detection of HS is now

routine using high-field-strength magnetic resonance imaging (MRI) magnets, and the scalp EEG is then viewed as a confirmatory tool in preparation for temporal lobectomy. Even the necessity of long-term monitoring in adult patients has been questioned at some centers because MRI evidence of HS in conjunction with the ictal semiology is deemed sufficient for establishing the diagnosis of the temporal lobe syndrome.

In contrast, medically resistant localization-related seizures in children are less often anatomically and functionally specific. Developmental anomalies of the cerebral cortex are particularly prevalent in children referred for surgical evaluation and arise throughout the cortical mantle.[27,100] Although a certain proportion of children have discrete lesions that are amenable to resection, multiple or poorly defined epileptogenic regions are common. Despite advanced neuroimaging techniques, there remain a significant proportion of children with cryptogenic seizures with normal imaging.

Even seizures arising in the temporal lobe pose a significant challenge in the child. Early-onset temporal lobe seizures are often neocortical in origin, and HS typically occurs as “dual pathology” with cortical dysplasia rather than as an isolated lesion. In these situations, the spike field may be less well defined on scalp EEG recording. Additional electrodes such as sphenoidal or nasopharyngeal recording are unlikely to yield definitive localizing data and are rarely employed at pediatric centers.

Magnetoencephalography (MEG) has recently been advocated for localizing seizure origin in pediatric epilepsy surgery candidates. In an MEG study of 11 children undergoing evaluation for intractable, nonlesional, extratemporal localization-related epilepsy, 10 demonstrated anatomic localization of epileptiform discharges that corresponded to the ictal onset zone established by intracranial EEG recording.[80] Three-dimensional magnetic source imaging (MSI) data has been successfully interfaced with neuronavigation in pediatric patients.[53] Ictal MEG identification of epileptic foci has also been correlated with zones of hyperperfusion on ictal SPECT studies.[103]

Invasive Recording

The limitations of the scalp-recorded EEG and the higher proportion of cryptogenic cases in childhood have led to the use of invasive EEG recording in many children. Depth electrodes record very few data points and are employed primarily in adults with temporal lobe epilepsy where targeted recording from mesial temporal structures provides adequate localization. Children with neocortical epilepsy are less likely to benefit from depth electrodes due to their limited ability to monitor widespread convexity and basal cortical surfaces. The pediatric epilepsy surgical evaluation therefore relies more on subdural electrodes accurately to localize seizure origin and functionally map the neocortex. Subdural electrodes accurately localize seizure origin while maintaining an acceptably low complication rate, even in very young children and infants.[29,101]

Potential indications for implanting subdural electrodes in children include the following:

- Normal or nonlocalizing neuroimaging. Without accurate localizing information, it is often difficult precisely to define a surgical target. Electrocorticography has been advocated for defining the epileptogenic zone but is often inadequate. Intraoperative recording under general anesthesia provides only limited interictal data. Furthermore, cortical malformations often present with diffuse borders that are not easily characterized. In a series of 53 children undergoing excisional procedures for intractable epilepsy, seizure freedom was achieved in 70% of patients who had complete resections. In contrast, only 10% became seizure free when the resection was incomplete, typically due to critical cortex precluding complete removal of the epileptogenic region.[58]
- Widespread epileptogenic zone. Lesionectomy guided by electrocorticography is generally adequate for evaluating developmental tumors and other noninfiltrative lesions rather than low-grade cortical dysplasia. If MRI and scalp EEG data are discordant, especially with regard to subtle developmental lesions, subdural recording may yield valuable information to help tailor the resection.
- Multilesional and multifocal epileptiform activity. This situation is not uncommon in children with intractable epilepsy. Subdural electrode placement assists in determining which lesion and which epileptogenic region are clinically relevant. For example, children with tuberous sclerosis complex may have so many tubers that it proves difficult to accurately identify the tuber responsible for seizure origin. Alternatively, more than one tuber may be triggering seizures, necessitating a more complex presurgical evaluation of multiple sites.
- Subcortical epilepsy. In rare situations, subcortical lesions may be responsible for intractable partial seizures. Hypothalamic hamartomas are most often defined on neuroimaging, but direct recording from the hamartoma reveals focal spiking and confirms seizure origin.[72] Heterotopic gray matter[71] and cerebellar gangliogliomas in infants[49] have also been implicated in intractable seizures through the use of invasive EEG recording.

Functional Cortical Mapping

The application of adult stimulation parameters to children has produced equivocal results. In childhood, the response to direct cortical stimulation using increments in stimulus intensity to a maximum of 15 mA can be inconsistent, and when studies of electrical stimulation are controlled for age, reduced motor responses are observed, especially in children younger than age 4 years.[84] Careful analyses of elicited responses reveal that the thresholds for afterdischarges and sensorimotor responses both have an inverse linear correlation with age.[4]

One solution to the problem of maturational influences on cortical responsiveness is to modify the standard adult stimulation paradigm by delivering stimulation in stepwise increments.[55] By alternating the stimulation sequence between increases in amplitude and time rather than amplitude alone, responses in children are reliably generated at the chronaxie, the point on the strength–duration curve corresponding to the lowest amount of energy. Eliciting responses at the chronaxie is especially welcome because there are no established guidelines for electrical safety using prolonged stimulation. The dual-stimulation paradigm successfully elicits sensorimotor responses in infants <2 years of age.[25]

Neuroimaging

The application of magnetic resonance imaging (MRI) and spectroscopy (MRS) protocols in the pediatric evaluation for surgery is similar to that in adults. For example, protocols for imaging hippocampal sclerosis are similar because the incidence of hippocampal sclerosis in children with intractable temporal lobe epilepsy is approximately 60%.[43] Recent evidence suggests that high-resolution MRI also enhances the detection of subtle surgically amenable lesions in children with intractable epilepsy. In a study of 13 children who underwent MRI examination using four-coil phased surface array MRI after a recent standard MRI evaluation, high-resolution MRI identified previously undiagnosed focal abnormalities in 5 of 9

nonlesional patients.[42] These included hippocampal dysplasia, hippocampal atrophy, and dual pathology.

MRS has been used successfully to lateralize seizure onset in children with temporal lobe epilepsy.[17] MRS findings generally complement the MRI exam, but rare children will demonstrate a previously undetected localized abnormality or evidence of bilateral involvement. Although no systematic studies of MRS have been performed in children with cortical malformations, studies conducted in adults indicate variability in the detection of metabolic abnormalities that are pathologically based. Patients with focal cortical dysplasia showed significant metabolic abnormalities corresponding to structural lesions, whereas patients with heterotopia and polymicrogyria did not.

Single Photon Emission Computed Tomography

The widespread availability of single photon emission computed tomography (SPECT) cameras in nuclear medicine facilities, the low cost of γ-emitting isotopes, and the introduction of more stable radiopharmaceuticals have facilitated SPECT studies at many pediatric epilepsy centers. SPECT has been employed successfully to evaluate a wide spectrum of pediatric epilepsy surgical syndromes, including Sturge-Weber syndrome,[11] tuberous sclerosis complex,[65] Rasmussen syndrome,[33] hemimegalencephaly,[96] and focal cortical dysplasia.[44]

Ictal SPECT studies remain the procedure of choice for localizing a high proportion of children with partial epilepsy.[51] Ictal SPECT revealed hyperperfusion in 14 of 15 children with temporal lobe epilepsy undergoing preoperative evaluation.[48] In 4 children, ictal SPECT provided additional localizing information that was absent from ictal EEG recordings. Similarly, Cross et al.[17] reported abnormalities on ictal SPECT in 13 of 14 children with both temporal and extratemporal seizures. The timing of injection was critical because injections >30 seconds postictally were less likely to yield reliable measurements of regional cerebral blood flow. Pediatric ictal SPECT studies also reliably colocalize the epileptogenic zone demonstrated by intracranial EEG recording and correlate with higher rates of surgical success.[64]

In contrast, interictal SPECT injections are a significantly less reliable localizing tool in pediatric patients.[47] Normal studies or uncertainty regarding regions of hypoperfusion may potentially be misleading and are rarely relied on for surgical decision making. Ictal SPECT studies may be used to confirm localizing data from EEG and MRI investigations or to define the epileptogenic region in children with normal or discordant EEG and imaging data. SPECT may also play a role in clarifying the extent of the epileptogenic region and assist in placing intracranial electrodes.

Positron Emission Tomography

Although it is less widely used in the pediatric setting, positron emission tomography (PET) studies successfully localize seizure origin in patients with West syndrome[14] and other epileptic encephalopathies,[87] Sturge-Weber syndrome,[13] tuberous sclerosis complex,[61] frontal lobe epilepsy,[21] and generalized tonic–clonic seizures.[67] PET studies are particularly useful in children with extratemporal epilepsy and childhood syndromes with apparently generalized epileptic discharges.

PET also has been used in the presurgical localization of eloquent cortex in children with seizures. PET mapping of eloquent language, motor, and visual areas was accomplished in 15 children by coregistering PET images of task-activated cerebral blood flow onto MR images.[30] All patients had lesional epilepsy. PET mapping was well tolerated in all cases.

The absolute reliability of PET as a stand-alone localizing tool in the pediatric epilepsy surgical evaluation has been questioned.[93] Whereas [^{18}F]fluorodeoxyglucose (FDG)-PET studies in older children and adolescents yield results similar to those in adults,[38] with one exception,[87] there are no longitudinal studies of PET in younger children. It has also been shown that [^{11}C]flumazenil PET is significantly more sensitive than 2-deoxy-2-[^{18}F]fluoro-D-glucose for detecting cortical regions of seizure onset and frequent spiking in children with extratemporal epilepsy and that both radioisotopes have low sensitivity with rapid seizure spread.[83]

Functional Magnetic Resonance Imaging

Functional MRI (fMRI) has reliably been used to localize language, sensory, motor, and visual functions in children and can influence surgical planning.[7]

Language mapping with developmentally appropriate paradigms generates localizing data in children that are similar to those in adults. Cooperative children as young as age 5 years have been studied successfully.[37] It is now clear that networks for auditory processing are regionally localized and lateralized by age 5 years.[2] Receptive language sites are located primarily along the superior temporal sulcus, similar to the case in adults, suggesting that language localization and network formation are established in early life. False lateralization of language cortex to the homologous nondominant hemisphere may occur in children in the postictal state.[56]

Sensorimotor cortex can be positively identified using paradigms in which the child taps a finger or toe, wiggles the tongue, or has an extremity brushed. All of these paradigms are simple to apply and achieve reliable results, even in very young children. The location of sensorimotor function by fMRI agrees with localization data obtained by direct cortical stimulation.

Surgical Procedure Issues

Neurosurgical procedures pose special challenges for smaller children, and this is especially true for epilepsy surgery, in which younger patients undergo larger cortical resections than do older children and adults. In 2004, the Pediatric Sub-Commission of the ILAE conducted a survey of 20 pediatric epilepsy surgery centers in Europe, Australia, and the United States, collecting presurgery information on >500 patients of age <18 years.[50] Of infants of age 1 year or less at surgery in the ILAE survey, 90% underwent multilobar resections or hemispherectomy, and the most frequent etiologies were multilobar cortical dysplasia (37%), hemimegalencephaly (30%), and Sturge-Weber syndrome (13%). By comparison, 65% of 10-year-olds had focal or lobar resections, and the substrates were tumors (20%), hippocampal sclerosis (20%), and focal cortical dysplasia (20%). In other words, the younger the child at epilepsy surgery, the greater was the likelihood that his or her symptomatic substrate involved hemispheric etiologies requiring large cerebral cortical resections.[78]

Large cerebral operations are associated with significant operative blood loss relative to total vascular volume in small children.[9,15,41,68,69] In children, brain weight is proportionally larger than body volume compared with adults. At age 2 years, for example, the brain is approximately 70% of its adult size, whereas body weight is about 12% of adult weight. At 10 years of age, brain weight is 95% of adult values and body weight is 50% of adult weight. Put another way, the vascular cerebral cortex receives a large proportion of cardiac output in infants and children compared with teenagers and adults. Of equal importance is that total vascular volumes are smaller in young children than in adults. Infants weigh between 6 to 10 kg at 6 months and 8 to 12 kg by 1 year. Estimated total blood volume (75 cc/kg) is 450 to 750 cc at 6 months and 600 to 900 cc at 1 year. By comparison, 10-year-olds weigh between 23 and 51 kg, and estimated blood volumes range from 1,700 to 3,800 cc.

Expected blood loss varies by operation, and generally ranges from 200 to 500 cc for a focal or lobar resection to 1,500 cc or more for an anatomic hemispherectomy.[88] Thus, in a 6-month-old, even relatively small epilepsy surgery procedures will result in blood loss equal to half or more of total blood volume, and larger operations, like hemispherectomy, will involve more than a total body transfusion of red cells and corresponding blood-clotting factors like fresh-frozen plasma. Blood loss and other complications appear to be more common in cases of hemimegalencephaly because the cortex is very vascular and dysmature.[6,23,60,77,91] Anticipating these operative and postsurgery problems requires a dedicated team of neuro-anesthesiologists and pediatric intensive care physicians who treat problems before they occur, adequate vascular access and monitoring for ongoing blood loss during surgery, and a surgical approach that minimizes operative blood loss.[19]

Waiting for the child to grow larger before performing surgery does not reduce operative risks over the first 3 years of life and significantly increases the probability for poorer cognitive outcomes in children at risk for epilepsy-induced encephalopathy. Two-year-olds weigh between 10 to 15 kg, whereas 3-year-olds weigh from 11.5 to 17.8 kg, and calculated vascular volumes are 750 to 1,100 cc for 2-year-olds and 860 to 1,300 cc for 3-year-olds. Thus, hemispherectomy operations, where blood loss is expected to range from 500 to 1,000 cc with newer disconnection procedures, is still associated with operative blood transfusion in young children, especially those with large regions of cortical dysplasia and hemimegalencephaly.[15,60] Thus, the risk of surgery is not significantly reduced in a 2- or 3-year-old compared with an infant. In addition, recent data indicate that operative delays in infants that exceed 12 to 18 months from seizure onset to surgery are associated with poorer development quotients compared to children with shorter seizure durations.[6,22,59] Hence, although operating in young children is riskier than in adolescents and adults, increased operative risks are justified to prevent permanent epilepsy-related cognitive and developmental deficits.

In infants, the earlier the surgery and the sooner the seizures are stopped, the better are the long-term cognitive outcomes. Surgery should be performed at epilepsy centers with the necessary experience and dedicated personnel to minimize operative risks, especially for infants and small children.[19]

At pediatric centers, close to 20% of surgical cases are performed on an urgent or emergent basis because the child presents with escalating seizure frequencies, including infantile spasms or status epilepticus, that require hospitalization or intensive care unit admission for continuous intravenous antiepilepsy medications or ventilator support.[3,66] These children require relatively rapid presurgical evaluations to detect symptomatic substrates, and the surgical team must be available to react promptly to these urgent situations. Fortunately, operative outcome in urgent cases in children are similar to more routine epilepsy surgery cases. Similarly, the pediatric epilepsy team should consider the risks of agents, such as valproic acid and aspirin, that interfere with platelet and clotting functions in the presurgery evaluation of surgery for children, especially younger children undergoing large resections in which operative blood loss must be minimized.[94] Similarly, the epilepsy team should be aware of diseases associated with epilepsy that affect other organ systems, such as the cardiac and renal tumors associated with tuberous sclerosis complex.[20,92,99] Comprehensive evaluation of these organ systems may be necessary before inducing general anesthesia.

Similarly, it is relevant to discuss the presurgical risk/benefit ratio for Wada or other language tests in young children. These procedures require participation and cooperation, which may be difficult in children with developmental disabilities, and in very young patients they might not be necessary because language cortex can be shifted to the nondominant hemisphere. Finally, it should be emphasized that the perioperative management of children should include sensitivity to reduce excessive intramuscular or subcutaneous injections, appropriate identification of pain in a nonverbal child, and staff ready to deal with children with significant emotional and behavioral issues.

Outcome of Pediatric Epilepsy Surgery

Seizure Outcome

Seizure freedom remains the primary aim of epilepsy surgery in children, although secondary aims may be equally if not of primary importance to some families and require careful consideration and consequent counseling prior to surgery. Seizure outcome in children undergoing resective surgery appears to relate to degree of resection, underlying pathology, and the type of procedure performed, with a wider range of procedures performed and greater proportion with developmental malformations compared to cases in adults.

Adult series suggest that individuals undergoing extratemporal resection have a lesser chance of seizure freedom than do those undergoing temporal lobe resection. Because pediatric series have a greater proportion of extratemporal procedures,[27,78,82,102] one may expect lesser chance of seizure freedom in overall series. Success appears to be related to the underlying pathology as well as the degree of resection. Studies of series of children undergoing focal resection for the treatment of epilepsy suggest that completeness of resection is relevant, whether electrically[86] or structurally[31] determined. Of course, the underlying pathology may influence this.

Some studies of series of children undergoing temporal lobectomy for hippocampal sclerosis have reported similar seizure outcome to adults.[79] These studies, however, appear to have selected children for temporal lobectomy on the basis of adult criteria. More inclusive series of children with higher rates of comorbidities indicate a lesser chance of seizure freedom,[79] but a more recent study reviewing the outcome of children undergoing temporal lobectomy for hippocampal sclerosis did not demonstrate that IQ predicted seizure outcome. Low IQ should therefore not be included in selection criteria for epilepsy surgery.[16] Other studies of a wider range of procedures have agreed with this.[39]

In children undergoing larger procedures such as hemidisconnection, seizure outcome appears to be primarily related to underlying pathology, with lower rates of seizure freedom reported for developmental malformations, particularly hemimegalencephaly,[22] although the completeness of disconnection is relevant. In such studies reporting seizure outcome, however, whether such has been determined is unclear. In addition, the choice of disconnection procedure performed—whether anatomic or functional hemispherectomy, hemispherotomy, or hemidecortication—depends on the neurosurgeon, who in turn may decide on a procedure relative to pathology and structure. Data to date give little comparison outcome figures for different procedures in the hands of a single neurosurgeon.[15]

One question that may arise is whether there is an optimal age for surgery; is outcome likely to be more favorable if surgery is performed at an earlier rather than a later age? Limited studies of surgery performed in the very young (<3 years) suggest that initial 12-month outcome with regard to seizure freedom is similar to that for the older child and again is more likely to be related to the underlying pathology and procedure performed.[27] In addition, many of these children have catastrophic epilepsies with multiple seizures per day, and significant seizure reduction and/or severity may be of equal importance to seizure freedom, which is achieved in the majority.

A further factor that needs to be considered with regard to seizure outcome following surgery is at which point in time outcome is measured. Studies vary according to the time over which seizure outcome has been determined—anywhere from 12 to 36 months—and there are limited studies of longer-term outcome. This of course is of a high degree of relevance when considering the very young for surgery. Two studies reviewed outcome at up to 10 years following surgery; they again found that pathology can determine whether seizure freedom is seen long term. Mathern et al.[78] reviewed children at 2, 5, and 10 years following surgery and found that those who underwent resection for cortical malformations were less likely to be seizure free at 10 years than were children who had other pathologies. Hamikwa and colleagues[46] reviewed seizure outcome at 10 years in a series of children undergoing surgery for cortical malformations and tumors; the outcome was 32% seizure free for the cortical malformation group as compared to 72% for those with tumors, although little difference was reported between 2 and 10 years.

This is also important when considering children with possible multifocal disease such as tuberous sclerosis.[54,74] It has become clear that when seizures are demonstrated to be arising from a likely single tuber, resection of that tuber may lead to significant reduction in seizures if not seizure freedom.[65] Some data have suggested that in a selected few patients, multiple procedures may lead to benefit.[90] It is difficult, however, to counsel the likelihood of long-term seizure freedom with few long-term outcome data. Jarrar et al.[54] reviewed 21 patients 1 to 14 years following surgery; at 12 months, 59% (13/22) were seizure free, as opposed to 42% (9/21) at 5 years. The likely developmental consequences of this are self-apparent although unproven.

Often, an overall parental aim of surgery is not necessarily seizure freedom, but reduction in anticonvulsant medication. Unfortunately, although there is accumulating data on seizure outcome, very little work has been done on antiepileptic drug reduction in children in particular. Different centers have varying practices with regard to perioperative and postoperative drug reduction. The data suggest that although there are predictive factors with regard to seizure freedom, reduction or withdrawal of anticonvulsants cannot be guaranteed, and such information should be included in the counseling of families preoperatively. In their report of 10-year outcome data for children undergoing surgery for cerebral malformations, Hamikwa et al.[46] noted that 71% were still taking anticonvulsant medication at this time, whereas Mathern et al.[78] reported that 75% were after 5 years.

Functional Outcome

Functional outcome is obviously important, and, in children, particularly the very young, the likelihood of functional reorganization needs to be taken into consideration. One major aim of presurgical evaluation is to determine whether functional deterioration may take place; certainly in the majority of cases that are to undergo focal resection, whether temporal or extratemporal, utmost evaluation is important to minimize the risk of this, proceeding to invasive EEG monitoring and functional stimulation if there is any concern. The advent of functional MRI has enabled this to be precluded in older selected cases.[75,76] Some consideration has been given to the presumption that with early onset of epilepsy in children with temporal lobe epilepsy, reorganization of memory is likely to have taken place. Presumptions cannot be made, however, and language has been found to be localized within malformed cortex even in the presence of early-onset epilepsy in contrast to epilepsy associated with early postnatal insults.[26]

In the case of hemidisconnection procedures, certain functional deficits may be inevitable, such as visual field defects in patients in whom they do not preexist (homonymous hemianopia) or increased motor dysfunction in cases in which preoperatively fine finger movement had been preserved. In the majority of cases, preexistent structural disease and contralateral hemiplegia indicate it as unlikely that deterioration will be seen. With regard to language dominance, again preexistent structural abnormality and early-onset epilepsy imply contralateral hemisphere dominance. In certain progressive conditions, however, such as dominant-hemisphere Rasmussen encephalitis, the likely timing of surgery will be influenced by the likelihood of language recovery, compared to the severity of the disease and degree of cognitive decline. Although the original data suggested that early onset of disease optimized outcome, cases have now been reported of later surgery with subsequent limited recovery of language.[8] Motor deficit is inevitable, and again the decision as to when this should be inflicted is influenced by the degree of clinical progression of the disease.

The decision to perform surgery is often challenging because the risk–benefit assessment requires considerable clinical experience and review of the individual. Such cases mandate careful review in centers experienced in the medical and surgical care of this condition. Children with Sturge-Weber syndrome (see later discussion) may also require risk–benefit decision making regarding the benefits of seizure control through surgery versus functional deterioration. Some children, however, may show improvement in motor function on the hemiplegic side with control of seizures.[22,32]

Developmental and Cognitive Outcome

The rate of cognitive dysfunction in those coming to surgery is high; Vasconcellos et al.[95] reviewed 100 children coming to resective surgery for epilepsy and showed that most had IQ <70, and that this was much more likely with seizure onset <2 years. This was unrelated to the underlying pathology. A further series of children presenting for temporal lobectomy showed 57% with intellectual dysfunction and a high degree of correlation with age of onset of epilepsy, with 82% of children with seizure onset younger than age 1 year showing intellectual dysfunction.[36] One argument for early surgery is the likely presumed improved developmental outcome with seizure control. There are, however, few prospective studies providing clear evidence for this. A recent study reviewed children who underwent resective surgery: 16 temporal lesionectomies, 9 frontal lesionectomies, and 25 more extensive resections (18 multilobar resections and 7 hemispherotomies). It reviewed developmental outcome at least 6 to 12 months following surgery (40 were reviewed for >2–3 years, 70% of whom were seizure free). Of the 40 who underwent longer follow-up, 29 continued to perform at their preoperative levels (gains of <15 and losses of <10 in IQ score) and 8 showed significant gains (>15 IQ points). The study implied that longer follow-up was required to see such changes.

Temporal Lobe Epilepsy

Early data from children undergoing temporal lobectomy suggested little overall risk to cognitive function.[98] A multicenter collaboration of centers in the United States accumulated data from 43 children who underwent left resection and 39 who underwent right resection. For the whole sample, there were no significant reductions in cognitive status. Analysis of individual scores showed that a small percentage either declined or improved in verbal or nonverbal functioning. By definition, all

children included in the study had a full-scale IQ >69. Gleissner et al.[40] examined whether children recovered from memory deficits better than did adults as a consequence of temporal lobe surgery. They matched children with adults for pathology, onset of epilepsy, side of surgery, and type of surgery. This study showed that only children undergoing left resections recovered verbal learning capacity, reaching preoperative levels 12 months following surgery. Children undergoing right resection showed improvement in visual memory compared to adults, who showed deterioration.

Hemispherectomy

Most studies report little longitudinal change in IQ following hemidisconnection procedures, although a "significant" change is regarded to be at least 15 IQ points, which would demonstrate an increased rate of progress relative to peers.[8,22,89] Some report gains, and very few report loss. However, even loss of IQ may reflect poor progress relative to peers and not necessarily frank regression. Pulsifer et al.[89] reported poorer developmental outcome following surgery for developmental pathology compared to acquired lesions such as Rasmussen encephalitis, stroke, or vascular pathology, although numbers in the last two groups were small. They determined that children with developmental pathology had a significantly lower IQ presurgery and did not evidence significant postoperative gains. It was also evident, however, that children undergoing surgery for developmental malformations had a significantly lower age of seizure onset (<12 months) than the postnatal group. A review of children who underwent surgery for epilepsy related to Sturge-Weber syndrome, the majority of which were hemidisconnection procedures, showed that early surgery was likely to improve developmental outcome.[5]

Comparative studies are required over a much longer duration of follow-up to determine the relative merits of surgery with regard to developmental outcome, although even the limited studies available suggest seizure outcome and age at surgery are likely to influence this.[36,89]

Behavioral Outcome

Behavior is often the most problematic issue in children with chronic epilepsy and developmental delay, providing the most challenging aspect for management. The rate of psychiatric diagnosis in children coming to epilepsy surgery is high; in a series of children coming to temporal lobe resection, Mclellan et al.[79] showed that 83% had a *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV),[4a] diagnosis at any time pre- or postoperatively. It is understandable that questions will arise as to how much impact resective surgery is likely to have. This is more difficult to predict. In the same series, 72% of cases showed at least one diagnosis preoperatively and a similar percentage postoperatively; in 16%, mental health problems resolved postoperatively, but in 12% they evolved. There was no clear relationship between seizure freedom postoperatively and psychiatric disorder, although there was a suggestion that children who were seizure free following surgery were more likely to lose a DSM-IV diagnosis (24%) than were those who continued to have seizures (4%). There was no correlation with antiepileptic drugs, type of surgery, or cognitive ability for the group as a whole.

In children undergoing hemispherectomy, the data are more encouraging. The procedure was originally advocated for infantile hemiplegia, epilepsy, and behavior disorder.[70] In a group of 33 children undergoing the procedure for a variety of pathologies, Devlin et al.[22] found 10 reported by parents to have preoperative behavior difficulty. Fifteen reported postoperative improvement. In a large series of 71 children who underwent hemispherectomy for cortical dysplasia, Rasmussen encephalitis, or vascular etiologies, there were no differences on the Child Behavior Checklist scores pre- and postoperatively.[89]

It is important to consider what realistic benefit may be conferred by surgery, with or without seizure freedom. For this reason, detailed neuropsychiatric evaluation should be advocated as part of the presurgical assessment.

Summary and Conclusions

Pediatric epilepsy surgery is an effective treatment modality for children with medically resistant seizures. Knowledge of pediatric seizure presentations and the natural evolution of defined pediatric epilepsy syndromes helps to facilitate case selection and the preoperative evaluation. In particular, the pathologic substrates of intractable pediatric epilepsy differ from those in adults in being more heavily weighted toward developmental lesions such as malformations of cortical development. Based on knowledge of how these lesions influence seizure patterns and brain functionality, it is possible to achieve rates of seizure freedom that rival the adult experience.

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Chapter 186

Overview: Clinical Biology of Epilepsy

Timothy A. Pedley

Introduction

Neither seizures nor epilepsy occur in isolation from the rest of the body's functions. Epilepsy is regularly associated with complex biologic interactions as a result of the seizures themselves, an underlying medical or neurologic disorder, or antiepileptic drug treatment. Epileptic seizures, especially when frequent or in the form of status epilepticus, result in significant physiologic stress to the autonomic nervous system and to the cardiovascular, pulmonary, and endocrine systems. The occurrence of seizures and epileptiform electroencephalographic (EEG) abnormalities is strongly influenced by circadian and ultradian rhythms. In some cases, this is sufficiently distinct that it is included among the features defining some epilepsy syndromes. Antiepileptic drugs can have profound consequences for reproductive health including hormonal effects, fertility, and pregnancy outcomes. Finally, seizures occur frequently with many medical conditions that affect the brain, either as part of a systemic disease process or secondarily as the result of he-patic or renal failure and other causes of metabolic dysfunction. Successful management of patients with epilepsy and seizures must take these broader biologic considerations into account, and that is the purpose of the chapters in this section.

Chronobiology and Wake–Sleep Cycles

Sleep and epilepsy are intimately related, at multiple levels and in multiple ways, as discussed in two chapters by Dr. Shouse et al. Hippocrates and Aristotle were perhaps the first to write of the occurrence of epileptic seizures during sleep. More modern views linking biologic rhythms, epitomized by the waking–sleep cycle, to epilepsy began to appear in the late 19th and early 20th centuries, both in the French (Echeverria, Fere) and English (Gowers) literature. Several biologic clocks influence the occurrence of epileptic seizures. A number of epileptic syndromes are strongly related to circadian (24-hour) rhythms. Representative examples include both primary generalized epilepsies, such as grand mal seizures upon awakening and juvenile myoclonic epilepsy, and focal epilepsies, such as autosomal dominant frontal lobe epilepsy. EEG epileptiform discharges may be even more entrained to the wake–sleep cycle than clinical events, as illustrated by the phenomenon of continuous spikes and waves during slow-wave sleep and the discharges of benign partial epilepsy with central-midtemporal spikes. Ultradian rhythms (shorter than 24 hours), such as the basic rest–activity cycle (BRAC), interact with the circadian rhythm to further influence the occurrence of both seizures and, especially, interictal discharges at shorter periodicities (e.g., 90 minutes). These effects have been described in both generalized and localization-related epilepsies. Infradian rhythms (longer than 24 hours) characterize the secretory patterns of hormones and hormone-releasing factors; their influence is evident in catamenial epilepsy. Among the exciting discoveries in neuroscience today is a growing understanding of the neurobiologic mechanisms underlying biologic clocks. The master circadian clock involves the suprachiasmatic nuclei of the anterior hypothalamus; other areas of the hypothalamus, such as the orexin-containing cells of the lateral hypothalamus, are specifically important in the sleep–wake cycle. Brainstem mechanisms are central to generation of the BRAC type of ultradian rhythm.

The distribution of ictal events and interictal discharges differs in rapid eye movement (REM) and non-REM stages of sleep, and the effects are different for primary generalized epilepsies and localization-related epilepsies. The effects of sleep and of sleep deprivation on interictal EEG discharges are well known and clinically useful.

Sudden Unexpected Death in Epilepsy

The recognition that patients with epilepsy have increased mortality rates has been an important finding. Part of this increase is related to underlying diseases (e.g., brain tumors) or to accidental death (e.g., drowning). In recent years, however, there has been growing awareness that death also occasionally occurs unexpectedly in otherwise healthy people for no apparent reason. Indeed, sudden unexpected death in epilepsy (SUDEP) is now recognized as the most common cause of seizure-related mortality in people with chronic epilepsy. Compared to persons without seizures, the incidence is particularly high in young adults with epilepsy. Early age of onset of epilepsy, frequent generalized tonic–clonic seizures, and intractability appear to be risk factors, and polytherapy may independently add additional risk, at least in adults. Drs. Nashef and Tomson provide a critical analysis of data related to SUDEP, and suggest that SUDEP is a direct consequence of an epileptic seizure, perhaps involving a cardiac mechanism. They conclude with an emphasis on optimizing seizure control and raising considerations that are important in informing patients about the condition.

Disturbances of Autonomic Function

Drs. Goodman, Stewart, and Drislane review the anatomy of the autonomic nervous system and the many clinical features of seizures (e.g., tachycardia, increased blood pressure, apnea, pupillary changes, sweating, salivation, incontinence, skin flushing or pallor) that indicate autonomic activation. Because the autonomic nervous system is controlled by a central autonomic network that involves the limbic system and lower brainstem, autonomic symptoms and signs are especially common with partial seizures that originate in the mesial temporal lobe, the cingulate gyrus, and other medial frontal cortical areas. Such autonomic features can occur before, during, or after a seizure. Occasionally, autonomic dysfunction may be life threatening, as in some cases of seizure-related neurogenic pulmonary edema or cardiac arrhythmias. Involvement of neurons that innervate the heart can produce tachyarrhythmias as well as heart block, and this particular manifestation of autonomic dysfunction may be a contributing factor to SUDEP.

Comorbidities

All patients with epilepsy will have a concurrent medical illness requiring treatment at some time. Whether benign and self-limited or severe and life threatening, comorbidity frequently complicates seizure management. Two chapters provide broad overviews of the importance of general medical disorders in children and adults. Drs. Aminoff and Parent review comorbidity in adults. Because seizures are among the most common symptoms of brain dysfunction, they occur frequently in medical disorders associated with encephalopathy (e.g., renal or hepatic failure). In addition, a number of systemic diseases, such as lupus erythematosus, nonketotic hyperglycemia, and HIV infection, also frequently involve the brain directly causing seizures as one manifestation. Seizures are also a well-known feature of substance abuse, especially alcohol and cocaine. Medical disorders can also complicate epilepsy treatment, especially when the liver or kidney is involved. Uremia, for example, affects protein binding and thus the proportion of bound and unbound antiepileptic drugs such as phenytoin and valproate. Renal failure reduces the clearance of drugs like gabapentin and topiramate that are excreted primarily through the kidneys. Advanced hepatic failure also affects protein binding and, of course, clearance of drugs metabolized in the liver.

In addition to the same interactions anticipated in adults with general medical disorders, children present unique comorbidities, especially in terms of complex developmental, behavioral, and psychiatric interactions, as discussed by Drs. Resnick and Duchowny. A major reason is undoubtedly the added dimension caused by the effects of recurrent seizures on the developing brain, although the details of this have not yet been fully specified. A few observations illustrate the point, however. Children with developmental disabilities have an increased risk of epilepsy, and behavioral problems are more common in children with epilepsy than in the general population. There is growing recognition that depression is more common in children and adolescents with chronic epilepsy than previously realized. Similarly, cognitive impairment due to diverse causes, and even cognitive deterioration occur with increased frequency in children with epilepsy. Nearly one third of children with autism or autistic spectrum disorder have seizures. Another aspect of childhood that is considered in this chapter is the impact of complications arising from immunizations on risk of seizures and neurologic dysfunction. This has been an extremely contentious area over the years, but several studies and careful analyses have brought clarity to some—but not all—allegations and assumptions about the adverse consequences of routine immunization, and this has allowed sensible recommendations to be made for the majority of children and circumstances.

Drs. Devinsky and Nordli discuss the important and practical topic of procedures and anesthesia in persons with epilepsy. This is a frequent and understandable source of concern raised by both patients and families. Although few studies have documented significantly increased risks for medical or dental procedures, providing specific information can lessen apprehension on the part of both patients and caregivers. This chapter reviews steps that can be taken to reduce the risk of seizures at the time of a scheduled procedure; the need for health care workers involved with procedures on patients with epilepsy to be familiar with first aid for seizures; and considerations for choice of drugs for premedication and anesthesia. Helpful guidelines are given for both medical and dental procedures. In children with severe epilepsy, it is especially important to exclude genetic defects that may lead to serious adverse metabolic effects from anesthesia.

Reproductive Biology and Health

In recent years there has been a substantial increase in knowledge about the modulatory effects of hormones on neuronal excitability on the one hand, and on the hormonal changes induced by seizures on the other. Four chapters summarize current knowledge of the relationships between hormones and epilepsy, the mechanisms underlying these changes, and the impact of these changes for reproductive health in men and women.

Drs. Harden and Frye review the disruptive effects that seizures have on endocrine function and the consequences of this. Neuroactive steroids that increase following seizures have mixed effects on brain excitability, with some being proconvulsant and others anticonvulsant. Alterations in the normal feedback loop between reproductive hormones and the hypothalamus may lead to infertility and an increased incidence of reproductive endocrine disorders in women with epilepsy including hypogonadotropic hypogonadism and polycystic ovary syndrome. Endocrine changes at the time of menopause affect seizure frequency, and menopause tends to be early in women with frequent seizures. Hormonal changes also underlie the particularly clustering of seizures seen in catamenial epilepsy.

Dr. Bäckström describes the effects of both endogenous and exogenous steroid hormones, including adrenocorticotropic hormone (ACTH), adrenal corticosteroids, and gonadal hormones. ACTH has anticonvulsant effects, whereas adrenal corticosteroids have both pro- and anticonvulsant effects. For example, desoxycorticosterone has anticonvulsant effects, but cortisol increases brain excitability. Estradiol is proconvulsant, whereas progesterone is anticonvulsant. In addition, the adrenocortical axis may be dysfunctional in patients with epilepsy. Finally, Dr. Bäckström discusses receptor actions for steroid hormone actions in the brain, as well as their distribution and metabolism, and the clinical changes that occur in hormonal profiles across the reproductive life span.

Dr. Herzog discusses the prevalence and mechanisms of reproductive dysfunction in men and women. Reproductive dysfunction is common in both men and women with epilepsy. Women experience an increased frequency of menstrual disorders and hirsutism, whereas men have increased rates of diminished libido and impotence. Infertility is more common in both men and women. Reproductive dysfunction is most likely the result of abnormal neuroendocrine regulation including gonadotropin secretion. Menstrual disorders occur in up to one third of women with epilepsy, and the polycystic ovary syndrome occurs in up to 20%. Antiepileptic drugs contribute to the development of reproductive endocrine disorders. Men with epilepsy have impaired gonadal function with low serum testosterone levels and/or decreased or abnormal sperm production. Enzyme-inducing antiepileptic drugs contribute to reduced testosterone levels by several mechanisms.

Both men and women with epilepsy appear to have increased rates of sexual dysfunction, although the exact frequency is not known. Dr. Morrell reviews the neuroendocrinology underlying sexual behavior (i.e., the interaction between desire and arousal) and then describes the sexual dysfunction that occurs in people with epilepsy. Both physiologic and psychosocial causes have been implemented, but in many patients, physiologic mechanisms (e.g., limbic brain dysfunction, antiepileptic drugs, seizure-related changes in pituitary and gonadal hormones) may be more important than psychosocial disability (depression, poor self-esteem, poor disease acceptance) in many patients, although both play a role sexual dysfunction. Because of the centrality of sexuality to quality of life, it is important to actively evaluate the possibility of sexual dysfunction in patients with epilepsy, as few will volunteer information. Depending on the results of this evaluation, a plan for therapeutic intervention can be designed.

Pregnancy

The final chapter is a discussion of the very special challenges that women with epilepsy face when they decide to have children. As noted in preceding chapters, infertility, sexual dysfunction, and reproductive disorders occur more frequently in women with epilepsy than in the general population, and thus pregnancy may be difficult to achieve. Antiepileptic drugs may adversely affect reproductive hormones and their regulation. Seizure frequency may increase during pregnancy, in part because of the decline in antiepileptic drugs levels. There are increased complications during pregnancy, including fetal death and spontaneous abortions, and both low birth weights and prematurity are increased in babies of mothers with epilepsy. Antiepileptic drugs increase the risk of fetal malformations and developmental delay. Despite these concerns, the great majority of women with epilepsy have successful pregnancies and healthy babies, and the chance of a successful outcome can be greatly enhanced by informed management of the unique issues presented by women with epilepsy who desire to become pregnant.

Summary and Conclusions

This section emphasizes the necessity for neurologists to maintain a broad perspective when evaluating and treating patients with epilepsy. Seizures and epilepsy occur in the context of multiple interacting factors, including the patient's general medical health, a woman's childbearing potential, concurrent medical disorders and treatments, and physiologic and psychological consequences of the seizures themselves. Some of these are readily apparent, but others are subtle and need to be actively sought. Treatment is optimal only when all of these factors are taken into account and addressed systematically. This section also illustrates that for patients with epilepsy (and probably other chronic neurologic disorders), neurologists are most effective when they assume the role of a primary health care provider.

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Chapter 187

Chronobiology

Margaret N. Shouse

Mark S. Quigg

Introduction

The term chronobiology refers to the clocking of biologic events. There are many biologic clocks that control behavioral and physiological processes.[54] Epilepsy is affected by biologic clocks, a phenomenon that has been documented for more than a century.[22,24,33,34,35,57,82,83]

This chapter focuses on three kinds of clocks or periodicities as they pertain to epilepsy: (a) circadian rhythms, which recur at about 24-hour intervals, (b) ultradian rhythms, which recur at <24-hour intervals, and (c) infradian rhythms, which recur at >24-hour intervals (e.g., monthly or seasonal).

More than one periodicity can exist. For example, some patients have 24-hour seizure peaks, whereas most have multiple peaks within 24 hours, sometimes at about 90-minute intervals defined by the basic rest–activity cycle (BRAC). Many patients with circadian and ultradian seizures also exhibit strong infradian patterns, as evidenced by multiple cyclic variations in hormonal secretions (Chapters 194,195,196,197,198). The way in which these periodic rhythms affect epilepsy depends on several interrelated variables that define epileptic syndromes,[15] including (a) seizure type, (b) etiology, (c) age-dependent course, and (d) prognosis.

Circadian (24-Hour) Rhythms/Variations and Seizure Events

A circadian rhythm in the strict sense refers to any periodicity (hormones, temperature, mobility, etc.) that fluctuates over the course of approximately a 24-hour day and does not necessarily refer to the sleep–wake cycle. The sleep–wake cycle is a circadian rhythm in many mammals, such as rats and humans, but it recurs several times a day in cats. The “time of day” difference does not alter the fact that interictal discharges (IIDs) and clinically evident seizures exhibit similar distributions during different sleep and waking states in all these species. Accordingly, most studies of epilepsy have focused on variables that exhibit variation in the sleep–wake cycle without examining the role of circadian “time of day” rhythms per se.

There are several reasons for the paucity of clear-cut data on circadian rhythms. Perhaps the most relevant is that, in contrast to the sleep–wake cycle, circadian periodicity is not directly measurable because it is not simply a matter of clock time. It requires robust circadian markers or reference points, the use of various mathematical constructs, and data collection over prolonged sampling intervals. True, endogenous circadian rhythms recur on a “free-running” basis regardless of exogenous cues, such as the light–dark cycle, or of any other endogenous factors, such as linkage to sleep versus waking states.

Findings on biologic events that are clearly under circadian rhythm versus sleep–waking state control are difficult to interpret. Masking effects, or perturbation of circadian markers, can complicate interpretation of observations on circadian seizure modulation. For example, cortisol secretion has a circadian periodicity, but seizures themselves elevate cortisol (e.g., Quigg[83]). Cortisol secretion is also modulated by stress, which is itself a seizure precipitant (e.g., Frucht et al.[27]). Melatonin is intimately involved in light-related circadian organization of the sleep–wake cycle and, by definition, is susceptible to masking effects by exogenous clues. Exogenous melatonin administration can improve seizure control in experimental animals[90] and in clinical trials.[23] However, the ameliorative effects of melatonin cannot be dissociated from improvements in sleep, which is disordered in epilepsy (see Chapter 188),[44] or from seizure-related factors (e.g., Bazil[5]).

These issues have been extensively reviewed by Quigg.[82,83,84] In this section, we review the evidence on circadian variation in seizure activity as function of the sleep–wake cycle vis-à-vis time of day (clock time) and show examples of endogenous circadian rhythm modulation, when available.

Clinical Findings

Three epilepsy categories are classified according to the timing of generalized myoclonic or tonic–clonic seizures in the sleep–wake cycle. Timing categories are referred to as awakening (diurnal), sleep (nocturnal), and diffuse epilepsies, the latter including epileptic syndromes in which seizures occur randomly in sleep or waking states as well as in the day or night.[44,46] These three epilepsy groups are also classified as a function of the different epileptic syndromes with which they are affiliated.[15,45,46,75,77]

Epilepsies Characterized by Seizures on Awakening (Diurnal): Primary Generalized Epilepsies

Epilepsies characterized by seizures on awakening are a special class of diurnal seizures, which are considered more entrained to the sleep–wake cycle than to endogenous circadian rhythms.[31] They are most often primary generalized epilepsies in which the etiology is assumed to be genetic. These include patients with typical absence, juvenile myoclonic epilepsy (JME), and generalized tonic–clonic seizures.[2,45,46,47,77]

Patients with absence and JME often have generalized tonic–clonic seizures.[29,30,48] Greater than 90% of these patients have generalized tonic–clonic convulsions (GTCs) only on arousal from sleep,[45,46] most frequently during prolonged drowsy periods occurring between 10 minutes and 2 hours after morning awakening.[8,45,46] Myoclonic and absence seizures are also common at this time. Table 1 shows the prevalence of generalized myoclonic seizures after awakening from nocturnal sleep.[119]

Table 1 Distribution of 51 primary generalized myoclonic seizures in relation to the time of predilection for occurrence of seizures and to the efficacy of treatment in 33 patients

Time of predilection for occurrence	Total (*n* = 33 patients)	Satisfactory control (*n* = 18)	Unsatisfactory control (*n* = 15)
Morning awakening	26	17	9
Evening period of relaxation	6	5	1
Sleep onset	3	2	1
Sleep	6	2	4
Nocturnal wakening	10	9	1

Adapted from Touchon J. Effect of awakening on epileptic activity in primary generalized myoclonic epilepsy. In: Sterman MB, Shouse MN, Passouant P, eds. *Sleep and Epilepsy.* New York: Academic Press; 1982:239–248; with permission.

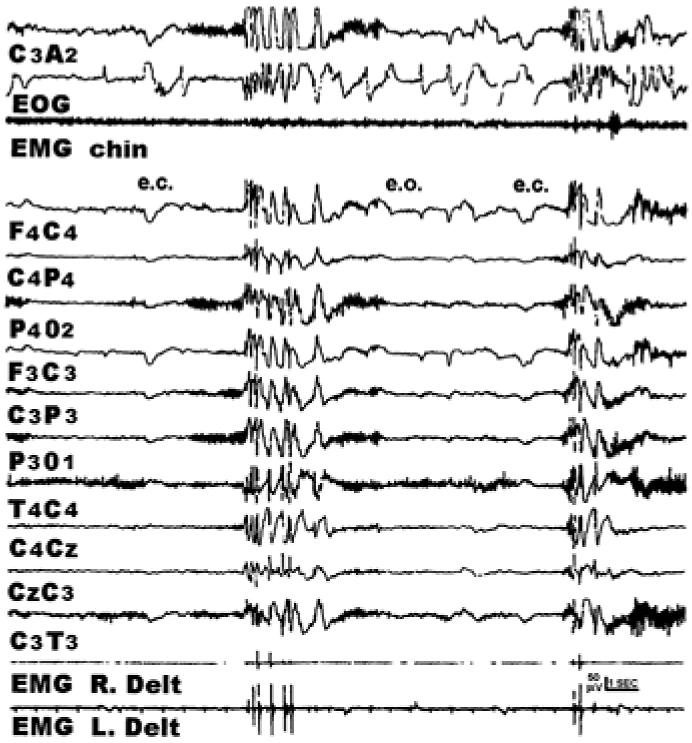

FIGURE 1. Electroencephalogram (EEG) recorded after morning awakening. Eye closure elicits a series of polyspike-and-wave (PSW) discharges associated with electromyographic (EMG) activity. Subsequent eye opening inhibited such EEG manifestations, which resumed again on closing the eyes. e.c., eyes closed; e.o., eyes opened; EOG, electrooculogram; L. Delt., left deltoid; R. Delt., right deltoid. (From Gigli GL, Calia E, Luciani L, et al. Eye closure sensitivity without photosensitivity in juvenile myoclonic epilepsy: polysomnographic study of electroencephalographic epileptiform discharge rates. *Epilepsia*. 1992;32:677–683; with permission.)

Many patients also exhibit more frequent and prolonged interictal epileptiform discharges after awakening.[37,51,52,77,78] Polyspike-and-wave complexes of JME often occur after awakening from nocturnal sleep, as depicted in FIGURE 1.[31] FIGURE 2 shows that the duration of 3/sec spike–wave complexes

associated with absence seizure disorders can be longer after awakening than at other times in the sleep–wake cycle.[52]

Ictal events are more entrained to awakening than are IIDs. Frequent polyspike-and-wave and spike-and-wave complexes also occur during non–rapid-eye-movement (NREM) sleep (e.g., Fig. 2), even when myoclonic and absence seizures occur only on awakening.

Epilepsies characterized by seizures on awakening typically exhibit an age-dependent clinical course.[15,70,73,97,98,99] Onset is usually between 4 and 15 years of age. Spontaneous remission, reduction of seizures, or complete medication control is common between puberty and 20 to 25 years of age, although some patients can be more drug refractory.[70,78,98]

These relatively benign epileptic syndromes are associated with normal developmental and neurologic functions. The presumed pathophysiology[32] is a disturbance in the electrophysiologic and neurochemical response of neocortical cell populations to synchronous synaptic inputs resulting from inhibition of arousal cells located in the hypothalamus and in the ascending reticular activating system (ARAS).[4,74,103,104]

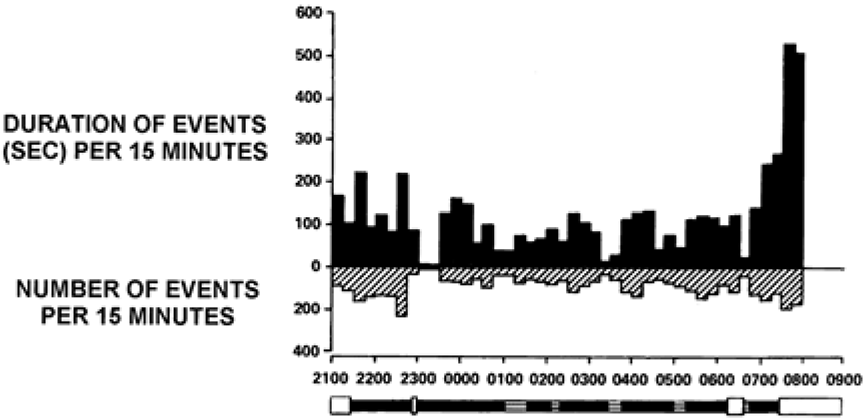

FIGURE 2. Circadian distribution of 3/sec spike-and-wave activity per 15 minutes. Discharge duration is longest at awakening and so is more likely to represent a clinical seizure. Discharge rate is also high at the beginning and end of sleep. Time of day along the abscissa is in terms of the 24-hour clock. The bar along the abscissa indicates the sleep or waking state: Unfilled, awake; filled, non–rapid-eye-movement (NREM) sleep; slanted lines, rapid-eye-movement (REM) sleep. (From Kellaway P, Frost JD Jr, Crawley JW. Time modulation of spike-and-wave activity in generalized epilepsy. *Ann Neurol*. 1980;8:491–500; with permission.)

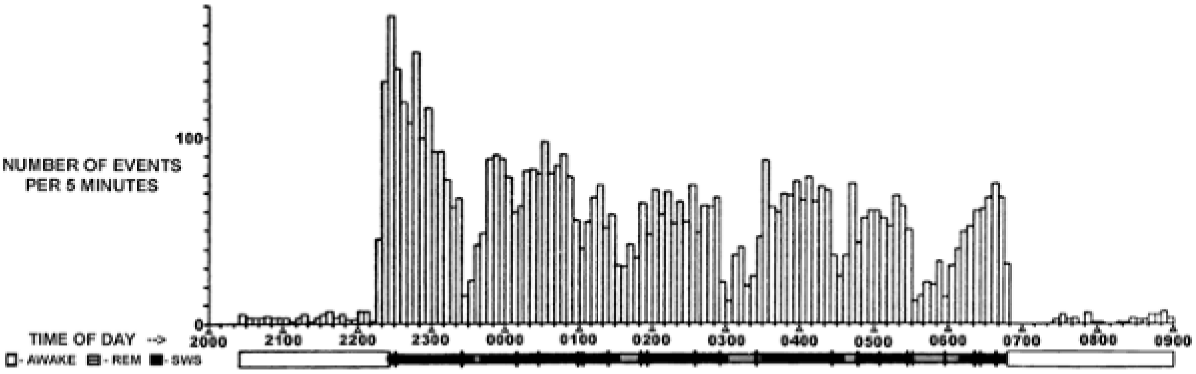

FIGURE 3. Spike density distribution at 5-minute intervals in benign epilepsy with centrotemporal spikes (BECT) showing a decremental pattern. An abrupt increase in spike activity is associated with sleep onset and is followed by an overall decline during subsequent non–rapid-eye-movement (NREM) sleep and particularly on awakening. Periodic troughs occur throughout sleep in relation to REM onset. SWS, slow-wave sleep. (From Kellaway P, Frost JD Jr. Biorhythmic modulation of epileptic events. In: Pedley TA, Meldrum BS, eds. *Recent*

Advances in Epilepsy, Vol. 1. London: Churchill Livingstone; 1983:139–154; with permission.)

Epilepsies Characterized by Seizures During Sleep (Nocturnal): Localization-Related Epilepsies

Circadian ictal and interictal discharge patterns occur during the "subjective night" and/or during sleep in epilepsies arising from a focal region of dysfunction (e.g., Frost et al.[26]). These may be relatively benign or not. For example, some frontal lobe syndromes, notably nocturnal paroxysmal dystonia[62,63,94] and autosomal-dominant nocturnal frontal lobe epilepsy (see Chapter 251), display bizarre partial motor seizure manifestations during NREM sleep. The seizures do not secondarily generalize in NREM sleep and are readily controlled by antiepileptic medication. Other "benign" localization epilepsies have an age-dependent course with a specific time frame for onset and spontaneous remission. The prognosis for spontaneous remission of seizure manifestations, is usually good.[2,6,7,15,70,78,98,99] These patients also display frequent IID and partial seizures with or without secondary generalization during NREM sleep. Examples are benign partial epilepsy with centrotemporal spikes (BECT, also called benign rolandic epilepsy),[58] benign epilepsies with occipital spikes,[6,7] Landau-Kleffner syndrome (acquired epileptic aphasia), and patients manifesting electrical status epilepticus during slow sleep (ESES).[113] FIGURE 3 shows an example of BECT in which the interictal spike discharge peaks at sleep onset.[51]

Simple partial or complex partial seizures, particularly those accompanied by secondary generalized tonic–clonic seizures, have long been thought to occur more frequently in sleep than in waking (e.g., Janz[45,46]). Greater than 50% of patients with temporal or frontal lobe foci reported secondary generalized tonic–clonic seizures only in sleep, whereas complex partial seizures without secondary generalization were reported to occur more often during waking.[45,46] Because localization-related epilepsies are more likely to be symptomatic than are primary generalized epilepsies,[15,45,46,78] it is not surprising that the prognosis is not always benign. For example, complex partial seizures of temporal or frontal lobe origin do not have an age-dependent course. Onset frequently occurs before the age of 20 years, spontaneous remission is rare, and seizures are often drug refractory.[15,45,46,78]

Recent findings using continuous electroencephalogram (EEG)-video monitoring for presurgical evaluation have revealed some interesting new developments in drug-refractory localization-related epilepsies.[17,39,48,81] Different timing patterns emerge when patients with drug-refractory complex partial seizures are evaluated as a function of the presence or absence of secondary generalized seizures and as a function of foci in frontal, temporal parietal, or occipital lobes (Fig. 4).[40] Partial seizures occur more frequently in waking than in sleep, regardless of the location of the seizure focus (Fig. 4A). Complex partial seizures with secondary generalization occur significantly more often in NREM than in waking at all seizure foci except in frontal lobe (Fig. 4B). It was concluded that different mechanisms govern the timing of seizure initiation versus propagation.

Quigg proposed that circadian diurnal rhythms govern the initiation of symptomatic partial seizures with *limbic* foci, whereas nocturnal sleep-related mechanisms trigger onset of focal seizures in symptomatic focal seizure disorders with *nonlimbic* foci. Several findings have been assembled to address this hypothesis:

1. The timing of symptomatic limbic seizures (mesial temporal lobe sclerosis) can be differentiated from that of nonlimbic (extralimbic) seizures with respect to linkage with circadian versus predominantly vigilance-related seizures. Table 2 summarizes this difference on the basis of recent studies dating from 1998 to 2004.[84]
2. Figure 5[83] illustrates the 24-hour distribution of seizures in two patients with left hippocampal sclerosis and temporal lobe onset of seizures (Fig. 5A, B) and in a single patient with dual pathology (Fig. 5C, D). The three patients with symptomatic mesial temporal lobe epilepsy (MLTE) (Fig. 5A–C) all showed complex

partial seizures during the subjective day, whereas the timing of symptomatic, parietal lobe seizures occurred nocturnally and during sleep (Fig. 5D).

3. Figure 6 contrasts the absence of a circadian rhythm in extratemporal focal seizures (Fig. 6A) with the presence of a circadian seizure distribution in an animal model and in patients with MTLE.[83] Findings are plotted as a function of clock time in humans (Fig. 6A, B) and with reference to the circadian temperature cycle in the 12-hour/12-hour light/dark cycle in animals (Fig. 6C). A comparison of findings in Figures 6B and 6C supports the conclusion that MLTE in both species is regulated by a circadian rhythm.[82,84,87] This circadian pattern was also maintained in rats during constant darkness when plotted in relation to the free-running circadian temperature cycle (Fig. 6D).[87]

The interpretation of these findings is complicated by the fact that rats are nocturnally active and humans are diurnally active. Thus, seizure activity seems dissociated from circadian rest–activity rhythm regulation. In addition, circadian entrainment disappeared when the data from free-running rhythms were plotted with reference to circadian rest–activity patterns (not shown in Fig. 6). Both discrepancies could suggest an underlying circadian modulation of limbic seizure occurrence that does not involve rest–activity or sleep–wakefulness patterns.

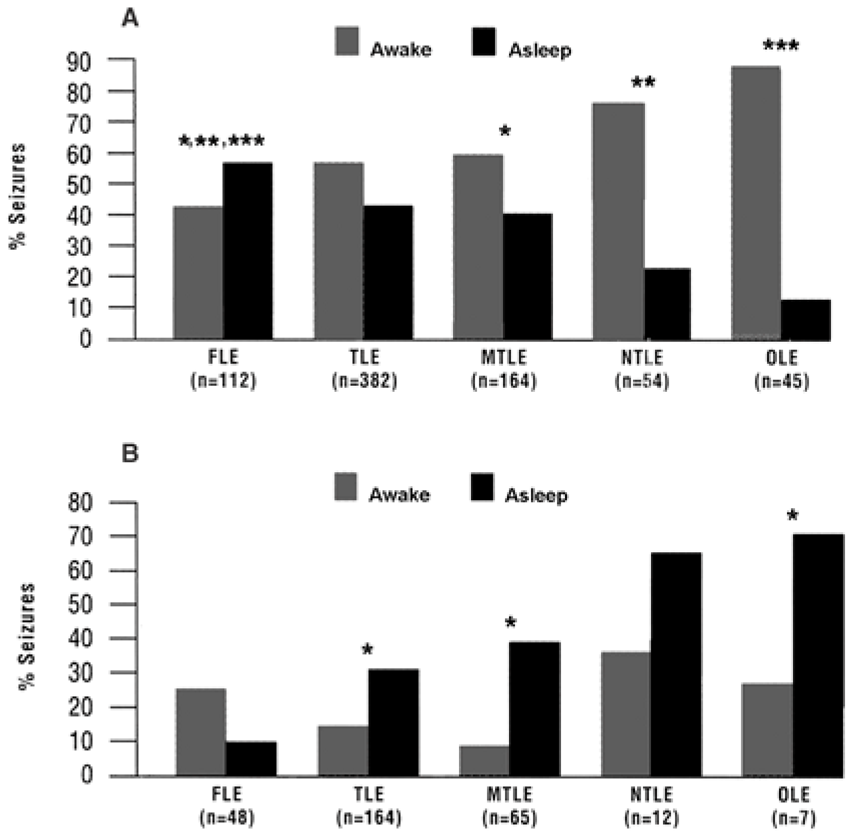

FIGURE 4. A: Percentage of partial seizures arising from various brain regions during waking (*gray bars*) or sleep (*black bars*). Partial seizures with or without secondary generalization of seizures (*n* = 579 of 613 partial seizures in 133 patients) were included. **B:** Percentage of partial seizures with secondary generalization (*n* = 396 of 613 partial seizures in 133 patients) during waking (*gray bars*) or sleep (*black bars*). In both histograms, data are presented for each location assessed. Overall, partial seizures were more likely to occur during wakefulness regardless of seizure onset site **(A)**, whereas partial seizures with secondary generalization were significantly more likely to occur in sleep at all onset sites except

fron-tal lobe **(B)**. Sleep refers to non–rapid-eye-movement sleep because no seizures were registered during rapid-eye-movement sleep. Data were obtained during in-patient monitoring of patients who were candidates for epilepsy surgery due to refractory complex partial seizures. FLE, frontal lobe; MLTE; mesial temporal lobe; NTE, neocortical temporal lobe; OLE, occipital or parietal lobes; TLE, temporal lobe. **p* <0.05; ***p* <0.001; ****p* <0.0001. (From Herman ST, Walczah TS, Bazil CW. Distribution of partial seizures during the sleep–wake cycle: differences by seizure onset. *Neurology*. 2001;56:1453–1459; with permission.)

Table 2 Distribution of focal seizures by location of seizure

Study	Location	Light (%)	Dark (%)
Quigg et al., 1998[87]	MTLE	60	40
	XTLE	54	46
Herman et al., 2001[40]	TLE	74	26
	FLE	43	57
Crespel et al., 1998[17]	MTLE	84	16
	FLE	39	61
Pavlova et al., 2004[81]	TLE	81	19
	XTLE	59	41

FLE, frontal lobe epilepsy; MTLE, mesial temporal lobe epilepsy; TLE, temporal lobe epilepsy; XTLE, nontemporal lobe neocortical epilepsy. Adapted from Quigg M. Chronobiology, sleep, and seizures (2004 Profiles in Seizure Management, Case 2). Princeton Media Associates; 2004(3);1–11. Available: http://www.princetonhcm.com/public/index.php?program=2004-79-6&rid=226; with permission.

Epilepsies in Which Seizures Occur Randomly (Diurnal and Nocturnal): Symptomatic Generalized Epilepsies

In these epileptic syndromes, ictal and interictal discharges occur in all sleep and waking states.[45,46,67] This random seizure distribution is often associated with diffuse, severe cerebral dysfunction.[43,52,79,97] Three well-known examples are West,[14,123] Lennox-Gastaut,[30,79] and progressive myoclonus[36] syndromes.

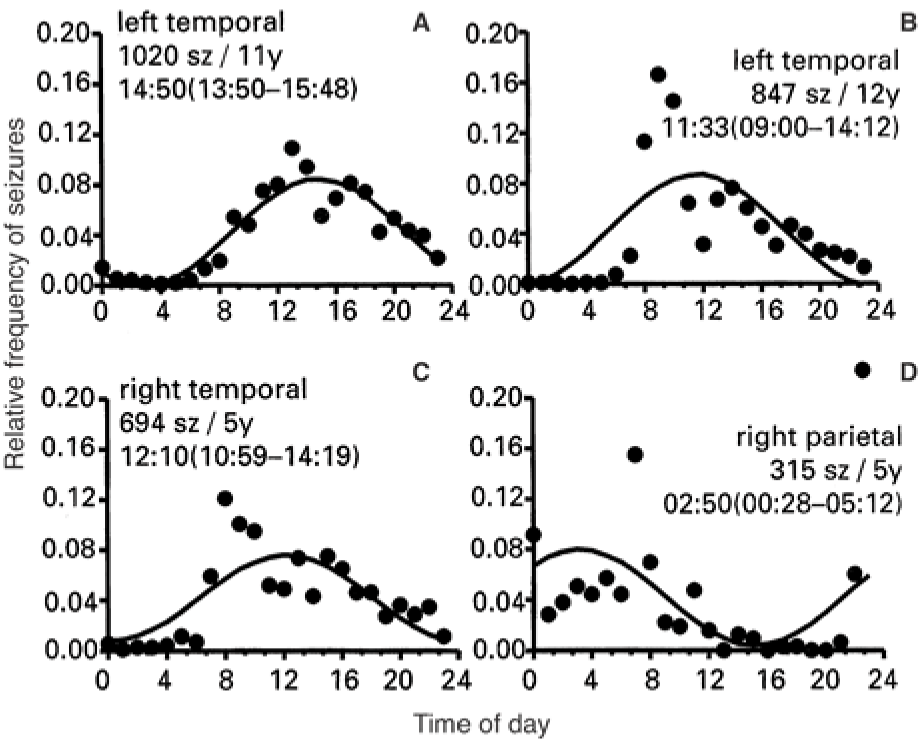

FIGURE 5. Daily distribution of seizures revealed by detailed, long-term diaries maintained by three subjects with medically refractory epilepsy and their spouses. Localization of seizures was later confirmed during epilepsy surgery evaluation. Curves provide the best-fit estimate of time of peak occurrence (95th confidence interval). **A, B:** Patients with left hippocampal sclerosis and left temporal lobe seizures. **C, D:** Patient with a pattern of seizures with different symptomatology and a dual pathology: Right temporal lobe seizures associated with ipsilateral hippocampal sclerosis occurred diurnally **(C)**, and parietal lobe seizures associated with a cortical malformation occurred nocturnally and out of phase with temporal seizures **(D)**. (Composite from Quigg[83] as follows: Panels A, B from Quigg M. Seizures and circadian rhythms. In: Bazil CW, Malow BA, Sammaritano MR, eds. *Sleep and Epilepsy: The Clinical Spectrum*. Amsterdam: Elsevier; 2002:127–142; panels C, D adapted from Quigg M, Straume M. Dual epileptic foci in a single patient express distinct temporal patterns dependent on limbic versus nonlimbic brain location. *Ann Neurol*. 2000;48:117–120; with permission.)

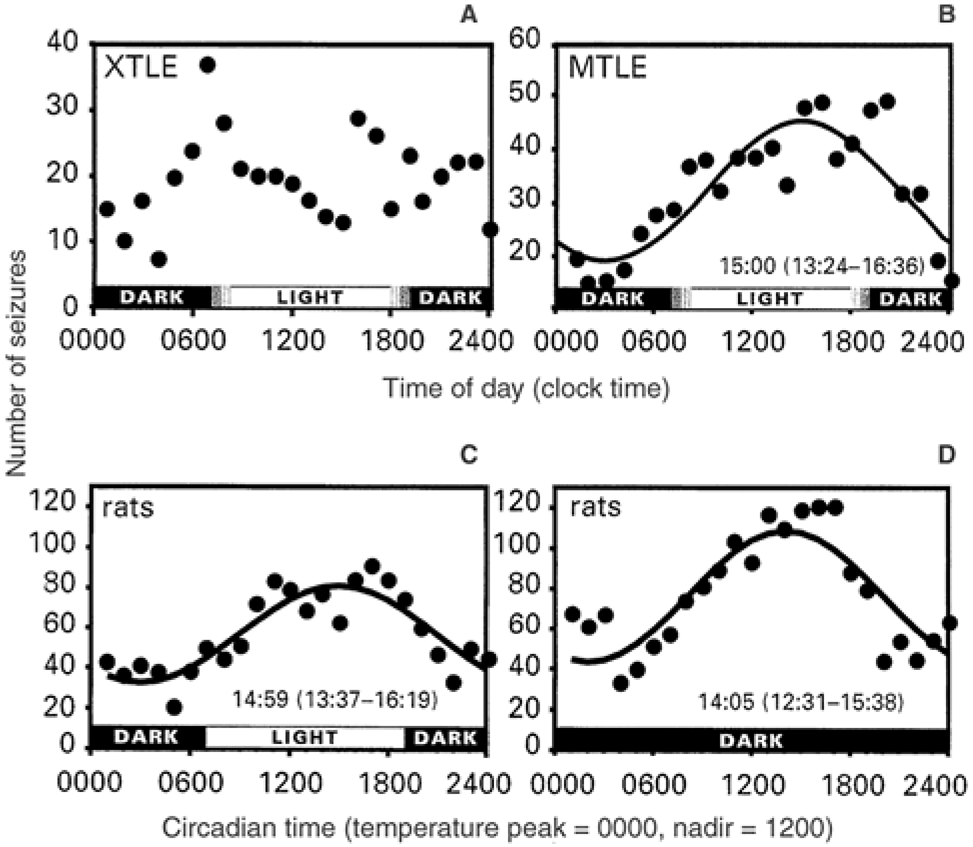

FIGURE 6. Distribution of spontaneous epileptic seizures in humans and in the self-sustained electrical status epilepticus rat model of limbic epilepsy. The times of seizure occurrence in humans were determined using continuous video-electroencephalogram (EEG) recordings from either scalp or intracranial electrodes. In rats, continuous EEG and hippocampal depth electrodes provided times of seizures. Where appropriate, data were fitted using cosinor-nonlinear least squares analysis. **A:** A biphasic distribution of seizures in patients with extratemporal lobe partial epilepsy (XTLE). When the observed distribution is compared with the expected uniform rate of seizure occurrence using chi-square analysis, the distribution is statistically random. In contrast, limbic seizures in humans with mesial temporal lobe epilepsy (MTLE) **(B)** and in rats **(C, D)** occur in similar patterns. Seizures of limbic origin are accurately modeled by a cosine function with the calculated time of peak occurrence reported with the 95% confidence limit. Both species have diurnally predominant seizures despite the fact that rats are nocturnal and humans are diurnal in activity. The limbic seizures of rats occur in similar distributions when entrained to a 12-hour/12-hour light/dark cycle **(C)** as compared to free-running circadian rhythms in constant darkness or a 12-hour/12-hour dark/dark cycle **(D)**. Note that the times of seizure occurrence are normalized to a 24-hour circadian clock provided by each animal's circadian rhythm of temperature because, once in constant darkness, the period of circadian rhythms may run slightly shorter or longer than exactly 24 hours. The plot in panel D confirms that the occurrence of limbic seizures is modulated in an endogenous, circadian fashion. (Composite from Quigg M. Seizures and circadian rhythms. In: Bazil CW, Malow BA, Sammaritano MR, eds. *Sleep and Epilepsy: The Clinical Spectrum*. Amsterdam: Elsevier; 2002:127–142; as adapted from Quigg M, Clayburn H, Straume M, et al. *Epilepsia*. 2000;41:502–509; and Quigg M, Straume M. Dual epileptic foci in a single patient express distinct temporal patterns dependent on limbic versus nonlimbic brain location. *Ann Neurol*. 2000;48:117–120; with permission.)

Onset can be early in life, but average age at onset in this category of seizure disorders is otherwise evenly distributed across the age spectrum.[45,70] Seizures tend to be medically refractory, and the prognosis is poor.[6,15,30,77,78,123] In some cases, morbidity and even death is expected (e.g., Lafora, essential hereditary myoclonus, or Unverricht-Lundborg syndrome).[36,78] In other cases, conversion to other serious seizure disorders is common (e.g., West syndrome, which is also called infantile spasms, to Lennox-Gastaut syndrome[79]). Spontaneous remission does not occur. Cases with extreme neurologic complications display substantial disruption of sleep states and of the sleep–wake cycle (see Chapter 188). Extreme neurodegenerative disorders also provide the only example in which endogenous circadian rhythm disorders are clearly manifested.[39,44]

Basic Mechanisms

Strong rhythms of circadian ictal and to some extent interictal discharge patterns arise in two groups of epilepsy.[26,33,34,35,36,37,41,42,43,45,46,47] In primary generalized epilepsies, ictal and interictal discharges often appear on awakening, although interictal discharge is common in NREM sleep as well. Localization-related epilepsies frequently exhibit generalized ictal and interictal discharges events during sleep, often at sleep onset or at the end of sleep. The same ictal and interictal patterns seen in humans have also been reported in experimental animal models of sleep versus awakening epilepsy (Fig. 7A vs. Fig. 7B).[99]

What is known about basic chronobiology mechanisms that might explain these differences? To address this question, it is necessary to consider two main hypothalamic regulatory systems: (a) the suprachiasmatic nuclei of the anterior hypothalamus, which is the “master” circadian clocking mechanism, and

(b) the anterior/preoptic, lateral, and posterior hypothalamic cell populations, which generate the sleep–wake cycle.

The suprachiasmatic nucleus (SCN) of the hypothalamus regulates nearly all circadian rhythms, including the subsystems linked to the sleep–wake cycle.[13,54,82,83] Sleep-dependent processes include NREM-related changes such as plasma growth hormone secretion and urinary calcium excretion. Lesions of either the SCN or its afferent retinal pathway eliminate most physiologic and behavioral circadian rhythms, including the sleep–waking circadian cycle.[21,73,102] Cells of the SCN continue to exhibit circadian discharge patterns in isolation[122] and also restore normal circadian patterns when transplanted into animals with genetically abbreviated periodicities.[88] These findings confirm that the SCN is the primary circadian clock. Various afferent and efferent anatomic interconnections have been identified to account for modulation of component circadian rhythms, such as the adjacent cell populations generating the sleep–wake cycle. Circadian oscillation in the SCN is genetically determined.[1,88] Several genes encode clocking proteins to create an autoregulatory feedback loop using transcription and translation.[61] γ-Aminobutyric acid (GABA) is the main transmitter.[69] GABA release is well known to have antiepileptic effects.

Considering the undisputed, pervasive influence of the SCN on circadian rhythms, it is difficult to understand why there is so little evidence linking this structure or the circadian light–dark cycle to ictal or interictal seizure events and vice versa. A number of reasons have been suggested (e.g., Quigg[83]). Examples are masking effects, which can occur as a result of extraneous environmental or internal factors, and the only fairly recent availability of prolonged polysomnographic and video recordings needed to capture sufficient seizure events for “time of day” analysis.

Independent oscillators also exist, even in structures normally entrained to discharge patterns of cells in the SCN. Destruction of the SCN abolishes circadian “time of day” rhythms, but the usual result is a replacement with other rhythms. FIGURE 8 shows the persistence of sleep–wake behaviors and unchanged overall percentages of sleep and wake time after SCN lesions. The circadian rhythm is replaced by an ultradian rhythm. It is curious that no one has attempted to differentiate “time of day” effects from sleep–waking-state effects on seizures before and after SCN lesions.

Another complication is that cells of the SCN discharge in the light phase of the light–dark cycle and are silent during the dark phase, regardless of whether mammals exhibit sleep nocturnally or diurnally. Taken alone, this fact is not disturbing because many circadian rhythms are totally out of phase with cellular discharge patterns of the SCN (e.g., melatonin release). The troublesome aspect is that rats, which are nocturnally active, still exhibit IIDs during diurnal sleep (e.g., Ascapone and Penry[2] and Kostopoulos[53]). In contrast, humans frequently exhibit seizures on awakening (primary generalized epilepsy [PGE]) or in sleep (most localization-related epilepsies), even though humans are typically awake diurnally and asleep nocturnally. Thus, with few exceptions, circadian effects on seizures and of seizures on circadian rhythms are so far primarily entrained to sleep and waking states.

The only way in which to eradicate or substantially diminish sleep or waking states is to destroy the generators of these states. Well-documented clinical (e.g., Von Economo[121]) and experimental findings, including transection, lesion, unit recording, microdialysis, *c-fos* expression, and/or regional blood flow studies, localize control of the sleep–wake cycle to the hypothalamus.[4,13,69,76,120] Histaminic cells in the tuberomammillary nucleus of posterior hypothalamus, orexin (hypocretin)-containing cells of the lateral hypothalamus, and cholinergic cells in the magnocellular region of the anterior hypothalamus generate awakening and maintain arousal, whereas GABAergic and galanin-containing cells of the anterior/preoptic hypothalamic areas (ventral lateral preoptic [VLPO]) generate sleep onset and maintenance.[60,69,88,95,110,111,112] These hypothalamic regions are reciprocally connected[60,95,96] and dominate all the EEG, behavioral, autonomic, and, conceivably, hormonal correlates of the sleep–wake cycle.

In the intact animal, these forebrain regions are also reciprocally interconnected and functionally interact with brainstem cholinergic, noradrenergic, and/or serotonergic cells originating in the pontine tegmentum. These brainstem cells also discharge during onset and maintenance of wakefulness and, with the exception of occasional bursts of cholinergic cell discharge (see Chapter 188), are silent during NREM

sleep.[4,10,49,69,76,120,121] For this reason, the coverage of basic mechanisms focuses on these particular regions.

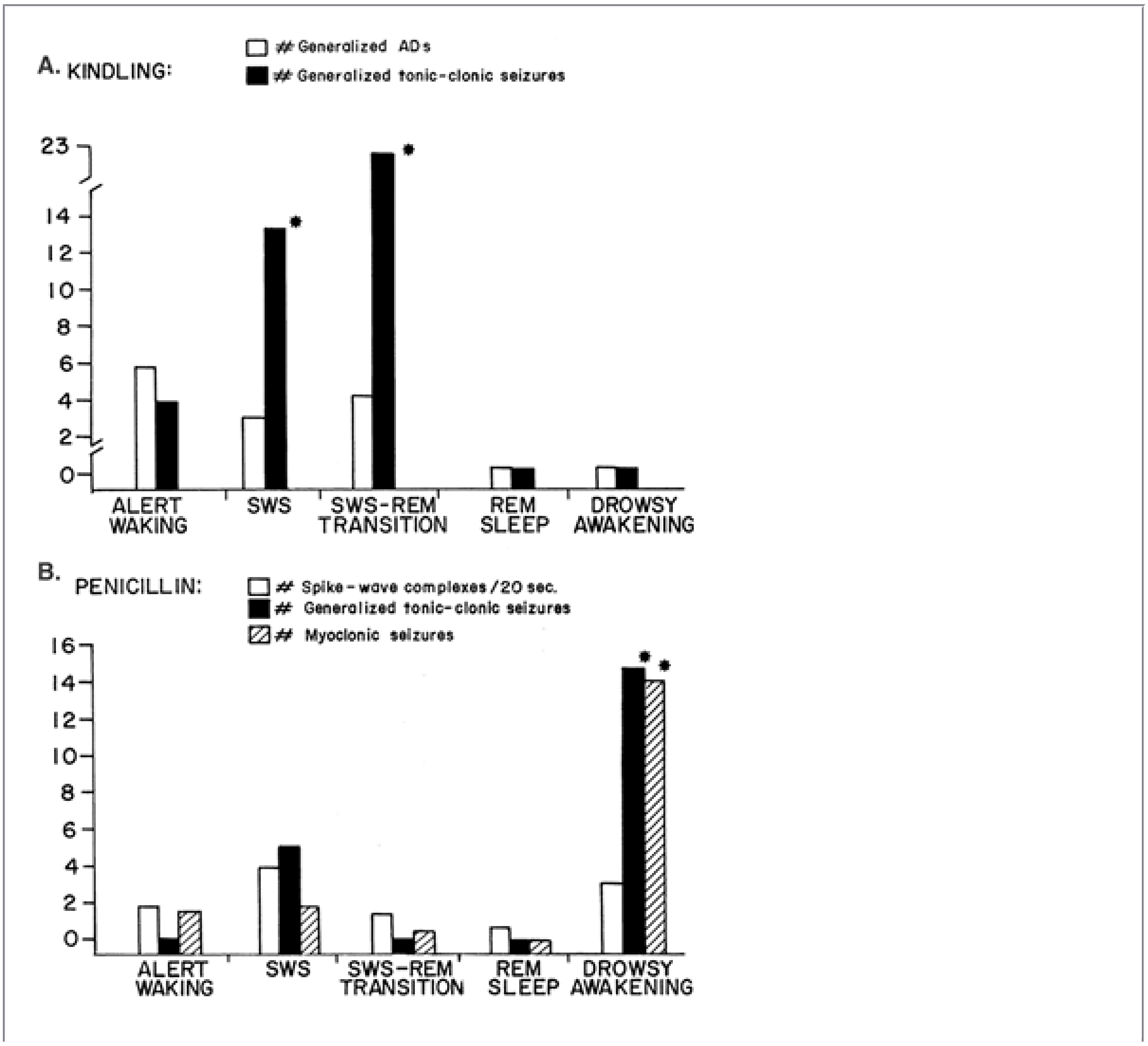

FIGURE 7. Timing of spontaneous seizures during the sleep–wake cycle in **(A)** 9 amygdala-kindled kittens and **(B)** 12 cats with systemic penicillin epilepsy (300,000–400,000 IU/kg). Temporal lobe kindling is a model of localization-related epilepsies, whereas systemic penicillin epilepsy is a model of primary generalized epilepsy. Slow-wave sleep (SWS) in cats is equivalent to non–rapid-eye-movement (NREM) sleep in humans. AD, afterdischarge. (From Shouse MN, King A, Langer J, et al. Basic mechanisms underlying seizure-prone and seizure-resistant sleep and awakening states in feline kindled and penicillin epilepsy. In Wada JA, ed. *Kindling 4*. New York: Plenum Press; 1990:313–327; with permission.)

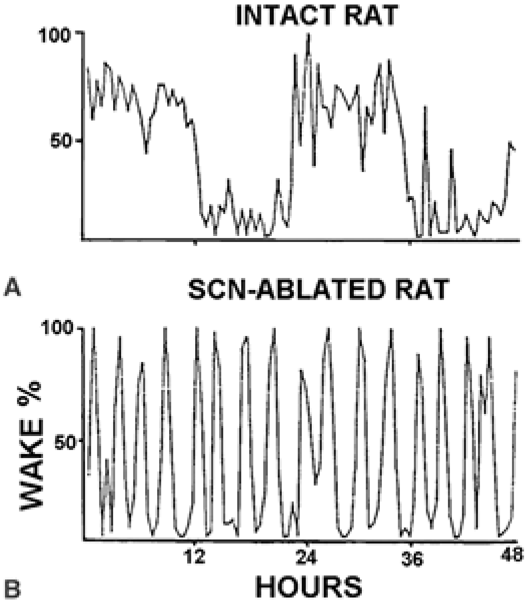

FIGURE 8. Percentage of polygraphically recorded wake time in each 30-minute period over 48 consecutive hours in two adult male rats recorded in constant dim light. **A:** An intact control rat, showing a typical 24-hour circadian rhythm of sleep–wake time. **B:** A rat with complete ablation of the suprachiasmatic nuclei (SCN). The 24-hour rhythm of sleep–wake time was completely lost. This rat shows prominent ultradian rhythms in the 3- to 4-hour range. (Modified from Mistlberger HE, Bergmann BM, Rechtschaffen A. Relationships among wake episode lengths, contiguous sleep episode lengths, and electroencephalographic delta waves in rats with suprachiasmatic nuclei lesions. *Sleep*. 1987;10:12–24; with permission.)

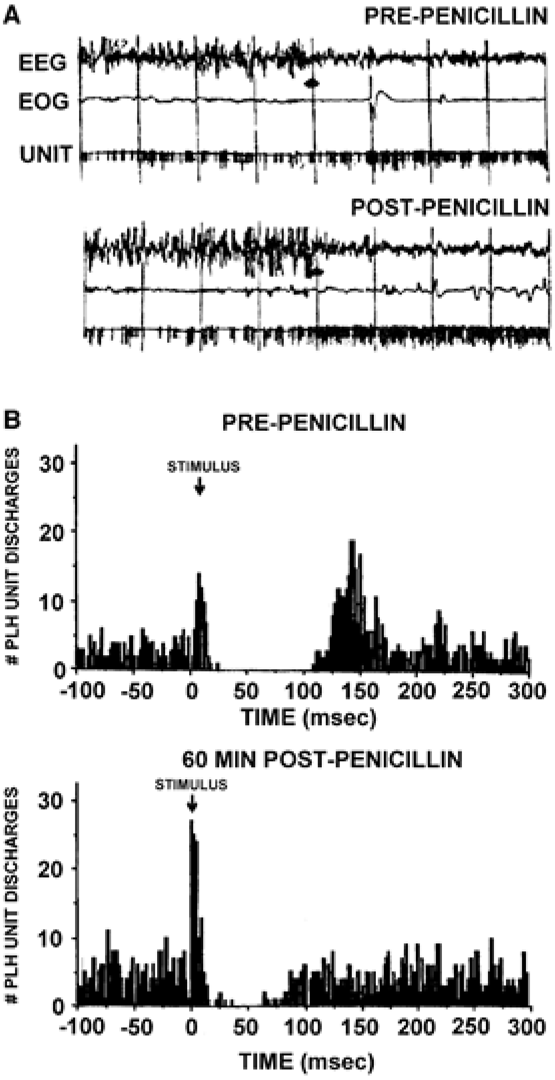

FIGURE 9. **A:** Spontaneous unit activity in a posterior lateral hypothalamic (PLH) neuron during slow-wave sleep (SWS), which here refers to non–rapid-eye-movement (NREM) sleep, and at awakening (*arrow*) before and during a subconvulsive dose of penicillin (200,000 IU/kg) in a cat. **B:** Evoked orthodromic response in a PLH neuron induced by stimulation of the external capsule (100 pulses, 0.8 mA), before and after penicillin (200,000 IU/kg) in a cat. Stimulus onset was at time 0. Note the increased amplitude of evoked excitation and the reduced duration of postexcitatory inhibition after penicillin when compared to the pre-penicillin record. (From Shouse MN, King A, Langer J, et al. Basic mechanisms underlying seizure-prone and seizure-resistant sleep and awakening states in feline kindled and penicillin epilepsy. EEG, electroencephalogram; EOG, electrooculogram. In: Wada JA, ed. *Kindling 4*. New York: Plenum Press; 1990:313–327; with permission.)

Epilepsies Characterized by Seizures on Awakening (Diurnal): Primary Generalized Epilepsies

The morphology of interictal discharges, including 3/sec spike-and-wave and polyspike-and-wave complexes,[15,29,77] is compatible with stimulus-evoked or recruited cortical EEG patterns resembling drowsiness. This may explain why interictal discharges arise during drowsy wakefulness.[32,37,77,78] Conversion to an ictal discharge pattern associated with myoclonic or tonic–clonic seizures could be precipitated by corticopetal influences originating in arousal cells of the hypothalamus, the brainstem reticular formation, or both, as follows.

Arousal cells in the magnocellular basal forebrain and in the posterior hypothalamus are also called waking-active neurons. These cells have direct projections to the entire neocortical mantle.[49,92,93] Sudden bursts of "excitatory" input from these arousal cells might exacerbate the diffuse, relatively mild cortical hyperexcitability thought to underlie this group of seizure disorders (e.g., Gloor[32]). One hypothesized mechanism is a direct (monosynaptic) effect mediated by normal or abnormal secretion of several transmitters such as acetylcholine (Ach) and/or histamine (e.g., Jones[49]).

Figure 9 shows spontaneous (Fig. 9A) and evoked (Fig. 9B) unit discharge of a waking-active neuron in the posterior hypothalamus during slow-wave sleep and awakening before and 1 hour after a subconvulsive dose of penicillin in a cat.[99] Note that spontaneous cellular discharge increases on awakening and is exacerbated at this time by penicillin (Fig. 9A). The

peristimulus histogram shows increased amplitude of evoked excitation and reduced duration of postexcitatory inhibition in the penicillin model of PGE on awakening (Fig. 9B; also see Fig. 7B).

Alternatively, indirect (polysynaptic) effects could be responsible. For example, waking-active neurons of the posterior hypothalamus and orexin-containing cells of the lateral hypothalamus also project to and synergize actions of the arousal cells in the ARAS,[74] including norepinephrine (NE), serotonin (5-HT), and/or Ach. These brainstem arousal cells in turn have widespread terminals in thalamus and cortex.[49,68,92,93,104] An impressive body of data supports the hypothesis that inhibition of arousal cells promotes synchronized thalamocortical discharges associated with NREM sleep and also the sleep-related interictal discharges in the penicillin and genetic models of awakening epilepsy.[3,28,53,103,104]

Sustained activation of the pontine arousal cells is thought to have tonic antiepileptic effects (e.g., Corcoran[16]; see Chapter 188), but the abrupt increase in discharge of these cells on awakening may be epileptogenic. For example, NE is thought to promote the ability to focus neuronal attention in wakefulness. The outcome is a coordinated sensorimotor act.[103] A surge of NE release on awakening might simply focus neuronal attention on and activate the epileptic neocortical cell populations in this group of seizure disorders. A similar effect could accompany the release of 5-HT and/or Ach.

Epilepsies Characterized by Seizures During Sleep (Nocturnal): Localization-Related Epilepsies

Seizures and interictal discharges arising during sleep could be provoked by monosynaptic and polysynaptic projections from sleep-active neurons of the anterior/preoptic hypothalamus to cortical or subcortical seizure foci. Hypothalamic sleep-active neurons suppress waking-active neurons located in the ARAS,[4,44,69] notably, the Ach, NE, and/or 5-HT cells of the pontine tegmentum. These cells in turn have widespread monosynaptic and polysynaptic projections to the entire neocortical mantle as well as to archicortical and subcortical limbic sites[49] and could thus precipitate seizure discharge during NREM sleep. The role of the thalamocortical system and its regulation of epileptogenic phasic events such as sleep spindles also cannot be overlooked (see Chapter 188).

Epilepsies in Which Seizures Occur Randomly (Day or Night): Symptomatic Generalized Epilepsies

Circadian patterns of ictal and interictal discharges are not prominent in these epileptic syndromes (e.g., Horita[41,42]). The extensive cerebral pathology associated with these syndromes could encompass the SCN, the hypothalamic generators of the sleep–wake cycle, and other brainstem and forebrain regions that ultimately express circadian rhythms.

Ultradian (<24-Hour) Rhythms and Seizure Events

Historically, the ultradian rhythm most often linked to epilepsy is called the basic rest–activity cycle

(BRAC).[12,105,107] The BRAC pervades the circadian sleep–wake cycle. During sleep, the synchronized EEG discharges of NREM sleep represent "rest" periods and alternate with the asynchronous EEG discharges of REM sleep, which represent "activity" periods. During waking, rest periods (drowsiness) alternate with activity periods (alert waking). In humans, this periodicity occurs at roughly 90-minute intervals. There is great individual variability, and 100- to 120-minute intervals have often been detected (e.g., Kellaway et al.[52]).

A second, more recently described ultradian rhythm refers to periodic microarousals, defined as a cyclic alternating pattern (CAP) of EEG desynchronization occurring on a background of prolonged, homogeneous EEG synchronization (noncyclic alternating pattern [NCAP]). CAPs have two components or phases.[114,115] Phase A corresponds to the initial or peak level of EEG desynchronization with sleep EEG transients, whereas phase B follows phase A and reflects a return to the stable synchronized-EEG NCAP state. Three different subtypes of CAP A have been identified and related to various seizure disorders. CAPs have been studied during NREM sleep, in which brief EEG microarousals are most readily detected (e.g., Parrino et al.[80]).

Clinical Findings

Ultradian BRAC seizure patterns are most evident in localization-related epilepsies of temporal or frontal lobe origin. In contrast to ictal events, IIDs with BRAC periodicities can occur in all seizure disorders. Ultradian CAP rhythms have been studied mostly in idiopathic epilepsies,[31,38,115,116] although studies have been performed in three types of localization-related epilepsies.[80,119] The observations are depicted in epileptic syndromes characterized by awakening, sleep, and random seizure patterns as follows.

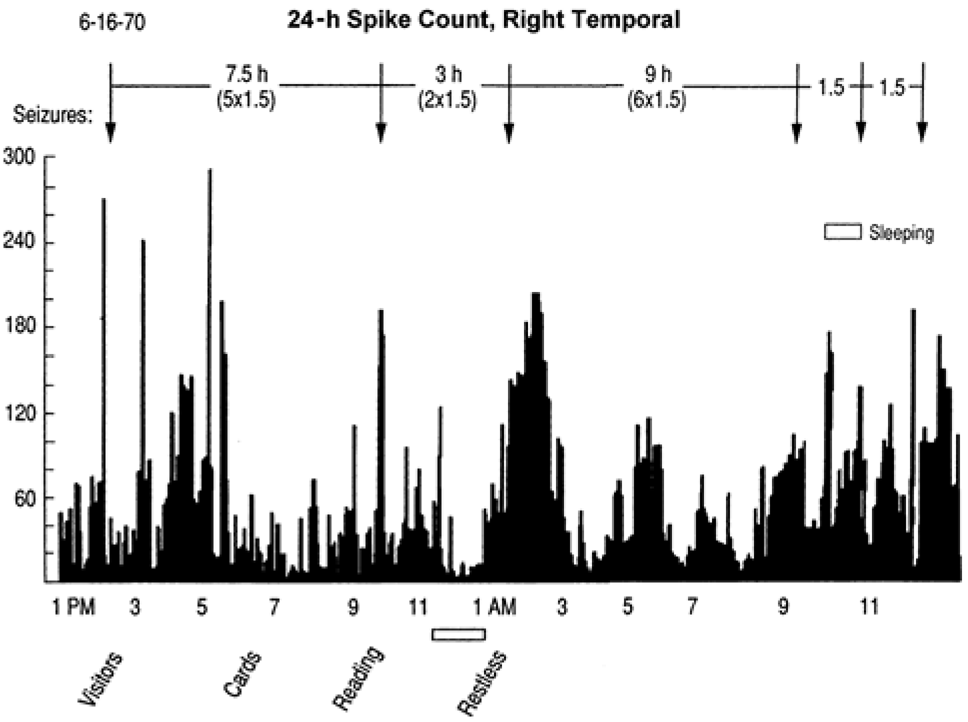

FIGURE 10. Timing of ictal and interictal discharges at 90-minute intervals in a patient with temporal lobe epilepsy. A 24-hour spike count per 4 minutes was recorded from the right temporal electrode of a patient with six seizures recorded during this period. Seizures (*arrows*) occurred at intervals or multiples of intervals of 1.5 hours. No distinct rapid-eye-movement sleep was recorded in the patient. (From Stevens JR, Lonsbury B and Goel SL. Seizure occurrence and interspike interval. *Arch Neurol*. 1980;26:409–411; with permission.)

Epilepsies Characterized by Seizures on Awakening (Diurnal): Primary Generalized Epilepsy

Seizures occur primarily on arousal from nocturnal sleep, but there are less prominent, secondary peaks on arousal from daytime naps and sometimes at sleep onset, as seen in Table 1.[33,57,119] The appearance of more than one peak constitutes an ultradian rhythm, but it does not reflect a BRAC pattern per se. Interictal discharges, on the other hand, can show strong ultradian rhythms corresponding to a BRAC pattern.[51,65,66,105,106,107,108]

Ultradian CAP patterns of IIDs have been studied most thoroughly in JME.[21] However, Terzano et al.,[114] who developed the CAP concept and methodology, studied a small and heterogeneous population of patients with various idiopathic (presumed genetic) seizure disorders[115,116] and found that the rate of spike-and-wave or polyspike-and-wave complexes is highest in the arousal phase (CAP A) and lowest in the sleep recovery phase (CAP B) when compared to NCAP. Seizure discharge is most often affiliated with k-complexes and bursts of slow waves, which are thought to represent phasic arousal events during CAP A.

Epilepsies Characterized by Seizures During Sleep (Nocturnal): Localization-Related Epilepsies

This group of epilepsies, especially those of temporal or frontal lobe origin, is known to be predisposed to ultradian seizures related to the BRAC.[11,106,107,108] Many authors have reported peaks in the timing of complex partial seizures and of interictal discharges, notably spikes and sharp waves, at about 90-minute intervals throughout the sleep–wake cycle,[11,106,107,108] as depicted in FIGURE 10.[107] Similar findings have been detected in animal models. An example is the prevalence of spontaneous convulsions emanating from kindled temporal lobe foci during the REM transition in FIGURE 7A.[99]

A CAP factor similar to that seen in awakening epilepsies also applies to certain sleep epilepsies, notably those of temporal or frontotemporal origin.[80] CAP modulation of IIDs in benign epilepsy with rolandic spikes (BERS) has not been detected.[118] The basis for this negative outcome is speculative. Amygdala-kindled kittens shows EEG microarousals associated with subclinical and possibly clinical seizures, which occur throughout the sleep–wake cycle at much shorter time intervals than the ~20-minute BRAC in cats and might reflect a CAP cycle.[100]

Epilepsies in Which Seizures Occur Randomly (Waking and Sleep): Symptomatic Generalized Epilepsies

These patients show weak ultradian seizure patterns. Some, such as those with West syndrome, can have demonstrable ultradian BRAC periodicities when a discernible REM cycle exists.[43,51,52,79]

Basic Mechanisms

The ultradian BRAC has been localized to the brainstem. This conclusion is based on its persistence in the brainstem but not the forebrain following transection at the midcollicular level (cerveau isolé preparation).[10,76,91,120] Transection findings are confirmed by other experimental methods such as selective lesion, extracellular unit, microdialysis, *c-fos*, and immunohistochemical studies (e.g., Baghdoyan and Lydic[4] and Beaussart[7]). The same brainstem neurotransmitters released during the awakening phase of the circadian sleep–wake cycle are also thought to serve as the brainstem generators of the BRAC. Discharge of NE and 5-HT cells in the medial and medial-lateral pontine tegmentum declines in the transition into REM, whereas Ach discharge in the dorsolateral pedunculopontine tegmentum increases and generates the phasic “arousal” events of the transition. These phasic arousal events are proposed to precipitate seizure discharge and its propagation at this time (Fig. 7A vs. Fig. 7B) (see Chapter 188).[37,99] The tonic discharge of Ach cells during REM is proposed to have antiepileptic effects in sustained periods of alert waking and REM (see Chapter 188). The combination of reduced cellular discharge and transmitter release of NE and 5-HT cells and increased Ach activity is mediated by local GABAergic interneurons (e.g., Baghdoyan and Lydic[4] and Lin et al.[60]).

Reduced NE and 5-HT release plus the phasic discharge bursts and chemical release of Ach cells at these times may promote ultradian ictal or IID manifestations or both. Because each cell type has widespread projections,[49,68] epileptogenic effects could be mediated by direct or indirect projections to epileptic cells anywhere in the brain. On the other hand, the periodic EEG microarousals associated with the arousal phase of CAP (i.e., CAP A) might reflect transient activation of the same brainstem arousal mechanisms regulating the BRAC or the forebrain hypothalamic mechanisms generating matutinal awakening.

Infradian (>24-Hour) Rhythms and Seizure Events

The existence of infradian or long-running rhythms, such as seasonal patterns, has been known for well more than a century.[22,24,34,35,56] Here, we provide two better-known examples relevant to seizure disorders.

Primary generalized epilepsies, which are characterized by seizures on awakening, have an age-dependent course paralleled by changes in the amplitude of EEG transients, such as the spike component of k-complexes. The k-complexes are associated with aborted arousals in sleep and with IIDs during sleep in this group of seizure disorders.[37,77,78] The clinical course also corresponds to the age-dependent secretory patterns of hormones and/or hormone-releasing factors such as melatonin, sex, and steroid-releasing factors. All of these chemicals have been implicated in arousal as well as in the ictal and interictal discharges in these epileptic syndromes.[83,91,125] Common genetic variables potentially related to an arousal dysfunction have been proposed to underlie these correlated age-dependent changes.[19,20,71]

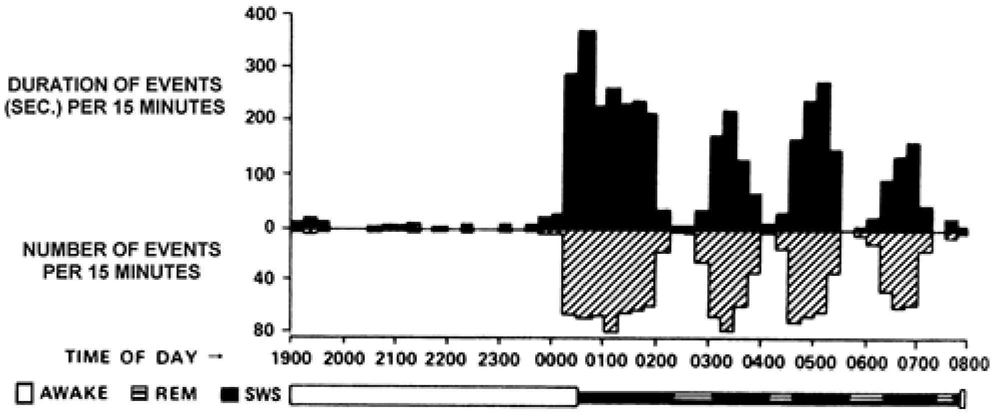

FIGURE 11. A decremental epileptic discharge pattern in which the duration and number of 3/sec spike-and-wave discharges per unit time peaks at the onset of non–rapid-eye-movement (NREM) sleep (here called slow-wave sleep [SWS]) and declines in successive NREM sleep cycles over the night. The suppression of spike-and-wave activity that occurs during REM sleep is comparable over successive REM cycles. Time of day on the abscissa is according to the 24-hour clock. The bar along the abscissa indicates the sleep or waking state: Unfilled, awake; filled, SWS; slanted lines, REM sleep. (From Kellaway P, Frost JD Jr, Crawley JW. Time modulation of spike-and-wave activity in generalized epilepsy. *Ann Neurol*. 1980;8:491–500; with permission.)

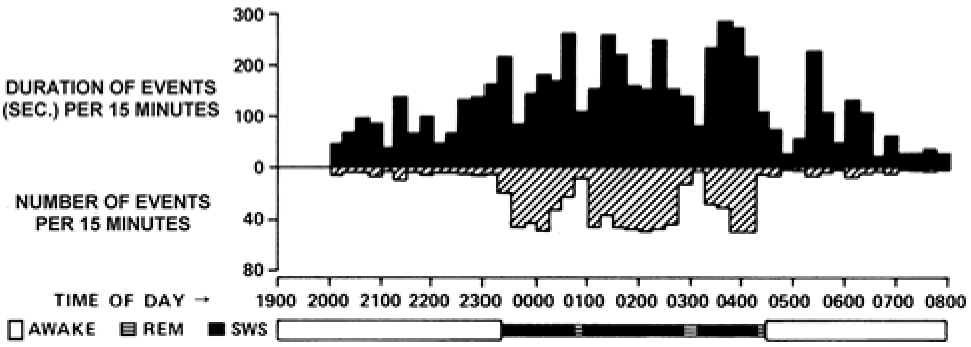

FIGURE 12. An incremental–decremental epileptic discharge pattern in the duration and number of 3/sec spike-and-wave discharges per 15 minutes. The augmenting effect of non–rapid-eye-movement (NREM) sleep (here called slow-wave sleep [SWS]) on 3/sec spike-and-wave discharges at first increases and then declines toward the end of sleep. An equivalent reduction in spike-and-wave activity occurs in each REM period. Time of day along the abscissa is according to the 24-hour clock. The bar along the abscissa indicates the sleep or waking state: Unfilled, awake; filled, SWS; slanted lines, REM sleep. (From Kellaway P, Frost JD Jr, Crawley JW. Time modulation of spike-and-wave activity in generalized epilepsy. *Ann Neurol*. 1980;8:491–500; with permission.)

Hormonal regulation of various seizure disorders is detailed elsewhere (see Chapters 194,195,196,197,198), including catamenial epilepsy. Hormonal changes associated with catamenial epilepsy also affect monoamines, as also covered elsewhere. Once menses develop, a monthly or near-monthly periodicity in seizures is exhibited before or during menstruation in 30% to

70% of women with epilepsy (e.g., Foldvary-Schafer et al.[25]). Once menopause occurs, a monthly cycle disappears.

Interactions Between Periodicities

Most ictal and interictal discharge patterns show admixtures of peaks and troughs related to circadian and ultradian variables as well as to different sleep stages (e.g., Kellaway and Frost[51] and Kellaway et al.[52]), sometimes regardless of epileptic syndrome. For example, circadian peaks are seen at sleep onset in centrotemporal spikes (Fig. 3) and in 3/sec spike-and-wave discharges (Fig. 11).[52] During subsequent ultradian NREM/REM cycles, a stepwise decline in seizure discharges may occur during successive NREM cycles (a so-called decremental pattern) and alternate with a near-complete suppression during REM epochs. FIGURE 12 illustrates a different pattern, in which spike-and-wave discharges at first increase and then decrease during successive NREM cycles (a so-called incremental–decremental pattern), again alternating with a suppression of spike-and-wave activity during REM sleep.[52] With this diversity, a logical question is: How do different biologic rhythms interact with state-related variables to generate different temporal seizure patterns?

This is a complex issue that is partially addressed by the statistical model of sleep-related epileptic discharges illustrated in FIGURE 13.[51] Here, the joint probabilities associated with hypothesized circadian (Fig. 13A) and ultradian (Fig. 13B) rhythms are calculated to predict the distribution of 3/sec spike-and-wave complexes during 8-hour sleep periods as a function of different sleep onset times (Fig. 13C–F). The model assumes a constant sinusoidal 24-hour circadian rhythm (Fig. 13A) and a sleep-related, sinusoidal 1.5-hour ultradian rhythm (Fig. 13B). The apexes of these curves correspond to peak circadian and ultradian effects. The 1.5-hour ultradian rhythm represents the NREM–REM cycle, which is shown only for one sleep onset time in FIGURE 13B but is assumed to be present throughout each hypothetical 8-hour sleep period depicted in FIGURE 13C–F.

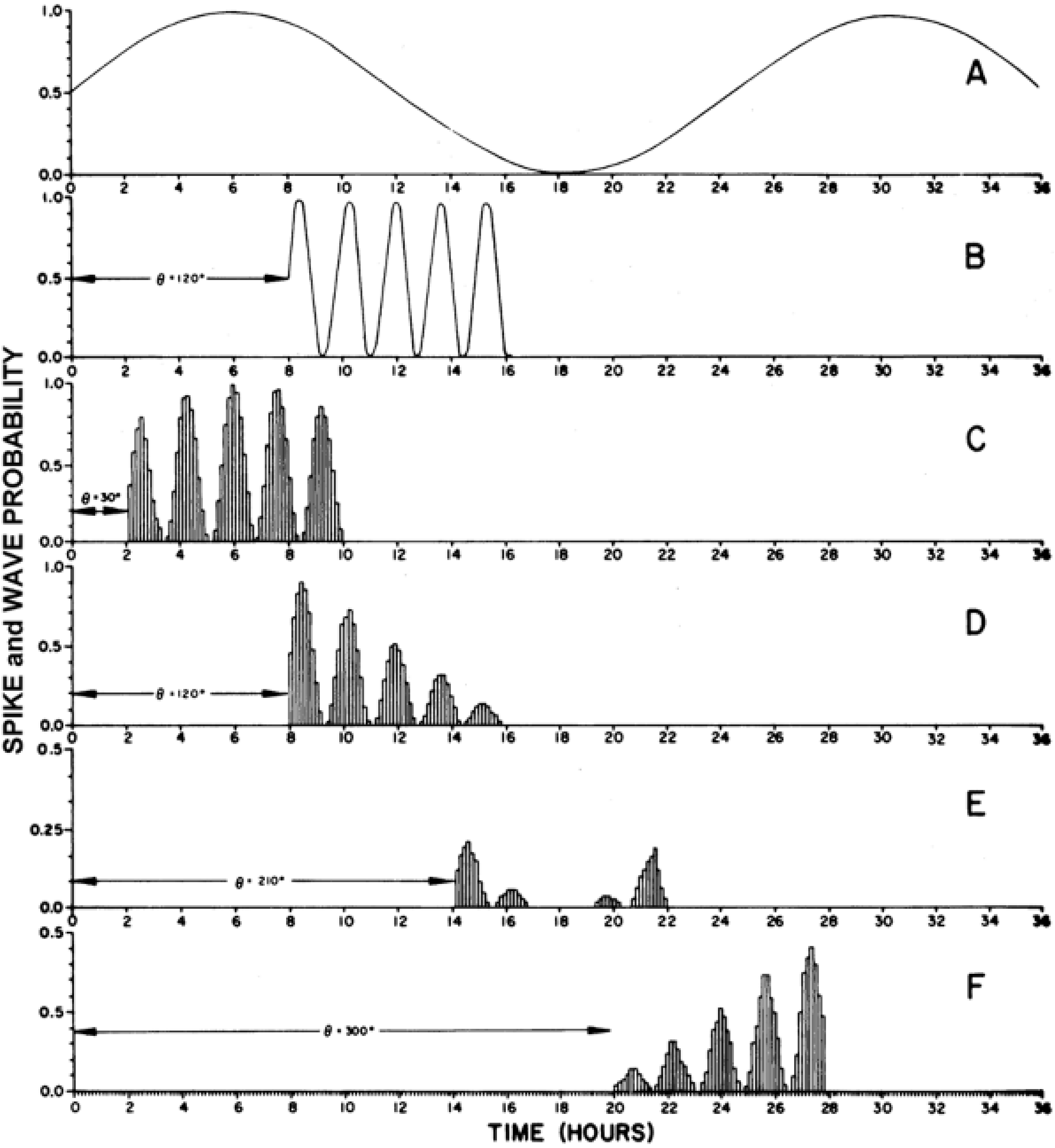

FIGURE 13. A statistical model showing the circadian (**A**) and ultradian (**B**) periodicities and how they predict the distribution of spike-and-wave probabilities over 8-hour sleep cycles as a function of sleep onset time. **C:** Sleep onset at 30° from A results in an incremental–decremental pattern in which spike-and-wave incidence at first increases after sleep onset and then subsides at the end of the sleep cycle. **D:** A 120° sleep onset lag results in a decremental pattern in which peak spike-and-wave discharge occurs at sleep onset and declines thereafter. **E:** A 210° sleep-onset lag with a bimodal pattern in which spike-and-wave incidence peaks at the beginning and end of the sleep cycle. **F:** A 300° sleep-onset lag produces an incremental pattern in which spike-and-wave incidence increases with the duration of sleep. (From Kellaway P, Frost JD Jr. Biorhythmic modulation of epileptic events. In: Pedley TA, Meldrum BS, eds. *Recent Advances in Epilepsy*, vol. 1. London: Churchill Livingstone; 1983:139–154, with permission.)

Spike-and-wave discharge probabilities range from 0.0 to 1.0 on the ordinate. The highest joint probabilities are generated when the apexes of circadian and ultradian curves coincide. Conversely, the lowest joint probabilities are predicted when the troughs of the two curves coincide. Intermediate probabilities reflect interaction between the heights of the

different curves at a given time. In FIGURE 13C–F, spike-and-wave probabilities are plotted as a function of different sleep onset times, expressed as phase angle θ from circadian time 0 on the abscissa.

Figure 13C shows that when sleep onset occurs at a 30° phase angle, the first two ultradian cycles occur on the ascending slope of the circadian curve, the middle cycle occurs at the apex of both the circadian and ultradian BRAC curves, and the last two ultradian cycles fall on the descending slope of the circadian curve. This interaction generates an incremental–decremental pattern like that depicted in FIGURE 12, in which spike-and-wave incidence at first increases in successive NREM sleep bouts, peaks in the middle, and declines toward the end of sleep.

Figure 13D shows that when sleep onset occurs at a 120° phase angle, the first ultradian cycle occurs at the apex of the circadian and ultradian curves, and the subsequent ultradian cycles fall on a progressively descending slope of the circadian curve. This generates a decremental probability pattern similar to those seen in Figures 3 and 11, in which epileptic discharge rates decline over successive NREM cycles.

Figure 13E shows that when sleep onset occurs at a 210° angle, the first two ultradian cycles occur on the descending slope of the circadian curve, the middle at the base of the circadian curve, and the last two on the ascending slope of the circadian curve. This generates a bimodal probability pattern similar to that seen in FIGURE 2, in which spike-and-wave discharge peaks at the beginning and end of sleep.

Figure 13F shows that when sleep onset occurs at a 300° angle, successive ultradian cycles fall on a progressively ascending circadian curve. This generates an incremental spike-and-wave probability distribution, which is the opposite of the pattern predicted in FIGURE 13D.

Notwithstanding limitations of this model (e.g., waking is ignored), it can predict epileptiform discharge patterns that are not explained by state-dependent variables such as NREM versus REM sleep stage alone. For example, sleep stage does not seem to explain distinctive patterns observed over the course of the sleep cycle, particularly during successive NREM sleep epochs. Effects of hypothesized phase advance and delay manipulations, as exemplified by irregularities in sleep habits in FIGURE 13, suggest how time-dependent factors associated with chronobiology, provide this modulation.[51,52]

Subsequent experimental findings did not support these hypotheses about sleep displacement effects.[50] For example, acute sleep delay (6 hours) sufficient to produce a 90° phase shift did not significantly alter the distribution pattern of 3/sec spike-and-wave discharges over successive NREM epochs during a 12-hour sleep recording period when compared to the two, preceding 12 baseline polysomnograms. The authors concluded that the presence of sleep per se is the critical regulatory factor and that the timing of spike-and-wave discharge is secondarily modulated by ultradian REM-NREM cycles.

Summary and Conclusions

Clinical Findings

1. There are no studies of interictal discharges and few studies of seizures in which endogenous circadian “time of day” patterns have been clearly differentiated from the sleep–wake cycle. This gap needs to be filled.

2. The timing of IIDs in sleep and waking states sometimes corresponds to the timing of seizures, but there is no

empirical basis for suggesting that IIDs routinely predict state-dependent seizure occurrence in humans or animals (e.g., Herman et al.,[40] versus Marlow et al.[64]). This dissociation prompted Stevens et al.[108] to state, “all that spikes isn't fits,” meaning that an IID is a seizure that did not occur. The reason that IIDs do not generate seizures, especially in seizure-prone sleep and waking states, is still enigmatic, although some aspects are addressed in Chapter 188.

3. Circadian (24-hour) state-related ictal and to some extent interictal discharge rhythms are strong in epilepsies with awakening seizures, which are primary generalized epilepsies of hereditary or idiopathic origin (e.g., absence and benign juvenile myoclonic epilepsy with or without tonic–clonic convulsions). Circadian state-related seizure patterns are also strong in sleep epilepsies, which often originate from temporal or frontal seizure foci, but also include BERS, benign epilepsy with occipital spikes, Landau-Kleffner syndrome, and ESES. Circadian sleep–wake seizure patterns are rarely seen in epilepsies with extensive organic complications (e.g., West syndrome).
4. Ultradian (<24-hour) state-dependent ictal patterns are most frequently detected in epilepsies with awakening or sleep seizures. Ultradian interictal discharge patterns also frequently occur in various seizure disorders regardless of the timing of ictal events. Ultradian interictal discharge patterns reflect both 90- to 120-minute BRAC cycles and the briefer CAP cycles associated with transient EEG arousals, especially k-complexes and bursts of slow waves.
5. Infradian rhythms, as seen in catamenial epilepsy, are not contingent on seizure type, timing, or etiology. Other long-running rhythms can be selective. For example, primary generalized epilepsies of hereditary origin and good prognosis show an age-dependent course, here meaning a relatively specific age at onset and spontaneous remission.
6. Multiple periodicities seem to interact with other factors, such as sleep stage, to generate diverse but predictable temporal seizure discharge patterns.

Basic Mechanisms

1. The circadian sleep–wake cycle has been localized to the hypothalamus. The posterior histaminic, anterior cholinergic, and possibly the lateral hypocretin-secreting areas induce awakening, whereas the GABAergic and galaninergic cells of the anterior hypothalamic/preoptic basal forebrain area induce sleep. These arousal- or sleep-active cells could provoke seizures via direct or indirect innervation of the epileptic cells involved in the genesis of awakening or sleep epilepsies.
2. The ultradian BRAC has been localized to the brainstem, likely the pontine tegmentum. Activation of BRAC-related ictal or interictal discharges could result from increased electrochemical activity via direct or indirect projections from these reticular formation neurons to epileptic cells anywhere in the brain. Similarly, activation of ultradian CAP-related interictal discharges could reflect transient increases in electrochemical activity of cholinergic, noradrenergic, and/or serotonergic cells in the brainstem ARAS or of the forebrain hypothalamic generators of arousal.
3. Infradian rhythms seem governed by age-dependent genetic and hormonal influences.

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Chapter 188

Sleep

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Introduction

Sleep states influence the expression or suppression of seizures. The two main sleep states, non–rapid-eye-movement (NREM) sleep and rapid-eye-movement (REM) sleep, have different physiologic components and contrasting effects on generalized ictal and interictal discharges (IIDs). Epileptiform discharges are likely to propagate during NREM sleep and its transitional EEG “drowsy” periods. In contrast, REM sleep is resistant to the propagation of epileptic potentials even though focal IIDs persist at this time.

This chapter describes the distribution of ictal and IID events during NREM versus REM sleep, differentiates NREM from REM sleep substrates, and suggests how the neural generators for seizure-prone or seizure-resistant sleep states modulate the timing of seizures. We also discuss the effects of seizures, antiepileptic drugs (AEDs), and vagus nerve stimulation on sleep. Finally, we consider the impact of sleep disorders and sleep deprivation on seizures.

Seizures and Interictal Discharges in Non-Rapid-Eye-Movement Versus Rapid-Eye-Movement Sleep

Clinical Findings

During NREM sleep, focal and generalized epileptic discharges are common, even if clinical seizures do not occur.[52,78,95] During REM sleep, generalized epileptiform discharges are infrequent. Focal interictal discharges are less numerous but persist during REM sleep and are highly localized (e.g., Sammaritano et al.[113]). Seizures are common during NREM sleep but rarely occur during REM sleep.[53,93,95] The effects of NREM sleep versus REM sleep on interictal and ictal epileptiform discharge depend somewhat on the epileptic syndrome (Table 1).

Primary Generalized Epilepsies of Genetic or Idiopathic Origin

In the primary generalized epilepsies (PGEs), interictal and ictal discharges begin simultaneously in all or most of the cerebral cortex bilaterally.[25,48,95] Most PGEs are thought to be genetic with age-related penetrance (e.g., Delgado Escueta et al.[32] and Niedermeyer[95]). Examples are childhood and juvenile absence epilepsy and juvenile myoclonic epilepsy (JME), which can occur with or without primary generalized tonic–clonic convulsions[2,25,95] (see Chapters 239, 240, and 244).

These primary generalized epilepsies presumably result from a diffuse abnormality of cortical excitability that is less severe than that seen with a focal epileptogenic lesion.[48,49] This concept is illustrated in FIGURE 1, which contrasts the surface electrographic and intracellular discharge patterns in cortex associated with normal rhythmic activity (Fig. 1A), PGE (Fig. 1B), and localization-related epilepsies (Fig. 1C).

In PGE, the membrane potentials of individual cells are within normal range, and intracortical inhibitory mechanisms are generally intact. The underlying neuronal hyperexcitability is expressed only in populations of cortical neurons entrained to a synchronous burst–pause firing pattern by the glutaminergic and aspartate-mediated thalamocortical volleys that normally evoke spindles and recruiting responses. Sequences of cortical excitatory postsynaptic potentials (EPSPs) alternate with inhibitory postsynaptic potentials (IPSPs) to generate spindles and recruiting responses. The sequential pattern persists in PGE but is altered by the increased amplitude of temporally and spatially summed EPSPs and IPSPs. The enhanced population excitatory response generates the action potentials underlying the spike or multispike component and is followed by a longer-lasting period of neuronal silence that gives rise to the slow-wave component of the complex (Fig. 1B, left). Preservation of γ-aminobutyric acid (GABA)-mediated intracortical inhibitory mechanisms is considered critical to the generation of the slow component and terminates the spike train, which, if unopposed, could lead to a convulsion (Fig. 1B, right).

Interictal and ictal discharges often arise during transitional “drowsy” arousal periods, which occur throughout the sleep–wake cycle.[52,57,95] For example, awakening from sleep presents a high risk for the occurrence of IIDs and/or ictal seizure events in idiopathic generalized epilepsies such as awakening “grand mal” seizures and juvenile myoclonic epilepsy. Such periodicities imply mediation of seizure events by both circadian and ultradian cycles. Chronobiology issues are primarily covered in Chapter 187.

This chapter focuses mainly on *stable* sleep, defined by the physiologic components that persist after initial onset of a specific NREM or REM sleep stage (e.g., Carskadon and Dement[21]) vis-à-vis IID and ictal events. Below, we describe sleep-related interictal and ictal discharges in this group of seizure disorders for (a) light NREM sleep (stages 1 and 2), (b) deep NREM sleep (stages 3 and 4), and (c) REM sleep.

Light Non–Rapid-Eye-Movement Sleep: Stages 1 and 2.

Interictal discharges, such as typical spike-and-wave (3/sec) and multispike-and-wave or polyspike-and-wave complexes, are more often detected in light NREM sleep (e.g., Niedermeyer[95]) than in deep NREM sleep or in REM sleep (e.g., Carskadon and Dement[21]). The longest trains of typical spike-and-wave complexes (>5 seconds) occur in stage 1 NREM sleep. Discharges of similar duration in an awake patient would typically be accompanied by a clinically evident seizure.

The next-most-prominent time for spike-and-wave and multispike- or polyspike-and-wave complexes is stage 2 NREM sleep. During this stage, IID complexes are frequent but of short duration. They usually coincide with sleep transients, which have an EEG configuration similar to epileptiform potentials[95] such as sleep spindles, K-complexes, vertex waves, and bursts of slow waves. Some evidence suggests that these events, particularly K-complexes, reflect aborted arousals during sleep.[95] For example, exogenous stimulation during NREM sleep, such as a loud noise, can evoke any of these transient waveforms.

Table 1 Generalized epileptiform discharges by sleep states in three epilepsy syndromes with convulsions at different times in the sleep-wake cycle

	Interictal discharges		Ictal discharges	
Epilepsy syndrome/circadian seizure rhythm	**NREM**	**REM**	**NREM**	**REM**
Primary generalized epilepsies of idiopathic or hereditary origin: awakening epilepsies	Common	Rare	Rare[a]	Rare
Localization-related epilepsies with or without known pathology: sleep epilepsies	Common	Rare[b]	Common	Rare
Symptomatic epilepsies with extensive encephalopathy: sleep and waking epilepsies	Common	Rare[c]	Common	Rare[c]

NREM, non-rapid-eye-movement sleep; REM, rapid-eye-movement sleep.

[a] Except stage 1 (≥ trains of spike-wave complexes would likely be associated with an absence seizure in waking).

[b] Note maximal focalization.

[c] As long as REM is intact.

Adapted from Shouse MN, da Silva AM, Sammaritano M. Sleep. In: Engel J Jr, Pedley TA, eds. *Epilepsy: A Comprehensive Textbook*, Philadelphia: Lippincott-Raven; 1997:1929–1942; **with permission**.

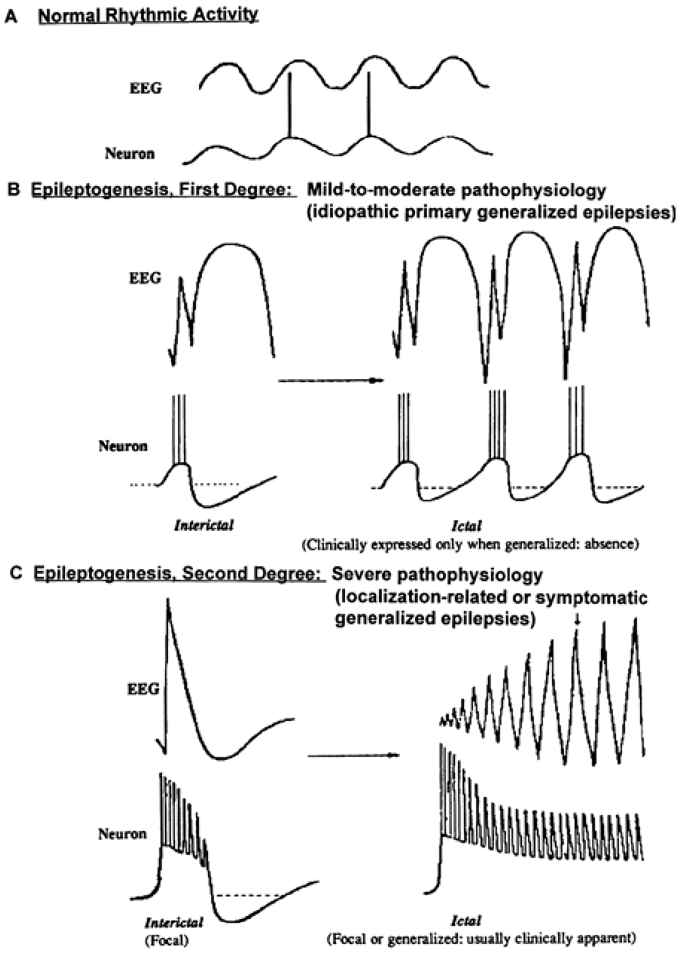
A Normal Rhythmic Activity
EEG
Neuron
B Epileptogenesis, First Degree: Mild-to-moderate pathophysiology (idiopathic primary generalized epilepsies)
EEG
Neuron
Interictal
Ictal
(Clinically expressed only when generalized: absence)
C Epileptogenesis, Second Degree: Severe pathophysiology (localization-related or symptomatic generalized epilepsies)
EEG
Neuron
Interictal
(Focal)
Ictal
(Focal or generalized: usually clinically apparent)

FIGURE 1. Relationship between surface electroencephalogram (EEG) and intracellularly recorded activity of cortical neurons in cats without epilepsy **(A)**, with primary generalized epilepsy (PGE) induced systemically or by diffuse, dilute cortical application of penicillin **(B)**, and with partial epilepsy induced by local application of higher-dose penicillin **(C)**. Normal rhythmic background activity **(A)** is contrasted with two types of interictal **(left)** and ictal **(right)** epileptic conditions representing two degrees of epileptogenesis seen in arousal-related **(B)** or in sleep-related and symptomatic **(C)** seizure disorders. (Adapted from Gloor P. Generalized epilepsy with spike-wave discharge: a reinterpretation of its electroencephalographic and clinical manifestations. *Epilepsia*. 1979;20:571–588; with permission.)

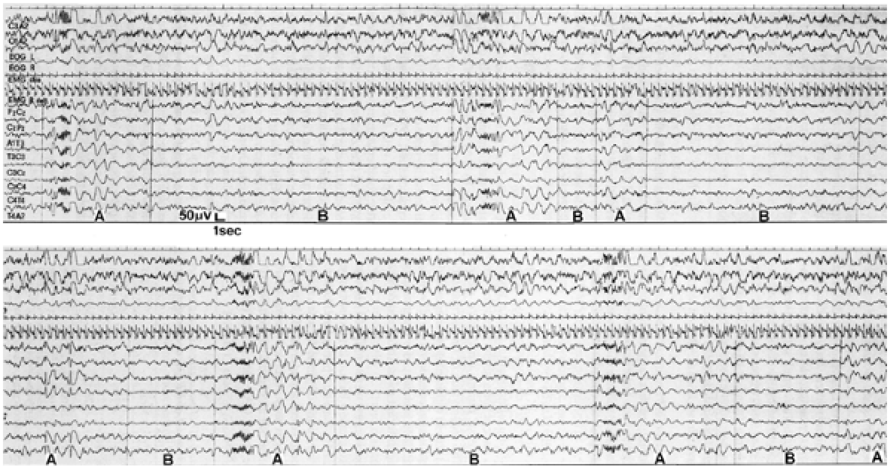

FIGURE 2. Polyspike-and-wave complexes associated with sleep spindles in juvenile myoclonic epilepsy (JME). Spindles and other sleep electroencephalogram (EEG) transients are thought to represent aborted arousals during sleep, and both aborted and actual arousals can provoke seizure events. This conclusion is supported by the higher incidence interictal discharges during the "arousal" phase **(A)** versus the reduced "arousal " phase **(B)** of Terzano's cyclic alternating patterns[142] (see Chapter 187 for more detail) and also by reports (e.g., Touchon[143]) that induced or spontaneous behavioral arousal from sleep most often provokes clinical seizure manifestations in JME. (Reprinted from Gigli GL, Calia E, Marciani MG, et al. Sleep microstructure and EEG epileptiform activity in patients with juvenile myoclonic epilepsy. *Epilepsia*. 1992;333:799–804; with permission.)

Figure 2 shows polyspike-and-wave complexes, which occur in relation to sleep spindles during the "arousal phase" of Terzano's cyclic alternating pattern (CAP) in a patient with juvenile myoclonic epilepsy (JME). CAP refers to sequences of transient electroclinical events that are distinct from homogeneous background EEG activity in NREM sleep and recur at up to 1-minute intervals.[142] See Chapter 187 for an explanation of ultradian rhythms, including CAPs (e.g., Parrino et al.[100] and Terzano et al.[142]). For the purpose of this chapter, note that induced or spontaneous behavioral arousals from sleep most often provoke clinical seizure manifestations in JME (e.g., Touchon[143]), regardless of CAPs.

Deep Non–Rapid-Eye-Movement Sleep: Stages 3 and 4.

Deep NREM sleep stages are usually considered least likely to activate typical spike-and-wave and multispike-and-wave or polyspike-and-wave complexes. However, some evidence suggests that deep NREM sleep is equally if not more conducive than light NREM sleep to these IIDs.[110,117] The IID trains are briefer and less organized in deep NREM than in light NREM sleep. This probably results from the prolonged hyperpolarization of thalamocortical cells[1,135,137] that generate the delta-wave oscillation of deep NREM and disrupt the rhythmic burst–pause discharge pattern as well as the morphology of spike-and-wave and multispike-and-wave complexes seen in light NREM sleep.

Rapid-Eye-Movement Sleep.

Generalized IIDs can occur during stable REM sleep (e.g., Billiard[17]) but are uncommon. "Breakthrough" generalized IIDs are less diffuse in REM than in NREM sleep. Even when generalized epileptic EEG potentials do occur in REM sleep, there is rarely clinical accompaniment.[53,93,113,114]

Localization-Related Epilepsies

This group of seizure disorders is thought to result from one or more focal regions of cerebral dysfunction (e.g., Commission Report[25]). Localization-related epilepsies are thought to reflect a more severe pathophysiology than that seen in PGE because individual neurons in the focus exhibit a sudden depolarization shift representing summated or giant EPSPs.[48] Depolarization shifts are characterized by high-amplitude, long-lasting depolarizations with superimposed high-frequency action potentials corresponding to spikes and sharp waves on the surface. Recurrent GABAergic inhibitory mechanisms are present but impaired, as evidenced by the absence of rebound inhibition during interictal discharge (Fig. 1C, left).[48,49] The intense hyperexcitability of focal epileptic neurons could increase the likelihood of seizure discharge propagation in response to synchronous bursts of excitatory synaptic inputs during NREM sleep (Fig. 1C, right).

Figure 3 shows that a spindle-like train of high-frequency epileptiform discharge in depth electrodes precedes seizure onset (Fig. 3A) and propagation during NREM in a patient with temporal lobe epilepsy (TLE).[73] It was concluded that, unlike PGE, EEG and behavioral arousal events most often follow seizure onset,[73] although others have concluded

that localization-related seizures are often precipitated by behavioral or EEG arousals during NREM sleep (e.g., Silvestri et al.[134]).

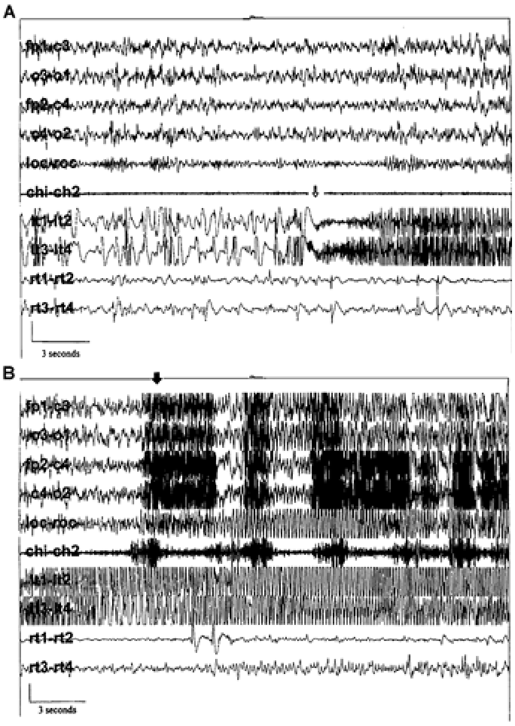

FIGURE 3. Combined scalp electrode (first six channels) and intracranial montage (last four channels). Lt1-lt2 and lt3-lt4, left temporal depth electrode contacts; rt1-rt2 and rt3-rt4, right temporal depth electrode contacts. Other depth electrode contacts are not shown. Calibration for scalp electrodes is 100 μV. Each figure represents 30 seconds. The open arrow in panel A indicates the intracranial electrode seizure onset in the left temporal depth electrode contacts, characterized by the cessation of interictal epileptiform discharges and their replacement by high-frequency sinusoidal activity. The solid arrow in panel B indicates the clinical arousal from sleep noted on the videotape, marked by myogenic artifact. (Reprinted from Malow BA, Bowes RJ, Ross D. Relationship of temporal lobe seizures to sleep and arousal: A combined scalp–intracranial electrode study. *Sleep*. 2000;23:231–234; with permission.)

There is significant variation in the severity of specific localization-related epileptic syndromes, based upon differences in medical refractoriness, spontaneous remission, and organicity.[91,121,123] Etiologies include but are not limited to trauma (see Chapter 253), lesions (see Chapter 251), and/or genetics (e.g., autosomal-dominant nocturnal frontal lobe epilepsy [ADNFLE] and some temporal lobe epilepsies; see Chapters 248, 249 and 255). Localization-related epilepsies with frontal or temporal lobe foci tend to be associated with more frequent clinically evident seizures, are more likely to be medically refractory[119] (although there are notable exceptions; e.g., nocturnal paroxysmal dystonia and ADNFLE), and are less likely to spontaneously remit than are the so-called "benign localization-related epilepsies." Regardless of these differences, localization-related epilepsies are most likely to display interictal and ictal discharges during NREM sleep.[7,8,9,40,53,57,58,78,91,95,121]

Table 2 Interictal discharges (IIDs) and visually scored sleep stage in 21 patients with medically refractory temporal lobe epilepsy

Sleep stage	IIDs	Total minutes	Average IIDs per minute
REM	179	1,327.5	0.135
Stage 1	393	1,118.5	0.331
Stage 2	2,193	4,284	0.512
Stage 3/4	882	883.5	0.998
Total	3,647	7,683.5	0.475

Arousals: Fewer than 1% of IIDs were preceded or followed by an arousal from sleep (defined as a shift of frequency to the alpha or theta range for at least 3 s).

Reprinted from Malow BA, Lin X, Kushwara R, et al. Interictal spiking increases with sleep depth in temporal lobe epilepsy. *Epilepsia*. 1998;39:1309–1316; with permission.

Frontal and Temporal Lobe Epilepsies.

Frontal and temporal lobe epilepsies comprise the largest group of localization-related seizure disorders[25,90] (see Chapter 25) and the largest group of "pure sleep epilepsies":[57,58] Up to 59% of patients have been reported to exhibit convulsions mostly or only during sleep.[57,91] Recent evidence indicates that secondary generalization during sleep is less prominent in frontal than temporal lobe epilepsies, although 55% of secondary generalized complex partial seizures occur in sleep regardless of onset site or the timing of other seizure types.[53] In addition, IIDs, such as anterior spikes or sharp waves, have higher amplitudes, longer durations, and rounder peaks in NREM than in other sleep or waking states (e.g., Frost et al.[40]).

Although both clinical seizures and IIDs are more common in NREM sleep than in REM sleep, evidence suggests that deep NREM sleep is the most vulnerable period for IID,[78,113] whereas lighter NREM sleep is the most vulnerable period for clinical seizures.[53,93] This dissociation between clinical seizures and IIDs is illustrated by comparing Table 2[78] to FIGURE 4.[53] Table 2 shows that the incidence of IIDs per minute peaks during NREM stages 3 and 4 sleep,[78] whereas FIGURE 4 shows a peak in the incidence of secondary generalized seizures in stage 2 sleep.[53]

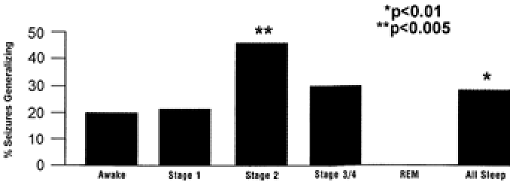

FIGURE 4. Percentage of partial seizures undergoing secondary generalization of complex partial seizures during various sleep stages. Sleep promoted the secondary generalization of seizures (*n* = 613 partial seizures in 133 patients) from all locations assessed (temporal lobe, mesial temporal lobe, neocortical temporal lobe, and occipital or parietal lobes) except the frontal lobe. REM, rapid-eye-movement sleep. (Reprinted from Herman ST, Walczak TS, Bazil CW. Distribution of partial seizures during the sleep–wake cycle: differences by seizure onset. *Neurology* 2001;56:1453–1459; with permission.)

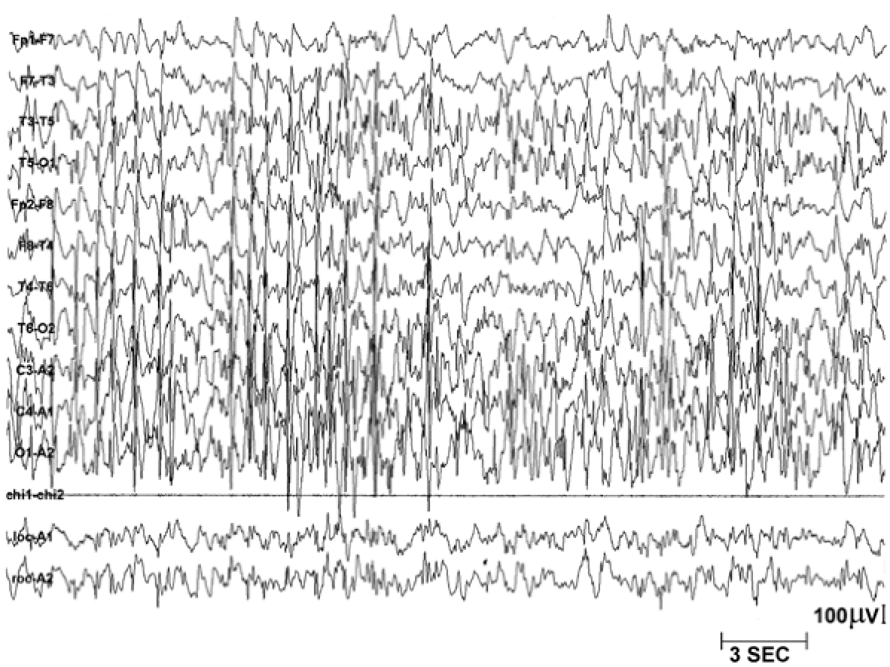

FIGURE 5. This 30-second epoch depicts non–rapid-eye-movement (NREM) sleep in an epileptic patient with electrical status epilepticus during sleep (ESES), also known as the syndrome of continuous spike-waves during slow-wave sleep (CSWS). The interictal discharges (IIDs) are so frequent that NREM sleep cannot be differentiated accurately into stages. Paroxysmal events in sleep and the EEG were recorded at 7 μV/mm. (Reprinted from Marzec ML, Malow BA. Approaches to staging sleep in polysomnographic studies with epileptic activity. *Sleep Med*. 2003;4:409–417; with permission.)

Several authors have emphasized a connection between REM sleep and partial or complex partial seizures originating from temporal lobe foci. However, most of these seizures occurred during NREM transitional states to or from REM rather than in stable REM sleep (e.g., Cadhillac[19] and Shouse et al.[123]). Because REM sleep transitions reflect an ultradian rhythm, this topic is described in more detail in Chapter 187. Herman et al.[53] saw few focal and no secondary generalized seizures during REM in a large series with 613 partial seizures in 133 patients regardless of seizure onset site, and Minecan et al.[93] noted that only 5% of seizures occurred during REM sleep in a separate series with 117 seizures in 55 patients. Neocortical seizures can be an exception (e.g., Mendez and Radtke[91]). Other evidence of the protective effects of REM sleep include the correlation between elevated REM percentages and reduced seizure incidence in human TLE[104] as well as the relative difficulty in evoking seizures[20] and the absence of

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spontaneous seizures during REM sleep in amygdala-kindled cats.[124,125]

Benign Localization-Related Seizure Disorders.

Examples of "benign" localization-related seizure disorders are benign epilepsy with centrotemporal spikes (BECT, also called benign rolandic partial epilepsy; see Chapter 236), benign occipital localization epilepsies (see Chapters 237 and 238), electrical status epilepticus during sleep (ESES; see Chapter 242), and Landau-Kleffner syndrome (acquired epileptic aphasia; see Chapter 242). Like seizure disorders of deep temporal or frontal lobe origin, these epilepsies are associated with diffuse IIDs during NREM sleep and maximal localization during REM sleep. Unlike many seizure disorders of temporal or frontal lobe origin, these childhood seizure disorders are considered benign because the seizures are responsive to AEDs and are likely to remit spontaneously (e.g., Mendez and Radtke[91] and Shouse[121]). Patients may be referred for a variety reasons other than seizures (e.g., slow progress in school in ESES, sudden deterioration of language skills related to auditory aphasia in Landau-Kleffner syndrome), and the seizure disorder may only be noted in a polysomnogram. FIGURE 5 shows an example of ESES, in which spike and wave discharges occupy at least 85% of NREM sleep. These types of pervasive seizure discharges in sleep are hypothesized to generate the nonepileptic symptoms of ESES and Landau-Kleffner syndrome as well, even though clinical seizures are rare and may not occur at all. In both ESES and Landau-Kleffner syndrome, cognitive, social, and linguistic anomalies tend to mitigate with seizure remission, but residual "nonepileptic" effects often persist (e.g., Mendez and Radtke[91] and Shouse et al.[121]).

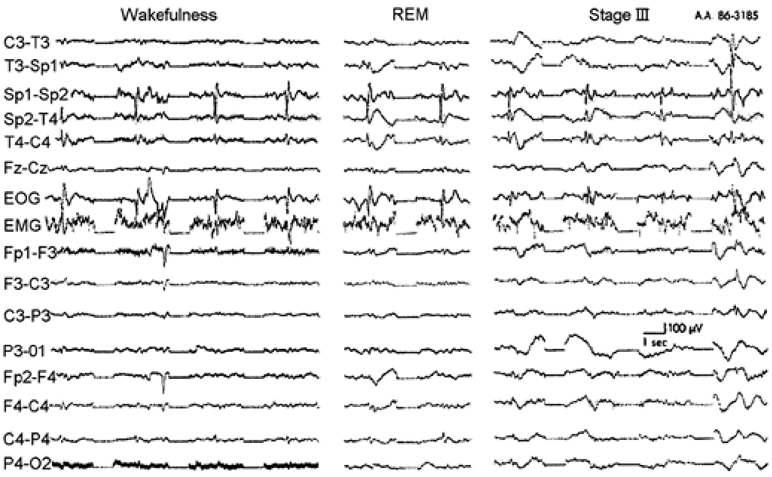

FIGURE 6. Electroencephalogram from scalp and sphenoidal electrodes during wakefulness, sleep stage 3, and rapid-eye-movement (REM) sleep for a patient with a temporal lobe focus. Sp1 and Sp2 are the left and right sphenoidal electrodes, respectively. Note the similarity of spiking fields in wakefulness and bilateral spiking in stage 3. Also note the maximal localization during REM. (Reprinted from Sammaritano M, Gigli G, Gotman J. Interictal spiking during wakefulness and sleep and the localization of foci in temporal lobe epilepsy. *Neurology*. 1991;41:290–297; with permission.)

Interictal Discharge Versus Ictal Seizure Discharge Propagation During Non–Rapid-Eye-Movement Sleep.

Differences in ictal seizure discharge propagation patterns cannot entirely be attributed to whether or not the localization-related seizure disorder is "benign." An unanswered question is why IIDs, which

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spread during NREM sleep, do not end in secondary generalized seizures. One possibility is the apparent location of the seizure focus. For example, many of the "benign" localization-related epilepsies appear to have neocortical foci. Ictal seizure discharge propagation seems to occur less often from neocortical foci than from subcortical sites during NREM sleep, as described previously. The presence of "inhibitory surrounds" has long been invoked to explain the confinement of cortical interictal and ictal discharges. This concept has recently been elaborated to include mechanistic interactions between glial and neuronal cell populations in neocortex and in deep cortical sites such as the hippocampus (e.g., Amzica and Steriade[1]). On the other hand, Herman et al.[53] found that seizures of mesial and neocortical temporal lobe origin exhibit secondary generalization more often than do those of frontal neocortical origin. See FIGURE 4 and the discussion of different findings between Herman et al.[53] and Crespel et al.[28] in Chapter 187. Another complication is the difficulty in verifying the actual site of the seizure focus and/or the propagation patterns even when subcortical leads are available. A third complication is that rapid seizure discharge propagation can occur in symptomatic localization-related syndromes, particularly those with neocortical tumors, and may initially present as primary generalized seizures (e.g., Malow et al.[79]).

Longitudinal Course of Sleep Epilepsies.

In temporal or frontal lobe epilepsies, seizures may occur initially only during sleep, although a random seizure pattern can develop later in the clinical course (e.g., D'Alessandro et al.[29]). For example, Janz reported that 38% of 100 patients with a 2-year or shorter history of epilepsy manifested complex partial seizures only during sleep, but a large percentage of these patients soon developed diurnal seizures as well.[58] Other studies[45,99] used patients with primary generalized, secondary generalized, and partial seizures that occurred only in sleep epilepsy at initial diagnosis. Over a 2-year follow-up, they found that patients with generalized seizures exhibited few seizures and tended to remit or to retain a sleep seizure pattern, whereas those with focal seizures tended to develop waking seizures as well. Effective medical management may also cause seizures to disperse across the sleep–wake cycle.[63]

The degree to which seizure patterns are state dependent may predict response to medication. Frequent seizures that are entrained to a specific sleep or arousal state usually respond better to medical treatment than epilepsies in which seizures are randomly distributed across the sleep–wake cycle.[55,84,99,152] Particular epilepsy syndromes are associated with different patterns of seizure occurrence. For example, benign or idiopathic localization-related epilepsies are more likely to retain nocturnal seizure patterns than are localization-related epilepsies with a documented lesion.[29,42,58]

The reason seizure patterns become random is uncertain. Frequent seizures may exacerbate cell dysfunction as well as response to synaptic input at the seizure focus and can ultimately influence cell discharge patterns in extrafocal brain areas (e.g., McNamara[90] and Shouse et al.[123]). Cells in certain limbic system areas, such as the hippocampus, are particularly sensitive to cerebral insult (e.g., McNamara[90]). Epilepsies in which there is widespread or progressive cerebral dysfunction usually have random distribution of interictal discharges and clinical seizures throughout the sleep–wake cycle.[16,42,44,50,57,58,84,98]

Regardless of the timing of clinically evident partial seizures, the rate, amplitude, and spread of IIDs peak during NREM sleep. Diffusion of spikes decreases during waking and further declines during REM sleep (e.g., Frost et al.[40]). The rate and amplitude of spikes may also be lower in REM sleep than in waking.[65,95,113] Because most partial seizure disorders are associated with focal cerebral dysfunction, it is not surprising that autonomous discharges persist during alert waking and REM sleep. Some authors suggest that optimal "focalization" occurs during REM, as seen in FIGURE 6.[113] Localizing epileptogenic foci during REM may assist in targeting the epileptogenic region for surgical resection.[71,113,114]

Symptomatic Generalized Epilepsies

This third group of seizure disorders is associated with variable degrees of diffuse cerebral dysfunction that can disrupt sleep, dissociate its components, and disperse IID and ictal discharges throughout the sleep–wake cycle (see footnote *b* of Table 1). Examples are West[42,54,98,159] (see Chapter 229) and Lennox-Gastaut[44,84,98] (see Chapter 241) syndromes and progressive myoclonic epilepsies such as Lafora-Unverricht-Lundborg syndrome[16,50] (see Chapter 252).

When NREM and REM states can be differentiated from waking, there is sleep-state modulation of IID and ictal seizure manifestations (e.g., Fukuyama et al.[42]). For example, hypsarrhythmia, the characteristic EEG manifestation of infantile spasms (West syndrome; Fig. 7), and the atypical slow spike-and-wave discharges of Lennox-Gastaut syndrome show a peak in NREM and subside during intact REM sleep. The prognosis for response to medical treatment is improved if IID or clinical seizures exhibit a sleep–waking state dependency, even if it is confined to a suppression of overt seizure activity in REM sleep.[42,54,55,84]

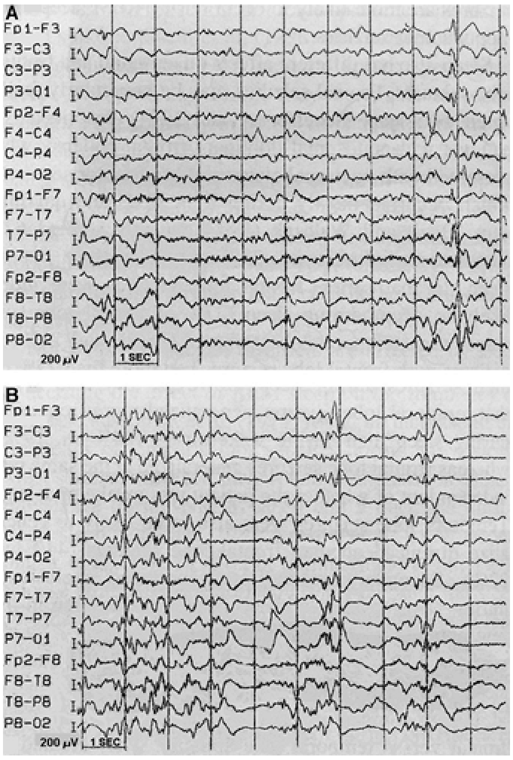


FIGURE 7. Effect of sleep on hypsarrhythmia. Electroencephalogram (EEG) from a 15-month-old girl with new onset of infantile spasms. **A:** EEG during waking shows multifocal high-amplitude sharp and slow-wave discharges, with intermittent periods during which a 5- to 6-Hz background could be seen. Note that the amplitude of this activity is 100 to 300 µV. **B:** The tracing from the same patient during sleep showed more prominent bursts of spike discharges, with periods of relative attenuation, which was not seen during wakefulness. Note that the high-voltage activity is in the range of 200 to 500 µV. (Reprinted from Mendez M, Radtke RA. Interactions between sleep and epilepsy. *J Clin Neurophysiol*. 2001;18:106–127; with permission.)

Basic Mechanisms

Three conclusions are supported by these clinical observations. First, in virtually all seizure disorders, interictal discharges are more likely to occur and to propagate during NREM sleep than in any other state. Second, the epilepsy syndrome, defined by seizure type, etiology, and prognosis, often determines whether clinically evident seizures occur exclusively or mainly during NREM sleep as opposed to waking. Finally, interictal discharges, particularly propagated IIDs, are least likely to occur during REM sleep. When epileptiform discharges do occur, they are unlikely to lead to a clinically evident seizure.

The contrasting effects of NREM and REM sleep on seizures and interictal discharges raise two questions: (a) which characteristics of NREM sleep account for the activation of interictal and ictal discharges and (b) which characteristics of REM sleep suppress them?

Many studies employing transections, lesions, pharmacologic manipulations, microdialysis, *c-fos* expression, regional blood flow, and individual cellular recordings indicate that different neural substrates mediate NREM and REM sleep states. These studies are summarized with references in Chapter 187 and are described in more detail in recent reviews.[3,22,60,89,131,135] Briefly, the NREM cell generators are localized to the forebrain, specifically the GABAergic and galaninergic cells of the anterior/preoptic hypothalamus (ventral lateral preoptic [VLPO]). The REM cell generators are localized to the brainstem, particularly the pontine tegmentum.[60,131]

Both NREM and REM sleep have a number of distinguishing physiologic characteristics, called components, that influence the likelihood that an electrographic or clinical seizure will occur. These include the degree to which cellular discharge patterns are synchronized and alterations in antigravity muscle tone.[105,128] NREM sleep differs from waking in that EEG activity is synchronized and postural muscle tone is diminished[21,60,131,135]; REM sleep differs from NREM in that EEG activity is desynchronized, and it differs from waking and NREM in that postural muscle tone is absent. REM sleep has sometimes been called “paradoxical sleep” because it is characterized by a “highly active brain in a paralyzed body.”[21]

During NREM sleep, virtually every cell in the brain discharges synchronously.[21,135,136,137] Lasting oscillations of rhythmic burst–pause firing patterns result in convergent synaptic actions. Synchronous synaptic effects, whether excitatory or inhibitory, are likely to augment the magnitude and propagation of postsynaptic responses, including epileptic discharges. During REM, cells discharge asynchronously.[131] The divergent synaptic signals of asynchronous discharge patterns are less likely to augment seizure magnitude or propagation.

Skeletal muscle tone varies by sleep state. Antigravity muscle tone is preserved in NREM[21] and thus permits seizure-associated movement.[24,128] Profound lower motor neuron inhibition occurs in REM,[21,22,131] creating virtual paralysis.

These different EEG and skeletal muscle tone components can be experimentally dissociated,[128] as depicted in FIGURE 8. FIGURE 8A shows normal feline REM sleep. FIGURE 8B shows that NREM-sleep–like EEG synchrony can be selectively induced during REM by systemic administration of atropine, which blocks acetylcholine (Ach) release from cells in the pedunculopontine and peribrachial nuclei of the brainstem and nucleus basalis of the forebrain. These cholinergic cells are one of the critical generators of global asynchronous EEG discharges in waking and particularly REM (e.g., Jones[60] and Siegel[131]; see also Chapter 187). FIGURE 8C shows selective loss of postural muscle tone induced by a lesion of the pontine generators of REM sleep atonia. Neural generators are thought to be cholinoceptive and glutaminergic cells in the brainstem atonia regions.[131]

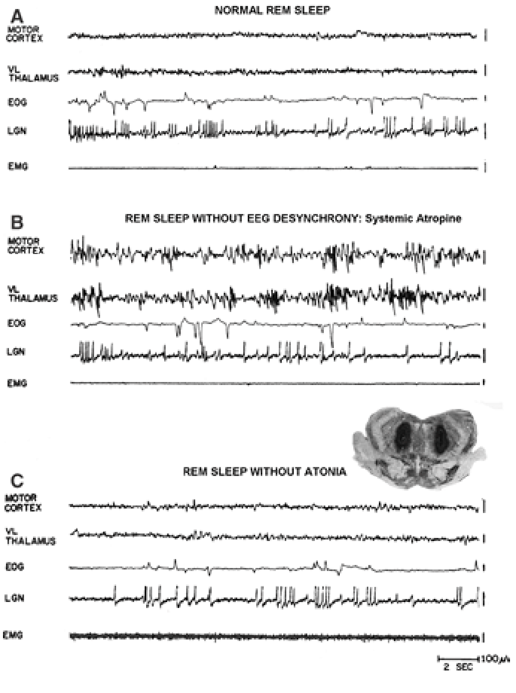


FIGURE 8. A: Normal feline rapid-eye-movement (REM) sleep, with electroencephalographic (EEG) desynchronization and atonia with periodic bursts of phasic events, including rapid eye movements and ponto-geniculo-occipital (PGO) spikes. **B:** Systemic atropine selectively abolishes EEG desynchronization. Instead, there is a non–rapid-eye movement (NREM)–sleep-like EEG with synchronized background and sleep spindles. However, atonia, eye movements, and PGO spikes persist. **C:** A pontine lesion selectively eliminates atonia. Note the presence of tonic EMG activity in the bottom channel of this tracing. EMG, electromyogram; EOG, electrooculogram; LGN, lateral geniculate nucleus; VL, ventral lateral nucleus of thalamus. (Reprinted from Shouse MN, Siegel J, Wu F, et al. Mechanisms of seizure suppression during rapid-eye-movement (REM) sleep in cats. *Brain Res.* 1989;505:271–282; with permission.)

Figure 9A shows the distribution of spike-and-wave complexes during intact NREM (left) and REM sleep (right) states. FIGURE 9B shows the effects of atropine administration. The REM-sleep EEG is synchronized, and seizure discharge rate is comparable to that in NREM (compare left and right panels). However, there is no clinical manifestation because of the skeletal motor paralysis in REM. FIGURE 9C shows that a pontine lesion eliminates REM sleep atonia so that a clinically evident seizure occurs in REM. These observations have been confirmed in three epilepsy models—penicillin

epilepsy (shown), electroconvulsive shock (ECS), and amygdala kindling[124,125,128]—suggesting that cellular discharge patterns and alterations in tone can affect electrographic and clinically evident seizure manifestations in diverse epileptic syndromes.

The effects of NREM and REM sleep on interictal and ictal discharges may also vary as a function of epilepsy syndrome. The question is, what accounts for the activation or suppression of selective seizure manifestations at different times? For simplicity, hypothesized basic mechanisms for only two classes of seizure disorders are considered. These are the primary generalized disorders of idiopathic or hereditary origin versus secondary generalized disorders originating from temporal lobe foci.

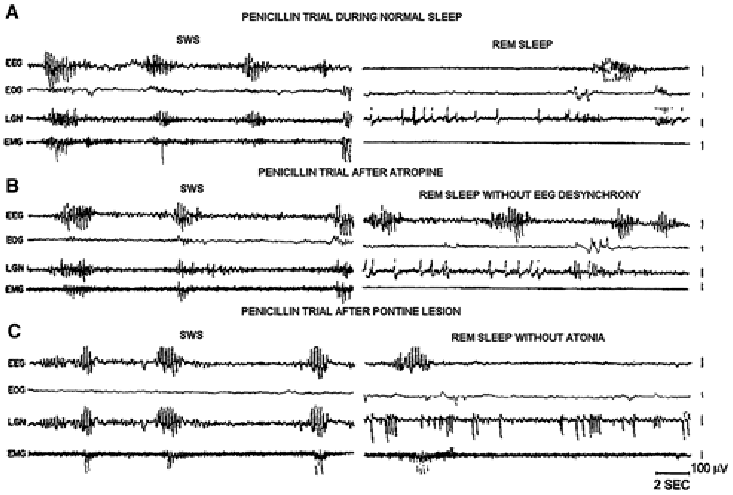

A
PENICILLIN TRIAL DURING NORMAL SLEEP
SWS
REM SLEEP
EEG
EOG
LGN
EMG
B
PENICILLIN TRIAL AFTER ATROPINE
SWS
REM SLEEP WITHOUT EEG DESYNCHRONY
EEG
EOG
LGN
EMG
C
PENICILLIN TRIAL AFTER PONTINE LESION
SWS
REM SLEEP WITHOUT ATONIA
EEG
EOG
LGN
EMG
100 µV
2 SEC

FIGURE 9. Systemic feline penicillin epilepsy during slow-wave sleep (SWS), the equivalent of non–rapid-eye-movement (NREM) sleep in humans, and REM sleep before and after dissociation of REM sleep components. Spike-and-wave paroxysms are visible in the electro-encephalogram tracing, and myoclonic seizures were associated with electromyogram (EMG) discharges in this cat. EEG, motor cortex EEG; EOG, electrooculogram; LGN, lateral geniculate nucleus. (Reprinted from Shouse MN, Siegel J, Wu F, et al. Mechanisms of seizure suppression during rapid-eye-movement (REM) sleep in cats. *Brain Res*. 1989;505:271–282; with permission.)

Cells of ascending reticular activating system are believed to promote propagation of interictal and ictal discharges in stable NREM sleep[1,4,123,124,125,126] (see Chapter 187 for a review), mostly via reduced cellular discharge and chemical release in cholinergic (Ach), noradrenergic (NE), and serotonergic (5-HT) cells. However, bursts of cholinergic cells in the pontine tegmentum generate arousal-related phasic events called ponto-geniculo-occipital waves (e.g., Shouse and Siegel[127]), which can provoke seizure discharge and sometimes its propagation in feline temporal lobe epilepsy (e.g., Shouse et al.[124,126]). Reduced electrochemical activity in reticulothalamic pathways appears conducive to IID propagation in primary generalized epilepsies,[1,41,136] probably by enhancing thalamocortical (EEG) synchronization patterns. Synchronized sleep transients, such as sleep spindles and possibly even delta waves, are contingent on sequenced hyperpolarizing GABAergic input from the thalamic reticular nucleus (RE) to thalamocortical relay cells.[1,41,135,136,137,149] Altered discharge patterns in RE cells are thought to inhibit thalamocortical neurons during cortically generated spike-wave discharge and also to explain the sensory isolation, lack of awareness, and behavioral arrest during absences as well as the absence of postictal depression afterward.[1,41,136] These synchronous thalamocortical discharge oscillations are abolished by activation of ascending brainstem afferents, particularly NE projections, which discharge maximally during alert waking, and cholinergic projections, which discharge maximally during alert waking and REM sleep.[60,89,132,135,136,149]

Reduced electrochemical activity in reticulolimbic pathways most parsimoniously explains interictal and/or ictal discharge propagation from temporal lobe foci during NREM sleep,[123,124,125,126] perhaps from direct or indirect innervation of focal epileptic neurons (refer to Jones[60] for anatomy). NE and 5-HT dialysates in pontine tegmentum and amygdala decline prior to sleep and spontaneous seizure activity after kindling.[129] Microinfusion studies indicate that local application of NE-receptor antagonists to limbic seizure foci promotes ictal discharge propagation, whereas NE-receptor agonists block seizure discharge generalization (e.g., Shouse et al.[122]). Microinfusion of cholinergic agonists into the pontine tegmentum promotes REM sleep and reduces amygdala-kindled seizure susceptibility.[67] The basis for reduced secondary generalization of frontal lobe foci is unclear and requires further investigation; however, similar mechanisms may be involved in the prevalence of partial and complex partial seizure during sleep. For example, Ach receptor dysfunction has been implicated in ADNFLE (e.g., Rodrigues-Pinguet et al.[108]).

Sleep Abnormalities

Clinical Findings

Just as sleep affects the expression of seizures, seizures influence sleep. Nocturnal seizures do not simply result in brief interruption of sleep; in fact, they can result in significant changes in sleep structure, particularly decreased sleep efficiency and decreased REM sleep (e.g., Bazil et al.[11]). The results are often seen clinically when patients with even very brief nocturnal seizures report inability to function adequately the following day. This may be confusing in the case of unrecognized nocturnal seizures. Treatment with anticonvulsant drugs can improve sleep by stopping seizures, but anticonvulsants can also have independent neuromodulatory effects that cause sleep disruption.[10,15,18,68,106,112,147,148]

Patients with epilepsy may, in addition, have a coincident sleep disorder such as periodic limb movements of sleep or sleep apnea that disrupts normal sleep, resulting in hypersomnolence. Disorganized and disrupted sleep may lead to complaints of poor sleep quality, excess daytime sleepiness, and a general decline in quality of life, including mood, cognitive, and memory deficits, as well as to increased refractoriness of the seizure disorder.[6,7,8,14,35,37,133,147] Once recognized, many of these complications may be improved or resolved by direct intervention aimed at treating the sleep disorder,[34,76,82,147] tailoring AEDs to avoid adverse side effects, or giving instructions on improved sleep hygiene with respect to routine sleep habits, reduced environmental distractions (e.g., exposure to light at times nonconducive for sleep), and other personal habits such as substance abuse.[7,8,37] A number of assessment tools are available to identify the nature of sleep disturbance in patients with epilepsy and to differentially diagnose epileptic from nonepileptic disorders. Many of these are discussed in more detail in related chapters, including those on sleep disorders (Chapter 276), affective disorders (Chapter 205), nonepileptic psychogenic seizures and epilepsy (Chapter 207), and nonepileptic psychogenic seizures (Chapter 282).

Briefly, there are several diagnostic tools ranging from patients' and significant others' logs, diaries, and questionnaires to polysomnography (PSG) with simultaneous behavioral video recordings. Particularly in patients with epilepsy and complicated histories or when differential diagnosis of nocturnal events is an issue, it may be helpful to include a full EEG array to detect and differentiate ictal and interictal abnormalities from other nocturnal disorders simultaneously with polysomnography. All may provide important information to supplement a thorough patient history and a routine EEG.[9,70,147] For example, the Epworth Sleepiness Scale is a simple questionnaire, and the outcome correlates positively with the multiple sleep latency test (MSLT), the gold standard of PSG for confirmation of excess daytime sleepiness (e.g., Foldvary-Schaefer[37]).

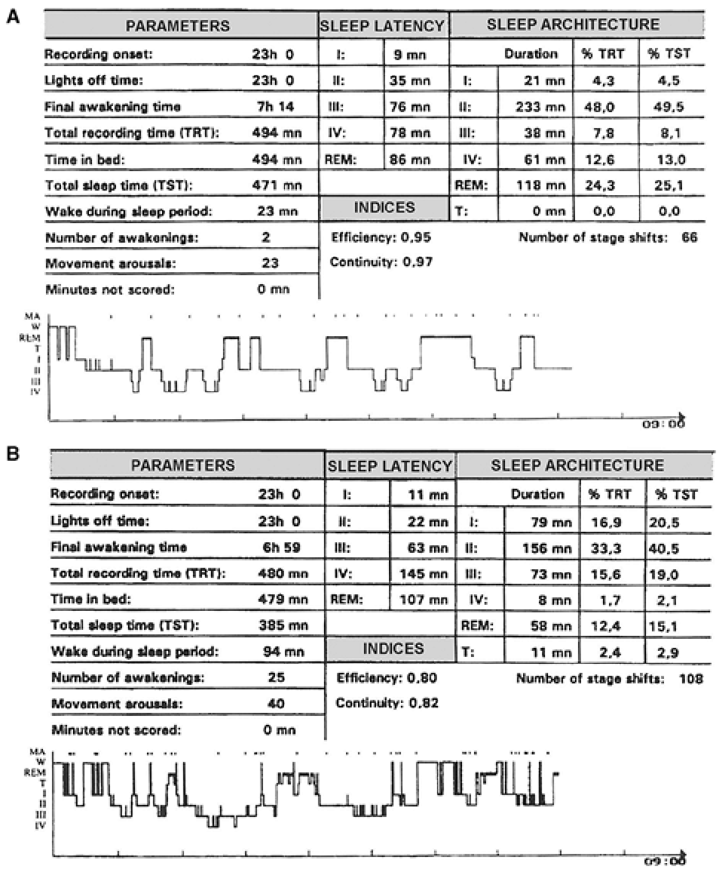
There are obvious limitations to the value of questionnaires, but they provide important data that may lead to referral for PSG. It seems generally accepted that patients with evidence of disordered sleep or a confusing clinical picture are candidates for a PSG, particularly when complaints of excess daytime sleepiness occur in epilepsy patients on monotherapy, with low AED serum levels, or with poor seizure control.[147] Simultaneous video can be particularly valuable in cases in which EEG seizure events are difficult to record or are absent in the waking EEG, clinical seizures are subtle, and differential diagnosis of seizures from sleep disorders or from pseudoseizures is difficult.[9,68,70] For example, epileptic seizures originating from mesio-orbito-frontal areas may have bizarre manifestations and ambiguous EEG correlates leading to a misdiagnosis of parasomnia.[8,70,88,101] Most patients with paroxysmal dystonia have sleep-related frontal lobe seizures, but the EEG alone is inconclusive (e.g., Montagna[94] and Sellal et al.[118]). In other cases, parasomnias coexist with limbic epilepsy without a common etiology.[43,51,141]

Sleep complaints are common in the general population and are particularly prevalent among those with epilepsy. In a study of 30 children with partial or generalized seizure disorders, 80% of sleep complaints were confirmed by PSGs indicative of obstructive sleep apnea, disturbance of sleep architecture, or sleep fragmentation. Sleep disturbance was more highly correlated with parent-reported daytime behavioral problems, notably inattention/hyperactivity, than was seizure incidence.[14] In other studies, large series of children with or without idiopathic epilepsy showed high ratings for poor quality sleep, anxiety about sleep, and disturbed breathing when compared to controls; correlations could be established with seizure frequency, incidence of IIDs and duration of seizure disorders, in addition to behavioral problems.[27,140]

Adults with focal seizure disorders with and without secondary generalization report sleep disturbances about twice as often as age-matched controls and also report a poorer quality of life than occurs with epilepsy alone.[35] Complaints of excessive daytime sleepiness have also been identified as predictors of seizures, particularly in relation to sleep disorders, such as sleep apnea, and have been also linked to increased seizure frequency and/or number of AEDs.[37,76,83] Poor sleep hygiene, such as irregular sleep habits, more substance abuse, and poor exercise, also has been related to excess daytime sleepiness and insomnia, particularly in younger patients, including children.[37]

Epilepsies prone to state-dependent IIDs or seizures are accompanied by similar sleep abnormalities, including increased sleep onset latency, increased number and duration of awakenings after sleep onset, reduced sleep efficiency, reduced or abnormal K-complexes and sleep spindles, reduced or fragmented REM sleep, and increased stage shifts.[4,16,55,65,95,144,145] FIGURE 10 illustrates some of these deficits by comparing statistics of a normal hypnogram (Fig. 10A) to those of a medically refractory patient with temporal lobe epilepsy during a seizure-free night (Fig. 10B). For an update of automated seizure detection programs, see Chapter 95.

Sleep abnormalities have been observed on PSGs in patients with juvenile myoclonic epilepsy,[47,145] primary generalized tonic–clonic seizure disorders,[148] and localization-related epilepsies of frontal or temporal lobe origin (e.g., Bazil et al.[11] and Versavel[148]). Reports are in conflict about sleep anomalies in patients with pure absence seizures (e.g., Ross et al.[110]). No sleep abnormalities have been reported in BECT.[29] Comprehensive reviews are also available.[91,121,123]



A

PARAMETERS		SLEEP LATENCY		SLEEP ARCHITECTURE			
Recording onset:	23h 0	I:	9 mn		Duration	% TRT	% TST
Lights off time:	23h 0	II:	35 mn	I:	21 mn	4,3	4,5
Final awakening time	7h 14	III:	76 mn	II:	233 mn	48,0	49,5
Total recording time (TRT):	494 mn	IV:	78 mn	III:	38 mn	7,8	8,1
Time in bed:	494 mn	REM:	86 mn	IV:	61 mn	12,6	13,0
Total sleep time (TST):	471 mn			REM:	118 mn	24,3	25,1
Wake during sleep period:	23 mn	INDICES		T:	0 mn	0,0	0,0
Number of awakenings:	2	Efficiency: 0,95		Number of stage shifts:	66		
Movement arousals:	23	Continuity: 0,97					
Minutes not scored:	0 mn						

B

PARAMETERS		SLEEP LATENCY		SLEEP ARCHITECTURE			
Recording onset:	23h 0	I:	11 mn		Duration	% TRT	% TST
Lights off time:	23h 0	II:	22 mn	I:	79 mn	16,9	20,5
Final awakening time	6h 59	III:	63 mn	II:	156 mn	33,3	40,5
Total recording time (TRT):	480 mn	IV:	145 mn	III:	73 mn	15,6	19,0
Time in bed:	479 mn	REM:	107 mn	IV:	8 mn	1,7	2,1
Total sleep time (TST):	385 mn			REM:	58 mn	12,4	15,1
Wake during sleep period:	94 mn	INDICES		T:	11 mn	2,4	2,9
Number of awakenings:	25	Efficiency: 0,80		Number of stage shifts:	108		
Movement arousals:	40	Continuity: 0,82					
Minutes not scored:	0 mn						

FIGURE 10. A comparison of hypnograms and related statistics using Somnis C software (AMISYSE), a semiautomatic method for sleep analysis of polysomnograms. Normally, the stages of sleep vary throughout the night in a somewhat predictable order.[19] Sleep onset typically begins with non–rapid-eye-movement (NREM) sleep, which predominates during the first one third of the night. Then, NREM and REM alternate with a periodicity of about 90 minutes. Finally, REM sleep predominates during the last one third of the night and is linked to the circadian rhythm of body temperature. A normal range of percentages for NREM stages 1 to 4 and for REM sleep in a young adult are as follows: stage 1, 25%; stage 2, 45% to 55%; stage 3, 38%; stage 4, 10% to 15%; REM, 20% to 25%, the latter occurring in four to six discrete episodes. **A:** Normal sleep organization in a typical young adult. Percentages of NREM and REM are normal. The REM latency of 86 minutes and number of REM cycles are within normal limits. Sleep efficiency, continuity, number of movement-related arousals, and awakenings are normal. **B:** Disorganized sleep architecture in a young adult with medically intractable temporal lobe epilepsy during a seizure-free recording. Sleep analysis shows a decrease in percentage of stage 4 and REM sleep together with increased stage 1 sleep. The increased number of movement-related arousals, number of awakenings after sleep onset, and stage shifts contribute to the fragmented sleep architecture. The REM latency (107 minutes) and number of REM cycles (four) are normal, but REM fragmentation is detectable. Sleep efficiency and continuity are decreased. I, stage 1 sleep; II, stage 2 sleep; III, stage 3 sleep; IV, stage 4 sleep; MA, movement arousal; REM, REM sleep; T, transitional stage; W, wakefulness. Time is indicated by h (hours) or mn (minutes). Recording started at 23 hours and ended at 7 hours, 14 minutes. Each line on the X axis divides the hypnogram into intervals of 1 hour. Sleep efficiency = total sleep time/(final awakening time-lights-off time). Sleep continuity = total sleep time/(final awakening time-time of sleep onset). (M. Sammaritano, reprinted from Shouse MN, da Silva AM, Sammaritano M. Sleep. In: Engel J Jr, Pedley TA, eds. *Epilepsy: A Comprehensive Textbook.* Philadelphia: Lippincott-Raven; 1997:1929–1942; with permission.)

Some sleep abnormalities, especially delayed REM onset, can occur as a result of recent daytime or nighttime convulsions (e.g., Bazil[5] and Bazil et al.[11]) or specific anticonvulsant drugs[5,6,7,8,9,10,146] (also see next section on anticonvulsant drugs), but sleep abnormalities can persist in spite of these factors. Sleep abnormalities have been reported to be more common in patients with primary or secondary generalized seizures than in those with simple or complex partial focal epilepsies,[91,121,123] but other studies have concluded that focal and complex partial seizures, especially in patients with temporal lobe epilepsy with frequent or medically refractory seizures, are also likely to have PSG-confirmed sleep disorders (e.g., Shouse[120,121] and Touchon et al.[145]).

Severe sleep abnormalities occur in symptomatic epilepsies that are associated with significant neurologic deficits. The sleep abnormalities described in the previous paragraphs are exaggerated, and sleep cycles may be poorly organized. In very severe epileptic disorders, a sleep cycle may not even be discernible.[16,42,44,50]

In conclusion, practitioners have in the past tended to dismiss patients' sleep complaints as unavoidable side effects of medications. The upsurge in the use of PSG and PSG-video during the last decade has confirmed sleep complaints as well as the chronic, deleterious effects of seizure-related or non–seizure-related sleep disorders on daytime activities, including exacerbation of seizure activity. It is appropriate and essential to consider treating the sleep abnormality and the seizure disorder as separate but related entities; however, both must be addressed before the patient will be able to perform at his or her best.[8,70,146]

Basic Mechanisms

Major motor seizures, especially tonic–clonic convulsions, substantially increase NE release. This presumably causes acute NE depletion in the postictal period. Norepinephrine release is normally suppressed during REM sleep,[103] which causes receptor upregulation or desensitization of NE receptors.[132] Postictal NE depletion may also lead to receptor upregulation. This is consistent with the hypothesis that seizures replace REM sleep (e.g., Stevens et al.[138,139]) and could also explain postictal delays in REM sleep onset.[4]

Other sleep abnormalities could result from neurotransmitter abnormalities associated with seizure disorders. For example, abnormalities of GABA synthesis and transmission have been implicated in the pathophysiology of most seizure disorders.[1,48,90,136] Fluctuations in other transmitters, such as Ach and NE, have been implicated in EEG and behavioral arousal.[3,60,89] Deficient GABA or increased Ach and NE could provoke the frequent stage shifts, increased wakefulness after sleep onset, and poor sleep efficiency seen in many epilepsy patients. The diffuse encephalopathies that accompany severe seizure disorders, such as infantile spasms and Lennox-Gastaut syndrome, seem likely to produce a significant neurochemical imbalance affecting sleep. Such an imbalance would be consistent with the notable disruption of sleep cycles recorded in these patients.

Antiepileptic Drugs

Clinical Findings

For many reasons, it is difficult to disentangle the effects of antiepileptic drugs (AEDs), sleep, and seizure disorders. AEDs have many side effects, which raises ethical considerations for testing in normal controls. Testing in normal individuals must in any case be limited to the relatively short term, unlike epilepsy patients, who typically take these medications for years. Seizures themselves (as described previously) have many effects on sleep, and therefore it can be difficult to isolate sleep benefits due to seizure control in epilepsy patients from other sleep effects (positive or negative). Particularly refractory patients often take more than one AED, further complicating results, but withdrawal of adjunct AEDs poses a risk for increased seizure activity, including status epilepticus. Most of the data are therefore based on findings in medicated epilepsy patients. An additional drawback is that AEDs are not site specific and thus affect neuronal networks involved in both sleep and seizure generation (recent reviews are available[7,37,81,91,102,146]).

State-dependent seizures are usually more responsive to AEDs than are seizures that occur randomly in the sleep–wake cycle.[91,99,121,152] AEDs can reduce seizure frequency but can also cause seizures to be randomly dispersed in the sleep–wake cycle.[63] The reason for this is unknown.

Table 3 summarizes effects of various AEDs on sleep architecture and complaints. Many traditional AEDs promote normalization and stabilization of sleep by increasing sleep latency, reducing stage shifts, and minimizing arousals during sleep (phenytoin,[107,151] carbamazepine,[47,107,148] pheno-barbital,[107] and benzodiazepines[26,115]). These AEDs rarely increase total sleep time or reduce complaints of daytime sleepiness because of the tendency to affect other components of sleep, including increasing light NREM stage 1 sleep, reducing deep NREM (stages 3 and 4) sleep, and reducing REM sleep. Other conventional AEDs, such as ethosuximide, promote arousals, elevate NREM stage 1 sleep, decrease NREM stages 3 and 4 sleep and REM sleep, and induce complaints of insomnia. Some of these medications are associated with weight gain (e.g., valproate) and diminished upper airway tone (e.g., phenobarbital and benzodiazepines), which promote sleep disorders such as sleep apnea. As mentioned previously, these drugs can improve sleep by stopping seizures, but anticonvulsants can also have independent neuromodulatory effects that cause sleep disruption.[10,15,18,68,106,112,147,148]

Table 3 Antiepileptic Medication Effects on Sleep Architecture and Complaints

Drug	Sleep efficiency	Total sleep time	Sleep latency	Arousals	Stage 1	Stage 2	Stage 3/4	REM sleep	Sleep complaints/ disorder effects
Phenytoin	Decrease	None	Decrease	Decrease	Increase	Increase	Decrease	None	Sleepiness
Carbamazepine	Increase	None	Decrease	Decrease	None	None	Increase	Transient decrease	Sleepiness; treats RLS
Phenobarbital	Decrease	None	Decrease	Decrease	Increase	Increase	None	Decrease	Sleepiness; OSA
Ethosuximide	Decrease	Unknown	Unknown	Increase	Increase	None	Decrease	Increase	Unknown
Valproate	None	None	None	Increase	Unclear	None	Increase	Mild decrease	Sleepiness; OSA
Felbamate	Decrease	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Insomnia
Lamotrigine	None	None	None	None	None	None	Unclear	Mild increase	Insomnia (rare)
Gabapentin	Increase	Increase	Decrease	Decrease	Decrease	None	Increase	Increase	Treats RLS

Topiramate	None	None	None	None	None	None	None	None	Unknown
Vigabatrin	Unknown	None	None	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown
Tiagabine	Increase	None	None	None	None	None	Increase	None	Unknown
Levetiracetam	None	None	None	None	None	Increase	Decrease	None	Insomnia (rare)
Zonisamide	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Insomnia (rare)
Pregabaelin	Increase	None	Decrease	Decrease	None	None	Increase	None	Unknown

OSA, obstructive sleep apnea; REM, rapid eye movement; RLS, restless leg sleep syndrome.

[a] Sleep efficiency is the ratio of total sleep time to total waking time after sleep onset.

Updated from Vaughn BV, D'Cruz OF. Sleep and epilepsy. *Semin Neurol*. 2004;24:301–313; with permission.

Acute and chronic effects of AEDs on sleep and epilepsy can sometimes be dissociated, as suggested in Table 3, and AEDs may affect sleep in ways that are not relevant to seizure control. Virtually all first-generation AEDs delay REM sleep onset or suppress REM sleep percentages,[7,8,147] even though many AEDs differentially affect specific seizure types. For example, "petit mal" AEDs can exacerbate complex partial seizures, and "temporal lobe" AEDs can exacerbate absence seizures.[109] Furthermore, since the early work in this area, many new anticonvulsant drugs have been developed that are also specific for seizure types. Their effects on sleep-related IID or clinical seizures and on sleep are not known, but preliminary evidence suggests that felbamate has stimulant effects, lamotrigine may have no effects on sleep, and gabapentin may increase NREM stages 3 to 4 sleep and also increases or has no effect on REM sleep.[8,9,10,37,68,115,147]

Vagus nerve stimulation (VNS) has been accepted for use in intractable seizure conditions. Although VNS has been shown to improve daytime alertness,[75] it can induce obstructive respiratory events in sleep (see Chapter 131).[74,86,147]

It is not possible to state whether the favorable or adverse effects of AEDs or VNS on sleep materially affect seizure control in general, although it is clear that in some patients, particularly those with juvenile myoclonic epilepsy,[57,59,95] seizure occurrence is extremely sensitive to sleep deprivation of any kind. However, sleep disorders do independently influence quality of life, and this should be taken into account particularly when seizures are refractory or when AEDs or alternative treatments that do not influence sleep or that can mitigate sleep

disturbance are available. Treatment of coexisting sleep disorders (e.g., obstructive sleep apnea, inadequate sleep hygiene) can improve both daytime sleepiness and seizures. In a subgroup of patients with epilepsy, changing AED to better treat coexisting sleep disorders may be warranted; the first step in this process is of course recognition of the sleep problem (e.g., Legros and Bazil[68] and Malow and Vaughn[81]).

Basic Mechanisms

The mechanisms of action of individual AEDs are covered in the section on antiepileptic drugs (Chapters 144,145,146,147,148,149,150,151,152,153,154,155,156,157,158,159,160,161,162,163,164). Many are thought to act on seizures by altering sodium, calcium, or chloride channels, sometimes in relation to specific transmitter binding, and may similarly influence sleep.[147] The systemic nature of effects, even with monotherapy, and the additional confounding influences posed by polytherapy significantly complicate evaluation of the basic mechanisms governing AED–sleep interactions. For example, the benzodiazepines act at $GABA_A$ receptors to increase neuronal inhibition. The resulting reduction in ictal and interictal discharges that results is associated with an increase in the rate of sleep spindles, with which many IIDs are associated. In contrast, ethosuximide, an AED that effectively suppresses absence seizures, reduces both the reticular thalamic Ca^{2+} spikes involved in the generation of sleep spindles and spike-and-wave complexes in some slice preparations.[135,149] This implies that ethosuximide might suppress spike-and-wave complexes by affecting the same mechanisms that produce sleep spindles. In humans and some animal models, however, ethosuximide suppresses spike-and-wave complexes without affecting spindle incidence (e.g., Kellaway et al.[63]), possibly by altering the Ca^{2+}-mediated t-current without eliminating it.[56] Caution must therefore be used in extrapolating proposed in vitro mechanisms to in vivo findings. Collectively, however, the clinical and basic findings suggest that AEDs can correct sleep and seizure anomalies concurrently, but they need not (see Table 3).

VNS has been hypothesized to improve daytime alertness through its effects on thalamocortical projection neurons. Even patients who did not show improvements in seizure control with VNS exhibited a reduction in daytime sleepiness as manifested by the Multiple Sleep Latency Test.[75] VNS may influence respiration during sleep via central pathways, peripheral mechanisms, or both. Activation of motor efferents alters neuromuscular transmission to the upper airway muscles of the pharynx and larynx to produce upper airway narrowing. Alternatively, VNS may influence respiration via central projections to the reticular formation of the medullar or medial pons, which connect with pontomedullary nuclei involved in regulating breathing and upper airway musculature.

Sleep Deprivation

Clinical Findings

Sleep deprivation can precipitate clinically evident seizures (e.g., Degen[30]). Methodologic problems, including control of extraneous seizure precipitating factors such as stress, fatigue, and substance abuse (e.g., Frucht et al.[39]), likely contribute to some clinical and self-report findings. Malow et al.[79] found no activation of seizures in patients with partial epilepsy after acute sleep deprivation and studied in the controlled setting of in-patient video monitoring of presurgical candidates. Other presurgical evaluation units have examined the utility and cost of sleep-deprived EEG, magnetic resonance imaging (MRI), and positron emission tomography (PET). PET was the most expensive and effective. It was concluded that sleep-deprived EEG and MRI should be done on an outpatient basis for presurgical evaluation.[33]

Most sleep deprivation studies have focused on activation of IIDs for diagnostic purposes in patients with normal, borderline, or minimal epileptiform discharges in routine waking EEGs. The range of experimentally induced sleep deprivation is usually briefer in children than in adults (3–4 hours vs. >24 hours), although partial sleep deprivation has been studied in adults as well. The results of sleep deprivation have been compared to routine waking EEGs and to natural or drug-induced sleep with or without hyperventilation and photic stimulation. Nearly all studies showed sleep deprivation activation exclusively in epilepsy patients with or without medication.[91]

The benefits of sleep deprivation, particularly when compared to waking and to natural or drug-induced sleep, have been debated. Methodologic issues include the longer duration of postdeprivation sleep versus waking records, the absence of baseline sleep recordings, and differences in composition of study populations. The majority of findings indicate that sleep deprivation increases IIDs by 30% to 50% in postdeprivation sleep versus ~15% to 30% in postdeprivation waking records.[38,145] However, Klinger et al.[66] controlled for sleep and waking state duration by analyzing rate rather than total percentage of activation and found more activation in postdeprivation waking records. Rowan et al.[111] evaluated patients with normal or borderline routine waking EEGs and found that epileptiform discharges were activated in 44% after sleep deprivation versus 14% during drug-induced sleep. Sleep deprivation is not necessarily superior to drug-induced or natural sleep, including naps,[85] as an activation technique. Eschenne et al.[36] found activation in 73% of sleep EEGs as compared to 36% of sleep deprivation records. However, other authors obtained lower yields from natural sleep (28.6% gain over waking EEGs) with a further gain of 10% after sleep deprivation.[111]

Sleep deprivation is effective in provoking all focal and generalized interictal discharges in patients with state-dependent or random seizures in the sleep–wake cycle.[30] Increased activation has been seen at all ages, although there is evidence that children <10 years of age are more responsive than 11- to 30-year-olds, who are in turn more responsive than adults >30 years of age.[30] These age-dependent effects are not surprising, given the increased sleep requirements in the young.[21] Unexpected gains in activation have been seen in the postdeprivation response to photic stimulation and sometimes hyperventilation (e.g., Rowan et al.[111]).

Basic Mechanisms

The mechanisms whereby sleep deprivation affects epilepsy are not well understood, mainly because it is difficult to control for other confounding variables such as stress and hormones.[39,57,97] The activating effects of behavioral sleep deprivation on seizures can be duplicated by lesions of NREM sleep generators in the preoptic basal forebrain.[130] Behavioral sleep deprivation also reduces spontaneous discharge rates of cells in the vicinity of the locus ceruleus in cats. These cells of the pontine tegmentum contain Ach, NE, or 5-HT.[60,61] Any change in these or other neuromodulators could account for the increased "drowsiness" and rapid NREM sleep onset in sleep-deprived subjects and for increased susceptibility to ictal and interictal discharges.

Summary and Conclusions

1. Both NREM sleep and drowsiness after awakening from NREM sleep are conducive to electrographic and clinically evident seizures, whereas REM sleep is not. Epileptic discharges are most focal during REM sleep and are also least prevalent.
2. Neural generators of synchronous EEG oscillations may provide a natural mechanism for electrographic seizure propagation during NREM and drowsiness, and antigravity muscle tone permits seizure-related movement.
3. Neural generators of asynchronous neuronal discharge patterns may reduce electrographic seizures during alert waking and REM sleep, and skeletal motor paralysis seems to block seizure-related movement in REM sleep.
4. Clinical neurophysiologic techniques, such as video-EEG polysomnography, can assess disturbances in nocturnal sleep or excessive daytime sleepiness. Sleep disturbances often parallel the severity of seizure disorders, possibly because seizures and the pathophysiology underlying epileptic syndromes may have disruptive effects on generators of sleep and arousal.
5. Antiepileptic drugs (AEDs) can lessen or exacerbate sleep disturbances and complaints. Improvement in sleep architecture is not usually a critical factor in seizure control, but efforts to ameliorate deleterious effects on quality of life should be taken seriously by practitioners.
6. Sleep deprivation appears superior to both routine waking EEGs and drug-induced sleep for activation of epileptiform discharges, possibly by inducing neuronal discharge patterns that normally promote drowsiness and NREM sleep.

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Chapter 189

Sudden Death in Epilepsy

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Introduction

Mortality in epilepsy is increased two- to threefold (see Chapter 10). Much of the excess mortality is due to associated or underlying disease, but there is also a smaller amount of excess related to the epilepsy itself, due to accidental injury, drowning, status epilepticus or sudden death. Sudden unexpected ("unexplained") death in epilepsy (SUDEP), in which an otherwise well person with epilepsy dies unexpectedly in benign circumstances with no cause found at autopsy, is the most important category of epilepsy-related deaths. As discussed in this chapter, we believe that such deaths are most likely related to epileptic convulsions. In recent years, some significant risk factors have been recognized through case–control studies. Nonetheless, it is not understood why some individuals are more at risk than others with a similar profile.

Historical Perspective

It has long been recognized that otherwise well individuals with epilepsy can die suddenly. Suffocation or asphyxia during a convulsion was considered a likely mechanism, as described in 1854 by Delasiauve[13] in his treatise on epilepsy, under the section Terminaisons:

> La mort est due souvent à une suffocation mécanique spéciale. Atteints dapops;accès dans leur lit, les malades se retournent instinctivement sur le ventre; le paroxysme les surprend dans cette position et les cloue, en quelque sorte, la face contre les oreiller ou le traversin. L'interruption de l'air ne tarde pas, si tous secours fait défaut, à provoquer l'asphyxie. On constate alors la bouffissure violacée du visage, du cou, et quelquefois de la partie supérieure de la poitrine; l'aplatissement des lèvres collées à la lange, qui se présente a leur ouverture; l'écrasement des narines et différents signes de congestion cérébrale et pulmonaire.

This description focuses on extrinsic mechanisms. It was also recognized that intrinsic mechanisms could account for such deaths. Early in the twentieth century, based on experience at the Craig Colony, Spratling[61] described epilepsy as

> a disease which destroys life suddenly and without warning through a single, brief attack, unaided by an accident to the patient at the moment, such as suffocation or fracture of the skull from falling, and does so in from 3% to 4% of all who suffer from it.

In Munson's mortality series[36] from the same colony, death from status epilepticus/series of seizures was relatively common and had declined compared to earlier years at the colony, unlike the category of sudden death. Nocturnal deaths were considered accidental and potentially preventable. Of note was "a definite and fairly large group where neither accident of any kind nor suffocation can be assigned as the cause of death which seemed to be intrinsic rather than extrinsic." He concluded "that death is imminent at the time of seizures, unless help is at hand. The cause may be traumatic, suffocation may take place, or deaths may occur without any apparent cause…. The epileptic should be by himself as little as possible." Many of the observations made by these earlier physicians are reflected in current knowledge. Despite a period of denial from some quarters in the second part of the twentieth century, SUDEP is now acknowledged as a real phenomenon and one that engenders concern. Not all that long ago, however, its existence was disputed. The efforts of investigators in the 1970s and 1980s, on both sides of the Atlantic, in drawing due attention to it should be acknowledged. These include Terrence, Hirsch, Brown, Earnest, Lathers, Schraeder, Leestma, Schwender, their colleagues, and others. SUDEP, however, is not a "cause." It is but a convenient category in which to classify such deaths. Different risk factors may operate through a final common pathway of cardiorespiratory compromise.

Definition of Sudden Unexpected Death in Epilepsy

This has been the subject of debate. To be classified as SUDEP, a death occurring in benign circumstances has to be sudden, unexpected, and without a clear cause. The latter requirement differentiates SUDEP from sudden death in general, in which autopsy may reveal a cause for death. Some investigators exclude observed peri-ictal deaths. However, most SUDEP cases are unwitnessed, with the person found dead, more often in bed, having been well the evening before. Evidence suggestive of a terminal epileptic seizure, such as tongue biting or incontinence, may be found at autopsy, but such evidence cannot be regarded as conclusive, nor indeed does its absence exclude an epileptic seizure. Thus, it is often not possible to be certain that the death occurred during or shortly after an epileptic seizure.

The following is a pragmatic, workable, if rather cumbersome, definition of SUDEP: Sudden, unexpected, witnessed or unwitnessed, nontraumatic and nondrowning death in patients with epilepsy with or without evidence for a seizure, and excluding documented status epilepticus, in which post mortem examination does not reveal a (structural or toxicologic) cause for death.[37] This definition makes no assumption of mechanisms(s) and allows similar deaths to be conveniently grouped. However, autopsies are not always performed, and, when they are, may be limited.[42] Annegers and colleagues[1] suggested that deaths in epilepsy should be classified into (a) definite (with autopsy), (b) probable (suggestive circumstances but no autopsy), or (c) possible SUDEP cases or (d) cases with a clear cause of death. The definition above has been helpful in case–control studies. It has a major limitation, however. By excluding cases with coexisting pathology that predisposes to sudden death, it does not allow us to assess any increased risk of sudden death from epilepsy in such cases.

Incidence of Sudden Unexpected Death in Epilepsy

This needs to be viewed with reference to the background risk of sudden death in the general population of around 0.05 to 0.1/1,000 for those <45 years of age and 3/1,000 for those older.[1] Reported rates of SUDEP vary depending on the cohort studied, as addressed in previous reviews.[46,63] Broad estimates are presented below. Most cohorts are selected. Population-based studies of adequate size are difficult to achieve. The U.K. prospective population-based study of newly diagnosed epilepsy[32] observed only 1 SUDEP case among 792 patients in 11,400 person-years of follow-up. One needs to consider, however, the excess mortality due to underlying or associated disease and the observation that 70% developed lasting remission. In a population-based study based on 9 SUDEP cases from Rochester, New York,[18] the rate observed was 0.35/1,000 person-years. Two SUDEP cases were observed in 5,000 person-years of follow-up in the Medical Research Council antiepileptic drug (AED) withdrawal study[35] among patients with controlled epilepsy randomized to continued treatment or gradual drug withdrawal after a minimum of 2 years of seizure freedom. A multicenter unselected hospital series from the United States reported a rate of 1.21/1,000.[73] Rates of 1 per 200 to 300 person-years of follow-up were reported for selected cohorts with epilepsy and other disability or cohorts seen at specialist centers.[46,63] These reflect more intractable epilepsy or associated morbidity. Higher rates are suggested for series considered for epilepsy surgery and for failed surgery cohorts as discussed in more detail later. Another group with severe epilepsy is that of patients undergoing vagal nerve stimulation. A sudden death rate of 4.5/1,000 for definite/probable SUDEP cases was reported (6/1,000 if possible cases were included). This is comparable to that expected in an intractable cohort. The rate seemed to decrease with longer follow-up, but this has not been studied further.[1] More publications reflect risk for younger adults rather than children or the elderly, and extrapolation to other age groups is not appropriate. In the elderly, sudden death as defined earlier is less amenable to study. Attribution is difficult in the presence of competing comorbidity, and epilepsy-related excess mortality is "lost" within much higher overall death rates. SUDEP is known to occur in children more often in symptomatic than idiopathic epilepsy and is thought to be rare, but studies are limited and sometimes small.[9,14,21,58,74] Mortality is considered more often related to the underlying neurologic disorder or associated deficit than to seizures. A long-term study of outcome in children with epilepsy, one that separates deaths in a seizure from SUDEP cases, observed an overall mean age of death of 18.6 years (range of 1–41 years), suggesting a greater risk as children enter adulthood.[58]

Epilepsy Surgery and Sudden Unexpected Death in Epilepsy

There has been increasing interest in SUDEP in relation to epilepsy surgery, discussed here in more detail. The risk of SUDEP appears to be particularly high among patients with refractory epilepsy considered as candidates for epilepsy surgery, with an estimated incidence of 1/100 patient-years.[12] Follow-up studies after epilepsy surgery have initiated a discussion on whether epilepsy surgery could reduce mortality and lower the incidence of SUDEP in this high-risk group.[55] Stavem and Gudlvog[62] reported survival in patients operated for focal epilepsy in Norway from 1948 to 1988. Operations for known brain tumors were excluded, but the pathology was otherwise not provided. With an average postoperative follow-up of 25 years, there were 34 deaths among 139 surgery patients (4 considered SUDEP and another 4 with "epilepsy" as cause of death). The risk ratio for death in relation to the general population was 6.2 (95% confidence interval [CI] 3.1–12.6). The survival of the epilepsy surgery group was not significantly different from that of matched controls with medically treated intractable epilepsy, although there was a trend toward a lower death risk ratio, 0.6 (95% CI 0.4–1.1). Patients who were seizure free 2 years after surgery did not differ from patients with recurrent seizures, but data on longer-term seizure control were not available. Unfortunately, the report does not clarify whether the postoperative SUDEP cases occurred among the patients rendered seizure free. The comparatively small number of epilepsy surgery patients included in this study may also have contributed to the failure to demonstrate a difference between surgery patients and controls. Furthermore, the fact that this cohort was operated on before the introduction of modern neuroimaging in presurgical workup calls for caution in generalization.

Outcomes have also been reported in 248 patients who had diagnostic evaluations for epilepsy surgery at UCLA from 1974 to 1990.[71] Of these, 202 underwent surgery (anterior temporal resection in 175) and 46 did not. On follow-up, 14 (7%) of the surgery patients had died compared to 9 (20%) in the nonsurgery cohort. Among those who died, 81% had seizures, whereas only 47% of the surviving patients had seizures. Unfortunately, no detailed account is given on the causes of death, and there is no mention of SUDEP in this report, although the observations indicate a lower mortality in patients with refractory epilepsy that undergo surgery, in particular among those who become seizure free. There were 11 deaths in a follow-up of 215 patients treated surgically for refractory temporal lobe epilepsy at another U.S. center.[56] Three patients died during seizures, another 3 were classified as SUDEP, and 2 patients died in accidents. Mortality was lower (2%) among patients rendered seizure free than among those who continued to have seizures after the operation (11.9%). Survival was assessed among 305 patients who had surgery for temporal lobe epilepsy from 1975 to 1995 at the Maudsley Hospital in London.[22] There were 20 deaths (6 SUDEP), resulting in a standardized mortality ratio (SMR) of 4.5 (3.2–6.6) and a SUDEP incidence of 2.2/1,000 person-years. Only 2 of the 6 cases of SUDEP were reported to be seizure free postoperatively. A population-based nation-wide Swedish study followed 596 patients who had undergone epilepsy surgery and 212 patients referred to epilepsy surgery evaluation that did not lead to an operation.[43] There were 14 deaths (6 SUDEP) in the surgery group, yielding an SMR of 4.9 (95% CI 2.7–8.3) and a SUDEP incidence of 2.4/1,000 person-years, very similar to the U.K. data. Among the nonsurgery patients, 5 died (4 SUDEP), resulting in an SMR of 7.9 (2.6–18.4) and an incidence of SUDEP of 6.3/1,000 person-years. Seizure outcome data for the entire cohort were available only at 2 years after surgery and did not seem to affect mortality or risk of SUDEP. However, none of the 6 cases of SUDEP were seizure-free.

A follow-up of 393 patients who had epilepsy surgery in the United States identified 11 deaths, of which 7 were epilepsy related (6 SUDEP).[59] None of the 199 patients who became seizure free after surgery died, whereas the SMR for those with recurrent seizures was 4.7 (2.3–7.9). This series has been extended to include 583 patients prospectively followed after epilepsy surgery.[60] In total, 19 deaths (10 SUDEP) were observed, 18 of which were in patients with recurrent seizures. The only death in the seizure-free cohort was due to breast cancer, and all 10 SUDEP deaths were among patients with recurrent seizures. The SMR was 5.8 (3.5–9.3) for the patients with seizures despite epilepsy surgery, whereas the mortality rate for those who stopped having seizures after surgery was indistinguishable from that of the general population.

Hence, available follow-up data after epilepsy surgery strongly suggest that SUDEP preferentially occurs among those with recurrent seizures, whereas the risk is remarkably low in patients that are rendered seizure free. The lower SUDEP risk is likely, at least in part, to be a consequence of the successful surgery, but other interpretations also need to be considered. Because these observations are from nonrandomized studies, it is possible that there may be underlying preexisting biologic differences between patients who respond favorably to surgery and those with recurrent seizures. Such difference, for example, in the spread of the epileptogenic zone, could be linked to the risk of SUDEP. The reported divergence in preoperative HRV between patients with good and poor outcome of surgery for temporal lobe epilepsy lends support to this latter interpretation.[50]

Is Sudden Unexpected Death in Epilepsy a Seizure-Related Event?

The previous definition, by being inclusive, acknowledges the difficulties of separating SUDEP cases directly related to a “terminal” epileptic seizure and those occurring independent of such a seizure. In an unwitnessed case, circumstances that suggest, but do not prove, an epileptic seizure include fresh tongue, cheek or lip biting, secretions, incontinence, disrupted environment or bedding, fall off the bed, contorted facial expression, or timing and triggers of per habitual seizures. The absence of such clues does not exclude a terminal epileptic event. Whereas a number of studies suggest that SUDEP is frequently a peri-ictal event, the evidence is mostly indirect. The proportion of witnessed cases varies among studies from 7% to 38%. Of those witnessed, between one third and all were reported to be related to convulsions.[29] A series of witnessed SUDEP cases,[30] among the first 135 ascertained for a case–control study, reported convulsions in 12 of 15 cases. An older study, based on detailed interviews of bereaved relatives or partners, addressed circumstances of death in 26 SUDEP cases (2 witnessed), and reported evidence suggestive of an epileptic seizure around the time of death in 23.[39] Signs of preceding seizures were reported in 67% in a case–control study of 42 SUDEP cases from Norway.[28] Monitored and reported SUDEP cases are rare. One such case occurred in a video telemetry unit during a secondarily generalized epileptic seizure.[6] Birnbach et al.,[7] in an early case–control study, reported an association with convulsive seizures. Observations from more recent case–control studies report a higher relative risk in people with more frequent seizures and in those with a history of generalized convulsive seizures (Table 1). This supports the premise that most SUDEP cases are seizure related. We believe that the majority of SUDEP cases are likely to be related to an epileptic seizure occurring close to the time of death.

Risk Factors, Descriptive Cohorts, and Case–Control Studies

The association with convulsive epileptic seizures accounts for some of the evidence only, and other risk factors need to be considered. Some individuals might be more at risk because of social factors, lifestyle, suboptimal management, and lack of adherence to treatment. Others might have additional biologic susceptibility. Descriptive cohorts suggested risk factors for study. These included youth, male gender, remote symptomatic epilepsy, structural findings on neuropathology, severe epilepsy, unwitnessed seizures, alcohol abuse, abnormal electroencephalograms (EEGs) with epileptiform changes and greater variations, mental disability, psychotropic medication, African American race, lack of adherence to treatment, abrupt medication changes, and low AED levels.

Certain risk factors have been shown to be associated with SUDEP in case–control studies. These studies have different methodologies and are not directly comparable. Some studies, for example, only include patients on long-term treatment for epilepsy or in specified age ranges. Not all studies are nested. Control groups vary and include living patients known to have epilepsy or patients with epilepsy who died of other causes. SUDEP cases are identified from a variety of sources, which could result in different data being available. Table 1 lists significant findings in some more recent case–control studies. Negative findings and older studies have not been listed.

Sudden Unexpected Death in Epilepsy and Antiepileptic Drugs

SUDEP was observed and documented well before the era of modern AED therapy, and we are not aware of data to suggest increased incidence in comparable populations. Medications taken by SUDEP victims in cohort studies appear to reflect prescribing practices. Nevertheless, potential risk factors relating to AED treatment, including drug levels, adherence to treatment, abrupt withdrawal, polytherapy, and choice of AED, are potentially very important because they are amenable to manipulation in routine management.

The Stockholm study,[35] which only included SUDEP cases with treated epilepsy, identified polytherapy and frequent medication changes as independent risk factors for SUDEP. These risk factors may still be surrogate markers for epilepsy severity, but they could make SUDEP more likely. Medication changes, prescribed or otherwise, particularly if abrupt, could result in instability both of the epilepsy and of the autonomic nervous system. AED therapy could, in theory, also affect post-ictal respiratory depression or predispose to cardiac arrhythmias.

The Swedish group further investigated the potential of AEDs to inhibit the cardiac rapid delayed rectifier potassium ion current (I_{Kr}) because other drugs known to have such an effect can be proarrhythmic, with their clinical use associated with sudden unexpected death due to cardiac arrhythmia. They recorded tail currents in I_{Kr} channels expressed from human ether-a-go-go–related gene (hERG) in a whole-cell patch-clamp technique. Phenytoin, phenobarbital, and lamotrigine had the potential to inhibit the I_{Kr} channel at potentially clinically relevant concentrations. Carbamazepine, topiramate, and gabapentin also had blocking effects but at concentrations outside the range usually associated with such a clinical effect.[10,11] The effect of AEDs on heart rate variability is discussed separately later.

The effect of medication changes on modifying seizure severity including the postictal phase, as opposed to seizure type or frequency, has not been adequately studied; anecdotally, such an effect is familiar to practicing clinicians and is often reported by caregivers. One of the authors recalls a patient with poorly controlled posttraumatic epilepsy who on a particular combination of AEDs was observed in hospital on more than one occasion to have a prolonged postictal phase lasting hours with deep coma and secondary obstructive apnea. Substituting one medication with another resulted in a “normal” postictal phase and later seizure freedom.

Table 1 Significant risk factors from different case–control studies with different designs

Reference	Cohort	SUDEP number (age)	Risk factor	Increased risk
Kloster et al. (1999)[28]	Hospital-based refractory; controls = non- SUDEP deaths	42	Body position	Prone > supine; see text
Nilsson	Hospital-based AED on treatment; controls = living epilepsy patients	57 (15–70 yr)	More frequent sizures	RR = 10.16 (95% CI 2.94–35.18), >50 seizures/yr vs. 2 seizures/yr

et al.[45]				
			Epilepsy type	Lower risk in symptomatic focal vs. idiopathic generalized epilepsy, but numbers are small
			Epilepsy age of onset	RR = 7.72 (95% CI 2.13–27.96) for age 0–15 yr vs. 45 yr
			Polytherapy	RR = 9.89 (95% CI 3.20–30.60), 3 AEDs vs. monotherapy
			Frequent medication changes	RR = 6.08 (95% CI 1.99–18.56), 3–5 changes/yr vs. none
Nilsson et al. (2001)[44]			Carbamazepine >usaual range	See text
Walczak	Hospital based; controls = non-SUDEP epilepsy patients	20	IQ <70 vs. >79	OR = 5 (95% CI 1.3–19.3)
			>2 AEDs vs. 0–2	OR = 4.0 (95% CI 1.4–11.7)
			Tonic–clonic seizure in last year	1–3 GTCS, or 2.4 (95% CI 1.8–30.5); >3 GTCS, or 8.1 (95% CI 2.2–30.0)
			>50 seizures/mo	OR = 11.5 (95% CI 1.3–99.3)

et al. (2001)[73]				
Langan et al. (2005)[30]	Through coroners, neurologists, and bereaved relatives; controls = living epilepsy patients in community	154 (16–50 yr)	>History of GTCS in last 3 mo Bedroom shared with supervising individual (protective)	OR = 13.8 (95% CI 6.6–29.1) OR = 0.4 (95% CI 0.2–0.8)
			Listening devices (protective)	OR = 0.1 (95% CI 0.0–0.3)
			>4 AEDs ever compared to 1–2	OR = 3.1 (95% CI 1.4–7)
			Never taken AEDs	OR = 21.7 (95% CI 4.4–106)
			Carbamazepine	OR = 2 (95% CI 1.1–3.8)

AED, antiepileptic drug; CI, confidence interval; IQ, intelligence quotient; OR, odds ratio; RR, relative risk; SUDEP, sudden unexpected death in epilepsy.
Note that relative risks/odds ratios are not comparable.

A large U.K.-based case–control study did not confirm polytherapy as a risk factor.[30] The study found, however, that total number of AEDs ever taken was associated with increased risk, most likely reflecting intractability of the epilepsy. The same study found untreated epilepsy to be a significant risk factor. This is an important observation, which, along with the association of SUDEP with convulsive seizures, supports active treatment of epilepsy with AEDs. Although we acknowledge that treatment interventions, surgical or medical, have potential adverse effects, including the potential to worsen seizure frequency and severity, we believe that the risk/benefit ratio clearly favors appropriate AED treatment.

Studies on adherence to treatment are contradictory, some supporting nonadherence to treatment as a risk factor, others not.[8,20,33,47,69] This is not surprising. Such studies have inevitable limitations. Historical details about medication taken or omitted by the patient during the last days preceding death often cannot be obtained from other sources. Post mortem AED blood levels can be unreliable, and interpretation needs to consider that levels below the usual quoted ranges can be therapeutic; it is not absolute levels that are important, but a difference in levels from usual. Furthermore, even if previous AED levels were available for comparison, the time of previous sampling would need to be taken into account as well as the degradation of post mortem samples. A recent study from Cardiff in the United Kingdom[31] avoids some of these problems by measuring AED levels in sequential 1-cm hair segment samples corrected for the washout effect. The results, however, do not reflect changes immediately before death. Interestingly, the study showed greater coefficient of variation in SUDEP cases than in three other cohorts studied: (a) An epilepsy cohort dying of other known causes, (b) an outpatient cohort, and (c) a residential cohort, with the latter showing the lowest variation. The difference, as far as the authors could ascertain, was not attributed to prescribed medication changes. This study suggests that nonadherence to treatment may indeed be a significant risk factor and amenable to modification.

It has been suggested that specific AEDs may be associated with a higher risk of SUDEP. Older descriptive series simply reflected the then-current prescribing practices. Walczak et al.'s study[73] did not identify any specific association with any particular AED. In a recent review, Walczak[72] argued that, on current evidence, there is no strong reason to avoid any particular AED, stressing the importance of preventing tonic–clonic seizures with as few AEDs as necessary to achieve complete control, a view with which we concur.

Timmings[66] reported that carbamazepine was disproportionately represented in patients suffering SUDEP. Further analysis of Nilsson et al.'s case–control study[44] suggested an increased risk in patients with frequent dose changes and polytherapy, with carbamazepine levels greater than the commonly quoted target range. There were only 6 such cases among 33 on carbamazepine and 57 SUDEP cases in total. Langan et al.'s case–control study also showed a small excess risk, with carbamazepine treatment just reaching significance.[30] Rare cases of heart block secondary to carbamazepine are documented, and carbamazepine has an effect on heart rate variability. The relevance of this association to the majority of people with epilepsy is uncertain. It is highly likely that patients with more-severe seizures were prescribed higher doses of carbamazepine, a mainstay of treatment in the last two decades. It is worth emphasizing, however, that AEDs needs to be appropriate to the epilepsy syndrome. In one study, some SUDEP cases on carbamazepine had uncontrolled idiopathic generalized epilepsy, whereas a broad-spectrum medication may have had better success.[39]

Mechanisms

Post mortem examination in SUDEP cases may reveal tongue bite or ptechial hemorrhages, a nonspecific finding in hypoxia and increased venous pressure. Pulmonary edema is very frequently noted, sometimes with other organ congestion. A study[65] of neuropathology in SUDEP cases showed microscopic evidence of hypoxic change in a small proportion of cases, suggesting that death may not be immediate in all cases. Routine autopsies in SUDEP cases, by definition, do not reveal a cardiac or other cause for death. Two studies reported on specialized cardiac pathology.[41,48] Perivascular and interstitial cardiac fibrosis, mainly subendocardial, was found in 4 SUDEP cases and myocyte vacuolization in a fifth but not in the control group.[41] In another study, morphologic abnormalities of the cardiac conduction system were observed in 4 of 10 SUDEP cases, a similar finding to 6 of 10 in the control group. This does not exclude these changes contributing to death in either group.[48] Nevertheless, the overall lack of evidence from pathologic studies suggests that the terminal event is likely to be due to functional disturbances.

Respiratory Mechanisms

Respiratory changes frequently occur in seizures, with well-documented central and obstructive apnea, excess bronchial and oral secretions, pulmonary edema, and hypoxia. Pulmonary edema is present in a large majority of SUDEP cases. Central apnea can occur secondary to the ictal discharge or postictally, perhaps, as has been suggested, due to secondary endogenous opioid release. During postictal coma, hypercapnea and hypoxia may be less potent respiratory stimuli. A sheep model of ictal sudden death supports an important role for ictal apnea/hypoventilation; animals that died were those with a greater rise in pulmonary vascular pressure and hypoventilation. When airway obstruction was excluded in a second study of tracheostomized sheep, central apnea and hypoventilation were observed in all animals, causing or contributing to death in two. A third animal developed heart failure with significant pathologic cardiac ischemic changes.[25,26]

Most unwitnessed SUDEP deaths occur in bed, presumably during sleep. One can postulate a number of different explanations for this observation, which are not mutually exclusive. It may reflect an individual's predisposition to sleep-induced cardiac arrhythmia. Nocturnal seizures may differ pathophysiologically; for example, they may be associated with an increase in vagal tone or with more marked respiratory depression. It may reflect lack of assistance at the time of the terminal event as Delasiauve believed. There is some evidence to suggest that he was at least partly right. A case–control study from Norway[28] found a significant difference in the position in which the body was found compared to that expected, with 71% of patients found prone and only 4% supine. In another study of circumstances,[29] in 11 of 26 SUDEP cases, the body was found in a position that predisposed to respiratory obstruction. In a study of a cohort of residential school children with epilepsy and other disability[53] in which children were monitored at night by awake staff aided by a continuous nocturnal sound monitoring system, 14 SUDEP cases occurring during the period of study all took place while the children were away from school. Finally, the use of listening devices or sharing the room with someone capable of giving assistance was associated with a reduced risk in Langan et al.'s case–control study.[30] The evidence that supervision within the community provides some protection favors an important primary role for respiratory factors, manipulated by relatively unskilled intervention such as adjusting position, ensuring an adequate airway, and perhaps physically stimulating respiration. An unknown proportion of SUDEP cases may be preventable by such intervention. Near-miss cases are recognized anecdotally but have not been systematically studied.

Cardiac Mechanisms

Primary or secondary cardiac mechanisms are also likely to be important through a number of possible scenarios as discussed later. Studies of routine interictal ECG changes in people with epilepsy have had a low diagnostic yield. ECG changes, both of rhythm and repolarization, are documented during seizures. The most common change is that of sinus tachycardia, but malignant tachyarrhythmias are relatively rare. Sinus bradycardia/arrest, although still infrequent, is more often documented.[63] One study observed ictal cardiac asystole in only 5 of 1,244 inpatients undergoing prolonged EEG-video recording.[53] Another study highlighted the potential yield, and dilemma, associated with long-term cardiac rhythm monitoring using an implantable device in a highly selected patient group with poorly controlled epilepsy.[55] This eventually revealed episodes of sinus arrest, for which pacing was carried out, in 4 of 19 patients studied. It remains to be seen how often such changes would be observed in a larger cohort and in other populations with epilepsy and what the indications for pacing should be in relation to preventing seizure-associated syncope and sudden death.

Sudden Unexpected Death in Epilepsy and Heart Rate Variability

Autonomic cardiac control can be assessed clinically by analysis of heart rate variability (HRV) based on ECG recordings. Reduced HRV has been shown to predict mortality and, more specifically, sudden death in other conditions than epilepsy.[5,64,67] HRV can be analyzed in time (standard deviation of RR intervals in the ECG) and frequency domains. Spectral analysis of HRV thus allows partly separate assessments of the sympathetic and vagal components of the power spectrum.[52] The high-frequency band (HF) is related to parasympathetic activity and low-frequency (LF) oscillations mainly with sympathetic activity, whereas the mechanism behind very low frequency (VLF) activity is not completely understood.

Several studies have assessed HRV in epilepsy. Interictal HRV has been analyzed in patients with chronic temporal lobe epilepsy and compared to age-matched healthy controls in cross-sectional studies with reduced HRV in the epilepsy patient groups as the major finding.[4,34,17,68] Adult patients with temporal lobe epilepsy were reported to have reduced total power, LF, and HF[60]; lower LF and LF/HF ratio[61]; or a decrease in all frequency-domain measures.[4] This reduction in HRV appears to be more pronounced during the night than during the day.[54] Sleep recordings in 11 children with different types of partial epilepsy revealed a decrease in HRV, most evident in the HF domain.[17] Another study of 30 children with unspecified epilepsy found other indications of disturbed autonomic modulation.[75]

The reason for the observed impaired autonomic cardiac regulation in patients with temporal lobe epilepsy is unclear. Treatment with antiepileptic drugs may contribute. Total power, LF, VLF, and HF all decreased after initiation of carbamazepine treatment in newly diagnosed partial epilepsy,[67] but little is known of the effect of other antiepileptic drugs. A Turkish study reported reduced HF and increased LF in young men with newly diagnosed generalized tonic–clonic seizures.[16] These patients, however, were not representative of new-onset epilepsy. Mean seizure frequency was 8/year for on average 5.6 years before diagnosis. An increase in LF/HF ratio during sleep, that is, enhanced sympathetic activity, was observed after sudden withdrawal of carbamazepine during seizure monitoring in patients with intractable seizures.[23] In another study, total power, VLF, and VF decreased when carbamazepine or phenytoin were withdrawn abruptly.[27] Although they slightly diverge, the results demonstrate the effects on HRV of sudden changes in medication.

Candidates for epilepsy surgery are at particularly high risk of SUDEP.[70] Patients with refractory temporal lobe epilepsy were also found to have significantly reduced HRV in all frequency domains before surgery, but only those that eventually continued to have seizures after temporal lobe surgery had so.[51] In contrast, patients with favorable outcome of surgery did not differ from their matched healthy controls in preoperative HRV measures, suggesting an a priori difference in autonomic cardiac control between good and poor candidates for epilepsy surgery. Differences in presurgical HRV patterns between poor candidates for epilepsy surgery and those with excellent outcome of temporal lobe resection have been reported.[19] A recent study assessed HRV in 16 patients who had undergone surgery for temporal lobe epilepsy, 8 with good outcome and 8 with poor outcome.[24] LF power and LF/HF ratio decreased after surgery in those rendered seizure free but increased in patients with persistent seizures. Decreased HRV might be a marker for an increased risk of SUDEP, in line with recent preliminary observations of lower HF in 9 patients who later died suddenly compared with epilepsy and nonepilepsy controls.[15]

In conclusion, epilepsy is associated with altered autonomic cardiac control. Although the impairment varies in extent and type, the most frequent finding is reduced HRV similar to that observed in other patient groups at increased risk of cardiac death. Several factors, for example, seizures, interictal discharges, underlying brain pathology, and drugs, may contribute. Most consistently, decreased HRV has been observed in patients at particular risk of SUDEP such as those with refractory epilepsy. This suggests that impaired autonomic cardiac control might contribute to the risk of SUDEP.

Can There Be a Coexisting Susceptibility to Epilepsy and Sudden Cardiac Death?

A number of hypotheses can be postulated, which are not mutually exclusive, as discussed in a recent review.[40] First, malignant cardiac tachy/bradyarrhythmias or cardiac failure might occur secondary to the ictal discharge and/or apnea/hypoxia. Second, long-term cardiac changes secondary to uncontrolled epilepsy might predispose to excess sudden death. Third, some individuals with epilepsy might have a coexisting "mild" susceptibility to sudden cardiac death that can manifest in the presence of uncontrolled seizures and, theoretically, can be modified by AEDs.

The third hypothesis could apply equally to acquired or genetic disorders. Of particular interest is the possibility of a coexisting "mild" genetic susceptibility to sudden cardiac death as a complex trait involving cardiac conduction/ion channel disorders. Such a genetic susceptibility might be unrelated to the epilepsy but become manifest because of uncontrolled seizures or medication, the latter less likely to be significant since inherited cohosts are at low risk. Alternatively and in theory, the same genetic variants may confer increased susceptibility to both epilepsy and to sudden cardiac death, both paroxysmal conditions in which similar disorders of ion channels, sometimes coexpressed in the brain and heart, are causally implicated. Against this suggestion is the lack of epidemiologic data indicating a higher incidence of epilepsy among relatives of those with inherited susceptibility to arrhythmia, the absence of reported family history of early sudden cardiac death in SUDEP cases, the uncommon observation of malignant tachyarrhythmias with seizures, and the clear pointers to respiratory mechanisms in SUDEP. These arguments can be addressed. Relevant epidemiologic data are not available. Studies looking at epilepsy in families of sudden cardiac death victims and at syncope in idiopathic epilepsy are needed. A clear family history of early sudden death in relatives of SUDEP cases, would not be expected in a complex trait. Finally, although inherited susceptibility to tachyarrhythmias is widely recognized, it is perhaps less widely appreciated among neurologists that such genetic susceptibility is also very well documented in sinus node dysfunction and bradyarrhythmias. As for respiratory mechanisms, one can draw an analogy with sudden infant death syndrome (SIDS). The dramatic success in reducing the incidence of SIDS through respiratory mechanisms simply by recommending the supine rather than the prone position at a vulnerable stage of the infant's life has not precluded other mechanisms being implicated, including genetic susceptibility to cardiac dysrrhythmias.

Summary and Conclusions

Our understanding of SUDEP has increased over the last two decades, but further research is needed. With the aim of prevention, we need to seek a better understanding of mechanisms and a better way to identify at-risk individuals. More generally, research into seizure prediction and detection could help to optimize response to seizures. The effects of therapy (mono or polytherapy) and its withdrawal on ictal and postictal states in relation to depressed consciousness and respiratory and cardiac parameters need to be explored. We also believe that further studies exploring the potential role of cardiac mechanisms outlined here are required.

The present focus in management, with the aim of preventing some SUDEP cases, is on seizure prevention and response to seizures. The former requires optimal medical and surgical therapy, guided by the studies mentioned earlier, as well as self-management and understanding by the patient of the importance of avoiding seizure triggers. The latter implies being with other people and impinges on hard-won independence. Informed patients will vary as to the level of risk they want to take, whether in considering independent living, or, if their condition is being controlled, in choosing to withdraw medication. It is important, however, to acknowledge that whereas some SUDEP deaths may be preventable, at present it is not possible to estimate the proportion nor is it possible to give more than broad estimates of risk in individual cases.

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Chapter 190

Autonomic Disturbances

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Introduction

Seizures are often accompanied by alterations in autonomic function such that any system controlled by the autonomic nervous system (ANS) has the potential to be disrupted before, during, or after the ictal event. Seizure-induced alterations in cardiovascular and gastrointestinal function occur most often, but pulmonary, sexual, pupillary, and cutaneous changes are also common. Symptoms can be subjective (sensory only) or the ictal event can actually change peripheral organ function. With simple autonomic seizures the sole clinical manifestation is an alteration in autonomic function, while complex partial seizures are often preceded by an autonomic aura. The ultimate manifestation of the autonomic disturbance is dependent on the type of seizure and the brain areas involved.

In order for a seizure to alter autonomic function, it must propagate to brain areas that comprise the central autonomic network (CAN). Limbic and cortical structures in the network control the output of the parasympathetic and sympathetic branches of the ANS through the hypothalamus and brainstem structures. Early clinical studies by Penfield and Kristiansen[87] and Van Buren[107,108,109] identified autonomic changes after stimulation of specific limbic and cortical structures. Van Buren also detected seizure-related autonomic changes in patients treated with the convulsant pentylenetetrazol (PTZ).[107,109] More recently, the experimental seizure models of kindling,[32,33,53] penicillin,[61,73,74] and PTZ[62,99] have been used to examine the mechanisms that underlie seizure-induced alterations in the ANS.

Seizure-related changes in autonomic function do not typically result from a generalized activation of one or both branches of the ANS. Symptoms are often restricted to an isolated system, which in some cases can be used as a diagnostic tool to localize seizure onset. However, the same set of symptoms can lead to misdiagnosis given that some seizure-induced changes mimic autonomic dysfunction related to other diseases. The proper diagnosis of syncope versus epilepsy and cardiac arrhythmias due to cardiovascular disease versus seizure-induced alterations in cardiovascular function remains a clinical challenge. Cardiovascular and respiratory disruption are particularly significant in that they have the potential to be life threatening and possibly play a role in sudden unexplained death in epilepsy (SUDEP).

Anatomy of the Autonomic Nervous System

The Central Autonomic Network

By definition, the ANS refers to the portion of the central and peripheral nervous systems that regulates autonomic function through the sympathetic and parasympathetic branches. The ANS is under the control of the CAN, whose anatomy and physiology have been extensively reviewed by Benarroch.[6] Structurally, the CAN consists primarily of the insular cortex, medial prefrontal cortex, amygdala, hypothalamus, and ventrolateral medulla. These areas can be functionally divided into those areas that relay sensory information and those that have a motor or effector action. There are reciprocal connections among all the structures within the CAN that help to integrate autonomic responses. The insular cortex is involved with visceral sensory function, while the anterior cingulate and other medial frontal structures appear to have primarily effector roles in autonomic seizures. Stimulation of the cingulate gyrus in humans can lead to intense vagal effects, including bradycardia and even cardiac arrest.[91] Deeper mesial temporal and limbic structures including the amygdala are also involved. Activation of the insular cortex and amygdala can produce cardiac arrhythmias, whether initiated by epileptic seizures or by other lesions such as stroke.[6,82] The amygdala is involved with the autonomic response to emotion. Stimulation of the amygdala can produce salivation and mydriasis in cats.[51]

In the diencephalon, the hypothalamus has a major role in visceral motor, neuroendocrine, and sexual function.[38] The hypothalamus controls both sympathetic and parasympathetic activity and is also involved in temperature regulation. There is evidence that subpopulations of neurons within the hypothal-amus can selectively activate subpopulations of preganglionic neurons.[16]

Finally, in the brainstem, the nucleus of the tractus solitarius (NTS) and the ventrolateral medulla are crucial. These medullary structures have major roles in regulating cardiovascular activity, respiration, and other autonomic motor phenomena. The NTS is important both in the afferent relay of viscerosensory information from the periphery to higher centers and in the efferent control of cardiovascular function.

Parasympathetic and Sympathetic Branches

Central control of autonomic function is mediated though the parasympathetic and sympathetic branches of the ANS.[5] Cells bodies for the parasympathetic branch are located for the most part in the brainstem. Parasympathetic innervation through cranial nerves III, VII, and IX mediates pupillary constriction, salivation, and lacrimation. Cranial nerve X (the vagus nerve) supplies parasympathetic innervation from the medullary structures of the dorsal motor nucleus of the vagus and the nucleus ambiguous to areas throughout the cardiovascular and gastrointestinal systems. Parasympathetic fibers in the second through fourth sacral spinal nerves largely influence genitourinary function.

Sympathetic innervation descends from the brainstem, synapsing on neurons in the intermediolateral cell columns located from T1 to L2 of the spinal cord. Axons from these cells exit the spinal cord through spinal nerves synapsing on neurons

in the paravertebral chain ganglia. These preganglionic neurons are organized into functional units such that different functions under sympathetic control can be selectively activated.[46] Postganglionic axons provide extensive innervation of the cardiopulmonary system and the smooth muscle of blood vessels throughout the body, playing a role in blood pressure maintenance and vasodilation.[5]

Clinical Symptoms

Many of the clinical phenomena associated with seizures are mediated by the ANS. Seizures often induce tachycardia, hypertension, apnea, borborygmi, altered gastric motility, decreased galvanic skin response, diaphoresis, mydriasis, increased secretions, or incontinence.[69,107]

Occasionally, simple partial seizures have solely autonomic manifestations, including cardiac rhythm disturbances; epigastric or intestinal sensations; skin changes such as flushing, pallor, or piloerection; and changes in pupillary or sexual function. In one series, one third of all simple partial seizures included autonomic features.[21] Complex partial seizures often begin with autonomic symptoms, especially those seizures with onset in mesial temporal areas (hippocampus and amygdala), medial frontal cortex (cingulate), or the insula. In one series of patients with refractory temporal lobe epilepsy, almost all had auras, which a large majority described as epigastric or abdominal.[27] Fear was the next most common aura.[10] The character of the aura symptoms can help with seizure onset localization, but not necessarily with lateralization.[84]

Cardiovascular Manifestations

Tachycardia and hypertension are impressively common in all types of seizures. In one study, 96% of seizures included increased heart rate; none produced bradycardia.[54] A study that recorded ambulatory electroencephalograms (EEGs) and simultaneous cardiograms during temporal lobe seizures showed an increased heart rate in 92% of 74 seizures; 30% had heart rates above 140.[12] These arrhythmias, consisting of irregular bursts of increased heart rate, occurred in 42% of seizures, typically late in the seizure. In a series of 145 seizures in 58 patients, 87% included tachycardia, which correlated with a mesial temporal seizure onset.[68] Only two (1.4%) had bradycardia, both with a left hemisphere seizure onset. Heart rate changes preceded EEG changes in 110 seizures, were simultaneous in five, and followed the EEG change in 30. Tachycardia preceded epileptic activity by a mean of 14 seconds in patients with temporal seizures and was more likely with a right-sided origin. With implanted depth electrode recording, there was no predominant laterality of seizures causing tachycardia, and tachycardia did not ensue from amygdala stimulation alone.[25] Rather, spread of seizures was necessary to produce tachycardia; its likelihood correlated with the extent of cortex involved.[25]

Bradycardia, generally considered to be mediated through the hypothalamus and vagus nerve, is far less common than tachycardia during seizures. However, it can be a more severe clinical problem, occasionally leading to sinus arrest[55] or asystole,[44] and in some cases necessitating placement of a cardiac pacemaker.[20] Bradycardia causing syncope often correlates with visceral symptoms and left hemisphere epileptogenic sites.[20] Antiepileptic drugs (AEDs) may treat the bradycardia by preventing seizures.[20] A literature review of ictal bradycardia in the setting of focal seizures indicated a modest but clear left-sided predominance for the epileptogenic site; seizures could originate in medial temporal or frontal areas.[104] Bradycardia is more likely to occur in temporal lobe seizures than in seizures of other origin.[29]

Other cardiac arrhythmias associated with epileptiform discharges include supraventricular tachycardia,[92] paroxysmal atrial tachycardia,[97] and sinoauricular heart block.[90] In one case report, paroxysmal atrial tachycardia occurred during seizures with a right frontal focus due to a tumor. The seizures and the arrhythmia ceased following tumor resection.[97] Sinoauricular heart block can accompany right temporal seizures, associated with an epigastric aura, diminished responsiveness, and syncope, presumed to represent a vagal effect.[90] This arrhythmia was treated successfully with anticholinergic agents, and with phenytoin.

Abnormal autonomic activity in patients with epilepsy is not restricted to the ictal state. Interictally, many patients with temporal lobe epilepsy have reduced heart rate variability, independent of AED use.[2,3] In another study, patients with complex partial seizures had large interictal fluctuations in heart rate that were not seen in controls.[28]

A major alteration in the variability of autonomic nerve activity innervating cardiovascular structures may be a risk for potentially serious arrhythmias.[61]

Analysis of the R-R interval (RRI), the period of time separating successive heartbeats, revealed RRI fluctuations at the respiratory frequency that were parasympathetically mediated, and RRI fluctuations at higher frequencies that were mediated by the combined effects of sympathetic and parasympathetic inputs to the heart.[80] In this analysis, complex partial seizures produced a marked imbalance in parasympathetic and sympathetic drive to the heart. Parasympathetic activity fell rapidly 30 seconds before seizure onset, while sympathetic activity continued to rise, peaking at seizure onset. In a report of two patients with temporal lobe epilepsy, investigators observed that a period of acute deterioration of seizure control was accompanied by increased parasympathetic function and that bradycardia began up to 40 seconds before seizure onset.[105]

Gastrointestinal Manifestations

Gastrointestinal symptoms are by far the most common epileptic seizure symptoms mediated by the ANS. While the most common gastrointestinal manifestation is the rising epigastric sensation initially described by Gowers,[34] other symptoms include vomiting, cramping, bloating, and diarrhea. Abnormal visceral sensations can arise from the normal perception of abnormal intestinal motor activity due to abnormal autonomic activity. However, most symptoms appear to remain restricted to altered sensory perception by the brain. Indeed, during complex partial seizures there is typically an inhibition of gastric motility.[109]

Van Buren[108] reviewed the histories of 100 patients who had depth electrode monitoring for refractory epilepsy and had chest, abdominal, or pelvic symptoms considered epileptic in origin. Symptoms characteristically began as partial seizures (auras) leading to complex partial seizures, with half of the patients reporting the spreading or rising epigastric sensation. Viscerosensory auras in patients with refractory seizures were temporal in onset in 90% of cases, with 10% from frontal and other areas.[84] In a series of patients with visceral symptoms, Mulder et al.[78] also noted that abdominal pain could be a manifestation of a sensory seizure alone or could be due to spasm induced by epileptic motor activity. Two thirds of these patients had gastrointestinal symptoms, especially nausea, which could occur in isolation. Abdominal discomfort occurred in another one third. In nine patients evaluated for epilepsy surgery with temporal lobe seizures and ictal vomiting, Kramer et al.[58] found a right-sided predominance of interictal and ictal discharges. In another study of patients with focal-onset seizures, one third

of auras that began in the right hemisphere were autonomic in nature versus only 8% from the left, and 84% of all autonomic auras originated on the right.[36] Almost all consisted of abnormal epigastric sensations.

Gastrointestinal manifestations of seizures can also include motor or effector autonomic phenomena such as vomiting, swallowing, and salivation, suggesting involvement of the hypothalamus and lower medullary structures that coordinate such motor activity through the nucleus of the tractus solitarius and dorsal motor nucleus of the vagus.[78,107] Vomiting is the most prominent autonomic motor manifestation of seizures, with cyclic vomiting a major symptom of partial seizures in children.[77] An anterior temporal focus can cause vomiting, accompanied by olfactory hallucinations followed by loss of consciousness or generalized convulsions. Especially in children, this has been labeled *abdominal epilepsy*. Many children have benign overlap syndromes including features of both epilepsy and migraine, often with occipital spike discharges.

Panayiotopoulos syndrome is a remarkably common “idiopathic susceptibility to early-onset benign childhood seizures” with primarily autonomic manifestations.[57] Patients (usually children aged 3 to 6) have recurrent gastrointestinal symptoms distinct from migraine.[85] Nausea and vomiting upon arousal from sleep are the primary clinical manifestations. Pallor and flushing are also common. Other epileptic manifestations include eye deviation and loss of consciousness, some with hemibody or generalized convulsions. Seizure-induced vomiting is presumed to represent epileptic activity transmitted from cortical areas through the hypothalamus and medulla. Epileptiform discharges are often occipital but may be multifocal, usually in posterior areas. Seizures may be prolonged to the point of status epilepticus,[57] but many children have just single episodes, and the prognosis is generally excellent. Most children recover without AED treatment. About 20% go on to have later epilepsy.

The sensation of *fear* (often localized by patients to intestinal sensations) has a strong correlation with seizures involving the amygdala,[31] and amygdala stimulation can produce such feelings in conscious patients. Ictal fear is usually accompanied by gastrointestinal or epigastric symptoms.[108] In one series, fear correlated better with amygdala atrophy than with hippocampal structural abnormalities.[17]

Genitourinary Manifestations

Urinary incontinence is common, but not invariant, in generalized convulsions, often occurring after the clonic phase. It occurs far less frequently in partial seizures, and fecal incontinence occurs even less often. Focal seizures can prompt a sensation of urinary urgency. We were unable to find unambiguous reports of urination as the sole manifestation of epileptic seizures.

Sexual Manifestations

Normal sexual function is dependent on the sensory nervous system and on motor and behavioral effector autonomic function. Seizures can affect sexual function in many ways. Epileptogenic foci in parietal or temporolimbic structures subserving sensation from genital and pelvic regions can produce “pure” sensations in those areas, without autonomic involvement or a more extensive sexual perception or feeling.[78] Erickson reported one woman with ictal sensations of pelvic “hotness,” proceeding to left leg jerking, left abdominal sensations, and loss of speech, all resolving after resection of a right frontal parasagittal tumor.[26]

More typical sexual sensations arise from epileptogenic areas in temporolimbic regions, more often in the right hemisphere.[93] Remillard et al.[93] reported a series of 12 women with such sensations—generally unpleasant at first but later pleasurable in many. Seven of the 10 localizable seizure foci were on the right side. They were able to produce such feelings (sometimes progressing to arousal or orgasm) with mesial temporal depth electrode stimulation in two. A female predominance of these phenomena (20 of the total 23 patients reviewed) suggested that limbic structure organization differs between the two genders and offered a partial explanation of the behavioral differences in men and women with temporolimbic seizures.[93]

Infrequently, seizures progress to the more complicated symptom of orgasm, involving motor autonomic nerves and implicating involvement of motor areas.[15] Women and men have reported orgasmic auras.[47,48] Ruff[96] reported two patients with right parietal tumors and unpleasant or even painful orgasm caused by seizures. This combination of sensory and autonomic motor components suggests spread of seizures to the hypothalamus and then peripheral autonomic nerves.

Cutaneous Manifestations

Seizures can also produce flushing, pallor, and pilomotor erection.[76] Unilateral flushing is rare but can arise from a contralateral seizure focus.[78] Pilomotor erection or “goose flesh” is seldom the sole manifestation of a seizure and is usually accompanied by other autonomic phenomena.[24] Some seizures cause bilateral pilomotor phenomena.[1] Occasionally, they are unilateral[78] and sometimes ipsilateral to the seizure focus.[35] Shivering and bilateral piloerection were traceable to left temporal seizures in 18 of 22 localizable cases.[103]

Pulmonary Manifestations

Episodes of apnea are common in temporal lobe seizures, usually with the chest in an expiratory position.[107] Especially when generalized, seizures can progress to include respiratory arrest.[78] Some seizures cause abnormal throat sensations that induce a feeling of shortness of breath or choking. Others lead to hypoventilation and oxygen desaturation.[11] Stimulation of the insula or hippocampal gyrus inhibited respiratory function in man.[52] Nevertheless, respiratory or pulmonary manifestations of seizures appear to be far less common than cardiovascular or intestinal symptoms.

Pupillary Manifestations

Unilateral mydriasis can occur with contralateral frontal seizures, but bilateral pupillary dilation is more common in seizures. Unilateral mydriasis is often presumed to arise from an ipsilateral seizure. In the largest series describing this phenomenon, this was the case in three patients, but five patients had mydriasis ipsilateral to the unilateral motor activity, thus from the contralateral hemisphere.[86] Unilateral mydriasis did not have localizing or even lateralizing value and was never the sole manifestation of seizures.

Experimental Observations: Clinical

In addition to the numerous clinical reports that describe seizure-related alterations in autonomic function, there have been a number of experimental clinical studies that have helped to elucidate the structures, pathways, and mechanisms that underlie these changes. PTZ is a γ-aminobutyric acid $(GABA)_A$ receptor antagonist initially used as an “artaleptic” to reverse the effects of sedatives, and was also used as a forerunner of electroconvulsive therapy. Early work that described many of the features of PTZ-induced seizures reported increases in heart rate, blood pressure, and cerebrospinal fluid pressure during the seizures.[107,109,113] In patients who were not pharmacologically paralyzed, periods of apnea were also reported.[30,107] Autonomic consequences resembled events associated with spontaneous seizures[107] and included many of the same visceral sensations reported during auras at the onset of seizures.[109]

Table 1 Lateralized Epileptic Autonomic Manifestations

All autonomic auras	85% right hemisphere[36]
Ictal vomiting	All right temporal (nine cases, depth electroencephalogram)[58]
Pilomotor erection (bilateral)	18 of 22 cases: Left temporal onset[103]
Sexual auras	More right hemisphere[93]
Bradycardia	Left hemisphere onset[104]
Tachycardia	*Not* lateralized[25,54]
Parasympathetic effects (bradycardia)	Left insula stimulation[83]
Sympathetic effects (tachycardia, hypertension)	Right insula stimulation[83]
Hypotension,	Right Wada testing[39]
decreased sympathetic effects	
Sympathetic effects, hypertension	Left Wada testing[39]

Electroconvulsive therapy (ECT) for psychiatric illness has also been used as a model system in which to examine autonomic changes associated with seizures. The period of electroconvulsive stimulation[14,110] caused intense seizure activity with a tonic phase lasting 10 to 12 seconds followed by a clonic phase lasting 30 to 50 seconds. Respiratory changes were marked by a period of apnea that outlasted the tonic phase, followed by expiration and then inefficient ventilation during and after the clonic phase, and finally hyperventilation. Heart rate changes were characterized by a brief initial sinus bradycardia that appeared to be due to vagal activity, followed by sinus tachycardia up to 190 bpm. Heart rate returned to normal over a period of several minutes. Similar life-threatening changes in blood pressure and heart rate were seen when convulsions were prevented by curare administration, indicating that the autonomic changes were central in origin and not provoked by motor activity.

Stimulation of the amygdala or mesial temporal region produced a typical abdominal aura, always with a rising character.[108] Similarly, right hemisphere suppression (in Wada testing) can cause hypotension without heart rate changes, suggesting that the right hemisphere is dominant for sympathetic effects.[39] Left-sided suppression led to hypertension (a presumed sympathetic excess) suggesting left-sided control of parasympathetic function. More recent intraoperative studies of patients undergoing epilepsy surgery found that left-sided insular stimulation caused bradycardia and blood pressure decreases, while right insular stimulation led to tachycardia and hypertension.[39,82] Oppenheimer[81] has suggested that insular cortex seizures might desynchronize the harmonious workings of the sympathetic and parasympathetic systems and lead to cardiac arrhythmias. A summary of lateralized epileptic autonomic manifestations can be found in Table 1.

Experimental Studies: Animal Models

Animal studies offer model systems that replicate features of human epilepsy and autonomic dysfunction, which can be used to study the mechanisms whereby interictal and ictal paroxysmal activity affect autonomic function. Goodman et al.[32,33] monitored blood pressure and electrocardiogram (ECG) in amygdala-kindled rats during the seizure. Kindled seizures activated both sympathetic and parasympathetic systems and produced ictal hypertension and bradycardia that could each be blocked pharmacologically. These changes were not observed when the kindling stimulus was delivered to the amygdala in naïve animals. There is also evidence that the baroreflex responses are altered interictally in amygdala-kindled rats.[53]

Oppenheimer et al.[83] examined the effects of left insular stimulation in rats on cardiac function and found an increasing degree of heart block and resultant ventricular escape rhythms that eventually resulted in asystole. Lathers et al.[62,99] observed autonomic changes during PTZ-induced seizures in anesthetized cats. During the seizure there was increased variability of cardiac autonomic nerve discharge rates. Cardiac sympathetic and parasympathetic activity was intermittently synchronized with interictal spike activity (lockstep phenomena).[63] It was also observed that “unstable lockstep” (periods when interictal spikes and synchronized autonomic activity occurred at irregular intervals) was associated with large fluctuations in blood pressure.[102] The following ECG abnormalities were observed during seizures induced by the direct injection of penicillin into the hippocampus of the cat: P-R interval changes, increased P-wave amplitude, QRS complex changes, T-wave inversion, and ST elevation.[62] Animal studies have shown that imbalance between the parasympathetic and sympathetic drive can produce ECG abnormalities, such as sinus pauses and prolonged QTc, which could predispose to malignant cardiac arrhythmias.[106]

Mameli et al.[73,74] used anesthetized and hemispherectomized rats to investigate which brain regions control cardiac function. These investigators found that application of penicillin G to the hypothalamus produced bradyarrhythmias and a small (4% to 6%) decline in systolic blood pressure. Creating an additional penicillin focus at the mesencephalic level increased paroxysmal activity, and produced second-degree atrioventricular (AV) block and impaired AV conduction, created bundle branch blocks, and caused an additional 17% reduction in systolic blood pressure. Coactivation of hypothalamic and mesencephalic centers by focal injection of penicillin G resulted in death in 25 rats.[73]

In a model of SUDEP, bicuculline was used to induce status epilepticus in chronically instrumented sheep.[49] The only parameter that correlated strongly with seizure-induced death was marked hypoventilation. In a subsequent study, Johnston et al.[50] showed that the hypoventilation was central in origin.

Autonomic Dysfunction as a Diagnostic Tool

Simple autonomic seizures can be defined as focal seizures with purely autonomic signs and symptoms. We have already described autonomic auras and autonomic consequences of seizures, particularly for focal limbic seizure activity. In circumstances where the aura is clearly followed by a seizure, the features of the aura can help with diagnosis. In other cases, where auras occur without an apparent seizure, diagnosis of a seizure disorder can be made more difficult, similar

to the difficulty in differentiation of syncope from seizure described below. Some epileptic abdominal pain can be difficult to distinguish from nonepileptic intestinal problems, prompting urgent medical evaluations.[88]

Seizure Versus Syncope

Transient loss of consciousness presents diagnostic challenges for the clinician because in many cases there are no detectable signs to identify an underlying disorder by the time a patient is seen. Part of the differential diagnosis for transient loss of consciousness is consideration of an isolated seizure or syncopal episode.[8,23,40,41,42] Reports by eyewitnesses are among the most valuable data for differentiating seizures from syncope. A rapid return to alertness reported by witnesses and specific autonomic symptoms (e.g., sweating, nausea) preceding attacks reported by patients are more commonly associated with syncope. By contrast, clonic movements or automatisms and early disorientation are more often reported in patients who have had seizures.[41] It has been argued that a syncopal episode of unknown origin may actually be one of the first signs of a developing seizure disorder.[4]

Although numerous reports suggest strategies for the differentiation of seizures from syncopal episodes, seizures, and syncope may occur in relation to one another[13] (see also Chapter 68, “Differential Diagnosis,” and Chapter 271, “Syncope”). Of course, many seizures cause loss of consciousness. In addition, seizures occasionally lead to typical syncope, through ictal bradycardia and other mechanisms. In turn, syncopal episodes often include a few brief jerking movements and may even trigger a seizure.[7] As described above, bradycardic episodes have been shown in a couple of examples to clearly precede patients' seizures.[105] In each of these examples, the seizure “trigger” may be increased neural activity that occurs during reperfusion. On the other hand, Saito et al.[98] have stopped seizures in rats by reducing blood flow to the forebrain.

Seizures Misdiagnosed as Cardiovascular Dysfunction

Cardiac manifestations of seizures have been widely reported because they can be life threatening and may explain some cases of sudden death in epilepsy patients.[22,56] Whereas most descriptions of bradycardia and arrhythmia suggest a predominantly parasympathetic outflow, tachycardia has been reported as the principal cardiovascular feature in some subclinical seizures.[111] The differential diagnosis for cases that involve bradyarrhythmias is similar to that described for the differentiation of syncope from seizures. Seizure-induced increases in sympathetic activity have been confused in some cases with pheochromocytoma,[76] but in some cases pheochromocytoma can trigger seizures.[67]

Autonomic Dysfunction, Neurogenic Edema and Sudden Unexplained Death in Epilepsy

Neurogenic Pulmonary Edema

Neurogenic pulmonary edema (NPE) is a rapidly developing increase in pulmonary interstitial and alveolar fluid due to an acute central nervous system catastrophe.[19,60,72,100] NPE includes dyspnea, sometimes hemoptysis, tachypnea, tachycardia, and rales on examination. Fortunately, NPE may resolve on its own within hours or days. Many cases may be subclinical.

Three conditions account for most cases of NPE: Hemorrhage, head injury, and epileptic seizures, especially status epilepticus.[60,70,95,100] Seizures appear less likely to cause NPE, but they are more prevalent than the other precipitants. Some diagnoses of postictal aspiration pneumonia may actually be mild forms of NPE. Postictal NPE may be recurrent in some children.[79]

The autonomic nervous system is clearly implicated in NPE. Major disruption of intracranial function is always present, frequently with hypothalamic dysfunction.[94] Consistent with other examples of altered autonomic effector function, the medulla (especially the NTS) is crucial in the pathogenesis of NPE.[18] Section or denervation of splanchnic sympathetic fibers to the lung or spinal cord transection at the C7 level or above (or α-adrenergic blockade) may abort NPE experimentally.[37,71]

There are two major theories to explain the development of the lung pathophysiology in NPE: (a) changes in systemic hydrostatic pressure and (b) changes in pulmonary capillary permeability.[43] Neither is required for all cases, and each can contribute.[101] Some patients have evidence of increased pulmonary vascular permeability,[70,75] including an elevated alveolar fluid protein concentration indicative of pulmonary capillary leak; others have low lymphatic fluid protein.[101] A combination of factors, with initial pulmonary hypertension damaging capillary linings and causing permeability changes, could be responsible.[112]

Sudden Unexplained Death in Epilepsy

ANS disruption is probably a major factor in SUDEP (see Chapter 189). Its incidence is about 1 per 1,000 people with epilepsy per year but 3.5 per 1,000 per year in refractory epilepsy.[64] Seizures may cause apnea directly, but respiratory failure is generally not considered the best explanation for SUDEP. At least some degree of pulmonary edema occurs in many cases of SUDEP,[66] but rarely does neurogenic pulmonary edema become life threatening from single seizures alone. Life-threatening cardiac arrhythmias accompany relatively few seizures, but they may be the best explanation for SUDEP given the overall occurrence of seizures in patients with refractory epilepsy.[65]

Even interictally, some epilepsy patients have cardiac rhythm disturbances that may implicate a greater vulnerability to arrhythmias. Some of this autonomic dysfunction may be related to AEDs,[45,59,89] but some patients have autonomic dysfunction even before treatment.[9] Nevertheless, dysfunction can be worse with refractory epilepsy, suggesting that it may be the *undertreatment* of epilepsy that is of greatest concern for SUDEP.[2]

Summary and Conclusions

In this chapter we have identified autonomic disturbances that commonly occur before, during, or after a seizure. The specific disturbance is dependent on the type of seizure, the brain areas involved, and propagation of the seizure to structures in the central autonomic network. While some autonomic changes have diagnostic value, seizure-induced changes in autonomic function can resemble autonomic changes associated with non–seizure-related diseases, leading to misdiagnosis and delay in treatment. Autonomic disturbances in cardiovascular and respiratory function are particularly significant given their possible role in SUDEP.

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Chapter 191

Comorbidity in Adults

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Introduction

Seizures commonly occur in the setting of general medical disorders, and their occurrence may then have significant implications regarding the prognosis and treatment of the primary disease. In addition, the treatment of seizures—whether secondary to some general medical disorder or the manifestation of a primary disturbance of central nervous system (CNS) function—may be complicated or influenced by nonneurologic factors. This chapter discusses these varying aspects.

Seizures and Renal Failure

Seizures occur in about one third of patients with acute or chronic renal failure. The seizures that occur in acute uremia tend to be associated with a severe encephalopathy, usually occurring between 7 and 10 days after the onset of renal failure and during its anuric or oliguric stages.[21,200] They are commonly generalized tonic–clonic seizures and are often multiple. Partial seizures also occur, and epilepsia partialis continua has been described.[158] When recurrent seizures or single partial seizures occur in uremic patients, however, investigations should be undertaken to exclude an underlying structural lesion.

The uremic convulsions complicating chronic renal failure are most likely to occur with advanced disease and develop especially in patients with a significant encephalopathy or who are preterminal.[21,158] Fewer than 10% of patients with chronic renal insufficiency now experience convulsions.[157,200] The decline in the incidence of seizures may reflect more aggressive treatment of renal failure and its various complications, such as hypertensive encephalopathy, abnormalities of fluid and electrolyte balance, and altered metabolism of proconvulsant medications such as penicillin.[21,158,200]

The convulsions associated with chronic renal failure are typically generalized tonic–clonic seizures; partial motor and generalized myoclonic seizures occur less often.[21,158] Treatment involves correction of renal failure and associated metabolic abnormalities, but it may also necessitate anticonvulsant treatment, especially when no specific cause of the convulsions is evident.[21,157] Phenytoin is commonly used, but other agents, such as phenobarbital and valproic acid, are also effective.[12,21,158] Status epilepticus, a rare complication of chronic renal failure, is managed as when it occurs from other causes.[158]

Treatment of renal failure may itself lead to seizures. Generalized convulsions sometimes occur during the late stages of hemodialysis or several hours after a session in patients with the dialysis disequilibrium syndrome.[157] They may relate to fluid shifts associated with the hemodialysis and resulting in cerebral edema.[59] With improved dialysis techniques, seizures are now a less common occurrence.[59,157]

Dialysis encephalopathy is characterized by a distinctive speech abnormality, psychiatric and cognitive disturbances, asterixis, myoclonus, gait ataxia, and seizures. It often has a fatal outcome. Clinical dysfunction is preceded by electroencephalographic (EEG) abnormalities, especially paroxysmal bursts of frontally predominant high-voltage delta or spike-and-wave activity.[86,143] The syndrome, which generally develops after treatment by dialysis for several years, may relate to increased aluminum levels in the brain.[10] The origin of the aluminum may be the water in the dialysate, phosphate-binding compounds that are ingested, or both. Treatment of the dialysate to remove aluminum has reduced the incidence of the disorder.[10,59,143,157] Seizures, usually of the generalized tonic–clonic variety, occur in almost two thirds of patients with dialysis encephalopathy and are especially likely during or immediately after dialysis. Myoclonic, simple partial, and complex partial seizures are less common.[21] Convulsions usually respond initially to diazepam, phenytoin, or carbamazepine but become harder to control as the disease progresses.[21,143,185]

The use of anticonvulsants in patients with preexisting renal disease is sometimes problematic. Uremia complicates anticonvulsant therapy because of altered protein binding and renal excretion of drugs; dialysis may also result in removal of anticonvulsant agents from the circulation. The situation is exemplified by phenytoin. This anticonvulsant is normally 90% protein bound, but in advanced renal failure, protein binding of phenytoin declines by as much as 20%, resulting in a greater volume of distribution and lower serum concentrations.[12,142] Nevertheless, the benefit of a given dose is maintained because the proportion of unbound (active) phenytoin increases. Consequently, in advanced renal disease, the optimal therapeutic range of phenytoin in the blood decreases from 10 to 20 µg/mL to approximately 5 to 10 µg/mL.[107] Therapy is best monitored in uremic patients by measurement of free phenytoin levels; the therapeutic range is 1 to 2 µg/mL. The total daily dose need not be reduced because phenytoin is unlikely to accumulate unless hepatic function is impaired. Because the half-life of phenytoin may diminish in uremia,[112] it may be appropriate to divide the daily dose rather than to take it all at one time.[12] Phenytoin is not removed to any significant extent by dialysis, and, therefore, the daily dose does not require adjustment.[107]

Valproic acid is especially helpful for myoclonic and generalized tonic–clonic seizures in uremic patients.[12] In renal insufficiency, plasma protein binding decreases, but the free fraction remains constant.[107] Careful clinical and laboratory monitoring is important when patients have severe renal failure. Dialysis does not necessitate additional doses.

Plasma phenobarbital levels are unaffected by uremia. The drug may accumulate,[107] however, and lower maintenance doses are used when it is given on a long-term basis to patients with severe renal failure.[12] Because it is 40% to 60% protein bound, phenobarbital may be partially removed by hemodialysis; some patients therefore require supplemental doses after dialysis.[107] Primidone and its metabolites may also accumulate and lead to toxicity in patients with renal failure.[12] Serum carbamazepine levels are unchanged by uremia, and doses do not need adjustment.[107] Ethosuximide levels are significantly reduced by hemodialysis, and supplementation may therefore be necessary.[107]

Many of the newer antiepileptic drugs show decreased clearance when renal function is impaired. These agents include felbamate,[68] gabapentin,[20] topiramate,[104] levetiracetam,[45] vigabatrin,[75] pregabalin,[16] and oxcarbazepine and its active metabolite monohydroxycarbazepine.[168] Gabapentin and pregabalin are excreted almost exclusively by the kidney with negligible metabolism,[16,20,156] and these drugs should be used with extreme caution and at reduced doses in patients with renal insufficiency. Topiramate also is eliminated mainly in the urine, although the percentage decreases somewhat in the presence of hepatic enzyme–inducing medications[11,104]; doses must be reduced in patients with kidney disease as with gabapentin and pregabalin. In patients on hemodialysis, supplemental doses of levetiracetam, typically 250 to 500 mg, are required.[45] Topiramate[104] and pregabalin[156] concentrations also decrease significantly after hemodialysis, and additional doses may be required. Gabapentin should be administered as a single 200- to 300-mg dose after each dialysis session.

Zonisamide is 40% to 50% protein bound and undergoes both hepatic metabolism and renal clearance.[11,110] Dose reduction may be necessary in patients with moderate or severe renal insufficiency. Protein binding may be lower in patients undergoing hemodialysis, and about 50% is removed during each dialysis session; however, supplemental doses often are not required if zonisamide is administered as a single daily dose after dialysis sessions, given the markedly reduced clearance in end-stage renal disease.[87] Tiagabine and lamotrigine pharmacokinetics appear largely to be unaltered even when renal function is severely impaired, and dose adjustment is usually unnecessary.[30,210] Occasionally, the half-life of lamotrigine is prolonged with severe renal insufficiency, however, and its elimination is more rapid in patients undergoing hemodialysis.[56]

Seizures and Liver Disease

Although early reports suggested that convulsions occurred in up to one third of patients with acute hepatic encephalopathy, Plum and Posner[152] found a smaller incidence and attributed many of the seizures in earlier reports to alcohol withdrawal rather than liver disease. Seizures may be generalized or partial and typically occur in stage III hepatic encephalopathy.[167] Treatment is directed at the underlying hepatic disorder and at relieving the hepatic encephalopathy with protein restriction and agents such as lactulose. Anticonvulsant therapy may not be required unless there is an underlying cause for the seizures, such as intracranial hemorrhage.

Chronic liver disease rarely causes seizures.[116] Seizures that occur in alcoholics with hepatic cirrhosis usually result from previous trauma, intracranial hemorrhage, or alcohol withdrawal. Seizures are common in Reye syndrome[151] and infrequent in Wilson disease.[167] When convulsions occur in patients with acute hepatic necrosis, they frequently relate to severe hypoglycemia.

Many anticonvulsant agents are metabolized by the liver and may cause hepatic toxicity. This is discussed elsewhere in this book and is not considered further here.

The effect of hepatic disease on anticonvulsant pharmacokinetics is usually clinically insignificant until the liver disease is advanced. The management of anticonvulsant drug regimens in patients with liver disease may be problematic. There is reduced protein binding of phenytoin and valproic acid, correlating with levels of serum albumin and bilirubin.[12,107] However, clearance is usually unaltered, and toxicity from drug accumulation is unlikely unless the liver disease is severe. In this latter circumstance, reduction in dose of phenytoin and valproic acid may be necessary, depending on serum drug concentrations. Free serum levels should be monitored closely. The hepatotoxicity of valproic acid mandates that it be used with caution in patients with preexisting liver disease.[12]

Hepatic encephalopathy may be precipitated by phenobarbital, benzodiazepines, and other sedatives in patients with otherwise compensated liver disease.[151] These agents, therefore, are best avoided or used very cautiously in patients with hepatic dysfunction; daily doses may have to be reduced to avoid their accumulation as a result of decreased hepatic metabolism.[107] The slightly decreased protein binding of carbamazepine that occurs in patients with liver disease is clinically insignificant, and serum carbamazepine concentrations are unaltered.[12]

Liver dysfunction alters the clearance of some newer antiepileptic agents. The elimination of lamotrigine decreases in the setting of significant hepatic insufficiency, and dose reduction therefore may be necessary.[123] Lamotrigine clearance also decreases by about one third in patients with Gilbert syndrome, or unconjugated hyperbilirubinemia, requiring the use of lower doses of the drug.[154] Tiagabine undergoes extensive hepatic metabolism, and its clearance is reduced by hepatic dysfunction; the dose should be lowered or the dosing interval increased in this situation.[106] The elimination of topiramate[104] and levetiracetam[45] is reduced only modestly with liver impairment, and the effect is usually clinically insignificant in the absence of concurrent renal dysfunction. Gabapentin[11] and pregabalin[16] undergo only minimal hepatic metabolism, and dose reductions are unnecessary in patients with hepatic insufficiency but preserved kidney function. Liver disease may increase the risk of felbamate-induced hepatic failure, and this medication should not be used in patients with liver disease under most circumstances.

Hepatic Porphyrias

The hepatic porphyrias are characterized by a partial defect in the heme biosynthetic pathway in the liver. The three autosomal-dominant forms with neurologic manifestations are acute intermittent porphyria, hereditary coproporphyria, and variegate porphyria. In acute intermittent porphyria, there is a partial deficiency of porphobilinogen deaminase, and this leads to the buildup of δ-aminolevulinic acid and porphobilinogen, which are excreted in the urine. Hereditary coproporphyria is caused by a partial deficiency of coproporphyrinogen oxidase, and variegate porphyria by a partial deficiency of protoporphyrinogen oxidase.

The neurologic features of these disorders are similar and include peripheral neuropathy, autonomic dysfunction, and behavioral disturbances. Seizures occur in 10% to 20% of patients with acute intermittent porphyria and may be its presenting feature.[93] They may be partial or generalized.[22,170] Status epilepticus may occur but is rare.[170] Cerebral dysfunction in porphyria may relate to γ-aminobutyric acid (GABA) receptor binding by δ-aminolevulinic acid,[14,136] which causes seizures when infused directly into rat brain.[93] In addition, defects in hepatic heme synthesis can affect levels of neurotransmitter substrates, such as tryptophan, in the CNS.[93] Patients with acute porphyric attacks may also have seizures as a result of fluid and electrolyte disturbances, usually from excessive vomiting and inappropriate secretion of antidiuretic hormone. Moreover, idiopathic or symptomatic epilepsy may coexist with porphyria,[64,81,105,118,192] so that anticonvulsant treatment may be required in both acute and chronic settings.

Unfortunately, many antiepileptic agents have been implicated in exacerbating hepatic porphyria by stimulating hepatic δ-aminolevulinic acid synthase activity in humans, in animal models, or in assays in vitro. The anticonvulsants implicated include phenobarbital, phenytoin, primidone, carbamazepine, valproic acid, succinimides, oxazolidones, and benzodiazepines.[22,64,81,105,118,130,160,161,170,176,192] The positions of clonazepam and paraldehyde remain unclear,[119,133] but bromides and magnesium sulfate do not have this enzyme-stimulating effect and their safe use in porphyria has been reported.[22,118,161,176,192] In vitro or animal studies of some of the newer antiepileptic agents, including lamotrigine, felbamate, topiramate, and tiagabine, suggest that they may exacerbate hepatic porphyrias[76,99]; one case report supports this idea for lamotrigine, which was implicated in inducing a porphyric attack that led to multiorgan system failure.[71] Other new agents, such as gabapentin, pregabalin, and levetiracetam, do not induce the relevant hepatic enzymes and may offer additional therapeutic options, as discussed later.

Seizures occurring during acute attacks of porphyria are managed by treating the underlying porphyrinogenic metabolic defect. This includes intravenous administration of a 10% dextrose solution, infusions of hematin or heme-arginate,[93] and correction of associated metabolic abnormalities such as hyponatremia. If seizures persist, magnesium sulfate, given as an intravenous infusion to maintain serum magnesium concentrations between 2.5 and 7.5 mEq/L, may be helpful.[170,176] Others prefer paraldehyde or intravenous benzodiazepines,[161] but this remains controversial.[176] More recently, successful treatment of seizures or status epilepticus in patients with hepatic porphyria has been reported with gabapentin[98,194,213] or levetiracetam,[149,212] although the numbers of cases are small.

Choices for long-term antiepileptic drug therapy in the setting of hepatic porphyria are likely to expand, given the availability of newer antiepileptic drugs without hepatic enzyme–inducing properties. In the past, bromides were commonly recommended despite their toxicity and narrow therapeutic index[22,64,118,161,176]; when using bromides, serum concentrations should be maintained <90 mg/dL.[176] Many reports suggest that low-dose clonazepam is safe for the long-term treatment of patients with hepatic porphyria.[22,64,105,176,192] The current agent of choice, however, is probably gabapentin or levetiracetam,[98,149,194,212,213] although clinical experience is limited. Pregabalin is not an enzyme-inducing agent and may eventually be a useful alternative. A single case report described the safe and effective use of oxcarbazepine in a patient with porphyria cutanea tarda,[62] but this safety profile may not extend to hepatic porphyrias because oxcarbazepine has some hepatic enzyme–inducing properties. Regardless of the treatment choice, levels of urinary δ-aminolevulinic acid and porphobilinogen should be followed closely during therapy.

Seizures and Connective Tissue Diseases

When seizures occur in patients with connective tissue diseases, it is generally because of a cerebral vasculitis or vasculopathy (Chapter 266). Both systemic and isolated CNS vasculitides may lead to seizures, sometimes accompanied by focal or diffuse cerebral abnormalities. Patients with Sjögren or Behçet syndrome occasionally have convulsions during a flareup of disease activity. Seizures reflecting cerebral involvement are rare in rheumatoid arthritis, scleroderma, and mixed connective tissue disease.[37,133,135] In many connective tissue diseases, seizures result from the effects of the disease on other organs, such as the kidneys, or from complications of therapy, especially with immunosuppressive agents, which predispose to CNS infections.

The connective tissue disease having the highest incidence of seizures and other neurologic manifestations is systemic lupus erythematosus (SLE). Seizures and behavioral abnormalities are probably the most common neurologic symptoms of lupus.[61,178] The incidence of seizures in SLE has ranged in different series from 10% to 54%.[27,61,178,208] Generalized convulsions are especially common, but simple partial, complex partial, absence, and akinetic seizures also occur, as may status epilepticus.[27] Seizures may be the initial feature of SLE, sometimes preceding systemic manifestations by several years.[198]

Pathologic examination in patients with SLE and seizures typically reveals cerebral microinfarcts and, less frequently, subarachnoid and intracerebral hemorrhages that have been attributed to an immunologically mediated vasculopathy.[77] Convulsions may also result from infections related to immunosuppressive therapy, uremia from lupus nephritis, or hypertensive encephalopathy and sometimes occur as a terminal event.[61,208] Evaluation must therefore include brain imaging, CSF examination, and investigation for metabolic abnormalities and systemic disease activity.

The treatment of seizures in patients with SLE depends on their etiology. Convulsions resulting from an exacerbation of cerebral lupus are frequently isolated, self-limited events for which anticonvulsant therapy is unnecessary; if several seizures occur over a period exceeding 48 hours, anticonvulsant medication is prescribed for a limited interval (e.g., 3 months) depending on the response to treatment of the underlying SLE. In cases of severe cerebral lupus associated with recurrent seizures, immunosuppression with corticosteroids, cyclophosphamide, or azathioprine may be required.[27] The occurrence of seizures or psychosis without other neurologic features or significant renal disease does not affect the prognosis for survival adversely.[27]

Many anticonvulsants, especially hydantoins, trimethadione, and ethosuximide, are known to cause drug-induced SLE.[78,206] There are also reports of an SLE-like syndrome associated with primidone,[206] carbamazepine, valproic acid,[3,19,48] and lamotrigine.[172] Symptoms typically occur many months after commencement of anticonvulsant therapy and clear days to weeks after its discontinuation, although they sometimes persist for months. Unlike idiopathic SLE, complement levels are usually normal, and antibodies to native DNA are rarely present.[206] There is no evidence that the implicated antiepileptics exacerbate idiopathic SLE,[85] and appropriate therapy should not be withheld from patients with seizures caused by SLE or with coexistent epilepsy and lupus.

Epilepsy and Cardiac Disease

Seizures caused by focal or global cerebral ischemia may occur in patients with cardiac disease (see also Chapter 275). Focal ischemia usually results from cardiogenic embolism, and global cerebral ischemia from cardiac arrest. Convulsive or myoclonic seizures are common after cardiac arrest, and clinical or electrographic status epilepticus is also well described.

Heart disease and epilepsy often coexist in the elderly, and this may pose therapeutic dilemmas. Thus, although intravenous phenytoin and benzodiazepines are important in the acute management of convulsions and status epilepticus, this approach must be used especially carefully in patients with cardiac disease because of the risk of inducing hypotension and cardiac arrhythmias. This risk depends on the rate of drug delivery, advanced age, and severity of underlying cardiovascular disease[44] and has been related to toxicity of the diluent, propylene glycol, a direct cardiotoxic effect of phenytoin, or both.[36,46] In patients at high risk, intravenous phenytoin should be infused at a rate of 25 mg/min rather than 50 mg/min, with continuous electrocardiographic monitoring and frequent blood pressure measurements.[36,46] Hypotension or an arrhythmia generally resolves with temporary discontinuation of the infusion; when restarted, the infusion rate may require reduction to 10 mg/min or less. Intravenous fosphenytoin appears to have the same therapeutic profile as intravenous phenytoin but with fewer cardiovascular effects.[155]

Table 1 Incidence of seizures after transplantation procedure

	Incidence of seizures (%)	Ref.
Bone marrow	3–11.5	65, 148
Kidney	1.5–5	141, 146
Liver	6–25	2, 26, 51, 114
Heart	2–15	72, 150

Long-term anticonvulsant therapy is rarely associated with significant cardiovascular complications. Symptomatic arrhythmias have developed, however, in association with plasma levels of carbamazepine in the optimal therapeutic range, usually in patients with underlying cardiac disturbances.[15,94] It seems appropriate, therefore, to obtain routine electrocardiograms in patients with known cardiac disease who are receiving either carbamazepine or phenytoin on a long-term basis. Any disturbance of consciousness in such patients may relate to a cardiac arrhythmia as well as to seizures, and investigations should be undertaken with this in mind.

The interaction of anticonvulsant and cardiac medications may complicate the management of epilepsy in patients with heart disease. Concurrent use of phenytoin and quinidine sometimes increases ectopy in patients with a history of ventricular arrhythmias.[201] Phenytoin and phenobarbital may increase the metabolism of quinidine, digoxin, lidocaine, and mexiletine through induction of hepatic microsomal enzymes.[46,201] Amiodarone may increase serum phenytoin levels,[126] and calcium channel blockers may increase serum carbamazepine concentrations.[46] It is therefore necessary to measure serum levels of anticonvulsant drugs frequently and to monitor cardiovascular function when introducing or adjusting antiepileptic or cardiac medications.

Seizures in The Transplant Patient

Seizures are frequent in transplant recipients, who may be put at risk by the nature of their underlying illness, prior treatments, perioperative metabolic abnormalities, and postoperative complications such as cerebral ischemia. Following the transplantation procedure, seizures may relate to immunosuppression, drugs, and rejection. The incidence of seizures after transplant procedures depends on the type and method of transplantation and the patient population under study (Table 1). Children are generally at greater risk than adults for posttransplant seizures.[2,66,91,125,129]

The etiology of seizures in transplant recipients is frequently multifactorial. Immunosuppressive agents, especially cyclosporine, may themselves cause seizures. Neurologic complications occur in up to 25% of patients receiving cyclosporine; in addition to seizures, tremor, ataxia, leukoencephalopathy, cortical blindness, neuropathy, quadriparesis, and dysesthesias are well described.[204] O'Sullivan[146] reported cyclosporine-induced seizures in 1.5% of kidney recipients and 5.5% of bone marrow recipients. Others have suggested higher rates, particularly in liver recipients[40,69] and in children.[66,91]

Cyclosporine-induced seizures occur regardless of whether serum levels are within or exceed the therapeutic range and have been attributed to a cyclosporine metabolite.[34] Metabolic and systemic abnormalities and other therapeutic agents may potentiate cyclosporine-related seizures. These various factors include concomitant methylprednisolone therapy,[23,49] hypertension,[89] hypomagnesemia,[2,69,196] hypocholesterolemia,[40] microangiopathic hemolytic anemia,[65,159] and, after renal transplantation, aluminum overload.[141] In many patients with suspected cyclosporine-induced seizures, however, none of these additional abnormalities is present.

Other immunosuppressive agents have also been implicated in the occurrence of seizures after transplantation procedures. Tacrolimus (FK506) has neurologic complications similar to those of cyclosporine, including seizures and encephalopathy.[51,60,174] It is interesting that sirolimus (rapamycin), a newer immunosuppressive agent, does not appear to cause seizures or other neurotoxicity so far as can be determined from an early report that included kidney and liver transplant recipients.[122] Seizures may occur with the antirejection agent OKT3 as one manifestation of a cytokine encephalopathy.[177] Busulfan alone or in combination with cytoxan may be a cause of seizures in bone marrow recipients.[41,197]

Seizures also may occur as an indirect complication of immunosuppressive treatment, for example, as a consequence of CNS infections. They may result from a wide variety of noninfectious structural lesions and metabolic disorders, such as cerebral ischemia or hemorrhage, hyponatremia with central pontine myelinolysis, hyperosmolar states, hypoglycemia, delayed malignancy related to prior treatment, and multiorgan system failure.[66] Finally, transplant rejection may be associated with, or even heralded by, an encephalopathic syndrome that includes seizures.[66,73]

The incidence (Table 1) and etiology of posttransplant seizures depend in part on the type of transplant performed. In bone marrow recipients, seizures may relate to prior irradiation, intrathecal or systemic chemotherapy, systemic complications such as thrombocytopenia, or disease relapse in conditions such as leukemia. Kidney recipients may be predisposed to seizures as a consequence of uremia or other metabolic abnormalities or as a result of cerebral reticuloendothelial tumors.[66] Heart, lung, or liver recipients are especially likely to have early postoperative seizures as a result of cerebral ischemia. New-onset seizures related to cerebrovascular disease or sepsis after orthotopic liver transplantation appear to portend a very poor prognosis.[33]

Seizures always require detailed evaluation to distinguish the many different etiologic factors that may be responsible. Hematologic and biochemical screening tests, determination of blood levels of immunosuppressive agents, cerebrospinal fluid (CSF) examination, EEG, and cerebral imaging studies (preferably magnetic resonance imaging [MRI]) may all be important.

Antiepileptic medication is not necessarily required for transplant recipients with seizures, especially if seizures are self-limited and relate to reversible abnormalities that are unlikely to recur. When seizures are prolonged or carry a risk of other complications, benzodiazepines may be given to control them acutely. Recurrent seizures require long-term anticonvulsant therapy. The choice of anticonvulsant agents is influenced by the type of transplant procedure and immunosuppressive drugs involved. For example, valproic acid should be avoided in liver recipients because of its potentially irreversible hepatotoxicity, and carbamazepine is best avoided in bone marrow recipients because of its myelosuppressive effects. During the 2 to 6 weeks required for bone marrow engraftment after transplantation, it is also appropriate to use phenobarbital rather than phenytoin or valproic acid.[66] Keppra appears efficacious in controlling seizures in liver transplant patients, typically at a dose of 500 mg twice daily, although the number of reported subjects is small.[32,67]

Anticonvulsants that induce hepatic enzymes will affect immunosuppressive agents that are metabolized by the liver.

Phenobarbital, phenytoin, and carbamazepine increase the clearance of cyclosporine and corticosteroids,[6,66,82,204] and this may decrease graft survival in kidney recipients.[205] When these anticonvulsant drugs are used, the dose of corticosteroids should be augmented by 25% to 30%, and cyclosporine should also be increased, depending on serum cyclosporine levels.[66] Some authors prefer to use valproic acid in such circumstances to avoid pharmacokinetic interactions.[82,179] A single case report describes decreased serum cyclosporine levels and sodium concentration after oxcarbazepine add-on treatment was initiated in a patient with epilepsy that predated a renal transplant, but these changes normalized after reduction of the oxcarbazepine dose.[164] Keppra is unlikely to affect immunosuppressive drug levels, has been used successfully in liver transplant recipients, and therefore may be a good initial choice for antiepileptic drug therapy in the overall transplant population. Gabapentin and pregabalin are potential alternatives, given their lack of hepatic enzyme–inducing properties.

Human Immunodeficiency Virus and Seizures

Seizures are a nonspecific but relatively common consequence of infection with human immunodeficiency virus (HIV) (Chapter 265). Convulsions occur at any stage of HIV disease[209] and are occasionally the presenting symptom of HIV infection.[83] However, seizures are an infrequent manifestation of CNS disease in children with HIV infection.[169]

Generalized convulsions are the most common seizure type in patients with HIV infection or AIDS,[83,209] but simple and complex partial seizures are also frequent. Generalized convulsive status epilepticus occurred at presentation in 8% and 10% of HIV-infected patients with seizures in two retrospective series,[83,209] and nonconvulsive status epilepticus has also been observed.[209] Seizure type does not correlate well with the etiology of HIV-related seizures, and the occurrence of partial seizures does not necessarily predict the presence of an opportunistic CNS infection or intracerebral mass lesion unless there are persistent lateralizing clinical signs.

In >40% of patients with AIDS or HIV infection who present with seizures, no cause other than the HIV infection is found. Many of these patients have evidence of HIV encephalopathy on neurologic examination or at autopsy.[209] Other CNS disorders associated with AIDS frequently result in seizures, however, such as cerebral toxoplasmosis, primary CNS lymphoma, cryptococcal meningitis, and cerebrovascular events. Therefore, a thorough diagnostic evaluation must be undertaken in HIV-infected patients who present with new-onset seizures, including biochemical screening tests, MRI of the brain, CSF analysis (including CSF cytology), and determination of serum and CSF cryptococcal antibody titers.

Because seizures frequently recur and status epilepticus may develop in this patient population, anticonvulsant treatment after an initial seizure is recommended.[83,209] However, antiretroviral therapy with protease inhibitors complicates antiseizure management. Protease inhibitors are extensively metabolized by the liver and also influence hepatic enzyme function; thus, antiepileptic drug toxicity or decreased serum levels of protease inhibitors were reported when HIV-infected patients were treated with anticonvulsants that induce or are metabolized by the same enzymes.[17,28,84,115] Therefore, monotherapy with one of the group of newer antiepileptic agents that do not undergo substantial hepatic metabolism or induce hepatic enzymes, such as levetiracetam, pregabalin, or gabapentin, is appropriate initially. In terms of older antiepileptic agents, in addition to the interactions with protease inhibitors, phenytoin is associated with a high incidence of hypersensitivity and other adverse reactions.[83,209] Phenytoin intoxication also has been observed with the concurrent administration of fluconazole,[29] an antifungal agent often used in AIDS patients. Phenobarbital poses a higher risk of adverse cognitive effects than many of the newer agents. Carbamazepine is suboptimal because of the potential for bone marrow suppression in patients who are often at risk for this complication as a result of concurrent medications. HIV patients with status epilepticus usually respond to typical urgent therapy with benzodiazepines and phenytoin.[109]

Seizures Related to Alcohol and Drugs of Abuse

Seizures are a frequent complication of alcohol and recreational drug abuse[50] (Chapter 268). Most alcohol-related seizures are self-limited generalized convulsions that occur in the first 72 hours after cessation of alcohol use, often in association with signs and symptoms of alcohol withdrawal. Seizures are isolated or occur in flurries typically lasting for no more than 12 hours.[50] Alcohol-related convulsions are generally attributed to brief abstinence or acutely declining ethanol levels in long-standing heavy drinkers. One study of alcohol-related first seizures found no association between the interval from last drink to seizure onset,[139] but this is not the general experience.

Seizures with focal features occurring in alcoholics are often the result of prior cerebral trauma. However, because alcoholics are at high risk for occult head injury, CNS infection, cerebrovascular disease, and metabolic derangements, a thorough clinical and laboratory evaluation is generally necessary whenever seizures occur. Hematologic, biochemical, and toxicologic testing is usually indicated, and brain CT or MRI studies should be obtained if a focal cerebral lesion is suspected or for a first convulsion.[50] Cerebrospinal fluid examination and EEG may also be necessary in certain clinical settings.

Because alcohol-related seizures are self-limited and medication compliance is poor in binge drinkers, acute or chronic anticonvulsant therapy is rarely indicated. Phenytoin is not effective for treating seizures in the setting of acute alcohol withdrawal,[5] but benzodiazepines are effective in treating ethanol withdrawal symptoms and may control seizures as well.[199] Convulsive status epilepticus may also result from alcohol withdrawal. In one urban medical center over the last two decades, alcohol was the major etiologic factor in 15% to 25% of cases of status epilepticus.[117] Alcohol-related status epilepticus should be treated with intravenous benzodiazepines and phenytoin according to standard protocols.

Patients whose seizures occur solely in the setting of alcohol or drug abuse do not, by definition, have epilepsy. However, approximately 2% to 4% of patients with alcohol-related seizures have preexisting epilepsy.[50] Although heavy alcohol intake may exacerbate seizures in epileptics for a variety of reasons,[127] light use of alcohol does not increase seizure frequency. Epileptic patients should be advised against chronic or heavy alcohol intake and instructed to avoid isolated drinking binges that are often associated with sleep deprivation.

Seizures may be induced by illicit drug use as a result of acute intoxication or, less frequently, as a withdrawal phenomenon similar to that occurring with alcohol. Seizures related to drugs of abuse are typically isolated, generalized convulsions that are self-limited and do not require acute or chronic treatment with antiepileptic medications; therapy should be directed at the problem of substance abuse itself. However, prolonged seizures and status epilepticus may rarely result from the administration of certain illicit drugs and necessitate urgent treatment. The occasional patient with preexisting epilepsy who abuses recreational drugs can be identified by a history of seizures occurring in the absence of alcohol or recreational drug use or by the presence of interictal EEG abnormalities.[50]

Cocaine is the drug of abuse most commonly implicated in recreational drug–related convulsions.[4,97] Seizures resulting from cocaine abuse have increased in recent years in association with the epidemic use of cocaine.[50] Proposed mechanisms for cocaine-induced convulsions include direct CNS stimulant effects via blockage of neurotransmitter reuptake at dopaminergic and noradrenergic nerve terminals, a possible kindling effect with chronic administration, acute cerebrovascular events or systemic effects, and as a terminal event in massive cocaine overdose.[50,63] Seizures manifest in 2.3% to 8.4% of patients presenting to the emergency room with cocaine toxicity.[97,147] They occur independent of the route of administration and are usually single, generalized tonic–clonic convulsions.[97,147] Most are self-limited, and anticonvulsant therapy is not required except for prolonged seizures or status epilepticus. In addition, seizures having a focal onset or associated with abnormal neurologic findings in cocaine users should raise suspicions of an acute intracranial process that requires evaluation by CT imaging and possibly MRI or cerebral angiography.[147] Neuroimaging should also be performed in patients with new-onset seizures.[50]

Seizures represent an infrequent manifestation of intoxication with other recreational drugs of abuse. Amphetamine intoxication is an uncommon cause of convulsions, which are typically generalized and occur more commonly after intravenous use and administration of high doses.[4] Focal features or abnormal findings on examination should raise concerns for the presence of a cerebral infarct, hemorrhage, or vasculitis.[50] Seizures are also uncommon after phencyclidine (PCP) administration. Generalized convulsions occurred in only 3.1% of 1,000 patients in the largest series of patients presenting to an emergency room with PCP intoxication, although 16% of seizure patients had status epilepticus.[128]

Heroin use has been associated with convulsions.[4,138] Although heroin may act directly as a convulsant agent, it is probably more often associated with seizures related to the concurrent administration of alcohol and other recreational drugs or to the systemic effects of heroin overdose.[4,50] Other complications of intravenous drug abuse that may result in seizures, including infectious endocarditis and HIV infection, should be sought in any patient presenting with convulsions associated with the use of heroin or other intravenous drugs. Marijuana is often used concurrently with heroin and other recreational drugs, but this agent appears independently to lower the risk of a first seizure.[138] Finally, an abstinence syndrome and withdrawal seizures similar to those observed in alcoholics may be induced after chronic administration of sedative agents.[63] Seizures caused by barbiturate and benozodiazepine withdrawal have become less common in recent years, although they are more likely to occur with short-acting agents and should be treated with parenteral benzodiazepines.[63]

Epilepsy and Pulmonary Disease

Pulmonary disease is associated only uncommonly with seizures. Because the prevalence of asthma and epilepsy are both relatively high, the two disorders occasionally coexist in the same patient. In rare instances, epilepsy may result from chronic cerebral injury after recurrent severe hypoxic episodes during asthmatic attacks, and hypoxia-induced seizures occur infrequently during acute asthma exacerbations.[137]

Seizures may result from certain medications used to treat pulmonary illnesses. They occur as a complication of theophylline toxicity in the setting of both chronic use and acute overdose,[13,63] probably from inhibition of phosphodiesterase, which may result in a reduction of adenosine-mediated CNS inhibition.[63] The elderly and patients with coexisting CNS dysfunction appear to be at increased risk for this complication, and seizures may occur with serum levels that are in the therapeutic range or mildly elevated.[13] Partial seizures, generalized convulsions, or status epilepticus occurs with massive acute overdose; when status occurs, it may be refractory to standard anticonvulsants and require hemodialysis or hemoperfusion therapy.[145] Theophylline should be used with caution in epileptics because of a possible risk of seizure exacerbation as well as pharmacokinetic interactions with anticonvulsant drugs.[166,173]

Isoniazid (INH) is another medication that may cause seizures during therapeutic use, although convulsions more frequently occur with overdose.[63] Multiple generalized seizures and status epilepticus are common after INH overdose.[132] Isoniazid probably induces convulsions by lowering brain GABA levels via antagonism of a pyridoxine-dependent cofactor used in its synthesis, and prolonged seizures should be treated with intravenous pyridoxine and benzodiazepines.[63]

Metabolic Causes of Seizures

Disorders of Glucose Metabolism

Seizures may occur in the setting of abnormal serum glucose concentrations (see also Chapter 267). Symptomatic hypoglycemia most often arises as a complication of insulin or oral hypoglycemic therapy, but it may also result from severe he-patic disease, sepsis, alcoholism, insulinoma, terminal cancer, hypothyroidism, fasting, and reactive hypoglycemia.[120,133] In a prospective study of 125 patient visits to the emergency room of an urban hospital for symptomatic hypoglycemia, Malouf and Brust[120] documented seizures in 7%. Seizures typically consisted of focal motor or generalized fits, but multiple seizures or convulsive status epilepticus also occurred. Other neurologic symptoms included depressed sensorium or coma, behavioral changes, tremor, and acute hemiparesis. Symptoms and signs did not correlate well with the degree of hypoglycemia, although most symptomatic patients have blood glucose levels <40 mg/dL.[133] Hypoglycemia should be considered in any patient presenting with seizures. Treatment consists of intravenous dextrose administration and correction of any associated metabolic abnormalities. Death or neurologic sequelae are rare with prompt therapy, but patients are best admitted to hospital for observation because significant hypoglycemia may recur hours after adequate initial treatment.[133]

Nonketotic hyperglycemia manifests with seizures in approximately 25% of patients,[183] and partial motor seizures or epilepsia partialis continua is often the first recognized feature of the disorder,[80,182,203] occurring in 19% of cases.[183] In addition to simple partial clonic or tonic motor fits, nonketotic hyperglycemia may cause complex partial, generalized tonic–clonic, and movement- or posture-induced seizures.[9,25,203] Patients are typically >50 years of age, may not have a known history of diabetes, and present with recurrent partial motor seizures involving one limb; confusion or mildly depressed sensorium and associated focal neurologic deficits may be present, but obtundation or coma is unusual early in the course of nonketotic hyperglycemia, when seizures occur. Serum glucose is often between 600 and 800 mg/dL, although the range of glucose elevation is very broad and is commonly associated with only mild elevation of serum osmolarity.[182,203]

Seizures associated with nonketotic hyperglycemia are refractory to conventional anticonvulsant therapy but respond rapidly to correction of hyperglycemia with insulin and intravenous fluid replacement. Associated focal neurologic abnormalities are usually transient,[203] and recovery typically occurs without sequelae if the condition is recognized and treated before coma ensues.[182] Significant underlying cerebral structural abnormalities are uncommon, even in the setting of epilepsia partialis continua. However, the occasional discovery of such lesions[182] makes it prudent to obtain neuroimaging studies when seizures first occur in association with nonketotic hyperglycemia or in any patient with persistent neurologic deficits. No role exists for acute or chronic anticonvulsant therapy in the setting of seizures related to nonketotic hyperglycemia. Convulsions may recur despite antiepileptic drug treatment if glycemic control in not maintained,[83] and phenytoin should be specifically avoided in these patients because it may exacerbate hyperglycemia through inhibition of insulin release.[119]

Possible mechanisms of seizures from nonketotic hyperglycemia include localized cerebral ischemia with or without a previous underlying structural abnormality, cortical deformation from brain dehydration, and increased metabolism of GABA via the succinic semialdehyde pathway as a result of depression of the Krebs cycle.[25,133] Depressed brain GABA levels presumably lower the seizure threshold by decreasing cortical inhibition. Although the Krebs cycle is also inhibited in diabetic ketoacidosis, seizures rarely occur in this setting, perhaps because of the anticonvulsant properties of ketosis and the resultant intracellular acidosis, which may lead to increased cerebral GABA concentrations.[25]

Hyponatremia

Hyponatremia, which is one of the most common electrolyte abnormalities found in hospitalized patients, is commonly manifest by an alteration of consciousness ranging from mild confusion to coma. Hyponatremic encephalopathy results from cerebral edema caused by an osmotic imbalance between the extracellular fluid and brain cells, and perhaps also from the effects of the compensatory loss of intracellular cations.[101] In general, symptoms correlate more with the rate of development of hyponatremia than with serum sodium levels,[162] and chronic hyponatremia may be well tolerated.[188] Mild manifestations, such as confusion and lethargy, occur when the serum sodium concentration falls acutely to below 125 or 130 mEq/L.[101] Severe symptomatic hyponatremia (resulting from an acute reduction of serum sodium concentration to <115 mEq/L) is associated with seizures, obtundation, and coma and has a mortality rate >50%.[101,162]

Both partial seizures and generalized convulsions may occur with hyponatremia and are sometimes the first sign of symptomatic water intoxication.[58] Hyponatremic convulsions are common in infants and children, and water intoxication is probably the most common cause of afebrile seizures in children <2 years of age.[171] Hyponatremic seizures constitute a medical emergency requiring aggressive treatment. Hypertonic saline should be administered intravenously but at a rate designed to increase the serum sodium concentration by no more than 1 mmol/L per hour until the patient is asymptomatic or the sodium concentration has increased by up to 12 mmol/L over the first day and 25 mmol/L in the initial 48 hours.[101,189] There is a risk of causing a pontine and extrapontine myelinolysis syndrome with more rapid correction of hyponatremia[108,188,189]; hypertonic saline should not be used once the plasma sodium concentration reaches 125 to 135 mEq/L.[101]

Hypernatremia

Neurologic manifestations occur in >50% of patients with significant hypernatremia.[193] Hypernatremia most commonly arises from conditions resulting in excessive dehydration, typically through gastrointestinal fluid losses or an inability to obtain water. Less frequently encountered causes include diabetes insipidus, hypothalamic lesions, and excessive salt intake.[162] Neurologic signs generally develop with serum sodium concentrations >160 mEq/L,[162] and their severity depends on the rapidity of change in serum sodium concentration.[193] Depression of consciousness is the most common neurologic abnormality in hypernatremic patients. Seizures, either generalized or partial, may occur and are commonly observed during rehydration.[133,193] Cautious correction of hypernatremia with half-isotonic saline may reduce the likelihood of convulsions occurring during treatment.[193]

Disorders of Calcium and Magnesium

Significant hypocalcemia is most frequently observed following thyroid or parathyroid surgery. However, it may also occur in other types of hypoparathyroidism (primary, secondary, and pseudohypoparathyroidism), as well as in other conditions such as renal failure or acute pancreatitis, and in neonates.[162] Altered sensorium and seizures are its most common neurologic manifestations.[162] Hypocalcemic seizures are typically generalized, but partial seizures occur in 20% of patients and may include either motor or sensory phenomenology.[39] Among patients with hypoparathyroidism, 30% to 70% experience seizures, typically in association with an altered sensorium and tetany,[133] although tetany is occasionally absent.[39] Movement disorders such as chorea or tremor may also be produced by hypocalcemia and must be distinguished from epileptic phenomena. Treatment of hypocalcemic seizures involves restoration of serum calcium levels and correction of the underlying disorder.

Deficiency of magnesium typically results from a combination of inadequate dietary intake and excessive gastrointestinal fluid and electrolyte loss. It may also relate to excessive renal excretion of magnesium because of diuretics and other medications, hyperaldosteronism, diabetic ketoacidosis, chronic alcoholism, and renal tubular acidosis.[162] Hypomagnesemia is associated with tetany similar to that occurring with hypocalcemia, and it is not uncommon for hypocalcemia to accompany hypomagnesemia. Multifocal and generalized seizures may be provoked by hypomagnesemia.[57] Seizures and other neurologic symptoms typically occur when the serum magnesium concentration decreases to <0.8 mEq/L.[162] Convulsions produced by hypomagnesemia require treatment with parenteral magnesium salt solutions,[57,162] which should be administered by slow intravenous bolus after the adequacy of renal function has been evaluated, and with calcium gluconate available to counteract transient hypermagnesemia.[162]

Seizures Caused by Anoxic–Ischemic Encephalopathy

Comatose survivors of cardiopulmonary arrest are frequently encountered in hospital intensive care units. Seizures resulting from global anoxic–ischemic cerebral damage occur in the acute setting after resuscitation in 15% to 44% of these patients.[24,100,113,207] Epileptic manifestations of anoxic–ischemic encephalopathy typically commence within 24 hours of cardiopulmonary arrest and include generalized tonic–clonic, tonic, myoclonic, and partial seizures.[100,186] Patients often have several types of seizure,[90,100,186] and status epilepticus and generalized tonic–clonic and myoclonic seizures are frequent.[31,90,100,207,211] In addition, electrographic status epilepticus, with clinical manifestations limited solely to extraocular or facial muscles, may occur in patients after cardiopulmonary arrest.[181]

Several reports suggest that the occurrence of seizures after cardiopulmonary arrest does not influence the eventual clinical outcome in comatose patients with anoxic–ischemic encephalopathy.[113,186] Even generalized tonic–clonic status epilepticus may not be predictive of a poorer outcome in this patient population, although the data are limited by the small number of cases reported.[100] However, myoclonic status epilepticus, generally defined as at least 30 minutes of continuous myoclonus with or without other seizure types,[31,90,100] appears to correlate with a poor prognosis after global cerebral anoxic–ischemic insult.[31,100,207,211] Myoclonic status epilepticus begins between 30 minutes and 5 days after cardiopulmonary arrest, but most often within 24 hours.[90,186,211] The myoclonus may be generalized and synchronous or asynchronous, with predominant involvement of axial muscles and extremities[90] or facial muscles.[90,211] The EEGs typically reveal either bursts of generalized spike- or polyspike-and-slow-wave discharges superimposed on an abnormal background or a burst-suppression pattern; a diffuse alpha-frequency pattern is found on occasion.[90,207,211] Neuropathologic examination shows diffuse anoxic–ischemic damage involving cerebral cortex, hippocampus, cerebellar Purkinje cells, thalamus, basal ganglia, and, to a lesser extent, the brainstem and spinal cord.[90,207,211]

Myoclonic status epilepticus is generally resistant to anticonvulsant therapy (Chapter 62).[90,207,211] Although aggressive treatment of this condition has been recommended to prevent additional cerebral damage from seizures,[100] it is likely that myoclonic status epilepticus represents a marker of severe cerebral anoxic injury that is incompatible with recovery except in rare patients. Treatment decisions in this setting should be individualized using data from the clinical examination and neurophysiologic studies.

Thyroid Disease and Epilepsy

The incidence of seizures in hypothyroidism is relatively high, approaching 20% in patients progressing to myxedema coma.[54] Seizures are usually generalized and resolve with correction to a euthyroid state.[1,134] The EEG in hypothyroidism typically reveals mild slowing of the background or voltage attenuation; abnormalities are reversible with correction of the hypothyroid state.[1,92] Anticonvulsants may decrease the values obtained in certain thyroid function tests, but patients usually remain clinically euthyroid.[1,102]

Seizures occur uncommonly in thyrotoxicosis,[1,70,96] although several lines of evidence suggest that hyperthyroidism or excess thyroxine may cause seizures or exacerbate preexisting epilepsy. Administration of thyroxine in several animal models of epilepsy reduces seizure threshold, whereas thyroidectomy protects against pharmacologically induced seizures.[175,184] Both partial and generalized seizures have been reported in patients with hyperthyroidism,[88,92,96] and generalized tonic–clonic seizures or absences may occur in individuals receiving thyroxine for hypothyroidism.[88,191] Smith and Looney[184] described a patient with thyrotoxicosis who developed generalized seizures only after treatment with high-dose propranolol. In addition, exacerbations of both partial and generalized epilepsies have been associated with increased thyroxine levels.[190,195] In two patients with juvenile myoclonic epilepsy and Graves disease, seizures could not be controlled by anticonvulsants until the hyperthyroidism was adequately treated.[190] Therapy for seizures that occur in the setting of thyrotoxicosis consists of correction of the hyperthyroid state; anticonvulsants are generally not required except sometimes in the acute setting.

Seizures Associated with Systemic Cancer

Table 2 Causes of seizures in the setting of systemaic cancer

Neoplasia

Direct effects: focal metastasis; carcinomatous meningitis

Remote effects: paraneoplastic encephalitis

Cerebrovascular events

Thrombosis (venous or arterial); embolism; hemorrhage

Central nervous system infection
Bacterial; viral; fungal; parasitic

Metabolic disorders
Hypoglycemia; hyponatremia; hypocalcemia; hypomagnesemia

Complications of therapy

Radiation therapy

Chemotherapy: alkylating agents; antimetabolites; cytokines

Symptomatic therapeutic agents: antibiotics; analgesics; antiemetics

Seizures are one of the neurologic complications of systemic cancer or its treatment (Chapter 264). Seizure prompted initial neurologic consultation in 5.4% of 851 (mainly adult) patients with systemic cancer in one prospective study.[35] Etiologies included intracranial metastasis in one half of cases and metabolic abnormalities in one third; the remainder was made up of intracerebral hemorrhage, longstanding epilepsy, or undetermined cause. Seizures appear more commonly in association with childhood systemic cancers. In one series of 158 children with systemic cancer, for example, seizures were the second-most-common reason for neurologic referral.[8] One third of the 29 cases with seizures were found to have a structural brain abnormality. Seizure types in patients with systemic cancer vary by etiology and may include simple or complex partial, secondarily generalized tonic–clonic, or primarily generalized tonic–clonic seizures. In addition, the diagnosis of nonconvulsive status epilepticus should be considered in cancer patients with an altered mental status.[47]

The differential diagnosis of seizure etiology in cancer patients is fairly long (Table 2). Direct effects of cancer, such as brain metastasis, must be excluded. Although brain metastases less commonly produce convulsions than primary brain tumors, those from melanoma, lung, breast, renal cell, gastrointestinal, or germ-cell tumors tend to be involved.[187] Leptomeningeal or dural metastatic disease also may induce seizures. Seizures caused by metastatic disease of brain or meninges are partial or secondarily generalized tonic–clonic in type. Epileptic seizures also may arise after cerebrovascular events in the setting of cancer-related hypercoagulable states or nonbacterial thrombotic endocarditis. Convulsions are often the first symptom of central nervous system infections, including fungal or parasitic abscesses, due to chemotherapy-induced immunosuppression. Seizures occasionally result from complications of chemotherapy, and may be seen with etoposide, L-asparaginase, alkylating agents such as chlorambucil or busulphan, immunotherapies, methotrexate, or cytosine arabinoside.[187] Other causes include delayed effects of cranial irradiation, cancer-induced metabolic disturbances, paraneoplastic encephalitis, and drugs used to treat cancer complications, such as pain medications or antibiotics.

The evaluation of new-onset seizures in patients with systemic cancer is relatively straightforward. Brain MRI with contrast should be obtained to exclude a cerebral structural abnormality. Lumbar puncture should be performed in the absence of a brain lesion, and CSF evaluated cytologically to exclude meningeal tumor involvement and for infectious causes. Coagulation studies and biochemical screening also are warranted,

and the cerebral venous system should be imaged if clinical suspicion exists for venous sinus thrombosis. EEG evaluation is helpful for determining the type of seizure and excluding nonconvulsive events. Finally, the medication list should be scrutinized carefully for any potential proconvulsant medications.

Antiepileptic drug treatment should be instituted unless a reversible cause of symptomatic seizures is present. Certain situations may, however, complicate the selection of the appropriate anticonvulsant agent. Phenytoin should not be used in patients receiving whole-brain cranial irradiation, because there may be an increased risk of Stevens-Johnson syndrome.[42] Carbamazepine, which often causes a mild leukopenia, is best avoided in those at risk for bone marrow suppression. The choice of antiepileptic drug is further complicated by potential interactions with chemotherapeutic agents for cancer. Many medications of both classes undergo hepatic metabolism and influence the hepatic cytochrome P450 metabolic enzyme system, leading to lowered effectiveness of cancer chemotherapy, inadequate seizure control, or anticonvulsant toxicity from drug interactions.[202] Thus, the use of newer antiepileptic agents that undergo limited hepatic metabolism and do not influence the hepatic P450 system, such as levetiracetam or pregabalin, may be preferable in individuals undergoing cancer chemotherapy.

Seizures and Central Nervous System Disease

Cerebrovascular Disease

Cerebral infarctions, both ischemic and hemorrhagic, are a common cause of seizures (Chapter 275). Stroke is the most frequent cause of epilepsy in the elderly.[52,111] Although the incidence depends on stroke type and duration of follow-up, seizures occur after cerebral infarction in approximately 6% to 25% of cases,[55,103,144] with some studies suggesting a higher incidence after embolic infarcts and primary intracerebral hemorrhage.[52,55,103,111] Seizures typically present immediately or in the first 48 hours after intracerebral hemorrhage[18,55]; at least one third of seizures occur within a few weeks in patients with ischemic infarcts.[74] Most fits caused by stroke occur in the first 2 years after the initial cerebrovascular event.[55,74,103]

Seizures occurring after stroke are typically of the secondarily generalized tonic–clonic or partial varieties; simple partial seizures, particularly with motor phenomenology, occur more frequently than complex partial spells.[52,74,111] Multiple seizures, as well as convulsive and nonconvulsive status epilepticus and epilepsia partialis continua, may also occur.[74,111] Risk factors for developing late epilepsy after stroke probably include the involvement of cerebral cortex by ischemic infarcts or lobar hemorrhages,[18,55,103,144] persistent hemiparesis,[144] and the occurrence of early (within the first 2–4 weeks) seizures.[52,95] Seizures recur in 32% to 40% of patients experiencing an early fit after cerebral infarction,[74,95] although this has not been a significant risk factor in some studies.[52] In addition, the presence of periodic lateralized epileptiform discharges in the EEG is associated with a high risk for the development of seizures.[74]

There is no justification for prescribing prophylactic anticonvulsant treatment routinely after a stroke.[18,95] When seizures do occur after stroke, however, these are typically well controlled with antiepileptic medications.

Infectious Diseases

Seizures are a relatively common symptom and consequence of CNS infections (see Chapter 265). In a population-based cohort study of 714 survivors of meningitis and encephalitis, Annegers and et al.[7] found a nearly sevenfold increase in the risk of developing late, unprovoked seizures. Viral encephalitis conferred a higher risk than bacterial meningitis, whereas the incidence of late convulsions after aseptic meningitis was not significantly increased compared to the rate in the general population. Most late seizures occurred within 5 years of the infection, although the seizure risk remained elevated for >10 years; 19% of patients experienced symptomatic fits during the acute illness, and this increased the likelihood of late seizures for all categories of CNS infection.

In a prospective study of 185 children with bacterial meningitis, late seizures (not associated with fever) occurred in 7%.[153] Most patients had their first late seizure within 2 years of the acute infection; seizures were either partial or secondarily generalized and were often difficult to control with anticonvulsant therapy. The occurrence of seizures during the acute illness and the presence of residual neurologic deficits significantly increased the risk of developing late seizures.

Seizures related to a preceding meningitic or encephalitic illness may be refractory to anticonvulsant medications and are sometimes amenable to surgical therapy for partial epilepsy. In a report of 38 patients undergoing presurgical evaluation for medically refractory seizures after bacterial meningitis or viral encephalitis, Marks et al.[124] found an association between the occurrence of infection before 4 years of age and mesial temporal sclerosis, a pathologic finding that is highly correlated with a good surgical outcome.

Other types of intracranial infections that frequently result in seizures include supratentorial brain abscess, subdural empyema, and parasitic CNS diseases. Convulsions occur in >25% of patients with bacterial cerebral abscesses[121,140] and in >50% of those with subdural empyema.[180] Late convulsions occur in >30% of patients with subdural empyema who survive the initial infection and usually commence within 18 months.[38]

Neurocysticercosis is the most common parasitic infection of the CNS and is the leading cause of late-onset epilepsy in developing countries.[131] Seizures are the most frequent manifestation of neurocysticercosis and are typically partial or secondarily generalized fits.[43,131] Both anticonvulsants and anticysticercal agents (praziquantel or albendazole) are required to control seizures in patients with active neurocysticercosis.[43,131] In patients with inactive disease (manifest solely by cerebral calcifications), convulsions typically respond well to antiepileptic drug therapy alone, although the relapse rate is high after medication withdrawal even in patients who have remained seizure free for several years.[43]

Degenerative Diseases

Neurodegenerative diseases are an important cause of seizures in the elderly. Alzheimer disease is associated with seizures, typically generalized tonic–clonic, in 10% to 16% of cases,[79,165] although even higher prevalences have also been reported.[163] Convulsions have been reported in both early and late stages of the disease,[79] although most reports suggest that seizures are more likely to occur late in the course of Alzheimer disease.[163,165] Convulsions arise much less frequently in the setting of neurodegenerative disease affecting mainly subcortical structures. Huntington disease is rarely associated with seizures in adults, although epilepsy is common in patients with juvenile Huntington disease and occasionally is the presenting symptom.

Summary and Conclusions

Seizures may result from a variety of medical conditions. Furthermore, the treatment of epilepsy may cause or complicate the course of other medical disorders. In general, acute seizures produced by endogenous or exogenous systemic disturbances require treatment directed at the underlying cause and do not necessitate antiepileptic drug therapy. Prolonged seizure activity or status epilepticus, however, requires immediate intervention. Certain medical illnesses influence the choice and manner of antiepileptic drug therapy, and comorbidity must be taken into account during the initiation of treatment and the chronic management of epileptic disorders. Seizures and epilepsy also frequently arise as a symptom of acute or chronic neurologic diseases. Recognition of the specific epileptic manifestations of various CNS disturbances serves to aid diagnostic and prognostic considerations and allows for the institution of appropriate therapy.

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Chapter 192

Comorbidity and Immunizations in Children

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Introduction

Comorbidity refers to the effect of other diseases and conditions on the management of epilepsy and to the special problems posed by the underlying condition of epilepsy and its association/causation with other disorders. This chapter is concerned with comorbidity in children; Chapter 191 addresses comorbidity in adults. Potential overlap between the two chapters is considerable with respect to drug interactions and the effect of systemic diseases on seizure control, especially those disorders that compromise hepatic and renal function. To avoid repetition, this chapter concentrates on child development and leaves much of the material on drug interactions and the effects of systemic disease to Chapter 191.

Multiple factors contribute to "comorbidity" in childhood epilepsy, and the relative contributions of these factors are a matter of continuing debate. The core issues that relate to comorbidity include the underlying substrate of the seizures, the effect of the seizures themselves, adverse effects of antiepileptic medications, and the psychosocial burden of coping with a stigmatizing paroxysmal disorder that limits employment, driving, and other "lifestyle" activities. This chapter reviews the extent to which these variables, both individually and together, affect developmental, cognitive, and psychosocial outcomes of childhood epilepsy.

Developmental Disabilities

Although epilepsy is widely known to be multifactorial in origin, a high proportion of seizures in childhood are developmentally based. Approximately two thirds of new-onset seizures in children have no apparent etiology.[23] This close relationship of childhood epilepsy with disordered brain maturation allows for significant and complex relationships with other developmental disorders, including behavioral problems, learning disabilities, attention-deficit hyperactivity disorder, autism, depression, and psychiatric disturbances. The frequent occurrence of one or more comorbid disability significantly complicates the management of the epilepsy and seriously impairs overall quality of life. It is therefore critical that clinicians caring for children with epilepsy understand comorbid conditions and be knowledgeable about their treatment.

Incidence

There are no studies that comprehensively define the incidence of all comorbid conditions in children with epilepsy. Methodologic difficulties arise because childhood epilepsy often occurs in developmentally disabled populations, making it difficult comprehensively to assess the entire spectrum of disability and epilepsy. General cohort studies report that a high proportion of children experience at least some degree of socially unacceptable behavior. In a study of 127 preadolescent children with chronic epilepsy, Austin et al.[3] noted that approximately half experienced some form of behavioral problem. A more recent population-based retrospective survey conducted over a 15-year period identified a similar prevalence rate in 134 children and adolescents.[24] This cohort was surveyed for a mean follow-up period of 117 months and found to have a psychiatric comorbidity of 51%, as defined by the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV).

It is also difficult precisely to time the onset of comorbid disorders, but several studies suggest that comorbidity can begin early in children with seizure disorders and occasionally pre-dates seizure onset. Both Austin et al.[2] and Oostrom et al.[42] found the incidence of behavior disorder to be significantly higher than in the general population. Although the incidence in newly diagnosed patients (32%) was slightly lower than the incidence in children with chronic epilepsy, the high incidence underscores the selective vulnerability of children as well as their potential to deteriorate further. Problems with attention and socializing were particularly prevalent.

Children with structural brain damage are at even greater risk of comorbid disability and, in general, experience risk proportional to the severity of the brain damage. Children with cerebral palsy who have four-limb spasticity have the highest incidence of seizures, whereas children with milder forms of cerebral palsy such as spastic diplegia affecting predominantly the lower limbs have the lowest incidence.[51] Factors responsible for the occurrence of cerebral palsy in most children are acquired prior to birth, confirming that in childhood, even seizures clearly attributable to brain damage are developmentally based.

Cognitive Impairment

Children with chronic epilepsy are at considerable risk for cognitive disability.[4,8] Learning problems and school failure are common and are due to heterogeneous causes. Impairment of attention plays a significant role and is affected by medication in conjunction with seizures. There is evidence, however, that cognitive deterioration in childhood epilepsy is a progressive process that is independent of medication and begins soon after seizure onset.[40]

Studies using standardized measures to assess attention suggest that as many as one third of children with epilepsy suffer some form of attentional impairment.[46] In a study of 175 children with epilepsy of at least 6 month's duration who were administered subscales for attention from the Child Behavior Checklist,[19] 58% were found to have some degree of attentional impairment and 37% had overt symptoms of attention-deficit hyperactivity disorder. The Analysis of the Child Symptom Inventory indicated that 24% were experiencing predominantly the inattentive type, 11% had the combined type, and 2% had the hyperactive-impulsive type. Of note, this

population had a gender ratio of 1:1 and a significant overrepresentation of the inattentive type compared to the general population.

Children with frontal lobe epilepsy are at even greater risk of developing cognitive dysfunction. In a comparison of 16 children with frontal lobe epilepsy to 8 children with temporal lobe epilepsy and 8 children with generalized absence seizures, Hernandez et al.[27] found that the frontal lobe group scored more poorly on tasks assessing attention, impulse control, and working memory. Poorer perceptual organization and a range of maladaptive behaviors were also observed. These observations suggest that school performance and social patterns of children with frontal lobe seizures may need to be monitored even more closely than those of children with other seizure types or other anatomic localizations.

The ways in which recurrent seizures contribute to cognitive and attentional impairment remain to be elucidated. There is experimental evidence that recurrent seizures affect the developing brain, leading to consequences in later life. Although seizures in early development may not produce discernible cellular loss, synaptic reorganization is known to follow neonatal seizures. Both pentylenetetrazol- and flurothyl-induced seizures alter mossy fiber distribution in the hippocampus of rats after neonatal convulsions.[30,37] Alterations in neuronal circuits render the brain more susceptible to further seizures and cognitive dysfunction. Lipp et al.[36] showed that conditioned learning in the rat is directly influenced by the extent of mossy fiber projections to the pyramidal layers of the CA3 region, with a larger number of fibers associated with poorer performance.

Even less is known about the direct effects of antiepileptic drugs (AEDs) on cognition and learning. Many studies are either poorly controlled for seizure type or use methodologies that do not lead to definitive conclusions. In clinical experience, higher rates of depression, learning problems, and negative behavior are associated with the long-term administration of barbiturates and benzodiazepines in children. Psychiatric and behavioral side effects are seen more commonly in AEDs with mechanisms that are associated with a γ-aminobutyric acid (GABA)-ergic component.

Genetic contributions to learning disabilities have recently been described in children with inherited forms of epilepsy. Chang et al.[13] reported a deficit in reading skill despite normal cognition in 10 patients with periventricular nodular heterotopia. All had a diagnosis of epilepsy, and most manifested partial seizures with or without secondary generalization. Patients with autosomal-dominant lateral temporal lobe epilepsy have been shown to have abnormal phonologic processing.[43] Genetic molecular analysis revealed a new LG11 missense mutation causing a Leu154Pro substitution in six affected and one unaffected individual.

Depression

Depression is a well-known accompaniment of adult epilepsy but has received relatively less scrutiny in children. The rate of depression in children and adolescents with chronic epilepsy as described by self-reporting instruments has been estimated at one fourth of patients.[18] Children and adolescents remain vulnerable to the same risk factors that exist in adults, whereas epilepsy may lead to further stress on their families. Using DSM-IV-R criteria, it has recently become possible to diagnose depression in children as young as age 6 years.[55] A detailed family history is an important part of the evaluation because rates of depression are higher in children with a family history of mood disorder.[54] Recognizing depression is an important element in the overall care of the child with epilepsy because treatment is available in the form of counseling and, in certain circumstances, pharmacotherapy.

Appropriate treatment is based on the proper evaluation of the biologic, family, social, and iatrogenic factors, including choice of AED. Unlike the situation in adults, the role of seizure type and lateralization of the epileptic focus has not been shown to influence the incidence of depression. Age of seizure onset and electroencephalogram (EEG) findings also do not appear to exert an influence. However, depression in children with epilepsy has been linked to seizure recurrence, high seizure frequency, and longer duration of epilepsy.[44]

The role of anxiety in children with epilepsy and depression is more controversial. Williams et al.[59] noted mild to moderate symptoms of anxiety in 23% of 101 children between the ages of 6 and 16 years who were administered the Revised Children's Manifest Anxiety Scale. The investigators noted, however, that a high proportion of their patients had other comorbid conditions. In contrast, Baki et al.[5] studied 35 children and adolescents with seizures and found higher rates of depression compared to normal controls but no differences in rates of anxiety. They also noted no differences in rates of depression or anxiety in mothers of children with epilepsy and controls.

In a structured psychiatric interview administered to 100 children with complex partial seizures (CPS), 71 children with childhood absence epilepsy (CAE), and 93 normal children ages 5 to 16 years and a behavioral checklist given to parents, Caplan et al.[10] found that significantly more patients had affective and anxiety disorder diagnoses and suicidal ideation compared to the normal group. Children with both CPS and CAE were five times more likely to have an affective or anxiety disorder. Despite this, very few patients were receiving mental health services, but there were no suicide attempts. These observations emphasize the importance of early detection and treatment of symptomatic children.

Psychosis

The diagnosis of psychotic thinking and behavior can be difficult in childhood, especially in the developmentally disabled population. Impaired thinking, delusions, and hallucinations may go unrecognized if there is significant language impairment. Despite these methodologic limitations, interictal psychosis in the children with epilepsy appears to be rare. The prevalence rate of interictal psychosis was reported to be 0.7% in Japanese children, but even this prevalence may have been biased in favor of patients with long-standing epilepsy.[38] One study of children with complex partial seizures found possible early symptoms of psychotic thinking including hallucinations.[10] Similar symptoms were not observed in children with generalized seizures.

The occurrence of interictal psychosis is generally regarded to be an adult-onset disorder. Several investigations have shown that seizures, especially of temporal lobe origin, must be present for at least 10 years before the onset of psychotic symptoms.[45] Thus, it is unlikely that frank interictal psychotic symptomatology will present in the preadolescent child. The onset of frank psychosis in a child with epilepsy should trigger a suspicion of another underlying neurologic disorder or adverse medication effect.

Autism

Almost one third of children with autistic spectrum disorder will experience at least one seizure in childhood.[57] Epileptiform discharges are noted in almost half during overnight video/EEG studies.[56] In a population of children at a tertiary care epilepsy clinic, Clarke et al.[14] noted that 32% fit criteria for autism spectrum disorder. Children with the higher risk had a younger age of seizure onset, approximately age 2 years. This interval correlates with the known timing of the onset of autistic regression.

Psychosocial Consequences

A comprehensive understanding of the consequences of unremitting seizures that have their onset in childhood is in its early stages. Apart from the social stigma attached to epilepsy and the potential consequences of long-term AED administration, the effects of recurrent seizures on the developing brain represent a major cause for concern. There is considerable evidence that when epilepsy is acquired in early life, multiple functional domains are affected to a degree that is often more severe than for other chronic childhood illnesses.[17,29] Even children who are intellectually normal are prone to emotional and social problems that may compromise their development and school performance.[44]

Social Consequences

A number of factors, both biologic and social, appear to increase the risk of poor psychosocial outcome. It has been shown, for example, that parental beliefs and attitudes concerning epilepsy may significantly affect adjustment and quality of life for both the child with epilepsy and the family.[60] Fastenau et al.[20] administered a comprehensive neuropsychological battery to 173 children ages 8 to 15 years. They noted a wide range of neuropsychological deficits and identified a subgroup of patients with a disorganized or unsupportive home environment who were at especially high risk for adverse academic outcomes.

Children with complex partial seizures have a greater risk for adverse long-term brain function. In a study comparing neurodevelopmental outcome in early versus late-onset childhood temporal lobe epilepsy compared to healthy controls, Hermann et al.[26] showed that the early-onset group exhibited widespread compromise in neuropsychological performance and substantial reductions in brain tissue volumes extending to the extratemporal regions compared to other groups. Reduction in total white matter volume was highly correlated with long-term cognitive deficiency. Further cross-sectional analyses indicated that longer duration of epilepsy in childhood-onset patients resulted in declining performance across both intellectual and memory measures, consistent with a progressive disorder.[25]

Outcome of Adults With Childhood-Onset Seizures

Many investigations have confirmed the poor social adjustment of many adults with epilepsy. However, there are few studies investigating the social outcomes of adults whose epilepsy began in childhood. The role of underlying neurologic dysfunction and comorbid disorders has also not been studied extensively. In one of the few well-controlled studies, Jalava et al.[34] prospectively studied a population-based cohort of childhood-onset epilepsy to ascertain the effect of early seizure onset on adult social adjustment and competence. They hypothesized that patients who had “only epilepsy” would not be at risk for impaired social adjustment and competence. They found the opposite—that many patients with seizures beginning in childhood who have no associated neurologic deficits exhibited poor social adjustment that was directly or indirectly related to individual seizures or chronic epilepsy. They also had lower rates of educational achievement despite the lack of evidence of learning impairment. Additional analysis of this cohort also revealed that patients with childhood-onset epilepsy have an unexpectedly high incidence of psychiatric and psychosomatic illness whether or not they were receiving concurrent AEDs.[33]

These early observations were confirmed in an independent investigation of a cohort of 243 consecutive newly diagnosed patients with epilepsy followed for average of 34 years.[48] A high proportion of the patients were diagnosed with epilepsy before age 15 years, and many experienced frequent seizures. Patients had a positive health evaluation, but although 55% had been seizure free for the previous 5 years, fewer patients married or had children and more lived at home or in foster homes or institutions. Acquiring epilepsy during school age had a particularly negative impact on school achievement. Sillanpaa et al.[49] also found that adults with childhood-onset epilepsy had significantly compromised quality of life despite being in remission and off medication.

These findings collectively lend strong support to the long-term impact of childhood-onset epilepsy on social functioning in later life. Problematically, social dysfunction occurs often in patients who do not have active epilepsy and are not taking medication. The reasons for this phenomenon are not well understood but attest to the negative effect of seizures that begin early in life.

Immunizations

Vaccines have had a profound effect in the eradication and control of many childhood infectious diseases; however, the risks have not been accurately defined. Over the last 10 to 15 years, concerns relating to the risks of immunization grew as case reports of neurologic and other complications associated with immunizations were published. As a result, some parents refused to have their children vaccinated, the incidence of lawsuits against vaccine manufacturers increased, and some companies threatened to stop vaccine production.

The National Childhood Vaccine Injury Act was passed in 1986; it established a federal compensation program for those judged to have incurred damage from a vaccine. In early reports, the major presumed offender in the causation of “immunization-induced encephalopathy” was pertussis. In published clinical descriptions, the terms encephalopathy and encephalitis are used interchangeably and include several symptoms and signs such as alteration in behavior or level of consciousness, seizures, headache, and focal neurologic deficits. When fever or cerebrospinal fluid pleocytosis is present, the term encephalitis is used.

Although no specific or consistent clinical presentation is evident in case studies of alleged vaccine-induced encephalopathy, the reported clinical patterns included (a) convulsions and coma occurring within 12 hours of immunization; (b) a “pertussis reaction syndrome” characterized by persistent screaming, irritability, refusal of feeds, seizures (usually associated with fever), and altered responsivity; and (c) a generalized seizure occurring within 2 days of the immunization and followed within days and or weeks by increasingly frequent seizures and developmental regression.

In 1948, Byers and Moll[9] reported on 15 cases of “pertussis-induced encephalopathy” characterized by fever, irritability, seizures, and coma occurring within 12 hours of pertussis immunization. All but one of the children suffered permanent neurologic deficits with seizures and/or mental retardation. Kulenkampff et al.,[35] in 1974, reported on 36 children with encephalopathic symptoms, mostly seizures, beginning within 24 hours of pertussis immunization. Two children died within 6 months, 30 had seizures and/or mental retardation, and 4 recovered completely. Subsequent case reports documented similar findings following measles, mumps, and rubella (MMR) vaccine, oral poliovirus vaccine (OPV), and diphtheria, tetanus, and pertussis (DTP) immunization.

The causal relationship of adverse events to immunization was questioned because no consistent encephalopathic pattern

was evident in the various case reports, and the possibility of a noncausal temporal relationship could not be excluded. Furthermore, the clinical manifestations of whooping cough encephalopathy differed from many of the case reports of immunization-induced encephalopathy.[52] Postmortem examination of brains from children dying with an encephalopathy during natural pertussis infection showed nonspecific changes usually associated with anoxia (brain edema, petechiae, small subarachnoid hemorrhages, and lymphatic plugs in veins and capillaries) and no evidence of inflammation. Corsellis and colleagues[16] reported the neuropathology of 27 postmortem examinations on individuals who were alleged to have suffered a pertussis-vaccine encephalopathy. No consistent pattern of brain damage was identified as a specific consequence of pertussis immunization. Similarly, animal studies have not supported a relationship between pertussis immunization and encephalopathy.

It was not until the 1980s that population-based epidemiologic studies were designed to objectively evaluate the relationship of immunizations to temporally-associated adverse events.

Population Studies

The National Childhood Encephalopathy Study (NCES) in Great Britain[1] is the most widely quoted epidemiologic study of the adverse effects of DTP vaccine. In a case–control design, 1,182 cases of acute encephalopathy in infants 2 to 35 months of age admitted to hospitals in England, Scotland, and Wales were registered in the study. Each index case was matched with two control children by gender, age, and geographic location. The study sought to address the relationship of DTP immunization to (a) acute serious neurologic events and (b) permanent brain damage. Immunization data were available for 1,167 of the 1,182 cases. Among these, 263 children had infantile spasms and are discussed separately. Of the remaining 904 children, 30 (3.3%) developed encephalopathy within 7 days of DTP immunization as compared to 23 (1.3%) of controls whose index date was within 7 days of immunization. The relative attributable risk of an acute encephalopathy associated with immunization was approximately 1 in 140,000 vaccinations, and the attributable risk of permanent brain damage was 1 in 310,000 vaccinations; the confidence limits for both risks were considerable. In three other controlled studies, only 2 cases of encephalopathy occurred within 7 days of immunization, and no statistically significant risk for encephalopathy was identified.[21,22,58]

The Institute of Medicine has critically reviewed and analyzed the studies concerned with a possible association of whole-cell pertussis vaccine and neurologic illness with particular reference to chronic encephalopathy. Notwithstanding criticism of the NCES methodology, they concluded that “the balance of evidence is consistent with a causal relationship between DTP and the forms of chronic nervous system dysfunction described in the NCES in those children who experience a serious acute neurologic illness within 7 days after receiving DTP vaccine.”[32]

Immunizations and the Risk of Epilepsy

Seizures are frequently reported as a solitary feature and as part of an encephalopathy following immunizations. Among 54,000 children followed in a prospective study by the National Collaborative Perinatal Project (NCPP), 2,766 experienced a seizure before age 7 years.[29] In 39 children (1.4%), the seizure occurred within 14 days of immunization. In 10, the seizure followed DTP, usually within 2 days. In 10 others, the seizure followed measles or smallpox vaccination, usually within 7 to 10 days. The seizures were mostly brief and generalized, and all but 1 was associated with fever. Twenty-three percent had a family history of febrile or afebrile seizures. The children were reevaluated at age 7 years; 2 had had a subsequent single seizure, but none developed epilepsy. All children who had experienced single generalized seizures were intellectually normal.

Cody et al.[15] compared the adverse effects following DPT in 15,752 children and DT in 784 children. Nine children had seizures following DTP and none following DT; 7 of the 9 seizures were associated with fever. Follow-up evaluations in 8 children showed that all were neurologically normal, and none had recurrent seizures.

Stetler et al.[52] evaluated data on 2,062 reports of adverse events following DTP immunization from the Monitoring System for Adverse Events Following Immunization (MSAEFI) at the Centers for Disease Control and Prevention (CDC). Children with a neurologic event (mostly seizures) after DTP had a 7.2-times higher risk for a personal history of seizures and a 4.5-times higher risk for a family history of seizures than children who did not have a seizure.

Griffin et al.[22] evaluated the risk of seizures and other neurologic events following DTP immunization in 38,171 children aged 0 to 3 years. Six children had febrile seizures within 6 days of immunization. The study did not show that immunization was associated with either a significant risk for febrile seizures or for later epilepsy.

Shields et al.,[48] in a retrospective epidemiologic study, reviewed the association of adverse neurologic events following DTP immunization in Denmark, where the immunization schedule was changed in 1970. The first group (pre-1970) received DTP at 5, 6, and 15 months and the second group at 5 weeks, 9 weeks, and 10 months. Epilepsy developed in 286 children from the first group and 268 from the second, but the age distribution at onset was the same in both groups. Febrile seizures occurred in 2,199 children, and in contrast to epilepsy, the association between age of febrile seizures and age at immunization was significant. Febrile seizures were more common in the second group and clustered around 10 months of age, suggesting that febrile seizures following immunization have their highest incidence at the age when children are most susceptible to seizures from febrile illnesses of any cause.

Adverse events occurring within 48 hours of DTP immunization were studied prospectively by Baraff et al.[6] in 15,752 children. Nine children had seizures and 9 had hypotonic–hyporesponsive episodes, which are generally regarded as syncopal rather than epileptic. Sixteen of the 18 children were contacted 6 to 7 years later, and all were considered normal by their parents and were doing well in school. Psychometric testing in 13 of the 16 children revealed normal performance IQ scores (104.3±15.8) but low verbal IQ scores (91.8 ± 18.4). The lower verbal scores were felt to be related to the high proportion of Hispanic and bilingual children.

As a group, these studies indicate a small but statistically significant risk of febrile seizures following immunization, especially in children with a personal or family history of seizures. As with other normal children who experience seizures with fever, the risk of subsequent nonfebrile seizures or neurologic disturbances is not increased.

Immunization and the Risk of Infantile Spasms

An association between routine immunization, especially DTP, and infantile spasms has been postulated repeatedly by single case reports and case series. The association is confounded, however, because the onset of infantile spasms is difficult to date and the usual age at onset of infantile spasms coincides with the recommended age of several routine childhood immunizations.

Table 1 Adverse events related to immunizations

Vaccine	Adverse event
DTP	Anaphylaxis[a]
Pertussis	Anaphylaxis[a] Persistent inconsolable crying[a] Acute encephalopathy[b] Hypotonic–hyporesponsive episodes[b]
Diphtheria	Anaphylaxis[a] Guillain-Barré syndrome[b] Brachial neuritis[b]
Tetanus	Anaphylaxis[a] Guillain-Barré syndrome[b]

	Brachial neuritis[b]
Rubella	Acute arthritis (adult women)[a] Chronic arthritis (adult women)[b]
MMR	Anaphylaxis[a] Thrombocytopenia[a]
Measles	Measles vaccine strain viral infection[a] Anaphylaxis[a]
Hepatitis B	Anaphylaxis[a]
OPV	OPV strain viral infection[a] Guillain-Barré syndrome[b]
Hib	Anaphylaxis[a]

DTP, diphtheria, tetanus, pertussis; Hib, *Haemophilus influenzae* type B; MMR, measles, mumps, rubella; OPV, oral polio vaccine.

[a] Evidence establishes causal relationship.

[b] Evidence suggests possible causal relationship.

The first epidemiologic study to address these issues was from Denmark,[39] where immunization schedules changed after 1967. Infantile spasms developed in 86 children immunized between 1957 and 1967, when DTP was given at 5, 6, and 10 months of age, and in 113 children immunized between 1970 and 1975, when whole-cell pertussis alone was given at 5 weeks, 9 weeks, and 10 months of age. The age at onset of infantile spasms was not influenced by the change in immunization practices.

The occurrence of infantile spasms was one of the index conditions studied by the NCES. Among 263 cases reported, no association with pertussis immunization was noted in the 28 days following immunization.[7] Some clustering of infantile spasms did occur in the first 7 days following immunization, but this was compensated for by fewer cases in the remaining 21 days, suggesting that DTP immunization is not a cause of infantile spasms but may bring it to attention.

Adverse Events Following Childhood Immunization

The National Childhood Vaccine Injury Act (Public Law 99-660) was passed by the U.S. Congress in 1986 and became effective in October 1988. Section 312 of Public Law 99-660 required a review and analysis of the available information pertaining to the possible adverse effects of routine childhood immunizations mandated for school entry. This review was conducted by the Institute of Medicine and published in two reports.[31,53] Their conclusions are summarized in Table 1.

Precautions and Contraindications of Immunizations

Immunization is mainly intended for use in healthy children, but children with chronic neurologic problems are especially vulnerable to infectious diseases and need protection. The standards of immunization practices are provided by the Advisory Committee on Vaccine Practices[12] and the American Academy of Pediatrics.[50]

In general, a vaccine that produces a serious adverse reaction should not be readministered. Epilepsy per se is not a contraindication to routine childhood immunizations. Parents of children who are at risk for febrile seizures should be warned that some immunizations cause fever and may trigger seizures. It is reasonable to suggest the use of acetaminophen on the day of DTP immunization.

Summary and Conclusions

Other diseases and conditions commonly affect the management of epilepsy in children; similarly, epilepsy and its treatment may confound treatment of systemic disorders. The effect of immunizations, especially DPT, on seizure susceptibility remains controversial. A large epidemiologic study from Great Britain demonstrated only minimal risk of persistent neurologic abnormalities following vaccination. The Institute of Medicine in the United States, however, concluded that DPT vaccination increased the risk of chronic encephalopathy. Febrile reactions following immunization increase slightly the risk of febrile seizures. Routine immunization, including DPT, does not increase the risk of infantile spasms. Acute encephalopathy, brachial neuritis, and Guillain-Barré syndrome have all been reported as adverse events following various immunizations.

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Chapter 193

Procedures and Anesthesia in Patients with Epilepsy

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Introduction

Patients with epilepsy are often considered to be at high risk for routine medical and dental procedures. This designation is based primarily on the risk of seizures occurring during or shortly after the procedure and, to a lesser degree, on the potential interaction between drugs for the procedure and those for seizure control. Although few procedures have been documented to have increased risks among patients with epilepsy, an increased level of concern is often present. Procedures in children and adults with epilepsy raise the following issues: (a) steps that can be taken before the procedure to reduce the risk of seizures associated with it, (b) education of health care workers involved in a procedure about a patient's seizures and medications and first aid for seizures, (c) defining the risks of the procedure for patients with epilepsy, (d) defining the effects of anesthetics or analgesics used for the procedure on seizure threshold and potential for interaction with antiepileptic drugs, which is the focus of this chapter, and (e) differential diagnosis of paroxysmal behavioral events occurring around the time of procedures.

Epileptic seizures during medical and dental procedures can be more dangerous (e.g., onset of uncontrolled clonic movements in an extremity in which a microsurgical procedure is being performed under local anesthesia) or less dangerous (e.g., onset of status epilepticus in a physician's office) than seizures occurring at other times (e.g., while sleeping alone in bed).

Some simple precautions should be employed before a person with epilepsy undergoes a procedure. First, factors that can precipitate seizures should be avoided. Because missed medications are a common cause of breakthrough seizures, the physician should emphasize compliance and ensure that patients continue taking medication up until shortly before the procedure (see later discussion). Although patients are instructed not to eat or drink for at least 8 hours before surgery, medications are often administered with sips of water within a few hours of surgery. Antiepileptic drugs should be given at this time as well. Sleep deprivation, common before many procedures, should be avoided. When needed, low doses of chloral hydrate or benzodiazepines can be safely used for insomnia the night before a procedure. Patients with epilepsy, who should always avoid excessive alcohol intake (i.e., more than two beverages per day), should avoid alcohol for 3 to 4 days before surgery to reduce the potential for withdrawal effects.

Much of the concern regarding patients with epilepsy results from perceived as well as real risks associated with seizures. Health care workers often receive little education concerning seizure classification and phenomenology, duration, and first aid. This lack of understanding fosters fear and conservatism that can lead to excessive precautions and restrictions and to management errors. Induced labor and cesarean section are examples in which interventions and procedures may be undertaken more often in women with epilepsy—two to four times more often than in other pregnancies—than medical reasons alone would justify.[115] Epilepsy alone is not an indication for either of these interventions. However, in selected cases, labor should be induced and cesarean section should be done on an elective (e.g., weekly tonic–clonic seizures during the last trimester) or emergency (e.g., tonic–clonic seizure during labor or lack of active maternal contribution) basis.[44]

Physicians, nurses, dentists, technicians, and other health care workers involved with procedures in patients with epilepsy should have a basic understanding of the patient's seizure types, medications, and first aid for the seizures. A complex partial seizure during a routine dental procedure can frighten both the dentist and technologist. If these professionals are informed of the possibility ahead of time and educated about the need for calm observation as opposed to intervention, fears and chances of inappropriate responses will be reduced. For example, restraint during a complex partial seizure or after a tonic–clonic seizure can provoke an aggressive reaction leading to a dangerous cycle requiring greater restraint. In such cases, restraint should be removed and the patient reassured in a comforting manner.

Paroxysmal behavioral events occurring during or after procedures have a differential diagnosis extending well beyond epileptic seizures.[75] An occasional patient with psychogenic seizures has events mainly around the time of medical procedures. More commonly, patients with convulsive syncope develop symptoms during painful or emotional procedures. In such cases, which can include such procedures as venipuncture, excision of moles under local anesthesia, and electromyography, the patient suffers a tonic–clonic seizure secondary to a fall in heart rate or blood pressure.[64] These seizures are typically brief, lasting <2 minutes, but may be followed by prominent postictal confusion. No specific therapy is required, and antiepileptic drugs should not be prescribed. In selected cases of recurrent convulsive syncope associated with medical procedures, anticholinergic agents may be beneficial.

Premedication and Assessment

During the preoperative interview, the anesthesiologist determines and prescribes premedication for the patient. Choice of premedication can have major implications for the patient with epilepsy. Considerations include the following:

1. Continuing the patient's prescribed daily medications. Administering medications either orally with a sip of water or via an acceptable alternate route (intravenous, intramuscular, or rectally) can avoid decreasing serum levels into the subtherapeutic range. Antiepileptic drugs (AEDs) are included in this category as well as antihypertensives and cardiac, diabetic, and asthma medications. When oral or parenteral administration of AEDs cannot be done (e.g., because of hyperemesis, gastrointestinal procedures, AEDs without parenteral forms), some may be given rectally (Table 1). Although clonazepam has an intermediate absorption rate,[53] the injectable forms of diazepam and lorazepam are rapidly absorbed rectally.[39,75] Carbamazepine can be given rectally with 80% absorption.[38] Ninety percent of rectal phenobarbital (liquid parenteral form) is absorbed in 4.4 hours.[39] Phenytoin (liquid parenteral form) given rectally is slowly absorbed in dogs.[35] Rectal absorption of oral forms of sodium valproate is complete, with peak concentrations occurring approximately 2 hours after administration.[47]

Table 1 Antiepileptic drugs available for rectal adminisration

Drug	Treatment usefulness	Dose (mg/kg per dose)	Preparation	Pharmacokinetics	Comments
Carbamazepine (CBZ)	Maintenance	Same as oral	Oral suspension (dilute with equal volume of water) Suppository gel (CBZ powder dissolved in 20% alcohol and methylhydroxy cellulose)[a]	Peak concentration 4–8 hr; 80% absorbed	Cathartic effect

Clonazepam	?Acute	0.02–0.1 mg	Suspension	Peak concentration 0.1–2 hr	Onset may be too slow for acute use
Diazepam	Acute	0.2–0.5 mg	Parenteral solution	Effect in 2–10 min; peak concentration 2–30 min	Well tolerated nordiazepam accumulates with repeated doses
Lorazepam	Acute	0.05–0.1 mg	Parenteral solution	Peak concentration 0.5–2 hr	Well tolerated
Paraldehyde	Acute	0.3 mL	Oral solution (dilute with equal volume of mineral oil)	Effect in 20 min; peak concentration 2.5 hr	Moderate cathartic effect; use glass syringe
Phenobarbital	?Acute	10–20 mg	Parenteral solution	Peak concentration 4–5 hr; 90% absorbed	Onset may be too slow for acute use
Secobarbital	Acute	5 mg	Parenteral solution	Peak concentration 0.5–1.5 hr	
	Maintenance	Same as oral	Same as acute	Same as acute	
Valproic acid	Acute	5–25 mg	Oral solution (dilute with equal volume of water)	Peak concentration 1–3 hr	Cathartic effect
	Maintenance	Same as oral	VPA liquid from capsules mixed into Supocire C lipid base	Peak concentration 2–4 hr; 80% absorbed	Well tolerated

(VPA)

These data are based largely on pediatric studies.
[a] Extemporaneously prepared using commercial products; all other preparations are commercial products given rectally.
Source: Adapted from Graves NM, Kriel RL. Bioavailability of rectally administered lorazepam. *Clin Neuropharmacol.* 1987;10:555–559; with permission.

2. Premedication for sedative or analgesic purposes. To calm the patient for transport to the operating room and smooth induction, benzodiazepines (diazepam, midazolam, lorazepam), antihistamines (hydroxyzine), barbiturates, and narcotics (meperidine, morphine) may be administered. Pro- and anticonvulsant considerations of these medications are addressed later.
3. Diminishing risks of perioperative problems or complications such as aspiration, hemorrhage, or postoperative nausea and vomiting. Complications associated with aspiration are related to both the volume (>25–30 mL) and the acidity (pH <2.5) of the aspirated gastric fluid. Medications are administered based on their ability to increase gastric pH or decrease gastric volume. H2 antagonists (cimetidine, ranitidine, and nizatidine) increase gastric pH and are often administered to patients at high risk for aspiration (e.g., obesity, hiatal hernia). Although H2 antagonists do not have proconvulsant activity, cimetidine can increase phenytoin plasma levels, and these should be monitored. Metoclopromide is also prescribed for patients at risk of aspiration because it increases lower esophageal sphincter tone, facilitates gastric emptying, and has an antiemetic effect. This medication works both centrally and peripherally as a dopaminergic antagonist. Metoclopromide should be used cautiously in epilepsy patients because it may increase the frequency and severity of seizures.[11]

Sodium valproate can cause thrombocytopenia and platelet dysfunction. The mechanism underlying these effects is unknown. Bleeding time and platelet count are essential in the presurgical evaluation of patients on sodium valproate.

Specific platelet function tests such as platelet adhesiveness or aggregation may also be helpful. The role of valproate-induced hemorrhage or exacerbation of surgically induced blood loss is not clearly defined. However, valproate has been suspected in the pathogenesis of hemorrhagic complications of surgery. In one study of 29 children with cerebral palsy who underwent bilateral femoral osteomy, platelet counts were lower and the need for transfusion was higher (50% of cases) in those who were on antiepileptic drug regimens including valproic acid.[17] For major surgical procedures, another AED should be substituted if possible. When valproate is used, doses of >40 mg/kg per day should be avoided because the hematologic effects of sodium valproate may be dose related.[65]

Anesthesia

Anesthetics may possess proconvulsant or anticonvulsant properties or both. The effects of local and general anesthetics on seizure threshold have been examined to determine intrinsic pharmacologic properties and mechanisms of action, interictal and ictal effects on surface, depth, and cortical electroencephalogram (EEG) recordings, and behavioral effects in animals and humans.

General Anesthetics

Inhalation and intravenous anesthetics possess proconvulsant and anticonvulsant properties. The mechanisms of these contrasting neural effects are not fully understood. Biologic differences in how patients respond may result from variations in bioavailability, relative effects on excitatory and inhibitory neurons, and the speed of delivery and changes in serum concentrations. With deepening levels of anesthesia, there are characteristic EEG changes, beginning with increased beta activity and followed by progressive slowing of the background until a flat line or burst suppression record is obtained (Table 2). Postoperatively, slowing often persists for several days, and occasionally for several weeks. As general anesthetics, all halogenated inhalational agents have anticonvulsant properties and can terminate status epilepticus.[82]

Table 2 Anesthetic drugs and the electroencephalogram (EEG)

Drug	Effect on EEG frequency[a]	Effect on EEG amplitude	Burst suppression?
Isoflurance			Yes, >1.5 MAC
Subanesthetic	Loss of alpha, ↑ frontal beta	↓	
Anesthetic	Frontal 4–8 Hz activity	↑	
Increasing dose >1.5 MAC	Diffuse theta and delta → burst suppression → silence	↑→0	
Enflurane			Yes, >1.5 MAC
Subanesthetic	Loss of alpha, ↑ frontal beta	↓	
Anesthetic	Frontal 7–12 Hz activity	↑	
Increasing dose >1.5 MAC	Spikes/spike-and-slow-wave → burst suppression; hypocapnia → seizures	↑↑	
Halothane			
Low dose	↑ Frontal 10–20 Hz activity	↓	Not seen in clinically useful dose range
Moderate dose	Frontal 10–15 Hz activity	↑	
Increasing dose >1.5 MAC	Diffuse theta, slowing with increasing dose	↑	
Desflurane	Similar to equi-MAC dose of isoflurane	Similar to equi-MAC dose of isoflurane	Yes, >1.2 MAC

Nitrous oxide (alone)	Frontal fast oscillatory activity (>30 HZ)	↑, especially with inspired concentration >50%	No
Barbiturates			Yes, with high doses
Low dose	Fast frontal beta activity	Slight ↑	
Moderate dose	Frontal alpha frequency spindles	↑	
Increasing high dose	Diffuse delta → burst suppression → silence	↑↑↑→0	
Etomidate			Yes, with high doses
Low dose	Fast frontal beta activity	↓	
Moderate dose	Frontal alpha frequency	↑	
Increasing high dose	Diffuse delta → burst suppression → silence	↑↑→0	
Propofol			Yes, with high doses
Low dose	Loss of alpha, ↑ frontal beta	↓	
Moderate dose	Frontal alpha waxing/waning alpha	↑	
Increasing high dose	Diffuse delta → burst suppression → silence	↑↑→0	
Ketamine			No
Low dose	Loss of alpha, ↑ variabillity	↑↓	
Moderate dose	Frontal rhythmic theta	↑	

High dose	Polymorphic delta, some beta	↑↑(beta is low amplitude)	
Benzodiazepines			No
Low dose	Loss of alpha, increased frontal beta activity	↓	
High dose	Frontally dominant delta and theta	↑	
Opiates			No
Low dose	Loss of beta, alpha slows	↔↑	
Moderate dose	Diffuse theta, some delta	↑	
High dose	Delta, often synchronized	↑↑	

MAC, minimum alveolar concentration.

[a] Delta, <4 hz; theta, 4–7 Hz; alpha, 8–13 Hz; beta, >13 Hz.

Source: Adapted from Black S, Mahla ME, Cucchiara RF. Neurologic monitoring. In: Miller RD, ed. *Anesthesia*. New York: Churchill Livingstone; 1994:1323.

Among the volatile anesthetics, methoxyflurane and halothane produce the least central nervous system (CNS) irritability and enflurane the most; isoflurane and desflurane are intermediate.[21,22] Changes in basicity of these compounds, which depends on the degree of fluorination of the carbon atoms adjacent to the ether oxygen, may parallel effects on cortical excitability. Isoflurane, the least fluorinated and most basic of these ethers, produces the least cortical reactivity.[21] The mechanism of enflurane-induced hyperexcitability in humans is unclear. In animals, enflurane inhibits synapses and stimulates excitatory neuronal transmission in cortical and subcortical areas.[13]

Patients on the ketogenic diet can safely receive general anesthesia.[11] Carbohydrate-free intravenous solutions should be used perioperatively. With more prolonged procedures, serum glucose and pH levels should be closely monitored. Although glucose levels are usually stable, metabolic acidosis can develop and patients may require intravenous bicarbonate.[11]

Enflurane.

Enflurane is the major inhalation agent that anesthesiologists usually avoid when caring for epilepsy patients because it lowers seizure threshold. In children and adults with no history of epilepsy, enflurane can cause epileptiform activity with concomitant facial or appendicular myoclonus or generalized tonic–clonic movements.[15,51,63] In epilepsy patients, the extent but not the frequency of spike activity on the electrocorticogram is increased.[51] Epileptogenic foci may be activated during epilepsy surgery.[33,74] As the depth of anesthesia is increased with enflurane, the EEG demonstrates high-voltage spikes and spike-and-slow-wave complexes—spike with burst suppression. Although low enflurane concentrations (1%–1.5%) administered to a normocarbic patient ($PaCO_2$ = 40 torr) are not frequently associated with seizure activity,[78] increasing enflurane concentrations (2%–3%) or hyperventilating an anesthetized patient enhances seizure activity. Hyperventilation to a $PaCO_2$ of 20 torr from 40 torr is associated with seizure activity at a 1% lower enflurane concentration. Because hyperventilation is frequently employed by neuroanesthesiologists to decrease cerebral blood flow and intracranial pressure, enflurane is avoided when hyperventilation is indicated. An increase in $PaCO_2$ from 40 to 60 torr increases the minimum enflurane concentration at which seizures occur by 1%.[13]

Generalized tonic–clonic and myoclonic seizures can occur within the immediate postoperative period and potentially occur a few days after enflurane anesthesia. The role of other CNS-active drugs is uncertain in these cases.[81] The convulsant effects may result from enflurane's organic and inorganic nonvolatile fluorinated metabolites.[20]

Although anesthesiologists consider diazepam and thiopental anticonvulsant agents and use them extensively to treat seizure activity, there is some evidence that both of these drugs may potentiate enflurane-related epileptiform activity in humans.[25] Nitrous oxide (N_2O) does not alter epileptiform activity induced by enflurane.[78]

Halothane.

Halothane has anticonvulsant properties and can terminate status epilepticus. When used alone, halothane does not cause CNS irritability.[12] In the few reports of halothane-related seizures, N_2O was also administered.[87] Rarely, sharp waves maximal over the vertex can appear during the first postoperative week, usually on the first two postoperative days. Persistence of an epileptogenic halothane metabolite (i.e., trifluoroacetic acid) may contribute to this sharp activity.[14]

Isoflurane.

Isoflurane, a commonly used inhalation agent, is an isomer of enflurane containing little or no epileptogenicity.[21] In the few cases of isoflurane-related seizures, N_2O was also administered.[43] Isoflurane has anticonvulsant properties, suppressing drug-induced convulsions in animals[56] and terminating status epilepticus in patients at inspired concentrations 0.5%–3%.[57,95] Isoflurane reduces both the frequency and field of spikes on the electrocorticogram of epilepsy patients.[51,57]

Desflurane.

Desflurane is an introduced inhalation agent structurally similar to isoflurane. Compared with isoflurane, it has a more rapid onset of action and recovery. The EEG patterns for desflurane are similar to those seen with equipotent doses of isoflurane. Burst suppression is easily achieved. There was some concern that EEG tolerance may develop to desflurane. However, this has not been demonstrated in humans.[90,116]

Sevoflurane.

Sevoflurane is an inhalation agent. Sevoflurane produces dose-dependent epileptiform discharges at surgical levels of anesthesia[52] and is more epileptogenic than isoflurane.[50] Sevoflurane induction can produce epileptiform activity without clinical evidence of seizure activity in children with or without a history of epilepsy.[23,59] In children of age 4 years and under without a history of seizures, sevoflurane induction has been rarely associated with convulsive seizures.[1] Patients with refractory epilepsy administered sevoflurane at a minimal alveolar concentration (MAC) of 0.5 had significantly fewer spikes than those with a MAC of 1.5.[61] In healthy individuals, electrographic and clinical seizures can result from MAC of 2.0.[52] The use of midazolam and thiopental, or nitrous oxide, prevents the appearance of epileptiform activity with sevoflurane induction.[51,79]

Nitrous oxide has very low epileptogenic potential and has been used extensively in both epilepsy and nonepilepsy patients.[74,80] It does not significantly affect neuronal firing in the human limbic areas.[4] Among 11 epilepsy patients undergoing dental procedures, there were no EEG changes during anesthesia in 9 patients and decreased frequency of paroxysmal discharges in 2 patients.[80]

Barbiturates

Barbiturates are anticonvulsants that can also have proconvulsant actions. Slight structural changes of a barbiturate (e.g., sulfuration or methylation of the 1 position) can convert it from an anticonvulsant into a convulsant.[55] Depending on the dose used, some barbiturates can have both pro- and anticonvulsant properties, with low doses associated with seizure activity in epilepsy patients[58] and higher doses leading to burst suppression.

Thiopental (Pentothal) and Ultrashort-Acting Barbiturates.

Thiopental is used to stop seizures, including those caused

by local anesthesia overdose. The proconvulsant action of thiopental is low compared to that of methohexital.[102] This drug is less effective than methohexital in activating existing epileptogenic activity on the electrocorticogram in epilepsy patients. Thiopental may be a safer induction agent than methohexital for patients with epilepsy.[94] Other ultrashort-acting thiobarbiturates such as thiamylal sodium, buthalitone, and thialbarbitone share common pharmacologic properties with thiopental.

Methohexital.

Methohexital is an ultrashort-acting methylbarbiturate that does not cause seizure activity in patients without epilepsy. However, it can be associated with some excitatory phenomena such as hiccoughing, tremors, and abnormal muscle movements.[74] In patients with epilepsy, electrographic and clinical seizures can occur following intravenous (0.5–1.0 mg/kg), intramuscular (10 mg/kg), and rectal (25 mg/kg) administration.[78,82] Low-dose methohexital (<0.5 mg/kg) can activate interictal and ictal discharges among epilepsy patients during electrocorticography.[86] The activating effect of methohexital may be largely restricted to patients with partial epilepsy, occurring in up to 72% of such patients.[77] Methohexital does not appear to cause seizures during anesthetic induction of patients with generalized epilepsy.[77,94] In higher doses, methohexital can suppress epileptogenic foci and cause electrical silence. This suppressive effect is used in the methohexital suppression test, which has been recommended as an adjunctive tool to distinguish the primary focus in patients with secondary bilateral synchrony or multifocal discharges.[102] This is most valuable in the investigation of temporal lobe epilepsy. Methohexital is administered in incremental doses of 0.5 to 1.0 mg/kg until EEG silence is obtained or only a single focus remains. If total EEG silence is obtained, as the EEG returns, it is hoped that a single focus will become evident.

Etomidate

Etomidate is a hypnotic nonbarbiturate ultrashort-acting anesthetic agent associated with involuntary muscle movements in 10% to 70% of patients. These movements can be violent and mimic seizure activity. Etomidate is often administered because of its cardiovascular stabilizing effect. In patients without epilepsy, surface electrode recordings during the myoclonic movements are not associated with epileptiform activity.[28,60] These myoclonic movements are dose related, occurring more often with higher doses.[28] Posttreatment myoclonus can be suppressed by pretreatment with a low dose of etomidate 50 seconds before the main dose.[28]

Etomidate (0.2 mg/kg) can activate seizure foci in epilepsy patients within 30 seconds[29] and has been used intraoperatively for this purpose. Despite lack of evidence that etomidate causes seizures in nonepilepsy patients, epileptiform activity occurred in 6 of 30 nonepilepsy patients who were induced with etomidate for heart valve replacement.[60]

Benzodiazepines

Benzodiazepines are potent anticonvulsants and are commonly used intravenously (and occasionally rectally) to treat status epilepticus.[74] Diazepam, midazolam, clonazepam, and lorazepam are all used as antiepileptic drugs.[58] Intravenous midazolam drip may be more effective for refractory status than other benzodiazepines.[85] Paradoxically, diazepam may induce seizures in patients with Lennox-Gastaut syndrome and lower the seizure threshold in epilepsy patients receiving enflurane.[107]

In patients with epilepsy, benzodiazepines can be used preoperatively to reduce anxiety. Furthermore, depending on the duration of the surgical procedure and the half-life and redistribution of the specific benzodiazepine, these agents may help to prevent seizures during the transition out of anesthesia. This transition is a withdrawal from central nervous system depressants, and in susceptible patients, can lower the seizure threshold sufficiently to cause a clinical seizure. In patients with a history of seizures during the withdrawal of anesthetics or during the postanesthetic state, use of low-dose benzodiazepines before the end of the procedure or an increase in their chronic antiepileptic drugs (before or intravenously during surgery) may help to prevent seizures.

Opioids

Patients without epilepsy are not at risk for seizures when they receive typical anesthetic doses of narcotics. However, high-dose opioids can elicit seizures. What practitioners observe as seizure activity may actually be myoclonic jerks, rigidity, and other nonepileptic drug–induced movements.[74] Simultaneous scalp EEG and electromyographic (EMG) recordings do not reveal epileptiform activity during abnormal movements. In epilepsy patients, high-dose narcotics may elicit seizure activity in isolated cases (see later discussion of fentanyl). However, scalp EEG recordings may not be adequate to determine this, and electrocorticographic recordings may be required to detect narcotic-induced seizure activity in epilepsy patients.[109]

Morphine.

In humans, routine oral or intravenous morphine doses have little or no effect on seizure threshold.[74] Seizures have occurred after epidural administration of morphine in an epilepsy patient[10] and after inadvertent intrathecal administration of a high dose to a cancer patient without prior seizures.[62] In animals, very high doses of intravenous morphine can cause epileptic seizures.[109]

Meperidine.

Myoclonus, seizures, jitteriness, and tremors are neurotoxic effects of meperidine. Myoclonus generally precedes seizures, but both resolve over several days with discontinuation of meperidine adminstration.[54] These neurotoxic effects are directly related to blood levels of normeperidine, the N-demethylated active metabolite of meperidine.[54,105] The half-life of normeperidine (14–21 hours) is longer than that of meperidine (3–4 hours), so continued use can result in high systemic normeperidine levels.[42,88] In patients receiving oral meperidine, normeperidine levels may increase at a faster rate because of hepatic metabolism.[71] Antiepileptic drugs that induce microsomal hydroxylation (e.g., phenytoin, phenobarbital) increase the conversion of meperidine to normeperidine.

If meperidine causes significant neurotoxicity, it should be discontinued. A short course of a benzodiazepine may help to control jitteriness and tremors, although myoclonus can be refractory.[45] Patients with renal disease have decreased normeperidine clearance and increased risk of toxicity.[105] Patients with sickle cell anemia and malignancy are also at increased risk.[54,106] Seizures have been reported in patients receiving long-term or high-dose meperidine via patient-controlled analgesia pumps (PCAPs).[42]

Seizure-like movements have not been reported in epileptic patients during either acute or chronic meperidine administration. It is unknown whether acute or chronic meperidine use activates epileptogenic EEG foci in epilepsy patients. Neither meperidine nor its metabolites have anticonvulsant properties.[74] Electroencephalogram changes in otherwise healthy individuals in whom seizures have occurred after repeated meperidine administration include diffuse slow activity and epileptiform discharges.[3,37]

Fentanyl, Sufentanil, and Alfentanil.

Myoclonic movements and rigidity occurring with fentanyl, sufentanil, and alfentanil prompted reports that high doses of narcotics can cause seizures. However, these reports have not been substantiated with EEG documentation of seizure activity.[91,99] Simultaneous EEG and EMG recordings during fentanyl, sufentanil, and alfentanil induction did not reveal epileptiform activity during intense rigidity and associated movements that might be interpreted as seizures.

Eight of nine patients with complex partial epilepsy had fentanyl-induced epileptiform activity on the electro-corticogram.[109] In four of these patients, epileptiform activity was recorded beyond the seizure focus. Alfentanil increases the mean temporal lobe spike frequency during temporal lobe electrocorticography.[18] Some groups use these agents to activate interictal epileptiform foci arising from the amygdala or hippocampus.[69]

Neuroleptic-Opioid Combination: Innovar (Droperidol plus Fentanyl)

Among 104 patients receiving neuroleptic anesthesia for various neurodiagnostic procedures utilizing metrizamide, there was no clinical or EEG evidence of seizures.[96]

Dissociative Anesthesia: Ketamine Hydrochloride

Ketamine hydrochloride has proconvulsant and anticonvulsant properties. Of eight epilepsy patients undergoing dental work, two had partial motor seizures and another had a generalized tonic–clonic seizure with ketamine.[6] In some patients with epileptiform activity on their baseline EEG, particularly those receiving 2 to 4 mg/kg intravenous doses, the activity progressed to electrical seizure.[32] The EEG recordings in all of these patients returned to their preanesthetic baseline within 1 week.[6] Ketamine should be used with caution in epilepsy patients. If a clinical seizure occurs during ketamine use, further administration of ketamine to deepen anesthesia should be avoided. Instead, a CNS depressant such as a barbiturate or benzodiazepine should be used.[114]

In other studies, ketamine did not increase epileptiform or seizure activity in epilepsy patients.[19,24] Because of the mixed depressant–stimulant effects of ketamine, epilepsy patients should be adequately premedicated with anticonvulsants and sedatives.

Propofol

Spontaneous movements can occur during induction with propofol without associated epileptiform abnormalities. These movements include dystonia, chorea, athetosis, twitches, and opisthotonus. Abnormal movements may mimic tonic and clonic movements during seizures, especially during the postoperative period.[16] In several cases, cortical epilepsy was activated during electrocorticography, with epileptiform activity beginning 20 to 30 seconds after a bolus of intravenous propofol.[46] In patients who receive baclofen, propofol can cause recurrent tonic–clonic seizures.[67] Seizures may recur for 7 to 23 days after propofol anesthesia, suggesting a proconvulsant metabolite.[12,48] Propofol also has anticonvulsant properties in animals[66] and humans.[9] Continuous propofol infusion can terminate status epilepticus refractory to other therapies.[73]

In epilepsy patients undergoing dental procedures, administration of propofol in subanesthetic doses to achieve conscious sedation did not provoke seizures or enhance any interictal epileptiform activity.[63] Propofol can also be used successfully in children undergoing the sodium amobarbital test to produce rapid induction of anesthesia without endotracheal intubation.[70] Neuropsychological testing could be successfully performed after angiographic testing was completed.

Local Anesthesia

Differences in CNS effects of local anesthetics are attributable to differences in potency, systemic rate of absorption from site of injection, speed of passage through the blood–brain barrier, rate of biotransformation, and speed of intravascular injection of the anesthetic.[111] Stimulation of the CNS by some local anesthetics may result from selective depression of inhibitory neurons. Rapid administration or large doses can depress all neuronal activity with only transient or no CNS signs of stimulation.[93]

Lidocaine

Lidocaine has proconvulsant and anticonvulsant effects, with CNS effects related to blood concentrations. Low doses of lidocaine (2–3 mg/kg) can terminate status epilepticus. With increasing blood levels, CNS symptoms and signs of toxicity occur from perioral numbness, lightheadness, dizziness, tinnitus, and fine tremors to generalized seizures and coma. In animals, lidocaine produces epileptiform activity limited to the amygdala and hippocampus.[26]

Lidocaine doses commonly used for local anesthesia can cause CNS toxicity if they are inadvertently administered intravenously. For example, when epidural anesthesia is administered, total doses of 5 to 8 mg/kg are commonly injected into the epidural space.[111] Accidental intravascular injection of this dose can cause epileptic seizures. In addition to direct intravascular injection and immediate toxicity, systemic lidocaine levels can rise to toxic levels by rapid systemic absorption from the area of injection. This can occur 10 to 20 minutes after injection. Anesthesiologists often add epinephrine, 5 g/mL, to the local anesthetic to decrease systemic absorption and decrease peak serum lidocaine levels. When a regional anesthesia block is unsuccessful, early reinjection of local anesthesia can cause toxicity (including seizures) because peak absorption of the first injection is occurring while additional medication is injected.

High doses of lidocaine cause sedation. Increasing $PaCO_2$ decreases the dose of lidocaine needed to produce a generalized electrical seizure.[113] Higher $PaCO_2$ levels increase cerebral blood flow, thus increasing the amount of anesthetic reaching the brain, and may directly excite the amygdala. In contrast to hyperventilation to activate seizure activity, by decreasing cerebral blood flow, hyperventilation may prevent seizures from occurring in patients with lidocaine overdose.

Lidocaine is injected intravenously to provide local anesthesia (intravenous regional anesthesia or Bier blocks). In this technique, after an extremity is exsanguinated and blood supply is arrested by a tourniquet, lidocaine is injected into a vein to provide anesthesia. Doses of lidocaine up to 3 mg/kg of 0.5% solution without preservatives or epinephrine are utilized. Premature tourniquet release (<20 minutes) can result in high systemic lidocaine levels and possible seizure activity. Release after 20 minutes can also be associated with toxicity. Some physicians cycle the deflation of the tourniquet with intermittent inflation–deflation–inflation in an attempt to decrease rapid absorption of lidocaine from the extremity.

Etidocaine HCl, a long-acting derivative of lidocaine, as well as mepivacaine and prilocaine HCl share common pharmacologic properties with lidocaine HCl. Seizures induced by lidocaine can be terminated with barbiturates.

Bupivacaine

Bupivacaine causes CNS toxicity at plasma level >4 g/mL. Seizures can occur with plasma levels of 2.3 and 3.0 g/mL after accidental intravenous injection during obstetric epidural anesthesia.[97] A more dangerous concern with bupivacaine toxicity is intractable ventricular fibrillation.

Cocaine

Cocaine produces electrical and clinical seizure activity in animals. Electrographic discharges arise in the amygdala. Protection against such cocaine-induced seizures is afforded by dibenamine, chlorpromazine, reserpine, pyridoxine, and hydroxylamine but not traditional anticonvulsants. Thus, cocaine may cause seizures by potentiating noradrenergic or dopaminergic activity in the amygdala.[31]

Seizures occurred in an 11-week-old infant receiving intranasal installation of a 4% cocaine solution[101] and in a child receiving topical cocaine solution through a bronchoscope.[100] Edematous and inflamed mucosa may absorb excessive amounts of anesthetic. In these settings, using benzodiazepines or short-acting barbiturates, using local vasoconstrictors, and rinsing the mucosal surface with water or normal saline to prevent further drug absorption have been recommended in managing cocaine-induced seizures in children.[101]

Procaine

At low doses, procaine has anticonvulsant properties.[7] Procaine, given at 18 to 29 mg/kg, causes generalized tonic–clonic seizures. In one study, thiopental pretreatment failed to prevent procaine-induced seizures but increased the dose of procaine necessary to produce seizures. Thiopental given during a procaine-induced seizure stopped the seizure.[111] *p*-Aminobenzoic acid is a procaine metabolite that can prevent seizures induced by local anesthetics.[92] This metabolite might explain the low incidence of generalized convulsions reported during the continuous infusion of intravenous procaine.

Chloroprocaine, a halogenated derivative of procaine, shares the same pharmacologic properties as procaine.

Tetracaine HCl, a derivative of *p*-aminobenzoic acid, is ten times more active and potent than procaine after intravenous injection.

Anesthetic Adjuvants

Muscle Relaxants

None of the Food and Drug Administration (FDA)–approved muscle relaxants used in clinical anesthesia is known to cause epileptiform activity or seizures, nor have there been reports regarding the anticonvulsant properties of these drugs in humans. Accumulation of laudanosine, a metabolite of atracurium, may slightly decrease the seizure threshold.[5] In Italy, three patients treated with thiocolchicoside, a centrally acting muscle relaxant, developed seizures.[27]

Most of the neuromuscular blocking agents are more rapidly metabolized in patients on chronic therapy with antiepileptic drugs that induce the hepatic enzymes. Resistance to metocurine-induced,[84] atracurium-induced, or vecuronium-induced[83] neuromuscular blockade has been demonstrated in patients chronically receiving phenytoin. Similarly, patients receiving chronic carbamazepine therapy have shortened recovery times from the neuromuscular blockage induced by vecuronium. The mechanism is a twofold increase in vecuronium clearance.[2] Children on chronic therapy with hepatic enzyme–inducing antiepileptic drugs have shorter recovery times with the neuromuscular blocker rocuronium.[104]

Anticholinesterases

Anticholinesterases used in clinical anesthetic practice have not been reported to cause or stop seizures.

Anticholinergics

Atropine can reduce abnormal discharges of the EEGs of epileptic patients.[41] It can also block spontaneous and hyperventilation-induced petit mal seizures.[110] These effects are probably related to its central anticholinergic action.

Analgesia: Nonopiate Analgesics

Acetaminophen

Phenytoin facilitates the elimination of acetaminophen by accelerating its biotransformation,[88] and phenobarbital induces acetaminophen metabolism, which can result in an increase in toxic metabolites.[89] This may increase the risk of acetaminophen overdose.

Salicylates

Salicylates compete with phenytoin for plasma protein–binding sites. One study showed an increase from 10% to 16% in the unbound fraction of phenytoin. Changes were proportional to the acetylsalicylic dose, which ranged from 900 to 3,600 mg/d.[34] Although high and repeated doses may cause slight increase in free phenytoin and a decrease in total phenytoin level, there is usually no need to adjust the phenytoin dose.[87] An increase of the free fraction but not of the total valproate concentration can occur in patients receiving 15 to 30 mg/kg of acetylsalicylic acid. This increase is not clinically significant in most cases.

Ibuprofen

Ibuprofen has not been reported to cause any significant interaction with anticonvulsants or to affect the seizure threshold.

Surgery and Recovery

Neurologists may be asked to provide clearance for an epilepsy patient to have surgery. A good history with particular emphasis on seizure types and frequency is important. History of status epilepticus should be sought because this may place the patient in a higher-risk group. Children with progressive neurologic dysfunction and epilepsy may have inborn errors of metabolism that place them at added risk for anesthesia and procedures. In particular, children with respiratory chain defects such as Leigh disease or other conditions that predispose to metabolic acidosis are at risk for sudden or delayed respiratory decompensation. This appears to be induced by anesthetic agents that interact with mitochondrial function.[30] We recently had experience with a pediatric patient with mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) who died during gastrostomy placement because of extreme fragility of her great vessels. Postmortem analysis revealed a large percentage of mutations in her vessels. Her mother had tragically died after minimal trauma to her vessels during a catheterization procedure.[108] Medication history including reactions, tolerance, side effects, and efficacy should also be obtained. Current medical problems requiring medications should be defined to anticipate possible interactions with habitual medications and anesthetics.

If the patient's epilepsy is in good control and there have been no recent medication changes, serum drug levels are unlikely to be clinically useful. In selected circumstances, it may be beneficial to check serum drug levels, but this need not be obligatory, and serum levels are of secondary importance to good seizure control and the absence of side effects.

Oral doses can be administered the morning of surgery with a small sip of water. Some antiepileptic drugs can be administered intravenously when surgical time exceeds the half-life of the maintenance antiepileptic drug. The decision to use an intravenous antiepileptic drug in patients maintained on antiepileptic drugs that only can be given orally depends on several factors, including degree of preoperative seizure control and the anticipated surgical time. Although intraoperative or postoperative seizures can occur in undiagnosed or undertreated epilepsy patients, it is rare, in our experience, to see substantial alterations in seizure control in well-planned circumstances.[36]

Serum drug levels may be significantly altered by anesthetics and the physiologic changes from surgery. These include antiepileptic drug distribution, enzyme saturation and competition, binding competition at the neuroreceptor level, carrier substances, pharmacokinetics, pharmacodynamics, and blood loss and volume changes. Carbamazepine level can increase up to twofold after surgery and returns back to normal in 7 to 10 days. Phenytoin level can also increase. Serum drug levels should be obtained after surgery to see this pattern. Clinical toxicity from an antiepileptic drug can cause a significant delay in postoperative recovery, and seizures may occur as a result of decrease in drug levels.[58]

Dental Procedures

Before a dental procedure is performed, drug levels should be obtained and adjusted based on the individual patient's history. Precipitating factors such as sleep deprivation or alcohol intake should be avoided before the procedure. The dental team should be informed about the patient's seizure type and first aid. The use of hospital-based dental programs for epilepsy patients can be helpful in patients with moderate to profound mental retardation or serious behavioral problems (31.1%) or if seizures are frequent and occurred during prior outpatient dental procedures.[49]

Methohexital was compared with local anesthetic in conservative dental procedures. Although only 1 seizure occurred among 200 patients, this drug had the additional disadvantages over local anesthetics of side effects that included tongue movements, coughing, hiccoughs, and prolonged lethargy after the procedure.[68] Seizures during or after a dental procedure can occur with nitrous oxide[36] or methohexital.[98] In these studies, seizures most often occur in undiagnosed epilepsy patients or those who missed a dose of their antiepileptic medications on the day of the dental procedure. Other studies demonstrate that nitrous oxide and propofol in subanesthetic doses for conscious sedation are safe for epilepsy patients with mental disabilities undergoing dental procedures.[80] Nitrous oxide and propofol are almost always safe in epilepsy patients who are adequately treated with antiepileptic drugs.

Summary and Conclusions

Proper history taking with attention to the seizure type and frequency as well as medication compliance and response is of basic importance. One priority of prescreening children with severe epilepsy is to exclude inborn errors of metabolism that may be exacerbated by anesthesia with tragic results. Other factors that may precipitate seizures must be identified. The health care provider should be able to identify different seizure types and understand principles of first aid for seizures. Antiepileptic drugs should be administered both before and after a procedure and adjusted individually (if needed) to minimize the risk of seizures or side effects. Drug interactions should be considered in adjusting maintenance doses.

Most general and local anesthetics have both pro- and anticonvulsant properties. Except for enflurane, which has been associated with a higher risk for seizures, all of the anesthetics in use may be administered safely to epilepsy patients if a proper approach to epilepsy patient care is made. The risk of seizures during or after a surgical or dental procedure is minimal when routine precautions and guidelines are followed.

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Chapter 194

Hormone Changes in Epilepsy

Cynthia L. Harden

Cheryl A. Frye

Introduction

The relationship between hormones and seizures has long been recognized with the observation of prolactin elevation immediately following generalized seizures. Furthermore, this clinical phenomenon has been diagnostically useful. More recently, however, studies of the effects of seizures on endocrine function have largely focused on reproductive issues. The disruptive effects of seizures on reproductive endocrine functioning are not immediate, however, and appear to develop as a result of chronic dysregulation of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) secondary to abnormalities in gonadotropin-releasing hormone (GnRH) from the hypothalamus. This chapter discusses evidence for effects of seizures on hormones and the clinical consequences of this relationship.

Effects of Epilepsy on Hormones in Animal Models

Stress-related Hormones

Stress produces an increase in circulating and brain concentrations of corticosteroids, most importantly cortisol and deoxyocorticosterone. Given that seizures themselves are stressful events, it is expected that stress hormones will increase with seizures. The hormones increased by stress have mixed proconvulsant and anticonvulsant effects. Both pregnenolone sulfate and dehydroepiandrosterone sulfate are increased by stress, and each has a proconvulsant effect in animal models. Deoxyocorticosterone is metabolized to allotetrahydrodeoxycorticosterone, however, which activates γ-aminobutyric acid A ($GABA_A$) receptors. Therefore, seizures may initiate the release of hormones that have mixed effects on brain excitability.[41] The $GABA_A$ receptors of hippocampal neurons in epileptic animals have diminished capacity for modulation by neuroactive steroids,[35] which supports the presence of an interaction between seizures and neurosteroid activity in the brain.

One hypothesis for the etiology of West syndrome and its accompanying infantile spasms is related to the presence of abundant corticotrophin-releasing hormone (CRH) receptors in the brain normally present at the critical infantile time period. Dysfunction of the brain's response to stress-induced CRH elevation triggers the syndrome and further explains the therapeutic response to a hormone that suppresses CRH production, adrenocorticotropic hormone (ACTH).[8]

Reproductive Hormones

Regulation of reproduction involves brain structures as part of a complex, multilocalized system termed the hypothalamic-pituitary-gonadal axis. A critical portion of the hypothalamic-pituitary-gonadal axis is the small and scattered population of GnRH-producing neurons within the diagonal band of Broca, the vasculosum of the lamina terminalis, and the preoptic area of the hypothalamus. When activated, these neurons secrete GnRH into the hypophyseal-portal vasculature, and this hormone then regulates the production and release of the two gonadotropins, LH and FSH. The synchronization and responsiveness of this hormonal system are essential for normal reproductive functioning.[15]

Seizures produce reproductive dysfunction in animal models of epilepsy, and these experiments provide further information about mechanisms of epilepsy-related reproductive dysfunction in humans. Kindling in the basolateral amygdala of intact rats produces reproductive alterations roughly analogous to polycystic ovary syndrome among women. Amygdala kindling disrupts ovarian cyclicity and produces cystic ovarian follicles, high E_2 levels, and increased pituitary weights.[13] The abnormalities in the target organs of the hypothalamic-pituitary-gonadal axis may be due to disruption of normal GnRH release in the hypothalamus due to seizure activity. The evidence for this is that GnRH fibers are reduced following pilocarpine-induced status epilepticus or focal application of kainic acid to the amygdala.[1,16] These findings suggest that temporal limbic structures, such as the hippocampus and the amygdala, that are involved in seizures alter reproductive function via the effects on gonadotropin secretion.

Effects of Epilepsy on Hormones in Humans

Acute Changes in Hormones Following Seizures: Prolactin, Follicle-stimulating Hormone, and Luteinizing Hormone

Further evidence for an effect of seizures on hypothalamic activity is the long-observed elevation in prolactin that occurs after generalized tonic–clonic seizures. Like that of LH and FSH, control of prolactin release from the pituitary is also under hypothalamic control. Acute changes following seizures include increases in prolactin for 20 minutes and serum LH (in women and men) and FSH (in women) for 60 minutes following generalized tonic–clonic seizures.[11,38,43] A recent, evidence-based report on the use of serum prolactin levels in diagnosing epileptic seizures recommended that an elevated prolactin within 10 to 20 minutes after a suspected event is a useful adjunct in differentiating generalized tonic–clonic or complex partial seizures in adults and older children from psychogenic nonepileptic seizures. Syncope may also elevate prolactin levels, however, limiting its diagnostic usefulness.[9] Furthermore, prolactin levels cannot be reliably used for this purpose in infants or in status epilepticus.[9]

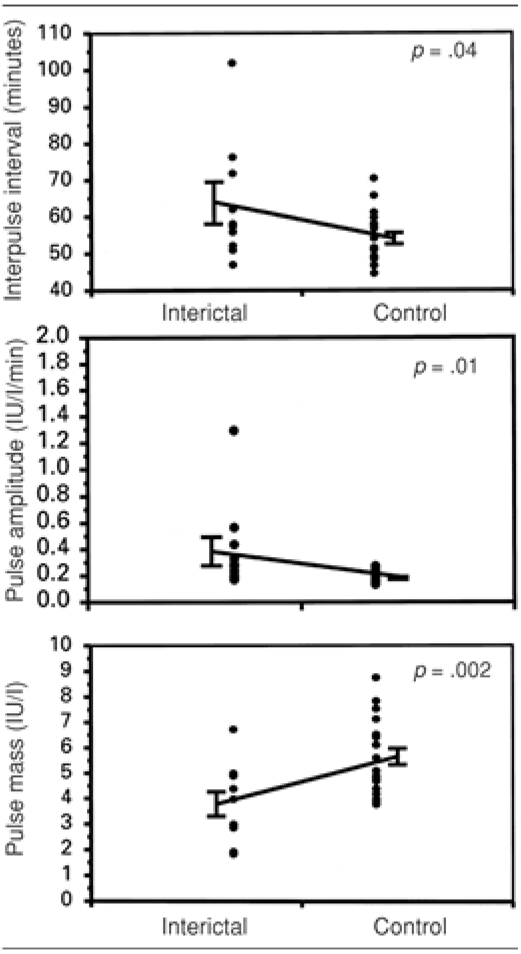

FIGURE 1. Scatterplot of luteinizing hormone interpulse interval, pulse amplitude, and pulse mass calculated from interictal epochs from men with mesial temporal lobe epilepsy compared with those of healthy controls. Error bars are equal to ± standard error of the mean, and *p* values are from Student's paired *t*-tests. (From Quigg M, Kiely JM, Shneker B, et al. Interictal and postictal alterations of pulsatile secretions of luteinizing hormone in temporal lobe epilepsy in men. *Ann Neurol*. 2002;51(5):559–566, with permission.)

Effects of Epilepsy on Luteinizing Hormone Pulsatility; a Possible Cause of Hypogonadotropic Hypogonadism

It is possible that the disruption in gonadotropin secretion produced by seizures, leading to a dysfunctional feedback system between reproductive hormones and LH and FSH secretion, is related to the increased incidence of reproductive endocrine disorders and infertility observed among those with epilepsy.[7] Epilepsy itself, incorporating the subclinical activity of interictal spikes, can also disrupt the finely tuned, pulsatile secretion of LH. It has been shown that LH secretion can be disrupted by interictal spikes in men and women (Fig. 1).[6,12,28,40] Recently, a differential effect of interictal and postictal effects on LH secretion in men with epilepsy was reported. The investigators reported that the circadian peak concentration of LH is delayed interictally compared to controls, and that burst amplitude is generally lower throughout the day. However, postictally, within 24 hours of a seizure, the peak concentrations of LH pulses were dispersed to a more random, rather than rhythmic pattern, with longer interburst interval.[39] These findings offer even more refinement of the evidence for a negative effect of seizures and epilepsy on reproductive functioning and indicate that this sensitive system can be easily disrupted, with clinical consequences.

The absent or decreased ability of the hypothalamus to secrete GnRH or of the pituitary gland to secrete LH and FSH leads to hypogonadotropic hypogonadism, which is a failure of gonadal function due to inadequate stimulation by LH and FSH. This syndrome, or at least partial features of it, has been reported in both men and women with epilepsy.[25,31,36] In one report, hypogonadotropic hypogonadism as defined by reduced gonadotropin release, loss of cyclicity, and/or infertility was present in 12% of women with temporal lobe epilepsy versus 1.5% in the general population.[25]

Polycystic Ovary Syndrome and Epilepsy

As an example of this dysfunctional feedback system, the incidence of polycystic ovary syndrome (PCOS), a form of hyperandrogenic chronic anovulation, which generates abnormal androgen levels and positive feedback at the level of the hypothalamus, ranges from 10% to 25% among women with temporal lobe epilepsy and from 4% to 6% in the general population.[25] One possible cause of this mysterious syndrome is thought to be centrally mediated as a result of abnormalities in LH and FSH stimulation of the ovary. This abnormal hormonal environment results in multiple immature ovarian follicles, which form cysts and secrete testosterone rather than estrogen, which is secreted from a matured follicle. Therefore, PCOS may also be a consequence of a dysregulated hypothalamic-pituitary-gonadal axis.

Although valproate has been associated with PCOS, it is unclear whether it causes, exacerbates, or imitates PCOS because it can elevate androgens in both men and women (see also Chapters 108 and 198). Valproate likely increases androgens, at least in part, by inhibition of aromatase, the enzyme involved in conversion of testosterone to estrogen.[19] In an evaluation of 93 women with focal epilepsy of long duration, PCOS (defined as elevated testosterone levels and oligomenorrhea or amenorrhea) occurred in 10.6%. No difference was found between women taking carbamazepine (*n* = 20; 10%), valproate (*n* = 18; 11.1%), or no antiepileptic drugs (AEDs) (*n* = 19; 10.5%).[4] This study confirms the finding that PCOS is present at a higher-than-expected rate in women with epilepsy, but it does not support a clear association with valproate use.

Epilepsy During Perimenopause and Menopause

During perimenopause, most women with epilepsy report seizure increase.[22] This may be due to an increased estradiol-to-progesterone (E_2/P_4) ratio, particularly at the beginning of perimenopause. At postmenopause, however, when E_2 and P_4 levels become very low and stable, women who had experienced a catamenial seizure pattern during their reproductive years in particular report decreased seizure frequency (Fig. 2).[22] This finding supports the presence of a subset of women with epilepsy who are sensitive to hormonal fluctuations both during reproductive years and after. Furthermore, women have reported increased seizures with hormone replacement therapy (HRT) during postmenopause,[22] and increased seizure frequency has been shown to occur with HRT using conjugated equine estrogens and medroxyprogesterone acetate in a double-blinded, placebo-controlled, randomized study of postmenopausal women with epilepsy.[20] This finding suggest that with this formulation of HRT, the brain milieu that was stable with low levels of reproductive hormones becomes sensitive to the seizure-promoting effects of estrogens.

Seizures and Age at Menopause

Table 1 Age at last menses in seizure frequency groups

Group	Mean ± SD age at last menses (yr)	95% CI
1, *n* = 15	49.9 ± 4.2	47.6–52.3

2, $n = 25$	47.7 ± 4.3	45.9–49.4
3, $n = 28$	46.7 ± 3.5	45.3–48.0

$p = .042$ ($p = .037$ between groups 1 and 3 using Bonferroni adjustment). CI, confidence interval; SD, standard deviation.

Groups 1 subjects had <20 seizures in their lifetime, group 2 subjects had >20 seizures in their lifetime but fewer than one seizures per month on average, and group 3 subjects averaged one or more seizures per month for most of their illness.

Source: From Harden CI, Koppel BS, Herzog AG, et al. Seizure frequently is associated with age at menopause in women with epilepsy. *Neurology*. 2003;61(4):451–455, with permission.

Women with epilepsy are at risk for early menopause,[21,23] and the timing of menopause may relate to seizure frequency (Table 1). Women with frequent seizures report an age at menopause of 3 to 4 years earlier than expected, whereas women with rare seizures become menopausal at the expected age of 50 to 51 years.[21] This finding is another example of an adverse effect on the reproductive system by seizures and epilepsy, and it may be due to chronic abnormal LH pulsatility, although the exact mechanism is unclear.

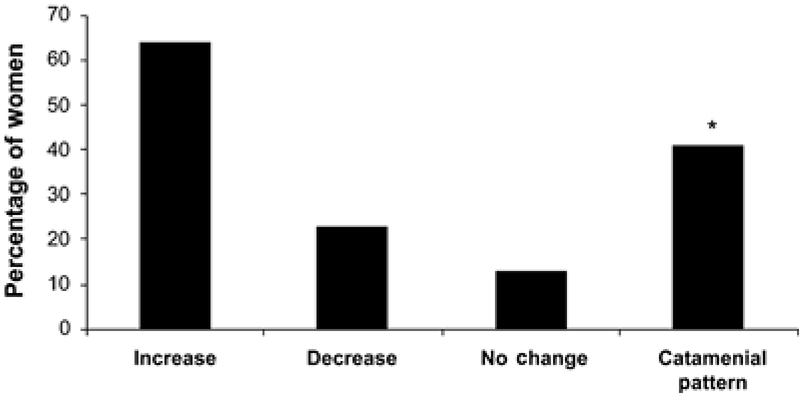

FIGURE 2. Seizure patterns in perimenopausal women with epilepsy. *Significantly associated with an increase in seizures ($p = .02$).

Effects of Epilepsy on Sexuality in Men and Women

It is noteworthy that men with epilepsy tend to have androgen deficiency more frequently and tend to have early and accelerated reductions in androgen levels compared to men without epilepsy.[26,31] Among men with epilepsy, the incidence of sexual dysfunction, hyposexuality, reduced potency, and/or infertility is reported to be as high as 70% and may be due to hypogonadotropic hypogonadism.[10,29,33] Although sexual dysfunction for persons with epilepsy is often evaluated in terms of an effect of antiseizure medications, it seems clear that an adverse effect of epilepsy itself is present, independent of treatment.[3]

A recent evaluation of the sexual development of a large group of adolescent males with epilepsy ($n = 130$)

reported that sexual development was delayed and free testosterone levels and testosterone-to-LH ratios were lower compared to controls.[14] In this study, polytherapy was associated with greater deviation from expected development and hormonal profiles. This confirms the effects of AEDs and likely epilepsy on sexuality in males and indicates a longitudinal adverse effect of these reproductive alterations.

Women with epilepsy also frequently report decreased sexual desire. In one study, 20% of women with epilepsy reported almost never having sexual desire, whereas this low level of sexual desire was reported only rarely among healthy control women.[5] Sexual dysfunction in women with epilepsy has been associated with right-sided epileptiform discharges and low bioactive testosterone levels.[27] (For additional discussion, see Chapter 197.)

Catamenial Epilepsy

It is recognized that seizures of men and women show clustering patterns[42]; exacerbation or clustering of seizures in relationship to the menstrual cycle is termed catamenial epilepsy. Catamenial epilepsy is best defined as a twofold increase in average daily seizure frequency that typically occurs perimenstrually when estradiol and progestin levels decline, around ovulation when estradiol and progestin levels increase, or during an inadequate luteal phase. The twofold increase in seizure frequency as a cutoff point for catamenial versus noncatamenial seizure exacerbation was derived from evaluating monthly seizure patterns in a large number of women with epilepsy. The authors found that a daily seizure increase of 1.6 to 1.8 times during perimenstrual days, at ovulation, or during the luteal phase compared to other days in the menstrual cycle reliably distinguished between women with seizure exacerbations at those times and those without them.[30] These findings indicate that an approximately twofold increase in seizure frequency during these days of the menstrual cycle is an appropriate amount of seizure increase to constitute a catamenial seizure exacerbation.

In relating these patterns to hormonal changes, seizure exacerbations at ovulation occur when P_4 levels are low relative to E_2 concentrations,[30] as described previously. Indeed, Backström, who was the first systematically to examine the relationship between gonadal steroid levels and seizure frequency, demonstrated a positive correlation between generalized seizures and E_2/P_4 ratio and a negative correlation between seizures and P_4 level (i.e., as P_4 concentration increased, the number of seizures decreased).[2] Seizure exacerbations perimenstrually, which is the most frequently reported pattern of catamenial seizure increase, are thought to be related to P_4 withdrawal.[17,32,42] Ovulation, when the E_2/P_4 ratio is highest, is the second-most-frequent time of seizure exacerbation. The third-most-commonly reported pattern of catamenial seizure exacerbation is during the entire luteal phase, particularly when FSH secretion is inadequate and P_4 levels are low.[30]

Stress Hormones in Epilepsy

Patient's report that day-to-day stress can increase their vulnerability to seizures[24]; whether this is related to alterations

in neurosteroids such as corticosteroids has not been ascertained. There are hints, however, that corticosteroids are related to epilepsy in important ways. In one series, women with epilepsy had higher cortisol levels than controls, and within the epilepsy group, women with frequent seizures in particular had high cortisol levels.[18] Furthermore, elevated basal cortisol prior to electroconvulsive shock therapy (ECT) has been associated with a greater decline in performance of executive function, visuospatial processing speed, and verbal memory after a standard course of ECT, suggesting that elevated glucocorticoids may increase the vulnerability of the brain to the adverse effects of repeated seizures.[37]

Summary and Conclusions

Stress-related Hormones

Corticosteroids have effects on brain excitability; however, the association between seizure occurrence or severity in persons with epilepsy and stress hormones requires further investigation.

Prolactin

Prolactin release following generalized tonic–clonic and complex partial seizures is further evidence of the hypothalamic involvement in these seizure types. This effect on hormones by seizure occurrence is so reliable that a prolactin level can be used to distinguish generalized tonic–clonic and complex partial seizures from psychogenic nonepileptic seizures in adolescents and adults. Caveats for the usefulness of a prolactin levels in this clinical situation are that it cannot be used to distinguish a seizure from syncope, reliably used for this purpose in infants, or used in status epilepticus.

Reproductive Endocrine Dysfunction

Seizures and interictal discharges are associated with abnormal FSL and LH secretion in men and women with epilepsy. This chronic effect of epilepsy-related effects on GnRH release and the secondary effect on gonadotropin release likely produces clinically significant but at times subtle effects on reproductive functioning over the long term. These effects include varying degrees of hypogonadotropic hypogonadism, polycystic ovary syndrome, anovulation, early onset of menopause, and a risk of sexual dysfunction in both genders as well as delayed sexual development in boys. The presence and occurrence of these reproductive abnormalities in persons with epilepsy should be monitored for and treated as they are recognized.

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Chapter 195

Effects of Hormones on Seizure Expression

Torbjörn Bäckström

Introduction

Epilepsy is a complicated condition that may affect different areas of life. For example, fertility, family planning, and pregnancy are affected by epilepsy in part because of epilepsy-related alterations in hormones. Seizures and epilepsy also have effects on thyroid and adrenal hormones. Thyroid, adrenal, and sex steroid hormones affect the central nervous system (CNS), ultimately altering seizures and epilepsy. This chapter examines how endogenous and exogenous steroid hormones affect the CNS. Metabolites of the gonadal steroid progesterone and the adrenal steroid desoxycorticosterone seem to be of great importance for the hormonal effects on CNS excitability. They have all a similar chemical structure in being 3α-hydroxy-5α-pregnane steroids. The nomenclature of these substances is somewhat confusing because the same steroid can have several names. The progesterone metabolite 3α-hydroxy-5α-pregnane-20-one is also called allopregnanolone; in this chapter we use the abbreviation 3α5α-P. The 3α-hydroxy-5α-desoxycorticosterone is also called tetrahydrodesoxycorticosterone, for which THDOC is often used as an abbreviation.

Adrenocorticotropic Hormone Effect on Seizure Expression

Adrenocorticotropic Hormone

An anticonvulsant effect of adrenocorticotropic hormone (ACTH) in epileptic patients was first described by Klein and Livingston.[87] Subsequently, ACTH was shown to be an effective treatment for patients with infantile spasms,[144,146] cryptogenic epilepsy, and symptomatic seizures following organic brain lesions.[118] Natural ACTH has fewer side effects than glucocorticoid hormones[144] and does not induce seizures.[86] Long-term glucocorticoid treatment, however, inhibits the activity of hypothalamic–pituitary–adrenal axis, which is a serious side effect. ACTH levels may be low in adult patients with epilepsy treated with antiepileptic drugs (AEDs), suggesting dysfunction of the adrenocortical axis.[49,118,122,132,145] In 27 men and women with epilepsy, the mean serum ACTH level was lower than that in a control group, and this reduction was most pronounced in those with more severe epilepsy of longer duration.[122] An ACTH level was evaluated in ten children before and after 6 months of therapy with valproic acid. Before treatment, ACTH values were normal, but they decreased significantly with treatment.[78] Seizures may also alter ACTH release. A significant increase in ACTH occurred in ten patients within 60 minutes of a generalized tonic–clonic seizure.[53] This elevation of ACTH suggests that the hypothalamic–pituitary–adrenal cortex axis may be affected by generalized seizures.

Corticosteroids

Adrenal cortical hormones exert regulatory effects on central nervous system (CNS) excitability.[174] There is a significant increase in serum cortisol level in patients after generalized tonic–clonic seizures. In the rat's brain, concentrations of neuroactive steroids increase with stress.[140] Changes in cortisol levels may respond to physiologic stress associated with seizures.[1] In a group of 45 men with epilepsy not treated with AEDs, cortisol levels were lower than in a control group.[132] After AED treatment, levels decreased further, suggesting that AEDs influence adrenal cortex function.[132] Further studies should evaluate the way in which alterations in the hypothalamic–pituitary–adrenal cortex axis are related to epilepsy or AEDs.

A relationship between adrenocortical steroids and seizures was found in several experimental and some clinical studies.[66,141] Both mineralocorticoids and glucocorticoids alter neural activity,[80] and the adrenal produces both pro- and anticonvulsant steroids[125] (see later discussion). Aird and Gordon[2] as early as 1951 showed that desoxycorticosterone has an anticonvulsant effect in patients with epilepsy. THDOC, a metabolite of desoxycorticosterone, is a potent γ-aminobutyric acid A ($GABA_A$)-receptor agonist with nearly the same inhibitory effects as 3α5α-P (see later discussion).[90,134,160] Although cortisol on its own increases brain excitability and decreases chloride flux through the $GABA_A$ receptor, when it is used together with 3α5α-P and THDOC the effect changes, and cortisol enhances the GABA agonistic effect of 3α5α-P and increases neural inhibition.[160,169] The classic hormonal mineralocortico- and glucocorticoid receptors are present in the brain, and their expression has effects on neural activity in the regions in which they are located, as in the hippocampus.[80] Several mechanisms are therefore likely to operate in parallel, but one can assume that rapid effects within minutes are mediated via the membrane-bound receptors whereas slower effects are via the classical hormonal receptors. More information is also needed regarding the direct role of adrenocortical hormones in seizure expression in patients with epilepsy.

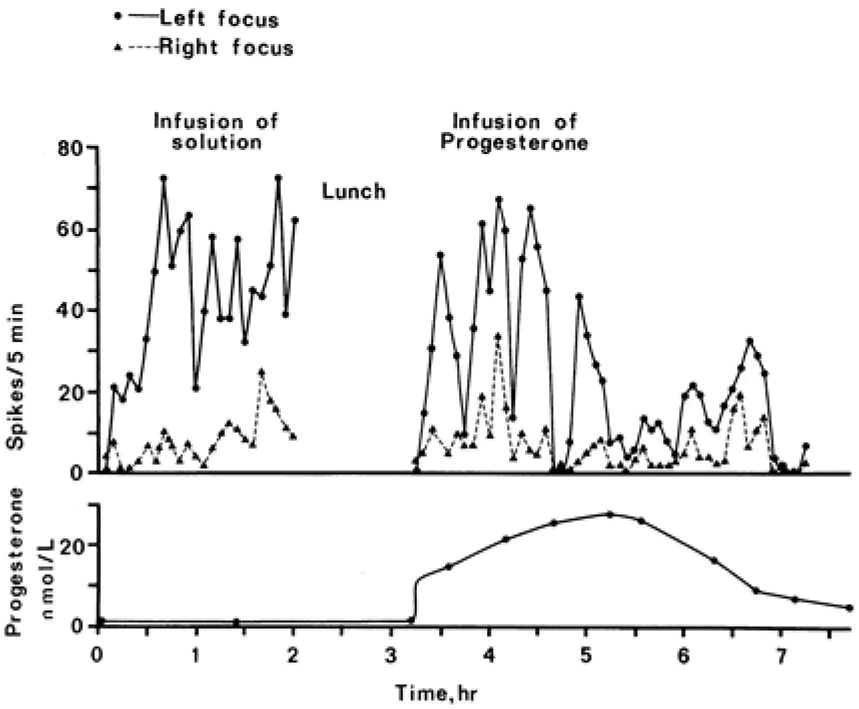

FIGURE 1. The effect of progesterone infusion in a patient with partial epilepsy. A continuous electroencephalogram recording was made to count the epileptic discharges. (Reprinted from Backstrom T, Zetterlund B, Blom S, et al. Effects of continuous progesterone infusion on the epileptic discharge frequency in women with partial epilepsy. *Acta Neurol Scand.* 1984;69:240–248; with permission.)

Sex Hormones

Experimental Data on Excitability

Estradiol decreases the electroshock seizure threshold in rats in a dose-dependent mode.[176] In humans, estrogen activates epileptiform electroencephalogram (EEG) discharges. Increased spike frequency occurred in 11 of 14 women with partial epilepsy given an intravenous (IV) injection of 40 mg of the estrogen Premarin. Generalized tonic–clonic seizures were provoked within 15 minutes in 4 of the patients.[102] An epileptic focus with 3/s spike-and-wave activity can be induced by applying estrogen directly on the cerebral cortex.[111] The convulsive estrogen effect is not consistent, however, and pretreatment with estrogen was neuroprotective against *N*-methyl-D-aspartate (NMDA)–induced seizures in female ovariectomized rats and did not affect any of the seizure parameters measured in the male rats.[82]

In contrast, progesterone in large doses induces anesthesia in humans[116] and animals,[58] increases the electroshock seizure threshold in animals, and protects against metrazol-induced seizures.[158] In oophorectomized cats, progesterone at plasma levels equivalent to those of pregnancy significantly decreased the frequency of interictal spikes from penicillin foci.[95] Progesterone at plasma levels similar to the luteal phase of the menstrual cycle significantly reduced interictal spike frequency in four of seven women with partial epilepsy. The women with low plasma protein binding progesterone showed the best response with the progesterone infusion, whereas women with the highest plasma protein binding did not respond.[15]

Progesterone metabolites that are reduced in the 5 position of the steroid molecule are very potent in their central nervous system (CNS)–depressant action, particularly those steroids with a 3α-hydroxy-5-reduced molecule.[47] The antiepileptic effects of progesterone are mediated by these metabolites.[119,142] In a rat model 3α5α-P is about eight times more potent, on a weight basis, in its anesthetic action than the most potent barbiturate known, methohexital.[129] The 5α derivative of the preceding steroid seems to be somewhat more potent than the 5ß derivative.[129] In oophorectomized cats with a penicillin-induced epileptic focus, 3α5α-P is more potent in inhibiting epileptic activity than clonazepam.[94] 5ß-Pregnenolone also acts as an anesthetic.[35]

In conclusion, estradiol increases brain excitability, whereas progesterone and some of its 5-reduced metabolites have potent inhibitory effects (Fig. 1). Wooley and Timiras[175,176] showed an estrus cycle–dependent variation in electroshock seizure threshold, and other studies have shown an estrus cycle variation and male versus female difference in pentylenetetrazol seizure threshold.[88] Interestingly, cycle-related changes and gender differences are described only for experimental models of epilepsy that use convulsant drugs specific for the GABA_A receptor complex (GRC).[75] In rats, sensitivity at the GRC also varies over the estrus cycle.[48]

Mechanisms Within the Brain

The classic target organ mechanism of steroid hormone action is via binding to an intracellular cytosol receptor, activating the genome for transcription and protein synthesis. Genome effects take at least 5 to 15 minutes, with some effects requiring hours to days.[137] Steroid hormone effects on sexual behavior are probably medicated via this nuclear mechanism of action.[137] Other possible CNS mechanisms of action of steroid hormones and their metabolites are by direct effects on neural membrane-bound receptors. Membrane effects are very rapid, occurring within a fraction of a second.[7,137]

The rapid antiepileptic effect is demonstrated with injections of 3α5α-P into the carotid artery of oophorectomized cats with an epileptic focus; epileptic spikes were instantaneously inhibited when the steroid solution reached the brain.[94] These steroid effects are too rapid to be mediated via genomic activation and protein synthesis and represent direct effects on neural membrane-bound receptors. In electrophysiologic studies, responses to the excitatory amino acids quisqualate and NMDA were augmented by estradiol.[89,155] Chronic treatment with estradiol may also sensitize the quisqualate system.[155]

3α5α-P acts as a receptor agonist at the GABA_A receptor complex in the brain,[52,109,110] similar to the action of benzodiazepines and barbiturates and some of the effects of alcohol. In mice, 3α5α-P inhibits convulsions induced by a number of convulsive substances acting at that GRC such as metrazol, (+)bicuculline, and picrotoxin but has no effect against maximal electroshock- and strychnine-induced seizures.[21] These rapid actions of 3α5α-P are mediated via actions on the GRC-chloride ionophore complex.[52] Progesterone metabolite effects on the GRC might mediate changes in seizure frequency over the luteal phase of the menstrual cycle. Metabolites of the adrenocortical steroid THDOC have similar effects on the $GABA_A$ receptor.[90]

Accumulating evidence suggests that the neuroactive steroids are very similar to benzodiazepines also in their acute side effects and long-term actions. 3α5α-P induces sedation in humans and inhibition of learning when given IV to rats in the Morris water maze.[81,161] Acute tolerance develops already after 90 minutes of 3α5α-P anesthesia.[179] Increased seizure frequency and decreased seizure threshold occur at 3α5α-P withdrawal.[143] At the molecular level, sustained high levels of neuroactive steroids reduce $GABA_A$ receptor responsiveness.[38,177] 3α5α-P effects in hippocampus vary between CA1 and dentate gyrus and change between different phases of the rat estrus cycle, indicating that a large diversity of effects and mechanisms can be expected.[96]

Another possible CNS mechanism of action of steroid hormones is by direct effects on monoamine turnover, metabolism, and receptors. Monoamines contribute to affective status and sexual behavior.[45] Monoamine oxidase (MAO) and catechol-*o*-methyl transferase (COMT) in the rat brain are decreased by estradiol and increased by progesterone.[32,75] In regularly menstruating women, platelet MAO, serotonin binding, and transport activity change during the cycle.[22,173] Platelet MAO is considered the best peripheral reflection of brain MAO activity. In certain discrete regions of the hypothalamus of the diestrus rat, noradrenaline and dopamine turnover correlate with plasma estradiol and progesterone levels.[100,101] Serotonin receptor expression changes in several brain areas during estrogen and estrogen plus progesterone treatments.[25] Estradiol given to oophorectomized rats increases the turnover rate of dopamine in the hypothalamus,[50] whereas progesterone increases serotonin turnover in limbic structures.[92] Estrogen also alters dopamine turnover in the striatum, increasing dopamine receptor sensitivity there.[76] The consequences of these effects on neurotransmission in relation to epilepsy are difficult to interpret.

Peripheral Neurosteroid Production

Estradiol and progesterone changes during the menstrual cycle and pregnancy are well described. Estradiol concentration increases tenfold from menstruation to ovulation. Progesterone increases 20 times from the follicular to the luteal phase. During menstruation, steroid hormones are at their lowest level. Both in humans and rats, 5α-reduced progesterone metabolites such as 5α-pregnane-3,20-dione (5-DHP) and 3α5α-P are produced peripherally and fluctuate in plasma and ovarian tissue in parallel with progesterone. In humans, 5α-DHP and 3α5α-P increase during the luteal phase of the menstrual cycle.[74,77,167] 3α5α-P and 5α-DHP are produced by the corpus luteum.[8,133,139] During pregnancy, 3α5α-P and 5α-DHP increase about ten times and achieve about one third of the plasma concentration of progesterone.[99,105] The concentration in fetal blood is about ten times that in maternal blood.[99] Enzymes necessary for 5-reduction of progesterone are in the CNS.[84] Brain concentrations of 5α-DHP in progesterone-induced anesthesia are much higher than those in plasma, indicating that progesterone is metabolized to 5α-reduced steroids within the brain.[27] During stress and diurnal variation 3α5α-P and THDOC are produced from adrenal cortex with a short delay after glucocorticoids in both animals and humans.[20,43,140]

In plasma, estradiol is largely bound to transport proteins, sex-hormone–binding globulin (SHBG), and albumin, and only a small fraction (1%-3%) is unbound.[157] Progesterone is bound to transcortin and albumin and about 10% is unbound.[10,171] The 5α-reduced progesterone metabolites bind to albumin with low affinity.[171] The unbound fraction exerts the normal effects in peripheral organs.

Steroid Distribution and Metabolism in the Central Nervous System

Estradiol[114,135,136] and progesterone[5,28] accumulate in specific brain regions in both rats and rhesus monkeys. The classic hormone-specific intracellular receptors have been identified in these regions[104,137] and fulfill all the criteria for classic steroid target organs.[114] The distribution of the estrogen alpha-receptor is different from that of the estrogen beta-receptor.[131] The estradiol concentrations vary with the phase of the menstrual cycle in humans and the estrus phase in female rats.[28,29] In addition, the progesterone CNS concentrations vary with ovarian steroid production. In rats the progesterone concentration in cerebral cortex is about 300 times higher during times of high ovarian progesterone production than during times of low ovarian production, whereas in hypothalamus the increase is 8 times and in plasma it is 12 times.[28] In humans the progesterone and 3α5α-P concentrations are also related to ovarian production and vary among CNS areas.[26] There is a significant correlation between the plasma and cortex, striatum, and cerebellum concentrations of progesterone, but not between the hypothalamus and plasma concentrations.[28,180] This raises the possibility that there are different mechanisms for progesterone accumulation depending on CNS area in the rat. In rhesus monkeys 60% of the luteal ovarian progesterone production is taken up by the brain.[24]

The synthesis and metabolism of progesterone in rat brain have been studied in vivo and in vitro. Progesterone is metabolized to 5α-DHP and further to 3α5α-P. This is the substance active on the $GABA_A$ receptor. The 3α5α-P is further 20α-reduced, and this diminishes the action on the $GABA_A$ receptor (for reviews see refs. 84 and 115). In the primate hypothalamus, progesterone is metabolized to 3α5α-P and 20α-hydroxypregnane-4-one-3-one.[23] The enzyme 5α-reductase is required for the synthesis of the progesterone metabolite 3α5α-P, and it is found in several areas of the mouse brain[152] and in the human fetal brain.[153] Neurosteriodogenesis seems to be important in the developing brain, and disorders of the developing brain are related to disturbed neurosteroid synthesis. This is perhaps not surprising, given that neurosteroid concentrations in fetal blood are very high.[55,72,99] Other steroids with $GABA_A$-receptor antagonist properties, such as pregnenolone sulfate, are also produced in the brain.[109]

Androgens are metabolized to estrogen in the brain of many species, including rats, monkeys, and humans. The aromatization takes place in the hypothalamus and limbic system and is more active in males than in females (for reviews see refs. 108 and 126). Major metabolic routes for estradiol in the brain involve 2- and 4-hydroxylation, forming the catechol estrogen. This metabolism is most active in the pituitary and hypothalamus in female rats (for reviews see refs. 18 and 126).

Central Nervous System Effects of Synthetic Steroids

Synthetic progesterone steroids, such as those contained in contraceptives, may not have the same effects as endogenous progesterone but they are all metabolized in the same way to 3α5α-steroids and are thus potentially active on the $GABA_A$ receptor. 3α5α-P is 20 times more potent than progesterone in reducing epileptic discharges from a cortical focus,[94] but medroxyprogesterone, a synthetic progesterone, is only one half as potent as progesterone in times of CNS inhibition, and levonorgestrel exerts no inhibitory effect.[117] That may be one reason that contraceptives do not significantly alter seizure frequency.

Estradiol, ethinylestradiol, and norethisterone have an excitatory effect on the CNS.[117,155]

Clinical Changes Across Reproductive Life

Puberty

At puberty there is a rapid and significant increase in pituitary gonadotropins, and gonadal steroids appear both in boys and girls. The female cyclical pattern of hypothalamic–pituitary–gonadal hormone release is established 2 years after menarche. In boys the hormonal production is steadier, and increases until the end of the teens. This period of hormonal change may coincide with seizure onset and influence existing epilepsy. A tendency for epilepsy to begin with puberty was first reported by Gowers[54] in 1893 and later by Turner in 1907[166] as well as by other authors.[103,181] Lennox and Lennox[98] found a relationship between first seizure and menarche in 25% of 387 women with epilepsy onset between the ages of 8 and 20 years. In a smaller group of 47 patients whose first seizure occurred during puberty (between 11 and 15 years of age), 60% had their first seizure within 6 months of menarche, 23% within 1 year, and 17% within 2 years. In this study age at menarche was not different from that of the general population (12.8 years). Another study found an association between delayed adolescence and late-onset epilepsy.[147] Other studies find that generalized tonic–clonic and partial seizures with and without generalization may occur at puberty.[63,91] Idiopathic generalized epilepsies and juvenile myoclonic epilepsy are common forms with adolescent onset.[172] However, some types of epilepsy, such as benign epilepsy with rolandic spikes, improve at puberty and may even disappear.[31,121] Adult women with catamenial seizures may be more likely to have experienced epilepsy onset during puberty.[102]

Increased seizure frequency, seizure recurrence, a change in seizure type, and even an improvement in seizure control may occur during puberty in girls.[40,51,91,103] Of 113 girls whose epilepsy began at an average age of 5 years, two thirds showed a change in their epilepsy at puberty.[40] In studies by Rosciszewska et al.,[151] two thirds of the girls had increased seizure frequency or a new type occurred; in one third the seizure frequency decreased or seizures remitted. Epilepsy was more likely to worsen in girls with generalized tonic–clonic seizures. In contrast, absence seizures rarely increased and sometimes disappeared, and there was no increase in complex partial seizures. Exacerbation of epilepsy was more likely to occur in girls whose seizure onset was at a younger age, who had a known etiology, neurologic or psychological abnormalities, EEG abnormalities, and a late menarche.[151] One retrospective study showed that changes in seizures during puberty were not related to antiepileptic drug (AED) treatment,[40] although another study found that increased severity of epilepsy was associated with suboptimal AED levels.[128] In many cases, however, a return to peripubertal seizure frequency has been observed later in life.[146]

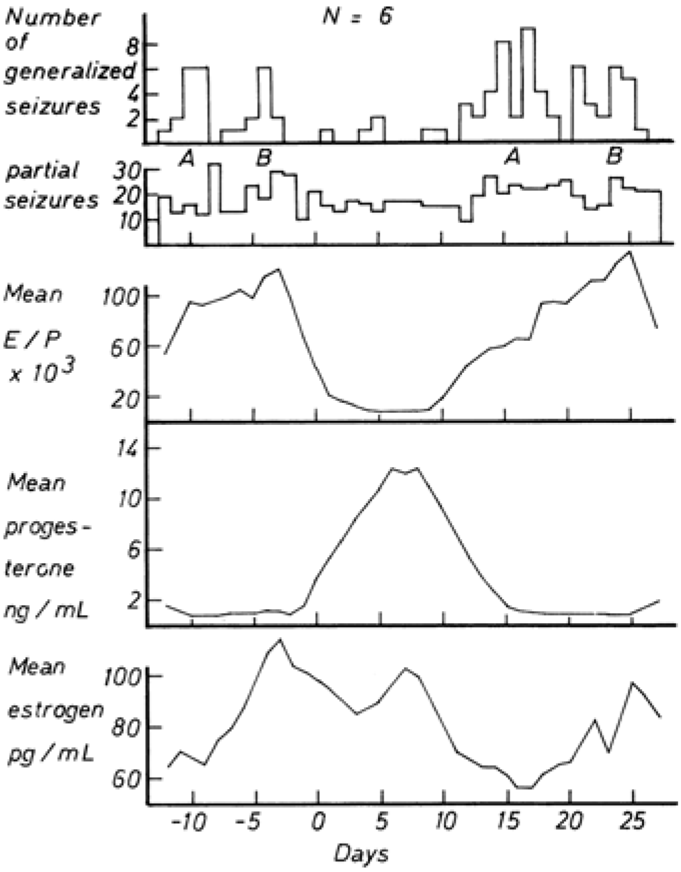

FIGURE 2. Seizure number and hormone concentrations in six women with partial epilepsy. The data are centered around the day of ovulation (day 0). A, peak of seizures during menstruation; B, peak of seizures during the preovulatory estrogen peak; E, estradiol; P, progesterone. Notice the low seizure frequency during the luteal phase. (Reprinted from Backstrom T. Epileptic seizures in women in relation to variations of plasma estrogen and progesterone during the menstrual cycle. *Acta Neurol Scand.* 1976;54:321–347; with permission.)

Menstrual Cycle Linkages

Several clinical studies show that seizure frequency changes at different phases in the menstrual cycle in a subset of women with partial epilepsy.[6,41,64,93,112,149] Discrepancies in the literature regarding the frequency of catamenial seizures may be due to the varied methodologies used to evaluate this relationship, such as using different methods for counting days of the menstrual cycle, lack of hormonal measurements to confirm cycle status, and not defining epilepsy type and severity.[127] The older literature reports large observational studies made at a time when the antiepileptic treatments were not as advanced as they are now, and perhaps it better shows the natural course. Laidlaw[93] found an increase in seizure frequency during menstruation. Almquist[3] found almost no evidence of any such relationship, whereas others describe catamenial seizures in 10% to 72% of women with epilepsy.[41,93] In a prospective study, Rosciszewska observed 69 women for 4 years and found that 63% experienced an increase in seizure frequency 2 days before or during the first day of menstruation. The distribution of 6,900 seizures during 1,237 menstrual cycles is shown in FIGURE 2.[149] In a few women, seizures occurred only during the days immediately preceding menstruation or during menstrual flow. Of 226 female epileptic patients, seizures occurred with menstruation exclusively in only 4 cases.[147]

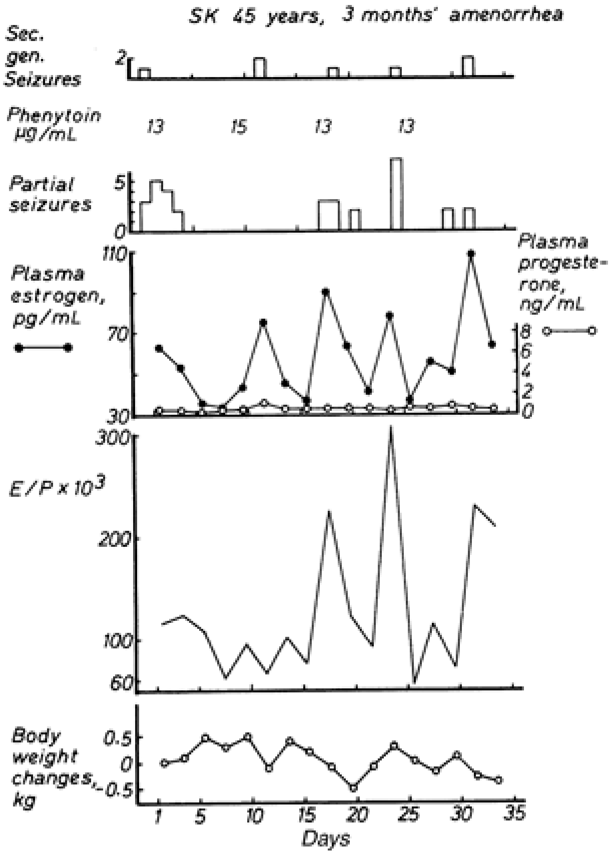

FIGURE 3. Seizure frequency in a patient with estradiol (E) peaks but with a low and constant progesterone (P) concentration. Notice the close connection between estradiol peaks and seizures. Sec. gen., secondary generalized. (Reprinted from Backstrom T. Epileptic seizures in women in relation to variations of plasma estrogen and progesterone during the menstrual cycle. *Acta Neurol Scand.* 1976;54:321–347; with permission.)

Herzog et al. identified three types of menstrual cycle–linked increase in seizure frequency in prospective seizure recordings in 184 women with intractable complex partial seizures.[71] In 87 women who recorded seizures and menses during three cycles, the average daily seizure frequency was significantly greater during the perimenstrual and preovulatory phases. Overall, 39.1% of the women showed catamenial epilepsy.[70] In ovulatory cycles, the most common pattern was an increase during menstruation shortly after the rapid decrease of progesterone and 3α5α-P from the corpus luteum. A second peak in seizure frequency occurred during ovulation when estradiol secretion is high but 3α5α-P is low. These data fit nicely to those from

a smaller prospective study of women with partial seizures, in which a relationship between seizure and hormonal variations during the menstrual cycle was noted (Fig. 3). The total number of generalized seizures increased at two time periods. The first occurred shortly after the rapid decrease of progesterone in the first several days of menstrual flow. The second seizure peak occurred during the preovulatory estrogen surge. During high-progesterone phases of the cycle, the number of generalized seizures was very low.[6] In a study by Rosciszewska, repeated EEG recordings during the menstrual cycle were evaluated in 41 women with mainly tonic–clonic seizures. A significant increase in paroxysmal discharges occurred on premenstrual days in 24 patients who had catamenial exacerbation of seizures. In 17 women without catamenial seizure patterns, the highest frequency of paroxysmal discharges was found on days close to ovulation. In both groups the discharges were least frequent on days 6 to 22 of the menstrual cycle.[56] Others have also noted changes in EEG with menstrual cycle.[73]

In patients with anovulatory cycles, estrogen peaks were associated with increased seizure frequency,[6] consistent with estrogen's activating effect. In Herzog et al.'s study, 1,523 seizures were recorded during 86 anovulatory cycles. The cycles were divided into four phases, and results showed a lower seizure frequency during the phase when low estradiol levels are expected compared to phases when higher estradiol levels are expected.[71] In a prospective study with daily recording of seizures in 87 patients, 39.1% of the women had catamenial epilepsy.[70] Results supporting an excitatory effect by estrogen also in humans were found by Logothetis et al.,[102] who provoked seizures with estrogen injections in women with epilepsy.

Decreased frequency of generalized seizures during the luteal phase of the menstrual cycle is most probably due to the CNS effects of progesterone metabolites, such as 3α5α-P, that reduce seizure susceptibility by enhancing $GABA_A$-receptor function and thereby inhibit neuronal excitability.[142] Increased seizures during menstruation could be caused by a rebound effect after a rapid decrease in progesterone or other antiepileptic factors premenstrually, similar to the seizure exacerbations that may occur when antiepileptic drugs are discontinued abruptly.[120] Although one study found that a premenstrual decrease in phenytoin concentrations coincided with an increase in seizure frequency,[150] changes in AED pharmacokinetics cannot explain menstruation-associated seizure cycles.[11] Further indications that the antiepileptic factor is progesterone or its metabolites comes from open studies to be discussed later.

Different types of epilepsy show different cyclical patterns of seizures. In the studies discussed earlier, the patients had partial and secondary generalized seizures. With absence seizures, patients seem to have a different pattern of seizure distribution during the menstrual cycle. Repeated 24-hour EEG recordings and hormonal analysis over one menstrual cycle in patients with absence epilepsy showed that highest seizure frequency occurred during the luteal phase when progesterone and 3α5α-P are high, with a peak during the last five premenstrual days. Seizure frequency decreased rapidly after onset of menstrual bleeding.[9] Similarly, primary generalized tonic–clonic seizures are also more frequent during the premenstrual period than in the rest of the cycle.[149] This seizure pattern is very similar to the menstrual cycle–associated pattern of mood changes in patients with premenstrual dysphoric disorder (PMDD) and premenstrual syndrome (PMS).[12] Progesterone given to women has been shown to exacerbate absence seizures.[57] In animal models of absence seizures both ganaxolone and 3α5α-P exacerbate the seizures.[19,156] Furthermore, in a genetic model of absence epilepsy 3α5α-P increases spike-wave discharges.[34]

Premenstrual syndrome coexisted in 84% of women with catamenial seizures but in only 22% of women with no catamenial exacerbation.[149] Therefore menstruation-associated seizure cycles may be associated with PMS. Progesterone and medroxyprogesterone given to postmenopausal women induces symptoms similar to those in PMDD and PMS. The symptom severity shows an inverted U-shaped relation to the progesterone dose and 3α5α-P concentration in serum.[4,30] All these data indicate that in certain conditions and under certain situations, neuroactive steroids like 3α5α-P acting on the $GABA_A$ receptor are seizure inducing and anxiogenic.[130] Psychological symptoms in patients with PMDD are effectively treated by inhibiting ovulation with a gonadotropin-releasing hormone (GnRH) agonist[60] or with selective serotonin-reuptake inhibitor (SSRI) preparations also in a sequential way only during the luteal phase.[42]

Menopause

Changes in the neuroendocrine system during menopause may influence epilepsy. Early observations suggested that menopause had no influence on epilepsy,[159,166] but other studies report an exacerbation in seizure frequency,[123] seizure recurrence,[51] or first seizures occurring with menopause.[33,147] An improvement after menopause was observed by Zara et al.[178] They reported that 27 of 29 patients experienced a decrease in seizure frequency. In another study of 41 women with epilepsy, 12 improved and 8 experienced an exacerbation.[148] Improvement was more likely if the seizures had started late in life, if they were well controlled, when the age of menopause did not deviate from that in the general population, and when the climacteric symptoms were mild or absent.[61,148]

Little is known about the effects of postmenopausal hormone therapy (HT). Logothetis et al.[102] reported seizure recurrence in a postmenopausal woman who was treated with unopposed estrogens. Seizures improved after the introduction of combined estrogen–progestagen treatment. Harden et al. reported that increase in seizure frequency is associated with estrogen-containing hormone therapy in postmenopausal women with epilepsy.[62]

Hormones and Epilepsy in Men

Androgens raise the seizure threshold in some experimental models of epilepsy.[163,170] Some testosterone 3α-hydroxy-5α/β-reduced metabolites are rather potent $GABA_A$-receptor agonists.[83] The production of the precursors and the 3α5α androgens occurs in the testis, but peripheral and CNS metabolism from testosterone is substantial.[115] The secretion of testosterone and thus also that of the metabolites from testis vary with season, age, and physical activity and decrease substantially on stress.[17,36,44] This indicates that also in men, variation in hormone concentrations can change seizure thresholds. Especially rapid withdrawal of the androgen metabolites, such as after acute stress, might provoke seizures, and this can interact with the effects of adrenal hormones (see earlier discussion).

Men with epilepsy may have low levels of free testosterone despite high concentrations of total testosterone[79,163] because of AED-induced increased concentrations of sex hormone–binding globulin (SHBG).[13,157] In men not treated with AEDs, testosterone concentration is similar to that in normal controls.[71] There are only a few studies that describe a relationship between testosterone therapy and course of epilepsy. In most investigations testosterone was given because of decreased libido.[71,163] Badalian et al.[16] reported that testosterone reduced seizure frequency by 50% to 70% in 8 of 15 men and improved the EEG. However, Herzog[66] found no significant effect in 12 male epileptic patients treated with intramuscular injections of testosterone enanthate, 200 to 400 mg every 3 to 4 weeks, although serum-free testosterone levels were normalized. From a clinical point of view there are some differences in epilepsy in female and male patients. Hormones play a more significant role in epilepsy in women. In men there is no obvious cyclical exacerbation in seizure frequency connected with hormone fluctuation. There are also suggestions that gender-related differences in drug responses, including anticonvulsants, may be due to hormones.[69,162]

Future Issues

Neurosteroids in Epilepsy Treatment

Natural and synthetic progesterone have been used to treat seizures, although so far only in open studies.[39,59,65,181] Mattson et al.[113] described a beneficial effect of medroxyprogesterone (Depo-Provera) as adjunctive therapy to AEDs in 7 of 11 women with epilepsy. The treatment was most effective in patients who became amenorrheic. We have also found that Depo-Provera treatment for patients with catamenial partial epilepsy has a beneficial effect on seizure frequency (Bäckström, unpublished data). In our experience, seizure frequency is less likely to be reduced in patients with persistent fluctuations in estrogen levels than in those with amenorrhea. Depo-Provera inhibits ovulation, and in higher doses it inhibits estradiol production. Depo-Provera has an additional benefit of acting as a contraceptive. This treatment may not be effective for patients with absence epilepsy. The usual dose of intramuscular medroxyprogesterone is 150 mg at intervals of 1 to 2 months to induce amenorrhea. The clearance of the medication is long, up to 1/2 to 1 year after last injection. Common side effects are increased appetite, weight gain, and irregular menstrual bleeding. A lifelong treatment can reduce mineralization in bone. Medroxyprogesterone is weaker, however, in its CNS action than progesterone (see earlier discussion). Oral medroxyprogesterone or norethisterone exerted no antiepileptic effects in open studies.[39,68]

Natural progesterone supplied in suppository form also had a beneficial effect in 6 of 8 women with complex partial seizures and an inadequate luteal phase.[65] Average monthly seizure frequency decreased 68%. In 23 of 34 epileptic women treated with synthetic progesterone, a decrease was noted both in tonic–clonic seizure frequency (an average of 62%) and in complex partial seizures (an average of 70%). In 8 women there was no improvement, and in 3 women seizure frequency increased during the time period examined (average 14 months).[46] In an open study with progesterone, 18 of 25 women (72%) experienced a decline in seizure frequency during a 3-month treatment period compared with the 3 months prior to therapy.[67] After a 3-year treatment period with cyclic natural progesterone, 200 mg three times daily, in 15 of 25 patients complex partial seizures decreased by 62% and secondary generalized seizures by an average of 74% compared to baseline.[68] The effect of intravenous progesterone infusion on epileptic discharge spike frequency was studied in 7 women with partial epilepsy. A significant decrease in spike frequency was shown in 4 of them, an effect related to the concentration of plasma progesterone.[15] None of the preceding studies was randomized and placebo controlled, so it is difficult to confirm the clinical value of such treatments.

Because of their enhanced potency, 3α5α-P metabolites of progesterone may be more suitable for use as antiepileptic therapy. One 3α5α-P metabolite (in the form of the anesthetic Althesin) has been used to successfully treat drug-resistant status epilepticus.[124] Eight of 11 patients with status epilepticus resistant to barbiturates and benzodiazepines were successfully treated with 3α5α-P derivative.[124] The 3α5α-P derivative also decreased intracranial pressure[165] and reduced oxygen consumption in the gray matter by 40%.[138]

In addition, one controlled study used the more potent orally active 3α5α-P–like substance ganaxolone and showed that this might be a new way of treating epilepsy.[37] Fifty-two eligible patients were randomized to receive ganaxolone (24 patients) or placebo (28 patients) for up to 8 days in a double-blind presurgical trial design. Ganaxolone monotherapy was well tolerated, and the results provided preliminary evidence that ganaxolone does have antiepileptic activity.[97] Ganaxolone has also been used to treat intractable infantile spasms in a multicenter, open-label, add-on trial with beneficial results.[85]

There are concerns, however, related to long-term use of progesterone/3α5α-P treatments. The neuroactive steroids act as agonists to the $GABA_A$ receptor, and accumulating evidence indicates that they have similar short-term and long-term side effects to all other $GABA_A$-receptor agonists. Patients develop tolerance and withdrawal symptoms.[143,179] The $GABA_A$-agonistic neurosteroids impair memory function and learning,[81] and long-term treatment with medroxyprogesterone in postmenopausal hormone treatment increases the frequency of dementia, mainly of Alzheimer type, compared to placebo.[154] In addition, several women experienced negative mood during treatment with progesterone, and the severity was related to the plasma concentration of 3α5α-P.[4]

This suggests that the neurosteroids might not be as useful in epilepsy treatment as has been hoped. Instead, antagonists to the agonistic neurosteroids may be useful to inhibit the tolerance and withdrawal that occur after cessation of endogenous 3α5α-P production. During the luteal phase or during a longer

period of stress, endogenous 3α5α-P is produced in such high amounts that a rebound occurs at withdrawal. If the effect causing the rebound at withdrawal could be blocked with an antagonist, such a substance may be used as a therapeutic agent. Such antagonists exist and are used in animal experiments to block negative effects of 3α5α-P.[14,106,164,168]

Summmary and Conclusions

Many studies using experimental models of epilepsy have shown that steroid hormones have strong effects on CNS excitability. In light of current knowledge, it seems that gonadal steroid hormones play a significant role in seizure expression. Given the endocrine influences on epilepsy in women throughout the lifetime, it is surprising that there are so few randomized, controlled studies concerning the use of agonistic neurosteroids in epilepsy treatment. These are urgently needed, as are controlled studies concerning hormone replacement therapy in postmenopausal women and hormonal treatment of epilepsy.

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Chapter 196

Disorders of Reproduction and Fertility

Andrew G. Herzog

Introduction

Reproductive dysfunction is unusually common among women and men who have epilepsy.[27,47,48] It generally manifests as menstrual disorders, hirsutism, and infertility in women[48] and diminished libido, impotence, and infertility in men.[47] Reproductive dysfunction is often associated with and may be the consequence of abnormal reproductive endocrine function.[28,47,48] Both epilepsy and antiepileptic drug (AED) use have been causally implicated.[28,38,47,48,50] Epilepsy and antiepileptic drugs can target a number of substrates to impact hormone levels. These include the limbic system, hypothalamus, pituitary, peripheral endocrine glands, liver, and adipose tissue.[33,43] Reproductive endocrine disorders, in turn, can lead not only to reproductive dysfunction, but also to exacerbation of epilepsy.[33,43] An understanding of these relationships and mechanisms is important to the comprehensive management of women and men with epilepsy.

Prevalence

Hospital-based[34,48] and community-based[91] studies have shown that menstrual disorders are more common among women with epilepsy than in the general population. Menstrual disorders can be categorized as amenorrhea (no menses for 6 months), oligomenorrhea (cycle intervals >32 days), polymenorrhea (cycle intervals <26 days), abnormal variation in cycle intervals (>4 days), and menometrorrhagia (heavy menses and bleeding between menses[40]). Cycle intervals between 26 and 32 days, rather than the currently popular broader range of 21 to 35 days, should be considered normal in women with epilepsy because ovulatory rates drop substantially and statistically significantly outside of the 26- to 32-day range, specifically from 75% to <50%.[40] Ovulation is considered to be an important criterion in this population because anovulatory cycles are associated with greater seizure frequency.[2,42,61] Menstrual disorders, using the foregoing definition, are estimated to occur in one third of women with epilepsy as compared with 12% to 14% of women in the general population.[34,40,46] More than one third of cycles in women with localization-related epilepsy (LRE) are anovulatory, as compared to 8% to 10% in controls.[12,40,63] There is conflicting evidence as to whether anovulatory cycles are more common with LRE or primary generalized epilepsy (PGE).[12,63] Reproductive dysfunction may be the result of reproductive endocrine disorders, especially those that are overrepresented in women with epilepsy.[12,34,46,48,63] These include polycystic ovarian syndrome, hypothalamic amenorrhea, functional hyperprolactinemia, and premature menopause.[6,27,34,48,56] Women with idiopathic epilepsy are only 37% as likely as unaffected female siblings to become pregnant.[86] This finding is not attributable to marital rate or to seizure type, age at onset, or family history of epilepsy.[86] In comparison to the general female population, fertility is reduced to 69% to 85% of the expected number of offspring among married women with epilepsy, primarily temporal lobe epilepsy (TLE).[14,98] One third of women with epilepsy have sexual dysfunction as determined by standardized questionnaire.[35] They may have sexual anxiety as well as deficits in arousal.[64] Sexual dysfunction is more common with right-sided rather than left-sided TLE[13,35] and is associated with lower serum testosterone levels.[35]

Sexual dysfunction (diminished sexual interest and/or potency) occurs in about 20% of men with epilepsy as determined by standardized questionnaire.[38] Older studies, using mostly structured or unstructured interviews, found higher frequencies ranging from 38% to 71%.[33] Abnormal semen analysis, including decreased sperm count, abnormal morphology, and impaired motility, has been reported in >90% of men with epilepsy.[8,34,53,92] Semen volume is reduced by 25% and sperm count by 67%.[95] Sperm morphologic abnormalities occur in 47%.[92] Although AED use is an important factor and differential AED effects on both sexual function[38] and semen characteristics[54] have been convincingly demonstrated, there is also considerable evidence to suggest that sexual dysfunction, reproductive endocrine disorders, and abnormal semen analysis are also common among untreated men with epilepsy.[38,92] Men with idiopathic epilepsy are only 36% as likely as male unaffected siblings to ever father a pregnancy.[86] This reduction is associated with LRE, onset of seizures before 20 years of age, and absence of a family history of epilepsy.[86] The effect is mitigated by reduced marital rates. Among married men with epilepsy, reproductive disadvantage was confined to those with onset before 10 years of age.[86]

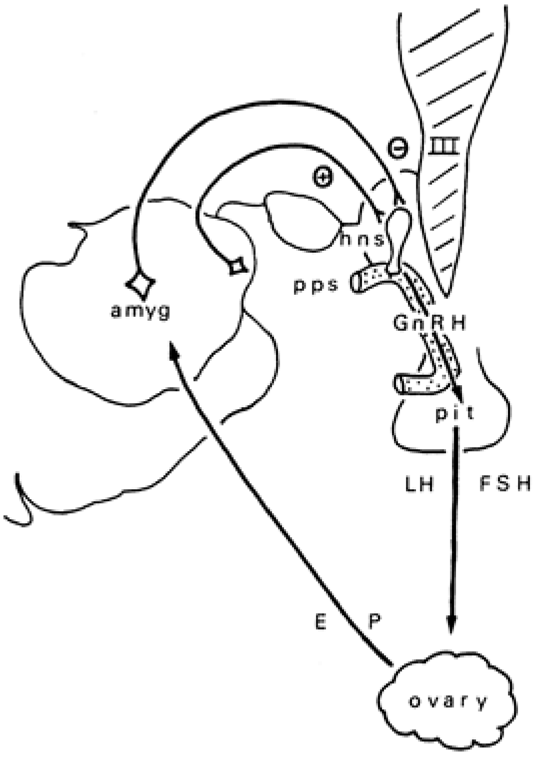

FIGURE 1. A cross section of the anterior temporal lobe and diencephalon. Shown are direct projections from the two anatomically distinct functional divisions of the amygdala (amyg) to the same arcuate hypothalamic neurons. The different influences of these projections on hypothalamic neurosecretory cells (hns) modulate pulsatile gonadotropin-releasing hormone (GnRH) secretion. Releasing hormones enter the pituitary portal system (pps) and regulate the pattern of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) secretion by the pituitary (pit). These gonadotropins induce ovulation and stimulate estradiol (E) and progesterone (P) production. Gonadal steroids, in turn, bind to specific amygdaloid hormone receptors and modulate γ-aminobutyric acid (GABA) and glutamate receptor–mediated conductance at the cell surface to influence neural activity, including epileptiform discharges.

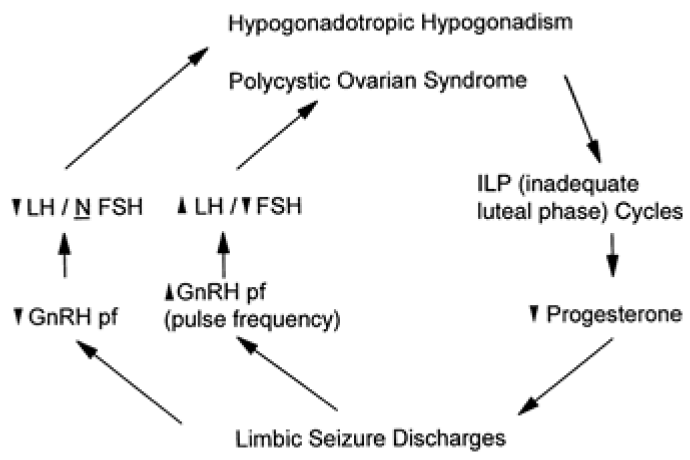
Hypogonadotropic Hypogonadism
Polycystic Ovarian Syndrome
▼LH / N FSH
▲LH / ▼FSH
ILP (inadequate luteal phase) Cycles
▼GnRH pf
▲GnRH pf (pulse frequency)
▼Progesterone
Limbic Seizure Discharges

FIGURE 2. Possible mechanisms by which limbic seizure discharges may promote reproductive endocrine disorders and how abnormal reproductive hormone levels may influence epilepsy. This is based on the hypothesis proposed by Herzog et al.[28,34,48] that involvement of limbic structures with epileptiform discharges may disrupt normal limbic modulatory influences on hypothalamic gonadotropin-releasing hormone (GnRH) secretion. Altered frequency or amplitude of GnRH may lead to patterns of pituitary luteinizing hormone (LH) and follicle-stimulating hormone (FSH) secretion that are found in hypogonadotropic hypogonadism (hypothalamic amenorrhea) and polycystic ovarian syndrome. Reproductive endocrine disorders that are associated with partial seizures of temporal lobe origin are characterized by anovulatory cycles and diminished progesterone secretion. An elevated serum estrogen/progesterone ratio may promote the development of seizure discharges in the brain.

Mechanisms in Women

Reproductive dysfunction is often associated with and may be the consequence of abnormal reproductive endocrine function.[28,34,48] This, in turn, may result from altered neuroendocrine regulation due to epilepsy itself.[7,34,48] Epilepsy may alter the hypothalamopituitary regulation of gonadotropin secretion (Figs. 1 and 2) or may have direct neurally mediated dystrophic effects on the ovaries, mediated by the autonomic nervous system.[25] The neurotrophic effects have been a much-neglected investigational topic but may warrant attention in an era in which vagal nerve stimulators are in common use. AEDs may alter peripheral steroid and binding protein synthesis as well as hormonal metabolism[53,62] and may produce direct gonadal toxicity.[78,94]

The most common reproductive endocrine disorder in women in general and in the epilepsy population in particular is polycystic ovarian syndrome (PCOS).[6,46,48] Its overrepresentation in women with epilepsy[6,27,34,46,48,56] (10%–20% in women with epilepsy vs. 5%–6% in general population studies) may be of considerable significance because in the general population, PCOS is associated with a higher prevalence of

migraine, emotional disorders, diabetes, cardiovascular disease, and female cancers.[46] Hypothalamic amenorrhea, functional hyperprolactinemia, and premature menopause have also been found to be overrepresented.[6,27,34,46,48,56] In an investigation of 50 consecutive women with clinical and electroencephalographic features of TLE, 28 (56%) had amenorrhea, oligomenorrhea, or abnormally long or short menstrual cycle intervals.[48] Nineteen of the 28 women with epilepsy and menstrual disorders (68%, 38% overall) had readily identifiable reproductive endocrine disorders: PCOS in 10, hypothalamic amenorrhea in 6 (12%), premature menopause in 2 (4%), and functional hyperprolactinemia in 1 (2%). The numbers of women with clinical and endocrine features of PCOS (20%) and of hypogonadotropic hypogonadism (HH) (12%) were significantly greater than the estimated frequencies (5% for PCOS and 1.5% for HH) in the general female population. The data showed no significant relationship overall between the occurrence of menstrual disorders and the use of AEDs (53% among users vs. 60% among nonusers). Moreover, PCOS was more common among the untreated (30%) than the treated (13%) women with epilepsy, although since then, a notable relationship between the use of valproate, not yet in common use at the time of the investigation, and PCOS[51] has been demonstrated.

PCOS is unlikely to represent a single nosologic entity but rather the failure of the ovarian follicle to complete normal maturation during the menstrual cycle or a series of cycles.[46] PCOS may represent a common endpoint for a number of pathophysiologic conditions, some of which may be attributable to epilepsy itself[6,34,48] or AED use.[50,63] The partially developed follicle is secretory but is deficient in aromatase, the enzyme that converts testosterone to estrogen, and, having failed to release its ovum, is retained in the ovary in the form of a cyst.[46] (The persistent occurrence of such cycles results in hyperandrogenic chronic anovulation, which is currently the simplest and perhaps the most utilitarian definition of PCOS.[46,59])

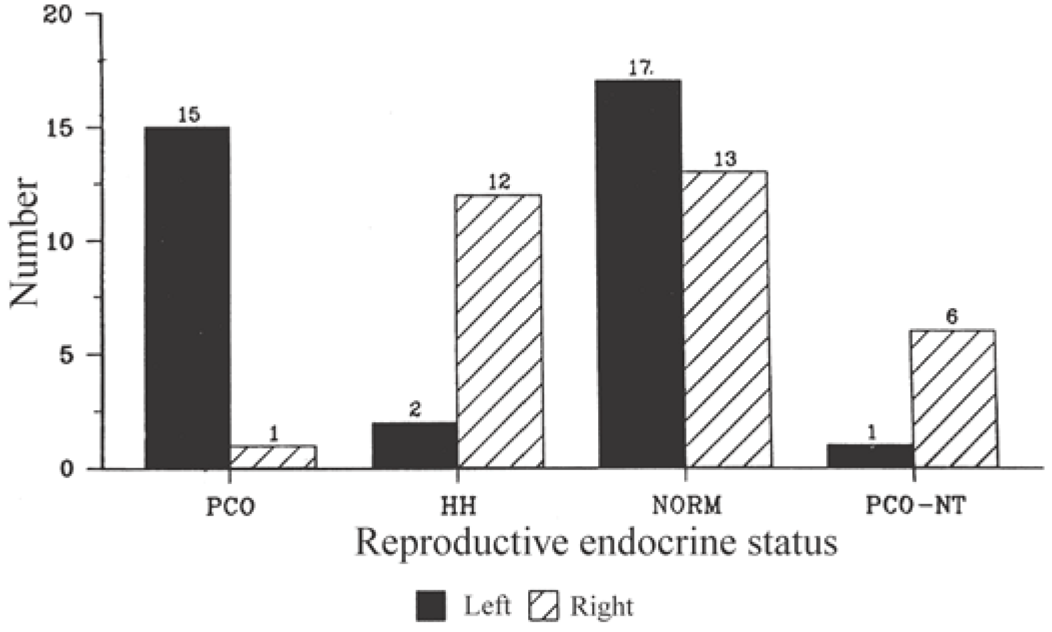

FIGURE 3. Laterality of epileptiform discharges in epileptic women with unilateral temporal lobe electroencephalogram (EEG) foci and polycystic ovarian syndrome (PCO), hypogonadotropic hypogonadism (HH), or normal reproductive endocrine function (NORM) as well as in those with unilateral non–temporal-lobe foci and polycystic ovarian syndrome (PCO-NT). PCO vs. HH: mean = 16.1, *df* = 1; *p* <.001. PCO vs. NORM: mean = 5.1, *df* = 1; *p* <.05. HH vs. NORM: mean = 5.4, *df* = 1; *p* <.02. PCO vs. PCO-NT; *p* <.001, Fisher's exact test.

There are findings that implicate epilepsy itself in the pathogenesis of PCOS. Herzog et al.[29,34,46,48] reported an association between particular reproductive endocrine disorders and the laterality of unilateral temporolimbic epilepsy. Specifically, left laterality has been associated with PCOS, whereas right laterality has been associated with hypothalamic amenorrhea. Nontemporal foci may have different laterality relationships (Fig. 3).[29] Herzog et al.[34] also evaluated reproductive endocrine function in women with unilateral temporolimbic epilepsy and normal controls to assess the effects of epilepsy, epilepsy laterality, and AED use on the cerebral regulation of hormonal secretion. The findings indicate that reproductive endocrine function differs between women with epilepsy and normal controls. Significant differences exist at all levels of the reproductive neuroendocrine axis, that is, hypothalamus, pituitary, and peripheral gland. Differences show significant relationships to epilepsy itself as well as to medication use. Sex hormone changes occur in a stochastic manner such that the laterality of unilateral temporolimbic discharges is associated with predictable directional changes in hormonal secretion at all levels of the reproductive neuroendocrine axis. These directional changes are consistent with the finding that different reproductive disorders may develop in relation to left- and right-sided temporolimbic epilepsy. Some hormonal changes can show close temporal relationship to the occurrence of interictal epileptiform discharges, and these vary in relation to the laterality of the discharges. Antiepileptic drugs differ in their effects on reproductive hormone levels. There are notable

differences between enzyme-inducing and noninducing drugs, with the former being associated with lower serum levels of some ovarian and adrenal steroids, such as estradiol, testosterone, and dehydroepiandrosterone sulfate. Menstrual disorders are more common among women with interictal discharges as well as among women with abnormal hormonal findings.

The role of AEDs in the development of reproductive endocrine disorders was first demonstrated in 1993 by Isojarvi et al.,[50] who found a strikingly high occurrence (>60%) of polycystic ovaries and/or hyperandrogenism in women with epilepsy who used valproate (VPA) alone or in combination. The frequency was significantly greater than among women with epilepsy who took carbamazepine (CBZ) alone (33%) or other drugs (14%) and was particularly high among women who started treatment before 20 years of age. Among 23 women who took VPA and had ultrasound and endocrine investigations, 4 (17%) had hyperandrogenism (i.e., elevated serum testosterone levels), with 3 (13%) of these having the combination of hyperandrogenism and menstrual disorder suggestive of PCOS. Murialdo et al.[68] demonstrated combined hyperandrogenism and ovulatory dysfunction in 15, that is, 15%, of 101 consecutive patients with epilepsy, with similar frequencies of menstrual disorders and polycystic ovaries in women with primary generalized epilepsy and LRE. In a comparison of 65 women who had epilepsy, 21 taking VPA monotherapy, and 20 normal controls, Murialdo et al.[67] found that VPA use was associated with substantially and statistically significantly higher body mass index and androgen levels and more anovulatory cycles than with CBZ or phenobarbital use or in normal controls. The role of VPA use was further highlighted in a study by Betts et al.[5] They compared serum hormone levels and ovarian magnetic resonance imaging among 54 women with epilepsy who had only ever taken VPA and for at least 1 year, 51 who had only ever taken either lamotrigine (LTG) or CBZ, and 50 normal controls. Women with epilepsy in general were significantly more likely to exhibit evidence of polycystic ovaries. Women taking VPA were significantly more likely to have hyperandrogenemia than women taking LTG or CBZ or normal controls. Further support for an important role for VPA comes from an investigation by Isojarvi et al.[52]) in which switching AEDs from VPA to LTG in women with epilepsy was associated with statistically significant reductions in weight, androgen levels, and number of ovarian cysts by the end of 2 months.

Although the relative importance of epilepsy versus AEDs, especially VPA, remains a topic of controversy with regard to the relationship between PCOS and epilepsy, the notion that VPA alone may not be entirely responsible draws support from a well-controlled investigation of primates. Ferin et al.[20] treated monkeys for 12 to 15 months with VPA monotherapy that produced serum levels of 88.7 ± 4.0 μg/mL. Monkeys continued to have regular 28-day ovulatory menstrual cycles throughout the time of VPA monotherapy. Follicular and luteal lengths and peak preovulatory estradiol and integrated luteal progesterone levels did not differ between controls and treated monkeys. Ovaries from VPA-treated monkeys showed histologic evidence of ovulation, and none had characteristic features of PCOS. Endocrine PCOS markers, such as increased early follicular ratio of luteinizing hormone to follicle-stimulating hormone (LH/FSH) and androgen levels, were not different in control and VPA treatment cycles. Luteinizing hormone and 17-hydroxyprogesterone responses to gonadotropin-releasing hormone agonist challenges and the insulin response to glucose tolerance tests were similar in control and VPA groups. Lipid profiles were not affected by VPA treatment. The data indicate that a 12- to 15-month therapeutic exposure to VPA does not induce cyclic hormonal or morphologic ovarian abnormalities or characteristics of PCOS when administered to nonepileptic, normally cycling nonhuman primates.

Data from clinical nonepileptic populations, specifically women with bipolar disorder, are conflicting[1,70,73] and complicated by the fact that women with atypical or type II bipolar disorder may have demonstrable brain dysfunction that may confound the conclusion that PCOS is or is not related to VPA use alone.

An alternative and possibly unifying consideration is that PCOS may develop as an interactional effect between AED use and epilepsy.[31,34,46] Specifically, there is the possibility that epilepsy may promote PCOS development and that enzyme-inducing AEDs (EIAEDs) treat not only the epilepsy, but also the PCOS by enzyme induction that increases the synthesis of sex hormone–binding globulin and the metabolism of testosterone, resulting in lower levels of bioavailable testosterone.[31,34,46] There is evidence that testosterone may sensitize the hypothalamopituitary response to estrogen feedback, thereby disrupting normal gonadotropin secretion.[17] In contrast, enzyme-inhibiting drugs, most notably VPA, may retard the aromatization of testosterone estrogen[93] and potentiate the development of epilepsy-related hyperandrogenism and hence PCOS.[31,34,46] Antiseizure medications other than VPA, therefore, may treat hyperandrogenism and thus PCOS, whereas VPA therapy may not. This mechanism, thereby, could contribute to a higher occurrence of PCOS in VPA-treated women with epilepsy. If this were an extant mechanism, then VPA would not be the primary cause of PCOS, yet its selection as treatment may be an important factor.

Mechanisms in Men

Hypogonadism in men refers to diminished gonadal function as determined by low serum testosterone level and/or decreased or abnormal sperm production.[33] It can manifest as diminished sexual interest, potency, fertility, energy, mood, competitive drive, bone and muscle mass, and secondary sexual characteristics. Physical signs include a loss of male escutcheon, gynecomastia, and testicular atrophy. The clinical impression of hypogonadism can be verified by laboratory testing. Testosterone exists in three major forms: (a) tightly bound to sex hormone–binding globulin (SHBG; 45%–50%), (b) loosely bound to albumin (50%–55%), and (c) unbound (1%–2%).[43] The albumin-bound and free portions are available to tissues and, therefore, constitute the clinically important bioavailable portion. Measures of bioavailable testosterone (BAT) suggest that hypogonadism may occur in greater than one third of men with temporolimbic epilepsy.[33,47,57,90] BAT shows a substantially earlier and greater age-related decline in men with epilepsy than in controls.[37,57] In a sample of men with localization-related epilepsy, we found that BAT fell below normal control levels in 11% of men between 20 and 30 years of age, in 27% of those between 30 and 40 years of age, and in 89% of those between 40 and 50 years of age.[37,38] Sexual dysfunction, as determined by standardized questionnaire, affects 20% of men with LRE.[38,90] Several[8,19,38,60,96] but not all[16] investigations have found significant relationship between reduced serum BAT measures and sexual dysfunction. Men with epilepsy may show evidence of sexual dysfunction in the setting of low-normal BAT levels at which men in the general population may not show clinical manifestations.[36,38] This may constitute an argument against the importance of the BAT level. Alternatively, higher BAT levels may be required for normal sexual function in the setting of the altered brain substrate of epilepsy. Semen analysis has consistently revealed a remarkably high frequency, perhaps as high as 90%, of decreased sperm count and/or abnormalities in sperm morphology and motility among men with epilepsy.[8,53,79,92] Men with epilepsy are only 36% as likely as male unaffected siblings to ever father a pregnancy.[86]

The etiology of hypogonadism in men with epilepsy has been attributed to a number of possible causes. These include (a) psychosocial stress, (b) antiepileptic drugs, and (c) epilepsy itself.[33,38,47,65] Each of these is recognized to alter reproductive endocrine secretion.

Psychosocial stress associated with epilepsy may play an important role in hypogonadism.[95] From a neuroendocrine perspective, stress response involves the activation of the hypothalamo–pituitary–adrenal (HPA) axis.[84] Cortisol levels are higher in individuals with epilepsy than in controls, not unlike individuals with depression.[23] Unlike depression, however, diurnal variation is often lost in epilepsy.[23] Factors that increase the activity of the HPA axis interfere with reproductive endocrine secretion as well as reproductive function[84] and may contribute to seizure exacerbation.[55] Stress increases the release of proopiomelanocortin (POMC), the precursor protein that is cleaved to form adrenocorticotropic hormone (ACTH) and endorphin,[9,97] both of which inhibit gonadotropin secretion and reproductive function.[84,85] ACTH increases cortisol secretion; endorphins increase dehydroepiandrosterone production. Both of these steroids have γ-aminobutyric acid (GABA)-negative allostearic modulatory properties that lower seizure thresholds and increase anxiety.[54]

Antiepileptic drugs differ from one another in their effects on reproductive endocrine secretion. Enzyme-inducing AEDs can directly suppress gonadal testosterone synthesis, increase the hepatic synthesis of

SHBG, and increase serum estradiol levels in absolute or relative terms. In vitro investigation suggests that therapeutic range concentrations of EIAEDs, including carbamazepine and phenytoin, act at various specific levels of the biosynthetic cascade to block testosterone production in Leydig cells.[58] EIAEDs increase the hepatic synthesis of SHBG, thereby decreasing the bioactive portion of total testosterone.[33,38,47,49,53,90] Total testosterone levels decrease with age.[37,38,76] SHBG levels increase with age.[53] Consequently, the age-related decline in bioactive testosterone is often significantly greater than the decline of total testosterone levels. EIAEDs can also raise serum estradiol levels, in absolute terms or relative to BAT, thereby producing increased negative feedback on the hypothalamopituitary axis.[44,66] Although it constitutes only 1% of the total reproductive steroid, estradiol exerts one half of the negative feedback on the hypothalamopituitary axis.[33] Therefore, a small increase in estradiol level, presumably as a result of AED-induced increase in aromatase activity, could have a disproportionately large negative feedback effect, thereby contributing to hypogonadism. Elevated estradiol may also lower the ratio of bioactive to immunoreactive luteinizing hormone.[4] Non–enzyme-inducing AEDs have received less attention. In animal investigations, valproate has been associated with testicular atrophy.[77] Although GABA generally suppresses gonadotropin secretion, men with epilepsy who use valproate have been found to have normal testosterone levels and free androgen index.[74] Androstenedione levels and estradiol/testosterone ratios are higher than in controls.[74] Enzyme inhibition by valproate may be a potential factor. The replacement of carbamazepine with oxcarbazepine is associated with a reduction of SHBG.[51] Free androgen index, a measure of bioavailable testosterone, however, does not increase even after 6 months.[51] This is consistent with our recent findings that, despite the more rapid normalization of SHBG, BAT as well as aromatized and reduced testosterone metabolite levels may remain altered as late as 3 years following the discontinuation of EIAEDs.[37,38] (AEDs differ in their effects on sexual function and reproductive hormone levels. In a comparison of sexual function and reproductive hormone levels among 85 men with epilepsy who took various or no antiepileptic drugs (25 on carbamazepine, 25 on phenytoin [PHT], 25 on lamotrigine, and 10 untreated for at least 6 months [no AED]) and 25 controls, Herzog et al.[38] found that sexual function scores (S-scores), hormone levels (bioactive testosterone, estradiol), hormone ratios (bioactive testosterone/bioactive estradiol), and gonadal efficiency (bioactive testosterone/luteinizing hormone) were significantly greater in the control and LTG-treated groups than in the CBZ- and PHT-treated groups. Sex hormone–binding globulin was significantly higher in the CBZ and PHT groups than in all other groups. The S-scores were below the control range in 20% of the men with epilepsy, including 32% on CBZ,

24% on PHT, 20% on no AEDs and 4% on LTG (X^2: $p = .08$ for all four groups; X^2: $p = .02$ for the three AED groups). Bioactive testosterone was below the control range in 28.2% of the men, including 48% on CBZ, 28% on PHT, 20% on no AEDs, and 12% on LTG (X^2: $p = .02$). Among men with epilepsy who had low S-scores, 70.6% had bioactive testosterone levels below the control range as compared to 17.6% among men with normal S-scores (X^2: $p < .0001$). Among men with epilepsy who had abnormally low bioactive testosterone, 50.0% had low S-scores; among men with normal bioactive testosterone, 8.2% had low S-scores (X^2: $p < .0001$). Bioactive testosterone decline with age was significantly greater among men with epilepsy than among controls and notably greater in the CBZ and PHT groups than in the LTG and untreated groups. Overall, sexual function, bioavailable testosterone levels, and gonadal efficiency in men with epilepsy who took lamotrigine were comparable to control and untreated values and significantly greater than with carbamazepine or phenytoin treatment.

The temporolimbic system plays an integral part in endocrine regulation and feedback, as well as in epilepsy.[28] It has massive direct anatomic connections to regions of the hypothalamus that are involved in neuroendocrine control, that is, the regulation, production, and secretion of peptides that control pituitary function (Fig. 1). The pulsatile secretion of gonadotropin-releasing hormone (GnRH) is an intrinsic feature of GnRH neurons in the preoptic and ventromedial hypothalamus and depends on the integrity of sodium, potassium, and calcium channel conductance, factors that may potentially be influenced by the direct action of some AEDs.[33,57] Synchronization of neurons may be accomplished by local circuit neuronal connections as well as diffusible chemical factors.[57] The neurons are sensitive to basal forebrain and brainstem modulatory influences mediated by glutamate, GABA, and other neurotransmitters.[57] Epileptiform discharges in medial temporal lobe structures may disrupt hypothalamic regulation of pituitary secretion and hence alter gonadal function.[28] Focal limbic seizures, as well as generalized seizures, disturb normal gonadal structure, physiology, and serum androgen levels in the male rat.[18] Animal studies demonstrate that unilateral amygdaloid seizures have a laterally asymmetric effect on hypothalamic reproductive endocrine nuclei.[21,88] There is significantly greater Fos activation[88] and loss of GnRH fiber immunoreactivity[21] ipsilaterally than contralaterally. These ipsilaterally predominating responses are of potential interest because there are lateralized asymmetries in the temporolimbic system with regard to reproductive effects[82] and in the hypothalamus with regard to GnRH content[26] and sexual function that may suggest potentially different consequences of unilateral left and right temporolimbic seizures. Clinically, there may be a greater occurrence of sexual dysfunction in men with right, rather than left, lateralized temporolimbic epilepsy.[3,13,69] Hormonally, temporolimbic seizures produce an abnormal elevation in prolactin levels, reaching a peak in 20 to 30 minutes and then returning to baseline over 1 hour.[89] Prolactin responses may reach higher levels with right- than left-sided epileptiform discharges.[30] There are clinical studies that also suggest that temporolimbic epilepsy may be associated with altered gonadotropin response to GnRH infusion regardless of AED use[45] and that mean baseline LH and LH pulse frequency are significantly more variable among men with epilepsy than among controls.[36] Quigg et al.[72] found that interictally, pulse frequency and mean concentration are lower and pulse amplitudes are higher than in controls. Postictally, they found no change in mean pulse frequency but did detect a significant change in the orderliness of the pulses. These seizure-related findings, as well as our demonstration of laterality effects and a close temporal relationship between discharges and endocrine events in women[34] and possibly in men,[33] provide clinical evidence to support a temporolimbic modulatory influence on GnRH secretion.

The temporolimbic system projects to dorsomedial and lateral regions of the hypothalamus that are the source of direct fibers to the intermediolateral column of the thoracic spinal cord that provides sympathetic innervation of the testes.[33,83] Similarly, the temporolimbic system projects to the dorsal motor nucleus of the vagus that is the source of the parasympathetic innervation of the testes.[33] Autonomic innervation plays an important trophic as well as endocrine regulatory role.[24] Reciprocally, the vagal afferents from the testis project to the solitary nucleus that provides direct afferents to the amygdala.[28] The amygdala shows sensitive electrophysiologic responses to vagal stimulation.[28] The effect of vagal nerve stimulation therapy for intractable seizures has not been formally evaluated with regard to reproductive endocrine effects.

Changes in reproductive steroid concentrations may affect seizure tendencies as well as reproductive function. Although estrogen is proconvulsant and progesterone is anticonvulsant in most adult animal models of LRE, the effect of testosterone on experimental seizures appears to be mixed.[55] This may be related to its ready metabolism by aromatase to estradiol, which has neuroexcitatory effects, whereas it can also be metabolized by reductase to dihydrotestosterone, which may block *N*-methyl-D-aspartate (NMDA)-mediated conductance,[71] and, by further reduction to androstanediol, a potent GABAergic steroid with antiseizure properties.[22] Although testosterone replacement has proven only moderately effective in restoring sexual function, possibly because of its ready metabolism to estrogen, especially in the setting of antiepileptic drugs, one pilot study has reported superior results using combined treatment with testosterone and an aromatase inhibitor that blocked the transformation of testosterone to estradiol.[41] Combined therapy was associated with seizure reduction as well.[41] The neuromodulatory role of reproductive steroids suggests that a greater understanding of neuroendocrine regulation in men with epilepsy may be important not only for reproductive function, but also for optimal management of seizure disorders.

Gonadal Steroid use for Family Planning and Treatment of Reproductive Dysfunction

It has long been recognized that the use of the older enzyme-inducing AEDs, such as barbiturates, phenytoin, and carbamazepine, is associated with higher failure rates of oral contraceptive pills (OCPs).[11] The failure rate was estimated to be 3.1 per 100 woman-years for the original 80-μg estrogen plus 1-mg progestin formulation in women on EIAEDs as compared to 0.7 per 100 woman-years in untreated epileptic women and women in the general population.[10] The failure rate is likely to be considerably higher for the currently popular formulations, which have less than half of this estrogen and progestin content. The use of these lower-dose pills is associated with unregulated cycles in about 10% of users. The greater failure rate is likely due to the induction of the catabolism and binding of reproductive steroids as well as the induction of hormone conjugation in the gut.[11] A newer enzyme-inducing AED, topiramate, has also been shown to lower serum OCP steroid levels.[15] Clinically significant interactions between OCPs and enzyme-neutral (e.g., lamotrigine, gabapentin) and inhibitory (e.g., valproate) drugs were not considered to be of concern until some recent reports suggested that the use of OCPs by women who take lamotrigine is associated with statistically significant and substantial (>50%) reductions in the serum levels of lamotrigine.[80,81] In one of these reports,[81] the introduction

of OCPs was associated with increased seizure frequency or recurrence of seizures in most of the cases. The possibility of a similar relationship between valproate and OCP use has been raised by a well-documented case report.[39] The change in lamotrigine levels has been attributed to the estrogen rather than the progestin component of the pill.[75] During the 7-day pill-free period of OCP use, lamotrigine levels have been noted to increase progressively by >100%.[87] By way of mechanism, both valproate and lamotrigine are largely inactivated by hepatic glucuronidation, a process that is induced by OCPs.[39,80,81] Further investigations of the reciprocal interactions between AEDs and OCPs are required to establish the optimal use of OCPs in women with epilepsy. Although interactions between AEDs and OCPs are increasingly recognized by the medical community in the setting of birth control, they must also be considered in women with epilepsy who take hormones for other reasons such as menstrual disorders and endometriosis, in which treatment failures may lead to needless hysterectomy, and in the use of hormone replacement therapy for menopausal women with epilepsy. Higher-dose, rather than minipill-formulation, birth control pills have been recommended for women with epilepsy who take AEDs, especially if they experience irregular cycles and breakthrough bleeding. The potential benefit of increasing OCP dose, however, must be weighed against the potential adverse effects of these higher doses on serum AED levels and seizures.

Summary and Conclusions

Reproductive dysfunction is unusually common among women and men with epilepsy. Reproductive endocrine disorders are a major cause. Both AEDs and epilepsy affect hormones and differences in levels and patterns of reproductive endocrine secretion vary with different AEDs and the characteristics of the epilepsy, including classification, laterality, and nature of paroxysmal discharges. Gonadal steroid use for family planning purposes or for the treatment of reproductive dysfunction is complicated by the concomitant use of both enzyme-inducing and some noninducing AEDs. Because hormones influence epilepsy and neuropsychological well-being[32] as well as reproductive function, the comprehensive management of women and men with epilepsy requires a clear understanding of the reciprocal interactions epilepsy, AEDs, and hormones.

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Chapter 197

Sexuality in Epilepsy

Martha J. Morrell

Introduction

Men and women with epilepsy are believed to be at high risk for sexual dysfunction, although the precise frequency with which sexual dysfunction occurs in epilepsy (and other chronic neurologic illnesses) is not known. However, a number of social and biologic variables that could negatively impact sexual behavior in people with epilepsy have been identified. These include low self-esteem, mood and anxiety disorders, a disruption to central nervous system regions mediating sexual behavior, and disturbances of hypothalamic, pituitary, and gonadal hormones. Sexual dysfunction in people with epilepsy can serve as a model to aid in understanding the neurobiology of sexual behavior. Most important, recognition of sexual deficits in this patient population is necessary for effective treatment to be developed and delivered.

The Sexual Response

Sexual behavior can be considered as comprising two main components—desire and arousal.[4] Sexual desire refers to the willingness to engage in sexual behavior when given an appropriate sexual stimulus. In animals, this is evaluated as willingness to engage in sexual activities when given a receptive mate. In humans, sexual desire is equated with libido or sexual drive. Sexual desire reflects the individual's psychological health, cultural expectations, and past sexual experiences and requires salient sexual stimuli. Hormones are also required to support sexual desire, including the gonadal sex steroids—estrogen, progesterone, and especially testosterone—as well as hormones of the pituitary, including the gonadotropins—luteinizing hormone (LH) and follicle-stimulating hormone (FSH)—and prolactin. In nonprimate mammals, the hypothalamic hormone gonadotropin-releasing hormone is required to maintain sexual desire.

The second component of the sexual response is defined as sexual arousal. This is strictly defined as the capacity to respond to an appropriate sexual stimulus with a series of stereotyped vascular, neural, and muscular responses. A normal physiologic sexual response requires an intact, functioning cerebral cortex, brainstem, spinal cord, and autonomic nervous system including the sympathetic and parasympathetic divisions. Genital structures must be anatomically and functionally normal. The physiologic sexual response also requires that the hormone milieu include adequate levels of gonadal steroids.

Sexual arousal is characterized by nonspecific physiologic arousal and by a series of stereotyped events in genital tissue, as first described by Masters and Johnson.[34] The male sexual response cycle begins with the excitement phase. A sexual stimulus elicits increases in heart and respiratory rates, blood pressure, and skin vascularity. Vasocongestion begins in the penis, eventually with attainment of erection and rigidity. This response is mediated by the parasympathetic branch of the autonomic nervous system and depends on sacral nerves 2, 3, and 4. When vasocongestion is maximal, the plateau phase begins and is then maintained for a variable period. The plateau phase terminates with orgasm, mediated by the sympathetic nervous system and by sacral nerves 2, 3, and 4. The resolution phase follows orgasm and is a refractory period during which no amount of sexual stimulation can elicit physiologic arousal. The refractory period is variable and tends to increase with age.

The sexual arousal cycle in women is quite similar to that in men. An excitement phase is characterized by generalized physiologic arousal and by vaginal vasocongestion and myotonia, which depends on the parasympathetic nervous system and sacral nerves 2, 3, and 4. Following the plateau phase, orgasm occurs, mediated by somatic and sympathetic nerves. The physiologic events of orgasm include rhythmic 0.8-second contractions of the pelvic floor, uterus, and fallopian tubes. In women, the refractory period is short, permitting multiple orgasms.

Neuroendocrinology of Sexual Behavior

Regions of the cerebral cortex that mediate sexuality include the medial frontal lobe, structures within the circuit of Papez, limbic tissues, the hypothalamus, and distinct regions of the brainstem. Stimulation of the septum, the circuit of Papez, including the dorsolateral tegmentum of the midbrain, the medial orbital gyrus,[33] and the hippocampus,[32] stimulates erections in primates, whereas ablative lesions in the medial forebrain bundle, the hypothalamus, and the dorsolateral tegmentum of the midbrain markedly depress or even eliminate erections and other sexual behaviors.[13,19] Lesions to the medial temporal lobe bilaterally result in the Kluver-Bucy syndrome, which is characterized by uninhibited sexuality.[30]

The amygdala appears to be critical in mediating sexual and emotional behavior. The amygdala is rich in estrogen and androgen receptors, as well as endocannabinoid, opiate, and catecholamine receptors, all of which affect sexual behavior.[46] Bilateral amygdala ablation causes sexual dysfunction as well as disruption in other social behaviors.[19,55] Amygdala lesions are also associated with reproductive dysfunction in animals, including aspermatogenesis, anovulatory menstrual cycles, and polycystic ovaries.[56]

Cortical representation of sexual behavior is not well understood in humans. One study in patients implanted with intracranial electrodes, however, reported that erections were elicited by stimulation in the circuit of Papez.[21] Sexual orgasm was associated with high-frequency rhythmic discharges in the hippocampus, whereas chemical stimulation of the hippocampus reproduced feelings of pleasurable sexual sensation.[20] The cerebral cortex, particularly limbic structures, also influences sexual behavior by modulating the hypothalamic-pituitary-gonadal axis. The amygdala, a region of limbic cortex, contains two distinct nuclear groups that are reciprocally connected with the hypothalamus. The corticomedial nuclear group relays excitatory impulses to the hypothalamus, increasing the release of hypothalamic trophic hormones. The basolateral nuclear group has an inhibitory effect on the release of these same trophic hormones. The cerebral neocortex also is directly connected with the hypothalamus, modulating the release of trophic hormones. In nonhuman mammals, gonadotropin-releasing hormone (GnRH) from the hypothalamus supports mating behavior.[40] In all mammals, GnRH acts on the pituitary to influence the release of the gonadotropins LH and FSH. The pituitary hormones LH, FSH, and prolactin affect sexual behavior. Elevated pituitary prolactin is associated with reduced libido and with impotence.[8] The pituitary gonadotropins LH and FSH may have direct effects on the cerebral cortex to support normal sexual behavior.

The gonadotropins stimulate the release of gonadal sex steroid hormones. The gonadal steroids—estrogen and progesterone in women and testosterone in men—exert positive and negative feedback at every level of the cortical–hypothalamic–pituitary axis. In addition, high-affinity receptors for all sex steroids are extensively distributed within the amygdala and other limbic tissues, thereby affecting hypothalamic functions.[42,43,47,52] Any disturbance to the cerebral cortex and to limbic structures could theoretically disrupt the dynamic relationship among the hormones of this neuroaxis. Finally, the dynamic equilibrium of the endocrine axis can be disturbed by medications, including many antiepileptic medications, that enhance or reduce the hepatic metabolism of steroid hormones.

Sex steroid hormones are required for normal sexual desire and arousal. Sexual desire appears to be supported by androgens in both men and women. Normal physiologic sexual arousal in males requires the support of androgens, although a relatively profound androgen deficiency is required before sexual arousal fails. In fact, at least 20% of castrates continue to maintain normal sexual potency. Testosterone and another androgen, dehydroepiandrosterone sulfate, contribute and may be essential to sexual desire in women. Estrogens appear to support the vaginal vasocongestive response associated with the first phase of the sexual response cycle.[36]

Sexual Dysfunction in Epilepsy

Sexual dysfunction, most often described as global hyposexuality, has been reported in people with epilepsy since 1956.[18] Disorders of desire and of arousal, typically impotence, have been described in 30% to 60% of men with epilepsy.[7,27,44,53] Interviews with 97 men with chronic epilepsy[16] found that 21% had never experienced sexual intercourse despite having had the opportunity to do so, and at least one third of sexually active patients had difficulty achieving and maintaining an erection or ejaculating. Sexual deviancy appears rarely in this population, and hypersexuality was found in only 1% of patients evaluated in one study.[53]

Deficits in women have not been as well described. By self-report, there is a high incidence of dyspareunia, vaginismus, and arousal insufficiency.[38] One third of women with epilepsy described themselves as dissatisfied with their overall sexual function, in contrast to a community prevalence of 8%. More subtle differences in sexual desire are appreciated in some women with epilepsy. One inventory, inviting subjects to imagine and rate their degree of arousal and of anxiety in response to a number of sexual activities, found that sexual arousal was similar in women with localization-related and primary generalized (presumed genetic) epilepsies, but that women with localization-related epilepsy imagined they would experience significantly more anxiety in sexual situations.

Sexual deficits may vary by culture. In Egypt, a psychosexual history obtained in 700 women patients of an outpatient epilepsy clinic found that 18% had sexual disorders, including inhibited desire and arousal.[12] Only 29% of epileptic women in a Scandinavian outpatient clinic complained of dysfunction, which was no different than the rate for healthy controls.[29]

Two studies have evaluated physiologic sexual function in people with epilepsy. Fenwick et al.[15] assessed nocturnal penile tumescence in men with epilepsy. The patients were divided into two groups—one with relatively low testosterone levels and one with higher testosterone levels. Nocturnal penile tumescence over two nights of monitoring was diminished and disorganized in the low-testosterone group relative to the high-testosterone group. Procedural difficulties of the study included the lack of measurement of rigidity and the relatively arbitrary division into high- and low-testosterone groups. The low-testosterone group did not have a testosterone reduction that would routinely be associated with sexual dysfunction.

Stimulus-induced physiologic sexual arousal was evaluated in men and women with localization-related epilepsy of temporal lobe origin and compared with that in similarly aged controls.[39] In this protocol, genital vasocongestion in response to erotic video stimuli was assessed by noninvasive devices. The genital blood flow response, corresponding to the excitement phase of the sexual arousal cycle, was significantly diminished in the men and women with epilepsy. Moderate subjective sexual arousal was reported by all subjects—both those with and those without epilepsy—suggesting that the men and women with epilepsy experienced a disorder of arousal rather than a disorder of desire.

Cmechanisms of Sexual Dysfunction in Epilepsy

There are a number of potential mechanisms by which sexuality may be disturbed in people with epilepsy. Psychosocial deficits, such as restricted social opportunities and poor self-esteem, limit the opportunity for normal sexual interactions. Poor disease acceptance is associated with sexual dysfunction in other chronic illnesses and may contribute to impaired sexuality in epilepsy.[29] Depression is common in persons with epilepsy and is associated with loss of sexual desire as well as arousal deficiencies. However, physiologic mechanisms may be more relevant than psychological variables. Disruption of cortical regions mediating sexual behavior, either by fixed lesions or by epileptiform discharges, could influence sexual desire and arousal. Changes in hormones supporting sexual behavior occur in epilepsy because of seizures and antiepileptic drugs. Antiepileptic drugs have direct effects on cortical regions mediating sexuality and may also cause sexual dysfunction by secondary effects on reproductive hormones.

Psychosocial disability can adversely impact sexuality in men and women with epilepsy. Individuals with epilepsy are susceptible to poor self-esteem. Recurrent seizures may lead to a sense of vulnerability and helplessness, impairing the capacity to form healthy, nurturing relationships. Having epilepsy may limit social development, particularly for patients with frequent seizures who have restricted access to usual educational and occupational experiences. Finally, sexual behavior may be negatively reinforced if sexual feelings are a component of the seizure. Many patients are also concerned that sexual activity will precipitate a seizure, particularly those whose seizures are sometimes triggered by hyperventilation or physical exertion.

Sexual experience may be limited in some individuals with epilepsy. A study in Philadelphia evaluating sexual experience in men and women with temporal lobe epilepsy found that these men and women had significantly fewer sexual experiences than similarly aged controls.[39] The same study repeated in Palo Alto, California, however, found no difference between the sexual experience of men and women with epilepsy and that of similarly aged men and women with no medical or

neurologic illness,[38] suggesting that experience may be more directly determined by prevailing cultural expectations.

Mood and anxiety disorders have a high prevalence in persons with epilepsy, affecting 49% of 174 patients participating in a multicenter investigation.[30] Major depression was the most common individual diagnosis, affecting 17.2% of patients. Mood and anxiety disorders are highly correlated with sexual dysfunction.

Several clinical observations suggest that dysfunction in limbic structures predisposes to sexual dysfunction. Sexual dysfunction usually arises after the onset of seizures[7,44,47] and may be most common in individuals with localization-related epilepsy, particularly those whose seizures arise from the amygdala and hippocampus.[6,12,23,26,47] Several authors report that sexual dysfunction improves after temporal lobectomy for medically intractable seizures, despite continued treatment with antiepileptic drugs.[6,9,14,49] Patients with extratemporal resections were less likely to experience an improvement in sexual function than were those with temporal lobe resections.[3] Patients treated with temporal lobe resection for medically intractable epilepsy were more likely to have postoperative sexual dysfunction if the volume of the contralateral amygdala was small compared to those patients with a large volume of the contralateral amygdala.[3]

The laterality of the epileptogenic focus may also influence the nature and extent of sexual dysfunction. Sexual dysfunction scores were significantly higher in women with right temporal lobe onset epilepsy than those whose seizures arose in the left temporal lobe.[23] Another study described a reduction in sexual interest in men and women with epilepsy of right temporal lobe origin but not in those with epilepsy of left temporal lobe origin.[11]

Antiepileptic drugs affect sexual behavior by at least two mechanisms: (a) alterations in hormone metabolism and binding and (b) direct cortical effects.[10,45,54] Antiepileptic drugs that induce or inhibit the hepatic microsomal enzyme system alter metabolism of sex steroid hormones. Many antiepileptic drugs also induce production of sex hormone–binding globulin (SHBG), a binding protein for steroid hormones. Increased binding reduces the free, biologically active fraction. These two mechanisms cause a reduction in the free level of steroid hormones.[10,28] Antiepileptic drugs are also associated with elevations in prolactin and gonadotropins. They may act as suppressants of sexual behavior. Diminished libido and arousal were described in 12% of men beginning an antiepileptic drug,[35] an effect that was most pronounced with barbiturates.

Antiepileptic drugs do not cause all sexual deficits observed in people with epilepsy. First, sexual dysfunction generally arises with the onset of epilepsy, before treatment;[27] occurs in men and women not treated with antiepileptic drugs;[25,26] and is not correlated with the number of antiepileptic drugs used or with their serum levels.[44] Sexual deficits may improve when seizures are controlled, even if this requires higher doses of antiepileptic drugs,[27] or after temporal lobectomy.[7]

Alterations in pituitary and gonadal hormones can negatively affect sexual behavior in people with epilepsy (see Chapter 194). Interictal elevations in prolactin are observed in men and women, both those treated and those not treated with antiepileptic drugs (AEDs).[45,51] Seizures can cause marked elevations in prolactin (see Chapter 194) that are maximal at 20 minutes and persist for approximately 1 hour. Whether these pulses of elevated prolactin contribute to sexual behavior and arousal deficits is not known; however, elevated prolactin is one of the most frequent causes of impotence in otherwise healthy males. Reductions in LH may also contribute to sexual deficits. Low LH appeared to be associated with low-desire disorder in one study of women with localization-related epilepsy of temporal lobe origin.[26]

Although total levels of sex steroid hormones are within the normal range in most individuals with epilepsy, the free fraction of sex steroid hormone, which is the biologically active component, may be reduced.[10,28] This is typically the case in individuals taking cytochrome P450 enzyme–inducing AEDs, which increase the level of sex hormone–binding globulin and reduce the concentration of circulating free hormone.

Sexual dysfunction in women with epilepsy appears to be related to levels of sex steroid hormones. Women with epilepsy and low testosterone levels are reported to be more likely to have disorders of sexual desire and arousal.[23,37] Serum estradiol is lower in women with epilepsy treated with phenytoin[37] and carbamazepine (cytochrome P450-inducing antiepileptic drugs)[23] but not with lamotrigine.[23,37] Low estrogen levels were associated with sexual dysfunction in women with epilepsy and may contribute to dyspareunia, vaginismus, and lack of lubrication.[37]

Men with epilepsy are also susceptible to endocrine-associated sexual dysfunction. Low levels of free testosterone have been associated with disorders of sexual desire[16,51] and arousal[5] in epileptic men, although the range of testosterone would still be considered adequate to maintain normal sexual function in most individuals. Men receiving the AED carbamazepine or phenytoin had significantly lower bioavailable testosterone levels and poorer sexual function than did men receiving lamotrigine, men with untreated epilepsy, and nonepileptic controls.[24]

Sexual dysfunction may be a consequence of ictal alterations in neurotransmitters, including γ-aminobutyric acid (GABA), opioids, and serotonin. Brain opioids and GABA are released after kindled seizures and after ejaculation, causing behavioral depression.[41] Elevations in GABA inhibit sexual behavior in rabbits,[1] and postictal elevations in GABA and opioids are associated with prolonged neuronal depression.[41] Serotonin agonists specific to one receptor subtype (5-HT$_{1B}$) inhibit sexual desire and sexual arousal in rats,[17] an action mimicked by serotonin reuptake inhibitors in humans.

Evaluation and Treatment of Sexual Dysfunction

Patients with epilepsy presenting with sexual complaints must be evaluated for other causes of sexual dysfunction. Psychogenic causes of sexual dysfunction include psychiatric disease, psychosis, and affective disorders, such as depression and bipolar illness. Sexual symptoms may also arise as a result of religious, social, or family taboos or because of negative early life experiences. A dysfunctional relationship involving a sexual partner is a common cause. Concomitant medication, such as psychotropic drugs and antihypertensive agents, can be associated with desire and arousal deficits. Medical conditions causing sexual dysfunction include those associated with small-vessel disease, such as diabetes, hypertension, and hyperlipidemia; endocrine disorders producing hyperprolactinemia, hyper- or hypothyroidism, or significantly low testosterone; and systemic illnesses, including renal, hepatic, cardiac, and pulmonary disease. Infections or injury to genital structures can impair sexual arousal. Neurologic causes of sexual dysfunction include injury or disease involving the spinal cord, peripheral or autonomic neuropathy, and nonepileptogenic cortical lesions, particularly those involving the frontal and temporal lobes.

Table 1 Evaluation strategy by type of sexual complaint

	Disorder of desire	Disorder of arousal
Medical and sexual history	X	X
Duration of symptoms		

Situational anxieties		
Affective symptoms		
Medication, substance abuse		
Review of systems		
Physical and neurologic exam	X	X
Gynecologic exam		X
Urologic exam		
Nocturnal penile tumescence	X	X
Penile hemodynamics		X
Laboratory tests		
Testosterone	X	X
Prolactin	X	X
Luteinzing hormone/follicle-stimulating hormone	X	X
Thyroid hormones	X	X
Complete blood count/chemistries		X
Triglycerides/cholesterol		X
Glucose tolerance test		X

An evaluation for sexual dysfunction can be modified according to the type of dysfunction—a disorder of sexual desire or of sexual arousal (as shown in Table 1)—but always begins with a thorough medical, neurologic, and sexual history. This requires that the physician ask specific questions about sexual well-being. Patients are unlikely to volunteer sexual complaints, particularly in a first or second visit. In one Danish study of 16,000 patients from general practitioner's clinics, the frequency of sexual complaints depended on the physician. Sexual dysfunction was more likely to be detected by female physicians who were <45 years of age and practiced in urban areas.[30] The physician determines whether symptoms are acquired or chronic. Situational anxieties are explored, as are phobias or avoidances. The patient is evaluated for an affective disorder. Medication use and substance abuse are carefully explored. The patient is asked about other physical complaints that might reveal systemic illness.

A complete physical and neurologic examination is always indicated. Screening laboratory tests at initial presentation include testosterone, prolactin, LH and FSH, thyroid hormones, complete blood count and chemistries, triglycerides and cholesterol, and a glucose tolerance test. The patient may also be referred for a gynecologic or urologic examination. The urologic evaluation may include tests of erectile capacity, including nocturnal penile tumescence and penile hemodynamics.

Therapeutic intervention begins with an explanation that sexual dysfunction is an epiphenomenon of epilepsy. This may prove tremendously relieving to the patient, who is likely to attribute sexual dysfunction to personal inadequacy. Educating the epileptic patient and his or her sexual partner about epilepsy in general and about the degree to which seizure control can be expected acutely and over the long term will improve disease acceptance, especially when combined with realistic and frank discussion about the impact of epilepsy on the lives of patient, family members, and friends.

An effort is made to improve seizure control with the patient's current antiepileptic drugs. If this is not successful, an alternative antiepileptic drug is considered, especially if the patient is taking a barbiturate. Individual patients may experience sexual deficits on one antiepileptic drug and be asymptomatic on another. Until further research clarifies the extent to which individual mediations affect sexual function, it is reasonable to switch to an alternative medication if seizure control is equivalent.

If other medical or psychological causes of sexual dysfunction are excluded and adjustment of antiepileptic drugs is not helpful or possible, specific sex therapy techniques may prove useful. Individual and couple psychotherapy may be indicated if there are problems in the relationship. If a woman complains of painful intercourse, relaxation techniques and lubrication products may be of benefit. For men with erectile difficulties, pharmacologic and surgical treatments are available.

Summary and Conclusions

A number of questions must be answered before the relationship between epilepsy and sexual dysfunction is better understood. The prevalence of sexual dysfunction and epilepsy must be contrasted with that in other chronic illnesses. The effects of individual antiepileptic drugs on sexual behavior must be elucidated. A better understanding of endocrine abnormalities associated with epilepsy must be achieved. Finally, and most important, attention must focus on treatments that can be offered to those men and women with epilepsy who experience sexual dysfunction.

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Chapter 198

Pregnancy and the Mother with Epilepsy

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Introduction

The management of women with epilepsy is an area that has received increased attention from neurologists. The discrimination and bias of past eras has gradually given way to an atmosphere in which marriage and child rearing is considered acceptable for women with epilepsy (WWE). We therefore tend to forget that in the not too distant past, most states had legislation prohibiting marriage for persons with epilepsy.

The advent of better neurologic training, improved diagnostic techniques, the development of vagal nerve stimulation, and a group of new and effective medications have vastly improved the management of epilepsy. The majority of women with this disorder can have healthy children. The management of women, however, presents unique issues not present for men. To be effective, neurologists need to understand these issues. Fluctuations in sex steroid hormones can have an impact on seizure control. Sexual dysfunction is seen more often in persons with epilepsy. Infertility is more common in women with epilepsy. It is unclear whether this is a function of the treatment or the underlying disorder. Enzyme-inducing antiepileptic drugs (AEDs) may reduce the effectiveness of hormonal contraceptives. Hormonal contraceptives may impact plasma concentrations of specific AEDs. Women with epilepsy are at greater risk for complications of pregnancy and adverse pregnancy outcomes. The following is a practical discussion of the management of these problems.

Infertility and Reproductive Abnormalities

Epidemiologic studies have demonstrated that women with epilepsy have only one fourth to one third as many children as women in the general population.[8,35] A variety of hypotheses have been developed to explain this phenomenon. A direct effect of seizures or epileptiform discharges on the pituitary and hypothalamus could disrupt ovulation. Electroconvulsive therapy increases prolactin concentrations over fivefold within 15 to 20 minutes, and in premenopausal women there is an acute increase in luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Generalized seizures also increase prolactin serum concentrations within 15 to 20 minutes by a factor threefold. This fact has been used to assist physicians in differentiating epileptic from nonepileptic seizures.[20]

Women with epilepsy have higher rates of reproductive and endocrine disorders (REDs) than expected. In a large clinical center, 50% of women with epilepsy were found to have menstrual abnormalities, 20% amenorrheic and 35% anovulatory.[24] Herzog et al. were among the first to demonstrate REDs in women with temporal lobe epilepsy.[25] Women with primary generalized epilepsies also have REDs. Five of 20 women studied by Bilo et al. had REDs, three with polycystic ovarian disease, and two with hypogonadotropic hypogonadism.[8]

Antiepileptic drugs may also interfere with the hypo-thalamic-pituitary axis. Amenorrhea, oligomenorrhea, and prolonged or irregular cycles have been described in WWE by Isojarvi et al.[35] Women with epilepsy taking valproate were overrepresented: 45% of those on valproate monotherapy and 25% on valproate polytherapy had menstrual disturbances. Polycystic ovaries were found in 43% of valproate-treated women and 80% of women treated with valproate before the age of 29 had polycystic ovaries.

Women with epilepsy have more variation in LH pulse frequency and lower LH concentrations than controls.[20] In addition, women with left-sided ictal epileptiform foci had polycystic ovarian disease, and those with right-sided foci hypogonadotropic hypogonadism.

Libido is significantly reduced in one third of men and women with epilepsy.[58] Increasing seizure frequency appears to decrease sexual desire, while there is no difference in libido between treated and untreated women with epilepsy. Hyposexuality and orgasmic dysfunction has been reported in 8% to 68% of women with epilepsy.[48] Persons with localization-related epilepsies appear to have higher rates of sexual dysfunction compared to those with primarily generalized epilepsies. Shukla et al. have demonstrated that 64% of women with partial epilepsies, compared to 8% with generalized epilepsies, report hyposexuality and sexual dysfunction.[79]

The problem of infertility in WWE is therefore complex. There are multiple factors: Seizure type, frequency, site of ictal onset, and use of AEDs, which may affect an individual patient. Infertility in a couple deserves a careful evaluation of both partners. For WWE, ultrasonography to rule out polycystic ovarian disease, serum LH and FSH concentrations, and an evaluation of AED use will help one narrow the focus of treatment. There is evidence that valproate may adversely impact the fertility of some women. If the patient's seizures are controlled, discontinuation of valproate is not warranted unless polycystic ovarian disease or hypogonadotropic hypogonadism is found.

Pregnancy

The majority of WWE can conceive and bear normal, healthy children. The pregnancies of WWE do present a greater risk for complications of pregnancy, they are more likely to have difficulties during labor, and there is a higher risk of adverse pregnancy outcomes.

Increased Seizure Frequency

One quarter to one third of WWE will have an increase in seizure frequency during pregnancy. This increase is unrelated to seizure type, duration of epilepsy, or seizure frequency in a previous pregnancy. While most studies have demonstrated that the increase tends to occur toward the end of pregnancy, recent reports find that a substantial number (31%) have their increase in the first trimester.[11]

Plasma concentrations of anticonvulsant drugs decline as pregnancy progresses, even in the face of constant and in some instances increasing doses.[63,72,92,93] Plasma concentrations tend to rise postpartum.[65,103] Although reduction of plasma drug concentration is not always accompanied by an increase in seizure frequency, virtually all women with increased seizures in pregnancy have subtherapeutic drug levels.[15,36,67,75] The decline of anticonvulsant levels during pregnancy is largely a consequence of decreased plasma protein binding, reduced concentration of albumin, and increased drug clearance.[14,36,63,68,69,93,104] The clearance rates are greatest during the third trimester.

Seizures during pregnancy increase the risk of adverse pregnancy outcomes. Generalized, tonic–clonic seizures increase the risk for hypoxia and acidosis as well as injury from blunt trauma.[85] Canadian researchers have found that maternal seizures during gestation increase the risk of developmental delay.[52] Although rare, stillbirths have occurred following a single generalized convulsion, or series of seizures.[10,27,87]

Generalized (though not partial) convulsions occurring during labor can have a profound effect on fetal heart rate.[90] The increased rate of neonatal hypoxia and low Apgar scores may be related to such events.[104] Partial seizures may also have similar effects, if less often.[74]

Complications in the Offspring

The infants of epileptic mothers are at greater risk for a variety of adverse pregnancy outcomes. These include fetal death, congenital malformations, neonatal hemorrhage, low birth weight, developmental delay, feeding difficulties, and childhood epilepsy.

Infant Mortality

Fetal death (defined as fetal loss after 20 weeks' gestation) appears to be as common and perhaps as great a problem as congenital malformations and anomalies. Studies comparing stillbirth rates found higher rates in infants of mothers with epilepsy (1.3% to 14.0%) compared to infants of mothers without epilepsy (1.2% to 7.8%).

Spontaneous abortions, defined as fetal loss prior to 20 weeks of gestation, do appear to occur more commonly in infants of mothers with epilepsy.[102] Women with localization-related epilepsies appear to be at greater risk for spontaneous abortions than those with other seizure types.[76] Other studies have demonstrated increased rates of neonatal and perinatal death. Perinatal death rates range from 1.3% to 7.8% compared to 1.0% to 3.9% for controls.

Malformations

Fetal malformations have been associated with in utero exposure to AEDs. Congenital malformations are defined as a physical defect requiring medical or surgical intervention and resulting in a major functional disturbance.

Infants of mothers with epilepsy exposed to anticonvulsant drugs in utero are twice as likely to develop birth defects as infants not exposed to these drugs. Malformation rates in the general population range from 2% to 3%. Reports of malformation rates in various populations of exposed infants range from 1.25% to 12.5%.[12,21,37,40,44,59,62,69,84,91,94,99] These combined estimates yield a risk of malformations in a pregnancy of WWE of 4% to 6%. Cleft lip, cleft palate, or both, and congenital heart disease account for many of the reported cases. Orofacial clefts are responsible for 30% of the increased risk of malformations in these infants.[1,22,43]

A wide variety of congenital malformations have been reported, and every anticonvulsant drug has been implicated as a cause. No anticonvulsant drug can be considered absolutely safe in pregnancy, yet most of these drugs do not produce any specific pattern of major malformations.

An exception to this is the association of sodium valproate with neural tube defects (NTDs). Methodologic problems make frequency estimates imprecise since most published data are case reports, case series, or very small cohorts from registries that were not designed to evaluate pregnancy outcomes. The prevalence of spina bifida (SB) with valproate exposure is approximately 1% to 2%, and with carbamazepine 0.5%.[28,53,73] However, a prospective study in the Netherlands found that infants of mothers with epilepsy (IMEs) exposed to valproate had a 5.4% prevalence rate of SB. Average daily valproate doses were higher in the IMEs with SB (1,640 ± 136 mg/day) than in the unaffected IMEs (941 ± 48 mg/day). Another group of investigators has found that valproate doses of 1,000 mg/day or plasma concentrations of 70 μg/mL or less are unlikely to cause malformations.[40,94]

Women with epilepsy should, as should all women of childbearing age, take folate supplementation. The dose recommended by the Centers for Disease Control and Prevention of 400 μg/day may not be high enough for many women who do not metabolize folate effectively. Even with folate supplementation, women taking valproate or carbamazepine should avail themselves of prenatal diagnostic ultrasound to rule out NTDs.

Neonatal Hemorrhage

For many years, it has been believed that infants of mothers with epilepsy are at greater risk of neonatal hemorrhage. This was reported first by Van Creveld, who suggested that vitamin K deficiency might be the cause.[95] Since then, there have been numerous reports that in utero exposure to AEDs is associated with neonatal hemorrhage.[9,19,46,50,81,83,86] Early reports attributed this to phenobarbital or primidone, but a hemorrhagic diathesis has subsequently also been described in children exposed to phenytoin, carbamazepine, diazepam, mephobarbital, amobarbital, and ethosuximide.

This has been differentiated from other hemorrhagic disorders in infancy in that the bleeding occurs internally, during the first 24 hours of life. Accurate prevalence figures are lacking.

The hemorrhage appears to be a result of a deficiency of vitamin K-dependent clotting factors II, VII, IX, and X. Maternal coagulation parameters are invariably normal. The fetus, however, will demonstrate diminished clotting factors and prolonged prothrombin and partial thromboplastin times. A prothrombin precursor, protein induced by vitamin K absence (PIVKA), has been discovered in the serum of mothers taking anticonvulsants.[16] Assays for PIVKA may permit prenatal identification of infants at risk for hemorrhage.[6,97]

The historical demonstration of an increased risk of neonatal hemorrhage coupled with a demonstrated deficiency of vitamin K and PIVKA led clinicians to believe that the relative lack of vitamin K and the presence of PIVKA was the cause of this particular neonatal hemorrhage. Three studies demonstrated that oral maternal supplementation increased neonatal vitamin K and reduced hemorrhage.[4,13,18] However, this practice has been challenged. Kaaja et al. found no difference in the rates of neonatal hemorrhage in 667 infants of mothers with epilepsy (0.7%) and 1,334 control infants (0.4%).[39] No

mothers in either group were supplemented with vitamin K, but all infants received intramuscular vitamin K at delivery. They concluded that on the basis of their experience, no evidence of a difference in clinical bleeding could be found; hence, supplementation was not recommended. Hey measured cord blood from 137 infants of mothers with epilepsy taking phenobarbital, phenytoin, or carbamazepine and found that 14 of 105 had prolonged prothrombin times but none had any clinical bleeding.[26] He believed that the lack of clinical bleeding in his series made supplementation with vitamin K inappropriate.

Some background may help clarify the apparent differences in conclusions made by these observers. Vitamin K deficiency is common in neonates. Maternal vitamin levels are not reflected in cord blood. When Shearer et al. measured vitamin K in mothers, they found values ranging from 0.13 to 0.29 ng/mL, but none in the cord blood.[80] Even after IV supplementation raised levels to 45 to 93 ng/mL, cord values rose only to 0 to 0.14 ng/mL. This discrepancy between maternal and neonatal vitamin K levels has lead researchers to look for PIVKA as a proxy for vitamin K deficiency. PIVKA is formed as a result of incomplete carboxylation of protein precursors of vitamin K and so is present when vitamin K is absent or present in very small concentrations.

The problem is, in part, that there has been confusion between vitamin K deficiency, laboratory evidence of abnormal coagulation parameters, and clinical bleeding. Vitamin K deficiency is common, the presence of PIVKA is less so, but clinical bleeding in neonatal life is rare. Shapiro et al. demonstrated that PIVKA presence is fairly uncommon in the general population of newborns (2.9%) and more common in premature infants.[78] We have no good data on prevalence of neonatal hemorrhage in infants of mothers with epilepsy, but we do have reasonably accurate case reports.

There is also reasonable causation. Anticonvulsants can act like warfarin and inhibit vitamin K transport across the placenta. These effects can be overcome by large concentrations of the vitamin. Despite lower coagulation factor levels, the fetus is generally able to obtain enough maternal vitamin K in utero. After birth the newborn must rely on exogenous sources of vitamin K because the newborn gut is sterile. Routine administration of vitamin K at birth is not adequate to prevent hemorrhage if any two of the coagulation factors fall below 5% of normal values.[83] Successful treatment requires fresh frozen plasma intravenously.

It is not so much that Kaaja and Hey are incorrect, but rather that it is extremely difficult to measure the effects of infrequent clinical outcomes. Neonatal hemorrhage is also unlikely to be identified unless it is severe and the child is clinically ill in those first 24 hours. The marked increase in PIVKA in infants of mothers with epilepsy suggests that they are at increased risk for hemorrhage, and the increase in developmental delay and need for additional educational assistance seen so often in this population suggests that small degrees of hemorrhage may affect the development of these infants.[3,52,55]

To make the matter more interesting, Howe et al. suggest that vitamin K deficiency in a developing embryo results in a failure of vitamin K–dependent carboxylation processes and an accumulation of compounds that affect embryonic cartilaginous development.[32] Such children are at risk for midface hypoplasia. They base this hypothesis on the clinical similarities between the midface abnormalities seen in warfarin- and phenytoin-exposed children. Howe et al. proposed that vitamin K supplementation should start prior to conception because maternal supplementation with vitamin K reverses the deficiency.

It is clear that one should offer maternal supplementation to pregnant women with epilepsy. The risks of neonatal hemorrhage, while low, clearly exist, as demonstrated by elevated PIVKA levels, particularly with enzyme-inducing AEDs. There is a lack of an effective intervention once a neonate bleeds. There is the additional possibility of small bleeds, which, while not clinically detectable at birth, may have long-term effects. There is a hypothesized possibility of an association of decreased carboxylation secondary to decreased vitamin K and the development of some types of malformations. There is a lack of risk with the recommended vitamin K supplementation (10 mg/day). There is also a clear need for better prevalence data on the true risk of clinical bleeding in infants of mothers with epilepsy.

Low Birth Weight

Low birth weight (<2,500 g) and prematurity have been described in infants of mothers with epilepsy. The average rates range from 7% to 10% for low birth weight and 4% to 11% for prematurity.[5,33,62,88,89] These studies do not analyze the effect of specific seizure types, frequency, or AEDs on this aspect of fetal development.

A prospective study that pooled data from three countries (Canada, Japan, and Italy) on 870 infants of mothers with epilepsy found that 7.8% were below the 10th percentile in weight at birth.[7] The risk was greater with polytherapy.

Body dimensions of infants of mothers with epilepsy have been studied by Wide et al.[100] Infants exposed to polytherapy, not surprisingly, were shorter and smaller than those exposed to monotherapy. Exposure to monotherapy with carbamazepine revealed a tendency toward small for gestational age, birth weight, and head circumference, but it was not statistically significant.

Table 1 IQ Scores of Children of Mothers with Epilepsy and Controls

Group	N	Mean VIQ	Mean PIQ	Mean FSIQ
Entire group	182	92.8	100.3	96.0
No AEDs	45	94.3	98.6	95.6
All monotherapy	107	94.4	101.9	98.0
CBZ monotherapy	86	96.2	103.1	99.7
VPA monotherapy	13	83.5	96.3	89.7
Other monotherapy	8	91.1	96.9	93.6
All polytherapy	30	84.9	97.1	89.5

VPA polytherapy	17	81.5	96.1	86.6
Control	141	94.9	102.4	97.6

AEDs, antiepileptic drugs; CBZ, carbamazepine; FSIQ, full-scale IQ; PIQ, performance IQ; VIQ, visual IQ; VPA, valproic acid.
From Gaily E, Kantola-Sorsa E, Hiilesmaa V, et al. Normal intelligence in children with prenatal exposure to carbamazepine. *Neurology*. 2004;62(1):28–32, with permission.

Developmental Delay

With a prevalence of 0.6% to 1%, it is estimated that there are 24,000 deliveries to women with epilepsy in the United States each year. If 75% to 95% of these persons take AEDs, we can expect 18,000 to 22,800 infants exposed to AEDs in utero per year. It is estimated that half of all AED prescriptions are used for conditions other than epilepsy. Though these patient populations may have fewer women of childbearing years, the numbers of exposed children is substantial.

Most investigators have focused on congenital malformations as the primary adverse outcome for children of mothers with epilepsy. The rates are approximately double those in the general population. I would argue that the magnitude of developmental delay is similar.

Infants of mothers with epilepsy have been reported to have higher rates of mental retardation than controls. This risk is increased by a factor of two- to sevenfold, according to various authors.[29,82] None of these early studies controlled for parental intelligence; although differences in IQ scores at age 7 between groups of children exposed (FSIQ = 91.7) or not exposed (FSIQ = 96.8) to phenytoin reached statistical significance, the clinical significance of such difference is unclear.[29] In comparing 76 IMEs with 71 unexposed control children, Wide et al. found no difference in scores on developmental tests, but did find a tendency for phenytoin-exposed children to have a greater reduction in tests of motor coordination.[98]

Leavitt et al. found that IMEs display lower scores in measures of verbal acquisition at both 2 and 3 years of age. Though there was no difference in physical growth parameters between IMEs and controls, IMEs scored significantly lower in the Bailey Scale of Infant Development's mental developmental index (MDI) at 2 and 3 years. They also performed significantly less well on the Bates Bretherton early language inventory ($p \leq 0.02$) and in the Peabody Picture Vocabulary's scales of verbal reasoning ($p \leq 0.001$) and composite IQ ($p \leq 0.01$), and they displayed significantly shorter mean lengths of utterance ($p \leq 0.001$).[51]

Infants exposed to polytherapy performed significantly less well on neuropsychometric testing than those exposed to monotherapy. Socioeconomic status had the strongest association with poor test scores, but maternal seizures during pregnancy was also a significant risk factor.[54]

Leonard et al. have in part addressed the question of whether maternal seizures or in utero exposure to AEDs are responsible for the developmental delay seen.[52] A group of children of mothers with epilepsy followed to school age were found to have a rate of intellectual deficiency of 8.6%. The Wechsler Intelligence Scale for Children revealed significantly lower scores for children exposed to seizures during gestation (100.3) than for children whose mother's seizures were controlled (104.1) or controls (112.9). All AEDs are clearly not created equal, and Koch et al. have demonstrated that primidone, particularly when used in polytherapy, is associated with a lower Wechsler score of intelligence.[45]

Both maternal epilepsy and AED exposure in utero appear to affect development of offspring in a study by Koch et al.[45] The severity of outcomes increased from control to “maternal epilepsy, no AED exposure” to "maternal epilepsy, AED-exposed" children.

A rigorous retrospective analysis of 100 consecutive pregnancies seen at a tertiary epilepsy center found that 3.9% of the children were premature, 1.1% had congenital malformations, and 6.2% developmental delay. This was despite the fact that 59% of the mothers were seizure free and 98% took folic acid during their pregnancy.[41]

Another retrospective study demonstrated that 16% of 594 children of mothers with epilepsy exposed to AED in utero, compared to 11% of 176 of children with no AED exposure, required additional educational assistance in school. This was felt to be a reasonable marker for developmental delay. In addition, differences between AEDs were found: 30% of children exposed to valproate monotherapy, 24% of children exposed to valproate polytherapy, and only 3.2% of carbamazepine monotherapy–exposed children required additional educational assistance.[3] Monotherapy with other AEDs had rates of 6% and polytherapy without valproate 16%. Children with no AED exposure had an 11% use of additional educational services.

The same cohort of children was studied to determine their IQ scores. Of 251 children tested, the mean IQ for valproate-exposed children was 82, compared to 95 for carbamazepine-exposed and 92 for AED-unexposed children.[96]

The authors followed up their initial cohort, eventually studying 249 children of mothers with epilepsy from ages 6 to 16. The numbers in monotherapy were modest: 41 were exposed to valproate, 52 to carbamazepine, 21 to phenytoin, and 49 to polytherapy, compared to 80 unexposed children. They used regression analysis to demonstrate that both exposure to valproate and frequent generalized tonic–clonic seizures in pregnancy increased the risk of low verbal IQ scores.[2]

Three other studies have found increased rates of developmental delay in children exposed to carbamazepine ranging from 8% to 20%.[38,66,77] One of these studies only used a single standard deviation from the mean to qualify developmental delay and thus overstates the risk.[38]

A retrospective study of mothers with epilepsy delivering in Scotland between 1976 and 2000 used the nonexposed siblings as controls. Developmental delay was demonstrated in 19% of 293 AED-exposed children compared to just 3% of their nonexposed siblings. The rate of delay in valproate-exposed children was particularly high at 37%. Congenital malformations were found in 14% of exposed and 5% of nonexposed siblings. The investigators also stated that facial dysmorphism was present in 52% of exposed and 25% of nonexposed siblings, which makes one wonder about the nature of this population.[17]

Reinisch et al. conducted double-blind studies examining intelligence in adult men with in utero exposure to phenobarbital.[71] Their mothers by and large had not had epilepsy but took the drug for other indications. Unexposed members of the same birth cohort, matched on a large number of variables, were used as controls. The first study used the Wechsler Adult Intelligence Scale (Danish version); the second, the Danish Military Draft Board Intelligence Test. The authors concluded that:

- Men exposed prenatally to phenobarbital had significantly lower verbal intelligence scores (approximately 0.5 standard deviation or 7 IQ points) than predicted.
- Lower socioeconomic status and being the offspring of an "unwanted" pregnancy increased the magnitude of the negative effects to a mean of 20 IQ points less than controls.
- Exposure during the last trimester was the most detrimental.

In one of the best designed prospective studies of outcomes of mothers with epilepsy, Gaily et al. measured the intelligence of 182 children of mothers with epilepsy and 141 controls.[23] The investigators performing the testing were blinded as to the child's exposure. Table 1 is from their report.

This suggests that children exposed to valproate and polytherapy are at higher risk for developmental delay than children exposed to carbamazepine or unexposed children.

Specific Effects of Antiepileptic Drugs and Other Interventional Therapies

New Antiepileptic Drugs in Pregnancy

Since 1993 a number of effective new AEDs have been introduced in North America. Their diminished side effect profiles have made them increasingly popular. Gabapentin, felbamate, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, and zonisamide are all now available in the United States. There is some tendency to think that since we know the older AEDs have hazards, the new ones might be acceptable substitutes. Unfortunately, there is little information to support their safety. The numbers of reported exposed pregnancies with these drugs is very low, and unfortunately not large enough for one to determine if there is an increased risk of adverse outcome with fetal exposure to these compounds. We know that lamotrigine and levetiracetam concentrations decline during pregnancy and expect that this is also true for the other new AEDs.[92] To follow is what we know to date.

Gabapentin

A study combining retrospective and prospectively collected cases evaluated 44 children born to 39 mothers with epilepsy taking gabapentin. Two of 44 or 4.5% had major malformations. One child had hypospadias and was exposed to gabapentin and valproic acid. The other was exposed to gabapentin monotherapy until the 16th week of gestation (the mother then switched to phenobarbital) and had only one kidney.[56]

Lamotrigine

The International Lamotrigine Pregnancy Registry has now identified 1,412 pregnancies reported in women taking lamotrigine in the first trimester. There is a significant difference in malformation rates when lamotrigine is used in monotherapy (2.8%; 20 of 707 with a 95% confidence interval of 1.8% to 4.9%) and polytherapy with valproic acid (11.8%; 14 of 119 with a 95% confidence interval of 6.8% to 19.3%) and polytherapy without valproic acid (2.7%; 7 of 256 with a 95% confidence interval of 1.2% to 5.8%).[49]

A recent report from the U.K. Pregnancy Registry found a dose-response effect with higher rates of malformations in infants exposed to doses >200 mg/day (5.4%) than those exposed to lower doses (1.9% at doses of 100 to 200 mg, and 1.5% at doses <100 mg).[60] An analysis of dosing from the Lamotrigine Registry did not find such a dose-response effect. Lamotrigine crosses the placenta and at delivery the fetus and mother have similar plasma concentrations. Elimination in infants appears to be rather slow. Seventy-two hours postpartum infant plasma levels are 75% that of the mother. Median milk:plasma ratios are 0.61.[65]

Oxcarbazepine

The only prospective series reported to date evaluated 42 oxcarbazepine-exposed pregnancies in Buenos Aires. There were no malformations in the 25 monotherapy-exposed cases. One child with a ventricular septal defect was exposed to oxcarbazepine and phenobarbital.[70] In a retrospective study from Finland of 133 women with epilepsy, 101 monotherapy exposures had no malformations and in 17 polytherapy exposures there was one malformation—a ventriculoseptal defect.[34] A recent review of the published world literature on oxcarbazepine exposure in pregnancy suggests that the risk of malformation is similar to that of the general population.[57] Oxcarbazepine crosses the placenta with equivalent maternal and fetal cord levels.[61]

Topiramate

There is little information on the number of pregnancies with topiramate exposure. There is one case report of a child exposed to topiramate monotherapy who developed growth deficiency, hirsutism, a third fontanelle, an upturned nasal tip, and distal digital hypoplasia. During the clinical trials, 28 pregnancies were reported in which there was one malformation and two anomalies. The manufacturer has collected 139 pregnancies during postmarketing surveillance. Of these, 87 resulted in live births, 29 were lost to follow-up, 23 had therapeutic abortions, and 5 cases had hypospadias (OthoMcNeil, personal communication). Topiramate crosses the placenta with cord and maternal plasma levels being equivalent at delivery. Milk:plasma concentration ratios average 0.86. Infant elimination appears to be substantial with little measurable drug found in the plasma of breastfed infants 2 to 3 weeks postpartum.[64]

Zonisamide

There have been 26 reported pregnancies with zonisamide exposure. Two of the 26 (7.7%) had congenital malformations. One child was also exposed to phenytoin and the other to both phenytoin and valproic acid.[47]

Zonisamide also freely crosses the placenta with transfer rates of 92%. Though data is available from only two children, milk:plasma ratios are 0.8 and elimination half-life ranges from 61 to 102 hours.[42]

Pregnancy Registries

The paucity of data on newer AEDs has led to the development of pregnancy registries. These prospective data collection centers can serve as an "early warning system" by looking for either clusters of specific abnormalities or rates of malformation in excess of expected. They are hampered by the fact that not all women with epilepsy who deliver will enroll, and there are poor data on the true number of exposed women. Therefore, no denominator exists to permit the estimation of rates. Such a system can only accurately capture major malformations of the type diagnosable at birth. Given these limitations, this remains the only method currently available for surveillance and physicians and patients are encouraged to enroll.

There are now two major regional pregnancy registries for AEDs: European (EURAP), and North American (NAREP). Both are prospective and collect information for all AEDs. They differ in the source of subjects. The NAREP requires patients themselves to report, while the other relies on physicians.

The North American registry has over 2,970 monotherapy prospective subjects and is the only registry with a concurrent control group. It has found an increased risk of malformations for phenobarbital (6.3%; odds ratio [OR] of 4) and for valproate (10.7%; OR of 7). In addition, it has determined that while lamotrigine has an overall malformation rate of 2.7%, it does appear to increase the rate of oral clefts to 8.9 of 1,000 compared to 0.37 of 1,000 in the general population.[30,31,101]

A Swedish birth registry study has reviewed 1,398 AED-exposed infants. The odds ratio for malformations in infants exposed to AED was 1.86 (95% confidence interval, 1.4 to 2.4). Malformation rates for specific AEDs in monotherapy were 4.0% for carbamazepine, 4.4% for lamotrigine, 6.8% for phenytoin, and 9.7% for valproic acid.[99]

An Australian pregnancy registry has combined prospective and retrospective data in an unusual approach. They have reported in oral platform sessions at the American Epilepsy Society meeting in 2004 on 565 completed cases. They reported a 15% malformation rate with valproate monotherapy, with higher rates seen with doses above 1,100 mg/day.[94]

A registry from the United Kingdom reported on 3,607 pregnancies. The malformation rate was 3.7% for those exposed to monotherapy and 6.1% for those exposed to polytherapy. There were higher rates of malformations in polytherapy with valproate than without (OR 2.49). Carbamazepine monotherapy exposures resulted in the lowest malformation rates (2.1%), followed by gabapentin (3.7%), lamotrigine (3.5%), phenytoin (4.1%), and valproate (6.1%).[60]

Summary and Conclusions

Those who care for WWE face a dilemma. Seizures need to be prevented, but fetal exposure to anticonvulsant drugs needs to be minimized. Though it might appear that the ideal situation would be to withdraw the patient from anticonvulsants prior to conception, for most women this is not a realistic option. Women today are more likely to be employed and the potential disruption of their lifestyle by seizures, such as the risk of loss of driver's license, makes elimination of anticonvulsants impractical. More importantly, maternal seizures increase the risk of injury, miscarriage, epilepsy in the offspring, and developmental delay.

The major organ systems have formed by late in the first trimester. The posterior neuropore closes by day 27 and the palate by day 47 of gestation. By the time most women realize they are pregnant, malformations already may have developed. WWE of childbearing age need to be informed of the risks of pregnancy associated with anticonvulsant use prior to conception if possible. They also need to know that seizures can be harmful to the mother and fetus, and that risks can be reduced with proper care.

Many people appear to be unaware that even healthy parents have a 2% to 3% risk of having a child with a malformation. Given the current state of the art, the best we can do is practice risk reduction. In general, risks can be minimized by the preconceptual use of multivitamins with folate, the use AEDs in monotherapy with the lowest effective dose, and the prevention of maternal seizures. Monitoring free drug levels both prior to and during pregnancy will permit accurate assessment of concentrations in a situation where plasma protein binding is in flux. Dose adjustment, however, should be made on a clinical basis. Plasma anticonvulsant drug concentrations will fall in pregnant women, but only a quarter to one third will have an increase in seizures. We tend to keep dosage as low as possible during conception and organogenesis, but will often raise dosage during the third trimester to reduce the risk of seizures during labor.

Supplementation with at least 0.4 mg/day of folate is recommended by the Centers for Disease Control and Prevention for all women of childbearing age, whether or not they have epilepsy.

Vitamin K1, 10 mg/day, should be initiated late in the third trimester to prevent neonatal hemorrhage. We usually prescribe it during the final month of gestation.

Breastfeeding is generally safe in term infants as they have been exposed to the AEDs for 9 months and have induced their hepatic microsomal enzyme systems. However, breastfeeding should be done cautiously by women receiving phenobarbital or primidone due to the risk of infant sedation.

Pregnant women taking valproate should avail themselves of the prenatal diagnostic techniques of ultrasound and *a*-fetoprotein measurement. Ultrasonography has become much more accurate and in experienced hands can identify the vast majority of structural defects. Current prenatal testing recommendations are as follows:

1. Anatomic ultrasound at 11 to 13 weeks. This can identify the most severe defects such as anencephaly.
2. Maternal serum *a*-fetoprotein
3. Repeat anatomic ultrasound at 16 weeks. This can identify abnormalities such as orofacial clefts, heart defects, and caudal neural tube defects.

When WWE initially present to their neurologist pregnant, their gestational age (GA) needs to be established with reasonable accuracy. One cannot rely on last menstrual period (LMP) alone; an early ultrasound should be obtained to date the pregnancy. Once GA is established, a calendar can be planned with dates for monthly AED level checks, prenatal testing, and initiating vitamin K supplementation determined ahead of time.

The management of women with epilepsy presents unique challenges. Confirmation of diagnosis and verification of the most appropriate AEDs for the individual are the starting points. With effective patient education and careful and consistent management, including a coordinated treatment plan with both neurologist and obstetrician, these patients can and do have successful pregnancies and healthy offspring. Neural tube defects are serious malformations lacking effective therapeutic interventions. Their risk can be reduced by careful management and theoretically eliminated by prenatal diagnosis and therapeutic abortion. In our role as advisors, we need to recognize that all patients may not share our value systems or even begin to perceive what it really means to care for a child with an NTD. Physicians must be sensitive to their patients' anxieties and be prepared to manage not simply their seizures, but also their emotional concerns.

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Chapter 199

Overview: Psychiatric Issues

Michael R. Trimble

Introduction

The links between epilepsy and psychiatry have a long and respectable history, but for reasons best deliberated on by historians, the growing gap between neurology and psychiatry in the 20th century led to a considerable divergence of opinion as to the relationships between psychiatric disorders and epilepsy. Part of this confusion was due to the eventually almost exclusive psychological approach taken to neuropsychiatric disorders by psychiatrists, and the relative neglect by neurologists of behavior problems that could be associated with neurologic disorders. Further, in the field of epilepsy there was confusion over the distinction between seizures and epilepsy. Many people equated the two, but seizures as signs and causing symptoms are quite distinct from the underlying pathologic process of the epilepsy. The ongoing interictal electrophysiologic disturbances, which presumably reflect on underlying electrochemical aberrations within the brain that are easily identifiable by various imaging techniques, may be expected to lead to continuing disturbances of cerebral function. If these occur in areas of the central nervous system that have an impact on emotion and behavior, then psychiatric disturbances may be the expected outcome of at least some people with epilepsy, depending upon the site and type of the underlying epileptic discharge.

By the midpoint of the 20th century, it was a strongly held view, particularly in the United States, that people with epilepsy, if they had psychiatric difficulties, had them because of secondary factors. These included not only the stigmatization of having a terrible condition such as epilepsy, with such a poor quality of life and considerable social disadvantage (which was known to occur then and still occurs now), but also drug factors (remembering that phenobarbitone was commonly employed in those times) or, for example, cerebral trauma from head injuries following seizures. The concept that the underlying neurologic disturbance that led to the epileptic seizures could also provoke psychiatric problems was hard for many to accept.

There was, however, a slowly growing literature that emphasized not only the possible neurologic underpinnings of psychiatric disorders generally, but also the psychiatric complications of neurologic disorders, including epilepsy. From a purely anatomic point of view, the unraveling of the concept of the limbic system, from the earlier circuitry proposed by Papez to the later, more sophisticated elaborations of people such as MacLean, emphasized that within the brain there were neuronal structures and circuits that had specifically to do with modulation of emotion. This was a new idea, because before the development of the limbic system concept, there was no clear cerebral framework for an understanding of how the brain felt and expressed emotion. It was crucial to elaborating on the link between epilepsy and emotion to realize that two key limbic structures, the hippocampus and the amygdala, were frequently involved in the underlying pathology of epilepsy, particularly in the localization-related epilepsies, and newly developed techniques of recording from sites within the brain revealed that in between seizures, interictal abnormalities were recorded from such structures. More recently, the uncovering and elaboration of the direct associations between medial temporal structures and limbic forebrain structures and the unraveling of the neuroanatomy of the limbic forebrain by authors such as Heimer et al. have given clear neurologic underpinnings for an understanding of the behavioral consequences of neurologic disorders, epilepsy being no exception.[1]

However, understanding the neuroanatomy in more detail is not sufficient. It is clear that people with epilepsy, like anybody else, can have a straightforward psychiatric problem. A number of these are classifiable in terms of standardized diagnostic schedules (for example DSM-VI or ICD-10) and, when present in people with epilepsy, should receive the same amount of attention for management as they would if the patient did not have epilepsy. However, the contention of the last 30 or so years has been that there are some psychiatric problems that are more intimately imbedded within the context of the underlying neurobiologic process of the epilepsy.

This underlying neurobiology of the behavior disorders is discussed at the very outset of this section. The first chapter essentially makes the point that at least some of the psychiatric presentations are potentially directly interwoven with either the ictus or the interictal neurologic changes, this underlying neurology giving a particular stamp to the clinical presentations that lead them to differ somewhat from the psychiatric presentations diagnosed in the absence of the underlying neurologic disorder.

A further complication arises from the fact that the patients with epilepsy who are most liable to psychiatric disorders are those who are treated with antiepileptic medications chronically, often with polytherapy, and the medications themselves can contribute considerably to some of the ongoing symptomatology. This includes not only some of the more florid psychotic presentations, but also one of the most interesting phenomena in neuropsychiatry, namely, the precipitation of a psychiatric disorder when an antiepileptic drug is prescribed and seizures are suddenly turned off (referred to as forced normalization—the Landolt phenomenon). Equally important, however, are the subtle changes of mood and cognition that can be induced by antiepileptic medications. These matters are noted in several of the following chapters, but need specific highlighting for certain populations, such as those with learning disorders. They form a vulnerable group for the development of behavior disorders, but often their management falls short of the optimum. This may be due to some physicians failing to recognize that patients with learning disorders and seizures do have epilepsy! It may be missed or dismissed on the grounds that this population of patients somehow lies outside of the neurologic limit. With language and motor abnormalities, their

psychopathology is sometimes simply not recognized. A second group that requires special consideration is children. The spectrum of clinical psychopathology is different in younger patients with epilepsy, and the management of such patients also requires different treatment strategies and agencies.

Some of the psychiatric disorders seen in people with epilepsy (e.g., the postictal psychoses) are simply not found in standardized diagnostic manuals for psychiatric disorders, and yet their presentation is highly characteristic and will be found only in people with seizure disorders. Other more subtle neuropsychiatric complications of epilepsy, including the schizophrenialike interictal psychoses (of Slater) and the interictal dysphoric disorder (of Kraepelin and Blumer), have been harder to define, but are now recognized as epilepsy-specific presentations, even if still requiring more elaboration and validity testing. To a large extent, these presentations no longer arouse the controversies that they used to in the past. A more vexed problem is the issue of the interictal personality disorder, particularly as it was described by Waxman and Geschwind in the 1970s.[3] At that time neurologists were becoming cognizant of the fact that patients with frontal lobe damage could develop personality changes reflective of the injuries, and the term *frontal lobe personality disorder* began to appear in neurologic texts. Further, with regard to the temporal lobes, the Klüver-Bucy Syndrome was described, initially in animals but then in patients, with central features to this being alterations of personality with taming of the emotions, alteration of spontaneity, and changes of mood and social behaviors. Thus, it does not seem out of keeping with the growing knowledge of clinical behavioral neurology, and the elaborations of the neuroanatomy of the limbic system, that an interictal personality syndrome may be defined and consequent of temporal/limbic/neuroanatomic/neurophysiologic disturbances. In fact, descriptions of an interictal personality syndrome can be found in the European literature from well over a hundred years ago, but it was well codified by Gastaut and Geschwind. The main features of the disorder, such as hypergraphia and hyperreligiosity, are discussed in the relevant chapter, but other, perhaps even more controversial topics such as the links between aggression and epilepsy are given appropriate space.

Geschwind et al. and followers gave to us the term *behavioral neurology*, essentially an offshoot of 19th-century neuropsychiatry. The paper that introduced the interictal personality syndrome pushed the field in new directions, as it touched on behaviors not usually discussed in neurologic circles (e.g., creativity and religiosity). Although the characteristics of the interictal personality disorder are now very well known, there are still many neurologists, even epileptologists, who find it hard to see the specimen when it flutters before them to be pinned down. In part, this still reflects on that confusion between seizures and epilepsy, which still in the minds of many remains conceptually muddled.

It is important that whatever the clinical problem, patients receive appropriate psychiatric care where necessary. At least part of this will involve psychopharmacology, and therefore, chapters on management and treatment of these problems are also included. All the chapters in this section emphasize the importance of recognizing c-morbid psychopathology in people with epilepsy. If the seizure is considered to be the only problem that patients face and the comorbidities are ignored, then an appropriate schedule of management cannot evolve, and the patient's untreated psychopathology may well undermine the ongoing attempts to manage the epileptic seizures.

David Taylor, in his overview on psychiatric issues of the first edition of this textbook,[2] pointed out that there had been an overcorrection of emphasis from the epoch of psychoanalysis, with the rise of biologic psychiatry, and noted the complexity of trying to disentangle brain–behavior relationships in epilepsy. While the lesion within the developing brain, present at a time when the anlage of the developing personality is being laid down, will be influenced and in turn influences interpersonal and familial relationships, he noted how accommodation and compensation within a brain, which has such developmental skews, may appear to lead to effective ways of coping at certain stages of development but not at others. There is, as he said, "a need to consider the complex interaction, over the course of the development of the individual, among impairments of cerebral structure, disorders of cerebral function, psychological deficits, and the sort of family and peer group functioning within which these deficits interact." He drew clear distinctions between diseases, illnesses, and predicaments, which bear not only on common sense, but also on our clinical experience. By disease he meant evidence of dysfunctions that are more often nowadays revealed through, for example, brain imaging than through postmortem analysis. By illness, he referred to the limitations of functioning and suffering that people experience as a consequence of the underlying disease, and he noted that psychiatric problems essentially are illnesses rather than diseases. The importance is to understand the illnesses and the predicaments that they present to the person who is ill and his or her family. Helping people with their predicaments, trying to understand their illnesses, and attending to their underlying discernible disease are all parts of the complexity of the neuropsychiatry of epilepsy.

Summary and Conclusions

In the 21st century we now have a much clearer understanding of the underlying neuroanatomy and neurochemistry of psychiatric disorders in general, but also of why a number of neurologic disorders, in which neuroanatomic changes are identifiable in limbic and forebrain structures, may lead to a susceptibility to the development of psychiatric syndromes. There is an overlap between psychiatry and neurology, and epilepsy has always been central to discussions about this interface. Most neurologists now accept that psychopathology is an integral part of some epilepsy syndromes, whether it be memory disturbances and other cognitive difficulties or more florid psychopathologies as one may see, for example, in the psychoses. A substantial portion of this comprehensive textbook has been devoted to these behavioral problems, and it is hoped that the chapters in this section will be of interest and importance to both neurologists seeking understanding and psychiatrists seeking enlightenment.

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Chapter 200

Neurobiology of Behavioral Disorders

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Introduction

Many persons with epilepsy suffer from interictal disturbances in behavior* that can contribute significantly to their illness and in some cases constitute the major disability. Although there remains some controversy on this subject, it is generally accepted by most workers in the field that the degree of behavioral problems associated with epilepsy is greater than would be expected on the basis of the existence of a chronic illness alone, both in adults[40] and in children.[64] To a certain extent, the psychiatric consequences of epilepsy can be attributed to external factors, specifically the predicament imposed by epilepsy not only as a traditionally stigmatizing disorder but also because the unpredictable nature of recurrent ictal events allows society to impose rather severe limitations on activities of daily living.[63] In addition, however, there are legitimate neurobiologic explanations for interictal behavioral disturbances in this patient population, including (a) nonepileptic factors, such as effects of the underlying pathologic substrate itself; (b) the unwanted effects of medical and surgical treatment on cerebral function; (c) epileptic mechanisms consisting of unrecognized prolonged ictal events that are witnessed as interictal behavioral disturbances; and (d) the ability of recurrent epileptic activity to cause enduring changes in neuronal function.

The concept that epileptic seizures themselves can effect a persistent disruption of normal neuronal function leading to the appearance of interictal behavioral disorders is not new[10,17,18,20,21,54,59] but is still not completely accepted and is even adamantly rejected by many. One socially sensitive justification for the contrasting point of view is that there are already too many negative associations with epilepsy, so that to add the fear of becoming "insane," without definitive proof, would impose a further unnecessary burden. On the other hand, formal recognition that epileptic mechanisms *might* contribute to transient and enduring changes of both function and structure in the brain is necessary before investigation of this possibility can begin. Appropriately designed clinical and animal research could lead to interventions that would reverse or prevent a major cause of epilepsy-associated disability.

Nonepileptic Organic Causative Factors

Symptomatic epilepsies result from a variety of underlying pathologic processes that might be localized or diffuse, unilateral or bilateral, static or progressive. These can produce epileptic seizures as their only clinically apparent manifestation. However, they might also give rise to chronic neurologic or psychiatric deficits related to (a) the nature of the pathophysiologic substrate, (b) its precise location in the brain, and (c) the time of its occurrence with respect to brain development. In idiopathic epilepsies, there is no obvious structural pathology, but the genetic defect responsible for the spontaneous recurrence of epileptic seizures presumably produces a disturbance in neuronal responsivity, transmission, or wiring that is continuously present between seizures and could have other, nonepileptic functional consequences manifesting as deficits in learning and skills, as well as interictal behavioral disturbances. Although focused research on this subject cannot begin until the specific defective gene or its aberrant products have been identified, this hypothesis offers a plausible explanation for the association of certain mild behavioral disturbances with some of the idiopathic generalized epilepsy syndromes that have been supposed to be only epilepsy and nothing more.[28,52] All current antiepileptic drugs act nonspecifically to alter excitatory or inhibitory influences or reduce neuronal synchronization, processes that are critical to normal cerebral function.[32] It is not surprising, therefore, that pharmacotherapy can be associated with sedation, cognitive impairment, and a range of psychiatric disturbances.

A hitherto unanswered question is whether psychiatric syndromes associated with antiepileptic drugs are a function of prior risk (i.e., faulty organization): Why are some, but not all, persons affected? Among a group of affected persons, a variety of psychiatric disorders might be associated with the use of any particular medication. This suggests that the specific disorder induced in an individual is that to which they are most genetically liable. Monitoring of these responses on a multicenter basis could be helpful in elucidating not only the problem of drug-induced disorders, but also the mechanism of the psychiatric disorders concerned. Surgical treatment, whether resection, ablation, or disconnection, also disrupts normal neuronal integration and new neurologic or psychiatric disturbances can emerge subsequently, either at the point in development when they normally occur (e.g., schizophrenia) or in direct reaction to tissue damage (e.g., specific learning deficits). Effects of pharmacotherapy and surgical therapy on behavior are dealt with in Chapters 208 and 209 and are not considered further here.

Nature of the Lesion

Epilepsy that is attributed to a lesion typically develops after a prolonged latent period, although brain organization could be adversely affected much earlier. Discrete, well-localized structural epileptogenic lesions in so-called silent brain areas may cause no perceptible disturbances other than recurrent ictal events, but more extensive lesions are likely to impinge on critical cortical areas and be associated with some degree of

interictal impairment. Consequently, cognitive deficits and neurologic signs and symptoms commonly accompany epileptogenic substrates that tend to be diffuse or multifocal. Disorders such as tuberous sclerosis or cortical dysplasia can be sufficiently mild that only a single localized lesion is identified on magnetic resonance imaging (MRI), but chronic behavioral impairment could suggest, in these cases, the presence of much more widespread aberrations in neuronal migration and differentiation that are beyond the resolution of current imaging techniques. For other lesions, disturbances in cerebral function could reflect distant cerebral abnormalities of a related disorder; for instance, the high incidence of schizophrenia reported to occur in women with hamartomas and gangliogliomas[61] was postulated to be caused by a karyotype abnormality associated with ectodermal dysplasias and abnormal behavior.[49] Progressive lesions that continue to destroy or disrupt neuronal function are clearly more likely to give rise to interictal behavioral problems than static lesions, the latter of which permit recovery of function through compensatory mechanisms. For the same reason, rapidly progressive disease processes cause more interictal disturbances than slowly progressive ones. It is also conceivable that some neoplastic lesions could secrete neuroactive substances that influence interictal behavior, and some vascular lesions can cause nonepileptic signs or symptoms by bleeding or a steal phenomenon. Lesions that were thought to be static, such as hippocampal sclerosis, are now reported to be common sequelae of stress in its widest sense.[56] Thus, stress would be an important factor in the epilepsies and in psychiatric disorders.

The Location of the Lesion

The neurologic signs and symptoms produced by focal structural lesions depend on the function of the brain area involved. Discrete neocortical lesions in primary areas produce very localized deficits, whereas diffuse bilateral abnormalities cause cognitive impairment and more global dysfunction. Lesions of the limbic system are of particular interest in epileptology because they are the most likely to produce epileptic seizures and because these lesions are associated with much more varied interictal behavioral disturbances than lesions of neocortex.[35]

The most common deficit associated with lesions of the mesial temporal limbic system is impairment of episodic memory, which is usually material specific for the hemisphere involved.[41] This is more noticeable, and therefore more disabling, when the lesion is in the language-dominant temporal lobe, and there is usually an associated verbal learning disturbance. The limbic system, however, also plays a key role in modulating mood and affect, basic drives (including sexual function), and motivation, functions that, when distorted by structural or functional lesions, could conceivably give rise to virtually every behavioral aberration attributed to epilepsy, including specific psychiatric illnesses.

It is important to note that lesions in certain locations that are epileptogenic might be more likely to cause enduring disturbances referable to the normal function of that area than lesions that are purely ablative.[61] Because there is a certain degree of plasticity of brain tissue, even in the adult, destructive lesions can cause transient deficits that eventually recover as other brain areas take over the function. When the neuronal disruption is intermittent, however, as with epileptic seizures, it is possible that natural compensatory mechanisms are not activated, and recovery of function does not occur. Furthermore, epileptic discharges propagate and can disrupt function at a distance from the primary epileptogenic region, including contralateral structures. Consequently, specific temporal lobe or frontal lobe signs and symptoms that require bilateral homotopic dysfunction would not occur with a nonepileptic destructive lesion in one hemisphere but are commonly seen with unilateral epileptogenic lesions. The existence of secondary bilateral involvement and its reversibility are readily demonstrated following successful anterior temporal lobectomy, when material-specific memory referable to the contralateral temporal lobe subsequently improves and patients may experience an overall increase in IQ.[47,62]

Developmental Considerations

Classical neurology has an adult perspective. Its premise is of some fault or accident that disrupts a previously normally functioning central nervous system (CNS). The lesson of epilepsy has been that the faults are often early prenatal or late prenatal or early postnatal, but the problem of interest (the epilepsy or the cognitive capacities or the behavior) becomes “eloquent” at some later stage. Models of this exist in syphilis, encephalitis, rheumatic heart disease, Huntington chorea, and many other conditions. The developmental perspective is to consider the possibility that the lesion or fault could have been “eloquent” in other ways before the condition of interest arose or could become “eloquent” in those ways later in development. This removes a need for thinking that a chronic lesion that arose in embryonal life has somehow acquired new powers at age 14 (or whenever) because “it has started to cause epilepsy.” It allows consideration that the condition of interest (e.g., epilepsy) arises from a constellation of circumstances that have not existed previously, a combination of aging and maturation together with hormonal and psychosocial factors.

Ordinarily, localized destructive cortical lesions that occur early in the course of development are less likely to cause lasting deficits than lesions occurring in later life because of the increased plastic potential of the immature brain. For instance, patients with extensive damage to the left hemisphere incurred within the first few years of life usually have a pathologic compensatory shift of language dominance to the right hemisphere, with little or no disturbance in speech or language.[48] On the other hand, more diffuse bilateral lesions occurring early in life are usually accompanied by a developmental delay that persists into adulthood. Taylor,[62] however, challenged functional shift as the only basis of handedness change, because alien tissue lesions are associated with left handedness whether they are in the left or right hemisphere. He suggested that an alien tissue lesion could act by reducing the effect of the gene for right-handedness bias. If this is confirmed in other studies, it would help our understanding of prenatal organization of cerebral functions.

As mentioned in the previous section, epileptogenic lesions may be more likely to produce a lasting effect on behavior than destructive lesions because intermittent disturbances could confound compensatory recovery processes. This appears to be particularly true during the period of cerebral development. Furthermore, the widespread electrical epileptiform electroencephalogram (EEG) abnormalities that characterize certain epileptic syndromes in infancy and early childhood, such as West syndrome, can reflect propagation of discharges from a localized epileptogenic lesion that also produces the same global behavioral disturbances usually associated with a diffuse bilateral destructive lesion. The evidence for this comes from the observation that some infants and small children with developmental delay who initially appear to have catastrophic secondary generalized epilepsy actually have a single lesion localized to one hemisphere, and surgical removal of this area not only eliminates the ictal events, but also helps to reverse the developmental delay.[53]

Epileptic Causative Factors

Unrecognized simple partial status epilepticus causes behavioral disturbances that can be mistakenly labeled "interictal," and prolonged convulsive status epilepticus can cause brain damage. There is an abundance of evidence for epilepsy-induced enduring functional disturbances from well-described phenomena in experimental animals.[10,14] The confounding effects of the pathologic process responsible for the epileptic condition on behavior and the effects of antiepileptic drugs, which are invariably present, make it extremely difficult to demonstrate, in a clinical setting, that recurrent, transient epileptic events alone can cause interictal behavioral disturbances.[59] If such changes do occur in patients, undoubtedly they are more likely to result from some types of epileptic abnormalities than others, and conceivably there are also ictal and interictal epileptiform events that pose no risk for persistent dysfunction. For this reason, it would be inappropriate to suggest that all epileptiform abnormalities are capable of inducing enduring neuronal dysfunction or that all epilepsies have the potential of being progressive in some way. On the other hand, it is of great practical importance to make every effort to document the occurrence of such epilepsy-induced behavioral disorders in patients in order to determine what types of seizures and epileptic syndromes are likely to give rise to persistent problems and at what point in the course of these conditions the disturbance might become irreversible. Such information would provide essential guidelines for early aggressive intervention in patients who are deemed to be at risk.

Unrecognized Prolonged Ictal Events

One inarguable cause of an inappropriate diagnosis of "interictal" behavioral disturbances, although perhaps rare, is nonconvulsive status epilepticus. Simple partial seizures of limbic origin can cause virtually any psychiatric sign or symptom in clear consciousness, and the scalp EEG in this condition is almost always normal.[71] Sensory symptoms caused by simple partial status epilepticus of neocortical origin can give rise to bizarre experiences that are acted on in strange ways to create a persistent interictal behavioral disturbance. These forms of simple partial status epilepticus (also called aura continua) are easy to recognize when they occur in patients with known epilepsy, and the ongoing signs and symptoms match those of the habitual simple partial seizures (auras) that usually precede more obvious ictal events. In patients who have never had an obvious epileptic seizure and who have a normal EEG, this diagnosis would be exceedingly difficult. Rapid reversal of signs and symptoms with intravenous benzodiazepines suggests, but in no way proves, a diagnosis of epilepsy because many nonepileptic conditions can also transiently respond to this treatment. Complex partial status epilepticus and absence status can also rarely be mistaken for a psychiatric condition when the clouding of consciousness is subtle. EEGs in these conditions, however, reveal the diagnosis, although sometimes only after extreme persistence.[2]

In patients with known epilepsy and well-documented, frequent interictal EEG abnormalities, the only surface EEG correlate of a simple partial seizure is, classically, disappearance of the interictal EEG spike. For instance, in temporal lobe epilepsy, a simple partial seizure is associated with an ictal discharge in mesial temporal lobe structures, which are then no longer able to generate interictal spikes that ordinarily would propagate to temporal neocortex and appear on the scalp EEG. Consequently, disappearance of the typical interictal EEG spike pattern in a patient with persistent behavioral disturbances could be used as supportive evidence for simple partial status epilepticus. Indeed, one postulated explanation for Landolt's so-called "forced normalization"[31] (the occasional observation that the EEGs of some patients with known epilepsy normalize during episodes of psychosis) is that the behavioral disturbance is actually simple partial status epilepticus.[72]

Epileptic Brain Damage

Another incontestable consequence of epileptic seizures is cell death from the excitotoxic effect of excessive release of excitatory amino acids during status epilepticus.[59] It is well known that susceptible cerebral structures, particularly the hippocampus, undergo irreversible damage in patients after prolonged convulsive status epilepticus, and studies in experimental animal models show that this occurs even when cerebral perfusion, ventilation, and normothermia are preserved.[39] Much is now known about the cellular mechanisms of excitotoxic cell death, but it is unclear whether (and if so, to what extent) this occurs in human epilepsy apart from the severe insult associated with convulsive status epilepticus.[59] Excitotoxic effects are associated with massive calcium influx, which may be insufficient to cause cells to die but, rather, turns on genetic mechanisms that could profoundly alter cell structure or function, perhaps inducing transsynaptic changes at a distance from the epileptogenic lesion. Such a mechanism could provide a ready substrate for persistent interictal behavioral disturbances.

Hippocampal sclerosis, believed to result, at least in part, from processes inducing excitotoxic cell death, has been associated with behavioral disturbances described mainly in terms of effects on personality, with evidence of immaturity, irritability, and trivial aggression, at that time recorded as psychopathy.[60,66] Hippocampal sclerosis has been shown to follow from conditions other than prolonged febrile convulsions, such as trauma, that occur early in life.[36] It is intriguing that there is now also considerable literature on the deleterious effect of high levels of cortisol, produced in response to stress, on the developing hippocampus.[56] It is possible that hippocampal sclerosis arising from prolonged febrile convulsions is a unique syndrome. Various other mental states have been associated with hippocampal sclerosis, including schizophrenia[7,42,58,69] and depression.[33,60] The behavioral syndrome associated with mesial temporal lobe epilepsy is subtle and deserves more research.[5,70] The immaturity, irritability, rigidity, stickiness, hypergraphia, and hyperreligiosity that most often are mentioned with this syndrome are, importantly, relieved by successful mesial temporal resection and disappear rapidly over the first 2 or 3 postoperative years.[66] Because the treatment is ablative, the effect must be through relief of seizures and/or obliging the rest of the limbic system to take over the tasks of the ablated tissue. Psychological evidence[47,62] suggests that successful surgery leads to generally improved functioning in other domains, too.

Kindling and Secondary Epileptogenesis

Although kindling[23] and secondary epileptogenesis[43] are extremely well documented in the animal laboratory, their relevance to human epilepsy remains controversial.[24,44] In virtually all vertebrate animals tested, from frogs to subhuman primates, subthreshold stimulation of susceptible limbic and neocortical structures, when repeated at appropriate intervals, gives rise to epileptiform EEG and behavioral abnormalities that become increasingly prolonged and severe, and eventually, spontaneous seizures occur. This phenomenon has been demonstrated with both electrical and chemical stimulation; there is crossover from one stimulation modality to the other, and the effect is persistent, at least to some degree, for as long as the animal is subsequently tested. The kindling paradigm brings under experimental control the more naturally occurring process of mirror focus development,[43] whereby a region capable of generating spontaneous epileptic seizures gradually develops contralateral and homotopic to an experimental epileptic focus, presumably as a result of continuous bombardment of epileptiform discharges across the corpus callosum. Nevertheless, despite years of research, there remains debate about the existence of significant secondary epileptogenesis in humans.

Some studies of patients undergoing surgical treatment for brain tumors provide evidence for mirror focus development,[44] and similar secondary epileptogenesis may account for the inverse relationship between duration of epilepsy and surgical outcome reported for anterior temporal lobectomies.[15] But the abrupt cessation of seizures and abnormal electrical discharges after successful surgery on patients who have had years of apparent provocation of secondary foci requires us to keep the issue open. There are a few scattered reports of seizures in patients following repeated brain stimulation that might mimic electrical kindling.[55] In a more general sense, the latent period between the occurrence of an epileptogenic insult and the appearance of spontaneous epileptic seizures that commonly occurs in humans,[29] what Penfield and Jasper[45] referred to as “ripening of the scar,” has been taken as evidence that some kindling process is necessary for seizures to occur spontaneously.[22] In some cases, however, this could reflect the time required to reach the stage of cerebral and physical development necessary to support the manifestations of seizures.

Whether or not kindling and secondary epileptogenesis occur in the human brain to produce additional independent epileptogenic areas, the fact that such activity-induced changes occur at all in the mammalian brain strongly suggests that they could also exist to some extent in the human epileptic brain. The exact mechanisms underlying these functional or structural transsynaptic changes are unknown; however, they must have some effect on normal neuronal function and certainly could provide a substrate for the development of interictal behavioral disturbances.[16]

One example of how kindlinglike modulatory influences could alter interictal behavior comes from studies of defensive rage in cats.[3] This is a stereotyped behavior that can be induced by electrical stimulation of hypothalamus or periaqueductal gray. The manifestations of stimulation-induced defensive rage can be modified by stimulation of the amygdala and hippocampus, and establishment of an experimental hippocampal epileptic focus not only exacerbated stimulation-induced defensive rage, but also caused this behavior to appear spontaneously in response to rough handling.[25] In the human, such “hard-wired” affective displays come under cortical control and may be more likely to manifest not as rage but as modified responses such as impulsiveness, depression, or other more socially acceptable, albeit disturbing, behaviors.

Another experimental example of kindling-induced interictal behavioral disturbances also derives from studies of cats that showed an enduring enhancement of methamphetamine-induced stereotypy following amygdala kindling.[51] This observation was interpreted to reflect a persistent up-regulation of dopamine receptors that could be another mechanism for the development of psychiatric disorders in patients with epilepsy.

The effect of kindling may depend upon the pre-existing affective state. For instance, amygdala kindling can reduce the manifestations of anxiety in high-anxiety rats, but exacerbates anxiety in low-anxiety rats.[1] The kindling effects of epileptiform discharges in patients with epilepsy, therefore, may depend not only on the location and type of the epileptogenic abnormality, but also on the predisposing behavioral state of the patient.

Some of the personality traits attributed in the literature to patients with temporal lobe epilepsy, such as hyposexuality and emotionality,[5,6,70] have been interpreted as being the opposite of the Klüver-Bucy syndrome[20]; changes in behavior, including taming and loss of affective responses, caused in primates by bilateral amygdalectomies; and seen in humans sometimes following head injuries or with certain dementias. One explanation for this effect could be a kindlinglike enhancement along amygdala projection fields.

Behavioral Effects of Natural Seizure-suppressing Influences

There are numerous inhibitory processes and other seizure-suppressing mechanisms that develop as a homeostatic reaction to the occurrence of epileptic seizures and presumably act to maintain the interictal state. These include the so-called inhibitory surround that limits the spread of localized epileptic activity,[46] the interhemispheric interference that opposes the development of secondary epileptogenesis,[38] and a variety of active mechanisms that terminate epileptic seizures.[8,12] These protective mechanisms persist between seizures and undoubtedly affect normal neuronal activity, conceivably contributing to the development of interictal behavioral disturbances.

Clinically, postictal changes are well documented, ranging from localized Todd paralysis[13] to profound global dysfunction following a generalized convulsion. In some patients, postictal behavior can involve complicated actions, such as the reactive automatisms that follow complex partial seizures, and may result in inappropriate semidirected responses, such as aggression toward someone attempting restraint. Other patients experience postictal psychosis.[6] It is easy to see how these behaviors, if persistent, could explain certain interictal disturbances. Such manifestations were evident in Hughlings Jackson's paradigmatic case of temporal lobe epilepsy, Dr. Z,[67] who diagnosed “pneumonia at the left base” in one of his own patients while totally amnesic after a seizure, a diagnosis that proved correct when he re-examined the child later.

Endogenous opioids are released during some types of epileptic seizures[27] and help to terminate seizures[8] but are also believed to be natural euphorogens, perhaps explaining the therapeutic effect of electroconvulsive shock therapy on clinical depression.[30] Also, there are people who feel much better after they have had a seizure, and parents who, enduring the escalating behavioral problems of their children between seizures, the so-called prodrome, look forward to the positive changes the seizure will bring. Opioid peptides have been shown to mediate several different postictal behaviors in rats, but the mechanisms are complicated. Whereas postictal hypofunction appears to be caused by a direct opioid effect, postictal explosive behavior is more likely the result of opioid withdrawal.[8] Different postictal behaviors appear to be mediated by different cerebral structures because seizures in rats increase opiate release in some brain areas and decrease opioid release in others.[50] Enduring changes in opiate mechanisms clearly occur in some patients with epilepsy, as shown by positron emission tomography (PET) evidence of increased μ-opiate-receptor binding in the neocortex of the epileptogenic temporal lobe.[19] If endogenous opioids are released in some brain structures during seizures and contribute to the appearance of postictal behaviors, it is conceivable that some patients could become dependent on high levels of endogenous opiates when they are having seizures and experience some degree of withdrawal when seizures stop. This might explain the transient depression that is often seen following successful surgical treatment of epilepsy.[14] The fact that depression can also be a side effect of antiepileptic drug treatment suggests that the same withdrawal phenomenon

following successful pharmacotherapy could contribute to what has largely been interpreted as a direct effect of medication on mood and affect.

Developmental Factors

Recurrent epileptiform discharges that disrupt function at a distance in the immature brain might interfere with critical phases of development and result in lasting behavioral disturbances.[16] Experimental evidence for epilepsy-induced disruption of normal development derives from a series of elegant experiments that demonstrated that lateral geniculate neurons in rabbits fail to acquire normal visual receptive properties when a chronic epileptic focus is created in the visual cortex to which they project.[4,9] Whether normal neuronal functional integration of the lateral geniculate body is disrupted by antidromic “backfiring” of the epileptiform discharges from visual cortex or orthodromic propagation from cortical neurons that feed back on the geniculate is not known. Conceivably, both mechanisms can influence behavior transiently and presumably effect more persistent functional or even structural changes. The reversibility of the noxious effect of epileptogenic tissue in the immature brain on distant normal structures, at least early in the course of the process, has been demonstrated by the observation that developmental delay is reversed in patients with infantile spasms caused by a unilateral localized lesion when resection of this lesion eliminates the habitual seizures,[53] as discussed earlier in this chapter.

There is a long history to the relationship between epilepsy and psychosis, particularly schizophrenia. Nonpsychiatrists should be aware of major changes in nomenclature, vocabulary, and interpretation that have taken place over the last 50 years when reading older texts.[34,69]

In the 1960s, the dominating influence was a paper by Slater and Beard,[54] some 50 pages long, showing a close association between epilepsy and “schizophrenialike” psychosis. (The label “schizophrenialike” was necessary because everyone important “knew” that schizophrenia was a functional disorder.) Falconer had operated on 16 such patients before deciding that the balance of benefit from surgery was such that it was not appropriate to continue. Taylor[61,62] showed that those patients, with chronic schizophrenic symptoms, were characterized by excesses of (a) females, (b) onsets of epilepsy at ages 5 to 15, (c) left handedness, and (d) alien tissue lesions (e) in the left temporal lobe. This unique material allowed him to suggest that brains that suffered schizophrenia had been biased from embryonal, prenatal life and had required compensations in the organization of speech and language that later proved to be problematic when the normal condensation and shifts in the organization of language occurred. This developmental hypothesis arose from the excess of prenatally acquired lesions, the excess of left handedness, and the relative excess of girls, whose language organization is different from that of boys. The emergence of a neuropathologic basis for schizophrenia in people without epilepsy tends to confirm these findings from patients with epilepsy.

It seems probable, in hindsight, that the benefit of surgery to these patients was underestimated and that their life situations and lack of appropriate modern management contributed to continuing chronicity of their psychoses.

Normally excluded from consideration is the whole issue of autisticlike syndromes and various degrees of language regression associated with Landau-Kleffner syndrome, continuous spikes and waves during slow sleep, and West syndrome. Because about a third of children with autism develop epilepsy, the association deserves urgent research. Taylor et al.[65] reported, in the Great Ormond Street series of patients considered for surgical treatment, a sequence of male children, mostly with dysembryoplastic neuroepithelial tumors of the right temporal lobe, who exhibited marked autistic features. Subsequently, a larger number of children with other lesions have been recruited to that series.[37]

Effects on Sleep and Endocrine Function

There is considerable evidence from both the animal and the clinical literature that certain types of epileptic seizures cause chronic disruption in sleep organization, particularly a reduction in rapid eye movement (REM) sleep.[57] It is well known that REM sleep deprivation can produce behavioral disturbances, including psychosis,[11] so the possibility that this could be an indirect means by which some forms of epilepsy produce lasting interictal disturbances in behavior needs to be further investigated.

Another potential source of epilepsy-induced interictal behavioral problems that has not been adequately pursued relates to the effect chronic epileptic seizures have on endocrine function.[26,68] Seizures are associated with release of prolactin and other hormones, altering diurnal fluctuations and absolute levels in brain and blood, which could have dramatic effects on behavior and might, for instance, account for the sexual dysfunction seen in some patients with epilepsy.

Summary and Conclusions

Suffering from epilepsy is not limited to having seizures. Indeed, it has to be emphasized that seizures are not the same as epilepsy, and are but one manifestation of the underlying neuroanatomic/neurophysiologic changes that represent the latter. The brain has a problem to deal with and is dealing with it all the time. Whether by developmental anomaly, scar, tumor, or the effect of trauma, the process by which persons come to declare their brain abnormality by having noticeable epileptic seizures will have originated at some point in time before that manifestation, and it is clearly present between each noted seizure. There are other ways in which the brain problem can manifest itself, such as gross or minor neurologic signs and, we argue, gross (or minor) behavioral signs and learning problems. The various expressions of the brain problem will not be constant over time. Just as seizures are not constant over time and are often reactive to circumstance, so too the behavioral problems are not constant and are reactive. Even severe psychoses can come and go. Medications will also affect the chemical manifestations of the brain problem, but so will other natural physiologic processes. As the brain changes radically over development, and those changes are often reflected in the scale, type, and frequency of seizures, so too the behavioral manifestations will change during the course of development. Furthermore, seizures can alter brain function in a manner that influences behavior just as behavior influences seizures. Behavioral changes are important because they are clinically relevant, but there is important research to be done not just on the mental states of people with epilepsy, but also in understanding these mental states, behavioral changes, serious psychoses in general, and their causes, using the models provided in the animal laboratory and by people with epilepsy.

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Chapter 201

Cognitive Side Effects of Antiepileptic Drugs

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Introduction

Cognitive impairment is the most common comorbid disorder in epilepsy.[13,28] Memory impairments, mental slowing, and attentional deficits are the most frequently reported cognitive disorders.[14,29] Such consequences may be more debilitating for a patient than the seizures; thus, it is worthwhile to explore the factors that lead to cognitive impairment. The exact cause of cognitive impairment in epilepsy has not been explored fully, but three factors clearly are involved: Etiology, the seizures, and the "central" side effects of drug treatment.[3] In this chapter we will concentrate on the unwanted effects of antiepileptic medication on cognitive function. When evaluating this factor separately, it is imperative to realize that in clinical practice most cognitive problems have a multifactorial origin and that, for the most part, the three aforementioned factors, combined, are responsible for the makeup of a cognitive problem in an individual patient. Moreover, the factors are related, which causes therapeutic dilemmas in some patients when seizure control can only be achieved with treatments that are associated with cognitive side effects.

The interest in the cognitive side effects of antiepileptic drug (AED) treatment is of recent origin. The possibility that cognitive impairment may develop as a consequence or aftermath of epilepsy was raised as early as 1885 when Gowers described "epileptic dementia" as an effect of the pathologic sequela of seizures. Nonetheless, the topic was not coupled to AED treatment until the 1970s,[27,38] probably stimulated by the widening range of possibilities for drug treatment during that period (i.e., the introduction of carbamazepine and valproate). Since then, a plethora of studies have been published, the majority on the commonly used AEDs: valproate (VPA), carbamazepine (CBZ), and phenytoin (PHT).

In the last decade, several new AEDs have been introduced. Although it is claimed that these drugs have different efficacy profiles and that some drugs are particularly efficacious in specific syndromes (e.g., vigabatrin [VGB]), head-to-head comparisons between the newer drugs and the commonly used drugs (such as CBZ and VPA) are rare. The types of studies used to investigate the newer AEDs are summarized in Table 1. Nonetheless, meta-analyses such as the influential Cochrane reviews[39,54] do not show significant differences in efficacy between these newer and commonly used drugs. Also, studies analyzing long-term retention do not show differences between the drugs.[78,90] Several studies have shown retention rate to be the best parameter of the long-term clinical usefulness of a particular drug.[47] Retention rate is considered to be a composite of drug efficacy and drug safety and expresses the willingness of patients to continue drug treatment. It is therefore the best standard for evaluating the clinical relevance of side effects. The 1-year retention rate is reported not to be higher than 55% for topiramate (TPM),[41] 60% for lamotrigine (LTG), 58% for VGB, and 45% for gabapentin (GBP).[53] Long-term (mostly 3-year) retention is about 35% for all newer AEDs.[52] Side effects appear to be the major factor affecting long-term retention for most drugs.[4,22] In clinical practice, tolerability is therefore a major issue and the choice of a certain AED is at least partially based on comparison of tolerability profiles of the drugs. Also, the tolerability profiles of the newer drugs have become a more important issue in drug development, stimulated by the interest of regulatory agencies.[4] Cognitive side effects have been demonstrated to be one of the most important tolerability problems in chronic AED treatment.

Method

In evaluating studies of the cognitive effects of AEDs, we will follow an evidence-based approach.[12,87] Randomized clinical trials with monotherapy in patients with newly diagnosed epilepsy represent the most accurate procedure for assessing the cognitive impact of AEDs.[4] These studies are not clouded by the effect of concurrent or previous AED use and permit the accurate collection of nondrug baseline data that is required for determining whether a particular treatment affects cognitive processing (i.e., to isolate drug-induced impairments from those due to other sources such as the seizures). Data from such studies can be supplemented with information from studies using add-on or polytherapy designs. In these studies, the use of two AEDs makes identifying the components of the treatment that are responsible for the observed effects more complex. In many cases, however, patients with epilepsy require dual AED therapy before adequate seizure control is obtained; therefore, data from add-on studies does warrant consideration. Also, data from healthy volunteers should be treated with caution. In general, the power of such studies is limited by small sample sizes, and drug exposure periods are typically brief. It is possible that chronic treatment results in entirely different types of cognitive impairment that cannot be observed during short-term treatment. For example, such differences in side effect profile between acute and long-term administration have been found with PHT. Finally, the differing cerebral substrate in patients with epilepsy and healthy volunteers suggests that cognitive responses to AEDs may be different in these populations. Nonetheless, volunteer studies may provide an early insight into the cognitive effects of an AED and therefore provide a foundation for further studies in patients with epilepsy (see reference 87 for a discussion of methodologic aspects of cognitive drug trials in epilepsy).

Table 1 Type of Study to Investigate the Cognitive Side-Effects of Newer AEDs

AED	Volunteer studies	Controlled studies in patients with newly diagnosed epilepsy	Add-on clinical studies in patients with epilepsy
OXC	Curran & Java (1993)	Laaksonen et al. (1985) Sabers et al. (1995) Äikiä et al. (1992) McKee et al. (1994)	
TPM	Martin et al. (1999)	Donati et al. (2006)	Meador (1997) Aldenkamp et al. (2000) Burton & Harden (1997) Bootsma et al. (2004) Thompson et al. (2000) Fritz et al. (2005)
LTG	Cohen et al. (1985) Hamilton et al. (1993) Martin et al. (1999) Meador et al. (2000)	Gillham et al. (2000)	Smith et al. (1993) Banks and Beran (1991) Aldenkamp et al. (1997)

	Aldenkamp et al. (2002)		
LEV			Neyens et al. (1995)
TGB		Dodrill et al. (1997)	Kälviäinen et al. (1996) Sveinbjornsdottir et al. (1994)
GBP	Martin et al. (1999) Meador et al. (1999)		Leach et al. (1997)
RUF			Aldenkamp and Alpherts (2006)

AED, antiepileptic drug; GBP, gabapentin; LEV, levetiracetam; LTG, lamotrigine; OXC, oxcarbazepine; RUF, rufinamide; TGB, tiagabine; TPM, topiramate.

Results

Phenobarbital

The main anticonvulsant mechanism of action is the increase of the duration (not the frequency) of the γ-aminobutyric acid (GABA)-activated chloride ion channel opening,[86] hence potentiating GABA-mediated inhibitory neurotransmission. Phenobarbital (PB) can also activate the $GABA_A$ receptor in the absence of GABA, which is sometimes considered to be a mechanism leading to its sedative properties. PB is used for the treatment of epilepsy since the discovery of its antiepileptic effect by Hauptman in 1912.

For PB one study[49] is available allowing the evaluation of the cognitive effects of PB relative to a nondrug condition. This study show relative serious memory impairment (short-term memory recall) in 19 patients with epilepsy.

Comparisons with other AEDs are available from four studies[21,35,60,88] of patients with epilepsy. One of these shows more impairment for PB than for PHT or CBZ on visuomotor and memory tests[35] and two other studies show convincing and clinically highly relevant impairments of intelligence scores after long-term PB treatment in comparison with VPA.[21,88] A randomized, double-blind, crossover study of healthy volunteers also found more impairment on some measures for PB compared to PHT and VPA.[61] Only the study by Meador et al.[60] does not show differences between PB and PHT or CBZ.

Phenytoin

The main anticonvulsant mechanism of action is use-dependent (voltage- and frequency-dependent) sodium channel blocking.[75] It binds to the fast inactivated state of the channel, reducing high-frequency neuronal firing. PHT has a stronger effect on the sodium channel than CBZ, delaying recovery stronger than CBZ. PHT may also have mild effects on the excitatory glutamate system and on the inhibitory GABA system. PHT has been used as an antiepileptic drug since it was introduced for the treatment of epilepsy in 1938 by Merritt and Putnam. For 20 years PHT was (together with PB) the universal treatment of epilepsy. PHT has excellent anticonvulsant properties and is used as a broad-range AED.

For PHT five studies are available[58,59,77,82,83] comparing PHT with a nondrug condition. These studies all reveal PHT-induced cognitive impairment in the areas of attention, memory, and especially mental speed. The magnitude of the reported effects is moderate to large. A caveat is in order, however, as all these studies were carried out in normal volunteers, which opens the possibility that these effects represent short-term outcomes of the drug.

The results of head-to-head comparisons with other AEDs are somewhat more confusing. Using an ingenious long-term treatment and withdrawal design, Gallassi et al.[35] found more cognitive impairment than CBZ. On the other hand, no difference with CBZ, VPA, oxcarbazepine (OXC), and even PB are reported.[2,33,58,59,60,74]

Ethosuximide

Ethosuximide (ESX) modifies the properties of voltage-dependent calcium channels, reducing the T-type currents and thereby preventing synchronized firing. The reduction is most prominent at negative membrane potentials and less prominent at more positive membrane potentials. Most effect is assumed to take place in thalamocortical relay neurons. ESX was introduced in 1960 and is mainly used for the treatment of generalized absence seizures.

No controlled studies are available to evaluate the cognitive effects of ESX.

Carbamazepine

The main anticonvulsant mechanism of action is similar to that of PHT with a less “slowing” effect in the recovery state than obtained for PHT. The mechanism of action is also voltage and frequency dependent. CBZ was first synthesized in the early 1950s[68,69] and introduced as an antiepileptic drug by Bonduelle in 1964 in Europe. CBZ is used for patients with partial complex seizures, with or without secondary generalization. Approval by the Food and Drug Administration (FDA) for use in the United States followed much later (1978) because of concerns about serious hematologic toxicity (e.g., aplastic anemia).

For CBZ two studies, one in normal volunteers[82] and one in patients with epilepsy,[6] report “no cognitive impairment” compared to a nondrug condition. This is challenged by the group by Meador et al.[58,59] that reported impairments of memory, attention, and mental speed, largely the areas that may also be affected by phenytoin.

When evaluating the comparisons of CBZ with other AEDs, there are the conflicting results of the Italian study by Gallassi et al., showing a more favorable profile compared with PHT and PB[35] and the U.S.-based study by Meador et al.[58,59,60] that showed no differences compared with PHT and PB.

Valproate

VPA, a fatty acid, is believed to possess multiple mechanisms of action. A number of studies have demonstrated an effect on sodium channels, however, different from PHT and CBZ. An effect on T-type calcium channels has also been demonstrated. Recent studies have, however, demonstrated that a predominant effect concerns the interaction with the GABAergic neurotransmitter system. More precisely, VPA elevates brain GABA levels and potentiates GABA responses, possibly by enhancing GABA synthesis and inhibiting degradation. Furthermore, VPA may augment GABA release and block the reuptake of GABA into glia cells. VPA is one of the most effective drugs against generalized absence seizures. It was introduced in approximately the same period as CBZ.

For VPA, three studies[24,71,84] allow the interpretation of absolute effects and show mild to moderate impairment of psychomotor and mental speed. The comparison with other drugs shows lower performance of memory and visuomotor function compared to CBZ[35] and a favorable profile compared to PHB on tests for intelligence.[21,88] One study does not show a difference with PHT.[33]

Oxcarbazepine

Oxcarbazepine (OXC) is essentially a prodrug, a keto homolog of CBZ, structurally very similar to CBZ, but with a different metabolic profile. In humans, the keto group is rapidly and quantitatively reduced to form a monohydroxy derivative that is the main active anticonvulsant agent during OXC therapy. Metabolism of OXC does not result in the formation of 10,11-epoxy carbamazepine that is sometimes considered to be the main metabolite causing side effects. The mechanism of action is similar to CBZ. However, OXC is also considered to reduce presynaptic glutamate release, possibly by reduction of high-threshold calcium currents. OXC was approved in the European Union in 1999 and is indicated for use as monotherapy or adjunctive therapy for partial seizures with or without secondarily generalized tonic–clonic seizures in patients 6 years of age or older.

The effects of OXC on cognitive function have been evaluated in one study in healthy volunteers and in four studies in patients with epilepsy. A double-blind, placebo-controlled, crossover study was conducted in 12 healthy volunteers.[25] The effects of two doses of OXC (300 mg/day and 600 mg/day) and placebo on cognitive function and psychomotor performance were assessed. The treatment duration for each condition was 2 weeks. Cognitive function tests were administered before treatment initiation and 4 hours after the morning doses on days 1, 8, and 15. In this study, OXC improved performance on a focused attention task, increased manual writing speed, and had no effect on long-term memory proces-ses.

In patients with epilepsy, four monotherapy comparative studies are available to evaluate the effects of OXC on cognitive functions in adult patients with newly diagnosed epilepsy. The first study[44] was a double-blind, active-control study evaluating the effects of CBZ and OXC on memory and attention in 41 patients with newly diagnosed epilepsy. The treatment duration was 1 year. Cognitive function and intelligence tests were administered before treatment initiation and after 1 year of treatment. The results indicated no deterioration of memory or attention with either CBZ or OXC. The second study was an active-control study that evaluated the effects of CBZ, VPA, and OXC on intelligence, learning and memory, attention, psychomotor speed, verbal span, and visuospatial construction in 32 patients with newly diagnosed epilepsy.[73] The treatment duration was 4 months. Cognitive function and intelligence tests were administered before treatment initiation and after 4 months of treatment. The results indicated no deterioration of cognitive function in any treatment group. Significant improvements in learning and memory tests were found for the CBZ- and OXC-treated patients. Improvements were also found in attention and psychomotor speed tests for the VPA-treated patients and partly for the CBZ-treated patients. The third study was a double-blind, randomized, active-control study that evaluated the effects of PHT and OXC on memory, attention, and psychomotor speed in 29 patients with newly diagnosed epilepsy.[2] The treatment duration was 1 year. Cognitive function tests were administered before treatment initiation and after 6 and 12 months of treatment. The results indicated no significant differential cognitive effects between PHT and OXC during the first year of treatment in patients with newly diagnosed epilepsy who achieved adequate seizure control. In the fourth study,[56] three groups of 12 patients taking either CBZ, VPA, or PHT took a single 600-mg dose of OXC followed 7 days later by 3 weeks of treatment with OXC 300 mg thrice daily and matched placebo in random order. Seven untreated patients, acting as controls, were prescribed the single OXC dose and 3 weeks of active treatment only. There were no important changes in cognitive function test results during administration of OXC compared with placebo. Finally a study in newly diagnosed children, randomized to OXC (n= 55), CBZ (n= 28), and VPA (n= 21$) was performed showing no differences between the three drugs.[29a]

In summary, the results of these studies indicate that OXC does not affect cognitive function in healthy volunteers and adult patients with newly diagnosed epilepsy. The effects of OXC on cognitive function, however, have not been systematically studied in children and adolescents. In accordance with the latest revision of the Committee for Proprietary Medicinal Products (CPMP) Note of Guidance (CPMP EWP/566/98 rev 1, dated November 16, 2000, Sections 2.5 and 5.2), a study has recently been launched (Protocol #: CTRI476E2337) to investigate the effects of OXC on cognitive function (i.e., psychomotor speed and alertness, mental information processing speed and attention, memory, and learning) in children and adolescents aged 6 to 17 years with partial seizures.

Topiramate

TPM is a sulfamate-substituted monosaccharide that has clearly multiple mechanisms of action.[89] TPM blocks neuronal sodium channels in a voltage- and frequency-dependent manner, inhibits CA, promotes the action of GABA at the $GABA_A$ receptor complex, and elevates GABA brain concentrations by about 60% at 3 and 6 hours after a single dose; this increase was maintained with 4 weeks of TPM administration.[70] TPM is a carbonic anhydrase–inhibiting drug. TPM has proved to be effective in patients with refractory chronic partial epilepsies.[32,72] It was recently introduced in the United States and Europe.

During the initial add-on clinical trials, central nervous system (CNS)-related "cognitive" subjective complaints were frequently reported, including mental slowing, attentional deficits, speech problems, and memory difficulties.[72] It should be mentioned, however, that higher target doses and faster titration schedules were used than are now common in clinical practice (see reference 32 for a discussion of dose and titration speed). Recent studies with TPM-treated patients have confirmed high levels of adverse cognitive effects based on subjective complaints.[42,80] A follow-up study[19] showed long-term retention of 30% for a 4-year follow-up. For about half of the 70% of patients who discontinued treatment, side effects were the major reason, with cognitive side effects being most frequently mentioned.

Only a few studies have psychometrically measured cognitive changes using neuropsychological tests. A study by Martin et al.[55] in six normal volunteers used an acute dose of 2.8 mg/kg (~200 mg/day) followed by a titration to 5.7 mg/kg (~400 mg/day) in 4 weeks, resulting in weekly dose escalations of about 100 mg. The rate at which TPM was escalated in this study was very similar to the dose escalation used in the initial TPM adjunctive therapy trials,[72] in which escalating the TPM dose to 200 or 400 mg/day over 2 to 3 weeks was associated with somnolence, psychomotor slowing, speech disorders, and concentration and memory difficulties.[19] Martin et al. showed neuropsychometric changes commensurate with these CNS effects. The cognitive effects of the acute starting dose of 200 mg/day were impairments of verbal function (word finding and verbal fluency) of approximately two standard deviations (which represents very serious impairment) and of sustained attention. Titration to 400 mg/day in 4 weeks resulted in impairments of verbal memory and mental speed of more than two standard deviations.

Six studies involving patients with epilepsy are available. In a study by Meador[57] with 155 patients with epilepsy, the effects of the gradual introduction of TPM as add-on (a 50-mg starting dose, followed by increments of 50 mg per week over 8 weeks) were compared with those of more rapid dose escalation (initial dose of 100 mg, followed by two consecutive weekly increments of 100 and 200 mg). In a test battery of 23 variables representing selective attention, word fluency, and visuomotor speed, the subjects who were on a slow-titration schedule and treated with one background AED displayed TPM-associated score changes of more than one third but less than one standard deviation. A study by Aldenkamp et al.[10] was specifically designed to compare cognitive effects of TPM and VPA added to therapeutic dosages of CBZ in 59 patients with epilepsy. In this study, a slow titration speed was used with a starting dose of 25 mg/day TPM and weekly increments of 25 mg. Moreover, the average achieved dose (approximately 250 mg) was relatively low. Neuropsychometric testing was conducted 8 weeks after the last dosage increase (20 weeks after the start of TPM therapy). The study therefore used optimal conditions (i.e., slow titration, relatively low dose, and a longer treatment period), allowing for patient habituation to the effects of TPM therapy. Nonetheless, cognitive impairment was found for verbal memory function both during titration and at end-point. In a study by Burton and Harden,[20] attention was assessed weekly in ten subjects receiving TPM over a 3-month period. Four of nine subjects showed significant correlations between TPM dosage and forward digit span measured weekly, such that higher dosage was associated with poorer attention. In a retrospective study by Thompson et al.,[81] the neuropsychological test scores of 18 patients obtained before and after the introduction of treatment with TPM (median dose 300 mg) were compared with changes in test performance of 18 patients who had undergone repeat neuropsychological assessments at the same time intervals. In those patients taking TPM, a significant deterioration in many domains was found. The largest changes were for verbal IQ, verbal fluency, and verbal learning.

A retrospective study by Kockelmann et al.[43] investigated the cognitive profile of 42 patients on AED polytherapy containing TPM compared to 42 patients taking LTG. Patients were assessed on an extensive battery of neuropsychological assessments and blood serum levels were obtained. The TPM-treated patients performed significantly worse on executive functioning measures such as working memory and verbal fluency. Significant correlations with blood serum levels were only evident for verbal fluency, verbal memory span, and verbal memory (delayed recall and recognition). A lack of correlation with other variables may be in part due to the small sample size.[43]

In an open, prospective study, 41 patients with intractable epilepsy initially received either TPM or tiagabine (TGB) as add-on treatment. Of these, 21 patients were assessed at baseline, after a 3-month titration phase, and after a 3-month maintenance phase. The patients were assessed on various aspects of cognitive functioning such as attention, memory, language, and self-report of mood and quality of life. The TPM group performed worse on measures of verbal fluency and working memory and reported more depression than the TGB group. They also felt that they were suffering from more adverse effects due to the TPM medication. However, TPM patients did report an increase in mental flexibility between titration and maintenance phase.[34]

In summary, there is clear clinical evidence for TPM-induced cognitive impairment. Not all studies are comparable because of the confusion about dose and titration speed (see reference 5 for a discussion). Moreover, the complete lack of controlled studies is remarkable.

Lamotrigine

LTG is a phenyltriazine with weak antifolate activity. The main anticonvulsant mechanism of action is to block voltage-dependent sodium channels that result in voltage- and frequency-dependent inhibition of the channel. This suggests that the mechanism of action is similar to that of PHT and CBZ. However, much attention is focused recently on the fact that this mechanism in LTG treatment results in preventing presynaptic excitatory neurotransmitter release. It is still in debate to what extent the mechanisms of action are different from CBZ.[46] Clinical evidence indicates that LTG is effective against partial and secondarily generalized tonic–clonic seizures, as well as idiopathic (primary) generalized epilepsy. LTG was introduced in Europe in 1991 and in the United States in 1994.

A large number of cognitive studies are available for LTG (see reference 11 for an overview). Five volunteer studies have been conducted with LTG. Doses of 120 mg and 240 mg did not produce a significant change in cognitive function compared with baseline when administered to 12 normal volunteers in an acute study of 1 day.[23] Similarly, five volunteers received LTG (acute dose 3.5 mg/kg and then titrated to a maximum of

7.1 mg/kg) in a single-blind manner and were assessed for change in cognitive function after 2 and 4 weeks.[55] There was no significant change in any of the neurocognitive measures relative to baseline performance. LTG and CBZ have been compared in 12 healthy male volunteers and associations were made between the observed cognitive effects and plasma concentrations of these drugs.[37] The effects of these drugs were examined by means of adaptive tracking, which assesses eye–hand coordination and effects of attention, and eye movement tests. LTG treatment was not significantly different from placebo, but increased CBZ saliva concentrations were significantly associated with impaired adaptive tracking and smooth and saccadic eye movements. The long-term effects of LTG and CBZ were compared in 23 volunteers in a 10-week crossover study.[63] The neuropsychological battery in this study consisted of 19 instruments yielding 40 variables, including both subjective and objective measures. LTG showed better performance or fewer side effects in 17 (42%) of the variables, while no statistically significant differences were seen in the remaining variables. Finally, a study by Aldenkamp et al.[8] in 30 volunteers (12 days of treatment, using a daily dose of 50 mg of LTG) showed evidence for a selective positive effect of LTG on cognitive activation, relative to both placebo and VPA. Although the results of these volunteer studies provide us with preliminary insight into the impact of LTG on cognition, the generalizability of the results from these studies to patients with epilepsy receiving long-term AED treatment is limited.

The effects of LTG on cognitive function have been compared with those of CBZ in patients with newly diagnosed epilepsy. Patients completed tests of verbal learning and memory, attention, and mental flexibility at baseline and then periodically for up to 48 weeks. Significant differences favoring LTG over CBZ were observed with semantic processing, verbal learning, and attention.[36] The authors concluded that LTG may have a favorable long-term effect on cognitive function when compared with CBZ. Other studies have reported positive cognitive effects of LTG used as adjunctive therapy. Two independent double-blind, randomized, crossover studies have examined the cognitive effects of LTG used as add-on therapy.[17,76] Both studies included patients with a history of partial seizures (at least once weekly during the preceding 3 months) who had received no more than two other AEDs or VPA monotherapy. Both studies also used two treatment periods (12 and 18 weeks), which were separated by a washout period (4 and 6 weeks). Despite the similarity in trial design and patients, there is some inconsistency between the findings of these two studies. One study showed a marginal reduction in general "cerebral efficiency" (an indirect measure of cognitive function) following LTG treatment.[17] Conversely, significant improvements were reported in the second study.[76] In an uncontrolled add-on study[15] using CBZ as baseline drug, no deterioration on any of the cognitive tests was found after introducing LTG (200 mg). LTG therapy in seven patients with epilepsy and mental retardation caused both positive and negative psychotropic effects.[31] These findings were based on the observations of parents and supervising staff. Positive effects included reduced irritability and increased compliance with simple instructions, while negative effects included behavioral deterioration with temper tantrums, restlessness, and hyperactivity. Similarly, a second study in 67 patients with mental retardation showed that following adjunctive treatment with LTG, social functioning was stable or improved in 90% of patients.[30]

In addition to clinical studies that have assessed the impact of LTG on cognitive function, further evidence can be obtained from examining the effect of LTG on electroencephalographic (EEG) parameters. Overt EEG discharges can occur without any visible clinical correlate in many patients with epilepsy. These epileptiform episodes may be associated with transient deterioration in cognitive function.[1,9] Data from several studies indicate that LTG may reduce spontaneous epileptiform discharges, which may partially explain the favorable cognitive profile of LTG. In five patients displaying spontaneous EEG discharges, a single dose of LTG (120 mg or 240 mg in addition to existing medication) resulted in a substantial reduction in spontaneous interictal discharges within a 24-hour period.[18] The long-term effects of LTG on paroxysmal abnormalities have also been monitored with a computer-based analysis system.[50] Twenty-one patients with intractable epilepsy (20 of whom were receiving multiple AED therapy) were evaluated before and after LTG treatment for EEG ictal events and number of spikes in a 10-minute period. Before LTG treatment, patients typically showed discharges characterized by diffuse spike-wave complexes. However, following a 4-month treatment period with LTG, ictal discharges disappeared and diffuse slow-wave activity was seen with no adverse effect on background activity. Nineteen of the 21 patients also showed a reduction in seizure frequency.

The effect of LTG add-on therapy in 11 patients with refractory partial seizures with or without secondary generalization has also been reported.[51] LTG was added to existing therapy consisting of CBZ with at least one additional AED. EEG recordings were made at rest with eyes closed, during an attentive task (blocking reaction induced by several episodes of eyes open lasting 8 to 9 seconds), during cognitive tasks, and while performing mental arithmetic. In addition, a battery of neuropsychological tests was carried out. Before LTG treatment, EEG data revealed a decrease in fast activity at rest and a reduction in α and β bands during attentive and cognitive tasks. LTG treatment resulted in a selective increase in α reactivity and β power during the attentive tasks with no other detectable changes. During cortical activation, subtle changes were observed that were taken as indicative of a slight improvement in attention. Neuropsychological evaluation revealed that following 3 months of LTG therapy, no deterioration in cognitive function had occurred.

LTG also shows a promising cognitive profile in elderly patients suffering from age-associated memory impairment.[64] A neuropsychological test battery in combination with auditory event-related potentials (ERPs) was used to measure the impact of LTG on cognitive function. LTG treatment caused a reduction in amplitude of the P300 component of the ERP and a corresponding improvement in immediate and delayed visual memory and delayed logical memory. LTG may therefore improve simple memory functions in a memory-impaired elderly population.

Levetiracetam

Levetiracetam (LEV) is a new AED, structurally and mechanistically dissimilar to other AEDs. It is believed to bind to a specific, as yet undetermined, site on the synaptic plasma membrane. Moreover, LEV seems to reduce the GABA turnover in the striatum by reducing GABA synthesis and increasing GABA metabolism. It is effective in reducing partial seizures in patients with epilepsy, both as adjunctive treatment and as monotherapy. LEV has many therapeutic advantages for patients with epilepsy. It has favorable pharmacokinetic characteristics (good bioavailability, linear pharmacokinetics, insignificant protein binding, lack of hepatic metabolism, and rapid achievement of steady-state concentrations) and a low potential for drug interactions. It is licensed for use as adjunctive treatment for partial seizures, with or without secondary generalization, in people aged over 16 years.

For its impact on cognitive function, we only have data from a small pilot study that does not allow definite conclusions.[66] An international (UK/The Netherlands) cognitive study is

presently being carried out. In this study a first-line add-on design is used, comparing the cognitive effects of LEV with CBZ and VPA.

Tiagabine

TGB is a GABA uptake inhibitor that is structurally related to the prototypic GABA uptake blocker nipecotic acid, but has an improved ability to cross the blood–brain barrier. TGB temporarily prolongs the presence of GABA in the synaptic cleft by delayed clearance. Clinical trials have shown that TGB is effective as add-on therapy in the management of patients with refractory partial epilepsy. TGB was recently marketed and some aspects of the development program are still not finished.

Three cognitive studies are available. Dodrill et al.[26] included 162 patients who received the following treatments: Placebo (n = 57), 16 mg/day TGB (n = 34), 32 mg/day TGB (n = 45), or 56 mg/day TGB (n = 26) at a fixed dose for 12 weeks after a 4-week dose titration period. Eight cognitive tests and three measures of mood and adjustment were administered during the baseline period and again during the double-blind period near the end of treatment (or at the time of dropout). The results showed no cognitive effects of monotherapy with TGB at a low or high dose, but there was some evidence for mood effects of add-on treatment with TGB at higher dosing, possibly related to titration speed. In the add-on polytherapy study by Kälviäinen et al.,[40] 37 patients with partial epilepsy were included. The study protocol consisted of a randomized, double-blind, placebo-controlled, parallel-group add-on study and an open-label extension study. During the 3-month double-blind phase at low doses (30 mg/day), TGB treatment did not cause any cognitive changes as compared with placebo. TGB treatment also did not cause deterioration in cognitive performance during longer follow-up with successful treatment on higher doses after 6 to 12 months (mean 65.7 mg/day, range 30–80 mg/day) and after 18 to 24 months (mean dose 67.6 mg/day, range 24–80 mg/day). Finally, a study by Sveinbjornsdottir et al.[79] was an open trial of 22 adult patients with refractory partial epilepsy followed by a double-blind, placebo-controlled, crossover trial in 12 subjects. Nineteen patients completed the initial open titration and fixed-dose phase of the study and 11 patients completed the double-blind phase. The median daily TGB dose was 32 mg during the open fixed dose and 24 mg during the double-blind period. Neuropsychological evaluation did not show any significant effect on cognitive function in the open or double-blind phase.

Gabapentin

GBP (1-(aminomethyl) cyclohexane-acetic acid) is a novel AED, currently used as add-on therapy in patients with partial and generalized tonic–clonic seizures. GBP is a cyclic GABA analog, originally designed as a GABA agonist.[48] Further research has clearly shown a specific effect of GBP on GABAergic neurotransmitter systems, especially influencing GABA turnover. Investigations using nuclear magnetic resonance imaging spectroscopy have confirmed that GBP elevates GABA concentrations, specifically in the occipital cortex of patients with epilepsy.[70]

Two volunteer studies and one clinical study are available to interpret the cognitive effects.

Martin et al.[55] used an acute dose and rapid titration in six volunteers and did not find cognitive effects of GBP. Meador et al.[62] compared the cognitive effects of GBP and CBZ in 35 healthy subjects by using a double-blind, randomized, crossover design with two 5-week treatment periods. During each treatment condition, subjects received either GBP 2,400 mg/day or CBZ (mean 731 mg/day). Subjects were tested at the end of each AED treatment period and in four drug-free conditions (two pretreatment baselines and two posttreatment washout periods [1 month after each AED]). The neuropsychological test battery included 17 measures yielding 31 total variables. Significantly better performance on eight variables was found for GBP, but on no variables for CBZ. Comparison of CBZ and GBP with the nondrug average revealed significant statistical differences for 15 (48%) of 31 variables. Leach et al.[45] studied GBP in 21 patients in an add-on polytherapy study after 4 weeks of adjunctive therapy and found no change in psychomotor and memory tests. Drowsiness was more often found in higher dosing (2,400 mg). Mortimore et al.[65] did not find a difference between continued polytherapy and an add-on with GBP in measures of quality of life.

Zonisamide

The anticonvulsant properties of zonisamide (ZNS) were discovered through extensive testing of a variety of sulfonamide compounds. Like TPM, it has multiple mechanisms of action: Blocking voltage-gated sodium channels, reducing sustained repetitive firing, blocking T-type calcium channels, and inhibiting ligand binding to the $GABA_A$ receptor. Like TPM, ZNS is a carbonic anhydrase–inhibiting drug. Although there is longer experience with ZNS in Japan (where it was developed), it recently was introduced in the United States and Europe for partial-onset seizures in refractory epilepsy.

Clinical anecdotal information and a pilot study by Ojemann et al.[67] show a cognitive side effect profile very similar to TPM, but no controlled studies are available. Also, no information is available about ongoing studies.

Rufinamide

Rufinamide (RUF 331; 1-(2,6-difluoro-phenyl)methyl-1H-1,2,3-triazole-4-carboxamide) is a structurally novel compound that limits the frequency of sodium-dependent neuronal action potentials. One study is available to assess the cognitive effects.[7] The study used a multicenter, multinational double-blind, randomized, placebo-controlled parallel study design with four different doses of rufinamide (based on prior studies): 200 mg/day, 400 mg/day, 800 mg/day, and 1,600 mg/day as add-on to the existing medication. Cognitive assessments were performed at baseline (before the start with RUF treatment) and at end-point (after 3 months of treatment). The most important finding is that for none of the cognitive tests, a statistically significant worsening occurs for any of the doses of rufinamide when the period after 12 weeks of treatment was compared with the baseline before introducing rufinamide. Also, none of the comparisons between dose and placebo showed a statistically significant difference.

Summary and Conclusions

A general conclusion that may be derived from meta-analyses[87] is that polypharmacy shows a relatively severe impact on cognitive function when compared with monotherapy, irrespective of the type of AEDs included. Two drugs that individually have mild cognitive effects may induce serious cognitive impairment when used together, possibly because of potentiation of tolerability problems.[85]

Possibly the most remarkable finding is that, although the severity of cognitive side effects is generally considered to be

mild to moderate for most AEDs,[87] all commonly used AEDs have some impact on cognitive function. Such mild impact may be amplified in specific conditions and may become substantial in some patients when crucial functions are involved, such as learning in children[14] or driving capacities in adults (often requiring millisecond precision), or when functions are impaired that are already vulnerable, such as memory function in the elderly.[85] Moreover, the cognitive side effects represent the long-term outcome of AED therapy; therefore, the effects may increase with prolonged therapy, which contributes to the impact on daily life functioning in refractory epilepsies.[16]

Definite evidence for drug-induced cognitive impairment has been established for phenobarbitone (memory impairment), phenytoin (mental slowing), and topiramate (mental slowing and dysphasia). Treatment with these drugs should consider these side effects and patients should be monitored on a regular basis. Mild effects (mostly psychomotor slowing) were found for carbamazepine, oxcarbazepine, valproate, and lamotrigine (with mild cognitive-activating effects). The effects for ethosuximide, tiagabine, gabapentin, levetiracetam, and zonisamide are inconclusive. It is clear, however, from the available evidence that there still exists a need to conduct studies that compare the relative effects of the neuropsychological consequences of AED treatment using standardized protocols. Further, the lack of well-designed studies of the neuropsychological effects of AED treatment means that we must remain cautious about our level of understanding about the impact of the newer drugs.

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Chapter 202

Learning Disorders

Michael P. Kerr

Mary Lou Smith

Introduction

The potential impact of epilepsy and its treatment on learning provides a considerable challenge for clinicians, patients, and families alike. In addition, the picture is often complicated by the association between the presence of epilepsy and apparently already coexistent disorders of learning and development. This poses important heuristic questions into the relative impact of epilepsy on the development of learning disorders.

It is beyond the scope of this chapter to address in detail this crucial question in the field of epileptology. For further reading please refer to the chapters on neonatal syndromes and syndromes of childhood and adolescence. This chapter will have as its focus the nature, impact, and management of epilepsy in those with an apparently coexistent intellectual disability (mental retardation). Such an approach helps the clarity of the chapter, yet it is important to reflect on how the populations of people who have intellectual disability are placed within the scope of learning disorders associated with epilepsy. This will be covered initially within our discussion on classification and terminology and later in the chapter within the section on the impact of epilepsy on people with an intellectual disability.

Key themes discussed in the chapter will include the association between certain syndromes of intellectual disability and seizure types, the impact of epilepsy, approaches to management, the association between epilepsy and behavioral disorders, and the multidisciplinary approach to care.

Classification and Terminology of Intellectual Disability

Considerable variation occurs in the terminology of intellectual disability. While *intellectual disability* is currently the internationally accepted term, *mental retardation* is favored in the United States and much of Europe, *learning disability* in the United Kingdom, *mental handicap* in much of the world during the 1990s, and *intellectual handicap* in Australia and New Zealand.

Definition of Disability

The American Association for Mental Retardation defines mental retardation as follows:

> "Mental retardation is a disability characterized by significant limitations both in intellectual functioning and in adaptive behavior as expressed in conceptual, social and practical adaptive skills…. The disability originates before the age of 18."

It adds five assumptions, which are essential to the application of the definition:

1. Limitations in present functioning must be considered within the context of community environments typical of the individual's age, peers, and culture.
2. Valid assessment considers cultural and linguistic diversity as well as differences in communication, sensory, motor, and behavioral factors.

3. Within an individual, limitations often coexist with strengths.
4. An important purpose of describing limitations is to develop a profile of needed supports.
5. With appropriate personalized supports over a sustained period, the life functioning of the person with mental retardation generally will improve.

From a clinical viewpoint, particularly in administrative terms, mental retardation is defined using the International Classification of Diseases rubric, currently in its 10th version. All codes for mental retardation are prefixed with F7. Assessment should include clinical findings, adaptive behavior, and the use of psychometric tests.

The range of disability is defined in Table 1.

The Nature and Impact of Epilepsy in People with Intellectual Disability

Epidemiology

Epidemiologic data for this population are particularly influenced by methodologic and sampling issues, raising concerns regarding the interpretation of results that vary significantly depending on the study's design.[41,91] These concerns focus on the usually selective nature of the population samples and difficulties in allowing for comparative levels of intellectual disability. The prevalence of epilepsy is significantly greater in people with intellectual disability than in the general population,[62] with estimates in intellectual disability populations ranging from 18% to over 60%.

The major influences on prevalence estimates are (a) age; (b) residence, institution, or community; and (c) the severity of disability.[18,57,84]

Table 1 Classification of Intellectual Disability (ICD-10)

Code	Definition	Attributes
F70	Mild mental retardation	1) Ability to use speech 2) Full independence in self-care 3) IQ range between 50 and 69
F71	Moderate mental retardation	1) Slow in comprehension 2) Immobility or restricted mobility 3) Retarded motor skills 4) IQ range between 35 and 49
F72	Severe mental retardation	1) Marked impairment of motor skills 2) Clinically significant damage to CNS 3) IQ range between 20 and 34
F73	Profound mental retardation	1) Severely limited understanding 2) Immobility or restricted mobility 3) Incontinence 4) Requiring constant supervision

	5) IQ <20 6) Usually organic etiology

CNS, central nervous system; ICD, International Classification of Diseases.

Table 2 Epidemiologic Surveys of the Prevalence of Epilepsy in People with Intellectual Disability (ID)

Sample	Prevalence
Children under age 14	
Community SMR[19]	20%
Children up to 22 yr Community[85]	Mild ID 24% Severe ID 44%
Institution[67]	All 32%
Children 6–13 yr Community[97]	Mild ID 14% Severe ID 24%
Adults, community based[108]	All ID 22.1%
Community identified pediatric sample[1]	All ID: 19% by age 10 years and 21% by age 22 years Severe ID: Fivefold risk as compared with mild ID
All ages, record-linked health data[71]	All ID 18.3%
Primary care health facilities[68]	Down syndrome 13.6% Cerebral palsy 40%

Cohort effects, due to year of birth, are important in defining prevalence in both intellectual disability[37] and epilepsy.[16]

A comparison between community and institutionally based surveys[67,108] show as much as a 10% discrepancy in the prevalence found. Table 2 describes a range of epidemiologic surveys of the prevalence of epilepsy in people with intellectual disability.

The increasing prevalence of epilepsy with increasing severity of intellectual disability is well recognized in both children[1] and adults.[4]

Definition of seizure type in populations of people with intellectual disability has proven difficult.[24,57] An example of this is seen in a community study of children with intellectual disability.[90] In this survey, there was evidence of a lack of investigation in the population, with only 10% having had electrophysiologic tests. Despite this, they showed an increase in generalized tonic–clonic and myoclonic seizures and a decrease in partial seizures with increasing handicap. The authors concluded that this increase in generalized seizure disorder was an artifact of the lack of investigation, though other explanations such as genetic causes may be valid.

A Japanese study focusing on people with severe intellectual disability[4] identified cerebral palsy as the most common etiology (42.3%); multiple seizure types were common (almost half had two or more seizures) and paroxysms were found on the electroencephalogram (EEG) in 90.6% of cases and abnormal computed tomography (CT) scan in 82.7% of cases. In a Finnish study in children,[1] prenatal causation was most frequent (47%), and seizures were most frequently partial (72%). As we shall see later, it is unrealistic when considering seizure type to take the intellectual disability population as a whole; individual etiologic characteristics are crucial in syndromal and seizure classification.

Etiologic Issues

Intellectual disability is caused by a range of pathologic processes, as, of course, is epilepsy. In particular, genetic advances into the individual causes of intellectual disability and of the epilepsies have expanded.[5,21]

It is beyond the scope of this chapter to highlight all the etiologic processes involved in the development of an intellectual disability. Two issues are, however, of particular relevance to this population: (a) are specific etiologies associated with recognizable epilepsy patterns? and (b) what impact do seizures have on development and learning?

Etiology Associated Patterns of Epilepsy

A further approach to investigating the etiology of epilepsy in people with intellectual disability has been to define the nature of the epilepsy in individual disability syndromes. This approach will hopefully lead to the matching of known genetic abnormalities with the individual's epilepsy and thus direct treatment options.

This section includes a brief overview of a select group of syndromes that have intellectual disability as a key feature, and that may also have epilepsy as a concomitant disorder. This section is not intended to provide a detailed analysis of the causes of the syndromes, or the etiology, features, or treatment of the associated epilepsies; these issues are reviewed in depth elsewhere in this textbook. This co-occurrence of epilepsy with these syndromes is important to recognize at a clinical level because the seizures add an additional burden to both the individual with the syndrome and to the caregivers.

Down Syndrome

Down syndrome (DS), or trisomy 21, is the most common genetic cause of intellectual disability.[93] In addition to intellectual disability, of which there is a range in severity, DS is characterized by growth retardation, hypotonia, a number of facial dysmorphologies, hypogonadism, an increased risk of cardiac disease and leukemia, and Alzheimer disease in those over the age of 35 years. A bimodal distribution in age of seizure onset has been described, with peaks in childhood and middle age.[82,98,105] The incidence of epilepsy increases with age, and the increase later in life is thought to be related to the onset and progression of Alzheimer disease.[54,63,105] A variety of seizure types have been reported, including infantile spasms, generalized tonic–clonic seizures, Lennox-Gastaut syndrome, and psychomotor seizures.[44,81,98]

Angelman Syndrome

Angelman syndrome (AS) is a genetic disorder that is estimated to account for up to 6% of all children presenting with severe intellectual disability and epilepsy.[42] Clinical findings present in all patients include developmental delay, which becomes apparent by 6 to 12 months of age; severely impaired expressive language; ataxic (“puppetlike”) gait; tremulousness of limbs; and a typical behavioral profile, including a happy demeanor, hypermotor behavior, and low attention span. Although development may appear almost normal or only slightly delayed during the first 6 months of life, all patients eventually develop severe intellectual disability. The typical lack of speech may not be due to the intellectual disability alone; oral motor dyspraxia and deficits in social interaction and attention also contribute to the lack of expressive language.[80] Sleep problems may affect a significant portion of individuals with AS and are persistent; parents report adverse effects of their child's sleep problems on their own well-being.[26,92]

Seizures, abnormal electroencephalography, microcephaly, and scoliosis are observed in >80% of patients, with onset of epilepsy typically occurring in infancy or early childhood.[30,34] A variety of seizure types are seen, including febrile, atypical absence, generalized tonic-clonic, myoclonic, and clonic unilateral seizures.[39,43,106] There are contradictory data on whether the severity of the developmental disturbance in AS is related to the severity of epilepsy,[58,77] and whether there is an improvement in epilepsy with age.[59,92,110]

Fragile X Syndrome

Fragile X syndrome (FXS) is the most common known cause of autism or “autisticlike” behaviors, and the incidence of cognitive impairment is quite high. The clinical phenotype in the male typically also includes tall stature, large testes, relative macrocephaly, characteristic facial features, and delays in speech and language development.[23,100,109] Up to 80% of males with FXS are described as cognitively delayed. In the older studies of males with FXS, almost all were described as having moderate or severe mental retardation. However, many of these studies were based upon institutionalized males, and with better ascertainment studies, it has become clear that 10% to 15% of boys with FXS have a less severe degree of developmental delay, with IQs in the borderline or mild intellectual disability range. A high number of boys with fragile X (80% to 90%) are described as distractible and impulsive, with symptoms of attention deficit hyperactivity disorder, and anxiety is a common personality feature.[38]

Girls with FXS tend to be less severely affected in terms of intellectual disability. Approximately 30% of girls with the full mutation have IQ scores above 85, with the other 70% mostly in the borderline or mild mental intellectual disability range.[23] However, those girls with normal intelligence are at higher risk for specific learning disabilities. The behavioral features in girls include shyness and poor eye contact.[100]

Seizures occur in approximately 15% to 20% of children with FXS.[6,53] Seizure types include absence, partial motor, generalized, and partial complex seizures; benign rolandic epilepsy is found frequently.[6,73,74] Epilepsy in individuals with FXS generally follows a benign course, and in a relatively high number, seizures remit before the age of 20.[86]

Rett Syndrome

In Rett syndrome (RS), there typically is normal development until 6 to 18 months (although as long as 30 months), after which development slows, or even deteriorates. The physical characteristics of RS include scoliosis, gait dyspraxia, and repetitive movements of the hands, often involving hand wringing. Individuals may have autonomic dysfunction, difficulty chewing, and teeth grinding, and eventually show growth failure and deceleration of head growth.[40,45] There is a high prevalence of behavioral and emotional disorders in RS, with anxiety, flat mood, self-injurious behavior, and autism seen frequently.[45,88] Frequently, there is a regression in cognition, behavior, and social and motor skills throughout the lifetime of patients with RS. The degree of developmental delay is usually within the severely to profoundly intellectually disabled range, although there is a spectrum of severity ranging from severe neurologic compromise to only minor neurologic symptoms.[51] There is a preserved speech variant, which shows the same course and stereotypic hand movements, but patients typically recover some hand use and speech; epilepsy is rare in this group.[22]

Epilepsy is common, occurring in between 80% and 95% of cases.[45,96] The severity of epilepsy may decrease with increasing age.[96] A variety of seizure types are found in RS, including generalized tonic–clonic, absence, myoclonic jerk, atonic, and tonic seizures. The incidence of true clinical seizures may be overestimated because the autonomic dysfunction may be incorrectly identified as absence or complex partial seizures.

The Impact of Epilepsy on Development and Learning

It is generally accepted that the causal process of epilepsy follows a path from brain damage through to the development of epilepsy.[57] Cognitive decline, as seen in a few patients with epilepsy, is usually associated with repeated head injury or through anoxic episodes in periods of status epilepticus. Other deterioration may be linked to seizures impacting information processing.[8]

However, increasing knowledge on conditions such as infantile encephalopathy (infantile spasms, myoclonic epilepsy) and the treatments for these devastating conditions seem to imply that epileptic phenomena can be associated with the development of intellectual disability.[27] A recent survey in Atlanta on the epidemiology and outcome of infantile spasms suggests that, at age 10 years, 83% will have intellectual disability.[103] The same survey suggested that 12% of 10-year-old children with profound intellectual disability had a history of infantile spasms.

Impact of Epilepsy

People with an intellectual disability are equally susceptible to the negative impacts of epilepsy on physical and psychological health, cognition, life expectancy, and social factors[10,32] as the general population. This impact should be seen as additional to their other impairments, if present. This is particularly important as underestimating the impact of epilepsy may lead to incomplete attempts at treatment.

Physical Health

The known impact of epilepsy on physical health as seen by an overrepresentation of hospitalization[20] and a range of antiepileptic drug (AED)-related morbidity holds true for people with an intellectual disability. An increase in admissions to accident and emergency rooms and to the hospital in general is seen.[71]

Psychological Health

Studies have found rates of behavior disturbance and psychiatric disorder to be significantly higher in people with epilepsy[24,50,64] and in people with intellectual disabi-lity.[11,28,64,66] Furthermore, a study in children[12] was able to identify decreasing IQ as a predictor of increasing mental health problems.

Considering the very strong evidence for an increased prevalence of emotional disturbance in individuals with epilepsy who do not have intellectual disability as compared with nonepilepsy controls,[50,64] it has proved much harder to find a similar link within populations who have epilepsy and intellectual disability. That is, it has been difficult to tease out any additional impact from epilepsy with the already high morbidity present in these populations.

Epidemiologic evidence does not support such a population link in adults or children. Deb and Hunter[25] showed an underlying prevalence of behavior disorder of 52.5% and that in the epilepsy population of 58%. An Australian study[61] showed in an epidemiologic-defined population of children with intellectual disability no difference in “caseness” of behavior and emotional disturbance between those with and without epilepsy. Other work has shown that aggression and self-injury were associated with frequent seizures and polytherapy. This approach is almost certainly missing the potential for epilepsy to impact on individuals' patterns of behavior. In particular, it may be that the particularly high frequency of mental illness, depression, and anxiety seen in general epilepsy populations may be underrecognized in people with an intellectual disability.

A study of a large epilepsy service database of people with intellectual disability[33] explored potential predictors of psychopathology within an epilepsy and intellectual disability group. They concluded that there was a relatively weak input from seizure factors such as frequency on psychopathology and that behavior disorders were more related to general disability factors than to seizure related factors.

The Family

Many factors associated with the burden of caring for someone with intellectual disability have been identified.[34,48] The most robustly replicated factor was behavior disorder. Caregiver burden is an important issue as the well-being of caregivers affects the prognosis of people in their care.[14]

The coexistence of epilepsy also seems to be a factor associated with caregiver burden.[32] Unfortunately, however, we know little about the precise impact of epilepsy on families of individuals who also have intellectual disability. A study of people with epilepsy without intellectual disability[102] found that levels of stress and dissatisfaction with their social situation were high, particularly in primary caregivers (mothers, in most instances). Respite periods away from home were few and the perceived level of support was low. Poor emotional adjustment was associated with severity of tonic and atonic attacks and periods of status epilepticus, and low levels of support were associated with depression.

Mortality

Patients with epilepsy are known to have increased risk of mortality over the population in general.[17,47] A recent Dutch cohort study demonstrated that patients with epilepsy have an increased risk ratio of 3.2 for all causes of mortality, and this rose to over 7 in those aged under 20.[89]

This is broadly similar to a Danish study, which demonstrated a standardized mortality ratio (SMR) of 3.6 for all deaths.[76] This excess risk is partly explained by underlying causes of epilepsy such as cerebrovascular disease, injuries, and poisoning. This probably explains the relatively higher SMRs in the year immediately after diagnosis of epilepsy.[17]

Patients with intellectual disability are also known to have a lower life expectancy than the general population[36] and an estimated SMR of 1.6.[35] Not surprisingly, the probability of survival decreases as the severity of intellectual disability increases.[49] This excess is increased for those patients with coexisting epilepsy[35,36] whose SMR may be as high as 5. It is possible that some of this increased mortality may be explained by an increase in sudden unexplained epilepsy death (SUDEP). An institutional review in North America revealed an increase in unexpected death of 1.3 deaths per 1,000 in the nonepilepsy group compared with 3.6 per 1,000 in those with epilepsy.[69] The impact of epilepsy on mortality in people with an intellectual disability appears to hold across all degrees of intellectual impairment.[79]

Management

Epilepsy management requires special skills and competencies for the epileptologist. These include (a) special communication skills specific to this population, (b) analysis of safety and communication of therapeutic interventions, and (c) knowledge of the care environment to work with multidisciplinary teams.

Communication Skills: Management by Proxy

Witness report from a caregiver or family member is common; a report from the individual is less so in people with intellectual disability. Thus, the history and management will commonly progress through, or at least be influenced by, another “management by proxy.” The degree of this will increase as the individual's communicative skills decrease.

Notwithstanding the need to manage third-party clinical consultations, a central aim should be to empower the individual to communicate his or her needs. Components of successful communication methods are highlighted below:

1. Nonverbal: Gaze, appropriate touch, use of gesture
2. Vocal: Appropriate tone, intelligibility
3. Verbal: Greeting, using individual's name, balance of communication with caregiver
4. Response: Recognizing the individual's responses and following leads, respecting information from the caregiver

5. Empathy: Showing appropriate respect and empathy

Table 3 Differentiating Seizure and Behavior Disorder

Seizure	Behavior disturbance
Identical behavior on each occasion	Variation in behavior with circumstances
No precipitant	Commonly that is a precipitant such as demands, need to avoid situation
Unresponsive to communication, calming	Responsive to calming, support, removal from stressor
Investigations:	*Investigations*:
Analysis of behavior: No relationship to behavior and environment	Analysis of behavior: Relationship found
Video: Shows typical seizure features	Video: Atypical picture seen
EEG: Positive interictal EEG	EEG: Negative interictal EEG of some use

EEG, electroencephalogram.

Specific Issues in Differential Diagnosis: Seizures or Behavior Disturbance?

In the majority of cases seizure disorder presents itself as paroxysmal episodes of abnormal behavior. In many cases, for example, a generalized tonic-clonic convulsion, the nature of these behaviors is well defined and cannot be confused with many other conditions. Other seizure disorders, however, are less well defined or are dependent on the verbal description of the individual and witnesses for a diagnosis. An example of the former is the pattern of behavior seen in complex partial seizures, particularly when they are associated with ictal or postictal automatisms. Differentiating these in the general population from psychiatric disturbance or, in some cases, from nonepileptic attack disorder is complex. Communication issues and the high prevalence of behavior and motor disorders in this population further complicate differentiating these in people with intellectual disability.

Repetitive episodes of manneristic or stereotyped behavior would be most unusual in many people without handicaps and the diagnosis of epilepsy would be highly likely. However, in a young man with autistic tendencies, for example, such behaviors may be reflections of the cognitive disturbance of the autism and not, in fact, epilepsy. Similarly, brief apparent losses of consciousness can be equally undiscriminating due to concurrent physical illness; an example of Sandifer syndrome misdiagnosed as complex partial seizure would be highly unlikely in an individual who could communicate his or her symptoms.[95] Clinicians need a structured approach to this differentiation. Table 3 highlights guidelines to this differential diagnosis, though in many cases behavioral analysis will be required to sufficiently differentiate the behavior.

Therapeutic Interventions

With such a strong case for the negative impact of epilepsy on individuals with an intellectual disability and their caregivers, there would appear to be a mandate for interventions to alleviate seizure-related morbidity. Such interventions should be guided by appropriate evidence and sensitive to the key concerns in this population that, in general, relate to the balance between seizure efficacy and concern over apparent side effects. Aspects of pharmacotherapy with antiepileptic drugs have been covered elsewhere in this book. We therefore will focus on those elements of particular relevance to this population: (a) recognition of the need for therapeutic intervention, (b) choosing an intervention, and (c) assessing therapeutic outcome.

Recognition of Need of Intervention

Seizures have a profound effect on this population, and intervention needs will usually be defined through an assessment that this impact exists and that a reduction would both reduce seizure-related risk and improve quality of life. Domains of impact as already described—physical, psychological, cognitive, and social—should be assessed on an individual basis.

Choosing an Intervention

Treatment guidelines[52] exist and can guide clinicians. As many of these patients already have longstanding complicated treatment histories, treatment choice will be influenced by which therapeutic options, either AEDs or surgical, remain available.

This therapeutic choice is mainly influenced by the same evidence base and decision-making process as in the general epilepsy population. FIGURE 1 shows a potential treatment pathway for people with intellectual disability who have epilepsy and can be used as a useful marker for judging the options available to an individual on his or her treatment pathway. This pathway relates to the use of AEDs. Surgical options are as relevant for this population both for potentially curative resective seizures and for procedures that may ameliorate the epilepsy, such as vagal nerve stimulation.

There does exist, however, a body of evidence relating to interventional studies in epilepsy and intellectual disability. Such evidence, while frequently hampered by its quality, can provide markers for treatment effect in terms of efficacy and safety.

Quality Evidence?

In general, therapeutic trials of AEDs use measures based on seizure frequency, seizure severity, quality of life, and side effect data. These measures, while appropriate in those without intellectual disability, may not be sufficient or may not be valid in those with intellectual disability.[31,56] It has been suggested that research in this population should use the following standard components:

1. Define the individual—use the Adaptive Behavior Scale.[75]
2. Define the individual epilepsy—etiology of intellectual disability, seizure type, and syndrome.
3. Use measures sensitive to change in the intellectual disability population.
4. Determine seizure frequency using seizure diaries.
5. Assess behavior using validated measure of behavior such as Aberrant Behavior Checklist,[3] or Developmental Behavior Checklist in children.[29]
6. Determine quality of life using specific mental retardation and epilepsy quality-of-life scales—Glasgow Epilepsy Outcome Scale (GEOS).[32]

Learning from the Evidence

Seizure Impact

Several high-quality randomized placebo-controlled trials have been published in populations of people with intellectual disability. The majority of these have been in people with Lennox-Gastaut syndrome. This syndrome is strongly associated with intellectual disability. However, the reproducibility of data from this specific seizure syndrome population into the total intellectual disability population is not proven.

Table 4[55,72,87,101] summarizes the data from these studies.

The advantage of these studies is that the placebo arm may provide some evidence of the natural course of seizure frequency in a trial setting. The studies show variation in seizure change within the placebo arms and by different seizure types. Atonic seizures ranged from a 9% decrease to a 5% increase. Tonic–clonic (recorded in one study) showed a 10% worsening and all seizure types showed from a 9% decrease to a 4% increase.

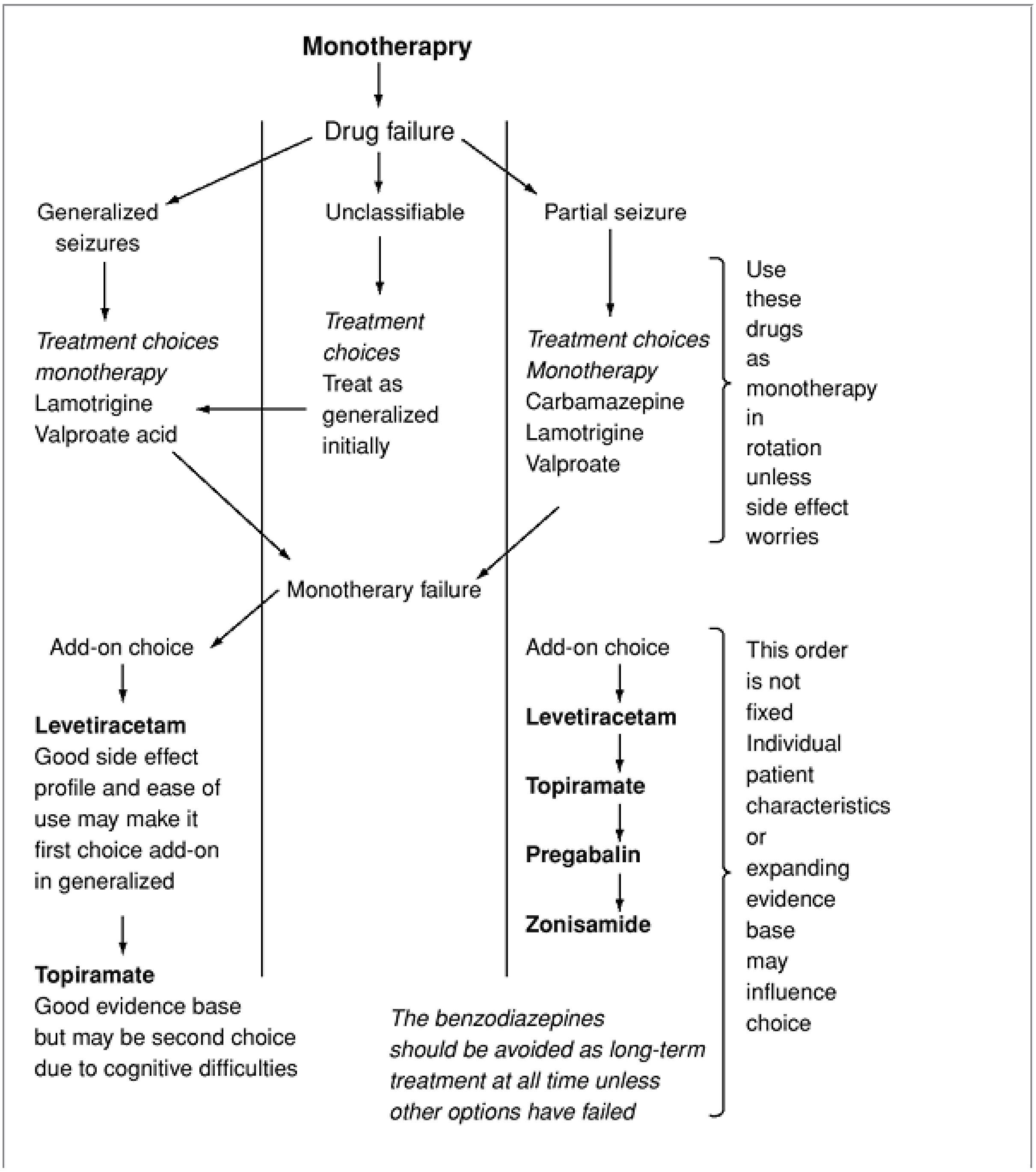
Monotherapry
Drug failure
Generalized seizures
Unclassifiable
Partial seizure
Treatment choices monotherapy
Lamotrigine
Valproate acid
Treatment choices
Treat as generalized initially
Treatment choices Monotherapy
Carbamazepine
Lamotrigine
Valproate
Use these drugs as monotherapy in rotation unless side effect worries
Monotherary failure
Add-on choice
Levetiracetam
Good side effect profile and ease of use may make it first choice add-on in generalized
Topiramate
Good evidence base but may be second choice due to cognitive difficulties
Add-on choice
Levetiracetam
Topiramate
Pregabalin
Zonisamide
This order is not fixed Individual patient characteristics or expanding evidence base may influence choice
The benzodiazepines should be avoided as long-term treatment at all time unless other options have failed

FIGURE 1. A treatment pathway for people with intellectual disability and epilepsy. (Published with permission of Clarion Press.)

A published study[7] used a retrospective case note review to assess the use of vigabatrin, lamotrigine, and gabapentin in adults with mental retardation. The study again showed variation in the percentage of patients reporting an increase in seizure frequency: Two (8%) of the patients on vigabatrin, six (24%) of the patients on lamotrigine, and zero (0%) of those on gabapentin.

It appears that seizure worsening occurs in Randomised Controlled Trials (RCTs) with novel AEDs in patients with intellectual disability, suggesting an association between seizure increase and natural fluctuation in seizure control.

The Impact of Antiepileptic Drugs on Behavior

Randomized placebo-controlled trials that have been published in populations of people with intellectual disability and Lennox-Gastaut syndrome may again offer some insight into safety issues. However, the reproducibility of data from this specific seizure syndrome population into the total intellectual disability population should again be treated with caution.

The studies showed a relatively high level of behavioral symptoms in placebo arms: Nervousness in 10% to 14%, somnolence in 22%, and “behavioral problems” in 10% (Table 4).

Data from the nonrandomized controlled trials are less valuable. However, a UK-based study[7] using a retrospective case note review showed behavior problems in 5 of 23 patients on vigabatrin, 2 of 25 patients on lamotrigine, and 1 of 23 patients on gabapentin.

The data on behavioral side effects in studies of AEDs in people with intellectual disability are particularly poor. The key problem is nonvalidated definitions of behavior. Where blinded control data do exist, they show that behavioral deterioration can occur and may be—in the case of topiramate—a specific drug effect.

Assessing Therapeutic Outcome

A judgment on treatment outcome has particular importance in people with an intellectual disability; there is certainly no “one size fits all” approach to this. In many instances very individualized approaches will be necessary, particularly in those with multiple physical and intellectual disabilities.

In a clinical context the assessment of treatment outcome will involve a more pragmatic approach. This is likely to have several broad aims. The first will be to analyze accurately any seizure change. To do this, accurate seizure charts are necessary. These will need space to identify several seizure types. Acquiring high-quality seizure frequency data can be a long-term and difficult process. Frequently, parents and caregivers will need guidance into differentiating varying seizure types and in accurate recording.

Table 4 Epilepsy and Intellectual Disability: Impact on Seizures and Behavior of AEDs from Controlled Trials

Trial	N	Seizure outcome	Behavioral outcome
Felbamate[101]	73	*Atonic seizures*	*Nervousness*

		Active—34% decrease Placebo—9% *Total seizures* Active—19% decrease Placebo—4% increase	Active—5 (14%) Control—5 (14%) No other behavioral outcome recorded, possibly due to side effects that occurred less than five times not recorded
Lamotrigine[72]	169	*All seizures* Active—32% decrease Placebo—9% decrease *Tonic-clonic seizures* Active—36% decrease Placebo—10% increase *Atonic seizures* Active—34% decrease Placebo—9% decrease	*Somnolence* Active—3 (4%) Control—4 (4%)
Topiramate[87]	98	*All seizures* Active—20.6% Placebo—8.8% *Atonic seizures* Active—14.8% reduction Placebo—5.1% increase	*Somnolence* Active—42% Control—22% *Nervousness* Active—21% Control—10% *Behavioral problems* Active—21% Control—10%
Topiramate[55]	88	*All seizures* Active—30% decrease Placebo—1% decrease	*Somnolence* Active—32.4% Control—10.8% *Nervousness* Active—2.7% Control—13.5% *Behavioral problems* Baseline change in Aberrant Behavior Checklist Active reduction in 7.3 points Control reduction by 9.3

Secondly, clinicians will have to assess any negative impact from the treatment change. This again can be a challenging task, especially in individuals who may have poor communication and a range of concurrent illnesses, all with symptoms not unlike those of potential drug side effects. Of these, the most concerning to clinicians and caregivers alike is the potential for behavior change. A structured approach is necessary to

identify those occasions where behavioral symptoms are likely to be treatment related (Fig. 2).

Surgery

For many years in the history of epilepsy surgery, patients with low IQ were excluded as candidates. One reason was that low IQ has been thought to be indicative of generalized cerebral dysfunction, suggesting that the prognosis for improvement of seizures after focal resection is low.[30,60,99] It has also been suggested that in patients with low IQ, the integrity of brain outside the area of focus may not be adequate to allow for compensation after surgery, thus making these individuals more prone to cognitive deterioration.[9,83] A third reason was the assumption that some patients with low IQ may be unable to cooperate or tolerate the preoperative procedures necessary for identifying good surgical candidates.[107] Despite these assumptions, present guidelines typically do not include intellectual status as an exclusion criterion for surgery.

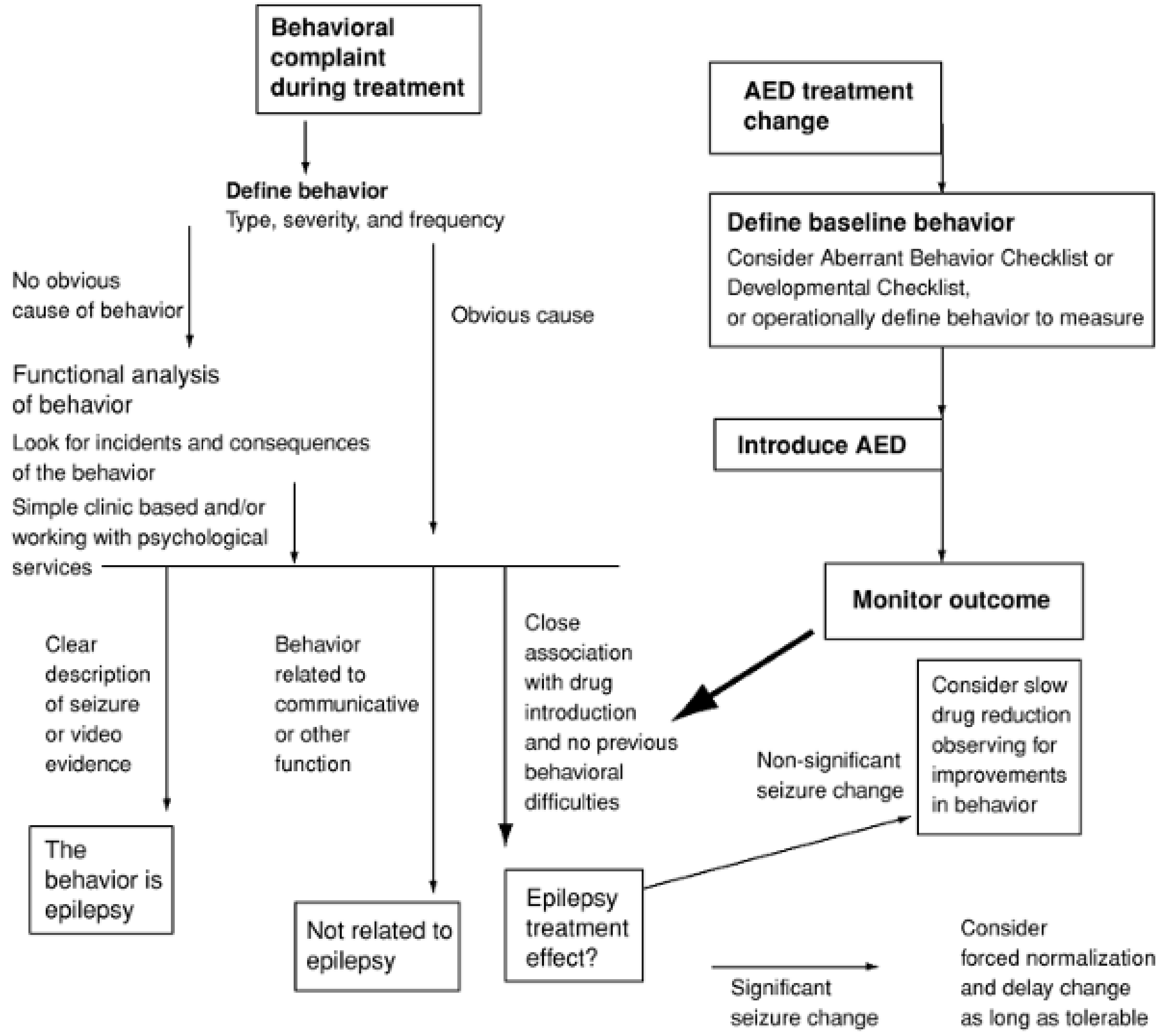
Behavioral complaint during treatment
Define behavior
Type, severity, and frequency
No obvious cause of behavior
Obvious cause
Functional analysis of behavior
Look for incidents and consequences of the behavior
Simple clinic based and/or working with psychological services
Clear description of seizure or video evidence
Behavior related to communicative or other function
Close association with drug introduction and no previous behavioral difficulties
The behavior is epilepsy
Not related to epilepsy
Epilepsy treatment effect?
AED treatment change
Define baseline behavior
Consider Aberrant Behavior Checklist or Developmental Checklist, or operationally define behavior to measure
Introduce AED
Monitor outcome
Non-significant seizure change
Consider slow drug reduction observing for improvements in behavior
Significant seizure change
Consider forced normalization and delay change as long as tolerable

FIGURE 2. Assessing behavioral change during antiepileptic drug treatment. AED, antiepileptic drug. (Published with permission of Clarion Press.)

Vasconcellos et al.[104] examined intellectual function in pediatric candidates for epilepsy surgery. Younger age at onset was associated with lower IQ, and mean IQ was significantly lower in patients with seizure onset at or before 2 years of age. The frequency of patients with intellectual disability varied with age of seizure onset, with 46% of those with seizure onset at or before 2 years of age having IQs lower than 70, compared with only 12% of those with onset after that age. This difference was independent of etiology of the epilepsy[9] reported on surgical outcome in 31 patients with IQ ≤70, approximately 15% of a consecutive surgical series in Norway. Two years after surgery, 52% of those with temporal lobe resections and 38% with extratemporal resections were seizure free. Unfortunately, the authors did not compare outcomes with the other patients in their own series, but comparison with other published series suggested that the seizure outcome was poorer than in patients with higher IQs.[15] An important finding was that the surgical result was related to duration of epilepsy, with greater likelihood of seizure freedom obtained with shorter duration of epilepsy prior to surgery. The authors suggested that when duration was taken into account, the rate of success was comparable to patients with normal intelligence.[60] Cognition did not improve in patients irrespective of IQ, a finding that has been demonstrated in other studies reporting neuropsychological outcomes of surgery in patients of all levels of intellectual

function.[70,94] A review[60] suggested that with careful presurgical evaluations, outcomes are similar between patients with normal IQ scores and those with low scores.

A high proportion of children with infantile spasms have mental retardation and behavior disorders. The UCLA Pediatric Epilepsy Surgery Research Group has compared surgical outcomes in these children with those of children with other forms of intractable symptomatic epilepsy.[13] At 2-year follow-up assessment, both groups continued to show impaired development of language, cognition, and social communication despite improved seizure control.

Vagal Nerve Stimulation

The effects of vagal nerve stimulation (VNS) have been investigated in a number of studies that have included children with intellectual disabilities associated with epileptic syndromes and developmental disorders. Despite reported improvements in seizure frequency and/or severity, mood, and quality of life, changes in cognitive function have not been found.[2,46,65,78] In a series of patients with Lennox-Gastaut syndrome, seizure reduction was highest in patients with highest baseline cognitive function,[2,65] leading these authors to conclude that intellectual disability is a negative prognostic factor for efficacy of VNS.

The Context of Care

Unfortunately, service delivery to individuals with an intellectual disability who have epilepsy has received little attention from the research community. However, five key areas exist around which multiagency care can be structured: Health advocacy, barriers and safety, quality of care, specialist provision, and the needs of the family (Table 5).

Table 5 Multiagency Areas of Need for Individuals with Learning Disability and Epilepsy

Area	Example issues
Health advocacy	Assistance in the communication of an individual's seizures Assistance in communication of an individual's response to treatment and past treatment history

Barriers and safety	Risk assessment of dangers of epilepsy such as bathing Assessment of the impact of epilepsy on an individual's social inclusion
Quality of care	Quality of care environment for individual Ability of environment to supply prescribed treatment Ability to administer rescue medication
Specialist provision	Education, housing Support services such as psychological or behavioral support Investigative services such as EEG and MRI under anesthesia
The family	Respite services Education Training Support

EEG, electroencephalogram; MRI, magnetic resonance imaging.

Health Advocacy

Due to the inherent difficulties in communication associated with intellectual disability, both the individual and the clinician can be disadvantaged. Parents frequently provide communication functions. However, when an individual lives in care, the agency will need to ensure that someone can describe the current seizures, their frequency, and the impact epilepsy is having on the individual. Additionally, services should be able to support the individual to make choices over epilepsy management where appropriate.

Barriers and Safety

Services have a responsibility to the safety of their charges; in particular, risk of bathing accidents must be carefully assessed. Additionally, where epilepsy has become a barrier to social inclusion, this should be identified and appropriate remedies sought.

Quality of Care

Any care setting for an individual with an intellectual disability should be able to meet his or her epilepsy management needs. In particular, medication, where prescribed, should be given, and where rescue medication is prescribed, appropriate management plans should exist.

Specialist Provision

The potential for specialist provision can read something like a wish list of potential services. This, of course, merely reflects the diverse needs of this population. An individual may need appropriate housing or education. Specific support services such as psychology or behavior support agencies may be needed. Completion of investigations will need appropriate disability-aware investigative electrophysiologic and imaging services.

The Family

Families provide much of the health advocacy and housing needs of this population. To deliver this, support is needed with education into epilepsy and its treatment, with the emotional effects on the family members, and with adequate respite services.

Coordinating Multiagency Care Delivery

The delivery of multiagency care does, of itself, need coordination. The availability of resources and trained staff will of course influence the ability to provide and coordinate multiagency care. Some of the key themes can be delivered relatively cheaply such as education on safety and education to caregivers. Where resource exists, other agencies can make a large impact into epilepsy care.

Summary and Conclusions

The interaction between epilepsy and learning disorder is complex and can be subtle and transient. Notwithstanding this for a large proportion of the population with epilepsy major intellectual disability coexists with severe refractory epilepsy. This combination of morbidities impacts on the individuals in their quality of life, and on the professional, demanding specific skills in assessment and treatment. Such skills include the use of communication strategies, recognition of phenotypes, the assessment of behavioural change, application of AEDs and surgical assessment. Our knowledge of this field is advancing as it is in the general epilepsy population. However this advancement is uneven, our chapter shows how the new genetic and aetiological knowledge can be readily applied to this group; yet there are relatively few data from interventional studies and as such the gap in our knowledge on the application and effectiveness of treatments in this group is widening as compared to the general epilepsy population. The challenge for the professional epilepsy community is to close this gap.

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Chapter 203

Personality Disorders in Epilepsy

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Introduction

At the turn of the 20th century, most of the lay and professional communities believed that people with epilepsy had pathologic personality traits and psychopathologic disorders such as aggression, sociopathy, and psychosis. However, from the medical perspective, this was partly an artifact of the main setting from which epilepsy was viewed: Chronically institutionalized patients, many of whom suffered comorbid disorders (e.g., head trauma, neurosyphilis). The concept of an epileptic personality—a ubiquitous and characteristically negative set of behavioral changes in epilepsy patients—was already established in antiquity, but continued to evolve slowly and relentlessly. Simultaneously, more humanistic and balanced views evolved during the 19th century. Based on extensive experience with a private outpatient population with idiopathic epilepsy, Reynolds[87] concluded that epilepsy does not invariably involve abnormal mental change, and Gowers[42] also recognized that many epilepsy patients had normal personality and intellect, but that many others could develop intraparoxysmal behavioral changes. He suggested that these changes resulted from many factors, but mainly from epilepsy.

The early 20th century brought diverse views concerning people with epilepsy and their behaviors. Wilson[121] offered a progressive psychosocial view: "On epileptic temperament inordinate stress has been laid. Life is difficult for these patients, and much that is attributed to temperament can with greater reason be assigned to chronic invalidism and unlucky circumstance." Sjobring[99] adhered to the negative, pervasive view: "A mental change of a specific nature takes place in individuals suffering from epileptic seizures. They become torpid and circumstantial, sticky and adhesive, effectively tense and suffer from explosive outburst of rage, anxiety, etc." Kraepelin[61] reported aggressiveness in some of his outpatient epilepsy patients: "Almost always an intensification of mental irritability occurs." The adhesive or viscous personality traits in which the patient has difficulty in disengaging from interpersonal exchanges was reviewed by many observers in the European literature under various terminologies such as the "enechetic constitution," "ixoid character," and "glischroid trait."

The Modern Era

Early in the 20th century, the term "epileptic personality" was used by psychoanalytic theorists to describe a set of character traits associated with epilepsy that focused on impulsivity, egocentricity, and affective viscosity.[17] These features were considered to result from hereditary factors, directly from seizures or treatment, or a reaction to painful social situations associated with epilepsy. Others believed that these particular personality features, in individuals with or without seizures, were a direct expression of epilepsy itself. Two coincident developments in the middle of the century helped reintroduce the highly controversial concept of personality changes in epilepsy: Identifying the role of the limbic system in emotion and behavior and localizing the onset of many partial seizures to the temporal lobe.

Papez[81] conceived a circuit of interconnected structures comprising the emotion system: Hippocampus—fornix—hy-pothalamus/mammillary bodies—mammillothalamic tract—anterior thalamic nuclei—thalamocingulate fibers—cingulate cortex—amygdala/hippocampus. This emotion circuit theory was based on anatomic connections, sham rage studies, and lesion studies. Yakovlev[124] conceived a basolateral circuit modulating emotional behavior, including the amygdala, insula, orbitofrontal cortex, and dorsomedial thalamic nucleus. MacLean[67] combined earlier ideas and conceived the limbic system with all the above regions, as well as the septum and nucleus accumbens.

The specific association of temporal lobe epilepsy (TLE) and psychopathology had its major genesis in the 1951 report by Gibbs[40] that up to 33% of patients with “psychomotor seizures” of temporal lobe origin exhibited interictal behavioral changes. Gastaut et al.[36] in 1954 reiterated common observations on the frequency of emotional viscosity, hyposexuality, hypoactivity, and aggressiveness in epilepsy patients, and first suggested that the stereotypic symptom complex was the antithesis of behaviors in the Kluver-Bucy syndrome (KBS). KBS is characterized by oral exploratory behavior, increased sexual appetite, decreased aggressivity, and continuous environmental exploration as a consequence of bilateral anterior temporal destructive lesions.[59]

Waxman and Geschwind[117] proposed a distinct subset of nonpathologic behaviors associated with TLE, which included deepened emotions, circumstantiality, altered religious and sexual concerns, and hypergraphia. They coined the term “interictal behavior syndrome,” sometimes referred to as Geschwind syndrome or Gastaut-Geschwind syndrome.[6] Bear and Fedio[4] expanded this syndrome to include the 18 traits based on a literature review. They found an increased frequency of all 18 traits in patients with TLE compared with non-neurologic controls. The interictal behavioral traits described by Bear and Fedio are summarized in Table 1. Some of these traits associated with this syndrome are described below in more detail.

Table 1 Proposed Personality Traits by Bear and Fedio

Hypergraphia
Hypermoralism
Altered sexuality
Religiosity
Aggression
Obsessionalism
Paranoia
Guilt
Humorlessness

Sadness
Emotionality
Circumstantiality
Philosophical interest
Personal destiny
Viscosity
Dependence
Elation
Anger

Viscosity

Viscosity is a tendency for prolonged interpersonal contacts; talking repetitively, circumstantially; and pedantically; and not ending conversations and visits after a socially appropriate interval. Bear and Fedio[4] reported viscosity to be significantly elevated in both right and left TLE compared to normal and neurologic controls. Brandt et al.[10] found increased viscosity among left TLE and generalized epilepsy (GE) patients, with no difference between right TLE and controls. Hoeppner et al.[51] presented the "cookie thief" picture from the Boston

Diagnostic Aphasia Examination, which shows a drawing of a boy stealing a cookie, to TLE, GE, and control subjects. Taped responses were reviewed blindly and all four individuals with verbose responses, characterized by trivial, circumstantial, and subjective details, had left temporal foci. A ten-item viscosity scale revealed significantly higher scores in the self-reports of patients with left TLE compared to right or bilateral TLE, absence seizures, panic disorder, or normal subjects.[86] Proxy raters reported a trend for increased viscosity scores in the left TLE group, endorsing items such as "when I have a phone conversation with him/her, I always find I am the one who wants to get off first." Seizure duration and viscosity score were significantly correlated for patients with left TLE.

Viscosity may result from some combination of linguistic impairment, social cohesion, mental slowness, and psychological dependence. Language dysfunction associated with left temporal lobe seizure foci may contribute to a verbal style characterized by circumstantiality and excessive discourse. However, there may be independent effects of left temporal foci on social behavior. Viscosity, the personality trait, may also result from an increased desire for interpersonal closeness, a need for affiliation with another being. Discrete limbic lesions can profoundly alter how animals maintain contacts with other members of their own or other species.[41,60,73] For example, rats with septal lesions will remain in contact with each other in an open field and, if left alone, will actively approach cats despite expressions of fear.[73] It is possible that some biologic effects of the epileptogenic process or recurrent seizures in a minority of patients with temporolimbic epilepsy, especially in the dominant hemisphere, fosters the development of viscosity.

Hyposexuality

Various changes in interictal sexual behavior occur in patients with TLE. Hyposexuality is frequently reported,[7,31,35,83,93,98,101,108] with anecdotal reports of hypersexuality[38,98] and deviant sexual behavior including exhibitionism,[7,52] transvestism,[27,84] transsexualism,[50] and fetishism.[26,74] Isolated cases of unusual sexual behavior occurring in patients with epilepsy could be chance associations. However, some cases develop profound changes in adulthood, shortly after the onset of epilepsy, raising the possibility of an etiologic relationship. Hyposexuality, including decreased libido and impotence, occurs in approximately half of TLE patients without gender bias. In many cases, especially those with seizure onset before puberty, patients may not marry or regard hyposexuality as a problem. Complaints are more likely to come from the spouse or parent who observes lack of interest in the opposite sex. Much of the original literature on hyposexuality from 1954 to 1985 was based on self-report[76] without detailed interviews to assess the relative roles of libido, arousal, erectile dysfunction, anorgasmia, and sexual satisfaction, as well as physiologic measures of endocrine and sexual function.

Most studies found higher rates of hyposexuality and sexual dysfunction in TLE than other epilepsy groups, although Fenwick et al.[31] did not observe any significant difference in sexual activity related to seizure type, type of epilepsy, or seizure frequency. Among those with TLE, no laterality effects were found for sexual behavior in left- versus right-sided seizure foci.[16] A well-designed study of six men with erectile dysfunction found abnormal nocturnal penile tumescence and rigidity in five.[44] The pattern of abnormality was consistent with neurogenic, not vasogenic, erectile dysfunction. In a self-report survey of 116 women with epilepsy, partial epilepsy patients experienced more dyspareunia, vaginismus, arousal insufficiency, and sexual dissatisfaction, whereas primary generalized epilepsy (PGE) patients experienced more anorgasmia and sexual dissatisfaction.[75] Sexual symptoms were not associated with seizure frequency, antiepileptic drug (AED) exposure, sexual experience, depression, or prepubertal seizure onset.

The pathogenetic role of temporal lobe seizures in hyposexuality is supported by animal models[30] and observations that sexual activity can increase following successful seizure control with AEDs[83] and temporal lobectomy.[7] In some postlobectomy subjects, marked hypersexuality similar to the Kluver-Bucy syndrome can develop occasionally.[9] However, AEDs modulate hypothalamic-pituitary-gonadal axis hormone activity and can directly inhibit sexual behavior.[64] Barbiturates may cause the greatest decrease in libido and sexual dysfunction.[70] Other hepatic enzyme–inducing AEDs are also associated with decreased testosterone levels and diminished libido and function.[49] Valproic acid is associated with menstrual disorders, hyperandrogenism, and polycystic ovaries.[54,78]

Religiosity

The ancient association between epilepsy and mystical/religious phenomena is paradigmatic of the difficulty reconciling dramatic anecdotes and long-standing medical opinion with limited clinical studies. Hippocrates began his monograph *On the Sacred Disease* by refuting the association between epilepsy and the divine. Despite his modern insights, religious and magical treatments of epilepsy predominated throughout the Middle Ages and Renaissance.[109] In the 19th century, psychiatrists stressed the religiosity of epilepsy patients and observed that Siberian medicine men preferred epileptic pupils.[64] Classic monographs on religious mysticism noted that “among the dread diseases that afflict humanity there is only one that interests us quite particularly; that disease is epilepsy.”[64] Intense religious experiences and beliefs are reported frequently by people with epilepsy. Many prominent religious figures allegedly had epilepsy, including prophets and founders of several religions.[116] The evidence supporting epilepsy in these people varies. Intense religious experiences can occur in association with seizures.[13,25,53,66,102]

Dewhurst and Beard[23] reported six TLE patients who underwent sudden religious conversions. There was a clear temporal relationship between conversion and increased seizure activity in five patients; one patient had a marked decrease in seizure frequency prior to conversion (she attributed her improved seizure disorder to the Almighty). Increased religious conviction and practice is not a consistent behavioral feature in patients with epilepsy. There is little evidence that epilepsy or TLE patients as a group are hyperreligious, although a subgroup may have unusually strong religious beliefs. Two studies with questionnaires on religion failed to differentiate patients with right versus left TLE, TLE versus GE, or epilepsy patients and controls.[110,120] However, one study found that patients with smaller right hippocampi had significantly higher ratings on a religiosity scale.[123]

Hypergraphia

Hypergraphia is not characteristic of interictal behavior among TLE or GE patients. However, several studies support that the subgroup manifesting this behavior most intensely are those with temporal lobe foci. Waxman and Geschwind[116] reported seven TLE patients with hypergraphia, which is a tendency toward extensive and sometimes compulsive writing. There was a striking preoccupation with detail—words were defined and redefined and underlined, parentheses were used to make word meaning absolutely clear—and the writers accorded great importance to their material. In four patients, the writings focused on moral and religious concerns. Hypergraphia was viewed as a component of the deepened emotions and especially viscosity of interictal behavioral changes.

Utilizing a mailed standard questionnaire, Sachdev and Waxman[92] demonstrated that TLE patients responded frequently and extensively (mean 1,301 words) as compared to other epilepsy patients (mean 106 words). Hermann et al.[47] replicated the higher response rates and longest letters in the TLE group, but they did not find that the average response was longer in TLE patients compared to other seizure patients. Duration of epilepsy, hypomania, and number of significant life events during the past year positively correlated with hypergraphia.[47,48] Hypergraphia occurs in 7% to 10% of TLE patients.[47,48]

Dostoyevsky was the most famous hypergraphic TLE patient,[39] although his prolific writing also reflected his pay per page and financial troubles. As a person, he was deeply emotional, irritable, angered over minor provocations, guilt ridden, depressed, and tortured over the question of God's existence. He described the relation between his writing and epilepsy in a letter to his brother (August 27, 1849): “Whenever formerly I had such nervous disturbances, I made use of them for writing; in such a state I could write much more and much better than usual.”[24]

Aggression

Interictal violence and aggression is a highly contentious topic, especially the relationship between TLE and aggression. There appears to be a relatively elevated incidence of interictal violence and hostility in patients with epilepsy as compared to healthy controls. The neurosurgical series of Serafetinides[97] and of Taylor[107] demonstrated rates of interictal aggression approaching 30% in TLE patients prior to temporal lobectomy. These studies were criticized for selection bias of refractory patients and those with psychiatric presentations. Rodin[91] identified 5% of patients presenting to an epilepsy center as manifesting aggressive behavior. Seizure type did not distinguish aggressive from nonaggressive patients. Gunn and Fenton[45] documented increased prevalence of epilepsy in British prisons relative to the general population. A study of the Illinois prison system documented a prevalence rate of epilepsy of 2.4%, elevated relative to the U.S. population at the time of the study. However, census of prisoners with epilepsy against matched nonepileptic controls did not reveal more serious violent crimes on the part of the epilepsy group.[118]

Violence and hostility in epilepsy is likely a consequence of an interaction of neurophysiologic as well as social factors. Male sex is a risk factor for violence and epilepsy, and Serafetinides noted that aggressiveness as a personality trait in TLE patients was more likely in those with seizure onset prior to age 10 years. Other risk factors identified in the TLE group include premature interruption of formal schooling, lower intellectual quotient, and lower socioeconomic status. These risk factors are associated with a greater risk of aggression in nonepileptic patients as well. Several studies found that ictal and interictal aggression appear to be more common in children than adults with TLE.[43,80,106] More specific neurobiologic factors were identified in a quantitative magnetic resonance imaging (MRI) analysis of mesial temporal structures in epilepsy patients with and without a history of interictal aggression.[112] Those with interictal aggression had less hippocampal atrophy. Two subgroups of those with aggression were identified: Those with severe amygdala atrophy and a history of encephalitis and those with left temporal lesions affecting the amygdala or periamygdaloid regions.[112]

Problems of Definition and Methodology

Defining specific personality traits and aberrations in patients with epilepsy is difficult and controversial. From a psychiatric standpoint, studies on interictal behavioral changes in epilepsy have not been "discipline neutral."[2] Over the past decades, stereotyped notions of personality attributes in patients with chronic seizures have been dominated by psychoanalysts and those performing trait analyses within the psychometric tradition of self-report methodologies and multivariate statistics. Debates in the literature center on complex personality concepts (e.g., hyperreligiosity) rather than attempt to integrate "first order" biologic variables that underlie the causality of complex behaviors (vide infra).

Considering the variety of epilepsy syndromes and their many etiologies, correlation of interictal behavior with a specific physiologic process or anatomic locus is difficult. Many studies on behavior and epilepsy were done before video-electroencephalographic (V-EEG) confirmation of a specific ictal onset zone and without high-resolution MRI. Many authors simplistically approach "TLE" as a monolithic entity primarily involving mesiotemporal structures. Analyses and speculations thereby focus exclusively on limbic-affective states. However, subdural grid electrode recordings frequently document TLE seizure onsets from neocortical extralimbic regions in isolation or together with mesial structures.[58,68] Even when invasive monitoring documents a temporal lobe "focus," there often is associated extratemporal glucose hypometabolism as defined by positron emission tomography (PET).[57] In patients with TLE, as an illustration, prefrontal metabolic asymmetry is associated with cognitive impairment and depression.[12,57]

Identifying behavioral changes confined to the interictal period is another methodologic challenge. Preictal (premonitory), postictal, and interictal behavioral alterations are less well circumscribed temporally than ictal changes. In the extreme case of partial status epilepticus, cognitive impairments form a continuum despite EEG evolution from discrete seizures to periodic discharges and finally re-emergence of normal EEG background.[88] For isolated seizures, transitions between ictal, preictal, postictal, and interictal behavioral states can be fluid, and clinical distinctions made may be artificial. These behavioral changes may morph over time and extend from their initial extent during the postictal period to more continuous disorders that fill the interictal periods.[105]

Studies from the pre-MRI/pre–V-EEG era are limited by methodologic issues, including the diagnosis of epilepsy (e.g., nonepileptic events), syndromic diagnosis (e.g., benign rolandic epilepsy vs. TLE in a child), and localization of the seizure focus (e.g., frontal vs. temporal), which may all be more problematic in older than more recent studies. Before high-resolution MRI, structural lesions such as cortical dysplasias, vascular malformations, and low-grade neoplasms were not identified. Studies of TLE patients in the pre-MRI era likely included patients with erroneous localization and lateralization.

Finally, past behavioral analysis of the population with ep-ilepsy focused on personality structure rarely assessed lifetime developmental, antiepileptic drug, or other variables.[14,79,96,104]

Interictal Behavioral Changes in Other Epilepsy Syndromes

Personality Changes in Primary Generalized Epilepsy

Personality changes in epilepsy are not restricted to patients with partial epilepsy; they also occur in patients with PGE syndromes such as juvenile myoclonic epilepsy (JME)[55] and absence epilepsy.[100] In JME, reported traits included irresponsibility and impaired impulse control, neglect of duties, self-interest, emotional instability, exaggeration, inconsiderateness, quick temper, and distractibility. Janz[55] found that many JME patients repeatedly exposed themselves to sleep deprivation and often failed to comply with AEDs, taking their illness lightly. They denied problems and conflicts, or often yielded to temptation against better judgment. There was limited support for Janz's clinical impression,[5] although scientific evidence is sparse and some of these behaviors may reflect adolescence, not JME. Other studies found high rates of psychiatric disorders among patients with JME.[82,113] Gelisse et al.[37] reported 45 (26.5%) of 170 consecutive JME patients with psychiatric disorders. Twenty-four of these 45 patients had personality disorders, including borderline (11 cases), dependent (five cases), histrionic (two cases), obsessive-compulsive (one case), and not otherwise specified (five cases).

Absence epilepsy, long considered one of the most benign forms of epilepsy, recently has been associated with significant behavioral changes in a very well-controlled study. Wirrell et al.[122] compared all children in Nova Scotia with typical absence epilepsy or juvenile rheumatoid arthritis (JRA) diagnosed between 1986 and 1997, who were aged 18 years or older at follow-up (mean age 23 years). Remission occurred in 32 (57%) of the patients with typical absence epilepsy but in only 17 (28%) of the patients with JRA. Five categories of outcome were studied: Academic-personal, behavioral, employment-financial, family relations, and social-personal relations. Patients with typical absence epilepsy had greater difficulties in the academic-personal and in the behavioral categories (p <0.001) than those with JRA. Those with ongoing seizures had the least favorable outcome. Most seizure-related factors showed minimal correlation with psychosocial functioning. Even patients whose epilepsy had remitted had significantly poorer outcomes than the JRA patients in the academic-personal and behavioral domains. Another recent study found that 54% of pediatric patients with PGE had psychiatric disorders.[12] Early age of onset and poor seizure control were significantly associated with the severity of illogical thinking in these children. Thus, the recent literature strongly supports prior research that PGE is a risk factor for cognitive and behavioral problems.

Personality Changes in Patients with Frontal Lobe Epilepsy

The frontal lobes are important in personality, as highlighted by the effects of prefrontal surgeries. Thus, as limbic disorders can alter emotion- and drive-related behavior (e.g., sex and aggression), frontal dysfunction can alter personality, judgment, and executive functions. Further, the posterior orbitofrontal cortex and anterior cingulate gyrus, two critical limbic (paralimbic) areas, are located within the frontal lobe. Patients with anterior cingulate seizure foci can develop interictal psychosis, aggression, sociopathic behavior, sexual deviancy, irritability, obsessive-compulsive disorder, and poor impulse control.[3,19,21,71] Orbitofrontal lesions can cause hyperphagia, failure to use autonomic cues to guide behavior, aberrant emotional responsiveness, increased aggression, dysfunctional social behavior (e.g., case of Phineas Gage[16,97]), behavioral disinhibition, and confabulation.[20] Systematic studies on interictal behavior in patients with orbitofrontal seizure foci are lacking; however, behavioral disorders such as attention deficit hyperactivity disorder can occur.[85] Given the critical role of this limbic cortex in social and emotional behavior, epileptic foci in this site could cause prominent interictal behavioral changes.

In the Vietnam Head Injury Study,[103] patients with tonic–clonic seizures had a higher frequency of psychiatric treatment than those with complex partial seizures, possibly reflecting greater frontal lobe involvement. The role of the frontal lobe in the personality and behavior of epileptic patients deserves greater attention. Functional imaging studies suggest that, even among patients with temporal lobe seizure foci, frontal dysfunction contributes to affective, personality, and cognitive disorders.[11,82,94]

Characterizing the Interictal Behavior Syndrome

The Bear Fedio Inventory

In the original study using this measure, all 18 self-rated traits were significantly higher in the TLE group than in neurologic and healthy controls. The most significant differences (p <0.0001) were humorlessness, circumstantiality, dependence, and sense of personal destiny. Proxy raters (i.e., family or friends) identified TLE patients as significantly different from controls on 14 traits, most strongly (p <0.0001) for circumstantiality, obsessionalism, and dependence. Patients with right temporal foci reported more emotional traits and minimized their behavioral changes (i.e., polished their image), whereas patients with left temporal foci had more ideational traits and often tarnished their image on self-report relative to proxy reports. The previously reported associations of right hemisphere lesions with denial and neglect syndromes and left hemisphere lesions with depression[33,34,89,90] were consistent with the right/left:polish/tarnish correlation.

Replication studies using the Bear Fedio Inventory (BFI) have produced mixed results.[11,22,46,77] Use of the BFI generally reveals increased rates of these behavioral traits in patients with epilepsy (TLE and GE) in comparison to healthy controls or some medical patients, but it does not distinguish epilepsy (TLE or GE) from psychiatric patients. Findings from TLE versus GE patient comparisons are inconsistent. When differences are present, the TLE group usually has higher scores than the GE group. Left–right differences in TLE are typically minor.

The complicating issue of frontal lobe seizure foci or frontal lobe involvement (e.g., seizure spread or interictal hypometabolism/neuronal dysfunction) should also be considered in patients with TLE. Although personality disorders are highlighted in the literature as elements of TLE, they would be expected to be features of frontal lobe epilepsy (FLE) as well. Indeed, in the literature on the BFI, the study by Wieser[119] was the only one to use invasive electrodes for localization and lateralization, and failed to replicate any laterality effects found by Bear and Fedio.[5] Interestingly, Wieser found a significant increase in humorlessness in the FLE group and a nonsignificant trend for an increase in all BFI behavioral traits in the FLE group.

The studies with the BFI nearly vanished after 1990, just as high-resolution MRI and V-EEG monitoring allowed more confident anatomic and physiologic diagnoses. As the BFI fell out of favor, so did much of the research on personality in epilepsy patients. Consequently, the subject of personality changes in epilepsy warrants further study.

The Neurobehavioral Inventory (NBI) is a more recent tool to specifically assess interictal psychopathology in epilepsy patients.[8] There has been relatively little use of the NBI, but it may prove valuable. In one study, patients with high ratings on the NBI religiosity scale had smaller hippocampi, while in another study, hyposexuality and hypergraphia were associated with bilateral hippocampal atrophy.[111]

Mazzini et al.[72] evaluated 143 patients with traumatic brain injury (TBI), of which 27 developed posttraumatic epilepsy (PTE), using another measure—the Neurobehavioral Rating Scale (NBHRS)—along with the Minnesota Multiphasic Personality Inventory (MMPI), Overt Aggression Scale, Back Depression Inventory (BDI), and *Diagnostic and Statistical Manual of Mental Disorders,* 4th ed. (DSM-IV) definitions for personality disorders. Patients with epilepsy showed a significantly higher incidence of severe personality disorders. Disinhibited behavior, irritability, and agitated and aggressive behavior were significantly more frequent and severe in PTE patients.

Feddersen et al.[29] examined 37 TLE patients, 38 with idiopathic generalized epilepsy with absence and generalized tonic–clonic seizures and 25 healthy controls using the Freiburg Personality Inventory/Form A (FPI-A-H)[28] and the Index of Personality Characteristics (IPC).[62] Patients with left TLE had increased emotional dependency, less externally judged composedness, increased depressive drive and mood, increased nervousness, increased search for information and exchange of disease experience, and greater tendency to persevere ($p < 0.05$). This study supported the differentiation made by Bear and Fedio[4] that patients with left TLE are more rational and tarnish their image, whereas patients with right TLE are more emotional and polish their image.

One study with the Millon Behavioral Health Inventory (MBHI) found that epilepsy patients have deficient coping styles.[115] Patients with epilepsy obtained higher scores on scales assessing inhibition and sensitivity and lower scores on scales evaluating sociability and confidence.

Table 2 Rate of Personality Disorders in Epilepsy

Schwartz and Cummings (1988)[95]	38% (4% controls)
Fiordelli et al. (1993)[32]	21% (0% controls)
Victoroff (1994)[114]	18%
Manchanda et al. (1996)[69]	18%
Arnold and Privitera (1996)[1]	18%
Lopez-Rodriguez et al. (1999)[65]	21%
Krishnamoorthy et al. (2001)[63]	47%
Koch-Stoecker (2002)[59a]	61%
Galimberti et al. (2003)[33a]	38%

DSM Axis II Disorders

Another approach to examining personality disorder in epilepsy is to turn to formal DSM-IV Axis II diagnoses. By definition, personality disorders are characterized by long-lasting patterns of thought and behavior that deviate from cultural expectations, inflexible and pervasive in nature, that result in impairment of function. To receive a diagnosis of personality disorder, the pattern of behavior must result in significant distress or impairment in personal, social, or occupational situations. Several criteria must be met in addition to the specific criteria for individually named personality disorders. These include the following:

1. Experience and behavior that deviates markedly from the expectations of the individual's culture. This pattern is manifested in two (or more) areas including cognition, affectivity, interpersonal functioning, and impulse control.
2. The enduring pattern is inflexible and pervasive across a broad range of personal and social situations.
3. The enduring pattern leads to clinically significant distress or impairment in social, occupational, or other important areas of functioning.
4. The pattern is stable and of long duration and its onset can be traced back at least to adolescence or early adulthood.
5. The enduring pattern is not better accounted for as a manifestation or consequence of another mental disorder.
6. The enduring pattern is not due to the direct physiologic effects of a substance or a general medical condition such as head injury.

There are ten specific personality disorders in DSM-IV, which are grouped into three clusters: *Cluster A* (odd or eccentric disorders) includes paranoid personality disorder, schizoid personality disorder, and schizotypal personality disorder; *cluster B* (dramatic, emotional, or erratic disorders) includes antisocial personality disorder, borderline personality disorder, histrionic personality disorder, and narcissistic personality disorder; and *cluster C* (anxious or fearful disorders) includes avoidant personality disorder, dependent personality disorder, and obsessive-compulsive personality disorder. Finally, *personality disorder NOS* is a category for behavior patterns that do not match these ten disorders but have the characteristics of a personality disorder.

A series of investigations have assessed Axis II disorders (not including mental retardation) in patients with epilepsy using contemporary diagnostic procedures. As can be seen in Table 2, the rate of Axis II disorders range from 18% to 61% across studies, with a mean of 31% (median = 21%). Only two studies incorporated controls. These rates are elevated overall and investigations that examined the distribution of clusters A through C reveal that most individuals with epilepsy with Axis II disorders exhibit cluster C disorders. Even biologically oriented researchers recognize that problems associated with living with epilepsy, particularly early-onset epilepsy, may lead to dependant and avoidant personality traits, although this contention has not been examined empirically.

Table 3 Distribution of Specific Personality Disorders in Epilepsy

Authors	N	A	B	C	Procedure
Lopez-Rodriguez et al. 1999	52	0.0%	5.8%	15.4%	SCID-II
Galimberti et al. 2003	69	1.4%	10.1%	26.0%	SCID-II
Koch-Stoecker et al. 2002	100	6.0%	15.0%	24.0%	DSM-III-R
Krishnamoorthy et al. 2001	35	17.1%	2.9%	22.9%	SAP

SCID-II Structured Clinical Interview for DSM-IV-TR
DSM-III-R Diagnostic and Statistical Manual of Mental Disorders-III-R
PSE Present State Examination
A Cluster A; odd or eccentric disorders
B Cluster B; dramatic, emotional, or erratic disorders
C Cluster C; anxious or fearful disorders

Axis II disorders are probably underrecognized and incompletely addressed in the traditional clinic setting (Table 3). There is little information regarding their consequences, but

the evidence available suggests that they are of consequence. Koch-Stoecker examined the predictors of postoperative psychiatric complications in 100 patients who underwent anterior temporal lobectomy (ATL).[59a] Patients were assessed for Axis I and II disorders preoperatively. Fourteen percent of their surgical patients were hospitalized for psychiatric reasons postoperatively and all these patients exhibited Axis II disorders preoperatively, either alone of in combination with Axis I disorders. No patients with just an Axis I disorder underwent postoperative psychiatric hospitalization.

Another indication of the maladaptive consequences associated with adverse personality features is demonstrated by Derry et al., who examined the impact of neuroticism on postoperative course in 45 individual ATL patients.[18] Those who were high in preoperative neuroticism exhibited significantly worse postoperative psychosocial adjustment and quality of life.

Summary and Conclusions

Personality disorders and other, less pathologic personality changes are common and often unrecognized in epilepsy patients. These disorders likely result from biologic factors such as structural and physiologic abnormalities as well as social and emotional factors. The specificity of certain personality traits or clusters and anatomic seizure foci (e.g., TLE or FLE) and epilepsy syndromes (e.g., partial vs. generalized) remains controversial, mired in methodologic issues and limited by a literature that often predated MRI and V-EEG studies. However, traits such as hypergraphia, although present in <10% of TLE patients, appear to be much more common in this form of epilepsy than others. Patients with FLE and idiopathic generalized epilepsy can also develop behavioral changes and personality disorders that can significantly impact their lives. The area remains ripe for additional studies using modern psychiatric and neurologic diagnostic tools.

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Chapter 204

Schizophrenia and Other Psychoses

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Introduction

Because the brain is the central organ that regulates behavior, a change of behavior may come about with disturbances of the brain, either through alteration of its structure or via functional change, functional here being used in its original meaning to emphasize disturbance of brain function.[92] Neurologists interested in behavioral disorders have mainly concerned themselves with patients with lesions that cause structural changes, whereas psychiatrists have dealt more with the consequences of disturbed function, where underlying structural lesions have been more difficult to discern. Epilepsy is one of a number of conditions in which there is often an underlying structural abnormality to be found if the appropriate technique is used (e.g., neuropathology, magnetic resonance imaging), but profound functional changes also occur, either as a consequence or independently. These may be reflected in the seizure, one manifestation of the epilepsy process, but may also be associated with some of the less dramatic but nonetheless clinically significant behavioral manifestations of epilepsy.

Definitions and Phenomenology

Psychosis, as used in the International Classification of Diseases (ICD)-10,[25] defines a disorder with the presence of “hallucinations, delusions, or a limited number of severe abnormalities of behavior, such as gross excitement and overactivity, marked psychomotor retardation, and catatonic behavior.” In the *Diagnostic and Statistical Manual of Mental Disorders,* 4th ed. (DSM-IV), the term psychotic refers to delusions, any prominent hallucinations, disorganized speech, or disorganized or catatonic behavior.[7]

Hallucinations and delusions, the hallmark of psychosis, suggest some deviant neurologic processing, underlying which are usually structural but sometimes solely functional alterations of activity. Although in epilepsy hallucinations and delusions may be experienced in certain settings for which patients have clear insight, in the majority of cases insight is lacking, and the condition is truly psychotic.

Historical Background

In the middle of the 19th century, European psychiatrists noted the high incidence of psychotic episodes in institutionalized patients with epilepsy. Several authors described the specific psychopathology of psychiatric complications occurring in the context of epilepsy using such terms as “épilepsie lavvée,”[50] “grand mal intellectual,”[9] “epileptoid states,”[18] and “epileptic equivalents.”[24] Samt[62] put forward the idea that the pathophysiology of certain psychoses occurring in the context of epilepsy, especially episodic twilight states, was identical to the pathophysiology of motor seizures. He suggested that in the absence of epileptic seizures, such epileptic equivalents could be sufficient for a diagnosis of epilepsy.

Some authors in the 19th century explicitly noted the rarity of chronic paranoia or true madness in patients with epilepsy. These observations resulted in intensive discussions on the nature of the relationship between epilepsy and schizophrenia, a subject frequently chosen in theoretical disputes on definitions of terms such as disease and symptom complex in psychiatry at the beginning of the 20th century.[20,30]

Combined seizures and schizophrenialike symptoms have generally been interpreted either as symptomatic seizures secondary to cerebral sequelae of insanity—for example, brain edema in catatonia—or as symptomatic psychoses caused by seizures or the underlying epileptic process.[32,36] In cases with no obvious temporal relationship between epileptic seizures and psychotic symptoms, it was speculated that both were not directly linked but were caused by the same underlying brain pathology.[54,73] Ganter,[13] Krapf,[32] and Glaus[16] published clinical case series with prevalence rates of combinations lower than expected. These studies, together with observations of alternating periods with seizures and seizure-free periods with psychosis in some patients and the improvement of psychotic symptoms after spontaneous seizures in others, led to the theory of functional dependency and biologic antagonism of schizophrenic and epileptic symptoms, a concept that influenced von Meduna[46] to introduce iatrogenic convulsions into the treatment of schizophrenia.

With progress in diagnosis and treatment in epilepsy, epileptology shifted conceptually to the realm of neurologists in many countries. Psychiatric aspects were neglected until they were "rediscovered" in the 1950s and 1960s.[14,38,82] American and English authors reported an excess of schizophrenialike psychoses in epilepsy patients, especially in those suffering from temporal lobe epilepsy.[15,55,70]

Slater et al. published a detailed analysis of 69 patients from two London hospitals who suffered from epilepsy and interictal psychoses. On the basis of this case series, the authors challenged the antagonism theory and postulated a positive link between epilepsy and schizophrenia. Although Slater was criticized for drawing conclusions on the basis of insufficient statistics,[77] the temporal lobe hypothesis soon became broadly accepted and stimulated extensive research into the role of temporal lobe pathology in schizophrenia. The use of epileptic psychoses as a biologic model or "mockup" of schizophrenia[59] is largely based on Gibbs and Slater's work.

Table 1 Clinical Characteristics of Psychoses in Relation to Seizure Activity

	Ictal	Postictal	Parictal	Alternative	Interictal
Relative frequency	~10%	~50%	~10%	~10%	~20%
Consciousness	Impaired	Impaired or normal	Impaired	Normal	Normal
Typical features	Mild motor symptoms	Lucid interval	Occurs often during presurgical evaluation	Initial symptom insomnia	Schizophrenialike psychopathology
Duration	Hours to days	Days to weeks	Days to weeks	Weeks	Months
EEG	Status epilepticus	Increased slowing, increased epileptic	Increased slowing, increased epileptic	Normalized	Unchanged
Treatment	Antiepileptic drugs IV	Spontaneous recovery, benzodiazepines, seizure control	Seizure control	Sleep regulation, reduction of antiepileptic drugs	Antipsychotics

EEG, electroencephalogram.

The possible impact of research into epileptic psychosis on the understanding of the pathophysiology of endogenous psychoses explains the bias in the literature toward study of interictal schizophrenialike psychoses. The spectrum of psychotic syndromes in epilepsy is, however, much more complex, and psychotic complications are not restricted to patients with temporal lobe epilepsy.

Epidemiology

Some of the earlier studies were reviewed in the first edition of this textbook (Chapter 197). The more recent studies have employed an improved methodology. Bredkjaer[2] in a record linkage study looked for associations between epilepsy from the national patient register of Denmark and the equivalent psychiatric register. The incidence of nonorganic, nonaffective psychoses, which included schizophrenia and schizophrenia spectrum disorders, was significantly increased in epilepsy, even when patients with learning disability or substance misuse were excluded.

Stefansson et al.[76] in a case-control study compared the prevalence of nonorganic psychiatric disorders in patients with epilepsy to those with other somatic diseases, the groups being taken from a disability register in Iceland. Although the difference in psychiatric diagnoses overall was not significant, there was a higher rate of psychoses, particularly schizophrenia and paranoid states, among males with epilepsy.

Qin et al.[56] in another study from Denmark have confirmed the increased risk of schizophrenia and schizophrenialike psychoses in epilepsy, and in this study a family history of psychoses and a family history of epilepsy were significant risk factors for psychosis.

Studies from Japan examining new referrals for epilepsy quote a 6% prevalence of psychoses in those with normal intelligence (in contrast to 24% in those with learning disability).[44]

There are several studies of much more selected populations, such as hospital case series. Thus, Gureje,[19] in patients attending a neurologic clinic, quoted that 37% of patients were psychiatric cases and that 29% of these were psychotic. Mendez et al.[48] in a retrospective investigation reported that interictal psychotic disorders were found in over 9% of a large cohort of patients with epilepsy in contrast to just over 1% in patients with migraine. The epilepsy sample had more complex partial seizures, more auras, and less generalized epilepsy.

None of the above studies has been able to examine issues related to epilepsy classification in any detail, cohorts being derived from case registers lacking detailed information from, for example, brain imaging. Certain risk factors have been defined, but not from these data, and are noted below.

Classification

There is no internationally accepted syndromic classification of psychoses in epilepsy. Most of the previously proposed classification systems for these psychoses[3,10,29,85] are based on a combination of psychopathologic, etiologic, longitudinal, and electroencephalographic (EEG) parameters. Unfortunately, because of a lack of taxonomic studies, our knowledge about regular syndromic associations is still limited.

"Atypical" syndromes are not unusual, and presentations such as those associated with forced normalization (see below) and postictal psychoses make simple divisions between what is ictal and what is interictal difficult to discern. In other words, the above two examples are of psychotic states closely tied to the biology of the ictus but which are interictal in their timing. A new multiaxial approach to the classification of psychoses in epilepsy can be found in the proposal by Krishnamoorthy.[33]

It is suggested that patients with epilepsy and psychoses receive two separate diagnoses according to either ICD-10 or DSM-IV,[7] but in addition, the relationships between onset of psychosis and seizure activity, antiepileptic therapy, and changes of EEG findings should be noted.

For pragmatic reasons, however, it remains convenient to group psychoses in epilepsy according to their temporal relationship to seizures.

Syndromes of Psychoses in Relation to Seizure Activity

The various syndromes are described in Table 1. The ictal psychoses are more likely to be linked to complex partial seizure status but have never been examined in any detail. In clinical practice they are not uncommon in seizures of temporal origin, but some of them are secondary to frontal lobe seizures. Simple focal status or aura continua may cause complex hallucinations, thought disorders, and affective symptoms. The continuous epileptic activity is restricted and may escape scalp EEG recordings. Insight usually is maintained, and true psychoses emerging from such a state have not been described. Nonconvulsive status epilepticus requires immediate treatment with intravenous antiepileptic drugs.

Table 2 Differences between Postictal Psychoses (PIP) and Interictal Psychoses (IIP) (Statistically Significant)

	PIP (n = 45)	IIP (n = 126)
Reduced intelligence (<70 IQ)	4	39
Complex partial seizures	37	84
Déjà vu aura[a]	10 of 43	10 of 103
Temporal MRI lesion	16	25
Temporal lobe epilepsy	39	74
Generalized spike-waves	1	21
Age at epilepsy onset (years)	16	11
Age at psychosis onset (years)	35	25
Interval between onset epilepsy and psychosis (years)	18	13

[a] Calculated for the subgroup of patients with focal epilepsies.

Data from Kanemoto K. Postictal psychosis revisited. In: Trimble MR, Schmitz B, eds. *The Neuropsychiatry of Epilepsy.* Cambridge: Cambridge University Press; 2002:117–134.

Postictal Psychoses

Most postictal psychoses are precipitated by a series or status of generalized tonic–clonic seizures. More rarely, psychoses occur after single grand mal seizures or following a cluster of complex partial seizures.[69] In the elderly, a postictal psychosis may be the first presentation of a new-onset epilepsy disorder.

Postictal psychoses account for approximately 25% of psychoses in epilepsy.[17,64]

The relationship to the type of epilepsy is not clear. Dongier[8] described a preponderance of generalized epilepsies, and Logsdail and Toone[41] noted a higher frequency of postictal psychosis in patients with focal epilepsies and complex focal seizures. One of the more comprehensive studies has been that of Kanemoto, and his distinction between postictal and interictal psychoses is shown in Table 2. Essentially, the postictal psychoses occur with later age of onset of epilepsy and at a later age than the interictal psychoses. They are significantly associated with temporal lobe epilepsy, complex partial seizures, and magnetic resonance imaging (MRI) temporal plus extratemporal structural lesions. Patients are less likely to have learning disability and are less likely to have generalized spike-wave abnormalities on the EEG. He also noted an association with déjà vu auras.[27] Others have suggested an association between ictal fear and postictal psychosis.[63]

A characteristic lucid interval is described in most patients during which time the mental state appears to be normal. This interval can last from 1 to 6 days between the epileptic seizures and onset of psychosis.[73] Failure to appreciate the presence of this lucid interval can lead to a misdiagnosis of this condition.

The psychopathology of postictal psychosis is polymorphic, but most patients present with abnormal mood and paranoid delusions.[41] Some patients are confused throughout the episode; others present with fluctuating impairment of consciousness and orientation; and sometimes there is no confusion at all. Kanemoto[27] suggests that up to 50% have a psychosis in clear consciousness. Dominant are delusions of grandiosity and religiosity often associated with an elevated mood when compared with interictal psychoses. Patients may also be anxious and a typical symptom is fear of impending death. Because patients often have a clear sensorium and may receive command hallucinations if the latter relate to violence or suicide, it is during such states that violent attacks on the self or others may occur.

The EEG during postictal psychosis is usually deteriorated, with increased epileptic as well as slow-wave activity, but there are few reliable studies since people with acute psychoses are difficult to examine.

The psychotic symptoms spontaneously remit within days or weeks, often without need for psychotropic drug treatment. However, in some cases, chronic psychoses develop from recurrent and even a single postictal psychosis[41,94]; this is estimated to occur in about 25% of cases.

The pathophysiology is not known. Savard et al.[63] noted the clinical analogy of psychoses following complex partial seizures to other postictal phenomena such as Todd paresis or postictal memory loss. Logsdail and Toone hypothesized that postictal psychosis results from increased postsynaptic dopamine sensitivity. Ring et al.[58] have tested this hypothesis using single-photon emission computed tomography (SPECT) and the D_2 ligand [^{123}I] iodobenzamide (IBZM). They noted that patients with epilepsy and psychoses had decreased binding to the ligand, suggesting that there was increased release of endogenous dopamine in the psychotic state. Kanemoto[27] suggested that we are dealing with a restricted limbic status epilepticus, but limited functional imaging studies produced contradictory results.[39]

Parictal Psychosis

Most authors do not distinguish between parictal and postictal psychoses.[63] In parictal psychosis,[94] psychotic symptoms develop gradually and parallel to increases in seizure frequency. The relationship to seizures is easily overlooked if seizure frequency is not carefully documented over prolonged periods. More rapid development of parictal psychoses can be seen, especially during the presurgical assessment of patients with intractable epilepsy, when series of epileptic seizures may be provoked by withdrawal of antiepileptic drugs. Impairment of consciousness is more frequent than in postictal psychosis.

Interictal Psychoses

Interictal psychoses occur between seizures and cannot directly be linked to the ictus. They are less frequent than peri-ictal psychoses, and account for 10% to 30% of diagnoses in unselected case series.[8,64] Interictal psychoses are, however, clinically more significant in terms of severity and duration than peri-ictal psychoses, which usually are brief and often self-limiting.

Slater and Beard stated that, in the absence of epilepsy, the psychoses in their study group would have been diagnosed as schizophrenia, and noted the frequent presence of the First Rank Symptoms of Schneider.[70] However, there have been persistent arguments as to the exact relationship between the two disorders and the phenomenology of the interictal epileptic psychoses. Slater maintained that there was a distinct difference between schizophrenia and the schizophrenialike psychoses associated with epilepsy, and they highlighted the preservation of affect, a high frequency of delusions and religious mystical experiences, and few motor symptoms.

Other authors have stressed the rarity of negative symptoms and the absence of formal thought disorder and catatonic states.[28] McKenna et al.[45] pointed out that visual hallucinations were more prominent than auditory hallucinations. Tellenbach[82] stated that delusions were less well organized, and Sherwin[67] remarked that neuroleptic treatment was less frequently necessary. There have been other authors, however, who denied any clear psychopathologic differences between epileptic psychosis and schizophrenia.[21,31]

Table 3 Risk Factors Associated with Interictal Psychoses of Epilepsy[a]

Sex	Bias to female patients
Age of onset	Early adolescence
Interval	Onset of seizures to onset of psychosis: Mean 14 years
Epileptic syndrome	Temporal lobe epilepsy
Seizure type	Complex focal
Seizure frequency	Low, diminished
Neurologic findings	Sinistrality
Pathology	Gangliogliomas, hamartomas
EEG	Mediobasal focus, especially left sided

EEG, electroencephalogram.

Using the Present State Examination and the CATEGO computer program, which is a semistandardized and validated method for quantifying psychopathology, it has been possible to compare the presentation of psychosis in epilepsy with process schizophrenia. Very few significant differences emerged from such studies,[53,84] which suggests that, assuming the

patients were representative, a significant number will have a schizophrenialike presentation virtually indistinguishable from schizophrenia in the absence of epilepsy.

Phenomenology apart, Slater argued that long-term prognosis of psychosis in epilepsy was better than that in process schizophrenia. In a follow-up study on his patients, he found that chronic psychotic symptoms tended to remit, and personality deterioration was rare.[17] Other authors have also described the outcome to be more favorable and long-term institutionalization to be less frequent than in schizophrenia.[28,67] Unfortunately, there have been no longitudinal studies comparing the long-term outcome of psychosis in epilepsy and process schizophrenia.

Risk Factors

The pathogenesis of psychotic episodes in epilepsy is likely to be heterogeneous. In most patients, a multitude of chronic and acute factors can be identified that are potentially responsible for the development of a psychiatric disorder. These factors are difficult to investigate in retrospect, and the interpretation of them as either causally related or simply intercorrelated is arguable.

The literature on risk factors is highly controversial; studies are difficult to compare because of varying definitions of the epilepsy, the psychiatric disorder, and the investigated risk factors. Most studies are restricted to interictal psychoses. Table 3 summarizes factors that have frequently been described to be associated with the interictal psychosis in epilepsy.[85]

Genetic Predisposition

With few exceptions,[26,56] most authors do not find any evidence for an increased rate of psychiatric disorders in relatives of epilepsy patients with psychoses.[11,53,69] This was one reason why Slater suggested that these psychoses were truly symptomatic, a representative phenotype of the genotype.

Sex Distribution

There has been a bias toward female sex in several case series,[80] but this has not been confirmed in controlled studies.[1,34,35]

Duration of Epilepsy

The interval between age at onset of epilepsy and age at first manifestation of psychosis has been remarkably homogeneous, in the region of 11 to 15 years, in many series.[85] This interval has been used to postulate the etiologic significance of the seizure disorder and a kindlinglike mechanism. However, some authors[5,77] have argued that the supposedly specific interval represents an artifact. They have drawn attention to the wide range, with a significantly shorter interval in patients with later onset of epilepsy. They also have pointed out that patients whose psychoses did not succeed their epilepsy were excluded in most series, and that there is a tendency in the general population for the age of onset of epilepsy to have an earlier peak than that of schizophrenia.

Type of Epilepsy

There is a clear excess of temporal lobe epilepsy in almost all case series of patients with epilepsy and psychosis. Among the pooled data of ten studies, 217 (76%) of 287 patients suffered from temporal lobe epilepsy.[85] The preponderance of this type of epilepsy is, however, not a uniform finding; in Gudmundsson's epidemiologic study, for example, only 7% suffered from “psychomotor” epilepsy. However, in many studies, especially the early ones, the classification of seizures and epilepsy is confused, and not supported by neurologic investigations.

The nature of a possible link of psychoses to temporal lobe epilepsy (TLE) is not entirely clear,[65] partly because of ambiguities in the definition of TLE in the literature, based on either seizure symptomatology (psychomotor epilepsy), involvement of specific functional systems (limbic epilepsy), or anatomic localization as detected by depth EEG or neuroimaging (amygdalohippocampal epilepsy). Unfortunately, most authors have not sufficiently differentiated frontal and temporal lobe epilepsy.

The temporal lobe hypothesis, although widely accepted, has been criticized for being based on uncontrolled case series, such as in the studies by Gibbs[15] and Slater and Beard.[70] It was argued that TLE is the most frequent type of epilepsy in the general population and that there is an overrepresentation of this type of epilepsy in patients attending specialized centers. However, there is a general consensus that psychoses are less common in patients with neocortical extratemporal epilepsies.[5,15,17,51,64,66,77] Adachi[1] suggested that psychoses in patients with frontal lobe epilepsy may be overlooked because of a differing psychopathology, hebephrenic symptoms in particular dominating the presentation.

The findings are less unequivocal regarding TLE and generalized epilepsies. Four studies[19,53,66,68] note significant differences in the frequency of psychoses in temporal lobe epilepsy, but several do not.[4,14,49,64,72,75,77] However, many patients with generalized epilepsy show pathology of temporal structures, making classification difficult, and again many reports lack the sophisticated brain imaging that is now required for such hypotheses to be tested.

There are several studies showing that psychoses in generalized epilepsies differ from psychoses in TLE.[85] The former are more likely to be of short duration and confusional.[4,8,77] Alternative psychoses, which are especially common in generalized epilepsy, are usually relatively mild and often remit before any development of paranoid-hallucinatory symptoms. Schneiderian first-rank symptoms and chronicity are more frequent in patients with TLE.[64,86] This has considerable significance for psychiatrists attempting to unravel the underlying "neurology" of schizophrenia, and the findings from epilepsy were

instrumental in altering the view of schizophrenia away from a psychosocial to a biologic model.

Type of Seizures

There is evidence from several studies that focal seizure symptoms that indicate ictal mesial temporal or limbic involvement are overrepresented in patients with psychosis. Hermann and Chabria[23] noted a relationship between ictal fear and high scores on paranoia and schizophrenia scales of the Minnesota Multiphasic Personality Inventory (MMPI). Kristensen and Sindrup[34,35] found an excess of dysmnesic and epigastric auras in their psychotic group. They also reported a higher rate of ictal amnesia. In another controlled study, ictal impairment of consciousness was related to psychosis, but simple seizure symptoms indicating limbic involvement were not.[64]

No seizure type is specifically related to psychosis in generalized epilepsies. Most patients with psychosis and generalized epilepsies have absence seizures.[64]

Severity of Epilepsy

The strongest risk factors for psychosis in epilepsy are those that indicate severity of epilepsy. These are long duration of active epilepsy,[70] multiple seizure types,[5,22,40,52,60,64,66] history of status epilepticus,[64] and poor response to drug treatment.[40] Seizure frequency, however, is reported by most authors to be lower in psychotic epilepsy patients than in nonpsychotic patients.[11,66,71,74] It has not been clarified whether seizure frequency was low before or during the psychotic episode. This may represent a variant of forced normalization (see below).

Laterality

Left lateralization of temporal lobe dysfunction or temporal lobe pathology as a risk factor for schizophreniform psychosis was originally suggested by Flor-Henry.[11] Studies supporting the laterality hypothesis have been made using surface EEG,[40] depth electrode recordings,[67] computed tomography,[6,83] neuropathology,[79] neuropsychology,[53] and positron emission tomography (PET),[91] and more recently with MRI. The earlier literature has been summarized by Trimble.[85] In a synopsis of 14 studies with 341 patients, 43% had left, 23% right, and 34% bilateral abnormalities. This is a striking bias toward left lateralization. However, lateralization of epileptogenic foci was not confirmed in all controlled studies.[8,34,35,68] Again, it may be that certain symptoms rather than any syndrome are associated with a specific side of focus. Trimble pointed out that a specific group of hallucinations and delusions, defined by Schneider and referred to as first rank symptoms, which usually (but not exclusively) signifies schizophrenia, may be relevant.[89,90] He suggested that these may be signifiers of temporal lobe dysfunction, representing disturbances of language and symbolic representation. In this sense, he then equated to a Babinski sign for a neurologist (i.e., pointing to a location and lateralization of an abnormality in the central nervous system).

These laterality findings have received support from brain imaging studies, especially SPECT and MRI. Mellers,[47] using a verbal fluency activation paradigm and HMPAO SPECT, compared patients with schizophrenialike psychoses of epilepsy (n = 12), with schizophrenia (n = 11), and epilepsy and no psychoses (n = 16). The psychotic epilepsy patients showed lower blood flow in the superior temporal gyrus during activation than the other two groups. Using MR spectroscopy, Maier et al.[42] were able to compare hippocampal-amygdala volumes and hippocampal *N*-acetyl aspartate (NAA) levels in patients with temporal lobe epilepsy and schizophrenialike psychoses of epilepsy (n = 12), temporal lobe epilepsy and no psychoses (n = 12), schizophrenia and no epilepsy (n = 26), and matched normal controls (n = 38). The psychotic patients showed significant left-sided reduction of NAA, and this was greater in the psychotic epilepsy group. Regional volume reductions were noted bilaterally in this group, and in the left hippocampus-amygdala in the schizophrenic group.

Flugel et al.[12] have recently examined 20 psychotic and 20 nonpsychotic cases with temporal lobe epilepsy using magnetization transfer imaging. They reported significant reductions of the magnetization transfer ratio (an index of signal loss) in the left superior and middle temporal gyri in the psychotic patients; this was unrelated to volume changes and best revealed in the subgroup with no focal MRI lesions.

Structural Lesions

The literature on brain damage and epileptic psychosis is very controversial. Some authors have suggested a higher rate of pathologic neurologic examinations, diffuse slowing on the EEG, and mental retardation,[34,35] but others could not find an association with psychosis.[11,26] Neuropathologic studies of resected temporal lobes from patients with TLE have suggested a link between psychosis and the presence of cerebral malformations such as hamartomas and gangliogliomas as compared with mesial temporal sclerosis.[4,59,80] These findings have been seen as consistent with recent findings of structural abnormalities in the brains of schizophrenic patients without epilepsy that arise during fetal development.

Bruton[4] has noted enlarged ventricles, periventricular gliosis, and an excess of acquired focal damage in brains of institutionalized psychotic epileptic patients compared with nonpsychotic controls. Bruton also reported that schizophrenialike psychoses were also distinguished by an excess of perivascular white matter softenings.

In a study specifically looking at hippocampal and amygdala volumes, Tebartz van Elst et al.[81] examined 26 patients with epileptic psychoses, 24 with temporal lobe epilepsy and no psychosis, and 20 healthy controls. The psychotic patients had significantly increased amygdala sizes in comparison with the other two groups, which were bilateral, not related to the laterality of the focus or length of epilepsy history. No hippocampal differences were noted in this study. In a complementary study on the same groups, Rusch et al.[61] were unable to find any neocortical cortical volumetric differences.

Forced Normalization

A full understanding of the relationships between epilepsy and psychosis requires appreciation of this concept.

Earlier this century, reports appeared that suggested that there was some kind of antagonism between epilepsy and psychosis. This was one of the reasons that led von Meduna to introduce convulsive therapy for the treatment of schizophrenia. In the 1950s, Landolt[37,38] published a series of papers on patients who had epilepsy who became psychotic when their seizures were under control. He defined forced normalization as follows: “Forced normalisation is the phenomenon characterised by the fact that, with the recurrence of psychotic states, the EEG becomes more normal, or entirely normal, as compared with previous and subsequent EEG findings.”

Forced normalization was thus essentially an EEG phenomenon. The clinical counterpart of patients becoming psychotic when their seizures became under control and their

psychosis resolving with return of seizures was referred to as alternative psychoses by Tellenbach.[82]

These phenomena have now been well documented clinically. The following are important to note, however. First, the EEG does not need to become “normal,” but the interictal disturbances decrease and in some cases disappear. Second, the clinical presentation need not necessarily be a psychosis but sometimes is. In childhood or in the mentally handicapped, aggression and agitation are common. Other manifestations include pseudoseizures or other conversion symptoms, depression, mania, and anxiety states. Third, the disturbed behavior may last days or weeks. They may be terminated by a seizure, and the EEG abnormalities then return. Fourthly, Landolt originally associated this phenomenon with focal epilepsies, but with the introduction of the succinimide drugs, he noted an association with the generalized epilepsies. Certainly, forced normalization may be provoked by the administration of anticonvulsants and has been reported with barbiturates, benzodiazepines, ethosuximide, tiagabine, topiramate, vigabatrin, levetiracetam, and more recently lamotrigine[5,85] (see Chapter 208).

The literature on antagonism between epilepsy and psychosis has been held to be incompatible with the suggestions outlined above that there is an increased association between epilepsy and psychosis. This has been resolved by more careful understanding of the original literature.[93] Thus, within the association or link between psychosis and epilepsy, there may be an antagonism of symptoms between seizures and the symptoms of psychosis (i.e., the hallucinations and delusions). It is the longitudinal course of the disorders that has to be followed, and forced normalization, as opposed to alternative psychosis, requires serial EEG recordings before the diagnosis can be made.

It is often denied that forced normalization occurs, probably with good reason. Thus, it is certainly rarer than made out by Landolt, and studies are few and far between. It is difficult to document cases precisely, EEG recordings being difficult to obtain at the right times. However, other less enlightened reasons to ignore such findings relate to the fact that the concept brings psychiatry uncomfortably close to neurology, revealing a close biologic link between seizures and psychosis. It also affects treatment. Thus, if in some patients suppression of seizures provokes psychopathology, it reinforces the fact, often ignored or misunderstood, that seizures and epilepsy are not synonymous, and that an understanding of the epileptic process and its treatment goes far beyond the control of seizures. In clinical practice, to ignore the fact that some patients manifest these problems as their seizures come under control can lead to the continuation of severe behavior disturbances, with all of the social disruption that then emerges, and a failure to manage the epilepsy appropriately.

Psychosis Following Surgery

Temporal lobectomy is an ever-increasing treatment for patients with intractable epilepsy. Ever since the early series, the possibility that surgery itself may be associated with the development of psychiatric disturbance, in particular psychosis, has been discussed. Some of the best evidence comes from the Maudsley series, initially described by Taylor[78] and more recently by Bruton.[4] Most centers have stopped operating on floridly psychotic patients, based on the observation that psychoses generally do not improve with the operation. A few centers, however, regularly include psychiatric screening as part of their preoperative assessment, but postoperative psychiatric follow-up is often nonexistent. Assessment of psychosocial adjustment is rarely performed, in contrast to the often scrupulous recording of neuropsychological deficits.

The Maudsley series show that some patients develop new psychosis postoperatively, and there is an increased reporting of depression. Bruton[4] has suggested that the development of postoperative psychoses may be more common with certain pathologies (gangliogliomas). Patients with right-sided temporal lobectomies may be more prone to these psychiatric disturbances.[85] In some cases, the sudden relief of seizures that occurs following surgery may suggest a mechanism similar to forced normalization, although no persistent clear relationship emerges between success of operation and the development of psychotic postoperative states. In recent times, there have been several small series reported of patients with psychoses who have been successfully operated on, without worsening of their seizures but with marked improvement in seizure control. This topic is discussed in much more detail in Chapter 209.[57]

Diagnosis

The principles of diagnosis of psychiatric problems in epilepsy are essentially the same as when a patient does not have epilepsy. However, as noted, it is not possible to apply the strict DSM-IV classifications,[7] and in many patients there are subtle aspects to the clinical picture that may suggest the underlying neurologic flavor of the phenomenology. These include in the schizophrenialike psychoses the retention of affective responses, lack of chronic personality and lifestyle deterioration, and development of some of the personality features noted in the interictal personality syndrome. An inclination to mysticism with developing religiosity is one of the most common.

Close attention to the relationship of the development of the psychoses to the seizure pattern is essential if the peri-ictal disorders are to be distinguished from the interictal, although in many patients this is not always clear, and the pattern may change with time. In particular, there are reports of ictally driven psychoses evolving to a chronic interictal syndrome, subtle at first but then more enduring. In other cases, the acute psychoses may erupt in the absence of an obvious cluster of seizures, even though on previous occasions the relationship has been obvious. The EEG in some cases is very important in clarifying the diagnoses, especially for nonconvulsive status and states of forced normalization.

Because many patients with psychoses of epilepsy display prominent affective symptoms, it is important to identify those patients with an affective disorder, as opposed to a schizophrenialike state or a paranoid illness, that may respond initially to effective antidepressant therapy.

Treatment

Essentially, management of psychiatric problems in patients with epilepsy is similar to that in patients without epilepsy, with a few caveats. Certainly, a number of nonmedical treatments are available. These should always be thought of in individual cases.

Patients with psychoses should be treated with neuroleptic medications, although these, like most antidepressants, can lower the seizure threshold. To date, all known neuroleptics have this potential, although some more than others; this is covered in more detail in Chapter 214.

Postictal psychoses may occasionally need neuroleptic drugs, although they usually settle rapidly. It is more important to prevent patients from damaging themselves or causing harm to others, but a drug such as haloperidol or one of the newer atypical antipsychotics at regular intervals may control behavior satisfactorily. Interictally, the paranoid or schizophrenialike states need to be evaluated in terms of their relationship to seizure frequency. Thus, in patients who stop having seizures in association with the onset of psychosis, a neuroleptic that increases the seizure threshold (e.g., chlorpromazine or even clozapine) may be the most logical prescription.

Where patients with epilepsy have no alteration of the seizure frequency or the psychosis is occurring in the setting of increased seizure frequency, a neuroleptic less likely to precipitate seizures, such as risperidone, an atypical antipsychotic, is logical. It should be recalled that patients taking anticonvulsants that increase hepatic metabolism will show lower serum levels of neuroleptics and may therefore require somewhat higher doses than patients not on these medications to achieve a similar clinical effect. Occasionally, the addition of an antidepressant or a neuroleptic to a patient's prescription may lead to increases in serum anticonvulsant levels.

Postictal psychoses often do not require psychotropic medication, resolving over a few hours. However, it is important to stress how dangerous these cases can be, and it is essential to take note of any command hallucinations or delusions of harm to the self or others and protect accordingly. In the first instance, treatment with a benzodiazepine is helpful, since there is a risk, especially with some of the antipsychotics, of precipitating further seizures and exacerbating the psychosis. Regular benzodiazepines for perhaps 48 hours are often sufficient. In the longer-term management it is important to realize that postictal psychoses have a tendency to recur. It is therefore important to warn about this, and to try with effective antiepileptic drug therapy to try to prevent clusters of seizures. It is sometimes possible to prevent such a cluster and hence the later psychosis by telling patients to take their benzodiazepine at the onset of any cluster and continue then for about 48 hours. Sometimes all these measures fail, and so intermittent or even continuous antipsychotic treatment becomes important.

As with all psychiatric problems, psychopharmacologic management alone is not sufficient. Although the role of psychotherapy in the management of psychotic conditions has not proven of any substantial value, it is important to acknowledge that epileptic patients with psychosis bear the burden of epilepsy in addition to their psychosis. Patients with intermittent psychotic states are often perplexed and embarrassed about what has happened to them while psychotic and fear further continuing bouts with a descent into insanity. Patients with continuous psychosis require the skills of paramedical intervention, and the full resources of community care may be needed to help them rehabilitate and to assist their families in coping with their difficulties. In many patients with chronic psychoses of epilepsy, the preservation of affect and lack of personality disintegration over years sustains them well in their communities and may enable them to live with their families or even marry. Maintaining them and bringing such support to them is important, sustaining them in the community and preventing their recurrent admission to the hospital. Further, in a good family environment with adequate medical facilities and follow-up care, patient compliance will tend to be good. Deterioration of an otherwise delicate situation induced by poor compliance, leading to more seizures and exacerbation of psychopathology with loss of control by the family and the physician, may thereby be avoided.

Summary and Conclusions

There is evidence that psychoses are overrepresented in patients with epilepsy, and few physicians who manage epilepsy have not seen patients with either an ictal, postictal, or interictal psychosis. The link to temporal lobe epilepsy is strong, both clinically and theoretically, because there is an acknowledged link between the limbic system and the modulation of emotional and social behaviors.[88] It has to be of profound interest that epilepsy, which is so often associated with lesions in medial temporal structures that tend to be present from an early phase in life, is linked to psychoses, which often resemble paranoid and schizophreniform states found in the absence of epilepsy. Thus, the latter can also be shown to have pathology in the same areas of the brain,[87] and schizophrenia is now viewed as a developmental disorder associated with anomalous central nervous system development in the fetal or perinatal era of life.

Although the underlying pathology may be different, the absence of gliosis in the hippocampus and related structures characterizing schizophrenia, the site of the pathology, the timing of the lesions, and the consequent functional changes in the brain may all be crucial to the later development of any behavior changes in both epilepsy and schizophrenia. Thus, the behavior changes should be viewed as an integral part of the process of epilepsy that are manifest in some patients. However, the recent evidence, especially from brain imaging studies, suggests that Slater's original hypothesis was part right but part wrong. Thus, the interictal psychoses seem different from schizophrenia, especially with regard to the admixture with affective symptoms and the long-term prognosis. While hippocampal changes may relate to both disorders, the increased amygdala size, bilateral and around 17% to 20%, and the lesser volumetric changes in the hippocampus suggest that the two psychopathologic states are biologically quite different. While the laterality findings with regard to the functioning of the left hemisphere seem to hold up, the data point away from fundamentally cortical abnormalities in these psychoses, and bring the amygdala and related structures as central in pathogenesis. Finally, it has to be repeated that epilepsy is not synonymous with seizures, and the latter are but one manifestation of the disordered cerebral function of patients with epilepsy.

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Chapter 205

Affective Disorders

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Introduction

Mood disorders are the most common comorbid psychiatric disorders associated with epilepsy, but their real incidence and prevalence have yet to be established. Some of the primary reasons for the lack of definitive epidemiologic data include the diversity in methodologies and sample populations across studies, the underreporting of symptoms of depression by patients and families, and the underrecognition by clinicians. Population-based studies, however, have clearly shown that the prevalence of depression in people with epilepsy (PWE) is significantly higher than in healthy controls, as well as in people with chronic medical disorders.[59,62,96,104,144]

There is an ongoing debate as to whether depression in PWE differs from that in people with primary mood disorders.[105] Proponents of both schools of thought are probably correct, as a significant percentage of PWE can experience any of the various forms of primary mood disorders (i.e., major depressive disorder, dysthymic disorder, bipolar disorder, cyclothymic disorder) indistinguishable from those described in the *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition (DSM-IV).[57] By the same token, several authors have identified atypical clinical manifestations of mood disorders in a significant proportion of PWE that fail to meet any of the diagnostic criteria suggested in the DSM-III, DSM-III-R, and DSM-IV.[19,105,110,134] Kraepelin and Bleuler were the first to recognize a "unique" clinical presentation of mood disorders in PWE consisting of recurrent episodes of "dysphoric symptoms"[18,115]; Gastaut expanded on Kraepelin's initial observations and Blumer coined the term *interictal dysphoric disorder*.[19,74,75] The purpose of this chapter is to provide a comprehensive review of mood disorders in epilepsy. The aim of this chapter is to provide a general review of the different aspects of affective disorder in PWE with special attention to epidemiologic and clinical data, the underlying pathogenic mechanisms with special attention to the existence of common pathogenic mechanisms that may be operant in depression and epilepsy, and the basic principles in their treatment. The chapter concludes with a brief discussion of interictal dysphoric disorder.

Epidemiologic Data

Lifetime prevalences for major depressive episodes in the general population have been reported to range between 3.7% and 6.7%, for dysthymic and minor depressive disorders between 2.1% and 3.8%, and for manic episodes 0.6% and 1.1%.[111] Recent population-based studies identified significantly higher prevalence rates of depression in PWE. For example, the Canadian Community Health Survey evaluated the existence of mental health problems in a large sample of the population (n = 36,984).[200] A total of 253 subjects were found to have epilepsy (corresponding to a prevalence rate of epilepsy of 0.6%). The investigators used the Composite International Diagnostic Interview (Short Form) to identify a history of depression and found a lifetime prevalence of depression of 22.2% (95% confidence interval [CI], 14.0% to 30.4%) compared with 12.2% in the general population, with higher rates of major depression in younger, but not older (>64 years), age groups. Furthermore, lifetime suicidal ideation was higher in PWE (25.0% [95% CI, 16.6 to 33.3]) than in the general population (13.3% [95% CI, 12.8 to 13.9]). In a separate population-based study, Ettinger et al. investigated the presence of symptoms of depression among 775 PWE, 395 people with asthma, and 362 healthy controls identified from a cohort of 85,358 adults aged 18 years and older using the Centers of Epidemiologic Studies-Depression (CES-D) Instrument.[62] PWE experienced symptoms of depression with a significantly greater frequency (36.5%) and severity than people with asthma (27.8%) and healthy controls (11.8%). Of note, 38.5% of PWE whose score on the CES-D suggested the presence of a depressive disorder and 43.7% of people with asthma and depression were never previously evaluated for depression. The same group of investigators compared the lifetime prevalence rates of bipolar symptoms and past diagnoses of bipolar I and II disorder with the Mood Disorder Questionnaire (MDQ) among subjects who identified themselves as having epilepsy and those with migraine, asthma, or diabetes mellitus or a healthy comparison group.[63] Bipolar symptoms, evident in 12.2% of epilepsy patients, were 1.6 to 2.2 times more common in subjects with epilepsy than with migraine, asthma, or diabetes mellitus, and 6.6 times more likely to occur than in the healthy comparison group. A total of 49.7% of patients with epilepsy who screened positive for bipolar symptoms were diagnosed with bipolar disorder by a physician, nearly twice the rate seen in other disorders. However, 26.3% of MDQ-positive epilepsy subjects carried a diagnosis of unipolar depression, and 25.8% had neither a uni- nor bipolar depression diagnosis.

The impact of seizure control on the prevalence of depression has been investigated in four population-based studies. Using the Hospital Depression and Anxiety Symptoms scale, Jacoby et al.[96] reported that of 168 patients with recurrent seizures, 21% met criteria for clinical depression. Using the same instrument, O'Donoghue et al.[144] showed that among 155 PWE identified through two large primary care practices in the United Kingdom, 33% with recurrent seizures and 6% of those in remission had depression. Edeh and Toone[59] used the Clinical Interview Schedule to demonstrate a depressive disorder in 22% of 88 epilepsy patients identified from general practices in the United Kingdom.

Clearly, the prevalence rates of depression are significantly higher in studies done in tertiary centers. For example, Victoroff et al. assessed the lifetime prevalence of psychiatric disorders meeting DSM-III-R diagnostic criteria by administering the Structured Clinical Interview for DSM-III-R—Patient Version (SCID-P) to 60 patients with medically intractable complex partial seizures.[207] The standard interview was enlarged by explorations of the relationship between psychiatric complaints and course of the epilepsy, of brief periods of depression and elation, and of atypical personality features that had been reported among patients with temporal lobe epilepsy (TLE). Of the 60 patients, 42 (70%) had histories of one or more DSM-III-R axis I diagnoses and 35 (58%) had histories of major depressive episodes or other depressive disorders.

Current diagnoses of depression can also be identified more frequently among patients followed in tertiary centers. In a recently completed study of 199 consecutive outpatients from five epilepsy centers,[103] the presence of an axis I diagnosis was identified according to DSM-IV criteria with the Structured Clinical Interview for DSM-IV diagnosis (SCID) and the Mini International Psychiatric Interview (MINI). Sixty-seven patients (34%) met a DSM-IV criterion of a mood and/or anxiety disorder: 37 (19%) met criteria for major depression, of whom 17 (8.5%) had a mixed major depression and anxiety disorder. Only four patients (2%) met criteria for dysthymic disorder and 27 (13.6%) for an anxiety disorder.

The relation between depression and epilepsy has traditionally been thought to be unidirectional, given the higher incidence and prevalence of depression in PWE and the recognition of several epilepsy-related pathogenic mechanisms, including (a) a reactive process to psychosocial stressors associated with a life with epilepsy, (b) neurophysiologic and neurochemical changes related to the seizure activity, and (c) iatrogenic pharmacologic and surgical factors. Yet, the higher prevalence rates of depression in PWE were based on cross-sectional studies, which do not necessarily establish causality between the two disorders. In fact, three recent population-based studies have questioned this long-held assumption of a unidirectional relation and suggested the existence of a "bidirectional" relation between depression and epilepsy, whereby the presence of a mood disorder can also be associated with an increased risk of developing epilepsy.[20,89,90] Of note, these investigators were not the first ones to suggest the existence of such bidirectional relationship; indeed, 26 centuries ago, Hippocrates wrote: "melancholics ordinarily become epileptics, and epileptics melancholics: what determines the preference is the direction the malady takes; if it bears upon the body, epilepsy, if upon the intelligence, melancholy."[124] Such bidirectional relationship may in fact reflect the existence of common pathogenic mechanisms shared by epilepsy and depression, which facilitate the development of one disorder in the presence of the other (see below).

Clinical Presentations

Symptoms of mood disorders in epilepsy are classified according to their temporal relation to seizure occurrence into peri-ictal and interictal symptoms. Peri-ictal symptoms include symptoms that precede (preictal), follow (postictal), or are the expression of a seizure (ictal), while interictal symptoms occur independently of seizures. Often, patients may experience symptoms of depression during both peri-ictal and interictal periods.

Peri-ictal Symptoms

Peri-ictal depressive symptoms and episodes are the least well studied with respect to their actual prevalence and are usually ignored by clinicians. Their occurrence has never been factored into any study investigating the prevalence of depressive symptoms/disorders in PWE despite the fact that their existence has been known to neurologists and psychiatrists for a long time.

Ictal Symptoms

It has been estimated that psychiatric symptoms occur in 25% of "auras"; 15% of these involve affect or mood changes.[54,209,212] For example, ictal symptoms of depression ranked second after symptoms of anxiety/fear, which are the most common type of ictal affect in one study. Ictal symptoms of depression are of short duration typically, are stereotypical, occur out of context, and are associated with other ictal phenomena. The most frequent symptoms include feelings of anhedonia, guilt, and suicidal ideation.

Preictal Symptoms

Preictal symptoms or episodes typically present as a dysphoric mood preceding a seizure by several hours to days. The best evidence is presented in the study by Blanchet and Frommer, who investigated mood changes in the course of 56 days in 27 PWE who were asked to rate their mood on a daily basis.[17] Mood ratings pointed to a dysphoric state 3 days prior to a seizure in 22 patients. This change in mood was more accentuated during the 24 hours preceding the seizure.

Postictal Symptoms

Postictal symptoms have been recognized for a very long time, but have been poorly studied in a systematic manner. Their detection can often be elusive as they do not occur necessarily on the same day as the seizure. Rather, symptom-free periods of up to 5 days can exist between the seizure occurrence and onset of psychiatric symptoms. The prevalence of postictal psychiatric symptoms was investigated in a study done at the Rush Epilepsy Center in Chicago in 100 consecutive patients with refractory epilepsy.[107] Only symptoms that occurred following more than 50% of seizures in the previous 3 months were included. In this study, the postictal period was defined as the 72 hours that followed a seizure. Symptoms that occurred during both interictal and postictal periods were also identified and compared in their severity during these periods. Since neurovegetative symptoms and fatigue are common postictal symptoms as well as symptoms of depression, they were analyzed separately so as not to inflate falsely the prevalence of postictal symptoms of depression (PSD).

Among the 100 patients, 43 experienced a mean of 4.8 ± 2.4 PSD (range 2 to 9; median = 5). The median duration of two thirds of symptoms was 24 hours. Twenty-five had a history of a mood disorder and 11 of an anxiety disorder. Table 1 shows the PSD and their respective median duration.

There was a significant association between a history of depression and the occurrence of the following PSD: Hopelessness, suicidal ideation, self-deprecation, and guilt. Furthermore, there was a significantly greater number of PSD in the presence of a history of depression and anxiety disorders.

Thirteen of these patients experienced a minimum of seven PSD lasting 24 hours or longer. Postictal suicidal ideation was identified in 13 patients. Eight patients experienced passive and active suicidal thoughts, while five only reported passive suicidal ideation. Ten of these 13 patients (77%) had a past history of either major depression or bipolar disorder, and this association was highly significant. Furthermore, the presence of postictal suicidal ideation was also significantly associated with a history of psychiatric hospitalization.

Among these 43 patients, PSD occurred together with postictal symptoms of anxiety (PSA) in 27 patients (63%) and seven other patients reported as well postictal psychotic symptoms. Table 1 shows the types of PSA and their median duration. Furthermore, 37 patients reported interictal symptoms of depression that worsened in severity during the postictal period in 30 patients.

Table 1 Prevalence and Median Duration of Postictal Symptoms of Depression and Anxiety

Postictal symptom	Prevalence	Median duration in hours (range)
Symptoms of depression, total	*43*	
Irritability	*30*	*24 (0.5-108)*
Poor frustration tolerance	*36*	*24 (0.1-108)*
Anhedonia	*32*	*24 (0.1-148)*
Hopelessness	*25*	*24 (1.0-108)*
Helplessness	*31*	*24 (1.0-108)*
Crying bouts	*26*	*6 (0.1-108)*
Suicidal ideation	*13*	*24 (1.0-240)*
Active suicidal thoughts	*8*	
Passive suicidal thoughts	*13*	
Feelings of self-deprecation	*27*	*24 (1.0-120)*
Feelings of guilt	*23*	*24 (0.1-240)*

Symptoms of anxiety, total	*45*	
Constant worrying	*33*	*24 (0.5-108)*
Panicky feelings	*10*	*6 (0.1-148)*
Agoraphobic symptoms	*29*	*24 (0.5-296)*
Due to fear of seizure recurrence	*20*	
Compulsions	*10*	*15 (0.1-72)*
Self-consciousness	*26*	*6 (0.05-108)*
Hypomanic symptoms, total	*22*	
Excessive energy	*9*	*2 (0.15-48)*
Thought racing	*15*	*2 (0.1-24)*

Postictal hypomanic symptoms (PHM) included excessive energy and racing thoughts, which were identified in 22 patients: 15 patients reported racing thoughts and nine reported increased energy, but only two reported both symptoms (see Table 1). The occurrence of PHM only correlated significantly with that of postictal psychotic symptoms. In contrast to PSD, a psychiatric history was not a risk factor of PHM.

Clearly, the occurrence of PSD is relatively high among patients with refractory epilepsy. Yet, in none of the studies on the prevalence of depression in epilepsy published so far has any investigator discriminated between an interictal, preictal, or postictal occurrence. The impact that PSD may have in “shaping” the psychiatric clinical phenomena of depression in PWE has yet to be established. Yet, it is likely that preictal symptoms and PSD may account for the frequent “atypical” characteristic of depressive disorders.

Interictal Depressive Disorders

Interictal depressive disorders have been the most commonly recognized. As stated above, there is an ongoing debate as to whether depressive disorders differ between people with and without epilepsy. In fact, some investigators have found that in up to 50% of PWE suffering from a depressive disorder, the depressive disorder failed to meet a DSM-III or -IV diagnostic criteria for one of the listed mood disorders.[134]

The following categories are included in the DSM-IV: Major Depressive Disorder, Dysthymic Disorder, Minor Depression, Bipolar Disorder, and Depressive Disorder Not Otherwise Specified or secondary to a medical condition or substance.[57] The difference between major depressive disorders and dysthymic disorder is based largely on severity, persistence, and chronicity. According to DSM-IV criteria, symptoms in both disorders may include combinations of depressed mood, anhedonia, worthlessness, guilt, decreased concentration ability, recurrent thoughts of death, and neurovegetative symptoms (i.e., weight loss or gain, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue). In patients with a major depressive episode, at least 2 weeks of either a depressed mood or anhedonia must accompany four of these symptoms. In contrast, dysthymic disorder is a more chronic but less intense process with symptoms persistent for more days than not for at least 2 years. Minor depression is a category that is similar to major depressive episode in duration but encompasses at least two but less than five of the depressive symptoms noted above.

Bipolar disorders are of two types, depending on the occurrence of manic (type I) or hypomanic (type II) episodes in addition to major depressive episodes. The DSM-IV diagnosis for manic episodes includes the requirement of a distinct period of abnormally and persistently elevated mood lasting at least 1 week and of sufficient severity to cause marked impairment in social functioning. The diagnosis for a hypomanic episode includes the requirement of a distinct period of persistently elevated mood lasting throughout at least 4 days and observable as a disturbance by others. The diagnosis of a cyclothymic disorder requires the presence of numerous hypomanic and minor depressive episodes for at least 2 years.

Concurrent Psychiatric Symptoms in Depressive Disorders in Epilepsy

Investigators have reported a frequent co-occurrence of mood and anxiety disorders in patients with and without epilepsy, with comorbid rates ranging between 50% and 80% in patients with primary mood disorders. The existence of comorbid anxiety symptoms or disorders has a significant impact on the quality of life of depressed patients and their recognition is of the essence as they significantly increase the suicidal risk of depressed patients.[29] Thus, any evaluation of mood disorders for clinical or research purposes are incomplete in the absence of an investigation of comorbid symptoms of depression and vice versa.

Similar observations have been made in PWE. In a study of 199 patients with epilepsy from five epilepsy centers, 73% of patients with a history of depression met also DSM-IV criteria for an anxiety disorder.[103] Furthermore, several investigators dating back to Kraepelin, Bleuler, Gastaut, and more recently Blumer and Kanner have made a point of emphasizing the pleomorphic nature of the symptomatology in depressive disorders in PWE, which in addition to symptoms of anxiety include irritability, increased energy, and physical symptoms.[18,19,74,75,110,115] To a significant degree, these authors attributed the atypical manifestations of depression in epilepsy to these symptoms. This point is discussed in greater detail in the section on Interictal Dysphoric Disorder.

Nonetheless, recent studies have shown that these additional symptoms can be identified in PWE suffering from depressive disorders that also meet DSM-IV diagnostic criteria. In the study by Jones et al. cited above,[103] a DSM-IV diagnosis of a mood and/or anxiety disorders was established with the MINI and SCID in 199 consecutive outpatients from five epilepsy centers. These patients completed a 46-item self-rating instrument the Mood and Anxiety Symptoms in Epilepsy (MASE), which includes symptoms from eight domains (depression, anxiety, irritability, self-consciousness, physical symptoms, disturbances in socialization, suicidal ideation, and increased energy) on two occasions, 2 weeks apart. Sixty-seven patients met criteria for a DSM-IV axis I diagnosis: Each one of the 37 patients that met criteria for major depression reported symptoms of irritability and anxiety; 36 experienced physical symptoms, primarily fatigue; and 31 reported periods of increased energy. Clearly, these data show that depression in epilepsy in its "typical" manifestations not only consists of symptoms of depression, but is more often than not accompanied by symptoms of anxiety and irritability and, paradoxically, symptoms of increased energy. Whether this pleomorphic semiology is specific to depression in PWE or may be present in other neurologic disorders has yet to be established.

Atypical Expressions of Depression in Epilepsy

As stated above, depressive disorders in PWE often fail to meet any of the DSM-III, -III-R, or -IV criteria. For example, using DSM-III-R criteria, Mendez et al. had to classify almost 50% of depressive disorders as atypical depression.[134] Wiegartz et al. found that the depressive episodes of 25% of PWE were also classified as atypical depression not otherwise specified.[211] The interictal dysphoric disorder is the classic example of the atypical expression of depression in PWE and is reviewed at the end of this chapter.

In a study of the semiology of depressive episodes severe enough to merit pharmacotherapy in 97 consecutive patients with refractory epilepsy, only 28 (29%) met DSM-IV criteria for major depressive disorder.[110] The remaining 69 patients (71%) failed to meet criteria for any of the DSM-IV categories. These 69 patients presented a clinical picture consisting of anhedonia (with or without hopelessness), fatigue, anxiety, irritability, poor frustration tolerance, and mood lability with bouts of crying. Some patients also reported changes in appetite and sleep patterns and problems with concentration. Most symptoms presented with a waxing and waning course, with repeated interspersed symptom-free periods of 1 to several days' duration. Their semiology resembled the most a dysthymic disorder, but the recurrence of symptom-free periods intermittently precluded DSM criteria for this condition. We therefore referred to this form of depression as *dysthymic-like disorder of epilepsy* (DLDE).

In 33 of these 69 patients, the predominant and most disabling symptom was anhedonia, while in the remaining 36 patients irritability and poor frustration tolerance were the most disabling symptoms. Of note, patients with DLDE in whom anhedonia was the predominant symptom (vs. irritability) were significantly more likely to have experienced a prior history of major depressive episodes (45.5% vs. 19.5%). Whether DLDE is a variant of the interictal dysphoric disorder has yet to be established in systematic studies (see below).

Subclinical or subsyndromic forms of depression are another presentation of atypical depression, both in primary mood disorders and in depressive disorders of PWE. In the study of 199 consecutive PWE cited above,[103,109] 132 patients (64%) failed to meet any DSM-IV axis I diagnosis according to the SCID and MINI; yet, using the self-rating instruments Beck Depression Inventory (BDI) or the CES-D, 32 patients (16% of the entire cohort) were also found to have been experiencing symptoms of depression of mild to moderate severity. Furthermore, symptoms of anxiety were identified in 31 of these 32 patients with the MASE, symptoms of irritability in 32, physical symptoms in 24, and symptoms of increased energy in 18.

Suicidality as an Expression of Depression in Epilepsy

The suicide rate in PWE is five times higher than the expected rate in the general population. However, among patients with TLE the suicide rate can be 25 times higher.[77] For example, Robertson reviewed 17 studies pertaining to mortality in epilepsy and found that suicide was ten times more frequent than in the general population.[166] Rafnsson et al. recently reported the results of a population-based incidence cohort study in PWE from Iceland in which suicide had the highest standard mortality rate (5.8) of all causes of death,[158] and it was 3.5 in a Swedish study carried out among 9,000 previously hospitalized PWE.[142] The topic of suicidality in PWE is reviewed in detail in Chapter 211 in this book.

Impact on Quality of Life

Depression has been found to yield a significant negative impact on the quality of life of PWE. For example, in a study of 56 consecutive patients with TLE, Lehrner et al.[123] found depression to be the most powerful predictor for each domain of health-related quality of life. Even after controlling for seizure frequency and severity and other psychosocial variables, there remained a significant association between depression and ratings indicative of poor quality of life. In another study of 257 patients with epilepsy, Perrine et al.[150] found that the mood factor had the highest correlations with scales of the Quality of Life in Epilepsy (QOLIE-89) and was the strongest predictor of quality of life in regression analyses, as the mood factor was responsible for 46% of the variance in overall quality of life.

Likewise, in a group of 125 patients who had undergone temporal lobe surgery at least 12 months previously, Gilliam et al. showed that mood status was the most significant predictor of the patients' assessment of their own health status.[78] In another investigation, Gilliam examined the variables responsible for poor quality of life identified with the QOLIE-89 in 194 adult patients with refractory partial epilepsy[80] and found that the only independent variables significantly related to poor quality-of-life scores were high levels of depression and neurotoxicity from antiepileptic drugs. Patients had a median 9.7 seizures/month (range 0.3 to 51), but the author saw no relationship between the type and/or the frequency of seizures and quality-of-life scores. Identical findings were replicated by Boylan et al. in a more recent study.[28] Cramer et al. also found

that depression was significantly associated with poor quality-of-life scores on the QOLIE-89 independently of the type of seizures; these investigators found, however, that seizure freedom for the last 3 months increased (i.e., improved) the quality-of-life ratings.[47] In the study of 199 patients described above, Kanner et al. found that the scores of the QOLIE-89 were significantly higher (i.e., better quality of life) among patients who had been seizure free for the last 6 months than those with persistent seizures.[109] These patients, however, were significantly less likely to have experienced a depressive disorder. The presence of a comorbid anxiety disorder with depression has also been associated with worse ratings in the QOLIE-89. In the same study cited above, patients with mixed anxiety/major depression had significantly lower scores than patients with major depression alone and these were in turn lower than those with only anxiety disorder.

Depression in PWE can also have a significant impact on health care costs associated with the management of the seizure disorder. For example, Cramer et al. investigated the impact of comorbid depression on health care utilization and health care coverage by PWE in U.S. communities using a postal survey questionnaire.[46] They found that people whose depression was untreated used significantly more health resources of all types, independently of seizure type and time since the last seizure. Furthermore, people with mild to moderate depression had a twofold and people with severe depression a fourfold higher frequency of medical visits than nondepressed people. Also, the presence and severity of depression was found to be a predictor of worse disability scores (Sheehan's Disability Scale), independently of duration of the seizure disorder. These data highlight the impact of comorbid depression on health care utilization by people with epilepsy.

Pathogenic Mechanisms

Is There a Bidirectional Relationship between Depression and Epilepsy?

Three studies published in the last 15 years have raised the possibility of a bidirectional relation between depression and epilepsy.[69,89,90] In the first study, Forsgren and Nystrom conducted a population-based case-control study of patients with newly diagnosed onset epilepsy in Sweden, and discovered that patients were seven times more likely to have reported a history of depression than were controls.[69] Hesdorffer et al. conducted a second population-based case-control investigation of the prevalence of new onset epilepsy among adults aged 55 and older, and showed that compared to controls, patients were 3.7 more likely to have had a history of depression *prior* to their first seizure.[89] The same authors conducted a population-based study in Iceland that included children and adults with newly diagnosed unprovoked seizures and/or epilepsy.[90] They found that patients with a history of major depression (by DSM-IV criteria) were significantly more likely than controls (odds ratio [OR] 1.7) to suffer from unprovoked seizures and epilepsy. Furthermore, a history of suicidal ideation was associated with a significantly greater risk of developing epilepsy (OR 5.5) independent of a history of major depression. These data do not indicate causality between the two disorders, but rather suggest the existence of common pathogenic mechanisms operant in depression and epilepsy.

Common Pathogenic Mechanisms in Epilepsy and Depression

Two classes of pathogenic mechanisms are likely to be operant in both disorders: (a) abnormal secretion patterns of neurotransmitter systems including serotonin (5HT), norepinephrine (NE), dopamine (DA), γ-aminobutyric acid (GABA), and glutamate; and (b) structural and functional abnormalities of common neuroanatomic structures in limbic structures, particularly in temporal and frontal lobes.

Abnormal Secretion of Neurotransmitters

Data from experimental animal studies.

Abnormal serotonergic, noradrenergic, and dopaminergic transmission in the brain has been recognized as a pivotal pathogenic mechanism of mood disorders and has been the basis for the development of antidepressant pharmacologic treatments.[191] By the same token, a decreased serotonergic and noradrenergic activity has been shown to facilitate the kindling of seizures, exacerbate seizure severity, and intensify seizure predisposition in some animal models of epilepsy as shown below.[98] Compelling data are derived from studies with two strains of genetic epilepsy-prone rats (GEPR), GEPR-3 and GEPR-9, which are characterized by genetically determined predisposition to sound-induced generalized tonic–clonic seizures

(GTCSs).[44,50,98,99,100,205] Both strains of rats have innate pre- and postsynaptic noradrenergic and serotonergic transmission deficits, the former resulting from deficient arborization of neurons arising from the locus coeruleus coupled with excessive presynaptic suppression of stimulated NE release in the terminal fields and lack of postsynaptic compensatory up-regulation.[44,50,98,99,100,205] GEPR-9 rats have a more pronounced NE transmission deficit and, in turn, exhibit more severe seizures than GEPR-3 rats.[215] Abnormal serotonergic arborization has also been identified in the GEPR's brain coupled with deficient postsynaptic serotonin$_{1A}$-receptor density in the hippocampus.[49] Of note, GEPRs display similar endocrine abnormalities to those identified in patients with major depressive disorder (MDD), such as increased corticosterone serum levels, deficient secretion of growth hormone, and hypothyroidism.[101]

Increments of either NE and/or 5HT transmission with the selective serotonin reuptake inhibitor (SSRI) sertraline resulted in a dose-dependent seizure frequency reduction in the GEPR, which correlated with the extracellular thalamic serotonergic thalamic concentration.[213,214] In addition, the 5-HT precursor 5-HTP has been shown to have anticonvulsant effects in GEPRs when combined with a monoamine oxidase inhibitor (MAOI),[98] while SSRIs and MAOIs have been found to exert anticonvulsant effects in genetically prone epilepsy mice and baboons as well as in nongenetically prone cats, rabbits, and rhesus monkeys.[133,152,153,213,217] Conversely, drugs that interfere with the release or synthesis of NE or 5HT exacerbate seizures in the GEPRs.[98,138] These include NE storage vesicle inactivators reserpine or tetrabenazine, the NE false transmitter *a*-methyl-m-tryosine, the NE synthesis inhibitor α-methyl-Δ-tyrosine, and the 5-HT synthesis inhibitor Δ-chlorophenylalanine, all of which have also been found to facilitate seizure occurrence in humans.[138,143,197]

An anticonvulsant effect of serotonergic activity has been reported in other animal models of epilepsy. Lopez-Meraz et al. studied the impact of two 5HT$_{1A}$ receptor agonists, 8-OH-DPAT and indorenate, in three animal models of epileptic seizures (clonic–tonic induced by pentylenetetrazol [PTZ], status epilepticus of limbic seizures induced by kainic acid [KA], and tonic–clonic seizures induced by amygdala kindling) in Wistar rats.[127] They found that 8-OH-DPAT lowered the incidence of seizures and the mortality induced by PTZ, increased the latency and reduced the frequency of wet-dog shake and generalized seizures induced by KA and at high doses diminished the occurrence and delayed the establishment of status epilepticus. Indorenate increased the latency to the PTZ-induced seizures and decreased the percentage of rats that showed tonic extension and death, augmented the latency to wet-dog shake and generalized seizures, and diminished the number of generalized seizures.

The antiepileptic effect of 5HT$_{1A}$ receptors has been associated with a membrane hyperpolarizing response associated with increased potassium conductance in hippocampal kindled seizures in cats, and in intrahippocampal kainic acid–induced seizures in freely moving rats.[13,148] Furthermore, antiepileptic drugs (AEDs) with established psychotropic effects (carbamazepine [CBZ], valproic acid [VPA], and lamotrigine [LTG]) have been found to cause an increase in 5HT.[41,42,51,52,53,189,210,216] In fact, the anticonvulsant protection of CBZ can be blocked with 5HT-depleting drugs in GEPRs.[216] Likewise, in a recent study, Clinckers et al. investigated the impact of oxcarbazepine (OXC) infusion on the extracellular hippocampal concentration of 5HT and DA in the focal pilocarpine model for limbic seizures.[41] When OXC was administered together with verapamil or probenecid (so as to ensure its passage through the blood–brain barrier), complete seizure remission was obtained associated with an increase in 5HT and DA extracellular concentrations.[42]

In addition, it has been suggested that the anticonvulsant effect of the vagal nerve stimulator (VNS) in the rat could be mediated by noradrenergic and serotonergic mechanisms, as deletion of noradrenergic and serotonergic neurons in the rat prevents or reduces significantly the anticonvulsant effect of VNS against electroshock- or pentylenetetrazol-induced seizures.[35,139] Furthermore, the effect of VNS on the locus coeruleus and raphe may be responsible for its antidepressant effects identified in humans.[3]

Data from studies in humans.

Depression in PWE has been associated more frequently with seizure disorders of temporal and frontal lobe origin, with prevalence rates ranging from 19% to 65% in various patient series.[6,74,75,95,104,163,207] In contrast to animal studies, the impact of pharmacologic augmentation or reduction in 5HT and NE transmission on seizures in humans has been rather sparse and mostly based on uncontrolled data. For example, depletion of monoamines with reserpine has been associated with an increase in frequency and severity of seizures in PWE,[143,197] while the use of reserpine at doses of 2 to 10 mg/day was found to lower the electroshock seizure threshold and the severity of the resulting seizures in patients with schizophrenia.[138] The tricyclic antidepressant imipramine, with reuptake inhibitory effects of NE and 5HT, was reported to suppress absence and myoclonic seizures in double-blind placebo-controlled studies.[71,72,73] Open trials with the SSRIs fluoxetine and citalopram yielded an improvement in seizure frequency, but no controlled studies with this class of antidepressants have been performed as of yet.[4,65]

Functional Neuroimaging Studies in Epilepsy and Primary Depression.

The use of positron emission tomography (PET) and single photon emission computed tomography (SPECT) studies has yielded significant data suggestive of abnormal 5HT activity in primary depressive disorders and in epilepsy, with particular involvement of $5HT_{1A}$ receptors. Deficits in 5HT transmission in human depression is thought to be partially related to a paucity of serotonergic innervation of its terminal areas suggested by a scarcity of 5HT levels in brain tissue, plasma, and platelets and with a deficit in serotonin transporter binding sites in postmortem human brain.[8,30,32,33,38,39,120,121,122,129,140,145,146,151,167,192,195] Serotonin stores and transporter protein are important components of serotonin terminals so that a combined deficit is a plausible indicator of reduced axonal branching and synapse formation.

With respect to abnormal serotonergic activity in functional neuroimaging studies of patients with primary major depression, Sargent et al. demonstrated a reduced binding potential of $5HT_{1A}$ receptors in frontal, temporal, and limbic cortex with PET studies using [11 C]WAY-100635 in both unmedicated and medicated depressed patients compared with healthy volunteers.[172] Of note, binding potential values in medicated patients were similar to those in unmedicated patients. Drevets et al., using the same radioligand, reported a decreased binding potential of $5HT_{1A}$ receptors in mesial temporal cortex and in the raphe in 12 patients with familial recurrent major depressive episodes compared to controls.[58] A deficit in the density or affinity of postsynaptic $5HT_{1A}$ receptors has been identified in the hippocampus and amygdala of untreated depressed patients who committed suicide.[147] In addition, impaired serotonergic transmission has been associated with defects in the dorsal raphe nuclei of suicide victims with major depressive disorder consisting of an excessive density of serotonergic somatodendritic impulse-suppressing $5HT_{1A}$ autoreceptors.[122]

Similar abnormalities have been reported in patients with epilepsy. In a PET study of patients with TLE using the $5HT_{1A}$ receptor antagonist [18F]trans-4-fluro-N-2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl-N-(2-pyridyl) cyclohexanecarboxamide reduced $5HT_{1A}$ binding was found in mesial temporal structures ipsilateral to the seizure focus in patients with and without hippocampal atrophy. Reduced serotonergic activity was independent of the presence or absence of hippocampal atrophy on magnetic resonance imaging (MRI), and reduced volume of distribution and binding remained significant after partial volume correction.[201] In addition, a 20% binding reduction was found in the raphe and a 34% lower binding in the ipsilateral thalamic region to the seizure focus. In a separate PET study aimed at quantifying $5HT_{1A}$ receptor binding in 14 patients with TLE, a decreased binding was identified in the epileptogenic hippocampus, amygdala, anterior cingulate, and lateral temporal neocortex ipsilateral to the seizure focus, as well as in the contralateral hippocampi, but to a lesser degree, and in the raphe nuclei.[174] Other investigators using the $5HT_{1A}$ tracer 4,2-(methoxyphenyl)-1-[2-(*N*-2-pyridinyl)-*p*-fluorobenzamido]ethylpiperazine ([^{203}F]MPPF) found that the decrease in binding of $5HT_{1A}$ was significantly greater in the areas of seizure onset and propagation identified with intracranial electrode recordings. As in the other studies, reduction in $5HT_{1A}$ binding was present even when quantitative and qualitative MRIs were normal.[135]

Reduction in $5HT_{1A}$ receptor binding is not restricted to patients with TLE. PET studies with the $5HT_{1A}$ receptor antagonist carbonyl-carbon 11-WAY-100635 ([11c]WAY-100635) found a decreased binding potential in the dorsolateral prefrontal cortex, raphe nuclei, and hippocampus of 11 patients with juvenile myoclonic epilepsy compared to 11 controls.[136]

With respect to abnormal DA activity as a common pathogenic mechanism, Tremblay et al. recently demonstrated abnormal dopaminergic function in the brain of patients with primary major depressive disorders.[203] Using functional MRI blood oxygen level-dependent activation during a controlled task and measurement of dextroamphetamine subjective effects, patients with major depression had a twofold increase in the response to the rewarding effects of dextroamphetamine, compared to a group of 12 healthy controls. Abnormal brain activation was identified in the ventrolateral prefrontal cortex and orbitofrontal cortex as well as in the caudate and putamen in the patient group.

Likewise, abnormal dopamine activity in the brain of patients with refractory epilepsy has been recently suggested in a PET study using 18F-fluoro-DOPA.[27] Three groups of patients were included: One consisted of 16 patients with a ring chromosome 20 (r20); a second group included 10 patients with absence-like epilepsy; and the third group was integrated by nine patients with intractable TLE. Compared to a group of ten healthy volunteers, patients from all three epilepsy groups displayed a decrease of 18F-fluro-DOPA uptake, but only in patients with TLE was the decreased uptake lateralized to the side of the seizure focus. A bilateral uptake was found in the substantia nigra in all three patient groups.

Involvement of frontal lobes in primary depression has also been demonstrated with functional neuroimaging (PET, SPECT) and neuropsychological studies.[11,114] For example, executive abnormalities are consistently found among studies,

and are more apparent in more severe depressive disorders. These neuropsychological disturbances correlated with reduced blood flow in mesial prefrontal cortex. Furthermore, in tests demanding executive function, cingulate cortex and striatum could not be activated in patients with major depressive disorders.[125] Functional disturbance of frontal lobe structures has been recognized in TLE and particularly among patients with TLE and comorbid depression, as they have been found to have bilateral reduction in inferofrontal metabolism.[31,102] Likewise, neuropsychological testing with the Wisconsin Card Sorting Test (WCST), which is highly sensitive to executive dysfunction, has revealed poor performance in patients with TLE and comorbid depression.[45,82,83,85,86,87,94,178] Of note, inferior frontal cortex is the main target of the mesolimbic dopaminergic neurons and provides input to the serotonergic neurons of the dorsal raphe nucleus.

The abnormal serotonergic secretion in the brain of PWE may account for the prominence of comorbid symptoms of anxiety and panic, irritability, and poor frustration tolerance, as well as the increased incidence rates of suicidality. Neumeister et al., using the selective $5HT_{1A}$ radioligand [18F]-FCWAY, found reduced $5HT_{1A}$ receptor binding in the anterior and posterior cingulate in patients with panic disorder with and without comorbid depression.[1] A relationship between abnormal serotonin activity and suicidal behavior associated with several psychiatric diagnoses has been suggested in multiple studies, including quantitative autoradiography studies of brain tissues obtained from suicidal victims, in studies of serotonin transporter sites, and in studies of $5HT_{1A}$ receptor binding, to name a few.[147] These studies suggest abnormal serotonergic function primarily at the ventral prefrontal cortex.

Common Neuroanatomic Structures Involved in Depression and Epilepsy

Structural changes in temporal lobes.

Structural neuro-imaging studies of patients with major depressive disorders revealed involvement of mesial temporal, orbitofrontal, and mesial frontal structures, as well as subcortical structures including basal ganglia and thalamic nuclei.[185] Sheline et al. reported bilateral smaller hippocampal volumes in two separate studies of patients with a history of primary major depressive disorders in remission when compared to hippocampal volumes of age-, sex-, and height-matched normal controls.[182,183,184] They also identified large hippocampal low-signal foci (≥4.5 mm in diameter) and their number correlated with the total number of days depressed. A significant inverse correlation between the duration of depression and left hippocampal volume was also demonstrated, suggesting that patients with more chronic and active disease were more likely to have hippocampal atrophy. More recently, Sheline et al. demonstrated that hippocampal atrophy was prevented with antidepressant drug therapy in a study of 38 female patients with a history of major depressive disorders.[180] They found a significant correlation between reduction in hippocampal volume and the duration of depression that went untreated, while there was no correlation between hippocampal volume loss and time depressed while taking antidepressant medication or with lifetime exposure to antidepressants. Similar findings have been reported by other investigators.[206]

Atrophy has also been identified in entorhinal cortex and amygdala.[15,154,185] Furthermore, in a neuropathologic study of amygdala and entorhinal cortex, a significant reduction of glial cells and of the glial/neurons ratio was found in left amygdala and to a lesser degree in left entorhinal cortex of patients with major depressive disorder and bipolar disorder (not treated with lithium and valproic acid) compared to those of controls.[181]

By the same token, abnormalities of mesial temporal structures are among the most frequently identified in PWE and comorbid depression. In three studies of patients with TLE, higher scores of depression were associated with the presence of mesial temporal sclerosis (MTS), decreased temporal lobe and frontal lobe perfusion on (99m) Tc-HMPAO SPECT scans, and greater abnormalities identified with magnetic resonance spectroscopy.[79,157,177]

It is important to notice, however, that the magnitude of hippocampal atrophy in TLE is significantly greater than that in major depressive disorder, while the neuropathologic findings are different. In MTS, neuropathologic findings consist of neuronal cell loss and astrocytosis in hippocampal formation (including areas CA1, CA2, CA3, and CA4, dentate gyrus, and subiculum), amygdala entorhinal cortex, and parahippocampal gyrus.[130]

Unfortunately, there have been very few neuropathologic studies of the human hippocampal formation in patients with primary major depressive disorder. Lucassen et al. carried out a neuropathologic study of 15 hippocampi of patients with a history of major depressive disorder and compared them to those of 16 matched controls and nine steroid-treated patients.[128] In 11 of 15 depressed patients, rare but convincing apoptosis was identified in entorhinal cortex, subiculum, dentate gyrus, CA1, and CA4. Apoptosis was also found in three steroid-treated patients and one control. However, no apoptosis of pyramidal cells in CA3 was identified. Other neuropathologic changes in brains from patients with major depression were reported by Stockheimer et al.[194] These investigators compared the density of pyramidal neurons, dentate granule cell neurons, and glia and the size of the neuronal soma from postmortem sections of right hippocampus obtained from 19 patients with major depressive disorders and 21 aged-matched psychiatrically normal controls. They found that in patients with major depressive disorders, the density of granule cells and glia in dentate gyrus and pyramidal neurons and glia in all cornu ammonis was significantly increased by 30% to 35%, while the average soma size of pyramidal neurons was decreased.

Hippocampal atrophy in primary major depressive disorders has been attributed to two potential pathogenic mechanisms: (a) an alteration in neurotrophic factors resulting from the mood disorder[40,141,187] and (b) high glucocorticoid exposure.[92,93,161,170]

Acute and chronic stress decreases levels of brain-derived neurotrophic factor (BDNF) in the dentate gyrus, pyramidal cell layer of hippocampus, amygdala, and neocortex, which may contribute to structural hippocampal changes.[187] These changes are mediated by glucocorticoids and can be overturned with antidepressant therapy, as chronic administration of antidepressant drugs increased BDNF expression and also prevented a stress-induced decrease in BDNF levels.[40,141] There is also evidence that antidepressant drugs can increase hippocampal BDNF levels in humans.[40,141] These data indicate that antidepressant-induced up-regulation of BDNF can hypothetically repair damage to hippocampal neurons and protect vulnerable neurons from additional damage.

The high glucocorticoid exposure mediating hippocampal atrophy is based on the excessive activation of the hypothalamic-pituitary-adrenal axis identified in almost half of individuals with depression resulting in impaired dexamethasone suppression of adrenocorticotropic hormone (ACTH) and cortisol. These changes are reversible to treatment with antidepressants.[93] In experimental studies with rats and monkeys, prolonged increased concentrations of glucocorticoids have been found to damage hippocampal neurons, particularly CA3 pyramidal neurons, possibly by reduction of dendritic branching and loss of dendritic spines that are included in glutamatergic synaptic inputs.[170] Hypercortisolemia has also been found to interfere with the development of new granule cell neurons in the adult hippocampal dentate gyrus. Deleterious effects of chronic glucocorticoid exposure may lead initially to a transient and reversible atrophy of the CA3 dendritic

tree and to an increased vulnerability to a variety of insults and finally result in cell death under extreme and prolonged conditions.[170]

Structural changes in frontal lobes.

Likewise, structural changes have been identified in the orbitofrontal and prefrontal cortex and cingulate gyrus, as well as in their white matter, including a smaller volume of orbitofrontal cortex in young adults and geriatric patients with major depressive disorder.[116,117,198,199] Of note, the magnitude of prefrontal volume changes was related to the severity of the depression, as elderly patients with minor depression had lesser changes than those with major depressive disorder.[116]

Neuropathologic studies have also documented structural cortical changes in frontal lobes of depressed patients. Raj-kowska et al. found a decrease in cortical thickness, neuronal sizes, and neuronal densities in layers II, III, and IV of the rostral orbitofrontal region in the brains of depressed patients.[159] In the caudal orbitofrontal cortex, there were significant reductions in glial densities in cortical layers V and VI that were also associated with decreases in neuronal sizes. Finally, in the dorsolateral prefrontal cortex, there was a decrease in neuronal and glial density and size in all cortical layers.

Other Pathogenic Mechanisms

Psychosocial causes of depression.

For many years, clinicians and patients have, erroneously, attributed and explained their patients' depressed mood solely as a “normal reaction” to the numerous social and personal obstacles resulting from epilepsy. These include (a) the patient's and/or family inability to accept and adjust to a diagnosis of epilepsy; (b) the stigma related to the diagnosis of epilepsy and the well-known discrimination patients face; (c) the lack of control in one's life resulting from the unpredictable occurrence of epileptic seizures; and (d) the patient's lack of social support and the need to make major adjustments in lifestyle, such as giving up driving privileges or changing jobs to maximize seizure precautions.[36,55,56,84,97,175] Any one or combination of these factors could result in an *initial* adjustment reaction with depressive and anxiety features, but they are unlikely *on their own* to result in *chronic* depressive disorder. Also, patients displaying comorbid depression may have less ability to cope with these obstacles. Additionally, even epileptic patients with a normal intelligence have been found to show a lower degree of flexibility of mental processing compared with normal controls in neuropsychological studies.[34,188] Nonetheless, a depressed state that persists after several months can no longer be diagnosed from a clinical standpoint as a “normal” reactive process and warrants a detailed psychiatric evaluation.

Depression as an iatrogenic process.

Every AED, including those with positive psychotropic properties, can trigger depressive symptoms in PWE, some more than others.[132] Phenobarbital (PB) can result in depression that may occasionally be complicated with suicidal ideation; primidone (PRM), tiagabine, vigabatrin, felbamate, topiramate (TPM), levetiracetam (LEV), and zonisamide (ZNS) have also been associated with symptoms of depression.[9,29,66,106,131,137,162,186] On the other hand, the presence of a current or prior depressive disorder may increase the risk of cognitive adverse events associated with topiramate.[106,137]

Depression following epilepsy surgery.

In the last two decades, depressive disorders have been recognized with increased frequency during the first year following an anterotemporal lobectomy.[23,173] It is common for patients to exhibit “mood lability” within the first 6 weeks after surgery, and usually these symptoms subside; however, overt depressive symptoms become clear within the initial 6 months in up to 30% of patients. Typically, symptoms of depression range in caliber from mild to very severe, including suicidal attempts. In general, pharmacologic treatment with antidepressant drugs is effective. Patients with a past history of depression are at increased risk. In a recent study of 90 consecutive patients that underwent an anterotemporal lobectomy at the Rush Epilepsy Center, 23 exhibited an exacerbation or recurrence of a previous depressive disorder and 11 experienced a de novo depressive disorder.[108] Remission of all symptoms was obtained in 22 patients, while in 12 symptoms persisted despite multiple pharmacologic trials with various antidepressants. There was no difference in the risk of developing a persistent depressive disorder among patients with de novo versus those with a prior history of depression. Postsurgical seizure freedom was associated with a lower likelihood of experiencing a postsurgical depressive episode. Thus, all patients preparing for epilepsy surgery should be warned of this possible risk, *prior to surgery*.

A paradoxic “iatrogenic” cause of psychopathology among epileptic patients includes the phenomenon of “forced normalization,” which consists of the development of psychiatric disorders following the cessation of epileptic seizures.[165] An interictal depression, therefore, may exacerbate or present de novo in patients as increased seizure control is attained, although the frequency of this phenomenon remains to be established. This problem is discussed in greater detail in section II.

A genetic predisposition.

A common risk to develop a depressive disorder in patients with and without epilepsy is a family history of depression. In fact, over 50% of PWE suffering from depression have been found to show a family history of psychiatric illness, affective disorders being the most frequent condition.[95,163]

Laterality of the seizure focus.

Despite having been raised as a potential pathogenic parameter, the laterality of the seizure focus remains a topic of debate. Certain authors have suggested, however, that a left hemispheric focus may be a predisposing factor of depression based on PET and SPECT studies.[165]

Treatment

Despite the relatively high comorbidity of mood disorders in epilepsy, they continue to remain unrecognized and untreated in a significant percentage of patients. Indeed, depression in epilepsy remains underrecognized and undertreated. For example, in a study of 97 patients with epilepsy with depressive disorders severe enough to merit pharmacologic treatment, 60% had been symptomatic for more than 1 year before any treatment was suggested.[110] Only one third of the 97 patients had been treated within 6 months of the onset of their symptoms. To our surprise, delay in recognizing the need for therapy was not related to the severity of the depressive disorder, as the proportion of untreated patients for more than 1 year did not differ between patients with major depression and dysthymic disorders. Wiegartz et al.[211] reported similar findings. Thirty percent of 76 patients with partial epilepsy met criteria of a lifetime-to-date diagnosis of major depressive disorder, 9% with a diagnosis of current major depressive episode, and 22% with a lifetime diagnosis of major depressive disorder. Twenty-five percent of these 76 patients reported symptoms of minor depressive disorders (dysthymic disorders, depressive disorder not otherwise specified). None of these patients had received treatment for their dysthymic disorder and commonly had not been trained to understand and treat the psychiatric complications of epilepsy.

Table 2 Efficacy of Selective Serotonin Reuptake Inhibitors and Serotonin Norepinephrine Reuptake Inhibitors in Primary Depression and Anxiety Disorders

Antidepressant drug	Depression	Panic disorder	Generalized anxiety	Starting dose	Maximal dose

Paroxetine	+	+	+	10	60
Sertraline	+	+		25	200
Fluoxetine	+	+		10	80
Citalopram	+			10	60
Escitalopram	+	+	+	5	30
Venlafaxine	+	+	+	37.5	300

Fluvoxamine was not included in this table due to the absence of any data in people with epilepsy.

Even when recognized, clinicians refrain from considering the use of pharmacologic treatment for (a mistaken) fear of worsening the patient's seizures. The hesitancy of using psychotropic medications in PWE has resulted in the absence of controlled studies on the efficacy and safety of antidepressants in these patients. Indeed, to date there has been only one controlled study published in the literature that compared under blind conditions the efficacy of two antidepressant drugs (amitriptyline and mianserin) to placebo in major depression of PWE.[179] Consequently, the data available for the management of mood disorders in PWE have to be derived from open uncontrolled trials, based on the experience obtained in the treatment of primary depression. Given the relatively high frequency of atypical depressive disorders in PWE, one cannot assume that efficacy in mood disorders in patients without epilepsy may apply to PWE. The absence of methodologically sound data has further compounded the clinician's reluctance to treat patients with psychotropic drugs, and in the end the persistence of a mood disorder ends up having a worse impact on the patient's quality of life than the actual seizures and increases their risk of suicide, which has also clearly surpassed the risk of death from a seizure, as documented in a separated chapter.

Some Preliminary Basic Concepts

Before starting any specific treatment strategy, it is important to consider the following questions:

1. Did the symptoms of depression and anxiety appear following the introduction or increase in the dose of an AED known to cause psychiatric adverse events?
2. Did the psychiatric symptoms follow the discontinuation of an AED with positive psychotropic (mood stabilizing, antidepressant, and anxiolytic) properties (i.e., CBZ, VPA, LTG, OXC)? In this case, the psychiatric symptoms may be the expression of recurrence of a latent psychiatric disorder that had been in remission (or masked) by the AED discontinued.[164] By the same token, it is important to investigate the existence of any psychiatric family history that places the patient at an increased risk when exposed to an AED with negative psychotropic properties (i.e., symptoms of depression following exposure to PB, PRM, or ZNS in patients with a family history of mood disorders).
3. Did the psychiatric symptoms occur after the introduction of an enzyme-inducing AED (CBZ, PHT, PB, PRM, high-dose TPM, or OXC) in a patient who was already taking a psychotropic drug for a previously recognized

depression or anxiety disorder? In such case, the symptom recurrence may have resulted from a pharmacokinetic interaction between the AED and the psychotropic drug on board that caused a drop in the psychotropic drug's serum concentration. Accordingly, a readjustment in the dose of the psychotropic drug may be sufficient to induce symptom remission.

4. Are the psychiatric symptoms temporally related to the seizure occurrence? That is, do they precede (preictal), do they follow (postictal), do they precede and follow, are they the expression of an ictal event, or do they occur interictally with a peri-ictal exacerbation in severity? In the case of pre- or postictal without interictal symptoms, pharmacotherapy may fail to yield any benefit. Postictal breakthrough symptoms may occur in patients whose interictal symptoms remitted with pharmacotherapy.
5. Are the psychiatric symptoms related to the remission of seizures following a period of persistent seizures, or are they associated with worsening of the patient's seizure disorder? In the former case, the symptoms may be the expression of the phenomenon known as “forced normalization” or “alternative psychopathology.”
6. Is the patient experiencing other psychiatric symptoms (i.e., symptoms of anxiety) that need to be targeted for treatment?

Pharmacotherapy of Depressive Disorders

Today, SSRIs and serotonin norepinephrine reuptake inhibitors (SNRIs) have become the first line of pharmacotherapy for primary major, dysthymic, and minor depressive disorders as well as for the treatment of generalized anxiety and panic disorders (Table 2).[37,112] These drugs are also being advocated for the treatment of these psychiatric disorders in PWE. Furthermore, the use of SSRIs is particularly relevant in PWE given the relatively high comorbidity of anxiety disorders and the prominence of irritability in which these drugs have shown marked efficacy.

Therapeutic Expectations of Pharmacotherapy of Depressive Disorders

A “primary” major depressive episode left untreated may last between 6 and 24 months in 90% to 95% of cases, while the remaining 5% to 10% could last more than 2 years.[37,60,91,112,202] When pharmacotherapy is started, “responders” to pharmacotherapy experience an improvement in their symptomatology (i.e., at least 50% reduction of severity of symptoms measured with a variety of rating scales) during the first 8 weeks. Two thirds of patients are expected to “respond” to antidepressant medication, and in controlled studies, one third are expected to respond to placebo. “Response to therapy,” however, does not imply a symptom-free state and persistence of symptoms increases significantly the risk of recurrence of future major depressive episodes. When such symptom-free state is achieved,

the patient is considered to have entered “remission.” It is estimated that approximately 50% of patients will reach remission within the first 6 months and about two thirds within 2 years of the start of therapy. When remission has lasted for a period of 6 to 12 months, the patient is considered to have reached a state of “recovery.” Approximately 15% to 20% of patients will fail to respond to any antidepressant trial. It has yet to be established whether pharmacotherapy of major depression in PWE yields the same efficacy as that in primary major depressive disorders.

The variables predictive of relapse include (a) multiple prior episodes; (b) severe episodes; (c) long-lasting episodes; (d) episodes with psychotic or bipolar features; and (e) incomplete recovery between two consecutive episodes. Furthermore, premature discontinuation of antidepressant medication can result in relapse. Indeed, only 10% of patients who had an initial response to antidepressant drugs and who were kept for at least 12 months on the drug are likely to experience a relapse, in contrast to 50% of patients in whom the antidepressant medication was discontinued within 6 to 12 months of the start of therapy. If psychotherapy is considered, patients can be referred to a psychologist or to a local mental health clinic for this type of treatment (see below). Many patients will require a combination of pharmacotherapy and psychotherapy.

Pharmacotherapy of Dysthymic-like Disorders

There are no controlled data available on the treatment of DLDE. In an open trial with the SSRI sertraline carried out at the Rush Epilepsy Center in 67 patients with DLDE, complete symptom remission was reached in 57% of patients. While these results are similar to those reported in primary dysthymia, they need to be replicated in randomized placebo-controlled studies in PWE.[110]

Role of the Neurologist in the Management of Mood Disorders in People with Epilepsy

Given their relatively high prevalence in PWE, neurologists should be able to identify the depressive and bipolar disorders described above. They should know how to *initiate* pharmacotherapy for major, dysthymic, and minor depressive episodes. However, the following are the mood disorders that deserve immediate referral to a psychiatrist: (a) any depressive episode associated with suicidal ideation. (b) Any major depressive disorder with psychotic features. Approximately 25% of major depressive disorders can present with psychotic features. In such cases, pharmacotherapy has to include antipsychotic and antidepressant drugs, and at times, the use of electroshock therapy (ECT) has to be considered. Furthermore, the presence of psychotic symptomatology increases significantly the suicidal risk of these patients. (c) Any major depressive or dysthymic episode that has failed to respond to a prior trial with SSRIs or SNRIs at optimal doses. These patients may require a combination of antidepressant drugs or the addition of lithium, thyroid drugs, or central nervous system stimulants to one or two antidepressants and occasionally ECT to reach a euthymic state. (d) Any bipolar disorder. The management of bipolar disorders is fret with a significantly lower therapeutic success and potential serious complications from an inappropriate use of psychotropic drugs such as the conversion of a bipolar disorder into a rapid cycling disorder.[60] Indeed, clinicians must keep in mind that the use of antidepressant medication in a bipolar disorder can facilitate the development of manic and hypomanic episodes and of a rapid cycling bipolar disorder (defined as the presence of four or more depressive, manic, or hypomanic episodes in a 12-month period). The American Psychiatric Association guidelines for the treatment of acute depression in bipolar disease advise against an initial use of antidepressant drugs.[60,202] Thus, in patients with “apparent” stable bipolar disorders, neurologists should at the least refer the patient for *one* psychiatric consultation to confirm that optimal treatment options are being prescribed.

Table 3 Incidence of Seizures in People without Epilepsy

Antidepressants	Incidence of seizures
Selective serotonin reuptake inhibitors	
Sertraline	0.08%
Paroxetine	0.1%
Fluoxetine	0.2%
Fluvoxamine	0.2%

Citalopram/escitalopram	<0.1%
Serotonin norepinephrine reuptake inhibitor	
Venlafaxine	0.3%

Choice of Antidepressant Drug

As stated above, there is a general consensus among psychiatrists that SSRIs and/or SNRIs are the drugs of choice to treat the various types of primary depression. However, when choosing an antidepressant drug in PWE, clinicians must also consider the following issues:

1. The potential of the antidepressant drug to worsen seizures
2. The pharmacokinetic and pharmacodynamic interactions of the AEDs with the antidepressant drug
3. The potential of the antidepressant drug to worsen underlying comorbid disorders specific to PWE

Do Selective Serotonin Reuptake Inhibitors and Serotonin Norepinephrine Reuptake Inhibitors Worsen Seizures?

The incidence of seizures in nonepilepsy patients exposed to SSRIs is presented in Table 3.

Clearly, the incidence of seizures is lower than that expected in the general population. Furthermore, in a recent critical review of the literature, Jobe and Browning concluded that not only is the use of SSRIs safe, but also that the proconvulsant effects of antidepressants cannot be accounted by their serotonergic or noradrenergic effects.[156] A recent study supports these conclusions. Khan et al. compared the incidence of seizures among patients randomized to SSRIs (citalopram, fluoxetine, fluvoxamine), the SNRI venlafaxine, and the α2-adrenergic antagonist antidepressant mirtazapine in regulatory trials. They found that patients randomized to the antidepressants were significantly less likely to have had an epileptic seizure than controls[2] (and Alper et al., submitted). These findings support the conclusions of Jobe and Browning as well as the data presented by Forsgren and Nystrom[103] and Hesdorffer et al.[89,90] in the sense that a history of depression increases the risk of seizures. These data raise the question of whether the seizures that occur after the start of SSRIs are in fact related to an increased risk associated with the depressive disorder. Yet, this question needs to be examined in prospective and controlled studies, as the occurrence of seizures has been occasionally reported to the introduction of an SSRI (see also Chapter 214).

The use of SSRIs in PWE has been investigated in the case of sertraline, citalopram, and fluoxetine.[4,65,110] In a study from our center, sertraline was found to *definitely* worsen seizures in only 1 of 100 patients.[110] In another five patients, a transient increase in seizure frequency was attributed to this antidepressant drug with a probable, but not definite, causality. Four of these five patients were maintained on sertraline therapy. Following adjustment of the dose of their AED, none of these patients experienced further seizure exacerbation. In the study that investigated the safety of citalopram in 45 PWE, none of the patients experienced a worsening of seizures[4]; in fact the authors noted a reduction in seizure frequency. Similar findings were reported in the study of fluoxetine in PWE.[65]

Blumer has also reported using tricyclic antidepressants (TCAs) alone and TCAs in combination with SSRIs in epileptic patients without seizure exacerbation.[19] No data have been published on the safety of SNRIs in PWE. We have used the SNRI venlafaxine in more than 100 PWE, a significant proportion of whom suffered from intractable epilepsy without observing any worsening in seizure frequency or severity (Kanner, unpublished data).

MAOIs are not known to cause seizures in nonepileptic patients; bupropion, maprotiline, and amoxapine are the antidepressant drugs with the strongest proconvulsant properties and should be avoided in epileptic patients.[48,113]

A review of the literature shows that the variables associated with an increased risk of seizure occurrence following exposure to TCAs in general *in nonepileptic* patients include (a) high plasma serum concentrations; (b) rapid dose increments; and (c) the presence of other drugs with proconvulsant properties.[48,113,196] There are four antidepressant drugs that should be avoided in PWE; these include maprotiline, bupropion, amoxapine, and chlorimipramine. Thus, to minimize the risk of seizures in PWE, antidepressant drugs should be started at low doses with small increments until the desired clinical response is reached; this will minimize the risk of causing and/or exacerbating seizures.

Pharmacokinetic Interactions between Antidepressants and Antiepileptic Drugs

All of the SSRIs and SNRIs are metabolized in the liver via the CP450 system and their metabolism is accelerated in the presence of AEDs with enzyme-inducing properties, which include phenytoin, carbamazepine, phenobarbital, and primidone at regular doses and oxcarbazepine and topiramate at higher doses. This pharmacokinetic effect is not observed with the new AEDs gabapentin, lamotrigine, tiagabine, levetira-cetam, and zonisamide. Thus, upon introduction of an enzyme-inducing AED, clinicians need to advise patients to be on the lookout for symptom recurrence, in which case the dose of the SSRI or SNRI may need to be increased.

Conversely, some of the SSRIs are inhibitors of one or more isoenzymes of the CP450 system. These include fluoxetine, paroxetine, and fluvoxamine and, to a lesser degree, sertraline.[81,149,204] Adjustment of some of the AED (primarily carbamazepine and phenytoin) doses may be necessary. Citalopram, escitalopram, venlafaxine, and mirtazapine are the antidepressant drugs with the least impact on CP450 isoenzymes.

Pharmacodynamic Effects of Antidepressant Drugs to Watch for in People with Epilepsy

The acute stimulation of four serotonin receptor subtypes (5HT-2 A, 5HT-2 C, 5HT-3, and 5HT-4) may account for the adverse events associated with SSRIs and SNRIs.[70,80] In addition, adverse events may result from a direct action of serotonin outside the brain, such as the spinal cord and gastrointestinal tract. The adverse events associated with these drugs include anxiety and agitation during the acute phase of treatment; gastrointestinal symptoms including nausea, abdominal cramping, and diarrhea; changes in appetite and weight; sexual disturbances; and, rarely, involuntary movements.[112] Among the SNRIs, hypertension is a potential adverse event identified in patients taking venlafaxine.[112]

A variety of sexual disturbances including decreased libido, anorgasmia, impotence, and disturbances in ejaculation as well as dyspareunia are more frequent among PWE than the general population, either as an expression of an iatrogenic effect of AEDs and/or as a direct impact of the seizure disorder. Adverse effects of SSRIs and SNRIs have been reported in about 20% to 30% of patients.[37,112] Citalopram and its s-enantiomer escitalopram and mirtazapine have the lowest incidence of sexual adverse events. Whether the adverse effects mediated by these drugs worsen already existing sexual disturbances in PWE has yet to be investigated. Patients, nonetheless, should be advised to report any of these adverse events, either whether occurring de novo or as a worsening of pre-existing disturbances. Tolerance may develop over time, and at times lowering of the dose or switching to another SSRI may improve these side effects.

By the same token, some SSRIs can cause changes in weight in the form of weight gain, as in the case of paroxetine, aggravating a weight gain problem triggered by AEDs like valproic acid, gabapentin, and carbamazepine. On the other hand, fluoxetine can cause weight loss in the first 3 months of therapy, but patients regain the weight lost thereafter.[37]

Finally, discontinuation of antidepressant drugs including TCAs, SSRIs, and SNRIs cannot be abrupt as it can result in withdrawal symptoms[70,112] including nausea, vomiting, tremors, and anxiety.

Other Treatments

Mood-stabilizing Agents

In the treatment of bipolar patients, mood-stabilizing agents have become the first line of drugs to prevent recurrence of major depressive and manic/hypomanic episodes. Fortunately for PWE, several of the AEDs, mainly CBZ, VPA, LTG, and OXC, have been found to show efficacy in this respect.[7,64,68,176,190] Often, however, administration of these AEDs may not be sufficient to cause remission of a major depressive disorder. In such cases a short-term use of an antidepressant may have to be considered, but always in the presence of a mood-stabilizing agent to minimize the risk of conversion to a manic or hypomanic episode. Occasionally, the use of lithium may be necessary to render the patient euthymic; this drug can be fraught with several problems including changes in electroencephalographic (EEG) recordings and proconvulsant properties at therapeutic serum concentrations in nonepileptic patients.[10,190] Its neurotoxicity and related increase in seizure risk increases with the concurrent use of neuroleptic drugs, in the presence of EEG abnormalities, and with a history of central nervous system (CNS) disorder, and thus should be used with caution in PWE. Furthermore, lithium can be associated with neurotoxicity (i.e., dizziness, diplopia, blurred vision, ataxia) when given in combination with CBZ, even when the serum concentrations of both drugs are in the therapeutic range, requiring the reduction in the dose of carbamazepine or a switch to another AED.

Electroshock Therapy

Electroshock therapy may need to be considered in very severe and treatment-resistant major depressive episodes.[14] ECT is not contraindicated in patients with epilepsy.[155] It is a well-tolerated treatment and is worth considering in patients with epilepsy with very severe depression or manic episodes that fail to respond to AD. Blackwood et al. found that the incidence of seizures in patients following treatment with ECT was no higher than in the general population.[155] In fact, several studies have shown that ECT increases seizure threshold by 50% to 100%.[5,16,43,168,169,208] Finally, there are case reports of ECT used successfully for the treatment of seizures in patients with epilepsy not responsive to multiple anticonvulsant medications.[160] Hence, it seems clear that ECT is not contraindicated as a treatment for depression in patients with epilepsy.

When Should Patients Be Referred for Psychotherapy?

Often, mood (and anxiety) disorders may benefit from a combination of pharmacotherapy and psychotherapy, above all when patients have been symptomatic for a protracted period of time and when the psychiatric symptoms have interfered with the patients' ability to maintain employment, a social life, etc. In fact, there are several studies that have established the efficacy of cognitive behavior therapy (CBT) for the management of depressive and anxiety disorders, either by themselves or in combination with pharmacotherapy. In general, CBT consists of short-term treatments of 16 to 20 sessions given during 12 weeks on average.[67] They should only be administered by health care professionals that have been trained specifically in this technique.

Concept of the Interictal Dysphoric Disorder

Modern studies of the interictal psychiatric disorders have usually attempted to identify their similarity to the psychiatric disorders that meet the current DSM-III/IV criteria. Our careful review has shown this to be a difficult task, particularly in view of the pleomorphic and intermittent presentation of the interictal psychiatric changes.

Modern psychiatry excluded epilepsy from its considerations when establishing the DSM classification; it has also omitted genetic considerations and based its classification on the descriptive symptomatology of psychiatric disorders. Admittedly, the current DSM is a work in progress.

Premodern psychiatry deemed epilepsy one of the major spheres of its interests, distinct by etiology and symptomatology from the spheres of manic depressive, schizophrenic, and sexual disorders. Kraepelin[115] precisely described the psychiatric changes among patients with epilepsy as they presented before the modern era of anticonvulsant therapy: Intermittent dysphoric episodes were characterized by irritability, depressive moods, and anxiety, as well as headaches, insomnia, and at times euphoric moods. These pleomorphic dysphoric episodes would occur every few days to every few months and would last from a few hours up to 2 days. Dysphoric symptoms were also observed in the prodromal and postictal phases of a seizure. Kraepelin identified the dysphoric disorder of epilepsy not by cross-sectional inquiries, but based on the daily observations of long-term inpatients with epilepsy at a university hospital. With an appropriate instrument, longitudinal assessment of the dysphoric symptoms in patients with chronic epilepsy has confirmed the pleomorphic and intermittent pattern of the interictal dysphoric disorder.[22,26]

Compared with the premodern psychiatric description of the dysphoric disorder, presumably as an undesirable result of modern antiepileptic drugs, the dysphoric symptoms now appear to be more protracted; for the same reason, chronic interictal psychoses are now more frequent, and suicidality has become a significant problem. This finding needs an explanation.

In 1951, Gibbs observed that the epileptic and psychiatric components of psychomotor epilepsy appeared to be physiologically antithetical.[207] A few years later, Landolt observed a patient whose epileptiform EEG had normalized each time he was dysphoric, ascribed the finding to a “supernormal braking action,” and developed the concept of “forced normalization.”[118,119] Related studies focused particularly on the alternating pattern of interictal psychoses and seizures, and the term “forced normalization” came into current use. Trimble, in particular, has emphasized the importance of forced normalization in several studies and a recent monograph.[205] Engel[61] and Stevens[193] postulated that the psychiatric disorders of epilepsy may result from the inhibitory activity that develops in reaction to the excessive excitatory activity of the chronic seizure disorder. The following findings are in accordance with this postulate[25]:

> (1) The development of the interictal dysphoric and psychotic disorders is delayed (by about 2 years and 12 years, respectively) following onset of epilepsy as inhibitory mechanisms become increasingly established. This finding accords with the particular linkage of the psychiatric disorders of epilepsy with its common relatively refractory form, mesial temporal lobe epilepsy. (2) Upon decrease, and particularly upon full control, of seizures, dysphoric or psychotic symptoms tend to be exacerbated or to emerge de novo (forced normalization or alternating psychosis). (3) Psychiatric changes emerge at times when severe exacerbation of the seizure activity engages an enhanced inhibitory response; thus, the prodromal phase of seizures may be associated with dysphoric symptoms (such as elated mood or heightened irritability), and the postictal phase is commonly associated with dysphoric symptoms (such as anergia, pain, depression, and, in rare cases, even suicidality) and at times (usually after a flurry of seizures) with a psychotic episode.

According to the above hypothesis of the pathogenesis of the psychiatric disorders of epilepsy, their pharmacologic treatment has to be directed primarily against the inhibitory mechanisms. Safety and effectiveness of prescribing the SSRI-type antidepressants for the mood disorders of epilepsy have been previously discussed. The more proconvulsant tricyclic antidepressant drugs, at modest doses, appear to serve as effective antagonists to excessive inhibition and, in fact, may be indispensable for successfully treating the interictal dysphoric disorders.[21,24] Gastaut et al.[74] pointed out that, as measured by their response to Metrazol, patients with temporal lobe epilepsy (in contrast to those with primary generalized epilepsy) show, surprisingly, a higher interictal seizure threshold than do persons without epilepsy. The bias against the use of antidepressants for the psychiatric disorders of epilepsy, on the grounds that they may cause seizures, is erroneous on both empirical and theoretical grounds. Modest amounts of tricyclic antidepressant medication do not increase the seizure frequency in patients with chronic epilepsy whose dysphoric disorder indicates the presence of marked inhibition, and the SSRIs, which we commonly use as adjuncts to the tricyclic antidepressants, are not known to lower the seizure threshold significantly. The combination appears more effective than the use of a tricyclic or of an SSRI alone.[24] Variations that may be necessary in the pharmacotherapy of the interictal dysphoric disorder have been described elsewhere.[21]

The mechanism of action of the antidepressant drugs in the interictal dysphoric disorder clearly is different than in traditional depressive disorders. The drugs are effective rapidly at lower doses and have a broad-spectrum effect for the entire range of symptoms of the limbic disorder, not just for depressive moods, anergia, and insomnia, but also for anxiety, fears, irritability, atypical pains, and euphoric moods.

It is of interest that DSM-IV recognizes the common premenstrual dysphoric disorder as an entity presenting with pleomorphic and labile symptomatology identical to that of the interictal dysphoric disorder.[20] More than two thirds of women with epilepsy experience their seizures predominantly or exclusively in a catamenial pattern, and many experience severe premenstrual dysphoria. This finding has been related to a shift in the estradiol/progesterone ratio in favor of the proconvulsant estradiol over the anticonvulsant progesterone.[88] It has been suggested that the premenstrual dysphoric disorder—as a subictal disorder—may be best treated, like the interictal dysphoric disorder, with the combination of an antidepressant and an anticonvulsant.[20]

Summary and Conclusions

In conclusion, mood disorders in PWE continue to be underrecognized and undertreated. It is of the essence that double-blind placebo-controlled studies be done in PWE with mood disorders to establish their safety and efficacy as well as ideal doses, more so because of the atypical manifestations exhibited by a significant percentage of patients. After all, as suggested by the data reviewed in this article, depression and epilepsy have a very close relationship, which most likely is bidirectional and not unidirectional, which is the expression of common pathogenic mechanisms shared by the two disorders.

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Chapter 206

Anxiety Disorders

Andres M. Kanner

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Introduction

Anxiety disorders are common in people with chronic medical disorders, including people with epilepsy (PWE). While population-based studies have suggested prevalence rates of 25%, equivalent to almost twice that of the general population, the actual incidence and prevalence rates of anxiety disorders in PWE is yet to be established.[54,96] The lack of such data stems from several methodologic problems including a paucity of population-based studies, the use of *screening* instruments that identify “anxiety symptoms” and not “anxiety disorders” (see section on epidemiology), and, to a large degree, an underrecognition of anxiety disorders by patients and families alike. Indeed, patients often misinterpret symptoms of anxiety as “a normal reaction to a life with epilepsy” or an “expected” response to the stresses associated with the multiple obstacles that PWE have to face, above all when their seizures fail to remit.

Deciding when anxiety symptoms are an appropriate response to stressful experiences or an expression of a pathologic disorder has been the source of debate, with some investigators suggesting a “continuum” between these two extremes. According to Hans Selye, stress is “a nonspecific response of the body to any demand.”[156] He added that stressful situations in daily life are not harmful and, in fact, may help individuals to adapt to new life circumstances. In support of these observations, Levine[106] found that young mice exposed to mild stress from time to time consisting of handling or weak electric shocks were better able to handle stressful events and became stronger and larger as adults than the mice that were not subjected to such stressors.

At what point does a “normal” response to stress become pathologic and symptomatic of an anxiety disorder? Selye postulated the existence of a “general adaptation syndrome” that includes three phases:[156] (a) alarm, (b) resistance, and (c) exhaustion. The alarm phase triggers a response of the sympathetic nervous system with activation of corticotrophin-releasing hormone (CRH), which in turn causes secretion of adrenocorticotropic hormone (ACTH), leading to a release of cortisol and norepinephrine (NE) from the adrenal glands. The resistance stage is considered to be aimed at overcoming the stress-producing event, by preparing the animal for fight or flight; during this phase, there is a significant increment of vesicles containing corticosteroids in adrenal glands available for release. According to Selye's theory, if resistance is not successful, the body reaches a state of “exhaustion,” during which no further corticosteroid vesicles can be identified, resulting in the animals' death. The corollary of these changes in humans is expressed in the development of mental illness in the form of depression, anxiety, and psychosomatic disorders. Some of these observations may be applicable to the development of anxiety in PWE. For example, Hermann et al. found that psychopathology was associated with poor adjustment to epilepsy, elevated number of stressful life events during the past year, financial stress, vocational problems, external locus of control with increased perceived stigma, and an earlier onset of epilepsy.[71] Multiple regression analyses identified three independent predictors of psychopathology: An increased number of stressful life events in the past year, poor adjustment to epilepsy, and financial stress.

The unpredictability of seizure occurrence can very well play an important role in the generation of anxiety symptoms or full-blown anxiety disorders facilitated by a perception of “loss” of the locus of control. Experimentally, this phenomenon can be studied in the animal model of fear conditioning.[74] This model is based on a classical conditioning paradigm consisting of 20-second conditioning stimulus trials in the animal (using a sound as a conditioning stimulus) that are terminated by onset of an aversive unconditioned stimulus consisting of a footshock of 0.5 second's duration. The resulting conditioned response is expressed by behavioral immobility (freezing) during the 20-second sound-conditioning stimulus. On the first trial, when the sound comes on the animal moves around freely. Within a few trials the animal freezes when the sound comes on, and remains still for most of its duration. The conditioned response—freezing—is used as a measure of fear. The manifestations of the inferred fear state in this animal model closely parallel the clinical criteria of generalized anxiety, as evidenced by increased heart rate and stroke volume, dry mouth/decreased salivation, stomach ulcers/upset stomach, altered respiration, scanning and vigilance, increased urination and defecation, grooming/fidgeting, and freezing/apprehension. Fear conditioning is a strikingly dramatic and reproducible phenomenon and can be elicited among many different animal species.

In addition to the above, it is important to consider the potential pathogenic role of neurophysiologic and neurochemical changes associated with the seizure disorder per se, particularly in temporal lobe epilepsy (TLE). Indeed, mesial temporal structures play a primordial role in the generation of symptoms of anxiety, as exemplified in the animal models of fear sensitization and kindling. Kindling refers to the gradual development and intensification of elicited motor seizures resulting from the repetitive administration of initially subconvulsive stimulations to particular brain regions.[61,87] Kindling of limbic structures has also been shown to effect lasting changes in affect in rodents and cats. For example, kindling of rodents' amygdala facilitates the development of behaviors suggestive of “symptoms of anxiety,” and partial kindling of amygdala and ventral hippocampus in cats leads to less predatory behavior. The question is then raised whether fear sensitization may result from hyperexcitation of fear circuits perhaps via long-term potentiation of excitatory amygdala efferents and whether kindling could be comparable to repetitive seizures, thereby inducing interictal anxiety.[1,2] In this chapter we review the available epidemiologic data, clinical manifestations, and treatment of the four most frequent anxiety disorders in PWE: Generalized anxiety disorder (GAD), panic disorder (PD), phobias, and obsessive-compulsive disorder (OCD). We devote a section to the discussion of the most relevant pathogenic mechanisms operant in the development of anxiety disorders in PWE, with special attention to the pathogenic mechanisms that may be shared by anxiety disorders and epilepsy.

Epidemiology

Together with mood disorders, anxiety disorders are the more frequent psychiatric comorbidity in PWE. The *Diagnostic and Statistical Manual of Mental Disorders,* 4th ed., text revision (DSM-IV-TR) lists 11 different types of anxiety disorders: GAD, PD (with and without agoraphobia), OCD, posttraumatic stress disorder (PTSD), acute stress disorder, specific phobias (i.e., to animals, injections, etc.), social phobia, anxiety disorders due to medical conditions, substance-induced anxiety disorder, and anxiety disorders not otherwise specified,[6] which include all those clusters of anxiety symptoms that fail to meet any of the above-cited categories (i.e., subsyndromic types).

As stated in our introduction, the real prevalence of each one of these anxiety disorders in PWE is yet to be established for the following reasons: (a) underrecognition by clinicians and underreporting by patients; (b) paucity of population-based studies; (c) use of diverse methodologies to identify psychiatric semiology, with some of the studies having relied essentially on the use of screening instruments that identify “symptoms,” while only a few studies having used structured interviews designed to establish current and past psychiatric syndromes (Axis I diagnoses) according to the DSM criteria; and (d) the use of relatively small case series, often derived from tertiary epilepsy centers, which attract patients with more severe forms of epilepsy and comorbid disorders. To make sense of published prevalence and incidence rates data, it is necessary to review separately those studies that screened for *symptoms* of anxiety from those that identified anxiety *disorders* with structured psychiatric interviews.

Prevalence of Anxiety Symptoms

In a review of the literature, Torta and Keller found anxiety symptoms in up to 66% of patients with epilepsy.[174] Using the Hospital Anxiety and Depression Scale in a study of 201 PWE, Cramer et al. found that 48% reported symptoms of anxiety; in 25% of these patients they were rated as mild, moderate in 16%, and severe in 7%.[36] In this study, anxiety symptoms were more prevalent than depressive symptoms, which were reported in 38% of subjects. Similar findings were reported in studies done in other cultures. For example, Nubukpo et al. investigated the presence of symptoms of depression and anxiety in 281 adults with epilepsy in West Africa using Goldberg's Anxiety and Depression Scale.[120] Compared to a control group, PWE had significantly higher depression and anxiety scores, which correlated with higher seizure frequency and lack of treatment.

Symptoms of OCD have been found to be more frequent among PWE than healthy controls in small case series. For example, Monaco et al.[114] investigated the presence of OCD symptoms among 62 patients with TLE, 20 patients with idiopathic generalized epilepsy, and 82 matched healthy controls. Symptoms of OCD were reported by nine of the TLE patients, none of the idiopathic generalized patients, and one control. In another small study, Isaacs et al. investigated the presence of OCD symptoms in 30 patients with TLE using the Obsessive-Compulsive Inventory (OCI).[75] As a group, patients with TLE had a higher prevalence of obsessive and compulsive symptoms than the nonpatient normative sample. In addition, TLE patients exhibited elevated scores on all but 3 of the 16 OCI scales and subscales.

Symptoms of anxiety disorders have also been found to be relatively frequent in children with epilepsy. For example, in a study of children whose age ranged from 7 to 18 years old, Ettinger et al. found elevated scores on the Revised Child Manifest Anxiety Scale in 16%,[50] while Williams et al. found this to be the case in 23%.[183] Alwash et al. found anxiety symptoms in almost 50% of Jordanian children or adolescents with epilepsy.[5]

Anxiety Disorders

Various studies have estimated the prevalence of anxiety disorders to range from 10% and 25%, with the higher prevalence rates found among patients with intractable epilepsy. In one of the few population-based studies, Gaitatzis et al. found a prevalence of anxiety disorders of 11% among 5,834 PWE compared with 5.6% among 831,163 people without epilepsy.[53] The psychiatric diagnoses were obtained from primary care records. In a study of 174 consecutive PWE from five epilepsy centers, current anxiety disorders were identified in 53 patients and comprised 52.3% of all Axis I diagnoses established with the Mini International Neuropsychiatric Interview (MINI).[83] Agoraphobia (15.5%), GAD (13.2%), and social phobia (10.9%) were the most common diagnoses among the anxiety disorders. Among these 53 patients, 27 (50.9%) exhibited symptomatology that met criteria for two or more anxiety disorders.

Several studies have been carried out in refractory patients being evaluated for epilepsy surgery. For example, Wrench et al. found a prevalence of 23% among 43 patients being evaluated for an anterotemporal lobectomy and 18% among 17 patients with an extratemporal seizure focus (mostly frontal).[184] In the largest case series of patients who underwent an anterotemporal lobectomy (N = 322), Devinsky et al. found an anxiety disorder diagnosed before surgery with a structured interview in 18%.[48] In a study of 300 patients with refractory epilepsy (231 patients with a temporal lobe focus, 43 with a nontemporal lobe focus, and 26 with a generalized and multifocal seizure onset), Manchanda et al. found that 88 (29.3%) met criteria for a psychiatric syndrome and 54 (18.0%) for a personality disorder, with anxiety disorders being the most common psychiatric diagnosis (10.7%).[109]

Panic disorder is significantly more frequent among PWE than the general population. In a review of the literature, Beyenburg et al. estimated that PWE were six times more likely to suffer from PD than the general population, with point prevalence rates ranging between 5% and 30%,[15] compared with 3.5% in the general population.[96]

Karno et al. have analyzed the prevalence data of obsessive-compulsive disorder measured in five U. S. communities among more than 18,500 persons in residential settings as part of the National Institute of Mental Health–sponsored Epidemiologic Catchment Area program. Lifetime prevalence rates ranged from 1.9% to 3.3% across the five Epidemiologic Catchment Area sites for obsessive-compulsive disorder diagnosed without DSM-III exclusions and 1.2% to 2.4% with such exclusions.[95] On the other hand, the actual prevalence of OCD in PWE is yet to be established as there are no population-based studies in this group of patients and most of the available data are based on small studies carried out in tertiary care centers.

Several studies have evaluated anxiety in children with epilepsy. In one study of 100 children aged 5 to 16 years with complex partial seizures and similarly sized groups of both children with childhood absence epilepsy and normal children, those with complex partial seizures and childhood absence epilepsy were five times as likely to have an affective or anxiety disorder as normal controls; these disorders were identified in 33% of the epilepsy group.[26,27] Of note, anxiety disorder was the most frequent diagnosis among children with suicidal ideation. Within the epilepsy group, children with absence epilepsy were more likely to have an anxiety disorder alone than the children with complex partial seizures, who were more likely to have comorbid depression with anxiety and depression alone. One additional study confirmed the increased rate

of anxiety disorders in children, as an anxiety disorder was present in 31% of 102 adolescents with epilepsy.[4]

Clinical Manifestations

People with epilepsy can present the same clinical manifestations of the anxiety disorders included in the DSM-IV-TR classification,[6] though anxiety episodes/disorders with atypical semiology is not unusual. Such is the case when anxiety episodes are restricted to peri-ictal periods (see below). Thus, it is essential to establish the temporal relationship between the occurrence of psychiatric symptomatology and the seizures, as the duration, course, and response to treatment varies depending on whether an anxiety episode is ictal, postictal, or interictal.[90]

Comorbid mood disorders can be identified in a significant percentage of patients with primary anxiety disorders, and this is also the case in PWE. Thus, any investigation of anxiety symptoms/disorders must always be coupled with a search for mood disorders. This important point is discussed in greater detail below. For example, in a study of 199 PWE from five epilepsy centers, Kanner et al. found that 73% of patients with a history of depression met also DSM-IV criteria for an anxiety disorder.[91]

Interictal Anxiety Disorders

Generalized Anxiety Disorder

To meet diagnostic criteria of GAD, patients have to have experienced the following symptoms for a period of at least 6 months, occurring more days than not: (a) excessive worry and anxiety about a number of events or activities; (b) difficulty in controlling the worry; (c) the focus of the anxiety is not related to another psychiatric disorder (i.e., panic disorder, social phobia, etc.); (d) three or more of the following symptoms: restlessness or feeling on edge, being easily fatigued, difficulty concentrating, irritability, muscle tension, sleep disturbance manifested by either difficulty falling asleep and/or staying asleep and/or restless unsatisfying sleep; (e) symptoms cause clinically significant distress or impairment in the patients' social, occupational, or other areas of functioning; and (f) symptoms do not result from the use of medication or substances of abuse (including alcohol) or a general medical condition (i.e., hyperthyroidism) and do not occur exclusively during a mood or psychotic disorder.

Panic Disorder

PD consists of recurrent panic attacks with a frequency of at least one attack per week for a period of at least 1 month.[6] These attacks are characterized by a subjective sense of dread (feeling of impending doom), associated with a variety of autonomic symptoms including palpitations, sweating, subjective dyspnea, paresthesias, dizziness, nausea, feeling faint, and a sense of abdominal or central chest discomfort. Each attack may last between 5 and 30 minutes and may not have a clear precipitant. Anticipatory anxiety is the second feature of PD, so that the patients fear a recurrence of attacks and may enter a state of chronic lower-grade anxiety. Finally, the patients may show phobic avoidance of situations that they feel may provoke an attack, which may reach total avoidance of leaving the home or fear of being left alone (in which case patients are diagnosed with PD with agoraphobia). Comorbid depression is found in up to 70%, as is the development of secondary psychosocial problems, agoraphobia, and social phobias.[112] It is important to keep in mind that ictal fear can be often confused and misdiagnosed as panic attacks (see below).

Phobias

According to the DSM-IV-TR criteria, specific phobias are described as "marked and persistent fear that is excessive or unreasonable, cued by the presence or anticipation of a specific object or situation (i.e., flying, heights, animals, etc.)." Exposure to the phobic stimulus can trigger an anxiety reaction that may reach proportions of a panic attack.[6] In PWE, agoraphobia or social phobias are among the more frequent types, resulting from fear of injury or social embarrassment should a seizure occur in public. For example, in a study of postictal psychiatric symptoms carried out in 100 consecutive patients with pharmacoresistant partial epilepsy, Kanner et al. found postictal symptoms of agoraphobia in 29 patients; 18 of these patients (62%) attributed these symptoms to the fear of seizure recurrence, but none of these patients experienced seizures in clusters to explain the agoraphobic symptoms.[90] Nonetheless, none of these patients developed full-blown interictal agoraphobia.

Obsessive Compulsive Disorder

OCD consists of the presence of obsessions and/or compulsions causing marked distress, being time-consuming (occurring for at least 1 hour per day) and significantly interfering with the individual's normal routine, occupational functions, or social activities or relationships.[6] The DSM-IV-TR classification defines obsessions as recurrent and persistent thoughts, impulses, or images that are experienced at some time during the disturbance as intrusive and inappropriate and cause marked anxiety or distress. It defines compulsions as repetitive behaviors or mental acts that the person feels driven to perform in response to an obsession or according to rules that must be applied rigidly. These criteria call for the individual to recognize that the obsessions and compulsions are excessive or unreasonable.[6]

There have been several case reports of complete remission of OCD or marked improvement following epilepsy surgery that have spurned hypotheses suggesting common pathogenic mechanisms between OCD and epilepsy. For example, Barbieri et al. reported a patient who had developed obsessive-compulsive symptoms shortly after the onset of temporal lobe epilepsy and who exhibited almost complete symptom remission after being rendered seizure free after a temporal lobectomy.[11] Kanner et al. reported the case of a woman with OCD consisting primarily of obsessions that had been intractable to various pharmacologic and psychotherapeutic interventions prior to surgery and that remitted in toto after a right temporal lobectomy.[88] Remission of OCD has been restricted to TLE surgery. Guarnieri et al. reported two male patients with medically intractable frontal lobe epilepsy and OCD symptoms who experienced remission of obsessive-compulsive symptoms after anterior cingulate cortex ablation.[66]

Peri-ictal Symptoms of Anxiety

Few studies have investigated in a systematic manner the prevalence of peri-ictal anxiety symptoms or episodes, and those available have been limited to selected populations in tertiary centers. The lack of these data is not accidental as clinicians in general fail to inquire about such symptoms in their evaluations of PWE.

Pre-ictal Symptoms

Pre-ictal symptoms of anxiety can precede a seizure by several hours to several days. For example, Blanchet and Frommer identified symptoms of anxiety intermixed with symptoms of depression and irritability in a study of 27 patients who were asked to rate their mood on a daily bases for 1 month.[19] Thirteen patients experienced a variety of dysphoric symptoms,

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including symptoms of anxiety 3 days prior to the seizure occurrence that increased in severity as the time of the seizure got closer.

Ictal Symptoms of Anxiety

Ictal fear or ictal panic is the most frequent psychiatric symptom presenting as an expression of a simple partial seizure (or aura). It was identified in 60% of patients with auras consisting of psychiatric symptoms.[44,180] As stated above, ictal panic has been confused and misdiagnosed as a panic disorder. For example, in a series of 112 consecutive PWE, Sazgar et al. identified five patients with ictal fear as part of a partial seizure disorder of right mesial temporal origin who had been misdiagnosed with PD.[150] The difficulty in distinguishing the two disorders stems from the following: (a) an inaccurate and/or incomplete clinical history. (b) The absence of epileptiform activity in scalp interictal recordings in patients whose seizures originate from amygdala, a structure that generates epileptiform discharges with very narrow electric fields. In such patients, the use of video-electroencephalographic (V-EEG) monitoring studies may be necessary to record the actual seizure. Often, sphenoidal electrodes inserted under fluoroscopic guidance may be necessary to identify the electrographic ictal pattern of the aura.[89] (c) Ictal fear occurs often in the setting of a partial seizure disorder originating in the nondominant hemisphere. In such cases, patients may continue to respond during the ictus (including during a complex partial seizure) and neither witnesses to the seizure nor the patients may be able to identify a period of confusion or loss of awareness of their surroundings, lest a careful testing of the patient is conducted.

A detailed history can help distinguish a panic attack from ictal panic.[163] Indeed, ictal panic is typically brief (<30 seconds in duration), is stereotypical, occurs out of context to concurrent events, and may be followed by other ictal phenomena such as periods of confusion of variable duration and subtle or overt automatisms when and if the seizure evolves to a complex partial seizure. The intensity of the sensation of fear is mild to moderate and rarely reaches the intensity of a panic attack. On the other hand, panic attacks consist of episodes of 5 to 20 minutes' duration, which at times may persist for several hours, during which the feeling of fear or panic is very intense, often described as a feeling of impending doom and associated with a variety of autonomic symptoms, including tachycardia, diffuse diaphoresis, and shortness of breath. During a panic attack, patients may become completely absorbed by the panic experience to the point where they may not be able to report what is going on around them; nonetheless, there is no real confusion or loss of consciousness as in complex partial seizures. Finally, patients with panic attacks are more likely to develop agoraphobia, while this is rare among patients with ictal panic unless they suffer from interictal panic disorder as well.

Given the relatively high comorbidity of interictal panic disorder in PWE, the concurrent occurrence of ictal fear and interictal PD has to be investigated in all patients. For example, in a small study of 12 patients with temporal lobe epilepsy, Mintzer and Lopez found ictal fear and interictal panic disorder in four of these patients.[113] Two other patients had other forms of interictal anxiety disorder and eight patients had depressive disorder.

Finally, the presence of ictal fear can herald the development of postsurgical mood disorders. Thus, Kohler et al. studied the association of ictal fear with mood and anxiety disorders before and 1 year after temporal lobectomy.[99] They compared 22 patients with ictal fear with matched groups of patients with other types of auras and no auras at all. Mood and anxiety disorders declined in the control groups, but not in the ictal fear group after surgery.

Postictal Symptoms of Anxiety

Postictal symptoms of anxiety are relatively frequent among patients with refractory partial epilepsy. In a study of 100 consecutive patients with pharmacoresistant partial epilepsy cited above, Kanner et al. investigated in a systematic manner the occurrence of postictal psychiatric symptoms during a 3-month period.[90] The postictal period was defined as the 72 hours that followed a seizure. Only symptoms that occurred after more than 50% of seizures were recorded. A median of two postictal symptoms of anxiety (range: 1 to 5) were identified in 45 patients with a median duration of 24 hours (range: 0.5 to 148 hours). In 30 patients, at least 1 postictal symptom lasted 24 hours or longer (15 patients [33%] reported a cluster of 4 symptoms of at least 24 hours); 10 patients reported at least 1 symptom of 1 to 23 hours' duration; and 5 patients had anxiety symptoms lasting <1 hour. Thirty-two patients reported symptoms of generalized anxiety and/or panic; an additional ten patients also reported symptoms of compulsions and 29 patients experienced postictal symptoms of agoraphobia. In 37 of these 45 patients, postictal symptoms of depression were also identified. A prior history of anxiety disorder was identified in 15 patients (33%). There was an association between a history of anxiety disorder and the occurrence of two postictal symptoms of anxiety: Constant worrying and panicky feelings. In addition, there was a significant association between a history of anxiety and depressive disorders and a greater number of postictal anxiety symptoms.

Comorbid Occurrence of Anxiety and Depression Disorders

In patients with anxiety disorders with or without epilepsy, investigation of symptoms of anxiety is not complete without also screening for symptoms of depression or carrying out structured interviews looking for mood disorders (and vice versa). Thus, in a meta-analysis of studies that investigated comorbidity between *primary* depression and anxiety disorders, Dobson and Cheung concluded that among patients with a depressive disorder, a mean of 67% (range: 42% to 100%) also experienced anxiety disorders concurrently or in their lifetime.[49] Conversely, in patients with anxiety disorders, a mean of 40% (range: 17% to 65%) also suffered from depression. By the same token, comorbid occurrence of primary social phobia and both major depression and dysthymia of up to 70% have been reported,[112] while higher comorbidity is also identified in first-degree relatives.[135] Furthermore, improvement in one condition can be expected to have a positive impact on the other. For example, in a study carried out in a general medical clinic setting, 880 patients were screened for depression by using the Diagnostic Interview Schedule version of the DSM-III and the Zung Self-Rating Depression Scale, as well as the Zung Self-Rating Anxiety Scale[192]; 112 patients (13%) were found to have a depressive disorder. Comorbid symptoms of anxiety of moderate severity were identified in 67% of depressed patients. After a follow-up period of 1 year, during which symptoms of depression and anxiety were monitored at five time points, depressed patients who improved showed a significant decrease in severity of comorbid symptoms of anxiety, while depressed patients who worsened showed a significant increase in their anxiety index; the decrease in the anxiety index of patients in the no-change group was not statistically significant.

In PWE, the occurrence of comorbid anxiety and depressive disorders is also common. In a study of 199 patients with epilepsy from five epilepsy centers cited above, 73% of patients with a history of depression met also DSM-IV criteria for an anxiety disorder.[91] In that study the DSM-IV-TR diagnosis of a mood and/or anxiety disorder was established with

the MINI and Structured Clinical Interview for Axis I Diagnosis (SCID). These patients completed a 46-item self-rating instrument, “The Mood and Anxiety Symptoms in Epilepsy” (MASE), that includes symptoms from eight domains (depression, anxiety, irritability, self-consciousness, physical symptoms, disturbances in socialization, suicidal ideation, and increased energy) on two occasions, 2 weeks apart. Sixty-seven patients met criteria for a DSM-IV Axis I diagnosis: Each of the 37 patients that met criteria for major depression reported symptoms of anxiety. Furthermore, several investigators dating back to Kraepelin, Bleuler, Gastaut, and more recently Blumer and Kanner have made a point of emphasizing the pleomorphic nature of the symptomatology of depressive disorders in PWE, in which symptoms of anxiety play a prominent role.[20,22,55,93,100]

Comorbid anxiety symptoms can also occur in subclinical or subsyndromic forms of depression. In the study of 199 consecutive PWE cited above,[91] 132 patients (64%) failed to meet any DSM-IV Axis I diagnosis according to the SCID and MINI; yet, using the self-rating instruments Beck Depression Inventory-II (BDI-II) or the Center for Epidemiologic Studies-Depression (CES-D), 32 patients (16% of the entire cohort) were also found to have been experiencing symptoms of depression of mild to moderate severity. Symptoms of anxiety were identified in 31 of these 32 patients with the MASE.

Screening of Anxiety Symptoms in the Clinic

Anxiety disorders in epilepsy *are not* homogeneous conditions, and often they occur in association with more than one type of anxiety and/or mood disorders. Thus, how can a neurologist identify an anxiety disorder in PWE? The use of self-rating *screening* instruments can be an *initial* step, but by themselves do not establish a diagnosis. Several instruments are available, but none has yet been validated in PWE. Self-rating screening instruments are obviously preferable to questionnaires that have to be administered by a health professional. In addition, instruments that also screen for symptoms of depression should be included for the reasons cited above. Among the multiple screening instruments available, the following can be considered:

1. Hospital Anxiety and Depression Scale[191]: This scale is specifically developed for use in patients with medical comorbidity, and consists of seven-item self-rated subscales for both depression and anxiety.
2. Beck Anxiety Inventory (BAI)[13]: The BAI is a 21-item self-report measure of anxiety severity. The scale consists of 21 items, each describing a common symptom of anxiety over the past week on a 4-point scale ranging from 0 (*Not at all*) to 3 (*Severely—I could barely stand it*). The items are summed to obtain a total score that can range from 0 to 63.
3. Goldberg's Depression and Anxiety Scales[62]: The instrument consists of nine questions assessing mood and anxiety over the previous month, and the full set of nine questions needs to be administered only if there are positive answers to the first four. The scales are devised specifically to be used by nonpsychiatrists in clinical investigations. Scores are from 0 to 9.
4. Hamilton Anxiety Rating Scale (HAM-A or HARS)[68]: This scale is a 14-item clinical interview scale (not self-reported) measuring somatic and psychic anxiety symptoms. The responses include five degrees of severity ranging from 0 (*None*) to 4 (*Frequent and severe symptomatology*). This instrument should be used with caution in PWE, given the large number of somatic symptoms included in this scale, which, in patients with epilepsy, can result from adverse effects of antiepileptic drugs (AEDs), potentially yielding false-positive suggestions of more severe anxiety symptomatology.

The Use of Screening Instruments in Research: A Cautionary Note!

One of the most frequent methodologic errors in research studies on psychiatric disorders and epilepsy is the sole reliance on *screening* instruments to establish a diagnosis. The argument for exclusively using screening instruments is that they have been “validated” to identify the condition at hand with acceptable levels of sensitivity and specificity and the severity of the depressive episodes. Yet, as stated above, patients may often experience more than one type of anxiety disorder at a given point in time and more often than not suffer from comorbid mood disorders. Accordingly, structured psychiatric evaluations are “a must,” aimed at identifying the complexity of current and past psychiatric disorders. Short of that, the conclusions that can be derived from studies that assess any treatment modality or the course of symptomatology are limited.

For example, the course and response to treatment of GAD or PD in a patient with a comorbid history of bipolar disorder is different from that of a patient with major depressive disorder or without a comorbid mood disorder. In short, *screening* instruments identify “*symptoms*”; *structured interviews* establish the presence of a psychiatric disorder, according to classifications like the DSM-IV-TR. Thus, if the aim of a study is to identify the presence of an anxiety disorder, a psychiatric structured interview is necessary. Only once the presence of psychiatric disorders have been established in this manner should screening instruments be used to follow changes of symptom severity over time.

Impact of Anxiety Disorders on Quality of Life

Primary mood and anxiety disorders have a negative impact on the quality of life in the general population. In PWE, research on the effect of psychiatric disorders on health-related quality of life (HRQOL) has been focused on mood disorders (see also Chapter 205) and five studies carried out in patients with pharmacoresistant epilepsy have consistently demonstrated depression to be *the most* powerful predictor for each domain of health-related quality of life, even after controlling for seizure frequency, severity, and other psychosocial variables.[58,59,102,105,128] Cramer et al. also found that depression was significantly associated with poor quality of life scores on the Quality of Life in Epilepsy Inventory-89 (QOLIE-89) independently of the type of seizures; these investigators found, however, that seizure freedom for the last 3 months increased (i.e., improved) the quality-of-life ratings.[35]

Few studies have investigated the impact of anxiety symptoms and/or disorders on HRQOL of PWE. In a study of 87 patients with TLE, Johnson et al. found that symptoms of depression and anxiety were the strongest predictors of poor HRQOL.[82] These investigators found an independent effect of each class of symptoms on HRQOL, however. Furthermore, the psychiatric comorbidity explained more variance in HRQOL than did combined groups of clinical seizure or demographic variables. Furthermore, in a study of 154 outpatient adults with epilepsy carried out in South Korea, Choi-Kwon et al. found that the presence of anxiety symptoms was the most important variable mediating lower quality of life in patients with epilepsy.[32]

In the study of 199 patients described above, Kanner et al.[91] found that the scores of the QOLIE-89 were significantly

lower (i.e., worse quality of life) among patients with anxiety disorders than those of asymptomatic patients. Furthermore, patients with comorbid anxiety and major depressive disorders had significantly lower scores in the QOLIE-89 than those with only major depressive episodes.

Impact of Anxiety on Suicidality

Suicidal ideation and attempts are significantly more frequent among PWE than in the general population.[84] Several studies have already established that anxiety disorders are risk factors for suicidal ideation and suicide attempts. For example, in a large population-based longitudinal study carried out in the Netherlands, Sareen et al. found that the presence of any anxiety disorder at the initial evaluation was significantly associated with suicidal ideation and suicide attempts in both the cross-sectional analysis (adjusted odds ratio [OR] for suicidal ideation, 2.29; 95% confidence interval [CI], 1.85 to 2.82; adjusted OR for suicidal attempts, 2.48; 95% CI, 1.70 to 3.62) and longitudinal analysis (adjusted OR for suicidal ideation, 2.32; 95% CI, 1.31 to 4.11; adjusted OR for suicide attempts, 3.64; 95% CI, 1.70 to 7.83).[149] Furthermore, the presence of any anxiety disorder in combination with a mood disorder was associated with a higher likelihood of suicide attempts in comparison with a mood disorder alone. Pilowsky et al. surveyed 2,043 patients attending a primary care clinic using the Primary Care Evaluation of Mental Disorders Patient Health Questionnaire, a screening instrument that yields provisional diagnoses of selected psychiatric disorders.[131] A provisional diagnosis of current panic disorder was identified in 127 patients (6.2%). After adjusting for potential confounders (age, gender, major depressive disorder, generalized anxiety disorder, and substance use disorders), patients with panic disorder were about twice as likely to present with current suicidal ideation, as compared to those without panic disorder (adjusted OR, 1.84; 95% CI, 1.06 to 3.18). After adjusting for panic disorder and the above-mentioned potential confounders, patients with major depressive disorder had a sevenfold increase in the odds of suicidal ideation, as compared to those without major depressive disorder (adjusted OR, 7.00; 95% CI, 4.42 to 11.08). Other studies have found that anxiety disorders may increase a suicidal risk only in the presence of comorbid mood disorders.[7]

The impact of anxiety disorders on suicidal ideation and suicide attempts has also been identified in children and adolescents but may not be as clear as in adults. For example, Strauss et al. carried out a study of 1,979 patients aged 5 to 19 years using the Schedule for Affective Disorders and Schizophrenia for School Aged Children–Present Episode at an outpatient mood and anxiety disorders clinic.[168] Subjects were stratified by age and categorized into mutually exclusive groups as being nonsuicidal (N = 817), having suicidal ideation (N = 768), or having attempted suicide (N = 394) in the current episode. After stratifying by age, the investigators found no differences among the ideators, attempters, and nonsuicidal youth in rates of an anxiety disorder in general or in specific rates of PD, agoraphobia, social phobia, simple phobia, and OCD. In older children (age >15 years), GAD was more prevalent in ideators (OR = 1.65; 95% CI, 1.03 to 2.66; $p = 0.03$) than in nonsuicidal patients. Whether similar findings would be identified in population-based studies is yet to be established.

The impact of anxiety disorders in suicidality of PWE has not been studied extensively. In one study by Jones et al. of 139 PWE, 17 met criteria for current suicidal ideation (12.2%), while a lifetime prevalence of suicidal attempts was found in 29 patients (20.8%).[84] Anxiety disorders were significantly more common among patients with current suicidal ideation (58.8%), while 41.2% of patients had comorbid anxiety and current major depressive disorders. On the other hand, lifetime major depressive disorder was the most frequent psychiatric disorder identified among patients with lifetime suicide attempt (51.7%).

Pathogenic Mechanisms

There are several operant pathogenic mechanisms of anxiety in PWE, which can be classified into three groups: (a) psychosocial; (b) endogenous, which include neurochemical, neurophysiologic, neuroanatomic, and functional changes related to the seizure disorder per se; and (c) iatrogenic, including adverse effects of AEDs and complications of epilepsy surgery.

Psychosocial Factors

Patients with epilepsy face multiple psychosocial obstacles that can facilitate the development of symptoms of anxiety and/or (in patients with a predisposition) full-blown anxiety disorder. Stigma, to name one of such obstacles, accounts for the development of symptoms of anxiety. For example, in a study of more than 5,000 patients living in 15 countries in Europe, Baker et al. found that 51% reported feeling stigmatized, with 18% reporting feeling highly stigmatized.[9] High scores were correlated with worry, negative feelings about life, long-term health problems, injuries, and reported side effects of AEDs. Unfortunately, PWE's perception of being stigmatized is not only a function of their “insecurity” resulting from the epilepsy, but is also a real phenomenon illustrated in a study by Harden et al.[69] These investigators developed a survey consisting of three vignettes briefly describing a coworker with depression, multiple sclerosis, or epilepsy. Of note, the epilepsy vignette *did not describe a seizure*. Each vignette was followed by eight identical questions addressing the level of comfort during interactions with the vignette subject. The surveys were hand-distributed in two companies in New York City and returned anonymously by mail. Seventy-four of 200 distributed questionnaires were returned. Respondents reported more discomfort at the thought of interacting with a coworker with epilepsy than with depression or multiple sclerosis, but this difference did not reach significance. However, worry about sudden, unpredictable behavior for the coworker with epilepsy was significantly greater than that with multiple sclerosis. Responders had a significantly lower level of comfort providing first aid for the coworker with epilepsy than for the coworkers with depression and multiple sclerosis. Lower job level and lower income level correlated with more social discomfort for all three illnesses.

People with epilepsy have also been found to suffer from more frequent comorbid physical disorders, some of which are closely associated with stress and anxiety. For example, Téllez-Zenteno et al. analyzed epilepsy-specific and general population health data obtained through two previously validated, independently performed, door-to-door Canadian health surveys, the National Population Health Survey (N = 49,000) and the Community Health Survey (N = 130,882), which represent 98% of the Canadian population.[172] PWE were found to have higher comorbid stomach and intestinal ulcers, bowel disorders, migraine, and chronic fatigue. Likewise, Strine et al. analyzed data obtained from 30,445 adults aged 18 years or older who participated in the 2002 National Health Interview Survey in the United States.[169] They identified an estimated 1.4% subjects who were told by a health care professional that they had seizures; these subjects were significantly more likely than those without seizures to report lower levels of education, higher levels of unemployment, pain, hypersomnia and insomnia, and psychological distress (e. g., feelings of sadness,

nervousness, hopelessness, and worthlessness). In addition, they were significantly more likely to report insufficient leisure time physical activity as well as physical comorbidities such as cancer, arthritis, heart disease, stroke, asthma, severe headaches, lower back pain, and neck pain. It is likely that the comorbid medical disorders play a significant role in the generation of symptoms of anxiety in PWE.

The Role of Seizure Frequency and Seizure Severity

As part of a large community-based study, Jacoby et al. investigated the variables associated with the clinical course of epilepsy and the development of anxiety and depression symptoms in an unselected population of people who had a recent history of seizures or were receiving AEDs.[76] Epilepsy data were collected from the medical records of the treating primary physicians and information about psychosocial functioning was obtained with questionnaires mailed to identified subjects, 71% of whom returned the questionnaire. Fifty-seven percent of the sample had had at least 2-year seizure-free periods and 46% were in a remission of at least 2 years' duration. There was a clear relationship between *current seizure frequency* and levels of anxiety and depression.

Smith et al. reported a study of 100 patients with medically refractory partial seizures who completed a quality-of-life questionnaire including measures of physical (seizure severity and frequency), social, and psychological well-being (anxiety, depression, self-esteem, locus of control, and happiness).[160] Multivariate analysis demonstrated that individual psychological variables were best predicted by other psychological variables. However, when these were removed from analysis, seizure severity, *but not seizure frequency,* was the most significant predictor of anxiety and self-esteem.

Similar findings have been reported in children with epilepsy, though data have been obtained from tertiary centers and not from population-based studies. For example, in a study of 35 children and adolescents aged 9 to 18 years and 35 healthy controls, Oguz et al. investigated the relationship between epilepsy-related factors and the development of symptoms of anxiety and depression.[123] Both study and control groups were divided into two age groups (9 to 11 and 12 to 18 years) to exclude the effect of puberty on anxiety and depression scores. Children and adolescents with epilepsy displayed higher scores on the measures of depression symptoms and suicidal ideation, and the mean trait anxiety score was significantly higher in the 9- to 11-year age group of epileptic patients than the corresponding control group, while the mean state, trait anxiety, and depression scores were significantly higher in the 12- to 18-year age group of epileptic children than in the control group. Duration of the epilepsy, seizure frequency, and polytherapy were the epilepsy-related factors associated with the development of anxiety and depression symptoms. Furthermore, in a study carried out in 102 adolescents aged between 12 and 18 from Nigeria, Abiodoun et al. identified an anxiety disorder in 32 (31.37%) of the adolescents with the Diagnostic Interview Schedule for Children Version IV (DISC-IV) and a depressive disorder in 29 (28.4%).[3] As in the above-cited studies, uncontrolled seizures, polytherapy, and felt stigma were identified as predictors of anxiety and depressive disorders by regression analysis. Family factors such as parents' psychopathology and family stress also played a moderately significant role. On the other hand, Williams et al. did not find a pathogenic role of seizure frequency in the development of anxiety symptoms. In a study of 101 children and adolescents between the ages of 6 and 16 years, mild to moderate symptoms of anxiety were reported by 23% of the patients.[183] The presence of comorbid learning or behavioral difficulties, ethnicity, and polytherapy were identified as the variables associated with increased anxiety scores.

Type of Seizure Disorder

The development of anxiety and mood disorders has been associated with seizure disorders involving limbic structures, such as seizures of temporal and frontal lobe origin. In fact, ictal fear can be identified in seizures originating in the amygdala, hippocampus, and cingulate gyrus.[28] Yet, anxiety symptoms can also be identified in primary generalized epilepsy. For example, among a group of 42 patients with idiopathic generalized epilepsy in adulthood, Cutting et al. found an anxiety disorder in nine patients (21%), seven of whom had GAD and two OCD.[40]

Endogenous Changes of Anxiety in Epilepsy

While it is tempting to conclude that anxiety in epilepsy is a simple reaction to having experienced the distress associated with seizures and living with the “Damocles sword” of future seizure risk, compelling evidence in the biologic realm would argue for a much higher degree of complexity to this association. While our understanding of the mechanisms underlying anxiety disorder is still in its infancy, knowledge of areas of potential commonality between anxiety and seizures has laid the foundation for better diagnosis and treatment of this distressing comorbidity. The common pathogenic mechanisms that may be operant in the development of anxiety disorders and epilepsy include (a) neurotransmitter abnormalities and (b) structural and functional abnormalities in common neuroanatomic structures, particularly the amygdala, hippocampus, and cingulate gyrus.

Neurotransmitter Abnormalities

Several neurotransmitters and neuropeptides have been found to play important pathogenic mechanisms in the development of anxiety disorders, including γ-aminobutyric acid (GABA), NE, serotonin (5-hydroxytryptamine, 5HT), and some of the hormones and neuropeptides involved in the hypothalamic-pituitary axis, particularly CRH. Interestingly enough, these neurotransmitters also play a significant pathogenic role in mood disorders and epilepsy and may explain the high comorbidity of these three disorders.

γ-Aminobutyric Acid

One area of obvious neurochemical commonality involves the neurotransmitter GABA, which promotes inhibition of neuronal excitability by its effect upon chloride ion channels. The important role GABA plays in the pathogenesis of epilepsy is well known. For example, commonly utilized AEDs such as benzodiazepines, barbiturates, and tiagabine have anxiolytic properties through a potentiation and prolongation of GABA's synaptic inhibitory actions.[167] Barbiturates, for example, inhibit action potentials, neurotransmitter release, voltage-regulated calcium channels, and glutamate-mediated inhibitory synaptic activity.[134] By the same token, the effect of tiagabine and vigabatrin is mediated by an increase of GABA synaptic concentrations, through an inhibition of its reuptake or its metabolism, respectively. Some AEDs may indirectly enhance GABA through action upon sodium or calcium channels. For example, pregabalin, a pharmacologically active S-enantiomer of 3-aminomethyl-5-methyl-hexanoic acid, is a structural analog of GABA, although it is not active at GABA receptors, nor does it acutely alter GABA uptake or degradation. It binds with high affinity to the a^{54}–δ subunit protein of voltage-gated calcium channels in central nervous system (CNS) tissues and acts as a presynaptic modulator of the excessive release, in hyperexcited neurons, of various excitatory neurotransmitters. Binding of pregabalin to the a^{54}–δ subunit appears necessary for its demonstrable anxiolytic, analgesic, and anticonvulsant activities in animal models.[126]

The convulsant pentylenetetrazol (PTZ; a model for generalized seizures), which blocks GABA_A receptor function, also promotes anxiety symptoms.[85] By the same token, anxiolytic effects of valproic acid identified in some animal models of anxiety are thought to be mediated through GABAergic processes as they can be reversed by the use of GABA_A receptor antagonists.[159] Valproic acid has been reported to display antipanic efficacy and an anxiolytic effect in an open trial,[8] but no controlled studies have been carried out as of yet.

One theory posits that anxiety disorders may be due to defective neuroinhibitory processes, mediated in part through GABA, while abnormalities in the benzodiazepine receptors have also been suggested to play a pathogenic role in epilepsy.[29] The potential relationship between abnormalities in the benzodiazepine receptor system and anxiety disorder is suggested by the induction of panic symptoms in panic disorder patients, when the benzodiazepine antagonist flumazenil is administered.[121] It is further supported by the demonstration of widespread decreased binding of flumazenil to benzodiazepine receptors in panic disorder patients. Indeed, Malizia et al. compared fully quantitative, high-sensitivity positron emission tomography (PET) studies with flumazenil radiolabeled with carbon 11 between seven patients with panic disorder who had been off medication for at least 6 months and who had never abused alcohol and eight healthy controls.[108] Patients' PET studies displayed a global reduction in benzodiazepine site binding throughout the brain compared with controls. In addition, the areas with the largest regional decrease in binding (right orbitofrontal cortex and right insula) were areas thought to be essential in the central mediation of anxiety. The question is then raised whether down-regulation of these receptors is a consequence of exposure to stress or whether a pre-existing low level of benzodiazepine receptor density may be a genetic risk factor for the development of stress-related anxiety disorders.

Noradrenergic Abnormalities

There are also very important links between the noradrenergic system and anxiety, since fear activates neurons of the locus coeruleus and increases NE secretion in the locus coeruleus; limbic structures such as the amygdala, hippocampus, and hypothalamus; and the cerebral cortex. With sustained stress in the learned helplessness animal model, depletion in norepinephrine can be demonstrated.[67] Furthermore, agents such as the norepinephrine reuptake inhibitor reboxetine are effective in the treatment of PD.[178] In fact, chronic symptoms experienced by anxiety disorder patients, such as panic attacks, insomnia, startle, and autonomic hyperarousal, are an expression of increased noradrenergic activity.[47] These symptoms can be alleviated with drugs that decrease the firing of neurons in the locus coeruleus, such as benzodiazepines, alcohol, and opiates, while drugs that increase its firing (i.e., cocaine) worsen these symptoms.[47]

Disturbances in the noradrenergic system have been found in epilepsy as well. For example, in animal models of epilepsy, the pathogenic role played by NE is illustrated in studies of two strains of genetic epilepsy-prone rats (GEPR), GEPR-3 and GEPR-9, which are characterized by predisposition to sound-induced generalized tonic–clonic seizures[34,79,81] and, particularly in GEPR-9 s, a marked acceleration of kindling.[78] Both strains of rats have innate noradrenergic pre- and postsynaptic transmission deficits. Noradrenergic deficiencies in GEPRs appear to result from deficient arborization of neurons arising from the locus coeruleus,[33,146] coupled with excessive presynaptic suppression of NE release in the terminal fields and lack of postsynaptic compensatory up-regulation.[78,187] GEPR-9 rats have a more pronounced NE transmission deficit and, in turn, exhibit more severe seizures than GEPR-3 rats.[80]

Increments of either NE transmission can prevent seizure occurrence, while reduction will have the opposite effect.[78,111] For example, drugs that interfere with the release or synthesis of NE exacerbate seizures in the GEPRs, including the NE storage vesicle inactivators reserpine or tetrabenazine and the NE false transmitter *α*-methyl-m-tryosine.

Another expression of the pathogenic role played by NE in epilepsy can be appreciated in the NE-mediated antiepileptic effect of the vagal nerve stimulator (VNS) in part through activation of the locus coeruleus.[117] Furthermore, a decrease in noradrenergic neurons reduces antiepileptic effects against electroshock or pentylenetetrazol-induced seizures.[25]

Serotonergic Abnormalities

An important pathogenic role has been identified in anxiety disorders and epilepsy. Serotonin's role in anxiety disorders is supported by the observation of potent anxiolytic effects of tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs), which enhance 5-HT synaptic concentrations. Serotonin's anxiolytic effects may relate to an inhibition of noradrenergic activation through raphe nuclei projections to the locus coeruleus, periaqueductal gray inhibition of the freeze/flight responses, hypothalamic inhibition of corticotropin-releasing factor, and the amygdala inhibiting excitatory pathways from cortex and thalamus. PET studies with the selective 5-HT_{1A} radioligand[183] trans-4-fluoro-N-2-(4-(2-methoxyphenyl)piperazin-1-yl)ethyl)-N-(2-pyridyl)cyclohexanecarboxamide (FCWAY) permitting in vivo assessment of central 5-HT_{1A} binding have been instrumental in identifying abnormal 5-HT function in PD in a study of 16 unmedicated symptomatic outpatients with PD (seven of whom also suffered from a mood disorder of mild severity) and 15 matched healthy controls.[118] Neumeister et al. found lower distribution volume in the anterior cingulate, posterior cingulate, and raphe in patients compared to controls, indicating a reduction of 5-HT_{1A} receptors in these structures. Not surprisingly, agents that mediate their therapeutic effect through an increase of serotonergic activity in the brain such as TCAs and SSRIs have become the first line of therapy of PD and other anxiety disorders.[64]

The role of 5-HT in epilepsy has also been demonstrated in the GEPR animal model of epilepsy. The brain of this animal has deficits in serotonergic arborization and decreased postsynaptic 5-HT_{1A} receptor density in hippocampus. Conversely, drugs that enhance serotonergic transmission, such as the SSRI sertraline, resulted in a dose-dependent seizure frequency reduction in the GEPR that correlates to the extracellular thalamic serotonergic thalamic concentration.[186] The 5-HT precursor 5-hydroxy-L-tryptophan has anticonvulsant effects in GEPRs when combined with the SSRI fluoxetine.[185] SSRIs and monoamine oxidase inhibitors (MAOIs) can exert anticonvulsant effects in experimental animals, such as mice and baboons, that are genetically prone to epilepsy,[104,111] as well as nongenetically prone cats,[133] rabbits,[130] and rhesus monkeys.[189] In addition, an antiepileptic effect of 5-HT_{1A} receptors has been correlated to a membrane hyperpolarizing response, which is associated with increased potassium conductance in hippocampal kindled seizures in cats and in intrahippocampal kainic acid–induced seizures in freely moving rats.[12,124]

As mentioned, AEDs with established psychotropic effects (carbamazepine, valproic acid, and lamotrigine) can cause an increase in 5-HT.[41,42,43,162,182,188] In GEPRs, the anticonvulsant protection of carbamazepine can be blocked with 5-HT–depleting drugs.[111,116,187]

Dysfunction of the Hypothalamic-Pituitary-Adrenal Axis in Anxiety Disorders and Epilepsy

As mentioned in our introduction, the hypothalamic-pituitary axis (HPA) plays a fundamental pathogenic role in anxiety, mood disorders, and epilepsy.[143] Neurons in the paraventricular nucleus of the hypothalamus secrete CRH, which stimulates the secretion of ACTH from the pituitary gland. ACTH, in turn, releases glucocorticoids from the adrenal gland, which have an impact on various brain regions, and once in the circulation they exert an inhibitory effect on the HPA axis.[137] Under normal conditions, the hippocampus and amygdala play a role in the inhibition of the HPA axis as well.[70] High levels of CRH and glucocorticoids occur in acute and chronic stress as well as in anxiety disorders, particularly PTSD, depressive disorders, and epilepsy.[177] Intraventricular administration of CRH can mimic stress-induced phenomena. These include an increase in plasma norepinephrine, epinephrine, and glucose concentrations as well as an increase in heart rate and arterial blood pressure, large bowel transit, increase of locomotor activity in familiar environment, increased acoustic startle, grooming, and shock-induced freezing. These phenomena are not reversible by adrenalectomy or hypophysectomy but can be achieved with the use of CRH antagonists, which indicate a “direct” effect of CRH on the brain. Of note, CRH receptors are found in large numbers in the amygdala, which activate fear-related behaviors.[30] CRH receptors also are widely distributed in the cortex, and their function is believed to reduce reward expectation in animal models. Furthermore, CRH inhibits neurovegetative functions involving sexual activity and food intake as well as endocrine functions associated with reproduction and growth. Several studies have shown that early life stressors result in long-term increase of CRH activity in the CNS.

By the same token, an activation of the HPA axis demonstrated by an increase in the secretion of CRH, ACTH, and cortisol has been found in humans postictally following generalized tonic–clonic and complex partial seizures, as well as interictally. Furthermore, Wang et al. found significantly higher brain concentrations of CRH in postmortem brains from children with epilepsy compared to controls.[179] A direct pathogenic role of CRH was suggested by Baram et al. in studies of infants with infantile spasms who were found to have low cerebrospinal fluid ACTH and cortisol, which reflects a high brain CRH.[10]

Abnormalities of Neuroanatomic Structures

Similarities in the nature of symptoms of panic or other anxiety disorders and symptoms of some seizure types suggest that similar brain structures and pathways are involved in both conditions. For example, the intravenous administration of procaine in healthy volunteers produced diverse emotional symptoms of euphoria, anxiety, depression, fear, and derealization, all of which may be encountered in seizures, especially those involving limbic structures. PET scanning during this procedure reveals increased metabolic activity in anterior limbic and paralimbic areas.[157]

Abundant evidence demonstrates the central role of the amygdala in the fear conditioning model. For example, administering bilateral lesions to the lateral nucleus of the amygdala of the rat attenuates fear-induced freezing response to a conditioned auditory fear stimulus.[103] Bilateral lesions of the central nucleus of the rabbit amygdala result in loss of the fear-induced bradycardia response to a conditioned auditory fear stimulus.[94] Lesions of the central nucleus of the rat eliminate fear-potentiated startle.[73]

The amygdala is primarily responsible for mediating fear (“emotional reaction to aversive events”) and anxiety (“the apprehension of an imminent aversive event”). The central nucleus is particularly crucial for this function. PET scan demonstrates increased perfusion to the amygdala when an individual is shown images of fearful as opposed to happy faces. Functional magnetic resonance imaging (MRI) can be used to show how individuals with social phobia exhibit increased amygdala activation in response to exposure to the stimulus of fearful faces, compared to healthy controls.[17]

The amygdala can be conceptually divided into three main groups of nuclei: The medial nucleus receives olfactory information and transmits excitatory signals to the hypothalamus. The lateral/basolateral nucleus receives diverse sensory information as well as information related to memories from the hippocampus. The central nucleus receives information from the lateral and basolateral nucleus of the amygdala and transmits excitatory signals to diverse regions that relate to arousal (e. g., hypothalamus, midbrain structures, pons, and medulla).[21,132]

There are numerous afferent and efferent connections to the basolateral nuclei. These connections may have important implications for response to fearful stimuli. Connections to the orbital frontal region play a role in the choice of behavioral responses to a fearful situation, providing an “emotional coloring” of events. Output to the dorsal and ventral striatum (structures believed to be integral to reward and motivation) is important for avoidance behavior and habitual behaviors. Connections to the central nucleus and/or lateral bed nucleus of the stria terminalis (BNST) lead to the "autonomic and somatic" manifestations of fear, and the individual's attention to specific stimuli.[30]

Efferent connections from the central nucleus of the amygdala may translate into many of the symptoms and signs commonly associated with anxiety. The role of the central nucleus in fear is further validated by the demonstration in animal studies of fearlike responses (freezing, shivering, and autonomic nervous system activation such as heart rate elevation and increase in blood pressure) in response to stimulation of this region.[30,60] This suggests that abnormal electrical activity, either experimental or spontaneous epileptiform in selective regions of the medial temporal lobe such as the amygdala, can produce intense sudden fear, reminiscent of the symptoms of panic disorder.[141]

Alternatively, lesions of amygdala nuclei reduce fearful behaviors. In a classic experiment in which the central nucleus is lesioned, the rat recurrently fails to react appropriately to the fearful stimulus of the ominous cat. In the face of danger, the rat no longer perceives sensory stimuli associated with the cat to be fearful and the normally expected autonomic nervous system activation is no longer produced.[18,86]

"Hyperexcitability" of fear circuits including the amygdala has been posited by some as a potential etiology for anxiety disorder. One might speculate then that seizures emanating from or involving the amygdala (as is commonly demonstrated on intracranial recordings in epilepsy surgery candidates) and its connections promote such a hyperexcitability, leading to heightened anxiety.[181]

Anxiety and the Hippocampus

Disturbances of structures other than the amygdala, such as the hippocampus, have been implicated in anxiety disorder.[129] High serum concentrations of corticosteroids, resulting from excessive CRH secretion, have been associated with damage to the hippocampal formation. Chronic exposure to high glucocorticoid serum levels has been blamed for hippocampal atrophy in patients with PTSD and major depressive disorders. Furthermore, in studies with rats and monkeys, prolonged increased concentrations of glucocorticoids have been found to damage hippocampal neurons, particularly CA3 pyramidal neurons, possibly by reduction of dendritic branching and loss of dendritic spines that are included in glutamatergic synaptic inputs.[147,153,158] Atrophy of CA3 pyramidal cells has been found following stress-induced secretion of glutamate in the hippocampus, which in turn resulted in high intracellular concentration of calcium, thus increasing the vulnerability of

these cells and in that manner potentially increasing the risk of seizures; this effect was attenuated by *N*-methyl-D-aspartate (NMDA) antagonists. The deleterious effects of chronic glucocorticoid exposure was found to lead initially to a transient and reversible atrophy of the CA3 dendritic tree and an increased vulnerability to a variety of insults and finally to result in cell death under extreme and prolonged conditions.[147,148,153]

The interplay between the impact of high glucocorticoid levels and glutamate secretion in the hippocampus is of significant relevance in our attempts to understand the relationship between anxiety disorders such as PTSD, major depressive disorders, and epilepsy.[23,24,148,190] The role of excitatory neurotransmitters and the glutamate receptor NMDA site has been well established in epilepsy. Indeed, NMDA antagonists have been shown to have antiepileptogenic properties in the "kindling" animal model and to also display antiepileptic properties.[155]

Hypercortisolemia resulting from chronic stress or a depressive disorder has also been found to interfere with the development of new granule cell neurons in the adult hippocampal dentate gyrus. This effect is thought to be mediated by a decrease in the secretion of brain-derived neurotrophic factor (BDNF) in the dentate gyrus, pyramidal cell layer of hippocampus, amygdala. and neocortex.[161] These changes can be overturned with chronic (but not acute) antidepressant therapy, as chronic administration of antidepressant drugs increase BDNF expression and also prevent a stress-induced decrease in BDNF levels.[31,119] There is also evidence that antidepressant drugs can increase hippocampal BDNF levels in humans.[31,119] These data indicate that antidepressant-induced up-regulation of BDNF can hypothetically repair damage to hippocampal neurons and protect vulnerable neurons from additional damage. Recent studies have suggested, nonetheless, that BDNF increases cell survival by inhibition of cell cascades.

On the other hand, other studies suggest that it is those individuals with pre-existing hippocampal atrophy who are predisposed to develop anxiety disorders such as PTSD.[57,190] So similar to the controversial debate whether seizures induce or are a consequence of hippocampal atrophy, the directionality of hippocampal abnormalities and anxiety symptoms remains unclear.

Iatrogenic Mechanisms

Pharmacotherapy

Iatrogenic effects associated with AEDs can be caused by two mechanisms: (a) the introduction of AEDs with anxiogenic properties and (b) the discontinuation (often abruptly) of AEDs with positive psychotropic properties, primarily among patients with an underlying mood and/or anxiety disorder that had been “masked” or “controlled” by the discontinued AED.[92] The AEDs with known anxiolytic properties include the barbiturates, benzodiazepines, tiagabine, valproic acid, gabapentin, and pregabalin.[15,110]

The AEDs with anxiogenic properties include ethosuximide, felbamate, levetiracetam, phenytoin, topiramate, zonisamide, and vigabatrin. Paradoxically, these AEDs have a GABAergic effect, particularly and to a lesser degree topiramate, zonisamide, and felbamate.[15,110]

Abrupt discontinuation of benzodiazepines and barbiturates is known to cause severe “withdrawal” anxiety symptoms including severe panic attacks.[14] However, abrupt discontinuation of AEDs with positive psychotropic properties can also cause anxiety.[97] Such symptoms are often observed in the course of V-EEG monitoring studies in which AEDs are stopped abruptly to facilitate the occurrence of seizures.

Epilepsy Surgery

Postsurgical development of anxiety symptoms following anterotemporal lobectomy has been reported by several investigators. Fortunately, these symptoms are transitory and occur during the first 3 to 6 months after surgery. For example, in a study of 60 consecutive patients who underwent a temporal lobectomy for intractable epilepsy, Ring et al. found that half of those with no psychopathology preoperatively had developed symptoms of anxiety or depression at 6 weeks after surgery and 45% of all patients were noted to have increased emotional lability.[140] By 3 months after surgery emotional lability and anxiety symptoms had diminished, whereas depressive states tended to persist. Patients with a left hemispheric focus were more likely to experience persisting anxiety. Reuber et al. evaluated 76 patients with TLE for symptoms of depression and anxiety before and 12 months after surgery.[136] At baseline, depression and anxiety scores were high in patients with TLE, while after surgery, depression ***but not anxiety*** scores were significantly lower than at baseline.

Postsurgical OCD has also been reported. Chemali et al. described the case of a young woman with a simple motor tic disorder who after right temporal lobectomy for medically intractable epilepsy developed Tourette syndrome with complex motor and vocal tics, severe obsessive-compulsive disorder, and paranoia.[30a] Kulaksizoglu et al. published a case series of five patients with TLE with obsessive personality traits before surgery who underwent an anterotemporal lobectomy.[101] Within the first 2 postsurgical months two of these patients fulfilled OCD diagnostic criteria. These two patients did not differ from the other three patients with respect to age, age of onset of epilepsy, seizure types, and seizure frequency. All patients stopped having seizures postoperatively, but the OCD patients had worse quality of life postoperatively than preoperatively.

Treatment

The treatment options of anxiety disorders include pharmacotherapy, a variety of psychotherapeutic modalities (i.e., cognitive behavior therapy, desensitization behavioral therapy, supportive and psychodynamically oriented psychotherapies) and a combination of psychotherapy and pharmacotherapy. Before addressing the specific treatment strategies, it is important to review these basic principles:

1. Did the symptoms of the anxiety disorder appear following the introduction or increase in the dose of an AED known to cause psychiatric adverse events?
2. Did the anxiety symptoms follow the discontinuation of an AED with anxiolytic properties? In this case, the psychiatric symptoms may be the expression of recurrence of an anxiety disorder that had remitted with the AED that was discontinued.
3. Did the symptoms of the anxiety disorder occur after the introduction of an enzyme-inducing AED (carbamazepine, phenytoin, phenobarbital, primidone, high-dose topiramate, or oxcarbazepine) in a patient who was already taking a psychotropic drug for a previously recognized anxiety disorder? In such case, the symptom recurrence may have resulted from a pharmacokinetic interaction between the AED and the psychotropic drug on board that caused a drop in the psychotropic drug's serum concentration. Accordingly, a readjustment in the dose of the psychotropic drug may be sufficient to induce symptom remission.
4. Are the psychiatric symptoms temporally related to the seizure occurrence; that is, do they precede (pre-ictal), follow (postictal), or precede and follow; are they the expression of an ictal event; or do they occur interictally with a peri-ictal exacerbation in severity? In the case of pre- or postictal without interictal symptoms, pharmacotherapy may fail to yield any benefit. Postictal breakthrough symptoms may occur in patients whose interictal symptoms had remitted with pharmacotherapy.

5. Is there a risk factor, other than epilepsy, for the development of the anxiety disorder, particularly a family history in first-degree relatives?
6. Is the anxiety disorder occurring in isolation or associated with other anxiety disorders (i.e., GAD and PD) and/or with a comorbid mood disorder?

Pharmacotherapy

Pharmacologic treatment of anxiety disorders in PWE follows the same drugs and dosages used in the treatment of primary anxiety disorders. Whether the anxiety disorder's response to pharmacotherapy differs between patients with and without epilepsy is yet to be established. Indeed, clinicians assume that primary anxiety disorders and those affecting patients with epilepsy are identical and hence should respond in the same manner, though such an assumption has yet to be proven. In short, pharmacotherapy of anxiety disorders in PWE remains empirical. We will therefore base our review on data from studies conducted in patients with primary anxiety disorders.

Pharmacologic treatment of anxiety disorders depends on the specific type of disorder. Five classes of drugs are typically used: (a) antidepressants, (b) benzodiazepines, (c) AEDs, (d) noradrenergic agents, and (e) buspirone. In the next section we will discuss the use of these drugs in the treatment of GAD, PD, social phobia, and OCD.

Antidepressant Drugs

Today, antidepressants have become the first line of therapy in the management of the four anxiety disorders under consideration. In patients with epilepsy, clinicians have often been reluctant to use antidepressant drugs for fear of causing breakthrough seizures in seizure-free patients or worsening of seizures in patients with refractory epilepsy.[175] Data have shown, however, that with the exception of four agents (amoxapine, maprotiline, clomipramine, and bupropion), TCAs, SSRIs, and MAOIs can be safely used in PWE with the following caveats: If TCAs are prescribed, patients need to be started at a low dose and increments must be done in a stepwise manner to avoid toxic serum concentrations.[38,98,175] In fact, animal models of epilepsy have suggested that serotonergic and noradrenergic properties of antidepressant drugs have anticonvulsant properties.[171] A study by Khan et al. supported these observations; these investigators compared the incidence of seizures in depressed patients who were randomized to placebo or the SSRIs citalopram, escitalopram, fluoxetine, and fluvoxamine as well as the α_2 antagonist mirtazapine in Food and Drug Administration (FDA) regulatory studies. Patients randomized to placebo had a significant-higher frequency of seizures.[77]

Little data are available on the safety of the newer classes of antidepressants, such as the serotonin-noradrenaline reuptake inhibitors (SNRIs) venlafaxine (Effexor) and duloxetine (Cymbalta) and the a_2 antagonist mirtazapine (Remeron). Venlafaxine has been prescribed in more than 100 adults with pharmacoresistant epilepsy at the Rush Epilepsy Center without any evidence of worsening of seizure frequency or severity (unpublished data). A detailed discussion of the safety of antidepressant drugs in patients with epilepsy can be found in Chapter 205 and on the use of psychotropic drugs in epilepsy in Chapters 204 and 214. From a safety standpoint, other than seizure-related concerns, the antidepressant drugs of the SSRI family are considered to be the drugs of choice.

The most frequent adverse effects of SSRIs include gastrointestinal and sexual disturbances.[173] The latter may be of greater significance in PWE, as these patients have a significantly higher prevalence of sexual disorders resulting from an iatrogenic effect of AEDs and/or as a direct impact of the seizure disorder. The SSRI-related sexual adverse effects include decreased libido, anorgasmia, impotence, disturbances in ejaculation, and dyspareunia and have been reported in about 20% to 30% of patients.[173] Citalopram and its s-enantiomer escitalopram have the lowest incidence of sexual adverse events. Of note, mirtazapine also has a lower incidence of sexual adverse effects. Whether the adverse effects mediated by these drugs worsen already existing sexual disturbances in PWE is yet to be investigated. Tolerance may develop over time, and at times lowering of the dose or switching to another SSRI may improve these side effects.

By the same token, some SSRIs can cause weight gain (i.e., paroxetine, sertraline) that could potentially aggravate a weight gain problem triggered by AEDs like valproic acid, gabapentin, pregabalin, and carbamazepine. On the other hand, fluoxetine can cause weight loss in the first 3 months of therapy, but patients regain the weight lost thereafter.[173]

Pharmacokinetic interactions between antidepressants and AEDs have to be considered carefully in PWE, in particular: (a) the drop in serum concentration of antidepressants following the addition of enzyme-inducing AEDs, such as carbamazepine, phenytoin, phenobarbital, primidone, topiramate, and oxcarbazepine at high doses; and (b) the decrease in the clearance of certain AEDs with some of the SSRIs and SNRIs mediated by the inhibition of some of the hepatic cytochrome isoenzymes, which may lead to an increase in the serum concentrations of AEDs that are substrates for these isoenzymes.[52,65] For example, venlafaxine and paroxetine have the potential to inhibit hepatic cytochrome isoenzymes 2C19 and 3A4, which may lead to an increase in the serum concentrations of carbamazepine, tiagabine, and zonisamide via a moderate inhibition of 3A4. Venlafaxine is minimally inhibiting of 3A4 and of 2C19 as well, which could affect phenytoin and barbiturate levels. Likewise, fluoxetine is an inhibitor of 3A4 and 2C9/10, which can result in an increase in the serum concentrations of carbamazepine and phenytoin, while sertraline is a mild inhibitor of 3A4, leading to a potential increase in carbamazepine blood levels. On the other hand, citalopram and its enantiomer, escitalopram, have no interactions with the isoenzyme systems involved in antiseizure medicine metabolism.[176]

Other Precautions on the Use of Antidepressants

1. Patients with anxiety disorders may be extremely sensitive to adverse effects of antidepressant drugs. Accordingly, these drugs need to be started at low doses.
2. The high comorbidity between anxiety and mood disorders and the efficacy of antidepressants in anxiety disorders have made these agents an attractive option that would result in the remission of depressive and anxiety disorders with the use of a single agent. However, in the case of mood disorders, the use of antidepressants is indicated in major depressive episodes that are an expression of major depressive disorders, in dysthymic disorder, or in double depression. On the other hand, the use of antidepressants is not recommended in patients with bipolar disorders, lest they are administered in the presence of a mood-stabilizing agent, since they can worsen the course of bipolar disorders, facilitating the development of rapid cycling bipolar illness (defined as more than four manic and or major depressive episodes in a 12-month period), in which case symptom remission is less likely.[72] Accordingly, prior to the start of any antidepressant drug, it is necessary to take a careful history of manic or hypomanic episode and a family

history of bipolar illness. Furthermore, a suspicion of potential bipolar illness increases in patients with a first major depressive episode before the age of 20. Indeed, Strober and Carlson

followed 60 adolescents hospitalized for major depressive episodes and followed them for a 3- to 4-year period. Twenty percent of these patients went on to develop bipolar illness.[170]

3. Discontinuation of TCAs, SSRIs, and SNRIs has to be carried out gradually through a tapering schedule to avert the development of discontinuation emergent symptoms.[152] These include somatic symptoms, such as nausea, vomiting, tremors, diaphoresis, ataxia, movement disorders, and sleep disturbances. SSRIs and SNRIs with the shorter half-lives are associated with a higher risk of developing these symptoms.

Efficacy of Antidepressants in Anxiety Disorders

All of the SSRIs have shown efficacy in GAD, PD, and OCD.[166] Given the lack of pharmacokinetic interactions with AEDs and better tolerance, we recommend the use of escitalopram or citalopram first and sertraline as an alternative.[16,45,115,142] In the case of GAD and PD, absence of efficacy with an SSRI should be followed by a trial with the SNRI venlafaxine.[46,56,139] The anxiolytic effect of these drugs may not be apparent until the first 4 to 6 weeks after the start of therapy, for which a temporary use of a benzodiazepine is often an option.

Among the older antidepressant drugs, the TCA imipramine is the agent of choice in PD with a comparable efficacy to that of SSRIs, and has also been found to be as effective as benzodiazepines in the treatment of GAD.[151] MAOIs have been also found to be effective in the treatment of PD. Their use in PWE has been relegated to third place, however.

The SSRIs are the drugs of choice in the treatment of OCD, and all have been found to show comparable efficacy. In contrast to the treatment of GAD and PD, a therapeutic effect may not be noticed for 6 to 12 weeks, however.

Benzodiazepines

Benzodiazepines occupied the first line of treatment of anxiety disorders before the antidepressants. Their efficacy has been demonstrated in GAD, PD, and anxiety secondary to life stressors or medical conditions.[39,51,122,138] The risk of physical dependence and development of tolerance after have limited their use to short-term trials. Typically, they are used in GAD and PD at the start of pharmacotherapy with antidepressants until the latter agents' therapeutic effect takes over. Alprazolam is the benzodiazepine preferred for PD, while clonazepam is used in GAD.

Noradrenergic Anxiolytics and Beta-Blockers

The “overactivity” of noradrenergic neurons underlying anxiety states and evidenced by tachycardia, tremor, and excessive sweating has been the basis for the consideration of drugs that limit the secretion of norepinephrine through stimulation of a_2 autoreceptors and for which the a_2 agonist clonidine has been used. While it is effective in blocking the noradrenergic aspects of anxiety, it is not as effective in improving its subjective and emotional aspects. The use of beta-blockers can achieve this goal in a more effective manner, and they are often used in the treatment of social phobia.

Antiepileptic Drugs

In addition to the benzodiazepines, tiagabine,[144,154,164] gabapentin,[165] pregabalin,[126] and valproic acid have been used by psychiatrists for anxiety disorders.[8,159] Tiagabine and pregabalin have been found to be effective in the treatment of GAD and gabapentin in social phobia in double-blind, placebo-controlled studies. Valproic acid, on the other hand, has been found to cause symptom remission in PD in a small study of 13 patients whose panic attacks failed to respond to antidepressant agents. These findings need to be confirmed in double-blind, controlled studies.[8] In PWE who suffer from seizures of frontal lobe origin, tiagabine should be used with caution as it can cause absence stupor.

Other Drugs

Buspirone is a 5-HT_{1A} agonist agent that has been found to be effective for the treatment of GAD.[127] It is favored over the use of benzodiazepines because it does not cause drug dependence or withdrawal with long-term use and there is a lack of any significant pharmacokinetic interactions with other agents. Its onset of efficacy is delayed by several weeks, like that of antidepressant drugs.

Psychotherapies

Various types of psychotherapy have been used for a very long time for the treatment of anxiety disorders. In the last decade, however, cognitive behavior therapy (CBT) has gained much favor among health professionals as it has been recognized as an effective treatment for anxiety and depressive disorders. This therapy involves dismantling the patient's false or exaggerated beliefs that lead to anxiety and interfere with daily functioning. This alteration in cognitive outlook is then coupled with gradual desensitization to the anxiety-provoking stimuli, in order to improve the patient's ability to cope with anxiety. For example, in a pilot study by Goldstein et al., CBT was undertaken with six adults with chronic, poorly controlled seizures and coexisting psychiatric and/or psychosocial difficulties.[63] After 12 sessions of CBT from an experienced CBT nurse specialist, participants rated their initial epilepsy-related problem as having less impact on their daily lives, and at 1-month follow-up reported less deleterious impact on everyday life in terms of their psychological difficulties. In addition, participants demonstrated significant improvements in terms of their self-rated work and social adjustment and in their decreased use of escape-avoidance coping strategies.

The efficacy of CBT as monotherapy in GAD has been shown in a recent study of 36 patients randomized to CBT and 36 to no therapy for a 25-week period. Significant decreases in anxiety were found in the treatment group compared to the untreated group using both clinician-rated and subject-rated anxiety scales.[107] The efficacy of CBT has been found to be comparable to that of pharmacotherapy in the treatment of primary mood and anxiety disorders by several investigators, and there is a consensus that a combination of CBT and pharmacotherapy yields better results than either treatment modality given alone.[37,125,145] Given its proven efficacy in patients with primary psychiatric disorders, CBT should be tested in large studies with PWE. In theory, given its efficacy, short duration, and the fact that it can be administered by health professionals from multiple disciplines (i.e., psychologists, nurses and nurse practitioners, and social workers), CBT can be expected to play a major role in the treatment of anxiety and mood disorders in all epilepsy clinics. Furthermore, it may help alleviate the pervasive problem caused by the limited access to psychiatrists.

Therapeutic Effect of Epilepsy Surgery

While no one advocates the use of epilepsy surgery for the treatment of anxiety disorders in PWE, various studies have found a marked improvement in anxiety disorders/symptoms following epilepsy surgery, particularly temporal lobectomy. Such improvements have been associated with the achievement of seizure freedom. For example, Devinsky et al. compared the rate of anxiety disorders before an anterotemporal lobectomy (ATL) in 332 patients and 278 patients 2 years postsurgically and found a drop from 17.5% to 10.4%.[48] Furthermore, epilepsy surgery has resulted in remission of OCD in several cases, as indicated above.[11,66,88]

Summary and Conclusions

Anxiety disorders are frequent psychiatric comorbidities in PWE and together with mood disorders account to a great degree for the poor quality of life of these patients. Their early

recognition and effective treatment should be part of the overall management of PWE. We have just begun to identify their multifactorial causes and multifaceted clinical expressions, but much research is needed to better understand their pathogenic mechanisms, identify the safest and most effective therapies, and establish the differences (if any) between anxiety disorders in epilepsy and primary anxiety disorders, as well as any difference in response to treatment.

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Chapter 207

Psychogenic Nonepileptic Seizures and Epilepsy

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Introduction

Psychogenic nonepileptic seizures (PNES) are similar to epileptic seizures (ES) in that they present as time-limited, paroxysmal alterations in behavior, sensation, motoric activity, autonomic signs, and/or consciousness. They differ from ES, however, in that they lack electroencephalographic ictal findings on EEG during the ictus. Treating the two disorders individually can present numerous challenges; the issues are multiplied in the 10% to 30% of patients with PNES who have comorbid ES. Much of the material on the diagnosis and treatment of patients with PNES is covered extensively in Chapter 282. In this chapter, we describe the epidemiology, diagnosis, and treatment of patients with mixed PNES/ES.

How frequently is it a problem? Epidemiologic Considerations

Medical writings from the 19th century describe how to differentiate ES from PNES (then known as hystero-epilepsy). There is a great deal of interest in and controversy about whether people with PNES have an increased incidence of coexisting or previous epilepsy. Of the 1% of the U. S. population diagnosed with epilepsy, 5% to 20% have PNES.[29] It is estimated that 10% of those with PNES have mixed ES/PNES,[54] and estimates for the coexistence of ES and PNES vary from less than 10% to more than 40%.[69] The incidence of PNES has been estimated to be 3.03 per 100,000,[79] and the prevalence of PNES is estimated to be up to 33 per 100,000.[5] Patients with PNES are usually women (~80%) and are between 15 to 35 years old (~80%),[76] although children and the elderly can develop PNES. It is estimated that up to 50% of patients admitted to an intensive care unit from the emergency department in status epilepticus in fact have pseudostatus, as one manifestation of PNES.[72]

The literature on comorbid ES/PNES is confusing because different populations of patients have been studied by different investigators with diverse methodologies and because of the uncertainty about the diagnosis of PNES. In an attempt to clarify the available data, the following three questions must be addressed:

1. In a population of people with established epilepsy in whom the primary diagnosis is clear, how many might also have PNES?
2. In a population of people with PNES in whom the diagnosis is clear, how many have previously had a history of epilepsy, and could some of their seizures still be of epileptic origin so that, if anticonvulsant medication is withdrawn, epilepsy would re-emerge?
3. How often is a “misdiagnosis” of PNES made in some of the seizures of patients with an established diagnosis of epilepsy?

The following sections attempt to answer these questions.

How Often Does PNES Occur in Patients with an Established Diagnosis

of Epilepsy?

The answer to this question is not known. If the cause of a particular patient's seizures is unclear, is it possible that two different types of seizure are present, one epileptic, the other not? The literature suggests that, in the assessment of a patient with an unknown attack disorder that has two different presentations, 5% to 30% of the time both with epilepsy and psychogenic PNES may be present.[69] The prevalence rates of concurrent ES and PNES may vary from one study to another according to whether a diagnosis of concurrent epilepsy was based on the capturing of actual seizures or on the recording of interictal epileptiform discharges only. For example, Devinsky et al. identified 20 patients with ES among a group of 99 PNES patients.[21] In contrast, in a study of 1,590 patients who underwent a video-electroencephalographic (V-EEG) study, Martin et al. found 514 (32.3%) diagnosed with PNES, of whom 29 (5.3%) were found to have both PNES and epilepsy.[55] Lesser et al. concluded that PNES and concurrent epilepsy occurred in about 10% of patients with PNES.[54] Using stringent criteria (as opposed to higher estimates in the past that based abnormalities—including slowing on EEG—as ictal evidence), Benbadis et al. identified three patients with interictal epileptiform activity among 32 patients (9.4%) with PNES.[4] These investigators did not record ES so it is not clear whether the seizure disorder was concurrent or the seizures had remitted with pharmacotherapy.

Studying the surgical population, Henry and Drury conducted a V-EEG in 145 patients who had temporal interictal EEG spikes, and they reported ictal semiology characteristic of temporal lobe seizures for presurgical evaluation of medically refractory seizures. PNES were unexpectedly identified in 12 (8%) of these patients.[37] A low prevalence was reported even in patient populations at greater risk. For example, Lelliott et al. found that, over a 5-year period, 7% of admissions to an epilepsy unit in a psychiatric hospital had PNES and concurrent epilepsy.[53]

An exception must be made among patients with cognitive developmental delay. Indeed, these are patients with epilepsy who may have found that their seizure activity can be reinforced or rewarded (i.e., having a seizure allows them to get out of unpleasant situations at school or workshop). As a result, they “learn to precipitate their epileptic seizures” at times when they try to avoid uncomfortable situations. These patients, therefore, are found to have higher prevalence rates of PNES and concurrent ES. For example, Neil and Alvarez

evaluated 124 mentally retarded persons with behaviors suggestive of epilepsy.[57] Patients were monitored using an eight-channel radio-telemetered V-EEG recording system. Twenty patients (16%) were found to have only ES, 50 (40.5%) to have PNES, 11 to have both epileptic and PNES (9%), and 43 were classified as inconclusive. Among the patients with only PNES 15 had abnormal EEGs and four (37%) had epileptiform EEGs. Thus, in this study, among the 61 patients with PNES, 24.5% had a concurrent or past seizure disorder.

How Often Does PNES Develop in Patients with Prior History of Epileptic Seizures?

As for the previous question, no clear answer is obtained from the available literature. For example, in some studies it is also sometimes unclear, when the prevalence of the two conditions is compared, whether the investigator is referring to patients with PNES and concurrent ES or merely a history of past epilepsy. It is likely, as Ramsey et al. have concluded,[69] that if the history is one of past as opposed to present epilepsy, the proportion of patients with both epilepsy and nonepilepsy is likely to be higher, particularly in patients with cognitive developmental delay.[57]

A review of the literature[8,69] and the clinical studies[42,47,71] suggest that 10% to 40% of patients who appear to have established PNES also have a past history of ES. Sometimes the question can only be answered by withdrawing antiepileptic drugs (AEDs) in those patients whose interictal recordings reveal epileptiform activity or in whom a history of paroxysmal events with clinical manifestations is highly suggestive of ES (also see the next section). If epilepsy re-emerges upon discontinuation of AEDs, the possibility exists of a patient who has a seizure disorder that remitted with the use of AEDs, and who, at some point, went on to develop PNES. On the other hand, failure to record an ES upon discontinuation of AEDs does not rule out a seizure disorder that remitted with AEDs, above all in the presence of epileptiform activity in interictal recordings.

One example of patients with both PNES and a past history of epilepsy is found in those patients who have had successful temporal lobectomies and then went on to develop PNES, presumably because of an inability to adjust to a seizure-free life. Fortunately, this is not a common occurrence. In a study of 166 consecutive patients who underwent epilepsy surgery, Parra et al. found three patients (2%) who experienced postsurgical de novo PNES documented by V-EEG.[62] The interval between the date of surgery and the development of the symptoms was variable (8–47 months range). Two of the three patients had become seizure free after surgery, and one had significant improvement of her seizures. The clinical phenomena of PNES differed from those seen for the ES preceding surgery. The diagnosis of PNES had not been suspected before the diagnostic V-EEG. Following the diagnosis of PNES, spells stopped in two patients and recurred rarely in one. Davies et al. found de novo postsurgical PNES in eight (3.5%) of 228 patients who underwent epilepsy surgery.[14] PNES occurred between 6 weeks to 6 years (mean, 23 months) after surgery. Six had undergone a resection, and two had complete callosotomy. There was a significant excess of postoperative interictal dysphoric disorder (IDD) and operative complications (bone flap infections) in the PNES group. Ney et al. identified five patients (5%) with PNES among a group of 96 consecutive patients who underwent epilepsy surgery.[58] Two patients experienced operative complications. Compared with the surgical cohort, patients had a higher frequency of preoperative psychopathologic conditions, lower mean FSIQ, and a greater occurrence of operative complications. In a recent study completed at the Rush Epilepsy Center, Kanner et al. found that seven of 94 patients (7%) who underwent an anterotemporal lobectomy developed de novo PNES. As in other studies, most patients (n = 6) were women; six of the seven patients had a pre- and postsurgical psychiatric depression/anxiety disorder, whereas the seventh patient had a history of attention deficit disorder and personality disorder that was present before surgery and worsened after surgery. Three patients had gainful employment before and after surgery, whereas the remaining four did not seek or obtain work either before or after surgery. Given the small number of patients with de novo PNES, no statistical analyses were carried out (Kanner AM, unpublished data).

Glosser et al. tried to identify risk factors of postsurgical PNES by comparing the demographic, neurologic, and psychiatric variables of 22 medically refractory epilepsy patients in whom PNES was documented by electroencephalogram (EEG) after resective surgery to those of a larger series of epilepsy surgery patients.[33] Patients with PNES were significantly more likely to have a seizure onset later in life, to have undergone epilepsy surgery in the right hemisphere, and to be women, but these subjects failed to differ with respect to age, IQ, or preoperative psychiatric diagnoses. PNES tended to become apparent in the first few months after surgery.

How Often Does Epilepsy Lie Behind an Erroneous Diagnosis of PNES?

This question is difficult to answer, because it depends on the accuracy of the diagnosis of PNES, which is often impossible to determine in published series. In the literature, completely different methods have been used for diagnosing PNES, based sometimes on EEG criteria (but not necessarily EEGs recorded during the ictus itself), clinical criteria, or a mixture of both. For example, people with epilepsy often show emotional reactions to their auras, so that they may become afraid of them and develop hyperventilation or panic attacks or have an emotional reaction during the ES itself. When auras fail to evolve to complex partial seizures, and their scalp recordings fail to reveal an electrographic ictal pattern,[22] clinicians may be prone to misdiagnose these patients with simple partial seizures as having PNES. In fact, in 1885, Gowers suggested that minor seizures can elaborate into hysterical seizures.[34] A century later, Devinsky and Gordon reported the case of four patients in whom V-EEG–documented ES were temporally associated with PNES.[20] In one woman, the nonepileptic event followed an absence seizure, whereas in the other three patients, the seizures were partial and arose from right frontotemporal regions. Kapur et al. described three patients who convincingly elaborated simple partial seizures during EEG monitoring in order to ensure a result that would lead to surgery.[43] Clearly, one of the problems of assessing the cause of a seizure is that, during a simple partial seizure, some of what is observed may well be a behavioral manifestation of the patient's emotional reactions to an unpleasant epileptic experience. This understandable emotional reaction may be mistaken for a nonepileptic event.

Paradoxically, as clinicians have become increasingly aware of the existence of PNES, patients with certain types of seizure disorders are increasingly being erroneously diagnosed as having PNES. For example, Parra et al. studied 100 consecutive patients who were undergoing a diagnostic V-EEG.[61] Referring physicians correctly suspected a diagnosis of ES in only nine (43%) of 21 patients, whereas 12 (57%) patients were incorrectly thought to have PNES. This misdiagnosis was especially likely in patients with clinical seizures of mesial frontal or parietal lobe origin and stemmed from their "bizarre" or "atypical" manifestations or from the absence of any electrographic ictal activity concurrent with the event during the V-EEG.[41,56,84] Furthermore, it should be remembered that the electrographic

ictal pattern on scalp recordings of simple partial seizures is identified in only 25% of these seizures.[22] The error rate in diagnosing PNES probably lies between 5% and 10% (i.e., in up to 10% of patients firmly diagnosed with PNES, the patient really has epilepsy).[69,85] This topic is reviewed in greater detail in Chapter 284.

Strategies in the Diagnosis of PNES in Patients with Epilepsy

Clinical History

Reaching a correct diagnosis of "only" PNES versus mixed PNES with concurrent or past ES is of the essence if a patient's AEDs are to be discontinued without placing her at risk of (epileptic) seizure recurrence. Clearly, a carefully obtained history and detailed description of all events witnessed by family members and the patient's own recollections are the first step in the diagnostic process and are of great importance when the existence of the two disorders in the same patient is suspected. The next step consists of a V-EEG to confirm the diagnosis. Unfortunately, few studies have investigated in a systematic manner the degree to which PNES and ES differ from one another in the same patient. The available data suggest that the two types of event differ clinically to a significant degree. In the Devinsky et al. study, analysis of PNES and ES on V-EEG revealed that the clinical features of PNES clearly differed from ES in 18 of 20 PNES cases.[21]

Although differentiating the two often is attempted by history, or even with observation of the ictal semiology, many epileptologists and neurologists know of cases in which a high suspicion for ES and V-EEG revealed PNES, or vice versa. Therefore, PNES is best diagnosed using the "gold standard" V-EEG, performed with the greatest humility because even the best have been fooled.

Differentiating PNES from ES Based on Ictal Semiology

This topic is reviewed in great detail in Chapter 282. We will therefore only refer to some of the salient clinical differences here. In many clinicians' minds, PNES presents as opisthotonic posturing with pelvic thrusting in a young female. Gates et al. showed that any presentation that epilepsy can have, PNES may have also,[30] but bedside examination reveals differences in the characteristics of the signs and movements.

During the ictus, some signs of PNES include geotropic eye movements, in which the eyes deviate downward to the side toward which the head is turned.[36] Eyelids are typically closed at the onset of PNES, and for a longer duration when as compared to temporal lobe epilepsy (TLE) or frontal lobe seizures (FLS) (20 seconds vs. ~2 seconds, respectively).[24] Along with ictal eye closure, weeping is associated with PNES.[7,27] Postictal nose rubbing and postictal cough are found in TLE, but not in PNES.[82] Pelvic thrusting has been reported to occur as commonly in FLS as it does in PNES. PNES and FLS differ, however, in that FLS are rarely associated with the overtly sexualized, often prolonged, display seen in some cases of PNES.[32]

It was once thought that absence of physical injury sustained during a seizure was a diagnostic indicator differentiating PNES from ES; however, more than half of all patients with PNES actually have a physical injury associated with their PNES.[40] PNES patients may have urinary incontinence and may injure themselves during the ictus. Tongue biting, self-injury, and incontinence are commonly associated with generalized seizures; however, two thirds of patients with PNES report one of these three signs, typically associated with ES.[15] Rug or floor burns on a patient's cheeks or body is viewed as being pathognomonic for PNES.[80]

Using Video-EEG

How Can the Video-EEG Monitoring Studies Help?

In ES, stereotyped ictal focal and generalized patterns appear on EEG. PNES, on the other hand, have a normal

EEG background before, during, and after the events. EEG sensitivity and specificity increase with repeated tracings.[73] Although seizures associated with impaired consciousness (e. g., generalized convulsive and nonconvulsive seizures) are associated with typical, widespread ictal EEG abnormalities, some focal seizures may not show features of seizures with scalp electrodes.[69] The limitation of V-EEG is the same as that of routine EEG—that is, simple partial seizures and FLS may not show ictal patterns using scalp electrodes. Without V-EEG, a neurologists' ability to differentiate an ES from PNES by history has a specificity of 50%.[16]

The judicious use of neurophysiologic studies can help establish whether the patient experienced PNES with a concurrent or past seizure disorder that may have remitted with the administration of AEDs, surgical treatment, or spontaneously. When suspecting concurrent PNES and ES, patients should undergo a V-EEG study and not an ambulatory EEG without video, because capturing the events on video to distinguish the two types of paroxysmal episodes is of the essence. In our opinion, patients should be admitted to a V-EEG monitoring unit, and recordings should be obtained without modifying the AED dose for the first 48 hours. Indeed, as shown by several studies, PNES tend to occur within the first 2 days in more than 90% of patients.[63] The use of induction protocols with conventional activation procedures (hyperventilation and photic stimulation) can facilitate the recording of PNES without raising the ethical concerns of other induction procedures sometimes used.[6] Furthermore, no evidence suggests that the use of induction protocols based on “placebos” such as IV infusion of saline solution or the application of alcohol swabs over the carotid artery yielded a higher rate of event induction than the use of the maneuvers typically used in all EEGs to facilitate seizures[63] (see also Chapter 282).

Interictal Epileptiform Activity

The recording of interictal epileptiform activity (IEA) in the course of a V-EEG is the first clue of a potential comorbid (present or past) ES disorder in patients with PNES. Yet, the recording of IEA does not help to establish the timing of the patient's ES (i.e., remote versus present) or whether the patient's seizures may be in remission as long as the patient is on AEDs. Furthermore, IEA may be recorded in individuals who may have never experienced any ES, and who may have a first-degree relative with a history of epilepsy, above all primary generalized epilepsy. For example, in a review of the literature that looked at the prevalence of IEA in people without epilepsy, Pedley et al. identified six studies with prevalence rates ranging between 0.5% and 2.5%.[64] Of note, IEA were more common in children (1.9%–3.5%) than in adults (0.5%), and future seizures went on to occur in healthy children more often than in healthy adults. Among children, central midtemporal IEA and generalized spike-and-slow-wave discharges were among the most frequent types of IEA recorded, which is suggestive of epilepsy in siblings or other first-degree relatives or of asymptomatic manifestations of genetic traits.[64] Delgado-Escueta et al. reported the presence of IEA in nonsymptomatic siblings from 5 of 33 families (16%) with symptomatic probands.[17] Ultimately, the clinical significance of IEA may have to be resolved by discontinuation of AEDs.

Tapering of AEDs During V-EEG

A rapid taper of most AEDs is reasonable as long as the patient is undergoing an inpatient V-EEG. Abrupt discontinuation of AEDs, however, is known to precipitate ES. Therefore, abrupt discontinuation of AEDs in nonepileptic people should be avoided, because they may cause a false-positive diagnosis of ES. This includes primarily any of the benzodiazepines. Furthermore, abrupt discontinuation of these drugs can trigger withdrawal panic attacks and psychotic episodes, thus leading to further confusion with PNES and underlying psychiatric disorders.

Ictal Data

The recording of spontaneous seizures before tapering the AED dose clearly establishes the concurrent existence of ES and PNES. The occurrence of seizures only after discontinuation of AEDs does not rule out ES coexisting with PNES, but it raises the possibility that the ES may have remitted with AEDs. This question can be clarified by showing the video of the captured seizure to family members and inquiring about their occurrence in the present versus recent or remote past.

The issue of the specificity of EEG in the diagnosis of PNES has not been formally established. Ramsay et al. tested whether altered clinical behavior in the absence of EEG changes was diagnostic of PNES.[69] They evaluated 281 ictal recordings in 194 sequential patients who underwent V-EEG. In 46 (23.3%), the initial scalp EEG showed no epileptiform EEG changes during the clinical event. Subsequent monitoring revealed that, of the 46 with initial negative EEGs, 28 (61%) had PNES, 12 (26%) had epilepsy, and 6 (13%) had mixed PNES/ES. Of the patients with epilepsy, depth electrode recording revealed mesial temporal or inferior frontal areas of seizure onset that were not recorded with scalp electrodes.

Also, failure to record seizures even after discontinuation of AEDs does not rule out a concurrent or past ES disorder. In such cases, the patient's family is asked to make a video of the patient's events when they occur at home.

Ideally, clinicians should aim whenever possible to have V-EEG recordings of PNES and ES available to guide the pharmacologic treatment of ES. Patients, family members, and, when appropriate, friends and coworkers should be shown the two types of events so as to avoid an unnecessary hospitalization for PNES when the patient could be treated aggressively with parenteral AEDs. It is also advisable to give the patient and close family member a copy of the video demonstrating both PNES and ES events in case the patient is taken to an emergency room. The availability of such videos can help emergency-room physicians decide on the course of treatment in a more judicious manner.

Role of Neuroimaging Studies

Neuroimaging allows in vivo visualization of central nervous system (CNS) lesions causing alterations of consciousness. No static and no functional neuroimaging abnormalities have yet been found associated with cases of PNES. Abnormalities on structural neuroimaging neither confirm nor exclude ES or PNES. As shown in the data presented earlier, patients with PNES may have abnormal neurologic examinations, including abnormal MRI studies. However, in patients diagnosed with PNES, the identification of a structural lesion in mesial or orbitofrontal regions should lead the physician to seriously reconsider the diagnosis of PNES. The use of an ictal SPECT or SISCOM study can help clarify whether ES may have been misdiagnosed as PNES (see Chapter 282 as well). A lack of abnormality on scan SPECT studies report an average sensitivity of 72% for PNES and an average of 59% specificity for ES.[13] Case reports exist describing patients with other forms of sensory or motor impairments. Patients with astasia-abasia motor conversion disorder had left temporal hypoperfusion abnormalities on SPECT; however, this has not been seen in PNES.[87]

Role of Laboratory Tests

Serologic measures have been helpful in differentiating ES from PNES. Prolactin (PRL) is secreted from the anterior pituitary and is inhibited by tuberoinfundibular dopaminergic neurons in the arcuate nucleus of the hypothalamus.[31] Trimble found that elevated serum PRL in patients with generalized seizures helped distinguish ES from PNES.[81] A number of studies have since been conducted measuring prolactin in PNES and, with a lack of elevation of PRL, the average sensitivity to PNES was 89%.[13] Further, prolactin ES versus PNES studies have since shown that serum levels are elevated on average in 88% of generalized tonic–clonic (GTC) seizures, in 64% of temporal complex partial seizures (CPS), and in 12% of simple partial seizures. False positives for epilepsy include treatment with dopamine antagonists and some tricyclic antidepressants, breast stimulation, and syncope, and false negatives occur with use of a dopamine agonist or with status epilepticus, because PRL has a short half-life and may attenuate in postictal release.[2] PRL also does not rise after frontal seizures. The American Academy of Neurology's Therapeutics and Technology Assessment Subcommittee published their report on the use of serum PRL in differentiating ES from PNES. The authors reviewed the PRL seizure literature and concluded that a twice-normal relative or absolute serum PRL rise, drawn 10 to 20 minutes after the onset of the ictus, compared against a baseline nonictal PRL, is a useful adjunct in the differentiation of GTC or PCS from PNES.[12] Unfortunately, this test is not useful for differentiating those ES that are more likely to be confused with PNES (i.e., FLS) from PNES proper.

Other serum measure studies to differentiate GTC seizures from PNES have included the use of elevations in peripheral white blood count,[75] cortisol,[66] creatine kinase,[86] and neuron-specific enolase.[67] However, Willert et al. discussed the limited discriminative power of these serological tests in differentiating ES from PNES.[83] Ictal heart rate on EKG monitoring is higher, and a change in ictal heart rate is associated with ES, but not PNES.[25,59,60] Capillary oxygen saturation on pulse oximetry is lower for ES than for PNES.[38]

Role of Neuropsychometric Testing

A large number of studies exist describing the cognitive, emotional, personality, and psychomotor differences between the ES and PNES groups. Cragar et al. reviewed the literature on adjunctive tests for diagnosing PNES and reported sensitivity and specificity of the different measures.[13] A summary of their findings noted that PNES and ES patients did not differ on intelligence tests or on neuropsychological (NP) measures consistently. Both PNES and ES groups did have cognitive deficits when compared to normal controls, and patients with PNES tended to perform better than patients with ES on various NP tests. Studies examining intelligence, psychomotor function, motivational measures, and personality features in PNES suggest the following:

- Intelligence measures and cognitive testing. Comparing patients with PNES to those with ES, Binder et al. found no significant differences on tests of intelligence or learning and memory, including the Wechsler Adult

  Intelligence Scale – Revised, Wisconsin Card Sort Test, or Rey Auditory Verbal Learning Test. Control subjects were significantly superior to both the PNES and ES groups.[9] Bortz et al. studied the California Verbal Learning Test results in PNES and ES patients, and the authors suggested that "failure to explicitly recognize words following repeated exposure" may be reflective of a negative response bias and psychological denial in patients with PNES.[11]
- Psychomotor measures. Kalogjera-Sackellares and Sackellares evaluated patients with PNES compared with matched normal controls and found reduced motor speed and grip strength in the PNES patients.[39] Some have interpreted this as a manifestation of motivation, which is discussed later. Dodrill and Holmes reported that patients with PNES performed better than those with ES on measures from the Halstead-Reitan Battery, with differences between Tactual Performance Test, Seashore Tonal Memory, and Trail-Making Part B.[23] Whereas finger tapping and grooved pegboard test results differed for controls compared with PNES and ES groups, Binder did not find differences between the ES and PNES groups on these measures.[9]
- Motivational measures. Motivational tests include the Portland Digit Recognition Test (PDRT), the Test of Memory Malingering (TOMM), and others; these tests are used to detect inadequate performance on NP testing. The presence of unconscious psychological stress is hypothesized as an explanation for variable effort in patients with PNES.[78] Binder et al. found that PNES patients performed more poorly when compared with patients with ES on the PDRT.[9,10] The authors noted that frank malingering occurs rarely in PNES, and the poorer performance in PNES may reflect a lack of psychological resources necessary to persist with a challenging NP battery.
- Personality testing. Results of the Minnesota Multiphasic Personality Inventory (MMPI/MMPI – 2) and Clinical Psychological Profiles and Family tests were reported. The majority of the MMPI studies in PNES report the "conversion V" profile, with elevations in Scales 1 (Hs, Hypochondriasis) and 3 (Hy, Hysteria), and depressions in Scale 2 (D, Depression).[13] Cragar et al. also reported an average sensitivity of 70% and specificity of 73% to PNES diagnosis using MMPI – 2 decision rules. The dramatic personality of patients with PNES was illustrated in a blinded pilot study of artwork drawn by patients with ES and PNES.[1] An 80% positive predictive value for PNES existed if subjects used 10 or more colors to draw their seizures. Galimberti et al. administered the Cognitive Behavioral Assessment (CBA) psychometric battery to patients with lone PNES, mixed ES/PNES, and ES controls. The CBA, which assesses personality characteristics and emotional adjustment, is comprised of scales rating introversion-extroversion, neuroticism, psychoticism, state-trait anxiety, psychophysiological distress, and depressive and other anxiety symptoms. These researchers found that the mean scores on the Psychophysiological Distress Scale for the PNES and the ES/PNES groups were higher than the mean scores of the ES control group.[28] The Rorschach test did not differentiate patients with PNES versus ES.[26] Krawetz et al. evaluated family functioning in patients with

ES and PNES and their families.

They found that individuals with PNES view their families as being more dysfunctional, particularly in the area of communication, whereas family members of patients with PNES reported roles as being dysfunctional.[46]

In summary, compared with healthy controls, patients with ES and with PNES perform worse on a number of NP measures. However, few differences exist between ES and PNES groups on tests that would reliably differentiate ES from PNES. The impairments are thought to be due to at least three factors: (a) both the ES and the PNES patients were on AEDs, which may affect cognition; (b) structural lesions in ES patients and in some of the PNES patients with ES; and (c) emotional factors contributing to cognitive impairment in the PNES group.[78] Psychologically, patients with PNES appear to have personality characteristics of anxiety, cognitive dysfunction, and somatic distress, and they have difficulty in expressing and communicating that distress to family and others.

Role of Pharmaco-Diagnosis

Prior to the use of EEG, neurologists and psychiatrists frequently used sedatives or other pharmacologic agents to distinguish ES from PNES. One of the earliest pharmaco-diagnostic accounts from the late 1800s reads: “I administered a hypodermic injection of hyoscine hydrobromate, which caused the fits to cease and produced five hours' sleep. On awakening the patient was very emotional and far from well, but there were no return of the fits.

Hyoscine, we know, is most useful in cases of status epilepticus and in the convulsions associated with general paralysis of the insane; it appears to be of service also in this condition of hystero-epilepsy, and certainly it is much less tedious than the old chloroform method.”[44]

Sodium Amytal and hypnosis were used in the mid-1900s to differentiate between ES and PNES.[52,65] Although these agents usually are not used diagnostically today, placebo saline injections and provocation techniques are used more frequently in some institutions.[3,18] The ethics of such procedures has been an issue of debate.[19,74,77] One acceptable technique incorporated at some epilepsy centers uses activation procedures (e.g., hyperventilation and photic stimulation) that are part of their routine EEG diagnostic protocol for PNES.[6]

Treatment strategies

We learn in medical school the physician's dictum, “Primum no nocere.” But in the case of the PNES population, many times harm *is* done through inappropriate treatments and aggressive therapy to stop seizures. Although PNES are not responsive to treatment with AEDs, most patients with PNES receive unnecessary AEDs, and only half pursue recommended psychiatric follow-up.[45] Extensive observational data suggest that AEDs are ineffective or may worsen PNES.[48] In some cases, potentially dangerous invasive diagnostic studies, toxic parenteral medications, or emergent intubation are administered.[35,70] The patients, their families, and society bear an enormous cost if psychiatric care is not provided or if inappropriate neurologic therapy is instituted for PNES.

Pharmacotherapy Using AEDs Only Targeting Recognized Epileptic Seizures

We ask patients and their family members to give a detailed description of seizure events; many times, PNES and ES have markedly different phenomenology in the same patient.[20] Once documented historically, we give the patient a seizure calendar and ask patients and family members to chart events prospectively, noting the characteristics of the seizures and any particular triggers or precipitants. The frequency of ES and that of PNES are established and, in the following visit, the results are discussed. This process clarifies treatment targets not only for the patient, but also for the physician. We explain that, for one

seizure type, we will use AEDs (e.g., “the seizure that occurs nocturnally, with lateral tongue biting, incontinence, and sore muscles upon regaining consciousness”). For the other type of seizure (e.g., “the one that occurs when watching a show on TV that reminds you of the past trauma of the assault, with ‘zoning out’ for a brief period of time and coming to just afterwards"), we will use a combination of medications for anxiety and psychotherapy. This method is a problem-oriented, practical approach that patients and their families understand and with which they can comply.

Psychiatric Treatment (Pharmacotherapy and Psychotherapeutic Interventions) for PNES

Intensive treatment using behavioral therapy, psychodynamic psychotherapy, occupational therapy, and education on an inpatient unit was the norm in earlier references to PNES treatment.[51,68] Success levels were higher than in the current outcomes reports, which incorporate a less intensive, outpatient treatment model, with up to 70% of patients with PNES continuing to have seizure events.[72]

Based on the clinical and research reports to date, we proposed the following assessment and treatment approach by a multispecialty neuropsychiatric team:[50]

- Proper diagnosis. Order a V-EEG for each patient with suspected PNES, or refractory or pharmacoresistant seizures.
- Presentation. Explain the PNES diagnosis in a clear, positive, nonpejorative manner. The patient may make the diagnosis presentation to the family members if cognitively and emotionally capable. This process helps reveal the level of understanding and initial acceptance of the diagnosis by the patient. Clarifications can be made by the physician, who is present. Communicate the diagnosis unambiguously to the referring physician and explain the need to eliminate unnecessary medications.
- Psychiatric treatment. Conduct a thorough psychiatric assessment to identify predisposing factors (including comorbid psychiatric disorders), seizure precipitants, and perpetuating factors. As diagnosis informs treatment, a dual-armed approach ensues using pharmacotherapy and/or psychotherapy, as indicated by the individual needs of the patient with PNES.

In patients with mixed ES/PNES, reduce high-dose or multiple AED therapy if possible based upon seizure calendar results. Use psychopharmacologic agents to treat mood, anxiety, or psychotic disorders. Enroll the patient in individual therapy with a psychiatrist or psychologist familiar with PNES and somatoform disorders, if a history of trauma, illness behavior, or specific interpersonal issues is identified in the assessment. Consider family therapy if the family functioning is found to be unhealthy, noting it to be a potential contributor to the symptoms.[49]

Summary and Conclusions

The majority of patients with PNES do not have epilepsy, and vice versa. In the 10% to 30% of patients who have mixed ES/PNES, diagnosis and treatment may present a significant challenge. A good history, documenting the various types of events the patient experiences, is an essential starting point. Long-term monitoring using V-EEG, to capture more than one of their typical events, aids in establishing the presence of mixed PNES and ES. Tapering AEDs during inpatient V-EEG greatly facilitates capturing the various seizure types. Provocation techniques using the routine activation procedures appear a safe and ethical procedure for seizure diagnosis.

Once the diagnosis of mixed ES/PNES is made, treatment entails addressing the patient and their family from a neuropsychiatric perspective. When ES coexists with PNES, this is most likely to occur in people with a previous history of epilepsy who have difficulty in adjusting to living without seizures and in patients who have coexisting psychiatric and physical disorders, which is not uncommon. Holistic assessment of the patient aids both diagnosis and management of coexisting epilepsy and nonepilepsy.

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Chapter 208

Psychiatric Side Effects of Antiepileptic Drugs

Bettina Schmitz

Introduction

Central effects of antiepileptic drugs (AEDs) are not restricted to the modulation of cortical excitability. AEDs may also modify systems that regulate mood and behavior. Anticonvulsant and psychotropic effects are not independent. Effects on seizure control have indirect effects on the mental state. Patients who are seizure-free have no risk of developing seizure-related psychiatric complications. On the other hand, the sudden cessation of seizures may lead to an imbalance in the mental state, as in "forced normalization" (FN). Some AEDs have dose-related paradoxical proconvulsive properties that may cause behavioral disturbances through underlying nonconvulsive status epilepticus.

Psychotropic effects may be negative or beneficial in individual patients. These effects depend on the antiepileptic strength, the mode of action of the anticonvulsant, and the patient's biologic and psychological predisposition. With the increasing variety of AEDs available, behavioral drug profiles have become very important for optimal treatment choices in epilepsy. Recent quality-of-life studies have shown that measurements of depression and the tolerability of AEDs are more important to patients than seizure reduction.[16] Furthermore, the high psychiatric comorbidity in epilepsy often requires psychopharmacologic interventions, which may be avoided when those anticonvulsants used have positive psychotropic properties.

In clinical praxis, the adverse psychiatric effects of AEDs are often not recognized. Often patients don't complain about behavior or mood changes unless they are specifically interviewed. Many neurologists are not competent in the exploration of a mental state, or they don't have the additional time needed to evaluate a patient's mental state. Many depressed patients are not primarily troubled by obvious depressive symptoms such as sadness or feelings of guilt. Depression in epilepsy often presents with sleep disorders or somatoform complaints and memory problems, which makes the diagnosis difficult unless the full psychopathologic status is explored. If delayed adverse psychiatric effects occur after months or years of exposure, the causal relationship with drug treatment is often not considered and is in fact difficult to prove, unless drug withdrawal is followed by the remission of psychiatric symptoms.

The exact prevalence of psychiatric AED events is difficult to estimate. In a consecutive series of patients with epilepsy and significant depression, about 30% were considered to have AED-related symptoms.[21,39] With respect to psychoses, the percentage of episodes triggered by AEDs has been calculated to be 40% in one study.[30]

Adverse Psychiatric Effects of Specific AEDs

Conventional Drugs

Barbiturates

Several studies suggested a link between depression and treatment with barbiturates, both in adults and in children.[5,36.] Forty percent of school children treated with barbiturates were diagnosed with "major depression," as compared with only 4% of children treated with carbamazepine.[4] In children, a conduct disorder resembling attention deficit hyperactivity disorder may be provoked by many AEDs, the most frequently implicated drug being phenobarbitone. Irritability and aggressive behavior are side effects particularly often seen when barbiturates are used in mentally retarded patients. Withdrawal problems, which present with nervousness, dysphoria, and insomnia, may occur even when barbiturates are very slowly tapered down.

Phenytoin

Phenytoin may provoke schizophrenia-like psychoses at high serum levels.[32] These psychoses are dose related—and are thus toxic syndromes—but they are not associated with the cerebellar signs that are the most common central nervous system side effects of phenytoin. In a study of 45 patients with drug-related psychoses, 25 (56%) cases were attributed to treatment with phenytoin.[20] A chronic encephalopathy has also been described with phenytoin use, and has been referred to as "Dilantin dementia."[44]

Ethosuccimide

Psychoses typically following cessation of seizures and associated with a normalization of the electroencephalogram (EEG) occur in 2% of children treated with ethosuccimide. The risk of FN is higher (8%) in adolescents and adults treated with ethosuccimide for persisting absence seizures.[45]

Carbamazepine

Affective problems are rare complications of treatment with carbamazepine.[8] These complications present as either depressive disorders or mania, the latter being explained as a paradoxical effect due to the antidepressant properties of carbamazepine, which is chemically related to tricyclic antidepressants.[9]

Valproate

Rarely, valproate is associated with acute or chronic encephalopathies.[37,40,47] These encephalopathies are related to dose and perhaps polytherapy, and they are reversible with dose reduction.

Table 1. Incidence rates of psychoses and depression in controlled trials (Besag,[2] Janssen-Cilag,[18] and Levinson and Devinsky[28])

	Psychoses (%)	Depression (%)
Vigabatrin	2.5	12.1
Lamotrigine	0.2	-
Felbamate	0.02	-
Gabapentin	0.5	-

Topiramate	0.8	9–18
Tiagabine	0.8–2	5
Levetiracetam	0.3–0.7	0.5–2

Newer AEDs

Table 1 summarizes data from premarketing controlled trials suggesting a relatively high frequency of depressive reactions in vigabatrin, tiagabine, and topiramate, and relative low rates for lamotrigine, gabapentin, and levetiracetam. Obviously psychiatric risks of the newer AEDs are not the same for all compounds. Some of the drugs seem to have neutral effects, some have a relevant risk for negative effects, and some may have predominantely beneficial psychotropic effects. A general comment is that the overall psychiatric risks of newer AEDs are not lower than those of older AEDs.

Vigabatrin

The risk of psychiatric complications caused by vigabatrin has been analyzed in two meta-analyses. The overall incidence of psychoses and severe behavioral reactions leading to drug discontinuation in seven placebo-controlled European studies was 3.4% in the vigabatrin group and 0.6% in the placebo group.[13] Another meta-analysis on the psychiatric risks of vigabatrin[28] translated psychopathologic symptoms described in the investigator forms into standardized psychiatric terminology, which was then summarized into a syndromatic diagnosis. This analysis of U. S. and non-U. S. double-blind studies demonstrated a significantly increased risk for psychosis and particularly for depression. Psychoses occurred in 2.5% of patients treated with vigabatrin compared to an incidence of 0.3% in the placebo group ($p < 0.05$), and depression occurred in 12.1% of patients treated with vigabatrin in contrast to only 3.5% in the placebo group ($p < 0.001$).

Lamotrigine

Severe psychiatric complications are rare with lamotrigine, and psychosis and depression occurred only in very few cases in trials.[14] Insomnia, which may be associated with irritability, anxiety, or even hypomania, is the only significant psychiatric side effect, occurring in 6% of patients treated in monotherapy, compared with 2% in patients treated with carbamazepine and 3% in patients treated with phenytoin.[6]

When first reports surfaced of caregivers complaining that handicapped patients had become more alert and demanding, it was interpreted as reflecting inadequate rehabilitation facilities, rather than a negative side effect.[3] Besag refers to this as a “release phenomenon.”[2] There are, however, a number of reports that children with learning difficulties and adults with mental handicaps develop behavioral problems such as aggression.[1,12] Reports have also noted the induction of a reversible Tourette syndrome, which in some cases was accompanied by obsessive compulsive symptoms.[29]

Felbamate

Felbamate is at present only used in a minority of patients, particularly those with Lennox-Gastaut syndrome, due to its hematologic and hepatic toxicity. Felbamate may lead to increased alertness, thus inducing sleep problems and behavioral problems related to agitation in some patients, particularly in children with learning disabilities.[31]

Gabapentin

Beyond somnolence, negative psychotropic effects have not been demonstrated in controlled studies of gabapentin. However, a number of studies suggest that gabapentin may induce behavioral problems such as aggression in children with learning disabilities and adults with mental handicap,[26,42,46] possibly related to rapid titration. In elderly people with reduced creatinine clearance, gabapentin may cause various neurotoxic symptoms due to its renal elimination.

Tiagabine

A specific problem with tiagabine is the paradoxical provocation of de novo nonconvulsive status epilepticus due to a relatively narrow therapeutic window.[38] Therefore, EEG registrations are necessary when behavioral problems arise, particularly when clinical signs such as mutism, qualitative change in consciousness, autisms, or myoclonia suggest status epilepticus.

In placebo-controlled add-on studies, nervousness and depressed mood were both increased in the tiagabine group[27] (12% vs. 3%, 5% vs. 1%). The incidence of serious adverse events presenting as psychosis was 2% versus 1% in the placebo group.

Table 2 Positive psychotropic effects of antiepileptic drugs demonstrated in controlled trials

	Depression	Mania	Bipolar disorder	Anxiety
Carbamazepine	0	+	+	0
Oxcarbazepine	0	+	0	0
Valproate	0	+	+	0
Lamotrigine	0	0	+	0
Gabapentin	0	-	-	+/ -
Topiramate	0	-	0	0
Tiagabine	0	-	0	0
Levetiracetam	0	0	0	-
Pregabaline	0	0	0	+
Zonisamide	0	0	0	0

+, positive results; -, negative results; 0, no published data.

Topiramate

In premarketing studies, and possibly related to aggressive titration schemes, topiramate was associated with a relatively high rate of neurotoxic side effects. Psychotic reactions were, however, relatively infrequent, with a prevalence of 0.8%. In a postmarketing study comparing the psychiatric side effects of topiramate, lamotrigine, and gabapentin, psychotic episodes occurred in 12% of patients treated with topiramate compared with 0.7% of patients treated with lamotrigine and 0.5% of patients treated with gabapentin.[7] These data suggest an increased vulnerability in selected patient groups. A significant proportion of topiramate-associated psychoses are explained as alternative syndromes in patients who become seizure-free.[34]

The rate of affective symptoms is clearly dose-dependent, with an incidence of 9% and 19% with a daily dose of 200 mg and 1,000 mg, respectively, found in one premarketing study.[18] In an analysis of topiramate-related psychiatric complications, depression was significantly correlated with rapid titration and high dosages.[34] Two studies demonstrated a correlation between psychiatric adverse events and cognitive side effects, suggesting that neuropsychological and affective problems are closely interlinked.[22,34] The neuropsychological disorders caused by topiramate resemble a frontal lobe problem, and have been interpreted as regional behavioral toxicity. It would be interesting to investigate whether patients with epilepsies and frontal lobe dysfunction are more vulnerable to these effects.

Levetiracetam

Levetiracetam is not associated with a high risk for severe psychotic or depressive reactions. Significant affective episodes were reported in 2% and psychoses in 0.7% of patients treated in preclinical trials. Some of the levetiracetam-associated psychoses were explained as a manifestation of FN.

A clinically relevant psychiatric side effect of levetiracetam is the provocation of aggressive behavior and irritability, which occurs both in adults and children. In an English series of 517 adult patients treated with levetiracetam, 10% developed a psychiatric complication, most frequently presenting with aggressive behavior.[35] Aggression occurs particularly often, but not exclusively, in patients with preexisting irritability and dysphoria. Mesad and Devinsky[33] analyzed cases of severe aggressive behavior, defined by objective verbal or physical aggression, leading to withdrawal of levetiracetam. The prevalence was 18 out of 460 consecutive patients (3.9%). Seven patients had previous episodes of aggressive behavior.

Children may be at an even higher risk to develop aggression, including suicidal behavior, with prevalence rates up to 68%.[11] In children with preexisting neuropsychiatric symptomatology, levetiracetam may provoke an exacerbation of behavioral problems.[17] Kossoff[24] reported on four adolescents who developed a psychosis secondary to treatment with levetiracetam, which was reversible following withdrawal. All patients had preexisting behavioral problems, and two had become seizure-free, supporting the role of FN.

Zonisamide

Outside of Japan and the United States, there is still limited experience with this broad-spectrum AED. There are, however, indications of significant psychiatric adverse events, including affective problems and psychoses. In a Japanese series of patients with psychotic episodes, half of drug-related episodes were triggered by zonisamide.[30]

Pregabaline

Controlled trials of pregabaline show no evidence for significant psychiatric adverse events. However, clinical experience with this recently introduced drug is still limited.

Positive Psychotropic Effects of AEDs

Carbamazepine and valproate are established drugs for affective disorders, and all novel anticonvulsants have been tested in primary psychiatric disorders with respect to potential mood stabilizing properties. The advantages of anticonvulsants compared to classical mood stabilizers are the lack of proconvulsive risks, the lower potential to induce a switch from depression into mania, and a superior efficacy in atypical syndromes such as rapid-cycling bipolar disorder. So far, only lamotrigine has been approved for bipolar disorder. Pregabaline has shown efficacy in anxiety disorders and insomnia (Table 2).

The potentially positive psychotropic effects of AEDs have not been systematically studied in patients with epilepsy. This is unsatisfactory because the experience with primary psychiatric patients cannot easily be transferred to epilepsy. Many psychiatric disorders in epilepsy are different in their phenomenology and most likely also in their pathogenesis from "endogenous" disorders.

The evidence for the mood-stabilizing effects of carbamazepine and valproate when used in patients with epilepsy is based on few observations.[36,39,44] With respect to the newer AEDs, the only convincing evidence with respect to positive psychotropic effects relates to lamotrigine.[10,15,19,41]

Risk Factors for Psychiatric Adverse Events

Patients with a biographic or genetic predisposition are presumably more at risk to develop AED-related psychiatric complications such as depression and psychosis (Table 3). Patients with previous depressive episodes are more likely to develop an affective disorder, whereas patients with previous schizophrenia-like psychoses are more likely to present with a psychotic reaction, suggesting that the clinical presentation of psychiatric adverse reactions depends on the individual psychopathologic predisposition. In patients with previous psychiatric problems, rapid titration should therefore be avoided, because aggressive titration schemes further increase the risk of behavioral toxicity.

Table 3 Risk factors for depression and psychosis with vigabatrin, topiramate, and levetiracetam

	Vigabatrin* depression/psychoses *n* = 22/28	**Topiramate** depression/psychoses *n* = 46/16**	**Levetiracetam*** depression/psychoses *n* = 13/6**
Psychiatric history	+/+	+/+	+/+
Febrile seizures	?/?	+/?	+/?
Status epilepticus	?/?	?/?	+/?
Titration/dosage	+/-	+/-	-/-

Seizure freedom	–/+ (13 cases)	–/+ (10 cases)	–/+ (4 cases)
Severity of epilepsy	–/+	+/ ?	–/ ?
Cognitive side effects	?/?	+/-	-/-

*Thomas,[43]
**Mula,[34] ***Mula[35]
+, significant relationship; –, no relationship; ?, not studied or too small numbers.

Some studies have shown that patients with severe epilepsies are at a higher risk for psychiatric side effects. Mula[34] demonstrated that hippocampal sclerosis is more common in patients who develop depressive episodes secondary to treatment with topiramate, compared with patients without affective side effects, another indication for the close links between limbic dysfunction and affective disorders.

Children and adults with learning disability and multiple handicaps are particularly vulnerable to the behavioral adverse effects of AEDs. In these patients, the exact psychiatric diagnosis may be difficult, and both depression and psychosis may manifest with aggressive behavior. Also, nonpsychiatric adverse events may lead to disturbed behavior because patients may have difficulties in otherwise expressing their discomfort. In these patients, drug changes should be monitored carefully, and it is recommended that the behavioral changes are carefully discussed with the health care/caregiver team. Occasionally, the interpretations of behavior changes are different within the team, particularly when patients become more alert and active because of positive psychotropic AED effects. These changes may be regarded as negative by some because they require attitude adjustments on the part of caregivers and make new treatment programs necessary.

Mechanisms

Four major mechanisms explain behavioral effects of AEDs: (a) dosage-dependant toxicity, (b) dose-independent idiosyncratic drug effects, (c) withdrawal effects, and (d) indirect effects via anticonvulsive actions. Of these, the two most important mechanisms are pharmacodynamic side effects related to the drug's mode of action and effects that arise with seizure control—those alternative syndromes associated with the phenomenon of FN.

Trimble's hypothesis of a link between psychiatric complications and the γ-aminobutyric acid (GABA)-ergic mechanisms of AEDs was extended by Ketter,[23] who distinguished two categories of AEDs. The first category are GABAergic drugs with sedating, anxiolytic, and antimanic properties. This category includes barbiturates, benzodiazepines, valproate, vigabatrin, tiagabine, and gabapentin. The second category are the antiglutamatergic drugs, which are claimed to have activating, an-xiogenic, and antidepressive effects: felbamate and lamotrigine. The authors suggest that anticonvulsant drugs have different psychiatric effects depending on the preexisting mental status of patients. They predict that patients who are primarily activated may benefit from drugs that belong to the “sedating” category and become worse with use of “activating” drugs. On the other hand, patients who are primarily sedated would benefit from a drug from the “activating” category, whereas the same patients would worsen with a “sedating” anticonvulsant. Taking the primary psychopathologic status of a patient into account explains the sometimes unexpected and seemingly paradoxical effects of some AEDs in individual patients. Based on clinical experiences, Table 4 suggests some "predictable" psychiatric AED risks that may depend on baseline psychopathology.

Forced Normalization

The concept of FN goes back to the publications of Landolt.[25] Cases of FN or alternative psychiatric syndromes have been reported with the use of all conventional and novel anticonvulsants, but seem to be particularly common with the more potent drugs such as vigabatrin, topiramate, and levetiracetam. FN has rarely been reported with tiagabine and lamotrigine, and is extremely rare with gabapentin. The best known manifestation of FN is a psychotic state. However, in a consecutive series by Wolf,[45] 50% of 36 consecutive patients presented with predominating affective symptomatology.

Table 4 Psychiatric risks of antiepileptic drugs in patients with preexisting psychiatric problems

Patient	Possible contraindication	Possible side effect
Dysthymia	PHB, VGB, TPM, TGB	Major depression
Paranoia	DPH, VGB, TPM	Schizophrenic psychosis
Agitation	LTG	Insomnia, anxiety, hypomania
Hypermotor	LTG	Tourette-syndrome
Dysphoric	LEV	Aggression
Learning disability	All AEDs	Behavior disorders

PHB, phenobarbitone; LEV, levetiracetam; LTG, lamotrigine; TGB, tiagabine; TPM, topiramate; VGB, vigabatrin; DPH, phenytoin; AED, antiepileptic drug.

Summary and Conclusions

The risk of AED-related psychiatric complications is likely linked to the severity of epilepsy, polytherapy, rapid titration, and high dosages of drugs. Patients with previous psychiatric problems or a familial predisposition seem to be especially prone to behavioral side effects. Another risk group includes children and adults with learning disabilities, and perhaps elderly patients. It is important to recognize patients at risk, inform them and their families about the possibility

of psychiatric side effects, apply a careful titration scheme, and make sure that patients are seen frequently—and that the appropriate questions are asked. When recognized at an early stage, psychiatric AED complications are mild and reversible in most cases. Risk factors for psychiatric complications are not a strict contraindication for any particular drug, and it is not always necessary to completely withdraw the responsible drug. Depending on the pathophysiology and the severity of the syndrome, a dose reduction or comedication with an antipsychotic or antidepressive drug may be a good compromise.

Behavioral drug-effect profiles, both negative and positive psychotropic effects, ought to be considered in the choice of the optimal drug for an individual patient. More studies are needed specifically devoted to the psychiatric effects of AEDs in patients with epilepsy. We need these studies to better identify patients at risk of severe behavioral reactions with the use of specific drugs, and also to identify patients who have a good chance of benefiting from the potentially positive psychotropic effects of certain AEDs.

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Chapter 209

Psychiatry and Surgical Treatment

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Introduction

More than half a century after its development, epilepsy surgery has become a routine procedure, especially for resection of mesiotemporal sclerosis. Indications for epilepsy surgery are now well-established, and expected physical benefits following epilepsy surgery can be shown with some certainty. Nevertheless, the implicit hope of patients is that "favourable outcomes in social and psychological domains" will follow seizure relief.[82] In light of this background, any attempts at prognosis must include more than a prediction of favorable seizure outcome by epileptologic methods. A more comprehensive neuropsychiatric view of epilepsy surgery outcomes is necessary, the importance of which is also underlined by the results of numerous studies from different countries that show a high psychiatric comorbidity in candidates for epilepsy surgery (Table 1). In the last few years, an increasing number of studies support the notion that this comorbidity exists not merely as the parallel existence of two unrelated diseases, but as a common etiology for epilepsies and psychiatric disorders. Examples include the association of fear auras with postoperative mood and anxiety disorders following a temporal lobectomy,[46] the prediction of seizures in later life by a history of depression,[31] and the correlation between postoperative psychopathology and the extent of temporal resection.[4] As a result, the gap between "organic" and "psychiatric" topics has begun to shrink, forcing neurologists and psychiatrists to work together—and producing some encouraging effects, as seen in reports from epilepsy surgery centers.

Table 1 Psychiatric morbidities pre- and postsurgery

Author (Ref.)	Total *n*	Preoperation	Postoperation	Time of assessment
Temporal				
Taylor 1972[81]	100	87%	68%	1–10y
Jensen 1979[36]	74	85%	69%	?
Polkey 1983[67]	40	—	58%	?

Stevens 1990[80]	14	38%	36%	2–3y<
Naylor 1994[63]	37	35%	38%	?
Manchanda 1996[57]	231	45%	—	—
Ring 1998[72]	60	20%	57%	3m
Ring 1998[72]	60	20%	20%	6m
Blumer 1998[11]	44	57%*	39%	1–3y
Glosser 2000[26]	44	65%	65%	6m
Anhoury 2000[4]	109	44%	58%	12m
Kanemoto 2001[40]	52	42%	37%	2–12y
Inoue 2001[34]	226	27%	24%	>2y
Cankurtaran 2005	22	27%	27%	6m
Extratemporal				
Naylor 1994[63]	10	20%	10%	?
Manchanda 1996[57]	43	44.2%	—	—
Blumer 1998[11]	6	67%	83%	1–3y FLE

FLE, frontal lobe epilepsy.
Total *n* = number of subjects; m/y, months/years.
*Described as interictal dysphoric disorder.

The Importance of Psychiatric Evaluation in the Context of Epilepsy Surgery

What do these promising developments mean for patients? The improvement in neuropsychiatric outcome prediction as a statistical piece of data is a helpful, although insufficient, frame in which to understand the complex situation of each individual patient. We know from psychiatric outcome studies[2,3] that mental instability may complicate the process of postoperative recovery. Following seizure cessation, affected patients may still suffer from their psychiatric disorders and may even acquire new ones. These patients face psychiatric disorder–related barriers that prevent them from making use of new opportunities in their seizure-free lives after surgery. Fortunately, individual outcome is not predicted by statistical data alone. We all know patients who transcend negative prognoses, profiting from the support and positive effects of relationships or internal strengths to make their way successfully through life post surgery. The best method for outcome prediction is a synthesis—a clinical psychiatric approach based on a balanced appreciation of the individual context and statistically evaluated group-predictors. The task of a neuropsychiatric assessment, beyond the evaluation of affiliation with special risk groups, is to understand the patient's motivations and aims within the frame of personal history, match them with realistic possibilities, communicate expected complications, treat actual disorders, and search for individual support strategies. Pre-, peri-, and postoperative psychiatric support during the process of surgery requires that the professional play the complex roles of physician, counselor, and container of hope simultaneously.

The majority of studies on this topic have focused on patients undergoing a temporal lobectomy or amygdalohippocampectomy because of the high proportion of temporal lobe epilepsies (TLEs) among epilepsy surgery candidates, but also of the prominence of psychiatric symptoms in patients with TLE. However, in the small number of reports that have mentioned the prevalence rate of psychiatric morbidities in temporal and extratemporal cases, no apparent difference has been found to exist when mental disorders are summed up as an entity.

This chapter does not cover the specific problems of epilepsy surgery in children, nor does it analyze in-depth psychosocial topics and questions concerning quality of life after surgery.

The Preoperative Phase: Mental Conditions of Surgical Candidates

As shown in Table 1, the reported prevalence of psychiatric morbidities among surgical candidates varies so widely (27%–85%) that no representative figures can be presented. With few exceptions, the mean numbers of psychiatric cases in recent studies exceed 40%, which is lower than the very early data obtained during the 1970s, although still clearly higher than in normal and nonselected epilepsy populations. Recent changes in selection strategies for epilepsy surgery to more strict exclusion criteria for patients with severe psychiatric morbidities, as well as progress in the treatment of epileptic seizures and mental problems, may have decreased the total number of patients. On the other hand, the increasing attention paid to mental disorders in the context of surgery and changes in assessment strategies (such as the use of structured clinical interviews) may account for a more complete perception of the whole situation, at least in recent series that have been reported. However, there are still no generally recognized psychiatric assessment methods for use in surgical centers. Further, the insufficiency of diagnostic systems for use in epilepsy populations has complicated the problem, because it is becoming increasingly clear that some of the most common and disabling psychiatric problems in patients with epilepsy are atypical and cannot be

classified easily within common psychiatric classification systems, such as the International Statistical Classification of Diseases and Health Related Problems (ICD) and the American Diagnostic and Statistical Manual of Mental Disorders (DSM).[11,89] Therefore, in the current situation, the variations of psychiatric morbidities among studies are due to the variety of selection methods used, improved treatment strategies, and investigation artifacts.

Although preoperative mental disorders may improve or even remit after surgery in some patients, a substantial portion of psychiatric morbidities emerge for the first time following surgical intervention, most within a few months after operation, with a limited timeframe of less than 1 year. As a net result, the prevalence rate of mental disorders after surgery tends to be close to that before surgery. Under the condition that epilepsy surgery is performed to cure epilepsy and not psychiatric disorders, practitioners should be content with these global outcome effects. However, the implicit expectations of patients, caregivers, and professionals transcend the expectation of mere freedom from seizures.

The Role of Surgical Expectations

Patients are subjected to a number of burdensome procedures during presurgical assessments. Strong motivation or a desire for surgery makes the stressful process more endurable for both patients and the doctors in charge. However, the beneficial effects of the strong desires seen prior to surgery often become a stumbling block after surgery, and might seriously undermine patient and caregiver satisfaction with a medically successful outcome, thus hindering social and psychological readaptation. Notably, Taylor et al.[84] designated such expectations as “desire beyond seizure freedom.” Furthermore, in a series of insightful investigations, Wilson et al.[95] revealed that the major components of this desire beyond seizure freedom consist of various expectations of a social and psychological nature (e.g., getting married, increasing self-confidence), and that those who aimed at more “practical” benefits (e.g., driving, employment, travel) tended to be more satisfied with the results of surgery. In a similar study, Wheelock et al.[92] showed that those with realistic aims and satisfaction with postoperative results had solid family backgrounds and more stable affective situations prior to surgery. These results suggest that desire beyond seizure freedom and implicit agreements between surgeons and patients should be explored, made explicit, and clearly stated and weighted before surgery. All who are involved in surgical procedures for intractable epilepsy should be aware of the simple fact that a surgical procedure, even a successful one, does not automatically make life happier.

Anxiety and Depression

For surgical candidates, the majority of studies agree that, among psychiatric disorders, depression and anxiety prevail, although the reported prevalence rates vary greatly from 27%,[14] to 33%,[26] to 77%.[2] In this regard, it is noteworthy that the rate of preoperative depression may change substantially, depending on the classification criteria and assessment procedures used. The atypical mixed-mood disorder is commonly encountered in patients with longstanding, intractable temporal lobe epilepsy (TLE) and, when the criteria are strictly applied, this disorder does not fit easily into any single standard diagnostic categories based on ICD and DSM. Blumer and Montouris[10] revived Kraepelin's concept of “epileptische Verstimmung” and designated the pleomorphic, intermittent, rapid cycling presentation of mixed-mood disorder as “interictal dysphoric disorder.” In addition to such a fundamental problem with diagnosis inevitably resulting from the insufficiency of the present standard diagnostic systems for neurobehavioral disorders, differences in assessment tools for affective symptoms as well as the observation period (whole life prior to the examination or a period at the time of examination) may well produce a profound effect on the results, which makes simple comparisons between studies virtually impossible.

Table 2 Outcome of preoperative psychosis (temporal lobectomy or amygdalohippocampectomy)

			Outcome of psychosis	
Author (Ref.)	Total *n*	Preoperative psychosis	Unchanged/aggravated	Improved/remitted
Simmel 1958[78]	44	11 (25.0%)	11 (100%)	
Taylor 1972[81]	100	12 (12.0%)	9 (75%)	3 (25%)

Jensen 1979[36]	74	11 (14.9%)	5 (46%)	6 (54%)
Sherwin 1981[77]	63	7 (11.1%)	7 (100%)	
Walker 1984[91]	50	5 (10.0%)	5 (100%)	
Bruton 1988[13]	248	18 (7.3%)	12 (66.7%)	6 (33.3%)
Stevens 1990[80]	14	3 (21.4%)	2 (66.7%)	1 (33.3%)
Kanemoto 2001[40]	52	12 (23.1%)	8 (66.7%)	4 (33.3%)
Cankurtaran 2005[14]	22	0 (0%)		

Supplemented and modified from Matsuura's[59] review.
Patients with postictal psychosis were excluded, if recognized as such from descriptions.
Total *n* = number of subjects.

It remains undetermined whether preoperative diagnoses of anxiety and depressive disorders are predisposed to postoperative anxiety and depressive disorders. Again, it seems plausible that a liability to depression or even a depressed personality structure will not automatically change following surgery for epilepsy, and contradicting data both for[2,68] and against[4,14,55] this argument have been provided. About one-third[26] to one-half[2] of all patients with presurgical depression experienced continuing relief from depression after surgery. In another report, virtually no overlapping was found between patients with depression prior to surgery and those after surgical intervention.[14]

As mentioned, in their study, Kohler at al.[46] added a special comment with regard to patients with ictal fear preceding temporal lobectomy. The authors observed that mood and anxiety disorders after a temporal lobectomy were more common in patients who had fear auras preoperatively, compared with patients with other auras or without auras, in particular if they were seizure-free. The role of the amygdala in fear conditioning, kindling, and the concept of forced normalization were suggested as a possible mechanism.

With regard to the laterality effect, some authors have postulated higher rates of depression in patients with left TLE at the time of the presurgical evaluation,[1,11,90] although more studies have suggested that serious affective dysfunction occurs predominantly in patients with right temporal lobe seizure focus.[22,24,26,47,81] There are also reports that deny any correlation between focus side and depression in surgical candidates.[2,55,57] However, a definitive trend is noted concerning postoperative depression, because right temporal surgery leads to a higher postoperative clinical depression index.[26,47,54,68,81]

Concerning the fate of patients with preoperative depression, the concept of “turning-in” proposed by Hill et al.[32] half a century ago is still worth noting. The authors found that some patients who had a reduction in outwardly turned aggressiveness that was apparent prior to surgery showed depressive mood swings that developed postoperatively, which recovered spontaneously in most cases within 18 months after surgery.

Thereafter, a number of authors reported results supporting that tendency for aggression and irritability to ameliorate following a temporal lobectomy.[19,35,67,81,91]

At our center in Bethel, however, we have also observed changes in the opposite direction, as patients who were emotionally withdrawn preoperatively have gained after surgery impulsive energy that turned into irritable, polemic behavior. The case of a man who lost emotional responsiveness to his family members after surgery, presented by Lipson et al.,[53] points in a similar direction.

Psychosis

Stable interictal psychotic disorders are notably absent in recent surgical series, because such patients have obviously been screened out during presurgical assessment on the assumption that they are less likely to improve functionally[36,37,71,79] or even deteriorate after an anterior temporal lobectomy.[22,36,52,54,81,86] However, since Fenwick[21] advocated surgical treatment even for patients with chronic psychoses, using the argument that seizure freedom alone can be worthwhile for patients even if their psychoses persist, this policy of excluding interictal psychosis has slowly started to change.

Recently, two multiple case studies summarized sequels of temporal lobectomy in patients with chronic psychosis. In one of those studies, Reutens et al.[71] described five patients who had been diagnosed with schizoaffective disorder or schizophrenia based on DSM-IV criteria and rendered seizure-free after surgery, with a 2- to 8-year follow-up period. In two of those patients, activities associated with daily living improved visibly. In another two patients, mental as well as social status remained stable, but unchanged. However, in one patient, psychotic symptoms continued and were so crippling that the patient needed repeated admission. Marchetti et al.[58] reported six patients, five of whom achieved Engel class I seizure outcome and relative improvement in their mental condition. Of those, four patients had a left epileptogenic lesion and two received an initial diagnosis of postictal psychosis, which developed into persistent chronic psychosis later during the course of illness. Although the psychotic symptoms were ameliorated in all four patients with a left-sided lesion, only one of the two with a right-sided lesion improved mentally.

Table 2 lists the ratios of patients with a history of episodic interictal psychosis prior to surgery and the outcome of

pre-existing psychotic symptoms after a temporal lobectomy reported in previous studies. The wide range (0%–25%) of rate of prevalence obtained at different surgical centers may well reflect different exclusion criteria for patients with intermittent (not persistent) psychotic episodes. Except for the Danish series, psychotic symptoms recurred in more than two-thirds of the patients after surgery. In our series, the average duration of postoperative psychotic disorders was far longer (7 months to 7 years; 50% longer than 2 years) than depression (2 to 17 months; 75% shorter than 6 months). It should be noted that a psychotic episode can recur even several years after surgery.[40,80]

In conclusion, treatment of interictal psychosis is not the aim of epilepsy surgery, and only seizure freedom (or improvement of seizure status) can be reasonably expected after surgical intervention. On this basis, patients should be informed that the postoperative development of their psychosis is unpredictable. However, with appropriate psychiatric support, patients can undergo epilepsy surgery and profit from seizure freedom in many respects.

In contrast to interictal psychosis, a number of studies suggest good outcomes for postictal psychotic episodes after a temporal lobectomy, thus rendering them as suitable surgical candidates.[19,22,40,74] The direct coupling of this type of psychosis to the occurrence of seizures predicts an excellent improvement under seizure-free postoperative conditions. In this regard, postictal psychosis has been described as a psychiatric indication for epilepsy surgery. However, in the postsurgical phase, those patients are especially liable to develop postoperative depression complicating their readaptation after surgery.[40] Two studies have reported frequencies of postictal psychoses in candidates for epilepsy surgery, which are rather high at 18%[87] and 13%.[40]

Other Psychiatric Disorders

In two case reports, rare associations of TLE and obsessive-compulsive disorder (OCD) were ameliorated after a right temporal lobectomy.[7,42] In contrast, Kulaksizoglu et al.[51] reported a worsening of preoperative obsessive-compulsive personality traits into a full-dressed OCD in two patients following an amygdalohippocampectomy. The authors hinted at the possible contribution of left-sided surgery to the development of OCDs.

Sexual behavior and function changes have also been listed as possible sequels after a temporal lobectomy. Postoperatively, both declines[12] and increases in sexual activity[5,6,9,12,65] have been reported, whereas abolition of aberrant sexual behaviors such as paraphilias[61] has also been noted. Postoperative sexual changes may persist several years after a temporal lobe resection and possibly more frequently after right-sided surgical intervention,[5,6] although the effect of laterality has been denied by others.[9]

Personality Disorders, Traumatic Stress, Nonepileptic Seizures

During the past decade, debate about the dubious character of the diagnostic category “personality disorder” (PD) has cooled down, possibly as a consequence of the descriptive, nonstigmatizing approach presented in the DSM classification system. Today, discussion tends toward a notion of PD as a result of maladaptive biographic developmental conditions, constitutional and/or experiential, which are expressed in behavior traits deviant from sociocultural norms. The capacity to cope with stressful life events is low in patients with a PD, and their liability to psychiatric decompensation is strengthened. It seems evident that, beyond other developmental risks, patients with chronic epilepsies are prone to additional personality problems due to their organic deficits, their epilepsy-specific social restrictions, and the side-effects of treatment. Candidates for epilepsy surgery with complex PDs could thus be expected to develop new psychiatric disorders. However, there are only a few studies on PDs in the context of epilepsy surgery. In 1957, Hill et al.[32] published a historical paper on personality changes after a temporal lobectomy. In that study, the authors investigated 27 patients both before and 2 to 5 years after temporal lobe surgery, of whom all but one had psychiatric disorders prior to surgery. Using a broad, not exactly specified definition of PD, the authors reported the following changes in personality: Loss of verbal learning abilities in dominant resections, reduction of aggressiveness by an increased tolerance of frustration, “turning-in” of aggressiveness with depressed mood (as mentioned earlier), changes in sexuality (mostly an increased sexual drive), and an increase of warmth in social relationships by a “lessening of egotism.”

Two more early, but very instructive, studies with diligent case-descriptions were presented by Horowitz and Cohen in 1968[33] and Serafetinides in 1975,[75] which focused on the meaning of PDs in the context of epilepsy surgery. However, from that time, the topic more or less vanished as a research subject in regards to epilepsy surgery. Since then, most of the studies on presurgical psychiatric morbidity have only focused on DSM axis 1, namely clinical syndromes, and excluded personality diagnoses. One study found PDs in 18% of the candidates for epilepsy surgery.[57] In a group of 100 patients who underwent temporal lobe surgery at our Bethel epilepsy center, we found that 60% had PDs. A detailed analysis revealed that 15% had a severe PD due to epilepsy—that is, directly correlated to the disease—which was formerly called “organic PD.” These patients, together with Cluster A patients (DSM-IV), showed a specific risk to develop new postoperative psychoses, whereas Cluster B patients were susceptible to dissociative disorders like depersonalization and nonepileptic seizures, but not to psychoses. The postoperative development of Cluster C patients was uncomplicated, except for those with additional cognitive deficits.[44] PDs also proved to predict severe postoperative psychiatric complications (defined by admittance to a psychiatric hospital during the first 2 years after surgery), because all psychiatrically hospitalized patients had suffered from PDs prior to surgery.[43]

As Ettinger[18] stressed in the editorial remarks to the recent re-edition of Hill's study, not only the topic of PDs but also Hill's scientific approach may need reactivation. The rigidity of the scientific community for only allowing the use of scales and scores as a basis for scientific publications too easily dismisses the detailed portrayals of patients' daily distress or missing skills, as well as analysis of their “essence.”

Another topic that remains unexplored in the context of PDs in epilepsy patients is the role of psycho-traumatization in the genesis of epilepsy and during surgical procedures. Research in this field has shown that chronic complex trauma experienced during the phase of brain development may induce borderline PD as well as dissociative disorders, and may have a damaging effect on mesiotemporal structures. It is an open question if the origin of TLE in those patients is accidental or causally related to trauma history, the latter being subjective evidence of many affected patients. As mentioned earlier, in our Bethel group, the development of new dissociative symptoms after surgery has shown a strong link to the diagnosis of borderline PD with a trauma history. This concurs with the findings of Ney et al.,[64] who reported that new dissociative nonepileptic seizures after surgery were predicted (among other factors like low IQ and surgical complications) by serious preoperative psychopathologic conditions.

Table 3 Postoperative depression (temporal or amygdalohippocampectomy)

Author (Ref)	Total *n*	Postop depression	New-onset only	Assessment time
Wrench 2005[96]	43		11 (26%)	1m
Ring 1998[72]	60	14 (24%)		1.5m
Ring 1998[72]	52	20 (38%)		3m
Glosser 2000[26]	39	3 (8%)		6m
Leinonen 1994[52]	57	5 (9%)		12m
Anhoury 2000[4]	109	35 (56%)	19 (17%)	12m
Naylor 1994[63]	37	5 (14%)	3 (8%)	23.5m*
Kanemoto 2001[40]	52		5 (10%)	24m–12y
Bladin 1992[9]	107	5 (5%)		4y*
Altshuler 1999[2]	49	14 (29%)	5 (10%)	9.6y*

Total *n* = number of subjects.
*Average follow-up duration at the last psychiatric assessment.
m/y, months/years.

It is unclear whether nonepileptic seizures should be considered an independent disorder or a symptomatic expression

of an underlying PD. To date, there is not much data on the percentage of patients with additional nonepileptic seizures in candidates for epilepsy surgery (ranging from 5%[64] to 10%[25]). Reuber et al.[70]

followed-up 13 patients (out of 1,342 surgery candidates) with both seizure types and reported good postoperative outcomes in terms of epileptic seizure control with a good match to those without nonepileptic seizures. Similar to Henry and Drury,[27] who recommended that an operation should only be planned if nonepileptic attacks are well treated by psychotherapeutic interventions, Reuber et al. concluded that additional psychogenic seizures should not be considered an absolute contraindication for surgery.

Postoperative Psychiatric Development

De Novo Acquired Disorders and Their Treatment

In general, improvement in seizure frequency after a temporal lobectomy may increase the possibilities of participation in social life and contribute to a well-balanced psychosocial state. However, especially during the first 3 to 6 months after temporal lobe surgery, many studies indicate that even patients who experience seizure freedom should be prepared for at least transient psychiatric deterioration.[11,26,39,40,48,72] Some authors have pointed out that even over the long term, some exceptional patients continue to suffer from postoperative worsening of their mental condition.[40,80,81] Among psychiatric disorders, depression and anxiety are listed as the most frequently encountered conditions in many reports. Psychogenic seizures are not so common; however, these could become a serious problem for some individuals. Single cases of OCDs that developed following surgery have also been described. The majority of recent studies that have addressed psychotic symptoms agree that new psychosis after a temporal lobectomy is less frequent than assumed earlier.[26,60,63] However, the acquisition of a new psychosis is such a serious burden for patients that it is imperative to observe carefully if psychotic symptoms develop. These may be potentially reversed when appropriate therapy is provided.

Generally, the explanations for the occurrence of new psychiatric disorders suggested so far can be summarized as biologic and sociopsychological, a consequence of disrupted functioning within the temporal lobe structure, such as the amygdala, which is known to be involved in the modulation and expression of emotion,[72] forced normalization.[26,50,90] This system collapses under increased expectations for new role functions once seizures have been abolished or reduced.[9,23] However, these theories remain to be elucidated with further evidence.

Postoperative Depression, Anxiety, and Manic Disorders

It is widely accepted that patients are especially prone to develop depressive or anxious states during the first 3 months after surgical treatment.[9,11,17,72,89] Thus, the prevalence rate of postoperative depression in outcome studies is highly dependent on the time schedule of the psychiatric assessment (Table 3). Within 3 months after the operation, depression occurred in one-third of patients, a prevalence rate that amounted to approximately half of the patients when anxiety disorder was added in two studies.[11,72] In contrast, many studies agree that the prevalence drops to 5% to 14% at 6 months after surgery.[9,26,40.52,63] Except for the report of Anhoury et al.,[4] showing 17%, the prevalence rate of new depression ranges from 8% to 10% after 6 months. Further, Wrench et al.[96] found that temporal patients reported significantly higher rates of anxiety and depression than did extratemporal patients, stressing the pivotal role of temporal lobe involvement in the genesis of new depression.

Although the highest incidence of anxiety was achieved within 1 to 2 months after surgery, the highest morbidity of depression was found within 3 months.[55,72] Except for some exceptions,[45] many authors agree that anxiety disorders tend to have a shorter duration than do affective disorders.[14,55,72]

In extreme cases, significant levels of postoperative depression and anxiety can lead to attempted suicide, paradoxically even in patients who have been rendered seizure-free.[9,26,36] After the first alarming report of Taylor and Marsh of nine suicidal cases from Falconer's large series of 193 patients, suicide attempts have been reported (4.6%–8.1%), especially in earlier series.[36,83] Most authors agree that postoperative mood disorders are transitory, with a remission within the first year after surgery,[26,40] and that the occurrence of postoperative depression is independent of seizure outcome.[32,96]

Table 4 De novo psychosis after epilepsy surgery

Author (Ref.)	Total (R/L) *n*	New-onset psychosis	Side of lobectomy
Simmel 1958[78]	44	4 (9.0%)	(R = 1, L = 2)
Taylor 1972[81]	100	7 (7.0%)	?
Jensen 1979[36]	74	9 (12.1%)	?
Polkey 1983[67]	40	2 (5.0%)	(R = 2)
Walker 1984[91]	50	6 (12.0%)	?
Bruton 1988[13]	248 (121/127)	9 (3.6%)	(R = 5, L = 4)
Stevens 1990[80]	14* (10/4)	5 (35.7%)	(R = 4, L = 1)
Mace 1991[54]	—	6	(R = 6, L = 0)
Bladin 1992[9]	107	2 (1.9%)	?
Leinonen 1994[52]	57	3 (5.2%)	(R = 2, L = 1)
Naylor 1994[63]	37	0 (0%)	
Anhoury 2000[4]	109	0 (0%)	
Kanemoto 2001[40]	52 (22/30)	2 (3.8%)	(R = 2, L = 0)
Mayanagi 2001[60]	70	2 (2.9%)	(R = 2, L = 0)
Cankurtaran 2005[14]	22	1 (4.5%)	?

Supplemented and modified from Trimble.[85]

Total *n* = number of subjects.
R/L, right/left.

In exceptional cases, mania can also occur de novo after a temporal lobectomy. Following the first case report,[38] a case control study[15] compared postoperative depression and mania

groups, and indicated that postoperative mania patients were more likely to yield findings of additional brain dysfunction in the hemisphere contralateral to the side of surgery, particularly in the electroencephalogram (EEG). Episodes of mania, just as depression, were usually transient and remitted within 1 year after onset. The prevalence rates in previous studies were 1.8%,[52] 3.8%,[39] and 3.9%.[15] Right temporal lobectomy was more common in patients exhibiting mania.[15,39]

New Nonepileptic Seizures and Somatoform Disorders

Nonepileptic seizures occurred newly after a temporal lobectomy in 1.8% to 8.8% of patients.[4,25,62,66] Following the first report of Ferguson,[23] which emphasized psychological aspects, new-onset nonepileptic seizures following surgery have been neglected in studies. However, the recognition of postoperative new seizure events as nonepileptic seizures, both in patients following a successful operation and in those with persistent epileptic seizures, is mandatory to prevent a delay in finding the most effective coping strategy. Since those patients who develop nonepileptic seizures frequently suffer from complex biographic burdens, extensive psychotherapeutic interventions may be necessary.

Previous reports agree that female patients with a right-sided temporal lobectomy are more susceptible to developing new-onset nonepileptic seizures, which tend to appear within 6 months after surgical intervention.[25] Although some reports have stressed early epilepsy onset as a risk factor for the emergence of new-onset nonepileptic seizures,[23,49] others have reported the reverse.[25] Low intelligence has been also suggested to promote new-onset nonepileptic seizures,[64] although that has been denied by another report.[25] As an explanation for that discrepancy, Glosser suggested the heterogeneity of such patients. Further, Naga et al.[62] described rare cases of postoperative occurrence of somatoform disorders other than conversion, such as pain disorder and body dysmorphia. They found new-onset somatoform disorders exclusively in patients following a temporal lobectomy, especially after right-sided resections, and not in those with an extratemporal resection.

De Novo Psychoses

Over the years, special attention has been paid to the risk of development of de novo psychosis following epilepsy surgery, because psychotic symptoms, once emerged, may decisively damage the quality of postoperative life and can become the main obstacle to social and psychological adaptations following surgery.[11,36,54,56,57,73,80,81,86] Furthermore, a new development of postoperative psychosis can be observed even in the setting of complete relief of seizures. As a result, several earlier reports stressed the risk of a development of postoperative psychosis.[36,81] However, the majority of recent studies suggest that new psychotic symptoms are less common following epilepsy surgery than assumed earlier.[26,60,63] Despite this, because of the severity of the disorder and the clinical significance of early detection and effective treatment of even subtle psychotic complaints, the new occurrence of psychotic episodes deserves special attention.

The prevalence rates of postoperative new psychosis in available studies range from 3.8% to 12.1%, except for the very high rate of 35.7% reported by Stevens[80] (Table 4). In Stevens' series, three patients who had exhibited strong paranoid behavioral patterns even prior to surgery were also included as postoperative new psychosis. By excluding those patients from analysis, the prevalence rate for that report drops to 14.3%. Several clinical parameters have been listed as predictors for the postoperative occurrence of new psychosis, and some authors have postulated that patients with ganglioglioma are more susceptible.[3,73,81] In a recent case-control study of patients with new psychosis after a temporal lobectomy, more bilateral abnormalities in preoperative EEG findings were detected, as well as pathologies other than mesial temporal sclerosis in the excised lobe and a smaller amygdala on the unoperated side.[76]

As Trimble suggested,[85] an association between postoperative psychoses and right-sided temporal lobectomy is rather clear when previous studies are listed together (see Table 4). This is all the more conspicuous when considering that schizophrenic-like psychoses are more common in patients with left or language-dominant temporal lobe seizure focus before surgery.[24,81,86]

Some psychoses following surgery occur with postoperative freedom from seizures. They may be interpreted as “alternative psychosis” under the postoperative condition of forced normalization,[54] whereas others occur in patients with ongoing seizures, frequently as new “postictal psychosis,” which has been reported to occur more often in male patients with right-sided surgery.[56] Recently, Christodoulou et al.[16] emphasized the significance of an emergence of new contralateral seizure foci after surgery, and suggested that new episodes of postictal psychosis were heralded by a new seizure type and originated from the side contralateral to the side of operation.

The Role of Seizure Outcome

Postoperative depression and psychosis can both occur with or without seizure freedom, and the relationship between seizure control and new psychiatric symptoms following surgery is still an open question. Glosser[26] noted a weak but noticeable trend that seizure-free patients may be at higher risk for the development of an early transient psychiatric worsening at 6 months after a temporal lobectomy. In contrast, seizure-free status is recognized to be the most powerful predictor of improved psychiatric and psychosocial adjustment outcome over the long term.[9,30,69,83,88,92]

On the other hand, several reports show weak but consistent evidence that the preoperative existence of a psychopathology is a negative predictor of seizure freedom. This supports the assumption of a common etiology between epileptic syndromes and psychiatric disorders.[4,63] At Bethel, we found seizure freedom in 89% of 100 patients without psychiatric comorbidities, whereas only 43% of patients with psychiatric disorders were seizure-free after temporal lobectomy.[44]

Postoperative Treatment, Role Changes, and Long-Term Adaptation

The first few postoperative weeks after epilepsy surgery are a vulnerable phase of irritability, anxiety, and the development of depression. One treatment strategy is to start early and broadly with antidepressants. Selective serotonin-reuptake inhibitors (SSRIs) are tolerated well and have been reported to be helpful, as have tricyclic antidepressants,[11] although control studies are missing.

If patients refuse to take antidepressants, it is necessary to instruct them to contact a neuropsychiatrist, at least when symptoms get stronger and indicate a manifest depressive episode. If patients, or more likely family members, should complain about withdrawal, delusions, and atypical suspiciousness, which are early symptoms of postoperative psychoses, an urgent outpatient contact is needed to plan careful treatment and convince the patient of the necessity of antipsychotic medication. Atypical substances, especially risperidone, in rather low doses are often sufficient, and instructions to the family along with clear advice about further treatment contacts are important. Generally, it is recommended to equip all patients with the phone number or e-mail address of a psychiatrist at the surgery center, which may also help to prevent suicide attempts during the first postoperative months. Although only a few patients make use of such contact offers, many report that the option to call or write is a substantial part of feeling secure during insecure times of change.

We concur with Wilson et al.,[94] in recommending a graduated return to work, starting no earlier than 6 to 8 weeks after surgery, to avoid the negative effects of early transient postoperative impairments (difficulties in word finding, memory, and concentration, distracted attention, affective lability) that may yield mistakes on the job and create a negative influence in the relationship between patients and employers.

Not only acute psychiatric complications bother patients and families after epilepsy surgery, but the complicated process of moving from chronically ill to normal and healthy. Since the early reports of Ferguson and Rayport,[23] who observed paradoxical worsening of behavior after successful surgery, and of Horowitz and Cohen,[33] who described that the loss of seizures may seem like the loss of “an old friend” during the process of readjusting to life without epilepsy, some papers have focused on the process of discarding roles associated with chronic epilepsy. Of special interest is the thoughtful application of the concept of “learned helplessness,” a known trigger for depression, to chronic epilepsy patients.[28] Recurrent uncontrolled seizures support the development of a self-concept as being without personal resourcefulness and efficacy. This negative self-concept tends to persist after surgery and may lead to a poor postoperative psychosocial adjustment.[17] Ongoing feelings of helplessness, especially in the surroundings of growing external demands and the loss of being excused by the epilepsy are expressions of the “burden of normality.”[9,93] Conversely, other patients have pushed themselves to their personal psychophysical limits before surgery to prove their normalcy. They may experience exhaustion after the cessation of seizures, instead of expected alleviation. Another hint that life remains complicated for patients who undergo surgery has been shown by Koch-Weser,[45] who found that the average burden of anxiety symptoms was higher in patients 2 to 7 years after surgery than in presurgical candidates. Over the long term, complete seizure relief is the best predictor of good psychosocial adaptation, and especially of an enduring remittance of depressive symptoms.[11,29]

Psychiatric Care in epilepsy Surgery Centers: History, State, and Perspectives

In the first Consensus Conference on epilepsy surgery at Palm Desert, Fenwick initiated a worldwide survey on psychiatric facilities in related centers.[20] At that time, 53 centers existed and 21 answered. The mean proportion of patients psychiatrically assessed before surgery was 31.7%, and after surgery the percentage was 41.5%. As a consequence, Fenwick advocated improvements in psychiatric facilities.

In their recommended standards, the International League Against Epilepsy (ILAE) commission on Neurosurgery (1993–1997) commented rather scantily on psychiatric necessities, saying that the preoperative workup should include “careful assessment of psychiatric state… using psychiatric rating scales when appropriate” and, with respect to the follow-up period, the recommendation was that “some form of psychiatric assessment should be used.”[8]

Recently, Kanner[41] has advocated for more involvement of psychiatrists in epilepsy centers. He complains that “only a minority of (U.S. surgical) centers performs a psychiatric evaluation as part of their presurgical evaluation” and “in less than 25% of major epilepsy centers surveyed, the epilepsy team includes a psychiatrist who is available to evaluate every patient.”

In the recent ILAE psychobiology commission (Trimble, Schmitz), a subcommission on epilepsy surgery (Koch-Stoecker, Krishnamoorthy, Kanemoto) has repeated a worldwide survey on psychiatric facilities in epilepsy surgery centers (unpublished data). The most important result is that 26 (43%) of the 60 responding centers stated that they perform both pre- and postoperative assessments for all patients, and another 40% at least have access to psychiatric crisis interventions. These results show substantial improvement; however, the survey did not cover the assessment strategies used, and it is probable that in many centers only standardized self-rating questionnaires are used which are no adequate substitute for a clinical diagnostic interview.

In times of economic pressure that lead to reductions in staff at most centers and no enhancement of psychiatric services, we recommend a psychiatric screening using rating scales for all patients, followed by an extensive interview with those who are screened out as belonging to a psychiatric risk group.

With respect to enhancement of psychiatric treatment options for epilepsy surgery patients, the development of specific psychiatric treatment manuals to be used in surgery centers as well as in local psychotherapies is desirable. These manuals should include topics such as a structured clearing of surgical expectations beyond seizure freedom; typical role-constellations and possible changes after surgery; education about symptoms of depression and psychosis; social skills training, along with instructions for the development of a reasonable self-concept; and education for coping with seizure recurrence.

Finally, psychiatric research in epilepsy surgery centers that stand at the interface between neurology and psychiatry must be promoted. In amplifying Ettinger's comments[18] on the rigidity of requirements for approval in peer reviews, more flexibility and creativity in study designs should be allowed to add new dimensions to our scientific knowledge. For example, individual case reports, in which psychosocial developments are extensively thought over and analyzed on the basis of the exchanges between patient and professional, or quality research strategies with expert discussion groups, are excellent and thoughtful means to supplement a statistically based understanding of mental disorders. Further, additional diversity in scientific exchange will inspire psychiatrists working in epilepsy surgery to participate in expanding the international network.

Summary and Conclusions

The close link between the epileptic condition and psychopathology, and the high frequencies of psychiatric disorders in epilepsy patients calls for psychiatric assessment and treatment in the context of epilepsy surgery. In addition, postoperative seizure freedom alone is no guarantee for an amelioration of quality of life, but mental stability and coping capacity are central preconditions in the challenging postoperative time of new role demands. Concerning depression, the most frequent disorder type, the predictive meaning of its preoperative existence is still equivocal, whereas postoperative depression is well-known as surgical complication during the first half year after surgery which occurs in about 10% of patients, especially after right sided resections.

Interictal psychoses are no longer seen as contraindications, because seizure relief can be of great value even if psychosis persists, and psychotic deteriorations after surgery are extremely infrequent. Postictal psychoses disappear together with seizures, but the probability of an episode of postoperative depression is high in this patient group. During the last decade the reports on new psychoses after surgery oscillate about a frequency of 2%. Despite this low incidence rate postoperative psychoses deserve special attention because of the severity of the disorder.

Personality disorders are very frequent in candidates for epilepsy surgery and complicate postoperative adaptation. The role of early traumatic experiences in the development of personality disorders, of the epilepsy causing lesion itself, and of non-epileptic dissociative attacks in epilepsy surgery candidates is not yet well understood.

In summary our knowledge about psychiatric disorders, their predictors and their treatment in the context of temporal lobe resections has grown during the last decade. Still there are many contradictory results, and conclusive etiological models are not available. Apart from future descriptive and controlled studies quality research and case studies could be helpful to create a more colourful picture of individual courses and to generate new hypotheses on psychobiological connections.

There is still too little presence of psychiatrists in epilepsy surgery units. Especially needed is more time for understanding patients' individual psychodynamics, the development of suitable assessment tools to meet the demands of atypical psychiatric disorders, and structured treatment instructions for special surgery related complications. If assessed and treated adequately mental disorders do not hinder patients on their way to a better quality of life after surgery in the long run.

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Chapter 210

Psychiatric Disorders in Children

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Introduction

The psychiatric and social aspects of epilepsy in childhood reflect the complex interaction of both general and specific illness-related factors on the child's life.[103] In terms of general factors, epilepsy is a chronic recurrent disorder and, like other chronic illnesses, this disorder affects the lives of the child and family. Among the specific illness-related factors, epilepsy involves brain function. In the developing child, chronic recurrent brief episodes of brain dysfunction might impact brain development, and, therefore, the development of behavior, cognition, and language. The maturation of these three areas of functioning has important implications for the psychiatric and social functioning of the child.

Two epidemiologic studies found a significantly higher rate of psychiatric disorders in children with neurologic disorders compared with children with chronic illnesses that do not involve the brain.[55,218] Furthermore, more specific seizure-related factors, such as type of seizure disorder, seizure control, the age of onset of seizures, and the number and type of antiepileptic drugs (AEDs) can impact the child's behavior.

This chapter summarizes the literature on these general and specific illness factors and how they are associated with psychopathology, cognition, and language in the child with epilepsy. It also presents the neurobehavioral aspects of selected early-onset epilepsy syndromes and how they affect children's behavior, cognition, language, and social skills.

The chapter then describes psychiatric disorders found in children with epilepsy. The chapter concludes by summarizing the most pertinent psychiatric and social issues of pediatric epilepsy. It also presents possible avenues for future research that would address the mental health needs of children with epilepsy.

Definition and Phenomenology

Psychological Impact of a Chronic Illness on the Child and Family

A chronic illness like epilepsy is a stress factor for the child and his family. The child and family need to recruit coping or behavioral, emotional, and cognitive strategies to decrease the illness related “mismatch” with the environment.[98,218] Adaptive or maladaptive use of these coping strategies depends on the complex interaction of a “multivariate multiprocess system”[143] that involves the child and family, as well as the social, educational, and medical environments.

Several studies have demonstrated that maternal and family functioning are important predictor(s) of psychological functioning in children with a chronic illness, whereas illness severity merely mediates (moderates) the effects of psychosocial variables; the reader is directed to two reviews on this subject.[248,269] In pediatric epilepsy, maternal depression and family functioning primarily reflect the presence of comorbid behavioral problems in the child rather than illness severity.[164,232] Limited family mastery and lower levels of confidence in managing child problems also predicted behavior problems in children with epilepsy at baseline and 24 months later.[11]

From the psychodynamic perspective, a child with epilepsy is faced with several stresses. The first stress factor, unpredictability, is a hallmark of epilepsy because the child never knows when a seizure is going to happen.[276] From the child's perspective, this unpredictability can lead to a sense of lack of control, fear, anxiety, or need to be dependent and protected by significant adults.

During development, children acquire self-esteem as they begin to master their environment and can do more things by themselves. This sense of mastery fosters a feeling of competence and control while decreasing the child's need for dependence. In contrast, the need for dependence produces a sense of helplessness and lack of self-esteem that can lead to feelings of inadequacy, poor self-worth, and ultimately to depression.[144]

In addition to unpredictability, the lapse in consciousness during a seizure or the child's experience of having his limbs do things that he has no control over further increases the sense of lack of control. Similarly, the unpleasant sensation of epigastric distress during the aura of a complex partial seizure can exacerbate the sense of lack of control, fearfulness, and dependence. Furthermore, the manifestations of a seizure are often perceived by others as frightening and grotesque.[163] The child's peers might, therefore, react to a seizure in a negative manner.[163] This could increase the child's feelings of being different.

Several older studies have shown that children with epilepsy, particularly those with temporal lobe epilepsy (TLE), were more dependent than children with other chronic illnesses.[96,109,243] In these studies, dependence was related to the presence of psychiatric disturbances,[96,109,243] a sense of lack of control, and attribution of failures and successes (particularly those in the social realm) to external unknown sources.[163] More recent studies have shown that children with newly diagnosed epilepsy feel shame and guilt about having epilepsy[196] and that adolescents with epilepsy are aware of a stigma to this illness.[9] Caplin et al.[36] demonstrated a positive correlation of self-efficacy with positive self-concept and positive attitude toward illness in youth with epilepsy and a negative association of child self-efficacy with child worries and symptoms of depression. Austin et al.[11] have shown that greater worry, negative attitude, poor self-concept, and symptoms of depression were associated with an increased sense of stigma in a large sample of children with chronic epilepsy.

Furthermore, the child has to contend with the possible behavioral and cognitive side effects of AEDs. Young children and sometimes adolescents are often unaware of the connection between these effects and their medication. These side effects could, therefore, contribute to the child's feeling of not being in control. Finally, despite the previously described stressors, children with epilepsy, like their peers, need to function adequately in the academic and social environment. These are far from trivial stressors.

Three main factors affect the coping skills of children with a chronic illness: the marginality of the sick status, the episodic nature of the disease, and the age of onset of the disorder.[100,202] If a child has visible physical impairments, a disease that is not episodic, and onset of the disorder from the preschool period, she self-identifies as sick and others identify her as different. If the disease has no visible impairments, is episodic, and begins after kindergarten, the child does not feel different from other children. When ill, the child tries to regain and/or achieve normal status.

The emotional burden on the child increases the less visible the handicap and the more normal the child is expected to be.[100] The need to meet these expectations becomes increasingly taxing for the child with epilepsy with recurrent rather than well-controlled seizures.

From the conceptual perspective, children's understanding of the nature of their disorder is age-related and can impact how well they cope with the illness.[220] Thus, 5- to 7-year-old children are aware of the external aspects of their disorder.[23] For example, they take medication, have repeated blood tests, and visit the doctor. Older children with epilepsy are more aware of the brain's role in their disorder, and this knowledge sometimes becomes a source of concern for them.

Sanger et al.[220] found that 41% of epileptic children and adolescents between the ages of 5 and 16 years identify epilepsy as a disease that involves the brain. Some children[10] fear that they might die during a seizure, and this fear makes them more anxious and dependent. Many children have misconceptions about seizure disorders and lack disease-related information. Only 41% of the children identified epilepsy as a disease involving the brain.[220]

Compared with children with asthma and diabetes, those with epilepsy have more unanswered questions about their illness and feel excluded from discussions with doctors.[119] Supporting this finding, McNelis et al.[157] reported that more than half of children with new-onset seizures want more information on seizures, the cause of seizures, treatment, handling future seizures, and protection from injury 6 months after their first seizure. They want to talk to other people with seizures, and need help handling seizures at school. More than 30% have fears or concerns about having another seizure and how to tell others about their seizures.

The impact and ramifications of the unpredictability of seizures is as important for the parents as for the child. It causes a sense of anxiety and is confounded by fear that the child could get hurt[10] or die[277] during a seizure. This unpredictability results in the difficult task of having to tread the fine line between what might be perceived as an overanxious or overprotective parent versus a neglectful parent. Thus, mothers of children with epilepsy are more stressed than are parents of children with other chronic illnesses.[68]

Parents vacillate between the need to protect and make sure their child is safe at all times versus the need to allow the child autonomy. The way parents cope with this stress affects the child's sense of dependence/independence, competence, and self-esteem. The findings of studies on the relationship of maternal anxiety and maternal adjustment with child quality of life, severity of epilepsy, and child adaptation highlight the role psychosocial variables play in how families cope with having a child with epilepsy.

For example, a study conducted on a relatively small sample described mothers as more emotionally involved in the lives of their children with epilepsy compared with their children without epilepsy.[111] This study also found increased maternal criticism toward the children with epilepsy, and this finding was related to more antisocial behaviors and poorer self-esteem in the children with epilepsy compared with their siblings.

Williams et al.[266] found that a significantly higher rate of parents of children with epilepsy sleep with their children than do parents of children with diabetes. They suggested that anxious parents might be more likely to perceive more risks for their children and misinterpret information about their child's condition, such as the need to sleep with the child to monitor for seizures. In a later study, Williams and colleagues[268] demonstrated that families most vulnerable to reduced quality of life were those in which a child has poorly controlled epilepsy, comorbid disabilities, and increased parental anxiety. Similarly, Austin et al.[15] reported that maternal adjustment and attitude was significantly related to the severity of the child's seizures.

In a large sample of children with epilepsy, Shore et al.[231] used a conceptual model based on prior findings in the literature to investigate the associations among maternal and child characteristics, maternal beliefs, and maternal adaptation. They found that most mothers adapt relatively well to their children having epilepsy. However, more than one-third of mothers were depressed and felt inadequate at managing their child's seizure disorder and maintaining the family's usual leisure activities. Child behavior problems, maternal satisfaction with family, and maternal learned helplessness had the strongest associations with maternal outcomes. This study did not examine the relationship between maternal and child adaptation.

In terms of child functioning and adaptation, Lotham and Pianka[154] found that measures of child–mother interaction and child self-reliance were significantly related to adjustment measures in children with epilepsy. Chapieski et al.[48] reported that poor adaptive functioning, based on the Vineland Adaptive Behavior Scale[238] in children with epilepsy was significantly associated with maternal anxiety, as well as with an overprotective and overly directive parenting style.

The few studies that have included both mothers and fathers find similar concerns in both parents of children with new-onset epilepsy.[233] Although these concerns decrease over a 6–month period, mothers maintain a higher level of concern than do fathers. Fathers have also reported that mothers are more concerned than they are about their child's epilepsy.[66] These parental differences can influence what children feel about the impact of their illness on their parents and family functioning. Therefore, studies are needed to determine how differences in parental concerns, anxiety level, and attitude are reflected in child functioning and adaptation.

In addition to the previously reviewed child and parent psychological variables, sociodemographic variables, such as social class, current and previous family stresses, and the presence of other children might also contribute to both the child's psychosocial adjustment and the family's coping skills.[110] Within the family context, there is a debate in the literature on the impact of chronic illness on healthy siblings; this topic is reviewed by Sharpe.[228] Hoare[108] demonstrated that the siblings of children with new-onset epilepsy are not more maladapted than the siblings of children with new-onset diabetes. However, the siblings of children with chronic epilepsy were more maladapted than the siblings of children with chronic diabetes. These findings led Hoare to conclude that chronic epilepsy has a marked impact on the behavior of the affected child, the siblings, and the family.[108]

In terms of the external environment, both the child and parents must deal with the school system. From the psychodynamic perspective, the occurrence of seizures at school can increase the child's sense of lack of control and present the child with the difficulty of dealing with stigma from peers and

teachers. The child is also often faced with repeated questions by peers after having a seizure at school and also with teachers' lack of knowledge and misconceptions about epilepsy.[24] Even though there is no medical indication, teachers sometimes send children home or to an emergency room when they have a seizure. As a result of repeated absences, the child has more work to catch up, and this may increase the already difficult work load.[202] Teachers also might underestimate the child's intellectual potential due to misconceptions about epilepsy.

From the parental perspective, their efforts to help the child deal with the school system might increase their stress and that of their child. Hoare and Kerley[110] have shown that families of children with epilepsy who attend special schools are under more stress than those of children in regular schools. Alternatively, Austin et al.[18] described a significant association between academic achievement and family mastery in children with epilepsy.

Regarding academic achievement, Fastenau et al.[72] demonstrated a moderating effect of family factors, particularly organized/supportive versus disorganized/unsupportive family structure, on the impact of neuropsychological deficits on the writing and reading skills of children with epilepsy. Supporting the importance of family functioning in the academic performance of children with epilepsy, Mitchell et al.[175] found that parental education rather than seizure variables plays an important role in the IQ of children with epilepsy. Taken together, these psychosocial factors could increase the demands facing the child and affect his academic functioning,[72] self-esteem,[162] and related social and school functioning.[42]

From the social perspective, the problems of adolescents with epilepsy deserve special mention. During adolescence, youth acquire more independence, yet vacillate between dependence and independence. Uncontrolled epilepsy could affect this process by increasing dependency. Alternatively, if adolescents experiment with the decision-making, they might make decisions that are potentially harmful for their illness.[33] For example, to conform to what they perceive as the expectations of peers, adolescents might be noncompliant with AEDs, go to sleep late, or use alcohol and drugs. These behaviors could lead to poor seizure control and possible denial of a driver's license. These circumstances can lead to a significant increase in family stress.[146]

In terms of coping skills, a study of a large sample of adolescents with epilepsy has shown increased negative attitude with increasing age and poor seizure control[99] using the Child Attitude Towards Illness Scale.[13] The authors of this study suggest that as youth get older, a better understanding of the restrictions and limitations of the illness might underlie the increased negative attitude. Despite seizure control, the mothers of adolescents with epilepsy report significantly more psychological, social, and school adjustment problems than do the mothers of adolescents with asthma.[14] Also, above and beyond the effects of seizure control, Sbarra et al.[224] found that adolescent perception of controlling maternal behavior was significantly associated with youth externalizing behaviors.

Dealing with the stigma of epilepsy during adolescence might also pose additional coping challenges, as reviewed by MacLeod.[157] Westbrook et al.[263] found that only one-third of 64 adolescents with epilepsy confirmed that they felt stigmatized, and this finding was associated with poor self-esteem. Similarly, using the Quality of Life in Epilepsy for Adolescents (QOLIE-AD-48), which includes a stigma scale, Devinsky et al.[57] found relatively low stigma and good quality of life in youth with epilepsy. In contrast, a 37-item questionnaire designed to measure familiarity with epilepsy, knowledge about epilepsy, and perceptions reflecting stigma filled out by 19,441 adolescents revealed lack of knowledge and misperceptions about epilepsy that suggest a high rate of stigma.[19] In addition, the finding that 70% of the epilepsy patients in the Westbrook et al.[263] study said that they do not talk with anyone about their epilepsy implies that they do not talk about their illness because of stigma.

Finally, the child and family also must interact with the medical system. Two studies, one conducted in the mid 1980s[50] and one in 2004 (Smith et al., in press) found a marked discrepancy between the concerns of parents of children with epilepsy regarding their children's needs compared to how the treating pediatric neurologists and pediatricians viewed the parents' concerns. Whereas the parents were mainly worried about their children's behavior and performance at school, physicians thought the parents were concerned primarily about the stigma of epilepsy and seizure control. This continued discrepancy, despite increasing evidence for behavioral, cognitive, linguistic, and quality-of-life difficulties experienced by children and adolescents with epilepsy, underscores the stresses faced by parents of children with epilepsy.

In summary, from the psychological perspective, the child's ability to cope with epilepsy is a function of his intrapsychic experiences, such as sense of mastery and understanding of the illness, how the child's parents and family deal with the illness, as well as how the school, peer group, and medical system respond to the illness.

The Effect of Seizure-Related Factors on the Child's Behavior

This section reviews studies on the association among seizure-related factors, such as seizure type, seizure control, AEDs, and age of onset with behavior, cognition, and language of children with epilepsy.

Psychopathology by Seizure Type

The landmark Isle of Wight epidemiologic study on psychopathology in children found an increased rate in children with TLE.[218] However, very few children in that study met criteria for TLE. Subsequent studies, albeit nonepidemiologic, of psychopathology by seizure type in childhood inconsistently found a relationship between type of epilepsy and psychopathology.

These discrepancies reflect limitations inherent in including relatively small sample sizes of children with epilepsy, and, therefore, small numbers of children with different seizure types. This, in turn, reduces the power to examine possible confounding effects of other seizure variables (e.g., seizure control, age of onset, duration of illness, type and number of AEDs), as well as of comorbid cognitive and linguistic deficits, demographic variables, and premorbid behavior problems.

Moreover, studies differ in whether they classify children by epilepsy syndrome, type of epilepsy, or localization-related epilepsy, or include type of epilepsy as one of several seizure severity measures. In addition, they also vary in the technique used to collect behavioral information on the children (e.g., structured psychiatric interviews, questionnaires), the source of information (e.g., child, parent(s), teacher), and the measures (psychiatric diagnoses, scores).

With these limitations in mind, the findings of earlier studies suggested that a relationship exists between type of seizure disorder and behavioral problems. For example, Nuffield[190] described neurotic traits in childhood absence epilepsy. Several studies suggested that children with TLE have characteristic behavioral disturbances,[94,110,151,217,241,246] particularly if they have left-sided foci.[151,241] Their behavior problems, hyperactivity, aggression, and antisocial behavior were

associated with male gender, poor seizure control, low IQ, and childhood rages.[94,110,151,217,241] However, other researchers were unable to identify differences in measures of psychopathology between children with temporal lobe and generalized epilepsy.[103,265]

Using structured psychiatric interviews, a recent study on a large sample of children with different types of seizure disorder has demonstrated similar rates of DSM-IV psychiatric diagnoses in 60% of the children with complex partial seizures and 58% of those with childhood absence epilepsy, compared with normal children.[198] Other than schizophrenia-like psychosis in 10% of children with complex partial seizures rather than childhood absence epilepsy,[41,150] children with complex partial seizures and childhood absence epilepsy have similar rates of disruptive, affective/anxiety, and both disruptive and affective/anxiety disorders. Controlling for seizure and demographic variables, IQ was the single predictor of a psychiatric diagnosis in children with complex partial and childhood absence groups.[198]

A long-term follow-up study of young adults with a history of childhood absence demonstrated that, compared with a control group of young adults with a juvenile rheumatoid arthritis history, they had a significantly higher rate of behavioral and school/academic problems.[270] This finding was unrelated to seizure variables. Thus, childhood absence epilepsy, considered by most neurologists to be completely benign, has both a high rate of psychopathology in childhood and poor outcome regarding behavior and academics by young adulthood.

In children with new-onset seizures, those with prior unrecognized seizures and subsequent development of partial or absence seizures have higher rates of behavior problems (based on Child Behavior Checklist [CBCL],[1] parent,[12] and teacher[65] total) internalizing, attention, thought, and somatic complaints scores than those with other types of seizures. Other studies on children with new-onset seizures, however, have not shown a relationship between severity of behavioral problems and type of epilepsy.[195] In fact, prior cognitive and behavioral problems, rather than seizure variables, predicted whether children with new-onset seizures continued to have behavior problems over time.[197]

A study on localization-related epilepsy describes parental reports of behavioral problems in 39% of 63 children with TLE.[97] However, this study did not include control groups of children with other types of epilepsy. A study comparing small samples of children with temporal, frontal, and absence epilepsy found increased attentional problems based on parent CBCL scores in those with frontal lobe epilepsy.[104]

Among the localization-related epilepsies, even the so-called “benign” epilepsies, benign epilepsy with centrotemporal spikes (BECTS) or benign occipital epilepsy (BOE) may be associated with psychopathology. In the last decade, more reports focus on the subtle behavioral alterations commonly seen with these syndromes. Nonspecific behavioral problems have been reported in 30% of children with centrotemporal spikes,[275] and these may be more prevalent in those with atypical features of BECTS.[260] Symptoms of attention-deficit hyperactivity disorder (ADHD) have also been reported and may be predicted by certain EEG characteristics.[161] Parents report more problems with attention, temper, and impulsiveness in children with BECTS compared with controls.[51] Of interest, centrotemporal spikes were found in 5% to 6% of a large sample of ADHD patients without a history of epilepsy,[117] and spike frequency appeared to be related to severity of symptoms.

In summary, irrespective of type of epilepsy, children with epilepsy, both new-onset and chronic epilepsy, have high rates of a wide range of behavioral disturbances. The small study sample sizes, wide age range, and different methods of assessing behavioral abnormalities in these studies highlights the importance of conducting prospective studies of large representative samples of children to demonstrate the consistency of the behavioral problems and their course, and whether type of epilepsy plays a role in the behavioral profile of children and adolescents with epilepsy.

Effects of Seizure Control on Behavior

Historically, Lindsay et al.'s[151] long-term outcome study of 100 pediatric TLE cases revealed that poor seizure control was associated with increased antisocial behavior in these children. Remission of seizures by age 12 years was associated with a better adult psychosocial outcome than remission after age 12.[150]

Hermann et al.[103] demonstrated that seizure control was the most robust predictor of total and externalizing CBCL scores in a large sample of children with epilepsy, controlling for the effects of demographic, biologic, and psychosocial variables. Numerous subsequent studies have examined this relationship using different behavioral instruments, control groups, informants, measures of seizure control, sample sizes, and youth cognitive ability. Some of these studies were cross-sectional and few were longitudinal. Only a few studies have controlled for possible confounding seizure variables to varying degrees. Retrospective and prospective treatment studies have also investigated the relationship between seizure control and behavioral outcome following intervention with AEDs and epilepsy surgery.

Due to space limitations, this section briefly summarizes the findings of the larger cross-sectional and longitudinal studies (including postsurgical intervention), conducted in children with epilepsy, that have examined the association with seizure control. It also indicates how these findings vary by type of behavioral instrument and informant.

In terms of cross-sectional studies there was no statistically significant relationship of seizure frequency with the presence and type of psychiatric disorders, as well as with CBCL scores in a large sample of children with complex partial seizures who have average IQ scores.[43] The DSM-IV psychiatric diagnoses of these children were based on information obtained on the child by a structured psychiatric interview administered separately to the child and to the parent.

In contrast to these findings, Schoenfeld et al.[225] reported significantly higher total and internalizing CBCL scores in children with complex partial seizures with the highest seizure frequency. However, they did not examine the possible effect of IQ on these findings.

Using CBCL scores, Austin et al.[16] also found significantly higher internalizing scores in children with epilepsy, aged 8 to 13 years, who had more severe seizures, a measure that includes seizure control. Follow-up of these children 4 years later revealed significantly higher internalizing CBCL scores in the girls with epilepsy who had more severe seizures both at baseline and follow-up.[9] These authors concluded that girls with more severe seizures might be more at risk for behavior problems as they moved through the teen years.

Children with new-onset seizures and subsequent recurrent seizures have significantly higher parent-[17] and teacher-based total and internalizing CBCL scores,[62] suggesting a relationship between seizure control and severity of behavioral problems. In contrast, Oostrom et al.[195] reported lack of persistence in behavior problems based on parent CBCL and teacher reports in their 3-, 12-, and 48-month follow-up study of children with new-onset epilepsy. Despite similar mean parent and teacher ratings, Oostrom et al.[195] found no agreement between parent and teacher ratings for individual children.

In terms of surgical studies, several older studies noted that some children with TLE become less aggressive, and their behavior improves once they attain seizure control after temporal lobectomy.[54,60,89,118,149] None of these studies, however, used standardized psychiatric instruments and control groups to follow the postoperative behavioral changes of a representative sample of children undergoing temporal lobectomy. In addition, these studies did not include a control group of medically treated children with epilepsy.

Using the CBCL,[1] Lendt et al.[145] found a significant decrease in the CBCL externalizing, internalizing, attention, and thought scores that had been within the clinical range 3 months after epilepsy surgery on 13 temporal and 11 extratemporal lobectomies, two hemispherectomies, and two callosotomies, compared with a control group of medically treated children with intractable epilepsy. Postsurgical seizure control rather than age, sex, onset, and duration of epilepsy; the site of the focus; and changes in AED regimen accounted for this finding.

In a 1-year follow-up study of a large sample of 30 children who underwent epilepsy surgery, Smith et al.[237] found no significant change in CBCL scores 1 year after surgery, compared with medically treated children with intractable epilepsy. Seizure control was unrelated to these findings.

In summary, the findings of cross-sectional and follow-up studies of children with new-onset and chronic epilepsy demonstrate an association of seizure frequency with the presence and severity of behavioral disturbances. However, recent evidence that verbal IQ predicts psychopathology, children with new-onset seizures have behavior problems prior to the onset of seizures, and children who undergo epilepsy surgery continue to have behavior problems irrespective of postsurgical seizure control suggest that psychopathology is a comorbid component of pediatric epilepsy irrespective of illness variables.

Effects of Antiepileptic Drugs on Behavior and Cognition

Although there are numerous reports on AED effects on behavior and cognition in children with epilepsy, no double-blind, randomized, controlled studies have examined these relationships in these children. For detailed information on extant studies and reports, the reader is referred to two reviews, one on the mechanisms of action of AEDs and the relevance to neurobehavioral adverse effects,[222] and the other on the cognitive side effects of AEDs in children with epilepsy (see also Chapter 201).[153]

This brief summary of the adverse effects of AEDs on cognition and behavior emphasizes the importance of controlling for these variables in neurobehavioral studies of children with epilepsy. In addition, different children appear to be vulnerable to these AED adverse effects. Thus, as described in adults with epilepsy,[138,181] increased risk for AED-related behavioral and cognitive side effects in children with epilepsy include AED polytherapy,[32,95,134,151,155] mental retardation or learning disabilities,[32,95] and a family history of psychiatric disorders.[28,30] Similarly, as shown in adults with epilepsy,[250] children with a past history of behavioral problems, as well as of prior adverse behavioral and cognitive effects to AEDs, might also be more vulnerable to these adverse effects.

It is important to note that children on high doses of combinations of AEDs might appear to be depressed because they are tired, apathetic, listless, and poorly motivated. Other children on polytherapy or high-dose monotherapy might respond with irritability, low frustration tolerance, poor impulse control, and hyperactivity.

However, AED polytherapy might also reflect the type or types of epilepsy, as well as comorbid cognitive and linguistic difficulties, all of which might increase the likelihood of behavioral problems. Therefore, clinicians should be aware that the functional impact of AED behavioral and cognitive side effects on the individual child's daily functioning and quality of life might be as severe as that of uncontrolled seizures.

In terms of specific behavioral side effects, AEDs that can trigger depression in children include phenobarbital,[28,30] primidone,[105] and valproic acid.[105] Adult studies also find depression associated with topiramate[182] and levetiracetam.[188] Manic behavior has been described in children with epilepsy treated with felbamate[45] and ethosuximide.

Case studies describe psychosis in children treated with topi-ramate,[206] levetiracetam,[134,274] vigabatrin,[35] and zonis-amide.[177] Several case reports describe irritability, hyper-activity, and aggression in children with epilepsy on gabapentin,[129,172] phenobarbital,[34,261] vigabatrin,[3,230] and benzodiazepines.[81,249]

Slowing of cognitive processes and motor reaction time are attributed to the older AEDs, such as phenobarbital and benzodiazepines.[26,34,105,261] In adults with epilepsy, these effects are dose-related for carbamazepine, phenytoin, and valproic acid.[59] However, there have been no well designed studies on the new AEDs and cognition in children. The impaired word retrieval and cognitive slowing found in children treated with topiramate,[91,229] and the possible association with the speed of titration[221] must be studied in children.

To date, most clinicians have been impressed by the lack of adverse cognitive effects in children treated with lamot-rigine.[221] The slow titration used in children with epilepsy to avoid the rash associated with lamotrigine treatment might contribute to this observation. However, well-designed studies are needed to examine the effects of the new AEDs on cognition.

In summary, double-blind, randomized studies using well-established behavioral and cognitive instruments sensitive to change are needed to determine which AEDs have behavioral and cognitive adverse effects and for which children with epilepsy. Studies of behavior and cognition in children with epilepsy, however, should include large samples of children to examine the possible role played by AEDs in the studies' findings. AED polytherapy and high therapeutic blood levels might be associated with more general behavioral problems, such as irritability, aggression, and hyperactivity, as well as slowing of cognitive processes in children.

Children with epilepsy at risk for the adverse neurobehavioral effects of AEDs are those with mental retardation, learning disabilities, poor prior behavioral and cognitive responses to AEDs, psychiatric history of past behavioral and cognitive problems, and family history of psychiatric disorders.

Age of Onset and Duration of Illness

Increasing evidence suggests connectivity and structural changes caused by seizures in the brain of young animals despite the lack of cell loss (see review by Holmes[114]), an age-related effect on synaptic function,[141] and long-term cognitive and behavioral changes.[223] Maternal deprivation in the young animal has synergistic effects, with recurrent seizures in inducing long-term damage in the developing brain.[121] Although the impact of early seizures on brain development might reflect the underlying cause of the seizures rather than the effects of seizures,[113] the findings of animal studies support the previously reviewed clinical data suggesting that the child's immediate environment (i.e., home, school), rearing practices, recurrent ongoing seizures, and AEDs might impact the development of behavior and cognition.

The age of onset of epilepsy might be an indicator of the severity of the underlying pathology. Thus, early-onset epilepsy is often associated with mental retardation, and children with mental retardation have an earlier onset of epilepsy.[218] These age relationships imply that epilepsy and mental retardation in children with early onset are epiphenomena of underlying pathologic processes in the brain.

In terms of psychopathology, two epidemiologic studies have demonstrated significantly higher rates of psychopathology

in children with epilepsy who have mental retardation[218] or complicated epilepsy, including learning disabilities[55] than those with normal intelligence or uncomplicated epilepsy. A population study of children with both mental retardation and epilepsy also revealed high rates of severe behavior problems.[239]

Nevertheless, it is still unclear how and to what degree recurrent seizures, both frequent and infrequent, and the need for high doses of AED polytherapy impair ongoing development of the brain and of emotional, social, cognitive, and linguistic skills in early childhood. It also remains to be determined through prospective studies if the behavioral, cognitive, and linguistic outcome in developmentally disabled children with earlier onset of epilepsy is worse than in children with later onset of their epilepsy. Whereas some studies suggest that epilepsy surgery and subsequent seizure control for early-onset intractable epilepsy changes the developmental course,[78] others do not.[44,133,135,237]

Regarding later onset of epilepsy, two of the most common types of pediatric epilepsy, complex partial seizure disorder and primary generalized epilepsy, typically begin in middle childhood. During middle childhood, acceleration occurs in the development of children's emotional, social, cognitive, and linguistic skills and continued maturation through adolescence. Ongoing seizures, high doses of multiple AEDs, and prolonged seizures might interrupt the functioning of the neural circuits involved in these maturational processes.

In children with onset of epilepsy in middle childhood, although the presence of psychopathology does not appear to be associated with age of onset,[43] earlier studies identify an association between early-onset and impaired cognitive functioning.[2,26,70,191] Yet, these findings might also reflect the confounding effects of poor seizure control, as well as AED polytherapy and high blood levels of treating drugs.[26]

More recent studies also find that cognition,[225] language,[225] verbal learning, and certain aspects of discourse skills[39,40] are associated with age of onset in children with complex partial seizures. For example, unrelated to lateralization of EEG findings, children with earlier onset of complex partial seizures have significantly lower scores on neuropsychological and linguistic tasks,[225] poor performance on long delay cued recall, and reduced monitoring and self-correction of errors in the organization of ideas during speech[39] than do those with later onset.

In summary, these findings suggest a dynamic interplay among brain development, age of onset, and maturation of cognition and language in children. They also highlight the importance of early treatment of seizures for optimal development of children's cognition, language, and discourse skills. Moreover, further studies are needed to determine if the higher rate of behavior problems found in studies of children with new-onset epilepsy[12] who had prior unrecognized seizures might represent the cumulative effects of early-onset seizures on the development of cognition, behavior, and language in these children.

Early-Onset Epilepsy Syndromes with Specific Behavioral, Cognitive, and Linguistic Impairments

Four early-onset epileptic syndromes, the West, Lennox-Gastaut, Landau-Kleffner, and continuous spike-and-slow wave syndromes and one disorder, tuberous sclerosis (TSC), are associated with behavioral social, cognitive, and linguistic impairments.

West Syndrome (Infantile Spasms)

The prototype for early-onset epilepsy syndromes is that of infantile spasms or West syndrome (Chapter 229). Seizure onset is usually by 4 to 6 months.[86] In the absence of seizure control, the developmental outcome for these children is usually poor both in the cognitive (see Caplan's review[38]) and behavioral domains, with varying degrees of impaired social relationships.[44,61,207]

Although the cause of the poor outcomes is still unknown, hypsarrhythmia, the severely epileptiform EEG found in this disorder, is present very early in development and has been implicated in the negative outcomes in these patients.[207] In fact, normalization of the EEG is thought to be the hallmark of successful treatment in this disorder.

Outcome studies in infantile spasms have mostly focused on cognitive rather than behavioral outcomes. Most studies show that a better cognitive profile at the onset (e.g., lack of significant regression), earlier treatment, and cryptogenic etiology are factors associated with improved cognitive outcome.[61,131,208]

More recently, early follow-up results from a large multicenter treatment trial[155] showed that the successfully treated subjects (those who showed cessation of spasms) had better scores on the Vineland Adaptive Behavior Scales than those who did not have cessation of spasms. Those with cryptogenic spasms also had better outcomes compared to those with symptomatic etiologies. But, in contrast to past results, there were no differences based on type of treatment, speed of normalization of the EEG, or time to treatment.

The behavioral or psychiatric abnormalities most strongly associated with infantile spasms are autism and autism spectrum disorders (ASD). According to a population study,[194] 6% of children with infantile autism had shown typical or atypical hypsarrhythmia with infantile spasms in the first year of life. Conversely, 13% of all children with infantile spasms were later diagnosed as suffering from infantile autism,[209] and several more showed severe degrees of autistic behavior. The autistic symptoms may be of a transient character in a large proportion of cases.[194,209] Another small prospective trial suggested that the etiology of the spasms was important in predicting later autistic behavior, with patients with symptomatic spasms showing a higher rate of autism.[8]

Given the high rate of infantile spasms in children with known genetic syndromes (e.g., TSC) and other brain abnormalities that are themselves associated with an increased rate of mental retardation and autism, this is undoubtedly a complex inter-relationship. The association with later autistic behavior in these patients, as well as the history of infantile spasms seen in ASD patients, points to the fact that epilepsy and, perhaps more importantly, epileptiform EEGs may play an important role in the development of autistic behaviors. Hyperactivity is another psychiatric disturbance seen in this syndrome. About two-thirds of those individuals with infantile spasms who have autism also meet criteria for hyperkinetic disorder. This is more than would be expected solely from the autism diagnosis.[209]

About 80% to 90% of children who had West syndrome in infancy will show cognitive delay either at the time of seizure onset or will be diagnosed with mental retardation later in childhood. Those with West syndrome, autism, and hyperkinetic disorders have mental retardation as often and of the same degree as children who do not. Thus, the well-known association of autism and hyperkinesis with cognitive impairment cannot in itself account for the link between these psychiatric disorders and West syndrome.

A meta-analysis of 67 studies showed that 17% of patients with infantile spasms developed Lennox-Gastaut syndrome (LGS).[120] The vast majority of these children will also appear severely withdrawn (autistic) and profoundly mentally retarded.

Lennox-Gastaut Syndrome

This syndrome is characterized by the early onset of intractable seizures (tonic, generalized tonic–clonic, atypical absence, atonic, and myoclonic) and bilateral slow spike-and-wave complexes on EEG (Chapter 241). Follow-up of children with LGS reveals that about half are retarded, in particular if they have minor motor seizures and multifocal independent spikes.[193] Treating clinicians all know that the behavioral aspects of this disorder are significantly impairing to the patient and family, but not much systematic study has been devoted to the area.[22] As in other cases of mental retardation, the children are sometimes irritable and hyperactive. These symptoms might decrease with seizure control or become exacerbated with some AEDs.

Landau-Kleffner Syndrome

Landau-Kleffner syndrome (LKS) is an acquired epileptic aphasia characterized by a gradual or rapid onset of aphasia that occurs in a previously normal child *plus* seizures and/or epileptiform changes on the EEG (Chapter 242).[142,257] The aphasia is often predominantly of a type referred to as “verbal auditory agnosia” (inability to understand spoken language).[205] All types of seizures have been reported in this syndrome, but nocturnal complex partial or simple motor may be most common.[21] The seizures are usually relatively infrequent and respond readily to AED treatment in most cases. EEG abnormalities frequently include focal or generalized spike-and-wave discharges that are activated during sleep.[161] At times, the patients meet criterion for electrical status epilepticus in sleep (ESES), with more than 80% to 85% of their sleep record consisting of spike-and-wave activity.[107]

The epidemiology of the disorder has not been properly studied. In clinical series, it appears to be about twice as common in boys as in girls. The etiology of LKS is unknown. There is a moderately increased rate of a family history of seizure disorder (10%–15%),[21] and the syndrome has been described in siblings. Taken together, these data suggest a genetic liability in some cases. However, it has also been described in conjunction with temporal lobe tumors,[186] cerebral arteritis,[199] and otitis media.[88] The possibility of electric dysregulation in several cortical areas as a pathophysiologic basis for this disorder has been emphasized by many authors, including Landau and Kleffner.[142]

The hallmark association is the language disturbance. This may fluctuate in severity, especially initially, when the impairment of verbal comprehension may first lead to suspicion of acquired deafness. Both receptive and expressive languages are affected.[236] Behavioral changes have also been reported. These include hyperactivity and inattentiveness,[107] psychosis and autistic behavior,[56] as well as oppositionalism, noncompliance, and frank aggression.[211,264]

LKS has been treated with traditional anticonvulsant medications,[56] corticosteroids,[147] intravenous immunoglobulin (IVIG),[173] and even epilepsy surgery[178] (see Tuchman[251] for review). Therapy that treats the EEG abnormalities has been associated with improved language[147,160] and behavior.[124,235] Robinson and colleagues reported that the duration of ESES was strongly correlated with language recovery, and that no child with prolonged ESES (>36 months) had a normal language outcome.[211] They also found that the severe behavioral disturbances in the acute phase were associated with frontal epileptiform activity during wakefulness.

On the other hand, the relationship between the seizures and/or the EEG abnormalities and the language and/or behavioral deficit is not completely clear. Many children do not begin to have seizures until after the period of regression, and some never have clinical seizures at all.[254] Some of the EEG abnormalities resolve spontaneously, and there are studies failing to demonstrate a correlation between EEG findings and the severity and course of the language impairment.[115,254,264] Van Hout[258] points out that, while the behavioral disturbances have been thought to be secondary to the severe language disturbance, there are cases where these disturbances precede the period of language regression. It has also been proposed that the epileptiform discharges are an epiphenomenon of the underlying brain abnormality rather than the actual cause of the language disturbance.[115]

Outcome in LKS is variable.[236] Seizure outcome is usually good, with resolution of seizures being the norm. But language and behavioral outcomes are more difficult to predict and range from muteness, persisting behavioral problems, and sometimes even intellectual impairment, to complete recovery in adult age. A considerable amount of variability of the clinical picture at the time of onset is supposedly a marker for relatively better outcome.

Continuous Spike-and-Wave Activity During Slow Sleep

Continuous spike-and-wave during sleep (CSWS) is the term most often used to describe a rare syndrome that strikes predominantly school-age males (Chapter 242). In 1971, Patry and colleagues[200] described the first patients, who presented with cognitive deterioration and the onset of epilepsy. The EEG showed a characteristic pattern of continuous spike-and-wave discharges during more than 85% of slow-wave sleep. The syndrome is now part of the epilepsy classification system as defined by the International League Against Epilepsy.[123] Individuals with the syndrome undergo severe language, behavioral, and global cognitive regression accompanied by epilepsy and the severely abnormal EEG pattern known as CSWS or ESES. Although the terminology is still not universal, most authors now use the term CSWS to refer to the clinical syndrome and ESES to refer to the EEG pattern.

As in LKS, this syndrome has its onset in childhood, shows a male predominance, and is associated with multiple seizure types. But unlike LKS, patients sometimes have preexisting developmental issues, the seizures are more frequent and harder to control,[236] the cognitive regression is significant and universal, and the behavioral difficulties are more prevalent.[79] Behavioral deficits include those similar to LKS (hyperactivity, inattentiveness, and aggression) but autism-like behavior has also been reported.[215] There are also motor impairments including weakness, dystonia, ataxia, and dyspraxia.[245] These more severe deficits in behavior, cognition, and motor function have been attributed to frontal and prefrontal dysfunction, perhaps as a result of the more frontal predominance of the EEG discharges.[33,215,236]

Outcomes are variable but overall are believed to be rather poor.[214] A recent study showed good behavioral outcome in all seven patients studied, but cognitive recovery (complete or partial) was seen in only three.[226] However, severe psychosis and lasting cognitive and motor impairment are also reported.[139,245]

Tuberous Sclerosis

TSC illustrates the complex relationship between brain malformations, epilepsy, behavior, and cognition. Epilepsy, both infantile spasms and partial epilepsy, and significant learning disability or mental retardation may be found in more than half the children with TSC.[52] Autistic disorder affects 25% to 50% of children with TSC.[25,94]

The severity of the neuropsychiatric problems associated with TSC seems dependent on the number and location of cortical tubers, although there are some inconsistencies in the literature. Bolton and Griffiths[25] found a strong association between temporal lobe tubers and autistic disorder. Positron emission tomography (PET) studies have shown decreased glucose metabolism in the temporal lobes, increased glucose metabolism in the cerebellar nuclei, and increased tryptophan uptake in the caudate nuclei.[7]

Age of seizure onset and seizure type also may be important. Both mental handicap and autistic disorder have been most consistently associated with infantile spasms and seizure onset before 2 years of age. Hunt and Dennis[122] found a history of infantile spasms in 40 of 45 children with TSC and autistic disorder.

The relative contribution of epileptiform discharges to autistic behavior remains a question. Tuchman and Rapin[255] found an association of autistic regression and epileptiform discharges in a population without TSC. Jambaqué et al.[125] treated seven children with TSC and infantile spasms with vigabatrin, with remission of the spasms in all the children. At follow-up, five of the six children with autistic symptoms showed improvement in behavior, and six of seven patients had improvements in developmental testing, thus suggesting some effect of epileptic discharges on cognitive function and behavior.

Thus, the brain areas that are dysfunctional in autism (and possibly certain variants of hyperkinetic disorder with cognitive impairment) may also be those that are affected in infantile spasms and in TSC with early symptom onset. According to one current theory for the development of autistic symptoms, dopaminergic (and other) nerve fibers arising in the brainstem and projecting onto structures in the striatum, medial temporal lobes, and prefrontal areas may be malfunctioning. Parts of these neural circuitries are also possibly involved in the pathogenic chain of events in infantile spasms. That they are often implicated in TSC has been known for a long time.[87]

Child Psychiatric Disorders Associated with Epilepsy

This section addresses the interface of behavior, cognition, language, social skills, and seizure variables as it pertains to psychiatric disorders commonly found in older children with epilepsy.

Autism, Asperger Syndrome, and Other Autism-Like Conditions

Autistic disorder, which occurs in about 1 to 2 children per 1,000, and about four times more often in boys than in girls,[77] is associated with a high rate of epilepsy, although reported rates have been extremely variable, with a range from 5% to 44%.[69,85,128,132,174,179,194,213,255,256,262,271] Seizure onset is usually either during the first 3 years of life,[194,262] or around the time of puberty.[80,82,218] New cases of epilepsy may also appear in early adult life.[53] The most common types of epilepsy encountered in autism are complex partial seizures, generalized tonic–clonic seizures, and combinations of seizures of various kinds.[53,194]

Autistic disorder is associated with mental retardation in approximately 70% of all cases.[76] Epilepsy is much more common in those individuals with autistic disorder who are also severely mentally retarded, but it is not a very rare phenomenon in those of low normal intelligence.[83,201,256]

The occurrence of epilepsy may also have a direct effect on language in ASD. The presence of a specific language profile (verbal auditory agnosia similar to that seen in LKS) predicts the presence of epilepsy and/or abnormal EEGs in autism.[256] Another, more controversial, association is that of language regression; conflicting reports exist regarding whether regression is or is not associated with a higher risk of epilepsy/EEG abnormalities.[128,132,148,152,156,183,184,213] For example, Tuchman and Rapin[255] found those with language regression had no increase in the frequency of clinical epilepsy, but did have significantly more isolated epileptiform EEG abnormalities compared with those without regression. Looking at this phenomenon in more detail, McVicar and colleagues[166,167] studied a sample with a high rate of ASD but that was ascertained for language regression; they showed that regression associated with pure language loss and occurring later was more frequently associated with epilepsy/EEG abnormalities than was more typical earlier autistic regression.

The variability in rates in the literature is likely due to sample heterogeneity. Factors such as differing ASD diagnostic classifications across the years,[58,210,256] variable epilepsy definitions,[85] differing age distributions in samples,[58,85,174,217,262,271] the inclusion of subjects with other specific genetic or neurologic disorders that are themselves associated with epilepsy,[201] as well as variability in the degree and type of associated cognitive or language deficits[20,253] could all influence rates of epilepsy in this population.

Asperger syndrome, which occurs in at least 3 to 4 out of every 1,000 children, and, again, much more often in boys than in girls,[67] may be associated with a slightly higher than expected rate of epilepsy,[47,81] but, to date, no large-scale epidemiologic study has been performed.

A group of autism-like conditions also exist that do not meet criteria for autism or Asperger syndrome. Some of these children are diagnosed as suffering from a “pervasive developmental disorder not otherwise specified” (PDD NOS). Others are never clinically diagnosed on the autism spectrum despite severe and typical problems, but receive diagnoses of “conduct disorder,” “attention deficit hyperactivity disorder,” or “hyperkinetic syndrome” instead, or have no other diagnosis than epilepsy (and possibly mental retardation). Just how frequently these autism-like conditions appear is not known. In a population study of all mentally retarded children with epilepsy, aged 8 to 12 years, several new cases of autism and autism-like conditions were found; these children had not been previously identified as suffering from a problem on the autism spectrum, and some had been missed in previous population studies of autism. Together they account for at least 1 in 1,000 children.[239] The gender ratio is almost equal in this group. It seems clear that the fact that they had early-onset epilepsy “deprived” them of recognition of the autistic symptoms. It is almost as though the specialists (often experienced child neurologists) treating these children for their epilepsy believed that the classical autistic symptoms evidenced were only to be expected in early-onset epilepsy and so required no additional diagnosis. The families, however, believed that, after the first year of diagnosis of the seizure disorder, they needed the most help with the autistic symptoms. However, no help was offered, because no diagnosis had been made. The children and their families were in a particularly difficult situation also because many of the AEDs (the benzodiazepines especially) tried appeared to contribute to enhancing the autistic symptoma-tology.

One of the many difficulties faced by the clinician caring for a family with a child affected by seizures and autistic behavior is to try to disentangle the effects of the neurologic from the psychiatric disorder. Many bizarre behaviors shown by children with autism are difficult to separate from clinical seizure activity. The empty, staring gaze might be mistaken for a “true” absence. Complex facial, hand, and arm mannerisms may suggest a complex partial seizure. Tics-like movements—very common in Asperger syndrome[67]—can be virtually impossible to separate from myoclonic jerks. The diagnostic problems are further enhanced by the fact that what is sometimes a symptom of epilepsy (for example, the upward turning of the eyes), may at other times be a stereotypic-catatonic phenomenon. An individual with an autism spectrum disorder may actually show the same—or a very similar—symptom as a consequence of epilepsy in one instance and of autism in another.

The EEG (including video monitoring) is sometimes very helpful in differential diagnosis, but this examination can be extremely difficult to accomplish in a child with severe behavior problems. A sleep EEG is sometimes all that can be obtained, but even the limited information one can get from this can be an essential part of the differential diagnostic work-up.

Literature also describes epileptiform discharges on EEGs in patients with autism without clinical seizure disorders. Tuchman and Rapin[255] reported 15% epileptiform sleep EEGs in patients without a history of epilepsy. Others report 20% to 30%[85,128,262] epileptiform EEG rates. Some evidence suggests that prolonged or overnight EEGs yield much higher rates of 46% to 60%.[49,252]

The exact association between the epileptiform discharges and the social, communication, and behavioral deficits seen in autism spectrum disorders is unknown. It is tempting to think there may be a causal relationship because that would have important implications for treatment. However, this has not been proven.

Pervasive Developmental Disorders Umbrella and the Spectrum Concept

The prevalence of epilepsy may be even higher in some of the other pervasive developmental disorders (PDD) umbrella disorders from the DSM. Rates in Rett syndrome range from 63% to 94%.[46,240] Patients also show an age-specific abnormal EEG pattern that may be related to the clinical disease progression.[86] Epilepsy rates of up to 77% are also seen in childhood disintegrative disorder.[179] Paroxysmal EEGs and ESES have been reported in higher numbers in CDD than in autism as well.[137,180,216]

These epilepsy and behavioral syndromes (e.g., autism with regression and epilepsy, other pervasive developmental disorders [Rett syndrome, CDD, developmental language disorder, LKS, CSWS, TSC]) all have in common characteristic seizures and/or epileptiform EEG patterns associated with specific behavioral, cognitive, and linguistic deficits. Thus, it has been the subject of much debate whether they could all exist along a single spectrum with a common underlying neuropathology and variable symptomatic presentation.[20,79,127,159,214,251,254,255] However, the exact role of the seizures and EEG abnormalities is still not understood. Given that the EEG pattern of ESES is seen in multiple epilepsy syndromes and not believed to be specific to the clinical syndrome of CSWS[259] it may be that the EEG pattern may affect behavioral, cognitive, and linguistic performance, regardless of the syndrome with which it is seen.

A better understanding of these phenomena is important both for elucidating pathophysiologic mechanisms underlying these disorders and for the development of proper treatment strategies. Indeed, some clinicians are adopting LKS and ESES treatment strategies, including drugs associated with significant side effects[251] and even epilepsy surgery,[185] for autistic patients with abnormal EEGs.

Attention-Deficit/Hyperactivity Disorder (ADHD)

Problems with attention and symptoms of attention deficit hyperactivity disorder (ADHD) are commonly reported in children with epilepsy. As previously described, children with TLE, particularly those with left-lobe TLE, were thought to demonstrate behaviors similar to ADHD (i.e., hyperactivity, distractibility, impulsivity) and conduct disorder (i.e., antisocial behaviors).[27,112,203,218,242] Using teacher and parent scales, Stores et al.[242] found that epileptic boys were more hyperactive and inattentive than nonepileptic boys. These two groups of subjects did not differ, however, on laboratory measures of attention, impulsivity, visual scanning, and distractibility.

Kinney et al.[130] concluded that epilepsy does not influence behavior adversely, because they did not find increased behavioral or learning disturbances in epileptic children with ADHD compared with nonepileptic children with ADHD. Hellgren et al.[101] found no increased rates of epilepsy in adolescents with a history of attentional deficits in preschool. However, the histories of these children indicated a significantly increased incidence of febrile seizures. Mitchell and colleagues[176] described decreased reaction time and inattention, but no impulsivity in children with epilepsy. These findings were unrelated to AEDs, IQ scores, duration of seizures, or seizure severity.

Reviewing ten recent studies of attention in children with epilepsy, Sánchez-Carpintero and Neville[219] found evidence of sustained attention deficits, particularly in children with complex partial seizures and BECTS. Deficits in divided attention were not found consistently. Studies using DSM criteria for the diagnosis of possible ADHD in children with epilepsy have reported prevalence rates of 30% to 40%.[63,102,227,247] There has been some suggestion that the inattentive type of ADHD may be more common than ADHD, combined type, in children with epilepsy.[63] As in the general population, children with epilepsy may have ADHD comorbid with other behavioral disorders. Caplan et al.,[43] in a study of children with complex partial epilepsy, found that 17% of children had disruptive behavior disorder (ADHD, oppositional defiant, or conduct disorders) and 23% had a disruptive disorder plus a mood or anxiety disorder.

Several risk factors are possible for attention problems in children with epilepsy. Neither gender nor seizure type have been consistent predictors. Early studies found more ADHD symptoms in boys with epilepsy, but in a recent study there was no difference by gender.[63] Similarly, although attention problems are often cited in children with partial complex seizures, some studies have found a higher rate in children with generalized seizures[102] or no effect by seizure type.[63] Seizure frequency may be important. Aldenkamp and Arends[4] found slowing of processing speed in children with frequent epileptiform discharges, and slow processing and attention problems in children with frequent nonconvulsive seizures. AEDs may be a factor. Attention problems have been reported with phenobarbital, benzodiazepines, and topiramate, but are less often found with newer AEDs.[26,153] ADHD may also be a risk factor for seizures. Hesdorffer et al.[106] found that ADHD, inattentive type, was a risk factor for subsequent unprovoked seizures, and Austin et al.[12] noted increased scores on the attention problem subscale of the CBCL at the time new-onset seizures were first recognized.

Treatment of attention problems in children with epilepsy is important. Williams et al.[267] have shown that problems with attention are better predictors of academic underachievement in children with epilepsy than are socioeconomic status, self-esteem, or measures of memory function. Although there have been concerns about the use of stimulants in children

with seizures, the more recent recommendations and studies of stimulants in children with epilepsy have shown that methylphenidate is effective for symptoms of ADHD, is safe in children with well-controlled seizures, and is probably safe in children with uncontrolled seizures.[73,90,93,244]

Affective and Anxiety Disorders

Although epilepsy markedly impacts children's coping resources,[13,64] only a few mood and anxiety disorder studies have been conducted in children and adolescents with epilepsy. They demonstrate depression and anxiety in 16% to 23% of patients, with more anxiety disorders in younger patients[42,192] and depression in older youth.[64,71] Evidence for suicidal ideation in 20% of children with epilepsy, most of whom have both affective and disruptive disorders,[42] underscores the potential morbidity of these comorbid diagnoses in this population. Moreover, the higher rate of depression, anxiety, and suicidal acts, together with the poor quality of life in adult epilepsy patients,[84,126] highlight the need for early detection and treatment of depression and anxiety disorders in youth with epilepsy.

In a large epidemiologic study, Davies et al.[55] found emotional disorders (e.g., mood and anxiety disorders) in 16% of children with epilepsy, a prevalence of more than twice that found in children with diabetes (6.4%) and four times the rate found in the general population of youth (4.2%) using a structured psychiatric interview. Based on the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS), Caplan et al.[42] found DSM-IV–based mood and anxiety disorder diagnoses in 33% of 171 children with epilepsy compared with 6% of 93 children without epilepsy. The most common diagnoses were anxiety (63%) and comorbid mood and disruptive disorders (26.1%), while only 5% had depression and 5% met criteria for both anxiety and depression.

Studies using the self-report Children's Depression Inventory[136] found depression in 25% of adolescents with epilepsy,[64] 26% of 7- to 18-year-old epilepsy youth,[71] as well as more depression in 12- to 18-year-old compared with 9- to 11-year-old children with epilepsy.[192] Although Ettinger et al.[71] reported anxiety in 16% of 7- to 18-year-old patients with epilepsy, both Caplan et al.[42] and Oguz et al.[192] found that anxiety, not depression, was more common in young children with epilepsy.

Inconsistent findings on the association of seizure variables with depression and anxiety disorders in youth with epilepsy could reflect methodological differences across studies, such as inclusion of different sample sizes and epilepsy variables, as well as use of different mood and anxiety instruments. Whereas several investigators report no association with seizure variables,[42,55,64] some find a relationship with duration of epilepsy and number of AEDs[192] and type of AED.[29,30] More children with complex partial seizures have depression than do those with absence epilepsy, who, in turn, have more anxiety disorders.[42]

Mood disorders also occur more frequently in children with epilepsy who have mental retardation[31,55] and lower average IQ scores.[42] Patients with comorbid psychopathology, depression and anxiety disorders, or disruptive and depression/anxiety disorders have significantly lower full scale and verbal IQ scores than do those with either depression or anxiety disorders alone.[42]

Finally, the association with demographic variables, such as gender and age, is similar to that described in the general population of youth with depression and anxiety disorders.[5,75] Thus, Dunn et al.[64] demonstrated more depression in adolescent girls with epilepsy. Younger children with epilepsy have more anxiety disorders, whereas adolescents have more depression.[41,192]

Psychosis

A recent epidemiologic study demonstrated a higher rate of a schizophrenia-like psychosis in epilepsy than in the general population.[204] They also found an association with both a family history of schizophrenia and a family history of psychosis. Unlike adults with epilepsy, postictal psychosis[189] has been rarely described in children. In contrast, about 10% of children with TLE[150] and complex partial seizures[37,41] have an interictal schizophrenia-like psychosis. These children present with hallucinations, delusions, and formal thought disorder, no negative signs, and poor seizure control.

Nonepileptic Seizures

Psychogenic nonepileptic seizures (PNES) can reflect a conversion disorder, a factitious disorder, malingering, or parental misinterpretation of the child's symptoms. The marked short- and long-term psychological morbidity associated with misdiagnosis of these disorders emphasizes the importance of recognizing these entities in youth with epilepsy.

Conversion Disorder (Pseudoseizures, Psychogenic Seizures, Nonepileptic Seizures)

In a conversion disorder,[8] the child's seizures or convulsions suggest that he has epilepsy and suffers significant distress or impairment from these attacks. Appropriate investigations do not confirm the epileptic basis for these episodes. Psychological factors, in the form of conflicts or stressors, however, initiate or exacerbate these attacks. The child with a conversion disorder does not intentionally produce or feign the seizures. This disorder is found in children and adolescents with normal IQ scores,[171] albeit varying degrees of learning difficulties, and in children with mild to moderate retardation.[116] Girls are affected more than boys,[74,92] and the incidence increases with age. The disorder is more common in children with a diagnosis of epilepsy and in those without epilepsy who have some exposure to epilepsy through a family member, a neighbor, or a friend.

The symptoms most commonly found in children and adolescents with PNES include: slow onset of seizures with a gradual build-up, prolonged duration, the absence of bodily injury or loss of continence, thrusting, jerking, or shaking motions rather than repeated fast flexion and extension, and the absence of a postictal period.[273]

These children often have difficulty expressing negative feelings, such as anger, or their expression of these feeling are unheard or minimized by family members. Social difficulties, strife with parents, learning difficulties,[234] or sexual abuse can give rise to the negative feelings associated with the primary conflict. The child's epileptic events increase the amount of attention the child gets and decreases demands, such as going to school. By reinforcing the child's symptoms, this secondary gain prevents the child from dealing with his problems in an adaptive manner. Although concerned about their seizures, these children minimize or deny any concern about the problems and difficulties in their lives even when these are significant.

Given the maladaptive nature of the symptoms of this disorder, a definitive diagnosis is needed as soon as possible. Wyllie et al.[273] reported a good outcome in 14 of 18 children and adolescents diagnosed with NES who had their symptoms for a mean duration of 7 months.

Factitious Disorders

Factitious disorders[8] involve intentional production or feigning of seizure symptoms specifically to assume the sick role. Unlike malingering, there are no external incentives for these

behaviors, such as avoiding a legal responsibility like going to school. More commonly, the parent rather than the child has the factitious disorder and imposes a diagnosis of epilepsy on the child, as in Munchausen syndrome by proxy. Many of the reported Munchausen syndrome by proxy cases have presented with seizures.[140,165,212,272] In Meadow's series of 76 cases, 32 children had a primary diagnosis of epilepsy. In 21 cases, the mothers fabricated the symptoms of the illness.[168,170] In 11 cases, the mothers caused seizures by suffocation, carotid sinus pressure, or use of drugs. Sixteen of the children in Meadow's sample had medical symptoms other than seizures. In Rosenberg's series, 42% of the 117 cases presented with seizures.[212] It is important to note that Munchausen syndrome by proxy can also occur in a child with genuine epilepsy.[170]

Unlike other disorders, clinicians do not usually observe the seizures of children with epilepsy and need to rely on parental report for a description of the clinical manifestations of the child's seizure.[165] Because it is difficult to confirm parental reports, it is relatively easy for a parent to fabricate a history of seizures and a lack of response to AEDs in the child.[168]

These cases present with a history of uncontrolled seizures; an inconsistent description of the child's seizures; repeated normal EEG recordings; repeated consultation with different physicians, particularly if the physician determines that no evidence suggests that the child has epilepsy. Other than the parent, no medical or school personnel have observed the child have a seizure. The mothers of these children,[165] sometimes employed in the healthcare field, are often very knowledgeable about epilepsy, EEG findings, and the use of AEDs. They are concerned and devoted to the child, and appear at ease in the hospital, even forming close relationships with hospital staff. The fathers usually are absent or play no role in the sick process, so that they appear to be in "passive collusion"[170] with the mother. In some cases of Munchausen syndrome by proxy, the father has been described as the perpetrator.[158]

Misinterpretation of Children's Behavior

Misinterpretation of the child's behaviors as epileptic seizures can reflect parental anxiety.[169] Several investigators have shown that the primary reason for nonepileptic events in children, particularly those with impaired intellectual function, was misinterpretation of behavior by parents and caretakers.[60,171,187] These behaviors included staring episodes, abnormal reactions to environmental stimuli, and repetitive movements, such as rocking, shaking, or arm waving. Unusual movements based on abnormal muscle tone were also often misinterpreted as seizures.[187]

Unlike Munchausen syndrome by proxy, these cases usually present with fewer episodes. In addition, the parent's main concern is that their child recovers rather than need repeated medical examinations and procedures.

Summary And Conclusions

In summary, epilepsy is a chronic and episodic disease of the brain that can affect the child's emotional, cognitive, and linguistic functioning and, therefore, his intrapsychic and interpersonal functioning within the family, with peers, and in the academic and social environment of school. The response of the child's family to these stressors affects the way the child copes with the disorder. In addition to these psychodynamic and social factors, seizure-related (i.e., type of seizure disorder, seizure control, seizure duration, number and blood level of AEDs) and developmental factors (i.e., age of onset of seizures, level of cognitive and language function) affect the child's functioning and ability to cope with his illness.

The research of the past decade has demonstrated that epilepsy is a biopsychosocial disorder and that children with epilepsy have comorbid difficulties with behavior, cognition, and language. They have also shown that parents shoulder a heavy burden. Studies are sorely needed to determine optimal approaches for early identification and treatment of these comorbid problems, as well as how best to implement them.

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Chapter 211

Suicide: Incidence, Psychopathology, Pathogenesis, and Prevention

Dietrich Blumer

Introduction

Suicide among patients with epilepsy has been widely recognized as a serious problem. In modern times, its frequency appears to approach the frequency of death from seizures. However, the frequency of its incidence is still debated, its psychopathology and pathogenesis remains unclear, and no proper method of prevention has been established.

Review of Literature

Frequency of Suicide

In a recent paper, Jallon[28] reviewed the significantly higher mortality of patients with epilepsy by status epilepticus, sudden unexplained death, and suicide, compared with the general population. He expressed concern that the reports on suicide were based on small samples from different populations and from highly selected groups of patients and used different methods of analysis. However, an analysis of the populations that differed in the numbers of suicide and an investigation (published in 2005) of the frequency of suicide in 29 cohorts of patients with epilepsy[44] provide answers to this concern.

Suicide is a rare event, occurring only slightly more than once among 10,000 persons annually in the United States.[41] In a review of completed suicide in manic-depressive patients, Goodwin and Jamison found a mean of 19% of deaths secondary to suicide in this population.[22] A similarly high suicide rate among patients with epilepsy has been documented: In a Danish study,[26] 164 of 2,763 patients with epilepsy suicided (an excess mortality rate of 273% compared with the number of deaths expected in Denmark); the case material included all adult patients discharged with the diagnosis of epilepsy at four neurologic clinics over 14 years, and any patient with a handicap other than epilepsy was excluded from the study. Although epilepsy was the immediate cause of death in 26%, suicide was the second leading cause of death in 20% (an excess mortality rate of 300%) at an average age at death of 32 years. According to eight reports, death by suicide occurs in 5% of patients with epilepsy, compared with 1.4% in the general population.[36] Based on a wider review of the literature, a fivefold increase in suicides among patients with epilepsy over the rate in the general population was found among those attending special clinics and was magnified to as much as 25-fold among patients with temporal lobe epilepsy (TLE).[1] A study by Hauser et al.,[24] on the other hand, included a general population of patients with epilepsy followed from the time of diagnosis, and not from the time of registration in a neurologic clinic; their patients were less severely affected, and they reported no suicides in excess of expected numbers. Suicide appears to represent a serious problem not in the general population of patients with epilepsy, but among those with more difficult epilepsy who require treatment in specialty clinics.

Since Jallon's review, Pompili et al.[44] investigated 29 studies of suicide in epilepsy, comprising 50,814 patients, of whom 187 committed suicide. Their meta-analysis showed that suicide in epilepsy is indeed more frequent than in the general population, but with significant exceptions. A study by Cockerell et al.[12] included patients with newly diagnosed or suspected epilepsy who were ascertained when attending a general practice, with a median follow-up of less than 7 years; a single suicide was registered among 792 patients. As in the study by Hauser et al.,[24] few severely affected patients were included. In contrast, the largest study cited by Pompili et al., 10,739 patients from our Epi-Care Center,[8] registered only five suicides (a rate lower than in the general population), not because of lack of severity of the epilepsy in the population, but because all patients with psychiatric complications were treated, at intake or as soon as needed, with proper psychotropic medication. This study will be fully reviewed, for a better understanding of suicide in epilepsy and to establish specific guidelines for its prevention.

Psychopathology Associated with Suicide in Epilepsy

The generally difficult psychosocial circumstances of patients with chronic epilepsy have often been considered the leading factor responsible for their elevated suicide rate, more important than the presence of psychiatric illness or the availability of drugs.[15] However, in general, psychiatric illness has been identified as the nearly universal antecedent of suicide, and psychosocial circumstances cannot be considered causes for suicide.[35,41] Very few reports have attempted to clarify the nature of the psychiatric disorder that may lead to suicide among patients with epilepsy.

Nilsson et al.[42] pointed out that studies are lacking in which persons with epilepsy who have committed suicide are compared with relevant controls to identify risk factors for suicide. In their case-control study of risk factors for suicide in epilepsy, they compared 26 cases of suicide and 23 cases of suspected suicide with 171 controls, within a cohort of 6,880 registered with a diagnosis of epilepsy in the Stockholm County Inpatient Register. They found a ninefold increase of suicide with mental illness and a tenfold increase in relative risk with the use of antipsychotic drugs. They arrived at a profile of the epilepsy patient who commits suicide as one with early onset, but not necessarily severe, epilepsy and with psychiatric illness (depression, psychosis, substance abuse).

Mendez et al.[40] studied the causative factors for suicide attempts by overdose in 22 patients with epilepsy (from 711 patients hospitalized for a suicide attempt) and concluded that interictal psychopathologic factors were of primary importance. A comparison of suicide attempts among patients with epilepsy and comparably handicapped controls with other chronic disabilities found that 30% of patients with epilepsy had attempted suicide, as compared with 7% of the controls.[38]

In 1992, Mendez and Doss[39] reported on the suicides in a substantial population of patients with epilepsy *and* included clinical details of all fatal outcomes. They documented the neuropsychiatric aspects of the four patients who died by suicide out of 1,611 patients with epilepsy followed in a neurology clinic over a period of 8 years: two male patients with chronic psychosis, depressive moods, and good seizure control; one male patient with brief psychotic episodes associated with confusion and increased bitemporal spikes and diffuse slowing on electroencephalogram (EEG) in the absence of seizures; and one female patient with episodes of profound ictal and postictal depression who suicided after three witnessed staring spells. The patient with brief psychotic episodes and one of the patients with chronic psychosis experienced voices commanding them to commit suicide. All four patients had suffered from complex partial seizures since childhood and committed suicide by medication overdose at a time when their seizures were controlled, except for the patient who suicided in a state of postictal depression.

Fukuchi et al.[17] reviewed the case records of all outpatients of two epilepsy centers who had died. Patients in one center were followed for 10 years and in the second center for 7 years. Those who had unclassified epilepsy or who died as the result of an underlying disease (such as neoplasm) were excluded. More than 4,000 subjects were reviewed, and the records of 43 deceased patients with well-classified epilepsy were analyzed. Suicide occurred in six patients (14% of the deaths), all with TLE, and three suicided by throwing themselves in front of an oncoming train in the midst of an episode of postictal psychosis. The authors noted the agreement of their findings with those of Mendez and Doss.[39] While providing fewer details, they concluded that most suicides in epilepsy were the result of an immediate causal relationship with ictal or interictal epileptic manifestations. The authors referred to reports of violent behavior directed outward following complex partial seizures, and proposed that this violence may eventually turn into a paroxysmal self-destructive impulse.[20,31]

Suicides After Successful Treatment of Seizures and After Surgical Treatment of the Epilepsy

For an understanding of the pathogenesis of suicide in epilepsy, evidence for the role of predominant inhibition ("forced normalization")[21,33,34,51] must be reviewed.

In 1969, Janz[29] stated that suicide does not occur among patients with severe epilepsy but does occur not infrequently among those patients who have just become free from seizures. With the guidance of Janz, Haltrich[23] studied the causes of death among 909 patients with epilepsy who had been treated at the neurology clinic of a German university during the preceding 8 years (1946–1953); his report includes a large number of suicides with highlights of their psychopathology. Of the 83 patients with symptomatic epilepsy, 51 died from brain tumors. The 11 recorded suicides all occurred among the 78 patients with cryptogenic epilepsy, and at 14.1% surpassed any other cause of death in this group; eight patients (10.3%) died from seizure status and six patients (7.7%) from single seizures. Among the 11 suicides, eight patients had complex partial seizures. Increased irritability was reported in six of the seven males (four with episodes of violence) and in one of the four females; four patients had a history of previous suicide attempts, and another three patients had experienced depressive moods with or without suicidal thoughts. Only one patient suicided during a psychotic state after three previous suicide attempts in psychotic or dysphoric states; he had been violence-prone and was the only patient requiring institutionalization among the 11 who suicided. Haltrich included three later cases of suicide when he reported that the 14 patients had responded well to treatment of their seizures; at the time of suicide, three had experienced only minor attacks, seven only very rare or no major seizures, and four had rare or no seizures of any type.

Taylor and Marsh[49] reported on the occurrence of suicide among 193 patients who had undergone temporal lobectomy and who were followed from 5 to 24 years. Of 37 deaths, nine were by suicide (24.3%). Including an additional six patients who died in unclear circumstances would have raised the suicide rate observed from 25-fold to 50-fold of that expected.[48] Five of the nine who definitely suicided had been rendered seizure-free by the surgery. The authors did not describe the mental state of the victims and merely documented the very high risk of suicide in their particular population.

In another series of surgically treated patients with epilepsy, Hennessy et al.[25] reported only one suicide among 20 deaths in their cohort of 305 consecutive patients who had TLE surgery over a 20-year period. A second patient ran onto a road and was killed by a passing car; both patients were seizure free. The authors suggested that the early series of Taylor and Marsh,[49] with its much higher postoperative suicide rate, had included many patients referred from the Maudsley psychiatric institution. However, the origin of the populations of patients surgically treated and with reports of postoperative mortality is usually not well defined. A large group surveyed from 1928 to 1973 by Jensen[30] includes 2,204 patients who had unilateral temporal lobectomy, with 164 postoperative deaths: due to epilepsy in 26%, suicide in 20%, and accidents in 11%; no details were provided about the suicides.

Of interest is the report by Bladin[2] who reported, with remarkable details of the psychosocial outcome, the results after temporal lobectomy of a series of 115 consecutive patients. They were followed as closely as possible for a mean of 4 years after temporal lobectomy. Five patients showed significant episodes of depression after the operation. In three of them, recognition and antidepressive therapy produced prompt improvement. Another patient, who was seizure-free, was rehabilitated by friends in a religious organization after two suicide attempts. The fifth patient, who lived at a distance and could not participate in the routine postoperative follow-up, was also free of seizures yet committed suicide following the unexpected death of mother and sibling. Three patients showed psychotic episodes more than 3 months after the operation and responded to appropriate therapy, including a neuroleptic. Postoperative anxiety was noted in about half the patients and responded to counseling, medication, or brief hospitalization. Increased sexual drive was reported only upon optimal seizure control. Bladin's report is unique in its report of the use of psychotropic medication for patients with epilepsy.

Psychopathology, Pathogenesis, and Prevention of Suicide: the Study of Patients Treated at the Epi-Care Center

In Chapter 205 on affective disorders of epilepsy, we concluded that the pre-modern psychiatrists, who commonly observed patients with epilepsy on a daily basis, were correct when they

recognized the interictal dysphoric disorder with its intermittent and pleomorphic symptomatology as the predominant specific psychiatric disorder of chronic epilepsy. The interictal dysphoric disorder includes episodes of anxiety, fear, elation, insomnia, anergia, pain, explosive irritability, and depressive moods that may be intense and associated with suicidality. The disorder, in its entirety, is well treated with low doses of antidepressant medication. Subsequent to the detailed report of our experience with suicide in a large population of patients attending our epilepsy center, the psychopathology, pathogenesis, and prevention of suicide in epilepsy will be discussed.

A total of 10,739 patients with epilepsy were treated at the Epi-Care Center in Memphis during a 12-year period (1987–1999). The population included a large number of referrals from the mid-South area and beyond. About 900 patients were surgically treated during this period. The comprehensive professional team of the Center consisted of a neurologist, neurosurgeon, electroencephalographer, neuropsychologist, and the same psychiatrist (D.B.) during the entire period. The tasks of the psychiatrist included evaluating all patients admitted for intensive neurodiagnostic monitoring (as candidates for surgical treatment of medically intractable epilepsy or for clarification of the differential diagnosis between epilepsy and nonepileptic seizures) and of every patient at the center who was judged by the team to have psychiatric difficulties. Every patient in need of psychiatric assistance was followed at the Center with the appropriate psychopharmacologic and supportive treatment regardless of geographic distance, as long as the patient and family were able to come for return visits. Patients who required psychiatric hospitalization were admitted under the care of the team psychiatrist in the same hospital where the team admitted its patients for evaluation and treatment of the epilepsy. The presence of a team psychiatrist at the Epi-Care Center and the effectiveness of the psychotropic treatment employed assured prompt referral of patients with psychiatric complications, who were not routinely evaluated by the psychiatrist, for early treatment beyond antiepileptic treatment. Neuropsychological testing of all patients admitted for intensive monitoring and of a large number of outpatients, as well as a weekly case conference, greatly facilitated the teamwork and the referrals to the psychiatrist for early treatment.

The gradual development of a standardized psychiatric evaluation by a comprehensive questionnaire for seizure patients using a semistructured interview of patients and next-of-kin and of an increasingly effective psychopharmacologic treatment has been reported elsewhere.[5,9,10,11] Initially, most patients with psychiatric complications of their epilepsy were treated by adding a modest dose of tricyclic antidepressant to the antiepileptic medication. With the development of treatment by double antidepressant medication (tricyclic plus serotonin-specific reuptake inhibitor) and the addition, if necessary, of a small dose of an atypical antipsychotic drug (risperidone), it became possible to treat successfully the vast majority of patients with any degree of psychopathology, including psychoses and suicidality.

The death of a patient with epilepsy at a treatment center is a memorable event. The number of patients who suicided was ascertained from medical records and the combined memories of the treatment team. The Epi-Care Center was the major center for treatment of epilepsy in the Mid-South and had a policy of careful follow-up of all patients. Thus, the death of one patient who had moved to a distant state about 1 year before her suicide (case 3) is included, as we had attempted to remain helpful.

Results

A total of five (four males, one female) of 10,739 patients attending the Center during the 12-year period committed suicide. The circumstances of these five treatment failures are reported here.

Case 1 (1989)

This male patient had had seizures since age 10. Following a 6-month marriage in late adolescence, he married two more times. His second wife had suicided following childbirth after 1 year of marriage; at that time, the patient became suicidal himself and required 2 months of psychiatric hospitalization. During the third marriage that lasted 4 years, he became suicidal when his wife left him with their child; he blamed his bad temper for the final breakup that had occurred 1 year prior to referral to the Center. His seizures became increasingly more frequent, occurring as often as three times daily. He was then treated by right temporal lobectomy at age 32.

After the operation, he experienced epileptic seizures on only two occasions after missing his medication. There had been a brief episode of feeling suicidal shortly after surgery, but soon he became enthusiastic about the success of the surgery, volunteered to talk to patients who were candidates for surgical treatment of their epilepsy, was active in the local chapter of the Epilepsy Foundation, and was working on a book about epilepsy. When he experienced an episode of dissociation with amnesia 12 months after his surgery, he was scheduled for psychiatric evaluation. Shortly thereafter, he developed frequent nonepileptic seizures.

He was first evaluated psychiatrically at age 33, 14 months after surgical treatment. He presented as an intensely emotional individual who felt he had a special mission in life and reported big mood shifts from very happy to very sad. He was at first treated with doxepin because of insomnia, then with the better-tolerated imipramine to 100 mg at bedtime, and he showed improvement. However, after 6 months of monthly visits, he felt accused of having “fake seizures,” abruptly severed his relationship with the Center, moved to a neighboring state, and discontinued the antidepressant medication. On two occasions, at 7 and 11 months after he had discontinued his visits, he returned to the Center for only neurologic follow-up visits, stating that he had no seizures and was doing well. Six months after his last visit, he called the Center from out of state. He stated that his girlfriend had left him, he feared going off in a rage attack, and for the past 8 days he had been driving around with a rope in his car looking for a tree to hang himself. He refused any help and, 10 days later, 3 years after the operation, committed suicide by hanging.

Comment: This patient had a dysphoric disorder with marked depressive moods, irritability, and insomnia. The occurrence of nonepileptic seizures is not uncommon in patients who have become free of seizures after surgery.[13] We did not have the experience to deal with this predicament at that time; the patient became noncompliant and discontinued the antidepressant medication.

Case 2 (1990)

This male patient had had frequent seizures since the age of 6 weeks. He had three to five seizures per week, lived with his parents, and was active in church life. When he became unable to work because of back pain, he became depressed, with marked anergia and recurrent episodes of feeling suicidal, which required a brief psychiatric hospitalization.

Four months after onset of his pain, at age 34, he was evaluated at the Epi-Care Center. No pathology was found for his back pain, but a right temporal tumor was detected, and a right temporal lobectomy for a ganglioglioma was carried out.

Subsequent to the operation, he remained seizure free. At discharge, he was prescribed imipramine but discontinued the drug when it did not help his insomnia. He was referred for psychiatric follow-up near his home. Initially, he seemed improved

but then continued to be depressed and preoccupied with his back pain. The psychiatric treatment consisted of counseling, fluoxetine, and a period of inpatient treatment 8 months after the operation. One year after the operation, he drowned himself. His family did not understand why this happened.

Comment: This patient had a dysphoric disorder with depressive moods, anergia, insomnia, and pain. He was treated psychiatrically near his home and, at that time, we did not have a more effective treatment to initiate or to recommend.

Case 3 (1991)

This female patient had had seizures since grammar school but was diagnosed only at age 18. After 18 years of education, she married but remained childless. She made one suicide attempt at age 38, and had several car accidents due to seizures.

She became a patient at the Epi-Care Center at the age of 43, initially for psychiatric treatment. Her main complaint was chronic pain with anergia and depressive moods of at least 5 years' duration; she also had insomnia and was hypochondriacal. Her primidone was phased out, and her pains and dysphoric symptoms vanished when the combination of carbamazepine and amitriptyline at 100 mg was prescribed. When her husband insisted on divorce, she regressed and had to be hospitalized for 1 month with a mixed manic and depressive state with recurrence of her pains. She again improved with the temporary addition of lithium.

Her seizures occurred perhaps every few weeks and, following finalization of the divorce, she had a right temporal lobectomy at age 45. The specimen showed hippocampal sclerosis, and she remained seizure-free. Six months after surgery, she felt great and decided to move to her far-away home state, where she did not find a supportive environment. Her pains and depression resumed, even though she maintained an antidepressant (trimipramine 100 mg daily). She returned to her original neurologist, who replaced the carbamazepine with primidone when she was found to have a low sodium level. At the age of 46, 18 months after surgery, she committed suicide by shooting herself.

Comment: This patient had a dysphoric disorder with depressive moods, anergia, insomnia, and pain. She did not seek local psychiatric help after her departure from the Center. The reintroduction of primidone possibly made her depressive moods worse.

Case 4 (1998)

This male patient began to have seizures at age 10, and was treated at the Epi-Care Center beginning at age 23. He underwent a left temporal lobectomy that showed hippocampal sclerosis, but he continued to have daily (although shorter) complex partial seizures. A further resection of the left hippocampus 6 months later was similarly ineffective. He was a serious and very religious young man, who admitted to some temper but showed no troublesome dysphoric symptoms at the time of his presurgical psychiatric evaluation at the Center, and he was not followed psychiatrically. He worked for 2 years after the operation and, after a failed marriage, resumed living with his parents. Over the subsequent 6 years, he was treated with all the latest antiepileptic drugs without any success until his seizures finally became controlled by the combination of zonisamide, gabapentin, and phenytoin. The subsequent follow-up was entirely by phone contact with the patient and his family. He resumed work and reported enjoying it. Following an unprecedented outburst of rage toward his parents 2 weeks after he had become seizure-free, he began to live in separate quarters on the family property. Antidepressant treatment suggested by our neurologist was not felt necessary by the family since he did well at work. Three months after becoming free of seizures, he was found dead, having inflicted a gunshot wound to the abdomen.

Comment: The first symptom of a dysphoric disorder in the form of an unexpected outburst of rage was reported after he had become seizure-free. There was no further warning or call for help.

Case 5 (1999)

This male patient suffered a head injury at age 6 and started to have seizures at age 17. He worked until age 35, and went to church faithfully. After age 41, he attended a family therapy center for a few years for depression and marital conflicts and took a drug overdose at the time of his divorce at age 45.

At age 48, he began treatment at the Epi-Care Center for complex partial seizures that tended to occur several times daily. On first evaluation, he was recognized as having a dysphoric disorder with intermittent depressive moods and occasional suicidal ideas, anergia, irritability, and anxiety. He refused antidepressant treatment. An anterior partial callosotomy early in his treatment at the Center did not improve the high daily frequency of his seizures.

At age 50, he married a domineering woman who had a history of skull fractures inflicted by her former husband and who had been treated for her own violent temper. Shortly thereafter, the couple elected treatment by vagal nerve stimulation (VNS) for his seizures, and he was reevaluated psychiatrically. Both the patient and his new wife admitted to being “hotheaded,” but they adamantly refused to comply with advice given for the treatment of his dysphoric disorder. His seizure frequency gradually decreased over the initial 15 months of VNS until it diminished to only two complex partial seizures per day. At that point, the VNS was increased. Four months later, we learned from his local physician that he had become seizure-free for the first time since the onset of the epilepsy 35 years earlier and that he had killed his wife and then himself.

Comment: This patient had a dysphoric disorder with depressive moods, anergia, anxiety, and irritability. Whereas irritability to the point of paroxysmal outbursts of anger is a key symptom of the dysphoric disorder, dysphoric patients, like the majority of patients with epilepsy, tend to be very conscientious and often highly religious, and their outbursts are followed by genuine remorse. Their extreme rage tends to be turned against themselves, and homicide, as opposed to suicide, is an exceptionally rare occurrence in epilepsy.[6]

Discussion

The five suicides among the population of 10,739 patients seen at the Epi-Care Center over the period of 12 years share a surprisingly common pattern. All had a history of early onset (mean age 9.5 years) of long-standing complex partial seizures (mean duration 29 years) with very high (often daily) seizure frequency in all but one. Suicide occurred in all patients after a short interval (3 months to 3 years, mean 13 months) of having obtained full control of seizures for the first time by temporal lobectomy (three patients), medication, or VNS. All had symptoms of an interictal dysphoric disorder, and three of the four males had a significant problem with episodes of violent anger. All but one (case 4) had a history of previous suicidal moods or suicide attempts, but in three of the five, the suicidal act was precipitate and not anticipated at the time. All had experienced worse psychosocial predicaments in the past than were present at the time of completed suicide.

The four patients from the series of Mendez and Doss[39] likewise all had an onset of epilepsy in early life, with a mean duration of the seizure disorder of 25 years, and two of the three patients who committed suicide in a psychotic state were under good seizure control. The third patient suffered from unusual psychotic episodes that coincided with the presence of increased electroencephalographic epileptiform potentials in the absence of seizures; he will be discussed in the section on pathogenesis. The fourth patient suicided in a state of postictal depression. The patients from the series of Taylor and Marsh[49] who suicided after temporal lobectomy were reported without any details of their psychopathology, but five of the nine had been rendered seizure-free after surgical treatment.

Among the three series, 12 of 18 patients committed suicide after a long-standing seizure disorder was under control. This finding confirms the early reports by Janz[29] and Haltrich.[23] Janz was already well aware of the finding of forced normalization noted by Landolt[34]: Control of seizures may usher in dysphoric or psychotic disorders. Particularly notable is Haltrich's finding that six of the seven male patients had been markedly irritable, with a majority suffering from episodes of violent temper. The same finding is evident in three of our four male suicides.

Suicide among patients with epilepsy clearly is not the result of psychosocial difficulties caused by having seizures, but rather occurs in the presence of significant interictal and at times postictal psychopathology. Prior to reviewing the pathogenesis of suicide in epilepsy, the phenomenology of the interictal and peri-ictal psychopathology and their relationship to suicide must be clarified.

Psychopathology Associated with Suicide in Epilepsy

Premodern psychiatrists recognized an intermittent and pleomorphic disorder, termed the *dysphoric disorder*, as the most common psychiatric disorder of epilepsy. The interictal dysphoric disorder is a distinct disorder that had to be rediscovered.[6] One of its key symptoms—intermittent depressive mood—is associated with the episodic suicidal moods of patients with chronic epilepsy, primarily those with mesial TLE.[3,6,9,18,19,37] Kraepelin[32] precisely described the dysphoric disorder of patients with epilepsy: Dysphoric episodes present with depressive moods ("very frequently with utter disgust of life and suicidal bent"), irritability, anxiety, headaches, insomnia, but also with euphoric moods. The dysphoric episodes occur without external triggers, with rapid onset and termination, and recur fairly regularly in a uniform manner in the absence of clouding of consciousness. Dysphoric symptoms commonly can be observed as prodrome or aftermath of an attack but, most important, they appear as phenomena independent of the seizures, as interictal dysphoric episodes, with a frequency varying from every few days to every few months. As a rule, the dysphoric state lasts from 1 to 2 days but may dissipate after just a few hours.

Based on our own observations, we added anergia and phobic fears to Kraepelin's six key symptoms of the dysphoric disorder and have defined it by the presence of at least three of the eight key symptoms, each present to a troublesome degree.[9]

The risk of suicide in patients with epilepsy is primarily associated with the often sudden episodes of intense depressive mood of the interictal phase; therefore, suicide in epilepsy tends to occur in a precipitate manner. As noted by Haltrich[23] and in our own series, the occurrence of marked irritability with outbursts of violent behavior appears to represent a particular risk factor for suicide among male patients. As noted early by Kraepelin, the dysphoric symptoms also tend to occur peri-ictally, during the prodrome or aftermath of a seizure. The postictal phase in particular may be associated with marked depressive mood.[4] A high suicidal risk has been observed in patients who experience ictal depressive mood that extends into the postictal phase for a period of 1 hour to 3 days. Williams[52] reported 21 such cases among his 100 patients with ictal emotional experience, and five of the 21 patients had made suicide attempts during their postictal phase. The fourth case of Mendez and Doss represents a well-documented postictal suicide.[39]

As noted earlier by Kraepelin, interictal psychoses tend to develop as expansions of interictal dysphoric disorders.[32] The dysphoric disorder persists during the psychotic state, and suicidal depressive moods may occur in the course of an interictal psychosis when reasoning is impaired. Presence of the hallucination of voices commanding a patient to suicide represents a particular risk.

Pathogenesis of Suicide in Epilepsy

The treatment of seizures during the first four decades of the 20th century consisted chiefly of potassium bromide; phenobarbital, available since 1913, was widely shunned by psychiatrists because of its psychotoxic effects. In a modern era that considers epilepsy a neurologic disorder and has focused with growing success on the control of seizures with an expanding score of antiepileptic drugs and surgical procedures, dysphoric symptoms and psychotic episodes appear to have become more severe and chronic. Kraepelin[32] had noted a very brief duration of the dysphoric episodes, and stated that interictal psychotic episodes as a rule last only a few days and may persist for weeks or even months only in isolated cases; he noted a very frequent suicidal urge, but not completed suicide, associated with dysphoric episodes. The relative infrequency of suicide in the premodern era is documented by Prudhomme,[45] whose research included approximately 77,000 patients with epilepsy from the period of 1893 to 1940.

The emergence or worsening of psychopathology upon suppression of seizure activity has been widely reported. Since the early reports by Gibbs,[20] Hill,[27] and Landolt,[34] evidence has been increasing that the interictal psychopathology may emerge or worsen upon improvement of the epilepsy, as measured by seizure frequency and EEG abnormalities. Persuasive evidence suggests that the psychiatric disorders of epilepsy may result from the inhibitory activity that develops in reaction to the excessive excitatory activity of the chronic seizure disorder, as postulated by Stevens[47] and Engel.[16] The precise nature of the seizure-suppressing mechanisms is insufficiently understood, and the phenomenon of emergence of psychiatric disturbance with normalization of the EEG or with suppression of clinical seizures, has been usually referred to as *forced normalization* or *alternating psychosis*, respectively.[10,34,50] Landolt's early observations included dysphoric disorders upon normalization of the EEG,[34] but when the concept of the dysphoric disorder was forgotten, psychiatric observations began to focus on the psychotic disorders and to a lesser extent on isolated symptoms of the dysphoric disorder.[46] Early reports that suicide may occur as an alternating phenomenon when seizures are suppressed[29] were widely ignored.

The evidence of a linkage of the psychiatric changes to inhibitory mechanisms can be summarized as follows: (a) The development of interictal dysphoric and even more so of psychotic disorders is delayed following onset of epilepsy,[18,19] as inhibitory mechanisms become increasingly established; this predicament accords with the particular linkage of the psychiatric disorders of epilepsy with its most prominent chronic form (i.e., mesial TLE). (b) Upon decrease, and particularly upon full control of seizures, dysphoric symptoms and psychosis tend to be exacerbated or to emerge de novo.[6,10,21,27,34,50,51] (c) The same psychiatric changes emerge also at times when

acute exacerbation of the seizure activity engages an enhanced inhibitory response, commonly in the prodromal and postictal phases, and rarely upon increased seizure activity as paraictal psychosis —a seeming opposite of forced normalization or alternating psychosis.[4,6,32,46] (d) After optimal surgical elimination of the epileptogenic zone, a delay of 6 to 18 months occurs before the psychiatric changes become phased out, presumably with only gradual fading of the inhibitory mechanisms.[10]

If predominance of inhibition results in persistent suppression of seizures in chronic epilepsy, some patients are at risk to develop the most severe psychiatric complications: A dysphoric disorder with suicidal depressive moods, psychosis, or a combination of both. On the other hand, the *acute* engagement of inhibitory mechanisms by the seizure event tends to result in peri-ictal dysphoric symptoms that may include postictal depressive mood with suicidality. The third case of Mendez and Doss[39] is exceptional: The patient's brief psychotic episodes would occur in the presence of *increased* epileptiform activity in the EEG in the *absence* of seizures, and the psychotic confusion was associated with voices commanding him to commit suicide. Demers-Desrosiers et al.[14] reported similar psychotic episodes in two patients who became psychotic shortly after discontinuing their antiepileptic medication, in association with *increased* epileptiform activity of the EEG in the *absence* of seizures; their psychotic state remitted upon resuming the antiepileptic medication. The authors correctly considered their findings as the antipode of forced normalization, since forced normalization is understood as the emergence of psychotic disturbance when the EEG is normalized. The three cases have in common that, in the presence of increased EEG abnormality, no seizures occurred, presumably as inhibitory mechanisms were acutely engaged, provoking psychotic episodes and suicidality as alternating phenomena.

A psychodynamic aspect in the pathogenesis of suicide is noteworthy. A core symptom of the dysphoric disorder, termed *irritability*, consists of the paroxysmal affect of anger that may be overcontrolled or range from short temper to the point of explosive rage; excessive anger conflicts with the notably conscientious and even hyper-religious personality of patients with epilepsy and may become intolerable,[6] prompting a precipitate and often unexpected act of suicide. Janz noted that a violent form of suicide (plunge from great height, throwing self under a train, drowning) occurred more frequently among patients with epilepsy than in the average population of suicides in Germany,[29] and similar reports came from Japan.[17]

Prevention of Suicide

If the hypothesis is correct that inhibition in chronic epilepsy may have a psychotoxic effect in many patients, then the treatment of psychopathology in epilepsy must aim to moderate the inhibitory mechanisms. Avoiding the antidepressant drugs that are most effective for this task for fear of lowering the seizure threshold of patients with epilepsy is ill-advised and carries the risk of fatal consequences.

The use of antidepressants for interictal psychiatric disorders was advocated as early as 1983.[43] We have successfully used antidepressants in modest doses for the psychiatric disorders of epilepsy for over 15 years in a large number of patients without increasing the seizure frequency, except in a rare patient with primary generalized seizures.[5,6,11] The proconvulsant antidepressant drugs at modest doses appear to serve as effective antagonists to the excessive inhibition and, in fact, are indispensable for successfully treating the interictal dysphoric and psychotic disorders. Gastaut et al.[19] pointed out that the interictal seizure threshold of patients with TLE (as measured by the response to Metrazol), in contrast to that of patients with primary generalized epilepsy, is higher than in nonepileptic individuals. The bias against the use of antidepressants for the psychiatric disorders of epilepsy, because they may lower the seizure threshold, is erroneous both on empirical and theoretical grounds. However, patients with primary generalized epilepsy who occasionally may experience dysphoric symptoms (presumably as a result of involvement of mesial temporal structures) still may have a lowered seizure threshold and need a more cautious dose of antidepressant medication.

In general, three of the eight key symptoms of the dysphoric disorder must be present before we initiate treatment with antidepressant medication. We add 100mg (up to 150 mg) of imipramine at bedtime to the antiepileptic medication, making sure that the sleep disturbance is corrected; amitriptyline, doxepin, trimipramine, or nortriptyline may have to be substituted for that purpose. If the patient does not respond well, we add a serotonin-selective reuptake inhibitory antidepressant (SSRI) to the tricyclic, which is usually kept at a dose of 100 mg. Paroxetine has been our preferred SSRI, at 20 mg once to twice daily, but at times a different SSRI may be more effective. One may also proceed in the reverse order by starting with the SSRI and then adding a tricyclic drug if necessary. As a third step, for severe dysphoric disorders, risperidone at about 2 mg daily may have to be added. The response to this treatment extends to all the symptoms of the dysphoric disorder, including the depressive moods as well as the irritability, and occurs within days once a therapeutic dose is reached, allowing a rapid escalation of the prescription if necessary. If an interictal dysphoric disorder is associated with suicidality or with psychotic features, treatment should be started promptly with double antidepressant medication; a small dose of neuroleptic (risperidone 1 to 4 mg daily) may need to be added. Treating the interictal psychoses—dysphoric disorders with predominant psychotic features—should generally be carried out in identical fashion as for the severe dysphoric disorders and not simply by neuroleptic drugs.[10]

The number of suicides at the Epi-Care Center is a fraction of what is expected from previous surveys. When the three early patients (cases 1–3) from the Epi-Care Center suicided after successful epilepsy surgery, we had not yet learned to use the more effective augmented antidepressant treatment for severe dysphoric disorders. Mendez and Doss[39] reported the low rate of four suicides out of 1,611 patients (0.25%) followed for epilepsy in a neurology clinic over a period of 8 years. We had two suicides among the estimated 7,160 patients (0.03%) followed at the Epi-Care Center over the last 8 years of the study period, when we had the more effective psychotropic treatment in place; both patients had eluded this treatment (cases 4 and 5). Case histories of patients with the highest suicide risk but successfully treated at the Center have been previously reported.[5,7]

Suicide in epilepsy tends to be precipitate, but there may be recurrent warning from earlier dysphoric episodes with suicidal mood. All such patients require prompt and vigorous intervention with augmented antidepressant medication to stabilize their dysphoric disorder. However, a suicidal mood may emerge without a previous occurrence in a patient who had shown other symptoms of a dysphoric disorder (e.g., the outburst of rage in case 4). Prompt treatment of significant dysphoric symptoms assures not only an improved quality of life but prevents a suicidal outcome. Finally, patients with severe postictal depression, in our experience, can be protected from a suicidal impulse if they are maintained on antidepressant medication.

Summary and Conclusions

The increased risk of death by suicide among patients with epilepsy, while rarely disputed, has often been viewed as the unfortunate result of the psychosocial difficulties imposed by a chronic neurologic disease and has received scant psychiatric attention.

The study of suicides among 10,739 patients seen at the Epi-Care Center over 12 years confirms earlier findings[23,39] of suicide in epilepsy resulting from the specific neuropsychiatric disorders that are associated with epilepsy. These disorders include intermittent depressive moods with suicidal intensity among patients with interictal dysphoric disorder, psychotic episodes with concomitant dysphoric disorder and at times with command hallucinations, and severe postictal depressive states. The suicides may occur particularly in patients with long-standing TLE with high seizure frequency once seizures finally became controlled. Although a majority of patients with epilepsy will reach long-term remission, some patients with chronic epilepsy experience serious psychiatric complications when their seizures become controlled. Mendez and Doss implied that interictal depression may be relieved by having seizures, similar to the effect of electroconvulsive therapy.[39] The evidence suggests that a predominance of inhibitory mechanisms, interictally or postictally, may be psychotoxic, favoring the emergence of dysphoric and psychotic states and of a suicidal risk. The findings from the Epi-Care Center indicate that the early treatment of patients with epilepsy and dysphoric symptoms by the appropriate psychotropic medication can prevent suicides.

Suicide is only the most striking problem among the sizable number of patients with chronic epilepsy who suffer from dysphoric and psychotic disorders, and are well treatable by modern psychopharmacologic intervention. A much improved collaboration is required between neurologists who recognize the scope of the psychiatric complications of epilepsy and of psychiatrists who do not shun the field of epilepsy as alien to their specialty. The modern advances in suppressing seizures must become paired with the competence to treat the psychiatric consequences of improved seizure control in order to achieve optimal quality of life and to prevent fatal outcomes.

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Chapter 212

Disorders of Impulse Control

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Introduction

Impulsivity in general is a frequent clinical problem that is related to many different primary psychiatric disorders as, for example, attention-deficit-hyperactivity disorder (ADHD), borderline personality disorder, bipolar disorder (in particular in hypomanic or manic states), and schizophrenia.[1,2] Furthermore, it is a common management problem in patients with mental retardation or organic brain disorders. Although the International Statistical Classification of Diseases and Health Related Problems (ICD-10) does not recognize specific independent disorders of impulse control,[1] the American Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) defines the category of impulse-control disorders not elsewhere classified[2] and includes the entities of intermittent explosive disorder (IED; DSM-IV 312.34), kleptomania (DSM-IV 312.32), pyromania (DSM-IV 312.33), pathologic gambling (DSM-IV 312.31), and trichotillomania (DSM-IV 312.39).

Because impulsive aggression is the most clinically important and most troubling form of these impulse control disorders (see also Chapter 283 and the review by Tebartz van Elst[73]), in this chapter we will concentrate on the problem of aggression in the context of epilepsy. This issue has been the topic of other recent publications.[73] We discuss the putative relationship between epilepsy and the other aforementioned impulse control disorders briefly at the end of the chapter.

Impulsive Aggression in Epilepsy

The relationship between epilepsy and aggressive behavior is a particularly controversial issue.[33] In Chapter 283, we discussed the issue of episodic dyscontrol and IED in the context of the differential diagnosis of epilepsy, and also as an independent psychiatric entity. Here we want to dwell on the more general and less specific forms of impulsive aggression that do not fulfil the criteria of episodic dyscontrol, but still are seen in patients with epilepsy.

The precise prevalence of aggressive and violent behavior in the context of epilepsy is very difficult to assess and subsequently is still unknown. In patients with episodic affective aggression, a history of epilepsy is reported to be more common.[4] On the other hand,[22] most of the community-based studies did not find an increased prevalence of aggressive behavior in patients with epilepsy.[43,48] Different papers report wide-ranging prevalence figures of aggression in epilepsy in general, do not note the specific epileptic syndrome, and cite figures from as low as 4.8%[65] to as high as 50%.[31]

Currie et al. reported aggression in 7% of the patients in a large survey of 666 patients with temporal lobe epilepsy (TLE).[15] Falconer's group reviewed 100 patients from London's Maudsley Hospital referred for temporal lobectomy and found a prevalence of outbursts of aggressive behavior in as many as 27% of these patients.[24] However, like most of the other studies addressing this issue, these studies were hampered by selection bias, and thus the real prevalence of aggressive behavior in epilepsy remains controversial.[48]

In epilepsy, three different types of aggressive behaviors should be distinguished on the basis of their relationship to the seizures: ictal, postictal, and interictal aggression.[27,42,73,74]

Ictal Aggression

Ictal aggression is very rare.[36,66] Delgardo-Escueta et al. found an incidence of about 1 in 1,000 seizures with ictal aggression in a large survey of several thousand seizures documented by video-telemetry.[18] However, it can be argued that as such, looking for ictal aggression in the context of the tightly controlled arena of an electroencephalogram (EEG) suite is not going to provide a true view on the frequency of the problem. This is because patients with aggressive episodes are less likely to be accepted for evaluation, and such episodes of aggressive release are more likely to occur in a community rather than a laboratory setting. In ictal aggression, hostile and verbal or physical aggressive behavior is often directed toward nearby objects or persons and may or may not be provoked.[27] The patients are generally amnesic for these aggressive episodes and often express remorse or feelings of shame for their behavior after the event.[19,28]

Postictal Aggression

Postictal aggression is more common than ictal aggression and, although it is still believed to be rare, it may be under-recognized and unreported.[77] Postictal aggressive behavior usually follows a cluster of complex partial seizures or secondary generalized seizures in patients in whom such episodes are not the usually expression of their epilepsy. Some evidence points to ictal pain or dysphoria as predisposing factors for the later development of postictal aggressive behaviour.[32] If the episode occurs in the context of a postictal confusional state, poorly structured aggressive behavior is not that rare. This aggression is poorly directed, and the patient, rather than someone who is attacked, is most likely to come to harm. If postictal aggression is part of a postictal confusional state, the disruptive behavior immediately follows the seizure without a lucid interval intervening between the ictus and the outbreak of the disruptive behavior. In this state, patients are often resistive, but within their confusion can be very aroused, angry, and fearful.[41,46]

Postictal psychosis typically follows a cluster of complex partial or secondary generalized seizures in patients with longstanding chronic and often therapy-refractory epilepsy. Generally these states follow a lucid interval—the calm before the storm—which might last anywhere between hours and days up to 1 week. Observers may notice an insidious onset of affective symptoms with arousal, restlessness, agitation, and often anxiety, fear, and anger, although the behavioral state can erupt quite suddenly. Subsequently, overt psychotic symptoms with delusions and hallucinations might follow. The latter might be accompanied by aggressive behavior that sometimes is very dramatic and dangerous.[29,40,49,78] Although aggressive behavior in the context of a delusional state is often rather disorganized if there is some clouding of consciousness, this is not necessarily the case. Over 50% of patients with postictal psychotic states have minimal or no such associated confusion, and aggressive behavior can be well-structured and goal-directed. Patients often feel angry and aroused, although they may appear calm and concentrated to the observer.[41,72]

Kanemoto et al. make the important observation that well-directed and self-destructive behavior might even be a hallmark of postictal psychosis.[41] The psychosis may be missed, either because it is not probed for, or because the behavior is such that it is not possible to obtain a good mental state evaluation. The latter is the more problematic in those with learning disabilities. The aggressive behavior might then be structured and goal-directed, but without any obvious sign of delusions or hallucinations.[41,46,72] The awareness of the problem of postictal psychoses and associated aggressive behavior is of particular importance for epilepsy-monitoring centers because, in this context, many patients with chronic therapy-refractory epilepsy are seen and diagnosed following an acute reduction of their medication for diagnostic purposes. If a history of previous postictal events exists, doctors should be aware of the risk of postictal psychosis and aggression, and should closely monitor the behavior of these patients. Outbursts of aggression, especially with psychotic intensity, are dangerous not only for the patients but also the nurses and attending physicians themselves.

Interictal Aggression

Interictal aggressions are the most common, but generally less dramatic forms of aggressive behaviors in patients with epilepsy. These can be seen in the context of an antisocial personality disorder which, in turn, might be the consequence of the sometimes difficult psychosocial background and upbringing of patients with epilepsy, Or it might be part of a prolonged psychotic episode, an interictal affective disorder, or a psychosis of a paranoid- or schizophrenia-like type.[49,41]

In patients with epilepsy and mental handicap, interictal aggression is a common management problem. In these patients, the aggressive behavior is often the result of poor social and communication competence in expressing personal needs and rarely results in severe violence.[37]

An interictal syndrome of episodic affective aggression, independent of observable ictal activity, major psychiatric disorder, or antisocial personality disorder, is well described and has been referred to as *episodic dyscontrol* or *IED*.[4,23,47,52,64,71] Episodic dyscontrol is characterized by several discrete epi- sodes of extreme arousal and rage that are out of proportion to any precipitating psychosocial stressor, but that result in severe aggressive and violent behavior. As mentioned earlier, this form of possible epilepsy-related aggression has been described and discussed in Chapter 283.

Irritability and impulsivity, in particular verbal aggression of mild to modest severity, might be a symptom of the dysphoric disorder of epilepsy (DDE). DDE is a specific form of epilepsy-related affective disorder characterized by symptoms like irritability, mood swings, anergia, diffuse pain, anxiety, fears, and disturbances of sleep. The paroxysmal affects, ranging from irritability through anger to rage, play a major role in DDE and make it an easy-to-recognize pattern of psychopathology for the experienced clinician.[10] Based on the relationship to the ictus, DDE can be subclassified as preictal, interictal, and postictal DDE.[44] In particular, in patients with learning disability, irritability and aggressive behavior might dominate the clinical picture of DDE and thereby obscure the diagnosis.

Finally, interictal aggression in the context of epilepsy can be a side effect of antiepileptic medication. Reports have been published, for example, for substances such as phenobarbital, several benzodiazepines, gabapentin (especially in adolescents), vigabatrin, topiramate, and levitiracetam.[3,8,16,20,30,54,57,67] This may be a part of a syndrome of forced normalization, an idiosyncratic reaction representing the precipitation of a nonconvulsive status epilepticus, or a manifestation of intoxication. However, from a different perspective, anticonvulsants may be quite helpful in treating impulsive aggression in patients with epilepsy, in whom aggression is postictal in nature or interictal as part of a mood instability syndrome, as they are in other aggressive patients without epilepsy.[5,6,39,58,59,68,69,75]

This complex constellation illustrates the need for a careful neuropsychiatric assessment of patients in whom impulsive aggression is a clinical problem, be it in the context of epilepsy or not.

Treatment of Aggression in Epilepsy

Establishing a correct diagnosis is the most important point in treating problems with aggression in the context of epilepsy (Fig. 1). A careful neurologic, psychiatric, and medical history and examination is a prerequisite to answer the following questions: Is there any medical condition that contributes to the aggressive behavior, such as an endocrinologic disease? Is there any medication that might contribute to the aggressive behavior—antiepileptic or otherwise? What is the correct neurologic diagnosis? Does the patient have epilepsy? Are there any other cerebral problems in addition to the epilepsy? Is there any specific epilepsy-related psychiatric disorder, either ictal or postictal, that might explain the aggressive behavior? Are any psychiatric diagnoses present, but possibly independent of the epilepsy, such as bipolar disorder or antisocial personality disorder?

With regards to the latter question, if the epilepsy started early in life, it is often impossible to establish if, for example, the clinical picture that fulfils the criteria for an antisocial personality disorder is or is not independent of the organic brain disease indicated by the epilepsy: Does the patient have an unassociated personality disorder or, alternatively, is the problem an organic personality disorder? A careful behavioral analysis, thorough anamnesis, and possibly video-telemetry should clarify if the aggressive behavior is ictal, postictal, or interictal and whether it occurs in the context of altered states of consciousness or psychosis.

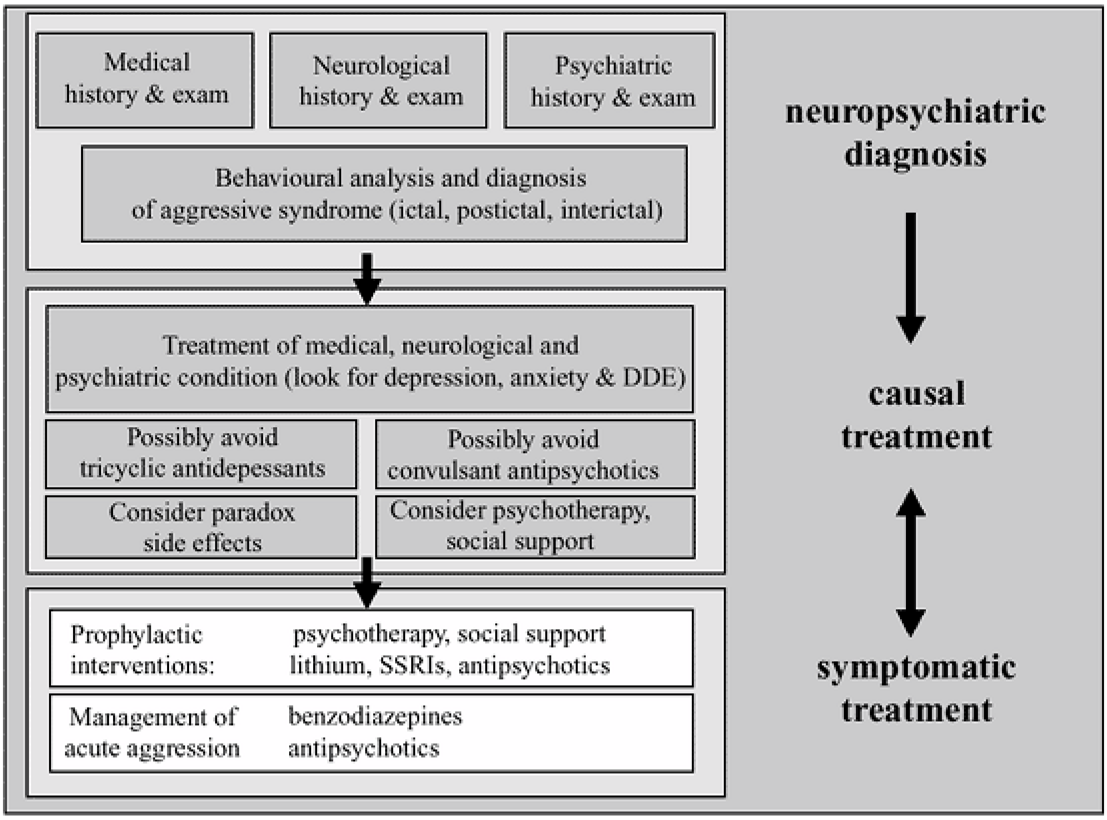
Medical history & exam
Neurological history & exam
Psychiatric history & exam
Behavioural analysis and diagnosis of aggressive syndrome (ictal, postictal, interictal)
Treatment of medical, neurological and psychiatric condition (look for depression, anxiety & DDE)
Possibly avoid tricyclic antidepessants
Possibly avoid convulsant antipsychotics
Consider paradox side effects
Consider psychotherapy, social support
Prophylactic interventions: psychotherapy, social support lithium, SSRIs, antipsychotics
Management of acute aggression benzodiazepines antipsychotics
neuropsychiatric diagnosis
causal treatment
symptomatic treatment

FIGURE 1. Therapeutic guidelines for the treatment of aggression in patients with epilepsy. (From Tebartz van Elst L. Aggression and epilepsy. In: Trimble M, Schmitz B, eds. *The Neuropsychiatry of Epilepsy.* Cambridge: Cambridge University Press; 2002: 81–106, with permission.)

Following syndromic and possibly nosologic diagnosis, treatment should be targeted to any treatable causes if possible, such as intervening medical problems like endocrinologic disorders. Neurological syndromes, such as the epilepsy itself, should be treated effectively, with as few medications as possible to avoid seizures, and with avoidance of medications most linked with alteration of mood and the release of aggressive behavior. Particular care should be taken to establish signs of depression, anxiety, or the common dysphoric disorder of epilepsy, because a close link exists between these psychopathologic states and affective aggression in epilepsy.[74] Affective symptoms should be treated medically and with psychotherapy at the same time.[34,50] In the medical treatment of depression in patients with epilepsy, selective serotonin reuptake inhibitors (SSRIs) or other new antidepressants such as venlafaxine should be preferred to the older tricyclic antidepressants (TCA) because the latter are more likely to provoke seizures.[9,45] The anticonvulsant effect of the SSRIs is well documented in animal models of epilepsy,[12,51,60,79] and is also described in humans.[26]

Following treatment of all medical, neurologic, and psychiatric conditions that may or may not contribute to the aggressive psychopathology, a symptomatic treatment of the aggression is mandatory. However, this depends on whether the aggression is an ictal, postictal, or interictal phenomenon.

Ictal aggression requires immediate attention to the seizures, and a nonconvulsive status epilepticus can be interrupted using, for example, benzodiazepines.[27] Apart from that, a patient who displays agitation and aggressive during a seizure should not be overly restricted, because defensive violence is more common in such situations, and the aggressive behavior is self-limited, as is the seizure.

The same is true for postictal confusional states: Even aggressive behavior in the context of postictal psychosis is self-limited. However, if the aggression is severe and disturbing or self-harming, medical treatment using benzodiazepines such as diazepam or clobazam and/or antipsychotics (usually one of the atypicals) should be started. Good seizure control that avoids clusters of complex partial or secondary generalized seizure is the best prophylactic intervention, because postictal confusional and psychotic states are more common after such episodes. If, after for example a cluster of attacks, the impending abnormal behavior can be predicted, the use of a benzodiazepine for about 48 hours may well be sufficient to abort the event. Patients or caregivers should have a supply of such medications and be given advice on how to use them judiciously.

In treating interictal aggression, one should again distinguish prophylactic and acute treatment. For the treatment of severe and etiologically unclear acute hyperarousal-dyscontrol syndromes, a combination of benzodiazepines, such as diazepam, and antipsychotics, such as haloperidol, is still the most effective and safest intervention. In cases of interictal psychoses, however, the antipsychotic medication should eventually be switched to one of the atypical antipsychotic agents with little proconvulsant potential, because these drugs are better tolerated. A good control of the psychosis is the best way to prevent aggression if it is part of the psychosis.

In cases of interictal aggressive syndromes like IED, no well-established medical prophylactic therapies are available. However, many anecdotal reports document the effective use of substances such as lithium, valproate, carbamazepine, phenyt-oin, antipsychotics, ß-blockers, clonidine, and even psychostimulants (see Chapter 283 and several reviews[25,35,81]). However, because there are hardly any well-conducted systematic treatment studies at the moment, the medical treatment still is very experimental and single-case driven. Nevertheless, in the light of the very severe burden that is put on the patients, their relatives, and caregivers by the sometimes devastating behavioral episodes, a systematic trial of these agents seems justified.

If aggressive behavior is part of interictal DDE,[10] this should be treated with SSRIs in the first instance. Substances such as citalopram or escitalopram have few interaction problems with other antiepileptic drugs and have a minimal problem with lowering the seizure threshold. If these drugs are not effective in controlling dysphoric depression, one should consider others, such as venlafaxine, a TCA, or even a combination of the two. In some cases, additional treatment with a very low-dose atypical antipsychotic might also be helpful. However, one should always avoid high doses of these drug and be very careful with combination therapy, because this might lower the seizure threshold,[9] provoking further irritability or further postictal episodes.

Finally, as mentioned in Chapter 283 in the context of episodic dyscontrol, it must be stressed that anger management, contingency management, and psychotherapy all can be very helpful and successful in treating impulsive aggressive behavior. Particularly in the context of mental handicap and personality disorders, aggression and impulsivity might be part of attention seeking behavior and role testing. In these cases, feedback strategies and the reactions of relatives and caregivers are very important, and methods of contingency management may be a critical element of any successful treatment.[7,14] Behavioral therapy, in particular in patients with epilepsy and mental handicap, has been proven very effective.[17,38,63]

Different methods of anger management, cognitive behavior therapy, or skills training that have been developed irrespective of the context of impulsive behavior may be very helpful in the therapy of aggression.[17,70,76,80]

Epilepsy and Other Disorders of Impulse Control

To our knowledge, no papers in the literature address the question of a specific link between epilepsy and syndromes such as kleptomania and pathologic gambling. However, a few case reports discuss a putative link between very specific forms of epilepsy and trichotillomania and, in particular, pyromania or arson.[11,13,21,53,55,56,61,62] The latter has been discussed to be possibly triggered by a putative mechanism called the *limbic psychotic trigger reaction* (LPTR). This is believed to be a form of nonconvulsive behavioral seizure (NCBS); following this theory, seizure-like limbic pathomechanisms that are kindled by memory stimuli result in brief psychotic episodes in which the affected patients impulsively set fire.[61,62] However, it should be stressed that these hypotheses are purely based on a few case reports, and that no solid epidemiologic data support the theory that these forms of impulse control disorder are truly more common in epilepsy as compared to the general population.

Summary and Conclusions

Aggression in the context of epilepsy is not common but, when it occurs, it often imposes an immense burden on the patient, his relatives, and caregivers. The neurobiology and precise pathomechanisms of aggressive behavior, be it in the context of epilepsy or not, are most likely heterogeneous and very complex. Nevertheless, it is important to appreciate the interplay of social, psychological, and neurobiologic factors, all of which may contribute to aggression and violent behavior in any given case.

Clinically, it is crucial to first establish a correct diagnosis. Intervening medical, neurologic, and psychiatric disorders—in particular, depression, anxiety, and DDE—should be recognized and treated adequately. A correct syndromic diagnosis of the aggressive syndrome and its relation to the seizures should be made. Treatment should aim at possible underlying medical, neurologic, or psychiatric disorders. In symptomatic treatment of aggressive outbursts, the management of acute aggression and prophylactic treatment to prevent further episodes should be differentiated.

Pharmacologic treatment is often the mainstay of therapy, but psychological therapies in the form of anger management or other variations of cognitive behavior therapy are an integral part of management in many patients.

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Chapter 213

Psychiatry and Residential Care

Stephen W. Brown

Frank M. C. Besag

> "Do poor Tom some charity, whom the foul fiend vexes."
>
> —William Shakespeare, "King Lear," Act III, Scene IV
>
> "What doubtless remained longer than leprosy, and would persist when the lazar houses had been empty for years, were the values and images attached to the figure of the leper as well as the meaning of his exclusion, the social importance of that insistent and fearful figure which was not driven off without first being inscribed within a sacred circle."
>
> —Michel Foucault, *Madness and Civilization: A History of Insanity in the Age of Reason*[11]

Introduction

Historical Perspective on the Rise and Fall of Confinement

Development of Institutions

Hospitals, hostels, and hotels share functions that are reflected in the common Latin root of these words (*hospitalia*, "guest chambers"). It is possible that in Europe during the Middle Ages some cities kept hostels for local people who were not capable of looking after themselves. Also, some people with behavioral problems that would now be attributed to psychosis, brain damage, or other psychiatric conditions might congregate around certain religious shrines. Custodial institutions that were separate from prisons appeared in Europe from the late 17th century onward and, during the 18th century, there emerged specialized asylums for the insane. The reason for the growth in asylum building during that period of history has been a subject of speculation in this century. One argument has been that a real increase occurred in the population with psychosis.[12] Alternatively, sociologic explanations have been advanced, suggesting that the development of psychiatry was a self-perpetuating means of social control.[25] For example, Foucault, noting that leprosy had recently disappeared from Europe, postulated that the "formulas of exclusion" persisted, so that "…poor vagabonds, criminals, and 'deranged minds' would take the part played by the leper …," and he refers to "…that major form of a rigorous division which is social exclusion but spiritual reintegration."[11] Houses of correction were established in England in 1575 by an act of Parliament for "the punishment of vagabonds and the relief of the poor," and in 1656 the Hôpital Général was founded in Paris to confine the poor. Foucault notes that this confinement included "the debauched, spendthrift fathers, prodigal sons, blasphemers, men who 'seek to undo themselves,' libertines, and, in about one-tenth of cases (Paris), the insane." There was, however, a gradual process of categorization whereby those in need of asylum were recognized as being respectively poor, insane, handicapped, or epileptic, and these groups in turn came to be regarded as separate from criminals. As asylums increased in number and became more concerned with mental illness, a more humane approach to care appeared. This was typified by the work of William Tuke (1732–1822) in York (who founded the York Retreat after the death of a fellow Quaker in the county asylum), and Philippe Pinel (1745–1826) in France. Both stressed moral aspects of treatment and advocated the avoidance of methods of physical constraint, such as chains. Pinel's pupil Maisonneuve studied epilepsy, and wrote that "…epilepsy, like all chronic diseases, can be studied well only in the hospitals; there alone is it possible to find all its varieties together, to see all its nuances, and to acquire in short time more experience of this disease than in the whole course of ordinary practice."[16] Another physician of Maisonneuve's generation, Jean Etienne Dominique Esquirol (1772–1840), advocated special facilities for people with epilepsy apart from the other asylum inmates. The reason for this, however, was not to protect those with epilepsy, but to protect the insane, for he believed "…that the sight of one epileptic attack might suffice to make a healthy person epileptic. Now if this held true of healthy people, how much greater was the danger for the mentally deranged, who were so much more impressionable."[27] Consequently, with the growth of provision for the insane there also came separate facilities within the asylums for people with epilepsy. It is not surprising that the next stage was the establishment of entirely separate institutions for people with epilepsy.

Epilepsy in Institutions and the Move Toward Colonies, Villages, and Schools

European writers of the 19th century became interested in the ways in which epilepsy might act on the mind and cause mental disorder. Morel[23] suggested that the disease could exist in a masked form (*epilepsie larvée*), in which the main features were of insanity, not seizures. Falret[10] attempted to classify the psychiatric disorders of epilepsy and, in addition to acknowledging the existence of interictal and peri-ictal phenomena, he followed Morel in proposing a category of epileptic insanity that was manifested as an alternative to seizures, the *folie épileptique*. Morel also offered the view that the behavioral disorders associated with epilepsy, in particular the "epileptic furore," might be a consequence of bad treatment, and that improvement of the patient's environment by segregation, recreation, and occupation would bring about improvement.[22] This debate added to the intellectual climate from which the argument for separate institutions for epilepsy was to emerge.

In 19th century Europe, the word *colony* did not carry a pejorative connotation. The notion of establishing separate living space for people with epilepsy was based on a belief that this would be therapeutic in itself. There was an understanding that the condition was perpetuated by restrictions placed on the activities of normal life, especially the opportunity to take part in work. This was the rationale for the colony movement,

exemplified by the foundation in 1867 of Bethel, near Bielefeld in Germany, and by the foundation later in England of the Chalfont, Lingfield, and David Lewis colonies, and in the United States of the Craig colony. The emphasis was on social management, with early intervention by admission to the colony; discharge back to society was a possibility. Alan McDougall, the first medical director of the David Lewis colony, wrote, "Most of our colonists come to us too late to be cured of their fits. The children give brilliant results; one third of them become free from fits. Our… experience seems to show that if all epileptic children, whatever their social position, were sent on the first appearance of epileptic symptoms to an epileptic colony, and kept there till the end of their school life, the benefits to themselves, to their relatives, and to the State would be enormous."[19] These epileptic colonies were sometimes, but not exclusively, situated in the countryside. They typically created a village-like atmosphere, and often included a residential school for children with epilepsy. Attention to lifestyle, as well as physical treatment, was considered important: "Most of the colonists take daily a 30-grain dose of Potassium Bromide. This appears in many cases to diminish the frequency of the fits, and the tendency to status. But other therapeutic means are even more important. Among these is the combined concert and dance that has been held without intermission every Saturday night of the year. Dancing (particularly the 'Lancers') is a valuable means of treatment, provided that it be practised frequently. On the first few occasions a fit may follow the dancing, but the patient soon becomes able to dance without unpleasant side effects. Classical treatment of Epilepsy follows the lines of forbidding the patient to do the things that might cause a fit; colony treatment attempts to rid the patient of fits while he is performing the acts of a normal person. The latter plan gives the better results."[17]

The development of colonies was the consequence of a philanthropic movement spearheaded by the social and religious conscience of the aristocracy and upper middle classes. Increasingly, the new wealthy class—the industrial bourgeoisie—undertook a scheme of building model villages for the working classes, exemplified by the work of the Cadburys in Bournville in the English Midlands, and in the building of Styal Village for the workers of Styal Mill in Cheshire. Also at this time, arts and crafts colonies developed, where a particular creative lifestyle could be followed, away from a society that Crichton-Browne described as "…a feverish and fidgety age in which an unappeasable restlessness pervades all ranks and classes."[7] This movement was not in any way the consequence of an overt desire to segregate or discriminate against elements of society regarded as difficult, dangerous, or undesirable. Thus, at this point, the history of the institutional management of epilepsy should diverge from that of institutional psychiatry. In particular, the epilepsy colonies (in Europe at least) were concerned from the beginning with destigmatization and normalization, with attaching value to people's social roles. The evidence is in stark contrast to that often offered by historians as explanations for the great confinement of the mentally ill in the 17th, 18th, and 19th centuries. Why is this? One explanation might be that some of the accepted historical cases in psychiatry have been overstated. Bynum wrote of Foucault, "…the power of his dark vision remains, although its empirical base has been questioned,"[3] and another modern historian noted, "…the view that the 17th and particularly the 18th centuries were a disaster for the insane in England has to be qualified…."[24] Alternatively, perhaps the epilepsy colony movement then was in opposition to social attitudes at the time. Indeed, the views of those advocating colony treatment are not congruent with ideas expressed by eminent psychiatrists much later in the 20th century. For example, in 1977, a leading English-language textbook of psychiatry contained the following passage describing personality deterioration in epilepsy: "There are also more constant and lasting affective changes. Most frequently these take the form of a mulish moroseness and rancour. Slights are felt to the quick, and malice is borne for months or years. In an epileptic ward gossip, lying or slander will all too easily reign…. Chronic epileptic patients are capable of actions of the most malicious and petty spite, and of combining them with self-justification and self-praise."[26]

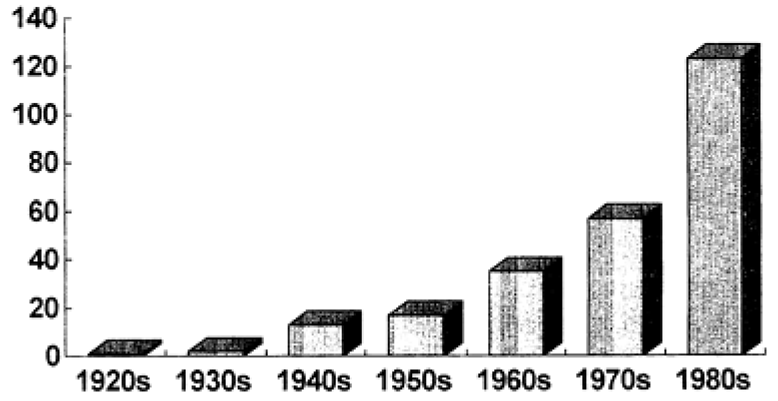

FIGURE 1. Admission rates to the Davis Lewis Centre for Epilepsy, 1920–1989.

Seven decades earlier, in 1909, Alan McDougall had noticed the opposite: "Each succeeding year, in spite of the constant increase in the population, there is less and less quarrelling among the colonists. Our experience leads us to believe that many of the unpleasant characteristics commonly ascribed to epileptics are due not so much to the disease as to the mishandling that the patient has received. When living with those who understand his special requirements, the epileptic is a very likeable person."[19] McDougall, however, did have a sanction that was not available to the alienist and, in the 1906 colony report, he noted, "Four have been discharged as unsuitable. Their persisting lack of consideration for their fellow colonists made it impossible to retain them. Yet had they entered a colony at an early stage of their illness, they would probably have been excellent colonists."[17]

Colonies for People with Epilepsy: Their Role and Development

Special Schools, Centers, and Villages: Their Maximum Development and Subsequent Decline

The epilepsy colonies of Europe have not died; rather, their work has changed to keep pace with new developments in treatment and social expectations. Their achievements have been recognized and envied in other parts of the world: "Residential and treatment facilities must be built and improved to accommodate the unique problems of persons with epilepsy and associated disorders, perhaps on the model of the many splendid public epilepsy comprehensive treatment centers of western Europe, which have not a single counterpart anywhere in the United States."[28]

The demand for services has not diminished. For example, analysis of admission rates to the David Lewis Centre from 1920 to 1989 shows an almost exponential rise (Fig. 1). Although during this period there was some rise in the overall numbers of residents, most of this increase was matched by a corresponding rise in the rate of discharges, as the length of stay decreased. The founding fathers of the colonies had apparently believed that a return to the terrors of the outside world was best avoided until cure was absolutely established: "It is very unwise to be hasty in removing from Colony conditions an improving patient; it is far wiser to wait till the improvement has become firmly established; otherwise there is great danger of relapse."[18] In these early days, however, probably the only effective medical treatment was bromide. Three factors developing during the 20th century were to influence the length of stay. These were treatment advances, secular social trends, and economics.

Treatment Advances

The introduction of barbiturates just before World War I, and of phenytoin just before World War II, made available a wider range of treatment options with potentially fewer side effects than bromides. Thus, an expectation of prolonged remission came to be part of the medical approach to epilepsy, with less medical objection to earlier return to the community. Those who still stayed behind would include a mixture of "good" colonists who had adapted well to colony life, so that neither the managers nor the clients themselves desired a change, together with those whose epilepsy or its associated problems failed to remit.

Secular Trends

The great confinement of the mentally ill began to end after World War II, probably mainly as a consequence of the introduction of phenothiazines in the 1950s, although the medicalization of psychiatry preceded this development by a century or so, with much of the intellectual impetus coming from the German-speaking world.[4] Similarly, the development of effective antituberculosis treatment at about the same time reduced the need for sanatoria. Thus, the concept of going away for long periods of time because of illness began to wither. It remained appropriate for sick people to spend time in the hospital for purposes of diagnosis and initiation of treatment, but after that the expectation was generally to return home. Although advances in epilepsy treatment were more modest, and despite the increased need for the services provided by epilepsy institutions as a consequence of increased numbers of cases of posttraumatic epilepsy resulting from two world wars, a view gradually began to emerge in parallel with these other developments, in which the emphasis shifted from fear of discharging too soon to fear of keeping patients too long.

Economics

Although most colonies were run as charitable institutions, and efforts were made to be as self-sufficient as possible in regard to providing food and services, residence always had to be paid for. Staffing and equipment costs increased along with the expectations of investigation, treatment, and care. Sponsors (families, insurance companies, national and local government agencies) were obliged to exert pressure to limit time spent during an admission.

Faced with these pressures, some establishments became smaller and a few closed, whereas others diversified their activities to meet the perceived needs of the changing market. During the 1960s, special short-stay assessment centers for epilepsy began to emerge within the colonies. Medical staff from epilepsy colonies became more involved in providing specialized epilepsy services in hospital settings. At about the turn of the decade, a significant change occurred; these venerable institutions faced the 1970s and beyond as "epilepsy centers," and the term *colony* was dropped forever. Since then, the larger centers have continued to provide more and more specialized facilities. The number of special residential schools declined, and those that remained came to include in their population an ever-larger proportion of children with severe learning disabilities. The charitable foundations responsible for the epilepsy centers began to become involved in wider issues, such as professional education and general public consciousness raising. In The Netherlands, the various epilepsy organizations, centers, and charities cooperated in producing an integrated epilepsy service for the nation that has remained a model of excellence. In the United Kingdom, the strength of the centers lay in their continuing independence from the state system in terms of business development, but their increasing reliance on statutory sources remained a weakness. In most parts of the world, an artificial distinction is made between health-related and social aspects of care, with different budgets available. A possibility arises for budget holders in health care or social services to attempt to shift the responsibility to the other area. No clearly accepted boundary exists at which social care takes over from "health." The situation is more complicated for children of school age in those areas where education authorities, faced with a bill for special education for a child with epilepsy, may be reluctant to fund aspects of care that are perceived as "medical" or "social." Thus, artificial difficulties may be put in the way of providing an integrated service. This is partly a consequence of social welfare and insurance systems that make no recognition of the particular issues in epilepsy. For example, the government of the United Kingdom, as part of a process of laying down minimum standards, sponsored a code of practice for residential care.[14] In this document, individual client groups are discussed, including the physically disabled, mentally ill, mentally handicapped, children and young people, the elderly, and people recovering from drug addiction and alcohol abuse. There is no mention of epilepsy. Therefore, there is no official "policy" for epilepsy—despite a number of expert reports, the recommendations of which have been largely ignored.[1,5,6,8] More recently, a further attempt at defining the scope of epilepsy services in the United Kingdom does seem to have had more impact, largely because of pressure from informed consumers.[2]

Current Residential Centers

At the beginning of the 21st century, the remaining residential epilepsy centers are the result of a heterogeneous evolution. The admission and discharge criteria and the range of services vary from country to country, and often from region to region, according to the prevailing social culture and the organization of health, education, and social services. Even so, some general themes are shared by most centers. The range of services includes (a) residential education for children, (b) residential assessment for children and adults, (c) long-stay provision and rehabilitation for adults, and (d) new areas of business.

Residential Education for Children

Some centers include a residential special school for children with epilepsy. There are, for example, currently three such schools in the United Kingdom, two of which are part of a larger center that also provides residential adult services. Admission criteria are the presence of a seizure disorder and educational failure. Many children arrive at residential special schools for epilepsy after a career of repeated failure in other settings. Frequently an additional psychiatric morbidity is present, manifested as a disorder of conduct, emotion, or both; however, in those cases where this has been studied, it seems that the rate of psychiatric disorders decreases with admission. This is probably a consequence of a mixture of efficient management of the seizure disorder, appropriate educational approach, and absence of stigmatization.[13] There is,

therefore, a possibility of return to mainstream education after a period in a residential school, and this is achieved in some cases. Geographic separation from the home area may be beneficial in the initial stages but can restrict opportunities for reintegration.

Residential Assessment for Children and Adults

Since at least the 1960s, epilepsy centers have developed a role in short-term residential assessment. Access to high-quality neurophysiologic investigations is often available, which allows the possibility of electroencephalographic (EEG) monitoring in a homelike, nonhospital environment. Each case of epilepsy can be investigated, and the most appropriate medical treatment plan agreed. Such an admission is also an opportunity to assess living skills and determine the level of care and rehabilitation needs. The individual's and the family's knowledge (or lack of knowledge) of epilepsy can also be addressed. Admission criteria include the presence of a refractory seizure disorder with or without other problems of living, and the outcome might include rediagnosis, a medical treatment plan, and a personalized statement of care and rehabilitation needs. In some centers, short assessment admissions are also used as part of an evaluation for epilepsy surgery.

Where units for assessment of children exist, the relationships between epilepsy, interictal EEG activity, drug adverse effects, behavioral problems, speech and language development, and learning difficulties (both generalized and specific) can be studied in classroom and home-type situations, so that an optimal educational approach can be developed for each patient. This information can then be used to identify the most appropriate placement after the child leaves the assessment unit.

In the case of both children and adults, assessment units may offer specialized services for patients with epilepsy and learning disabilities or other coexisting psychiatric morbidity. Assessment units are therefore staffed by epileptologists, specialist nurses, educational and clinical psychologists and neuropsychologists, speech and language therapists, and social workers. Some centers also provide nonverbal approaches, such as art therapy and music therapy. Periods of admission for assessment vary from 2 to 12 weeks, and may depend on the reason for referral.

Long-stay Provision and Rehabilitation for Adults

Despite the trend toward deinstitutionalization in the last few decades, a long-stay residential population still remains in the epilepsy centers. It is slowly dwindling in size (Fig. 2), and comprises two groups of patients. First, there is an old long-stay group of patients who were admitted many years ago (and who would not have been admitted in modern times). These are people who have spent a large part of their lives in the epilepsy centers, are now growing old, and know no other home. Their numbers will continue to decrease, and this group will eventually disappear. Although their needs for care will increase with age, they do not make high demands on services compared with other groups in the epilepsy centers. Second, a new, small, but significant long-stay group of people is emerging who have particularly complex care needs as a result of refractory epilepsy, learning disability, challenging behavior, coexisting organic psychosyndromes, or any combination of these. Members of this group may eventually be able to return to the community as a clinical and social rehabilitation program achieves slow progress over a number of years. The final size of this group has yet to be determined.

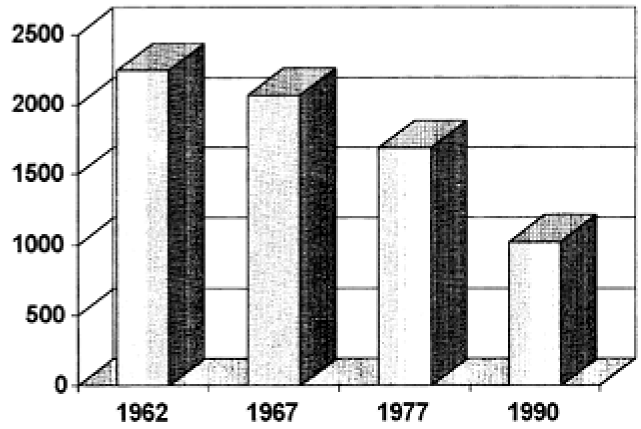

FIGURE 2. Numbers of patients living in epilepsy centers on a long-term basis. (From Duncan JS, Hart YM. Medical services. In: Laidlaw J, Richens A, Chadwick D, eds. *A Textbook of Epilepsy*. 4th ed.

London: Churchill Livingstone; 1993:705–722, with permission.)

New Areas of Business

Keeping pace with secular trends in social care policy as well as advances in epilepsy management, the medical staff of epilepsy centers have developed working relationships with established neurology and psychiatry units, both academic and clinical. Epilepsy centers are now often involved in research and teaching in epileptology, and in the management of tertiary outpatient facilities. In some areas, epilepsy center staff members have started working directly with primary care physicians. Some residential epilepsy schools have developed links with mainstream education and send staff members to advise on educational approaches to children with epilepsy in mainstream schools, and they have also become involved in training teachers who will work in the educational mainstream. Finally, there is a trend to replace, wherever possible, the large, institutional-type housing of the long-stay clients with small, family-sized units that may be situated within the local community close to the facilities of the epilepsy center.

Current Trends and Purposes in Epilepsy Institutions

Discharge of People with Epilepsy into the Community

Although actual discharge rates are difficult to determine on a large scale, the decline in total numbers of beds in the United Kingdom during the last years, set against the rise in overall admission rates mentioned previously, indicates a fairly marked process of deinstitutionalization (Fig. 2). The population remaining in residence does so for any of the following reasons: (a) A patient does not wish to be discharged; (b) there is no appropriate facility in the home area, even though the care needs are not excessively high; (c) care needs—whether social, medical, or both—are high, and the local services would be unable to provide the same level of support and, when appropriate, medical intervention.

Coassessment of Learning Disability (Mental Handicap)

Another problem arises in some cases for which service must provide guidance. Different professional groups may have varying views about a patient's primary problem; for example, neurologic services may see the main problem as psychiatric or social, and so on. This is why, in the United Kingdom, mental handicap (learning disability) services are increasingly taking on the management of learning disabled patients with complex epilepsy, although this currently identifies a need for training in staff working in this area. People with learning disability should have the same quality of investigation and treatment as the rest of the population. Epilepsy is very common among these individuals and, because of their special needs, intensive investigation may be necessary. The residential centers have the capacity to offer an integrated approach in which epilepsy and learning difficulties are assessed together. Medical assessment involves detailed observation of behavior and seizures in conditions that approximate those of everyday life. Education of both caregivers and clients can be achieved, and the needs of caregivers taken into account.[15] With children, the residential setting can provide a detailed multidisciplinary assessment for a prolonged period in a nonclinical environment, and then continued management with a true 24-hour curriculum. A detailed neuropsychiatric study of the children in one residential special school for epilepsy showed that, although nearly two-thirds had been referred because of behavioral problems, the rate of observed psychiatric disorder while they were at the school was only 42%. Given the overall disabilities of the sample population, (low IQ, brain damage, frequent seizures, poor family background), it was considered surprising that the prevalence of psychiatric disorder was not higher. The authors commented, “It may be that the stable environment of a residential school involves fewer stresses that might precipitate or maintain psychiatric disturbance…. Absence of stigma, efficient management of seizures and minimizing their effect on school attendance could also be beneficial in this respect.”[13]

Outcome on Discharge from Special Schools, Centers, and Hospitals

Surprisingly little follow-up research has been done on the results of discharge from residential centers. Meyer and Gray[21] drew attention to the lack of community provision for people with epilepsy, which affected quality of life in their sample. Nearly a quarter of former residents were living independently, whereas half were in supported accommodation. Regular employment had been found only in 5% of cases. On the other hand, 50% reported a continuing decrease in seizure frequency, and 32% felt more alert. Medagoda and Brown[20] found that failures of successful rehabilitation were mainly related to inadequate medical follow-up or the inability of caregivers in the community to cope with behavioral problems or seizures. Breakdown of community placement after discharge was caused by a combination of inappropriate selection of placement by the receiving social services and a lack of appropriate medical services for epilepsy. It was possible, however, to readmit patients to the epilepsy center and achieve a successful, planned discharge later when these needs were met.

Summary and Conclusions

The former colonies remain repositories of expertise in the multifactorial assessment and management of epilepsy because they continue to carry a positive culture of destigmatization. The need for their services has not diminished, but the environment in which those services are provided is changing. On the site of the traditional countryside residential setting, services are being developed to provide residential assessment away from the clinical atmosphere of the hospital. People with epilepsy who also have challenging behavioral and learning disabilities can undergo specialized assessment and treatment in this setting. A special role in the future might be found for work in the field of forensic neuropsychiatry. Certainly the trend to shorter, focused admissions will continue, with the center at the same time reaching out into the community and offering preadmission services and postadmission follow-up. Some epilepsy centers in Europe are actively developing in-community care projects by establishing small living units that are closer to patients' friends and families. This last development, if successful, will further integrate the long-stay residential facility, which has the advantage of being able to provide prompt, appropriate medical and social care, in the tradition of the best colonies, into the mainstream of the community. Although residential schools are taking on the function of short-term assessment and rehabilitation, it is likely that at least some children with complex epilepsy and associated neuropsychiatric problems will receive a large part of their education in such places. Epilepsy centers will continue to be involved in teaching and research. The question remains whether truly integrated services comprising health, social work, and education can continue to thrive in a social market. Only time will tell.

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Chapter 214

Psychopharmacology of Patients with Behavior Disorders and Epilepsy

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Introduction

Psychiatric disorders are common in patients with epilepsy, and they encompass the spectrum of conditions from those that are a direct consequence of the epileptogenic activity to others that are simply comorbid.[45]

Therapy for behavioral disorders still remains unsatisfactory, and many patients with epilepsy receive psychotropic medications (Table 1) not always based on their psychiatric symptoms.[81] Effective therapy depends on a correct diagnosis and a combination of psychotropic drug treatments and behavioral interventions when other factors, such as emotional stressors, are present. In addition, antiepileptic drugs (AEDs) are important psychotropic agents with positive and negative psychotropic properties in their own right that should be taken into account when evaluating psychiatric symptoms in patients with epilepsy.

The present chapter focuses on the main problems that a clinician may encounter when treating psychiatric disorders in patients with epilepsy. We examine the effects of AEDs on mood and behavior, and we briefly review main factors that may affect choice of therapy, and patient's response and compliance, when prescribing antidepressants or antipsychotic drugs. In reviewing these agents, we concentrate specifically on drug interactions and any potential proconvulsive risk they may pose.

Antiepileptic Drugs as Psychotropic Agents

During the last 15 years, the number of AEDs available clinically has nearly trebled,[71] thus providing the possibility of providing better-tailored therapy according to patients' needs but also revealing a wide spectrum of adverse effects.

In some cases, emergent psychiatric symptoms may be side effects of the AED therapy,[5,42] the result of interactions between the drug and some biologic vulnerabilities of the patient. Subjects with more severe forms of epilepsy are generally more at risk to develop psychiatric adverse events (PAEs),[60,62] whereas specific lesions in the limbic system, such as hippocampal sclerosis, seem to be associated with the liability to develop depressive symptoms.[61] The *forced normalization phenomenon* is well known to be an idiosyncratic reaction to a sudden seizure cessation that may happen with different AEDs in predisposed patients, but whose characteristics are largely unknown.[59]

On the other hand, we have to take into account the fact that AEDs are extensively used in psychiatric practice for a broad spectrum of psychiatric disorders, especially bipolar disorders, and some are well known to stabilize mood. Since its introduction into the clinical management of epilepsy, carbamazepine has been reported to have psychotropic properties. Over time, several controlled studies have been carried out comparing the effects of carbamazepine in acute mania with placebo, lithium, or neuroleptics.[15] These studies have shown that carbamazepine is equivalent to lithium over a period of 8 weeks, and that the time course of the antimanic effect is a little slower than with neuroleptics but equivalent to lithium. This is relevant for those patients who are refractory to lithium and require an alternative to it. Carbamazepine has also been shown to be an effective treatment for the prophylaxis of bipolar disorder, with controlled studies suggesting that patients who are referred to as rapid cyclers (namely, patients with an unstable bipolar disorder with rapid fluctuations of more than four episodes a year), do best on carbamazepine or a combination of carbamazepine and lithium.[93] This approach has several advantages over the use of neuroleptics for such conditions, such as the avoidance of tardive extrapyramidal symptoms.

Valproate has been used in manic episodes, depressive episodes, and the maintenance therapy of bipolar disorder.[96] The strongest supporting evidence is for it use in acute mania, with somewhat less supporting evidence for the other conditions. Valproate may have an adverse effect on behaviors such as affective lability, aggression, and impulsivity across a range of different clinical contexts but, at the moment, controlled studies are available mainly for bipolar depression.

Among the new AEDs, some of them (e.g., tiagabine) have failed to show any efficacy in primary psychiatric disorders whereas others (e.g., topiramate) may have adjunctive uses, such as weight loss in the management of obesity. The data on the effects of oxcarbazepine on psychiatric disorders are limited and definitely less conclusive than those regarding carbamazepine. However, oxcarbazepine seems to be less effective than lithium but as effective as carbamazepine in acute mania; oxcarbazepine is probably better tolerated than carbamazepine.[94] The lack of efficacy of gabapentin in bipolar disorders has emerged from controlled studies have failed to detect such an effect.[29]

During clinical trials in the development of lamotrigine as an AED, it was observed that it had antidepressant properties. The cumulative results of the studies done so far provide evidence that lamotrigine is effective in the management of the depressed phase in bipolar disorder type II and in the long-term stabilization of mood in patients with rapid-cycling bipolar disorder.[36]

Among AEDs in development, pregabalin is probably the most interesting molecule. Controlled studies have demonstrated that it is better than placebo in anxiety disorders such as generalized anxiety disorder.[69]

Table 1 Brief classification of psychotropic drugs

ANTIDEPRESSANTS
Mono-Amino-Oxidase Inhibitors (IMAOs)
Moclobemide
Tricyclic antidepressant drugs (TCAs)
Amitriptyline, nortriptyline, clomipramine, imipramine, desipramine
Selective Serotonin Reuptake Inhibitors (SSRIs)
Fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, escitalopram

Noradrenergic uptake inhibitors (NARIs)

Reboxetine

Noradrenaline-Serotonin Uptake Inhibitors (NSRIs)

Venlafaxine, duloxetine

Noradrenaline-Selective Serotonin Antidepressants (NASSAs)

Mirtazapine

Serotonin Antagonist and Reuptake Inhibitors (SARIs)

Trazodone, nefazodone

ANTIPSYCHOTICS

Typical

Phenothiazines

Thioridazine, mesoridazine, chlorpromazine, prochlorperazine

Butyrophenones

Haloperidol

Atypical

Benzisoxazoles and benzisothiazoles

Risperidone, ziprasidone, perospirone

Thienobenzodiazepine, dibenzothiazepine, dibenzothiazepine derivatives

Clozapine, olanzapine, quetiapine

MINOR TRANQUILLIZERS – Barbiturates, Benzodiazepines, Others

MOOD STABILIZERS – Lithium

OTHERS – ß-Blockers, buspirone

Thus, data published to present suggest an important role for AEDs in psychiatric disorders. Unfortunately, it is difficult to extrapolate findings from these studies, performed with psychiatric patients, directly to patients with epilepsy. Obviously, it would be very useful to know whether AEDs have a positive influence on the psychic status of patients with epilepsy beyond their influence on seizure activity. However, there is little scientific evidence for this; most of the studies are uncontrolled and based on quality-of-life parameters rather than on a formal psychiatric evaluation. Because the simultaneous use of an AED as an anticonvulsant and antidepressant or mood stabilizer should be an important option for a rational pharmacotherapy in patients with uncontrolled epilepsy and comorbid psychiatric disorders, the need is great for further studies.

During the last few years, lamotrigine is the only AED investigated also as a psychotropic drug in patients with epilepsy. A randomized, placebo-controlled, double-blind, cross-over study of lamotrigine in 81 patients with refractory partial seizures showed some improvement in two subscales (happiness and alertness) in a health-related quality of life model but not on the other four scales specific for self-esteem, mood, anxiety, and depression.[82] Two double-blind studies of la-motrigine verus, respectively, carbamazepine[27] and valproate[16] demonstrated some improvement in quality of life outcomes. An open study[40] reported a significant antidepressant effect of lamotrigine in 13 patients with uncontrolled epilepsy and depression. Moreover, in two different studies, we have observed that lamotrigine significantly reduced the occurrence of PAEs during therapy with topiramate[60] or levetiracetam.[62] All these studies taken together suggest a possible role of lamotrigine as an antidepressant or mood stabilizer in those patients with uncontrolled epilepsy and depressive symptoms.

Pharmacokinetic Interactions Between Antiepileptic Drugs and Psychotropic Drugs

Pharmacokinetic Interactions with Antidepressants

Several factors must be taken into account when predicting the outcome of a potential interaction: Patient-related (sex, age, ethnicity) and drug-related (the presence of active metabolites, the activity and potency at the enzyme site, the therapeutic window).[70] The role of the CYP450 enzyme system and glucuronosyltransferases (UGTs) in clinical psychopharmacology is increasingly recognized, and many papers have been published about pharmacokinetic interactions between AEDs and psychotropic drugs.[55,57,58]

Tricyclic antidepressants (TCAs) such as amitriptyline, clomipramine, and imipramine, are mainly metabolized by CYP1A2, -2D6, and -3A4 (Table 2). Nortriptyline and desipramine are, respectively, the active metabolites of amitriptyline and imipramine and are subsequently metabolized by CYP2D6.[80] Moclobemide is primarily metabolized by the CYP2 C subfamily, of which it is probably an inhibitor,[28] whereas the atypical antidepressants mianserin and trazodone are metabolized by CYP2D6.[11]

The selective serotonin reuptake inhibitors (SSRIs) fluoxetine and paroxetine are metabolized by CYP2D6, whereas sertraline, fluvoxamine, and citalopram are respectively metabolized by CYP3A4, -1A2, and -2 C.[64] Paroxetine and fluvoxamine are inhibitors of CYP2D6[74] and -1A2,[7] respectively (Table 3). Fluoxetine is a moderate inhibitor of CYP3A4, but, like paroxetine, is a potent inhibitor of CYP2D6. No clinically significant induction-inhibition properties have been demonstrated for sertraline and citalopram.[64]

Among the new generation of antidepressant drugs, venlafaxine is primarily metabolized by CYP2D6,[17] whereas CYP3A4 metabolizes nefazodone and reboxetine.[87] Nefazodone is a potent inhibitor of this enzymatic pathway.[87]

Generally, phenobarbital, carbamazepine, and phenytoin stimulate the metabolism of TCAs, whereas valproate can increase their plasma levels[55] (Table 4). An open-label study investigated the effect of valproate on amitriptyline and its active metabolite nortriptyline.[97] The mean area under curve (AUC) and the peak plasma concentration, for the sum of nortriptyline and amitriptyline, was 42% and 19% higher, respectively.

In a case series of 13 patients with major depression, the effects of carbamazepine on imipramine and desipramine serum concentrations have been investigated.[89] The authors demonstrated that carbamazepine affects not only the metabolism of both drugs but also their protein binding, thus leading to a significant increase in the free fraction.

Table 2 CYP enzymes involved in psychotropic drug metabolism

CYP1A2	CYP2C9/10	CYP2C19	CYP2D6	CYP3A4
Antidepressants	**Antidepressants**	**Antidepressants**	**Antidepressants**	**Antidepressants**
TCAs	Sertraline	Citalopram	Fluoxetine	Nefazodone
Fluvoxamine	Fluoxetine	Escitalopram	Fluvoxamine	Sertraline
Mirtazapine	Amitriptyline	Sertraline	Citalopram	Venlafaxine
Duloxetine	Bupropion	Clomipramine	Escitalopram	Reboxetine
Antipsychotics	**Anticonvulsants**	Imipramine	Duloxetine	Escitalopram
Chlorpromazine	Phenytoin	Moclobemide	Paroxetine	Mirtazapine
Haloperidol	**Antipsychotics**	**Anticonvulsants**	Mianserin	Trazodone
Clozapine	Thioridazine	Phenytoin	Venlafaxine	TCAs
Olanzapine	Olanzapine	Mephenytoin	Trazodone	**Antipsychotics**
Ziprasidone		Esobarbital	Nefazodone	Haloperidol
		Mephobarbital	Maprotiline	Clozapine
		Phenobarbitone	Mirtazapine	Risperidone
		Primidone	TCAs	Ziprasidone
			Antipsychotics	Iloperidone
			Chlorpromazine	Quetiapine
			Thioridazine	Aripiprazole
			Haloperidol	**Anticonvulsants**
			Olanzapine	Carbamazepine
			Risperidone	Zonisamide
			Iloperidone	Tiagabine

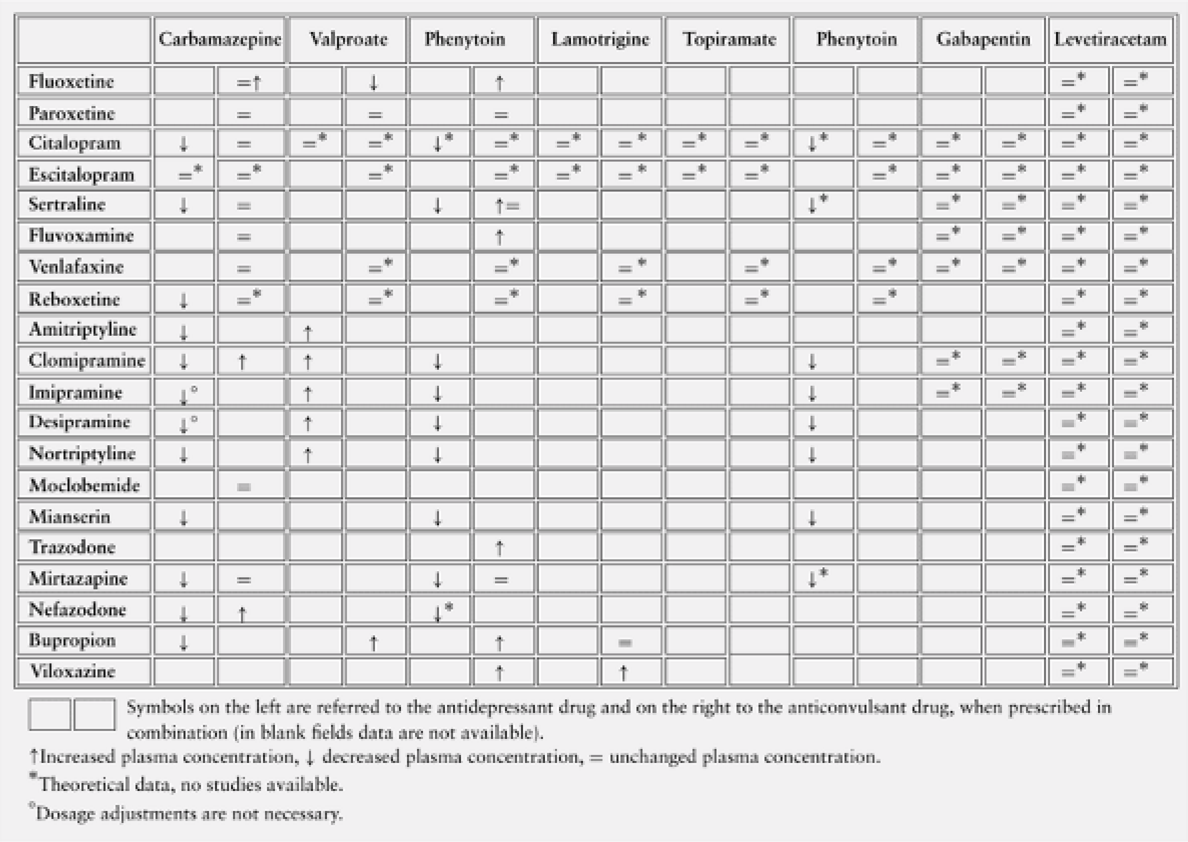
Table 3 CYP enzymes inhibited or induced by different psychotropic drugs

	Inhibitors		
CYP isoenzyme	**Antidepressants**	**Antipsychotics**	**Inducers**
CYP1A2	Fluvoxamine Fluoxetine Paroxetine Sertraline		St. John's wort
CYP2C9/10/19	Fluoxetine Sertraline Fluvoxamine	Thioridazine Clozapine	Phenobarbital Carbamazepine
CYP2D6	Fluoxetine Paroxetine Sertraline Bupropion Duloxetine Clomipramine	Thioridazine Haloperidol Clozapine Olanzapine Risperidone	
CYP3A4	Norfluoxetine Nefazodone Fluvoxamine	Chlorpromazine Thioridazine Haloperidol Risperidone	Carbamazepine Barbiturates Phenytoin St. John's wort

Data about fluoxetine-carbamazepine interactions are contradictory and are still based on two old studies. The first one is a formal pharmacokinetic study using healthy male volunteers, in which the authors observed a slight increase in carbamazepine AUC levels and a decrease in 10,

11-carbamazepine epoxide AUC.[30] The second study is a small series of eight patients with epilepsy who showed no modifications in carbamazepine plasma levels before and after fluoxetine administration.[85] These two studies are not comparable mainly because the activity of CYP enzymes is influenced by different factors, namely age, sex (in the first study the authors used only male patients), ethnicity, and so on.

The inhibition properties of several SSRIs on phenytoin metabolism have been tested in an in vitro study with human liver microsomes.[86] The risk for a phenytoin-SSRI interaction seems to be higher with fluoxetine and less likely with the others (paroxetine and sertraline).



	Carbamazepine		Valproate		Phenytoin		Lamotrigine		Topiramate		Phenytoin		Gabapentin		Levetiracetam	
Fluoxetine		=↑		↓		↑									=*	=*
Paroxetine		=		=		=									=*	=*
Citalopram	↓	=	=*	=*	↓*	=*	=*	=*	=*	=*	↓*	=*	=*	=*	=*	=*
Escitalopram	=*	=*		=*		=*	=*	=*	=*	=*		=*	=*	=*	=*	=*
Sertraline	↓	=			↓	↑=					↓*		=*	=*	=*	=*
Fluvoxamine		=				↑							=*	=*	=*	=*
Venlafaxine		=		=*		=*		=*		=*		=*	=*	=*	=*	=*
Reboxetine	↓	=*		=*		=*		=*		=*		=*			=*	=*
Amitriptyline	↓		↑												=*	=*
Clomipramine	↓	↑	↑		↓						↓		=*	=*	=*	=*
Imipramine	↓°		↑		↓						↓		=*	=*	=*	=*
Desipramine	↓°		↑		↓						↓				=*	=*
Nortriptyline	↓		↑		↓						↓				=*	=*
Moclobemide		=													=*	=*
Mianserin	↓				↓						↓				=*	=*
Trazodone						↑									=*	=*
Mirtazapine	↓	=			↓	=					↓*				=*	=*
Nefazodone	↓	↑			↓*										=*	=*
Bupropion	↓			↑		↑		=							=*	=*
Viloxazine						↑		↑							=*	=*

☐☐ Symbols on the left are referred to the antidepressant drug and on the right to the anticonvulsant drug, when prescribed in combination (in blank fields data are not available).

↑Increased plasma concentration, ↓ decreased plasma concentration, = unchanged plasma concentration.

*Theoretical data, no studies available.

°Dosage adjustments are not necessary.

Table 4 Pharmacokinetic interactions between anticonvulsant and antidepressant drugs

Possible kinetic interactions between paroxetine and carbamazepine, valproate, and phenytoin have been investigated in a single-blind, placebo-controlled, cross-over trial.[3]

Paroxetine caused no change in plasma concentrations and protein binding of the anticonvulsants. Studies of paroxetine plasma concentrations are lacking, but the major enzymatic pathway is a non-inducible enzyme (CYP2D6); therefore, modifications in plasma levels are unlikely when paroxetine is coadministered with AEDs with inducing properties.

Leinonen et al.[51] observed an increase in citalopram levels when carbamazepine was substituted with oxcarbazepine in two patients, demonstrating a significant induction effect of carbamazepine on citalopram metabolism. Steinacher et al. confirmed this observation in an open study of six patients, showing that a 4-week treatment with carbamazepine decreased the plasma concentration of S-citalopram and R-citalopram by 27% and 31%, respectively.[88]

The potential interaction between carbamazepine and fluvoxamine has been evaluated in a small open study of eight patients with epilepsy in steady-state for carbamazepine; no significant changes in carbamazepine and carbamazepine-10,11-epoxide occurred.[85] There are no studies of valproate-fluvoxamine interactions.

In the literature, two studies have investigated a possible effect of sertraline on phenytoin and carbamazepine metabolism. A double-blind, randomized, placebo-controlled study with 30 healthy volunteers showed no modifications in phenyt-oin pharmacokinetics.[77] The same authors, in a double-blind, randomized, placebo-controlled study on 14 healthy volunteers, observed no significant effects of sertraline on carbamazepine metabolism.[78] Conversely, Pihlsgard and Eliasson clearly showed that phenytoin and carbamazepine significantly reduced sertraline plasma concentrations.[72] Bonate et al.[6] demonstrated no drug interaction between clonazepam and sertraline in a randomized, double-blind, placebo-controlled, cross-over study with 13 subjects.

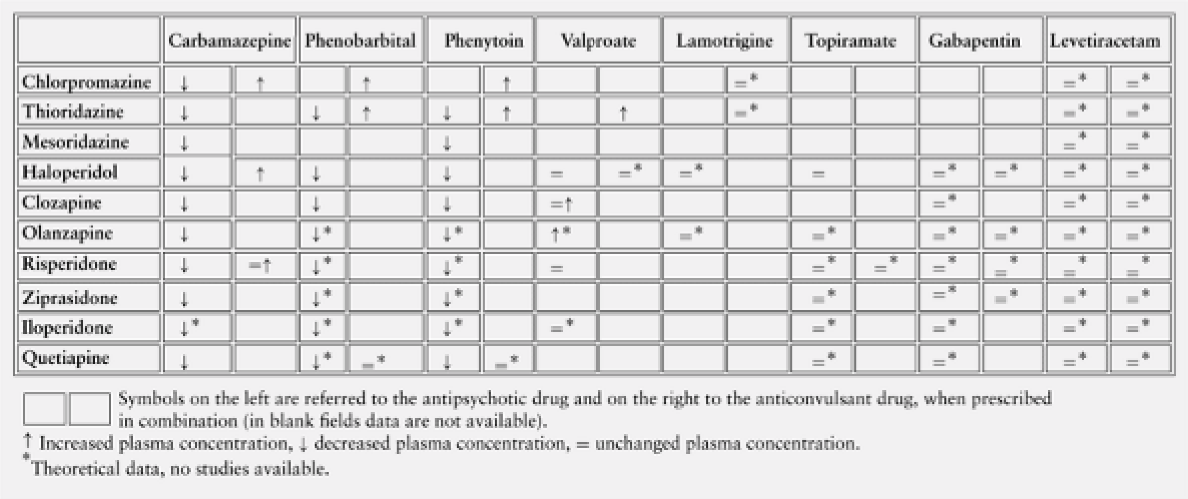
No clinical studies are available about potential interactions between venlafaxine and AEDs, whereas a randomized, cross-over study with 18 male subjects showed no pharmacokinetic interactions between venlafaxine and diazepam.[92]

Laroudie et al.[48] investigated kinetic interactions between nefazodone and carbamazepine in 12 healthy subjects. They observed a significant decrease in nefazodone AUC and an increase in carbamazepine AUC, demonstrating a potential inhibition property of nefazodone on carbamazepine metabolism.

An open-label, randomized, parallel group study in healthy male subjects investigated the possibility of pharmacokinetic interactions between mirtazapine and phenytoin. Coadministration of the antidepressant does not alter the steady-state pharmacokinetic of phenytoin, which, conversely, can decrease mirtazapine plasma levels by 46% on average.[83]

Ketter et al.[41] investigated the safety and efficacy of carbamazepine-moclobemide cotreatment in a double-blind study. The combination was well tolerated, with no modifications in carbamazepine kinetics, but they did not assess moclobemide plasma concentrations.

It has been well established that AEDs with induction properties determine a significant reduction in mianserin plasma concentrations.[58]



	Carbamazepine		Phenobarbital		Phenytoin		Valproate		Lamotrigine		Topiramate		Gabapentin		Levetiracetam	
Chlorpromazine	↓	↑		↑		↑				=*					=*	=*
Thioridazine	↓		↓	↑	↓	↑		↑		=*					=*	=*
Mesoridazine	↓				↓										=*	=*
Haloperidol	↓	↑	↓		↓		=	=*	=*		=		=*	=*	=*	=*
Clozapine	↓		↓		↓		=↑						=*		=*	=*
Olanzapine	↓		↓*		↓*		↑*		=*		=*		=*	=*	=*	=*
Risperidone	↓	=↑	↓*		↓*		=				=*	=*	=*	=*	=*	=*
Ziprasidone	↓		↓*		↓*						=*		=*	=*	=*	=*
Iloperidone	↓*		↓*		↓*		=*				=*		=*		=*	=*
Quetiapine	↓		↓*	=*	↓	=*					=*		=*		=*	=*

☐☐ Symbols on the left are referred to the antipsychotic drug and on the right to the anticonvulsant drug, when prescribed in combination (in blank fields data are not available).
↑ Increased plasma concentration, ↓ decreased plasma concentration, = unchanged plasma concentration.
*Theoretical data, no studies available.

Table 5 Pharmacokinetic interactions between anticonvulsant and antipsychotic drugs

The use of bupropion is limited in patients with epilepsy because of a high seizure risk. Carbamazepine is a potent inducer of its metabolism, reducing the antidepressant plasma concentrations to undetectable levels.[75] On the other hand, bupropion has shown marked inhibition properties on valproate[75] and phenytoin metabolism.[90] In a randomized, open-label, cross-over study with 12 healthy subjects, the kinetic parameters of a single 100-mg lamotrigine dose were not modified by steady-state, slow-release bupropion therapy.[65]

Pharmacokinetic Interactions with Antipsychotics

Neuroleptics, such as phenothiazines, are metabolized by intestinal sulfoxidases, although CYP2D6 plays an important role in chlorpromazine and thioridazine metabolism.[67] They are also partially metabolized by CYP1A2 and -2C, respectively, and partially inhibit CYP3A4.[12] Phenothiazines, in particular thioridazine, are potent inhibitors of CYP2D6.[67] Haloperidol is metabolized by CYP3A4 and -1A2, and only partially by -2D6.[46]

Among the atypical antipsychotics, clozapine undergoes extensive hepatic metabolism; multiple CYP enzymes are involved, however, the two most prominent are CYP1A2 and -3A4.[76,77]

The newer generation of antipsychotic drugs seem to have more favorable pharmacokinetic profiles. Risperidone is primarily metabolized by CYP2D6, although a correlation study using a panel of human microsomes suggested that CYP3A4 may also be involved.[22] Olanzapine undergoes extensive hepatic metabolism and shares some of its metabolic routes with the structurally and pharmacologically related clozapine, but UGTs appear to be a major metabolic pathway.[79] Quetiapine shares some pharmacologic and structural characteristics with clozapine and olanzapine, but CYP3A4 is most likely the main isoenzyme involved in its metabolism.[17]

Thioridazine is metabolized by intestinal sulfoxidases that are induced only partially by AEDs such as carbamazepine, phenytoin, and phenobarbital, but some authors have reported an increased clearance of thioridazine and a relevant decrease of mesoridazine (the active metabolite of thioridazine) levels in patients taking carbamazepine and or phenytoin.[70] On the other hand, thioridazine, as chlorpromazine and prochlorperazine, inhibits phenytoin, phenobarbital, and valproate metabolism[31] (Table 5).

Several studies have shown that haloperidol plasma levels decrease by 50% to 60% after carbamazepine coadministration, with concomitant worsening of the psychiatric clinical features.[37,38,43] In one study, therapeutic drug monitoring data from 231 schizophrenic inpatients demonstrated that haloperidol levels were 37% and 22% lower in patients comedicated with carbamazepine or phenobarbital, respectively.[35] Carbamazepine seems to decrease haloperidol concentrations in a dose- or concentration-dependent manner, even at subtherapeutic doses of the drug.[100] Interestingly, Iwahashi et al.[37] observed that serum carbamazepine concentrations in patients treated without haloperidol were significantly decreased (on average 40%), as compared with those treated with both carbamazepine and haloperidol. In a controlled clinical trial on the effects of carbamazepine and valproate cotreatment on the plasma levels of haloperidol and on the psychopathologic outcome in schizophrenic patients, valproate led to no significant effects on haloperidol plasma levels, and its use was associated with a better psychopathologic outcome.[34]

As far as new AEDs are concerned, the use of topiramate did not lead to clinically significant modifications on haloperidol pharmacokinetics in a formal pharmacokinetic study with healthy volunteers.[14]

Spina et al.[84] compared the risperidone total active moiety (risperidone plus its active metabolite, tamoxifen steady-state plasma concentrations in patients treated with risperidone alone and in patients comedicated with carbamazepine or valproate, matched for age, sex, body weight, and antipsychotic dosage. Although carbamazepine caused a significant decrease in active moiety concentrations, valproate (at dosages up to 1,200–1,500 mg/day) had minimal and clinically insignificant effects on plasma levels of risperidone-tamoxifen, suggesting

that valproate could be added safely to an existing treatment with risperidone.

Recently, the relationship between CYP2D6 genotype and carbamazepine-risperidone interaction has been investigated, suggesting that the decrease in risperidone concentration is dependent on the CYP2D6 activity.[66] In an open study with eight patients with epilepsy, a mild increase in carbamazepine plasma levels has been described after the addition of risperidone 1 mg.[57] Although this interaction seems not to be clinically relevant, it may suggest that the antipsychotic, or more likely its metabolites, could modulate CYP3A4 activity and, interestingly, a different enantioselective 9-hydroxylation of risperidone by CYP2D6 and CYP3A4 has been shown in a separate study.[26]

Ziprasidone and perospirone are newly available antipsychotic drugs, and there are few clinical studies about their interactions. An open, randomized, parallel-group study using healthy volunteers showed a clinically insignificant reduction (<36%) in steady-state ziprasidone levels after carbamazepine prescription.[54]

Generally, phenytoin, phenobarbital, and carbamaze- pine[21,77] cause a decrease in clozapine plasma concentrations. However, carbamazepine is rarely used in combination with clozapine because of the high risk of hematologic side effects. Existing data on the effect of valproate coadministration are contradictory.[8,20] According to some authors, valproate may have a moderate inhibiting effect on the demethylation of clozapine (catalyzed by CYP1A2 and -3A4), but clozapine disposition is characterized by a large interindividual variability, being affected by age, gender, body weight, dose per kilogram, smoking habits, and ethnicity.[10]

Olanzapine plasma concentrations are decreased by carbamazepine,[53] but the authors of the study did not consider this interaction clinically relevant because of the wide therapeutic index of the antipsychotic. However, other authors have pointed that carbamazepine increases the metabolism of olanzapine, with a decrease in plasma concentrations of the latter by 38%.[52]

Quetiapine is a newly introduced atypical antipsychotic, and clinical data about pharmacokinetic interactions are lacking. Phenytoin seems to induce the metabolism of quetiapine, suggesting that dosage adjustment of quetiapine may be necessary when it is coprescribed with other AED enzyme inducers such as carbamazepine or phenobarbital.[98] Interestingly, Fitzgerald and Okos reported two patients who experienced markedly elevated levels of the carbamazepine active metabolite (carbamazepine-10,11-epoxide) with the occurrence of symptoms of neurotoxicity such as ataxia and agitation. The authors suggested that quetiapine may inhibit the epoxide hydrolase and/or glucuronidation of carbamazepine-10,11-trans-diol in the same way as valproate and lamotrigine possibly do.[23]

Pharmacokinetic Interactions with Anxiolytics

Generally, anxiolytics have a wide therapeutic index; therefore the clinical relevance of pharmacokinetic interactions is very limited. AEDs with enzyme-inducing properties may stimulate the biotransformation of many benzodiazepines. Carbamazepine has been reported to induce clobazam and diazepam metabolism,[86] and has also been demonstrated to enhance the clearance of clonazepam and alprazolam.[25,81] A clinically relevant interaction occurs between AEDs-inducers and midazolam and triazolam,[4] which are extensively metabolized by CYP3A4. Conversely, newer hypnosedatives such as zopiclone, zolpidem, and zaleplon are biotransformed by several CYP isoenzymes in addition to CYP3A4, resulting in CYP3A4 inducers having a lesser effect on their biotransformation.[33]

The Risk of Seizures with Psychotropic Drugs

Antidepressants

The association of antidepressants with the provocation of seizures is quite well known in medical literature. However, most of the data arise from studies using in vitro techniques, animal studies, and clinical observations; few specific clinical studies exist.[91] Within the therapeutic range for serum levels, the incidence of seizures is less than 0.5% for most antidepressants when other risk factors are excluded.

Table 6 Seizure risk for some antidepressant and antipsychotic drugs

High risk	Intermediate risk	Low risk
Antidepressants	Mianserin	SSRIs
Bupropion	Amitriptyline	Trazodone
Clomipramine	Imipramine	Venlafaxine
Maprotiline		IMAOs

		Mirtazapine
		Desipramine
		Nortriptyline
Antipsychotics	Haloperidol	Risperidone
Chlorpromazine (dose related)	Quetiapine	Ziprasidone
Clozapine (titration and dose related)	Olanzapine	

It has been known ever since their introduction that TCAs are proconvulsant and lead to seizures. This predilection, for example in overdose, is one method of fatality.[73] However, the mechanism responsible for inducing seizures with these heterocyclic antidepressants remains unclear. The most obvious explanation would be that the increase in serotonin and noradrenaline neurotransmission mediates this effect, because all antidepressants appear to display one or both of these properties. However, both these neurotransmitters have also been demonstrated to have some anticonvulsant effects in animal and human models. Such findings may explain those papers that suggest a possible therapeutic effect of antidepressants such as TCAs and newer antidepressants in low doses in the treatment of seizures.[99] Such observations have led to the suggestion of a biphasic effect, with lower levels being anticonvulsant and higher levels proconvulsant. Further, Leander[49] demonstrated, in an animal model of epilepsy, that the selective inhibition of serotonin uptake by fluoxetine can enhance the anticonvulsant potency of phenytoin and carbamazepine.

Antidepressants that pose a higher risk of seizures include mianserin, clomipramine, and maprotiline (Table 6). The risk associated with bupropion appears to be acceptably low when recommended prescribing practices are used. Of the newer generation of drugs, the SSRIs are considered to provoke less in the way of seizures than do TCAs.[32] Extensive clinical and research experience with all the SSRIs suggest that the epileptogenic potential of this class of drugs is quite low and not much different from placebo. However, a special caution should be mentioned with regard to the risk of hyponatremia. This idiosyncratic phenomenon has been associated with all the SSRIs and represents an important variable that may precipitate seizures.

Antipsychotic Drugs

Traditional antipsychotics have long been recognized as a class of drugs that can increase the risk of seizures. To determine the risk for drug-induced seizures, different approaches have been adopted: Observational studies (case-control studies and case reports), drug-induced electroencephalographic (EEG) changes, animal models, and in vitro techniques in isolated tissue samples. One of the problems of the recent literature is that most of the studies have been performed on psychiatric patients, and it is not known whether drug related seizures in non–epileptic patients really predict risk in patients with epilepsy, and whether different epileptic syndromes have different risks for psychotropic-induced seizures.

Generally, chlorpromazine and clozapine are considered proconvulsant in epileptic patients, the former only at high doses (1,000 mg/daily) and the latter at medium and high doses (>600 mg/daily).[2] Clozapine frequently causes epileptiform EEG changes and seizures in 3% to 5% of patients treated, even at therapeutic doses. Devinsky et al.[13] observed a mean prevalence of seizures of 2.9% with clozapine and, considering different doses, the prevalence was respectively given at 1%, 2.7%, and 4.4% for doses of less than 300 mg, 300 to 600 mg, or 600 to 900 mg per day. Pacia and Devinsky[68] analyzed only patients without a previous history of seizures, and the prevalence of seizures was respectively 0.9%, 0.8%, and 1.5% for the same range of doses as in the previous study. Thus, with clozapine, the proconvulsant effect seems to be a dose-related phenomenon but the role of the titration time and rate of increase of dose probably is also important.[47] Although the incidence of seizures rises to about 5% at doses 600 mg and EEG changes may be recorded at lower doses, it should be noted that these results emerge from patients with schizophrenia, and not epilepsy.[2] The seizures are often myoclonic, but can be generalized tonic–clonic or partial, depending on the individual patient.

Although, olanzapine is structurally related to clozapine, it is in the thienobenzodiazepine class of atypical antipsychotics and, along with quetiapine, premarketing studies showed a seizure rate of 0.9%.[50] Risperidone seems to have a low risk of seizures (about 0.3%), but data are taken from premarketing and postmarketing studies[2,50] (Table 6).

The use of Lithium in Patients with Epilepsy

Lithium carbonate is frequently used for manic episodes in bipolar disorder, in association with valproate and carbamazepine. Carbamazepine also demonstrates antimanic properties, and a possibly favorable pharmacodynamic interaction could be suggested; however, carbamazepine can increase the incidence of lithium toxicity. Kramlinger and Post[44] studied the effects of this combination in 23 patients with affective disorders. They observed a significant increase in many hematologic parameters (mainly the mean white blood cell count; lithium likely counteracts the neutropenic properties of carbamazepine) and a significant modification in thyroid function, with decreases in T4 and free T4. The opposing effects of carbamazepine and lithium on electrolyte regulation are well-known, with the potential occurrence of severe hyponatremia when lithium alone is stopped.[95]

The combination of lithium and valproate is widely used in rapid-cycling, manic, depressive, and mixed episode in bipolar disorder. This combination has a higher tolerability than the coadministration with carbamazepine, and a pharmacodynamic synergistic interaction has been suggested.[32] However, the combination of lithium and valproate may induce additive side effects, such as weight gain, sedation, and tremor.[24]

Chen et al.[9] investigated lithium pharmacokinetics when coprescribed with lamotrigine in 20 healthy subjects. There were no significant differences in lithium pharmacokinetic parameters. Abraham and Owen described a single case of lithium toxicity associated with topiramate cotherapy.[1] The authors suggested that topiramate, as a carbonic anhydrase inhibitor, may reduce lithium clearance and lead to toxic plasma levels.

The neurotoxic and convulsant effects of lithium are well known, but seizures are most common when plasma levels exceed 3.0 mEq/L. At therapeutic levels, the effect of lithium on seizure frequency in individuals with epilepsy is inconsistent.[19,39] Thus, although reports are conflicting, it appears that lithium can be prescribed in patients with epilepsy when mood-stabilizing therapy is necessary and alternative agents either fail or are not tolerated. In these situations, vigilant monitoring of lithium blood levels and for clinical signs of neurotoxicity is warranted.

Prescribing Psychotropic Drugs for Patients with Epilepsy

As noted earlier, most studies on the effects of AEDs on mood, or of psychotropic drug effects on seizures have been gathered from patients with psychiatric disorders and not from patients with epilepsy. However, some cross generalizations may be expected; for example, there is little reason to believe that a drug that is proconvulsant in psychiatric populations will not also be proconvulsant in people with epilepsy.

To minimize side effects and increase compliance, it is important to first of all discuss potential problems with the patient and, in particular, to settle any worries that the patient may have difficulty getting off the drugs because they may be addictive. Actually, the addictive potential of the antidepressant and the antipsychotic drugs is negligible, and some AEDs such as phenytoin are much more likely to be addictive and cause problems of abuse.

The psychotropic drugs should be introduced at low dosages, and the escalation rate should be slow (low and slow adage), but the patient's clinical progress must be carefully monitored. There is no point in prescribing the psychotropic and not seeing the patient again for several weeks.

Choice of drug is always difficult, especially because of so many newer agents from which to choose. The SSRIs are the favored antidepressants, and the atypical antipsychotics are best chosen for psychoses and in some settings for mood stabilization. If a patient has responded to a particular drug before, then it is sensible to opt for that prescription again.

The risk of an increase in seizures must always be mentioned, but this is not usually a problem in clinical practice, partly because patients are on AEDs, and partly because patients most susceptible to depression and psychoses are likely those with difficult-to-treat epilepsy, who have quite frequent seizures. In some patients who respond to the psychotropics but who do experience an exacerbation of seizures, a judicious increase in the AED therapy may be warranted.

A problem arises in the patient who has been seizure-free for a long time, but who develops a psychiatric disorder requiring treatment. Such patients are susceptible to the provocation of a seizure either on account of the proconvulsant potential of the drugs or because of a pharmacokinetic interaction. Careful discussion of the possibility of a seizure with the patient is mandatory.

Pharmacokinetic interaction possibilities are legion, as this chapter has demonstrated. Psychotropic drugs are not equivalent in their potential for drug interactions with AEDs. Each combination should be carefully considered, while taking into account all relevant variables related to the patient such as gender, age, ethnicity, smoking habits, body weight, and any associated renal or hepatic diseases.

Among antidepressants, the combination of nefazodone-carbamazepine is contraindicated because of the occurrence of toxic concentrations of the anticonvulsant. In other cases, from a clinical point of view, there are no particularly troublesome combinations. However, clinicians must be aware that fluoxetine has a long half-life, and the clearance of most antidepressants can be accelerated by enzyme-inducing AEDs.

As far as antipsychotic drugs are concerned, it must be kept in mind that the doses of neuroleptics should be always tailored on the patient's response. In almost all cases, enzyme inducers reduce the plasma levels of these drugs. The use of clozapine must be carefully monitored because its metabolism has high inter- and intraindividual variability and, especially in combination with valproate, interactions are difficult to predict. If there is concern about possible interactions, then serum AED levels should be taken before the administration of the psychotropic for later comparison.

Antidepressants must be given for at least 6 months to patients who have developed major depressive disorders, but variants, such as interictal dysphoric disorder (see Chapter 205), may resolve without therapy after a few days, or become repetitive and persistent, requiring longer-term mood stabilization. Antipsychotic drugs will be given at various schedules depending on the classification of the psychoses (see Chapter 204) and the severity. Stopping, as with starting these drugs, should be carried out slowly, and under adequate supervision.

Finally, the special role of clozapine in the psychoses should be noted. This drug may seem contraindicated in patients with epilepsy, especially on account of its proconvulsant liability. However, it has been used successfully in the management of the interictal psychoses of epilepsy, with certain provisions.[47] It is a remarkably useful antipsychotic in patients whose psychosis fails to respond to other atypical antipsychotics. The side effects of drooling and weight gain are further problems to its use, and it should not be used in patients who are on carbamazepine. However, a change of the latter to oxcarbazepine is an acceptable clinical maneuver. An EEG should be done before the administration of clozapine, in case of a deterioration of behavior, so that the development of a nonconvulsive status epilepticus can be identified and managed appropriately. The clozapine should be introduced slowly, white cell counts monitored, and increased in dose to between 300 and 600 mg if necessary, although some patients respond to lower doses.

The use of clozapine is most successful when given to a patient who has developed a psychosis and become seizure free, suggesting some variant of the theme of forced normalization and requiring perhaps a more proconvulsant antipsychotic for a clinical effect.

Summary and Conclusions

Although the mainstay of drug therapy in epilepsy relates to antiseizure medications, many patients have an associated psychopathology and receive psychotropic medications. In the past two decades the choice of such agents has increased considerably, and the introduction of new antidepressants such as the SSRIs and the atypical antipsychotics has allowed more patients to receive such drugs with a lessening of side effects. However, no psychotropic is free from treatment emergent effects, and they should only be prescribed when the clinical situation justifies it. It seems to be the case that many patients with epilepsy have unidentified psychiatric needs, and if anything psychotropic drugs are underprescribed.

Used judiciously, antidepressants and antipsychotic drugs can help bring resolution of psychopathology, but their use is always seen as part of a package of care which must also address social and psychotherapeutic needs.

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Chapter 215

Overview: Social Issues

Robert T. Fraser

Introduction

There has been longstanding concern in the field of epilepsy that, although progress continues to be made relative to medical management of the disability, including the development of new generations of antiepileptic medications, attention is less focused on the social adjustment of individuals with the disability. A survey of 420 individuals drawn from affiliates of the Epilepsy Foundation of America[17] suggests a number of ongoing concerns, including employment, marriage and money management, and diverse health-related concerns. An earlier study by Schacter et al.[16] indicates that 65% of the 150 respondents in an Epilepsy Association of Massachusetts study responded that they were psychosocially adversely affected by seizures and that this was true for even half of those with one seizure or less per year. A recent review by Theodore et al.[18] regarding epilepsy in North America describes poor quality of life, a high number of depression and anxiety days, marked unemployment and underemployment, continuing perceived stigma, and higher suicide rates. Although adults with well-controlled epilepsy[8] may not be as significantly affected as those with more active seizure conditions, this appears to be the minority of the epilepsy population.

The field of epilepsy is at a crossroads relative to addressing the psychosocial needs of people with this disability and their significant others. The impact of managed care, a lack of U.S. federal support for multidisciplinary centers, and other factors are reducing the emphasis on diverse aspects of social adjustment and needed psychosocial interventions. There is an increasing concern, however, about quality-of-life assessment related to medication or surgical intervention and diverse aspects of neuropsychological functioning, but a review of the presentations at the American Epilepsy Society's 2005 Annual Meeting in Washington, D.C., suggests less coverage and research investment in some of the areas discussed in this section of the book. There were almost no studies relating to psychosocial intervention. This underscores that clinical service demands and financial constraints are affecting the investment in psychosocial research and demonstration projects.

Overall, there are a number of areas in which the epilepsy population appears to be making some significant gains. In Chapter 216, Jacoby, Snape, and Baker make a helpful distinction between “felt” and “enacted” or actually experienced stigma. On an overview, attitudes toward people with epilepsy are continuing to become more positive. There are a number of mediators of attitudes toward epilepsy, including the educational levels of respondents and their perceptions of disability-related limitations. Jacoby et al. stress the importance of family support and clear intrafamily communication as being preventive of perceived stigma by offspring. They also endorse the importance of “target-specific change models,” for example, geared to adolescent attitudes, involving multiple and multitiered strategies within each efforts.

Although employment continues to be an international concern, in Chapter 219, Thorbecke and Fraser highlight the various aspects of the vocational assessment process, workplace accommodation, different model programs, and relevant national legislation that affect employability for those with epilepsy. Employment rates through specialized programs have been recorded to be as high as 89% for referrals with “epilepsy only” as a disability.[6] There is no question, however, that associated cognitive deficits, behavioral difficulties, and so on, are making successful employment outcomes more challenging. Specialized epilepsy vocational programs, however, will continue to be more effective, particularly for individuals with more involved epilepsy and associated disabilities. Unfortunately, there has been a lessening of emphasis on provision of employment services by the national Epilepsy Foundation (EF) in the United States. Today in the United States, specialized epilepsy vocational programs exist only at the University of Washington-Seattle, the University of California-San Francisco, and some EF affiliate agencies. Germany and Holland are among the few other countries that have specialized programs of this nature.

As Beran and colleagues indicate in Chapter 221, a number of gains have been made in the areas of legislation, driver licenses, and access to insurance. The Americans with Disabilities Act (ADA), signed into law in 1990, not only forbids discrimination in employment, but also requires reasonable accommodation (e.g., job restructuring) if an individual cannot perform the essential functions of a job. This type of legislation, although not necessarily affecting initial hiring decisions, can assist people with epilepsy to maintain their job position within the context of discriminatory or whimsical employer decisions to terminate. Eligibility for coverage under ADA has been difficult to establish for persons with good seizure control, but advocacy efforts by the U.S. EF and collaborators are being made to rectify this situation.

In relation to driver licenses, there is a general trend toward shorter seizure-free periods and a review of favorable modifiers prior to categorical driver licensing suspensions. This is not to say that advocacy and targeted physician effort will not be necessary in different areas of the world or within some U.S. states. Some countries, such as Japan and Russia, preclude driving after one seizure.[4] There remains a delicate balance between patient benefit and acknowledging risk factors and general safety.

Within the area of legislation, however, there is a continuing international need for advocacy, specifically in relation to health care coverage and reform. A number of U.S. insurance companies have used outdated actuarial data and failed to note the advances in diagnosis and treatment of epilepsy in making their health care access and financial rate decisions. This issue is not unique to the United States. Beran et al. emphasize the need to advocate in other areas such as epilepsy research and development and services to families. They end their chapter with a helpful section on strategies for use with political representation.

Over the years there has been a growing recognition of the need for social support for individuals with epilepsy. In Chapter 217, Austin, de Boer, and Shafer review the plethora of issues affecting psychosocial adjustment in epilepsy and a range of issues that can be targeted for intervention. Of particular value are guidelines for dailing living both inside the home and within the community. They also draw attention to the need for more “self-management” education in relation to the disability and research into the value of group versus individual educational programs or programs combining education, counseling, and even recreation, among other isues.

Despite the fact that psychosocial gains are being made in a number of areas, certain issue areas deserve increasing attention. Although there is a dramatic increase in quality-of-life assessment and an effort to measure the impact of seizure severity on patients' lives, there is a continuing theme in the literature[1,2,7] that patients feel poorly educated not only about epilepsy, but also about medications and potential side effects. As Buck et al.[2] indicate, patients place a significant premium on physicians who are not only knowledgeable, but are also communicative and approachable. Within the current managed care context in a number of countries and given the institutional demands on the physicians' time, it can be very difficult for physicians to make the effort carefully to explain epilepsy and issues in medical management to a patient and family members. Somehow, however, this needs to be done because it directly relates to patient compliance, among other care variables, in the prevention of the disabling condition. Several studies[5,10] show sample noncompliance rates exceeding 50%. It appears that time spent educating each patient about epilepsy and medication is well spent.

In general, there is a need for more educational programs for individuals with epilepsy and their significant others. In Chapter 217, Austin et al. point out that although the literature supports the need for epilepsy education, few educational programs (exceptions are the Modular Service Package Epilepsy [MOSES] and Sepulveda Epilepsy Education [SEE] programs) have been presented and systematically evaluated. Internationally, only a few clinics have formal educational programs for their patients with regard to their epilepsy and medications, and only one program could be identified in the literature[11,12] for children with epilepsy and their parents. The SEE program[17] has shown some very beneficial results on quality of life and seizure management for adolescents with epilepsy and their parents.

Although the U.S. Epilepsy Foundation and other national epilepsy associations have quality educational materials available (e.g., on cognition and epilepsy), significant marketing efforts through the media might be needed to promote their utilization. An obvious role for epilepsy organizations internationally is the development of formal educational programs about epilepsy and associated issues that also help physicians to take the time required to discuss their patients' concerns. Medication noncompliance and continuing advances in medication management are areas that need to be attacked simultaneously.

Marriage and family concerns also deserve continued emphasis. Educational programs for both patients and the general public could be very helpful in improving the prognosis for marriage—particularly for men. As Thompson and Upton indicate,[19] levels of stress and dissatisfaction within families can be high because those with epilepsy often face difficulties in maintaining primary work careers or even receiving respite care for their children. Within the context of psychosocial research, interventions with families and their impact on medical and social adjustment have been largely overlooked.

In Chapter 218, Seidenberg and Clemmons discuss issues relating to school functioning and school-to-work transition. They present a comprehensive review of seizure and neuropsychological correlates of academic dysfunction and discuss subtypes of learning disabilities and a comprehensive perspective on educational and vocational assessment. They also offer approaches to working with parents, teachers, and state vocational rehabilitation representatives. Again, there is a paucity of recent research on school functioning or successful school-to-work transition.

Of particular interest in this section is Chapter 220 by Rubin, Wiebe, and Gilliam on health outcomes. The chapter underscores the importance of adverse medication effects and depression/anxiety on quality of life and the need to assess and intervene with regard to these issues. Although it is understood that other health-promoting behaviors such as sleep quality and exercise also can affect quality of life, we do not yet have an integrated model of effects on quality of life.

Summary and Conclusions

Although progress has been made relative to the social adjustment of people with epilepsy, there remains much to be done. Considerable challenges face those in less industrialized countries, in which some of the issues in discrimination, employment, and so on, are only recently becoming obvious and receiving media attention. As discussed by Collings,[3] we remain at the early stages of examining international differences in psychosocial well-being and quality of life for this population. The challenge remains not only to identify these differences, but also to find funds to mount education and other psychosocial intervention efforts that currently are lacking. Although it appears that intervention during childhood and particularly adolescence[15] is crucial within this population, most existing intervention efforts appear to be conducted within short-term summer camp structures.[5] Although these are valuable, they are insufficient. More comprehensive and sustained psychosocial interventions need to be pursued and evaluated.

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Chapter 216

Social Aspects: Epilepsy Stigma and Quality of Life

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Introduction

In this chapter, we turn from consideration of epilepsy as a biomedical condition and the province of health professionals to consideration of epilepsy as a negative social label and the concern of social theorists, social policy makers, and disability activists. Epilepsy has long been considered as "undesired differentness,"[44] and, as a consequence, it has involved the application of formal and informal rules and sanctions against those affected by it. Legal discrimination against people with epilepsy dates back centuries and operates still,[56] even though in many countries persons with epilepsy are now considered as having a prescribed disability and so are offered protections under the law. A significant literature traces the history of epilepsy as stigma and documents the role of stigma and discrimination in its present-day social reality. From this, it is clear that the social problems arising from a diagnosis of epilepsy and the repercussions for quality of life, especially for those in whom it proves to be clinically benign, can represent a greater challenge than its medical management. How these problems can be minimized thus represents an important aspect of the overall management of epilepsy.

Epilepsy as a Social Label

Although considered the "sacred disease" by the ancient Greeks, in many ancient and primitive societies epilepsy was believed to originate from malignant causes and to be associated with sin and demonic possession. Seizures were often considered bad omens. There are references in the New Testament to epilepsy as a form of madness, and the notion of people with epilepsy as "lunatic" held widespread currency throughout the mediaeval period. Theories of epilepsy as contagion can also be traced back to antiquity.[108] Temkin[108] saw epilepsy as representing the historical struggle between magical and scientific conceptions of disease, with its medicalization in the Western world a victory for the latter. It is apparent, however, from studies of lay attitudes and beliefs toward epilepsy (see later discussion) that remnants of the former attitude continue to inform popular concepts of the condition even through to the present day. What is more, even when biomedical explanations for epilepsy emerged as triumphant during the Enlightenment,[82] the evolution of epilepsy from "badness to sickness"[22] brought with it its own associations to stigma, with studies linking epilepsy to aggressive or even criminal behavior, abnormal sexual activity, hereditary degeneracy, and a specific "epileptic personality," all of which have had power to reinforce negative stereotypes and hence perpetuate stigma.

Although the biomedically driven concept of the epileptic personality may have been discounted in recent years, Scambler[97,98] proposed an alternative sociologic construct of "epileptic identity" resting firmly on the view of epilepsy as not just a clinical problem but also a social label. Scambler suggested that people with epilepsy react symbolically to having seizures and develop a special identity or "view of the world" underpinned by their expectations of stigma. This world view is not generally present in their lives, and is triggered by particular events; when it is triggered, however, it has the effect of predisposing them to try to cover up the signs of their condition and pass themselves off as “normal.” Scambler found that almost everyone he interviewed was distressed by receiving a diagnosis of epilepsy because “they showed a more or less clearly defined awareness that a physician's diagnostic statement… had transformed them from ‘normal’ persons to ‘epileptics’ and this was first and foremost a stigmatising condition.” Their perceptions of epilepsy as stigmatizing were clearly anchored in what they believed to be the predominantly negative attitudes of others, which constituted a major source of anguish to them, but for which, Scambler argued, there was actually little empirical support.

Based on his analysis, he proposed a “hidden distress” model wherein the stigma of epilepsy and its repercussions for quality of life are best understood by making a distinction between “felt” and “enacted” stigma.[100] Felt stigma here refers to the shame of being epileptic and the fear of encountering epilepsy-linked enacted stigma, that is, enacted stigma to actual episodes of discrimination against people with epilepsy *solely* on the grounds of them having epilepsy. Scambler concluded that felt stigma was far more prevalent than enacted stigma, with almost everyone in his study appearing to suffer from it, even if only intermittently. It was also, in effect, a self-fulfilling prophecy inasmuch as their fear and shame about epilepsy led people to attempt to conceal their condition from others, denying themselves the opportunity to test whether the enacted stigma and discrimination they expected would, in fact, materialize.

The power of the social label of epilepsy is also illustrated in the work by Schneider and Conrad,[101] who reported that the people they interviewed with epilepsy saw it as a kind of “moral weight” they had to carry and so was far worse than simply having seizures. Some, described as “unadjusted” to their diagnosis, appeared to be overwhelmed by the shame of having epilepsy; they saw it as precluding or limiting their access to important personal and social resources, negatively affecting different aspects of their quality of life and preventing their happiness. For some people, referred to by Schneider and Conrad as “debilitated,” it appeared that the label of epilepsy totally defined them, and their response was often to withdraw from contact with the nonepileptic world.

Table 1 Dimensions of stigma according to jones et al.[66]

Concealability	Extent to which the stigmatizing condition is visible to others
Course of the mark	Whether the condition becomes more salient over time
Disruptiveness	Degree to which it interferes with social interactions
Aesthetics	Subjective reactions of others to the unattractiveness of the stigmatizing condition
Origin	Whether seen as congenital, accidental, or intentional
Peril	Perceived danger of the condition to others

Theories of Stigma in the Context of Epilepsy

Goffman[44] defined stigma as “an undesired differentness.” People are stigmatized because they possesses an attribute, such

as epilepsy, that is undesired and deeply discrediting and by virtue of which they represent a discrepancy between the persons they might be and the persons they are—in Goffman's words, between their virtual and actual social identities. Goffman identifies three different types of stigma: (a) the tribal stigmas of race and religion, (b) blemishes of individual character, and (c) what he refers to as abominations of the body. Whichever of these prevails, Goffman argues that those who are stigmatized are seen by others as “not quite human” and the legitimate target for discrimination. Goffman notes that even though people who are stigmatized may attempt to rid themselves of their “contaminated” social identity, they cannot reacquire the status of normal, only that of someone who was once “contaminated.” This problem is thrown into relief in the context of epilepsy by the fact that, in clinical terms, the condition may not be considered curable, only controllable, so that the threat of “contamination” can never be entirely eliminated. Because the possibility exists “that the offensive behaviour will recur,”[2] the stigma of epilepsy is irreversible and ineradicable.

Recent theoretical work on the concept of stigma has tended to emphasize two key dimensions, visibility/concealability and course/controllability,[29,65,66] both of which are highly relevant to epilepsy. Seizures, the “symptoms” of epilepsy, may be difficult to conceal and may become more salient over time depending on the clinical course of the condition and the degree to which it can be controlled. Four further dimensions, within each of which the stigma of epilepsy can be located, are disruptiveness, aesthetic aspects, origin, and peril (Table 1).[66] Seizures are clearly often highly disruptive to social interaction, causing those observing them to stand by powerlessly as “the terrified watcher.”[116] Depending on their specific manifestations, they may also be aesthetically unpleasant to those observing them. The legacy of the old ideas about epilepsy as the product of malign forces or sinful behavior results in the issue of origin remaining ambiguous: It might be thought that people with epilepsy are somehow morally culpable for their condition. Moreover, although seizures present far greater dangers to those with epilepsy than to bystanders, the issue of peril is echoed in old ideas of epilepsy as contagion. Such ideas are still often dominant in resource-poor countries where the majority of those affected by epilepsy live, which commonly leads to their social ostracism.[21,64,83]

Table 2 Components of stigma according to link and phelan[73]

Component 1	People distinguish and label *socially relevant* human differences
Component 2	Dominant cultural beliefs link labeled persons to *negative* stereotypes (e.g., “People with mental illness are a danger to others”)
Component 3	Labeled persons are placed in distinct categories (e.g., “fat,” “disabled,” “epileptic”) to separate them from others
Component 4	Labeled persons experience status loss and discrimination (and unequal health and socioeconomic outcomes)
Component 5	Social, economic, and political power allows components 1–4 to operate (those in positions of *low* power cannot impose labels, stereotypes, separation, status loss)

Even in resource-rich countries, the fact that often no definitive cause for epilepsy can be found creates the possibility for continuing misattributions. As shown in a recent study by Austin et al.,[5] 22% of American adolescents were uncertain whether epilepsy was a contagious condition.

Social theorists have commented that a reason that conditions such as epilepsy are almost universally stigmatizing is that they represent some kind of tangible or symbolic danger either to individuals or entire cultures, including physical, moral, and health dangers.[32,104] With regard to epilepsy specifically, it has been argued[1,6,98,112] that seizures can be seen as uniquely dangerous to normal social interaction both by violating cultural norms or values and by representing human weakness and unpredictability and even "anomic terror." Recently, stigma theorists have also recognized the previously neglected role of power relations in the social construction of stigma.[73,99] Link and Phelan[73] commented, "it takes power to stigmatise." The social labeling, stereotyping, separation from others, and consequent status loss that are the key elements of stigma are only relevant in a power situation that allows them to unfold; in other words, they cannot be imposed by those in positions of low power (Table 2). How does this play out in epilepsy? Certainly within the current culture of biomedicine, clinicians hold power to impose a diagnosis of epilepsy on a set of often nebulous neurologic events or symptoms and, in so doing, to legitimize a historically based negative social label and its associated stereotypes. This then allows imposition of rules and sanctions that reinforce the differentness of having epilepsy.

Because it was developed in the context of epilepsy stigma specifically, it is worthwhile reevaluating Scambler's "hidden distress" theory in view of subsequent epilepsy-related research. Jacoby[54] revisited the concepts of felt and enacted stigma and found, like Scambler, that the former was far more commonly experienced than the latter, with few people able to recall any instances of enacted discrimination. Other research on epilepsy stigma in similar cultures supports this. It has been argued, however,[90] that much of the research reported has been concerned with identifying episodes at the hard end of enacted stigma only, for example, in relation to employment, while failing to document its more subtle expressions.

Furthermore, whereas felt stigma appears to be a much more pervasive element in North European cultures, it should not be assumed to be universally of greater relevance.[89] In some cultures, for example, sub-Saharan African ones,[87] enacted stigma may be of far greater concern, perhaps in part because the treatment gap increases the visibility of epilepsy. If we are to advance our understanding of the nature of epilepsy stigma, it will

therefore be important to develop a shared theoretical framework and set of measurement tools that allow for cross-cultural and contextual adaptation.

Views About Epilepsy as a Social Label

Views of People With Epilepsy

Labeling theorists maintain that the impact of a negative social label, for example, being "epileptic," can be quite profound inasmuch as the label overrides other aspects of a person's identity. In a sense, it becomes what has been termed the "master" status,[72] making it difficult for the affected person to continue to think of himself or herself as just "like everybody else."[30] Given that all illness can be defined negatively as a state of "deviance" from good health,[81] having epilepsy can be said to represent a state of double deviance,[55] its particular characteristics and social connotations ensuring that deviance also attaches to the condition per se. The process by which people with epilepsy come to acknowledge their deviant status and accept that they are not like everyone else has been the focus of attention of several authors.[98,101,118]

Parents emerge as key figures in these analyses because their reactions to a diagnosis of epilepsy in their child seem effectively to set the stage for the child's subsequent interpretation of its significance. When parental reactions are negative, their affected child learns to think of epilepsy as something shameful; when parental assumptions are that epilepsy will inevitably attract hostile reactions from others, their affected child learns to think of it as something to keep quiet about. Other key figures are likely to be teachers and health care professionals, both of which groups are known as sometimes having less-than-positive attitudes about the condition and limited knowledge about its implications (see later discussion).

It is not surprising, consequently, that people with epilepsy sometimes resort to trying to “renegotiate” the diagnosis into something more socially benign[98] or to taking active steps to conceal it from others.[74,98,101,120] Among the adult participants in the studies by Schneider, Conrad, and Scambler, concealment constituted a key management strategy. Similarly, in their study of adolescents with epilepsy, Westbrook et al.[119] found that more than half kept their condition a secret from others and almost three fourths said they rarely or never talked about it to others, even though denying that having epilepsy affected their friendships and perceived likeability among their peers.

Views of Other Groups

As noted, even today epilepsy remains shrouded in misinformation and misbeliefs.[78] Misattributions about the causes of epilepsy, for example, are common (Table 3). Historically, studies have presented a less-than-favorable picture for people with epilepsy. For example, Bagley[6] compared public attitudes toward people with epilepsy with those toward people with cerebral palsy and mental illness and found that people with epilepsy were much more often rejected than the other two groups. Both Vinson[115] and Harrison and West,[47] who interviewed people in two cities as part of the U.K. National Epilepsy Week, found that significant numbers of the people with whom they talked held images of people with epilepsy that were essentially negative. These included the views that people with epilepsy were violent, retarded, antisocial, and physically unattractive. Similarly negative traits were identified as peculiar to people with epilepsy in later street surveys carried out in the United Kingdom.[67,96]

Table 3 Lay understanding of causes of epilepsy

Resource-rich countries	Resource-poor countries
• Stress/pressure • Tiredness • Heat • Mental illness • Brain/nervous system disorder • Congenital problem • Old age	• Sorcery, witchcraft • Possession by devils, ancestral spirits • Infection, contagion • Saturation by foams • Insect/lizard in stomach/head

In the United States, Baumann et al.[10] found that one fourth of respondents to a telephone survey believed there would be deterioration in the classroom environment were a child with epilepsy to join it. In the 1987 American Institute of Public Opinion survey,[70] 7% thought people with epilepsy were dangerous, 12% that they should not have children, and 33% that people think less of a person with epilepsy and their families. With regard to particular groups within the general population, research has also identified lack of knowledge and accompanying negative attitudes among employers,[40,50,91,94] coworkers,[46] health professionals,[11,109] and teachers.[13,31,42,75]

Rather more encouragingly, numerous surveys have documented improvements over time in attitudes to epilepsy,[19,20,33,39,51,52,61,63,79,80] indicating that its weight in some, if not all, “local moral worlds”[32] has lessened. For example, in the United States,[20] affirmative responses to questions asking people whether they would object to a child of theirs playing with one who had epilepsy and whether people with epilepsy should be barred from employment in the same jobs as others declined between 1949 and 1979 from 24% to 6% and from 35% to 9%, respectively. Jensen and Dam[63] reported that social acceptance of people with epilepsy was high in Denmark; Dawkins et al.[33] reported similarly in the United Kingdom. In a recent study carried out as part of the U.K. Omnibus Survey and involving >1,600 randomly selected members of the general public,[61] those questioned appeared generally well-informed about epilepsy, its causes, and its treatment, and most held highly favorable attitudes toward people with epilepsy, although one fifth thought people with epilepsy were more likely to have personality problems. Likewise, increasingly positive attitudes have been noted among key subgroups. For example, among primary and secondary level teachers surveyed in Greece,[68] most believed that children with epilepsy were as capable as others of achieving academically. Nonetheless, the continuing challenge of stigma is highlighted by a study published in the same year[95] documenting persistent widespread negative attitudes and bias toward epilepsy among teachers in Nigeria.

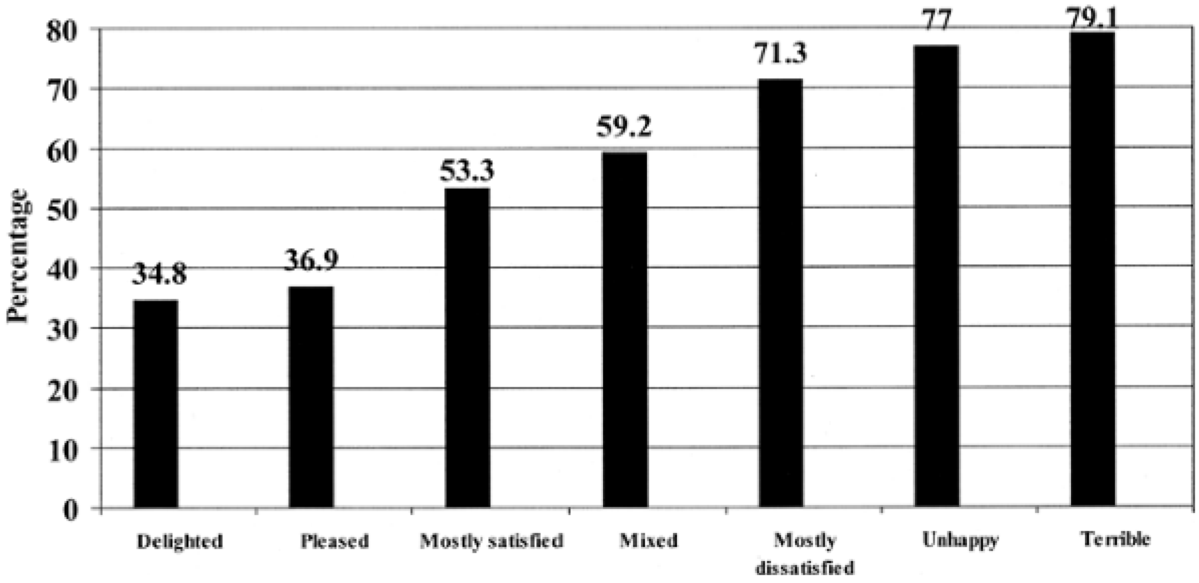

FIGURE 1. Stigma and overall quality of life. (From Baker GA, Brooks J, Buck D, et al. The stigma of epilepsy: a European perspective. *Epilepsia.* 2000;41:98–104, with permission.)

In a survey of 200 randomly selected U.K. employers, Jacoby et al.[60] found that although epilepsy continues to generate anxiety in the work context, the majority (and a larger proportion than in earlier surveys) reported that there were jobs in their companies suitable for people with epilepsy and were aware of the need and expressed clear willingness to comply with the principle of "reasonable adjustment." Overall such studies suggest significant improvements in public attitudes. It is interesting that, despite positive public attitude shifts, it has also been shown that epilepsy still sometimes evokes greater responses to rejection than other chronic conditions, even conditions such as AIDS/HIV infection and mental illness, which are recognized as deeply stigmatizing.[6,10,26,85] Reis[88] concluded that although the classic stereotypes of epilepsy may have less

resonance today, they have tended to be replaced by new ones in which people with epilepsy are regarded as introverted, overanxious, and less open than others. Such present-day stereotypes, even if they are in any degree supported by available research, are inevitably disquieting to those against whom they are directed.

Role of Stigma in Quality of Life

Stigma has long been thought of as predisposing to psychopathology in people with epilepsy, although the relative lack of published studies involving formal and scientifically robust investigation of its role means that its supposed effects are less evidence based than a "taken for granted" assumption.[48] Studies that have attempted to examine the relationship between stigma and psychological health specifically, and quality of life more broadly, include those by Arnston et al.,[4] Hermann et al.,[49] Jacoby,[53,58] Baker et al.,[8] and Suurmeijer et al.[106] Jacoby[57] noted that consistent with sociologic theories about "the illness trajectory"[23] for people with epilepsy, the clinical course of their disease is important for their quality of life, including the degree of their stigma sense. She and her colleagues documented rates of stigma in persons starting to have seizures, experiencing seizures that prove to be intractable, and having seizures that go into remission. Among those newly diagnosed with epilepsy,[59] one-fourth reported feeling stigmatized despite the recency of application of the negative social label of "being epileptic." Two years later, only one tenth of those who had remained seizure free reported feeling stigmatized, compared with 45% of those experiencing continuing seizures. In contrast, among a separate cohort of persons with seizures in remission, only 14% reported feeling stigmatized, and this group also reported minimal impairments in other life domains.

The relationship between epilepsy stage or severity and stigma is also supported by Baker et al.'s study,[8] in which the percentage of people reporting feeling highly stigmatized rose from 10% of those who had been seizure free in the previous 12 months to 29% of those reporting ongoing seizures occurring more than once monthly. Competing evidence about the importance of factors other than these clinical ones is available, however; for example, the study by Ryan et al.[92] showed that the relationship between stigma perceptions and epilepsy severity was highly dependent on other mediating factors such as attained level of education and the perceived limitations imposed by epilepsy-related vulnerabilities. Such findings help to explain why a sense of stigma may persist for a small minority of people with apparently excellent seizure control and, conversely, are absent among some people with even very frequent seizures. They highlight the need for a psychosocial as well as a medical approach to the management of epilepsy.

Stigma was positively associated with impaired self-esteem, self-efficacy, sense of mastery, perceived helplessness, increased rates of anxiety and depression, increased somatic symptomatology, and reduced life satisfaction in studies by Arnston et al.,[4] Jacoby,[54,58] Westbrook et al.,[119] and Dilorio et al.[36] Baker et al.[7,8] also demonstrated a link between felt stigma and medication side effects, supporting Scambler's proposition about the potential for antiepileptic drugs to act as stigma cues. Both Baker et al.[7] and Youn and Hong[121] found that overall quality of life was poorer for persons reporting higher levels of stigma, either felt or enacted (Fig. 1). Suurmeijer et al.[106] used hierarchical regression analysis to demonstrate that perceived stigma was fourth in importance in predicting quality of life, after psychological distress, loneliness, and adjustment; it accounted for twice the amount of variance in quality-of-life scores as did clinical variables such as seizure frequency and antiepileptic drug side effects.

It is interesting that several hypotheses were not supported by the findings in the study by Westbrook et al.,[119] which focused on the link between stigma and self-esteem. For example, focal seizures, rather than tonic–clonic seizures, were predictive of lower self-esteem. In addition, contrary to the role proposed for it in stigma theory—namely, that the issue of disclosure management would be forced by the threat of frequent, visible symptoms—no relationship was shown between it and seizure type or frequency or epilepsy duration. These findings raise questions about the limitations of theory for lived experience and the need for more in-depth approaches to identify alternative and previously unrecognized mechanisms by which stigma exerts its effects.[74]

Stigma may also be implicated *indirectly* in quality of life by virtue of the fact that the quality of health and social care received by persons with stigmatizing health conditions may be suboptimal. Stigmatized conditions may fail to attract investment both for service provision and for research.[117]

There is also some evidence to suggest that health and social care professionals, like other members of the general public, are susceptible to negative attitudes and beliefs about epilepsy. Recent surveys in the United Kingdom have suggested that health care for people with epilepsy is fragmented and underresourced, with many receiving care that is substandard in relation to published guidelines.[62,109,113] Significant levels of dissatisfaction with the quality of their medical, social, and educational care has been expressed by members of the United Kingdom's largest epilepsy support organization, Epilepsy Action.[15,16] The U.K. Clinical Standards Advisory Group[113] concluded that levels of disability and social exclusion for people with epilepsy would be considerably lessened by relatively simple and inexpensive changes in the delivery of their care. Among their suggestions were that formal mechanisms for eliciting the views of service users should be incorporated and that simple care protocols should be introduced for nonneurologic staff, for example, those working in accident and emergency departments.

DiIorio et al.[36] examined the relationship between felt stigma and perceptions of the quality of health care among adults with epilepsy living in the United States. They found that persons with higher levels of felt stigma reported lower levels of satisfaction with their care across a whole range of areas, including interpersonal, communication, technical competence, time spent with the doctor, and the accessibility of their care. They also experienced greater difficulty with managing their medication regime, reported less medication adherence, and reported less positive outcomes associated with taking medication. This lack of satisfaction may therefore reflect a combination of underresourcing and negative attitudes among care providers. As the authors acknowledge, however, the cross-sectional nature of their study precludes firm conclusions about the direction of effects.

Managing Epilepsy Stigma

Helping People With Epilepsy to Manage a Negative Social Label

Dell[35] noted that although identity politics is not "a comforting strategy" for those concerned, it does seek to establish society as the locus of stigma against people with epilepsy and force a reevaluation of their societal worth. Although people with epilepsy may have been slower than some other stigmatized groups to respond to the call, the epilepsy associations are moving rapidly from a view of their function as that of support and information to an increasingly political and campaigning role, agitating for better services and less discrimination for their members.[71]

Campaigns such as the Global Campaign Against Epilepsy[43] are raising its profile with governments and their health systems planners and providers worldwide.

At the individual level, there is evidence that whereas some people with epilepsy appear to admit to the permanence of epilepsy stigma, others show resourcefulness and resilience in putting it aside whatever the clinical prognosis.[92] Among factors identified as critical for developing such resilience are unconditional family support and clear intrafamilial communication.[1] Ablon[1] noted that living in such a positive environment helps to instill confidence and security in early life and encourages positive illness-coping behaviors in the affected person. Family members who openly discuss the practical and emotional issues associated with having a stigmatizing condition and who actively seek out high-quality health care for the affected person can do much to empower that person. Ablon commented that lack of knowledge on the part of other family members can seriously hamper the ability of persons with stigmatizing conditions to cope with them and make a positive adjustment, as can lack of knowledge on the part of affected persons themselves.[37] This suggests a need for targeted educational programs for people with epilepsy and their families; a number that have been formally evaluated are accessible for use.[76]

The importance of counseling as a means of helping people with epilepsy manage stigma had been stressed.[41] Although one-to-one counseling is expensive and therefore may be difficult to fund, Floyd-Richard and Gurung[38] studied the effect of group counseling for people with another chronic stigmatizing condition, leprosy, and concluded that this was a time-efficient and productive method of reducing the effects of stigma. They also argued, however, that counseling alone will not improve the self-image and acceptance of a stigmatized person, and other interventions, such as economic rehabilitation for the whole family and health education for the affected individual, their family, and the community, are also essential.

As shown earlier in this chapter, in the face of possible hostility and stigma, concealment appears to be a key management strategy adopted by people with epilepsy. Although this may make felt stigma "a self-fulfilling prophecy,"[98] disclosure is recognized as a potentially risky course of action[46,111] and is therefore a source of some considerable anxiety to people with epilepsy.[77] The advice from the epilepsy support organizations tends to be that people with epilepsy should approach the issue of disclosure carefully and thoughtfully.[12,17,86] Of course, people with epilepsy are often under a legal imposition to disclose their condition, for example, if they drive or are engaged in particular types of employment in which seizures would put them or others at risk.

Ultimately, however, the decision of whether disclosure or nondisclosure is the wisest and least stressful course of action for managing possible stigma and discrimination must be made on an individual basis, although preferably with proper support.

Changing Negative Public Attitudes

With regard to improving public attitudes toward epilepsy, possible strategies include education and information provision, advocacy, inducing a greater degree of empathy toward epilepsy, and increasing the level of contact between people with epilepsy and people without epilepsy. The most frequently used strategy appears to be that of education, and findings from reviews[18,114] and single studies related both to epilepsy[5,14,64] and other health conditions[24,27,28,69,84,102,103,107] support it as an effective one. Evaluation, however, is often limited to fairly short-term assessments, and different kinds of educational interventions show mixed effects on patterns of attitude and behavioral change and stigma reduction. Interventions targeted at specific population subgroups appear more promising and cost-effective than broad-based public educational campaigns.[105] The overarching message appears to be that the type and content of educational interventions needs to be shaped within peoples' traditional way of thinking and must take account of the context in which stigma operates.

Advocacy focuses on provision of a supportive, enabling environment within which attempts can be made to influence legislative and policy change and is proposed as an important strategy for stigma reduction by several authors.[1,3,25] Given that attitude and behavior change initiatives appear to be more effective when targeted, Corrigan[25] proposed that advocacy groups should use a target-specific stigma-change model to ensure organization of diverse information into a coherent framework. The principle is to identify the group and stigmatizing attitudes that influence discriminatory behavior and the social context within which the group interacts with the stigmatized

person(s). This, in turn, enables a specific change strategy to be identified. The success of the U.S. Epilepsy Foundation's “Entitled to Respect” campaign, targeted at young people, is a current example of advocacy at work.[110] Another good example is the U.K. group Epilepsy Bereaved, as a result of whose work the U.K. Department of Health commissioned the first U.K. audit into epilepsy-related death,[45] which led to a series of recommendations for the care of people with epilepsy.

Inducing empathy for a member of a stigmatized group can improve attitudes toward members of that group as a whole.[9] The assumption here is that by inducing others to see the world from the perspective of a stigmatized group member, they can be led to *feel* for this person and these empathetic feelings will generalize, resulting in a more positive attitude toward the group as a whole. Similarly, interventions based on increasing contact have been proposed as a means of reducing social distance toward affected persons. Such interventions can be targeted at individuals, groups, or the wider community; for example, the Horizon initiative in the Netherlands[34] involved placing people with epilepsy into employment and so exposing employers to them as employees directly. This initiative showed some degree of success despite findings from studies within other health contexts that increased contact in real-world settings, for example, job training, is largely ineffective. Brown et al.[18] argued that a contact strategy in conjunction with education is one of the most promising approaches to reducing negative attitudes.

Whatever strategy is adopted, the literature makes it clear that conducting stigma intervention programs requires diverse skills to engage and interact with targeted communities and community agencies. It also suggests that multistrategy, multilevel approaches are more effective in improving knowledge and reducing stigmatizing attitudes than are single interventions.[114] Furthermore, several studies report evidence of superficial changes in attitude based on improved knowledge but limited change in deep-seated fears, and little is known about what is required to bring about long-term attitude change. Within the field of epilepsy specifically, there is still limited evidence for the effectiveness of interventions to reduce stigma, despite the length of its history, but research suggests that stigma reduction must go hand in hand with improving access to health care and supporting treatment adherence.

Summary and Conclusions

In this chapter, we have focused largely on the literature relating to epilepsy stigma as played out in countries in the developed world. As we have tried to make clear, however, the implications of having epilepsy vary with time, geographic place, and sociocultural context, as do the ways in which people with epilepsy, their families, and their communities respond to the condition. What is without question is that for a significant proportion of those affected, stigma remains a real and present, if intangible, danger. Weiss and Ramakrishna[117] noted that a reformulation of the concept of stigma for health research would be that it is a process in which adverse social judgments are made that are medically unwarranted. This is a very relevant definition of stigma for the great majority of people with epilepsy whose condition can be easily and effectively controlled.[93] At a recent meeting on stigma and global health supported by the U.S. National Institutes of Health (available at www.stigmaconference.nih.gov), family, local community, health and social care systems, educational institutions, legal systems, employment, and insurance were all identified as areas in which people with epilepsy might encounter stigma. Continuing to challenge stigma in all these areas must remain a priority.

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Chapter 217

Disruptions in Social Functioning and Services Facilitating Adjustment for the Child and the Adult

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Introduction

The impact of epilepsy on social functioning, or the ability to participate in a broad range of social activities and interpersonal relationships, can be quite varied. Although many people with epilepsy have few, if any, disruptions in social functioning, others have severe problems that prevent them from engaging in fully productive lives. The exact prevalence of social problems is difficult to establish because most studies have been carried out on clinic samples in which persons with more difficult-to-control epilepsy are served. Studies show that rates of social dysfunction are substantially higher in samples from clinics than in community samples.[104] Nevertheless, social problems are common in persons with epilepsy, and these problems need to be addressed by health care professionals.

In this chapter, we present an overview of the disruptions in social functioning that can be experienced by children and adults with epilepsy. We also describe factors associated with social problems and consider them within the context of tasks of normal psychosocial development. We conclude with guidelines for daily living, an overview of areas that need to be addressed in a comprehensive assessment, and the types of services that can facilitate social functioning in persons with epilepsy.

Disruptions in Social Functioning

Social Problems

Persons with epilepsy have a higher prevalence of social problems than those from the general population. A longitudinal study of adults with childhood epilepsy indicated that epilepsy had a negative impact on social functioning.[97] Problems most commonly reported in persons with epilepsy include anxiety, poor self-esteem, social isolation, and symptoms of depression.[7,19,60,74,79,90,92,93]

Comparison studies show that children with epilepsy have poorer social functioning than children with other chronic physical conditions[89] such as asthma,[7,19] diabetes,[75] or learning disabilities.[74] In a recent study, adolescents with epilepsy showed greater social anxiety and interpersonal problems than adolescents without epilepsy.[20] Adults with epilepsy have also been found to have higher rates of social problems than the general population. Social problems include social isolation and problems with adaptation.[28,30,44,58] Problems in living with epilepsy related to social adjustment (e.g., driving and lack of employment opportunities) are also frequently reported in adults with epilepsy.[53,64] Long-distance travel can also be difficult for adults with epilepsy, especially for those with severe or frequent seizures. Social problems are important because they reduce quality of life and contribute to mental health problems such as depression, anxiety, and psychopathology in persons with epilepsy.[5,57]

Factors Associated With Social Problems

Empirical research carried out to identify factors associated with social dysfunction in persons with epilepsy identifies the following as risk factors:

- Severe and frequent seizures
- Presence of other chronic conditions or deficits
- Cognitive impairment and academic underachievement
- Negative attitudes toward epilepsy
- Inadequate knowledge about epilepsy
- Lack of a supportive family environment

Although social problems are more common in persons who have a chronic physical condition, youth with epilepsy have been found to have a poorer social functioning than youth with other chronic physical conditions.[4,19,88] Studies indicate that disruption in social functioning is greater for persons with severe epilepsy and other neurologic deficits or disabilities[29,56,100] than for those with epilepsy alone. Moreover, higher seizure frequency is generally found to be related to poorer social functioning.[6,17,20,59,60] Other seizure variables have not been found to be consistently associated with poorer social functioning. For example, Camfield et al.[25] did not find epilepsy-related variables (e.g., age at onset, seizure type, cause of seizures), neurologic deficits, and encephalographic data (e.g., focal slowing) to be strong predictors of social dysfunction in a sample of children and young adults with normal intelligence. Furthermore, even remission of epilepsy did not significantly predict social dysfunction. Only a learning disorder and >21 seizures before initiation of treatment were associated with at least one unfavorable social outcome in this population-based study.[25] In addition, poor cognitive functioning[26] and poor academic achievement[101] have also been found to be positively related to social problems in children with epilepsy.

Although most research identifying high rates of social problems are carried out on samples of persons with chronic epilepsy, studies of persons with new-onset epilepsy also indicate that social difficulties occur very early with the disorder. For example, Chaplin et al.[29] found that >10% of adults with recently diagnosed epilepsy rated four problems related to social functioning (fear of seizures, employment concerns, concerns about leisure, and decreased energy) as severe.

Negative attitudes toward having epilepsy have been found to be related to psychosocial problems in children with epilepsy.[13] Sometimes, negative perceptions about epilepsy are caused by excessive fears about seizures.[80] Austin and colleagues[8,16] found that children with new-onset epilepsy and their parents had many unfounded fears about seizures and their treatment, and greater concerns and fears have been associated with more-negative attitudes about having seizures.[11] Lack of accurate knowledge about epilepsy has been found to be associated with greater social anxiety and lower self-esteem in adolescents.[20]

The whole family is confronted with coping with the epilepsy. Studies exploring relationships between the family environment and social functioning in children indicate that family factors are related to social functioning in the child.[88] Austin et al.[17] found family stress, extended family social support, and family mastery and control to be related to psychosocial functioning. Lothman et al.[72] found praise in mother–child interactions to be related to child competence. What is not as well delineated is the nature of the relationship between the family environment and social functioning because most of the research is cross sectional. It is not known whether both the family and the child are reacting to the epilepsy, whether environment leads to social problems for the person with epilepsy, or whether the family is responding to the child's problems.

Few studies have been conducted on family environments of adults with epilepsy to identify whether there are factors that are associated with social problems. Thompson and Upton[103] found that caring for an adult with intractable epilepsy is quite stressful for the family. Approximately two thirds of the primary caregivers were dissatisfied with limitations on their social activities and intimate relationships. Caregivers identified the need for respite and increased social support.

In summary, although more research is needed to identify all the factors that lead to problems with social dysfunction, research has identified broad categories of variables that place persons at risk for social problems. It appears that a chronic, difficult-to-control condition and the presence of other deficits or disabilities are risk factors for social problems. Moreover, knowledge about epilepsy, how persons feel about having seizures, and characteristics of the family environment are related to social functioning in persons with epilepsy.

Developmental Tasks and Social Problems

Disruptions in social functioning in children need to be considered within the context of normal psychosocial development because epilepsy can interfere with the accomplishments of age-appropriate tasks. Furthermore, because epilepsy affects the whole family, it is important to consider how family factors influence the psychosocial adjustment to epilepsy.

Early and Middle Childhood

In early childhood, children need an environment in which they are able to become increasingly independent. They have daily routines and learn to master toilet training and other self-care activities, communicate with others, and become socialized.[22] For optimal psychosocial development, these children need an environment in which they can develop autonomy and initiative.[51] If parents are overly protective and concerned about the possibility of a seizure, they may overrestrict the child's activities and hinder the development of life skills. A recent study found increased levels of parental anxiety about their child's epilepsy was associated with poorer socialization in the child.[27] In middle childhood, children become more independent of parents. There is empirical evidence that children with epilepsy can have problems with completion of some of these developmental steps. For example, children with epilepsy have been found to be more dependent than children with tonsillectomies.[52]

Child social development has been found to be associated with parenting behaviors. Social maturity and social skills in children with epilepsy were found to be positively related to parental strictness. Lothman et al.[72] studied parenting behaviors in mother–child interactions and found praise to be related to child competence and child positive affect. Conversely, intrusive and overcontrolling parenting behaviors were related to decreased child autonomy and child confidence. In a recent longitudinal study, parent support of the child's autonomy predicted a better psychosocial adjustment.[10]

Adolescence

The primary developmental challenge of adolescence is identity formation.[22] Ideally, adolescents should begin adulthood with a strong sense of self and physical competence. Failure to develop a strong sense of self as competent can lead to problems with poor self-esteem and feelings of being different from others. Another important developmental task for adolescents is becoming independent and separating from the family of origin. Peer-group membership plays an important role in the social development of adolescents and in their becoming independent of their family. A recent study,[18] however, suggested that the social environment might not be supportive of the social development for the adolescent with epilepsy. In that study, adolescents in the general population were found to have a poor understanding of epilepsy. Almost three fourths believed that adolescents with epilepsy would be more likely to be bullied or “picked on” by others than other adolescents, and less than one third indicated that they would date an adolescent who had epilepsy.[18]

Young people with epilepsy can have problems meeting the developmental accomplishments of adolescence. The presence of a chronic condition such as epilepsy can interfere with the development of a strong sense of physical competence. Parental overprotection can deprive the child of experiencing the feelings of competence and, subsequently, affect later self-esteem.[76] The occurrence of seizures and the need to take medication can lead to a reduced sense of physical competence. The stigma associated with epilepsy can negatively impact how adolescents perceive themselves, socially and physically. A recent study indicated that adolescents with intractable epilepsy perceived that their having epilepsy set them apart from their peers.[47] Even adolescents with newly diagnosed epilepsy have been found to feel different from their peers and worry about being teased by them.[8] The episodic loss of control caused by seizures also can make it more difficult to become independent and separate from families. The inability to drive a car at an age-appropriate time can be a major problem for adolescents with epilepsy because it limits opportunities for developing independence and participation in social activities.[33]

A final way the presence of epilepsy might affect social functioning is poor academic performance. Success in school facilitates the development of initiative. School achievement also provides an opportunity for young people to receive recognition from others and to derive a sense of accomplishment. The school problems found in adolescents with epilepsy[19,79] reduce opportunities for the development of a sense of pride and accomplishment at school and also place these children at risk for later vocational problems.

Adulthood

Studies of psychosocial function of adults with epilepsy have many methodologic problems. Studies regarding these issues

have mostly been clinic based, thus limiting generalization to the whole population of people with epilepsy. Recent research[102] was carried out in the north of the Netherlands concerning the quality of life reported by 210 adults with epilepsy and an average IQ of 101; 75% had a high school education or more. Of this group, 69.5% reported no social problems, 25.1% mentioned problems with adaptation, 5.5% reported feeling isolated or suffering from other problems in this area, and 89.7% mentioned no financial problems. Various subscales on health, self-confidence, coping, loneliness, stigma, life fulfillment, and psychological problems did not show many problems. It appeared as if early-onset epilepsy leads to adaptation and does not much influence the quality of life. The outcome of this study differed from those of many others probably because this was performed among a group of people with epilepsy living in the community rather than a clinic-based sample.

Being employed is an important predictor of quality of life of people with epilepsy. The World Health Organization also mentions the importance of employment for social health and, therefore, improved quality of life. It is widely recognized that a large number of people with epilepsy experience particular difficulties in gaining access to employment and vocational training on equal terms with other sections of the population, and it is also acknowledged that this situation is likely to get relatively worse, not better. Most figures concerning employment rates of people with epilepsy indicate that they do not perform as well on the labor market as others do. Although both research figures and research groups vary, unemployment rates generally are higher for people with epilepsy than for the general population.

Early employment studies showed that the situation for people with epilepsy was discouraging. Jacoby[64] found that 50% of people with epilepsy were unemployed, and Scambler and Hopkins[91] reported that 42% were unemployed. A research project set up among people with epilepsy in The Netherlands who were being treated at 10 special outpatient epilepsy clinics showed that compared to the general population, the study group tended to have a lower educational and a lower vocational level than the general Dutch population.[102] Of the study group, 44% were employed and 49% were unemployed (7% were in school).[34,86] A more recent study by Jacoby showed that when seizures are well controlled and there are no other handicaps, people with epilepsy do not experience employment problems.[65]

Young people with epilepsy especially are at a disadvantage when it comes to obtaining and retaining employment and may need special assistance and training to enable them to deal with difficulties they are likely to encounter. Even when the epilepsy is controlled, many find that their epilepsy is a barrier to employment.

Concerning marriage, Dutch research showed that 66.2% of patients were married and 14.8% were still living with parents.[102] This figure may be influenced by age, or there may be a regional (cultural) effect. Data from Montreal[32] showed that among study participants who developed seizures after the age of 20 years, 91.7% of women and 76.2% of men were married before the onset of seizures. These proportions were similar to those for the general population. However, if seizures occurred in the first decade, marriage were lower than expected for the general population. The rates were 32% for men and 58% for women. Ounsted and Lindsay[82] found that among their sample of 100 young people diagnosed as having temporal lobe epilepsy, the prognosis for marriage was good for girls (92% of them married), whereas only 41% of the boys married, even though they were not heavily handicapped. Pierzchala and Grudzinska[83] reported that of a group of 243 patients with epilepsy, 50.6% of men were married, which is a lower rate than both women with epilepsy and the general population. Follow-up studies on people with epilepsy in the 1946 British birth cohort show very little difference concerning marriage between both uncomplicated and complicated cases and their controls at the age of 26 years.[23]

For many (young) people, marriage is one of the main goals in life. For a person with epilepsy, however, the chances of getting married can be particularly slim in the Third World. In some countries, a woman with epilepsy has virtually no chance of getting married at all, or when she does, epilepsy is a reason for an immediate divorce. In India, although the law forbidding people with epilepsy from getting married was repealed recently, such people still stand no chance of an arranged marriage, which is customary in that part of the world. Fundamentalist groups in many religious cultures, following ancient laws, still believe that epilepsy is inheritable, and of course these laws were originally intended to prevent the disease from spreading. Having epilepsy appears to affect the chances of marriage in the developing world as well as in the developed world, based on the erroneous idea that people with epilepsy are uneducable, unemployable, and a danger to the community; epilepsy is widely considered to be an inheritable disease requiring restriction of its spread. The severity of the epilepsy does not seem to make any difference in relation to marriage: Having seizures at all diminishes the chances.

There is a large literature on the medical aspects of pregnancy and epilepsy; however, the social aspects seem to be a neglected area. For the future mother with epilepsy, there are even more questions concerning having children than for other women. The questions include the following:

- Will my children also have epilepsy?
- What will happen to my seizures during pregnancy? Will they harm the baby?
- What is the effect of my medication on the baby?
- What happens if I have a seizure during delivery?
- Can I take care of a child safely?
- What changes do I need to make to take care of the child?

Up-to-date information concerning these often emotional questions is extremely important because the fear that they cause might not be verbalized. It is of the utmost importance that future mothers be able to discuss their desire for a child with the physician who treats their epilepsy. The importance of a good relationship between doctor and patient is vital.

Various practical measures for taking care of a baby may include sitting on the floor during feeding and washing and dressing the baby on the floor as well. Bathing should not be done when the mother is alone with the baby. When common sense and practical precautions as just described are applied, much of the fear of future mothers is in fact not necessary.

Epilepsy in a parent may have an impact on the family system. Few studies have explored the effects on child development of having a parent with epilepsy. Aldenkamp et al.[2] found acceptable patterns of communication about epilepsy between parent and child; 80% of the children were informed about their parents' seizure before witnessing one. This is contrary to the results from a study by Lechtenberg and Alkner,[68] which found little communication about the epilepsy. Information about epilepsy given before a child witnesses a seizure proved to be important for the adaptation of the child and prevention of serious personality disorders. The findings of the Aldenkamp study support the belief that children benefit from adequate information given in open and frank communication with their parents.

People with epilepsy sometimes state that it is very difficult, or even impossible, for them to make friends. This maybe caused, however, by their own attitude toward the disorder. Some people wear their epilepsy as a shield in front of them, thus creating a self-fulfilling prophecy, almost introducing themselves as a person with epilepsy. Friends probably

should know about the epilepsy, but only when it is active. The following points to should be kept in mind:

- Do not scare the other person with your epilepsy.
- Only talk about your own epilepsy and your own seizures.
- Explain what happens when a seizure occurs.
- Explain what people can do to help.

When these rules are applied, neither the epilepsy nor the seizures should stand in the way of friendship.

Guidelines for Daily Living

Risks at Home

Most accidents happen at home; this generalization applies to everyone, simply because we spend so much time there. Still, for people with epilepsy, there are extra risks, some of which can easily be avoided, as the following suggestions show:

Living Room

- An open fire or stove should be surrounded by a shield; sharp radiators should be covered (e.g., a wooden shield).
- Furniture should not have sharp edges.
- Unbreakable glass should be used in any windows below neck level.

Kitchen

- Gas or electric stoves can be protected with a low shield on top, as used for children.
- Microwave or induction cooking may be used.
- The hot water tap should be fitted with a temperature-control device.
- Electric tea- or coffeemakers are less risky than a hot water kettle.

Bathroom

- The door should be made to open from the outside.
- Baths should not be taken when the person is alone in the house.
- Showering is safer than bathing; any glass windows in the shower should be of unbreakable glass.
- The water taps must be fitted with a temperature-control device.

Bedroom

- If a person tends to fall out of the bed following seizures, a mattress may be placed on the floor. This is less restricting than a shield around the bed and it is quite safe.

Risks at School

Parents and teachers should avoid implementing rules for a regular and quiet life for children with epilepsy. Although fatigue and sleep deprivation may provoke seizures in some people with epilepsy, nothing should be left out of the lives of children with epilepsy unless it would be dangerous in that particular person. Education of parents, teachers, and children with epilepsy should decrease unsubstantiated fears about the condition and the implementation of unnecessary restrictions on their activities. Decisions must be made about participation in activities. The children should participate in this decision making about their participation in activities from a young age; otherwise, they might have difficulty in accepting real restriction or precautions. It is obvious that living a full, independent life between the seizures involves taking risks for everybody, and taking risks implies that, with statistical certainty, accidents will occur.

Risks at Work

The vast majority of jobs are suitable for people with epilepsy. When medical advice is sought about the suitability of particular jobs for people with epilepsy, the guidance given should take into account the requirements of the job, known facts about epilepsy, and the nature of the individual's seizures. More specifically, decisions should take into account information concerning the individual's epilepsy, such as the following:

- The diagnosis and prognosis of the individual's epilepsy
- Description of the seizures, including aura
- Seizure frequency
- Time pattern in which seizures occur (e.g., only during sleep)
- Recovery time
- Date of last seizure
- Any safety issues
- Medication

One area of misunderstanding is the prevalence of seizures caused by visual stimuli.[78] A recent comprehensive review of the empirical literature indicated that the chance of having a seizure caused by light or pattern is only 2% to 14% in people with epilepsy.[50] Children appear to be more vulnerable to visual stimuli than are adults. Therefore, blanket prohibitions should be avoided. Besides, often simple precautions can be taken to reduce the risks in the workplace, such as providing a chair with armrests to prevent the person from falling when having a seizure. In jobs known to carry a high degree of physical risk to the individual worker or to others, the organization of work practice should be examined to reduce this potential risk to an acceptable level. Only in those situations in which this cannot be achieved are restrictions on the employment of people with epilepsy justified.[63]

Traveling

Many people have the vague notion that persons with epilepsy are unfit to travel alone. Parents have nightmares of their children having a seizure in front of a train. In fact, traffic accidents caused by seizures are rare, and using public transport is possible for most people with active epilepsy. Traveling abroad is another issue of concern for many people with epilepsy and their caregivers. Having a seizure in a train or an airplane, however, is no more dangerous than having a seizure at home. An epilepsy "passport" assisting people with epilepsy when traveling abroad containing information on epilepsy in many languages may be very useful and is available in a number of countries. The International Bureau of Epilepsy (IBE) had developed such a passport, but this is now out of print. It would be useful to develop such passports either on a national or a regional basis. Holidays are organized by a number of IBE member organizations. All of these programs have one thing in common: They prove that epilepsy presents no constraint to traveling. Individuals who have frequent seizures, however, need to make sensible travel arrangements. Some general rules apply:

- Travelers need to take medication with them, preferably two sets, with one packed in the hand luggage and one in the checked bag.
- A letter from a doctor explaining the epilepsy and medication can be helpful (especially when dealing with

customs).

- Travelers need to have appropriate travel insurance.
- Taking an epilepsy "passport" (as mentioned previously) is useful.
- Information issues concerning travel can be sought from a national epilepsy association or the IBE.

Cycling

In the literature, cycling is not considered more dangerous to people whose seizures are well controlled than to anybody else, and normal precautions should be taken, which may include wearing a helmet. If seizures are active, busy roads are best avoided, and cycling in the company of a supervisor may be advisable. All children will want to ride bicycles; in some countries, it is a regular part of growing up, and blanket restrictions may result in covert cycling in unsupervised situations, causing a greater danger than properly managed cycling. Furthermore, the use of tandem or properly fitted three-wheeler bikes can enable people who have frequent and severe seizures to ride a bike, thus offering them the feeling of freedom that comes with this activity.

Leisure Activities and Club Membership

Health professionals are often asked to give opinions about the risks for people with epilepsy engaging in leisure activities. Although this is an understandable question, there are no rules concerning risks for people with epilepsy in general, and no systematic study into such areas of ordinary daily activities has been made. It is, however, a well recognized that leisure activities such as going out and joining a club are highly desirable, especially for young persons when growing up and learning social skills, whether they have epilepsy or not. It also adds to the quality of life for adults. Going out may involve going to discotheques, which is a normal part of growing up and should not be avoided by young people with epilepsy who seek a full social life. Some people may find flashing or flickering lights unpleasant, but generally it is only bright white "strobe" lights operating at >5 flashes per second that may induce a seizure in some people with epilepsy.

Sports

Interest and active participation in sports is growing. Although studies do not indicate that people with epilepsy are at greater risk of developing seizures during various types of sports, it is assumed that fewer of them participate actively than might want to do so. Information on this or the advice given to people with epilepsy about active sports is not available. A survey in the Netherlands among patients and doctors showed that people with epilepsy are relatively interested in sports. Active participation is limited when either the doctor or the person with epilepsy sees epilepsy as a restricting factor. Clear advice from the professional is essential.[62] This advice should be based on the following rules:

- The risks following a seizure during sports depend on the type of seizure.
- When advising people with epilepsy concerning active participation, three categories of sports can be distinguished:
  - Sports with no restrictions.
  - Sports with some restrictions (safety precautions).
  - Sports that are prohibited.
- The risk of having a seizure during sports is usually smaller than during the relaxation period afterward.
- Sports, including contact sports (team sports) and fighting sports, generally do not provoke more, or more serious, seizures.
- Epilepsy is never a reason for not partaking in competitive sports at any level.
- Epilepsy is never a reason for denial of membership in a sports club.

- Besides to normal safety precautions, special guards need to be available with sports in or around water.
- Instructors and trainers need to know what to do when a seizure occurs.

(This list is the outcome of a symposium on epilepsy and sports organized by the Dutch League Against Epilepsy in 1989.)

Swimming

Most fatal accidents in epilepsy occur in the water (60%). However, very few people with epilepsy drown during swimming. Most accidents occur in the bath, while fishing, or from falling into water. As noted, research shows that very few seizures occur during active sports. They do occur, however, in the rest period afterward (e.g., when resting alongside the swimming pool). Still, certain precautions need to be taken in or around water when a person is not seizure free:

- Swimming in open waters is ill advised because first aid, in the case of a serious seizure, presents extra difficulties.
- Supervision is necessary.
- A person with epilepsy should never go into the water alone.
- When people have active seizures, they should have a person with lifesaving skills present.

Services for Facilitating Social Adjustment

The increased prevalence of social problems in people with epilepsy emphasizes the need for a comprehensive approach to treating people with this condition. Although seizure control is a critical factor affecting social function, managing the consequences of seizures on one's daily life is often the most challenging component of epilepsy care. Health care professionals must be aware of the multiple causes of social problems, how to screen for their occurrence, and how to provide appropriate referrals, education, and treatment. In addition, recent research highlighting the increased incidence of cognitive, mood, and behavior problems in children and adults with epilepsy stresses the need to identify and treat these problems early before the psychosocial consequences become intractable.

The ultimate goal of support services is to help persons with epilepsy and their families become as socially capable and competent as possible and live independent self-directed lives. Ideally, models of care and support systems will "foster empowerment and independence for people with epilepsy and support their efforts towards improved seizure control and a positive quality of life."[49] Critical elements that must be considered when making decisions about services include the following:

- Comprehensive assessments should be carried out on a regular basis.
- Early referral to services is recommended to prevent and treat social difficulties.
- Support services should be matched to specific needs of the persons with epilepsy and their families.

- Services should embrace the concepts of self-management and self-determination for persons with epilepsy and their families.

Comprehensive Assessment

Because a full explanation for the development of social problems is not available and persons with new-onset seizures have social concerns, it is important that the social functioning of all persons with seizures be assessed on a regular basis in the clinical setting. Moreover, persons with epilepsy can have different needs at different developmental stages. Therefore, it is important regularly to complete a comprehensive assessment of patient and family needs to obtain information critical to planning services to prevent and reduce social problems. A comprehensive assessment should provide the basis for designing intervention programs and services to enhance the quality of life of persons with epilepsy and their families. In the assessment, it is important to include both psychosocial functioning and the factors that are associated with social problems.

Assessments incorporating a functional status approach commonly used by nurses and rehabilitation specialists are easy to use in clinical settings and can help patients and families to identify target concerns, individualized goals, and treatment strategies. Assessments are generally carried out using structured interviews, rating scales, and self-report questionnaires. Some assessment instruments have norms, so results can be compared with general population norms or other populations. Areas of assessment and examples of scales to use in each area include the following:

Knowledge About Epilepsy and Its Treatment

- Fear of Seizures[80]
- Epilepsy Myths and Misunderstandings Questionnaire[48]
- Information Needs of Parents of Children with Epilepsy[31]
- Parent Need for Psychosocial Care Scale[9]
- Child Need for Psychosocial Care Scale[9]
- Learning Needs of People with Epilepsy[39]
- Knowledge of Women's Issues in Epilepsy[71]

Attitudes and Psychosocial Problems

- Rosenberg Self-Esteem Scale[90]
- Child Behavior Checklist[1]
- Child Depression Inventory[66]
- Washington Psychosocial Inventory (Adolescents)[21]
- Washington Psychosocial Inventory (Adult)[45]
- Child Attitude Toward Illness Scale (CATIS)[13]
- Quality of Life in Epilepsy[35]
- Child Stigma Scale[14]
- Parent Stigma Scale[14]
- Epilepsy Self-efficacy Scale[38]
- Epilepsy Self-management Scale[37,40]
- Epilepsy Regimen Specific Support Scale[40]

Family Environment

- Family Support Scale[46]
- Family Inventory of Resources for Management[77]
- Family APGAR[12,98]

Matching Services With Needs

Early referral to health care professionals, rehabilitation specialists, and educators is recommended for proper recognition and treatment of both seizures and their consequences. Because needs of patients and families may be assessed and prioritized differently by health care professionals and patients, incorporating the patient's perspective into the care planning is critical. Services and interventions can then be tailored to the individual and patient-centered goals established.

Types of Services

Programs and services for addressing social functioning may include various educational approaches, counseling, social skills training, cognitive rehabilitation, support networks, peer mentoring, vocational rehabilitation, and independent living programs. Many different health care providers and community-based rehabilitation and educational specialists may provide these services, depending on their areas of expertise and practice setting (i.e., nurses, social workers, psychologists, psychiatrists, educators, vocational rehabilitation therapists, recreation therapists, and resource specialists).

With the changing health care environment in many countries, care is increasingly being provided in outpatient settings. Residential programs, however, are still available in some countries. Specialized epilepsy centers offer the ability to provide education, counseling, and supportive services in both inpatient and outpatient settings and by professionals with expertise in epilepsy. Guidelines have been established by the National Association of Epilepsy Centers in the United States that incorporate the critical services that should be provided at level three and four epilepsy centers to provide education, counseling, neuropsychological evaluations, educational and vocational assessments, and rehabilitation services.[81]

Unfortunately, many people do not have access to specialty centers, lack insurance coverage, or are not referred to these services until secondary disabilities and social problems are difficult to treat. In these instances, a “shared control” concept of care between general neurologist and a specialized epilepsy program or between the person's health care providers and community-based agencies, support services, and rehabilitation specialists is often implemented.[95]

The Internet is increasingly becoming a major source of information, education, support, and resources. When used to supplement medical care, the Internet serves as a fascinating way to connect people with resources and support previously not accessible to many. Online support groups via community forums, information and education provided by reputable epilepsy organizations, academic distance learning, and job search programs hold the promise of overcoming major barriers for people with epilepsy such as the need to drive to be able to access needed services.

Self-management Education

Educating people with epilepsy and their families should be geared to more than just imparting information and should involve skill development and resource identification. Ideally, education should assist people in managing their epilepsy and its consequences. This process, often termed epilepsy self-management, can also be thought of as taking the steps necessary to manage seizures and their impact.[36]

Common components of self-management have focused on seizure, medication, and lifestyle management.[24,96] A psychosocial model of self-management has focused lifestyle management on stress and safety while adding the critical need to manage information and disclosure.[41,42] Other issues involving accessing care, managing health needs, and addressing social relationships and community living suggest that psychosocial concerns need to be addressed as an integral part of epilepsy education and care.[94]

Research into predictors and outcomes of self-management programs are sparse. Self-efficacy, or self-confidence in managing epilepsy, and patient satisfaction have been found to be important variables in epilepsy self-management, particularly medication management, and social support, stigma, depressive symptoms, and outcome expectancies influence self-efficacy.[43] Self-efficacy, together with locus of control and social support, has important influences on quality of life as well.[3]

Tailoring epilepsy education to individual needs is considered a critical element of program planning. Because responsibility for caring for children with chronic conditions rests primarily with the family,[61] the best way to enhance social functioning in children is to provide needed services to families. According to Dunst et al.,[46] addressing families' needs helps to empower them to successfully manage chronic conditions in family members. Interviews with families of children with new-onset epilepsy indicated that they had many learning needs, including the need for education about epilepsy, treatment issues, and strategies for managing the epilepsy.[16] Included in the strategies for management were parents' needs to handle the responses of others to their child's seizure disorder and to help their children to cope successfully. A recent psychoeducational intervention in which the information and support were tailored to the individual needs of the family members showed significant increases in knowledge about epilepsy for both children with epilepsy and their parents. In addition, after the intervention, these children had fewer worries and need for information, and their parents had significantly less need for information and support related to their child's epilepsy.[15]

DiIorio et al.,[39] in an assessment of learning needs, found that adults with epilepsy had a strong wish for information about the condition and how to manage it. Needs were identified in the following rank order: Information on medication, seizures, psychological factors, basic brain functioning and seizure causes, and general lifestyle factors.

Very few educational programs have been systematically evaluated for effectiveness and reported in the literature. Studies of psychoeducational groups for adults with epilepsy using the Sepulveda Epilepsy Education (SEE) and Modular Service Package Epilepsy (MOSES) programs have demonstrated positive outcomes (e.g., knowledge, coping, and seizure outcomes).[55,73] Study of 6-week structured program for adolescents with epilepsy and their parents using cognitive–behavioral strategies and support suggests a positive influence on quality of life; however, the sample size was quite small.[99] Finally, Lewis et al.[69,70] evaluated an intervention program for children with epilepsy and their parents and found that an educational program increased parents' knowledge about epilepsy, decreased parents' anxiety, and increased children's perceived social competence.

There are many other educational materials and programs that have been developed by specialized epilepsy centers or national organizations, such as the International Bureau for Epilepsy and country-specific organizations such as the Epilepsy Foundation in the United States. Most often programs are implemented on the community level and tailored to the needs of the learner for maximum effectiveness.

Unfortunately, research into the benefits of individual epilepsy education is sparse. A study of community-based specialty nurses demonstrated improved knowledge of people with newly diagnosed epilepsy, supporting the benefits of shared care in epilepsy between specialists and community-based professionals.[87] In addition, a recent nurse-led education intervention for adults with uncontrolled epilepsy showed a significant improvement in quality of life compared to a control group.[54] In this study, the areas of greatest improvement were physical limitations, health discouragement, and medication effects.

Recent advances in our understanding of self-management and health education have important implications for educational programming. In addition to giving information, improving the learner's self-efficacy or confidence and building social support networks also may be important strategies for managing social problems.

Counseling

Counseling approaches in epilepsy care are frequently used to address social problems, both individually and in group settings. Mental health counseling may help people to adjust to the challenges of living with epilepsy and treat comorbid conditions such as anxiety and symptoms of depression. Desired outcomes include improved attitudes related to the epilepsy and social functioning, as well as treatment and/or prevention of psychiatric complications. People who experience changes in seizures with emotional distress or stress may also use counseling to improve seizure control. Finally, group counseling can provide important opportunities for learning social skills and gaining support from others with similar problems.

Approaches may include psychotherapy, cognitive–behavioral techniques, and other stress management approaches. Combining or supplementing self-management education with counseling can help to build a person's self-efficacy or confidence in living with epilepsy. Because epilepsy affects more than just the individual with seizures, addressing family dynamics and problems is an important part of epilepsy care.

Counseling can also be provided by specialists in recreation therapy. Recreation therapy appears to be especially appropriate for persons with epilepsy because of their problems with social isolation and lack of satisfactory peer relationships. For example, Regan et al.[85] combined education and counseling with a recreational activity (a ski trip) and found improvement in self-concept.

Social Skills and Cognitive Rehabilitation

Some people with epilepsy have impaired social skills and cognitive problems that may be due in part to underlying brain dysfunction complicated by the effects of seizures and medications on their brain function. Rehabilitation professionals with expertise in brain injury and epilepsy can teach social awareness and help patients to learn social skills and develop specific strategies to compensate for cognitive problems such as memory deficits. These services can be provided within many specialized epilepsy centers, outpatient rehabilitation settings, and community-based programs.

Self-help and Support Groups

Self-help groups generally are groups of peers who have joined together to help each other with a common problem. Self-help groups can lead to improved social function by extending social networks, providing new opportunities for social learning, and changing cognitive perceptions about one's condition.[67] Courses have been organized to standardize methods for self-help groups in Italy.[84] In the United States, support groups can be found in many communities, established by individuals, health care facilities, or nonprofit agencies. The Epilepsy Foundation and affiliates offer support groups and networks that are often targeted to specific groups such as parents, teens, and women. Increasingly, varied ways of providing support are being tried, such as phone networks, online forums, and individual mentoring.

Vocational Rehabilitation

Because employment is a major problem for many people with epilepsy, all adolescents and adults should receive vocational counseling. Needs can include help in identifying medical and social factors that may affect employment, assisting people to become job-ready, educating potential employers about epilepsy, assisting with job searches, teaching people to develop new vocational skills that will build on strengths, and teaching people new vocational skills and how to find reasonable accommodations.

Independent Living Programs

Independent living programs aim at enhancing independence and self-determination for people with epilepsy. These programs may be provided in residential settings for people with significant difficulties living independently. Many people with less severe functional problems may still experience difficulties living on their own and can benefit from teaching and assistance in developing critical skills such as personal care, budgeting, home management, transportation, shopping, and other independent living skills. Funding for these services may be problematic, but some federal health or disability insurance or private agencies may help.

Summary and Conclusions

We have outlined some of the major social problems found in persons with epilepsy and placed them within the context of tasks of normal psychosocial development. We also have identified some of the risk factors for social dysfunction, provided some examples of instruments that might be used for a comprehensive assessment, and reviewed different types of services for facilitating social functioning. Although many persons with epilepsy function well socially, others experience difficulties. We propose that comprehensive assessments be carried out on a regular basis to facilitate early identification of social problems and referral for rehabilitation services. In addition, recent studies suggest that educational interventions can be helpful for persons with epilepsy.

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Chapter 219

The Range of Needs and Services in Vocational Rehabilitation

Rupprecht Thorbecke

Robert T. Fraser

Introduction

The employment concerns for individuals with epilepsy have been repeatedly documented in the literature. The Epilepsy Foundation generally cites an unemployment rate of 13% to 25% for people with epilepsy in the U.S. labor force.[43] An earlier study by Emlen and Ryan[25] suggests that this statistic pertains to those who are maintaining an active job search. If persons who have been discouraged from seeking work were additionally included, the unemployment statistic would be closer to 34%. In the study of Emlen and Ryan, individuals having one or more generalized tonic–clonic or complex partial seizures a year had an even higher unemployment rate of 50%.

From an international perspective, the situation does not look appreciably different. A study from the United Kingdom[24] revealed an unemployment rate for vocationally active patients with epilepsy of 46%, compared with 19% in an appropriate age- and sex-matched group. A study from an Irish clinic[9] showed, for a period of 12 months, an unemployment rate of 34% in men, which compared poorly with the unemployment rate of 13% in the general population. A German study[7] found that 24% of a group of epileptic persons were unemployed, with unemployment in the general population being 8% to 10%. Mean duration of unemployment was 30 months, compared with 11.6 months in the general population. In an epidemiologic study in Germany in 1995, 29% of persons with epilepsy in the labor force were unemployed, with general unemployment being 10.4%, and 15% for persons with a disability certificate.[60] In a Finnish study, a cohort of 245 children younger than 16 years was recruited for a long-term follow-up. Thirty years later, of those with uncomplicated epilepsy 64% were seizure free for 5 years or more. In comparison to a matched control group 31% of those with epilepsy were unemployed, while 8% of the controls were unemployed. Further analysis gave hints that nonidiopathic etiology and learning disability might be relevant for these differences.[70,71] A caveat in understanding unemployment rates among this disabled group is that many studies have used populations from epilepsy clinics that are more severely impaired. For the United States, the Emlen and Ryan study,[25] which utilized a pharmacy register, and for Germany the Pfaefflin May study would be most representative.

Earlier studies have indicated that people with epilepsy can also be overrepresented in unskilled and semiskilled positions.[47,62] They may also drop out of the workforce prematurely.[59] In Germany in 2004, the mean age for early retirement because of illness or disability was 50.4 for men and 49.1 for women years, whereas for those with epilepsy it was 45.6 and 43.2 years, respectively. In addition, 12.1% of all men and 14.4% of all women with illness or disability retiring early were below 40 years of age, compared with 27.2% of men and 35.4% of women retiring because of epilepsy. These employment statistics are chiefly from industrialized countries, and the work difficulties experienced by persons with epilepsy in developing countries are not well documented.

It is of interest that in a German study up to 60% of employees with epilepsy had active seizures, but 70% had them outside work.[22] In an English study,[11] 51% of employees with epilepsy had a seizure at work, and this was even higher in a Tunisian study.[39] It is also of interest that risk of accident related to seizures in the workplace is either not higher than the nondisabled[52] or slightly higher and yet inconsequential as compared to impairing injury.[81,84] It is interesting to observe that in the European study 3% of persons with epilepsy (PWE), in contrast to 1% of controls, had an accident at the workplace in 24 months ($p < .01$); however, when seizure-related accidents were omitted the accident rate of PWE fell only to 2.5% ($p < .05$), indicating that medication side effects and neurologic deficits could be a more important factor.[81]

There is broad agreement in the literature that the employment problems of people with epilepsy cannot be reduced to one factor (i.e., seizure severity), but that they are rather the result of a bundle of adversive factors interacting with each other in a complex fashion. These factors include a lack of education and vocational training, neuropsychological deficits, lack of information, social isolation and resulting social skills deficits, and negative attitudes on the part of the family or employers. Unemployment appears to be minimally two to three times that of the general population (e.g., as shown in the 1979 Emlen and Ryan general pharmacy sample[25]) and still worse within the populations of specialized epilepsy clinics.

There appears to be two major issues. One is that of initial job access after secondary school. For example, at the University of Washington Epilepsy Center, vocational clients requesting services have approximately 13 years of education, which usually comprises high school and some additional community college course work. The common theme is that no specific vocational entry or transition plan exists, and youngsters with the disability simply "go on" to further community college training because it is considered "normative" despite often pronounced impairments. A second major issue is that people with epilepsy in the workforce often must deal with repeated and long periods of unemployment. It seems that these persons are a group with a specific cluster of problems and that their employment situation can be definitively improved by employment services addressing these problems as a whole rather than focusing on one simple concern, such as seizure status.

It is important to note that there is not one, but several profiles for job-seeking groups with epilepsy. Chaplin,[12] for

purposes of understanding intervention needs, has proposed four categories of employment seekers with MS:

> Group 1: Individuals with seizure control, a good work/educational background, and requiring minimal intervention other than some disclosure training.
>
> Group 2: Those with acceptable seizure control, but unrealistic career goals based upon personal capacity. Vocational assessment (to include situational) can be very helpful.
>
> Group 3: Those with unsatisfactory seizure control and interactive cognitive and emotional difficulties. They require comprehensive vocational and psychosocial intervention to achieve employment.
>
> Group 4: Individuals who are typically not able to maintain competitive work due to seizure type, frequency, cognitive deficits, etc., and have typically required sheltered and supported work.

Traditionally, the latter group has been employed in sheltered workshops. There is now, however, a strong movement in bringing this group out of sheltered employment into the open labor market, and it is important to consider the implications of this movement for those currently in sheltered settings. It is beyond the scope of this chapter to review in detail vocational strategies for persons with epilepsy and associated disabilities—the associated disabilities can be a greater source of impairment than the epilepsy. New movements and legislation have brought about exciting developments in vocational rehabilitation for persons with epilepsy, but substantial challenges remain to include funding.

Postsecondary School Vocational Assessment

Unquestionably, a successful transition after secondary school into suitable employment or targeted vocational training is the best groundwork for stable employment in adult life. Nevertheless, studies or demonstration projects attempting to isolate the factors relevant for successful transition are surprisingly scarce.

Vocational Interests/Work Values

Some research is available that is specific to the vocational interests of individuals with epilepsy. Schultz and Thorbecke,[67] in a study of 116 people with epilepsy, including young adults, being assessed vocationally, found that initially 47% desired training for an occupation in the field of social sciences, for example, nurse or educator. As a result of the assessment, however, no one was recommended for training in this area. Fraser et al.[34] studied the vocational interests of 47 male and 24 female patients with epilepsy attending the University of Washington Regional Epilepsy Center using primarily the six major occupational scales and three special scales of the Strong-Campell Interest Inventory. Male patients with major motor seizures had lower Academic Orientation and Investigative scores than male normal controls (p <.01), and male patients with early-onset epilepsy had lower Investigative scores than normal controls (p <.01). Female vocational interests were not significantly different from those of the normal control group. The authors concluded that in line with previous research, male patients appear to be more greatly affected developmentally by epilepsy and that disability alone does not influence vocational orientation, but rather severity of the disability and age at disablement. The authors suggest supportive counseling, social experiences, and involvement in “hands on” and exploratory types of tasks for young men in the home and within the academic setting. Presently, there remains a need for further and more comprehensive studies of this type. It should be noted that work values or reinforcers (“things about the job”) may be more important than interests in actual job choice. In one study,[29] securing a job close to home was significantly more important (p <.01) for those who found work than the unemployed. If this need couldn't be met, job outcome was less successful.

Pattern of Abilities

Studies of aptitudes or abilities present a number of other interesting issues. Clemmons[13] used the General Aptitude Test Battery (GATB), which has been in use throughout state employment and rehabilitation services in the United States. Fifty patients at the University of Washington Epilepsy Center were tested. Test scores did not discriminate between the successfully employed and unemployed. Furthermore, when the mean scores of the employed group were compared with the published GATB norms, all scores of the employed people with epilepsy were found to be significantly lower. The author emphasized that factors such as social support and appropriateness and psychosocial status might be more crucial job access variables than aptitudes.[13] Specialized vocational assistance and placement may also compensate for lesser abilities in highly motivated job seekers with epilepsy.

In a study by Clemmons and Dodrill,[16] the vocational outcome of 40 high school students with epilepsy 4.5 years after graduation was assessed. When looking for factors discriminating the unemployed from the employed, no influence of sex, age, or time since high school graduation could be detected. However, mean scores on the Wechsler Adult Intelligence Scale (WAIS) and the Halstead Impairment Index were significantly different across the groups (p <.01), with the strongest discriminator being the Aphasia Test (p <.001). The unemployed did significantly more poorly on these tests than those who were working. The working and nonworking groups were easily distinguished on the basis of neuropsychological and intelligence measures. The authors suggest identifying those at risk for unemployment based on these variables before they enter the workforce and offering them specialized and intensive vocational services.

Epilepsy-related Restrictions and Limitations

Scharfenstein and Thorbecke,[65] while performing a secondary analysis of vocational rehabilitation by the Department of Vocational Rehabilitation of the Berlin Labor Exchange, found severe epilepsy-related job restrictions in the records (Table 1). Only 11% of the records indicated the type of seizure and only 19% the seizure frequency. Such restrictions are in sharp contrast to the consistently reported low accident rates of people with epilepsy as noted previously. This holds true for persons known to the employer as having the disability and also for persons who do not disclose epilepsy.[77] Therefore, the development of approaches to assess the work-related risks of persons with epilepsy on an individual basis should be of high priority.

Table 1 Work Restrictions for People with Epilepsy (Department of

Vocational Rehabilitation—Berlin)

	Adults with epilepsy (*n* = 32)	Controls (*n* = 32)	Youths with epilepsy (*n* = 32)	Controls (*n* = 32)
No “dangerous tasks” (working with machinery, working in high places)	100%	22%	67%	11%
No “shift work”	94%	44%	60%	
No “piece work”	44%	22%	60%	
No “responsibility”	13%	9%	7%	11%
No “intellectually demanding tasks”	25%		27%	

Behavioral Problems and Social Skills Deficits Associated with Epilepsy

In addition to some of the issues described above, there appear to be a number of variables affecting social and interpersonal behavior and competency for youth and adults coming into epilepsy rehabilitation programs. Work at the University of Washington Epilepsy Center[30] indicates that through several years (1988–1990) during which participants entered vocational services, additional disabilities were prevalent in 89% of this population. Mild to moderate neuropsychological impairment was salient; 37% to 54% (depending on the study group) had a specific documented brain insult, and 26% to 40% had an additional psychiatric diagnosis. The percentages of those with physical disability were minor. Wada et al. in a series of 278 patients in the unemployed found a significantly higher proportion with neuropsychiatric complications.[82]

Earlier work by Goldin et al.[38] suggests that children and adolescents with additional disabilities are more socially isolated and less involved in extracurricular and school social activities. Consequently, they have not had the exposure to social organizational activities through which social skills and competencies are developed. It would appear that youths with active seizures have increased dependency and are less involved in normal risk-taking and social activities, with a subgroup further restricted by additional emotional and cognitive limitations.

A lack of social skills development can be exacerbated by frequent seizure activity and side effects of drugs. As individuals with a seizure disorder mature, emotional and behavioral difficulties can become more pronounced as they react to isolation and failure in the social environment. Curly et al.[17] restricted their study of risk factors for psychosocial maladjustment to a sample of boys (*n* = 60) because they observed that boys seemed to have more adjustment difficulties than girls.[74] This has also been the experience of Fraser et al.[34] In the study by Curly et al., neuropsychological impairment, divisive parenting styles, and number of lifetime seizures accounted for approximately 50% of the variance related to the boys' behavioral disturbances—neuropsychologic impairment for 28% and the other two variables for 13%. Young boys in particular may be a subgroup having greater adjustment difficulty because of lack of support and greater expectations for performance within sports and the vocational areas.

Services

Job access after school may vary between different countries because of different traditions. Therefore, the structure of some services will be outlined without a description of specific features.

Prevocational Intervention (Work Preparatory Courses, Social Rehabilitation)

Freeman and Gayle in 1978[36] initiated in Baltimore a school-based program to facilitate transition from school to employment. During the first 3 years of the program, 333 students with epilepsy were identified, with a mean age of 16 years (range, 12–21 years). The program provided counseling, epilepsy education, and work experience. Students in a first step participated in vocational training courses within their schools and then were offered job opportunities. When the employment outcome was evaluated 2 years after graduation, only 18% of the participating adolescents with epilepsy but 31% of the students without disabilities were identified as program dropouts (i.e., not holding a job or being in school or training).

The key factor to the success of this project was that it enabled the school system personnel to meet the requirements of the law (Public Law 94-142) in developing individualized programs for students with disabilities. In other words, the program assisted overworked and underfunded school personnel to complete required work activity.[35] It was "housed within the school system." Other projects, in Cleveland[80] and Seattle,[14] have encountered more significant difficulties in securing the cooperation of school personnel in obtaining access to youths with epilepsy for enrollment in school-to-work transition programs.

Similar programs were offered in the United Kingdom and in the Irish Republic. A work preparation course by the British Epilepsy Association[6] is conducted during 4 to 6 weeks and offers, in addition to epilepsy education, a comprehensive program of counseling, industrial visits, and work experience. Carroll[10] reported on a 6-month training program from Ireland, during which the trainees were assisted in developing social and communication skills and allowed to sample basic activities in art, drama, home management, and woodworking. On completion, 60% of the trainees with epilepsy versus 72% of the trainees without epilepsy were placed. One year later, 40% of the participants with epilepsy still were employed. When interviewed, participants with epilepsy found the program helpful in increasing their self-confidence and social skills.

At the Heemstede Center in Holland,[18] group training is provided in the following areas, considered vital to good vocational preparation: (a) Coping with seizures in work situations, (b) educating colleagues at work about epilepsy, (c) coping with colleagues' attitudes, and (d) interviewing techniques (role playing). As part of the group training, participants

are given work experience during which they practice what has been learned. Similarly, in Germany, work preparatory courses lasting 1 or 2 years have been designed to integrate adolescents with disabilities into the general labor market as unskilled or semiskilled workers. In 2005 these courses were changed to a more open and flexible form including more practical work experience and allowing continuing with formal vocational training if the young adult shows sufficient capabilities.

Such courses are a valuable trajectory from school to employment for young adults with epilepsy for whom seizures are the main handicap. However, for those having additional physical or neuropsychological handicaps, vocational assessment and training are necessary to identify job goals more appropriately.

Vocational Assessment and Its Components

Around the world in rehabilitation centers or epilepsy centers, assessment units have been set up for people with disabilities, including epilepsy. Vocational assessment typically involves the use of vocational interest inventories, work values inventories, academic achievement testing, intelligence assessment, assessment of emotional and personality functioning, and (depending on job goals) assessment of visual-spatial abilities, motor speed, and dexterity. For individuals with a known or suspected brain insult or impairment of functioning, a full neuropsychological evaluation is requested. For individuals more severely compromised by epilepsy and neuropsychological impairment, a number of commercially available or devised work samples may be utilized to identify a skill that might be transferable to repetitive work (e.g., filing by numbers). If an individual has no specific work goal that can be identified, time should be spent in identifying work-related values (e.g., aspects of work—an esthetically pleasing environment, working with a mixed group of young men and women) that might draw them into some type of work. At a number of the European rehabilitation or sheltered work facilities, a wide range of work activity that can be sampled is often available.

At the University of Washington Epilepsy Center Vocational Services, job tryouts are planned as they relate to a client's job goal, either in a volunteer setting within the hospital or within the private sector under a special 1993 U.S. Department of Labor waiver that allows unpaid work for up to 215 hours. In addition to a rehabilitation counselor monitoring this job tryout or community-based assessment, a job coach often is present to coach the client and take performance data. In the United States, sheltered work facilities are generally used for evaluation or training purposes only with the most impaired clients. Vocational assessment of people with epilepsy must always have two main components: (a) Evaluation of seizure-related restrictions and (b) Evaluation of abilities based on work samples and often neuropsychological testing (if there is a known brain insult).

A first step is always *a complete description of seizure variables* to assess vocational risks. Is there an aura or warning that allows the patient to prepare for a seizure? What is the state of consciousness during a seizure? Does the person with epilepsy fall, and what is the typical pattern of behavior during a seizure? How does the person behave after a seizure (e.g., confusion, disturbance of speech, paralysis of limbs, sleep)? How long does it take until the person is able to resume usual activity? At what time do seizures tend to occur (e.g., during sleep, after awakening), or are they completely unpredictable? Have seizure triggers been observed (e.g., sleep deprivation, alcohol intake, emotional issues)? Has the individual experienced other injuries secondary to a seizure incident? These are representative issues in assessing vocational concerns or risks.

A German group of epileptologists and professionals from rehabilitation centers, large companies, and state accident insurances recently suggested five categories of increasing risk that can be used to evaluate the occupational suitability of persons with epilepsy (Table 2).[1] Seizure frequency was grouped into four categories: More than one seizure per month, three to 11 per year, no more than two per year, and seizure free.

To demonstrate the practicality of these categories, vocations in electromechanics, metal work, health care, and pedagogics were assessed.[1]

Table 2 Epilepsy Risk Categories of the German Task Force

"O"	No loss of consciousness; no loss of posture; control of own actions (seizures only with subjective symptoms)
"A"	No loss of consciousness; no loss of posture; impairment of ongoing activity
"B"	Impaired consciousness; interruption of ongoing activity; no loss of posture
"C"	No loss/loss of consciousness; loss of posture; interruption of ongoing activity

"D"	Impaired consciousness; no loss of posture; actions not in accordance with demands of the situation

Such guidelines facilitate assessment of suitability for certain "dangerous" vocations on an individual basis. However, before such an evaluation is performed, a person's drug regimen and compliance should be assessed to be sure that the person with epilepsy is grouped into the most appropriate category. In the United States, legislation requires consideration of workplace accommodations (adaptive procedures, physical modification of the job site, adaptive equipment that lowers risk). Nevertheless, there may remain situations in which the individual risk must be assessed using such a categorization.

Vocational planning traditionally has been done with the help of psychological testing. For people with epilepsy, however, such a strategy seems to be successful only if procedures are used that are sensitive to the specific abilities and deficits often found. As mentioned earlier, the GATB, which has been universally used in the United States, was not very predictive of the employment status of adolescents with epilepsy. On the other hand, neuropsychological tests predict job success at 1 year reasonably well[15] for those with epilepsy and known brain impairment.

In Germany, 46 rehabilitation centers now exist for young adults—all with a vocational assessment unit. Assessment is done both by evaluation of work samples from different occupational fields and by psychological testing. Finger[27] did an extended study within the assessment unit of the Bethel Epilepsy Rehabilitation Center. Seventy-eight young adults (mean age, 20.25 years; standard deviation [SD], 3.52) were given an extended battery of neuropsychological tests. In addition, epilepsy variables were documented carefully. The dependent variable was recommendation of formal training as a manual worker by the professional team (master educators or social workers) after evaluation of 3 months of work samples. The result was that none of the 10 persons with a history of status epilepticus was given a recommendation for training (p <.05).

The neuropsychological test battery, comprising Picture Arrangement, Digit Symbol Test, Concentration Endurance Test/d2, Stroop (Naming of Color Dots, Naming of Color Prints), Controlled Oral Word Association Test, Name Writing Preferred Hand, Trail Making Test Part B, and Purdue Pegboard Test (Preferred Hand and Both Hands Assembly), discriminated well between the trained and untrained groups. Stepwise discriminative function analysis correctly classified 73% of the persons without and 89% of those with training recommendation (81% and 60% in the cross-validation sample). These results underscore the importance of sensorimotor coordination, motor speed of the dominant side, speed of information processing of selective stimuli, cognitive flexibility, and mastery of abstract language concepts for vocational training.

It can be seen from these results that neuropsychological tests are a very effective tool for rehabilitation planning that includes special training considerations or appropriate job accommodations. It is important, however, not to ignore other capabilities of a client (e.g., compensatory capabilities or social skills). The final goal of vocational training is not successful training but successful placement, which can require additional abilities not measured through neuropsychological tests.

Vocational Training Courses for Young Adults with Epilepsy

Germany has a developed system of vocational training centers for young adults with disabilities. State legislation guarantees every young person with a disability vocational training that takes into account the limitations of the disability. To offer such training, 42 centers have been established, some with a focus on epilepsy and one (Bethel) specializing in assessing those with severe epilepsy or with epileptic and pseudoepileptic seizures. About 7% of the trainees in these centers (about 1,000 persons) have epilepsy.

Rehabilitation, as a rule, begins with an initial assessment by the Department of Vocational Rehabilitation (DVR). Skilled training in a rehabilitation center is proposed for about 60%, and a 3-month extended assessment for 40%. If the DVR counselor or the staff in the assessment unit concludes that it is still too early to enter formal training, a 1-year preparatory course may be offered through a rehabilitation center. During these courses, basic social and vocational skills are developed. Formal training as a rule takes 3 years. At the end, the trainees have to pass an examination in which they must solve the same tasks as an apprentice in a workshop or company elsewhere. The rate of success is high (see above), a consequence of careful selection during the different stages before formal training. Depending on the general unemployment rate between 1995 and 2003, between two-thirds and three fourths have been placed into competitive employment. There are, however, studies from the rehabilitation centers at Heidelberg and Bethel[83] showing that placement of young adults with epilepsy after successful training is more difficult than for trainees with other handicaps. This problem underscores the importance of specialized placement services being available.

School-to-work Transition

There remains a continuing need for developing and evaluating more integrated models of school-to-work transition in which the previously discussed issues are addressed at the same time (i.e., family education and family acceptance of new roles, vocational goal setting based an individual interests and work values, neuropsychological tests, and paid work experience with on-site support and assessment). At the end of such a sequence of activity, reassessment should be done with the aim of confirming or redesigning long-range employment goals.[68]

Unemployment, Underemployment, and Work-related Difficulties of the Employed

It has long been understood that persons with epilepsy have much higher rates of unemployment than persons without epilepsy (see Introduction). Unemployment statistics, however, provide only one perspective. Another perspective relates to difficulties at work for those who are employed (e.g., being underemployed because of undue concern about a seizure disorder, or being “encouraged” toward early retirement because of disability).

Subgroups of the Unemployed and Underemployed

Chronically unemployed persons with epilepsy very often have additional handicaps, such as specific neurologic or neuropsychological deficits, physical handicaps, and emotional and behavioral difficulties. Fukoshima,[37] in a sample of 136 patients at Hirosaki University Hospital in Japan, found 100% of patients with controlled epilepsy and without additional handicaps in the regular workforce. On the other hand, 15% of those with uncontrolled seizures, 29% of those with an additional personality disorder, 36% of those with subnormal intelligence, and 41% of those with additional physical disability were unemployed. Dennerell et al.[19] analyzed in depth differences between 177 employed and unemployed adult patients with seizures. Utilizing verbal IQ, performance IQ, and education as predictors, they could correctly classify 67% of the patients as employed or unemployed. When scores from the Halstead-Reitan Neuropsychological Battery and the California Personality Inventory were included, 78% were correctly classified. It is likely that accurate employment classification would increase with additional information regarding disability or psychiatric status. It is the “epilepsy and additional disability” information that is generally unavailable relative to employment, but is available at the Michigan clinic.

Seizures and Unemployment

The influence of type and frequency of seizures as a risk for unemployment is controversial. Some studies[25,37,42,45,68] show a clear and consistent influence of type and frequency of seizures on rate of unemployment. In an epidemiologic study in Germany for a group of 660 persons between 15 and 60 years old, a consistent relation between seizure frequency and employment could be shown. Interestingly, unemployment of PWE aligned the general unemployment rate not before having become seizure free for 3 years or more.[60] Conversely, studies from epilepsy centers could not detect any significant influence of seizure frequency on unemployment, underscoring the larger role of psychiatric and neuropsychological factors in unemployment.[3,16] One explanation for this finding could be that specialized centers attract patients in whom psychiatric and neuropsychological difficulties are overrepresented. Another explanation could be that there has been a relative increase or identification of psychiatric difficulties in the last

30 years, as can be seen in the studies of Penin.[59] This author followed adults with epilepsy receiving early retirement between 1960 and 1979. In 1960, 75% of all early retirements were a consequence of high seizure frequency, whereas in 1979 this was true for only 25%. Instead of seizure frequency, psychiatric and neuropsychological variables were more in evidence. This is attributed by the author to better seizure control at the end of his study, in 1980, than at the beginning, in 1960.[59]

Some insight on the relationship between unemployment and seizure frequency comes from studies of the social outcome of surgical treatment. In a Norwegian study,[40] 156 surgically treated patients were followed for 17 years and then compared in regard to employment status with a group of nonsurgically treated patients. Treated patients who were employed at the time of surgery were significantly more involved in work at follow-up. On the other hand, those with epilepsy who were unemployed at the time of surgery were not better employed at follow-up than controls, although their seizure status was better than that of the controls and their self-reported "working ability" had improved highly significantly. A study from the Seattle group[28] showed similar results concerning the effects of surgery on employment. Furthermore, it was observed that those patients who remain employed after surgery gain a higher functional level—higher earnings, more working time, and wider responsibilities. In a U.S. study measuring long-term outcome after anterior temporal lobectomy, employment of the surgical group had significantly improved in comparison to the control group; there were, however, no differences between those having become seizure free and those with continuing seizures.[49]

A field of growing interest is changes in the psychosocial situation after a first epileptic seizure or with newly diagnosed epilepsy. There was one study on socioeconomic prognosis after a newly diagnosed unprovoked seizure. Unemployment was higher for those with continuing seizures.[53]

In sum, the relationship between seizure frequency and employment seems to be complex. Among the employed, some with severe epilepsy are not dismissed because of protective legislation in countries such as the United States and Germany. Seizure frequency may also be overshadowed by other factors—neuropsychological and psychiatric—important to employability. However, this does not mean that seizures can be neglected when the issue of unemployment is discussed. It would appear extremely important not to overlook seizure factors relevant for employment, such as the timing of seizure occurrence, potential warnings, provoking factors, falling, duration, and postictal confusion.[57]

Neuropsychological Deficits and Employability

Commonly used neuropsychological batteries include the Luria-Nebraska Neuropsychological Battery and the Halstead-Reitan Battery. Dodrill[21] established a comprehensive battery of 16 discriminative measures sensitive to brain impairment and epilepsy. This battery includes the Halstead Neuropsychological Battery for Adults; the Aphasia Screening Test; the Trail Making Test; the Logical Memory and Visual Reproduction parts of the Wechsler Memory Scale, Form 1; the Sensory-Perceptual Examination; the Stroop Test; and the Seashore Total Memory Test. This battery or others should enable an assessment of a broad range of capabilities, including motor performance, sensory-perceptual abilities, memory performance, attention span, language skills, visual-spatial abilities, problem-solving capacities, and general cognitive efficiency. For individuals referred to a regional or tertiary resource epilepsy center, it is these kinds of difficulties that will affect employability as much or more than seizures. It is common at the University of Washington Regional Epilepsy Center to refer an individual for a neuropsychological evaluation if there is a history of job losses and pronounced emotional difficulties. Sometimes individuals with both emotional problems and suspected cognitive deficits are also referred for assessment. Approximately 40% of the vocational program participants at the University of Washington Regional Epilepsy Center have experienced a head injury. In these cases, the importance of a neuropsychological assessment is further emphasized. Before neuropsychological information was utilized more carefully in vocational planning, it was very common for individuals to lose jobs because of memory difficulties, abstraction deficits, motor and visual-spatial problem-solving concerns, and general cognitive inefficiency.

In a cross-sectional validation study of 58 persons with epilepsy,[8] the neuropsychological scores of the Dodrill battery differentiated very well between the unemployed, the underemployed (working in sheltered employment settings or in competitive settings <20 hours per week), and the employed. The percentage of total test measures outside normal limits was 64% in the unemployed, 53% in the underemployed, and 22% in the employed (p <.001). When the subtests were inspected, the greatest differences could be found in tasks emphasizing motor performance and visual-spatial skills.[8] In another study from the University of Washington Epilepsy Center at Seattle,[32] 46 outpatients were followed prospectively in regard to employability. The best discriminators were the Digit Symbol Test from the WAISR Scale and the Name Writing Procedure. The neuropsychological battery for epilepsy correctly classified 70% of both employed and unemployed.[28] From this finding and general test data trends in the study, a picture emerged showing the unemployed having more difficulties with tasks requiring tactile, motor, perceptual, and spatial integration skills and having more neuropsychological deficits in general.

It is interesting to speculate on the development of such deficits in the course of epilepsy. Rodin[62] reported on 90 patients who were reassessed 6 years after their first evaluation at the Epilepsy Center of Michigan. Those who were unemployed at follow-up had several additional problems: Drug resistance, behavioral abnormalities, and neuropsychological deficits that had not been observed at the first examination 6 years earlier.[62] Dodrill,[20] in a very careful study assessing the association between number of generalized tonic–clonic seizures and neuropsychological functioning, reported a significant increase of neuropsychological deficits in comparing persons with two to 10, 11 to 100, and more than 100 generalized tonic–clonic seizures, and a history of status epilepticus. The sharpest loss of abilities was noted in the group of patients with a history of status epilepticus. It appears that neuropsychological variables are the most important predictors of employment stability or instability, and neuropsychological assessment tools are of immense practical value for rehabilitation planning.

Interactions with Employers and Colleagues

In one hypothesis for the high rate of unemployment among people with epilepsy, misinformation and the negative attitudes of employers are considered to be important causal factors. A study by Sands and Zalkind[63] of employment policies and attitudes toward persons with epilepsy showed that feelings about hiring people with epilepsy were more unfavorable than they were about hiring persons with heart disease, cancer, or diabetes. A similar result was found in a study from the United Kingdom,[48] in which the attitudes of 52 personnel officers

toward employees with epilepsy were compared with their attitudes toward persons with heart conditions, loss of one eye or leg, diabetes, or chronic bronchitis. A recent study from the United Kingdom in which 240 employers were endorsed qualifies these findings.[46] About one fifth said that a prospective employee's epilepsy would be a major issue (mainly in respect to safety). When asked to consider a series of six conditions, epilepsy caused “the greatest overall concern” after depression or heart disease and the highest concern after depression with respect to absenteeism and accidents. About one fourth of the companies had experience employing PWE. In those companies the proportion of jobs deemed to be suitable for PWE and the willingness to make workplace accommodations were greater, and the belief that insurance costs could increase less likely. A higher proportion of jobs in larger businesses were regarded as suitable for PWE than in small ones.

It seems that the basis for negative employer attitudes is the lack of practical information about epilepsy. Holmes and McWilliams,[44] when surveying 116 employers in Tennessee, asking them, “If your company physician told you that an applicant with epilepsy was physically able to work, would you hire him?” got 72% positive answers and only a small proportion of negative responses; however, a relatively high proportion (24%) of employers expressed the view that they were unsure. From an earlier UK study,[48] it was also obvious that information deficits were one of the main barriers to employment; 43% of employers wrongly believed that insurance companies would not provide normal liability insurance rates.[48] The above findings suggest that employers could profit from basic educational to improve their hiring practices.

When looking at interactions with employers, there are also the emotional aspects that cannot be overseen. In all studies cited, there are prejudicial hints—high percentages of “unsure” answers or contradictions between positive and negative attitudes toward hiring in more specific questions. Sands and Zalkin,[63] in their demonstration project, undertook a rigorous education campaign over 1 year to change employer attitudes. The outcome was totally negative. There were no meaningful differences when the experimental (educational intervention) city was compared with the control city. From this the authors concluded the following:

> "Modification of employer attitudes toward hiring the epileptic may therefore require something more than the usual public education program. Employers must be actively involved in education campaigns by their actually seeking and providing jobs for qualified epileptics. As a result of such involvement in placement, the policy-level business executive will learn about epilepsy on an emotional level, which we postulate should result in an attitude change."[63]

It is just this approach that is often followed in modern vocational rehabilitation training and placement services. It would also be important to establish rules to prevent discriminatory hiring practices toward those with disabilities. A general framework for this is provided in the Americans with Disabilities Act, and specific guidelines are presented in the "principles for good practice" of the Employment Commission of the International Bureau for Epilepsy.[3]

There is now also a study in which the reactions of coworkers to PWE have been addressed.[41] When comparing the reactions to persons with depression, multiple sclerosis, and epilepsy, it seemed that coworkers are especially worried about sudden unpredictable behavior of PWE ($p <.013$) and feeling uncomfortable providing first aid to them ($p =.081$). This finding in accordance with the studies tapping employer attitudes suggests that educating people about epilepsy, especially about the concrete features of seizures and how to give first aid, could decrease worry and social avoidance.

Predictors of Long-term Employment Success

Prior sections of this chapter have dealt with seizures, neuropsychological deficits, behavioral abnormalities, additional handicaps, and employer attitudes as factors independently influencing the chances of persons with epilepsy to obtain or hold a job. From a broader perspective, it becomes obvious that these factors are interrelated. Frequent seizures may increase the likelihood of seizures occurring at work, which increases the risk for unemployment[76] and psychosocial problems.[20] Frequent seizures at the same time increase the risk for neuropsychological deficits,[20,62] and these in turn increase the risk for unemployment. It is also well known that unemployment increases the risk for psychiatric disorders and psychosocial problems, the latter being correlated with a bad seizure prognosis.[23]

Thus, it appears that services aimed at reducing the risk for unemployment will be effective only if they address joint factors at the same time and as early as possible. A second presupposition for long-term employment success is compensation for poor education and insufficient vocational training, which seem to be fundamental deficits in the unemployment status of people with epilepsy. Finally, it is insufficient simply to place these people in competitive, unsubsidized employment; they also need support to maintain steady employment and overcome periods of only cyclic employment.[33]

Vocational Services

To address the employment problems of people with epilepsy, four types of services seem to be necessary:

1. Programs for assessment and short-term rehabilitation
2. Vocational retraining programs for those in occupations or trades unsuitable for anyone with a seizure disorder
3. Training and placement services for those who have completed vocational training or for those with poor work records
4. Services directed at keeping people with epilepsy employed (postplacement services)

It is obvious that such services in different countries may have different structures. For example, they may be separated or integrated, specialized for people with epilepsy, or specific for those with neurologic deficits or diverse disabilities.

Programs for Assessment and Short-term Rehabilitation

In 1983 in the United States, and then 15 years later in Germany, a type of service was launched that connected on the one hand high standard diagnosis and treatment approaches (including surgical treatment of the epilepsies) and on the other hand neuropsychological and psychiatric assessment and first steps of rehabilitation such as work experience, preparing structured vocational rehabilitation measures like retraining into a more suitable profession, or placement into competitive employment.

First data on the outcome of the U.S. program were given in 1983 by Fraser et al.[31]

From the German program, designed very similar to the American one, first data were given in 2004[73] comparing social and employment situations for a consecutive series of the first 96 patients before admission and 18 months after the 4- to 6-week enrollment in the program. Seventy-nine patients (82%) had focal epilepsy. Physical comorbidity was found in 21%, and psychiatric comorbidity in 53% of the cohort. Compared with time point 1, seizure frequency and number of hospital admissions due to epilepsy were reduced at time point 2 (p <0.01). Significant improvements were found in six out of seven quality-of-life domains (epilepsy-related fear, emotional adaptation, perceived restrictions, perceived stigma, mobility/independent living, and physical/emotional health) and in performance in daily life (e.g., going out alone, driving a car).

The employment situation also changed significantly: Unemployed, preadmission 48%, postenrollment 20%; employed, preadmission 33%, postenrollment 37%; sheltered employment, preadmission 6%, postenrollment 10%; vocational rehabilitation measures, preadmission 3%, postenrollment 11%; early disability pension, preadmission 2%, postenrollment 14%; homemaker, preadmission 8%, postenrollment 8%. Those who were employed preadmission and postenrollment reported significantly fewer problems at the workplace—time on sick leave, concentration and memory problems, and seizures at the workplace (p = .014).[72]

Retraining Centers for Adults

During the last 40 years in Germany, a network of centers has been developed; today, 28 centers have 14,500 retraining slots. They offer vocational retraining for a great number of occupations and trades. As a rule they have three components: (a) An assessment unit to assess interests and abilities over a 2- to 6-week period. At the end of the assessment, it is decided whether the client should be retrained, receive a disability pension, or be placed in unskilled or semiskilled employment without retraining. The decision to send a person to a retraining center is the responsibility of the local labor exchange's department of vocational rehabilitation or the rehabilitation department of the state pension insurance. (b) Retraining may begin with a 3-month preparatory course in which basic (school) abilities are retaught. (c) Two-year retraining follows. This is equivalent to 3 years of vocational training of young adults without disability after high school.

The proportion of people with epilepsy in these institutions is 1% to 3%. Some are specialized for persons with neurologic diseases, including epilepsy. Fifteen to 20% of the trainees drop out.

Schultz and Thorbecke[67] observed 73 people with epilepsy within the assessment unit of a Berlin retraining center for adults. Prognostic factors suggestive of training potential and level of retraining were age, number of additional handicaps, intellectual capacity, working pace, and drawing skills. Psychopathologic abnormalities sharply discriminated between those accepted versus not accepted for retraining.[67] No influence of seizure variables, which were carefully documented in the study, could be found.

In a study from the large retraining center at Heidelberg, Germany, Wöhrl[83] reported that 2 years after retraining, 68% of the persons with epilepsy (n = 151) were employed, whereas 79% of the persons with other disabilities (n = 757) were employed (p <.01), the level of vocational qualification being equivalent in both groups. This draws some attention to a need for specialized placement assistance for those with epilepsy.

Training and Placement Services

The most effective training and placement service for people with epilepsy worldwide has been the 20-year-old TAPS (training applicants for placement success) program of the Epilepsy Foundation of America (EFA). Over this time span, it grew continuously and became more specialized to the needs of special groups of people with epilepsy while simultaneously increasing the placement rate from about 55% at the beginning of the 1980s to nearly 70% at the beginning of the 1990s.

The background of the TAPS program was an EFA demonstration project in the 1960s in which group counseling was proved to be highly effective for the placement of job seekers with epilepsy and numerous other problems.[66] In 1976, with funding from the U.S. Department of Labor, the EFA started the TAPS program, which worked according to the same principles. The *client-oriented component* of TAPS is based on the principles of active peer support and shared responsibility. After intake and orientation sessions, participants received *training in job-seeking skills.* In the weekly meeting of the *job club,* they shared their actual job-seeking experiences and encouraged each other to continue the job search. During job club meetings, employers familiarized participants with their views of job applicants or did exercises with them to improve their job-seeking skills. Additionally, every participant received individual assistance as needed. *Placement* was achieved if an individual found part-time (15–29 hours) or full-time (30–40 hours) unsubsidized employment. *Follow-up services* were provided for 1 year following placement.

A second component of TAPS was aimed at *employer development and interagency collaboration.* Employer participation was to be found in all parts of the program. In *employer development,* staff gained information on current job opportunities and required qualifications through employer visits. Every regional TAPS had *a local advisory committee* composed of employers and representatives of relevant local agencies. Finally, staff provided *education and mediation services* for local employers regarding employment and epilepsy issues.

TAPS programs existed in 13 American cities, largely supported by the U.S. Department of Labor.[5] There were 1,351 persons with epilepsy enrolled in 1994, with 914 (68%) being placed in unsubsidized employment. Among these, 77% maintained employment 90 days after placement. Placement of women, however, reached only 39%, and placement of youth only 7%. Average cost per placement was approximately $750. Because of the great success of the TAPS methodology, EFA established further regional TAPS that were privately funded (e.g., by the Coelho Jobs Fund).

Troxell[79] reviewed a number of highlights from this large effort by the EFA and U.S. Department of Labor. It is of interest that seizures seemed to contribute little to employment outcome or retention. People receiving social funding assistance had more difficulty securing jobs and those unemployed for more than 1 year at intake had more difficulty keeping jobs. It is also important to note that although more than 65% achieved placement, only 70% of these maintained the job even at 90 days. Troxell ended his retrospective review of TAPS activities by calling for earlier vocational intervention, more comprehensive and intensive services for enrollees on social financial assistance programs, more in-depth assessment at intake, and the need for more intensive job-site support and follow-up postplacement.

Unfortunately, the U.S. Epilepsy Foundation is less involved in vocational programming today. Much of this relates to reduced available funding.

Fraser et al. conducted two studies[31,33] to evaluate the effectiveness of specialized training and placement services for people with epilepsy. In the first,[31] the vocational services program of the University of Washington Regional Epilepsy Center, which has nearly the same components as TAPS, was evaluated. Of 106 persons with epilepsy, 50 (47%) could be successfully placed. The strongest discriminators between the employed and dropouts were “months employed in the last 24 before entering the program” and treatment for psychiatric conditions or addictions before entering the program. The group achieving employment had an average of 12 months in

employment of the prior 24, whereas dropouts approximated only 7 months. In later cross-validation, only months employed before entering the program proved to be a significant discriminator, the psychiatric and addiction category losing its influence because of program refinements targeting these issues.[31]

In the second study,[33] outcome from seven state placement agencies was compared with the outcome from the University of Washington placement program. State agencies had a placement rate ranging from 9% to 21%, except for one state with a 44% placement outcome. The University of Washington specialized program placement rate was about 50% (see above). There were no differences in client characteristics that could account for these differences. These authors provided some interesting explanations:

1. In state agencies, the client-to-rehabilitation counselor ratio is about 1:100, whereas in specialized TAPS programs it is between 1:30 and 1:40.
2. In the state agency with a placement rate as high as 44%, special efforts were made to increase placement of persons with epilepsy, such as hiring only counselors with a Master's degree and having a counselor with the disability provide detailed education on epilepsy for fellow counselors (also having an emotional impact).

From these experiences, the authors concluded that specialized agencies should be established in local epilepsy centers and associations. At the same time, specialized training should be developed for the state counselors so that they may better meet the needs of the job seeker with epilepsy. Through specialized training, counselors also acquire empathy for the cause.

Postplacement Services

After a person with epilepsy is assisted to placement, several problems may occur: Frequent sick leave, inadequate performance, conflicts with supervisors or colleagues, and uncertainty of supervisors and colleagues about an individual having epilepsy if this has not been previously disclosed. Different kinds of assistance may be needed: Medical treatment, accommodation of some type at the job site, transfer to another workplace, counseling of the person with epilepsy by supervisors or colleagues, medical leave, or early retirement. Support and counseling may be provided by different services. External services are affiliated with state agencies, epilepsy societies, or epilepsy clinics. Other services are situated at or near the work site, such as occupational health services. These services may be specialized for epilepsy or may accommodate persons with various disabilities.

As previously described, TAPS provided postplacement support until 1 year after placement. In Germany, external postplacement services for persons with mental illnesses and disabilities, which also support people with epilepsy, have been developed by the state. These services cooperate closely with psychiatric clinics, and in many cases support can begin before placement and be continued, if necessary, for years. These services seem to be effective in opening doors for unemployed persons, because the employer may rely on the service if there are difficulties after placement. It has also been observed that these services are effective if a chronic disorder develops in an employee. In this situation, an employer is generally in need of specific information concerning the disorder and is ready to accept suggestions from an external service (e.g., to look for specialized medical treatment or to retrain). If an employee with a chronic disorder, such as epilepsy, is employed for many years, support from the external postplacement services seems less applicable, because the company itself may have attempted many accommodations. Nevertheless, the external service can still give meaningful support, such as counseling, suggestions for transfer to another work site, or recommendations for specialized medical treatment.[54] These services seem to be highly effective for maintaining people with chronic illness on the job.

Postplacement support may also be given by occupational health services. Kleinsorge[50] reported on 65 persons with epilepsy in a large German chemical company. Only one of six had been known to have epilepsy when starting to work because of lack of disclosure. No one with epilepsy was dismissed when the epilepsy condition was disclosed; however, 25 of 65 had to be transferred to a more suitable workplace. Espir et al.[26] recently reported on 93 subjects with epilepsy who were referred to the British Civil Service Occupational Health Service during an 18-month period. Reasons for referral were prolonged or frequent sick leave, unsatisfactory work performance, and epilepsy starting during employment. After each case was inspected, it became evident that many referrals were not a consequence of epilepsy but of associated illness or handicaps. Twenty-six instances of prolonged sick leave were reported: Six caused by epilepsy, nine caused by side effects and disorders associated with epilepsy, and 11 caused by other disorders, such as internal medical problems, psychiatric problems, or alcohol abuse. Of 23 cases of unsatisfactory work performance, 14 were a consequence of epilepsy and nine were not.

It is interesting to review the results of the Occupational Health Service interventions. Of the six persons with epilepsy who had prolonged or frequent sick leave caused by epilepsy, only three continued to work. Of the 14 persons with epilepsy who had an unsatisfactory work performance caused by epilepsy, 12 continued to work. Among the 22 persons with epilepsy whose disability began during employment, 12 continued working. Of eight persons with undisclosed epilepsy, seven continued working, and of the 35 needing advice on working conditions, 28 continued. The authors emphasize the important role of the Occupational Health Service in solving these problems. However, the fact that only 12 of 22 persons with new-onset epilepsy occurring during employment continued to work engendered some criticism. This is not what would be expected for new-onset epilepsy, which has an excellent prognosis, and results could have been different with the advice of an experienced epileptologist.[26]

More research and demonstration project efforts with regard to specialized postplacement services are presently needed. It would be misleading to believe that only unemployed persons with epilepsy are a problem group. A second group, employed people with epilepsy, is at risk for dismissal or retirement, or these people are gradually losing their abilities because of lack of appropriate medical interventions. Postplacement services should be targeted at these groups.

Workplace Accommodations

There are several categories of work-site accommodation, which include procedural accommodations, physical modifications to the workstation itself, and the use of adaptive or assistive technology (equipment that enables an individual to perform on the job). For most individuals with a seizure disorder, the primary issue falls within the first two categories.

Procedural changes can be easily implemented and are very helpful to an individual with a seizure disorder. Individuals with occasional loss of consciousness, particularly when there is no warning, may need to avoid certain physically hazardous work activities. Without consistent warning, there may be no way to ensure safety in a specific activity. For example, part of a job involving working in high places or driving might be reassigned to another worker. For some individuals with seizures, changing shifts can be detrimental to functioning. A regular day shift can at times be arranged so as not to disrupt sleep patterns or the manner in which drugs are absorbed. Individuals may also require work-site modifications specifically for safety purposes. This might involve some type of floor covering or matting, a machinery guard, or an automatic cutoff switch that would ensure safety if a seizure occurred. In sum, accommodation needs are primarily for those individuals with marginal seizure control and the potential for an accident or injury on the job. However, some individuals with new-onset epilepsy take some time (up to 1 year) to achieve reasonable control. During this period, procedural changes or work-site modification can help to keep them on the job.

Assistive equipment is primarily for individuals with epilepsy and neuropsychological impairment. Equipment can include electronic cueing devices and watches, telepagers, and other memory aids. For individuals with both memory and problem-solving deficits, computer software programs can be helpful in organizing work and improving cognitive efficiency. Other individuals may use palm-top computers to organize work and otherwise aid memory. Again, assistive equipment is not a typical work-site accommodation for an individual with a basic seizure disorder but is more commonly used for clients with additional cognitive or physical limitations.

Birgit's Case

Birgit S. came to the center at Bethel when she was 19 and in the third year of training as a lathe operator. Complex partial seizures preceded by an epigastric aura were diagnosed. Her aura, however, was too short to protect her from the seizures. Therefore, the foreman, the occupational physician, and the rehabilitation specialist decided to install a box of acrylic glass over the lathe to prevent the machine from starting without the box in the right position. Birgit completed her training as a lathe operator successfully and after several changes of drugs has achieved good seizure control.

Others who can profit from workplace accommodations are persons with epilepsy who have been employed for a long time in one company, persons with late-onset epilepsy, or those whose epilepsy status deteriorates. Such persons are often too old for retraining, cannot be dismissed because of seniority, and are often considered desirable by the employer for their long-term performance and contribution.

Christina's Case

Christina W. was employed as a production assistant. Her job was to take containers formed with synthetic material out of machinery, put away the metal-forming edges, and store the containers. When generalized tonic–clonic seizures developed and these tasks became too dangerous for her, the machinery was adapted. She is now using a new machine with an automatic starting button placed some distance away. The cost of this accommodation was paid by the Office for Handicapped People in the Work Force (Germany).

National Legislation Affecting Job Access

Germany

In 2001 the federal government bundled all rehabilitation laws and regulations in a complex rehabilitation act, which is based on the principles of the ICF (Sozialgestzbuch IX). The rehabilitation act also contained new forms of support (e.g., "work assistance"). An example for this would be that a person with epilepsy who sometimes to fulfill his or her professional tasks has to drive would get funded a driver. Persons who cannot reach their workplace because they are not able to use public transportation can ask for cost-free private transportation. Support of disabled persons at the workplace is organized by regional (state) offices for the disabled. These offices are also responsible for workplace accommodations and therefore provide technical services. They also have highly specialized outreach services to support persons with disabilities at the workplace. One shortcoming is that these institutions give only support to people who have the status as handicapped. One consequence of this is that persons after a first epileptic seizure cannot get support even though this is a group in high need of work-site accommodations or procedural changes for a limited time period.

Americans with Disabilities Act

The Americans with Disabilities Act, enacted between 1992 and 1994, is benchmark legislation in the United States extending the prohibition on disability-related discrimination to the private sector. Title 1 of the Act covers employment and companies with as few as 15 employees. A company cannot discriminate in employment practices against a person who has epilepsy (or even a record of experience with the disability). Persons with a seizure disorder cannot be discriminated against in employment if they can perform the *essential* functions of the job with or without *reasonable accommodation* (a change in procedure, physical modification to the work site, or some type of adaptive equipment). People with epilepsy do not have to disclose their disability in the interview unless it affects performance of the job's essential functions. A person with a seizure disorder no longer has to submit to a medical examination unless a job has been offered.

In a review of the claims[17] filed under the Act with the Equal Employment Opportunity Commission during the first year, McMahon et al.[58] determined that 86% of the complaints were related to individuals already on the job. The law seems to be helping people with disabilities to keep jobs, but not necessarily to be hired.

Sheltered Employment Versus Employment of Persons with Epilepsy in the Open Labor Market

Sheltered employment, or special work facilities for persons who are considered unemployable in the competitive labor market, exists in nearly all countries of the world. Typically, certain products or services are provided or subcontracted from a manufacturing company, but in recent years more sheltered workshops have developed their own products, such as toys. Although nearly universal, the types and extent of sheltered employment differ sharply between countries with comparable economic structures. In 1990, 5 of 1,000 workers in Germany, 14 of 1,000 in The Netherlands, and 1 in 1,000 in the United Kingdom and the United States were employees in sheltered workshops. The extent of sheltered employment seems to be more a reflection of national philosophies toward employing people with disabilities than an objective employment phenomenon.[75] In two sheltered facilities in Berlin, Thorbecke found that 5% to 10% of their employees had epilepsy, depending an each workshop's production structure. This result was congruent with findings in other countries.[2]

In a study on seizures and epilepsy within a mentally retarded population,[61] 26% of those with mental retardation, 6% of a borderline IQ group (IQ below 75), and 2% of the comparison group experienced two or more seizures. The authors have found not only persons with epilepsy and mental retardation in sheltered workshops, but also a second group who have epilepsy and other problems, such as learning disabilities, behavioral problems, and severe drug or cognitive side effects, or who have frequent uncontrolled seizures—a subgroup of persons with epilepsy who are chronically unemployed. Members of the first group as a rule enter sheltered workshops directly after school, whereas those in the second group come to them after integration efforts in the open labor market have failed, which may have serious consequences for their perception of the sheltered employment opportunity.

People with epilepsy in sheltered work are a minority. Therefore, their special needs can easily be neglected. For example, in Germany the responsible consulting physician in a sheltered workshop as a rule is neither an epileptologist nor a neurologist, and treatment status is assessed only on first entrance into sheltered employment, with no requirement for epilepsy education for supervisors. As a consequence, persons with epilepsy may be needlessly excluded from work at machinery that is highly valued and can pay better in the sheltered workshop setting. A further consequence may be that persons with epilepsy in sheltered employment who

are not mentally retarded, after their epilepsy is well controlled, may not be sent for further vocational rehabilitation or placed in the open labor market, but rather remain in the sheltered workshop. These observations should, however, be grounded in more systematic studies (see also studies cited below).

New Services

Models to Change Sheltered Employment

In the early 1970s, a U.S. movement arose for reducing sheltered employment and finding ways less conducive to segregation of employing those with severe disabilities. As a consequence, new forms of employment for this group in the open labor market, known as supported employment, were established. In the United States, supported employment emerged quickly because of amendments to the Developmental Disabilities Act in 1984. The concept of supported employment can be divided into four steps: (a) Placement, (b) training on the job by a job coach, (c) stabilization, and (d) maintenance. The time spent on job-site assistance decreases continuously from step one through step four.

Models of Supported Employment Placement

It should be noted that there is more than one model of supported employment:

1. Individual placement. Employer pays the client minimum federal wage or above while the client receives specific training with a job coach.
2. Enclave model. A group of individuals (usually fewer than eight) work together or at diverse work stations for one company and receive training or support from a job coach. Wages are usually at the minimum level. In some cases, individuals are integrated into the mainstream workforce on an individual basis.
3. Mobile crew model. In a single-purpose business, a general manager or trainer works with a group of four to five employees out of a mobile vehicle, such as a van. The work can involve activities such as landscaping or janitorial services, with wages at a minimum level or higher.
4. Entrepreneurial benchmark model. In a small, single-purpose business located in an integrated community setting, eight to 15 clients receive training or actively work. Wages are at a minimum level or higher and

the workforce may be integrated, involving employees without disabilities.

Much work has been done to clarify supported employment program components: Community job analysis, job match and placement, job training with specific techniques of applied behavior analysis, and follow-up services and interagency coordination. (See special issues of the *Journal of Rehabilitation,* 1987;53[3]; the *American Journal of Applied Behavior Analysis,* 1989;Winter[4]; and the *American Journal on Mental Retardation,* 1989;94[1].)

A survey covering the years 1984 to 1985 and 1985 to 1986 in the United States showed that 17% to 19% of clients were transferred from sheltered into supported employment.[64] This trend within the United States has continued, so that the majority of clients are being served under a model of supported employment. Several benefit–cost analyses indicate positive results: The supported employee earns better pay and is more a part of mainstream life.[51,56,78] Three German federal states have large demonstration projects on ongoing supported employment: One aimed at direct transition from special school to employment in the open labor market, and the other two at transition from sheltered employment to competitive employment. In the Westfalian project including 141 persons, more than four/fifths of them had visited a special school for children with mild or severe learning disability and were placed in the general labor market. Twenty percent were in sheltered employment, the remaining unemployed or in work preparatory courses. Eighteen percent had epilepsy. Seven years later 125 could be revisited. Sixty-six percent still were employed in the general labor market, and 80% had been regularly employed for >50% of the follow-up time. No negative effects of epilepsy on the chances to keep employment could be detected; 93.6% got practical work experience before entering regular employment and got, if necessary, extensive support at the workplace organized by the integration service of the Westfalian office for the disabled. There was also an economic cost efficiency study showing that that there would be strong economic arguments for this approach, resulting in better funding of such services.[4]

Transition of People with Epilepsy from Sheltered Employment into the Open Labor Market

From the cited surveys, primarily persons with mild mental retardation or ratings of dull–normal on full-scale IQs (approximately the lower 70s) are served in supported employment. The proportion of persons with severe disabilities, such as traumatic brain injury, cerebral palsy, or autism, is low.[69] No specific data are available for persons with epilepsy. However, it is safe to assume that people with moderate or severe mental retardation as a primary disability who have epilepsy as an additional handicap are being served. It seems that issues concerning control of epilepsy in this group are the same as for persons without mental retardation, if treatment follows the principles of an effective anticonvulsant regimen.[55]

There is an urgent need for research to address the specific problems of those with epilepsy in sheltered employment who are truly candidates for supported employment in the open labor market.

Summary and Conclusions

In this chapter, the specific vocational needs of people with epilepsy and the services designed to meet them have been outlined. The background for this chapter has largely been experiences in vocational rehabilitation within the United States and in Germany. The service structure in these two countries is considerably different. In the United States, specific services exist for persons with epilepsy to a limited degree at certain affiliates of the national Epilepsy Foundation or at university epilepsy programs (e.g., University of Washington-Seattle or University of California-San Francisco).

In Germany, specific services are rare, while at the same time the “welfare state” makes intensive efforts to integrate all people with disabilities into the labor force. As a consequence, a network of labor-mediation agencies and integration services dealing with disability issues and rehabilitation centers for adolescents and adults has been developed. In Germany, the state agencies and training institutions try to remain sensitive to the specific needs of persons with epilepsy who are a minority, whereas in the United States, the vocational support such people receive depends more on the specialized vocational rehabilitation services that are available in their region. In some cases these services are exceptional, but in other cases within the United States, persons with epilepsy miss the benefits of a German type of integrated training or retraining system.

It is the authors' conviction that both approaches are needed: Specialized services for persons with epilepsy that are sufficiently flexible to accommodate their unique requirements and a network of integrated work access and training services for all people with disability with staff that knows and understands the special needs of those with epilepsy.

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Chapter 220

Issues in Health Outcomes Assessment

Zarya A. Rubin

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Introduction

Epilepsy is a multidimensional disorder with potential consequences for nearly every aspect of a patient's life, from physical effects, to social and vocational challenges, to personality and mood changes. In addition, total estimated health care costs are $12.5 billion in the United States annually.[12,46] Results of recent large clinical studies indicate that 25% to 40% of patients diagnosed with partial epilepsy will not be controlled with medication,[37,60,72,73,74,88] and a larger proportion experience adverse antiepileptic medication effects. Epilepsy patients are also more likely to suffer from comorbid depressive disorders than the general population or patients with other chronic illness, with prevalence rates of depression estimated to be 20% to 40%.[11,33,50,61,78,84] The comprehensive picture of the experience of epilepsy is more complex and detailed than is often assumed, reaching beyond the seizures themselves and extending into multiple domains of patients' overall health.

The Concept of Health-related Quality of Life in Epilepsy

Measures of success in treating medical illness have traditionally been characterized as freedom from disease or other intermediate quantifiable endpoints such as reduction in systolic blood pressure, serum glucose, or seizures.[21] Over the last decade, however, the emergence of health-related quality of life as a reliable, valid, and significant indicator of overall outcome in patients with epilepsy has begun to alter that perception.[28,41,49,95,101]

The concept of quality of life is not new, and dates back at least to the time of Aristotle, who attempted to define the attributes of happiness.[4] The Constitution of the World Health Organization defines health as “A state of complete physical, mental and social well-being and not merely the absence of disease or infirmity.”[102] The current definition of quality of life encompasses both the concept of health and functional ability, as well as the patient's perceived satisfaction with this level of functioning. Thus, both objective and subjective measures are incorporated into the final assessment of overall quality of life.

As defined by Gotay et al.,[45]

> Quality of life is a state of well-being that is a composite of two components: (1) the ability to perform everyday activities that reflect physical, psychological and social well-being and (2) patient satisfaction with levels of functioning and the control of disease and/or treatment-related symptoms.

The initial formulation of an instrument designed to measure quality of life in health care occurred in 1948 with the development of the Karnofsky Performance Status Scale. The 100-point scale defined a patient's ability to perform various activities of daily living (where 100 is *capable of performing all normal activities* and 0 is *deceased*).[19,58] In 1992, Vickrey et al.[95] developed one of the first reliable and valid measure of quality of life in epilepsy, the Epilepsy Surgery Index-55. Baker et al.[9] concurrently constructed a model of assessment of physical, social, and psychological impairment related to refractory epilepsy. In 1995, Devinsky et al.[29] developed the Quality of Life in Epilepsy Inventory (QOLIE-89), an 89-item, disease-specific inventory to help characterize the impact of epilepsy on patients' global functioning. Since then, a QOLIE-10[25] has been developed in addition to other more specific inventories relating to aspects that contribute to overall quality of life in epilepsy such as medication side effects (Adverse Events Profile)[6] and the NDDI-E (Neurologic Disorders Depression Inventory for Epilepsy),[38] a newly developed tool for differentiating depression in epilepsy from antiepileptic drug (AED) and cognitive effects.

In a study of 81 consecutive epilepsy patients, Gilliam et al.[40] systematically assessed the specific concerns of patients with recurrent seizures. The most frequently cited concern was driving, at nearly 70%, whereas

other significant factors listed by more than one third of patients included independence, work and education, social embarrassment, medication dependence, mood/stress, and safety (Table 1).

Although these patient-oriented outcome measures are not intended to replace traditional indicators of health status in epilepsy such as seizure frequency or severity, they may offer additional information that allows us to expand our knowledge of the experience of epilepsy and better treat our patients. This review examines the contributions of seizure status, outcomes of epilepsy surgery, mood effects, medication toxicity, and other comorbidities to overall health-related quality of life (HRQOL) in epilepsy.

Seizure Frequency and Health-related Quality of Life

Although seizure frequency was previously believed to predict overall quality of life and seizure reduction continues to be a goal of therapeutic interventions for epilepsy, there in fact exists no clear gradient establishing a direct correlation between number of seizures and degree of HRQOL improvement or worsening. In fact, the only true amelioration in quality of life can be observed when patients are rendered entirely seizure free.[14,63,69,96]

Table 1 Quality of Life in Epilepsy-89 (QOLIE-89) total and subscale score differences between groups according to depression diagnosis

	Difference between no and major	Difference between no and moderate	Difference between moderate and major
Total QOLIE-89	31	19	12
Health Perception	27	20	7
Overall Quality of Life	30	16	13
Physical Function	23	21	2
Role Physical	40	31	9

Role Emotional	54	24	29
Pain	29	18	11
Social Function	27	17	10
Energy-Fatigue	29	17	12
Emotional Well-Being	37	19	18
Attention-Concentration	32	17	15
Health Discouragement	38	20	17
Seizure Worry	24	15	8
Memory	27	18	9
Language	23	13	10
Medication Effect	21	8	13
Social Support	25	11	14
Social Isolation	37	21	16

Score difference >12 points are considered clinically significant. ANOVA, $p < .0001$, for all QOLIE-89 total and subscale raw scores by depression group.
Source: From Cramer JA, Blum D, Reed M, et al. The influence of comorbid depression on quality of life for people with epilepsy. *Epilepsy Behav*. 2003;4:515–521; with permission.

In the multicenter study by Leidy et al.,[63] patients were classified according to seizure frequency and evaluated on the Medical Outcomes Short Study Form (SF-36), a "gold standard" measure of quality of life. Scores for seizure-free patients were similar to those of the general population, whereas increasing frequency of seizures predicted a small but inverse shift in HRQOL across all domains.[63] Although some differences were observed between groups with differing seizure frequency, these differences were subtle, and the greatest discrepancy in quality-of-life scores was observed in the seizure-free group versus all seizure groups.[63] In a recent study by Birbeck et al.,[14] these results were confirmed using the QOLIE-31, QOLIE-89, and SF-36, with positive changes in HRQOL occurring only in the group that achieved seizure freedom and not in the groups that achieved seizure reduction. Thus, although many AED trials use a 50% reduction in seizure frequency as a desirable endpoint, it appears that the complete eradication of seizures provides the only definitive HRQOL benefits for patients with epilepsy.[14,63]

Vickrey et al.[95] compared the health status of patients who had undergone epilepsy surgery with those who suffered from other chronic illnesses such as hypertension, diabetes, and heart disease (Fig. 1). Although patients who were rendered completely seizure free scored higher on all measures than patients with chronic illness, patients who continued to have seizures, even without alteration in consciousness, scored similarly to patients with other chronic medical conditions in terms of social and emotional well-being; patients with residual complex partial or generalized tonic–clonic seizures scored significantly worse than patients with myocardial infarction or congestive heart failure on overall QOL and social and emotional well-being.[95]

These results further emphasize the importance of eliminating seizures to achieve adequate quality of life; even occasional auras impair quality of life to a degree similar to a chronic medical condition such as diabetes.[33] By achieving total cessation of seizures, through medical or surgical interventions, patients with epilepsy may attain of a level of quality of life that approaches or surpasses that of the general population.[14,63]

Surgery and Health-related Quality of Life

In the first randomized, controlled trial comparing epilepsy surgery to conventional therapy, Wiebe et al.[100] demonstrated that surgery was far superior to medical treatment in terms of rendering patients free of disabling seizures (58% vs. 8%), with correlative improvements in quality of life. In a recent multicenter observational study with long-term follow-up by Spencer et al.,[90] 66% of patients experienced a 2-year remission. Success rates for temporal lobe epilepsy with corresponding mesial temporal sclerosis and supportive electroencephalographic (EEG) findings may be considerably higher.[39,83]

Despite compelling evidence in favor of epilepsy surgery, few patients who are possible candidates are being offered this potentially curative treatment, and those who are being considered for surgery may wait an average of 20 years from diagnosis.[42,61] The risks of delaying epilepsy surgery are not insignificant, given that the rate of epilepsy-related death may exceed 1%,[91] whereas the reported rate of mortality for epilepsy surgery is <0.2%.[13]

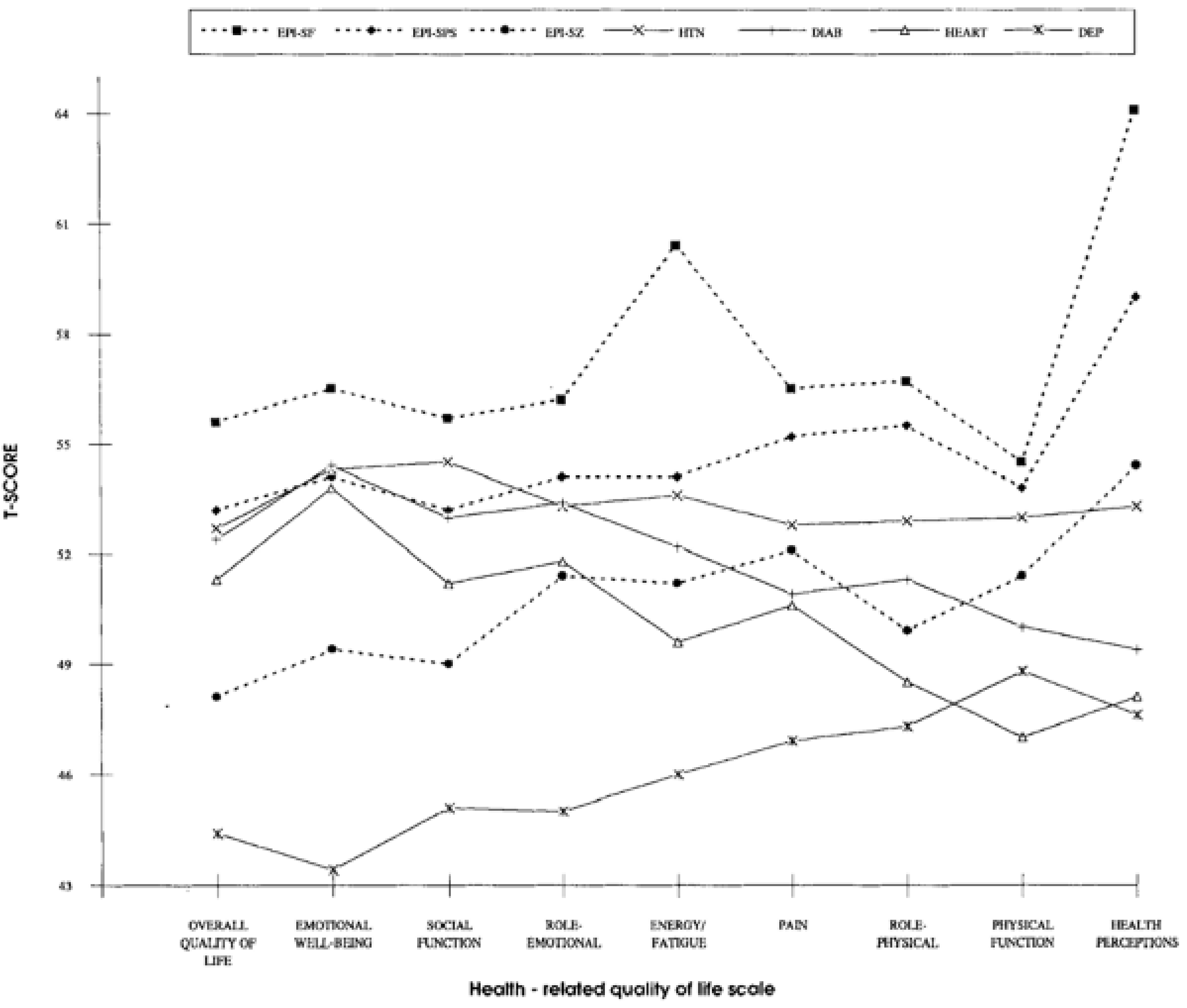

FIGURE 1. T-score distribution across nine health-related quality-of-life (QOL) domains in epilepsy surgery patients and Medical Outcomes Study Patients. EPI-SF, seizure free (*n* = 55, *solid squares*); EPI-SPS, simple partial seizures (*n* = 44, *solid diamonds*); EPI-SZ, one or more complex partial or generalized tonic–clonic GTC seizures or both (*n* = 67, *solid circles*); HTN, hypertension (*n* = 1,224, ×); DBT, diabetes (*n* = 548, +); DEP, depressive symptomatology (*n* = 906, *). (From Vickrey BG, Hays RD, Rausch R, et al. Quality of life of epilepsy surgery patients as compared with outpatients with hypertension, diabetes, heart disease, and/or depressive symptoms. *Epilepsia.* 1994;35:597–607; with permission.)

In addition to freedom from seizures, which is associated with significantly improved health outcomes, Gilliam et al.[42] looked at patient-oriented measures after temporal lobectomy for refractory epilepsy, using validated instruments for assessing HRQOL such as the Epilepsy Foundation of America's (EFA) Concerns Index, the Epilepsy Survey Inventory-55, the Adverse Events Profile, and the Profile of Mood States (POMS).[42] In a comparison of a presurgical group of 71 patients to 125 patients who had previously undergone anterior temporal lobectomy, 65% of postoperative patients were found to be seizure free (vs. 0%) and 60% (vs. 27%) were driving.[42] Multivariate regression analysis in the postoperative group

demonstrated that factors associated with improved quality of life included mood status, employment, driving, and AED cessation but did not include seizure freedom or IQ status.[42]

Markand et al.[69] found improvement in overall score and 10 of 17 scales of the QOLIE-89 in patients who had undergone temporal lobectomy versus those treated with conventional medical therapy. However, these improvements were dependent on achieving total seizure freedom.

These studies suggest a complex interaction among variables contributing to HRQOL in patients with epilepsy. By assuming that freedom from seizures, although a primary goal, is the only valuable postsurgical endpoint, we may be missing additional opportunities for intervention in the domains of transportation options, vocational counseling, and treatment of mood symptomatology with medication or psychotherapy. Through examination of the influence of patient-oriented outcomes on postoperative measures of success, we may better be able to characterize the impact of these factors on overall HRQOL in epilepsy and tailor therapeutic approaches accordingly.

Medications and Health-related Quality of Life

Several recent studies have emphasized the importance of medication effects on overall HRQOL in epilepsy. Baker et al.[7] surveyed >5,000 European patients with epilepsy and found that 44% of respondents had changed their medications at least once in the last year due to unsatisfactory control. Only 12% of patients reported no side effects from medication; common side effects included tiredness (58%), memory problems (50%), difficulty concentrating (48%), sleepiness (45%), difficulty thinking clearly (40%), and nervousness or agitation (36%). Thirty-one percent of patients had changed their medication at least once in the last year due to side effects.[7] This study included patients' self-report of adverse effects from medication. Baker and colleagues also developed an instrument to systematically evaluate medication-related toxicity: The Adverse Events Profile (AEP).[6] This 19-item instrument was tested and evaluated for internal consistency and was then administered to 200 consecutive epilepsy patients, 62 of whom met enrollment criteria. Patients were then randomized to receive usual care from a neurologist (no AEP) or to have the AEP provided to their neurologist at each visit. Baseline scores on the AEP correlated with scores on the QOLIE-89, and significant improvements in both the AEP and QOLIE-89 were observed in the group for which the neurologist had access to the AEP.[6,40] Availability of the AEP also resulted in a significant reduction in seizures as well as more adjustments in medication by their physician compared to patients for whom this additional information was not available.[6] These results emphasize the importance of measuring and evaluating medication toxicity as part of the overall care of the epilepsy patient, not only to control for side effects, but also to potentially reduce seizure frequency and improve overall quality of life.

Gilliam et al. specifically evaluated medication side effects and their association with HRQOL in a prospective study of 195 consecutive patients.[37] Patients were screened with the AEP, the QOLIE-89, and the Beck Depression Inventory (BDI). After controlling for age, gender, generalized tonic–clonic seizure frequency and depressive symptoms, adverse medication effects were the strongest predictor of HRQOL. Severity of depression was also found to be independently correlated with overall HRQOL; seizure frequency, however, was not.[37]

There has been equivocal evidence in the literature as to the relative superiority of monotherapy over “rational polypharmacy” in the treatment of medically refractory epilepsy.[82] Although monotherapy may be felt to be insufficient, polytherapy may not necessarily reduce seizure frequency but may incur a host of other, undesirable effects.

A recent study by Pirio Richardson et al.[82] looked at QOL and monotherapy in a group of patients with medically refractory epilepsy who had been converted to monotherapy and maintained on treatment for at least 12 months. Forty percent of patients became seizure free and experienced statistically significant improvements in quality of life in several domains, including memory loss, concern over medication long-term effects, difficulty in taking medications, trouble with leisure time activities, and overall state of health.[82] Despite methodologic issues in this small study, it suggests that further consideration be given to the notion of monotherapy in medically refractory epilepsy.

In a large study of 547 patients with partial-onset epilepsy and inadequate seizure control or intolerable side effects, conversion to monotherapy was achieved with lamotrigine. Patients were evaluated with the QOLIE-31 and showed significant improvement in multiple domains after conversion to monotherapy. This improvement was independent of seizure control.[24]

Baker et al.[7] conducted a cross-sectional community survey that compared 514 patients <60 years of age to 155 patients >60 years of age across various quality-of-life domains. Medication effects were assessed using the AEP, and results were significant for increased rates of dizziness, upset stomach, disturbed sleep, and memory problems among older patients. Older patients were also more likely to be taking older AED medications. Although senior adults (>60 years of age) represent the group with the highest age-specific rates of epilepsy and are likely to be the most vulnerable to drug interactions and AED-related side effects, few studies have specifically examined the effects of epilepsy treatment on HRQOL in this particular group.[70]

These studies emphasize the need methodically to approach the choice and monitoring of pharmacologic interventions for the treatment of epilepsy. By increasing our awareness of medication toxicity through careful, systematic screening and questioning of our patients at each office visit, we may be able significantly to improve health outcomes and overall quality of life. Instruments such as the AEP are ideally designed for such ends and should be employed routinely and without hesitation.

Depression and Health-related Quality of Life

Psychiatric comorbidities, particularly depression, have long been shown to negatively affect health outcomes and health-related quality of life in a variety of neurologic and nonneurologic conditions.[18,22,48,97,98,99] Epilepsy has extremely high rates of psychiatric illness, with depression being the most common comorbidity, with a prevalence of up to 55% among patients with refractory epilepsy.[43,50,61,78] Recent studies have consistently shown a negative correlation between mood status and overall quality of life in epilepsy, often with depression alone accounting the majority of variance in quality-of-life scores.[16,65,81]

In 1995, Perrine et al.[81] examined the relationship among neuropsychological functioning, mood, and quality of life in epilepsy patients at 25 centers across the United States. Results demonstrated that mood had the highest correlation and explained the greatest amount of variance (46.7%) in validated quality-of-life measures (QOLIE-89).

Lehrner et al.[62] studied patients with refractory epilepsy and measured degrees of depression and overall HRQOL using instruments validated for native German-speakers. Forty-five percent of patients were found to suffer from depression, and on multiple regression analysis, depression scores proved to be the major predictor on all six HRQOL scales. This was a linear correlation, with more severe depression scores predicting a lower quality of life. Seizure frequency was not found to predict either depressive mood or HRQOL score.[62]

Cramer et al.[23] studied the influence of comorbid depression on HRQOL for people with epilepsy using a postal survey and the QOLIE-89 and CES-D (Center for Epidemiologic Studies Depression Scale) (Fig. 2). Other variables, such as seizure frequency, medications, degree of disability, and economic factors, were also incorporated into the analysis. Depending on CES-D scores, patients were categorized into one of three groups: (a) no depression, (b) moderate depression, or (c) major depression. All QOLIE-89 subscales and total score were determined by degree of depression but were not significantly influenced by seizure type. Total scores decreased by 17 to 23 points between major and moderate depression, 8 to 13 points between moderate and no depression, and 30 to 32 points between major and no depression (Table 1).[23]

In a recent study, Loring et al.[65] examined the relative contribution of epilepsy-specific concerns, cognitive variables, and other clinical factors to overall HRQOL in patients undergoing evaluation for epilepsy surgery. Patients were evaluated with the QOLIE-89, Minnesota Multiphasic Personality Inventory-2, BDI, EFA Concerns Index, and various measures of general intelligence and cognitive function. Regression analysis revealed that the two most important factors associated with overall score on the QOLIE-89 were depressive symptomatology (accounting for 57% of the variance) and seizure worry (accounting for 42% of the variance) (Figs. 3 and 4).[65]

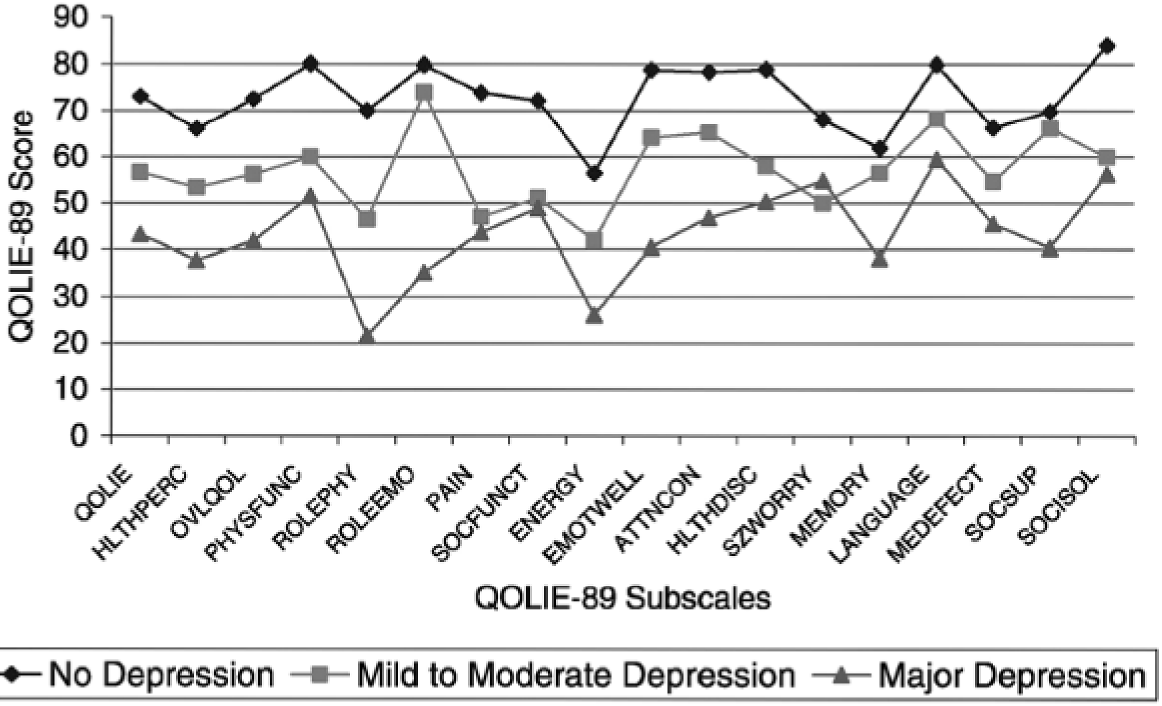

FIGURE 2. Quality of Life in Epilepsy Inventory-89 (QOLIE-89) total and subscale scores for patients with partial seizures by depression category. All scores significantly different by ANOVA across all groups. QOLIE, QOLIE-89 total; HLTHPERC, Health Perception; OVLQOL, Overall QOL; PHYSFUNC, Physical Function; ROLEPHY, Role Physical; ROLEEMO, Role Emotional; SOCFUNCT, Social Function; EMOTWELL, Emotional Well-Being; ATTCON, Attention-Concentration; HLTHDISC, Health Discouragement; SZWORRY, Seizure Worry; MEDEFECT, Medication Effect; SOCSUP, Social Support; SOCISOL, Social Isolation. (From Cramer JA, Blum D, Reed M, et al. The influence of comorbid depression on quality of life for people with epilepsy. *Epilepsy Behav.* 2003;4:515–521; with permission.)

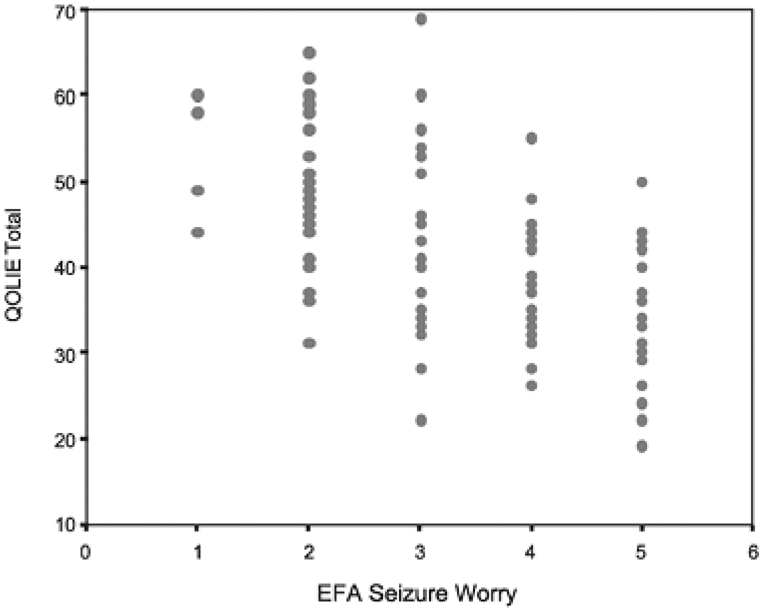

FIGURE 3. Correlation between Quality of Life in Epilepsy Inventory-89 (QOLIE-89) total score and the Epilepsy Foundation of America's Seizure Worry scale. (From Loring DW, Meador KJ, Lee GP. Determinants of quality of life in epilepsy. *Epilepsy Behav.* 2004;5:976–980; with permission.)

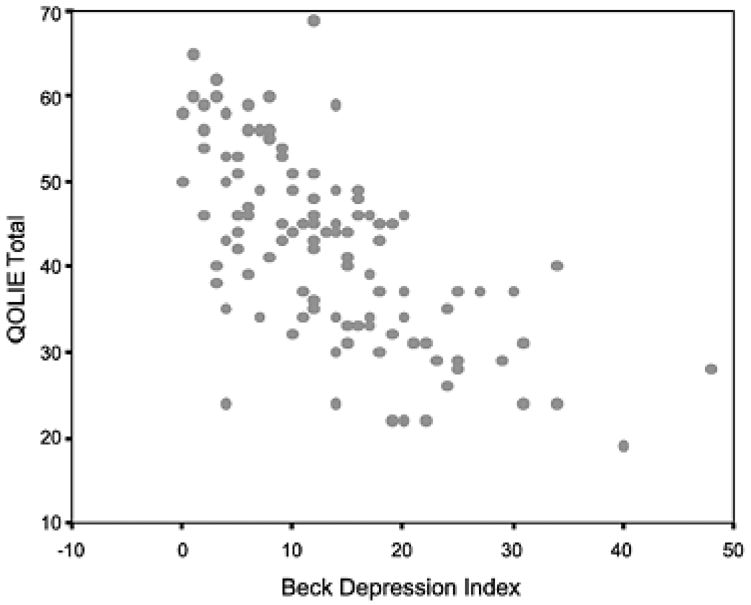

FIGURE 4. Correlation between Quality of Life in Epilepsy Inventory-89 (QOLIE-89) total score and Beck Depression Inventory score. (From Loring DW, Meador KJ, Lee GP. Determinants of quality of life in epilepsy. *Epilepsy Behav.* 2004;5:976–980; with permission.)

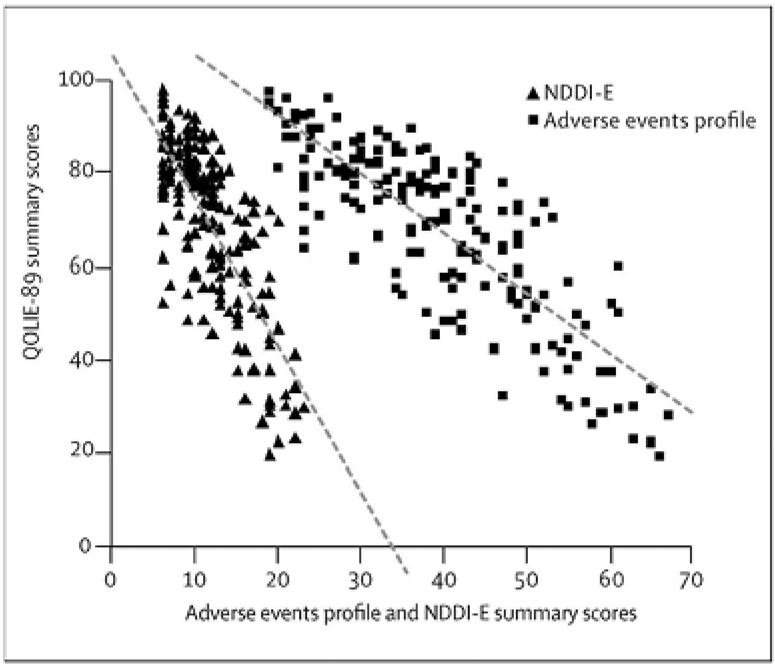

FIGURE 5. Correlation between Quality of Life in Epilepsy Inventory-89 (QOLIE-89) total score with Neurological Disorders Depression Inventory for Epilepsy (NDDI-E) score (partial $r = -0.39$, $p < 0.0001$) and Adverse Events Profile score (partial $r = -0.60$, $p < 0.0001$). Adjusted $R^2 = 0.72$ ($p < 0.0001$) on logistic regression with QOLIE-89 as the dependent variable. (From Gilliam F, Barry J, Hermann B, et al. Rapid detection of major depression in epilepsy: A multicentre study. *Lancet Neurol.* 2006:5;399–405, with permission.)

Until very recently there had been no specific diagnostic instrument for reliably and consistently diagnosing depression in patients with epilepsy, distinguishing mood status from other cognitive and medication-related effects. In a multicenter, multidisciplinary study by Gilliam et al.,[38] a six-item screening instrument, the NDDI-E (Neurological Disorders Depression

Inventory for Epilepsy), was developed. Discriminant function analysis determined the items most likely to predict a diagnosis of depression based on *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition[3] (DSM-IV)–based criteria and validated screening instruments (the Mini International Neuropsychiatric Interview [MINI] and the Structured Clinical Interview for DSM-IV [SCID]). The NDDI-E predicted major depression with a 90% specificity and 81% sensitivity, and together with drug toxicity, independently predicted 72% of the variance on the QOLIE-89 (adjusted $R^2 = 0.72$; $p < 0.0001$). Subjective health status as measured by the QOLIE-89 was independently predicted by total NDDI-E score (Fig. 5).[37]

Although depression is the most common psychiatric comorbidity in epilepsy,[53] a recent multicenter study by Jones et al.[54] found a very high prevalence of DSM-IV anxiety disorders (52%) among patients attending tertiary care epilepsy clinics. Johnson et al.[52] looked at not only depression, but also the relative impact of anxiety and clinical seizure features on HRQOL in patients with temporal lobe epilepsy. Patients with temporal lobe epilepsy completed self-report measures of mood, anxiety, QOL, and seizure severity, including the Symptom Checklist-90 Revised, the BDI, the QOLIE-89, and the Liverpool Seizure Severity Scale. Significant inverse relationships were observed between depression and anxiety scores and overall HRQOL.

Although there is often considerable overlap of these two conditions, partial correlations demonstrated independent contributions by depression and anxiety symptoms to scores on the QOLIE-89. In addition, depression and anxiety independently accounted for the most variance in QOLIE-89 scores when compared to seizure variables and demographic characteristics.[53] These findings replicated the “dose-dependent” phenomenon of psychiatric illness on HRQOL measures seen previously for both depression and anxiety.[37,53]

Psychiatric illness is a highly prevalent, relatively underdiagnosed, and undertreated comorbidity in epilepsy that has the potential to significantly impact QOL.[43,56,57] There now exist highly specialized screening tools, such as the NDDI-E, that can rapidly and reliably detect depression in epilepsy patients, as well as differentiate symptoms of depression from those of medication toxicity and cognitive effects of epilepsy.[37] By recognizing the presence of this interictal phenomenon through systematic screening of epilepsy patients, we have the opportunity to intervene via psychotropic medications or psychotherapy and effect positive change in the overall HRQOL of patients with epilepsy.

Other Comorbidities

In a recent population-based, nationwide Canadian study, Tellez-Zenteno et al.[93] found that people with epilepsy had a two- to fivefold higher risk of somatic comorbidities such as stroke, migraine, intestinal ulcers, and chronic fatigue than the general population. Although the reasons for these patterns were not directly explained in the study, this information further emphasizes the need to conceptualize epilepsy as a complex condition with diverse medical and psychiatric comorbidities, requiring a multidisciplinary, integrated approach.[93]

Sleep

A reciprocal relationship between sleep and epilepsy has been described over the last several centuries.[77] Circadian rhythms can affect the expression of epilepsy, and epilepsy itself has the potential to alter sleep patterns.[77] In addition, many antiepileptic drugs used to treat seizures have a disruptive effect on sleep architecture. There is a significant association between the presence of epilepsy and a comorbid sleep disorder, with rates of sleep apnea approaching 30% among patients with epilepsy.[34,51,66,67,68]

De Weerd et al.[26] examined the prevalence of various sleep disorders in patients with partial epilepsy and found significantly higher rates of disturbances such as insomnia, periodic leg movements, and excessive daytime sleepiness, with an overall twofold increase in sleep disorders compared to controls (38.6% vs. 18%; $p < 0.0001$). This study also examined the impact of sleep disturbances on overall quality of life in patients with epilepsy. The presence of epilepsy and a comorbid sleep disorder in the last 6 months was associated with the most substantial decrease in quality of life as measured by the SF-36, compared to patients with epilepsy alone and normal controls.[26]

In a large study of Mexican patients with epilepsy, patients were surveyed for factors contributing to quality-of-life scores as measured by the QOLIE-31.[1] On multiple regression analysis, the most significant factors predictive of lower QOLIE-31 scores were sleep disturbance and socioeconomic status. These factors were independent of seizure frequency, thus suggesting an independent association. Although this study was limited by the lack of screening instruments for detecting depression and medication toxicity, it further emphasizes the potential importance of comorbid sleep disturbances in determining quality of life in epilepsy.[1]

The increased prevalence of sleep disorders, particularly sleep apnea, among patients with epilepsy and their perceived impact on HRQOL should prompt increased awareness and screening by physicians who treat epilepsy.[44] Questioning regarding adequacy of sleep or excessive daytime somnolence may necessitate referral to a sleep specialist for polysomnography. General measures pertaining to proper sleep hygiene may also prove beneficial.[44] Because specific AEDs have the potential to both alter sleep architecture and increase daytime somnolence, judicious choice of medications favoring stimulating agents such as lamotrigine and felbamate, as well as the timing of medication with more-sedating agents used at bedtime, may also aid in restoring sleep.[10,44,51,77]

Exercise

Epilepsy patients have traditionally been counseled to avoid physical activity due to fear of physical injury or provocation of seizures, and as a result they tend to suffer from inactivity and general lack of physical fitness.[15,52,76,92] The issue of whether exercise exacerbates seizures is somewhat controversial, however; many studies point to a reduction in seizures in patients participating in regular exercise.[27,32,79] Several studies have examined fitness levels in epilepsy patients and results of exercise interventions on seizure control and overall health.

Steinhoff et al.[92] quantified objective measures of physical fitness such as body mass index, muscle strength endurance, and flexibility. Patients were also questioned about leisure time activities. Although leisure time activities did not differ considerably between epilepsy patients and normal controls, results based on the objective physical indicators reflected a significantly lower level of fitness in the epilepsy patients, including measures of aerobic endurance, muscle strength endurance, physical flexibility, and body mass index (BMI).[92]

Eriksen et al.[32] examined a small group of women with intractable epilepsy who were given an exercise regime of aerobic dance and strength training for 60 minutes, twice weekly, for 15 weeks. Seizure frequency was significantly reduced during the treatment phase, and a decrease in muscle pain, sleep disturbance, and fatigue was also observed.[32]

Roth et al.[85] studied associations among exercise levels, depression, and stressful life events in 133 adults with refractory epilepsy. Statistical analyses demonstrated lower levels of depression among the group who was more physically active, as well as an independent contribution of exercise and stressful life events on depression. This effect was separate from the influence of other predictor variables such as seizure frequency, age, and gender, suggesting that regular exercise and the avoidance of stress may lower depression in patients with epilepsy.[85]

In the first randomized, controlled trial of exercise in epilepsy, McAuley et al.[76] examined 23 patients with epilepsy who were randomized to either a 12-week, supervised, outpatient exercise program or to continue their current level of activity. Both clinical (seizure frequency, AED concentrations) and behavioral outcomes (QOLIE-89, POMS, Physical Self-Description Questionnaire, Self-Esteem) were measured. Results showed no appreciable difference in either seizure activity or AED levels; there were, however, significant improvements in overall score on the QOLIE-89 and significant decreases in mood disturbance among patients in the exercise group.[76]

These studies suggest a role for the implementation of an exercise program to promote overall HRQOL among patients with epilepsy without the risk of exacerbating seizures.

Migraine

Significant overlap between epilepsy and migraine is well known, in terms of both clinical presentation and prevalence of comorbid conditions in the same individual or family; having one disorder doubles a patient's risk of having the other disorder.[47,80]

Ottman and Lipton[80] investigated the comorbidity of migraine and epilepsy in a population-based study of >3,000 patients and found a greater-than-twofold increase in the rate of migraine among patients with epilepsy (24%) as well as their relatives with epilepsy (23%) compared to relatives without epilepsy (12%). Despite this increased association, no definitive causative factors, either genetic or environmental, have been identified, making this increased comorbidity likely the result of multiple contributory events.

Lipton et al.[64] examined the influence of migraine and depression on HRQOL in an international study involving patients in both the United States and the United Kingdom. Three hundred 89 migraine cases and 379 controls completed the SF-12, a generic measure of quality of life, and the Primary Care Evaluation of Mental Disorders, a mental health screening inventory. Patients with migraine had significantly lower scores on the SF-12 in both the physical and mental health domains. Depression was highly comorbid with migraine (adjusted prevalence ratio 2.7; 95% confidence interval 2.1–3.5), and both depression and migraine were independently correlated with lower HRQOL scores.[64]

A Turkish study by Velioglu et al.[94] specifically looked at the impact of migraine on epilepsy and prognosis. Cases with epilepsy and migraine and controls with epilepsy alone were followed prospectively over a 5- to 10-year period and assessed for medication use and seizure frequency. Despite similar initial baseline characteristics, the epilepsy-migraine group had a lower chance of becoming seizure free, a higher incidence of intractable seizures, a longer duration of illness, and a lower treatment response than did epilepsy controls. The reasons for poorer prognosis in the epilepsy-migraine group are not known; however, previous evidence suggesting neuronal hyperexcitability as the underlying pathophysiologic mechanism in migraine may explain the adverse outcomes in relation to seizure control.[5,47,59,94]

Given the increased prevalence of migraine and epilepsy, the adverse association with prognosis, quality of life, and depressed mood, and possible shared pathophysiology, it seems sensible to screen epilepsy patients for comorbid migraine headache and to prescribe pharmacologic treatments that target both disorders. Both topiramate[17,88] and valproate[35,87] have been shown to be effective in migraine prophylaxis and are approved by the U. S. Food and Drug Administration for this indication. Other antiepileptic drugs that may be useful in the treatment of migraine but lack evidence from large-scale trials include gabapentin,[71] levatiracetam,[33] tiagabine,[20] and zonisamide.[30] Very preliminary data in a small number of patients may show the efficacy of vagus nerve stimulation in refractory migraine.[75]

Summary and Conclusions

Traditionally, the study and treatment of epilepsy has considered the ictus itself to be of paramount importance. Whereas attempting to reduce or eliminate seizures is a worthy goal, the last decade of research in epilepsy, and particularly research relating to health outcomes, has begun to shift the focus from the ictal to the interictal period. By recognizing that pervasive and persistent interictal factors such as medication toxicity and comorbid psychiatric illness are responsible for the greatest amount of variance in overall HRQOL, we can see that the mere cessation of seizures may not be sufficient to positively affect HRQOL in patients with epilepsy.[16,37,65,81] The available instruments for measuring predictors of HRQOL should be employed routinely and frequently by neurologists and the epilepsy health care team at each outpatient encounter.

Numerous research-proven, validated instruments exist for measuring indicators of quality of life in epilepsy, including general measures such as the QOLIE-89 and instruments that target the most significant contributory subcategories, such as medication toxicity and mood status.[29,36,55,86] Current evidence from randomized, controlled trials suggests that instruments such as the Adverse Events Profile[5] for measuring medication toxicity and the newly developed Neurological Disorders Depression Inventory for Epilepsy[37] for screening for depression are relatively short, are easily completed in a busy neurologic practice, and may be the most valuable tools for improving the comprehensive care of patients with epilepsy.

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Chapter 221

Legal Concerns and Effective Advocacy Strategies

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Introduction

For too many years, people with disabilities—particularly people with epilepsy—were a voiceless minority. These individuals had many unmet needs in the areas of civil rights, education, employment, residential and community services, and provision of appropriate health care. Many lived at home, rarely venturing out. Too many were segregated from society and they were forced to live in large state residential institutions for the intellectually disabled or mentally ill. Until recent decades, laws, even in countries whose citizens pride themselves on liberal views about such matters, such as the United States, restricted the rights of people with epilepsy to marry and provided for their involuntary sterilization.[3] The prevailing belief was that people with epilepsy could not be employed because they might have a seizure on the job and hurt themselves or others.

Over the years, these beliefs and conditions have been challenged in various countries by advocacy efforts led by citizens with disabilities, family members, professionals, policy makers, and the courts. Gradually, society is coming to recognize that many of the problems faced by those with disabilities are not inevitable but are rather the result of discriminatory policies based on unfounded, outmoded stereotypes and perceptions deeply grounded in irrational fears and prejudices toward such people.

In recent decades, some countries have enacted laws specifically prohibiting discrimination on the basis of disability. One example of a broad-reaching antidiscrimination law is the Americans with Disabilities Act (ADA), enacted in 1990, which prohibits discrimination on the basis of disability in employment, in the programs and services of state and local governments, by places of public accommodation, in public and private transportation services, and in communications. The ADA grants all individuals with disabilities uniform protection, regardless of the state in which they live.[2]

Even with the passage of laws like the ADA and its international equivalents, epilepsy raises a variety of legal concerns, including employment discrimination, driver licensing requirements, access to appropriate educational services, access to insurance, and even possible arrest for seizure-related behavior. This chapter summarizes some of the legal issues that patients with epilepsy face, some of the legal remedies, the issues physicians may face as they advocate for their patients, continuing areas of legislative advocacy, and effective advocacy strategies for those wishing to change current laws.

This chapter emphasizes U.S. law because space does not permit a full discussion of legal issues from the perspective of each country and because insufficient recent information exists about legal issues from an international perspective, except in the area of driver licensing. Additional publications on legal or psychosocial issues in various countries may be of interest.[1,4,6,9,10,11,12,15,16,19,21,23,24,25]

The Americans with Disabilities Act—Employment Provisions

Although laws do not eliminate discriminatory attitudes, antidiscrimination statutes such as the ADA have forced many employers to reevaluate and subsequently change their employment practices and have given employees important legal tools with which to seek redress from unfair employment practices.

The concept of disability under the ADA encompasses three parts: (a) does the individual have, does the individual have a record of, or is the individual regarded as having, a physical or mental impairment? If so, does the physical or mental impairment the individual has, has a record of, or is regarded as having (b) substantially limit (c) one or more of that individual's major life activities?

Under the ADA, employers with 15 or more employees are prohibited from discriminating on the basis of disability against individuals who can do the essential functions of the job or who could do so with reasonable accommodation. Reasonable accommodation is a flexible concept. Examples of accommodations that might be appropriate for individuals with epilepsy include job restructuring (e.g., if driving is a marginal duty, driving tasks could be reassigned to another employee); permitting part-time or modified work schedules; allowing time off for doctor's visits and to recover from seizures; installing a safety device around a piece of machinery; padding a concrete floor at the employee's work site; and allowing the individual to work at a job site close to home or, in some cases, at home.

Employers are not required to provide an accommodation under the ADA if it would be an “undue hardship” on the employer, that is, if it would cause the employer significant difficulty or expense. This is evaluated in light of the employer's overall business. If a particular accommodation would impose an undue hardship on an employer, the employer may be required to provide other reasonable accommodations. The ADA does not require employers to accommodate the needs of employees who miss work to care for family members with medical problems. However, in the United States, employees who need to miss a significant amount of work because of their serious health problems or those of family members may benefit from the Family and Medical Leave Act (FMLA), which requires employers with 50 or more employees to provide up to 12 weeks of unpaid leave to eligible employees and to retain the employee's benefits. It is recognized that this may be a uniquely U.S. situation, but it highlights the way in which the rights of individuals are becoming protected by law. Further information about FMLA can be obtained from the Wage and Hour Division of the U.S. Department of Labor.

Safety Issues

For most jobs, simply having occasional seizures will not significantly affect the person's ability to do the job's essential functions. Having seizures does not render a person unqualified under the ADA simply because seizures require occasional use of sick time, do not look good, or may result in injury or possible use of worker's compensation. In the U.S. example, employers do not have to offer a job or retain an individual in a job because of a disability if the individual poses a “direct threat” to safety. Direct threat is defined as “a significant risk of substantial harm which cannot be lessened by reasonable accommodation.”

Except in very limited circumstances (e.g., commercial airline pilots), a mere diagnosis of epilepsy will not mean that an individual poses a direct threat. Similarly, a possibility or even a probability that an individual will experience a seizure at work is usually not enough to make that person a direct threat without showing that the individual's workplace or essential job duties pose a particular risk of harm. An evaluation must also be made as to whether the factors causing the increased risk can be reduced through a reasonable accommodation. Using laws similar to the ADA, people with epilepsy have successfully obtained and retained such high-risk jobs as firefighter, police officer, and butcher (see, e.g., the case of *Jansen v Food Circus Supermarkets*[13]).

Unsubstantiated fears about risks from the employment environment may not be used by an employer to disqualify a person with epilepsy. Under the ADA, employers must evaluate the individual and the specific situation using reasonable medical judgment that relies on the most current knowledge and best objective evidence. If the specific job tasks suggest possible safety concerns, the treating physician may be asked by the employer or employee for advice about whether the employee should avoid certain tasks. In evaluating a person with epilepsy for a position that might pose safety concerns, it is important to consider the type of job, the essential job duties, the degree of seizure control, the types of seizures (whether the person has simple partial onset to warn of possible evolution), the person's reliability in taking prescribed seizure medication, any side effects of medication, and any accommodations that might lessen the risk.[17]

The ADA's focus on individual capabilities is especially important for the individual with epilepsy because the term epilepsy refers to a broad range of symptoms and underlying causes. Depending on their individual circumstances, some people with active seizures should avoid certain job tasks, such as driving, or certain environmental conditions, such as exposure to open fire, hot substances, dangerous moving objects, mechanical and electrical hazards, and situations in which a danger of falling exists. If an employee is no longer able to do the job for which he or she was hired, even with reasonable accommodations, an employer may be required to reassign that employee to another position, if one is available, for which the employee is qualified. The position should be equivalent in terms of pay and other job status. Within this scheme, an employer is permitted to reassign an individual to a lower-grade position if that is the only position available for which the individual is qualified.

Medical Inquiries by Employers

Employers who are covered by the ADA are prohibited from asking any questions about whether an applicant has a medical condition or about the nature and severity of the condition until after they have extended the applicant a job offer. This is particularly important for individuals with epilepsy, who historically have been denied interviews and refused employment solely because an employer learned of their epilepsy. Again focusing on the U.S. situation, once a job offer has been made, an employer may ask medical questions or request that an individual have a medical examination, so long as all employees selected for that job classification are required to do so. Once an individual has been employed and is on the job, medical inquiries must be job related and consistent with business necessity. In other words, the need for the examination must be triggered by some evidence of problems related to job performance or safety, or an examination may be necessary to determine whether individuals in physically demanding jobs continue to be suitable for duty. In addition, a request for reasonable accommodation by an employee may trigger medical inquiries to verify the need and scope of accommodation. All medical information must be kept separate from an employee's personnel file, and the information must be kept confidential.

Many countries have enacted privacy laws, and transgression of these may provide an alternate source of remedy if the person with epilepsy has been exposed against his or her will.

Complaint Process Under the Americans with Disabilities Act

Individuals may file employment discrimination complaints under the ADA with the U.S. Equal Employment Opportunity Commission (EEOC) or, in many cases, with their state Human Rights Commission. If an employer is not covered by the ADA, because the business does not have 15 or more employees, one should investigate whether there is a state law that applies. Further information about state antidiscrimination laws should be available from the state Human Rights Commission (HRC), and most industrialized countries now have local equivalents of the EEOC and HRC. These bodies have international legitimacy because their host nation is usually a signature nation of the International Parent Body run under the auspices of the United Nations. The U.S. example is far from unique, and was merely provided as a focus on which local proceedings can be examined and used to protect the rights of people with epilepsy.

The Supreme Court's Interpretation of the Americans with Disabilities Act—Important Limitations

It is important to note that, despite the apparently clear nature of protection against discrimination afforded by the ADA, its recent interpretation by the Supreme Court of the United States has limited the protection provided by the Act. In a trilogy of cases (*Sutton v United Airlines, Inc*; *Murphy v United Parcel Service, Inc*; and *Albertson's Inc v Kirkinberg*), the Court held that, in determining whether a person was suffering from a disability, mitigating factors (such a medication) must be taken into account. Thus, in *Sutton*, although the applicants had poor eyesight (20/200 in the right eye and 20/400 in the left eye), when corrected with glasses or contact lenses, their vision was 20/20. The applicants were not disabled. Similarly, the applicant in *Murphy* had chronic hypertension, which, without medication, was extremely high. With medication, it was within acceptable ranges. A recent reaffirmation of these cases is *Cutrera v Board of Supervisors of Louisiana State University* (429 F.3 d 108, 2005).

The effect of these cases on people suffering from epilepsy is obvious. A person whose epilepsy is controlled by medication will not be regarded as having a disability, and thus will not be afforded the protections of the ADA.

Driver Licensing

Driver licensing laws and policies vary significantly from country to country. There is, however, a consensus among experts worldwide that driving should be permitted when seizures are adequately controlled. There is less consistency among different countries as to the length of time considered to be adequate following seizure activity.

Most countries require a seizure-free period of 1 to 3 years.[20] In the United States, most states use a firm seizure-free period of 1 year, 6 months, or 3 months. Many states also provide for exceptions to the usual seizure-free requirement, for example, when an individual has a breakthrough seizure due to medication change or withdrawal and is back on the original medication.[14]

Experts in the international community and in the United States have recently developed separate reports on driving and epilepsy.[18,20] In general, these experts recommend that licenses should be granted after a short prescribed period of freedom from seizures, the decision should be based on an assessment of the medical history of the individual and there should be room for exceptions to the prescribed period of seizure freedom. This assessment should be done either by an independent neurologic specialist or by a Medical Advisory Board on which a neurologic specialist serves. Variations in determining whether to license an individual come from differences in the seizure history, type of seizure, and causative factors. Reassessments should occur periodically or when the individual reports changes in seizure experience.

Current practice in the United States is that, whereas the ultimate licensing decision lies with the state Department of Motor Vehicles (DMV), the agency looks to the treating physician for a variety of information ranging from details about the patient's seizure disorder to the physician's opinion about the patient's ability to drive safely. Most states also require periodic medical updates, at least for several years.

There has been a general trend in recent years to move toward shorter seizure-free periods and exceptions to the general rule. Those U.S. physicians who want to influence DMV policies may want to join their state DMV's medical advisory board, if one exists. In states where the criteria for licensing people with epilepsy was enacted by the legislature, any major changes would be made on the legislative level, but in many places the rules are controlled by regulations pertaining to the act; thus, alteration is far simpler. Physicians may want to contact a local epilepsy organization about state-wide legislative initiatives. A model driver licensing law developed by the Epilepsy Foundation of American (EFA), the American Academy of Neurology (AAN), and the American Epilepsy Society (AES) is available from the EFA.[18] The EFA, AAN, and AES support the use of a 3-month seizure-free interval in driver licensing with consideration of the following favorable and unfavorable factors that may modify that interval:

Favorable modifiers

- Seizures during medically directed medication changes
- Simple partial seizures that do not interfere with consciousness or motor control
- Seizures with consistent and prolonged auras
- Established pattern of pure nocturnal seizures

- Seizures secondary to acute metabolic or toxic states not likely to recur
- Sleep-deprived seizures
- Seizures related to reversible acute illness

Unfavorable modifiers

- Noncompliance or lack of credibility
- Alcohol or drug abuse within last 3 months
- Increased number of seizures in the last year
- Prior bad driving record
- Structural brain lesion
- Noncorrectable brain functional or metabolic condition
- Frequent seizures after seizure-free interval
- Prior crashes due to seizures in the last 5 years

According to their report on driving and epilepsy, international experts from the International Bureau for Epilepsy (IBE) and the International League Against Epilepsy (ILAE) have not recommended a specific seizure-free period but generally describe a range from 3 months to 2 years as appropriate, depending on various factors.[20] The medical issues critical to licensing, and which they recommend should be assessed, are generally similar to the criteria described here. For example, the report on driving suggests that no restrictions on driving may be necessary if the seizure follows an acute cerebral illness from which there has been full recovery or in cases of sensory-evoked seizures. Only a short period of seizure freedom may be necessary prior to licensure if a seizure is the result of physician-supervised medication changes. Whether to license individuals who have seizures due to metabolic disorders depends on the nature of the underlying condition or disease. The report thus clearly emphasizes an individualized assessment based on various factors.

Some people who suffer from seizures have incurred civil or criminal liability as the result of seizure-related accidents. In the United States, such liability has occurred when individuals have driven against medical advice, without a valid license, without the state DMV being aware of their medical condition, or with the knowledge that there was a particular reason that they should not be driving at that time.

In a disturbing trend that is yet to show up in the United States, a court in New South Wales, Australia, in deciding the unreported case of *R v Gillett*, disregarded physician- and state-endorsed guidelines established to determine fitness to drive in assessing the liability of a man with epilepsy who had a motor vehicle accident causing death to others.

In the United States, few reported cases exist on the issue of physician liability to third parties for certifying a patient to drive. Those cases that have been brought in the area of certifying fitness to drive suggest that the risk of liability is minimal. In the United States and internationally, experts recommend that physicians should not be liable for recommendations to the state driver licensing agency as long as those recommendations were arrived at in a reasonable manner and consistent with the prevailing standard of care.[18,20]

Some cases brought by third parties against physicians have been based on the theory that the physician did not use due care in the diagnosis or treatment of the patient. Most courts that have considered these cases in the United States have recognized that physicians cannot "control" their patients; thus, they do not have a duty to prevent them from driving. They may, however, have a duty to warn their patients not to drive due to recent seizures or side effects of medication, and they may be liable to third parties if they fail to give such instructions. Physicians should provide the warnings and advice that are required under prevailing standards of care. Patients who should not be driving, or who should be driving only under certain circumstances, should be so advised in writing. Similarly, confirmation of having given such advice should be written in the patient's medical records as an added protection, should the physician be faced with litigation.

As long as the physician is using reasonable medical judgment and proper documentation, a third-party suit should not result in liability. If a physician has specific concerns, however (such as a patient who is driving against medical advice), he or she may want to consult with an attorney.

The EFA, the IBE, and the ILAE oppose laws requiring physicians to report their patients with epilepsy to the state. In the United States, states currently having such laws include California, Delaware, Nevada, New Jersey, Oregon, and Pennsylvania. Instead, the EFA, the IBE, and the ILAE support laws that give physicians "good faith" immunity for participating in the driver licensing process and for voluntarily reporting those patients who pose an imminent threat to public safety because they are driving against medical advice. In Australia, physicians are not required to report (except in South Australia and the Northern Territory) and are protected against invasion of privacy, except in Western Australia.[5]

Education

The educational process can pose significant obstacles to children with epilepsy. Obstacles include the physical and psychosocial effects of seizures, the effects of antiepileptic medications, underlying cognitive difficulties, and an educational system that, all too often, does not provide the necessary support or understanding.[22]

In 1975, in response to pressure from organized groups, the U.S. Congress passed the Education of All Handicapped Children Act (PL. 94–142), which guarantees that all children shall receive a free, appropriate public education in the "least restrictive environment." The underlying notion was that children with disabilities were to be educated alongside their nondisabled peers whenever possible. This law was yet another step in the evolution of a public policy goal of total integration of people with disabilities into U.S. society. In 1990, this law was renamed the Individuals with Disabilities Education Act (IDEA).

The Individuals with Disabilities Education Act is the central vehicle through which the U.S. federal government maintains a partnership with the states and localities to provide an appropriate education for children with disabilities requiring special education and related services. To receive funds, state and local education agencies must follow the law's requirements for identifying, evaluating, and providing services to eligible children aged 3 to 21 years. Children with epilepsy are eligible for services if their epilepsy adversely affects their educational performance. Infants and toddlers who have developmental disabilities or who are at risk of having a disability may be eligible for early intervention services.[8] Treating physicians play an important role in establishing a child's need for services.

Arrest for Seizure-Related Behavior

Some seizure-related behaviors, particularly those associated with complex partial seizures, may result in the individual with epilepsy being arrested and charged with such offenses as public intoxication, trespassing, breaking and entering, shoplifting, resisting arrest, and assault. Assault charges sometimes result when an individual having a seizure is restrained and reacts reflexively. Whether the behavior in question was consistent with the individual's seizures is an issue best addressed by the treating neurologist. Sometimes, intervention by a medical professional will result in charges being dropped. If charges are brought, the individual should seek the advice of a criminal defense lawyer. The type of defense that is appropriate varies from country to country. Some countries and some U.S. states recognize an "automatism" defense for individuals who were not aware of their actions at the time of the alleged criminal behavior. Expert opinion at trial will be crucial in proving a defense. In some countries, one must be careful of the concept of "sane" versus "insane" automatism, and legal judgment is mandatory.

To reduce the number of inappropriate arrests of those with epilepsy, the EFA, in conjunction with the Police Executive Research Forum, has developed training materials for police officers. The materials encourage police to consider the possibility that certain types of behaviors stem from seizures. Police should consider information from bystanders or family members or from observation at the scene that give clues that a person's confusion or unusual behavior was seizure related. Other national bodies, such as the National Epilepsy Association of Australia (NEAA), as it was then called, have also developed police training materials.

In a number of cases, individuals have sought to use epilepsy as a defense against charges of serious violent crimes. The circumstances under which violent or aggressive behaviors occur, as the result of epileptic seizures, is controversial, and the types of legal defense that would be used vary from country to country and from state to state.[26] In a text such as this, it is not possible to fully debate such defense strategies, but it is vital that the rights of both the individual with epilepsy and the public at large be protected and that the defense provided by "epilepsy" be correctly applied and not abused.

Continuing Areas of Advocacy

Health Care Reform

Issues of access to health care services are central to ethical concerns regarding quality of life for people with epilepsy in all countries. Decisions about access and adequacy of services made at executive and legislative levels, as well as in the private sector, affect the choices that are available to clinicians and patients. A major public policy priority for the epilepsy community in the United States is comprehensive reform of the health care system. The existing mix of public and private insurance in the United States has failed to provide insurance to an estimated 39 million Americans, including many individuals with chronic health conditions such as epilepsy. Private health insurance is increasingly priced beyond the reach of individuals and businesses. Benefits for individual consumers are being trimmed in an attempt to control costs, yet the costs of health care continue to skyrocket. The greatest flaw in the existing health care delivery system in the United States is the fact that those individuals who most need access to health care, namely people with chronic health conditions or disabilities, are the most likely to be denied health insurance.

In 1989, the EFA commissioned a study of insurance industry practices toward people with epilepsy. This study found that most, if not all, companies base their underwriting decisions on medical outcome data that are seriously outdated. The report concluded that existing underwriting guidelines used by U.S. insurance companies fail to reflect the major advances in the diagnosis and treatment of epilepsy. Clearly, the question that lies at the heart of today's U.S. health care debate is, "How do we ensure access to appropriate health care for everyone?" Many options have been considered by the U.S. Congress, including mandating health insurance coverage at the workplace and significantly restructuring the health care system in a comprehensive way. Some have advocated for a single-payer national health plan patterned on the Canadian system. Clearly, passage of legislation ensuring universal access to health insurance would have a profound effect on the lives of thousands of people with epilepsy who currently are unable to obtain coverage. Although Congress has failed to pass appropriate health care reform legislation, disability rights advocates will continue to press for comprehensive reform.

Epilepsy Research and Drug Development

Enormous advances in our understanding of epilepsy have occurred in the last 20 years that have already affected, or will affect, the care of patients with epilepsy and their quality of life. Particularly in the 1990s, dubbed the "decade of the brain," there was enormous enhancement of tools available with which to treat epilepsy, such as vigabatrin, lamotrigine, gabapentin, felbamate, and topiramate.

Concurrent with these developments has emerged a need to examine commitment to research and a review of ethical questions and indemnification of those, namely researchers, ethics committees, and people who take part as volunteers, within such research programs. Each of the antiepileptic medications mentioned encountered problems in development (addressed elsewhere in this text), but, coupled with these difficulties, the issues of legal standing, for all concerned, emerge. This is highlighted by the case of felbamate, the development of which has been arrested on a worldwide scale, even though there are still 150,000 people in the United States who depend on this medicine to achieve better seizure control. A similar, though quite different, situation existed with zonisamide, an agent whose U.S. development was initially stopped while the drug was still in use in Japan, before it reemerged in the United States.

The epilepsy movement, through its international parent bodies of the ILAE and the IBE, and local agencies such as the EFA and the AES, has long been committed to supporting research at all levels of society with its own programs and those of national bodies such as the National Health Scheme (United Kingdom), the National

Institutes of Health (United States), and the National Health and Medical Research Council (Australia).

Where problems arise as a result of federal (national) government regulation or intrusion into the availability of or access to existing or new agents, the local chapters of the ILAE and the IBE have proven highly persuasive. This is evidenced by the Australian experience in which the government restricted access to valproate to authority-only prescription, which made it difficult to get the drug. The combined efforts of the NEAA (as it was then called) and the Epilepsy Society of Australia (ESA) reversed this decision and ensured ongoing easy access to this effective treatment. Similarly, the EFA interacts with the U.S. Food and Drug Administration on a frequent basis to improve the regulatory function of evaluating the safety and efficacy of medications, including the standards used to determine the therapeutic bioavailability of generic antiepileptic drugs.

The international epilepsy movement has also demonstrated its commitment to the exchange of ideas within the scientific community at all levels with the sponsorship of international meetings that provide a forum to consider not only the pure science of epileptology, but also advocacy and legal ramifications, as evidenced by the 1987 and 1995 meetings, during which the main themes examined were epilepsy and the law.

Family Support Services

The literature on the psychosocial adaptation of children with epilepsy indicates that the adjustment of the child to his or her disability is significantly affected by the attitudes of the adults in the family, community, and educational environment.[27] Families of children with disabilities experience enormous stress on a day-to-day basis. Lack of family support often renders even the strongest family unable to cope effectively. In the face of complicated medical, social, and educational issues, families in this situation may not be able to provide the support and nurturing a child with epilepsy needs to reach his or her full potential. In addition, families often do not have a clear understanding of the right of their children to an appropriate education in the least restrictive environment and how to advocate effectively for these services. For these reasons, the epilepsy community is actively advocating for greater family support services in the following areas: information, respite care, counseling support and communication, evaluation, and coordination of services.

In the United States, efforts are underway in several states to establish programs providing families of people with disabilities with financial support, the specific uses of which are to be determined by the family, not the government. At the federal level, legislation has been passed that would provide eligible families with assistance. Efforts are underway to secure funding for the initiative. The epilepsy community and other disability organizations have been working very hard on these types of initiatives at the state and federal levels.

Effective Strategies with Political Representatives

In an era of diminishing public resources and increasingly complex public policy debates, it is especially important for the epilepsy community to expand on its current advocacy activities and relationships with public policy makers. The following strategies have proven effective in building such relationships:

- Write letters and make phone calls to policy makers on issues of concern. Similarly, write or call to thank legislators for supporting an issue.
- Conduct meetings on a regular basis with legislators in their home district offices.
- Invite elected representatives to local activities, such as board meetings, support group meetings, fund-raising events, and medical conferences.
- Include articles about public policy issues and legislators in organizational newsletters.
- Get involved in local political campaigns; however, these activities must be conducted only on personal time and cannot include contributions or expenditures by tax-exempt organizations.
- Develop or join coalitions of groups with coinciding interests or positions.
- Develop local grass-roots letter-writing and telephone networks that can be activated to influence decision

makers when issues arise.

- Add legislators to mailing lists for newsletters and special event announcements.
- Write letters to the editors of local newspapers on issues of importance to the epilepsy community.
- Organize rallies and events when important issues are being considered by your state or federal legislators and invite the press to attend.

A strong advocacy network, at national and local levels, is needed to protect the rights of people with epilepsy and to ensure that their specific concerns will be fully considered as new policies are developed. To accomplish this, continuing contacts and interactions with legislators and other policy makers are essential.

Summary and Conclusions

Although one can point to significant gains in the areas of legal rights, education, employment and training, and development of safer, more effective therapies, much remains to be done if people with epilepsy truly are to be given the opportunity to reach their full potential in our society. An area of particular need in some countries continues to be access to appropriate health care services. No longer should those with epilepsy be routinely denied the benefits of timely and quality health care services. The epilepsy community will continue to advocate strongly in this and other areas, with the goal of further reducing the burden of this serious disorder.

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Chapter 222

Overview: Neonatal Syndromes

Jean Aicardi

Introduction

The neonatal period is conventionally limited to the first 28 days of life. However, some seizures with onset in the first 2 to 3 months of life display similar features and will be considered here. The vast majority of neonatal seizures, however, occur during the first 10 days of life. Most neonatal seizures are short-lived events, lasting only a few days, and usually do not herald a chronic convulsive disorder unless structural damage is present whether due to malformations or acquired disease. Therefore, the term *epilepsy,* meaning a chronic, recurrent disorder with unprovoked paroxysmal events, is only rarely adequate, and the noncommittal term of *neonatal seizures* or *convulsions* is more appropriate. Seizures are one of the most common neurologic problems in the first days of life. Their real frequency is not known because it is becoming clear that all abnormal, stereotyped, and periodically recurring movements may not be epileptic seizures in the sense of excessive discharges of the gray matter, but they can be due to other mechanisms, such as release of brainstem tonic mechanisms from cortical control as a result of lesions or dysfunction of the cortex.[5] The clinical features of neonatal seizures are often relatively unimpressive (see Chapter 56). Generalized seizures are rare, although occasionally cases of infantile spasms or massive myoclonias may occur.[1,3] Focal or multifocal seizures are the rule and several types are recognized. Focal clonic seizures may remain in a fixed location or may involve several focal areas at the same time or in succession (migratory seizures). Clonic seizures are usually associated with typical rhythmic electroencephalographic (EEG) discharges, although these may also occur with tonic or subtle seizures. Tonic seizures may be localized to a single segment; when generalized, they are more often the result of nonepileptic tonic liberation than truly epileptic. *Subtle seizures*,[30] sometimes referred to as *motor automatisms*,[19] are frequent and may include random and roving eye movements, sucking, chewing motions, tongue protrusion, rowing or swimming or boxing movements of the arms, and pedaling or bicycling movement of the lower limbs. Apneic seizures are relatively common.[31] Although some subtle seizures are associated with rhythmic ictal EEG discharges and are clearly epileptic, ictal EEG often does not show typical epileptic activity, and the nature of the clinical events is difficult to determine. In some cases, such ictal phenomena can be provoked by external stimuli that can demonstrate temporal and spatial summation, or they can be inhibited by restraint or repositioning of the involved part. Such features may be more suggestive of brainstem release phenomena, and these events are mainly interpreted as nonepileptic. The absence of an EEG discharge, however, does not completely rule out the possibility of an epileptic phenomenon, thus raising a difficult diagnostic problem.

Ictal EEG discharges in neonates may be highly polymorphic. The two main components, which may be associated withone another, are repetitive sharp waves or spikes and abnormal paroxysmal rhythms including beta, alpha, theta, or delta rhythms that usually remain focal or involve only one hemisphere.[13,16,21] Almost all paroxysmal EEG activity in the neonate begins focally. Ictal discharges are extremely variable in appearance, voltage, frequency, and polarity, and their aspect can change suddenly. Unrelated discharges of various shapes and rhythms frequently occur independently at different locations in both hemispheres. Bilateral symmetric discharges are rare and are associated specifically with unusual ictal phenomena such as myoclonias or spasms. In benign familial neonatal convulsions, they may consist of generalized flattening of the tracing, followed by high-amplitude, slow theta waves,[12,26] but these events follow a focal onset.

Although such differences between neonatal epileptic versus nonepileptic seizures can be of practical value because the use of anticonvulsant drugs that depress cortical activity might be contraindicated in nonepileptic release phenomena,[5] a firm differentiation of epileptic from nonepileptic seizures in neonates may be impossible.

From a clinical viewpoint, seizures must be differentiated from jittering or tremulations, shuddering, and benign neonatal sleep myoclonus.

Ictal EEG recording is helpful when showing clear paroxysmal activity. Ictal EEG events may not be easily differentiated from other patterns that are not infrequently seen in the neonatal EEG. These include brief intermittent repetitive discharges (BIRDS). Most investigators, therefore, require discharges of at least 10 seconds to accept their ictal nature.[28,29] Isolated interictal sharp waves should not be regarded as pointing necessarily to a diagnosis of seizures. However, some seizures with all the clinical features of classical epileptic seizures are not accompanied by typical discharges on the scalp.[8] Conversely, many characteristic EEG discharges are not associated with any clinical manifestation,[13] and such electroclinical dissociation seems to occur especially following long series of seizures. It is not currently possible to decide whether such purely electrical seizures have the same significance as electroclinical attacks, carry the same risk of brain damage, and require the same treatment.

Neonatal seizures rarely occur as isolated events. In most cases, the seizures are frequently repeated over a period of a few days and may result in status epilepticus.[28] They then subside, irrespective of whether the cause is a major brain lesion—as in hypoxic-ischemic encephalopathy—or a benign, purely functional disturbance—as in benign familial neonatal convulsions. The duration of individual seizures is usually brief, even in cases of status. An average duration of 137 ± 11 sec was found in one study.[7] This brief duration may be one reason for the absence of residual damage in such cases as hypocalcemic seizures that leave no residua even if they are repeated over several days.

The causes of neonatal seizures differ considerably from those of seizures in older children. A majority are due to organic brain damage of prenatal or perinatal origin or to acute metabolic disturbances. The role of neonatal hypoxic-ischemic encephalopathy is probably less than formerly thought because of improvements in prenatal and obstetric care. Moreover, a significant proportion of seizures attributed to anoxia are of the subtle type and may not be epileptic. A relatively poor correlation has been found between such variables as Apgar scores, cord pH, and abnormalities of cardiac rhythms and the occurrence of convulsions.[20] Conversely, emphasis has been put more recently on the etiologic role of brain damage of prenatal origin[27] and congenital brain anomalies.

Other significant lesional causes include intracranial hemorrhage and neonatal and fetal infections such as bacterial meningitis and sepsis that require emergency treatment. Strokes due to arterial thrombosis or embolism of undetermined origin have proved to be a frequent cause of focal seizures of fixed location occurring in the first few days of life. These are usually of clonic type and are often repeated in long series or status epilepticus. A persisting hemiplegia is observed in about half of the cases, but the neurodevelopmental outcome is relatively favorable.[30] Strokes of venous origin may also be observed.[9]

Acute metabolic disturbances are relatively uncommon with the virtual disappearance of late hypocalcemia and the decrease in frequency of electrolytic derangements and of hypoglycemia. Hypoglycemia remains an important cause, however, because it is a treatable condition that is observed mainly in post-term infants often following prolonged labor and difficult birth. It may rarely reveal pancreatic disease or may result from other metabolic errors. An abnormality of the transport of glucose[10] usually becomes manifest later in the neonatal period and is responsible for hypoglycorrhachia without hypoglycemia, thus requiring CSF level of glucose study for diagnosis.[10]

There are a number of chronic metabolic diseases with neonatal manifestations. Disorders of organic acids and amino acid metabolism most often manifest in the neonatal period with subtle seizures or abnormal movements that, in most cases, do not seem to be of a true epileptic nature. True epileptic attacks can be observed perhaps more commonly in urea cycle disorders.[2] They are also a feature of glycine encephalopathy in which erratic myoclonus is frequent. Rare disorders of neurotransmitters and sulfite oxidase and manganese cofactor occur. Pyridoxine dependency is another treatable cause and occurs selectively in the first days of life.[11] Convulsions responding to pyridoxal-phosphate but resistant to pyridoxine, which are also treatable, have been recently described.[15] These causes individually, in rare cases collectively, form a sizable group and are important because treatment is possible in some situations, or at least diagnosis is possible for counseling purposes. Other nonlesional causes include drug withdrawal and inadvertent injection of local anesthetics in the fetus during peridural anesthesia.[14]

Benign syndromes of infantile seizures have emerged during the last two decades and their recognition is important because, in contrast with most neonatal convulsions, their outcome is favorable and families should not be given the poor prognosis that is applicable to many neonatal seizures (see Chapter 227). They include two groups. *Benign familial neonatal seizures* have recently attracted considerable attention (see Chapter 223). Such cases are dominantly transmitted and in some families have been shown to result from ion channel dysfunction affecting usually K^{2+},[18] but also Na channels.[4] Whether these cases form one or several clinical syndromes is not clear. Genetically, they are heterogeneous, with at least three different loci, and responsible genes have been located most commonly on chromosome 20 and, rarely, on chromosome 8, although many cases do not demonstrate any of these linkages.[18,24] However, in most families no gene is currently known. They are dominantly inherited. The seizures have some special characteristics[12,26] and disappear, usually in a few days or weeks, although some 15% of affected children may have other types of seizures in later life.

Despite their rarity, these cases are of great significance because they represent the first known disease of pure epilepsy of monogenic origin and may be significant for the understanding of the mechanisms of more common forms of epilepsy. They are also of theoretical interest as demonstrating the role of ion channels, in this case K channels. *Benign nonfamilial seizures*, sometimes termed fifth-day fits[24,25] because their most common occurrence consists of episodes of repeated brief seizures of clonic and apneic types in the normal newborn between days 3 and 7, recur for 24 to 48 hours and disappear without leaving apparent sequelae. Their features do not differ from those of the familial seizures. No cause has been consistently found, and the frequency of the syndrome may be fluctuating with time, suggesting the possibility of environmental causes. The definition of the syndrome, however, is loose, and this may account for the discrepant frequencies reported.[17] Nonetheless, its existence underlines the fact that some syndromes in neonates are benign.

The outlook of neonatal convulsions varies with their cause. Seizures due to brain damage are of unfavorable significance when associated with structural brain defects. Predictors of poor prognosis include the persistence of abnormal neurologic signs at the end of the first week of life[17] and the presence of marked interictal EEG anomalies, such as inactive or depressed tracings and periodic bursts of paroxysmal activity on a generally inactive background (paroxysmal tracings). The major problem is the development of mental retardation or cerebral palsy rather than the persistence of seizures. The frequency of later epilepsy varies between 18% and 26% following convulsions of hypoxic-ischemic origin. In many cases, late seizures develop after a free interval and are often infantile spasms.[3] The persistence of partial seizures is the rule with brain malformations.[19] In rare cases, infantile spasms may begin in the neonatal period.[3] They are a part of Ohtahara syndrome, in association with a burst-suppression EEG (see Chapter 225). The syndrome is often due to extensive brain malformations and has a very poor outlook.[21] The same sort of burst-suppression tracing may be associated with erratic myoclonus and partial seizures in the syndrome of neonatal (or early) myoclonic encephalopathy.[21] The two syndromes may be related, although the latter seems to be more often of genetic, perhaps metabolic, origin. This is definitely the case of glycine encephalopathy, a common cause of neonatal myoclonic encephalopathy.

Treatment of neonatal seizures hinges mainly on etiology (see Chapter 123). Many uncertainties persist concerning the significance of the seizures themselves as a cause of possible additional brain damage[17,30] and, consequently, concerning how important it is to control seizures (with the additional unsolved problem of purely EEG discharges, as discussed earlier). Therefore, a rapid but complete assessment of the infant with special attention to infections and possible metabolic disturbances such as hypoglycemia, hypocalcemia, and electrolyte disturbances is essential and should lead to appropriate correction treatment. More severe metabolic diseases should be vigorously treated. There is no agreement on the anticonvulsant drugs to be used.[16] Many investigators[22] favor phenobarbital or phenytoin in large doses, with initial loading, followed by maintenance therapy for variable periods. In general, short-term treatment is advised, but actual duration may be a few days to a few months. Recently doubt has been raised concerning the innocuousness and effectiveness of large doses of phenobarbital.[23] An alternative method is to use diazepam or lorazepam by intravenous route as the first anticonvulsant agent.

Summary and Conclusions

The clinical significance of neonatal seizures is more of an indicator of underlying serious brain damage or dysfunction than a predictor of chronic seizure persistence despite the recent realization that benign "idiopathic" cases do exist. Much remains to be learned about the basic mechanisms of neonatal seizures such as answers to such fundamental issues as the ability of the seizures to produce brain damage and the role of brain maturation in their electroclinical expression and response to therapy. In any case, their significance is more of an indication of brain damage than in terms of etiology. Pending the answers, empirical therapy and supportive treatment will remain essential.

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Chapter 223

Benign Familial Neonatal Seizures and Benign Idiopathic Neonatal Seizures

Perrine Plouin

Introduction

In 1989, the International Classification of Epilepsies, Epileptic Syndromes and Related Disorders[15] included two neonatal syndromes among idiopathic conditions in the section on generalized epilepsies and syndromes: *benign familial neonatal convulsions* and *benign neonatal convulsions*. At that time, no video-electroencephalogram (EEG) recording of seizures had been reported, and newborn infants were considered as presenting more generalized than focal seizures. Nevertheless, since 2001, it has been proposed to consider at least benign familial neonatal convulsions as a focal clonic or adversive epilepsy. Plouin[47] proposed that the appellation *benign neonatal convulsions* was not sufficiently precise: Some symptomatic cases such as hypocalcemia may also be benign, and it would be more accurate if the word *idiopathic* was added: *benign idiopathic neonatal convulsions.* Since then, the word “convulsions” has been replaced by the word “seizures” because “convulsions” refer only to the motor components of seizures, excluding the autonomic components. These two syndromes are now called benign familial neonatal seizures (BFNS) and benign idiopathic neonatal seizures (BINS). Only the first remains in the proposed classification because it seems that no new cases of BINS have been reported in the last 15 years.

These two syndromes do not strictly fulfill the criteria for idiopathic generalized epilepsies; the typical trait of generalized spike-and-wave discharge is not present. It can be argued that the immaturity of the central nervous system is responsible for this absence. Nevertheless, since 2001, it has been proposed that at least BFNS be considered a focal clonic or adversive epilepsy.

Benign neonatal seizures are defined by a favorable outcome, that is, normal psychomotor development and the absence of secondary epilepsy. Benign familial neonatal seizures and benign idiopathic neonatal seizures fulfill these criteria, even if some questions remain open.

Recognition of these syndromes allows the prediction of a favorable outcome from the neonatal period, and long-term antiepileptic treatment is not indicated.

Benign Familial Neonatal Seizures

Historical Perspectives

In 1964, Rett and Teubel[51] reported the first BFNS family, with eight cases over three generations. On the third day of life, the male proband developed an initial tonic phase with cyanosis followed by clonic movements of the whole body including the face and eye muscles, and he had 15 to 20 seizure events on the following day. A brother born 16 months later had a similar experience. Several interictal EEGs were reported for these two boys and single EEGs for three other affected relatives. No ictal EEG was recorded. The authors noted the familial history, the normality of the interictal EEG, and the favorable outcome.

In a second family, 14 members in five generations had similar clinical histories.[9] After a normal delivery, seizures (sometimes with cyanosis) usually started on the third day of life but stopped within 1 month. A few seizures were observed up to 7 months in three children and up to 10 years in two others.

In 1979, Quattlebaum[50] reported a family in which 11 individuals had seizures that started on or before 3 days of age, 1 at 3 weeks, and 3 at 3 months. Most had seizures until 6 or 8 months, but all were otherwise normal.

Between 1964 and 1989, 26 families were reported, with all authors agreeing on a probable autosomal-dominant inheritance.

In 1989, Leppert et al.[32] studied 48 individuals in four generations of a family (Quattelbaum's family), 19 of them having the characteristics of BFNS. They localized the gene on the long arm of chromosome 20, possibly to 20q13.2, the first linkage to be reported for an epilepsy syndrome. This was soon confirmed in a Newfoundland, Canada, family with 69 affected inviduals,[53] in a northern European family,[55] and in six French families.[38] The BFNS syndrome that maps to chromosome 20q has been designated EBN1. Since then, >25 families have been genetically studied in different countries. For 20 of them, the same genetic localization on the long arm of chromosome 20 has been proved.

In 1991, however, Ryan et al.[55] studied two families with BFNS that did not link to chromosome 20 and concluded that the syndrome of BFNS was genetically heterogeneous. Further study of that family[34] demonstrated tight linkage to a locus on 8q, thus verifying heterogeneity (the BFNS syndrome on 8q is designated EBN2). In other families, no linkage could be found on either 20q or 8q.[35]

In 1995, Anderson et al.[1] characterized a candidate gene for BFNS: the human alpha 4 subunit of the nicotine acetylcholine receptor (hCHRNA4). In 1998, the sequencing of genes that are mutated in EBN1 and EBN2 was reported.[58] The new gene was named *KCNQ2*, and analysis of five other ENB1 families yielded two transmembrane missense mutations, two frameshifts, and one splice-site mutation.

A search of the human genome databases for sequences homologous to *KCNQ2* detected one in the chromosome 8q24 region.[14] The new gene was named *KCNQ3*, and a mutant DNA fragment from it was found to segregate perfectly with the EBN2 phenotype in a *Mexican-American family*.[58]

New EBN1 kindreds have been reported with variations in seizure history or in types of mutation. A wide range of clinical manifestations has been observed, including partial seizures in later life with corresponding focal neurologic deficits. Thus far, however, there is little evidence for a correlation between type of mutation and seizure history.[8,33]

The condition of benign familial neonatal seizures is a rare, dominantly inherited epileptic syndrome with a penetrance as high as 85%.

For more details about the genetics of this syndrome see Chapter 18.

Definitions

The diagnosis of BFNS can be considered as a diagnosis by exclusion if every other etiology has been excluded and if there is a family history of neonatal seizures without any severe epilepsy in family members.

Epidemiology

No epidemiologic study of infant or childhood epilepsy has determined the prevalence of BFNS. Among a population of 76 newborns with seizures referred to the neuropediatric unit of Saint Vincent de Paul Hospital between 1994 and 2002 and with video-EEG–recorded seizures, we had only 2 cases of BFNS. The best estimate thus far of the population rate for BFNS comes from a recent prospective, population-based study that involved all obstetric and neonatal units across the province of Newfoundland.[52] Five cases of BFNS (none of whom were part of the kinship reported by Ronen et al.[53]) were observed among 34,615 live births from 1 January 1990 to 31 December 1994. Thus the incidence of BFNS was reported as 14.4 per 100,000 live births.

All reported families represent isolated cases. It is probable that families with BFNS are more numerous than would appear from the medical literature; families with this syndrome often know that the outcome is favorable and do not always report the occurrence of seizures to their physician.

Three hundred and fifty-five cases have been reported in the medical literature since the first article by Rett and Teubel.[51] These neonates belong to 44 families. The number of affected generations varies from one to five (Table 1).

Etiology and Basic Mechanisms

By definition, an idiopathic syndrome does not have a specific underlying etiology. This is the case for BFNS.

Basic mechanisms in this syndrome are probably close to those involved in other types of neonatal convulsions. Immature brain is more likely to respond to any kind of injury with epileptic seizures. In this syndrome, genetic susceptibility during the first week of life in full-term neonates is responsible for the appearance of seizures; the cause is a deficit of a specific channelopathy, but the precise mechanism is unknown. The fact that seizures occur in premature infants when they reach 39 to 41 weeks of gestational age means that a step in maturation has to be reached for the channelopathy to be expressed.

Table 1 Benign familial neonatal seizures

	6	2
	3	2
Pavone et al. 1982[44]	7	2
Giacoia 1982[23]	7	4
Plouin 1984[46]	2	2
	2	1
Kaplan and Lacey 1983[31]	12	4
Palencia and Berjon 1985[43]	4	2
Shevell et al. 1986[57]	5	3
	4	3
Nieto Barrera et al. 1986[41]	14	3
Calero Garcia et al. 1988[11]	17	4
Cunniff et al. 1988[17]	8	2
Giroud et al. 1989[24]	2	2
	2	2
	2	1
Malafosse et al. 1990[37]	6[a]	3

	4[a]	2
Webb and Bobele 1990[63]	9	5
Camfield et al. 1991[12]	5	2
Ryan et al. 1991[55]	14[a]	3
	15[b]	3
Schiffmann et al. 1991[56]	4	1
Wakai et al. 1991[61]	5	2
Aso and Watanabe 1992[4]	3	2
Malafosse et al. 1992[38]	9[a]	4
	3[a]	2
	9[a]	4
Mami et al. 1993[39]	4	2
Ronen et al. 1993[53]	69[a]	5
Hirsch et al. 1993[30]	6[a]	2
Bye 1994[10]	5	3
Berkovic et al. 1994[6]	10[a]	4

Total 1964–1995: 355 cases, 44 families

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[a] Families mapped to chromosome 20 (linkage analysis of Quattelbaum's family by Leppert et

al.[32]).

[b]Family mapped to chromosome 8 (linkage analysis of Lewis et al.[34]).

Clinical Presentation

One can consider the diagnosis of BFNS as a diagnosis by exclusion reinforced by the familial history of neonatal seizures.

The clinical data come from the 44 families reported between 1964 and 1996, including 355 cases (Table 1). Since 1996, more isolated families have been reported, but mostly by geneticists, and few details appear in these papers about the electroclinical presentation of seizures.

In documented cases, birth was always at full term (except for three cases of Ronen et al.[53]), with a normal birth weight and an Apgar score >7 at the first minute of life. None of these neonates was in an intensive care unit. There was always a seizure-free interval between birth and occurrence of seizures.

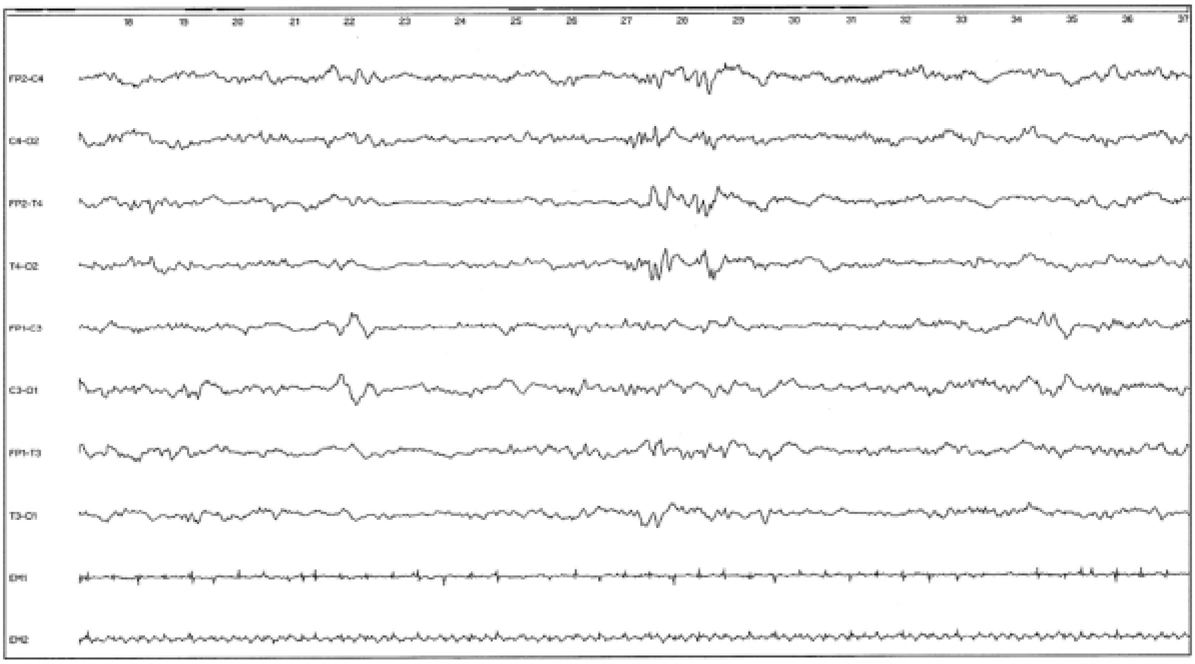

FIGURE 1. Interictal waking electroencephalogram (EEG) in a 5-day-old full-term neonate with benign idiopathic neonatal seizures (BFNS); short bursts of theta rhythms are more marked on the right hemisphere.

The gender ratio shows an equal distribution between boys and girls.

In 80% of cases, seizures start on the second or third day of life, but some infants start having seizures later, during the first or even up to the third month of life. Ronen et al.,[53] in their large family, report that two of the individuals in whom seizures started at 1 month of age were premature. Premature infants would not be able to have seizures before reaching full-term neurologic state; this point is important, given the strict age dependence of the syndrome.

The neurologic state of the infants remains normal in most cases, and they can nurse or drink from a bottle between seizures; a mild transitory hypotonia can be noticed in some cases. None of these infants was transferred to neonatal intensive care units.

In the first reported families, before the use of video-EEG monitoring, seizures were described as a clonic type, sometimes with apneic spells. Tonic seizures were reported in two cases. Clonic or tonic seizures were short (lasting from 1 to 3 minutes) and frequently repeated within a period of 7 days, whereas isolated seizures could occur in some cases during the following weeks.

Seizures had already been described in previous reports,[12,16,23,57] but there was no evidence in these cases for a homogeneous presentation. More recently, Ronen et al.[53] listed all the clinical components of the 70 seizures they could analyze in their large family. They concluded that most of the time, seizures started with tonic, autonomic, or oculofacial features, being of a mixed type. Hirsch et al.[30] recorded 14 seizures in three neonates with video-EEG monitoring. All seizures started with a tonic phase, with a right or left maximum. Seizures varied from one to the next in a given infant and were always accompanied by tachycardia and a short period of apnea. The clonic phase (partial or generalized) was introduced by vocalization or chewing. We had the opportunity to record seizures in five cases with video-EEG monitoring (unreported families): Seizures were stereotyped, starting with a diffuse hypertonia and a short apnea, followed by autonomic or oculofacial features and symmetric or asymmetric clonic movements of the limbs. In 1994, Bye[10] reported a new case of BFNC, with two seizures recorded and videotaped. Both seizures started with an arousal, but in one, groping and clonic movements of the limbs remained localized to the left side, whereas in the second, these movements were generalized. From these different video recordings, it appears that in most cases, seizures start with a diffuse tonic component, followed by various autonomic and motor changes, which can be unilateral or bilateral, symmetric or not. The only cases without an initial tonic component are those of Bye.[10] No myoclonic seizures or spasms have been reported nor in fact true generalized tonic–clonic seizures.

When described, interictal EEG was normal, discontinuous, or included focal or multifocal abnormalities or a *théta pointu alternant* pattern (Figs. 1 and 2). Patterns suggesting a poor prognosis, such as a paroxysmal, inactive, or suppression-burst pattern, were never reported.

In first reports, some seizures were recorded, but the EEGs were not published or were incomplete. In the cases we recorded, the ictal pattern was very similar to the one published by Ronen et al.[53] and to the cases of Hirsch et al.[30] On the EEG, seizures started with a generalized flattening of the background activity followed by focalized or generalized spikes or slow waves lasting as long as the clinical manifestations. A prolonged flattening of the EEG could follow the seizures. Hirsch et al.[30] studied the ictal EEG very carefully and found that the length of the flattening could vary from 5 to 19 seconds and the complete seizure from 59 to 155 seconds. All of these individuals had BFNS mapped to chromosome 20. The electroclinical presentation of these seizures suggests that they are of

a generalized type. Aso and Watanabe[4] discussed this point because they recorded a unilateral seizure in a 3-month-old infant having had BFNS.

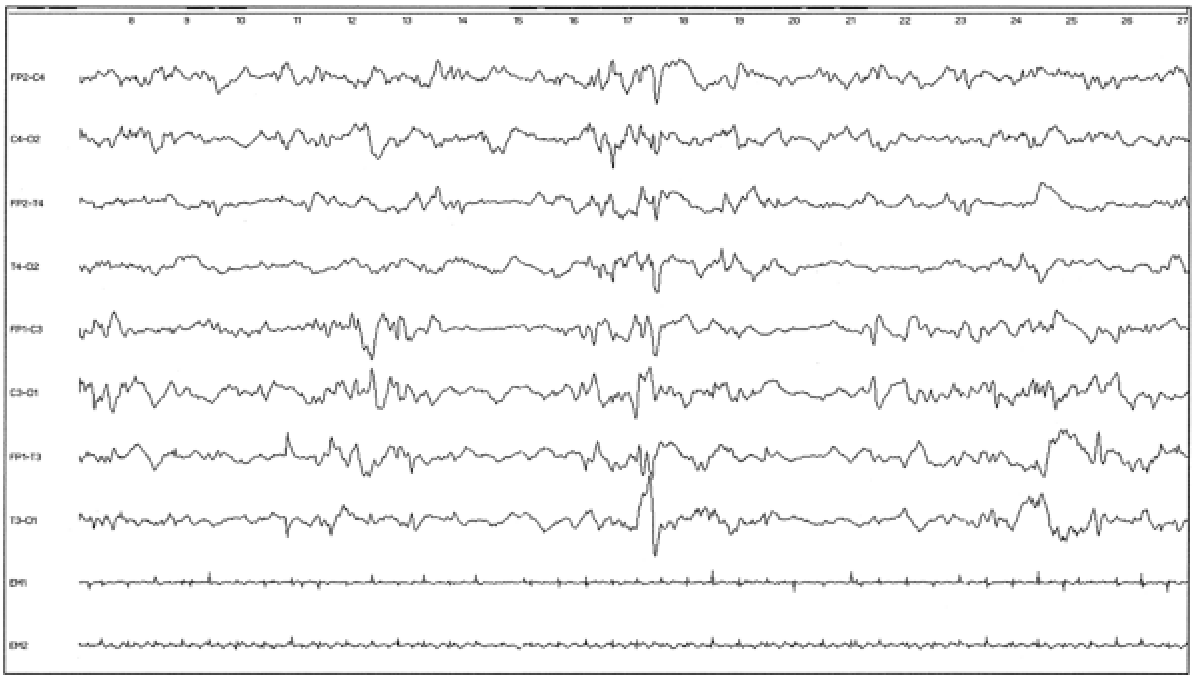

FIGURE 2. Interictal sleep electroencephalogram (EEG) in the same neonate with benign idiopathic neonatal seizures (BFNS); short bursts of bilateral asynchronous theta rhythms are more marked on the left hemisphere.

The publication of Hirsch et al.[30] emphasized that the initial flattening of the EEG is generalized from the start and that the successive symptoms occurring during a seizure (tonic, apnea, clonic phases) are identical to those reported in generalized tonic clonic seizures in children and adults. The same authors suggested that the asymmetric character of some clinical and EEG signs during the tonic or the clonic phase could be related to the absence of maturation of the corpus callosum during the first weeks of life.[5] In all of our recorded seizures we noticed a unilateral predominance of the EEG pattern, even if the initial flattening seemed to be generalized, and at the end of the seizures, we noticed a focal temporal discharge, the same side as the frontal initial spikes and slow waves (Fig. 3). Bye[10] and Hirsch et al.[29] discussed the place of BFNS among idiopathic generalized epilepsies: At the time the classification was adopted (1989), no videotape of BFNS existed, whereas it now appears that some partial seizures may be present, but most of them are of a generalized type.

We suggest nonetheless that this syndrome not be included among the generalized ones: The electroclinical presentation is closer to partial epilepsies such as benign infantile familial seizures or epilepsy with centrotemporal spikes, both benign age-dependent focal epilepsy syndromes. This opinion is shared by Watanabe et al.[62] and Engel.[22]

Diagnostic Evaluation

The diagnosis of BFNS is based on the clinical presentation and the familial history. Cases of BFNS will be found in the family history, but whereas only cases of BFNS are seen in some families, in other families, cases of BFNS are found along with other types of seizures, mostly belonging to the idiopathic generalized epilepsies. The EEG is normal or mildly abnormal. If recordings are made, the electroclinical presentation of seizures is relatively stereotyped.

Nevertheless it seems necessary to exclude any other etiology—metabolic or infectious—and for that purpose a clinical workup and a lumbar puncture should be done. Computed tomography (CT) is not indicated as long as the neurologic state of the infant remains normal.

Differential Diagnosis

Benign familial neonatal seizures must be differentiated from nonepileptic paroxysmal phenomena of neonates (see Chapter 273) and from other types of neonatal convulsions (see Chapter 56).

Among nonepileptic phenomena in neonates, tremulousness and benign sleep myoclonus should be eliminated. Tremulousness occurs in normal neonates during waking and sleep; it can be very intense, and its main characteristic is that it can be stopped by restraining the involved limb and the EEG is normal. Benign neonatal sleep myoclonus occurs only during quiet sleep. The EEG is strictly normal between and during the fits. This phenomenon disappears spontaneously within days to weeks, and the child develops normally.[20]

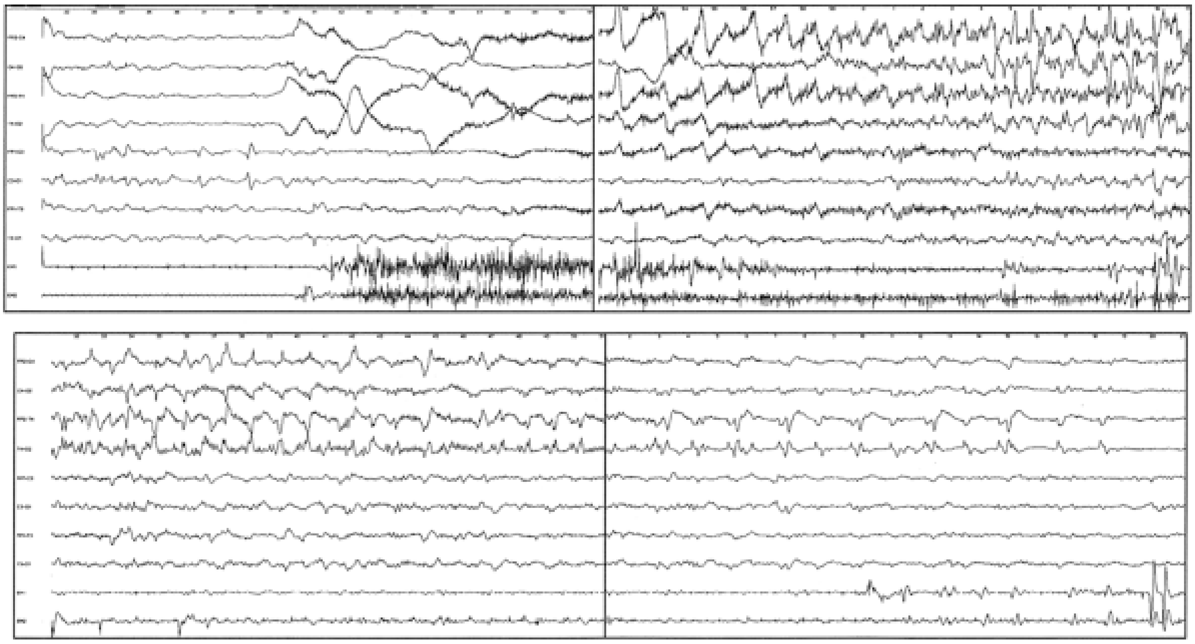

FIGURE 3. Polygraphic recording of a focal seizure in the same neonate. Initial flattening is more marked on the right hemisphere, followed by frontal delta waves; notice the right temporal spikes at the end of the seizures; the duration of the seizures is 80 seconds.

Symptomatic neonatal convulsions are the most frequent, occurring secondary to hypoxo-ischemic encephalopathy, metabolic disturbances, or infectious processes. These etiologies can be assessed with different diagnostic tools, and the convulsions do not have the typical clinical presentation of BFNC, differing in regard to day of onset, clinical type of seizures, duration and repetition of seizures, and neurologic

state. Interictal and ictal EEGs also show different patterns according to etiology and severity of the pathology, from normal to very abnormal tracings.

A new sodium channelopathy was reported in 2002[27] in a family with benign neonatal-infantile seizures, the phenotype being described later by Berkovic et al.[6] In this situation, the members of a given family may have neonatal or infantile seizures, with a favorable outcome in all cases. This could be considered an intermediate situation between BFNS and benign familial infantile seizures.[60]

Treatment and Outcome

No guideline has been proposed concerning the treatment of BFNC. In the past, probably no treatment was given. In some families, mostly coming from around the Mediterranean Sea, the best reported treatment was to put a cold key in the neck of the infant. Different authors give their own experience in the treatment of these infants. The drug used depends on country, continent, and year of publication.

Most infants were given phenobarbital for 2 to 6 months, rarely longer. In our experience, sodium valproate is effective, leading to a rapid cessation of seizures. Some authors have also used diphenylhydantoin. The question remains open about the usefulness of an antiepileptic drug treatment: Grandparents of these infants were not treated and did well. If a treatment is initiated at the time of the seizures, it seems reasonable to interrupt it by the third or sixth month.

Long-Term Prognosis

No longitudinal study has been published of BFNC. When we reviewed the literature,[47] we found that infants with BFNS have a 5% risk for febrile convulsions, which is not very different from the general population risk. Concerning secondary epilepsy, the mean risk is around 11% among these infants, higher than in the general population. However, no case of severe epilepsy was noticed in this population. In 1999 Maihara et al.[36] reported two siblings with BFNS who later developed epilepsy with centrotemporal spikes: Both stopped having seizures with carbamazepine and had a normal psychomotor development. No case of psychomotor retardation or mental impairment has been reported among this population of BFNS.

Benign Idiopathic Neonatal Seizures

Historical Perspectives

The first report about BINS was by Dehan et al. in 1977.[19] They described 20 neonates with convulsions occurring around the fifth day of life, no specific underlying etiology, and a favorable neurologic outcome in an article entitled “Les convulsions du cinquième jour: un nouveau syndrome?” (“Fifth day's fits: a new syndrome?”). Other French authors reported similar cases.[2,3,21,40,48] The first non-French study was by Pryor et al.[49] from Australia, followed by that of North et al.[42]

During the 1980s, the only reports were French and Australian. In 1992, however, Herrmann et al. from Germany reported 21 recent cases.[28] No study of this syndrome came from the United States.

Table 2 summarizes the 299 published cases.

Table 2 Benign idiopathic neonatal seizures

Study	Collection period	Cases
Dehan et al. 1977[19]	1973–1976	20
André et al. 1978[3]	1972–1976	4
Pryor et al. 1981[49]	1973–1977	90
Dreyfus-Brisac et al. 1981[21]	1974–1979	11

Plouin et al. 1981[48]	1966–1980	39
Navelet et al. 1981[40]	1976–1980	18
North et al. 1989[42]	1972–1985	94
André et al. 1990[2]	1980–1981	2
Herrmann et al. 1993[28]	1989–1991	21
Total	1966–1991	299

Definitions

The diagnosis of BINS is made in full-term infants who are neurologically normal and have no familial history of neonatal convulsions, negative findings on workup, and a favorable outcome with respect to both psychomotor development and the absence of secondary epilepsy. Again, this diagnosis is made by exclusion of any specific underlying etiology.

Epidemiology

The incidence of BINS is not clearly apparent in epidemiologic studies dealing with childhood epilepsy. This condition is quite well known among neonatologists and neuropediatricians but not among epileptologists.

Plouin[46] tried to determine the prevalence of BINS among neonatal convulsions. Studies of neonatal convulsions or neonatal status epilepticus published between 1959 and 1982 were analyzed to identify those that could be defined as BINS. Among these studies, special attention was paid to the description by Dehan et al.[18] of neonatal convulsions with unknown etiology occurring around the fifth day of life.

The 15 published studies exhibited a great disparity regarding material and methods. Among the 2,042 cases reported in these 15 studies, a majority of the cases of neonatal convulsions of unknown etiology had a good outcome (120 of 195 documented cases; mean, 62%; range, 28%–93%), and cases with unknown etiology and favorable outcome account for 6.6% of all neonatal convulsions (range, 0%–28%).

This suggests that cases of BINS were already present in the literature before their formal description by Dehan et al. in 1977.[18] Their prevalence can be estimated to be about 7% of neonatal convulsions; this percentage decreases to 2% if only the cases for which the date of occurrence of seizures and the interictal EEG patterns are reported are taken into account. In reported series of BINS, the prevalence varies from 4% to 38% of neonatal convulsions, and this large scatter probably reflects differences in patients' referral and recruitment—intensive care units, maternity clinics, and departments of neonatology or pediatric neurology. The true prevalence of BINS is in good agreement with the range of 2% to 7% cited previously.

Finally, North et al.[42] insisted on the fact that no case of BINS has been observed in their department since 1982. Moreover, the incidence of neonatal convulsions, which was very high during the 1970s, has decreased since the beginning of the 1980s. Others in Australia noted the same facts, leading to the hypothesis of an epidemic phenomenon of BINS, with the etiology undetermined.

In 1990, Dehan, Navelet, and D'Allest carried out a retrospective study to determine the number of cases of BINS referred to neonatology and pediatric department intensive care units as well as maternity units each year between 1979 and 1989. The results were presented at the first Réunion d'Actualités en Epileptologie in Geneva in 1991. The authors concluded that sporadic cases existed among all departments (0.5 to 1.5 cases per year per department), with an important peak in 1981 (comparable with the one of 1975 that led to the first report of BINS).

Herrmann et al.[28] also reported the epidemic occurrence of BINS, with 21 cases referred between 1989 and 1991. The fact that they found a rotavirus infection associated with 95% of their cases reinforces the hypothesis of an epidemic phenomenon but does not explain the relationship to the convulsions.

Etiology and Basic Mechanisms

Metabolic, viral, other infectious, and toxic etiologies have been looked for in this syndrome.

Goldberg and Sheehy proposed one etiologic hypothesis.[25] After a 3-year prospective study, they found an acute zinc deficiency in the cerebrospinal fluid of infants with BINS when compared with a group of infants in whom a cause of convulsions had been identified and with another group of infants without convulsions but with other health problems. This hypothesis has not been confirmed. Moreover, in Australia and France, very complete metabolic, toxic, and viral inquiries have been performed, without any significant results.

More recently, Herrmann et al.[28] reported 21 cases of BINS referred between 1989 and 1991 among 1,917 neonates hospitalized during the same period. They tested for rotavirus in the feces of 19 infants with BINS, 30 healthy controls (age, 4–6 days), and 202 sick neonates without convulsions. They found rotavirus in the feces of 18 of the 19 infants with BINS (95%), whereas only 40% of the healthy controls ($p < 0.001$) and 48% of the sick neonates without convulsions ($p < 0.001$) had positive findings. The authors suggested a causal relationship between BINS and rotavirus infection, although rotavirus was not present in the cerebrospinal fluid of 6 rotavirus-positive infants with BINS. They concluded that pathogenic mechanisms remain unclear. This syndrome remains idiopathic.

Clinical Presentation

The gender distribution reveals a majority of boys (62%). Only full-term infants have been reported. Pregnancy and delivery were normal, and seizures started after a seizure-free interval. In all cases, seizures occurred between days 1 and 7; 90% occurred between days 4 and 6, and 97% between days 3 and 7. No videotape recording has been reported for any of these cases.

When described, the seizures were always of the clonic type, mostly partial, with or without apnea, but never tonic. North et al.[42] reported apneic seizures in 31% of their cases. Clonic seizures were often lateralized, starting on one side and then affecting the other side, and rarely of a generalized type. They lasted from 1 to 3 minutes. They were frequently repeated, leading to status epilepticus. The mean duration of status epilepticus was about 20 hours, but it could be shorter (2 hours) or longer (up to 3 days).

The neurologic state of the infants is usually normal at onset of convulsions. Infants then become drowsy and hypotonic, the various antiepileptic drugs given to stop the convulsions being partly responsible for this evolution. Drowsiness and hypotonia may last for several days after the end of status epilepticus, but the infants soon recover to a normal neurologic state.

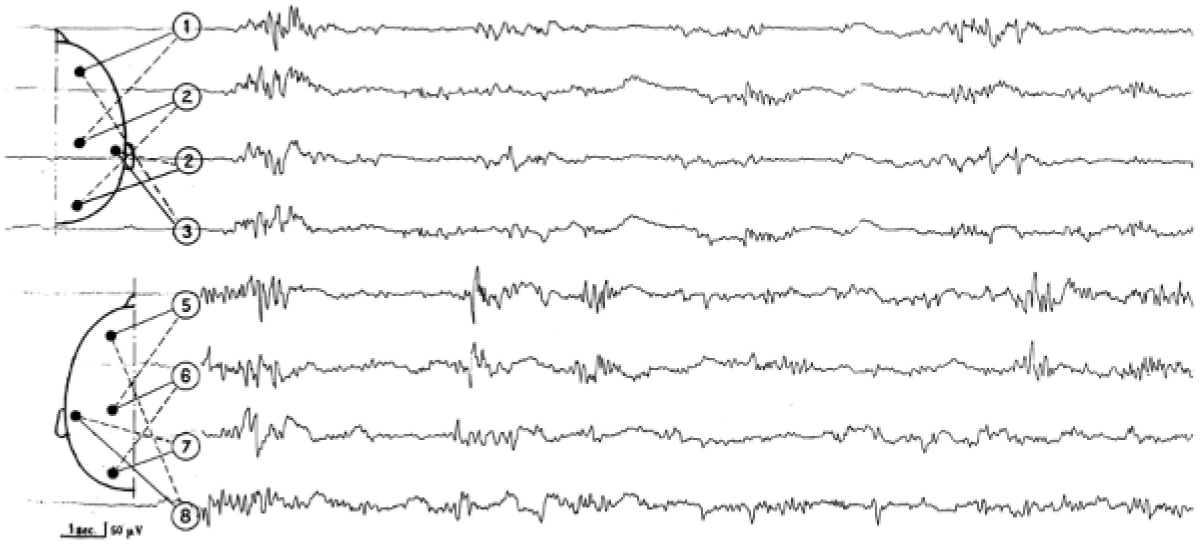

FIGURE 4. Interictal electroencephalogram (EEG) of a *théta pointu alternant* pattern in an infant with benign idiopathic neonatal seizures (BINS).

Interictal EEG patterns were described in 101 of the 299 published cases. The interictal EEG was normal in 10 infants, discontinuous in 6, and showed "focal or multifocal abnormalities" in 25. The *théta pointu alternant* pattern was present in the remaining 60 infants. This pattern was first described by Dehan et al.[18] as a dominant theta activity, alternating or discontinuous, unreactive, with sharp waves and frequent interhemispheric asynchrony. The *théta pointu alternant* pattern may be present in cases of status epilepticus of different etiologies (hypocalcemia, neonatal meningitis, subarachnoidal hemorrhage) and cannot be considered as specific for BINS.[40,46] Nevertheless, it is associated with a favorable neurologic prognosis (Fig. 4).

Seizures have been recorded in most of the 101 cases. They last from 1 to 3 minutes and have no remarkable EEG features—mostly rhythmic spikes or rhythmic slow waves. They can be localized to any area but are more frequently present in the rolandic areas. They can be strictly unilateral, immediately generalized, or first localized and then generalized. Electroclinical seizures or subclinical discharges (so-called electroencephalographic seizures) can be recorded; clinical seizures without EEG modifications have also been reported.

Diagnostic Evaluation

The diagnosis of BINS is based on the clinical presentation, the ictal and interictal EEG, and the elimination of any specific underlying etiology, such as metabolic disturbances, neonatal meningitis, viral infections, or malformations of the central nervous system.

Differential Diagnosis

The differential diagnosis of BINS is not different from that of BFNS. The familial convulsions are different from the idiopathic convulsions in several ways: BFNS is a familial disease having an autosomal mode of inheritance linked to genetic markers localized to the long arm of chromosome 20, at least in the majority of cases; conversely, a family history is very rare in BINS (0.2%). Seizures start earlier in BFNS (days 2–3) and persist longer than in BINS (starting on days 4–5, and lasting no more than 20 hours). Occurrence of secondary epilepsy is more frequent in BFNS (11%) than in BINS (0.5%). Minor neurologic impairment is more frequent in cases of BINS.

Treatment and Outcome

Many antiepileptic drugs have been used for BINS (phenobarbitone, phenytoin, diazepam, paraldehyde, chloral hydrate, clomethiazole), often in combination, without a consistent effect on the duration of seizures. The seizures usually stop without treatment, but occasionally the end seems to be related to administration of diazepam or phenytoin. Dehan et al.[19] suggested that these infants not be treated if alternative diagnoses have been eliminated.

Long-Term Prognosis

The long-term favorable outcome must be confirmed by more numerous and more extensive studies. The 90 cases reported by Pryor et al.[49] have not been followed beyond the neonatal period. The 92 cases reported by French authors were followed from 6 months to 6 years. In five cases, a transitory psychomotor retardation was noted until the age of 1 year; one child had a simple febrile convulsion, and another had a convulsion without fever at the age of 3 years.[18]

Among the 94 cases reported by North et al.,[42] 33 (38%) were followed between the ages of 6 months and 2 years. In roughly half of these 33 infants, the authors found abnormalities. Although there is no control group, the percentage of abnormalities seems excessive in this study. One can consider that children with medical problems were exposed to more frequent consultations than were children without any problems. These authors concluded that their results do not allow assessment of the benignity of this syndrome.

Summary and Conclusions

Benign Familial Neonatal Seizures

Recognizing the phenotype of BFNS is important, first because of the prediction of a favorable neurologic outcome, and second for the contribution to genetic studies, which comprise a dynamic area of epilepsy research, especially for the idiopathic epilepsies.

The classic phenotype of BFNS comprises the following features: (a) normal pregnancy and delivery; (b) seizure-free interval before onset of seizures (mostly on days 2 and 3); (c) neurologically normal state between seizures; (d) normal interictal EEG; (e) tonic–clonic seizures, symmetric or not; and (f) familial history of BFNS or other types of epilepsy (mostly idiopathic epilepsies). The families of such infants should be considered appropriate for genetic studies.

Benign Idiopathic Neonatal Seizures

Benign idiopathic neonatal seizures can be recognized by the clinical and paraclinical characteristics that comprise the syndrome. Diagnosis allows one to predict a favorable neurologic outcome. However, the *théta pointu alternant* EEG pattern is present in only 60% of cases and is not specific. Further reports with a longer follow-up period will perhaps lead to a better understanding of this syndrome and more precise determination of the outcome. The "episodic character" of this syndrome and the nonspecific EEG pattern as well as the type of seizures make it questionable to maintain it in the International Classification of Epilepsies and Epilepsy Syndromes.

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Chapter 224

Early Myoclonic Encephalopathy (Neonatal Myoclonic Encephalopathy)

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Introduction

In 1978, Aicardi and Goutieres described a group of five patients with "neonatal myoclonic encephalopathy" commencing in the hours immediately after birth and consisting of erratic, asynchronous, nonperiodic myoclonus associated with generalized jerks and a distinctive electroencephalogram (EEG).[3] Since then, the syndrome has been referred to as early myoclonic encephalopathy and also as myoclonic encephalopathy with neonatal onset,[8] neonatal epileptic encephalopathy with periodic EEG bursts, and early myoclonic epileptic encephalopathy[9] and neonatal myoclonic encephalopathy.[3,39]

In 1989, the ILAE Commission of Classification and Terminology recognized the syndrome as "early myoclonic encephal- opathy (EME)" and classified it as generalized symptomatic epilepsies of nonspecific etiology.[16] In 2001 the entity was finally recognized as one of the "epileptic encephalopathies" together with early infantile epileptic encephalopathy with suppression-bursts (EIEE, Ohtahara syndrome), West syndrome, and Lennox-Gastaut syndrome. Since 1978, there have been published reports on 50 patients with the characteristic clinical picture—onset of symptoms during the first month of life consisting of erratic, fragmentary myoclonus, massive myoclonus, partial seizures, suppression-burst EEG pattern, and, later, tonic spasms; the prognosis is grave.[4] Some controversial issues on differential diagnosis from EIEE and physiopathology remain; there are several cases of early encephalopathy with seizures and a suppression-burst pattern that do not fulfill the criteria for either EIEE or EME.[4,10,18,33]

Epidemiology

The syndrome is rare. An epidemiologic study of childhood epilepsy in Japan detected 4 cases of EME (0.168%) among 2,378 children with epilepsy >10 years of age.[6,28] In a study of 75 infants with epilepsy of neonatal onset, Watanabe et al.[42] observed 2 cases (2.7%) of EME. A gender difference, with female-to-male ratio of 1:1.3, is seen in the 30 cases published in the English literature.[10]

Etiology

In most cases, the etiology of EME is unknown. Although EME is assumed to be associated with inborn errors of metabolism, even the most frequently reported diagnosis—nonketotic hyperglycinemia—is rarely documented.[2,5,9,13,27,33,38,39] Other identified inborn errors of metabolism are D-glyceric acidemia, propionic acidemia, molybdenum cofactor deficiency, methylmalonic acidemia, mitochondrial dysfunction, and abnormal urinary oligosaccharides.

Structural brain malformations (cerebellar hypoplasia, migrational disorder with cortical dysgenesis) have also been reported.[11,23]

Wang and colleagues reported a patient with a clinical picture of early myoclonic encephalopathy and an atypical suppression-burst pattern, with full recovery after administration of pyridoxine.[40] The syndromes of retinal pigmentary degeneration and nephronophthisis, congenital nephrotic syndrome, and Zellweger disease have all also presented with EME.[2,5,9,13,15,19,21,23,27,33,39,40]

Familial occurrence has been reported,[2,9,33,40] reflecting the genetic nature of the underlying diseases. Because the gene locations for these metabolic errors vary widely, however, it is more likely that EME does not develop due to a specific genetic abnormality but rather due to extensive cortico-subcortical dysfunction as a consequence of a severe metabolic disorder.[27]

Clinical Presentation

Seizure Characteristics

In this condition, a child usually born without dysmorphic features and after an uneventful delivery undergoes a regression as the seizures emerge and becomes less alert and irritable and with poor interactions.[9] The distinctive clinical characteristic of EME is myoclonias, which are the first presenting symptom, starting usually within the first week of life. The majority of the patients present within the first month of life. Onset during the prenatal period and during the second or third month of life has been reported but is rare.[9,11,40]

Myoclonus is fragmentary and erratic and shifts from one to another body part in a random, asynchronous fashion; it can become massive and generalized in some cases.[4] Initially, it involves eyelids, face, and limbs in the form of twitches of small to moderate amplitude. Sometimes, twitches are restricted to a very small territory (eyebrow, corner of the mouth). The frequency of myoclonic jerks also varies from occasional to almost continuous from the onset. It may persist during sleep.[9]

Shortly after the onset, partial seizures occur and can be subtle, consisting of only eye deviations or autonomic phenomena according to Dalla Bernardina et al.[9] Tonic seizures are observed later, usually around 3 to 4 months of age.[2,4]

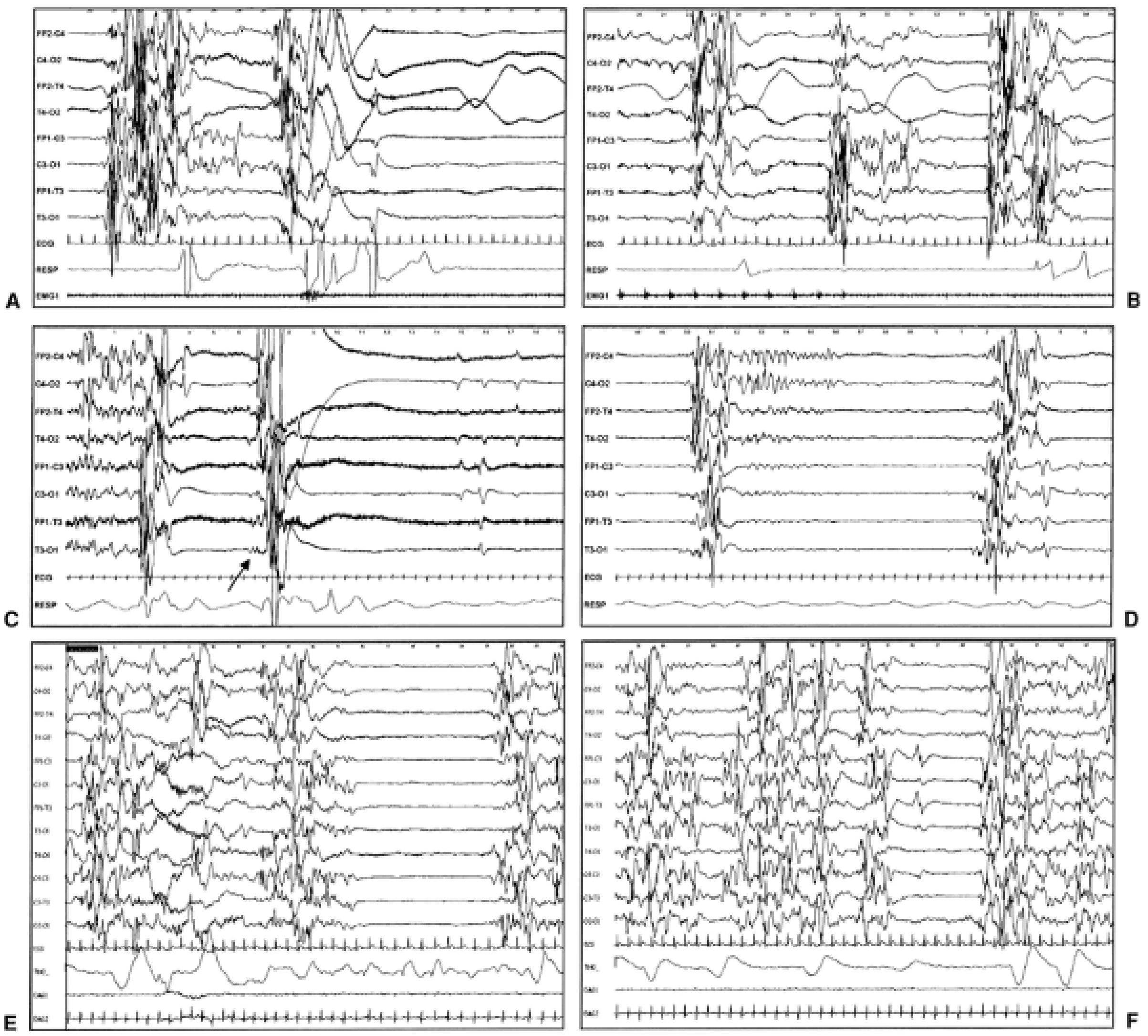

FIGURE 1. Electroencephalograms (EEGs) from an infant with early myoclonic encephalopathy. Panels A to D were obtained when the infant was 1 month old. **A, B:** Awake state. **C:** The occurrence of a myoclonic jerk (*arrow*). **D:** Asleep. Panels E and F were obtained when the infant was 3 month old **E:** Awake. **F:** Asleep. Notice that the burst-suppression pattern is present during wakefulness and sleep. Time scale is 15 mm/s; sensitivity is 100 µV/cm.

Diagnostic Evaluations

Electroencephalographic Features

There is no normal background activity during wakefulness or sleep.[2] There is a burst-suppression EEG pattern characterized by bursts of spikes, sharp waves, and slow waves irregularly intermingled and separated by periods of electrical silence. The duration of the bursts is usually 1 to 5 seconds, and the duration of the silent periods is 3 to 10 seconds (Fig. 1A–D). The EEG paroxysms may be either synchronous or asynchronous over both hemispheres. This pattern is often more marked during sleep. Usually after a few months, it evolves into hypsarrhythmia (more or less typical) or into multifocal paroxysmal discharges without normal patterns. In some cases the burst-suppression pattern may persist for a few months (Fig. 1E, F).

Erratic myoclonus generally may not have an ictal EEG correlate. Axial myoclonias that can be recorded with surface electromyography (EMG) on both deltoid muscles are immediately preceded by a burst of bilateral polyspikes.[3] They occur more frequently during wakefulness and may occur in clusters (Fig. 1). These myoclonias can be differentiated from epileptic spasms: The clinical manifestation is a short tonic contraction, and the EEG pattern consists of a complex of slow waves associated with fast rhythms. Later, multifocal seizures may emerge and the interictal EEG pattern evolves to hypsarrhythmia.[29]

Imaging Findings

Computed tomography (CT) and magnetic resonance imaging (MRI) in most cases are initially normal. In some cases, serial brain imaging shows development of diffuse brain atrophy even in those children with normal imaging findings at onset. Malformations have been reported as a cause of EME. The imaging may show the different pattern of brain malformation cited in the section on etiology.

Other Laboratory Investigations

Because the inborn errors of metabolism are the major cause of EME, a metabolic workup (amino acids, organic acids, lactate, and pyruvate) should be considered in all patients in the blood and in the cerebrospinal fluid (CSF). A pyridoxine challenge should be performed because the association of massive and erratic myoclonias leading to a very hyperexcitable infant with a suppression-burst EEG pattern can be the expression of B6 dependency. In these cases myoclonic jerks stop as soon as the B6 is administered intravenously. To confirm this diagnosis, the specific treatment should be stopped later; if the myoclonic seizures recur, the diagnosis is definite.

Developmental Course

Psychomotor development becomes arrested. The prognosis is grave. In 91% of the patients described in sufficient detail, the outcome is poor: Death occurs during the first years of life in at least 50%; those surviving have severe psychomotor retardation or remain in a persistent vegetative state.[2,10] In rare cases, signs of peripheral neuropathy were reported.[2] Normal developmental outcome has been limited to one case with pyridoxine dependency.[40] The progressive nature and the high fatality of EME cases can be attributed to the progressive nature and systemic influences of conditions with inborn errors of metabolism that remain undetected or untreated in addition to an electroencephalographic abnormality.

Seizure control is poor. The erratic myoclonus usually disappears after a few weeks or months,[4] and partial seizures become intractable. Tonic seizures develop at age 3 to 4 months. Once tonic seizures occur, the overall poor prognosis becomes even graver. In review of 30 patients from the literature, Djukic et al.[10] found that of 22 patients with EME and tonic seizures, 11 died, whereas none of the patients without tonic seizures did. The burst-suppression EEG pattern evolves into hypsarrhythmia in one third of patients. Focal or multifocal abnormalities develop in the remaining patients.

Pathophysiologic Basis

Neither the occurrence of the constellation of symptoms and findings in EME nor the pathophysiologic basis of the changing clinical picture that follows the progression of the disease have been well explained.

Ohtahara et al.[25] approached the problem from the standpoint of the characteristic EEG findings. They drew an analogy to the pathophysiologic basis of the other, more common conditions with suppression-burst EEG (deep anesthesia, normal premature infants <30–32 weeks of gestation, severe hypoxic ischemic encephalopathy). They pointed to a theory of abnormal "neuronal connectivity, suggesting that a disconnection in brain circuits may be involved in the genesis of EEG" and emphasized the "indispensable role of brain lesions both at the subcortical and cortical level."[27]

An alternative hypothesis is more symptom oriented, based on evidence from experimental studies and analysis of the clinical stages in the evolution of EME; it proposes that EME and EIEE may represent a continuum based on the burden of disease at the onset of symptoms.[10] Rodin's animal studies[31,32] clearly showed the brainstem structures associated with the onset of generalized seizures, such as tonic seizures, with the earliest sustained discharges appearing in the pons. During clonic seizures, the cortical discharges lead. Thus, there it has been suggested that clonic seizures originate in the forebrain, whereas tonic seizures originate in the brainstem.[36] This conclusion is supported by studies using precollicular transections: Tonic seizures also occurred when seizures were induced in animals with transections, whereas clonic seizures required forebrain connections.[1,7,12] Other studies show that repeated generalized seizures in experimental animals can kindle secondary seizure foci.[43] These secondary epileptic foci may persist even after the bilateral or generalized seizures abated, because descending inhibition from the hemispheres increases with maturation.[22]

Thus, it is tempting to speculate that in EME, there is initially involvement of cortical structures. The repeated myoclonic seizures may “kindle” the development of focal seizures, and with time there may be a spread to the brainstem (in some cases). Tonic seizures develop once the brainstem lesion burden exceeds the threshold for seizures. Patients with EIEE may have already exceeded this threshold at birth and present with tonic seizures early. In EME, brainstem involvement may be less severe, and tonic seizures are not the presenting symptom. Over time, the brainstem alterations may allow the emergence of tonic seizures possibly as a result of a kindling process increasing seizure susceptibility or as a release of the brainstem from cortical inhibitory control as the metabolic disease progresses.

The pathologic data are consistent with this view. Autopsies were performed in five patients with EME.[11,14,15,17,20,24,30,34,35] All patients had tonic seizures, and clinical signs of brainstem anomalies were present in all of them.

Genetic mapping of an autosomal-recessive form of EME to chromosome 11p15.5 led to the identification of a missense mutation (p.Pro206Leu) in the gene encoding GCI, a protein in the mitochondrial inner membrane that cotransports glutamate with H^+.[21] Expression of this protein has an age-specific distribution: At 20 weeks of gestation, the highest gene expression is identified in the cortex, brainstem, and cerebellum. A moderate to high level of expression is observed within the brainstem in the red nuclei, the substantia nigra, and the olivary complexes and the dentate nucleus in the cerebellum. It is interesting that many of these structures, especially the substantia nigra pars reticulata and its output circuits, play a prominent role in the control of seizures as a function of age and gender.[37] The observation that EME results from a defect in GC1 suggests a role for either glutamate metabolism, mitochondrial pathology, or both in EME.

Differential Diagnosis

Early myoclonic encephalopathy and Ohtahara syndrome share many common clinical and EEG characteristics such as onset in the first few months of life, suppression-burst pattern on EEG, and grave prognosis. The boundary between the two syndromes unfortunately is not always clear,[18,33,40] and the classification is sometimes questionable even among the published cases.[4] Once tonic seizures occur in patients with EME, the differential diagnosis becomes even more difficult, perhaps implying common pathogenetic mechanisms as discussed earlier. Perhaps the term *neonatal epileptic encephalopathy* is more appropriate to encompass both conditions.

The critical difference between EME and EIEE appears to be in the presumed etiologies and the prevailing seizure type at the onset of the clinical seizures. EIEE typically manifests with tonic seizures at onset, whereas EME is most associated with myoclonic seizures. However, erratic myoclonus may be absent even in the most frequently identified cause of EME: glycine encephalopathy (J. Aicardi, personal communication). In its classification, the International League Against Epilepsy emphasizes the symptomatic nature and nonspecific etiology of both syndromes.[16] The majority of cases of EIEE are associated with structural brain anomalies, whereas the majority of EME cases are associated with metabolic disorders.[4,9,19,26,38,40] There is an overlap, however, and often the underlying etiology remains unclear.[42] The observation that under some circumstances multiple etiologies can produce either syndrome suggests that EIEE and EME may represent a continuum.

The initial differentiation of EIEE and EME based on the presence or absence of myoclonic or tonic seizures at onset may better indicate the stage of the progression of the brainstem pathology/dysfunction than a phenotype specific to one syndrome or another. A major differentiating point is the absence of myoclonias in EIEE. A common unifying feature is the eventual appearance of tonic seizures. As the brainstem disease burden approaches the threshold for tonic seizures, EME patients become less distinguishable clinically from patients with EIEE.

The EEG pattern and persistence of "burst-suppression" distinguishes EME and EIEE from other conditions that produce neonatal burst-suppression, such as hypoxic–ischemic encephalopathy and neonatal convulsions.

Treatment

With the exception of cases with pyridoxine dependency, there is no effective management for EME. Neither the conventional antiepileptic medications nor adrenocorticotropic hormone or corticosteroids alter the progressive nature of the disease and improve the poor outcome. Treatments directed at correcting the underlying metabolic deficit may improve the outcome. A trial of treatment with pyridoxine is justified in all cases with EME because it is still the only efficient treatment for the small subgroup of patients in whom it is effective.

Summary and Conclusions

EME is a malignant epileptic syndrome with typical onset during the neonatal period. The main seizure type at onset is erratic myoclonus, but as the disease progresses, other seizure types develop, including tonic seizures at 3 to 4 months of age. The EEG is characterized by a suppression-burst pattern and often evolves into hypsarrhythmia. The etiology of EME is diverse: Congenital errors of metabolism are the most frequently identified, followed by cryptogenic and cases with structural brain malformations. Except in rare cases responsive to treatment with pyridoxine, control of seizures is poor. Prognosis is grave, with high early mortality and severe neurologic handicap in survivors.

It is possible that EME presents a continuum with EIEE and the phenotypic differences reflect the severity of the underlying pathologic process. In the future, a systematic approach including comprehensive evaluations (morphometric and functional imaging studies, neurophysiologic evaluations with multimodal evoked potentials, and possibly CSF neurotransmitter studies) performed during different stages of the diseases and especially during periods of clinical transitions could help to provide a better understanding of the underlying pathophysiologic processes. Shifting the goal of the diagnostic evaluation from detecting a specific abnormality to detecting a progressive pathologic change might permit the identification of more subtle changes before they become significant and allow the introduction of new treatments.

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Chapter 225

Ohtahara Syndrome

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Introduction

Epileptic or chronic seizures occurring during the neonatal and early infantile periods are rarely observed compared with those occurring during other stages of childhood, because of the morphologic and biochemical immaturity of the central nervous system. Only a few epileptic syndromes begin in these periods, most of them refractory and catastrophic epilepsies.[3,7,21] Of these, this chapter describes the Ohtahara syndrome (OS): Early infantile epileptic encephalopathy with suppression-burst.

This syndrome, which has not only characteristic clinical and electroencephalographic (EEG) features, but also a distinct age dependence and evolution of epileptic syndromes with age, is considered the youngest form of the age-dependent epileptic encephalopathy.

Historical Perspective

In 1976, Ohtahara et al.[27] first described OS as an independent epileptic syndrome. It is the earliest form of the age-dependent epileptic encephalopathies, which include OS, West syndrome, and Lennox-Gastaut syndrome. Although each of these is an independent clinicoelectrical entity with individual clinical and EEG features, they have the following characteristics in common: (a) predominance in a certain age group (age dependence); (b) a peculiar type of frequent, minor, generalized seizure; (c) a severe and continuous epileptic EEG abnormality; (d) heterogeneous etiology; (e) frequent association with a mental defect; and (f) poor response to treatment and grave prognosis.[25,26,29] Furthermore, these syndromes often evolve with age. During their clinical course, a considerable number of cases of OS evolve into West syndrome and then from West syndrome into Lennox-Gastaut syndrome.[25,28,49] Because of their common characteristics and their transitions with age, Ohtahara applied the inclusive term *age-dependent epileptic encephalopathy* to this group of three syndromes.[25,26,29]

We adopt the term "epileptic encephalopathy" instead of "epilepsy" based on the following characteristics: (a) the presence of serious underlying disorders, (b) extremely frequent seizures, (c) continuously appearing marked epileptic EEG abnormality, and (d) mental stagnation or deterioration often manifesting with the persistence of seizures.

Although the etiologies of these syndromes are heterogeneous, each syndrome occurs predominantly within a certain age range and is associated with specific clinical and EEG traits. Because the clinical and electrical characteristics of each syndrome are based on a diverse group of etiologies, age should be considered the common factor underlying the manifestation of specific features. Thus, these syndromes may represent an age-specific epileptic reaction to various nonspecific exogenous insults to the brain occurring at an age-specific developmental stage.

Definitions

Ohtahara syndrome is characterized by very early onset, within a few months of birth, frequent tonic spasms, and a suppression-burst pattern in the EEG.[27,29,31,32] This periodic EEG pattern is consistently observed in both awake and sleep states. The main seizure pattern is tonic spasms but not myoclonic seizures. Tonic spasms appear often in clusters but sometimes sporadically. Partial motor seizures may occur. Although the etiologies are heterogeneous, neuroimaging usually discloses gross structural abnormalities due to mainly prenatal cerebral dysgenesis. The prognosis is serious: For example, early death or marked psychomotor retardation and intractable seizures with frequent evolution to West syndrome and still further to Lennox-Gastaut syndrome in some cases[28,29,49] or to severe epilepsy with multiple independent spike foci.[51] The Commission on Classification and Terminology of the International League Against Epilepsy (ILAE)[7] placed this syndrome among "symptomatic generalized epilepsies and syndromes with nonspecific etiology," and the proposed diagnostic scheme of the ILAE[10] categorized it as "epileptic encephalopathy."

Epidemiology

Several dozen cases of OS have been reported, but occurrence has been rare in comparison with West syndrome (WS) and Lennox-Gastaut syndrome. An epidemiologic study of childhood epilepsy carried out in Okayama Prefecture, Japan, detected 1 case of OS (0.04%) among 2,378 epileptic children <10 years of age.[36] The prevalence of this syndrome was much lower than that of West syndrome (40 cases, or 1.68%). Similarly, Kramer et al.[18] described 1 case of OS (0.2%) and 40 cases of WS (9.1%) in a cohort of 440 consecutive children <15 years of age with epilepsy in Tel Aviv, Israel. Thus, the relative prevalence of OS to WS may be 1:40 or less. On the other hand, in a study of 75 infants with epilepsy of neonatal onset who were monitored intensively, Watanabe et al. observed 8 cases (10.7%) of OS and no case of WS.[46]

No obvious racial differences have been observed in the respective incidences. No significant gender difference was confirmed, but male slightly exceeded female cases by 9:7 in our series.[50]

Etiology and Basic Mechanisms

Although the etiologies of OS are heterogeneous, the majority are static gross brain pathologies such as cerebral dysgenesis, although some are cryptogenic. Development of neuroimaging techniques, particularly magnetic resonance imaging (MRI), has disclosed that various types of cerebral dysgenesis are the greatest underlying pathologies of this syndrome.[40,50] It is also important that asymmetry is often

observed in structural abnormalities of the brain. Porencephaly, Aicardi syndrome,[34,50] cerebral dysgenesis, olivary-dentate dysplasia,[13,39,44] hemimegalencephaly,[12,33,50] linear sebaceous nevus,[15] Leigh encephalopathy,[42] and subacute diffuse encephalopathy[29] have been reported.

Of 16 cases in our series, 5 (31.3%) were cryptogenic.[50] With regard to genetic factors, no sibling case was reported except for Leigh encephalopathy.

With regard to metabolic disorders, although they are very rare, Williams et al.[14,48] first reported a case with cytochrome oxidase deficiency. This case, however, had only transient reversible deficiency that may have caused impaired neuronal migration or demyelination due to energy depletion during a critical period. Miller et al.[20] reported the absence of γ-aminobutyric acid (GABA) in cerebrospinal fluid (CSF) in a case with diffuse cerebral migration disorder. Fusco et al.[11] described one case each with pyridoxine dependency and carnitine palmitoyltransferase deficiency.

Fundamentally, the age factor should be emphasized, on the basis of polyetiology.

The pathophysiologic mechanisms underlying suppression-bursts are not fully elucidated. Aso et al.[4] found that the suppression-burst pattern correlated with multifocal severe brain damage, although no one structure was consistently affected. Any of these anomalies can prevent the establishment of normal neuronal connectivity necessary for the EEG ontogeny. This hypothesis is corroborated by the observation that a normal EEG pattern at any age can revert to a suppression-burst pattern after catastrophic events that cause laminal necrosis of the cortex, as in severe hypoxic-ischemic encephalopathy.[47] Similar but less readily identifiable cortical and subcortical abnormalities must be invoked to explain cryptogenic cases of OS and those with olivary-dentate dysplasia. Spreafico et al.[41] suggested that in OS and early myoclonic encephalopathy (EME) the suppression-burst (SB) pattern primarily reflects a diffuse structural or junctional disturbance of gray matter connectivity.

Its similarity to tracé alternant in neonatal quiet sleep and to burst-suppression in brain-damaged neonates may suggest an excessive subcortical neuronal discharge modified by subcorticocortical dysregulation or disconnection and by cortical lesions.[27,29] Trinka et al.[44] also considered that in olivary dentate dysplasia or focal cortical dysplasia, mild additional supratentorial/cortical anomalies or infratentorial anomalies contribute to the SB pattern in OS.

The markedly asymmetric and sometimes unilateral SB pattern reported in hemimegalencephaly further suggests the indispensable role of brain lesions at both the subcortical and cortical levels in generating the SB pattern.[23,33,35]

Two types of mechanisms have been suggested in the pathogenesis of SB, as mentioned later.

Clinical Presentation

The onset of the initial seizures or tonic spasms is early, within the first 3 months after birth, mainly within 1 month. Du Plessis et al.[9] extended the earliest age of onset into the intrauterine period. Clarke et al.[6] also suspected an intrauterine onset in four of their eight cryptogenic cases based on observations of violent fetal movement.

The main seizure type is tonic spasms with or without clustering. These occur not only during the waking state, but also during sleep in most cases. In 6 of our 16 patients (37.5%), hemiconvulsions, tonic seizures, or clonic seizures preceded one to several weeks before the onset of tonic spasms.[50] Myoclonic seizures are rare.[29,50]

An evolutionary pattern is characteristic: From OS to West syndrome in the middle period of infancy (between 3 and 6 months of age in many cases) and from West syndrome to Lennox-Gastaut syndrome in early childhood.[28,29,30,45,50]

Diagnostic Evaluation

Electroencephalographic Findings

The most characteristic feature of EEG in OS is the suppression-burst pattern, which is consistently seen during both awake and sleep states (Fig. 1). The suppression-burst pattern is characterized by high-voltage bursts alternating with nearly flat periods at an approximately regular rate. Bursts last 1 to 3 seconds and comprise high-voltage (150–350 μV) slow waves intermixed with spikes. Duration of the suppression phase is 3 to 5 seconds. The interval measured from beginning to beginning of bursts ranges from 5 to 10 seconds. The suppression-burst pattern shows some asymmetry in approximately two thirds of cases, presumably reflecting the underlying brain lesions. There is no awake/sleep differentiation. The suppression-burst pattern evolves to hypsarrhythmia in many cases, and then from hypsarrhythmia to diffuse slow spike-waves in some cases.[28,30]

The EEG pattern of OS needs to be differentiated from (a) the periodic type of hypsarrhythmia, in which periodicity becomes remarkable in the sleeping state and sleep spindles may be observed in the interburst phase, and (b) the burst-suppression pattern in severely abnormal neonates, which is characterized by a longer depressed phase with irregular and atypical appearance of bursts including fewer spike components.

The ictal EEG during tonic spasms shows desynchronization with or without fast activity. Tonic spasms in OS often appear concomitant with burst, but the SB pattern often disappears during a cluster of spasms. Partial seizures show focal repetitive or rhythmic discharges, which are often followed by a series of tonic spasms.

Neuroimaging and Other Laboratory Examinations

Computed tomography (CT) and MRI reveal structural abnormalities that are often asymmetric, even at an early stage of the disorder. Single-photon emission computed tomography and positron emission tomography often show corresponding abnormalities.

No abnormalities are found in serum and urine amino acids, cerebrospinal fluid, bone marrow, enzyme assay of white blood cells, serum pyruvate and lactate, ammonia, liver function, serum immunoglobulin, or TORCH (antibodies of *Toxoplasma*, rubella virus, cytomegalovirus, and herpes simplex virus).[29]

With evoked potentials, abnormalities are often found in auditory brainstem responses and visual responses in OS.[29]

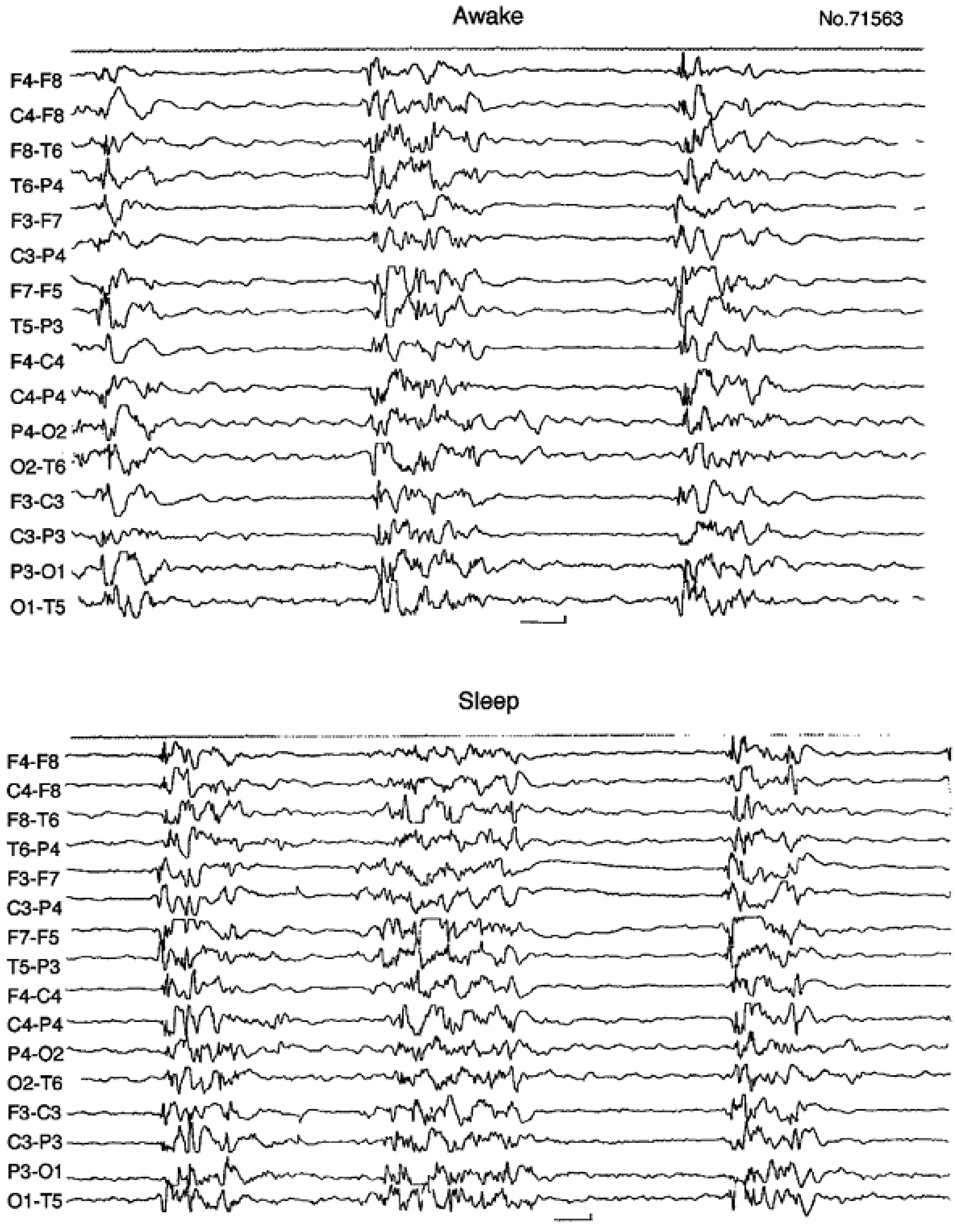
Awake
No.71563
F4-F8
C4-F8
F8-T6
T6-P4
F3-F7
C3-P4
F7-F5
T5-P3
F4-C4
C4-P4
P4-O2
O2-T6
F3-C3
C3-P3
P3-O1
O1-T5
Sleep
F4-F8
C4-F8
F8-T6
T6-P4
F3-F7
C3-P4
F7-F5
T5-P3
F4-C4
C4-P4
P4-O2
O2-T6
F3-C3
C3-P3
P3-O1
O1-T5

FIGURE 1. Interictal electroenceph-alogram. Suppression-burst pattern in a 2-month-old boy with Ohtahara syndrome. **Top:** Awake. **Bottom:** Natural sleep. The horizontal calibration mark denotes 1 second, the vertical one, 50 μV.

Differential Diagnosis

Ohtahara Syndrome and West Syndrome

The age of onset is different in the two syndromes. It is between the neonatal and early infantile periods in OS and between middle and late infancy in West syndrome (see Chapter 229). Lombroso[19] claimed that OS might be regarded as an early form of West syndrome. There is a close relationship between OS and West syndrome, and in a considerable number of cases OS evolves to West syndrome. However, OS is certainly a different epileptic syndrome than West syndrome. Although

the main seizure type is tonic spasms in both syndromes, tonic spasms in OS appear during both awake and sleep states, and also with and without clustering in many cases. Partial seizures are also more often observed in some OS cases. Most cases with OS show severe cortical pathology, often with asymmetric lesions displayed on neuroimaging.

With regard to EEG findings, the suppression-burst pattern is seen in OS, in contrast to hypsarrhythmia in West syndrome. The suppression-burst pattern differs from the periodic type of hypsarrhythmia, in which periodicity becomes distinct only during sleep. Seizures are more intractable in OS, and adrenocorticotropic hormone (ACTH) is poorly effective in most cases. Prognosis is far less favorable in OS than in West syndrome.

Ohtahara Syndrome and Early Myoclonic Encephalopathy

Because OS and EME[1,2,3,8] have both clinical and electrical characteristics in common, such as onset during the neonatal and early infantile periods and the EEG suppression-burst pattern, differential diagnosis of these syndromes warrants discussion (see also Chapter 224).[31,32]

Clinical Features

Tonic spasms are the main seizure type in OS, whereas EME is characterized by myoclonia, especially erratic myoclonia, and very frequent partial seizures. In contrast, episodes of myoclonia are rarely seen in OS.

Electroencephalographic Findings

The suppression-burst pattern is a common feature of both syndromes, although its form and the mode of its appearance and its period of persistence differ considerably between the two. With regard to mode of appearance, the suppression-burst pattern in OS appears consistently and unchangingly during both the awake and sleep states; in EME, the suppression-burst pattern is enhanced during sleep and often is not apparent in the awake state.[32] Regarding the period of its persistence, the suppression-burst pattern appears at the onset of disease and

disappears within the first 6 months of life in OS, whereas in EME, the suppression-burst pattern appears at 1 to 5 months of age in some cases and characteristically persists for a prolonged period.[22,31,32]

Evolution During the Clinical Course

Evolution of the EEG pattern during the clinical course is a characteristic feature of OS: From the suppression-burst pattern to hypsarrhythmia in many cases, and then from hypsarrhythmia to diffuse slow spike-waves in some cases.[29,31,32,45,50] In contrast, the suppression-burst pattern in EME reappears and persists for a prolonged period after a transient appearance of atypical hypsarrhythmia that may be observed during the clinical course in some cases.[22,32] Thus, the patterns of EEG evolution with age differ considerably between the two syndromes.

As already mentioned, considering the evolution of disorder type with age and the mode of appearance in relation to the wake-and-sleep cycle, the existence of two types of SB, those observed in OS and EME, is a very interesting and important finding, one that might contribute to the understanding of the mechanism of SB.

With regard to the evolution of epileptic syndromes, OS shows a specific pattern of evolution into other forms of the age-dependent epileptic encephalopathies, whereas EME has no such age-related evolution. Furthermore, it is also significant that no transition is observed between OS and EME.

Etiology

In OS, obvious brain lesions, such as malformations, are often seen, and CT and MRI abnormalities are usually detected even at an early stage. No familial cases of OS have been reported. In contrast, the frequent occurrence of familial cases of EME suggests some congenital metabolic disorders as the etiology.[3,40,43]

These findings strongly suggest that OS and EME are separate clinicoelectrical entities. Schlumberger et al.[40] found definite clinical and symptomatologic differences between these two syndromes and no overlap. However, there are cases that are truly difficult to separate because they have cerebral malformation and metabolic/genetic disorders.

Treatment and Outcome

Seizures are intractable. Synthetic ACTH exerted a limited efficacy in some cases.[50] Phenobarbital,[37] pyridoxal phosphate or vitamin B6, valproate, benzodiazepines, and a ketogenic diet were poorly effective in general.

There are recent reports of cases responsive to zoni- samide[24,50] and vigabatrin.[5] Successful resection has been reported in patients with focal cortical dysplasia and has been associated with relatively improved neurologic development after surgery.[16,17,38]

Although they are intractable, seizures come under control by school age in approximately half of the patients. Prognosis for psychomotor development remains very poor; all survivors have severe disabilities, both mental and physical. Many such patients died, especially in the early stage of the disease.[50] One fourth of our patients died before 2 years of age.

Long-Term Prognosis

In 8 survivors of 16 OS cases in our series, the age at follow-up ranged from 5 years and 0 months to 28 years and 0 months.[50] All but 2 were >10 years of age. All survivors had severe mental retardation. Six were bedridden with quadriplegia; only 2, with hemiplegia, were ambulant. Seizures persisted in 2 of the survivors: Tonic spasms in 1 and focal motor seizures in the other.

With EEG follow-up, only 2 of 8 survivors were spike-free. Focal spikes were detected in 6 others: Multiple independent spike foci were found in 4 and other cortical foci in 2; 3 of them showed diffuse generalization.

Summary and Conclusions

OS is a peculiar epileptic syndrome with strong age dependence in the neonatal period and very early infancy, and it is the earliest form of the age-dependent epileptic encephalopathies. In describing the clinicoelectrical characteristics of this syndrome and its evolution with age, we stressed the importance of taking a developmental approach in epilepsy research. This approach is very effective for establishing new syndromes and differentiating them from related disorders/syndromes as well as clarifying prognoses. In discussion differential diagnosis focused particular attention on early myoclonic encephalopathy.

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Chapter 226

Overview: Syndromes of Infancy and Early Childhood

Jean Aicardi

Introduction

The incidence of epilepsy is very high in the first years of life, reaching a peak in the first year and remaining at high levels throughout infancy and early childhood. The epilepsies with onset in infancy, although a heterogeneous group, share some special characteristics, and this applies up to the age of approximately 3 to 4 years. The following chapters, therefore, are concerned with all epilepsies that begin before the age of 4 years.

The special features of the epilepsies of early onset are the result of several etiologic, anatomic, and neurophysiologic factors. One major factor is the immaturity of the infant's brain. At this period, dendritic development is actively proceeding, and myelin formation and deposition are far from complete, which may be responsible for imperfect synchronization of the hemispheres. Brain circuitry is different from that in later life. In particular, the number of synapses increases rapidly during the first years of life and far exceeds the ultimate number.[16] A high proportion of these synapses is eliminated before 8 to 10 years of age, and this pruning process depends on activity and, therefore, on environmental stimuli. There is evidence that functional synapses become stabilized, whereas unused ones disappear; this is probably one of the mechanisms of brain plasticity. Development and maturation of the brain are associated with changes in neurotransmitters and receptors and their effects. For example, some γ-aminobutyric acid (GABA) receptors have been shown to be excitatory during fetal life and the early postnatal period,[19] and glutamate receptors may not be sufficient to produce brain damage through activation of the glutamate cascade. Such changes are likely profoundly to modify the excitability of the infant's brain. The conjunction of these factors undoubtedly accounts for some of the features of early seizures, such as the generally imperfect organization of seizure discharges, the rarity of full-fledged tonic–clonic attacks, and the higher frequency of unilateral or predominantly unilateral seizures in response to diffuse systemic disturbances such as fever or metabolic imbalances. However, the infant's brain is capable of occasionally producing 3-Hz spike-wave discharges and massive myoclonias and even, although rarely, absence attacks.[2] Seizures of focal origin are the most common seizures in this age range. They may be associated with focal clinical manifestations and electroencephalogram (EEG) discharges of several forms with different degrees of propagation. Many focal seizures are associated with extensive brain lesions, indicating that the infant brain may be unable to organize complete seizure sequences as observed at a later age. The atypical clinical expression of many seizures in the infantile range probably results from the neurophysiologic factors already mentioned, from the late maturation of some areas of the brain such as the frontal lobe, as well as from the inability of infants to experience or express some of the more complex features of seizures and the difficulty or impossibility for observers to detect such symptoms as loss or impairment of consciousness.[20] Conversely, focal brain lesions or abnormalities may be associated with diffuse clinical symptoms and with extensive EEG paroxysms, one common type being infantile spasms with the so-called hypsarrhytmic pattern of high-amplitude disorganized tracing, suggesting that focal origin of seizures may be expressed in generalized attacks and is probably even more common in young children than previously thought.[13]

The etiology of early-onset epilepsies is also responsible for many of their clinical and evolutive characteristics. As in older patients, the two main factors are a propensity to fitting (mostly genetically determined) and the presence of brain lesions; however, both have age-specific peculiarities.

The *epileptogenic lesions* are often extensive, even when they give rise to partial seizures. Some are destructive and may be related to mechanical or hypoxic-ischemic injuries. A majority, however, are of developmental origin, the most common being abnormalities of cortical development. These include heterotopias, diffuse pachygyria-lissencephaly, hemimegalencephaly, and focal cortical dysplasias, the latter being the most common cause of epilepsy at this age.[15] It is of interest that the nature, location, and extent of organic brain damage—and not only the age of the child—are responsible, at least in part, for the ictal symptomatology. Thus, tuberous sclerosis often determines infantile spasms, and Aicardi syndrome determines a mixture of focal seizures and spasms.

The propensity to seizures of infants is mainly expressed by febrile convulsions (see Chapter 227) and less often in the form of other benign epilepsy syndromes. Febrile convulsions (FCs) are by far the most common frequent manifestation of a genetic predisposition to seizures. Although febrile seizures are not termed *epilepsy* because they do not fulfill the definition of a chronic unprovoked condition but are classified as *occasional seizures* or *situation-related seizures*,[1,14] they have undoubted physiopathologic and genetic relationships with the epilepsies and may be regarded as a benign expression of the main basic phenomenon. This genetic relationship is best illustrated by the occurrence of afebrile convulsions following FC, which, although rare, are much more common than in the general population and in rare instances by the syndrome of generalized epilepsy with febrile seizures plus (GEFS+).

The importance of age in the expression of infantile epilepsy is clearly shown by the age dependence of several types of seizures. West syndrome rarely begins after 1 year of age and has a well-defined modal age of onset at 5 to 6 months (Chapter 229). Several types of seizures may occur in succession in the same patient with an unchanged pathologic basis; for example, Ohtahara syndrome can precede infantile spasms, followed by the development of the Lennox-Gastaut syndrome; focal or unilateral seizures may precede the development of West or Lennox-Gastaut syndrome. Such changes may reflect not only the maturation of the brain, but perhaps also the plasticity of the central nervous system. Some of the changes could result from the capacity for reorganization of the infant's brain following an insult or even a prolonged dysfunction without any lesion. It is conceivable that unusual regulation and development of receptors or preferential stabilization of certain synapses as a result of prolonged abnormal epileptic activity in certain pathways may lead to altered connectivity, with corresponding clinical changes. Such a mechanism could account for some of the characteristics of epileptic deterioration, such as its spontaneous arrest after disappearance or improvement of epileptic activity and incomplete recovery in spite of apparent cure of epilepsy. Deterioration associated with, and possibly resulting from, intense epileptic activity, whether marked by seizures or only by EEG alterations, is a remarkable feature of some early epilepsies,[3,5,11] sometimes termed *epileptic encephalopathies* or *catastrophic epilepsies* (see Chapter 230). Although epileptic deterioration is not limited to young children, as shown by its occurrence in such syndromes as the Landau-Kleffner syndrome or that of continuous spike-waves of slow sleep,[5] it is clearly prominent in this age bracket (see Chapter 242). Other factors possibly responsible for deterioration include evolution of the underlying lesions, frequency and consequences of seizures, psychological problems, side effects of drugs, and other environmental influences.

Finally, epilepsy in infants is often associated with other neurologic problems, such as cerebral palsy or mental retardation, and seizures not only add to children's difficulties, but also multiply the total impairment so that attempts at control are particularly important.

The seizures of early-onset epilepsies often differ from those in older patients (see Chapter 56). Some types of seizures observed in later life are sometimes seen in children <3 years of age. These include generalized—especially myoclonic—seizures that may have their onset from a few months of age.

Tonic–clonic seizures tend to be less well organized and less symmetric and to feature a longer tonic phase than in older children. Atypical absences often feature changes in tone, and their EEG manifestations (slow spike-wave complexes or fast rhythms) are completely different from those of typical absences, which are very rare in the first 2 to 3 years.[3] Partial seizures are probably more common, but they often have unusual clinical features with predominance of head deviation and unilateral or asymmetric tonic phenomena over clonic jerks.[12] More precise classification of partial seizures is difficult because of the difficulties of assessing awareness and the limited register of motor manifestations, even though some investigators have reported on "complex" focal seizures in infants.[26,27] Some types of seizures are particularly characteristic of young children, although none is completely restricted to them. These include infantile spasms, tonic and atonic seizures, atypical absences, and episodes of nonconvulsive status epilepticus often with myotonic manifestations. Such seizures are major components of the catastrophic epilepsies or epileptic encephalopathies.[3,11] Other seizures have a very limited clinical expression, such as simple arrest of activity, subtle changes in tone (hypertonia or hypotonia), simple staring, pallor, perioral cyanosis, blinking of eyelids, or isolated eye deviation.[22] Such atypical attacks often evolve into more characteristic partial seizures when the children grow older.

The frequency of the various types of seizures is not well known. In two large series of epilepsy in infants <1 year of age,[7,8] infantile spasms were the most frequent type (230 of 437 and 183 of 387, respectively), followed by other generalized seizures (99 and 87, respectively) and partial seizures (57 and 51, respectively). In a large group of 504 children <3 years old, Dalla Bernardina et al.[10] ascribed 163 patients to the group of the epileptic encephalopathies, 189 to the partial epilepsies, and 80 to the generalized epilepsies (34 with myoclonic seizures). These figures were drawn from specialized referral centers, so the proportion of severe seizures is likely to be less in the general population.

As in other age groups, epilepsy syndromes, that is, clusters of signs and symptoms occurring customarily together,[11,14] are recognizable among infantile epilepsies. However, syndromic classification is more difficult than in older patients because of the uncharacteristic features of many cases and the fact that the clinical and EEG manifestations are rapidly changing in many cases, so that several syndromes may evolve in succession in the same child. For example, partial seizures may precede infantile spasms, and these frequently herald the development of the Lennox-Gastaut syndrome. The most common epilepsy syndromes in infants are described in the following chapters. The best characterized are West syndrome (Chapter 229), severe myoclonic epilepsy (Chapter 230), and the Lennox-Gastaut syndrome (Chapter 241) (although its onset is often slightly later in life). These syndromes usually have a poor prognosis. West syndrome and the Lennox-Gastaut syndrome are of lesional origin in most cases, and abnormalities of cortical development are a major etiologic factor, especially in the case of infantile spasms.[13] Despite their generalized clinical and EEG features, seizures in these two syndromes are probably due in a significant proportion of cases to localized lesions, some of which may be amenable to surgical treatment. Severe myoclonic epilepsy (renamed Dravet syndrome because myoclonic seizures may be absent in some cases) is a clinically well defined syndrome with onset in the first year of life with febrile convulsions, often prolonged and frequently recurrent, followed in the second or third year by myoclonic attacks and multiple seizure types. It is due in most cases to a new sodium channelopathy.[21] Other tentative syndromes have been proposed. One is the syndrome of partial migrating infantile seizures,[9] whose specificity has been debated.[17]

More-benign syndromes of infantile seizures have been recognized more recently, indicating that the outcome of infantile seizures is not always poor and this has to be taken into account when giving a prognosis. Their frequency is much lower than that of the more severe types but may be greater than shown by statistics coming from referral centers and may be higher in some Asian countries[18] (Chapters 236 and 238). Clinical manifestations are brief partial seizures occurring in clusters in the first 2 years of life and disappearing before the age of 2 years. In some cases, a benign movement disorder may supervene after several years.[23] Benign partial infantile seizures are often genetically determined.[24,25] Some have been mapped to different loci on chromosomes 16, and the mutant gene has been isolated in one family.[6] Nongenetic benign syndromes have also been described.[12]

Summary and Conclusions

Infantile epilepsies have distinctive clinical characteristics due in large part to neurophysiologic features related to age. Their treatment is often unsatisfactory as a result of the lesional nature of many cases, the extent of responsible brain damage, and the consequences of epilepsy for cognitive and behavioral development. The respective indications of conventional and new drug treatment and of agents such as adrenotropic hormone or steroids are not yet clear. Surgical treatment has been shown to be possible and to give results on seizures similar to those obtained in older patients. However, its effects on neurodevelopment are yet to be assessed.

The important point is that experience with the catastrophic epilepsies of this age shows that epilepsy is more than simply having seizures and may have pervasive effects on development, even when paroxysmal manifestations are absent or mild.

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Chapter 227

Benign Familial and Nonfamilial Seizures

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Introduction

Benign familial and nonfamilial forms of infantile seizure and partial epilepsies of infancy are significant categories of pediatric epilepsies. In the past, seizures with onset during the first months of life were considered to have a bad prognosis and a symptomatic etiology. Since the first description by Fukuyama, the existence of infantile seizures with a benign evolution has been defined and accepted.

The international classification of epilepsies and epileptic syndromes[17] includes benign infantile seizures, which are divided into familial and nonfamilial forms. In recent years, variants of these two forms and similar entities have been described.

Historical Perspective

In 1963, Fukuyama was the first to report cases with onset within the first 2 years of life that were characterized by generalized convulsions, absence of etiologic factors, and benign outcome.[18] This type of infantile convulsion was the subject of many subsequent studies, but only after 20 years were the true clinical entities clarified. Reports have specified the localization and semiology of seizures, which have been defined as being of partial type[69,71,72] and in terms of the presence or absence of familial occurrence.[6,7,8]

Vigevano and coworkers focused on cases exhibiting a family history of convulsions with benign outcome during infancy and autosomal-dominant inheritance, and they proposed the term *benign infantile familial convulsions* (BIFC).[67] Later, other such cases were reported in many different parts of the world,[16,21,35,40,45] thus confirming them as new epileptic syndromes. When these entities were included in the list of epileptic syndromes by the International League Against Epilepsy (ILAE) Task Force on Classification and Terminology, it was suggested that the term “seizure” should be used rather than the term “convulsion.”[17] Just like benign seizures with neonatal onset, benign infantile seizures are divided into familial and nonfamilial forms.[17] These two forms, however, can have overlapping features.[39] Genetic studies of familial forms led to the identification of a chromosome marker on chromosomes 19,[23] 16,[11] and 2.[42]

An association between *benign familial infantile seizures* (BFIS) and variably expressed paroxysmal choreoathetosis was reported in 1997 by Szepetowski et al.[61] A specific marker on chromosome 16 has been identified in this familial variant, called *infantile convulsions and choreoathetosis* (ICCA).

Heron et al.[25] in 2002 and later Berkovic et al.[3] proposed a new entity and coined the term *benign familial neonatal-infantile seizures* (BFNIS) to describe families with onset at an intermediate age between neonatal and infantile forms.

Considering that convulsive manifestations are limited to a short period of time, some authors hypothesized the existence of particular etiologic factors in some sporadic cases such as cases of benign infantile convulsions associated with episodes of diarrhea caused by rotavirus infections.[12,28,30] Finally, Capovilla et al. described a peculiar form of benign epilepsy occurring within the second year of life and with a typical sleep electroencephalographic (EEG) pattern.[5,6]

Definition

Benign partial seizures in infancy are a group of diseases characterized by onset during the first 2 years in otherwise normal children. They could be familial, with a characteristic autosomal-dominant trait of inheritance and a typical onset around 6 months, or nonfamilial, which usually occur later. Seizures are partial with or without secondarily generalization and are typically grouped in clusters of many per day. In most cases, interictal EEGs are normal, except for the midline spikes during slow sleep described by Capovilla, but this form of epilepsy is under discussion. Outcome is always excellent, with a normal psychomotor development after seizures.

Epidemiology

Several cases with this syndrome have been described from all over the world. Data on prevalence and incidence are not available. In a series described by Caraballo et al.,[9] benign infantile seizures were listed as the third-most-common type of epilepsy in the first 2 years of life.

Etiology and Basic Mechanisms

Autosomal-dominant transmission is evident in BFIS. Due to the close similarity to *benign familial neonatal seizures* (BFNS), researchers first tried to find the chromosome markers described in this latter syndrome.[37,55,57] In 1994, Malafosse et al.[43] demonstrated that BFIS is not an allelic form of BFNS, excluding the marker on chromosome 20.

In 1997, linkage analysis was carried out in five Italian BFIS families, and a locus was mapped on chromosome 19q12–13.1 between markers D19S49 and D19245.[23] Gennaro et al.[20] later conducted a linkage analysis of seven families of Italian origin and demonstrated the presence of linkage to chromosome 19q in a single family, suggesting genetic heterogeneity within the examined families. Studies of familial cases with ICCA are particularly interesting. Szepetowski et al.[61] demonstrated linkage to the pericentromeric region of chromosome 16 in the families with this syndrome. This finding was then confirmed by Lee et al.[36] in a family of Chinese origin. In 2001, Caraballo et al.[11] found linkage on chromosome 16p12-q12, the same region as

for ICCA, in seven families with only benign familial infantile seizures. There was a previous report describing a large family affected by paroxysmal kinesigenic dyskinesia without infantile convulsions with linkage to the ICCA region.[33] Therefore, Caraballo et al. hypothesized that chromosome 16p12-q12 is a major genetic locus underlying both benign familial infantile seizures and paroxysmal dyskinesias.[11] Weber reported similar results in 14 families with benign familial infantile seizures without paroxysmal choreoathetosis.[73]

In 2001, Malacarne et al.[42] mapped a novel locus to chromosome 2q24 in eight Italian families, thus demonstrating a genetic heterogeneity, as in other autosomal-dominant idiopathic epilepsies.

In cases described as having *benign familial neonatal-infantile seizures*—an intermediate form between BFIS and benign familial neonatal seizures—a missense mutation in the *SCN2A* gene has been found, leading to the hypothesis of the existence of a third form,[20] although recently a similar mutation of the same gene has been described in a family with clinical features typical of BFIS.[58]

A particular etiologic factor has been recognized in some infantile seizures associated with mild gastroenteritis, with positivity to the rotavirus antigen. In the other nonfamilial forms, no clear etiologic factors have been described.

Clinical Presentation

Benign Nonfamilial Infantile Seizures

Watanabe et al.[3] described a series of infants having focal seizures with benign evolution. The majority of the cases were not familial. They described nine infants with benign complex partial seizures as diagnosed by simultaneous electroencephalogram and video recording. At ages of 3 to 10 months, most of these infants presented with clusters of seizures consisting of motion arrest, decreased responsiveness, staring, or blank eyes, mostly with simple automatisms and mild convulsive movements associated with focal paroxysmal discharges, most frequently in the temporal area. Carbamazepine or phenobarbital was used to control the seizures, and all patients were seizure free for >3 years. All patients showed normal interictal electroencephalogram and psychomotor develop-ment.

Later, the same authors described the cases of 7 infants with benign idiopathic partial epilepsy presenting with apparently generalized tonic–clonic seizures (GTCs), which turned out to be partial seizures evolving to secondarily generalized seizures (SGS).[69] In subsequent years, other reports confirmed this syndrome, for example, Berger et al.[2] and Capovilla et al.,[7] who reported the cases of 12 children with complex partial seizures having similar electroclinical features.

The term *benign partial epilepsy in infancy* (BPEI) was proposed to combine the two previously described entities.[2,69] Clinical characteristics of benign partial epilepsy in infancy, which is now classified as benign nonfamilial infantile seizures, are summarized in Table 1.

Table 1 Clinical characteristics of benign nonfamilial infantile seizure, which comprises benign partial epilepsy of infancy with complex partial seizures and benign partial epilepsy with secondarily generalized seizures in infancy

Benign Partial Epilepsy of Infancy With Complex Partial Seizures	Benign Partial Epilepsy With Secondarily Generalized Seizures in Infancy
• Normal development before onset	• Normal development before onset
• No underlying disorders or neurologic abnormalities	• No underlying disorders or neurologic abnormalities
• Onset mostly within the first year of life	• Onset mostly within the first year of life (3–20 mo)
• Complex partial seizures, often occurring in clusters	• Partial seizures (stare, blank eyes, or crying)
• Normal interictal EEG	• With secondary generalization, often occurring in clusters

• Ictal EEG most often showing temporal focus	• Normal interictal EEG
• Excellent response to treatment	• Ictal EEG most often showing a centroparietal origin
• Normal developmental outcome	• Excellent response to treatment • Normal developmental outcome

EEG, electroencephalogram.

Benign Familial Infantile Seizures

Vigevano and coworkers described cases with benign epilepsy in infancy and a family history of convulsions.[69] All of them had a benign outcome and autosomal-dominant inheritance, and the authors suggested the term *benign infantile familial convulsions*.[67] In subsequent years, autosomal-dominant familial cases have been reported by other authors, confirming the existence of this syndrome.[10,21,35,40,46,65]

The first series described by *Vigevano et al*.[67] consisted of five infants—three girls and two boys. All of them had one or more paternal relatives with a history of benign seizures occurring at the same age. It was found that 13 of their relatives had analogous seizures. Age at onset ranged from 4 to 7 months in the probands, whereas in their relatives it was 4 to 8 months, and peaked around 6 months. Onset was never in the neonatal period or after the eighth month of life.

This syndrome is included in the most recent classification and terminology proposed by the ILAE under the term *benign familial infantile seizures*.

Clinical characteristics are summarized in Table 2. Psychomotor development of all children before the onset of seizures is absolutely normal. A common characteristic to almost all cases is the occurrence of seizures in a cluster—mostly brief and successive seizures, a maximum of 8 to 10 per day, which do not reach a true status epilepticus. Interictal clinical condition is normal, with occasional stupor, most probably caused by drugs. Seizures are usually longer in the beginning, lasting 2 to 5 minutes, and become shorter as treatment takes effect. The cluster can last 1 to 3 days.

Table 2 Clinical and electroencephalographic characteristics of benign familial infantile seizures

- Family history of seizures (similar age at onset, autosomal-dominant trait)
- Normal development before onset
- No underlying disorders or neurologic abnormalities
- Onset between 4 and 8 mo of age
- Seizures in clusters
- Partial seizures localized in the occipitoparietal areas

- Semiology: psychomotor arrest, cyanosis, head/eye deviation to one side (variable), tonic contraction, bilateral clonic jerks
- Normal interictal electroencephalogram
- Ictal electroencephalogram: fast activity originating in the occipitoparietal area
- Postictal electroencephalogram: lateralized occipitoparietal delta waves and spikes
- Normal developmental outcome
- Benign course

Vigevano's patients presented with seizures that were clinically characterized by psychomotor arrest, slow deviation of the head and eyes to one side, diffuse hypertonia, cyanosis, and unilateral limb jerks, which became bilateral and synchronous or asynchronous. Although the seizures were highly stereotyped, the direction of the head and eye deviation sometimes changed from seizure to seizure in the same patient.

Benign Familial Infantile Seizures Associated With Other Neurologic Symptoms

In 1997, Szepetowski et al.[61] identified and described in four French families an association of BFIS with paroxysmal choreoathetosis appearing later in life, and they proposed a new syndrome called *familial infantile convulsion and choreoathetosis* (ICCA). Linkage to chromosome 16 and dominant transmission were also clearly defined.[61] This entity has been confirmed by other authors.[1,4,6,8,60,63]

Familial hemiplegic migraine (FHM) is a rare, severe autosomal-dominant subtype of migraine with aura associated with hemiparesis.[29] Most of the families that have been reported were linked to chromosome 19p13 and had missense mutations in the *CACNA1A* gene.[16] In two families with FHM linked to 1q23, two missense mutations in the *ATP1A2* gene were identified.[65] Two novel mutations in the *ATP1A2* gene were also found. In particular, one mutation was detected in a Dutch-Canadian family in which FHM was associated with BFIS.[45,62] In this family, BFIS were followed at an older age by FHM and cosegregated to chromosome 1q23.[65] This finding suggests that BFIS may have a wider association with other neurologic diseases.

Benign Familial Neonatal-Infantile Seizures

A seizure onset occurring between neonatal and infantile ages was reported by Kaplan and Lacey in 1983.[32] The onset of seizures varied from 2 days to 3.5 months.[32] The authors used the term *benign familial neonatal-infantile seizure* (BFNIS). In 2002, Heron et al.[25] described two families with afebrile, secondarily generalized partial seizures occurring between 1.9 and 3.8 months of life and having an autosomal-dominant mode of inheritance, and they described a missense mutation in *SCN2A*, the gene coding for the α2 subunit of the voltage-gated sodium channel. In 2004,[3] a novel missense mutation in *SCN2A* gene was found in five similar families in addition to the first family described by Kaplan and Lacey: a new sodium channelopathy was identified. Clinical characteristics are summarized in Table 3. The semiology of the seizures was characterized by a predominant focal motor manifestation, with head and eye deviation followed by tonic and clonic movements. Most of the seizures were relatively long, lasting up to 4 minutes, and were of variable frequency, with some patients having few seizures per day and others having clusters of seizures. Interictal EEGs were normal or showed some epileptiform discharges in the posterior areas. When ictal EEGs were recorded, they showed a focal posterior onset of discharges. All patients had a normal development before and after the seizure occurrence. The authors concluded that this mutation represents a new sodium channelopathy, despite the possible overlap with the previously described cases of BFIS.

Table 3 Clinical characteristics of benign familial neonatal-infantile seizure

- Family history of seizures (autosomal-dominant trait)
- Normal development before onset
- No underlying disorders or neurologic abnormalities
- Onset between 2 d and 7 mo of age
- Frequency ranging from few attacks to clusters
- Afebrile secondarily generalized partial seizures
- Ictal electroencephalogram: onset in the posterior areas
- Remission within 12 mo
- Benign course

Recently, Striano et al.[58] reported a novel heterozygous mutation c3003 T→A in the *SCN2A* gene in a family with three affected individuals over three generations. All individuals experienced clusters of partial seizures with or without secondary generalization and onset between 4 and 12 months of life. They have been diagnosed with BFIS. No patients developed other seizures later in life, and all of them had a normal development outcome. This report provides new evidence that BFNIS and BFIS may show some overlapping clinical and genetic characteristics.

Benign Infantile Seizures Associated With Mild Gastroenteritis

Morooka[46] was the first to describe this entity (BIS with MG) in Japan in 1982. It is characterized by nonfebrile generalized seizures associated with symptoms of gastroenteritis in previously healthy patients between 6 months and 3 years of age. Seizures often occurred in clusters, and laboratory examination results, including blood and cerebrospinal fluid (CSF) glucose, were normal. Interictal EEG was normal in all patients, and all of them had an excellent outcome.

After the first report by Morooka, numerous (>60) reports have been published in Japan[30,31,33,36,49,53,56,64,67] but only nine from other countries.[20,22,27,38,42,54,61,68,76] Cases of BIS with MG are likely to fall within the category of situation-related seizures, although they are not described in the proposed ILAE classification and seizure terminology.[17] Seizure recurrence, also without prophylactic antiepileptic treatment, has not been reported in BIS with MG, although it can occur in a few cases when an infant has repeated episodes of gastroenteritis.[19] In a recent study by Okumura et al.[51] on the efficacy of antiepileptic drugs during a cluster, lidocaine was reported as the most effective drug for seizure cessation.

Table 4 Clinical characteristics of benign infantile seizures associated with mild gastroenteritis

- Healthy patients
- Age between 1 and 2 yr
- Brief partial seizures evolving to secondary generalization
- Symptoms of gastroenteritis

- Seizures in clusters
- Seizures within the first 5 days of gastroenteritis
- More than 50% positive to rotavirus antigen
- Seizure recurrences rare, only during recurrence of mild gastroenteritis
- Benign course

BIS with MG are characterized by mostly brief and partial seizures evolving to secondary generalization, often occurring in clusters, in infants and children aged 1 to 2 years. Seizures occurred within the first 5 days of the gastroenteritis episode, and the proportion of positive rotavirus antigen was greater than half.[64] Table 4 summarizes the clinical characteristics of this condition.

Benign Infantile Focal Epilepsy With Midline Spikes and Waves During Sleep

First Bureau and Maton[4] and later Capovilla and Beccaria[5] and Capovilla et al.[6] described a form of epilepsy in children with homogeneous electroclinical features and a benign course that they hypothesized to be a new form of benign focal epilepsy. A distinctive aspect of this condition was that all of the described children presented particular interictal EEG abnormalities that were detectable during sleep and characterized by isolated or grouped spikes and waves from the midline region to the central regions. The authors pointed out that these abnormalities could be an EEG marker that is clearly distinct from other typical EEG markers at an older age. They highlighted, however, that it could not be only an EEG marker because it was found in a group of infants presenting with homogeneous clinical features, thus suggesting a possible new epileptic syndrome. Capovilla had previously described this syndrome with the term *benign partial epilepsy in infancy and early childhood with vertex spikes and waves during sleep*.[5] He later[6] proposed to replace *vertex spikes* with *midline spikes* in order not to confuse them with physiologic sleep vertex spikes.

The general features of this condition (Table 5) are neurologic and neuroradiologic normality, a normal psychomotor development, a positive family history, and a benign evolution in all cases. With regard to clinical features, age at onset is between 4 and 30 months, with a peak between 13 and 19 months (more than two thirds of cases are within this age range). The frequency of seizures is low; some children have a single episode, and others have multiple episodes per year. The seizure length is between 1 and 5 minutes. The episodes usually occur during wakefulness; in one fourth of cases, they occur during sleep. The age of the last seizure is between 24 and 43 months. The semiology of seizures is characterized by loss of contact— staring as a rule—and cyanosis. Perioral cyanosis and motion arrest are among the main clinical symptoms. Instead, lateralizing signs and automatisms are rarely observed. EEG is normal when awake, with typical sleep EEG abnormalities, well differentiated from the typical high-voltage diphasic spikes followed by a slow wave found in benign epilepsy with centrotemporal spikes.[13] All of the children reported had a normal development during the follow-up period.

Table 5 Clinical and electroencephalographic characteristics of benign infantile focal epilepsy with midline spikes and waves during sleep

- Normal psychomotor development

- Family history (half of patients)
- Age between 4 and 30 mo
- Semiology: cyanosis, staring, rare lateralizing signs, automatisms
- Electroencephalographic marker: spike followed by bell-shaped slow wave (midline region) during sleep
- Sporadic seizures
- Favorable outcome
- Majority of patients not treated
- Benign course

Diagnostic Evaluation

As a general rule, it is not necessary to perform many diagnostic evaluations in these forms of epilepsy except for prolonged wake and sleep EEGs. All of these children have a normal psychomotor development and in some cases a clear familial recurrence: this history since onset can help to bring the clinician to a diagnosis of idiopathic epilepsy. The follow-up and the EEG evaluations of these patients confirm the diagnosis of benign forms. Magnetic resonance imaging (MRI) is always normal, as are all other diagnostic evaluations. In cases in which mild gastroenteritis is suspected as an etiologic factor, it is necessary to look for rotavirus antigen, which has been found in half of the cases.

Electroencephalographic Findings

Interictal EEG is normal or fails to show any diagnostic elements in all forms except for the midline spikes during sleep reported by Capovilla, who hypothesized the existence of this peculiar and rare form.[6]

The EEG characteristics are well defined in BFIS as described by Vigevano et al.[67]; during a cluster of seizures, interictal EEGs showed lateralized slow waves and spikes in the occipitoparietal areas, whereas outside the cluster of seizures, the interictal EEG is normal. Ictal EEG disclosed a focal discharge characterized by a recruiting rhythm of increasing amplitude with onset in the occipitoparietal regions, spreading over the hemisphere and involving the entire brain. Recordings in the same patient of seizures with onset sometimes on the right hemisphere (Fig. 1) and sometimes on the left (Fig. 2) confirmed the alternating clinical pattern. The site of seizure origin seems to be a characteristic distinguishing this form from that described by Watanabe. The temporal area is the site of origin in cases described as BPEI with CPS,[71] whereas in cases described as BPEI with SGS, the site of origin is centroparietal.[69] In familial cases, the seizures originate mostly in the parieto-occipital area, with the side varying from one seizure to another.[66]

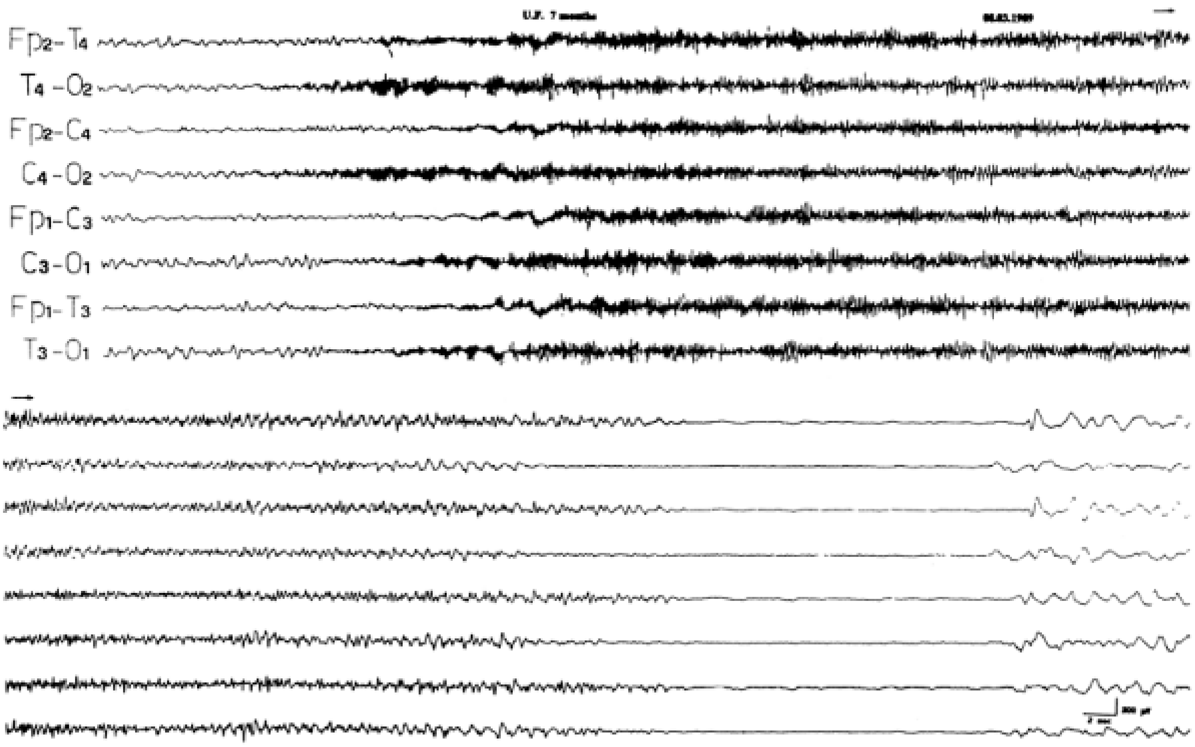
U.F. 7 months
Fp2-T4
T4-O2
Fp2-C4
C4-O2
Fp1-C3
C3-O1
Fp1-T3
T3-O1
200 µV
2 sec

FIGURE 1. A 5-month-old boy affected by a familial form of benign infantile seizure. The seizure starts over the right parieto-occipital region.

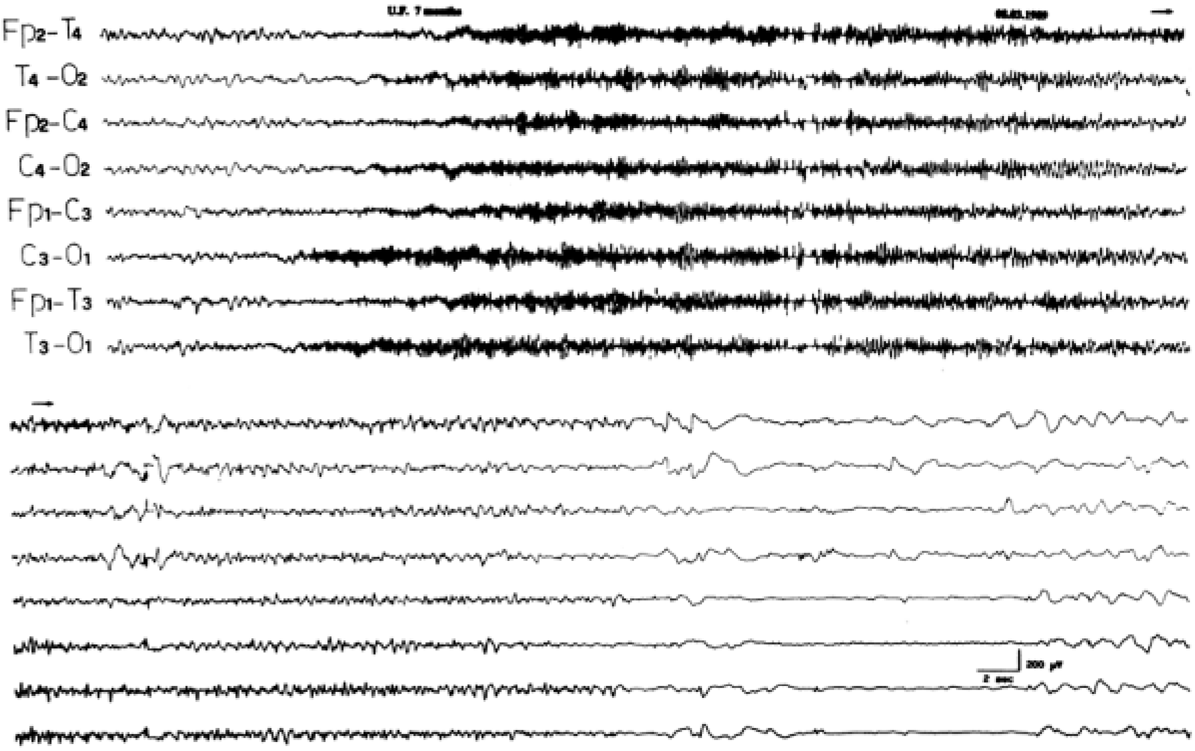
U.F. 7 months
Fp2-T4
T4-O2
Fp2-C4
C4-O2
Fp1-C3
C3-O1
Fp1-T3
T3-O1
200 µV
2 sec

FIGURE 2. The same patient after 2 hours, experiencing a second seizure, which in this case starts over the left parieto-occipital region, thus demonstrating the alternating clinical and electroencephalographic pattern.

The distinctive aspect of benign infantile focal epilepsy with midline spikes and waves during sleep is that all of the described children presented particular interictal EEG abnormalities that are detectable during sleep and characterized by isolated or grouped spikes and waves from the midline region to the central regions; Capovilla described these abnormalities as fast spikes, followed by a slow wave, in the midline region. They tend to spread to both central regions and are followed by a higher, bell-shaped slow wave.

Neuroimaging and Laboratory Assessment

Brain MRI is normal in all patients. The need to perform such examinations is based on the difficulty of diagnosing these epilepsies as benign from the onset. In cases with a clear autosomal-dominant pattern of inheritance and clear clinical features of benignity, it is possible to postpone the brain MRI. There are no particular indications for the laboratory assessment: Cardiovascular and respiratory function parameters have to be carefully monitored in children with BFIS or BNFIS during the cluster. A determination of glycemia could be useful at the onset and during the cluster of seizures.

In cases with BIS and MG, it is necessary to monitor the patient's hydration and general clinical conditions and investigate the presence of rotavirus antigen.

It is useful to collect such familial cases for linkage studies. The aim of genetic studies is to confirm the mutations that have been identified and provide genetic counseling. The possibility of new genetic mutations responsible for benign infantile seizures is sufficiently important to justify proposing a genetic study of these families.

Differential Diagnosis

The different forms of benign epilepsy in infancy recently have been examined by the ILAE in a proposed classification,[17] although their nosologic definition presents some difficulties.

The first report on the possible existence of benign forms of epilepsy in infancy dates back to 1963. In that year, Fukuyama[18] described a series of infants having apparently generalized seizures and benign course, as confirmed by Sugiura et al.[59]

On the other hand, partial epilepsies in infancy had long been considered as epilepsies with an unfavorable prognosis and as an expression of brain injury. Some authors also doubted the existence of partial idiopathic epilepsy in early infancy.[15] With the work of Watanabe et al.,[69,71,72] who reported cases of infants with complex partial seizures and seizures evolving to secondarily generalized seizures, a form of benign epilepsy was identified with partial seizures and onset in infancy. Afterward, Vigevano et al. focused on cases with similar features but also having a clear familial origin. They identified a specific form of benign epilepsy with onset within the first year of life and autosomal-dominant inheritance.[67] After the first study by Vigevano et al.,[67] a number of other reports confirmed the existence of such a benign epileptic syndrome. Furthermore, inheritance patterns have been confirmed with the identification, through linkage analysis of numerous families, of gene loci on chromosomes 19, 16, and 2.[11,23,42,58]

In this regard, other clinical entities with similar features to that described by Vigevano et al. but associated with other neurologic symptoms have been mapped to the same chromosomes where the syndrome described by Vigevano et al. was mapped.

ICCA, in which BIS are associated with paroxystic choreoathetosis,[61] has been mapped in various families on chromosome 16 in a region very close to that identified in families with BFIS.

The distinction between BFIS and other forms of benign epilepsy with neonatal onset (BFNS) appeared to be clear due to both the tight correlation with age and the difference in linkage analysis showing the existence of two genes, *KCNQ2* and *KCNQ3*, on chromosomes 20 and 8 responsible for BNFS.[37,55] Genetic studies failed to demonstrate the same gene defect in families with BFIS, thus dispelling all doubts about a possible overlap between BFIS and BFNS,[43] which are now also clearly distinct in the latest classification proposed by the ILAE.[17]

In 2004, a form of benign epilepsy with an intermediate onset between the neonatal and infantile forms was identified as BFNIS.[3] For this syndrome, a mutation of the gene *SCN2A* has been demonstrated. The onset of seizures in families affected by BFNIS is reported to occur between 7 days and 4 months of age. Although the mutation of the gene *SCN2A* appears to be distinctive to these families, age of onset and seizure semiology seem to overlap with BFNS and BFIS. We believe that it is of crucial importance to study new families with the described clinical picture to confirm the actual existence of a third form of benign familial epilepsy. To this purpose, we recently reported a new mutation of the gene *SCN2A* in a family with clinical features of BFIS, demonstrating a clinical and genetic overlap between BFNS and BFIS.[58]

From the clinical point of view, benign epilepsies of infancy are entities for which it is not easy to make a diagnosis. Clinical criteria described for BNFS and BFIS are not indicative for the diagnosis, although the presence of familiality may be helpful information. Sporadic forms may be even more difficult to diagnose. As reported by Okumura et al.,[50] recognition of BPEI is possible, to some extent, at the first presentation, but a confirmation can actually be obtained only by following these children over time to verify whether other seizures occur and other EEG abnormalities are found. These concepts are also relevant to pharmacologic treatment: It is difficult not to treat these epilepsies at the onset because these infants present with clusters of seizures. After the acute phase, many infants continue to follow a chronic therapy. In familial forms, the tendency is to interrupt the therapy as early as possible. In nonfamilial forms, instead, the indication is to wait and follow the evolution; should the benign diagnosis be confirmed, it is possible to stop the treatment within 18 months after the last seizure.

The phenotype of familial and nonfamilial forms is likely to be very similar. There may be some differences in the seizure semiology and in the site of the seizure onset (more anterior in the sporadic forms and more parieto-occipital in the familial forms).

It is certain, however, that there are familial forms with an autosomal-dominant trait as well as sporadic forms. Therefore, in our opinion, the major criterion for distinguishing these forms of benign epilepsy should be the presence or absence of familiality, as proposed in the most recent classification.[17]

All of the aforementioned entities do not present any interictal EEG abnormality and are characterized by seizures occurring exclusively in a short period of infancy. For all of these reasons, we agree with the proposal of the ILAE Task Force on Classification and Terminology that these conditions be defined with the term *seizures* and not *epilepsy*.[17]

Benign infantile focal epilepsy with midline spikes and waves during sleep (BIMSE) can be distinguished from other infantile benign forms because infants with this syndrome, as reported by Bureau and Maton[4] and later by Capovilla et al.,[5,6] have a slightly later onset, with no seizures in clusters, and with characteristic sleep EEG abnormalities. This syndrome is more similar to other benign epilepsies with partial seizures generally occurring at older ages, such as early-onset benign occipital seizure susceptibility syndrome (EBOSS) and benign epilepsy of childhood with centrotemporal spikes (BECTS), in which the interictal EEG shows particular epileptiform abnormalities.

Table 6 Benign non familial infantile seizures

	BNFIS	BFIS	BFNIS	BIS AND MG	BIMSE
Genetic	Sporadic	AD	AD	Sporadic	Sporadic
Onset					
Typical		5-6 mo	Within 3rd mo	?	17 mo
Range		3-9 mo	2 d -7th mo	5-36 mo	4-30 mo
Type of seizure	Focal sometimes with SGS	Focal with SGS	Focal with SGS	Focal	Focal
Occurrence	Cluster	Cluster	Cluster	Repetitive	Rare
Other type of seizure	—	—	—	—	—
Other clinical features	—	Paroxysmal choreoathetosis migraine	—	—	—
Interictal EEG	NS	NS	NS	NS	Midline spikes during sleep
Chromosomal loci	—	16,19,2	2	—	—
Gene	—	*SCN2A*	*SCN2A*	—	—

AD, autosomal dominant; BFIS, benign familial infantile seizures, BNFIS, benign non familial infantile seizures, BIS and MG, benign infantile seizures and mild gastroenteritis; BIMSE, benign infantile focal epilepsy with midline spikes and waves during sleep; EEG, electroencephalogram; NS, not significative; SGS, secondarily generalized seizures.

Although in BIMSE, as in the other epilepsies described, there seems to be a characteristic EEG pattern, a wider number of patients should be studied to confirm the actual existence of this new form of benign epilepsy. At present, this entity is being studied and is not included in the international classification of epilepsies.

In contrast to the previously discussed entities, benign infantile seizures associated with mild gastroenteritis (BIS with MG) are more likely to be considered as situation-related seizures than as epilepsy. This syndrome can be misdiagnosed as epilepsy because seizures are nonfebrile and may occur in clusters. It is important further to study and understand this entity.

In conclusion, benign epilepsies of infancy encompass a wide spectrum of entities with differences in age at onset, genetic aspects, seizure semiology, and EEG characteristics (when available). Table 6 summarizes the main features of benign epilepsies. Follow-up of these infants is important because it allows us to confirm the benign outcome over time.

Treatment and Outcome

Although, as in other benign forms of infant epilepsy, seizures in these forms should not be treated, in clinical practice it is difficult to not treat these patients. At the very beginning these children present seizures in clusters (seizure every 2–3 hours), which sometimes require a rapid intervention with drugs. Patients not treated after the first cluster can have other seizures or clusters. When such children arrive at the emergency department, the etiology of their seizures may appear clearly only after EEG monitoring and with a normal neurologic evaluation. For these reasons, the majority of children receive antiepileptic treatment. In cases that exhibit a familial recurrence, it is possible to withhold the treatment because the diagnosis is simpler. In anecdotal reports, all drugs have demonstrated efficacy in benign infantile seizures (valproate, carbamazepine, phenobarbital, and phenytoin), with apparently no differences. Recently, Japanese authors[44] reported the efficacy of low doses of carbamazepine in a series of patients with benign infantile seizures. In this study, carbamazepine was administered at a once-daily dose of 5 mg/kg; seizures did not recur in any patient. The treatment can be withdrawn 1 year after onset.

Long-Term Prognosis

Unpublished data from the Division of Neurology, Bambino Gesù Children's Hospital, of a 14 year-follow-up period confirm that any patients have had seizure recurrence without treatment. Neuropsychological development appears to be normal in all of them, except for one patient, who has mild mental retardation, which was evident before the seizure onset. Most of the patients have had several follow-up EEGs that failed to show any abnormalities. Some data have been published that confirm the benign prognosis for these patients.[49,52]

Summary and Conclusions

Benign epilepsies during infancy are a large topic needing both clinical and nosologic clarification. In 1963, Fukuyama reported patients with seizures during infancy with a benign outcome. In the late 1980s and early 1990s, Watanabe reported series of infants with complex partial seizures or partial seizures with secondary generalization, with a normal development before onset and a benign outcome. In the same years, Vigevano focused on familial cases: He described several families with seizures with onset around 6 months of age and an autosomal-dominant mode of inheritance. To define this condition, he coined the term *benign familial infantile seizures* (BFIS). Later studies of families with this phenotype detected loci on chromosomes 19, 16, and 2 responsible for it. Similar loci were found in families affected by BFIS and subsequent choreoathetosis and BFIS associated with familial hemiplegic migraine. More recently, a new form of benign epilepsy has been proposed with an intermediate onset between the neonatal and infantile ages, *benign familial neonatal-infantile seizures* (BFNIS). This condition might have some clinical and genetic features overlapping with BFIS. Seizures with a benign outcome also have been reported in infants during episodes of mild gastroenteritis (BIS with MG), frequently with positive rotavirus antigen. Finally, Capovilla et al. reported sleep EEG abnormalities in children

with a peculiar form of epilepsy that they defined as *benign infantile focal epilepsy with midline spikes and* *waves during sleep* (BIMSE). Some of these entities have been included in the most recent classification proposed by the ILAE and have been differentiated into familial and nonfamilial forms.

We believe that there is a series of clinical entities with seizures in clusters that are limited to a short period of life. All of these entities are idiopathic, without EEG interictal abnormalities, and benign, and we define them as “seizures” and not “epilepsies.”

Benign infantile focal epilepsy with midline spikes and waves during sleep should be placed at the upper border of this age range. Infants with this syndrome have a later onset, and it has more similarities with benign focal epilepsies appearing later in life such as early-onset benign occipital seizure susceptibility syndrome (EBOSS) and benign epilepsy of childhood with centrotemporal spikes (BECTS).

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Chapter 228

Migrating Partial Seizures In Infancy

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Introduction

Epileptic syndromes with onset in the neonatal period or infancy with very poor prognosis have been recognized or better defined in recent years due to developments in diagnostic techniques, including video-electroencephalography, brain imaging, and cytogenetics. Migrating partial seizures in infancy (MPSI) is a rare, newly recognized, age-specific epileptic syndrome first described in 1995 by Coppola et al.[3] In the proposed revision of the International League Against Epilepsy (ILAE) diagnostic scheme for people with epileptic seizures and with epilepsy, MPSI was labeled as a syndrome in development and included among symptomatic and probably symptomatic focal epilepsies.[7] It is characterized by onset in the first 6 months of age, after a normal early development, of nearly continuous multifocal partial seizures arising independently and sequentially from both hemispheres, progression through a period of intractable seizures, subsequent neurologic deterioration or arrest with complete loss of both cognitive and motor abilities and, in most children, progressive decline of head circumference percentile.

Historical Perspectives

MPSI was first reported in 1995 by Coppola et al.,[3] who described 14 infants with a severe epileptic disorder characterized by seizure onset in the first year of life; nearly continuous multifocal seizures involving both hemispheres; no identifiable immediate or remote cause; normal neuroimaging studies at onset; and intractability to conventional antiepileptic drugs (AEDs), including phenobarbital, phenytoin, carbamazepine, valproate, vigabatrin, clobazam, nitrazepam, biotin, vitamin B_6, and corticosteroids. In this first description, the outcome was very poor with regard to both the seizure disorder and psychomotor development. Only 2 of 14 patients stopped having seizures with a combination of stiripentol and clonazepam and showed some neurologic improvement. Eleven patients developed microcephaly during the first year of life, and three patients died. After this original report, additional cases from Australia, Europe, Japan, and the United States were published.[4,10,11,13,15,17,22] Thirty-three cases have now been reported. In particular, two cases have been reported from Australia[22] that fulfill the diagnostic criteria proposed by Coppola et al.[3] Both infants presented with intractable partial seizures arising independently from multiple regions of both hemispheres, with interictal electroencephalograms (EEGs) revealing multifocal epileptiform activity. There was no response to AEDs, pyridoxine, and corticosteroids, and developmental arrest followed seizure onset. Extensive investigations failed to identify an underlying cause. Both infants died. One of them underwent postmortem examination, which was normal.

Veneselli et al. reported three infants in whom seizure onset occurred before 3 months of age and was characterized by focal motor manifestations with a gradually increasing frequency.[17] Either hemibody was alternatively and randomly involved, and secondary generalization was evident only during the evolution of the disease. Conventional AEDs were uneffective. No etiologic factors have been identified. Neurologic status and evolution were highly unfavorable, resulting in death in one case and severe neurodevelopmental morbidities in the others. The same malignant course, with regard to both seizure disorder and ultimate outcome, was described by Gross-Tsur et al. in two additional cases.[10] One infant, microcephalic at birth, developed at age 4 months clusters of nearly continuous multifocal seizures with secondary generalization, refractory to antiepileptic drugs. By the age of 4.5 years she was seizure free but remained without any cognitive or motor function. The other, born with a normal head circumference, began seizures at the age of 3 months, never became seizure free, and died at age 18 months. Neuroimaging findings showed progressive subcortical atrophy. In both cases, extensive evaluation including skin and muscle biopsy did not clarify the etiology. However, more recently, Marsh et al.[13] reported six new patients with the same clinical and electroencephalographic characteristics as those described by Coppola et al.[3] but with the prospect of a more optimistic developmental outcome, raising the difficult distinction at onset with benign infantile or neonatal-infantile seizures. Each patient underwent comprehensive brain imaging and neurometabolic evaluations, which were unrevealing. Five patients had a long-term follow-up. Whereas all had some degree of neurodevelopmental sequelae, a few of them appeared to be less severely affected: One was able to walk, one developed some degree of spoken language, two showed developmental quotients between 50% and 100%, and only one was profoundly impaired. In terms of seizure outcome, one was still having intractable seizures when lost to follow-up. For five of six patients, six or more AEDs failed. Two patients received adrenocorticotropic hormone (ACTH); two were treated with folinic acid, and two were placed on ketogenic diet. None of them was more successful than the others. In contrast, successful seizure control was obtained with potassium bromide by Okuda et al. in two patients with a diagnosis of MPSI and refractory to conventional AEDs.[15] Moreover, once seizures were controlled, both patients showed some degree of neurologic recovery. A recently published case report by Hmaimess et al. in 2006 described the first neonatal case of MPSI and documented a positive response to levetiracetam.[11] Unfortunately, despite the dramatic decrease in seizure activity, which paralleled a positive clinical evolution in terms of psychomotor development, the child died unexpectedly at 14 months of age. The most recent three cases at the time of this review have been reported by Coppola et al., who performed a mutational scanning of potassium, sodium, and chloride ion channels (KCNQ2, KCNQ3, SCN1A, SCN2A, and MECP2) but

failed to find any mutations.[4] Finally, it is important to consider that studies on drug-resistant seizures with early onset classified as “catastrophic infantile epilepsy” may include cases of MPSI. Ishii et al.[12] investigated clinicoelectrical and etiologic characteristics of 15 patients with catastrophic infantile epilepsy. Although some of these patients did not belong to MPSI, a number of them, mainly those without a clear etiology, clinically and electroencephalographically resemble this syndrome.

Definitions

MPSI is a severe, probably symptomatic, age-dependent focal epilepsy defined by the following diagnostic criteria: (a) normal development before seizure onset; (b) seizures beginning before age 6 months; (c) migrating focal motor seizures at onset; (d) multifocal seizures becoming nearly continuous; (f) intractability to conventional AEDs; (e) lack of demonstrable etiology; and (g) severe psychomotor delay on follow-up. The clinical features and EEG pattern suggest that MPSI may rank among the catastrophic epilepsies of infancy. Moreover, due to the high frequency of seizures and the intense epileptiform activity that contribute to the progressive disturbance of cerebral function, MPSI could also be included in the epileptic encephalopathies.

Epidemiology

Its prevalence is unknown because only small series of patients have been published.[4,10,11,13,15,17,22] Both sexes are equally affected.

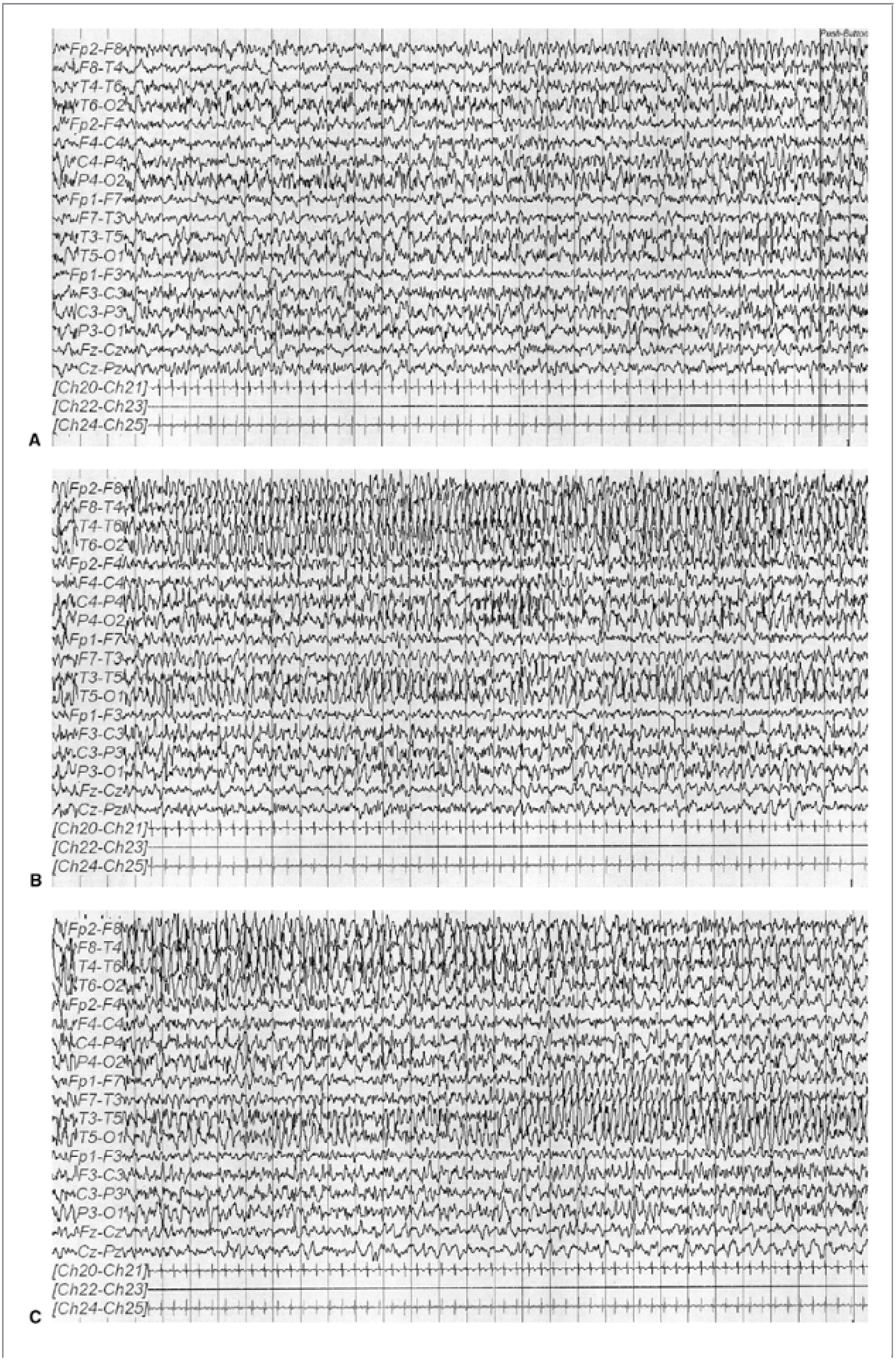
Etiology and Basic Mechanisms

The etiology is not known, but a functional or metabolic disorder is suspected. All reported patients had normal magnetic resonance imaging (MRI) and computed tomography (CT) scans at the onset of seizures. There is no evidence of familiarity because no familial recurrence of migrating seizures has been reported, and there is no consanguinity. In the series reported by Coppola et al., three patients had family history of febrile seizures and four of epilepsy.[3] Veneselli et al. reported one patient with a family history of first-degree seizures.[17] Neurometabolic evaluations performed in all cases have excluded inborn errors of metabolism. In those cases that were examined with postmortem, neuropathology failed to demonstrate cortical dysplasia, neuronal migration defects, or cortical vacuolation.[3,22] Preliminary genetic studies excluded any abnormality in the coding region of several relevant sodium, potassium, and chloride ion channel gene involved in other epileptic syndromes of the first year of life, suggesting lack of any molecular link between benign familial neonatal or neonatal-infantile seizures or Dravet syndrome and MPSI.[4]

Clinical Presentation

The first seizure occurs before 6 months of age (1 day to 6 months; mean 25 days) in normal infants, who have no antecedent risk factors. Seizures begins with focal motor movements that can alternate from one side of the body to another with lateral deviation of the head and eyes and eye jerks, twitching of the eyelids, limb myoclonic jerks, and increased tone of one or both limbs.[3,4,10,11,13,15,17,22] At the beginning, many of the motor manifestations are relatively subtle and easily overlooked both by parents and the nursing staff, such as fixed sight, psychomotor arrest, lateral deviation of the eyes, and chewing-like movements. Sometimes, electrical seizures are not associated with any clinical manifestations, although they may spread and involve both hemispheres.[13,22] It is also worth mentioning that in very young patients motor and autonomic signs are often the only clinically relevant symptoms of seizures. Focal motor components are often accompanied by autonomic signs including flushing of the face, salivation, and apnea.[3,13,15,17] Epileptic spasms have been described in only one patient, appearing during the course of the disease and associated with a focal discharge.[3] Truly generalized tonic–clonic seizures are very rare.[22] The combination of these various manifestations produces a wide range of ictal semiology that may vary in a given infant from one seizure to another, although there are predominant focal motor components. Prolonged observation soon shows that both sides are alternatively affected, which demonstrates the involvement of the whole brain cortex. Seizures are relatively brief, but often last several minutes, and thus are longer than observed in patients with benign seizures in infancy. In addition, they tend to recur in series of 5 to 30 seizures during drowsiness and/or at awakening, several times a day. Such clusters may last up to 2 to 5 days. Initially seizures are rare, occurring roughly once a week. Nevertheless, two patients presented with status epilepticus.[3] Soon after, seizure frequency tend to increase and, at an age ranging from 24 days to 10 months, become almost continuous in most of the reported cases. These consecutive seizures can overlap, with one seizure beginning before the end of the previous one (Fig. 1).[3,11] At this stage, seizures tend to cluster, and clusters of seizures may last up to 2 to 5 days. Between seizures during these clusters, infants are floppy, drooling, often somnolent, and unable to drink and swallow. Between clusters, the infant may recover partially. As patients recover slightly, however, the next cluster occurs and patients regress. Moreover, with time, seizures tend to generalize more frequently.

Psychomotor development before seizure onset has been normal in most cases.[3,4,10,13,17,22] One patient presented with microcephaly at birth,[10] and two patients had evidence of mild psychomotor delay before onset of seizures.[3] However, in some cases the first symptoms appear as early as the first days of life, making developmental evaluation prior to the seizure onset more difficult. There is progressive neurologic deterioration with the development of major axial and limb hypotonia, loss of visual contact, inability to grasp, and complete loss of other motor and social skills in most children. Most patients show progressive loss of head circumference percentiles over time and development. In most cases, the condition is progressive, and patients lose all skills within a few months of onset of the illness. However, in a few cases,[3,11,13,15] seizures were eventually controlled, and these children partly recovered motor and cognitive abilities. In all series, developmental outcome is better when seizures are controlled compared to those with continued intractable seizures. Some patients die.[3,10,11,17,22] Although death can be a consequence of very frequent seizures complicated by respiratory distress and[17] intercurrent infections,[3,22] the cause of death often remains unclear and is largely undocumented.[10,11] Marsh et al. published a series of infants with MPSI and a slightly better outcome than previously reported, underscoring the difficult distinction with benign conditions at onset.[13] In particular, although all of their patients had a period of intractable seizures and developmental plateau or regression, the developmental outcome was borderline mild mental retardation in one patient and mild to moderate retardation in another. Three patients had developmental quotients between 50% and 100%, and only one was profoundly impaired. These findings are not dissimilar to those of other types of early-onset epileptic encephalopathies, such as West syndrome, in which a few children may recover without severe adverse sequelae.[6]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F8-T4
T4-T6
T6-O2
Fp2-F4
F4-C4
C4-P4
P4-O2
Fp1-F7
F7-T3
T3-T5
T5-O1
Fp1-F3
F3-C3
C3-P3
P3-O1
Fz-Cz
Cz-Pz
[Ch20-Ch21]
[Ch22-Ch23]
[Ch24-Ch25]
C

FIGURE 1. Ictal recording of a 6-month-old girl affected by migrating partial seizures in infancy showing apparently random onset of electroencephalographic discharges. **A:** A seizure starts over the right frontotemporal region. **B:** Another seizure starts in the left frontotemporal region, before the end of the first event. **C:** Simultaneous discharges involve two different areas, the right frontotemporal region and the left temporal region. **D:** The seizure over the right hemisphere ends, whereas the seizure over the left hemisphere persists.

Diagnostic Evaluation

Electroencephalographic Findings

At onset, interictal EEG background varies from normal to diffuse slowing,[3,13] and epileptiform discharges may be rare, with unifocal or multifocal interictal patterns. Initial EEGs and video-EEGs may indicate a localized onset of seizures if only few seizures are recorded. The multifocal character of the seizures becomes evident only with prolonged video-EEG monitoring,[22] suggesting that long-term monitoring has an important role in the diagnosis of this disease. EEGs reflect the escalation of seizure activity, because no infant continues to have a normal EEG. Soon, the EEG background activity becomes slow with fluctuating asymmetry, one hemisphere exhibiting slow activity on one recording, the other one on the next recording. Multifocal spikes are present in all instances. When seizures become very frequent, an interictal state can no longer be identified. All patients have electrographic seizures with a monomorphic pattern that is identical from seizure to seizure in each patient. It consists of focal rhythmic theta or alpha activity beginning in one region and progressively involving the adjacent areas. The location of the ictal onset varies not only from side to side, but also within a hemisphere. Electrographically, the single ictal event can shift from one region to another and from one hemisphere to the other, and additional seizures beginning in other areas in either hemisphere could start before the end of the first event or immediately follow it (Fig. 1).[3,11] The centrotemporal region seems to be the most common site of seizure onset,[10,13] although posterior temporal, frontal, and occipital onsets are also observed. Most seizures are electroclinical, but frequent subclinical discharges also occur.[3,13] Although in some studies video-EEG makes it possible to define the correlation between the topography of the EEG ictal discharge and the clinical manifestations,[2,3] in others the clinical features did not correlate with the hemisphere involved.[10] When there is a good clinical/EEG correlation,[2,3] occipital EEG seizures correlate with lateral deviation of head and eyes and lateral eye jerks; rolandic discharges correspond to contralateral limb clonus; temporal discharges are associated with chewing movements and staring; and frontal seizures are related to limb hypertonia of either side. In older children, the amplitude of ictal discharge tends to increase, more seizures generalize, and the frontal areas are more frequently affected. In children EEG documented the disappearance of spikes and sharp waves and the reappearance of sleep/wake differentiation.[11,15] In contrast, if seizures continue, stopping only when they “burn out,” EEG is characterized by low-voltage, slow activity, as described by Gross-Tsur et al.[10]

Neuroimaging and Laboratory Examinations

CT and MRI performed at the beginning of the illness are normal, as are single photon emission computed tomography (SPECT),[15] fluoro-2-deoxyglucose/positron emission tomography (PET) scan,[11] and MRI with spectroscopy.[13] On follow-up, CT and MRI, when abnormal, show progressive atrophy of both the cortex and subcortical white matter with enlargement of subarachnoid and ventricular spaces.[3,10] MRI spectroscopy discloses decreased *N*-acetyl aspartate in the frontal cortex and basal ganglia.[10]

Laboratory findings, including karyotype, cerebrospinal fluid (CSF) biochemistry and neurotransmitters, liver function tests, extensive metabolic evaluation with ammonia, serum lactate and pyruvate, serum amino acids, urine organic acids, CSF amino acids, CSF lactate/pyruvate, serum folate, sulfocystein, succinylpurine screening, serum copper level, ceruloplasmin, chromatography purine and pyrimidine, uricemia, ß-galactosidase, ß-hexosaminidase A and B, as well as respiratory chain enzymes, are unrevealing. Skin, muscle, and liver biopsies are normal. In most cases, brainstem auditory-evoked responses (BAERs), electroretinogram, visual- and somatosensory-evoked potentials (VEPs and SEPs), as well as nerve conduction velocities are also normal. In one case, SEP showed a mild increase in central conduction time,[17] and in another, BAERs had absent waves I and II in the left side, right interpeak latency prolonged, and decreased amplitude of wave V bilaterally.[15] Autopsy was performed in three cases.[3,22] Although neuropathologic examination manifested no evidence of hippocampal sclerosis, cortical dysplasia, or neuronal migration defects in one case,[22] there was revealed severe hippocampal neuronal loss and accompanying gliosis in the two others.[3] In particular, in those cases, there was almost

complete neuronal loss, with reactive gliosis of the CA1 sector of the pyramidal layer of the Ammon horn in the hippocampus and also a mild neuronal loss and gliosis in the hilus of the dentate gyrus. The neocortex exhibited only minimal lesions, consisting of microvacuolization and gliosis in discrete areas of the molecular layer in one case, whereas it was normal in the other. The cerebellum was normal in both.

Differential Diagnosis

The spectrum of neonatal and early infantile epilepsy syndromes is broad and ranges from relatively mild to severe.[1,6,16] In addition, there are symptomatic and cryptogenic focal epilepsies beginning in the neonatal period. MPSI may be misdiagnosed as refractory focal epilepsy, which could lead to inappropriate surgical procedures.[8] Indeed, initial EEGs and video-EEG monitoring may initially suggest a localized onset for the seizures, and their multifocal character becomes evident only later, and when prolonged video-EEG monitoring. Whereas in symptomatic or probably symptomatic focal epilepsies seizures alway arise from the same cortical area, indicating a localized pathologic process, seizures in MPSI, originate from multiple focal areas, demonstrating the involvement of the whole cortex. Given the unique clinical and EEG features exhibited by children with MPSI, it is extremely unlikely that this condition could be mistaken for one of the severe epileptic syndromes of neonatal or infantile periods, such as early myoclonic encephalopathy (EME),[1] early infantile epileptic encephalopathy (EIEE),[1] or West syndrome.[6] All of these entities have typical interictal EEG patterns, such as burst-suppression in EME and EIEE and hypsarrhythmia in West syndrome. In contrast to EIEE and West syndrome, spasms are lacking in MPSI.

Multifocal electrographic seizures in the neonate are a common nonspecific feature following various types of brain insults, such as infections, metabolic disorders, or hypoxia-ischemia.[20] However, in these conditions, frequent seizures tend to be confined to the acute phase of the illness. Cerebral damage from hypoxic-ischemic encephalopathy or infection is readily demonstrated with neuroimaging, which is normal in MPSI.

Pyridoxine and pyridoxal phosphate dependencies should be considered, especially in those cases with onset of multifocal seizures within the first hours or days of life and no apparent cause. The differential diagnosis is made by a therapeutic trial of intravenous pyridoxine with simultaneous EEG monitoring or oral pyridoxal phosphate, the lack of response excluding these hypotheses.

Alpers disease is a rare autosomal recessive hepatocerebral syndrome of early onset characterized by progressive neuronal degeneration with liver involvement. This entity has been recently associated with mitochondrial DNA depletion and mutations.[5,14] Neurologic symptoms of Alpers disease include loss of previously learned skills and intractable myoclonic seizures. Progressive liver failure is considered an important hallmark of Alpers disease, and in the reported patients with MPSI, liver function tests and/or liver biopsy were normal. However, none of them underwent mitochondrial DNA testing.

The normal development before onset of seizures, absence of an identifiable cause, time of onset, tendency of seizures to occur in clusters, as well as the clinical and EEG features of the seizures may overlap similiar features in the benign partial epilepsies in neonates or infants, such as benign partial epilepsy in infancy,[21] benign familial and nonfamilial neonatal seizures,[16] and benign infantile familial seizures.[9,18,19] Even in the most benign conditions, such as benign neonatal seizures and benign infantile familial seizures, seizures can occur in clusters involving various areas of the cortex. The ictal manifestations in these benign syndromes show many similarities to those of MPSI, including eye deviation, head rotation, clonic movements of the face and limbs, tonic stiffening, and secondary generalization. However, although intense, the period of seizure activity is usually brief and there is a marked difference in outcome. Giordano et al.[9] described a large family with benign familial infantile seizures in which seizures began at 3 to 4 months of age and stopped by 11 months in every infant with no treatment. All were seizure free with normal psychomotor development at follow-up, in contrast to MPSI, in which seizures are almost continuous for several months, there is developmental regression, and interictal EEG becomes progressively more abnormal with both multifocal epileptiform activity and slowing.

Treatment and Outcome

Conventional AED treatments, including phenobarbital, phenytoin, carbamazepine, valproate, vigabatrin, clonazepam, nitrazepam, midazolam, lamotrigine, steroids, and ACTH, have proved ineffective. Vigabatrin and carbamazepine may worsen seizures. These data should help in avoiding overtreatment with conventional AEDs that are consistently ineffective. Trials with various vitamins, including pyridoxine, biotin, and folinic acid, have been done without success. Four patients have been placed on the ketogenic diet with little or no improvement.[13,15] Among the new antiepileptic drugs, zonisamide and topiramate (C. Chiron, personal communication) have been tried and found to be ineffective. Successful control of seizures was reported with a combination of clonazepam and stiripentol in two patients[3] and with potassium bromide in two others[15] but was not confirmed in another.[11] The first use of levetiracetam was recently reported in a newborn with MPSI[11] and proved to be well tolerated and effective in reducing the seizure frequency even if complete seizure control was never achieved. Among the 33 cases with MPSI, death has been reported in 8 patients (25%), mostly before the age of 1 year.[3,10,11,17,22] The majority of these patients failed to respond favorably to various AED combinations. Nevertheless, one of them died unexpectedly despite a positive evolution over several months in terms of seizure control and clinical improvement.[11] The cause of death in this syndrome remains unclear and largely undocumented. In many cases, the parent's denial of postmortem examination precluded a proper investigation into the causes of death.

Long-Term Prognosis

In most cases, the prognosis has been poor. Seizures remained severely intractable, patients develop microcephaly and hypotonia during the first year of life, and all skills are typically lost within a few months of onset of the illness. There is a trend toward progressively diminishing head-circumference percentiles, hypotonia, and developmental delay, but a few patients are occasionally less severely affected, with only mild to moderate mental retardation. These findings of a slightly better outcome are not dissimilar to those of other types of early-onset catastrophic epilepsies such as West syndrome, in which a few children may escape the expected sever outcomes.

Summary and Conclusions

Various epileptic syndromes with onset in the neonatal period or infancy have been identified by age of onset, seizure types, and interictal clinical and EEG characteristics.[7] MPSI is a newly recognized epileptic syndrome, unusual but often overlooked, that begins in the first 6 months of life in apparently normal infants, and in which very frequent seizures involve multiple independent areas of both hemispheres with arrest of psychomotor

development. No causes have been identified, and no familial cases have been reported. Clinical, EEG, and follow-up data suggest that MPSI may rank among the catastrophic seizure syndromes of infancy. It is unclear whether the progression of the disease is the cause of the intractable seizures or its consequence. In our opinion, the high frequency of seizures and epileptiform abnormalities is a major cause of the psychomotor deterioration observed in these infants in coincidence with the onset of seizures. For this reason, we believe that MPSI should be included among the epileptic encephalopathies as defined by the ILAE in 2001.[7]

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Chapter 229

West Syndrome

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Introduction

The occurrence of clusters of axial movements in the first year of life, combined with major and subcontinuous electroencephalographic (EEG) paroxysmal activity called hypsarrhythmia, is the most frequent cause of psychomotor deterioration in infancy. This condition, usually termed either infantile spasms (IS) or West syndrome (WS), is a model for the study of epilepsy, because although the etiology, clinical and EEG expression, and outcome vary greatly from one patient to another, there is growing evidence that the etiology determines both expression and outcome in each given patient. The term *IS* denotes a specific age of onset and is therefore a syndromic concept. Because the concept of *West syndrome* usually includes hypsarrhythmia, this term should be considered more restrictive than the term *IS*. The clinical and EEG pattern is described in Chapter 54 (Spasms). This chapter concentrates on recent findings concerning correlation with etiology and the contribution of these findings to the understanding of pathophysiology.

Historical Perspectives

Over 160 years ago, West reported a condition that is probably the first epilepsy syndrome ever described. It was characterized by spasms as a particular seizure type not reported earlier and also by occurrence in infancy and mental deterioration. The condition did not become widely recognized as an epilepsy syndrome until 100 years later, however, when the particular EEG pattern was defined. Nevertheless, epileptic spasms were not recognized as a particular type of seizure and were therefore not included in the international classification,[80] although it is clear that their occurrence is not restricted to West syndrome, and they may occur beyond infancy.

Basic Mechanisms

A large variety of cerebral lesions may cause IS. Classic concepts of basic mechanisms suggest that IS are generated in subcortical structures, with ascending activity producing hypsarrhythmia and descending activity producing the seizures, a concept very similar to that of so-called centrencephalic epilepsy.[39,43] This view fails to take in account the predominantly cortical lesions determined radiologically and by neuropathologic studies. According to a newer concept, based on the potential recovery following removal of cortical lesions, the subcortical structures supposedly producing hypsarrhythmia and spasms are triggered by discharges in the cortical lesion.[10,15] During an ictal event, electrocorticography recording detects a focal spike triggering the fast-wave burst[2] and near-infrared spectroscopy multiple cortical areas activated simultaneously or sequentially.[70] However, this hypothesis does not clarify the age relationship, the variability of outcome, and especially the correlation of clinical and EEG pattern with etiology. The neurobiologic characteristics of the developing brain cortex, including age-dependent hyperexcitability and anteroposterior gradient of maturation, are the features most likely to contribute to the clinical and EEG pattern, including variations in outcome of epilepsy and cognitive disorders.[26] According to this hypothesis, continuous paroxysmal activity in the cortex, resulting from cortical damage, age-related functional instability, or both, produces nonconvulsive status epilepticus, accounting for the psychomotor deterioration, and determines the disinhibition of subcortical structures that generate the spasms. A model based on an unbalanced maturational pattern in brain structures leading to developmental desynchronization has recently been proposed for IS.[38] A transient developmental particularity is also the key of Baram's hypothesis at the origin of IS: The excessive secretion by hypothalamus of a highly convulsant peptide in immature brain, cortico-releasing factor, would be reduced by feedback using adrenocorticotropic hormone (ACTH) as treatment of IS.[4]

Clinical Characteristics of the Syndrome

For these, see also Chapter 54.

Seizures

Epileptic spasms consist of axial contractions that may occur in flexion, extension, or both, and that may be symmetric or asymmetric. Asymmetry may involve the upper limbs, head, or eyes, and video recording is often required for detailed analysis. The contractions are usually brief and differ from myoclonic and tonic fits. They occur in clusters, occasionally combined with a focal discharge. Between spasms of a cluster, the interictal EEG pattern may or may not recur, which distinguishes "independent" from "nonindependent" spasms. Other types of seizures—myoclonic, tonic, or partial—may occur before, in combination with, or after the cluster of spasms.

Psychomotor Development

Psychomotor development can be been normal or abnormal before the first spasms. Deterioration at onset of spasms is a usual feature. However, some patients do not deteriorate and may even make further progress in development after onset of the disorder.

Interictal Electroencephalogram

The interictal EEG pattern is quite variable. Hypsarrhythmia as defined by Gibbs and Gibbs,[40] consisting of more or less continuous activity of high-amplitude, asynchronous spikes-and-slow-waves without any physiologic activity, involves only a small proportion of cases. Other patterns consist of asymmetric hypsarrhythmia, focal or multifocal spikes with secondary generalization during sleep, and patterns that are more specific to particular causes of the disorder, including suppression bursts.

Age of Onset

Onset of IS usually occurs in the middle of the first year of life. Onset is rare before 3 months and after 1 year of age, which is considered to be the upper limit of occurrence of the syndrome in the classification of epilepsy syndromes.[80] In one series, however, >2% of patients with IS had their first seizure after the age of 12 months, and cases with onset in the fourth year of life are on record.[5]

Outcome

The range of outcomes is wide; spontaneous recovery may occur in 6% to 16% of patients. Others still have spasms after the end of the first decade of life. Different types of seizure disorders may occur, including partial epilepsy with one or more foci, Lennox-Gastaut syndrome, and other types of symptomatic generalized epilepsy. Mental retardation and various types of specific cognitive disorders are involved.

Thus, the pattern of IS is extremely variable from patient to patient in terms of clinical and EEG features and outcome. Etiology seems to be the major factor determining the characteristics of each component. Whatever the cause, age of onset and seizure type are similar among patients. The syndrome can therefore either be subdivided according to specific patterns or considered as a single disorder. The following discussion will show that both approaches are productive in terms of understanding clinical expression and outcome.

Pattern of Infantile Spasms According to Etiology

Malformations

Aicardi Syndrome

Aicardi syndrome is characterized by IS, chorioretinal lacunae, and callosal agenesis. Although often overlooked, the presence of widespread polymicrogyria probably contributes to the severe epilepsy; paraventricular heterotopia and occasional plexus papilloma are also frequently observed.

Initial seizures occur before 3 months of age in 68% of patients and before 1 month in 23%. Partial seizures usually precede epileptic spasms by 1 to 6 weeks, and spasms most often are characterized by asymmetry of contraction of the upper limbs and lateral deviation of the head and eyes.

Interictal EEG is characterized by asymmetry or asynchrony of both hemispheres with unilateral hypsarrhythmia, a pattern called *split brain*[34]; it is now clear, however, that the pattern does not result from callosal agenesis, because patients with callosal agenesis and IS of other etiology do not exhibit a similar pattern. At disease onset, patients often have a diffuse, asymmetric, or unilateral suppression-burst pattern. Focal discharges may arise from the smaller or more malformed hemisphere.[21] Electroencephalographic recordings of ictal events demonstrate that in many instances the cluster of spasms is combined with a focal discharge.[9,10] Spasms prove to be extremely resistant to treatment, and they often persist after the end of the first decade. Most patients exhibit severe mental retardation and remain bedridden, and the mortality rate is high. However, some patients acquire the ability to walk.[65]

Agyria, Pachygyria, and Laminar Heterotopia

Various forms of diffuse disorders of cortical development, ranging from the four-layered cortex of agyria to laminar heterotopia, may produce IS. Agyria with microcephaly resulting from chromosomal deletion of 17p13 and agyria-pachygyria with no obvious chromosomal deletion produce IS in most cases.[8,24] Laminar heterotopia mainly involves female infants and rarely produces IS.[74,75] A few families have been reported with girls exhibiting laminar heterotopia and boys agyria, with X-linked dominant transmission.[22,78]

In cases of agyria and pachygyria, epilepsy may be manifested by early partial seizures before epileptic spasms occur. Interictal EEG demonstrates diffuse, high-amplitude rhythmic activity in the theta or alpha range that becomes discontinuous during sleep.[32] A similar pattern is occasionally seen in laminar heterotopia. Polygraphic recording shows the disappearance of high-amplitude interictal activity between spasms of a cluster. A functional imaging study with single-photon emission computed tomography (SPECT) showed no anteroposterior gradient of cerebral blood flow and no modification with age, in contrast with the maturation observed in normal infants, thus demonstrating the lack of normal maturation of the cortex.[14] This is correlated with the persistence of spasms, which may last beyond the end of the first decade.

Hemimegalencephaly, Focal Cortical Dysplasia, and Hamartoma

In hemimegalencephaly, one hemisphere and the corresponding lateral ventricle are larger than the other, and the cortex on the affected side is thick with giant neurons and abnormal lamination.[83] In focal cortical dysplasia, similar but less extensive histologic abnormalities are observed.

Epileptic spasms occur in half of cases of hemimega- lencephaly.[104] During a spasm, contraction of the upper limbs is asymmetric. The period of IS is usually preceded and followed by partial seizures. A similar pattern may be produced by focal cortical dysplasia, particularly when it is located in the occipital lobe[58] or recently individualized as hemi-hemimegalencephaly if extended to the posterior quadrant.[20] Here, the asymmetry involves eye deviation rather than the upper limbs. Electroencephalographic findings may include triphasic spikes in the first week of life. During the period of IS, EEG usually demonstrates an asymmetric suppression-burst pattern.[73] Detection of focal cortical dysplasia may be difficult, even on new-generation magnetic resonance imaging (MRI machines). Functional imaging is helpful,[16] but IS are often associated with transient cortical, especially occipital, hypometabolic foci that are not necessarily associated with structural lesions and do not indicate a poor prognosis.

Several cases of prepeduncular hamartoma have been reported with IS.[37]

Bilateral Perisylvian Microgyria

Bilateral perisylvian microgyria appears to result from some ischemic event related to rapid growth of the perisylvian area in the second trimester of gestation. A small proportion of patients are affected with IS.[56] The EEG pattern consists of asymmetric hypsarrhythmia.

Neurocutaneous Syndromes

Tuberous Sclerosis

Half of all patients with tuberous sclerosis have IS, and tuberous sclerosis is the major cause of IS,[49] accounting for 7% to 25% of cases. The IS are often asymmetric or are preceded by or combined with partial seizures. Most patients with partial seizures in the first month of life progress to IS. This pattern is rare when partial seizures begin after 6 months of age.[27] Interictal EEG demonstrates diffuse spike-and-slow-wave activity that is rarely of the typical hypsarrhythmic pattern type. Waking traces usually show one or several spike-and-slow-wave foci with generalization during sleep. During drowsiness, spikes associated with physiologic hypnagogic hypersynchrony simulate the hypsarrhythmic pattern.[27] Even patients who exhibit true hypsarrhythmia have focal spikes or slow waves in a significantly higher proportion than do patients with cryptogenic West syndrome, particularly after administration of diazepam. Polygraphic recordings show that clusters of spasms may be initiated by a tonic or a focal discharge. The tracing between spasms does not return to the pattern seen before the onset of the cluster. Few spasms are isolated. Video recording shows that during the spasm the eyes or head may turn to the side opposite the interictal focus.

In 75% of patients, epileptic foci are correlated with the topography of large cortical tubers, suggesting that these malformations are the main epileptogenic cause.[17] The correlation is stronger for occipital than for frontal foci[96] because frontal foci are rare before the age of 2 years and because bilateral synchrony predominates in the frontal regions.[16] A functional imaging study in 25 patients used SPECT and MRI and showed that cortical tubers are hypoperfused, even before the first seizure occurs.[11] In active epilepsy, the area of hypo- perfusion may be wider than that of the corresponding tuber. Patients with intractable epilepsy exhibit hypoperfused areas without corresponding cortical tubers, localized mostly in the temporal regions. This suggests that secondary epileptogenic foci contribute to intractability.

In the past, more than two thirds of patients with tuberous sclerosis and IS were left with mental retardation and behavioral disorders, and more than half exhibited autistic traits,[45] a rate twice that for all patients with IS. Mental retardation is linked to the number of tubers together with IS.[71] Intellectual outcome is significantly improved by the control of spasms and subsequent seizures.[41,48] Early treatment with vigabatrin, which controls spasms in >90% of cases,[13] prevents the development of autistic features in most instances, even in patients who still have intractable partial seizures.[47] Topography of tubers also plays a major role. Autistic traits with TS were linked to bilateral and combined anterior and posterior tubers,[49] whereas mental retardation is associated more with other generalized seizures in patients with bilateral anterior tubers. Patients with selective cognitive defects had had either transient IS rapidly controlled by therapy or infrequent partial seizures, and they had a single detectable cortical tuber.

Neurofibromatosis

The combination of neurofibromatosis and West syndrome is not coincidental.[69] Spasms are usually symmetric, with a typical hypsarrhythmic EEG, “independent” spasms on ictal EEG and no focal features. This is the only symptomatic condition having the clinical and EEG characteristics of “idiopathic West syndrome” in most patients. A single case of hemimegalencephaly with neurofibromatosis has been reported.[18]

Perinatal Hypoxia-Ischemia

Severe hypoxia-ischemia in full-term newborns producing convulsions in the neonatal period and IS in infancy has become a rare condition in developed countries. Electroencephalographic features are a markedly depressed tracing followed by a progressive return to normal or near normal before focal or multifocal spikes or sharp waves appear and foretell hypsarrhythmia.[107] The outcome of the spasms is rarely favorable,[103] and partial epilepsy with multiple foci or generalized epilepsy may occur in more than half of patients.

In premature infants, numerous positive rolandic spikes lasting several weeks indicate a high risk for periventricular leukomalacia. In two of nine patients, the spikes were followed by development of West syndrome.[72] Outcome of the epilepsy is favorable in most patients following steroid treatment, although they are left with spastic diplegia.[88] Regarding patients with periventricular leukomalacia, the occurrence of paroxysmal discharges as irregular spikes-and-waves and polyspikes-and-waves, mainly in bilateral parietooccipital areas, is predictive of the development of WS.[93] The timing of brain insult in premature infants who develop WS is determined by maturation, not by the term of delivery.[72]

Porencephaly

Among 173 patients with IS investigated by computed tomography (CT), Cusmai et al. found 10% to have focal lesions, mainly porencephaly.[19] Most patients had spasms as the first seizure type, although occasionally partial seizures preceded them.[1] Epileptic spasms are asymmetric in one third of cases, and the EEG shows asymmetric hypsarrhythmia with striking focal features.[19] Outcome is favorable, but partial epilepsy may occur by 2 to 3 years of age, mainly in patients with frontal porencephaly.

Chromosome Disorders

Down Syndrome

WS involves 1% to 3% of patients with Down syndrome. WS may result from ischemic brain lesions produced during delivery or may be caused by congenital heart disease. Nonetheless, the combination of Down syndrome and WS is not coincidental. In a series of 14 patients with Down syndrome who were followed from their first spasms,[89] spasms had begun at a mean age of 8 months, spasms were symmetric and associated with no other type of seizure, and mental deterioration involved tone and eye contact. Hypsarrhythmia was typical in 13 cases, asymmetric in 1. The spasms of 8 patients were recorded; these were “independent,” and intravenous diazepam failed to show any focal feature. Therefore, the neurophysiologic features were those of idiopathic WS. However, unlike idiopathic WS, this condition is particularly resistant to treatment when its onset is delayed by >2 months, with significantly increased risk of autistic features and pharmacoresistance.[33,81] During the following years, patients often exhibited other types of seizures—myoclonic, tonic–clonic, or absences—that were usually easy to control. Thus, in contrast to brain malformations and tuberous sclerosis, and despite the fact that the gyral pattern in the temporal lobe is abnormal, Down syndrome does not exhibit the features of focal or diffuse brain malformations; rather, the characteristics are mainly those of a functional phenomenon, as in idiopathic epilepsies. However, functional consequences may be severe, possibly related to diagnostic delay with postural delay and the development of autistic features.

Deletions and Mutations

Sex-linked dominant inheritance involves incontinentia pigmenti; other families had Xp11.4-Xter, Xp11.4-Xp22.11[92] chromosomal translocation, and others had Williams[68] syndrome. Dysmorphia, hypotonia, and pyramidal signs are combined with inversion duplication[6] and partial hexasomy[44] of chromosome 15q. The 1p36 deletion with characteristic craniofacial abnormalities and mental retardation includes epilepsy, which often consists of severe IS when there is loss of the potassium channel beta-subunit gene, KCNAB2. Various familial dysmorphias are combined with IS, including broad thumbs,[98] cleft lip, and exophthalmos.[101] Familial

IS with microcephaly and nephrotic syndrome[84] has been reported. Monogenic conditions are being recognized. Various abnormalities of Aristaless-related homeobox gene, ARX, produce IS in 12.5%[76] to 34% of the cases.[91] However, IS are not the only type of seizures, and myoclonic epilepsy does occur,[100] with some apparent genotype–phenotype correlation.[53] Missense mutations,[97] frameshift deletions,[87] and de novo balanced X autosome translocations[52] in the X-linked cyclin-dependent kinase–like 5 (CDKL5/STK9) gene produce early-onset severe IS. Mutation of the ATPase-sensitive potassium channel Kir6.2 is associated with IS.

Inborn Errors of Metabolism

They are rare and comprise a wide variety in which IS are but one expression of infantile convulsions. However, Menkes disease,[94] phenylketonuria and biopterin deficiency, and mitochondrial disease due to NARP mutation[62] comprise a high proportion of patients who develop IS. In Menkes disease, West syndrome is constant following the first occurrence of status.[4a] In phenylketonuria, WS affects 1 patient of 6, and the phenylalanine-free diet can only prevent its occurrence when started before the age of 3 months.[108] In biopterin deficiency with WS, the diet does not permit solution of the epilepsy, which needs steroid therapy.[66] The NARP mutation produces pharmacosensitive WS.[23] Complexes I, III, and IV and combined I and IV have also been reported in combination with WS.[7] Spasticity, nystagmus, apnea, and cardiac problems are usually combined in these cases.[99] The latter is easily recognized based on T2 hypersignal in the basal ganglia. Blood lactate is usually normal in patients with IS.[86] Schinzel-Giedion syndrome, which comprises several facial dysmorphisms, midface hypoplasia, and multiple skeletal anomalies, produces IS in one fourth of the cases.[42] In some families, hypsarrhythmia was combined with congenital encephalopathy, edema, and optic atrophy (PEHO) and was inherited as an autosomal recessive trait.[36,55,102]

Cryptogenic/Idiopathic West Syndrome

Of patients with IS, 15% to 32% have a normal development before the onset of spasms and exhibit no evidence of brain lesion.[54,63] These cases are classically designated as cryptogenic[39] or idiopathic.[50] According to the 1989 classification of epilepsies and epileptic syndromes, the terms are not synonymous; *cryptogenic* indicates that the origin is hidden, whereas *idiopathic* means that there is no cause other than the disease itself. In addition, according to this classification,[80] West syndrome may be either symptomatic or cryptogenic, but not idiopathic. However, a number of patients with West syndrome exhibit spontaneous disappearance of epilepsy and complete recovery of mental development.[3] The proportion of cryptogenic/idiopathic cases varies in the reported series from 15% to 53%, probably as a result of varying definitions of the condition. For idiopathic cases, the figures are 26% and 6% in the only two available series.[28,105] The latter series also show that based on clinical and neurophysiologic characteristics, it is often possible to differentiate cryptogenic from idiopathic cases.

Cases are considered to be *cryptogenic* when indirect evidence of focal or multifocal cortical involvement exists. Focal ictal discharges may be recorded between clusters of spasms by 24-hour ambulatory EEG.[79] During a cluster, a focal discharge may occur, and hypsarrhythmia does not usually recur between consecutive spasms.[25] In most instances, however, no focal discharge is recorded during a cluster, but again hypsarrhythmia does not recur between spasms, thus showing that the whole cluster is a single seizure. Parents often notice that the child's behavior changes before the first spasm, as an “aura” easily overlooked by the medical staff. Focal interictal abnormalities can be evidenced by reducing the amplitude of the recording or by the intravenous administration of diazepam. Neuropsychologic investigation at the onset of the disease may demonstrate loss of eye tracking or babbling, or asymmetry of grasping.[29] Focal dysplasia may be overlooked by MRI until myelination shows the blurred border between gray and white matter by the end of the second year of life. Inversion recovery or thin slices may be helpful. Functional imaging by SPECT[12] and positron emission tomography (PET)[15] may detect single or multiple abnormal cortical areas. Cases with demonstrated abnormalities should then be considered as symptomatic and treated as such. A majority of the remaining patients later exhibit partial or generalized epilepsy, including Lennox-Gastaut syndrome, associated with development of mental retardation, autistic features, speech delay with hyperkinesia, and visual disorders. The latter disorders are correlated with the topography of EEG and functional imaging foci, and a correlation could be found between subscores of the Brunet-Lézine test battery at onset of West syndrome and on follow-up.[46] Very few neuropathologic investigations have been reported. In patients with focal abnormalities, cortical dysplasia is usually observed. The pathologic significance of more widespread heterotopic neurons remains to be demonstrated.[64]

The term *idiopathic West syndrome* is used to designate the condition of patients who are considered to have no brain lesion and for whom epilepsy is a purely functional phenomenon. Identification of these patients at onset of the disease is based on lack of indirect signs of brain lesion. Normal development before spasms is extremely difficult to determine. In a prospective study, 12 of 14 patients had acquired the ability to grasp objects and all had acquired smiling and eye tracking; loss of milestones was mild, with only 1 patient having lost eye tracking.[31] Hypsarrhythmia is symmetric, with no spike-and-slow-wave focus after intravenous diazepam. Recorded clusters show reappearance of hypsarrhythmia between spasms and no focal discharge. In a later article, it was shown that significant diagnostic features include no loss of eye tracking and smiling. In regard to ictal EEG, it was shown that 12- to 14-hour ambulatory recording is necessary to analyze the characteristics of the cluster of spasms.[79]

"Lumping" Versus "Splitting"

It has become clear that the clinical and EEG features of IS mainly depend on its cause. Asymmetric spasms indicate a cortical brain lesion, thus demonstrating the cortical contribution to the genesis of the spasms. The EEG pattern may be specific for a given brain malformation, thus showing that it is determined by the cortical abnormality, not by the epilepsy. Secondary generalization may result from single focal or multifocal epileptogenic brain lesions, such as tuberous sclerotic lesions or anoxoischemic lesions after term delivery.

Hypsarrhythmia is an age-related dysfunction of the brain cortex occurring around a focal lesion or without any evidence of structural lesion.[26]

This correlation of clinical and EEG expression with etiology has three implications: (a) The diagnosis may be suspected based on clinical and EEG characteristics, which may contribute to an improved imaging workup; (b) evaluation of the prognosis may be improved, particularly when the characteristics of idiopathic West syndrome are present; and (c) therapeutic decisions may be made more specifically, according to etiology. For instance, vigabatrin has been shown to be better than steroids in tuberous sclerosis in a randomized, prospective trial.[13]

Treatment

The major drugs that have been shown to be effective in IS are steroids and vigabatrin. Considering an evidence-based approach, ACTH is "probably" effective in the short-term treatment and vigabatrin (VGB) "possibly" effective.[61] They both have side effects, although different in potential severity: Vigabatrin may induce bilateral restriction of the peripheral visual field in around 20% of cases, whereas steroid therapy carries a mortality rate from 2.3%[57] to 4.9%.[82] Most conventional antiepileptic compounds are ineffective, but some patients respond to valproic acid, lamotrigine, high doses of pyridoxine, topiramate, sulthiame, and zonisamide. Carbamazepine may even worsen the condition, which is an important finding in view of the possible combination of IS with focal seizures.[95] Very little has been reported with ketogenic diet in WS. In our hands, it proved occasionally but rarely effective in patients who had not responded to VGB and steroids. The evidence for an effect as first-line treatment remains to be evaluated.[85]

It has been advocated not to give aggressive treatment, that is, steroids, to patients with IS symptomatic of brain injury because the side effects would exceed the mild benefits. However, this assertion mainly results from the major dispersion of mental functions before the first spasms, of psychomotor regression at the onset of the disorder, and of the ability of treatment to control seizures and interictal paroxysmal activity. When focusing on a single etiology, it appears that treatment schedules are not equal. For instance, vigabatrin as initial therapy proved to be more efficient than steroids in tuberous sclerosis[13] but less in other etiologies[59] at 2-week treatment. Developmental and socialization outcomes are favorably influenced by early and rapid control of spasms with vigabatrin in tuberous sclerosis[47] but with steroids in cryptogenic cases.[35,60] On the other hand, up to 10% of patients seem to recover spontaneously.[3,30] Therefore, early, tailored and sometimes aggressive treatment is required to achieve total control of seizures and paroxysmal EEG abnormalities.

Treatment strategy mainly depends on drug availability in different countries. In most countries, VGB is considered the drug of choice as first-line monotherapy, the major remaining question being for how long. In cryptogenic cases, 6 months seems reasonable. For tuberous sclerosis, the risk of a severe and intractable relapse persists until the age of 5 years. Adding steroids to VGB seems to be more effective than steroids alone, but, again, whether VGB should be continued for a long period needs to be clarified. In a prospective population study, it could be shown that tailored choices are useful for steroid treatment, using hydrocortisone for 2 weeks and then switching to ACTH in case of failure. Recovery is only considered when both the spasms and EEG paroxysmal activities have ceased.[106]

Surgical removal of an epileptogenic cortical brain lesion can be effective, provided it is the only lesion. Patients with tumors, focal dysplasia or hemimegalencephaly, and porencephaly have all benefited from removal or disconnection of the lesion, with cessation of epilepsy and improvement in psychomotor development.[67,90] The earlier the surgery, the better is the developmental outcome.[51] Identifying the lesion by imaging may be an issue before the age of 18 months, when myelin has become mature, thus showing properly the white/gray border. Total callosotomy was useful in 80% of children who underwent this procedure after having acquired walking. However, if the child is able to speak, it should be performed before the age of 10 years to avoid the risk of deterioration of this ability. Both anterior and posterior sections proved to be ineffective.[77]

Summary And Conclusions

Although each of the various causes of IS is associated with quite specific features, the age of onset, main seizure type, and occurrence of generalized paroxysmal activity are similar for all patients. The similarity of these three characteristics among patients is sufficient to delineate a syndrome, although other characteristics vary widely according to underlying cause.

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Chapter 230

Severe Myoclonic Epilepsy in Infancy (Dravet Syndrome)

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Michelle Bureau

Introduction

Severe myoclonic epilepsy in infancy is one of the most severe epilepsies affecting the infants and deserves to be recognized as soon as possible in order to manage it appropriately. However, the diagnosis is not easy and every infant who presents with long and repeated febrile convulsions before the end of the first year of life must be carefully followed because he is at risk for this epilepsy. Up to now, no antiepileptic drug has allowed controlling the seizures completely and almost all the childern have an abnormal psychomotor development and cognitive impairment at the adult age. In the last years, the genetic origin of this epilepsy has been demonstrated, most of the patients being carriers of a *de novo* mutation in the SCN1A gene, but not all. Currently, many studies aim to discover either the other mutations that could be responsible or the function of the known mutations.

Historical Perspectives

Severe myoclonic epilepsy in infants (SMEI) was first defined in 1982[14] and recognized as a syndrome in the most recent international classification of the epilepsies.[9] Since 1982, about 445 cases have been published in the literature. Most cases are reported from Southern Europe and Japan, but descriptions also come from other regions.[3,26,30] The name of the syndrome was used in the first description to underscore the ictal and interictal, myoclonic component, which allowed differentiating this syndrome from the Lennox-Gastaut syndrome. In the latter, the ictal hallmarks are occurring by generalized tonic seizures, mainly during sleep, and atypical absences. Later, it appeared that myoclonus could be absent in some patients. Seizures were polymorphic, and it was more difficult to find an appropriate semiologic designation.[1] For this reason the Commission on International Classification has proposed using the eponym “Dravet syndrome.”[9] Since 2000, because of the discovery of a mutation in the sodium channel gene *SCN1A* in some patients,[8] this syndrome has been the target of a number of genetic studies that have given new insights to its pathophysiology.

Definition

Severe myoclonic epilepsy in infants is characterized by febrile and afebrile, generalized and unilateral clonic or tonic–clonic seizures that occur in the first year of life in an otherwise normal infant. Later there is with myoclonus, atypical absences, and partial seizures. All seizure types are resistant to antiepileptic drugs. Developmental delay becomes apparent within the second year of life and is followed by definite cognitive impairment and personality changes. The disorder has been categorized among “epilepsies and syndromes undetermined as to whether they are focal or generalized” because the syndrome shows both generalized and localized seizure types and electroencephalographic (EEG) paroxysms.[9] In the most recent proposal it is placed among the “epileptogenic encephalopathies.”[15]

Many children have been reported with a similar picture but without myclonus, and this condition has been designated as “borderline SMEI” (SMEIB).[33] These patients can have different EEG features but have the same course and outcome as patients with myclonus, and they can be included in the same syndrome. Recent genetic studies have demonstrated of *SCN1A* mutations in SMEIB patients but with differences in the type and the site of these mutations.

Epidemiology

SMEI is a rare condition. In the patient population of the Centre Saint-Paul, SMEI was diagnosed in 63 of 6,300 patients (1%) between 1970 and 1990. Hurst[26] estimated an incidence of at least 1 case in 40,000 children <7 years of age in the general population, and Yakoub et al.[50] gave a slightly higher figure (1/20,000 or 1/30,000). In children with seizure onset in the first year of life, the proportion varies from 3%[2] to 5%.[50] These findings show that this syndrome deserves to be recognized in infants with early convulsions. Mild male predominance has been reported.[13]

Etiology and Basic Mechanisms

SMEI shares some characteristics with the idiopathic epilepsies (genetic predisposition, photosensitivity, generalized seizures, and generalized spikes-and-waves on EEG), but they are also associated with features of localization-related epilepsies (focal seizures, focal EEG anomalies, cognitive impairment). Moreover, the course of the disease—progressive during the first stage and always severe—could suggest a metabolic disease. However, none has been identified.

Until recently, magnetic resonance imaging (MRI) was said to be normal, even when repeated some years after the onset. However, in 2005, new data were published by Siegler et al.,[40] who performed the first systematic neuroimaging study with repeated MRI at different ages. They found hippocampal sclerosis (HS) in 10 of 14 patients with SMEI. In 6 of them, HS was not present on the first MRI, performed during the first 2 years in 5 patients and at 11 years in 1 patient, but developed later, between 14 months and 16 years. In the other 4 children, the first examination was not performed before the age of 4 years. In the last 4 children, MRI, performed between 6 and 17 years, remained normal. Because all the patients had a history of

numerous hemiconvulsions and generalized tonic–clonic seizures (GTCS) during the first year, these results support the hypothesis that HS is a consequence of prolonged febrile seizures, even if it is unclear why 4 of the patients did not show HS.

Neuropathologic findings reported by Renier and Renkawek[37] from an autopsied case included cerebellar microdysgenesis, irregular lamination of cerebral cortex, and threefold spinal cord canals. There are no other neuropathologic studies.

A mitochondrial cytopathy was suspected in three patients who presented with an extremely severe picture.[5,6,16] However, according to Dravet et al.[13] and Giovanardi-Rossi et al.[20] no structural or histochemical abnormality was present in the biopsy samples from muscles in respectively five and nine patients.

A family history of epilepsy or febrile seizures is often present, ranging from 25% to 71%.[13] Five families have been reported with two affected siblings in each.[13,33,47]

Monozygotic twins have been reported by Fujiwara et al.,[17] Musumeci et al.,[31] and Ohki et al.[35] Recently, several publications described SMEI cases in the syndrome of generalized epilepsy with febrile seizures plus (GEFS+).[41,42,47] Thus, a genetic etiology could be suspected and was confirmed by the recent discovery of a de novo mutation in the sodium channel gene *SCN1A*.[8] Several publications have reported analogous findings in a high proportion of patients with SMEI but not in all. The percentage varies from 35% among 93 patients,[32] to 62% among 76 patients[19] (in part already published in the Nabbout et al. study[32]), to 71.4% among 12 patients,[44] to 82.7% among 29 patients.[36] Only two studies reported a *GABRG2* mutation,[25,28] which was not found by Madia et al.,[29] in 53 patients without the *SCN1A* mutation. Different mutation types were reported (truncating, missense, nonsense) in different sites of the gene. Correlations of phenotypes to genotypes were variable in different studies. Mutations were observed also in SMEIB,[18] but truncating mutations were largely predominant in the typical form.

Clinical Presentation

Initially, prolonged, generalized, or unilateral clonic seizures are typically but not always triggered by fever. In some patients, isolated episodes of focal myoclonic jerking are noted by parents. Shortly thereafter, seizures also appear without fever. These convulsive seizures tend to be long (>20 minutes), recur in clusters in the same day, and evolve to status epilepticus. Their lateralization is variable, from one side to the other, either in different episodes or even in the same episode (alternating seizures). Generalized or erratic myoclonus, or both, appear between the ages of 1 and 4 years in typical cases. Jerks are usually mild, and falling is infrequent.

Other seizure types are observed during the course of the disease. Atypical absences accompanied by myoclonus occur in 40% of patients, often as absence status associated with convulsive seizures. The status consists of impaired consciousness, variable in intensity, with fragmentary and segmental, erratic myoclonias of low amplitude involving the limbs and the face, sometimes associated with a slight increase in muscular tone. According to the degree of altered consciousness, patients can or cannot react to stimuli, and have simple activities interrupted by short episodes of complete loss of contact and staring. Convulsive seizures can either initiate, occur during, or terminate the status. The EEG is characterized by diffuse slowing, intermixed with focal and diffuse spikes, sharp waves, and spike-wave discharge, of higher voltage in the frontal areas and the vertex, with random correspondence between spikes and myoclonias. Simple partial motor seizures or complex partial seizures, with prominent vegetative symptoms, occur in 46% of children observed as a complex partial status in one case.[48] Without EEG video recordings it is often difficult to differentiate between atypical absences and complex partial seizures. Generalized tonic seizures are exceptional but can be observed in the later stage of the disease. Other clinical paroxysmal events are described by parents, but we do not know if they are epileptic seizures.

Psychomotor delay becomes progressively evident. After children have started walking and producing first words at a normal age, they develop an unsteady gait for an unusually long time, and language skills are delayed, if acquired at all. After the age of 2 years, children become hyperkinetic, with recalcitrant behavior and major learning problems. About 60% of children have an ataxic gait, and 20% show mild pyramidal signs. Interictal EEGs are usually normal at the beginning. However, postictal recordings show asymmetry after unilateral seizures, and a photoparoxysmal response is evident before the age of 2 years in 20% of patients (Fig. 1). Interictal generalized spike-and-wave (SW) complexes appear within the second year of life in most children and can be frequent or infrequent, and only slightly activated by sleep. They are associated with focal and multifocal abnormalities in the majority of cases. Background activity is also usually normal at the beginning. Myoclonus is easily demonstrated by polygraphic recordings, accompanied by generalized SW or polySW when generalized, and without detectable EEG changes if erratic (Figs. 1 and 2).

Neuroimaging does not show any definite abnormality at the onset.[13]

Treatment and Outcome

Typically, the course of SMEI is characterized by three phases, as emphasized by Lambarri San Martin et al.[27] The first phase ("febrile phase" according to these authors) covers the first year, with onset of seizures in a normal infant, often febrile or related to infectious episodes and vaccinations. The second phase ("catastrophic phase") extends from the second to the fourth year, with explosion of frequent and various types of seizures, myoclonus, status epilepticus, psychomotor delay, behavioral disturbances, neurologic signs, and EEG worsening. After 4 years ("sequelae phase"), progressive improvement is observed with decreased seizures and EEG discharges, slow cognitive improvement, and attenuation of the neurologic signs.

However, other periods of worsening are not actually excluded. Although results of medical treatment are in general disappointing, valproic acid (VPA) and benzodiazepines are preferable to other drugs at the very beginning. The first seizures should be treated vigorously, whether, febrile or not, to avoid development of status with its deleterious consequences. Rectal diazepam is the drug of choice and can be used by parents and caretakers. Phenobarbital (PB) can be necessary in case of status. Phenytoin does not offer any advantage and may produce more severe side effects than PB. Continuous oral treatment by VPA should be given when febrile seizures are long and repeated, and when afebrile seizures and myoclonic jerks occur.[38] Among the newer antiepileptic drugs, topiramate is the most promising and should be used as soon as VPA resistance appears.[10] In case of repeated status, stiripentol is the best choice, combined with VPA and clobazam.[7,46] Other options are possible, such as bromides[13] and ketogenic diet.[2,3] Ethosuximide may be helpful in reducing myoclonus and atypical absences. In older patients (third phase), vigabatrin has given promising results, reducing convulsive seizures in patients in whom myoclonus was not a prominent symptom.[23] Conversely, severe worsening of convulsive seizures and myoclonus has been observed with add-on carbamazepine and

lamotrigine, and these should be avoided.[21,48] Particular attention should be given to avoiding intercurrent infections and to prevent the occurrence of status epilepticus because any febrile episode may be complicated by convulsive status.

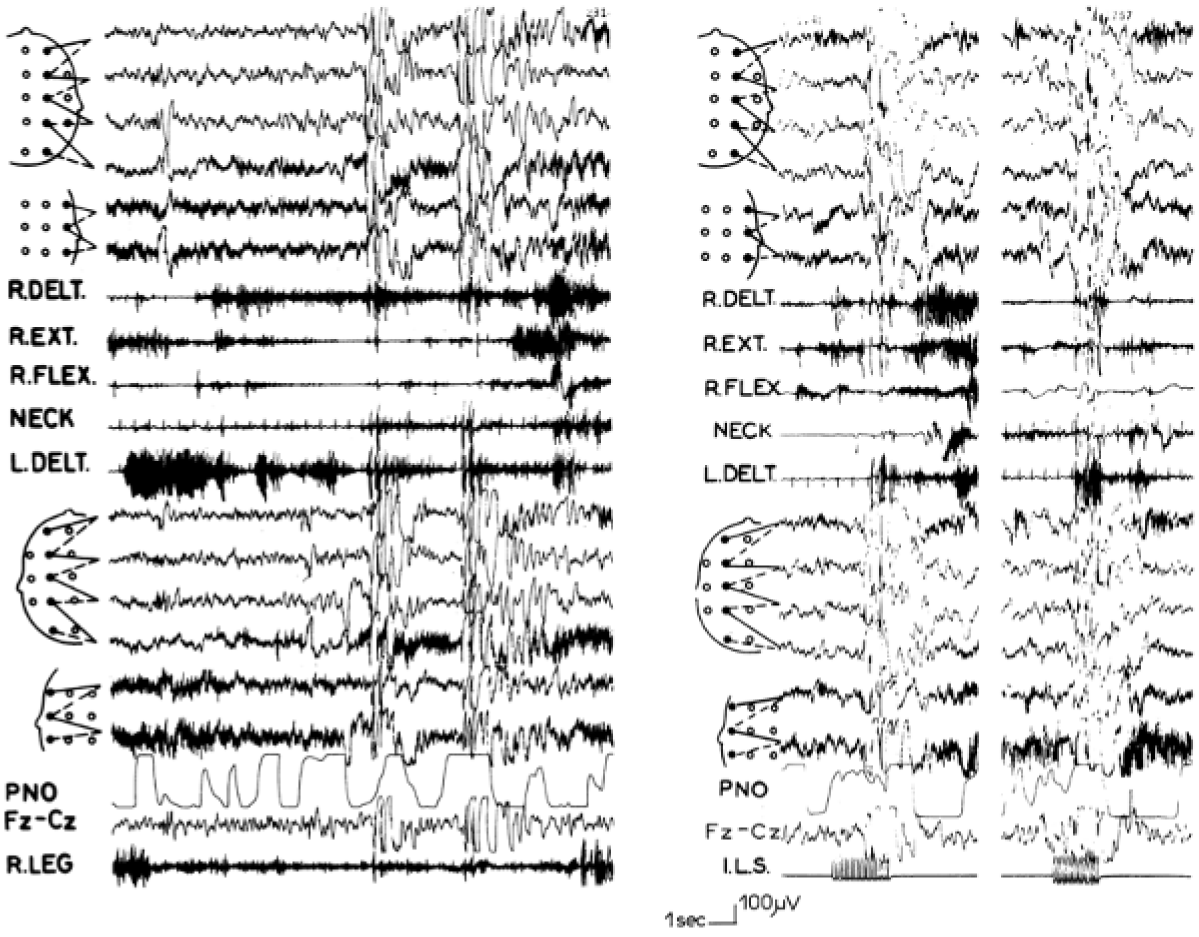

FIGURE 1. Boy, age 1 year, 8 months. **Left:** Polygraphic recording of spontaneous myoclonic attacks is accompanied by generalized spike-and-wave complexes. **Right:** Electroclinical findings of intermittent light stimulation (ILS)–induced generalized myoclonus are similar to those of the spontaneous attacks. L. DELT., left deltoid; R. LEG, extensor of the right leg; R. DELT., right deltoid; R. EXT., extensors of the right wrist; R. FLEX., flexors of the right wrist; PNO, pneumogram.

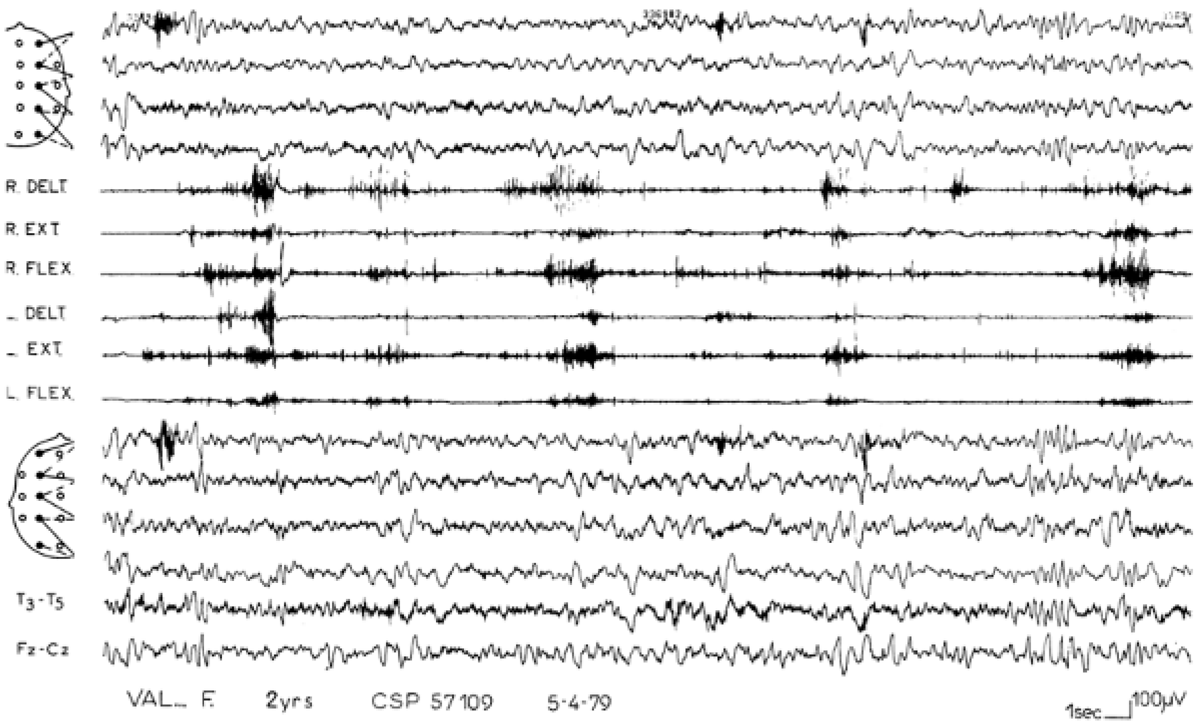

FIGURE 2. Girl, age 2 years. Polygraphic recording of segmental myoclonus at rest and during muscular contraction. Myoclonic potentials are not accompanied by time-locked paroxysmal electroencephalographic abnormalities. L. DELT., left deltoid; L. EXT., extensor of the left wrist; L. FLEX., flexor of the left wrist; R. DELT., right deltoid; R. EXT., extensors of the right wrist; R. FLEX., flexors of the right wrist.

Peculiar features are remarkable temperature, sensitivity and photosensitivity. Seizures can be triggered by slight variations in the body temperature of only few degrees (e. g., going from 36.5°C to 37.5°C) without associated infection, sometimes related to external temperature or physical efforts. In Japan, hot baths are a frequent triggering factor.[45] Other triggering factors are variations in the environmental light, eye closure, and pattern fixation leading to self-stimulation.

Long-Term Prognosis

Follow-up in the series by Dravet et al.[13] varied from 2 years, 6 months to 33 years, 8 months (median, 11 years, 6 months). Long-term outcome was always unfavorable. Convulsive seizures persist, with a tendency to be localized at night. They are described as generalized but often have a localized onset, proved by ictal video-EEG recordings. The course of myoclonus is variable. It may persist, more or less attenuated, disappears, or occur only just before a convulsive seizure. Complex partial seizures usually no longer occur after the first years but the age of disappearance is not homogeneous.[13,35] Atypical absences and absence status also tend to cease. Electroencephalographic findings may vary by age from one patient to another. Generalized SWs tend to disappear. Focal abnormalities, often localized in the central areas, are activated during sleep. Background activity can deteriorate during the course of the disease, mainly when convulsive seizures are frequent, especially between the ages of 5 to 10 years, and then return almost to normal. Temperature sensitivity decreases. Photosensitivity and pattern sensitivity can be constant during the course or occur inconsistently. All patients are cognitively impaired, with 50% of those 10 years and older having severe retardation. The mental impairment constitutes itself progressively during the first 4 to 6 years and then remains more or less equal without further deterioration. A single neuropsychological study was conducted in Marseille, France,[4,49] on 20 patients aged from 11 months to 16 years, with a follow-up of >3 years in 10 cases. Cognitive and behavioral difficulties were always present at varying degrees. Neuropsychological deficits involved all skills, with motor, linguistic and visual abilities being most affected. Behavior was

marked by hyperactivity, psychotic type of relationships, and some autistic traits. The appearance of neuropsychological disorders seemed to be related to the severity of epilepsy during the first 2 years of life.

The mortality rate is very high, around 15% in our most recent series.[13] Several other authors have also reported this high incidence of early deaths.[11,33,34] Causes of death are various, and include drowning, accident, status epilepticus with hepatic or multiorgan failure, severe infection, and sudden unexpected death.

In adulthood, these patients present as dependent persons with mental disabilities, with poor language, poor fine motor function, generalized slowness, sometimes autistic features, and rarely aggressiveness or other psychiatric features. They have few or no school skills, are unable to work, and live in specialized institutions or with their family. However, we underline that therapeutic possibilities have strongly increased with the use of new and more efficacious drugs and strategies. We can hope to see a better outcome for these patients due to these improvements.

Differential Diagnosis

The first seizures must be differentiated from febrile convulsions. Long duration and clustering of attacks despite treatment should lead one to suspect SMEI. Appearance of myoclonus, established by EEG and electromyographic recordings, and photosensitivity are typical. However, in some children with a similar outcome, myoclonus is a minor feature or is absent.[43] Differentiation from benign myoclonic epilepsy is quite easy and is based on three major features: (a) onset with brief generalized myoclonic attacks, (b) which represent the only ictal manifestation in a normal child, (c) with generalized SWs on the EEG.[12] In the rare patients having benign myoclonic epilepsy with febrile seizures, these seizures are always simple and infrequent. The differences between SMEI and Lennox-Gastaut syndrome are clear enough (see Chapter 241). On the contrary, more difficulty arises in differentiating SMEI from myoclonic-astatic epilepsy (MAE),[22,24] a syndrome category in which some children are first seen with early-onset generalized convulsive seizures triggered by fever.

Although this onset is very similar to that of SMEI, it is not the most common in MAE, and the course is different, with myoclonic-astatic seizures (drop attacks) becoming a major feature with absence of any focal clinical or EEG manifestation. The long-term outcome is variable. Some of the affected children remain intractable and have a severe cognitive impairment, but others improve and become seizure free. Another condition that must be ruled out is a progressive myoclonic epilepsy resulting from metabolic disorders, mainly the neuronal ceroid lipofuscinoses. The absence of visual disturbances and of abnormalities of the fundus coupled with negative results of relevant laboratory investigations eliminate this diagnosis. The last differential diagnosis is with a cryptogenic focal epilepsy, which may have the same onset, with febrile seizures rapidly associated with focal seizures. However, these patients do not present atypical absences and myoclonic jerks in the later course, and their EEG shows focal abnormalities that remain localized in the same area. Moreover, this diagnostic is very improbable when the hemiclonic seizures are alternating.[39]

Summary and Conclusions

Severe myoclonic epilepsy in infants is characterized by febrile and afebrile generalized and unilateral clonic or tonic-clonic seizures that occur in the first year of life in an otherwise normal infant and are later associated with myoclonus, atypical absences, and partial seizures. All seizure types are resistant to antiepileptic drugs. Developmental delay becomes apparent within the second year of life and is followed by definite cognitive impairment and personality disorders. Some cases do not present with all the features and are described as borderline or atypical forms. In the most recent proposal it is placed among the “epileptogenic encephalopathies."

In more than 60% of patients in the most recent studies, mutations in the sodium channel gene SCN1A have been found. In more than 60% of patients in the most recent studies, different mutations types were reported in different sites of the gene. Correlations of phenotypes to genotypes are not well established.

Initial prolonged, generalized, or unilateral clonic seizures are typically but not always triggered by fever, and seizures also appear without fever. They tend to evolve into status epilepticus. They are generalized or lateralized (alternating seizures). Later on, myoclonic seizures, atypical absences, absence status, simple partial motor seizures or complex partial seizures, with prominent vegetative symptoms, are observed. Interictal erratic myoclonus also appears between the ages of 1 and 4 years in typical cases. Psychomotor delay and behavioral disturbances become progressively evident, often associated with ataxia and pyramidal signs. Interictal EEGs are usually normal at the beginning. Later on, generalized spike-and-wave discharges associated with focal and multifocal abnormalities appear in the majority of cases, and photosensitivity is frequently observed. Neuroimaging does not show any definite abnormality at onset.

Typically, three phases characterize the course of the disease: the “febrile phase" (first year), the “catastrophic phase" (from the second to the fourth year), and the “sequelae phase" (after 4 years) with decrease in seizures and EEG discharges, slow cognitive acquisitions, and attenuation of the neurologic signs, other periods of worsening being not actually excluded. Triggering seizure effect of temperature variations persists all over the life, whereas photosensitivity is fluctuating.

Treatment is disappointing. Valproate, benzodiazepines, topiramate and stiripentol are the most useful antiepileptic drugs. Carbamazepine and lamotrigine should be avoided during the first phases. Particular attention must be given to avoiding intercurrent infections and to vigorously treating the febrile seizures to prevent the occurrence of status epilepticus (rectal and intravenous diazepam).

In published series, long-term prognosis was always unfavorable, and no adult patient became seizure free. All patients were cognitively impaired, with 50% of those 10 years and older having severe retardation. The mental impairment remained more or less static without further deterioration after the age of four. Mortality rates are very high, around 15%, ofen due to sudden unexpected death. Differential diagnosis mainly includes febrile seizures, myoclonic astatic epilepsy, progressive myoclonus epilepsies, cryptogenic focal epilepsies.

Dravet syndrome should be recognized in infants with early convulsions because it affects 3% to 5% of children seizures in the first year of life. Early diagnosis could allow improved management and, perhaps, a less severe prognosis.

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Chapter 231

Idiopathic Myoclonic Epilepsy in Infancy

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Federico Vigevano

Introduction

The syndrome of benign myoclonic epilepsy in infancy (BMEI) was not clearly identified before its first description in seven infants in 1981.[10] These authors defined it as the occurrence of myoclonic seizures (MS) without other seizure types, except rare simple febrile seizures (FS), in the first 3 years of life in otherwise normal infants. These myoclonic seizures were easily controlled and remitted during childhood. Psychomotor development remained normal, and no severe psychological consequences were observed. Many other cases have been published since. BMEI was classified among the generalized idiopathic epilepsies in the 1989 international classification.[4] Some authors have described cases with reflex myoclonic seizures, triggered by noise or contact, and have proposed to distinguish two separate entities, the second one being named “reflex myoclonic epilepsy in infancy.”[24] We do not think this distinction is necessary,[11] and we will describe all cases as BMEI.

As of 2006, there were 155 cases published in the literature, of which 123 corresponded to the classical description and 32 were reported as “reflex BMEI” (for a review, see Auvin et al.[2] and Dravet and Bureau[11]). The 22 cases reported by Darra et al.[6] are not counted because it is not known how many were already included in other reports. In the first description, onset was before 3 years of age, whereas in subsequent reports, some cases had a later onset, up to 4 years 8 months.[17] This means that the same type of epilepsy may appear at different ages but tends to be more frequent in some periods.[18] The adjective “benign” is considered problematic, because some patients do not have an actually benign evolution, particularly from the neuropsychological point of view.[2,22] For this reason, the name “myoclonic epilepsy in infancy” has been proposed, but it is ambiguous. This BMEI is idiopathic, and to distinguish this syndrome from other myoclonic epilepsies, we propose replacing the *benign* by *idiopathic.* Thus, the condition should be termed “idiopathic myoclonic epilepsy in infancy (IMEI),” but, in this chapter, we continue to use BMEI, which is the designation best known to epileptologists.

In this chapter, the numbers reported without reference citation are taken from the extensive review of the literature by Dravet and Bureau,[11] supplemented by the paper of Auvin et al.[2]

General Considerations

Epidemiology

According to the few available epidemiologic data, BMEI seems to represent <1% of all epilepsies[20] (unpublished data from the Centre Saint-Paul, 1999), 2% of all idiopathic generalized epilepsies (unpublished data from the Centre Saint-Paul, 1997), and around 2% of epilepsies that begin in the first 3 years of life.[5]

Gender Distribution

There is a prevalence of male patients, with a male-to-female ratio of 2:1.

Genetics

The genetics of BMEI are unknown. Cases are rare, and no family cases of BMEI have been described. A family history of epilepsy or FS is present in 50.5% of cases. Epilepsy types found in relatives are difficult to assess. In one case, the mother presented with juvenile myoclonic epilepsy (JME).[6] In another case, the mother had a myoclonic-astatic epilepsy (EMAS). In the case described by Arzimanoglou et al.,[1] the proband was the second of two brothers, and the oldest was affected by typical EMAS. A similar situation was reported in 2006 by Darra et al.[6]

Personal History

Most patients do not have any relevant history prior to the onset of the myoclonic seizures. Only two (1.9%) had an associated disease: Down syndrome[13] and hyperinsulinic diabetes.[3] However, the occurrence of FS is not uncommon (28%). They are always simple, usually rare (one or two), and are observed before the onset of myclonus and before initiation of treatment. In one patient, two isolated nocturnal orofacial seizures occurred 6 months before appearance of myoclonic seizures.[6]

Clinical and Electroencephalographic Manifestations

The age at onset is usually between 4 months and 3 years; earlier onset is uncommon. Rarely, later onset, between 3 and 5 years, is reported.[17,18]

Initially, the myoclonic seizures are brief, often rare, and involve the upper limbs and the head, rarely the lower limbs. In infants, they may be barely noticeable, and the parents sometimes have difficulty determining their exact onset and their frequency. They often speak of “spasms” or “head nodding.” Later, the frequency increases.

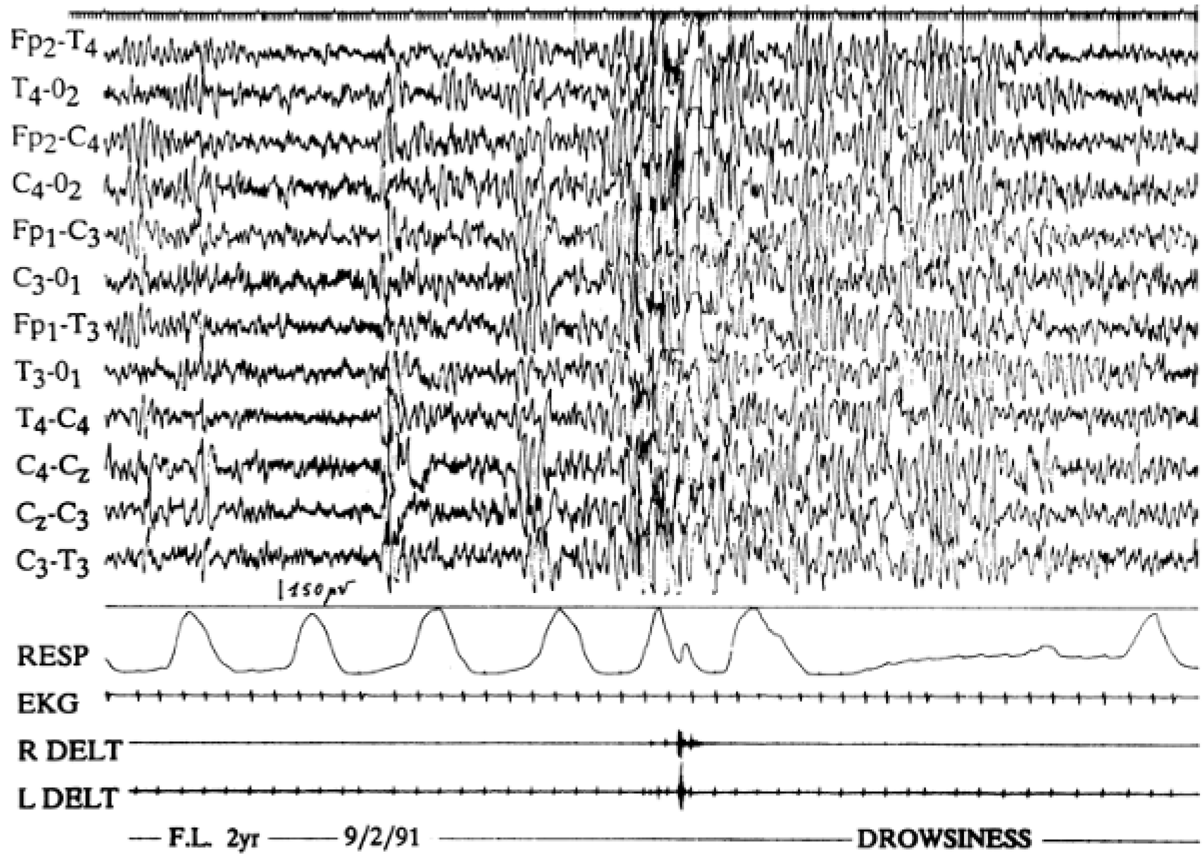

FIGURE 1. Infant with benign myoclonic epilepsy. A spontaneous massive myoclonic jerk was recorded during drowsiness. The ictal EEG shows a brief discharge of generalized spike-wave and polyspike-wave complexes. EKG, electrocardiogram; L DELT, left deltoid; R DELT, right deltoid; RESP, respiration.

Video-electroencephalographic (EEG) and polygraphic recordings have facilitated precise analysis of these seizures. They are more or less massive myoclonic jerks, involving the axis of the body and the limbs, provoking a head drop and an upward-outward movement of the upper limbs, with

flexion of the lower limbs, and sometimes a rolling of the eyes. Their intensity varies from one child to another and from one attack to another in the same child. The most severe forms cause a sudden projection of objects held in the hands and sometimes a fall. The mildest forms provoke only brief forward movement of the head or even a simple closure of the eyes. As a rule, seizures are very brief (1–3 seconds), although they may be longer, especially in older children, consisting of pseudo-rhythmically repeated jerks lasting no more than 5 to 10 seconds. They occur several times a day at irregular and unpredictable times. Unlike infantile spasms, they do not occur in long series. They are not activated by awakening, but rather by drowsiness, except in some cases. In some patients, they can be triggered by intermittent photic stimulation (IPS). In patients with the reflex BMEI, myclonus is triggered by a sudden noise, more often by a sudden contact. The state of consciousness is difficult to assess in isolated seizures. Only when seizures are repeated is there slight impairment of consciousness without interruption of activity. In reflex myoclonic seizures, the myoclonus is elicitable both in wakefulness and in sleep, with a threshold lower in stage I and increasing gradually during the slower stages.[24] No rapid eye movement (REM) sleep has been recorded and tested in patient with reflex myoclonic seizures.

As development continues normally, parents and pediatricians tend not to consider these movements as pathologic events.

When an EEG is performed, it can be normal during the awake state if no myoclonic fits are recorded.

However, myoclonias are always associated with an EEG discharge. Polygraphic recordings demonstrate that myclonic are accompanied by a discharge of fast generalized spike-waves (SW) or polyspike-waves (PSW) at >3 Hz, lasting for the same time as the myoclonia (Figs. 1 and 2). This discharge is more or less regular and can start in the two frontal areas and the vertex. Myoclonias are brief (1–3 seconds) and usually isolated. Each myoclonic jerk may be followed by a brief loss of time. Sometimes, after the attack, there is a voluntary movement, visible as a normal muscular contraction. In only one patient did we observe the association of myclonus in the deltoid muscle with pure atonia in the neck muscles. During drowsiness, there is enhancement of the myclonic jerks; they usually, but not always, disappear during slow sleep. The myoclonic seizures triggered by tactile and acoustic stimuli have the same characteristics (Fig. 2). Ricci et al.[24] noted that the initial manifestation generally, but not always, consisted of a blink, followed 40 to 80 msec later by the first myoclonic arm jerk. After a myoclonic attack, there was a refractory period, lasting 20 to 30 seconds to 1 to 2 minutes, during which sudden stimuli did not provoke attacks, even when the startle reaction was easily elicitable. IPS can also provoke myoclonic seizures.

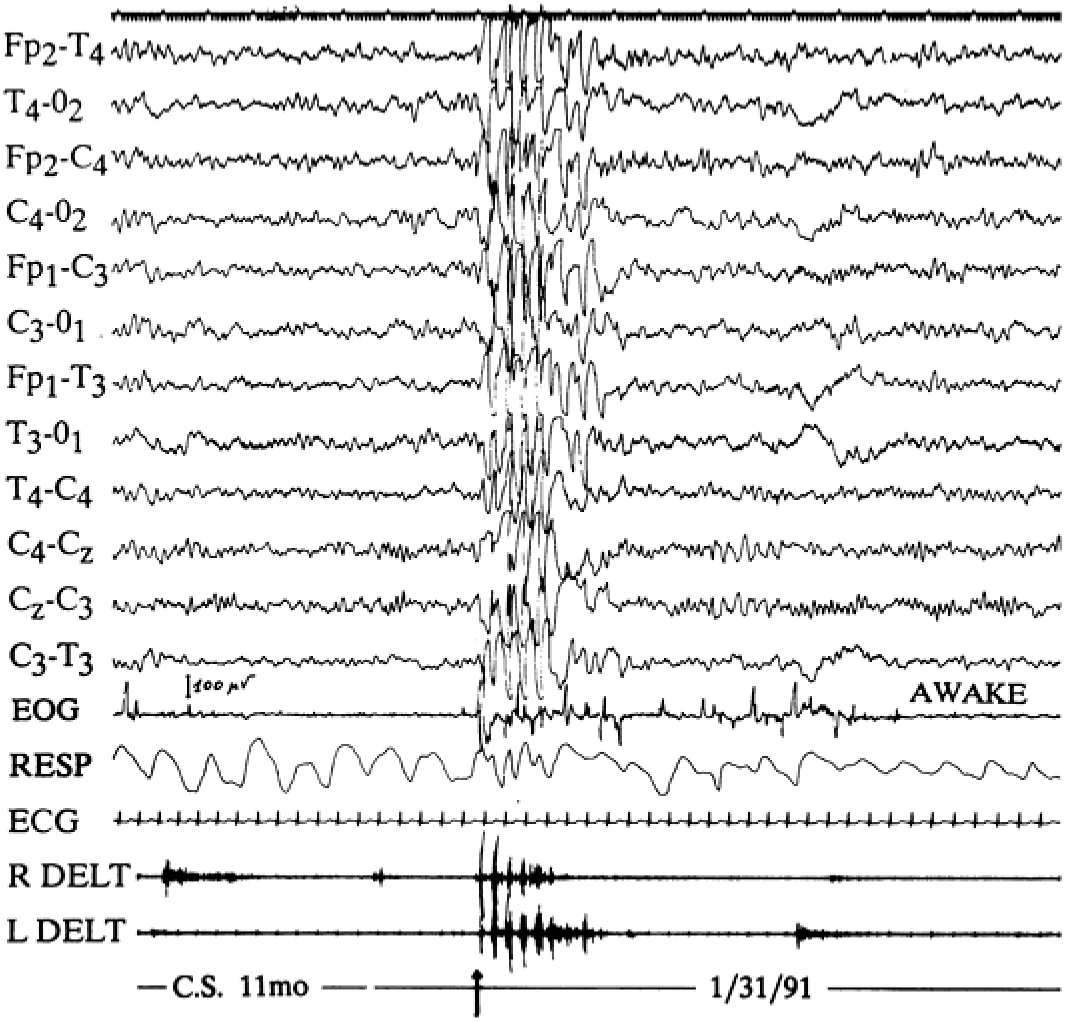

FIGURE 2. Patient affected by reflex benign myoclonic epilepsy in infancy. A sudden noise (*arrow*) triggers a brief cluster of myoclonic jerks; ictal electroencephalogram consists of generalized spike-and-wave complexes. ECG, electrocardiogram; L DELT, left deltoid; R DELT, right deltoid; RESP, respiration.

The interictal EEG is normal. Spontaneous SW discharges are rare; some slow waves may be found over the central areas. Darra et al.[6] described rhythmic, 4- to 5-Hz theta activity over the rolandic regions and the vertex in 4 of 22 children. IPS does not provoke SW without concomitant myclonus at the onset. Nap sleep recordings have shown a normal organization of sleep; generalized SW discharges may occur during REM sleep.

Evolution and Treatment

No other type of seizure is observed in children with BMEI, even if they are left untreated (for up to 8.5 years in one of our patients). In particular absence or tonic seizures do not occur. Clinical examination is normal. Interictal myoclonus was described only by Giovanardi-Rossi et al.,[17] in 6 patients. In reviewing our patients, we found mild interictal myoclonus in 2 patients, revealed by polygraphic recordings. Many patients were not investigated, but when computed tomography (CT) scan and magnetic resonance imaging (MRI) were performed, they were normal (46 patients).

The outcome seems to depend on an early diagnosis and treatment. Myoclonic jerks are easily controlled by valproate (VPA), and the child may then develop normally. If left untreated, patients continues to experience myoclonic attacks, and this may lead to impaired psychomotor development and behavioral disturbances.

The therapeutic modalities have been reported in 131 patients. Monotherapy was used in 109 patients (104 with VPA), polytherapy in 15, and no therapy in 7. Ninety-nine (95.2%) became seizure free on monotherapy. All of the others became seizure free using, usually including VPA and one benzodiazepine, rarely phenobarbital (PB), ethosuximide (ESM), or lamotrigine (LTG). Only in 1 patient did myoclonic seizures persist in spite of various drug combinations and even one ketogenic diet.[23] Finally, 7 patients, 4 of whom presented with reflex seizures, did not receive any treatment and became seizure free spontaneously. On the whole, 125 (95.4%) became seizure free. The study of Darra et al.[6] confirmed these findings, the control of myoclonic seizures having been achieved in all 22 patients.

These data support the VPA as the drug of first choice in BMEI. Treatment must be monitored using plasma drug levels, because irregular intake can lead to relapse and falsely mimic drug-resistant epilepsy. Lin et al.[19] gave a well-detailed account of treatment in their patients. They also underscored the necessity of monitoring and of using high doses at the onset (30–40 mg/kg) to obtain levels >100 mg/L at 3 hours after the morning intake in some patients. The daily dose was reduced to usual therapeutic plasma levels (50–100 mg/L) after seizures were controlled.

Long-Term Outcome and Prognosis

The length of follow-up is known in 112 cases, from 9 months to 27 years, and ≥5 years in 85.

In all these cases, myoclonic seizures disappeared. Their duration is known in 69 cases. In most patients they lasted <1 year. The longest duration (6 years 4 months) was observed only in the first publication, before recognition of the syndrome and its treatment.[13] When duration of follow-up is longer, the number of patients who have other seizure types after the end of the myoclonic seizures increases. Excluding FS, there were 17 reported among the 112 cases with known follow-up (15.2%). They were rare generalized tonic–clonic seizures (GTCS) in 12 patients, without associated myoclonic seizures. It is interesting that only 2 patients with BMEI evolved to juvenile myoclonic epilepsy (JME) at 9 and 12 years, respectively, with seizures well controlled by VPA.[2] Two other patients presented absences, respectively, at 10 and 11 years.[23] They were described as “petit mal” in the first patient and as absences with marked eyelid myoclonia in the second. The last patient, with reflex BMEI, had complex partial motor seizures from 6 years on, with normal EEG, with good response to the combination of carbamazepine and PB.[2] In a series of 22 patients,[6] 4 presented occasional isolated seizures after the age of 5 years: 1 spontaneous GTCS, 1 IPS-induced massive myoclonic seizures, 1 IPS-induced GTCS, and 1 television-induced GTCS.

The EEG outcome is known for 88 patients. EEGs remained abnormal after myoclonic seizures have disappeared, with generalized SW, sometimes focal without clinical correlate (frontal, frontocentral, frontoparietal, frontotemporal), but they became normal later in the majority of patients. It is interesting to note that photosensitivity can appear after the disappearance of myoclonic seizures, as reported by several authors, and can persist for many years after cessation of myoclonic seizures even to adult ages. In once older patients, photo sensitivity is only an EEG response without clinical correlate. Darra et al.[6] confirmed the persistence of photosensitivity. They reported one case with association of generalized SW and typical rolandic spikes, the latter persisting at 9 years, several years after seizure remission and withdrawal of treatment.

These findings affirm the usual good prognosis of BMEI. Attacks provoked by noise or contact were more easily controlled than spontaneous ones. Conversely, photosensitivity was more difficult to control and persisted several years after cessation of seizures.

On the whole, psychological outcome is favorable, and most patients are normal. Outcome is known in 96 cases. Seventy-nine (82.3%) were normal, of whom 56 were age 5 years or older. Twelve (12.5%) presented with mild retardation and attended specialized schools, but none was institutionalized. Five patients (5.2%) had cognitive deficits and personality disturbances. One of them had Down syndrome and strong photosensitivity, and another had myoclonic seizures until age 5 years, with sensitivity to IPS and eye closure.

The psychological outcome of cases reported by Darra et al.[12] was also favorable, and 77% had normal cognitive skills at follow-up.

One recent study[22] analyzed of the neuropsychological and behavioral outcomes in seven patients affected by BMEI, with an average follow-up of 6 years 9 months (range: 4 years 9 months–9 years 2 months). The mean full-scale intelligence quotient of the group was 74, with a significantly higher verbal IQ score in all but one patient. Five were within normal limits, one had slight mental retardation, and one had moderate retardation. All but one also had attention-deficit disorder. The authors underlined the young age at onset of the disease in the patients who had neuropsychological deficits.

In our opinion, the psychological outcome partly depends on an early diagnosis, allowing appropriate treatment and reassurance of the family for the future. The early occurrence of epilepsy often generates great anxiety and leads to wrong educational attitudes. There are, however, also other factors related either to an associated pathology or to an abnormal family structure and a disturbed mother/infant relationship. Finally, it cannot be excluded that the biologic process that causes the myoclonic attacks also interferes with the development of cognitive functions when it occurs in a very immature brain.

Differential Diagnosis

Differential diagnosis must be made with respect to the other epileptic and nonepileptic manifestations that appear in the first years of life. These include *benign nonepileptic myoclonus* described by Lombroso and Fejerman.[21] In this condition, both ictal and interictal EEG patterns are always normal, and the ictal manifestation is not a true myoclonus, but rather a movement similar to a shiver.

When myoclonic seizures start in the first year of life, the other diagnosis that comes to mind is that of *cryptogenic infantile spasms* (IS). IS are clinically different from benign myoclonias: They are more intense, and they involve a strong flexion (or extension) of the whole body, which is never observed in BMEI. In addition isolated, sporadic spasms are always associated with serial spasms in the same infant, and long serial spasms are more likely with awakening. Polygraphic recordings of IS show a typical pattern of a brief tonic contraction, well described by Fusco and Vigevano,[15] only rarely a prolonged myoclonia. The ictal EEG is not a fast, generalized PSW. It is variable, accompanied by a sudden flattening with or without superimposed fast rhythms, or a large slow wave followed by a flattening, or even no visible change. The occurrence of IS is associated with behavioral changes, poor quality of contact, and psychomotor delay leading to arrest and regression. Interictal EEGs are always abnormal, demonstrating either hypsarrhythmia or modified hypsarrhythmia, or focal abnormalities; they never show the isolated or brief bursts of bilateral synchronous SW as in BMEI.

In the first year of life, *severe myoclonic epilepsy of infancy* (see Chapter 230) might be considered, but it always starts with long and repeated febrile and afebrile convulsive seizures. Exceptionally, they can be immediately preceded by myoclonic attacks, more often focal.[12] They are drug resistant and associated with other seizure types. Psychomotor development becomes delayed during the second year of life with behavioral disturbances.

When myoclonic seizures begin after the end of the first year of life, the diagnosis of a *cryptogenic Lennox-Gastaut syndrome* (LGS) may come to mind. In LGS (see Chapter 241), seizures are typically tonic, leading to sudden falls and injuries, and atypical absences, sometimes associated with atonic seizures. Myoclonic seizures are rare. The ictal EEG shows either a recruiting rhythm, a flattening, or a high slow wave followed by runs of low-voltage rapid rhythms. Interictal awake EEGs are characterized by bursts of diffuse slow SW, and sleep EEGs by PSW and diffuse, high-voltage, rapid rhythms. When these EEG features are not present at the very beginning, the diagnosis is based on the rapid association of different types of seizures such as atypical absences and axial tonic seizures, constant impairment of behavior and learning, and lack of efficacy of antiepileptic drugs.

If myoclonic seizures remain isolated or are associated with GTCS, the diagnosis *of epilepsy with myoclonic astatic seizures* (EMAS) (see Chapter 232) must be entertained, although the onset of myoclonic astatic seizures in this syndrome is rare before the age of 3 years.[8] There are two essential differences. The first one is the clinical aspect of the seizures, which associate myoclonic jerks without fall and myoclonic-atonic or pure atonic seizures leading to violent drop attacks. In BMEI, only rarely do the myoclonic seizures provoke falls on the ground. In EMAS, the myoclonic seizures are combined with other seizure types, such as repeated GTCS, atypical absences, and minor epileptic status with stupor, which are never observed in BMEI. The second difference lies in EEG features. SW and PSW are more numerous, often interictal, and grouped in long bursts with an irregular frequency. They are activated by sleep where polyspikes can predominate. The typical theta rhythm over the centroparietal areas described in the seminal Doose's study[8] is not always present. Other differential criteria appear during the following months, including pharmacoresistance and slowing down of psychomotor delay. Some cases included by Doose,[8] however, should probably be classified as BMEI. In the same way, the group studied by Delgado-Escueta et al.[7] under the name of early childhood myoclonic epilepsy (ECME) seems to include cases of both EMAS and BMEI. On the other hand, some relationship between the two syndromes is strongly suspected (see later discussion).

A recent study[23] emphasized the relationship between BMEI and the syndrome of *eyelid myoclonias with absence* because the authors observed eyelid myoclonias with myoclonic seizures in three children. One of them later, at 10 years of age, had this seizure type. Other authors have not observed this evolution.

Finally, one should consider other epilepsies beginning in the first 3 years of life in which myoclonias are the main seizure type and which have a variable prognosis. They are heterogeneous: There is a combination of other types of seizures,

constant presence of EEG focal abnormalities, previous delayed psychomotor development, poor response to drugs, and uncertain prognosis.[9,11] Most probably those are cases of symptomatic myoclonic epilepsies. We also mention the *autosomal-recessive benign myoclonic epilepsy of infancy* described in a single family,[27,28] in which myoclonic seizures were associated with GTCS persisting in adulthood. The locus was mapped to chromosome 16p13 in this family.

Diagnostic Evaluation

The diagnostic workup is simple. It requires a good clinical description and repeated polygraphic video-EEG recordings to demonstrate the presence of myoclonic seizures with generalized SW discharges, either spontaneous or facilitated by drowsiness, noise, contact, or IPS. A sleep recording shows slight activation of discharges without change in morphology, without appearance of rapid rhythms and focal abnormalities. Neuroimaging can be useful to confirm the absence of brain lesions but is not mandatory when the symptomatology is typical. Neuropsychological assessment is more useful to check psychomotor development and follow its evolution. Biologic investigations may be necessary in cases where associated symptoms suggest another disease.

Management

Treatment of choice is VPA monotherapy, which must be prescribed as soon as possible. The use of solution is preferable to that of syrup because it is better tolerated by the infant. Plasma levels must be monitored carefully. A dose of 30 mg/kg divided three times a day is usually sufficient, but higher doses are necessary in some patients.[18] VPA is also effective against possible febrile seizures. If myoclonias are not completely controlled by VPA, the addition of either a benzodiazepine (clobazam or nitrazepam) or ESM can be considered, and the diagnosis must be reviewed. Treatment should be continued for 3 to 4 years if it is well tolerated. In cases of purely reflex seizures, drug therapy may be avoided. When used, seizures can usually be stopped early, except in cases of photosensitivity. The occurrence of a GTCS at adolescence can require another brief period of treatment. The medical treatment must be associated with psychological help to the family, who may be extremely anxious and need to be reassured concerning the good prognosis of this epilepsy.

In practice, the diagnosis of BMEI should be restricted to patients fulfilling the following criteria:

- Brief myoclonic seizures, spontaneous or provoked by noise or contact
- Onset between 4 months and 3 years

- Previously normal infant, often with a family history of epilepsy or FS
- Not associated with other seizure types, except rare simple FS
- In the EEG:
    - Generalized fast SW and PSW during myoclonic seizures
    - Rare interictal SW when awake
    - SW enhanced by drowsiness and slow sleep, sometimes by IPS
    - Normal background
    - Absence of focal discharges
- Good response to VPA monotherapy

In patients with this typical picture, treatment given without delay leads to a good clinical outcome in terms of seizures and cognitive function. In cases with less typical features, particularly in the presence of focal EEG discharges, the diagnosis remains uncertain until a long remission is observed.[26] When the onset is later than 3 years, the diagnosis may be the same.[18]

Nosology

This syndrome belongs to the group of idiopathic generalized epilepsies.[4] It seems to be the infantile equivalent of JME. Auvin et al.[2] reported the first two cases in whom the two syndromes were observed successively, and Darra et al.[6] reported a single case of a mother affected by JME. Delgado-Escueta et al.[7] did not find cases of JME in their study of 24 affected family members with ECME, although they found 76% with other types of idiopathic generalized epilepsies. The relationship with EMAS should be investigated as suggested by the case reported by Arzimanoglou et al.[1] and Darra et al.[6] Moreover, Doose[8] mentioned the case of a patient with EMAS who had two children. The first was affected by EMAS and the second by BMEI.

The last problem is that of the terminology this syndrome. In 1981, it was legitimate to name it “benign” because of the constant disappearance of seizures and the usually good psychological outcome. Today, how benign it is questionable, in light of the definition given by the ILAE Commission report[14] “a benign epilepsy syndrome is a syndrome characterized by epileptic seizures that are easily treated, or require no treatment, and remit without sequelae.” It is now established that a small proportion of patients with BMEI have other seizures later (15.2%) or are not psychologically normal (17.7%) after remission of epilepsy. Whether the cognitive and personality disorders described in rare patients are the sequelae of their epilepsy is difficult to establish, however, given the early age of onset. In some patients, the syndrome can be associated with another conditions, as is accepted in other idiopathic and benign epilepsies, such as the benign epilepsy with centrotemporal spikes.[16,25]

We had the opportunity to read the paper by Zuberi et al.[29] only after the end of our work and have not included their six cases in our analysis.

Summary and Conclusions

In this chapter we have used the name “benign myoclonic epilepsy in infancy" (BMEI), and the terminology is discussed because it has recently been proposed as a substitute for “isdiopathic myoclonic epilepsy in infancy.”

BMEI epilepsy is defined as the occurrence of myoclonic seizures (MS) without other seizure types, except rare simple febrile seizures (FS), in the first 3 years of life in otherwise normal infants. These myoclonic seizures are easily controlled by a simple treatment and remit during childhood. The psychomotor development remains normal, and no severe psychological consequences are observed. Some patients present with a reflex form, in which the myoclonic seizures are usually triggered by noise or contact.

BMEI was classified among the generalized idiopathic epilepsies in the 1989 international classification. It seems to represent <1% of all epilepsies and around 2% of epilepsies that begin in the first 3 years of life. Genetics is unknown. A family history of epilepsy or FS is present in 50.5% of cases. Juvenile myoclonic epilepsy (JME) and epilepsy with myoclonic astatic seizures (EMAS) were reported in four families.

Age at onset is usually between 4 months and 3 years, exceptionally between 3 and 5 years.

The myoclonic seizures consist of very brief shock-like seizures, affecting mainly the upper limbs and the head, isolated or grouped in short clusters, accompanied by a generalized spike-wave discharge of the same duration in the EEG.

Interictal EEG discharges are rare, more often during drowsiness and sleep. An extensive clinical and EEG description of the myoclonic seizures is given.

The outcome seems to depend on early diagnosis and treatment. Myoclonic seizures are easily controlled by valproate (VPA) alone, and the child may then develop normally. If left untreated, the patient continues to experience myoclonic attacks, and this may lead to impaired psychomotor development and behavioral disturbances. On the whole, 95.4% of the patients reported in the literature became seizure free. However, the use of high doses of VPA and the monitoring of the plasma levels are necesssary at the onset. After seizures are controlled, the dosage can be reduced. In the reflex form, pharmacological treatment can be avoided.

Other types of idiopathic generalized seizures can occur after the disappearance of the myoclonic seizures (15.2% of the published patients) and these respond well to treatment. In two patients BMEI evolved to JME, well controlled by VPA. One patient, after a reflex BMEI, had complex partial motor seizures with a normal EEG.

On the whole, psychological outcome is favorable, and about 80% of the patients are normal. The others have slight to moderate mental retardation. Attention-deficit disorders are also described.

Differential diagnosis includes non-epileptic benign myoclonus of infancy, infantile spasms, severe myoclonic epilepsy in infancy (Dravet syndrome), and epilepsy with myoclonic astatic seizures.

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Chapter 232

Epilepsy with Myoclonic Astatic Seizures

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Introduction

Epilepsy with myoclonic–astatic seizures (EMAS) is a recently identified type of idiopathic, potentially severe epilepsy. It is characterized by a combination of seizures, including drop attacks, and psychomotor deterioration beginning in early childhood. These features are similar to those of Lennox-Gastaut syndrome, and the syndrome's nosologic limits, particularly with regard to the Lennox-Gastaut syndrome, are still not clearly determined. A "myoclonic variant of Lennox-Gastaut syndrome" has even been reported that most likely corresponds to one subtype of EMAS. Epilepsy with myoclonic–astatic seizures was identified on the basis of two distinct approaches by two different schools of epileptology: German researchers in Kiel identified genetic predisposition as an etiologic factor in severe pediatric epilepsy at the same time that researchers in Marseille were developing the concept of epilepsy syndromes.[5] A clear definition therefore needs to be established distinguishing EMAS from both the Lennox-Gastaut syndrome and other kinds of myoclonic epilepsy occurring in childhood.[8]

In this chapter, we describe the development of EMAS as a syndrome, delineate it nosologically, describe the specific pattern of cognitive and motor dysfunction, define the therapeutic strategy, and describe the present pathophysiologic hypo- theses.

Historical Perspectives

To understand the apparent contradictions that have paved the way for the identification of EMAS, one has to consider two major schools of epileptology following parallel pathways. The German school—Janz and Christian for adults[9] and Doose and coworkers for children—was making considerable effort to clarify the genetic basis of epilepsy.[7] Careful neurophysiologic analysis played a major role, particularly for children. Doose established a correlations between several electroencephalographic (EEG) patterns and familial antecedents of epilepsy, namely theta rhythms, generalized spike waves, spontaneous or triggered by hyperventilation, and photosensitivity (for a review, see Doose[6]). This allowed him to identify epilepsy conditions affecting early childhood that were thought to be due to genetic predisposition with polygenic inheritance. He called this group, in which myoclonic seizures causing drop attacks were a predominating feature, "centrencephalic myoclonic–astatic petit mal."[7] The main practical interest in the recognition of this group was to show that children with severe epilepsy involving the whole brain and producing drop attacks and cognitive deterioration did not all have Lennox-Gastaut syndrome, and thus some kind of brain lesion, but they could have genetically inherited epilepsy in an undamaged brain.

Patients within "centrencephalic myoclonic–astatic petit mal (CMAPM)" exhibited a range of different types of seizures: tonic–clonic, myoclonic, myoclonic–astatic, tonic, absence, and various types of epilepsy status, mainly myoclonic and absence. However, within this group, Doose distinguished various patterns correlated with different courses[5]:

- Patients who exhibit only generalized myoclonic seizures as the sole seizure type usually have good outcome.

- Patients with clonic seizures from the first year of life experience a severe course and the occurrence of long-lasting clonic status epilepticus contrasting with very few or even no spike waves on EEG.
- Poor outcome is also the case for patients who develop frequent tonic seizures in sleep and for those who have episodes of myoclonic status and develop dementia. Such cases usually begin after the second year of life.
- However, other patients, beginning after 2 years of age, may completely recover, even if they have experienced tonic seizures and daily drop attacks for weeks and their EEG shows a very active spike and wave pattern.

Therefore, although CMAPM features myoclonic seizures and generalized spike-waves, which are assumed to express genetic predisposition, it is completely heterogeneous in terms of clinical presentation, EEG characteristics, and outcome. It is thus not a syndrome, but an etiologic concept of difficult-to-treat generalized epilepsies resulting from genetic predisposi-tion.

In the meantime, the Marseille school developed the concept of epilepsy syndromes following the observation that patients with epilepsy have a variable course ranging from full recovery to pharmacoresistance with major impact on cognitive and motor functions, and that this variability is not related solely to age of onset, seizure type, interictal EEG, or etiology. Indeed, etiology is identified in only one fourth of patients, and the variability also affects both patients without identifiable etiology and those with a given etiology. The type of seizure is not linked to etiology or the course because a given seizure type may occur in epilepsies with the most benign as well as those with the most severe outcome. Children with epilepsy usually exhibit several types of epileptic seizures, and therefore it is not possible to distinguish the various types of epilepsy according to seizure types only. In addition, the neurologic condition prior to onset of seizures, the age of onset, and the interictal clinical and EEG phenomena also vary greatly. However, there are groups of patients that have similar age of onset, seizure types, interictal EEG pattern, and course. These characteristics form the basics of epilepsy syndromes. This concept appeared soon after the clinical introduction of EEG. It became possible to distinguish between two major EEG patterns of generalized spike waves, respectively “petit mal” and “petit mal variant” patterns, which were correlated with different seizure types and distinct courses. In addition, the “hypsarrhythmic” EEG pattern was linked to infantile spasms. This approach to the separation of various epilepsy patterns with distinct courses was then systematized in Marseille. In Lennox-Gastaut syndrome, drop attacks result from tonic seizures or atypical absences, whereas myoclonic seizures are rare. Therefore, it differs from conditions that include mainly myoclonic seizures. When myoclonic epilepsy has begun in infancy without any identifiable cause, two groups with respectively severe (Dravet syndrome) and benign courses could be distinguished. In the last decade of the twentieth century, it became clear that these two conditions were included in Doose's “centrencephalic myoclonic–astatic petit mal.”

In addition, in some patients, “centrencephalic myoclonic–astatic petit mal” starts later in life, after the age of 2 years, in which severe myoclonic seizures cause the patient to fall, as in Lennox-Gastaut syndrome. Indeed, that can be difficult to distinguish this from Lennox-Gastaut syndrome. Patients with Lennox-Gastaut syndrome and EMAS share age of onset (early school age, various kinds of seizures including absences and drop attacks), generalized spike waves, and a major impact on cognitive functions. Thus, the usual understanding, expressed by Aicardi, was that there is a range from Lennox-Gastaut syndrome to myoclonic epilepsy, with myoclonic–astatic epilepsy between these two extremes.[1] This concept of a continuum was similar to that of the Montreal school regarding idiopathic generalized epilepsy (e. g., Berkovic et al.[3]). However, the concept of a continuum was inconsistent with the idea that one condition was genetically determined, whereas the other resulted from a brain lesion. Some difference should therefore exist. The difficulty in making reliable and reproducible distinctions lies to in the fact that the number of characteristics to be taken in account challenges our ability to identify possible differences. By applying a special mathematical method called “multiple correspondence analysis,”[10] it proved possible to recognize reproducible differences. This method can identify within a group of items belonging to a population those clusters of individuals that differ from the rest of the population for specific items and identify these items.[2] This method was applied to patients with various types of generalized seizures and various patterns of generalized spike waves, including either 3-Hz spike waves (SW) or slow spike waves (SSW), negative brain imaging, and first seizures between 1 and 10 years of age; two groups could be distinguished:

One group had onset between 5 and 7 years of age had mainly tonic and absence seizures together with SSW, and the course was unfavorable. There was an excess of focal EEG abnormalities. The sex ratio in this group was equal. This is the usual pattern of the Lennox-Gastaut syndrome.

The other group began slightly earlier, between 2 and 5 years of age, with tonic–clonic seizures before the occurrence of myoclonic–astatic seizures and 3-Hz SW. There was an excess of boys. The course was favorable in a majority after 2 or 3 years, although one third had recorded tonic seizures, a feature previously not mentioned in patients who recover. However, in a sizeable proportion, vibratory tonic and absence seizures and long-lasting myoclonic status occurred and the course was unfavorable: Following the disappearance of myoclonic status, clusters of vibratory tonic seizures at the end of night sleep and slow spike waves persisted for years together with major cognitive impact.

Definitions

Epilepsy with myoclonic–astatic seizures is defined by the combination of myoclonic–astatic seizures and other kinds of generalized seizures, including tonic–clonic, myoclonic, and eventually tonic seizures, absences and erratic myoclonus, and generalized spike-waves beginning in early childhood, between 2 and 5 years of age. The outcome ranges from complete recovery to intractable epilepsy persisting after the end of the second decade and consisting of tonic seizures in sleep with dramatic deterioration of cognitive and motor functions. This syndrome is not related to any brain lesion, but rather to genetic predisposition combined with brain maturational features.

Epidemiology

The epidemiology is not known because this condition has long been confused with Lennox-Gastaut syndrome. It is likely that the incidence is at least in the same range as that of Lennox-Gastaut syndrome if not higher.

Etiology and Basic Mechanisms

Although the etiology is unknown, familial studies suggest that some genetic predisposition is at work. However, the variable course has no explanation, and the search for gene mutations has been negative.[13] The only differences between favorable and unfavorable cases have been with regard to gender, with a poorer prognosis for boys than girls, and the age of onset, with poorer prognosis in case of late onset.[10]

Mechanism of Intractability and Cognitive Difficulties

The clinical presentation and course mentioned earlier are characteristic and result from the combination of two groups of factors:

- Generalized tonic–clonic seizures, myoclonus, and bursts of 3-Hz generalized SW seem to be determined mainly by genetic predisposition to idiopathic generalized epilepsy thought to involve the thalamocortical circuits. The rhythmicity in this model is generated by the thalamic reticular nuclei and the cortical contribution mainly involving the rolandic strip, generating myoclonus.
- Tonic seizures, atypical absences, and slow spike-waves suggest epileptogenicity-related and age-related hyperexcitability, and therefore a relation to brain maturation, which involves mainly both frontal lobes at that age. Irregular and slow spike-waves probably result from secondary bilateral synchrony involving both frontal lobes through the corpus callosum.

The pattern in patients with early onset but unfavorable course is consistent at onset with the pattern of the first group (genetic). In terms of the course of the disorder, it is consistent with the second group (maturation of frontal lobes) in the course of the disorder.

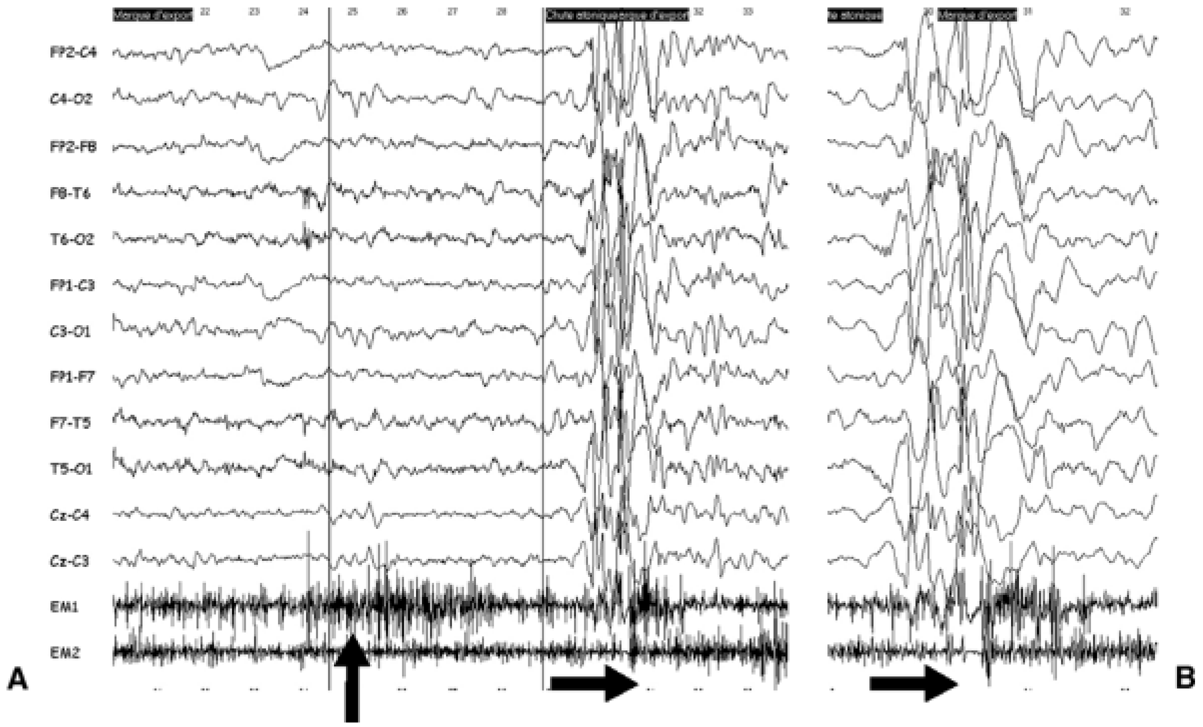


FIGURE 1. Polygraphy in a 3-year-old boy with drop attacks due to epilepsy with myoclonic–astatic seizures (EMAS). Notice that the jerk indicated by the arrow coincides with the spike and precedes the disappearance of muscle tone that coincides with the slow wave, which explains why the child is unable to protect his face from the injury. **A:** 15 mm/s; **B:** 30 mm/s.

The relative contribution of these two factors determines the severity of the condition: The combination of both epileptogenic factors could explain the long-lasting episodes of myoclonic status with drowsiness. The interaction of two distinct paroxysmal activities, respectively rhythmic at 3 Hz and irregular and slow at 2 Hz, could generate the apparently chaotic, irregular, and asynchronous spike and slow-wave activity and replace massive myoclonus by erratic myoclonus. The predominance of the latter in the perioral and tongue areas and in distal parts of the upper limbs is consistent with involvement of pyramidal pathways, because these areas are those mainly represented in the rolandic strip. In addition, the combination of two epileptogenic factors could also generate pharmacoresistance.

This formulation also clarifies similarities with Lennox-Gastaut syndrome, because in the latter, there is a combination of some cortical lesion with the same age-related hyperexcitability involving frontal maturation, ensuring pharmacoresistance. Therefore, in Lennox-Gastaut syndrome, pharmacoresistance would result from the combination of two etiologic factors— focal cortical lesion and maturation—whereas in unfavorable cases of EMAS, it would result from the combination of genetic predisposition with maturation. Because one factor is shared by Lennox-Gastaut syndrome and EMAS, the clinical and EEG patterns have similarities that have generated long-lasting confusion. Finally, in favorable cases of EMAS, the contribution of maturation factors would be milder, explaining the neater clinical pattern and lack of pharmacoresistance.

Neuropsychological findings are also consistent with this understanding of pathophysiology: Major features are dysarthria and apraxia, in addition to the ataxia that is often linked to myoclonus. Dysarthria and apraxia both involve areas of the cortex that are adjacent to the rolandic strip. Cases with unfavorable outcome exhibit in addition slowness and attention deficit, which are eventually additional features of frontal lobe dysfunction. The latter is shared with Lennox-Gastaut syndrome.

What Is the Precise Nature of the Genetic Predisposition?

The identification of a specific genetic predisposition to Dravet syndrome may open another way to understand the difference between favorable and unfavorable cases because a specific monogenic predisposition might apply only to unfavorable cases of EMAS.[4] The slightly lower incidence of familial antecedents of epilepsy in unfavorable cases would be consistent with this hypothesis. However, it is also consistent with the hypothesis previously mentioned of a combination of genetic and maturational features. In the case of Dravet syndrome, the characteristic pattern in patients with the mutation in *SCNA1* can be recognized from the beginning of the disorder because they exhibit unilateral clonic seizures. The only way to answer the questions thus opened on the neurobiologic basis of the various aspects of EMAS is through extensive search of the molecular predisposition in this disorder combined with very precise phenotyping. To date, however, such search has been negative.[13]

Clinical Presentation

Seizures

Myoclonic–astatic epilepsy begins between 2 and 5 years of age in a previously healthy child, usually with repeat tonic–clonic seizures that may repeat on the same day. Febrile seizures may have occurred, but this is not the rule.

Within a few days or weeks, the patient starts to have falling episodes due to myoclonic seizures. These drop attacks may be very severe, causing face injuries.

At this point, the child exhibits tonic–clonic, clonic, absence, myoclonic flexor, and atonic, and myoclonic–astatic seizures. The child becomes hyperkinetic and inattentive.

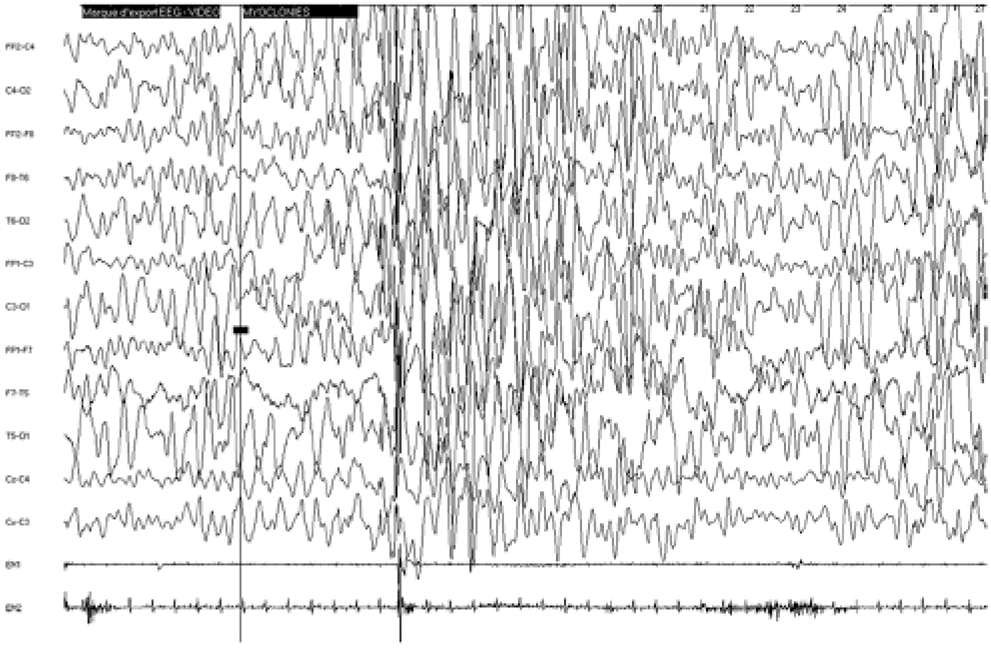
Pattern of Cognitive and Motor Dysfunction

The main findings in patients who are mildly affected are ataxia together with abnormal fine movements due to dyspraxia, and speech difficulties. Many patients suffer from attention deficit disorder with hyperkinesia that may persist for many months after the last seizure has occurred. Patients who undergo prolonged episodes of myoclonic status develop dementia.[11]

Diagnostic Evaluation

Electroencephalographic Findings

At onset, the interictal EEG shows slowing of the background activity, and generalized spike-waves increase when the patient is falling asleep (Fig. 1). When drop attacks have occurred, videopolygraphic recording shows different mechanisms underlying the falling: myoclonic flexor seizures, atonic seizures, and particularly myoclonic–atonic seizures, which are very particular because they combine myoclonic and atonic components (Fig. 1).[14]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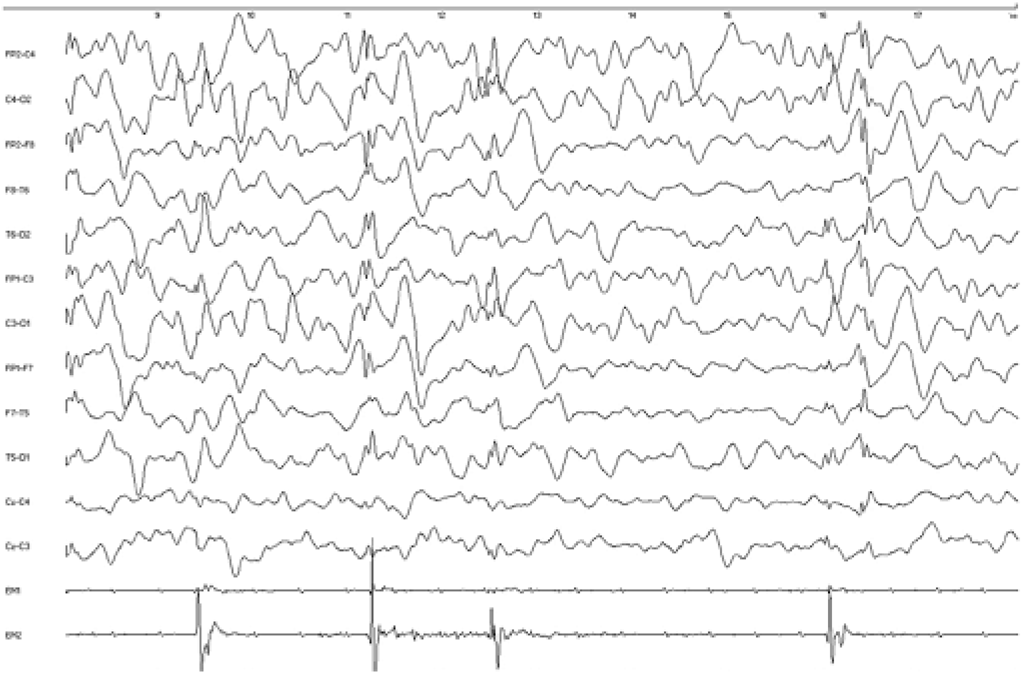
MYOCLONIES
FP2-C4
C4-O2
FP2-F8
F8-T6
T6-O2
FP1-C3
C3-O1
FP1-F7
F7-T5
T5-O1
Cz-C4
Cz-C3
EM1
EM2

FIGURE 2. Myoclonic status. 1 cm = 100 μV, 15 mm/s; lack of physiologic rhythms, high-amplitude slow waves, and spike waves. Segmentary myoclonus.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FP2-F8
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FP1-C3
C3-O1
FP1-F7
F7-T5
T5-O1
Cz-C4
Cz-C3
EM1
EM2

FIGURE 3. Myoclonic status. 1 cm = 200 μV, 1 cm = 30 mm; slow waves with multifocal spikes correlated with erratic myoclonus. Note that the spike activity is very mild.

Therefore, the combination of video-EEG and simultaneous recording of the surface EMG is most useful in this situation. It makes it possible to show that the drop attacks are due to the

patient being thrown forward and losing the ability to protect himself or herself with the upper limbs. This is the cause of severe injury to the face.

Neuroimaging and Other Laboratory Examinations

Neuroimaging is by definition negative, including in those cases with unfavorable outcome. Other laboratory investigations are also negative.

Differential Diagnosis

At this early stage, there are a few diagnostic issues. Some patients exhibit occasional partial seizures in addition to the generalized tonic–clonic seizures. They are distinct from partial seizures of focal epilepsy because they do not appear as repeated and stereotyped with an interictal EEG focus, as would be the case in focal epilepsy. The distinction is of major importance for the choice of medication. At onset of the disease, it is more dangerous to miss EMAS than to miss partial epilepsy, because the risk of iatrogenic worsening mainly concerns EMAS. On the other hand, the EEG may exhibit major slowing of the background activity, suggesting acute brain damage instead of epilepsy. Again, the physician treating a 2- to 5-year old child who starts having generalized tonic–clonic seizures should always consider the possibility of EMAS because it is highly treatable and, if overlooked, may destroy brain functions.

Treatment and Outcome

The Risk for Worsening

One characteristic of this disorder is drug-induced worsening, which has been reported by a number of research groups, including situations before the nosologic characteristics were identified (for review, see Perucca et al.[16]). Carbamazepine was long considered as the drug of first choice for children with epilepsy. It is now clearly established that this drug aggravates EMAS. It is difficult to give the incidence of aggravation due to the lack of controlled data, but Kaminska et al. found in their series that this occurred in more than half of the cases.[10]

The same applies to phenytoin, although this is less often administered to children. It is, however, an excellent drug for the treatment of status epilepticus, and it is then tempting to switch from the intravenous to the oral formulation.

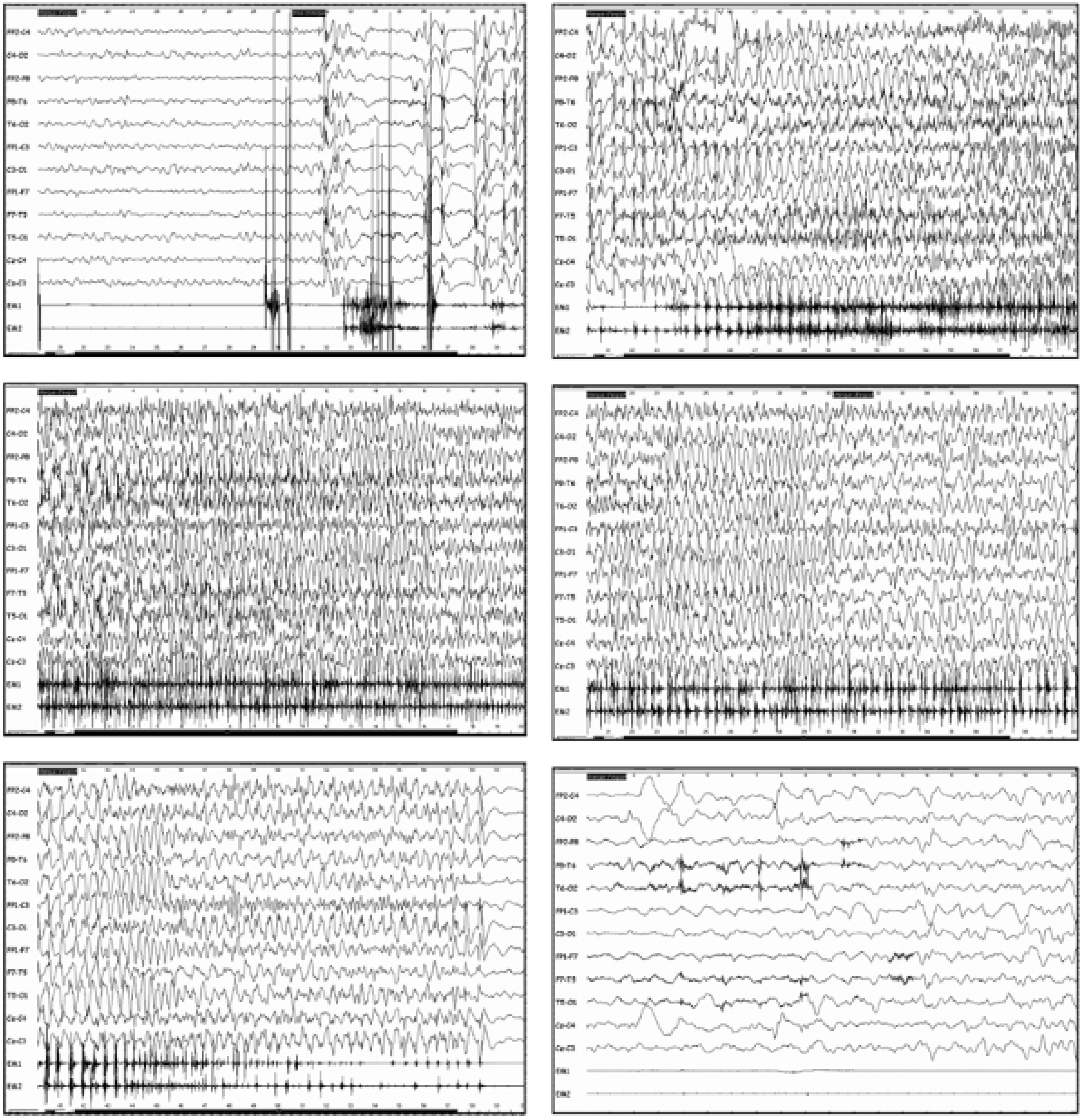

FIGURE 4. Myoclonic–tonic–clonic seizure. 1 cm = 200 μV, 1 cm = 30 mm. Note the complexity of the pattern compared to a classic tonic–clonic seizure observed in adolescence or adulthood, and the major postictal slowing.

Vigabatrin is also likely to worsen the condition.[12] Although the use of this drug has been restricted due to its potential retinal toxicity, it is very helpful for infants and children with pharmacoresistant epilepsies.

The risk related to the administration of phenobarbital is not as clear. However, given the high incidence of absence seizures in this type of epilepsy and the ability of phenobarbital to precipitate nonconvulsive status epilepticus, this compound clearly represents a theoretical risk for aggravation.

Benefits From Therapy

Valproate has some effect on tonic–clonic, absence, and myoclonic seizures. Ethosuximide is helpful for absences and myoclonic seizures. Benzodiazepines are indicated for the treatment of status epilepticus, but the benefit of long-term everyday administration is less clear for two reasons: These compounds may increase the incidence of tonic seizures or even precipitate tonic status epilepticus, and the chronic administration of the compound may reduce the potential of these compounds to interrupt status epilepticus. In addition, withdrawing benzodiazepines following chronic administration may be challenging because of progressive dependence; it needs to be done over several months. The introduction of lamotrigine has led to a revolution in the treatment of EMAS, with more than three fourths of patients experiencing >75% decrease in seizure frequency and many stopping seizures altogether.[10] Topiramate was effective, reducing seizure frequency by half in more than half of the cases.[18] Levetiracetam seems promising, provided moderate doses are administered at onset, but wider experience is required before it can be advised early in the course of the disorder.

In practice, the occurrence of a first tonic–clonic seizure in a 2- to 5-year-old child requires an EEG, in contrast to later age ranges. Slow basic activity, and even more so the presence of spike waves, indicates the need for administration of valproate. The occurrence of further seizures indicates the addition of lamotrigine. Although the epilepsy may prove intractable for months and could encourage dropping this therapy in favor of less appropriate compounds, seizure frequency tends to decrease progressively. The ketogenic diet is useful in this context, particularly in cases of recent worsening of seizure frequency.[15] Steroids may be useful in cases of frequent absence seizures or myoclonic status.

Long-Term Prognosis

The course is variable, with total recovery within a few months to 3 years in most cases, although behavioral abnormalities improve only slowly. A number of patients develop myoclonic status in which the child is drowsy with erratic myoclonus involving the mouth and tongue, the hands, and eventually the rest of the body. The EEG shows high-amplitude polymorphic delta slow waves, with rare and erratic spikes. Other kinds of motor seizures appear mainly at the end of the night, between 5 AM and 7 AM, in clusters consisting of axial hypertonia with a rapid clonic, vibratory component (Figs. 2,3,4). When unrecognized this status may last several weeks. The term status itself may not be appropriate because the long duration of this kind of seizure activity is also seen in epileptic encephalopathy. Following this episode of epileptic encephalopathy, erratic myoclonus disappears and consciousness improves, but the patient has lost cognitive abilities and become very slow in thoughts and behavior. The long-term unfavorable course is characterized by the persistence of clusters of vibratory tonic seizures at the end of night sleep many years later, even by the beginning of the third decade.

Mental retardation and persisting seizures are the two major features that prevent the patients from normal social integration (p <0.001).[10] The major factors for developing mental retardation are lack of familial antecedents and presence of short 3-Hz SW bursts, as shown with univariate analysis of electroclinical variables. Logistic regression analysis added the presence of tonic and absence seizures at onset as major risk factors (p = 0.01). On follow-up, univariate analysis showed that the main factors were duration of epilepsy >3 years (p <0.001), presence of vibratory tonic seizures (p <0.001), and myoclonic status epilepticus (p = 0.02). Factors relating to poor school performance in children with epilepsy were shown to include behavior problems, early onset, and polytherapy.[17] Although these children have onset of epilepsy after age 2 years, they have the two other risk factors.

Summary And Conclusions

Severe, generalized cryptogenic epilepsies comprise a particularly important model for understanding the respective roles of the three major categories of factors predisposing to epilepsy in childhood: (a) cortical lesions, (b) genetic predisposition, and (c) maturation of the brain. They also contribute to the understanding of factors of intractability in this age range. In addition, they make it possible to apply a mathematical method—multiple correspondence analysis—that is particularly useful in distinguishing discrete groups of patients with epilepsy that may appear as a continuum to the clinician, even though they result from distinct etiologic factors and thus from distinct neurobiologic mechanisms. This has made it possible to confirm mathematically the existence of EMAS as an epilepsy syndrome distinct from Lennox-Gastaut syndrome. The impression of a continuum is given by the combination of several factors in some patients. In addition, recent findings concerning the genetic predisposition to epilepsy suggest that genetic predisposition is heterogeneous due to several monogenic conditions, and thus this heterogeneity also contributes to the impression of a continuum. In addition, modulating genetic factors yet to be identified could also increase the clinical variability and thus the impression of a continuum.

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Chapter 233

Hemiconvulsion-Hemiplegia-Epilepsy Syndrome

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Introduction

Hemiconvulsion-hemiplegia-epilepsy (HHE), described by Gastaut et al.[17] in 1957, was not considered as a syndromic entity in the 1989 International League Against Epilepsy (ILAE) classification of epilepsies and epilepsy syndromes. Indeed, one could argue that the initial episode of a prolonged unilateral convulsion can be classified as a unique episode of a motor partial status, with hemiplegia as the main sequela. The later development of focal seizures can be considered, and consequently classified, as a form of partial symptomatic epilepsy. In 2001, HHE was introduced as a syndrome in the published report of the ILAE Task Force on Classification and Terminology.[12] In fact, it is *the stereotyped sequence of events* (hemiconvulsions followed by hemiplegia and leading to a focal epilepsy) that makes HHE "a complex of signs and symptoms that defines a unique epilepsy condition," that is, a syndrome.

As mentioned, taken separately each of its components cannot be considered as an identifiable syndrome because they can be classified into other categories. However, as for progressive myoclonic epilepsies, maintaining HHE as a syndrome is still useful because of the unique characteristics of the condition and their importance when dealing with complex issues and concepts such as secondary epileptogenesis, role of febrile convulsions, and neuroprotection.

Historical Perspectives and Definitions

The sequence of prolonged hemiconvulsions (the term *unilateral status* could be used to differentiate them from focal status restricted to a body segment) immediately followed by hemiplegia and, secondarily, focal epileptic seizures was identified by Pierre Marie[26] in 1885 within the setting of infantile infectious disorders and described by Gowers in 1886 as "posthemiplegic epilepsy."[18] Similar descriptions advocated a vascular[13] or "acute encephalitic"[7] etiology.

In 1957, Gastaut et al.[17] grouped cases of hemiplegia in childhood following convulsions due to various causes (excluding cases of preexisting brain damage) and were the first to use the term HHE. In their series of 150 patients, they found that >80% of cases of chronic epilepsy occurred after a free interval of <1 year and 50% of cases of "psychomotor" epilepsy after >3 years. Partial seizures were considered to be of temporal origin. Further studies[8,9,33,34] have demonstrated that the initial episode may be observed in various situations and that the subsequent partial epilepsy can be temporal, extratemporal, or multifocal.

The term hemiconvulsion-hemiplegia (HH) is often used to describe the initial stage of the syndrome. It is considered as appearing in a child without antecedents, usually before the age of 4 years. Using current ILAE classification criteria for the definition of syndromes, one cannot consider HH as an epilepsy syndrome, because it corresponds to a unique paroxysmal episode.

The incidence of HHE has declined considerably over the last 20 years. Between 1967 and 1978 the number of

HHE cases in the district of Geneva decreased from 7.7 to 1.64 per 10,000 children (Beaumanoir, cited by Roger et al.[35]). A *PubMed* search reveals that the most recent publication of a series on HHE dates back in 1988[21]; it reported on computed tomography (CT) and electroencephalogram (EEG) abnormalities in 25 children with post-hemiconvulsive hemiplegia hospitalized between 1968 and 1980. Since 1995 not more than ten small series or isolated case reports have been published. It is expected that it would be difficult for isolated cases to be accepted for publication. The lack of published large series, however, probably reflects the dramatic improvement in the acute treatment of prolonged seizures in young children. As a consequence, some children who experienced HH avoid motor sequelae and late-onset epilepsy, whereas others do not develop the full HHE clinical picture and are considered as focal epilepsies with antecedents of an acute, usually febrile, convulsive episode.

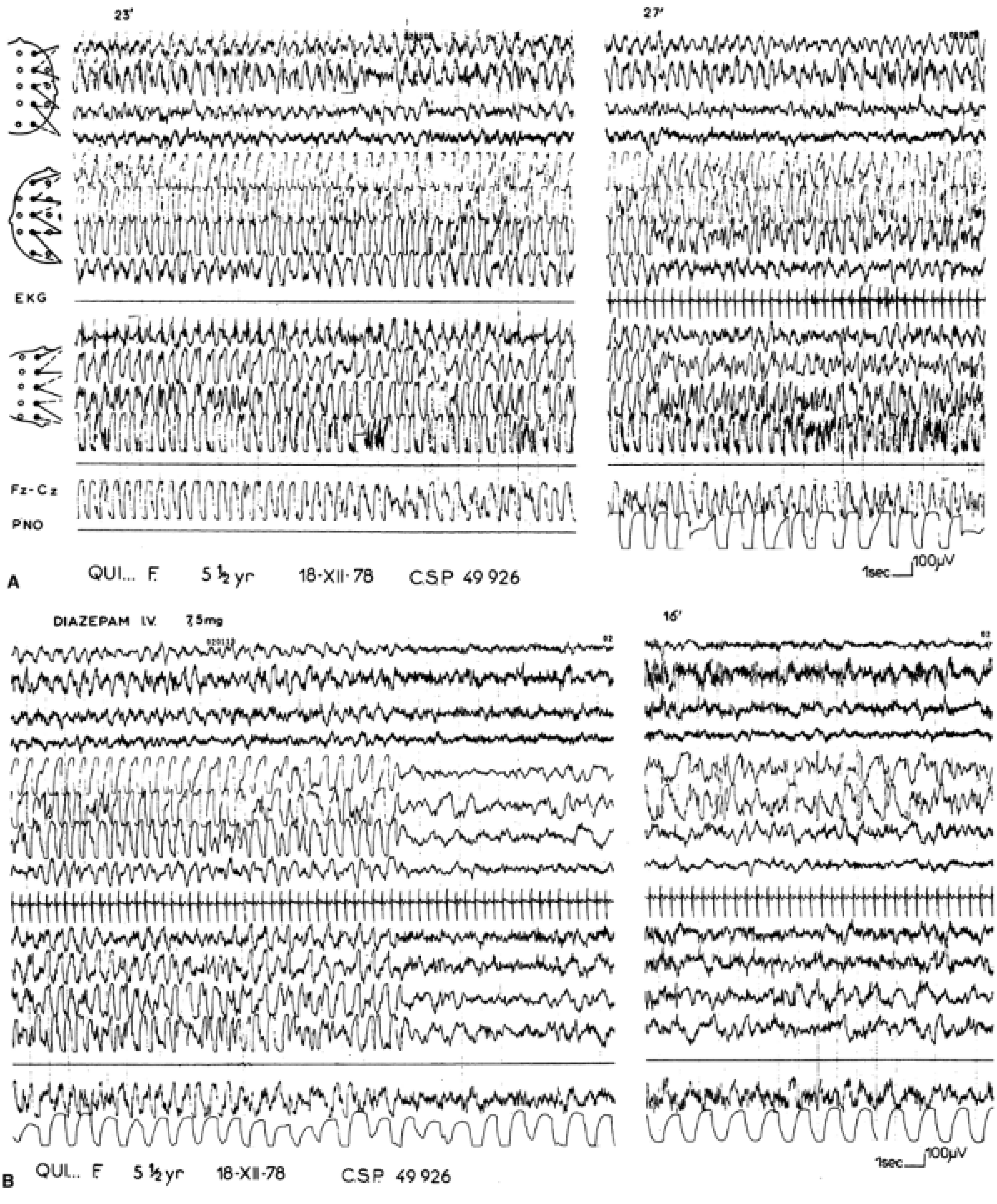
Age at Onset

The HH initial episode has its peak of incidence during the first 2 years of life; 60% to 85% of the cases occur between 5 months and 2 years of age, with only few patients who are 4 years or older.[3,36] In approximately three fourths of patients, the HH episode evolves to the secondary appearance of partial epilepsy. The average interval from the prolonged initial convulsion to chronic epilepsy was 1 to 2 years, with 85% of the epilepsies having started within 3 years in one study.[3] However, this series was biased in favor of the early onset of complex partial seizures, and these often occur 5 to 10 years after the initial episode.

Clinical Presentation and Diagnostic Evaluation

The first stage of the syndrome, *hemiconvulsion*, constitutes a particular form of status epilepticus corresponding to the *unilateral seizures* described by Gastaut et al.[15] As stated in the previous edition of this book and by Arzimanoglou et al.,[6] this type of seizure deserves to be distinguished because it occurs frequently in infants and young children, diffuses to the whole of the affected side and can last 30 minutes or more (up >24 hours if untreated). In children, most of the long-lasting hemiconvulsions, particularly in the presence of fever, are the initial epileptic manifestations,[2,3,30] which explains the impossibility of prevention. Recognition of this type of seizure by general practitioners, pediatricians, and nurses is of primary importance because in most of the cases the outcome is favorable,[27,39] provided treatment is administered early in the course of the seizure. The seizure is predominantly of the clonic type, with saccadic adversion of head and eyes to one side and unilateral, more or less rhythmic jerks of the limb muscles (with contralateral involvement), variable degree of impairment of consciousness, and autonomic symptoms (cyanosis, hyersalivation, respiratory dysfunction) of variable severity.

The ictal discharge consists of rhythmic (2–3/s) bilateral slow waves, with higher amplitude on the hemisphere contralateral to the clinical seizure. On this side they are intermingled with recruiting rhythms of 10 cycles/s, which predominate posteriorly (Fig. 1). Ictal EEG is variable because of changes in shape, frequency, and topography of the slow and fast components. Pseudorhythmic Spike-waves (SWs) contralateral to the clinical seizure, periodically interrupted by electrodecremental events of 1 to 2 seconds' duration, also may occur. Polygraphic recordings do not demonstrate any consistent relationship between muscle jerks and spikes. Spontaneous seizure termination is brisk, with a brief extinction of all rhythms followed by delta waves of higher amplitude on the ictally engaged hemisphere alternating with short periods of suppression. On the opposite side, physiologic rhythms progressively reappear. At this time the hemiplegia is noted. When the seizure is stopped by intravenous diazepam, arrest of muscle jerks is immediate. The ictal discharge progressively vanishes, persisting longer on the ictally engaged hemisphere. Postictal asymmetry is obvious, with abundant drug-induced rapid rhythms invading the contralateral hemisphere.[8]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B
QUI.. F 5 ½ yr 18-XII-78 C.S.P 49 926
1sec 100μV

FIGURE 1. Right hemiclonic seizure in course in a 5-year-old boy afflicted with this type of seizure since the age of 3 years. **A:** Recordings 23 and 27 minutes after seizure onset. On the left hemisphere, high-amplitude rhythmic slow waves with superimposed small spikes; on the right hemisphere, rhythmic slow waves over the frontocentral area, with superimposed myoclonic jerks recorded from scalp electrodes. Tachycardia and slight irregularities in respiration. **B:** End of the seizure following intravenous injection of 7.5 mg of diazepam. On the left hemisphere, rhythmic slow waves stop abruptly; 16 minutes later, SW appear over the frontal area. On the right hemisphere, slow waves are replaced at the end of the seizure by fast rhythms caused by diazepam. Respiration becomes more regular. EKG, electrocardiogram; PNO, pneumogram.

The second stage of the syndrome, *hemiplegia*, immediately follows the prolonged convulsive episode. It is initially flaccid and fairly massive but tends to become spastic and less marked as time passes. The minimum duration of the hemiplegia is arbitrarily set at <7 days, to separate it from the more common postictal or Todd paralysis. In 20% of the cases of Gastaut et al., the hemiplegia was not permanent and disappeared within 1 to 12 months. In our experience,[6] some degree of spasticity, increased deep tendon reflexes, and pyramidal tract signs persist, even when the paralysis clears. The hemiplegia is usually predominant in the arm, but the face is constantly involved, an important sign that differentiates an acquired hemiplegia from a congenital one in cases of early onset.

The third component of HHE is *focal epilepsy*. The average interval from initial convulsions to chronic epilepsy is 1 to 4 years,[17] with 85% of the epilepsies having started within 3 years of the first hemiconvulsive episode in one study.[3] Vivaldi,[43] in his series of 45 cases, reported a range of 1 month to 9 years after the acute episode. Approximately two thirds of the late seizures are focal seizures with alteration of consciousness.[36,43] Focal seizures without alteration of consciousness, mainly clonic motor seizures, occur in approximately 30% of the patients; secondarily generalized seizures are reported in 20% and other episodes of status in approximately 10%.[36] Gastaut et al. considered that the epilepsy is always made of focal seizures originating from the temporal lobe (previously called “psychomotor seizures”).

In an attempt to further characterize the types of epilepsy within the setting of HHE syndrome, Chauvel and Dravet[8] analyzed a series of 37 adult patients investigated in Sainte-Anne Hospital in Paris for surgical therapy. They were selected based on having a history of convulsions in infancy or early childhood, immediately followed by a hemideficit, and after a free interval (ranging from 1 month to 19 years; mean 5.6 years), having developed epilepsy. They had all underwent a stereotactic neuroradiologic investigation as part of the epilepsy surgery evaluation. The age of HH syndrome ranged from 1 month to 9 years. Only 19% presented the initial episode after the age of 3 years. The majority of the patients had several seizure types, whereas only 9 (24%) had one type of seizure. All the patients presented focal seizures, but 3 of them also had “absences” and seizures generalized at onset. The epileptogenic zone was considered unifocal in 29 and multifocal in 8. In the unifocal group, a striking predominance of suprasylvian localizations was found as compared to the pure temporal lobe epilepsies (5 patients). In 14 of those 29 (nearly 50%) the epileptogenic zone included the frontocentral and parietocentral regions; prefrontal epilepsies were rare, and no pure occipital epilepsy was reported. In the multifocal group, a predominant involvement of the parietal lobe was noticed (7 of 8 patients). These results clearly show that epilepsy in HHE is not always of temporal origin, as initially suggested by some authors.

Diagnostic evaluation following the initial acute episode mainly consists in identifying the cause or triggering event responsible (see the later section on the etiology of HHE). Immediately after the HH episode, CT scan may evidence swelling and edema of the hemisphere involved in the epileptic discharge. Later, a rather characteristic uniform hemiatrophy with midline displacement is observed. This evolution was initially reported using pneumoencephalography[2,17,20] or CT scan.[16,21] Case reports including magnetic resonance imaging (MRI) investigation confirmed this pattern.[14] Morimoto et al.'s case[29] showed a unilateral swelling and damaged cortex and subcortical white matter with a high-intensity signal in T2-weighted images at day 17 from status, followed, on day 25 and day 36 neuroimaging, by a severe hemispheric atrophy. Kawada et al.[22] reported a similar evolution, with atrophy being detected from day 15. Follow-up reports on the evolution of hemiatrophy are lacking, but in our experience it remains relatively stable (Fig. 2).

To our knowledge, the longitudinal evolution of interictal EEG abnormalities during the free interval period has not been studied in detail. In the Sainte-Anne series,[8] when the patients were seen for intractable epilepsy, interictal EEG showed multifocal spikes and sharp waves, as well as generalized and bilateral slow waves, in 56% of 37 patients. Widespread interictal abnormalities were more frequently encountered in the symptomatic category (see later discussion) of HHE patients. Even when radiologic studies suggested a strictly unilateral pathology, the distribution of EEG slow waves frequently suggested a more extended lesion (especially in the contralateral hemisphere), and interictal spiking frequently suggested multiple epileptogenic zones.[8]

Etiology

Prolonged clonic convulsions with a marked unilateral predominance usually occur in the course of a febrile disease. A number of acute cerebral disorders have been occasionally related to the occurrence of the syndrome (meningitis, subdural effusions, head trauma, etc.). In many cases no cause is obvious (*idiopathic hemiconvulsion-hemiplegia* according to Roger et al.[33]), and such cases may represent only prolonged (complicated) febrile convulsions that do not otherwise differ from common febrile convulsions. In such cases the seizure activity itself could be responsible for the appearance of new lesions occurring in a previously normal brain. As Aicardi and Chevrie[3,4] pointed out, "febrile, cryptogenic status epilepticus is only the most severe expression of idiopathic febrile convulsions and differs from the common brief, benign seizures in severity, not in nature." They proposed that "epilepsy and neurological sequelae might be the direct consequence of seizures *per se*." In the same way, Lennox-Buchtal[25] insisted that in cases in which febrile convulsions were focal and prolonged there was a definite risk for mental and neurologic sequelae as well as for subsequent development of epilepsy. The two preceding studies stressed the importance of prompt treatment of febrile convulsions to prevent their sequelae. Furthermore, they stressed the importance of prevention with prophylactic treatment of febrile status in children at risk.

Alternatively, the presence of a preexisting asymptomatic lesion, of perinatal or prenatal origin, may be responsible in a number of cases (*symptomatic hemiconvulsion-hemiplegia* according to Roger et al.[33]) for the initiation or localization of the seizure. The prolonged seizure would then produce or contribute to the development of irreversible brain damage with resultant partial epilepsy.[3,4,5,25,35,37]

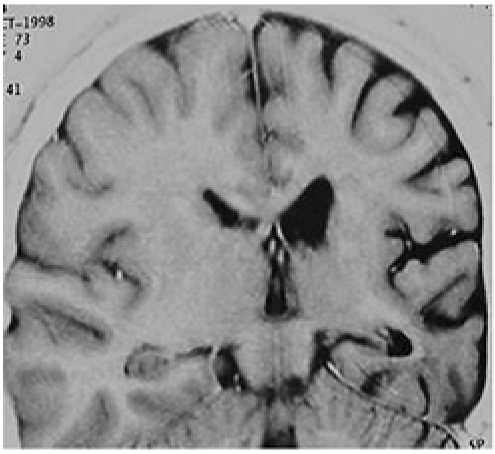

FIGURE 2. Magnetic resonance imaging (MRI) scan of a patient with hemiconvulsion-hemiplegia syndrome. The left hemisphere is diffusely atrophic with ventricular dilation and cortical atrophy. The MRI picture corresponds to the neuropathologic aspect known as hemiatrophia cerebri. It differs from the localized atrophy observed in congenital hemiplegias resulting from arterial occlusion, and it is seen only with acquired post-convulsive hemiplegia. (Reproduced from Arzimanoglou A, Guerrini R, Aicardi J. Epilepsies characterized by partial seizures. In: *Aicardi's Epilepsy in Children*, 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2004, with permission.)

The difference between "idiopathic" and "symptomatic" forms is not always easy to establish. As for "probably symptomatic" focal epilepsies, one could expect that showing some of the related lesions (particularly those due to a migration disorder) depends on the quality and capacity of the means of investigation. Particularly for cases investigated only by pneumoencephalography, CT scan, or early-generation MRI machines, a minor lesion would be difficult to detect. The combination of an "idiopathic" febrile seizure and a potentially epileptogenic lesion would then favor the prolonged character of the convulsive episode and the development of a "symptomatic" HHE syndrome.

The role of long-lasting febrile convulsions, as part of a hemiconvulsion-hemiplegia episode, in the genesis of hippocampal sclerosis and consequent mesial temporal lobe epilepsy also remains disputed. A statistical association is well demonstrated,[32] and there are strong arguments in favor of an etiologic relationship,[19] although the presence or absence of other contributing factors is not clearly established.[5,38,41]

Pathophysiology

The pathophysiologic mechanisms involved are not clearly elucidated. They most probably involve issues related to the pathophysiology of complicated febrile seizures (genetic factors, the triggering or predisposing role of a preexisting lesion, etc.), the duration of the initial event, the cortical structures involved in the propagation of the initial seizure, and the epileptogenicity of the brain lesions resulting from the initial event.

Chauvel and Dravet[8] recently reviewed the hypotheses on the pathogenesis of the syndrome. They underscored that radiologic studies appear to establish a sequential relation between early repetitive seizures, brain edema, cortical and subcortical atrophy. and, in a good proportion of the cases, chronic epilepsy. For that reason, pathogenesis of the HHE syndrome is of special interest, relating directly to major controversies in the pathogenesis of brain damage in human epilepsy. The principal arguments in this controversy center around two extreme positions: On one hand, it is argued that hypoxic damage (diffuse or selective) would be the result of deficient blood supply (directly by mechanical distortion of the brain at birth, or vascular thrombosis; indirectly by arterial or venous thrombosis of infectious origin[42] or secondary to brain edema); on the other hand, as emphasized by Meldrum and Corsellis,[28]

> insults such as a severe infection or a head injury may well be important factors in some cases, but the most sinister event commonly found to have occurred in epileptic patients with “hypoxic” brain damage is the onset of fits in infancy or in childhood.

The existence of a predisposing genetic factor has been discussed.[31] A high incidence of family history of febrile convulsions is frequently present. Tanaka and colleagues reported ictal and postictal single photon emission computed tomography (SPECT) findings in a 5-month-old boy.[41] When the SPECT was realized during left-sided hemiconvulsions and during the third day after partial status, diffuse hyperperfusion was revealed in the right hemisphere. On the seventh and tenth days after status, diffuse hypoperfusion was exhibited in the right hemisphere. Striking neuroimaging findings suggestive of diffuse cytotoxic edema confined to one hemisphere, including extensive diffusion-weighted imaging abnormalities, were reported by Freeman et al.[14] following early MRI screening. Japanese authors discussed the possible role played by hypercytokinemia[44] and elevated level of interleukin-6 in the cerebrospinal fluid,[23] whereas Scantlebury et al.[37] reported two patients for whom the HHE syndrome could be attributed to the factor V Leiden mutation.

Management

The incidence of hemiconvulsion-hemiplegia-epilepsy syndrome has declined considerably in countries in which emergency care is highly developed.[5,8,35]

Most cases of fever and prolonged convulsions occur during the first 18 months of life. The most important factor is the prompt recognition and early vigorous treatment of prolonged infantile seizures of whatever origin, especially of febrile convulsions. This seems to be the only way to reduce the incidence of postconvulsive hemiplegia and late-onset partial epilepsy. Symptomatic therapy of the acute convulsive episode uses mainly benzodiazepines, particularly diazepam. It can be easily administered by either venous or rectal route. The usual dose is 0.5 to 1 mg/kg given as a single dose. The dose may be repeated after 10 to 20 minutes. Clonazepam, midazolam, or lorazepam may also be used. Antithermic drugs are used in combination. According to the eventual causal agent, additional anti-infectious therapy is required. Prophylactic treatment of febrile convulsions is necessary after HH, but it does not prevent later epilepsy. The outcome of the HH syndrome has become less severe, and subsequent epilepsy seems to be less frequent in idiopathic cases.

In the complete form of the syndrome, partial seizures of temporal or extratemporal origin should be treated like any other type of focal symptomatic epilepsy, using antiepileptic drugs. Surgical treatment is an alternative. However, epilepsies due to extended brain damage may prove difficult to handle surgically. The possibility for a limited cortectomy will usually need an invasive presurgical evaluation performed by a group specialized in epilepsy surgery. Of the 37 patients explored in Sainte-Anne,[8] it was estimated that surgery was possible in only 20. Following surgery, 9 patients (45%) became seizure free or experienced <1 seizure per year; three patients (15%)

showed a significant reduction (40%) in seizure frequency, and no change was obtained in 7 patients (35%). One patient died during a postoperative status.

Hemispherectomy (total, subtotal, or “functional”) may be another surgical alternative, particularly when limited cortectomy is not feasible. Delalande et al.[10] included 7 children with HHE syndrome in a series of 53 patients submitted to hemispherotomy. Indications and clinical outcomes of hemispherectomy for epilepsy of various etiologies have been recently reviewed.[11]

Kwan et al.[24] reported on 4-year follow-up in three children who underwent callosotomy. All patients experienced a significant reduction of “generalized tonic seizures,” whereas partial seizures of the sensory type were unchanged.

Summary and Conclusions

Hemiconvulsion-hemiplegia-epilepsy syndrome can be considered as a unique epilepsy condition because of the stereotyped sequence of events that characterize it. Onset is in the form of an isolated episode of motor partial status (unilateral status) followed by hemiplegia. The seizure is predominantly of the clonic type, with saccadic adversion of head and eyes to one side and unilateral, more or less rhythmic jerks of the limb muscles (with contralateral involvement), variable degree of impairment of consciousness, and autonomic symptoms (cyanosis, hyersalivation, respiratory dysfunction) of variable severity. Hemiplegia, immediately follows the prolonged convulsive episode. It is initially flaccid and fairly massive but tends to become spastic and less marked as time passes. After a free interval the patient will develop focal seizures and neuroimaging will evidence a rather characteristic cerebral hemiatrophy. The complete sequence of event defines HHE. The HH initial episode has its peak of incidence during the first two years of life. The average interval from the prolonged initial convulsion to chronic epilepsy is one to three years. Diagnostic evaluation, following the initial acute episode, mainly consists in identifying the cause or triggering event responsible. The pathophysiological mechanisms involved are not clearly elucidated.

The most important factor that can influence long-term outcome is the prompt recognition and early vigorous treatment of prolonged infantile seizures of whatever origin, especially of febrile convulsions. This seems to be the only way to reduce the incidence of post convulsive hemiplegia and late onset partial epilepsy. In the complete form of the syndrome, partial seizures of temporal or extratemporal origin should be treated as any other type of focal symptomatic epilepsy.

Hemiconvulsion-hemiplegia-epilepsy syndrome is a form of focal epilepsy, more often symptomatic. It is the stereotyped sequence of events that justifies its recognition as a syndromic entity. The HH initial prolonged episode has its peak during the first two years of life and may or may not be related to fever. After a free interval of usually not more than 2 to 3 years approximately three fourths of the children will develop a focal epilepsy, temporal, extratemporal or multifocal.

Vigorous and early treatment of the initial episode, usually with rectal administration of a benzodiazepine, is the most appropriate way to reduce neurological sequelae. The incidence of HHE syndrome has declined considerably in countries in which emergency care is highly developed.

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Chapter 234

Myoclonic Status in Nonprogressive Encephalopathy

Bernardo Dalla Bernardina

Introduction

Despite the existence in the literature of proof of the possible occurrence in infants and young children of an absence status with myoclonias of variable severity and duration called by various names, such as "minor epileptic status," "minor motor status," "myoclonic status," "obtundation with myoclonias," "nonconvulsive states with ataxia," "myoclonic state with impaired consciousness," "myoclonic status in symptomatic cases of myoclonic astatic epilepsy," and so on,[1,2,3,6,9,10,24,27,28,32,36,38,42] reports documenting the existence of an epileptic syndrome characterized by the recurrence of long-lasting or subcontinuous myoclonic status in children with a nonprogressive encephalopathy are relatively rare.[7,11,13,15,16,18,19,20,21,25,33] In fact a very similar electroclinical picture has been described in children with Angelman syndrome,[8,25,33,34,35,37,39,41,43,45,47,52] in some children with 4p- syndrome,[44,46,53] and in some children with Rett syndrome,[17] but very few authors have stressed how, in these cases, the electroclinical picture was typically that of "myoclonic status in nonprogressive encephalopathy,"[15,16,17,18,19,22,40,44] a syndromic entity recently proposed by the ILAE Task Force on Classification and Terminology[41] in its category "syndromes in development."

Definitions

The syndrome is characterized by the recurrence of long-lasting myoclonic status, that is often difficult to recognize and frequently refractory to different treatments, in children with a nonprogressive encephalopathy of variable etiology.

Epidemiology

The prevalence of this condition is unknown; it seems to be rare because the only three series available[7,11,17] account for a total of 96 cases. The true prevalence is probably higher than reported, considering that many similar cases can remain misdiagnosed particularly in the absence of polygraphic recordings. There appears to be a female predominance, with a male:female ratio of 1:2. Familial antecedents for epilepsy are present in about 15% of cases.

Etiology and Basic Mechanisms

A genetic disorder (4p- syndrome, Rett syndrome, and especially Angelman syndrome) is present in nearly half of the reported cases. In such cases, nonsignificant abnormalities are neuroradiologically detectable.

A history of prenatal anoxic injury is well documented in about 15% of the cases. In about half of these cases, the neuroradiologic investigation shows cortical atrophy of variable degree that maximally affects the frontal regions.

In about one third of cases, neuroradiologic investigations reveal brain developmental malformations such as unilateral or bilateral micropolygyria, complete or partial callosal agenesis, vermis hypoplasia, or bilateral hippocampal dysgenesis, in most cases probably genetically determined.[7,17]

In the remaining 10% of cases, the etiology is unknown, with normal neuroradiologic and other laboratory investigations.

In some of the genetic cases, as in Angelman syndrome and 4p- syndrome, hyperexcitability of the motor cortex might be related to reduced GABAergic inhibition. In pre and perinatal anoxic cases, a similar "localized" hyperexcitability could be induced by a circulatory disturbance in late pregnancy causing selective dysfunction in the motor cortex.[11]

Electroclinical Presentation

Neurological impairment, which may be severe, has been observed at onset in almost three fourths of the cases. There is axial hypotonia of variable degree associated with abnormal movements, presenting a picture of "ataxic" cerebral palsy of a dystonic dyskinetic syndrome, severe mental retardation and, in some cases, microcephaly with dysmorphisms.

In one fourth of the cases, the neurologic impairment at onset is less obvious, characterized only by delayed postural acquisitions and language skills.

Age at first seizure ranges between 1 month and 5 years, with a mean age of 10 months.

Onset of epilepsy in several cases has been characterized by a myoclonic status with very frequent daily or subcontinuous "absences" accompanied by periorbital and perioral myoclonias and rhythmic and arrhythmic jerks of distal muscles in nearly half of the cases. In other childern, the initial seizures are mostly partial motor, brief myoclonic absences, massive myoclonias, and, more rarely, generalized or unilateral clonic seizures. Massive startles frequently occur at rest and during drowsiness.

The average age at which myoclonic status is recognized is 14 months (range: 3 months–5 years). Because of severe mental retardation and continuous abnormal movements, both the paroxysmal attention disturbances ("absences") and the myoclonias can remain unrecognized for several months. Considering its insidious appearance, it is probable that the age of onset of the status, in many cases, may be significantly earlier than when it is recognized.

In many cases, the myoclonias are subcontinuous but asynchronous in different muscles, and their relationship to the paroxysmal electroencephalographic (EEG) activity is difficult to appreciate because they are arrhythmic and subtle and also because the paroxysmal nature of the EEG pattern is often difficult to recognize.

In some cases the myoclonias are more obvious, involving rhythmic contractions of both arms and orofacial muscles. In other cases, the myoclonias are followed by a brief silent period constituting a mixture of positive and negative phenomena. In others, negative myoclonus is predominant, continuously fragmenting the voluntary movements and inhibiting the maintenance of any fixed antigravitary postures.

Even when the child is awake, the EEG is characterized by slow and poorly reactive activity with paroxysmal abnormalities. These consist of relatively monomorphic subcontinuous delta-theta activity (3–6 c/s) that varies in amplitude and occurs asynchronously over the frontocentral regions. In addition, there are brief sequences of rhythmic delta waves with superimposed spikes constituting unusual spike and wave complexes.

When the myoclonias are rhythmic, synchronous on the two sides, and strictly related to the diffuse paroxysmal bursts, they constitute an ictal pattern similar to that of a brief myoclonic absence.

The myoclonias become easier to recognize when there is motor arrest, such as during absence or drowsiness when all other abnormal movements disappear.

During drowsiness and slow wave sleep, spikes and waves become continuous to the point that sleep spindles are not recognizable. During stages II and III of the following nocturnal cycles, the paroxysmal activation ceases and spindles are clearly represented. During slow wave sleep, the myoclonias vanish, reappearing briefly at arousal. During rapid eye movement (REM) sleep when the diffuse discharges disappear, there is continuous rhythmic theta activity involving mainly the vertex and rolandic regions. The same theta activity strictly related to myoclonias is transitorily observed during alerting.

Based on the electroclinical picture, three main subgroups can be recognized.

The *first group* consists of patients who show a mixed pattern of brief myoclonic absences and subcontinuous rhythmic positive jerks, eventually followed by a brief silent period related to subcontinuous delta-theta activity involving the central areas accompanied by brief sequences of rhythmic delta waves with superimposed spikes mainly involving the parieto-occipital regions and often elicited by eye closure.

In this group, the status can be recognized during the first year of life. These are events of variable duration recurring sporadically in about half of the cases, whereas they are more "chronic" (lasting for years) in about one fourth of the cases. No other types of seizures are observed except for rare unilateral or generalized seizures that often occur in the setting of a febrile illness.

This electroclinical picture has been observed mainly in children with Angelman syndrome and with 4p-syndrome.

As we have described previously,[16,17,18,19,22,23] and as confirmed by other authors,[7,25,33,40] we consider this electroclinical picture to be the earliest diagnostic indicator of Angelman syndrome. Many authors have, in fact, described a very similar status in cases of Angelman syndrome, but they didn't recognize the preeminent myoclonic character.[5,30,37,39,41,43,45,47,48]

The *second subgroup* is made up of patients showing a pattern characterized by the marked predominance of inhibitory phenomena mixed with a severe fragmented dystonic component and sudden irregular, fast, lightning-like jerks. In these cases, the status is often difficult to recognize because of the very severe mental impairment, which is present from onset, and the abundance of continuous polymorphic and coarse abnormal movements. The jerks are mostly erratic and are therefore difficult to distinguish from violent dyskinetic movements. Moreover, the EEG paroxysmal abnormalities consist of subcontinuous multifocal slow spike waves that predominate in the frontocentral regions but fluctuate in amplitude and extent, making it very difficult to correlate with the positive and negative myoclonias. The result is an epileptic status characterized by a complex dysregulated motor pattern inducing a peculiar "hyperkinetic complete motor inhibition."

Except for brief generalized tonic-clonic seizures sometimes in clusters, other types of seizures are very rare.

Patients showing this electroclinical picture are females affected by a nonprogressive encephalopathy of unknown etiology or by associated with a cortical malformation.[7,17]

The *third subgroup* is made up of children who have only mild neurologic impairment at onset. Initially they have partial motor seizures or brief myoclonic absences. More or less rapidly and more or less subtly, a progressive myoclonic status begins, characterized initially by a subcontinuous sequence of generalized spike-wave paroxysms related to the rhythmic myoclonias of face and limbs. With time, there is progressive deterioration of the electrical activity and a morphologic modification of the paroxysms to sharp theta wave type with very slow pseudorhythmic continuous spikes in the central regions and vertex. At the same time, motor function is progressively compromised and pyramidal signs and intention tremors appear. In addition, continuous myoclonic inhibitory phenomenon appears that sometimes can be recognized clinically and polygraphically only when postural tone is increased. Complete motor inhibition is invariably the result.

In one fourth of the cases, magnetic resonance imaging (MRI) shows a probable disturbance, in gyration such as focal bilateral micropolygyria. Some children have Rett syndrome.[7,17]

Partial motor seizures, predominantly tonic and only sometimes followed by generalization, are frequent even at long follow-up intervals, whereas other types of seizures are absent.

Differential Diagnosis

Because of the significant progressive increase of both neurological impairment and EEG paroxysmal abnormalities as well as worsening polymorphic myoclonic manifestations, the first and often most complex step is the need to exclude a progressive disease, particularly the late infantile form of neuronal ceroid-lipofuscinosis.[4,49,50] The absence of progressive visual impairment with persistence of normal visual evolved potentials (VEP) even when, as frequently observed, the somatosensory evoked potentials (SEP) are abnormal, there is an absence of a paroxysmal response to photic stimulation and there is persistence of recognizable spindles can help to suggest a correct diagnosis.

Neuropathologic and molecular genetic analyses are required to rule out a progressive disease, particularly neuronal ceroid-lipofuscinosis.

Another somewhat difficult differential diagnosis can be with the cases reported in the literature as having a "newborn continuous partial epilepsy,"[14] "early-onset progressive encephalopathy with migrant continuous myoclonus,"[29] or "migrating partial seizures of early infancy"[12,31,51] because many of these can present, soon after onset, long-lasting status characterized by continuous discharges of diffuse spikes and waves accompanied by bilateral asynchronous myoclonias with obtundation and drooling.

Treatment and Outcome

In children showing the first electroclinical picture, the status frequently lasts for years refractory to treatment, and even benzodiazepines and adrenocorticotropic hormone generally have only a transitory effect. Nevertheless, in many cases ethosuximide plus valproic acid and levetiracetam leads to a significant improvement, and as the status resolves the clinical picture

improves dramatically. Continuous disabling jerks are reduced and some children become able to walk. In about one third of cases, even if the status disappears, intention myoclonus becomes predominant, constituting the picture described by Guerrini et al.[33,35,36] as cortical myoclonus.

In children with the second electroclinical picture, the long-term prognosis is always unfavorable. The status is refractory to different therapies and permanent in evolution, with definitive aposturality and severe mental deficit. Some patients die in long-lasting motor status.

The third electroclinical pattern is a pharmacoresistant progressive epilepsy not associated with a progressive disease. The neurologic impairment increases dramatically over a few years: In one third of the cases, cortical-subcortical and cerebellar atrophy becomes recognizable on MRI.

Summary and Conclusions

This particular type of symptomatic myoclonic epilepsy, characterized essentially by the recurrence of long-lasting atypical status associated with an impaired attention and continuous polymorphic jerks mixed with other complex abnormal movements in infants suffering from a nonprogressive encephalopathy, constitutes a unique syndromic entity.

Although this condition is difficult to diagnose clinically, it can be easily recognized by polygraphic recordings, which show rhythmic discharges of diffuse slow spike-waves accompanied by more or less rhythmic asynchronous myoclonias that are continuous during wakefulness and, in many cases, persist during sleep.

It is probable that becuase it is not routine to perform polygraphic recordings in clinical practice, the frequency of this condition has been underestimated.

This status is invariably accompanied by concomitant worsening of the child's neurological condition. The etiology can be varied, and is probably mainly malformative and genetic.

Electroclinical analysis makes it possible to distinguish three subsets of the disorder that have important diagnostic and prognostic significance. The first is characterized by the association of absences, subcontinuous jerks, at times rhythmic or arrhythmic and mainly positive, brief myoclonic absences, and hypnagogic startles. These suggest a diagnosis of Angelman syndrome or the up-syndrome.

The second affects mainly females and is characterized by the association of absence status and continuous rhythmic myoclonus, mainly negative, mixed with sudden, uncontrolled continuous dyskinetic movements leading to a clinical picture of hyperkinetic aposturality, generally sustained by a cortical malformation.

The third is characterized by continuous spike activity over the rolandic regions that persists throughout life accompanied by bilateral rhythmic myoclonias followed by an inhibitory phenomenon leading to a progressive neuromotor deterioration. This presents as a form of myoclonic progressive epilepsy in the absence of a progressive disease. In these cases, cortical dysplasia involving the motor area is frequently recognized.

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Chapter 235

Overview: Syndromes of Late Childhood and Adolescence

Jean Aicardi

Introduction

The incidence of epilepsy declines after the first few years of life but remains higher than in adults.[21] Greater maturity of the brain is associated with an increasing frequency of the classic types of seizures, such as generalized tonic–clonic, absence, and simple or complex partial seizures, and with a decreased incidence of the seizure types characteristic of infancy, such as infantile spasms, atypical absences, and febrile convulsions. Although lesional epilepsies of various causes can begin in this age range, a remarkable feature of many of the epilepsies of late childhood and adolescence is their occurrence in a previously normal child without neurologic or neurodevelopmental defects. Even more remarkable is the fact that a significant proportion of the epilepsies of late childhood and preadolescence tend to be self-limited and disappear after a few years without any detectable sequelae, and several such epilepsy syndromes with variable degree of benignity are described in the following chapters.

Such benign or favorable courses reflect the nonlesional nature of many of the epilepsies of this age, which are mainly determined by genetic factors.[14,16,32] Familial grouping of cases is well recognized, but there is still considerable uncertainty regarding the modes of inheritance of various types and the identification and localization of the responsible genes. Several monogenic syndromes have been described, but in most epilepsies of childhood and adolescence, only a few loci or genes have been characterized, and multigenic determination is considered probable. Even clinically homogeneous syndromes such as juvenile myoclonic epilepsy are genetically heterogeneous, and the current trend is to think in terms of susceptibility genes rather than of direct causation. This applies, for instance, to juvenile myoclonic epilepsy[23] and even more clearly to the syndrome of generalized epilepsy with febrile seizures plus (GEFS+), for which at least three genes have been identified,[17] and probably to other epilepsies.[32]

Two major groups of nonlesional, probably genetically determined, epilepsies are recognized: (a) the idiopathic generalized and (b) the benign partial epilepsies. The first group includes epilepsies with primary generalized tonic–clonic convulsions and several forms of myoclonic and absence epilepsies. The most common types in childhood and adolescence are childhood absence epilepsy (Chapter 239) and juvenile myoclonic epilepsy (Chapter 244). Absence epilepsy appears to be a clinically heterogeneous syndrome, and several distinct syndromes of absence epilepsy exist, whose recognition is probably important for prognostic purposes.[27] Childhood absence epilepsy has an excellent outcome, whereas juvenile absence epilepsy[34] and absences associated with juvenile myoclonic epilepsy are likely to persist into adult life. The exact nosologic place of some rare syndromes, such as eyelid myoclonia with absences[4] and absences with prominent perioral myoclonus between absence and myoclonic epilepsies, is not definitely determined. Juvenile myoclonic epilepsy is a common and well-defined syndrome in adolescents. The characteristic myoclonus on awakening easily goes unrecognized, and the diagnosis is often missed, so that the correct prognosis and treatment might not be given.[9,23] Juvenile myoclonic epilepsy, idiopathic grand mal epilepsies, and juvenile absence epilepsy may represent a spectrum of related syndromes (sometimes termed primary generalized epilepsies) with some types presenting only tonic–clonic seizures (awakening grand mal) and others with associated juvenile absences. It is not clear whether these different clinical presentations form different electroclinical and/or genetic entities or more likely belong to what is basically a single condition due to a common predisposition with specific factors determining the seizure expression, so that the group might be better termed primary generalized epilepsy.[30] Despite these different clinical aspects, the epilepsies in this group are benign in terms of neurodevelopment but tend to be persistent and not to remit for many years. They may even be lifelong, thus requiring continuous treatment.

The second group of partial idiopathic epilepsies has proved to be one of the most common types of epilepsy in older children. *Benign rolandic epilepsy* (Chapter 236), first described in the 1960s,[24] has been extensively studied.[5] The charactristic nocturnal sensorimotor facial seizures of short duration occurring in healthy children has now become familiar to neurologists and is easily recognized, even though the paroxysmal electroencephalogram (EEG) abnormalities may be more variable than initially thought.[34] The virtually complete benign nature of the syndrome has been repeatedly confirmed, although exceptional cases of an identical clinical syndrome in association with focal opercular lesions are on record.[3] However, recent studies have shown that disturbances of language and of other cognitive and behavioral functions may often be found, usually to a mild degree.[11,12] Long- term follow-up studies are necessary to assess the significance of these findings.

Cases closely related to benign rolandic epilepsy but with unusual features have received recent attention, and different aspects have been described. Opercular status epilepticus applies to rare cases with dysarthria, drooling, and pseudobulbar features lasting days to weeks, which might be considered as status of benign rolandic epilepsy, as confirmed by EEG recording.[8,11] Atypical benign partial epilepsy[1,20] is marked by the appearance of atonic seizures following a period of typical facial seizures, associated with intense spike-wave activity in slow sleep, and may wrongly suggest the diagnosis of Lennox-Gastaut syndrome. Electrical status epilepticus of slow sleep (ESES) is defined mainly by the EEG features and clinically by cognitive and behavioral deterioration. It is a heterogeneous group of patients, with approximately half of the cases having lesional causes.[18,19] The Landau-Kleffner syndrome (Chapter 242) often shares the EEG features of ESES and is clinically characterized by prominent language disturbances.[7,10] The very delineation of these syndromes is not entirely clear, and their relationship to benign rolandic epilepsy, which is suggested by the interictal EEG findings and the ultimate remission of epilepsy, is not straightforward because some cases may be due to brain lesions and the reasons for the different clinical expression and course are obscure. The mechanism of epileptic encephalopathy outlined here is probably an important causal factor.

Benign childhood epilepsy with occipital paroxysms (Chapters 237 and 238) is a second form of idiopathic focal epilepsy. Its clinical presentation is variable. Most commonly it presents in young children with infrequent nocturnal seizures, vomiting, loss of consciousness, and eye deviation. Most seizures are brief, but some may last several hours, with prominent autonomic manifestations, and they may simulate abdominal emergencies.[26] Visual symptoms are more common in older children, mainly in the form of transient loss of vision. Striking EEG abnormalities include continuous spike-wave complexes arrested by eye opening. Less typical abnormalities may be more common, however, in the form of spikes over the posterior part of the head. The course is consistently benign. Similarities and sometimes coexistence between rolandic and occipital epilepsy have suggested the concept of benign seizure susceptibility syndrome. Other syndromes, such as epilepsy with evoked parietal spikes and benign psychomotor epilepsy, have not been validated.

New syndromes of partial nonlesional epilepsies have been recently reported. Nocturnal frontal lobe epilepsy[2] presents with nocturnal seizures and is often misdiagnosed as sleep disorder (Chapter 249). It is transmitted as an autosomal-dominant trait and, in some families, has been shown to be due to mutations in the gene for α- and ß-nicotinic cholinergic receptors or of the γ-aminobutyric acid (GABA) receptor GABRG2.[17] No linkage to these loci was present in other families, however, indicating further genetic heterogeneity. Several distinct syndromes of dominant partial epilepsy are now recognized. They include benign multifocal partial epilepsy,[2] benign rolandic epilepsy with pseudobulbar features,[31] and benign dominant mesial and lateral temporal lobe epilepsies,[6] which may not be rare but have not been recognized before adolescence (Chapter 248).

The benign couse and even the nonlesional nature of some of the newly described partial epilepsy syndromes are difficult to establish because similar cases can be of lesional origin. In general, the use of the term *benign* should be reserved for those cases in which a favorable outcome of the epilepsy and normal neurodevelopment have been consistently found. The term is not synonymous with *idiopathic* or *genetic* because cases belonging to the latter categories may have a severe outcome.

Seizures of lesional origin in children and adolescents may have quite variable manifestations. Late cases of the Lennox-Gastaut syndrome (Chapter 241) and even of epileptic spasms may appear. Well-defined complex partial seizures tend to become increasingly frequent as the patients grow older. The causes of lesional seizures in this age range differ from those found in adults. Developmental brain abnormalities are still common.[18] Cases of mesial temporal lobe epilepsy (Chapter 247) with typical temporal lobe seizures and evidence of hippocampal sclerosis on neuroimaging begin to appear in the latter part of the period. In younger children, cortical dysplasia and related migration abnormalities tend to predominate. They can involve any part of the brain, which explains the greater frequency of extratemporal epilepsies in children than in adults. Frontal lobe seizures are especially common and may be difficult to distinguish both from temporal lobe seizures and from pseudoseizures. In many frontal lobe seizures, consciousness is preserved despite unresponsiveness of the child and complex movements and attitudes.[5] Tumors are rare as a cause of seizures in children and adolescents. A majority are developmental tumors, commonly associated with neighboring dysplasias (developmental neuroepithelial tumors and gangliogliomas). Their diagnosis by neuroimaging has been reviewed.[29] A rare but important form of partial lesional epilepsy is Rasmussen syndrome (Chapter 243), a progressive inflammatory brain disorder of unknown origin that often causes epilepsia partialis continua and a progressive neurologic deficit requiring surgical therapy.

Summary And Conclusions

An important proportion of the epilepsies of childhood and adolescence are of idiopathic origin and relatively benign. Overtreatment should be avoided in these cases, and some epileptologists believe that drug treatment is unnecessary when the outcome can be firmly predicted. Intractable lesional epilepsies may be medically intractable and amenable to surgical therapy. However, the majority of the epilepsies with onset in late childhood and adolescence respond well to antiepileptic agents and are compatible with a reasonably normal quality of life in the cases in which no definitive remission is to be expected.

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Chapter 236

Benign Childhood Epilepsy with Centrotemporal Spikes

Natalio Fejerman

Introduction

The recognition that some epilepsies in children have focal clinical manifestations and unilateral electroencephalographic (EEG) discharges with benign evolution has been one of the most interesting contributions to pediatric epileptology in the last 50 years.

The concept of idiopathic and benign focal epilepsies of childhood is relevant not only from the theoretical point of view, but also as a practical tool, because the term implies both absence of structural brain lesions and a genetic predisposition associated with age-dependent seizures. Benign childhood epilepsy with centrotemporal spikes (BCECTS) is the most frequent of the benign focal epilepsies of childhood and represents 15% to 25% of epilepsy syndromes in children <15 years of age. In addition, it is the most frequent epilepsy syndrome in school-age children.[25,101,125]

Historical Perspectives

Yvette Gastaut was the first to state, in 1952, that "pre-rolandic spikes" could be "functional" instead of an indicator of a cortical lesion.[48] In 1958, Bancaud et al.[6] and Nayrac and Beaussart[91] reported the first series of patients, emphasizing that rolandic or pre-rolandic spikes or spike-waves constituted EEG features that were typical of childhood, and that should not induce "neurosurgical behaviors," although they did not describe a clear electroclinical correlation. In 1960, Gibbs and Gibbs[51] stated that prognosis was much better in children with centrotemporal spikes than in those with spikes in the anterior temporal regions. In the same year Faure and Loiseau[39] wrote of "Rolandic spike-waves without focal significance," referring to age of onset and sleep as a trigger of seizures, and to spontaneous electroclinical normalization in puberty. Clinical features of seizures were not defined, however, because they found generalized seizures in 13 of their 15 cases. In 1966, Trojaborg[114] published a longitudinal study in a cohort of 519 children with focal spike discharges. Two hundred and eighty of these patients had cerebral palsy. The main purpose of this work was a detailed analysis of the significance of acute sharp waves in the EEG and their correlation with brain lesions. The author recognized that one prognosis was good in children with centrotemporal spikes, but did not determine their clinical correlates. Also in 1966 the most important series of children with temporal lobe epilepsy was published.[97] Among the 100 children followed, 33 constituted a subgroup without pathologic history and with mean age of onset of seizures between 7 and 8 years. It is now easy to imagine that a significant proportion of these 33 children might have had the diagnosis of BCECTS.

One year later, two independent groups reported their series of patients with a peculiar form of epilepsy to be differentiated from other focal epilepsies, mainly from temporal lobe epilepsy. Loiseau et al.[78] presented 122 cases with onset of seizures at school age and rolandic sharp waves in the EEG. In 80% of their patients, seizures occurred during sleep and were frequently motor with predominant involvement of the face. Lombroso[81] provided a clear description of the seizures, emphasizing somatosensitive symptoms in tongue, oral mucosa, and gums, along with speech arrest, and proposed the term "sylvian seizures," recognizing also the particular focal EEG features. Both Loisseau et al. and Lombroso stressed the benign character of the condition in terms of the evolution of seizures and normalization of the EEG. In 1972, Blom et al.[13] reported a prevalence and follow-up study and proposed that the condition be named “benign epilepsy of children with centrotemporal EEG foci.” Several long-term follow-up studies confirmed the good prognosis.[8,9,72,80] Atypical and not-so-benign evolutions have been reported in some patients.[1,40,43,44,46,54] This form of epilepsy is now called benign childhood epilepsy with centrotemporal spikes and is placed in the group of idiopathic localization-related (focal, local, partial) epilepsies in the International Classification of Epilepsies and Epileptic Syndromes.[21,36]

Definitions

The most common name besides BCECTS appearing in the literature referring to this condition is “benign rolandic epilepsy.” The term “benign” has been questioned for other epilepsy syndromes because some epileptologists believe that benign implies a natural evolution to remission of seizures and EEG abnormalities even without treatment. In this sense, BCECTS conforms to the aforementioned concept, even if we must accept that there are exceptions to the rule.

Onset during childhood with hemifacial motor, seizures, speech arrest, and sialorrhea, occurring mostly during sleep, along with distinctive centrotemporal spikes in the EEG are well-defined features that allow a prompt diagnosis and assure a good prognosis, although subsets of atypical cases with slight compromise of neurological functions are increasingly being reported.[102,120,122]

Epidemiology

Benign childhood epilepsy with centrotemporal spikes accounts for between 15% and 25% of all epileptic syndromes in children between the ages 4 and 12 years.[19,25,101,121] Its annual incidence has been reported to be between 7.1 and 21 per 100,000 in children <15 years of age.[56] Because nocturnal seizures can be overlooked in diagnosis, this disorder may be even more common than generally suspected. There is a slight male predominance.[82]

The prevalence of epilepsy is much higher among close relatives of children with BCECTS than in a matched control group.[17] In one study, 15% of siblings had seizures and rolandic spikes, 19% of siblings had rolandic spikes without attacks, and 11% of the parents had had childhood seizures that had disappeared by adulthood.[57]

In an epidemiologic study of epilepsy in a cohort of 440 consecutive children, benign rolandic epilepsy of childhood accounted for 8% of patients (neonatal seizures were excluded from the analysis).[67]

Etiology and Basic Mechanisms

The high incidence of a positive family history for epilepsy and focal EEG abnormalities indicates the importance of genetic factors in the etiology of BCECTS.[13,17,27,82] Most authors speak of an autosomal-dominant trait with variable penetrance.[17,57] This type of inheritance was also suggested by studies of monozygotic twins with rolandic discharges[64] and of HLA antigens and their haplotypes.[34] However, in another study of clinical and genetic aspects in children with benign focal sharp waves, including 134 probands with seizures (24% of which had typical rolandic seizures), the findings agreed with a multifactorial pathogenesis with “benign” focal epileptiform sharp waves.[32] Epileptic seizures appear in only 25% or less of individuals with this EEG trait.[82] Expression of the gene may be influenced by other genetic and environmental factors.[79] Linkage to chromosome 15q14 was found in 54 patients of 22 families with benign childhood epilepsy with centrotemporal spikes.[92] However, in a study of 70 families with BCECTS in Italy, the same linkage could not be found.[104] Approximately 10% of patients have a history of febrile seizures, and this also supports a genetic predisposition for febrile seizures expressed at earlier ages in children with BCECTS.[63,71]

A family with nine affected individuals in three generations was reported showing the features of rolandic epilepsy associated with oral and speech dyspraxia and cognitive impairment.[109] Similar seizures and the EEG phenotype of BCECTS were found in three children with de novo terminal deletions of the long arm of chromosome 1q, and the authors suggested that it could be a potential site for a candidate gene.[118]

Although the pathophysiology of BCECTS is unknown, and there is no associated structural lesion, the typical ictal clinical behavior and EEG discharge indicate a disturbance in the sylvian and rolandic areas.[37] Electrophysiologic studies, however, fail to demonstrate a discrete generator, and a large, shifting area of regional cortical dysfunction may be present. In some patients with BCECTS, the occurrence of generalized spike-wave EEG discharges, as well as focal spikes in other areas, suggests a relationship between BCECTS and the idiopathic generalized epilepsies, as well as with other idiopathic localization-related partial epilepsies.[73,82] Between 10% and 20% of patients with centrotemporal spikes may also have sharp slow wave complexes in other cortical locations.[100]

Combined recording of interictal spikes and somatosensory-evoked potentials led to the conclusion that in some patients multiple simultaneous neuronal populations are active within the central region.[7]

Magnetoencephalographic (MEG) analysis of generator sources and propagation of rolandic discharges in BCECTS using three-dimensional dipole localization suggested that rolandic discharges are generated through a mechanism similar to that of somatosensory-evoked responses.[86] A localization analysis of spontaneous magnetic brain activities also suggested the value of MEG for pathophysiologic studies.[65] Six children with bilateral centrotemporal synchronous discharges were studied using MEG and EEG with equivalent current dipole modeling. Results implied cortical epileptogenicity in bilateral perirolandic areas.[75] Interictal spikes were recorded in seven children during functional magnetic resonance imaging (fMRI) acquisition using a MR-compatible digital EEG system. Spike-related activation in the perisylvian central region was found in three of them.[14] High-resolution EEG and MEG and a realistic volume conductor model were used to study the spatiotemporal aspects of the sources of spikes in children with benign rolandic epilepsy. Results for EEG and MEG were different. Both high-resolution EEG and MEG revealed that in some cases there were multiple sources for spikes that were well separated in space and time, whereas in other cases only single-source activity was present.[61]

Recent papers considered BCECTS, Landau-Kleffner syndrome, and electrical status epilepticus in sleep as a spectrum of disorders with a common transient, age-dependent, nonlesional, genetically based epileptogenic abnormality, involving a perisylvian epileptic network. Halasz et al. refer to “mild to severe epileptic encephalopathy limited to the perisylvian network, where the cognitive impairment is caused by epileptic discharges interfering with cognitive development.”[55]

Clinical Presentation

We discuss the main clinical features of BCECTS, assuming that this is an idiopathic focal epilepsy that appears in children with normal neurological development, although this syndrome has also been reported in patients with nonevolutive brain lesions.[108]

1. BCECTS begins between 4 and 10 years of age in 90% of patients, and the median age of onset is approximately 7 years. There are no reports of BCECTS occurring during the first year of life or after age 15 years, and cases with seizure onset before the age of 2 years are extremely rare.[25,42]
2. BCECTS is seen more frequently in males, with a male-to-female ratio of 3:2.
3. Seizures are clearly related to sleep, whether during the night or the day. This is seen in 80% to 90% of patients. Seizures during waking hours are more likely to occur shortly after awakening,[82] although on many occasions, during the early morning the child wakes up with a seizure that really started during sleep. Seizure frequency is usually low, and around 10% of cases have only one seizure. In about 20% of the children, however, seizures are frequent and may even occur several times per day.[25] Most patients have a single type of seizure, but 20% to 25% of children experience more than one type.[79] Loiseau and Beaussart[77] described 35 signs or components of 275 seizures analyzed in 190 children with BCECTS. We can reduce this number to a small group of characteristic manifestations of seizures:
    a. *Orofacial motor signs*, especially tonic or clonic contractions of one side of the face, with predilection

for the labial commissure (contralateral to the centrotemporal spikes). There are also contractions of the tongue or jaw, guttural sounds, and drooling from hypersalivation and swallowing disturbance.

b. *Speech arrest,* most probably due to tonic contractions of pharyngeal and buccal muscles, constituting anarthric seizures. In fact, the patient cannot speak during the seizure because either he or she wakes up with hemifacial contractions or while awake opens his or her mouth with the intention to speak but stays blocked in that position.

c. *Somatosensory symptoms*, namely unilateral numbness or paresthesia of the tongue, lips, gums, and cheek, are frequent, but sometimes have to be looked for in the context of recalling previous events.

d. The three mentioned groups of manifestations are related to an epileptic activation of lower rolandic motor and somatosensory areas. In terms of sialorrhea, it is not clear whether it corresponds to increased salivation, a swallowing disturbance, or both. In general, these seizures only last a few minutes. Although partial seizures are characteristic of this disorder, generalized seizures are not infrequently observed, particularly in younger children.[71,82] The initial event is often a nocturnal hemifacial convulsion, which may spread to the arm and the leg or may become secondarily generalized. It is highly probable that in these cases a focal seizure begins during sleep with a rapid generalization and loss of consciousness, which makes it difficult for the child to remember what happened. This is in line with the fact that almost all seizures that start while the person is awake are focal.

4. Behavioral and learning problems are less frequent than in other forms of childhood epilepsy.[58] It is often mentioned that children with BCECTS are free of neurological and psychological impairments.[45,46,71] In recent years, however, several reports based on meta-analyses of published series, retrospective analysis of patients, or prospective cohort studies have reported a higher incidence of learning and/or language difficulties in these children. In a study of 40 children with centrotemporal spikes with and without seizures compared with 40 healthy controls, patients were significantly impaired in IQ, visual perception, short-term memory, and psychiatric status. The deficits in IQ correlated more with frequency of EEG spikes than with the frequency of seizures.[122] Similar findings were reported in 19 children with this syndrome.[29] An increased frequency of rolandic spikes has been reported in children with attention deficit hyperactivity disorder.[59] One study found a consistent pattern of language dysfunction in 13 of 20 children with BCECTS, suggesting interictal dysfunction of the perisylvian language areas.[113] A longitudinal study of one boy with acquired epileptic dysgraphia was reported. Most probably, in this case, the acquired regression of graphomotor skills was associated with an increase in spike frequency as happens in cases with atypical evolution of this syndrome.[33] In a more recent report, written language skills were compared in 32 children with typical BCECTS with 36 controls. As a group, the patients with BCECTS performed significantly worse than controls in spelling, reading aloud, and reading comprehension, presented dyslexic-type errors, and frequently had below-average school performance.[102] Language assessment in 16 children with BCECTS also showed that the domains of expressive grammar and literacy skills were affected in a significant proportion of the cases.[89] A comprehensive study of neuropsychological and language profiles of 42 children with BCECTS selected using strict clinical and EEG criteria showed that the patients have normal intelligence and language ability, although a specific pattern of difficulties in memory and phonologic awareness was found. No correlation between EEG features and the aforementioned impairments was demonstrated.[94]

   Atypical features in benign childhood epilepsy with centrotemporal spikes can be seen both clinically (daytime-only seizures, postictal Todd paresis, prolonged seizures, or even status epilepticus) and in EEG features (atypical spike morphology, unusual location, or abnormal background). In a retrospective case series, atypical clinical features were seen in 50% of patients and atypical electrographic features in 31%.[123] In a follow-up study of 74 children with typical rolandic epilepsy and 14 with atypical features, a significantly higher percentage of learning and behavioral disabilities was found in the second group.[120]

   Several cases of partial status epilepticus have been reported. The manifestations include hemifacial seizures, dysarthria or anarthria, and persistent drooling.[20,43,44,52,66,106,107]

Diagnostic Evaluation

Electroencephalographic Findings

After recognition of typical clinical features, the cornerstone of the diagnosis of BCECTS lies in the characteristic interictal EEG pattern, which include the following features:

1. Background EEG activity is symmetric, well organized, and normally reactive during wakefulness, and the physiologic patterns of sleep are also normal.[25,26]
2. Interictal epileptic discharges and location of spikes are characterized as follows:
    a. *Characteristics of spikes*: Typical centrotemporal spikes (CTS) are located in centrotemporal or rolandic areas (Fig. 1). They are broad, diphasic, high-voltage (100–300 µV) sharp waves, with a transverse dipole, and they are often followed by a slow wave. The spikes may occur isolated or in clusters, with a rhythm of about 1.5 to 3 Hz.[79] Focal rhythmic slow activity is occasionally observed in the region in which the spikes are seen, especially when spikes are frequent.[87] They may be seen in only one hemisphere or independently on both sides of the head (Fig. 2).[37] The CTS tend to spread to adjacent regions. Several authors emphasized the characteristic dipole orientation in the EEG.[53,76,115] Two groups of patients have been found based on EEG findings (maximal negativity was registered in high- and low-central regions, but never in midtemporal regions): (a) a high-central-region group with more frequent hand involvement and (b) a low-central group with common orofacial symptoms.[70] The source distribution of benign rolandic spikes along and across the central sulcus was examined in 15 patients between 7 and 15 years of age. The equivalent current dipoles of the spikes measured by whole-head MEG were compared to the spike distributions detected by simultaneous scalp EEG. Rolandic spikes are consistent with by a precentral origin, assuming that the surface negative potential is continuous from the gyral to fissural cortices.[62]

    b. *Enhancement of discharges*: The centrotemporal spikes are not enhanced by eye opening or closure, hyperventilation, or photic stimulation. Moreover, hyperventilation sometimes reduces the frequency of rolandic spikes.[45,121] The discharge rate is increased in drowsiness and in all stages of sleep, and in about one third of children, the spikes appear only in sleep.[81] Sleep EEG organization is preserved.[23] In spite of their increasing frequency during sleep, the CTS show the same morphology as during wakefulness. A change in morphology, particularly the appearance of fast spikes or polyspikes, a marked increase in the slow component, or a brief depression of voltage, suggests an organic etiology even when the ictal features are suggestive of BCECTS.[25] There is no correlation between intensity of spike discharges in the EEG and

frequency, length, or duration of clinical seizures.[72] In fact, extreme discrepancies between the rarity of seizures and the activity of the EEG foci are not uncommon, and clinical experience indicates that the EEG is often relatively unchanged, even with effective treatment.[5]

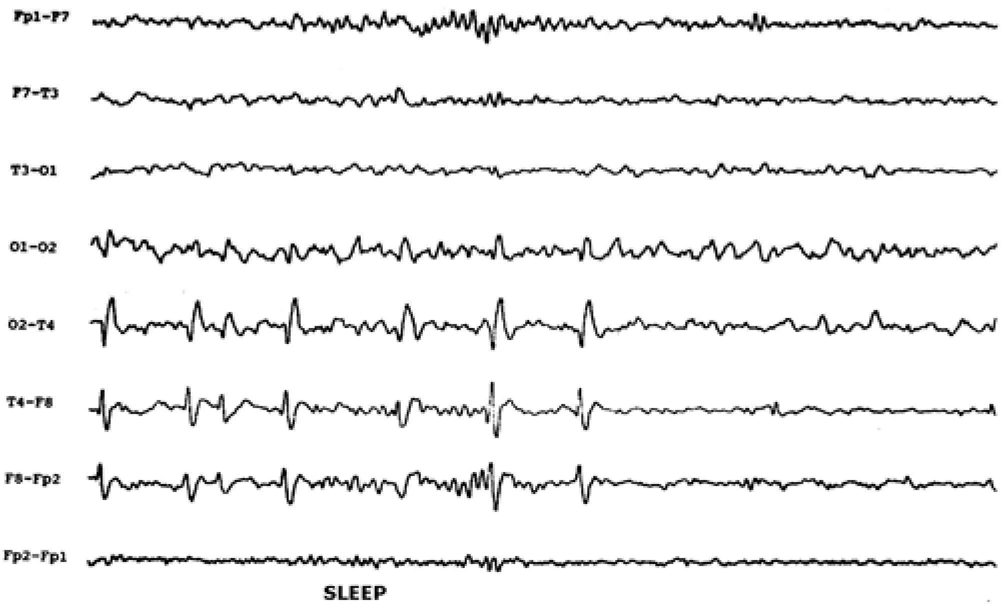

FIGURE 1. Sleep electroencephalogram (EEG) in a 6-year-old girl with typical seizures and right centrotemporal spikes.

c. *Spikes in other areas and spike-wave discharges*: Spike foci may coexist in other areas independent of their clinical correlation.[71,100] Generalized spike-wave discharges are rarely seen in the waking state but are not infrequent during drowsiness and sleep.[11,45] The real incidence of spike-wave discharges in children with BCECTS is not established; numbers vary between 7% and 65%.[25,27] One must be cautious in interpreting this because bursts of slow waves with spikes in drowsiness are seen in up to 20% of children between 3 and 6 years of age, especially those with history of febrile seizures.[2] We will see later that the coexistence of BCECTS with the Panayiotopoulos type of benign occipital epilepsy is not rare, whereas its association with absence epilepsy is exceptional.

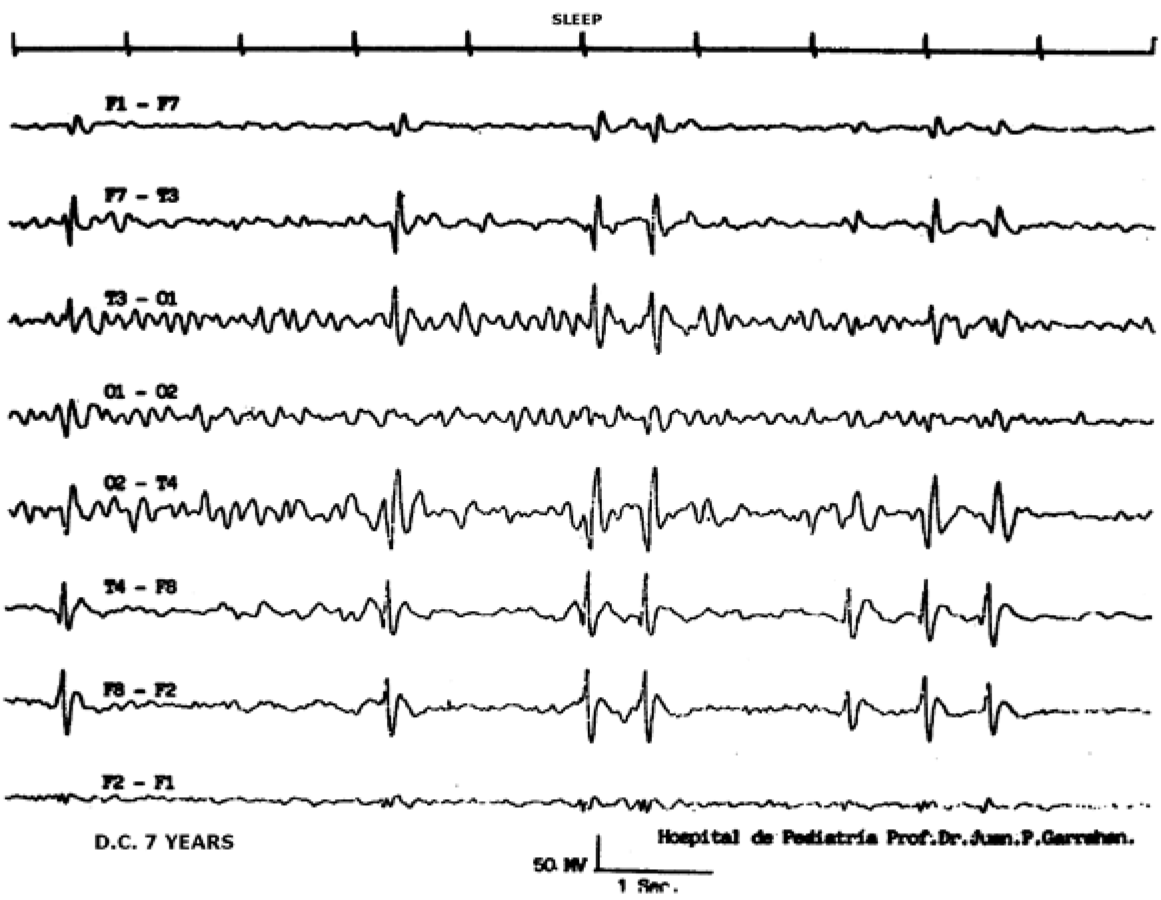

FIGURE 2. Sleep electroencephalo-gram (EEG) in a 7-year-old boy with typical seizures and bilateral centro- temporal spikes.

3. With regard to the frequency of discharges and the correlation with cognitive deficits, the association of more frequent discharges or multifocal paroxysms with complicated evolution in BCECTS is a debated subject.[25,85] It is clear, however, that the appearance of bilateral synchronies leading to continuous spikes and waves during sleep are frequently associated with severe cognitive and language impairment.[43] In a recent study of 20 children with benign partial epilepsies who were studied by combined EEG, MEG, and MRI, location of spikes was determined by dipole source estimates. There was a correlation between location of spikes and selective cognitive deficits, with left perisylvian spikes associated with poorer language test results in 11 cases, whereas 6 children with right perisylvian location performed within normal ranges in all parts of the tests.[124] In a small group of patients with status epilepticus in BCECTS, the finding of independent right and left seizures was considered a risk factor.[52]

4. EEG studies in large numbers of healthy children revealed centrotemporal spikes in 2.1% of 533 children between 6 and 15 years of age;[35] in 2.4% of 3,726 children between 6 and 13 years of age;[19] and in 3.5% of 1,057 children between 6 and 12 years of age.[95] Considering that in many of the cases the EEGs were performed in the waking state, we may assume that the actual figures should be higher. The fact is that in a vast majority of children with CTS, a genetically determined cortical excitability produces the EEG abnormalities, which in a few patients are associated with clinical seizures. It has been estimated that <25% of children with CTS have seizures.[82] The presence of CTS was also reported in children with Rett syndrome and fragile X syndrome and even in children with brain tumors.[69,90,93]

5. Reports in the literature on ictal EEGs in children with BCECTS are scarce and only deal with isolated cases.[3,26] The ictal pattern is generally characterized by a sequence of rhythmic spikes remaining quite monomorphic throughout the discharge. Lerman described a diurnal seizure with local decremental activity followed by dense spikes confined to the centrotemporal area during the tonic phase and with spike-waves during the clonic phase.[71]

Neuroimaging and Other Laboratory Examinations

When the clinical and EEG features are typical, the diagnosis is certain, and therefore neuroimaging in BCECTS has been regarded as superfluous by many authors.[5,71] However, several reports called attention to a higher percentage of brain abnormalities in children with typical BCECTS. Gelisse et al.[50] presented the case of a 10-year-old-boy with marked right hippocampal atrophy, although they concluded that the seizure disorder could not be ascribed to this abnormality. The same group reported computed tomography (CT) or MRI abnormalities in 10 of 71 consecutive patients with BCECTS, but the sample was most probably biased because 2 of the 5 children showing enlargement of the lateral ventricle had shunted hydrocephalus.[49] Hippocampal asymmetries and white matter abnormalities in MRI have been reported in 33% of 18 children with BCECTS, but the relationship was considered unclear.[83,84] On the other hand, because of a few cases that have presented the clinical and EEG phenotype of BCECTS in whom cortical dysplasia[3,40,110] and even brain tumors[111] were found, one might question whether an MRI study is indicated. Based on these findings and the evaluation of what happens in everyday practice, it is legitimate to obtain an MRI study to avoid the possibility of ignoring existing abnormalities.

Very few studies using positron emission tomography (PET) have been performed in children with BCECTS. De Saint-Martin et al.[30] reported a longitudinal study of a child with BCECTS using F-fluorodeoxyglucose (FDG) PET. They found a bilateral increase of glucose metabolism in the temporal opercular regions interictally during the “active” phase of the epilepsy. In 11 children with BCECTS studied with FDG-PET, no interictal side differences in glucose metabolism were demonstrated.[117]

Differential Diagnosis

Several series of children with BCECTS have included some patients with cerebral palsy.[13,72,82] Distinction between benign childhood epilepsy with centrotemporal spikes and more serious nonidiopathic epileptic conditions, such as mesial temporal lobe epilepsy, can usually be made easily on the basis of history and the unique dipole pattern of the centrotemporal spike. However, benign focal epileptiform discharges were found in 2 of 17 preadolescent children who eventually underwent anteromesial temporal resection for refractory temporal lobe epilepsy due to hippocampal sclerosis, and the authors suggested that it might not have been an incidental finding.[98] Because of their prevalence, fortuitous associations may be found between benign childhood epilepsy with centrotemporal spikes and nonprogressive brain lesions.[108] Isolated cases of children with BCECTS and unilateral opercular neuronal migration disorders have been published.[3,40,110] Cerebral tumors presenting as pseudo-benign partial epilepsy in childhood with centrotemporal spikes were reported in five patients.[111] Five children with a so-called “malignant rolandic-sylvian epilepsy” secondary to neuronal migration disorders and gliosis were reported as presenting similar clinical and EEG features of benign childhood epilepsy with centrotemporal spikes. The authors emphasized the role of MEG in the differential diagnosis.[96]

The pathophysiologic relationships that may exist between benign childhood epilepsy with centrotemporal spikes and other benign partial nonrolandic epilepsies can make differential diagnosis difficult. The coexistence of two types of benign partial epilepsies in children, namely Panayiotopoulos type of benign occipital epilepsy and BCECTS, has been reported, presenting either in sequence one after the other or at the same time,[18,22,99] although treatment and prognosis are the same.[73]

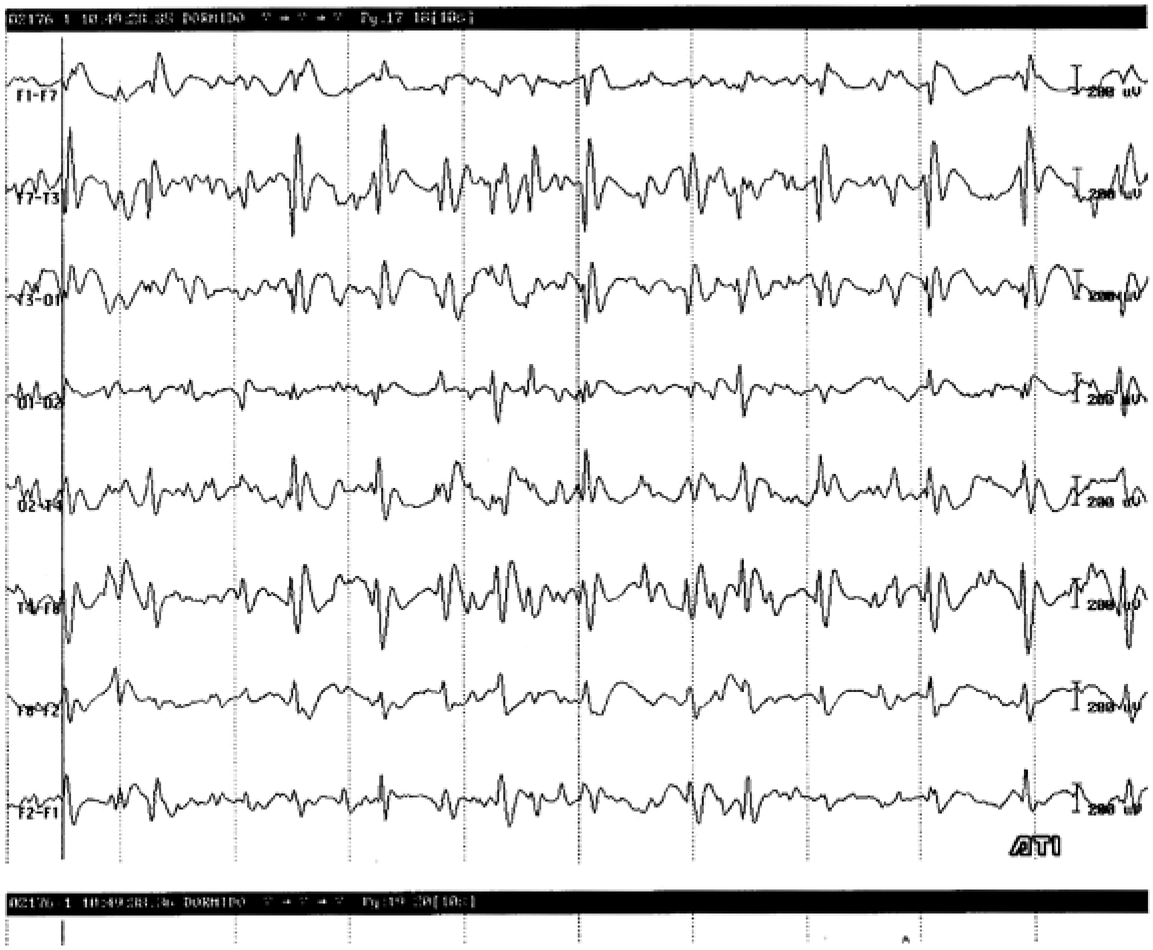

FIGURE 3. Sleep electroencephalogram (EEG) in a 7-year-old boy with a history of typical benign childhood epilepsy with centrotemporal spikes and onset of inhibitory seizures. Bilateral, almost continuous spike-wave discharges are seen.

Treatment and Outcome

In considering outcome in children with BCECTS, it is necessary to consider control of seizures on one hand and the incidence of neurological impairments, either transitory or persistent, on the other. Antiepileptic drug treatment is usually effective, although many authors believe that drug treatment is not necessary in the benign focal epilepsies of childhood.[25,47,100] Therefore, continuous treatment should be considered only in patients with frequent seizures and when the ictal events are disruptive to the patient or family. Carbamazepine was always the drug of choice. However, the use of benzodiazepines at night may be considered in those children who have seizures only during sleep. Benzodiazepine treatment for several weeks was also recommended.[28] In comparison with valproate and carbamazepine, clonazepam was found to be more effective in suppressing rolandic discharges after 4 weeks of treatment.[88] Sulthiame has been recommended in several reports.[31,71,74] In a double-blind, placebo-controlled study of 66 children with BCECTS, sulthiame was found to be remarkably effective in preventing seizures and was well tolerated.[105] A more recent report also showed the benefits of sulthiame.[38] Among new drugs, oxcarbazepine and levetiracetam showed good results.[10,116] Curiously enough, an ictal clinical and EEG study in one child suggested that voluntary protrusion of the tongue could stop seizures and EEG discharges.[119]

A meta-analysis of outcome in 794 patients in 13 cohorts, concluded that early prediction of seizure outcome in a new patient cannot be given with certainty.[15] It was stated that the only predictor for a disease course in children with multiple seizures is onset before 3 years of age.[68]

In a prospective study of treatment in childhood epilepsy, it was concluded that 1 year of treatment can be recommended in children with benign childhood epilepsy with centrotemporal spikes.[16] In fact, once the decision to treat is made, it is not possible to make a firm recommendation regarding duration, but there is no need to wait for normalization of the EEG to stop medication. Relapse of seizures, however, may occur after premature withdrawal.[79]

If it is considered that there is risk of an atypical evolution due to worsening of the EEG, an increase in the number of seizures, the presence of inhibitory seizures, or evidence of neuropsychologic abnormalities, the following steps should be taken: First, stop the medication if it is carbamazepine, oxcarbazepine, phenytoin, or valproic acid, and then switch to a benzodiazepine, ethosuximide, or sulthiame. Two of our cases of BCECTS status only responded to treatment with steroids.[44] Sulthiame seems to be the drug of choice in patients presenting atypical evolution associated with secondary bilateral synchrony in the EEG.[41,43]

Long-Term Prognosis

In general, benign childhood epilepsy with centrotemporal spikes is associated with an excellent prognosis. Seizures are difficult to control in only a small number of cases.[9,12] The prognosis is favorable even in patients whose seizures are difficult to control as seizures almost always remit spontaneously in adolescence. In their investigation of 168 patients 7 to 30 years after cessation of epilepsy with centrotemporal spikes, Loiseau et al. reported that seizures persisted in only 3 cases after adulthood.[80] The seizures were all generalized tonic–clonic seizures. Two of the 3 had obviously isolated incidences. This incidence of generalized seizures in adults with a history of epilepsy with centrotemporal spikes in childhood is nevertheless higher than that of seizures in the general population.[80] Cognitive functions were evaluated in 23 adolescents and young adults in complete remission from BCECTS and showed no significant differences from controls. However, qualitative analysis suggested a different organizational pattern for cerebral language in adolescents and young adults in remission.[60]

The presence of atypical interictal epileptiform EEG patterns does not appear to alter prognosis.[11] However, atypical evolutions may cause doubt about the prognosis. For example, in the cases of benign atypical partial epilepsy described by Aicardi and Chevrie,[1] affected children showed partial or generalized atonic fits leading to multiple daily falls. These inhibitory attacks appeared in clusters that lasted for weeks, and the EEG showed continuous spikes-and-waves during slow wave sleep (Fig. 3). Status lasting days or weeks including motor facial seizures and anarthria with persistent drooling constitute other complications of this syndrome.[43,44] Both complications were still associated ultimately with a good prognosis. However, acquired epileptic aphasia and the syndrome of continuous spikes-and-waves during slow sleep have also been associated with BCECTS, and in these cases the risk of permanent language dysfunction or neurological abnormalities is clearly present.[40,43] EEG activity in these atypical evolutions seems to be a kind of secondary bilateral synchrony, but it is not understood why some children develop this EEG pattern. In some cases, certain antiepileptic drugs seemed to be responsible.[18,103,112]

Summary and Conclusions

Benign childhood epilepsy with centrotemporal spikes is an idiopathic childhood epilepsy characterized by well-defined

electroclinical features, including brief hemifacial motor seizures, with sialorrhea and speech arrest, occurring more frequently during sleep, associated with centrotemporal spikes in the interictal EEG. It is the most frequent epilepsy syndrome in children between 4 and 12 years of age.

In general, BCECTS is associated with very good prognosis, with electroclinical normalization in puberty. There are rare cases (approximately 2%) with atypical evolutions leading to significant neuropsychologic impairments. This event should be recognized as early as possible.

Treatment is not always necessary. Common antiepileptic drugs can be used, but in the presence of atypical features such as increase in the number of seizures, onset of inhibitory seizures, continuous spike and waves during slow sleep in the EEG, and language or behavioral involvement, the best choice is benzodiazepines or sulthiame.

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Chapter 237

Early-onset Benign Childhood Occipital Epilepsy (Panayiotopoulos Type)

Natalio Fejerman

Introduction

In the first edition of this book, only a few lines mentioned this condition under the heading of Childhood Epilepsy With Occipital Spikes and Other Benign Localization-Related Epilepsies.[33] At present, early-onset benign childhood occipital epilepsy (Panayiotopoulos type) (EOCOE) is not only a clearly recognized syndrome, but it also represents the second-most-frequent benign focal epilepsy syndrome in childhood after benign childhood epilepsy with centrotemporal spikes (BCECTS). The characteristic clinical features of this syndrome should be known not only by epileptologists and neurologists, but also by pediatricians. An early diagnosis would avoid undue interventions and concerns on account of its really benign outcome.

Historical Perspectives

In the International League Against Epilepsy (ILAE) classification of Epilepsy syndromes,[11] besides the well-known BCECTS, only childhood epilepsy with occipital paroxysms (CEOP), as described by Gastaut, is recognized.[29] In comparison with BCECTS, which has a prevalence of approximately 15% among children with epilepsy,[15,18,52] the Gastaut type of CEOP is rare, of uncertain boundaries, and often of unpredictable prognosis.[8] This condition is characterized by brief seizures with mainly visual symptoms such as elementary visual hallucinations, illusions, or amaurosis, followed by hemiclonic convulsions. Postictal migraine headaches occur in half of the patients. Age at onset is approximately 8 to 9 years. The electroencephalogram (EEG) shows occipital spike-wave paroxysms that attenuate or disappear when the eyes are open.[11,29,30,47]

In 1989, two significant papers of Panayiotopoulos based on an already long follow-up of his patients called attention to the particular cluster of symptoms present in what he called “benign nocturnal childhood occipital epilepsy.”[49,50] He had already emphasized vomiting as an ictal symptom in epileptic seizures in children 1 year earlier.[48] Another peculiar clinical feature of EOCOE was the “cerebral insult–like” partial status epilepticus including autonomic symptoms.[38,57,64] To stress the variable phenotypes of benign focal epileptic syndromes in childhood, Panayiotopoulos and coworkers used the term “benign childhood seizure susceptibility syndromes.”[51,52] After 1996, Fejerman and coworkers proposed naming this syndrome early-onset benign childhood occipital epilepsy (Panayiotopoulos type) as opposed to late-onset childhood occipital epilepsy (Gastaut type).[7,8,19,20,21,22] Three important series of children with this syndrome were published about this time.[25,37,45] Retrospective analysis of the clinical histories allowed the authors to study the variants of childhood epilepsies with occipital paroxysms and to recognize this early-onset variant. In the same year, the first prospective study of 66 children with EOCOE was published.[8] In 2001, the task force on Classification and Terminology of the ILAE published a proposed diagnostic scheme for people with epilepsy.[17] It adopted the names proposed by Fejerman including eponymic designations to emphasize the differences between the Gastaut type and the Panayiotopoulos type of childhood epilepsy with occipital paroxysms, keeping intentionally the term “benign” only for this early-onset form.[19,20] Thereafter, several authors preferred the eponymic term “Panayiotopoulos syndrome” (PS) to include patients with and without occipital spikes or occipital ictal origins.[3,8,13,14,16,26,27,28,36,42,54,56,59] Considering the emphasis given in recent years to the presence of autonomic seizures and autonomic status epilepticus in this condition, that occipital EEG abnormalities are not found in a certain proportion of the cases, and that there is no clear documentation of an occipital origin of seizures, we agree that the name PS might be more appropriate. As a practical measure, we will continue to refer to EOCOE as PS in this chapter.

Definitions

Types of seizures, age of onset, normal neurologic status of patients, and spontaneous evolution allow us to define the PS as a benign, age-related focal epilepsy syndrome occurring in early and mid-childhood. The analysis of several large series of published cases and our own present series clearly demonstrates the significant frequency of PS, which is seen about one third as often as BCECTS.

Epidemiology

PS is seen only in children, with a peak incidence between 4 and 5 years of age. Given that the official recognition of EOCOE or PS took place only in 2001, it is very difficult to find epidemiologic studies in a childhood population that include PS among the diagnoses. Additionally, most studies are based more on seizure types than syndromes. One study included a mix of seizures and syndromes for the recognition of epilepsies in 440 consecutive pediatric patients. Thirty-six (8%) of the cases were diagnosed as benign rolandic epilepsy of childhood and 8 cases (2%) as benign occipital epilepsy of childhood. We may assume that this last group was underevaluated, and we do not know how many of the cases corresponded to PS.[39] A cohort of 407 children with their first unprovoked seizure was followed for a mean of 9.4 years, and distribution of epilepsy syndromes was reported: Of 114 children with localization-related

epilepsy syndromes, 26 were idiopathic, 24 were rolandic, and only 2 were occipital.[60] Another study of a population-based, active-prevalence cohort in children <16 years of age was able to classify syndromes in 235 (96%) of the 245 patients followed for many years. However, no specific data about PS were included in any of these three studies because they were based on the 1989 ILAE Classification.[61] Therefore, one has to credit the everyday experience of active epileptologists caring for children, who have become aware of this condition in the last few years:[3]

- Oguni et al. 1999: Among 649 children with localization-related epilepsy selected from their database, 62 met the criteria for diagnosis of PS.
- Kivity et al. 2000: A file review of patients with occipital EEG paroxysms disclosed 72 children with typical PS.
- Caraballo et al. 2000: A prospective study selected 66 patients with PS with strict criteria for inclusion.
- Lada et al. 2003: A retrospective analysis of clinical and EEG records included 1,340 children with focal seizures; 43 who had PS and >2 years since they were seizure free were followed-up.
- Caraballo and Fejerman 2005: The addition of new cases after the 66 reported in 2000 provided a total of 156 children with typical PS who were followed prospecti-vely.
- Panayiotopoulos 2005: In an ongoing hospital-based, prospective study at the end of 3 years, 228 children aged 1 through 14 years with one or more seizures had one or more EEGs. Fourteen of them (6.1%) had Panayiotopoulos syndrome.[54]

Etiology and Basic Mechanisms

As an idiopathic epilepsy syndrome, PS is by definition not associated with remote symptomatic or acute symptomatic etiology. Most likely, it is genetically determined, although neither a gene nor a chromosomal locus has been found in PS. Linkage with chromosome 15 has been reported in BCECTS,[43] although in another study this locus was not found.[58] One affected sibling with PS was reported in one series,[25] and two pairs of affected siblings were seen in each of two other series.[8,42] Three siblings were reported in 1987 as having benign occipital epilepsy as described by Gastaut, although the paper indicates that the three siblings showed seizures starting at ages 4 and 5 years, and the clinical features were quite compatible with PS.[40]

There is a high prevalence of febrile seizures in children with PS, ranging from 16% to 45%.[8,13,14,25,45,64] A family history of epilepsy was found in 30.3% of the cases.[8] The finding of several children with PS who at the same time or later had rolandic seizures and centrotemporal spikes typical of BCECTS as well as siblings who had either rolandic epilepsy or PS speaks in favor of a genetic linkage of these two syndromes, perhaps expressed as a reversible functional derangement of the brains cortical maturation.[6,8,13,14,24,50,52,54,56] Basic mechanisms and pathophysiology of PS are largely unknown. Clinical findings indicate that there is a diffuse cortical hyperexcitability, which is related to maturation.[14,26,54] Even when the majority of cases show occipital spikes, a significant number of patients have spikes in other areas, and according to the mentioned reference of PS and BCECTS in the same children, spikes may appear in two areas at the same time or over the course of time.[6,13] In addition, the high frequency of ictal vomiting indicates that epileptic discharges are generated at various cortical locations. The same concept is valid for other autonomic manifestations. As we will see later, different cortical locations in patients with PS were also documented with magnetoencephalo-graphy.[36]

Table 1 Frequency of seizure types in children with Panayiotopoulos syndrome

Core clinical features

- Ictal emetic symptoms and other autonomic manifestations
- Deviation of the eyes
- Impairment of consciousness

Frequent types of seizures

- Unilateral clonic or tonic–clonic seizures
- Secondary generalized tonic–clonic seizures
- Encephalopathy-like status epilepticus (focal motor—unilateral or generalized—and autonomic)

Less frequent but not rare symptoms and signs

- Visual symptoms
- Migraine-like headaches
- Incontinence of urine and feces
- Syncope-like symptoms
- Other

Clinical Presentation

Panayiotopoulos syndrome occurs in children who are otherwise normal; it is not associated with neurodevelopmental problems. Although it has been described as starting as early as 1 year of age and as late as 14 years of age, the large majority of patients have their first seizure around the age of 4 to 5 years. Three fourths of patients have their first seizure between the ages of 3 and 6 years. It affects boys and girls almost equally. Seizures occur predominantly during sleep, and only in sleep in two thirds of patients. In seizures occurring while the patient is awake, onset may be inconspicuous with pallor, agitation, feeling sick, and vomiting. At this stage, the epileptic nature of the event can hardly be suspected in the absence of motor convulsive symptoms that, if present, may be rightly considered as secondary to an ongoing serious brain insult. It is only the normal postictal state of the child that should be reassuring.

The duration of the seizures is usually long, commonly >5 minutes, and in approximately 40% of the cases, >30 minutes, constituting then a focal or secondarily generalized status epilepticus. Three groups of symptoms are recognized, as shown in Table 1.

Core Clinical Features

Ictal Emetic Symptoms and Other Autonomic Manifestations

Ictal vomiting, which is considered to be exceptional in other epilepsies, occurs in approximately 80% of the cases with PS.[8,13,25,42,45,48,49,50,54,55] In one prospective study, vomiting was considered a criterion for inclusion, although we now know that vomiting is not present in 100% of the cases.[8] In nocturnal seizures, it is usually the first apparent symptom, whereas in seizures occurring while the patient is awake, other symptoms of the emetic spectrum such as nausea or retching may appear along with or before vomiting.[13]

Vomiting may occur repetitively or only once during the seizure.

Pallor is the most frequent autonomic manifestation. It occurs mainly at onset and commonly together with vomiting. In seizures starting while the patient is awake, pallor, nausea, and “feeling sick” are frequent symptoms.

Deviation of the Eyes

Unilateral deviation of the eyes is as common as vomiting and also occurs in approximately 80% of the patients.[8,25,45,48,49,54,56] The eye deviation may be brief or prolonged and is frequently accompanied by head deviation. It may be continuous or, less often, intermittent. Consciousness is often but not invariably impaired at this stage. It should be noted that exact details of this symptom are rarely witnessed because seizures occur mostly at night.

Impairment of Consciousness

Consciousness is usually intact at seizure onset but becomes impaired in 80% to 90% of cases as the seizure evolves. Impairment of consciousness may be mild or moderate, with the child retaining some ability to respond to verbal commands but often talking out of context. In seizures with motor components occurring during sleep, complete loss of consciousness may be seen, especially in all those that are prolonged into status. In diurnal seizures, clouding of consciousness usually starts after the appearance of autonomic and behavioral symptoms. Awareness may be preserved throughout the ictal state in 10% to 20% of the seizures.[25,45,46,50,54,56]

Frequent Features of Seizures

Unilateral Clonic or Tonic–Clonic Seizures

Unilateral clonic convulsions in face and extremities at onset or following vomiting and eye deviation are seen in 25% to 30% of the cases.[8,54,55]

Secondarily Generalized Tonic–Clonic Seizures

This type of seizure rarely appears at onset and usually follows seizures starting with focal motor manifestation. In one series of patients, this course was seen in nearly 40% of the cases.[8]

Status Epilepticus

This is usually nonconvulsive, lasts >30 minutes, and occurs in approximately 30% of cases in all series.[8,25,45,49,54,55,56] This "encephalopathy-like" form of status epilepticus may progress to hemiconvulsions. We will show under the heading of differential diagnosis how important it is to recognize PS when it may mimic other pathologies caused by true cerebral insult.

Less Frequent, but Not Rare, Symptoms

Visual Symptoms

Visual symptoms are typical of the Gastaut type of CEOP. However, in patients with PS, elementary visual hallucinations, illusions, and blindness were registered in <10% of children who were able to describe them.

Migraine-Like Headaches

These are rarely present, and in older children may sometimes cast doubt on a differential diagnosis with the Gastaut type of CEOP.

Incontinence of Urine and Feces

This may occur when consciousness is impaired.

The occurrence of syncope-like symptoms is another autonomic manifestation that has been emphasized more recently. Children becoming completely irresponsive and flaccid, often without convulsions, are not considered rare by many authors.[13,14,26,54,56]

Diagnostic Evaluation

Neuroimaging and Other Laboratory Examinations

By definition of an idiopathic epilepsy syndrome, neurologic and neuropsychological evaluations of children with PS are normal. Some of the initial symptoms may mislead the pediatrician regarding the nature of the condition, mainly when vomiting and other autonomic symptoms are present. Excessive laboratory examinations might then be undertaken. When syncope-like manifestations occur, cardiology consultation is required.

Brain imaging studies are normal. However, the spectacular nature of ictal features, and especially the frequency of status epilepticus, makes magnetic resonance imaging (MRI) necessary to rule out conditions that can provoke focal, unilateral, or generalized seizures.

Electroencephalographic Findings

The most useful laboratory test is EEG. Ictal EEG reports are rare because seizures are infrequent. The ictal discharge in PS is characterized by rhythmic monomorphic decelerating theta or delta activity that is markedly different from the episodic fast activity of visual seizures of the Gastaut type CEOP and starts either from the posterior[2,16,45,64,65] or frontal regions.[14,45] We recently registered an ictal EEG in a 4-year-old girl with a seizure consisting of vomiting, pallor, and loss of consciousness; rhythmic spike discharges could be seen starting in the right occipital region and propagating to frontal areas (Fig. 1).[4]

Because most patients with PS are first seen between ages 3 and 6 years, many of these EEGs are obtained during sleep. Sleep activates the appearance of occipital spikes in these children (Fig. 2).[8] Occipital spikes are bilateral and synchronous, often with voltage asymmetry, or unilateral. In awake EEGs, occipital paroxysms of high amplitude with sharp and slow-wave complexes that occur immediately after closing the eyes are often registered. These paroxysms are eliminated, or markedly attenuated, when the eyes are opened, a phenomenon due to fixation of sensitivity.[47,54,55] This phenomenon, which should be sought in every EEG laboratory, was considered pathognomonic of the Gastaut type of CEOP, but it is not. It has been reported not only in patients with PS, but also in patients with other conditions.[12,44]

Even when occipital spikes and spike-wave paroxysms are the main EEG feature, their absence does exclude the diagnosis of PS. It has been emphasized that extraoccipital spikes (centrotemporal, frontal, parietal) may also be found in children with PS.[14,45,52] Generalized spike and wave discharges are not seen in children with PS as frequently as they are in children

with BCECTS.[18] Normal EEGs during sleep are exceptional according to a recent consensus report.[26]

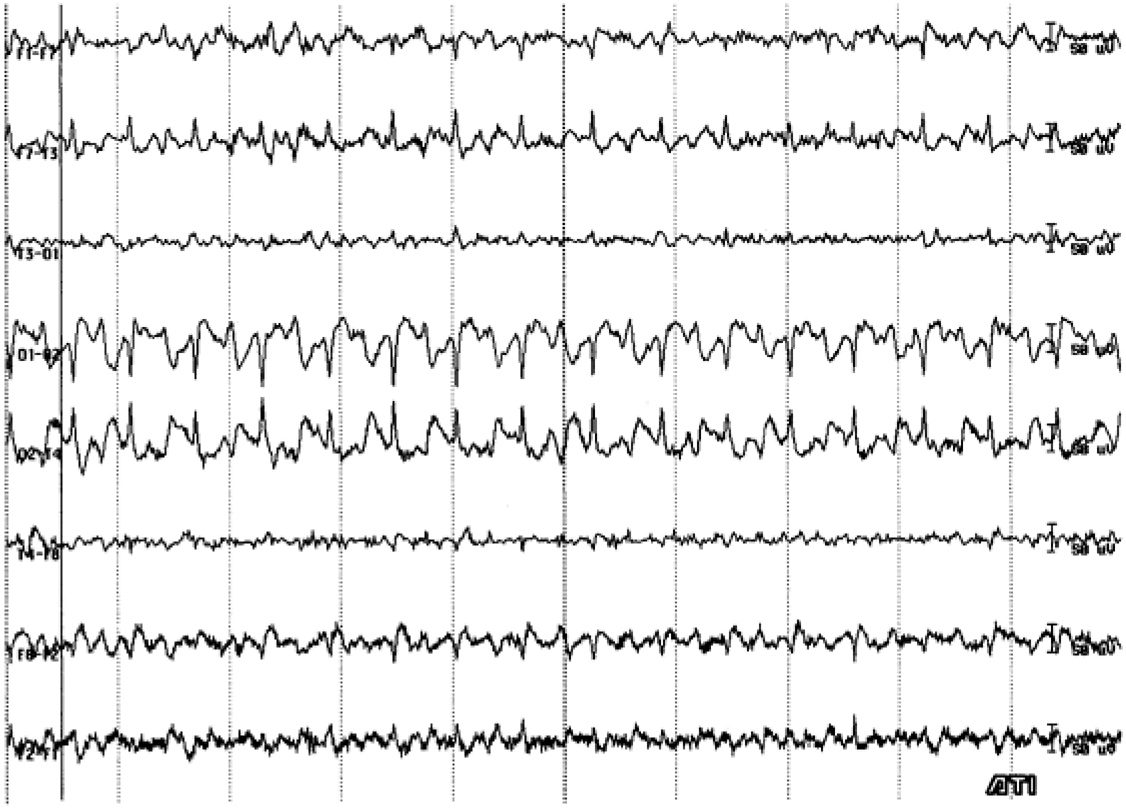

FIGURE 1. A 4-year-old girl. Ictal EEG: The seizure started 5 seconds before the discharges seen in this sample, with rhythmic spikes in the right occipital area and propagated to frontal areas.

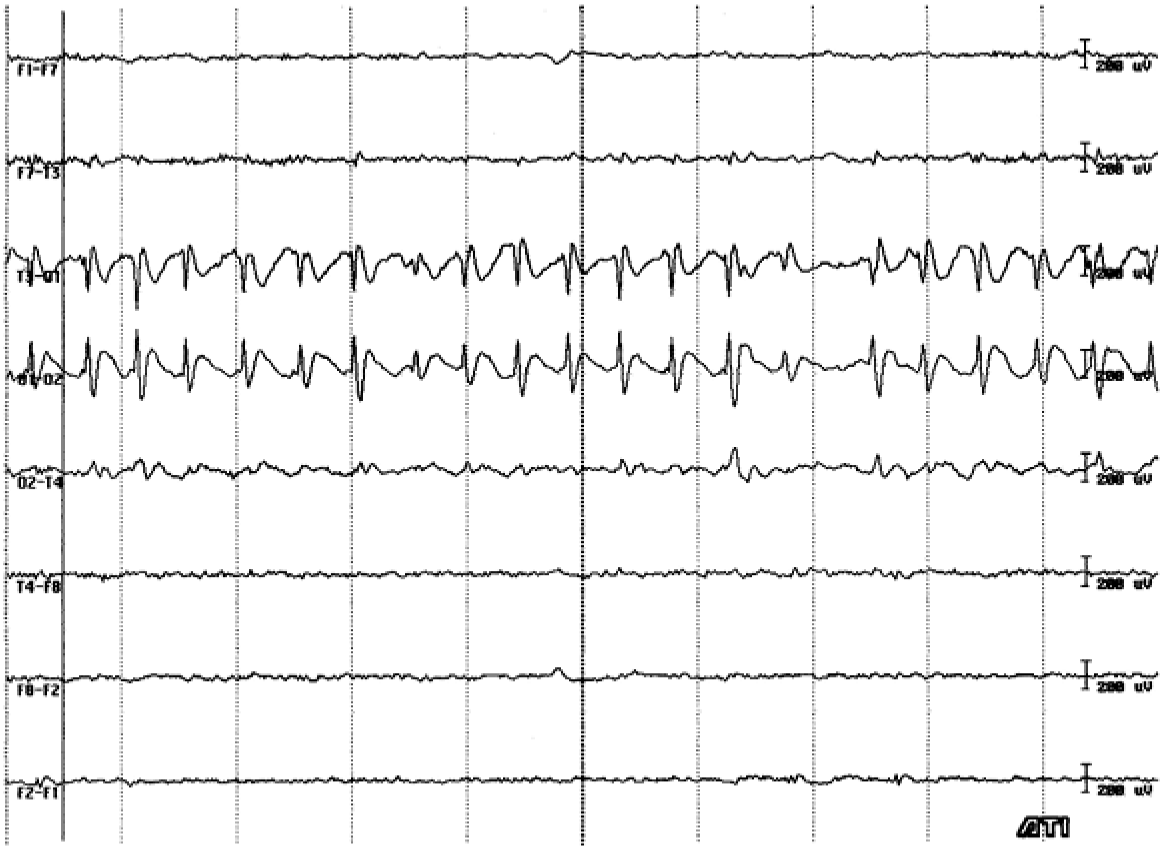

FIGURE 2. A 7-year-old boy. Left occipital spikes activated by sleep.

The evolution of EEG discharges in 76 children with PS was followed with repeated sleep EEG examinations. These showed that the occipital spike pattern was prevalent in the first few years of the diagnosis and later became associated with frontal or centrotemporal spikes.[46]

An interesting recent paper related to EEG in PS showed that a group of EEG technicians trained on the clinical features of PS were able to diagnose the condition in 14 children, and in 9 of the cases their information was crucial to achieving a diagnosis.[59]

In a recent study of eight children with PS, dipole analysis of the interictal spike discharges was performed. The various types of spikes observed in PS had similar and stable dipole locations. The dipoles showing high stability were located in the mesial occipital area and were accompanied by dipoles located in the rolandic area, suggesting a possible pathogenetic link between PS and BCECTS.[66]

Other Neurophysiologic Studies

In 13 children with PS who ranged in age from 3 to 14 years, the localizations of equivalent current dipoles (ECDs) of spike discharges by magnetoencephalography were examined. Eleven patients (84.6%) showed clustered ECDs in areas alongside the parietooccipital sulcus and/or the calcarine sulcus. Five of the children who also presented rolandic seizures showed in addition clustered ECDs in rolandic areas.[36]

Studies of visual-evoked potentials (VEPs) were performed in 9 children with PS and 10 children with the Gastaut type of CEOP. High-amplitude VEP responses attributed to hyperexcitability of the occipital cortical structures were present in all 19 patients.[34]

Table 2 Differential diagnosis of Panayiotopoulos syndrome

With other neurologic conditions

- Encephalitis
- Acute toxic encephalopathy
- Acute disseminated encephalomyelitis (ADEM)
- Mitochondrial encephalopathy with lactic acidosis and stroke (MELAS)
- Acute cerebrovascular event
- Migraine (basilar artery migraine)
- Diseases of the autonomic nervous system

With other epilepsy syndromes

- With other idiopathic epilepsy syndromes
  - Childhood epilepsy with occipital paroxysms (Gastaut type)
  - Benign childhood epilepsy with centrotemporal spikes
  - Idiopathic photosensitive occipital epilepsy

- With symptomatic occipital epilepsies
  - Celiac disease, occipital calcifications, and epilepsy
  - Occipital epilepsy after neonatal hypoglycemia
  - Other symptomatic occipital epilepsies

Differential Diagnosis

Despite sound clinical-EEG manifestations, for many years Panayiotopoulos syndrome escaped recognition, for many reasons. Ictal vomiting is rarely considered as an ictal event. When this is associated with deteriorating level of consciousness followed by convulsions, encephalitis or other acute cerebral insults are the prevailing diagnoses at the acute stage. If the seizures are hemigeneralized, a more focal cerebral insult is always looked for. If the child is seen after complete recovery, atypical migraine, gastroenteritis, or a first seizure is a likely diagnosis. Table 2 lists the main differential diagnoses of PS. The presence of prolonged seizures in a previously healthy child inevitably leads to consideration of acute cerebral insults due to encephalitis; intoxication; acute disseminated encephalomyelitis; mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS); or acute cerebrovascular event. Complete recovery after ≥1 hours of seizures makes these diagnoses improbable, although, as stated before, brain imaging studies are usually obtained. Basilar or other infrequent forms of atypical migraine are among the main differential diagnoses in cases with prolonged or repeated vomiting with other autonomic symptoms. Both conditions may appear abruptly, and in both, full recovery is seen. Impaired consciousness does not rule out the diagnosis of migraine.[53] However, it is extremely rare for migraine to start with vomiting interrupting sleep in young children.

Syncope-like episodes with pallor, irresponsiveness, and flaccidity may lead to consideration of real syncopal attacks and to ask for cardiology examination. Of course, common syncope in children does not appear during sleep, but nausea, pallor, and sick feeling in an awake child can be the first symptoms of a syncopal attack.

Table 3 shows the differential diagnosis between PS and the Gastaut type of CEOP.

The mean age of onset of BCECTS is approximately 7 to 8 years of age, and its typical features differ clearly from those of PS. However, we will note later that it is not rare to see children presenting at the same time ictal symptoms of both syndromes. As for the idiopathic photosensitive occipital lobe epilepsy, its mean age of onset is around 11 years, and all ictal events are preceded by the exposure to photic stimulation, either intermittent lights or TV or computer game screens.[35] This condition is quite rare and less frequent than other reflex epilepsies secondary to visual stimuli.

Symptomatic occipital epilepsies may present clinical features similar to those of the idiopathic occipital epilepsies. The EEG may even show the occipital spike-and-wave discharges disappearing after eye opening that is so typical of the Gastaut type of CEOP but may also be seen in PS.[12,44] There are two particular conditions to consider in children with seizures manifested by visual symptomatology and occipital spikes or spike-waves. One is celiac disease with occipital calcifications and epilepsy. The majority of patients with this condition do not have overt symptoms of celiac disease. That is why, in the presence of occipital discharges and seizures, posterior cerebral calcifications have to be discarded. If they are present, specific studies for celiac disease are mandatory because in these children their epilepsy improves with a gluten-free diet.[1,32] Silent celiac disease was investigated in a study of 72 patients observed consecutively over a 5-year period with an initial diagnosis of idiopathic partial epilepsy. In the 47 children with BCECTS, specific antibodies were not found, but in 2 of the 25 cases with childhood partial epilepsy with occipital paroxysms (CEOP), the results were positive and later confirmed by jejunal biopsy.[41] This study did not attempt to distinguish between the Gastaut type and the Panayiotopoulos type of CEOP.

In a recent series of 12 patients, we showed a clear association between history of neonatal hypoglycemia and posterior cerebral lesions provoking seizures. Epileptic seizures in these children were usually well controlled by antiepileptic drugs (AEDs), but most of the cases presented intellectual impairment.[8]

Association of Panayiotopoulos Syndrome With Other Idiopathic Epilepsy Syndromes

Isolated cases with electroclinical features of BCECTS are occasionally found in children with idiopathic occipital epilepsies.[24,38,49,54] In 1998, idiopathic partial epilepsies with both rolandic and occipital spikes appearing were reported in ten patients. Five of them had first PS and after ≥2 years presented hemifacial motor seizures with anarthria typical of BCECTS. The other five patients presented anarthria and hemifacial contractions with sialorrhea and ictal vomiting with head deviation as typical seizures of PS and BCECTS in the same epoch and even in the same episodes.[6] This finding was later confirmed by another group of authors.[13]

Another small series of cases reporting the presence of two idiopathic epilepsy syndromes in the same children showed that absence epilepsy was associated with the Gastaut type of CEOP in five patients and with PS in one child.[10]

Table 3 Differential Diagnosis Between Panayiotopoulos Syndrome and Gastaut-Type Childhood Occipital Epilepsy

	Panayiotopoulos syndrome	Gastaut-type childhood occipital epilepsy
Prevalence among benign focal epilepsies in childhood (%)	27	3

Age at onset (yr)	1–14 (mean: 4–5)	3–16 (mean; 8–9)
Duration of seizures		
• <2 min	Exceptional	As a rule
• >5 min	As a rule	Rare
High seizure frequency	Rare	As a rule
Seizures during sleep	>2/3 of cases	<1/3 of cases
Features of seizures		
• Ictal vomiting	Frequent	Exceptional
• Deviation of the eyes	Frequent	Rare
• Impairment of consciousness	Frequent	Rare
• Visual hallucinations	Rare	As a rule
• Loss of vision	Exceptional	Frequent
• Autonomic disturbances	Not rare	Rare
• Postictal headache	Rare	Frequent
Seizures evolving into status	Frequent	Exceptional
Interictal electroencephalogram	Frequent occipital spikes; less frequent spikes in other areas.	Spike-wave occipital paroxysms reactive to eye opening
Prognosis		

• Remission within 1–3 yr from first seizure	As a rule	Rare
• Evolution into Continuous spike and waves during slow sleep	Rare (3 cases reported)	Rare (2 cases reported)
• Overall prognosis	Excellent	Uncertain

Treatment and Outcome

There is no consensus about treatment in PS. Because approximately one third of the patients only have one seizure, either brief or prolonged, many authors recommend not starting AED treatment.[14,56] However, it is not so easy for pediatric neurologists to advise parents after their child has had a prolonged seizure that there is no need to try to prevent further events using medication. Even when both authors of this chapter agree about the good outcome in patients without medication, one of us prefers to medicate after the first seizure when it was prolonged. Carbamazepine and valproic acid are the drugs of choice, and the latter is preferred when the EEG shows spike-and-wave discharges instead of spikes. At any rate, clear instructions should be given to parents on how to use rectal diazepam immediately after onset of a new seizure.

Long-Term Prognosis

Despite the high incidence of seizures evolving into status epilepticus, PS is a remarkably benign epilepsy syndrome.[8,14,54,56,62] One third of the patients have only a single seizure, and most of the cases present no more than two to five seizures. Remission usually occurs 1 or 2 years after the first seizure, and there are no comparable data on whether there is a significant difference in cases treated with AEDs.

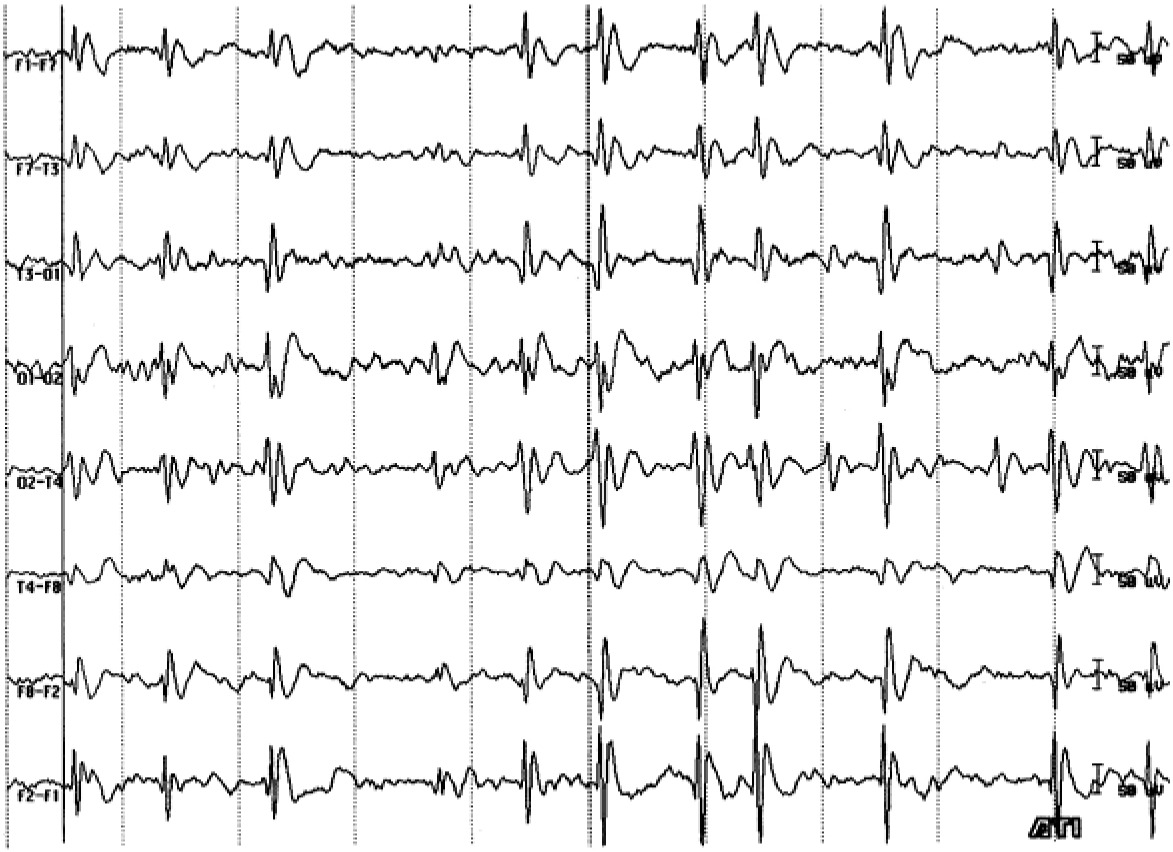

FIGURE 3. A 5.5-year-old boy. Atypical evolution of Panayiotopoulos syndrome with frequent bilateral spike-wave discharges in sleep.

Regarding the risk of persistence of seizures or of developing other types of epilepsy in adult life, except for the personal experience of Dr. Panayiotopoulos, no series has reached a sufficient long-term follow-up to provide information.

A need for caution in reference to neuropsychological findings has recently been raised. A study of 22 children with PS showed that intellectual quotients were within normal limits, but selective dysfunctions were found relating to verbal and visual-spatial memory, visual-motor integration global abilities, reading and writing, and arithmetic ability.[31]

Atypical Evolutions in Patients with Panayiotopoulos Syndrome

As stated before, a number of cases presenting BCECTS after the onset of PS are well documented, and even one case with typical absence epilepsy following PS was recently reported. The concept is that even when these associations occur, long-term prognosis is almost always benign. We say “almost” because nothing is absolute in medicine. We showed three cases with typical features of PS that presented atypical evolutions quite like those described in BCECTS.[23] The three children started with inhibitory seizures and drops, atypical absences, and language and behavioral impairment associated with continuous spike-and-waves discharges in the sleep EEG (Fig. 3). They were well managed with appropriate changes in AEDs, but we do not know what the natural evolution of this complication would have been.[5,28] Moreover, ictal cardiorespiratory

arrest was recently reported in a patient with PS,[63] an exception confirming the rule of very good long-term prognosis.

Summary and Conclusions

- Early-onset benign childhood occipital epilepsy (Panayi- otopoulos type), or Panayiotopoulos syndrome, is a clearly identifiable epilepsy syndrome that is second in frequency to benign childhood epilepsy with centrotemporal spikes among idiopathic focal epilepsies with onset in childhood.
- Vomiting and other autonomic ictal manifestations are very frequent and should call attention to the possibility of PS. The other frequent seizure features are eye deviation and impairment of consciousness.
- Approximately one third of patients present prolonged seizures evolving into status; one third of children have only one seizure.
- Sleep EEG shows occipital spikes in a majority of patients, although spikes in other areas can also be seen in more than one third of patients.
- There is no clear understanding of the mechanisms of vomiting and other autonomic ictal features and their association with interictal epileptiform discharges in the EEGs of these children.
- Prognosis is excellent despite prolonged seizures or the rare event of atypical evolutions with continuous spike-and-waves during slow sleep and its clinical correlations.
- Future research should clarify the not rare association between PS and BCECTS, perhaps based on a finding of genetic linkage explaining the different phenotypic expressions within a wider group of benign focal epilepsies in infancy and childhood.

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Chapter 238

Late-onset Childhood Occipital Epilepsy (Gastaut Type)

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Introduction

Occipital epilepsies commonly start in childhood or adolescence and include two etiologic groups: Symptomatic and idiopathic epilepsies. Symptomatic occipital epilepsies may be caused by brain malformations (focal cortical dysplasia, polymicrogyria, subcortical band heterotopia, periventricular heterotopia), metabolic disorders (Lafora disease, juvenile neuronal ceroid lipofuscinosis, mitochondrial disorders such as MERRF [syndrome of myoclonus epilepsy and ragged red fibers] and MELAS [syndrome of mitochondrial encephalopathy, lactic acidosis, and strokelike episodes]), and occipital bilateral calcifications (often associated with celiac disease).[95] Among the idiopathic group, the new classification system of the International League Against Epilepsy (ILAE) Task Force[30] recognizes three epilepsy syndromes: (a) the early-onset benign childhood occipital epilepsy (Panayiotopoulos type), (b) the late-onset childhood occipital epilepsy (Gastaut type), and (c) the idiopathic photosensitive occipital lobe epilepsy. The latter is included among the reflex epilepsies.

The late-onset childhood occipital epilepsy–Gastaut type (LOCOE-Gastaut type) is the topic of this chapter, while the early-onset benign childhood occipital epilepsy (Panayiotopoulos type) and the idiopathic photosensitive occipital lobe epilepsy are described in Chapters 237 and 257.

Historical Perspectives

Benign occipital epilepsy was first described by Gastaut.[35] It was considered an epilepsy syndrome with a typical clinical history and interictal electroencephalographic (EEG) pattern. The existence of an idiopathic/cryptogenic benign childhood occipital epilepsy was already evident in the first reports of Gastaut in 1950[34] and Gibbs and Gibbs in 1952.[42] Further observations corroborated the identification of "benign occipital epilepsy,"[10,25,68,93] but discussions about a new "benign migraine-epilepsy syndrome" developed among authors.[1,16,71,78,90,94] The controversy regarding whether the origin of this syndrome was epileptic or migrainous was resolved by Gastaut,[35,36] who critically reviewed the four children reported by Camfield et al.[16] and concluded that their benign occipital epilepsy constituted "a primary and independent epileptic disorder." Gastaut[36] and Gastaut and Zifkin[39] considered both visual ictal symptoms and the interictal occipital spikes and waves that appeared upon closing the eyes as the main clinical and EEG signs of the benign childhood epilepsy with occipital paroxysms (CEOP). However, it was already known that occipital foci in young children might also be a sign of a "maturational" factor in a variety of cerebral dysfunctions.[63] In fact, occipital lobe epileptogenesis with occipital spikes may occur in genetically predisposed children with visual defects at a critical stage of development.[67,73] Reactive occipital spikes have been reported in children without epileptic seizures[2,11,60,76] as well as in patients having cryptogenic or symptomatic occipital epilepsies[2,23,27,36,41,51,76,98] and those having occipital epilepsies associated with progressive disorders.[29,49,50,74,89,91] Finally, visual symptoms and reactive occipital paroxysms may be absent in CEOP.[41,54] These data cast some doubt on the existence of a true benign and idiopathic occipital epilepsy as defined, using the clinical and EEG criteria proposed by Gastaut.[35] Among patients with occipital epilepsy and occipital EEG abnormalities suppressed by eye opening, a series emerged with "nonlesional" epilepsy, remarkable age-dependent seizure onset, familial predisposition, and benign evolution.[6,23,98] According to these criteria, CEOP was included in the ILAE classification[21] as an idiopathic form having the clinical and EEG findings suggested by Gastaut,[35,36] but with an uncertain long-term prognosis. More recently, Panayiotopoulos[80,81] described a form of CEOP characterized by early onset, nocturnal seizures with tonic deviation of the eyes, and vomiting,[80,81] which has an excellent prognosis with seizure remission occurring within 1 to 2 years. On that basis, Caraballo et al.[17] proposed designating this early-onset CEOP as "Panayiotopoulos-type benign childhood occipital epilepsy," and "Gastaut type of benign childhood occipital epilepsy" the occipital epilepsy described by Gastaut.

Finally, the latest diagnostic scheme for people with epilepsy proposed by the ILAE Task Force on Classification and Terminology[30] recognized this syndrome as "late-onset childhood occipital epilepsy–Gastaut type."

Definition

LOCOE-Gastaut type is an age-related, possibly genetically determined, epilepsy syndrome, with onset ranging from 4 to 13.2 years, and with a peak of incidence at 8 years. Girls and boys are equally affected.[85]

Epileptic seizures are characterized by brief, frequent, diurnal visual hallucinations; blindness; or both. Although commonly preserved, the consciousness is mainly impaired when seizure progresses toward a hemiclonic or generalized convulsion or automatism. In 25% to 50% of cases, visual seizures are followed by pulsating headache, associated with nausea and vomiting in about 10% of patients.

Interictal EEG features consist of high-voltage spikes-and-wave complexes or sharp waves recurring rhythmically in the occipital and posterior temporal areas of one or both hemispheres, but only when the patient's eyes are closed. Fixation-off sensitivity is typical. Ictal EEG is characterized by the sudden appearance of an occipital discharge consisting of fast activity and/or spikes, which may spread to the central or temporal regions.[85]

Since both clinical and EEG findings do not exclude a symptomatic epilepsy, neurophysiologic, neuropsychological, neuroimaging, and laboratory assessment are always indicated. At

present, no definite statement on prognosis is possible,[21] even though it seems to be relatively benign, especially using rigid criteria of selection.[99]

Epidemiology

LOCOE-Gastaut type is a rare condition with a probable prevalence of 0.2% to 0.9% of all epilepsies, and 2% to 7% of benign childhood partial seizures. On average, LOCOE-Gastaut type is considered five times less frequent than Panayiotopoulos type.[85] Higher figures have been reported by Gokcay et al.,[52] who observed ten patients with LOCOE-Gastaut type among 29 cases presenting with idiopathic occipital epilepsies. A slightly higher frequency of LOCOE-Gastaut type than the Panayiotopoulos type has also been found by Tsai et al.,[99] which was attributed to the inclusion of patients with migrainous headache with focal occipital paroxysms and the exclusion of patients with adversive seizure and EEG foci beyond the occipital area.

Etiology and Pathophysiology

Gastaut[36,37] stressed the presence of genetic or functional factors, such as a predisposition to epilepsy and febrile convulsions, in 36.6% to 47% of the cases. However, patients with lesional epilepsy related to premature birth, mild perinatal distress, and HHE (hemiconvulsion-hemiplegia-epilepsy) syndrome were also included in LOCOE-Gastaut type.[36,37,41] A thalamocortical mechanism, similar to the reticulocortical mechanism of idiopathic generalized epilepsies[46] but limited to a localized thalamocortical area, was hypothesized.[34] According to the concept of "idiopathic" epilepsy, symptomatic cases are no longer included in this group of patients.

A role of genetic factors as part of the etiology is still presumed, and the recognition of familial cases strongly suggests this hypothesis. A family history of epilepsy varying from 33% to 43% in patients with occipital epilepsy has been reported by several authors.[6,60,98] Kuzniecky and Rosenblatt[65] suggested "an autosomal dominant pattern for the EEG abnormalities with age-dependent expression and variable penetrance of the seizure disorder." Nagendran et al.[75] reported a family in which two siblings had visual seizures and occipital paroxysms, and another presented with centrotemporal spikes on the EEG. Moreover, there may be an association between idiopathic generalized epilepsies and LOCOE-Gastaut type. In fact, generalized spike-wave discharges in addition to occipital epileptiform activity were noted in this group of patients.[36] In turn, in idiopathic generalized epilepsies there may be focal activity, which is typically frontal but may also occur in posterior areas.[77] Caraballo et al.[18] reported the occurrence of childhood absence epilepsy in 5 out of 35 children with LOCOE-Gastaut type. Patients with both types of epilepsy have also been reported by Sofue et al.[92] and by Grosso et al.,[53] respectively. Typical absences have mainly been found in patients with LOCOE-Gastaut type (14% of patients) rather than in the much larger group with the Panayiotopoulos type (0.6%). Therefore, it has been suggested that childhood absence epilepsy may have a closer genetic relationship to LOCOE-Gastaut type than to the Panayiotopoulos type.[18]

From a pathogenetic point of view, mechanisms underlying LOCOE-Gastaut type remain to be established. The primary visual cortex (VI or Brodmann area 17) represents the site where elementary visual hallucinations are generated. Simple visual symptoms can also be evoked by stimulation of extra-striate and prestriate (Brodmann areas 18 and 19) cortical regions. The stimulation of the latter areas can also provoke visual illusions. Recently, it has been confirmed that both the mesial and lateral occipital lobe may be involved in generating elementary visual phenomena, and that there is a wide semiologic overlapping of visual symptoms between seizures originating from these occipital areas.[15] In fact, mesial foci rapidly spread to the lateral occipital region and vice versa.[20] Occipital epileptogenic activity spreads extensively to the adjacent neocortex and to limbic structures through the projections from the occipital cortex to lateral and mesial temporal areas.[15]

In particular, reciprocal connections between temporal neocortex and the primary visual cortex have recently been confirmed.[3,62] Complex visual seizures have been considered to represent seizure spread to the temporal lobe. Blume et al.[15] suggested that structured visual phenomena require the involvement of both neocortical and limbic regions. This is consistent with the clinical occurrence of initial occipital symptoms followed by structured visual hallucinations and other temporal lobe findings.[5,102] Actually, the role of the temporal lobe in determining visual symptoms appears to be more complex. Indeed, it should be remembered that simple visual phenomena have also occasionally been reported in temporal (lateral or medial) epilepsy. Motor phenomena of both lateral and mesial occipital epileptogenesis may be explained by their access to supra-Sylvian or to brainstem motor regions.[15]

The pathophysiologic mechanisms leading to postictal headache remain also to be clarified. Migraine is considered a paroxysmal and unique neurovascular disorder.[101] According to Goadsby,[47] migraine is a disorder of sensory dysmodulation that involves the trigeminovascular system and central nervous system modulation of the pain-producing structures of the cranial structures. A multitude of factors able to increase neuronal and network hyperexcitability may trigger migraine attack. Thus, it is possible that an occipital ictal discharge triggers a genuine migraine headache through trigeminovascular or brainstem mechanisms.[84] It has been pointed out that postictal migraine headache occurs in predisposed children with impaired or labile cerebrovascular autoregulation. On that basis, occipital ictal activity may result in a persistence of vasodilation in the posterior territory of cerebral and basilar arteries with subsequent plasma extravasation and neuropeptide release.[101]

Clinical Presentation

The mean age at onset ranges from 3 to 4 to 13 to 16 years.[85,99] Gastaut and Zifkin[41] reported an upper age at onset of 19 years.

The main clinical findings of LOCOE are represented by *visual seizures*. Usually, they occur in the daytime, but are not invariably present. In some instances, triggering or facilitation stimuli have been reported: Extinction of light,[69,79] passage from light to darkness or vice versa,[8,37] and darkness.[86] In some teenage girls, seizures seem to occur with menstruation.[37,41] *Elementary visual hallucinations* are brief (5 to 20 seconds, rarely more than 3 minutes or even 15 to 20 minutes) seizures, which usually occur as an initial ictal symptom, and may represent the only seizure type (30% of the patients)[64,84] or be associated with other occipital symptoms such as illusions of ocular movements, tonic deviation of the eyes, and eyelid fluttering. This type of seizure may also be prolonged, especially when visual symptoms are followed by autonomic-migrainous postictal symptoms, and may progress to hemiconvulsions or generalized tonic–clonic seizures. *Positive elementary visual hallucinations* may consist of perception of white flashes or colored (bright red, yellow, blue, and green are prominent) unformed or formed phenomena, usually circular, commonly appearing in the periphery of a hemifield, evolving into multicolored circular patterns that multiply and enlarge during seizure progression, flashing or static, with a possible horizontal movement toward

the other side.[84] Sometimes the patient may turn his or her head and eyes to look at them.[64] In each patient elementary visual hallucinations have a stereotypic appearance regarding morphology, colors, location, and movement. *Negative elementary visual seizures*[6,36,37] are the second most common seizure type. They consist of a sudden ictal blurred vision or amaurosis, lasting up to 5 minutes. Ictal amaurosis may be the sole event in a patient who, during other seizures, has visual hallucinations without blindness. Blindness may involve the whole visual field or be confined to a part of it (quadrantanopia, hemianopia). Hemianopia may be both ictal and postictal. The elementary visual seizures in nontreated patients may be frequent, up to several per day or week. Responsiveness is commonly preserved. Loss of consciousness usually occurs at the onset of other ictal manifestations following visual hallucinations or amaurosis, such as eye deviation or convulsions.[85]

Complex visual hallucinations and visual illusions are rare in LOCOE-Gastaut type patients, occurring in <10% of the patients. *Complex visual hallucinations* represent the progress of elementary visual seizures, and consist of hallucinations of animals, people, or scenes, or of numerals or letters, stationary or moving. In complex hallucinations an evident emotional component, such as elements from memory, unfulfilled wishes, or intense affects related to them, which is lacking in simple hallucinations, is experienced by the patient. *Ictal visual illusions* may be simple with alteration in perception of objects, such as micropsia/macropsia (dysmegalopsia), dyschromatopsia, achromatopsia, metamorphopsia, plagiopsia, kinetopsia, and teichopsia, or may be complex, such as palinopsia, teleopsia, macroproxiopia, and microtlepsia.[6,36,37,38,39,41,78,81] *Sensory hallucinations of ocular movements and pain* without detectable motion usually occur with progression of ictal elementary visual hallucinations

Nonvisual ictal seizures with occipital lobe origin may also be present in

the context of the clinical picture. *Adversive seizures with contralateral eye deviation*, often associated with head turning, is the most common nonvisual symptom. Kivity et al.[64] reported that 79% of patients with visual symptoms experienced adversive manifestations, either independently, as a separate entity that preceded or followed the visual symptoms by weeks or months or even years, or as a part of the same event. In the latter, usually they start after visual hallucinations or occur while hallucinations persist. More often these events are severe with impairment of consciousness and may evolve into secondary generalizations or hemiconvulsions with or without secondary generalization. *Forced eyelid closure and eyelid blinking* occur in approximately 10% of LOCOE patients.[84,85] They may precede by months the onset of elementary visual hallucinations (personal observations). Other nonvisual seizures may occur as a result of seizure propagation. Visual symptoms may be followed by *hemiclonic* (44%), *complex partial* (19%), or *generalized tonic–clonic seizures* (8%).[34,35,36,37,38,39,40,41] *Partial status epilepticus* is rare.[64] Contrary to what occurs in symptomatic occipital epilepsies, progression to hemiclonic seizures is more frequent than to complex partial seizures,[24,98] and symptoms related to the temporal lobe are more evocative of a symptomatic cause.[85] *Ictal vomiting* is rare in LOCOE-Gastaut type.[32]

Rarely, *migraine-type headache* with photophobia, nausea, and vomiting with or without impairment of consciousness preceded the seizures,[2] sometimes by several hours.[41,69] Some patients may have headache during their seizures at the same time as visual symptoms.[66] It is unclear whether these were migraine-triggered seizures or migrainelike ictal symptoms. Undoubtedly, headache as an ictal event is rare.[85] By contrast, *postictal headache* is common and observed in 30% to 50% of LOCOE-Gastaut type patients. Headache is bilateral, throbbing, and often associated with nausea and vomiting, photophobia and phonophobia, and sometimes obfuscation of consciousness.[36,37,78,98] Postictal headache may be indistinguishable from migraine, especially when it follows a simple visual seizure, which may be considered as the presenting visual event of migraine with aura attack.[41] Duration ranges from 30 minutes to several hours, and appears to be proportional to the duration and severity of the preceding seizures. Postictal headache may also be present in the cases of symptomatic occipital seizures.[85]

Finally, an association between LOCOE-Gastaut type and *typical absences* has been reported. In these patients typical absences appeared at the same time as visual seizures or after 1 year. All patients had typical occipital paroxysms and a 3-Hz generalized spike-wave on the EEG.[18,53,92] *Febrile convulsions* have been reported in 14% of the patients as well.[85]

Diagnostic Evaluation

Interictal EEG

EEG shows normal background activity[6] and typical occipital dysphasic spike-and-wave complexes, spikes, or sharp-wave paroxysms of high voltage (200 to 300 µV) with a strong negative peak followed by a small-amplitude positive peak and a negative slow wave.[35,36,37,38,39] The occipital spike component has been found to be usually higher in amplitude than the negative slow waves, often exceeding 100 µV, with a duration <70 msec.[96] Occipital paroxysms are rhythmic at a frequency of 1 to 4 Hz in bursts or sequences.[36,37,81] In 5% of cases, occipital paroxysms consist of rhythmic posterior slow waves.[41] Distribution of paroxysmal abnormalities is over the occipital and posterior temporal regions of one hemisphere or over both hemispheres, synchronously or independently. When bilateral, the spikes are frequently asymmetric.[81] Topographic mapping may show the focus mainly at the occipital area mostly spreading to the parietal or temporal area. No superficial dipole field was noted by the voltage mapping of scalp EEG.[99] Other independent epileptiform discharges may be found, in addition to occipital spikes.[99] Photic stimulation does not usually affect occipital paroxysms[36,37,82] but may occasionally have an inhibitory effect.[66,82] Activation during hyperventilation has occasionally been reported.[60,66,98] Discharges are usually, but not invariably, increased during non–rapid eye movement (REM) sleep.[6,41] In some patients, discharges appear only during sleep.[66] Usually, occipital spikes disappear upon eye opening and reappear 1 to 20 seconds after eye closure.[35,36,37] Panayiotopoulos[79] and Lugaresi et al.[69] found that occipital spikes are also activated by darkness, and that in darkness they were suppressed by fixation on a very small light source (fixation-off sensitive spikes). This would indicate that the abolition of central vision (macular vision) is responsible for the appearance of occipital paroxysms.[79] The absence of the typical EEG paroxysms does not exclude the diagnosis[41,55,81,96] if the other clinical and EEG criteria are present. Moreover, occipital spikes may often occur only between the ages of 3 and 5 years.[61] Occipital paroxysms may remain in the same location during follow-up or may shift from side to side, and they sometimes may be replaced by, or associated with, bilateral rolandic spikes.[43,45,54,55,82,98] Spikes and seizures usually disappear simultaneously,[6] but epileptiform EEG abnormalities may outlast seizures.[37,54,80,96]

Although the normal background and the suppression of occipital paroxysmal discharges operated by eye opening were considered to be distinctive and characteristic of LOCOE-Gastaut type,[40,60,95] further studies showed that these features were not very specific, since they may also be observed in symptomatic epilepsies[49,50,56] and in epilepsies with undefined complex partial seizures.[70]

Ictal EEG

Electroencephalographic seizure patterns do not differ from those of other occipital epilepsies.[6] In general, in the case of brief seizures there are ictal discharges localized in one or both occipital areas and characterized by rapid spikes that slow progressively.[6,36,37] Panayiotopoulos[81,84,85] observed that in complex visual seizures the discharges are slower than in simple ones, and that ictal EEG anomalies during amaurosis are represented by pseudoperiodic slow waves and spikes, which are different from those observed during visual hallucinations. Brief seizures recorded during sleep show disappearance of interictal occipital discharges, followed by repetitive spikes of about 10 Hz that sometimes spread to the parietal region.

Other Neurophysiologic Investigations

Visual-evoked potentials (VEPs) and somatosensory-evoked potentials (SEPs) had a higher amplitude in the involved hemisphere.[41,87] Gokcay et al.[52] also reported that P100 potential amplitude values of LOCOE-Gastaut type patients were significantly higher than those recorded in healthy subjects and mostly attributed to hyperexcitability of the occipital cortical structures.

Neuroimaging and Other Laboratory Examinations

Neuroimaging is normal by definition. However, since both clinical and EEG findings do not exclude a symptomatic epilepsy[2] with unfavorable outcome, especially at the onset of the disorder,[48,51] further diagnostic investigation is needed, including neuroimaging, especially with high resolution, visual field assessment, and full laboratory evaluation (see Differential Diagnosis section).

Neuropsychological Assessment

Neuropsychological assessment could be important in children for diagnostic purposes, as well as early detection of possible cognitive disturbances accompanying nonidiopathic forms. However, to our knowledge, apart three reported cases with evolution to continuous spike-wave during sleep (CSWS) and cognitive deterioration,[31,97] any data available are on the neuropsychological profile in patients with LOCOE-Gastaut type. The few studies addressing that topic included patients presenting with both early- and late-onset childhood occipital epilepsy.[19] Since the occipital lobes are mainly involved in both low-level and high-level visual processing, including object identification and localization and face recognition, it is possible that any interictal dysfunction of occipital circuitries may have visuoperceptual difficulties as a clinical counterpart. In fact, lower performance in visuoperceptual tasks, attention, memory, and verbal functions were reported in idiopathic childhood occipital epilepsy,[58] even though studies that compared the neuropsychological outcome of patients with idiopathic childhood epilepsy with occipital paroxysms with normal controls revealed no significant differences in basic neuropsychological functions. However, a cognitive profile with relatively better verbal than performance abilities, a high incidence of scholastic disabilities, and the presence of psychiatric disturbances in the form of anxiety and depressive disorders was found in a cohort of patients with idiopathic occipital epilepsy.[19]

Differential Diagnosis

LOCOE-Gastaut type has to be differentiated from the Panayiotopoulos-type childhood-onset epilepsy, photosensitive idiopathic occipital epilepsy, symptomatic occipital epilepsies (including malformations of cortical development), temporal epilepsies, idiopathic generalized epilepsy, and migraine.

Concerning the Panayiotopoulos-type childhood-onset epilepsy, cardinal differences are age at onset of seizures, higher frequency, shorter duration, and daily occurrence of seizures. Ictal vomiting is commonly lacking, even though it may sometimes occur after visual symptoms.[33,99]

In the case of photosensitive idiopathic occipital epilepsy, age at onset is around the fourth year of life with visual symptoms consisting of either blurred vision or ictal amaurosis followed by secondary tonic–clonic generalization. Seizures are typically triggered by televisions or less often by video games. Interictal EEG shows occipital paroxysms activated by intermittent photic stimulation. Ictal EEG is characterized by spike-and-wave occipital paroxysms spreading to the temporal areas.[57,82,83,84,85]

Symptomatic occipital epilepsies often imitate LOCOE-Gastaut type. In fact, although Gastaut and Zifkin[41] stated that the ictal symptoms are different in idiopathic and in symptomatic occipital lobe epilepsy, seizure semiology analysis cannot invariably help to distinguish between different forms of occipital lobe epilepsy.[84,85,100] Therefore, clinical examination; neurophysiologic investigations; neuroimaging studies, including high-resolution magnetic resonance imaging (MRI) for the detection of subtle lesions; and neuropsychological assessment are needed for a correct etiologic diagnosis. Interictal EEG in symptomatic forms may show focal or diffuse abnormal background activity,[98] occipital polymorphous delta activity,[41] and prolonged bursts of sharp waves in temporo-occipital regions,[23] frequently associated with secondary generalization, occipital bursts of fast activity,[48] or multifocal spikes that are semiologically different from those of benign childhood epilepsy with centrotemporal spikes. The interictal abnormalities are enhanced during sleep and often show morphologic modification into rapid rhythms or polyspikes and waves.[51] Sleep interictal EEG is especially useful in the differential diagnosis of some symptomatic cases in whom the clinical and waking EEG features resemble those of a LOCOE-Gastaut type at the beginning of disease[44,51,76] but in whom progressive severity becomes apparent after a benign onset (Fig. 1). In this "malignant variant," occipital polyspikes or rapid rhythms during sleep are the only early warning sign.[48,51] Brain mapping of the occipital spikes in LOCOE-Gastaut type shows the spike maximum in the occipital area, while in symptomatic occipital lobe epilepsy it is located away from the occipital pole, often in the temporo-occipital or the parieto-occipital areas.[72] Clinical and EEG findings in the different forms of occipital epilepsy are summarized in Table 1.

Finally, among the symptomatic occipital epilepsy causes should be considered celiac disease[49,50] Lafora disease[89]; neuroaxonal dystrophy with myoclonus epilepsy; mitochondrial diseases, such as MELAS and MERRF[4,29,91]; and metabolic disorders such as hyperglycemia,[59] in which occipital lobe seizures and EEG abnormalities may be present in the early stages, before other clinical features are present; and hypercalcemia, nonketotic hyperglycinemia, hypoglycemia (in neonatal age), and glycogenosis.

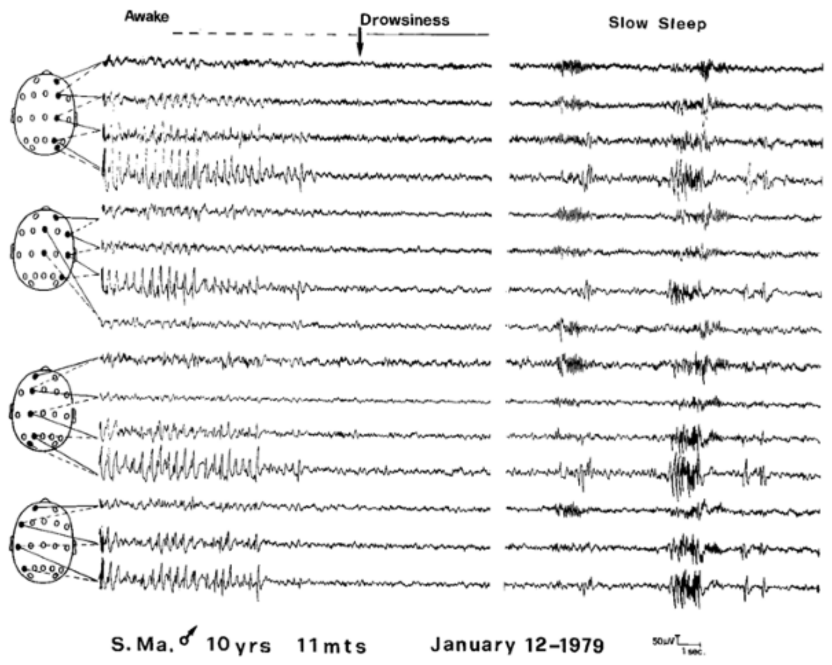

FIGURE 1. Patient with cryptogenic occipital epilepsy and severe evolution, 5 months after the epilepsy onset. **Left** (awake to drowsiness): Rhythmic bilateral occipital spikes and waves disappear in drowsiness. **Right:** Bilateral occipital polyspikes and rapid rhythms appear during slow sleep instead of occipital spikes and waves.

Childhood epilepsies with posterior temporal seizure onset[28,41,66] and complex partial seizures accompanied by illusions or hallucinations, followed by motor ictal phenomena, also have to be assessed. The so-called "concentric changes of visual field" seizures, which consist of continuous progressive restriction of the visual field, referred to as "tunnel vision" by patients and often associated with emotional distress, are strictly related to either the hippocampus or the temporolateral neocortex.[12] In these cases ictal and interictal EEG abnormalities are usually localized over the temporal, central, and posterior frontal region.

There may be diagnostic confusion between idiopathic occipital epilepsy and idiopathic generalized epilepsy. In fact, in idiopathic occipital epilepsies of childhood there may be generalized spike-wave discharges, and, conversely, EEG of idiopathic generalized epilepsies may show focal activity, which typically occurs in the frontal regions but may also occur in posterior areas. Moreover, patients with absences or even myoclonus may report brief "blacking out" of vision, mimicking a simple visual seizure. Distinction is possible through careful electroclinical analysis.[96]

Differential diagnosis between migraine with aura, basilar migraine, and LOCOE-Gastaut type should not be difficult if all of their components are present and properly evaluated.[85] In general, the age at onset of basilar migraine is during adolescence.[7,9,13] The persistent occipital abnormalities of LOCOE-Gastaut type have rarely been reported in cases of basilar migraine.[16,78,90,94] However, elementary visual seizures followed by headache and vomiting may be especially confusing. In fact, classic distinctive criteria, suggesting that in migraine the prodrome is usually longer than 5 minutes, as opposed to the very brief epileptic aura,[26] have proved to be unreliable.[14,56,57] On the other hand, visual auras, when of epileptic origin, are multicolored with circular or spherical patterns, as opposed to the predominantly black-and-white linear pattern of migraine attacks,[83] and are followed by eye deviation and lateralized or generalized convulsions, and there are no brainstem or cerebellar symptoms.[98] Eventually, postictal EEG commonly return quickly to the pre-ictal state, in contrast to the prolonged postcritical EEG abnormalities of migrainous attacks.[6]

Treatment and Outcome

Unlike other benign childhood partial epilepsies that may not need treatment, LOCOE-Gastaut type should be treated because seizures, although brief and mild, are frequent with possible secondary generalization, and the active period is variable. Most of the available data on treatment are based on studies performed when the distinction between early- and late-onset variants had not yet been defined, and the results reported could therefore be biased. In prospective studies of patients with strictly defined diagnoses, carbamazepine was able to control visual seizures.[84,85,100] It may be possible that delaying appropriate medication may adversely affect prognosis. Antiepileptic drugs do not necessarily normalize EEGs, and the epileptiform abnormalities may persist for a few years after the cessation of seizures and withdrawal of drugs.[36,54] Clusters of seizures do not seem to be influenced by antiepileptic drugs. Clobazam seems to control the seizures and spikes and waves after a few days in some difficult cases.[41,66]

Table 1 Clinical and EEG findings differentiating the idiopathic and symptomatic occipital epilepsies

Occipital epilepsies	Age at onset of occipital seizures, y	Main seizure patterns	Photoparoxysmal response	Photically induced occipital seizures	Interictal EEG findings	Outcome	References
EOBCOE- Panayiotopoulos type	2–14, peaks 4–5	Sleep-related—tonic eye deviation, unresponsiveness, vomiting	Never reported	Never reported	Normal background, occipital S or SW reactive to eye	Remission within 1–2y, before 12 y	90,91
LOCOE-Gastaut type	3–16, mean 8	Diurnal visual seizures, followed by postictal headache and often by CPS or hemiclonic seizures	Never reported	Never reported	Normal background, occipital S or SW reactive to eye	Seizures persisting into late adolescence	40,41
Idiopathic photosensitive occipital lobe epilepsy	5–17, peak at about 15	Visual symptoms, epigastric discomfort, headache, version, vomiting	Constant posterior, generalized, or both	Constant	Normal background, occipital S or SW reactive to eye opening	Good in most patients; seizures may persist with wide photosensitivity range	50,79
Symptomatic/cryptogenic epilepsy (unspecific etiology)	Variable	Varies with suprasylvian/intrasylvian spread	Not infrequent: posterior	Sporadic	Usually abnormal background, S or SW reactive or not to eye opening evolving in to rapid rhythm or pSW during sleep	Variable, with progressive occipital lobe severity (malignant variant)	56,60
Special conditions that may be associated with recurrent occipital seizures:							
Occipital lobe epilepsy (with and without occipital calcifications) and occipital lobe epilepsy with occipital calcifications (without celiac disease)	2–14	Visual and versive first; tonic, atypical/atonic absences if worsening	Not infrequent: posterior	Not infrequent	Normal or abnormal background, occipital S or SW reactive or not to eye opening, in celiac disease	Variable: favorable, or steady orprogressive severity	5,54,55
Lafora disease	6–19, peak at about 11	Visual, clonic, GTC, myoclonus	Almost constant: occipital, generalized, or both	Sporadic	Normal or abnormal background, occipital and generalized S and pSW	Progressive myoclonus, epilepsy, and mental deterioration	106
Hyperglycemia	Adulthood	Visual and versive	Never reported	Never reported	Normal or abnormal background, occipital slow waves	Drug-resistant if glucose levels abnormal	61

Among patients who had been treated, drugs were successfully withdrawn before the age of 16 in 33% of cases. According to Panayiotopoulos,[85] slow reduction of medication 2 to 3 years after the last visual or other minor or major seizure may be advisable, but if visual seizures reappear, treatment should be restored. However, a relapse at drug withdrawal is possible even after a 2-year seizure-free period,[54] and long-lasting spontaneous remission is not guaranteed. The duration of the active phase may be difficult to predict, and consequently optimal duration of treatment is hard to assess.

Long-term Prognosis

Prognosis of LOCOE is not firmly established. Prognosis variability may depend on the selection criteria of the patients. In the early series of Gastaut, seizures were completely controlled by medication in only 60% of cases.[36,41] Beaumanoir reported seizure control before the age of 13 years, whereas Gastaut found 19 years to be the upper limit.[10] Patients initially classified as having idiopathic epilepsy but with a less favorable course turned out to have minor lesions on high-resolution MRI, which had not been detected in earlier neuroimaging studies.[72] When strict inclusion criteria such as normal neurologic examination and normal imaging studies are fulfilled, most patients have a favorable outcome.[99] Brain mapping seems to be valuable predictor of seizure outcome.[72]

Summary and Conclusions

In general, occipital epilepsies constitute a rare condition, but it is common opinion that they are probably underestimated because, especially at the onset, they may emulate other epilepsies since the visual hallucinations, which are the most important symptom for diagnosis, may lack or may be difficult to elicit on history, especially from younger children. The typical EEG abnormalities may also be absent, and if the no-visual seizures are the predominating ictal event, a different localization-related epilepsy may be supposed.

The usual clinical picture of LOCOE-Gastaut type is a normal child within the typical age range having either short visual seizures or eye-adversive seizures accompanied by visual ictal phenomena, which may be followed by hemi- or generalized convulsions. Elementary visual seizures are frequent, up to more than one per day. In about 50% of the patients, ictal hallucinations are followed by unilateral and pulsating headache, and in 10% of the cases they are associated with nausea and vomiting, making visual seizures indistinguishable from migraine with aura or basilar migraine attacks. Even though specific studies are needed to draw definite conclusions, these patients might be at risk for lower intellectual performance, scholastic disabilities, and psychiatric disorders. In particular, specific deficits in the visuoperceptual domain might occur.

LOCOE-Gastaut type has to be differentiated from the Panayiotopoulos-type childhood-onset epilepsy, photosensitive idiopathic occipital epilepsy, symptomatic occipital epilepsies, temporal epilepsies, idiopathic generalized epilepsy, and migraine. Especially important differential diagnoses are symptomatic occipital epilepsies. The following features should be considered as indications of a symptomatic or cryptogenic origin: Neuropsychological and neuroradiologic abnormalities, brief (>30 minutes) and persistent frequent partial seizures that may be associated with an alteration of consciousness, polymorphous seizures, abnormal background EEG activity, focal slowing, multiple spike foci, secondary generalization, and a change in the morphology of paroxysmal abnormalities during sleep.[6,22,51,61,88,98] A full neurophysiologic, neuropsychological, neuroimaging, and laboratory assessment is invariably mandatory in all patients with occipital epilepsy.

Prognosis and outcome of LOCOE-Gastaut type is not more firmly established than in other benign idiopathic epilepsies. This variability may depend on the selection criteria of the patients. When strict inclusion criteria are fulfilled, most patients have a favorable outcome. Because of prognosis uncertainty; seizures, though brief and mild, are frequent with possible secondary generalization; and the active period is variable, LOCOE-Gastaut type should be early treated. It may also be possible that delaying appropriate medication may adversely affect prognosis. Carbamazepine seems able to control visual seizures.

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Chapter 239

Childhood and Juvenile Absence Epilepsies

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Introduction

Typical Absences: The Symptoms

Typical absences (TAs) are epileptic seizures manifested by impairment of consciousness and 2.5- to 4-Hz generalized spike-and-slow-wave discharges[47,85,187] (see Chapter 49). Impairment of consciousness may be mild (requiring special testing)[1,7,27,112,122,161,162,199,205,206,208] or severe and may be associated with other clinical manifestations, such as automatisms,[184] regional or widespread myoclonia (rhythmic or random), and autonomic disturbances.[46] Furthermore, the electroencephalographic (EEG) discharge may be brief or long, continuous or fragmented, with multiple or single spikes that are consistently associated or not associated with the slow wave. The intradischarge frequency may be relatively constant or vary.[161]

Thus, the term *typical absences* does not refer to a stereotyped symptom, but to a cluster of clinico-EEG manifestations that may be syndrome related. It should be appreciated that like any other physical symptoms in medicine, a detailed study of the manifestations of TAs is a prerequisite for a meaningful syndrome-related diagnosis. The clinico-EEG manifestations of absences have been best described in the eminent video-EEG studies by Penry et al.[185] and Stefan et al.,[211] but it is only recently that an attempt has been made for their syndrome-related characterization with video-EEG analysis.[108,109,158,159,160,161,170,171,172] It has been shown that some of the manifestations of TA may be more specifically related to an epileptic syndrome than others, but no single symptom is sufficient to define an epileptic syndrome.[173]

Epileptic Syndromes with Typical Absences

An epileptic syndrome, by definition, requires the nonfortuitous clustering of many symptoms and signs.[48]

Four epileptic syndromes with TAs have been recognized by the International League Against Epilepsy (ILAE)[48]: Childhood absence epilepsy (CAE), juvenile absence epilepsy (JAE), juvenile myoclonic epilepsy (JME), and myoclonic absence epilepsy (MAE). The first three (CAE, JAE, JME) are considered as part of idiopathic generalized epilepsies (IGEs), whereas the fourth (MAE) is categorized among the symptomatic or cryptogenic generalized epilepsies.

There may be more epileptic syndromes with TAs, such as eyelid myoclonia with absences (EMA), perioral myoclonia with absences, and others awaiting further studies and confirmation.[166,168,171,177,178] Furthermore, idiopathic generalized tonic–clonic seizures on awakening are often associated with mild absences.[175] Many of these syndromes are different in presentation, severity, and prognosis. Children with CAE in their majority will remit, those with MAE are affected by or may develop mental and behavioral problems, and those with JME in their midteens may develop lifelong myoclonic jerks and generalized tonic–clonic seizures (GTCSs). Other patients may have subtle clinical manifestations during the typical 3-Hz spike-and-wave discharges of which they are not aware (phantom absences); often they seek medical consultation only after a generalized tonic–clonic seizure develops, probably a long time after the onset of absences.

Some investigators[11,21,23,24,25,26,117,192,193] have proposed that all these disorders, not only idiopathic (for which some theoretical justification may exist) but also those whereby the seizures arise from known brain damage, constitute a neurobiologic continuum.

Historical Perspectives

This topic has been discussed in detail elsewhere.[66,67,116,125,127,134,135,139,194] According to Temkin,[216] the first description of absences was made in 1705 by Poupart. Tissot in 1770[217] described a girl with absences "*avec un très léger mouvement dans les yeux*" associated with frequent GTCSs. The term *epileptic absences* was first used by Calmeil[35] in his doctoral thesis of 1824. The term of *petit mal* was introduced by Esquirol in 1815.[73] Gowers in 1881[97] gave the most accurate description of absence seizures "without conspicuous convulsions," and Hughlings Jackson in 1879[115] discussed the differences between absences and complex partial seizures. Absences also have been described on clinical grounds, without EEG, by Friedmann.[83] Although he believed that these absences were not epileptic, he gave an excellent description of the attacks and a long-term favorable prognosis. Sauer[204] originated the term *pyknolepsy* (from the Greek *pyknos* indicating closely packed, dense, aggregated). Adie.[2] based on his own observations but mainly, as he admitted, on those of Friedmann,[83] Heilbronner,[106] and Stier,[212] defined pyknolepsy in the most admirable way as follows:

> "A disease with an explosive onset between the ages of 4 and 12 years, of frequent short, very slight, monotonous minor epileptiform seizures of uniform severity, which recur almost daily for weeks, months or years, and which are uninfluenced by anti-epileptic remedies, do not impede normal and psychical development, and ultimately cease spontaneously never to return. At most the eyeballs may roll upwards, the lids may flicker and the arms may be raised by a feeble tonic spasm. Clonic movements, however slight, obvious vasomotor disturbances, palpitations and lassitude or confusion after the attacks, are equivocal symptoms strongly suggestive of oncoming grave epilepsy, and for the present they should be considered as foreign to the more favourable disease."

The electroclinical characteristics of absences were described by Gibbs.[94,95] The petit mal triad of Lennox,[126,127] which was misused and misunderstood, was finally clarified by the ILAE[47] with the differentiation of typical and atypical absences.

The present ILAE distinction[48] between CAE and JAE is mainly based on the pioneer work of Doose et al.[61] and Janz.[116] Doose et al.,[61] in a study of 149 children with absences, found three different groups with emphasis at the age of onset: (a) an absence epilepsy of early onset from birth to 4 years of age, (b) CAE (pyknolepsy) with onset at 4 to 8 years of age, and (c) JAE with onset before puberty and with absences occurring in clusters (cycloleptic) or sporadically (spanioleptic). Janz[116] emphasized the significance of the frequency of the absences in a comparative study of 505 pyknoleptic and 197 nonpyknoleptic cases and confirmed Doose's conclusions regarding differences of age at onset and sex.[116,118,119]

Tassinari et al.,[215] by describing myoclonic absences, and Jeavons,[121] by describing eyelid myoclonia with absences, were probably the first authors to report absences starting in childhood but having different characteristics and prognoses than in CAE.

Definitions

Childhood Absence Epilepsy

According to the international classification of epilepsies,[48] CAE represents an idiopathic generalized epilepsy defined as follows: Pyknolepsy occurs in children of school age (peak manifestation age 6 to 7 years), with a strong genetic predisposition in otherwise normal children. It appears more frequently in girls than in boys. It is characterized by very frequent (several to many per day) absences. The EEG reveals bilateral, synchronous symmetric spike-waves, usually 3 Hz, on a normal background activity (Fig. 1). During adolescence, generalized tonic–clonic seizures often develop. Otherwise, absences may remit or, more rarely, persist as the only seizure type.

This brief definition of the ILAE Commission[48] mainly based on retrospective studies was a source of confusion. Thus, many authors make the arbitrary interpretation that CAE is any type of epilepsy with onset of absences in childhood. Therefore, epidemiology, genetics, age at onset, clinical manifestations, other types of seizures, long-term prognosis, and treatment do not accurately reflect the syndrome of CAE. A more precise definition of childhood absence epilepsy has been recently proposed by the ILAE Task Force on Classification defining inclusion and exclusion criteria.[140] It takes into account several important diagnostic points, such as the degree of impairment of consciousness, the morphology of spike-wave discharges, and the place of generalized tonic–clonic seizures. Clear exclusion criteria were also proposed[140]: Eyelid myoclonia (which is predominantly myoclonic and has minimal consciousness impairment) and TAs consistently provoked by specific stimuli. The same applies for multiple spikes (more than three spikes per wave) that also indicate a bad prognosis and coexistent myoclonic jerks or GTCSs.[160]

The following definition may better represent CAE (Table 1):

> Childhood absence epilepsy is an age-related idiopathic generalized epilepsy, which occurs in otherwise normal children, more frequently girls, with a strong genetic predisposition. Age of onset is between 4 and 10 years of age, with a peak at 5 to 7 years. Absences are frequent, tens to hundreds per day. Their duration varies from 4 to 20 seconds, though most of them last around 10 seconds. Clinically, there is abrupt and severe impairment (loss) of consciousness, with cessation of voluntary activity, which is not restored during the ictus. The eyes spontaneously open; overbreathing, speech, and other voluntary activity stop within the first 3 seconds from the onset of the discharge. Automatisms are frequent but have no significance in the diagnosis. The eyes stare or move slowly, and random eyelid blinking (usually not sustained) may occur.
>
> Persistent eyelid myoclonia, rhythmic massive limb jerking, and single or arrhythmic myoclonic jerks of the head, trunk, or limbs are probably not compatible with childhood absence epilepsy. However, milder myoclonic elements, particularly at the onset of the seizure discharge, may be a feature of childhood absence epilepsy. Generalized tonic–clonic seizures and other types of seizures like myoclonic jerks should not be featured in childhood absence epilepsy. Visual (photic) and other sensory precipitation are most likely against a diagnosis of childhood absence epilepsy. Mild or no impairment of consciousness is not compatible with childhood absence epilepsy.
>
> The EEG has a normal background, with sometimes rhythmic posterior delta activity. Ictal discharges consist of generalized high-amplitude spike- and double (maximum occasional three spikes are allowed)-spike-and-slow-wave complexes. They are rhythmic at around 3 to 4 Hz (>2.5 Hz) with a gradual and regular (0.5 to 1 Hz) slowdown from the initial to the terminal phase of the discharge. The first 1 to 2 seconds of the onset of the discharge is usually fast and unreliable for these measurements. There are no marked variations in the relation of spike to the slow wave, no fluctuations in the intradischarge frequency, and certainly no fragmentations of the ictal discharges.
>
> Remission usually occurs before the age of 12 years but infrequent GTCSs may develop in adolescence.

Juvenile Absence Epilepsy

According to the Revised International Classification of Epilepsies and Epileptic Syndromes,[48] JAE is one of the age-related idiopathic generalized epilepsies. The following description is given:

> The absences of JAE are the same as in pyknolepsy, but absences with retropulsive movements are less common. Manifestation occurs around puberty. Seizure frequency is lower than in pyknolepsy, with absences occurring less frequently than every day, mostly sporadically. Association with GTCS is frequent, and GTCSs precede the absence manifestations more often than in childhood absence epilepsy, often occurring on awakening. Not infrequently, the patients also have myoclonic seizures. Response to therapy is excellent.

A similar but slightly more restrictive definition has been proposed by Panayiotopoulos.[166]

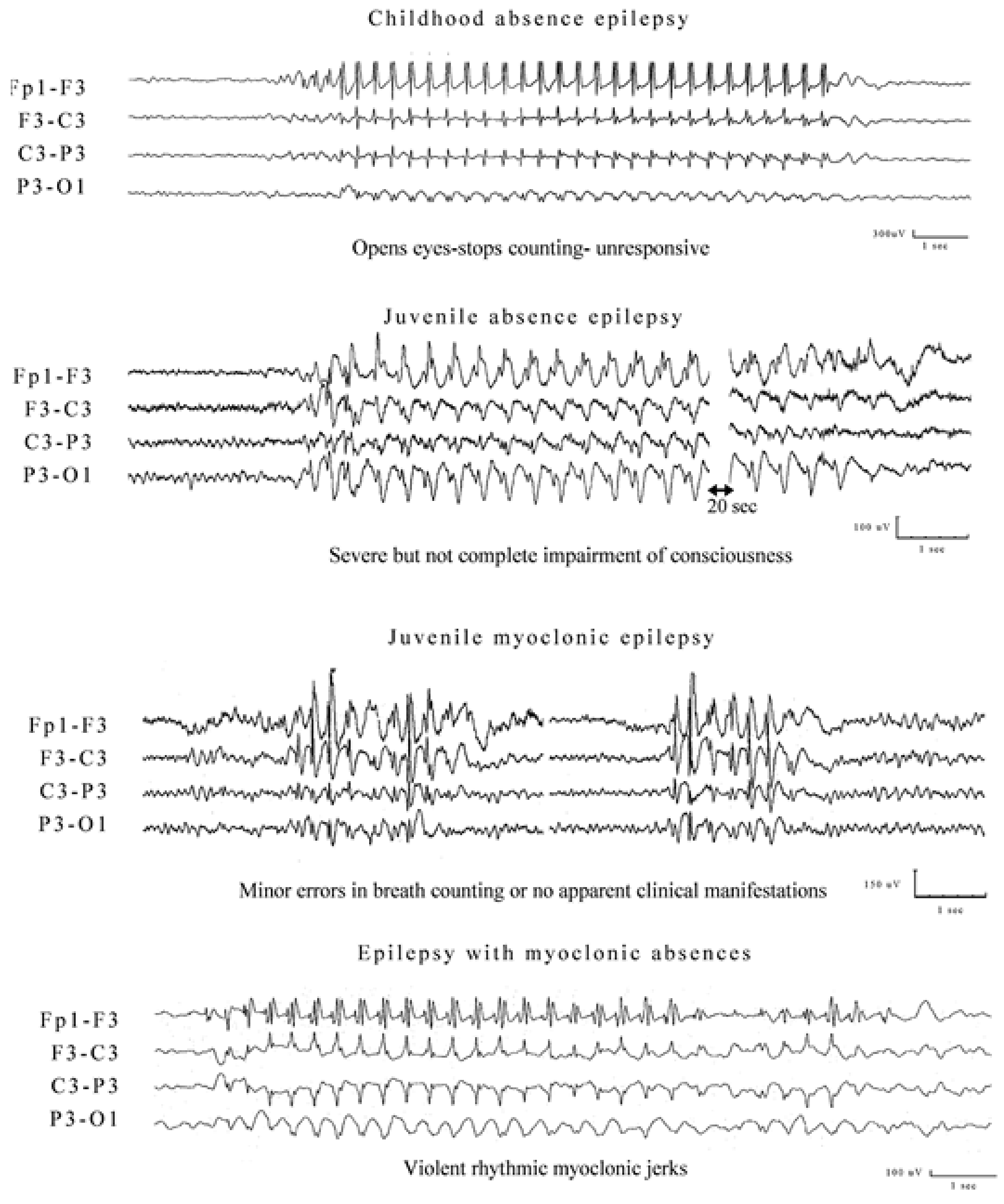
Epidemiology

Childhood Absence Epilepsy

The annual incidence of CAE is low and may vary from 1.9 to 8 per 100,000 children below the age of 16 years, and the prevalence is probably in the range of 2% to 10% of children with epileptic disorders.[23,30,133,200,201] A twofold preponderance in girls than boys may be a realistic estimate, although some studies have reported that boys and girls are equally affected.

Juvenile Absence Epilepsy

There are no population-based epidemiologic data on this syndrome. According to Janz,[118] JAE represented 10% of the age-related epilepsies with petit mal seizures.


Childhood absence epilepsy

Opens eyes-stops counting- unresponsive

Juvenile absence epilepsy

Severe but not complete impairment of consciousness

Juvenile myoclonic epilepsy

Minor errors in breath counting or no apparent clinical manifestations

Epilepsy with myoclonic absences

Violent rhythmic myoclonic jerks

FIGURE 1. Video-electroencephalographic (EEG) recordings. **Upper:** This trace is from a 7-year-old girl with frequent daily typical absences (TAs). She stops overbreathing and counting within the first 3 seconds after onset of the EEG 3-Hz spike-and-slow-wave discharge, she is unresponsive, and she demonstrates features described in the text for CAE. Automatisms are seen in some of her seizures, but there is no eyelid or perioral or limb myoclonia. She is not photosensitive. Note the regularity and rhythmicity of the ictal paroxysm. **Upper middle:** This trace is from a 33-year-old woman who has experienced frequent daily absences that were highly resistant to treatment since 8 years of age. Ten long spontaneous absences were recorded during the 3-hour video-EEG session, but they were mainly provoked by overbreathing. She experiences severe impairment of consciousness, but she may recall events occurring toward the end of the ictus, usually keeps her eyes closed, and may restore counting during the discharge. The long ictal EEG is as rhythmic and regular as that of CAE. **Lower middle:** This image is from a 38-year-old woman with juvenile myoclonic epilepsy (JME). Note the brief fragmented discharges with "W's. Impairment of consciousness may be detected with breath counting (annotated

with numbers) where there is a significant delay in pronouncing the next number after a discharge. **Lower:** This trace is from an 11-month-old boy with mild developmental delay and a 1-month history of absences. In video-EEG these were manifested with 3-Hz rhythmic multiple spike-and-slow-waves with rhythmic myoclonic jerking of the head, body, and shoulders.

Table 1 Inclusion and Exclusion Criteria for Childhood Absence Epilepsy

INCLUSION CRITERIA FOR CHILDHOOD ABSENCE EPILEPSY

1. Age at onset between 4 and 10 years and a peak at 5–7 years
2. Normal neurologic state and development
3. Brief (4–20 seconds, exceptionally longer) and frequent (tens per day) absence seizures with abrupt and severe impairment (loss) of consciousness. Automatisms are frequent but have no significance in the diagnosis.
4. EEG ictal discharges of generalized high-amplitude spike- and double (maximum occasional three spikes are allowed) spike-and-slow-wave complexes. They are rhythmic at around 3 Hz with a gradual and regular slowdown from the initial to the terminal phase of the discharge. Their duration varies from 4 to 20 seconds.

EXCLUSION CRITERIA FOR CHILDHOOD ABSENCE EPILEPSY

The following may be incompatible with childhood absence epilepsy:

1. Other than typical absence seizures such as generalized tonic–clonics seizures or myoclonic jerks prior to or during the active stage of absences
2. Eyelid myoclonia, perioral myoclonia, rhythmic massive limb jerking, and single or arrhythmic myoclonic jerks of the head, trunk, or limbs. However, mild myoclonic elements of the eyes, eyebrows, and eyelids may be featured—particularly in the first 3 seconds of the absence seizure.
3. Mild or no impairment of consciousness during the 3- to 4-Hz discharges
4. Brief EEG 3- to 4-Hz spike-wave paroxysms of <4 seconds, multiple spikes (more than three), or ictal discharge fragmentations
5. Visual (photic) and other sensory precipitation of clinical seizures

From Loiseau P, Panayiotopoulos CP. Childhood absence epilepsy. In: Gilham S, ed. *Neurobase*. San Diego, CA: Arbor Publishing Corp.; 2000, with permission.

Etiology and Basic Mechanisms

According to Tissot,[217] “To produce epilepsy, two things are necessary: (i) a tendency for the brain to fall into spasm more readily than during health; (ii) a source of irritation that can precipitate this tendency.” These two factors (genetic factor and acquired factor) exist with a very unequal significance in absences epilepsies.

Genetic Factors

Childhood Absences

Although CAE is genetically determined, the precise mode of inheritance and the genes involved remain largely unidentified.[9,10,84,154] A positive family history of epilepsy was found in 15% to 44% of cases.[20,53,59,62,63,108,127,205] Ascertainment of family history of epilepsy has to be considered: When keeping only epilepsy in parents and siblings, the frequency decreases from 42.6% to 20.7%.[111] In two series, epilepsy in first-degree relatives was found in 17% of CAE.[36,137] These seizures are TAs and GTCSs. In studies on twins, 84% of monozygotic twins had 3-Hz spike-waves, and TA developed in 75% of pairs and dizygotic twins 16 times less often.[127] An Australian study of epilepsy in twins confirmed that in concordant pairs, twins developed a similar syndrome.[26] Bianchi et al.[28] found that in 24 families with a CAE proband, there was a high concordance (33.3%) for the same clinical form in first-degrees relatives, while febrile convulsions (46.7%) and GTCSs (30%) were more common in distant relatives. Epilepsy risk in children of patients with CAE would be 6.8%.[17]

Currently, various chromosomal loci have been identified in families with absences of childhood onset (not necessarily equated with CAE). Linkage to chromosome 1 was found in families with absences starting in childhood and the later development of myoclonic jerks and GTCSs, as in JME.[58] Linkage analysis in five generations of a family in which affected patients had childhood absences and GTCSs provided evidence of a locus on chromosome 8q24.[58,81] The candidate region for this locus, designated ECA 1, has been refined, but a gene remains to be identified. According to the criteria proposed in this chapter, neither of these groups is CAE. There are also reports implicating chromosome 5q31.1 and 19p13.2.[52] Furthermore, there is now evidence available to suggest that mutations in genes encoding GABA receptors[145] or brain-expressed voltage-dependent calcium channels[44] may underlie CAE. Marini et al.[145] found $GABA_A$ receptor γ-2 subunit gene mutations on chromosome 5 in a large family with CAE and febrile seizures (including febrile seizures plus and other seizure phenotypes). This gene mutation segregated with febrile seizures and CAE, and also occurred in individuals with the other phenotypes. The clinical and molecular data suggested that the $GABA_A$ receptor subunit mutation alone could account for the febrile seizure phenotype, but an interaction of this gene with another gene or genes was required for the childhood absence phenotype in this family. Linkage analysis for a putative second gene contributing to the childhood absence phenotype suggested possible loci on chromosomes 10, 13, 14, and 15. Chen et al.[44] found 68 variations, including 12 missense mutations in the calcium channel *CACNA1H* gene in CAE patients. The identified missense mutations occurred in the highly conserved residues of the T-type calcium channel gene.

Juvenile Absences

A family history of epilepsy is frequent, and identical twins who both have the syndrome have been reported.[26] Obeid[156] reported that in a Saudi Arabian population where consanguineous marriages are frequent and can be found in 47% of the families of patients with JME,[152] this was only true for 1 out of 14 JAE families. This could indicate that a recessive gene is important in JME but not JAE. In the clinical genetic study of families with idiopathic generalized epilepsy,[146] phenotypic concordance within families of JAE was 10%, which was low compared to families of other IGE syndromes. Because 31% of JAE relatives had CAE but only 2.5% had JME, the authors suggested that CAE and JAE share a close genetic relation, whereas JME may be a more distinct entity. There are several reports of mutation of the CACNA1 A *α*-1 subunit of the CaV2.1 Ca2+ channel, or the CACNB4 *β*-4 subunit, with the phenotype of absence seizures with ataxia,[72,114] which does not fit in any of the known absence epilepsies. The paper of Escayg et al.[72] comprises an observation of a mutation in a family with an identical locus in CACNB4 as in the *lethargic* mouse mutant but which resulted in a quite different human phenotype. Findings with the genetically well-defined series of mouse mutants with absences can probably not be easily transferred to human epilepsies.

Acquired Factors

As concordance in monozygotic twins is not 100%, nongenetic factors are likely.[26] Perinatal complications, postnatal head trauma, and cerebral inflammatory disease were found in the

case histories of 7% to 30% of patients,[146,225] and only 3.9% in the Janz series.[118] However, these cerebral aggressions are very common in children and were not risk factors in a population-based case-control study.[196] A history of febrile convulsions is frequent: 20% to 23% of cases.[196,205] More than a risk factor, febrile convulsions are probably the first manifestation of an epileptic diathesis.[196] This is in accordance with results of studies on the phenotype of families with "febrile convulsions plus" related or not to mutations of voltage-dependant sodium channel gene mutations (SCN1A or SCN1B). In such families, tonic–clonic, tonic, and absence seizures have been reported.[14,128]

Pathology and Structural Brain Imaging

Autopsy[147,148] and magnetic resonance imaging (MRI)[225] studies found microdysgenesis and other cerebral structural changes in some patients with CAE. Meencke and Janz[148] reviewed autopsy findings in CAE and confirmed their previous reports on microdysgenesis[147] with the frontal lobe more severely affected. Using quantitative MRI, Woermann et al.[225] found that patients with idiopathic generalized epilepsy had significantly larger cortical gray matter volumes than control subjects. Abnormalities of the regional distribution of cerebral gray and subcortical matter were frequent in other patients with IGE but only in 1 out of 10 patients with childhood absence epilepsy. However, all cases of Meenke[149] had frequent absences from childhood to adulthood and GTCSs, which would not conform to a strict diagnosis of the syndrome of CAE. Similar may be the single patient with abnormal MRI of Woermann et al.[225] Recently, thalamic atrophy was demonstrated, using optimized voxel-based morphometry in a series of absence epilepsy patients. Bilateral thalamic atrophy may be either a result of damage from seizures (as in hippocampal sclerosis) in this group of patients with difficult to treat absences or a reflection of a primary underlying pathology as the cause of absence seizures.[41]

Basic Mechanisms

Current thinking about the pathogenesis of absence seizures dates to the landmark experiments of Jasper and Drooglever-Fortuyn.[120] They demonstrated that 3 c/s stimulation of the midline and intralaminar nuclei of the thalamus in cats could produce bilaterally synchronous spike-wave discharges in the cortical EEG of those animals. Over the next 50 years, a debate ensued in the literature as to which was pre-eminent in controlling synchronous spike-wave discharge that characterized absence seizures: The cortex, the thalamus, or both. With the advent of number of animal models of generalized absence seizures, this controversy has been at least partially resolved.[210] Moreover, the availability of these models has advanced our understanding of the basic mechanisms of absence seizures. The unifying hypothesis coming from animal data and in vitro neurophysiologic data will be briefly summarized in this chapter.

Animal Models of Generalized Absence Seizures

A valid animal model of generalized absence seizures should reflect the clinical and pharmacologic characteristics of this disorder.[42,113,144,155] The criteria for animal models of absence seizures are EEG findings and behavior analogous to human absence epilepsy; reproducibility; predictability; ability to standardize and quantitate; attenuation or blockage by ethosuximide, trimethadione, valproic acid, and benzodiazepines; appropriate ontogeny; exacerbation by γ-aminobutyric acid (GABA)-ergic drugs; blockage by GABA_B antagonists; spike-wave discharges that originate in the thalamus, cortex, or both; and hippocampus silent during seizure activity. There are two main genetic models of absence seizures in rats: WAG/Rij[46] and GAERS (genetic absence epilepsy rats from Strasbourg).[56] A number of other well-characterized genetic mouse models of absence seizures are reported. However, these models manifest a variety of neurologic abnormalities and in some cases other seizures types besides absence epilepsy. Several pharmacologic models of generalized absence seizures are described (γ-hydroxybutyrate [GHB], pentylenetetrazol, penicillin, etc.). These pharmacologic models are all electrographic models because bilaterally synchronous spike-wave discharges are observed.

Unifying Hypothesis

The animal data suggest that three interacting neuropharmacologic forces within the context of the thalamocortical circuitry are involved in the pathogenesis of absence seizures: (a) postsynaptic events required for the occurrence of generalized absence seizures are glutamate-mediated excitatory postsynaptic potentials (EPSPs) followed by $GABA_A$- and $GABA_B$-mediated inhibition that triggers a low-threshold calcium current in nuclear reticularis thalamus neurons; (b) the overall setpoint of thalamic and cortical excitability is modulated by means of ascending cholinergic pathways that project to the thalamus and noradrenergic and dopaminergic neurons projecting to the cortical end of the thalamocortical loop; and (c) presynaptic $GABA_B$ and GHB receptors may contribute to the regulation of thalamocortical rhythmicity by means of precise control of excitation and inhibition through modulation of GABA and glutamate release within the involved thalamocortical circuitry.

Genetic Identifiers of Animal Models of Absence Epilepsy

Studies have uncovered the causative genes for absencelike mice models. Tottering and leaner mice have defects in the calcium channel *α* subunit, lethargic mouse in the calcium channel *β*-4 gene, and stargazer and waggler mice in the calcium channel *γ* subunit gene. These mice mutants show some characteristics of absence epilepsy; however, all affected mice show some degree of cerebellar degeneration, which is quite different from human absence epilepsy.[110] Attempts to identify the genetic defects in calcium channel genes that underlie human absence epilepsy have so far failed.[201] Similar mutations of P/Q-type voltage-gated calcium channel CaV2.1 have been reported in a family with autosomal dominant transmission of absences and episodic ataxia.[114] Genetic studies in GAERS suggest a polygenic mode of inheritance of the EEG phenotype with at least three gene loci on chromosomes 4, 7, and 8.[197]

Clinical Presentation

Childhood Absences

The age at onset of CAE is classically between 4 and 8 years, with a peak at 6 to 7 years, although some investigators have suggested a much wider range reflecting differences in definition criteria. For example, Janz et al.,[118] using frequency of absences as a selection criterion, found that pyknoleptic absences first occur at 3 to 16 years of age, with a peak at 7.5 years. Girls are affected twice as frequently as boys.

The description of Gowers[97] probably best describes the clinical manifestations of TA in CAE:

> "Transient loss of consciousness without conspicuous convulsions. A patient stops for a moment whatever he or she is doing, very often turns pale, may drop what ever is in the hand…. There may be a slight stoop forward, or a slight quivering of the eyelids…. The attack usually lasts only a few seconds. The return of the consciousness may be sudden and the patient after the momentary lapse, may
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> be in just the same state as before the attack, may even continue a sentence or action which was commenced before it came on, and suspended during the occurrence."

The absences of CAE are easily precipitated by hyperven-tilation,[34] which may be used during clinical examination for observation. They are easily studied with EEG because untreated children with CAE invariably manifest clinical absences with 3-Hz generalized spike and slow waves during well-performed overbreathing.

A typical case of CAE is of a girl with normal intelligence and development who at the age of 6 years started having absences with severe impairment of consciousness. They were brief, lasting around 8 seconds, and occurred many times (tens or hundred) per day. The EEG, as nearly always with CAE, demonstrated 3-Hz regular spike-and-slow-wave generalized discharges that were mainly provoked by hyperventilation.[33] Video-EEG confirmed exclusion and inclusion criteria for CAE. There was no evidence of photosensitivity.

Cessation of seizures was achieved by administration of sodium valproate, but because of body weight increase this was changed to ethosuximide, which also successfully controlled her absences. Two years later, ethosuximide was gradually withdrawn. At 21 years of age, she is well, attends college, and plans to start a family.

Juvenile Absence Epilepsy

Age of onset is mostly in the range of 7 to 17 years with a peak at 10 to 12 years.[69,174,227,228] The seizure frequency is lower than in pyknolepsy, with clinical absences occurring less frequently than every day, mostly sporadically. The same types of absence occur as in CAE, but absences with retropulsive movements are less common. In one video-based study,[160,161] language functions in JAE absences were less rapidly abolished, consciousness was less severely impaired, and hyperventilation stopped later than in CAE. Spontaneous eye opening was rare, and simple absences were more common. However, this study is based on only three cases of JAE and is therefore not necessarily representative.

The majority of patients also have GTCSs, but it may be that the diagnosis is often missed if absences are the only seizure type. If the patients also have GTCSs, their manifestation precedes that of the absences more often than in CAE. Most frequently, they belong to the awakening type. Association with myoclonic seizures of the type seen in JME is more common than in CAE, probably in the order of 15% to 20%.

Diagnostic Evaluation

Electroencephalographic Findings

Childhood Absence Epilepsy

Video-EEG studies showed that CAE demonstrates the following ictal symptoms[108]:

1. The impairment of consciousness is severe. There is no verbal or other response to commands, and recollection of verbal ictal events is lost.
2. The eyes are open, overbreathing stops, and speech discontinues within 3 seconds after the onset of the discharge.
3. Automatisms occur in two thirds of the seizures but are not stereotyped. The same patient may have simple and complex absences. Automatisms may be evoked by passive movements. Automatisms in absences indicate severe impairment of consciousness and do not occur in patients with mild impairment of cognition, even if the discharges last for more than 8 seconds.
4. Rhythmic blinking at 3 Hz is an infrequent, unsustained feature. The eyes may stare, but they also may move during the ictus, particularly if the child is loudly called by name.
5. Retropulsive movements of the eyes and head, which characterize eyelid myoclonia with absences, are not a usual clinical feature of CAE but may occur at the onset of the absence.
6. The duration of absences in CAE is shorter than in JAE (mean 12.4 and 16.3 seconds, respectively).

The clinical manifestations of CAE are associated with the following EEG features:

1. The interictal EEG is normal or shows rhythmic posterior delta activity. Occasionally, centrotemporal or occipital spikes may be seen.
2. The ictal EEG shows generalized, spike- or double-spike (no more than three spikes are seen)-and-slow-wave complexes at 3 Hz (no less than 2.7 Hz and no more than 4 Hz at the initial phase of the discharge with gradual and smooth decline in frequency from the initial to the terminal phase). The discharge is regular, with well-formed spikes that retain a constant relationship with the slow waves. The duration is usually around 10 to 12 seconds, no less than 4 seconds, and no more than 20 seconds (Fig. 1).

Partial seizures, myoclonic jerks, GTCSs, and other more bizarre fits have been described with absences starting in childhood (not necessarily CAE).[14,75] GTCSs occurring before the onset of TAs should not be accepted in CAE.

Juvenile Absence Epilepsy

In the EEG, the background activity is usually normal. The characteristic feature of the interictal and ictal EEG is generalized symmetric spike-and-waves discharge with frontal accentuation. The spike-and-waves frequency is usually faster than 3 Hz (3.5 to 4 Hz), the first complex of a group sometimes being even faster.[220] Often, the slow wave is preceded by two or three spikes. The above-mentioned preliminary study of Panayiotopoulos et al.[160] indicated that the ictal discharges may be longer in JAE (16.3 ± 7.1 seconds) than in CAE (12.4 ± 2.1 seconds) and in JME (6.6 ± 4.2 seconds). They were more regular than in JME but could show fragmentation unlike in CAE. In one study,[226] photosensitivity was less common than in other idiopathic generalized epilepsies, but this was not confirmed in the only other study.[220,229]

Neuroimaging

Functional imaging with positron emission tomography demonstrates normal cerebral glucose metabolism and benzodiazepine receptor density in absence epilepsies with diffuse hypermetabolism during 3-Hz spike-and-wave dis-charges.[71,188,198] There is no evidence of any interictal overall abnormality of opioid receptors, though typical absences have been found to displace 11 C-diprenorphine from the association areas of the neocortex. In contrast, binding of 11 C-flumazenil to cBZRs has been shown not to be affected by serial absences.[71] Functional MRI-EEG study of absences seizures in adult patients with JAE demonstrated bilateral activation of the thalamus and widespread deactivation of the cortex maximal in frontal regions.[6,124,199] Substraction interictal-ictal single photon emission computed tomography (SPECT) coregistered to MRI (SISCOM) was used to evaluate cerebral blood flow changes during the ictal and immediate postictal phase in

four children with CAE.[153] The authors reported a widespread decrease of cerebral blood flow during ictal phase and an increase during post ictal phase. Those studies confirm in humans data observed in animal models, which suggest a crucial role of the thalamo-cortical loop and specific metabolic modifications during absence seizures.

Differential Diagnosis

The diagnosis of CAE may be difficult, even by specialists. Three child neurologists independently classified epilepsy syndromes in a cohort of children with newly diagnosed epilepsy and 7 of 74 CAEs were not diagnosed as such by one of the three.[18] In practical terms, a child suspected of typical absences should be asked to overbreathe for 3 minutes counting his or her breaths. Hyperventilation will provoke an absence in nearly all untreated children with CAE.[224] This procedure should preferably be videotaped for documentation of the clinical features.

CAE and JAE are epileptic syndromes that have to be distinguished from a variety of conditions such as nonepileptic manifestation (attention disturbance and daydreaming)[80] or focal epilepsies. Differential diagnosis of absence epilepsies from focal epilepsies should be easy, though alteration of consciousness and automatisms may be common in both. Temporomesial seizures could be characterized by staring and automatisms, reasons that in the past it was improperly called “pseudoabsences” or “temporal lobe absences.” However, in temporal mesial seizures, loss of consciousness is preceded by vegetative aura; seizure ending could be characterized by postictal signs (asthenia, aphasia). A main problem is “typical absence seizures” from frontopolar lobe origin that may also have concomitant more or less regular bilateral 3-Hz spike-wave discharges.[75,77,219] Focal motor components, asymmetric ictal discharges, or stable interictal frontal foci in the EEG may help in their differentiation. MRI may demonstrate frontal abnormalities[77] or subependymal gray matter heterotopia.[190] However, rare focal EEG abnormalities are possible in CAE.[16,141,231] Loss of consciousness of milder intensity is observed during atypical absences in Lennox-Gastaut syndrome. Lennox-Gastaut syndrome is characterized by the association of atypical absences with tonic and atonic seizures, runs of rapid spikes in non-REM sleep, and status epilepticus. Resistance to therapy and persistence of epilepsy are among the most frequent features. Mental retardation is a leading symptom, occurring on average in 90% of cases.

Other Epilepsies with Typical Absence Seizures Starting in Childhood or Early Adolescence

The differentiation of CAE from other IGEs with absences may be difficult without video-EEG comparisons (Fig. 2). Eyelid myoclonia with absences is the easiest of all to differentiate from CAE because of brief, mainly eyelid myoclonia; minor impairment of consciousness; EEG generalized discharges of predominantly polyspikes; and photosensitivity. Myoclonic absence epilepsy and absences with perioral myoclonia have clinically apparent myoclonic jerks, and EEG discharges usually show polyspikes. The major problem is with JAE and JME that may start with typical absence seizures long before the appearance of myoclonic jerks and GTCSs.

Juvenile Myoclonic Epilepsy (Janz Syndrome)

Absence seizures occur in one third of JME patients, but these are usually very mild, are often inconspicuous, and have different EEG patterns.[100,160,165,167] The main seizure type of JME is myoclonic jerks upon awakening, and these do not occur in CAE. The problem is when JME starts with absences prior to the onset of myoclonic jerks, but again, there are a number of clinico-EEG differences such as milder impairment of consciousness, frequent polyspikes, and fragmentations of the EEG discharges in JME.[160,207] Some authors consider these cases as CAE evolving or progressing to JME.[58,223] In our opinion, this is JME starting with absences in childhood. In the majority of these patients with JME starting with TAs in childhood, video-EEG studies would clearly differentiate them from the TAs of CAE.[160] However, there may be cases where their differentiation is difficult and JME will not be diagnosed until many years after with the appearance of myoclonic jerks and GTCSs.

Absence Epilepsy of Early Childhood

A syndrome of absence epilepsy of early childhood was proposed in the 1960s[61] and later,[8,29,38,40,55,57,65] that included a heterogenous group of patients, some of whom had CAE. It was characterized by an onset before the age of 5 years; possible occurrence, at the onset or later, of GTCSs and/or myoclonic-astatic seizures; irregular 2- to 3-Hz spike-and-waves discharges on the EEG; and often an unfavorable prognosis. Later, its heterogeneity was admitted.[64] Age at onset artificially covers various idiopathic generalized epilepsies with a polygenic inheritance. Absence epilepsies of early childhood include early-onset CAE and other absence epilepsies in which more important environmental factors explain the frequency of GTCSs and a less favorable outcome. The "intermediate petit mal" described by the Bologna school[142] probably corresponds to similar situations.

Myoclonic Absence Epilepsy

This syndrome described by Tassinari et al.[214,215] is also incorporated in the ILAE Classification[48] as a rare generalized cryptogenic/symptomatic absence epilepsy. Severe bilateral rhythmic clonic jerks, often associated with a tonic contraction, occur during the absence.[143] Awareness of the jerks may be maintained. Seizures occur many times a day. Other types of seizures are rare. Age of onset is around 7 years, and there is a male preponderance. Prognosis is not good because of resistance to therapy, mental deterioration, and possible evolution to other types of epilepsy such as Lennox-Gastaut syndrome.[215]

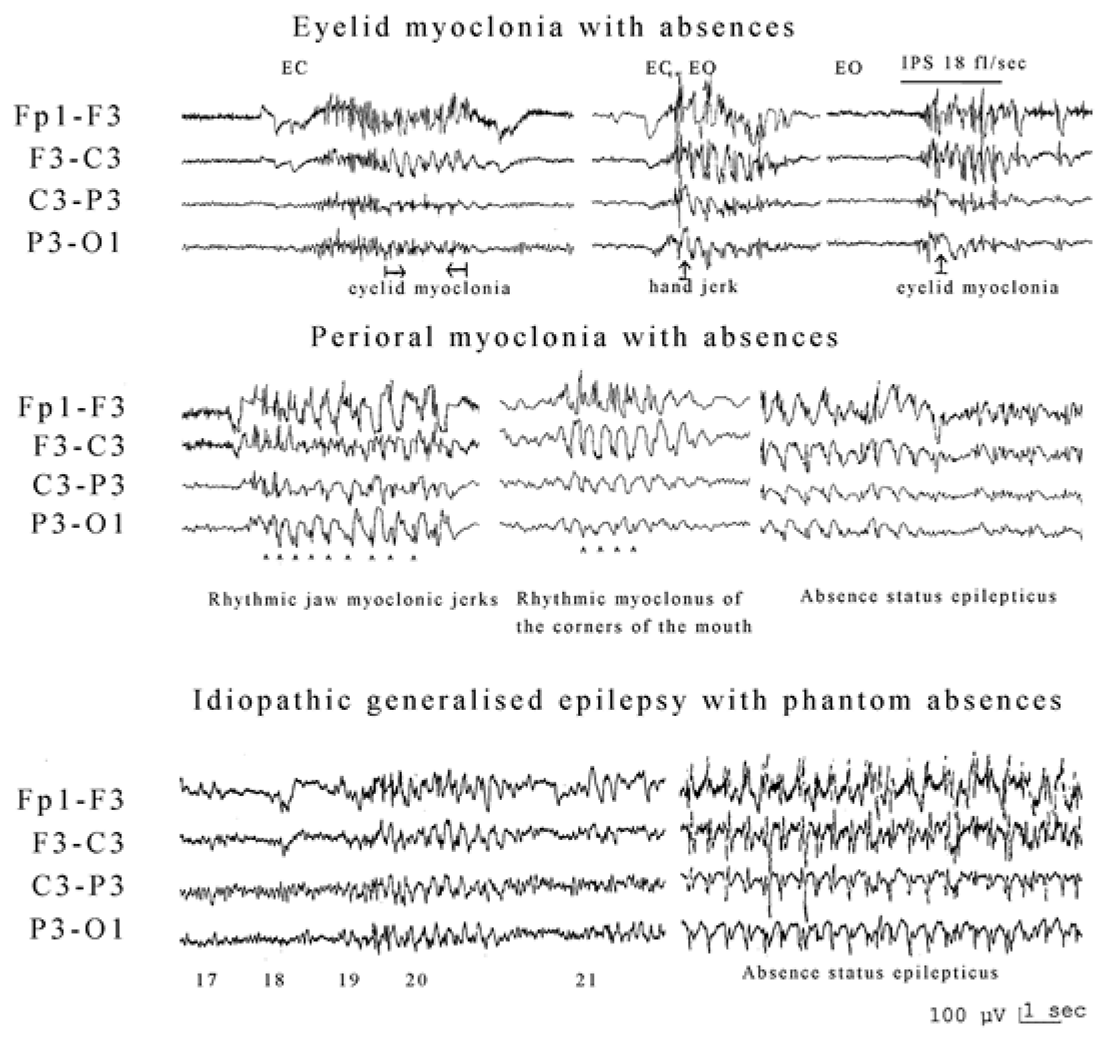
Eyelid myoclonia with absences
EC
EC, EO
EO
IPS 18 fl/sec
Fp1-F3
F3-C3
C3-P3
P3-O1
eyelid myoclonia
hand jerk
eyelid myoclonia
Perioral myoclonia with absences
Fp1-F3
F3-C3
C3-P3
P3-O1
Rhythmic jaw myoclonic jerks
Rhythmic myoclonus of the corners of the mouth
Absence status epilepticus
Idiopathic generalised epilepsy with phantom absences
Fp1-F3
F3-C3
C3-P3
P3-O1
17
18
19
20
21
Absence status epilepticus
100 μV
1 sec

FIGURE 2. Video-electroencephalographic (EEG) recordings. **Upper left:** Brief ictal discharges consisting mainly of polyspikes and slow waves are induced after eye closure in a 32-year-old woman with eyelid myoclonia with absences (EMA). They are associated with eyelid myoclonus and occasionally mild impairment of consciousness. Similar abnormalities are seen in a 17-year-old girl on eye closure **(middle)** and intermittent photic stimulation **(right)**. In the latter case, mild myoclonic jerks of the hands also were seen. Details of these patients have been reported by Giannakodimos and Panayiotopoulos.[50] **Middle left:** Rhythmic jaw jerking (annotated with *arrows*) with mild impairment of consciousness were the characteristic clinical features during these brief discharges in an 18-year-old woman with intractable absences, generalized tonic–clonic seizures (GTCSs), jerks, and possible absence status. Similar EEG abnormalities associated with rhythmic contractions of the depressor anguli oris were recorded in a 37-year-old man with infrequent absence status followed by GTCSs **(middle)**. An episode of absence status with perioral myoclonia and cloudiness of consciousness ending in a GTCS was recorded via EEG in a 29-year-old woman with frequent absences and absence status with GTCSs **(right)**. Details of these patients have been reported by Panayiotopoulos et al.[102,103] **Lower right:** Phantom absences manifested with delays in counting during overbreathing (numbers) in a 17-year-old girl with a single GTCS at 17 years of age **(left)**. Similar brief and mild absences were recorded in another 56-year-old woman who also had two episodes of de novo absence status of late onset **(right)**. Details for these patients have been reported by Panayiotopoulos et al.[106]

Eyelid Myoclonia with Absences (Jeavons Syndrome)

The syndrome of eyelid myoclonia with absences was first described by Jeavons in 1977 as a form of photosensitive epilepsy[70,121] and was confirmed by other investi-gators.[12,13,15,55,79,90,91,96,99,103] Eyelid myoclonia with absences is frequently familial.[182] It is considered more a myoclonic than an absence syndrome.[177,213] The following definition was proposed by Panayiotopoulos[181]: Jeavons syndrome (eyelid myoclonia with absences) is an idiopathic epileptic syndrome manifested by frequent (pyknoleptic) seizures, consisting of eyelid myoclonia often associated with absences. Onset is usually in early childhood. The seizures are brief (3 to 6 seconds) and occur mainly after eye closure.[169,176,222] They consist of eyelid myoclonia, which persists throughout the attack with or without absences. Absences without eyelid myoclonia do not occur. The eyelid myoclonia consists of marked, rhythmic, and fast jerks of the eyelids, often associated with jerky upward deviation of the eyeballs and retropulsion of the head. There is probably an associated tonic component of the involved muscles. If the seizure is prolonged, impairment of consciousness occurs. The latter is mild or moderately severe

without associated automatisms. Milder seizures of eyelid myoclonia without absences are common, particularly in adults and treated patients, and may occur without EEG accompaniments. All patients are highly photosensitive in childhood, but this declines with age. Infrequent GTCSs, either induced by lights or spontaneous, are probably inevitable in the long term and are likely to occur after sleep deprivation, fatigue, and alcohol indulgence. Myoclonic jerks of the limbs may occur, but are infrequent and random. The eyelid myoclonia of Jeavons syndrome is resistant to treatment and may be lifelong. However, clinical absences may become less frequent with age.

The EEG ictal manifestations consist mainly of generalized polyspike-waves at 3 to 6 Hz, which are more likely to occur after eye closure in an illuminated room. Total darkness abolishes the abnormalities related to eye closure. Photoparoxysmal responses are recorded from all untreated young patients.

Perioral Myoclonia with Absences

Panayiotopoulos et al.[168] reported that TAs associated with marked perioral myoclonia may constitute a new epilepsy syndrome defined as follows:

> Perioral myoclonus with absences is a syndrome of idiopathic generalized epilepsy with onset in childhood or adolescence, characterized by frequent typical absences with variable severity of impairment of consciousness and ictal localized rhythmic myoclonus of
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> the perioral facial muscles (lip myoclonus) or occasionally of the masticatory muscles (jaw myoclonus). TA duration is usually brief, ranging from 2 to 10 seconds. Ictal EEG shows generalized discharges of spikes, more often irregular polyspikes and slow waves at 3 to 5 Hz. They are not associated with eye closure and photosensitivity. Perioral myoclonia with absences often associates with absence status.[5] GTCSs always occur either early or several years after the onset of TA; they are usually heralded by clusters of TAs or absence status and may be infrequent. The syndrome is lifelong and often resistant to medication. A family history of epilepsy is common.[181]

Lips and chin myoclonia are by themselves insufficient symptoms to justify a syndromic individualization, because of a possible moderate myoclonic component in CAE and JAE.[37,108] However, a unique combination of characteristic clinico-EEG features is likely in perioral myoclonia with absences.

Phantom Absences and Generalized Tonic-Clonic Seizures

Phantom absences is the term we have coined to denote TAs that are so mild that they are inconspicuous to the patient and imperceptible to the observer.[76,88,180] They have been known for many years as “subclinical or larval absences.”[1] The absences are simple, occasionally with eyelid blinking. They are common in patients with idiopathic generalized epilepsies but are often unrecognized. Based on patient information, the absences often start after patients' teen years. The absences were shown on video-EEG recordings with breath counting and consisted of brief (3 to 4 seconds) generalized discharges of 3- to 4-Hz spikes or multiple spike-and-slow-wave discharges, during which mild impairment of cognition manifested with consistent errors and discontinuation of breath counting. Absence status occurred, either in isolation or terminating in GTCSs.[209] In these patients GTCSs were consistently preceded by absence status. After recognition of this sequence, GTCSs were often preventable with rectal benzodiazepine, self-administered while in absence status. Long-term prognosis may be the same as in other syndromes of IGE with TAs and GTCSs. In view of the high incidence of absence status, patients should be advised to use rectal diazepam.

Symptomatic Absence Seizures

In genetically predisposed individuals, brain damage may precipitate TA occurrence, most often associated with neurologic signs and/or mental retardation. This category comprised 10% of patients with TA in a Swedish population-based study.[158] Ferrie et al.[77] made a list of diffuse and focal cerebral pathologies in which TAs have been reported. They are as follows, in alphabetic order: Arteriovenous malformations, autism, biochemical disturbances, brain tumors, cerebral abscess, congenital microcephaly, craniostenosis, Down syndrome, drugs/drug withdrawal, encephalitides, endocrine disturbances, head injury, hemiplegia, hydrocephalus, hypothalamic lesions,[152] juvenile Batten disease, mitochondrial encephalopathies, neonatal intracranial hemorrhage, precocious puberty, progressive myoclonic epilepsy, Sturge-Weber syndrome, subacute sclerosing panencephalitis, tuberculous meningitis, and tuberous sclerosis. Most of these reports are old and, hence, poorly documented, and one may wonder how many patients fitted with CAE characteristics. Subtentorial lesions[189,191] are noteworthy, because they may disturb the corticothalamic oscillatory networks. Prognosis is that of the underlying pathology. In most cases, the association is probably coincidental. However, cerebral pathology may modify the expression of genetic seizure susceptibility.[77] In these cases, the correct diagnosis is not CAE, but symptomatic absence epilepsy, with a less favorable outcome.

Treatment and Outcome

Childhood Absence Epilepsy

Childhood absence epilepsy needs treatment because absences are very frequent throughout the day and may adversely affect cognitive functioning.[32,68] However, clinicians should avoid overtreatment with antiepileptic drugs (AEDs), which may induce cognitive side effects. First-line drugs are ethosuximide, sodium valproate, and lamotrigine, alone or in combination.[78,164,195] Clonazepam, clobazam, and acetazol- amide are second-line drugs for CAE, sharing a similar risk of tolerance and adverse effects.[98,179] Amantadine could be effective in association as a third-line drug in pharmacoresistent absence epilepsies with few adverse events. Despite this clear-cut evidence of antiabsence drug efficacy, many children with typical absence seizures would still be treated with inappropriate drugs.[183] Sodium valproate controls absences in 75% of patients[22] and has the advantage also of controlling generalized tonic–clonic seizures (70%) and myoclonic jerks (75%), but may be undesirable for women. Rare cases of paradoxical aggravation in CAE with valproate have been reported; this might be related to a genetic heterogeneity of CAE.[129] Similarly, lamotrigine may control absences in possibly 50% to 60% and GTCSs in 50% to 60%, but may worsen myoclonic jerks; hypersensitivity immune reaction are possible.[49,50,82,89] Ethosuximide controls 70% of absences, but it is undesirable as monotherapy if other generalized seizures are at risk. Combination of any of these three drugs may be needed for resistant cases. Minute doses of lamotrigine added to sodium valproate may have a dramatic beneficial effect. Clonazepam, particularly in absences with myoclonic components, acetazolamide, and amantadine may be useful adjunctive drugs. Diones are no longer used.[186] Conversely, carbamazepine, vigabatrin, gabapentin, and tiagabine are contraindicated because of their proabsence effect.[39] Phenytoin and phenobarbital are contraindicated because of their usual inefficacy.[179,181] The place of topiramate, levetiracetam, and vagal nerve stimulation is still unknown.

Monotherapy with sodium valproate, ethosuximide, or lamotrigine should be the choice and should not be abandoned before making sure that the maximum tolerated dose has been achieved if smaller doses have failed. There are anecdotal reports whereby children may not respond to syrup of sodium valproate despite adequate levels, but seizures stop if this is replaced by tablets or microspheres of sodium valproate. If monotherapy fails or unacceptable adverse reactions appear, then replacement of one by the other is the alternative. The best possible combination is adding small, minute doses of lamotrigine to adequate doses of sodium valproate. Gradual withdrawal of medication is recommended in patients with CAE who are seizure free for 1 to 2 years and have a normalized EEG. EEG confirmation of the seizure-free state is needed during this withdrawal period.

Juvenile Absence Epilepsy

First-line drugs are sodium valproate and lamotrigine, alone or in combination. When there is concern about teratogenicity, lamotrigine can be given as first-line monotherapy,[82] although onset of action is much slower compared to

valproate.[49] There is at present no study specifically investigating the newer AEDs such as topiramate and levetiracetam in JAE. Carbamazepine and oxcarbazepine may aggravate the seizures of JAE.[87]

Long-term Prognosis

Childhood Absence Epilepsy

Most of the available evidence is inconclusive regarding evolution and prognosis of CAE. This is because of markedly different classification criteria in the relevant reports or of too-short follow-up periods. Most authors include in CAE any child with absences before the age of 10 years, which may not be CAE.[19,31,140,181] Retrospective studies in adults may lack accurate initial data. Patients must be followed beyond 18 or 20 years of age.[132,136,138] Our view is that CAE, if properly defined, has an excellent prognosis.

Prognosis of Typical Absence Seizures

At a time when no antiabsence drug existed, Adie[2] concluded that even if absence seizures in pyknolepsy persisted for a long time, they ultimately ceased, never to return. This is consistent with recent findings that absences of CAE, even if they may persist several years, finally disappear with age in more than 90% of cases.[132,136,138,202,203] In a Swedish population-based study, a 91% remission rate was found when patients with absence epilepsy had only absences.[105]

Typical absence seizures persist for a mean time of 6.6 years[53] and disappear between age 3 and 19 years, with a mean age of 10.5[107] or 14 years.[53] "The tendency for petit mal to cease is present at all ages and not just at puberty. In about a quarter of patients the attacks cease before the age of 15 and by the age of 30 years petit mal had ceased in about three quarters of the patients."[92,93] In this study, with a follow-up of about 5 years, only 3% of patients experienced TAs beyond 50 years of age. In another study,[130] of the 92 controlled patients, 89 were aged 20 or younger at the time of cessation of absence seizures.

Thus, TA persistence is rare, reported to occur in about 6% of patients.[157] In adults, attacks tend to be infrequent and milder, and occur with precipitating factors such as fatigue, sleep deprivation, and menstruation,[53,86,161,181] though in some cases absences may be very severe.[5]

Two favorable prognostic signs are age at onset of TAs and medication efficacy. In patients diagnosed early and followed beyond 20 years of age, TAs had disappeared in 95% and 90% of cases according to an age at onset of 8 or 10 years, respectively.[135,136] Their cessation soon after prescription of a convenient antiepileptic drug is considered as a favorable sign.[53,131]

Generalized Tonic–Clonic Seizures

However, cessation of absence seizures may not mean remission. This again depends on diagnostic inclusion and exclusion criteria. Considering all absences with onset in childhood as CAE, prognosis is uncertain and with great variations.[31,181] GTCSs may appear and patients may develop juvenile myoclonic epilepsy.[223] Absence seizures in these patients may persist, improve, or disappear.

It has been estimated that GTCSs occurs in 36% to 60% of patients with onset of TAs in childhood.[53,130] Most often, GTCSs occur 5 to 10 years after onset of TAs,[132] that is, mainly between 8 and 15 years of age,[43,60,130] and sometimes beyond 20 and even 30 years of age.[86] They have been considered as infrequent and easily controlled.

Different risk factors have been suggested, as follows:

- Age at onset of TAs: The later the onset of TAs, the higher the risk is for subsequent convulsive seizures.[20,43,51,54,102,127,130]
- Absence status, especially when absences occur late in the course of epilepsy,[60] but this may not be childhood absence epilepsy.[3,4,5,104]
- Sex: TAs are more frequent in girls and TAs + GTCSs are more frequent in boys.[157]
- EEG: Usually, clinical/EEG correlation is fair. However, the predictive value of the EEG is not absolute; spike-wave discharges may persist after clinical recovery, and conversely GTCSs may occur in spite of a normalized EEG.[105] When initial tracings show posterior delta rhythms, GTCSs rarely occur.[45,105,157] An abnormal background activity, multiple spikes,[74] and focal abnormalities are considered as unfavorable signs, but are likely to correspond to erroneous diagnoses.
- Therapy: With an early institution of effective therapy, GTCSs occurred in 30% of cases, and 68% after incorrect therapy.[20] GTCSs manifested in 85% of incorrectly treated patients.[60]

A change of CAE into epilepsy with focal seizures has been reported. It probably corresponds to erroneous diagnosis: Either TAs with automatisms or absence epilepsy other than CAE such as in febrile seizures plus.[123]

Complete Remission

A wide range of remission rates has been given: 78% to 33%. The reasons for this are as follows: (a) patients with absence epilepsies other than CAE were included; (b) patients' age at last clinic visit, with, for instance, inclusion of 82% of patients when beyond 18 years of age but only 65% in those beyond 20[60]; (c) follow-up duration, with relapse in 19% of patients who had been seizure free for 2 years or more; and (d) therapy[60]: With early and adequate therapy, 70% of patients were included, whereas 18% with an incorrect therapy were included.[20]

Social Prognosis

Social adaptation of patients having had CAE would be poor in one third of patients, even when in remission.[60,102,107,142] In childhood absence epilepsy, TAs are very frequent and the EEG shows brief discharges of bilateral spike-waves without apparent clinical impairment. Neuropsychological studies have documented cognitive dysfunctioning (reaction time tasks and sustained attention tests) during these discharges. "The transitory bursts of spike-wave activity represent the tip of an iceberg. Below the surface there may be a more or less continuously active pathophysiological process, which is reflected in impaired performance on tests of attention and in alterations in event-related brain potentials."[150,151] Therefore, long-term sequelae of scholastic difficulties are not surprising. Furthermore, a psychomotor slowing beginning late in follow-up has been found in some patients with TAs persisting after the age of 30 to 61 years.[86] It was supposed to be multifactorial in origin.

Juvenile Absence Epilepsy

The response to therapy is good in spite of the frequent combination with GTCSs. Wolf and Inoue,[230] in their cross-sectional study of 229 adolescents and adults who had a diagnosis of absences and still were in treatment, reported that all were seizure free if they had only had absences (n = 21), and 87% were seizure free if there had not been more than ten GTCSs. If there were more GTCSs (which was the case in 123 patients), the response was still very good, but 24% were not seizure free. The response was better in JAE (85% seizure free) than in CAE (80%, p <0.02), and combination with myoclonic seizures did not affect the therapy prognosis. In these patients, the absences were mostly treated with ethosuximide, valproate, or both—and in some cases with mesuximide—and if necessary the doses were increased to the maximum the patients could tolerate. If GTCSs were present, these were often treated with an additional drug, especially with succinimide treatment for absences. In the study of Trinka et al.,[218] 40 (62%) of 64 JAE patients were seizure free for at least 2 years, which was almost similar to the seizure-free rate of CAE patients (56%).

Summary and Conclusions

Childhood absence epilepsy is an idiopathic generalized epilepsy that should not be equated with any type of absences first appearing in childhood. It may be as benign as the benign childhood partial seizures,[163] but further prospective studies must be conducted with strict clinico-EEG criteria of the classification. A better definition of CAE and related syndromes allows a better classification of patients with idiopathic absence epilepsies. However, 33% of patients are still difficult to classify.[101] This syndromic approach is necessary for the improvement of genetic and pharmacologic studies. Juvenile absence epilepsy is an idiopathic form of epilepsy that is probably lifelong. It is characterized by frequent absences with severe impairment of consciousness (imitating CAE) associated with GTCSs and occasionally with myoclonic jerks (imitating JME). Thus, the phenotypic manifestations of JAE are intermediate between CAE and JME. Whether this is also the case for their genotypes remains to be seen. Incidence, prevalence, long-term prognosis, genetics, and what is the most realistic treatment (which may be lifelong) need to be studied.

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Chapter 240

Epilepsy with Myoclonic Absences

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Introduction

Epilepsy with myoclonic absences (MAs) is an epileptic syndrome characterized clinically by absence seizures associated with rhythmic, bilateral myoclonic jerks of severe intensity. The diagnosis is based on clinical observation and ictal video-polygraphic recordings. Indeed, in video-polygraphic investigations (recording an electroencephalogram [EEG] and electromyogram [EMG] from upper limb muscles, such as deltoids), MAs are characterized by rhythmic, bilateral, synchronous, symmetric 3-Hz spike-wave (SW) discharge, as in typical absences, associated with EMG myoclonic bursts at 3 Hz, superimposed to a progressively increasing tonic contraction.

Demonstration of MA seizures is essential for the diagnosis; thus, epilepsy with MAs belongs to the group of epilepsy syndromes that is defined by a specific seizure type (as, for example, juvenile myoclonic epilepsy or myoclonic astatic epilepsy [Doose syndrome]). Indeed, since the early description of MAs,[13,15,16] it has been believed that this seizure type could characterize a distinct epileptic condition that could be identified and separated from other forms of generalized epilepsy, such as childhood absence epilepsy. The Commission on Classification and Terminology of the International League Against Epilepsy (ILAE) accepted this view, recognizing epilepsy with MAs as an autonomous syndromic entity that was included, in the 1989 ILAE Proposal for Revised Classification of Epilepsies and Epileptic Syndromes,[6] in the group of cryptogenic or symptomatic generalized epilepsies, due to an overall dismal and heterogeneous prognosis. On the other hand, in the more recent Proposed Diagnostic Scheme for People with Epileptic Seizures and with Epilepsy produced by the ILAE Task Force on Classification and Terminology,[9] it has been tentatively placed among idiopathic generalized epilepsies. Recent reviews on this epileptic condition by Bureau and Tassinari[2,3] and Tassinari et al.[21] acknowledged the existence of at least two forms of epilepsy with MAs: one with a more benign course, and eventually disappearance of seizures, in which MAs are the sole, or predominant, seizure type; and the other with MAs associated with other seizure types (particularly, frequent generalized tonic–clonic seizures) that bears a more severe prognosis, as compared to other idiopathic generalized epilepsies. Furthermore, cases with "atypical" features in which MAs were part of a clinical picture characterized by some degree of mental retardation, neurologic deficits (e.g., congenital hemiparesis), and chromosomopathy[7,8,11] have been reported.

Clinical Data

General Remarks

Epilepsy with MAs is a rare condition; in a selected population of epileptic patients attending the Centre St. Paul in Marseilles, it accounts for 0.5% to 1% of all epilepsies. There is a male preponderance (69%), at variance with childhood absence epilepsy in which females are more frequently affected. Etiologic factors reported in about 35% of cases are prematurity, perinatal damage, consanguinity, congenital hemiparesis, and chromosomopathy.[2,3] The evidence in some cases of associated chromosomal dysfunction has led to the hypothesis that abnormal expression of genes located in the affected chromosome segments may play a role in the pathogenesis of myoclonic absence epilepsy.[7,8] A genetic susceptibility, as demonstrated by a positive family history of epilepsies, has been observed in about 20% of cases.

The mean age of onset of MAs is 7 years, with a range between 11 months and 12.2 years. Reports describing cases with onset of MAs in the first year of life have been published in the last years.[1,14,19,22]

Myoclonic Absences

MAs are characterized by the following:

> *Impairment of consciousness*, which can vary in intensity, ranging from a mild disruption of contact to a complete loss of consciousness. Sometimes the patients are aware of the jerks and may recall the words pronounced by the examiner during the seizures.
>
> *Motor manifestations*, which consist of bilateral myoclonic jerks, often associated with a discrete tonic contraction that has been clearly documented in proximal upper limb muscles. The myoclonias mainly involve the muscles of the shoulders, arms, and legs; facial myoclonias, when present, are more evident around the chin and the mouth, whereas eyelid twitching is typically absent or rare. Due to concomitant tonic contraction, the jerking of the arms is accompanied by a progressive elevation of the upper extremities, giving rise to a quite constant and recognizable pattern. When the patient is standing, falling is uncommon. In some patients, asymmetric features, such as head and trunk deviation, may occur.

> *Autonomic manifestations*, which consist of an arrest of respiration and inconstant loss of urine.

MAs last for 10 to 60 seconds, and recur at a high frequency (many seizures per day), being often precipitated by hyperventilation or awakening. MAs may also be observed during the early stages of sleep. Episodes of MA status are distinctly rare.

Seizures Other Than Myoclonic Absences

MAs represent the only seizure type in about one third of patients. The remaining cases can suffer from other seizure types, which can appear before the onset of MAs or occur in association with MAs. They consist of generalized tonic–clonic seizures, absences, or epileptic falls.

Neurologic and Neuropsychologic Examination

Neurologic examination is normal, except in those cases with congenital hemiparesis. Mental retardation is present in about 45% of cases before the onset of MAs. During the course of MAs, mental retardation may worsen, or even appear, in patients previously normal, particularly in those patients with frequent tonic–clonic seizures associated with MAs. These data constitute a very significant difference for this subgroup of patients when compared with the cognitive status observed in childhood absence epilepsy.

Neurophysiologic Data

Interictal EEG

The interictal EEG shows a normal background activity in all cases. In one third of cases, bursts of generalized SWs or, more rarely, focal or multifocal SWs are present. It is noteworthy to point out that the sinusoidal posterior slow rhythm has never been observed, as reported in childhood absence epilepsy.

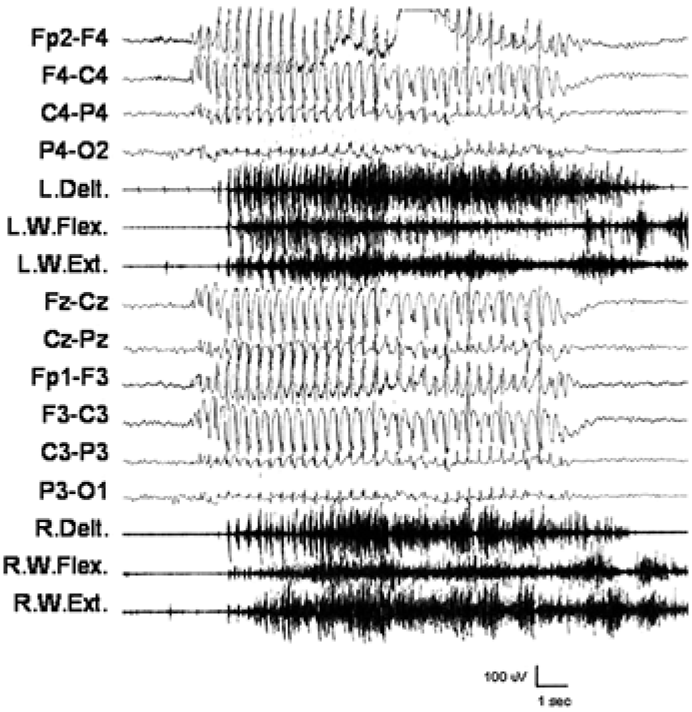
Fp2-F4
F4-C4
C4-P4
P4-O2
L.Delt.
L.W.Flex.
L.W.Ext.
Fz-Cz
Cz-Pz
Fp1-F3
F3-C3
C3-P3
P3-O1
R.Delt.
R.W.Flex.
R.W.Ext.
100 uV
1 sec

FIGURE 1. Spontaneous myoclonic absence. Electroencephalogram (EEG): Rhythmic spike-wave (SW) discharge at 3 Hz, bilateral, synchronous, and symmetric, as observed in typical absences. Electromyogram (EMG): Rhythmic myoclonia, at the same frequency of the SW, involving the upper extremities, and starting about 1.5 seconds after the onset of the EEG paroxysmal discharge, associated with a tonic contraction with progressively increasing intensity. Delt., deltoid; W.Flex., wrist flexor; W.Ext., wrist extensor; R., right; L., left.

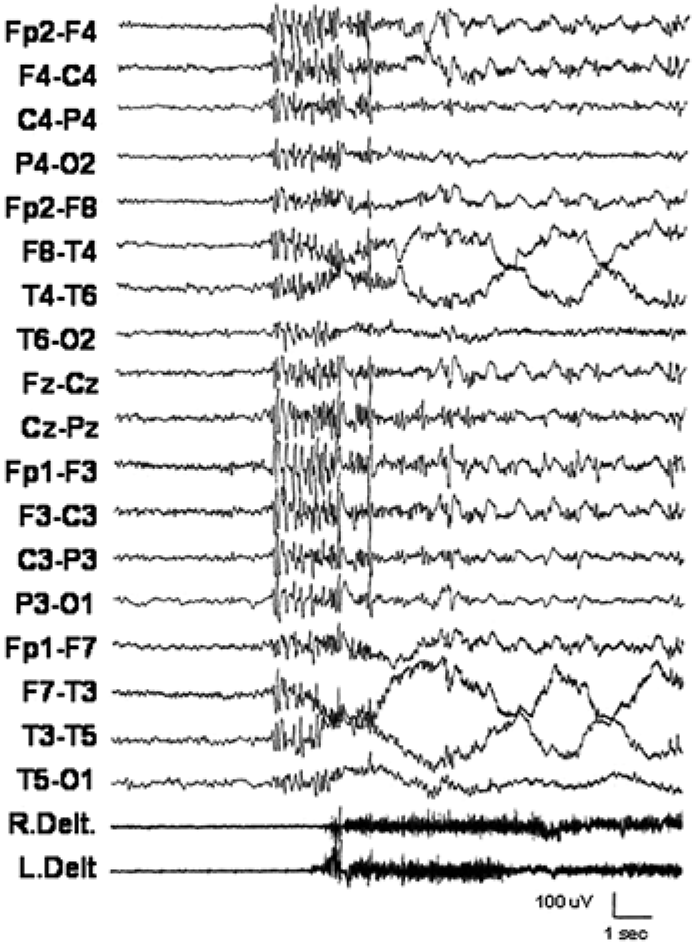

FIGURE 3. Tonic seizure during light sleep in a 45-year-old patient who started to suffer from myoclonic absences when she was 11 years old. Tonic muscular activity appears about 1 second after the onset of a rhythmic polyspike discharge. Delt., deltoid; R., right; L., left.

Ictal EEG

The ictal EEG consists of rhythmic SW discharges at 3 Hz, which are bilateral, synchronous, and symmetric, as observed in typical absences. The onset and the end of SWs are abrupt. Polygraphic (EEG-EMG) recording discloses the appearance of bilateral myoclonias, at the same frequency as the SW, which begin around 1 second after the onset of EEG paroxysmal discharges and are followed by a tonic contraction, maximal in the shoulder and deltoid muscles (Fig. 1). Original investigations by Tassinari et al.[16,17] by means of high-speed oscilloscopic analysis provided a detailed description of the relationships between the EEG SW and motor events, showing a strict and constant relation between the spike of the SW discharge and the myoclonia (Fig. 2). These studies emphasized the relationships between the positive transient encompassed in the SW complex,[24] which in MAs is of high amplitude and is followed on the EMG by a myoclonia with a latency of 15 to 40 msec for the more proximal muscles and of 50 to 70 msec for the more distal muscles. This myoclonia is itself followed by a brief silent period (60 to 120 msec), which breaks the tonic contraction. Recently, Gardella et al.[10] demonstrated that the first myoclonic jerks were restricted to the facial musculature, then spreading to the neck and upper limbs muscles. Back-average of the EEG activity triggered from the onset of the first myoclonia confirmed the correlation of the

myoclonic phenomenon with the positive transient of the SW complex.

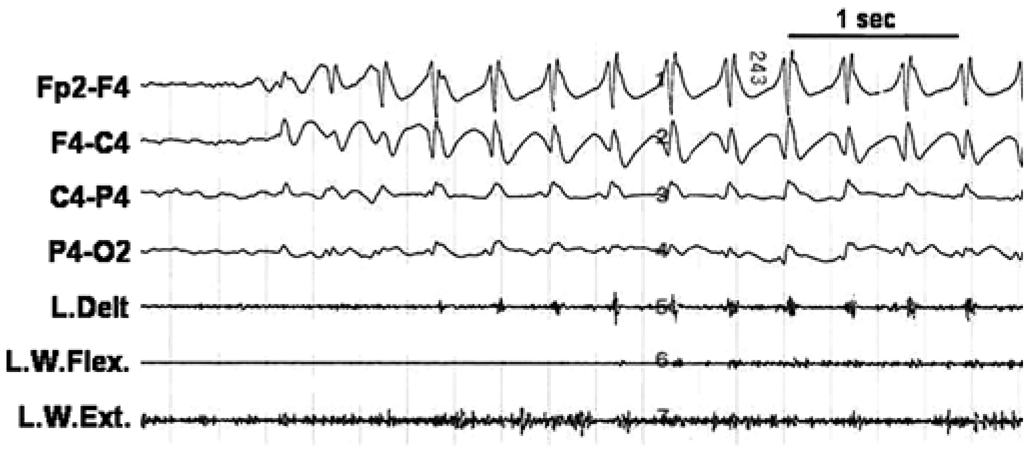

FIGURE 2. High-speed polygraphic recording of a myoclonic absence (MA) seizure, showing the relationship between the spike of the spike-wave (SW) complex and the myoclonic potential. The first three SW complexes are not associated with any evident myoclonic activity. Delt., deltoid; W.Flex., wrist flexor; W.Ext., wrist extensor; L., left.

Physiopathogenetic hypotheses on the peculiar muscular pattern that characterizes MA seizures admit that the tonic muscular contraction component that is superimposed on the myoclonic activity might be related to the involvement of secondary motor areas,[3] possibly in the frontomesial cortex.[12] Indeed, tonic contractions occur always in MAs, but after the appearance of few SW complexes, possibly suggesting a spread of paroxysmal activity to frontomesial areas. During the evolution, some cases may evolve to a “Lennox-Gastaut–like syndrome” with tonic seizures, particularly during wakefulness or light sleep, associated in the EEG with rhythmic polyspike waves (Fig. 3). In these patients, the disappearance of SW complexes might be observed, replaced by focal frontal spikes; although infrequently, a frontal partial status may occur that can be controlled by phenytoin administration.

Sleep EEG

Sleep organization is constantly normal and physiologic patterns are symmetrically present. During sleep the evolution of the SW discharges is similar, on the whole, to that observed in childhood absence epilepsy.[18] MAs may occur during stage I of sleep, awakening the subject. During stage II, SW discharges, of brief or long duration, are also observed, sometimes associated with bursts of myoclonias.

Evolution

Classical data on the evolution of MAs indicate that these are still present in about two thirds of the cases followed up for a mean period of 10 years, whereas they disappear in the remaining patients after a mean period of 5.5 years from the onset.[2,3,21] The two groups of patients differ in the frequency and type of associated seizures: in fact, patients with “refractory” MAs have a high incidence (80%) of associated seizures, mainly of generalized tonic–clonic and atonic types. On the contrary, patients with remitting MAs have a lower incidence (40%) of associated seizures, mainly of the absence type. The long duration of MAs is likely to be an important factor for the appearance of mental retardation, since intellectual functions are always preserved in children with rapid remission of MAs. In rare cases, the disappearance of MAs has been followed by the onset of other seizure types, namely absences with atypical SW discharges and clinical and subclinical tonic seizures, giving rise to a clinical picture similar to the Lennox-Gastaut syndrome.[19,20]

Diagnosis

The diagnosis of MAs mainly rests on the polygraphic demonstration of SW discharges at 3 Hz (as in typical absences) accompanied by rhythmic myoclonias. Therefore, polygraphic recording is mandatory when the clinical suspicion of MAs is raised. Since the anamnestic data may sometimes be misleading (asymmetric MAs may be misdiagnosed as partial motor seizures, MAs with mild myoclonias may be misdiagnosed as typical petit mal absences, etc.), we suggest that polygraphic recording should be performed also in patients with “drug-resistant” absence seizures and in cases with refractory “myoclonic” or “partial motor seizures.”

Capovilla et al.[4] reported a group of patients with childhood absence epilepsy exhibiting absence seizures associated with mild myoclonic jerks, involving mainly the facial and neck muscles (eyebrows, nostrils, perioral region, chin, sternocleidomastoideus). Indeed, the electroclinical characteristics (particularly, benign course with excellent response to treatment, and possible drug withdrawal in the evolution, and mild myoclonia without a background of tonic contraction) differentiate this clinical picture from epilepsy with MAs. Moreover, myoclonic phenomena have also been described in children with early-onset typical absences (before age 2 to 3 years).[5]

Finally, MAs must be differentiated from absence seizures with more or less rhythmic myoclonias associated with 2.5–3 Hz irregular SWs observed in nonspecific diffuse epileptic encephalopathies.[20]

Treatment

Data on outcome suggest that the correct medical therapy for MAs consists of the associated use of valproic acid and ethosuximide at high doses, with serum plasma levels ranging from 80 to 130 µg/mL and 70 to 110 µg/mL, respectively. Recent studies found lamotrigine, particularly in combination with valproate, or in one case ethosuximide, to be useful when other measures had failed.[14,23] In individual cases, good seizure control was achieved by using a combination of phenobarbitone, valproic acid, and benzodiazepines. It must be pointed out that since epilepsy with MAs is a relatively rare condition, no comparative or controlled clinical trials have ever been performed; therefore, the only available data are of retrospective nature. In particular, the efficacy of more recent antiepileptic drugs that are currently used in the treatment of refractory absences or in myoclonic epilepsies, such as levetiracetam, topiramate, and zonisamide, has not been adequately investigated in epilepsy with MAs. Finally, it should be mentioned that drugs such as carbamazepine or phenytoin (and possibly vigabatrin, gabapentin, tiagabine, and oxcarbazepine) might theoretically worsen MAs; however, as above mentioned, in patients who present with partial status, phenytoin may be useful to stop seizure activity.

Summary and Conclusions

The syndrome of epilepsy with MAs is a distinct form of childhood epilepsy characterized by a peculiar seizure type that identifies this epileptic condition. Recognition of MAs relies on direct clinical observation and polygraphic recording; in particular, the EEG-EMG ictal pattern bears specific features that allow differential diagnosis with other generalized seizure types. It can be stated that the demonstration of MAs is sufficient for the diagnosis. Regarding the natural history and prognosis of epilepsy with MAs, two forms may be identified: a form in which MAs are the sole or predominant seizure type and a form in which MAs are associated with other seizure types and particularly with numerous generalized tonic–clonic seizures; this latter form bears a poor prognosis in terms of seizure control and neuropsychological deterioration.

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Chapter 241

Lennox-Gastaut Syndrome

Pierre Genton

Charlotte Dravet

Introduction

Among childhood epilepsies, Lennox-Gastaut syndrome (LGS) is one of the most severe. It is characterized clinically by frequent seizures, including sudden falls, marked resistance to therapy, and progressive mental and behavioral disturbances. The syndrome is difficult to treat, even with the most recent antiepileptic drugs. Although the physiologic and pathogenic mechanisms of LGS are not fully understood, it has precise, well-defined clinical and neurophysiologic characteristics that restrict the diagnosis to a fairly homogenous, albeit rather uncommon entity. Historically, its main trait (i.e., the presence of diffuse slow spike-wave discharges), has led to overdiagnoses and confusion with other encephalopathic epilepsies; not all diffuse slow spikes-and-waves, not all epileptic drop attacks, and not all severe, polymorphic encephalopathic childhood-onset epilepsies are caused by LGS. Indeed, some cases previously diagnosed as LGS would nowadays be reclassified into other categories, like myoclonic astatic epilepsy or the Dravet syndrome.

LGS has many possible causes, and modern concepts have stressed the major part played in the genesis of LGS by secondary bilateral synchrony originating from the frontal cortex. In spite of its relative rarity, LGS has in recent years been the object of specific clinical trials evaluating the efficacy of newer antiepileptic agents, probably because it still represents the archetype of a recognizable, yet severe, intractable childhood epileptic encephalopathy.

Historical Perspective

Early authors had already noticed the poor prognosis of some types of childhood seizures (i.e., atypical absences, tonic seizures, and astatic seizures), when Gibbs in 1938[38] and then Gibbs et al.[39] in 1939 identified an electroencephalographic (EEG) pattern characterized by slow (about 2-Hz) spikes-and-waves. They called this the *petit mal variant* as opposed to the less severe *petit mal absence*, characterized by 3-Hz spikes-and-waves. Lennox in 1945[57] and Lennox and Davis in 1950[59] established the clinical correlates of this pattern and described a symptomatic triad comprising slow diffuse spikes-and-waves, mental deficiency, and three seizure types: Myoclonic jerks, atypical absences, and head drops or falls, the latter successively described as *akinetic seizures*, *astatic seizures*, and finally *drop attacks*.

The further studies by Sorel[80] and Doose et al.,[25] and the MD dissertation of Dravet, published by Gastaut et al.,[33] allowed precise characterization of the electroclinical features of the syndrome. Different denominations were used over the years (including such complex ones as *childhood epileptic encephalopathy with diffuse slow spike-waves*) until the consensual denomination of *Lennox-Gastaut syndrome* was proposed by Margaret Buchtal-Lennox in 1966, in tribute to both the initial work of Lennox[57,58] and the thorough clinical description performed by the Marseille school. Further investigations included the long-term studies of large series reported by Oller Daurella,[69] Gastaut et al.,[34] Loubier,[60] Ohtahara et al.,[68] Beaumanoir,[11] and Chevrie and Aicardi.[18] Of particular interest from a clinical, genetic, and therapeutic perspective is the progressive delineation of LGS from other encephalopathic epilepsies like myoclonic astatic epilepsy (the Doose syndrome), severe myoclonic epilepsy of infancy (the Dravet syndrome), the syndrome of continuous spikes-and-waves during slow-wave sleep, and specific encephalopathies like the Angelman syndrome.

Definitions

In the International Classification of Epilepsies and Epileptic Syndromes,[20] LGS is classified among the symptomatic or cryptogenic generalized epilepsies. It is defined by several criteria:

a. Onset during childhood

b. Coexistence of several seizure types, with mainly atypical absence, axial tonic, and atonic seizures; the presence of tonic seizures during sleep is a constant feature; other seizures (myoclonic, generalized tonic–clonic, focal) can occur

c. Diffuse slow spikes-and-waves and bursts of fast rhythms at 10 to 12 Hz during sleep

d. Permanent psychologic disturbances with psychomotor delay, personality disorders, or both

The seizure frequency is high, and episodes of status are not uncommon. In the EEG, focal and multifocal abnormalities can be associated with the diffuse slow spikes-and-waves. These electroclinical features may occur in a previously normal child, without pathologic antecedents and without signs of brain lesion, usually between the ages of 1 and 8 years, and constitute the cryptogenic form of LGS. They also can occur in a child with prior signs of brain damage, sometimes in the wake of another type of epilepsy, such as infantile spasms or focal epilepsy, and constitute the symptomatic forms of LGS. In the latter cases, the range of ages at onset may be wider (between 1 and 15 years, rarely more).

In the 2001 proposal of the ILAE,[29] LGS was classified among epileptic encephalopathies, a category of epilepsies *in which the epileptiform abnormalities may contribute to progressive dysfunction.*

Epidemiology

Epidemiologic data on LGS vary greatly. Different criteria were used in selecting cases. Some studies have included all forms of severe childhood epilepsies associated with slow spikes-and-waves on the EEG. Others have restricted the criteria to those defined above. Its frequency has thus been estimated to range

from 3% to 10.7% of all cases of childhood epilepsies.[4,11,34] In the population observed in the Centre St. Paul, which specializes in the treatment of severe epilepsies, the figure is 3.7% in the whole population (children and adults) and 6.6% in patients with onset before age 10 (personal data from a prospective registry of all newly referred epilepsy cases seen between 1986 and 1996). A study performed in metropolitan Atlanta, GA, found a prevalence of 4% among children aged <10.[84] Another study performed in Finland found a yearly incidence of 2 per 100,000 of “broadly defined” LGS among children aged 1 to 14 years.[47]

There is no particular geographic or ethnic distribution. Boys are slightly more often affected than girls.[60,61,68] A closer look at patient registries would probably show that the incidence has declined in recent years, due to stricter diagnostic criteria, leading to other specific diagnoses and to changes in the early treatment of severe childhood epilepsies that may have avoided the progression of symptomatic cases into the full-blown LGS. In our recent experience, the incidence of LGS has been comparable to that of myoclonic astatic epilepsy and the Dravet syndrome.

Etiology and Basic Mechanisms

LGS can be symptomatic or cryptogenic. Numerous etiologies can be found in the symptomatic forms[12]: Perinatal anoxic ischemia; antenatal or perinatal vascular accident; antenatal, perinatal, or postnatal cerebral and cerebromeningeal infection; HHE (hemiconvulsion-hemiplegia-epilepsy) syndrome; both diffuse and lateralized or even focal brain malformation and migration disorders; tuberous sclerosis, Down syndrome, hydrocephalus, head trauma, brain tumor and radiotherapy for brain tumor, and many others. There are numerous publications on uncommon etiologies, and a sample may be quoted here to underline the etiologic heterogeneity of this syndrome. LGS may, for instance, occur following chemo- and whole-brain radiotherapy for acute lymphocytic leukemia[63]; in an encephalitic form of neurocysticercosis[1]; or in common variable immunodeficiency with acute disseminated encephalomyelitis.[53]

In some cases, despite psychomotor retardation before the onset of seizures or of mild to moderate, nonspecific cerebral atrophy demonstrated by computed tomography (CT) and magnetic resonance imaging (MRI), there is no recognizable etiology. When epilepsy starts in the first year of life, it is often in the form of infantile spasms, followed by LGS. Otherwise, LGS can be preceded by focal seizures, or all the features of LGS may be manifesting at onset or soon thereafter. It must also be stressed that the typical features of LGS can be observed only transiently in some patients.[11] In the cryptogenic forms, there is no etiology by definition. However, "cryptogenicity" may depend on the amount of investigation, and this category may have shrunk since the availability of MRI. Some authors have been enticed to subdivide LGS patients in three categories: Symptomatic, noncryptogenic, and cryptogenic, the latter category referring to individuals with strict criteria of normal development, lack of dysmorphism, and normal MRI[41]: Using such criteria, these authors found no difference in seizure outcome between these etiologic categories.

The mechanisms underlying LGS are not well understood. In 1987, Theodore et al.[82] used positron emission tomography (PET) to investigate the cerebral metabolism of ten patients, and Chugani et al.[19] that of five, without considering the various etiologies. Their results appear too heterogeneous to be significant. Microscopic studies of samples obtained at autopsy and brain biopsy from 15 patients were reported by Roger and Gambarelli-Dubois.[75] Selective neuronal necrosis was observed in the neocortex, hippocampus, thalamus, and cerebellum, but in eight cases the necrosis was restricted to the cerebellum. Electron microscopic examination of biopsy material from eight patients showed that neuronal loss occurred mainly at postsynaptic sites. Quantitative analysis confirmed the rarefaction of cortical dendrites and synaptic contacts. In two cases studied by Renier,[73] there were a few swollen astrocytes around the neurons in the deeper cortical layers, poor dendritic arborization, and disturbed synaptic development of the pyramidal cells restricted to the inner cortical layers. He hypothesized that these findings were the origin and not the consequence of LGS, and were perhaps related to an autoimmune process. A virologic and immunologic approach was adopted by Smeraldi et al.,[79] but the results of their studies were not significant. Eeg-Olofsson[28] discussed the relationships between a genetic defective immune mechanism and the occurrence of LGS.

Genetic factors do not seem to play a major part in LGS, and no multiplex families with LGS have been reported. The frequency of cases with a family history of epilepsy ranges from 2.5%[18] to 28%.[60] Boniver et al.[16] noted that 48% of patients with cryptogenic LGS had a family history of either epilepsy or febrile convulsions, but their series may have included patients with myoclonic astatic epilepsy. Interestingly, no case of LGS has been reported in large generalized epilepsy with febrile seizures plus (GEFS+) families, which include patients with Dravet syndrome or myoclonic astatic epilepsy. Among genetically determined cortical brain malformations, LGS may occur in patients with micropolygyria and in those with the XLIS mutation, which causes subcortical band heterotopia in females and pachygyria in males. In the latter example, the occurrence of LGS seems to be correlated with the thickness of the band or severity of pachygyria.[42]

The neurophysiologic processes leading to the production of interictal EEG changes and seizures in LGS have received some attention. Processes related to those occurring in idiopathic generalized epilepsies play a limited part, since abnormal sleep patterns found in patients with cryptogenic LGS seem to originate outside the usual thalamocortical circuit.[88] Secondary bilateral synchrony (SBS), which is of cortical origin, appears to be at the origin of the apparently generalized EEG changes: In their study comparing myoclonic seizures found in LGS and in (truly idiopathic) myoclonic astatic epilepsy, Bonnani et al.[15] convincingly demonstrated propagation from a lateralized origin in LGS. There is no satisfactory explanation for the genesis of this abnormal tendency to SBS and related inhibition of function, but this phenomenon clearly plays a major part in the genesis of both seizures and cognitive impairment. The occurrence of the LGS at a crucial stage of neurodevelopment is of course a major factor of the learning difficulties and progressive retardation, and Blume[14] has hypothesized that the intensity of interictal and ictal discharges diverts the brain from normal developmental processes toward seizure control mechanisms.

In the light of recent data, LGS appears to be an acquired, nonspecific, age-dependent diffuse encephalopathy, occurring without specific familial predisposition, and the reason why it appears in either normal or brain-damaged patients is not known.[12] There is evidence of major focal factors, related to the frontal lobes, but these coexist with a predisposition to bilateral synchrony, which accounts for most of the clinical features. Until we know more, this epileptic encephalopathy should thus still be ranked among the "generalized" syndromes.

Clinical Presentation

The onset is before the age of 8, with a peak between 3 and 5 years. Onset after age 10 is unusual. In cryptogenic cases,[16] the first seizures can be myoclonic, atypical absences, or falls, sometimes repeated in status. Sometimes, an isolated seizure—tonic, clonic, tonic–clonic, or even a unilateral seizure—has preceded the typical seizures by several months. Nocturnal tonic attacks are usually not observed at the very onset. Psychological and cognitive disturbances can be concomitant with the first seizures or can develop later, insidiously. Thus, it is not easy to make the diagnosis of LGS very quickly. The EEG features at onset can consist of either diffuse slow spikes-and-waves or only more or less diffuse slow waves. A single case study of nocturnal sleep at this stage has been published,[21] demonstrating the presence of bursts of low-voltage rapid rhythms evoking subclinical tonic seizures. When LGS follows infantile spasms, there are two possible modalities: Either infantile spasms are replaced by tonic seizures without a free interval, or infantile spasms disappear and both the EEG and the psychomotor development improve for some time before falls, atypical absences, and diffuse slow spikes-and-waves appear, accompanied by a new slowing of development. When LGS complicates other types of epilepsy, the diagnosis is marked by the onset of falls and behavioral/cognitive changes. Several authors have reported the occurrence of LGS in adolescents and young adults who previously had an idiopathic type of generalized epilepsy.[59,68,74]

Interictal Symptomatology

The neuropsychological and psychiatric symptoms consist of arrest or slowing of psychomotor development, apparent deterioration of cognitive abilities, and appearance of psychiatric conditions, the expression of which depends on age. The youngest children are seen with physical and intellectual instability, mood lability, inability to acquire new skills, and progressive disharmony. Older children exhibit slowness of ideation and expression; language deterioration resulting from motor dysfunction, particularly changes in muscular tone of the orolaryngopharyngeal area[10]; aggression; irritability; loss of social relationships; tendency to isolation; and sometimes psychotic outcome. Personality disorders are always present in the cryptogenic forms.[89] There are no neurologic signs that can be considered specific to LGS, apart from transient cerebellar, pyramidal, or extrapyramidal signs during prolonged status. However, in some patients the recurrent episodes of status are so long and so frequent that this semiology can become permanent after more than 10 years of evolution. Iatrogenic factors may contribute to neurologic deterioration.

On the EEG, the background can be disorganized, with diffuse slow waves, poor reactivity, and lack of topographic differentiation. Such disorganization can be permanent (67% of patients) or transient, appearing only during periods of worsening of seizures. Constant disorganization is a sign of poor prognosis. Hyperventilation can elicit slow spike-and-wave discharges with or without clinical correlates (atypical absences), whereas intermittent photic stimulation has no effect. Paroxysmal changes are frequent, with discharges of diffuse slow spikes-and-waves and slow polyspikes-and-waves. In 75% of children, they are associated with focal and multifocal changes (spikes, slow spikes, slow spikes-and-waves), with constant or variable focalization, frequently frontal or temporal. They are increased during slow sleep, when the diffuse slow spikes-and-waves become more synchronous and rhythmic, with prominent polyspikes. During sleep, specific bursts of fast rhythms appear (see below). The differentiation of sleep stages can be preserved or can be blurred[7] (Fig. 1).

Ictal Symptomatology

In order of decreasing specificity, LGS, a disorder associated with multiple seizure types, includes tonic seizures, atypical absences, atonic seizures, and other types. Both tonic and atonic seizures may cause falls.

Tonic seizures are the main feature of the syndrome and are reported in 74%[11,34] to 90%[60] of patients. They can be axial, axorhizomelic, or complete, and symmetric or markedly unilateral. They can occur while patients are awake or asleep. The neck and body are suddenly flexed, the shoulders and arms are raised in a semiflexed or extended position, the legs are extended, the facial muscles (sometimes only of the lower lip) contract, and the eyes roll up. Apnea and facial flushing are apparent. The victim may fall suddenly. Loss of consciousness does not always occur and is rarely the initial symptom. Return to normal consciousness always coincides with the end of the EEG discharge. Enuresis can occur. The pupils are usually dilated. When these seizures are short and involve only rolling of the eyes and respiratory changes (which is usually the case during sleep), they may remain unnoticed. When they last for more than 10 seconds, they can culminate in a tremor that affects the whole body (resulting in a "vibratory" seizure). In tonic–automatic seizures, described by Oller Daurella[70] in 72% of late-onset cases, there is a final phase of gestural, sometimes ambulatory automatisms. Slow-wave sleep facilitates the occurrence of tonic seizures. The EEG during tonic seizures (Fig. 2) consists of either a bilateral discharge of fast rhythms, predominantly in the anterior areas and at the vertex, or a flattening of the background, or a combination of these two patterns, sometimes preceded by generalized spikes-and-waves, followed by diffuse slow waves and slow spikes-and-waves, that last longer in patients with "tonic–automatic" seizures. There is no postictal silence. The fast discharges are particularly common during slow-wave sleep, when they can be nearly subclinical. Gibbs[38] inappropriately described this ictal pattern recorded during sleep as the *grand mal pattern*.

Atypical absences are observed in a vast majority of patients. Clinically, they are often difficult to diagnose: The onset and end are gradual, contact is impaired but not completely lost, a simple activity can be continued, eyelid myoclonus is not rhythmic, perioral myoclonus is frequent, and slow forward motion of the head caused by loss of tone, as well as drooling, is also frequent. In the EEG, atypical absences are associated with often irregular, more or less symmetric discharge of diffuse slow spikes-and-waves at 2 to 2.5 Hz (Fig. 3), or with a burst of rapid rhythms, or with a mixed pattern.

Atonic, myoclonic-atonic, and myoclonic seizures are not easy to differentiate by clinical observation alone. Most authors group these seizures with falls under the name of *akinetic* or *astatic* seizures,[32] or *drop attacks*. They may provoke a sudden fall, either of the head only or of the whole body, which may cause injuries. This is followed by an immediate recovery (there may, however, be loss of consciousness and progressive recovery in case of significant head concussion). The EEG correlates are polymorphous: Slow spikes-and-waves, slow polyspike-and-waves, and decremental events. The simultaneous video-EEG and polygraphic recordings allow an accurate characterization of the seizure type. They occur together in the same patient in 95% of cases.

Other seizure types, not specific for LGS, can be observed: Generalized tonic–clonic, generalized clonic, and focal seizures. Reflex seizures may be seen in some cases, like seizures provoked by eating[56] or, more commonly, in Down syndrome patients with LGS, in whom a "startle" reaction may trigger tonic seizures or atypical absences.[43]

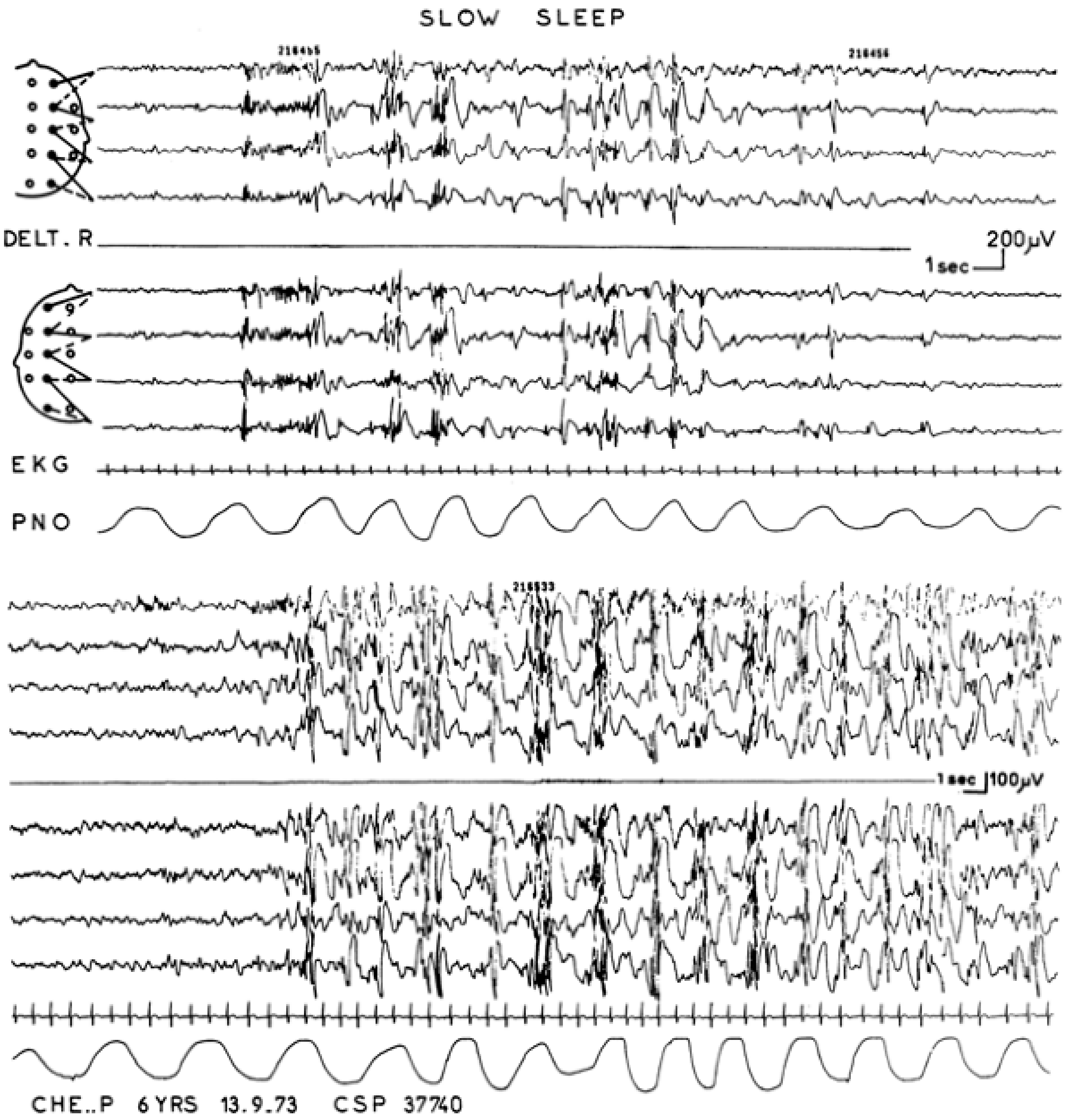

FIGURE 1. Electroencephalographic recording during sleep in cryptogenic Lennox-Gastaut syndrome. **Top:** Typical bursts of subclinical rapid rhythms, variable in amplitude and duration, recorded with decreased amplification. **Bottom:** Other runs of rapid rhythms recorded with the normal gain, accompanied by a slight change in respiration. DELT R, right deltoid; PNO, pneumogram.

All the seizure types occur as status in a majority of patients (54%,[60] 75%[11]). Status consists of periods of more or less profound obtundation/stupor, intermixed with serial tonic attacks, sometimes with myoclonic–atonic falls. When tonic attacks are predominant, they constitute a tonic status. The main characteristics of status episodes are their long duration

(days to weeks), resistance to treatment, and tendency to occur repeatedly. During status, the EEG becomes almost hypsarrhythmic. It has been suggested that this represents only a temporary worsening of the usual interictal symptomatology.[11,26] The occurrence and frequency of nonconvulsive status is considered to contribute to the poor cognitive outcome of LGS.[48]

Clinical Variants

In the myoclonic variant of LGS, which represents 18% of the cases of Chevrie and Aicardi,[18] massive myoclonus and myoclonic–atonic attacks are the prominent seizure types. Tonic seizures are mainly nocturnal, and epileptic status is characterized by stupor and myoclonus. The awake EEG is not different from the typical form, but there are fewer runs of rapid rhythms during sleep. This myoclonic variant is cryptogenic in 64% of cases, and its mental prognosis is more favorable. Probably some of the patients reported to have “myoclonic LGS” in the literature actually had myoclonic astatic epilepsy.[24]

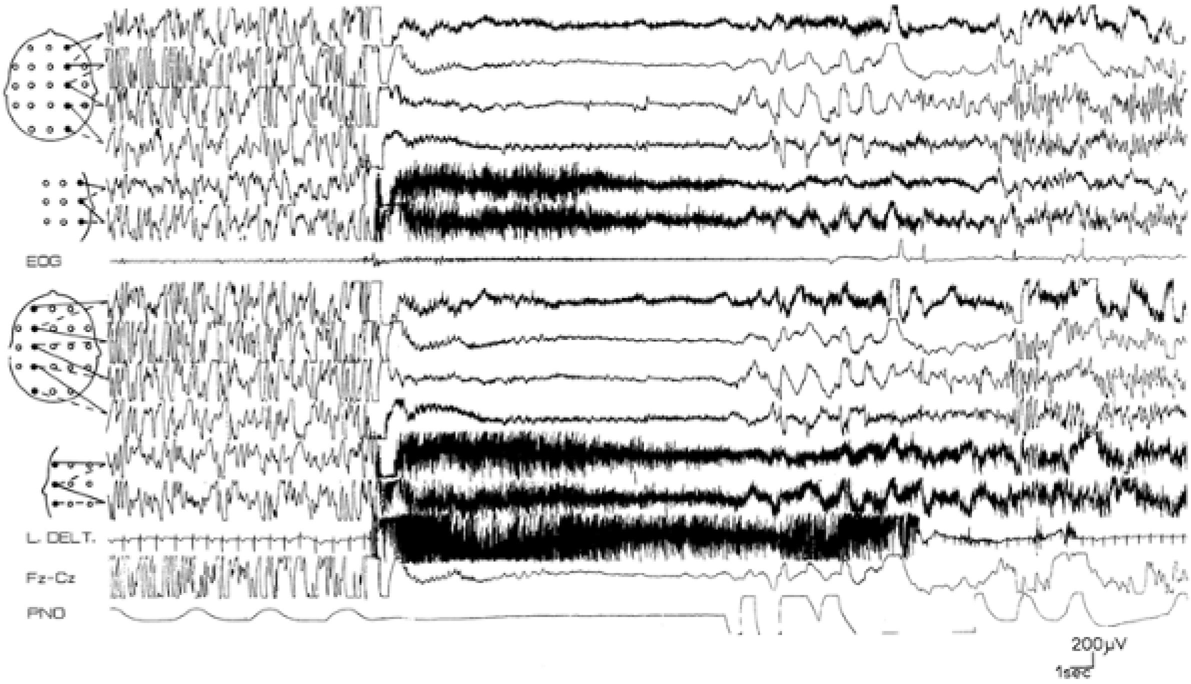

FIGURE 2. Awake recording of a tonic seizure in a boy with symptomatic Lennox-Gastaut syndrome. Interictal slow spikes-and-waves are abruptly interrupted by flattening, with superimposed rapid rhythms and muscular artifacts, for 15 seconds, followed by diffuse slow waves and then a burst of sharp waves. Polygraphy shows intense tonic contraction of the deltoid and apnea. (Note the decreased recording amplification used here.) EOG, oculogram; L DELT, left deltoid; PNO, pneumogram.

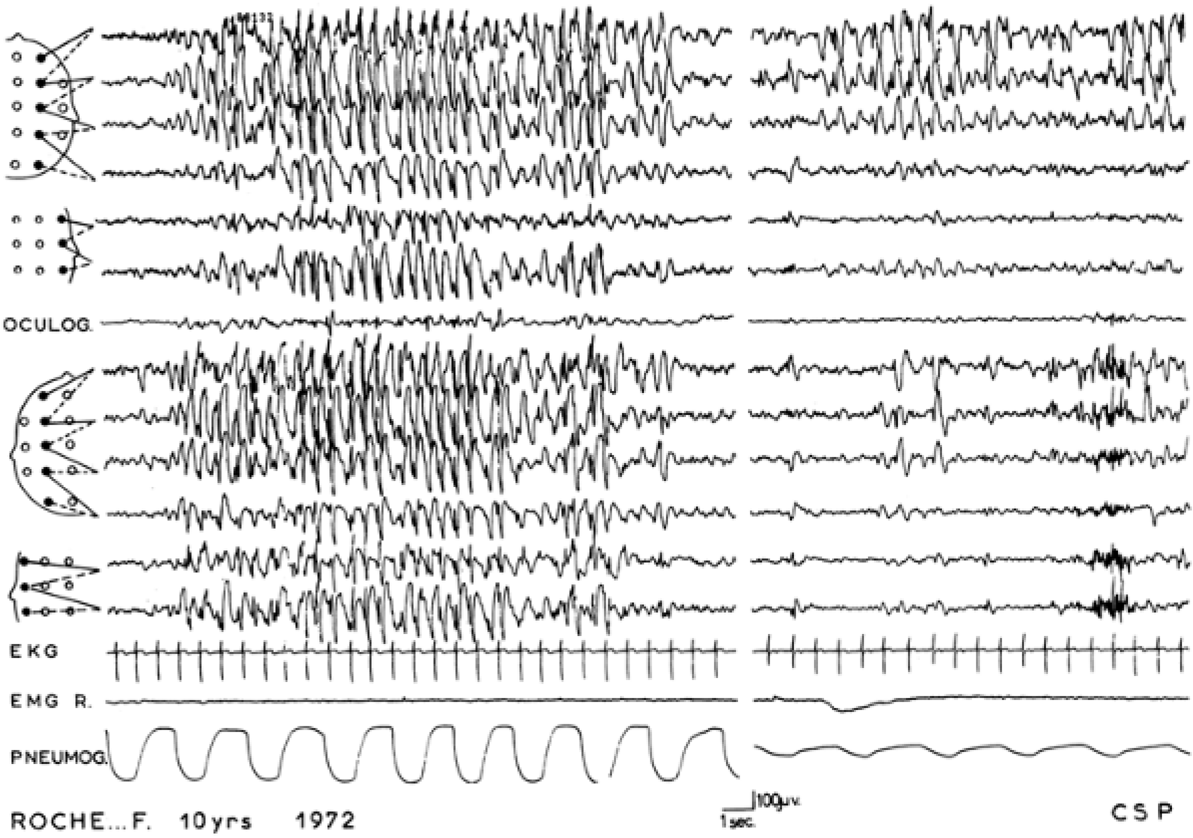

FIGURE 3. Left: Atypical absence with asymmetric, irregular, slow spikes-and-waves. **Right:** During slow sleep, one burst of frontal slow spikes-and-waves in the right hemisphere and a burst of rapid rhythms in the left hemisphere. In this girl, Lennox-Gastaut syndrome was preceded by partial seizures. EMG R, electromyogram of right deltoid.

Late-onset LGS has been studied by Oller Daurella,[69] Bauer et al.,[9] and Roger et al.[74] These authors have distinguished between LGS following idiopathic generalized epilepsy, LGS following partial epilepsy, and LGS appearing initially as the typical cryptogenic syndrome. The age of onset is usually between 10 and 20 years but in some cases was between 20 and 30 years. Patients with Down syndrome will usually initiate LGS with reflex seizures, between the ages of 8 and 12 years.[43] The clinical characteristics of late-onset LGS are the presence of tonic–automatic and generalized tonic–clonic seizures in addition to drop attacks and atypical absences. The psychologic features are mainly ideomotor slowness and psychotic change of personality. In the EEG, slow spikes-and-waves are often associated with fast spikes-and-waves.

Diagnostic Evaluation

The diagnosis of LGS is based on electroclinical findings, which must be carefully collected. A precise description of seizures must be obtained so that atypical absences and nocturnal tonic seizures can be detected. A sleep EEG must be performed, and an afternoon sleep recording after partial sleep deprivation is usually sufficient. If the results are not informative, the EEG must be repeated, as the whole clinical and EEG picture can establish itself progressively over time. Given the subtle nature of atypical absences and sometimes of the atonic or tonic seizures, polygraphic recording with axial EMG leads is compulsory, and the importance of video-EEG monitoring has been stressed.[8] Simultaneous etiologic investigations (neurocognitive, fundus, MRI, biology) help distinguish symptomatic from cryptogenic cases.

Criteria for an early diagnosis were proposed by Boniver et al.[16] Existence of one or several seizures typical for the syndrome, presence of diffuse slow spikes-and-waves in the EEG, and cognitive impairment were considered major criteria; high frequency of seizures, drug resistance, and atypical seizures were considered minor criteria. The presence of at least two major criteria during the first 6 months of the epilepsy was strongly predictive of the diagnosis.

During the course of the disorder, the diagnosis rests on the demonstration of tonic seizures or subclinical runs of fast rhythms at 10 to 12 Hz during sleep, not on the presence of diffuse slow spikes-and-waves alone. Thus, at least one EEG must be recorded during sleep. The best way to confirm the diagnosis is to make a long video and polygraphic EEG recording with the patient awake and engaged in some activities, and again with the patient asleep (recording during an afternoon nap may be sufficient), so that interictal and ictal patterns can be studied. It is also necessary to follow the psychomotor and cognitive development of the child by the appropriate psychometric testing in order to react quickly to special educational needs.

Differential Diagnosis

Diffuse slow spikes-and-waves do not constitute a sufficient criterion for the diagnosis of LGS; they can appear secondarily during the course of other types of epilepsy,[59] as reported by Beaumanoir[11] in 38 of 103 patients seen with severe epilepsy resembling LGS. They can also be observed in cases of idiopathic generalized epilepsies modified by iatrogenic factors, and in other specific settings like the Angelman syndrome, which should be easily recognizable. A multiple seizure-type disorder with cognitive decline like the Dravet syndrome (severe myoclonic epilepsy in infancy) should not be confused with LGS, due to its own many specific diagnostic features. The main characteristics of encephalopathic epilepsies of childhood are summarized in Table 1.

The main nosologic and clinical problems involved in the differential diagnosis of LGS are different in cryptogenic and symptomatic forms, and depend partly on age at onset.

For cryptogenic LGS, the main differential diagnosis is myoclonic astatic epilepsy of early childhood (MAE, Doose syndrome), which has often been poorly separated from LGS, especially in patients with MAE and an unfavorable course, which may be associated with tonic seizures during sleep.[24] Contrary to LGS, MAE is a truly idiopathic type of epilepsy, with a strong genetic component. An in-depth clinical evaluation[52] has stressed the differential features of MAE, all of which are apparent within 1 year from seizure onset: A family history of idiopathic epilepsy, earlier onset, fast spike-and-waves, and myoclonic and generalized tonic–clonic seizures are markers of a benign type of MAE with good outcome. Additionally, children with MAE may exhibit myoclonic status, vibratory tonic seizures, and marked slow components on the EEG, and may have a less favorable outcome. In this series, patients with a final diagnosis of LGS had atypical absences, no vibratory tonic seizures, no myoclonus, and a later age at onset, and all experienced mental degradation. Neurophysiology may also help in this differential diagnosis, with the evidence, on back-averaging studies of the EEG correlates of myoclonus, of SBS in the LGS versus a truly generalized aspect in MAE.[15]

Another condition has long been confused with LGS: Epilepsy with continuous spikes-and-waves during slow sleep (CSWS). Like LGS, CSWS, first described by Patry et al.,[71] can occur in children who were previously normal or already retarded, and in children with brain lesions or with normal MRI. It can succeed to partial or generalized epilepsy. It is characterized by atypical absences, drop attacks, mental deterioration, and diffuse slow spikes-and-waves in the EEG, especially pronounced during sleep. However, children with CSWS never have tonic seizures, either awake or during sleep, nor are runs of rapid rhythms or subclinical tonic seizures apparent in their sleep EEG. The typical sleep EEG pattern is one of continuous diffuse slow spikes-and-waves, which occupy at least 85% of slow sleep and are fragmented during rapid eye movement (REM) sleep. This pattern also occurs in children with acquired aphasia with auditory agnosia (Landau-Kleffner syndrome), which is not observed in patients with LGS. In CSWS, the epileptic seizures and EEG changes are strictly age related and always disappear at the latest during puberty.

Atypical benign partial epilepsy, described by Aicardi and Chevrie,[2] is difficult to diagnose at first, because it differs from CSWS only by its outcome and the absence of mental deterioration. It can be confused with LGS when electroclinical symptomatology worsens. At this stage, it is essential to look for factors that might explain these changes, such as inappropriate treatment or intercurrent disease, and to perform sleep EEG recordings to demonstrate the absence of tonic seizures and fast activities. This type of childhood epilepsy clearly overlaps with benign epilepsy with centrotemporal spikes and with CSWS. In the German-speaking area, the term of “pseudo-Lennox” syndrome is often used, even recommended, to describe such patients.[45]

There are severe focal epilepsies, usually of frontal lobe origin, in which seizures consist of sudden falls that resemble the drop attacks observed in the generalized epilepsies. However, in these disorders the electroclinical symptoms do not mimic those of LGS. In some cases, however, the diagnosis of focal epilepsy with SBS must be considered, to the point that the diagnosis may fluctuate between focal epilepsy with SBS and LGS at various moments during follow-up, as some age-dependent traits of LGS may disappear with maturation or may become less prominent due to medication.

Table 1 Distinctive Features of Encephalopathic Childhood Epilepsies

	Age at onset	First seizure	Other seizures	EEG changes	Mental outcome
LGS	2–8 yr	Variable	Falls Tonic, atonic Atypical absence Other (GTC, focal) Frequent status	Abnormal BA Slow SW 10–12 activities during sleep Multifocal changes	Abnormal
MAE	1–5 yr	Myoclonic, myoclonic astatic	Falls, GTC Myoclonic Atonic Obtundation state	Normal BA Centroparietal theta Generalized SW	Normal or abnormal
SME	<1 yr	Febrile clonic	Clonic, GTC, unilateral, Pseudogeneralized Myoclonic, absence, other	Normal BA at onset Multifocal Photosensitivity	Abnormal
ABPE	3–8 yr	Partial	Falls, focal Atypical absence neg. myoclonus	Normal BA Focal and diffuse	Normal

ABPE, atypical benign partial epilepsy; BA, background activity; GTC, generalized tonic–clonic; LGS, Lennox-Gastaut syndrome; MAE, myoclonic-astatic epilepsy; SME, severe myoclonic epilepsy; SW, spike-and-wave.

The concept of SBS was introduced by Jasper[51] and Tükel and Jasper.[85] SBS was described as bursts of high-amplitude, synchronous, slow spike-and-wave complexes, more or less symmetric over both hemispheres, caused by a unilateral epileptogenic lesion of the mesial surface of the frontal or temporal lobe. SBS is contrasted with *primary* bilateral synchrony, which is manifested by more rapid symmetric and synchronous spike-and-wave discharges over both hemispheres and is caused by a generalized epileptic process independent of any focal hemispheric lesion. Many authors have discussed this concept. Gastaut and Zifkin[35] and Blume[13] tried to establish the differences between epilepsy with SBS and LGS. According to the former, epilepsy with SBS begins later (mean age of onset, 10 years and 9 months); focal neurologic signs are much more frequent (hemiplegia in 30% vs. in 9% of those with LGS); obvious mental retardation is less frequent (35% vs. 87%); seizure frequency is lower; multiple seizure types are less often present in the same patient; partial seizures are more frequent; astatic seizures are less frequent; atypical absences are not observed; bursts of slow spikes-and-waves are more often asymmetric (50% vs. 23%); a constant, localized epileptic focus is seen in all cases of epilepsy with SBS versus a rather variable localized predominance of slow spikes-and-waves in LGS; and runs of rapid recruiting rhythms in slow sleep are less frequent (15% vs. 79%). The same EEG aspects were described by Niedermeyer et al.[65] in cases of severe head trauma associated with generalized tonic–clonic and complex partial seizures. Lesions are mainly frontal and temporal, and SBS can be the significant mechanism in such posttraumatic epilepsies. Epilepsy with SBS can be as severe as LGS. It is, however, important to recognize this situation, because surgery may be the treatment of choice in epilepsy with SBS— with either removal of the primary lesion when possible or callosotomy. Thorough functional imaging investigations can help determine the diagnosis and indication for surgery. Indeed, a study using ^{18}F-fluorodeoxyglucose (FDG)-PET in children with epileptic encephalopathies showed the absence of abnormal focal findings in five children with cryptogenic LGS, while focal changes were present in three fourths with an atypical LGS, and five sixths in LGS following infantile spasms.[30] It is clear that there is no tight border between LGS and epilepsy with SBS, especially in symptomatic, lesional cases.

Treatment

LGS is highly drug resistant. Classic antiepileptic drugs (AEDs) usually do not bring total seizure control, and the "gold standard" of monotherapy can seldom be applied.[12] Polytherapy, with a combination of drugs respectively active against the main seizure types, is the rule. A mixed seizure disorder with frequent attacks that requires polytherapy, like LGS, is a likely candidate for paradoxic aggravation of seizures,[37] and this phenomenon may escape attention due to the subtle character of seizures, to the unlikelihood of self-reporting, and to the spontaneously fluctuating course of the condition. Drugs that may aggravate typical absences are likely to increase atypical absences as well as myoclonic or astatic seizures. Specific aggravation has been described in LGS following the use of IV clo-nazepam, which may induce tonic status,[81] and following the use of gabapentin,[90] but these reports concern only the tip of the iceberg. Clinicians should thus remain acutely aware of the possibility of drug-induced aggravation in patients with LGS. Moreover, unwanted side effects of AED are more likely to occur in LGS, due to polytherapy and use of high daily doses, and they may be overlooked because of the spontaneous severity of the condition and the lack of adequate communication with the patient. Clinicians should also be aware of this. Recent considerations about treatment attitudes have stressed that individual risk–benefit considerations should apply.[77] Overtreatment is probably common, and may contribute in part to the unfavorable long-term evolution. Treatments used in LGS include classic MAE, recent MAE, and nonpharmacologic treatments like the ketogenic diet, vagus nerve stimulation, and surgery.

Among the classic AEDs, carbamazepine, valproate, and benzodiazepines are often used, mostly in combination. Despite their metabolic interactions, carbamazepine and valproate give interesting results when given in combination. Carbamazepine (like phenytoin) is effective against tonic seizures, but may increase absences, while valproate (like ethosuximide) is effective against atypical absences and myoclonic or atonic seizures, but has little effect on tonic seizures. Clobazam and nitrazepam have fewer side effects than clonazepam and may need to be prescribed alternatively because tolerance may occur. Nitrazepam, which has been recommended by the Marseille

school in the treatment of LGS nearly 40 years ago, is seeming to enjoy a revival, with estimated responder rates above 50% and few side effects besides sedation and drooling.[49] Phenyt-oin can be used in adolescents and adults for the vibratory tonic and tonic–clonic attacks, and is often initiated during a tonic status.

Ethosuximide can also help control the atypical absences.

Among the newer AEDs, vigabatrin has not proved very useful. However, it is worth trying, and some good results have been reported in LGS associated with cortical dysplasia.[44] La-motrigine has proven efficacy in open studies[23,83] and in controlled trials,[64] apparently mostly when used in combination with valproate, which matches our own experience. Felbamate retains selective indications in LGS, with proven efficacy,[6] and a favorable effect on cognitive function and behavior[36]; its efficacy may be due in part to its combination with valproate.[78] Topiramate has been proven efficacious, especially against drop attacks, both in open-label, long-term studies[40] and in shorter controlled trials.[76] However, its efficacy is less prominent in LGS than in other epileptic encephalopathies like the Dravet syndrome.[62] There is a single study alluding to a possible positive effect of levetiracetam in LGS, especially against myoclonic and generalized tonic–clonic seizures, without effect, however, on tonic seizures.[22] Zonisamide has been used for more than 15 years in Japan, and is considered appropriate for use in LGS.[67] Among AEDs still in development, rufinamide has received an orphan drug designation in Europe for patients with LGS.[5]

The course of the disease is characterized by a succession of bad and better periods. During the better periods, only nocturnal seizures are observed, and patients are less handicapped in their daily life. But series of tonic seizures can occur suddenly, without obvious reason, particularly in the early morning. Even when epilepsy has improved, cognitive impairment and behavioral disturbances persist, requiring educational and psychological support. The degree of mental deficit is variable, from slight to profound. In cryptogenic cases, it increases with age and repetition of seizures, but it is less marked than in symptomatic cases.

One of the aims of treatment is to avoid episodes of status. Sometimes they are provoked by triggering factors, such as intercurrent illness, changes in drug regimen, and psychological stress.[26] In case of impending status, it is better not to change the treatment dramatically and not to hospitalize the patient in a nonspecialized unit. Rectal injections of diazepam or oral intake of a high dose of clobazam (30 to 40 mg) can stop serial attacks and avoid hospital admission. Overt status can be treated with IV benzodiazepines and/or phenytoin, sometimes with concomitant steroids, and with respiratory assistance if necessary. It must be noted that status is much less life threatening in LGS than in other types of epilepsies. Recovery is relatively swift. Steroids may be tried in children early in the course of the disease, as in infantile spasms.

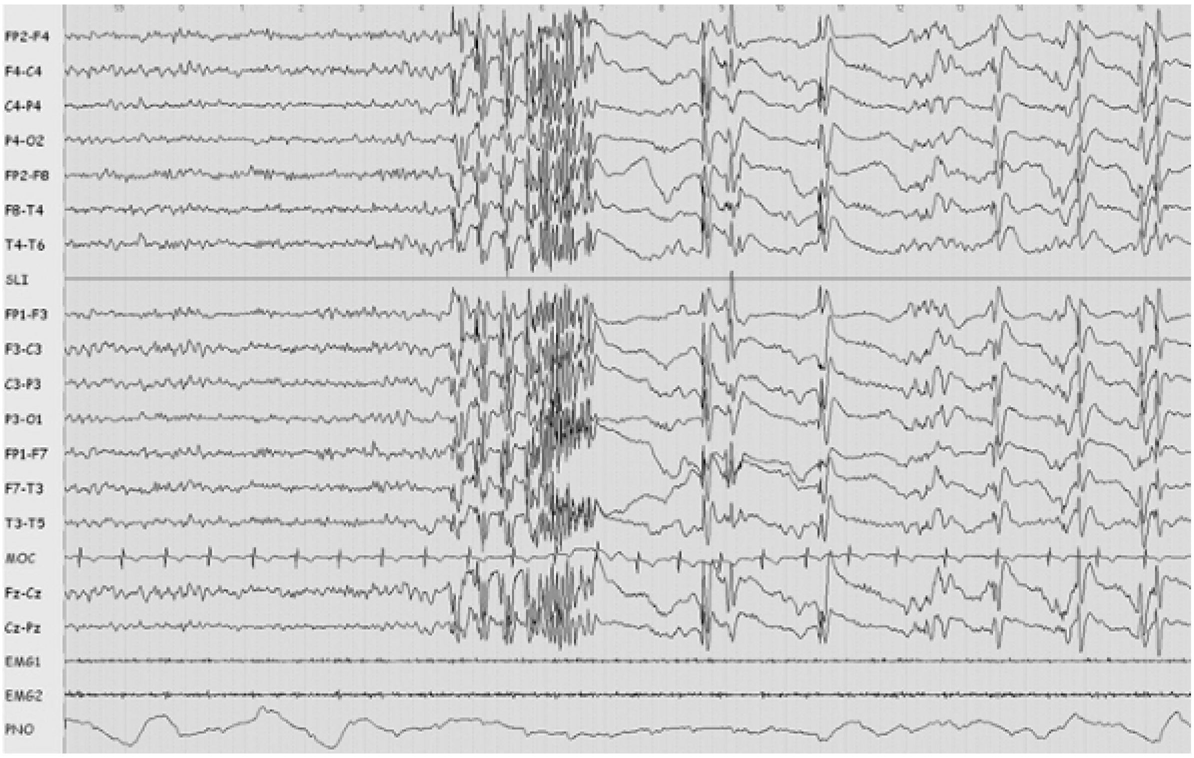

FIGURE 4. Sleep electroencephalogram (EEG) in a 48-year-old patient with cryptogenic Lennox-Gastaut syndrome since the age of 5. She lives in a home for the handicapped and has part-time sheltered employment. She still has several falls per month, atypical absences, and frequent nocturnal tonic seizures (usually several per night), with rare generalized tonic–clonic seizures. She receives a combination of valproate, felbamate, phenobarbital, and clobazam. Her waking EEG shows normal background *α* activity and is devoid of paroxysmal changes (not shown). During an afternoon sleep recording, there were few physiologic sleep transients and numerous high-amplitude bursts of fast activities, as well as suppressions and isolated spike-waves.

Other treatments have been used in LGS, without controlled trials. IV *γ*-globulins have been proposed,[17] as has thyrotropin-releasing hormone.[54] The ketogenic diet has been used, but not in controlled trials.

Surgical procedures are not often considered as treatment options. Callosotomy brought significant seizure relief to 31 of 48 (64.6%) patients with LGS,[55] but is reputedly less efficacious than in focal epilepsies with SBS. There are only isolated reports on successful lesional surgery in patients with focal brain pathology and LGS.[27] Conversely, vagal nerve stimulation (VNS) has been used quite extensively in LGS, and is considered well tolerated. A Dutch study showed marked cognitive improvement, which did not correlate with the modest effect on seizures (26.9% average seizure reduction).[3] This contrasts with the 52.2% seizure reduction observed in a U.S. study,[50] in which 3 of 13 patients reached a 90% reduction in seizure frequency. Indeed, the response may increase over time, with seizure reduction of 42% at 1 month, 58.2% at 3 months, and 57.9% at 6 months.[31] Stimulation procedures differing from VNS, especially deep brain stimulation, have been tried in selected patients,[88] apparently with some positive results against atypical absences and tonic seizures.[86,87] Modern recommendations are that the baseline treatment for LGS should rely on valproate, benzodiazepines, and either lamotrigine or to-piramate as second-line add-ons,[77] with the valproate + la-motrigine or valproate + topiramate probably representing the most logical, synergistic combinations. They carry their own risks, cumulating the potential side effects of either drug with the specific side effects of these combinations. According to a recent Cochrane review, none of the recent AED has shown spectacular power against LGS, and each case should be considered individually.[46] Indications for nonpharmacologic treatments should also be assessed individually. The multiplicity of therapeutic proposals does not really mask—and indeed, rather underlines—the relative impotency of medical intervention in LGS. Practical management is also a matter of common sense and restraint.

Long-term Prognosis

As stressed by all authors who have studied this syndrome, its long-term prognosis is unfavorable, and it is too soon to know whether it will be improved by recent advances in epilepsy treatment. Unfortunately, the availability of many new treatment options has not changed the global outlook for patients with LGS, in contrast with the apparently improved prognosis of MAE and Dravet syndrome.

Complete seizure-free recovery is rare: 13.7% of patients for Ohtahara et al.,[68] 6.7% for Gastaut et al.,[34] and none of the cryptogenic cases followed up for more than 15 years by Beaumanoir.[11] Among 72 patients followed over more than 10 years, 33% of the cryptogenic and 55% of the symptomatic cases had lost the characteristics of LGS, turning into nonspecific generalized symptomatic epilepsies, severe epilepsy with multiple independent spike foci, or localization-related epilepsies.[66] In another long-term study, with an average follow-up of 16 years, only 33% of 102 patients retained LGS.[91] Few studies have considered the epilepsy outcome in adulthood. Roger et al.[74] reported that only 47% of patients maintained a complete LGS profile in adulthood. Most had cryptogenic LGS with an onset before the age of 4 years. In 16%, generally those with symptomatic LGS, the syndrome as such disappeared, but an often severe, mostly unifocal epilepsy persisted, together with symptoms of frontal lobe dysfunctions. In 20%, seizures were rare, probably partial, but gross psychological disturbances were present. In 17%, epilepsy seemed to be nearly completely cured, with a normal or subnormal mental state. Rai et al.[72] reported on 17 patients institutionalized in an epilepsy center for a period of 16 years. The severity of epilepsy decreased even though the seizure types remained more or less unchanged. However, an attempt to reduce polytherapy failed, and a global improvement was observed only in three patients who had a relatively late onset of LGS between ages 5 and 10.

Mental deficiency is observed in 85% to 92% of patients. Major changes in behavior may occur at adolescence, with onset of violence, often directed against close family members. Frequently, but not consistently, patients become psychotic. Many patients are finally institutionalized, either in centers for epileptic patients or in homes for mentally handicapped people. Some children who are absolutely normal before the onset of cryptogenic LGS have a relatively good social outcome, with normal or near-normal schooling, and reach employment (often in a sheltered context) despite persisting seizures. The EEG features often attenuate with age, but some patients will retain

the full-blown LGS symptomatology, including the typical EEG traits, especially during sleep (Fig. 4), while awake EEGs may show only a slow background without slow spike-and-wave discharges.

Death is caused by intercurrent disease or accident, rarely by epilepsy itself. The mortality rate is difficult to assess: About 3% in the series of Gastaut et al.[34] with a mean follow-up of 8 years and 7 months, and 7% in that of Loubier[60] with a mean follow-up of 9 years and 9 months.

The main factors for a poor prognosis are the symptomatic nature of the syndrome, particularly after infantile spasms; early age at onset, before 3 years; high frequency of seizures; long duration of worsening periods; frequent status; and the presence of constantly slow background activity and multifocal localized abnormalities on the EEG.

Summary and Conclusions

Lennox-Gastaut syndrome is a well-defined epilepsy syndrome that can be easily recognized using a careful clinical and EEG approach and applying consensual diagnostic criteria. It is still overdiagnosed due to the prevalent concept that slow spike-waves and mental handicap is synonymous with LGS. It may be difficult to distinguish from myoclonic astatic epilepsy, and from epilepsies with secondary bilateral synchrony. It stands out among epileptic encephalopathies as a true syndrome, with multiple etiologies and a fairly homogenous presentation and prognosis. The multiplicity of therapeutic proposals does not really mask—and indeed, rather underlines—the relative impotency of medical intervention in LGS. Practical management is a matter of common sense and restraint. Here, as in other difficult-to-treat epilepsies, one shouldn't do anything just because not much can be done.

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Chapter 242

Landau-Kleffner Syndrome and CSWS

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Introduction

Landau-Kleffner syndrome (LKS) and the syndrome of continuous spikes-and-waves during slow sleep (CSWS) were described independently and have been considered separate disorders. Both have been given distinct recognition by the Commission on Classification and Terminology of the International League Against Epilepsy[13] and by the World Health Organization in the International Classification of Diseases.[74] More recently, however, emphasis has been placed on the possibility that there may be common features in the pathophysiology of these two syndromes[15,25,27,28,41,43,62,71] and that LKS may actually be a subtype of CSWS.[25,43,46,62] A major symposium on this subject was held in Venice in 1993 and published in 1995.[8]

LKS and CSWS appear to represent points on a spectrum of functional age-related epilepsies ranging from the "benign" idiopathic localization-related childhood syndromes, such as benign childhood epilepsy with centrotemporal spikes (BECT), to full-blown continuous spikes-and-waves in slow sleep associated with behavioral disturbances.[62] They differ from the secondary generalized epilepsies, such as Lennox-Gastaut syndrome (LGS), in being a truly functional disturbance induced by age-related, self-limited paroxysmal activity.

Historical Perspectives

In 1957 Landau and Kleffner[37] reported six children with a syndrome of "acquired aphasia with a convulsive disorder." One of the children became aphasic and hemiplegic after a head injury, but the other five children's developmental aphasia was related to their convulsive disorder. These five children were presented in detail, with one added as an addendum. Landau and Kleffner described an aphasia that developed over days to months that then persisted from 2 weeks to several years. The associated seizures included grand mal, petit mal, and myoclonic seizures, and the paroxysmal abnormality was usually bilateral, most prominent over the temporal lobes.

They felt that although the relationship was not perfect, the severity of the paroxysmal disturbance on the electroencephalogram (EEG) did correspond to the severity of language disturbance. Landau and Kleffner noted that the seizures were easily controlled and the prognosis was generally good. They hypothesized that persistent convulsive discharge in brain tissue responsible for linguistic communication results in the functional ablation of these areas for normal language behavior. Their thesis was supported by the fact that these children did not have clouded consciousness like patients in petit mal status and had good performance on nonverbal intelligence tests.[37]

Since that time there have been over 350 published cases of acquired aphasia associated with a paroxysmal EEG.[4] The EEG abnormality is a predominantly bilateral posterior temporal spike or spike-and-wave discharge that is activated by slow-wave

sleep. Most observers agree that the ultimate language outcome correlates with the age of onset of this epileptic disturbance, as well as its severity, bilateral anatomic location, and duration of the active phase.[15,28,41,62]

In 1971 Patry et al.[52] described "subclinical electrical status epilepticus" induced by sleep in children. They reported on six children who displayed seizures; cognitive decline, including language dysfunction; and severe paroxysmal EEG disturbance. The patients ranged in age from 7 to 12, four boys and two girls. There was a history of birth trauma in three, consanguinity in two, and epilepsy in the family of one. All displayed continuous spikes-and-waves in 85% of the non–rapid eye movement (REM) sleep record for an extended period of time. Seizures were described as atonic, generalized tonic–clonic, convulsive, clonic, and atypical absence. Five of the six children were mentally retarded and two failed to acquire language. The authors noted that the degree of mental retardation was related to the age of onset of the seizures and hypothesized that this syndrome represented a form of encephalopathy secondary to a focal or multifocal brain lesion. The activation of the paroxysmal activity during sleep, especially slow-wave sleep, was due to a particularly active synchronizing system during slow sleep.[52]

Tassinari et al. later retitled this syndrome electrical status epilepsy during sleep (ESES)[69] and then CSWS,[67] as a result of the criticism that clinical seizures were not seen during the spike-and-wave discharges. Tassinari et al. concluded that the persistent continuous spike-and-wave discharges over years were responsible for the complex and severe neurologic impairment.[67]

Definitions

LKS is a functional disorder of childhood usually described as having the following features: Acquired aphasia, paroxysmal EEG that is usually bitemporal, seizures that are easily treatable and self-limited, no demonstrable brain pathology that is sufficient to explain the behavioral symptomatology, and some degree of improvement when the epileptic condition resolves.[17,25,36,46,49,53,57]

Although these features are commonly cited in the literature, there are exceptions. The language disturbance is described as an acquired aphasia, but both these terms have been challenged. Rapin et al. argued that it is not an aphasia, but a verbal agnosia.[56] In fact, recent evidence suggests that it is an auditory agnosia.[49] Acquired aphasia implies a demonstrable age-appropriate language prior to onset of the CSWS. Early onset of the same process could prevent language function before any language is clearly demonstrable; however, a diagnosis of LKS would be impossible in this situation unless the aphasia is reversed by stopping the epileptic activity.

The paroxysmal EEG is commonly described as predominantly bitemporal and activated by sleep, especially slow-wave sleep. It usually becomes continuous in slow-wave sleep and persists for an extended period.[46] However, the paroxysmal disturbance may be interrupted by normal sleep EEG patterns, and eventually the epileptiform EEG disturbances disappear completely.[29] Furthermore, as will be discussed later, there is evidence to suggest that the primary epileptogenic region is unilateral.[46,49] Awake EEGs may be normal, even in the active phase of spike-and-wave during sleep. Seizures are not always seen, and when present may be quite subtle and not reported.[17,27,49]

Although there is no demonstrable brain pathology sufficient to explain the language dysfunction, multiple nonspecific structural abnormalities have been associated with LKS,[63] which presumably accounts for the epileptiform disturbances.

There is improvement in language function in all patients with the resolution of the active phase of spike-and-wave discharges; however, permanent sequelae in language function are usually seen, especially when there has been early onset of epileptic EEG activity[8,25,53,62] and when the epileptic activity is not eliminated before the critical period for language development is over.[44,49,57,58] LKS therefore represents an age-dependent functional disruption of language induced by a localized paroxysmal EEG disturbance.

CSWS is a functional disorder of childhood with the following features: Severe paroxysmal EEG disturbance, occupying at least 85% of sleep (sleep index 85%); seizures that may be severe but self-limited; behavioral deterioration, with or without premorbid developmental disturbances; no demonstrable brain pathology sufficient to explain the behavioral deterioration; and stabilization or improvement of behavior once the epileptiform EEG abnormalities resolve.[9,68]

These features are not invariably agreed upon. Although Tassinari et al.[68] have maintained that a sleep index of 85% is a necessary component of the diagnosis, the ILAE definition did not require it (ILAE 1989). There may be fluctuations, fragmentation, and variability in the continuity of the spike-and-wave discharges over time. Seizures are usually seen, but they may be subtle and go unreported.[9,68] Traditional antiepileptic drugs usually prevent the expression of the seizures but do not eliminate the paroxysmal EEG abnormality. Although behavioral deterioration is seen in all patients, it may not be as marked in those with previously abnormal development.[68]

Prior abnormal neurologic development is not uncommon in CSWS. Demonstrable brain pathology is seen, but it is insufficient to explain the deterioration of function. There is spontaneous resolution of the epileptiform discharges by the midteenage years with stabilization and often improvement of the neuropsychological and behavioral deterioration. However, significant permanent sequelae are seen in the majority of patients that appear to be related to the duration of the active phase of spike-and-wave activity.[9,53,73] CSWS, therefore, also appears to be an age-dependent disturbance of brain function, induced by a severe paroxysmal disturbance that resolves over time.

Epidemiology

The frequency of Landau-Kleffner syndrome cannot be accurately ascertained. Using the strict diagnostic criteria discussed earlier, LKS is a rare disorder. There have been over 350 published cases since 1957. There were 81 cases reported between 1957 and 1980, but 117 cases were reported between 1980 and 1990.[3] Dugas et al.[21] observed one new case per year in a Parisian psychiatric clinic. Males are affected more commonly than females, with a peak onset between 5 and 7 years of age.[10]

The frequency of CSWS is also unknown. Using the strict criteria of continuous spike-and-wave discharge during 85% of sleep associated with cognitive and behavioral decline, CSWS is a rare disorder. Between 1971 and 1984, Tassinari et al. reported 19 personal cases from the Centre St. Paul in Marseille and an additional 25 from the literature.[67] Since 1984, ten new cases have been seen at the Centre St. Paul, a rate of one to two per year.[68] Males are affected more commonly than females, with a peak onset between 5 and 7 years of age.[10]

Etiology and Basic Mechanisms

A convergence of evidence suggests that LKS and CSWS are due to a common pathophysiologic mechanism,[14,25,27,29,41,43,46,62,71] and a specific hypothesis has been proposed for LKS.[46,49] Both disorders develop during a period of cortical synaptogenesis when the basic functional circuitry is being established (age 1 to 8). Synaptogenesis involves an overabundant growth of axonal processes and synaptic contacts thought to be twice the number found in mature adults.[31,32,54,55] Neuronal activity or synaptic use is the major factor that determines which synapses will be strengthened and which will be pruned.[31,54] The environment, more than genetic programming, plays the crucial role in the establishment of permanent synaptic contacts. If a significant paroxysmal EEG disturbance is present during this age-dependent synaptogenesis, it acts to strengthen synaptic contacts that should have degenerated in order for the neuronal aggregates to mediate normal behavior.[49] In the case of LKS, the paroxysmal activity reinforces inappropriate contacts in the developing temporoparietal cortex, thus producing a permanent language dysfunction.[49] In addition, the disturbance must have a bilateral effect to prevent transfer of function to the contralateral homotopic cortex. In CSWS, the most prominent paroxysmal activity appears to be in the frontal area, which would disrupt higher cognitive and executive function and attention before producing language dysfunction. Because the functional disruptions induced by paroxysmal EEG activity can spread to involve a larger cortical area, the symptom complexes of LKS and CSWS tend to merge as the disease goes on, producing severe cognitive, behavioral, and social dysfunction, much like the child with severe autism.

This proposed underlying mechanism predicts that, if unsuccessfully treated, those children affected earlier in this period of synaptogenesis will suffer the most serious neuropsychological sequelae after the epileptiform disturbances remit. Several authors have reported this in their series.[8,23,57,58,70] The importance of overactive inhibition as well as overactive excitation in these syndromes has been recently highlighted. This combination results in coexistence of a lack of overt seizures at the same time as severe cognitive/language dysfunction—a hallmark of the epileptic encephalopathies.[27]

Multiple nonspecific pathologic abnormalities can be associated with these syndromes and, although insufficient to explain the behavioral deterioration, may be responsible for the epileptic disturbances. Common etiologies in CSWS include congenital hydrocephalus, periventricular, and diffuse atrophy.[7,20] The pathologic findings associated with LKS in the literature are similar to those seen in other partial epilepsies; they include encephalitis, vasculitis, subpial gliosis, cysticercosis, and neuronal migration disorders.[12] The biopsy material taken from the temporal pole, at a distance from the primary epileptic site, in one surgical series of 14 patients with LKS revealed a variety of pathologic abnormalities in 13.[63]

The mechanistic hypothesis presented here raises the question of whether other epilepsies might also induce progressive behavioral dysfunction. BECT and other idiopathic localization-related epilepsies involving frontal, temporal, parietal, and occipital lobes all could have deleterious effects on cortical development and function where the abnormality

is maximal. It may be that we cannot clinically detect the permanent sequelae because of the poor sensitivity of our testing.

Clinical Presentation

Landau-Kleffner Syndrome

LKS is an acquired epileptic aphasia or auditory agnosia, occurring in a previously normal child, in language function, in association with paroxysmal EEG abnormalities with or without clinically apparent seizures, and without a structural substrate sufficient to account for the behavioral deterioration. The disorder begins most commonly between the ages of 3 and 8 in children who have already developed age-appropriate speech. The onset may be subacute or stuttering and initially consists of a loss of verbal understanding (i.e., receptive disturbances predominate). Soon, however, speech output is affected and paraphasias and phonologic errors appear. In the most severe cases, the child becomes entirely mute and will fail to respond to even nonverbal sounds—such as the ring of a telephone, a knock on the door, or a dog barking—that were previously well attended to. Behavioral disorders such as hyperactivity and attention deficit are common. Rarely, there is progression to severe disinhibition and psychosis.[3,46,49]

Seizures vary in type, but most commonly are associated with eye blinking or brief ocular deviation, head drop, and minor automatisms with occasional secondary generalization. They bear a variable relationship to the language deficit, and, indeed, from 20% to 30% of patients do not exhibit behavioral seizures.[4] The seizures have a benign course, are readily responsive to antiepileptic drugs, and generally subside by the age of 15 years. The language disturbance, as a rule, has a much less satisfactory prognosis, although early on the symptoms may show marked fluctuation, and even complete recovery, within weeks or months of onset.[15] However, if the aphasia persists for more than 2 to 3 years, complete recovery is most unusual; such patients may expect a lifelong linguistic defect.[8,36,46,49,53,57]

A critical component of LKS is the presence of continuous 1.5- to 5-Hz spike-and-wave EEG discharges in slow sleep that fragment or disappear during REM sleep[29,41,42,46,49] (Fig. 1). It is this latter feature that links the two conditions under discussion and provides the impetus to seek clinical similarities. A distinctive feature of LKS, however, is that the spike-and-wave discharges predominate in the posterior temporal regions. Most patients do not show spike-and-wave activity for 85% or more of slow sleep at the time of study, and some may not show continuous spike-and-wave during sleep at all; however, it has been assumed that this condition was met at some point during the course of the disorder.[46] During the active phase, brief posterior temporal epileptiform discharges can also be seen during wakefulness on the routine EEG, which can be localized to one posterior temporal region. With the use of the methohexital suppression test,[47,64] intracarotid amobarbital, EEG dipole mapping, and magnetoencephalogram (MEG), it can be shown that most, if not all, children have a unilateral primary epileptogenic region.[39,46,49,51,65] This can involve either side, since the contralateral propagation of paroxysmal discharges creates bilateral dysfunction that disrupts normal language development, regardless of the side of origin.

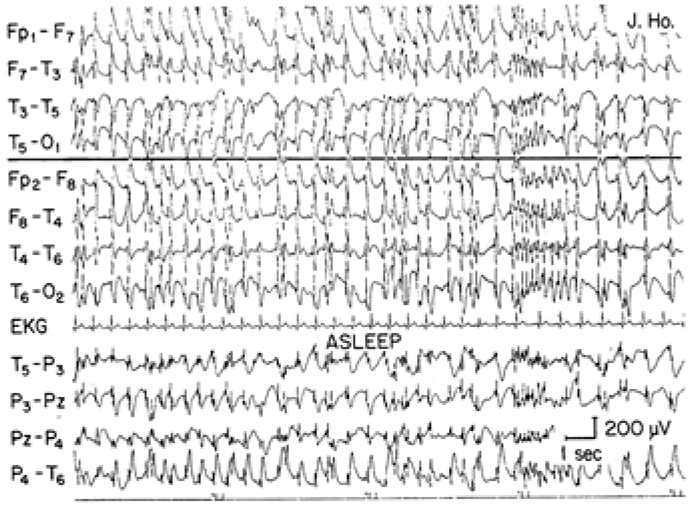

FIGURE 1. Electroencephalogram tracing taken during sleep in a patient with Landau-Kleffner syndrome prior to treatment. Such patterns may occupy 80% to 90% of the hours normally given to slow-wave sleep. The first four channels derive from the left hemisphere, the second four from the homotopic regions on the right. The lowest four channels show a transverse array, left to right, across the parietal region. Electrode designations are those of the standard “10 to 20” international system. (From Morrell F, Whisler WW, Smith MC, et al. Landau-Kleffner syndrome: treatment with subpial intracortical transection. *Brain.* 1995;118:1529–1546.)

Continuous Spikes-and-Waves during Slow Sleep

The EEG pattern of CSWS consists of bilateral generalized, 1.5- to 5-Hz spike-and-wave discharges strongly activated by sleep, being present for 85% to 90% of slow-wave sleep and interrupted during REM episodes or in the waking state. REM and wakefulness are characterized by focal or multifocal paroxysmal EEG activity, or by brief bursts of bilateral spike-and-wave discharges.[52] Focal spikes tend to be frontal.

Generally, the seizures associated with CSWS are focal motor or hemiclonic, partial motor, complex partial, absence, or secondarily generalized tonic–clonic. Tonic seizures do not occur. Although the seizures may be frequent, they are usually responsive to medical management and disappear entirely in the middle teens.[10,68]

Much more serious are the cognitive disturbances. These may include aphasias and apraxias, but generally embody widespread multisystem cognitive decline leading to substantial retardation and dementia.[9,68] Although the cognitive symptoms are highly correlated in time with the onset of CSWS, antiepileptic drugs do not improve them.

Tassinari et al.[68] have distinguished three groups of patients with CSWS based on clinical seizures. The first group suffers rare orofacial, generalized tonic–clonic, and myoclonic seizures in sleep. These patients resemble children with BECT. The second group suffers unilateral partial, generalized tonic–clonic, and absence seizures. The frequency of seizures in this group is greater, and seizures occur in wakefulness. The third group has unilateral partial and generalized tonic–clonic seizures in sleep and absence, absence status, and atonic seizures with falls in wakefulness.[68]

Table 1 Comparison of LKS versus CSWS[a]

	LKS	CSWS
Sex	**(Sex) 68% male**	**(Sex) 63% male**
Antecedent history	3% encephalopathy	31%; 36% cerebral palsy; 36% encephalopathy
FH epilepsy	3%	10%
Age of onset	Peak, 5–7; 5% after 9 years of age	Peak, 5–7; 20% after 9 years of age
First symptom	Seizure, 60%	Seizure, 80%
Second symptom	Neuropsychological, 40%	Neuropsychological, 40%
Seizure types	GTC seizure, 35%; unilateral, 26%; unilateral status, 6%	Unilateral, 50%; unilateral status, 6%; absence, GTC, CPS
During active phase of spike-and-wave	(-) atonic seizure, not significant ↑ seizure, clonic/unilateral, CPS	+ atonic seizure/with fall, significant ↑ in seizures, ↑ absence, ↑ atonic seizure, ↑ atypical absence
After active phase of spike-and-wave	19% rare seizure: 81% seizure free	16% rare seizure; 84% seizure free
Neuroimaging	13% abnormal	33% abnormal
Meet criteria for 85% spike-and-wave in sleep	<50%	78%
Frequency of spike-and-wave	2 Hz	2 Hz
Ictal discharge awake	26%	67%

Focal discharges	Centrotemporal/parietal, 60%	Frontal, 60%
Regional predominance of continuous spike-and-wave during sleep	Posterior	Anterior

[a] = 103. CSWS = 71; LKS = 31. FH, = family history; GTC, generalized tonic-clonic convulsions; CPS complex partial seizures.
Adapted from Refs. 3 and 10.

When reviewing the psychomotor development and neuropsychological disturbances, Tassinari et al.[68] distinguished two groups. The first has a normal development prior to the CSWS. During the active phase of epileptic discharge, there is a severe decrease in IQ, marked reduction in language function in the majority, severe disturbance of temporospatial orientation, and a marked behavioral disturbance in all. The behavioral disturbance includes reduced attention span, hyperactivity, aggressiveness, disinhibition, and difficulty in contact with the environment. The second group has pre-existing abnormalities of psychomotor development. These patients suffer deterioration of function and worsening of behavior, but this condition

is not as marked from pre-existing baseline as that of the first group. Long-term outcome in a CSWS patient is generally poor, with significant mental retardation common and frontal lobe syndrome and frontal lobe epilepsy described.[53,73]

Overlap between the Syndromes

A major problem in our understanding of this spectrum of age-related functional cognitive disorders induced by paroxysmal activity has been the low frequency of reported cases in a given institution. At the Venice colloquium,[6] case reports from an international group were analyzed, yielding 103 patients. Of this group, 71 best fit the syndrome of CSWS and 31 best fit that of LKS. One could not be classified. This substantial body of information allows a direct comparison of these two syndromes.[10] Not all the cases could be used in each reported analysis because of the insufficient or poorly described information. Nonetheless, these data confirm the significant overlap between these proposed separate syndromes (Table 1). The reported differences in clinical presentation, seizure type, and neurologic and behavioral sequelae appear to be due to the primary cortical area involved; the age of onset of epileptiform EEG abnormalities in relation to age-dependent synaptogenesis; severity of the continuous spikes-and-waves during sleep, as measured by the sleep index; and length of time the EEG abnormality persisted.[66] Because of the commonality of features and the more specific localization of the epileptogenic region in LKS, it might be considered a subtype of CSWS.[46]

Diagnostic Evaluation

In the evaluation of children with suspected LKS or CSWS, a careful developmental history is taken and physical and neurologic examinations are done. Documentation of premorbid language and of cognitive and behavioral performance is sought, including school testing and intelligence testing.[49]

All children with suspected LKS or CSWS should undergo careful neuropsychological testing by a specialist team experienced in both linguistic and nonlinguistic capacity. This testing allows one to judge whether there are specific deficits in cognitive function, as expected in LKS in the language domain, or whether there is frontal dysfunction, as expected in CSWS.

Laboratory testing includes structural and functional neuroimaging. Routine EEG is essential, and either closed-circuit television (CCTV)-EEG monitoring or ambulatory monitoring can be helpful.[3,46,49] More sophisticated investigations, which are of value for LKS when surgical treatment is considered, can include MEG,[39,51,65] computerized amplitude mapping of EEG, and intracranial EEG recordings, as reviewed by Morrell et al.[49]

In general, structural neuroimaging is usually normal in LKS but abnormal in CSWS, reflecting the prior neurologic insult.[49,68] The structural abnormalities reported in CSWS include unilateral atrophy, focal porencephaly, focal pachygyria, diffuse atrophy, congenital hydrocephalus, and minor white matter abnormalities. The abnormalities reported in LKS include focal pachygyria and mild diffuse atrophy.[7,10,20]

Functional neuroimaging has been reported in only a minority of patients with LKS and CSWS. An important point in interpreting these results is to know whether radionucleotide injection and scan was performed during the active phase of spike-and-wave and whether it was performed in the wake or asleep state. In general, if scans are performed in the wake state or after the period of active spike-and-wave activity, both single photon emission computed tomography (SPECT) and positron emission tomography with ^{18}F-fluorodeoxyglucose (FDG-PET) show an area of decreased blood flow or glucose utilization, whereas if they are done in sedated patients with induced continuous spikes-and-waves, they show a focal area of increased blood flow or glucose utilization.[41,49] Hirsch et al. reported increased glucose metabolism during the active phase of spike-and-wave during both the asleep and wake states in both disorders, though the area of increased metabolism was greater in sleep.[28] It is not noted whether the paroxysmal activity was present during the wake scan. The hypermetabolism was restricted to focal or regional cortical association areas and the type of neuropsychological impairment was in good agreement with the topography of this disturbance.[28,41] The pattern seen in both LKS and CSWS combined features of immature brain with superimposed focal abnormalities. The metabolic abnormalities of these two syndromes displayed significant overlap, suggesting that they represent two parts of the same spectrum of functional disorders of childhood.[28,41] Some patients who underwent FDG-PET scans after the active phase of spike-and-wave discharges had resolved showed persistent regions of hypometabolism in areas that previously showed hypermetabolism, documenting enduring metabolic change.[41]

EEG recordings in slow sleep are important in the diagnosis of LKS and CSWS, but, because of the short recording time, routine studies rarely record slow-wave sleep. Amitriptyline at a dose of 1 to 2 mg/kg and a prolonged recording of 3 hours significantly improves the chance of observing slow sleep. The Venice colloquium provided direct comparison of EEG data in LKS and CSWS[6] (see Table 1). During the active phase of spike-and-wave discharges, more patients with CSWS met the criteria of a sleep index of 85% than those with LKS. The average frequency of the spikes-and-waves was 2 Hz in each disorder. Sleep spindles were absent in 10% of patients, more commonly in the CSWS group than in the LKS group. If a patient had a frontal EEG spike focus, he or she was more likely to have a sleep index of 85% or greater, suggesting that intrinsic circuitry and dense callosal connections of the frontal lobe predispose to generalization during sleep. Patients could be divided into two groups, depending on the severity of the EEG abnormality. The first group had a sleep index of 85% or greater, frequently disrupted sleep spindles, only rare focal discharges during sleep, and bursts of spikes-and-waves in wakefulness. This EEG pattern was seen in 70% of patients with CSWS and in 40% of those with LKS. The second, less severely affected group, showed a sleep index between 50% and 80%, often recognizable sleep spindles, more frequent focal spiking during sleep, and absent or rare spike-and-wave discharges during wakefulness. This set of EEG findings was seen in 30% of the CSWS group and in 60% of the LKS group. These data support the significant overlap in EEG findings, although those with CSWS are more likely to have a severely affected EEG.[6] In addition, focal spikes tend to be frontal in CSWS and are temporoparietal in LKS.

Magnetoencephalography on a number of patients with LKS revealed a focus of slow waves and epileptiform activity in the posterior temporal area adjacent to the sylvian fissure, supporting an origin in the dorsal surface of the superior temporal gyrus[24,39,49,53,65] (Fig. 2). Computerized amplitude and polarity mapping has also been performed in a few patients with LKS and CSWS. In LKS, isolated unilateral spikes during the methohexital suppression test or the first spike in a burst of spikes-and-waves displays a tangential dipole with suprasylvian negativity and infrasylvian positivity, also indicating the origin to be in the dorsal surface of the superior temporal gyrus.[30,41] Amplitude mapping of spikes during wakefulness in three cases of CSWS showed two to be predominantly left frontal with temporal spread and one right frontal with frontal and temporal spread. The sleep spikes tended to have a more diffuse distribution.[24,62] Although the number of cases studied is small, they support differences in maximal cortical areas involved in these syndromes.

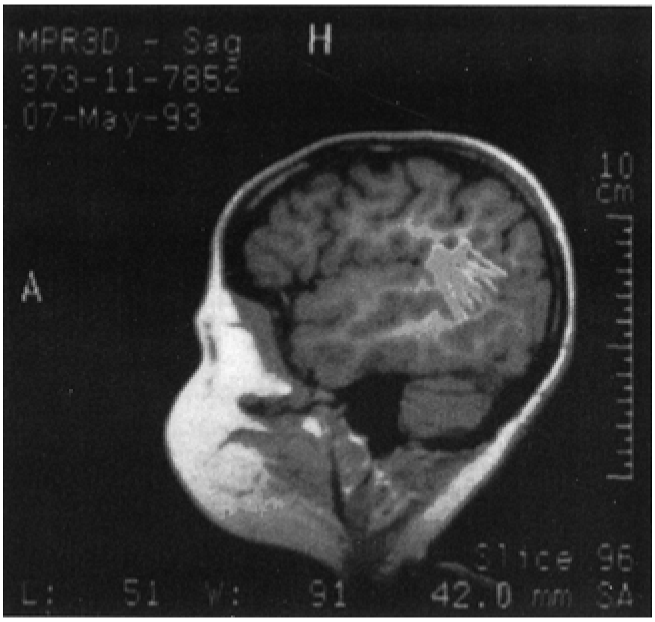

FIGURE 2. Magnetic resonance image (MRI) of another patient with Landau-Kleffner syndrome. In this example, the entire dipole, including its orientation, is displayed on the MRI. In (A) a sagittal section of the left sylvian region is shown. The dipolar orientation is perpendicular to the sylvian fissure and is angled in the anterior–posterior dimension, the suprasylvian projection being anterior to the intrasylvian one.

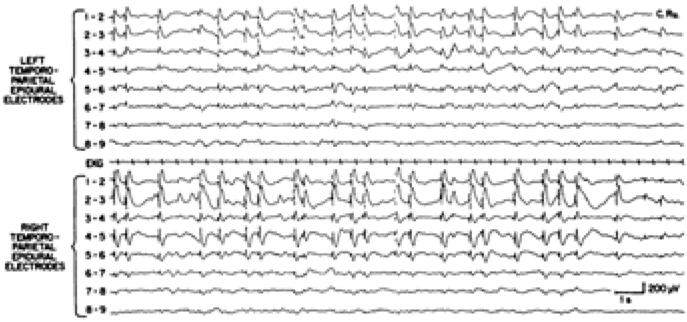

FIGURE 3. Electroencephalogram derived from implanted epidural electrodes in a 5-year-old child. The bilateral spike and spike-wave pattern is well seen. Electrodes were placed symmetrically over the sylvian fissure in each hemisphere. (From Morrell F, Whisler WW, Smith MC, et al. Landau-Kleffner syndrome: treatment with subpial intracortical transection. *Brain.* 1995;118:1529–1546.)

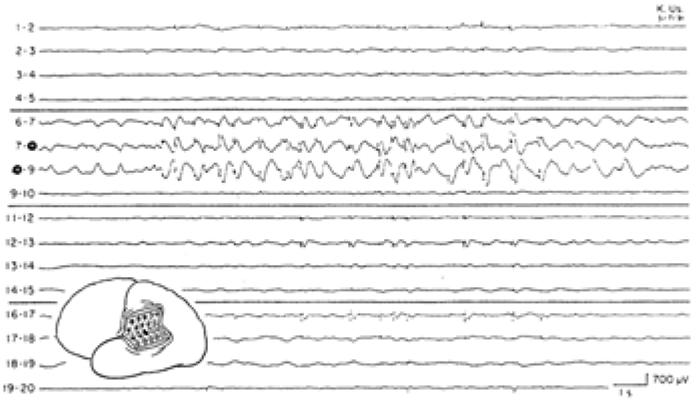

FIGURE 4. Electrocorticographic recordings derived from a pad of electrodes inserted between the lips of the surgically opened sylvian fissure. A vigorous epileptiform discharge was encountered at electrode number 8, whereas highly attenuated spikes were detected in adjacent electrodes of the pad. Electrode 8 lay directly on the dorsal surface of the superior temporal gyrus immediately posterior to the transverse gyrus of Heschl. (From Morrell F, Whisler WW, Smith MC, et al. Landau-Kleffner syndrome: treatment with subpial intracortical transection. *Brain.* 1995;118:1529–1546.)

A few children with LKS have undergone chronic intracranial electrode and intraoperative recordings in the course of surgical treatment.[33,49,59] These studies confirmed that the common paroxysmal abnormality is in the area of the posterior temporal lobe, often maximal on the superior temporal gyrus (Fig. 3). At times the epileptogenic region is confined within the sylvian fissure near the Heschl gyrus (Fig. 4).

Differential Diagnosis

The differential diagnosis between LKS and CSWS, whether or not the former is considered to be a subtype of the latter, is difficult (see Table 1). LKS tends to affect a slightly younger population, presenting first with language dysfunction and only later with other cognitive and behavioral deterioration. In CSWS the children affected tend to be slightly older, presenting with more global neuropsychological and behavioral deterioration before language dysfunction appears.[9] The severity of the seizures and EEG abnormality is not as pronounced in LKS as in CSWS. The spike-and-wave discharges are maximal in the centrotemporal and posterior head region in LKS and in the frontal head region in CSWS.[6]

The disorders most commonly confused with LKS and CSWS are pervasive developmental delay (PDD) and autism.[25,62,71] The most important distinguishing feature is the loss of previously achieved developmental milestones with LKS and CSWS. In contrast to LKS, children with PDD and autism display abnormal, nonverbal intelligence as well as language dysfunction. Children with early-onset and persistent CSWS may deteriorate more globally and begin to mimic autism. However, although PDD and autism may be associated with paroxysmal EEG abnormalities, they do not have the continuous spike-and-wave discharges during slow sleep of CSWS.

Mental retardation from a wide variety of causes can occasionally be misdiagnosed as LKS or CSWS. A careful history will usually document that motor developmental milestones were not met and suggest the child was affected from birth. The neurologic examination is often abnormal, demonstrating abnormalities in the motor and other systems. These children may also display EEG abnormalities reflecting the underlying cortical pathology; however, these abnormalities rarely meet criteria for continuous spikes-and-waves.[17]

Developmental dysphasia is another disorder that may mimic LKS. Children with this condition do not develop language skills in the usual time frame. They often have a normal neurologic examination and nonverbal intelligence. EEG abnormalities are uncommon, and a continuous spike-and-wave abnormality has not been described.[17] If a child presented with continuous spikes-and-waves in sleep and developmental dysphasia, early-onset LKS is possible.

Once seizures and EEG recordings have indicated the presence of an epileptic disorder, other epileptic syndromes must be considered. These include BECT; other idiopathic, localization-related epilepsies; and Lennox-Gastaut syndrome.[9] Although clear features distinguish LKS and CSWS from Lennox-Gastaut syndrome, there is an overlap with BECT and related disorders.

Classic CSWS and Lennox-Gastaut syndrome (see Chapter 241) share some common features. These include the presence of atypical absence and atonic seizures. The EEG of Lennox-Gastaut syndrome typically shows slow spikes-and-waves that may activate with sleep, but not to the extent of CSWS. In addition, the EEG of Lennox-Gastaut syndrome, but not CSWS or LKS, typically includes polyspikes-and-waves as well as bursts of rhythmic fast activity.[9,25,62,68] Finally, children with Lennox-Gastaut syndrome, but not with CSWS or LKS, display tonic seizures as a prominent component of their disorder.[25,62,68]

Although there are clear clinical differences in these syndromes, a common feature may be that severe epileptiform activity is responsible for progressive cognitive dysfunction. In CSWS and LKS, the paroxysmal abnormality is more restricted and time dependent, whereas in Lennox-Gastaut syndrome the epileptiform activity is multifocal, persistent, and secondary to central nervous system (CNS) injury that also contributes to cognitive disturbance that is not time dependent; this results in a chronic seizure disorder and permanent cognitive dysfunction.[9,68]

The idiopathic localization-related epilepsies (see Chapters 236, 237, and 238) are more difficult to distinguish pathophysiologically from LKS and CSWS but are readily separated clinically.[9,25,43,62,71] These disorders may have less of an effect on cognitive function because the active spike-and-wave activity is less severe, or because it involves different, more “silent” cortical areas. Aicardi and Chevrie[1] reported a syndrome that displayed active spike-and-wave discharges that became continuous with sleep. These children had no detectable cognitive or intellectual deterioration. However, the sleep index and the duration of the active phase of spike-and-wave were not documented.[7] Deonna et al.[19] had six similar cases, but documented increasing neuropsychological dysfunction at the time of EEG deterioration. Polypharmacy may have worsened the clinical status, and all of Deonna's cases improved with antiepileptic drug (AED) taper. It is probable that this syndrome is a subset of CSWS with an older onset and a shorter course of the active phase of continuous spikes-and-waves. It may also be that more careful neuropsychological testing would be able to detect cognitive deficits.[10]

Benign childhood epilepsy with centrotemporal spikes is easily distinguished from LKS by the absence of acquired aphasia; however, BECT may also be a subset of CSWS.[25,62] In Tassinari's clinical division into various subsets of CSWS, one type with orofacial and generalized tonic–clonic seizures in sleep mimics BECT. Absence seizures have been reported with BECT.[68] There are differences, however, in EEG manifestations. In CSWS, focal abnormalities predominate in the frontal areas, whereas in BECT they are maximal in the centrotemporal areas. There is a clear activation of epileptiform activity in BECT during sleep, at times becoming continuous spikes-and-waves; however, the sleep index never reaches 85%.[9,11,25,62] There was one reported case of BECT that worsened with the introduction of carbamazepine and reached a sleep index of 85%; clinical deterioration with atypical absence and falls resolved with withdrawal of the carbamazepine.[11] Mental retardation and a history of prior neurologic insult are commonly seen in CSWS but not in BECT. Family history of epilepsy is reported in 40% with BECT but in only 10% with CSWS.[9] Despite these clinical differences, it is probable that a child with early-onset and persistent BECT with a high sleep index would display cognitive or motoric deficits if carefully tested.

Treatment and Outcome

As previously noted, the clinical seizures in LKS and CSWS, as with the other idiopathic localization-related epilepsies, are, for the most part, not severe and are easy to control.[10,25,41,46,49,62]

The one important exception to this is in the subgroup of CSWS with daily atypical absences and drop attacks.[68] In this group, clinical seizures are severe and at times difficult to treat. The clinical seizures in both groups are self-limited, with only rare seizures in about 20% of both groups once the active phase

of spike-and-wave has resolved.[10] All available AEDs have been used individually and in combination for the treatment of LKS and CSWS. The Venice colloquium confirmed this and listed the medications used by participating investigators.[72] During the active phase of spike-and-wave, polytherapy was the rule, with only 9% of patients treated with monotherapy. Efficacy was difficult to judge, because in general, all AEDs were effective in treating the clinical seizures, but there was poor response of the paroxysmal EEG. There have been reports of carbamazepine causing a worsening of seizures, especially atypical absence and atonic falls.[11] In reviewing which AEDs, if any, were being used at the time of resolution of the CSWS, there were data on 88 patients. Seven of these patients were not on any medication at the time of resolution of CSWS, documenting its self-limited nature. Of the other 81 patients, 55 were taking valproate, 19 as monotherapy. Thirty-nine of the patients were on a benzodiazepine, mostly clobazam. A small number were on phenobarbital, vigabatrin, ethosuximide, and carbamazepine. These data indicate that valproate alone or in combination with a benzodiazepine has been the treatment of choice.

Corticosteroid therapy, either with adrenocorticotropic hormone (ACTH) or prednisone, appears to have favorable and long-lasting effects.[61,72] Although there were too few cases and insufficient follow-up time to permit a definitive conclusion on their effectiveness, some authors suggest that ACTH or corticosteroids should be the treatment of choice, especially in new-onset disease in a young patient.[18,29,38] Lerman et al.[38] reviewed the literature and reported on four cases with LKS that they treated with either ACTH or corticosteroids. They tended to use a high dose for a prolonged period of time (ACTH 80 IU/day with a 3-month taper; prednisone 60 mg/day with a 3-month taper). They noted, and this was confirmed in the Venice colloquium,[72] that there may be relapses with steroid reduction and some children may need to be on steroids for months to years. A commonly accepted dose is 3 to 5 mg/kg/day of prednisone for at least 3 months. It appears that the earlier treatment is initiated, the shorter the duration of steroids required, and the better is the ultimate outcome.[38] With steroid wean, most of these children were on additional AEDs, most commonly valproate or benzodiazepines. Lower-dose protocols with fewer adverse effects have been reported to be helpful.[61]

The long-term use of corticosteroids is fraught with side effects, including weight gain, cushingoid appearance, hypertension, glucose intolerance, electrolyte abnormalities, sleep disturbance, mood changes, and more serious conditions, including cataract formation, proximal myopathy, pathologic fracture, and immune dysfunction (see Chapter 144). The risks versus benefits must be clearly thought out and explained to all concerned parties, including patients, parents, and primary care physicians. Side effects of steroids may be acceptable in patients with an early onset of the active phase of spike-and-wave discharges and a severe and persistent epileptic disturbance because this group is at highest risk for significant residual neuropsychological sequelae.

Current practice is to treat initially with valproate with or without a benzodiazepine. If epileptiform EEG abnormalities and cognitive dysfunction persist despite high therapeutic AED levels, a course of prednisone 3 to 5 mg/kg/day[1] with careful laboratory and physical examination follow-up is usually offered. It is important to obtain serial EEGs that include slow-wave sleep in order to judge the efficacy of therapy. An attempt can be made to convert to every-other-day dosing in the second month of therapy, if there is therapeutic success. A slow wean during the third month is performed, although relapses are not uncommon.[18,38,46]

Morrell et al. originally reported on the surgical treatment by multiple subpial transection (MST) of 14 children suffering from LKS.[49] All children had been unable to use language meaningfully for more than 2 years and displayed continuous spike-and-wave discharges that were demonstrated to arise unilaterally in the superior temporal gyrus and surrounding perisylvian cortex. After MST resolved the paroxysmal EEG abnormality, there was dramatic improvement in language function over time, with 50% recovering age-appropriate language and returning to regular classroom school and 29% showing a marked improvement in language function but still undergoing speech therapy. They concluded that success in restitution of language function depended on proper selection of patients and resolution of the severe epileptiform EEG abnormality.[49] Presurgical evaluation requires delineation of an epileptogenic region involving one posterior temporal lobe, which is usually accomplished not only by standard imaging and electrophysiologic investigations, but also by the methohexital suppression test, and occasionally intracarotid amobarbital, electrical dipole mapping, and magnetic resonance imaging.[49]

Longer-term follow-up on the original 14 patients found that 11 of 14 demonstrated significant postoperative improvement in receptive-expressive language and that gains in language function are most likely to be seen years rather than months after surgery.[26] These results indicate that early accurate diagnosis and effective treatment optimizes outcome. This series has been recently extended to 24 children treated with MST to treat severe persistent language disturbance of more than 18 months' duration. MST resulted in recovery of functional language (speaking in complex sentences) in two thirds of children treated.[35]

Other investigators have confirmed these original findings that MST is an effective treatment in children with active CSWS and acquired aphasia despite treatment.[33,59]

The clinical response to MST in atypical LKS or autistic regression with epileptiform EEG, at times CSWS, had been reported, but long-term functional language improvement had not been demonstrated,[39,50] making accurate diagnosis critical in patient selection for MST.[62]

There is now a better understanding of treatment options in LKS and CSWS. It is necessary to eliminate the severe paroxysmal EEG disturbance to prevent serious neuropsychological sequelae in some patients.[41,46,66] Aggressive treatment is indicated in those with early onset of the active phase of spike-and-wave discharges who have a severe and persistent paroxysmal disturbance affecting neocortex that is critical to language and other higher cognitive function. In these children, high doses of traditional AEDs, corticosteroids, and occasionally surgery are justified because of the risk of serious and permanent cognitive dysfunction that will affect education, occupation, and activities of daily living.

Long-term Prognosis

Long-term prognosis for the seizure disorder in both conditions is good, with <20% suffering from persistent, usually rare, seizures.[10] However, the long-term prognosis for neuropsychological consequences is not nearly as good as was once thought.[17] In general, most patients who suffer from LKS or CSWS have some permanent sequelae that limit their activities. Those with the earliest onset of spike-and-wave discharges and longest persistence over time are most affected.

In 1980 Mantovani and Landau[40] reviewed the long-term prognosis of nine patients with LKS 10 to 28 years after onset. They found that the overall clinical status and language were normal in <50%. Many other studies agree that aphasia persists in the majority.[2,3,14,16,34,53] Only half of patients with a history of LKS are able to live a normal life.[2,34,41,49,53]

Long-term outcome with CSWS has also been reported as poor in most patients.[53] Again, outcome appears to be related to the age of onset and duration of the active phase of spike-and-wave discharges.[68] All four cases reported by Morikawa et al.[45] continue to have neuropsychological sequelae, with IQ ranging from 35 to 60, and require special schools or sheltered workshops.

The Venice colloquium confirmed that permanent neuropsychological sequelae are seen in the majority; in fact, only a few of the 59 children with adequate follow-up intelligence tests achieved a global IQ within the normal range.[44] Disturbances included short attention span, hyperactivity, affective symptoms, and language dysfunction, as well as intellectual impairment. Although there was a global improvement in all intellectual areas after resolution of CSWS, this did not lead to complete restoration of function, particularly in verbal ability, attention, and executive function.[44,53]

Summary and Conclusions

LKS and CSWS are two points on a spectrum of age-related functional disorders of childhood characterized by a severe paroxysmal EEG disturbance that can permanently alter critical synaptogenesis by strengthening synaptic contacts that should be pruned. They appear to be linked to other idiopathic localization-related epilepsies by a common pathophysiology. Although prognosis for seizure control is good, cognitive function deteriorates and serious permanent neuropsychological consequences are reported in the majority. At highest risk for permanent sequelae are those with the earliest and longest exposure to the active phase of continuous spike-and-wave discharges during sleep. In LKS the paroxysmal activity permanently affects the posterior temporal area and results in auditory agnosia and language deficits, whereas in CSWS the frontal lobes are more involved and other cognitive disturbances predominate. Aggressive treatment approaches to abolish the paroxysmal disturbance—such as high-dose AEDs, corticosteroids, or, in select LKS patients, surgery—should be seriously considered in the high-risk group.

Acknowledgment

This chapter is dedicated to the life and work of Frank Morrell (1926–1996), our teacher, mentor, colleague, and friend. The ideas and concepts contained in this work were greatly influenced by him.

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Chapter 244

Juvenile Myoclonic Epilepsy

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Introduction

Juvenile myoclonic epilepsy (JME) is a common type of idiopathic generalized epilepsy (IGE). The major landmark of JME is the occurrence of adolescent-onset myoclonic seizures. JME is both genetically and clinically heterogeneous, suggesting that different pathophysiologic mechanisms might be involved.[84]

Historical Perspectives

The first description of a patient with JME came from the French literature in 1867 by Herpin,[38] but the myoclonic jerks were only properly characterized in 1899 by Rabot.[63] The intermittent character of these jerks as compared to the myoclonus occurring in progressive myoclonic epilepsy, a neurodegenerative disease, was emphasized by Lundborg[47] in 1903.

The description of JME as a specific IGE syndrome was established almost at the same time by Janz and Christian in Germany[42] and by Castells and Mendilaharsu in Uruguay,[16] almost a century after the first patient was reported in the literature. However, because of varying terminologies employed by previous authors, the syndrome was only recognized as JME in the English-speaking literature in the mid-1980s.[5,22]

Definitions

JME is the most common form of IGE, and the myoclonic seizures are the hallmark of the syndrome. Isolated myoclonic jerks of the arms, especially shortly after awakening, are characteristic. Generalized tonic–clonic seizures (GTCSs) occur in most patients, and one third of individuals also have absences. Seizure occurrence is more likely with sleep deprivation, fatigue, and alcohol withdrawal. Onset is usually in adolescence but seizures may begin or be diagnosed only in the early 20s. Patients frequently come to medical attention only after a generalized convulsion, and the history of earlier myoclonic jerks is often obtained retrospectively. More recently, myoclonic epilepsy with adult onset (37 to 39 years) has been highlighted by different groups.[20,30,49]

Epidemiology

Prevalence

JME accounts for up to 26% of patients with IGE and up to 10% of all cases of epilepsy,[43] but misdiagnosis and delayed diagnosis remain common.[34]

Based on a 1% population risk for epilepsy by age 20,[36] the Risk of JME in the general population would be 1 per 1,000 to 2,000. It is less frequently seen in children and more frequently in adolescents and adults.[43] In adults with IGE, JME should be strongly considered, and detailed inquiries regarding a history of myoclonus beginning in the teens are essential.

Sex Ratio

Although an equal sex ratio is generally assumed in JME, there is a slight female predominance, with 515 males to 615 females, based on the summation of ten different studies.[43] Only one of the studies showed male preponderance (33 males to 20 females),[22] whereas another study showed marked female preponderance (77 males to 104 females).[24] A recent Irish study also showed significant female predominance for JME.[55] A large family study has also confirmed a very high female-to-male risk ratio.[59]

Age of Onset

The onset of JME is clearly age related. It varies between 8 and 26 years, with the majority between 12 and 18 years.[43] The average age of onset of myoclonic jerks is usually earlier than that of generalized tonic–clonic seizures.[24] The onset age of JME is generally earlier in photosensitive than in nonphotosensitive patients.[70,83]

Etiology and Basic Mechanisms

The pathophysiology of JME is unknown. Although clinically a well-defined syndrome, detailed investigations of JME suggest that this stereotyped clinical pattern may be the result of different genetic, pathologic, and pathophysiologic processes.[5a,84]

The electroencephalographic (EEG) pattern and other neurophysiologic studies, including those conducted in patients with reflex seizures induced by thinking, writing, or “action programming,” suggest a variable focal or regional frontal hyperexcitability in many cases.[84] Even so, although subtle frontal morphologic changes can be found, they are not universal in JME, and neither is sensitivity to various cognitive triggers, which may be absent in a typical case or present in a patient with another IGE syndrome. The association with photosensitivity is also variable.

An association with clinical and EEG findings of a clearly focal epilepsy, namely, idiopathic photosensitive occipital epilepsy (IPOE, described below), also raises questions about the nosologic purity of JME as a generalized epilepsy syndrome.

The classic electrophysiological studies conducted by Gloor[31] led to the corticoreticular theory of generalized epilepsy: This theory postulates an underlying cortical hyperexcitability and abnormal response to thalamocortical input, which would operate in the absence of any lesional substrate. Genetic animal models of generalized epilepsy confirm the role played by thalamocortical circuits in cortical spike-wave generation, and it has been proposed that genetically determined dysfunction of reticular thalamic neurons is responsible for the abnormal excitation. Since then, evidence has also been accumulating suggesting that subtle but probably significant neurochemical and morphologic alterations exist in both cortex and thalamus in IGE. Meencke and Janz[52] and Meencke and Veith[53] described subtle cortical neuropathologic changes in IGE (“microdysgenesis”) believed to be migrational disturbances, but this has not been confirmed in other small series.[57]

Furthermore, there is much genetic heterogeneity in JME. A positive family history of epilepsy is common, and there is recent evidence that JME constitutes a single gene syndrome in some families,[19,23] although most families show complex inheritance. Some JME cases are apparently sporadic, others occur in families with other IGE syndromes, and occasional families have a pure autosomal dominant JME phenotype. However, the patients in these various groups are otherwise clinically indistinguishable by usual diagnostic criteria. Different genetic results may relate to different diagnostic criteria, including the importance given to detailed classification of EEG patterns, differing estimates of penetrance, and choice of models for linkage analysis.[9] Linkage to chromosomes 6p and 15q has been described,[25,33,46,79] and mutations in the CACNB4 gene (on chromosome 2q),[26] in the CLCN2 gene (on chromosome 3q),[21,35] in the GABRA1 gene (on chromosome 5q),[19] and in the EFHC1 gene (on chromosome 6p)[71] have been identified in JME patients.

The various mutations suggested for JME are all believed to influence neuronal excitability but involve different mechanisms. Both direct ion channel mechanisms and nonionic mechanisms have been proposed. How these interact with other possible susceptibility genes and with environmental factors is not yet clear. Vijai et al.[77] suggested that a potassium channel gene polymorphism may predispose to JME and that later gene expression of KCNQ3 may account for the striking age dependence that is typical of JME. Another potassium channel gene polymorphism in KCNJ10 has been associated with susceptibility to several common seizure types.[13] Chloride currents, which affect inhibition, are implicated in some studies. Families linked to chromosome 3q and with mutations in the ClCN2 gene, which encodes the ClC-2 voltage-dependent chloride channel, suggest a defect in γ-aminobutyric acid (GABA)-mediated inhibition. Altered GABA-mediated inhibition is also implicated in autosomal dominant JME. The GABRA1 mutation found in autosomal dominant JME encodes a mutant α_1 subunit of the GABA_A receptor, but the functional effect, altered chloride current, and thus altered neuronal inhibition depend on the number of mutant subunits and their position within the pentameric structure of the ligand-gated chloride ion channel.[29]

Mutations in EFHC1 have more complex effects that may be associated with the pathogenesis of JME.[71] In animals, EFHC1 protein is not an ion channel protein but increases calcium currents in R-type voltage-dependent calcium channels and promotes calcium-related apoptosis; these effects are partly reversed by the mutations associated with JME.[71] Such mutations may thus interfere with apoptotic activity and prevent the normal elimination of neurons during postnatal development of the central nervous system in humans. This may result in increased density of neurons and formation of hyperexcitable circuits. Microdysgenesis, reported in JME, may be a visible manifestation of such a process, which may also be associated with age-dependent seizure onset. Mutations may also destabilize calcium homeostasis with resulting effects on sensitivity to sleep deprivation and other clinical triggers of seizures in JME. However, mutations in EFHC1 were found in only 6 of 44 families, and the authors suggested that unidentified mutations may exist in intronic or regulatory regions.[71] Similarly, the BRD2 gene, in which a mutation in JME was reported by Pal et al.,[60] is a putative nuclear transcription regulator and a member of a family of genes that are expressed during development and may thus be relevant to the reported abnormalities in imaging and age-related onset of JME.

Clinical Presentation

This is an age-dependent disorder with onset usually in the second decade, but occasionally earlier and not infrequently later. It is important to recognize this group of patients since they are generally fully controlled on valproate in about 80%,[14] but require lifelong treatment.

Myoclonic seizures, mainly involving the arms and occurring preferentially in the postawakening period, are the main feature of JME and are correlated with short bursts of generalized spike-wave or polyspike-wave complexes.[22] The myoclonus is quite variable in intensity, often unreported by patients until a GTCS occurs, and then identified only after specific questioning. It is often not considered to represent a major inconvenience to patients, who frequently prefer not to take medication in order to suppress it. Others, however, prefer not to be frequently reminded of their epilepsy by these minor symptoms. When minor manifestations such as myoclonus or absence coexist with major seizures, treatment with antiepileptic drugs (AEDs) such as valproate or clonazepam is mandatory.

The myoclonus usually responds quite readily to antimyoclonic agents such as valproate, clonazepam, piracetam, or levepiracetam, but it may be difficult to control during certain periods of the patient's life. The reasons for this are not entirely clear, but loss of seizure control may be correlated with emotional factors. The generalized attacks are often precipitated by the concurrence of sleep deprivation and being woken up from sleep, and this sequence should obviously be avoided, if at all possible. Further clinical features are discussed in recent detailed reviews of JME.[75,84]

In an effort to better define syndromes for genetic study, Taylor et al.,[74] working with Berkovic and Scheffer in Australia, showed overlap between the clusters of clinical features used to diagnose JME and IPOE, suggesting a relationship with this focal epilepsy syndrome, especially with respect to visual auras and conscious head version (which are typical of IPOE) in patients with JME. They identified coexistence of myoclonic seizures and occipital EEG spikes in the same individuals in both syndromes. The probands and their families were evaluated in detail by highly skilled observers, and one may suspect that such overlap exists more commonly than is currently realized but that patients are not usually questioned as carefully.

Diagnostic Evaluation

Although JME is considered a typical generalized epilepsy, earlier and more recent reports of clinical, EEG, and imaging studies have raised questions regarding the degree to which this classification can be strictly maintained. Clinical and EEG studies of JME and of reflex seizures in generalized epilepsies have suggested localized or regional hyperexcitability in generalized epilepsy syndromes, especially in JME.[5,15,40]

Electroencephalographic Findings

The typical abnormality on EEG is bilateral multiple spike- or polyspike-wave complexes at a rate of four to six per second, with anterior predominance. Photosensitivity occurs in about 30%, especially in women, but the two disorders appear to be inherited separately.

Scalp EEG showed focal interictal epileptiform discharges in 30.3% of JME patients studied in detail by Panayiotopoulos et al.,[61] and focal EEG abnormalities of all kinds in 36.7%.[2] In

our experience, frequent unilateral or bilateral temporal EEG abnormalities are seen as patients age.[66] Panayiotopoulos et al.[61] also commented on the precipitation of seizures by mental activation as part of the syndrome, which may represent seizures induced by thinking. Wolf emphasized the typical frontocentral predominance of the ictal EEG activity recorded with the myoclonic jerks of JME.[82] This regional predominance and cognitive activation have been discussed by several authors (for review, see Matsuoka et al.[51]).

Neuroimaging

Although JME is classified under the so-called idiopathic epilepsies, evidence from structural and functional imaging highlights the existence of underlying abnormalities. Studies in patients with JME have shown abnormalities in mesial frontal structures in many[81] and some have more widespread abnormalities of cortical gray matter. Using magnetic resonance spectroscopy (MRS), Savic et al.[68] showed reduction in frontal lobe *N*-acetyl aspartate (NAA) in JME, and later confirmed that frontal NAA was reduced in patients with JME but not in those with generalized epilepsy with tonic–clonic seizures.[69] These investigators also showed reduced thalamic choline and myoinositol concentrations in both IGE syndromes. Mory et al.[54] studied thalamic MRS in JME and reported reduced NAA/phosphocreatine ratios in nine out of ten patients. Similar findings were reported by Bernasconi et al.[11] in 12 out of 20 patients with IGE. Twelve patients had JME, but these cases were not analyzed separately.

Combined EEG and functional magnetic resonance imaging (fMRI) in patients with IGE, including JME, has demonstrated bilateral thalamic activation, with increased blood oxygenation level–dependent (BOLD) signal during bilateral spike-wave activity in most individuals and deactivation in bilateral frontal, parietal, and posterior cingulate regions.[1] Thus, although MRS and fMRI studies support a role for thalamic abnormalities in IGE, they also implicate more localized cortical neuroanatomic mechanisms in JME in particular. MRI and MRS studies thus support the suggestions made on clinical and EEG grounds that the frontal cortex is in some way preferentially involved in JME.

Biochemical Studies

Biochemical studies have also sought evidence of systemic metabolic abnormalities that would, when expressed in the brain, alter cortical function in generalized epilepsy. Platelets have been used as a model of GABAergic neurotransmission. Rainesalo et al.[65] reported reduced platelet GABA uptake in patients with JME and increased activity of the catabolic enzyme GABA-transaminase, which may indicate impaired cerebral GABAergic function. They also reported increased interictal plasma glutamate in JME patients, with no significant change in the postictal period.[64] This study confirms earlier findings in both generalized and focal epilepsies.[41]

Genetic Studies

Genetic studies have also contributed to our understanding of JME. Based on family and twin data, respectively, Andermann,[3] Berkovic et al.,[10] and other investigators concluded that most IGEs, as well as most idiopathic focal epilepsies, are inherited as multifactorial or complex traits, with the additive effects of several or many susceptibility genes and interaction with environmental factors to produce the final phenotype. Even in so-called monogenic epilepsies, the variation in phenotype among family members and between families is attributed to the effects of modifying genes and environmental or developmental factors. Multiple IGE subsyndromes may exist in the same family, even in those with a single gene defect.[4,12] Marini et al.[50] reported that, although childhood and juvenile-onset absence epilepsies share a close genetic relationship, JME appears to be genetically more distinct. A recent study also demonstrated different genetic influences between IGE families with absences and those with myoclonic seizures,[80] and other studies showed different linkage groups for childhood and adolescent absence epilepsy and for JME.[37]

The discovery that some well-defined epilepsy syndromes are channelopathies has also fueled efforts to describe the mechanisms underlying JME. Several genetic models have been proposed for generalized epilepsies and for JME in particular, and mechanisms of epileptogenesis have also been proposed based on these findings. Mulley et al.[56] pointed out that "all but one of the idiopathic epilepsies with a known molecular basis are channelopathies. Where the ion channel defects have been identified, however, they generally account for a minority of families and sporadic cases with the syndrome in question. The data suggest that ion channel mutations of large effect are a common cause of rare monogenic idiopathic epilepsies, but are rare causes of common epilepsies."

When a positive family history of epilepsy can be obtained, most JME occurs in families with a variety of IGE syndromes. Several loci have been mapped for IGE in such families, including 8q, 3p, and 1p (for review, see Gourfinkel-An et al.[32]). Sander et al.,[67] in a large genome-wide scan of families with IGE, reported linkage to chromosome 3q among other loci. The candidate interval on 3q includes the gene ClCN2 coding for the ClC-2 voltage-dependent Cl^- channel, largely expressed in cerebral neurones and inhibited by GABA. Haug et al.[35] reported three different heterozygous mutations in this gene in three unrelated families with IGE. These mutations segregate with the epilepsy phenotype in each family and all cause changes in function associated with neuronal excitability. These authors also detected a novel polymorphism in the ClCN2 gene based on 115 parent–child trios. ClCN2 is the first epilepsy gene with both rare major gene mutations and a common sequence variation (polymorphism) conferring a range of phenotypic effects. Mutations in this gene have also been reported in two other families: In one family the proband had JME and in the other the proband had focal epilepsy, thus confirming ClCN2 as a major gene for more than one type of epilepsy.[21]

Another gene located in the 3q26 region, KCNMB3, codes for regulatory subunits associated with calcium-activated potassium channels (B channels). Four polymorphisms in this gene were detected in a variety of patients with epilepsy including JME. These variants were found to be associated with functional deficits of the BK channel.[39]

A recent genetic study of a large French-Canadian family with autosomal dominant JME (ADJME)[19] showed that affected individuals are heterozygous for a missense mutation (A322D) in the gene coding for the α_1 subunit of the $GABA_A$ receptor (GABRA1) on chromosome 5q34. It is also of interest that this region overlaps the locus for GABRG2, one of the genes responsible for GEFS+ (generalized epilepsy with febrile seizures plus) syndrome as well as for absence epilepsy with febrile seizures.[8,78] As is often the case in genetic studies of epilepsy, autosomal dominant JME accounts for only a small proportion of JME, and studies of other families have yielded different results. Although the same mutation in GABRA1 was not found in a study of Indian JME families,[44] these investigators[77] suggested that polymorphisms in a potassium channel gene, KCNQ3 (EBN2, 8q24), may be important in predisposing to JME in South Indian families. They also suggested that the later expression of the KCNQ3 gene may help to explain the characteristic adolescent onset of JME, as compared with the neonatal onset of seizures in benign familial neonatal convulsions (BFNC) associated with major mutations in KCNQ2. However, major mutations in KCNQ3 have been identified in Mexican-American families with BFNC.[17] Susceptibility to seizures of many kinds has also been proposed in relation to a missense variation in the human potassium ion channel gene KCNJ10.[13]

Other investigators using linkage studies have proposed that susceptibility loci for JME exist at 6p11–12,[6,45,46,62] HLA-6p21.3 region,[33] 15q14,[25] and 5q34.[19] Recent studies conducted in Dutch families narrowed the region on 6p11–12,[62] known as EJM1. Suzuki et al.,[71] reviewing previous studies from Belize, Los Angeles, and Mexico[6,45,46] and extending them, described a novel gene, EFHC1, in this region. Five mutations in EFHC1 segregated with JME in 6 out of 44 families and were not found in healthy control individuals. EFHC1, unlike other epilepsy genes, does not encode ion channels but modulates and interacts with voltage-dependent calcium channels and has apoptotic activity. The authors proposed that EFHC1 is the gene on 6p12 that is associated with JME. Although mutations in both GABRA1 and EFHC1 are rare causes of JME,[48] disease-causing mutations in EFHC1 have been identified by other groups[48,69a] both in JME and in other forms of IGE.

Other families exhibit linkage to the 6p21.3 region associated with HLA rather than to 6p12. Pal et al.[60] suggested that JME at the 6p21 locus may be caused by a mutation in the BRD2 gene. The authors noted that the abnormal MRI in JME[81] would be consistent with involvement of BRD2.

Association studies suggest that the $\alpha_{1\,A}$ subunit of the voltage-gated calcium channel gene (CACNA1A) may affect susceptibility to IGE.[18] This channel is responsible for seizures and ataxia in tottering and leaner mice[28] and has also been implicated in human episodic ataxia type 2, spinocerebellar ataxia type 6, and a form of familial hemiplegic migraine.[58] Escayg et al.[26] found coding and noncoding variations of the human calcium channel gene CACNB4 in patients with IGE and epithotic etaxia.

In summary, although several major genes have recently been identified for IGE, and for JME in particular, only mutations in the ClCN2 and EFHC1 genes have been replicated by different groups. Furthermore, no consistent genetic pattern has been revealed by association studies for any common idiopathic epilepsy syndrome.[73] A number of association studies of other ion channels in IGE, including JME, have yielded negative results.[7,27,72]

Differential Diagnosis

Two main differential diagnoses have to be considered here. In the cases where myoclonus is not well characterized, it may be confounded with a partial seizure with motor manifestations and, in this situation, a detailed clinical history is important. The main implication of the misdiagnosis of JME as a partial epilepsy is, of course, the choice of the wrong AED, and further classification of the epilepsy as a refractory one. The second differential diagnosis is for those patients who do not clearly report myoclonus, which may delay the diagnosis of JME. These patients may be diagnosed as having one of the various forms of idiopathic generalized epilepsies with generalized tonic-clonic seizures.[4] Again, a detailed clinical history is the essential tool. Other rare differential diagnoses include the progressive myoclonus epilepsies, especially Lafora disease and Unverricht-Lundborg disease, which also present in adolescence and may resemble JME in the early stages.

Treatment and Outcome

Valproate is the drug of choice. The newer AEDs, such as lamotrigine and topiramate, result in variable control of the myoclonus, but good efficacy for the GTCSs in JME. Levetiracetam appears to have significant antimyoclonic effect. Clonazepam is a good add-on drug for myoclonis, and can be used in monotherapy only in patients who have never had GTCs. The lack of responsiveness of JME to AEDs such as carbamazepine or phenytoin with, in some patients, even an increase in myoclonus due to these agents should be emphasized. In the European literature, the activation of minor epileptic manifestations of IGE such as absence or myoclonus by carbamazepine or oxcarbazepine as well as phenytoin, vigabatrin, and gabapentin has been stressed,[76] but this has only recently been accepted in North America.

Long-term Prognosis

The prognosis of myoclonus in this form of epilepsy is not entirely clear. Although AEDs can be withdrawn in only a minority (10% to 20%) of patients,[14,61] it is generally accepted that there may be improvement over time, particularly with respect to myoclonus, and that the process may be less active, but without complete remission in adult life. The great majority of patients responds to treatment with appropriate antimyoclonic and antiepileptic medication, and has an otherwise benign outcome with no other neurologic disturbances. Since most patients continue to be on medication, it is difficult to know how often the myoclonus remits spontaneously over time.

Summary and Conclusions

JME is a frequent type of IGE characterized by myoclonic seizures, most often implicating a lifetime use of valproate. Recent work suggests that JME may represent several different disorders with different genetic and pathophysiologic signatures found in patients who are clinically or practically indistinguishable.

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Chapter 245

Overview: Non–Age-Related and Special Syndromes

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Introduction

Each of the chapters in this section uses a different approach to address one of two challenges in epileptology: (a) the relationship connecting seizure semiology, the structures involved in epileptogenesis, and related lesions and (b) the interplay between predisposing and precipitating factors in igniting seizures. In addition, chapters on familial epilepsies involving the temporal lobe (Chapter 248), frontal lobe (Chapter 249), and variable foci (Chapter 255) reflect the increasingly recognized role of genetics in the etiology of seizure disorders, including those without an apparent familial seizure history.

Semiology, Epileptogenesis, and Related Lesions

The precise definition of the structures or systems responsible for ictal phenomena has long posed a challenge to the best efforts of distinguished investigators. For Hughlings Jackson, "the study of partial seizures became the starting point for the study of localization of function within the central nervous system."[31] As described by Jasper,[31] Sherrington electrically stimulated the cortex of anthropoid apes to examine functional–structural relationships. The early stimulation studies in humans performed by Foerster[17] preceded the exhaustive studies carried out by Penfield and Jasper in the course of evaluating patients for epilepsy surgery; these culminated in their classic work, *Epilepsy and the Functional Anatomy of the Human Brain*.[31] Interictal electroencephalography (EEG) has provided helpful correlative data to clarify the localizing significance of ictal symptomatology,[11,31] as has intracranial recording.[3] However, Williamson and Engel (see Chapter 246) caution that sophisticated techniques for correlating ictal electrical activity with clinical phenomena have only revealed the complexities of anatomic–symptomatologic relationships.

A second method of identifying structures or systems responsible for ictal phenomena has been to correlate the latter with structural lesions. In Chapter 246, the authors indicate that Hughlings Jackson first recognized the correlation between ictal behavior and the location of structural abnormalities in the brain. Defining "specific lesions" as "discrete focal (or regional) structural pathologies that are associated with chronic partial epilepsy," Chapter 251 examines such relationships. These authors review changes in neurotransmitters in the vicinity of tumors, favoring excitation over inhibition. They cite the finding of Awad et al.[5] that lesionectomy alone more often renders patients seizure free than resection of epileptogenic cortex without regard to lesion, supporting a direct relationship between structure and ictogenesis. Fortunately, improved neuroimaging now more accurately identifies focal or regional epileptogenic lesions (Chapters 247 and 251).

However, several factors complicate such relationships. Penfield[31] demonstrated that the form of the attack is considered to be due to the functional characteristics of the local area of onset within the brain, the strength of initial discharge, and the path of its spread to other brain areas. Rasmussen[32] acknowledged this factor of propagation in elaborating a concept of secondary localizational aspects of epileptic phenomena. His review of seizure-free patients after frontal lobe resection found no correlation between surgery site and seizure characteristics. Variability of propagation patterns is a principal factor in confounding any anatomic classification of seizures.

Williamson[41] indicated that rapid spread of frontal seizures clouds the localizing value of many ictal phenomena. Varying and bilateral motor ictal phenomena may be consequent to multiply targeted intracortical and corticofugal projections within the motor system, including ipsilateral projections to proximal limbs.[8,14,41] Abundant projections from the occipital cortex to anterior temporal areas[24,35] effect the dyscognitive seizures from occipital epileptogenesis. More recently demonstrated temporal-to-occipital projections[4,16,25] are likely among factors producing visual auras from extraoccipital seizure origins.[7] In addition, a seizure disorder beginning while the brain is developing may lead to abnormal patterns of innervation.[19,38] For example, a seizure-related failure of “pruning” through apoptosis may produce a permanently abnormal connectivity.[22]

Moreover, epileptogenic regions may be remote from a lesion that is also epileptogenic (Chapter 251). Temporal epileptogenic regions may coexist with epileptogenic occipital lesions[10,29] or with parietal arteriovenous malformations.[43] For undetermined reasons, lesions may be unevenly epileptogenic around their peripheries. Thus, O'Brien et al. (Chapter 252) cite works indicating that resection of a lesion as well as epileptogenic cortex is necessary for optimal seizure reduction.[6,39,44] A further confounding factor impeding the establishment of structural–semiologic relationships is the possibility that lesions may extend beyond their manifestations on neuroimaging studies. This factor may underlie the relative ineffectiveness of surgery as treatment for epileptogenic neuronal migration disorders (Chapter 251).

Defining seizures or epilepsies according to lobes of the brain is inexact because none is fully functionally distinct from the others. This sharing of functions partially underlies the overlap of symptoms of seizures arising from different regions. Several examples of seizure types that transcend lobar boundaries are described in Chapter 246.

The aforementioned impediments suggest that epileptic seizures should be analyzed according to the systems involved rather than discrete cortical loci. For example, the intimate connections of thalamic nuclei with circumscribed cortical regions suggested to Penfield[31] that the cortex be divided according to thalamic projection areas. Rapid propagation of cortical discharge to related thalamic nuclei[36] and the decrease of cortical discharges by thalamic lesions[15,21,27,28] support this concept. The term “system” is applied here in the same way in which we otherwise speak in neurology about system disorders, actually referring to subsystems of the nervous system.

Probably the best example of an epilepsy involving a system is that of mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE-HS), described in Chapter 247. In contrast to anatomically based descriptions of seizure types, this is a localization-related syndrome with a semiology centered around the limbic system. The characteristic ictal semiology and mesial temporal pathology—hippocampal sclerosis—are the fundamental components of MTLE-HS. This is likely the most common correlate between semiology and structure encountered in practice. However, the persistence of auras after successful temporal lobectomy reflects the complex genesis of symptoms caused by epileptic discharge centered in the mesial temporal regions, which is a further example of a seizure type that transcends lobar boundaries. The system concept is further exemplified by the shared semiology of seizures propagating to the limbic system and those originating in that same system.[9,40] However, ever more precise stereoncephalography can disclose ictal semiologic distinctions within the temporal lobe. Thus, in some studies, laterally originating temporal seizures have been found to be shorter, more likely to have auditory symptoms, and secondarily generalize more than those originating mesially.[26]

The idiopathic localization-related epilepsies afford an additional opportunity to link systems involved in epileptogenesis with seizure symptomatology. Syndromes with focal seizures unrelated to any identifiable or presumed brain pathology but with associated characteristic EEG abnormalities, often in homotopic regions of both hemispheres, and with spontaneous remission have been described principally among children.[2]

Inherited channelopathies are associated with several epilepsy syndromes, usually with onset in childhood.[20] Some become lifelong disorders. “Febrile seizures plus,” a genetic disorder involving mutant neuronal sodium channels, begins in childhood as febrile seizures and may continue into adulthood as one or more types of afebrile generalized motor seizures.[33] Similarly, autosomal-dominant nocturnal frontal lobe epilepsy, associated with mutations in genes encoding neuronal nicotinic acetylcholine receptors, begins in childhood but persists into adulthood despite its usually mild nature. Chapters 249 and 256 further describe these entities. The homogeneity of ictal semiology of these conditions and the lack of "contamination" of ictal genesis by associated lesions suggest that such benign conditions may clarify semiologic–structural relationships if newer methods of tracing an ictal pathway—such as functional magnetic resonance imaging—can be applied.

Predisposing and Precipitating Factors in Epilepsy

The second group of chapters deals with the complex interplay between predisposition for epileptic seizures and immediate provocative factors. As Dreifuss[13] stated, "The reason a person who is epileptic all the time does not manifest seizures all the time is that the necessary provocation sufficient to trigger the individual seizure is intermittent and is frequently the result of concatenations of circumstances." The proportion of seizures that occur spontaneously is difficult to establish because triggering events may pass unrecognized or unappreciated. Nonetheless, the balance of each pathogenetic component—predisposition and provocation—varies with the epilepsy. These chapters describe various conditions, each with different proportions of predisposing and triggering components.

In posttraumatic seizures (Chapter 253), predisposing components predominate. The authors document forms of trauma that put a patient at a higher risk for the development of late seizures, the common factor being the presence of intracerebral blood. However, stress or lack of sleep may provoke the first late seizure.

Berkovic (see Chapter 252) presents a valuable update on the concepts and data pertinent to the progressive myoclonus epilepsies. These conditions provide convincing evidence of predisposing factors for the development of seizures. Features usually include myoclonic and tonic–clonic seizures, ataxia, and dementia. The distinctive features of each condition producing the syndrome, along with aspects relevant to differential diagnosis, are presented. The increasing importance of obtaining a family history and examining relatives of patients is emphasized. Even in conditions associated with a strong tendency for seizures, provocative factors are involved. Thus, the myoclonus of Unverricht-Lundborg disease may be precipitated by movement, stress, or sensory stimuli. Similar stimuli may evoke the myoclonic seizures of Lafora disease.[1]

Dreifuss' concept[13] of the relationship between predisposing factors and precipitants is again relevant to Chapter 254, in which solitary seizures are defined as events that may occur once in a lifetime or very rarely. Apart from seizures accompanying acute conditions, such as trauma or encephalitis, it may be assumed that a predisposition for an isolated seizure has existed for some time. Indeed, data from Wolf's series disclosed an identifiable predisposing factor in the majority of patients. Moreover, at least one seizure-provoking factor could be identified in 80 of his 104 patients. As in other studies,[18,23] lack of sleep was a common precipitant of isolated seizures.

Chapters 256 and 257 discuss forms of epilepsy in which an identifiable agent, such as fever, flashing lights, lack of sleep, or drug withdrawal, precipitates many or all of the seizures. Most such seizures are of the generalized tonic–clonic type. The relative importance of predisposition and precipitant factors varies among the broad categories described in each chapter, among entities, and among individual patients. In all cases, the sum of these factors intermittently exceeds the seizure threshold. For patients with these epilepsies, avoiding the precipitants helps to control the seizures.

The seizures of simple reflex epilepsies (Chapter 257) are associated with the most apparent and immediate specific provocators. As the authors emphasize, the seizure history must be scrutinized to discern and establish the relationship. Chapter 257 also describes precisely how visual stimulation should be applied during clinical EEG to confirm light- and pattern-sensitive epilepsy and presents clinical data concerning the photoparoxysmal response.

Photosensitive epilepsy is a model for the interplay of factors leading to tonic–clonic seizures. Although a genetic defect specific for photosensitive seizures has not been discovered, data suggest an autosomal-dominant inheritance.[12,30,37] Withdrawal of alcohol and benzodiazepines may be causes of temporary photosensitivity.

Startle epilepsy is a particularly crippling condition; its mechanism and effective management have proved elusive to investigators.

This section concludes with an interesting review of complex reflex epilepsy, in which precipitants also play essential roles in causing seizures. The attacks are triggered by relatively elaborate stimuli whose specific pattern is the determining

factor in seizure evocation. Reading, musicogenic, praxis-induction, and thinking epilepsies fall into this group. Because the precipitating stimuli involve higher cortical function, the relationship may be less immediate or obvious and may include anticipation of the stimulus complex. Discovering such epilepsies may be the reward for an ingenious historian or a perceptive patient. As in other precipitant-related epilepsies, these compound stimuli may evoke generalized tonic–clonic seizures. However, they may also elicit more restricted forms, such as myoclonus of the jaw in reading epilepsy and dyscognitive seizures in musicogenic epilepsy. Perhaps even more than the simple reflex epilepsies, the complex variety likely requires participation of several cortical and subcortical regions, further supporting the system concept of epileptogenesis.

It is of special interest, complex precipitating mechanisms like praxis induction of reading and talking seem to be particularly related to the syndrome of juvenile myoclonic epilepsy (JME). Perioral reflex myoclonias provoked by talking and reading are probably related genetic traits that JME shares with primary reading epilepsy, that is, an idiopathic localization-related epilepsy.[34,42] This observation is thought provoking because it seems to open a new view onto ictogenesis in the so-called generalized epilepsies, which are likely also to become redefined according to the concept of system epilepsies.

Summary and Conclusions

These chapters examine two relationships in epilepsy of importance to clinicians and basic scientists: (a) epileptogenesis and epileptic lesions on one hand and (b) predisposition and provocation of epileptic seizures on the other.

The intricate interaction between epileptogenic lesion and host, the surrounding brain, exhibits properties common to many patients but often harbors components unique to a particular patient. How this interaction produces the epileptic seizures may be understood by scrutiny of not only the histology and situation of the lesion, but also of the systems so engaged in the epileptogenesis. Several chapters in this section examine these aspects.

Why seizures occur only intermittently in a patient chronically harboring a seizure tendency, that is, predisposition versus provocation of epileptic seizures, is of interest in a second series of chapters. Greater realization of this interaction will improve clinical management and also shed light on several significant pathophysiologic mechanisms.

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Chapter 246

Anatomic Classification of Focal Epilepsies

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Introduction

The International Classification of Epilepsies, Epileptic Syndromes, and Related Seizure Disorders[2] recognizes five symptomatic localization-related epilepsies, four of which are anatomically defined: Temporal lobe epilepsies, frontal lobe epilepsies, parietal lobe epilepsies, and occipital lobe epilepsies. Only the fifth, chronic progressive epilepsia partialis continua of childhood, is not classified by location. If we accept the definition of an epileptic syndrome as a complex of signs and symptoms, with only one feature being the occurrence of electroclinically characteristic epileptic seizures.[1] then we can make a cogent argument for the existence of a syndrome of mesial temporal lobe epilepsy (MTLE)[47,55,208,218,222] (see Chapter 247). Otherwise, the classification of epilepsies by anatomic lobe appears to refer predominantly to conditions with characteristic seizure types as the only unifying feature. Recent reports of the International League Against Epilepsy (ILAE) argue against the view that these conditions are syndromes rather than seizures.[51] However, as there is as yet no new classification of syndromes, anatomically defined epilepsies with variably specific seizure types will be retained in this chapter. Other than MTLE, there may be a few examples with constellations of findings that do constitute true syndromes. These possible exceptions will be discussed later.

Much effort has gone into creating an anatomic classification of epileptic seizures, based largely on data obtained from epilepsy surgery centers. The anatomic classification has been greatly assisted by the introduction of high-resolution magnetic resonance imaging (MRI) more than 20 years ago, enabling the detection of small, circumscribed, potentially epileptogenic lesions in many patients with symptomatic localization-related epilepsy. Nevertheless, the validity, or for that matter, clinical value of devising an anatomic classification of epileptic disorders remains the topic of considerable debate. This chapter will review the subject, but emphasis, of necessity, will be placed on seizures rather than syndromes.

Historical Perspectives

John Hughlings Jackson is credited with being the first neurologist to recognize the correlation between ictal behavior and the location of structural abnormalities in the brain.[190] His work derived largely from observations of ictal signs and symptoms, followed by identification of lesions at postmortem examination, in an era of pioneering investigations of localization of function within the brain.[48] This work led directly to the application of surgical treatment for refractory partial epilepsy,[82] which, in turn, provided opportunities for invasive investigations of the human brain, such as direct stimulation to delineate anatomic substrates of specific ictal manifestations.[151] With the advent of the electroencephalogram (EEG), the location of focal interictal spikes was used as evidence for the site of origin of habitual seizures, and surgical treatment for “temporal lobe epilepsy” was introduced on the basis of EEG evidence alone.[11] Shortly thereafter, the pioneering efforts of Bancaud et al. related intracranial seizure recording to clinical seizure characteristics.[12]

The development of sophisticated electrophysiologic techniques for recording spontaneous seizures with intracranial electrodes and correlating this information precisely with videotaped ictal behavior has made anatomic classification of seizures more, rather than less, controversial. Because of variability of propagation patterns of ictal discharge, the area of brain giving rise to clinical signs and symptoms can be at considerable distance from the actual site of seizure onset. Consequently, virtually no signs or symptoms can be considered pathognomonic of the anatomic localization of the primary epileptogenic region.[4,121,124] Although the timing or sequencing of seizure manifestations may be as important as their presence or absence, this feature fails to localize precisely because of the potential for seizure origin in clinically "silent" brain regions.

Improvements in structural imaging also have not definitively clarified anatomic classification. High-resolution MRI can identify many structural cerebral lesions in patients with localization-related epilepsy,[107] and they are usually indicative of the epileptogenic region.[25] Many patients with partial seizures, however, have normal MRI evaluations; others have lesions that are unrelated to their epilepsy. Furthermore, it has become increasingly apparent from intracranial recordings of patients under evaluation for surgical treatment that a discrete, well-circumscribed epileptogenic region often does not exist in the human brain; instead there are diffuse or multiple areas of functional abnormality capable of generating interictal, and even ictal, discharges, even in patients for whom a specific localized structural lesion has been identified.[46,214,220] For these reasons, anatomically classifying a seizure disorder merely on the basis of the location of an observed structural abnormality is not always justifiable. Nevertheless, a continued effort to categorize epileptic seizures, and even epileptic disorders, according to a presumed anatomic substrate can be considered a reasonable exercise of some value, particularly for devising presurgical diagnostic strategies, as long as the limitations of such a classification are recognized and surgical interventions are not undertaken on the basis of ictal manifestations or MRI lesions alone. Combining clinical seizure characteristics, structural neuroimaging findings, and EEG results, however, has improved our understanding of partial seizures and helped to better define an anatomic classification.

Functional imaging using positron emission tomography (PET) has been employed at a few medical centers for many years and is currently becoming available at many more institutions. While early results in patients with temporal lobe seizures were and still are promising,[28,117] PET utility in patients with seizure origin outside of the temporal lobe

has been less consistent.[128] Newer radioligands and improved technologies will almost certainly improve results in extratemporal epilepsy with normal MRI[77,117] (see Chapter 80).

Ictal single positron emission computed tomography (SPECT) is being used widely to help identify regions of seizures origin.[75,92,101,117,130,143,182,201] Early injection is essential, particularly with brief seizures that propagate rapidly.[113,201] The subtraction product of interictal SPECT from ictal SPECT coregistered with MRI improves the resolution of this relatively difficult-to-obtain procedure.[141,142,143] Ictal SPECT has become an integral part of the presurgical evaluation in some centers. This is particularly relevant when the MRI is normal.

Magnetoencephalography (MEG)[45] superimposed on MRI and EEG-triggered functional MRI[104] have great promise for localizing sources of ictal, as well as interictal, epileptiform activity. In the former, dipole localization is easier than with EEG because differences in conductivity between brain, cerebrospinal fluid (CSF), bone, and skin do not need to be taken into account. In the latter, simultaneous EEG and MRI recording permit MRI acquisition during epileptiform discharges to be subtracted from MRI acquisitions in the absence of epileptiform discharges, so that the difference in blood oxygenation can be used to localize tissue activated during the EEG events of interest. Magnetic resonance spectrometry (MRS) is also being used to identify metabolic changes associated with interictal disturbances, and this has been particularly useful for confirming hippocampal epileptogenic lesions.[109,186]

Definitions

With the exception of MTLE, the designation of an epileptic condition by anatomic location denotes the occurrence of a specific type of seizure or seizures, rather than a complex of signs and symptoms that would ordinarily constitute a syndrome. In the purest sense, a temporal lobe epilepsy, for example, would be an epileptic condition in which seizures originate somewhere in the temporal lobe, as indicated directly by invasive electrophysiologic monitoring, or inferred indirectly from clinical seizure characteristics, scalp EEG monitoring, perhaps the presence of a discrete lesion on structural neuroimaging, functional disturbances revealed by neurologic examination, neuropsychological testing and functional neuroimaging, and disappearance of habitual events following a temporal lobe resection of some type. There remains some controversy, however, with this terminology. In much of the published literature on temporal lobe epilepsy, some patients are given this diagnosis when extratemporal ictal onsets preferentially project to mesial temporal structures that, in turn, are responsible for mediating the characteristic ictal manifestations. In many cases, such patients are diagnosed as having temporal lobe epilepsy because the extratemporal origin of their seizures is unrecognized, but in others the actual site of the primary epileptogenic region is ignored and classification is based on ictal characteristics.[208] If a temporal lobe seizure is one that is caused by seizures involving temporal lobe structures, then this could result from ictal initiation within the temporal lobe or an extratemporal “silent area” that preferentially projects to the temporal lobe. Thus, if temporal lobe epilepsy is characterized by the existence of temporal lobe seizures, then the broader definition is acceptable. Rather than dwell on the semantic difficulties associated with anatomic classification, this example can be used to argue the folly of attempting to construct an anatomic classification of epileptic disorders at all. On the other hand, if a specific temporal lobe epilepsy syndrome can be defined, then seizures originating elsewhere can, in part, be identified by virtue of not fulfilling all the characteristics of this syndrome.

Attempts to define seizures or epilepsies according to anatomic lobes of the brain are also confounded by the fact that none of the classical four lobes represents functionally homogenous or unique regions. For instance, parts of the frontal lobe, such as the precentral gyrus, are capable of generating specific ictal signs and symptoms, whereas others, such as the orbital frontal cortex, belong, in part, to the limbic system and can give rise to ictal signs and symptoms by virtue of propagation to other frontal regions or mesial temporal structures, or both (see section on frontal lobe seizures). The International Classification of the Epilepsies divides frontal lobe epilepsy into seven anatomic subtypes and temporal lobe epilepsy into two anatomic subtypes, based on the belief that these areas give rise to different characteristic ictal manifestations.[2] However, there are also functional areas of the brain that give rise to relatively stereotyped clinical seizure characteristics, despite the fact that they encompass more than one anatomic lobe. Thus, seizures arising from the perirolandic area can generate indistinguishable signs and symptoms from motor or sensory cortex, and there may be characteristic features associated with ictal discharges in the temporal-parietal-occipital junction, as well as regions of frontal parietal operculum and insula.

Nevertheless, as our understanding of the various specific and anatomically originating seizures improves, there may emerge clearer evidence on how these clinical characteristics can help localize regions of seizure origin, both by virtue of their uniqueness and their masquerading qualities. This may be particularly true of some, but not all, seizures of frontal lobe origin.

Epidemiology

Among the localization-related epilepsies, the relative incidence and prevalence of temporal lobe, frontal lobe, parietal lobe, and occipital lobe epilepsy have not been adequately determined, due largely to the recognized inaccuracies of identifying anatomic substrates without sophisticated diagnostic evaluation. Data from epilepsy surgery centers indicate that temporal lobe epilepsy is by far the most common of the four when only medically refractory patients are considered. In a review of surgical procedures performed worldwide for medically refractory epilepsy, approximately 70% have involved resections of temporal lobe abnormalities, whereas <20% involved resection of extratemporal cortex.[49,162,163,212] Of the latter group, frontal lobe resections are more common than occipital resections, and parietal lobe resections are least commonly performed. It is important to note, however, that these figures reflect the ease of identification of temporal lobe, frontal lobe, occipital lobe, and parietal lobe epileptogenic regions; the degree of intractability and disability of seizures associated with these areas; and the desirability of their surgical resection, as much as they reflect the incidence of epileptogenic abnormalities in these cerebral areas.

Mesial temporal lobe epilepsy may well be the most common epileptic syndrome, partly because of the peculiar epileptogenicity of hippocampal sclerosis (see Chapter 247). Studies of regional differences in epileptogenicity have shown that temporal lobe EEG spike foci are the most likely, and central EEG spike foci the least likely, to be associated with clinical seizures in children,[98] although these data are biased by the inclusion of patients with the benign centrotemporal spike EEG trait.[26] A different pattern of epileptogenicity is revealed by studies of posttraumatic epilepsy, which indicate that injury to the perirolandic region is most likely to give rise to seizures[87] and that frontal and temporal lesions are more epileptogenic than those in parietal and occipital areas.[31,91]

Etiology and Basic Mechanisms

There are no specific causes or pathophysiologic substrates of the various anatomically defined epileptic disorders, with the exception of hippocampal sclerosis, which underlies most cases of MTLE (discussed in Chapters 13, 41, and 247). Any insult, lesion, or primary genetic abnormality capable of producing a localized epileptogenic region can account for the localization-related epileptic disorders classified by cerebral lobe. There are, for example, variants of the idiopathic benign childhood epilepsy with centrotemporal spikes that appear to originate in other cortical areas.[122]

Clinical Presentation

The symptomatic localization-related epilepsies discussed in detail below include only those for which there is reasonable documentation. Much of the information is derived from recently reported series using currently available technologies with localization often confirmed by surgery.

Clinical Characteristics of Seizures Related to Anatomic Region of Origin

Temporal Lobe Epilepsy

Wieser[206] extensively evaluated a limited number of carefully studied patients and concluded that there were five different types of “psychomotor” seizures. Four of these were of temporal lobe origin. While this concept failed to achieve wide acceptance, much of what he concluded remains valid, and it did direct attention toward the possibility of different temporal lobe epilepsy syndromes.

Mesial Temporal Lobe Seizures

Currently, temporal lobe epilepsy is divided into two types: Those with seizures originating in the medial temporal structures (MTLE), and those with seizures beginning elsewhere in the temporal lobe (e.g., neocortical temporal lobe epilepsy or lateral temporal lobe epilepsy). MTLE refers to a specific subset of patients with seizures originating in the medial temporal lobe structures (mesial temporal lobe seizures [MTLSs]); MTLE with hippocampal sclerosis (MTLE-HS) comprises the great majority of patients with MTLE. Although MTLE-HS is characterized by many features that are not shared by conditions with MTLS caused by other lesions, the seizures themselves are indistinguishable. For purposes of this chapter on anatomic classification, therefore, MTLE, with and without HS, need not be further discussed here, as the phenomenology is described extensively in Chapter 247. MTLE, however, serves as a prototypical benchmark for localization-related epilepsies. As noted previously, one of the first steps used to identify other anatomic symptomatic focal epilepsies is to examine them in comparison to MTLE to determine how far they stray from the typical syndrome.

Neocortical Temporal Lobe Epilepsy

Since the lateral temporal cortex only comprises a portion of the temporal neocortex, the preferred terms here are neocortical temporal lobe epilepsy (NTLE) and neocortical temporal lobe seizures (NTLSs).

Several reviews of temporal lobe epilepsy do not even attempt to differentiate medial from neocortical temporal lobe seizures.[102,133,208] A review specifically addressing the issue of neocortical temporal lobe epilepsy concludes that currently there is very little information about this type of epilepsy and that distinguishing seizure characteristics do not exist.[203] Patients with neocortical temporal lobe seizure origin are rare, particularly if examples with obvious epileptogenic lesions are excluded. Although exact statistics are not available, a reasonable estimate would be that <10% of patients with temporal lobe epilepsy, who do not have obvious circumscribed lesions, have seizure origin in the temporal neocortex. Patients with seizures due to temporal neocortical lesions are also uncommon. In one study spanning 14 years from a large epilepsy center, only ten examples of neocortical temporal lesional epilepsy were identified.[173]

One study comparing mesial versus neocortical temporal lobe seizures found very little difference in terms of risk factors, demographics, and scalp EEG patterns.[27] The only significant difference was increased lateralized memory impairment during intracarotid Amytal testing in patients with MTLSs. There was a trend toward early risk factors (below age 2 years) in the patients with MTLSs. Clinical seizure characteristics were not examined. An important contribution of this study is that patients with lateral temporal lobe seizure origin (none of whom had detectable lesions) had surgical outcomes as good as those associated with mesial temporal lobe seizure origin. This is in contrast to other studies reporting less favorable postsurgical results in patients with nonlesional lateral temporal lobe epilepsy.[76,184]

Extensive reciprocal connections between lateral temporal neocortex and medial limbic structures might explain why clinical features of seizures could be similar and possibly indistinguishable from both regions.[22,69,207] Even the auras may require participation of both areas.[22,69]

Nevertheless, despite some generally negative results obtained in attempting to define lateral temporal lobe seizures, there are some features that may help identify them. Auditory, vertiginous, and complex visual hallucinations have been equated with lateral temporal origin.[12,212] No one in a large “pure culture” of patients with MTLSs had this type of aura.[55] One study comparing patients with hippocampal sclerosis and temporal lobe tumors, however, did report auditory, visual, and vertiginous auras in both patient groups.[173] Three studies have noted that the motor manifestations observed in MTLSs are less common in lateral temporal seizures.[52,67,173] There are some scalp EEG and neuroimaging findings that might help distinguish the two types of temporal lobe seizures.[43,44,76,202]

During the past 10 years, additional converging evidence has been provided that there are some characteristics that can help differentiate seizures associated with MTLE from those originating in the temporal neocortex.[29,53,68,119,126,148] Patients with NTLSs have no history of febrile convulsions and have experiential auras (auditory and other sensory/experiential illusions and hallucinations, but not fear), early contralateral dystonic posturing in the absence of oral alimentary automatisms, early loss of contact and shorter seizure duration, and greater propensity to generalize compared to patients with MTLSs. Patients with MTLSs often have a history of febrile seizures (usually complicated), younger onset, evidence of hippocampal sclerosis on MRI, auras of visceral sensations, fear or olfactory hallucinations (rare), dreamy state, early oral alimentary automatisms, delayed contralateral dystonic posturing, and less tendency to generalize compared to patients with NTLS. All authors stress the importance of early findings in differentiating the two conditions. Many of the clinical seizure characteristics described in autosomal dominant lateral temporal epilepsy are the same as described here in neocortical temporal lobe seizures.[132]

Frontal Lobe Epilepsy

Patients with seizures originating in the frontal lobes are the second most common to have localized surgical resections.[93,99,161,162,163,223] Frontal lobe seizures are not rare but, because of lack of familiarity with some of the clinical manifestations, they are often misdiagnosed.[96,205,211,214,217,219,220] Before 1985, scattered reports described different types of frontal lobe seizures,[4,63,65,125,151,193] but during the past 20 years, there has been heightened interest in frontal lobe seizures as reflected in the publications from two symposia specifically concerning this topic.[34,90] A current PubMed search of frontal lobe seizures from 2000 to 2006 yields 907 citations.

Whereas MTLSs are all similar with differences representing variations on a theme, the same is not true for frontal lobe seizures. A number of entirely different seizure types are associated with frontal lobe origin. Initially, because of protean clinical seizure manifestations, frontal lobe seizures seemed to defy classification into subtypes,[213] but recently some order has begun to shape this formerly chaotic situation. Frontal lobe seizures can now be grouped into six broad categories: Focal clonic motor seizures, asymmetric tonic seizures, frontal lobe hyperkinetic (psychomotor, hypermotor, complex partial) seizures, frontal lobe absence seizures, frontal opercular seizures, and frontal lobe seizures that closely resemble typical MTLSs, recognizing that there can be some admixture among the different types.[32,33,92,99,205,211,212]

Focal Clonic Motor Seizures

When focal clonic motor seizures occur in isolation, they are not associated with impaired consciousness and reflect ictal activity in the primary motor area. Focal clonic motor seizures are often part of other frontal and extrafrontal secondary activations of the primary motor cortex. They are discussed in detail in Chapter 44.

Asymmetric Tonic Seizures

Supplementary motor area (SMA) seizures are the classic type of asymmetric tonic seizures. SMA seizures were first described over 50 years ago.[5,150,151] Renewed interest in this relatively uncommon seizure type is reflected in recent publications describing both clinical seizure manifestations and cortical stimulation studies.[13,14,38,56,58,72,92,113,135,159,164,212,214,220] Despite the often dramatic and identifiable clinical seizure manifestations, the frequent absence of EEG abnormalities can still lead to the erroneous diagnosis of nonepileptic psychogenic attacks in patients with SMA seizures.[58,96]

SMA seizures can have subjective symptoms that include bilateral, contralateral, and ipsilateral somatosensory sensations of tightness, pressure, numbness, or tingling. This is fairly common, causing some investigators to prefer the term "supplementary sensorimotor area."[38] A nonspecific general feeling of constriction or tightness can immediately precede visible motor activity. Because the majority of patients do not report specific somatosensory symptoms, the preferred term remains *SMA seizures*.[92] The objective manifestations of SMA seizures usually begin with the sudden, often explosive, assumption of a fixed posture, classically with the arm contralateral to the side of seizure origin abducted at the shoulder, externally rotated, and flexed at the elbow with the head and eyes deviated as if looking at the up-raised hand.[4] The leg on the side contralateral to seizure origin can be held in rigid extension or can be flexed at the hip. Forced vocalization can occur, usually repeated vowel sounds rather than formed words. More often, there is speech arrest. Seizures are brief, lasting seconds, and only rarely last longer than 1 minute. Toward the end of the seizure, there can be clonic motor twitches of the hand or face. These seizures can secondarily generalize into tonic–clonic seizures. Even when generalized convulsive seizures occur, the postictal clinical and EEG suppression is often surprisingly short when compared to other convulsive generalized seizures.[220] If they do not secondarily generalize, they stop as suddenly as they start. They can occur in clusters of many seizures per day. Nocturnal preponderance is common, but there are many exceptions. Patients with SMA seizures are often conscious during seizures. There seems to be no fundamental difference in terms of lateralization or clinical seizure characteristics that determines whether or not consciousness is impaired during SMA seizures. Responsiveness, however, often is not tested during these typically brief seizures. When given test phrases or words during these seizures with intense bilateral motor activity, one is often surprised to discover that patients clearly recall the test phrase during the immediate postictal period.

The classic motor manifestations of SMA seizures are probably the exception rather than the rule. Although to some extent representing variations on a theme, the motor manifestations of SMA seizures among different patients can differ widely, though they are usually stereotyped for a given patient.[14,38,58,92,99,135,145,164,220] Motor manifestations in relatively well-documented examples of SMA seizures can include symmetric tonic or dystonic posturing of both upper and lower extremities; unilateral rigid straight tonic upper extremity posturing; adducted, flexed posturing of the upper extremity with the fist clenched; flailing, thrashing movements of the ipsilateral arm; kicking and stepping activity of the lower extremities; tonic/dystonic posturing involving the contralateral lower extremity; and athetoid dystonic movements of the contralateral hand, arm, leg, or both.[214,217,220] SMA seizures can rarely present with automatisms without tonic motor activity.[92,211]

Startle epilepsy with asymmetric tonic seizures of presumed SMA origin has been the topic of several reports.[36,92,144,177] SMA origin was documented in some, but not all, of the reported patients. Similarly, reflex seizures due to more casual somatosensory stimuli (i.e., movement or rubbing) have been attributed to SMA seizure origin,[95,154] but SMA origin was not documented in any of these patients. In some of these patients seizures probably began in the parietal cortex.[95]

Both positive (tonic) and negative (atonic) motor activity have been attributed to SMA seizure activity.[95,131] Gelastic seizures in the absence of mirth have been described as a part of SMA seizures.[19,33] Finally, many of the features of SMA seizures seen in adults are also seen in children.[13]

Despite a wealth of reports on SMA seizures, some confusion persists, largely because asymmetric tonic seizures can be evoked practically anywhere in the neocortex.[3,83,215,216] In many of the reports of SMA seizures, origin of seizures is not well documented. In a careful study of four patients with asymmetric tonic seizures, various MRI lesions, and good surgical results, seizure origin was documented in the SMA in only one patient.[86] Two of these patients had seizure origin in the lateral frontal regions and the other patient had seizures beginning in the medial parietal cortex. All propagated to the SMA. These authors emphasized that asymmetric "SMA-type" seizures do not equate with SMA origin. These same authors, in a later report, examined clinical progression patterns in ten patients with presumed SMA seizures. SMA origin was based on clinical seizure characteristics and scalp EEG findings. Only three patients had intracranial studies, while two patients had parietal lesions on MRI. In an earlier report, they described two patients with parietal lesions and asymmetric tonic seizures.[83] Another study of SMA seizures with tonic limb posturing found the posturing to have poor localizing and lateralizing results in 14 patients studied with intracranial electrodes. Eleven patients had surgery and only three became free of seizures.[3] The lack of specificity of asymmetric tonic seizures has been well documented in earlier reports.[64,214,215,216,220] Although it is often assumed that these tonic motor manifestations represent spread to the SMA,[3,83,84] this has seldom been proven[215] and sometimes has been specifically denied.[64]

Considering the sometimes confusing and conflicting data associated with seizures of SMA origin, can they be diagnosed with any degree of accuracy? The scalp EEG in patients with SMA seizures is notoriously inaccurate and may be misleading or completely uninformative.[15,33,54,179,184,200] A recent paper describing ictal and interictal magnetoencephalography in patients with medial/frontal lobe epilepsy reported good results but provided no evidence to verify the findings.[179] Ictal SPECT was used to study eight patients with presumed seizure origin in the SMA.[113] The importance of early (5 seconds or less) isotope injection was emphasized. Excellent results were realized in all eight patients. The ictal SPECT results in part explained the clinical seizure characteristics. Outcome was excellent in the five patients who had surgery. In a recent paper examining frontal lobe seizures in general, seven had seizure origins located in the SMA.[92] While not specifically stated, ictal SPECT was used to direct intracranial electrode placements in many of the patients included in this study. Of the seven patients with SMA seizure onset who had surgery, five are seizure free and one has had brief nocturnal seizures. The one patient with a poor result had a major postoperative complication that resulted in death 2 years later. No seizures occurred after surgery, but the patient was in a persistent vegetative state. Although normal MRI is said to predict less favorable outcomes,[50] the six patients from the Dartmouth series with good outcomes all had normal MRIs.[92] A small series of patients with presumed SMA seizure origin studied with invasive recording all experienced good results following surgery.[14]

SMA seizures, because of associated findings, may be a diagnostic entity. SMA seizures can often be recognized by the company they keep. Patients with brief, asymmetric tonic seizures with a sudden explosive onset and maintenance of consciousness, usually with speech arrest, nocturnal clustering, and normal or nonspecific EEG findings, have what might be considered to be an SMA epilepsy syndrome. This will not define all patients with SMA seizures. One of the seven patients with well-documented SMA seizure origin in the report by Jobst et al.[92] had the bizarre frontal lobe hyperkinetic seizures described in the next section.

A syndrome of autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) has been well defined recently[37,156] (Chapter 249). This phenotypic expression of ADNFLE is the result of at least three different genetic mutations with the majority of patients having, as yet, no recognized genetic marker. Seizure types associated with ADNFLE include asymmetric tonic seizures and hyperkinetic behavioral seizures described in the next section. Most of these patients respond well to antiepileptic drugs, so documentation of SMA origin has not been possible. Until recently, many of these patients, as well as nonfamilial forms, were thought to be suffering with a sleep disorder labeled nocturnal paroxysmal dystonia.[10,157,175]

Frontal Lobe Hyperkinetic Seizures (Frontal Lobe Seizures with Bizarre Behaviors, Hypermotor Seizures, and Frontal Lobe Complex Partial Seizures)

Certain types of peculiar nonconvulsive frontal lobe seizures occur with prominent motor activity but without tonic posturing. These seizures have been variably labeled frontal lobe complex partial seizures, frontal lobe seizures with bizarre behaviors, hypermotor seizures, and hyperkinetic seizures. The current preferred term is *hyperkinetic seizures*.[23] Isolated reports of these seizures date back to 1972,[193] and hints of their recognition can be found as early as 1954.[151] Several subsequent reports described patients with very unusual seizures of presumed frontal lobe origin.[62,63,65,125] The first detailed report of a series of these patients carefully studied with intracranial electrodes appeared in 1985.[211] Later reports confirmed the existence of this peculiar type of frontal lobe seizure disorder, which has now been extensively well defined.[40,92,103,188,205,213,214,217,220] The peculiar hyperkinetic automatisms are thought to be fairly specific for this type of frontal lobe seizure.[103] A recent report, however, did describe nocturnal hyperkinetic seizures of temporal lobe origin.[140] Although not specifically described, the frontal lobe system responsible for these ictal behaviors can presumably be accessed by other cortical areas as well.

Frontal lobe hyperkinetic seizures (FLHSs) usually occur frequently, often in clusters of many per 24 hours. As with SMA seizures, a nocturnal preponderance is common. The seizures are brief, lasting <1 minute with little or no postictal confusion. Motor automatisms are prominent and complex, beginning suddenly with a frenetic or agitated appearance. In some patients, aggressive sexual activity is a prominent part of the automatic motor activity.[63,185] Vocalization commonly occurs, varying from simple humming to growling and barking to shouted obscenities. Warnings are frequent but usually nonspecific. In approximately half of the patients with FLHSs, there is a history of nonconvulsive status epilepticus, which is often documented during evaluation[92,210] (see also Chapter 59). These attacks have a very bizarre, hysterical appearance, but they are stereotyped for each patient. As with other types of frontal lobe seizures, there can be transition forms between this seizure type and those of SMA origin, with some patients exhibiting components of both. Another important transition form occurs when there is delayed spread to medial temporal structures. In this situation, seizures will begin as FLHSs but then transition into the less dramatic MTLSs.[92] Focal clonic motor activity can also occur, but it is usually not a part of FLHSs. There is no specific region within the frontal lobe in which these seizures originate. They have been described with seizures of orbital frontal origin,[32,92,125,193,211] with seizures of mesial frontal origin (including the SMA),[92,205,211] and with seizures of frontal polar and dorsal convexity origin.[92,160]

Similar to SMA seizures, interictal and even ictal EEGs are often unrevealing in patients with FLHSs. This, coupled with the usually bizarre atypical appearance of these seizures, frequently leads to the erroneous diagnosis of psychogenic, nonepileptic seizures.[211,217] These seizures, however, are recognizable by virtue of their clinical characteristics alone; therefore, awareness of these characteristics is essential. Some specific features may help differentiate frontal lobe seizures in general from psychogenic seizures.[172] Features such as pelvic thrusting, side-to-side head movements, and kicking and a history of psychiatric diseases that have been used to define psychogenic seizures are also seen in FLHSs, whereas nocturnal preponderance, short seizure duration, young age at seizure onset, and prone position during seizures are more characteristic of FLHSs.

Analogous to SMA seizures, FLHSs are associated with a constellation of findings. These include often bizarre but stereotyped seizures, frequent brief seizures that occur in clusters with a nocturnal preponderance, normal or nonspecific interictal and ictal EEG patterns, and often normal MRI. All of these characteristics taken together could also constitute a syndrome. As noted previously, these seizures are also a part of the ADNFLE syndrome (see Chapter 249).

Frontal Lobe Absence Seizures

Rarely, frontal lobe seizures can present with absence seizures.[93,105,112,167] A variety of absence status of the elderly may be of frontal lobe origin.[194,195]

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Frontal Opercular Seizures

Seizures beginning in the frontal operculum have been described infrequently.[92,171,180,189] Opercular seizures consist of profuse salivation, oral facial apraxia, and possibly some focal facial clonic activity. To some extent, they resemble the opercular syndrome due to fixed lesions.[35]

Frontal Lobe Seizures Resembling Temporal Lobe Seizures

Seizures confined to the frontal lobes will have features resembling those previously described (i.e., frontal lobe absence, asymmetric tonic seizures, frontal lobe hyperkinetic seizures, and frontal opercular seizures).[93] Some FLHSs, particularly those originating in the orbital frontal region, will spread to the medial temporal structures. As previously discussed clinically, a bizarre FLHS will evolve into a more bland, temporal lobe–type seizure.[214,220] Other examples of orbital frontal seizure origin present with pure temporal lobe seizure manifestations, including scalp EEG findings.[92,178,183] This may be a particular feature of seizure origin in the medial posterior orbital frontal cortex. When this happens in patients without MRI-detected lesions, the potential for diagnostic error is very high.

Occipital Lobe Epilepsy

The prevalence and incidence of occipital lobe epilepsy documented with modern diagnostic technology is not known, but it is generally considered rare. In an older series reported by Gibbs and Gibbs,[66] occipital lobe seizures were thought to occur in 8% of 3,271 cases with focal partial epilepsy. In the large Montreal surgical series between 1928 and 1973, 25 of 1,702 patients without tumors, who underwent surgery for epilepsy, had occipital lobe seizures.[162] Six contemporary series of patients with well-documented occipital lobe seizure origin have been reported: Two examining seizures from the posterior hemispheres[21,39] and four specifically looking at occipital lobe seizures.[24,118,168,216] There have also been several reviews of occipital lobe seizures and epilepsies.[20,169,187,191,219] All contemporary reports on occipital lobe epilepsy are remarkable in the consistency of their findings, recognizing that many of the symptoms have been observed for more than 100 years,[70,71,88] and some of the “newly discovered” observations were reported 50 years ago.[5]

Occipital lobe seizures, as defined by subjective symptoms and objective signs, can be recognized by clinical seizure characteristics in most cases. Some clinical symptoms and signs reflect occipital lobe seizure origin, whereas others are indicative of spread anteriorly from the occipital lobe medially and laterally, above and below the sylvian fissure and contralaterally via the splenium of the corpus callosum with the potential for multiple additional spread patterns.[20,39,168,169,191,216] The manifestations of these multiple and highly variable seizure spread patterns are often the most prominent feature of these seizures, tending to overshadow more subtle findings of occipital lobe origin, leading to diagnostic error.

Elementary visual hallucinations, usually consisting of flashing or steady spots or simple geometric forms, either colored or achromatic, are the most common occipital lobe seizure symptoms. When lateralized, they occur contralateral to the side of seizure origin. They may be stationary or move across the visual field. Ictal amaurosis is the second most common symptom of occipital seizure origin.[24,168,187,216] This symptom, though not universally appreciated, has been consistently described.[7,9,20,149,166,168,198,216] Blindness can be limited to one visual field, but more often is bilateral, consisting of visual blackouts of vision or, rarely, whiteouts.[216] Bilateral (complete) ictal amaurosis implies early spread to the contralateral occipital lobe as previously discussed. An aura of eye movement sensation without detectable eye movement has been reported.[81,216]

Forced blinking or eyelid flutter at the very beginning of seizures can be objective evidence of occipital lobe origin.[24,136,146,216] Both tonic and clonic eye deviation have been noted, with the former much more common than the latter.[18,136,168,216] Concurrent head deviation may or may not be present. Oculoclonic status epilepticus has been reported.[94] Although eye deviation is usually contralateral to the side of seizure origin, ipsilateral eye deviation can occur.[168,216] Other features of occipital lobe epilepsy include ictal vomiting and other autonomic manifestations.[24,73,191] A series of carefully studied surgical patients were examined to determine whether there were differences between medial and lateral occipital seizure origins.[24] The only clear difference was absence of a field cut with lateral onset. There were no clinical seizure features that distinguished the two.

The important fact that seizures originating in the occipital lobe can have the potential for multiple different spread patterns was recognized almost 50 years ago,[5] and has been a consistent finding in recent reports.[20,24,73,118,168,191,216] Symptoms of spread outside of the occipital lobe include somatosensory auras and complex visual and auditory hallucinations. Signs of anterior spread from the occipital lobe include focal clonic activity (lateral, superior), asymmetric tonic seizures (medial superior), and various types of automatisms (inferior). These latter seizures are said to be indistinguishable from those seen in temporal lobe epilepsy.[149,168,169,216] Since most of the clinical seizure characteristics that occur after seizure origin reflect specific spread patterns, occipital lobe seizures can present with a wide variety of clinical patterns that do not reflect occipital lobe seizure origin but that do suggest seizure activity elsewhere. To further confound the issue, some patients exhibit different spread patterns during different seizures, thereby suggesting multifocal disease.[118,216] Static visual field defects, which help identify occipital lobe seizures, are reported in over half the patients in most recent studies.[168,216]

Neuroimaging detects occipital lobe structural abnormalities in up to three quarters of patients with occipital lobe seizures.[118,168,169,216] Focal cortical dysplasia, as a cause of occipital lobe epilepsy, may be undetectable, although newer high-resolution MRI makes this less common. Older literature included birth injury with anoxia in a high proportion of patients with occipital lobe epilepsy.[162] Other causes of occipital lobe seizures include Sturge-Weber variant or celiac disease with occipital lobe calcifications.[9,137,152,197] Occipital lobe seizures can occur in patients with hyperglycemia[78,204] and in women with eclampsia.[155]

Three benign idiopathic childhood epilepsy syndromes with occipital lobe seizures have been described.[59,60,61,106,110,196] These consist of an early type (Panayiotopoulos syndrome), a late type (Gastaut type), and a juvenile type with photic sensitivity (for a review see Taylor et al.[191]; also see Chapters 236, 237, and 257). The early-onset childhood epilepsy may not always have occipital features.[110] The early type is also noteworthy for the propensity to develop nonconvulsive status with pronounced autonomic features.

The prognosis of occipital lobe epilepsy usually relates to the cause. Permanent cortical blindness can occur following repeated occipital lobe seizures.[7] The prognosis of the benign childhood forms, as the name implies, is usually benign with complete resolution, in most but not all, by 19 years.[61] The clinical characteristics of the late childhood type (Gastaut type) of benign occipital epilepsy are identical to those with chronic symptomatic occipital lobe epilepsy, and the two must be differentiated if surgical intervention is being considered.

Occipital lobe resection can be very effective in controlling medically intractable occipital lobe seizures, particularly when lesions are present.[20,168,169,216] This includes patients with celiac disease and occipital calcifications.[137] Partially or completely intact visual fields contralateral to the side of seizure origin can be converted to complete homonymous hemianopsias. Because most patients adjust to this visual neurologic deficit, homonymous hemianopsia is usually acceptable if medically intractable disabling seizures can be eliminated.[216] However, because postoperative field cuts are often not as severe as would be predicted, there may be reorganization of the visual cortex in some patients.[108] Patients with lateral occipital epileptogenic lesions can often be spared visual field deficits.[24,169] Patients with occipital lobe seizures consistently spreading into the ipsilateral temporal lobe usually do not do well following temporal lobectomy,[149,216] but there are exceptions.[146] Finally, cortical resections in the posterior regions are not associated with cognitive impairments, provided language areas are spared.[123]

Parietal Lobe Epilepsy

Certain clinical characteristics of seizures arising in the parietal lobes have been recognized since antiquity,[192] but patients with these kinds of seizures are uncommon. Parietal lobe seizures constitute no >5% of all partial seizures from surgical series.[162]

There have been several recent reports and reviews examining the clinical seizure characteristics, electroencephalographic findings, and neuroimaging results in patients with well-documented parietal lobe seizure origin.[6,21,30,39,80,100,187,215] Although there were some minor differences among these recent reports on parietal lobe seizures, most findings were consistent.

As with most focal seizures, there are subjective and objective manifestations of parietal lobe seizures. The most common symptoms are paresthesias consisting of numbness and tingling, sometimes described as a “pins and needles” sensation and, less commonly, as a feeling of crawling or itching. Ictal paresthesias, however, occurred in less than half of the patients reported in some series, and were not always correctly lateralizing.[30,80,215] One study, however, found somatosensory auras reliably lateralizing.[89]

Although pain has been recognized as an ictal phenomenon at least since Jackson's time,[88] it is considered rare.[114,199,209,224] Young and Blume[225] examined ictal pain in a series of patients and three types of pain were recognized. The most common was a burning dysesthetic sensation involving part or all of the hemibody opposite to the side of parietal lobe seizure origin. The second type was abdominal pain, sometimes severe, associated with temporal lobe seizure origin. The third type was ictal headache or head pain that had no localizing value. Other reports examining parietal lobe seizures described lateralized abdominal pain.[30,187] Other reports on epileptic pain described lateralized dysesthesias, abdominal pain, and head pain, all in patients with parietal lobe seizure origin.[181,221] Ictal abdominal pain has also been related to an intracranial parietal hemorrhage.[153]

Because pain is not thought to be a cortical sensation, this ictal manifestation might involve activation of corticothalamic circuits. Painful epileptic symptoms, however, have also been equated with seizure activity in the second sensory area,[225] as has widespread numbness.[224] Ictal pain can also be a manifestation of primary sensory cortex involvement.[153]

In a review of parietal lobe seizures, Sveinbjornsdottir and Duncan,[187] in addition to paresthetic, dysesthetic, and painful symptoms, described parietal lobe ictal sensations that included sexual sensations, apraxias, and disturbance of body image. Ictal vertiginous sensations have been attributed to seizure activity in the temporal parietal junction.[97] Gustatory hallucinations have been equated with seizures in the parietal operculum.[79] Some ictal parietal lobe dysfunction would never be detected except in extraordinary circumstances. For example, a patient in the Montreal program[151] had a seizure restricted to the parietal lobe while undergoing electrocorticography under local anesthesia. Two-point discrimination was impaired during the seizure but returned to normal when the seizure terminated. Some parietal lobe seizure symptoms can resemble panic attacks.[8] Parietal lobe seizures can occasionally be induced by complex somatosensory stimulation.[215] There is a case report of hot water–induced seizures related to a focal area of parietal cortical malformation.[116] Other unusual reported findings associated with parietal lobe seizure origin include expressive aprosody and amusica,[16] autoscopy,[127] kinetopsia,[111] and atonic seizures.[170]

Objective manifestations of seizures in the more anterior inferior aspects of the language-dominant parietal lobe would include the expected disorders of speech. If a seizure discharge remained confined to the parietal lobe and produced various apraxias and agnosias, the patient might present in a confused, disoriented state, but this could be true for seizures from almost anywhere. Most objective ictal manifestations of parietal lobe seizures reflect spread of seizure activity anteriorly into the frontal lobe, inferiorly into the temporal lobe, or posteriorly into the occipital lobe.[6] Tonic motor activity, automatisms, or both can occur in patients with documented parietal lobe seizure origin.[64,80,215] In a patient studied with intracranial electrodes, asymmetric tonic posturing occurred with spread to the ipsilateral supplementary motor area,[215] but another study using invasive monitoring did not find that relationship.[64] Subsequently, asymmetric tonic posturing in parietal lobe seizures resembling frontal lobe seizures has been reported repeatedly.[6,100,138] Secondary involvement of the medial temporal structures with associated automatisms has been documented during intracranial recording in patients with parietal lobe seizure origin.[57,64,215] Based on intracranial recording, two patients with unsuspected parietal lobe seizure origin underwent unsuccessful temporal lobectomy in the series reported by Ho et al.,[80] as did two patients from the Yale series.[215] Parietal lobe seizure origin was determined by detecting lesions using previously unavailable MRI and verified by successful surgery in the latter two patients. Ho et al.[80] determined parietal lobe seizure origin in their patients with ictal SPECT, including the two with previous unsuccessful temporal lobectomies.

There is a possible relationship between the location of parietal lobe seizure origin and the clinical seizure manifestations. Anterior parietal lobe lesions or seizure origin can be associated with initial ictal sensorimotor phenomena, whereas posterior seizure origin can be associated with more complex symptomatology.[30,80] Posterior parietal lobe complex partial seizures were described as "psychoparetic,"[80] which implied a psychic aura, such as fear or déjà vu followed by motionlessness and loss of consciousness. Parietal lobe onset seizures are associated with short postictal periods, even if they progress to complex partial seizures or secondarily generalized seizures[80] similar to that reported for frontal lobe seizures.[211,220] Some patients had elementary visual symptoms, presumably due to posterior spread, suggesting occipital lobe onset.[30,215]

Patients from several studies aimed at defining parietal lobe epilepsy all had epileptogenic parietal lobe lesions.[6,30,215] Because most of these patients had no clear lateralizing parietal sensory aura and the clinical seizure manifestations reflected spread outside of the parietal lobe, it can be concluded that a parietal lobe syndrome cannot be well defined. Although it can be argued that patients who present with consistently lateralized paresthesias and dysesthesias and possibly abdominal pain as part of their seizures may be identified as having a high likelihood of having parietal lobe seizure origin, focal tonic

seizure activity and seizures with automatisms cannot be considered criteria for or against parietal lobe seizure origin. The salient point regarding parietal lobe seizures is that they can present with all these variable manifestations, and sometimes with more than one seizure type occurring during different seizures in the same patient analogous to that seen in occipital lobe seizures.[100,215,216] Parietal lobe origin should therefore be considered in those patients who do not have clear evidence for seizure origin elsewhere. Ictal SPECT may provide localizing data not otherwise obtainable in these difficult cases[80] (see Chapter 81).

When parietal lobe seizures are refractory to medications, surgery is an option. Because, with the exception of the postrolandic gyrus, much of the parietal lobe is silent with respect to seizure symptoms, initial clinical manifestations will often reflect seizure spread outside of the parietal lobe.[6,139,215] Furthermore, scalp EEG findings may not be helpful and may even be misleading. Therefore, in the absence of a detectable parietal lesion, the presurgical evaluation can proceed in the wrong direction.[80,215] Although ictal SPECT can be helpful, lack of early seizure manifestations could preclude early injections. Nevertheless, when parietal lobe seizure origin could be documented, surgical results were good.[6,21,30,39,100,120,215] There is a report of a remarkable case of atypical Lennox-Gastaut syndrome that was dramatically improved by removing a parietal convexity dysembryoplastic tumor.[158] A patient with painful seizures who developed medically refractory nonconvulsive status epilepticus was cured following a medial parietal resection.[138] New cognitive deficits after parietal surgery have been evaluated and found to be relatively minor.[123]

Insular Lobe Seizures

Insular lobe involvement in temporal lobe seizures is a recognized common spread pattern.[85] In the past, the clinical features of seizures starting in the insula were thought to be indistinguishable from medial temporal lobe seizures, thus accounting for some of the surgical failures following temporal lobectomy.[74,147] Furthermore, surgery was often considered too risky because the insula is located just lateral to the lenticulo-striate arteries.[174] Recent reports dispute these assumptions by providing evidence that insular surgery can be done safely, albeit not without risk.[42,86]

Isnard et al.[85,86] described a series of patients with presumed temporal lobe epilepsy who were carefully studied with intracranial electrodes. They found that 10% of these patients had consistent seizure origin in the insula and not the hippocampus. A fairly stereotyped sequence of clinical events was observed, including a sequence of unpleasant, sometimes painful laryngeal constriction followed by dysesthesias, perioral or involving extensive cutaneous areas, then dysarthria, and culminating in focal clonic activity of the face and arm, all with full consciousness. Another case report of insular seizures documented these sensory phenomena and associated them with an unpleasant taste.[165]

Two reports by Duffau et al.[41,42] address the issue of resective surgery in the insular lobe in a series of patients with low-grade gliomas. Postoperative morbidity was high but cleared completely in 3 months in most patients. Three patients, however, were left with a permanent hemiparesis due to compromise of lenticulostriate arteries.

Diagnostic Evaluation

Accurate localization of the anatomic substrate of an epileptic disorder, as opposed to identification of a specific pathologic substrate, is only of clinical value when resective surgical treatment is being considered. In this situation, classification merely by lobe is inadequate to plan a resective procedure, and localization by clinical seizure characteristics and interictal scalp EEG is too often misleading to be used alone as an indication for surgical intervention.[120] When a discrete structural lesion is identified on MRI, the ictal clinical characteristics and location of interictal EEG spikes may be sufficient to confirm an anatomic diagnosis, although ictal EEGs are also usually performed prior to surgery to be sure that the intractable habitual seizures are the same as those arising from the presumed epileptogenic lesion. Focal functional deficits, as demonstrated by neurologic examination, neuropsychological testing, and functional neuroimaging such as PET, can offer additional confirmatory evidence when localization is equivocal. Ictal SPECT is becoming increasingly important in presurgical evaluations, particularly when the MRI is normal.[16,75,92,101,182,201]

The importance of very early injection in rapidly propagating neocortical seizures cannot be overemphasized.[115,201] It is important to recognize that structural lesions in patients with localization-related epilepsy occasionally may be fortuitous findings and unrelated to the epileptogenic process, and that interictal EEG spikes can propagate widely to predominate at a distance from the primary epileptogenic region. When localization is uncertain, particularly in patients with focal epilepsy who have normal MRI scans but stereotyped clinical seizure characteristics indicating the likelihood of a single discrete epileptogenic region, chronic recording with intracranial electrodes is generally performed. Depth electrodes are usually preferred when the epileptogenic region is presumed to be in deep limbic structures of the brain, whereas subdural grids or strips are commonly used to delineate neocortical epileptogenic regions. Because all these diagnostic approaches are those used in presurgical evaluation, the reader is referred to the chapters on diagnosis (Chapters 167,167,168,169,170,171,172,173,174,175) in the section in this book on surgical treatment for epilepsy. The objective of the presurgical evaluation is to precisely locate and delineate the epileptogenic region, and not merely to make an anatomic diagnosis.[124]

Differential Diagnosis

No specific issues of differential diagnosis are peculiar to the anatomic classification of focal epilepsies. The distinction between these disorders and those associated with paroxysmal nonepileptic phenomena that can be mistaken for epilepsy is the same as for epilepsy in general. Certain types of focal epilepsies, such as those discussed under frontal lobe epilepsy, are particularly prone to misdiagnosis, and only familiarity with them will prevent mistakes. It is worthwhile to note, however, that seizures can arise from a single anatomic location when MRI reveals a diffuse cerebral structural abnormality that would not permit a discrete anatomic classification. Conversely, patients can have seizures arising from a discrete epileptogenic region that propagate so rapidly that they appear to be generalized from the start, making a correct anatomic classification difficult. An example of the former would be a patient with a large developmental lesion, such as schizencephaly, where only a small part is responsible for generating the habitual ictal events; such patients can often benefit from localized resective surgery,[115] but invasive electrophysiologic recording is usually necessary to characterize the anatomic localization of the epileptogenic region. An example of the latter would be a patient with a localized frontal lobe lesion that gives rise only to generalized seizures that appear to have no electroclinical localizing features. In this situation, evidence of a localized disturbance, either from structural neuroimaging or tests of focal

functional deficit, is necessary before invasive electrophysiologic studies can be recommended.

Treatment and Outcome

Pharmacotherapy for focal epilepsy is not dependent on anatomic diagnosis, and there is no evidence of differential responses to medication based on anatomic localization of a neocortical epileptogenic region, although mesial temporal lobe epilepsy may be uniquely refractory.[176] In patients with medically refractory seizures, surgical treatment depends largely on precise localization and delineation of the epileptogenic region rather than anatomic diagnosis, and outcome reflects the accuracy of this process and the ability to resect the abnormal tissue completely. Total resection may be limited by involvement of adjacent essential primary neocortex, which cannot be damaged, or by failure to correctly map the epileptogenic substrate, as can often be the case with MRI-negative localization-related epilepsy. When the epileptogenic region involves essential cortex, seizures may be relieved by removal of a structural lesion without cortical margins,[29] or by multiple subpial transection, which is designed to disconnect propagation of epileptic activity along the surface of the brain without disrupting functional columnar cortical organization.[134] Results of the surgical intervention are excellent in a condition where a discrete epileptogenic lesion is identified and a circumscribed adjacent area of epileptogenicity can be delineated; this is considered to be one of the surgically remediable syndromes, with 70% to 80% of patients becoming seizure free,[25] and surgical intervention is recommended as soon as first-line medications fail[50] (Chapters 127 and 168).

Long-Term Prognosis

The long-term prognosis of localization-related epilepsy is determined by the pathophysiologic nature of the underlying substrate, and not by its anatomic location. Patients with discrete structural lesions as the cause of medically refractory epilepsy have the greatest chance of becoming seizure free, and remaining seizure free, following surgical resection, as opposed to patients with mesial temporal lobe epilepsy, who have a higher incidence of postoperative simple partial seizures, and patients with cryptogenic localization-related epilepsy, who are much more likely to have postoperative disabling seizures as well.[17,129] However, surgical results in MRI-negative localization-related epilepsy are also improving dramatically in some centers as we gain better understanding of clinical seizure patterns and develop new diagnostic techniques.[92,182]

Summary and Conclusions

The International Classification of Epilepsies and Epileptic Syndromes recognizes temporal lobe, frontal lobe, parietal lobe, and occipital lobe epilepsies as subtypes of the focal symptomatic epilepsies. With the exception of mesial temporal lobe epilepsy, these disorders describe seizure types rather than complexes of signs and symptoms that might be considered discrete syndromes. Some conditions with frontal lobe seizures and associated constellations of findings could, however, eventually be recognized as syndromes. A number of different characteristic seizures can be identified as indicative of epileptogenic regions in functionally distinct regions of these broad lobar designations. Furthermore, some seizure types are characteristic of epileptogenic regions that transcend lobar boundaries, particularly those arising in the perirolandic region, the perisylvian operculum and insula, and the temporal-parietal-occipital junction. Anatomic classification is of clinical value when surgical treatment is considered, but much more precise localization of the epileptogenic region is necessary before resection can be performed. In this situation, clinical seizure characteristics, routine EEG, and structural neuroimaging provide important localizing information, but more accurate delineation of a primary epileptogenic region for surgical resection usually requires ictal video-EEG monitoring, functional imaging, other tests of focal functional deficit, and, occasionally, intracranial EEG recording. Treatment and outcome are dependent more upon pathophysiologic substrate than anatomic localization, except in situations where surgical resection is limited by involvement of essential primary cortical areas or an inability to accurately define the boundaries of the epileptogenic region. Patients with medically refractory seizures due to discrete resectable structural lesions have an excellent long-term prognosis; this constitutes a surgically remediable form of epilepsy and is an indication for early surgical intervention. An understanding of the variety of focal seizure manifestations originating in different anatomic locations also helps prevent erroneous diagnoses of nonepileptic seizures by identifying specific unusual epileptic seizure types such as those originating in parts of the frontal lobes.

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Chapter 247

Mesial Temporal Lobe Epilepsy with Hippocampal Sclerosis

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Introduction

The term *temporal lobe epilepsy* (TLE) has been used for many years to denote a variety of conditions associated with complex partial seizures of presumed temporal lobe origin. The 1985 International Classification of Epilepsies and Epileptic Syndromes[21] divided symptomatic localization-related epilepsies according to the cerebral lobe of origin and recognized a syndrome of temporal lobe epilepsy defined purely on an anatomic basis. However, anatomic localization was usually determined purely from electroencephalographic (EEG) evidence, which could be misleading.[39]

It has also been known for many years that the most common pathologic substrate of mesial TLE (MTLE), as loosely defined in the 1985 International Classification, is hippocampal sclerosis (HS).[5] Data have accumulated in recent years strongly suggesting that MTLE with HS (MTLE-HS) represents a discrete syndrome that can usually be recognized in life.[33,47,127,133,138] The International League Against Epilepsy (ILAE) recently convened a workshop of experts to discuss the natural history, pathologic features, pathogenesis, electroclinical, neurophysiologic, neuropsychological, structural, and functional imaging findings of MTLE-HS and to determine whether it should be considered a disease, a single syndrome, or a group of clearly distinct syndromes.[134] Their conclusion was that MTLE-HS should be considered a subtype of a greater syndrome of MTLE due to many causes, and that much more work is needed before MTLE-HS could be specifically characterized. Diagnosis of MTLE, and specifically MTLE-HS, early in the course of the disorder, however, is now considered important because disabling seizures and their consequences can be eliminated by anteromesial temporal lobectomy in 60% to 80% of patients, and early surgical intervention provides the greatest opportunity for complete psychosocial rehabilitation.[34,127,130,133]

Historical Perspectives

Bouchet and Cazauvieilh[11] first described the association between epilepsy and a sclerotic hippocampus in 1825, based on gross pathologic examination of brains from patients with "mental alienation seizures." These lesions were believed to be an effect, rather than a cause, of epilepsy, which at that time referred only to generalized convulsions believed to originate in the medulla oblongata. In the latter part of the 19th century, however, Hughlings Jackson[63,64] recognized that partial seizures also represented epileptic phenomena and made an association between limbic-type seizures, which he called "intellectual auras" or "dreamy states," and lesions in mesial temporal structures. During the same period of time, the neuropathologists Sommer[117] and Bratz[12] suggested that HS might be an epileptogenic lesion.

With the advent of EEG, Gibbs et al.[52] reported an ictal discharge pattern that they considered characteristic of psychomotor seizures; however, because they referenced all their electrodes to linked ears, they believed this phenomenon to be generalized. It was Jasper et al.[65,66] who pointed out that interictal and ictal epileptiform EEG abnormalities in psychomotor dreamy states and other phenomena now known to be limbic seizures originated in mesial temporal structures. Bailey and Gibbs[6] were the first to perform anterior temporal lobectomy on the basis of EEG evidence alone, but it was the en bloc resection of Falconer,[43] which included mesial temporal lobe structures, that made it possible to perform systematic pathologic analysis of resected tissue. Not only was HS identified as being present in a high percentage of patients with medically refractory temporal lobe epilepsy, but also surgical outcome in patients in whom this pathologic abnormality was demonstrated was exceptionally good, supporting the argument that this structural lesion was the cause, and not the effect, of recurrent epileptic seizures. Falconer[44,45] also recognized the association between HS and both febrile convulsions and a family history of epilepsy, which suggested the existence of a specific syndrome.

In large part as a result of the success of EEG monitoring in identifying mesial temporal epileptogenic tissue, anterior temporal lobectomy became, and has remained, the most common surgical treatment for medically refractory epilepsy. Crandall et al.[24] subsequently took advantage of the en bloc resection and long-term depth-electrode recording to initiate basic research on temporal lobe epilepsy.[37] HS is now the most studied epileptogenic lesion, and thus the fundamental neuronal mechanisms responsible for MTLE-HS are the best understood of any form of human epilepsy. The elucidation of a unique pathophysiology coupled with characteristic clinical features and an increasing ability to identify hippocampal disturbances noninvasively with functional and structural imaging have all helped to establish MTLE-HS as a discrete epileptic syndrome.[22,134]

Definitions

Definitions of temporal lobe epilepsy and temporal lobe seizures have varied through the years, and confusion persists concerning their usage.[35] The terms *temporal lobe seizure*, *psychomotor seizure*, and *limbic seizure* are often used interchangeably to denote seizures with signs and symptoms that derive from ictal activation of mesial temporal limbic structures. According to some workers, these terms are reserved only for seizures that originate in mesial temporal structures; other investigators, however, interpret the terms more loosely and use them also to define seizures that might originate in temporal or extratemporal neocortex but rapidly and preferentially propagate to mesial temporal structures.[31]

Whereas the 1970 International Classification of Epileptic Seizures introduced the term *complex partial seizure* in place of *temporal lobe seizure*,[49] the 1981 revision of this classification[20] redefined *simple* and *complex partial seizures* phenomenologically such that the latter term would be used to describe any partial seizure associated with impairment of consciousness. Because partial seizures can be associated with altered consciousness without involvement of mesial temporal limbic structures, not all complex partial seizures are temporal lobe seizures. Furthermore, because ictal discharges limited to one mesial temporal limbic area can produce characteristic symptoms such as epigastric rising, emotional and psychic experiences, and olfactory hallucinations during clear consciousness, temporal lobe seizures can also be simple partial seizures.[54] Consequently, whereas the 1981 International Classification of Epileptic Seizures has had definite clinical utility, the ILAE is now recommending that the concept of simple and complex partial seizures be abandoned. Seizures associated with MTLE are more correctly referred to as limbic seizures, whether or not consciousness is impaired.[36]

The 1985 International Classification of Epilepsies and Epileptic Syndromes divided partial epilepsies according to the cerebral lobe of onset and recognized a number of subcategories of temporal lobe epilepsy based on characteristic patterns of ictal onset and propagation as recorded with depth electrodes.[21,131] Because of controversy regarding the precision of such electrophysiologic localization, the 1989 classification[22] abolished anatomic categorizations but retained a syndrome of temporal lobe epilepsy based on associated clinical features, such as increased incidence of febrile convulsions and family history of epilepsy, as well as characteristic anterior temporal interictal EEG spikes and temporal lobe hypometabolism on positron emission tomography (PET). The term *temporal lobe epilepsy*, however, did not account for various etiologic factors and was used to denote the condition of patients both with and without apparent structural lesions. In some cases, patients with a diagnosis of temporal lobe epilepsy could conceivably have extratemporal epileptogenic regions that preferentially propagated to mesial temporal structures, producing characteristic temporal lobe seizures.

Before the advent of high-resolution magnetic resonance imaging (MRI), the term *cryptogenic temporal lobe epilepsy* had been frequently used to describe the condition of patients with the characteristic features of MTLE but no obvious lesions on structural imaging. Pathologic studies of mesial temporal tissue resected from patients with cryptogenic temporal lobe epilepsy revealed HS in most, so that the adjective *cryptogenic*, as opposed to *lesional*, was used tacitly to denote a subtype of MTLE that has now been more clearly defined as the syndrome of MTLE-HS.

Ammon's horn sclerosis and *mesial temporal sclerosis* are the two most common pathologic terms that have been used more or less synonymously with HS, although strictly speaking they imply different degrees of anatomic involvement.[4] The term *hippocampal sclerosis* refers to a specific type of hippocampal cell loss involving CA1 and hilar neurons most and CA2 neurons least, which distinguishes this entity from nonspecific cell loss with other causes.[5] Other characteristic features, such as mossy fiber sprouting[123] and selective loss of somatostatin and neuropeptide Y–containing hilar neurons,[25] also help to identify this distinct pathologic entity.

Epidemiology

Because the syndrome of MTLE-HS has only recently been clearly defined, and because only the medically refractory forms of this disorder referred to epilepsy surgery centers are usually identified, no epidemiologic information is available. It has been reported that 40% of patients with epilepsy experience complex partial seizures[50]; however, not all these patients necessarily have temporal lobe epilepsy, let alone MTLE-HS. In surgical series, careful pathologic analysis of hippocampal specimens, including cell counts and special staining procedures, reveals that as many as 70% of patients with medically refractory temporal lobe epilepsy may have HS,[5] indicating that the vast majority of patients with medically refractory temporal lobe epilepsy have MTLE-HS. Because of the probable increased incidence of a family history of epilepsy among patients who have MTLE-HS,[133] there may be some relationship between this syndrome and the recently described benign familial form of MTLE, which can also be associated with HS.[10,16] Although it is currently impossible to estimate the number of patients with MTLE-HS whose seizures are adequately controlled by antiepileptic drugs, two studies provide some evidence from nonsurgical series evaluated with high-resolution MRI. Semah et al.[114] reported on patients seen in a Paris epilepsy clinic over a 7-year period, approximately one half of whom had a diagnosis of temporal lobe epilepsy. Of these, half had evidence of hippocampal atrophy on MRI. At least one quarter of their population, therefore, could be given a diagnosis of MTLE-HS, and the percentage was probably higher because not all patients with this condition have sufficient atrophy to be visible on MRI. More importantly, of all the diagnostic categories, the most refractory to antiepileptic drugs was MTLE-HS. Only 11% of patients with this diagnosis, and only 3% with dual pathology (that is, HS and some other MRI lesion), had been seizure free in the previous year. This report suggests that MTLE-HS may be the most common, and most medically refractory, form of epilepsy. Another report from Glasgow by Stephen et al.,[121] however, found a similar proportion of patients with MRI evidence of HS, but only 46% of these were medically refractory (although this group was still the most intractable). The difference may be due to the fact that the Paris clinic included tertiary referral patients. The time at which patients with MTLE were referred may also influence the prevalence of intractability, because this condition typically has a stuttering course with long periods of remission. Berg et al.[8] reported on a large cohort of patients undergoing surgical treatment for medically refractory focal epilepsy, most of whom had MTLE, and found that it took an average of 9 years for the establishment of medical intractability.

Etiology and Basic Mechanisms

The epileptogenicity of this disorder results from loss of specific neurons in the hippocampus and synaptic reorganization of surviving cellular elements to cause hypersynchronization and hyperexcitability. The characteristic features of cell loss and reorganization, as well as the electrophysiologic aberrations that ultimately give rise to spontaneous seizures, are described in detail in Chapters 13 and 41. Although the pathophysiology of HS in fully developed MTLE-HS has been relatively well defined by studies of patients in epilepsy surgery centers and some very good experimental animal models exist, the events that initiate this process in humans are as yet unknown.

An association between mesial temporal sclerosis and febrile seizures was reported more than 30 years ago,[44] suggesting a causal relationship. Subsequent studies in both animals and humans have challenged this concept; some patients with MTLE-HS do not have a history of febrile convulsions,[47] and prolonged seizures in immature animals do not produce HS.[94] There are methodologic concerns with these studies, however, and more recent series of patients having MTLE-HS report a strong association with early risk factors, with as many as 66% of patients having prolonged febrile convulsions[14,15,47,60,61,115,116,138] and a variety of other early insults, such as trauma and infection.[83] Furthermore, there is

evidence that the process, once begun, does not stop after seizures appear but rather continues to progress over time.[47,82]

Also of etiologic importance is the observation that HS is sometimes associated with microdysgenesis[85] and occurs in patients with dysplastic lesions, such as hamartomas and heterotopias, but only rarely in patients with neoplasms.[79] This association, coupled with the increased incidence of a family history of epilepsy and febrile convulsions, suggests a genetic or congenital predisposition to epilepsy. Consequently, familial or congenital disturbances could be a necessary precursor that permits early noxious insult to give rise to the characteristic cell loss and neuronal reorganization necessary for the development of MTLE.

Clinical Presentation

The current characteristic clinical features of MTLE-HS are derived almost exclusively from patients with medically intractable seizures who are being evaluated for surgical intervention. Onset of habitual seizures typically begins toward the end of the first decade of life, and seizures often initially respond well to antiepileptic drug treatment. Characteristically, patients do well for several years, but seizures then return in adolescence or even early adulthood and become refractory to medical treatment. Of these patients with medically intractable seizures, the great majority have a history of complicated febrile convulsions or other initial precipitating injury.[47,83]

Evidence for Progression

Debate exists concerning the possibly progressive nature of MTLE-HS despite the fact that some animal models, such as kindling, clearly progress.[124] Based on the known pathophysiology, there is evidence that cell death and neuronal reorganization continue with recurrent seizures.[82] The latent period between occurrence of a precipitating event and onset of habitual seizures, and the period of control between initiation of medical therapy and development of medical intractability, also suggest an ongoing process.[47] The fact that some patients with MTLE-HS have persistent auras following extensive mesial temporal lobe resection that is successful in eliminating disabling complex partial seizures indicates that more than the sclerotic hippocampus is epileptogenic. Evidence that the degree of hippocampal atrophy on MRI[15] and persistence of auras and occasional seizures[38] correlate with duration of MTLE-HS further supports the existence of a progressive process. Progressive worsening of cognitive dysfunction in MTLE-HS, particularly involving memory and learning, has been disputed.[113] However, some degree of cognitive disability can be reversed by successful surgical intervention, indicating that it is related to recurrent seizures.[19,91,98,101,112,120] Although the subject is controversial, much has also been written about the possibility that patients with temporal lobe epilepsy are at greater risk for personality disturbances, depression, and psychosis, and numerous possible neurobiologic mechanisms have been put forth to justify a concept of epilepsy-induced enduring dysfunctions. It is conceivable that progressive changes peculiar to HS could make the appearance and exacerbation of nonepileptic psychologic and psychiatric disturbances reportedly seen in temporal lobe epilepsy a more specific feature of MTLE-HS in particular.

Clinical Seizure Characteristics

Mesial temporal lobe seizures (MTLS) occurring with MTLE-HS are generally thought to be indistinguishable from MTLS resulting from other forms of MTLE and therefore do not characterize the syndrome per se but are an important part of the symptom complex. Recent evidence refutes this concept in part, as there may be some differences between the seizures of MTLE-HS and other varieties of MTLE.[111] For example, ipsilateral limb automatisms, contralateral dystonic posturing, and oral-alimentary automatisms may be characteristic of MTLE-HS but not of MTLE resulting from neoplasms. More work is clearly needed to define this issue better.

The following descriptions of MTLS are based heavily on several reports from a relatively "pure culture" of patients with MTLE-HS,[47,135,138] as well as on recent studies describing various lateralizing or localizing features of these seizures.[1,41,72,73,74,88,93,99,140,142]

Ictal clinical characteristics can be divided into subjective and objective components. The subjective component in MTLS is the warning or aura. Auras in MTLS are very common, occurring in more than 90% of patients.[47,69] They can occur as the first manifestation of a complex partial seizure, and they often occur in isolation as simple partial seizures.[118,119] Auras in isolation may be a defining feature of MTLE, but not necessarily of MTLE-HS. By far the most common type of aura is a visceral sensation, usually in the epigastrium and often with a rising component.[27,47,81,95,129,132] Fear as an aura is a distant second. Other frequently described auras, such as déjà vu, jamais vu, micropsia, macropsia, olfactory hallucinations, and feelings of depersonalization, do occur, but they are uncommon.[47] Some aura symptoms may not have a counterpart in human experience and cannot be described. Patients who cannot describe their seizures verbally can sometimes do so in writing. Formed visual hallucinations and auditory hallucinations of any kind are not part of these seizures. Some patients have experienced auras in the past but no longer have them. This could be a consequence of seizure-related retrograde amnesia.[30] For example, during intensive monitoring, an occasional patient will consistently press the alarm button at the beginning of a seizure, yet deny any warning afterward.

The objective manifestations of MTLS, described by observers or recorded on videotape, usually occur when consciousness is impaired, so the patient is seldom aware of them. The objective manifestations of MTLS often begin with motor arrest, staring, and pupillary dilation. The seizure may not progress beyond this point (temporal lobe absence), but more often semipurposeful coordinated motor activities (automatisms) are a prominent part of MTLS. Oral-alimentary automatisms, although not seen exclusively in MTLS, are highly characteristic. They consist of lip smacking, chewing, licking, and tooth-grinding movements. Lip smacking can be so pronounced as to be audible on videotaped seizures, as can tooth grinding. Stereotyped automatisms that consist of fumbling, picking, and gesticulating movements are another common feature of MTLS. Automatisms suggesting reactions to environmental objects or situations are also common. Other, less common, automatic activity includes vocalization,[142] spitting,[56,68] and bicycling movements[122]; these, however, are also seen in seizures originating elsewhere. Ictal piloerection has also been reported in patients with MTLS.[26,107]

Emphasis has recently been placed on objective seizure characteristics that may have lateralizing or localizing value. These include lateralized motor manifestations, language signs, and postictal findings.

Head and eye deviation have long been recognized as clinical seizure manifestations,[2,55,97,125] but their lateralizing significance, particularly in MTLS, has been disputed.[92,100,106,140] Many reports suggest that head deviation, eye deviation, or both, occurring in temporal lobe seizures have lateralizing value, but this depends on when during the seizure such deviation takes place.[41,67,73,140] Early, relatively casual head deviation can be ipsilateral to seizure origin, whereas forced head

and eye deviation occurring later in the seizure, often as a prelude to a secondarily generalized convulsive seizure, is almost always contralateral.

Unilateral tonic or dystonic posturing occurs in 15% to 70% of patients with MTLS and is reliably contralateral to the side of onset.[41,73,88] Studies using ictal single-photon emission computed tomography (SPECT) have equated this dystonic posturing with increased activity in the basal ganglia ipsilateral to seizure onset.[88] Although unilateral dystonic posturing has been considered a relatively new lateralizing sign, it was actually described 50 years ago.[2,81] Ajmone-Marsan and Ralston[2] provided illustrations of dystonic posturing (and ipsilateral/contralateral head turning) on pages 86 and 95 of their classic monograph, *The Epileptic Seizure*. This posture, termed *larval M2e*, was seen primarily during temporal lobe seizures. Contralateral dystonic posturing can include the leg and even the face and is often associated with ipsilateral automatisms.[73] Ipsilateral automatisms occurring alone are not as consistently lateralizing as dystonic posturing.[73] Conversely, contralateral ictal paresis has recently been reported as a reliable lateralizing sign.[92]

Ictal vomiting in MLTS has been related to right temporal lobe onset.[72,74,87] Unilateral eye blinking reportedly occurs on the same side as seizure origin.[7]

Language disturbance during seizures has been critically examined infrequently. Both ictal aphasia and ictal speech arrest have been equated with seizure onset in the language-dominant temporal lobe.[1,42] Ictal vocalization has been reported to have no lateralizing value,[142] whereas verbalization of coherent speech is associated with seizure onset in the temporal lobe that is not speech dominant.[142] Although uncommon, ictal automatisms with preserved consciousness occur with seizure origin in the nondominant hemisphere.[3,96]

Postictal aphasia as a lateralizing sign in MTLS has been controversial. Two early studies examining clinical features of temporal lobe seizures provided contradictory results: One reported that postictal language disturbances had no localizing value,[128] whereas the other noted highly accurate lateralization of seizure origin to the language-dominant side.[69] The controversy in part must be related to methodology. Postictal language disturbance is often difficult to separate from confusion, and it will be missed completely unless specifically tested for by trained examiners. More recent reports that specifically evaluated postictal language function following temporal lobe seizures confirm that postictal aphasia reliably lateralized seizure origin to the language-dominant side.[42,99] Although seldom evaluated, lateralized postictal motor deficits can occur in patients with MTLS. When detected, they are contralateral to seizure origin and usually follow seizures associated with prominent unilateral dystonic posturing. Patients occasionally wipe their nose at the end of an MTLS, and when they do, they almost always use the hand ipsilateral to ictal onset.[51,78]

Since MTLS with HS usually present with typical seizures, series with this condition in young children do not exist. Two recent reports examined temporal lobe seizures in children, some with documented HS.[103,126] In general, children under the age of 3 have tonic motor and clonic motor activity, while children over 10 years have the same clinical characteristics as adults. In between these years, seizures tend to be relatively simple (hypokinetic seizures) with progressive elaboration of automatisms as they grow older. This pattern was seen in children with HS.[103]

Mesial temporal lobe seizures are typically followed by postictal dysfunction of variable duration, as opposed to some extratemporal seizures with a minimal postictal phase or none.[59,136,137,139] The postictal state is usually obvious at the end of the seizure, often accompanied by visible relaxation; automated semipurposeful motor movements can persist. The postictal state is further characterized by confusion, disorientation, and, as noted above, disturbances of language. Reports have suggested that the duration of the postictal period that follows MTLS beginning in the language-dominant side is much longer than that following seizures originating in the nondominant side.[42,99] This is unquestionably related to gradual clearing of postictal language disturbance.

All these potentially lateralizing signs are helpful during the presurgical evaluation of patients with medically intractable MTLSs. Whether or not these signs also occur in other types of temporal lobe seizures, or in seizures originating outside the temporal lobes, and with what frequency, is not clear, but recent evidence suggests that they occur less often.[46,53,111] Further verification is needed.

Diagnostic Evaluation

Results of the neurologic examination are usually normal, with the exception of mild to moderate memory deficit that is generally material specific for the involved hemisphere. Formal neuropsychological testing is useful for demonstrating typical memory and learning disturbances.[139] When surgical treatment is being considered, the neuropsychological evaluation often includes an intracarotid amobarbital procedure to demonstrate that the temporal lobe contralateral to the planned resection is capable of supporting memory.[102] Dysfunction of the ipsilateral mesial temporal structures can be confirmed when injection of amobarbital into the contralateral carotid artery results in a global memory deficit.

Results of routine EEGs in patients with MTLE-HS can be normal or nonspecific, but only rarely will no epileptiform abnormalities be revealed during prolonged monitoring.[138] The characteristic interictal EEG abnormality is anterior temporal sharp waves, spikes, and slow waves. These can be bilaterally independent in up to one third of patients.[33,133,138] The discharges demonstrate a characteristic field with a maximum in basal derivations, such as sphenoidal, true temporal, or earlobe electrodes. Although bilateral synchronous interictal spikes and sharp waves are usually not a part of the MTLE-HS syndrome, occasionally bilateral frontal polar spikes are seen, but they are not considered clinically significant.[108] Ictal EEG onset usually consists of a characteristic unilateral 5- to 7-Hz rhythmic discharge, seen best in one basal electrode derivation and appearing within 30 seconds of the first ictal EEG abnormality.[105] Occasionally the scalp ictal pattern can be seen over the temporal lobe contralateral to obvious HS.[86] In this case, intracranial studies reveal seizure origin in the abnormal hippocampus ("burned-out hippocampus") without spread to the ipsilateral temporal neocortex but with contralateral spread. Specific ictal patterns can help differentiate mesial from lateral temporal lobe epilepsies.[29] Auras are usually not associated with any EEG changes, although frequent interictal spikes may be seen to disappear during the simple partial seizure. Stereotactic depth-electrode studies demonstrate that simple partial seizures usually are associated with hypersynchronous hippocampal discharges, with a transition to a low-voltage fast recruiting rhythm just before contralateral propagation and onset of the clinical complex partial ictal event.[32] Depth-electrode recordings reveal that hypersynchronous hippocampal ictal discharges can also occur without noticeable signs or symptoms.[119]

High-resolution MRI can demonstrate hippocampal atrophy in a high percentage of patients with medically refractory MTLE.[9,75,138] Volumetry is used by some investigators to demonstrate asymmetry,[13] although controversy exists as to the need for this quantitative technique. As technology for structural imaging improves, it may also be possible to diagnose hippocampal sclerosis by loss of the normal architectural pattern. T2-weighted images often show increased signal in the

area of hippocampal sclerosis, and this is also a useful finding for confirmation of a diagnosis of MTLE-HS.[9,75]

Positron emission tomography with ^{18}F-fluorodeoxyglucose (FDG-PET) remains the most sensitive interictal imaging technique for identifying the focal functional deficit associated with hippocampal sclerosis.[39,70] The area of hypometabolism can be quite large, involving more than the epileptogenic temporal lobe and including the ipsilateral thalamus, basal ganglia, and other cortical structures.[57] It is not clear at this time, however, whether such patterns might help to distinguish MTLE-HS from MTLE due to other lesions. Other PET tracers demonstrate zones of decreased cerebral perfusion approximating the area of hypometabolism,[141] increased binding of μ-opioid receptors[48] in lateral cortex of the involved temporal lobe, and decreased benzodiazepine receptor binding[117] of the sclerotic hippocampus. Bilateral reduced benzodiazepine binding suggests subtle damage in up to one third of contralateral hippocampi in patients with unilateral HS on MRI.[71] Bilateral limbic system dysfunction was also suggested in patients with unilateral HS by investigating MRI diffusion properties.[23] Interictal SPECT is also capable of showing unilateral temporal hypoperfusion in MTLE-HS, but with a much lower yield than PET. Ictal SPECT, however, demonstrates a characteristic pattern of hyperperfusion of the involved temporal lobe when the tracer is injected during a seizure, and of lateral hypoperfusion with persistent mesial hyperperfusion when it is injected shortly after a seizure, during the early postictal phase.[89,90] Again, it remains to be demonstrated whether this pattern has any specificity for MTLE-HS.

Magnetic resonance spectroscopy has demonstrated that HS is associated with a decrease in *N*-acetylaspartate.[77] Magnetic source imaging (MSI) with magnetoencephalography (MEG) can localize interictal and ictal epileptiform discharges to mesial temporal structures in patients with MTLE.[28]

Differential Diagnosis

Both MTLE and benign childhood epilepsy with centrotemporal spikes (BCECTS) can first appear in childhood as a single generalized convulsion and interictal temporal EEG epileptiform discharges. The broad centrotemporal spikes of BCECTS with a characteristic transverse dipole are located more posteriorly and superiorly, and morphologically they are easily distinguished from the characteristic, sharper anterior spike and spike-and-wave discharges of MTLE. The partial seizures of the benign childhood syndrome typically begin with sensory or motor phenomena around the mouth or upper extremity, and they are not likely to be confused with the complex partial seizures of mesial temporal origin.

The features of MTLE-HS most likely to distinguish this syndrome from MTLE caused by other lesions in mesial temporal structures include the earlier age of onset, history of complicated febrile convulsions and other early insults, increased incidence of seizures among family members, material-specific memory deficit, characteristic sphenoidal ictal onset pattern, and hippocampal atrophy on MRI. The same features help to distinguish patients with MTLE-HS from patients with complex partial seizures caused by lateral temporal or extratemporal lesions. In addition, the latter may have auras that indicate a site of origin closer to primary sensory or motor cortical areas.

Treatment and Outcome

The medical treatment of choice for MTLE-HS includes carbamazepine, oxcarbazepine, lamotrigine, topiramate, and levetiracetam. Seizures usually respond well for several years.[8] However, because a diagnosis of MTLE-HS is rarely made until the condition becomes medically refractory and the patient is referred for surgical treatment, there is no definitive information concerning the percentage of patients who remain adequately controlled with pharmacotherapy.

Once seizures return (usually in adolescence or early adulthood), high-dose monotherapy or combinations of drugs often result in intolerable side effects and fail to control disabling seizures.

Surgical treatment, on the other hand, is now reported to abolish all disabling complex partial seizures in 60% to 80% of patients with MTLE.[40,130] A report that patients with MTLE-HS are more likely to experience late postoperative seizure recurrence than patients with other forms of MTLE has now been refuted.[84] The presurgical evaluation can usually be achieved noninvasively with video-EEG monitoring, MRI, neuropsychological evaluation, and often functional imaging with either PET or SPECT.[34] At most epilepsy centers, surgical resection is now limited to the involved mesial temporal structures, the temporal pole, and only a small amount of lateral neocortex, resulting in no significant additional neurologic deficit. When material-specific memory is already impaired, this does not change postoperatively, but contralateral material-specific memory may improve and IQ may increase.[101] If material-specific memory is intact, however, anteromesial temporal resection will result in a postoperative deficit, particularly when performed on the language-dominant side. This can cause additional disability for highly functional patients who depend on verbal memory.[18,58,76,80,109]

The reason for the 20% to 30% surgical failure rate in MTLE-HS has not been extensively studied. Insular lobe seizure origin has been documented in a few cases,[62] whereas the importance of the temporal polar cortex has been emphasized by others.[17]

Long-term Prognosis

Patients in whom medically refractory MTLE-HS develops have a relatively poor prognosis with medical treatment. Seizures often become worse and interictal behavioral disturbances can ensue. MTLE-HS is, however, the prototype of a surgically remediable syndrome, as presurgical evaluation can now usually be accomplished noninvasively and a high percentage of patients become free of disabling seizures postoperatively.[34,127] Early surgical intervention, as soon as possible following demonstration of failure of two appropriate drugs at maximum tolerable doses, yields the best psychosocial outcome if patients are relieved of disabling seizures before these events interfere with critical social and vocational development during adolescence and early adulthood. If seizures continue through this period, irreversible psychosocial disturbances often result, so that seizures may be abolished by surgical treatment later in life but complete or even partial rehabilitation cannot be achieved, and the patient remains dependent.[104,120]

Summary and Conclusions

MTLE-HS is now generally recognized as a distinct syndrome, representing a subtype of MTLE caused by a variety of lesions. The incidence and prevalence of MTLE-HS are unknown, as patients with medically refractory seizures are preferentially identified; however, this is likely to be the most common single form of human epilepsy. Although HS is believed to be the epileptogenic lesion, its etiology is unknown. There is a strong association with an early precipitating insult, particularly complicated febrile convulsions, and a genetic predisposition. The

pathophysiology of MTLE-HS is now relatively well understood, and there is evidence that the disturbance can be progressive. The syndrome can be easily recognized in most patients by the characteristic presentation, seizure type, and diagnostic findings, which include increased incidence of febrile convulsions and family history of epilepsy, onset toward the end of the first decade of life, typical simple and complex partial limbic seizures, material-specific memory deficit, anterior temporal interictal EEG spikes and a characteristic ictal EEG onset pattern, temporal hypometabolism on FDG-PET, and hippocampal atrophy on high-resolution MRI. Once seizures become refractory to two appropriate antiepileptic drugs, further pharmacotherapy is not likely to be of benefit; disabling, irreversible psychosocial disturbances can result if aggressive treatment is not instituted. Surgical treatment, however, can abolish disabling seizures in 60% to 80% of patients with MTLE-HS, making this a surgically remediable syndrome. Early surgical intervention, therefore, offers the greatest potential for restoring a patient to a normal life.

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Chapter 248

Familial Temporal Lobe Epilepsies

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Introduction

A positive family history of seizures and/or epilepsy is frequently observed among patients with temporal lobe epilepsy (TLE).[67] These families cannot be included in only one group, however, and detailed characterization of affected family members is crucial for defining the familial epilepsy syndrome. Patients with TLE can be identified in the context of familial mesial temporal lobe epilepsy (MTLE),[9,16,19,37,43] familial TLE with auditory features,[34,49,50] familial partial epilepsy with variable foci (FPEVF),[56,69] and generalized epilepsy with febrile seizures plus syndrome (GEFS+),[23,45,55,58,66]

There are two groups of familial TLE, according to the evidence for involvement of mesial or neocortical structures. The majority of affected individuals with *familial MTLE* have a benign clinical course, and in some families all affected members have good seizure control, much like those originally described by Berkovic et al.[9,11] However, as in patients with nonfamilial MTLE, some affected family members may have poor seizure control and require surgical treatment.[19,40] Although hippocampal atrophy (HA) and other signs of hippocampal sclerosis (HS) were more frequent and more severe in those patients with refractory seizures, these changes were also observed in patients with good outcome[41,43] and even in asymptomatic family members (Fig. 1).[42] These are strong indicators that genetic factors play a role in the genesis of hippocampal pathology in patients with *familial MTLE*. The genetic background in familial MTLE, however, does not suggest a more widespread structural abnormality on magnetic resonance imaging (MRI).[25]

Familial TLE with auditory features, also described as *autosomal-dominant partial epilepsy with auditory features* (ADPEAF), and *familial lateral temporal lobe epilepsy* (FLTLE)[38] was first reported by Ottman et al.,[49] and additional families have been described by the same group and by other authors.[34,48,50,52,68] Seizure semiology pointed to an extrahippocampal epileptogenic area in the temporal lobes, and, characteristically, most patients had auditory auras. Patients have good seizure control, and epileptiform discharges may be observed over posterior temporal regions. No clear signs of HA have been described in different series, but abnormalities in the neocortical aspects of the temporal lobes may be present (Figs. 2 and 3).[44] Molecular studies identified linkage to chromosome 10q (ch10q),[49,52,68] and mutations in the *leucine-rich, glioma-inactivated 1* gene (*LGI-1*) have been identified.[34,48,50]

There is no evidence to suggest that partial epilepsy with auditory features, familial partial epilepsy with variable foci, or temporal lobe variants of benign childhood epilepsy with centrotemporal spikes ever evolve into MTLE with HS; this is further evidence for a clear distinction between familial MTLE and these other familial epilepsy syndromes.

Historical Perspective

Genetic factors in epilepsy have long been recognized. Until very recently, however, only generalized epilepsies were thought to be genetic in origin, whereas focal or partial epilepsies were largely attributed to environmental factors, such as birth injuries, infections, postnatal head trauma, and brain lesions such as tumors or vascular insults.

As in the generalized epilepsies, partial epilepsies were found to fit a model of multifactorial inheritance (now termed complex inheritance), in which there is an interaction of one or more genes and environmental factors.[2,3,6]

In the last decade, several autosomal-dominant forms of partial epilepsy were described (reviewed by Berkovic and Steinlein[13] and more recently by Andermann et al[6a]). These include autosomal-dominant nocturnal frontal lobe epilepsy (ADNFLE), familial MTLE, ADPEAF, FPEVF, and autosomal-dominant rolandic epilepsy with speech dyspraxia.

The first description of familial occurrence of TLE was in 1994 by Berkovic et al.; they described it as a benign syndrome with late seizure onset without a history of prolonged febrile seizures (FS) or MRI evidence for mesial temporal sclerosis (MTS). However, in subsequent FTLE series, patients had a less benign clinical course, and a high proportion of individuals with HA were described. Some of these patients required surgical treatment for their epilepsy.[19,40,43] These families showed phenotypic heterogeneity in different family members, as well as between families, with respect to a history of prolonged FS, severity of the epilepsy, and presence of HA. The original series of Berkovic et al.[9,11] was population based, arising from a twin study, whereas the later series were hospital based.

Recently, FTLE was included in the new proposal for classification of epileptic syndromes by the International League Against Epilepsy (ILAE), supporting it as a well-defined syndrome.[22]

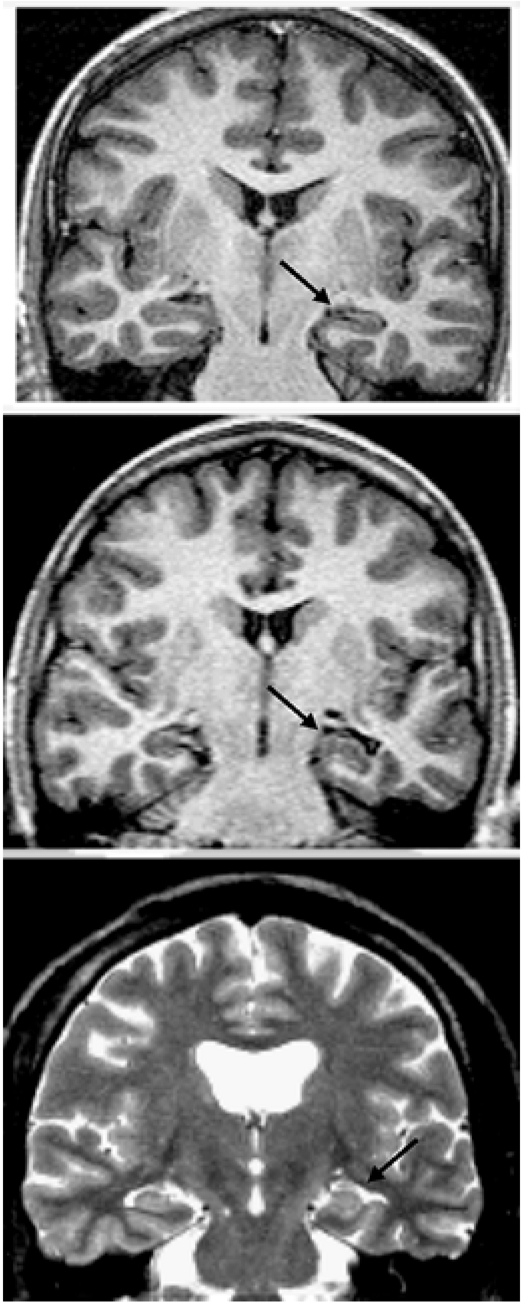

FIGURE 1. Hippocampal abnormalities in three asymptomatic individuals from families with mesial temporal lobe epilepsy. **Top**: Coronal T1-IR image of a 14-year-old boy, showing flattened and atrophic left hippocampus (*arrow*). **Middle**: Coronal T1-IR image from a 15-year-old boy. The left hippocampus is atrophic and bent clockwise and has an abnormal, "irregular" shape (*arrow*). **Bottom**: Coronal T2-FSE image from a 26-year-old man. The left atrophic hippocampus has an abnormal, "rounded" shape (*arrow*). In addition, the fusiform gyrus and collateral sulcus on the left have an abnormal shape. Note also the absence of septum pellucidum. (Reproduced, with permission, from Kobayashi E, Li LM, Lopes-Cendes I, et al. Magnetic resonance imaging evidence of hippocampal sclerosis in asymptomatic first-degree relatives of patients with familial mesial temporal lobe epilepsy. *Arch Neurol*. 2002;59(12):1891–1894. Copyright © 2002, American Medical Association. All rights reserved.)

With the description of the neocortical form of familial TLE or ADPEAF[49] associated with mutations in the *LGI-1* gene on chromosome 10q,[34,48] the distinction between mesial and lateral forms became more obvious.[7,10,37,38,43,63]

It is important to emphasize that it is impossible to distinguish familial from nonfamilial TLE patients based solely on the clinical presentation, in both mesial and lateral forms. Because the family history is not always accurately documented, many so-called "sporadic" or "isolated" patients may actually have a familial epilepsy syndrome.

Definitions

Familial Mesial Temporal Lobe Epilepsy

The best definition of familial MTLE is based on the familial recurrence of MTLE, according to the ILAE clinical-electroencephalogram (EEG) criteria,[53] in the absence of any suggestion of other partial (including lateral TLE symptoms) or generalized epilepsy syndromes in other affected family members. Thus, the finding of at least two MTLE patients in one family is suggestive of familial MTLE. The observation of an autosomal-dominant inheritance pattern with incomplete penetrance implies the presence of asymptomatic carriers of the genetic abnormalities who can transmit the disease to their offspring. Therefore, we should consider inclusion not only of families with affected first-degree relatives, but also those with affected second- and third-degree relatives. This criterion has not been employed in some reported series, leading to exclusion of many possible familial MTLE kindreds.[51]

Familial Temporal Lobe Epilepsy with Auditory Features

Familial TLE with auditory features is a benign epilepsy syndrome, characterized by auditory auras (buzzing, roaring, radio- or motor-like sounds, distortions in sounds and words). Although other manifestations such as psychic, cephalic, and other sensory and motor phenomena can occur, the auditory auras are a landmark for this syndrome. Sometimes ictal aphasia and visual misperceptions can occur and, in some families, secondarily generalized tonic–clonic seizures (GTCS) are frequent.[16,29,47,52,68] The pattern of inheritance observed is autosomal dominant with incomplete penetrance.

Age of onset is variable, usually in the second or third decade of life, and seizures are easily controlled by antiepileptic drugs (AEDs). EEGs may show posterior temporal epileptiform discharges but are frequently normal. No signs of HA are found on MRI studies, but a lateral temporal malformation pattern has been observed in 45% of affected individuals, including one asymptomatic carrier of the mutation.[44] The left temporal lobes of these individuals seemed enlarged, and sometimes there was protrusion of the brain parenchyma laterally, with an "encephalocele-like" appearance. Anterior temporal lobe volumetry showed a significant global increase in volumes in only two individuals. The epileptogenic significance of these structural abnormalities is unknown.

Epidemiology

The prevalence and incidence of these two forms of familial TLE are unknown. However, familial MTLE is apparently more common than familial TLE with auditory features. There is no predominance in any particular ethnic group. Families with MTLE have been described in Australia, Canada, Brazil, Italy, Belgium, and France. FLTLE has been studied in the United States, Brazil, Japan, Germany, France, Italy, Spain, and Australia. This is probably an underestimate of the real prevalence of both forms of familial TLE worldwide, especially in families with predominantly good outcomes.

Ascertainment of these families requires detailed questioning of patients and family members. This has only been emphasized recently because, in the past, MTLE as well as other partial epilepsies were considered to be symptomatic and due largely to environmental factors. A preliminary hospital-based study found that familial MTLE represented 7% of all MTLE patients.[43]

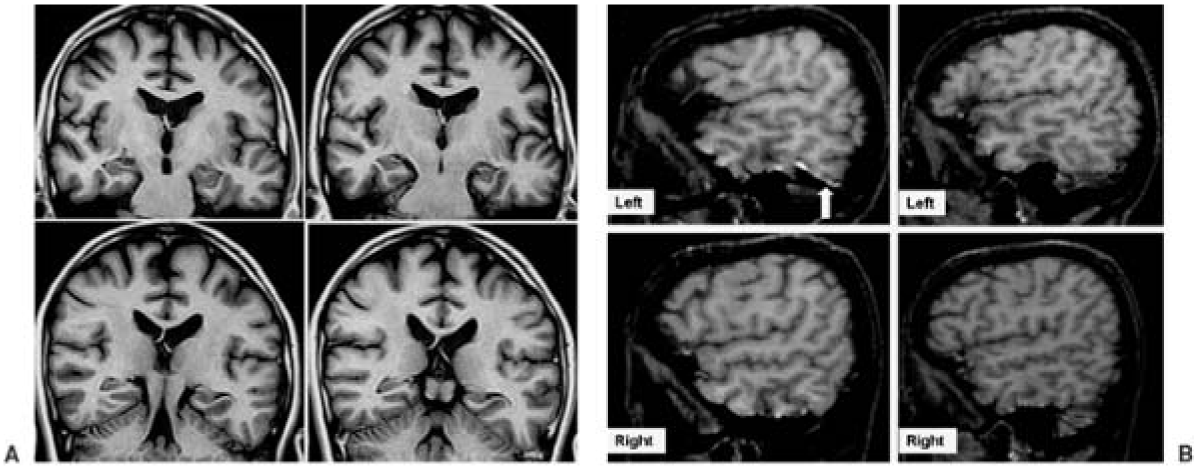

FIGURE 2. A: T1-IR coronal images from a patient with *LGI-1* mutation showing left temporal lobe dysgenesis, characterized by enlargement of the lateral temporal lobe, with small gyri (although not characterizing polymicrogyria). **B:** T1 sagittal images from the same patient showing absence of first and second temporal sulcus on the anterior and middle portions of the left temporal lobe. The posterior basolateral aspect of the left temporal lobe is also abnormal, with a protrusion of parenchyma downward, with an "encephalocele-like" appearance (*arrow*). (Reproduced, with permission, from Kobayashi E, Santos NF, Torres FR, et al. Magnetic resonance imaging abnormalities in familial temporal lobe epilepsy with auditory auras. *Arch Neurol*. 2003;60(11):1546–1551. Copyright © 2002, American Medical Association. All rights reserved.)

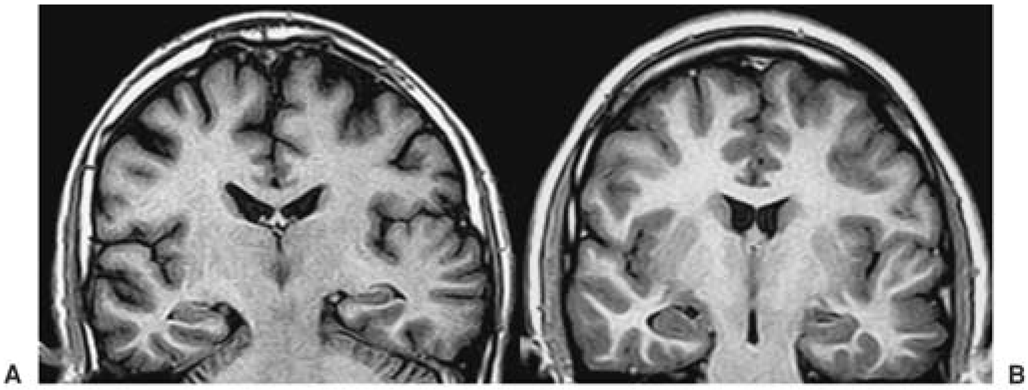

FIGURE 3. T1-IR coronal images from two patients with *LGI-1* mutation, showing left temporal lobe malformation, with a dysgenetic aspect of temporal gyri and enlargement of the lateral aspect of the temporal lobe. (Reproduced with permission, from Kobayashi E, Santos NF, Torres FR, et al. Magnetic resonance imaging abnormalities in familial temporal lobe epilepsy with auditory auras. *Arch Neurol*. 2003;60(11):1546–1551. Copyright © 2002, American Medical Association. All rights reserved.)

Etiology and Basic Mechanisms

The etiology of familial epilepsies is first determined by the genetic pattern that indicates an inherited disease and second

by the structural/functional abnormalities that are associated with this genetic background.

Pathogenetic mechanisms underlying familial MTLE remain unknown. Seizures and HS in familial MTLE may result from interactions between genetic and environmental factors. No locus for familial MTLE with HS has been identified.

No single-gene molecular defect has been confirmed, although several loci for familial TLE have been mapped. Digenic inheritance with loci on chromosomes 1q25–q31 and 18qter was described in a large family with febrile seizures and familial TLE without HS,[8] as well as a locus on chromosome 12q22–q23.3 in another large family with autosomal-dominant familial TLE with febrile seizures without HS.[21] Whether these loci represent susceptibility for febrile seizures or for TLE remains to be determined. A more recent locus was described on chromosome 4q in a four-generation kindred with familial MTLE.[31] MRI data, however, did not show signs of HS in this family.[31] Investigation of these loci in other families has not been reported.

No families with familial MTLE were found to have an *LGI-1* mutation, even in those families in which one or more family members had auditory features alone or in association with mesial symptoms.[7,10,54] This further supports the determination that familial MTLE and familial TLE with auditory features constitute distinct genetic syndromes.

Some polymorphisms have been found in association with MTLE,[62] but these could not be replicated in a recent large cohort of patients.[18] Kanemoto et al.[35] found an increased frequency of the T allele at the 511 position of the interleukin 1ß gene among TLE patients with HS as compared with TLE patients without HS and with controls. The frequency of this polymorphism was further increased in patients with a history of prolonged FS. Stogmann et al.[59] found an overrepresentation of a functional polymorphism in the prodynorphin gene promoter (possibly related to seizure suppression) in patients with TLE and a positive family history of epilepsy as compared to controls. Gambardella et al.[27] recently demonstrated an overrepresentation of a $GABA_B$ receptor 1 polymorphism (G1465A) in patients with MTLE as compared to the normal population, especially in those with refractory seizures. However, more recent studies failed to replicate these findings.[46,61] The presence of all these polymorphisms would suggest a polygenic or multifactorial mode of inheritance, as first suggested by Andermann.[2,3,4]

The presence of clear-cut HA in both affected and asymptomatic family members in familial MTLE suggests that the

hippocampal abnormalities themselves could be inherited, and not necessarily lead to epilepsy.[42] The phenotype would then depend on interaction with other modifying factors. Two papers addressed the possibility of inherited hippocampal abnormality. Fernandez et al.[24] studied families of patients with a previous history of FS, including asymptomatic individuals. They observed subtle abnormalities in hippocampal configuration, internal structure, and volume in individuals with and without FS. This suggested the presence of preexisting hippocampal malformations as an associated factor leading to FS and subsequent HS. A study of children with prolonged FS and their monozygotic asymptomatic twins did not confirm these findings.[33] Volumetric studies of the temporal lobes showed similar patterns of atrophy in familial and nonfamilial MTLE patients.[25]

Qualitative pathology from surgical specimens obtained from operated familial MTLE patients showed the typical pattern of MTS: Selective neuronal loss in CA1, CA3, and CA4 with relative preservation of CA2, and variable involvement of the amygdala and parahippocampal region.[40] The observation of MTS in operated familial MTLE patients who became seizure free suggests that MTS represents the epileptogenic substrate, at least in some of these families; analogous to what is observed in nonfamilial or “sporadic” cases.

Most likely, Familial MTLE will be found to have a major gene leading to hippocampal abnormalities, and the phenotype could be influenced by additional genetic and environmental modifying factors.

The mechanism by which LGI-1 causes familial TLE with auditory auras is unknown. LGI-1 is not homologous to any known ion channel, and it is likely to be involved in brain development.[34,50] The *LGI-1* gene was cloned from a glioblastoma cell line and, although previous studies have suggested that *LGI-1* represents a tumor suppressor gene,[20] a more recent study was unable to establish a correlation between the gene and malignant glioma suppression.[28] *LGI-1* codes for a putative membrane-anchored protein of unknown function. The LGI-1 protein is characterized by a central leucine-rich repeat region,[32] which is involved in regulation of cell growth, adhesion, and migration. More recent studies have shown that *LGI-1* mutations in patients with familial TLE with auditory features are associated with loss of function, with the LGI-1 protein either not secreted or unstable.[57] The association of lateral temporal malformation patterns in some families may indicate a probable role of LGI-1 in the development of the temporal lobes.[44]

The *LGI-1* gene is mutated in approximately 50% of families with familial TLE with auditory features.[10,50] Although *LGI-1* mutations appear to be specific for familial TLE with auditory features, the identification of *LGI-1* mutations in only one half of families presenting the typical phenotype[10,50] suggests genetic heterogeneity. No mutations in *LGI-2*, *LGI-3*, and *LGI-4* have been identified in 71 families with various types of TLE, including 4 who had familial TLE with auditory features.[10]

Clinical Presentation

Familial Mesial Temporal Lobe Epilepsy

Familial MTLE is a well-characterized syndrome, with different degrees of seizure severity, although the majority of patients have good seizure control.[9,11,19,43] The mode of inheritance is autosomal dominant with incomplete penetrance. Patients with familial MTLE present with simple partial or complex partial seizures (CPS) or both, with characteristics of mesial temporal lobe origin (such as rising epigastric sensation, fear, *déjà vu*, *jamais vu*) that are indistinguishable from the sporadic form of MTLE.[1] Auras of *déjà-vu* and *jamais-vu* are particularly frequent, especially in families with benign outcome, and may be the only feature in some family members.[5] Memory impairment is often associated, even in asymptomatic family members with HA.[1] Secondary GTCSs are uncommon in patients with familial MTLE taking AEDs. Age at onset and the presence of a silent period follow initial febrile seizures are also similar to sporadic MTLE. However, an antecedent of febrile seizures in childhood is less frequent in patients with familial MTLE as compared to sporadic MTLE.[40,41,43]

Familial Temporal Lobe Epilepsy With Auditory Features

Seizure semiology in familial TLE with auditory features is characterized by auditory auras preceding complex partial and secondarily generalized seizures in many, but not all, patients.[50] Visual auras may occur,[52] and ictal aphasia has also been described.[16,29]

The most common initial ictal manifestations are described as buzzing, roaring, radio- or motor-like sounds, and distortions in sounds and words. Sometimes ictal aphasia and visual misperceptions can occur, and, in some families, secondarily generalized seizures are frequent.

The pattern of inheritance is autosomal dominant with incomplete penetrance. Age of onset is variable, usually in the second or third decades of life, and seizures are easily controlled with AEDs.

Diagnostic Evaluation

Electroencephalographic Findings

EEGs in patients with familial MTLE show interictal epileptiform discharges over mid- and inferomesial temporal regions with similar characteristics to those of sporadic MTLE. Ictal EEG recordings in familial MTLE patients undergoing presurgical evaluation also show the same pattern observed in sporadic MTLE. A normal EEG, however, does not exclude the diagnosis of familial MTLE.

EEGs in familial TLE with auditory features may show posterior temporal epileptiform discharges but are frequently normal.

Neuroimaging and Other Laboratory Examinations

Familial Mesial Temporal Lobe Epilepsy

MRI evaluation in familial MTLE has shown a high frequency of HA and other signs of HS,[19,41,43] even in individuals with seizure remission and asymptomatic family members (Fig. 1).[42,43] The identification of MRI signs of HS in familial MTLE patients with a benign clinical course confirms that the presence of HA is not always associated with refractory epilepsy.

Data indicate that MRI abnormalities are similar in familial and sporadic MTLE with HS.[25]

Familial Temporal Lobe Epilepsy With Auditory Features

There have been no signs of HS in MRIs of patients from the reported families with *LGI-1* mutation.[10,44,50] Enlargement and abnormal gyration suggesting developmental abnormalities in the lateral cortex of the temporal lobes was described in 53% of affected individuals in one family with *LGI-1* mutation[44] (Figs. 2 and 3), a finding that requires confirmation. However, the MRI findings in that family are clearly distinct from the MRI findings in familial MTLE and are consistent with the distinct seizure semiology in these two forms of familial TLE.[44]

Differential Diagnosis

A family history of seizures is common among TLE patients. Many of them have one or more relatives who have experienced a single episode compatible with either CPS or GTCS, and a history of FS is also frequently found. Unless there are two individuals in the family with well-defined MTLE, however, a diagnosis of familial MTLE cannot be made.

In addition, there are other familial epilepsy syndromes in which patients with MTLE are found. In FPEVF,[12,17,56,69] most reported families mapped to chromosome 22q, but the gene has not yet been identified. Affected family members may present with various forms of partial epilepsy, including frontal lobe epilepsy and MTLE.[39]

In GEFS+, related to mutations in genes *SCN1A*, *SCN2A*, *SCN1B*, and *GABRG2*,[23,30,45,60,64,65,66] patients may present heterogeneous epilepsy phenotypes. FS are the most common phenotype, followed by FS plus (FS+), in which individuals have seizures with fever that may persist beyond the age of 6 years and/or may be associated with afebrile GTCS.[55,58] Less frequent phenotypes seen in GEFS+ involve other generalized and partial seizure types, including MTLE.[55,58,65]

A new partial epilepsy syndrome with some individuals presenting seizure semiology consistent with MTLE has been described in one large Brazilian kindred and named partial epilepsy with pericentral spikes.[36] The majority of affected individuals, however, presented hemitonic or hemiclonic seizures, and molecular analysis showed linkage to chromosome 4p15.

It is essential to evaluate the phenotype of all possibly affected individuals before classifying the family as having a specific familial syndrome. In addition, because the severity of the phenotypes in family members may vary, we can never be absolutely sure that an “isolated” or “sporadic” MTLE patient does not have familial MTLE. Molecular studies can be helpful in excluding other familial epilepsies with already identified gene mutations.

The two main differential diagnoses for familial TLE with auditory features are sporadic neocortical TLE and familial MTLE, which can be clarified most of the time with a detailed history and seizure description.

Recently, the presence of patients with neocortical TLE but without a positive family history was highlighted by Bisulli et al.[14] The authors termed this syndrome idiopathic partial epilepsy with auditory features (IPEAF) and performed a clinical and genetic study in 53 sporadic cases. Mutations in *LGI-1* were excluded in all these IPEAF patients, although, except for the absence of family history, these patients had identical clinical manifestations to those seen in familial TLE with auditory features, including the always-good prognosis.[14] After the first description of their large series, the same authors reported a de novo mutation in the *LGI-1* gene in one patient with sporadic neocortical TLE,[15] but another, more recent series of similar patients found no *LGI-1* mutations.[26]

Since the severity of the phenotype in family members with familial TLE with auditory features may vary, and mild cases may not be known to other family members, we can never be absolutely sure that an “isolated” or “sporadic” neocortical TLE patient does not have familial TLE with auditory features. Molecular studies with testing for mutations of the *LGI-1* gene and of other genes associated with related familial epilepsies can be helpful.

In summary, in the differential diagnoses, a familial MTLE and familial LTLE, one may consider familial partial epilepsies with variable foci, temporal lobe variants of benign childhood epilepsy with centrotemporal spikes, and GEFS+.[58]

No family with familial MTLE has been found to have an *LGI-1* mutation, even in those families in which one or more family members had auditory features alone or in association with mesial symptoms.[7,10,54] This further supports the observation that familial TLE with auditory features and familial MTLE constitute separate genetic syndromes.

Patients with TLE are found in other familial epilepsy syndromes. In FPEVF, different family members may present with various forms of partial epilepsy, including TLE,[39] but the focus remains the same in each affected individual. Most reported families mapped to chromosome 22q, but the gene has not been identified.[12,17,56,69]

Treatment and Outcome

Treatment should be based on the patient's response to AEDs, and the rationale is similar to that in nonfamilial patients. Familial MTLE patients may have refractory seizures, and surgical treatment should be considered, based on clinical-EEG-MRI data, despite the context of a familial epilepsy syndrome.[19,40]

The majority of patients with familial MTLE have good seizure control, with low doses of AEDs indicated for partial epilepsies.[11,19,43] A large number of patients undergo seizure remission and maintain seizure freedom off medication. However, approximately 24% of our patients with familial MTLE were considered refractory to medical treatment.[19,37,43] Patients with refractory familial MTLE have excellent surgical outcome when unilateral or clearly asymmetric HA is identified on MRI.[40] The investigation of patients with familial MTLE should not differ from that of patients with sporadic MTLE, and the surgical decision should be based on the same clinical-EEG-imaging evidence for seizure lateralization and localization.

Seizures in patients with familial TLE with auditory features are easily controlled with small doses of AEDs indicated for partial epilepsies. Some of the affected family members with *LGI-1* mutation may present only a few seizures during their life time, with clear-cut precipitating factors, such as sleep deprivation or alcohol intake, and a decision to treat these patients with AED should be taken on an individual basis.

Long-Term Prognosis

Although the first description of familial MTLE defined it as a benign condition,[9,11] it is now well known that some patients may be refractory to medical treatment. In our series, 81% of familial MTLE patients achieved good seizure control on medication or remitted spontaneously. Refractory seizures were observed in 19%, and surgical treatment was considered in these cases.[40] When unilateral or clearly asymmetric bilateral EEG-MRI abnormalities were observed, familial MTLE patients had an overall likelihood of 85% of becoming seizure free following surgery.[40]

Whether the long-term prognosis for familial MTLE differs from that for sporadic MTLE is still to be determined. For those patients ascertained in epilepsy surgery programs, it appears that the long-term prognosis is similar in the familial and sporadic forms of MTLE. For the majority of patients with familial MTLE who have good seizure control on AEDs or seizure remission, it appears that the long-term prognosis is better than in the sporadic form of MTLE; however, this may represent an ascertainment bias.

Patients with familial MTLE with refractory seizures present a similar degree of memory impairment to patients with sporadic MTLE. In addition, we have shown that individuals with familial MTLE and hippocampal atrophy who have never had seizures also show significant memory-specific impairment on neuropsychological evaluation.[1] It remains to be determined whether this memory impairment in familial MTLE progresses independent of the seizures.

Familial TLE with auditory features has a benign clinical course, with no refractory patients reported.[16,47,49,52,68] Many patients may present only a few episodes and then have spontaneous remission. No neurologic disabilities are known in this syndrome. Long-term prognosis in familial TLE with auditory features is excellent, with most individuals being free of seizures with low doses of AEDs or off medication. There have been no patients with familial TLE with auditory features and *LGI-1* mutation described with refractory seizures requiring surgical treatment.

Summary and Conclusions

Two genetically distinct autosomal dominant familial TLE syndromes have been reported: (a) Familial MTLE and (b) Familial TLE with auditory features, ADPEAF, or familial LTLE.

Familial MTLE is a well-characterized syndrome, with different degrees of seizure severity, although the majority of patients have good seizure control. There is a high frequency of MRI signs of HS in affected individuals, including those with seizure remission or who have never developed seizures. The data suggest that the development of hippocampal abnormalities in these families may be related to genetic factors, although there is no gene mutation described so far. Whether familial MTLE without HS is part of the spectrum of the same condition or a distinct syndrome remains to be determined.

Familial TLE with auditory features, ADPEAF, or familial LTLE is characterized by auditory auras preceding complex partial and secondarily generalized seizures. The most common initial ictal manifestations are described as buzzing, roaring, radio- or motor-like sounds and distortions in sounds and words. The clinical course is usually favorable, with most patients being well controlled with AEDs. MRI investigations in this syndrome have not shown signs of HS. Half of the described families have mutations in the *LGI-1* gene, which is probably related to an abnormality in brain development.

It is essential to evaluate the phenotype of all possibly affected individuals before classifying the family as having a specific familial syndrome. To make a diagnosis of familial MTLE or familial TLE with auditory features, at least one family member should have the same clinical syndrome as the probant.

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Chapter 249

Familial Frontal Lobe Epilepsies

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Introduction

Frontal lobe epilepsies, as with other focal epilepsies, were formerly invariably considered to be the consequence of an overt or obscure brain lesion. However, this view has changed during the last 10 years, as large families comprising several individuals with non–age-related partial seizures without manifest organic cause have been identified. Today, the genetic origin of nonlesional focal epilepsies is well accepted. Several familial focal epilepsy syndromes with an autosomal dominant mode of inheritance have successively been recognized, such as autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE), familial temporal lobe epilepsies, and familial focal epilepsy with variable foci.[46] They are considered idiopathic, like the classical benign localization-related epilepsies of childhood, since affected individuals do not exhibit any other etiology than a presumed genetic cause.

ADNFLE constitutes a reasonably homogeneous clinical syndrome. Mutations have been identified in genes coding for subunits of the cerebral nicotinic acetylcholine receptor (nAChR) in some families, establishing a clear link between ADNFLE and this ion channel. The many cases of sporadic nonlesional nocturnal frontal lobe epilepsy (NFLE) present similar clinical and electroencephalographic features.[66] It is likely that some of them represent unrecognized familial cases or are related to de novo mutations. Yet, others possibly share similar pathophysiologic mechanisms, even if their etiology is not predominantly genetic.

Historical Perspectives

In the last 30 years, several reports have described patients with sudden, brief nocturnal episodes of complex motor activity and a family history of similar attacks.[18,27,68] This clinical picture was originally thought to represent a movement disorder, so-called *paroxysmal nocturnal dystonia*,[32,33] but was later recognized as epilepsy.[23,37] In 1993, Vigevano and Fusco used the term *partial idiopathic epilepsy of frontal lobe origin* to describe otherwise healthy children presenting with nocturnal tonic postural seizures with a strong family history of epilepsy.[72] When families with a clear mendelian inheritance later were identified by Scheffer et al. in 1994, this disorder was designated ADNFLE.[59] The first reported families originated in Australia, Canada, and the United Kingdom. In the Australian family, linkage studies revealed mapping to the long arm of chromosome 20.[44] Subsequent sequencing demonstrated a missense mutation in the gene coding for a subunit of the neuronal nAChR.[63] This finding was a surprise, as it was not previously known that this receptor was involved in epileptogenesis. ADNFLE was the first epileptic syndrome with a proven monogenetic origin, a finding that may be considered a milestone in epileptology. Various mutations in genes coding for subunits of nAChRs have later been demonstrated in different families with this condition (Table 1).[4,8,14,21,24,30,34,35,36,39,42,43,44,55,56,58,59,62,63,64]

Definitions

ADNFLE was first described on the basis of its familial character, but does not differ clinically from the more frequently occurring sporadic cases of nonlesional NFLE. An attempt to define the general characteristics of frontal lobe epilepsy was part of the 1989 Classification of Epilepsies and Epileptic Syndromes by the International League Against Epilepsy (ILAE)[11]:

> "Frontal lobe epilepsies are characterized by simple partial, complex partial, secondarily generalized seizures or combinations of these. Seizures often occur several times a day and frequently occur during sleep. Frontal lobe partial seizures are sometimes mistaken for psychogenic seizures. Status epilepticus is a frequent complication."

A list of features strongly suggestive of the diagnosis was given:

> "(1) generally short seizures, (2) complex partial seizures arising from the frontal lobe, often with minimal or no postictal confusion, (3) rapid secondary generalization (more common in seizures of frontal than of temporal lobe epilepsy), (4) prominent motor manifestations which are tonic or postural, (5) complex gestural automatisms frequent at onset, (6) frequent falling when the discharges are bilateral."

ADNFLE contains several elements from this general outline. However, the unique seizure semiology in this disorder was found to fit poorly with the 1981 ILAE seizure classification.[12,31] Hence, the concept of hypermotor seizures was introduced in the more recent proposal of a semiologic seizure classification[31]:

> "Hypermotor seizures are seizures in which the main manifestations consist of complex movements involving the proximal segments of the limbs and trunk. This results in large movements that appear 'violent' when they occur at high speeds. The 'complex motor manifestations' imitate normal movements, but the movements are inappropriate for the situation and usually serve no purpose. Frequently, the movements are stereotypically repeated in more or less complex sequences (e.g. pedalling). Consciousness may be preserved during these seizures."

Finally, the term hyperkinetic seizure was included in the new glossary of descriptive terminology for ictal semiology by the ILAE Task Force on Classification and Terminology[6]:

> "(1) Involves predominantly proximal limb or axial muscles producing irregular sequential ballistic movements, such as pedalling, pelvic thrusting, thrashing, rocking movements. (2) Increase in rate of ongoing movements or inappropriately rapid performance of a movement"

ADNFLE follows an autosomal dominant inheritance with incomplete penetrance. The first identified families allowed the

delineation of the main clinical features,[58] which later have been refined (Table 2). Subsequently, other focal idiopathic epilepsies with an autosomal dominant transmission pattern were described: The familial temporal lobe epilepsies[2] and the autosomal dominant partial epilepsy with variable foci.[60] ADNFLE has together with these syndromes been included within the subgroup of "familial focal epilepsies" in the list of epilepsy syndromes recently proposed by the ILAE Task Force on Classification and Terminology.[15]

Table 1 Clinical Characteristics in Autosomal Dominant Nocturnal Frontal Lobe Epilepsy Families with Mutations in Genes Coding for Subunits of Nicotinic Acetylcholine Receptors

Mutation (references)	Number of patients	Mean age of onset, yr (range)	Pharmacoresistance	Intellectual disability	Psychiatric or behavior disturbance	Siezures while awake	Status epilepticus	Secondary generalization	Abnormal interictal EEG
CHRNA4 mutations									
S248F[44,58,59,63]	27	8.5 (0.2–28)[a]	nr	0/25	nr	nr[b]	nr	nr[b]	nr[b]
S248F[64]	11	8.6 (4–13)	8/11	1/11	1/11	3/11	2/11	8/11	4/11
S248F[56]	11	7.6 (3–12)	4/8	0/11	0/11	0/11	nr	1/9	2/8
S248F[36]	6	12.5 (6–15)	1/6	0/6	In a few	nr	nr	1/6	0/6
776ins3[34,35,39,62]	10	8 (1–11)	1/8	0/10	4/10	2/10	0/10	0/10	1/8
S252L[21,24]	5	(0.3–10)	2/4	2/5	3/5	0/5	0/5	1/5	2/3
S252L[43]	2	1.3 (0.7–2)	1/1	0/2	nr	0/2	nr	0/2	1/1
S252L[55]	3	2.5 (0.5–5)	2/3	0/3	nr	1/3	nr	3/3	0/3
S252L[8]	9	11 (4–14)	6/7	6/6	nr	0/9	nr	1/7	5/9
T265I[30]	2	18 (15–20)	1/2	nr	nr	0/2	0/2	0/2	2/2
CHRNB2 mutations									
V287L[14]	8	9 (8–12)	0/8	nr	nr	0/8	nr	0/8	4/8
V287M[36,42]	10	10 (6–18)	0/10	0/10	In a few	nr	nr	3/10	1/7
I312M[4]	2	7	nr	2/2	2/2	0/2	nr	nr	0/2

EEG, electroencephalogram; nr, not reported.

[a] In the 24 patients in whom age of onset was known.

[b] Data not provided separately for this family.

Table 2 Main Clinical Features of Autosomal Dominant Nocturnal Frontal Lobe Epilepsy

- Onset age is variable, although generally in childhood.
- There are brief hyperkinetic seizures, almost exclusively during sleep.
- Attacks may be numerous every night for long periods.
- Awareness during seizures is often retained.
- The course is nonprogressive and seizures may remit.
- Good response to antiepileptic drugs, especially to carbamazepine, is common.
- Pharmacoresistance occurs in almost one third of patients.
- Clinical neurologic examination and magnetic resonance imaging are normal.
- Cognitive deficits and psychiatric comorbidity may occur.

Epidemiology

To date, the number of reported ADNFLE families exceeds 100.[4,8,10,14,21,24,25,30,34,35,39,40,41,42,43,45,46,55,58,62] Undoubtedly, they only represent a small fraction of ADNFLE families worldwide and the prevalence of this disorder is obscure. Several known families have probably not been reported when genetic analyses have not been performed or have been inconclusive. In addition, it is likely that there still are families in which the epileptic nature of the paroxysmal nocturnal events has remained unrecognized or misdiagnosed. The reported ADNFLE families all comprise at least two affected first-degree relatives with an inheritance pattern suggestive of autosomal dominant transmission. Twenty-seven affected individuals have been reported in the largest and first described family in Australia.[44] Up until now, mutations have been found in genes encoding subunits of nAChR in 12 families and in one sporadic case (Table 1). Thus, identified mutations currently account for only a minority (10% to 12%) of published ADNFLE families. Sporadic NFLE cases are relatively common,[51] and some may harbor the same mutations that have been identified in ADNFLE.[43]

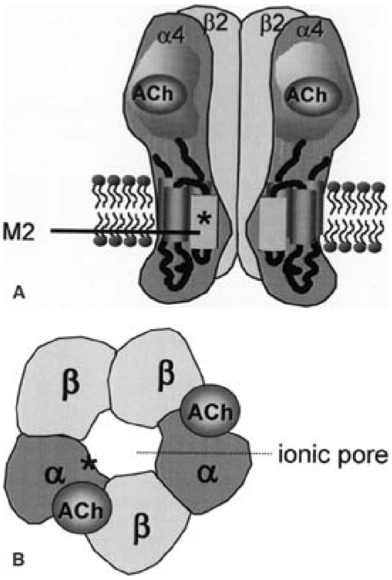

FIGURE 1. Schematic illustration of the neuronal α4 ß2 nicotinic acetylcholine receptor (nAChR), a pentameric ion channel. **A:** Coronal section. **B:** Axial section. The α4 ß2 nAChR results from the assembly of two *α* and three *ß* subunits. The wall of the ionic pore is lined by the M2 segment of each subunit (second transmembrane domain). When acetylcholine binds to the nAChR, the ion channel opens and lets cations enter. The *asterisk* indicates the location of the mutations in the α4 subunit.

Etiology and Basic Mechanisms

ADNFLE was the first idiopathic epilepsy for which a responsible gene was recognized.

Mutations have been identified in the *CHRNA4* gene encoding the nAChR α4 subunit and in the *CHRNB2* gene encoding the nAChR ß2 subunit (Table 1). Up until now, four different mutations have been described in *CHRNA4*: (a) S248F, a missense mutation replacing serine with phenylalanine in position 248 in the amino acid sequence, observed in an Australian, a Spanish, a Norwegian, and a Scottish family[36,56,63,64]; (b) 776ins3, an insertion of three nucleotides at nucleotide position 776, leading to the insertion of a leucine in the amino acid sequence, in another Norwegian family[62]; (c) S252L, a missense mutation replacing a serine by a leucine in position 252 in the amino acid sequence in a Japanese, a Polish, and a Korean family, and in a sporadic case of Lebanese origin who subsequently had an affected son[8,21,24,35,43,55]; and (d) T265I, another missense mutation, in a German family.[30] Some authors use an alternative codon numbering, which may cause nomenclature confusion.[10,55,56] Three different mutations (V287L, V287M, and I312M) are described in the *CHRNB2* gene in an Italian, a Scottish, and an English family, respectively.[4,14,42]

The nAChRs are pentameric ligand-gated ion channel receptors consisting of different functional subunit combinations (Fig. 1). When acetylcholine (ACh) binds to the nAChR, the ion channel opens and lets cations enter. The known ADNFLE mutations are located within the second transmembrane domain (M2) of the subunits, which constitutes the walls of the ionic pore, except for the mutation ß2-I312M, which is in the third transmembrane domain. Thus, it appears that mutations with a principally direct effect on the ionic pore may cause ADNFLE. The fact that the major nAChRs in humans are made from an assembly of α4 and ß2 subunits explains well that defects in both subunits are associated with the same disorder. The α4ß2 nAChRs are the most abundant form and are found in the entire brain, with a predominance in the thalamus. They may have a presynaptic or a postsynaptic location. The first have a neuromodulatory role (facilitation of neurotransmitter release), whereas the latter induce a depolarization of the postsynaptic neuron. To assess the changes in the electrophysiologic properties of the mutant receptors, a system of

heterologous expression in frog (*Xenopus*) oocytes has been used. These cells were injected with an equivalent amount of the mutant and nonmutant allele, in addition to cDNA coding for the other normal subunit, in order to obtain mutant "heterozygous" receptors mimicking an autosomal dominant disorder. Six different mutations led to a significant increase in sensitivity to ACh of the mutant receptors.[4,5,30,38,42] The seventh mutation, the *CHRNB2* V287L mutation, caused retardation of channel desensitization.[14] Thus, contrary to the first conclusions obtained from the assessment of homozygous mutant receptors, the current studies suggest a gain of function of the mutant nicotinic receptor for the various mutations. In contrast, another study of five mutations proposed a reduction of the Ca^{2+} dependence of the ACh response, which could explain an increase of glutamate release during bouts of synchronous activity, as an alternative common mechanism.[52] However, the precise cellular mechanisms leading to epileptogenesis in ADNFLE remain elusive. In particular, it is not clear how an alteration of an nAChR subtype that is present in the thalamus and in the entire cortex may cause a partial epilepsy.

Currently, it is assumed that the mutant nAChRs alter the activity level of frontal thalamocortical loops, which play a major role during sleep. A positron emission tomography (PET) study using 2-[^{18}F]-F-A-85380, a high-affinity agonist of the heteromeric (α4β2) nAChRs, has recently offered an opportunity to investigate some in vivo consequences of the molecular defect.[48] Eight ADNFLE patients with an identified mutation in nAChRs were studied. Their pattern of nAChR brain distribution was clearly different compared to healthy volunteers. A significant decrease in nAChR density in the right dorsolateral prefrontal region and a significant increase in the epithalamus, ventral mesencephalon, and cerebellum were demonstrated. The regional decrease in the nAChR density in the prefrontal cortex appears congruent with a frontal lobe epilepsy. We propose two explanations for the regional increase in the nAChR number in the mesencephalon: (a) a regional malformation of central nervous system (CNS) circuits, with an increase of synaptic density, since nAChRs may have a role in the migration of neocortical neurons and in synaptogenesis[53]; and (b) a regional nAChR up-regulation, related to the hypersensitivity of the mutant nAChRs to ACh and the richness of local ACh release sites. A consequence of the increased nAChR density in mesencephalon could be an overactivated cholinergic pathway ascending from the brainstem. This pathway acts on postsynaptic nAChRs on thalamocortical cells and participates in "desynchronization" and interruption of the sleep physiologic oscillations at the time of the arousals.[13,28,65] Thus, the findings of the recent PET study[48] support the theory that ADNFLE seizures are due to a defective interruption and a pathologic transformation of synchronized sleep oscillations.

Other in vivo functional studies using transgenic animal models have also enhanced the understanding of ADNFLE pathogenesis. A *CHRNA4* knockout mouse showed increased anxiety compared with the behavioral phenotype of the wild type, but did not exhibit spontaneous seizures.[54] *CHRNB2* knockout mice showed abnormal functional organization in the dorsal lateral geniculate nucleus,[19] reduced sensitivity to nicotine-induced locomotor depression,[70] and reduced fragmentation of non–rapid eye movement (REM) sleep by micro-arousals.[29] This last phenotypical trait is an interesting finding, as sleep microstructure analysis of NFLE and ADNFLE patients has revealed sleep fragmentation with an increase in arousals and sleep instability in all non-REM sleep stages.[67,74] Knockin mice containing a point mutation in the pore-forming M2 domain of the α4 subunit (Leu9′Ser) showed increased anxiety, increased sensitivity to induced seizures by agonists (such as nicotine, the nicotinic agonist epibatidine, but not the γ-aminobutyric acid (GABA)$_A$ receptor blocker and proconvulsant bicuculline), but no spontaneous epileptic seizures,[16] and also dopaminergic deficits.[26] When tested in oocytes, the α4β2 nAChRs with this specific mutation displayed an increased ACh sensitivity, as observed with the human ADNFLE mutations.[5,26] In addition to these mice models, a new transgenic rat model harboring a true ADNFLE mutation is currently under investigation.[22] This model appears more interesting as it expresses spontaneous seizures resembling those of ADNFLE.

For a long period of time, no other genes than those coding for nAChR subunits were reported to be responsible for this condition. Just recently, mutations have been identified in the promoter of the corticotropin-releasing hormone (CRH) gene.[9] The first mutation, a polymorphism present in 3% of the general population, was detected in three families and in two sporadic cases. The second, not present in 115 healthy subjects, was detected in one ADNFLE proband. However, in vitro the first mutation caused an increase in the protein level, whereas the second resulted in a decrease.[9] Although the nAChRs are known to activate CRH release,[7,57] the pathophysiologic link between CRH and nAChRs in ADNFLE is still obscure.

Clinical Presentation

The main clinical features are listed in Table 1. Mean age of onset of ADNFLE varies between 8 and 11.5 years, according to clinical studies. It starts below 20 years in 85% of cases. Onset ages as low as 2 months and as high as 56 years have been reported.[46,58] The penetrance appears to be up to 80%. Males and females are equally affected.[10] Seizures arise from sleep. They are more or less stereotyped in each patient over the years. It is remarkable that sudden arousals are characteristic for ADNFLE[4,39,56,64] in contrast to the reduced consciousness that typically occurs in seizures with medial temporal lobe onset. Some patients describe an aura. They are nonspecific and include a broad variety of phenomena: Somatosensory (shivering/tingling, either diffusely or localized, mostly in the head, sometimes in the limbs; and also epigastric discomfort), special sensory (e.g., sensations of light, auditory hallucinations, vertigo), psychic (fear, malaise, déjà vu, dreaming activity), and autonomic (breathing difficulty).[58,64]

The motor manifestations are characterized by a wide range of clinical features, which in part can be regarded as a release of subcortical activity. Extrapyramidal features are often prominent. Behavior and autonomic elements may reflect limbic overactivity. The mildest form consists only of a sudden awakening with an elevation of head and trunk, often associated with the expression of fear. Abrupt and rapidly changing movements of the limbs and the trunk may occur, leading to a bizarre sequence of various brief dystonic postures, reminiscent of a mechanic puppet. Hyperkinetic activity (frantic movements with bipedal activity, pelvic thrashing) or tonic stiffening are common features. During the seizure, a breathless sensation is reported by many patients.[36,42,43,46,56,58] Seizures usually last less than 1 minute, with a mean duration of 30 seconds,[46,58] but some seizures are prolonged and may take the form of nocturnal wanderings. Postictal symptoms are absent or very brief. Rare secondarily generalized seizures are observed in about half of the patients, but the unusual semiologic pattern may cause classification difficulties. Some patients report that awareness is partly retained even during apparent generalized convulsions, a phenomenon that may wrongly raise the suspicion of psychogenic seizures.

Seizures frequently occur in clusters, predominantly during the first few hours after falling asleep or early in the morning. Some patients have attacks every night, while others report mild and rare symptoms. Periods with high seizure frequency may alternate with seizure-free intervals. In one study, the mean seizure frequency was around eight episodes per night.[58]

Diurnal seizures, apart from during naps, are very rare, but may be observed in the most severe cases, particularly during periods of poor seizure control.[40,46,64] Some patients may also experience status epilepticus. Stress, sleep deprivation, and menstruation may increase seizure frequency. Sensory stimulation during sleep (e.g., shaking the body of the patient or a sudden sound) may sometimes provoke seizures.[24,43,55] On the background of a video-polysomnographic study of a large number of patients, the attacks were classified into four categories according to duration, semiology, and complexity of motor behavior (minimal, minor, major, and prolonged episodes).[40,41] The mildest form is described as paroxysmal arousals, consisting of a sudden awakening with dystonic posturing of upper or lower limbs.[49,50,69] They can recur with a periodic repetition, every 30 seconds to 2 minutes during light sleep. Paroxysmal arousals are probably the most frequent type of seizures, but, due to their short duration, many patients remain unaware of them. The information from relatives about apparently unaffected individuals is thus hampered with a high degree of uncertainty. Structured interviews of all pedigree members and their proxies, particularly their bed partners, are thus necessary to recognize the true penetrance of this disorder. The clinical observation is the major diagnostic tool in NFLE, particularly since even ictal electroencephalograms (EEGs) may be inconclusive. Nocturnal video recordings, preferably with polysomnographic parameters, may be necessary for the clinical diagnosis.

Clinical neurologic examination is normal. A normal intelligence was one of the ADNFLE features originally described.[58] Nevertheless, subsequent descriptions reported neuropsychological deficits in some patients. In four families with typical ADNFLE, most patients also suffered from mild to moderate intellectual disability.[4,8,24,25] Two of these families had an α4-S252L mutation, one the β2-I312M mutation and one no identified mutation. The patient with the de novo α4-S252L mutation was reported to be of low average intellect.[43] Several of the cognitively affected patients had pronounced memory deficits. A neuropsychological study of two other patients from ADNFLE families without identified mutations showed specific frontal lobe neuropsychological disturbances.[46] Currently, it is unknown whether the observed neuropsychological deficits are a consequence of the seizure disorder or a behavioral phenotype primarily associated with the genetic defect. In addition, in some families psychiatric disturbances have been reported in up to half of the patients during the active phase of their epilepsy.[4,24,35,36,46] Behavioral disorders with hyperactivity, irritability, aggressiveness, and impulsive behavior are the most frequent findings, but psychosis have also been reported in some patients.[35] The psychiatric impact may contribute to the diagnostic confusion, which still may occur in this disorder.

No obvious clinical elements seem to differentiate mutation-positive from mutation-negative families.

Diagnostic Evaluation

Electroencephalographic Findings

Many patients have a normal interictal EEG. Most studies report waking EEG abnormalities in only 10% to 25% of patients.[8,40,56,58] Other authors who retrospectively looked at all previous EEGs of their patients reported waking EEG abnormalities in up to 60%, mostly recorded during periods of frequent seizures.[46,64] When present, the abnormalities consist of focal intermittent theta or delta slow waves and/or sparse focal sharp waves or spikes. They are usually located over the frontal regions and exceptionally over the temporal areas.[8,46] Interictal sleep EEG sometimes demonstrates abnormalities in patients with a normal waking EEG.[40,46] In a study of 40 patients, 10% had an abnormal waking EEG and 50% an abnormal interictal sleep EEG.[40] When unilateral interictal or ictal EEG abnormalities are identified, they appear to remain lateralized on the same side throughout the evolution of the disorder. Ictal EEG recordings may also fail to show specific discharges. Cortical activity is often concealed by movement artefacts. An ictal pattern appears in 40% to 80% of the patients, according to studies, but rarely consists of clear-cut epileptiform activity in the frontal regions. Most often a diffuse flattening or a rhythmic theta or delta activity with predominance over anterior quadrants is seen. Thus, at least a quarter of the patients have normal interictal as well as ictal scalp EEGs.[40] Video-EEG-polysomnographic recordings show that almost all seizures arise during stage 2 non-REM sleep. Intracerebral EEG recordings performed in a patient with a typical ADNFLE surprisingly demonstrated that seizures originated from the left insular cortex, whereas ictal surface EEG showed diffuse flattening or left frontoprecentral fast activity at the onset of seizures.[46]

Neuroimaging and Other Laboratory Examinations

Brain magnetic resonance imaging (MRI) is normal in all patients with ADNFLE. Functional imaging studies include single photon emission tomography (SPECT) and positron emission tomography (PET) studies. ^{18}F-fluorodeoxyglucose (FDG)-PET was described in eight patients with ADNFLE from three different families.[8,20] The study was considered normal in seven patients and showed a hypometabolism in the frontopolar region in one.[20] A statistical parametric mapping (SPM) analysis was performed in six patients with a normal PET and permitted the detection of glucose hypometabolism in the left superior and middle frontal gyrus in five of them, but also in the left central and parietal regions and the right anterior superior frontal gyrus.[8] Recently, a PET study using a tracer of the nicotinic receptors has been performed in eight ADNFLE patients with an identified mutation[48] (see Etiology and Basic Mechanisms). An interictal SPECT using 123I-IMP (*N*-isopropyl-p-iodoamphetamine) showed no abnormality in a patient from Japan, while an interictal SPECT using 99mTc-ECD (ethyl cysteinate dimer) showed low perfusion in both frontal lobes in another patient from the same family.[24] Another study using ^{99}Tc-HMPAO (technetium-99m hexamethyl-propylamineoxime) showed perfusion changes on interictal and ictal SPECT in the left frontopolar region, congruent with the focal hypometabolism observed in interictal PET in one patient, and right parasagittal, midfrontal hyperperfusion on ictal SPECT with a hypoperfusion in the same area on interictal SPECT in another patient with an identified mutation.[20]

Differential Diagnosis

Diagnostic difficulties have been recurrent problems in many families with ADNFLE. Nocturnal seizures often occur without eyewitnesses, and if present, the beginning of even dramatic episodes is often not seen. Darkness and covers frequently restrict the detailed observation by bedroom partners. Even ictal EEG recordings may be inconclusive. Previously, many patients with NFLE were considered to suffer from a primary movement disorder termed *paroxysmal nocturnal dystonia*[32,33] (see Historical Perspectives). Misdiagnoses as parasomnias, in the form of night terrors, nightmares, and somnambulism, have been common. Based on the history alone, the differential diagnosis

from benign parasomnias may be difficult in children. Attack frequency differs and symptoms usually occur as single or isolated recurrent episodes in the parasomnias in contrast to the frequent clustering of nocturnal frontal lobe seizures. Due to pronounced autonomic and emotional symptoms with arousal and fear, psychiatric disorders such as panic attacks and hysteria may also be suspected. REM behavior disorder is characterized by agitated, sometimes violent movements occurring during REM sleep. The majority is males above age 60 and other neurologic disorders such as Parkinson disease or multisystem atrophy are common.[1,10,24,50,58,69] Other members within the same family can certainly be afflicted with these disorders, but hardly with a distinct autosomal dominant transmission pattern. Besides hypnagogic myoclonias, short nocturnal movements resembling mild seizures can be present in healthy subjects. However, in NFLE the episodes are more stereotypical and include sudden movements with dyskinetic or dystonic components. When characteristic hyperkinetic seizures during sleep are video-recorded, the diagnosis of NFLE is usually readily made.

A careful pedigree analysis confirms the familial occurrence of the disorder and differentiates ADNFLE from the more common sporadic forms of NFLE. Other autosomal dominant focal epilepsies (e.g., from the temporal lobe) may also manifest themselves with nocturnal seizures, but have otherwise different ictal semiologies. However, families with autosomal dominant partial epilepsy with variable foci may contain patients with a seizure pattern similar to NFLE. They can thus wrongly be considered as ADNFLE families before the phenotypic variability is appreciated. In this syndrome, seizures arise from different cortical regions in different family members and a predominance of seizures while awake may be observed in some individuals.[3]

Treatment and Outcome

Carbamazepine has been postulated to be the drug of choice in ADNFLE. It has been reported to be more effective than valproate and appears to suppress seizures completely in about two thirds of patients with this syndrome.[46,58] Low doses of carbamazepine (around 600 mg/day in adults) are often sufficient. The detection of an association between nAChR mutations and ADNFLE gave the opportunity to compare the effect of carbamazepine on mutated and wild-type receptors in vitro. Studies in *Xenopus* oocytes demonstrated that carbamazepine most probably acts as an open channel blocker and generally inhibits α4β2 nAChRs, but that most mutants display a higher sensitivity to this effect.[5,47] Carbamazepine may shut down the mutant receptors, whereas remaining wild-type receptors are less affected.[47,64] Pharmacoresistance to carbamazepine and other antiepileptic drugs has nevertheless been observed in one third of patients. Most reported families have at least had one pharmacoresistant individual, whereas other affected family members have had a good therapeutic response.[10] There is indeed considerable interfamilial and intrafamilial clinical variability concerning epilepsy severity and effect of antiepileptic therapy in this condition.

Acetazolamide was reported to reduce or control seizures in one family without evidence for nAChR mutations.[71] In one single patient with uncontrolled seizures from the original Australian family, transdermal nicotine appeared to be very effective when added to carbamazepine in both an open and a double-blind placebo-controlled fashion.[73] These preliminary data encourage attempts to treat patients who prove to be refractory to standard antiepileptic therapy with these agents.

The effect of surgical treatment has not been reported in ADNFLE in spite of its localization-related clinical manifestations. A priori, resective surgery does not appear to be an appropriate option in disorders caused by mutations affecting receptors with widespread distribution in the brain. Prudence should also be exercised in sporadic NFLE.

Long-term Prognosis

The phenotypic expression of this condition spans from a persistent, severe disability to only a mild intermittent sleep disruption, not recognized as an epileptic manifestation by either the affected individuals or their proxies. Even with frequent seizures, remissions can occur during adolescence and adulthood, without seizure recurrence after discontinuation of drug therapy.[17,34,36,39,42,46,64] However, relapses may occur after many years, and in some families, ADNFLE persists through adult life in many of the affected individuals.[58,62,64,66] Genetic or environmental factors that determine penetrance or remission are not yet identified. The reported efficacy of nicotine administration[73] is interesting in this respect, and to date it is not known to what extent chronic consumption of nicotine could influence the course and prognosis of this disorder. The fact that the attacks are exclusively sleep related in most patients and usually do not change their chronodependency is important when assessing these patients for motor vehicle driving.

Summary and Conclusions

ADNFLE was the first idiopathic epilepsy for which a distinct genetic basis was identified. Mutations in two genes (*CHRNA4* and *CHRNB2*) coding for neuronal nicotinic receptor subunits (α4 and ß2) have been identified. ADNFLE is characterized by nocturnal attacks that tend to cluster and can recur several times during one night. Seizures have prominent motor features and mainly occur during non-REM sleep, particularly shortly after falling asleep, before waking up in the morning, and during daytime naps. Onset age varies, but is usually within the two first decades of life. Currently, it is hypothesized that the pathogenetic mechanism is linked to overactivity in ascending cholinergic circuits that control arousal, leading to an imbalance of function in the frontal lobes. The ictal symptoms are thought to represent a paroxysmal disinhibition of subcortical activity in the form of automatic motor and limbic activity. The hyperkinetic sleep-related seizure is the clinical hallmark of the disorder. Interictal cognitive and psychiatric symptoms have been described in some families, but it is uncertain whether these features are true phenotypic traits. Most patients respond to antiepileptic therapy, especially carbamazepine, but one third of patients are pharmacoresistant. Some patients report long seizure-free periods. Unknown factors influence penetrance, treatment response, severity, and remission. Further studies, clinical as well as on the molecular level, are needed for a more complete understanding of ADNFLE. Nevertheless, the recent discoveries in ADNFLE have suggested new neurobiologic mechanisms for familial epilepsy and throw new light on the pathogenesis of epilepsy in general.

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Chapter 250

Hypothalamic Hamartoma with Gelastic Seizures

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Introduction

The syndrome of hypothalamic hamartoma (HH) with gelastic (laughing) seizures (GSs) is a rare but important epileptic syndrome (HHGS), being one of the most refractory, disabling, and poorly understood seizure disorders affecting children and adults. Over the last decade, much has been learned about the nature of HH and its often progressive neurologic and behavioral manifestations, and effective surgical treatments have also been developed.

Historical Perspectives

Le Marquand and Russell[44] first used the term hamartoma in 1934 to describe a tumor-like lesion of the hypothalamus found at postmortem in a boy with precocious puberty. Chronic epilepsy associated with a hypothalamic lesion, designated an astrocytoma but likely an HH, was first reported 2 years earlier[86] in a boy with precocious puberty and mental retardation who died from status epilepticus. The first report of GS in a patient with HH was in 1938,[18] the patient also having precocious puberty and pervasive developmental delay. Isolated reports of probable or proven HH with gelastic seizures followed.[27,45,50,59,60,66,78] In 1988, the association was better characterized by Berkovic et al. as a recognizable and possibly progressive epileptic syndrome, their series incorporating neuroimaging diagnosis.[4] The first report of a patient surviving surgical resection of an HH was in 1967,[59] but it was not until the mid-1990s that GSs were shown conclusively to arise in the HH[39,41,54] and surgical treatment for refractory seizures flourished. Over the last 10 years, there has been great interest in the nature of HH and its association with GSs, and great efforts in developing minimally invasive surgical techniques for treatment of the refractory seizure disorder. For further details concerning GSs, see Chapter 53.

Definitions

A hamartoma is a focal malformation that resembles a neoplasm, composed of an abnormal mixture or proportion of tissue elements normally present in that site, which develop and grow at virtually the same rate as normal tissue.[71] HHs are usually spherical in shape with a diameter between 0.5 and 4 cm, in most cases <1.5 cm. HHs arise from the tuber cinereum or from one or both mammillary bodies, and if large, may bulge into the third ventricle and compress (but not disrupt) the hypothalamic nuclei and fiber tracts.[45] Asymmetric location and attachment are seen in about two thirds of patients.[21]

Several anatomic classifications of HH based on magnetic resonance imaging (MRI) features have been proposed, distinguishing different sizes and patterns of hamartoma attachment to the hypothalamus.[1,8,15,85] The most important separation from clinical, pathophysiologic, and surgical perspectives seems to be the distinction between HHs sitting within the third ventricle that are attached to the mammillary bodies and/or the hypothalamic walls (sessile, intraventricular, intrahypothalamic) from those HHs beneath the third ventricle with attachment to the tuber cinereum (pedunculated, extraventricular, parahypothalamic). HHs associated with epilepsy are almost always intraventricular, at least in part, with a significant mammillary body attachment.

Histologically, HHs resemble normal gray matter,[57] though some neurons may show variation in size and shape[8,14,37,59,62,75] and may appear in discrete nests or nodules of cells.[8,29,59] Fibrillary gliosis is also found,[8] and cystic changes have been observed in large lesions.[70] Dysplastic neurons and balloon cells are not seen in HHs.

Epidemiology

HHGS is an uncommon epileptic syndrome, with a prevalence in childhood of about 0.5 in 100,000.[9] Most early reports of HHs were in patients with central precocious puberty,[91] but most recent reports concern HHs and GSs. The current literature is biased toward surgical patients with severe seizure and other neurologic manifestations, making it hard to determine the proportion of patients with different clinical features. Also, it is likely that there are patients with HHs who are asymptomatic or have only mild or undiagnosed seizure manifestations,[81] leading to underreporting of HH. A greater number of males with HHs and epilepsy is reported.[82]

Etiology and Basic Mechanisms

HHs are a nonfamilial, congenital malformation usually occurring in isolation. They are rarely associated with other intracranial malformations such as callosal dysgenesis, heterotopias, arachnoid cysts, and microgyria.[8,21,30] Rarely, HHs may occur as part of a multiple congenital malformation syndrome, most notably the autosomal dominant Pallister-Hall syndrome, which includes HH, polydactyly, hypopituitarism, imperforate anus, and dysplastic nails.[7] Seizures occur in about 15% of patients with Pallister-Hall syndrome and are often mild, despite HHs often being very large. Patients with Pallister-Hall syndrome have mutations of the zinc-finger transcription factor gene *GLI3* on chromosome 7p13,[35,40] but the role of *GLI3* mutation in patients with sporadic HHs[24] is unconfirmed and so the etiology of sporadic HHs remains uncertain.

The genesis of seizures associated with HH is also incompletely understood. Mechanical irritation or distortion of the adjacent hypothalamus or midbrain by the HH was initially believed to be the cause of seizures.[45] The severity and

generalized nature of seizures and associated neurologic and behavioral problems in many patients with HHs, and the early poor results of HH surgery,[10,49,69,75] led to speculation that patients with HHs had widespread occult cerebral dysgenesis.[4,79] GSs were eventually shown to arise from the HH by stereotactic depth electroencephalographic (EEG) recording of seizures from the HH, by reproduction of symptoms with electrical stimulation of the HH, and by demonstration of HH hyperperfusion with ictal single photon emission computed tomography (SPECT).[34,36,37,38,39,41,54] This led to a change in view from the HH simply being an epiphenomenon to the HH being intrinsically epileptogenic.[6] Such intrinsic hyperexcitability has been documented with single cell studies of small neurons within cell clusters in resected HHs exhibiting pacemaker-like spontaneous repetitive firing,[90] similar to that seen in focal cortical dysplasia.[48,63]

The reasons for marked variability of the neurologic manifestations of HHs, and the relationship between the size and attachment of the HH, and the neurologic manifestations remain uncertain. Some reports suggest that seizures are more frequent or severe in patients with larger HHs.[47,81] A connection of the HH with the mammillary bodies seems to be integral to epileptogenesis.[1,21,85] Tonic seizures that develop in a proportion of children do not seem to arise from the HH,[37] but rather occur as a related but independent neocortical phenomenon. The whole electroclinical picture of symptomatic generalized epilepsy, with slow spike-wave on EEG and generalized tonic seizures, may develop in patients with HHGS as a consequence of secondary epileptogenesis in the neocortex.[22]

Clinical Presentation

GSs are the characteristic epileptic manifestation of HH, occurring in nearly all patients (see Chapter 53). Early onset of GSs is characteristic[9,82] and onset from the day of life is well known.[4,16,17,41,62,78] The sound produced during GSs associated with HH is described variously as laughter, chuckling, or giggling, often qualified by words such as unnatural, mechanical, mirthless, and inappropriate. Dacrystic (crying) seizures are noted in many patients,[10,28,37,45,65,78,80,87,89] invariably accompanied by GSs. Very frequent, brief GSs occurring during wakefulness and sleep are common in infancy. A mild form of GSs is described in adults with small HHs, the patients sometimes describing only a “pressure to laugh”[81] or an “urge to giggle.”[52] Consciousness is said to be preserved during brief gelastic seizures.[4,12,78] Often accompanying laughter in gelastic seizures are autonomic features such as facial flushing and pupillary dilation, hypermotor automatisms, oro-alimentary automatisms, head and eye deviation, and tonic or clonic facial contraction.[4,78]

West syndrome is reported in association with HH,[3,9,22,53] such that HH should be included in the differential diagnosis of infants presenting with epileptic spasms.

An epileptic progression with development of focal seizures, tonic/atonic seizures, and tonic–clonic seizures occurs in more than half of patients.[82] Many patients develop Lennox-Gastaut syndrome with disabling drop attacks. There is a paucity of detailed clinical and EEG descriptions of these associated seizures occurring in patients with HHs, in contrast to GSs. The interrelationship of these different seizure types is uncertain, but focal seizures associated with HHs often have frontal and temporal lobe features, tonic seizures and spasms associated with HHs often have focal motor features, and laughter may precede or follow all of these.

Cognitive and behavioral impairments are common in patients with HHGS who have seizures beginning in childhood, especially refractory seizures that begin in infancy and evolve to focal and generalized seizures with marked EEG disturbances. These vary in severity from mild impairments of memory, attention, and learning[4,20,52,81] to severe intellectual disability.[15,33,62] Aggressive behavior, rage attacks, and other psychiatric comorbidities are widely reported in patients with HHGS.[4,88] The relationship of behavior disturbance to GSs and intrinsic hypothalamic dysfunction is uncertain.

Central precocious puberty is common in patients with HHGS (see below), occurring in 30% to 40% of patients with epilepsy,[21,82] usually following the onset of seizures and associated with larger HH size and involvement of the tuber cinereum.[21] Treatment of central precocious puberty with gonadotropin-releasing hormone (GnRH) agonists is usually effective, and patients rarely undergo surgery for this indication alone.

Diagnostic Evaluation

The diagnosis of HHGS is usually based on the recognition of pathologic laughter attacks and the finding of an HH on MRI; EEG is rarely informative early in the course of the epilepsy. The diagnostic evaluation for patients undergoing epilepsy surgery is similar to that for patients with refractory epilepsy of cortical origin except for the need for perioperative endocrine assessment, the need for precise anatomic imaging of midline brain structures, and less attention paid to scalp EEG localization of seizures and interictal discharges.[32]

EEG Findings

Scalp EEG in patients with HHs is variable, reflecting the age of the patient and the evolution of the seizure disorder. In young children with only GSs, and in adults with mild symptoms, the interictal EEG is usually normal,[60] potentially leading to missed diagnosis. Interictal EEG abnormalities may not appear until later childhood,[46] coinciding with the appearance of additional seizure types.[82] Initially, the interictal record may only be abnormal during sleep.[12] Spike-wave activity is prominent over the frontal and temporal regions initially and may be bilaterally synchronous or predominantly unilateral.[11,82] Unilateral abnormalities tend to occur on the side of predominant HH attachment. In patients with tonic and other generalized seizures, background slowing is common and multifocal or generalized spike-wave activity, paroxysmal fast activity, and electrodecremental patterns are recorded, often with electrical status in sleep.[22] The interictal EEG abnormalities in patients with HH must be secondary neocortical phenomena, as a small mass of nonlayered gray matter deep in the middle of the cranium cannot generate electrical potentials of significant amplitude to be recorded on the scalp surface. In fact, intracranial EEG recordings show that interictal discharges arise independently in the HH and the neocortex.[22,37] Furthermore, interictal discharges persist over the neocortex immediately following resection of the HH,[22] though they may subside in the weeks and months that follow successful surgery.

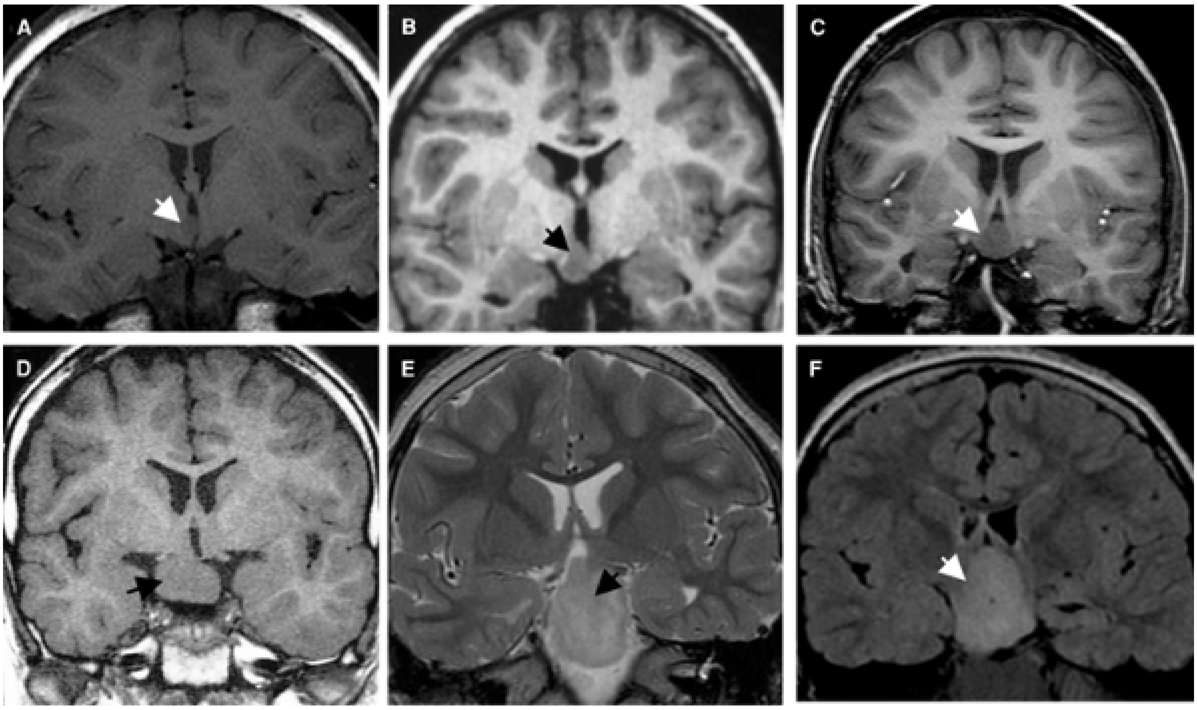

FIGURE 1. Coronal magnetic resonance images of six patients with gelastic seizures and hypothalamic hamartoma (HH) of different sizes and attachments. **A, B:** Small, unilateral, intraventricular HHs. **C:** A moderate size, bilateral, intraventricular HH. **D, E:** Large, unilateral HHs attached broadly to the ventricular wall and tuber cinereum. **F:** A large, bilateral, intraventricular HH, which distorts the hypothalamus and extends into the interpeduncular cistern.

Ictal scalp EEG may show no change during brief GSs,[60] or just a desynchronization of the background activity.[9] Later, as tonic seizures and interictal slow spike-waves develop, GSs are marked by suppression of the interictal discharges and attenuation of background rhythms, with or without widespread low-voltage fast activity.[4] In patients with partial seizures, ictal EEG recordings may show focal rhythms or spike-wave activity, either unilaterally or bilaterally. Misleading focal ictal onsets in the frontal or anterior temporal lobes of patients studied with intracranial EEG recordings, but without electrodes in the HH, once led to unsuccessful focal cortical resections.[11] Depth EEG recordings from the HH[37,38,39,41,54] show that GSs are associated with an ictal discharge within the HH that, in most

cases, remains confined to the HH. Electrical stimulation of the HH via the depth electrodes in these cases may provoke the characteristic ictal laughter. In contrast, depth EEG recording of tonic seizures reveals discharges remote from the HH involving various cortical areas.[37]

MRI

MRI (Fig. 1) is far superior to computed tomography (CT) of the brain in revealing and characterizing HHs.[4] Small HHs may be difficult to detect unless the hypothalamic region is specifically examined. HHs usually have increased signal compared to gray matter on T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences, and low signal on T1, but do not enhance with contrast and remain in proportion with the rest of the brain over time.[21] T2-weighted sequences in the three orthogonal planes are well suited to displaying the high-signal HHs in relation to the low-signal, heavily myelinated hypothalamic nuclei and tracts. Proton magnetic resonance spectroscopy suggests neuronal attenuation and relative gliosis compared with normal gray matter.[21]

PET and SPECT Imaging

Positron emission tomography (PET) studies are few and show either scattered areas of focal cortical or regional hypometabolism, with lateralization usually being concordant with the side of HH attachment.[62,74] Ictal SPECT studies during GSs demonstrate focal hyperperfusion in the region of the HH[17,34,41,43]; HH hypermetabolism is reported in a patient studied with ^{18}F-fluorodeoxyglucose (FDG)-PET during status epilepticus.[64] Asymmetric cerebral perfusion during seizures is common in HHGS,[9] with hyperperfusion ipsilateral to the side of predominant HH attachment, suggesting preferential cortical spread of seizure activity from the HH.[23]

Differential Diagnosis

Pathologic laughter is reported as an epileptic and nonepileptic manifestation of various lesions and processes affecting the temporal lobe, frontal lobe, and brainstem (see Chapter 53). Craniopharyngiomas and tumors of the hypothalamus and third ventricle are imaging differentials of HHs but are generally distinguishable on MRI and rarely present with chronic epilepsy. A search for associated cerebral malformations on MRI and a clinical examination for midline malformations and polydactyly should be undertaken in a patient with seemingly isolated HHs to look for syndromic features.

Surgery and Outcome

Antiepileptic medications are generally ineffective in the management of epilepsy associated with HHs.[4,9] While they may have some impact on the severity or frequency of partial and generalized seizures, antiepileptic drugs generally have little impact on GSs. Vagal nerve stimulation may provide partial benefit in some patients.[9,55]

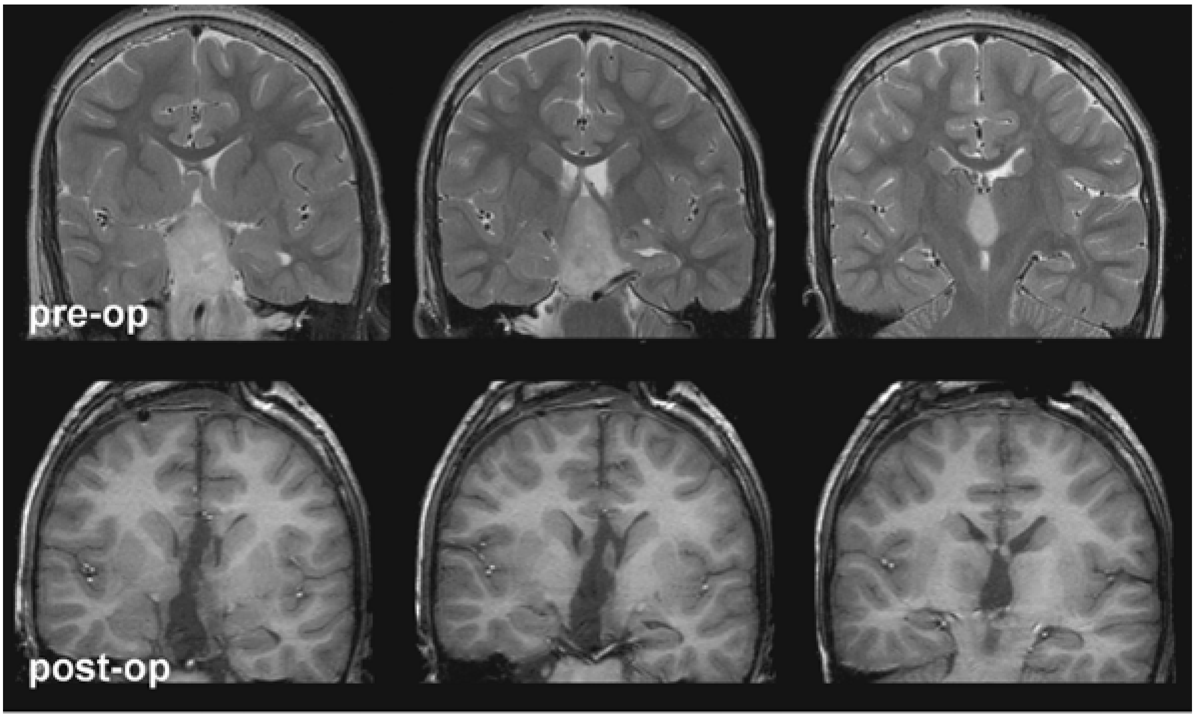

FIGURE 2. Coronal magnetic resonance images of a child with a large bilateral hypothalamic hamartoma and intractable gelastic seizures, before **(top row)** and after **(bottom row)** transcallosal resection.

Early attempts at HH removal were not particularly successful,[10,69,75,78] but with refinements in technique and advances in technology, epilepsy surgery has since become the

accepted treatment of choice for refractory epilepsy associated with HHs.[5,6,31,68] Several operative approaches are currently reported, including open craniotomy (pterional, frontotemporal, paramedian) for either microsurgical or endoscopic resection or disconnection of the HH, and minimally invasive stereotactic approaches with endoscopic, radiofrequency, or radiosurgical ablation.

Open Craniotomy

Pterional and large frontotemporal craniotomies provide access to the inferior part of the HH via a transsylvian, transfrontal, subtemporal, or subfrontal approach.[15,46,51,58,62,85] In some cases the temporal pole or orbital cortex is resected. Such surgical approaches to HHs have proven ineffective in many cases, as only the subventricular component of the HH can be removed, leaving the intraventricular component attached to the mammillary bodies.[5,6,62] Furthermore, there is significant risk of endocrine complications, stroke, and oculomotor paresis with these approaches.[15,62] Delalande proposed disconnection as a safer alternative to resection during frontotemporal approaches.[15]

An interhemispheric, transcallosal approach to intraventricular resection of HHs was developed by Rosenfeld et al.,[73] with superior results and fewer neurovascular complications reported. This approach passes between the columns of the fornices to access the HH within the third ventricle, allowing direct vision of the intraventricular component of the HH under the operating microscope, and complete or near-complete resection or disconnection of the intraventricular HH with the ultrasonic aspirator (Fig. 2). In a series of 29 consecutive young patients undergoing transcallosal surgery for HHs, complete or near-complete resection was achieved in 22. Seizure freedom was achieved in 15 patients and >90% seizure reduction in seven.[33] Most striking in this series was the improvement in patients with symptomatic generalized epilepsy, in whom tonic seizures were frequently abolished and generalized, multifocal spike-wave on scalp EEG was improved, and improved language and behavior were observed.[22,33] “Running down” of generalized seizures was observed in several patients.[22,33] These results dispel the notion that these HHGS have diffuse and irreversible cerebral dysfunction or dysplasia. Morbidity consisted of short-term memory impairment, weight gain, hypothyroidism, and transient hypernatremia.[25,33] Similar results are reported from another center.[56]

Stereotactic Radiofrequency Ablation

Stereotactic radiofrequency thermocoagulation was employed early in the development of surgical treatments for HHs with intractable epilepsy.[26,41,65] Multiple lesions are produced in the HH, often after seizures are recorded from the implanted electrode and symptoms are reproduced with electrical stimulation. The need for repeat procedures is not uncommon and low seizure-free rates are reported, most likely reflecting the limited impact of the small lesions induced. Stereotactic radiofrequency thermocoagulation may only be suitable for small HHs.[42]

Neuroendoscopy

Neuroendoscopy is being increasingly utilized to resect or disconnect HHs,[13,15,42,62] with access to the third ventricle being obtained via a transcortical approach through the frontal horn of the lateral ventricle and the foramen of Monro.

Radiofrequency thermocoagulation can be combined with endoscopic access to disconnect or lesion HHs. Postoperative hospital stay is reduced with such minimally invasive procedures, but whether efficacy and safety are comparable with open craniotomy and resection is yet to be demonstrated in large series.

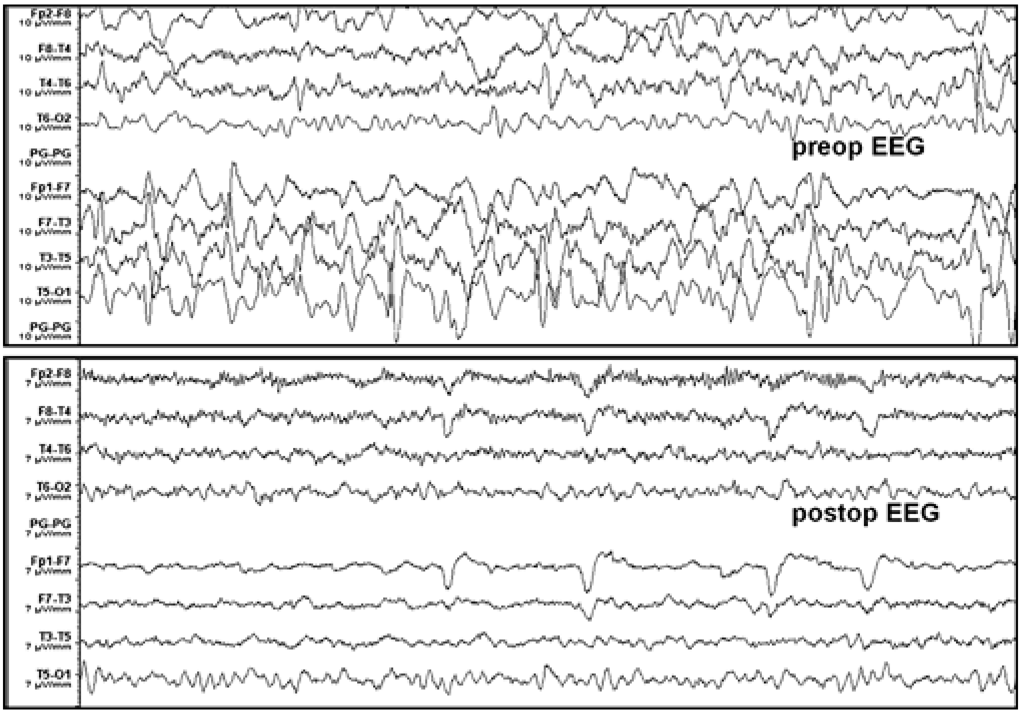

FIGURE 3. Interictal scalp electroencephalographic (EEG) recordings in a child with gelastic seizures and hypothalamic hamartoma who underwent transcallosal resection of the hamartoma. The preoperative awake EEG 8 days before surgery **(top)** showed multifocal epileptiform discharges predominantly on the left, which were abolished on the postoperative awake EEG 21 days following surgery **(bottom)**.

Stereotactic Radiosurgery

Stereotactic radiosurgery, such as with the Gamma Knife, delivers high-dose, ionizing radiation to a stereotactically defined intracranial target, with a steep radiation fall-off outside of the treated volume. Gamma Knife radiosurgery has been extensively applied to the treatment of HHs.[2,19,72,83,84] Like stereotactic radiofrequency ablation, Gamma Knife surgery is probably best suited for small HHs or for the hypothalamic attachment of larger HHs. Minimal morbidity and short hospital stays are clear advantages, whereas delayed seizure reduction is a disadvantage. Seizure-free rates are difficult to determine as large series are lacking. Stereotactic implantation of ^{125}I seeds into the HH is an alternative radiosurgical approach.[76,77]

Surgery Outcomes

If seizure outcomes are compared in patients undergoing only one surgical technique, and analysis is confined to series with adequate reporting and minimum 1-year follow-up, Engel class I or II outcome (seizure freedom, auras only, rare seizures only) is reported in 66% of patients undergoing transcallosal resection, 60% of patients undergoing endoscopic procedures, 38% of patients undergoing Gamma Knife surgery, 36% of patients undergoing pterional or frontotemporal approaches to resection or disconnection, and 27% of patients undergoing stereotactic radiofrequency ablation.[31] Neurovascular complications are significantly greater for operative compared with stereotactic approaches, especially for pterional and frontotemporal approaches. Endocrine and memory disturbances appear to be more common with the transcallosal approach. Seizure outcome does not seem to be related to patient age, the presence of generalized seizures, or HH size[33] such that all patients with HHs and refractory epilepsy should be considered for surgery. More data with longer patient follow-up are required to properly evaluate radiosurgery. Callosotomy and neocortical resection are failed operative approaches that are no longer advocated in patients with HHs.[11,61]

Improvements in behavior, school performance, and aspects of development are reported in many patients undergoing HH surgery, regardless of approach and seizure outcome. Amelioration of autistic features has also been noted in one case with postoperative seizure freedom.[67] Reduction of interictal spike-wave following HH surgery is reported[22] (Fig. 3) and is associated with improvements in alertness, language, and behavior. However, reversal of intellectual impairment is not reported.

Long-term Prognosis

In patients with HHs in whom seizures begin early in childhood, the prognosis for seizure control and neurologic development and behavior seem poor, especially if seizures begin in infancy and there is early evidence of seizure evolution. Favorable treatment outcomes seem only to occur in patients who undergo successful surgery early in childhood, before the development of severe neurologic sequelae.

Summary and Conclusions

A rare, severe, and once untreatable epileptic syndrome, HHGS is now better understood and being effectively treated with surgery. Early diagnosis is important and requires recognition of pathologic laughter and adequate MRI imaging and interpretation. While controlled trials of surgical treatments are unlikely, greater experience with transcallosal, endoscopic, and radiosurgical approaches should lead to a better understanding of the most effective and safe treatment for this condition.

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Chapter 251

Localization-related Epilepsies Due to Specific Lesions

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Introduction

The localization-related epilepsies are epileptic syndromes in which seizures arise in a geographically restricted area within a part of one or alternate hemisphere(s) (partial or focal seizures).[30] Lesional localization-related epilepsies are the most common group of medically intractable epilepsies seen in adults and are also an important cause of intractable seizures in children.[58,162] Magnetic resonance imaging (MRI) is the most sensitive and specific modality for imaging lesions in patients with focal epilepsies and has greatly improved our understanding of the nature and frequency of these lesions.[19,31,72,85]

Approximately 30% of patients who undergo surgical treatment for intractable epilepsy have a foreign tissue lesion detected on pathologic examination.[6] There is a strong correlation between the site of the lesion and the site of the epileptogenic zone.[5,14,25,119] The identification of an epileptogenic lesion on MRI has been cited as being as predictive of a poor response to antiepileptic drugs.[43] Furthermore, such patients are more likely to become seizure free postoperatively than those in whom no structural abnormality is found.[94,127,144] In a randomized, controlled trial for surgery versus medical treatment for medically refractory mesiotemporal lobe epilepsy, 58% of those treated surgically in addition to drugs were seizure free at 12 months compared with 8% in the only conservatively treated group.[159]

Historical Perspectives

Focal structural lesions, particularly brain tumors, have been recognized as a cause of seizures since ancient times.[148] Hughlings Jackson[73] wrote extensively of the relationship between partial seizures and underlying focal brain pathology. He stressed that seizures could be the first and only manifestation of the tumor, that ictal behavior may predict the cerebral localization of the lesion, and that the severity and type of seizures were not predictive of the nature of the underlying pathology. Horsley in 1886[66] reported three patients who had been cured of seizures by surgical excision of an underlying focal structural lesion. In the earlier part of this century, it was particularly the work of Penfield and colleagues[87,121] at the Montreal Neurological Institute (MNI) and of Falconer and Serafetinides[48] in London that advanced our understanding of localized cerebral lesions and epilepsy and of the surgical treatment of these conditions. It has been only since the advent of modern neuroimaging, however, that the true importance of local structural lesions as a common, surgically treatable cause of both temporal and extratemporal focal epilepsy has been appreciated.[6]

Definitions

For the purposes of this chapter, "specific lesions" are defined as discrete local (or regional) structural pathologies that are associated with chronic focal epilepsy. These local lesions most commonly occur in an otherwise structurally normal brain. More diffuse cerebral pathologies that may be associated with partial seizures but do not typically present as discrete mass lesions (e.g., diffuse neuronal migration disorders, Rasmussen encephalitis) are discussed elsewhere (Chapters 259 and 243). Mesial temporal sclerosis is discussed fully in Chapter 247.

Epidemiology

A large surgical series of patients with focal structural lesions comes from the MNI; Table 1 summarizes the results of this series and other selected epilepsy surgery series along with reported pathology. Surgical series, however, are subject to significant biases because patients with a known mass lesion are more likely to be referred to an epilepsy center and then proceed to surgery.[101] There is also a bias regarding the sites of the lesions reported in these series, with patients having temporal lobe seizures more likely to undergo epilepsy surgery. Furthermore, most of the patients in these series were collected before the advent of modern neuroimaging, when only large masses could be detected preoperatively. It is important to note that a number of pathologies associated with focal epilepsy, notably focal cortical dysplasias (FCDs) and dysembryoplastic neuroepithelial tumors (DNETs), were not recognized until the advent of high-quality magnetic resonance imaging.

Studies using high-resolution MRI have the potential to reduce some of the biases of these surgical series, and they may give a more accurate representation of the incidence and sites of occurrence of neocortical lesions in focal epilepsy. Because these series also come from large epilepsy referral centers, however, they are subject to some of the same referral biases. Ta-ble 2 summarizes four large, high-resolution MRI series. In comparison with the pathologic series, it is noteworthy that the proportion of extratemporal lesions is higher, as is the incidence of certain types of lesions, particularly FCDs and DNETs.

Table 1 Selected series of lesions detected on pathologic examination following surgery for intractable partial seizures

	Le Blanc and Rasmussen 1974	**Spencer et al. 1984**	**Wolf et al. 1993[a]**	**Fried et al. 1994[b]**	**Britton et al. 1994[a]**	**Xiao et al. 2004**
Reference	87	140	163	52	15	166
Number of cases (% Total Cases)[c]	265 (20%)	27 (15%)	125 (58.1%)	65	51	1,650
Institution	MNI	Yale	Bonn	Yale	Mayo Clinic	Xiangya
Time Period	1928–1966	1972–1982	1987–1993	1978–1991	1984–1990	1991–2000
Site						
Temporal	NS	12 (41.3%)	125 (100%)[a]	41 (63%)	39 (76%)	904 (55%)
Extratemporal	NS	15 (58.7%)	—	24 (37%)	12 (24%)	746 (45%)
Frontal	NS	7	—	7	10	—
Frontoparietal	NS	3	—	—	—	—
Parietal	NS	1	6	2	—	—

Occipital	NS	2	—	11	—	—
Other	NS	2	—	—	—	—
Pathology						
Primary brain tumors	171 (79.5%)	19 (70.3%)	75 (60%)	65 (100%)[c]	51 (100%)	247 (15%)
Low-grade astrocytoma	127	8	23	40	18	117
Oligodendroglioma	NS	3	9	5	15	76
Ganglioglioma	NS	1	34	4	4	24
Miscellaneous low-grade gliomes	44	1	2	5	10	—
Glioblastoma	24	3	1	11	—	—
DNET	NS	NS	6	—	4	—
Meningiomas	20	2	—	—	—	30
Other	—	1	—	—	—	—
Vascular malformations	NS	3 (11.1%)	13 (10.4%)	—	—	292 (17.7%)
Arteriovenous malformations	14 (5%)	3	2	—	—	70
Cavernous hemangiomas	NS	—	11	—	—	222
Disorders of cortical development	—	—	1 (3.2%)	29 (23.2%)	—	122 (7.4%)
Cystic lesions	—	3 (11.1%)	4 (3.2%)	—	—	63 (3.8%)

Metastatic tumor	6 (2%)	—	—	—	—	—
Miscellaneous lesions	20 (8%)	1 (3.7%)	4 (3.2%)	—	—	926 (56.1%)[d]

DNET, dysembryoplastic neuroepithelial tumors; MNI, Montreal Neurological Institute; NS, not stated.

[a] This series reported temporal lobe specimens only.

[b] This series was restricted to glial tumors.

[c] Number of cases of lesional epilepsy and percentage of total surgical specimens examined.

[d] Miscellaneous lesions included scar, hippocampal sclerosis, gliosis, infection, calcification and encephalomalacia lesions.

Table 2 Selected series of high-resolution magnetic resonance imaging in patients with partial epilepsy

	Jackson 1994	Li et al. 1995	O'Brien et al. 1996	Velasco et al. 2006
Reference	72	91	109	153
Total number of cases	340	341	468	512
Number of Lesional cases	117 (34.4%)	117 (34.3%)	213 (45.6%)	179 (35%)
Site				
Temporal	58 (58%)[a]	28 (23.9%)	36 (62.1%)[b]	NS
Extratemporal	42 (42%)[a]	89 (76.1%)	22 (37.9%)[b]	NS
Frontal lobe	NS	41	15	—
Central lobe	NS	—	4	—
Parietal lobe	NS	19	1	—
Occipital lobe	NS	5	2	—

Multilobar	NS	24	—	—
Lesion Type				
Low-grade tumor	46 (39.3%)	40 (34.1%)	58 (27.2%)	51 (28.5%)
Disorders of cortical development	35 (29.9%)	43 (36.8%)	82 (38.5%)	62 (34.6%)
Focal cortical dysplasia	NS	NS	71	NS
Nodular heterotopia	NS	NS	11	NS
Vascular malformations	14 (12.0%)	28 (23.9%)	39 (18.3%)	2 (1.1%)
Cavernous hemangiomas	12	NS	NS	NS
Arteriovenous malformations	—	2	NS	NS
Cystic lesions	5 (4.3%)	—	10 (4.7%)	33 (18.4%)[d]
Focal encephalomalacia	—	20 (17.1%)	20 (9.4%)	31 (17.3%)
Miscellaneous	17 (14.5%)	—	4 (1.9%)	—

NS, not stated.

[a] Sites are not given for patients with miscellaneous lesions.

[b] Figures for the sites in this study are for 58 lesional patients with complex partial seizures proved by video telemetry.

[c] Figures available for “brain tumors” only.

[d] Includes porencephaly and neurocysticercosis cases.

[e] Defined as gliosis.

Epidemiologic population-based studies of epilepsy have the potential to reduce the biases seen in both the surgical and MRI series.[57,71] Hauser and Kurland,[58] in one of the largest such studies (Rochester, Minnesota, from 1935 through 1967), found a focal mass lesion in only 27 (5.2%) of 516 cases given a diagnosis of epilepsy during this period. Of these patients, 21 had brain tumors (18 primary and 3 metastatic), 4 had vascular malformations, and 1 patient had tuberous sclerosis. This study was also performed before the advent of modern neuroimaging, however, and therefore it is likely to have underestimated the true incidence of lesions because most are indolent and produce

no focal clinical impairment or electroencephalographic (EEG) slowing.[150]

The incidence of cerebral tumors in children undergoing epilepsy surgery may be higher than in adults, with estimates as high as 46%.[13,101] Studies using MRI also suggest that before the age of 12 years, lesional epilepsy, particularly gangliomas and disorders of cortical development (DCDs), may be more common and mesial temporal sclerosis (MTS) less common.[85,119,122]

Etiology and Basic Mechanisms

The pathophysiologic mechanisms by which intracranial mass lesions cause chronic seizure activity is poorly understood, but a number of theories have been advocated. One proposed mechanism is "denervation hypersensitivity," which results from the partial isolation of a part of the neocortex through tumor growth or brain scarring, thus creating enhanced excitatory status and epileptogenic potential.[41] The degree of mass effect of the lesion, however, is unrelated to the incidence of epilepsy.[8,95] There is some evidence that there may be a familial predisposition to epilepsy developing with mass lesions, but much of the data on this are conflicting.[14,109]

Low-grade tumors, which predominate in series of chronic lesional epilepsy, are rarely associated with pathologic evidence of hemorrhage, necrosis, inflammation, or ischemia, nor are they usually associated with significant mass effect.[101] Cerebral tumors may induce changes in the surrounding neocortex that affect the balance of neurotransmitter levels, synaptic receptors (especially for *N*-methyl-D-aspartate [NMDA] or γ-aminobutyric acid [GABA]), or ion channels (e.g., increased leakage of axonal calcium or chloride channels).[21] In support of this theory, Bateman et al.[8] demonstrated an increased concentration of glutamine (the precursor to the excitatory neurotransmitter glutamate) in the gliomas of patients with epilepsy compared with gliomas from patients without seizures. Glutamine has been shown to be released and taken up by glioma cells.[106,156] Decreases in concentrations of the inhibitory

neurotransmitter GABA have also been demonstrated in gliomas of patients with seizures[8] and in the surrounding non–tumor-infiltrated neocortex.[10] Expanding tumors may also interfere with vascularization of the surrounding cerebral cortex, creating a region of relative cerebral ischemia having an increased epileptogenic potential.[126]

In vascular malformations, pathologic studies have shown the presence of neuronal loss, gliosis, demyelination, and hemosiderin deposition in the surrounding cerebral cortex, which may act as a focus for epileptogenesis.[97,145] It has been suggested that the increased epileptogenic potential associated with these lesions is caused at least in part by the effects of repeated subclinical hemorrhage and resultant hemosiderin deposition.[21,145,169] Dodick et al.,[38] however, showed that hemosiderin deposition could not be the sole mechanism of epileptogenesis in patients with vascular malformations. Alternatively, ischemia in the brain surrounding an arteriovenous malformation (AVM) caused by arteriovenous shunting of blood may result in an area of epileptogenic encephalomalacia.[167]

Clinical Presentation

It has been appreciated for more than a century that the clinical history and ictal behavior may give a clue to the site of the underlying epileptogenic lesion.[73] Since the advent of MRI, however, it has become clear that a large overlap exists in the ictal symptomatology produced by lesions at different cortical locations. Lesions at any site may result in simple partial, complex partial, or secondarily generalized seizures. Complex partial seizures are often thought to indicate temporal lobe seizures, but in a study of high-resolution MRI in 129 consecutive patients with video-EEG-proven complex partial seizures, discrete neocortical lesions were detected in 58 (45%), of which 22 (37.9%) were extratemporal (15 frontal, 4 frontoparietal, 1 parietal, and 2 occipital).[108] Boon et al.,[14] in 51 patients with lesions, found that although all patients with temporal lesions had complex partial seizures, 74% of patients with extratemporal lesions also had complex partial seizures. This study also found that although visual auras may give a clue to the presence of an occipital lesion, the nature of the aura was not otherwise useful in predicting the location of the lesion.

The clinical features, including seizure type, age of patient at onset, and duration of epilepsy, response to antiepileptic drugs, and findings of neurologic examination, are not useful in predicting the nature of the underlying lesion.[126] Patients tend to have a long history of seizures before surgery, and even patients with tumors do not commonly have an increasing frequency of seizures.[87,101,140] Careful neurologic examination in patients with low-grade tumors may occasionally detect focal signs, such as visual field loss, unilateral facial weakness, or progressive sensory loss or hemiparesis, but findings are normal in the vast majority of patients.[21,101]

Diagnostic Evaluation

The identification of a lesion in a patient with intractable epilepsy is not sufficient grounds to proceed directly to surgical excision, because the zone of seizure onset may occasionally be at a site remote from the lesion.[5,14,20,85]

Furthermore, patients with potentially epileptogenic lesions have been found after evaluation to have idiopathic generalized epilepsy or nonepileptic seizures. It is therefore important that all patients with intractable epilepsy have a comprehensive presurgical evaluation to ensure that the identified lesion is the source of the seizures. A great deal of caution, however, should be exercised before determining that the MRI lesion is *not* the source of the seizures; both extracranial and intracranial EEG can be misleading in lesional epilepsy,[5,23] and if the apparent epileptogenic zone is excised without the lesion, the results are likely to be poor in these patients.[50] Of course the reverse also holds true. The second important aspect of the presurgical evaluation is precise definition of the location and extent of the lesion, so that an operative strategy can be planned allowing maximal potential for a seizure-free outcome while minimizing the chance of a disabling postsurgical neurologic deficit.

Clinical Evaluation

As with all epilepsy patients, it is very important that a thorough history be taken. Questions should specifically be asked about factors that may suggest another source of seizures than the identified lesion—for example, a history of febrile convulsions, significant head trauma, intracranial infections, other neurologic disorders, or a family history of epilepsy. A careful neurologic examination should be performed in which focal deficits that may help to localize or lateralize the lesion are sought with particular care. It is now generally accepted practice that all patients also undergo visual perimetry, neuropsychological, and psychiatric evaluation before undergoing epilepsy surgery.

Neuroimaging

High-resolution MRI seizure protocols have virtually a 100% detection rate for tumors and vascular malformations, and improvements in technique have allowed the vast majority of focal DCDs also to be detected.[31,71] It may be difficult from the MRI appearance to predict the precise histologic tumor type, and FCD can sometimes be difficult to distinguish from low-grade cortical tumors.[71] The presence of a lesion on MRI concordant with the site of seizure onset has proved to be the best prognostic factor for a good postsurgical outcome if the lesion is included within the planned resection.[5,12,14,23,60,139]

The MRI data should be acquired using a seizure protocol that includes thin (1.5 or 1.6 mm), T_1-weighted volumetric slices of the *whole brain*.[71] This maximizes structural resolution and allows for reformatting, which is essential for the accurate detection of small cortical dysplasias, in which the only abnormality may be a subtle thickening of the cortex that is difficult to distinguish from volume averaging of normal cortical gyration.[31,71] T_2-weighted spin-echo and spin-density sequences may reveal areas of high signal in small cortical tumors, cortical dysplasias, and cortical sclerosis in some patients that are not obvious on the T_1 images.[71] Certain pulse sequences, especially fast fluid inversion recovery imaging (FLAIR), may increase the sensitivity for small cortical abnormalities.[132]

Even after the detection of one lesion, the whole-brain MRI needs to be carefully examined for the presence of coexistent hippocampal atrophy or a second neocortical lesion because a number of patients with lesional epilepsy may have dual pathology.[6,21,26,51] Cendes et al.[26] found that 15% of 167 patients with lesional epilepsy also had hippocampal atrophy. The incidence was particularly high in patients having DCDs (25%), porencephalic cysts (31%), and reactive gliosis (23.5%) compared with those having tumors (2%) or vascular malformations (9%), which suggests a common etiology during embryogenesis or early development. The identification of coexistent hippocampal atrophy in a patient with lesional epilepsy can alter the surgical strategy because these patients may have a worse outcome following lesionectomy alone.[24,51]

A carefully analyzed high-resolution MRI is essential for presurgical planning and accurate definition of the site and extent of the lesion.[31] This is especially important if a stereotactic lesionectomy is planned rather than epilepsy surgery with excision of the surrounding epileptogenic cortex.[25] Functional MRI can be used to localize eloquent cortex when the planned excision may impinge on these areas.[86]

Functional Neuroimaging

^{18}F-Fluorodeoxyglucose Positron Emission Tomography

There is evidence from studies of patients with MTS that the focal region of hypometabolism seen on ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) in many patients with focal epilepsy represents a functional rather than a structural change.[60,110] Therefore, FDG-PET may potentially have a role in defining the extent of the surrounding epileptogenic zone in lesional epilepsy. Traditionally, studies had found a poor correlation between the extent of the hypometabolic area and the extent of electrically abnormal cortex.[42] Due to major technical improvements in PET imaging, however, recent studies have demonstrated correct localization of the seizure focus, as correlated with MRI or EEG, in 62% to 100% of patients.[76,103,146,164] O'Brien et al.[107] demonstrated that FDG-PET had a significant effect on changing management in 45% of patients with intractable epilepsy, with a further 13% benefiting through increased confidence in localization and ultimately epilepsy surgery, despite the availability of other localizing information. The evidence is suggestive that localization of epileptogenic lesions by PET is greater for temporal lobe lesions than for extratemporal lobe lesions, especially when PET is assessed visually.[100,107]

Single Photon Emission Computed Tomography

Weis et al.[158] found that in temporal lobe epilepsy (TLE), the sensitivity of ictal single photon emission computed tomography (SPECT), in which the radiotracer (^{99m}Tc-D, L-hexamethylpropylene amine oxime [HMPAO]) is injected during a seizure, was lower in patients with structural lesions of the temporal lobe (56%) than in those with MTS (92%) or a normal MRI (88%). Coregistration of the ictal SPECT and MRI (SISCOM) constructs a difference image between the ictal and interictal SPECT and then coregisters it to the patient's MRI for anatomic localization. SISCOM aids in accurately identifying the regions of activation with ictal SPECT and also provides an objective way to quantitatively compare images from different patients or groups of patients.[111,112,113,114,115] SISCOM can play a role in lesional epilepsy when other data about the relationship of the structural lesion to the epileptogenic zone are conflicting and might aid in identifying the epileptogenic lesion in the case of dual pathology, but this requires further study.

Interictal Electroencephalography

Focal polymorphic delta activity, which is said to be the EEG hallmark of cerebral mass lesions, is relatively uncommon in patients with chronic lesional epilepsy.[14,67,140] Boon et al.[14] found that interictal focal sharp waves were more common than focal slow waves, but that 34% of patients had neither. O'Brien et al.,[109] comparing TLE patients having temporal neocortical lesions with those having MTS, found that the lesional patients have a higher incidence of interictal epileptiform activity (60% vs. 37%) and focal slowing (66% vs. 41%). However, no interictal EEG abnormality was found in 27% of lesional patients.

Boon et al.[14] found that unilateral temporal spikes predicted the side of the lesion correctly in 29 of 30 patients; however, the correlation of location of the spikes with site of the lesion was poor, being correct in only 30% of patients. A similar proportion of patients with temporal and extratemporal lesions had ipsilateral temporal spikes (44% vs. 39%), with bilateral independent spikes occurring in 22%. Other studies have also demonstrated that bilateral independent temporal spikes are not uncommon with unilateral lesions but that this does not correlate with a poor surgical outcome.[21,125,127]

Video-electroencephalography

Closed-circuit video-EEG is an important part of the routine presurgical evaluation of a patient with lesional epilepsy. At least one typical seizure should be recorded. In most cases, careful analysis of the seizure semiology and the ictal EEG will allow a confident determination that the site of seizure onset is concordant with the site of the lesion.[21,162] It is important to note, however, that extratemporal neocortical lesions can spread rapidly to the mesial temporal structures, producing semiology and ictal EEG findings that are indistinguishable from those of temporal seizures.[50,160,161]

The scalp ictal EEG is often poorly localizing in patients with lesional epilepsy.[21] O'Brien et al.,[109] analyzing 46 seizures in 15 patients with temporal neocortical lesions, found a clearly localized ictal EEG onset in only 14 (30.4%), with another 15 (32.6%) having an onset that began diffusely in the temporal lobes. The ictal EEG was more accurate in lateralization, with the onset being correctly lateralized in 31 (78%), nonlateralized in 8 (20%), and incorrectly lateralized in only 1 (3%). However, Boon et al.[14] found an unequivocally lateralized scalp ictal EEG in only 58% of their patients, and one of these cases was falsely lateralized. Morris and Estes[101] reported that in their series of patients with brain tumor, the combination of ictal and interictal EEG agreed with the lobe of the lesion in 72% of cases and was correctly lateralized in another 17%.

Intracranial Electroencephalography

Intracranial EEG monitoring is not routinely required for all patients with lesional epilepsy.[21] If the results of the noninvasive evaluation are concordant with the site of the lesion, then surgery can be recommended without invasive studies being required. Intracranial studies are principally reserved for two situations: (a) Results of the noninvasive evaluation give conflicting information or suggest that the lesion is remote from the source of the seizures, and (b) preoperative mapping of the eloquent cortex using subdural strips is required when the planned resection may involve these areas.

Unfortunately, even intracranial EEG is often nonlocalizing or misleading in patients with lesional epilepsy.[41] Williamson et al.[160] studied 9 patients having parietal mass lesions with depth electrodes, parietal grids, or both, and consistently found a localized seizure onset in the parietal lobe in only 3. In 4 patients, the onset was diffuse and poorly localized, and in 2 the seizures were apparently of mesial temporal onset (1 bilateral independent).

Intraoperative Neurophysiologic Techniques

Intraoperative electrical cortical stimulation can accurately define the speech area and the motor strip and allows the cortical resection to be performed to within 1 cm of these areas.[101] Intraoperative mapping requires a very cooperative patient, however, because it is performed under local anesthetic, and the complexity of the language tasks that can be tested is limited. Intraoperative somatosensory-evoked potentials can also be helpful in defining the motor strip.[102] Functional mapping can also be performed using an implanted subdural electrode array.[14,94] This technique has the dual advantage of enabling the recording of interictal and ictal intracranial EEG and allowing the patient to be evaluated in a more comfortable setting with more complex and extensive tests.[21]

Differential Diagnosis

Tumors

Epilepsy caused by brain tumors represents 3.5% to 5% of all cases of epilepsy and 16% of cases seen in adults, and tumors are the most common cause for new-onset epilepsy in persons between the ages of 35 and 55 years.[46] Low-grade or slow-growing or indolent tumors are the most highly epileptogenic.[157] In their review of the MNI series, Le Blanc and Rasmussen[87] determined that the incidence of epilepsy in patients with supratentorial tumors was approximately 50%. The site of tumors in the hemispheres is related to their epileptogenicity; individuals with tumors of the centrotemporoparietal region have the highest incidence of epilepsy (approximately 75%). Lund[95] found in 615 cases that the depth of the tumor also was related to the incidence of epilepsy, with epilepsy occurring in association with 63% of “superficial and cortical” tumors and only 29% of “deep and noncortical” tumors.

Gliomas

Gliomas account for 72% to 88% of tumors in patients with chronic epilepsy, of which 50% to 70% are low-grade astrocytomas; oligodendrogliomas, gangliomas, and mixed gliomas account for the remainder.[80,127] Le Blanc and Rasmussen[87] found that oligodendrogliomas had the highest epileptogenic potential (92%), followed by astrocytomas (70%) and glioblastomas (35%). High-grade glial neoplasms and metastatic tumors are rare in series of patients with chronic epilepsy.

Astrocytomas most often appear in the third and fourth decades, and seizures are the most common clinical manifestation.[101] Oligodendrogliomas tend to appear in the fourth to fifth decades, although they can occur in children.[28,93] Some calcification is present in up to 90% of patients, and therefore many are seen on CT. Gangliomas represent only 0.7% to 6% of brain tumors overall, but they are overrepresented in series of patients with chronic focal epilepsy, with estimates of their incidence ranging from 10% to 50%.[4,81,101,163] These tumors seem to occur preferentially in the temporal and frontal lobes.[70]

Meningiomas

Meningiomas are the most common benign intracranial tumor, especially in middle age, representing about 15% of all primary

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brain tumors.[46] Seizures are estimated to occur in 60% to 75% of all patients with these tumors.[79,87]

Dysembryoplastic Neuroepithelial Tumors

Dysembryoplastic neuroepithelial tumors are an important cause of focal epilepsy that has only relatively recently been recognized.[35] A number of the patients that were classified as having low-grade gliomas or hamartomas in older series probably had DNETs. A recent series of 216 temporal lobectomies found that DNETs comprised 8% of lesional cases.[163] They have a predilection for the temporal lobes, but they also often occur extratemporally, especially in the frontal lobes.[35] These lesions usually develop within dysplastic cortex, and it is thought by some authors that they would be better classified as a neuronal migration disorder rather than as a tumor.[71]

Disorders of Cortical Development

Taylor et al.[147] first recognized cortical dysplasia in their pathologic study of postsurgical specimens of patients with intractable epilepsy. The importance of DCDs as a cause of focal epilepsy, however, has been widely appreciated only since the development of high-resolution MRI. The derangement of cortical structure associated with these lesions can be relatively subtle and is not well detected by CT or earlier MRI methods.[31,71,85,119] Even with high-resolution MRI, these lesions are easily overlooked because they are often difficult to detect on standard planar images acquired with thick slices (see Chapter 79 for further discussion).

The DCDs have been classified according to MRI findings as generalized, unilateral hemispheric, and focal.[20] In this chapter, the focal DCDs are emphasized; these include FCDs, focal subependymal heterotopias, polymicrogyria, and schizencephaly (see Chapter 259 for a more complete discussion).[20,85,119] In a series of 49 patients with DCD and chronic focal epilepsy reported by Andermann and Palmini,[3] 30 had unilateral localized areas of abnormalities (either FCD or tuberous sclerosis in forme fruste), 10 had bilateral abnormalities, and 9 had a generalized DCD.

Focal cortical dysplasias, schizencephaly, and microdysgenesis usually have no apparent inheritance pattern and are likely caused by cerebral insults occurring during perinatal development.[71] The initial seizures in patients with focal DCD usually occur in the first decade of life.[119,147]

Focal cortical dysplasia is the most common type of focal DCD. Definitions of the term *cortical dysplasia* have varied from a subtle degree of disorganized cortical architecture with or without neuronal cytomegaly to profound abnormalities, such as lissencephaly and polymicrogyria.[154] Tuberous sclerosis in forme fruste is usually classified as a DCD because clinical and imaging studies cannot reliably differentiate it from FCD, and pathologically it is also often very difficult to make the distinction.[80]

Neuronal heterotopias may include several patterns, but nodular and laminar heterotopias are most frequently associated with epilepsy.[80] Nodular heterotopias consist of discrete, isolated regions of gray matter that occur in the periventricular region. They may also be associated with other abnormalities, such as polymicrogyria or pachygyria. Laminar heterotopias are elongated islands of neurons that occur as bands in the white matter separated from the cortex or ventricular wall. Heterotopias are believed to result form an arrest during neuronal migration.

Focal schizencephaly is characterized by a communication between the ventricle and the surface of the brain, which is often lined by polymicrogyrous cortex.[3] Focal unilateral schizencephaly is commonly associated with epilepsy, and surgical excision of the most epileptogenic areas can lead to a reduction in seizure frequency.[89]

Cerebral Vascular Malformations

The estimated seizure risk in patients with vascular malformations is 1.5%/person-yr.[34] The types of vascular malformations are, in decreasing order of frequency, arteriovenous malformations (AVMs), cavernous hemangiomas, venous angiomas, and capillary telangiectasias.[142] Venous angiomas and capillary telangiectasias are only rarely associated with seizures.[6]

Arteriovenous Malformations

Arteriovenous malformations are congenital vascular abnormalities consisting of communicating arteries and veins without intervening capillary beds. Seizures represent the second-most-common presenting feature of AVMs after cerebral hemorrhage (17%–40% of cases).[63,88,168] In an international multicenter trial, Hofmeister et al.[63] demonstrated that 30% of all patients with AVMs experienced generalized seizures, with 10% experiencing focal seizures. Hoh et al.[64] reported that male gender, age <65 years, AVM size <3 cm, and temporal lobe AVM location were significantly associated with an increased incidence of seizures. Posterior fossa and deep locations were not statistically associated with seizures.

Others have also confirmed that patients with larger AVMs (>3 cm) are more likely to have seizures.[88,123] Seizures are more frequent with AVMs situated in the posterofrontal and temporal lobes.[123]

Cavernous Angiomas

This benign vascular anomaly consists of a tangled mass of tightly arranged abnormal vessels made of common hypocellular walls,[80] and it represents about 5% to 20% of all vascular malformations of the central nervous system.[49] Seizures, estimated to occur in 40% to 70% of patients, are often the most common and only clinical manifestation of cavernous angiomas,[29,151] typically commencing in the 30- to 40-year age group.[49] On MRI, these lesions have a characteristically high T_2 signal core surrounded by a low signal halo (caused by hemosiderin deposition in macrophages), which results in a "targetlike" appearance.[141] It is theorized that the excess iron deposition may act as an electron donor providing free radicals and lipid peroxides, which can lead to neuronal excitability and hence seizures.[82,155] In some patients the coexistence of hippocampal sclerosis may be present (dual pathology), complicating potential surgical management.[24]

Cysts

Several studies have found a higher-than-expected frequency of seizures in patients with porencephalic cysts.[1,149] Porencephalic cysts have also been found in surgical specimens from patients undergoing resective surgery for intractable partial seizures.[1] One study of 10 patients with arachnoid cysts and intractable seizures found no other explanation for the seizures in 8.[129] Accurate localization of the epileptogenic foci has been difficult traditionally, and hence either surgical resection has been discouraged or functional hemispherectomy has been performed, especially on patients with significant deficits.[62,68]

Infectious Lesions

Neurocysticercosis

In countries where it is endemic, neurocysticercosis may affect from 2% to 4% of the population.[36] It is estimated that 50% to 70% of patients with neurocysticercosis have epilepsy, and it is the most common cause of adult-onset epilepsy in developing countries.[37,99] It is now being increasingly recognized as a cause of epilepsy in Western countries as a result of increased migration from endemic areas and of improved neuroimaging, which can detect the typical multiple cystic lesions.[126] In most patients with neurocysticercosis, epilepsy is the only clinical manifestation, with only a minority of patients having focal neurologic symptoms or signs.[37]

Cerebral Tuberculoma

Cerebral tuberculomas are now very rare in Western countries, but they still represent up to 20% to 40% of intracranial tumors in developing countries.[126] They can appear even after the apparently successful treatment of systemic or central nervous system tuberculosis, and seizures are not uncommonly the first manifestation.[56]

Treatment and Outcome

Antiepileptic Drugs

The medical treatment of lesional epilepsy does not essentially differ from that of other localization-related epilepsies. Monotherapy with carbamazepine or phenytoin is generally accepted as the first line of treatment in many countries, and the drugs are probably of equal efficacy.[96] Valproic acid, alone or in combination with one of the aforementioned drugs, is also effective in some patients. Phenobarbital and primidone may control seizures, but they frequently result in unacceptable behavior and cognitive disturbances and therefore are no longer recommended as first-line therapy. Many patients with lesional epilepsy continue to have poorly controlled seizures despite treatment with antiepileptic drugs (AEDs),[43] and these patients need not be subjected to prolonged, unsuccessful trials of multiple different drugs, or polypharmacy, before surgical therapy is considered.

Surgical Treatment

It is well documented that surgery is a successful treatment for medically intractable localization-related seizures associated with structural lesions.[21,39,55,159] As mentioned previously, in a randomized, controlled trial comparing surgical resection with medical treatment for intractable temporal lobe epilepsy, 58% of those undergoing surgery in addition to continued AED treatment were seizure free compared with 8% in the purely medical group at 12 months.[159] The greatest controversy in the surgical treatment of lesional epilepsy is the relative importance of excision of the structural lesion as opposed to the epileptogenic zone. The nature of the relationship between the two is relatively poorly understood, and hence the surgical strategy lacks an irrefutable physiologic basis.[51]

Resection of the Epileptogenic Region

A number of series have found that up to 90% of patients with intractable seizures secondary to tumors become seizure free when both the structural lesion and the epileptogenic cortex are resected ("seizure surgery").[10,13,14,15,18,165] There is some evidence that epileptogenic cortex may develop independently secondary to a noncontiguous structural lesion and that the epileptogenic zone may not be restricted to the lesion site.[5,39,54] Some authors have also found that complete excision of both structural lesion and epileptogenic cortex is necessary for worthwhile seizure reduction.[11,135,167]

However, resection of the epileptogenic zone in addition to the structural lesion involves a larger area of brain excision. The rate of operative morbidity increases dramatically when eloquent cortex is removed in an attempt to resect the epileptogenic zone,[117] and this approach does not necessarily improve postoperative seizure control.[128,138] Resection of the epileptogenic cortex alone, without the structural lesion, is likely to result in an unfavorable outcome. Siegel et al.[135] found that seizure freedom occurred in their patients only when a second operation was performed to resect an epileptogenic zone surrounding a previously resected cavernous angioma. Fish et al.[50] found that of 19 patients with small posterior structural lesions who had had resections limited to the epileptogenic zone in the anterior temporal lobe, only 2 became seizure free. The epileptogenic zone is likely to be a direct consequence of the structural lesion,[157] and therefore epilepsy surgery should include excision of the structural lesion whenever possible.

Lesionectomy

Patients often become seizure free, or have a decrease in seizure frequency, after simple lesionectomy.[22,61] Furthermore, the structural impact of the lesion appears to be reversible in some patients following lesionectomy, so that the previously epileptogenic cortex is free of electrical activity.[157] In addition, Falconer et al.[47] showed that even when the EEG abnormalities remain after the structural lesion is removed, clinical seizures often do not persist.

The studies of both Casazza et al.[17] and Zevgaridis et al.[171] did not find that the additional excision of hemosiderin-stained tissue around a cavernous angioma improved seizure freedom compared with resection of the lesion alone. Goldring et al.,[55] in a study evaluating the surgical outcome of 20 patients undergoing temporal lobe lesionectomy mainly for low-grade tumors, found that only one patient continued to have long-term postoperative seizures. Awad et al.[5] found that 79% of patients became seizure free when the epileptogenic cortex was completely resected without regard to the structural lesion, compared with 90% following lesionectomy alone regardless of complete excision of epileptogenic brain tissue. An alternative to standard neurosurgical lesionectomy is stereotactic lesionectomy. This is particularly useful in reducing morbidity in patients with deep-seated intra-axial lesions and lesions encroaching on functional cortex.[2,25,78] Cascino et al.[25] found that 74% of 23 patients who underwent stereotactic lesionectomy had a marked reduction in seizure activity, with 5 patients able to discontinue antiepileptic drugs.

Table 3 Results of surgical series of patients undergoing lesionectomy only

Study (ref.)	Structural lesion	Number of cases	Follow-up	Seizure free (%)
al-Rodhan et al. 1992[2]	Mixed lesions	30	24–66 mo	50
Awad et al. 1991[5]	Mixed lesions	18	20–114 mo	94
Baumann et al. 2006[9]	Cavernous angiomas	14	12–36 mo	77

Cascino 1990[8]	Mixed lesions	30	3–46 mo	53
Fried et al. 1994[52,a]	Glial tumors	54[a]	>12 mo (median, 46 mo)	85
Giulioni et al. 2006[53]	Gangliogliomas	21	1.25–10 yr	67
Goldring et al. 1986[55]	Mixed lesions	35	12–120 mo	82
Kalyan-Raman and Olivero 1987[77]	Ganglioglioma	8	30–84 mo	50
Murphy 1985[104]	AVM	20	2–36 yr	55
Silver et al. 1991[136]	Ganglioglioma	14	1–19 yr	50

AVM, arteriovenous malformation.

[a] Only patients with complete lesion excision were included.

Table 4 Results of surgical series involving patients undergoing resection of the epileptogenic cortex

Study (ref.)	Structural lesion	Number of cases	Follow-up (mo)	Seizure free (%)
Awad et al. 1991[5]	Mixed lesions	6	20–114	83
Baumann et al. 2006[9]	Cavernous angiomas	17	12–36	65
Daumas-Duport et al. 1988[35]	DNET	37	12–216	81
Estes et al. 1988[45]	Mixed lesions	11	6–72	82
Jooma et al. 1995[75]	Mixed lesions	14	12–84	93
Nakasato et al. 1992[105]	Glioma	11	12–348	64

Rasmussen 1975[128]	Mixed lesions	261	NS	47
Wyllie et al. 1987[165]	Mixed lesions	6	12–42	83
Yeh et al. 1990[167]	AVM	27	24–72	78

AVM, arterivenous malfromation; DNET; dysembryoplastic neuropeithelial tumors.

Unfortunately, few studies have directly compared lesionectomy with more extensive epilepsy surgery. Awad et al.[5] found no significant difference in seizure-free outcome between patients who underwent simple lesion removal and those who underwent surgery directed at removal of the epileptogenic zone (Tables 3 and 4). Weber et al.[157] used meta-analysis to compare studies reporting outcomes of simple lesionectomy with those reporting more extensive epilepsy surgery, and found that more patients were seizure free 2 years after "seizure surgery" than after lesionectomy. Tables 3 and 4 compare selected studies reporting postsurgical outcome in patients undergoing lesionectomy alone and those undergoing surgery involving resection of the epileptogenic cortex.

Treatment and Outcome for Different Lesions

Tumors

Older AEDs, including phenytoin, carbamazepine, and phenobarbital, have been reported to produce more idiosyncratic effects in patients with brain tumors than in the general epilepsy population.[130] These anticonvulsants induce cytochrome P450 enzymes, and it has therefore been proposed that they interfere with other commonly used drugs and increase chemotherapeutic agent clearance.[152] Most cerebral tumors are considered for surgical resection. In 51 patients who were operated on at the Mayo Clinic for intractable epilepsy caused by low-grade neoplasms, 66% were rendered seizure free and 88% experienced a significant reduction in seizure frequency.[15] Le Blanc and Rasmussen[87] reported that of 171 patients with astrocytomas and other low-grade cerebral neoplasms treated with tumor resection and excision of the epileptogenic cortex, 41% were rendered seizure free and 70% had at least a marked reduction in seizure frequency. Most patients in this study also had postoperative radiotherapy; this is of unproven benefit, however, in patients with low-grade gliomas in whom a complete tumor resection has been achieved and is generally reserved for cases of tumor recurrence.[101] In patients with unresectable gliomas, radiotherapy alone, after biopsy conformation of the pathologic diagnosis, may result in a significant reduction in seizure frequency, with some patients being rendered seizure free.[55,131]

Complete resection of meningiomas is usually curative.[46] Surgical excision of meningiomas can achieve seizure freedom in up to 63% of patients.[92] Patients with gangliomas generally have a good postsurgical prognosis with regard to seizures, and Otsubo et al.[118] found that 22 of 25 surgically treated children were either seizure free or had >50% reduction in seizures. In a series of 29 adult and pediatric patients experiencing intractable seizures associated with gangliogliomas, Im et al.[69] reported that 76% were rendered seizure free and 59% had completely ceased anticonvulsant medications after surgical resection.

Radiotherapy is usually reserved for patients with postsurgical tumor recurrence, or the rare patient with an anaplastic ganglioma.[74] Complete surgical excision is usually curative for DNETs, and an excellent outcome with respect to seizures can be expected in about 90% of patients.[35] Chan et al.[27] demonstrated that temporal lobectomy for DNETs was significantly better associated with seizure freedom than was lesionectomy (83% Engel class 1). In contrast, however, only 10% of patients with glioblastomas and other aggressive malignant lesions become seizure free postoperatively.[128]

Disorders of Cortical Development

There is some evidence that focal DCD have a worse outcome following epilepsy surgery than other lesional types, with only 2 of 26 patients reported by Andermann and Palmini[3,119] becoming seizure free and 9 having >90% reduction in seizure frequency. They found a good correlation between outcome and amount of the lesion removed. Sisodiya et al.[137] demonstrated that in 15 of 18 patients with FCD, the abnormalities in distribution of gray and subcortical white matter volumes extended beyond the margins of the lesions as visualized on MRI. Therefore, the apparently worse outcome in patients with focal DCD may be a result of the lesion often being more extensive than the region of surgical excision. More recently, other authors report better postsurgical results, with Kral et al.[83] finding that 38 of 53 patients with focal cortical dysplasia who had cortical resections became seizure free postoperatively; a similarly good outcome was found by Hong et al.[65]

Vascular Malformations

Arteriovenous malformations are associated with a significant lifelong risk of hemorrhage and a significant risk of morbidity and mortality; prevention of this complication is the most common indication for surgical excision in these patients.[16] The efficacy of surgery in treating seizures associated with AVMs is more controversial. A number of earlier authors report disappointing results, with some even finding an increase in seizure frequency postoperatively.[33,104,120] Most recent surgical series, however, have found that many patients with AVMs have a good postoperative outcome with respect to seizures.[38,64,123,150,167,169] Dodick et al.[38] found that three fourths of patients with epilepsy secondary to a vascular malformation were seizure free after lesion resection, and most of the remaining patients had a significant reduction in seizure frequency. Yeh et al.[169] found that several factors correlated with outcome, including age at seizure onset, duration of seizures, location of lesions, and cortical excision of the epileptogenic zone. Radiosurgery is an accepted treatment measure for AVMs not suitable for surgical resection and is largely reserved for lesions <3 cm in size.

In cases of intractable seizures caused by cavernous hemangiomas, Cohen et al.[29] advocated lesionectomy alone for patients having fewer preoperative seizures and shorter seizure histories (<1 year) but an increased margin of resection for patients with longer seizure histories or more frequent seizures. In cases of dual pathology, however, lesionectomy has not resulted in seizure control, and subsequent resection of the mesial temporal structures is necessary to achieve a satisfactory outcome.[17,24,90]

Neurocysticercosis

Patients with inactive calcified neurocysticercosis can usually be adequately controlled on standard monotherapy for most localization-related epilepsy, for example, with carbamazepine or phenytoin. However, Del Brutto et al.[37] found that seizure control was significantly improved in patients with active neurocysticercosis by simultaneous treatment with anticysticercal drugs (praziquantel or albendazole), with 83% of such treated patients remaining seizure free compared with only 26% of those treated with antiepileptic drugs alone. In patients with multiple cysts, increased seizures and neurologic signs may develop soon after commencement of anticysticercal drugs as a result of an intense inflammatory reaction to the dying cysticerci in the surrounding brain. Coadministration of cortico-steroids may minimize this complication.[36] Occasionally, large cysts causing significant mass effect may require surgical removal (see also Chapter 265).

Long-Term Prognosis

When seizures are adequately controlled with antiepileptic drugs, patients must usually continue to take them indefinitely. Recurrence of seizures will occur in most patients on withdrawal of antiepileptic drugs because they merely suppress seizures, whereas the underlying epileptogenic lesion remains unchanged.

Following epilepsy surgery, patients who have discrete structural lesions (including mesial temporal sclerosis) have a better long-term outcome with respect to seizures than those who do not.[44] An earlier study by Berkovic et al.[12] using actuarial analysis to assess the outcome at 60 months in 135 surgically treated patients with TLE found that 69% of patients with a foreign tissue lesion on the preoperative MRI had no postoperative seizures, compared with 50% of those with hippocampal sclerosis and 21% of those with normal findings on MRI. In a more recent publication by the same group assessing long-term outcome, 328 patients underwent anterior temporal lobectomy over a 20-year period.[98] This study reported that 59.6% of lesional patients achieved seizure freedom at 10 years, with 47% of patients with hippocampal sclerosis achieving the same in this time period. The group with no discernible lesions on preoperative studies did most poorly, with 18.2% achieving seizure freedom at 10-year follow-up. These results are confirmed by other studies.[40,170]

Tumors

As previously discussed, tumors resulting in chronic epilepsy are usually of low grade and slowly growing. In patients with gliomas in whom seizures are the sole clinical manifestation, the clinical course tends to be more protracted and indolent than in other patients with gliomas, and survival for 10 to 20 years is not uncommon.[124,134] Depending on the grade, patients with oligodendrogliomas have been reported as demonstrating 5-year survival of 73% and 10-year survival of 49%,[59] with median survival time of 11.6 years.[116] Overall, patients with gangliogliomas have a better prognosis for long-term survival than those with histologically similar astrocytomas or mixed glial tumors, but gangliogliomas arising in the midline may be more aggressive and are associated with a poorer prognosis.[74]

Serial MRI is mandatory to follow patients with low-grade tumors in whom surgery has not been performed, and the appearance of such lesions can remain remarkably constant on repeated examinations over time.[55,140] An increase in size, mass effect, or degree of contrast enhancement of the lesion or the development of surrounding cerebral edema, however, suggests transformation to a higher-grade tumor. Serial MRI is also mandatory in following patients who have had surgery because recurrence of the tumor may be an indication for further treatment such as radiotherapy. Tumor recurrence may also be suggested by return of seizures in a patient who was initially rendered seizure free following surgery.[101]

Disorders of Cortical Development

Most patients with DCD reported in the literature have had medically intractable seizures, but this is likely to reflect at least in part a selection bias because almost all these series are from large epilepsy referral centers.[3] More recent studies report that among patients with focal cortical dysplasia, up to 72% may be rendered seizure free with epilepsy surgery.[84] Routinely, studies examining outcome from medical treatment alone report lower rates of seizure freedom, ranging from 24% to 54%.[7,133,143]

Vascular Malformations

Crawford et al.,[32] in a long-term follow-up study of 217 patients with unoperated AVMs, found that those without a history of hemorrhage in whom epilepsy was the primary clinical manifestation have a somewhat lower long-term risk for hemorrhage than other patients with AVMs (30% vs. 42% at 20 years). If there was a history of hemorrhage, however, the risk for a further hemorrhage increased to 51% at 20 years. Of the patients in this study who had a hemorrhage during the follow-up period, 25% died as result of that hemorrhage. The risk for cerebral hemorrhage with cavernous hemangiomas is lower than that for AVMs but is reported to occur in 10% to 30% of patients.[49]

Hoh et al.[64] demonstrated that in AVMs treated via a multidisciplinary approach, short seizure history, seizures linked to intracranial hemorrhage, generalized tonic–clonic seizures, deep and posterior fossa AVMs, and surgical resection and complete AVM obliteration were associated with Engel class 1 seizure frequency outcome. Thorpe et al.[150] found that multiple seizures and poor neurologic outcome postoperatively were independent factors predictive of the incidence of postoperative seizures.

Neurocysticercosis

Despite the fact that excellent control of seizures is usually obtained with antiepileptic and anticysticercal drugs, achievement of a long-term seizure-free state without drug therapy is difficult. Del Brutto et al.[37] found that 16 of 21 patients with epilepsy and neurocysticercosis who had been seizure free for 2 years while taking antiepileptic drugs relapsed when the drugs were withdrawn.

Summary and Conclusions

Of all patients who undergo surgery for chronic intractable epilepsy, 30% have a discrete structural lesion. There is a strong correlation between the site of epileptogenesis and the epileptogenic zone. Common structural lesions include low-grade neoplasms, vascular malformations, and disorders of cortical development. Cysticercosis and tuberculomas are increasingly being seen in developed countries and they are still a prevalent cause of epilepsy in endemic regions.

The pathophysiology of lesional epilepsy is uncertain, but a number of explanations have been proposed, and the mechanisms may vary for different lesional types.

Magnetic resonance imaging is the most sensitive and specific investigation in the detection of structural lesions. Evaluation for surgery involves careful clinical assessment, structural neuroimaging, and video-EEG in all patients. Intracranial monitoring, functional neuroimaging, and intraoperative neurophysiologic techniques may be useful in some cases.

Epilepsy surgery is the treatment of choice for intractable partial seizures caused by focal structural lesions. In most reported series, more than 50% of patients are rendered seizure free. It is controversial whether resection of the epileptogenic cortex in addition to the structural lesion is required for optimal seizure control. Stereotactic lesionectomy is a useful technique for minimizing morbidity with deep-seated lesions and those involving eloquent cortex.

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Chapter 252

Progressive Myoclonus Epilepsies

Samuel F. Berkovic

Introduction

Progressive myoclonus epilepsy (PME) is an uncommon epilepsy syndrome caused by a large number of rare specific disorders. In its fully developed form with florid, unremitting myoclonic seizures and progressive neurologic deterioration, the syndrome can hardly be missed. Diagnosis of the PME syndrome can be more difficult in the early stages, and confusion with more benign epilepsies is common. Diagnosis of the specific type of PME is challenging, as most individual clinicians' experience with these rare disorders is limited. Molecular genetics has had an enormous impact on the clinical approach to these disorders, and PME is the clinical syndrome par excellence showing the value of careful clinicomolecular correlations leading to advances in practical clinical diagnosis and fundamental biologic understanding. This chapter will focus on diagnosis of the PME syndrome and of the more common specific causes.

Historical Perspectives

The rarity and complexity of the disorders causing PME have resulted in a confusing literature since the first description by Unverricht in 1891 (Fig. 1).[130] Eponymous names were used in conflicting ways, and there were often erroneous putative clinicopathologic correlations. In particular, the term *Ramsay Hunt syndrome* generated enormous confusion (for review see references 11, 18, 84, and 95).

Pathologic studies since the 1930s established that there were at least three separate pathologic substrates of the PME syndrome: Lafora bodies, lipid storage, and “degenerative” changes.[36,54,56] However, in clinical practice, PME was often the final clinical diagnosis, as there was no way to diagnose specific forms during life.

Over the last three decades a number of clinical, pathologic, genetic, biochemical, and molecular advances have led to considerable clarification of this subject, allowing a sophisticated and rational approach to diagnosis in life of the patient with PME.[7,14,46,84,116] First, in many of the specific causes of PME, characteristic clinical patterns have been recognized. Second, ethnic and geographic clusters of certain disorders have been identified, accounting for the different perspective of PME by authors in various countries. Third, the broad pathologic group of “lipidoses” causing PME has been classified by clinical, biochemical, and pathologic studies into neuronal ceroid lipofuscinoses, sialidoses, and Gaucher disease. Fourth, the mitochondrial disorder MERRF (myoclonus epilepsy and ragged red fiber syndrome) was discovered and found to be a major cause of PME. Fifth, the “degenerative” type of PME was found to be heterogeneous, comprising at least three distinct conditions: Unverricht-Lundborg disease, MERRF, and dentatorubral-pallidoluysian atrophy. Sixth, minimally invasive methods for diagnosis during life were developed. Finally, important molecular genetic findings have further refined understanding of these disorders and are playing an increasing role in routine diagnosis.

Definitions

The syndrome of PME consists of myoclonic seizures, tonic-clonic seizures, and progressive neurologic dysfunction, particularly ataxia and dementia. Onset can be at any age, but is usually in late childhood or adolescence. There are a large number of causes of the PME syndrome; most are due to specific genetic disorders, which can now be accurately diagnosed in life.[7,46]

Myoclonus in PME is typically fragmentary and multifocal, and often precipitated by posture, action, or external stimuli such as light, sound, or touch. It is particularly apparent in facial and distal limb musculature. Bilateral massive myoclonic jerks, which tend to involve proximal limb muscles, may also occur.

The origin of and generators for myoclonus in PME is a confusing and controversial area. Neurophysiologic studies show that some but not all myoclonic jerks are accompanied by obvious electroencephalographic (EEG) spikes, polyspikes, or spike-and-wave complexes. Where EEG accompaniments of jerks are not obvious, back-averaging techniques may reveal preceding EEG changes. These data, coupled with the frequent finding of giant somatosensory-evoked potentials (SSEPs) and of evidence suggesting abnormal cortical hyperexcitability using transcranial magnetic stimulation, suggest that the myoclonic jerks are often of cortical origin—*cortical reflex myoclonus*. Electrophysiologic studies of bilateral jerks suggest that some are generated in the cortex unilaterally and spread rapidly contralaterally via the corpus callosum, whereas others may be generated in the brainstem—*reticular reflex myoclonus*.[50,109,118,119] The lack of demonstrable EEG change with some jerks might lead to the conclusion that these are examples of “nonepileptic” myoclonus, akin to that seen in certain movement disorders. Unfortunately, no absolute clinical or indeed experimental technique exists to determine the epileptic nature or otherwise of particular jerks. Moreover, the coexistence of “epileptic” and “nonepileptic” myoclonus in one patient is counterintuitive. From a pragmatic clinical viewpoint, therefore, “epileptic” myoclonus can be diagnosed in cases where tonic–clonic or other seizures coexist or where obvious epileptiform discharges accompany some, but not necessarily all, myoclonic jerks.

FIGURE 1. Heinrich Unverricht of Magdeberg (1853–1912). First clinical description of progressive myoclonus epilepsy in 1891. (Reproduced from Berkovic SF, Andermann F. The progressive myoclonus epilepsies. In: Pedley TA, Meldrum BS, eds. Recent advances in Epilepsy. Edinburgh: Churchill Livingstone; 1986:157–187.)

Epidemiology

PMEs account for <1% of people with epilepsy seen at specialist centers.[46] Series from different countries reveal considerable

geographic and ethnic variability in the occurrence of specific types of PMEs.[1,36,40,46] Details of known geographic clusters of specific PMEs are given below. Knowledge of the patient's ethnic background can provide an essential clue to the likely differential diagnosis of the type of PME.

The incidence and prevalence of specific PMEs are largely unknown. In Finland, Unverricht-Lundborg disease has an incidence of at least 1 per 20,000,[95] but outside the Baltic region the incidence is probably at least an order of magnitude less, although a recent study in The Netherlands using molecular methods suggested that Unverricht-Lundborg disease is underdiagnosed.[35]

Specific Disorders

Unverricht-Lundborg Disease

Etiology and Basic Mechanisms

Unverricht-Lundborg disease is the prototypic cause of PME.[65,77,130] No storage material is present but there is neuronal loss and gliosis particularly affecting the cerebellum, medial thalamus, and spinal cord.[51]

It is an autosomal recessive condition[95] initially recognized as a geographic cluster in Finland and eastern Sweden (*Baltic myoclonus*). An erroneous, but frequently held, view is that this disorder is confined to the Baltic region. Clusters of a phenotypically identical disorder occur in Southern Europe and North Africa, so-called “Mediterranean myoclonus.”[47] It is also found sporadically worldwide in Caucasians, Blacks, and Japanese.[40,84] Indeed, it appears that Unverricht's original family was of Baltic German extraction, and not Estonian as widely believed.

The disorder was linked to the long arm of chromosome 21 in Finnish cases in 1991[71] and cystatin B was identified as the responsible gene in 1996.[104] The clinical prediction that similar cases seen outside the Baltic region have the same condition was confirmed by showing the identification of mutations in cystatin B (*CSTB*) in families from around the world. The most common mutation, responsible for about 90% of abnormal alleles, is an unstable expansion of a dodecamer repeat in the 5′ untranslated promoter region. The remaining mutations are missense mutations.[69,70,72] CSTB is a cysteine protease inhibitor. The *CSTB* mutations lead to marked reduced expression of *CSTB* mRNA. Development of a mouse model with targeted disruption of the mouse *Cstb* gene has shown increased apoptosis affecting particularly cerebellar granule cells. It has been suggested that deficiency of CSTB protein results in increased activity of cathepsins with increased apoptosis in specific neuronal cell types.[72,103,117]

A variant has been described where *CTSB* has been excluded as the causative gene. This form maps to chromosome 12 but the gene is presently unknown.[15]

Clinical Presentation

Clinical onset is with myoclonus or tonic–clonic seizures between the ages of 8 and 13 (mean 10, range 6 to 16 years). The myoclonus is usually quite severe and may be precipitated by movement, stress, and sensory stimuli. Repetitive morning myoclonus is also typical, frequently building up and culminating in a major tonic–clonic seizure.[63,64] Seizures may be difficult to control, but progression in terms of ataxia and dementia is mild and late. The clinical course is variable and there may be considerable intrafamily variation in the

severity of the seizures. Some patients are relatively mildly affected and survive to old age.[78] A more fulminant course with death within a few years of onset has been observed; this outcome is rarely if ever seen now and may have been due to unrecognized deleterious effects of phenytoin.[40,58]

The EEG background may show some diffuse theta that increases over years, as well as some frontal beta activity. Epileptic activity comprises 3- to 5-Hz spike-wave or multiple spike-wave activity with the maximum field being anterior. Sporadic focal spikes, particularly in the occipital region, may be seen but are usually not prominent (Fig. 2). Photosensitivity is typically marked. During non–rapid eye movement (REM) sleep the spike-wave activity is diminished.[18,64]

Diagnostic Evaluation

Unverricht-Lundborg disease is recognized clinically by its characteristic age of onset and clinical pattern, with an absence of other clinical or pathologic features. Diagnosis is confirmed by molecular analysis of the cystatin B gene.

Myoclonus Epilepsy and Ragged Red Fibers

Etiology and Basic Mechanisms

The MERRF syndrome has emerged as one of the most common causes of PME. It may be familial or sporadic. Most familial cases of MERRF are transmitted through the maternal line and are examples of mitochondrial inheritance.[111] The peculiarities of mitochondrial inheritance provide an explanation for the wide phenotypic variability in patients with MERRF and for the extraordinary intrafamily variation.

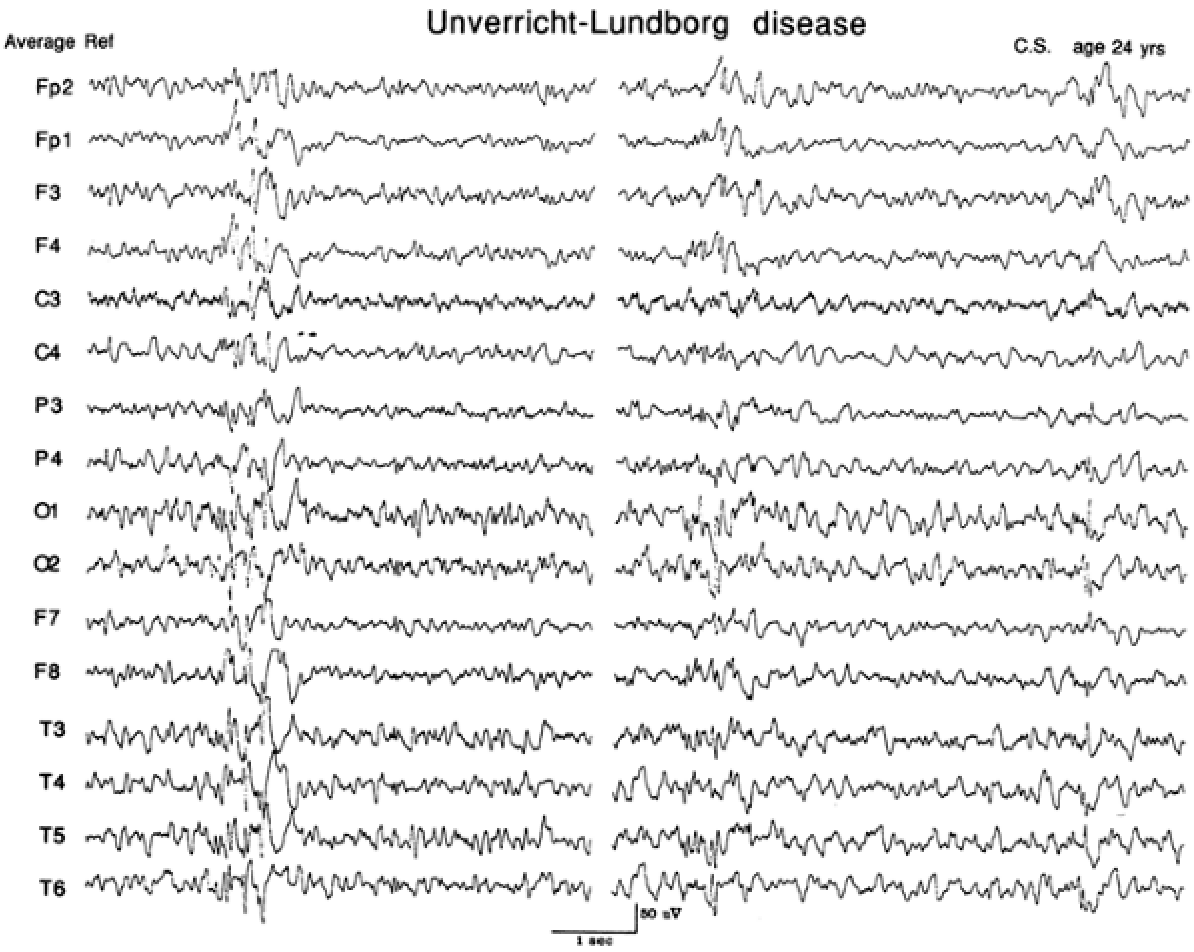

FIGURE 2. Unverricht-Lundborg disease. Waking electroencephalogram in a 24-year-old woman showing generalized polyspike-and-wave discharges on a slow background (**left panel**) with occasional focal occipital discharges (**right panel**).

A single base substitution at nucleotide pair 8344 of mitochondrial DNA, causing an A-to-G substitution in the tRNA^{Lys} gene, occurs in many familial cases of MERRF.[120] The fact that this mutation affects tRNA, rather than a gene for a respiratory enzyme, probably explains the heterogeneous results for respiratory enzyme assays reported in MERRF. This tRNA^{Lys} mutation appears to underlie most, but not all, familial cases and some sporadic examples of MERRF.[17,52,53,138] Other rare identified molecular causes of MERRF also affect the tRNA^{Lys} gene.[121] Recently, autosomal recessive mutations in the nuclear encoded mitochondrial gene polymerase-*γ* (POLG) have been identified in some MERRF cases.[129]

Pathologically the brain shows “degenerative” changes, particularly affecting the dentate nucleus and inferior olive. In more severely affected cases, lesions typical of Leigh disease are also found. Positron emission tomography shows decreased metabolism for glucose and oxygen with relatively preserved cerebral blood flow, findings compatible with a respiratory chain defect.[13] Phosphorus magnetic resonance spectroscopy of the brain is normal but studies of resting muscle show an increase of inorganic phosphate and a decrease of the phosphocreatine-to-inorganic phosphate concentration ratio.[86]

Clinical Presentation

MERRF was first described in cases with a florid clinical myopathy and myoclonus epilepsy.[43,128] It is now clear that the clinical spectrum of MERRF is extremely broad. It should be suspected in a wide variety of situations, even when clinical and pathologic evidence of myopathy is absent.[8,13] Symptoms can begin at any age and there may be marked intrafamily variation in the age of onset and clinical severity.[13,111] The clinical features include myoclonus, tonic–clonic seizures, dementia, ataxia, and less common findings of myopathy, neuropathy, deafness, and optic atrophy. Some cases show striking axial lipomas. Occasional patients or families have focal neurologic events and there is an overlap with the syndrome of mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes (MELAS), where strokelike episodes frequently preceded by migrainous headaches with vomiting are characteristic.[8,102]

It has been previously suggested that a wide variety of cases of PME known by eponyms, clinical signs, or particular patterns of system degeneration were examples of mitochondrial disease.[4,7,13] This has now been confirmed for PME with lipomas,[13,39] and for at least some cases of PME and deafness[87,131] and of so-called Ramsay Hunt syndrome.[4,10,84] PME with Friedreich ataxia[122] and PME with deafness, focal cerebral deficits, alopecia, and a transient response to biotin[21] may also be due to mitochondrial disease.

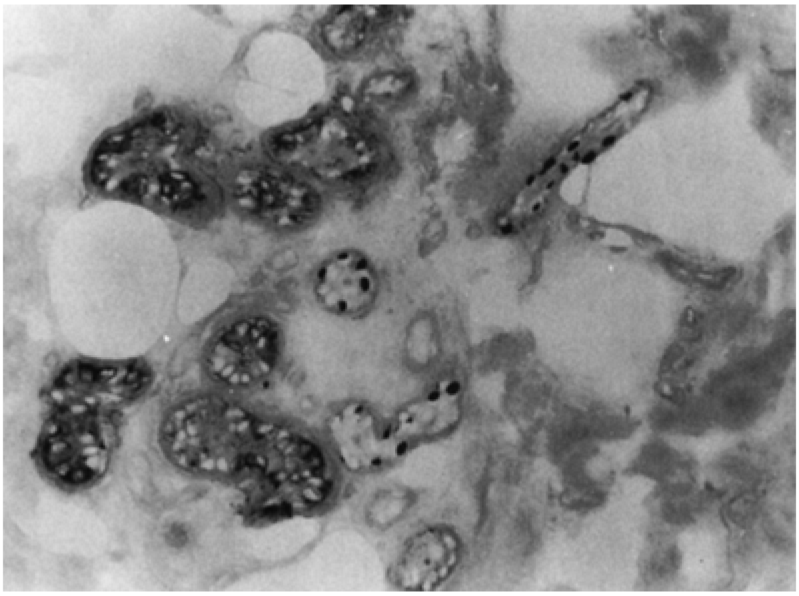

FIGURE 3. Lafora disease, skin biopsy. Cryostat section of skin stained with periodic acid-Schiff showing oval densely staining inclusions in eccrine duct cells. The secretory ascini (on the **left**) show normal glycogen staining (×225). (Reproduced from Berkovic SF, Andermann F. The progressive myoclonus epilepsies. In: Pedley TA, Meldrum BS, eds. Recent advances in Epilepsy. Edinburgh: Churchill Livingstone; 1986:157–187.)

The EEG shows slowly progressive background slowing paralleling degree of clinical deterioration. There are generalized spike-and-wave discharges at 2 to 5 Hz or multiple spike-and-wave discharges. Sporadic occipital spikes and sharp waves may be seen. Prominent photosensitivity may occur. Non-REM sleep is disorganized and spike-and-wave discharges are diminished.[18,123]

Diagnostic Evaluation

The unifying feature of these cases is dysfunction in the mitochondrial respiratory chain. This is most simply demonstrated by ragged red fibers in skeletal muscle, although these can be absent. Biochemical assays of the mitochondrial respiratory enzymes may show abnormalities, but these too may be normal.[13,134]

Diagnosis can usually be suspected clinically and may be difficult to confirm with laboratory markers. The clinical clues to the diagnosis include deafness, optic atrophy, myopathy, lipomas, intrafamily variation in age of onset and severity, and a pattern of inheritance compatible with maternal transmission.[13] Serum lactate, ragged red fibers, and respiratory enzyme activities in muscle can all be normal in patients known to be affected (e.g., family members of proven cases). Magnetic resonance spectroscopy of muscle may show elevated levels of inorganic phosphate and a decrease of the phosphocreatine-to-inorganic phosphate concentration ratio.[86] Molecular defects in mitochondrial DNA or POLG can be detected, when present, in peripheral blood or muscle.[53,138] Screening for the mitochondrial DNA 8344 mutation should be done first; if negative, then more extensive DNA testing of mitochondrial DNA or POLG may be indicated.

Lafora Disease

Etiology and Basic Mechanisms

Lafora disease is characterized by the presence of Lafora bodies, which are polyglucosan inclusions found in neurons and in a variety of other sites including heart, skeletal muscle, liver, and sweat gland duct cells[25,68] (Fig. 3).

It is an autosomal recessive condition. The largest series have been reported from Southern Europe,[125] but it is found worldwide, apparently without a marked racial or ethnic predilection. Approximately 90% of cases have mutations in the gene *EPM2A,* which encodes a dual phosphatase known as laforin,[89,114] or in *EPM2B* (also called *NHLRC1*), which codes for an E3 ubiquitin ligase known as malin.[28,48] There is evidence for a third as yet unknown locus.[27]

Clinical Presentation

Onset is between the ages of 10 and 18 years with a mean age of onset of 14. Clinical features are myoclonus, tonic–clonic seizures, and relentless cognitive decline. Focal seizures, particularly arising from the occipital regions, occur in about half the patients. Recognition of Lafora disease in its fully developed form is not difficult. At the onset, however, the disorder can resemble a typical benign adolescent generalized epilepsy with no evidence of cognitive decline. It may also present as a dementing illness with relatively infrequent seizures, or it may mimic a nonspecific secondary generalized epilepsy because myoclonus is not obvious.[11,107,110] The prognosis of Lafora disease is dismal, with death occurring 2 to 10 years after onset and the mean age of death being 20 years.

The clinical picture, including the relatively narrow age range of onset and relentlessly progressive course to death within 2 to 10 years of onset, is constant in all reports with the exception of a few cases. These cases, sometimes erroneously labelled as "type Lundborg," had symptoms beginning in late adolescence or early adult life with a milder protracted course.[36,60,66] Certain mutations in *EPM2B* may cause a milder course.[6] Conversely, an early-onset form with marked cognitive decline has been reported with mutations in exon 1 of *EPM2A*.[44]

At onset the EEG background is well organized and there are multiple spike-and-wave discharges that are increased by intermittent photic stimulation. Erratic myoclonus is seen without EEG correlation. Spike-and-wave discharges are not accentuated during sleep. Over the next few months to years, the background deteriorates, the physiologic elements of sleep become disrupted, and only REM sleep can be identified. Multifocal, particularly posterior, epileptiform abnormalities appear in addition to the generalized bursts, and in the terminal phase of the illness the EEG is quite disorganized.[125]

Diagnostic Evaluation

The age of onset, eventual inexorable dementia, and frequent occurrence of focal occipital seizures are clinical clues to the diagnosis.[110,127] Lafora bodies can be demonstrated in many tissues, but diagnosis is most simply made by examination of eccrine sweat gland ducts by a simple skin biopsy[25] and can

now be confirmed in most cases by molecular study of *EPM2A* and *EPM2B*.[57]

Neuronal Ceroid Lipofuscinoses

Etiology and Basic Mechanisms

The neuronal ceroid lipofuscinoses (NCLs) are characterized by the accumulation of abnormal amounts of lipopigment in lysosomes. There are four classical clinical forms: Infantile, late-infantile (Jansky-Bielschowsky), juvenile (Spielmeyer-Vogt-Sjögren), and adult NCL (Kufs), of which all but the infantile form may present as a PME syndrome. The infantile form presents differently with regression, hypotonia, and impaired vision and is not considered here. The childhood forms are sometimes collectively referred to as Batten disease.

The various forms are genetically distinct and occur worldwide, but with peculiar patterns of geographic clustering. In Finland there are large numbers of infantile and juvenile cases, whereas in Newfoundland late-infantile and juvenile cases are seen with increased frequency.[3,108] All forms have autosomal recessive inheritance. Kufs disease, however, also occurs in families with dominant inheritance.[20]

The storage material proved extremely difficult to characterize, and for many years was thought to be lipid. Subunit c of mitochondrial adenosine triphosphate (ATP) synthase, a very hydrophobic protein, was subsequently identified as the major storage protein in an ovine model[99] and in human late-infantile, juvenile, and adult cases.[49,98] Clinicomolecular studies have now designated eight variants (*CLN1 to 8*) for which the gene has been isolated in six.[90]

Clinical Presentation

The classic late-infantile form (*CLN2*) has an onset between 2½ and 4 years. Seizures are usually the first manifestation with myoclonic seizures, tonic–clonic seizures, atonic seizures, and atypical absences. Within a few months of onset, ataxia and psychomotor regression are seen with visual failure generally developing late. Examination of the optic fundi reveals attenuated retinal vessels and macular degeneration. The seizures are usually intractable, dementia is relentless, and there is progressive spasticity with death about 5 years after onset.[11,107] The EEG shows background slowing and disorganization with generalized epileptiform discharges. Photosensitivity is marked and single flashes may provoke giant posterior-evoked responses. Visual-evoked potentials (VEPs) are abnormally broad and of high amplitude, and SSEPs are enlarged. The electroretinogram

(ERG) becomes progressively attenuated.[101,107,136] *CLN2* encodes a lysosomal enzyme tripetidyl peptidase (TPP1).[90]

The late-infantile variant form, described in Finland (*CLN5*), differs in the following ways. Onset is later, between 5 and 7 years; psychomotor regression and visual failure occur earlier, with myoclonic and tonic–clonic seizures generally appearing at around age 8 years; and progression is somewhat slower.[113] Electrophysiologic findings are similar to those of the late-infantile form except that the marked response to photic stimulation develops around age 7 to 8 years and disappears by ages 10 to 11 years, and the visual-evoked response (VER), which is initially large, progressively attenuates.[113] *CLN5* encodes a glycosylated lysosomal protein.[90]

CLN6 encodes a membrane protein found in the endoplasmic reticulum and is associated with a late-infantile variant form, which presents between 5 and 7 years with seizures and motor impairment, while visual failure occurs later. This disorder has been described in many countries.[90] Late-infantile cases are frequent in Turkey; some have mutations in *CLN8,* which encodes a membrane protein found in the endoplasmic reticulum, and others have been designated as *CLN7*, but the gene has not been identified.[90]

Juvenile NCL (*CLN3*) begins between the ages of 4 and 10 years. The majority of patients present with visual failure, and have the gradual development of dementia and extrapyramidal features, with seizures being a relative minor manifestation. Funduscopy reveals optic atrophy, macular degeneration, and attenuated vessels. Inheritance is autosomal recessive. The course is variable, with death about 8 years after onset.[107] The EEG shows background slowing and generalized epileptiform discharges that are often of the slow spike-and-wave type. Sleep activates the epileptic abnormality but photic stimulation does not. VEPs are of low amplitude and sometimes cannot be elicited. The ERG is flat.[101,107,136] The gene encodes a glycosylated membrane protein probably localized to lysosomes.[90]

The adult form (*CLN4*) is considerably rarer. It can present as a PME syndrome around the age of 30, although other cases present with a picture of dementia and extrapyramidal or cerebellar disturbance. Visual auras may occur before some seizures. Blindness is notably absent and the optic fundi are normal. The clinical course from onset to death is approximately 12 years.[12] The EEG shows generalized fast spike-and-wave discharges with marked photosensitivity. Single flashes may evoke paroxysmal discharges. The background activity may be normal in the early stages, and ERGs are normal.[9,12] The genes have not been identified.

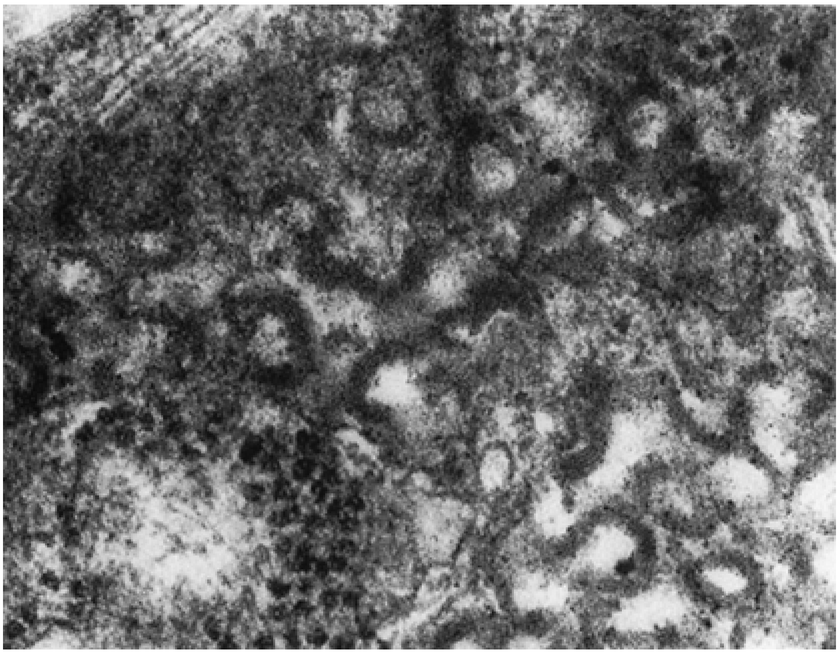

FIGURE 4. Late-infantile neuronal ceroid lipofuscinosis, skin biopsy. Electron micrograph of a skin biopsy showing curvilinear profiles from an eccrine secretory cell (×120,000). (Reproduced from Berkovic SF, Andermann F. The progressive myoclonus epilepsies. In: Pedley TA, meldrum BS, eds. Recent advances in Epilepsy. Edinburgh: Churchill Living Stone; 1986:157–187.)

Diagnostic Evaluation

Diagnosis can often be suspected clinically, particularly if there are visual changes. The electrophysiologic findings described above can be helpful. Vacuolated lymphocytes may be noted in the juvenile form. Neuroradiologic studies show cerebral and particularly cerebellar atrophy. Diagnosis can be made by the demonstration of characteristic inclusions by electron microscopy. These can be found in a variety of cell types including eccrine secretory cells. The inclusions take various forms, with curvilinear profiles being characteristic of a late-infantile NCL, fingerprint profiles being usual in the juvenile and adult forms, and granular osmiophilic deposits occurring in the infantile form (Fig. 4). A number of variations occur, however, such as rare cases of the adult and juvenile cases showing granular osmiophilic deposits. Considerable expertise may be required in the pathologic interpretation of the electron micrographs.[24,26] In the case of suspected *CLN2*, enzymatic assays for TPP1 are available and molecular testing can be performed for *CLN2, CLN3, CLN5, CLN6,* and *CLN8.*[90]

Sialidoses

Etiology and Basic Mechanisms

The sialidoses are the least common of the major forms of PME. They are autosomal recessive disorders associated with deficiencies of *a-N*-acetyl-neuraminidase. Sialidosis type I is due to a primary deficiency in a neuraminidase. Many of the published cases were of Italian origin.[75] Sialidosis type I is due to mutations in the *a-N*-acetyl-neuraminidase gene *(NEU1)* on chromosome 6.[115]

Sialidosis type II comprises a complex group of phenotypes. The juvenile form presents as a PME and occurs predominantly in Japan. In addition to the neuraminidase deficiency, a partial deficiency of ß-galactosidase is also found in most if not all cases.[75,85] The combination of neuraminidase and ß-galactosidase deficiency (galactosialidosis) is due to a lack of a 32-kilodalton protein that is required to protect

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galactosidase from degradation and is essential for the catalytic action of neuraminidase.[34,100] Missense mutations in the gene lysosomal protective protein/cathepsin A (PPCA) on chromosome 20 cause the juvenile form with PME.[91,139]

Clinical Presentation

In sialidosis type I (*cherry red spot-myoclonus syndrome*), there is onset in adolescence with myoclonus, gradual visual failure, tonic–clonic seizures, ataxia, and a characteristic cherry-red spot in the fundus. The myoclonus is usually very severe. Lens opacities and a mild peripheral neuropathy with burning feet may occur. Dementia is absent.[42,75,106,107,124]

Juvenile sialidosis type II presents as a PME with features like sialidosis type I except that onset is sometimes a little later. There may be additional features of coarse facies, corneal clouding, dysostosis multiplex, hearing loss, and low intellect, which can be present from early life.[75,85]

The EEG background comprises low-voltage fast activity, but some slowing can be seen in demented patients. Generalized spike-and-wave bursts are absent or infrequent; rather massive myoclonus is associated with trains of 10- to 20-Hz small vertex positive spikes preceding the EMG artefact. Non-REM sleep is disorganized, and although myoclonus diminishes, the vertex spikes persist and become very frequent in deep sleep.[41,107]

Diagnostic Evaluation

Sialidoses should be identified clinically because of the characteristic optic fundus. Periodic acid-Schiff–positive inclusions may be seen in lymphocytes, bone marrow cells, neurons, and Kupffer cells. Diagnosis is confirmed by grossly elevated urinary sialyloligosaccharides and by a deficiency of cryolabile α-N-acetylneuraminidase in leucocytes or cultured fibroblasts.[75]

Rare Causes of Progressive Myoclonus Epilepsy

Dentatorubral-pallidoluysian atrophy (DRPLA) is an autosomal dominant condition that has been extensively studied in Japan. It is caused by a triplet repeat expansion in a gene on chromosome 12p; the function of the gene is as yet unknown.[62,93] DRPLA has a distinct pathology with neuronal loss and gliosis in the dentatorubral and pallidoluysian systems. A variety of clinical phenotypes occur, which may all be seen in one family. PME is one mode of presentation and tends to occur in cases with onset in childhood or adolescence. Other patients, usually with onset in adulthood, present with ataxic-choreoathetoid or chorea-dementia (mimicking Huntington disease) phenotypes.[59,94] Diagnosis is by detection of the abnormal triplet repeat expansion. DRPLA was previously thought to be extraordinarily rare outside Japan. Molecular diagnosis has recently revealed a number of non-Japanese families, although the PME phenotype appears to be uncommon.[23,105,135]

Noninfantile neuronopathic Gaucher disease presents as a PME, with supranuclear gaze palsy and splenomegaly without dementia. Neurologic manifestations may appear in childhood or as late as 38 years.[61,137] Pancytopenia, elevated serum acid phosphatase, and low leukocyte β-glucocerebrosidase activity are found. Inheritance is autosomal recessive. The glucocerebrosidase gene is on chromosome 1. A large variety of mutations causing disease have been identified.[19]

Atypical inclusion body disease has inclusions that are limited to the brain and are histochemically and ultrastructurally different from Lafora bodies.[30,37] Clinical onset is between 7 and 31 years, and dementia is prominent. Diagnosis requires brain biopsy. The initially reported cases were sporadic, but it has been suggested that at least some of these cases may be related to familial encephalopathy with neuroserpin inclusion bodies.[32,33]

A remarkable autosomal recessive disorder has been described in French Canadians with tremor and a PME syndrome beginning at around the age of 19, followed shortly by renal failure with proteinuria. Dementia is absent. An unusual pattern of pigment deposition is seen in astrocytes. EEGs show typical features of a PME with marked photosensitivity.[2] This condition has recently been recognized outside French Canada in a number of countries.[5,132]

Neuroaxonal dystrophy rarely presents in late childhood or adolescence as a PME. Additional clinical features include dementia, ataxia, chorea, and lower motor neuron involvement.[38,126] Diagnosis is made by demonstrating the presence of axon spheroids, which may be seen in peripheral nerves, in brain and by electron microscopy around eccrine secretory coils.

Celiac disease can be associated with generalized myoclonus, seizures, and ataxia,[76] although palatal myoclonus, rather than a PME syndrome, is more common in the malabsorptive disorders of celiac and Whipple diseases. Other very rare causes of PME are atypical late-infantile or juvenile forms of GM_2 gangliosidosis,[22] an unusual form of β-galactosidase deficiency with normal neuraminidase activity,[92] familial encephalopathy with neuroserpin inclusion bodies,[33] and possibly pantothenate kinase-associated neurodegeneration.[112] Alzheimer disease beginning in the third or fourth decade can present as a typical PME.[16]

Differential Diagnosis

Distinguishing Progressive Myoclonus Epilepsy from Other Epilepsies and Myoclonic Syndromes

It is usually not difficult to diagnose the syndrome of PME some years after onset with the distinctive diagnostic triad of myoclonic seizures, tonic–clonic seizures, and progressive neurologic decline. At the beginning of the illness, however, the clinical and EEG features may be similar to that of benign idiopathic generalized epilepsies, particularly mimicking juvenile myoclonic epilepsy. Response to therapy may be relatively favorable initially. With the passage of time, however, seizures may become more frequent, and progressive neurologic decline occurs. Failure to respond to therapy and progressive neurologic signs should lead to consideration of the presence of a PME. Conversely, the clinical picture of patients with idiopathic generalized epilepsies may mimic those of PME if they are inappropriately treated and intoxicated with antiepileptic drugs leading to ataxia, impaired cognitive function, and poorly controlled seizures.

Myoclonus in PMEs is usually quite severe, but in some patients, it may be relatively inobvious with convulsive seizures and intellectual decline dominating the clinical picture, leading to a misdiagnosis of a nonspecific symptomatic (secondary) generalized epilepsy or Lennox-Gastaut syndrome. In such cases, a careful search for myoclonus should lead to consideration of the PME syndrome.

Neurophysiologic assessment may also provide clues to the presence of a PME. The EEG background rhythm may be relatively well preserved in the early phases, but as the condition progresses generalized slow activity appears. This is particularly so in those forms of PME associated with relentless dementia, such as Lafora disease and NCL. Generalized epileptiform abnormalities are seen during the resting record, usually in the form of fast spike-and-wave, multiple spike-and-wave, or multiple spike discharges. Photosensitivity is common and may be marked. Focal, particularly posterior, epileptiform abnormalities are common in Lafora disease but also may occur in other forms.[18] SSEPs frequently show giant responses.[118,119]

PMEs should be distinguished from degenerative disorders where seizures and/or myoclonus can occur but do not form part of the clinical core or usual initial presentation of the disorder. The causes of such progressive encephalopathies with seizures are numerous and include GM_2 gangliosidosis, nonketotic hyperglycinemia, Niemann-Pick type C, juvenile Huntington disease, and Alzheimer disease. The distinction between this diverse group of disorders and the PMEs, while not absolute, is clinically useful and provides a practical framework on which to begin specific differential diagnosis.[11] For example, typical Alzheimer disease may have myoclonus as a relatively late feature, and would not be confused with a PME. Rare early-onset cases may, however, present as a PME in early adult life. Myoclonus is also prominent in certain static encephalopathies, of which postanoxic myoclonus (Lance-Adam syndrome) is the best known. The absence of progression and the usual clear history of the causative encephalopathy enable clear distinction from PME.

The PME syndrome should also be distinguished from the progressive myoclonic ataxias. This term was introduced to denote a group of patients, usually adults, with progressive ataxia and myoclonus but with few if any tonic–clonic seizures and little or no evidence of dementia.[84] Previously, some authors used the term *Ramsay Hunt syndrome* for these patients, although others used this term for quite different clinical groups, leading to considerable confusion in the literature.[4,83] The causes of progressive myoclonic ataxia partially overlap with the causes of PME but also include spinocerebellar degenerations, celiac disease, and Whipple disease. While it is now possible to specifically diagnose most patients with the PME syndrome in life (see below), a larger proportion of carefully studied cases with progressive myoclonic ataxia remain without a specific cause being established.[82,84]

Japanese authors have highlighted a condition of benign myoclonic epilepsy of adulthood. In this autosomal dominant disorder, onset is usually between 20 and 40 years, with myoclonus and rare tonic–clonic seizures.[88] Generalized epileptiform EEG abnormalities and giant SSEPs are present, but there is little or no evidence of progression. A number of other families have been described, under various names, that share adult onset, distal action tremor and myoclonus, epileptic seizures, autosomal dominant inheritance, benign course, effectiveness of antiepileptic drugs, and possibly cognitive decline, and the term *familial cortical myoclonic tremor with epilepsy* has been suggested.[133] This condition may be the same or similar to that previously described in the German literature as myoclonus epilepsy of Hartung type.[36]

Finally, the condition of benign familial myoclonus needs to be distinguished. In this autosomal dominant disorder, nonepileptic myoclonus begins in the first three decades of life, but is not associated with major seizures, epileptiform EEG abnormalities, or neurologic deterioration.[31,80]

Diagnosing the Specific Type of Progressive Myoclonus Epilepsy

Once the clinician is convinced that a patient has the PME syndrome, the critical question is to determine which specific disorder is present. This is essential for proper clinical and genetic counseling of the family (see below).

It is now possible to provide a specific diagnosis in life for the vast majority of patients with PME using clinical methods and minimally invasive investigations. An approach to this problem has been described previously.[7,14] The clinician should first consider the five major disorders causing PME, with the addition of DRPLA in patients of Japanese origin. Once these conditions are excluded, the rarer disorders should be considered.

Clinical Features

Although patients with the PME syndrome may appear superficially to have similar clinical features, knowledge of the specific clinical patterns of the common causes of PME often allows the differential diagnosis to be narrowed. Age at onset of symptoms provides some guidance in making the diagnosis, although MERRF may begin at any age. Certain seizure patterns are helpful; very prominent myoclonus suggests Unverricht-Lundborg disease, MERRF, or sialidosis. Partial seizures, particularly of occipital origin, can occur in a variety of the disorders but are often noted in Lafora disease. Characteristic fundal changes are almost invariable in sialidosis and are frequent in the neuronal ceroid lipofuscinosis. Dementia is a constant feature of Lafora disease, the neuronal ceroid lipofuscinoses, and neuroaxonal dystrophy, whereas it is characteristically absent or mild in Unverricht-Lundborg disease, sialidosis type I, noninfantile Gaucher disease, and the action myoclonus-renal failure syndrome. The presence of deafness, lipomas, optic atrophy, myopathy, or neuropathy is a clinical pointer to MERRF. Neuropathy may also occur in sialidosis and neuroaxonal dystrophy. Dysmorphic features are usual in sialidosis type II and may occur in MERRF. Chorea can occur in dentatorubral-pallidoluysian atrophy, neuroaxonal dystrophy, and MERRF. Splenomegaly and supranuclear gaze palsy suggest Gaucher disease. Transient alopecia was seen in biotin-responsive encephalopathy.

Family History

A detailed family history, including examination of relatives, is essential. Recessive inheritance is usual, and the finding of parental consanguinity or early clinical signs in asymptomatic siblings would support this pattern. Maternal transmission is characteristic of MERRF. In MERRF and in the autosomal dominant disorders, older relatives may be found to have mild, incomplete forms of the condition.[14]

Neurophysiology

Findings that may be useful in specific diagnosis include the finding of vertex spikes as the main epileptiform abnormality in sialidosis, activation of epileptiform abnormalities in non-REM sleep in the sialidoses and the late-infantile and juvenile forms of NCL, photosensitivity to single flashes in late-infantile and adult NCL, and absent ERG in late-infantile and juvenile NCL.[18]

Laboratory Findings

Hematologic examination may reveal lymphocyte vacuolation in sialidosis and in certain cases of neuronal ceroid lipofuscinosis. Pancytopenia is common in Gaucher disease.

Routine biochemical tests are not helpful, with the exception of findings of elevated lactate levels in blood and cerebrospinal fluid in some cases of MERRF, elevated serum tartrate-resistant isozymes of acid phosphatase in Gaucher disease, and proteinuria with impaired renal function in the action myoclonus-renal failure syndrome. More sophisticated testing includes assays for TPP1 in leukocytes or fibroblast culture to diagnose late-infantile NCL, urinary thin-layer chromatographic oligosaccharide screen to detect sialidosis, urinary organic acid estimation for biotin-responsive encephalopathy, and β-hexosaminidase A and B screens of serum and leukocytes for GM_2 gangliosidosis. Specific enzyme assays for the sialidoses (α-*N*-acetylneuraminidase and β-galactosidase) and Gaucher disease β-glucocerebrosidase) and definitive assays for the various forms of β-hexosaminidase deficiency in GM_2 gangliosidosis using fibroblast cultures and special substrates are performed only when the relevant diagnosis is strongly suspected.

Pathologic Studies

A tissue diagnosis is essential for a number of these disorders. Skin biopsy with or without skeletal-muscle biopsy is the initial procedure. Lafora disease can be reliably diagnosed by examining eccrine sweat gland duct cells with stains for polysaccharides.[25] The diagnosis of neuronal ceroid lipofuscinosis may be suggested by an acid phosphatase stain, but electron microscopy of the skin biopsy specimen is essential for the definitive identification of inclusions. These inclusions are detectable in many cell types in the late-infantile form of the disease, but in the juvenile and adult varieties, diagnostic inclusions may be limited to eccrine secretory cells.[24] False-negative skin biopsies in Lafora disease and in late-infantile and juvenile NCL are, in our experience, due to failure to examine the appropriate cell type properly. In suspected Lafora disease it is essential to ensure that sweat gland ducts are included in the biopsy and properly examined. Where doubt remains, skin biopsy should be repeated because of the serious prognostic implications of the diagnosis of Lafora disease. The reliability of diagnosis of Kufs disease from skin biopsy is not yet clear.

Axon spheroids may be seen in autonomic terminals around eccrine secretory coils in cases of neuroaxonal dystrophy, but the sensitivity of this finding has not been established. Study of muscle biopsy specimens with modified Gomori trichome and oxidative enzyme reactions may demonstrate ragged red fibers in MERRF. Abnormal mitochondria may be identified in muscle or skin using electron microscopy. Normal light and electron microscopic studies of muscle do not rule out the diagnosis of MERRF and, in clinically suspicious cases, a second biopsy may be indicated.

Molecular Genetic Studies

Molecular genetic studies are playing an increasing role in the diagnosis of the PMEs. Simple DNA tests for the dodecamer repeat in Unverricht-Lundborg disease and mitochondrial DNA mutations in MERRF and for the triplet repeat expansion in DRPLA are readily available. Testing for mutations associated with Lafora disease, neuronal ceroid lipofuscinoses, and sialidoses is available from more specialized or research-orientated laboratories (see http://www.genetests.org).

Treatment and Outcome

Treatment of these disorders may be distressingly difficult. Accurate diagnosis is the first step as informed genetic counseling must be given. It is very important to distinguish MERRF, which may show maternal inheritance, from autosomal recessive disorders such as Unverricht-Lundborg disease, Lafora disease, sialidoses, and the neuronal ceroid lipofuscinoses, and from dominant disorders such as DRPLA, familial encephalopathy with neuroserpin inclusion bodies, and rare dominant families with Kufs disease. Genetic counseling may now be extended to prenatal diagnosis in some cases. Specific diagnosis also allows an accurate prognosis to be given, including a realistic appraisal of the educational and vocational goals of the patient.

For symptomatic control of myoclonus, valproate and/or clonazepam should be used. Phenytoin has a clear deleterious effect in Unverricht-Lundborg disease.[40,58] Phenytoin should not be used in the other PMEs either. Small doses of barbiturates may be helpful, but sedation should be avoided. Piracetam may be useful in certain cases.[96] Care must be taken not to render the patient intoxicated with drugs, although there is some evidence that carefully monitored polytherapy may be more effective in some patients as opposed to the usual practice of aiming for monotherapy.[97] Combinations of L-tryptophan or 5-hydroxytryptophan with carbidopa have been used[73,74] but are not generally of long-term benefit. Zonisamide[55,67] and levetiracetam[29,79,81] may be quite effective. Drugs that may exacerbate myoclonus, including carbamazepine, vigabatrin, and gabapentin, should be avoided.

Programs of physical therapy may be of benefit, and attempts should be made to search for strategies allowing movement without precipitating myoclonus in individual patients. Alcohol may provide symptomatic benefit in some patients, but must be used judiciously.[45]

Strategies for replacing enzymes in the storage disorders and for augmenting mitochondrial function in the mitochondrial

disorders are being developed, but presently they remain in the experimental phase and results to date have been disappointing.

Long-term Prognosis

The prognosis of all the PMEs is poor, and is discussed under the specific diseases. In general, the worst prognosis is seen in the storage disorders (NCL and Lafora), where there is an associated relentless dementia. The prognosis is somewhat better in Unverricht-Lundborg disease, where some patients can remain ambulant and active for many years or even decades after diagnosis. The prognosis of MERRF is highly variable; cases with an earlier onset generally have a more rapid course.

Summary and Conclusions

The PMEs are a group of rare genetic disorders previously shrouded in nosologic confusion. Recent advances have clarified the features of these disorders and provided a rational approach to diagnosis. The major causes of PME are now known to be Unverricht-Lundborg disease, MERRF, Lafora disease, neuronal ceroid lipofuscinoses, and sialidoses. In the last 15 years a series of molecular genetic findings have further refined the understanding of the PMEs. The genes responsible for most forms of PME have been identified. Precise diagnosis in life is now possible in virtually all cases using clinical methods, biochemical tests, skin and muscle biopsies, and molecular genetic techniques. Accurate diagnosis allows determination of prognosis, rational genetic counseling, possible prenatal diagnosis, and consideration of emerging therapeutic strategies. Although the PMEs are among the rarest of the inherited epilepsies, because of molecular genetic discoveries, they are best understood at a molecular level. It is hoped that the great strides that have recently been made in the biochemical and molecular genetics of these disorders will soon transfer into rational and effective therapeutics.

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Chapter 253

Posttraumatic Seizures

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Introduction

The risk for epilepsy is increased at least threefold in patients with head injury compared with the general population.[4] Head injury is a major risk factor, comparable with bacterial meningitis, heroin abuse, or a family history of seizures.[32,33] Each year in the United States, about 1.5 million people sustain a traumatic brain injury.[64] Although trauma accounts for only about 5% of all epilepsy cases, this is still a problem of considerable magnitude. More importantly, it is a potentially preventable cause of epilepsy.

The link between head trauma and epilepsy raises a number of important issues. A rational approach to treatment and prevention requires knowledge of the incidence of posttraumatic seizures and the specific aspects of injury that are associated with the development of epilepsy. How should posttraumatic seizures be treated, and is there a role for prophylactic antiepileptic drug therapy? Finally, because seizures develop after a known injury to the brain, posttraumatic seizures offer the opportunity to investigate mechanisms of epileptogenesis.

Historical Perspectives

That head injuries could be associated with acute seizures was known to Hippocrates. Duretus (1527–1586) attributed epilepsy in an 18-year-old man to a skull fracture that had occurred 6 years earlier. Head injury appears in 19th-century tabulations of causes of epilepsy, although it ranked well behind fright and masturbation in importance.[61] Modern concepts of head injury and epilepsy derive from studies of British and American veterans of four major 20th-century wars.[11,55]

Definitions

Implicit in the designation *posttraumatic seizures* is the notion that the injury not only preceded, but also caused the seizures. Posttraumatic seizures are classified as *early* (occurring within 1 week of injury) or *late* (occurring more than 1 week after injury); in some studies "early" encompasses a longer interval, or means the phase of recovery from the acute effects of injury. Early seizures include a subgroup of immediate or impact seizures, which occur at the time of, or immediately after, the injury. Early seizures are acute symptomatic seizures. Late seizures are remote symptomatic seizures; they may be single or multiple. Conventionally, only recurrent late seizures represent *posttraumatic epilepsy*. In practice, posttraumatic seizures and posttraumatic epilepsy are sometimes used interchangeably.

Head injuries have traditionally been divided into two categories: *Penetrating* injuries from "missile" damage (mostly gunshot wounds) and *closed* injuries from "blunt" trauma (mostly caused by falls, motor vehicle accidents, and assaults not involving firearms). There has not been uniform agreement about what constitutes mild, moderate, and severe head injury. *Mild* injury generally excludes evidence of intracranial structural pathology and neurologic abnormalities other than brief loss of consciousness or amnesia. *Severe* injury implies significant structural damage to the brain (either focal or diffuse), or coma, encephalopathy, or amnesia lasting more than 24 hours. Victims of head injury can be stratified more objectively based on the neurologic examination using the Glasgow Coma Scale.[36]

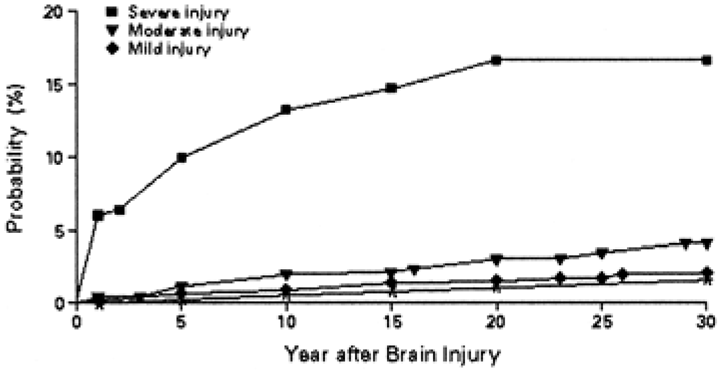
Epidemiology

Head Injury

In the United States, the annual incidence of hospitalization or death from traumatic brain injury is about 100 per 100,000 population.[64,65] Men are more often affected than women. The age-related incidence peaks are in young adults 15 to 24 years of age and in the elderly. Next most affected are young children. The incidence of fatal head injury is about 20 per 100,000. Among survivors of moderate to severe head injury, only about half recover to baseline in such functional domains as home management, financial independence, and social integration.[18] It is estimated that 5.3 million Americans (2% of the population) are living with disability as a result of a traumatic brain injury.[64]

Seizure Studies

It is difficult to establish the incidence of posttraumatic seizures accurately because of a number of methodologic pitfalls. Case ascertainment varies from study to study. For example, head injuries may be noticed only because of a seizure. In some patients, other risk factors for seizures may be present, including pre-existing epilepsy, previous head injury, or alcoholism. Ascribing acute seizures to the effects of brain injury may be confounded by alcohol withdrawal, medication toxicity, or metabolic encephalopathy. In determining the incidence of late posttraumatic seizures, acute symptomatic seizures should be excluded, and the expected incidence of unprovoked seizures occurring in the general population must be taken into account. Many patients are lost to follow-up, and these may not be representative of the study population. As a result of all of these pitfalls, estimates of posttraumatic epilepsy tend to be inflated.



No. of Patients				
Mild injury	2,758	1,751	1,191	609
Moderate injury	1,455	934	660	351
Severe injury	328	181	136	74
Total	4,541	2,866	1,987	1,034

FIGURE 1. Cumulative probability of unprovoked seizures in 4,541 patients with traumatic brain injuries, according to the severity of the injury and the incidence of seizures in the general population. The cumulative incidence in the population was derived from incidence rates with the use of the density method to convert the rates to risk estimates. The *asterisks* indicate the incidence in the general population at specified points in time. (From Annegers JF, Hauser WA, Coan SP, et al. A population-based study of seizures after traumatic brain injuries. *N Engl J Med.* 1998;338:20–24, with permission.)

Early Seizures

Early seizures occur in 2% to 5% of all patients with head injuries,[3,15,37] and they are more common in children than

adults. After severe head injury, the frequency of early seizures is 10% to 15% for adults and 30% to 35% for children.[3,28,58] Most early seizures occur within 24 hours of injury.

Late Seizures

In the Vietnam Head Injury Study,[55] 53% of veterans who suffered a missile injury eventually experienced at least one seizure, with multiple seizures occurring in the great majority. The relative risk in the first year was 580. In about half the patients, the first seizure occurred within 12 months of injury, but in more than 15% of patients, seizures did not develop until 5 or more years later and the relative risk remained elevated at 10 years. In earlier studies of veterans with military head injuries, late seizures occurred in 35% to 45%.[11]

In Jennett's large series of patients in Oxford and Glasgow who were hospitalized because of nonpenetrating head injury, late seizures occurred in 5%.[34] However, of those patients with severe trauma, late seizures occurred in up to 35%.

In a seminal work, Annegers et al. studied civilian head injury (mostly, but not exclusively, nonpenetrating injury) in Olmsted County, Minnesota, and determined the incidence of late seizures, taking into account the incidence of unprovoked seizures in the general population.[3,4] Children under 15 constituted 38% of the study population. The 5-year cumulative probability of seizures for mild, moderate, and severe injury was 0.7%, 1.2%, and 10%, respectively (Fig. 1). Late seizures occurred in 7.4% of children and 13.3% of adults with severe trauma, with the elderly at still greater risk. The relative risk of late seizures (single or multiple) for mild, moderate, and severe injury was 1.5, 2.9, and 17.0, respectively. After severe injury, about half of the first seizures occurred in the first year, but the risk of a first late seizure remained elevated even 10 years later. After mild injury, this risk had largely subsided at 4 years.

The demonstration (for the first time) of a link between mild head injury and seizures is tempered by the very low relative risk. It follows from a relative risk of 1.5 that an unprovoked seizure following a mild head injury is twice as likely to be unrelated to the injury as it is to be related.

Seizure Recurrence

Early seizures are followed by late seizures in 25% to 35% of adults; early seizures are less predictive of late seizures in children.[3,16,37] The relative risk is in the range of 3 to 5,[4,5,19] but risk factors for early and late seizures are similar, and early seizures did not appear to confer a large independent risk of late seizures in a multivariate analysis.[4]

A first late seizure will have a high risk of recurrence.[3,12,55] In one study of moderately to severely injured patients (penetrating and nonpenetrating) with a first late seizure, recurrence occurred in 47% at 1 month and 86% at 2 years, with at least four additional late seizures in half of these patients.[30]

Immediate seizures have been studied phenomenologically and epidemiologically in Australian rugby players. When not associated with other evidence of significant injury, they appear not to significantly increase the risk for later seizures. They may be no more than a transient symptom of concussion.[45,46]

Risk Factors

For penetrating injury, retained metal fragments, intracranial hematoma, persistent neurologic deficits, and degree of brain volume loss as estimated from computed tomography (CT) images were all associated with increased seizure risk.[55] For nonpenetrating injury, depressed skull fracture and intracranial hematoma (both subdural and intracerebral) are risk factors for both early and late seizures.[4,15,34] Multiple cerebral contusions may place a patient at particularly high risk.[20] The presence of parenchymal blood, whether caused by trauma or stroke,[39] appears to be an important element in the development of seizures. Coma duration and Glasgow Coma Scale score correlate with occurrence of both early and late seizures.[20] There is some controversy as to whether intracerebral hemorrhage[14,16] or severity of diffuse encephalopathy[42] best predicts seizures. Seizures are seen in a higher proportion of abusive injuries than accidental injuries in children; the abusive injuries were more serious by other measures as well.[8]

Genetic influences have long been suspected as a factor in the development of posttraumatic seizures. Although some investigators have reported that a family history of epilepsy is more common in subjects in whom epilepsy does develop following head injury than in those in whom it does not,[12,21] the most careful studies to date were unable to demonstrate any increase in the frequency of seizures among relatives of probands with head injury.[50,56] Similarly, the Vietnam Head Injury Study failed to show any increase in family history of seizures among those in whom posttraumatic epilepsy developed.[55] Despite a lack of evidence, it is possible that genetic susceptibility increases the risk for epilepsy in people with milder injuries, individuals who constitute a small proportion of the posttraumatic seizure population.

The use of seat belts and helmets substantially decreases the severity of brain injuries resulting from bicycle, motorcycle, and automobile accidents.[1,49,63] Although it has not yet been shown directly that these measures also reduce the occurrence of late posttraumatic seizures, a mitigating effect can be assumed. The current proliferation of firearms ominously forecasts an increase in the most severe category of head injury, with a consequent increase in posttraumatic epilepsy. Firearm deaths related to head injury are clearly increasing in the United States.[64]

Etiology and Basic Mechanisms

Trauma produces many structural, physiologic, and biochemical changes in the brain. Acceleration and rotational forces shear nerve fiber tracts, rupture blood vessels, and produce diffuse axonal injury characterized histologically by gliosis, microglial scar formation, axonal retraction balls, and wallerian degeneration.[25] Both contusions (focal injuries characterized by a mixture of blood, edema, and necrosis) and frank hemorrhage may occur. Damage to the hippocampus, especially the CA1 region, occurs in a high proportion of fatal head injuries[40] and may be important in the development of epilepsy in survivors. Interestingly, Lowenstein et al.[43] demonstrated that even a brief, relatively minor percussive blow to the dura of rats could result in selective hilar cell loss and hyperexcitability of granule cells that may be a necessary substrate for some kinds of partial seizures. In another rat model of head injury, selective hippocampal cell loss (hilus and area CA3), granule cell hyperexcitability, and mossy fiber sprouting could be seen, and these rats demonstrated enhanced susceptibility to seizures.[23] The findings in the hippocampus are similar to those of mesial temporal lobe epilepsy.

Parenchymal blood with subsequent hemosiderin deposition is a major risk factor for epilepsy, and experimental studies have demonstrated that neocortical injection of ferrous or ferric chloride produces focal electroencephalographic (EEG) epileptiform discharges and seizures.[70] The epileptogenic effect of iron is related to the formation of free radicals, and development of seizures can be blocked by antiperoxidant compounds.[27,71,72] The exact mechanisms of this process are unknown. Low levels of hemoglobin-binding protein have been described in families with epilepsy (although not posttraumatic epilepsy).[52] Because individuals with low levels of hemoglobin-binding protein may clear intracerebral blood less efficiently, this could prolong iron exposure and increase the risk for posttraumatic seizures.

In rats, seizures occurring immediately or shortly after traumatic injury are accompanied by increased glutamate and aspartate levels,[48] a finding documented with seizure onset in humans as well.[54] Excitatory amino acids are highly epileptogenic as well as cytotoxic to neurons; these effects can be blocked by *N*-methyl-D-aspartate (NMDA) antagonists.[13] Release of excitatory amino acids may also be responsible for the large, calcium-dependent increase in extracellular potassium seen after experimental brain injury.[38] Increased extracellular potassium further increases neuronal excitability and may contribute to interictal–ictal transitions. It is unlikely, however, that a unitary mechanism for posttraumatic seizures will be found.

That there is generally a latent or "silent" period between the actual brain injury and first seizure has been known since Gowers. It is most likely that trauma initiates a dynamic epileptogenic process that progressively alters neuronal excitability, establishes or obliterates critical interconnections, and perhaps results in critical structural remodeling so that an epileptogenic network of sufficient size is established, resulting in clinical seizures. It is also possible, however, that head injury resets the seizure threshold downward relatively rapidly. In this case, the delay between injury and the first posttraumatic seizure would not necessarily reflect a progressive, evolving process but rather the outer fringe of a probabilistic spread of first seizure latencies.

With head injury (unlike brain tumor), the moment of onset of a potentially epileptogenic process is known with precision. This would allow for the early initiation of neuroprotective agents. There appears to be a critical period for intervention in rats.[24] However, the successful use of antioxidants and NMDA receptor blockers as neuroprotective agents in rats, as mentioned above, has not so far translated into human head injury trials.

Clinical Presentation

Seizures caused by head injury have similar semiologies to those occurring in other contexts. Thus, the full spectrum of simple and complex partial seizures as well as generalized tonic–clonic seizures can be seen following head injury. Both cortical ("epileptic") myoclonus[29] and epilepsia partialis continua[62] have been described. Generalized absence seizures probably do not occur as a consequence of head injury.

Because individual patients may have both partial and generalized seizures, it is difficult to estimate the relative frequency of different seizure types with accuracy. Recognized early seizures are predominantly generalized tonic–clonic in type,[15,41,44] particularly seizures on the very first day.[6] A study of continuous EEG monitoring for an average of 1 week after moderate to severe injury revealed electrical seizures without clinical accompaniment in 11 of 94 patients.[66] These subclinical, typically unrecognized seizures could not, however, be temporally correlated with increased intracranial pressure or decreased cerebral perfusion pressure, nor did they predict poorer outcome. The majority of patients with late posttraumatic seizures have at least one generalized tonic–clonic convulsion.[34,55] Perhaps a quarter will have complex partial seizures,[6] though this particular seizure type is probably underrecognized in the head-injured population.

Diagnostic Evaluation

Electroencephalographic Findings

Electroencephalography plays only a limited role in the evaluation of early posttraumatic seizures. It is usually most useful in clarifying the basis of intermittent behavioral changes in obtunded or semicomatose patients. It is not of value in predicting the development of posttraumatic epilepsy.[35] The EEG is also less helpful in predicting recurrence after a first late posttraumatic seizure than it is in predicting recurrence after a first idiopathic seizure.[9]

Neuroimaging and Other Laboratory Examinations

The initial diagnostic approach to head trauma is based on the characteristics of the injury and the assessment of the patient's neurologic and general medical status. Patients with moderate or severe head injury require urgent CT imaging. Because intracerebral hemorrhage, subdural hematoma, and hydrocephalus may be delayed, repeated imaging is mandatory in patients who do not improve as expected or deteriorate in the face of appropriate treatment. Development of seizures after the initial CT scan is also an indication for repeated imaging. The role of brain imaging after mild head injury is more controversial, but it is certainly indicated if a seizure occurs or if there is any other unexpected turn in a patient's course. In a large study of adults with mild head injuries,[41] 47% of those with early seizures had intracranial abnormalities; 7% of these required surgical intervention. In a meta-analysis, seizures predicted intracranial pathology in relatively mild injuries.[19] The need for magnetic resonance imaging (MRI) in the acute phase depends on factors other than the presence of seizures.

The first late seizure should be evaluated as any new, unprovoked seizure, including consideration of other etiologies.

Differential Diagnosis

Fluctuations in level of consciousness and intermittent changes in behavior may pose diagnostic problems, especially in the first 1 to 2 weeks after injury, when patients with severe head injuries are likely to be encephalopathic or otherwise neurologically abnormal. Momentary lapses without other symptoms or signs, emotional outbursts without alteration of consciousness, and attacks of directed violence should not be attributed to seizures. Persistent emotional, cognitive, or behavioral changes are likewise unlikely to be caused by seizure activity. On the other hand, the behavior of an individual with frontal lobe partial seizures may be bizarre, and such seizures are frequently misdiagnosed as nonepileptic events. Even the more typical complex partial seizures may be hard to recognize if they occur in a setting clouded by underlying encephalopathy. Determining which changes may be caused by seizure activity is important for management. Video-EEG monitoring may be necessary for definitive diagnosis in some cases.

Nonepileptic seizures (NESs; also psychogenic seizures, pseudoseizures) can occur in head-injured adults[7,69] and children.[51] Indeed, head injury seems to be a risk factor for NES, though the precipitating head injury is usually minor. Most head-injured NES patients have pre-existing or concomitant psychiatric disorders. Some may be malingering or involved in litigation.

Treatment and Outcome

Patients with moderate and severe head injuries are often medically unstable and especially vulnerable to such physiologic consequences of seizures as metabolic acidosis, sudden increases in cerebral blood flow and intracranial pressure, and compromised respiratory function, including pulmonary edema. Convulsive movements may further injure a patient with multiple trauma. Postictal depression complicates neurologic assessment. For these reasons, antiepileptic medication is appealing, at least in the early phase.

Several prospective, randomized, controlled trials[47,53,58,59,73,74] examined the efficacy of antiepileptic drugs in preventing early or late seizures, with mixed results owing to methodologic problems, particularly underpowering. The topic of antiepileptic drug prophylaxis was, for some time, controversial. The most comprehensive studies are those of Temkin et al. In a study of phenytoin in head injury patients at high risk for seizures,[58] phenytoin levels were maintained in the high therapeutic range; side effects were modest.[31] Phenytoin was very effective in suppressing early seizures, with a relative risk of 0.25 at 1 week. However, phenytoin was ineffective in reducing the incidence of late seizures, with no difference between treated and untreated groups at 2 years (Fig. 2). In a second study, valproate was not statistically different from phenytoin in preventing early seizures (though with a trend to less efficacy), but was ineffective late, after 6 months of treatment.[59] For unclear reasons, the valproate group had a trend toward higher mortality. An earlier study found that carbamazepine was also ineffective in preventing development of late seizures.[22] These data imply that although phenytoin, valproate, and carbamazepine are useful *antiseizure* drugs, they do not affect mechanisms involved in the development of posttraumatic epilepsy—they are not *antiepileptogenic* drugs. The situation is similar in patients with other disease processes that promote epileptogenesis, such as brain tumors: long term antiepileptic drug prophylaxis does not prevent the development of a first seizure.

The use of glucocorticoids was examined in the data set of the phenytoin study described above. The early exposure to glucocorticoids did not appear to affect the rate at which late seizures developed.[68] A study of magnesium sulfate has recently been completed. It showed no positive effects on late seizures or neurobehavioral outcome. Almost all participants received phenytoin for the first week, so the early seizure rate was too low to evaluate any effect of magnesium on early seizures.[60]

Recommendations

Patients with severe head injuries should be treated with phe-nytoin for the first week after injury to minimize complications from seizures occurring during acute management. Phenytoin (or fosphenytoin) should be given intravenously in a dose equivalent to 20 mg/kg; subsequent doses should be adjusted to an unbound (“free”) blood level of 2.0 to 2.5 μg/mL. It is not appropriate to continue phenytoin beyond 1 week or the acute phase of injury, if no seizures have occurred, given its neurobehavioral effects.[17] Phenytoin is the drug of choice for preventing and treating early seizures because of its demonstrated efficacy and the availability of an effective formulation for intravenous administration. The hepatic metabolism of phenytoin may be increased and its plasma protein binding decreased in patients with severe head injury.[10,26,75] It is therefore advisable to monitor unbound ("free") phenytoin levels in these patients. While the cause of increased mortality in valproate-treated patients is unclear, it makes valproate a much less attractive alternative to phenytoin. The clearance of valproate in head-injured patients is increased.[2]

In patients who have a single posttraumatic seizure, treatment decisions should be based on the anticipated risk for further seizures. Late seizures follow early posttraumatic seizures no more often than they do a first unprovoked seizure in the general population.[3,9,16,22,37] Thus, long-term antiepileptic drug treatment after early seizures is usually not indicated. In contrast, a first late posttraumatic seizure is usually followed by recurrent seizures, and long-term treatment is usually indicated. There is no settled doctrine on duration of treatment. Antiepileptic drug treatment of early seizures can usually be stopped after a period of weeks or months. Treatment of late seizures, particularly recurrent late seizures, would generally continue for a minimum of 2 years.

Standard antiepileptic medications should all be effective for late seizures; a choice is made as in other contexts, with particular attention to the sedating and behavioral effects of the medications.

Status epilepticus related to head injury is treated in the same manner as in other contexts.

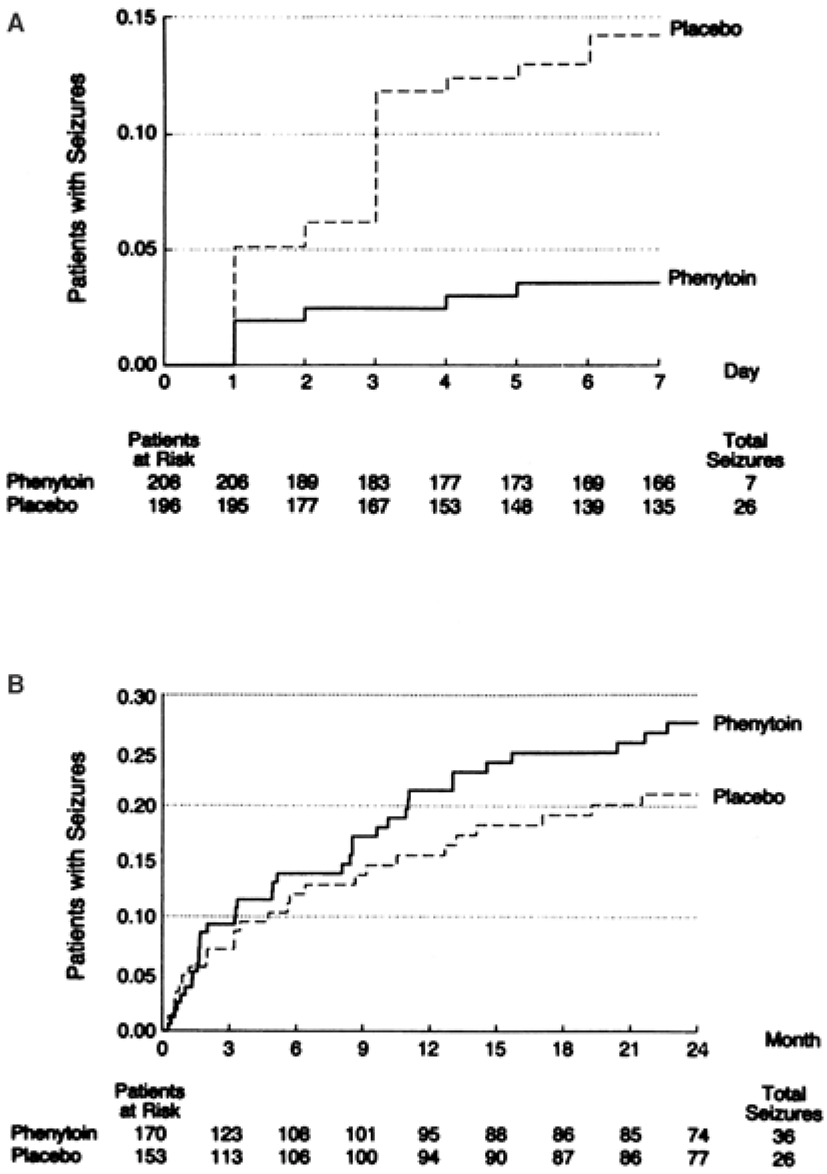


FIGURE 2. Treatment of patients with severe head injury with phenytoin or placebo. Cumulative fraction of patients with early **(A)** or late **(B)** seizures in the two groups. (From Temkin NR, Dikmen SS, Wilensky AJ, et al. A randomized, double-blind study of phenytoin for the prevention of post-traumatic seizures. *N Engl J Med.* 1990;323:497–502, with permission.)

Long-term Prognosis

The same problems that plague incidence studies of late seizures make it difficult to assess prognosis. About half of head-injured patients with late seizures have prolonged remissions, although it is not always clear if patients with early seizures or single seizures were excluded.[12,55,67] Remission rates for epilepsy are somewhat higher (70% or so) in the general population.[32] In the Vietnam Head Injury Study, the average duration of active seizures was 93 months.[55] Intracranial hematoma, partial seizures, and frequent seizures during the first year substantially decrease the chance for extended remission.

Summary and Conclusions

Seizures complicate about 50% of penetrating head injuries and about 5% of closed head injuries. Early seizures are related to the acute effects of trauma and are more common in children than adults. The risk for both early and late seizures is increased by depressed skull fracture, intracranial hematoma, and severe encephalopathy. Early seizures increase the likelihood of late seizures, and late seizures have a high recurrence rate. Iron deposition related to hemosiderin, cytotoxic effects of excitatory amino acids, and free radical formation may all play a role in the pathogenesis of posttraumatic seizures. Phenytoin is effective in reducing the chance of early seizures but does not prevent development of posttraumatic epilepsy.

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Chapter 254

Isolated Seizures

Peter Wolf

Introduction

All epilepsies begin with a first seizure. However, a first seizure does not necessarily mean that epilepsy will develop (Chapters 7 and 122). It may turn out to be an isolated event, symptomatic of some other pathologic condition (Chapter 8), or indicative of an inherent increased risk for development of epilepsy and the need to prevent such development.

This chapter does not deal with the first of these possibilities—the epileptic seizure as an acute symptomatic event—but rather with the second, which is often discussed under the heading of “first unprovoked seizures.” The discussion of these has mostly addressed two questions: How probable is it that a first “unprovoked” seizure signifies epilepsy, and should treatment begin after a first seizure? In this literature, treatment is always conceived of as pharmacotherapy, and a thorough definition of seizure provocation is rarely given. Important as these aspects may be, the theoretically more interesting question of nosology—the relation of isolated seizures to the established epileptic syndromes—is asked rarely, if at all, although apart from dealing with the occasional patient in such a situation, physicians hear about isolated seizures perhaps most frequently when taking the family histories of patients with epilepsy.

Historical Perspectives

The statement of Gowers[10] that “we have no means of ascertaining, on any considerable scale, the frequency with which a single epileptic fit occurs without successors” clearly shows that he and his contemporaries were quite aware of the possibility of isolated seizures. However, this was not a major concern with the classic epileptologic writers. Apart from the specific subgroup of febrile seizures in infants, isolated seizures mostly were mentioned in epidemiologic and genetic investigations. These were briefly reviewed by Janz[16] in a section on *Gelegenheits-Epilepsien*. His remarkable conclusion was that this is “at the same time the most frequent and mildest form of epilepsy, and the one with the highest rate of heredity.”

It was mainly for epidemiologic, prognostic, and similar statistical purposes and quantitative studies of therapy that epilepsy was defined as a minimum of two unprovoked seizures. This definition left isolated seizure events as a separate group that logically—and provided that the diagnosis of an epileptic seizure was reliable—had to be included in the classification of epilepsies and epileptic syndromes.[4] The new International League Against Epilepsy (ILAE) and International Bureau for Epilepsy (IBE) definition of epilepsy as a disorder “characterized by an enduring predisposition to generate epileptic seizures” and requiring “the occurrence of at least one epileptic seizure”[9] gives the possibility in certain instances of coming to a diagnosis of epilepsy even after one seizure, but these cases will probably be the exception rather than the rule.

Definitions and Nosologic Place

Isolated seizures can be defined as solitary seizure events that may occur once in a lifetime or very rarely, at lengthy intervals. A seizure event according to this definition would be one single seizure or a short series of two or more seizures in the course of 24 hours, or an isolated episode of status epilepticus.[14]

The best-known type of isolated seizure, febrile convulsions of early childhood, is considered to be a separate entity and is not discussed here.

The relationship of isolated seizures to other epilepsy syndromes has rarely been given much attention, let alone systematically considered. However, it appears that the rare recurrences of seizures in later life among patients with idiopathic localization-related childhood epilepsies are usually isolated generalized tonic–clonic seizures.[19] The same seems to be true for another benign idiopathic epilepsy syndrome, benign familial neonatal convulsions,[22] and isolated seizures may be found in the pedigree of patients with this syndrome.[3]

Epidemiology

Stress convulsions, defined as epileptic attacks in adults exposed to various “stressing” exogenous influences who have not previously had unprovoked epileptic attacks, were diagnosed in 37 of 1,250 patients with convulsive disorders studied during a 13-year period by Laue Friis and Lund.[18] These patients can be considered a subset of the patients discussed here.

Hauser et al.[12] reported 244 patients with a first idiopathic or remote symptomatic seizure. These were drawn from a total of 1,047 patients with newly diagnosed seizures who had been enrolled during a 4 1/2-year period. They compared them with 334 patients who had acute symptomatic seizures and 435 who had had two or more seizures at first diagnosis; 34 patients were excluded from study. After 36 months of follow-up, seizures had recurred in 27% of the persons with only one seizure—that is, in 73%, the seizure had been an isolated event.

In the National General Practice Study of Epilepsy,[23] which was a prospective, population-based cohort study of 1,195 patients with newly diagnosed or suspected epileptic seizures, 220 patients had febrile seizures, and definite epileptic seizures were diagnosed in 564. Of these, 252 were registered at the time of their first seizure, 89 of whom were followed for 3 or more years. Of the latter group, 56% had had a seizure recurrence at 3 years of follow-up—that is, in 44%, the seizure had remained isolated.[11]

The focus of these and similar studies, however, differs slightly but significantly from the subject of this chapter. They were aimed at establishing the risk for recurrence after a first seizure and did not ask whether a second seizure signifies epilepsy or is only the recurrence of an isolated event, or *Gelegenheitsanfall*.

When seizure types are considered, it turns out that in all studies of this matter, generalized tonic–clonic seizures are by far the most frequent type. Percentages ranged between 61% (27% with simple and 10% with complex partial seizures; the remainder were unclassified, although these figures apply only to the cryptogenic group, the semiology of remote symptomatic seizures not being recorded)[12] and 97.5%.[15] This important difference from the usual distribution of seizure types in clinical cohorts is probably attributable to the fact that with minor and less frightening seizures, a physician is frequently not seen after a first seizure, but is seen only later. These cases are frequently lost for studies of first seizures.

However, as Loiseau et al. pointed out, partial seizures also may occur as isolated events, and these have been reported in several studies.[20]

Etiology and Basic Mechanisms

Apart from the bias toward generalized tonic–clonic seizures, it would appear that these patients are not nosologically homogeneous. Rather, they comprise both a group with an innate risk for development of some type of idiopathic generalized epilepsy and a mixed bag of patients at risk for development of symptomatic localization-related epilepsies of various etiologies.

Of the 564 patients with first seizures in the series of Sander et al.,[23] the seizures of 346 were classified as idiopathic/cryptogenic, those of 119 as remote symptomatic, those of 83 as acute symptomatic, and those of 16 as associated with neurologic deficit.

In the extended follow-up study of Hauser et al.[13] of 208 patients with first seizures, the seizures of 149 were diagnosed as idiopathic and those of 59 as remote symptomatic. There were no acute symptomatic cases in this study.

The prospective cohort of adolescents and adults with first seizures of Wolf[26] comprised 104 patients as of January 31, 2002. Of these, 26 (25%) had a positive family history of epilepsy or febrile convulsions. Febrile convulsions were a previous manifestation of seizure susceptibility in 5 (4.8%), and 1 patient had had benign rolandic epilepsy in childhood. Twenty-five (24%) were photosensitive and thus revealed a trait most frequently seen in association with idiopathic generalized epilepsy syndromes.[24] In an additional 20 (19.2%), the electroencephalogram (EEG) showed some other type of generalized epileptiform discharge. On the other hand, indications of a remote symptomatic etiology were present in 15 (14.4%), and 41 (39.4%) displayed some focal trait (clinical, EEG, or both). In 16 patients (15.4%), no definite indicators of either a focal or a bihemispheric onset were found.

Clinical Presentation

There is good reason to assume that the manifestation of epilepsy of any type is often preceded by a stage of increased risk for development of seizures. This risk may be discovered on EEG if for some reason it happens to be performed. More often, risk becomes apparent through a first seizure. In a continuum stretching from no risk through low risk and high risk to active epilepsy, an isolated seizure would identify a person as belonging to a high-risk group for development of any type of epilepsy.

Risk for Relapse

The usual approach to this issue is to define the risk for relapse after a first seizure, which is the inverse expression of the chance of its remaining isolated. The discussion of this risk is highly controversial. The percentages in various recent studies vary from a low of 16% in the first year of follow-up and 27% in 3 years[12] to a maximum of 67% after 1 and 78% after 3 years.[11]

The reasons for these variances are not entirely clear. They could not be explained by differences in therapy. In the study of Annegers et al.,[1] 60.6% of 424 patients received drugs. In cryptogenic ("idiopathic" in the authors' terminology) cases, the relapse rates in patients taking drugs were considerably higher after 3 years (44% vs. 36%) and 5 years (60% vs. 41%), whereas in remote symptomatic cases there was no difference (70% for each group at 3 years and 80% vs. 76% at 5 years). In the Royal College of Physicians Study,[15] 41 of 306 patients (13.4%) had had drugs prescribed by their family doctor or neurologist, and this had no influence on the relapse rate.

It has been suggested that the figures for recurrence in the optimistic studies were unrealistically low because the patients who had already had a second seizure were excluded from them at the onset of a prospective follow-up—thus excluding the group with the highest risk for relapse.[8] This is certainly true, but when Hauser et al.[13] in a second study included such patients who had been excluded from their previous one, only a minor increase in the relapse rate resulted. According to Berg and Shinnar,[2] with retrospective ascertainment, the success of follow-up may depend on the outcome because the patients who have recurrence are easier to find and follow. In addition, they pointed out that in such studies, "the investigator may have little control over the quality of the initial assessment."

A serious methodologic weakness of the British studies showing a high relapse rate is indeed that most[15] or even all[11] patients were not given their diagnoses by the investigators; rather, the diagnoses of other physicians were relied on, and no special precautions were taken to exclude the possibility that a patient with a first major seizure leading to a diagnosis had previously been subject to minor seizures. Some of these, such as absences, myoclonic seizures in juvenile myoclonic epilepsy, or isolated auras, can easily escape the attention of an inexperienced observer. In the study of Sander et al.,[23] which relied on information collected by general practitioners, only 3% of 564 patients with "definite epileptic seizures" were given diagnoses of "true absences or myoclonic jerks with or without generalized tonic–clonic seizures." Obviously, these diagnoses were frequently missed, as can also be seen in another article from the same investigation.[21] In this study of 1,195 primarily registered patients, only 9% were excluded because it was determined that they had already had seizures. In contrast, in the investigation of Hauser et al.,[13] who are the only authors who discussed this problem and provided for it, 74% of patients "with newly identified unprovoked seizures had experienced multiple seizure episodes prior to their first medical contact"; these authors even excluded 13 patients referred by neurologists after a "first seizure" because a history of complex partial seizures had been overlooked—a diagnosis that would be thought hard to miss. It cannot be ruled out and seems even probable that the studies reporting high relapse rates comprise an unknown and potentially large number of patients with established but undiagnosed epilepsy.

Several studies have tried to identify subgroups with higher and lower risks for relapse. Hauser et al.[12] reported that risk was significantly higher in patients with remote symptomatic than with cryptogenic seizures. In the latter group, it was

increased if the patients had generalized slow-wave activity in the EEG (*n* = 13) but not focal EEG abnormalities (*n* = 61). (These results may very well be a question of numbers.) Risk was increased if patients had a sibling with seizures (*n* = 17) but not a parent with seizures (*n* = 6).

Annegers et al.[1] found that the risk increased for patients whose seizures had a presumed etiology, and among their "idiopathic" (cryptogenic) cases, EEG abnormalities, neurologic findings, and initial partial seizures were significant independent predictors of higher recurrence risks.

In the study of Hopkins et al.,[15] the only clinical variable associated with recurrence was seizure occurrence between midnight and 9:00 AM.

According to Hauser et al.,[13] the risk for recurrence was increased by the history of an identified insult to the central nervous system. Further factors in cryptogenic cases were generalized slow-wave activity in the EEG, a history of acute symptomatic seizures, and a sibling with epilepsy; in remote symptomatic cases, they were a history of acute symptomatic seizures, a history of status epilepticus or multiple seizures, and Todd's paresis.

In the National General Practice Study,[11] the risk was increased when the age at first seizure was <16 or >59 years, when a neurologic deficit was presumed present at birth, or when the first seizure was simple or complex partial. (Seizures of partial onset evolving to generalized tonic–clonic seizures seem in this study for unexplained reasons to have been lumped together with primarily generalized tonic–clonic seizures.) The risk was decreased in this study when the seizure was precipitated acutely by an insult to the brain (occurring within 3 months) or by alcohol. In this same study, relative risks are given for many subgroups (etiology, seizure type, age, index seizure first, or subsequent seizure).

Donselaar et al.[5] found that against an overall 2-year risk for relapse of 40% in 151 patients, 15 of 16 patients with epileptiform discharge in the standard EEG and 12 of 19 additional patients with discharge in the EEG after sleep deprivation had a relapse. They concluded that "the decision to initiate or delay treatment should be based on EEG findings." In this investigation, however, no particular efforts were made to exclude a history of minor seizures, and no steps were taken to ensure that the epileptiform EEG activity was only subclinical. Especially in the case of generalized spike-and-wave discharges, absences may be difficult to rule out. Sometimes this requires a video-EEG investigation with tests of reaction and awareness, which were not part of this study.

In the study of Wolf,[26] in which all measures, including those mentioned in the preceding paragraph, were taken to exclude preexisting epilepsy with difficult-to-diagnose seizures, the relapse rate was not influenced by EEG, antecedents, or focal versus generalized seizure onset.

Of course, the ultimate question behind these studies is not how often a second seizure occurs, and the concept of "isolated seizures" is not identical to the concept of one single seizure in a whole lifetime. The substantial question is how often epilepsy develops. However, most studies stop at the second seizure, probably because two unprovoked seizures, in studies of epidemiology and therapy, are often considered sufficient for a diagnosis of epilepsy, and "unprovoked" is frequently understood to mean no indication of an acute symptomatic background.

Elwes et al.,[7] however, looked at retrospective sequences of up to five initial generalized tonic–clonic seizures in 183 patients. They found that the intervals between seizures of 82 patients with more than two seizures decreased in 48 individuals, did not change in 16, and increased in 18. They concluded that "in many patients… an accelerating disease process may occur at least in the early stages.” However, they also believed that this was not an invariable phenomenon, and “as well as processes of acceleration of epilepsy the brain may generate processes of remission.”

Donselaar et al.[5] investigated the outcome of 58 of 151 patients with an idiopathic first seizure and no drug treatment who had had a relapse during the 2 following years. Of these, 6 had no further seizures although they remained untreated, 25 were started on drug treatment immediately after their second seizure, and 26 were started on drugs following additional seizures. One patient refused drugs despite several recurrences and was excluded. Forty patients (70%) became seizure free (including the aforementioned untreated 6), and 17 (30%) continued to have seizures—only sporadically in 8 cases.

An analysis of factors influencing the risk for relapse after a first seizure would thus suggest that a variety of candidate factors exist, some of which have reached statistical significance in some studies and some in others. None of them is surprising, and none would sort out isolated seizures in any specific way. Rather, they seem to corroborate the conclusion of the previous nosologic considerations that across epileptic syndromes, isolated seizures characterize a group of patients with an increased relative risk for the development of seizures and, eventually, some specific syndrome.

The question arises whether this risk can be enhanced by any specific or nonspecific precipitating factors. The more important the influence of nonspecific precipitating factors, the closer we come to the concept of isolated seizures, and the more important the influence of specific precipitating factors, the closer we come to the concept of reflex epilepsies.

Provocation of Isolated Seizures

Provocation of the first seizure is an aspect not uniformly dealt with in the literature. Some studies exclude all provoked seizures, others some, and still others none. More important, there is no uniform definition of seizure provocation. Seizures occurring “in the context of uncertain precipitants such as sleep deprivation or ‘stress’ were considered unprovoked” by Hauser et al.[13]

Sander et al.[23] stated that “the circumstances of the… first seizure [in 252 cases] were explored but did not suggest any striking precipitating factors”—a surprising statement from an investigation that did not include any expert interviews and had therefore no means to look into this question seriously.

Others[16,17,25] consider lack of sleep as a potent and common seizure precipitant. Even if many of the provoking factors have not yet been discovered, some epileptologists could imagine that provocation of seizures is the rule.[6]

In addition to such nonspecific provocative or facilitating factors of seizures, the role of specific sensory precipitants has received little attention in the literature, although early identification of such risk factors for the development of reflex epilepsy is, of course, important.

In the most recent update of the follow-up study of Wolf,[26] on January 31, 2002, at least one facilitating or precipitating factor could be identified in 80 of 104 patients (Table 1), and this knowledge was used therapeutically (see later discussion). In only 10 patients (9.6%) was the seizure unprovoked beyond suspicion.

Table 1 Facilitating or precipitating factors of first seizure in life in 104 adolescents and adults

Nonspecific (facilitating)

Disturbances of the sleep–wake cycle	69	(66.3%)
Extraordinary physical or emotional stress	23	(22.0%)
Acute excessive intake of alcohol	11	(10.6%)
Fever, infectious disease	3	(2.9%)
Hunger, hypoglycemia	3	(2.9%)
Miscellaneous (migraine, hyperhydration)	3	(2.9%)
Specific (precipitating or reflex epileptic)		
Intermittent lights (environmental) and television	14	(13.5%)
Video games, praxis induction	4	(4.8%)
Other specific movement, complex visual)	2	(2.0%)
Questionable	14	(13.5%)
No probable or suspected factors	10	(9.6%)

Epilepsy Evolving From a First Seizure

Berg and Shinnar[2] tried to distinguish methodologically between “first-seizure” studies and “new-onset epilepsy” studies, but this distinction is not always as clear as these authors would have us believe. All epilepsy starts with a first seizure, and it is a mere convention when physicians start to call a condition *epilepsy*. It is surprising to see what little attention the question

of how epilepsy evolves from a first seizure has received from modern writers.

Not much progress seems to have been made since Gowers,[10] who, in his chapter on the course of epilepsy, differentiated three modes of onset. The first is:

> by minor seizures which occur alone for months and years before there are severe attacks…. The second mode of commencement is by severe fits recurring at short intervals, without any preceding *petit mal*…. The third mode of onset is with a single severe fit, and no other fit or sign of epilepsy for months and even years, when another attack occurs, after which they usually become frequent. Between the last two forms there is every gradation of varying interval between the first and second fit.

The situation addressed in this chapter clearly is closest to the third mode of onset.

Elwes et al.[7] pointed out the possible interaction of factors of "acceleration" and remission in the development of epilepsy, and according to Janz,[17] the development of epilepsy with grand mal on awaking is characterized by a shift from initial seizures with clearly exogenous precipitating factors to a much more spontaneous mode of seizure recurrence. Would it, then, be possible to prevent the development of at least this particular type of epilepsy by "isolating" the first one or few seizures by preventing further recurrences? This question is discussed later.

Diagnostic Evaluation

The first and immediate question to be answered after a first epileptic seizure is whether it was the symptom of an acute or undiscovered progressive illness. Alcoholic and other toxic/metabolic causes have to be ruled out. The diagnostic program, beyond history and physical investigation, normally comprises the usual tests for exclusion of an acute inflammatory disorder; the EEG, mainly in view of possible signs of acute conditions such as encephalitis or metabolic-toxic disorders, or indicators of existing epilepsy or such specific traits as photosensitivity; and magnetic resonance imaging (MRI), now the most reliable method for detecting any morphologic changes. Only if MRI is unavailable or in case of emergency would computerized tomography (CT) be performed.

Differential Diagnosis

Frequently, when a first seizure takes everybody by surprise, there is little reliable information about what really has happened. Often there is no witness at all, or only a fraction of the seizure has been seen, perhaps by a poor observer. Patients may give the most important clues when they remember a typical—epileptic or vasomotor—aura. Indirect indicators of an epileptic seizure are a sudden fall without an aura, lateral tongue biting and enuresis (infrequent!), a slow recovery with Todd's paresis, feelings of physical exhaustion or muscular aches, and periocular petechiae. It is better to leave the diagnosis unresolved when the obtainable information is poor than to jump to rapid conclusions and take incorrect therapeutic measures. When a seizure is unmistakably a generalized tonic–clonic seizure, it is extremely important to remember that a first convulsive seizure may be just the tip of an iceberg and that minor seizures may long have been present. Intense, pointed, knowledgeable, and sometimes repeated questioning is often required. Isolated epileptic auras and absences are the types that most frequently go unnoticed by patients and relatives, and the jerks of juvenile myoclonic epilepsy are the type that physicians most often forget to ask about. They are practically never volunteered by patients, who usually are unaware that they are a pathologic phenomenon.

The EEG may be an important indicator of established epilepsy. Seemingly subclinical groups of bilateral spikes-and-waves require intensive monitoring, including video registrations and cognitive tests (tapping, counting, response to an acoustic stimulus), to be sure that they do not represent actual seizures. It is quite amazing how many patients with a presumed first seizure actually have epilepsy!

Treatment and Outcome

After a first seizure, "secondary prevention" rather than "therapy" seems the appropriate term for the recommended interventions because no disease has yet developed. The controversial question of whether antiepileptic pharmacotherapy should be recommended after a first seizure is discussed in Chapter 122.

In the longitudinal investigation of Wolf,[26] the only systematic interventions were the detailed and close instructions given to patients regarding avoidance of precipitating factors that had been identified individually. These were given verbally to patients and, if at all possible, to relatives or friends. In addition, patients received a printed memorandum (Table 2) explaining the significance of a single epileptic seizure, the risk for development of epilepsy, and the necessity and principles of preventing recurrences.[25] The question of drugs was not treated dogmatically. Possible benefits and risks of available antiepileptic drugs were explained, as well as the necessity, if drugs were to be given, of regular intake for a period of at least 2 years. The patients were invited to make their own choice regarding drug treatment. However, if no precipitating factor for the seizure could be defined, drug treatment was recommended. Of the 104 patients in this study, 29

(27.9%) were already taking some antiepileptic drug at enrollment, and these all chose to continue taking drugs for variable periods of time.

Table 2 Items to be discussed with patient and handed out in print

Single seizures (*Gelegenheitsanfälle*) do not yet mean the diagnosis is epilepsy.
They indicate a high risk that epilepsy will develop unless preventive measures are taken.
Every additional seizure is one step in the development of epilepsy.
A special danger with seizures is the risk for accidents; even a single seizure means temporary unfitness for driving.
Drug treatment is not always necessary but may be advisable, depending on the individual circumstances.
Several antiepileptic drugs are available; they are usually well tolerated, but no effective drug is without possible untoward effects.
Even in the best case, drug treatment has to be pursued for several years, and regular intake every day is necessary; missed doses mean a risk for withdrawal seizures.
In most instances, first seizures do not occur “out of the blue sky” but are precipitated by factors such as disturbances of the sleep–wake cycle; recurrences can often be prevented by control of precipitating factors.
Rules to be followed concerning the use of alcohol.
Rules to be followed concerning sleep–wake habits on workdays and holidays. Night shifts must be discontinued, if applicable.
Rules to be followed concerning specific precipitating mechanisms (e.g., photosensitivity).

Table 3 Calculated and observed recurrences in first year of follow-up in patients whose treatment consisted of avoiding precipitating factors

Fifty-Two patients with 1 seizure expected rate of 37%	19.2
Thirty-five patients with >1 seizure expected rate of 47%	16.5
Total recurrences expected	35.7 (41%)
Total recurrences observed	15 (17%)

Eighty-seven patients were followed for ≥1 year; the expected rates of recurrence are according to Hart et al.[11]

As of January 31, 2002, 87 patients of this cohort had been followed for a minimum of 12 months and a maximum of 10 years. Because 35 of these patients had already had more than one seizure when they were enrolled, the expected number of recurrences in the first year of follow-up was 35.7 (41%), calculated from the respective risk rates reported by Hart et al.[11] for patients with one and with more than one seizure (Table 3). A slightly higher rate would have been expected from Hauser et al.,[13] who estimated the recurrence rate after more than one seizure to be greater than 65%. In contrast, the observed rate was 15, or 17%. Sixty-three of these patients had been followed for at least 2 years, and 6 cases of recurrence were observed in the second year. Forty-six patients were followed for at least 3 years, and another 5 recurrences were observed in the third year. The majority of recurrences were provoked by factors similar to those associated with the previous seizure, and this was true for all of the few recurrences after >3 years. Spontaneously recurrent seizures requiring treatment, that is, epilepsy, developed in 13 patients (15% of those followed for at least 1 year), 2 with a diagnosis of idiopathic generalized epilepsy, 1 with an idiopathic focal epilepsy (a remanifestation at age 33 years after a history of probable childhood rolandic epilepsy), 2 with generalized tonic–clonic seizures without clear focal or generalized signs, 1 with both generalized and focal signs, and 7 with symptomatic or cryptogenic focal epilepsy. Considering that 42 of these patients at onset presented with generalized signs and symptoms, 27 with focal ones, and 18 could not be assigned to either category, a relapse in the presence of focal features is more likely to indicate the establishment of epilepsy, whereas in the presence of generalized features it is more likely to represent another isolated seizure or *Gelegenheitsanfall.*

It can therefore be concluded that appropriate preventive measures taken after first seizures, including the avoidance of specific and nonspecific precipitating factors and, probably, administration of antiepileptic drugs in selected cases, can be highly successful in keeping seizures isolated and preventing the transition to epilepsy, especially in the patients who are at risk of developing an idiopathic generalized type of epilepsy.

Long-Term Prognosis

In the majority of cases, the question of whether a first seizure will remain isolated or mark the onset of epilepsy is resolved within 1 to 2 years. If by then epilepsy has not developed, a good prognosis can be expected. The data from existing studies do not indicate that epilepsy is likely to develop once this period of time has elapsed after one or a few isolated seizures. On the other hand, there are sufficient observations of late recurrences of isolated seizures to indicate that the increased risk for seizures is lifelong (see also Chapter 7).

Summary and Conclusions

A first seizure may signify the onset of epilepsy, but it may also remain an isolated event. Isolated seizures can be defined as solitary seizure events that may occur once in a lifetime or very rarely, at lengthy intervals. In the literature, the most common approach is to define the risk for recurrence after a first seizure, which is the inverse expression of the chance of its remaining isolated. However, most studies of first seizures analyze recurrence risk but not the development of epilepsy with ongoing seizures. Therefore, the epidemiology of isolated seizures cannot be definitely determined at present. Their relation to other epileptic syndromes has never been systematically investigated. Isolated seizures, apart from the febrile seizures of early childhood, may not be a separate syndrome, but rather they may represent, across syndromes, the group of patients having the most benign course and the lowest risk for seizures.

In studies of first seizures, by far the most common seizure type is generalized tonic–clonic. The most important and often rather difficult diagnostic task, besides exclusion of an acute symptomatic or progressive etiology, is to make sure that the patient does not already have epilepsy, hitherto manifested only as unrecognized minor seizures. Once this possibility is safely ruled out, the therapeutic aim is the secondary prevention of epilepsy in those patients who, by having had a first seizure, can be identified as individuals with a clearly increased risk for epilepsy.

The indication for antiepileptic drug treatment after an isolated seizure is controversial. An often neglected aspect is the precipitation of isolated seizures by specific or nonspecific factors. Control of these seems to be the most important therapeutic intervention, and it drastically reduces the risk for recurrence, especially in patients with a risk of idiopathic generalized epilepsy.

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Chapter 255

Familial Partial (Focal) Epilepsy With Variable Foci

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Introduction

Familial partial (focal) epilepsy with variable foci (FPEVF) is a distinct syndrome among the familial partial epilepsies, in that different clinical and electroencephalographic (EEG) features can be observed in different family members, suggesting that different epileptic foci may be determined by the same genetic mutation. On the other hand, the epileptic focus in any one individual remains the same.

Recently, FPEVF was included in the new diagnostic scheme for epileptic syndromes proposed by the International League Against Epilepsy (ILAE). Although it is displayed as a syndrome in development, this inclusion supports its uniqueness.[8]

Historical Perspectives

FPEVF is a unique syndrome first reported in 1998 in an Australian kindred by Scheffer et al,[28] and in the following year in two French–Canadian kindreds by Xiong et al.[36] Other more homogeneous familial partial epilepsy syndromes, including autosomal-dominant nocturnal frontal lobe epilepsy (ADNFLE),[27] familial temporal lobe epilepsy (FTLE),[1a,2] and autosomal-dominant partial epilepsy with auditory features (ADPEAF)[21] had been described (reviewed in Andermann et al.[1]). To date, only 10 pedigrees of FPEVF have been identified and reported in the literature.[3,4,25,28,35,36]

Definitions

Due to its uniqueness, FPEVF can only be defined on the basis of family rather than individual phenotypes. The occurrence of at least two different partial epilepsy syndromes in first- and second-degree relatives with no identifiable structural brain abnormality and segregating in a sufficient number of individuals in more than one generation is suggestive of FPEVF. Nevertheless, it has to be highlighted that, since the first report by Scheffer and colleagues,[28] many small families have been ascertained that could indeed have represented FPEVF, but both the diagnosis and the inheritance pattern could not be definitely confirmed.

Epidemiology

FPEVF kindreds have been identified in Australia, Canada, Spain, Holland and other European countries. Three of the 10 families are French-Canadian, originating from the region around Quebec City and sharing the same haplotype on chromosome (chr) 22q, suggesting a founder effect (Figs. 1 and 2).[3,35] FIGURE 2 demonstrates that a Spanish family has a completely different haplotyes than the French-Canadian families. Several small families have also been identified in the Eastern Townships region of Quebec, where linkage to the same region on chr22 is suggested, but these families have a different haplotype (P. Cossette, personal communication). Another Spanish family, which links to chr22, has also been described.[19] This family originates from a different region of Spain and has a different haplotype from the first Spanish family (J. Serratosa, personal communication).

Due to the variable seizure pattern among affected family members and the usually benign clinical outcome, FPEVF might often be underdiagnosed, as is the case for other familial partial epilepsy syndromes. It seems to be less frequent than other familial partial epilepsies, but, in the absence of genetic confirmation, it is impossible to estimate its frequency at present.

Etiology and Basic Mechanisms

In terms of etiology, it should again be emphasized that only 10 pedigrees have been reported in the literature.[3,4,25,28,35,36] All are compatible with an autosomal-dominant inheritance pattern with approximately 70% penetrance. Two different loci have been associated with FPEVF, the first with suggestive linkage on chr 2q,[28] and the second on chr 22q.[36] However, the gene(s) have not been cloned. Only one reported kindred had suggestive linkage to chr 2q,[28] but the family was not large enough to confirm linkage. Although linkage to chr 22q has now been confirmed in six families,[3,4,19,35,36] the gene has not been identified. Sequencing with mutation analysis has excluded the coding regions of >60 genes in the region on chr22q (A. Kerstin Lindblad-Toh, personal communication).

The mechanisms by which these molecular abnormalities can present as different types of idiopathic partial epilepsy within the same family are intriguing. Modifying genes and environmental factors should be further investigated.

Clinical Presentation

In FPEVF, affected family members may present with different types of partial epilepsy, which are, however, invariable within each subject. Frontal lobe seizures are the most frequent manifestation, but they have a different pattern in FPEVF as compared to that observed in ADNFLE (Table 1): The seizures are less frequent, clusters and auras are rare, and daytime seizures as well as secondarily generalized seizures are more frequent.[3] Age at seizure onset is variable; onset usually occurs in the first three decades, with two peaks at approximately 5 and 25 years of age.[35,36] Although temporal lobe seizures are also commonly found, centroparietal and occipital seizures are less frequent. There is also marked intrafamilial heterogeneity in seizure severity and outcome.

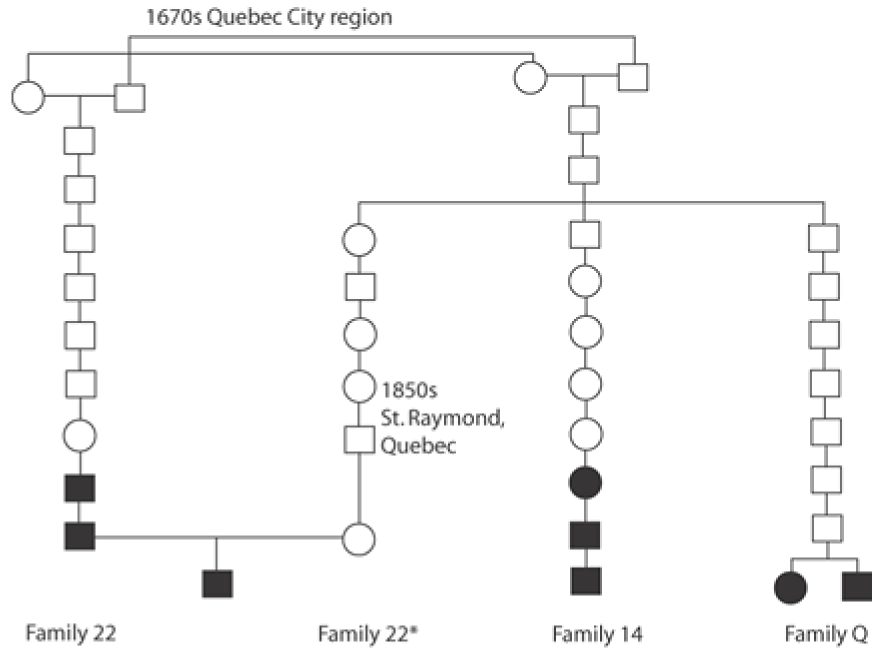
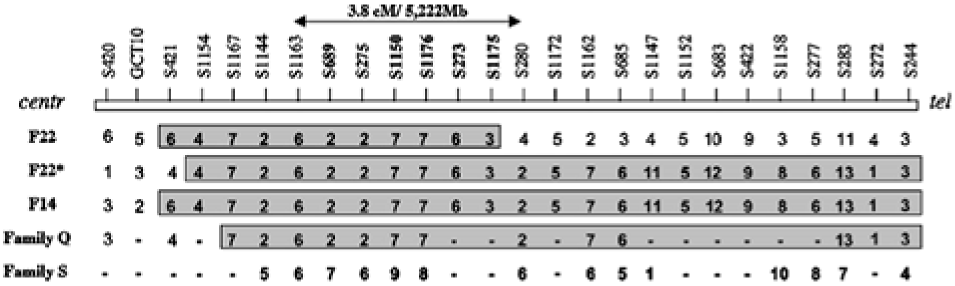


FIGURE 1. Genealogic representation of three French-Canadian families (F22, F22*, F14) demonstrating a founder effect.



	S420	GCT10	S421	S1154	S1167	S1144	S1163	S689	S275	S1150	S1176	S273	S1175	S280	S1172	S1162	S685	S1147	S1152	S683	S422	S1158	S277	S283	S272	S344
F22	6	5	6	4	7	2	6	2	2	7	7	6	3	4	5	2	3	4	5	10	9	3	5	11	4	3
F22*	1	3	4	4	7	2	6	2	2	7	7	6	3	2	5	7	6	11	5	12	9	8	6	13	1	3
F14	3	2	6	4	7	2	6	2	2	7	7	6	3	2	5	7	6	11	5	12	9	8	6	13	1	3
Family Q	3	-	4	-	7	2	6	2	2	7	7	-	-	2	-	7	6	-	-	-	-	-	-	13	1	3
Family S	-	-	-	-	-	5	6	7	6	9	8	-	-	6	-	6	5	1	-	-	-	10	8	7	-	4

FIGURE 2. Disease haplotypes in familial partial epilepsy with variable foci (FPEVF) families. The order of markers is based on the DNA sequence of chromosome 22. F22, F22*, F14, and family Q all represent haplotypes of French-Canadian families from the Quebec City region (same families as shown in Fig. 1). Shared haplotype portions are shaded. Note that the Spanish family (S) has a totally different haplotype. Markers within the candidate interval defined by recombination analysis are in bold. The 3.8-cM candidate region is marked by an arrow. Dashes indicate that the marker was not typed. (From Berkovic SF, Serratosa JM, Phillips HA, et al. Familial partial epilepsy with variable foci: clinical features and linkage to chromosome 22q12. *Epilepsia*. 2004;45(9):1054–1060, with permission.)

Diagnostic Evaluation

A detailed clinical evaluation with clear description of the seizures by the patient and close relatives is the first important requirement for diagnosis of FPEVF.

Electroencephalographic Findings

Electroencephalograms (EEGs) in patients with FPEVF may disclose temporal, frontal, and, less frequently, occipital and centroparietal foci. Although the variable foci are a landmark of this familial syndrome, the focus remains stable throughout life in each affected patient.

Neuroimaging and Other Laboratory Examinations

No structural magnetic resonance imaging abnormalities have been described in kindreds with FPEVF. In large families, studies to search for linkage to the chr 2 or chr 22 loci can be performed. In French-Canadian families with two or more individuals having different forms of focal epilepsy, origin from the same geographic region and/or the finding of the same haplotype as described in the original three families[36] is strongly suggestive of the diagnosis.

Differential Diagnosis

Sporadic benign partial epilepsies constitute the main differential diagnosis, but it is impossible at present to know whether these individuals may have mutations in the same gene or genes as patients with FPEVF. It should be noted that some sporadic patients could in fact be part of an FPEVF kindred in which the other family members are only mildly affected and sometimes unrecognized. In the case of sporadic French-Canadian patients, however, origin from the same region of Quebec and/or identification of the same haplotype on chr 22q as in the previously reported French-Canadian families[3,35,36] constitutes a high probability for a positive diagnosis of FPEVF. Even in smaller families, linkage to the two loci for FPEVF can be excluded but not confirmed.

Table 1 Comparison of clinical and genetic features in two forms of familial partial epilepsy with variable foci (FPEVF) and autosomal-dominant noctural frontal lobe epilepsy (ADNFLE)

	ADNFLE	FPEVF	
Genetics			
Inheritance	AD	AD	AD
Penetrance	~70%	~70%	~60%
Linkage (gene if known)	20q (*CHRNA4*) 1q (*CHRNB2*)	22q	?2q
Age at onset			
Mean	12yr	12 yr	13 yr
Median	8 yr	10 yr	10 yr
Range	2 mo–35 yr	1 mo–52 yr	9 mo–43 yr
Seizure features			
Frontal origin	Always	Often	Often
Temporal origin	No	Often	Often
Centroparietal origin	No	Rare	Rare
Occipital origin	No	Occasional	Rare

Nocturnal clusters	Almost always	Occasional	No
Seizures when awake	Very rare	Present in some	Common
Secondarily generalized	Rare	Common	Common
Interictal discharges			
Frequency	Rare	Occasional	Common
Localization	Frontal	Variable foci or poorly localized	Variable foci
Structural imaging	Normal	Normal	Normal
Intrafamily variation			
Seizure localization	No	Yes	Yes
Epilepsy severity	Yes	Yes	Yes

AD, autosomal dominant.
(From Berkovic SF, Serratosa JM, Phillips HA, et al. Familial partial epilepsy with variable foci: clinical features and linkage to chromosome 22q12. *Epilepsia*. 2004;45(9):1054–1060, with permission.)

For differential diagnosis of the two commonest clinical presentations FPEVF patients might have, genetic testing to exclude mutations in the known genes for ADNFLE and FTLE could also be helpful.

Among the genetically determined partial epilepsies, the most important differential diagnosis is ADNFLE because frontal lobe seizures are the most frequent type found in affected family members with FPEVF. However, frontal lobe seizures have a different pattern in FPEVF as compared to that observed in ADNFLE: The seizures are less frequent, clusters and auras are rare, and daytime seizures as well as secondarily generalized seizures are more frequent (Table 1).[3,36]

For ADNFLE, three loci and two genes have been identified: ENFL1 (chr 20q13.2), with four different mutations in the *CHRNA4* gene, coding for the alpha 4 subunit of the neuronal nicotinic acetylcholine receptor (nAchR)[12,17,23,30]; ENFL2 (chr 15q24, gene unknown)[24]; and the *CHRNB2* gene on the ENFL3 locus (chr 1q), coding for the beta 2 subunit of the AchR.[7,10,22] However, most families with ADNFLE do not map to any of these loci and do not have mutations in either the *CHRNA4* or the *CHRNB2* gene. Thus, in the absence of genetic confirmation, the differential diagnosis between FPEVF and ADNFLE should be based on the clinical and EEG characteristics of the frontal lobe seizures, as well as family members with seizure patterns that indicate foci outside the frontal regions in the former.

The familial temporal lobe epilepsies, both familial mesial temporal lobe epilepsy (FMTLE)[1a,2,5,6,14,16] and familial lateral temporal lobe epilepsy (FLTLE) or ADPEAF,[5,15,21] also should be considered in the differential diagnosis if one or more affected individuals in the family presents clinical and EEG features of temporal lobe epilepsy.[5] A confirmed extratemporal focus in a family member would exclude the diagnosis of FMTLE or FLTLE and suggest FPEVF. Genetic testing is only possible for FLTLE, in which mutations in the *LGI1* gene on chr 10q[13,20] have been found in about half of the families investigated.

In generalized epilepsy with febrile seizure plus (GEFS+), related to mutations in genes *SCN1A*,[9,18,32] *SCN2A*,[31] *SCN1B*,[33,34] and *GABRG2*,[11] different family members also present heterogeneous epilepsy phenotypes, as in FPEVF. Febrile seizures (FS) are the most common phenotype, followed by FS+, in which individuals have seizures with fever that may persist beyond the age of 6 years and/or may be associated with afebrile generalized tonic–clonic seizures.[26,29] Less frequent phenotypes seen in GEFS+ involve other generalized and partial seizure types, including MTLE.[5,16,26,29,33]

Treatment and Outcome

Treatment should be based on the patient's response to antiepileptic drugs (AEDs), and the rationale is similar to that in nonfamilial patients with partial epilepsies. Usually, patients with FPEVF are well controlled with small doses of the same AEDs indicated in other partial epilepsies, and the seizures may remit spontaneously.

Long-Term Prognosis

FPEVF has an overall benign clinical course, although some patients with refractory seizures have been reported. One of our refractory French-Canadian patients was homozygous for the haplotype, having received it from both parents,[35,36] although only one of the parents had epilepsy (1 and 2). Only one individual from another French-Canadian family underwent a temporal lobectomy, but this was not effective in controlling his seizures.[3,35] No neurologic disabilities are known in this syndrome.

Summary and Conclusions

FPEVF is a characteristic epilepsy syndrome with different types and localization of focal epilepsy within families, in the absence of any structural lesion.[28,36] Seizures and epileptic EEG abnormalities are consistent over time in each affected family member and may be frontal, temporal, or occipital, but they vary among family members, which may lead to the misdiagnosis of other familial partial epilepsy syndromes. Two different loci have been associated with FPEVF, an unconfirmed locus on chr 2q,[28] and a confirmed locus on chr 22q.[36] The gene(s) have not yet been identified.

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Chapter 256

Generalized (Genetic) Epilepsy with Febrile Seizures Plus

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Introduction

Generalized epilepsy with febrile seizures plus (GEFS$^+$) is a familial epilepsy syndrome characterized by heterogeneous epilepsy subsyndromes or phenotypes within families.[50] GEFS$^+$ has been key in advancing understanding of the genetic interrelationship between epilepsy and febrile seizures. The clinical concept of GEFS$^+$ led directly to the discovery of the role of sodium channels in epilepsy and has also highlighted the importance of γ-aminobutyric acid (GABA)$_A$ receptor subunits in causing seizure disorders.

The majority of families with GEFS$^+$ have generalized seizure types and generalized spike-wave activity on the electroencephalogram (EEG) in addition to febrile seizures.[7,9,37,45,50,54,55] Studies of families around the world have highlighted that focal seizures may also occur, leading some authors to question the nomenclature of "generalized" in generalized epilepsy with febrile seizures plus.[3,7,9,30,51,58] We suggest that the nomenclature be altered to "*genetic* epilepsy with febrile seizures plus" to reflect this observation. It must be emphasized that generalized epilepsies are considerably more frequent in GEFS$^+$ families.

Historical Perspectives

GEFS$^+$ was originally described in 1997 in a large Australian family comprising many affected individuals who showed a spectrum of phenotypic severity.[50] The phenotypes ranged from febrile seizures to mild generalized epilepsies to the severe end of the GEFS$^+$ spectrum, which included myoclonic-astatic epilepsy (MAE, or Doose syndrome; see Chapter 232). This work built on the extensive clinical genetic studies of Doose, where he concluded that MAE was a polygenic disorder.[17] Doose showed that family members of MAE probands most commonly had febrile and afebrile convulsions in early childhood. Evidence to support Doose's hypothesis that MAE has a genetic basis has been gained from the conclusive findings of mutations found in some GEFS$^+$ families, including family members with MAE.

Subsequently, the clinical spectrum of GEFS$^+$ was further elucidated in a study of nine families, the majority of whom were identified through probands with MAE.[54] The clinical genetics of GEFS$^+$ were extrapolated further with the study of probands of families with severe myoclonic epilepsy of infancy (SMEI, or Dravet syndrome; see Chapter 230) where family members with seizure disorders had GEFS$^+$ phenotypes.[53,60]

In 1998, the first gene for GEFS$^+$ was discovered in another large Australian family. This was a mutation of the sodium channel ß1 subunit gene, *SCN1B,*[64] and was the first time that sodium channel genes were implicated in epilepsy. In 2000, Escayg et al. reported mutations in *SCN1A*, the gene encoding the α1 subunit of the sodium channel, in GEFS$^+$ families,[21] a finding later confirmed by other groups.[3,20,30,63] The recognition that patients with SMEI, also known as Dravet syndrome, began with febrile seizures led Claes et al. to find that all seven of their patients with Dravet syndrome had *SCN1A* mutations.[13] This work led many others to replicate the findings, highlighting the importance of *SCN1A* in the severe epileptic encephalopathies[47] as well as in milder GEFS$^+$ phenotypes.

The $GABA_A$ receptor γ2 subunit gene, *GABRG2*, has also been implicated in $GEFS^+$ in several kindreds.[7,27,62] More recently, mutations in possible "susceptibility genes" have been reported in the $GABA_A$ receptor *δ* subunit gene *GABRD* and the calcium channel subunit gene *CACNA1H*; these observations require confirmation.[16,29]

Definitions

$GEFS^+$ is defined as a "familial epilepsy syndrome." This syndrome is diagnosed on the basis of more than one individual within a family with a history of seizures that fits into a specific subsyndrome or phenotype of the $GEFS^+$ spectrum (Fig. 1). It remains to be seen whether the phenotype of febrile seizures plus (see below) can be diagnosed in isolation and whether the same genes will be implicated. $GEFS^+$ is best conceptualized as a spectrum of phenotypes seen within a family ranging in severity from mild to severe seizure disorders.

Febrile seizures (FSs) are defined as convulsive seizures with fever above 38°C that occur between 3 months and 6 years of age at their broadest limits.[2]

The phenotype of febrile seizures plus (FS^+) refers to a number of different presentations. The most straightforward example is where febrile seizures continue past the defined upper limit of FS of 6 years. Rarely, seizures with fever may start before 3 months of age and would also be called FS^+. Additionally, afebrile convulsions may occur in the setting of a child who has febrile seizures. These afebrile seizures may occur during the typical age range of FS (i.e., from 3 months to 6 years), or alternatively, they may follow on from the febrile seizures after 6 years. The afebrile convulsions may also occur after a break of several years after the last febrile seizure.

FS or FS^+ may occur with afebrile generalized or partial seizures. For example, individuals may have FS/FS^+ and absence, myoclonic, or atonic seizures or a constellation of generalized seizure types.[50]

Partial seizures emanating from the temporal or frontal lobes may also occur with FS or FS^+.[3,7,30,52] Although temporal lobe epilepsy (TLE) may occur in the context of hippocampal sclerosis (HS), presumably secondary to FS/FS^+, TLE may also occur with normal neuroimaging and pathology and in the absence of preceding FS.[51]

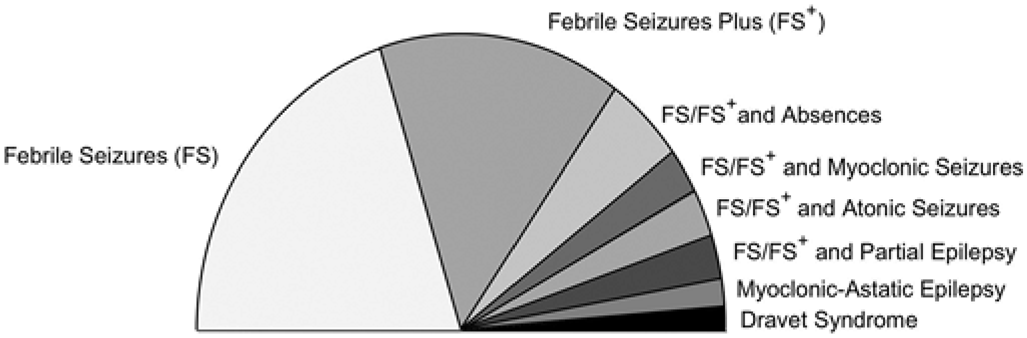

FIGURE 1. Generalized epilepsy with febrile seizures plus ($GEFS^+$) spectrum: The spectrum illustrates the phenotypic heterogeneity seen in $GEFS^+$ families ranging from benign phenotypes such as febrile seizures to severe epileptic encephalopathies such as Dravet syndrome.

At the severe end of the $GEFS^+$ spectrum are MAE and the epileptic encephalopathy Dravet syndrome.[18,26] It is unusual for a family to have multiple severely affected individuals with these syndromes, as most family members have more benign phenotypes.

Epidemiology

The idiopathic generalized epilepsies (IGEs) account for about 15% to 20% of all epilepsies.[28,32] The IGEs can be divided into two major subgroups: The classic IGE and GEFS$^+$. Families in which a number of individuals have IGE typically show phenotypic heterogeneity. However, GEFS$^+$ families show different phenotypic patterns compared with the classic IGE where childhood absence epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy, and "generalized tonic–clonic seizures alone" segregate within families.[1,42] Although overlap between the classic IGE and GEFS$^+$ phenotypes does occur within families,[41,54] this is not frequent, suggesting that these major subgroups arise due to distinct, but at times overlapping, groups of genes. No formal epidemiologic studies of GEFS$^+$ have been performed.

Etiology and Basic Mechanisms

GEFS$^+$ is a genetic disorder that has been recognized through study of large multiplex families where there is clinical genetic evidence of a gene of major effect. It sometimes is erroneously stated that GEFS$^+$ is an autosomal dominant syndrome based on the initial genetic discoveries. Whilst autosomal dominant families do occur, the majority of GEFS$^+$ families have clinical genetic evidence of complex inheritance. The rare dominant families led to the appreciation of the phenotypic variation seen in GEFS$^+$ families and the genetic relationship between these phenotypes. However, even in these large kindreds, there is evidence for "complex monogenic" inheritance, which would explain why one family member has a benign phenotype such as FS while another has MAE or Dravet syndrome. In these latter cases, presumably other genes, with or without environmental factors, contribute to produce a severe phenotype.

Mutations of a number of ion channel genes have been identified in GEFS$^+$ kindreds. These include sodium channel subunit and GABA$_A$ receptor subunit genes. The most frequently reported is *SCN1A,* which encodes the pore-forming α subunit of the sodium channel and comprises four transmembrane domains. Missense mutations spread throughout the gene have been associated with the full spectrum of GEFS$^+$ phenotypes including MAE, Dravet syndrome, partial seizures, FS, and FS$^+$ with other generalized seizure types.[3,20,21,30,63]

In contrast, *SCN1A* mutations usually arise de novo in Dravet syndrome and are truncation mutations in at least 50% of cases. Only about 5% of *SCN1A* mutations occur in patients with Dravet syndrome who have familial missense mutations where other family members have milder GEFS$^+$ phenotypes.[22,47,48] Recent reports of low levels of parental somatic and germline mosaicism explain cases of apparently de novo mutations in affected siblings; the parent may be unaffected or have a mild phenotype such as FS.[15,23]

Studies of the functional effects of *SCN1A* mutations yield variable results, with some mutations leading to loss of channel function while others suggest gain of function.[38,39,57] Indeed, different functional effects have been demonstrated using the same mutation in different expression systems.[4,39] In general, missense mutations may lead to gain of channel function, whereas truncation mutations in Dravet syndrome cause loss of function; however, this is by no means universal.[44] Computer simulation of the effects of several GEFS$^+$ mutations suggests a unifying functional endpoint, with each showing an increased propensity to fire repetitive action potentials and thus hyperexcitability.[56]

The first gene implicated in GEFS$^+$ was *SCN1B,* which encodes the β1 subunit of the sodium channel, the auxiliary subunit with a role in channel-gating kinetics and localization of the ion channel.[43] There are now four different mutations of *SCN1B* reported, three missense and one deletion mutation.[6,51,61,64] An analysis of six families with *SCN1B* mutations highlighted that the most common of the known mutations, C121W, is associated with TLE, including patients with and without HS.[51] Functional studies suggest that these mutations cause loss of function.[6,64] The C121W mutant causes subtle effects on channel function and subcellular distribution; initial studies suggested that the major effect was due to slowing of the sodium current inactivation time course.[64] More recent studies showed increased sodium channel availability at hyperpolarized membrane potentials and reduced sodium channel rundown during high-frequency channel activity, as well as altered protein–protein interactions critical for sodium channel localization.[43]

One small family with a GEFS$^+$-like phenotype has been reported with a missense mutation in the sodium channel gene *SCN2A*,[59] and there is one report of a more severe childhood encephalopathy in a child with a nonsense *SCN2A* mutation.[34] Missense mutations in *SCN2A* have been clearly associated with the benign familial neonatal-infantile seizure syndrome, which is unrelated to GEFS$^+$, and in our experience, SCN2A mutations have not been found in GEFS$^+$ families.[8]

The second group of genes associated with GEFS$^+$ encodes subunits of the GABA$_A$ receptor, the ligand-gated chloride channel, which mediates fast synaptic inhibition. The γ2 subunit gene, *GABRG2,* has been confirmed to play a role in GEFS$^+$ families, in some cases in association with classic childhood absence epilepsy.[7,27,41,62] The latter is an intriguing finding given the key role of GABA$_A$ receptors in corticothalamic pathways that mediate generalized spike-wave activity. Functional studies of *GABRG2* mutations suggest loss of function or abnormal trafficking, whereby the receptors do not reach the cell surface.[7,10,27,35,36,40]

Although GEFS$^+$ has been recognized through large dominant families, in most cases GEFS$^+$ follows complex

inheritance where a number of genes are presumed to be involved with or without an environmental contribution. Initial insights into susceptibility genes that contribute to complex inheritance are just developing through discovery of alleles in small kindreds where there is evidence of a functional effect of gene variants. It is not known how many such susceptibility genes are needed to produce a GEFS$^+$ phenotype, either for a mild picture such as FS or a severe one such as MAE.

Interestingly, different changes in the *GABRD* gene encoding the *δ* subunit of the GABA$_A$ receptor were found in small families with GEFS$^+$ and IGE.[16] These changes showed reduction of GABA current, suggesting increased excitability given the central role of GABA in inhibition. The *δ* subunit confers different characteristics to the heteropentameric GABA$_A$ receptor compared with the γ2 subunit. The *δ*-containing receptor has a perisynaptic or extrasynaptic localization and has a role in tonic inhibition, whereas the γ2-containing receptor is subsynaptic and mediates phasic inhibition.[16] The finding of *GABRD* changes in GEFS$^+$ and the classic IGE reinforces the concept that GABA$_A$ receptor subunits are involved in both major subgroups of IGE, whereas sodium channel subunits appear to be primarily involved with GEFS$^+$ phenotypes.

The genes currently known for GEFS$^+$ account for <20% of large families studied[44,63]; thus, there remain many genes of major effect to be discovered. Moreover, the number of genes contributing to complex inheritance is not known, nor is the effect size of each gene. Does a GEFS$^+$ phenotype require five or ten genes? Do the molecular permutations and combinations explain phenotypic differences? How do we distill the environmental effects that may underlie aspects of phenotypic heterogeneity? Current molecular and mechanistic insights into GEFS$^+$ highlight how much we are yet to understand regarding the neurobiology of this complex familial syndrome.

Clinical Presentation

Clinical evaluation in GEFS$^+$ involves a detailed history and examination with careful attention to the presence of a documented fever, rather than the presumption of a fever, when attacks occur. This may require sourcing the ambulance and emergency department notes to determine if a fever was present as families often equate fever with the observation that a child feels hot, yet the child may be afebrile when his or her temperature is formally taken.

The nature of the attacks needs to be determined ideally through an eyewitness account. Many attacks may mimic febrile seizures such as febrile delirium, febrile syncope, rigors, and breath-holding attacks. It is important to accurately determine that a convulsion occurred. Clues to unwitnessed convulsions should also be sought such as a bitten tongue or rare enuresis in a child not prone to enuresis.

Specific questioning regarding other seizure types is necessary as myoclonic seizures, atonic seizures, or staring spells may not be mentioned spontaneously; indeed, a child may just be considered to be a day-dreamer, “nervous,” or jumpy. Absence seizures may be less frequent than in typical childhood absence epilepsy, with rare but definite attacks lasting <30 seconds and occurring several times per year, rather than several times per day. Symptoms of focal seizures should also be sought with emphasis on temporal lobe auras and complex partial seizures.

When considering phenotypes at the severe end of the GEFS$^+$ spectrum, the electroclinical presentation of syndromes such as myoclonic-astatic epilepsy of Doose and Dravet syndromes is quite specific (see Chapters 232 and 230).

Family History

The key to a diagnosis of GEFS$^+$ is the family history as this is a *familial* epilepsy syndrome and requires at least two affected individuals in a family to have GEFS$^+$ phenotypes.

The family history should explore the presence of seizures in family members and consanguinity. One should always ask specifically about febrile seizures or febrile convulsions in addition to epilepsy, as families often do not think the former is of relevance. Frequently the matriarchs of the family hold the key to this knowledge and the family should be encouraged to speak with older family members and report back to the clinician at subsequent visits. Where there is controversy about attacks, the clinician may need to directly contact family members, with the permission of the proband's family, to understand the nature of the attacks in other branches of the family. This aids in diagnosing whether a specific individual's phenotype is likely to be part of the GEFS$^+$ spectrum. As epilepsy is common, it is not unusual for an individual with epilepsy in a GEFS$^+$ family to have an unrelated seizure disorder such as symptomatic epilepsy; this must be carefully considered when performing and interpreting genetic studies.[64]

Diagnostic Evaluation

Electroencephalographic Findings

Although no systematic EEG studies in GEFS$^+$ have been performed, the EEG is often normal in the milder phenotypes in GEFS$^+$. Irregular generalized spike wave can occur in FS$^+$ individuals and is likely to be an age-dependent abnormality. Similar changes were reported in a cohort of children with seizures with fever; it is possible this cohort included cases that we would now regard as FS$^+$.[5] With the more severe phenotypes, the EEG findings are as anticipated by their seizure types. For example, epileptiform discharges emanating from the region in which the seizures originate may occur in focal seizures. Similarly, fast generalized spike wave would be seen in MAE, and generalized spike wave and focal discharges in Dravet syndrome.[19,25]

Neuroimaging and Other Laboratory Examinations

Magnetic resonance imaging (MRI) of the brain is almost always normal in GEFS$^+$ phenotypes. Where ongoing focal seizures occur, MRI is indicated as HS has been found in certain cases, including some with known sodium channel mutations, and has typically followed a history of FS or FS$^+$.[31,51] Some patients with TLE and *SCN1B* mutations have been rendered seizure free following anterior temporal lobectomy,[51] but they still require comprehensive presurgical characterization as with other patients undergoing epilepsy surgery.

Mutational analysis of *SCN1A* is indicated in Dravet and related syndromes such as the borderline variant of Dravet syndrome. Mutations are found in about 70% to 80% of children with classic Dravet syndrome, and around 95% arise de novo. Very recently, exonic deletion of *SCN1A* has been shown to be a novel mechanism underlying Dravet syndrome, responsible for some patients negative by conventional mutational analysis.[46] In these children, the discovery of a mutation obviates the need for other potentially invasive investigations such as lumbar puncture and muscle and liver biopsy. It also supports more aggressive strategies to achieve seizure control to potentially improve developmental outcome.

Mutational analysis in GEFS$^+$ is more controversial. While mutations have been found in GEFS$^+$ in sodium channel and GABA$_A$ receptor subunits, these are uncommon and do not modify treatment approaches. Further research is needed, as with current knowledge the presence of a familial mutation does not inform the clinician regarding phenotype or outcome. Indeed, the finding of a mutation in a family does not explain the phenotypic heterogeneity that is the hallmark of $GEFS^+$. Deeper understanding of the complex genetics of $GEFS^+$ is necessary to explain why one family member has a benign versus a severe phenotype.

Differential Diagnosis

The differential diagnosis of $GEFS^+$ includes an understanding of the phenotypic variation that occurs in $GEFS^+$ families and those phenotypes that are not regarded as part of the spectrum. For example, malformations are not seen in $GEFS^+$ and are unlikely to be due to the same genetic mutations.

Diagnosis of FS requires an understanding of attacks that can be misdiagnosed as FS such as febrile delirium and febrile syncope. It cannot be emphasized sufficiently that a clear description of the event is necessary, ideally from an eyewitness. Moreover, distinction of different phenotypes within $GEFS^+$ may require additional effort, such as establishing whether a fever was actually present at the time of the attack.

There are many childhood epilepsy syndromes that are not characteristically seen in $GEFS^+$ families. These include benign childhood epilepsy with centrotemporal spikes and the benign occipital epilepsies of childhood. As they are relatively common disorders, they may occur in a $GEFS^+$ family just by chance; a mutation common to both disorders would need to be demonstrated to prove a molecular relationship.

Treatment and Outcome

Children with FS and FS^+ usually do not require medication. Recognition of FS^+ allows the clinician to defer antiepileptic therapy where infrequent brief convulsions with fever persist after 6 years in a developmentally normal child. If, on the other hand, frequent or afebrile seizures occur at any age, the clinician should consider antiepileptic therapy. There are no trials of the efficacy of treatment; however, our experience suggests that valproate is effective in FS^+ or where the child has FS/FS^+ with other generalized seizure types. If seizures are refractory to valproate monotherapy, lamotrigine should be considered. The usual principle of treating the child until he or she has been seizure free for 2 years should guide therapy. If convulsions are prolonged, benzodiazepines may be considered acutely. If convulsions occur frequently, interval use of benzodiazepines may be used when fever occurs prophylactically.[49]

For the phenotypes at the more severe end of the $GEFS^+$ spectrum, choice of antiepileptic drug should be based on the seizure types and syndromes. For example, seizures in Dravet syndrome may be exacerbated by lamotrigine,[24] whereas, seizure control is often better with clobazam and topiramate.[14] The experimental drug stiripentol was effective in one double-blinded study of Dravet syndrome suggestive of a syndrome-specific effect.[12]

Long-term Prognosis

The outcome is usually good, with most $GEFS^+$ phenotypes being benign. Seizures settle by adolescence in FS^+, although rare adult convulsions may occur under conditions of stress or sleep deprivation. Where other generalized or focal seizures occur in addition to febrile convulsions, the outcome is often, but not universally, good. For example, TLE may cease by midchildhood or, alternatively, prove refractory, warranting surgical consideration.[51]

MAE is known for its variable cognitive outcome from normal to severe intellectual disability, and this is clearly evident where MAE occurs in $GEFS^+$ families.[54] Seizure frequency improves with age although may not cease altogether. The majority of patients with Dravet syndrome have poor cognitive outcome, although rare individuals have normal intellect. Seizures typically continue into adult life and comprise nocturnal tonic–clonic seizures, although partial, absence, and myoclonic seizures may also occur.[33] These patients often have pyramidal signs and ataxia, and rarely manage to live independently as adults.

Genetic Counseling

Genetic counseling is an important aspect of management of patients and families with $GEFS^+$. The diagnosis of a GEFS$^+$ phenotype acknowledges the relationship with other familial seizure disorders but does not allow the clinician to predict prognosis. A finding of a mutation, if present, cannot be used alone to offer prognostic counseling because of the wide phenotypic and outcome variability; thus, prognostic counseling should be based on the clinical phenotype. Familial mutations are usually associated with a penetrance of 60% to 80%, so it is difficult to predict the outcome in carrier offspring.[37,54]

Genetic counseling is critical in Dravet syndrome, where *SCN1A* mutations are found in 70% to 80% of children with Dravet syndrome and 95% arise de novo. It is rare for families to have two children with severe phenotypes such as Dravet syndrome and the borderline variant of Dravet syndrome. This rare occurrence has recently been explained by the finding of parental germline and somatic mosaicism.[15,23]

A recent pertinent issue is the risk to offspring of adults with Dravet syndrome who have an essentially normal cognitive outcome. Such questions have only arisen since recognition that this may occur.[11,33] For example, in the case of a familial GEFS$^+$ mutation where the patient has Dravet syndrome, the outcome for offspring may be relatively good as the severe phenotype is likely to have a polygenic basis. On the other hand, where the adult has a de novo *SCN1A* mutation, it is more likely that offspring may have a similarly severe phenotype. Whether this is indeed the correct interpretation will depend on careful observation of such patient groups.

Summary and Conclusions

GEFS$^+$ is an important form of idiopathic epilepsy recognized throughout the world and forms one of the major subgroups of the IGEs. GEFS$^+$ is a clinical diagnosis that depends on recognition of the clinical syndrome in the familial context. The concept of a familial epilepsy syndrome aids in understanding the interrelationships of seizure disorders such as epilepsy and febrile seizures. Recognition of the phenotypes that fit into the GEFS$^+$ spectrum helps in diagnosis and may inform investigations, treatment selection, and prognostic and genetic counseling.

GEFS$^+$ led directly to the discovery of mutations of sodium channels and GABA receptors in epilepsy, further reinforcing the key role of ion channels in the pathophysiology of the epilepsies. The finding of *SCN1A* mutations in Dravet syndrome is of significant clinical importance and is the key investigation in these individuals. Nevertheless, the diagnosis of Dravet syndrome is based on electroclinical features and is not dependent on molecular testing. Equally, the finding of an *SCN1A* mutation does not necessarily mean that a child

has Dravet syndrome; this diagnosis depends on the clinical setting. New genetic counseling issues are arising with recent discoveries. GEFS$^+$ has opened many doors to understanding the genetics of the epilepsies but has also highlighted the large task ahead in solving this complex area.

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Chapter 257

Reflex Seizures

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Introduction

Reflex seizures are reliably triggered by some identifiable factor.[200] Reviews include Beaumanoir et al., Zifkin et al., and Wolf et al.[11,210,213] The identification of a patient with reflex epilepsy depends on the physician's awareness and on the observations of the patient and witnesses. The epileptogenic trigger must occur often enough in everyday life so that its relation to the resulting seizures can be suspected. If the trigger is ubiquitous, however, the seizures appear to occur by chance or with no obvious antecedent.

The study of reflex seizures has also furthered understanding of cortical organization in man and has implications for our understanding of how and why some apparently generalized seizures may begin.

Definition and History

Seizures induced by light stimulation were known from classical antiquity, and in the 20th century before the electroencephalographic (EEG) era.[166,189] The use of the term *reflex* has been controversial. Hall[85] first applied it to epilepsy in 1850. Arguing that no reflex arc is involved in reflex epilepsy, others proposed terms such as *sensory precipitation*[65,156] or *stimulus-sensitive epilepsies*.[42] Wieser noted that sensory precipitation epilepsy is a misnomer because some reflex seizures, for example, those triggered by cognition, are not precipitated by sensory stimuli.[197] In the 19th century, Brown-Séquard[27] noted that "certain parts of the central nervous system possess an elevated excitability so that any minimal stimulation may cause a crisis." Both Gowers[77] and Hughlings Jackson[95] described reflex seizures triggered by various causes including sudden noise, bright sunlight, movement, and tapping the head, which are still accepted reflex seizure types. In the 20th century, Adrian and Matthews[1] first documented the effect of light on the normal EEG. The stroboscope became available after World War II and rapidly led to further progress as flicker stimulation and its clinical and EEG effects could be easily studied. Important studies by Walter and Walter,[195] and later by groups led by Gastaut in France and by Bickford in America, yielded basic information about those EEG responses to stroboscopic flicker (intermittent photic stimulation [IPS]), which were reliably linked to seizures. Television screens and sunlight are the most common environmental triggers of visual-sensitive seizures; triggering by television broadcasts and video games has become notorious in recent years, leading to increased interest in reflex seizures.

Classification

Some earlier classifications and the publications on which they were based described "simple" and "complex" reflex epilepsies. Binnie[19] noted: "A distinction should be made between seizures evoked by simple, unstructured sensory stimuli and those precipitated by complex cognitive activities, often with an emotional component. The former are interpretable in terms of known physiological events (not strictly reflex processes) following a stimulus, whereas the latter may offer insights into the complex mechanisms underlying cognition." Wolf and Inoue[209] described reading epilepsy and praxis induction as complex reflex epilepsies.

Complex reflex epilepsies are characterized by seizures triggered by relatively elaborate stimuli whose specific pattern is the determining factor in seizure evocation. The attacks are precipitated by stimuli involving integration of higher cortical function, rather than by relatively simple sensory stimuli, and may be evoked by anticipation of the stimulus. Latency from stimulus onset to the clinical seizure or evoked abnormal paroxysmal EEG activity is typically longer than in simple reflex epilepsies, such as photosensitive epilepsy, in which the response to flicker is usually almost immediate. These properties, enunciated in the 1985 proposal for classification of epilepsies,[42] had been systematically described in the pioneering work of Forster.[61] To avoid confusion, it should also be emphasized that the term *complex*, as applied to reflex epilepsy, does not refer to a classification of the induced seizures. Although many varieties are not accepted as epileptic syndromes in the current international classification, partly because of the occurrence of spontaneous seizures in the same patients, they are described as "epilepsies characterized by specific modes of seizure precipitation."[43] Despite this, the induction of attacks in these patients is prominent and often quite stereotyped, and the Commission's 1989 definition of a syndrome—"a cluster of signs and symptoms customarily occurring together"—may be met. In others, for example, with "language-induced seizures," the clinical pattern may overlap other more clearly defined entities.

The current classification proposal[55] defines reflex epilepsy syndromes as those "…in which all epileptic seizures are precipitated by sensory stimuli. Reflex seizures that occur in focal and generalized epilepsy syndromes that are also associated with spontaneous seizures are listed as seizure types." Thus, this proposal also recognizes few reflex epilepsy syndromes:

- Idiopathic photosensitive occipital lobe epilepsy
- Other visual-sensitive epilepsies
- Startle epilepsy
- Primary reading epilepsy
- Musicogenic epilepsy

Reflex seizures are often classified according to the stimuli that trigger them rather than by the type of seizure that is triggered. The classification proposal also includes, under seizure types, a list of precipitating stimuli for reflex seizures. These stimuli are:

- Visual stimuli
- Flickering light—color to be specified when possible
- Patterns
- Other stimuli
- Thinking

- Praxis
- Reading
- Somatosensory
- Proprioceptive
- Eating
- Music
- Hot water
- Startle

It is important to note that reflex seizures are not distinguishable from spontaneous seizures except for the fact that they are triggered in some identifiable way; that is, a reflex generalized tonic–clonic seizure is clinically the same as one that occurs spontaneously.

Basic Mechanisms of Reflex Epilepsy

Animal Models

There are two types of animal model of reflex epilepsy. In the first, diffuse or regional cortical hyperexcitability is induced chemically or by the creation of a lesion. The second model involves naturally occurring reflex epilepsies or seizures induced by specific sensory stimulation in genetically predisposed animals.

The first approach has been used since 1929, when Clementi[38] induced convulsions with intermittent photic stimulation after applying strychnine to the canine visual cortex. Strychninization of auditory,[39] gustatory,[40] and olfactory cortex[140] also produced focal irritative lesions that could produce seizures with the appropriate afferent stimulus. EEG studies showed that the clinical seizures (chewing movements), which were induced by photic stimulation in rabbits with strychnine lesions of the visual cortex, resulted from rapid transmission of the epileptic discharge from the visual cortex to masticatory areas.[190] Paroxysmal discharge from visual cortex may also spread to frontorolandic areas during seizures.[63,66] The ictal EEG spread was thought to represent corticocortical conduction,[38,63] although later work with pentylenetetrazol also implicated thalamic relays[66] and demonstrated spread of the visual-evoked potential to the brainstem reticular formation.[64] Hunter and Ingvar[96] identified a subcortical pathway involving the thalamus and reticular system and an independent corticocortical system for radiation of visual-evoked responses to the frontal lobe. In cats and monkeys, the frontorolandic region was also shown to receive spreading-evoked paroxysmal activity from auditory and other stimuli.[18,28]

The second approach, the study of naturally occurring or induced reflex seizures in genetically susceptible animals, has been pursued in chickens with photosensitivity,[45,105] rodents susceptible to sound-induced convulsions,[35] the E1 mouse sensitive to vestibular stimulation,[179] and the Mongolian gerbil sensitive to a variety of stimuli.[126,127] Most of these are of limited relevance to human epilepsy but are of interest to the drug industry as rodent models are useful as relatively cheap and standardized methods for testing possible antiepileptic drugs.

The only species in which naturally occurring reflex seizures and EEG findings are similar to those in humans is the baboon Papio papio,[113] but the light-induced epileptic discharges in baboons occur in the frontorolandic area, rather than in the occipital lobe as they do in human photosensitive epilepsy.[112] EEG, visual-evoked potentials, intracerebral recording, and lesion and pharmacologic studies show that visual afferents are necessary to trigger frontorolandic light-induced epileptic discharges in these animals. Unlike human photosensitivity in which the occipital cortex is hyperexcitable, in the baboon the occipital lobe does not generate this abnormal activity, but sends corticocortical visual afferents to hyperexcitable frontal cortex, which is responsible for the epileptiform activity.[137] The interhemispheric synchronization of the light-induced paroxysmal EEG activity and seizures depends mainly on the corpus callosum and not on the brainstem. Brainstem reticular activation depends initially on frontal cortical mechanisms until a seizure is about to begin, at which point the cortex can no longer control reticular activation. The genetically determined hyperexcitability may be related to cortical biochemical abnormalities, involving regulation of extracellular calcium concentration,[51,161] or an imbalance between excitatory and inhibitory neurotransmitter amino acids[124] similar to those described in feline generalized penicillin epilepsy and in human epilepsy.[74]

Visual-sensitive Epilepsies and Seizures

Reflex seizures and epilepsies sensitive to visual stimulation, especially flashing light, are the commonest and longest known, and will be described first. Visual sensitivity has been defined as “having seizures evoked by the physical characteristics of a visual stimulus in daily life or by IPS.”[111] Recognition of seizures induced by flashing light predates the EEG. Before clinical EEG, seizures were reported with environmental flicker or with sudden changes in light intensity. Gastaut et al. reported an early series of patients investigated with stroboscopic IPS during EEG recording.[68] Historically, photosensitivity has meant an abnormal response to light and since the development of the stroboscope, an abnormal response to flicker stimulation during EEG recording is generally called photosensitivity. This flicker sensitivity is common to different types of seizures induced by visual stimuli, but subtypes in which patients are reproducibly sensitive to more complex visual stimuli can be distinguished among patients, who are almost always sensitive to intermittent photic stimulation at some time. Pure photosensitive epilepsy, in which seizures occur only with environmental light stimulation, is the most common reflex epilepsy. The induction of focal occipital lobe seizures by the same types of visual stimuli is more common than previously thought. Television and sunlight are the most common environmental triggers of visual-sensitive seizures; triggering by television broadcasts and video games has become notorious in recent years. Visual-sensitive epilepsy is included as a reflex epilepsy syndrome in the most recent proposed classification of epilepsy syndromes.[55]

Several types of EEG response to flicker have been described. An epileptiform EEG response to IPS is a photoparoxysmal response (PPR). These may be restricted to the occipital area or be apparently generalized. Different responses may occur in the same patient depending on the stimulator used, the stimulation protocol, age, and medication effects. In untreated subjects, only generalized paroxysmal epileptiform discharges in response to IPS (spikes, polyspikes, and spike-and-wave complexes) are clearly linked to epilepsy: Apart from those with idiopathic photosensitive occipital epilepsy (IPOE), less is known about patients with clinically evident visually triggered seizures but who have only focal occipital PPRs. These responses are most common with stimulation from 10 to 30 flashes per second.

Epidemiology of Visual Sensitivity

Most studies are retrospective and target specific patient groups. Following seizures triggered by the video game Mario World in 1992, Quirk et al.[163] prospectively studied the

incidence of visually-induced seizures and PPRs in newly diagnosed epilepsy patients in the United Kingdom. For all ages, a conservative estimate was that the incidence of epilepsy with PPRs was 1.1 per 100,000, about 2% of all new cases of epilepsy. Incidence rose to 5.7 per 100,000, or 10% of all new cases, in patients from 7 to 19 years old.

PPRs and clinical photosensitivity show marked age dependency. They are very rare before age 2 years. In Dravet syndrome (severe myoclonic epilepsy of infancy), responses may be abnormal before age 2 but without evident seizures, and Oguni et al.[148] reported a subgroup in whom myoclonic seizures and atypical absences could be triggered by constant illumination, rather than by IPS, depending on the brightness of the light. This sensitivity tended to disappear before age 5 years. Only one case has been reported of an infant aged 15 months who experienced about 20 seizures in 3 weeks when brought into a bathroom with bright white walls and shiny bright chromed plumbing; he showed the following symptoms: Motion arrest, deviation of the head and eyes to the left, jerks of the eyelids, looking afraid, and right occipital seizure on the EEG. He had no further seizures until he was 11, when occipital seizures recurred.[172]

Both PPRs and visually induced seizures show a clear female preponderance of about 60% of cases, and photosensitivity appears to peak at around puberty. Whether photosensitivity declines with age in patients is debated; several report that it declines in the third decade, while others found no decline with age.[111] PPRs occur in normal subjects, especially in children up to 16 years old, in whom a prevalence of 1.3% has been reported, and this photosensitivity declines with age. Studies in young adult male aircrew candidates in several countries yielded PPR rates of 0.5% to 0.7%.

Genetics of Photoparoxysmal Responses

Genetic studies of photosensitivity have been hampered by differences in stimulation methods and in classification of the EEG responses. The reduction of sensitivity with age, especially in asymptomatic children, also makes transgenerational studies impossible or difficult to interpret. Monozygotic twins have shown almost 100% concordance for PPRs. Waltz and Stephani reported that photosensitivity is significantly more common in 5- to 10-year-old siblings of proband offspring of a photosensitive parent (50%) than in siblings of photosensitive children without parental photosensitivity (14%). The highest risk of seizure (33%) was in photosensitive siblings of a proband with parental photosensitivity, and the lowest (4%) in nonphotosensitive siblings of probands without parental photosensitivity.[196]

A single gene for photosensitivity has not yet been identified. Three different loci have been found, one on each of chromosomes 2 (in a single family), 7q32, and 16p13, and the last two in families with prominent myoclonic epilepsy.[158] Photosensitivity occurring in some patients with identifiable epileptic syndromes (e.g., juvenile myoclonic epilepsy [JME]) is inherited separately from the other epileptic disorder.

Clinical Aspects of Visual Sensitivity

The proposed classification recognizes idiopathic photosensitive occipital lobe epilepsy and “other” visual-sensitive epilepsies as reflex epilepsy syndromes, requiring that all seizures be triggered. Other cases are classified as seizure types, which are more common, and it is not specified whether these represent generalized or focal epilepsy.

Pure Photosensitive Epilepsy

Pure photosensitive epilepsy is characterized by seizures exclusively provoked by flicker. These patients do not have spontaneous seizures. Forty percent of patients with seizures and photosensitivity studied by Jeavons and Harding, Binnie et al., and Kasteleijn-Nolst Trenité et al. are reported to fall into this group. In one study, 84% of patients had seizures reported as generalized tonic–clonic, whereas absences occurred in only 6%, partial motor seizures (possibly asymmetric myoclonus in some cases or unrecognized idiopathic photosensitive occipital epilepsy) in 2.5%, and myoclonic seizures in 1.5% of patients.[104] However, these proportions are subject to bias; patients will come to medical attention after a convulsion in front of the television but may have already had many subtle unobserved reflex seizures with brief myoclonic or absence-like events. Patient self-reporting of these triggered seizures can be extremely inaccurate: Over half of known photosensitive epilepsy patients questioned immediately after stimulation denied having had brief but clear-cut seizures induced by IPS and documented by video-EEG monitoring.[110] In laboratory studies with video monitoring, most events are myoclonic jerks[110] and patients commonly report eye pain and feelings of eyestrain. The developmental and neurologic examinations are normal.

Idiopathic Photosensitive Occipital Epilepsy

IPOE[84] is recognized as a reflex epilepsy syndrome in the proposed diagnostic scheme. IPOE is a relatively benign, age-related syndrome without spontaneous seizures. Seizures evoked by visual stimuli were formerly thought to be almost exclusively generalized despite the clear occipital localization of visual function, though asymmetric myoclonus could occur. Induction of partial seizures by visual stimulation, including typical complex partial seizures, is now well recognized.[92] Intermittent photic stimulation can induce clear-cut partial seizures originating in the occipital lobe.[81,92] As in more typical photosensitive subjects, environmental triggers include television and video games. The symptoms may remain localized to the occipital area for several minutes even after the stimulus has ceased: Visual blurring, blindness, or elementary visual hallucinations may occur.[81,169,188] The clinical seizure pattern depends on the pattern of spread. The initial reflex visual symptoms may be followed by versive movements and motor seizures. Myoclonus is not typical, but migraine-like symptoms of throbbing headache, nausea, and, sometimes, vomiting are common and can lead to delayed or incorrect diagnosis.

Photosensitive Epilepsy with Spontaneous Seizures

The remaining 60% of patients with epilepsy and photosensitivity also have spontaneous seizures, and photosensitivity gives rise to attacks precipitated by environmental visual stimulation in 33% of the total. A further 7% have demonstrable seizures during IPS but report no visually precipitated attacks in everyday life. Thus, 80% of photosensitive people with epilepsy have some form of visually precipitated seizures. These are often associated with idiopathic generalized epilepsies and especially with juvenile myoclonic epilepsy, in which 30% to 48% are photosensitive, and childhood absence epilepsy, in which 18% were reportedly photosensitive.[125,208] Typical absence seizures may be triggered by IPS: These are rare and may be resistant to treatment.[10]

Photosensitivity in Other Epileptic Disorders

Photosensitivity may be found in several epileptic disorders. It is rare in symptomatic occipital epilepsies but has been described with triggered focal occipital seizures in patients with

occipital calcifications and celiac disease.[4] It also may occur with symptomatic generalized epilepsies such as severe myoclonic epilepsy of infancy (SMEI, Dravet syndrome); with the progressive myoclonus epilepsies such as Lafora disease, Unverricht-Lundborg disease, Kufs disease; or with the neuronal ceroid lipofuscinoses, in which photosensitivity at low flash frequencies such as 1/s is typical. These syndromes are associated with photic cortical reflex myoclonus, and the patients also have clear-cut action myoclonus.

Pattern-sensitive Seizures

Pattern-sensitive epilepsy consists of seizures triggered by viewing patterns, typically stripes. The seizures are generalized convulsions, absences, or brief myoclonic attacks provoked by viewing patterns such as patterned video screen content, escalator steps, striped wallpaper, or patterned clothing.[22] Television is now the most common precipitant, reported in 41% of 73 patients.[165]

Initially described in a single child by Bickford, it was considered an interesting rarity. Bickford et al.[17] reported a low rate of EEG sensitivity to stationary pattern of 0.25% in 40,000 patients. Chatrian showed that the nature of the pattern affected its epileptogenicity, and the classic studies of Wilkins et al.[22] further described the characteristics of epileptogenic patterns. With stimuli designed for maximum effect, pattern sensitivity is more common than previously reported, found in 17% to 54% of photosensitive subjects with static patterns.[21,109,144,160] Patterns oscillating orthogonal to their line orientation are more provocative and elicit sensitivity in 60% to 70%.[21] Clinical pattern sensitivity is much less common, found in about 2% of photosensitive subjects by Jeavons and Harding[104] and in 6% by Kasteleijn-Nolst Trenité.[109] Some subjects sensitive to pattern are not sensitive to flicker.[90] Radhakrishnan et al.[165] noted this in 11% of 73 subjects, but their first EEGs were performed in 1950 and this may be partly related to different methods of IPS and age-related changes in photosensitivity.

Interictal epileptiform EEG activity has been reported in 84%. Two thirds had generalized epileptiform activity with pattern stimulation, and in one third, this was confined to posterior head regions.[165] These authors also found that 14 of 73 (19%) had JME, three had progressive myoclonus epilepsy, and one had SMEI.

Other

Some photosensitive patients are sensitive to eye closure alone. Reflex absences or brief myoclonic attacks, and visual disturbances (“scotosensitive seizures”) can occur with eye closure or in darkness in patients not sensitive to intermittent photic stimulation and are thought to be precipitated in some by the abolition of central vision and fixation.[151,152] Others may not require total darkness or abolition of fixation. However, most subjects with the florid posterior epileptiform EEG activity abolished by fixation, and typical of the Panayiotopoulos and Gastaut types of idiopathic childhood occipital epilepsy, do not have reflex seizures.

Eyelid myoclonia with absences, described by Jeavons[103] and reviewed by Gobbi,[75] is characterized by eyelid jerks with eye closure in a photosensitive patient, with bilateral fast spike-and-wave EEG activity. The seizures can occur even in darkness. Some have no spontaneous seizures. Often, only the EEG change can be seen. Not all patients have absences and not all are photosensitive. It is not yet clear whether this forms a discrete clinical entity: The trigger mechanisms are complex and not well defined, and many may have another epileptic disorder such as JME. Harding and Jeavons[90] suggested that most such cases were examples of self-induction, but a detailed definition of a syndrome of eyelid myoclonia with absences has been suggested by Panayiotopoulos.[153]

Seizures reportedly triggered by eye movement[183,191] are a heterogeneous group. Some may represent scotosensitivity, and others may be cases of self-induction. Others triggered by conjugate eye movement may depend on proprioceptive input, and anterior, occipital, and parietal EEG discharges have been reported with these.

Self-induction of Visual-sensitive Seizures

Patients with all types of visually induced seizures may induce attacks with visual stimulation and may be compulsively drawn to sources of flicker or pattern stimulation such as television screens. Patients sensitive to eye closure may use a compulsively repeated eye rolling and eyelid flicker movement to self-stimulate.[47] Monitoring has shown that the stimulatory behaviors indeed trigger the seizures rather than being manifestations of the seizures. Intensely pleasurable sensations have been reported with these, and some patients induce seizures to relieve stress or to gain attention.[188] Monitoring indicates that 24% to 30%[21] engage in self-induction when placed in a well-lit environment, particularly if stressed. Diagnostic features are:[19]

1. The eye movement precedes the epileptiform EEG discharge.
2. The oculographic artifact is larger and slower than that accompanying normal spontaneous eye closure and often shows a superimposed ocular tremor at about 6 Hz.
3. The maneuver is carried out less frequently in darkness, where it fails to produce epileptiform discharge.
4. The behavior is increased by stress.
5. Patients display guilt when the phenomenon is discussed.
6. Patients admit to carrying out the maneuver, variously describing it as voluntary or compulsive.
7. A pleasant sensation is often reported; this may have a sexual component leading to orgasm in some subjects.
8. There may be a history of seizures induced by hand waving in the past, or patients may use hand waving in combination with slow eye closure to enhance or prolong the discharge, as documented on film by Ames.[5]

These can be distinguished by EEG monitoring from nonepileptic paroxysmal eyelid movements that may occur in children and adults with generalized photosensitive epilepsy. These may be mistaken for absence seizures. There is often a family history of eyelid movements.[29]

Seizures Triggered by Television and Video Displays

Reflex seizures triggered by television, computer screens, and video games have become notorious. The Pocket Monsters cartoon episode that triggered a nationwide outbreak of photosensitive seizures in Japan is a well-known example,[87,102] but broadcasting of dangerous screen content had already led to outbreaks of photosensitive seizures, and guidelines to prevent the broadcasting of screen content likely to trigger seizures were already in place in the United Kingdom. These have become more widespread since the Pocket Monsters episode. Many of these events represent pure photosensitive epilepsy with or without pattern sensitivity. Some have occurred in subjects not previously known to have epilepsy, and others have occurred in known photosensitive patients. Some were likely focal occipital visual reflex seizures with autonomic manifestations (see IPOE above). Ferrie et al.[59] found that 29% of a group of subjects with video game–induced seizures had photosensitive partial seizures. In patients with seizures recurring after an initial Pocket Monster seizure, juvenile myoclonic epilepsy was the most common diagnosis in those not known to have epilepsy before the triggered event, while those with a history of epilepsy and recurrent seizures often had frontal lobe epilepsy.[149]

Guidelines in Japan and the United Kingdom now prohibit such program material.[91] These have been shown to successfully control potentially harmful TV screen content.[186] Special electronic filter devices are also effective in reducing PPRs induced by television.[185] Seizures associated with video screens may also have occurred by chance or in nonphotosensitive individuals in relation to other reflex seizure triggers, such as thinking, with or without manipulation of objects (action programming or praxis, see below) during computer use or game play.

Mechanisms of Visual-sensitive Seizures

Several approaches have been taken to studying human photosensitivity and seizures induced by visual stimuli. Visual stimulation resembling reported environmental stimuli such as video games can be modified and responses studied. Properties of elementary and subthreshold visual stimuli can be manipulated to enable inferences to be drawn about physiologic trigger mechanisms in both EEG and evoked potential studies and more recently in magnetic resonance and magnetoencephalography studies.

Television-induced seizures and others triggered by video displays can be understood in relation to the properties of video screens and to the images on the screen. Visual reflex seizures and the characteristics of the effective triggers have been recently reviewed.[214] Flicker rate, pattern, luminous intensity, size, location, and duration of the stimulus need to be considered. A television screen produces flicker at the alternating current (AC) frequency, effectively generating IPS at 60 Hz in North America and 50 Hz in Europe. Photosensitivity is more common at the lower frequency, with nearly 50% of patients sensitive to 50-Hz intermittent photic stimulation,[104] and television sensitivity has indeed been a greater problem in Europe than in North America. Television-induced seizures, however, are not only related to AC frequency flicker. Wilkins et al. studied patients who were not sensitive to this flicker but who responded to the vibrating pattern of interleaved lines at half the AC frequency (25 Hz in Europe and 30 Hz in North America) to which about 75% of photosensitive subjects are sensitive and which can be discerned only close to the screen.[205] Special 100-Hz television screens, marketed in Europe, reduce the risk of television-induced seizures.[169] Color is important even without luminance changes; photoparoxysmal EEG responses can be elicited in sensitive subjects by non–color-opponent stimuli even if they are isoluminant.[88] Sensitivity is greater with red stimulation at wavelengths greater than 700 nm, and red stimulation was important in the Japanese cartoon incident.[87] Red-cyan flicker, even when isoluminant, is reportedly even more provocative of epileptic discharge.[180] Thus, seizures can be triggered even at greater distances and by 100-Hz TV sets and modern noninterlaced screens without intrinsic flicker. Flashing or patterned screen content has been implicated in these. Although the 50-Hz television screen is an important determinant of screen sensitivity and 100-Hz screens reduce the ability of the screen to trigger seizures, it is important to note that all systems are equally dangerous if dangerous screen content is broadcast.

Most patients sensitive to IPS can be shown to be sensitive to pattern, and studies on pattern-sensitive patients have enabled several inferences to be drawn, based also on animal studies of single unit responses. These have recently been reviewed by Wilkins et al.[203] and can be summarized as follows:

The seizure trigger involves cortical cells. A paroxysmal EEG response occurs in the majority of patients with a history of photosensitive seizures when they are exposed to IPS. In about 30% of patients, bright, large, continuously illuminated patterns of high-contrast stripes evoke a similar, though usually less pronounced, response. The response is probabilistic and depends on the spatial and temporal properties of the visual stimuli that evoke it. Studies of length of line contour of effective patterns, pattern orientation, and the effect of binocularity indicate a cortical trigger. Further evidence comes from studies of effects of spatial frequency and of pattern motion: These suggest that the trigger involves neurons whose spatial tuning is independent of position in the visual field, and the first point at which this independence occurs is at the level of the complex cell in the visual cortex. EEG studies using patterns presented in only part of the visual field, such as hemifield stimulation, are also consistent with an occipital cortical event, and also indicate that seizure onset involves one cerebral hemisphere or both hemispheres independently. Often the response is generalized, involving many brain areas other than the visual cortex, but even in these circumstances the trigger may be cortical and unilateral because when the response is suppressed with sodium valproate, focal occipital activity can remain.[48] All these are consistent with an epileptic discharge triggered in the visual cortex, which sometimes remains within the visual cortex and sometimes spreads to involve other areas.

The triggering mechanism requires the physiologic activation of a critical area of cortical tissue. Any region of the visual cortex can evoke an epileptiform discharge, provided a sufficiently large area is stimulated. Wilkins[201] noted that the probability of a response to patterns differs in each patient, but in such a way as to indicate that each patient's threshold can be expressed in terms of the area of cortex necessary to trigger a discharge.

Synchronization of the physiologic activation is necessary for epileptogenesis. Patterns that vibrate back and forth, orthogonal to their line orientation, become more epileptogenic, but a pattern that drifts steadily in the same direction ceases to be epileptogenic. This difference suggests an important role for the synchronization of large neuronal aggregates in the induction of a discharge. When the pattern alternately changes direction, the neurons sensitive to one direction of motion should fire, followed by a period during which cells sensitive to the opposite direction of motion should fire. The very marked difference in the epileptogenic properties of drifting and vibrating patterns suggests that the synchronization that occurs with a vibrating or phase-reversing pattern is critical at the initiation of the epileptic discharge.

The trigger involves the magnocellular pathways, but the resulting discharge may be more diffuse and involve both magnocellular and parvocellular divisions. Several characteristics of epileptogenic patterns suggest this involvement. The stripes differ in brightness rather than color, and are more epileptogenic if they move in certain ways and fuse in binocular vision. They have a rather low spatial frequency. Magnocellular neurons do not generally code for color, are directionally coded, and are tuned for binocular disparity. They have a lower spatial resolution and a higher temporal resolution than parvocellular neurons. The magnocellular system is thought to be part of the “dorsal stream,” and in pattern-sensitive patients, the isolated spikes in response to a pattern tend to be most marked over parietal electrodes. The cortical hyperexcitability need not be confined to this system but the discharge may start there. Harding and Fylan[88] also provide evidence for the participation of the parvocellular system.

The visual system in visual-sensitive epilepsies is normal with respect to acuity, stereopsis, and color vision. However, evidence of visual cortical abnormality is found in pattern reversal visual-evoked potentials; these show a lack of luminance contrast gain control at low spatial frequencies in subjects with IPOE.[159] This is seen only at temporal frequencies lower than those that are typically epileptogenic. Functional magnetic resonance imaging (fMRI)[94] and magnetoencephalography (MEG)[154,168] also suggest regional occipital cortical hyperexcitability, regional activations, and abnormal neuronal synchronization in photosensitive subjects. MEG in photosensitive subjects showed enhanced phase synchrony in the gamma band (30 to 120 Hz) preceding those photic stimulation trials that evolve into PPR compared with trials not followed by PPR and compared with phase synchrony in nonphotosensitive controls, possibly reflecting a pathologic synchronization of gamma oscillation that mediates the transition to PPR.[154]

An important feature of most visual-sensitive seizures and of pattern sensitivity in particular is that a stimulus that activates a well-defined cortical area subserving a specific function will produce seizures usually thought of as generalized and often occurring within a typical generalized epilepsy syndrome such as JME. This paradigm will be encountered with complex reflex seizures, discussed below, and appears to operate in seizures induced by thinking and praxis and in many cases of reading epilepsy. Studies of reflex seizures suggest that cognitive triggering occurs mostly with idiopathic generalized epilepsy (IGE). These and other observations in both reflex and spontaneous epileptogenesis[20,58] suggest that the postulated cortical hyperexcitability in IGE is not necessarily uniform: Specific activities can activate specific cortical systems and produce focal discharges or partial seizures, which may generalize. This does not invalidate a diagnosis of underlying generalized epilepsy but shows that the biologic substrate of generalized epilepsy can be complicated.

Treatment of Visual-Sensitive Seizures

All reflex seizures may be treated by avoiding the triggering stimulus. This is not always practical or possible, but modification of the stimulus may reduce or eliminate its epileptogenicity. Increasing the distance from the television set, watching a small screen in a well-lighted room, using a remote control so that the set need not be approached, and monocular viewing or the use of polarized eyeglasses to block one eye should provide protection.[204] Colored eyeglasses may be useful in selected cases.[32,202] Prevention of seizures induced by video screens is effective but requires adherence to guidelines that reduce the likelihood of a visually triggered seizure or the use of special electronic filter devices, which is less practical as these would be required on all screens. A recent draft consensus developed by the Epilepsy Foundation of America[91] noted:

> "A pattern with the potential for provoking seizures contains clearly discernible stripes, numbering more than five light–dark pairs of stripes in any orientation. When the light–dark stripes of any pattern collectively subtend at the eye from the minimal-expected viewing distance a solid angle of >0.006 steradians, the luminance of the lightest stripe is >50 cd/m2, and the pattern is presented for ≥0.5 s, then the pattern should display no more than five light–dark pairs of stripes, if the stripes change direction, oscillate, flash, or reverse in contrast; if the pattern is unchanging or smoothly drifting in one direction, no more than eight stripes."

Drug treatment is needed if preventive measures are impractical or unsuccessful, if photosensitivity is severe, or if spontaneous attacks occur. The drug of choice is valproate, which in one study[89] abolished photosensitivity in 54% of patients and markedly reduced it in a further 24%. Lamotrigine, topiramate, ethosuximide, benzodiazepines such as clobazam,[34] and levetiracetam[111] also may be useful. Quesney et al.[162] proposed a dopaminergic mechanism in human epileptic photosensitivity based on the transient abolition of photosensitivity with apomorphine, and bromocriptine and parenteral L-dopa have been reported to alleviate photosensitivity.[37,139] Appropriate treatment for photosensitivity is generally successful and noncompliance or self-induction should be considered if it is not.

Startle Epilepsy

Startle epilepsy is characterized by seizures triggered by unexpected sensory stimuli, usually auditory. Startle epilepsy was described in the 1989 International Classification of Epilepsies and Epileptic Syndromes as a symptomatic epilepsy in which seizures occur with a specific mode of precipitation. The most recent proposed classification[55] includes startle epilepsy as a reflex epilepsy syndrome. The effective stimulus is usually a sudden sound.[3] Most patients are sensitive to a single sensory modality but the suddenness of the stimulation, which must be unexpected, is crucial. The seizures usually last <30 seconds and consist of a startle response followed by a brief tonic posture, which is usually asymmetric. Many subjects fall, and clonic jerks may occur. Injury is common when the seizures occur in patients who are standing or able to fall while seated, or while they are in bathtubs or similar risky locations. The seizures may be frequent but habituation is typical: If the stimulus is repeatedly presented over several minutes, it becomes temporarily ineffective. Patients with startle epilepsy usually have static cerebral lesions arising prenatally or within the first 2 years of life and intellectual handicap. Many are hemiparetic; in these, the weak side is preferentially involved in the seizure. Spontaneous seizures occur, reportedly in all cases, but may be infrequent. Startle epilepsy is typically intractable.

Brain imaging may show localized lesions (mesial hypodensity) or diffuse lesions.[2,82] The lateralized lesions usually involve sensorimotor and premotor cortex and white matter, but normal scans have been reported without neurologic deficit.[128] Such patients have precentral or perisylvian dysplastic lesions on MRI. Schizencephaly has also been found. Startle epilepsy often occurs with Down syndrome.

Scalp EEG ictal recording shows an initial vertex discharge followed by diffuse relative flattening or low-voltage rhythm at about 10 Hz. Ictal depth electrode recordings have shown an initial high-amplitude evoked response over motor areas corresponding to the vertex scalp activity, followed by ictal EEG discharge, which begins in lesioned motor or premotor cortex and spreads to mesial frontal, parietal, and contralateral frontal regions.[12,13,192] Subdural recordings in a patient with a small lesion next to the right supplementary sensorimotor area showed seizure onset in the right dorsolateral premotor cortex and the right supplementary sensorimotor area.[178]

The seizures resemble supplementary motor seizures. Localized lesions and seizure onset often involve that area or its surroundings: The epileptogenic lesion may be in the dorsolateral frontal lobe or in the perirolandic area (for a recent example with video illustration see Nolan et al.[146]).

Differential diagnosis includes startle disease (hyper-ekplexia).[6] Touch-evoked or tap seizures in children[50,212] may have a startle component, but are not startle epilepsy as currently defined. Startle stimuli can cause nonepileptic falls in Coffin-Lowry syndrome. Startle myoclonus, though not clearly startle epilepsy, has been reported in association with GM2 gangliosidosis[143] and startle epilepsy has been reported with aspartylglucosaminuria.[119] Seizures induced by sudden dousing with hot water may also have a startle component at some time in their course but are not to be confused with startle epilepsy.[15,174] Other reflex seizures, produced by cutaneous or proprioceptive stimulation, should also be distinguished from startle epilepsy.[107,192]

Startle epilepsy can be treated with drugs appropriate for focal seizures. Reports discuss carbamazepine, lamotrigine, clobazam, and clonazepam.[2,41,56,119,171] Psychological intervention has also been proposed.[136] Startle epilepsy is usually intractable, however, and surgery has been reported to control startle epilepsy associated with infantile hemiplegia.[33,131,147]

Reading Epilepsy

Primary reading epilepsy (RE) consists of seizures triggered exclusively by reading, without spontaneous seizures.[17] The current proposed diagnostic scheme defines it as a reflex epilepsy syndrome without specifying a generalized or focal subtype.[55] Seizures usually begin in adolescence. Patients report jaw jerking or clicking and other sensations or movements in orofacial muscles, usually after reading for some time, representing partial seizures or localized myoclonus. They may thus appear to stutter.[138] If reading then continues, even for a very short time in some patients, a generalized convulsion may occur. Seizures are not induced by mental activity without reading. The developmental history, neurologic examination, interictal EEG, and computed tomography (CT) scan are normal. A family history of epilepsy is common, and familial reading epilepsy may occur.[134,209] The syndrome is relatively benign and often goes undiagnosed, mistaken for harmless tics or stuttering.

Both unilateral and bilateral orofacial myoclonus may be triggered by reading and either may be seen with unilateral or bilateral EEG discharges.[209] In an important review of 111 patients by Wolf and Inoue,[209] 77% had triggered epileptiform discharges consisting of short bursts of sharp waves, spikes, or spike-and-wave complexes that are bilateral and symmetric in 32%, bilateral but asymmetric in 38%, and unilateral or focal in 30%. Lateralization is more frequent to the language-dominant hemisphere (78%), preferentially over the temporoparietal region (80%).

Radhakrishnan et al.[164] found generalized and symmetric ictal discharges in 15 of 20 patients (75%) with RE and asymmetric or unilateral discharges in five (25%) with lateralization to the dominant hemisphere. They suggested that RE be classified among the idiopathic generalized epilepsies. Mayer and Wolf[135] found that the triggered perioral reflex myoclonus thought to be exclusive to RE was also found with bilateral spike-and-wave EEG activity in juvenile myoclonic epilepsy, and was also recorded, triggered by talking more than by reading, in patients with a variety of epileptic disorders.[211] Koutroumanidis et al.[117] monitored 17 patients with RE. During the triggered myoclonic jerks, eight had bilateral synchronous epileptic discharges. Two patients had alexia or possibly speech arrest as the only ictal manifestation, associated on the EEG with focal abnormalities over the left posterior temporal area.

Koepp et al.[115] performed [11C]-diprenorphine positron emission tomography (PET) in a patient with RE and found decreased peri-ictal opioid binding in both temporal lobes and the left frontal lobe, regions that had shown PET activation during normal reading. Archer et al.[7] performed spike-triggered fMRI in a patient with reading epilepsy. During activation tasks, spike-related activity was found in the left precentral gyrus and bilaterally in the central sulcus and globus pallidus. Comparison of fMRI activation seen during spiking with that during reading showed overlap in the posterior dorsolateral prefrontal cortex. This area was shown to be activated during specific cognitive tasks with a working memory component, and evidence for the involvement of this region in RE also comes from a patient who developed RE after removal of a left premotor arteriovenous malformation.[170] Archer postulated that the ictal activity of RE spread from working memory into nearby motor cortex. The facial myoclonus typical of RE may also be triggered by language tasks in symptomatic epilepsies.[30]

Thus, it appears that reading can activate generalized epilepsies, similar to activation by pattern sensitivity with its occipital trigger. RE is not, however, exclusively a generalized epileptic phenomenon but involves a functional system over both hemispheres. Reading requires bihemispheric cooperation, with dominant hemisphere predominance for phonologic processing and nondominant hemisphere predominance for semantic representation. Pegna et al.[155] reported a case of RE and suggested lexical and nonlexical forms of RE, and RE seems less common in Japanese, which uses a logographic writing system.

Language-induced epilepsy involves seizure precipitation by speaking, reading, and writing.[71] The seizures are similar to those of primary reading epilepsy, and patients may report one or several seizure triggers related to language (e.g., recitation or writing only).[8,93] The nosologic position of language-induced epilepsy is not clear: Reported cases most closely resemble reading epilepsy but are more heterogeneous than those of primary reading epilepsy, whose definition should probably be expanded to include them.

RE may be treated by partial avoidance of the stimulus, especially if the patient does not develop generalized seizures or has a useful delay before one occurs. Interruption or limitation of reading can then be effective. Maneuvers that briefly disrupt comprehension or increase arousal may be helpful, but social and educational handicap may arise from all of these. Audiotaped texts may be useful. Text masking may help those in whom pattern or eye movement contribute to seizure occurrence.[206] Wolf and Inoue[209] reported that valproate is the drug of choice and that clonazepam can be a useful adjunct.

Musicogenic Seizures

Induction of seizures in humans by unstructured sound apart from startle stimuli is very unusual. Musicogenic epilepsy is characterized by seizures induced by hearing certain sounds, typically music.[9,46] Patients with musicogenic seizures alone may have a reflex epilepsy syndrome, but most also have spontaneous seizures. The reflex seizures then often begin over a year after the onset of the spontaneous attacks.[198] Seizures have also been reported while the subject is exposed to the musical trigger during sleep or while thinking about it. The effective stimulus can be stereotyped for each patient. It can be restricted to a single musical work, but there is no clear common pattern among patients. An affective component of the stimulus must be present in some, yet nonmusical sounds, such as whirring machinery, can be effective triggers in others. The seizures are of simple or complex partial type, with interictal and ictal epileptiform activity recorded from either temporal region,[176] usually the right. Often, the seizure does not begin immediately and the patient must be exposed to the trigger for several seconds or minutes. Musicogenic seizures have been reported in infancy.[122] Some patients with autosomal dominant lateral temporal lobe epilepsy have reported triggering by sound or by hearing speech.[26]

A right temporal predominance for musicogenic seizures has been reported by several authors.[69,70,198] They also documented right anterior and mesial hyperperfusion during ictal single photon emission computed tomography (SPECT) of musicogenic seizures.

The mechanism of musicogenic seizures is not clear. Although cortical processing of music has been studied extensively, subjects have been normal controls or patients with lesions or intractable spontaneous seizures. Chronic temporal lobe depth electrode studies in epileptic subjects without musicogenic epilepsy suggest different lateralizations for different components of a musical stimulus.[199] Creutzfeldt and Ojemann showed that musical stimuli may have widespread effects on neuronal activity in human temporal lobes extending well beyond the primary auditory area,[44,121] that different components of music have different effects possibly with specialized lateralization and localization, and that the effects of music are different from those of speech. Studies of the cerebral representation and processing of music have been extended, and are reviewed in Peretz and Zatorre.[157] PET studies in patients and others[106] show predominant involvement of right hemisphere structures in networks involved in processing musical information, extending well beyond the classical auditory cortex of the Heschl gyrus. Studies in subjects with musical hallucinations show that the primary auditory cortex is not “a sufficient substrate for higher-order pattern perception.”[79]

The primate auditory cortex consists of a central core of primary cortex that receives thalamic projections, linked to several “belt” areas. Primary cortex has multiple tonotopically organized areas and is especially sensitive to pure tones. Belt regions are more sensitive to complex stimuli and are less tonotopically organized.[106] Zifkin and Zatorre also noted that more complex musical processing tasks activate more cortical and subcortical territory bilaterally but with right hemisphere predominance.[215] Thus, hyperexcitable cortical areas could be stimulated to different degrees and extents by different musical stimuli in patients sensitive to musical triggers. Gloor suggested that responses to limbic stimulation in epileptic subjects depend on widespread neuronal matrices linked through connections that have become strengthened through repeated use, of interest in considering the delay from seizure onset to the development of sensitivity to music.[73]

Musicogenic seizures can be treated by stimulus avoidance or modification in many cases, especially if there is a useful latency from stimulus onset to seizure onset or if the stimulus is very specific. If this is not possible or effective, or if spontaneous seizures occur, drugs for focal seizures are indicated and intractable cases should be assessed for surgical treatment.

Reflex Seizure Types Usually Associated with Generalized Epilepsies

Touch-evoked ("Tap") Seizures

Otherwise normal infants and toddlers may develop seizures induced by tapping, often by a single touch on the head ("tap epilepsy") or by a sudden sound.[50,212] Age of onset is usually from 6 months to 3 years. These are typically manifestations of an idiopathic generalized epilepsy and consist of an initial blink followed by bilateral myoclonic jerks mostly involving the arms, with flexion of the head and upward deviation of the eyes. If intense, they can cause a fall. They can occur isolated or in clusters. The interictal EEG is usually normal and there is no photosensitivity. The ictal EEG shows bilateral spike-and-wave EEG discharges usually predominant anteriorly. Differential diagnosis includes hyperekplexia, symptomatic disorders such as startle epilepsy and focal reflex seizures induced by cutaneous stimulation, and benign myoclonic epilepsy of infancy, which is not triggered and has somewhat later onset and longer duration of the disorder with other seizure types.[54] Imaging is normal. These seizures appear to represent an early-onset idiopathic generalized epilepsy, and many such cases remit without drug treatment. Valproate may be used when drug treatment is needed. These attacks are not remarkably different from the benign early infantile reflex absence seizures illustrated with video recording by Voskuil.[194]

Seizures Induced by Thinking and Praxis

Seizures induced by thinking[207] occur in response to higher cortical function and have been reported with a variety of stimuli, including arithmetic, drawing, playing cards or chess, decision making, solving Rubik's cube, and using the soroban (a Japanese abacus). Goossens et al.,[76] in an extensive review, have proposed this as a separate epileptic syndrome. These patients are not sensitive to reading. Although a patient may report only a single trigger, detailed testing shows that about 80% have more than one effective stimulus. Unlike those with primary reading epilepsy, most have spontaneous seizures, and the reflex and spontaneous attacks include bilateral myoclonus, absences, and generalized tonic–clonic seizures. Partial seizures have been reported but are the exception. Seizures related to "praxis," clinically and electroencephalographically similar to these,[98] have been reported, strongly associated with juvenile myoclonic epilepsy (Herpin-Janz syndrome) and at times with other generalized epilepsies. Patients with seizures induced by thinking almost always have an idiopathic generalized epilepsy syndrome but without any specific variety associated.

Seizures induced by thinking are typically associated with both spontaneous and evoked generalized bilaterally synchronous spike or multiple spike-and-wave complexes. These may reappear only after reduction of medications in some patients. Though patients often report mental arithmetic as a trigger, other effective stimuli have included parts of standard neuropsychological test batteries such as Block Design. While occasional patients have temporoparietal or frontal spontaneous nonspecific EEG abnormalities, typically over the right side, these are at times mixed with generalized epileptiform activity. Clearly localized induced epileptiform activity is very unusual.[76]

The essential component in the seizure trigger appears to be nonverbal thought, the processing of numeric or spatial information, and possibly sequential decision making. Recent studies provide more detail on the cerebral representation of calculation and spatial thought and document a bilateral functional network activated by such tasks.[181]

The term *praxis induction* was introduced by Japanese authors who described seizures triggered when subjects "are obliged to contemplate complicated spatial tasks in a sequential fashion, to make decisions, and to practically respond using a part of their body."[99] Writing is reported to be a frequent precipitating factor[98] although reading is not. Hand or finger movements without "action-programming activity" (defined as "higher mental activity requiring hand movement" and apparently synonymous with praxis) are not effective triggers. Matsuoka et al.[132,133] noted, "The dependence of hand movements in the seizure-inducing tasks differentiates the action-programming activity from the thinking activity." Reflex upper limb myoclonus occurs and may spread. This pattern occurs very predominantly in juvenile myoclonic epilepsy. It does not seem prominent in patients with thinking-induced seizures who do not also have prominent myoclonic reflex attacks. In its milder or most restricted forms, such as the morning myoclonic jerk of the arm manipulating a utensil, this phenomenon resembles cortical reflex myoclonus as part of a "continuum of epileptic activity centered on the sensorimotor cortex,"[192] and back-averaging of chess-induced spikes with unilateral myoclonia in a patient with JME has shown localization to bilateral frontocentral regions.[129] The motor component, either imagined or performed, is crucial in praxis induction, whereas seizures induced by thinking are activated by tasks such as purely mental calculation of orally presented arithmetic tasks with no motor component in either the stimulus or the response.

Seizures induced by thinking and praxis, many cases of reading epilepsy, and photosensitive epilepsy are all examples of specific brain activities involving definable cortical areas triggering generalized seizures or epileptiform EEG activity, often in the context of known idiopathic generalized epilepsy. Inoue and Kubota[97] postulated on the basis of MEG and sensory-evoked potential studies that increased, but spatially different cortical hyperexcitability operates in photosensitivity and praxis sensitivity. Binnie[20] has discussed the implications of such studies of reflex seizures for the understanding of generalized epilepsy.

Treatment of Seizures Induced by Thinking and Praxis

Avoidance of triggering stimuli is usually impractical. These seizures are almost always found as part of an idiopathic generalized epilepsy, particularly juvenile myoclonic epilepsy, and drugs appropriate for these syndromes are the treatment of choice.

Reflex Seizure Types Usually Associated with Focal Epilepsies

Seizures Induced by Eating

Eating epilepsy is characterized by seizures closely related to one or several parts of eating. Although described as eating epilepsy, seizures triggered by eating often occur in patients who also have spontaneous seizures and are not now classified as a separate epileptic syndrome but as a seizure type in the most recent proposal.[55] Some cases may be described as epilepsies characterized by specific modes of seizure precipitation.[43] A prevalence of approximately 1 per 1,000 to 2,000 epileptic patients has been reported.[142,193] The unusually high figures reported for Sri Lanka[177] may be related to ascertainment methods. Seizures induced by eating have been reported in childhood, youth, and adult life. The clinical triggers of a seizure are usually stereotyped for each patient but may have a few points in common. Thus, some patients have seizures at the very sight or smell of food, while others may have them immediately after a heavy meal. Most typically, the seizure occurs shortly after beginning to eat and does not recur during the same meal. In some, the seizures may be related to emotional or autonomic components of eating, and in others to gastric distension or to stimulation of the mouth or pharynx and with possible participation of autonomic, somatosensory, or proprioceptive afferents.

Seizures with eating are typically of complex or simple partial type, almost always related to a symptomatic localization-related epilepsy. Rémillard et al.[167] suggest that patients with temporolimbic seizures activated by eating have fewer spontaneous attacks and are more likely to have such attacks from the onset of their epilepsy than are those with extralimbic, usually suprasylvian, seizure onset who have less constant activation by eating, more obvious extratemporal structural lesions, and possible activation by specific thalamocortical afferents. The latter may also have seizures with other forms of buccal stimulation such as tooth brushing or kissing and may represent particular examples of sensitivity to somatosensory or proprioceptive stimulation. Koutroumanidis et al. reported a case of adult-onset sensitivity to tooth brushing only, with normal imaging and interictal left frontal epileptiform activity, and suggested that this was a cryptogenic reflex epilepsy.[118] The role of malformations of cortical development in reflex seizures has been recently discussed by Palmini et al.,[150] who found eating-related seizures in patients with perisylvian lesions and noted functional anatomic correlation with the reflex seizure types.

Eating epilepsy is usually associated with localized or regional epileptiform activity either from temporolimbic structures or from suprasylvian regions in association with larger lesions. Patients considered to have idiopathic generalized epilepsies are exceptional, and cases in which seizures have been shown to be generalized from the start are less frequent.[60,116]

The seizures of eating epilepsy can be affected by modifying the trigger. It is our impression that patients with eating epilepsy and extralimbic seizure onset are more sensitive to either somatosensory or proprioceptive stimuli during eating and are more likely to report that seizure induction can be prevented by altering the sensory characteristics of their food. Some will drink through a straw rather than from a cup or will avoid biting into a whole fruit by cutting it into small pieces. Such stimulus modification can reduce seizure frequency in what may otherwise be an intractable or socially disabling condition. Some patients also take advantage of a refractory period after a reflex seizure and will induce an attack in private to avoid having a seizure later in a more embarrassing setting. Some patients have prolonged periods of heightened susceptibility to reflex attacks and may then refuse to eat adequately. Drugs effective for partial seizures are usually necessary, but medically intractable patients should be recognized early and assessed for surgical treatment.

Seizures induced by eating in infancy are unusual, may present as acute life-threatening events (ALTEs), and appear to have a poor prognosis. Navelet et al.[145] reported four infants with onset before 6 months, attacks provoked by meals, cyanosis, hypo- or hypertonia, and apnea followed by clonic movements of the limbs. Gastroesophageal reflux (GER) was present in the four cases but attacks remained frequent despite anti-GER treatment and all infants developed a severe epilepsy. The first interictal EEG was normal but repeated polygraphic EEG recordings documented the seizures. The trigger in these patients is unknown and the relationship between GER, ALTEs, and epilepsy remains unclear. One of us (P.P.) studied three children with epileptic spasms beginning in the first year who developed seizures with the approach or ingestion of food at 3 to 4 years old. The triggered seizures were spasms in two cases and tonic seizures in one. The last child had cryptogenic epilepsy, the others had symptomatic epilepsy with early large opercular lesions, and all had lateralized or regionally predominant ictal and interictal EEG abnormalities. They continued to have reflex and spontaneous seizures. It is possible that a network responsible for the reflex attacks may not have matured until several years of age.

Seizures Induced by Proprioceptive Stimuli (Movement Induced)

Reflex seizures apparently induced by movement were reported before the EEG era.[78] Early reports emphasized induction by movement,[123] but later experiments showed the determinant role of proprioceptive afferents.[36,72] Thus, seizures originally described as movement induced or gait induced are usually more accurately described as “proprioceptive induced.” These reflex seizures are rare[192] and may be most commonly seen as a transient occurrence with nonketotic hyperglycemia.[23]

Proprioceptive-induced seizures involve the sensorimotor area of the hemisphere contralateral to the clinical seizure onset. This has been confirmed by imaging and intensive monitoring. The supplementary motor area may also be involved. Maximum EEG electronegativity appears to be at the central vertex electrode in a published EEG of seizures induced by walking.[101] Cerebral lesions are often evident and may have occurred long

before the onset of attacks. Acute cerebral lesions or acute diffuse encephalopathies may also be accompanied by self-limited proprioceptive-induced seizures. In nonketotic hyperglycemia or other metabolic encephalopathies, neurologic deficit related to a remote lesion may be transiently unmasked during the period of seizures.[23] New-onset proprioceptive-induced seizures thus require rapid medical and neurologic evaluation.

Reflex drop attacks elicited by walking[53] are seen rarely in patients with reflex interictal spikes evoked by percussion of the foot.[49,187] These may be a variety of seizures induced by proprioceptive stimulation. However, individuals with these evoked spikes, generally considered a benign finding, do not usually have epilepsy or reflex seizures.[120] This disorder likely represents a form of idiopathic focal epilepsy of childhood, distinct because of the parietal lobe involvement. Participation of a more elaborate network involved in motor programming cannot be excluded in some cases, especially if the effective stimulus seems restricted to activities such as walking, although "gait epilepsy"[101] is not now a recognized seizure type or epilepsy syndrome.

Seizures Induced by Somatosensory Stimuli

Seizures induced by somatosensory stimulation are typically triggered by repeatedly tapping, rubbing, or pricking part of the body. There is often a localized or regional cutaneous trigger zone. The seizures begin with a sensory aura; a sensory jacksonian seizure occurs often followed by tonic motor manifestations suggesting a supplementary motor area seizure. Generalization may occur. Consciousness is preserved at least at the onset. Ictal pain and autonomic disturbances have also been reported.[175] Compulsive somatosensory self-stimulation with self-induced epileptic spasms has also been demonstrated in children with severe developmental delay.[83] Somatosensory-induced seizures typically occur in patients with postrolandic cortical lesions that may be subtle.[192] Malformations of cortical development have also been implicated.[150] Normal MR imaging has been reported in patients with "rub" epilepsy, but detailed imaging was not described[107] and current imaging methods are more refined.

These focal-onset seizures must be distinguished from the typically more benign generalized reflex seizures induced by tapping in infants and young children (see above) that are not associated with lesions. Patients with somatosensory reflex seizures must be investigated for brain lesions and treatment is as for other symptomatic or cryptogenic focal epilepsies.

Hot Water Epilepsy

Seizures induced by immersion in or contact with hot water have until recently been reported predominantly in older children and adolescents from south India, where ritual bathing involves repeatedly pouring hot water over the head from a jug.[173,174] Indian patients are typically boys, with adolescence-onset complex partial or generalized tonic–clonic seizures during ritual bathing. Hot water epilepsy (HWE) has been thought to be a relatively benign age- and situation-related disorder akin to febrile seizures. This is often so when seizures start in infancy or early childhood. Ictal recordings are rare and interictal EEG abnormalities have been recorded over temporal areas in half of the patients. Imaging has been unremarkable in most, but focal cortical malformations have been reported.[80] Differential diagnosis includes nonepileptic events such as startle and vasovagal syncope, and startle epilepsy. Some older patients report pleasurable feelings with these events, and self-induction has been reported. Prophylactic clobazam is reportedly helpful.[52] Studies in non-Indian subjects[15,100] report onset from infancy to adult life and spontaneous seizures in 62% of patients in whom onset was after infancy. These series include younger children than in India, with complex partial seizures occurring as soon as the child is immersed in hot water rather than when hot water is poured over the head; sensitivity often diminishes with time.[100]

HWE beginning in infancy appears to have a better prognosis. Seizures begin in the first year and are always triggered by immersion in hot bath water with a temperature around 37.5°C. Parents describe some nonspecific malaise and when recorded these are complex partial seizures; general pediatricians may be unfamiliar with these seizures in such young children.

In infantile HWE, the neurologic and developmental examinations are always normal. There is no personal or family history of epilepsy. Interictal EEG is normal, including during sleep. CT scan and MRI are reported as normal, and no interictal or ictal SPECT has been reported in these infants. Treatment is by lowering the temperature of the bath. No antiepileptic drugs are needed and in more than 3 years of follow-up, no further seizures have developed in five cases we have evaluated (P.P.), some of whom were also reported by Ioos et al.[100] Differential diagnosis of HWE in infants includes gastroesophageal reflux, which, however, would be rare in the bath; syncope; startle events; and aquagenic urticaria. Sensitivity to visual stimuli such as the light reflections in the bathroom or the color of the bathtub would not be expected in otherwise normal children at this age.

A mechanism involving defective thermoregulation has been proposed.

Miscellaneous Reflex Seizures

Psychogenic seizures are triggered by specific thoughts, either self-induced attacks (e.g., by thinking sad thoughts) or those unintentionally triggered by specific mental activity.[57] This use of the term *psychogenic* does not refer to nonepileptic seizures. A report of temporal lobe seizures induced by thinking of the family home documented such seizures during monitoring and a subtle malformation of cortical development in the resected temporal structures.[130]

Seizures with extremely specific visual stimuli have been reported. Recurring self-induced brief tonic seizures triggered by looking at round objects occurred in an 18-month-old boy. Later he developed sensitivity to other patterns and secondary generalized seizures, which were difficult to control. He was not photosensitive.[25] A child with generalized seizures self-induced by looking at his own hand was reported. By 4 years of age, medications were withdrawn, and no further seizures, reflex or otherwise, occurred in 26 years of follow-up.[114] The EEG was said to be normal. A similar case has been reported.[62]

Vestibular stimuli, caloric or rotatory, have been reported to produce EEG discharges, generally nonspecific but at times in the contralateral temporal region,[14,24,31,141] but seizures induced by these stimuli, as distinguished from startle effects or syncopal events, appear to be very rare.[16,108]

Olfactory stimuli have elicited seizures in experimental animals.[140] Stevens[182] reported that strong odors increased interictal epileptiform EEG activity in 26% of patients with temporal lobe epilepsy, but triggering of seizures is much rarer.[184]

Presumed enteroceptive seizures are very unusual. Occasionally, seizures induced by eating may be shown to depend on gastric distension,[67] but this is not typical. Defecation has been reported to induce seizures, confirmed by EEG, but not immediately after emptying the rectum,[86] and was the most common trigger reported by Schubert and Cracco[175] in a case of induction by tactile stimuli.

Summary and Conclusions

Reflex seizures have been considered interesting rarities, but are probably more frequent than we realize, especially in some relatively common syndromes that are now believed to be generalized epilepsies. Study of reflex seizures has been important in understanding some basic brain mechanisms of seizure occurrence. Neurologists, pediatricians, and family or general practitioners can expect to encounter patients with these seizures. A detailed history is the first step to proper diagnosis of seizure type and epilepsy syndrome, so that effective treatment may be prescribed.

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Chapter 258

Overview: Diseases Associated With Epilepsy

Timothy A. Pedley

Introduction

Seizures and epilepsy are common manifestations of disturbed cerebral function; thus, they may be symptoms of other diseases that involve the brain and not of epilepsy *sui generis*. This association has long been recognized in the case of brain tumors and tuberous sclerosis, for example, but the modern era of brain imaging and molecular diagnosis has greatly expanded our recognition of specific disease entities in which epilepsy is a major feature. This section reviews major categories of disease that present with seizures or in which epilepsy constitutes a significant aspect of the illness. Certain presentations or evolution should always raise the question of a specific underlying disorder.

Clues from Epilepsy Syndromes

The diagnosis of infantile spasms (West syndrome; Chapter 229) or Lennox-Gastaut syndrome (Chapter 241) should always lead to a search for a specific cause. Both syndromes can occur as either idiopathic or symptomatic conditions, and therein lies one of the disadvantages of the current classification. Both are electroclinical syndromes and therefore etiologically heterogeneous. Neither is a singular pathologic entity, and cerebral malformations, perinatal asphyxia, anoxic encephalopathy from cardiopulmonary arrest, central nervous infection, postimmunization encephalopathy, and progressive degenerative or metabolic syndromes have all been implicated in individual children. Tuberous sclerosis is the most common disease entity causing infantile spasms,[7] but untreated phenylketonuria, nonketotic hyperglycinemia, and other metabolic and structural disorders are also encountered occasionally.[4] A small subgroup of children with spasms but no identifiable causes have normal developmental outcome and may represent an idiopathic condition.[3] Similar disorders are found in children with Lennox-Gastaut syndrome (Chapter 241),[1,8] and of course infantile spasms and Lennox-Gastaut syndrome are not fully independent entities: The 6-year-old child designated as having Lennox-Gastaut syndrome may well have carried a diagnosis of West syndrome as an infant. Indeed, with computed tomographic (CT) and magnetic resonance (MR) brain imaging and the availability of sophisticated and highly specific biochemical and genetic tests, the percentage of cryptogenic cases has steadily declined.

Intractable Epilepsy

Persistent seizures despite appropriate therapy are often an indication to consider medical illnesses or treatments that can contribute to or cause recurrent seizures, such as systemic lupus erythematosus, hypoglycemia, drug abuse, and theophylline toxicity (Chapters 127, 191, and 192). The use of molecular techniques to establish linkage or a gene defect has clearly demonstrated that variability in phenotype is common and that syndromic fidelity, defined traditionally by seizure semiology and electroencephalographic (EEG) features, is not invariable. Thus, older children and even adults with seemingly stable (or only very slowly progressive) neurologic abnormalities are now found to have progressive metabolic or degenerative encephalopathies due to adrenoleukodystrophy, ceroid lipofuscinosis, storage diseases such as Tay-Sachs or sialidosis, various aminoacidurias and urea cycle disorders, or one of the progressive myoclonus epilepsies. Other genetic disorders (also referred to as chromosomal abnormalities), including trisomy 13 and 21, fragile X syndrome, and Aicardi syndrome, as well as cortical malformations such as lissencephaly (e.g., Miller-Dieker syndrome) and Angelman ("happy puppet") syndrome, may present with seizures that prove to be drug resistant (Chapter 261). Associated physical abnormalities often provide clues to the diagnosis in most of these conditions.

Seizures are a common manifestation of the mitochondrial encephalopathies, although the frequency is highly variable among the different mitochondrial syndromes. Specific gene defects in many of these disorders have been identified, and they include both mitochondrial and nuclear mutations. In some cases, the type of mutation is quite different in patients that commonly present with seizures than in those in which epilepsy is rare. Thus, seizures are the rule in MELAS (mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes) and MERRF (myoclonus epilepsy with ragged red fibers), which are almost always associated with point mutations in the tRNA^{Lys} gene.[10] However, seizures are rare in Kearns-Sayres syndrome, which is related to large deletions or duplications of mtDNA. Hirano and colleagues (Chapter 262) believe that the spatial distribution within the brain of the mitochondrial mutation underlies the association of particular mutations with epilepsy.

Seizures occur in the majority of children with Rett syndrome,[6] and these can sometimes be intractable. Some of these patients also have syncopal episodes that are occasionally misdiagnosed as epilepsy, and the characteristic stereotypic movements (e.g., hand-wringing) also may be erroneously considered to reflect seizure activity.

Importance of Brain Developmental Abnormalities

Except for major malformations such as anencephaly, holoprosencephaly, and schizencephaly, abnormalities of cortical development were largely unrecognized as a common cause of epilepsy until high-resolution MR brain imaging became widely available and part of the routine diagnostic evaluation

of patients with seizures. Cortical developmental malformations are now known to be common, especially as a cause of intractable epilepsy. They are found in up to 20% of adults[2] and >50% of children referred to epilepsy centers because of drug-resistant seizures or as possible surgical candidates.[5] Of equal interest is the growing recognition that cortical dysgenesis can be found in a wide spectrum of patients, including some without seizures, in patients with only one or a few seizures, and as associated pathology in patients with temporal lobe epilepsy due to mesial temporal sclerosis. The movement of cortical developmental abnormalities from the domain of the neuropathologist to that of the neurologist has been one of the most significant changes in modern epileptology (Chapter 259). Some critical questions are beginning to be addressed:

1. To what extent is cortical dyplasia in a given patient coincidental, an associated marker of epileptogenic mechanisms, or the direct cause of seizures?
2. Why do seizures often seem to arise from a single epileptogenic region even when the developmental abnormalities are multifocal or bilateral?
3. How do developmental malformations cause epilepsy?

Miscellaneous Considerations

Seizures are the presenting symptom in the majority of patients with astrocytomas and oligodendrogliomas, but they are also common at some point in the course of more malignant brain tumors (Chapter 264). With slowly growing neoplasms, seizures typically occur early, when there may be no other clinical symptoms or signs to suggest a tumor. CT may be normal at the time of a first seizure caused by well-differentiated, relatively benign tumors, so MRI is essential. Seizures are also common in many infectious and inflammatory diseases (Chapter 265). Parasitic, bacterial, and viral agents all cause various syndromes in which seizures or chronic epilepsy are common, including as the presenting manifestation. Both mental retardation and cerebral palsy (Chapter 263) are major risk factors for epilepsy, probably because they are markers of brain damage, and the risk for epilepsy is additive when both conditions are present. Alcohol and drug abuse are common causes of symptomatic seizures, but alcohol use itself is also a dose-dependent risk for chronic epilepsy (Chapter 268). Heroin and cocaine, but usually not marijuana, also raise the risk of unprovoked seizures, although symptomatic seizures related to acute toxic effects on the brain are far more common.

Summary and Conclusions

Certain epileptic syndromes, associated neurologic abnormalities, age at first seizure, drug resistance, and associated morphologic or systemic abnormalities should warrant a search for a specific diagnosis. High-resolution brain MR imaging will generally establish structural causes of epilepsy, including cortical developmental malformations and brain tumors, although serial scans and special imaging sequences may be necessary fully to define the abnormality. In those circumstances in which epilepsy is due to or associated with an underlying disease, proper treatment, genetic and prognostic counseling, and clinical investigation depend on accurate diagnosis.

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Chapter 259

Malformations of Cortical Development

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Graeme D. Jackson

Introduction

The development of the human brain is a long and complex process that begins with the induction of the neural plate from the undifferentiated surface ectoderm and continues after birth.[115] Any disruption of the normal mechanisms responsible for the formation of the cerebral structures can result in malformations due to abnormal cortical development.[81,85] A wide variety of genetic and environmental factors can cause disturbances in these developmental processes and can therefore lead to an abnormality in the mature brain.

Until the advent of high-resolution magnetic resonance (MR), malformative disorders of the nervous system were almost exclusively the domain of the pathologist. With magnetic resonance imaging (MRI), abnormalities of cortical development can be identified in life, and understanding these conditions, their clinical consequences, and outcome has become essential for appropriate management. The physician's goal is to diagnose these disorders accurately, using information that is available in the clinical setting. This chapter presents an approach that we believe is helpful to clinicians dealing with these disorders, especially in the setting of epilepsy.

The clinical circumstances in which these disorders are encountered are many but primarily involve developmental delay, epilepsy, skin lesions in specific neurocutaneous disorders, and associated organ malformations. From the perspective of epilepsy, there are two common presentations. First, a patient with epilepsy has an abnormal MR brain scan suggesting a malformation of cortical development (MCD). In this case, the issue is largely one of diagnosis, appropriate classification, knowledge of the relevant condition, and genetic testing, if available. This is important for prognosis, treatment, and genetic counseling. Second, a patient with epilepsy has a “normal” brain MR scan, but the clinician suspects, perhaps on the basis of family history, seizure intractability, or other findings on clinical examination, that there may be an underlying abnormality of cortical development. In this case, one is usually dealing with a subtle, localized cortical malformation, and the challenge is to identify the abnormal brain region(s). This is not an uncommon problem for epilepsy centers that deal with surgical treatment.

Clinical Presentation

Disorders of cortical development encompass many types of malformations with a comparably wide range of etiologies that produce different effects depending on the stage of brain development that is affected. Not surprisingly, then, clinical presentations are quite heterogeneous and can manifest at almost any age. As a result, the practical problem is that because there are actually many disorders of cortical development, there are no specific clinical features associated with MCDs when considered as a group.

While MCDs are a common cause of epilepsy, there are many cases in which seizures are not a feature of these disorders. Why almost identical brain abnormalities can have such variable clinical phenotypes is not known. Yet while there are no clinical features that are specific for MCDs taken as a whole, there are within this group some specific syndromes recognized on the basis of characteristic patterns of genetic, clinical, and imaging findings.

Seizure type usually reflects the topology of the malformations. That is, focal seizures occur with focal or multifocal MCD, and secondarily generalized seizures with diffuse or bilateral MCDs.

Almost any epilepsy presentation, at almost any age, can be due to an MCD. However, in focal epilepsy, some features create a strong suspicion of an underlying MCD and encourage thorough investigation to exclude this possibility if no other cause has been identified. These features include developmental delay, static focal neurologic deficits, a family history of developmental delay or epilepsy, frequent seizures from onset, and focal status epilepticus. While the presence of such elements may raise the suspicion of an MCD, it must be emphasized that none of them is specific. In surgical series of patients, such characteristics will likely lead to detailed high-resolution MRI with special techniques in an effort to define an abnormality of cortical development.

The severity of seizures in patients with MCDs also varies greatly. There are many individuals with extensive cortical malformations who have no seizures. On the other hand, some individuals with apparently small developmental malformations have severe and intractable epilepsy. The mechanisms of epileptogenesis associated with these abnormalities are complex and generally poorly understood.

Epidemiology

Few studies have addressed the epidemiology of MCDs in detail, and little information can be obtained from studies using the modalities, including MRI, that are currently available. One series based on pathology findings revealed that 46.5% of patients had developmental malformations at autopsy.[95] A case ascertainment study of lissencephaly showed a prevalence of 11.7 per million births.[40] No data are available for heterotopia, focal cortical dysplasia, or other malformations of cortical development.

Recent clinical and neuroimaging studies in special populations have suggested that cortical malformations are much more common than was previously appreciated. In children referred to epilepsy centers for intractable seizures, more than half have some type of developmental abnormality, with focal cortical dysplasia discovered in approximately 25% of those with intractable focal seizures.[79] The prevalence of these disorders in the adult population with intractable focal epilepsy is 15% to 20%.[6,10]

Terms and Definitions

A number of terms are commonly used in referring to patients with developmental malformations.[10] For example, *dysplasia* in this context is an encompassing term that usually means abnormalities of the cortex that have a particular histopathology and are developmental in origin. *Neuronal migration disorder* is generally used in a similar context, but this is clearly incorrect as a general term, as it describes only one embryologic stage in cortical development. We consider all of these disorders to be *malformations of cortical development* and prefer this as the general term for referring to this category of conditions. All of these disorders seem to result from disturbed organogenesis (and, hence, are malformations), and all involve cells that under normal circumstances would participate in formation of the cerebral cortex. The most common malformative disorders involve abnormal stem cell formation in the germinative zone or abnormal cortical organization. Some result from faulty neuronal migration, whereas still others are postmigratory in origin.

We believe that establishing a single nomenclature and classification system for these disorders is essential to their understanding and management. The classification proposed in the following discussion provides a means by which similar disorders can be logically grouped together.[10]

Classification Principles

MCDs can be classified according to a number of different criteria emphasizing clinical phenotype, imaging findings, pathology, and genetic defects. The overall classification scheme that we favor (Table 1) is based on the three fundamental events of cortical formation: (a) proliferation of neurons and glia in the ventricular zone and subventricular zones; (b) multidirectional migration of immature but postmitotic neurons to the developing cerebral cortex; and (c) cortical organization, which consists of vertical and horizontal organization of neurons within the cortex and elaboration of axonal and dendritic ramifications. For those malformations with abnormalities involving more than one of these processes, classification is based on the first identified abnormal step. Diffuse and focal malformations that were classified separately in the past are no longer separated since genetic studies have shown that the same gene defects can cause focal or generalized MCDs.

Table 1 Classification Scheme of Malformations of Cortical Development

I. Malformations due to abnormal neuronal and glial proliferation or apoptosis
    A. Decreased proliferation/increased apoptosis or increased proliferation/decreased apoptosis—abnormalities of brain size
        1. Microcephaly with normal to thin cortex
        2. Microlissencephaly (extreme microcephaly with thick cortex)
        3. Microcephaly with extensive polymicrogyria
        4. Macrocephalies
    B. Abnormal proliferation (abnormal cell types)
        1. Nonneoplastic
            a. Cortical hamartomas of tuberous sclerosis
            b. Cortical dysplasia with balloon cells
            c. Hemimegalencephaly
        2. Neoplastic (associated with disordered cortex)
            a. Dysembryoplastic neuroepithelial tumor
            b. Ganglioglioma
            c. Gangliocytoma
II. Malformations due to abnormal neuronal migration
    A. Lissencephaly/subcortical band heterotopia spectrum
    B. Cobblestone complex/congenital muscular dystrophy syndromes
    C. Heterotopia
        1. Subependymal (periventricular)
        2. Subcortical (other than band heterotopia)
        3. Marginal glioneuronal
III. Malformations due to abnormal cortical organization (including late neuronal migration)
    A. Polymicrogyria and schizencephaly
        1. Bilateral polymicrogyria syndromes
        2. Schizencephaly (polymicrogyria with clefts)
        3. Polymicrogyria or schizencephaly as part of multiple congenital anomaly/mental retardation syndromes
    B. Cortical dysplasia without balloon cells
    C. Microdysgenesis
IV. Malformations of cortical development, not otherwise classified
    A. Malformations secondary to inborn errors of metabolism
        1. Mitochondrial and pyruvate metabolic disorders
        2. Peroxisomal disorders
    B. Other unclassified malformations
        1. Sublobar dysplasia

2. Others

Thus, with advances in molecular genetics, we have moved from a purely phenotypic approach to a combined phenotypic/genetic classification. The basis of this change has been the recognition that malformations of varying severity can result from the same underlying processes, specifically from mutations of the same causative genes. This was shown first for classical lissencephaly[38,93,94,111,112,113,114,123] and more recently in the brain malformations associated with congenital muscular dystrophies.[15,16,17,88,89,108,132,133,134] For example, patients with large deletions and truncations of the *LIS1* and *DCX* mutations have diffuse or severe lissencephaly, while those with less severe *LIS1* mutations may only have posterior pachygyria or posterior-predominant subcortical band heterotopia. Those with less severe *DCX* mutations have anterior pachygyria or frontal subcortical band heterotopia of variable thickness,[27,49,50,51,87,92,111,114,123] or they may even have normal brain MRI scans.[57] Further support for this approach has been the recent discovery of mutations of multiple genes each causing very similar clinical syndromes, and the finding that mutations of different genes can cause the phenotype of Walker-Warburg syndrome or muscle-eye-brain disease.[123]

Developmental Malformations Associated with Epilepsy: Specific Disorders

We have restricted the following discussion to an overview of the most common and relatively distinct entities that affect patients with epilepsy.

Focal Cortical Dysplasia

Focal cortical dysplasia (FCD) is probably the most common form of focal developmental disorder diagnosed in patients with intractable focal epilepsy.[24,67,83,86,100] The lesions consist of disruption of cortical lamination with poorly differentiated glial cell elements. Since its original description, FCD has been recognized to encompass a spectrum of changes.[130] These range from mild cortical disruption without apparent giant neurons to the most severe forms in which cortical dyslamination, large bizarre cells, and astrocytosis are present.[75,79,130] It is the presence of balloon cells that differentiates FCD type I (without balloon cells) from FCD type II (with balloon cells) and that lead to the distinction in our classification scheme (see Table 1).

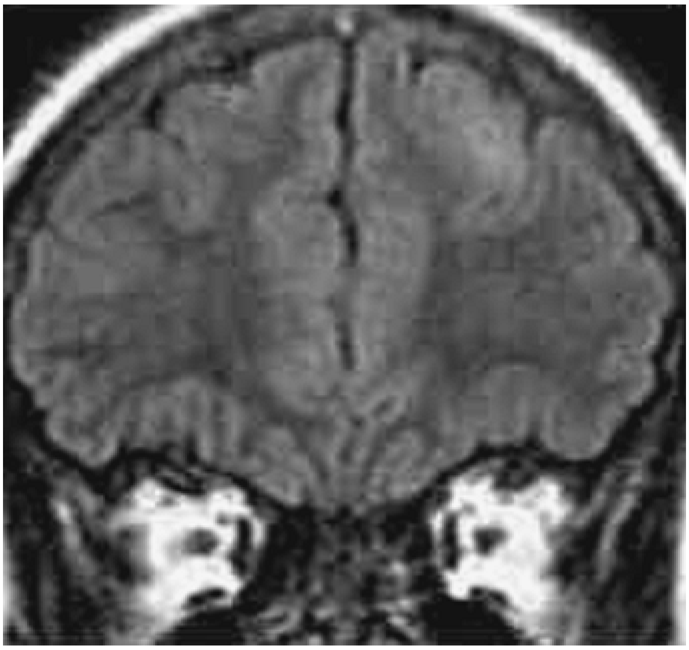

FIGURE 1. Focal cortical dysplasia (FCD). Left frontal lobe shows in this coronal fluid-attenuated inversion recovery magnetic resonance image a subtle signal abnormality and thickened cortex representing FCD. Pathology showed balloon cells.

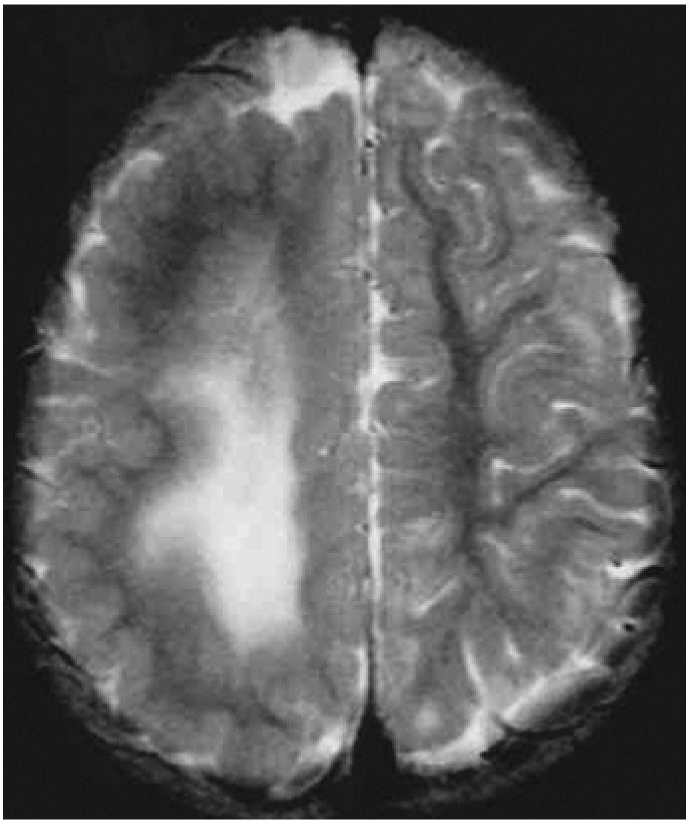

FIGURE 2. Hemimegalencephaly. Axial T2-weighted magnetic resonance image shows abnormal left hemisphere with smooth cortex and white matter changes.

The clinical manifestations of patients with cortical FCD are variable. Seizures usually begin between the ages of 2 and 10 years. Sometimes, however, seizures may be the presenting clinical problem in the second decade or even later. Focal and secondarily generalized attacks are common. Interestingly, seizures often occur in clusters, but generalized status epilepticus is rare except in patients with FCD involving the central region.[76] In our experience, the majority of patients have extratemporal cortical dysplasias that affect the pre- and postcentral regions most often. Interictal scalp electroencephalography (EEG) may demonstrate focal subclinical ictal discharges over the dysplastic lesions, underscoring the high epileptogenicity of these lesions.[103] FCD involving the frontal lobe has also been reported, and lesions can occur in both mesial and lateral neocortical structures as well.[77]

The MRI findings consist of abnormal gyral thickening with underlying T2-weighted white matter changes. These abnormalities are often circumscribed in nature, and they can sometimes be extensive, involving more than one gyrus or lobe. High-resolution MRIs with thin slices and multiplanar reconstruction are often necessary to identify these[24,25,55] (Fig. 1). Location can be quite unpredictable, as in the example of a very small lesion that was restricted to the bottom of a sulcus. Correlating clinical manifestations with the spectrum of changes seen in FCD has been limited, because histopathology is usually required before subtypes of FCD (e.g., FCD without balloon cells and microdysgenesis) can be firmly established.[10]

Hemimegalencephaly

Hemimegalencephaly is a rare malformation characterized by predominantly unilateral cerebral pathology typically associated with an enlarged hemisphere. It can be seen in isolation or in association with epidermal nevus syndrome[105] or hypomelanosis of Ito.[91,104,128] Pathologic findings are diverse and include cortical dysplasia, white matter abnormalities with abnormal cell types, or polymicrogyria usually restricted to one hemisphere. Most children with hemimegalencephaly associated with cortical malformations have not had other associated congenital anomalies.

Seizures and hemiparesis are common presenting symptoms.[101,107,118] Developmental delay is also common. Seizures usually appear within the first 6 months of life. They are often unilateral but can secondarily generalize, and they are frequently intractable to medical therapy. Continuing seizure activity is associated with the appearance or worsening of unilateral neurologic findings, such as hemiparesis and hemianopias. Occasionally there is only minimal neurologic dysfunction.

Diagnosis is based on the predominantly focal epileptic syndrome, the unilateral hemispheric EEG discharges, and the presence of unilateral neurologic abnormalities. MRI findings provide definitive diagnosis. Mild to severe enlargement of at least one lobe is present in all patients (Fig. 2). In more than half of the patients, the entire hemisphere is enlarged with thick gray matter and broad, flat gyri.[23,83,136] The underlying hemispheric white matter usually demonstrates abnormal MRI signal intensity. Heterotopia and other malformations are sometimes detected throughout the abnormal hemisphere, and there may be ipsilateral ventricular enlargement.

Focal Transmantle Dysplasia

Transmantle dysplasia is a developmental malformation characterized by abnormal brain tissue that extends through the entire mantle of the cerebrum, from the pia to the ventricular surface.[12] On MRI brain scans, areas of signal abnormality extend radially inward from the cortical surface toward the lateral ventricle. When the imaging plane is parallel to the tract, the T2 imaging signal abnormality involves the deep cortex and subcortical white matter.

Patients with this malformation present with focal seizures at different ages. Ictal semiology and neurologic deficits resemble those that accompany FCD. EEG abnormalities are usually lateralized to the areas of cortical malformations. Mild motor signs may be present if the lesions are in close proximity to the central cortical area. This malformation likely represents a subtype of FCD as pathology obtained during resections for epilepsy show a lack of normal cortical lamination, neuronomegaly, and hypomyelination with atypical reactive astrocytosis in the white matter.

Tuberous Sclerosis

Tuberous sclerosis (TS) is an autosomal dominant, genetically determined multisystem disorder with high penetrance and variable expression.[35,36,37,71] Genetic heterogeneity is observed with gene defects reported in both chromosome 9q34 and chromosome 16p13 with genetic classification into TSC1 and TSC2.

Pathologically, TS is a disorder of cellular migration, proliferation, and differentiation, resulting in hamartomata formation that involves a large number of neural crest derivatives. Histologically, two major abnormalities are seen. Cortical tubers are characterized by cortical dyslamination, large cells (neurons and glial cells or neuroastrocytes), and abnormal neuropil with hypomyelination. Subcortically, subependymal nodules projecting into the ventricles are typical. Microscopically, densely aggregated larger cells are present, often resembling neoplasms. Electron microscopic (EM) studies of cortical tubers have demonstrated that glial cells predominate near the pial surface, whereas small neurons are more prevalent inferiorly. Underneath the tubers, a rudimentary cortical plate is seen. The presence of the most undifferentiated cell types in the subependymal zone (giant cells) and more differentiated cells in the cortical tubers with intermediate lesions between them suggest a spectrum of abnormalities in neural and glial differentiation and migration.

Seizures are the most common neurologic symptom in TS: More than 90% of patients have seizures during their lifetimes.[71,120,142] Infantile spasms and partial seizures are highly prevalent, and secondary generalization occurs more often after age 2 years. Myoclonic seizures and mental retardation are very frequent. Over time, clinical deterioration is common, with seizures becoming more frequent and difficult to treat.

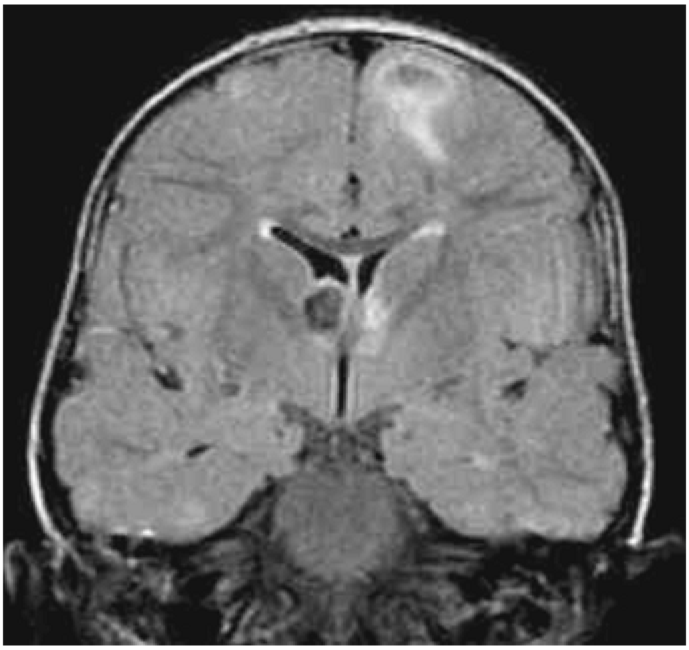

FIGURE 3. Tuberous sclerosis complex. Coronal fluid-attenuated inversion recovery magnetic resonance image shows multiple hamartomas and a large subependymal nodule.

MRI scans often demonstrate subependymal nodules with varying degrees of contrast enhancement.

Calcifications are frequent and are best demonstrated using gradient-echo sequences. Cortical tubers, ranging in size from 1 to 2 cm, are located at the gray–white matter interface. The parietal and frontal lobes are affected most often (Fig. 3). Tubers are isointense on T1 images but hyperintense using T2 sequences. Gyral core tubers may resemble an empty gyrus due to hypointensity of the white matter.[3,48,129]

The location of certain size tubers appears to correlate with EEG epileptogenic foci and prognosis. Patients with posteriorly located lesions have early onset of seizures as opposed to those with frontal lesions.[31] The presence of multiple and large cortical tubers, early onset of multiple seizure types, and multifocal EEG abnormalities correlate with unfavorable prognosis.

Lissencephalies

Lissencephaly refers to brains without normal sulcation (i.e., smooth brains).[43,72] The lissencephalies are a group of different disorders with distinct pathologic substrates and multiple causes. The major distinction is between classical lissencephaly and cobblestone lissencephaly, terms that reflect the appearance of the brain and that, in turn, derive from different genes. The various types of lissencephaly are classified according to the gene defect and associated malformations. For example, instead of classifying *LIS1* mutations and *DCX* mutations as subcategories of the isolated lissencephaly sequence, the classification includes Miller-Dieker syndrome, isolated lissencephaly syndrome, and subcortical band heterotopia as subcategories under *LIS1* mutations.[10] Instead of listing *POMT1* mutations and *FKRP* mutations under Walker-Warburg syndrome, the classification lists muscle-eye-brain disease and Walker-Warburg syndrome under *FKRP* mutations. As a result of this reclassification, many syndromes are listed more than once. For example, isolated lissencephaly sequence and band heterotopia are listed under both *LIS1* and *DCX* mutations and Walker-Warburg syndrome is listed under *POMT, FKRP,* and *FCMD* mutations.

Classical Lissencephaly

Classical lissencephaly or generalized agyria-pachygyria is a severe brain malformation manifested by a smooth cerebral surface, abnormally thick cortex with four abnormal layers,

diffuse neuronal heterotopia, enlarged ventricles, and often hypoplasia of the corpus callosum. Mutations in the *LIS1* gene result in Miller-Dieker syndrome (MDS), isolated lissencephaly sequence (ILS), and subcortical band heterotopia (SBH). Similar phenotypes also occur with *DCX* mutations, although in patients with *DCX* mutations, the frontal lobes are most affected; whereas in patients with *LIS1* mutations, the posterior areas are more involved. Mutations of the *ARX* gene cause X-linked lissencephaly with ambiguous genitalia and anomalies of the corpus callosum.[65,69,70,127]

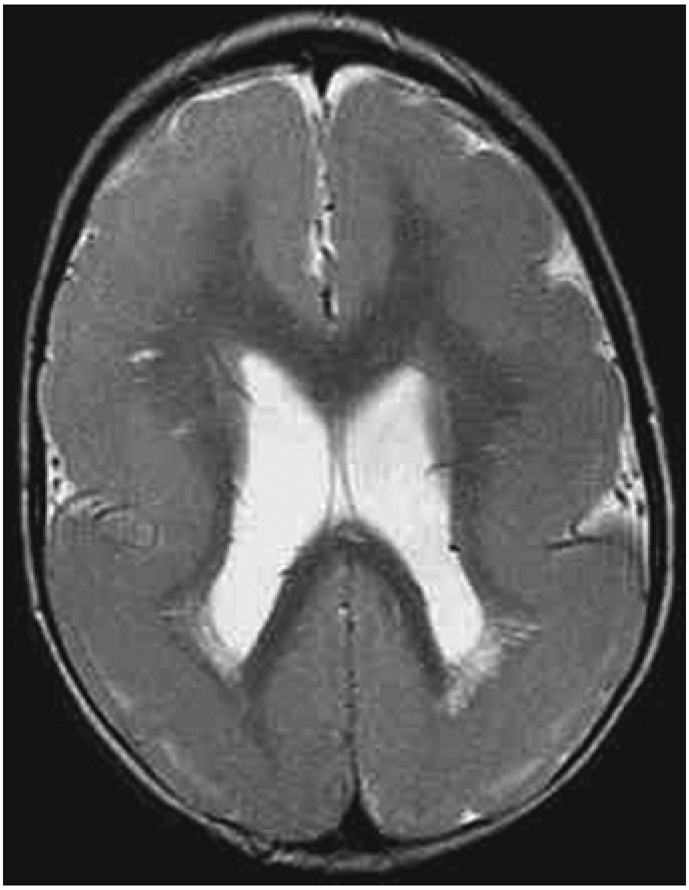

FIGURE 4. Lissencephaly. Miller-Dieker syndrome. *LIS1* mutation. Axial T2-weighted image shows smooth cortex.

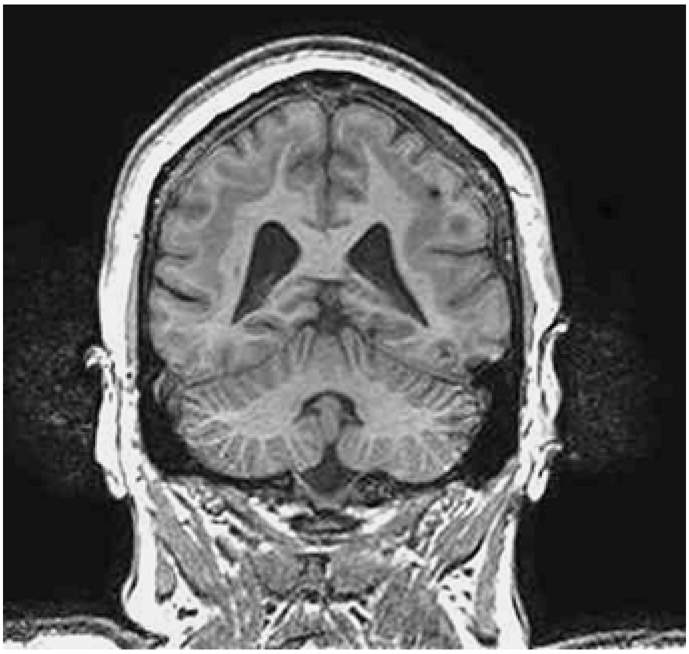

FIGURE 5. Subcortical band heterotopia (SBH). Coronal T1-weighted image shows typical subcortical band of gray matter with relative normal cortical infolding; *DCX* mutation.

Children with classical lissencephaly present with feeding difficulties or hypotonia. By 6 months of life, most of these children will have seizures, and the evolution of the epilepsy is similar in all patients. Infantile spasms with hypsarrhythmia and typical paroxysmal fast activity on the EEG appear in the first year of life. Response to treatment with adrenocorticotropic hormone (ACTH) or other anticonvulsants is variable, but most children will continue to have frequent seizures accompanied by severe developmental delay. Typical seizure types also include myoclonic, tonic, and tonic–clonic seizures. Profound mental retardation and spastic quadriplegia are present.

Diagnosis of classic lissencephaly is based on the typical clinical, EEG, and MRI features. MRI demonstrates a thickened cortex, loss of white matter, and vertical sylvian fissures, which result in the typical 8-shaped appearance of the brain (Fig. 4). Cortical thickness is in the range of 11 to 20 mm compared to 3.5 mm in normal controls.[11] In some patients there are regions of pachygyric cortex. Barkovich et al.[11] have also reported the presence of incomplete inversion of the hippocampi, a marker of arrest of neuronal migration.

Band Heterotopia (Double Cortex)

Subcortical band heterotopia or "double cortex syndrome" (Fig. 5) consists of symmetric and circumferential bands of gray matter located just beneath the cortex and separated from it by a thin band of white matter. The inner margin of the band is usually smooth, while the outer margin may be smooth or follow the interdigitations of the true cortex and white matter. Pathologic specimens have demonstrated normal lamination in cortical layers one through four; layers five and six usually cannot be seen; and layer six is merged with the U-fibers of the white matter.[90] Underneath, clusters of ganglion cells are present. Cortical thickness overlying the heterotopia is mildly increased or normal, and the temporal lobes, in particular the hippocampal structures, are normal as opposed to lissencephaly.

Band heterotopia is an X-linked recessive trait, and thus it is usually found only in females, although a few affected males have survived.[112] The risk for carrier females is high: 50% of their sons will have lissencephaly, and 50% of their daughters will have band heterotopia. Patients have mild to moderate developmental delay, upper motor neuron signs, and, in some, dysarthria. Full-scale IQs ranging from severely low to normal have been reported.[5] EEG investigations usually demonstrate frequent bilateral focal and multifocal spikes, although generalized discharges are also seen, including slow spike-wave patterns.

MRI findings are fairly stereotyped and demonstrate a circumferential band of subcortical gray matter heterotopia underlying the cortical mantle and separated from it by a thin rim of white matter. This is usually more obvious over the frontocentral parietal region. Barkovich et al. have suggested that the thickness of the heterotopic gray matter correlates with severity of the clinical syndrome.[5,66,90]

Cobblestone Lissencephaly Complex

Cobblestone lissencephaly, so called because of the pebbled appearance of the cortical surface due to leptomeningeal neuronal and glial heterotopia, is less common than classical lissencephaly. It is a complex brain malformation that consists of cobblestone cortex, polymicrogyria, pachymicrogyria, abnormal white matter, enlarged ventricles, small brainstem, and cerebellar vermian atrophy with cerebellar polymicrogyria.[43] It is often associated with eye malformations and congenital muscular dystrophy.

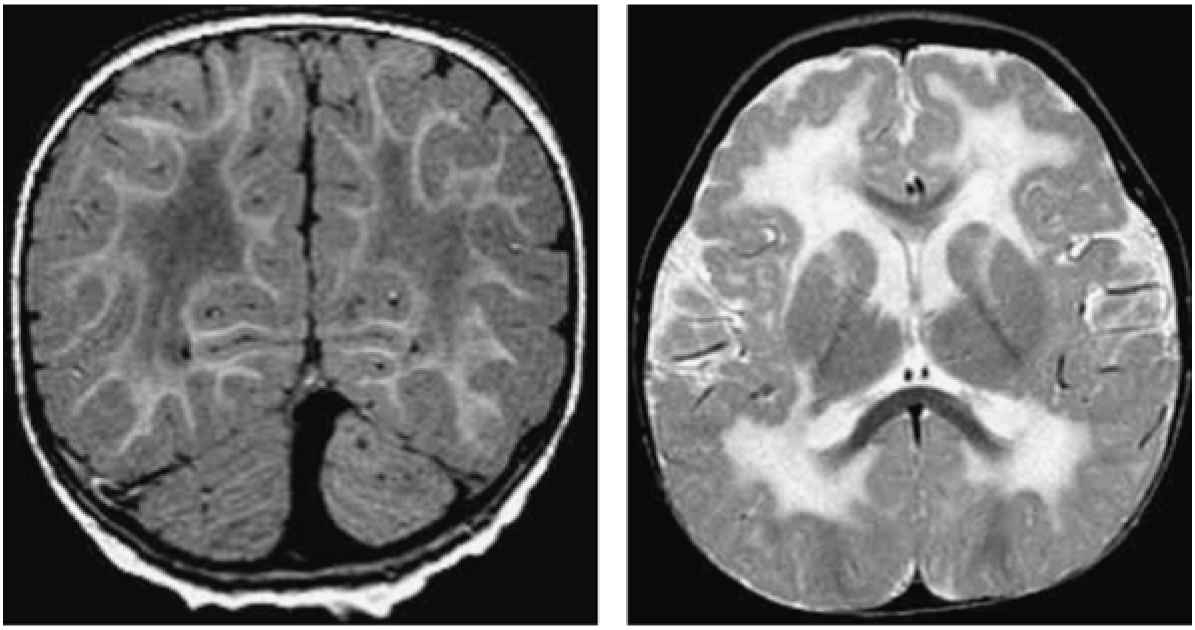

FIGURE 6. Cobblestone lissencephaly in Fukuyama congenital muscular dystrophy with *FKTN* mutation. Note white matter changes, smooth cortex, and cerebellar cyst.

Syndromes associated with cobblestone lissencephaly include Fukuyama congenital muscular dystrophy (FCMD) (Fig. 6), muscle-eye-brain disease (MEB), and Walker- Warburg syndrome (WWS). The classification of cobblestone lissencephalies changed significantly when it was discovered that congenital muscular dystrophies result from abnormalities of protein glycosylation.[2,22,143] Mutations in any of the genes involved can cause several different clinical syndromes. For example, Fukutin-related protein (*FKRP*) mutations can cause the clinical phenotypes of limb-girdle muscular dystrophy, muscle-eye-brain disease, and Walker-Warburg syndrome.[15] Fukuyama (*FCMD*) mutations can cause Walker-Warburg syndrome in addition to FCMD and MEB (Fukuyama CMD plus retinal abnormality) phenotypes.[14,124] Thus, the clinical phenotype may be related more to the severity of the mutation than to the precise gene.

Most children with cobblestone lissencephaly have severe mental retardation and hypotonia, mild distal spasticity, and often poor vision. Most patients do not survive beyond the first decade. Seizures have not been well studied.

Heterotopia

Heterotopia is, by definition, the presence of normal cells in improper locations.[8,47] In cases of epilepsy associated with MCDs, this definition usually refers to neurons within the periventricular or subcortical white matter. At the present time, there are two major groups of heterotopia that are recognized as syndromes: Periventricular nodular heterotopia (PNH) and focal subcortical heterotopia.

Periventricular Nodular Heterotopia

Periventricular nodular heterotopia, or subependymal nodular heterotopia, is the most common form of developmental disorder seen in patients with epilepsy.[8,21,44,58,68] The condition is caused by the failure of a group of neurons to either initiate or complete the migration process toward the cortical mantle. PNH can range from a few nodular clusters of neurons to diffuse lining of the ependymal regions. Bilateral periventricular nodular heterotopias (BPNHs) are usually contiguous and symmetric but occasionally are isolated and asymmetric. Ninety percent of reported patients with PNH had diffuse, narrow involvement of all subventricular regions.[44,63,84]

Patients with PNH usually have normal neurologic development. A few have had symptoms that were probably overlooked, such as headaches or psychiatric complaints, while other persons discovered during family evaluations have been asymptomatic. The majority of patients have normal intellectual and motor function or mild mental retardation. Seizures are common, and epilepsy occurs in almost 80% of cases. Interestingly, seizures usually begin in adolescence. In patients with seizures, temporal and parieto-occipital symptomatology is common. EEG findings are generally nonspecific, and interictal discharges are infrequent.[57]

Typical MRI features consist of multiple smooth ovoid nodules of cortical gray matter lining the lateral ventricles but sparing the third and fourth ventricles (Fig. 7). Approximately 75% of patients have bilateral lesions, and 30% have additional focal subcortical heterotopia. Callosal and cerebellar malformations are present in 25% of cases. Signal intensity from the nodules is isointense with gray matter in all MRI sequences, and the nodules do not enhance with contrast, distinguishing features from subependymal hamartomas seen in tuberous sclerosis. In 20% of patients, other cortical malformations may be detected.

Classic PNH can be associated with FILA (Filamin) mutation on chromosome Xq28.[46] Because it is an X-linked mutation, men are only rarely affected.[45,57,59,97] Most pregnancies carrying male fetuses terminate in spontaneous abortions.

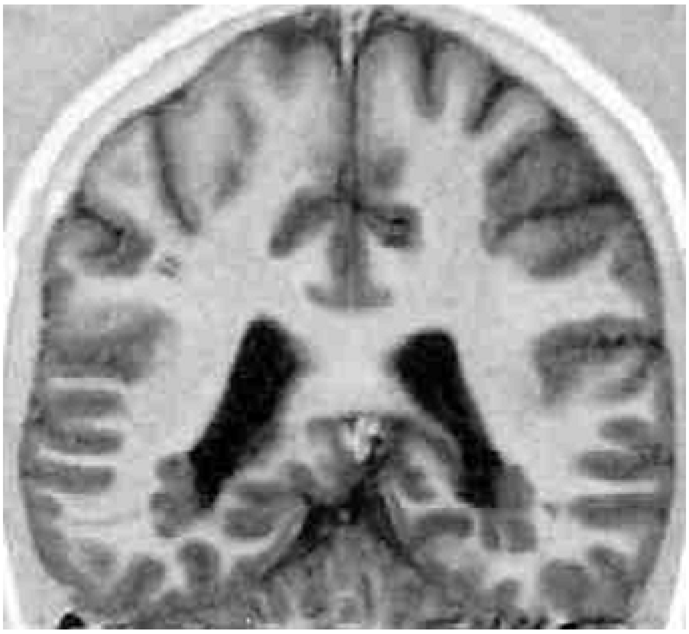

FIGURE 7. Periventricular nodular heterotopia due to Filamin 1 mutation. Note periventricular gray matter nodules.

Focal Subcortical Heterotopia

Although the majority of patients with subependymal heterotopia have diffuse nodular lesions, occasionally patients may present with few focal lesions involving one hemisphere. According to reviews,[13,45,83] the frequency of focal subcortical heterotopia is <20%. In a patient without neurologic symptoms, such lesions may be just coincidental findings, but the true incidence of seizures in these patients is unknown. Most patients have been sporadic occurrences, and subcortical heterotopias are probably secondary to mosaic mutations or to true environmental injuries.

Clinically, patients may present with normal development, but at times, depending on the size of the lesions, contralateral pyramidal signs may be present. Approximately 50% of patients with focal subcortical heterotopia are developmentally and cognitively delayed. Developmental delay is more common among patients who have concomitant callosal agenesis. Speech appears to be normal in some patients, but when lesions are extensive and involve the dominant hemisphere, speech delay is observed. Seizures in these patients are a mixture of focal motor and secondary generalized convulsions. Infantile spasms have also been described. The ultimate neurologic and seizure outcome not only depends on the type, location, and size of lesions, but also on the type of developmental disorder.

Imaging features in these patients are quite characteristic. Heterotopia appears as clusters of nodules of gray matter with irregular margins (Fig. 8). The surrounding white matter is usually normal and has normal-intensity signal. At times, the heterotopia may appear as masses with ventricular compression. On some occasions, cerebrospinal fluid (CSF) signal may be seen within these malformations. Corpus callosum abnormalities have also been reported.

Polymicrogyria

Polymicrogyria (PMG) refers to an abnormal macroscopic appearance of brain gyration that is characterized by excessive numbers of small gyri. In some cases, the gyri are shallow and very small, separated by slight sulci, whereas in other cases the gyri are wider.[1,86,108]

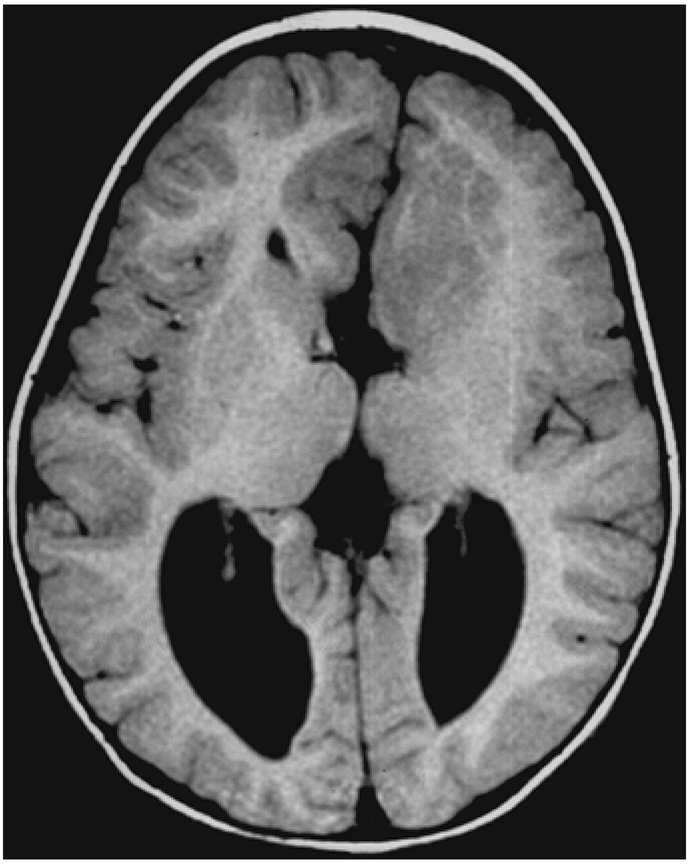

FIGURE 8. Subcortical nodular heterotopia. Axial T1-weighted magnetic resonance image shows large subcortical mass of gray matter in the mesial frontal lobe associated with partial agenesis of corpus callosum and ventricular changes.

The histologic changes in polymicrogyria are midcortical laminar necrosis in layer five resembling ischemic change. Superficial to this cortical band, the cortex consists of normal layers four, three, and two. Because late-migrating neurons reach their normal positions before laminar necrosis takes place, this type of malformation most likely originates in some cases after the 20th fetal week and is thus postmigratory in origin.

Histologic classification divides polymicrogyria into four-layered and unlayered types. Although most of the experimental data and pathologic findings in human fetuses suggest that polymicrogyria is the result of a postmigratory ischemic mechanism, this has been disputed and some investigators[1,99] have postulated that at least some forms of PMG are premigratory in origin. In fact, the best known cause in humans is intrauterine cytomegalovirus (CMV) infection, which is also usually associated with diffuse or patchy white matter changes and often diffuse or multifocal calcifications.

Several new unilateral and bilateral polymicrogyria syndromes have recently been described, and several others have had the causative genes mapped or identified. Reports of *bilateral perisylvian polymicrogyria* had commented on a significant male preponderance.[96] This was subsequently confirmed in a large series that localized a gene to Xq28.[135] Unilateral and bilateral perisylvian polymicrogyria has been observed in several chromosomal aneuploidy syndromes, most prominently with deletion of the chromosome 22q11.2 DiGeorge syndrome critical region,[18,19] and in families with presumed X-linked inheritance.[20] Additional bilateral polymicrogyria syndromes include bilateral *frontal polymicrogyria,*[60] *bilateral parasagittal parieto-occipital polymicrogyria,*[61] *bilateral lateral parietal polymicrogyria,*[7] *bilaterally generalized polymicrogyria,*[30] and two distinct malformations with periventricular nodular heterotopia and overlying polymicrogyria, one with frontal-perisylvian predominance and another with posterior-temporal predominance. A recent report described a malformation designated *bilateral frontoparietal polymicrogyria* associated with abnormalities of myelination and dysplasia of the cerebellum and brainstem.[29] This has been mapped to chromosome 16q12.2-21 and subsequently associated with mutations of the *GPR56* gene.[109]

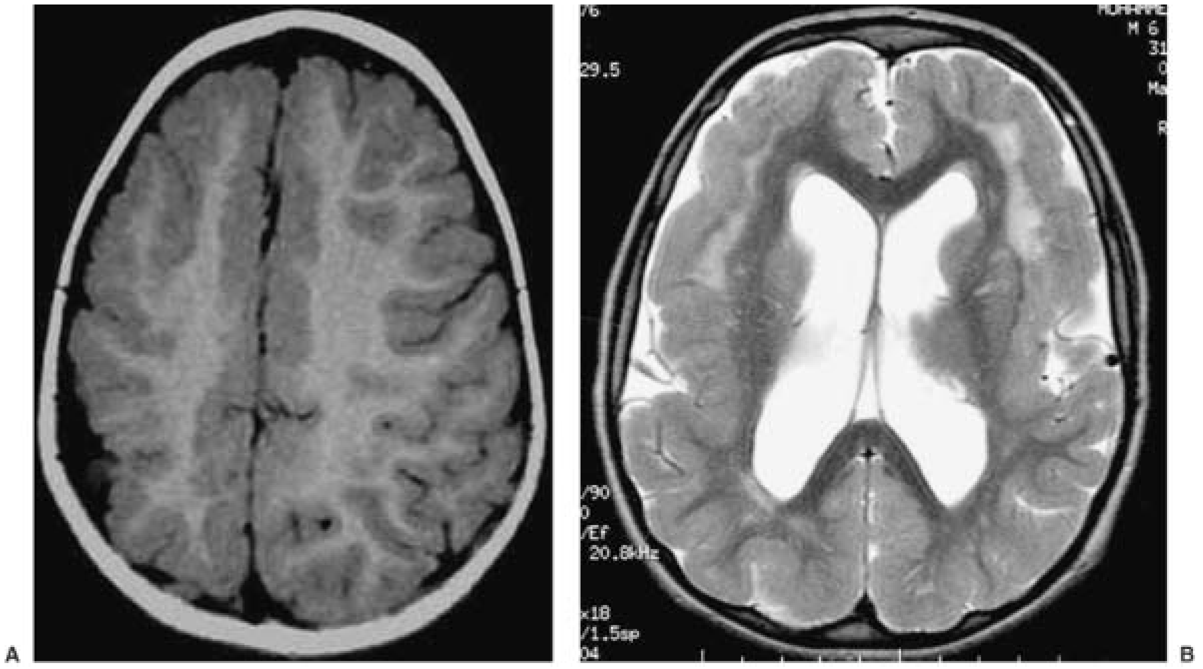

FIGURE 9. A: Unilateral polymicrogyria (PMG). Note extensive atrophy and PMG cortex in the left hemisphere. **B:** Bifrontal PMG syndrome with *GPR56* mutation. Note PMG and abnormal white matter changes.

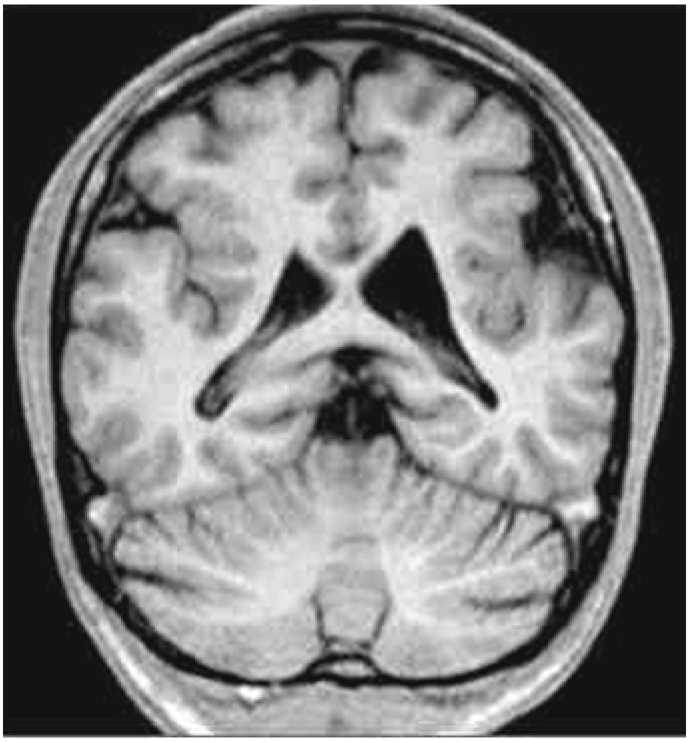

FIGURE 10. Polymicrogyria (PMG), bilateral perisylvian syndrome. Coronal T1- weighted magnetic resonance image shows bilateral perisylvian PMG.

The clinical presentation depends on the location and extent of polymicrogyria, and whether the contralateral hemisphere is involved. It is thus highly variable. Diffuse polymicrogyria may present with severe developmental delay, microcephaly, and hypotonia. Polymicrogyria can be limited to one hemisphere (*unilateral hemispheric polymicrogyria*) (Fig 9); it can also be one of the pathologic changes associated with hemimegalencephaly.

MRI findings demonstrate a seemingly thick cortex that can be interpreted as pachygyria. However, cortical thickness in polymicrogyria is less than that observed in pachygyria. The sulci are shallow, and the underlying white matter may show abnormal T2 signal. (Figs. 9 and 10).

As indicated by the foregoing descriptions, PMG syndromes have been classified by the anatomic distribution of the abnormal gyri. Some syndromes can also now be identified on the basis of clinical and imaging features. The most common of these is *bilateral perisylvian polymicrogyria,* also known as *congenital bilateral perisylvian syndrome* (CBPS).[52,56,73,74,98] Clinical features include congenital pseudobulbar paresis, intellectual delay, and characteristic bilateral lesions on computed tomography (CT) or MRI. Almost 90% of patients present with seizures, and half of them have intractable epilepsy. A unique seizure pattern consists of perioral and bilateral facial involvement. Other seizure types include atypical absences attacks, tonic/atonic seizures, and generalized tonic–clonic seizures. EEG findings include generalized spike-wave or multifocal abnormalities, but 20% have had localized epileptogenic discharges. The diagnosis can be made on the basis of the clinical features; brain MRI provides confirmation.[74] The imaging findings are distinctive with involvement of the sylvian,

opercular, and perisylvian regions (Fig. 10). Except for unilateral hemispheric polymicrogyria, the other bilateral polymic-rogyria syndromes do not have characteristic clinical or EEG features.

Schizencephaly

Although schizencephaly has been considered a condition different from polymicrogyria, most authorities today classify them as *polymicrogyria/schizencephaly complex*. The term *schizencephaly* is used to describe clefts in the cerebral hemispheres that are lined with gray matter and extend from the pia to the ependymal lining.[42,54,64] The clefts may be in apposition to each other (closed lip or type I schizencephaly) or separated (open lip or type II schizencephaly).[126] The cortex surrounding the clefts can be normal or have underlying polymicrogyria. The gray matter lining the cleft itself is usually composed of polymicrogyric cortex. Subependymal heterotopias are common. The pathogenesis of schizencephaly is probably similar to that of polymicrogyria and porencephaly. It is, rather, the extent of cortical injury that determines if a lesion becomes polymicrogyria or schizencephaly. Injuries that extend more deeply into the cortex and destroy the superficial portions of the glial fibers produce cortical infoldings lined by polymicrogyria. When the injury involves the entire thickness of the developing hemisphere, schizencephaly results. The septum pellucidum is absent in 70% to 90% of patients.[9,117]

Schizencephaly has many features resembling those of polymicrogyria. As with polymicrogyria, schizencephaly can be bilateral or unilateral. Furthermore, bilateral lesions can be either symmetric or asymmetric. In our experience, approximately 30% to 40% of patients with schizencephaly have bilateral lesions. They are often asymmetric, however, with type I schizencephalic lesions in one hemisphere and type II lesions in the opposite hemisphere (Fig 11).

Patients with bilateral schizencephaly often have a moderate to severe spastic quadriparesis. Severe mental retardation and language disorders are also common. Infantile spasms may be the presenting seizure type in these patients, and focal motor seizures with and without secondary generalization are common. A minority of patients with bilateral lesions are controlled on drugs.

Unilateral schizencephalies are evenly distributed between the two hemispheres. The frequency of type I versus type II lesions is similar. Developmental delay, intellectual impairment, and hemiparesis contralateral to the cleft are common findings. We have not observed any significant differences in language dysfunction between left and right dominance in persons with schizencephaly, probably because these patients most likely transfer language to the more normal hemisphere. Seizures are usually focal motor, but sensory and complex partial seizures also occur. EEG investigations may reveal focal temporal discharges when the lesions are localized to the temporal-parietal convexity. However, EEG spikes may occur beyond the area of malformation, including the opposite hemisphere (see below). The location of lesions by MRI appears to be evenly distributed, with the majority located in pre- and postcentral regions.

An interesting issue concerning patients with unilateral polymicrogyria or schizencephaly is the presence of subtle cortical developmental malformations of the opposite hemisphere. The contralateral lesions are usually present in the mirror regions of the opposite hemisphere. This may explain why some patients with unilateral lesions may present with severe developmental delay. These findings underscore the possible pathogenic mechanism for cortical dysplasia, polymicrogyria, and schizencephaly.

Management of Patients with Malformations of Cortical Development

The first step is to make a correct diagnosis of the specific MCD. This is important for several reasons. First, accurate identification of the underlying MCD permits proper genetic counseling. Second, a syndromic classification assists in making rational decisions about the medical and surgical treatment for seizures. The best example of such a case is the congenital bilateral perisylvian syndrome. Third, proper diagnosis may permit assessment of ultimate prognosis. In the following section we will discuss management issues pertaining to specific problems and conditions.

Infantile Spasms and Malformations of Cortical Development

MCD is recognized with increasing frequency in children with infantile spasms (ISs) because high-resolution imaging has permitted improvement in the detection of MCDs. In fact, MCDs are the most frequent cause of ISs. However, the ultimate prognosis for these children is variable and more likely to be associated with the extent and type of underlying MCD (see Chapter 229, West Syndrome).

A number of observations have modified the treatment options in patients with ISs and MCDs.[36] It is likely that corticosteroids may be the treatment of choice in patients with focal developmental lesions and ISs associated with hypsarrhythmia. In contrast, open studies have shown that vigabatrin (VGB) is effective in patients with diffuse malformations such as TS. VGB in combination with carbamazepine or benzodiazepines is effective in TS. The response to drug treatment in patients with ISs and diffuse malformations such as lissencephaly is poor.

Surgical treatment of patients with ISs and MCDs is dependent on the underlying condition. The presence of a tumor or porencephalic cyst is usually associated with good results.[4,138] Large multifocal resections have provided improvement in a number of children with ISs and focal features.[32,33] Modified hemispherectomy is also effective in patients with ISs and hemimegalencephaly.[39,106] Callosal sections performed in some children with diffuse MCDs and ISs have given disappointing results.[140]

Other Seizure Types

Apart from the clear difference in response of TS patients with ISs to VGB treatment, there have been no randomized drug trials to prove that any particular drug regimen is superior in treating patients with MCDs.

The response to antiepileptic drugs (AEDs) is generally dismal in diffuse malformations such as Aicardi syndrome; it is more variable among patients with lissencephaly. Among patients with bilateral lesions or focal malformations, about 35% respond to AEDs.[125] It is estimated that the response rate to AEDs is approximately 35%. Valproic acid and other broad-spectrum drugs are generally chosen in patients with diffuse malformations.

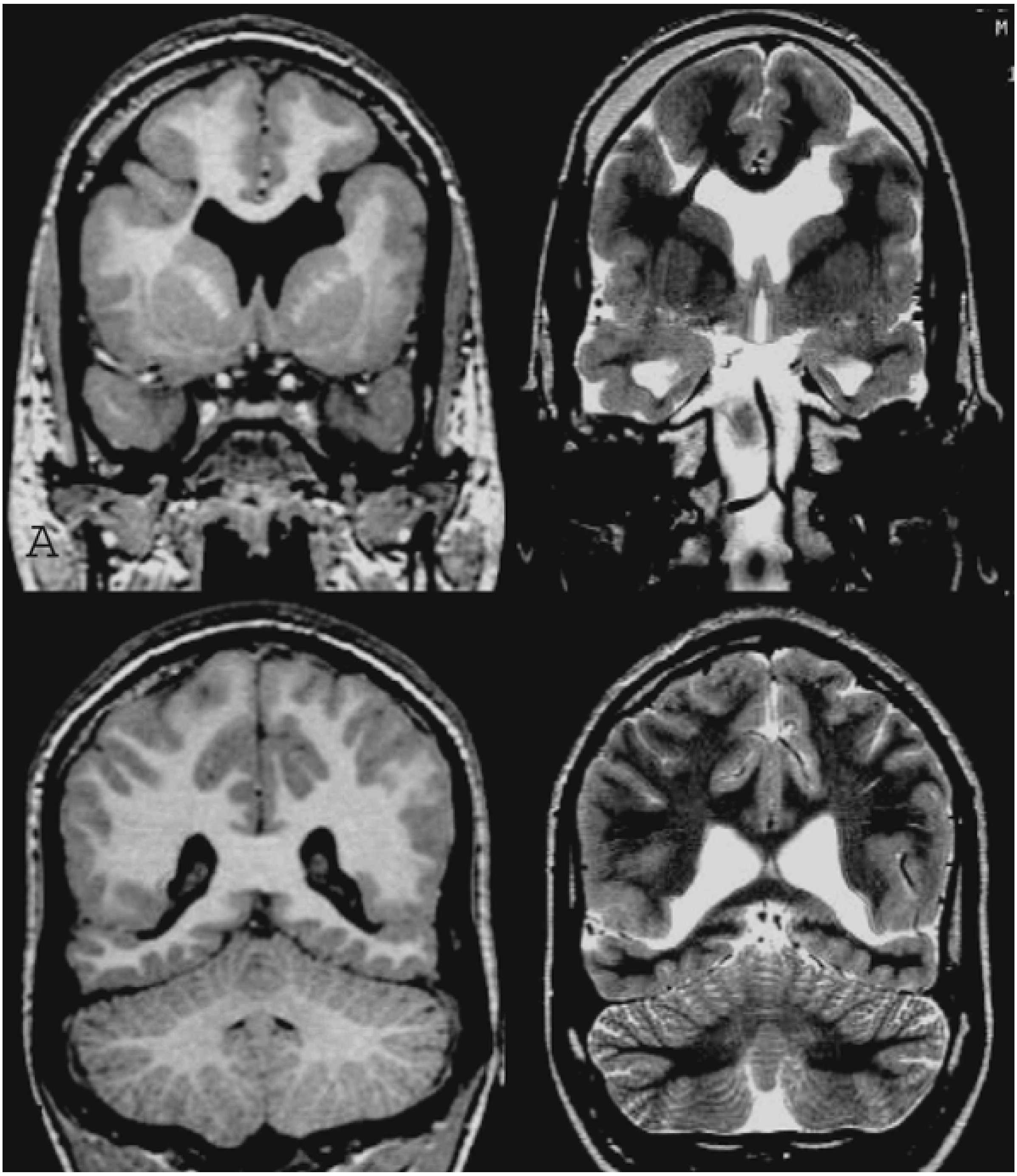

FIGURE 11. Schizencephaly/polymicrogyria syndrome, bilateral symmetric clefts involving frontal and parietal regions.

Surgical Strategies

In some cases of MCDs, depending on the specific clinical and investigative findings, surgical procedures may be appropriate

for treatment (see Chapters 178 and 179). In general, any defined abnormality (usually on MRI) is only a small part of the disturbance of the brain due to abnormal development. Therefore, resections need to extend beyond just the clearly defined abnormality; outcome is generally not as good as that following resections of focal lesions such as benign tumors or cavernomas.

Focal resections in patients with MCDs have been performed with variable results. Several groups[78,80,102,137,139,141] reported good outcome if the visualized lesions were completely resected. In our experience, the best outcome is seen among patients with small developmental abnormalities in the temporal lobe. Unfortunately, focal MCDs are commonly localized in the perisylvian region, and thus, motor or language vital cortical areas limit resections. In such cases, outcome is more variable. Recent data have indicated that 52% of patients with temporal lobe dysplasias were seizure free compared with 29% of those with frontal lobe dysplasias.[102] reported excellent outcome when ictal-like EEG activity was eliminated by surgery. Therefore, it would appear that the outcome following surgical resection of focal MCDs depends on the extent of lesion removal and elimination of highly epileptogenic discharges on EEG.

Table 2 Genetic Basis of Malformations of Cortical Development

Syndrome	Locus	Gene (Testing)	Protein
ARMCP^{MCPH1}	8p23	**MCPH1***(R)*	Microcephalin
ARMCP^{ASPM}	1q31	**ASPM** *(R)*	Abnormal spindle—like microcephaly
ARMCP^{CDK5RAP2}	9q34	**CDK5RAP2** *(R)*	Cyclin-dependent kinase 5 regulatory associated protein 2
ARMCP^{CENPJ}	13q12.2	**CENPJ** *(R)*	Centromere associated protein J
ARPHM	20q13.13	**ARFGEF2** *(R)*	ARFGEF2
MCPHA	17q25.3	SLC25A19 (R)	Nuclear mitochondrial deoxynucleotide carrier
SCKL1	3q22-q24	**ATR** *(R)*	FRAP-related protein 1
ILS^{DCX}	Xq22.3-q23	*DCX=XLIS* (C)	DCX or doublecortin
SBH^{DCX}	Xq22.3-q23	*DCX=XLIS* (C)	DCX or doublecortin
MDS	17p13.3	Several contiguous	PAFAH1B1, 14-3-3ε, and others

ILS^{LIS1}	17p13.3	*LIS1* (C)	PAFAH1B1
SBH^{LIS1}	17p13.3	*LIS1* (C)	PAFAH1B1
LCH^{RELN}	7q22	*RELN* (R)	Reelin
XLAG^{ARX}	Xp22.13	*ARX* (C)	Aristaless-related homeobox protein
FCMD^{FCMD}	9q31	*FCMD* (R)	FCMD or Fukutin
MEB^{POMGnT1}	1p33-34	**POMGnT1** *(C)*	Unknown
MEB^{FKRP}	19q13.3	**FKRP** *(R)*	Fukutin-related protein
MDC1C^{FKRP}	19q13.3	**FKRP** *(R)*	Fukutin-related protein
MDC1D^{LARGE}	22q12.3-q13.1	**LARGE** *(R)*	
WWS^{POMT}	9q34.1	**POMT1** *(R)*	O-mannosyl-transferase 1
WWS^{FKRP}	19q13.3	**FKRP** *(R)*	Fukutin-related protein
WWS^{FCMD}	9q31	**FCMD** *(R)*	FCMD
BPNH^{FLNA}	Xq28	*FLNA* (R)	Filamin-A
BPNH with microcephaly	20q13.3	**ARFGEF2** *(R)*	BIG2
BPNH^{5p}	5p15	Unknown	Unknown
TSC1	9q32	*TSC1* (C)	Hamartin
TSC2	16p13.3	*TSC2* (C)	Tuberin

BFPP	16q13	*GPR56* (R)	Unknown
WARBM1	2q21.3	RAB3GAP (R)	
BPSP	Xq28	Unknown	Unknown

ARMCP, autosomal recessive microcephaly; ARPHM, autosomal recessive periventricular heterotopia and microcephaly; BFPP, bilateral frontoparietal polymicrogyria; BPNH, bilateral periventricular nodular heterotopia; BPSP, bilateral perisylvian polymicrogyria; C, clinical testing available for gene; FCMD, Fukuyama congenital muscular dystrophy; ILS, isolated lissencephaly sequence; LCH, lissencephaly with cerebellar hypoplasia; MCPHA, Amish lethal microcephaly; MDC, congenital muscular dystrophy; MDS, Miller-Dieker syndrome; MEB, muscle-eye-brain disease; R, research testing available for gene; SBH, subcortical band heterotopia; SCKL1, Seckel syndrome 1; WWS, Walker Warburg syndrome.

In cases of hemimegalencephaly, high seizure-free rates have been reported with early hemispherectomy.[119] Although there has been controversy regarding the optimal timing of surgery, an increasing number of investigators advocate early surgical intervention with the aim of protecting the normal hemisphere from the damaging effects of seizures and subsequent abnormal development. Another point of contention has related to the type of surgery. Some have argued that complete hemispherectomy is the procedure of choice,[34,119] whereas others recommend functional hemispherectomy.[28,34,131] Unfortunately, there have been no randomized trials to assess this issue. The complications of complete hemispherectomy, which include hydrocephalus and hemosiderosis, appear to be higher than with functional hemispherectomy.

Callosotomy has been used in patients with severe diffuse MCDs, but the results have been disappointing. However, benefit has been observed in some patients with specific types of malformations. For example, we previously reported good outcome in cases of congenital bilateral perisylvian syndrome,[73] although results have not been predictable. Recent experience with individual patients suggests that multiple subpial transactions may be a potential treatment for selected patients with bilateral lesions. In such cases, the surgical approach should be viewed as a palliative procedure that offers the possibility of a good outcome. Finally, vagus nerve stimulation (VNS) has been carried out in patients with various types of MCDs. Although some reports have described improved seizure control, there are no prospective studies. Our own experience indicates that outcome with VNS is unpredictable.

Genetic Counseling

MCDs often affect children, and thus, genetic counseling becomes extremely important for their families. Much has been learned about the genetics of MCDs, but diagnostic testing is available for only a few (Table 2). Among malformations of neuronal and glial proliferation/apoptosis, routine tests are only available for the two causal genes for tuberous sclerosis (*TSC1* and *TSC2*).

All forms of lissencephaly/subcortical band heterotopia are genetic, and tests are available that are applicable to at least 80% of patients, although this varies with the specific phenotype. When lissencephaly is suspected, chromosome analysis and fluorescent in situ hybridization (FISH) using a probe that contains the *LIS1* gene should be done followed by sequencing of *LIS1* and then *DCX* if *LIS1* is negative. When band heterotopia is suspected, the order of testing should be changed to sequencing of *DCX*, followed by FISH with a probe containing *LIS1*, and finally sequencing of *LIS1*. In a child with lissencephaly whose brain imaging also reveals callosal agenesis, or whose physical examination demonstrates abnormal genitalia, *ARX* testing should be done first. When mutations of any of the aforementioned genes are found, parents should generally be tested to determine their carrier status, as this is important for genetic counseling. Parental testing is especially important for the two X-linked genes, *ARX* and *DCX*, as mothers are often carriers. The frequency of postzygotic mosaicism is high in mothers, probably at least 5%, which must be taken into account for genetic counseling. When genetic tests for lissencephaly or band heterotopia are negative, later siblings have nonetheless been affected in several instances.[41,50,82,116] Counseling should include acknowledging a 10% to 15% risk in such situations. Without testing, counseling is more difficult.

Two genes associated with PNH, *FLNA* and *ARFGEF2*, have been discovered, but no labs currently offer clinical testing. Classic PNH with cerebellar hypoplasia and no dysmorphic features occurs much more frequently in females than in males, and mutations of the X-linked *FLNA* gene account for >80% of familial PNH, ~20% of sporadic PVNH in females, and ~10% in sporadic males.[121] The large size of the gene, which would make clinical testing very expensive, probably accounts for the lack of testing by clinical labs. Among women carriers, ~50% have de novo mutations of *FLNA*, whereas the remaining 50% have inherited mutations. Although maternal transmission is much more likely, father-to-daughter transmission is possible, implying that either parent can transmit the mutation to a female proband.[62] An affected man with PNH caused by an *FLNA* mutation would be expected to transmit the mutation to all of his daughters unless somatic mosaicism is present. To date, all individuals harboring *FLNA* mutations have been found to have PNH, although they can be asymptomatic. Because germline mosaicism of *FLNA* has never been reported in PNH, the recurrence risk is probably low when a mutation is found in the proband but neither parent is a carrier. Microcephaly with PNH is a rare malformation associated with mutations of *ARFGEF2* in a few patients.[122]

So far, five genes have been identified that are associated with the cobblestone cortical malformation found in Fukuyama congenital muscular dystrophy, muscle-eye-brain disease, and Walker-Warburg syndrome (*FCMD*, *FKRP*, *LARGE*, *POMGnT1*, and *POMNT1*). Testing is not yet available clinically. However, enzyme analysis has been developed for POMGnT1 in muscle,[144] and it should be possible to use the same assay in fibroblasts. Similar assays for other enzymes in this group could be developed as well.

There are few laboratory tests to identify genes associated with malformations of late migration and cortical organization. A few patients with perisylvian polymicrogyria have had small chromosomal deletions or duplications, the most common being deletion of chromosome 22q11.2. We therefore recommend chromosome analysis, FISH using a probe from 22q11.2, and FISH using a subtelomeric probe set. The yield with the 22q11.2 probe appears to be high if the polymicrogyria is asymmetric. The causal gene for bilateral frontoparietal polymicrogyria has been identified (*GPR56*),[110] but it cannot yet be tested for clinically. Several years ago, mutations of the *EMX2* gene were reported in a few patients with schizencephaly,[26,53] but these results have not been confirmed. There is now doubt that *EMX2* is a causal gene for schizencephaly.

Summary and Conclusions

Malformations of cortical development are an important cause of drug-resistant epilepsy. High-resolution MRI now permits detection and classification of MCDs, and advances in molecular genetics are identifying causal gene mutations. It is important today to view MCDs within a coherent framework that integrates the clinical phenotype, imaging findings, and genetic cause (if known). Antiepileptic drug treatment provides benefit in some cases, and surgical intervention is useful in others. However, treatment is often frustrating and the results of various therapeutic interventions unpredictable.

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Chapter 260

Chromosomal Abnormalities

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Introduction

About 30 years ago, chromosomal abnormalities, as detectable by classic cytogenetics, were estimated to cause approximately 6% of central nervous system (CNS) malformations.[31] Today, the use of current techniques such as high-resolution chromosome banding, fluorescent in situ hybridization (FISH), and molecular genetics would certainly increase this percentage; it was estimated recently that genome-wide molecular cytogenetics techniques (array-CGH) can detect cryptic deletions/duplications in no less than 20% of individuals with mental retardation and dysmorphic features but apparently normal karyotype (Fig. 1).[139] It is likely that array-CGH at higher resolution will increase this percentage even further.

Most syndromes associated with chromosomal abnormalities are caused by duplications (with duplication of a segment of chromosome), deletions (absence of a segment), or breakpoint disruptions (only one or a few genes are disrupted). Virtually all known chromosomal abnormalities lead to anatomic and functional impairment of the CNS and, especially those involving autosomes, are accompanied by mental retardation. Tharapel and Summit[155] found 6.2% of cases of mental retardation to be associated with chromosomal abnormalities, as contrasted with the 0.7% rate found in controls.

The risk of epilepsy is greater in individuals with chromosomopathy than in the general population.[74] However, chromosomal abnormalities do not represent a frequent cause of epilepsy.[78]

Epilepsy as a complication of a chromosomal abnormality syndrome should be considered in a twofold perspective. First, symptomatic epilepsies have a high probability of causing intractable seizures, leading to further disability in these patients. Severe epilepsy may significantly reduce a low-IQ patient's potential for autonomy in everyday life.[64] Second, when seizures are the main manifestation of a chromosomal disorder or present with peculiar electroclinical patterns, it is important to establish whether these associations result from structural CNS abnormalities caused by the chromosomal changes or from the effect of loci that specifically affect seizure susceptibility. Careful attention to chromosomal abnormalities associated with seizures, together with detailed analysis of electroclinical patterns, may help to detect specific genes affecting seizure susceptibility.[2,142] It seems likely that the association between cryptic deletions/duplications and epilepsy will improve our ability to clone new critical genes.

Only those chromosomal abnormalities of special importance for their high frequency or association with epilepsy are considered in this chapter.

Standard Cytogenetic and Molecular Techniques for Diagnostics

Standard Karyotype and High-Resolution Chromosome Analysis

The karyotype of an individual can be ascertained from readily accessible somatic cells, such as peripheral blood lymphocytes or skin fibroblasts. Each chromosome can be identified by special staining techniques, using fluorescent dyes or Giemsa staining after treatment with a proteolytic enzyme (trypsin). A typical standard karyotype from metaphase cells contains 400 to 550 bands per haploid genome. "High-resolution" chromosome analysis makes it possible to visualize up to 2,000 bands, although a high-resolution chromosome analysis of standard quality allows the detection of about 850 bands. Given the greatly increased amount of work, the difficulty of the analysis, and the cost, high-resolution chromosome analysis should not be considered as a routine cytogenetic assay.

Molecular Karyotyping with Array-CGH

Several techniques defined as molecular cytogenetics have, over the course of the last 10 years, improved the resolution capability of the chromosome banding. The latest technology is the array-CGH, which represents a powerful modification of classical comparative genomic hybridization (CGH) based on metaphases. Using CGH, the DNA of a patient (to be tested) and the DNA of a control are labeled with green and red fluorochromes, respectively, and hybridized on metaphase spreads. The images of both fluorescence signals are captured, and the ratio of DNA intensities quantified using a dedicated software along each chromosome. The chromosome regions represented in the same amount in both DNAs (patient and control) appear yellow, the deleted regions appear red, and the duplicated regions appear green. The difficulty of obtaining sufficiently long metaphases limits the resolution power of this technique to a maximum of 3 Mb. Array-CGH technology replaces the use of chromosome spreads with clones or oligomers (targets) that cover the entire genome, and its resolution power depends only on the amount of targets and their distribution. Recently, microarrays using bacterial artificial chromosome (BAC) clones separated by 100 Kb have been used. Other platforms, using oligomers as targets, have a higher resolution that theoretically can reach up to a few hundreds of base pairs. The use of these arrays might allow the detection of deletions and duplications below the size of 1 Mb and precisely define their

breakpoints (Fig. 1). This technology has also revealed that the human genome may harbor deletions and duplications, having an average size of 2 Mb and being devoid of phenotypic effects, which may play a role in multifactorial diseases. It seems obvious that microarray-CGH will have a crucial role in pre- and postnatal cytogenetics as well as in oncology; its potential in the etiologic diagnosis of epilepsy associated with mental disability and dysmorphic features is extremely high.

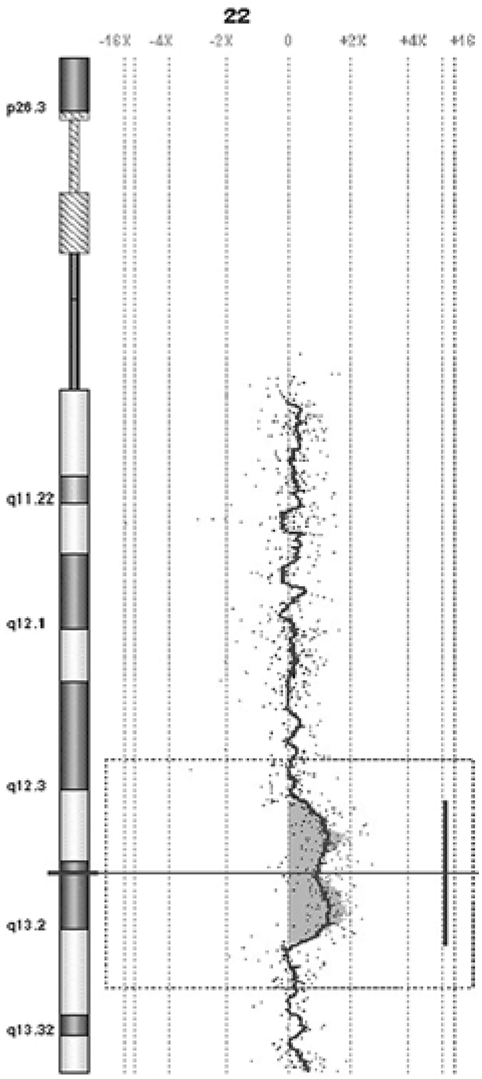

FIGURE 1. Eight-year-old girl with early-onset focal epilepsy and dysmorphic features. 6.9 Mb duplication at 22q13.1q13.2 detected through oligo-array-CGH at 75 kb resolution; log2 ratio of signals intensity is increased in the duplication region where red signals are located more proximal to the +2x line than are the remaining ones. This interstitial duplication had not been detected at conventional karyotyping nor, obviously, after FISH with subtelomeric probes. (See color insert.)

Fluorescent in Situ Hybridization

The hybridization of a labeled DNA probe for spreading metaphase chromosomes allows the detection of small deletions, duplications, or cryptic translocations involving the chromosomal segment complementary to a probe labeled with a fluorochrome. The probe signal can be visualized by fluorescence microscopy. Double or multiple hybridizations can be carried out at the same time using different fluorochromes. Although this is a sensitive technique, it allows the investigation of only a few loci in one experiment, thus it can be requested when the clinician already has a specific clinical suspicion known to be associated with the deletion/duplication of that gene/region (i.e., Angelman syndrome and 15q11–q13 deletion).

Southern Blot Analysis

Differences in the DNA sequences at the same locus in different individuals can be detected by restriction enzyme digestion and Southern blot analysis. The diversity in DNA sequences among different individuals will result in either the introduction or loss of specific restriction sites, thereby causing DNA fragments of different sizes. The DNA is subsequently electrophoresed on an agarose gel, denatured with alkali, transferred to a nylon filter, and hybridized with a radiolabeled probe. The resulting X-ray film permits a comparison among the segments of DNA from different individuals.

Polymerase Chain Reaction

Polymerase chain reaction (PCR) allows the amplification of DNA fragments of 100 to 2,000 bp in length. The reaction is carried out in the presence of oligonucleotides flanking the region of interest, free deossinucleotides, template DNA, thermostable DNA polymerase from *Thermophilus aquaticus* (TAQ), and an appropriate saline buffer. The reaction requires 25 to 35 cycles of denaturing, annealing, and synthesizing DNA strands complementary to the template, thus allowing an exponential increase in the amount of target DNA for each cycle. The PCR product can be visualized on an agarose gel stained with ethidium bromide or labeled with a radioisotope, run on a polyacrylamide gel, and detected after exposure of the gel to an X-ray film.

Main Chromosomal Abnormalities Associated with Epilepsy

Trisomy 21 (Down Syndrome)

General Clinical Findings

Down syndrome (DS) has an approximate incidence of 1 in 650 births.[144] In 95% of cases, the cause is a nondisjunction of chromosomes 21 during meiosis; in about 4% of cases, there is an unbalanced translocation. Approximately 1% of patients are mosaics and show a less severe phenotype. The region that, if triplicated, results in the typical phenotype maps to 21q22.3.[41] The risk of carrying a child with DS increases with increasing maternal age and with very young maternal age.[79]

The main clinical features of this condition include growth retardation, mental retardation of variable degree, hypotonia, flat facies, brachycephaly with flat occiput, upward-slanting eyes, epicanthal folds, small ears, speckling of the iris (Brushfields spots), simian crease, and hypogonadism. About 40% of patients have congenital heart disease. There is a marked risk of leukemia. All individuals above the age of 35 years show features of Alzheimer disease.

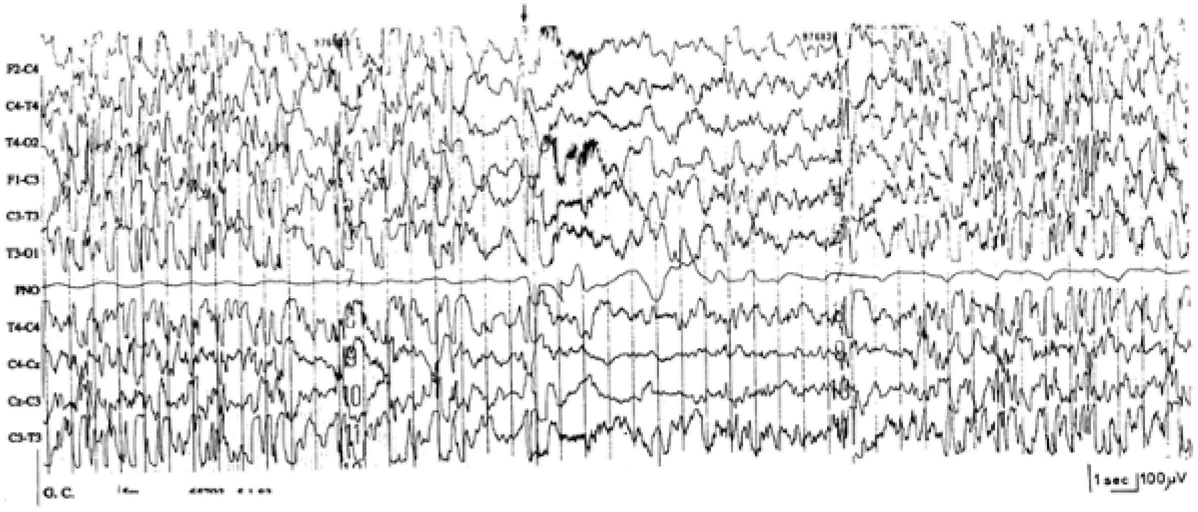

FIGURE 2. Five-month-old girl with Down syndrome and infantile spasms. Typical and symmetrical hypsarrhythmia that is interrupted after a spasm (*arrow*) initiating a cluster of spasms (not shown). Note rapid rebuilding of hypsarrhythmia after the spasm.

Epilepsy

Epilepsy in DS has been extensively investigated.[45,60,66,83,135,147] The incidence of epilepsy in children with DS was estimated to be 1.4%.[153] However, the overall prevalence of epilepsy increases with age, reaching 12.2% in patients over 35 years

of age.[159] About 40% of patients have seizures since the first year of life, and another 40% experience their first seizure during the third decade.[116] This trend seems to be related to the early medical complications of DS, such as hypoxic ischemic encephalopathy and congenital heart disease,[129] and the development of neuropathologic changes typical of Alzheimer disease[36] have a specific etiology, most often related to common medical complications of DS such as hypoxic–ischemic perinatal suffering, hypoxia from congenital heart disease, or infection. Febrile seizures have a low frequency (0.9%) in comparison with the general population.[60,93,129,153] When only cases without known causes were considered, 2.5% of patients presented with seizures, a frequency still greater than that in the general population. Although many patients in both groups had their first seizure in the first year of life, seizures occurred significantly later in infants without a known etiology. Generalized tonic–clonic (GTC) seizures predominated in both the known and unknown etiology groups. Myoclonic seizures and infantile spasms with hypsarrhythmia were also common, the latter predominating in the unknown etiology group. Partial seizures usually occurred in patients with an identifiable etiology. Prognosis for recurrent seizures varied with the etiology. Patients with seizures related to cardiovascular disease were usually well controlled by anticonvulsants. Neonates with hypoxic–ischemic injury had poor outcomes. None of the patients who developed seizures as a result of CNS infection had persistent attacks. Patients with idiopathic seizures had generally good outcomes. The authors concluded that children with DS have an increased susceptibility to seizures early in life, and superimposed systemic illness increased the risk.

In a review of studies in which population estimates were possible, infantile spasms occurred in 0.6% to 13% of children with DS, representing 4.5% to 47% of all seizures (reviewed by Stafstrom and Konkol[146]). Infantile spasms probably represent the most common seizure type in DS and, in most children, they appear without any evidence of additional brain damage.[60,113,141,146] Prognosis is usually good with regard to seizure control. Remission was obtained on conventional antiepileptic drugs (AEDs), adrenocorticotropic hormone (ACTH), or steroids, without relapse of seizures[60,113,146] or with later onset of pharmacologically controllable, age-related generalized seizure disorders[141] (Fig. 2). Conversely, spasms proved to be resistant, progressing to other forms of intractable epilepsy in most of the patients who suffered hypoxic insults.[60,146]

The occurrence of reflex seizures in the context of startle epilepsy is particularly frequent (Fig. 3).[54,66,115,130] Age at seizure onset is variable, and there is usually no evidence for etiologic factors other than DS. Most of the patients described presented "pure" forms of reflex epilepsies, with almost all seizures being precipitated by acoustic or tactile stimuli. However, the epileptic syndrome varied in type and severity, with a predominance of Lennox-Gastaut–type patterns.[66] The mechanism leading a high incidence of reflex phenomena in DS patients is unclear. A central deficit of inhibition of afferent stimuli has been proposed.[29]

Lennox-Gastaut syndrome (LGS) has been well documented in DS, but is not frequent. Quite characteristic is its de novo appearance at a mean age of 10 years, not preceded by other forms of epilepsy.[60,66]

Only a few studies have analyzed adult or late-onset epilepsy in DS, despite its high frequency.[90,159,164] Although in most late-onset epilepsies seizures appeared infrequently but were intractable,[60] no precise indications on seizure severity are available. Late-onset generalized epileptic myoclonus has also been reported.[53]

Neuropathology and Neurogenetic Basis of Seizures

Brain weight is in the lower normal range, and the gyral pattern is simplified.[39] A narrow superior temporal gyrus is observed in about 50% of patients. The insula is exposed because of hypoplasia of the inferior frontal gyrus.[86] Changes typical of Alzheimer disease appear above the age of 30 years.[51,64] Several cytoarchitectonic abnormalities have been found from birth, including a 20% to 50% decrease in the number of small granule cells, mainly inhibitory γ-aminobutyric acid (GABA)ergic interneurons, with lower neuronal density, abnormal neuronal distribution, and dysgenesis of dendritic spines.[18,81,98,127,166] The relation among these structural abnormalities and increased susceptibility to certain seizure types, particularly infantile spasms and reflex seizures, is poorly understood.

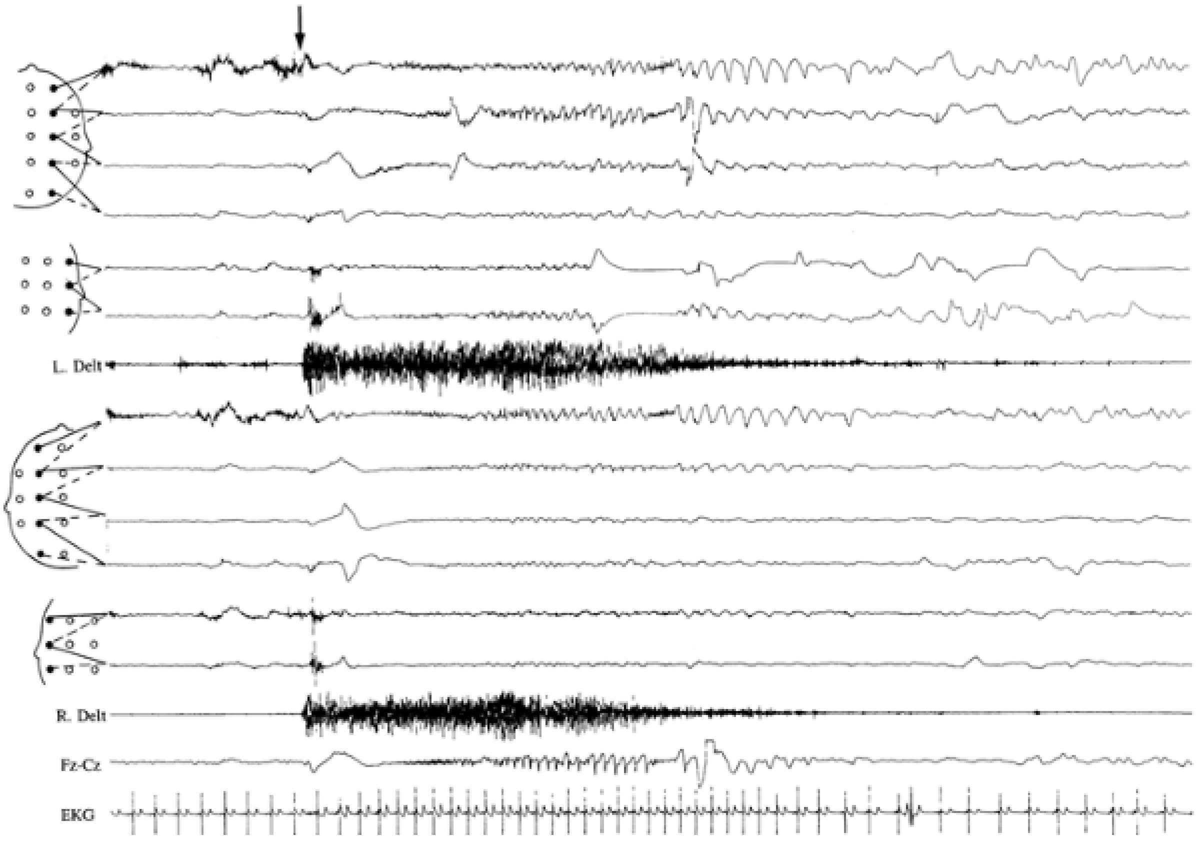

FIGURE 3. Twenty-year-old male Down syndrome patient with startle epilepsy. A sudden, unexpected noise induces a tonic seizure lasting 15 seconds, accompanied by tachycardia; the patient, who is sitting on the bed, is projected violently backward. Tonic contraction, visible on the deltoid muscles (R and L Delt), is accompanied on the EEG by a decremental event, followed by low-voltage fast activity, with increasing amplitude and decreasing frequency, well recognizable over the vertex and frontocentral electrodes, more on the right.

Diagnostic Evaluation

Most patients have a free trisomy 21, detectable on standard chromosome analysis. In such circumstances, chromosome study in the parents is not indicated. Parents should be given a 1% recurrence risk, based on the calculation of the recurrence of DS in a sibship. This slightly higher recurrence risk, when compared to the expectation based on the maternal age is likely due to a germinal mosaicism present in a few parents or to a general failure in the chromosomal disjunction mechanisms normally occurring at meiosis.[110]

If DS results from a translocation, this usually occurs between acrocentric chromosomes, termed a *robertsonian translocation*. In such circumstances, one of the parents might be a balanced carrier of the translocation, and a chromosomal study is strongly indicated for both parents. The most common robertsonian translocation found in healthy carriers involves chromosomes 14 and 21. Virtually all the (21;21) translocations are de novo. The involvement of chromosome 21 in translocations with nonacrocentric chromosomes[101] is very rare. The calculation of the recurrence risk for DS in the carriers of robertsonian translocation is based on the gender of the transmitting parent and the chromosome involved.

Fragile-X Syndrome

General Clinical Findings

Fragile-X syndrome has an approximate incidence of 1 in 1,500 males[163] and is the most common chromosomal abnormality associated with heritable mental retardation. Both genders may be affected, but the phenotype is notably more severe in males. It is estimated that 1 in 1,000 females are carriers.[23] The X-chromosome of patients affected with the syndrome shows a "fragile" site at Xq27.3 when cells are grown in a folic-deprived medium. The condition results from a dynamic mutation in heritable unstable DNA,[124] because of variation in the copy number of a trinucleotide repeat p(CCG)n within the *FMR1* gene. This fragile site is termed *FRAXA*. The disorder has an unusual mode of inheritance. About 20% of males who carry the mutation are clinically and cytogenetically normal (normal transmitting males). About 30% of female carriers have mental impairment. Transmission is consistent with an X-linked semidominant condition. The main clinical features include moderate mental retardation, poor language, hypotonia, growth retardation, macrocephaly, prominent forehead, long, narrow facies, large ears, macroorchidism, pectus excavatum, a floppy mitral valve, and hyperactive or autistic behavior.[50,165]

Epilepsy

The prevalence of epileptic seizures is approximately 25%.[167] Seizures usually appear before the age of 15 and tend to disappear during the second decade of life.[65,167] In most patients, seizures are fairly rare or are controllable with simple drug regimens.[59,65,105,167] The most frequently mentioned seizure types are generalized tonic–clonic seizures.[50,165] However, no specific epilepsy syndrome is observed.[65] Background electroencephalographic (EEG) activity is slow.[105,167] An EEG pattern of midtemporal spikes, possibly age related, similar to the waveform of benign rolandic epilepsy, has been described in some affected males, with or without seizures.[104] This EEG pattern has been confirmed by other investigators, but only in a minority of cases.[60,167] The fragile-X locus has been excluded as the candidate gene for benign rolandic epilepsy.[118]

Neuropathology and Neurogenetic Basis of Seizures

The variety in seizure types in the fragile-X syndrome may reflect extreme clinical polymorphism as a consequence of the variability of amplification of the trinucleotide repeat among patients.[52] A somatic variation in DNA amplification during development is also possible.[168] Little is known of the neuropathology. Anomalous synapses and abnormal development of dendritic spines have been observed using Golgi impregnation.[129,167] Neuroimaging studies have shown hypoplasia of the cerebellar vermis[121] and periventricular heterotopia in rare patients.[103]

Diagnostic Evaluation

The fragile site at Xq27.3 is not expressed in cell culture media employed for standard karyotypes. The induction of the fragile site in stimulated lymphocytes can be achieved using culture media free of folic acid and thymidine. The fragile site is detected only in a proportion of metaphase cells, with most fragile-X males expressing their fragile site in only 5% to 50% of their lymphocytes. Normal transmitting males usually do not express the fragile site. Fragile-X females with mental impairment express their fragile site, but in a lower proportion of cells than do fragile-X males. The majority of female carriers do not express the fragile site, but some of them might show an expression in 5% or less of their cells. The fragile-X syndrome is due to the expansion of a p(CGG)n repeat within the 5′ untranslated region of the *FMR1* gene. Normal chromosomes are polymorphic, containing 6 to 52 copies of this repeat, whereas males with more than 200 copies have the disease (full mutation). Normal transmitting males have 50 to 200 copies (premutation). Females bearing the premutation are phenotypically normal and do not express the fragile site. Females with more than 200 copies may be normal or mentally retarded and can show facial features of fragile-X syndrome. Premutations tend to expand when transmitted to offspring through female carriers, and the risk of expansion to a full mutation correlates with the size of the premutation.[52,73] In association with the full mutation, the promoter region of the *FMR1* gene is hypermethylated, and the transcription of the gene is repressed.[112,160] DNA studies have improved the accuracy of testing for fragile-X syndrome. By looking at the size of the trinucleotide repeat segment, as well as the methylation status of the *FMR1* gene, the genotype can be determined for both affected individuals and suspected carriers. Two main approaches are used: Polymerase chain reaction (PCR) and Southern blot analysis. PCR analysis utilizes flanking primers to amplify a fragment of DNA spanning the repeat region. Thus, the sizes of the PCR products are indicative of the approximate number of repeats present in each allele of the individual being tested. The efficiency of the PCR reaction is inversely related to the number of CGG repeats, so that large mutations are more difficult to analyze and may fail to yield a detectable product in the PCR assay. An additional limitation to the PCR approach is due to the fact that it provides no information about *FMR1* methylation. On the other hand, PCR analysis permits accurate sizing of alleles in the normal and premutation size ranges. *FMR1* analysis by Southern blotting allows both size of the repeat segment and methylation status to be assayed simultaneously. A methylation-sensitive restriction enzyme that fails to cleave methylated sites is used to distinguish between methylated and unmethylated alleles. Southern blot analysis is more labor intensive than PCR and requires larger quantities of genomic DNA. Southern blot accurately detects alleles in all size ranges, but precise sizing is not possible. Many laboratories can use both methods, and choose the type of analysis that is most appropriate to the circumstances. A few patients with fragile-X harboring deletions in the *FMR1* have been described.[117,152]

Two additional fragile sites reside in the distal Xq, termed *FRAXE* and *FRAXF*. Although *FRAXF* is not clearly associated with a specific phenotype, those with *FRAXE* show mental impairment, usually milder than that observed in patients with *FRAXA* mutations. Because no clinical overlap occurs between patients with mutations at the *FRAXA* and the *FRAXE* loci, other than mental retardation, the details about the diagnostic procedures for identifying *FRAXE* will not be discussed here.

Del 4p (Wolf-Hirschhorn) Syndrome

General Clinical Findings and Genetic Background

Wolf-Hirschhorn syndrome (WHS) is a multiple congenital anomalies/mental retardation syndrome[34] with a frequency of 1 in 50,000 births and a female:male predilection of 2:1.[57,96] It is caused by partial loss of material from the distal portion of the short arm of chromosome 4. The minimal deleted segment causing the phenotype is 4p16.3.[96] Although about 75% of patients have a de novo deletion[96] of preferential paternal origin,[38,157] about 12% have an unusual chromosome abnormality (such as ring 4), and about 13% have a deletion of 4p16 resulting from an inherited unbalanced chromosome rearrangement from a parent with a balanced rearrangement. The main features of monosomy 4p are the typical “Greek warrior helmet appearance of the nose,” microcephaly, pre- and postnatal growth delay, congenital hypotonia, severe mental retardation, and seizures.[13] In at least one-third of cases, death occurs during the first year of life because of severe systemic malformations, cardiac failure, or pulmonary infection.

Epilepsy

Seizures constitute a major medical concern during the first years of life, and occur in 50% to 100% of patients.[10,13,32,40,68,149] Seizure onset usually occurs within the first 2 years of life, with a peak incidence around 9 to 10 months of age. These seizures may be clonic or tonic, unilateral with or without secondary generalization, or generalized tonic–clonic from the onset.[5,8,9,10,11,12,13,47,108,119] They are frequently triggered by fever, may be prolonged, and often occur in clusters.[5,11,12,136,171] More than 50% of the patients experience early unilateral or generalized clonic or tonic–clonic status epilepticus (SE), despite adequate treatment.[13] Two-thirds of the subjects develop, between 1 and 5 years of age,

atypical absences, often accompanied by a mild myoclonic component, mainly involving the eyelids and axorizomelic muscles.[5,11,12,13,14,136] Such episodes are accompanied by generalized slow spike-and-wave complexes. The interictal EEG shows high-amplitude, fast spikes, polyspikes, and wave complexes over the posterior third of the head on eye closure. Other seizure types have been described in a minority of patients (Fig. 4).[80,171]

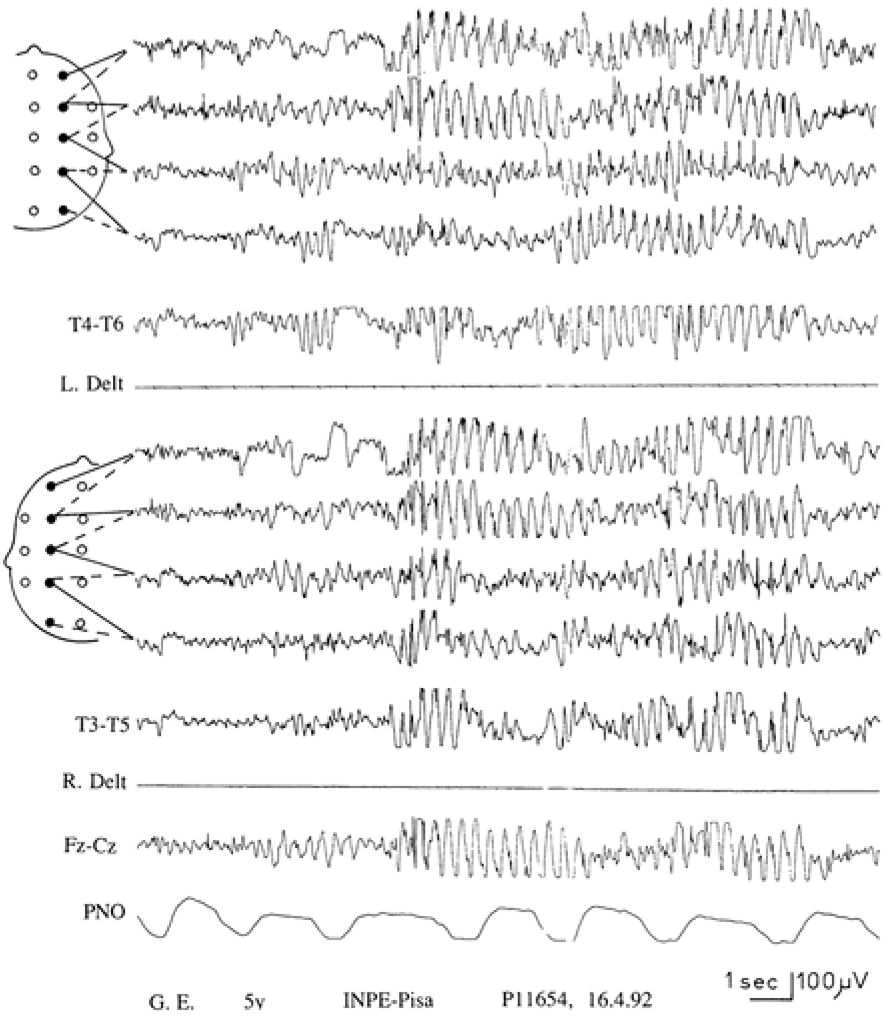

FIGURE 4. Five-year-old girl with 4p- syndrome. An atypical absence seizure is accompanied by diffuse atypical slow spike-and-wave complexes. Interictal EEG preceding the episode shows multifocal spikes and spikes and spike-and-wave complexes.

In our experience, the seizures observed in WHS can be effectively controlled by valproate alone or associated with ethosuximide and, in patients who continue to have seizures, add-on benzodiazepines are usually effective. Carbamazepine may cause seizure worsening. Despite early severity, the long-term outcome of epilepsy is relatively good, because seizures tend to disappear with age.[7,10]

Neuropathology and Neurogenetic Basis of Seizures

Corpus callosum hypoplasia is the most frequent brain abnormality (rarely associated with decreased white matter volume) and hypoplasia or agenesis of the posterior lobe of the cerebellum also is seen. Hypoplastic brain with narrow gyri, heterotopia, and dysplasia of nuclear structures has been described in some cases.[58,92]

The $GABA_A$ receptor gene maps proximal to the critical deletion region (WHSCR), specifically, 4p12–p13[27] and is probably not involved in epileptogenesis in this condition. *LETM1*, a gene possibly involved in calcium (Ca^{2+})

signaling or homeostasis, seems to be a good candidate for seizures and neuromuscular problems in WHS.[46,158] Initially, *LETM1* was suggested to flank the WHSCR,[13,46] but a recent report implies that it falls within the newly proposed critical region of WHS nearer the telomere.[173]

Diagnostic Evaluation

Standard cytogenetics detects about 60% to 70% of deletions, whereas FISH (using the WHSCR probe) detects more than 95%. Subtelomeric FISH analysis can be useful to determine if a deletion is the result of an unbalanced translocation.[14]

Partial Monosomy 15q (Angelman Syndrome)

General Clinical Findings

Angelman syndrome (AS) has a prevalence of about one in 12,000 to 20,000 of the population,[148] accounting for up to 6% of all cases with severe mental retardation and epilepsy.[87] The main clinical features of AS may not be apparent early in life. All patients have developmental delay, which becomes apparent by 6 to 12 months of age, microcephaly, severely impaired expressive language, ataxic gait, tremulousness of limbs, and a typical behavioral profile including a happy demeanor, hypermotoric behavior, and low attention span. About 90% have epilepsy.[3,161,174]

Seventy percent of patients show a deletion involving the maternally inherited chromosome 15q11–q13, encompassing a cluster of GABA receptor subunit genes; 5% show chromosome 15 paternal uniparental disomy (UPD); 5% harbor a mutation in the imprinting center (IC), a transcriptional regulatory element; and 10% harbor intragenic mutations of the *UB3A* gene. A few patients have no detectable genetic abnormality. The rare cases of familial recurrence of AS show either IC or *UBE3A* mutations.[62]

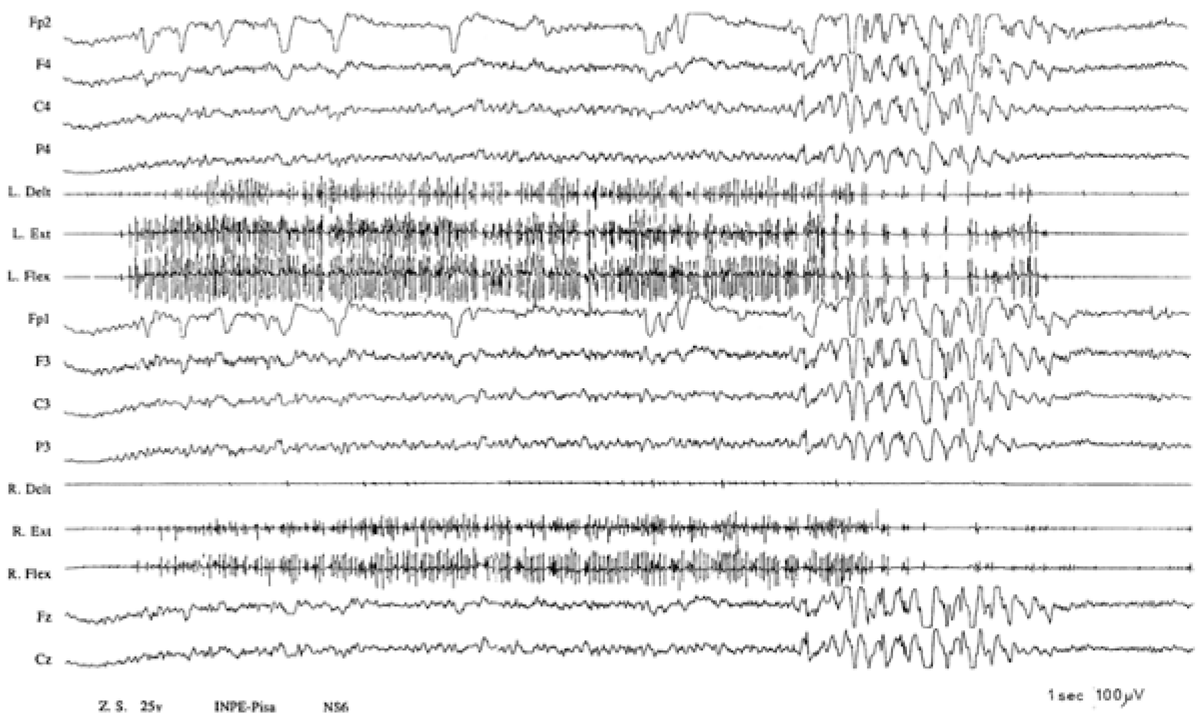

FIGURE 5. Twenty-five-year-old female patient with Angelman syndrome and 15q11–13 deletion. Polygraphic

recording. Rhythmic 12- to 15-Hz myoclonus (fast-bursting cortical myoclonus) involving all muscles recorded, is accompanied by 5- to 7-Hz rhythmic activity recorded from all EEG electrodes. A discharge of generalized, irregular polyspike-and-wave complexes lasting 3 seconds is accompanied by rhythmic bursts of two or three myoclonic potentials; each burst is time-locked with the spike component of the discharge. Clinically, the fast-bursting cortical myoclonus resembles tremor. The generalized spike-and-wave discharge is accompanied by a short myoclonic absence.

Epilepsy

It is estimated that about 90% of patients have epilepsy.[174] Viani et al.[161] reviewed 155 published patients, of whom 130 (84%) had experienced seizures. Viani's review[161] and subsequent reports suggest that the first seizures occur between the ages of 3 months and 20 years,[63,100,150,161,174] although onset is in infancy or early childhood in most. The first seizures are often precipitated by fever.[100,150] Infantile spasms are exceptional. Complex partial seizures with eye deviation and vomiting, possibly indicating occipital lobe origin, were estimated to occur frequently.[161] Atypical absences, myoclonic seizures, GTC, and unilateral seizures are among the main seizure types.[63,100,150,161] Over half of the patients suffer from episodes of decreased alertness and hypotonia lasting days or weeks, described as nonconvulsive SE.[100,150] Often there is concomitant mild jerking, rhythmic or not,[37,63] typical of myoclonic status. Polygraphic recordings reveal diffuse, slow, irregular spike-and-wave complexes at about 2 Hz, accompanied in some patients by myoclonic potentials that are time locked to the EEG spikes (Fig. 5). This clinical and EEG pattern has also been described by Dalla Bernardina et al.[37] as *myoclonic status* in nonprogressive encephalopathies. In other patients, myoclonus may remain erratic, showing no apparent relation with EEG discharges. Myoclonic jerks typically cease during sleep.[63,161] Myoclonic status is rare after the age of 6 years. In addition to myoclonic seizures or status, AS patients exhibit quasicontinuous rhythmic cortical myoclonus at about 11 Hz, mainly involving hands and face, and producing a mild jerking or twitching, easily mistaken for tremor (see Fig. 5).[63]

Individuals with chromosome 15q11–q13 deletions have more severe impairment and are more prone to develop severe epilepsy. Uniparental disomy, IC, and *UB3A* mutations are associated with a milder phenotype.[62,102]

Although seizures are generally difficult to treat in infancy and early childhood, they are usually less severe in later childhood,[174] although complete seizure remission is rare.[89] The exact percentage of patients continuing to suffer seizures as adults is unknown.

Episodes of myoclonic status and of nonconvulsive status are usually stopped with intravenous benzodiazepines,[63,161] although they frequently relapse.[100] Chronic treatment using benzodiazepines achieve fairly effective control of myoclonus. Particularly effective is the association clobazam-valproate for the long-term treatment of epilepsy.[63,161] Valproate and ethosuximide in association are also effective in patients presenting recurrent myoclonic status.[37] Worsening of myoclonus and absence seizures may be produced by carbamazepine or vigabatrin.[85,161] If cortical myoclonus is particularly disabling, generous doses of piracetam are often effective in reducing it.[63]

Neuropathology and Neurogenetic Basis of Seizures

Neuroimaging does not disclose conspicuous CNS abnorm- alities.[63,174] Available neuropathologic data derive from the study of the brains in two patients in whom the AS had not

been confirmed by genetic analysis. Jay et al.[77] found cerebellar atrophy with loss of Purkinje and granule cells and extensive Bergman gliosis. Neurochemical study of the cerebellar cortex demonstrated markedly reduced GABA content, possibly related to failure to develop or a loss of Purkinje cells and inhibitory GABAergic interneurons. Kyriakides et al.[88] reported small temporal and frontal lobes with disorganized and irregular gyri, irregular distribution of neurons in layer 3, and minor cell heterotopia in both the cerebrum and cerebellum. There is some evidence that the motor cortex in AS is hyperexcitable. Because the deletion involving the maternal 15q11–13 chromosome eliminates a cluster of $GABA_A$ receptor genes (β3, α5, γ3), it has been suggested that cortical hyperexcitability might result from reduced GABAergic inhibition.[63] A 60% to 80% reduction in benzodiazepine binding has been shown in most brain regions of a mutant mouse exhibiting a deletion involving a chromosomal region that is syntenic to the AS region.[106] The antiabsence and antimyoclonic action of benzodiazepines, which is based on their GABAergic properties, is confirmed in AS.[62]

Diagnostic Evaluation

About 80% of cases are detected through the CpG methylation at 15q11.q13 genes through "bisulfite" tests, which allows the detection of deletions, UPD, and IC mutations. The test is based on the different parentally derived methylation patterns at specific loci. If the methylation test is abnormal, a FISH assay should be run in the search of a 15q11–q13 deletion. If the FISH assay is normal, a UPD study should be performed to distinguish UPD from an IC mutation. If an IC mutation is suspected, the case should be referred to a research laboratory for the identification of the IC mutation. Mutation analysis of the *UBE3A* gene should be performed in those cases matching the clinical criteria for AS in the presence of a normal methylation test. This analysis is not 100% sensitive, because mutations involving the promoter or intronic regions might remain undetected.

The results of genetic testing have important implications for genetic counseling, because de novo deletions and UPD can be assigned a very low recurrence risk, whereas IC mutations and *UB3A* mutations can be inherited in a dominant fashion and may be causative disease mutations according to the gender of the transmitting parent. It is important to point out that about 5% of patients do not show any molecular or cytogenetic abnormality. Most such cases are sporadic but, due to the few reported familial cases, recurrence risk in siblings may be as high as 50%.

Ring Chromosome 20 Syndrome

General Clinical Findings and Genetic Background

Ring chromosome 20 (r20) is a rare chromosomal disorder, of which epilepsy is a striking feature. Although some patients may have microcephaly, mild to moderate mental retardation, and behavioral abnormalities,[114] the lack of specific phenotypic features in most individuals makes diagnosis difficult. Dysmorphic signs are exceptional. Psychomotor development tends to be initially normal. The description of about 50 cases has drawn attention to the uniqueness of the electroclinical presentation,[142] which should always prompt a request for karyotype. The chromosomal abnormality can occur in mosaic. Most cases are sporadic, but a few are familial.[30] The severity of cognitive impairment seems to correlate with the percentage of mosaicism, whereas that of epilepsy does not.[76]

Epilepsy

Seizures occur in almost all subjects, with onset between infancy and age 17 years, and these seizures are usually refractory to treatment.[142,175] The typical presentation is with repetitive episodes of confusional state, lasting from several minutes to 30 minutes, also described as "complex partial" or "nonconvulsive" status, during which patients appear to be confused and unresponsive to a variable degree. Motionlessness and staring or, conversely, complex automatisms or wandering have been described.[76,142] Perioral jerking and eyelid myoclonus are often observed.[30,76,91,111,142] Such episodes often occur daily and are accompanied on the EEG by long bursts or trains of rhythmic θ-waves and high-amplitude, 2- to 3-Hz rhythmic, notched slow waves with frontal predominance.[30,76,111] Typical spike-and-wave discharges are rarely seen. Hyperventilation, specific mental activities, or adverse psychological situations can act as triggers in some children.[128] Frontal lobe ictal-onset was shown by means of subdural electrodes during typical confusional episodes.[76] On the basis of ictal single positron emission computed tomography (SPECT) studies, a possible role of subcortical structures has been hypothesized in the genesis of such a characteristic ictal pattern. Mainly in young children, the prolonged seizures are misinterpreted as behavioral nonepileptic manifestations, unless video-EEG recording is available.[76] Partial motor and generalized tonic–clonic seizures have also been reported. Interictal EEG, normal in some individuals, can show spikes over both frontotemporal areas in others.

Diagnostic Evaluation

A standard karyotype should be performed examining at least 100 mitoses, considering that the percentage of lymphocytes carrying the chromosome rearrangement may be low.[128] In most cases, the locus of fusion between the deleted short and long arms in the ring chromosome was p13q13, p13q13.3, or p13q13.33.[76,142] The loss of telomeric material on both arms of chromosome 20 is usually identified by FISH.[26] Cases with a mosaicism for r20 have also been observed.

Del 1p36 Syndrome

General Clinical Findings and Genetic Background

The incidence of del 1p36 syndrome is estimated to be 1 in 5,000 to 1 in 10,000, with a female predilection of 1.5:1.[17,71,137] About 100 cases have been reported.[71,97] It appears that 1p36 deletions account for as much as 0.5% to 0.7% of “idiopathic” mental retardation.[56] Intrauterine growth retardation and/or postnatal growth deficiency,[19,21,55,69,82,97,120,125,138,143,170] as well as obesity and hyperphagia[48,82,132,138] have been observed.

The craniofacial features represent a hallmark of the disorder, and are characterized by microbrachycephaly, large and late-closing anterior fontanel, prominent forehead, straight eyebrows, deep-set eyes, short palpebral fissures, broad/flat nasal bridge, midface hypoplasia, pointed chin, abnormal ears, and short hands and feet.[17,71,120,138] Moderate to profound mental retardation and very poor language skills are observed in most individuals.[17,71,137,138]

Epilepsy

Seizures occur in over 50% of patients.[17,71] Different seizure types, such as infantile spasms, simple and complex partial seizures, generalized tonic–clonic, myoclonic, and absence seizures, have been reported.[21,55,82,84,120,125,138,143] Infantile spasms associated with a hypsarrhythmic EEG are observed in about 50% of cases and are usually responsive to ACTH.[4] In about 30% of patients, complex partial seizures or tonic seizures may occur, often having a favorable outcome.[17,48,143] Seizure onset is usually within the third year of life. Background EEG shows poverty of the usual rhythmic activities. Interictal EEG abnormalities are variable, including hypsarrhythmia, focal and multifocal spikes, generalized slow spike-and-wave complexes.[15]

Neuropathology and Neurogenetic Basis of Seizures

Cerebral atrophy, ventricular dilatation, hydrocephalus, delay in myelination, focal cortical dysplasia, and a leukodystrophic picture have been documented on brain neuroimaging.[6,17,49,69,72,82,125,138,143,170] A severe seizure phenotype has been associated with hemizygosity for the voltage-gated potassium (K^+) channel β-subunit gene, *KCNAB2.*[72]

Diagnostic Evaluation

Monosomy 1p36 may be the result of pure terminal deletions, interstitial deletions,[169] derivative chromosome 1, and more complex rearrangements.[6,17,71] Conventional cytogenetics may not detect these different rearrangements, particularly those that are derivative chromosomes. FISH analysis with subtelomeric region-specific probes is necessary in most cases. CGH microarray can be used as an alternative. Determination of the parental origin has provided discordant results.[17,71] Overall, deletions of paternal origin seem to be larger than deletions derived from the maternally inherited chromosome.[17,71]

Other Chromosomal Disorders Associated with Seizures

Inv Dup(15) or Idic(15) Syndrome

The chromosome region 15q11–q13 is known for its instability,[43] and many rearrangements may occur in this imprinted segment, such as deletions, translocations, inversions, and supernumerary marker chromosomes formed by the inverted duplication of proximal 15. Interstitial duplications and triplications are much less frequent. The inv dup(15) accounts for about 60% of supernumerary marker chromosomes.[35] Of the two identified cytogenetic types, one is a metacentric chromosome, smaller or similar to a G group chromosome, not containing the PWS/AS critical region (PWS/ASCR); it is found in children without dysmorphic features who are usually studied because of mild mental retardation or behavioral abnormalities.[75] However, a normal phenotype is also possible. The second type of inv dup(15) is as large as or larger than a G group chromosome, contains the PWS/ASCR,[22,126] and is associated with an abnormal phenotype.[16] Its cytogenetic description is dic(15)(q12 or q13). Most dic(15)(q12 or q13) derive from the two homologous maternal chromosomes at meiosis and are associated with increased maternal age at conception. The presence of large inv dup(15) results in tetrasomy 15p and partial tetrasomy 15q. Incidence at birth is estimated to be 1 to 30,000, with an equal sex ratio.[133]

Patients with large inv dup(15), extending to q15, usually have severe epilepsy, mental retardation, autistic-like behavior, and minor dysmorphic features.[16,25,28,151] A clinical presentation of infantile spasms in children with minor dysmorphic features has been reported in some patients, whereas LGS with very poor outcome has been observed by several authors.[16,28,151,156] Focal epilepsy has also been reported.[25] Milder presentations with mild mental retardation, generalized epilepsy with onset in adolescence of absence seizures, and an interictal pattern of generalized spike-and-wave discharges have been reported even in patients with large duplications.[33]

Various genetic mechanisms have been hypothesized to explain clinical heterogeneity (beyond the size of chromosomal duplication), including dosage effect of genes located within the duplication.[33,156] Considering that a mild epilepsy phenotype is possible, it has been suggested that inv dup(15) be ruled out as a possible, although rare, cause of “cryptogenic” or seemingly idiopathic generalized epilepsy.[33]

To distinguish between inv dup(15)s and the other supernumerary marker chromosomes, the simple distamycin A/4′-6′-diamidino-2-pheylindole hydrochloride (DA-DAPI) staining technique is sufficient, but FISH or array-CGH may be useful, although more expensive. The majority of inv dup(15)s are dicentric, with one centromere inactivated; these are also referred to as *pseudodicentric chromosome 15* or *SMC(15)*. By conventional cytogenetics, they can be classified into two main groups: (a) small SMC(15)s, which are metacentric chromosomes without euchromatic material; and (b) large SMC(15)s, which are acrocentric chromosomes containing two copies of the 15q11–q13 region. Small SMC(15)s can be familial or de novo. In contrast, large SMC(15)s are almost always de novo in origin, maternally derived, and associated with an abnormal phenotype that includes severe mental retardation, developmental delay, behavioral problems, and epilepsy. For this reason, it is important to discriminate between small and large inv dup(15), especially in prenatal diagnosis. To this aim, FISH performed on a gene within the critical Prader Willi/Angelman syndrome region allows the precise discrimination of whether the supernumerary chromosome is harmful or without any effect. However, the molecular confirmation that inv dup(15) belongs to the “small” category is not sufficient to exclude that the fetus will be affected by Prader Willi or Angelman syndrome, because cases have been reported with small inv dup(15) associated with uniparental disomy for chromosome 15 or with 15q11–q13 deletions.[94]

Ring Chromosome 14

Ring chromosome 14 (r14) is a rare chromosomal abnormality consistently associated with epilepsy. Reviews of reported cases suggest that early onset epilepsy, which is often intractable, is a constant feature of the syndrome, but does not have typical clinical or EEG features.[142] Generalized tonic–clonic seizures, myoclonic, and complex partial seizures have been reported.[95,134] General clinical features include moderate to severe mental retardation, microcephaly and facial dysmorphism with narrow elongated face and retrognathia.[122] Ocular abnormalities involving cataract and retinal pigmentation have been observed in about 50% of cases.[172] Most patients show a mosaic chromosomal abnormality. Familial occurrence is possible.[99] There is no indication of the brain histopathology that underlies such severe neurologic presentation, and neuroimaging seems to be of little help.[109]

Trisomy 12p and Tetrasomy 12 (Pallister-Killian Syndrome)

Trisomy of the short arm of chromosome 12 can be caused either by a malsegregation of a balanced parental chromosomal rearrangement or can occur de novo.[1]

Trisomy 12p is characterized by severe mental retardation, early hypotonia, turricephaly, flat occiput, short neck, round facies with prominent cheeks, prominent forehead, hypertelorism, epicanthal folds, and other dysmorphic facial features. Lateralized microgyria, internal hydrocephalus, cortical dysplasia, and ectopic glial tissue in the leptomeninges have been reported.[107]

Particularly striking was the finding of generalized 3-Hz spike-and-wave discharges in four patients, three of whom had childhood onset myoclonic absences or myoclonic seizures that appeared well controlled by AEDs.[44,61] It is of interest that three voltage-gated K^+ channel genes are clustered together, probably in the 12p13 band.

Pallister-Killian syndrome (PKS) is a rare, sporadic disorder caused by a mosaic supernumerary isochromosome 12p (i[12p]). The i(12p) is infrequently present in peripheral lymphocytes, but it is found in cultured fibroblasts and other tissues such as bone marrow and lungs. Children present with peculiar dysmorphic features including coarse and flat facies, prominent forehead, scarcity of scalp hair over frontal and temporal regions, hypertelorism, broad nasal bridge, small nose with anteverted nostrils, highly arched palate, microretrognathia, cupid bow-shaped upper lip, and low-set ears.[20,70,123] A combination of these features, with severe to profound cognitive impairment and epilepsy, characterizes the syndrome.[20,70,123,145,162] Seizures have been reported in 40% of 67 cases,[20] but their frequency is probably underestimated because most patients had a short follow-up.[20,123,145,162] For the same reason, no information is available on the seizure semiology and electrophysiologic correlates of epilepsy in these patients. Epileptic spasms have been reported in some patients.[131]

Klinefelter Syndrome (XXY Syndrome)

The prevalence of seizures in Klinefelter syndrome ranges from 2% to 10% in major series.[67] Some patients have been reported with generalized epilepsy with absence seizures or generalized tonic–clonic seizures, and a 3-Hz spike-and-wave EEG pattern.[24] However, the most common profile of patients with Klinefelter syndrome and seizures includes mental retardation, behavioral problems, epileptiform EEGs, and generalized tonic–clonic seizures. In one series, the seizures of six of 11 patients with epilepsy were well controlled with AEDs; the electroclinical spectrum was heterogenous, and outcome with AED treatment was often favorable.[154]

Partial Monosomy 17p (Miller-Dieker Syndrome)

The main clinical and genetic findings of Miller-Dieker lissencephaly are discussed in Chapter 228. We present here some guidelines for diagnostic evaluation of patients with both Miller-Dieker syndrome (MDS) and lissencephaly related to chromosome 17p (more severe in the posterior part of the brain). More than 90% of the MDS patients show a cytogenetically visible or a submicroscopic deletion involving the 17p13.3 band. About 40% with the LIS1-type lissencephaly show a submicroscopic deletion at the same chromosomal locus. Because these deletions are not observed under standard chromosome banding analysis, they are referred to as “submicroscopic.” *LIS1*, a gene mapping to 17p13.3 and encoding for the noncatalytic 45-Kd subunit of the platelet-activating factor (PAF) acetylhydrolase, is the lissencephaly causative gene, based on the finding of subtle mutations involving this gene in some patients with LIS1-type lissencephaly.

FISH using commercial probes containing the *LIS1* gene is required in all patients in whom a chromosome 17 lissencephaly is suspected on the basis of the appearance of magnetic resonance imaging (MRI).[42] In particular, it is recommended that a FISH study be performed using the *LIS1*-specific probe PAC 95H6. The search for point mutations consists of the direct sequencing of the *LIS1* gene, following PCR amplification of the entire coding region. About 25% of patients with classic lissencephaly show an intragenic mutation of *LIS1*. Gene sequencing is not 100% sensitive because the promoter and transcription regulatory regions of the gene are not routinely investigated, and a mutation in these regions could be missed. Southern blot analysis reveals gross rearrangements of the *LIS1* gene, which can be detected in about 4% of patients. The recent demonstration of mosaic mutations of the *LIS1* gene in individuals with posterior band heterotopia-pachygyria[140] suggests that a highly sensitive technique, such as denaturing high pressure liquid chromatography (DHPLC), can be useful in identifying low-level mosaicism that may escape recognition by direct sequencing or other standard techniques.

Summary and Conclusions

Chromosomal abnormalities are relatively common, genetically determined conditions that increase the risk of epilepsy. However, the likelihood of developing seizures varies greatly among the different chromosomal disorders. Chromosomal abnormalities almost constantly result in rearrangements or deletions/duplications that affect the function of more than one gene. As a consequence, even when very high-resolution techniques, such as microarray-CGH, are used, patients with chromosomal abnormalities always have a combination of clinical features and only exceptionally have isolated epilepsy. The ring chromosome 20 syndrome represents the most striking example in which a highly specific epilepsy phenotype can be the only expression of the chromosomal disorder. Most often, mental retardation and dysmorphic features, even subtle, coexist with epilepsy. Although some conditions are associated with a risk for epilepsy only slightly greater than that of the general population, others carry a risk of close to 100%, and the epilepsy is part of the phenotype. Some chromosomal abnormalities result in intractable seizures, whereas others have a more favorable epilepsy prognosis. Susceptibility to developing epilepsy does not necessarily correlate with the severity of structural abnormalities in the brain or with the extent of the chromosomal derangement. Depending on the specific genes involved, seizure susceptibility is more likely to be related to factors that alter cortical excitability, such as gene dosage effect in genes involved in ion channel and neurotransmitter function or neural development. Awareness of the associations between syndromes due to chromosomal abnormalities and epilepsy, together with knowledge of their response to treatment and the expected outcome, should be of help in planning rational treatment and counseling families.

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Chapter 261

Inherited Metabolic Disorders

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Introduction

There are a wide variety of disorders of metabolism, approximately 50 of which are associated with seizures or epilepsy. From the epileptologist's perspective, many present similarly, with indistinguishable seizure semiology and electroencephalographic (EEG) findings. The clinical presentation may be influenced more by the age of the child than the specific etiology. In some children with inborn errors of metabolism and recurrent seizures, the epilepsy can be categorized into one of the recognized epileptogenic encephalopathies, such as early myoclonic epilepsy or West syndrome. In other cases, precise syndromes are lacking and terms like "generalized symptomatic epilepsy, not otherwise specified" and "epilepsies with focal and generalized features" are used. Clearly, more work needs to be done to accurately identify children with inborn errors, and we suspect that there are novel epilepsy syndromes yet to be described in this interesting group of patients. In the meantime, useful clues sometimes present that might alert one to the correct diagnosis. In some cases, this might be a relatively unique clinical feature, in others a characteristic of the epilepsy, and, finally, in some, a particular detail of the interictal EEG (Table 1). We have tried wherever possible to include these details, but we recognize that these definitive features seldom present themselves. For this reason, it is usually necessary to consider a relatively broad differential diagnosis. To organize the thought process, it is useful to think in terms of the age of the child and broad characteristics of the presentation. These have been organized into a table for ready reference (Table 2). The differential can be refined with the use of judiciously chosen screening tests. The results of these tests further guide the selection of definitive enzyme studies or genetic testing.

The acquisition of genetic information is proceeding at an exciting pace. Although this is stimulating to the neurologist, it presents a challenge for the traditional textbook format to contain up-to-date information. For this reason, we include a reference number from the Online Mendelian Inheritance of Man (OMIM) Web site so that the interested reader can quickly obtain the most current data (this source also links to Medline references). Wherever applicable, the OMIM number is given in parentheses in each heading. Another useful site is http://www.genetests.org, which provides a comprehensive listing of gene tests and the associated laboratories.

Metabolic Disorders of The Neonatal Period

The neonatal period comprises the first month of postnatal life, and a number of metabolic disorders that appear at this time include seizures as a major clinical feature.

Nonketotic Hyperglycinemia (#605899)

In this condition, glycine accumulates in the central nervous system and elsewhere in the body because of a primary biochemical defect involving the glycine cleavage system. There are four enzymes that cleave glycine: (a) P protein, a pyridoxal phosphate–dependent glycine decarboxylase (GLDC), (b) T protein, a tetrahydrofolate-requiring enzyme (GCST), (c) H protein, a lipoic acid–containing protein (GCSH), and (d) L protein, a lipoamide dehydrogenase. Disease can be caused by defects in any of these enzymes, although mutations involving GLDC and GCST are most common. Mutations that involve the pore region of the T protein appear to particularly impair function. [7] The mode of transmission is autosomal recessive, with an estimated prevalence of 1/250,000. Neonatal nonketotic hyperglycinemia (NKH) is characterized by an initial variable symptom-free interval of 1 to 42 days. Clinical symptoms are at first lethargy, poor feeding, apneic spells, altered muscular tone, and intermittent ophthalmoparesis that occasionally progresses to bilateral external ophthalmoplegia. Erratic myoclonus is another major symptom that may appear early; hiccups and coma follow. The electroencephalogram (EEG) demonstrates a suppression-burst pattern that correlates with brainstem-evoked potential abnormalities and intrinsic brainstem pathology seen on postmortem examination (Fig. 1).[54] Similar EEG abnormalities are characteristic of phenylketonuria, maple syrup urine disease, and molybdenum cofactor deficiency (Table 2). Clinical seizure patterns include infantile spasms and generalized tonic seizures. Progressive brain atrophy, delayed myelination, incomplete development of the corpus callosum, gyral malformations, cerebellar hypoplasia, and culpocephaly are common. Elevated glycine concentrations in the cerebrospinal fluid (CSF) during the first hours of life and a partial suppression-burst EEG pattern detected as early as 30 minutes after delivery in an asymptomatic patient indicate that the abnormal glycine metabolism has been present prenatally. A CSF-to-plasma glycine ratio >0.08 is diagnostic of nonketotic hyperglycinemia. The disease usually has a severe outcome, but milder cases have been reported. Some of these are due to abnormal splicing with slightly preserved enzyme function. [72] Transient nonketotic hyperglycinemia is associated with similar clinical and biochemical findings initially, but glycine concentrations normalize between 2 and 8 weeks of life, and the prognosis is generally more favorable. [10]

Treatment of NKH has focused on three compounds: (a) glycine, (b) benzoate, and (c) carnitine. Glycine is known to stimulate the *N*-methyl-D-aspartic acid (NMDA) receptor, and dextromethorphan is a noncompetitive agonist of this same receptor, which has been used with some clinical success. High doses of benzoate can lower the CSF concentration of glycine, and there are anecdotal reports of responses. Carnitine deficiency has been documented in patients treated with benzoate, and therefore supplementation with L-carnitine has been advocated in patients receiving benzoate. Despite prompt administration of these treatments, some children may still suffer lasting neurologic sequelae.[8]

Table 1 Metabolic disorders in late infancy

Disorder	Seizure frequency	Seizure type	EEG	Dysmorphism	Neuroimaging	Laboratory findings	Treatment
Metachromatic leukodystrophy	++/+++	P	Diffuse slowing; asymmetric, slow-wave activity	Absent	White-matter lesions	High CSF protein; arylsulfatase deficiency	Not available (bone marrow transplant)

Schindler disease	+++	GTC, M	Multifocal spike-and-wave complexes	Absent	Severe atrophy of cerebellum, brainstem, and cervical spinal cord	Abnormal oligosaccharide pattern; α-*N*-acetylgalactos-aminidase deficiency	Not available
Mucopoly-saccharidoses	++	G	No specific pattern	Present	Cortical atrophy; ventricular dilation	Abnormal oligosaccharide pattern; several enzyme defects	Bone marrow transplant
CDG syndrome	+++	IS (CDG type III), P	Focal slow activity; hypsarrhythmia	Absent	Cerebellar atrophy; pons atrophy; demyelination (type III)	Low thyroxine-binding protein; abnormal serum and CSF disialotransferrin; phosphomannomutase deficiency	Not available

+, 0%–25% seizure activity; CDG, carbohydrate-deficient glycoprotein; CSF, cerebrospinal fluid; EEG, electroencephalogram; G, generalized; GTC, generalized tonic-clonic; IS, infantile spasms; M, myoclonic; P, partial.

Table 2 Metabolic disorders in the neonatal period

Disorder	Seizure frequency	Seizure type	EEG	Dysmorphism	Neuroimaging	Laboratory findings	Treatment
Urea cycle	++	P	Theta/delta waves; suppression-burst	Absent	Cerebral edema	High ammonia; low plasma urea	Dietary and pharmacologic
Nonketotic hyperglycinemia	++++	M, G, IS	Suppression-burst	Absent	CNS malformations	High CSF/plasma glycine ratio	Symptomatic
Maple syrup urine disease	++	M, P	Suppression-burst; comblike rhythm activity	Absent	Cerebral edema	Elevated Leu, Ile, Val; abnormal OA pattern	Dietary
Pyroxidine dependency	++++	P, G, M, IS	Multifocal spikes	Absent	Normal	Low CSF GABA	Pyridoxine
Organic acidurias	++	P, G	Trace alternans pattern; delta-wave paroxysms	Absent	Cerebral edema, white-matter hypodensity	Metabolic acidosis/ketosis; abnormal OA pattern	Dietary and pharmacologic
Pyruvate dehydrogenase deficiency	++	P, G, M	Bursts of slow spikes-and-waves	Present	CNS malformations; high CSF and plasma lactate	Metabolic acidosis	Symptomatic
Molybdenum cofactor deficiency	++++	P, G, M	Suppression-burst; multifocal paroxysms	Present	Progressive atrophy	Abnormal plasma and urinary amino acid profile: *S*-sulfocysteine and taurine	Not available
Peroxisomal disorders	++++	P, G, M	Multifocal paroxysms	Present	Cerebral dysplasia	High VLCFA	Not available
Fructose-1, 6-diphosphatase deficiency	+++	P, G	Diffuse slowing; intermittent burst; fast activity	Absent	Normal	Hypoglycemia; lactic acidosis; ketosis	Dietary
Biotin disorders	+/++	P, M	Suppression-burst; multifocal paroxysms	Absent	Cerebral edema	Ketoacidosis; hyperammonemia; organic aciduria	Biotin

+, 0%–25% seizure activity; CNS, central nervous system; CSF, cerebrospinal fluid; EEG, electroencephalogram; G, generalized; GABA, γ-aminobutyric acid; IS, infantile spasms; M, myoclonic; OA, organic acids; P, partial; VLCFA, very-long-chain fatty acids.

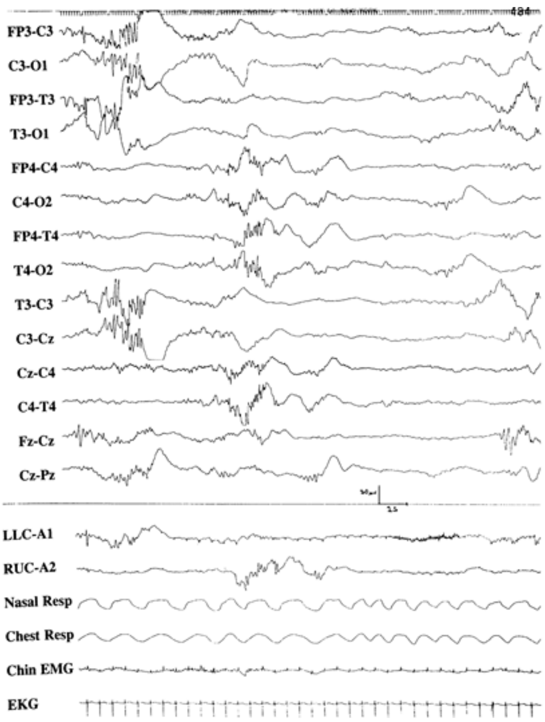

FIGURE 1. Suppression-burst electroencephalogram with interhemispheric asynchrony in a newborn. The sup- pression-burst pattern is characteristic of a variety of disorders, including nonketotic hyperglycinemia, phenylketonuria, maple syrup urine disease, and molybdenum cofactor deficiency. EKG, electrocardiogram; EMG, electromyogram; Resp, respiration.

Pyridoxine-dependent Epilepsy (#266100)

This disorder, transmitted as an autosomal-recessive trait, was previously believed to be due to a defect involving glutamic acid decarboxylase, but linkage studies have excluded this enzyme and implicated other pathways that do not appear to be primarily involved with this reaction.[5] Instead, mutations in an enzyme, antiquitin, in the lysine degradation pathway are responsible for the condition. An accumulated substrate inactivates pyridoxal 5-phosphate by forming a Knoevenagel condensation. The diagnosis can be suspected by finding elevated pipecolic acid in the blood, urine, or CSF.[41]

Typically, recurrent and long-lasting seizures occur in the neonatal period that are refractory to treatment with conventional antiepileptic drugs. The seizure types vary, and include persistent partial seizures with variable preservation of consciousness, recurrent status epilepticus, generalized myoclonic and atonic seizures, and infantile spasms. Progressive irritability, restlessness, and vomiting often precede seizures. The EEG may be diagnostic, showing an unusual paroxysmal pattern consisting of bursts of diffuse but asynchronous high-vol- tage delta activity intermixed with spikes or sharp waves. Other EEG findings include focal and multifocal spikes, bursts of generalized delta waves, and paroxysmal complexes of sharp and slow waves.[40] Intravenous administration of pyridoxine usually produces rapid control of seizures, but some cases may require several days of oral administration to show clinical effect. Patients remain dependent on pyridoxine supplementation to maintain seizure control and normal neurologic development.

Atypical cases of pyridoxine dependency have been described. Onset may be delayed into early infancy. As a rule, all infants of this age who have idiopathic seizures should be given a test dose of pyridoxine (75–100 mg) to determine responsiveness. Occasionally, a patient with vitamin B6–dependent conditions will become apneic after the test dose is administered, and so it is important to anticipate the need for transient respiratory support. Decreased concentration of γ-aminobutyric acid (GABA) in the CSF is the defining biochemical abnormality. This finding, coupled with elevated CSF concentration of glutamate and response to administration of pyridoxine, is diagnostic.

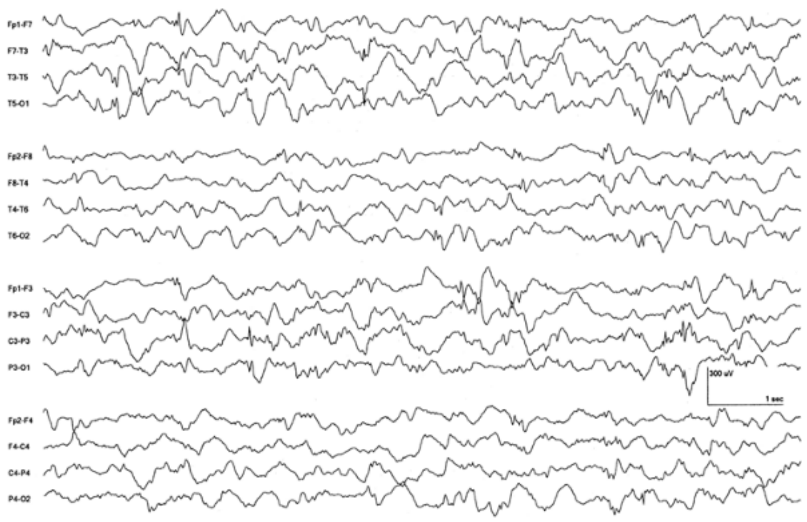

FIGURE 2. Electroencephalogram (EEG) in a patient with dihydropyrimidine dehydrogenase deficiency. The infant is 6 months old. Note the background slowing, the asymmetry with reduced complexity on the right, and the presence of multifocal spikes. A prior EEG had shown reduced complexity on the left, indicating that this feature presents with shifting laterality. (Courtesy of Dr. Kent R. Kelley.)

Some patients with neonatal encephalopathies do not respond to B6 but do respond to pyridoxal phosphate. [9,67] Pyridoxal phosphate is the biologically active form of the B6 vitamins, but the defect in these patients is not precisely known. Some advocate giving neonates or infants with intractable seizures and encephalopathy a test dose of pyridoxal phosphate (either 50 mg for a neonate or 30–50 mg/kg/d for infants) for 2 weeks because of these rare cases of pyridoxine resistance and the observation that pyridoxal phosphate appears to be superior to B6 in idiopathic epilepsies. [4,68]

P.2607

Dihydropyrimidine Dehydrogenase Deficiency (#274270)

Dihydropyrimidine dehydrogenase (DPD) is used in the first step of the pyrimidine degradation pathway, converting uracil and thymine to ß-alanine and the R-enantiomer of ß-aminoisobutyric acid. This conversion primarily takes place in the liver, and DPD is the rate-limiting enzyme of the catabolism. This enzyme is absent in the brain, but it is believed that alanine may be converted from carnosine owing to the presence of tissue carnosinase in brain. There is a wide range of clinical presentation, but nearly all children present with neurologic abnormalities, including hypertonia, hyperreflexia, tremor, seizures, and developmental delay. Severely affected children present as newborns with hypertonia, stiffness, and feeding difficulties.[2] Details of the EEG features and characteristics of the seizures have yet to be described. In our own patient, erratic myoclonias were present. The EEG showed bursts of semirhythmic delta and attenuation of the expected background complexity over either hemisphere with shifting laterality. Multifocal interictal epileptiform discharges were present (Fig. 2). No treatment has been shown to be effective.

Molybdenum Cofactor Deficiency (#252150)

This condition is exceedingly rare. Molybdenum is a trace element that serves as an essential cofactor for the reactions of three different enzymes: (a) sulfite oxidase, (b) xanthine dehydrogenase, and (c) aldehyde oxidase. Deficiency of molybdenum cofactor can result from mutations in four separate genes: *MOCS1*, *MOCS2* (which codes for molybdopterin synthase), *MOSC3*, and *GEPH* (which codes for gephyrin).[36] Absence of hepatic molybdenum cofactor results in a combined enzyme deficiency. A progressive encephalopathy develops in affected infants, with recurrent and refractory seizures appearing shortly after birth. Focal seizures, diffuse tonic seizures, and erratic myoclonic jerks are common. Jitteriness, abnormal cry, and intermittent irritability are other neurologic findings. Dysmorphic features, ectopia lentis, and hepatomegaly are associated somatic manifestations. The EEG is characterized by multifocal paroxysms and a suppression-burst pattern. Brain magnetic resonance imaging (MRI) demonstrates initial signal changes consistent with white matter edema, then curvilinear signal changes in the gray–white junction suggestive of hemorrhage and laminar necrosis, and ultimately multiple subcortical cystic areas scattered throughout the brain. [16]

Isolated sulfite oxidase deficiency is clinically and pathologically indistinguishable from molybdenum cofactor deficiency, suggesting that decreased sulfite oxidase activity is central to the clinical syndrome.[59] In both conditions, the serum concentration of uric acid is abnormally low, and sulfur-containing products are evident in the urine. Serum urate may be the more sensitive screening test. [3] There is no effective treatment for this condition. Recent work suggests that sulfites might have a direct impact on glutamate dehydrogenase function, thereby reducing the adenosine triphosphate (ATP)-producing capacity of cells. [75] In theory, a severe impairment of energy production could account for the MRI appearance and the burst-suppression pattern apparent on EEG tracings.

P.2608

Peroxisomal Diseases

These disorders are invariably associated with seizures in the neonatal period. Zellweger (cerebrohepatorenal) syndrome (ZS) is the prototype of this group of conditions. Neonatal adrenoleukodystrophy and infantile Refsum disease are progressively milder presentations. Most cases of ZS are caused by mutations in the *PEX1* gene, and the severity of the mutation correlates with the clinical severity, although to an imperfect degree. [66] Severe encephalopathy with failure to thrive, hypotonia, hyporeflexia or areflexia, and seizures are the major features. Seizures develop in the neonatal period in 80% of patients. Seizure types include focal, myoclonic, and atypical flexor spasms. The EEG shows multifocal spikes or, less frequently, hypsarrhythmia. Dysmorphic features are distinctive and often permit diagnosis by inspection. These include a high, prominent forehead; shallow orbital ridges; high palatal arch; deformities of the external ear; micrognathia; presence of epicanthal folds; low, broad nasal bridge; and redundant skin folds of the neck. Cataracts, glaucoma, pigmentary retinopathy, optic nerve dysplasia, and amaurosis are usually present, as are hepatomegaly, polycystic kidneys, and calcific stippling of the patellae. Laboratory abnormalities include absence of peroxisomes on liver biopsy and high levels of very-long-chain fatty acids in the serum.

Disorders of the Urea Cycle

These conditions involve 1/30,000 live births.[24] Except for ornithine transcarbamoylase deficiency, which is transmitted as an X-linked dominant trait, the other five urea cycle disorders are autosomal-recessive diseases. Hyperammonemia, respiratory alkalosis, absence of ketoacidosis, and decreased blood urea nitrogen concentrations are laboratory findings that strongly suggest a urea cycle disorder. The concentrations of citrulline and argininosuccinic acid in the plasma and of orotic acid in the urine help to differentiate among six different enzyme defects of the urea cycle.

Approximately 60% of infants with urea cycle defects become symptomatic within 24 to 72 hours of birth. Symptoms include progressive lethargy, vomiting, hypothermia, and hyperventilation. Seizures are not usually seen initially but are manifested later, as cerebral edema develops. The EEG is characterized by low-voltage, asymmetric delta and theta activity. A suppression-burst pattern may develop, and the duration of intervals between bursts may correlate with the degree of hyperammonemia. Brain imaging reveals cerebral edema with small ventricles, and intracranial hemorrhage has been reported. Primary treatment is dietary, with various drugs administered to lower the blood and tissue concentrations of ammonia.

Maple Syrup Urine Disease (#248600)

There are five subtypes of maple syrup urine disease (MSUD), but the classic severe neonatal form presents with poor sucking, lethargy, and coma, beginning sometime between the fourth and seventh days of life. Intermittent hypertonus and opisthotonus, gross tremor, myoclonic jerks, and repetitive flexion–extension movements of the limbs are common. It is the result of a defect of the branched-chain α-ketoacid dehydrogenase complex, and mutations in at least four different genes can cause the clinical syndrome. This mutation is expressed as an autosomal-recessive trait, with an estimated prevalence of 1/200,000 live births. The branched-chain amino acids (leucine, isoleucine, and valine) accumulate together with the α-ketoacid derivatives. Clear focal seizures, seizures with diffuse clinical expression, and uncontrolled cerebral edema are common in untreated subjects. A mu-like rhythm characterized by bursts of 7- to 9-Hz spindle-like sharp waves of moderate amplitude is distinctive. [18] Fast rolandic rhythms have also been described.

Organic Acidurias

The disorders of organic acid metabolism comprise a large number of inborn errors, including isovaleric aciduria and several ketotic hyperglycinemic syndromes (propionic acidemia, methylmalonic acidemia, and β-ketothiolase deficiency).

Symptoms develop during the neonatal period in approximately 50% of children who have isovaleric aciduria (#243500), with poor feeding, vomiting, dehydration, and a progressive encephalopathy manifested by lethargy, tremors, seizures, and coma. Cerebral edema is present, and seizures are most often focal motor or diffuse tonic posturing. The EEG shows dysmature features during sleep. Distinctive biochemical findings include metabolic acidosis, ketosis, lactic acidosis, hyperammonemia, and transient bone marrow suppression. Isovalerylglycinuria is diagnostic. The disorder is due to a defect in isovaleryl CoA dehydrogenase. It is of note that recent newborn screening has led to the identification of asymptomatic individuals with identical genetic mutations. This is important information for genetic counseling. [44]

The symptoms of propionic acidemia (#606054) also appear during the neonatal period, and 20% of affected newborns have seizures as the first symptom. The defect is in propionyl-CoA carboxylase. Again, both focal seizures and manifestations that appear more diffuse have been reported. The EEG shows diffuse delta wave activity, with generalized or focal temporal spikes during the encephalopathic phase. Intractable epilepsy may develop. In 40% of affected children, generalized convulsions and myoclonic seizures develop in later infancy, and older children may have atypical absence seizures. A recent workshop showed that modern mortality rates are about one in three, but the degree of dietary protein restriction used as treatment varies considerably among centers worldwide. [65] Biochemical findings include metabolic acidosis, ketosis, and elevation of branched-chain amino acids and propionic acid.

Methylmalonic acidemia is the metabolic signature of several biochemically distinct entities, all of which show decreased activity of methylmalonyl-CoA mutase. [48] Stomatitis, glossitis, developmental delay, failure to thrive, and seizures are the major features. Diffuse tonic postures and focal seizures with apparent secondary generalization are the most frequently described seizure types. Methylmalonic acidemia also occurs in association with homocystinuria. Seizures involve repetitive clonic eyelid blinking and simultaneous upward deviation of the eyes. Lesions of the globus pallidus on computed tomography (CT) or MRI are classic. [57]

Defects of carnitine palmitoyltransferase types I and II may be manifested in the newborn period by diffuse neurologic signs and seizures. [39] Hypsarrhythmia has been described in one case. Deficiency of carnitine acylcarnitine translocase also may produce seizures, apnea, and bradycardia in the neonatal period, and seizures may occur in other defects of fatty acid oxidation. [28]

Pyruvate Dehydrogenase Deficiency (#312170) and Pyruvate Carboxylase Deficiency (#266150)

The clinical manifestations of pyruvate dehydrogenase (PDH) deficiency are extremely heterogeneous. The spectrum ranges from neonatal lactic acidosis with severe neurologic dysfunction to a slowly progressive, chronic neurodegenerative disorder. [6] Structural abnormalities, such as agenesis of the corpus callosum, are frequently revealed by brain imaging. Mutations most often affect the E_1 α subunit gene located on the short arm of chromosome X. [11] The pyruvate dehydrogenase complex catalyzes the irreversible conversion of pyruvate into acetyl-CoA. The PDH complex is composed of multiple copies of three enzymes: E1 (PDHA1), dihydrolipoyl transacetylase (DLAT or E2), and dihydrolipoyl dehydrogenase (DLD or E3). The E1 enzyme is made up of two α and two β subunits. The E1 α subunit contains the active site and plays a key role in the function of the PDH complex. Complex malformations of the nervous system are common in girls with neonatal onset, and seizures are a frequent feature, including infantile spasms and myoclonic seizures. Electroencephalographic abnormalities are usually severe and include multifocal slow spike-and-wave discharges. Patients with defects in E2 have been recently reported. The clinical expression is quite different, and affected individuals may present with episodic dystonia and few or none of the classical features of PDH deficiency. [26] Patients are treated with the ketogenic diet because use of ketone bodies for oxidative metabolism bypasses the primary defect. A zebrafish model was developed that demonstrates the effectiveness of this approach. [60]

Pyruvate carboxylase deficiency also may be devastating in the neonatal period, being associated with severe lactic acidosis, hypotonia, failure to thrive, and seizures. [11] The combination of lactic acidosis and ketosis is a distinctive metabolic disturbance, and when hyperammonemia, citrullinemia, and hyperlysinemia are also present, it is diagnostic of the disorder. Seizures are related to the associated hypoglycemia and failure of the Krebs cycle. Treatment with adrenocorticotropic hormone (ACTH) can worsen infantile spasms associated with this disorder, and treatment with the ketogenic diet can be lethal. [52]

Other disturbances of mitochondrial function have been linked to Leigh syndrome (LS) and Alpers syndrome. Symptoms of these two syndromes, which appear in infancy, include convulsions. Leigh syndrome is better understood and may be related to various biomolecular defects. [14] Maternally inherited Leigh syndrome (MILS) is frequently associated with convulsions and pigmentary retinopathy. The common mutation associated with MILS is a thymine–guanine transition at nucleotide position 8993 in complex V of the mitochondrial genome. Other mitochondrial DNA mutations may produce the MILS phenotype. Leigh syndrome associated with deficiency of pyruvate dehydrogenase is characterized by convulsions about 50% of the time. In contrast, convulsions occur infrequently (7% of cases) in LS associated with cytochrome *c* oxidase.

The pathophysiology of Alpers syndrome is more obscure. This condition is transmitted as an autosomal-recessive trait and is invariably associated with convulsions. Liver failure with cirrhosis follows in the Huttenlocher variant. [27] Whether Alpers syndrome is mitochondrial in origin had been a subject of debate. [24] Mutations in the POLG gene have been reported. [45]

Disorders of Carbohydrate Metabolism

Hypoglycemia in the neonatal period is often caused by an inborn error of gluconeogenesis, such as deficiency of fructose-1,6-bisphosphatase. Fifty percent of affected children show symptoms during the first week of life, including periodic hyperventilation, hepatomegaly, irritability, apnea, somnolence, and coma. Other patients become symptomatic during the early infantile period. Seizures are common, and the initial EEG reveals diffuse slowing and low-amplitude background activity with intermittent bursts of fast activity. Less frequently, there are multifocal sharp waves and spikes. Profound hypoglycemia, lactic acidosis, ketosis, elevated plasma concentrations of alanine, and presence of abnormal urinary organic acids with glycerol and glycerol-3-phosphate are characteristic biochemical findings. The diagnosis can be made using cultured lymphocytes, thereby eliminating the need for a liver biopsy. [31] Neurologic symptoms and permanent brain damage can be avoided by preventing hypoglycemia.

Other disorders are caused by abnormalities of fructose and galactose metabolism. Galactosemia can be caused by defects in the products of three genes. The most commonly involved enzyme is galactose-1-phosphate uridyltransferase (#230400). Deficiency occurs in 1/62,000 births. The precise cause of the neurologic disability is not known. Despite prompt recognition and appropriate dietary management, long-term disability may still result. [55] Hyperchloremic metabolic acidosis, hyperaminoaciduria, albuminuria, abnormal liver function, and elevated blood concentrations of galactose are diagnostic of this condition. Neonatal screening can be performed.

Disorders of Biotin Metabolism

These conditions may produce seizures in the neonatal period (Table 2).[7] Holocarboxylase synthetase binds biotin covalently to four apocarboxylases (propionyl-CoA carboxylase, pyruvate carboxylase, ß-methylcrotonyl-CoA carboxylase, and acetyl-CoA carboxylase) (#253270). The gene map locus is 21q22.1. Biotinidase, in turn, cleaves biotin from biocytin, a short biotinylated peptide that is formed during the proteolytic degradation of the holocarboxylases. Holocarboxylase synthetase deficiency is also known as early-onset multiple carboxylase deficiency, and biotinidase deficiency is also termed late-onset multiple carboxylase deficiency. Symptoms of holocarboxylase synthetase deficiency appear in the neonatal period; diffuse tonic seizures, brief focal motor seizures, and multifocal myoclonic jerks develop in 25% to 50% of cases. In addition, Thoene et al.[61] reported lactic acidosis, alopecia, keratoconjunctivitis, and perioaral erosions. Seizures are usually refractory to treatment with antiepileptic drugs but may improve with large doses of biotin. The EEG shows a suppression-burst pattern and multifocal spikes (Fig. 1).

Metabolic Disorders of Early Infancy

Several inborn metabolic errors of which seizures are a manifestation become symptomatic after the first month of life. All patients with GM_2 gangliosidosis, disorders of folate metabolism, glucose transporter protein deficiency, fumarase deficiency, and Menkes disease have seizures as part of the clinical picture. In the other metabolic disorders of early infancy, seizures occur in 25% to 75% of cases (Table 3).

Lysosomal Disorders

GM_2 gangliosidosis is a lysosomal disorder that invariably includes seizures as a prominent feature. The infantile form of GM_2 gangliosidosis includes Tay-Sachs disease (#272800), caused by deficiency of hexosaminidase A, and Sandhoff disease, caused by deficiency of hexosaminidase A and B. Classic Tay-Sachs disease is characterized by developmental regression, paralysis, blindness, seizures, and death in the second or third year of life.[46] An exaggerated startle response, often associated with myoclonic jerks, is one of the earliest neurologic signs, and is a distinctive feature of this disorder. Focal and atypical absence seizures have been described and respond poorly to antiepileptic drugs. The EEG shows central spikes with a very sharp morphology (Fig. 3). The classic cherry red spot is present in the ocular fundi of nearly all patients. One report in the literature based on autopsy findings suggested an exaggerated sensitivity to phenytoin neurotoxicity.[42] Nonetheless, phenytoin should be avoided in patients with Tay-Sachs disease because of the high incidence of myoclonus and the availability of other agents effective against multiple seizure types.

Table 3 Metabolic disorders in early infancy

Seizure disorder	Seizure frequency	type	EEG	Dysmorphism	Neuroimaging	Laboratory findings	Treatment
GM_2 gangliosidosis	++++	SM, P, M	Multifocal paroxysms	Absent	Progressive ventriculomegaly	Abnormal urinary oligosaccharide pattern; hexosaminodase A deficiency	Not available
Krabbe disease	+++	M, SM, IS	Asynchronous spike-polyspike paroxysms	Absent	White-matter demyelination	Increased CSF protein; galactosylceramidase deficiency	Not available
Biotinidase deficiency	+++	G, M, IS	Suppression-burst; spike-and-slow-wave paroxysms	Absent	Nonspecific	Abnormal urinary OA pattern	Biotin
Folate disorders	+++/++++	IS, M, P	Multifocal paroxysms; hypsarrhythmia	Absent	Cortical atrophy; leukoencephalopathy; calcifications	Abnormal amino acid pattern: homocystinuria, low methionine, normal or low CSF folate	Folate, betaine
Glucose transporter protein deficiency	++++	M, A	Normal	Absent	Normal	Low CSF glucose and lactate; normal serum glucose	Ketogenic diet
Branched-chain organic acidurias	+++	P, G, M, IS	Generalized or focal delta slowing	Present (3-OH-isobutyric aciduria)	Cerebral edema; hypodensity BG; heterotopias; cerebral dysplasia	Ketonuria or hypoketosis; hypoglycemia; abnormal urinary OA	Dietary, carnitine
Fumarase deficiency	++++	P, IS, M	Multifocal spikes; spike-and-wave complexes; hypsarrhythmia	Absent	CNS malformations	Lactic acidosis; fumaric aciduria	Symptomatic
Hyperpheny-alninemias	+++	G, P, M, IS	Generalized or focal paroxysms; hypsarrhythmia	Absent	White-matter lesions; cerebral atrophy	High phenylalanine; abnormal CSF biopterin ratio	Dietary, biopterin

Fructose-1, 6-biphosphatase deficiency	+++	P, G	Diffuse slowing; intermittent burst; fast activity	Absent	Normal	Hypoglycemia; lactic acidosis; ketosis	Dietary
HHH syndrome	+++	G, P, M, IS	Spike-and-wave complexes; diffuse slowing	Absent	Normal	Increased orotic acid, glutamate, alanine; homocitrullinuria; hyperammonemia	Dietary
Urea cycle	++	P, G	Generalized theta-wave paroxysms	Absent	Cerebral edema; white-matter lesions	Hypera- mmonemia; abnormal amino acid pattern	Dietary, phenylbutyrate
Menkes disease	++++	M	Multifocal paroxysms	Absent	Cerebral, cerebellar atrophy; focal areas of necrosis	Low serum copper and ceruloplasmin	Symptomatic
Histidinemia	+++	M, IS, SM	Atypical hypsarrhythmia	Absent	Normal	High histidine	Symptomatic, histidine restriction
Hyper-prolinemia	++	P, IS	Slow delta-wave activity	Absent	Normal; leukodystrophy (1 case)	High proline	Symptomatic

+, 0%–25% seizure activity; BG, basal ganglia; CNS, central nervous system; CSF, cerebrospinal fluid; EEG, electroencephalogram; G, generalized; IS, infantile spasms; M, myoclonic; OA, organic acids; P, partial; SM, startle myoclonic.

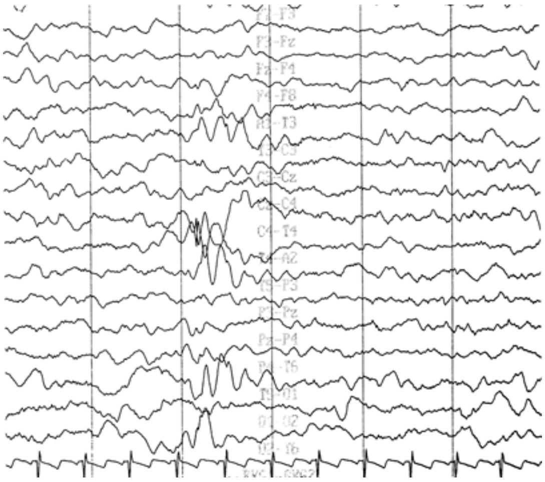

FIGURE 3. Electroencephalographic tracing showing very fast central spikes in an infant with Tay-Sachs disease.

Other lysosomal disorders occurring at this age include globoid-cell leukodystrophy (Krabbe disease; #245200), caused by a deficiency of galactocerebrosidase. Presentation in early infancy is characterized by developmental regression, increasing irritability, progressive spasticity, and opisthotonic posturing.[20] Myoclonic jerks, startle myoclonus, and extensor spasms are common, and infantile spasms with hypsarrhythmia have been reported in several cases. The EEG is usually characterized by increasingly severe bilateral, symmetric delta activity and asynchronous spike-polyspike discharges. Increased CSF protein and peripheral neuropathy are distinctive features of this disease of white matter. In contrast to what is observed in most classic white-matter diseases, seizures occur early in the course of 50% to 75% of infants with Krabbe disease. Bone marrow transplantation has been used and is most promising in the presymptomatic newborns.[17,70]

Disorders of Vitamin Metabolism

Disorders of vitamin metabolism with symptoms that appear in early infancy include biotinidase deficiency (#253260) and disorders of folic acid. As described in a previous section, biotinidase deficiency produces multiple carboxylase deficiency. Thirteen different mutations have been described in the gene.[73] Seizures occur in 50% to 75% of patients and are the presenting clinical symptoms in one third of cases. Apparently generalized clonic seizures, infantile spasms, and myoclonic seizures are seen. Electroencephalographic findings may include a suppression-burst pattern, absence of physiologic sleep patterns, poorly organized and slow waking background activity, and frequent spike and spike-and-slow-wave discharges. A deficiency of biotinidase is diagnostic, and patients respond dramatically to supplementation with high-dose biotin. Newborn screening is used to make the diagnosis, but not all individuals identified will develop clinical symptoms.[74]

Methelyne tetrahydrofolate reductase deficiency (#236250) is the most common inborn error of folate metabolism, with a clinical spectrum from early neurologic deterioration and death to asymptomatic adults, even within the same family.[25] In affected individuals, a progressive neurologic syndrome develops with regression in infancy. Clinical features include acquired microcephaly and seizures. Intractable infantile spasms, generalized atonic and myoclonic seizures, and partial motor seizures are seen. Electroencephalographic findings vary from diffuse slowing of background activity to continuous spike-and-wave complexes or multifocal spikes. The early-onset form differs from the late-onset form. The latter presents with progressive motor deterioration, schizophrenia-like psychiatric symptoms, and recurrent strokes; seizures are uncommon. Homocystinuria and elevated serum concentrations of homocystine and methionine are the main biochemical features. Treatment with folate can reverse white matter lesions, but this response may be variable, even within families of affected members. [58]

Defects in methionine biosynthesis are also associated with seizures. Convulsions are frequent and are predominantly generalized, although myoclonic seizures with a hypsarrhythmia on the EEG have been reported. Diagnostic laboratory findings are megaloblastic anemia, homocystinuria, decreased methionine, and normal folate and cobalamin concentrations in the absence of methylmalonic aciduria.

Seizures are common in congenital folate malabsorption, a rare condition that is believed to be caused by a defect in the folate transporter system. Folate is concentrated in the nervous system, and the CSF concentrations of folate are higher than serum concentrations. Sometimes, calcifications form in the occipital lobes and basal ganglia. Without folate supplementation, a slowly progressive encephalopathy develops with refractory seizures. Other clinical features include megaloblastic anemia, diarrhea, mouth ulcers, and failure to thrive. High-dose folate or folinic acid may improve seizure control.

Inherited defects of vitamin B12 metabolism also may produce severe megaloblastic anemia in early infancy. Generalized tonic convulsions occur almost invariably and are refractory to conventional treatment. Methylmalonic aciduria without homocystinuria suggests this diagnosis.

Glucose Transporter Type 1 Deficiency Syndrome

The glucose transporter type 1 deficiency syndrome is a prototypic example of a defect in energy supply. [12,64] Affected infants become encephalopathic, with seizures and delayed motor and mental development. Seizures typically begin after the second month of life and are of diverse types but are probably multifocal in origin. Later, generalized nonconvulsive seizures, myoclonic jerks, and atypical absence seizures are common. Developmental clumsiness, impaired early language and behavioral development, and deceleration of head growth with acquired microcephaly are additional findings. Low CSF glucose and lactate concentrations in the presence of a normal blood sugar concentration are diagnostic. The EEG is often normal early in the course or may show scattered multifocal interictal epileptiform discharges (Fig. 4B). As the child matures, bursts of generalized spike-and-wave discharges are seen in about one third of patients (Fig. 4A).[35] Another useful EEG clue to the diagnosis is the marked enhancement of the interictal epileptiform abnormalities in the fasting state and, in turn, the marked improvement of the EEG after a meal. [29] The disease can be diagnosed by assaying glucose transport in isolated intact erythrocytes. Seizures generally respond well to a ketogenic diet, but they tend to be refractory to conventional antiepileptic drugs. Phenobarbital should be avoided because of its potential to interfere with transport of glucose into the nervous system. [34]

Early infantile seizures can be seen in other disorders of carbohydrate metabolism, including hereditary fructose intolerance, d-glyceric aciduria, and galactokinase deficiency.

Congenital Disorders of Glycosylation

Congenital disorders of glycosylation (CDGs) are caused by deficiencies in glycoprotein biosynthesis and usually result in severe cognitive dysfunction. CDG type I (CDG-I) disorders are an increasingly expanding group of conditions caused by disturbances in the synthesis of the lipid linked glycan precursor or in the attachment of glycans to proteins. CDG-II disorders are caused by impairments of either the trimming of the protein-bound oligosaccharide or the addition of sugars. Seizures can be seen in infants with CDG-IE and CDG-IL. Patients with CDG-IE have had onset of seizures within the first year of life. Additional features are development delay, hypotonia, and acquired microcephaly. Laboratory evaluations showed hypoglycosylation on serum transferring and cerebral spinal fluid β-trace protein. The disorder is due to dolichol phosphate mannose synthase (DPM1) mutations.[32] Detailed descriptions of the seizures and EEG features are not available. CDG-IL is caused by deficiency of the ALG9 α1,2-mannosyltransferase enzyme and results in delay, seizures, hypotonia, diffuse brain atrophy with delayed myelination, failure to thrive, pericardial effusion, cystic renal disease, hepatosplenomegaly, esotropia, and inverted nipples. Detailed descriptions of the seizures are lacking. One report stated that the initial EEG shortly after onset of seizures was normal.[71] Febrile seizures are a common feature of CDG-IA, but afebrile seizures are only variably seen in this disorder. [33]

Organic Acidurias

Seizures in early infancy may be the presenting symptom of branched-chain organic acidurias. These include isovaleric aciduria, 3-methylcrotonyl-CoA carboxylase deficiency, 3-methylglutaconic aciduria with normal 3-methylglutaconyl-CoA hydratase, and 3-hydroxy-3-methylglutaryl CoA lyase deficiency (#246450).[76] In the latter condition, the urine has been observed to smell like a cat. The common mutation associated with this condition may alter the three-dimensional structure of the enzyme. [50] Seizures, including convulsions and infantile spasms, tend to be prominent in 3-methylcrotonyl-CoA carboxylase deficiency. The typical abnormal organic acid includes 3-hydroxyisovaleric acid and 3-methylcrotonyl glycine. Serum concentrations of free carnitine are very low.

Severe developmental delay, progressive encephalopathy, and seizures are the most common features of 3-methylgluta- conic aciduria, but the biochemical features can also be identified in asymptomatic individuals. [1,19] Seizures occur in one third of cases, and infantile spasms have been reported early on. The typical organic acid abnormality includes marked elevations of 3-methylglutaconic acid and 3-methylglutaric acid in the urine.

Seizures are the presenting symptom in 10% of patients with 3-hydroxy-3-methylglutaric aciduria, a metabolic disorder caused by a deficiency of the lyase enzyme that mediates the final step of leucine degradation and plays a pivotal role in hepatic ketone body production.

Infantile spasms have been reported in patients with 3-hydroxybutyric aciduria. Facial dysmorphism and brain dysgenesis are prominent manifestations. The enzyme deficiency causing this condition is unknown. Urinary excretion of 3-hydroxyisobutyric acid in the absence of ketosis is diagnostic.

Glutaric acidemia type I is a more common autosomal recessive disorder of lysine metabolism that is caused by a deficiency of glutaryl-CoA dehydrogenase. Seizures often are the first clinical signs of metabolic decompensation following a febrile illness. Valproate and carnitine with a low-protein diet and riboflavin supplementation are recommended.

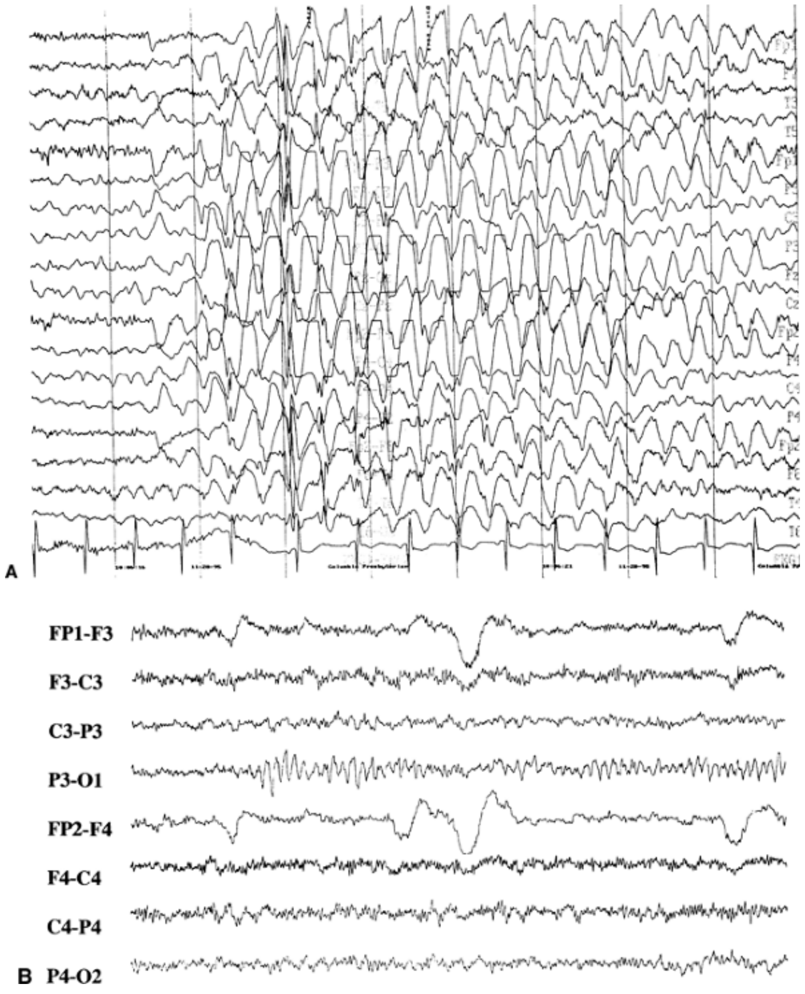

FIGURE 4. Typical electroencephalogram from a patient with glucose transporter type 1 deficiency syndrome. **A:** Bursts of generalized irregular spike-and-wave discharges and runs of rhythmic delta activity are associated with altered responsiveness. Similar discharges have been encountered in approximately one third of patients with glucose transporter protein deficiency. In other patients (not shown), multifocal spikes with very sharp morphology, rapid repetition, and a proclivity for the posterior head regions have been seen. **B:** Electroencephalogram showing a depression of the alpha rhythm on the right, consistent with a focal disturbance of cerebral function in the right posterior head region.

Aminoacidurias

Phenylketonuria (PKU; #261600) is typical of several disorders of amino acid metabolism whose symptoms appear in early infancy.[2] Phenylketonuria is caused by phenylalanine hydroxylase deficiency and is associated with mental retardation, microcephaly, psychotic behavior, and seizures.[47] Generalized seizures occur in 25% of patients. The majority of children with classic PKU who are treated early will have normal EEGs.[51] Focal and generalized slowing and epileptiform discharges have been reported in patients with abnormal EEGs. Increased delta activity may occur with oral phenylalanine loading. PKU may be successfully treated by dietary restriction of phenylalanine.

A hyperphenylalaninemic state may be the consequence of disorders of phenylalanine metabolism or tetrahydrobiopterin (BH_4) homeostasis. A disorder of BH_4 recycling produces severe neurologic regression and epilepsy that is refractory to antiepileptic drugs. Recurrent episodes of status epilepticus have been reported during the first year of life. The EEG may show hypsarrhythmia in early infancy. The typical biochemical profile is hyperphenylalaninemia, associated with decreased urinary and CSF biogenic amines.

A disorder of BH_4 synthesis secondary to deficiency of guanosine triphosphate cyclohydrolase (#233910) produces early developmental regression and infantile spasms. Control of seizures and improvement in the clinical condition can follow BH_4 replacement. Central replenishment of dopamine and serotonin can also lead to further improvement. The EEG of a patient followed at our institution revealed diffuse background slowing and multifocal spikes (Fig. 5). Deficiency of 6-pyruvoyal tetrahydrobiopterin synthase is characterized by progressive encephalopathy, pyramidal and extrapyramidal signs, and myoclonic seizures. Treatment with BH_4 and central neurotransmitter precursors controls seizures and normalizes the EEG.

Inborn errors of tyrosine metabolism cause seizures in patients of this age group. Tyrosinemia type III (4-hydroxy- phenylpyruvate dioxygenase deficiency) was reported in a newborn with recurrent seizures and in children in whom infantile spasms developed. Electroencephalographic findings included generalized voltage attenuation with single-spike and polyspike discharges in the parietal-occipital areas.

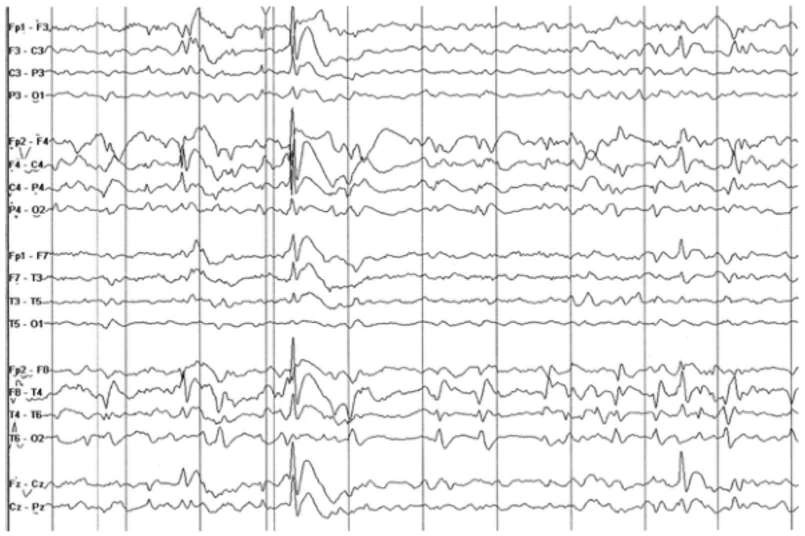

FIGURE 5. A 9-year-old child with guanosine triphosphate cyclohydrolase deficiency. Note severe background slowing with admixed multifocal spikes.

Mental retardation and seizures occur with histidinemia or histidase deficiency. Infantile spasms and myoclonic seizures are frequent. Delayed development and an exaggerated startle response are additional features. Seizures are refractory to the

usual drugs, and only one patient has responded to a diet low in histidine. A few patients with hyperprolinemia type I (proline oxidase deficiency) have mental retardation, seizures, and severe encephalopathy. Hyperornithinemia-hyperammonemia-homocitrullinuria (HHH) syndrome is manifested by ataxia, myoclonus, chorea, spasticity of gait, mental retardation, and seizures.[15] Infantile spasms have been reported in association with this defect of intramitochondrial ornithine transport. Restriction of protein and supplementation with ornithine, arginine, and citrulline are recommended as treatment.

Defects of the Urea Cycle

Presenting symptoms of disorders of the urea cycle and disorders of branched-chain amino acid and keto acid metabolism can appear either in the neonatal period, as discussed previously, or during infancy.

Disorders of γ-Aminobutyric Acid Metabolism

4-Hydroxybutyric aciduria is an example of an inborn error of GABA metabolism that results from a defect in succinic semialdehyde dehydrogenase function (#271980).[30] Psychomotor retardation, language delay, hypotonia, and ataxia develop in affected children between the ages of 6 months and 11 years. Seizures may be the presenting symptom in about 50% of patients. Accumulation of 4-hydroxybutyric acid in urine, plasma, and CSF and variable elevations of glycine are characteristic. Valproic acid is effective in controlling the seizures. Although it should theoretically work, our personal experience with vigabatrin treatment in one case was very disappointing. Others have also found lack of a good effect.[20,22]

Menkes Disease

This is an X-linked inherited disorder that results from a defect in the Cu^{2+}-transporting ATPase α polypeptide.[39] As a result, copper-dependent enzymes, including cytochrome *c* oxidase, are catalytically less active. The disturbance in cerebral oxidative metabolism is reflected in elevated CSF concentrations of lactic acid. Affected infants have a progressive encephalopathy with characteristic facial features, abnormalities of the hair, and various skin manifestations, including cutis laxa, seborrheic dermatitis, recurrent rash, and hypopigmentation. Myoclonic seizures are common during the first 2 months of life and are generally refractory to treatment. The EEG shows multifocal epileptiform discharges. Details regarding the EEG findings are not often reported, but evolution to infantile spasms has been observed.[56] Copper histidinate, the only available treatment, may be effective if begun in the presymptomatic phase.

Metabolic Disorders of Late Infancy

In general, metabolic diseases that cause seizures in late infancy are disorders affecting the structural components of the nervous system. These conditions are inexorably progressive, and the most important ones are lysosomal (Table 1).

Metachromatic Leukodystrophy

Metachromatic leukodystrophy is the result of a deficiency of arylsulfatase A. There are at least five allelic forms, including the characteristic late-infantile variant. Gait disorder and ataxia are the most common presenting symptoms, which are followed by a progressive decline in mental and motor skills.[21]

Partial seizures develop late in the clinical course in 25% of patients with the late-infantile form of metachromatic leukodystrophy and in 50% to 60% of patients with the juvenile-onset form. Electroencephalographic findings include diffuse high-voltage slowing and occasional bursts of spikes. Slow-frequency activity may be asymmetric. Focal interictal epileptiform discharges predominate in the late-infantile form.[69]

Schindler disease (#609241) results from a deficiency of α-*N*-acetylgalactosaminidase and is an extraordinarily rare condition.[62] Affected patients appear normal at birth, but progressive neurologic decline becomes evident after 1 year of age. Manifestations include spasticity, cerebellar signs, and extrapyramidal dysfunction. Generalized tonic–clonic seizures and myoclonic jerks are common. Electroencephalographic abnormalities include multifocal spikes and spike-and-wave complexes.

Mucopolysaccharidoses

The mucopolysaccharidoses are a family of lysosomal storage disorders caused by the deficiency of several enzymes involved in the degradation of glycosaminoglycans. The various mucopolysaccharidoses share many clinical features, including a chronic and progressive course, multisystem involvement, organ enlargement, dysostosis multiplex, and abnormal facial features. The most frequently occurring mucopolysaccharidosis is Sanfilippo syndrome; four different subtypes have been described, each associated with a different enzymatic defect. Generalized seizures develop in about 40% of patients with Sanfilippo syndrome, but these are often easily controlled by antiepileptic drugs. Progressive dementia and severe behavioral disorders are other features. Bone marrow transplantation has been successful in several cases.

Neuronal Ceroid Lipofuscinoses

The neuronal ceroid lipofuscinoses (NCL) are a group of diseases with the common feature of storage of lipopigments in the brain and other tissues. At least seven clinical subtypes as well as additional rare atypical forms have been reported, and virtually all these are transmitted as autosomal-recessive traits.[53] Infantile NCL (#256730), also referred to as Santavuori-Haltia-Hagberg disease, is particularly common in Finland, with an incidence of 1/13,000 live births. The disease is caused by a defect in palmitoyl-protein thioesterase (PPT). Infants are normal in the neonatal period, but at about 1 year of age, rapid neurologic deterioration with ataxia occurs. Initially, patients may be given a misdiagnosis of Rett syndrome because of the deceleration of head growth and stereotypic abnormal hand movements. However, myoclonic jerks become increasingly evident, and the appearance of macular and retinal degeneration with optic atrophy allows cases of infantile NCL to be distinguished clinically from cases of Rett syndrome. The electroretinographic findings are abnormal, and the EEG shows progressive slowing and loss of amplitude. Some cases of Lennox-Gastaut syndrome have been caused by NCL. Symptoms of the late-infantile form of NCL, known as Jansky-Bielschowsky disease (#204500), appear in late infancy or early childhood, and epilepsy is the dominant clinical manifestation. This is due to a mutation in the CLN2 gene. Other features are ataxia and dementia. The EEG shows multifocal spikes and slow background rhythm and a highly characteristic response to photic stimulation. Stroboscopic light flashed at rates of <4/s produce high-voltage spike discharges over the posterior scalp regions. Visual-evoked potentials and somatosensory-evoked potentials are also of very high voltage. A pseudoperiodic pattern with absence of sleep spindles may be highly suggestive of the disorder in the early stages of presentation.[63] Seizures are difficult to control, and the diagnosis may be hard to establish. Skin or conjunctival biopsy specimens demonstrate abnormal cytosomes containing curvilinear bodies.

Metabolic Disorders of Childhood and Adolescence

Numerous metabolic disorders make their presence known in later childhood or adolescence. These conditions largely represent variants of disorders discussed in the preceding sections. Seizures may occur, but not invariably, as shown in Table 4.

Homocystinuria

Disorders of transulfuration include cystathionine β-synthase deficiency, the most frequent cause of homocystinuria (#603174). Some patients respond to pyridoxine administration. Mental retardation, behavioral disturbances, and seizures are manifestations of nervous system involvement; ectopia lentis, osteoporosis, and scoliosis are other common clinical findings. Generalized seizures occur in about 20% of patients with pyridoxine-nonresponsive homocystinuria and in 16% of patients with the pyridoxine-responsive form. Electroencephalographic abnormalities are more common than seizures and may consist of either mild diffuse background slowing or focal interictal epileptiform discharges. These abnormalities may not respond to B6 administration.[13] Thromboembolism, malar flush, and livedo reticularis reflect vascular system involvement. Biochemical abnormalities include homocystinemia, methioninemia, decreased cystine concentration, and homocystinuria.

Diabetes Mellitus

Diabetes mellitus is the most common metabolic disorder. Seizures are generally not a feature except during metabolic crisis with ketoacidosis and cerebral edema. Nonketotic hyperosmolar diabetic coma has a high mortality, and generalized or partial seizures are common in this setting. Epilepsia partialis continua has been reported with nonketotic hyperglycinemia. Generalized tonic–clonic seizures have also been reported in a patient with diabetes mellitus who had an intracerebral hemorrhage during ketoacidosis.

Adrenoleukodystrophy

There are seven different clinical presentations of adreno- leukodystrophy (#300100).[43] It is caused by mutation in the *ABCD1* gene, which encodes an ATPase-binding-cassette protein. Symptoms of the X-linked form of adrenoleukodystrophy classically appear in early childhood. Partial motor seizures, often with secondary generalization, and generalized tonic–clonic seizures are common in this peroxisomal disorder. Status epilepticus has been the initial presenting symptom, and epilepsia partialis continua has also been reported. The EEG is characteristic, with high-voltage polymorphic delta activity and loss of faster frequencies over the posterior regions.[38]

Lysosomal Disorders

An example of this group of diseases is neuraminidase deficiency (#256550), characterized by progressive loss of vision, presence of a macular cherry red spot, and progressive and

disabling myoclonus but relative preservation of cognition. The condition is also known as the cherry red spot-myoclonus syndrome. Generalized seizures are common, and the EEG is characterized by low-voltage, fast background activity and positive spikes that correlate with massive myoclonic jerks. This form of neuraminidase deficiency is referred to as sialidosis type I. Sialidosis type II is subdivided into two groups, an infantile form with early onset and a juvenile form with early normal development.[37] The infantile form is characterized by progressive encephalopathy, visceromegaly, course facial features, dysostosis multiplex, and presence of macular cherry red spots. Seizures are uncommon. Symptoms of the juvenile form appear in childhood, and include progressive mental regression, myoclonus, short stature, dysostosis multiplex, course facial features, and cherry red spots. The EEG is abnormal in 50% of patients, with an irregular slow background activity and spike-and-wave complexes.

Table 4 Metabolic disorders in childhood and adolescence

Disorder	Seizure frequency	Seizure type	EEG	Dysmorphism	Neuroimaging	Laboratory findings	Treatment
Tyrosinemia type I	+/++	G	Slow-wave acitvity in acute phase	Absent	Cerebral edema (rare)	Hyponatremia; aminoaciduria; high tyrosine; abnormal coagulation profile	Dietary, liver transplant
Homocystinuria	+/++	GTC	No specific abnormalities	Marfan-like; ectopia lentis	Normal	High methionine and homocysteine; low cystine; homocystinuria	Pyroxidine
Diabetes mellitus	++	P, EPC (nonketotic hyperglycemia), GTC	Diffuse or focal slow activity; focal paroxysms (sharp/slow wave)	Absent	Cerebral edema	Hyperglycemia; hyponatremia; hyperosmolarity	Mannitol therapy; fluid restriction

Pyrimidine disorders	+++	GTC, A	Generalized paroxysms; photic response	Absent	Hypoplasia CC; BG calcifications	High thymine and uracil	Symptomatic
X-linked adrenoleukodystrophy	+++	P, GTC, SE, EPC	Slow theta-delta waves of large amplitude	Absent	White-matter lesions	High VLCFA	Symptomatic; immuno-suppression; bone marrow transplant
Sialidosis	+++ (type 1)	M	Abnormal background	Present (type II)	Cerebral, cerebellar atrophy	Abnormal urinary oligosaccharide pattern	Symptomatic
Niemann-Pick type C	++	GTC, P, akinetic	Diffuse theta slowing; bursts of spike-and-wave complexes; multifocal spikes	Absent	Cerebellar atrophy; large fourth ventricle; white-matter lesions	Accumulation of unesterified cholesterol; normal or elevated sphingomyelinase activity	Drug therapy
Gaucher disease	+++	P, GTC	Slow background; spike-and-wave paroxysms	Absent	Normal	Glucocerebrosidase deficiency	Enzyme replacement; bone marrow transplant
Krabbe disease	++	M, atonic, RSE	No specific pattern	Absent	White-matter lesions; enhancement of the splenium CC; low-density gray matter	Galactosylceramidase deficiency	Not available
Galactosialidosis	+++	M, GTC	Multiple spike-and-slow-wave paroxysms	Present	Normal	Abnormal oligosaccharides; combined ß-galactosidase and neuraminidase deficiency	Not available
GM_2 gangliosidosis	++	P, GTC, M, gelastic	Spike-and-wave complexes; slow waves (anterior region)	Absent	Cerebellar atrophy	Abnormal oligosaccharides; hexosaminidase A deficiency	Not available

+, 0%–25% seizure activity; BG, basal ganglia; CC, corpus callosum; EEG, electroencephalogram; EPC, epilepsia partialis continua; G, generalized; GTC, generalized tonic-clonic; M, myoclonic; P, partial; RSE, recurrent status epilepticus; SE, status epilepticus; VLCFA, very-long-chain fatty acids.

Niemann-Pick disease type C is an autosomal recessive lipidosis caused by a defect in cholesterol esterification (#257220), specifically a mutation in either the *NPC1* or *NPC2* gene.[49] The sphingomyelinase activity is normal or elevated. Neurologic manifestations are striking and include a progressive ataxia, supranuclear vertical gaze palsy, progressive extrapyramidal symptoms, and seizures.[27] Complex partial seizures, partial seizures with secondary generalization, and primary generalized tonic–clonic convulsions occur frequently. Akinetic seizures, often precipitated by sudden laughter, are less frequent but suggestive of the disorder. Conventional antiepileptic drugs are rarely effective.

Gaucher disease is another lysosomal disorder; it results from a deficiency of acid ß-glucosidase. There are three clinical types. Type I (#230800) is characterized by hepatosplenomegaly, hypersplenism, and bone lesions. Type II (#230900) involves the nervous system, with early onset of progressive encephalopathy and visceromegaly. Type III (#23100) represents an intermediate form, characterized by early normal development, ocular apraxia, and slowly progressive mental and motor deterioration with ataxia. Complex partial seizures and generalized tonic–clonic seizures occur almost invariably. Some patients have early progressive myoclonus. Current treatment is enzyme protein replacement and bone marrow transplantation.

Finally, GM_2 gangliosidosis may appear in early to late childhood as a progressive ataxic syndrome associated with mental and motor deterioration and seizures. Partial complex seizures and generalized tonic or tonic–clonic seizures are particularly common. Generalized atonic seizures and gelastic seizures also have been described. Seizures are generally refractory to treatment.

Diagnostic Investigation

The diagnosis of genetically determined metabolic diseases is straightforward in many instances but complicated in others. For example, the classic aminoacidopathies and organic acidurias, once suspected, can be easily diagnosed by appropriate blood or urine measurements. Conversely, the diagnosis of an obscure condition, such as the carbohydrate-deficient glycoprotein syndrome, may require specific isoelectric focusing of the serum sialotransferrin isoform pattern in a specialized research laboratory.[23] Before obtaining appropriate metabolic, biochemical, or tissue specimens, the physician must have a reasonable differential diagnosis. Age of onset, clinical findings, family history, and neurologic examination continue to be the cornerstones of diagnosis. Experienced neurologists can often diagnose many of the disorders discussed in this chapter at the first clinical encounter. In such situations, laboratory studies serve only to confirm the clinical diagnosis. The presence of macular cherry red spots, abnormal appearance of the hair, or a peculiar distribution of fat over the posterior flanks or thighs immediately suggests the diagnosis of Tay-Sachs disease, Menkes disease, or the carbohydrate-deficient glycoprotein syndrome. Deceleration of head growth during infancy with consequent acquired microcephaly implies a defect of energy metabolism, the infantile form of NCL, or Rett syndrome, among other possibilities. Dislocated lenses and a seizure followed by a stroke are virtually diagnostic of homocystinuria.

Genetically determined metabolic diseases often have a saltatory historical pattern, in contrast to neurodegenerative diseases, which are inexorably progressive.

A complete blood cell count with differential and platelet count should be obtained in every case. Bone marrow depression occurs in the ketotic hyperglycinemic syndromes. A review of the peripheral smear may reveal important clues, such as a macrocytic anemia or vacuolated lymphocytes. A complete serum chemistry profile will uncover carbohydrate and electrolyte disturbances or specific organ dysfunction. Calcium and magnesium concentrations should be determined in every case. Low uric acid concentration raises the possibility of molybdenum cofactor deficiency, and low blood urea nitrogen suggests a defect involving the urea cycle. Quantitative measurement of plasma and urinary amino acids is necessary to identify the various aminoacidopathies. A urinary organic acid profile should be obtained based on the first morning urine specimen.

A lumbar puncture is required to measure various CSF metabolites. Elevated CSF protein concentration is characteristic of metachromatic leukodystrophy and globoid-cell encephalopathy. Low CSF glucose concentration is consistent with hypoglycemia caused by a defect of gluconeogenesis or a defect in the transport of glucose across the blood–brain barrier (glucose transporter type 1 deficiency syndrome). Low CSF folate concentration suggests a defect involving folate metabolism. The presence in CSF of amino acids, specifically glycine, glutamate, and GABA, may be diagnostic of nonketotic hyperglycinemia or pyridoxine-dependent epilepsy. Lactate and pyruvate values are elevated in CSF in disorders of cerebral energy metabolism, including pyruvate dehydrogenase deficiency, pyruvate carboxylase deficiency, numerous disturbances of the respiratory chain, and Menkes disease. A low CSF lactate value may be seen in the glucose transporter protein deficiency syndrome. Abnormal findings on measurement of CSF biogenic amine and measurement of biopterin metabolism suggest several disorders associated with the hyperphenylalaninemic state.

Tissue biopsy specimens also provide important information in establishing a diagnosis. Specimens of skin, conjunctiva, rectum, peripheral nerve, and skeletal muscle may provide useful clues. Only rarely would a brain biopsy be necessary.

Electroencephalographic abnormalities are frequently helpful in establishing a diagnosis. A suppression-burst pattern is characteristic of nonketotic hyperglycinemia, phenylketonuria, maple syrup urine disease, and molybdenum cofactor deficiency. Distinctive EEG features include the comblike rhythm with 7- to 9-Hz central activity in maple syrup urine disease, vertex positive spikes in sialidosis type I, bioccipital polymorphic delta activity in X-linked adrenoleukodystrophy, and 14- to 22-Hz invariant activity with infantile neuroaxonal dys- trophy.

Structural brain imaging provides important information, although findings are frequently nonspecific. Progressive atrophy is characteristic of NCL. White-matter signal abnormalities are characteristic of metachromatic leukodystrophy, globoid-cell encephalopathy, phenylketonuria, some mitochondrial diseases, Canavan disease, and some organic acidurias. Calcification of the cerebral cortex and basal ganglia is seen with many inherited metabolic diseases. Magnetic resonance spectroscopy may demonstrate elevated concentrations of lactate in brain tissue in various mitochondrial diseases or elevated concentrations of *N*-acetylaspartic acid in Canavan disease.

Treatment

The treatment of seizures associated with inherited metabolic diseases should focus primarily on the metabolic disturbance whenever possible. For example, seizures associated with a hypoglycemia are correctly treated with administration of glucose to maintain a normal blood glucose concentration. Similarly, seizures associated with hyponatremia, hypocalcemia, or hypomagnesemia respond best to correction of these electrolyte disturbances. Dietary treatment is appropriate for many inherited metabolic diseases, including defects of the urea cycle, defects of fatty acid oxidation, gluconeogenic defects, aminoacidopathies, organic acidurias, and the glucose transporter deficiency syndrome. The ketogenic diet is effective in controlling seizures in patients with the glucose transporter protein deficiency syndrome, and it provides some benefit in the management of patients with pyruvate dehydrogenase deficiency. Phenylketonuria can be well treated with a diet low in phenylalanine. Protein restriction is recommended for defects of the urea cycle, and fat restriction is advised for defects involving fatty acid oxidation. Pyridoxine-dependent epilepsy and other vitamin-responsive syndromes can be cured by early diagnosis and prompt administration of the specific vitamin or cofactor. Enzyme protein replacement has proved to be effective in Gaucher disease. Bone marrow transplantation has been used effectively to treat patients with mucopolysaccharidoses and adrenoleukodystrophy. Conventional antiepileptic drugs are useful adjuncts to these more direct therapeutic interventions but are often ineffective by themselves. Patients with certain inherited metabolic diseases (e.g., defects of fatty acid oxidation) may be less tolerant of some antiepileptic drugs, notably valproic acid, particularly because it interferes with fatty acid oxidation and depletes tissue stores of carnitine.

Summary and Conclusions

Seizures often are part of the clinical picture of inherited metabolic disorders, particularly when these conditions first appear in the neonatal period or during infancy. Why seizures commonly accompany some metabolic diseases and are infrequent in others is incompletely understood, but certain correlations are intuitively obvious. Defects of energy metabolism commonly are associated with seizures—witness the hypoglycemic syndromes and defects involving pyruvate metabolism, the Krebs cycle, and the respiratory chain. In addition, seizures frequently accompany inherited metabolic disorders that affect neurotransmission, such as nonketotic hyperglycinemia and pyridoxine-dependent epilepsy. A more fundamental common mechanism may be operative in many of these conditions. For example, an alteration in the ratio of glutamic acid to GABA may exist in conditions associated with cerebral energy failure and in conditions affecting the GABA shunt. Any inherited metabolic condition in which the extracellular glutamate concentration is elevated and the extracellular GABA concentration is lowered would lower the seizure threshold. Recent studies have confirmed this speculation in cases of symptomatic hypoglycemia, nonketotic hyperglycinemia, and pyridoxine-dependent epilepsy.

In contrast, defects of fatty acid oxidation are less likely to be associated with epilepsy. Fatty acids do not serve as oxidizable fuels for brain metabolism. Brain function is compromised principally when the patient is subjected to fasting and hypoketotic hypoglycemia develops. Under these conditions, the brain is deprived of its two primary fuels—glucose and ketone bodies. Disturbed consciousness and seizures may occur under these circumstances.

All infants and young children seen with unexplained seizures should be evaluated for an inherited metabolic disorder. A positive family history may provide an important clue, and careful studies of blood, urine, and CSF may uncover important diagnostic clues. Primary correction of the metabolic disturbance is the optimal treatment of the associated seizure disorder, even though conventional antiepileptic drugs may blunt the expression of the seizure disorder. In certain situations, antiepileptic drugs are ineffective, as is the case with the glucose transporter protein deficiency syndrome. Providing an alternative fuel source for brain metabolism by placing the patient on a ketogenic diet is effective in controlling seizures in this syndrome, whereas conventional antiepileptic drugs are ineffective.

It can reasonably be assumed that seizures in the neonatal period or infancy have a metabolic basis until it is proved otherwise. Careful study of this patient population will continue to identify novel inherited metabolic disorders and lead to more direct and effective treatments of these conditions.

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Chapter 262

Mitochondrial Diseases

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Introduction

Since the initial discovery of mitochondrial DNA mutations in 1988, our understanding of the mitochondrial encephalomyopathies has advanced at an astoundingly rapid pace. Numerous scientific and clinical reports have documented the discoveries, while review articles[19,23] and even several books[20,104] have summarized much of this progress. The purpose of this chapter is not to describe the mitochondrial encephalomyopathies comprehensively, but rather, to illustrate some of the fundamental clinical and scientific themes in these diverse disorders that often manifest epilepsy.

Mitochondria are vital organelles, because they (a) produce energy in the form of adenosine triphosphate (ATP) through oxidative-phosphorylation of carbohydrates, fats, and amino acids,[57,70,128] (b) are essential for intracellular calcium homeostasis,[28] (c) contribute to the synthesis of important metabolic precursors [e.g., uridine,[54] amino acids, and iron-sulfur (Fe-S) clusters[34]], and (d) finally, participate in cell death pathways.[39] Much has been learned about the functions of these organelles, and defects of specific processes provide an elegant and rational biochemical classification system of the mitochondrial diseases (Table 1). A prime example of a specific biochemical defect of mitochondria is carnitine palmityl transferase (CPT) II deficiency.[21] Transport of fatty acids through the mitochondrial membranes is impaired by specific mutations in CPT II. By contrast, mitochondrial respiratory chain disorders often do not conform to single-enzyme defects because multiple enzymes can be affected; therefore, this biochemical classification scheme has limitations.

Molecular genetics provides an alternative perspective of mitochondrial diseases. One can gain a better understanding of mitochondrial disorders by considering the several unique genetic characteristics of mitochondria. Mitochondria are unique mammalian organelles because they possess their own genetic material, mitochondrial DNA (mtDNA), which is a small (16.5 kilobases) circular molecule encoding 13 polypeptides, 22 transfer RNAs (tRNA), and two ribosomal RNAs (rRNA).[4] The mtDNA-encoded polypeptides are vital subunits of the respiratory chain. In addition, more than 1,000 mitochondrial proteins are encoded in the nuclear DNA (nDNA). Because mitochondria are the products of two genomes, defects in either genome can cause mitochondrial dysfunction. To date, most of the respiratory chain defects that have been characterized at the molecular genetic level are due to mtDNA mutations.[19,20,23]

An important principle of mtDNA genetics is *heteroplasmy.* Each mitochondrion contains two to ten copies of mtDNA and, in turn, each cell contains multiple mitochondria; therefore, there are hundreds to thousands of mtDNA molecules in each cell. Alterations of mtDNA may be present in some of the mtDNAs (heteroplasmy) or in all of the molecules (*homoplasmy*). As a consequence of heteroplasmy, the proportion of a deleterious mtDNA mutation can vary widely. An individual who harbors a large proportion of mutant mtDNA will be more severely afflicted by the mitochondrial dysfunction than a person with a low percentage of the same mutation. As a consequence, a given mtDNA mutation can produce a diverse spectrum of clinical severity among patients.

A second factor that can influence the expression of a mtDNA mutation in a person is the *tissue distribution* of that mutation. The best example of tissue distribution variation is offered by large-scale mtDNA deletions. Infants with a high proportion of deleted mtDNA in their blood can develop Pearson syndrome, a sideroblastic anemia often accompanied by exocrine pancreatic dysfunction.[68,92] Presumably, these infants have a high proportion of deleted mtDNA in the bone marrow stem cells. Some children survive the anemia with blood transfusions and subsequently recover, because the stem cells with a high proportion of deleted mtDNA are eliminated through a negative selection bias. Later in life, however, those children may develop the multisystem mitochondrial disorder Kearns-Sayre syndrome (KSS), characterized by ophthalmoplegia, pigmentary retinopathy, and cardiac conduction block.[53,93] Thus, variable tissue distribution broadens the clinical spectrum of pathogenic mtDNA mutations.

The third factor that determines clinical expression of a mtDNA mutation is tissue *threshold effect*. Cells with high metabolic activities are more severely affected by relatively lower levels of mtDNA mutations; therefore, these disorders tend to affect disproportionately the brain and muscles (encephalomyopathies).

A fourth unusual characteristic of mtDNA is *maternal inheritance*. During the formation of the zygote, the mtDNA is derived exclusively from the oocyte. Thus, mtDNA is transmitted vertically in a nonmendelian fashion from the mother to both male and female progeny. A single exception to this rule has been described; a man with exercise intolerance and two base-pair deletions in the mitochondrial-encoded gene for subunit 2 of complex I (nicotinamide adenine dinucleotide [NAD] dehydrogenase 2 [ND2]) showed paternal inheritance of mtDNA in skeletal muscle.[56,108] Because paternal inheritance of mtDNA appears to be exceedingly rare,[29,109,122] maternal inheritance is important to recognize in determining whether a family is likely to harbor a mtDNA mutation. A caveat to this principle is the fact that maternal relatives who have lower percentages of a mtDNA mutation may have fewer symptoms (oligosymptomatic) than the proband, or they may even be asymptomatic. Therefore, in taking the family history, it is important to ask about the presence of subtle symptoms or signs in maternally related family members who might be oligosymptomatic.

Table 1 Biochemical classification of mitochondrial encephalomyopathies

1. **Defects of transport**
    a. CPT deficiency
    b. Carnitine deficiency
    c. Defects of FAD uptake (?)
2. **Defects of substrate utilization**
    a. Pyruvate carboxylase deficiency
    b. Pyruvate dehydrogenase complex deficiency
    c. Defects of ß-oxidation
3. **Defects of the Krebs cycle**
    a. Fumarase deficiency
    b. α-Ketoglutarate dehydrogenase (dihydrolipoyl dehydrogenase) deficiency
4. **Defects of oxidation-phosphorylation coupling**
    a. Luft syndrome (loose coupling of muscle mitochondria)
5. **Defects of the respiratory chain**
    a. Complex I deficiency
    b. Complex II deficiency
    c. Complex III deficiency
    d. Complex IV deficiency

e. Complex V deficiency
f. Combined defects of respiratory chain components

From DiMauro S, et al. Mitochondrial encephalomyopathies. *Neurol Clin*. 1990;8:483–506, with permission.

These peculiar features of "mitochondrial genetics" contribute to the clinical complexity of human mitochondrial disorders. Variable heteroplasmy of mtDNA mutations produces an extensive range of disease severity, whereas tissue distribution and tissue threshold of mtDNA mutations explain the frequent but variable involvement of multiple organ systems.

In addition to mtDNA mutations, nuclear DNA (nDNA) defects can also cause mitochondrial dysfunction. In fact, nDNA encodes most of the components of the respiratory chain and, since 1995, many nDNA mutations associated with defects in oxidative-phosphorylation have been identified.[19,20] In this chapter, we review the major mitochondrial encephalomyopathy syndromes associated with seizures. We will not quote or summarize the vast literature on mitochondrial encephalomyopathies; rather, we will try to convey some of the principles of evaluation, diagnosis, and treatment of these disorders with emphasis on epilepsy.

Clinical Description

The mitochondrial encephalomyopathies comprise a heterogenous group of multisystem disorders that typically affect infants, children, or young adults. Among these diverse conditions, specific clinical syndromes were recognized. Because clinicians are confronted with patients, the clinical classification of the mitochondrial disorders is of pragmatic significance in guiding the diagnostic evaluation, determining prognosis, and in directing therapy. The discovery of distinct mtDNA and nDNA mutations has demonstrated that, in general, clinical phenotypes have specific genotypes; however, some patients do not fit into any clinical syndrome, or they have an atypical presentation for a particular mutation.

Table 2 Seizure incidence in specific mitochondrial encephalomyopathy syndromes

Syndrome	Incidence	Percent	References
MERRF	62/62	100	44
MELAS	97/102	96	43
KSS	5/156	3	44

MERRF, myoclonus epilepsy with ragged-red fibers; MELAS, mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes; KSS, Kearns-Sayre syndrome.

Common to all mitochondrial disorders with prominent epilepsy is involvement of the central nervous system (CNS), particularly the cortex. Imaging techniques have confirmed that gray matter involvement is an early feature of myoclonus epilepsy with ragged-red fibers (MERRF) and of mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS); white matter abnormalities are also seen at later stages, but usually not in isolation.[15] Maternal inheritance is pathognomonic of mtDNA point mutations, whereas patients with single large-scale rearrangements tend to be sporadic. In addition, phenotypic variability in families is the general rule rather than the exception with pathogenic mtDNA point mutations.

Mitochondrial Encephalomyopathies Associated with mtDNA Mutations

Kearns-Sayre Syndrome

Rowland and colleagues defined Kearns-Sayre syndrome (KSS) by the obligate triad of ophthalmoplegia, pigmentary retinopathy, and onset before age 20, with at least one of the following additional features: Cardiac conduction block, ataxia, and cerebrospinal fluid (CSF) levels of greater than 100 mg/dL.[93] The existence of KSS as a clinical entity is supported by the fact that more than 150 patients with these characteristics have been reported.[43] About 90% of the KSS patients have single large-scale rearrangements of the mtDNA, either deletions, duplications, or both.[72,85] Typically, KSS patients are sporadic, because the mtDNA rearrangements seem to originate in oogenesis or early zygote formation. Despite the clear evidence of encephalopathy (dementia, basal ganglia calcifications, and spongy changes of the brain white matter), seizures are uncommon in KSS (5/156 patients) (Table 2).[43]

Myoclonus Epilepsy with Ragged-Red Fibers Syndrome

In contrast to KSS, MERRF includes epilepsy as a defining clinical feature. In addition, these patients have myoclonus, ataxia, and ragged-red fibers in the muscle biopsy.[32] Other common clinical manifestations associated with MERRF are hearing loss, dementia, peripheral neuropathy, short stature, exercise intolerance, lipomas, and lactic acidosis.[118] The majority of MERRF patients have a history of affected maternally related family members, although not all have the full syndrome.

In 1990, Shoffner et al. identified a mtDNA A-to-G transition mutation at nucleotide (nt) 8344 of the *tRNA*^{Lys} gene[113]; that mutation has been found in about 90% of MERRF patients tested.[118] This mutation was the first molecular genetic defect to be associated with a hereditary epilepsy syndrome. A second mutation in the same gene at nt-8356 was identified in a pedigree with typical MERRF[117] and in another family with overlap features of MERRF and MELAS.[134] In addition, a mutation at nt-611 in the *tRNA*^{Phe} gene has

been also associated with MERRF.[63] Within families with a MERRF proband, oligosymptomatic and asymptomatic members harbor the same mtDNA mutation, but the phenotype is presumably attenuated by heteroplasmy and tissue distribution of the mtDNA mutation.[118]

Table 3 MtDNA mutations associated with epilepsy

	tRNA$^{\text{Lys}}$	8356	T-to-C	117, 134
	tRNA$^{\text{Phe}}$	611	G-to-A	63
Atypical MERRF	*tRNA*$^{\text{Leu(UUR)}}$	3255	G-to-A	78
	tRNA$^{\text{Ser(UCN)}}$	7472	Ins C	86
	tRNA$^{\text{Asp}}$	7543	A-to -G	114
	tRNA$^{\text{Lys}}$	8342	G-to-A	126
	tRNA$^{\text{His}}$	12147	G-to-A	124
	ND3	10191	T-to-C	122
	ND5	13042	G-to-A	75
Seizures, PEO, diabetes, and deafness	*tRNA*$^{\text{Leu(UUR)}}$	3256	A-to-G	72
Cardiomyopathy, deafness, and seizures	*tRNA*$^{\text{Ile}}$	4269	A-to-G	120
	tRNA$^{\text{Ile}}$	4320	C-to-T	99
ME with recurrent episodes of epilepsia partialis continua	*tRNA*$^{\text{Ser}}$	7512	T-to-C	50, 106
	COX I	6489	C-to-A	130
Leigh syndrome	*ATP 6*	8993	T-to-G	13
		8993	T-to-C	17
	tRNA$^{\text{Lys}}$	8363	G-to-A	115
LHON	*ND1*	3460	G-to-A	11

	ND2	4640	C-to-A	11

Table 4 Mitochondrial encephalomyopathies with epilepsy due to nuclear DNA mutations

Biochemical defect	Clinical phenotype	Defective gene or gene product
1. *Mutations in genes encoding structural subunits of respiratory chain enzymes*		
Complex I deficiency	Encephalomyopathy or Leigh syndrome	*NDUFS1, NDUFS2, NDUFS3, NDUFS4, NDUFS6, NDUFS7, NDUFS8, NDUFV1, NDUFV2*
Complex II deficiency	Leigh syndrome	Flavoprotein subunit of SDH
2. *Mutations in genes encoding assembly factors for respiratory chain enzymes*		
Complex I deficiency	Encephalopathy	*B17.2*
Complex III deficiency	Encephalopathy, tubulopathy, and hepatopathy	*BCS1L*
Complex IV deficiency	Leigh syndrome	*SURF1*
	Infantile cardioencephalopathy	*SCO2*
	Infantile encephalopathy	*SCO1, COX10*
3. *Defects of intergenomic communication*		
Autosomal recessive	MNGIE	Thymidine phosphorylase
	arPEO	*POLG1*
	ARCO	Unknown

PEO with multiple Δ-mtDNA		
Autosomal dominant PEO with multiple Δ-mtDNA	adPEO	*ANT1*, Twinkle, *POLG1*
MtDNA depletion	Infantile encephalopathy and hepatopathy	dGK
	Alpers disease	*POLG1*
	Infantile encephalomyopathy	ADP-forming succinyl-CoA synthase
4. *Defects of the mitochondrial membrane*		
Coenzyme Q10 deficiency	Myoglobinuria, encephalopathy, ragged-red fibers	Unknown
	Cerebellar ataxia	Unknown
	Infantile encephalomyopathy nephropathy	COQ2

Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-like Episodes Syndrome

MELAS is another maternally inherited disorder whose defining clinical features include (a) stroke-like episodes at a young age (typically before age 40); (b) encephalopathy manifest as seizures, dementia, or both; and (c) mitochondrial dysfunction with lactic acidosis, ragged-red fibers, or both.[44,82] Other commonly encountered manifestations include normal early development, migraine headaches, myopathic weakness, exercise intolerance, myoclonus, ataxia, short stature, and hearing loss.[44,82] It is uncommon for more than one family member to have the full MELAS syndrome; in most pedigrees, there is only one MELAS patient with oligosymptomatic or asymptomatic relatives in the maternal lineage.

Other Mitochondrial Encephalomyopathies with Epilepsy Caused by mtDNA Point Mutations

In addition to the three aforementioned common and well-defined phenotypes of mitochondrial diseases, several other epilepsy syndromes have been associated with point mutations of mtDNA (Table 3). These mutations reside predominantly in mitochondrial tRNA genes.[50,64,78,86,99,106,114,115,125] Although less common, mutations in polypeptide-coding mitochondrial genes have also been reported in patients with epilepsy.[11,13,17,65,75,124,130] Some of these mutations are associated with multisystem disorders such as maternally inherited Leigh syndrome (MILS),[17,115] neuropathy ataxia retinitis pigmentosa (NARP),[13] or Leber hereditary optic neuropathy

(LHON).[11] In addition to epilepsy, other common manifestations include dementia, cardiomyopathy (typically hypertrophic) skeletal myopathy, and hearing loss.[99,120]

Mitochondrial Encephalomyopathies Associated with Nuclear Mutations

Leigh Syndrome

Subacute necrotizing encephalomyelopathy was originally described in 1951 by Dr. Denis Leigh, who reported a 6.5-month-old infant presenting with developmental regression that progressed quickly and led to death 6 weeks later.[61] At autopsy, Dr. Leigh observed multiple symmetric foci of spongy degeneration with microvascular proliferation in the brainstem tegmentum, thalami, cerebellum, posterior columns of the spinal cord, and optic nerves. He astutely noted that the neuropathologic alterations resembled those of Wernicke syndrome but spared the mamillary bodies, a consistent feature that distinguishes the two disorders.

The clinical presentations of Leigh syndrome (LS) are heterogeneous, due to variations in age-at-onset, rates of progression, frequency of epilepsy, and presence or absence of pigmentary retinopathy. The onset is often acute and may coincide with a febrile illness or may follow a seizure. Most LS patients present in infancy with psychomotor regression, whereas some present in childhood or adolescence. Adult-onset LS is uncommon. In infants with LS, in addition to developmental regression, generalized hypotonia, feeding problems, progressive vision loss due to optic neuropathy or pigmentary retinopathy, progressive external ophthalmoplegia, hearing loss, nystagmus, ataxia, and seizures are typical manifestations. In addition, failure to thrive, dysarthria, vomiting, and diarrhea are common manifestations. Respiratory dysfunction is often prominent and frequently causes death. Most infantile-onset LS patients die before age 2 years. In older infants or young children, LS may begin with ataxia, dystonia, or intellectual decline.

The clinical diagnosis of LS is usually made by brain magnetic resonance imaging (MRI) scans, which reveal increased signals in the basal ganglia and brainstem on T2-weighted or FLAIR images. The lesions are typically symmetric and commonly affect the putamen, globus pallidus, caudate, thalami, substantia nigra, inferior olivary nuclei, periaqueductal gray matter, and brainstem tegmentum. Magnetic resonance spectroscopy (MRS) scans reveal decreased N-acetylaspartate and increased lactate in the affected brain regions.

The causes of LS are biochemically heterogeneous and, to an even greater extent, genetically diverse (Table 4). LS has been associated with defects of pyruvate carboxylase, pyruvate dehydrogenase complex (PDHC), and mitochondrial respiratory chain complexes I, II, IV, and V.[10,98,126,129,135] The inheritance pattern depends on the specific mutated gene, but may

be autosomal recessive, X-linked recessive, or, as previously mentioned, maternally inherited.

Alpers Syndrome

Alpers or Alpers-Huttenlocher syndrome was reported in 1931 by Bernard Alpers, who described a previously healthy 3-month-old girl, who developed intractable seizures, blindness, and became stuporous before dying at age 4 months.[3] Neuropathology revealed widespread degeneration of the cortex and basal ganglia. Huttenlocher et al. described the pathologic findings in liver, which included microvesicular steatosis, proliferation of bile ducts, and cirrhosis.[48] Clinically, Alpers syndrome is characterized by autosomal recessive inheritance, normal early development, episodic neurodegeneration with psychomotor regression, seizures that become intractable, and hepatopathy. The occipital lobe is frequently affected, leading to cortical blindness. Onset is usually in infancy or childhood, but can be as late as 25 years. In patients with Alpers disease, valproic acid should be avoided because this drug can precipitate fulminant hepatopathy.

Ultrastructurally abnormal mitochondria in cerebral neurons suggested that the disease might be a mitochondrial encephalomyopathy[97]; this notion was confirmed by the identification of mtDNA depletion in association with pathogenic mutations in the gene encoding the catalytic subunit of mitochondrial DNA polymerase-γ (*POLG1*).[77]

Coenzyme Q_{10} Deficiency

Coenzyme Q_{10} (CoQ_{10}) is a small lipophilic molecule located in the inner mitochondrial membrane and composed of a quinone group and a poly-isoprenoid tail.[127] CoQ_{10} transfers reducing equivalents from complexes I and II to complex III. Deficiency of CoQ_{10} in skeletal muscle has been associated with four major phenotypes. A predominantly myopathic form is characterized by the triad of recurrent myoglobinuria, ragged-red fibers, and encephalopathy with seizures, ataxia, or mild mental retardation.[81] A more common ataxic form presents with cerebellar ataxia and atrophy with variable involvement of the peripheral nerves, muscle, and other CNS functions.[59,74] The third variant is a rare infantile encephalomyopathy with nephropathy.[92,96] Finally, a pure myopathic variant without epilepsy exists.[58] Presumably, all the CoQ_{10} deficiencies are due to defects of biosynthesis. The first mutation directly affecting CoQ_{10} biosynthesis was identified in a pair of siblings with the infantile form; the homozygous missense mutation resides in the *COQ2* gene, which encodes *para*-hydroxybenzoate-polyprenyl transferase.[87] It is important for clinicians to recognize patients with CoQ_{10} deficiency because the syndrome responds dramatically to CoQ_{10} supplementation (150–3,000 mg daily in adult patients).

Epileptic Seizures

Seizures are a common manifestation of mitochondrial encephalomyopathies (Table 2). As with other clinical features, the frequency and severity of seizures varies with the syndrome and even among affected individuals within a family with a single mtDNA point mutation.

Kearns-Sayre Syndrome

Seizures have been rarely described in KSS. Of 156 reported patients, only five (3%) were noted to have seizures and, in four of these, epilepsy was attributed to electrolyte imbalance secondary to hypoparathyroidism.[43] The infrequency of epileptic seizures in KSS illustrates an important clinical point; although seizures are a common feature of MELAS and a defining symptom of MERRF, their relative absence in KSS reinforces the concept that distinct clinical syndromes do exist although overlap features sometimes occur. It is very likely that the spatial distribution of the mitochondrial defect in the CNS is the responsible factor that determines the association of certain mtDNA mutations with epilepsy.[56,123] This seems to be in line with the fact that KSS is a white matter disorder affecting preferentially brainstem tegmentum, white matter of cerebellum and cerebrum, cervical spinal cord, basal ganglia, and diencephalon,[56] which are brain areas with low epileptogenicity.

Myoclonus Epilepsy with Ragged-Red Fibers

Myoclonus epilepsy with ataxia comprises a classical neurologic triad originally described by Ramsey Hunt as *dyssynergia cerebellaris myoclonica*.[47] We now label idiopathic cases of that triad as Ramsey Hunt syndrome, which is one form of progressive myoclonus epilepsy (PME).[6] PME syndromes include a well-characterized set of disorders that are described earlier in this volume. Since 1980, when Fukuhara et al.[32] first defined MERRF, this syndrome has been increasingly recognized as a major form of PME.

Symptoms and signs in isolated MERRF patients may be clinically indistinguishable from other PME disorders such as Unverricht-Lundborg disease and Lafora body disease. The myoclonus typically affects limbs, and can be severe enough to interfere with normal voluntary functions such as writing, speaking, or walking.[7,32,91] The myoclonus can be virtually constant,[91] but is usually spontaneous and intermittent, and it may be photosensitive.[60] In one unusual patient, the myoclonus correlated with EEG spikes: Both manifestations were seen with eyes closed and disappeared when the patient opened her eyes.[33]

Patients with MERRF typically have generalized tonic–clonic seizures, which are responsive to conventional antiepileptic therapy. Focal clonic and akinetic seizures have been reported.[7,60] Visual or somatosensory auras may precede the generalized seizures.[7] Both myoclonus and seizures may be precipitated by photic stimulation, such as watching television.[33,91]

Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-Like Episodes

Patients with MELAS frequently manifest seizures, myoclonus, and ataxia; therefore, they may closely resemble individuals with MERRF. In a review of 110 reported MELAS patients, myoclonus was noted in 38% (23/72), seizures in 96% (97/102), and ataxia in 33% (23/70)[44]; however, stroke is the distinguishing clinical feature of MELAS.

Seizures are extremely common in MELAS patients and are not infrequently the initial clinical manifestation (28% in one series).[44] The seizures are sometimes associated with stroke-like episodes. It is possible that the increased metabolic demands imposed by the seizures provoke some MELAS strokes, and it is likely that the cerebral lesions cause the seizures, thus establishing a vicious cycle. Sometimes, febrile episodes accompany the seizures, raising the hypothetical possibility that the added metabolic stress of the febrile illness can precipitate seizures.

Information about seizures was available in 42 of the 110 reported MELAS patients we identified.[44] Of those patients, 26 had both generalized and partial seizures, and 10 had generalized epilepsy (including one patient with absence seizures).[22,31,46,49,66,67,80,103]

Partial seizures were predominantly motor, (21 patients), and, less commonly, visual (six patients), temporal (three patients), auditory (one patient), or sensory (one patient).[22,31,46] At least six individuals developed status epilepticus.[22] Myoclonus is generally less common and less severe in MELAS patients than in MERRF patients.[44]

Other Mitochondrial Encephalomyopathies with Epilepsy Due to mtDNA Point Mutations

In addition to the common clinically delineated mitochondrial conditions, atypical or overlap encephalomyopathy syndromes with epilepsy—atypical MELAS, atypical MERRF, MELAS/MERRF, or MERRF/KSS—have been reported in association with mutations in genes encoding tRNA^{Ser},[86] tRNA^{Leu},[78] tRNA^{Lys},[125] tRNA^{Asp},[115] tRNA^{His},[123] and the polypeptides ND3[124] and ND5.[75] Epileptic seizures have been also described in patients harboring mtDNA mutations that typically cause clinical syndromes without epilepsy, such as LHON.[11] Although more frequently caused by nDNA mutations, LS can be a manifestation of mtDNA point mutations[13,17,115] and is often associated with epilepsy. Furthermore, mitochondrial encephalomyopathies with recurrent episodes of epilepsia partialis continua have been linked to mutations in tRNA^{Ser} genes[50,106] and subunit 1 of cytochrome C oxidase (COX) (CO1).[130]

Mitochondrial Encephalomyopathies Associated with Nuclear Mutations

Leigh Syndrome

Seizures are common in LS, but are particularly frequent in patients with MILS due to the T8993G or T8993C NARP mutations or with PDHC deficiency.[98] In contrast, seizures are less prominent in LS due to COX deficiency.

Alpers Syndrome

In Alpers syndrome, seizures are a clinical hallmark and include simple and complex partial, generalized tonic–clonic, epilepsia partialis continua, and status epilepticus. The seizures typically become intractable. EEGs often reveal very slow activity (≤1 Hz) of high-amplitude (0.2–1 mV) with polyspikes of lower amplitude.[41] In patients with this condition, valproic acid should be avoided because this drug can precipitate fulminant hepatopathy.

Coenzyme Q_{10} Deficiency

Seizures have been observed in three of the four clinical phenotypes associated CoQ_{10} deficiency: The predominantly myopathic form, the ataxic form, and the infantile encephalomyopathy with nephropathy.[59,74,81,92,96] Although detailed descriptions of the epileptic syndromes in CoQ_{10} deficiency are lacking, complex partial and generalized seizures have improved with oral CoQ10 supplementation.[18,74,96]

Diagnostic Investigation

Clinical Issues

As with any patient with a neurologic disorder, one must begin with the clinical evaluation. These disorders are typically multisystemic and clinically variable. The wide clinical diversity provides diagnostic challenges even for experienced neurologists. In obtaining the medical history of patients suspected to have a mitochondrial encephalomyopathy, clinicians should inquire about the following clinical features: Normal infancy and early development, premature exercise-induced fatigue, migraine headaches, diabetes mellitus, short stature, and hearing loss. Multiple lipomas are not uncommon in MERRF syndrome and hypoparathyroidism in KSS. Family history is important, but may be very subtle when dealing with a mtDNA point mutation. For example, in families with MELAS syndrome, relatives in the maternal lineage may have migraine-like headaches or diabetes mellitus as the only manifestation of the genetic defect.

A careful physical examination may reveal subtle clues to the correct diagnosis. Patients are often short and thin. Multiple lipomatosis can be disfiguring in patients with MERRF or in their maternal relatives.[7] Dementia can be a prominent finding in KSS, MELAS, and MERRF.[43] Cranial nerve functions may be impaired and affect particularly extraocular muscles, with ptosis and progressive external ophthalmoplegia (PEO), which are necessary to diagnose KSS, but are sometimes seen in MELAS patients. Funduscopy may reveal pigmentary retinopathy in KSS and, less commonly, in MELAS and MERRF. Optic atrophy is sometimes detected in MERRF patients. Peripheral neuropathy is frequent in MERRF and MELAS. Sensorineural hearing loss is common in many mitochondrial encephalomyopathies.

Clinical Laboratory Tests

The laboratory evaluation should begin with routine blood tests, including complete blood count, serum electrolytes (including calcium and phosphate), liver function tests, blood urea nitrogen, creatinine, lactate, and pyruvate. These tests may reveal parathyroid, kidney, or liver dysfunction. Lactate and pyruvate at rest are commonly elevated in patients with mitochondrial encephalomyopathies, and these values may increase dramatically after moderate exercise.

Electrocardiograms may reveal preexcitation in MELAS or MERRF, and heart block in KSS or MELAS. Lumbar puncture may show elevated CSF protein, especially in KSS patients, in whom it is often greater than 100 mg/dL. CSF may also reveal elevated lactate and pyruvate levels. Electromyography and nerve conduction studies are typically consistent with a myogenic process, although neurogenic changes may be detected in MERRF or MELAS. Brain imaging with CT or MRI scans may reveal basal ganglia calcifications and atrophy in all three major syndromes. In MELAS patients, neuroimaging often reveals lesions compatible with strokes that typically affect the posterior cerebrum and generally do not conform to the distribution of major arteries.[1,2,67]

Electroencephalogram findings are usually not specific. Of 27 MELAS patients with seizures, EEG demonstrated diffuse slowing in 20 individuals and focal slowing in seven; epileptic activity was diffuse in 12 patients and focal in 15.[22] One MELAS patient had clinical and radiologic evidence of a left occipital stroke and a normal EEG.[67]

In 62 reported MERRF patients, we were able to identify descriptions of 32 EEGs; all were considered ab-normal.[7,9,25,27,30,32,33,44,60,62,76,84,89,90,91,110,118,119,132] Although details of the EEGs were not available in all cases, 13 showed slowing (12 generalized, one focal and generalized) and 14 revealed epileptiform activity

(12 generalized, one focal, one bitemporal). Photic stimulation was elicited in seven of nine MERRF patients, whereas hyperventilation produced epileptiform activity in one of three patients. The relationship of myoclonus and EEG discharges was unclear in several

cases.[119] As in other forms of progressive myoclonus epilepsy, somatosensory evoked responses typically reveal giant cortical evoked responses.[119]

Special Laboratory Tests

Clinical research has contributed greatly to our understanding of mitochondrial disorders and to our diagnostic capabilities. Specialized evaluation for oxidative-phosphorylation defects has evolved from laboratory research and includes histology (particularly skeletal muscle), measurement of oxidative-phosphorylation enzyme activities, and molecular genetic analyses.

Histology

Histology has focused on skeletal muscle, but mitochondrial changes have been noted in other tissues. In the mid-1960s, Shy, Gonatas, and Perez described the typical ultrastructural alterations seen in mitochondrial myopathies.[116] These changes include (a) an overabundance of ultrastructurally normal mitochondria ("pleoconial myopathy"), (b) enlarged mitochondria with disoriented cristae ("megaconial myopathy"), and (c) "paracrystalline" and "osmiophilic" inclusions within mitochondria.[116] Engel and Cunningham developed a modified Gomori trichrome stain,[24] which has been commonly used to identify fibers with subsarcolemmal accumulations of mitochondria, which are commonly referred to as "ragged-red fibers."

Histochemical stains for mitochondrial enzymes are also used to identify excessive mitochondrial proliferation and to demonstrate specific enzyme defects. These stains include succinate dehydrogenase (SDH), nicotinamide dehydrogenase-tetrazolium reductase (NADH-TR), and cytochrome *c* oxidase (COX). Immunohistochemical techniques are used to identify defects in specific mitochondrial polypeptides.

In KSS, MELAS, and MERRF, RRF with ultrastructurally abnormal mitochondria are almost always identified in skeletal muscle by the Gomori trichrome stain. SDH histochemistry reveals mitochondrial proliferation as hyperintense staining in subsarcolemmal regions of muscle fibers. In MELAS patients, excessive SDH staining often occurs within blood vessel walls, so-called strongly SDH-reactive vessels or SSVs.[42,94] Another characteristic of skeletal muscle from MELAS patients is the relative preservation of COX staining in RRF, in contrast to muscle from KSS and MERRF, which generally shows an abundance of COX-negative RRF on serial or double-stained (SDH and COX) sections. Nevertheless, histologic abnormalities in skeletal muscle biopsies are absent in some patients with MERRF[113] or other mitochondrial disorders.[45,46]

Unfortunately for clinicians, the histologic abnormalities described are neither specific nor sensitive enough to define all mitochondrial diseases. Morphologically abnormal muscle mitochondria have been detected in many conditions that are not primary oxidative-phosphorylation defects, for example, inflammatory myopathies[14] and myotonic dystrophy.[26] Conversely, some conditions with defects of respiratory chain enzymes do not have morphologically abnormal mitochondria, including LHON, LS, and Alpers syndrome.

Biochemistry (Enzyme Assays)

Activities of mitochondrial respiratory chain enzymes can be measured in vitro using crude extracts or isolated mitochondria. In KSS, MELAS, and MERRF, one can detect various combinations of respiratory chain enzyme deficiencies; however, the pattern is often not consistent, and normal enzyme activities have been reported. Factors influencing the activities of mitochondrial respiratory chain enzymes are the degree of heteroplasmy[37] and the distribution pattern of the mutation within the skeletal muscle biopsy sample.[38]

Molecular Genetics

Since the initial discoveries of the first mtDNA point mutation and large-scale deletions in 1988,[45,131,133] there has been an outburst of information relating molecular genetic defects to human disorders. Numerous mtDNA mutations have been identified including duplications, depletion, single and multiple deletions, and more than 100 pathogenic point mutations.[19,20,23]

Holt et al. first identified large-scale mtDNA deletions in mitochondrial myopathy patients[45] and, soon thereafter, Zeviani et al. pointed out the specific association with KSS.[133] Approximately 90% of KSS patients have large-scale mtDNA deletions, duplications, or both.[72,85] The mtDNA deletions generally range from about 2.0 to 10.4 kb in length,[45,72] and are mainly confined to an 11-kb region that does not include the origins of mtDNA replication or mtDNA promoter regions. About one-third of the mtDNA deletions involve an identical 4,977 base pair (bp) segment, which is often referred to as the “common deletion.”[72] The majority of the mtDNA deletions are flanked by direct DNA sequence repeats, which suggests that they may originate from homologous recombination events.[45,51,69,105,112] The large-scale mtDNA deletions are often undetectable in leukocytes, so that molecular diagnosis requires muscle biopsy.

MERRF was the first multisystemic disorder to be associated with a mtDNA point mutation, specifically, A8344G in the transfer RNA lysine ($tRNA^{Lys}$) gene.[113] A second $tRNA^{\mathrm{Lys}}$ mutation at nt-8356 was associated with both MERRF and MERRF-MELAS phenotypes,[117,134] and a $tRNA^{\mathrm{Phe}}$ mutation at nt-611 has been associated with MERRF.[86] These point mutations can be easily identified in blood leukocytes from patients.

MELAS was also associated with a specific mtDNA point mutation, an adenine-to-guanine transition in the $tRNA^{Leu(UUR)}$ gene at nt3243 (A3243G). About 80% to 90% of MELAS patients have been found to harbor this mutation. Fifteen other mtDNA mutations have been identified in patients with MELAS, and a large number of other mtDNA point mutations have been associated with epilepsy (Table 3). As in MERRF, blood leukocytes can be screened for epilepsy-associated mtDNA point mutations.

Although the identification of mtDNA mutations has simplified diagnosis in most cases of mitochondrial encephalomyopathies, it has created new dilemmas. Genetic counseling of patients and their maternal relatives is difficult because heteroplasmy and variability of mutation loads in different tissues make clinical outcome predictions tenuous. Similarly, prenatal diagnosis is also perilous. The molecular genetic information should be handled carefully, because it can adversely affect medical insurability, employment opportunities, and the emotional status of patients.

Treatment

The medical management of mitochondrial myopathy has lagged behind research and diagnostic knowledge. Treatment can be divided into two types: Symptom management and metabolic therapy.

Symptom Management

Seizures in MERRF and MELAS typically respond to conventional antiepilepsy drugs[119]; however, they may be difficult to control in the setting of metabolic disarray. There have been reports that valproate therapy can cause adverse effects in certain patients with mitochondrial encephalomyopathies and particularly in individuals with Alpers syndrome.[8,107] The electrolyte disturbances related to hypoparathyroidism and diabetes mellitus should be corrected. Thyroid hormone replacement will alleviate the hypothyroidism. Cardiac pacemaker placement can prolong life in KSS patients with cardiac conduction defects.

Metabolic Therapy

Treatments aimed at the primary biochemical defects in mitochondrial encephalomyopathies have been tried; however, the evidence of efficacy has been anecdotal. We generally recommend CoQ_{10}, 50 to 200 mg t.i.d. and L-carnitine, 1,000 mg t.i.d. Idebenone, a related quinone, has also been administered to patients and has the theoretical advantage of better crossing the blood–brain barrier.

Dichloroacetate, a lactate-lowering agent, was shown to cause or exacerbate peripheral neuropathy, which overshadowed potential benefit in a randomized double-blind placebo-controlled trial in MELAS patients.[52]

Vitamins that may donate electrons directly to COX include phylloquinone (vitamin K_1), menadione (vitamin K_3), and ascorbic acid (vitamin C).[111] Vitamin C has also been used as an antioxidant because the impaired oxidative-phosphorylation pathway may generate increased amounts of free radicals. Nicotinamide and riboflavin have been used to improve electron chain functions.[83]

In cultured human cells, ketone body treatment reduced the amount of deleted mtDNA.[101] This finding, coupled with the fact that ketogenic treatment has been effective in children with intractable epilepsy,[55] suggests that a ketogenic diet may be an effective treatment for patients with heteroplasmic mtDNA mutations and seizure disorders, but clinical trials have not yet been conducted to demonstrate safety and clinical efficacy.

Summary and Conclusions

Since the seminal publications of the first pathogenic human mtDNA mutations in 1988, the field of mitochondrial encephalomyopathies has expanded at a rapid rate. Molecular genetic research has led the way through the identification of numerous mutations including more than 100 different mtDNA point mutations, numerous single mtDNA large-scale deletions and duplications, multiple mtDNA deletions, mtDNA depletion, and a growing number of nuclear DNA mutations. Seizures are common manifestations, and the first epilepsy syndrome to be defined at the molecular genetic level was MERRF.[113] Modern histology with histochemistry, immunohistochemistry, and ultrastructural analysis has provided further insight into the pathogenesis of these disorders. Correlations of genotypes and phenotypes revealed general relationships between specific mutations and clinical syndromes; however, we learned that there can be wide variability of the clinical manifestations of a given mtDNA mutation. Due to this clinical complexity, neurologists must carefully evaluate patients with suspected mitochondrial encephalomyopathies to reach the correct diagnosis. Genetic counseling is important, but is imprecise in families with heteroplasmic mtDNA point mutations. Treatment is primarily symptomatic, and seizures are generally amenable to conventional antiepileptic agents. Clearly, there is a large gap in our understanding of how the mtDNA defects lead to human disease; however, as our knowledge expands, more rational and specific therapies may develop.

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Chapter 263

Cerebral Palsy

John B. P. Stephenson

Introduction

Understanding epilepsy is a necessary part of the management of individuals with cerebral palsy.[45] Epilepsy is common in all types of cerebral palsy and, in some varieties, it is the rule.

Definitions

The definitions of *epileptic seizures, symptomatic epileptic seizures*, and *epilepsy* are the same as those used in other chapters throughout this book. The definition of *cerebral palsy* (CP) is a little more difficult, insofar as some variation occurs in the way in which the term is used between different authors and different studies. The most frequent definition of *cerebral palsy* is “a disorder of posture and movement due to a static lesion of the developing brain.” Most authors include cerebral malformations as examples of static lesions of the brain but, in at least one study, cerebral malformations were excluded.[20] Many authors include the aftereffects of acute cerebral insults and injuries in infancy and even in early childhood, whereas others would exclude from the CP definition any condition presumed not to have been present before the age of 4 weeks.[20] There is considerable force in the argument for limiting the definition of cerebral palsy in this way, insofar as the prognosis with respect to epilepsy differs between those whose brain lesion is of perinatal or prenatal origin and those children with unequivocally postnatal cerebral insults.

A new definition of cerebral palsy was proposed in 2005[5]: “Cerebral palsy (CP) describes a group of disorders of the development of movement and posture, causing activity limitation, that are attributed to nonprogressive disturbances that occurred in the developing fetal or infant brain. The motor disorders of cerebral palsy are often accompanied by disturbances of sensation, cognition, communication, perception, and/or behavior, and/or by a seizure disorder.” From the point of view of this chapter, it is disappointing to see the term “seizure disorder” employed. This sloppy and ambiguous term deserves to be deleted from scientific discourse.[38]

Authors have exhibited some variability on the definition of the various subtypes of CP but, on the whole, these differences in classification do not materially affect the understanding of epilepsy in the context of CP. The main divisions in the Edinburgh classification were[23]: (a) hemiplegia, (b) bilateral hemiplegia, (c) diplegia (which might vary from virtually paraplegic to tetraplegic), (d) ataxic CP (including ataxic diplegia and ataxia), (e) dyskinesia (including dystonia and athetosis), and (f) any other form of CP, including mixed forms. Many authors now include ataxic diplegia within the diplegia categories. Certainly, for the purposes of discussion of epilepsy, dystonic CP should be strongly distinguished from athetoid CP, insofar as the liability to epilepsy may be high in the former and low in the latter type. The group described by the Edinburgh School as bilateral hemiplegia will have severe mental retardation, as discussed in the section Risk Factors for Epilepsy.[13]

Recent studies[31,37] of the etiology of CP (with or without epilepsy) have shown a much higher diagnostic yield than was thought likely in the past. This should make one wary of the CP label without firm foundation.

Problems in Diagnosis of Cerebral Palsy

Many conditions can masquerade as cerebral palsy but turn out to be something else.[21,40] Most such conditions are individually rare, but parents do not commonly judge the rarity of a condition as a justification for pediatricians or neurologists to make an incorrect diagnosis. Fortunately for the present issue, cerebral palsy imitators complicated by epilepsy or epileptiform attacks are few. Pelizaeus-Merzbacher disease is one such confusing condition.[6] One might argue that this is actually an example of cerebral palsy but, of course, the important point is that it is an X-linked disorder and may recur in a future male child.

Another condition with an unequivocally progressive cerebral pathology is the Aicardi-Goutières syndrome.[39] Affected children may behave much like patients with cerebral palsy without regression.[39] Confirmation of the diagnosis of Aicardi-Goutières syndrome depends on finding elevated cerebrospinal fluid (CSF) and serum α-interferon in the absence of any congenital viral infection.

Another confusing condition is hyperekplexia[47] in which affected neonates may be very stiff and troubled by severe nonepileptic convulsions. When a family history of dominantly inherited startle disease is present, the diagnosis presents no difficulty, but in sporadic cases it can be difficult.

Rare, potentially treatable inborn errors of metabolism leading to cerebral palsy and epilepsy have been described. These include defective serine biosynthesis[24] deficiency,[4] and GAMT deficiency.[28a]

New conditions will continue to be recognized, and it behooves the child neurologist to question the diagnosis in every patient with "cerebral palsy." This is particularly so in so-called *ataxic cerebral palsy*, which some have suggested should not be called cerebral palsy at all,[26] insofar as genetic etiologies abound.

Problems in Epilepsy Diagnosis

Having cerebral palsy is no insurance against exhibiting or suffering from the various nonepileptic attacks that may affect the general population.[38] We suspect that children with cerebral palsy are more at risk of having epilepsy misdiagnosed in this way because epilepsy is common in cerebral palsy and so expected to be seen. For example, a young child with spastic diplegia may have what we term *reflex anoxic seizures*[38] after falling over and bumping his head just like anyone else who is similarly genetically predisposed. In addition, patients with cerebral palsy may have a predilection for various movements having a superficial resemblance to epileptic seizures. In all these situations, keen clinical judgment must be used. The interictal electroencephalogram (EEG) cannot be relied on to assist in the differential diagnosis. Although it has been attested that spikes or epileptiform discharges are more common in children with cerebral palsy who have epileptic seizures, cerebral palsy individuals who have never had epileptic seizures may not uncommonly show spike discharges also.[35] When an individual with cerebral palsy has had one or more previous epileptic seizures, it is even less rational to expect that an EEG examination will help to diagnose a new unexplained paroxysmal event.[38] On the other side of the coin, those with startle epilepsy[36] may not show spikes at all in the ictal EEG; however, such individuals always have other epileptic seizures without the startle provocation.[28]

Nonepileptic Paroxysmal Disorders in Sleep

It is particularly important not to mistake nonepileptic paroxysmal phenomena associated with sleep for epileptic seizures. Repetitive sleep starts are serial, sleep-related nonepileptic jerks or spasms that may occur in young neurologically impaired children.[16] As these children may *also* have epilepsy,[16] the recognition of these nonepileptic sleep starts is necessary to avoid needless increases in antiepileptic therapy.

Second, because of their cerebral palsy, affected individuals may have obstructive sleep apnea with tonic nonepileptic seizures, easily misdiagnosed as the expected nocturnal epileptic seizures.[3]

In both these clinical situations polygraphy during sleep may be necessary, recording EEG, electrocardiogram (ECG), respiration, and electromyogram (EMG).[3,16]

Anoxic-Epileptic Seizures: Epileptic Seizures Induced by Syncope

Epileptic seizures induced by syncopes—what we call anoxic-epileptic seizures—may not be rare in children.[22]

When this occurs in cerebral palsy, diagnosis may be exceptionally difficult. A recent report describes a boy with Cornelia de Lange syndrome diagnosed as having symptomatic epilepsy until it was realized that his clonic and hemi-clonic epileptic seizures—including status epilepticus—were always triggered by obstructive apnea[29] and ceased without the need for antiepileptic medication once recurrent upper airways obstruction was prevented.[29]

Problems in Combined Cerebral Palsy and Epilepsy Diagnosis

The Special Case of Glucose Transporter Deficiency

It has become apparent that one of the most important etiologies of "cerebral palsy" and epilepsy or "epilepsy" is the genetic disorder of glucose transport now known as GLUT-1 deficiency syndrome or GLUT1DS.[46] The importance lies not in the frequency of this disorder but in its potential treatment by ketogenic diet, albeit such treatment is not universally successful.[25] Affected individuals mostly—but not always[34]—have epilepsy, and many have a motor disorder that could be described as cerebral palsy. Presumed nonepileptic movement disorders and other paroxysmal events are also seen.[46] Insofar as the ketogenic diet is potentially useful for the treatment of these various phenomena, clinicians should consider this disorder early and make careful simultaneous measurements of fasting blood and CSF glucose when in doubt.[46]

Risk Factors for Epilepsy

The early studies of Ellenberg and Nelson[14] indicated that knowledge of the etiology of epilepsy not associated with cerebral palsy was very limited. A number of later studies have addressed such a question in various ways.

Goulden et al.[20] studied a cohort of mentally retarded individuals born in Aberdeen, Scotland, between 1951 and 1955. By 22 years, 15% of these had epilepsy. With their definition of *cerebral palsy* as "having a presumed prenatal or perinatal onset," the cumulative risk for epilepsy was 28%, 31%, and 38% at 5, 10, and 22 years of age, respectively. This compared with a much lower risk for individuals with mental retardation and no associated disabilities, and a much higher risk of epilepsy in those with postnatal brain injury (defined as a significant brain insult after 28 days of life which might reasonably account for the child's later functioning). This particular study included a separate group with cerebral malformations but, in fact, the only malformation determined was described as an occipital meningocele.

A careful Italian study[9] focused on the risk factors for the co-occurrence of partial epilepsy, cerebral palsy, and mental retardation. In a studied population of 64 children with these three conditions, neuroimaging identified 32 with cerebral malformations and 32 without but with encephalomalacia, periventricular leukomalacia, or diffuse atrophy. These two groups were compared with a much larger population of normal children. The definitions in this study were as follows:

Partial epilepsy met the International League Against Epilepsy (ILAE) criteria. Such seizures had to have begun in the first 3 years of life. Apparently generalized seizures at onset did not exclude a child if persistent partial motor or complex partial seizures appeared within the first 3 years, but partial seizures in West syndrome or Lennox-Gastaut syndrome excluded a child from this study. *Cerebral palsy* was defined as "a disorder characterized by abnormal control of movement or posture starting early in life and without any recognized underlying progressive disease." *Mental retardation* was defined as an IQ of less than 70.

Significant relative risks were found for both familial factors and for maternal and neonatal factors. Any kind of epilepsy occurred in 0.5% of first-degree relatives of controls, whereas in both the groups with cerebral malformation and without cerebral malformation, the epilepsy risk in first-degree relatives was over 7% (95% confidence interval did not include one). Similarly significant maternal and neonatal factors for both groups (with and without cerebral malformation) were: Maternal diseases in the 2 years before pregnancy (such as diabetes, heart disease, hyperthyroidism, and gynecologic disorders), placental pathology, prematurity with delivery later than 31 weeks' gestation in those who were small for their gestational age, and neonatal convulsions. An enormously increased risk was found for those born at or before 31 weeks' gestation, all of these from the group without cerebral malformation. The need for cardiopulmonary resuscitation in the neonatal period, used as a measure of presumed asphyxia, was a high risk factor in the group without cerebral malformation, but not a risk factor in those with cerebral malformation. The findings of this study indicate that a number of genetic and prenatal risk factors interact in the genesis of early partial epilepsy with cerebral palsy and mental retardation.

Ottman et al.[32,33] looked at the etiology of epilepsy from a different perspective. In this study of about 2,000 individuals, all had epilepsy but none had severe mental retardation. Of these, 80% had either idiopathic or cryptogenic epilepsy; 18% had postnatal symptomatic epilepsy, defined as having had a cerebral insult 7 or more days before the first unprovoked seizure. Of interest in the present context was the smallest group with neuro deficits (1%). This group consisted of 28 individuals with cerebral palsy and one with mild intellectual impairment. Although the 95% confidence intervals did not include one because of small numbers, the standard morbidity ratios for epilepsy or for idiopathic or cryptogenic epilepsy was 3 or over in the group with neuro deficits from birth. This was no different from the standard morbidity ratios in the case of those with idiopathic or cryptogenic epilepsy, but different from the situation in postnatal symptomatic epilepsy, where the standardized morbidity ratio was 1.

These studies are consistent with other results such as those of Aicardi[1] in demonstrating that, whereas postnatal brain damage is frequently the cause of subsequent epilepsy, similar genetic and prenatal factors underlie both cerebral palsy not of postnatal origin and epilepsy when it coexists.

The relationship of mental retardation is complex. Those with mental retardation are more likely to have epilepsy if they also have cerebral palsy, and those with cerebral palsy are more likely to have epilepsy if they are mentally retarded. To a certain extent, these relationships reflect a common etiology, but by no means is enough known. A simple method of demonstrating the relationship of neurologic deficit severity to IQ has been proposed for individuals with childhood hemiplegia.[19]

The risk of epilepsy in different subtypes of cerebral palsy also varies. It is highest[13] in those with what some call *double hemiplegia* and some *quadriplegia*, perhaps not surprisingly. Those with dystonic cerebral palsy who may not be easily distinguishable from those in the former group will also have a high incidence. In those with spastic hemiplegia, the relative incidence is intermediate,[42] with the lowest frequency in those with preterm related diplegia or athetoid cerebral palsy.

Clinical Features of the Epilepsy

Considerable difficulties arise in classifying the epilepsies in individuals with cerebral palsy, according to the previous international classification. It might be argued that the epilepsies in cerebral palsy ought to be either partial or localization-related, or secondarily generalized. However, there is no *a priori* reason why genetic epilepsy, such as the primary generalized epilepsies, or even benign partial epilepsy, such as benign rolandic epilepsy,[27] should not occur in those with cerebral palsy, with or without mental retardation. For instance, typical absences with 3 per second spike-and-wave can be seen in children with cerebral palsy,[1] and one cannot on clinical and EEG grounds say whether that individual has secondary generalized absences or whether there is coincident primary generalized absence epilepsy. This applies to many of the epilepsies in the context of cerebral palsy. Perhaps the argument is specious insofar as, as indicated earlier in the sections Problems in Combined Cerebral Palsy and Epilepsy and Risk Factors for Epilepsy, a common genetic etiology may exist for the cerebral palsy and the epilepsy.

Certain seizure types, such as infantile or juvenile spasms (otherwise called *periodic spasms*[17]), or atonic or startle seizures,[36] may be more likely to occur in those with cerebral palsy, but almost any type of epileptic seizure is possible.[1,2] It is important to recognize that although normal intellect may be preserved when cerebral palsy and epilepsy are combined (see Case 2) even with startle epilepsy,[30] intellectual stagnation or decline may occur (see Case 4).

A study from London[44] showed that in children with hemiplegic cerebral palsy and overall intelligence within normal limits, the presence of epileptic seizures in the first 5 years of life was associated with defects of cognition, language, and memory. In this study, when hemiplegia was unaccompanied by early seizures, nonverbal functions were almost exclusively impaired. The authors inferred that language displaced spatial abilities. By contrast, when hemiplegia was accompanied by early seizures, nearly all measures of psychologic function were affected, nonverbal and verbal alike. The presence of seizures seemed to be more important than the presence of EEG discharges. Furthermore, the presence of early seizures was more important than the size of the lateralized lesion on imaging: Children with severe neuroradiologic deficits and no seizures did better on verbal IQ, memory quotient, and third-trial paired associate learning than did those with mild neuroradiologic deficit and early seizures. Case 4 provides a more extreme example with documented regression and loss of skills.

Therapy of the Epilepsy and of the Cerebral Palsy

The principles of medical therapy of the epilepsies complicating cerebral palsy are generally similar to those that pertain in other clinical contexts. Little has been written about the use of corticosteroid, but this is alluded to in a case example below (Case 4). The use of rectal diazepam or buccal midazolam has become widespread in the management of children with cerebral palsy and epilepsy, perhaps in part because of the frequency of long hemiclonic seizures.

The place of epilepsy surgery in cerebral palsy has remained rather small, despite impressive reports on the value of hemispherectomy in refractory epilepsy with complicating hemiplegia (see Chapter 178). Section of the corpus callosum and subpial transection are discussed elsewhere (see Chapters 180 and 182). An impressive recent report from Utrecht has shown that epilepsy surgery in children and adolescents with or without prior spasticity does not harm motor performance.[43]

Baclofen by intrathecal route has increased in popularity as a treatment for spastic and other forms of cerebral palsy. There has been concern that this use of baclofen—insofar as it is a GABA-B antagonist—might be epileptogenic. However, a recent controlled study concluded that in children with spasticity of cerebral origin intrathecal baclofen does not seem to aggravate or induce epilepsy.[7]

Prognosis

The prognosis of the neurodevelopmental features, in particular cognitive function and the development of mental retardation, has been discussed earlier in "Risk Factors for Epilepsy." This section focuses on the prognosis for the epilepsy, with brief mention of mortality.

Prognosis of the Epilepsy

Clinical impression of the intractability and unremitting continuation of epileptic seizures in many children with cerebral palsy is undoubtedly biased by patient referral and differential follow-up of those with good and bad outcomes. In a report[11] from Dallas, around 25% (531 of 2,086 children with cerebral palsy actively followed) had epilepsy at the time of writing or previously had epilepsy. Since 1985, only 69 or 13% of these children with cerebral palsy and epilepsy had been seizure free for 2 years or more. These children were studied prospectively

on antiepileptic drug withdrawal. Electroencephalography was done before the antiepileptic drug discontinuation. In all children, therapy was tapered off by 15% to 20% every 2 weeks. Four were lost to follow-up, but the remaining 65 were followed after antiepileptic drug discontinuation until seizure relapse or until at least 2 years without seizures. In the event, the seizure relapse rate was about 41% (i.e., the remission rate was about 60%). Many factors appeared to have no significant effect on whether remission would or would not take place, although, as the authors point out, nonsignificance means only that we are yet unable to state with a high degree of confidence that the factor does have prognostic value. Paradoxically, there is a higher frequency of relapse in those with normal mental development than in those with mental retardation, but this was likely due to the higher incidence of epilepsy relapse in those with hemiplegic cerebral palsy. In this study spastic hemiparesis was the only factor identified that significantly increased the risk of epilepsy relapse after discontinuation of antiepileptic drug therapy. These hemiplegic individuals were more likely to have normal intelligence than were those having other forms of cerebral palsy.

Thus, the vast majority of children with cerebral palsy do not become seizure free, but of those who do, the majority will be able to discontinue antiepileptic drugs. Children with hemiplegic cerebral palsy seem to be an exception to this rule.

Mortality

Epilepsy significantly increases the mortality rate in those with mental retardation,[15] and it has been shown[8] that independent predictors of this increased mortality are: The type of cerebral palsy (spastic quadriplegia and double hemiplegia having the worst prognosis); the presence of epilepsy (of any type); and the presence of severe or profound mental retardation. In remote symptomatic epilepsy as a whole mortality is increased,[10] seizure severity seemingly a factor.[41] By contrast, the prognosis for survival in those with hemiplegic cerebral palsy and epilepsy but without mental retardation is excellent (96% at 30 years).[8]

Case Examples

For those who appreciate the value of detailed clinical observations on individual children, four case studies are provided in this section. One child represents a condition that successfully masquerades as cerebral palsy but has different implications. The other three case studies are of three children with congenital left spastic hemiplegia, with different trajectories and outcomes. These clinical studies may suggest to others further ways of refining the excellent type of epidemiologic studies referred to earlier.

Case 1: Progressive "Cerebral Palsy"

A girl was born at term in 1991 to unrelated parents who had two previous normal children. She presented at age 10 weeks because she was not holding up her head and did not smile. Her left limbs jerked repetitively as she fell asleep. Her development was very slow, but her parents and medical attendants did not observe loss of skills. She smiled once at 3 months and then more so at 9 months, smiling very readily at age 3 years. Initial hypotonia changed to spastic tetraplegia from her second year of life. Seizures consisting of extension of her limbs with quivering for about a minute occurred daily in infancy, at which time the EEG was normal, but diminished to once a week at age 3 years, EEG then showing a considerable quantity of slow spike-and-wave activity. Chilblains (pernio) were prominent, particularly on her toes. The only clinical evidence of a progressive disorder was failure of head growth. Initially, head circumference was on the mean, albeit 2 cm below that expected from her parental and sibling head circumferences, but after age 4 months, growth further declined; by 4 years of age, head circumference was 4 standard deviations below the mean.

Computed tomography head scans demonstrated progressive encephalopathy with periventricular calcifications, later also in basal ganglia and dentate locations, associated with white matter hypointensity. Cerebrospinal fluid contained 40 lymphocytes/mm^3. There was no evidence of viral infection, and the huge level of cerebrospinal fluid α-interferon confirmed the diagnosis of autosomal recessive Aicardi-Goutières syndrome.[35a,39]

Comment

Epilepsy, yes; cerebral palsy, no!

Case 2: Hemiplegic Cerebral Palsy, West Syndrome, and Good Outcome

A first-born male did not show signs of asphyxia after a long labor but was very jumpy at noise at the age of 2 hours and from age 2 days had a tendency to tenseness of his left limbs, with his fontanel bulging when he was upset. Thereafter, his behavior and development seemed normal except that there was a tendency for his left hand to be fisted.

When he presented at the age of 7.5 months, his parents said that about a month previously he had lost his happy disposition and had become lethargic, docile, and unsmiling. At about the same time, he had begun to have runs of spasms five or so times a day, with ten or more spasms in each run about 10 seconds apart. On admission to the hospital, runs of spasms were observed, sometimes with a degree of asymmetry. His head circumference was on the second percentile, and his skull transilluminated excessively on the right. He had a left hemianopia and absent optokinetic nystagmus when the drum or tape was moved to his right. His left hand did not have full voluntary control, only briefly retaining an object. Brain imaging was not done at that time, but years later showed infarction in the right middle cerebral territory. Electroencephalography showed hypsarrhythmia without convincing asymmetry.

He was treated with adrenocorticotropic hormone (ACTH) gel, 40 units daily for 2 weeks, and nitrazepam 1 mg twice daily. He had no further infantile spasms after the first dose of ACTH, and 3 days later he was smiling and taking an interest in his toys again. Repeat EEG after 2 weeks showed no discharges but reduced rhythmic activity over the right.

He received nitrazepam in the same dose until the age of 2 years. He developed intellectually, having a verbal comprehension at the age of 1.5 years of more than 2 standard deviations above the mean. He had left spastic hemiparesis and required lengthening of his Achilles tendon at the age of 3 years. An additional medical complication was an atrial septal defect, which was closed without use of blood at the age of 9 years.

From the age of 4 years, he had occasional episodes of altered consciousness, sometimes with some motor disturbance on the left. These tended to be preceded by a “funny feeling in his tummy”; instances of “sick tummy” were more frequent. Antiepileptic therapy for these simple and complex partial seizures was not required until the age of 11 years, when carbamazepine was introduced. At the age of 12 years, he replied to a letter sent to his parents inquiring about him: “Thank you

for the letter of interest. My Mum and Dad thought that it would be appropriate for me to write because I am the person you are so considerate of…” At about age 15 years, he began to have startle-induced alterations in the tone of his left limbs, lasting 15 to 30 seconds, the startle stimulus being solely an accidental scuffing of the toe of his left foot on the ground. He was improved by an increase of carbamazepine dose in the sustained release form. At the age of 17 years, he had two episodes of left limb stiffness without startle, but since the addition of vigabatrin, 500 mg daily, he has remained seizure free.

When he was aged 17 years, he discovered that he would have difficulty obtaining a driving license because of his left hemianopia. However, the combination of a life-long habit of frequently shifting his gaze to the left and training in blind sight in his left visual field has enabled him to drive commercially and to achieve complete independence.

When in his 20s, he suffered several attacks of loss of consciousness, preceded by a funny feeling in his abdomen. These were misdiagnosed as a return of his epilepsy, and an EEG was inappropriately requested. In fact, his mother had a long history of vasovagal syncopes with an identical abdominal aura.[38]

Comment

Aside from illustrating determined human qualities, this case illustrates that neither symptomatic West syndrome nor epilepsy complicating hemiplegic cerebral palsy are bars to intellectual achievement and success in life.[18]

It is also a powerful reminder that individuals who have had epilepsy may have syncopes as well.

Case 3: Congenital Hemiplegia with Secondary Generalized Myoclonic Epilepsy

This boy's mother sustained a motor vehicle accident in pregnancy at 22 weeks' gestation, after which she was unconscious for 2 hours and required an infusion to maintain her blood pressure. He was born normally at term, but a left hemiparesis became apparent later in the first year of life. His development appeared to be otherwise normal.

At age 3.5 years, he first had simultaneous head nods with right arm jerk. Soon after, he had one clonic epileptic seizure from sleep. At age 4 years, jerks became very frequent daily. They appeared to involve head nodding and abrupt dropping of the right upper limb, suggesting negative myoclonus (although surface EMG polygraphy was not undertaken). Interictal EEG showed very frequent runs of high-voltage 2/sec spike-and-wave; this slow spike-and-wave was generalized but of even higher voltage on the right. Computed tomography brain scan showed a smaller right cerebral hemisphere with abnormal gyration and a deep cleft consistent with polymicrogyria. His attentiveness varied with the frequency of his seizures but intellectual assessment showed normal intelligence.

Carbamazepine was associated with worsening of his seizures, and sodium valproate with or without lamotrigine had no consistent beneficial effect. A 2-week course of betamethasone led to marked reduction in seizures and an increase in attentiveness; he went into normal school and has continued on lamotrigine monotherapy with only occasional jerks.

Comment

An example of prenatal origin hemiplegic cerebral palsy with intelligence in the normal range despite severe secondary generalized epilepsy, probably negative myoclonic.[7a] Selective learning difficulties were expected to become more apparent in school years.

Case 4: Congenital Hemiplegia with Epileptic Encephalopathy

After an uneventful pregnancy, this girl was born at term by emergency cesarean section because of a maternal straight sacrum. There was said to be fetal distress with meconium staining and type 2 dips in labor. The APGAR score was 3 at 1 minute, and she was intubated at 3 minutes for 2 minutes. However, she was well as a neonate except that when about 1 week old, it was noted that whenever she fought out of her shawl or cot covers, it was always with the right hand. Thereafter, although she developed evidence of a left spastic hemiparesis (shown later to be due to a large right middle cerebral infarct), her general development was distinctly advanced, and she spoke many meaningful words, including “what's that?” before the age of 1 year.

Just after the age of 2.5 years, she had an episode of staring with left hand twitching. At the age of 3.5 years, she had a bilateral clonic seizure of at least 25 minutes' duration. At the age of 4 years, she began to have blanks, which increased in frequency and began to be described as periods of confusion. EEG from before the age of 4 years showed runs of generalized spike-and-wave discharges, which were nearer to 2 per second but were often at 2.5 to 3 per second with blinking and probable absence. By the age of 5 years, there was also bifrontal slow activity. She received sodium valproate in a dose of 400 mg daily from 4 years 4 months, and 800 mg daily from 4 years 8 months, changing to ethosuximide 500 mg daily, 2 months later.

Cognitive and behavioral decline was noticed by her mother from about the age of 4 years 4 months. Although there was some fluctuation, the girl would no longer sit down and draw people and faces if requested but would run about most of the time. Professional evaluation confirmed the decline. At the age of 4 years 2 months, her expressive language was well above average, and her verbal comprehension not less than 4 years 9 months (the ceiling had not been reached in the tests). By 4 years 11 months, both expressive language and verbal comprehension had dropped to 2 years 6 months. She had also become disorientated and declined in nonverbal skills, and had various behavioral abnormalities.

Short courses of betamethasone initially reduced spike-and-wave activity on EEG and were associated with improved cognition and behavior such that, for example, her Stanford-Binet intelligence was raised from 2 years 11 months at 5 years 2 months up to 3 years 11 months at 5 years 5 months, but such improvements became less and of shorter duration after each successive betamethasone course. In due course, although the atypical absences were eliminated by the betamethasone, her cognition and behavior did not much improve. Over the next 5 years, these atypical absences fluctuated and were often not observed. Very occasional night seizures, possibly tonic–clonic, were reported, but there have been no further seizures of any type observed since the age of 10 years on ethosuximide monotherapy. At the age of 15 years, she has just begun to read but has no road sense, is too friendly with strangers, and has other behavioral difficulties.

Comment

In this previously very intelligent girl with hemiplegic cerebral palsy, severe cognitive and behavioral decline was associated with rather subtle epileptic manifestations. Although cortico-steroid administration at first led to improvement, this was temporary, and she is now not likely to be able to live independently, despite remission of her epilepsy. Whether more modern medical or surgical antiepileptic approaches might have prevented this dismal prognosis remains speculative. A good discussion of cognitive and behavioral disturbances as epileptic manifestations is to be found elsewhere.[12]

Summary and Conclusions

It is essential to make sure that the diagnosis of cerebral palsy is correct and that the diagnosis of the epilepsy is correct. In the case of cerebral palsy diagnosis, both genetic disorders with high recurrence risk and rare treatable cerebral disorders should be excluded. In the case of the epilepsy diagnosis, special attention should be paid to nonepileptic events in patients with cerebral palsy that masquerade as epileptic seizures. Even epileptic seizures do not always imply epilepsy, as the section on anoxic-epileptic seizures has illustrated. Obviously, antiepileptic therapy should be avoided when it is not appropriate.

It appears that cerebral palsy and epilepsy are linked both by etiology and prognosis. The outlook is not universally bad, but we have little evidence on which to make improvements. Especially terrible are regressions in mental capacity linked in some way to the epileptic component of the cerebral palsy.

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Chapter 264

Neoplastic Diseases

Lawrence D. Recht

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Introduction

Seizures are frequently the first symptom in patients with brain tumors, and they represent an important cause of potentially preventable morbidity. They thus present a clinical problem requiring specific treatments that do not necessarily affect the course of the brain tumor but that generally improve quality of life.

Historical Perspectives

The first reports of a relationship between brain tumor and epilepsy were published before the 18th century, and a number of clinicians, including J. Russell Reynolds, drew attention to this problem in the early 19th century. Hughlings Jackson, however, was the first to point out a direct association between partial epilepsy and tumors.[40] Jackson also recognized the relationship between epileptogenicity and tumor involvement of the cortical gray matter.[40,41]

Since then, the evolution of neurosurgical techniques and the development of new imaging techniques have greatly facilitated the management of tumor-associated epilepsy. Nevertheless, controversy over optimal pharmacologic and surgical therapies persists, and seizures still represent one of the more commonly encountered problems in neuro- oncology.

Epidemiology

Although neoplasms of the brain account for only 1% of cases of epilepsy, seizures occur in approximately 50% of children with supratentorial tumors,[4,39,50] and seizures develop in approximately 35% to 40% of adults with brain tumors.[48] The rate is much lower for tumors of the infratentorial or pituitary region, and consequently even higher for supratentorial lesions. Furthermore, because physicians who are not neurologists are apt to miss seizures with other than motor manifestations, these figures are probably underestimates.

In the majority of patients with supratentorial low-grade gliomas, seizure is the initial manifestation.[47,66] Seizures occur especially commonly in association with oligodendrogliomas. A recent retrospective study found seizures to be the first symptom in three quarters of patients with oligodendrogliomas.[91] Seizures are also commonly encountered in patients with meningiomas. Although earlier workers reported that seizures were less frequently encountered in cases of more malignant glial neoplasms,[27] recent studies demonstrate that up to 60% of patients with malignant gliomas experience seizures at some time during their clinical course.[57] In contrast, the incidence of seizures in patients with cerebral metastasis is much lower; most reports suggest an incidence of 20% at time of presentation.[18,28,63,96]

Clinical Presentation

Clinical Correlates of Tumor-Associated Epilepsy

Despite the variable frequency of seizures as a function of histologic subtype, the most important factor associated with the development of seizure is probably tumor location.[44,52] Seizures occur much more frequently in supratentorial (22%–68%) than infratentorial (6%) lesions.[31,64,78] Moreover, the incidence of seizures increases as the site of tumor approaches the rolandic fissure.[90] As the distance from the central sensorimotor region increases, early-onset seizures are less likely to occur.[65] Similarly, superficial and cortical tumors are associated with a much higher incidence of epilepsy than are noncortical deep lesions (63% vs. 29%), and lesions entirely within the white matter infrequently produce seizures.

Other factors aside from location are also probably important determinants. Both the chronicity of tumor growth and patient age affect the incidence of epilepsy in intra-axial supratentorial neoplasms.[23,24,25,30,31,34,54,64,69,70] Slowly growing tumors, such as gangliogliomas and dysembryoplastic neuroepithelial tumors, are overrepresented in patients with brain tumors who have seizures, whereas more rapidly growing tumors are less often epileptogenic. Thus, a seizure incidence of 70% is reported for astrocytoma, but only 37% for glioblastoma multiforme.[4,70,90] Young age also is correlated with the presence of epilepsy.[91]

Seizure Types in Tumor-Associated Epilepsies

Since Jackson first noted, at the end of the last century, the relationship between uncinate seizures and tumors of the frontotemporo-orbital regions, many reports have documented the important relationship between the type of seizure and the presence of tumor. Despite occasional disagreement,[48,86] a correlation between a specific seizure type and either a particular neoplasm or specific tumor location has been commented on repeatedly. In an analysis of psychomotor attacks in 80 untreated patients with and without tumor, for example, olfactory and gustatory hallucinations were very suggestive of tumor.[43,52] Muller (cited in Jackson[40]) noted olfactory hallucinations, increasing frequency of attacks, and random variations in the type of attack (especially of motor seizures) to be particularly characteristic of tumor. For children, the probability of diagnosing an underlying tumor is higher in those with complex partial seizures (10%–46%) than in those with other seizure types.[7,82,90]

In a recent series of patients with oligodendroglial tumors, seizures were approximately equally divided between generalized, partial, and mixed types.[91] In contrast, localization-related motor seizures, characterized by a clonic jerking of

the face or one extremity, are often characteristic of patients with intracranial metastases or malignant gliomas,[44,48] and these seizures are almost always seen in association with focal neurologic abnormalities.[57] Multifocal or bilateral neoplasms more often produce seizures than solitary neoplasms do,[57] and seizures tend to occur more frequently with lesions of the central nervous system (CNS) caused by metastatic melanoma, because these lesions involve gray matter and tend to be multiple.[11] Furthermore, partial seizures in patients with brain tumors are clinically significant, because they are rarely falsely localizing and thus provide a clue to tumor location.[1] Following partial or secondarily generalized seizures, many patients with underlying brain tumors exhibit a significant Todd's paralysis; although usually transient, this may be permanent.[56]

Diagnostic Evaluation

Because seizures are a presenting complaint in approximately 20% of patients with newly diagnosed brain metastases,[68] neuroimaging, preferably magnetic resonance imaging (MRI), is required in every patient with cancer in whom seizures develop. Since seizures also occur in up to 40% of neutropenic patients with infectious meningitis,[51] are a common manifestation of leptomeningeal carcinomatosis, and have been reported as an early manifestation of limbic encephalitis, a spinal fluid analysis with careful assessment of the patient's prior clinical course for possible epileptogenic drugs and metabolic aberrations is always indicated.

Before the advent of modern neuroimaging, the significance of a seizure as a first manifestation of brain tumor was insufficiently recognized, and the average delay between first seizure and tumor diagnosis was about 3 years.[16,44,89] In recent years, however, scanning with computed tomography (CT) and MRI has made it possible to document that many low-grade gliomas have relatively benign pathologic features and, although they produce chronic epilepsy, tend to be associated with long survival.[26,71] Furthermore, low-grade gliomas are serendipitously noted in up to 20% of resected surgical specimens from the brains of patients with chronic temporal lobe epilepsy.[10,58,79,84] Therefore, it is the authors' recommendation that all patients with a first seizure have a CNS imaging study, preferably an MRI scan, at the time of presentation.

Electroencephalography (EEG) is also useful in assessing these patients. Findings correlate with tumor location, and in approximately 40% of patients, the EEG abnormalities are lateralized to the side of the tumor.[17] On the other hand, in the authors' experience,[32] EEG does not predict in which patients with supratentorial lesions late seizures will develop. Nevertheless, because EEG is relatively inexpensive and helps to localize the epileptogenic foci by a method different from neuroimaging, it remains a useful test for attempting to localize the physiologic seizure focus.

Differential Diagnosis

In patients with established cancer, the differential diagnosis of either isolated or multiple seizures includes more than just mass lesions, and the appropriate work-up must be designed accordingly. Although the differential diagnoses of a seizure in cancer patients are similar to those in patients without cancer, certain etiologies are specific to or more frequent in a patient with preexisting cancer. For example, hyponatremia, hypomagnesemia, and hypocalcemia all occur more frequently in patients with cancer owing to a number of factors, including dehydration and chemotherapy. These metabolic aberrations in turn predispose to seizures. Similarly, the immunosuppression associated with cancer and its treatment predisposes patients to meningitis, often with less common etiologic agents, such as *Listeria* and *Cryptococcus*. A partial list of potential causes of seizures in patients with cancer is given in Table 1.

Treatment and Outcome

Pharmacotherapeutic Aspects of Tumor-Associated Epilepsy

Seizures can be especially detrimental to patients with tumors because they can lead to breakdown of the blood—brain barrier[61] and subsequent formation of brain edema. This process is probably related to seizure-induced arterial hypertension. Because the increase in blood flow and blood volume may worsen elevated intracranial pressure, leading to focal ischemia and sometimes infarction, the Todd's paralysis that frequently follows these seizures tends to be more protracted (even permanent on occasion) than that occurring in patients with partial seizures and no tumor. This potential complication alone justifies instituting aggressive antiepileptic measures for these patients once a seizure has occurred.

As in the treatment of idiopathic seizures and secondary seizures not related to tumor, however, the efficacy of anticonvulsant therapy for tumor-associated epilepsy falls well short of complete control. Tumor-associated epilepsy tends to be relatively refractory to antiepileptic drugs (AEDs), and significant remission of seizures is rare.[34,57,78] Primary tumors tend to be more difficult to control than metastatic lesions (M. Glantz, *unpublished observations*), but seizures with onset late in a patient's clinical course tend to be easier to control than those that are an initial manifestation of tumor.[57]

A number of unique problems also complicate the use of AEDs in cancer patients. For example, a rash develops in approximately 25% of patients taking either phenytoin or carbamazepine, a figure twice the reported incidence in the population without tumors.[57] Even more serious, both of these agents have been reported to cause Stevens-Johnson syndrome, particularly in patients who receive radiation therapy while taking a decreasing dose of steroids.[19]

Moreover, it is difficult to maintain therapeutic levels of conventional AEDs (e.g., phenytoin, carbamazepine, phenobarbital) in cancer patients. A number of chemotherapeutic agents, including bischloroethylnitrosourea (BCNU), cisplatin, carboplatin, and Taxol, cause antiepileptic drug levels to decrease, either because of induction of microsomal enzymes or decreased absorption.[9,22,29,36,60] Complex mutual interactions of these agents with the commonly coadministered dexamethasone also exist; as a result, corticosteroid requirements are increased[15,38] and phenytoin levels are decreased, necessitating close monitoring of antiepileptic drug levels.[93] To compensate for lower AED levels, dosages may have to be increased, only to have the level overshoot into the toxic range. Toxicity, in turn, may mimic the symptoms of brain tumor progression, including seizure.[12,81] Lethargy and cognitive dysfunction do not occur only as manifestations of drug toxicity; they can also occur when drug levels are in the therapeutic range. Finally, in approximately 20% of patients with brain tumor who are taking phenobarbital, pain and dysfunction develop in the shoulder and sometimes the entire upper extremity (shoulder-hand syndrome) on the tumor-affected side.[83]

Table 1 Causes of seizures other than tumor masses in cancer patients

Etiology	Setting	Comment
Metabolic	Hypomagnesemia	Occurs 2–7 days after cisplatin chemotherapy.
	Hyponatremia	Often occurs after craniotomy. Usually caused by hydration with hypotonic fluids. Sometimes occurs with vincristine chemotherapy.
	Hypocalcemia	Occurs after cisplatin chemotherapy.
Drug-induced	Methotrexate	Especially with concurrent RT and in patients with abnormal CSF flow.
	Cisplatin	May be caused by electrolyte disturbance.
	Ifosfamide	Especially common in setting of renal failure.
	BCNU (high-dose), IL-2, VP-16 (high-dose)	Uncommon.
	Anticonvulsants	Associated with abrupt decreases or increases; frequently caused by interactions with other drugs.
Intracranial hemorrhage	Coagulopathy	Also occurs with chemotherapy-induced thrombocytopenia.
Radiation	Radiation necrosis	May mimic recurrent tumor.
Infectious	Meningitis	Especially *Listeria*; occurs frequently in patients with ventricular reservoirs.

Neoplastic	Leptomeningeal carcinomatosis	
Paraneoplastic	Limbic encephalitis	Most common with small-cell cancer of lung; very rare.

RT, radiation therapy; CSF, cerebrospinal fluid; BCNU, bischloroethylnitrosourea (carmustine); IL-2, interleukin-2; VP-16, etoposide.

Furthermore, AEDs address only a minority of the possible pathophysiologic mechanisms purported to be important in generating tumor-associated epilepsy. Specifically, these agents tend to act on excitatory mechanisms by blocking and inactivating Na^+ or Ca^{++} channels or on inhibitory ones through increasing γ-aminobutyric acid (GABA)ergic activity.[21] They do not address other possible causative factors such as morphological changes, altered receptor and connexin patterns and changes in cytokine expression.[73]

To complicate matters even further, no published studies address whether AEDs prevent further seizures in patients with brain metastases or whether any one epileptic agent is superior. In earlier work, Posner[68] recommended phenytoin as an initial agent, followed by carbamazepine, phenobarbital, and valproate. However, because brain tumor patients with epilepsy suffer from a number of neuropsychological and psychological problems that are aggravated not only by the severity of epilepsy, but also by the intensity of treatment,[46] use of some of the newer agents such as levetiracetam, which has less allergenicity and fewer medical interactions, seems an attractive alternative that is more frequently being recommended.[85] However, no agent has been proven clearly superior, and the failure of one agent does not predict failure of another.

Should Patients with Brain Tumors Receive Prophylactic Antiepileptic Drugs?

Although the risk for perioperative seizures after neurosurgical procedures is 10% to 15% in the first week,[20,55] this does not necessarily justify the long-term use of prophylactic antiepileptic drugs in patients with brain tumors. Only one study suggests that prophylactic administration of antiepileptic drugs can prevent seizures in patients with glioma.[8] Other retrospective studies have failed to demonstrate decreased seizure frequency in patients with brain metastases or gliomas treated with antiepileptic drugs.[18,53,57] Recently, two prospective studies also failed to indicate a difference in the frequency of first seizures in patients having either primary or metastatic tumors treated with either phenytoin or valproic acid.[32,88] A similar recommendation was made for patients with malignant gliomas by Moots et al.,[57] who recommend that these agents be withheld except for patients at high risk (multiple or hemorrhagic lesions). This has led to a general consensus that was published as an American Academy of Neurology practice parameter that prophylactic drugs not be prescribed in this situation,[33] a recommendation further supported by a subsequent controlled study on the topic.[24]

The practice of the authors therefore has been not to prescribe antiepileptic drugs until a seizure occurs. On the other hand, prophylactic antiepileptic drugs have proved effective in at least one specific instance: Prevention of contrast-induced seizures at the time of CT. Five to ten milligrams of diazepam given orally 30 minutes before contrast administration decreases the likelihood of seizures.[62]

Surgical Treatment of Tumor-Associated Epilepsies

Tumor-associated epilepsies can also be ameliorated by resection. Even a lesion in or near the sensorimotor or language cortex is not an absolute contraindication to surgery.[34] Intractable seizures can often be controlled by gross total removal.[13,34,79] Of patients with low-grade gliomas, for example, 40%

become seizure-free and another 30% have a marked reduction in seizure frequency after surgery.[48] Tumor removal or lesionectomy alone provides effective relief in many patients. In numerous series, from 30% to 60% of patients with brain tumors are rendered seizure free after surgery,[3,13,14,25,34,35,39,74] even though up to 35% of these patients retain their auras after surgery.[80] When surgery failed to control seizures, incomplete resection of the lesion was usually found.

The most favorable seizure-free outcomes following lesionectomy have been reported for patients with indolent glial neoplasms. Complete seizure remission can be obtained in 65% to 80% of these patients, and doses of antiepileptic drugs can be tapered in half of them.[13,14,39] When surgery involves subtotal lobectomy and removal of the medial temporal or frontal structures, at least a 95% reduction in seizure frequency is seen in virtually every patient.[79] Best results are seen in patients undergoing extensive resections soon after the development of epilepsy.[2,94,95] Results are poorer, however, for patients with meningiomas and malignant gliomas.[48] Seizures in patients with brain tumors can also be reduced using either radiation therapy[34,72] or chemotherapy.

Lesionectomy Versus More Extensive Surgery

Although lesionectomies are generally effective, many investigators feel that more extensive surgery produces better results. This contention is supported by the frequent finding on intraoperative electrocorticography in patients with low-grade gliomas of epileptogenic foci remote from the tumor nidus that are devoid of tumor infiltration.[6] Furthermore, a statistically significant decrease in both GABA and somatostatin neurons has been noted in epileptogenic tissue not infiltrated by tumor, compared with nonepileptic cortex not infiltrated by tumor.[37] These findings suggest that cortex surrounding a slowly growing tumor may become isolated, lose inhibitory neurotransmitters, and develop into an independent, tumor-free epileptogenic cortical focus. The not infrequent persistence of seizures following complete tumor resection further suggests that the epileptogenic zone responsible for the initiation and propagation of seizures is sometimes separate from the area of tumor-involved brain removed during lesionectomy.

Whether resection of separate seizure foci, using intraoperative electrocorticography, in addition to radical resection of tumor optimizes seizure outcome remains controversial. Penfield et al.[64] demonstrated a seizure-free outcome in only 21% of patients undergoing lesionectomy and therefore subsequently recommended electrocorticography and more extensive surgery.[65] Many other workers have since reported optimal results when both tumor and epileptogenic foci are identified and removed. If the region of epileptogenicity involves the amygdala-hippocampal complex, results can be improved even further.[5,42,45,67] Furthermore, others[3,34,39,91,92] have reported that routine tumor resection performed without electrocorticography is inferior to more monitored procedures in terms of attaining postoperative seizure control, but this issue remains unsettled.

Part of the difficulty in attaining remission of epilepsy associated with brain tumor can be attributed to progressive, reactive changes taking place in the brain surrounding the lesion, in contrast to the regressive neuronal changes commonly found in seizure foci in idiopathic epilepsies. Thus, failure to control seizures is usually related to persistent disease. In some patients, an initially satisfactory result is followed by a relapse; second surgeries tend to be ineffective.[91] In this situation, if electrocorticography is used, large contiguous and noncontiguous areas of brain surrounding the lesion are found to be dysrhythmic. Paradoxically, however, in patients whose focal neurologic deficits become worse, seizure disorders frequently become easier to control, presumably because of progressive neuronal loss in previously epileptogenic brain.[91]

Prognosis

Although the Brain Tumor Cooperative Group (BTCG) trials for patients with malignant gliomas did not demonstrate a correlation between the occurrence of seizures at diagnosis and improved survival,[77,87] a number of other observations suggest that at least for patients with primary brain tumors, presentation with a seizure is a favorable prognostic sign. In the era before CT, for example, reports of cases of long-standing seizures in patients with benign tumors of the temporal lobe abound. List[49] and Penfield et al.[64] both felt that the prognosis of patients with brain tumors who had seizures was better, because less aggressive neoplasms are commonly seen in these patients. This observation has been substantiated in recent years. Convulsions tend to occur more frequently and earlier in patients with lower-grade gliomas, whereas more malignant tumors tend to produce other signs first. Tumor calcification, which occurs more frequently in lower-grade neoplasms, also correlates with seizure frequency.[76] In fact, a number of recent studies have identified presentation with a seizure as a favorable prognostic sign.[59,75,78] Possible explanations for this observation include relative surgical accessibility (because tumors tend to have a cortical location), earlier detection and diagnosis, and overrepresentation of lower-grade tumors. Interestingly, although most glial neoplasms producing intractable epilepsy are not clinically aggressive, almost 20% have anaplastic histologic features.[26]

Summary and Conclusions

Seizures are frequently the first symptom in patients with brain tumors, or seizures develop later in the clinical course. Thus, they represent an important cause of potentially preventable morbidity in these patients. Determining the cause of the seizure using neuroimaging and other diagnostic tests is critical, because multiple potential etiologies exist in patients with cancer. Unfortunately, pharmacologic therapies are often ineffective in the absence of surgery or other antitumor therapy, and no one antiepileptic drug is clearly superior in terms of efficacy. Furthermore, antiepileptic drugs probably do not prevent seizures from occurring in those patients with brain tumors who have not yet had a seizure. Therefore, for most patients, prophylactic antiepileptic drugs are not recommended. In contrast, surgery, either lesionectomy or more extensive epilepsy-type surgery, frequently produces long-lasting remission of epilepsy, especially in patients with lower-grade primary tumors of the brain.

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Chapter 265

Infection and Inflammatory Diseases

Oscar H. Del Brutto

Introduction

Infectious and inflammatory diseases of the central nervous system (CNS) cause a wide range of clinical manifestations, including decreased level of consciousness, behavioral changes, increased intracranial pressure, focal neurologic deficits, and seizures. The latter may occur as the primary manifestation of the disease or as part of a diffuse encephalopathy. Pathogenesis of the seizure disorder varies widely from one disease to another. In some of these conditions, seizures appear in close temporal association with the acute disease process, although in others, seizures may occur from several weeks to months later, and tend to recur over the following years. Recognition of infectious- or inflammatory-related acute or remote symptomatic seizures has important therapeutic and prognostic implications. Here, we review the most common CNS infectious and inflammatory disorders associated with seizures.

Parasitic Infections

Neurocysticercosis

Neurocysticercosis (NCC) is defined as the infection of the CNS by the larval stage of *Taenia solium*. The disease occurs when humans become intermediate hosts in the life cycle of this cestode after ingesting its eggs in contaminated food or by the fecal–oral route in individuals harboring the adult parasite in the intestine. Although the former was previously considered the most common form of transmission, recent studies showing clustering of NCC patients around taeniasic individuals have changed previous concepts crediting food and the environment as the main sources of human contamination with *T. solium* eggs.[21] *Taenia* carriers are contagious sources of cysticercosis, endangering everyone coming into contact with them. Human cysticercosis must be considered a disease resulting from contagion from an infected human; therefore, the patient's close environment should be investigated to eradicate the source of contagion.

NCC constitutes a threat to millions of people in Latin America, sub-Saharan Africa, and Asia. Massive immigration of people from endemic areas has also caused a recent increase in the prevalence of this parasitic disease in the United States and some European countries.[68] NCC is a leading cause of late-onset epilepsy and a major cause of seizures in developing countries, where the prevalence of active epilepsy is twice that seen in industrialized nations. Indeed, population-based studies have shown that NCC accounts for up to 30% of this excess fraction of epilepsy in the developing world.[14,39,41] It is estimated that 50,000 deaths due to NCC occur every year, and many times that number of patients survive but are left with irreversible brain damage. Despite the magnitude of these numbers, they are but the “tip of the iceberg” because the actual prevalence of NCC is not known.

Pathophysiology

Cysticerci may be located in brain parenchyma, subarachnoid space, ventricular system, and spinal cord. After entering the CNS, cysticerci elicit few inflammatory changes in the surrounding tissues. In many patients, cysticerci remain in this vesicular stage for years. In others, parasites enter, as the result of the host's immune attack, in a process of degeneration. Stages of involution through which cysticerci pass during this process are called colloidal, granular, and calcified. Inflammatory reaction around cysticerci induce pathological changes in the CNS serving as a substratum for the further development of seizures. Within the brain parenchyma, such a reaction is usually associated with edema and reactive gliosis. At the subarachnoid space level there is thickening of the leptomeninges with entrapment of cranial nerves and blood vessels located at the base of the skull. Luschka and Magendie's foramina may be occluded with the subsequent development of hydrocephalus. Ventricular cysticerci elicit a local inflammatory reaction if they are attached to the ventricular wall. In such cases, ependymal cells proliferate and may block cerebrospinal fluid (CSF) transit at the level of the cerebral aqueduct or Monro's foramina; this process of granular ependymitis causes obstructive hydrocephalus.[49]

Epilepsy is more frequently observed in patients with cysticerci located in the brain parenchyma or in the depth of cortical sulci. Cysticerci in all stages of involution may induce seizures, although the mechanisms of epileptogenesis are different. Vesicular cysts cause seizures due to compression of the surrounding brain parenchyma and colloidal cysts cause seizures due to acute inflammatory changes. In contrast, granular and calcified cysticerci cause seizures due to the intense astrocytic gliosis that usually surrounds these lesions.[44]

The concept that cysticerci play a role in epileptogenesis comes from epidemiological studies showing a correlation between populations with increased prevalence of both cysticercosis and epilepsy, and from neuroimaging studies showing NCC in patients with epilepsy in the absence of other etiologies. Also, the episodic appearance of edema surrounding cysticerci after a seizure episode unquestionably links cysticerci with seizures (Fig. 1). This phenomenon occurs not only in patients with living cysts but also in those with calcifications, suggesting that calcified cysticerci should not be seen as inert lesions causing no symptoms.

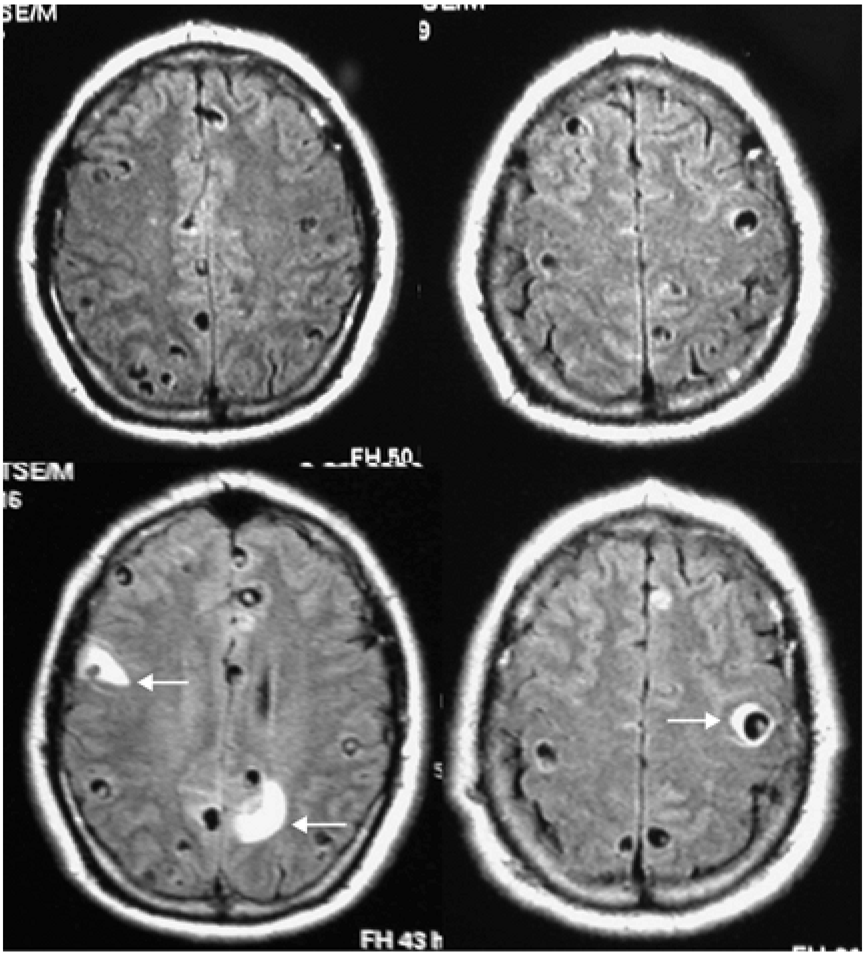

FIGURE 1. Fluid attenuated inversion recovery MRI of patient with parenchymal NCC before (*upper panel*) and 6 hours after (*lower panel*) a seizure episode, showing new hyperintense areas in brain parenchyma, some of which are surrounding cystic lesions (*arrows*).

The pathogenesis of edema around calcified cysticerci is not fully understood.[44] One hypothesis is that periodic remodeling of calcifications exposes the host's immune system to residual antigens still present in these lesions. Direct calcium toxicity is another possibility as it has been suggested that brain lesions that calcify are associated with increased seizure activity compared to those that fail to calcify. It is also possible that brain gliosis left during the death of the parasite explain recurrent

seizure activity. Another hypothesis is that edema is not the cause but the result of the seizure, as has been documented in a few patients after a cryptogenic partial status epilepticus. However, this is improbable because the magnetic resonance imaging (MRI) pattern of perilesional edema in cysticercosis is most consistent with vasogenic edema resulting from breakdown of the blood–brain barrier, and does not have the imaging appearance of cytotoxic edema resulting from cell swelling associated with prolonged seizures.

Clinical Manifestations

NCC is highly pleomorphic owing to individual differences in the number and location of the lesions. Seizures, focal deficits, cognitive decline, and increased intracranial pressure are common manifestations of NCC. Seizures occur in more than 70% of NCC patients.[15] Most of these patients have a normal neurologic examination, and differ from patients with epilepsy due to other cerebral lesions, who usually present with focal signs.

Seizures due to NCC are most commonly simple partial or generalized tonic-clonic, although some patients may present with complex partial or myoclonic seizures. The seizure type has been considered to be related to the number and location of the parasites, whereby patients with a single lesion present with partial seizures, although patients with multiple lesions have generalized seizures.[15] However, other studies have shown no difference in the frequency of partial seizures in patients with single cysts as compared with those with multiple cysts.[40] It is possible that most NCC patients with generalized seizures actually have partial seizures with rapid secondary generalization, an assumption based on the fact that focal brain lesions rarely course with genuine generalized seizures. Not all NCC patients with seizures develop epilepsy. Indeed, there are some patients with a single colloidal cyst who after a bout of two or three seizures remain free of seizures even without antiepileptic drug (AED) therapy.[53] Nevertheless, if we consider the population of patients with NCC-related seizures at large, the vast majority actually have epilepsy because the epileptogenic focus is already developed when the patient is first seen.

Diagnosis

NCC is often diagnosed on the basis of information provided by neuroimaging studies and serology. Both computed tomography (CT) and MRI give objective information on the number and location of lesions as well as on the stage of evolution of cysticerci.[19] Although MRI has better accuracy than CT, it may miss some small calcifications and has the shortcoming of being less available in endemic areas for NCC. From the many immune diagnostic tests, current evidence favors the use of serum immunoblot using purified glycoprotein antigens.[21] A major problem using the immunoblot is that almost 50% of patients with a single intracranial cyst may test negative, and that some patients with taeniasis (but not NCC) may test positive. A set of diagnostic criteria has been proposed to homogenize the diagnosis of NCC.[13] Proper interpretation of these criteria permit two degrees of diagnostic certainty, definitive or probable (Table 1).

Table 1 Diagnostic criteria for neurocysticercosis

DIAGNOSTIC CRITERIA

Absolute Criteria:

- Histologic demonstration of the parasite from biopsy of a brain or spinal cord lesion.
- Cystic lesions showing the scolex on CT or MRI.
- Direct visualization of subretinal parasites by funduscopic examination.

Major Criteria:

- Lesions highly suggestive of neurocysticercosis on neuroimaging studies.
- Positive serum immunoblot for the detection of anticysticercal antibodies.
- Resolution of cystic lesions after therapy with albendazole or praziquantel.
- Spontaneous resolution of small single enhancing lesions.

Minor Criteria:

- Lesions compatible with neurocysticercosis on neuroimaging studies.
- Clinical manifestations suggestive of neurocysticercosis.
- Positive CSF enzyme-linked immunosorbent assay (ELISA) for detection of anticysticercal antibodies or cysticercal antigens.
- Cysticercosis outside the central nervous system.

Epidemiologic Criteria:

- Evidence of household contact with *T. solium* infection.
- Individuals coming from or living in an area where cysticercosis is endemic.
- History of frequent travel to disease-endemic areas.

DEGREES OF DIAGNOSTRIC CERTAINTY

Definitive Diagnosis:

- Presence of one absolute criterion.
- Presence of two major plus one minor and one epidemiologic criteria.

Probable Diagnosis:

- Presence of one major plus two minor criteria.
- Presence of one major plus one minor and one epidemiologic criteria.
- Presence of three minor plus one epidemiologic criteria.

Treatment

Characterization of NCC according to the viability and location of lesions is important for a rational therapy, which usually includes a combination of symptomatic and cysticidal drugs, surgical resection of lesions, or placement of ventricular shunts.[20] Albendazole and praziquantel have changed the prognosis of most patients with parenchymal brain and

subarachnoid cysts presenting with seizures. However, because pioneer studies of NCC therapy focused on the number of cysts before and after the trial, some authors affirmed that cyst disappearance did not necessarily mean improved clinical outcome. Thereafter, two studies showed a strong association between cysticidal treatment and fewer seizures in NCC patients, a finding that was also questioned due to the non-randomized design of these studies.[15,66] During the past few years, placebo-controlled trials have shown that the use of cysticidal drugs not only results in better resolution of lesions but in a lesser risk of seizure recurrence in patients with NCC, providing Class I evidence favoring therapy in these cases.[2,22]

The control of epilepsy in NCC patients not only depends on the use of cysticidal drugs, but on the chronicity of the disorder and the presence of brain calcifications. These patients must be treated with an AED regardless of the use of cysticidal drugs. The optimal length of AED therapy has not been settled. A prospective study showed that up to 50% of NCC patients had relapses after AED withdrawal.[11] Such patients had been free of seizures during two years, and their brain cysts had been successfully destroyed with albendazole. Prognostic factors associated with seizure recurrence included the development of calcifications, and the presence of both recurrent seizures and multiple brain cysts before cysticidal drug therapy.[11,52] Calcified cysticerci are potentially active epileptogenic foci that may cause recurrent seizures after AED withdrawal. Although epilepsy due to NCC may be easily controlled with AEDs, a seizure-free state without medications cannot always be achieved.

Cerebral Malaria

Of the four species of malaria parasites, only *Plasmodium falciparum* invades the CNS and causes cerebral malaria. Because all species may cause fever associated with delirium or seizures, definition of cerebral malaria requires all of the following conditions to be present: unarousable coma, evidence of acute infection with *P. falciparum*, and no other identifiable cause of coma.[69] Humans acquire the infection when parasites are inoculated through the skin during a blood meal by a female *Anopheles* mosquito. Malaria is a public health problem around the world. Up to 500 million people are infected by *Plasmodium spp*. every year, with 3 million fatal cases, most of which occur in African children. Due to increased travel, many cases of cerebral malaria have also been recently recognized in developed countries.[63]

Pathophysiology

The brain of patients dying from cerebral malaria shows diffuse swelling and small ring hemorrhages in the subcortical white matter. These are related to extravasation of erythrocytes resulting from endothelial damage which, in turn, is caused by the liberation of cytokines and vasoactive substances. Another common neuropathologic finding in cerebral malaria is the plugging of capillaries by parasitized erythrocytes due to an increased adherence of these cells to the endothelium. This causes brain damage as a result of obstruction of the cerebral microvasculature, increased concentrations of lactic acid, and ischemic hypoxia.[53]

Clinical Manifestations

Cerebral malaria is an acute encephalopathy characterized by headache, seizures, somnolence or agitation that rapidly progresses to stupor and coma, and extensor posturing. Seizures occur in up to 70% of cases, and are most often tonic-clonic generalized, although some patients present with partial seizures.[54] Pulmonary edema, renal failure, hypoglycemia, and disseminated intravascular coagulation are common during the acute phase of the disease. Most patients who do not die during the first few days recover without sequelae. Some others are left with hemiplegia, blindness, psychiatric symptoms, speech disturbances, recurrent seizures, and extrapyramidal manifestations.[69]

Diagnosis

P. falciparum may be seen by examining blood smears with Giemsa stain; repeated examinations may be needed, because parasitemia is cyclic. Dipstick antigen-capture assay may be of diagnostic value in patients with low levels of parasitemia.[67] Although the cytochemical analysis of CSF is normal in these patients, a spinal tap is mandatory to exclude other causes of encephalopathy. Neuroimaging studies may show brain swelling, hypodense areas in the thalamus or cerebellum, small hemorrhages, or dural sinus thrombosis.[36]

Treatment

Because of chloroquine-resistant strains of *P. falciparum*, quinine is the drug of choice for cerebral malaria.[6] The association of quinine plus pentoxifylline may be better than quinine alone for therapy of cerebral malaria in adults. Mefloquine is effective against *P. falciparum* but has not been evaluated in patients with cerebral malaria. Recent evidence favors the use of artemether as a first-line therapeutic agent for cerebral malaria.[43] Symptomatic therapy includes fluid replacement, sedatives, and osmotic diuretics. Corticosteroids are harmful to comatose patients with cerebral malaria and should be avoided. Although phenobarbital is often used to treat malaria-related seizures in endemic areas, the common loading dose of 20 mg/kg may be deleterious for children with cerebral malaria. A recent study suggested that an initial dose of 15 mg/kg followed by two doses of 2.5mg/kg after 24 and 48 hours is safe and effective in these patients.[30] Despite therapy, up to 25% of patients with cerebral malaria die. Factors adversely affecting the prognosis include coma, retinal hemorrhages, recurrent seizures, renal failure, disseminated intravascular coagulation, respiratory distress, arterial hypotension, severe anemia, hypoglycemia, altered liver function tests, presence of malaria pigment in peripheral white blood cells, high levels of parasitemia, and co-infection with HIV.[8,69]

Other Parasitic Diseases of the Central Nervous System

Almost any parasite invading the CNS may cause seizures. These may occur as the result of the pressure effects of a parasite growing within the brain parenchyma (as in the case of cerebral hydatid disease or coenurosis), due to the irritative effects of a larva migrating through the brain (as in gnathostomiasis or sparganosis), or as part of a diffuse encephalopathy (as in patients with cerebral amebiasis or African trypanosomiasis). In any case, seizures may occur during the acute phase of the disease or as a chronic sequelae of the infection.[12,58] AED therapy should be promptly started in these cases to stop seizures and to avoid recurrences, irrespective of the specific therapy used for each of these conditions. Duration of AED therapy and the risk of seizure recurrence after AED withdrawal will vary depending on the severity of the initial infection and the occurrence of residual structural brain damage.

Bacterial Infections

Pyogenic Meningitis

Causal agents of pyogenic meningitis vary according to the age and the immune status of the patient, and the route by which the infection gains access to the CNS. *Haemophilus influenzae*, *Neisseria meningitidis*, and *Streptococcus pneumoniae* are the most common pathogens causing this condition. Bacteria may reach the subarachnoid space by the hematogenous route from a remote infection, or by contiguity from an infection of paranasal sinuses or ears.[56]

Pathophysiology

Pyogenic bacteria induce the formation of a purulent exudate within the subarachnoid space related to migration of neutrophils and other immune cells.[53] Such exudate, together with direct effects of bacterial toxins, may cause seizures by a number of pathogenetic mechanisms, including: (a) occlusion of small pial arteries with the subsequent development of cortical infarctions, (b) venous thrombosis, (c) diffuse brain swelling, (d) toxic effects of bacteria accumulation within the subpial space, and (e) acute metabolic changes.

Clinical Manifestations

Pyogenic meningitis is an acute disease mainly characterized by fever, headache, cloudiness of consciousness, and seizures. Neurologic examination usually shows neck stiffness or other signs of meningeal irritation. Less common signs include cranial nerve palsies, papilledema or focal deficits. Acute symptomatic seizures occur in up to 40% of patients and are more often of the tonic-clonic generalized type, although some patients present with partial seizures. Only a few patients develop chronic epilepsy after the acute infection. In two large series of children with pyogenic meningitis, epilepsy occurred in 2% and 7% of cases, and was most often associated with the occurrence of permanent neurologic deficits.[50,64]

Diagnosis

A spinal tap usually shows a turbid CSF under increased opening pressure. CSF examination reveals increased polymorphonuclear cells (>1,000 mm^3), decreased glucose levels (<20 mg/dL), and high protein contents (from 100–500 mg/dL). Gram stains and cultures are helpful for identifying the offending microorganism but may be negative in some patients, especially in those receiving antibiotics prior to admission. Polymerase chain reaction (PCR) amplification techniques are useful for detecting bacterial antigens in patients with partially treated infections.[17] CT or MRI should be performed to rule out a cerebral abscess.

Treatment

Patients must be treated with antibiotics according to the causal agent. When the etiology is not know, antibiotics should be chosen according to the age of the patient and the suspected portal of entry of bacteria.[56] Current knowledge does not favor the routine use of corticosteroids in most cases. Acute seizures should be treated with intravenous phenytoin of fosphenytoin; most of these patients will not need long-term AED therapy. However, patients with late seizures should be managed according to the guidelines of treatment of symptomatic epilepsies. Some patients, particularly those developing mesial temporal sclerosis as a late sequela may course with intractable epilepsy, and may require surgery for seizure control.[33]

Brain Abscess

Abscesses are localized infections occurring as the result of invasion of the brain parenchyma by pyogenic bacteria. Most common causal agents include *Bacteroides spp.*, *Staphylococcus aureus*, *Streptococcus spp.*, *Proteus spp.*, and *Enterobacter spp*. These lesions are most often related to the direct spread of bacteria from an adjacent focus of infection (paranasal sinuses, ears, orbits, or teeth), but may also be the result of hematogenous spread of microorganisms from distant foci of infection, usually located in the heart and lungs.[7]

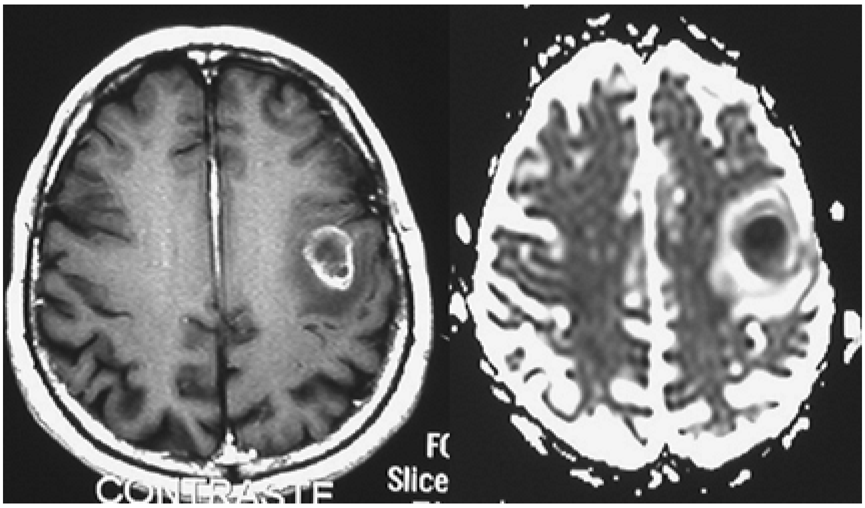

FIGURE 3. Gadolinium-enhanced, T1-weighted MRI (*left*) and apparent diffusion coefficient (ADC) map (*right*) of patient with brain abscess. Reduced ADC helps to differentiate abscesses from brain tumors (courtesy of Dr. Julio Lama, Guayaquil, Ecuador).

Pathophysiology

Most abscesses are located in the cerebral hemispheres at the cortico-subcortical junction. These lesions evolve into four stages: Early cerebritis (days 1–3), late cerebritis (days 4–9), early capsule formation (days 10–13), and late capsule formation (after 14 days). Once fully developed, an abscess consists of a necrotic center and a capsule composed of fibro-blasts, macrophages, and collagen fibers. The surrounding brain parenchyma shows severe swelling and gliosis, providing a substrate for the occurrence of seizures.[31]

Clinical Manifestations

A brain abscess may cause fever, signs and symptoms of increased intracranial pressure, and focal deficits that vary according to the location of the lesion.[7] Fever may be lacking, especially in the elderly or immunosuppressed patients. Seizures occur in more than 50% of patients during the acute phase of the disease, and almost 40% of survivors are left with residual epilepsy. A retrospective series showed that brain abscesses located in the temporal lobe were associated with the highest risk of developing late epilepsy.[31]

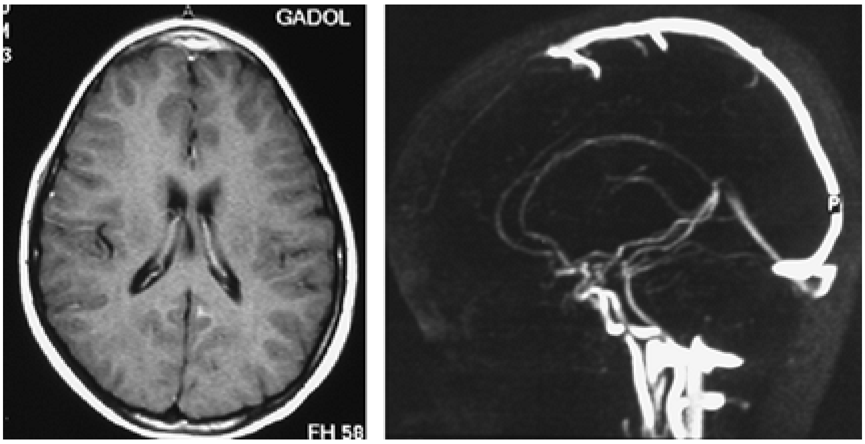

FIGURE 4. Gadolinium-enhanced, T1-weighted MRI (*left*) and MR angiography (*right*) showing epidural empyema and occlusion of anterior half of superior sagittal sinus in patient presenting with tonic–clonic generalized status epilepticus.

Diagnosis

Abscesses appear on CT and MRI as ring enhancing lesions surrounded by edema. The rim of enhancement is usually thicker at the cortical than at the ventricular side of the abscess. Lesions may be multilobulated, due to the formation of the so-called “daughter abscesses” (Fig. 2). New MRI techniques such as MR spectroscopy, diffusion-weighted imaging, and apparent diffusion coefficient (ADC) maps have been shown to be of value in the differentiation of abscesses from other space-occupying brain lesions such as brain tumors and tuberculomas.[24] The purulent center of a brain abscess has a reduced ADC as opposed to necrotic or cystic brain tumors presenting with elevated ADC values (Fig. 3).

Treatment

Patients usually require a combination of medical and surgical management. Antibiotics must be started without knowing the causal agent and their spectrum of action should cover both aerobic and anaerobic bacteria.[4] Increased intracranial pressure should be treated with mannitol or corticosteroids; the latter may reduce the concentration of antibiotics in the necrotic center of the lesion. Seizure prophylaxis is indicated as soon as a brain abscess is diagnosed, and most patients will require prolonged AED therapy.

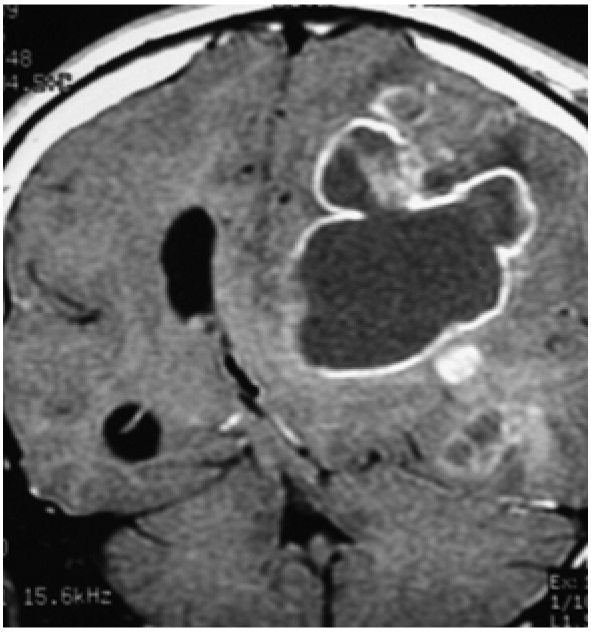

FIGURE 2. Gadolinium-enhanced, T1-weighted MRI of patient with brain abscess showing multilobulated ring-enhancing lesion displacing midline structures.

Empyemas

Empyemas are collections of purulent material at the subdural and epidural spaces. They occur as the result of direct spread from an adjacent focus of infection and, in cases of brain abscesses, empyemas are most often caused by anaerobic bacteria.[28]

Pathophysiology

Empyemas distend the dura and cause septic thrombosis of intracranial dural sinuses. Cortical veins may also be occluded with the subsequent development of cortical infarctions. Seizures may occur as the result of these infarctions or due to direct irritation of the cerebral cortex by the infectious process, as occurred in patients with meningitis.

Clinical Manifestations

Intracranial hypertension and seizures are common manifestations of empyemas.[16] Focal neurologic deficits occur in patients with cortical venous infarctions. Careful examination usually reveals an infectious process of paranasal sinuses, orbits, or ears.

Diagnosis

Neuroimaging studies usually allow the visualization of the empyema and the extent of compromise of intracranial dural sinuses (Fig. 4). A spinal tap is contraindicated in these patients due to the high risk of cerebral herniation.

Treatment

Most patients require surgical drainage of the purulent collection.[4,60] Broad-spectrum antibiotics should be given for several weeks, especially if osteomyelitis is present. AEDs should be started in all cases due to the high risk of seizures during the acute disease. The need of long-term AED therapy will be guided by the development of cortical infarctions.

Tuberculosis of the Central Nervous System

Tuberculosis is most often caused by *Mycobacterium tuberculosis*, an acid-fast bacillus that enters the body through the respiratory tract, settles in the lungs, and then reaches the CNS by the hematogenous route. The first step of brain invasion is the formation of small parenchymal brain tubercles called Rich foci. Then, tubercles may rupture into the subarachnoid space to cause meningoencephalitis or may grow in the brain parenchyma to form tuberculomas.[23]

Pathophysiology

Tuberculous meningitis is characterized by the formation of a thick exudate that encroaches cranial nerves and subarachnoid blood vessels causing arterial narrowing and cerebral infarctions. Luschka and Magendie's foramina may be occluded with the subsequent development of hydrocephalus. Also, damage of the cerebral cortex adjacent to areas of subarachnoid exudate may occur. These pathological changes are responsible for the occurrence of seizures as well as other manifestations of the disease.[47] Intracranial tuberculomas are space-occupying lesions composed of a core of caseation necrosis and a capsule of collagen tissue and inflammatory cells. The surrounding brain parenchyma shows edema and astrocytic proliferation, providing a substrate for the occurrence of seizures.[10]

Table 2 British Medical Research Council classification of severity of tuberculous meningitis

STAGE I

- Fully conscious and rational patient, who does not have any neurologic sign.

STAGE II

- Confused but not comatose patient, who may present with some focal neurologic signs such as hemiparesis or a single cranial nerve palsy.

STAGE III

- Stuporous or comatose patient, who has hemiplegia, paraplegia, or multiple cranial nerve palsies.

Clinical Manifestations

Tuberculous meningitis is a subacute disease characterized by fever, malaise, behavioral changes, headache, seizures, focal neurologic signs, and stupor or coma. The disease has been classified into three stages according to its severity (Table 2). Seizures occur in approximately 20% of cases, are more common in children than in adults, and may represent a predictor of poor outcome.[26,65] Intracranial tuberculomas present as mass lesions, with increased intracranial pressure, focal signs, and seizures.[23]

Diagnosis

Data provided by CSF analysis and neuroimaging studies usually allows a correct diagnosis of tuberculous meningitis.[23] The CSF shows lymphocytic pleocytosis, low glucose levels, and increased protein contents. Acid-fast bacilli may be seen in less than 50% of cases, but cultures are positive in 80%. PCR detection of mycobacterial antigens is of diagnostic value in doubtful cases. CT and MRI show hydrocephalus, abnormal leptomeningeal enhancement, and small cerebral infarctions.[45] In contrast, diagnosis of intracranial tuberculomas is more complex because they resemble other space-occupying lesions on neuroimaging studies, and CSF examination is most often unrevealing. On MRI, some tuberculomas are visualized with a hypointense center surrounded by concentric rims of different intensities (Fig. 5).

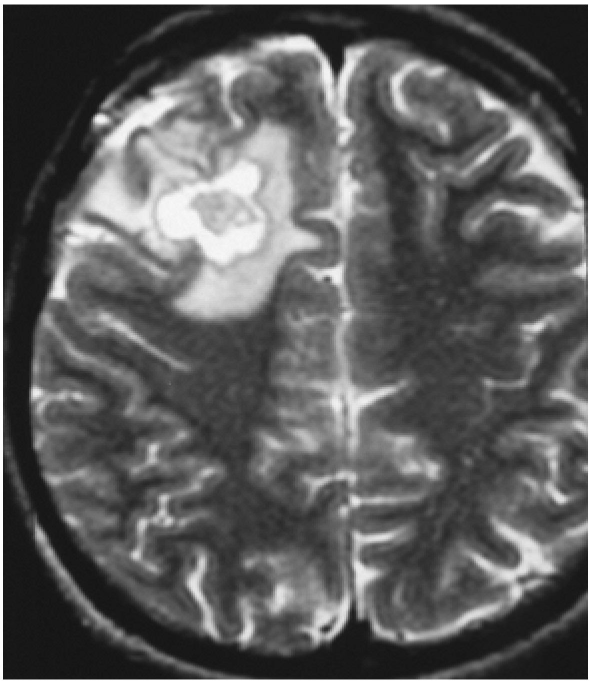

FIGURE 5. T2-weighted MRI of patient with intracranial tuberculoma showing characteristic “target” appearance of lesion.

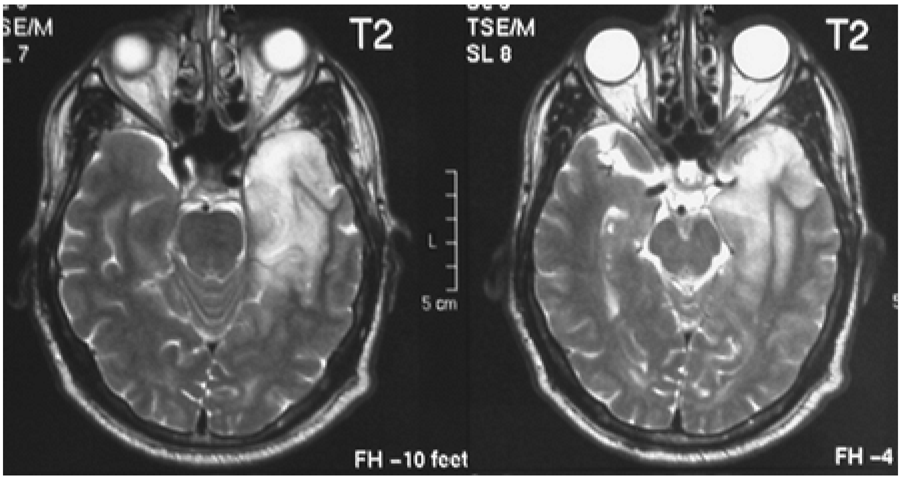

FIGURE 6. T2-weighted MRI of patient with herpes simplex virus type 1 encephalitis showing hyperintense lesion in left temporal lobe.

Treatment

Prompt therapy with antituberculous drugs is associated with decreased morbidity and mortality in patients with meningitis. Corticosteroids ameliorate the inflammatory reaction and reduce the risk of angiitis. Tuberculomas should also be treated medically because of the risk of disseminated disease after surgery. AED therapy is indicated in patients with seizures.

Viral Infections

Viral Encephalitis

A number of viruses may cause encephalitis, defined as a diffuse inflammation of the brain parenchyma.[57] Some of these conditions are mosquito-borne, whereas others are transmitted by rodents, ticks, non-human primates, or by direct human-to-human contagion. Some encephalitides result from direct viral invasion of the CNS, whereas others are related to the occurrence of postinfectious immune disorders. In some other cases, reactivation of a latent viral infection may cause encephalitis. Viral encephalitis may occur sporadically or in epidemic bouts, and some are cosmopolitan whereas others are restricted to certain areas. Herpes simplex virus type 1 (HSV-1) is the most common cause of sporadic viral encephalitis worldwide. Of the geographically restricted viral encephalitis, the most important are Japanese B encephalitis, Venezuelan equine encephalitis, Eastern equine encephalitis, and West Nile virus encephalitis, a formerly restricted disease that is currently spreading from Africa to Europe and America.[38]

Pathophysiology

Once in the CNS, viruses spread to involve the cerebral cortex, basal ganglia, cerebellum, and brainstem. Severity of brain damage is influenced by both the virulence of the offending agent and the immune status of the host. Pathological abnormalities in the brain parenchyma of patients with viral encephalitis include diffuse swelling, vascular congestion, demyelination, inflammatory infiltrates of mononuclear cells, microglial proliferation, formation of glial nodules, and diffuse necrosis of the cerebral cortex and basal ganglia. These changes explain clinical manifestations of viral encephalitis, including seizures.

Clinical Manifestations

Viral encephalitides usually have an acute or subacute onset followed by a rapidly progressive course that may kill the patient in a few days. Occasionally, encephalitis evolves over months, causing a slowly progressive brain damage. Clinical manifestations include fever, seizures, behavioral changes, cloudiness of consciousness, rigidity, and focal neurologic deficits related to the development of cerebral infarctions.[1,29] Some patients present myalgias, sore throat, conjunctivitis, skin rash, bleeding diathesis, and respiratory dysfunction.[9,29] Seizures may be generalized or partial, are most often recurrent, and may persist after the acute disease, especially in patients left with permanent brain damage.

Diagnosis

Viral encephalitis is diagnosed on the basis of virus isolation or detection of specific antibodies in serum, in the proper epidemiological context.[62] CSF examination is abnormal in about 90% of patients, and usually shows a lymphocytic pleocytosis associated with mildly increased protein contents and normal glucose levels.[57] Neuroimaging studies most often show diffuse brain swelling or multiple small cerebral infarctions. In some conditions, MRI findings may suggest the diagnosis by showing hyperintense lesions in the temporal lobe, as in the case of HSV-1 encephalitis (Fig. 6), or bilateral necrosis of the thalamus and striatum, as in patients with Japanese B and other flaviviruses encephalitis.[18,51]

Treatment

Antiviral agents are of value in some conditions such as in HSV-1 encephalitis (acyclovir or foscarnet), cytomegalovirus encephalitis (ganciclovir and foscarnet), and Lassa fever (ribavirin). Other viral encephalitides as well as those in which the etiology cannot be established may be treated initially with acyclovir and then with foscarnet if the patient deteriorates despite therapy.[29] Seizures must be aggressively treated with intravenous AEDs.

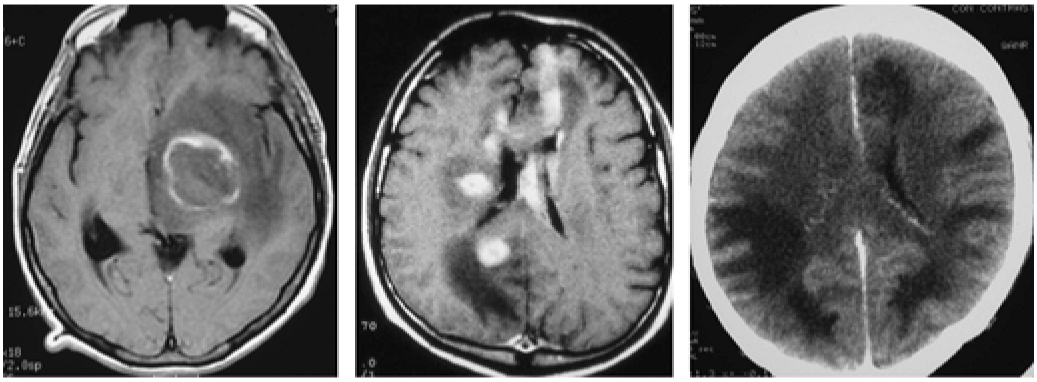

FIGURE 7. Neuroimaging findings in AIDS patients with seizures. Gadolinium-enhanced, T1-weighted MRI showing toxoplasma brain abscess (*left*) and intracranial lymphoma (*center*), and contrast-enhanced CT showing progressive multifocal leukoencephalopathy (*right*).

Acquired Immunodeficiency Syndrome

Acquired immunodeficiency syndrome (AIDS) affects millions of people worldwide. It represents the late stage of infection with the human immunodeficiency virus (HIV), a nononcogenic retrovirus that is acquired by sexual contact, blood transfusions, needle sharing, or vertically from the mother to the fetus. Neurologic complications of AIDS are protean, and may be caused by the HIV itself or by a number of opportunistic microorganisms or neoplasias.[37] Seizures may occur as the result of different pathogenetic mechanisms, including direct neuronal damage induced by HIV, the presence of space-occupying infectious or tumoral lesions within the brain, metabolic abnormalities, or even as a collateral effect of antiretroviral therapy.[55] Seizures may be the presenting symptoms of CNS involvement or may occur late in the course of the disease. It has been estimated that seizures occur 10 times more frequently in HIV-positive patients than in the general population.[25] In most cases, neuroimaging studies show toxoplasma brain abscesses, lymphomas, or progressive multifocal leukoencephalopathy (Fig. 7). Some patients presenting with seizures and no discernible mass lesion develop HIV-related encephalopathy in the short-term.[25,70]

HIV-positive patients with seizures must be treated with AEDs because of the high risk of recurrences. However, traditional AEDs should not be used. Phenytoin is associated with an increased prevalence of cutaneous reactions, valproic acid may favor HIV replication, and carbamazepine or phenobarbital interact with protease inhibitors.[25,27,42] Newer AEDs, such as topiramate or gabapentin, are the preferred drugs in these patients.[55]

Noninfectious Inflammatory Disorders

Rasmussen Encephalitis

Rasmussen encephalitis (RE) is a sporadic focal encephalopathy of unknown cause. A viral etiology has been postulated but never proved, and it has been suggested that the disease may be related to autoimmune mechanisms or to depletion of cellular immunity.[5] These hypotheses are supported by the fact that most patients had an infectious disease before the start of symptoms.

Pathophysiology

The brain of patients with RE shows astrocytic gliosis, microglial nodules, spongy degeneration, and perivascular inflammation. Pathological changes are always localized to the cerebral cortex of one hemisphere.[46] There is no sound pathogenetic mechanism explaining these findings, although it has been suggested that antibodies against subunit 3 of the inotropic glutamate receptor (GluR3) cause brain damage.[5] Those antibodies would be produced after an infectious process, and would enter the brain through a focal breach in the blood–brain barrier, thus explaining the unilateral nature of RE.

Clinical Manifestations

The disease most often affects children and has an acute onset characterized by partial seizures, followed by progressive hemiparesis and cognitive decline. Epilepsia partialis continua is common, with many patients dying with severe intellectual deterioration a few years after the onset of symptoms.[59]

Diagnosis

RE should be considered in children with a typical clinical picture in whom neuroimaging studies show unilateral cerebral atrophy. Electroencephalograms (EEGs) may show delta waves or multifocal spikes in the affected cerebral hemisphere. CSF examination reveals a mild mononuclear pleocytosis associated with increased protein contents.

Treatment

Antiviral agents, interferon-α, immunoglobulins, plasmapheresis, and corticosteroids have been empirically used in some cases. Many patients develop intractable seizures despite aggressive AED therapy, and will require cerebral hemispherectomy.[48]

Neurosarcoidosis

Sarcoidosis is a systemic granulomatous disease that more often affects African-American, middle-aged women. Although the etiology is unknown, it is accepted that exposure to certain infectious agents or environmental toxins triggers, in a susceptible host, a severe inflammatory response leading to noncaseating granuloma formation.[71] Sarcoidosis usually affects the lungs, the liver, and the eyes. CNS involvement occurs in 5% of cases, and does not necessarily occur in patients with systemic manifestations of the disease. Neurosarcoidoses usually present with cranial nerve palsies, peripheral neuropathy, or diabetes insipidus. Seizures may occur in patients who develop parenchymal brain or subdural granulomas.[34,61] Children are more prone to develop seizures than adults

(15% vs. 40% of cases, respectively).[3,32] Diagnosis is difficult in patients who do not have systemic disease, and is often disclosed after a brain biopsy.[34] Therapy includes corticosteroids and AEDs. The risk of developing recurrent seizures is related to the occurrence of fibrotic scars in the brain parenchyma after granuloma resolution.

Summary and Conclusions

Almost any infectious agent invading the CNS, and a number of inflammatory conditions affecting the brain parenchyma, may cause seizures. In this setting, seizures may be related to the pressure effects of a focal infection growing within the brain, to the irritative effects of a given infectious agent, or as part of a diffuse encephalopathy. In any case, seizures may occur during the acute phase of the disease or as a chronic sequelae of the infection. Initial therapy should be directed to stop seizures and to treat the specific infection. In many cases, AEDs must be given for years to avoid seizure recurrences irrespective of the successful management of the infectious process. Duration of AED therapy and the risk of seizure recurrence after AED withdrawal vary according to the severity of the infection and the occurrence of structural brain damage.

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Chapter 266

Connective Tissue Diseases

Barbara S. Koppel

Introduction

Seizures occur in several connective tissue diseases, most frequently systemic lupus erythematosus (SLE), and in forms of vasculitis that involve the brain. Often, however, seizures are not due to the primary disease process itself, but rather to secondary conditions. For example, seizures may occur in the setting of hypoxic or metabolic encephalopathy. Chronic hypertension and accelerated atherosclerosis, even in the absence of antiphospholipid syndrome or cerebral vasculitis, increase the risk of stroke and hemorrhage, which in turn predispose to seizures. Both the underlying disease and its treatment with immunosuppressive drugs increase the risk of brain or meningeal infection, which can cause seizures. Finally, some therapeutic agents used in the management of collagen-vascular disease or vasculitis, such as tacrolimus and cyclosporine, cause an encephalopathy of which seizures are a manifestation.[29]

This chapter reviews the incidence of seizures in connective tissue and vasculitic diseases; when in the course of these illnesses, and under what circumstances, seizures can be expected; and pathophysiology, diagnostic testing, and treatment guidelines. The role of antiepileptic drugs in causing chemical and clinical signs of lupus is also discussed briefly.

General Principles of Autoimmunity in Epilepsy

Seizures occur in autoimmune disorders of the brain such as Hashimoto encephalopathy, Rasmussen encephalitis, paraneoplastic limbic encephalitis, and probably Landau-Kleffner syndrome.[87] In addition, in the absence of structural pathology, antibodies against membranes or ion channels have been proposed as causes for some cases of epilepsy. Some antibodies that are found may be just disease markers, but if there is a clinical response to treatments that lower antibody levels, or if animals immunized with the target antigen develop signs similar to those of the human disease, pathogenesis due to an immune reaction to a targeted antibody is confirmed.[105] In a study of 139 epilepsy patients, 26 had known autoimmune diseases (most often SLE and antiphospholipid syndrome) with antibodies to nuclear antigens. Although these antibodies did not correlate closely with seizure frequency, patients with antibodies against voltage-gated potassium channels and glutamic acid decarboxylase (GAD) generally had more seizures. This suggests a role for these antibodies in causing seizures, especially given that antibodies to voltage-gated calcium channels, gangliosides, glutamic receptor 3, and cardiolipins were not found.[70]

Systemic Lupus Erythematosus

Clinical Manifestations

Collagen-vascular disorders, including SLE, rarely present with seizures. Seizures almost always appear later in the course of active disease, especially during flares of systemic and central nervous system (CNS) lupus.[79] SLE is one of the most common autoimmune diseases, with an annual incidence of 1.8 to 7.6/100,000 and a prevalence of 39 to 51/100,000.[79] Onset is most common in early adult life, women account for 80% of patients, and non-whites (Asians and African-Americans) are disproportionately affected.[62,81] In addition to the nervous system, SLE affects, in order of frequency, joints, mucous membranes and skin (discoid lupus, malar rash, photosensitivity, alopecia), kidneys, pleura, heart, and bone marrow. Neurologic or neuropsychiatric complications have been reported in all series since Kaposi[53] first described them in 14% to 75% of patients >100 years ago.[2,13,46,71] Psychiatric symptoms include depression and psychosis. Neurologic syndromes include dementia, aseptic meningitis, seizures, stroke, movement disorders (especially chorea), myelopathy, and peripheral neuropathy.[2,14,37] Headache can be prominent due to benign intracranial hypertension, aseptic meningitis, and venous thrombosis.[46,61] Even in the absence of dementia or depression, neuropsychological testing reveals high frequencies of cognitive dysfunction.[46,47,71,72] Neurologic complications are a common cause of hospitalization in patients with SLE[89] and the second leading cause of death.[14,107] Early neurologic involvement, especially stroke, has a worse prognosis, but seizures also contribute to poor outcome when they occur in children with arthritis.[90] Seizures double the rate of mortality when found with nephritis in adults.[107]

Both partial and generalized seizures occur in SLE. Generalized seizures can be the sole evidence of brain involvement in diffuse CNS lupus [the term “cerebritis” is no longer used by the American College of Rheumatology (ACR) due its lack of specific pathologic findings], or they may occur as part of hypertensive or metabolic encephalopathy. Status epilepticus also occurs, especially in critically ill patients, in whom it may be a preterminal event.[109] Partial seizures can be a manifestation of cerebrovascular complications (hemorrhage, ischemic stroke, venous thrombosis), abscess, or meningitis.[110] Reflex epilepsy induced by acoustic and patterned visual stimuli has been reported,[16] as has photosensitive myoclonic epilepsy,[74] both in children with SLE. Psychiatric symptoms, especially psychosis and delirium, commonly coexist with seizures[14] and are reported to occur at some time in up to 50% of patients. Partial complex (nonconvulsive) status epilepticus presents with confusion, delirium, or hallucinations; electroencephalographic monitoring is often necessary to confirm the diagnosis,[14,86] which suggests that it may have been missed in the past.

Because of the multiple causes of neuropsychiatric symptoms, it is difficult to obtain meaningful incidence figures for seizures occurring in SLE. However, the fact that seizures are listed first on the SLE activity index devised by the ACR,[12] even after this was updated to separate persistent from acute symptoms,[40] indicates their importance in this condition. In one series of 91patients with SLE, 22% experienced generalized seizures and an additional 5% had partial seizures.[37] Multiple factors, including renal failure, coagulopathy, and hypertension, contributed to seizure occurrence, whereas 3 patients had seizures completely unrelated to SLE. Of interest, 2 patients had seizures only during flares of their SLE, and 8 of the 14 patients who had had strokes experienced seizures during the course of their illness. Most series do not provide sufficient detail to conclude whether the reported seizures are due to SLE or to other conditions.

Diagnostic Tests

In patients with seizures, brain imaging should be done promptly to look for evidence of intracranial hemorrhage (parenchymal or subarachnoid), cerebral infarction, or other structural pathology. Hemorrhage is associated with vasculitis, which occurs in only a minority of patients with SLE.[78] Cortical atrophy is a frequent finding[46,49] and may relate to either long-term steroid use or disease duration.[41] Abnormalities detected by brain magnetic resonance imaging (MRI) scans have been reported in up to 75% of patients with active disease, but the findings are frequently nonspecific subcortical and periventricular punctuate areas of increased T2 signal that most likely reflect small-vessel disease or, possibly, demyelination with gliosis.[41,92] In patients with chronic SLE, abnormal MRI scans were found in 57% of cases; many of the findings were clinically silent.[41] SLE patients with neuropsychiatric symptoms have increased cerebral atrophy and more T1- and T2-weighted lesions compared to both controls and SLE patients without such symptoms.[3] However, only 4 of 43 patients had seizures in this study. Similar lesions have been reported in neurologically asymptomatic patients.[13] Acute inflammatory lesions are enhanced with gadolinium, and in symptomatic patients, serial MRI scans can document loss of enhancement or complete resolution as clinical improvement occurs.[71,110] MR venography and computed tomography (CT) angiography are useful in detecting thrombosis, especially given the dangers of invasive angiography in patients with anticardiolipin antibodies. Transcranial Doppler can be used to follow ischemic changes over time.[57]

Functional brain imaging modalities that have been used in patients with SLE include single photon emission computed tomography (SPECT), positron emission tomography (PET), and MR spectroscopy.[27,92,108] SPECT is abnormal in patients with ischemic stroke, showing focally reduced perfusion in areas that correlate well with both CT and clinical findings. At times, SPECT may be an even more sensitive indicator of cerebral ischemia than MRI, with hypoperfusion preceding clinical symptoms in patients undergoing serial scans.[50,111] Loss of the vascular response to acetazolamide detects marginally perfused areas that are at risk for infarction.[43] In patients with psychosis, SPECT has revealed decreased perfusion in the frontal lobes.[56] PET scans using fluorodeoxyglucose (FDG) demonstrate hypometabolic areas in regions of ischemia or infarction.[22,92]

Serologic markers have been studied in both generalized and CNS lupus. Positive antinuclear antibody (ANA) is found in 95% of patients with SLE, and anti–double-stranded DNA is found in 30% to 75%.[76] Although anti-Sm (smith) antibody is found in <30% of patients, it is specific for SLE. Other laboratory abnormalities that are useful in following active disease are elevated CSF complement 3 and 4,[52] and anti–single- or anti–double-stranded RNA.[33] Serum markers of autoantibodies, especially antiphospholipids (aPL), are increased in SLE patients with neuropsychiatric symptoms compared to those without them.[110] The tests most often used to distinguish among the different connective tissue disorders and types of vasculitis are summarized in Table 1. Anticardiolipin antibody levels, especially immunoglobulin G (IgG), correlate with the occurrence of seizures,[48] whereas antiribosomal P seems to be a marker of psychosis without other neurologic symptoms or signs.[14,33,113] The presence of antibodies to native DNA rather than to the histone complex favors idiopathic rather than drug-induced lupus.[16,21,36,79] Although antineuronal antibodies reflect diffuse pathology and have been reported in 60% of patients with neuropsychiatric SLE, they are also found in patients without neurologic symptoms, raising doubt as to their role in "cerebritis."[27,71,99]

In patients with cerebral ischemia or infarction, the following findings on blood tests can be helpful: The presence of anticardiolipin antibodies, of which IgG is more significant for stroke[79,116] protein S or C deficiency (this is sometimes caused by the nephrotic syndrome[61] when kidney damage is prominent); thrombocytopenia; and lupus anticoagulant using kaolin clotting time or lupus anticoagulant (LAC)-prolonged activated partial thromboplastin time (aPTT). Echocardiography can assist in determining whether there is a cardiac source for cerebral emboli, although marantic (Libman-Sacks) endocarditis is only rarely responsible for stroke in SLE.[46]

Lumbar puncture is required whenever infection is suspected, although significant thrombocytopenia or other clotting abnormalities need to be corrected before it can be performed to avoid producing a lumbar epidural hematoma. Up to one third of patients undergoing a lupus flare with CNS involvement have nonspecific findings in the cerebrospinal fluid (CSF) including increased numbers of white cells (usually lymphocytic) and elevated protein levels.[46] CSF antiribosomal-P and anticardiolipin antibodies correlate with disease activity,[112] but they can also be related to vascular damage that produces breakdown of the blood–brain barrier. Similarly, CSF interleukin-6 (IL-6), a regulator of autoantibody production, can be elevated in patients with infection and is thus best viewed as a nonspecific inflammatory marker.[46,103,112] CSF antineuronal antibody, oligoclonal bands (seen in 25% of one series, produced locally in half),[72] and IgG levels decline with treatment,[110] suggesting that they play a role in the pathogenesis of neuropsychiatric symptoms.

Electroencephalographic abnormalities have been reported in up to 65% of patients with SLE,[69] including those without symptomatic cerebral involvement.[110] The most common finding is generalized slowing, which correlates better with cognitive dysfunction than with the occurrence of seizures.[14,46] For example, in one series of 42 patients, 11 of whom had seizures, EEG recordings did not reveal epileptiform activity in any, although focal slowing was present in 29%, and diffuse slowing was seen in 26%.[49] In contrast, however, a study of 120 patients with SLE found that epileptiform activity occurred in one third, but none of these patients had seizures.[69] Monitoring critically ill SLE patients using continuous EEG is useful in discovering reversible causes of altered mental state or coma, including seizures and metabolic encephalopathy.[86]

Pathophysiology

There are diverse causes of seizures in patients with SLE. Cerebral involvement by lupus itself results in seizures through immune, vascular, and inflammatory mechanisms. Generalized seizures, often accompanied by neuropsychiatric symptoms and headache, are associated with increased titers of antineuronal antibodies, elevated levels of CSF IgG, and oligoclonal bands,[72] as well as cytokine production.[46] Whether these are simply markers of cerebral lupus or are actually pathogenic is not known,[110] although loss of self-tolerance leading to increased cytokine and T- and B-cell production undoubtedly plays some role. Antibodies against brain reactive antibodies,[99] synaptosomes,[46] and gangliosides[67,88] are also increased, especially in patients with seizures or psychosis.[99] Anticardiolipin antibodies from patients with SLE reduce γ-aminobutyric acid (GABA)-mediated chloride currents in snail neurons, a finding that may be relevant to development of seizures.[64]

Table 1 Features of Syndromes with Primary or Secondary Vasculitis

	Patients (%)					
Disease	**CNS**	**Seizures**	**When**	**Vessel size**	**Laboratory**	**Radiology**
PACNS	95	30	Anytime	Small, medium, large; granulomata, stenosis, beads	CSF: > 10 WBC, Pro > 100; culture, Ag, Ab, + oligoclonal bands	MR: subcortical ↑signal T2, meningeal enhancement, mass lesion +/-MRA, SPECT changes
SLE	11–75	12-50	Early or with flares	Small artery vein, capillary Rare stenoses in large arteries (vasculitis rare)	Pancytopenia, +ANA, +/- anticardiolipin, + n-dsDNA (homogeneous), + Sm or RNP (speckled) + RNA (nucleolar), antiribosomal P, ↓complement during flare; CSF: ↑protein, few lymphs, ↑IgG, oligoclonal bands	Hemorrhage with vasculitis; CT, MRI: nonspecific ↑signals; wm, resembles hypertensive; rare abnormal angiogram; MRA; atrophy (diffuse involvement) PET ↓ metabolism
APA			With CVA	Rare vasculitis, medium, large, thrombosis	+ Antiocardiolipin Ab (IgG, IgM), +LA or ↑pTT, ↓plt	Multiple cortical and subcortical strokes, SPECT diffuse and focal ↓ uptake
WG	3		Late	Arteriole, venule, rare medium large	Anti-cANCA>>pANCA; kidney, lung, sinus involvement	Sinusitis
RA	Rare	<1	Anytime	Any size, near involved meninges	+RF	Enhanced meninges, granuloma, or pachymeningeal plaque,

						hemorrhage
SS	Rare	<1	Anytime	Small outside CNS	Anemia, ↑ESR, +RF, +ANA, anti- Ro(SSA), La(SSB), hyperyglobulinemia	MS-like lesions
Behçet	5–20	<1	With flare	Capillories, veins, often brainstem	Mucous membrane lesions, uveitis, CSF: few L or N, sl ↑ Pro, oligoclonal bands	Meningeal thickening; small irregular lesions brainstem; spinal cord, deep wm
Cogan	3–5	<1	Rare	Aorta, any	Eye findings, CSF lymphs	Rare cavernous sinus thrombosis
PAN	3–28	1.5	Rare	Small, medium, branch-point aneurysms	↑ESR, ↑WBC, anemia + HepB, HepC, HIV, pANCA	Single or multiple strokes, often normal, irregular vessels with aneurysms on angiogram
MPA	8	<1	Rare	Small artery, capillary, venule	+pANCA, no Hep B	CXR pulmonary hemorrhage, normal CNS studies usually
TA	1.5	<1	Anytime	Medium, large carotid (external) rare intracranial	↑ESR, ↑CRP	Rare infarct, angiogram beading

Ab, antibody; ANA, antinuclear antibody; APA, antiphospholipid antibody; cANCA, cytoplasmic-staining antineutrophil cytoplasmic autoantibody; CNS, central nervous system; CRP, C-reactive protein; CSF, cerebrospinal fluid; CT, computed tomography; CVA, cerebrovascular accident; CXR, chest x-ray; ESR, erythrocyte sedimentation rate; GA, granulomatous angiitis; HepB, hepatitis B; HepC, hepatitis C; IgG, immunoglobulin G; IgM, immunoglobulin M; L, lymphocyte; LA, lupus anticoagulant; La(SSB); MPA, microscopic polyangiitis; MR, magnetic resonance; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; MS, multiple sclerosis; N, neutrophil; n-dsDNA, non double stranded DNA; PACNS, primary angiitis central nervous system; PAN, polyarteritis nodosa; pANCA, perinuclear staining antineutrophil cytoplasmic autoantibody; PET, positron emission tomography; plt, platelet; Pro, protein; PT, prothrombin time; pTT, partial thromboplastin time; RA, rheumatoid arthritis; RF, rheumatoid factor; RNP, ribnonuclear protein; Ro(SSA); sl, slight; SLE, systemic lupus erythematosus; Sm, Smith antibody; SS, Sjogren syndrome; SPECT, single photon emission computed tomography; TA, temporal arteritis; WBC, white blood cells; WG, Wegener granulomatosis; wm, white matter

After brain involvement by lupus itself, the next-most-common cause of partial and secondarily generalized seizures is cerebral infarction. Infection may also occasionally be a cause. Infarcts can occur from vasculitis caused by immune-complex deposition, emboli from Libman-Sacks endocarditis, enhanced platelet aggregation—due either to endothelial damage or antiphospholipid antibodies—and hypercoagulable states.[14,37,61,109] Cerebral hemorrhage is associated with hypertension, renal failure, and vasculitis. Ironically, accelerated atherosclerosis in patients receiving long-term corticosteroid therapy also contributes to increased risk of cerebrovascular disease, although the role of inflammation promoters (cytokines, proteases, adhesion molecules) is probably paramount.[66] Cerebral ischemia of any cause can be associated with seizures, either at the time the infarct occurs (acute symptomatic seizures) or much later (remote symptomatic seizures). Microinfarcts due to vasculopathy contribute to generalized seizures and depression of mental status.

Seizures can occur as symptoms of a metabolic encephalopathy that is most often related to uremia[109] or as a consequence of lupus-related cardiac disease causing heart block with secondary cerebral ischemia.[75] Because multiple potential causative factors can contribute to seizures even in individual patients, it is frequently difficult to identify SLE as the primary cause. For example, in a review of 91 SLE patients with neurologic dysfunction, more than one third of those with seizures had had a stroke, 2 patients had probable idiopathic epilepsy, and 1 had posttraumatic seizures.[37] Two patients had seizures only during lupus flares.

Treatment

Antiepileptic drug (AED) therapy is not always needed, especially in circumstances in which underlying causes, such as metabolic abnormalities, hypertension, or infection, can be quickly and successfully treated.[93] Seizures occurring with systemic lupus exacerbations often respond to intravenous pulsed methylprednisolone alone. When seizures are frequent, short-term treatment with AEDs is necessary until the lupus flare is suppressed. Seizures occurring in the context of neuropsychiatric symptoms without other factors indicate cerebral parenchymal involvement by lupus and require immunosuppression.[79] Children with SLE who have depression or behavior problems almost always respond to corticosteroids, which suggests that immune-mediated neuronal dysfunction, not a reactive psychiatric condition, is responsible.[62] The incidence of steroid-induced psychosis is often exaggerated. Most patients who develop hallucinations and other psychotic symptoms require increased doses of steroids, not a decrease.[25,55] In addition to oral and intravenous steroids, other immunosuppressive drugs in common use include cyclophosphamide, azathioprine, and cyclosporine.[102] Cyclosporine must be used with caution in patients with seizures both because it can provoke seizures and because it interacts with antiepileptic drugs that are hepatic enzyme inducers. Intravenous immunoglobulin has also been effective.[101] Stroke prevention includes anticoagulation, with or without antiplatelet aggregants.[79,81] Patients with remote-symptomatic seizures generally require long-term antiepileptic drug therapy.

Drug-Induced Lupus

SLE has been attributed to almost all anticonvulsant drugs, as well as to other medications such as procainamide, chlorpromazine, isoniazid, and hydralazine.[7,21,32,39] Clinical manifestations are mild, appear only when the suspected medication is being used, and subside quickly after it is discontinued. Symptoms and signs are usually limited to the skin and joints with accompanying fever and malaise. Visceral, kidney, and CNS involvement is extremely rare. The immune mechanisms underlying drug-induced lupus have been reviewed recently.[117] Although antibodies to the histone complex of DNA are present in 90% of drug-induced cases, they are also found in up to one third of idiopathic SLE patients. Other laboratory abnormalities that drug-induced cases share with idiopathic SLE include cytopenia, positive ANA, prolonged PTT, and rheumatoid factor.[32] Antibodies to single-stranded DNA are common in drug-induced lupus, but antibodies to native double-stranded DNA do not occur. Complement levels are normal.[36] Symptoms resolve soon after the offending drug has been withdrawn, although antibody production may persist for months. In patients with SLE and seizures, AEDs should be prescribed as clinically indicated without undue concern about exacerbating the underlying condition, because only isolated cases of drug-induced lupus attributed to AEDs have been reported.[15,36,110]

Cerebral Vasculitis: Clinical Syndromes

Vasculitis with CNS involvement occurs alone or in combination with several diseases, all of which produce symptoms by inflammatory mechanisms that create structural damage to blood vessels that may lead to ischemia or hemorrhage. In addition to primary autoimmune processes, vasculitis is seen with several collagen-vascular diseases, infections, tumors, or paraneoplastic syndromes, as a consequence of amphetamine, cocaine, or other stimulant use, and with other drugs. The annual incidence of vasculitis is about 4/100,000.[78] Ischemia results from several pathologic processes, including deposition of antigen–antibody complexes in vessel walls, infiltration of blood vessel walls by inflammatory cells, and formation of antibodies to platelets and other cell-mediated immune mechanisms.[17,63,78,115,116] Different conditions affect blood vessels of a particular size and at various sites.[111] Some types of vasculitis affect the brain primarily; others are systemic and involve multiple organs, including the brain. In addition to ischemic strokes, hemorrhage can occur, especially in the presence of aneurysm.[78,80] When many small blood vessels become occluded, diffuse encephalopathy and even coma results. Other symptoms include fluctuating level of consciousness and systemic signs such as fever, diffuse muscle or joint pains, weight loss, anemia, and headache.[17,78] An international consensus group recently updated the classification of the various forms of vasculitis.[98] Several types (polyarteritis nodosa, Churg-Strauss syndrome, temporal arteritis) mainly involve the skin, peripheral nerves, and muscle.[59] Seizures occur as complications of cerebral infarction, metabolic encephalopathy related to hepatic or renal failure, or steroid encephalopathy.[59] Seizures occur in about 4% of patients with polyarteritis nodosa.[28] Although brain involvement is common in Behçet disease, seizures are rare.[23,80] Electroencephalography may be necessary to exclude subclinical seizures in patients with confusion, behavioral changes, and depressed levels of consciousness.[4,86] Some authors have suggested that a vasculitis may be the cause of Landau-Kleffner syndrome,[87] although the evidence for this is weak (see Chapter 242). In general, children who have cerebral vasculitis are less likely to have seizures than are adults.[8]

Connective tissue diseases are among the causes of secondary CNS vasculitis that can lead to seizures. Arteritis is also a complication of some infections (most notably cytomegalovirus, tuberculosis, herpes simplex, herpes zoster, and aspergillosis), vasoactive drugs (phenylpropanolamine, ergotamine, amphetamines, and cocaine), malignancies (lymphoma), and drug hypersensitivity reactions.[17,45,98,114] In these conditions, patients usually have a subacute or chronic course characterized by headache, behavioral or psychiatric symptoms, confusion and altered mentation, as well as generalized seizures. Large-vessel ischemia produces prominent focal neurologic signs and partial seizures. The presence of systemic signs such as fever, nausea, weight loss, and fatigue is variable.

Granulomatous Angiitis (Primary Central Nervous System Angiitis)

Seizures are most often a feature of primary (isolated) granulomatous angiitis of the brain: They occur in 20% to 44% of patients.[1,17,19] Seizures are less often encountered in a recently described “benign” form of granulomatous angiitis that often lacks angiographic evidence of vasculitis and is associated with a better outcome.[20] The incidence of seizures is much higher than can be accounted for by stroke alone, which occurs in no more than 15% of cases, usually those with medium- and large-vessel involvement. Onset of the disorder is subacute, and the course is consistent with a progressive encephalopathy. Focal signs are common but can be transient. Children with primary angiitis have seizures, cumulative neurologic deficits, and headache due to granulomatous invasion of small cerebral vessels.[60] Laboratory findings include CSF pleocytosis and high protein content with normal glucose.[17,114] Meningeal or brain biopsy is required for definitive diagnosis because similar clinical and arteriographic findings can occur in other inflammatory and neoplastic diseases.[17,114]

Diagnostic Tests

When cerebral vasculitis is suspected as a cause of seizures, laboratory testing should be directed to obtaining evidence of an autoimmune disorder and to determining whether there is systemic as well as brain involvement. Blood tests should include erythrocyte sedimentation rate (ESR), C-reactive protein,[66] autoantibody titers (antinuclear, antineutrophil, anticardiolipin), complement levels, creatinine, liver enzymes, and creatine phosphokinase.[98] In granulomatous angiitis, the ESR is normal in 30% of patients.[45,78] Cerebrospinal fluid should be obtained for evidence of inflammation and to exclude infection and neoplasia. In up to 80% of patients with granulomatous angiitis, the CSF shows a lymphocytic pleocytosis, elevated protein, and normal glucose.[45] Brain MRI may show findings consistent with small-vessel disease and stroke,[111] gyral or parameningeal enhancement and edema, and mass lesions in 10% of cases that may mimic abscess or sarcoid.[79,111] Cerebral angiography, although insensitive for changes affecting smaller vessels, can sometimes be helpful and generally should be performed.[45,54,106] Brain and meningeal biopsies are necessary for definitive diagnosis,[31] although these have a false-negative rate of about 25%.[17,114]

Treatment

Treatment of cerebral vasculitis is based on immunosuppression using corticosteroids or cytotoxic agents such as cyclophosphamide.[1,18,44,45,77,98] There is little evidence, however, that these drugs are effective in primary granulomatous angiitis of the brain. When vasculitis is secondary to an infection or neoplasia, the underlying disease must be treated. Plasmapheresis has helped in some cases of steroid failure.[26] Seizures can generally be controlled by carbamazepine or phenytoin; there is less experience with newer AEDs. Because encephalopathy is usually present, benzodiazepines and barbiturates, which can further depress mental status, should be avoided.

Wegener Disease

Wegener granulomatosis results from immune-mediated necrotizing granuloma formation in the mouth, nose, ears, upper and lower respiratory tract, and sinuses, sometimes accompanied by vasculitis and glomerulonephritis.[84] Neurologic complications occur in one third of patients. Cranial or peripheral neuropathies are most common, but stroke and seizures are not rare.[84] Multifocal myoclonus has been described in one child.[44] Wegener granulomatosis is associated with seizures in up to 10% of patients.[84] Vasculitis involving small and medium blood vessels is the presumed etiology of both strokes and seizures, although renal hypertension is associated with cerebral hemorrhage. Direct intracranial extension of the granulomatous pathology can occur from involved sinuses. Seizures are also seen as a preterminal event in patients with severe pulmonary or renal disease, sepsis, and disseminated intravascular coagulation.[104]

Diagnosis of Wegener granulomatosis is based on demonstration of oral ulcers or purulent, bloody nasal discharge, pulmonary involvement with a characteristic X-ray picture, microhematuria, and biopsy demonstrating perivascular granulomatous inflammation. The condition is classically associated with antineutrophil cytoplasmic antibodies (ANCA) in many but not all patients.[42] Cytoplasmic antibodies (cANCA) are more frequent than perinuclear antibodies (pANCA).[51] ANCA titers decline following immunosuppressive treatment but do not correlate reliably with disease activity. CT or MRI of the brain may show meningeal disease or parenchymal destruction consistent with stroke.[100] The most common MRI finding is diffuse white matter hyperintense signals on T2-weighted images[44] that are maximal posteriorly.[85] Treatment includes corticosteroids and cyclophosphamide, with immune globulin reported as having helped one child.[97]

Behçet Syndrome

Behçet syndrome is a form of vasculitis that affects small, medium, and large vessels; both arteries and veins can be involved. This disease occurs mainly in young adults, men more often than women, and classically manifests with the triad of mouth ulcers, genital ulcers, and inflammatory iritis, uveitis, or keratoconjunctivitis. The brain, especially the brainstem, is involved in about 5% of cases.[23] The picture is one of meningoencephalitis. Cranial nerve palsies, focal cerebral signs (aphasia, hemiparesis), encephalopathy, and seizures have been reported. Neurologic dysfunction appears late in the course, although rarely it is the presenting problem.[73] In one study, seizures

occurred in 4.5% of 223 patients with CNS involvement.[9] Half of these patients had other risk factors for seizures, such as insertion of ventriculoperitoneal shunts, brain biopsy, or unrelated surgical interventions. Patients with seizures had a high mortality rate, attributable to the underlying meningoencephalitis.

Rheumatoid Arthritis

Rheumatoid arthritis is an inflammatory disease that produces erosive arthritis of many joints; the viscera are occasionally involved. Neurologic manifestations, although uncommon, sometimes occur in patients with long-standing disease. Cases of polyneuropathy, myopathy, atlantoaxial dislocation with spinal cord compression, myelopathy caused by rheumatoid nodules in the spinal dura, meningitis, and, rarely, rheumatoid nodules in the brain parenchyma[15] have been described in addition to secondary complications of vasculitis.[24,83] Seizures are extremely rare, and when they occur, they are most often a consequence of stroke caused by immunoglobulin, complement, or amyloid deposition in arterioles. Seizures have also been attributed to parenchymal rheumatoid nodules.[15] Rheumatoid cerebral involvement is treated by immunosuppressive therapy such as cyclophosphamide.[79] When seizures are present, AEDs are usually required.

Sarcoidosis

The nervous system is involved in approximately 5% of patients with sarcoidosis.[91,96] Neurologic symptoms usually appear within the first 2 years following diagnosis, although in Sponsler et al.'s review of the literature, they occurred late in the course in almost one third of patients.[95] Seizures occur in about 20% of patients with CNS sarcoidosis. Partial seizures suggest a mass lesion.[58,95] Most, however, are secondarily generalized.[96] Generalized seizures accompanying meningitis or hydrocephalus are associated with a poor prognosis and increased mortality,[30,58] a correlation that presumably reflects more severe parenchymal involvement. Focal seizures that are related to isolated mass lesions have a better prognosis.[95] Seizures occur at higher frequency in children <13 years of age (38% of one series) than in adults[10] without deleterious effect on prognosis. Seizures may also be symptomatic of hyponatremia due to hypothalamic dysfunction or inappropriate antidiuretic hormone (ADH) secretion due to lung disease.[96] Patients with sarcoid are at risk for opportunistic infections and malignancies that may also cause seizures.

Angiotensin-converting-enzyme (ACE) levels are usually elevated in the serum and may be increased in the CSF as well.[94] Brain MRI demonstrates inflammatory changes and granulomata in the majority of patients with neurologic symptoms or signs.[94] Oligoclonal bands are found in the CSF in about one half of these patients.[72]

Patients with sarcoidosis who have seizures require treatment with AEDs, but seizures are often refractory until the underlying disease remits.[30,65]

Scleroderma

Neurologic manifestations of scleroderma (also known as *progressive systemic sclerosis*) are uncommon and usually limited to myopathy and neuropathy. Seizures or other manifestations of brain involvement are rare,[11,49] probably because the antigenic targets in scleroderma are components of collagen, which in the brain occurs only in the basement membrane of some blood vessels and in the leptomeninges.[49]

In the few published case reports, seizure etiology has been unclear but may have been stroke related, due to carotid or intracranial arteritis, or due to hypoperfusion secondary to cardiac involvement.[82]

Sjögren Syndrome

Sjögren syndrome is common and often complicates other connective tissue diseases.[118] Diagnostic criteria include dry mouth (xerostomia), lack of tearing (keratoconjunctivitis sicca) causing dry eyes (xerophthalmia), and characteristic pathologic findings in a salivary gland biopsy. It has been estimated that Sjögren syndrome affects 3% of adults, mostly women.[5] The most common neurologic complications are peripheral neuropathy and polymyositis. CNS manifestations are rare,[34,49] although meningitis and cerebral involvement with cognitive impairment and mental symptoms were seen in 15% of patients with Sjögren syndrome at one tertiary referral center.[5]

Seizures have been estimated to occur in up to 1.5% of patients and are most often partial or secondarily generalized. They are usually attributed to vascular involvement,[6] although autopsy findings in one patient with partial seizures were limited to leptomeningeal lymphocytic infiltrates and laminar cortical necrosis and gliosis without evidence of vasculitis.[38]

MRI scans are abnormal in up to 80% of patients with Sjögren syndrome who have CNS symptoms.[68] Findings include multiple, small, T2-weighted signal abnormalities in the subcortical white matter and periventricular areas (similar to findings in multiple sclerosis), as well as cerebral infarcts and cortical atrophy. The white matter lesions do not resolve with treatment. Cerebral angiography demonstrates changes consistent with arteritis in about 20% of CNS cases.[5] EEG abnormalities are common, and both epileptiform and nonspecific changes have been described.[5,49] Patients with CNS involvement frequently have anti-Ro antibodies in serum.

The pathophysiology of the neurologic manifestations of Sjögren syndrome is unknown, although immune-mediated damage to blood vessels is hypothesized.[5] Vasculitis is commonly presumed to be present, although neither immune-complex deposition nor vasospasm has been excluded as possible mechanisms. Anti-Ro (SSA) antibodies have been implicated; antineuronal antibodies have not been found. Treatment includes corticosteroids, plasmapheresis, and monthly injections of cyclophosphamide.[34]

Sneddon Syndrome

Sneddon syndrome was identified in 1965 in patients who had livedo reticularis (a fishnet-like mottling of the skin) and vasculitis involving medium-sized cerebral blood vessels.[35] About one half the patients have antiphospholipid (aPL) antibodies, which are associated with strokes in patients <45 years of age, headache, and chorea. Seizures have been reported to occur more often in aPL-positive patients (14%–37%) than in aPL-negative patients (0%–11%). They have not been associated with clinical or MRI ischemic events, which suggests an immune etiology. Some patients with Sneddon syndrome have features of SLE. Treatment with steroids can worsen vascular complications; antiplatelet agents have been as effective as anticoagulation with warfarin in aPL-positive patients.[35]

Summary and Conclusions

Seizures can occur in many connective tissue diseases and vasculitis syndromes, although the incidence varies considerably across the different disorders. Seizures are seen most often as a feature of SLE and primary granulomatous angiitis of the brain. Generalized seizures are usually associated with signs of

encephalopathy reflecting diffuse brain involvement by the vasculitis or metabolic or infectious complications. Partial seizures usually indicate ischemic complications or, less often, inflammatory lesions. An infectious cause must always be considered before starting or intensifying immunosuppressive regimens. AED therapy must be individualized, based on usual clinical practice. Drug-induced lupus is rarely serious or permanent.

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Chapter 267

Electrolyte, Sporadic Metabolic, and Endocrine Disorders

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Introduction

Acute and chronic metabolic, electrolyte, and endocrine disorders may cause dysfunction or impairment of the central nervous system, including epileptic seizures.

Occasional seizures resulting from metabolic and electrolyte imbalances are typical and well-recognized events in neonates. However, seizures may develop in later childhood and adulthood as the presenting symptom of an endocrine or metabolic disturbance, and these have been reported with increasing frequency, sometimes in newly recognized clinical conditions such as primary magnesium deficiency. Metabolic disorders in which seizures are one of the main symptoms also occur with liver and kidney transplantation.[4]

Epilepsy as an initial and prominent symptom of unrecognized gastrointestinal disease has been described in cases of gluten intolerance.[11,31,88202] Finally, there have been anecdotal reports of patients affected by concomitant endocrine, metabolic, and gastrointestinal disorders in whom seizures were the presenting manifestation.

In this chapter, the main metabolic, endocrine, and gastrointestinal disorders in which seizures or epilepsy may occur are reviewed based on the literature. The following conditions are considered:

- Electrolyte disorders of sodium (hyponatremia) and magnesium (hypomagnesemia).
- Renal failure (uremic encephalopathy, aluminum encephalopathy, dialysis disequilibrium syndrome, dialysis encephalopathy syndrome).
- Endocrine disorders, including pituitary disorders, hypothalamic hamartoma, thyroid disorders (primary hyperthyroidism, primary hypothyroidism, Hashimoto encephalopathy), parathyroid disorders (hypoparathyroidism, hyperparathyroidism), pancreatic disorders (diabetes mellitus or nonketotic hyperglycemia, diabetic and nondiabetic hypoglycemia), and reproductive disorders.
- Gastrointestinal diseases (celiac disease, orthotopic liver transplantation).

Electrolyte Disorders

Electrolyte disorders can be associated with seizures especially in neonates, but also in children and adults. Seizures may be the presenting symptom of an isolated disorder or of a disorder associated with renal or endocrine disease. Seizures may be present in cases of sodium, magnesium, and calcium imbalance. Seizures associated with sodium and magnesium imbalance are described in this section on electrolyte disorders; disturbances of calcium balance are discussed in the section on endocrine disorders.

Sodium Electrolyte Disorders: Hyponatremia

General Findings

Hypotonic hyponatremia is an electrolyte disturbance characterized by low plasma osmolality (<280 mosm/kg).[29] Hyponatremia may be mild (serum sodium concentration <130 mEq/L) or severe (serum sodium concentration <120 mEq/L). Mild hyponatremia commonly occurs in about 3% to 5% of hospitalized patients[14] and in 1.5% of hospitalized children.[37] Usually, it is asymptomatic and requires no specific therapy. Severe hyponatremia is rare (occurring in only 0.2%),[37] but it must be corrected immediately because of the risk for severe neurologic sequelae.[14] Hypotonic hyponatremia may be hypovolemic, euvolemic, or hypervolemic (Table 1).

The clinical consequences of hyponatremia uncommonly manifest primarily as neurological symptoms but may occur in cases of *acute (symptomatic) hypotonic hyponatremia*. In this condition serum sodium concentration falls rapidly (in <24 hours) to levels <120 mEq/L, without the brain having time to adapt to the electrolyte disturbance. When an osmotic gradient occurs in the brain within a few hours, equilibrium is restored by movement of water molecules into both extracellular fluid and cells. Cerebral edema consequently develops, inducing convulsions followed by tentorial herniation, respiratory arrest, and death. The rate of change is a key element in the appearance of convulsions, and is more important than the degree of hyponatremia. The same mechanism causes seizures during rapid rehydration in cases of hypernatremia.[17] Some authors[18] have suggested that the ability of the brain to adapt to hyponatremia is gender related and that androgens may augment such adaptation. In children, in whom hormonal concentrations are minimal or absent, no gender difference has been found.[19] Of course, the pathogenesis is complicated, and there may be other contributing factors, such as concomitant hypomagnesemia,[180] a combination of hypokalemia and elevated levels of antidiuretic hormone (ADH) (diuretic-induced hyponatremia), a combination of excessive water intake and impaired renal excretion of free water caused by inappropriate secretion of ADH syndrome (SIADH),[19] increased tubular sensitivity to ADH (e.g., in psychotic patients taking neuroleptics),[52] and a combination of extensive extrarenal loss of electrolyte-containing fluids and intravenous replacement with hypotonic fluids in the presence of ADH activity (as in postsurgical patients).

Table 1 Classification of hypotonic hyponatremia

Hypovolemic hypotonic hyponatremia	Extrarenal losses	Vomiting, diarrhea, sweating, pancreatitis, peritonitis, ascites, burns, muscle trauma	Low urinary sodium concentration (<20 mEq/L)	Loss of sodium exceeds loss of water
	Renal losses	Primary renal disease, drug- and hormone-induced renal dysfunction	High urinary sodium concentration (>20 mEq/L)	Loss of sodium exceeds loss of water
Euvolemic hypotonic hyponatremia		Excess of ADH (SIADH), reset osmostat, water	High urinary sodium concentration	Near-normal total body sodium and

	intoxication, endocrine disturbances	(>20 mEq/L)	slightly increased extracellular fluid volume
Hypervolemic hypotonic hyponatremia	Acute renal failure, chronic renal failure	High urinary sodium concentration (>40 mEq/L)	Water retention markedly exceeds sodium retention
	Congestive heart failure, cirrhosis of the liver, nephrotic syndromes	Low urinary sodium concentration (<20 mEq/L)	Water retention exceeds sodium retention

ADH, antidiuretic hormone; SIADH, syndrome of inappropriate secretion of ADH.

Epileptic seizures have been reported in cases of *diuretic-induced acute hyponatremia*, *SIADH acute hyponatremia*, and *acute water intoxication*.

Diuretic-induced acute hyponatremia may be caused by a thiazide or a combination of hydrochlorothiazide and amiloride.[141]

The syndrome of inappropriate secretion of ADH (SIADH) is a form of chronic hyponatremia sustained by constant or intermittent secretion of ADH that is inappropriate in relation to both osmotic and volume stimuli.[37] SIADH is characterized by hyponatremia without extracellular dehydration and edema and by plasma hypo-osmolality without urinary hypo-osmolality. Renal, thyroid, or adrenal insufficiency is absent. Causes of SIADH may be any of the following: Central nervous system disorders (infections, trauma, tumor, sarcoid psychosis), tumors (leukemia; lymphosarcoma; and carcinoma of prostate, ureter, pancreas, or duodenum), drugs (vincristine, vinblastine, carbamazepine, oxcarbazepine, barbiturates, amitriptyline), or pulmonary diseases (infection, tumors, asthma, pneumothorax).[37] In particular, acute hyponatremia and generalized tonic–clonic seizures have been observed in infants with respiratory syncytial virus bronchiolitis. Therefore, fluid therapy in these vulnerable infants should be tailored to reduce the risk of hyponatremia.[93] The syndrome has also been observed in postoperative patients with water retention caused by heart, liver, or kidney failure and in cases of excess salt depletion, as occurs in adrenal insufficiency, malnutrition, or diuretic therapy. Seizures have been reported only in cases of SIADH acute hyponatremia associated with *Salmonella* infection,[47] ingestion of 3,4-methylenedioxymethylamphetamine (MDMA, "ecstasy"), or febrile convulsions.[178]

Acute water intoxication is a rare condition occurring in a variety of clinical settings, all of which involve excessive and rapid intake of free water resulting in a sudden fall of serum sodium levels to <120 mEq/L. Acute oral water intoxication is increasing in frequency, especially in infants <6 months of age, in whom it follows inappropriate administration of low-solute formula or excessive administration of water to infants who are denied formula or breast-feeding.[140] In some cases, water had been given because of mistaken ideas about the correct management of diarrhea in infants or because of infant irritability (perhaps caused by neglect).[140] The risk for this problem may be increased among infants of parents living in poverty. Oral water intoxication is rarer in children (0.4%) and adults (1%-4%); it has been reported in cases of children being forced to drink water or swallowing swimming pool water[114] and of psychogenic polydipsia.[95] Acute non-oral water intoxication has been reported following tap water enemas or excessive parenteral administration of water in hospitalized patients receiving intravenous fluid.[114] It is also seen in postoperative patients with extrarenal loss of electrolyte-containing fluids undergoing parenteral replacement with hypotonic fluid, which normally leads to an increased plasma ADH concentration and a decrease in urinary output.[74] In postoperative patients, excessive ADH secretion may be caused by pain or emotional stress. Most of these patients have a superimposed condition that impairs excretion of free water.[37] Acute hyponatremia followed by seizures may also occur after desmopressin treatment. Desmopressin is an ADH analogue used to improve hemostasis in patients with bleeding disorders and in patients suffering from nocturnal enuresis. Therefore, fluid restriction, avoidance of hypo-osmolar fluid, and close monitoring of fluid and electrolytes are recommended in patients who undergo desmopressin therapy.[59,143] The risk of imipramine administration also has to be taken into account in patients who are given desmopressin.[92]

In *chronic hyponatremia*, the osmotic gradient occurs gradually, so that diffusion of sodium chloride is sufficient and the respective volumes are kept constant. As a result cerebral edema and convulsions do not occur. On the other hand, during these adaptive changes, sodium and potassium are lost from the brain, rendering it susceptible to dehydration during correction of hypersalinity if this occurs more rapidly than the brain can recover solute.[195] The suddenly higher plasma osmolality may cause dehydration and injury of the brain, leading to *osmotic demyelination syndrome* with central pontine myelinolysis and extrapontine demyelination.[195]

In addition, acute or chronic hyponatremia may occur as a side effect of antiepileptic drugs. Oxcarbazepine and carbamazepine are able to lower serum levels of sodium in 29.9% and 13.5% of patients, respectively.[65] Symptomatic hyponatremia may also be induced by levetiracetam.[149]

Clinical Description

Typical neurologic manifestations of acute symptomatic hyponatremia consist of generalized tonic–clonic seizures, hypothermia, and respiratory failure. Nausea, vomiting, muscular twitching, and, in later phases, coma may also occur.

In diuretic-induced acute hyponatremia, hyponatremic seizures are usually generalized tonic–clonic, with frequent progression to status epilepticus.[110] In SIADH acute hyponatremia, neurologic manifestations are headache, incoordination, disturbances of consciousness, and especially generalized tonic–clonic seizures.[47,178] Persistent simple partial motor seizures and multifocal seizures have been reported in a patient with SIADH, acute intermittent porphyria, hyponatremia, and hypomagnesemia; seizures were controlled by magnesium therapy.[180]

Infants affected by acute oral water intoxication exhibit persistent, severe generalized tonic–clonic seizures, usually with progression to status epilepticus. The seizures are intermixed with periods of reduced responsiveness, which have been considered to represent a postictal state or persistent, clinically unapparent seizures.[114] Seizures may be preceded by twitching of the eyes. Brief seizures lasting <10 minutes are rare (9% in the series of Farrar et al.[74]). Clinical features may also include opisthotonic posturing, restlessness, weakness, nausea, vomiting, diarrhea, polyuria or olyguria, and muscle fasciculations. Seizures are rare in older children and adults. However, in 84 of 121 cases in the literature with psychogenic self-induced acute water intoxication, generalized tonic–clonic seizures were the presenting symptom.[52] Partial jacksonian seizures were reported in only one case.[108] In contrast to oral water intoxication, acute nonoral water intoxication is not characterized by seizures as the presenting symptom, and generalized tonic–clonic seizures lasting several minutes have been reported only anecdotally as the presenting symptom.[39] Seizures are similar to those of oral acute intoxication.

A relationship has been demonstrated between lower serum sodium levels and an increased risk of developing recurrent seizures within the same febrile illness. In fact, sodium levels were significantly lower in children with recurrent "simple" febrile seizures as compared with single febrile seizures.[117] Because this finding has not been confirmed by other authors, the American Academy of Pediatrics Practice Parameter does not recommend routinely obtaining electrolytes in patients with febrile convulsions.[200]

The outcome is usually favorable, and in series of both infants and adults, almost all patients recovered completely after prompt correction of the electrolyte imbalance; severe brain damage is usually prevented.[52] Coma and death resulting from respiratory failure, brainstem herniation, and permanent brain damage occurred only in patients who underwent treatment after respiratory failure and coma had already occurred. Permanent brain damage may take the form of diabetes mellitus, central diabetes insipidus, mental retardation, or vegetative status.[18,19] Mortality has been reported in 50% of adult patients, especially women,[18] and 8.4% of children.[19] Vulnerability to water intoxication seems to be greater in postoperative patients, especially children[19] and adult women,[18] in whom the incidence of death or permanent brain damage is higher. These figures appear to be an overestimate, however, because a more recent review found a much lower mortality rate and only few cases of permanent neurologic sequelae.[74]

Chronic hyponatremia is less symptomatic, brain edema is not severe, and neurologically these patients may experience only minor symptoms. Nonetheless, osmotic demyelination syndrome may occur during the correction phase, producing convulsions, fluctuating levels of consciousness, and behavioral disturbances that progress to pseudobulbar palsy.[195] Thus, patients with chronic hyponatremia may be more likely to become permanently impaired than those with acute hyponatremia.

Diagnostic Evaluation

Because acute hyponatremia was the cause of seizures in 56% of infants <2 years of age who experienced seizures without any obvious cause,[74] a diagnosis of hyponatremia should be strongly considered in infants with long-lasting seizures or status epilepticus that is poorly responsive to antiepileptic drugs in whom evidence of another cause is lacking. Similarly, generalized seizures in psychogenic patients should be suggestive of acute hyponatremia. An accurate history is useful in investigating the vast number of possible causes of acute hyponatremia but not in emergent cases, for which only laboratory evaluations are of diagnostic value. Clinically, hypothermia associated with drug-resistant seizures or status epilepticus (in contrast to the more common situation of a rising temperature in such cases) may be a predictor of hyponatremia.[74]

Moreover, because hyponatremic seizures are usually occasional seizures that occur only once either as an isolated attack or in the form of repeated convulsions, a correct diagnostic evaluation first must consider all the main causes of occasional seizures, such as bacterial and viral infections, intoxication, trauma, cerebrovascular diseases and accidents, burn encephalopathy, and metabolic disturbances, including electrolyte imbalance. Laboratory determinations of serum electrolytes, urea nitrogen, creatinine, glucose, and osmolality and of urinary electrolytes, urea, creatinine, and osmolality are more important and may provide sufficient data for a correct diagnosis. In general, a condition characterized by hypovolemia and low plasma osmolality (<280 mosm/kg) together with excessive levels of total body water and sodium and an abnormally high urinary sodium concentration (>20 mEq/L) is suggestive of a primary renal disorder or of drug- or hormone-induced renal dysfunction, which is associated with renal salt wasting. Low serum sodium associated with low urinary sodium concentration (<20 mEq/L) is caused by extrarenal losses, such as vomiting, diarrhea, sweat, pancreatitis, peritonitis, ascites, burns, and muscle trauma. Water intoxication is confirmed by euvolemia associated with low plasma osmolality (<280 mosm/kg), dilute urine, and low serum sodium levels despite normal or near-normal total body sodium, whereas low serum sodium levels with high urinary sodium concentration (>20 mEq/L) suggest SIADH. A full clinical and laboratory examination is needed to investigate all the possible causes of SIADH, and the diagnosis is confirmed by normal adrenal, pituitary, thyroid, and renal excretory function. Finally, excessive levels of total body water and sodium with low plasma osmolality and low urinary sodium concentration (<20 mEq/L) may suggest nephrotic syndromes, congestive heart failure, or cirrhosis.

Electroencephalographic (EEG) examinations have not been commonly performed in acute water intoxication. Nevertheless, lack of alpha activity and presence of high-voltage slow waves requiring long periods to disappear[155] and diffuse and bilateral periodic lateralizing epileptiform discharges (PLEDs) occurring in relation to hemispheric ischemic disturbance have been reported.[108]

Treatment

Acute hyponatremia must be promptly corrected, even when the cause is unknown, because rapid correction of sodium levels is usually well tolerated before brain adaptation against osmotic swelling is complete.[199] The empiric use of hypertonic saline solution (2–6 mL of 3% sodium solution per kilogram of body weight),[52] producing a rapid increase of 3 to 5 mmol/L in the serum sodium concentration, corrects hyponatremia within 4 hours, may prevent death and brain damage,[183] and should be strongly considered. Further correction toward a normal serum sodium concentration should be continued during the

next 20 to 48 hours. Similar successful correction of acute hyponatremia has been demonstrated in psychogenic water drinkers, either by saline infusion alone or by a combination of saline infusion and fluid restriction,[52] although cases of presumed pontine myelinolysis following fast correction of self-induced water intoxication have been reported in alcoholic, malnourished psychogenic water drinkers.[199] Patients who are potentially more vulnerable to osmotic demyelination are similar to patients with polydipsia-hyponatremia syndrome, which is a chronic hyponatremic condition. Even though they experience episodes of acute water intoxication, these patients may be at risk for osmotic demyelination syndrome if an aggressive therapeutic approach with hypertonic saline solution is administered.[195] Therefore, a more conservative approach, with slow correction of hyponatremia, must be taken. In addition to hypertonic correction, treatment may include intubation and assisted mechanical ventilation in cases of respiratory failure.[19] Finally, special care must be taken if carbamazepine or barbiturates have been administered as treatment of recurrent seizures before hyponatremia was diagnosed. These drugs may cause SIADH, which induces water retention and complicates the clinical outcome. On the other hand, phenytoin has been reported to be the therapy of choice for SIADH, reducing seizures in neonates with SIADH developing refractory hyponatremic seizures.[154]

Magnesium Electrolyte Disorders: Hypomagnesemia

General Findings

The location of magnesium in the body is chiefly intracellular, and about half of the body content is located in bone, with high concentrations also in liver, muscle, and brain. Magnesium is the second-most-abundant intracellular cation in the body and plays an important role in neuromuscular excitability. Magnesium produces a curare-like action on neuromuscular function and has a depressant effect on the central nervous system. A direct correlation between low plasma magnesium concentrations, seizure frequency, and status epilepticus has been demonstrated in generalized idiopathic epilepsies.[33] However, the reason that hypomagnesemia causes seizures is unknown. It has been suggested that hypomagnesemia may remove an inhibitory influence from the *N*-methyl-D-aspartate (NMDA) glutamate receptors. Then, this process may trigger neuronal depolarization. Magnesium specifically inhibits sodium flux through NMDA-type glutamate receptors.[64] Chronic hypomagnesemia, as an isolated abnormality, may be caused by a reduced intestinal absorption due to transport defect or a reduced tubular filtration rate. It may be asymptomatic or symptomatic, depending on the patient's age.[77] Normal serum concentration is between 1.6 and 2.1 mEq/L. In cerebrospinal fluid the normal concentration is 2.4 mEq/L because of active transport of the ion. Symptomatic magnesium deficiency is an electrolyte disturbance defined as a serum magnesium concentration of <1.4 mEq/L (usually between 0.7 and 1.4 mEq/L). A secondary hypocalcemia caused by the inhibitory effects of magnesium deficiency on the parathyroid gland[12] is frequently present, and it is associated with inappropriately low parathyroid hormone levels for the degree of hypocalcemia, as has been found in both primary and secondary hypomagnesemia.[26,175]

Primary hypomagnesemia (*congenital hypomagnesemia*, *familial hypomagnesemia or primary hypomagnesemia with secondary hypocalcemia*, *isolated intestinal magnesium malabsorption*) is a rare condition in infants. Phenotypic characterization of clinically affected patients and experimental studies of appropriate animal models have contributed to a growing knowledge of renal magnesium transport mechanisms. In that context, both autosomal-dominant and recessive models of inheritance have been reported. The autosomal-dominant variant has been found to be associated with hypocalciuria and linked to the gene *FXYD2* on chromosome 11q23, which codes for a subunit of the basolateral Na-K-ATPase on the distal collecting tubule.[120] In the recessive variant, defects and mechanisms for hypomagnesemia are unknown.

Hypomagnesemia may also be associated with other abnormalities in the context of specific syndromes. For example, hypomagnesemia in association with hypokalemia is suggestive of Gitelman syndrome, which also manifests with metabolic alkalosis and high renin and aldosterone levels. Gitelman syndrome is caused by an inactivating mutation in the electroneutral cation-chloride–coupled cotransporter gene *SLC12A3*, which is located on human chromosome 16q13 and functions as a sodium/chloride thiazide-sensitive cotransporter.[138]

Familial hypomagnesemia with secondary hypocalcemia is an autosomal-recessive inherited disorder related to mutations in the *TRPM6* gene located on chromosome 9q21, which encodes for a transient receptor potential ion channel and leads to defects in both intestinal and renal handling of magnesium.

Finally, hypomagnesemia, hypercalciuria, and nephrocalcinosis also comprise a rare autosomal-recessive disorder in which polyuria and hyperuricemia may occur. Mutations in the paracellin-1 or *CLDN16* gene located on chromosome 3q, which encodes for paracellular transport pathways, have been found.[64]

Secondary hypomagnesemia has been reported after removal of parathyroid neoplasm and in cases of diabetic acidosis, malabsorption syndromes caused by intestinal injury, bowel resection (for carcinoma, enteritis, mesenteric thrombosis), prolonged loss of gastrointestinal fluids, hyperaldosteronism,[10] excessive use of diuretics, prolonged treatment with platinum compounds,[26] and closed heart surgery.[184] Frequently, it is associated with concurrent metabolic disorders, such as electrolyte deficiencies, hypo-osmolality, and septicemia, which may make it difficult to recognize hypomagnesemia. In neonates, transient hypomagnesemia is known to occur in children of toxemic and diabetic mothers, intrauterine growth retardation (IUGR) infants, or infants with transient hypoparathyroidism or maternal hypomagnesemia due to celiac disease.

Generalized or partial seizures have also been described in patients with hypomagnesemia induced by the ketogenic diet for intractable epilepsy,[9] cyclosporin A therapy,[9] and ibuprofen overdose.[7]

Clinical Description

In general, magnesium depletion is characterized by an epileptic syndrome consisting of generalized seizures or partial seizures with single or multiple foci. There is a complicated symptomatology associated with neuromuscular irritability resulting in action-intention tremor, myoclonic jerks, startle response, generalized tendon hyperreflexia, Chvostek's sign without concomitant Trousseau's sign or carpopedal spasm (which may be found in primary hypomagnesemia with secondary hypocalcemia; see later discussion), tachycardia, and rarely athetoid and choreiform movements.

Infant patients are classically seen with partial seizures that have one or multiple foci. They are conscious and hyperactive. Diarrhea and secondary hypocalcemia are present.[3] Seizures occur repeatedly and are resistant to antiepileptic drugs. Stiffness of all four extremities and hypertonia also have been reported.[50] In children and adults, generalized tonic–clonic seizures associated with nonepileptic massive myoclonic jerks and carpopedal spasm, without diarrhea, were the presenting

symptoms.[175] Sudden-onset aphasia and no clear initial motor seizure activity have also been reported.[64]

Convulsions and diarrhea are intractable, and children may die if the magnesium disorder is not recognized and corrected early.[3] Otherwise, the prognosis is relatively good with normal psychomotor development as long as magnesium supplements are maintained.

Diagnostic Evaluation

Hypomagnesemia should be strongly suspected in infants with generalized or partial seizures with one or multiple foci of unknown cause that are resistant to treatment and are associated with diarrhea and tetany that do not respond to calcium replacement. Given that older patients are less symptomatic, isolated magnesium malabsorption has to be investigated at any age. Finally, complete investigation of magnesium metabolism should also be considered in cases of idiopathic epilepsy because of reports[91,193] concerning a direct correlation between low levels of serum magnesium and the frequency of seizures and status epilepticus in patients with idiopathic generalized epilepsies.

Intestinal malabsorption of magnesium is confirmed by markedly elevated fecal magnesium levels and low serum magnesium levels, even if serum magnesium concentrations do not reflect total body magnesium stores. A 24-hour urine collection and intravenous magnesium loading test for total body magnesium determination are very sensitive. When facilities for serum magnesium determinations are not available, a trial of parenteral magnesium sulfate may serve as a therapeutic test if renal function is not impaired. Comprehensive intestinal and renal investigations to detect intestinal malabsorption and renal failure or tubulopathy, hormone and electrolyte determinations to detect hypoparathyroidism, hyperaldosteronism, and conditions associated with hypokalemia or hypocalcemia, and X-ray of the carpal bones to detect other metabolic diseases are also required.

In addition, because of the associated movement disorders, specific investigations to detect disease of the basal ganglia (computed tomography, magnetic resonance imaging, neurophysiologic evaluations, and laboratory tests for liver disease, metabolic disorders, and immunologic disease) should be considered.

Treatment

Elective therapy in isolated magnesium malabsorption consists of high-dose oral or parenteral magnesium supplements. Typically, magnesium administration alone controls convulsions and low serum levels of magnesium and calcium in primary hypomagnesemia; administration of calcium and vitamin D is not effective. The major complication of magnesium supplementation appears to be diarrhea caused by the magnesium itself.

Renal Failure

Renal failure leads to disturbances in the function of every organ system in the body. Complications of renal failure become increasingly prevalent as the glomerular filtration rate decreases below 5 mL/min/1.73 m^2, the level of function that defines end-stage renal disease. Neurologic disorders remain an important source of morbidity and mortality in this vulnerable patient population. With the introduction of dialysis and renal transplantation, the spectrum of neurologic complication has changed. On one hand, the incidence and severity of uremic encephalopathy, neuropathy, and myopathy have declined.[40] On the other hand, dialytic regimen or renal transplantation may determine neurologic disorders such as dialysis dementia, dialysis dysequilibrium syndrome, cerebrovascular accident, and hypertensive encephalopathy, which are thought to be the consequence of ultrafiltration-related arterial hypotension directly related to dialysis. Moreover, hemorrhagic stroke, subdural hematoma, osmotic myelinolysis, opportunistic infections, intracranial hypertension, Wernicke encephalopathy and peripheral neuropathy can also occur. In patients who undergo renal transplantation, immunosuppressive drugs may cause encephalopathy, movement disorders, opportunistic infections, neoplasms, myopathy, and atherosclerosis. The neurologic manifestations of renal failure are summarized in Table 2.

Table 2 Neurologic manifestations of renal failure

Neurologic manifestations of uremia
- Uremic encephalopathy
- Hypertensive encephalopathy
- Aluminum encephalopathy in infancy and childhood

  - Uremic polyneuropathy
  - Cranial nerve dysfunctions
  - Autonomic dysfunctions
- **Neurologic complications of uremia treatment**
  - Dialysis disequilibrium syndrome
  - Dialysis encephalopathy syndrome
- **Neurologic complications of transplantation**
  - Rejection encephalopathy

This section discusses epileptic seizures in *uremic encephalopathy*, *aluminum encephalopathy in infancy and childhood*, *dialysis disequilibrium syndrome*, and *dialysis encephalopathy syndrome*.

Neurologic Manifestations of Uremia

Uremic Encephalopathy

General Findings.

Uremia can be defined as "systemic intoxication caused by severe glomerular deficiency associated with disturbances in tubular and endocrine functions of the kidney. It is characterized by retention of toxic metabolites derived mainly from proteins associated with changes in volume and electrolyte composition of the body fluids and excess or deficiency of various hormones."[35] The pathophysiology of uremic encephalopathy is complex and poorly understood. Renal failure results in a gradual accumulation of several substances, but no single metabolite has been identified as the sole cause of uremic encephalopathy.[204] Accumulation of urea, uric and hippuric acids, phenols and conjugates of phenols, phenolic and indolic acids, glucuronic acid, various amino acids, polyamines, polypeptides, carnitine, sulfates, phosphates, and "middle molecules" has been observed.[61] It may also depend on guanidino compounds; acidosis; hyperhydration and dehydration; electrolyte disorders (hyponatremia, hypomagnesemia, hypocalcemia, hyperkalemia); hormonal disturbances (parathyroid hormone, thyrotropin, prolactin, luteinizing hormone, growth hormone, insulin, and glucagon); disturbances of cerebral amino acid metabolism; decreased concentration of γ-aminobutyric acid (GABA); increased concentrations of dopamine and serotonin; diminished cerebral uptake of glutamine, valine, and isoleucine; and increased extraction of glycine and cystine.[38] Seizures may be related to hypertension, electrolyte imbalance, aluminum toxicity, drug toxicity, and infections. Inhibition of cerebral sodium-potassium adenosine triphosphatase (ATPase) has been demonstrated in experimental animals, which might be correlated with elevation of intracellular sodium and seizure activity.[142] A main role is thought to be played by guanidino compounds such as methylguanidine and guanidinosuccinic acid, which were found to be highly increased in cerebrospinal fluid (CSF) and brain of uremic patients.[61] They may also induce a disorder similar to the "twitch-convulsive" syndrome, including epilepsy.[144] Activation of the excitatory NMDA receptors and concomitant inhibition of inhibitory $GABA_A$-ergic neurotransmission have been pointed out as underlying mechanisms.[61] Intrahippocampal guanidinosuccinic acid injection in unanesthetized rats triggered partial clonic seizures leading to generalized tonic–clonic seizures and eventually status epilepticus.[158] Moreover, inhibition of cerebral sodium-potassium-ATPase was shown in experimental uremic animals.[42] This might correlate with the elevation of intracellular sodium and might therefore be associated with the epileptogenicity affecting this population.[40] In this context, the pathophysiologic role of parathyroid hormone should also be considered. Although the mechanisms are unknown, parathyroid hormone is able to facilitate the entry of calcium in brain tissue.[42] Because calcium is an essential mediator of neurotransmitter release and plays a major role in intracellular metabolic and enzymatic processes, alterations in brain calcium may possibly take part in determining cerebral dysfunction and seizures. Focal or multifocal and stimulus-sensitive myoclonus is supposed to originate in the brainstem reticular formation.[49] Uremic encephalopathy is reversible on correction of renal insufficiency, consistent with the failure of histopathologic studies to find a specific anatomic lesion.[156]

Clinical Description.

Uremic encephalopathy almost invariably complicates both chronic and acute uremia, its severity depending on the rate of renal failure. Neurologic manifestations of acute and chronic renal failure do not differ qualitatively, but clinical symptomatology is usually more severe and progresses more rapidly in patients with an acute deterioration of renal function.[42] The clinical course is characterized by variability from day to day. Presenting symptoms may be subtle and represented by apathy, irritability, inattentiveness, clumsiness, and fatigue. Tests show that attention span is impaired at this stage.[42] "Frontal lobe" dysfunction manifests with deficient abstract thinking, behavioral disorders, paratonia, and palmomental reflex.[42] Recent memory deficits indicate a more advanced stage of disease. Later, remote memory fails, and confusion, lethargy, stupor, and ultimately coma develop. Typical features of delirium (toxic psychosis), such as hallucinations, agitation, confusion, and disorientation, are especially frequent in acute renal failure. Mental impairment is greater in children who experience onset of chronic renal failure during the first year of life, especially within the first 2 months.[166] Psychomotor and mental development are delayed, and a small head circumference and progressive decrease in IQ may be encountered, even in the absence of neurologic signs.[4] Even in patients who have been treated with renal replacement therapy, memory deficits and sleep disturbances are not uncommon. Neuropsychological investigations showed significant deviation from normal controls in areas of attention/response speed, learning and memory, and perceptual coding.[42] Movement disorders and epilepsy constitute a very characteristic clinical feature of uremic encephalopathy and define the so-called "*uremic twitch-convulsive*" syndrome,[2] which consists of intense asterixis and multifocal myoclonic jerks that are accompanied by fasciculations, muscle twitches, and seizures.[60] Early manifestations include muscle cramps, tremors, and asterixis. Muscle fasciculations and myoclonus appear in advanced encephalopathy. Asterixis or "flapping tremor" is probably caused by sudden loss of tonus, originating from cortical dysfunction and clinically consists of multifocal action-induced jerks that can even mimic drop attacks in severe cases. In uremia, both spontaneous action myoclonus and stimulus-sensitive myoclonus with good response to benzodiazepines can occur. Uremic myoclonus may be caused by a dysfunction in the lower brainstem reticular formation due to water-electrolyte imbalance leading to microcirculatory and degenerative changes.[40] Thiamine deficiency is thought to determine chorea by interfering with basal ganglia function.[106] "Alternating hemiparesis" can occur in up to 45% of patients.[42]

Epileptic seizures have been reported in about one third of patients with uremic encephalopathy. In cases of chronic renal failure, they are most often a late manifestation and sometimes a preterminal event.[169] In acute renal failure, seizures occur within the first 15 days of disease.[60] Late-onset seizures have been rarely observed in association with hemiparesis and transient blindness as a result of a posterior reversible encephalopathy syndrome.[34] Usually, seizures are generalized tonic–clonic or myoclonic, but focal motor seizures and even epilepsia partialis continua have also been reported.[60] Nonconvulsive status epilepticus characterized by acute confusion or stupor without motor seizures has also been observed in patients with end-stage renal failure.[53]

Neurophysiologic Investigations.

The EEG is abnormal in the setting of acute encephalopathy due to renal failure. EEG background activity becomes progressively disorganized. Decreased alpha activity is associated with the appearance of intermittent paroxysmal bursts of bilaterally synchronous slow waves, with largest amplitudes over the frontal regions (projected rhythm). In chronic renal failure, changes are less dramatic. As the uremic state progresses, the EEG becomes slower, with a recognizable correlation between the percentage of frequencies <7 Hz and the increase in creatinine. Bilateral spike and wave complexes, in the absence of evident clinical seizure activity, have been reported in up to 14% of patients with chronic renal failure.[42] A paradoxical response to eye opening and an abnormal arousal response to afferent stimuli consisting of bursts of slow waves may occur. Photic driving, photomyogenic response, and photosensitivity manifested by paroxysmal epileptiform discharges are more characteristic of uremic encephalopathy. They may be elicited just before the onset of convulsions. Electroencephalographic features correlate with alteration in consciousness to a greater degree than with the degree of uremia, electrolyte imbalance, and acidosis.[185] Asterixis is electromyographically characterized by typical silence, which follows a biphasic wave in the backaveraged EEG activity.

The N75 and P100 components of one visual-evoked potential (VEP) are significantly prolonged in chronic renal failure.[57] Peak V and I–V and III–V interpeak latencies of brainstem auditory-evoked responses (BAERs) were significantly prolonged in one third of chronic renal failure patients.[176] Unfortunately, no significant correlations have been documented between the degree of prolongation of various VEP or BAER component latencies and the severity of chronic renal failure or its associated metabolic complications.

Visually-evoked event-related potentials (ERPs) in neurologically asymptomatic patients affected by chronic renal failure clearly showed an increased P3 latency and decreased P3 amplitude. After hemodialysis, P3 latency showed a significant decrease, and P3 latency habituation during the ERP measurement was also significantly decreased. These data suggested that impaired cognitive processing can be disclosed by ERP even in neurologically asymptomatic chronic renal disease. Removal of uremic toxins by hemodialysis leads to an improvement in cognitive function.[73]

Somatosensory-evoked potentials (SEPs) after median nerve stimulation are enhanced bilaterally. Both the biphasic wave and the giant SEP are believed to have a common origin in the sensorimotor cortex in brain-mapping recordings.[22]

Diagnostic Evaluation.

A combination of clinical signs of depression and signs of cerebral excitation, such as multifocal myoclonus and epilepsy, is strongly suggestive of uremia.

When seizures are present, a series of investigations, including determination of bone and plasma aluminum concentrations and plasma and urinary electrolyte concentrations, osmolality, volume, and levels of ADH, has to be performed to exclude other, superimposed causes of seizures, such as hypertensive encephalopathy, electrolyte imbalance (water intoxication, hypocalcemia, hyponatremia, hypomagnesemia), or aluminum encephalopathy. Computed tomography followed by lumbar puncture (unless intracranial pressure is increased), which may show elevated protein concentrations or pleocytosis, can aid in the diagnosis of infection of the central nervous system. Papilledema, focal neurologic signs, and elevated opening pressure at lumbar puncture may suggest hypertensive encephalopathy or intracranial hemorrhage. If no causes are demonstrated, an idiopathic seizure disorder must be differentiated. When a patient with acute or chronic renal failure experiences an unexpected onset of seizures, asterixis, myoclonus, and behavioral disturbances such as agitation and confusion (toxic psychosis), a drug-induced encephalopathy should be suspected. In the case of renal failure, the availability of certain drugs, such as vigabatrin, acyclovir, chlorpromazine, cyproheptadine, salicylates, phenytoin, barbiturates, and benzodiazepines or their metabolites, is increased by the diminished urinary elimination of active metabolites or diminished protein binding, which increases their plasma concentrations. Immunosuppressive-associated encephalopathy has been described with cyclopsorin,[51] tacrolimus,[161] and muromonab-CD3.[159] The clinical picture involves tremor, cerebellar and and/or extrapyramidal signs, and headache. Sometimes a reversible posterior leukoencephalopathy syndrome may complicate the clinical course,[161] with white matter changes. Subcortical and cortical involvement has also been described.[31] Recognition of immunosuppressant-associated encephalopathy is crucial because modulation in immunosuppressive drugs administration may result in resolution of clinical symptoms and neuroimaging abnormalities.

Finally, possible thyroid disorders have to be investigated (see section on endocrine disorders). Video-polymyographic-EEG recordings and electromyographic (EMG) examinations must be performed to differentiate epileptic events from other, nonepileptic movement disorders such as asterixis, tremor, and myoclonus.

Treatment.

Clinical symptoms of uremic encephalopathy may improve following dialysis and renal transplantation. The development of uremic encephalopathy is an indication for prompt initiation of dialysis and consideration of renal transplantation.

Seizures may be treated with standard antiepileptic drugs, taking into account the changes in renal excretion and reductions in plasma protein binding that may occur in renal insufficiency. Therefore, monitoring of blood levels of drugs is advisable; levels of unbound antiepileptic drugs, which increase during renal disease, are most informative. In general, oral doses of all the antiepileptic drugs should be reduced and the intervals of administration modified. Sodium and magnesium valproate and phenytoin free plasma fractions increase, whereas lamotrigine clearance is not significantly modified in renal disease. Carbamazepine (which may exert a significant antidiuretic effect, causing increased danger of fluid retention), vigabatrin, and felbamate (which are excreted almost entirely by the kidneys) should not be given.[129] Benzodiazepines, and especially clonazepam, are effective against myoclonus,[4] whereas piracetam and l-5-hydroxytryptophan cannot be used in renal failure. Sedative hypnotics and antipsychotic tranquilizers, which may cause toxic psychosis,[122] and antibiotics, which may induce myoclonus, asterixis, seizure, and coma, must be administered with extreme care.[172] With respect to the newer antiepileptic drugs, zonisamide and oxcarbazepine are cleared by both the renal and hepatic routes. The clearance of both drugs has been shown to decrease with decreasing creatinine clearance. No specific guidelines for dose adjustment have been provided for zonisamide. Oxcarbazepine should be initiated at one half of the usual starting dose and increased to achieve clinical response.[41,128] More than two thirds of levetiracetam and topiramate is excreted in the urine. A reduction in the dosing rate for both drugs is recommended for patients with moderate or severe renal impairment.[41]

Aluminum Encephalopathy Syndrome in Infancy and Childhood

General Findings.

Aluminum encephalopathy syndrome is a progressive encephalopathy that tends to occur in infants and children with chronic renal failure following prolonged exposure to aluminum-containing solutions and compounds, such as aluminum-containing phosphate binders.[165] It has also been described in adults.[177] Although the mechanisms for the entry of aluminum into the central nervous system (CNS) are poorly understood,[174] the aluminum content of brain gray matter of these patients has been found to be markedly elevated in comparison with controls.[6] It has mainly been found in the nerve cells of the cerebral cortex.[6] Neuropathologically, the brain shows cortical atrophy and stromal spongiosis.[190] The mechanisms associated with the pathogenesis of the neurotoxicity of aluminum are unknown.[174] The increased bioavailability of aluminum in chronic renal failure seems to be related to decreased urinary excretion and enhanced gastrointestinal aluminum uptake induced, in turn, by secondary hyperparathyroidism, which is common in infants and children with chronic renal failure. Aluminum in individuals with chronic renal failure is stored in bone tissue, from which it may be mobilized during intercurrent stress, thereby causing acute aluminum intoxication.

Clinical Description.

Usually, aluminum encephalopathy syndrome develops in children with chronic renal failure who have been exposed to aluminum for several years. Clinically, aluminum encephalopathy syndrome is closely similar to both uremic encephalopathy and dialysis dementia syndrome. Features are a progressive encephalopathy with arrest or regression of psychomotor development, disturbances of motor function (such as dysmetria, tremor, hypotonia, focal or generalized myoclonus), seizures, speech disturbances, and ultimately vegetative status. Seizures are usually generalized, but simple and complex partial seizures with secondary generalization have also been reported.[177] Subacute aluminum encephalopathy with loss of consciousness, myoclonic jerks, and status epilepticus leading to the exitus was related to the direct exposure of CNS to aluminum.[170] Computed tomography shows cortical atrophy. Electroencephalographic features, which evolve simultaneously with clinical features, consist of diffuse slowing of background activity with superimposed bursts of high-amplitude slow waves and multiple paroxysms of triphasic contoured waves, sharp waves, and complexes of spikes and slow waves.[103]

Diagnostic Evaluation.

The presence of typical clinical features in children with chronic renal failure who have been taking aluminum-containing phosphate binding gels or formulas suggests aluminum encephalopathy syndrome. Computed tomography showing cortical atrophy, presence of specific EEG features, and demonstration of high bone and plasma aluminum concentrations confirm the diagnosis. Aluminum encephalopathy syndrome has to be differentiated from uremic encephalopathy, which also causes mental retardation, myoclonus, and seizures. This differential diagnosis is very important because uremic encephalopathy promptly improves with dialysis, whereas aluminum encephalopathy syndrome does not in all cases. Electrolyte determinations may differentiate aluminum encephalopathy syndrome from

acute hypercalcemia, severe phosphate depletion, and other electrolyte imbalances that may complicate chronic renal failure. Finally, aluminum encephalopathy syndrome must be differentiated from the rare cases of aluminum intoxication in nonuremic patients.[102,174] Video-polymyographic-EEG recordings and EMG examinations are mandatory in the differential diagnosis of movement disorders, such as asterixis, tremor, and myoclonus, and other epileptic events.

Treatment.

Prompt discontinuation of the use of aluminum gels is indicated. Dramatic improvement in advanced stages has been achieved by aluminum chelation (deferoxamine). The combined use of deferoxamine and appropriately timed hemodialysis has been proposed in the rare patients presenting with severe acute aluminum intoxication.[147] Common antiepileptic drugs and especially benzodiazepines are effective in the treatment of myoclonus and seizures, but the same risks are encountered as in the treatment of uremic encephalopathy (see earlier discussion). Because the main cause of aluminum encephalopathy syndrome is gastrointestinal absorption of aluminum, infant diets should consist of low-phosphate formulas with the addition of calcium carbonate. Calcium citrate– and aluminum-containing antacids should be avoided.

Neurologic Complications of Uremia Treatment

Dialysis Dysequilibrium Syndrome

General Findings.

Dialysis dysequilibrium syndrome is an acute reversible neurologic syndrome caused by exacerbation of the neurologic manifestations of renal failure during a patient's first few dialysis maintenance treatments. Dialysis disequilibrium syndrome has been attributed to the “reverse urea effect” during rapid hemodialysis. Urea is believed to be cleared less rapidly from the brain than from the blood, producing an osmotic gradient and shift of extracellular water into the brain to cause cerebral edema.[115] Experimental data showed a reduced expression of urea transporter (UT-B) and increased expression of aquaporins in brain cells. Urea exit from astrocytes is therefore delayed during rapid removal of extracellular urea through fast dialysis. An osmotic driving force that promotes water entry into the cells is also favored by abundant expression of aquaporins.[203] Moreover, it has been demonstrated that cerebral edema may result from the generation of idiogenic osmoles in association with a decrease in intracellular pH of the cerebral cortex.

Clinical Description.

The symptoms of dialysis dysequilibrium syndrome are irritability, restlessness, headache, nausea, emesis, hypertension, blurred vision, epileptic seizures, muscular twitchings, fasciculations, asterixis, and confusion. Seizures usually are generalized tonic–clonic, and status epilepticus may also occur.[189] When delirium appears, it tends to persist for several days. Death from brainstem herniation has been reported in the past, while in more recent years only milder symptoms have been reported. After a general trend toward normalization, marked EEG changes may develop during dialysis, consisting of increased slow-wave activity, bursts of bilateral symmetric rhythmic slow waves, and increased photosensitivity.[185] Patterns of VEPs are exaggerated, with abnormal prolongation of P100;[57] BAER latencies are abnormal.[176] Computed tomography demonstrates cerebral edema. Brain magnetic resonance imaging (MRI) may show white matter changes in the posterior area mimicking a reversible posterior leukoencephalopathy syndrome (RPLS).[189] Central pontine and extrapontine myelinolysis has also been reported in children.[25]

Diagnostic Evaluation.

Diagnostic evaluation must exclude all other causes of irritability, headache, nausea, hypertension, muscular twitchings, fasciculations, asterixis, confusion, and seizures that can occur in patients on maintenance dialysis. Seizures are a key symptom. When seizures occur with various degrees of impairment of consciousness, headache, nausea and vomiting, hypertensive encephalopathy, intracranial hemorrhage, and subdural hematoma[127] should be investigated. Papilledema, focal neurologic signs, typical findings on computed tomography, and elevated opening pressure at lumbar puncture confirm the diagnosis of these conditions. When seizures are generalized or partial and are associated with irritability, headache, restlessness, or twitchings, special consideration must be given to disorders of electrolyte imbalance, including hyponatremia and hypernatremia (which in renal insufficiency may induce seizures more frequently than hyponatremia), hypocalcemia and hypercalcemia, hypophosphatemia, abrupt increase in blood pH (which can lower the serum concentration of ionized calcium), and nonketotic hyperosmolal coma in nondiabetic patients, which is caused by increasing levels of glucose after repeated peritoneal dialysis. Determination of plasma and urinary electrolyte concentration, glucose concentration, osmolality, volume, ADH levels, and presence of acidemia may aid in the differential diagnosis. Full neurophysiologic monitoring is useful to differentiate epileptic myoclonus and seizures from other, nonepileptic movement disorders and detect any sudden changes of central nervous system electrical activity during dialysis.

Treatment.

If a patient experiences seizures during dialysis, treatment must be discontinued immediately until vital signs have stabilized. Standard therapy of movement disorders and epileptic seizures may improve the patient's course but must be monitored carefully in renal failure (see earlier discussion of treatment of uremic encephalopathy). Hypocalcemic seizures may be controlled with calcium gluconate administration.

Dialysis Encephalopathy Syndrome

General Findings.

Dialysis encephalopathy syndrome has been described in patients receiving maintenance hemodialysis. The syndrome usually occurs in patients dialyzed for periods >3 years. It is considered to be the most dramatic manifestation of aluminum toxicity, and is caused by an increase in brain levels of aluminum secondary to a high content of this metal in the dialysis bath.[6] Its incidence has sharply decreased with the use of aluminum-free water.[4]

Clinical Description.

Presenting symptoms consist of dysarthria, apraxia, and slurred speech with stuttering and hesitation. The speech disorder is intensified during and immediately after dialysis and at first may be seen only during these periods. Cognitive disturbance usually occurs, and the EEG shows bursts of high-amplitude slow waves in the frontal regions. Within months, myoclonus, asterixis, movement dyspraxia, seizures, memory loss, personality changes, and psychosis develop.[78] In most cases, the disease progresses to apneic spells, tonic–clonic seizures, focal neurologic deficits, and death within months from sepsis or suicide.[6]

After a short and transient improvement, usually following dialysis, the EEG shows progressive abnormalities that become indistinguishable from those seen in aluminum encephalopathy syndrome (see earlier discussion).[185]

Diagnostic Evaluation.

Dysarthria, myoclonus, delirium, and seizures are possible symptoms of clinical conditions that may exist concomitantly with hemodialysis, such as acute hypercalcemia[173] and severe hypophosphatemia,[164] and these must be differentiated from dialysis encephalopathy syndrome. Video-polymyographic-EEG recordings and EMG examinations must be performed to differentiate epileptic myoclonus from other, nonepileptic movement disorders.[105] Water-soluble vitamin deficiency, especially pyridoxine deficiency (removed from blood during hemodialysis), should always be considered

in cases of drug-resistant seizures. Clinical and EEG features similar to those of dialysis encephalopathy syndrome have been described in patients not on dialysis who are receiving large quantities of aluminum salts.[187] The CSF is unremarkable. No distinct abnormalities have been found in brain at autopsy. In all these cases, only the history and laboratory investigations may aid in the differential diagnosis.

Treatment.

The presence of clinical and EEG evidence of dialysis encephalopathy syndrome is a clear indication for discontinuation of aluminum-containing phosphate binders (especially in infants with chronic renal failure) and initiation of chelation therapy. Dramatic improvement in advanced stages has been achieved by aluminum chelation (deferoxamine). Associated myoclonus responds well to clonazepam and diazepam, which are also able to improve speech disorders. Common antiepileptic drugs may be effective in the treatment of seizures, but as with other conditions of renal failure, special care must be taken. Phenytoin usually is used for tonic–clonic seizures. Because a relatively little amount is removed by hemodialysis, it can be given intravenously in loading doses to maintain a desired plasma concentration. Pyridoxine supplementation must be administered in cases of pyridoxine deficiency. Before initiating dialysis, avoidance of aluminum-containing formulas should be recommended. It is also mandatory to test for secondary hypoparathyroidism (frequent in children with chronic renal failure) and iron-deficiency anemia to minimize gastrointestinal absorption of aluminum and restrict dietary phosphate to prevent hyperphosphatemia. Finally, in patients undergoing maintenance dialysis, the aluminum concentration of the dialysate should be monitored periodically.

Endocrine Disorders

Epileptic seizures may occur in patients affected by many endocrine disorders and sometimes constitute the presenting symptom. Epileptic seizures may be caused directly by hormones (as in thyrotoxicosis) or indirectly by metabolic disequilibrium associated with hypoglycemia, hyperglycemia, or electrolyte imbalance (hyponatremia, hypomagnesemia, hypocalcemia), which causes an increase in neuronal excitability. Alternatively, as in the case of hypothalamic-pituitary tumors, epilepsy can result from a temporal lobe extension of the tumor or from the tumor itself (i.e., hypothalamic hamartoma). Finally, epilepsy and an endocrine disorder may both result from one genetic immunologic disease. In general, seizure control is obtained with correction of the endocrine disorder or the related metabolic disturbances. If not, administration of antiepileptic drugs may become necessary, with the associated risk for adverse effects on the endocrine system.

Endocrine disorders associated with epileptic seizures or epilepsy are summarized in Table 3.

Hypothalamic-Pituitary Disorders

Pituitary Disorders

Pituitary disorders can occasionally be associated with epileptic seizures, as in conditions of the posterior pituitary affecting water metabolism, such as SIADH, or in panhypopituitarism with hypoglycemia. Generalized epileptic seizures have been anecdotally reported as the presenting or unique symptom in a case of incidental pituitary macroadenomas or incidentalomas,[48] in a case of normotensive primary aldosteronism with hypopituitarism,[122] and in an infant with panhypopituitarism secondary to hypoplasia of the anterior pituitary.[55] Temporal lobe epilepsy resulting from pituitary adenoma with temporal extension has also been described. Temporal extension of an adenoma might disturb the uncinate gyrus and the medial surface of the temporal lobe, resulting in complex partial seizures.[27]

Table 3 Endocrine disorders associated with epileptic seizures or epilepsy

Hypothalamic-pituitary
  Pituitary neoplasms/hypoplasia
  Hypothalamic hamartoma/precocious puberty
  Inappropriate secretion of antidiuretic hormone (ADH) syndrome
Thyroid
  Primary hyperthyroidism/thyrotoxicosis
  Primary hypothyroidism/myxedema
  Hashimoto encephalopathy
Parathyroid
  Hypoparathyroidism
  Hyperparathyroidism
Pancreas
  Diabetes mellitus
Reproductive system
  Polycystic ovaries/hypogonadotropic hypogonadism

Hypothalamic Hamartoma

General Findings

Hypothalamic hamartomas (HHs) are nonneoplastic, heterotopic nodules resembling the normal gray matter of the hypothalamus. They mainly consist of mature neurons and rare large dysplastic neurons, intermingled with glial cells. Myelinated and unmyelinated fibers have been identified, and some of these connect to hypothalamic nuclei.[20] Mature and differentiated ectopic neurosecretory cells secreting luteinizing hormone–releasing hormone (LH-RH) have also been observed. Etiology of HHs is unknown. No genetic anomaly has been found, except for patients with Pallister-Hall syndrome (PHS).

The two main manifestations of HHs are central precocious puberty (CPP) and seizures, and the latter may be the predominant clinical symptom (see Chapter 250). Among 277 sporadic patients with HHs, 63% had CPP, 61% presented with seizures (of any type), and 25% had both CPP and seizures.[151] Typical seizures consist of brief stereotyped attacks of laughter, also known as gelastic seizures (GS) (see Chapter 53). Although a neocortical origin has been found in some cases, GS are pathognomonic of HHs.[36,151] The pathogenesis of the epileptic syndrome occurring in HHs is unknown. It has been suggested that it may result from a general dysgenetic process that includes cortical abnormalities. The size of the lesion and the secondary mechanical compression on hypothalamus and the mammillary bodies seem to play roles in generating seizures.[20] However, several pieces of evidence suggest that the source of GS is HHs per se. In fact, when associated with GS, HH tissues contain predominantly small GABAergic inhibitory neurons that exhibit intrinsic "pacemaker-like" behavior.[213] Moreover, the HH can have a pedunculated stalk or a sessile one. The latter is associated with epilepsy, whereas the former is associated only with precocious puberty. It appears that the epileptiform activity generated inside the hamartoma leads to clinical manifestations only when a sessile attachment to the hypothalamus allows its propagation to the diencephalon.

Clinical Description.

The characteristic epileptic syndrome occurring with HHs begins in infancy, even in the first days of life. Brief episodes of pleasant laughter or giggling last a few seconds, and at the beginning occur without loss of consciousness, recurring many times a day, with both diurnal and nocturnal attacks.[36] In the clinical course, GS are more frequently associated with alteration of consciousness and associated with autonomic phenomena, automatisms, epigastric auras, déjà vu, déjà vecu, and motor symptoms. Some patients may also show a pattern of symptomatic generalized epilepsy. Absence, tonic, atonic, and tonic–clonic seizures occur mimicking Lennox-Gastaut syndrome with intractable seizures, progressive cognitive impairment, and severe behavioral disturbances.[196] HHs may determine a less severe epileptic disorder. Indeed, only some cases progress to an epileptic encephalopathic picture, and cognitive disturbances may be mild or absent. Therefore, the severity of the epilepsy syndrome related to HHs may range from mild, drug-resistant epilepsy with a simple “pressure to laugh” in otherwise normal patients up to a catastrophic epileptic encephalopathy.[13,196] Pathogenetically, such an evolution has been related to the anatomic and physiologic connections of the hypothalamus to the thalamus and cortex.[182] Interictal EEG shows generalized and focal frontal or temporal spikes.[36] Neurophysiologic and clinical studies have demonstrated that when the hamartoma connects to the mamillary bodies, a secondary involvement of the temporal lobe is present, suggesting that the projection of the paroxysmal activity to the cortex is due to a specific pathway connecting the hypothalamus with the temporal lobe. By contrast, when the hamartoma connects to the medial hypothalamus, a frontal lobe epileptic activity is recorded. The existence of direct projections of several neuronal groups in the middle and posterior supramamillary hypothalamus to the frontal lobes (bilaterally) has been described, which could provide such a selective propagation of spike activity.[182]

Initially there are no significant EEG abnormalities detected during a gelastic seizure. Subsequently, generalized onset with low-voltage rhythmic fast activity, generalized suppression of background rhythms, or both, sometimes preceded by single or multiple generalized spike-and-wave complexes, are recorded.[36]

Diagnostic Evaluation.

Diagnosis of HH can be evoked in patients affected by gelastic epilepsy and/or PP. The presence on MRI of a nonprogressive, noncalcified, nonenhancing hypothalamic mass that appears isointense to gray matter on T1-weighted images, isointense to mildly hyperintense on proton density-weighted images, and often hyperintense on T2-weighted images confirms the diagnosis.[151] As the seizures become more complex with clinical features of secondary generalized epilepsy, background activity can show variable diffuse slowing, and interictal findings can include unilateral or bilateral temporal/frontal independent epileptiform discharges and/or irregular generalized slow spike-and-wave discharges. Ictally, diffuse nonlocalizing electrographic changes such as generalized low-voltage rhythmic fast activity (LVFA) and/or generalized suppression of background activity have been described. Intracranial studies can be misleading if the hypothalamic lesion is not sampled itself. Depth electrodes advanced into the lesion have revealed LVFA discharges well localized in the hamartoma during GS and more widely extended LVFA in atonic seizures.[151]

Treatment.

The therapeutic approach must consider the risk for death after attempted operative removal and the very slow-growing or nonprogressive nature of the hamartoma. The precocious sexual development can be controlled by treatment with LH-RH agonists, but epileptic seizures are usually resistant to antiepileptic drugs and deaths from status epilepticus have been reported.[36] However, focal seizures and tonic and atonic attacks are at best moderately controlled by antiepileptic drugs. Treatment with clonazepam and, more recently, lamotrigine has resulted in significant abatement of seizures. Epilepsy surgery may be considered when drop attacks occur.[36]

Long-lasting control of seizures can be achieved by complete removal, destruction, or disconnection of the hamartoma. The debate has therefore shifted to the best means of treatment with a variety of surgical approaches and the possibility of destruction of the lesion with radiofrequency probes or gamma-knife surgery. A transcallosal approach reaching the lesion from above through the third ventricle has been performed with low morbidity. At 1 year, 90% of cases are free or essentially free of all seizures. Marked behavioral improvement has been reported, and cognitive decline appears to stop. Dissection of the hamartoma from the wall of the third ventricle and infundibulum or mammillary bodies may be achieved in selected patients under direct vision. All forms of surgery can be associated with transient diabetes insipidus, but no other major endocrinologic or hypothalamic complications have emerged as hazards of these procedures. Destruction of the lesion by focused ionizing radiation (gamma knife) is an approach that does not require conventional surgery. Although the follow-up periods are short, early results suggest an excellent seizure response. Gamma knife has the lowest morbidity rate of all treatments with comparable seizure-free rates. Concerns exist about the long-term effects of radiation in the hypothalamic region. Overall, authors agree that the surgical approach must be tailored to the specific surgical anatomy of the hamartoma.[13]

Thyroid Disorders

Primary Hyperthyroidism

General Findings.

Studies of experimental animals and humans have provided evidence that thyroid hormones can lower seizure thresholds.[198] Epileptic EEG discharges have been found in many patients with *thyrotoxicosis*. Epileptic seizures associated with thyrotoxicosis have been considered an infrequent event: 9% of all admitted patients with thyrotoxicosis.[109] Nevertheless, epilepsy associated with thyrotoxicosis remains a possible infrequent event,[167,181] and thyrotoxicosis must be considered among the causes of adult-onset epileptic disorders.[121]

Thyrotoxicosis (or thyrotoxic crisis) is an uncommon but severe complication of hyperthyroidism that occurs in *Graves disease* (an autoimmune disorder associated with the HLA-DQA1*0501 allele and characterized by thyrotoxicosis and ophthalmopathy in the presence of autoantibodies to thyroglobulin, microsome, or thyroid peroxidase[30]) and *toxic multinodular goiter*, which is almost always precipitated by an intercurrent illness.[181] *Iatrogenic thyrotoxicosis* may occur after treatment of hypothyroidism.[109] The association between juvenile myoclonic epilepsy and Graves disease may be not fortuitous but rather an indication of a shared genetic immunologic etiology.[198]

Clinical Description.

Both generalized tonic–clonic and partial motor epileptic seizures (including visual-adversive and partial motor seizures with secondary generalization and prolonged postictal coma) associated with or followed by signs of hyperthyroidism (irritability, tachycardia, tremor, anxiety, confusional state) have been reported as presenting symptoms of thyrotoxicosis.[109,167] Juvenile myoclonic epilepsy has recently been reported in two unrelated patients with untreated Graves disease.[198] Typically, in these cases epilepsy begins during adolescence with characteristic clinical, laboratory, and ictal EEG findings; the latter consist of 3- to 3.5-Hz diffuse polyspikes-and-waves and spike-and-wave bursts. Often epilepsy in hyperthyroidism may be secondary to neurologic disorders such as stroke, Moyamoya disease, and superior sagittal sinus thrombosis induced by thyrotoxicosis rather than to hyperthyroidism per se.[116,168] Recurrent generalized seizures, preceded by an encephalopathy state, coinciding with relapses of the thyrotoxicosis have been reported in a patient. EEG showed bilateral slowing of activity. Characteristically, antithyroid drug treatment was able to control symptoms. Convulsive[126] and nonconvulsive status epilepticus[132] may also represent the first manifestation of thyrotoxicosis. In this context, status epilepticus is often resistant to conventional antiepileptic drugs.[181] The situation is obviously life threatening, requiring vigorous and comprehensive management.

Interictal EEG findings of thyrotoxicosis consist of diffuse slowing, sharp discharges, and occasional bilateral triphasic waves.[167]

Diagnostic Evaluation.

Although seizures are not especially frequent in thyrotoxicosis, thyroid hormone levels should be evaluated during diagnostic investigation at the onset of an epileptic disease.

Differential diagnosis must exclude other metabolic (nonketotic hyperosmolal state) or endocrine (hypoparathyroidism) disorders that may significantly increase focal cerebral excitation.

Treatment.

Treatment of thyrotoxic crisis should begin as soon as the diagnosis is suspected. The aim is to correct both severe thyrotoxicosis and any precipitating intercurrent illness and to provide general supportive therapy. Effective therapy of the endocrine disorder and epileptic seizures comprises administration of antithyroid drugs (propylthiouracil, methimazole, or both), dialysis, plasmapheresis, hemoperfusion (to lower circulating levels of thyroid hormones), administration of glucocorticoids and adrenergic antagonists, supportive therapy (intravenous administration of glucose, saline, vitamin B complex, and sedatives), and correction of hyperpyrexia and heart failure.[181] Common antiepileptic drugs may be useful in controlling seizures, but careful evaluation of other organ systems is required to estimate the risk for adverse effects of antiepileptic therapy.

Primary Hypothyroidism

General Findings.

Primary hypothyroidism is characterized by the combination of low levels of thyroid hormone and high levels of thyroid-stimulating hormone (TSH). Possible causes are Hashimoto thyroiditis (see later discussion), treatment with radioiodine, thyroidectomy, drugs, and thyroid lymphoma; primary hypothyroidism may also be congenital. Decreased TSH resulting from tumor or infiltrative disease of the pituitary causes secondary hypothyroidism.[125] Decreased thyrotropin-releasing hormone (TRH) resulting from hypothalamic tumor causes tertiary hypothyroidism.[125] The most important consequence of *primary congenital hypothyroidism* is impaired brain development, which, if not treated, leads to severe mental retardation. Psychotic manifestations and terminal myxedematous coma are the most common central nervous system manifestations in *primary acquired hypothyroidism*; epileptic seizures only rarely occur. In these cases, convulsions may be the presenting symptom or may occur in untreated cases of myxedema of long duration.[43]

A paroxysmal triad consisting of high fever, seizures, and coma with a flulike prodrome can rarely occur in patients with scleromyxedema and is termed “dermato-neuro” syndrome. It has been found that the incidence of febrile convulsions among patients with congenital hypothyroidism under therapy with L-thyroxine since the age of 1 month was significantly lower than that of normal control children. It seems therefore that patients with congenital hypothyroidism on regular L-thyroxine replacement are less prone to experience febrile convulsions.[23]

Although epileptic seizures do not usually occur in *primary hypothyroidism*, experimental data demonstrated that the number of stimuli necessary to produce lidocaine-kindling seizures (i.e., tonic attacks followed by tonic–clonic movements) in congenital hypothyroid rats was significantly lower than in the control group for both ages.[157] Moreover, it is well known that early-onset hypothyroidism produces audiogenic seizure susceptibility in rodents, in which TR α1 and TR ß thyroid hormone receptors seem to play a role.[150]

Clinical Description.

In primary acquired hypothyroidism, generalized tonic–clonic seizures and EEG findings of low-voltage slow waves and dysrhythmic background suggest a nonspecific encephalopathy. Seizures may be characterized by an unexplained prolonged postictal recovery.[43]

Diagnostic Evaluation.

Although hypothyroidism is an uncommon cause of epilepsy, thyroid assessment must be considered in the etiologic diagnosis of cryptogenic generalized seizures, especially when followed by a prolonged postictal recovery. Differential diagnosis should exclude other metabolic or endocrine disorders. However, coarse facies, bradycardia, dry skin, and hair loss (when present) are clearly suggestive of hypothyroidism.

Treatment.

Treatment with L-thyroxine leads to normalization of the endocrine disorder and abatement of epilepsy. Therefore, antiepileptic drug treatment seems to be unnecessary. However, it should be remembered that rapid correction of a hypothyroid state during administration of thyroxine might constitute a risk for thyrotoxicosis, with epileptic seizures as a consequence. In fact, a causal relationship has been presumed between high-dosage thyroxine therapy and a nonconvulsive status epilepticus characterized by absence seizures with eyelid and distal myoclonic twitchings, triggered by spontaneous or passive eye closure and generalized convulsive seizures.[109] These seizures appeared to respond to valproate. Thyroxine-induced epilepsy with hypermotor seizures was also controlled by reducing thyroxine doses.[24]

Hashimoto Encephalopathy

General Findings.

Hashimoto encephalopathy (HE) is a steroid-responsive neurologic disorder associated with antithyroid antibodies. Frequently, epileptic seizures are a presenting symptom.[28,83,98] The term "Hashimoto encephalopathy" is not considered appropriate by some authors because the thyroid condition has not been proved to have a direct relationship with the neurologic process, and the role of thyroid antibodies in the pathogenesis of encephalopathy has not been defined. The term "autoimmune encephalopathy associated with Hashimoto thyroiditis" is considered a more accurate definition. "Nonvasculitic autoimmune encephalopathy" and "corticosteroid-responsive encephalopathy associated with Hashimoto thyroiditis" are also used. In fact, although in some patients thyroiditis is diagnosed before Hashimoto encephalopathy, the disease may affect euthyroid patients with normal levels of thyroid hormones and TSH. At present, HE is suspected whenever symptoms of acute or subacute encephalopathy or myelopathy are associated with high serum levels of antithyroid antibodies.[28]

Several theories have been proposed to explain the pathogenesis of HE. They include autoimmune vasculitis, autoimmune reaction to common antigens between the thyroid gland and the CNS, cerebral hypoperfusion, and toxic effects of thyrotropin-releasing hormone. The presence of antithyroid antibodies in CSF of patients with encephalopathy and myelopathy associated with Hashimoto disease was reported, and indirect evidence was provided to suggest intrathecal synthesis of antithyroid antibodies. Therefore, it has been proposed that the diagnosis of Hashimoto encephalopathy should be based on this CSF finding.[76,83] Specific high

reactivity against human α-enolase has been found to be in patients with Hashimoto encephalopathy. Some authors suggest that the detection of an anti–α-enolase antibody is useful for defining encephalopathy-related pathology.[153]

Postmortem examination in a patient with Hashimoto encephalopathy complicated by fatal status epilepticus demonstrated mild perivascular lymphocytic infiltration throughout the brain and leptomeninges with diffuse gliosis of gray matter in the cortex, basal ganglia, thalamus, and hippocampus.[66]

Clinical Description.

The clinical picture of Hashimoto encephalopathy with epilepsy includes generalized and partial seizures as distinguishing features. Myoclonus, tremor, choreic movements, central nystagmus, gait disturbance and ataxia, and hallucinations may be present, as well as transient aphasia or somnolence, headache, fatigue, confusion, and unilateral sensory loss. Strokelike episodes, palatal tremor, musical hallucination, and cerebellar dysfunction have also been reported in some cases. The symptoms may improve spontaneously or after corticosteroid therapy. Two distinct clinical forms of HE have been suggested: (a) a *vasculitic type* characterized by multiple strokelike episodes and (b) a *diffuse progressive* type characterized by dementia and psychiatric symptoms. Both forms may be associated with tremor, seizures, stupor, and myoclonus. The myoclonic syndrome may be so prominent that Hashimoto encephalopathy has also been defined as *Hashimoto myoclonic encephalopathy*.[28,83]

Recurrent generalized convulsive status epilepticus and recurrent generalized absence status with blinking and/or twitching resistant to antiepileptic medications but successfully treated with corticosteroids have been reported.[139]

The interictal EEG findings are also variable. Most commonly the EEG shows generalized abnormalities including generalized slow wave activity, slow posterior background, and frontal intermittent rhythmic delta activity (FIRDA). Triphasic waves and focal slow waves have been described in some patients. The EEG findings seem to subside with the improvement of the encephalopathy, although the EEG tends to lag behind the clinical improvement.

Ictal recordings showed bitemporal discharges and focal mesial-basal temporal seizure discharges. In the latter patient, the ictal seizure semiology, with gradual onset and slow secondary generalization, was consistent with a temporal onset.[16,83,98,205] Ghika-Schmid et al. considered the clonazepam-induced synchronous paroxysmal monomorphic rhythmic delta activity associated with transient myoclonus recorded in a patient as a peculiar finding and suggested caution in the administration of antiepileptic drugs.[83]

Magnetic resonance imaging findings vary. A review of MRI findings on 82 patients found abnormalities in 49%. Findings are nonspecific and include subcortical white matter abnormality and T2 cortical signal abnormalities and are reversible with recovery or after corticosteroid therapy.

Cerebral angiography has been reported to be normal; in contrast, cerebral blood flow single-photon emission computed tomography (SPECT) scans have shown areas of reduced perfusion in cortical areas and basal ganglia.

Brain biopsy findings were normal in one patient. Patchy myelin pallor, scant perivascular chronic inflammation, mild gliosis, and lymphocytic infiltration of the venous brain system have been reported.[75,152]

Diagnostic Evaluation.

An adult-onset encephalopathy of unknown origin with focal neurologic signs, myoclonus, drug-resistant epileptic seizures, and mental impairment is strongly suggestive of Hashimoto thyroiditis. Therefore, screening for antithyroid antibodies should be performed. Viral and bacterial infections must be excluded. The CSF protein concentrations are high in 78% of patients. Mild lymphocytic pleocytosis may be present occasionally. Differential diagnosis between movement disorders (tremor and myoclonus) and epilepsy requires video-polygraphic-EEG recordings and EMG examination. EEG anomalies are found in 98% of patients. The progressive chronic evolution associated with seizures, myoclonus, and strokelike episodes[98] may cause problems in the differential diagnosis of mitochondrial encephalopathy. Finally, possible kidney disorders must be investigated (see section on renal failure).

Treatment.

Although some patients have been found to be corticosteroid nonresponsive, both high doses of oral prednisone and shorter courses of intravenous methylprednisolone were reported to be very effective in controlling HE symptoms.[83,98] Azathioprine, methotrexate, cyclophosphamide and hydroxychloroquine sulfate, plasmapheresis, and intravenous immunoglobulin have been used with clinical benefit. Spontaneous improvement without corticosteroid therapy occurred in some cases.[75] Because of this rapid seizure control, antiepileptic drugs are not usually given.

Parathyroid Disorders

Hyperparathyroidism

Hyperparathyroidism, characterized by hypercalcemia and elevated levels of parathyroid hormone (PTH), is not usually associated with epileptic seizures. However, a *grand mal* epileptic seizure associated with psychiatric symptoms has been reported anecdotally in patients with hypercalcemia secondary to neoplastic hyperparathyroidism and basal ganglia calcifications.[70]

Hypoparathyroidism

General Findings.

Hypoparathyroidism is a clinical disorder characterized by hypocalcemia and hyperphosphatemia. It manifests when PTH secreted from the parathyroid glands is insufficient to maintain normal extracellular fluid calcium concentrations or, less commonly, when PTH is unable to function optimally in target tissues, despite adequate circulating levels. Deficiency of PTH may occur following thyroidectomy or other surgical procedures involving the neck. Infections, glandular infiltrations by granulomatous processes, heavy metals, or more commonly autoimmune disorders may cause deficiency of PTH. Congenital parathyroid hypoplasia or agenesis causes congenital hypoparathyroidism. Autosomal-dominant and autosomal-recessive familial idiopathic hypothyroidism have also been identified. Hypocalcemia is the characteristic biologic consequence of hypoparathyroidism. Because low calcium levels result in hyperexcitability of neural membranes, the prominent clinical neurologic manifestations of hypoparathyroidism are those related to hypocalcemia with neuromuscular irritability, perioral paresthesias, tingling of the fingers and toes, and tetany. Generalized tonic–clonic seizures and laryngeal spasm also occur. In a chronic setting, hypocalcemia can be asymptomatic. Alternatively, mild neuromuscular irritability, calcification of the basal ganglia, extrapyramidal disorders, cataracts, alopecia, abnormal dentition, mental retardation, or behavior disorders may be present. From a biochemical point of view, hypoparathyroidism is mainly characterized by hypocalcemia and hyperphosphatemia with normal renal function. Serum levels of PTH are low, except in the setting of PTH resistance, in which case levels are high-normal or elevated. Serum levels of 1,25-dihydroxyvitamin D are usually low or low-normal. The 24-hour urinary excretion of calcium is decreased. Nephrogenous cAMP excretion is low, whereas renal tubular reabsorption of phosphorus is elevated.

DiGeorge syndrome, 10p deletion syndrome, Hallermann-Streiff syndrome, and familial nephrosis with nerve deafness constitute different genetic syndromes with congenital hypoparathyroidism. In particular, hypoparathyroidism with short stature, mental retardation, and seizures (or Sanjad-Sakati syndrome) is characterized by congenital hypoparathyroidism, growth and mental retardation, and seizures as a prominent finding. Recent studies demonstrated that both Sanjad-Sakati syndrome and the autosomal recessive Kenny-Caffey syndrome are allelic variants caused by mutations in the *TBCE* gene.[160]

Anecdotal reports describe the association between idiopathic hypoparathyroidism and systemic lupus erythematosus[82] or subacute sclerosing panencephalitis,[54] in which the authors suggest a common pathogenetic mechanism. In these reports, epileptic seizures occurred in the period of idiopathic hypoparathyroidism.

Here we present data regarding epileptic seizures in hypoparathyroidism occurring after the neonatal period.

Clinical Description.

Typically, clinical signs of hypoparathyroidism include tetany, epileptic seizures, and, when basal ganglia calcifications are present, hemichorea, choreoathetosis, and parkinsonism.[146] Epileptic seizures may occur at any age and are usually generalized tonic–clonic with loss of consciousness.[54,81,82] Nonconvulsive status epilepticus has also been described in this group of patients.[118]

Seizures may be the presenting symptom, preceding other signs of hypocalcemia such as chorea and tetany. Normally, tetany develops after calcium levels decline further. Generalized convulsive epileptic seizures may also be the presenting symptom in elderly patients with hypoparathyroidism, in association with confusion and then with signs of tetany. In fact, iatrogenic hypoparathyroidism needs to be considered in the differential diagnosis of adult-onset, generalized tonic–clonic seizures even if the thyroidectomy was performed years earlier.[145] Several types of partial motor seizures, including jacksonian seizures, may also be observed. If not treated, the outcome of these conditions may be very severe. Among the members of a familial idiopathic hypoparathyroidism, some untreated members died in infancy because of convulsions. Paroxysmal kinesigenic choreoathetosis and convulsions occurring in clusters at age 2.5 months have been observed in a child with idiopathic hypothyroidism. The clinical picture was indistinguishable from that of infantile convulsions and choreoathetosis syndrome.[96] Reported EEG findings show irregular high-voltage delta activity that is increased on hyperventilation. Paroxysmal abnormalities may also occur during wakefulness and sleep.[111]

Diagnostic Evaluation.

Hypoparathyroidism with hypocalcemia as a cause of epileptic seizures should be considered and investigated in patients of any age. The condition can be treated successfully, whereas if it is untreated, it may be fatal in infants. Tetany, generalized epileptic seizures, and movement disorders may occur at the same time in hypocalcemic states, posing problems of differential diagnosis. Differential diagnosis of partial epileptic seizures and hemitetanic carpopedal spasm may be difficult, as may be the differential diagnosis of reflex epilepsy and paroxysmal kinesigenic choreoathetosis associated with hypoparathyroidism.[29] Finally, the differential diagnosis of primary hypomagnesemia with secondary hypocalcemia must be considered (see section on electrolyte disorders). In all these cases, correct diagnosis requires direct observation of the motor phenomena and ictal EEG investigation during hyperventilation maneuvers. Computed tomography and magnetic resonance imaging of the brain are mandatory to investigate basal ganglia lesions.

Treatment.

The aim of therapy in all hypoparathyroid states is to restore serum calcium to levels sufficient to alleviate symptoms of acute hypocalcemia and prevent the complications of chronic hypocalcemia and hypercalcemia. The main pharmacologic agents available are calcium and vitamin D preparations. Neurologic findings disappear on normalization of calcium levels with calcium supplementation and vitamin D therapy in all cases, including those with extrapyramidal signs and basal ganglia calcifications. Magnesium replacement should also be considered routinely in patients with hypocalcemia because hypomagnesemia induces functional hypoparathyroidism. When antiepileptic drugs are required, it must be emphasized that they may lower circulating calcium concentrations. Regular monitoring of plasma calcium levels is recommended.

Disorders of the Pancreas

Diabetes Mellitus

The most important disease of the pancreas associated with epileptic seizures is diabetes mellitus. Seizures may be induced in diabetes mellitus during nonketotic hyperglycemia or during hypoglycemia resulting from iatrogenic hyperinsulinism; in ketotic hyperglycemia, epileptic seizures are rare.

Nonketotic Hyperglycemia

General Findings.

Seizures associated with nonketotic hyperglycemia were first reported in 1965.[133] Many other subsequent reports confirmed the occurrence of seizures in nonketotic hyperglycemia. Cases in non–insulin-dependent diabetes mellitus may exhibit a spectrum from asymptomatic hyperglycemia without ketosis (which may be clinically asymptomatic for months or years[90]) to hyperosmolal nonketotic diabetic coma (representing the extreme end of a biochemical continuum). Hyperosmolar nonketotic diabetic coma is associated with a high mortality in adults (range, 20%–70%) and children, but it is more common in the elderly and rarer in children.[208] Diabetes is often detected before severe hyperosmolality develops. Neurologic manifestations such as seizures, focal neurologic signs (usually postictal), myoclonic twitches, nystagmus, and meningeal signs often provide the first clinical clues to the presence of nonketotic hyperglycemia.[133] Age at onset of nonketotic hyperglycemia ranges between 48 and 72 years. Epileptic seizures have been rarely reported in juvenile nonketotic hyperglycemia.[179] As a rule, seizures occur when hyperglycemia is not severe and osmolality is normal or only slightly increased, with normal to moderately decreased sodium levels.[191] In this phase, patients are usually alert. If diabetes mellitus is not treated, however, hyperosmolality with progressive impairment of consciousness develops while seizures stop. The pathogenetic mechanism of the association between hyperglycemia and seizures is still debated. Most authors attribute the partial seizures to a preexisting structural lesion activated by hyperosmolality and hyperglycemia.[56,133] An entirely metabolic cause of epilepsy, such as hypertonicity or hyperglycemia, appears unlikely because in diabetic ketoacidosis partial seizures are rare. However, experimental studies demonstrated that susceptibility to clonic and tonic–clonic flurothyl-induced seizures positively correlates with blood glucose concentrations and that the increased glucose concentration is associated with proconvulsant effects.

Similarly, in the in vitro experiments, epileptiform activity was promoted by increased and suppressed by decreased glucose concentrations. Therefore, extracellular glucose itself has proconvulsant activity even without a previous focal lesion.[186] Hyperglycemia may precipitate seizures by lowering γ-aminobutyric acid levels, resulting in a lower seizure threshold. Moreover, the parietal lobe seems to play a role in epilepsia partialis continua, which is often associated with nonketotic hyperglycemia. Ictal SPECT studies in humans[104] and experimental studies, which found that diabetic hyperglycemic animals have more severe neuronal necrosis in the parietal cortex than do normoglycemic animals,[130] corroborate that hypothesis. The apparently protective effect of ketoacidosis may be

attributed to an increase in GABA bioavailability secondary to acidosis, which is known to increase glutamic acid decarboxylase activity.[56,94]

Clinical Description.

Seizures occur in about 25% of patients and are the chief initial manifestation in 6%.[94] Seizures are most often partial motor seizures, occurring in 75% to 86% of cases.[94] The seizures are frequent and repetitive and are often followed by transient postictal paralysis.[90] Occipital visual and adversive seizures have been described[92] and have been considered to be a relatively common early manifestation of nonketotic hyperglycemia. Typical jacksonian seizures have also been reported.[97] Epilepsia partialis continua has been described in some cases as the initial symptom of nonketotic hyperglycemia.[56,99,179] Contrary to data in the literature, in some of these cases epilepsia partialis continua could not be attributed to any structural cerebral lesion but seemed to be caused solely by metabolic dysfunction; results of neuroimaging were normal.[56] Nonconvulsive status epilepticus of frontal origin has also been observed.[113,201] Generalized tonic–clonic seizures have been described less frequently.[94] Some patients have reflex or posture-induced epileptic seizures.[99,207] Such seizures are relatively rare and have been defined as kinesigenic seizures[99] or fencing-posture seizures.[207] Characteristically, the seizures are partial, simple, or complex in type, last <5 minutes, and appear within seconds after onset of the triggering maneuver. This maneuver may consist of passive or active elevation of an arm or leg or walking. Seizures are followed by a refractory period during which no further seizures can be elicited.[207] Gaze-evoked sensory visual occipital seizures have been described in an anecdotal case.[67] Ictal stereotypic visual experiences consist of flashing lights followed by formed objects or unfamiliar human faces and may be consistently elicited by having the patient look to one side. Usually, the EEG is normal in uncomplicated diabetes. Focal EEG abnormalities have been found only in nonketotic hyperglycemia, related to an underlying focal cortical lesion, likely vascular in nature, as a consequence of hyperglycemia and hyperosmolarity.[112,133]

Diagnostic Evaluation.

Patients with partial seizures, fencing-posture seizures, and even epilepsia partialis continua without any detectable cause and with normal findings on neuroimaging examinations should be investigated for diabetes mellitus. Consequently, it is very important to check glucose levels in all patients with seizures, especially if they are elderly, to detect the early manifestations of nonketotic hyperglycemia associated with mild or minimal hyperosmolality. In cases of occipital seizures, celiac disease must be excluded (see section on gastrointestinal diseases). Of course, neuroimaging investigations must be performed in patients with partial seizures and epilepsia partialis continua to detect more frequent causes, such as cerebral tumor, infarction, encephalitis, brain malformations, and abscess. CT scans in cases of nonketotic hyperglycemia–related seizures often fail to reveal relevant focal cerebral disease. Hyperintensities in T_2 and fluid attenuated inversion recovery (FLAIR) related to seizure activity have frequently been seen in the cortices. Transient T_2 and FLAIR subcortical hypointensity with or without abnormalities in the overlying cortex in the setting of partial status epilepticus associated with NKH was reported in three patients. The mechanisms of T_2 and FLAIR hypointensities are unclear. These changes may be due to an accumulation of free radicals and iron deposition, as has been described in early cortical ischemia. The decreased N-acetyl-aspartate in the same region observed in some patients suggests reduced vital neuronal tissue.[56,188]

Treatment.

As long as biochemical disturbances remain uncorrected, the seizures are refractory to antiepileptic drug therapy. Patients become seizure free after administration of insulin and rehydration, and they remain seizure free while the diabetes mellitus is controlled. Moreover, patients who receive prompt treatment, before nonketotic hyperglycemic coma develops, have a better prognosis. If antiepileptic drugs are used for seizures, it should be noted that plasma free fractions of valproate are increased in diabetes mellitus, and phenytoin should be avoided because it inhibits insulin secretion and may aggravate hyperglycemia and nonketotic hyperglycemia, precipitating diabetic ketoacidosis.[94]

Diabetic Hypoglycemia

General Findings.

Diabetic hypoglycemia is a common problem in adults and children with diabetes who are treated with insulin and other oral hypoglycemic agents.[123]

Nondiabetic hypoglycemia may have many causes, such as alcoholism, sepsis, fasting, terminal neoplasms, and insulin-secreting neoplasms. There are also anecdotal reports of patients affected by gastroenteritis with diarrhea and dehydration, hypoparathyroidism, and adrenocortical insufficiency.[81,123]

Clinical Description.

Initial clinical symptoms of hypoglycemia are caused by excessive adrenergic activity; patients may be dizzy, tremulous, anxious, and profusely sweating. Hypotonia, motor restlessness, and generalized seizures appear later. Confusion, bizarre behavior, obtundation, stupor, or coma occur in more severe degrees of hypoglycemia. At times, for unknown reasons, the neurologic deficits are of a focal nature, producing partial motor epileptic seizures, focal sensory deficit, and hemiplegia with or without dysphasia.[79,123] Some authors[123,210] have suggested that several mechanisms, including selective sensitivity of neurotransmitters, selective neuronal vulnerability, and loss of autoregulation of cerebral blood flow leading to vasospasm are involved in hypoglycemia associated with focal neurologic deficits.

Hypoglycemic seizures occur in 10% to 20% of adults and more frequently in children.[107] Usually, seizures are generalized, tonic, and tonic–clonic in type. Partial seizures typically occur in adults.[79] There are only two reports of nocturnal partial seizures in children,[123,210] one of them with transient postictal hemiparesis (Todd paralysis).[123] It is well known that unrecognized nocturnal hypoglycemic events are frequent in diabetics, with blood glucose levels returning to normal by morning (Somogyi effect). Therefore, unrecognized nocturnal hypoglycemic seizures may occur in patients with no previous history of fits and hypoglycemic symptoms during waking hours.[123] It appears that severe hypoglycemic events mainly affect the youngest patients and boys (the latter of all ages) rather than adolescents girls, who mainly suffer from ketoacidosis.[171] In this context, Strudwick et al.[197] investigated whether severe hypoglycemic episodes in young children with early-onset type 1 diabetes (T1DM) were associated with subsequent abnormalities in cognitive status. They found that there was no clear evidence that episodes of seizure or coma, even those occurring in very early childhood, resulted in broad cognitive dysfunction, nor was there evidence of specific memory difficulties at the time of testing in children and adolescents with early-onset T1DM.

From a pathogenetic point of view, elegant experimental studies demonstrated that insulin doses of 8 IU/kg were able to induce seizures in 100% of animals and that insulin-induced hypoglycemic convulsions could be mediated by serotoninergic, dopaminergic, and excitatory amino acid pathways.[15]

Interictal EEG findings show different degrees of generalized slowing of background activity, exaggerated response to hyperventilation, increasing of preexisting epileptiform abnormalities, and/or appearance of paroxysmal patterns, such as 3-Hz spike-and-wave discharges or focal abnormalities.[185,192] Blood sugar levels of 50 to 80 mg/dL are associated with slowing of background activity and appearance of diffuse theta activity. At lower glucose levels, EEG shows intermittent bursts of bisynchronous slow waves.[185] Electroencephalographic abnormalities are more frequent in hypoglycemic children,

especially younger ones, and in the case of repeated severe hypoglycemic episodes.[192] Usually, these abnormalities disappear rapidly when blood sugar levels return to normal levels, but they may persist after more severe and prolonged hypoglycemic events.[123] The pathogenesis of these EEG abnormalities is unknown. Repeated hypoglycemic episodes alone do not seem to be the major factor in causing EEG abnormalities, and it has been hypothesized that a diabetic encephalopathy caused by microvascular lesions may be involved.[69]

Diagnostic Evaluation.

Nocturnal generalized or partial seizures in diabetic patients should be strongly considered as evidence of possible unrecognized insulin-induced hypoglycemia. It has been postulated that these seizures are more common than generally thought and that they may be a presenting symptom of diabetes mellitus.[123] Because such seizures are not symptomatic of a brain lesion and because results of computed tomography were normal in all patients,[79,123] seizures could mistakenly be diagnosed as idiopathic epilepsy, leading to unnecessary treatment with antiepileptic drugs, which must be administered with special care to diabetic patients (see section on nonketotic hyperglycemia). Because of its characteristic pattern, the EEG may aid significantly in the diagnosis. Otherwise, laboratory and clinical investigations are strongly recommended to rule out all other causes of hypoglycemia, especially neoplasms secreting insulin.

Treatment.

Reducing the daily dose of insulin and other oral hypoglycemic agents is strongly advised because this is sufficient to prevent hypoglycemia. Antiepileptic drugs should not be considered as elective therapy and must be monitored closely, and it should be remembered that various drugs interact with insulin and other hypoglycemic agents, such as phenothiazine, aspirin, phenylbutazone, sulfa drugs, haloperidol, propranolol, and lithium.

Reproductive Endocrine Disorders

Epileptic seizures as a symptom of reproductive endocrine disorders are problematic. Although there is evidence that reproductive endocrine disorders (especially hypogonadotropic hypogonadism with infertility, hyperprolactinemia, and polycystic ovarian syndrome) and epilepsy (especially temporal lobe epilepsy) frequently occur together, the pathogenesis is controversial.[101,214] Experimental evidence that the temporal lobe modulates sexual, reproductive, and neuroendocrine functions has been obtained in animals, and anatomic-functional pathways connecting the amygdala and hypothalamus have also been defined.[100] Thus, in temporal lobe epilepsy associated with reproductive endocrine disorders, altered impulses arising as epileptiform discharges from the amygdala have been postulated to disrupt normal secretion of gonadotropins and prolactin. In this context, endocrine disorders can be considered as secondary to temporal lobe epilepsy, and so they are beyond the scope of this chapter. However, because experimental animal and human clinical evidence suggests that estrogen and testosterone may precipitate epileptic seizures, and because there are many patients who have temporal lobe epilepsy and reproductive endocrine disorders without taking antiepileptic drugs, it is possible that the presence of a reproductive endocrine disorder may favor the development of temporal lobe epilepsy.[101]

Finally, because of the frequent familial occurrence, a possible contribution of genetic factors to the development of both temporal lobe epilepsy and reproductive endocrine disorders has been hypothesized.[101] A relationship between the type of endocrine disorder and the laterality of temporal epileptiform EEG discharges in women with temporal lobe epilepsy occurs, suggesting the existence of a lateralized asymmetry in cerebral influences on reproductive endocrine function.[100]

Gastrointestinal Diseases

The relationship between epilepsy and gastrointestinal diseases is a very intriguing problem. Apart from vomiting, which may be a common symptom of either gastrointestinal illness or neurologic disturbances such as migraine, epilepsy, increased intracranial pressure, and metabolic disorders, epilepsy and epileptic seizures may be the presenting symptom in some gastrointestinal diseases. Some authors have reported seizures associated with gastroesophageal reflux and suggested that it could be a part of the autonomic dysfunction that accompanies temporal lobe seizures. Afebrile partial or generalized seizures as a presenting symptom have been reported in children with mild gastroenteritis.[119] Generalized tonic–clonic seizures are nearly the most common extraintestinal manifestation of shigellosis.[46] The reported incidence ranges from 12% to 45%.[87]

Epilepsy and epileptic seizures may be a relevant symptom in celiac disease and orthotopic liver transplantation.

Celiac Disease

General Findings

Celiac disease (CD) is characterized by permanent gluten intolerance. Clinically, the “classical or typical” form appears in the first 2 years of life with diarrhea, weight loss, dystrophic appearance, and anorexia. Irritability and vomiting occur in one third of patients. On the other hand, CD may be silent, latent, or potential. These “atypical” forms are more frequent in children older than 2 years and may present with extraintestinal features such as dermatitis herpetiformis and dental enamel defects. Neurologic disorders have been extensively observed in patients with CD. Among them, epilepsy is the most frequent, and its prevalence in CD patients has been estimated to be between 1.2% and 5%. In 7% of newly diagnosed CD patients, neurologic disorders may be the presenting symptoms of the disease, especially in the case of silent and latent CD.[58,67,88,136] Epilepsy as a presenting symptom of celiac disease has also been reported.[88]

In the case of epilepsy and CD, three groups of patients have been identified: (a) patients with celiac disease, epilepsy, and cerebral calcifications (CEC), or “typical form”; (b) patients with celiac disease and epilepsy without cerebral calcifications; and (c) patients with celiac disease and cerebral calcifications without epilepsy. The latter two groups are considered “atypical forms.” There is a fourth group of patients with epilepsy and cerebral calcifications without celiac disease, who are believed to be affected by a latent or silent form of celiac disease.[87]

The *CEC syndrome* was first hypothesized in 1988 and then defined in 1992.[86,88] The majority of patients reported in the literature came from Italy, Spain, and Argentina.[87] Fewer patients have been reported in Australia, Canada, Israel, and Sweden. On the other hand, patients from outside Italy do not have an Italian origin. These data demonstrate that this syndrome, although most widespread in Italy, is generally found all over the world. The Italian diet is rich in gluten, but there may be other reasons for the reported high incidence of CEC in the Italian population, such as the particular interest in this condition in Italy. Whether the association between CD and epilepsy and cerebral calcifications is merely a coincidence or a genetic condition, or whether epilepsy and/or cerebral calcifications are a consequence of an untreated CD, still has to be demonstrated. On one hand, clinical and histopathologic findings, which seem to be the expression of vascular calcified malformation instead of the inflammatory lesion, of CEC syndrome are similar to those found in Sturge-Weber syndrome.[202] On the other hand, the high number of cases reported in the literature and the much higher-than-expected frequency of CD (77.5% of cases in the series of the Italian Working Group on Celiac Disease and Epilepsy[88]) in patients with cerebral calcifications and epilepsy, the progressive growth of cerebral calcifications or their late occurrence during evolution before the adoption of a gluten-free diet,[5,44] and the increasing prevalence with age of epilepsy and cerebral calcifications in patients with undiagnosed CD (from 0.79% at mean age of 5.9 years to 3.5% at mean age of 10 years[206]) lead us to consider that the two conditions are related. Epilepsy and cerebral calcifications might be the consequence of an autoimmune disorder affecting the central nervous system triggered by gliadin in predisposed subjects (HLA phenotype) and originating from the jejunal mucosa. In fact, it has been suggested that an altered expression of jejunal mucosa-activated circulating T cells, secreted cytokines, and tissue transglutaminase may initiate an immune response in the CNS tissue and might play a pathogenetic key role in seizures and cerebral calcifications in these patients.[85]

Concerning the genetic predisposition, CD is strongly associated with HLA class II genes. HLA-DQ2 was found in 90% of CD patients and HLA-DQ8 in 10% of cases. Another association with CD is the DR53 heterodimer, which seems to have affinity with gliadin-A peptides. In a minor percentage of patients, DQ2 is not present and CD is associated with DQ8 heterodimer. Those rare CD patients lacking these HLA markers may exhibit the DR4 allele.[85] It has been suggested that different aspects of the syndrome (with or without CD, with or without epilepsy, and with or without cerebral calcifications) might depend on involved genes and their combination.[80]

Epileptogenesis in CD patients does not appear to be directly dependent on the local deposit of calcium. In fact, seizures may occur early in CD patients before the development of cerebral calcifications.[21] Cerebral calcifications might depend also on deposit of calcium due to chronic immune complex–related endothelial inflammation. Chronic folic acid deficiency has also been hypothesized, similar to what occurs in non-CD conditions such as congenital disease, methotrexate therapy, and radiotherapy. Chronic folic acid deficiency could also depend on the effect of antiepileptic drugs, but that seems less probable because antiepileptic drug–induced folate deficiency is rare.[85] Preferential occipital involvement is an unexplained issue, but it could be related to a selective vulnerability of the occipital lobe.[97] According to Martinez-Bermejo et al.,[137] considering that most CEC patients are from the Mediterranean area (Italy and Spain) and Argentina, it could be hypothesized that CEC may represent a genetic, noninherited, ethnically and geographically restricted syndrome associated with environmental factors.

Atypical forms include patients with celiac disease, epilepsy without cerebral calcifications, and patients with CD and cerebral calcifications without epilepsy. Sixty-nine patients of the latter group were reported up to 1996,[87] and one third of them had partial occipital epilepsy. Labate et al.[122a] found that in a cohort of 72 newly diagnosed patients with idiopathic partial epilepsy, 9% of those with occipital epilepsy were affected by silent CD. Of course, it is possible that cerebral calcifications were lacking because of the early age at diagnosis of celiac disease. In fact, it is well known that some CEC patients with an initial normal CT scan may develop bilateral parieto–occipital calcifications later during the evolution.[44,85,86,87,124,135]

Finally, 9 cases in the Italian Working Group (IWG) series and 24 literature patients[87] had *epilepsy and cerebral calcifications without celiac disease*. Some of these patients had strong similarities with the CEC patients. In fact, imaging characteristics of cerebral calcifications overlapped those of CEC patients, appearing to be progressive in one case, and epilepsy was localization related in 24 cases (7 from the IWG and 17 from the literature). Of these, 18 showed partial occipital epilepsy, with evolution toward epileptic encephalopathy in 2. The fact that 7 of 9 cases of the Italian Working Group series had the HLA DQW2 and DR3 phenotype, as in CEC patients, suggested that some of these patients might be affected by a CEC syndrome in which CD is in a latent state, perhaps with mucosal patchiness.[85,87]

Recently, Pengiran Tengah et al.[162] ascertained the prevalence of active epilepsy in a cohort of 801 CD patients by patient interviews and retrospective case note review. All the CD patients had diagnostic confirmation by small bowel biopsy. Twenty-one patients had a history of epileptic seizures, but only 9 (1.1%) had active epilepsy. No specific epileptic syndrome was identified, suggesting that a causal relation between gluten sensitivity and active epilepsy is unlikely.

Clinical Description

In CEC syndrome, epilepsy may start at any age, with a peak between 5 and 6 years. In a more recent Argentinean series, mean age at onset of epilepsy was 6.13 years (range 1–16 years).[21] On the basis of clinical and EEG findings and evolution, the epilepsy was classified as localization related in 109 cases. Among them, 78 patients had occipital epilepsy. The semiology of the seizures may consist of versive and/or visual seizures (simple hallucinations, amaurosis, blurred vision, loss of focus, vision of colored dots, complex visual hallucinations such as seeing unfamiliar faces or scenes).[163] Visual seizures followed by complex seizures or secondary generalization may also occur. Two anecdotal cases had reflex epilepsy, with reading reflex seizures in one[87] and eating-induced seizures in the other.[134] The remaining 31 cases showed other varieties of partial epilepsy, with complex seizures in 15, motor seizures in 9, and partial seizures with secondary generalization in 7.[85] Although clinically heterogeneous, epilepsy in these patients is usually pharmacoresistant, frequently characterized by an early and apparently benign initial phase followed by an epileptic encephalopathy after a seizure-free interval.[89] Nevertheless, in many cases the evolution is benign (20 cases in a review of the literature).[87] In 9 benign cases, the outcome of occipital epilepsy was similar to that of early- and late-onset benign childhood epilepsy with occipital paroxysms. Progressive myoclonic ataxia syndrome with a cortical myoclonus has been reported in 7 cases.[32] Progressive mental impairment has been found in patients having epilepsy with a severe evolution. Typical generalized epilepsies have also been reported.

In patients with CD and epilepsy without cerebral calcifications, one third had partial occipital epilepsy and one half had a benign evolution of the seizures. Some of these patients were believed to have a form of benign occipital epilepsy. In two patients, occipital epilepsy was progressive toward epileptic encephalopathy.

Electroencephalographic recordings mainly showed focal occipital spike-and-wave abnormalities; rarely, focal abnormalities were outside the occipital regions. Bilateral slow spike-and-wave activity occurred in the cases of occipital epilepsy with progression toward epileptic encephalopathy. The EEG normalized in patients in whom the seizures disappeared.[88]

Typical CT features of CEC syndrome consist of bilaterally subcortical, roughly symmetric or asymmetric, occipital calcifications, absence of contrast enhancement, and absence of brain atrophy. Calcifications may also be observed in the frontal region, and scattered cases of unilateral occipital calcifications

have been reported.[21,85,88,134] Calcifications are extremely variable in size, and no correlation between the extension of calcifications and the severity of disease has been demonstrated.[88]

Diagnostic Evaluation

Considering the apparently specific involvement of the occipital lobe in patients with untreated celiac disease, careful investigation of CD in all patients with occipital epilepsy of unknown cause, even if cerebral calcifications are absent, should be performed.[11] Testing for celiac disease is strongly advised also because, as stated earlier, CD is a gluten-dependent syndrome that may be silent, latent, or potential, and clinical signs of malabsorption may be lacking. Pediatric neurologists may be the only specialists who can detect CD early in these patients.[88]

Complete evaluation to identify CD includes xylose load test, determination of serum folic acid, antigliadin immunoglobulin G (IgG) and IgA antibodies, and antiendomysium antibodies (EmA). Transglutaminase antigen (tTG) has recently been identified as the main autoantigen recognized by antiendomysial antibodies in celiac disease. Low CSF folate levels with alteration in the CSF/serum folate ratio associated with increased CSF and serum levels of cystathionine have been described.[45] Peroral biopsy (with a Crosby capsule) of the jejunal mucosa at the ligament of Treitz (crypt hyperplasia and unequivocal flat mucosa were accepted as markers of celiac disease according to the criteria of Dunnill and Whitehead[68]) should be performed before luten-free diet and 1 year later. Determination of HLA phenotype also should be included in the diagnostic evaluation process.

Moreover, all other known causes of cerebral calcifications must be excluded, including encephalitis, purulent meningitis, ossifying meningoencephalitis, leukemia, chemotherapy, neonatal hemorrhage, congenital infections, TORCH group (toxoplasmosis, rubella, cytomegalovirus, herpes simplex) diseases, and disturbances of calcium and phosphate metabolism. The following examinations should be performed: hematology; urinalysis; blood chemistry; serum electrolytes (sodium, potassium, calcium, and phosphate); serum parathyroid hormone; calcitonin; urinary oligosaccharides and mucopolysaccharides; lysosomal enzyme activities; blood antibodies to herpes simplex virus, cytomegalovirus, mumps virus (parotitis), rubella virus, measles virus, Epstein-Barr virus, and *Toxoplasma*; and vitamin B12.

Finally, enhanced CT scan and MRI must be performed to differentiate these cases from the other phacomatoses, such as tuberous sclerosis complex and Sturge-Weber syndrome, especially when port wine facial nevus is absent. In particular, in patients with celiac disease there is no enlargement of the choroid plexus or local or diffuse brain atrophy, which are common imaging findings in Sturge-Weber syndrome.[88]

Treatment

The epilepsy is usually drug resistant, sometimes evolving into epileptic encephalopathy; it is only rarely benign. Reduced efficacy of common antiepileptic drugs because of malabsorption has been supposed but not demonstrated.

The role and the effectiveness of a gluten-free diet as therapy for epilepsy have yet to be established, although there is no doubt that a correct diet may prevent long-term health risks in unrecognized celiac disease.[103] Nevertheless, it has been demonstrated that the chances of seizure control after gluten-free diet (GFD) seem to be significantly inversely related to the duration of epilepsy before GFD, the age at onset of epilepsy, and the age at the beginning of GFD.[88] When GFD is started late during the evolution, epilepsy may be more severe and epileptic encephalopathy may develop.[63,134]

Lesionectomy might be considered in those patients with drug-resistant epilepsy related to unilateral occipital calcifications.[148]

Hepatic Disorders: Orthotopic Liver Transplantation

General Findings

Seizures are not reported in hepatic encephalopathy, which is usually characterized by varying degrees of confusion, tremor, dysarthria, ataxia, and asterixis. In contrast, seizures are a frequent complication of liver transplantation, even though this procedure usually produces a striking improvement in brain function in patients who have preoperatively hepatic encephalopathy. Nevertheless, neurologic complications are frequent and important causes of morbidity and mortality following orthotopic liver transplantation (OLT). The frequency of neurologic complications after a second OLT is significantly greater than after a first or a third transplant.[131] Seizures represent a main complication of OLT. Although seizures may often be related to focal brain injury, metabolic abnormalities may represent a predisposing factor in these patients. Commonly, underlying factors causing seizures in OLT patients include metabolic derangements, drugs such as cyclosporine and muromonab-CD3 (OKT3), hypoxic–ischemic injury, cerebral structural lesions, and infection. The more frequent electrolyte disturbances in these patients are represented by hypomagnesemia, hypocalcemia, and hyponatremia. Hypomagnesemia may also be secondary to cyclosporin A, which can cause magnesium wasting. The latter drug as well as other immunosuppressant medications (OKT3 and tacrolimus [FK 506]) may trigger seizures per se. Dose reduction or discontinuation of the drug usually leads to complete recovery. It has also been hypothesized that the high dose of steroids used in the therapy of graft rejection may play a role in causing seizures. Cerebral structural lesions that may occur in OLT patients, such as cerebral infarction, pontine or extrapontine myelinolysis, hemorrhagic or ischemic infarct, intracerebral hemorrhage, subarachnoid hemorrhage, and brain abscess and viral and mycosis infections of the central nervous system may also contribute to seizures.[1,71,72,131,194,212] In addition, several reports in the transplantation literature link seizures and other neurologic signs such as confusion, blindness or other visual abnormalities, tremor and paresthesias to immunosuppressive therapy, especially with cyclosporine.[1,101a,131,136a,209] Because of MRI findings (see further on), this has been referred to as a “reversible posterior leukoencephalopathy syndrome.” Children seem to be more susceptible than adults to cyclosporine-related seizures[1,206] especially in the presence of synergistic factors such as electrolyte disturbances, structural damage, high-dose steroid treatment for rejection,[8] or low serum cholesterol levels.[62]

Clinical Description

Epileptic seizures are a frequent neurologic complication of liver transplantation, affecting 10% to 29% of cases.[131,209] Single or recurrent generalized tonic–clonic seizures are the most common ictal manifestation. Myoclonic seizures, partial motor seizures, partial seizures with secondary generalization, and status epilepticus have been reported.[1,72,131,209] Unlike hepatic encephalopathy, an increased frequency of seizures may occur within the first week after transplantation, especially after the second orthotopic liver transplantation, but not after subsequent transplant procedures.[131] The cause is undetermined. Conversely, alteration in mental status may increase with each successive orthotopic liver transplantation, progressing to coma. Only a few reports describe the postoperative EEG after orthotopic liver transplantation. Usually, the EEG shows nonspecific generalized slowing of cerebral activity consistent with the development of a metabolic encephalopathy. Interictal generalized or focal spikes and sharp waves have been reported.[1,72,209,211] These epileptiform abnormalities have not been found in all patients. They are associated with serious, often irreversible brain damage, and their incidence has been estimated as fivefold higher in patients who died than in those who survived.[211] EEG was performed after seizure onset in the majority of patients, and partial and generalized electroclinical seizures have also been recorded.[211]

Diagnostic Evaluation

Development of seizures after orthotopic liver transplantation should alert the clinician to investigate for one of the cerebral complications listed earlier. Case history and laboratory tests may aid in the differential diagnosis with other associated metabolic disorders. Usually, computed tomographic findings are described as normal in orthotopic liver transplantation patients.[209] In some patients receiving immunosuppressive drugs (e.g. cyclosporine, tacrolimus), MRI scans show extensive bilateral white matter abnormalities consistent with edema involving mainly the parietal-occipital regions that resolve within 2-3 weeks if immunosuppressive therapy can be reduced, changed or withdrawn. This has been termed a *reversible posterior leukoencephalopathy.*[1,62,101a,136a] MRI is difficult to obtain in these critically ill patients, particularly when they are intubated or unable to remain still.[212] Electroencephalographic monitoring is indicated for its prognostic value.[211]

Treatment

Treatment of the underlying cause of the seizures should always be undertaken together with the administration of anticonvulsant medication. Special attention should be given to the correction of electrolyte imbalances, treatment of infection, and intracranial hemorrhage. Neurosurgical management may be necessary in selected cases such as those with cerebral abscess or subdural hematoma.[212]

Usually, seizures can be controlled by antiepileptic drugs such as phenytoin, phenobarbital, carbamazepine, or benzodiazepines.[1,72] However, phenobarbital, diazepam, phenytoin, and lamotrigine, which are highly bound to albumin, and carbamazepine and ethosuximide, which are primarily eliminated by hepatic oxidation, must be administered carefully because their metabolism is impaired in liver insufficiency, and doses need to be reduced. The most useful anticonvulsant in OLT patients remains phenytoin. Higher doses (18–20 mg/kg) than usual may be necessary to achieve high therapeutic levels. Both total and free phenytoin levels should be measured because hypoalbuminemia and decreased protein binding of phenytoin may result in a toxic free phenytoin level even when the total level is in the subtherapeutic range. Phenobarbital can also be considered. However, because of the excessive sedation, hypotension, and respiratory suppression that may occur during intravenous administration, phenytoin remains the drug of choice. The intravenous loading dose of phenobarbital is not well established, but it is generally in the range of 8 to 20 mg/kg. Carbamazepine can be used in patients with a history of epilepsy and on carbamazepine preoperatively. Carbamazepine, phenobarbital, phenytoin, and primidone may decrease cyclosporine blood levels by induction of P450IIIA (cyclosporine oxidase).[212] Sodium and magnesium valproate and felbamate should be avoided because of their hepatotoxic effects. Gabapentin and vigabatrin, which are not metabolized in the liver, are not bound to albumin, and are exclusively excreted by the kidneys, may also be preferable for these patients.[129]

Anecdotal reports showed that levetiracetam might be an attractive treatment because of its efficacy, lack of hepatic enzyme induction, and rapid attainment of serum levels. It is significant that levetiracetam-treated patients require significantly lower doses of immunosuppressant medications to achieve an equivalent antirejection effect.[84]

Summary and Conclusions

Occasional seizures due to metabolic electrolyte and endocrine disorders may occur more frequently in neonates but are also seen in children and adults. Based on the review of the literature presented in this chapter, three different situations must be considered. First, seizures may be an occasional and transient event concomitant with the toxic effect of a metabolic or endocrine disorder; in this case, they usually disappear following correction of the disorder, as in uremic encephalopathy,[156] electrolyte disturbances,[74,195] hypoparathyroidism, hyperthyroidism, and hypothyroidism,[43,167,181] and hypoglycemia and nonketotic hyperglycemia. Second, seizures may be the symptom of a brain lesion produced either by the toxic effect of a metabolic or endocrine disorder on cerebral tissue, as in hyperglycemia and hyperosmolarity,[133] aluminum encephalopathy,[165] and dialysis disequilibrium syndrome,[127] or by an immune-mediated mechanism, as in Hashimoto thyroiditis and probably celiac disease.[88] Third, brain tumors that cause an endocrine or metabolic disorder, as in pituitary incidentalomas and hypothalamic hamartomas, may produce seizures by a mechanical effect on the cortex.

All of these disorders indicate that epilepsy may be a symptom not only of a disease that primarily affects the brain, but also of systemic disorders or diseases that primarily affect other organ systems. Frequently, epileptic seizures may be the presenting symptom in these systemic disorders and also the predominant or sole clinical manifestation.

Consequently, in the presence of new-onset epileptic seizures, clinicians should carefully investigate not only for brain disease, but also for metabolic, endocrine, or gastrointestinal diseases that may be clinically silent. Such investigations may improve the etiologic diagnosis and thereby indicate a more correct therapeutic approach.

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Chapter 268

Alcohol and Drug Abuse

John C. M. Brust

Introduction

Worldwide, a variety of drugs are used recreationally, and they differ in their ability to produce either psychic dependence (compulsive drug-seeking behavior, "craving," "addiction") or physical dependence (an adaptive state in which cessation of drug use or administration of an antagonist produces physical withdrawal signs).[5] Many of these agents, by either indirect or direct mechanisms, increase the risk of seizures. This chapter addresses those drugs most often used recreationally in North America and Europe, exclusive of tobacco and caffeine (Table 1). Although agents are discussed individually, it is important to recognize that polydrug use (including ethanol) is common and, in fact, a person may be simultaneously overdosed on one drug while withdrawing from another.

Indirect Mechanisms

Drug users are frequent victims of cerebral trauma: in alcoholics usually associated with intoxication and in illicit drug users with lawlessness and violence. Post-traumatic seizures can be early or late in onset, and, depending on the agent, intoxication or withdrawal can further reduce seizure threshold.

Parenteral drug abusers are subject to systemic and central nervous system (CNS) infection. Endocarditis causes meningitis, brain abscess, and infected ("mycotic") aneurysm. Seizures in patients with AIDS may reflect opportunistic CNS infection or neoplasm, or direct infection of the brain by human immunodeficiency virus (HIV). Illicit drug users and alcoholics are often immunocompromised in the absence of HIV infection.

Independent of endocarditis, illicit drug users are at risk for ischemic and hemorrhagic stroke; mechanisms include embolization of foreign material, vasculitis, coagulopathy, and, with psychostimulants (especially cocaine), hypertensive crisis and direct cerebral vasoconstriction. Although mild-to-moderate doses of ethanol are protective against ischemic stroke, high doses increase risk, and any dose of ethanol is a risk factor for hemorrhagic stroke.[51]

Metabolic derangements are frequently encountered in drug users, including hyponatremia, hypocalcemia, and renal failure. In particular, hypoglycemic seizures, which in alcoholics tend to occur during binges, are often mistakenly attributed to ethanol withdrawal.

Direct Mechanisms: Toxicity, Withdrawal, and Individual Agents

Opioids

Opioid drugs include a large number of agonists, antagonists, and mixed agonists/antagonists (Table 2). Heroin, the most commonly abused opioid, can be injected, snorted, or smoked. Commercial street heroin contains a variety of pharmacologically active and inactive adulterants.

Heroin overdose, with coma, pinpoint pupils, and respiratory depression, is sometimes associated with seizures, but their occurrence in that setting is so unusual that other possible causes such as concomitant cocaine use, ethanol withdrawal, or CNS infection should be sought. In a case-control study, heroin use, either past or current, was a risk factor for new-onset seizures independent of head trauma, infection, stroke, ethanol, or other drugs.[45] For provoked seizures (i.e., caused by an underlying precipitant such as infection or trauma) the odds ratio (OR) was 3.65; for unprovoked seizures it was 2.57. The risk was greatest if heroin had been used on the same day as the seizure, but in no patient was there clinical evidence of overdose, and the risk persisted after a year of abstinence.

The pharmacologic basis of this risk is unclear. In animals, opioids are variably proconvulsant or anticonvulsant depending on species, seizure model, rate of administration, and particular agent (e.g., μ-, δ-, or κ-agonist). In some models, effects are blocked by the antagonist naloxone; in others they are not.[4,55]

Seizures or myoclonus are a well-recognized feature of meperidine toxicity, attributable to its active metabolite normeperidine.[29] Seizures are also anecdotally described as a toxic effect of fentanyl, pentazocine, and propoxyphene.

Except in neonates seizures are not a feature of opioid withdrawal, which produces flu-like symptoms and intense craving. In newborns of opioid-dependent mothers, withdrawal causes tremor, screaming, fever, tachypnea, tachycardia, vomiting, explosive diarrhea, and sometimes death.[21] Seizures and myoclonus are described, but can be difficult to distinguish from jitteriness. The diagnosis requires exclusion of hypoglycemia, hypocalcemia, intracranial hemorrhage, CNS infection, and withdrawal from other drugs or ethanol.

Table 1 Categories of recreational drugs

- Opioids
- Psychostimulants
- Sedatives/hypnotics
- Cannabis
- Hallucinogens
- Inhalants
- Phencyclidine
- Anticholinergics
- Ethanol
- Tobacco

Table 2 Major opioids

- Agonist
  - Camphorated tincture of opium (paregoric)
  - Morphine
  - Heroin
  - Methadone
  - Fentanyl
  - Meperidine
  - Oxymorphone
  - Hydromorphone

- Codeine
- Oxycodone
- Hydrocodone
- Levorphanol
- Antagonist
  - Naloxone
  - Naltrexone
- Mixed agonist-antagonist
  - Pentazocine
  - Butorphanol
  - Buprenorphine

Table 3 Major psychostimulants

- Dextroamphetamine
- Methamphetamine
- Methylphenidate
- Pemoline
- Ephedrine
- Pseudoephedrine
- Phenmetrazine
- Diethylpropion
- Benzphetamine
- Phenylpropanolamine
- Methylenedioxymethamphetamine (ecstasy)
- Cocaine

Psychostimulants

Psychostimulant drugs include amphetamine-like agents, whose principal action is to release monoamines at synaptic nerve endings, and cocaine, which blocks monoamine synaptic reuptake (Table 3). Cocaine is the only recreationally used psychostimulant with local anesthetic properties, which probably contributes to its epileptogenicity. Amphetamine-like drugs are taken parenterally or orally, and methamphetamine is often smoked. Cocaine hydrochloride is taken parenterally or intranasally; alkaloidal cocaine ("crack") is smoked.[5]

Amphetamine-like drugs tend to cause seizures in the setting of obvious overdose (fever, hypertension, cardiac arrhythmia, delirium, or coma).[3] With cocaine, seizures more often occur in the absence of other signs of toxicity; they can appear immediately or several hours after use, perhaps attributable to pharmacologically active metabolites.[25,34,43] A focal signature to seizures suggests a structural lesion such as cocaine-related intracerebral hemorrhage. Status epilepticus (SE) following cocaine use is often refractory to conventional anticonvulsant therapy.

In different reports, the prevalence of seizures among cocaine-intoxicated patients ranged from 1% to 9.3%.[8,34,48,52] Seizures are more likely to occur after smoking crack than after snorting cocaine hydrochloride, probably a dosage effect. A seizure can be new onset with no other contributing factor than cocaine, or it can be triggered by cocaine in a known epileptic.[48] In animals (and probably humans), repeated administration of cocaine progressively lowers seizure threshold until seizures occur at doses that were originally subthreshold ("kindling," "reverse tolerance").[13,41]

Methylenedioxymethamphetamine ("ecstasy") has pharmacological properties of both amphetamine-like psychostimulants and hallucinogenic agents such as mescaline. Popular on college campuses, it is usually taken orally in groups, including "rave" parties (dancing to loud fast music for hours at a time). Overdose can cause seizures, delirium, coma, and death.[30,59]

Phenylpropanolamine, available over-the-counter as a decongestant or appetite suppressant, and sold by mail order as a "legal stimulant," was banned by the U.S. Food and Drug Administration (FDA) after it was shown to increase the risk of stroke. Seizures are described at recommended doses.[42]

"Dietary supplements" containing ephedra alkaloids ("ma huang") became popular in North America and Europe during the 1990s, and both seizures and stroke were described in users. In 2003, the FDA banned these products.[24]

Sedatives and Hypnotics

Sedative/hypnotic agents include barbiturates, benzodiaze- pines, and nonbarbiturate/nonbenzodiazepine agents. Recreational barbiturate use is either parenteral or oral; short-acting agents are most popular. Although available as street drugs, benzodiazepines have much less abuse potential. Other sedative drugs vary in their addiction liability. Glutethimide, for example, is a well-recognized street drug, often combined with codeine ("hits," "loads"). Buspirone, by contrast, does not appear to be abused.[5]

Barbiturates and benzodiazepines potentiate γ-amin- obutyric acid (GABA) neurotransmission through stereospecific receptors on the GABA receptor–chloride channel complex. GABA receptor downregulation is probably a major mechanism of seizures during barbiturate or benzodiazepine withdrawal.

Short-acting barbiturates are most likely to produce seizures on the second or third day of abstinence; full-blown delirium tremens sometimes follows. In a study of human volunteers, abrupt withdrawal from secobarbital or pentobarbital after several months of a daily dose of 400 mg produced paroxysmal EEG changes without symptoms in one-third of the subjects. Withdrawal from 600 mg daily produced minor symptoms in half the subjects and a seizure in 10%. Withdrawal from 900 mg daily produced seizures in three-fourths and delirium tremens in two-thirds.[20]

Following withdrawal from benzodiazepines, anxiety and tremor are common but can be difficult to distinguish from the symptoms for which the drug was being taken in the first place. Seizures and delirium tremens do occur, however, usually within 24 hours of stopping a short-acting agent and within several days of stopping a long-acting agent.[18] As with barbiturates, seizures are dose-related and unlikely in patients taking recommended therapeutic doses.[6]

Withdrawal seizures have been described with a number of nonbarbiturate/nonbenzodiazepine sedatives, including meprobamate and chloral hydrate. Tolerance and physical dependence are infrequent among users of zolpidem, America's most popular sleeping pill, but tremor, agitation, and seizures are described during withdrawal.[35] Glutethimide-induced

seizures were reported as an acute toxic effect, possibly related to the drug's anticholinergic properties.[44] Seizures are also a feature of acute toxicity in recreational users of antihistamines. During the 1980s, parenteral administration of tripelennamine combined with pentazocine was a popular fad ("Ts and blues"), and seizures were a frequent complication.[7]

γ-Hydroxybutyrate, or its precursors γ-butyrolactone or 1,4-butanediol, is popular at "rave" parties and as a "date rape" drug. Acting at its own receptors as well as at GABA receptors, it produces ethanol-like effects, including a life-threatening abstinence syndrome. Myoclonus and seizures can be features of intoxication, however.[38,54]

Marijuana

Marijuana, made from cut tops and leaves of the hemp plant, *Cannabis sativa,* contains many cannabinoid compounds, of which Δ-9-tetrahydrocannabinol (Δ-9-THC) is the principal psychoactive ingredient. A more potent preparation, hashish, is made from resin covering the leaves. Marijuana can be smoked or eaten. In the brain, Δ-9-THC acts at stereospecific cannabinoid receptors (called CB-1) on synaptic terminals containing either excitatory or inhibitory neurotransmitters.[5]

A case-control study found marijuana use protective against new-onset seizures in men (OR = 0.42); for women there was a trend toward risk reduction that did not achieve statistical significance.[45]

In animal studies, cannabinoid compounds are variably proconvulsant or anticonvulsant depending on species and seizure model.[50] The nonpsychoactive compound, cannabidiol, is more consistently anticonvulsant.[9,49]

Anecdotal reports describe either improved or worsened seizure control temporally associated with marijuana use.[10,16,17,23] In a placebo-controlled study of 16 epileptics refractory to other drugs, cannabidiol acutely exacerbated EEG abnormalities but not behavioral seizures; after several months, however, seven of eight patients receiving cannabidiol were seizure-free compared to one of eight controls.[11]

Hallucinogens

Worldwide, dozens of hallucinogenic plants are used ritualistically or recreationally for their hallucinogenic properties. In North America and Europe, the most popular agents are peyote cactus containing mescaline, mushrooms containing psilocybin and psilocin, and the synthetic ergot compound D-lysergic acid diethylamide (LSD). The visual illusions and hallucinations produced by these agents—including those that spontaneously recur days or weeks after last use ("flashbacks")—are not considered epileptiform.[1] True seizures can follow very high doses, however.[19]

Inhalants

The recreational inhalation of volatile substances is a popular form of drug abuse, especially among children and adolescents. Products include solvents, cleaning fluids, glues, aerosols, bottled fuel gas, deodorizers, marker pens, petroleum, anesthetics, and nitrites, and the intoxicating compounds include hydrocarbons, esters, and ketones. Despite the variety of agents, the effects they produce resemble ethanol intoxication. A difference is that hallucinations and seizures can occur with overdose and are not features of inhalant withdrawal.[39,53]

Phencyclidine

Phencyclidine ("PCP", "angel dust") and the related compound, ketamine, are classified as "dissociative anesthetics." Their principal pharmacologic action—inhibition at glutamate receptors—is anticonvulsant, yet myoclonus and seizures including SE occur with overdose. Additional signs of intoxication—fever, tachycardia, hypertension, nystagmus, psychosis, delirium, dystonia, and stupor or coma with a blank stare—are likely to precede or accompany the seizures.[31,37]

Anticholinergics

Plants containing scopolamine and atropine are used recreationally worldwide. In North America and Europe, *Datura stramonium* (jimsonweed) is especially popular among adolescents, who ingest the seeds, leaves, or roots. Drugs with anticholinergic properties (e.g., amitriptyline) are also abused. The syndrome of anticholinergic poisoning—hallucinations, delirium, dilated unreactive pupils, hot dry skin—may include myoclonus or seizures.[40]

Ethanol

As with other drugs, seizures associated with ethanol may be the consequence of acute or remote head injury, CNS infection, stroke, or toxic/metabolic derangement. In many heavy drinkers, seizures are a direct effect of the ethanol ("alcohol-related seizures"), especially as a withdrawal phenomenon.

In a study of alcoholics presenting to an emergency room with either incident (new onset) or prevalent seizures, 78% of seizures occurred between 7 and 30 hours after the last drink. Excepting three subjects whose seizures occurred after 2 or more weeks, 99% of seizures occurred within 72 hours. A few seizures happened during active drinking. Forty-one percent of subjects had a single seizure; 21% had more than three, usually within a few hours after the first. SE occurred in 3%. Seizures were generalized in 95%; 5% had a focal onset. These seizures could occur alone or accompanied by other withdrawal signs. One-third of the patients subsequently developed delirium tremens. (Seizures, however, are not commonly present during delirium tremens.) The authors concluded that alcohol-related seizures were a withdrawal phenomenon, and that subjects whose seizures occurred beyond the withdrawal period or had focal signature probably had underlying structural pathology such as a remote cerebral contusion.[57]

In a study of volunteers, six subjects drank ethanol every few hours (including a 3:00AM dose) for at least 48 days. Withdrawal produced seizures in two subjects and delirium tremens in two.[28] The pattern of drinking in this study would be unusual for most alcoholics, who do not customarily awaken themselves in the middle of the night to have a drink. Moreover, the high percentage of subjects who experienced seizures was not encountered in other studies. For example, of over a thousand alcoholics who were detoxified without pharmacologic support, only 1% developed seizures.[58]

Consistent with the view that withdrawal might not be the sole mechanism for alcohol-related seizures is a case-control study of incident seizures, in which chronic daily ingestion of 50 g absolute ethanol raised the odds ratio (OR) above one, and 200 g daily increased the OR to 20. The minimal duration of drinking necessary to increase seizure risk could not be determined. In that study, many seizures occurred either during active drinking or more than a week after stopping, and statistical analysis failed to demonstrate a clear-cut temporal relationship between seizures and early abstinence. Moreover, those who had recently increased their ethanol consumption tended to have seizures earlier during abstinence than those who had decreased their consumption.[46]

Another case-control study found similar dose relationships for ethanol and incident seizures, with an increased risk appearing at 50 g daily absolute ethanol for men and 25 g for women, but that study did not address temporal relationships between seizures and active drinking.[33]

Animal studies demonstrate the existence of ethanol withdrawal seizures, and selective breeding can produce genetic susceptibility.[22] Alcohol-related seizures in animals, however, often occur with low doses of ethanol, and their variable time courses and semiology suggest multiple mechanisms. In both animals and humans, repeated bouts of ethanol withdrawal increase the risk of eventual alcohol-related seizures.[32]

A common neuropharmacologic mechanism to explain both withdrawal and nonwithdrawal alcohol-related seizures might be glutamate toxicity. Acutely, ethanol blocks glutamate neurotransmission, with receptor upregulation.[14,56] Abrupt abstinence would then produce a hyperglutaminergic state, resulting in withdrawal symptoms, including seizures. Repeated bouts of withdrawal might result in more lasting excitotoxicity, thus lowering the threshold for seizures independent of acute withdrawal.

Should brain imaging be performed in patients with alcohol-related seizures? In a study of 259 patients with incident alcohol-related seizures and no obvious explanation other than ethanol withdrawal, computerized tomography (CT) identified intracranial lesions in 16 (6.2%).[15] Four had subdural hematomas, four subdural hygromas, two vascular malformations, two cysticercosis, and one each aneurysm, possible neoplasm, skull fracture with subarachnoid hemorrhage, and cerebral infarction. Seven (44%) of the 16 patients were alert and had no focal signs or evidence of trauma. In 10 patients, the identified lesions altered management. The answer to the above question is therefore, yes, as far as new-onset seizures are concerned. More problematic is the patient with repeated alcohol-related seizures. Although imaging may not be necessary in every instance, the clinician must consider the possibility of underlying new treatable pathology in such patients.

Should alcohol-related seizures be treated acutely? Because ethanol withdrawal seizures tend to occur singly or in a brief cluster, the likelihood of recurrence has often passed by the time a decision is made whether to treat. In a controlled trial, either intravenous lorazepam 2 mg or placebo was given to alcoholic patients following a single generalized seizure. Over the next 6 hours, 3% of those receiving lorazepam had a second seizure, compared with 24 % of those receiving placebo (OR = 10.4). Of those not admitted, one receiving lorazepam and seven receiving placebo had a second seizure within 48 hours.

Should alcohol-related seizures be treated prophylactically? Anticonvulsants for seizure prevention are usually not indicated in alcoholics. Abstainers do not need them, and drinkers do not take them. Phenytoin, carbamazepine, and valproate, moreover, are probably ineffective in preventing withdrawal seizures.[2,26,36] For those whose seizures are not temporally associated with drinking, who have an additional lesion that by itself could account for seizures, or who have epileptiform electroencephalographic (EEG) abnormalities, prophylactic anticonvulsants may be required even though patient compliance is unlikely.

Can epileptics safely drink ethanol? In one report, one or two drinks daily appeared to precipitate seizures in 5% of epileptic patients; five or six drinks daily precipitated seizures in 85%.[36] In another study, however, epileptics given one to three glasses of vodka over a 2-hour period daily for 16 weeks were no more likely to have a seizure than those given orangeade; there was no change in seizure frequency or in EEG epileptiform activity.[27] Although these observations are reassuring, it is probably advisable to discourage ethanol use by an epileptic.

Management Strategies in Substance Abusers with Seizures

Medical or surgical conditions that might be causing or contributing to seizures—trauma, infection, stroke, metabolic derangement—must be identified and treated. For example, cocaine intoxication might entirely explain fever, delirium, and seizures, but not until an image and a spinal tap have excluded meningoencephalitis or intracranial hemorrhage.

Seizures accompanied by other signs of drug toxicity tend to be refractory to treatment. SE in such patients is nonetheless managed in the usual fashion. Other than naloxone for opioid overdose, flumazenil for benzodiazepine overdose, and physostigmine for anticholinergic poisoning, there are no available pharmacologic agents that specifically reverse the signs of recreational drug overdose, including ethanol.

The treatment of drug withdrawal should include an agent from the same pharmacologic class (e.g., methadone for heroin withdrawal) or with a degree of cross-tolerance (e.g., a benzodiazepine for ethanol withdrawal). Seizures observed during neonatal opioid withdrawal respond more predictably to opioid substitution therapy (e.g., methadone or paregoric) than to anticonvulsants.[47] Phenytoin is an inappropriate agent for either preventing or treating seizures during sedative or ethanol withdrawal, and neuroleptics given for anxiety or agitation in such patients may do nothing more than lower seizure threshold. Ethanol itself is a direct neurotoxin and therefore also an inappropriate agent to use in the prevention or treatment of ethanol withdrawal, including seizures.

As with ethanol, prophylactic anticonvulsants are seldom indicated when drug toxicity or withdrawal is the sole explanation for single or even multiple seizures.

Summary and Conclusions

Alcohol and recreational drugs can cause seizures by indirect mechanisms such as trauma, stroke, CNS infection, or metabolic derangement. Depending on the agent, seizures can also be the result of either direct toxicity or withdrawal. Such patients should be thoroughly assessed for underlying cerebral pathology, but if toxicity or withdrawal is then considered the sole cause of a seizure, anticonvulsant prophylaxis is usually not indicated.

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Chapter 269

Disorders of Pregnancy

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Introduction

Few conditions occurring during pregnancy give rise to epilepsy, but some pregnancy-associated conditions give rise to seizures. Seizures developing during pregnancy may herald an acute central nervous system (CNS) event, such as cerebrovascular disease, neoplasia, or infection. Fortunately, these occurrences are rare. Most commonly, new-onset seizures in later pregnancy are associated with eclampsia. This chapter reviews the pregnancy-related disorders that may present with seizures; the clinical presentation of each is described, along with a suggested diagnostic evaluation and treatment approach. Because of their frequent occurrence and the controversy regarding the treatment of seizures associated with pre-eclampsia and eclampsia, much of the chapter is devoted to a discussion of the approach to these seizures.

Pregnancy and Epilepsy: Approach to the First Seizure

Seizures may first appear during pregnancy in women who later are given a diagnosis of epilepsy. How often this occurs is not known, although Suter (as described by Lennox and Lennox[33]), in a study of 200 women with epilepsy, found that seizures had begun during pregnancy in 40. It is not clear how many of these women actually experienced eclampsia. Some women with epilepsy have seizures only during pregnancy (gestational epilepsy), but the frequency with which this occurs also is not known. Sleep deprivation and the physiologic stresses associated with pregnancy may lower the seizure threshold and precipitate the first seizure in women with an underlying epileptogenic lesion or genetic predisposition to epilepsy. The hormonal changes of pregnancy may also provoke seizures. The pregnant woman experiences a dramatic increase in the production of estrogens and progestogens. The population of sex steroid hormones also changes during pregnancy; whereas estradiol is the principal sex steroid hormone in women who are not pregnant, estriol is the most prevalent hormone of pregnancy. Some women may be susceptible to changes in cortical excitability triggered by these endocrine changes.[43]

Recommended Evaluation Strategy for the Pregnant Woman With a First Seizure

The appropriate neurologic evaluation for a pregnant woman with a first seizure does not substantially differ from the evaluation indicated for any patient with a first-time seizure. A careful neurologic history is taken and an examination performed to detect any neurologic symptoms or signs that would indicate increased intracranial pressure, a CNS infection or hemorrhage, or a focal CNS lesion. The history is explored for risk factors for seizures and for epilepsy. The basic evaluation should include a complete blood cell count, measurement of electrolytes, liver and renal function tests, and a toxicology screen—particularly to detect cocaine or alcohol, which are the most common substances of abuse associated with seizures.[42] The obstetric history includes determination of dates and an evaluation for hypertension, proteinuria, and edema to exclude pre-eclampsia and eclampsia.

Electroencephalogram (EEG) and neuroimaging are indicated in any woman seen with a seizure in the absence of eclampsia. If it has been determined that the seizure arose from pre-eclampsia/eclampsia and the presentation is otherwise not complicated, then EEG and neuroimaging are not usually required. However, if the patient with pre-eclampsia/eclampsia has focal neurologic symptoms or signs and partial seizures, EEG and neuroimaging should be obtained. Magnetic resonance imaging (MRI) is generally preferred to computed tomography (CT). Magnetic resonance imaging is the most sensitive technology for detecting CNS pathology and is safer for the pregnant woman. There is no known risk to humans from MRI scans using <2.0tesla.[56] The remainder of the evaluation is guided by the differential diagnosis.

When an antiepileptic drug is used in pregnant women, a dosage adjustment may be required from what is customary in the nonpregnant woman. Because of a reduction in protein binding during pregnancy, highly protein-bound antiepileptic drugs may have higher free, or non–protein-bound, fractions than would usually be anticipated. This translates into a higher CNS concentration. For example, during pregnancy the non–protein-bound fraction of phenytoin may represent 15% of the total fraction, in contrast to 10% in the nongravid state. The standard load of phenytoin (20 mg/kg) may prove excessive for the pregnant woman. A suggested regimen for pregnant women is to give 10 mg/kg and repeat with 5 mg/kg in 2 to 6 hours.[54]

Disorders of Pregnancy Associated with Seizures

Cerebral Ischemia

Seizures may be a sign of cerebral ischemia. The risk that a pregnant woman will experience a cerebral infarction varies from 1/481 in India to 1/26,099 in Rochester, Minnesota.[68] In one retrospective and prospective study of strokes associated with pregnancy and the puerperium in women delivering in public hospitals in Ile de France, 31 cases of stroke were identified among 348,295deliveries.[57] Arterial occlusion represents 50% to 80% of all cerebral infarctions occurring during pregnancy, with central venous thrombosis next most common. Arterial infarctions tend to occur in the second and third trimesters, whereas venous infarctions are more likely to occur in the first trimester. In the Ile de France study, nonhemorrhagic strokes (47%) and intracranial hemorrhage (44%) were most likely to occur in association with eclampsia.[57]

Stroke during pregnancy resulting from an arterial thrombosis usually arises in individuals with an identifiable risk factor for stroke. Most arterial infarctions are a consequence of arteropathy associated with premature atherosclerosis, moyamoya disease, Takayasu arteritis, fibromuscular dysplasia, and, rarely, isolated CNS vasculitis. Stroke and seizures may also be the initial manifestation of hematologic disorders, such as hemoglobinopathy (sickle cell disease), antiphospholipid antibody syndrome, thrombotic thrombocytopenic purpura, and deficiencies in antithrombin III and proteins C and S. The factor V Leiden mutation is a hereditary abnormality of the coagulation system that appears to enhance resistance to activated protein C, which inhibits coagulation. Up to 5% of the population exhibits resistance to activated protein C, and about 20% of patients with venous thromboembolism carry the factor V Leiden mutation.[30,71] Evaluation of a patient with stroke and seizures would also consider cardioembolism and paradoxic embolism from a patent foramen ovale, deep venous thrombosis, thrombosis of the pelvic or ovarian vein, or fat embolism. During labor and delivery, amniotic fluid and air embolism are considered in the differential diagnosis.

The clinical syndrome of cerebral venous thrombosis is characterized by headache, nausea and vomiting, visual symptoms, encephalopathy, lateralized neurologic deficits, and focal or generalized seizures.[21] Unlike arterial thrombosis, cerebral venous thrombosis develops in pregnant women who have no other specific risk for stroke. Cerebral venous thrombosis appears to be caused by the combination of the hypercoagulable state of pregnancy and the decrease in cerebral blood flow consequent to blood loss during labor and delivery. Other conditions associated with cerebral venous thrombosis include infection; hyperviscosity syndromes; sickle cell anemia; leukemia; antiphospholipid antibody syndrome; protein C, S, and antithrombin III deficiency; and factor V Leiden mutation. Malignancies and arteriovenous malformations should also be considered.[68] Although cerebral venous thrombosis may require acute treatment for seizures, the long-term prognosis is good. In one series of 77 patients with cerebral venous thrombosis, of 28 patients who experienced seizures acutely, seizures recurred in only four.[45]

Cerebral Hemorrhage

Cerebral hemorrhage occurs in between 1 and 5 pregnancies per 10,000. Associated mortality is 30% to 40%.[69] The risk for intracranial hemorrhage appears to be increased in pregnant women,[57,70] although data from Rochester, Minnesota, found no evidence of a gestational increase.[67] Pregnant women are likely to experience conditions that increase the risk for hemorrhage, however, such as eclampsia, metastatic choriocarcinoma, cerebral emboli, and coagulopathies. In addition, physiologic changes occur in pregnancy that predispose to intracranial hemorrhage, such as hypertension and increases in cardiac output, blood volume, and venous pressure. High concentrations of circulating estrogens may cause arterial dilation and be an additional risk factor for cerebral hemorrhage.[69]

Subarachnoid hemorrhage in the pregnant woman is most likely to be caused by cerebral aneurysms and arteriovenous malformations. Other causes of subarachnoid hemorrhage are eclampsia, cocaine abuse, coagulopathy, subacute bacterial endocarditis, and choriocarcinoma.[69] Aneurysmal bleeding is most likely to occur in older patients (25–35 years of age) and in the second and third trimesters of gestation. Bleeding is unlikely to occur in the postpartum period. In contrast, hemorrhages from arteriovenous malformations are more likely to occur in younger women (18–25 years) and are uniformly distributed throughout gestation, with a higher risk during labor and the puerperium.

Subarachnoid hemorrhage in a pregnant woman, as in a patient who is not pregnant, may be associated with severe headache, nausea, vomiting, focal neurologic signs, and seizures. Transient hypertension and proteinuria are often present and must be differentiated from pre-eclampsia/ eclampsia. Diagnosis is established based on the clinical presentation and CT of the brain. If the brain CT findings are negative and intracranial hemorrhage is still suspected, then a lumbar puncture to detect hemorrhage is indicated. If hemorrhage is detected, the patient requires either an MR angiogram or four-vessel angiography, depending on the institution's technical capabilities and experience, and a brain MRI to evaluate for aneurysms and arteriovenous malformations.

Intracerebral hemorrhage in pregnancy is most often attributable to hypertension occurring in the setting of eclampsia. Other causes include bleeding from an arteriovenous malformation, hemorrhagic transformation of an ischemic stroke, cocaine or alcohol abuse, and coagulopathies. The presenting symptoms of intracerebral hemorrhage are usually focal neurologic deficits, headache, nausea, vomiting, and seizures. A noncontrast CT of the head is generally the imaging test of first choice, followed by MRI to detect any structural lesion underlying the hemorrhage.

Treatment of seizures in the setting of subarachnoid or intracranial hemorrhage does not differ in pregnant and nonpregnant patients. The risk for teratogenic effects of antiepileptic drugs is far outweighed by the risk for repeated hemorrhage following a major motor seizure.

Rheumatologic Disease

Patients with immunologic and rheumatologic diseases, such as systemic lupus erythematosus (SLE), may experience an exacerbation of CNS disease during pregnancy.[41] Unlike most rheumatologic disorders, which spare the CNS, SLE involves the CNS in as many as one half of patients.[12] Neurologic disease is the second-leading cause of death in SLE[53] and frequently causes neuropsychiatric disturbances such as seizures, encephalopathies, psychosis, and lateralized motor deficits.[20] The risk for development of pre-eclampsia, hypercoagulability, and antiphospholipid antibodies is also increased in SLE. The CNS lesion in SLE is principally a small-vessel vasculitis with vascular hyalinization, endothelial proliferation, thrombosis, and capillary wall thickening.[1] Low-dose corticosteroids are the preferred treatment for SLE, with or without aspirin or heparin. Lupus of the CNS may require treatment with higher doses of corticosteroids. Antiepileptic drugs for seizures may be required only during acute flares.

Antiphospholipid antibodies may be associated with neurologic disease, either in the context of SLE (30% of patients) or within the primary antiphospholipid antibody syndrome.[35] The syndrome is characterized by deep venous and arterial thrombosis and stroke, repeated miscarriages, and thrombocytopenia. Seizures may occur. Cerebral events during pregnancy associated with anticardiolipin antibodies are generally treated with heparin anticoagulation. Seizures usually require antiepileptic treatment.

Thrombotic thrombocytopenic purpura is a rare disorder that may occur more frequently during pregnancy. Presenting features are thrombocytopenic purpura, microangiopathic hemolytic anemia, renal disease, and neurologic symptoms, which may include headache, encephalopathy, paresis, visual disturbance, and paresthesias. Seizures occur

in 20% of patients and are treated acutely with antiepileptic drugs.[48] The outcome of thrombotic thrombocytopenic purpura has substantially improved with plasmapheresis and plasma exchange.[55]

Neoplasia

The types of brain tumors that occur in pregnant women are not different from those in nonpregnant women—most commonly gliomas, then meningiomas and acoustic neuromas.[11] Pregnancy does not appear to be a risk for development of a specific neoplasm, but it can exacerbate tumor growth. Symptoms associated with increased intracranial pressure, such as nausea and vomiting, may be confused with "morning sickness," especially during the first trimester. However, persistent headache and neurologic deficits should raise concern for neoplasia. Seizures are a common presenting symptom of cranial neoplasms and may be partial or generalized. Any patient who has a seizure and in whom neurologic signs and symptoms are present warrants evaluation with an MRI.

Infections

Seizures may be the presenting symptom of infections of the CNS during pregnancy. The frequency of viral meningitis and encephalitis is not increased during pregnancy. However, pregnant women are at higher risk for infections caused by intracellular organisms because specific immune responses are altered to permit maternal adaptation to fetal and placental antigens.[23] The agents most likely to cause CNS infections and seizures during pregnancy include bacteria (*Mycobacterium tuberculosis*, *Listeria monocytogenes*), fungi (*Coccidioides immitus*), protozoa (*Toxoplasma*, *Plasmodium*), and viruses (influenza, varicella-zoster [chicken pox only], and polio).[27] The increased incidence of HIV seropositivity and AIDS in pregnancy should prompt consideration of this entity in any pregnant patient with opportunistic infections of the CNS. Treatment of these infections is the same as for nonpregnant women, with choice of antibiotic guided by information regarding the relative teratogenicity. Seizures are treated with antiepileptic drugs as required during the acute illness.

Pre-eclampsia and Eclampsia

Pre-eclampsia and eclampsia are diseases of pregnancy that occur most often in nulliparous women. Most seizures occurring during pregnancy are a sign of eclampsia. Eclampsia is defined as the development of convulsions and/or unexplained coma during pregnancy or postpartum in patients with signs or symptoms of pre-eclampsia. Pre-eclampsia is a multisystem disorder associated with hypertension, proteinuria, edema, hemoconcentration, hypoalbuminemia, abnormalities of hepatic function or coagulation, and increased urate levels.[32] In a recent study, 3.9% of 467 women with untreated pre-eclampsia progressed to seizures (eclampsia).[7]

Eclampsia is associated with seizures, cerebral bleeding, and death. The diagnosis of eclampsia is made when an antepartum or postpartum woman presents with generalized edema, hypertension, proteinuria, and convulsions. The spectrum of presentation, however, includes severe to minimal or even no hypertension, proteinuria, or edema.

Eclampsia most commonly occurs at or beyond week 28 of pregnancy. However, some cases occur between weeks 21 and 27 (7.5%) or at 20 weeks' or earlier (1.5%). Eclampsia occurring before 20 weeks' gestation is usually associated with molar or hydropic degeneration of the placenta. Eclampsia may also present within 48 hours postpartum and even as late as 4 weeks postpartum.

The incidence of eclampsia in Europe and other developed countries is 1/2,000 deliveries. In developing countries, estimates vary from 1/100 to 1/1,700. Maternal mortality ranges from 1.8% to 5%.[10,16] Eclampsia accounts for approximately 50,000 maternal deaths and is a leading cause of maternal deaths in the United States, Scandinavia, Iceland, Finland, and the United Kingdom.[50]

In the classification scheme of hypertension in pregnancy of the National Institutes of Health, pre-eclampsia and eclampsia are diagnosed according to the following criteria: increase in blood pressure to 140/90 mm Hg or greater in late pregnancy if no early reading is available, plus proteinuria (>300 mg/24 h), edema, or both.[32] Pathologic changes in pre-eclampsia and eclampsia involve multiple organ systems and arise because of vasospasm caused by exaggerated vascular responsiveness to circulating angiotensin II and catecholamines. Cardiac output, intravascular volume, and renal hemodynamics may be decreased. Uteroplacental perfusion may be compromised, leading to fetal growth retardation. A subset of pre-eclampsia is designated the HELLP syndrome: H for hemolysis, EL for elevated liver enzymes, and LP for low platelets.[61]

Neurologic abnormalities associated with eclampsia are usually acute and transient. These may include cortical blindness, focal motor deficits, and coma, although there is usually no permanent neurologic deficit. Seizures are most often generalized, but they may be partial.

During an eclamptic convulsion, the EEG shows spike-and-wave discharges. In one series of 65 patients with eclampsia,[60] a transient neurologic deficit was the presenting symptom in 5% of cases, and another 5% had transient cortical blindness. Electroencephalographic abnormalities were present acutely in 75% of cases, consisting primarily of excessive diffuse slow activity (67%), focal slow activity (33%), and paroxysmal spike activity (10%). These abnormalities were evident during administration of therapeutic doses of magnesium. The EEG abnormalities resolved at follow-up between 1 week and 6 months in all the patients. Other authors have described similar transient EEG abnormalities.[64]

Brain imaging in eclampsia shows vasogenic cerebral edema in 93% to 100% of women.[36,71] Extensive bilateral abnormalities of white matter are described in the posterior regions of the cerebral hemispheres as well as cerebellum and brainstem.[25] In addition, foci of infarction may be present. Angiography has shown spasm in large and medium-caliber arteries.[15] Results of CT are usually normal, but scans may show regions of decreased density corresponding to areas of cerebral edema.[15] The findings are similar to results with imaging in hypertensive encephalopathy. MRI abnormalities can persist for 6 to 8 weeks after resolution of symptoms.[36,71]

Pathologic examination of eclamptic brains usually reveals multiple petechial hemorrhages in cortical patches or subcortical hematomas. Areas predisposed to hemorrhages are the parietooccipital regions and the occipital lobes. Microscopically, these lesions correspond to ring hemorrhages about capillaries that are occluded by fibrinoid material.[15]

The treatment of eclamptic seizures associated with maternal hypertension has been controversial. There is wide consensus that the therapy for pre-eclampsia is delivery if the pregnancy is appropriately advanced. Hypertension is treated as necessary with antihypertensive drugs. The prevention of and treatment of seizures associated with pre-eclampsia and eclampsia has varied across countries and medical centers. The National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy[32] recommends the use of magnesium sulfate for women with pregnancy-induced hypertension to prevent eclamptic seizures during labor and the immediate puerperium. Although most obstetricians in the

United States have traditionally used magnesium sulfate to prevent eclamptic seizures in pregnant women with hypertension, obstetricians in the United Kingdom have favored diazepam and phenytoin.[18,26,47] A number of clinical studies have found magnesium sulfate treatment to be efficacious in preventing recurrent seizures in women with eclampsia.[24,46,58]

A randomized, placebo-controlled trial was performed in women from 33 countries diagnosed with preeclampsia and randomized to receive magnesium (5,071) or placebo (5,070).[2] Primary outcomes were eclampsia and, for women randomized before delivery, death of the infants. A total of 1,201 of 4,999 (24%) women given magnesium sulfate reported side effects versus 228 of 4,993 (5%) given placebo. Women allocated magnesium sulfate had a 58% lower risk of eclampsia (95% confidence interval [CI] 40–71) than those allocated placebo (40, 0.8%, vs. 96, 1.9%; 11 fewer women with eclampsia per 1,000 women). Maternal mortality was also lower among women allocated magnesium sulfate (relative risk 0.55, 0.26–1.14). For women randomized before delivery, there was no clear difference in the risk of the infant dying (576, 12.7%, vs. 558, 12.4%; relative risk 1.02, 99% CI 0.92–1.14). This trial established that magnesium sulfate halves the risk of eclampsia and probably reduces the risk of maternal death. There do not appear to be substantive harmful effects to mother or infant in the short term.

Whether antiepileptic drugs are appropriate to use in the treatment of seizures in this population has been debated. Arguments in favor of using antiepileptic drugs have stressed that magnesium is not antiepileptic, and it affects only the overt manifestations of seizures through neuromuscular blockade without altering the epileptic discharge.[14,28,29] Magnesium may have some unwanted obstetric effects as well. Inhibition of labor and impairment of postpartum hemostasis as a consequence of uterine smooth muscle relaxation have been described,[22] although others have not found that use of magnesium (or phenytoin) is associated with prolonged labor or an increased number of cesarean deliveries.[4]

A number of small trials have evaluated obstetric and seizure outcomes after phenytoin treatment in pre-eclamptic and eclamptic patients. Phenytoin was associated with more rapid cervical dilation and a smaller fall in hemocrit compared with magnesium in 105 pre-eclamptic and eclamptic women.[22] Slater et al.[62] treated 26 women who had eclampsia or pre-eclampsia with intravenous phenytoin and reported no convulsions. Robson et al.[52] treated 5 women who had eclampsia and 67 women who had severe pre-eclampsia with a phenytoin dose of 15 mg/kg or a loading dose of 17.5 mg/kg and found that some women had seizures despite therapeutic levels. Dommisse[13] assigned 22 women with eclampsia to receive either intravenous phenytoin or magnesium. Four of the women on phenytoin (levels of 10–25 mg/mL) had seizures, but none of the women on magnesium had seizures. Appleton et al.[3] randomized 50 patients with pre-eclampsia to phenytoin or magnesium for seizure prophylaxis. No differences were found in patient tolerance, adverse reactions, or neonatal outcomes between groups. No patient in either group had seizures.

Small trials have also evaluated the efficacy of prophylactic benzodiazepine treatment. Fifty-one women with eclampsia were randomized to magnesium or diazepam as an anticonvulsant.[9] Convulsions occurred in about one fourth of the women in each group, and there was no statistically significant difference in maternal morbidity, although significantly fewer infants in the magnesium group had low Apgar scores compared with those in the diazepam group.

Recently, several randomized, large-scale trials have permitted objective comparison of the efficacy of alternative medical treatments for pre-eclampsia/eclampsia. These represent the best information concerning the relative efficacy of magnesium and phenytoin for seizure prophylaxis and improving maternal and fetal outcome.

The Eclampsia Trial Collaborative Group[19] was an international multicenter, randomized trial that compared magnesium sulfate, diazepam, and phenytoin as treatment for eclampsia. This trial included 1,687 women with eclampsia from South Africa, Argentina, Colombia, Zimbabwe, Uganda, Brazil, Ghana, India, and Venezuela. Women were randomized to receive either magnesium or diazepam, or magnesium or phenytoin. Each center chose the comparison pair. Women receiving magnesium had a 54% lower risk of recurrent convulsions than did those receiving diazepam. There was no difference in maternal morbidity or perinatal morbidity and mortality. Women receiving magnesium had a 67% lower risk of recurrent convulsions than did women receiving phenytoin. Maternal mortality was not significantly lower in the women receiving magnesium. However, women on magnesium were less likely to be ventilated, contract pneumonia, and be admitted to an intensive care unit than were those receiving phenytoin. The infants of the mothers on magnesium were less likely to be intubated and to require admission to a special care nursery. Infant mortality remained high in the trial. Overall, 27% of infants died, with a mortality rate of 49% to 58% for those delivered before 34 weeks' gestation. This high infant mortality rate may be a reflection of the multinational nature of the trial. In the United States, mortality rates at 28 weeks or more are 10% or less.[51]

A second trial,[37] based in the United States, evaluated magnesium and phenytoin as prophylaxis for eclampsia in hypertensive pregnant women. Women admitted to labor and delivery with hypertension received either magnesium or phenytoin. Magnesium was administered as 4 g intravenously, followed by 10 g intramuscularly and 5 g intramuscularly every 4 hours thereafter as needed and as tolerated by protocol. Phenytoin was given as 1,000 mg intravenously, then at a maintenance dose 10 hours later of 500 mg orally. In this intention-to-treat analysis, 178 women randomized to the phenytoin group were given no phenytoin or received only partial loading doses. None of these women experienced an eclamptic seizure. Although there were no significant differences in any risk factors for eclampsia between the two groups or in maternal and fetal outcomes, 10 of 1,089 women receiving phenytoin had convulsions, compared with none of the 1,049 women receiving magnesium sulfate. These women had a number of peripartum complications: 5 had cesarean sections, 6 had infants with low birth weight, 1 had abruptio placentae, and 2 required transfusions. Several women who underwent neuroimaging had areas of low density, a finding that has been previously described with eclampsia,[8] but otherwise showed no structural abnormalities. Phenytoin levels in the women who had seizures ranged from 5.8 to 24 mg/mL; 9 of the 10 women with seizures had phenytoin levels of at least 10 mg/mL. The past experience of this center[37] predicted that the incidence of eclampsia after admission for hypertension and during magnesium sulfate prophylaxis would be 1/750 women. In this study, the observed incidence in the magnesium-treated group was 1/1,384, whereas the phenytoin failure rate was 1/100. This can also be compared with an incidence of 1/78 in one study in which women with proteinuric hypertension received no treatment.[8]

Magnesium sulfate may have other beneficial effects in high-risk infants and after neuronal injury in other patient populations. Magnesium is associated with improved survival in infants weighing <1,000 g.[6] Magnesium also appears to protect against hemorrhage into the germinal matrix or ventricles in infants of very low birth weight.[31] In an experimental model of birth asphyxia, magnesium was associated with less evidence of brain injury.[39,65] In one observational study, in utero exposure to magnesium sulfate appeared to be associated with a protective effect against cerebral palsy in infants of very low birth weight.[44] Magnesium administration also decreases secondary neuronal damage after experimental traumatic brain injury.[40,66]

What are the mechanisms by which magnesium effectively treats seizures in these patient populations? Seizures are an expression of dysfunctional cortical excitability and arise in a variety of pathophysiologic conditions. Magnesium may be most effective against seizures and brain injury that arise as a result of increased excitatory neurotransmitters.[34] Magnesium suppresses activity at the *N*-methyl-D-aspartate (NMDA) receptor, blocks calcium influx at the NMDA receptor, and reduces calcium-dependent presynaptic neurotransmitter release. Phenytoin blocks sodium channels but has no significant effect on calcium channels. Although there is no accepted animal model for eclampsia, stimulation at the NMDA receptor may reproduce some of the neurochemical events responsible for the eclamptic seizure. In one experimental model of eclamptic seizures, rats were cannulated in the lateral cerebral ventricle and given NMDA to elicit seizures. Magnesium sulfate was more effective in terminating these seizures than was phenytoin.[38] Seizures in amygdala-kindled rats, however, representing a model more typical of human localization-related epilepsy, responded to phenytoin but not to magnesium in terms of seizure duration, duration of postictal depression, and behavioral seizure stage.[63] Sibai et al.[59] also found that magnesium did not suppress epileptiform potentials as recorded on the EEG.

Seizures in pre-eclampsia and eclampsia may also occur in response to intense vasospasm. Magnesium sulfate is a potent vasodilator and increases cerebral blood flow as measured by Doppler ultrasonography of intracranial vessels.[5] Vasodilation appears to be greatest in the smaller-diameter intracranial vessels distal to the middle cerebral artery. This effect would be anticipated to relieve cerebral ischemia. The vasospasm in pre-eclampsia and eclampsia is thought to be partly related to endothelial dysfunction. Magnesium increases the production of prostacyclin, an endothelial vasodilator, and also protects against endothelial injury mediated by free radicals—perhaps by substituting for calcium and preventing the influx of calcium that is induced by free radicals.[49]

Magnesium has been the standard treatment for pre-eclampsia and eclampsia, reducing maternal and neonatal morbidity and mortality.[49] The largest number of fetal deaths occur as a consequence of maternal hypertension, which is associated with retardation of intrauterine growth, low birth weight, and prematurity as well as a significant rise in fetal death rate.[17] Magnesium addresses the maternal hypertension and improves fetal outcome. It appears that in most cases, magnesium also effectively treats eclamptic seizures. This should not be surprising. The optimal treatment of any seizure corrects the specific neurochemical events triggering the epileptic discharge. The events in seizures arising with pre-eclampsia/eclampsia appear to differ from those in seizures arising with epilepsy. Whether treating eclamptic seizures with magnesium and an antiepileptic drug confers additional benefit has not been directly evaluated. Further understanding of the pathophysiology of seizures associated with pre-eclampsia/eclampsia will better define the best therapy.

Summary and Conclusions

The diagnostic and treatment approach to the pregnant woman with seizures follows the same basic principles as the approach to any patient with a first seizure, although the diagnostic differential must be expanded. The need for emergent antiepileptic treatment is assessed. Results of the medical and neurologic history and the physical and neurologic examination are combined with findings of a comprehensive obstetric history and examination. Laboratory examinations include urinalysis for proteinuria, complete blood cell count with platelets to exclude infection and evaluate for a hematologic disorder or HELLP syndrome, determination of electrolytes, liver function tests, and a toxicology screen for cocaine and alcohol. Except in situations in which the diagnosis is clearly pre-eclampsia/eclampsia, EEG and MRI are indicated. In cases of complicated eclampsia or in the setting of focal neurologic deficits, neuroimaging should also be obtained.

Seizures occurring in the later part of gestation in a hypertensive woman are most likely a manifestation of pre-eclampsia/eclampsia. Other potential causes of seizures during pregnancy include acute cerebrovascular disease, infection, exacerbation of a neoplastic lesion or SLE, or hematologic disorders.

In a pregnant woman with seizures in whom the diagnosis of pre-eclampsia/eclampsia has been excluded, treatment of seizures proceeds as would be appropriate for a nonpregnant woman. Although antiepileptic drugs are teratogenic, seizures—particularly convulsive or prolonged seizures—pose a greater risk to the well-being of both mother and fetus. Care should be taken in figuring the doses of highly protein-bound drugs because the non–protein-bound fraction active in the CNS is relatively higher in a pregnant woman.

In the pre-eclamptic patient, magnesium sulfate is indicated for both prophylaxis and treatment of seizures. The question of whether an antiepileptic drug should be administered as well must be answered by future research. In the meantime, it appears prudent to obtain an EEG (or EEG monitoring) in any woman in whom seizures recur after treatment with magnesium sulfate or in any woman whose mental status is not normal. The EEG permits persistent electrographic seizures to be detected; these may be difficult to diagnose clinically in a patient with obtundation and neuromuscular blockade. Patients with clinical or electrographic seizures who are receiving magnesium should be treated with an antiepileptic drug as well. Phenytoin or a benzodiazepine appears to be an acceptable choice because of the relatively good safety profile in both mother and fetus.

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Chapter 270

Overview: Disorders That Can Be Confused with Epilepsy

Frédérick Andermann

Introduction

The history is crucial in suggesting a diagnosis of epilepsy. The value of the interview hinges largely on the availability of an accurate history from both the patient and a witness to the event. In the absence of either of these essential features, the information is usually incomplete or inadequate, and every effort should be made to obtain a complete and detailed account before attempting to formulate a diagnosis.[2]

The last quarter-century has witnessed a great increase in the number of neurologists sophisticated in the treatment of epilepsy, and such neurologists are now available in many practice groups and academic departments. Many neurologists developed sophisticated monitoring units, to which patients with unexplained paroxysmal events are often referred. It soon became obvious that many of these individuals did not have epileptic seizures, and this led epileptologists and other neurologists to focus on the wide range of disorders presenting for differential diagnosis. More recently this increased awareness and accuracy in diagnosis by referring physicians has led to a reduction in the number of patients with clinically recognizable nonepileptic paroxysmal events who are referred to epilepsy centers.

Nonepileptic seizures present the most common problem in differential diagnosis (see Chapter 282). Increasingly available information and sophistication coupled with ready access to medical literature and the Internet, along with the individual's ability to learn from previous interviewers and examiners, has led to the appearance of complex accounts of what might be called "pseudoepileptic nonepileptic seizures." Thus, such patients often provide a history that contains many features of temporal lobe epilepsy or of other specific epileptic disorders. They may have a background of study in a field related to epilepsy, which obviously makes diagnosis difficult. The patients' social and cultural backgrounds are important determinants not only of the pattern of nonepileptic seizures, but also of their response to treatment. In many settings and localities the majority of patients respond to appropriate psychiatric treatment with remission of the attacks. In other environments with different levels of psychiatric sophistication and social problems, the disorder is much more refractory and the percentage of patients who cannot be relieved of their nonepileptic attacks is higher.[43]

Systemic Disturbances

Anoxic convulsions, or "ischemic convulsions" as they are sometimes termed, continue to present a diagnostic problem. They occur most often as a sequel to syncope and are related usually to the person being kept in an upright or standing position. Sometimes, however, syncope may occur in individuals who are recumbent. The circumstances of the event and the family history will provide clues to the diagnosis.[18,21,29,43] Not only might patients with asthma during an acute attack have cerebral ischemia, but they also might present with tonic episodes, whose mechanism is analogous to that of anoxic convulsions.[27] When there is some lateralization, the differential diagnosis is, of course, more difficult. However, lateralization of clinical features is not uncommon and has long been recognized in generalized processes such as idiopathic epilepsy.[24] It may be erroneously inferred by the observer, depending on the patient's position during the attack. It is important to distinguish between persistent or habitual lateralization and less significant and inconstant asymmetries in body and limb postures and movements.

Many individuals with migraine present features that make diagnosis difficult (Chapter 274). Acephalgic migraine occurring in older individuals is often not accompanied by headache, and these patients are not infrequently referred for diagnosis because of the suspicion of intermittent cerebral ischemic attacks or an epileptic etiology. Acephalgic migraine, however, does also occur in younger individuals and children.[45]

The march of the migrainous aura has a time course that frequently is different from that of the recruitment of symptoms in epilepsy, and in a majority of individuals distinguishing between the two is not difficult.[12,38,45] After the migrainous aura, however, the patient may have convulsive seizures, so-called intercalated attacks.[3,47] These are most likely related to spreading depression crossing the central sulcus, but proof of the specific mechanism is lacking. Whether these attacks require treatment with antiepileptic medication is not clear. Patients with a habitual tendency to develop such epileptic manifestations in the course of their migraine attacks eventually may develop seizures, usually temporal in pattern, which no longer occur in relation to clear-cut migrainous events. The mechanism of this form of secondary epileptogenesis is not clear.[1] Confusional migraine may also result in an epileptic seizure occurring during the acute event.[1,19] Here, too, the possibility of eventual development of independent epileptic attacks exists.

Patients with basilar migraine not infrequently present difficult diagnostic problems. It is usually the sequence of symptoms pointing to brainstem involvement, such as diplopia and ataxia, that provides clues to the diagnosis.[9,39,46] Neuro-otologic investigation during an attack documenting the very prominent nystagmus is also helpful.

Patients with basilar migraine also may have epileptic events or in rare instances status epilepticus. Here, too, the account of symptoms preceding the seizure will lead to clarification.[14]

The unresponsiveness that is not uncommon during basilar migraine attacks may be interpreted as loss of consciousness; however, the patients generally can be aroused by vigorous stimulation, only to relapse into stupor when stimulation ceases.[9]

In addition to the clinical problems, the recognition that the migraine aura may be manifested by electroencephalographic (EEG) spike discharge (usually over posterior head regions) may lead to diagnostic difficulty.[6,33,44]

Migraine is an extraordinarily common disorder, and despite the efforts of the International Migraine Society, there is still considerable disparity in deciding on its prevalence. It seems fairly clear that migraine and epilepsy have different mechanisms but that relationships between the two conditions, at times of a causal nature, exist. An interesting example is the association between benign rolandic epilepsy or benign occipital epilepsy and migraine.[10] Surprisingly, there is no unanimity among pediatric neurologists and epileptologists about the high and probably consistent association of these two disorders. Clarification must await advances in molecular genetics, which, it is hoped, will provide markers for these conditions.

Recent advances in molecular biology have shed some light on the nature of hemiplegic migraine with coma; it is notable that these patients do not have clear epileptic events. The hallucinations that occur as they recover from the coma are similar to those of peduncular hallucinosis.[26,36,50]

Patients with peduncular hallucinations are often considered to have epilepsy and are so treated. The hallucinations are usually vivid, stereotyped, prolonged, and not associated with overt epileptic manifestations. They are caused by mesencephalic lesions or abnormalities and do not respond to antiepileptic drugs.[15,25,37] The hallucinations of patients with parkinsonism are probably similar to if not identical to those of peduncular hallucinosis and also may raise questions as to their nature.[16,20] The auditory hallucinations of the deaf or the visual hallucinations of the blind are occasionally misinterpreted as epileptic in nature.

Neurologic Disturbances

Patients with episodic hypothalamic dysfunction or the Kleine-Levin syndrome have varied behavioral abnormalities, including hallucinations and excessive sleep. The patients often have some disturbance of awareness and memory, although they remain fully conscious.[11,42] An epileptic twilight state is at times suspected, but when the examiner is aware of the condition, a detailed history stressing associated features such as excessive eating and inappropriate sexual behavior should lead to the diagnosis.

Paroxysmal events occurring exclusively during sleep have led to diagnostic difficulties for some time (see

Chapter 276).[22,35] The identification of nocturnal paroxysmal dystonia as a specific entity arose at a time when there was little awareness of the various patterns found in frontal lobe epilepsy. It now appears that paroxysmal nocturnal dystonia is not an entity that can be distinguished from partial epilepsy of frontal origin. The recent recognition of familial frontal epilepsy has further helped to clarify the diagnosis in a number of individuals.[41] It is not a homogeneous condition, however, and although in some families the attacks are always nocturnal and easily controlled by antiepileptic medication, in others there is variation in the occurrence of attacks in relation to the sleep/waking cycle, and medical control is difficult to achieve. This disorder, or rather this group of disorders, occurs in the absence of visible lesions and most likely is related to regional disorders of channel function or other, unidentified molecular abnormalities.[32,41]

Rapid-eye-movement (REM)–related sleep disorder may be mistaken for epileptic or postepileptic confusion and aggression but has become increasingly recognized as a consequence of the development of sleep medicine.[22] Hypnagogic and hypnapompic myoclonus is often misinterpreted as epileptic by patients with epilepsy and their families. The nature of myoclonus occurring during sleep is often difficult to interpret and to relate to a patient's known epileptic disorder.

Myoclonus has recently been intensively studied by epileptologists and movement disorder specialists, and its neurophysiologic basis is much better understood, but gaps still exist (see Chapter 277). Although the myoclonic component of idiopathic generalized epilepsy is usually easy to recognize, the diagnosis is often missed until generalized tonic–clonic or clonic–tonic–clonic seizures supervene.

The progressive myoclonic epilepsies subsume a number of disorders that share an association with generalized seizures, photosensitivity, and sometimes occipital epileptic discharge, ataxia, and some degree of neurologic deterioration (see Chapter 252). The most common disorders are Lafora disease, Unverricht-Lundborg disease, neuronal ceroid lipofuscinosis, myoclonus epilepsy with ragged red fibers (MERRF), and sialidosis. There are also several other entities that may present in this way.[8,13,30,40,49] Despite recent progress, particularly in the area of molecular biology, the neuronal networks in brainstem and cerebellar structures leading to these manifestations have not been identified. This is surprising considering the great disparity in their biochemical and neuropathologic abnormalities.

Myoclonic ataxia as defined by Marsden et al.[34] implies that these patients do not have overt epileptic seizures. It is likely that at least a percentage of these individuals suffer from MERRF or a related mitochondrial disorder (Chapter 262). Patients presenting in this way should have a detailed investigation of mitochondrial function.[34]

Benign essential myoclonus is an ill-defined disorder. Affected family members may have an occasional seizure, which casts doubt on the nonepileptic nature of the syndrome.[17]

The nature of some of the paroxysmal movement disorders has been intensely debated recently. Benign paroxysmal kinesigenic choreoathetosis (PKC), perhaps the most common of these, is easily recognized if one is aware of the clinical symptomatology. Attacks are classically induced by initiation of movement, are brief, and are not associated with any impairment of awareness. The disorder gradually improves with age. The episodes respond remarkably to low levels of antiepileptic medications such as carbamazepine and phenytoin. However, stopping the small dose of medication usually leads to recurrence.[28] This disorder is clearly not epileptic in the classical sense. Until its mechanism is more clearly understood, the relationship to epilepsy will remain uncertain (see Chapter 278).[7,31]

Symptomatic choreoathetosis may well have a different pathophysiologic basis.[23] The symptoms are more varied than in PKC, triggers are less obvious and not stereotyped, and an epileptic etiology is more frequently assumed. Examination with depth electrode recording in one patient showed spike discharges, which prompted the investigator to assume a relationship of the disorder to epilepsy, at least in the patient so studied.[7] Certainly the presence of such spiking in subcortical structures may be related in some way to the effectiveness of antiepileptic drugs in low doses in some of the individuals with paroxysmal movement disorders.

Alternating hemiplegia of childhood is almost invariably still diagnosed initially as an epileptic disorder. The progressive deterioration and the lack of response to antiepileptic drugs eventually lead to the diagnosis. Perhaps as many as half the children later develop epileptic seizures as well, and in most instances these are easily controlled. This disorder is probably also migraine related, although its cause remains a mystery. The attacks of hemiplegia are associated with only mild or no definite slow-wave electroencephalographic changes during the event. This pattern of alternating hemiplegia is not limited to the classical syndrome, and several disorders may manifest in this way. Benign nocturnal alternating hemiplegia is not associated with mental deterioration and is even more clearly

migraine related. Pyruvate dehydrogenase deficiency, undiagnosed basal ganglia disorders, and episodic dystonic attacks in infancy also may present with similar motor symptoms and share what seems to be a common subcortical or brainstem mechanism.[4]

Shuddering attacks are not uncommon in children and are often considered to be myoclonic or epileptic. They may be related to a family history of essential or familial tremor, and this has again been suggested in the recent literature.[5,48] Benign nocturnal myoclonus recently was recognized in infants who continue to develop normally (see Chapter 280).

Summary and Conclusions

The clinical features of the epilepsies and of epileptic seizures and epileptic syndromes have been well delineated in recent years. This has led in turn to more accurate diagnosis and increasing recognition of a variety of paroxysmal events of a nonepileptic nature. The progress reported in this overview and in the following chapters is not merely an idle theoretical exercise; rather, it has prevented the needless use of antiepileptic drugs with their known side effects in situations in which these agents cannot be expected to be helpful.

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Chapter 271

Syncope

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Thomas P. Bleck

Introduction

The term *syncope*, from the Greek for "cutting short," refers to an abrupt and transient loss of consciousness accompanied by loss of muscular tone. It is usually caused by a sudden, global reduction in cerebral perfusion, and clinical recovery occurs with restoration of normal cerebral blood flow. The very transience of this syndrome and the variety of medical disorders that can cause or mimic it are at the core of the diagnostic problems that the neurologist faces.

Definitions

Patients and physicians alike use a variety of terms to describe an occurrence of syncope. The term *fainting* is often used synonymously with syncope and captures the essential criteria— loss of consciousness and muscle tone. If the symptoms differ only in degree, so that there is partial loss of consciousness with a near fall, the term *presyncope* is often used. Less specific terms, such as *passing out*, *blackout*, or *dizziness*, need further clarification to become diagnostically useful. Some clinicians restrict the meaning of *drop attacks* to episodes of transient loss of tone with preservation of consciousness, a definition that carries a different burden of etiologies than does syncope.

Incidence and Prognosis

When measured in studies of consecutive emergency room visits, syncope prompts about 3% of emergency room evaluations, a proportion that has changed little over the last 25 years.[9,14,56] Multicenter surveys estimate that of 865 million emergency room visits between 1992 and 2000, 6.7 million (0.77%) were related to syncope.[78]

Although no age is spared, the incidence of syncope is highest among the elderly. A study of 711 elderly patients revealed a 10-year prevalence of 23% and a yearly incidence of 7%.[52] Of those who are admitted to hospital, 59.9% are age 70 years or older.[79] In addition to increasing age, other factors leading to higher rates of hospitalization are female gender and white race.[78]

The incidence of syncope among children and adolescents is 1.25%, peaking in the 15- to 19-year-old group.[20] Young athletes at a mean age of 16 years report that 6.2% had syncope within the last 5 years.[10]

Diagnosis is important because the mortality of syncope varies widely with the underlying etiology. Kapoor determined the 5-year outcome of 433 patients evaluated for syncope.[41] Mortality is >50% in patients with a cardiac cause of syncope, compared to 30% in patients with a noncardiac cause and 22% with an unknown cause.

Data from the Framingham Heart Study emphasize that syncope from cardiac causes is often a harbinger of significant coronary disease.[76] In this study, 822/7,814 (10.5%) individuals reported syncope over a 24-year period, for an overall incidence of first report of syncope of 6.2/1,000 person-yr. The relative hazard rate experienced by those with syncope from any cause compared to those without syncope is 1.31. Cardiac syncope has the highest relative risk of death than any other cause of syncope at 2.01 and an especially high risk of death related to coronary artery disease (relative risk 2.66). The Framingham study also emphasizes that those whose etiology of syncope remains unknown do not necessarily experience a benign course, having a relative risk of death from any cause of 1.32.

Older age appears to increase the risk of mortality in cardiac syncope. Another study by Kapoor that compared mortality rates of patients <60 and >60 years of age found that although the 2-year mortality rate was 27% in the older and 8% in the younger group, cardiovascular causes remained the most significant risk factor for mortality in either.[43] In the elderly, syncope carries a greater mortality despite etiology. In elderly patients hospitalized for syncope, the 4-year mortality was 41%, with the relative risk of cardiac syncope not varying significantly from that of noncardiac syncope.[30]

Morbidity associated with trauma from syncopal falls also contributes to the costs related to syncope. Between 16% and 36% of patients presenting with syncope experience a range of injuries from minor lacerations and bruises to fractures of the hip, face, or limbs.[14,41]

The morbidity of syncope goes beyond the physical. Assessments of the functional status of patients with chronic syncope show degrees of psychosocial impairment similar to those experienced by patients suffering from other disabling diseases such as rheumatoid arthritis or low back pain.[51]

The frequency of recurrence of syncope is not especially helpful in characterizing patients by etiology or prognosis,[41] although each syncopal episode increases the probability of serious injury. In Kapoor's study of 433 syncopal patients followed for 5 years, 153 had one or more recurrences, and the mean number of recurrences was greater than six.[41] Whether the diagnosis was cardiac, noncardiac, or unknown, recurrences were common in every category.

The 2000 Healthcare and Utilization Project estimates the annual cost of syncope-related hospital admissions in the United States at $2.4 billion, placing syncope on par with asthma ($2.8 billion) and human immunodeficiency virus ($2.2 billion).[78] The estimated cost per patient is $5,400. The high cost reflects the difficulties in establishing a diagnosis of a syndrome having both a wide range of possible etiologies and a high rate of studies returning nondiagnostic results. These problems have led to the publication of guidelines on evaluation and hospitalization of syncope, the adherence to which, some report, leads to higher yields in diagnostic accuracy but to no clear reductions in cost.[16,26] Other clinicians, however, report success in cost reduction, test reduction, and health benefits in the use of specialized syncope units and protocols of risk stratification and evaluation.[45,74]

Clinical Description

Classic Symptoms

The prodromal symptoms of classic syncope are familiar to most physicians and consist of nausea, “clammy” sweating, visual blurring and “graying out,” tinnitus, lightheadedness, and dizziness. The patient appears ashen or pale and becomes diaphoretic. Mydriasis may occur with tachypnea and bradycardia. Witnesses frequently note that the victim's “eyes rolled back into the head,” reflecting fading extraocular muscle tone. The patient becomes diffusely weak and hypotonic and, as consciousness is lost, falls to the ground with lack of protective reflexes if unsupported. Within seconds to minutes, once the patient is horizontal, color, pulse, and consciousness return. During the anoxic phase, before the patient recovers consciousness, a few myoclonic jerks or even more rhythmic, clonic movements may appear. Such a syncopal convulsion is common and often leads to erroneous reports of epileptic seizures. Sequelae include continued nausea and generalized malaise, but drowsiness, confusion, and amnesia are limited.

Syncopal Myoclonus

These common clinical features have been confirmed by video analysis of syncope induced in healthy volunteers through ocular pressure, hyperventilation, and Valsalva maneuver.[49] Typical prodromal symptoms were blurred vision, dizziness, vertigo, and nausea. Average duration of loss of consciousness was about 12 seconds, and myoclonic activity (syncopal convulsions) occurred in 38/42 syncopal episodes. Automatisms were observed in nearly 80%. Opened eyes and upward eye deviation were also common. Auditory and visual hallucinations, not usually elicited in previous studies, were reported in 60%. Postictally, transient amnesia occurred in 1 of 42 individuals, but cognitive sequelae were otherwise unremarkable. In none of these normal individuals nor in other studies of induced syncopal convulsions in patients did incontinence occur.[2,34,49]

Of the manifestations of syncope, convulsive movements are potentially the most confounding because they raise the question of epileptic seizures. Studies of syncopal convulsions induced in patients during cardiac electrophysiology studies,[2] positive tilt-table studies,[34] and in healthy volunteers[49] describe a prevalence of 45% to 90%.

Myoclonic activity during a syncopal convulsion is usually multifocal and arrhythmic, but generalized, rhythmic myoclonus is also common.[36,49] In our experience, biased by patients admitted for diagnosis in epilepsy monitoring units, dystonic posturing similar to that of a complex partial seizure is not unusual and adds further difficulty in the purely visual distinction between syncopal and epileptic motor activity. This opinion is supported by a large study (694 individuals) of symptoms provoked by tilt-table testing; 8% of participants with positive results ($n = 222$) had “neurologic events” consistent with the clinical behaviors of tonic–clonic seizures, focal seizures, or dysarthria or aphasia.[63]

Electroencephalographic Appearance

Electroencephalographic recordings document the electrophysiologic correlates of syncopal convulsions. In patients with vasovagal syncope who have attacks induced by tilt-table, the electroencephalogram (EEG) demonstrates gradual development of high-amplitude 3- to 5-Hz slowing during prodromal symptoms. Slow-wave frequency decreases to 1- to 3-Hz activity with loss of consciousness.[36] In recordings of cardiac syncope caused by ventricular arrhythmias,[2] electrographic findings are more variable and sometimes feature marked attenuation of cortical activity with loss of consciousness, although in most cases, rhythmic slowing occurs before voltage attenuation. The changes in EEG occur about 10 to 15 seconds after development of arrhythmia. It is of interest that brain-slice preparations deprived of oxygen show a time of onset to isoelectric activity of about 7 minutes,[64] which implies that corticothalamic activity comprising scalp EEG is more susceptible to hypoxia than individual cortical neurons. Normal background activity returns quickly with restoration of circulation and return of consciousness. Myoclonic activity has no consistent relationship with the EEG changes, and could occur either before or after EEG attenuation.[2] In neither study were epileptiform or ictal discharges observed.[2,36] Both the duration of loss of consciousness and postsyncopal confusion are linearly related to the duration of cardiac dysfunction.[2] Figures 1 and 2 demonstrate typical EEG accompaniments in syncope induced by cardiac asystole and in reflex bradycardia induced by breath-holding.

Differential Diagnosis

Because neurologists and epileptologists can be expected to see a more selected patient group than cardiologists, general practitioners, and emergency room physicians, the bulk of this discussion focuses on the separation of neurologic causes of syncope from other etiologies. However, because neurologic causes are relatively infrequent, a discussion of the differential diagnosis of syncope is undertaken first.

As Table 1 shows, even a brief listing of causes of syncope can be daunting. A more concise method is to group the myriad causes onto five main categories: (a) disorders of orthostatic intolerance; (b) primary cardiac dysfunction; (c) transient neurologic dysfunction; (d) metabolic derangement; and (e) psychiatric syndromes. The relative frequency of these diagnostic groups as they present in emergency rooms and other primary care facilities is shown in Table 2.

Disorders of Orthostatic Intolerance

Disorders of the homeostatic mechanisms of blood pressure maintenance comprise a large portion of syncope seen by physicians. In these disorders, the unifying pathophysiology is the abnormal or insufficient response of the peripheral vascular system and in reflex cardiac mechanisms to internal or external stimuli.

To briefly review, on standing, about 300 to 800 mL (about 25% of total blood volume) is displaced downward from the thorax. Reduced pressure is detected by receptors in the carotid sinus and aortic arch and within cardiac and pulmonary tissues. Tonic central sympathetic inhibition decreases, which allows an increase in peripheral vascular resistance and an increase in heart rate as mediated by medullary cardiovascular control centers.[81] Defects in this regulatory system lead to orthostatic hypotension, which can be due to degeneration of the autonomic nervous system either centrally, as in Shy-Drager syndrome, or peripherally as the result of acquired or hereditary neuropathies. An intact autonomic nervous system, on the other hand, may be unable to compensate for conditions causing hypovolemia, such as anemia or dehydration. Elderly patients have particular problems with compensatory cardiovascular regulation and are vulnerable to orthostasis whatever the cause.[43]

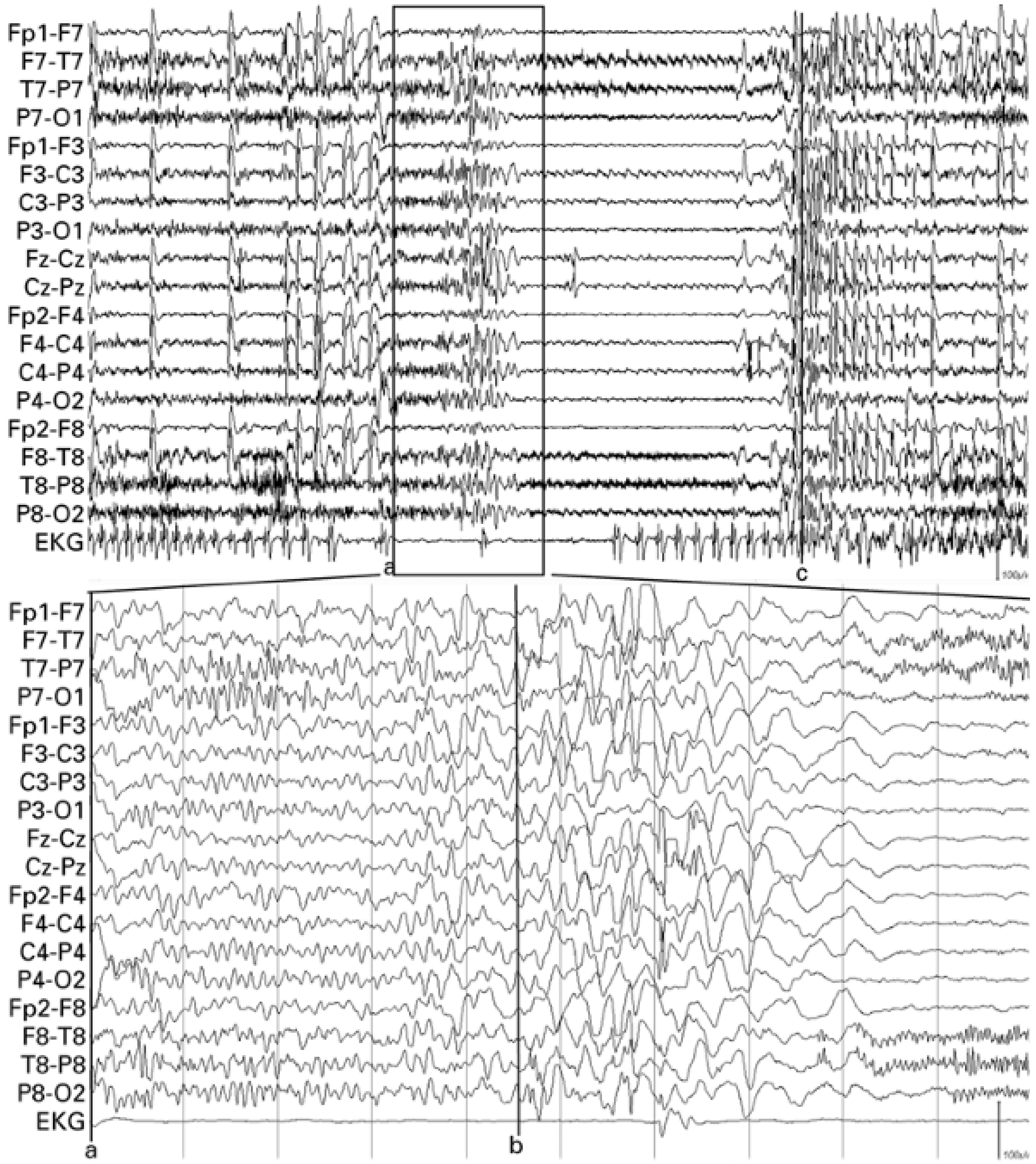

FIGURE 1. Electroencephalographic (EEG) excerpts from intensive video-EEG diagnosis of syncopal convulsion following spontaneous asystole in a patient who had undergone treatment for 1 year for presumptive epileptic seizures. The top panel shows a 60-second page with the box indicating the 10-second page excerpt in the bottom panel. The EEG starts with the patient in her normal, awake state while lying in bed. At time point a, the ECG channel shows the onset of asystole. The patient experiences clinical onset at point b marked by behavioral arrest and bilateral, dystonic posturing. The EEG, typical in response to cerebral hypoperfusion, develops abrupt, generalized slowing approximately 5 seconds after the last heartbeat, followed by generalized attenuation. Note the lack of epileptiform discharges despite the apparent motor activities of a complex partial seizure. Symptoms resolve at point c about 10 seconds following the return of normal sinus

rhythm. The lags from ECG to EEG and clinical changes are typical for syncope and represent a combination of cardiac output and cerebral perfusion volume.

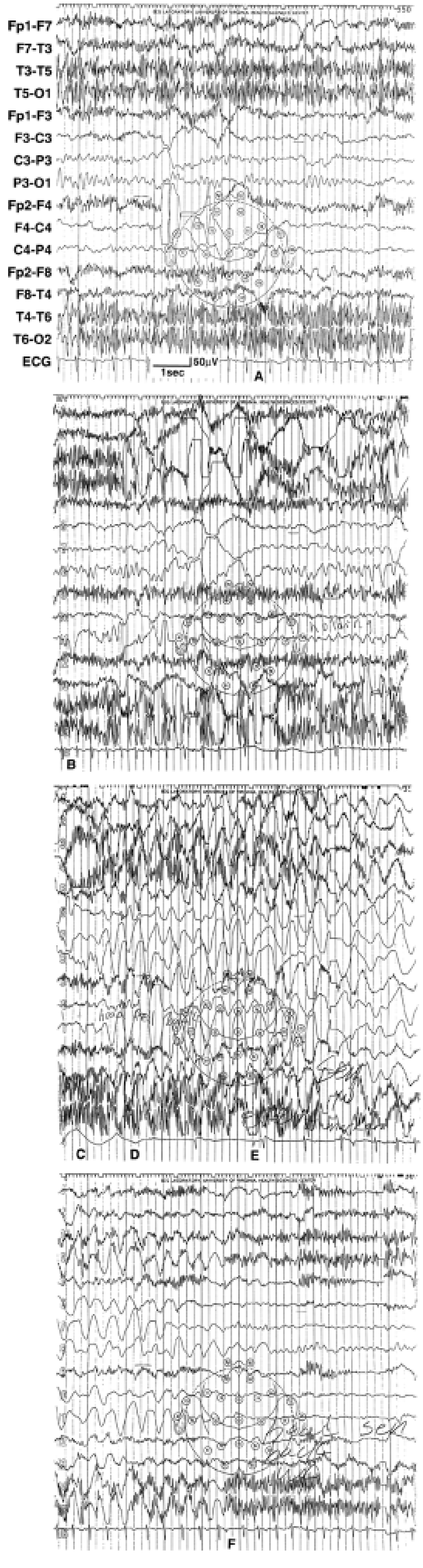
Fp1-F7
F7-T3
T3-T5
T5-O1
Fp1-F3
F3-C3
C3-P3
P3-O1
Fp2-F4
F4-C4
C4-P4
Fp2-F8
F8-T4
T4-T6
T6-O2
ECG
1sec
50µV
A
B
C
D
E
F

FIGURE 2. Breath-holding spell in a 15-month-old resulting in asystole, syncope, and brief convulsion recorded with continuous-telemetry electroencephalogram and simultaneous video recording. **A:** Patient, held in mother's arms, is crying while the technician re-gels the electrodes. **B:** Crying abruptly stops, and several seconds later, the technician notes that the patient is not breathing. **C:** The patient becomes limp and is unresponsive. **D:** A single axial myoclonic jerk is seen. **E:** The patient abruptly resumes crying. **F:** Normal tone returns. The tracing demonstrates that breath-holding precedes bradycardia/asystole by approximately 6 seconds. Generalized rhythmic delta activity gradually builds up during the event and, after ECG activity and crying resume, gradually resolves. (Adapted from figures provided courtesy of Ted Burns, M.D., Neuromuscular/Autonomic Testing Division, Department of Neurology, University of Virginia.)

One of the more important causes of syncope in older people is orthostatic hypotension induced by drugs. In a study of elderly, institutionalized patients, hypotensive adverse effects

of drugs caused 8 of 32 cases of noncardiogenic syncope.[52] Nitrates, levodopa, and thioridazine were cited this study, but any new medication, especially one that antagonizes the alpha-1 receptor such as amitriptyline or chlorpromazine, should be suspect in any elderly patient with syncope.

Current consensus divides disorders of orthostatic intolerance into three groups, as follows.[3]

Reflex Syncope

Reflex syncope is a group of disorders that occur because of a sudden failure of the cardioregulatory system to maintain adequate vascular tone during orthostatic stress, resulting in hypotension that is frequently associated with bradycardia.

Neurocardiogenic syncope (or vasovagal syncope) is a reflex syncope believed to result from an inappropriately hypercontractile response of the heart to abrupt venous pooling. The resulting state mimics hypertension and causes a compensatory but pathologic bradycardia, initiating syncope.[35] In susceptible individuals, neurocardiogenic syncope is triggered by strong emotions such as fear or follows painful stimuli such as venipuncture, dental procedures,[22] or prostate exams.[5] Sometimes the precipitating event is merely a prolonged upright stance, as is frequently required of soldiers standing at attention. In this situation, there is also the confounding variable of venous pooling in the legs because gastrocnemius and soleus muscle contraction ceases. Soldiers who are taught to keep their knees slightly flexed and to intermittently contract their leg muscles are at much lower risk of syncope.

Hypersensitivity of peripheral visceral afferents, whether idiopathic or the result of trauma or tumor, is another mechanism of reflex syncope. Asystole after carotid massage is the hallmark of carotid sinus hypersensitivity. Neuralgic syncope is associated with tumors or other pathology of the

glossopharyngeal nerve, and there are rare cases of syncope associated with trigeminal neuralgia well.[40]

A variety of seemingly prosaic activities such as coughing, micturition, defecation, and breath-holding are all subsumed under the term situational syncope. Each stimulus, as in the Valsalva maneuver, leads to syncope through neurally mediated vasodepression analogous to vasovagal syncope. Micturition syncope may in addition reflect the relief of pressure exerted by the bladder on the inferior vena cava producing a transient decrease in venous return.

Autonomic Failure

Autonomic failure, either from primary degeneration of the autonomic nervous system, as in Shy-Drager syndrome (multiple-system atrophy) or that secondary to peripheral neuropathies, is the second major category of disorders of orthostatic intolerance.

Pure autonomic failure syndrome[27] is a chronic, insidious-onset disease with syncope as one major symptom accompanied by other failures of the autonomic nervous system (anhydrosis, impotence, etc.) that, unlike multiple-system atrophy, is not accompanied by a movement disorder or cognitive deficits.[27]

Other autonomic failure syndromes are usually attributable to small-fiber peripheral neuropathies resulting from such diseases as diabetes mellitus or paraneoplastic syndromes. In the case of diabetes mellitus, autonomic neuropathies can present quite early and severely coincident with other evidence of the disease.[72]

Postural Orthostatic Tachycardia Syndrome

Postural orthostatic tachycardia syndrome (POTS) is the third major category of orthostatic intolerance and consists of excessive increases in heart rate in the upright position.[35] The partial dysautonomic form is believed to be due to insufficient increases in peripheral vascular resistance on standing and may be a precursor to more severe primary autonomic failure. The second form consists of an initially appropriate tachycardic response to standing that does not "turn off," thus causing symptoms of presyncope and palpitations along with postural hypertension and tachycardia. The latter is often called beta-hypersensitivity syndrome because isoproterenol infusion causes a marked increase in heart rate. Investigation is underway to confirm a genetically mediated basis for these disorders.[73]

Primary Cardiac Dysfunction

Cardiac causes comprise disorders of pump failure caused by obstructed outflow, impaired cardiac filling, shunting, myocardial ischemia, or arrhythmias. The large but not all-inclusive list shown in Table 1 includes typical primary and secondary causes of episodic pump failure. Most of these disorders are distinguished from epilepsy by standard and invasive electrophysiologic tests or by specific aspects of the history or physical examination.[41]

The long-QT syndrome of Romano-Ward is an autosomal-dominant disorder of cardiac repolarization that results in ventricular tachycardias leading to palpitations, syncope, and sudden death. It is a channelopathy of cardiac hERG potassium or voltage-gated sodium channels[71] that is easily confused with epilepsy because patients are often young and usually have had unprovoked syncopal convulsions and the family history reveals similarly affected relatives. Other genetic long-QT syndromes, such as the Jervell-Lange-Nielsen syndrome, have different modes of inheritance and different channel abnormalities.[1] The electrocardiogram (ECG) is diagnostic, demonstrating a long, corrected QT interval. A large number of drugs and other precipitants have more recently been associated with acquired prolonged-QT syndromes.[69] These latter patients may not have prolongation of repolarization at baseline. One should also consider the Brugada syndrome, an autosomal-dominant disorder consisting of syncope, sudden death, ECG with ST-segment elevation, and an appearance similar to a right-bundle-branch block in the anterior leads.[80]

Especially in adolescents and young adults, one should also consider arrhythmogenic right ventricular dysplasia as a cause of syncope.[12]

Metabolic Disorders

Metabolic disorders usually cause loss or alteration of consciousness that is more indolent and longer lasting than the relatively abrupt, transient impairment with rapid, spontaneous resolution that characterizes typical syncope. As a correlate of this observation, brain-slice preparations take five times longer to reach isoelectric potentials when deprived of glucose as opposed to oxygen.[64] Thus, most metabolic disorders are more suited to a discussion of delirium or coma. For example, although hypoglycemia is frequently cited as a cause of syncope, reports of proved hypoglycemic syncope are rare.[7] Glucose tolerance tests were not positive in any of 121 patients tested in one study.[42] More common in the modern emergency room is intoxication due to alcohol or other drugs presenting as syncope.[1,21,41]

Table 2 Causes of syncope by frequency as seen in emergency rooms

	Kapoor 1990[41]	Eagle et al. 1985[21]	Day et al. 1982[14]	Total	Percent
Cardiovascular volume/tone					
Vasovagal	35	64	57	156	19.3
Other	89	16	9	114	14.1
Cardiac	110	15	17	142	17.6
Neurologic					
Seizure	7	2	58	67	8.3
Other	8	3	5	16	2.0
Metabolic/other	5	7	27	39	4.8
Unknown	179	69	25	273	33.8
Total	433	176	198	807	100.0

Psychiatric Disorders

Psychiatric disorders, especially depression and panic disorder, were the cause of syncope in 24% of patients referred to a specialized syncope clinic.[50] Conversion reaction and somatization are other psychiatric causes of syncope.[14,21,41] In contrast to patients with physiologic syncope, psychiatric patients are said to be relatively younger, have a higher recurrence rate, and are more often disabled by attacks.[50] Vertigo, rather than lightheadedness and disequilibrium, is more frequent in younger patients with psychiatric syncope.[75]

Table 1 Causes of syncope by etiology

Disorders of orthostatic intolerance

  - Reflex syncope
    - Neurocardiogenic/vasovagal
    - Carotid hypersensitivity syndrome
    - Neuralgic
    - Situational
      - Micturation
      - Deglutation
      - Tussive
      - Breath-holding
      - Postexercise/postprandial
  - Autonomic failure
    - Shy-Drager/multiple-system atrophy
    - Parkinson disease
    - Pure autonomic failure
    - Peripheral and autonomic neuropathies
    - Postural orthostatic tachycardia syndrome
    - Partial dysautonomia
    - Primary beta-hypersensitivity
    - Hypovolemia
    - Drug induced
- Disorders of cardiac function
  - Impaired outflow
    - Idiopathic hypertrophic subaortic stenosis
    - Atrial myxoma
    - Aortic stenosis/dissection
    - Pulmonary hypertension
  - Impaired filling
    - Pericardial effusion
    - Pulmonary embolus
  - Shunt
    - R to L Shunt (tetrology of Fallot)
  - Ischemia
  - Bradyarrhythmias
    - Sick sinus
    - Second-degree heart block
    - Atrioventricular heart block
  - Tachyarrhythmias
    - Supraventricular
    - Ventricular
  - Long-QT syndromes
    - Familial (Romano-Ward, Lang-Jervell-Nielsen)
    - Drug induced
- Transient neurologic dysfunction
  - Seizure
  - Seizure-induced bradycardia/asystole
  - Migraine
  - Transient ischemic attack
- Transient metabolic dysfunction and other
  - Drug effects or intoxication
  - Hypocapnia/hyperventilation
  - Hypoglycemia
  - Psychiatric
    - Conversion disorder

Panic disorder

Epilepsy and Other Neurologic Disorders

Epileptic Seizures That Mimic Syncope

Transient neurologic causes of syncope, especially epileptic seizures, are relatively infrequent. In a study of cost-effectiveness, tests of neurologic function in 121 occurrences of syncope were not diagnostic in any.[42] Nevertheless, the more unusual neurologic causes of syncope must be differentiated from the more common nonneurologic etiologies.

Complicating the differential diagnosis is the fact that convulsions following syncope are commonplace.[2,36,49] Syncopal convulsions are briefer than generalized tonic–clonic seizures, do not have extended rhythmic clonic jerking, recover rapidly, and lack postictal symptoms.[36] Normal orientation immediately or shortly after the event is a helpful clue to the diagnosis of syncope,[37] although recovery after atonic or frontal lobe seizures may be rapid. Conversely, if hypoxia produced by syncope is more severe or prolonged than usual, recovery may be slower than anticipated.

A variety of epileptic seizures may mimic the loss of tone and consciousness that are salient features of syncope. Some seizure types are more frequently confused with syncope than others. A subset of complex partial seizures, misleadingly termed temporal lobe syncope, can present with sudden drops or falls with or without prodromal symptoms but are followed by confusion, amnesia, and gradual recovery.[15] Scalp recordings suggest that temporal lobe syncope may have an extratemporal localization despite the name.[15] For example, six of seven epilepsy surgery patients who experienced drop attacks and who also suffered from focal motor seizures of the face and arm had seizures localized to the sensorimotor facial area.[48] On the other hand, temporal localization has been described in patients with temporal lobe epilepsy who developed drops and falls late in the course of previously manageable complex partial seizures.[28,67] The development of epileptic drop attacks is a poor prognostic sign, not only of the morbidity from fall-related injuries, but in its implication for future seizure control in the face of loss of inhibitory mechanisms that mediate rapid secondary propagation of seizure activity. Studies of volumetric magnetic resonance imaging (MRI) in patients with mesial atrophy demonstrate that extensive mesial atrophy, especially amygdalar atrophy, correlate with secondary generalization and temporal lobe syncope.[32]

Patients with the Lennox-Gastaut syndrome and other epileptic encephalopathies commonly have atonic seizures. These are frequently the source of greatest morbidity and are usually refractory to antiepileptic drug treatment. They can take the form of brief head nods or of sudden myoclonic jerks followed by atonia (myoclonic–astatic seizures).[19] EEG/video recordings of epileptic drop attacks reveal that the majority take the form of tonic “axial spasms,” analogous to an adult version of infantile spasms, with rapid, moderate flexion axially followed by a tonic phase during the fall. The anatomic substrate for these events may be the lower brainstem.[23] Care must be taken in evaluating an exacerbation of epileptic drop attacks because drug intoxication or vasovagal syncope and other form of syncope can coexist.

Table 3 Emergency room risk stratification of syncope based on history, physical examination, and electrocardiogram findings

High-risk group
Chest pain compatible with acute myocardial infarction
Signs of congestive heart failure
Valvular disease

History of ventricular arrhythmias
Electrocardiogram findings of ischemia
Prolonged QTc (>500 ms)
Trifascicular block
Persistent sinus bradycardia between 40 and 60 bpm
Atrial fibrillation and nonsustained ventricular tachycardia without symptoms
Cardiac devices (pacemaker or defibrillator) with dysfunction

Intermediate-risk group
Age ≥50 yr
With previous history of:
  Coronary artery disease
  Myocardial infarction
  Congestive heart failure
  Stable cardiomyopathy
Bundle-branch block or Q wave without acute changes on electrocardiogram
Family history of unexplained sudden death
Symptoms not consistent with a vasovagal cause
Cardiac devices without evidence of dysfunction
Physician's judgment that suspicion of cardiac syncope is reasonable

Low-risk group
Age <50 yr
With no previous history of:
  Cardiovascular disease
  Symptoms consistent with reflex-mediated or vasovagal syncope
  Normal cardiovascular examination
  Normal electrocardiogram findings

Source: Adapted from Shen WK, Decker WW, Smars PA, et al. Syncope Evaluation in the Emergency Department Study (SEEDS): a multidisciplinary approach to syncope management. *Circulation.* 2004;110:3636–3645, with permission.

Seizure-induced Asystole, Bradyarythmias, or Ventricular Tachycardias

A rare cause of syncope is a seizure-induced cardiac asystole or arrhythmia. Simultaneous EEG/ECG recordings have documented cases of asystole following photic-stimulation–induced spike-wave[60] and asystole, supraventricular tachycardia, and bradyarrhythmias following temporal lobe ictal discharges,[11,31,66,68,70] to give a few examples. Asystole during seizures is probably more frequent with left hemispheric foci.[68]

The pathophysiology of ictal arrhythmias is not well understood but may involve cardiac efferents that are stimulated by insular, limbic, and midbrain cardiopedal pathways.[58] Autonomic instability and subsequent cardiac arrest induced by an ictal discharge has been invoked as a mechanism of sudden unexpected death in epilepsy,[46] a finding supported by animal studies that show that epileptic triggering of hypothalamic and mesencephalic cardiovascular control centers by focal application of penicillin G causes cardiovascular instability and bradyarrhythmias.[53]

Ambulatory EEG/ECG monitoring of patients with epilepsy, however, has demonstrated that cardiac dysrhythmias do not occur at an increased rate compared to the general population.[44] The frequency of ictal and interictal discharges has little relation to the generation of cardiac rhythm abnormalities.[44] The usual cardiac response to a seizure is sinus tachycardia that seems to be more dependent on the volume of brain involved in the ictal discharge than on the location of seizure onset.[25] Thus, despite well-documented "epileptic syncope," such cases appear to be more like unlucky exceptions rather than useful models for sudden epileptic death.

One epileptic syndrome in which syncope is a frequent complication is Panayiotopoulos syndrome.[61] In this idiopathic, childhood epilepsy, autonomic seizures start with emesis and may proceed to ictal syncope. Because symptoms may last >30 minutes (thus qualifying as autonomic status epilepticus),[61] the prolonged course and prominent parasympathetic involvement are helpful in differentiating it from the shorter course of typical syncope. It is not clear whether syncope in Panayiotopoulos syndrome results from bradycardia, decreases in peripheral resistance, or both.

Hypoperfusion-induced Seizures

The inverse problem to seizure-induced arrhythmias is the occasional seizure that is provoked by a cardiac arrhythmia,[39,57] presumably from the triggering of a latent seizure focus by decreased cerebral perfusion. Review of both confirmed and suspected cases of hypoperfusion-induced seizures in children shows that rare cases of prolonged bilateral clonus following syncope can be epileptic in origin rather than strictly limited to more typical, brief nonepileptic convulsions.[39] Because nonepileptic syncopal convulsions often mimic epileptic seizures,[63] simultaneous EEG/ECG recordings are the only way reliably to make these diagnoses.

Cerebrovascular Attacks

Neurologic syndromes other than epilepsy can be confused with syncope. Cerebrovascular disease and, specifically, transient ischemic attacks of vertebral-basilar origin can cause abrupt and transient loss of consciousness following interruption of blood flow to the brainstem. Concurrent symptoms helpful in diagnosis are vertigo, ataxia, and parasthesias. Although the posterior circulation is often the site for such symptomatic ischemic disease, bilateral carotid atherosclerosis has also been described.[13] As in cortical stroke syndromes, such patients have a high incidence of hypertension and heart disease.[13]

Basilar migraine is a syndrome that is most common in adolescents and young adults. Some patients have syncope before a severe occipital or vertex headache, but they usually have a variety of associated symptoms, including dizziness, visual phenomena, nausea, disequilibrium, and ataxia. The EEG occasionally shows occipital spikes or intermittent rhythmic delta activity.[17] Patients with basilar migraine can be confused with those with Panayiotopoulos syndrome[61] or other forms of benign occipital epilepsy.[29]

Cataplexy

Finally, cataplexy may occasionally be confused with syncope. As with vasovagal syncope, an emotional trigger sets off a typical attack. Unlike syncope, however, the loss of tone in cataplexy is not clearly accompanied by loss of consciousness. The other hallmarks of narcolepsy—daytime somnolence, hypnogogic hallucinations, and sleep paralysis—help to identify cataplexy as well.

Diagnostic Evaluation

History

Because of the significant morbidity and mortality of cardiac syncope, the acute, emergency room evaluation of syncope centers on the distinction between cardiac and noncardiac causes. Risk stratification and protocols have come to bear on syncope evaluation. Table 3 divides syncope into high-, intermediate-, and low-risk groups based on history, physical, and baseline ECG findings used in prospective studies of the efficacy and cost–benefit relation of syncope protocols and specialized syncope units.[74]

Eliciting the critical elements of loss of consciousness and tone of a putative syncopal spell are important during

tertiary evaluation. Certain clinical characteristics indicate particular syndromes. In a comparison of historical features that distinguished among ventricular tachycardia, atrioventricular block, and vasovagal syncope,[8] cardiac etiologies were suggested by male gender, old age, infrequent recurrence, and short or no prodromal symptoms. On the other hand, vasovagal syncope was more likely when prodromal symptoms were complex, including palpitations. Symptoms from vasovagal syncope tended to persist longer than those from cardiac syncope.

A key to distinguishing reflex syncope from other disorders is a “trigger,” that is, an event such as sudden standing, fright, or pain that can initiate an abnormal or insufficient response of the autonomic nervous system. Other triggers may be elusive, and diagnosis may hinge on uncovering subtle signs such as grunting before episodes, as occasionally happens with children who have breath-holding spells.

The timing of certain triggers, specifically exercise, in relationship to syncope is a particularly important historical feature. In a study of 474 young athletes who were surveyed on aspects of syncope, syncope was nonexertional in 87%, postexertional in 12%, and exertional in 1.3%. Two of the 6 athletes with exertional syncope had structural cardiac disease, and the remaining 4 had positive tilt-table tests. In contrast, no adverse events occurred in nonexertional or postexertional syncope despite recurrence rates of ~20 events per 1,000 person-years.[10]

One confounding factor is that patients often cannot provide important historical details and witnesses may be lacking. Retrograde amnesia for the event, especially in the elderly, may be severe enough to have the patient present with falling with no memory of loss of consciousness.[62] In one study of carotid hypersensitivity syndrome, 95% of patients who presented with falling rather than syncope could not recall loss of consciousness following symptomatic carotid massage. In comparison, 12% of patients who presented with syncope recalled loss of consciousness. Similarly, in the evaluation of 65 patients in a specialty syncope clinic, 15% denied loss of consciousness despite subsequent typical syncopal episodes induced by a tilt table. Furthermore, only 58% of patients could recall events immediately before the attack, suggesting that retrograde amnesia may be frequent,[55] although postictal confusion is either brief or absent following syncope in contrast to an epileptic seizure.[36,49]

The presence and quality of prodromal symptoms can be confounding. Falls, lightheadedness, and vertigo often overlap in the presenting symptoms.[55,75] “Dizziness,” for example, is a confusing term both linguistically and diagnostically, and patients mean different things by them, as do physicians.[55,75] Up to two thirds of patients with syncope say that their main problem is “dizziness.”[75] When prompted by a standard questionnaire, 68% of patients with proved syncope had presyncopal lightheadedness, 55% reported disequilibrium, and 35% had vertigo, with some patients having more than one symptom.[75] Patients who complained solely of vertigo tended to be young and have a psychiatric cause for their symptoms.[75]

Some clinicians emphasize that the predictive value of prodromal symptoms are too low to usefully distinguish cardiac from other causes. Instead, they emphasize event triggers. Of note, no prospective assessment of the predictive value of history has been performed.

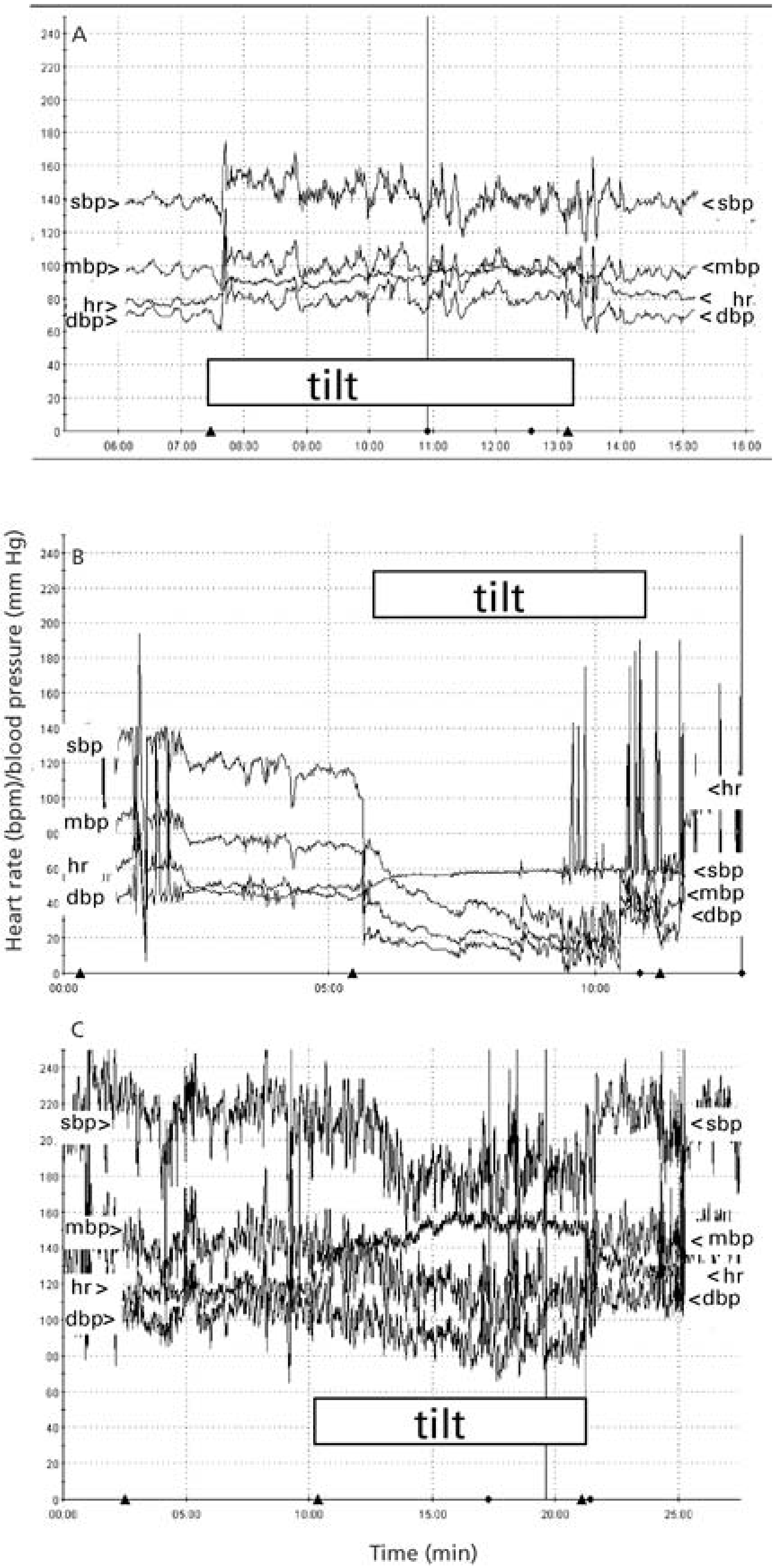

FIGURE 3. Findings in tilt-table testing. **A:** Normal tilt-table response. In response to abrupt vertical positioning of the tilt table, heart rate (hr) increases are limited to 15% to 30% of the horizontal rate because of the appropriate compensatory increase of peripheral vascular resistance, as denoted by the

~10% increase in diastolic blood pressure (dbp). **B:** A patient with Parkinsonism demonstrates central and peripheral postural hypotension marked by a severe drop in peripheral vascular resistance (with corresponding drops in systolic [sbp], mean [mbp], and diastolic blood pressures) accompanied by insufficient compensatory tachycardic response. **C:** A woman with small-cell breast cancer demonstrates positional tachycardia syndrome (POTS) marked by baseline hypertension, a relative hypotension with tilt, and an excessive tachycardic response. (Adapted from figures provided courtesy of Ted Burns, M.D., Neuromuscular/Autonomic Testing Division, Department of Neurology, University of Virginia.)

Physical Examination

Findings on physical examination help to diagnose some cases of syncope. Orthostatic hypotension is defined as a 20-mm Hg drop in systolic pressure or sinus bradycardia when standing.[55] Carotid massage followed by 3 or more seconds of asystole or a 50-mm Hg drop in blood pressure suggests carotid hypersensitivity.[55] Although one should be cautious in the patient with carotid bruits or at a high risk for carotid atherosclerosis, carotid massage is generally a safe procedure under supervised circumstances with appropriate monitoring. Bárány or Hallpike maneuvers can help to identify patients with vestibular dysfunction and vertigo. Nystagmus may suggest drugs or indicate central or peripheral vesicular dysfunction, depending on the direction, latency, and reproducibility.

The ECG is the significant helpful screening electrophysiologic test for cardiac causes of syncope.[41] Although one half of 433 patients with syncope had ECG abnormalities, these were diagnostic in only a small number of cases. In patients with arrhythmias, the routine ECG was diagnostic in 30% of cases.

Prolonged ECG monitoring using a Holter monitor, event recorder, or loop recorder is another common diagnostic test. Although <5% of patients have symptomatic arrhythmias during extended ECG, Kapoor[41] reported a diagnostic yield of 22% when screening for arrhythmias.

Implantable loop recorders have recently become available and marketed to neurologists. These devices have a battery life of approximately 14 months and record and store a

single-lead ECG when activated by a patient event button at the time of symptoms. Some clinicians recommend early use of implantable loop recorders when cardiac syncope is suspected and when events are rare rather than withholding it until other modes of testing have been exhausted. In early use, implantable recorders yield positive diagnoses in >50% of cases after a 1-year recording duration and in >80% after 2 years.[54]

Invasive electrophysiologic testing has been advocated in the subset of syncopal patients with heart disease[41] because these patients are most likely to have a positive test and the worst

prognosis if untreated. With any of the electrophysiologic tests, the diagnostic value of an arrhythmia that does not reproduce symptoms is debatable.

Echocardiography, although frequently used in the diagnostic evaluation of patients with syncope, is best reserved for patients found to have cardiac abnormalities on physical examination or in the course of other studies.[65]

Head-up tilt-table testing, with or without augmentation using isoproterenol, has gained favor because of its usefulness in diagnosing vasovagal syncope.[36] Tilt-table testing (Fig. 3), performed in combination with testing of vagal function, allows localization of orthostatic insufficiency into sympathetic or parasympathetic systems. Although controversies sur- round its specificity and sensitivity, tilt-table testing is safe in experienced hands. Guidelines for its application have been published.[4]

In most cases, routine EEG has a low diagnostic yield, especially in initial screening.[41] In those patients in whom a seizure is suspected, however, the EEG is of course a useful tool. In one study, the EEG provided useful information in only 12% of patients with suspected nonneurologic causes. On the other hand, the EEG yielded diagnostically helpful findings in 41% of patients suspected of having neurologic disease.[14] A comparison of patients with either epilepsy or syncope demonstrated that findings of focal epileptiform discharges, generalized epileptiform discharges, or focal slowing offered a sensitivity of 40% and a specificity of 95% in distinguishing between these two groups.[38]

The utility of routine brain imaging is also limited. Most studies evaluating the emergent diagnosis of syncope[14,21,41] have found that head computed tomography, when not guided by clinical data, had a poor diagnostic yield. Information is not available, however, regarding MRI, MR angiography, and functional MR.

If the clinical event occurred within 1 hour, elevated serum prolactin levels have been proposed to aid in the distinction between seizure and syncope,[18,82] but the most recent studies give conflicting results, suggesting that this assay may not reliably aid in differential diagnosis.[59]

Finally, as mentioned earlier, intensive telemetry with simultaneous EEG/ECG recording may establish a definitive diagnosis if the events are frequent and confounding enough to merit the costs incurred in such a study. Of note, most cases in which unusual cardioarrhythmic seizures have been documented were captured fortuitously, not through purposeful prolonged monitoring. With the development of implantable electrocortigraphy devices, perhaps long-term monitoring analogous to that of implantable ECG loop recorders will fill this clinical need.

Treatment

Treatment of syncope is as varied as the range of possible etiologies. A few statements regarding the treatment of autonomic insufficiency, such as found in the Shy-Drager syndrome, severe polyneuropathy, or idiopathic orthostatic hypotension, deserve mention. Measures to expand volume, such as increased fluid intake and salt ingestion, are often sufficient to ameliorate mild cases. The addition of compression stockings or, with more severe cases, of leg-to-waist customized support garments may be necessary. Fludrocortisone, a mineralocorticoid, will aid in volume expansion provided that due caution is allowed for possible congestive heart failure or recumbent hypertension. Biofeedback training may occasionally be a useful adjunct to more traditional measures.[6]

The development of the tilt-table test has led to a variety of pharmacologic treatments for refractory vasovagal syncope.[77] Beta-blockade is usually tried first, although the use of a beta-blocker for syncope seems at first counterintuitive. Nonetheless, the strategy works in a majority of patients with tilt-table–positive vasovagal syncope,[77] although the mechanism of efficacy is not clearly understood. Beta-blockade may attenuate the hyperactive response of cardiac mechanoreceptors thought to be in part responsible for vasovagal syncope.[36,77] Disopyramide has combined inotropic, anticholinergic, and vasoconstrictive effects and is occasionally used.[77] Anticholinergic drugs such as scopolamine are sometimes efficacious but are poorly tolerated by the elderly as a rule. A double-blind clinical trial failed to show efficacy of transdermal scopolamine.[47] Cardiac pacing is sometimes performed for severe and refractory cases but is often ineffective.[77] Methylphenidate is occasionally worth trying.[33]

When syncope is unpredictable, the patient and other people may be placed at risk by common activities such as driving. A position statement on this issue is available.[24]

Summary and Conclusions

In conclusion, syncope consists of loss of consciousness and muscle tone that is abrupt in onset, of short duration, and followed by rapid recovery. Syncope occurs in response to transient impairment of cerebral perfusion. Typical prodromal symptoms often herald onset of syncope, and postictal symptoms are minimal. Syncopal convulsions, resulting from cerebral anoxia, are common but are not a form of epilepsy, nor are there any accompanying EEG ictal discharges. Diagnosis is based on the history, physical, examination, and ECG findings. A major emphasis should be on distinguishing cardiac from noncardiac causes of syncope because of excess mortality of the former. Despite intensive study, one third of all syncope cases remain undiagnosed.

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Chapter 272

Metabolic and Endocrine Disorders Resembling Seizures

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Shehzad Basaria

Introduction

Patients frequently consult a physician because of alarming “spells.” These may consist of symptoms such as sudden malaise, a feeling of faintness, flushing, a perceptibly irregular or rapid heart beat, dizziness, sweating, confusion, as well as myriad other alarming complaints. The physician's task is to differentiate psychological from organic complaints and potentially dangerous from benign symptoms and to localize the symptoms to a particular system of the body—cerebrovascular, neurologic, endocrine, or other. When patients are seen with lip smacking, loss of consciousness, prolonged jerking movements, and tongue biting, the diagnosis of a tonic-clonic seizure is straightforward. More difficult diagnostic problems occur when the complaints are subjective, as with symptoms of autonomic or sensory origin, because objective confirmation of disease may be lacking, and the subjective perceptions (e.g., feelings of dissociation, anxiety, or panic) are often difficult to put into words.

Among the many entities considered in the differential diagnosis of “spells” are those associated with metabolic and endocrine disturbances, some of which have proved to be among the “great imitators” of other diseases, including hysteria. Endocrine or metabolic disturbances may in themselves cause seizures, or they may exacerbate epilepsies by lowering seizure thresholds. The primary emphasis of this chapter is on metabolic and endocrine disturbances that result in symptoms that may be mistaken for seizures.

General Comments Regarding Patient History

Spells associated with many endocrine disturbances are characteristically accompanied by other features of the endocrine disease. For example, patients with spells caused by thyrotoxicosis usually have tremulousness, weight loss, and sweating in addition to palpitations and anxiety attacks. In other endocrine or metabolic disturbances, however, few clinical signs may be present. In such cases, attention must be paid to the particular precipitating factors, pattern, course, duration, and resolution of the spell in the context of the patient's medical history. For example, in a patient who has undergone gastric surgery, the malaise, sweating, and light-headedness occurring at fixed intervals after meals should alert the physician to the possibility of reactive hypoglycemia with “dumping syndrome.” Similarly, patients with diabetes who are taking oral hypoglycemic agents or insulin may have the same symptomatology resulting from episodic hypoglycemia. Typical settings would be a lower-than-usual caloric intake, or unanticipated exercise without appropriate changes in insulin. In these cases, symptomatic hypoglycemia may supervene over the ensuing hours. Conversely, hyperglycemia may appear with intercurrent illness and decreased insulin dosage.

Particular inquiry into dietary habits, medications, and prior medical problems or surgery, therefore, is essential in making the appropriate diagnosis.

With some diseases, the constellation of signs and symptoms may provide the physician with a diagnosis through “pattern recognition.” For example, intermittent severe abdominal pain and episodes of limb paralysis, delirium, and “port wine”-colored urine are typical features of an acute intermittent porphyric crisis. A history of previous similar attacks, possibly triggered by drugs, should be sought. In a similar vein, the simultaneous occurrence of paroxysmal headache, facial flushing, and hypertension will evoke the diagnosis of pheochromocytoma.

Specific Metabolic and Endocrine Disorders

Hypoglycemia

Because the central nervous system requires a constant supply of glucose, hypoglycemia may produce transient neurologic dysfunction[51] that can be mistaken for or even precipitate seizures. When delivery of glucose to the central nervous system is insufficient, a number of signs and symptoms may appear (Table 1). The particular array of clinical features may vary with the rapidity of development of hypoglycemia and the depth of hypoglycemia, as may the degree of impairment and level of consciousness. The symptoms of hypoglycemia are generally divided into adrenergic symptoms and neuroglycopenic symptoms. The former include anxiety, nervousness, palpitations, diaphoresis, and tremors. Neuroglycopenic symptoms include lethargy, disorientation, confusion, blurry vision, stupor, and in severe cases seizures and coma. In rare cases, focal weakness may also be seen.

Table 1 Symptoms of hypoglycemia in insulin-dependent diabetes mellitus

Sweating	Tremor
Blurred/double vision	Weakness
Confusion	Vertigo
Odd behavior	Anxiety
Perioral paresthesias	Hunger
Sensation of cold	Ataxia
Slurred speech	Palpitations

Source: From Bouloux P, Kaplan PW. *Imitators of Epilepsy.* New York: Demos; 1994:201, with permission.

Table 2 Causes of hypoglycemia

Fasting hypoglycemia
Exogenous hyperinsulinism

- Sulfonylureas
- Alcohol

Endogenous hyperinsulinism
- Insulinomas
- Tumor production of insulin-like activity (IGF-2)

Endocrine causes

Adrenal insufficiency

Growth hormone deficiency

Miscellaneous disorders
- Hepatic disease
- Renal disease

Hypoglycemias of infancy and childhood
- Neonatal hypoglycemias
- Congenital deficiencies of glucogenic enzymes
- Ketotic hypoglycemia of childhood

Reactive hypoglycemia

Enzyme deficiency of carbohydrate metabolism
- Galactosemia
- Hereditary fructose intolerance
- Functional postprandial hypoglycemia

Source: Adapted from Bouloux P, Kaplan PW. *Imitators of Epilepsy.* New York: Demos; 1994:202, with permission.

The symptoms of falling levels of blood glucose usually occur episodically, and the diagnosis rests on demonstrating subnormal levels of blood sugar in the symptomatic patient. Some patients may lose the warning symptoms[17] and adapt to the sensations that accompany hypoglycemia. This is known as “hypoglycemia unawareness.” Patients particularly at risk are the elderly,[70] those taking adrenergic blocking agents,[47] and patients who have a history of frequent hypoglycemic attacks. The variability in the threshold at which particular patients experience symptoms is marked. Normal individuals when fasting may have a blood glucose concentration that falls below 45 mg/dL and remain asymptomatic; in contrast, some patients who have insulin-dependent diabetes mellitus and certain elderly patients become symptomatic when blood glucose

levels descend toward 45 mg/dL.[50,51] Diagnosis of symptomatic hypoglycemia, therefore, lies in determining a low plasma glucose level in the symptomatic patient, with relief effected when blood glucose concentrations are normalized (Whipple's triad).[73] It is important to appreciate that some poorly controlled diabetics (who have marked hyperglycemia) experience hypoglycemic symptoms (mostly adrenergic symptoms) even when their glucose levels are lowered toward normal. It is interesting that with better glycemic control, these symptoms resolve.

Causes of Hypoglycemia

The differential diagnosis of hypoglycemia includes the array of causes leading to the condition (Table 2). Because plasma glucose concentrations are affected by a number of agents, imbalance in these dynamic forces may cause hypoglycemia. In humans, there is a dynamic and often delicate balance between factors that increase blood glucose levels, such as epinephrine, cortisol, growth hormone, and glucagon, and factors that decrease glucose levels, including oral hypoglycemic agents, exogenous or endogenous insulin, and concurrent he- patic or renal disease. An excess of glucose-lowering agents or insufficiency of gluconeogenic mechanisms may result in symptomatic hypoglycemia. Common causes are oral hypoglycemic agents, excess exogenous or endogenous insulin, he- patic or renal disease, heavy alcohol use, a decrease in food intake, or unanticipated exercise in an insulin-dependent diabetic patient.[45] A number of drugs when taken concurrently may enhance or prolong the hypoglycemic effect of oral hypoglycemic agents or inhibit compensatory mechanisms of hepatic glucose release.[2] These include anticoagulants, beta-blockers, clofibrate, isoniazid, phenylbutazone, salicylates, and sulfonamides. Other drugs may precipitate hypoglycemia, including colchicine, disopyramide, haloperidol, paracetamol, pentamidine, perhexiline, and quinine. Insulin-treated patients may have hypoglycemic attacks as a result of missed meals, excess insulin dose, and exercise not compensated for by an increase in food intake or adjustment in insulin dose.

Of the oral hypoglycemic agents, the sulfonylureas are the most notorious in causing hypoglycemia. The elderly and the patients with renal disease are particularly sensitive to sulfonylurea-induced hypoglycemia (due to decreased clearance of the drug). They are also the most common cause of factitious hypoglycemia. This surreptitious use is most commonly seen in medical personnel and persons with family members on these agents.[15]

Excessive long-term alcohol intake, resulting in chronic disease of the liver, also predisposes to hypoglycemia because glycogen stores are depleted.[42] Similarly, patients who have not eaten for several days and who have a binge of moderate to heavy drinking may also experience transient or even prolonged hypoglycemia up to 1 day after the end of the binge.

Hypoglycemia may occur in patients after gastric surgery, later than the symptoms of "dumping syndrome." Overactivity of the "enteroinsular axis" is thought to result in excessive release of glucose-dependent insulinotropic peptide (GIP) and other hormones, which in turn increase insulin secretion after ingestion of glucose.[66]

Other rare causes of hypoglycemia include endogenous hyperinsulinism caused by insulin-secreting tumors (insulinomas) of the pancreas.[34] Of such tumors, 10% are malignant, 10% are of questionable malignancy, and the rest are benign.[53] Patients with multiple endocrine neoplasia type I may have multiple tumors that secrete a variety of hormones, including pancreatic polypeptide, glucagon, gastrin, and somatostatin. Symptoms typically include blurred vision, double vision, sweating, palpitations, weakness, confusion, behavioral changes, obtundation, and tonic–clonic seizures. Patients with adrenal insufficiency and growth hormone deficiency may also present with hypoglycemia. Finally, tumor (nonislet)-induced hypoglycemia is seen in rare retroperitoneal mesenchymal tumors that elaborate insulin-like growth factor II (IGF-II). Surgical resection is the treatment of choice in these patients.

Diagnostic Investigation

When the diagnosis of symptomatic hypoglycemia has been made, determination of the particular cause depends largely on the medical and surgical history, evaluation of medications that are known to impair glucose regulation, and a physical examination.

In insulin-treated patients, the query is directed at the dose, timing, method, and location of subcutaneous administration (e.g., thigh, which has greater absorption, especially if the patient exercises). A frequent cause of inappropriate dosing is self-administration of insulin by patients with impaired vision. Syringes with larger writing are now available. Attention should also be directed at patients taking oral hypoglycemic agents or other newly introduced drugs that may interfere with glucose regulation. Surreptitious injection of insulin may be deduced by a high plasma insulin level with a low plasma C-peptide concentration. This contrasts with excessive endogenous insulin production, in which a high plasma insulin level is accompanied by an appropriately high C-peptide level. Both sulfo- nylureas and insulinomas result in elevated levels of plasma insulin and C-peptide levels. Hence, measurement of serum levels of sulfonylureas is an important part of the workup of hypoglycemia. If insulinoma is suspected, endoscopic ultrasound, magnetic resonance imaging of the abdomen, and arteriography are the main imaging modalities. Octreotide scan is not very sensitive. Percutaneous transhepatic portal venous sampling may be needed in some cases.

Treatment

Treatment of episodic hypoglycemia is based on treatment of the underlying cause. In patients treated with insulin and hypoglycemic agents, careful attention to modification of the regimen may prevent hypoglycemic dips. The aid of a specialist in diabetes should be sought. After gastric surgery, "dumping syndrome" may be avoided by more frequent and smaller meals containing complex carbohydrates. Insulin-secreting tumors are usually resected; if they are inoperable, octreotide, a long-acting somatostatin analog, may be used. If hypoglycemia is a manifestation of adrenal insufficiency, physiologic glucocorticoid replacement results in the resolution of hypoglycemia.

Association with Epileptic Seizures

Hypoglycemia itself may be the cause of seizures. In infants, these usually occur on the second postnatal day in newborns who are small for gestational age. Occasionally, hypoglycemia may be seen in infants of diabetic mothers and in cases of syndromes associated with defects of gluconeogenesis, defects of organic or amino acid metabolism, and mitochondrial dysfunction. Hypoglycemia may trigger tonic–clonic seizures and cause paroxysmal electroencephalographic (EEG) activity that can be confused with seizure activity.

Hyperglycemia

Hyperglycemia is a state that develops gradually, typically during a period of days to weeks. Because changes are gradual and usually progressive, these events are not often mistaken for an epileptic disturbance. Hyperglycemia in the absence of ketosis, however, may be associated with a number of abnormal movements, including asterixis, paroxysmal choreoathetosis, hemiplegia, and partial epileptic seizures.[38,56] Such partial seizures are typically motor, often exhibit a jacksonian march, and may be reflex seizures or effort induced. The seizures are resistant to antiepileptic drugs, but they usually regress on treatment of the hyperglycemia within a few hours to a few days.[7] Occasionally, partial seizures may continue for long periods in the state of epilepsia partialis continua.[22,56] Ketotic hyperglycemia is much less frequently associated with seizures, possibly because of the antiepileptic effect of ketosis.

Hypocalcemia

The predominant clinical features of hypocalcemia are the consequence of a decrease in ionized serum calcium, which in turn leads to an increase in neuromuscular excitability. This may be accompanied by numbness and tingling in the fingers, paresthesias, stiffness, muscle cramps, carpopedal spasm, and perioral numbness. Associated clinical features include papilledema, cataracts, developmental defects, and mental retardation in the congenital forms of the disease and calcification of the basal ganglia with dyskinesias. The electrocardiogram may show prolonged QT_c intervals and T-wave changes.

Several conditions may be accompanied by hypocalcemia, each with its own constellation of clinical features. Well-described causes include thyroid and parathyroid surgery, chronic renal failure, renal tubular acidosis, malabsorption, hypomagnesemia, blood transfusion, acute pancreatitis, osteomalacia or rickets, vitamin D deficiency, intake of chelating agents, and pseudohypoparathyroidism.

Bedside diagnostic features include the Chvostek sign (twitching of the lips or nasal alae, or even of the entire half of the face, produced by tapping the branches of the facial nerve as it passes through the parotid gland above the angle of the jaw). The diagnostic indicator is a low level of ionized serum calcium. The underlying cause of hypocalcemia should be sought.

Tetany is characterized by flexor spasms in the arms and extensor spasms in the legs; it may resemble tonic-clonic seizures and can be induced by hyperventilation. Both tetany and partial or tonic–clonic seizures may supervene.[18] Tonic–clonic seizures can be treated by administering a slow intravenous infusion of 15 mL of 10% calcium gluconate under cardiac monitoring.

Hypercalcemia

The most common cause of hypercalcemia is primary hyperparathyroidism. In this condition, hypercalcemia is generally mild and typically develops over a period of months to years; in most cases, patients are asymptomatic. In contrast, malignancy-induced hypercalcemia usually develops rapidly and can be severe and is accompanied variably by anorexia, nausea, vomiting, weight loss, and constipation. Neurologic symptoms are general fatigue, muscular weakness, and proximal myopathy, with mental status changes that include personality changes, depression, stupor, coma, and tonic–clonic seizures. The major causes of hypercalcemia are primary or tertiary hyperparathyroidism, humoral hypercalcemia of malignancy, multiple myeloma, paraneoplastic disorders, bone metastases, thyrotoxicosis, milk-alkali syndrome, vitamin D intoxication, immobilization, and rarely Paget disease of bone. Adrenal insufficiency and acromegaly are other rare endocrine causes of hypercalcemia.

Occasionally, a more acute hypercalcemia is characterized by paroxysmal headache, nausea, vomiting, abdominal pain, and constipation. Muscle weakness, lethargy, and coma may supervene. There may be visual impairment, tonic–clonic seizures, and spike-and-wave discharges over the occipital regions.[26]

The diagnosis of hypercalcemia is based on the finding of a raised level of ionized calcium. The next step is to measure serum levels of intact parathyroid hormone (iPTH). This test is fundamental to differentiating between parathyroid and nonparathyroid causes of hypercalcemia. An electrocardiogram may show a shortened QT_c duration.

The underlying cause should be sought and treated. Acute management of hypercalcemia includes hydration with saline, subcutaneous calcitonin, and intravenous bisphosphonates.

Excess of Growth Hormone

Paroxysmal attacks of sweating that occur with excess levels of growth hormone may be mistaken for autonomic seizures.[25] Sweating occurs due to increased concentration of sweat glands as a result of growth hormone excess. In contrast to autonomic seizures, paroxysms are not associated with other ictal manifestations.

Hyperthyroidism

The acute malaise, anxiety, sweating, tremulousness, and tachycardia of hyperthyroidism may mimic partial seizures,[52] as may choreiform movements and encephalopathy.[1,24] Features of the illness that suggest thyrotoxicosis include heat intolerance, weight loss despite a healthy appetite, hyperdefecation, goiter, exophthalmos, palpitations, atrial fibrillation, and muscle wasting and weakness. Proximal myopathy is the classical presentation of Graves disease. Patients with severe thyrotoxicosis (thyroid storm) may present with fever, stupor or coma, pyramidal and bulbar dysfunction, and convulsions.[31,41] It is important to appreciate that many elderly patients may not have any of the typical clinical features of hyperthyroidism (apathetic hyperthyroidism). Cardiac arrhythmias, like atrial fibrillation, may be the initial presentation in these subjects.

The most common causes of hyperthyroidism include Graves disease, solitary toxic adenoma, and toxic multinodular goiter (Plummer disease) Other etiologies of thyrotoxicosis include iodine-induced thyrotoxicosis, various thyroiditides, factitious thyrotoxicosis, and central hyperthyroidism (TSHomas). Large metastases of follicular thyroid cancer are a rare cause of thyrotoxicosis. The diagnosis is based on finding an undetectable or suppressed thyroid-stimulating hormone (TSH and increased T_3 or free T_4 levels. Imaging with radioactive iodine is the gold standard in determining the etiology of thyrotoxicosis.

Occasionally, choreiform movements and encephalopathies occur. Clinical seizures may rarely supervene, and partial motor, adversive, and tonic–clonic seizures are reported. A rare manifestation of hyperthyroidism is hypokalemic periodic paralysis, which may be confused with a seizure. This entity is predominantly seen in individuals of Asian decent, and Graves disease is the most common underlying etiology. The attacks may last for minutes to hours. Ingestion of a carbohydrate meal is a well-known trigger (the release of insulin being responsible for shifts in potassium).

Hypothyroidism

Hashimoto thyroiditis is the most common cause of primary hypothyroidism. Other causes include history of thyroid surgery, neck radiation, lithium therapy, and central hypothyroidism. General symptoms include dry skin, constipation, cold intolerance, sallow skin discoloration, ovulatory dysfunction, and minimal weight gain. Hypothyroidism may be accompanied by neurologic complaints, including neuropathy, myopathy, choreoathetosis, dementia, or even coma.[10,37,57] Sudden falls from arrhythmias secondary to hypothyroidism rarely occur.[40] There may be nocturnal jerking movements from obstructive sleep apnea and, more rarely, central sleep apnea. Comatose, hypothyroid patients may have tonic–clonic seizures. In severe hypothyroidism, patients may develop psychosis with hallucinations (myxedema madness). Myxedema coma remains the dreaded complication of severe hypothyroidism. It usually occurs in the elderly and has a high mortality rate. Intravenous thyroxine therapy is indicated in these cases.

Diagnosis rests on finding elevated TSH and low T_3 or free T_4 levels in cases of primary hypothyroidism. In secondary hypothyroidism due to pituitary dysfunction, TSH levels are low or inappropriately normal. Imaging of the pituitary with magnetic resonance imaging (MRI) is mandatory in such cases to rule out mass lesions. Treatment involves replacement of thyroid hormone.

Hashimoto Encephalopathy

Very few entities in neurology and endocrinology have puzzled and at the same time fascinated clinicians (more neurologists than endocrinologists). Hashimoto encephalopathy is one such entity. The story began in 1966 when Lord Brain, a famous English neurologist, described a case of a man with confusion, disorientation, and seizures.[6] The patient also had transient episodes of fluctuating hemiparesis of different extremities and aphasia, which completely resolved. Investigations revealed abnormalities in EEG, and cerebrospinal fluid (CSF) showed elevated levels of protein. Brain antibodies were not detected in the serum. This patient had known Hashimoto thyroiditis with positive antithyroid antibodies and was on optimal thyroxine therapy during these episodes. According to Lord Brain, “the apparent onset of Hashimoto's disease—was followed by an extraordinary and puzzling neurological illness which waxed and waned for over a year.” He concluded, “antibody studies in future cases of unexplained encephalopathy should show whether we have described a syndrome or a coincidence.”

Hashimoto encephalopathy remains a diagnosis of exclusion, which is usually entertained by a neurologist when a case of acute or subacute encephalopathy is seen in a patient with no evidence of other etiologies (infectious and metabolic causes excluded), positive antithyroid antibodies, and good clinical response to steroids. It is important, however, to appreciate that positive antithyroid antibodies are present in 10% of the U.S. population.[23] Hence, it is debatable whether Hashimoto encephalopathy is a distinct clinical entity or a coincidence of a rare encephalopathy that occurs in an individual with a common endocrinologic condition and a not uncommon circulating antibody. Furthermore, there is no evidence that antithyroid antibodies are directly responsible for the encephalopathy. As a result, some have suggested that this entity should be called “steroid-responsive encephalopathy associated with Hashimoto thyroiditis.”

Three fourths of the cases of Hashimoto encephalopathy occur in women. Although many cases have mild hypothyroidism, many patients with encephalopathy are adequately treated with thyroxine. Furthermore, there is no correlation between the degree of hypothyroidism and the severity of encephalopathy. Clinical manifestations include headaches, fatigue, memory loss, confusion, and transient aphasia. Movement disorders like tremors, myoclonus, ataxia, and chorei- form movements may be seen. Some patients experience auditory hallucinations. It is important that, as described by Lord Brain, many patients have signs and symptoms suggestive of stroke. The majority of these symptoms are episodic, with most of them resolving either spontaneously or with glucocorticoid therapy. Approximately 80% of the patients have elevated levels of protein in the CSF; however, pleocytosis is only seen rarely.[9] Abnormalities in the EEG are present almost universally and include diffuse slowing of the waves or epileptiform abnormality. The findings on MRI are nonspecific and include white matter changes. In some cases, cerebral angiography shows perfusion abnormalities of the cortex and basal ganglia.[16] The majority of the cases respond to steroids, an important aspect of this condition.

Carcinoid Tumors

The carcinoid syndrome is characterized by paroxysmal flushing, gastrointestinal hypermobility, bronchoconstriction, and

right-sided cardiac valvular disease.[63] The paroxysmal flushing typically involves the face, neck, and upper trunk, producing a transient erythema and sensation of warmth, occasionally with palpitations. With more severe paroxysms, dizziness and rarely syncope can occur.[12] Other associated symptoms of gastrointestinal origin include diarrhea and abdominal cramps. This syndrome is produced by the release of serotonin from carcinoid tumors located in structures of the embryonic foregut (bronchus, pancreas, and stomach), midgut (duodenum and transverse colon), or hindgut (descending colon and rectum).[74] Rarely, carcinoid tumors only produce histamine, in which case, pruritis is the most common manifestation.

Carcinoid attacks may be induced by exertion, eating, emotional upset, and alcohol. The diagnosis is made by the finding of elevated levels of 5-hydroxyindoleacetic acid (5-HIAA), a serotonin metabolite, in the urine.[43] Recently, assays have been developed that measure serotonin levels in blood. Differentiation from simple partial seizures or auras in patients who experience flushing or heat sensation is made by the absence of subsequent confusion, automatisms, and convulsions that typify the progression of simple partial seizures to complex partial seizures; further distinguishing characteristics are the absence of bronchoconstriction, cardiac disease, diarrhea, and abdominal cramps. Nonetheless, ill-defined flushing or sensations of heat with upper gastrointestinal discomfort are seen with epileptic auras, and diagnostic confusion may occur.

Spiral computerized tomography (CT) of the chest and abdomen and an octreotide scan are the imaging modalities available. Treatment involves excision of the carcinoid tumors, when possible. Medical treatment, which is disappointing, involves blockade of the effects of secreted 5-hydroxyindoles with serotonin antagonists such as methysergide, α-methyldopa reduction of 5-hydroxytryptophan, or chemotherapy.

Pheochromocytomas

Pheochromocytomas are tumors that produce catecholamines, including norepinephrine, epinephrine, l-dopa, and dopamine. Ninety percent of these tumors arise in the adrenal medulla; the remaining 10% arise from extramedullary chromaffin tissue and are known as paragangliomas. In 10% of the cases the tumors occur bilaterally and may be malignant. Some are inherited as part of a multiglandular neoplastic syndrome (multiple endocrine neoplasia type II [MEN II]), von Hippel-Lindau disease, and von Recklinghausen disease.

Clinical presentation is typified by sudden headache, blurring of vision, hypertension, pallor, sweating, and malaise (Table 3).[59]

Poorly definable symptoms of sudden onset are suggestive of autonomic partial seizures or anxiety or panic attacks. The absence of confusional states, automatisms, and tonic–clonic seizures differentiates the spells from complex partial seizures and secondarily generalized tonic–clonic seizures. The clinical manifestations of pheochromocytoma, caused by tumor secretion of catecholamine,[32,54] which in turn stimulates adrenergic receptors, depend on the catecholamine or vasoactive neuropeptide produced: vasoactive intestinal peptide (VIP), calcitonin gene–related peptide (CGRP) and endothelin, neuropeptide Y, angiotensin II, and rarely corticotropin-releasing factor (CRF) and corticotropin (ACTH). Headaches occur in 80% of patients and are often accompanied by a sense of apprehension, tightness in the chest and abdomen, palpitations, and sweating.[62] Less frequently, nausea, vomiting, and generalized paresthesias occur. During the paroxysms, pallor or flushing and a sensation of warmth may occur with changes in heart rate. In rare cases in which the tumor preferentially secretes epinephrine or dopamine, the patients are normotensive and may even experience episodes of hypotension.

Table 3 Symptom complex in pheochromocytoma

Headache	Sweating
Palpitations	Pallor
Tremor/trembling	Feeling of exhaustion
Anxiety	Epigastric and chest discomfort

Dyspnea	Flushing/warm feeling
Paresthesias	Tightness of throat
Convulsions	Nonspecific dizziness
Syncope	Faintness

Source: From Bouloux P, Kaplan PW. *Imitators of Epilepsy.* New York: Demos; 1994:205, with permission.

With their sudden brief onset (typically 15–20 minutes), often associated with a sensation of impending doom, these spells may resemble complex partial seizures, but the absence of true confusional states and the more frequent occurrence of sudden headache, hypertension, visual dysfunction, and vomiting differentiate the symptoms of pheochromocytoma from those of complex partial seizures.

The diagnosis of pheochromocytoma is based on the demonstration of inappropriate catecholamine secretion in blood and urine or abnormal secretion of urinary metabolites. Computed tomography or magnetic resonance imaging may localize tumors, as may the chromaffin-seeking radioactive nuclide ^{131}I-metaiodobenzyl guanidine.[55]

Paroxysms may occur spontaneously or with movement that induces release of vasoactive peptides/catecholamine from the tumors. Movements that displace abdominal contents including straining, lifting, and bending forward, and any strenuous exercise may precipitate spells.

Treatment is by surgical excision of the tumors after complete pharmacologic alpha- and beta-blockade.

Menopausal Vasomotor Flushes

Menopause is frequently accompanied by agitation, anxiety, depression, and hot flushes, associated with increases in levels of gonadotropins.[8] Flushes are not accompanied by impaired consciousness or other features of complex partial seizures. Autonomic seizures, for which they may be mistaken, are usually accompanied by sweating, dilated pupils, salivation, and changes in heart rate, respiration rate, and blood pressure, and they rarely occur without other seizure manifestations. Symptoms may be alleviated by estrogen replacement therapy.

Porphyrias

Porphyrias are disorders of porphyrin metabolism and heme biosynthesis caused by inherited enzyme defects.[5,35] The absence of particular enzymes in heme synthesis leads to the accumulation of psychoactive and neurotoxic metabolites that produce a wide spectrum of acute, subacute, and chronic neurologic changes. The manifestations of subacute changes may resemble seizures.

Table 4 Clinical features of acute intermittent porphyria: comparison of percentage incidence before puberty, in adolescence, and in adulthood

	Adult cases				Pediatric cases	
	Waldenström[68] (321 cases)	**Markovitz[33] (69 cases)**	**Goldberg[19] (50 cases)**	**Stein and Tschudy[58] (46 cases)**	**0–14 yr (37 cases)**	**15–19 yr (35 cases)**
Male patients	40	39	38	26	57	26
Female patients	60	61	62	74	43	74
Abdominal pain	85	95	94	95	97	94
Vomiting	59	52	78	43	70	49
Constipation	48	46	74	48	46	37
Limb pain				50	22	40
Fever	37	36	14	9[a]	51	43
Hypertension	40	49	54	36	38	57
Tachycardia	28	51	64	80[a]	68	66
Mental changes	55	80[b]	58	40[a]	51	74
Limb paresis	42	72	68	60[a]	51	74
Bulbar/respiratory paresis		37		10	14	34
Hyporeflexia	16[c]		54	29[a]	57	69
Seizures	10		16	20[a]	30	34
Death	30	58	24	9.5	16	37

[a] Based on 34 cases.

[b] Includes seizures.

[c] Areflexia.

Source: From Kaplan PW, Lewis DV. Juvenile acute intermittent porphyria with hypercholesterolemia and epilepsy: a case report and review of the literature. *J Child Neurol*. 1986;1:38–45, with permission.

Acute Intermittent Porphyria

Acute intermittent porphyria (AIP), the porphyric syndrome most frequently confused with seizures, is most commonly seen in Sweden.[68,69] Inherited as a mendelian dominant trait, the syndrome can occur with a number of mutations that result in defectiveness of the enzyme porphobilinogen deaminase (PBGD). Although it was originally described in young adults after the onset of puberty, it has been increasingly recognized in children. Among adults, it affects women twice as often as men, whereas in children, it affects both sexes equally.[27] The incidence of clinical features and seizures in pediatric and adult patients undergoing medical treatment is given in Table 4.

Acute attacks may be heralded for years by “nervousness” and tiredness. Attacks may last for days to weeks and are characterized by symptoms that can be referred to psychic, autonomic, and peripheral nerve dysfunction.[68] Dominating the clinical picture are abdominal pain, constipation, and tachycardia. Other clinical features are optic atrophy, ocular palsies, hoarseness, general malaise, lethargy, and coma. During the attack, there may be an agitated delirium with hallucinations and psychosis. Isolated neuropathies, with wrist or foot drop progressing to a flaccid limb paralysis, may supervene and take months to regress.

In the early stages of the crisis, the psychosis and encephalopathy may dominate in the absence of the other typical features of porphyria, although the classic “port wine”-colored urine may appear.[35,65,71]

Porphyria Cutanea Tarda

Porphyria cutanea tarda (PCT), caused by a deficiency of uroporphyrinogen decarboxylase in the liver, is characterized by the presence of urocarboxylic and heptacarboxylic porphyrins in the urine and isocoproporphyrin in the feces. It usually does not occur with acute neuropsychiatric symptoms, but it may be associated with hallucinations and dysphoria and, occasionally, seizures.[29,30] Seizures may be precipitated in patients with epilepsy from other causes who are being treated with porphyrinogenic antiepileptic drugs. It is differentiated clinically from AIP by the presence of skin lesions. Exposed areas of the skin, face, and hands are photosensitive, resulting in ulcerative vesicular eruptions. Coexisting liver disease and diabetes further complicate the diagnosis, which is based on a urinary porphyrin screen. Valproate and gabapentin have been safely used to treat seizures in PCT,[11,29] but valproate has precipitated attacks in AIP.

Variegate Porphyria

Variegate porphyria is the term used by Dean and Barnes[13] to denote the condition of patients from South Africa, who have a mixed clinical picture of photosensitivity, as in PCT, and neurologic episodes, as in AIP. Variegate porphyria is associated with urinary porphobilinogen and D-aminolevulinic acid (D-ALA) and fecal protoporphyrin and coproporphyrin. Episodes can result in sudden hallucinosis, psychosis, and catatonic states, as well as seizures.[13,44] It may be precipitated by oral contraceptives.

Hereditary Coproporphyria

Hereditary coproporphyria (HC), the rarest of the hepatic porphyrias, is characterized by fecal and urinary excretion of coproporphyrin. It may start in childhood, be precipitated by barbiturates and sulfonamides, and be manifested in crises with hypertension, abdominal pain, tachycardia, constipation, confusion, and delirium.[4] Subacute and acute neuropathies may lead to limb paralysis. Epileptic seizures frequently occur, often predating the first diagnosed porphyric crisis.[20]

Treatment

There are three aspects to the treatment of porphyria: (a) avoidance of all drugs known to be porphyrinogenic;

(b) interruption of an attack by preventing induction of D-ALA synthetase with a high intake of carbohydrate or administration of intravenous glucose and reducing porphyrin production by the administration of intravenous hematin, and (c) symptomatic management of autonomic symptoms and pain with propranolol, chlorpromazine, meperidine, and morphine.

Porphyric crises can be precipitated by many drugs, including most antiepileptic drugs (AEDs), estrogens, alcohol, and oral contraceptives.[65] Some AEDs without porphygenic effect in a rodent model are levetiracetam, gabapentin, zonisamide, and possibly low doses of oxcarbazepine. The diagnosis is made with the Watson-Schwartz test and enzyme assays that reveal decreased activity of PBGD.

Problems in Diagnosis of Seizures and Management

Although porphyric crises may resemble simple partial sensory seizures, simple partial psychic seizures, and complex partial seizures, the prominence of abdominal pain, tachycardia, constipation, and paralysis distinguish them from ictal syndromes. The porphyric crisis itself, however, may precipitate partial or tonic–clonic seizures. In children, AIP and HC may be associated with mental retardation, itself a risk factor for epilepsy.[27,68] The cause of the psychic and epileptogenic manifestations is unknown, but some investigators have suggested that toxicity is a consequence of the structural similarity of porphobilinogen and D-ALA to γ-aminobutyric acid (GABA) and glutamate.[39] Some authors suggest that porphyrins are endogenous ligands for mitochondrial benzodiazepine receptors.[67]

The management of patients with porphyria who are in or between crises is complicated by the frequently marked porphyrinogenic qualities of most antiepileptic drugs. Barbiturates, carbamazepine, clonazepam, diazepam, ethosuximide, the hydantoins, primidone, paraldehyde, and valproate may all induce crises and are porphyrinogenic in chick embryo hepatocyte cultures.[46,49,60,61] Triggering of the first porphyric crisis around puberty derives from the fact that steroids, including estradiol, containing a 5-β configuration induce D-ALA synthetase, thus precipitating the porphyric crisis.[28,72] Oral contraceptives also increase urinary enzyme excretion in normal patients, and asymptomatic relatives of patients with porphyria should avoid contraceptive pills.[14] The cyclic nature of AIP attacks of varying severity, usually late in the luteal phase or during ovulation, may simulate the catamenial exacerbation of seizure disorders.[65] As with catamenial seizures, attempts to suppress ovarian cycling by oral contraception to reduce porphyric crises have met with variable success.[3]

The chick embryo hepatic cell culture has been used to test the potential of antiepileptic drugs to induce porphyria.[21,46] Reynolds and Miska[46] found that phenytoin, phenobarbital, carbamazepine, clonazepam, and valproate may all increase porphyrin levels. Benzodiazepines (diazepam), bromides, magnesium sulfate, and gabapentin have been suggested as alternatives in the treatment of porphyria based on single case reports and small reviews of the literature.[27,46,49,60,61]

Table 5 Safe drugs for patients with porphyria

- Analgesics
  - Codeine
  - Narcotic analgesics
- Antibiotics
  - Penicillins
  - Streptomycin
  - Tetracycline
- Antiemetics
  - Chlorpromazine
  - Prochlorperazine
  - Promethazine
  - Diphenhydramine

- Trifluoperazine
Anticonvulsants
- Bromides
- Clonazepam
- Diazepam
- Gabapentin
- Levetiracetam
- Zonisamide
- Vigabatrin
Others
- Chloral hydrate
- Corticosteroids
- Propranolol

Independent of the acute porphyric attack per se, partial or generalized seizures in children[27] or adults may supervene in about 1% to 30% of hospitalized patients or patients brought to medical attention. In genetically susceptible individuals, the incidental intake of one of the many drugs thought to precipitate porphyria may induce a porphyric crisis, which may, in turn, be associated acutely with partial or generalized seizures. However, seizure onset may appear after the original crisis or even between crises. Some patients may have both conditions, apparently occurring independently, with the onset of epilepsy preceding the first porphyric attack. Common drugs and antiepileptic agents that can usually be safely used in porphyria are listed in Table 5.

Idiopathic Recurring Stupor

Idiopathic recurring stupor (IRS) is a rare disease that has only recently been elucidated. It is a syndrome of recurring obtundation or coma unassociated with a known toxic, metabolic, or structural abnormality.[48,64] Events in the few cases described occur in early middle age or in older male patients who are light drinkers. Characteristics are drowsiness that is not associated with alcohol intake, slurred speech, drunken gait, and aggressiveness upon challenge. Lethargy deepens to sleep, from which the patient can be briefly aroused only with vigorous stimuli. Spells, which may occur weekly but are usually infrequent, can last up to 3 days, after which the patient may appear stunned and be amnestic.

During stupor, there may be up to a 300-fold increase in levels of endozepine-4, an endogenous ligand for benzodiazepine recognition sites on $GABA_A$ central nervous system receptors, with normalization of levels between attacks.[48] Ictal EEGs reveal a fast (14- to 16-Hz) unreactive background activity without apparent epileptiform activity.[64]

The stuporous state can be reversed by the pure benzodiazepine antagonist flumazenil.

Table 6 Metabolic and Endocrine imitators of epilepsy

Hypoglycemia	Relation to meals or fasting Hunger Characteristic prodrome Hypoglycemia correlated with symptoms Response to glucose
Hyperglycemia	Elevated blood glucose and osmolarity Prolonged confusion

	Movement disorder syndromes Epilepsia partialis continua
Hypocalcemia	Acral and perioral paresthesias Tetanic spasms and Chvostek sign Low serum calcium Response to calcium
Hyperthyroidism	Anxiety, tremor, sweating, weight loss, tachycardia Choreiform movements Rare periodic paralysis Suppressed thyroid-stimulating hormone, elevated serum T_4, T_3
Hypothyroidism	Choreoathetoid movements Confusion, stupor, or coma Sleep apnea Decreased serum T_4, elevated thyroid-stimulating hormone
Pheochromocytoma	Hypertension, headache, malaise, pallor Episodes resembling panic attacks Secretion of catecholamines Computed tomography, magnetic resonance imaging, or radionuclide tumor identification
Carcinoid	Flushing with transient erythema Bronchoconstriction, diarrhea Increased serotonin metabolites in urine Radiologic localization of gastro- intestinal or bronchial tumor
Porphyria	Paroxysmal hyperautonomic symptoms Abdominal pain, delirium, neuropathy Generalized seizures, provoked by drugs Porphyrins in the urine
Hyponatremia	Fluctuating confusion or stupor Generalized seizures Low serum sodium and osmolarity Syndrome of inappropriate antidiuretic hormone

Source: From Bouloux P, Kaplan PW. *Imitators of Epilepsy.* New York: Demos; 1994:210, with permission.

Movement Disorders

A marked tremor may be confused with an epileptic seizure. Several metabolic and endocrine disorders include tremor, such as hypoglycemia and pheochromocytoma. Choreiform movements may be seen with hypocalcemia, hypoglycemia, hyperglycemia, hyperthyroidism, and porphyria. Hypoglycemia and hyperglycemia may induce myoclonus.

Acute Confusional States

Acute confusional states or delirium may also resemble complex partial seizures. Many metabolic and endocrine disorders, including hyponatremia and hypernatremia, hypocalcemia and hypercalcemia, hypothyroidism and hyperthyroidism, hypocortisolemia and hypercortisolemia, hypoparathyroidism and hyperparathyroidism, hepatic insufficiency, and porphyria, may cause delirium.

Summary and Conclusions

Many metabolic, endocrine, and vasoactive/autonomic disturbances share clinical features with simple partial and some complex partial seizures. Differentiating them from myoclonic or tonic–clonic seizures usually poses little difficulty. The key to differentiating partial seizures from metabolic, endocrine, and vasoactive/autonomic dysfunctions is usually the constellation of signs and symptoms associated with the two respective categories. Although rare, simple psychic, autonomic, or sensory seizures not infrequently progress to complex partial seizures or secondarily generalized tonic–clonic seizures. Metabolic or endocrine conditions may lower seizure thresholds, but typically they cause generalized tonic–clonic seizures that are not preceded by partial symptomatology. Similarly, most endocrine and metabolic dysfunctions are associated with other clinical features that distinguish them from partial seizures. Prominent malaise, sweating, anxiety and palpitations, diarrhea or constipation, and abdominal pain or cramping occur relatively infrequently with partial seizures.

Hypoglycemia is one of the most important mimics of epilepsy. The temporal relationship of the cardinal features of hypoglycemia to fasting, food intake, or intake of hypoglycemic drugs should alert the physician to the correct diagnosis, despite the fact that the symptoms of anxiety, clamminess, tachycardia, sweating, and confusion are also associated with anxiety states, hyperventilation, and rare conditions such as pheochromocytoma and carcinoid syndrome. Differentiation rests on demonstration of hypoglycemia and the symptomatic relief provided by reestablishment of normal glucose levels. Rarer causes, including carcinoid syndrome, pheochromocytoma, and porphyria, may be tested for on an individual basis, with a higher diagnostic probability during an attack. Typically, the array of multisystem features, including sudden headache, hypertension, and marked sweating (pheochromocytomas), diarrhea and abdominal cramps (carcinoid syndrome), and abdominal pain, constipation, and paralysis (acute porphyrias), helps to differentiate these conditions.

A more complex issue is the coincidence of epileptic seizures. Carcinoid tumors and pheochromocytomas are rarely associated with seizures. Tonic–clonic seizures, however, are seen with hypoglycemia, as are characteristic partial motor seizures and epilepsia partialis continua in nonketotic hyperglycemia. Similarly, the porphyric syndromes, in addition to resembling certain seizure types, may be associated with epileptic seizures or be precipitated by antiepileptic drugs. The management of these conditions, therefore, involves not only diagnostic differentiation, but also the appropriate management of metabolic and endocrine disorders on the one hand and intercurrent seizures on the other.

Blanket testing for rare endocrine or metabolic disorders is neither justified nor cost-effective. The tests are frequently invasive. It is only with justifiable suspicion of the rare entities that costly and morbid investigation should be undertaken. Table 6 summarizes the characteristic presentations of endocrine and metabolic disorders.

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Chapter 273

Systemic Nonepileptic Paroxysmal Disorders From Neonatal to Childhood Periods

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Introduction

Paroxysmal phenomena during neonatal and childhood periods cause intermittent or recurrent motor or behavioral signs or symptoms that must be distinguished from epileptic disorders. The clinician's diagnostic acumen can be especially challenged by specific behaviors. Nonepileptic paroxysmal disorders can be on either a neurologic or a systemic basis. The clinical context may help to distinguish paroxysmal nonepileptic disorders from epileptic seizures. Before committing to a specific pharmacologic intervention with medications, which may both be unnecessary and place the child at risk for adverse effects, alternative etiologies first must be considered. Home videography of the suspicious event can be pivotal for the clinician to reach a prompt and correct diagnosis with minimal investment in time and resources. Synchronous video-neurophysiologic monitoring either in the inpatient or outpatient setting[1,65,70] may also be necessary more definitively to categorize the event as epileptic or nonepileptic.

The child's age, state of arousal, and organ system involvement and an accurate description of the event by a witness will lead, in most cases, to the correct diagnosis. One must always be alert to nonepileptic disorders that occur in the context of a child who also has epilepsy. An early classification by Prensky[53] utilized functional categories to subdivide disorders: Disease-related behaviors, altered tone or consciousness, respiratory disturbances, perceptual disturbances, behavioral disorders, and unusual movements (see Table 1). Recent reviews further highlight selected disorders in young children.[18,19,22,48] Discussion of specific epileptic and nonepileptic paroxysmal events of neurologic origin such as nocturnal frontal lobe epilepsy, migraine, tic disorders, sleep disorders, psychogenic seizures, and cerebrovascular events are reviewed elsewhere in this book.

Relative to maturation, these paroxysmal disorders can be referred to as transient, paroxysmal, and/or chronic in presentation.[19] The proportion of transient events is highest during childhood, with the preponderance occurring during the first year of life. Many disorders remain idiopathic and unassociated with other neurologic diseases. When investigations are performed, test results are often normal. The clinician must therefore rely on clinical experience and consider a functional mechanism without known pathophysiologic explanations. Knowledge of these conditions is essential for the pediatric neurologist to avoid unnecessary tests and treatment while alleviating family anxiety (Table 1).

Disease-Related Behaviors

Various systemic disease states present with recurrent signs and symptoms during infancy and childhood that may be misdiagnosed as epilepsy. Alteration of consciousness or muscle tone, focal neurologic deficits, and diffuse weakness may be clinical signs of systemic nonepileptic paroxysmal disorders.

Tetralogy Spells

This phenomenon is characterized by episodes of cyanosis, dyspnea, and unconsciousness and can present during the first several years. The repertoire of events occurs in 10% to 20% of children with congenital heart disease and may result in seizures. Anoxia-induced seizures occur in such individuals who suffer chronic and significant hypoxemia. Such episodes are labeled "tet spells" because young children with the especially cyanotic congenital heart lesions (such as tetralogy of Fallot) usually present in this manner. The pathogenesis for "tet spells" is the sudden increase in right-to-left shunting of blood through the heart with sudden oxygen desaturation. On careful history taking, attacks of hyperpnea and cyanosis are seldom misinterpreted as epileptic seizures. Loss of consciousness may result from anoxia or hypoxia, however, which then may precipitate seizures in certain children and, therefore, may be confusing to the clinician. For those children old enough to be ambulatory, taking a squatting position and then remaining nearly motionless is a maneuver for recovering cardiac reserve.[49]

Table 1 Systemic NonEpileptic Paroxysmal Disorders

Disease-related behaviors	**Behavioral disorders**
Tetrology spells	Head banging or nodding
Cardiac arrhythmias	Rumination
Poststreptococcal autoimmune disorders	Nightmares
Hypoglycemia	Night terrors
Hypocalcemia	Sleepwalking
Hydrocephalic spells	Confusional states
Hyperthyroidism	Panic attacks
Periodic paralysis	Dyscontrol syndrome or rage attacks
Gastroesophageal reflux	Munchausen syndrome by proxy
Drug poisoning (e.g., neuroleptics)	Psychotic states (i.e., fugue spells, hallucinations)
Cerebrovascular events	Stereotypic behavior
Loss of tone or consciousness	**Unusual movements**
Syncope	Jitteriness or tremulousness

Drop attacks	Shuddering
Narcolepsy/cataplexy	Benign sleep myoclonus (neonate or infant)
Attention-deficit hyperactivity syndrome	Exaggerated startle responses (i.e., hyperekplexia)
Respiratory disturbances	**Other unusual self-stimulator behaviors**
Infant apnea	Paroxysmal torticollis
Apparent life-threatening events	Masturbation
Breath-holding (including vagotomy)	Withholding, constipation
Hyperventilation	Transient dystonia, choreoathetosis
Perceptual Disturbances	Paroxysmal choreoathetosis or dystonic spasms
Headache (i.e., migraine)	Kinesigenic or nonkinesigenic
Abdominal pain	Tic disorder or Tourette syndrome
Vertigo, dizziness	Paroxysmal tonic up gaze

Cardiac Arrhythmias

Children with recurrent episodes of loss of consciousness or alterations in arousal may suffer from cardiac arrhythmias. Disturbances of cardiac conduction of either intracardiac or extracardiac origin include sick sinus syndrome,[60] Jervell-Lange-Nelson syndrome, which is genetically determined and includes an associated deafness,[29] and Ward-Romano syndrome.[51] Therefore, careful history taking and examination may reveal characteristic features such as hair hypopigmentation, hearing loss, or dysmorphea. Syncope may frequently include convulsive movements similar to an Adams-Stokes attack. The prolonged-QT syndrome should be suspected in children particularly with underlying cardiac disease on a genetic basis such as the velocardiofacial syndrome (i.e., chromosomal 22q 11.2 deletion).[31] Prolonged-QT syndrome may be benign and transient or prolonged with risk for sudden death.[67] Prognosis is guarded because sudden unexpected death may occur at any time. True epileptic seizures may ensue in affected children as a result of asphyxia-induced brain injury incurred during prolonged episodes of hypoxemia during cardiac arrest. A cardiologic evaluation, including a prolonged electrocardiographic (ECG) recording and/or ECG during exercise may be required.

In a recent study of adults, 20% of patients referred to a neurologic department with possible idiopathic epilepsy were subsequently found to have cardiac arrhythmias that caused or significantly contributed to their symptoms.[60] Pediatric populations referred to neurology or epilepsy clinics may reflect comparable percentages, but few studies are available for comparisons with older populations. A report of sudden death in the young presenting with presumed cardiac arrhythmias was the most common cause of mortality in people 5 to 35 years of age. The two most common noncardiac causes of sudden death were epilepsy (23.8%) and intracerebral hemorrhage (23.8%).[55] In another study of adult epileptic patients, one third showed ictal bradycardia, with greater than one half experiencing serious cardiac events meriting pacemaker placement.[58] In general, sinus tachycardia accompanies approximately 90% and bradycardia or asystole 0.5% of all seizures.[72]

Metabolic Abnormalities: Hypoglycemia and Hypocalcemia

Hypoglycemia may occasionally challenge the clinician because of its association with unusual symptomatology. Both seizures and nonepileptic behaviors occur with hypoglycemia at any age, including the neonatal period. Neonates with hypoglycemia may present with tremulous behavior. Rare metabolic disorders can present early in life with hypoglycemia associated with, for example, hyperammonemic states, leucine intolerance, and hereditary fructose intolerance. Particularly after 1 year of age, unusual episodes of unconsciousness, stupor, or even seizures may occur during the early morning hours after an all-night fast. Postevent confusion or stupor can be prolonged after hypoglycemia-induced seizures. Such events may occur after episodes of vomiting, diarrhea, or transient reduced food intake, sometimes in the setting of a transient illness. The combination of symptoms associated with the condition of ketotic hypoglycemia[8] accounts for approximately 50% of cases of hypoglycemia that occur during early childhood. The child appears grossly ketotic during the attack and may exhibit marked hyperventilation. Acetonuria is an essential feature, which is rapidly corrected by administration of glucose. Hospitalization with carefully controlled provocation tests are suggested to induce hypoglycemia, such as with the administration of a ketogenic diet. Treatment consists primarily in preventing ketosis by adhering to regular mealtimes, particularly during times of illness, together with glucose supplementation. Of course, hypoglycemia and seizures may coexist; children may have epileptiform discharges on electroencephalogram (EEG), which may support a seizure diagnosis but not be interpreted in the context of the patient's clinical history. For example, neonatal hypoglycemia can result in injury to parietal-occipital cortical regions, which may later present as one form of focal epilepsy, involving posterior pathways.

Hypocalcemic stress usually results in seizures and can be secondary to primary or secondary hypoparathyroidism (with or without genetic cardiac syndromes). Severe nutritional deficiencies may be associated with poor feeding practices, starvation, or chronic diseases such as malabsorption syndromes or rickets.[2] A rare genetic disease of familial hypomagnesemia may be associated with hypocalcemia.[68] Rarely, profound hypocalcemia can result in nonepileptic tetanic spells,

including generalized clonic activity, jaw rigors, and tremulousness.

Gastroesophageal Reflux

Infants may demonstrate episodic extension and lateral flexion of the head, usually in association with feeding. This syndrome was first described by Kinsbourne[34] and is sometimes termed “Sandifer syndrome” because the first patient described by Kinsbourne was under the care of Dr. Paul Sandifer. Although these seizure-like episodes suggest epilepsy, gastroesophageal reflux disorder (GERD) should be suspected after a careful history is obtained. In a retrospective review of 342 infants presenting with symptoms suggestive of GERD, all were <1 year of age; they presented with regurgitation, choking, irritability, failure to thrive, an apparent life-threatening event (ALTE), or wheezing.[64] In a study of 69 infants with ALTE, GERD was diagnosed in 38 cases and gastric volvulus in 21.[45]

Gastrointestinal radiographs, such as barium swallow study, document reflux with or without hiatal hernia or other morphologic abnormalities of the upper airway or gastrointestinal tract. Surgical correction is sometimes required to correct such attacks. The age range for these events is wide, beginning during the neonatal period and extending into adolescence. For infants, choking, apnea, laryngospasm, and opisthotonos also commonly occur,[25] whereas other gastrointestinal complaints, weight loss, or sleep disturbances are noted for older children.

Altered Muscle Tone or Consciousness

The following discussion of syncope does not include neurologic conditions, such as cataplexy associated with the sleep disturbance of narcolepsy, or the inattention associated with attention-deficit hyperactivity disorder.

Syncope

Syncope is a common occurrence for adults and older children and is usually distinguished from true epileptic seizures by the historical description of a witness (see Chapter 271).[5] Patients describe warning signs of lightheadedness, dizziness, or visual dimming, such as graying out or browning out. Nausea may also be described after the event. Subjective feelings of temperature change and profuse sweating are also described. Sometimes a specific stimulus such as the sight of blood, minor trauma, or enclosure in a confined space may precipitate an attack. Orthostatic syncope may follow after prolonged standing or sudden change in posture. A careful review of a family history may document similar events in other relatives.[6]

Reflex syncope may also be described with certain physiologic maneuvers such as coughing, swallowing, or micturition.[32] Table 2 lists some causes of syncope, some of which are described elsewhere in this chapter, such as cardiac arrhythmias.

Table 2 Causes of Syncope

Menstruation in females	Decreased blood volume
Anemia	
Vasovagal	Fear Pain Unpleasant sights
Reflex	Cough Micturition Swallowing Carotid sinus pressure
Decreased venous return	Orthostatic with Valsalva maneuver
Disease states Cardiac Cerebrovascular insufficiency	Arrhythmia, obstructive outflow
Familial undetermined causes	

Syncopal events in the neonate, infant, or preverbal children have unique diagnostic challenges. Events may occur precipitously following surprise, pain, or prolonged crying. Breath-holding spells are discussed later, given the prominent respiratory component to this event. Underlying illnesses such as cardiorespiratory or metabolic-genetic causes may suggest a pathophysiologic mechanism. Neurocardiogenic syncope and neurologic disorders (80% and 9%, respectively) are the most common diagnoses for pediatric patients presenting to an emergency department.[41] Cardiogenic studies such as prolonged ECG monitoring, ultrasonography of the heart, or a tilt-table test may help to document associated abnormalities or capture events. Serum studies during an attack may document metabolic disturbances, such as hypoglycemia. Rarely, syncope triggers epileptic seizures, requiring both cardiologic treatment such as antiarrhythmic medication or cardiac pacing, as well as antiepileptic medications.[28] Patients with syncope, however, may have a few clonic jerks or even incontinence during or following the syncopal event[52] without evolving to seizures.

The physical examination of syncopal patients yields normal results. Blood pressure changes from supine to standing positions, however, may demonstrate a substantial drop in the diastolic component, supporting the diagnosis of orthostatic syncope. A tilt-table test may also be helpful. If one documents a blood pressure reduction of more than 15 points or the presence of a sinus bradycardia on standing, orthostatic hypotension should be suspected. A cardiologic evaluation including investigation for a heart murmur or dysrhythmia should be considered. Exceptional cases of congenital heart block have been associated in children with chronic myopathy, ophthalmoplegia, deafness, and ataxia, termed the Kearne-Sayne syndrome.[3]

If an attack is prolonged, a tonic motor seizure may occur. In a review of 77 patients appearing in an emergency room, 40 had syncope, 17 had near-syncope, and 20 did not have a syncopal episode. Vasovagal (50%) and orthostatic hypertension (20%) were the most common causes of syncope. Near-syncopal episodes occurred with lightheadedness (29%), seizures (18%), tension headaches (12%), and migraine (6%).[52] Adolescents, particularly those who lift weights or perform gymnastics, may induce syncope by stretching or straining the musculature, including inducing a neck-hyperextended position.

Children with recurrent symptoms should be evaluated by a cardiologist. Autonomic functioning of patients with beta-adrenergic hypersensitivity should be tested. A tilt-table test is particularly useful, sometimes with administration of isoprotosenol infusion as a provocative agent to induce blood pressure changes.[23]

Respiratory Disturbances

Primary respiratory disorders most commonly occur without associated seizures. These symptoms, however, may be confused with seizures. At times, clonic jerks or isolated seizures may follow primary apnea.[69] An electroencephalogram or polysomnogram during such events will help to distinguish a respiratory disorder from a true seizure.

Infant Apnea or Apparent Life-threatening Events

Apnea usually occurs during sleep and may be associated with centrally mediated hypoventilation, airway obstruction, or aspiration. Paroxysmal events are sometimes commonly referred to as apparent life-threatening events (ALTEs). On polysomnography, central apnea is defined as the absence of both chest and abdominal movements, as well as a cessation of airflow at the nares. Obstructive apnea usually involves movement of the chest and abdomen without airflow at the nares. Clonic or myoclonic jerks may occur during the apnea episode but do not represent true epileptic seizures. Most do not define apnea until it reaches durations of 15 to 20 seconds. Apnea associated with preterm infants is the most common presentation, but it also may occur in older infants.

If apnea occurs while a child is fully awake, this may be associated with gastroesophageal reflux.[26,63] Such an event is common usually when the infant is laid supine after a feeding, and aspiration may result following the reflux event.

Apparent life-threatening events predominantly affect children younger <1 year of age. This syndrome is characterized by a frightening constellation of symptoms in which the child exhibits some combination of apnea, color change, change in muscle tone, coughing, or gagging.[24] Recent studies highlight that a diagnostic testing strategy should depend on the outcome of the initial clinical assessment.[4,42] Together the two studies found that 50% to 70% of patients were correctly diagnosed based on the history and examination. Suggested algorithms follow a stepwise approach, with investigations initially directed by historical and clinical findings. The first step is consideration of child abuse. Based on information from six studies, baseline studies were suggested as follows: (a) basic blood tests, (b) infection screens, (c) metabolic workup, (d) cardiologic evaluations or ancillary organ system monitoring such as EEG, (e) polysomnography, and (f) pH probe studies.[42] It has also been recently emphasized that there are clear differences in epidemiology and risk factors between ALTE and sudden infant death syndrome (SIDS).[33]

Breath-holding Spells

This phenomenon is common between 6 months and 6 years and is often confused with tonic seizures. The child is described as falling, followed by tremulousness or convulsive, clonic-like movements. Two forms—cyanotic and pallid spells—have been reported, both resulting from reflex vagal changes that produce bradycardia and decrease cerebral blood flow. The cyanotic form of breath-holding spell is typically more common, beginning during the second or third year of life in response to anger, fear, excitement, or minor injury. The child will cry and suddenly stop breathing, often during expiration. Cyanosis ensues within seconds, followed by a loss of consciousness, limpness, and loss of postural tone. After 1 to 2 minutes of unresponsiveness, consciousness rapidly returns with the resumption of normal activities without postictal alterations in arousal.

The pallid form of breath-holding spells (BHS) often follows minor trauma or surprise, but crying is minimal or absent. There is rapid loss of consciousness or limpness as with the cyanotic form. Attacks may be longer, however, and frequently involve clonic movements associated with cerebral hypoxia.[39] Children with the pallid form may have more profound bradycardia or even asystole. Both cyanotic and pallid forms of BHS can be associated with autonomic nervous system dysregulation,[14] and children with myelodysplasia and Arnold-Chiari malformations exhibit various brainstem abnormalities manifesting in abnormal control of breathing, upper airway dysfunction, aspiration, pneumonia, and cor pulmonale. Severe and sudden bradyarrhythmia or asystole may also result, necessitating treatment with beta-adrenergic antagonists such as atropine.

Unwitnessed attacks may be difficult to distinguish from seizures, but observers often describe an association between precipitating causes as the historical key to the diagnosis. Electroencephalographic recordings do not demonstrate epileptiform discharges, but may show paroxysmal slowing of background EEG activities during an induced syncopal episode.

The optimal treatment is usually behavioral modification without the need for medication, although atropine may be rarely recommended for frequent pallid spells and a trial of iron supplementation is usually recommended for children with BHS and hematologic evidence of iron-deficiency anemia.[9,47]

The presumed pathogenesis of breath-holding spells involves an acute reduction of cerebral blood flow because of increased intrathoracic pressure. This mechanism is analogous to syncope induced by the Valsalva maneuver, which occurs in addition to acute oxygen desaturation caused by respiratory arrest. Some clinicians describe the pallid form as “vagotonia,” which may reveal genetic transmission after obtaining a family history. Children with posterior fossa malformations, such as the Arnold-Chiari anomaly, have also been described as having this physiologic abnormality.[46]

For a typical pediatric population who present with breath-holding spells, 76% of the attacks occur between 6 and 18 months of age.[38] Eighty-five percent of affected children are free from attacks by the age of 5 years. There is generally no relationship with mental retardation and later epilepsy, but it can occur in children with developmental disorders, in whom such attacks are repetitive and stereotypic.

Hyperventilation Syndrome

This phenomenon is most commonly noted in older children, particularly during adolescence. Children with the complete clinical presentation breathe rapidly with shallow, irregular breathing, whereas others complain of an inability to obtain satisfying deep breaths. The initial complaints are commonly dyspnea, chest pain, and lightheadedness. Syncope or pseudoabsence seizures have been described and may be mistaken for true epileptic events. The clinician must have a high index of suspicion in the presence of the typical symptoms, which often include thoracic pain, shortness of breath, and muscle pain. Having the patient rebreathe in a paper bag permits the clinician quickly to control the symptoms of the impending attack. Such a syndrome, however, should alert the clinician to the presence of an anxiety disorder or other significant psychological disturbance. For recurring or chronicity of events, antianxiety medications may help; long-term psychiatric intervention may also be required.

Behavioral Disorders

Rumination

These attacks involve hyperextension of the neck, repetitive swallowing, and protrusion of the tongue and may overlap with the syndrome of gastroesophageal reflux. Although some situations may be due to abnormalities of esophageal peristalsis on an anatomic basis, other patients manifest this behavior as a developmental disturbance because of a dysfunctional relationship between the caretaker and child. The child is usually described as alert but sometimes appears under stress and uncomfortable. Variable feeding techniques are helpful to correct this disorder, depending on the etiologic possibilities. Intensive psychotherapy with both the caretaker and child may be required before long-term benefits result.

Panic Attacks

Panic attacks occur as acute events associated with a chronic anxiety disorder (see Chapter 285). Patients suffering from depression, schizophrenia, or hyperthyroidism may present with these events. The possibility of substance abuse should also be considered. Attacks last from minutes to hours and are accompanied by palpitations, sweating, dizziness or vertigo, and feelings of unreality. Other symptoms have also been described such as dyspnea or a smothering sensation, unsteadiness or faintness, palpitations or tachycardia, trembling or shaking, choking, nausea or abdominal distress, depersonalization or derealization, numbness or tingling, flushes or chills, chest pain or discomfort, and fears of dying, aura, going crazy, or losing control.[50] Specific situational experiences may bring on panic attacks, such as agoraphobia. Children with developmental disturbances, such as those with pervasive developmental disorders with autistic signs, may also manifest stereotypic behaviors that suggest seizures.[12]

Episodic Dyscontrol Syndrome (Rage Attacks)

Episodic dyscontrol syndrome is characterized by recurrent attacks of uncontrollable rage. Such attacks occur despite minimal or absent provocation, often totally out of context with the personality of the patient or the situation.[17] Although this can be seen in younger children, this is more often noted in teenagers and young adults. Younger children with specific language delay or developmental disorders in multiple domains may present with rages. Many patients may have impaired mental status and other neurologic abnormalities on examination, but the history provided by a family or witnesses document that such attacks occur suddenly, are explosive, and are characterized by uncontrollable behavior. Behavior may include primitive physical violence such as kicking, striking, or biting, or even verbal abuse with profanity. Patients display uncharacteristic strength and speed and appear to be psychotic, claiming amnesia, fatigue, or remorse following the episode. At times, such attacks may be difficult to distinguish from complex partial seizures; however, directed violence is very unusual during a true epileptic seizure. Patients rarely describe an aura, and their EEG examination is noncontributory. Some authors indicate that patients with complex partial seizures also have a higher-than-expected incidence of rage attacks.[36,54]

Munchausen Syndrome by Proxy

Clinicians must be cognizant of children with false events or illnesses invented or induced by a relative or caretaker. Meadow[43,44] described children whose mothers fabricated signs and symptoms of illness; a false history of seizures ranging from 1 month to 20 years with an average of 4 years was described. These “seizures” are reported to occur as generalized events at night during sleep, poorly controlled by a wide variety of antiepileptic medications, leading to repeated hospitalizations and multiple diagnostic studies.

The physical examination of these children is usually completely normal. In addition to the commitment and expense of diagnostic studies and prolonged hospitalizations, emotional trauma, prolonged absence from school, and unnecessary restrictions in sports and recreational activities are the consequences to the child of this condition.

The mothers of children with Munchausen syndrome by proxy are medically sophisticated and spend long hours in hospital settings. Knowledge about medical procedures and other factual minutiae allows these individuals to be conversant in sophisticated discussions involving different diagnoses. Fathers, on the other hand, keep a low profile, rarely visit the child in the hospital, and are quite passive by description.[20]

It is essential to diagnose this condition promptly because it is considered a form of child neglect or abuse. The clinician must maintain a high index of suspicion and conduct a methodical review of all medical records with a case conference with as many health care providers as possible.[59] Covert video surveillance of infants in pediatric hospitals is now more widely recommended, although ethical and legal dilemmas have been discussed.[21] Some children are at risk of being asphyxiated or poisoned to induce spells, and mortality is estimated at 10%. Prompt psychiatric intervention for the caretaker is required.

Unusual Movements

Tremulousness or Jitteriness

Neonates and young infants commonly present with rapid generalized tremulousness. Infants appear alert, and gentle flexion of the affected body part will extinguish or diminish these movements. The movement is a to-and-fro movement of the limb, which is contrasted with the fast and slow movement phases characterized by clonic activity. Tremors or jitteriness may persist up to 4 to 6 weeks postconceptional age but usually resolve after this time. This movement is a benign pattern during infancy, with a high rate of normal neurodevelopmental outcome.[62] The movements may occur spontaneously or be provoked by stimulation. Older children may also exhibit tremors. In the absence of cerebellar or motor neuron signs, dystonia, family history of cerebellar disease, or a history of hyperthyroidism, childhood essential tremor can be considered. Other entities such as drugs with tremor-inducing properties must be considered. One in 20 essential tremor cases arise during childhood, with an age range at onset of 1 to 14 years.[40] Neonates who are small for gestational age, hypoglycemic infants, infants of diabetic mothers, and infants withdrawing from prenatal substance exposure may present with jitteriness.

Shuddering, Myoclonus, Hyperekplexia, Dyskinesias

Shuddering is an exaggerated movement resembling shivering. Events occur both during waking and sleep states. Video-EEG monitoring may be required to capture the events.[30] There is a rapid tremor involved in the head, arms, and trunk or even the lower extremities. Such episodes have been described as early as 3 to 4 months of age but decrease gradually in frequency and intensity by 10 to 11 months of age. Essential tremor may be more common in families of children with shuddering spells.[27,66] Young children show an abrupt onset of shuddering movements with flexion of the head, elbows, trunk, and knees and abduction of the elbows and knees. Some describe provocation with excitement, fear, anger, or an urge to void.

A more frequent nonepileptic condition described in infants is benign neonatal myoclonus (BNM)[56] or benign myoclonus

of early infancy (BMEI),[18] which may include shuddering of the upper limbs in approximately 50% of children. Fejerman[18] suggested that shuddering attacks are a variant of BMEI. Children with BNM resolve by 6 months of age. Myoclonic jerks are only present during sleep and mainly during non–rapid-eye-movement sleep. Arousal always terminates the jerks. By definition, the neurologic examination and electroencephalogram are normal.

Hyperexplexia or hyperekplexia is a relatively benign disorder consisting of exaggerated startle responses and hypertonicity that may occur during the first year of life, and in severe cases presents during the neonatal period. As a relatively uncommon disorder, it is usually sporadic, but familial inheritance has been reported. Thirty-nine patients were recently reported[61] with an average age at onset of 3.3 months. Children usually present with marked irritability and recurrent startles in response to handling or sounds. Severely affected infants had severe jerks and stiffening, sometimes with breath-holding spells. Symptoms gradually resolved by 2 years of age with normal neurodevelopment.

Paroxysmal dyskinesia is a general descriptive term that encompasses a number of clinical phenomena of adults and children.[10] Abnormal movements may be induced by sudden voluntary movements (i.e., paroxysmal kinesigenic choreo-athetosis). Some movements may be dystonic, choreic, ballistic, or choreoathetotic. Three other dyskinesias are nonkinesigenic, exertion induced, or hypnogenic. Seven children were recently described, with the earliest onset at 18 months.[35] Most cases are idiopathic with a benign course, diminishing in frequency and severity with age. Video-EEG monitoring may be required to exclude epilepsy, but antiepileptic medications may be required for the specific child.

Paroxysmal Eye Movements: Spasm Nutans, Benign Paroxysmal Tonic Upward Gaze, Eye Fluttering

Spasm nutans is a syndrome occurring in early childhood. It consists of a triad of symptoms: (a) head nodding,

(b) ocular oscillations, and (c) anomalous head position. Ophthalmologic and neurologic findings are otherwise normal. This syndrome is benign and has spontaneous resolution.[16] Age of onset ranges from 1 to 15 months, with both head nodding and nystagmus, which most of the time are intermittent. Neuroimaging is required for the rare association of brainstem masses or malformations.

Benign paroxysmal tonic upgaze is an ill-defined neuro-ophthalmologic disorder with onset in infancy.[11] It consists of sudden ocular movements with sustained upward deviation of the eyes. Episodes disappear with time with normal neurodevelopment,[57] although ataxia has been reported in a child.[37]

Although eye fluttering may be part of typical childhood absence epilepsy, nonepileptic eyelid movements have been described in 19 children and adults with well-controlled generalized epilepsy.[7] Eye movements in children began 2 to 4 years before epilepsy was noted and did not resolve with age. Twelve patients had a family history of the eyelid disorder without epilepsy.

Self-stimulatory Behavior

Some behaviors may be mistaken for seizures, especially in neurologically impaired children. Donat and Wright[15] described head shaking and nodding, lateral and vertical nystagmus, staring, tongue thrusting, chewing movements, periodic hyperventilation, tonic postures, ticks, and excessive startle reactions in some children. Self-stimulatory behavior, such as rhythmic hand shaking, body rocking, and head swaying performed during a time of apparent unawareness of the surroundings, are commonly noted in children with mental deficits, as well as those with pervasive developmental disorders such as autism. The clinical syndrome Rett syndrome should be suspected in young girls who are delayed in development and exhibit “hand washing” movements. Deaf and blind children frequently resort to self-stimulatory behavior, such as hitting their ears or eyes. Developmentally normal children with constipation or refusal to urinate may present with unusual behaviors that may appear to be seizure-like or self-stimulatory but instead reflect the child's discomfort and distraction because of his or her resistance to voiding or defecating.

Finally, masturbatory behavior, even in the very young, may give the appearance of seizures. Referrals for neurologic consultation may have requested evaluations for seizures or movement disorders. Infantile masturbation may mimic pain, inattention, or fear. Infants of either gender, for instance, may be found in a sitting position with their legs held tight together or straddling bars of the crib or playpen and rocking back and forth.[71] Direct observation is crucial, and video-monitoring at home or by the neurology team can be diagnostic.

Diagnostic Methods and Differential Diagnosis

The paroxysmal events discussed here represent, for the most part, transitory functional disorders not associated with any particular disease. As already mentioned, specific investigations should be performed only for organ-specific clues by history and examination, such as cardiopathies causing syncope or gastrointestinal pathologies causing gastroesophageal reflux. In other situations, there are no particular examinations that can lead to an etiologic diagnosis.

The cardinal element for diagnosis is a precise history of the event. It is important to investigate favoring or triggering factors that preceded the event and the patient's subjective sensations, motor manifestations, and postictal state. Differential diagnosis with tonic–clonic generalized epileptic seizures can be particularly difficult in a syncope that can present a tonic contraction of the entire body and sometimes arrhythmic myoclonic limb jerks. Family history must be reviewed for the presence of nonepileptic paroxysmal disorders, such as syncopes or other paroxysmal events. Careful attention must paid to discover any family history of sudden death. The objective examination will be normal, except in cases with cardiopathy, as will the neurologic examination.

The clinician must consider that patients with a suspected convulsive seizure should undergo an EEG or video-EEG study that can provide additional information. Home videography can also prove helpful.

The EEG will characteristically show an absence of interictal epileptogenic abnormalities or the presence of abnormalities not relevant to the symptomatology, for example, rolandic spike discharges in children with episodes of loss of consciousness.

An optimal routine should always include a recording of cardiac activity, by which it is sometimes possible to detect cardiac arrhythmias, especially during a hyperventilation test. There should be an increase in heart rate during the hyperventilation test that can favor the triggering of arrhythmias (Fig. 1).

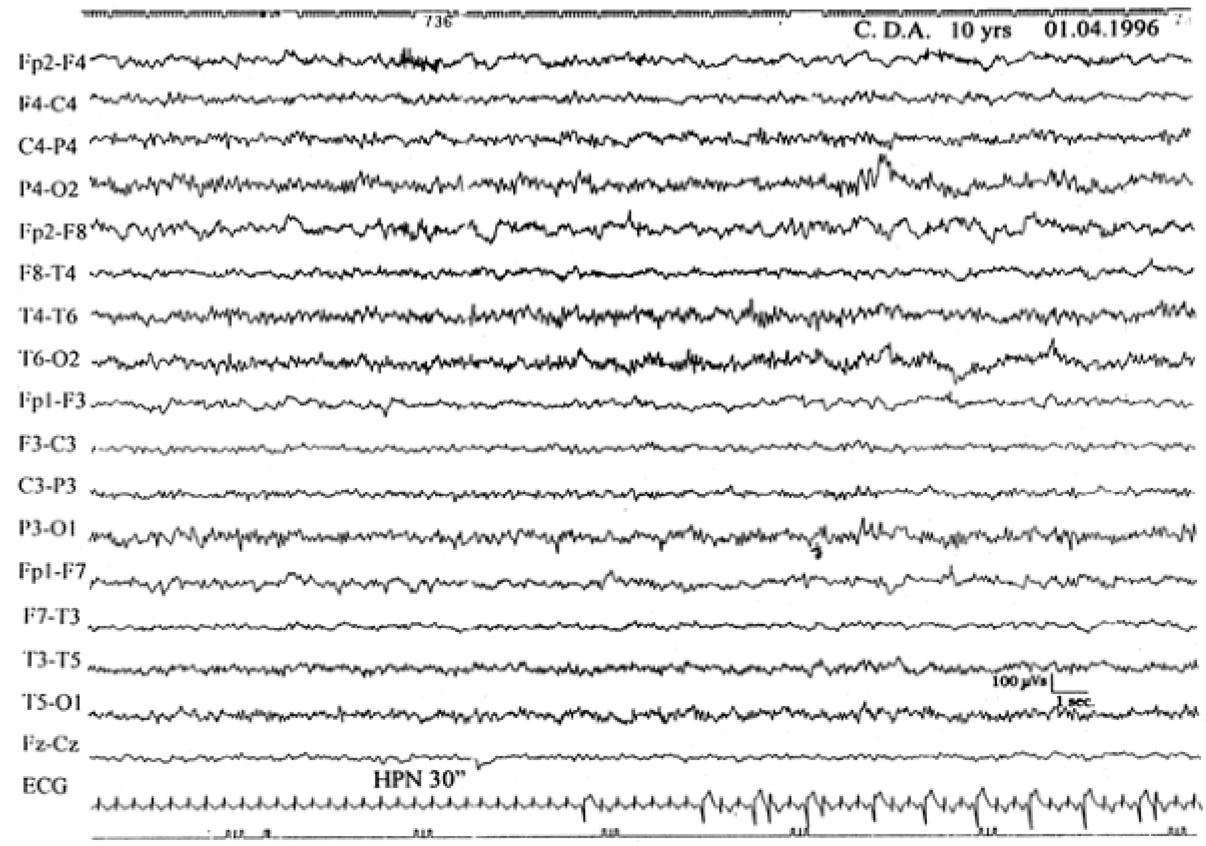
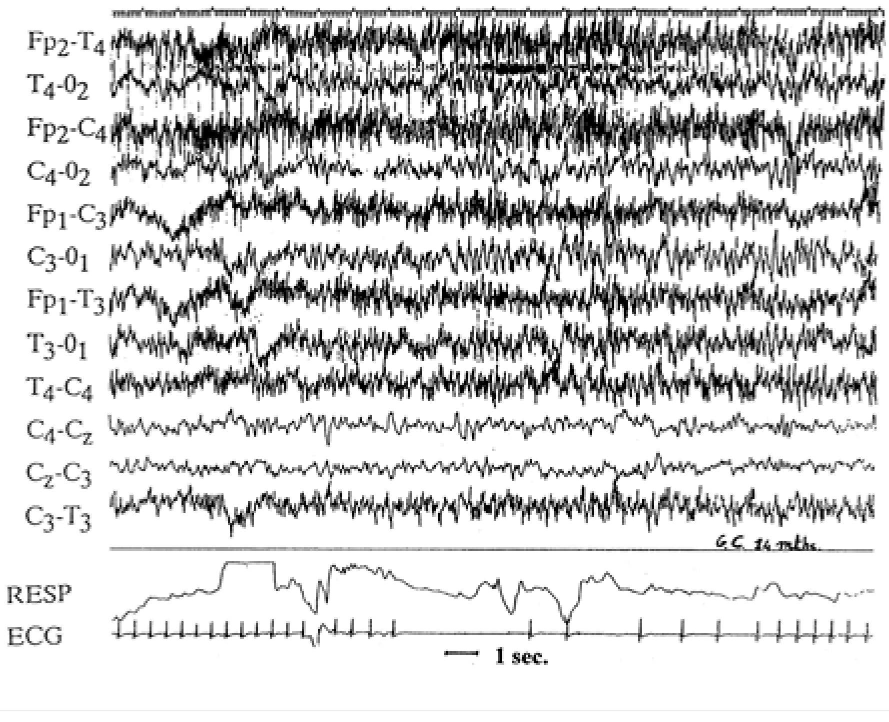

736
C. D.A. 10 yrs 01.04.1996
Fp2-F4
F4-C4
C4-P4
P4-O2
Fp2-F8
F8-T4
T4-T6
T6-O2
Fp1-F3
F3-C3
C3-P3
P3-O1
Fp1-F7
F7-T3
T3-T5
T5-O1
Fz-Cz
ECG
HPN 30"
100 µVs
1 sec.

FIGURE 1. A 10-year-old girl who presented with a seizure with loss of consciousness and diffuse tonic contraction. A sister died suddenly at age 13 years. The electroencephalogram is normal; extra systoles appear after 30 seconds of hyperventilation (HPN). Diagnosis: exercise-induced ventricular tachycardia.


Fp2-T4
T4-02
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C4-02
Fp1-C3
C3-01
Fp1-T3
T3-01
T4-C4
C4-Cz
Cz-C3
C3-T3
G.C. 14 mths.
RESP
ECG
1 sec.

FIGURE 2. A 14-year-old boy with pallid form of breath-holding spells, triggered by emotion or fear. His brother presented with the same phenomenon. A strong emotion (the father leaving the recording room) provoked crying and, after a few seconds, bradycardia to a cardiac pause of 7 seconds. This type of reaction is an expression of "vagotonia."

Even more useful is the polysomnographic study with recording of EEG, ECG, and nasal, oral, and chest breathing, in addition to other parameters. In cases of ALTE, this test is mandatory while the patient is awake and asleep because it helps to identify any central or obstructive apnea.

The best diagnostic method is undoubtedly the documentation of the paroxysmal manifestation. In cases of frequent and unprovoked paroxysmal manifestations, it could be useful to ask the parent to try to record the phenomenon with a video camera at home.

One can try to provoke the event in the neurophysiology laboratory. Use of the tilt table can provoke syncopes caused by orthostatic hypotension; crying can provoke either a cyanotic or pallid type of breath-holding spell (Fig. 2); contraction of the scapular girdle muscles can provoke a stretching syncope.

When it is possible to record the event, EEG generally does not evidence any change or only nonepileptic changes (Fig. 3).

The first observation during the syncope is a slowing in background activity, then a diffuse synchronization with appearance of diffuse, wide-amplitude 1- to 2-c/s waves. Clinical manifestations include dizziness and visual dimming, pallor with cold sweating, and loss of consciousness. If the syncope is prolonged and there is significant decrease in arterial pressure or severe bradycardia, electrical activity decreases abruptly until an isoelectric pattern is reached. In this phase, the patient is unconscious and can have a diffuse tonic contraction, generally in extension with cyanosis and sometimes even clonic jerks. Subsequently, with the return to baseline cardiac activity and arterial pressure, slow electrical activity with wide amplitude reappears and progressively desynchronizes until normal characteristics are resumed. From a clinical point of view, the patient returns to normal respiration and coloring and regains consciousness (Fig. 4). Epileptic-type abnormalities should not be noted in any phase.

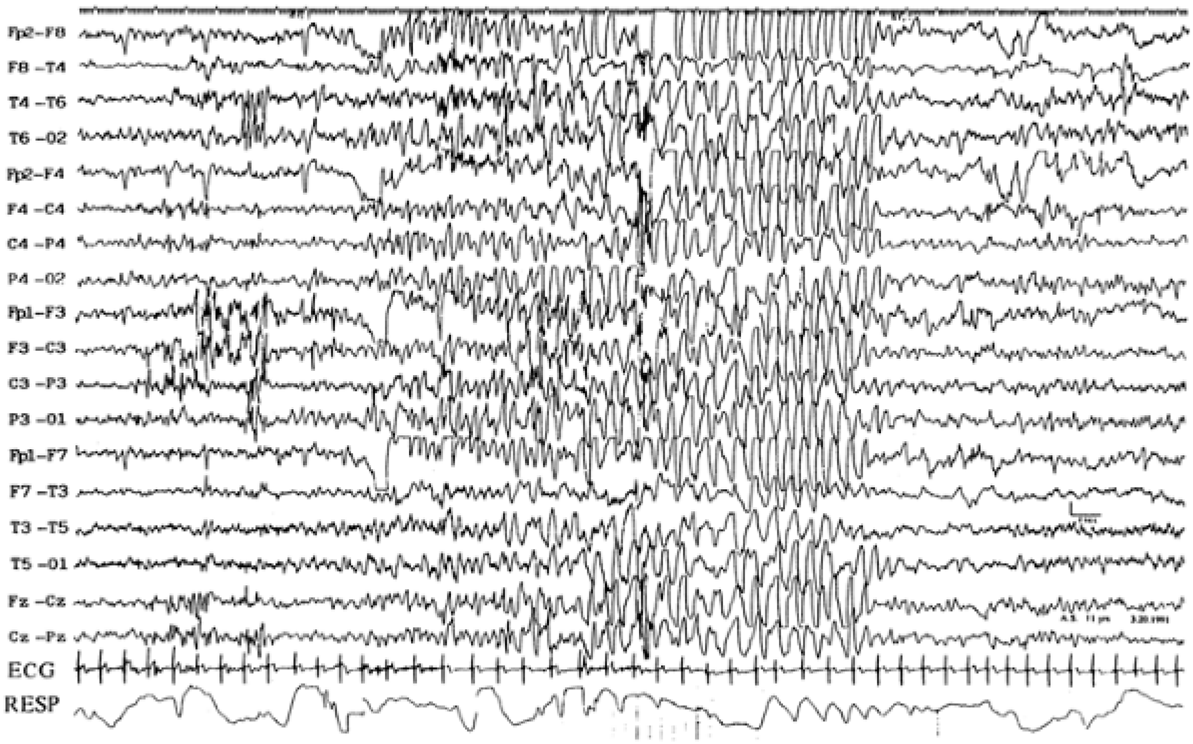
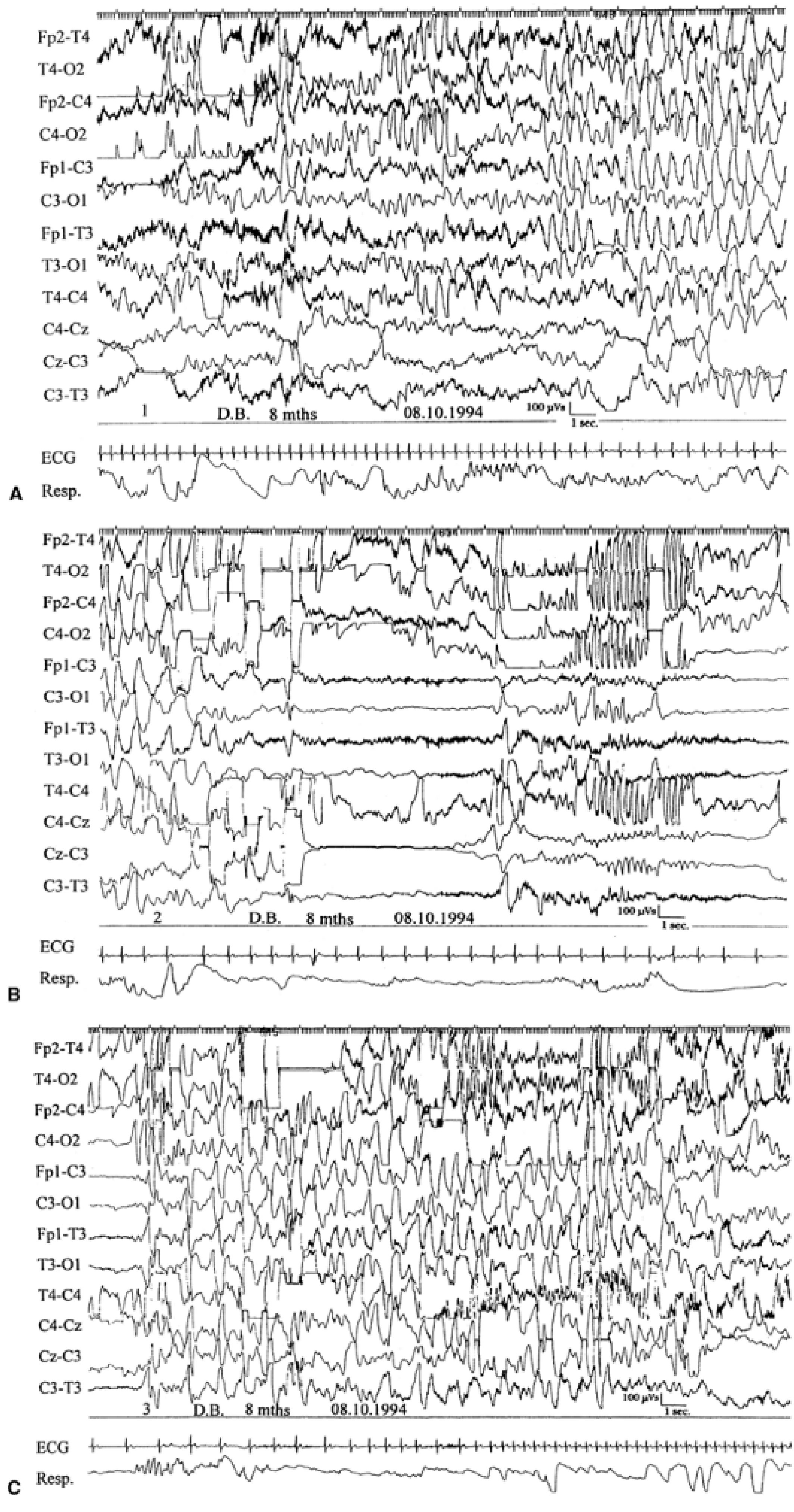

Fp2–F8
F8 –T4
T4 –T6
T6 –O2
Fp2–F4
F4 –C4
C4 –P4
P4 –O2
Fp1–F3
F3 –C3
C3 –P3
P3 –O1
Fp1–F7
F7 –T3
T3 –T5
T5 –O1
Fz –Cz
Cz –Pz
ECG
RESP

FIGURE 3. An 11-year-old girl with a history of loss of consciousness. The electroencephalogram is performed standing. The patient presented a syncope caused by orthostatic hypotension. Cerebral electrical activity synchronized progressively to 1 to 2 c/s, then progressively desynchronized as symptoms disappeared.


Fp2-T4
T4-O2
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C4-Cz
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C3-T3
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Cz-C3
C3-T3
2 D.B. 8 mths 08.10.1994
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ECG
Resp.
B
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T4-O2
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C4-O2
Fp1-C3
C3-O1
Fp1-T3
T3-O1
T4-C4
C4-Cz
Cz-C3
C3-T3
3 D.B. 8 mths 08.10.1994
100 µVs
1 sec.
ECG
Resp.
C

FIGURE 4. An 8-month-old boy with tetralogy of Fallot and frequent cyanotic spells. **A:** After crying briefly, the child stops breathing and rapidly becomes cyanotic. Polygraphic recording shows progressive synchronization of background activity and bradycardia. **B:** The child shows diffuse tonic contraction with apnea and cyanosis. The electroencephalogram (EEG) shows an isoelectric-type pattern; bradycardia is always very significant. There are some artefacts on the EEG due to resuscitation maneuver. **C:** Respiratory and cardiac activities slowly return to normal and the child regains consciousness. The EEG shows slow, wide-amplitude electrical activity that progressively desynchronizes.

Summary and Conclusions

This overview describes nonepileptic systemic paroxysmal disorders during neonatal and childhood periods. Some of these nonepileptic phenomena may be challenging to the clinician. In most situations, however, a careful history by a reliable observer leads the clinician to a successful diagnosis. Home video recordings, synchronous video-neurophysiologic monitoring, or cardiologic testing in the hospital or clinic may document the episodes in question for the clinician, who can then make an accurate diagnosis.

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Chapter 274

Migraine

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Introduction

Migraine and epilepsy are the most common of the chronic neurologic disorders with episodic manifestations. Each group includes a highly variable family of clinical features, natural histories, and patterns of treatment response.[6,99] Therefore, there are many types of migraine, as there are many types of epilepsy. Both disorders are characterized by episodes of neurologic dysfunction that are sometimes accompanied by headache, as well as gastrointestinal, autonomic, and psychologic features.

This chapter focuses on the relationship between migraine and epilepsy for several reasons. First, abundant clinical and epidemiologic data demonstrate that migraine and epilepsy are highly comorbid, in that individuals with one disorder are at least twice as likely to have the other.[5,6,7,60,61,67] Secondly, the clinical presentation of migraine and epilepsy may overlap, creating a challenge in differential diagnosis. Finally, the disorders share overlapping risk factors, brain mechanisms, and treatments.[61] We will begin by describing the migraine attack, dividing it into four traditional stages—the premonitory phase, the aura, the headache phase, and the resolution phase[31]—and contrast the seizure using this framework. We will then review the diagnosis of migraine using the International Classification of Headache Disorders (ICHD)-2 criteria, emphasizing the variants of migraine most frequently mistaken for epilepsy. Finally, we will summarize the epidemiologic evidence that migraine and epilepsy are associated, and provide treatment considerations.

Classification

Each family of disorders has an internationally recognized classification system. The classification system for headache, developed by international consensus, was updated in 2004, and will be referred to herein as the ICHD-2.[40] The classification system utilized in epilepsy was developed by the International League Against Epilepsy (ILAE).

The ICHD-2 criteria divide headache disorders into two broad groups: Primary headache disorders and secondary headache disorders.[40] In a somewhat similar manner, epilepsies are regarded as idiopathic, symptomatic, or cryptogenic by ILAE criteria. In the secondary headache disorders, the headache is symptomatic of an underlying condition, such as a stroke or a mass lesion. This group is analogous to the symptomatic epilepsies in that an underlying cause has been identified. In the primary headache disorders, the headache does not have an identifiable underlying cause. Primary headaches are divided into four major categories: Migraine; tension-type headache; the trigeminal autonomic cephalgias, including cluster headache; and a group of headache disorders analogous to the idiopathic epilepsies. There is no group of headache disorders akin to cryptogenic epilepsies. Furthermore, there is no classification of headache types analogous to the classification of seizure types.

Migraine

Migraine is an extremely common disorder. Recent population-based studies have yielded remarkably consistent

1-year period prevalence estimates of about 6% in men and 15% to 18% in women.[87,62,97] Most studies find that migraine is about three times more common in women than in men.[62,64,97]

Headache diagnosis is usually based on the retrospective reporting of attack characteristics. The results of general medical and neurologic examinations, as well as laboratory studies, are usually normal and serve to exclude other, more ominous, causes of headache. The ICHD-2 classification of migraine subtypes is presented in Table 1. The most important International Headache Society (IHS) subtypes of migraine are “migraine without aura” (formerly common migraine) (Table 2) and “migraine with aura” (formerly classic migraine) (Table 3). In migraine, the aura is a complex of focal neurologic symptoms that precedes or accompanies an attack.[116] About 20% to 30% of migraineurs have migraine with aura.[63] The same patient may have headache without aura, headache with aura, and aura without headache.

The migraine attack can be divided into four phases: The premonitory phase, which occurs hours or days before the headache; the aura, which comes immediately before the headache; the headache itself; and the postdrome. Although most people experience more than one phase, no one phase is absolutely required for a diagnosis of migraine, and most people do not experience all four phases.[17] The epilepsy attack may also have a premonitory, aura, attack, and postictal phase. The similarity in terminology does not imply similarity in mechanisms.

Premonitory, or prodromal, phenomena occur in approximately 60% of migraineurs, often hours to days before the onset of headache.[3,4,17] The phenomena of the premonitory phase has been elucidated using an electronic diary.[33] Features include constitutional, autonomic, psychological (depression, euphoria, irritability, restlessness, mental slowness, hyperactivity, fatigue, and drowsiness), and neurologic (photophobia, phonophobia, and hyperosmia) features. Some patients report a poorly characterized feeling that a migraine attack is coming. Although features vary widely among individuals, they are often consistent within an individual. The most common premonitory symptoms were feeling tired/weary (72%), difficulty concentrating (51%), and stiff neck (50%). Poor functioning commonly predicted headache.[35] Migraineurs who reported premonitory symptoms accurately predicted their full-blown headaches 72% of the time. Among patients who were almost certain that attacks would occur, 93% had attacks.

Table 1 International Classification of Headache Disorders (ICHD)-2 Migraine Classification

1. Migraine
  1.1 Migraine without aura
  1.2 Migraine with aura
    1.2.1 Typical aura with migraine headache
    1.2.2 Typical aura with nonmigraine headache
    1.2.3 Typical aura without headache
    1.2.4 Familial hemiplegic migraine
    1.2.5 Sporadic hemiplegic migraine
    1.2.6 Basilar-type migraine
  1.3 Childhood periodic syndromes that are commonly precursors of migraine
    1.3.1 Cyclical vomiting
    1.3.2 Abdominal migraine
    1.3.3 Benign paroxysmal vertigo of childhood
  1.4 Retinal migraine
  1.5 Complications of migraine
    1.5.1 Chronic migraine
    1.5.2 Status migrainosus
    1.5.3 Persistent aura without infarction
    1.5.4 Migrainous infarction

    - 1.5.5 Migraine-triggered seizures
  - 1.6 Probable migraine
    - 1.6.1 Probable migraine without aura
    - 1.6.2 Probable migraine with aura
    - 1.6.3 Probable chronic migraine

From Headache Classification Committee. The International Classification of Headache Disorders. 2nd ed. *Cephalalgia.* 2004;24:1–160.

Table 2 Migraine without Aura

Diagnostic Criteria

- A. At least five attacks[87] fulfilling criteria B–D
- B. Headache attacks lasting 4–72 hours (untreated or unsuccessfully treated)
- C. Headache has at least two of the following characteristics:
  1. Unilateral location
  2. Pulsating quality
  3. Moderate or severe pain intensity
  4. Aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)
- D. During headache at least one of the following:
  1. Nausea and/or vomiting
  2. Photophobia and phonophobia
- E. Not attributed to another disorder

From Headache Classification Committee. The International Classification of Headache Disorders. 2nd ed. *Cephalalgia.* 2004;24:1–160.

Table 3 Migraine with Aura (41)

Diagnostic Criteria

- A. At least two attacks fulfilling criterion B
- B. Migraine aura fulfilling criteria B and C for one of the subforms 1.2.1–1.2.6
- C. Not attributed to another disorder

Typical aura with migraine headache
Diagnostic Criteria

A. At least two attacks fulfilling criteria B–D
B. Aura consisting of at least one of the following, but no motor weakness:
    1. Fully reversible visual symptoms including positive features (e.g., flickering lights, spots, or lines) and/or negative features (i.e., loss of vision)
    2. Fully reversible sensory symptoms including positive features (i.e., pins and needles) and/or negative features (i.e., numbness)
    3. Fully reversible dysphasic speech disturbance
C. At least two of the following:
    1. Homonymous visual symptoms and/or unilateral sensory symptoms
    2. At least one aura symptom develops gradually over ≥5 minutes and/or different aura symptoms occur in succession over ≥5 minutes
    3. Each symptom lasts ≥5 and ≤60 minutes
D. Headache fulfilling criteria B–D for 1.1 *Migraine without aura* begins during the aura or follows aura within 60 minutes
E. Not attributed to another disorder

From Headache Classification Committee. The International Classification of Headache Disorders. 2nd ed. *Cephalalgia.* 2004;24:1–160.

Premonitory symptoms have also been reported prior to seizure onset.[30] Although less commonly present than in migraine, patients with epilepsy often report a constellation of symptoms prior to a seizure, including irritability, gastrointestinal upset, heaviness, or depression.

Aura

The migraine aura consists of focal neurologic symptoms that precede or accompany an attack. Approximately 20% to 30% of migraineurs experience auras. Most aura symptoms develop slowly over 5 to 20 minutes and usually last for <60 minutes. The aura almost always includes visual features but somatosensory, motor, language, and brainstem disturbances are not rare.

The visual aura often has a hemianoptic distribution and includes both positive (scintillations, fortification spectra, photopsia) and negative (scotoma) features. Elementary visual disturbances include colorless scotoma, photopsia, or phosphenes. Simple flashes, specks, or hallucinations of geometric forms (points, stars, lines, curves, circles, sparks, flashes, or flames) occur and may be single or number in the hundreds. More complicated hallucinations include teichopsia, or fortification spectrum, which is the most characteristic visual aura and is almost diagnostic of migraine. An arc of scintillating lights classically begins near the point of fixation and may form a herringbone-like pattern that expands to encompass an increasing portion of a visual hemifield. It migrates across the visual field with a scintillating edge of zigzag or flashing lights that are often black and white; on occasion colored dots appear at the end of the white stripe. A scotoma is a negative phenomenon consisting of a blanking or graying out of vision. Scotomas are usually accompanied by a positive visual display, but may occur independently. Complex disorders of visual perception include metamorphopsia, micropsia, macropsia, zoom vision, and mosaic vision.[99,100]

Numbness or tingling (paresthesia) over one side of the face and in the ipsilateral hand or arm is the most common somatosensory phenomena. Hemiparesis and dysphasia or aphasia may develop. Olfactory hallucinations are rare, unpleasant, and short lived (5 minutes to 24 hours). Anxiety, déjà vu, and jamais vu have been reported as migraine auras and are presumably of temporal lobe origin.[90] One type of aura may follow

another: Sensory phenomena may occur as visual phenomena fade, or motor phenomena may develop as sensory phenomena dissipate. Although visual auras are relatively specific for migraine, related phenomena may occur in cerebrovascular disease, including carotid dissection, and in epilepsy, especially of the occipital lobes.

Nonvisual association cortex symptoms also occur; these include complex difficulties in the perception and use of the body (apraxia and agnosia), speech and language disturbances, states of double or multiple consciousness associated with déjà vu or jamais vu, and elaborate, dreamy, nightmarish, trance-like or delirious states.[38,51,59,90,95]

In epilepsy, the aura, representing an actual seizure discharge, is typically rapid in development and brief. In contrast to the common visual auras of migraine, epileptic auras are often associated with more unusual symptoms. Auras are estimated to precede up to 80% of temporal lobe seizures; in this setting, autonomic and psychic phenomena, such as a rising abdominal sensation, nausea, fear, or déjà vu, are common.[103]

Mechanisms of Aura

Cortical spreading depression (CSD) is believed to underlie the migraine aura. CSD consists of a wave of excitation followed by a wave of inhibition that moves across the cortical mantle at a rate of 3 mm/min. Best studied as an animal phenomenon, it can be induced by pricking the cerebral cortex with a pin, by applying potassium chloride, and in other ways.[56] CSD is characterized by transient increases in metabolic and electrical activity and transient increases in cerebral blood flow (CBF), followed by sustained decreases.[75] The aura is associated with an initial hyperemic phase followed by reduced CBF, which moves across the cortex (spreading oligemia).[76]

Several lines of evidence in humans suggest that CSD is a mechanistic substrate of migraine aura. Olesen and Lauritzen[74,76] found 17% to 35% reductions in posterior CBF, which spread anteriorly at 2 to 3 mm/min. It crossed brain areas supplied by separate vessels and is, thus, not due to segmental vasoconstriction.[74] Reduced CBF persisted from 30 minutes to 6 hours, then slowly returned to baseline or even increased. The rates of progression of spreading oligemia could account for the rate of expansion of the scotoma in migraine, suggesting that they are related.[55,56,69,77]

Magnetoencephalographic studies show similar profiles in humans during migraine aura and in experimental animals during CSD,[101] implying that spreading depression may be the mechanism that produces the aura.[18,53,86,87,111] Subjects with spontaneous migraine visual auras have also been studied with functional magnetic resonance imaging (fMRI).[23] Interictally, using perfusion-weighted imaging, CBF, cerebral blood volume, and mean transit time were normal and symmetric. During visual auras, CBF decreased 15% to 53%, cerebral blood volume decreased 6% to 33%, and mean transit time increased 10% to 54% in the occipital cortex gray matter contralateral to the affected visual hemifield. When multiple perfusion images were obtained during the same aura, the margin of the perfusion defect moved anteriorly. The absence of diffusion abnormalities in these patients suggests that ischemia does not occur during the migraine aura.[22]

Blood oxygenation level–dependent (BOLD) fMRI reflects the relative concentration of deoxyhemoglobin in venous blood. Visual stimulation was used to trigger headache in migraineurs.[20] A wave of increased (hyperoxygenated blood) and then decreased (possibly reflecting neuronal metabolic-flow coupling) BOLD signals propagated into the contiguous occipital cortex at 3 to 6 mm/min. When visual stimulation was used to test the visual cortex response, the BOLD signal and the BOLD response to visual activation diminished following progression of the visual aura.[39]

Using transcranial magnetic stimulation–applied magnetic fields of increasing intensity to evaluate occipital cortex excitability, Aurora et al.[9] and Young et al.,[115] but not Afra et al.,[1] found that phosphenes were generated in migraineurs at lower thresholds than controls, and that it was easier to visually trigger headaches in those with lower thresholds. Other evidence of increased central nervous system (CNS) excitability comes from studies of visual and brainstem auditory-evoked potentials.[93] Migraine with aura may be due to neuronal hyperexcitability, perhaps due to cortical disinhibition.

The aura of epilepsy is a simple partial nonmotor seizure that typically precedes an observable seizure, but may occur alone. The patient experiences the aura prior to loss of consciousness, and memory of it may be retained. The aura is associated with the electroencephalographic correlate of the seizure type in which it occurs[27]; however, the EEG pattern is often not evident on surface recording until the seizure has progressed to involve a larger area of cortex.

Headache Phase

The typical migraine headache is unilateral and described as throbbing by 85% of patients. Headache severity ranges from moderate to marked and is aggravated by head movement or physical activity. The onset is usually gradual and the attack usually lasts 4 to 72 hours in adults and 2 to 48 hours in children.[99] Anorexia is common, although food cravings can occur. Nausea occurs in up to 90% of patients, and vomiting occurs in about one third of migraineurs.[63] Many patients experience sensory hyperexcitability manifested by photophobia, phonophobia, and osmophobia, and seek a dark, quiet room.[28,95] To make a diagnosis of migraine, the pain must be accompanied by other features. The ICHD-2 selects particular associated features as cardinal manifestations for diagnosis (Table 2).[98]

Postdrome or Postictal Phase

With migraine, the patient may feel tired, washed out, irritable, and listless and may have impaired concentration. Many patients report scalp tenderness. Some people feel unusually refreshed or euphoric after an attack, whereas others note depression and malaise. In epilepsy, during the postictal phase, there may be a depressed level of awareness or focal neurologic deficits that sometimes provide clues to the site of seizure onset.

Formal International Classification of Headache Disorders-2 Classification

Migraine without Aura (Common Migraine) **(Table 2)**

To establish a diagnosis of ICHD-2 migraine without aura (1.1), five attacks lasting from 4 to 72 hours are required. The attacks must have two of the following four pain characteristics: Unilateral location, pulsating quality, moderate to

severe intensity, and aggravation by or causing avoidance of routine physical activity. In addition, the attacks must be associated with at least one of the following: Nausea or vomiting or photophobia and phonophobia. No single characteristic is mandatory for a diagnosis of migraine. A patient who has photophobia, phonophobia, and severe pain aggravated by routine activity meets these criteria, as does the more typical patient with unilateral throbbing pain and nausea.[98] Attacks that persist for more than 3 days define status migrainosus. Although the frequency of attacks varies widely, the average migraineur experiences one to three headaches a month. Like epilepsy, migraine is, by definition, a recurrent phenomenon. The requirement for at least five attacks is imposed because headaches simulating migraine may be caused by such organic diseases as brain tumors, sinusitis, or glaucoma.[98]

Migraine with Aura (Classic Migraine) **(Table 3)**

Descriptively, auras are focal neurologic symptoms that usually develop gradually over 5 to 20 minutes and last for <60 minutes. The diagnosis of migraine with aura (1.2) requires at least two attacks meeting the criteria of one of the subforms. In addition, it cannot be attributed to another disorder. Migraine with aura is subclassified into typical aura with migraine headache (1.2.1) (homonymous visual disturbance, unilateral numbness or aphasia); typical aura with nonmigraine headache (1.2.2); typical aura without headache (1.2.3); familial hemiplegic migraine (FHM) (1.2.4); sporadic hemiplegic migraine (1.2.5) (see Table 6); and basilar-type migraine (1.2.5). Some of these variants will be discussed in detail since they may be confused with epilepsy.

Typical aura with migraine headache (1.2.1) requires at least two attacks with the aura consisting of at least one of the following (but no motor weakness): Fully reversible visual symptoms including positive; fully reversible sensory symptoms including positive; and fully reversible dysphasic speech disturbance. Additionally, it requires at least two of the following: Homonymous visual symptoms and/or unilateral sensory symptoms; at least one aura symptom developing gradually over ≥5 minutes and/or different aura symptoms occurring in succession over ≥5 minutes; and each symptom lasting ≥5 and ≤60 minutes. Fewer attacks are required to make a diagnosis of migraine with aura because a typical aura is highly specific for migraine. Headache with the features of migraine without aura usually follows the aura symptoms. Less commonly, headache lacks migrainous features or is completely absent.[40,98]

If the aura includes motor weakness, it is coded as 1.2.4 *Familial hemiplegic migraine* or 1.2.5 *Sporadic hemiplegic migraine*.

The headache and associated symptoms of migraine with aura are similar to those of migraine without aura but may be less severe and/or of shorter duration. Most people who have migraine with aura also have migraine without aura. The aura usually lasts 20 to 30 minutes and typically precedes the headache, but occasionally it occurs only during the headache.

Migraine Variants

The variants of migraine as classified by the ICHD-2 have been discussed in detail elsewhere.[40] In this section we will describe the migraine variants that are most commonly confused with epilepsy, using ICHD-2 terminology when possible.

Basilar-type Migraine

Originally called basilar or basilar artery migraine,[40] the term *Bickerstaff syndrome* has also been applied to this disorder.[13] It affects all age groups and both sexes, with the usual female predominance. The aura often lasts <1 hour and is usually followed by a headache. In basilar-type migraine, the visual aura is usually followed by at least one of the following: Ataxia, vertigo, tinnitus, diplopia, nystagmus, dysarthria, bilateral paresthesia, or a change in the levels of consciousness and cognition. If marked, these alterations in consciousness define confusional migraine.

The aura symptoms described above are often, but not always, followed by a severe, throbbing occipital headache and vomiting. Although attacks are usually infrequent, they can last for 1 to 3 days. These headaches can be very frightening and difficult to diagnose. On occasion, the attacks can lead to cardiac arrhythmias and brainstem stroke. A diagnosis of basilar migraine should be considered in patients with paroxysmal brainstem disturbances. Basilar migraine may be difficult to differentiate from simple or complex partial seizures and the postictal state following a primary or secondary generalized seizure. The differential diagnosis, besides occipital lobe epilepsy, includes posterior fossa tumor or malformation, urea cycle defects, and mitochondrial disorders.[84]

Confusional Migraine[40,43]

No longer part of the ICHD-2 classification, confusional migraine is probably a form of basilar-type migraine or hemiplegic migraine. It is characterized by a typical migraine aura, a headache (which may be insignificant), and confusion, which may precede or follow the headache. During the confused period the patient is inattentive, is distracted, and has difficulty maintaining speech and other motor activities. The electroencephalogram (EEG) may be abnormal during the attack. Agitation, memory disturbances, obscene utterances, and violent behavior have been reported. Single attacks are most common; multiple attacks rare. Attacks may be triggered by mild head trauma. A more profoundly disturbed level of consciousness may lead to migraine stupor, which can last from hours up to 5 days. The confusional state is usually followed by sleep, resembling postictal depression of mental status. Confusional migraine may be difficult to diagnose. The differential diagnosis includes drug ingestion, metabolic encephalopathies (Reye syndrome, hypoglycemia), viral encephalitis, and acute psychosis. Acute confusional states also occur during complex partial seizures and in the postictal state. The patient may be delirious, hyperactive, restless, and, on occasion, combative. Acute migraine confusional states may recur over a period of days or months and then evolve into typical migraine episodes. A history of typical migraine aura supports a diagnosis of migraine.[52]

Benign Paroxysmal Vertigo of Childhood

Now classified as one of the "childhood periodic syndromes," this condition is a precursor of migraine (1.3.3). This disorder is characterized by recurrent, brief episodic attacks of vertigo. Attacks occur without warning and resolve spontaneously in otherwise healthy children. Children with this disorder cannot stand, and lie silently on the floor or wish to be held during attacks. Attacks last a few minutes and tend to recur at irregular intervals over a period of 6 to 12 months. While headache may not be present at the onset, as the disorder evolves the vertigo may be replaced by attacks of headache and vomiting, facilitating diagnosis. When simple partial seizures give rise to vertigo, the vertigo is usually less prominent than it is in migraine.

Aura without Headache

Migraine aura can occur without headache,[112] although diagnosis is more difficult in this setting. These periodic neurologic phenomena (scintillating scotomata or recurrent sensory, motor, or mental phenomena) should be accepted as migraine only after a full investigation. Headache occurring in association with some attacks will help confirm the diagnosis.[88] Ziegler and Hassanein[116] reported that 44% of their patients who had headache with aura had aura without headache at some time.

Late-life migrainous accompaniments are characterized by attacks of aura without headache beginning in late life.[31,32] Many patients have a history of migraine in early or midlife, often with an attack-free hiatus. Because focal neurologic defects occur without headache, they can be confused with transient ischemic attacks (TIAs) or seizures. Late-life migrainous accompaniment remains a diagnosis of exclusion.

Migraine-triggered Seizure

New to the ICHD-2 is a seizure triggered by a migraine aura (1.5.5). This diagnosis requires migraine that fulfills the criteria for 1.2 Migraine with aura and a seizure fulfilling diagnostic criteria for one type of epileptic attack that occurs during or within 1 hour after a migraine aura. This phenomenon is sometimes referred to as *migralepsy*.

Epidemiologic Connections between Migraine and Epilepsy

Andermann and Andermann[5] summarized a number of studies that examined the association between migraine and epilepsy. The prevalence of epilepsy in persons with migraine ranged from 1% to 17% with a median of 5.9%, substantially higher than epilepsy's population prevalence of 0.5%. Migraine prevalence in patients with epilepsy ranged from 8% to 15%. Many of these studies were limited by the method of patient identification, the lack of appropriate control groups, and poorly specified definitions of migraine and epilepsy. Nonetheless, these studies powerfully argue that migraine and epilepsy are associated.

Ottman and Lipton[79] examined the association between migraine and epilepsy using data from Columbia University's Epilepsy Family Study. Subjects with epilepsy (probands) who were over 18 years of age were identified and recruited from voluntary organizations for persons with epilepsy. Among the probands with epilepsy, migraine prevalence was 24%. Migraine prevalence was 26% in the relatives with epilepsy. In the control group of relatives without epilepsy, only 15% had migraine. The gender-adjusted rate ratio for migraine in probands with epilepsy compared with relatives without epilepsy was 2.4 (95% confidence interval [CI]: 2.0 to 2.9). For relatives with epilepsy compared with relatives without epilepsy the rate ratio was also 2.4 (95% CI: 1.6 to 3.8). These statistics indicate that the incidence of migraine is 2.4 times higher in persons with epilepsy than in persons without epilepsy.

Risk of migraine was not associated with the age of onset of epilepsy. The risk of migraine was elevated in both partial and generalized seizures, although the risk was higher for probands with partial-onset versus those with generalized-onset seizures (relative risk [RR] = 1.3; 95% CI: 1.00 to 1.86). The risk of migraine was elevated in both idiopathic and symptomatic epilepsy. Probands with epilepsy caused by head trauma had a higher risk of migraine than probands with idiopathic/cryptogenic epilepsy (RR = 1.8, 95% CI: 1.32 to 2.43). Nonetheless, migraine risk was elevated in every subgroup of epilepsy defined by seizure type, age of onset, and etiology of epilepsy.[70]

Although migraine and epilepsy are associated, the mechanisms of the association are complex and may be multifactorial. One possibility is a simple unidirectional causal explanation. For example, migraine may cause epilepsy by inducing brain ischemia and injury. Under this hypothesis, we would expect the incidence of migraine to be elevated before, but not after, the onset of epilepsy. Alternatively, epilepsy may cause migraine by activating the trigeminovascular system. This hypothesis leads us to expect an excess risk of migraine after, but not before, the onset of epilepsy. The data show that there is an excess risk of migraine both before and after seizure onset, leading to the rejection of both unidirectional causal models.

Marks and Ehrenberg[67] explored the timing and features of headache in patients with epilepsy. They found that of 79 of 395 patients with epilepsy, 20% also had IHS migraine. In 84% of patients with both migraine and epilepsy (66 of 79), the attacks were completely independent. In 16% of patients (13 of 79), a seizure immediately followed the migraine aura (migralepsy); 11 of 13 were women, seven of whom had a catamenial pattern. Migralepsy was also seen in refractory patients with both migraine and epilepsy in Andermann's series,[6] although this phenomenon does not account for the majority of the comorbidity.

Velioglu and Ozmenoglu[109] studied the relationship between migraine and epilepsy in 412 adults with epilepsy. Fourteen percent of adults with seizures had IHS migraine. Migraine-induced epilepsy (migralepsy) was found in seven patients (1.7%); all had migraine with aura. The authors at times found it difficult clinically to distinguish the aura of migraine from the aura of epilepsy. Patients were at increased risk for both conditions if they had migraine with aura and catamenial epilepsy. Three of the patients with refractory seizures had improved control with the combination of antimigraine and antiepilepsy drugs.

Lenaerts[57] evaluated the degree of comorbidity and tried to establish the pattern of temporal relationship between migraine and epilepsy in 201 patients from tertiary care clinics. He systematically reviewed charts, obtained additional information by telephone interviews where necessary, and applied IHS and ILAE diagnostic criteria. Two-tier grouping according to reason for referral (migraine or epilepsy) was done. Adequate information was obtained from 185 patients (113 females, 72 males). In the epilepsy-referred patient group (n = 103), 23% had migraine, a risk ratio of 1.9 ($p = 0.01$). In the migraine-referred group (n = 82), 11% had epilepsy, a risk ratio of 21 ($p = 0.05$). Of the 33 comorbid cases, 21 had their attacks in close temporal relation. The migraine attack preceded the seizure in 12 patients (nine migraine with aura) (57%) and followed it in nine (six migraine with aura) (43%). Migraine attacks equally precede or follow seizures, but migraine aura more often precedes the seizure (migralepsy).

Shared environmental risk factors may contribute to comorbidity. The risk of migraine is higher in subjects with epilepsy caused by head injury. Since head injury is also a risk factor for migraine,[8] comorbidity may result, in part, from an effect of head injury on the risk of both disorders. Because risk is also significantly increased in persons with idiopathic/cryptogenic epilepsy, known environmental risk factors cannot account for all of the comorbidity.

Table 4 Migraine and Epilepsy Relationships

1. Coexisting epilepsy and migraine Both disorders occur together at an increased prevalence, but attacks occur independently
2. Migraine-induced epilepsy (migralepsy) Seizures are triggered by migraine aura
3. Epilepsy-induced headache (ictal or postictal) Headache occurs as part of seizure or postictal state
4. Primary epilepsy–migraine syndromes Syndromes with features of both migraine and epilepsy without a specific underlying cause
   –Occipital epilepsies (e.g., benign occipital epilepsy)
   –Benign rolandic epilepsy
5. Secondary epilepsy–migraine syndromes Both migraine and epilepsy occur in the same individual with a common underlying cause
   –Mitochondrial disorders (MELAS)
   –Symptomatic (e.g., arteriovenous malformation of occipital lobe)
   - Neurofibromatosis
   - stürge-Weber

Modified from Andermann F. Migraine and epilepsy: an overview. In: Andermann F, Lugaresi E, eds. *Migraine and Epilepsy*. Boston: Butterworths, 1987:405–421; and Welch KM, Lewis D. Migraine and epilepsy. *Neurol Clin.* 1997;15:107–114.

Ottman and Lipton[79] tested the alternative hypothesis, that shared genetic risk factors might account for comorbidity. They

argued that the risk of migraine should be higher in families with genetic versus nongenetic forms of epilepsy if genetic factors account for comorbidity. They further argued that the risk of epilepsy should be greater in the relatives of probands with migraine and epilepsy versus the relatives of probands with epilepsy alone. In a series of analyses, they adjusted for a number of potentially confounding factors including age, gender, the familial aggregation of migraine, and the comorbidity of migraine and epilepsy. The analyses failed to confirm either of the authors' hypotheses, leading them to reject the idea that genetic susceptibility accounts for comorbidity.[79]

Having rejected the unidirectional model, the environmental model, and the genetic hypothesis, they proposed that an altered brain state (increased excitability) might increase the risk of both migraine and epilepsy and account for comorbidity. Enhanced neuronal hyperexcitability and a reduced threshold to attacks figure prominently in the pathophysiologic models of migraine and epilepsy. Reduction in brain magnesium or perturbations in neurotransmitter systems may provide a basis for these alterations in brain excitability. In theory, genetic or environmental factors could produce these alterations. Regardless of mechanisms, these findings are important for clinical practice.

Interrelationships between Headache and Epilepsy

Apart from the causal epidemiologic issues discussed above, there are many possible clinical interrelationships between headache and epilepsy (Table 4). The disorders may exist independently. Migraine may trigger epilepsy (migralepsy) or epilepsy may initiate headache. Seizure and headache seem to be associated in certain syndromes, such as benign occipital epilepsy of childhood with occipital paroxysms (BOEP). In addition, both disorders may have a common underlying cause such as head trauma, an arteriovenous malformation,[66] or neurofibromatosis.[21,85] Finally, migraine may be a predictor of poor outcome in persons with epilepsy. We will now consider some of these interrelationships.

Headache as a Consequence of Seizures

Although headache is commonly associated with seizures as a preictal, ictal, or postictal phenomenon, it is often neglected because of the dramatic neurologic manifestations of the seizure. Patients with migraine-triggered epilepsy seek medical attention because of seizures, which may overshadow the migraine and be overlooked by the patient and physician.

Preictal and Ictal Headache

Palmini and Gloor[80] presented a descriptive study of auras in partial seizures. Cephalic auras, defined by the symptoms of nonvertiginous dizziness, lightheadedness, or head pressure, occurred in 22 of 196 patients. In Blume and Young's epilepsy unit, 2.8% of 858 patients had brief ictal pain and 1.3% (11 patients) had headache. Only two patients described the pain as throbbing; the others described it as sharp or steady. Headache preceded the seizure in eight patients and accompanied the other ictal symptoms in three; all three of these patients had partial seizures, although the nature and location of EEG abnormalities varied considerably from patient to patient.

Isler et al.[47] found that hemicranial attacks of pain coincided with seizure activity and lasted for seconds to minutes (hemicrania epileptica). Two exceptions were noted: One a case of complex partial status in which the headache lasted for hours and another in which the headache lasted most of the 20 minutes of a recorded seizure. Overall, 20% of this group of drug-resistant epileptics had cephalic symptoms.

In a more recent study,[114] nearly half of patients undergoing continuous EEG monitoring for intractable epilepsy experienced peri-ictal headache, the majority being postictal. Interestingly, preictal headache lateralized to the side of seizure focus in 9 of 10 patients.

Headache can also be the sole or most predominant clinical manifestation of epileptic seizures, although this is a relatively rare situation.[54] Headache was noted to be a true ictal manifestation during intracranial monitoring, in two cases relieved by resective epilepsy surgery.[54]

Postictal Headache

In a telephone interview of 372 patients attending an epilepsy clinic, 45% had experienced postictal headache (PIH) and 21% always had PIH. Of those who always had PIH, headache was severe 39% of the time; in contrast, it was severe in only 10% of patients with occasional PIH. Twenty-seven percent of patients had independent headaches that were usually similar to their seizure-related headache. Headaches lasted <6 hours in 81% of patients, 12 to 24 hours in 11%, and >24 hours in 8%.[92] The headache was throbbing in over two thirds.

Schön and Blau[94] reported on 100 epileptic patients, 51 of whom had PIH either always (n = 35), usually (n = 5), or 25% to 50% of the time (n = 11). PIH was more commonly associated with generalized tonic–clonic seizures than with focal seizures; 9% of the patients with PIH also had independent migraine attacks. The headaches were either bilateral or unilateral. They were associated with photophobia and phonophobia, throbbing pain, vomiting, nausea, and visual aura, and lasted 6 to 72 hours. Epileptic migraineurs recognized these headaches as being similar to their migraine. Postictal headaches with migraine features respond to triptans.[49]

Ito et al. reported that 40% of 364 patients with partial epilepsies had PIH and that 26% had postictal migraine.

Migraine-like PIH was more likely in temporal and occipital lobe epilepsy and less likely in frontal lobe epilepsy.[48]

The mechanism of ictal and postictal headaches is uncertain. In recent years, the theory of migraine pathogenesis has focused on the trigeminovascular system; activation of this system gives rise to neurogenic inflammation of cranial blood vessels and pain.[70] In animal models, Moskowitz et al. have shown that seizures activate the trigeminovascular system, providing a potential mechanism for the associated headaches. This mechanism would account for the triptan response in postictal headache.[46] Velioglu et al. examined the effect of migraine on the prognosis of epilepsy in a prospective study of 59 patients with both disorders and a control group of 56 patients with epilepsy but not migraine. The group with migraine and epilepsy was less likely to become seizure free and more likely to have intractable seizures and medication problems than patients with epilepsy alone. Thus, comorbid migraine may be a predictor of poor outcome in epilepsy.[108]

In summary, preictal and ictal headaches are relatively rare and short lived. The seizure itself may limit the patient's ability to observe or recall the manifestations of these headaches. In contrast, PIH is common and can impact the quality of life of the person with epilepsy. It is most common with generalized tonic–clonic seizures, but is also common in complex partial seizures; it is less common with simple partial seizures.[92]

Migraine–epilepsy Syndromes

Benign Epilepsy of Childhood with Occipital Paroxysms

BEOP is a clinical syndrome characterized by a partial seizure with visual symptoms, followed by postictal migraine and occipital spikes on EEG. A rare disorder, it accounts for <5% of epilepsy in children (mean age of onset 7.5 years).[24,33,82] BEOP has features of both epilepsy and migraine.[33,35,105] The visual symptoms may include amaurosis, elementary visual hallucinations (phosphenes), complex visual hallucinations, or visual illusions, including micropsia, metamorphopsia, or palinopsia.[11,33,73] The visual symptoms are often followed by hemiclonic, complex partial, or secondarily generalized tonic–clonic seizures. Following the seizure, approximately 25% to 40% of the patients develop migraine-like headaches.[105]

The interictal EEG is characterized by normal background activity and distinct occipital discharges. The occipital spikes typically have a high voltage (200 to 300 μV), diphasic morphology, and a unilateral or bilateral occipital and posterior temporal distribution. The spikes disappear with eye opening and reappear 1 to 20 seconds after eye closure.

Gastaut reviewed the clinical and EEG features of 53 patients with BOEP. Only 55% had the “complete” syndrome of occipital spikes, ictal visual symptoms followed by a partial seizure, and postictal migraine. In patients with nocturnal seizures, motor symptoms predominated; in those with daytime seizures, visual symptoms were more common. Nocturnal seizures are more common in younger children and bear a good prognosis.[33,82] Seizures starting after 8 years of age are more likely to be frequent, diurnal, and persistent,[33,82] although overall, complete seizure control is achievable in about 60% of patients.

Occipital spikes are not specific for BOEP. They have been reported in people with migraine, and in children under 4 they may not be associated with epilepsy or any other defined disorders.[41,58,102] Occipital spikes can also be seen in other disorders, including myoclonic, absence, and photosensitive epilepsies, as well as celiac disease.[19,33]

Benign Rolandic Epilepsy

Benign rolandic epilepsy is characterized by unilateral somatosensory or motor seizures and centrotemporal spikes; both clinical and electrographic features can shift from side to side. Speech arrest, pooling of saliva, and (usually) preservation of consciousness are also typical, although secondary generalization may occur. Most patients respond well to anticonvulsant medication. In one series, 75% of patients were seizure free after 5 years.[10] The seizures almost invariably disappear by age 15. An association with migraine has been reported in some, but not all, studies.[15,16] Rossi et al.[89] found that migraine prevalence in male controls (11.1%) was much higher than one would expect in boys between the age of 6 and 15 years. Giroud et al.,[36] in a control study, found that epilepsy with rolandic paroxysms and migraine were associated. Migraine incidence was studied in four groups of patients: Patients with centrotemporal epilepsy, patients with absence epilepsy, patients with partial epilepsy, and nonepileptic patients with a history of cranial trauma. Migraine was present in 62% of the patients with centrotemporal epilepsy, 34% of the patients with absence epilepsy, 8% of the patients with partial epilepsy, and 6% of the patients with cranial trauma. These results suggest that centrotemporal epilepsy and, to a lesser degree, absence epilepsy are associated with migraine.[36] The association between benign rolandic epilepsy and migraine may be part of the comorbidity of migraine with all forms of epilepsy.[85]

Differential Diagnosis and Concomitant Diagnosis of Migraine and Epilepsy: Clinical and Electroencephalographic Features

The most important tool in differentiating between migraine without aura and epilepsy is the history.[82] Table 5 illustrates high levels of symptomatic overlap between migraine and epilepsy. Tables 6 and 7 present the features most useful in distinguishing them. In general, in comparison with epilepsy, attacks of migraine are more gradual in onset and of longer duration. Nausea and vomiting are more commonly associated with migraine, while prolonged confusion or lethargy after the attack favors epilepsy.

Table 5 Symptoms Common to Both Migraine and Epilepsy

Symptom	Migraine	Epilepsy
Systemic		
Vomiting	+	+/-
Nausea	+	+/-
Diarrhea	+/-	-
Headache	+	+/-
Visual disturbances		

Colored circles	-	+
Black and white lines	+	-
Blindness	+/-	+/-
Blurred vision	+	+
Visual triggering factors	+	+
Other neurologic		
Olfactory	+/-	+
Vertigo	+	+/-
Confusion	+/-	+
Loss of consciousness	+/-*	+
Impaired consciousness	+/-	+
Loss of memory	+/-	+
Postevent lethargy	+	+
Depersonalization	+/-	+
Paresthesias	+	+
Hemiparesis	+/-**	+
Hemisensory loss	+/-**	+
Aphasia	+/-**	+

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*More complex.
**Hemiplegic migraine.

At times, differentiating migraine with aura from epilepsy can be difficult, particularly when motor manifestations such as tonic or clonic movements are absent. The characteristics of the aura may help[29]: The migraine aura is longer (5+ minutes) and the aura of epilepsy is brief (usually <1 minute).[5] In addition, the aura symptom profiles differ. Autonomic, psychic, or somatosensory features favor epileptic auras, while a mix of positive and negative visual features, such as a scintillating scotoma, favors migraine.[81]

Table 6 Prodrome and Aura in Migraine and Epilepsy

Symptom	Migraine	Epilepsy
Premonitory	Common	Often
Duration of aura	15–60 min	Brief, often <1 min
Automatisms	Unusual	Absent in aura, present in complex partial seizures
Gastrointestinal aura	Abdominal pain (rare); nausea (common)	"Butterflies"—rising epigastric sensation
Visual disturbances	Positive/negative	Complicated visual phenomenon
Paresthesias	Common (5–60 min)	Common (seconds to minutes)
Altered consciousness	Usually responsive	Responsive during aura, altered responsiveness during complex partial seizure
Olfactory	Very uncommon	More common
Aphasia	Common	Common
Déjàvu	Rare	Common

The characteristics of the visual features present in migraine and epilepsy bear further discussion. Colorless glittering scotomata are typical of migraine, as are black-and-white zigzag patterns that appear concentrically around the point of fixation, usually unilaterally. (These are also termed fortification spectra.) The phenomenon of a geometric pattern with expansion from the center to the periphery of the visual field (rarely in the reverse direction) and a simultaneous increase in size over a period of several minutes suggests CSD and migraine. The regular angular patterns in the photopsias that accompany migraine correspond to the cortical structures that generate them.[44,45,46] Photopsias in migraine may evolve into a scotoma or a temporary homonymous hemianopia. Resolution of the visual field

defect typically occurs without any positive visual phenomena. Colors may be seen as well, or spots, circles, and beads with or without colors. When these occur, they are usually part of the scintillating scotoma or teichopsia and not a predominant independent feature of the migrainous visual hallucination.

In contrast, visual epileptic auras are predominantly multicolored, with a circular or spherical pattern, as opposed to the predominantly black-and-white zigzag pattern of migraine.[83] During a seizure, hallucinations that begin unilaterally may later encompass the whole visual field, and simple hallucinations may develop into complex forms. In contrast to migraine, epileptic visual auras last for only seconds (with the rare exception of persistent visual auras),[113] thus limiting the patient's opportunity to observe and describe the hallucinations. The auras are often associated with head or eye movement and alteration of consciousness. Formed visual hallucinations are rare in migraine; when present in epilepsy, this manifestation may localize the seizure onset to the temporal or temporo-occipital region.[14]

The sensory auras of migraine and epilepsy also differ. In migraine, the auras are paresthesias (pins and needles) that typically begin in the hand, move up the arm, skip the shoulder, and move into the face and tongue over a period of 10 to 15 minutes. They are often associated with a visual aura.[92] The sensory aura of epilepsy is typically briefer and is often described as burning, cramping, stinging, aching, electric, or throbbing.

Correctly diagnosing and separating epilepsy and migraine can be more difficult in children than in adults. Young children may give incomplete descriptions of their symptoms; features useful in diagnosing epilepsy or migraine in adults may be absent or difficult to elicit in children. Hemicranial pain and visual auras occur less often in children with migraine than in adults. In children, the first symptoms of migraine may not even be associated with headaches.[42] Children are also less likely to experience feelings of déjà vu or to have olfactory hallucinations as part of a simple partial seizure or temporal lobe epilepsy. Furthermore, the epilepsies most commonly mistaken for migraine are childhood syndromes, as discussed above.

While the EEG is extraordinarily useful in diagnosing epilepsy and differentiating subtypes, it is less valuable in diagnosing migraine. EEGs recorded during an attack of migraine with aura, unlike those recorded during a clinical seizure, are usually normal. Focal slowing sometimes occurs during migraine auras, although this is not a consistent finding. Previously recommended EEG markers of migraine, such as robust photic driving at high flash frequencies and slowing with hyperventilation, can be seen in children without a history of migraine and are not very specific.[37]

Table 7 Features of Epilepsy and Migraine

Clinical features	Migraine	Epilepsy
Consciousness	Usually clear	Usually clouded
Duration	Hours	Minutes
Family history	Often positive for migraine	Sometimes positive for epilepsy
Onset	Gradual	Sudden
Electroencephalogram	Nonspecific abnormalities	Spikes and sharp waves, ictal patterns

The incidence of epileptiform activity in patients with migraine appears to be higher than that of the general population. In a large multicenter study, the incidences of spikes and paroxysmal rhythmic events in 10-hour overnight EEGs of normal adult volunteers (*n* = 135) was 0.7%, as compared to 12.5% for subjects with a history of migraine and 13.3% for subjects with a family history of epilepsy.[86] However, this finding does not contribute to the diagnosis of patients with migraine, and may in fact confuse the issue. Currently, the Quality Standards Subcommittee of the American Academy of Neurology has concluded that the EEG is not useful in the routine assessment of headache patients.[2] It does not identify headache subtypes or effectively screen for structural causes of headache. The EEG is useful if headache patients have symptoms that suggest a seizure disorder, such as atypical migrainous aura or episodic loss of consciousness. Assuming head-imaging capabilities are readily available, EEG is not recommended to exclude a structural cause for headache.[2,91]

There is, however, clearly a role for 24-hour closed-circuit television EEG recording; when differentiating migraine aura from epileptic aura is difficult on clinical grounds, these procedures can also facilitate the diagnosis of comorbid epilepsy and migraine as well as the migralepsy syndrome. Marks and Ehrenberg[29] studied patients with migralepsy using multiple 24-hour video EEG telemetry recordings. The entire migraine–epilepsy sequence of two patients was captured, showing changes during the clinical migraine aura that were atypical for electrographic epilepsy. During migraine aura, bursts of spike activity may resemble the ictal EEG during an epileptic seizure. In most reported cases, however, the EEG does not show the usual temporal evolution with progressive increases and declines in the frequency and amplitude of rhythmic, repetitive epileptiform activity typical of ictal EEGs in epilepsy. In addition, the EEG during migraine aura may show “waxing and waning” patterns, separated by completely normal EEG activity despite the persistence of clinical symptoms.

Manzoni et al.[65] and Terzano et al.[106,107] coined the term intercalated seizures to denote epileptic seizures occurring between the migrainous aura and the headache phase of migraine. They found that 16 of 450 patients with migraine (3.6%) also had seizures. The two conditions appeared to be coincidental in 4 of the 16 patients. In another five patients, the two types of attacks were quite distinct, but often an epileptic seizure was followed by a migraine attack and vice versa. The remaining seven patients had intercalated seizures. All had a family history of migraine and two also had relatives with epilepsy. All had visual seizures consisting of highly stylized contours of plain figures, or single or multicolored spots that often rotated. The seizures lasted for 1 to 2 minutes and came out of a scintillating scotoma, slowly developing in the visual field and evolving into unilateral or bilateral hemianopia. DeRomanis et al.[25,26] studied patients who had brief ictal visual hallucinations of “colored dots or discs” and interictal occipital paroxysms on EEG. EEG during a seizure showed that they had occipital epilepsy and not migraine with aura.[85]

Striking EEG patterns have been described in specific subtypes of migraine.[12] The brain regions most often involved in the published EEG samples in basilar-type migraine include the posterior temporal, parietal, and occipital regions. The posterior electrographic localization may not pertain to other forms of migraine.[71] Paroxysmal lateralized epileptiform discharges (PLEDs) or PLED-like activity has been associated with hemiplegic migraine, prolonged migraine aura, or incipient migrainous infarction. Those patients with PLED-like activity did not have any of the usual entities associated with PLEDs, such as stroke, brain abscess, glioblastoma, or viral encephalitis; their PLEDs usually resolved within 24 hours. Certain migralepsy patients had clinical seizures when PLEDs were present on their EEGs.[67]

Treatment Considerations

Because migraine and epilepsy are associated, clinicians should be sensitive to the issue of concomitant diagnoses. When diseases are comorbid, the principle of diagnostic parsimony does not apply. Individuals with one disorder are more likely, not less likely, to have the other. In the Epilepsy Family Study, only 44% of probands with epilepsy who were classified as having migraine on the basis of their self-reported symptoms reported physician-diagnosed migraine.[78] In the general population, 29% of men and 40% of women with migraine reported a medical diagnosis.[63] The proportion of probands reporting a physician's diagnosis of migraine was surprisingly low, given that all were already being treated for epilepsy.

Why is the comorbidity of migraine and epilepsy not recognized? Epilepsy may be viewed as a more serious disorder than migraine. As a result, the migrainous symptoms of patients with a diagnosis of epilepsy may have been overlooked or attributed to the seizure disorder. In addition, the diagnosis of atypical migraine symptoms can be quite difficult, and a number of epileptic and nonepileptic syndromes may mimic migraine. Some patients with epilepsy and migraine may not report their headaches because the headaches are being effectively treated with an antiepileptic drug without a diagnosis of migraine. Finally, the interview used in the Epilepsy Family Study may lead to overdiagnosing migraine in some patients.

When planning treatment strategies for epilepsy and migraine, the possibility of comorbid disease should be considered. Although tricyclic antidepressants and neuroleptic drugs are often used to treat migraine in patients with comorbid epilepsy, caution is advisable, as these medications may lower seizure thresholds. When selecting drugs for migraine prophylaxis, it is sometimes advantageous to treat comorbid conditions with a single agent; for example, when migraine and hypertension occur concomitantly, a beta-blocker or calcium channel blocker is commonly used.[97] In the same way, anticonvulsants with efficacy for both migraine and epilepsy (divalproex sodium and topiramate) should be considered in patients with both disorders.

Divalproex sodium is a Food and Drug Administration (FDA)-approved anticonvulsant for migraine prophylaxis. The efficacy of divalproex has been supported by recent open and double-blind, placebo-controlled studies.[50,68,96,104] The doses that are effective in migraine are generally lower than those used for epilepsy; 500 mg/day is often sufficient. Topiramate is a second FDA-approved anticonvulsant for migraine prophylaxis. In both open and small, placebo-controlled, double-blind trials, doses of 50 to 100 mg/day have been shown to be effective for migraine.[99] Other antiepileptic drugs that have been shown to be superior to placebo for migraine include gabapentin, levetiracetam, tiagabine, and zonisamide, but large-scale studies are needed. Lamotrigine may be effective for migraine aura, but not headache.

An advantage to the use of anticonvulsants as migraine prophylactic agents is that they can be administered to patients with depression, Raynaud disease, asthma, and diabetes, circumventing the contraindications to beta-blockers.[98]

In addition, the recognition of potentially similar mechanisms and response to therapy between the disorders has led to crossover of other treatment modalities. For example, the vagal nerve stimulator, an FDA-approved device for the add-on treatment of intractable partial epilepsy, is under investigation for migraine.[72] Similar efforts are likely to continue.

Summary and Conclusions

In summary, migraine and epilepsy are comorbid conditions, and the presence of one disorder increases the likelihood of the other. Because of its greater prevalence, migraine is very common in persons with epilepsy, while epilepsy is rare in migraineurs. The comorbidity of migraine and epilepsy presents both pitfalls and opportunities, and the diagnosis and treatment of each disorder must take into account the potential presence of the other.

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Chapter 275

Cerebrovascular Disorders

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Introduction

The relationship between cerebrovascular disease and epilepsy has long been appreciated since Hughlings Jackson first reported partial seizures in the setting of acute stroke.[7] Indeed, cerebrovascular disease has been found to be the most common cause of secondary epilepsy. In a population-based study from Rochester, Minnesota, cerebrovascular disease accounted for 11% of cases.[37] This chapter will review the limited data on the epidemiology and treatment of poststroke seizures and epilepsy. Because the differentiation between cerebrovascular disorders and seizures is sometimes difficult, the chapter will also aim to make the clinical distinction between epileptic syndromes, transient ischemic attacks (TIAs), and other minor ischemic stroke syndromes. The nosology and natural history of TIAs, the more common TIA syndromes, and some less common clinical syndromes of TIAs and minor strokes that might be confused with paroxysmal epileptic syndromes will be discussed.

Epidemiology

Seizures can be a complication of an acute stroke. Traditionally, poststroke seizures have been divided into early and late based on presumed differences in pathophysiology.[41] Early seizures are thought to result from acute biochemical disturbances and may result in part from the damaging effects of the excitatory neurotransmitter glutamate in response to ischemia.[14,17,58] In contrast, late seizures are attributed to gliosis and cortical scarring with resulting selective neuronal loss and hyperexcitability of the surrounding tissue.[39,58] Some authors have argued that early seizures are not reliably related to the strokes themselves because of other concurrent metabolic problems.[38,57] The International League Against Epilepsy (ILAE) defines early poststroke seizures as those that occur before 1 week, but studies have used widely varying definitions, from under 24 hours up to 1 month after stroke.[46,49] Despite varying definitions of what constitutes an early poststroke seizure, several studies have found that the risk of epilepsy is significantly increased among those patients who have seizures within 2 weeks of the onset of a stroke.[71] Late poststroke seizures have also been associated with an increased risk of epilepsy.[10,15,48,71]

Data from five prospective studies have shown that the rate of epilepsy after ischemic stroke ranges from about 2% to 4%.[10,15,48,57,71] However, the reported incidence of epilepsy varies between studies with the definition. Using the ILAE definition of two or more unprovoked seizures more than 1 week after stroke, a study from Rochester, Minnesota, found an overall rate of poststroke epilepsy of 3.3%, and 66% of those that developed an initial late seizure after ischemic stroke went on to develop epilepsy by 4.5 years.[71] In a study from Norway, the overall incidence of poststroke epilepsy was 3.1%, while 11 of 28 subjects with poststroke seizures developed epilepsy (55%).[57]

Limited data are available regarding risk factors for poststroke seizures and more is known about those that occur early than late. Involvement of the cortex is the most well-recognized predictor of early seizure occurrence, having been found to be an independent risk factor in several prospective studies.[8,10,15,47,48,71] Stroke severity and infarct size have also been found to be independent risk factors.[10,48,57,65] Few studies have examined independent predictors of late poststroke seizures or epilepsy.[17] Early seizures appear to be a risk factor for late seizures and possibly epilepsy, and a few studies have found that infarct size, cortical involvement, and recurrent stroke have been independent predictors.[10,48,71] However, in a large prospective study from Norway, stroke severity was an independent risk factor for epilepsy while cortical location was not.[57] Thus, further data are needed to clarify the relative importance of these modifying factors.

Treatment

Treatment of poststroke seizures and epilepsy is complicated by a lack of clinical trial data to support the use of a particular antiepileptic drug on the one hand, and evidence that some commonly used drugs may be detrimental to stroke recovery on the other. For example, treatment with antihypertensive drugs that block the adrenergic system, such as prazosin and clonidine, or those that stimulate γ-aminobutyric acid (GABA) receptors, such as benzodiazepines, have been shown to impair recovery after brain injury in the rat, and the antiepileptic drugs phenytoin and phenobarbital have been implicated as well.[33] Less is known about the effect of these drugs on recovery in humans. One study examining the control group of an acute ischemic stroke treatment trial found that subjects administered any of a group of "detrimental drugs" including benzodiazepines, dopamine receptor antagonists, α-1 blockers, α-2 agonists, phenobarbital, or phenytoin had worse motor recovery and less independence in activities of daily living than those that did not receive any of these drugs.[33] Recovery after subarachnoid hemorrhage may also be impeded by such treatment. In a prospective case series, greater phenytoin exposure was associated with worse functional outcome at 14 days and worse cognitive outcome at 3 months.[60] However, treatment after experimental ischemia in rodents has shown that many antiepileptics may be neuroprotective if given very early.[17] For example, phenytoin when given 30 minutes after experimental occlusion of the rat middle cerebral artery was neuroprotective, but not if given after 2 hours.[22] Separately, diazepam given 30 and 90 minutes after induced forebrain ischemia in the gerbil resulted in protection of hippocampal neurons.[69] Neuroprotective properties have also been reported for lamotrigine, topiramate, levetiracetam, and zonisamide.[17] Thus, further data are needed to clarify the importance after stroke of the doses, timing, and length of treatment with antiepileptic drugs that may be helpful or harmful to patients.

Nosology of Transient Ischemic Attacks

The term *stroke* generally describes a group of vascular disorders diverse in etiology and includes ischemic brain infarction, intracerebral hemorrhage, and subarachnoid hemorrhage.[4] The term *transient ischemic attack* has been limited to the description of a brief episode of neurologic dysfunction resulting from ischemia and was introduced in 1957 by C. Miller Fisher. TIA is formally defined as "an abrupt onset of focal loss of brain function lasting less than 24 hours that localizes to a portion of the brain supplied by one vascular system and for which no other cause can be found."[2] The arbitrary 24-hour time limit was selected on the basis of prospective studies in the 1970s prior to the widespread use of brain imaging.[3] It was thought that focal deficits lasting beyond 24 hours would be expected to result from a focus of ischemic infarction. This definition now requires revision, based upon recent brain imaging evidence of infarction in a substantial proportion of episodes classified by the 24-hour time limit as TIAs.[11,24] The term *reversible ischemic neurologic deficit* (RIND) was created to define those patients with neurologic dysfunction lasting longer than 24 hours but resolving completely within 1 to 3 weeks.[4] Neurologic deficits in the minor ischemic stroke syndromes conversely persist beyond these arbitrary time periods. Ischemic stroke may be more appropriately viewed as a continuum that encompasses TIA, RIND, and minor ischemic stroke.[18] As similar risk factors and vascular pathologies underlie these diagnostic subgroups, their continued separate distinction from each other is employed primarily for the purposes of differential diagnosis and prognostic risk strati- fication.[23]

Prevalence and Incidence of Transient Ischemic Attacks

Differing methods and ambiguities of definition have resulted in a wide disparity in reported prevalence and incidence rates of TIAs.[13] Estimated prevalence has varied from 1.1 to 77 per 1,000 persons, but three recent studies have dealt more effectively with the ascertainment bias inherent in capturing transient episodes, and data have shown incidence rates that are more consistent. Population-based data from Rochester, Minnesota, for the period 1985 to 1989 led to a calculated annual age- and sex-adjusted incidence rate of 68 per 100,000 population.[13] The incidence rate was somewhat higher in the Greater Cincinnati/Northern Kentucky Stroke Study at 83 per 100,000, but 15% of the sample is of black race and may be at higher risk of cerebrovascular disease.[42] Similar rates were seen in the United Kingdom. In the Oxfordshire study the overall age- and sex-adjusted incidence rate for TIA was 51 per 100,000.[66] In addition, annual incidence rates for TIA appear to be reasonably stable over time, taking into account lower ascertainment in earlier studies. The incidence rate did not change appreciably in Rochester between the periods 1960 and 1972 and 1985 and 1989, although the rate increased slightly in Oxfordshire, U.K., between 1981 and 2004 (relative incidence 1.27).[13,66] The incidence of TIA was strongly related to age in all three studies.

Natural History of Transient Ischemic Attacks

Transient ischemic attacks precede 11% to 50% of strokes, depending on the specific stroke subtype.[3] They have been reported most frequently in association with large artery atherothrombotic disease and less commonly with small vessel disease.[30,59] Approximately 50% to 75% of patients who experience a stroke from extracranial carotid atheromatous disease have a prior TIA.[59] Perhaps the most important finding in recent studies has been the very high rate of stroke following TIA. Data from a large health maintenance organization in California found that roughly 10% of those presenting with TIA went on to have an ischemic stroke within 90 days and half of these occurred within the first 48 hours after the index event.[40] Similarly, data from the Greater Cincinnati/Northern Kentucky Stroke Study found a 17% ischemic stroke rate within 6 months after TIA, 65% of which occurred within the first month.[42] The results from the North American Symptomatic Carotid Endarterectomy Trial (NASCET) helped clarify the outcomes for TIA patients.[1] Patients with TIAs and symptomatic extracranial carotid stenosis exceeding 70% were followed prospectively over a period of 18 months. During this time period, 24% of the medically treated group had a stroke or died, compared with a 7% rate in the endarterectomy-treated group. This striking difference proved that surgery was effective in reducing the risk of stroke after TIA and that TIAs should be regarded as a marker of significantly increased stroke risk. Certain subgroups of TIAs carry a higher stroke risk than do others. Data from NASCET showed that hemispheric TIAs with known high-grade ipsilateral carotid stenosis had a stroke risk exceeding 40% over 2 years.[75] Early stroke risk is probably greater in those patients with “crescendo” TIAs (multiple and frequent) and in the subgroup with ventricular thrombi.[2]

Clinical discrimination between TIAs and nonvascular causes of transient neurologic dysfunction is crucial as the occurrence of a TIA is a reliable warning signal of an impending stroke. An episode consistent with a TIA should be rapidly evaluated to determine the cause. Prompt clinical recognition of TIAs and timely institution of appropriate therapy can help prevent stroke. Furthermore, the possibility of occult coronary artery pathology should be considered in the workup of these patients as the occurrence of TIAs may indicate generalized atherosclerosis; ischemic heart disease is the leading cause of death in elderly TIA patients.[2,25]

Diagnostic Difficulty

Less than one in ten TIAs are witnessed by a physician; therefore, accurate diagnosis usually depends on a careful interpretation of the patient's history.[26] Health care professionals tend to formulate a preliminary diagnosis within the first few minutes of history taking, which works well when the symptoms follow classic textbook descriptions.[68] However, many patients cannot offer a clear, concise account of abrupt onset of focal neurologic dysfunction, as required for the diagnosis of TIA. Details are often forgotten or unappreciated regarding time, mode of onset, and subsequent course of symptomatology. Historical reliability becomes more questionable when patients consult a physician weeks or months following the event. Nondominant hemispheric TIAs are particularly susceptible to misclassification because the event may be ignored or misinterpreted by the patient.[78] The lack of uniform diagnostic criteria for TIA is reflected in significant interobserver disagreement. The Cooperative Group for the study of TIA found that 30% of patients hospitalized with a diagnosis of TIA had been misclassified.[16]

This finding has been confirmed in other series.[43] Questionnaires on TIA symptomatology have documented a high positive response rate, both in the elderly and in a group of young adults.[56,81] These surveys indicate that episodes of transient central nervous system dysfunction are common. Follow-up of those patients whose transient symptoms were considered too vague to represent TIA has revealed a stroke rate comparable to the TIA group, suggesting that current empiric criteria for TIA are too narrow.[82] Standardized checklists using nonmedical terminology and computer-based diagnostic algorithms offer useful alternatives to enhance diagnostic consistency.[44,63] There is a need for improved diagnostic guidelines for TIAs with enhanced reliability, sensitivity, and specificity.

Table 1 Frequency and Type of Symptoms[a] in Carotid Transient Ischemic Attacks

Frequency left carotid[b]		Frequency right carotid[c]	
67%	Sensorimotor (arm)	70%	Sensorimotor (arm)
56%	Weakness (face, arm, or leg)	50%	Weakness (face, arm, or leg)
45%	Aphasia	N/A	
44%	Sensory (arm)	53%	Sensory (arm)
21%	Dysarthria	24%	Dysarthria
20%	TMB	27%	TMB

N/A, not applicable; TMB, transient monocular blindness.

[a] Only symptoms reported by at least 20% of patients are tabulated.

[b] n = 171.

[c] n = 142.

Data derived from Futty DE, Conneally M, Dyken ML, et al. Cooperative study of hospital frequency and character of transient ischemic attacks. V. Symptom analysis. *JAMA.* 1977;238(22):2386– 2390.

Typical Transient Ischemic Attack Symptoms

Traditionally, TIAs have been classified according to the vascular territory involved: Carotid or vertebrobasilar. This differentiation is important for management and prognosis.[55] Carotid territory TIAs occur more frequently and may result in the following: Weakness, paralysis, or clumsiness of one side of the body or face; numbness or paresthesias affecting one side of the face or body; loss of vision affecting one eye or, less frequently, one visual field; language disturbance (aphasia); and dysarthria.[4] Analysis of a large series of carotid TIAs has proved helpful in determining the relative frequencies of various symptoms typical of TIAs (Table 1).[31]

Mixed sensorimotor disturbances of the distal arm and hand were the most frequent carotid TIA symptoms, followed by motor weakness variably affecting the face, arm, or leg; aphasia with left carotid territory syndromes; and isolated sensory dysfunction of the arm. Transient monocular blindness (TMB) or amaurosis fugax and dysarthria were less frequent manifestations. Neurologic evaluations during the occurrence of TIAs confirmed the presence of motor or language disturbance. Sensory complaints were found to have less objective associated signs on examination, and reflex asymmetry or Babinski signs were found infrequently. Patients with visual field deficits were often unaware of their deficit, and the examiner found evidence for deficits in addition to the presenting symptom.

Table 2 Frequency and Type of Symptoms[a] in 97 Vertebrobasilar Transient Ischemic Attacks

60%	Ataxia (appendicular or gait)
43%	Vertigo
39%	Diplopia
37%	Blurry vision
27%	Dysarthria

[a] Only symptoms reported by at least 20% of patients are tabulated.

Data derived from Futty DE, Conneally M, Dyken ML, et al. Cooperative study of hospital frequency and character of transient ischemic attacks. V. Symptom analysis. *JAMA.* 1977;238(22):2386– 2390.

Table 3 Atypical Transient Ischemic Attack Syndromes That May Mimic Epileptic Activity

Syndrome	Vascular territory	Localization
Limb shaking	Carotid	Hemisphere
Asterixis	Vertebrobasilar	Diencephalon
Dyskinesia	Carotid Vertebrobasilar	Hemisphere Diencephalon
Pure sensory	Vertebrobasilar Carotid	Diencephalon Hemisphere
Speech arrest	Carotid	Hemisphere
Visual inversion	Vertebrobasilar	Brainstem

Auditory hallucinosis	Vertebrobasilar	Brainstem
Anosognosia	Carotid	Hemisphere
Akinetic mutism	Carotid	Hemisphere
Drop attacks	Vertebrobasilar	Brainstem

Vertebrobasilar TIAs may cause the following symptoms: Weakness, paralysis, or clumsiness with or without sensory deficit affecting the face or limbs; gait imbalance; vertigo; diplopia; dysarthria; or dysphagia.[4] Complaints may alternate from side to side, be bilateral from onset, or affect one side of the face and the opposite body (crossed syndromes). Symptom analysis from a large series of vertebrobasilar TIA patients is presented in Table 2.[31] Vertigo, diplopia, dysarthria, dysphagia, and disequilibrium occurring alone were considered less likely to be a TIA. Whether nonrotatory dizziness may have a vascular etiology remains unclear.

These large clinical series have demonstrated that motor symptoms accompany most TIAs, that typical TIA symptoms are "negative" (loss of function), and that dysarthria can result from either anterior or posterior circulation dysfunction. Symptoms considered unlikely to represent TIAs include loss of consciousness without other vertebrobasilar signs, tonic or clonic activity, light-headedness, syncope, incontinence, and focal symptomatology with migraine headache (e.g., "march" of a sensory deficit, scintillating scotomata). Less typical TIA symptoms that include positive clinical manifestations and can cause diagnostic confusion will be discussed further (Table 3).

Typical Time Course of Transient Ischemic Attacks

Eliciting historical information regarding the temporal course of the TIA symptoms is as important as the nature of the actual

symptoms in making an accurate diagnosis. There is now general acceptance that the arbitrarily defined time period of 24 hours for the definition of TIAs is too long.[55] Most TIAs are rapid in onset and extremely brief, with one series reporting that 24% resolved within 5 minutes, 39% within 15 minutes, and 50% within 30 minutes.[56] Only 40% of TIAs in this series lasted longer than 1 hour. The Cooperative Group for the study of TIAs found that carotid TIAs lasted, on average, 14 minutes, whereas vertebrobasilar events lasted approximately 8 minutes.[5] The prognosis of those patients with longer-lasting TIAs may differ from the subset with brief spells, with reports suggesting that longer-duration TIAs are more likely to exhibit ischemic infarction on more sensitive brain imaging.[11,24] The term *cerebral infarction with transient signs* (CITS) has been developed to describe this subgroup.[79]

Atypical Transient Ischemic Attack Presentations

Limb-shaking Carotid Transient Ischemic Attacks

It is generally assumed by physicians that motor TIAs cause limb weakness, whereas focal motor seizures produce convulsive limb movements; however, focal limb shaking resembling a partial motor seizure has been described in association with carotid occlusive disease. Fisher first recognized this unusual manifestation in his observations on carotid TIAs.[27] He noted that the patients described the involved limb as "trembling, shaking, twisting, drawing up, or moving irregularly." His observations have since been corroborated by several investigators.[9,36,84] Russell and Page reported one patient who had involuntary jerking movements affecting the left arm and leg in association with carotid occlusive disease.[66a] Yanagihara and Klass described six patients with involuntary limb jerking, all in association with high-grade stenosis or occlusion of the contralateral carotid artery.[84] They concluded that cerebral ischemia due to diminished cerebral perfusion was the underlying pathogenic mechanism. All of their patients benefited from cerebral revascularization, either carotid endarterectomy (CEA) or extracerebral-intracerebral (EC-IC) bypass grafting. Eight patients were described by Baquis et al. in whom involuntary repetitive movements affected the arm/hand alone or arm and leg opposite to a diseased carotid.[9] The movements had a coarse, wavering, nonrhythmic character with a frequency of 3 to 12 Hz, and seven of the patients had additionally experienced more typical carotid TIAs. In one of their patients, the episodic limb shaking was temporarily related to postural changes in the absence of documented orthostatic hypotension. Cerebral revascularization procedures performed in six of eight patients produced resolution or reduction in the episodic limb-shaking spells. The authors suggested that ischemia affecting the distal field of the atheromatous carotid artery and resulting in perfusion insufficiency was the pathogenic mechanism.

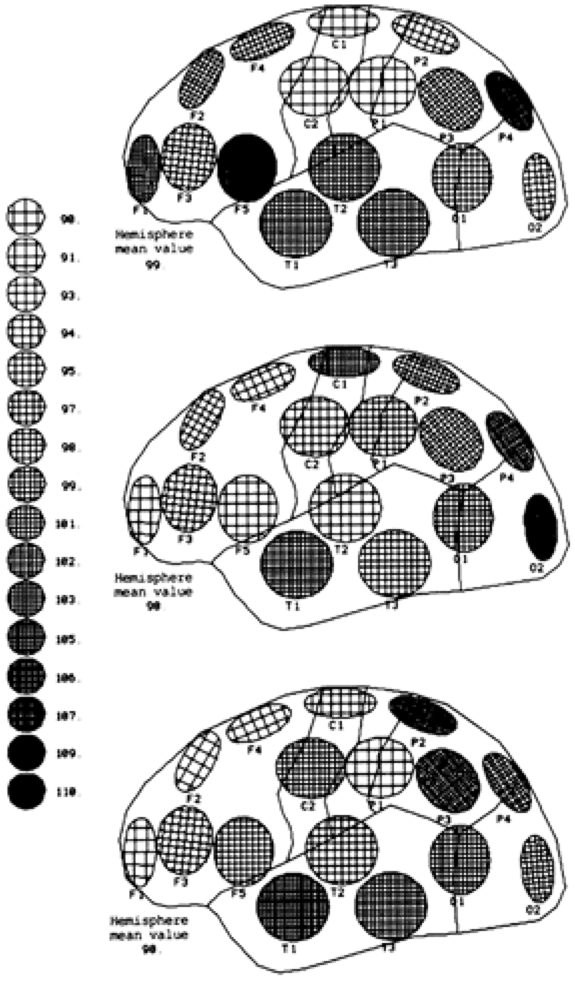


FIGURE 1. Map of cerebral blood flow asymmetry (right initial slope index ([ISI] ÷ left ISI × 100) before carotid endarterectomy under normocapnic (**upper**), hypercapnic (**middle**), and hypotensive (**lower**) conditions. Asymmetry is indicated by intensity of shading, quantified by scale (**left**), given as a percentage. Under normocapnic conditions, there was hypofrontality and reduced perfusion focally in right dorsofrontal and upper rolandic regions (detectors *C1, C2, P1,* and *P2*). With hypercapnia, more extensive zone in right dorsofrontal region was apparent, extending to superior and inferior frontal regions (detectors *F4, F2, F1, F3, F5,* and *T2*). During hypotension, blood flow deficit in right dorsofrontal and prerolandic regions (detectors *C1, P1, F4, F2, F1,* and *F3*) was further accentuated. (From Tatemichi TK, Young WL, Prohovnik I, et al. Perfusion insufficiency in limb-shaking transient ischemic attacks. *Stroke.* 1990;21(2):341–347.)

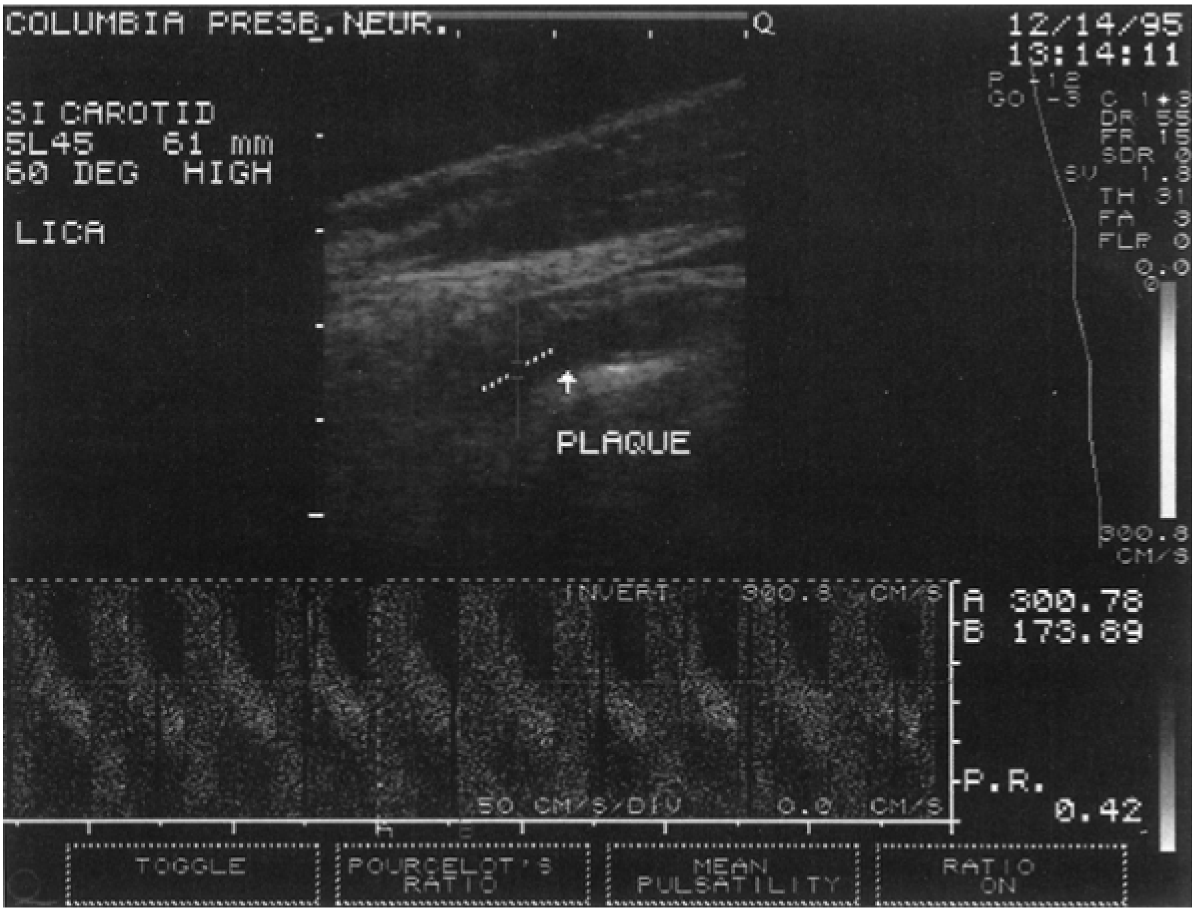


FIGURE 2. Duplex Doppler of the left internal carotid artery showing severe stenosis with plaque obstructing the lumen (*arrow,* **upper**). The Doppler wave form spectra confirm the hemodynamically significant stenosis (**lower**).

Subsequent investigators have confirmed the mechanism of perfusion insufficiency as the probable cause of focal limb shaking. Levine et al. studied cerebral blood flow (CBF) reactivity to induced hypercapnia using fluoromethane positron emission tomography (PET) scanning in 32 patients with carotid TIAs.[54] Reactivity was found to be significantly diminished in a hemodynamic subset of eight patients whose clinical manifestations included orthostatic limb shaking. Tatemichi et al. reported on a patient whose limb-shaking episodes occurred repeatedly on standing up. Cerebral blood flow was measured using inhaled Xenon-133, and a focal decrease was observed in the right frontal convexity, representing the distal fields between the anterior cerebral artery and the middle cerebral artery.[77] Impaired reactivity was demonstrated in response to hypercapnic challenge using CBF and transcranial Doppler (TCD). A circumscribed loss of cerebral autoregulation was also demonstrated in the same patient, with exacerbation of the perfusion deficit in the right frontal region during hypotension (Fig. 1). The abnormal CBF response to both hypercapnia and hypotension was felt to reflect maximum vasodilation in the distal fields or watershed territory of the involved hemisphere with poor hemodynamic reserve.

These cases illustrate that limb shaking as the first manifestation of a carotid TIA correlates with hemodynamically significant carotid artery disease, with perfusion failure being the most likely mechanism. The patients typically have risk factors for cerebrovascular disease, and the spells are often triggered by postural change or exertion. The movements tend to be coarse and irregular, lasting minutes, and occurring from once a week to several times a day. Other neurologic deficits

rarely occur during the spells, and the interepisode examination is usually normal. A seizure mechanism is not supported in these patients, based on the following observations: No associated clinical seizure phenomena (e.g., impairment of consciousness, rhythmic tonic–clonic jerking, head or eye deviation); no epileptiform activity recorded on electroencephalograms (EEGs) between and during such attacks; a lack of response to trials of antiepileptic medication when such a mechanism was entertained; and, finally, the prompt and favorable response to cerebral revascularization. It remains unclear how ischemia produces the positive motor symptoms, with release of subcortical motor pathways proposed as a possible explanation. Failure to recognize that focal limb shaking can occur secondary to ischemia could lead to delay in diagnosis of the associated severe carotid atheromatous disease (Fig. 2).

The converse situation, where focal seizure activity may cause limb weakness and be misdiagnosed as a TIA, has also been described.[53,64] Fisher referred to this situation as “nonconvulsive seizure paralysis,” and noted that it may give rise to diagnostic confusion.[29] Lee and Lerner reported on a 70-year-old diabetic man who presented with recurrent episodes of short-lived right arm weakness and numbness.[53] These spells lasted from 3 to 5 minutes and occurred without warning or other obvious precipitating factors. The patient also noted some speech difficulty during these spells. Neurologic evaluation at the time of admission revealed only a mild right pronator drift, and a computed tomography (CT) scan of the brain was normal. An initial diagnosis of crescendo left carotid TIAs was made, and the patient was anticoagulated with intravenous heparin. Despite therapeutic heparin, the patient continued to have spells at a frequency of three or four hourly. During a typical attack, the patient was noted to first complain of vague right arm discomfort, followed by right arm paralysis; he was described as alert throughout the episode, but with mild word-finding difficulty. An EEG obtained during one such episode demonstrated intermixed spike-and-sharp-wave activity in the left parietal region, which resolved after return of motor function to the affected arm. The presence of these EEG abnormalities was confirmed during subsequent spells. The patient was treated with phe- nytoin, and the spells decreased in frequency and resolved completely over several days. The authors proposed that a seizure discharge involving the motor region of the left parietal lobe was responsible for the limb paralysis in their patient.

Primavera et al. described a 56-year-old woman with multiple vascular risk factors who presented with recurrent bouts of weakness affecting the right face and arm.[64] Neurologic examination disclosed a right pronator drift, and a CT scan showed multiple old lacunar infarcts. Anticoagulation was begun for a presumptive diagnosis of carotid TIAs, but the intermittent attacks of limb weakness continued. An EEG obtained during a typical attack revealed intermittent high-amplitude slow-wave activity of 2 to 3 Hz intermixed with spikes and sharp waves in the left frontotemporal regions. The attacks decreased in frequency and eventually ceased after treatment with phenobarbital.

These case reports emphasize that the differential diagnosis between TIA and seizure is not always straightforward, even in the presence of vascular risk factors and established ischemic cerebrovascular disease. High-grade carotid stenosis may produce limb shaking, mimicking a focal motor seizure, whereas somatic inhibitory seizures can result in motor weakness, simulating an ischemic TIA.

Unilateral Asterixis

Asterixis is the sudden failure in maintenance of posture, characterized by transient electrical silence in muscles activated to maintain the posture.[80] Clinically it is manifested by asynchronous jerky or flapping movements of the outstretched hands. It was first described by Adams and Foley in a group of patients with hepatic encephalopathy.[6] However, unilateral intermittent asterixis may occur in association with focal cerebral ischemia and be confused with partial motor epilepsy.

Lazzarino and Nicolai described a 56-year-old man who presented 5 months after a left posterior cerebral artery stroke with sudden onset of involuntary movements of the right hand:

> The right hand, when outstretched, showed a movement characterized by sudden flexion of the wrist with loss of position, followed by its sudden restoration. This movement was repeated intermittently at regular intervals, but brief periods of sustained posture between the flaps were present. Active movements abolished these involuntary movements.[52]

Another report described the onset of unilateral asterixis in a 73-year-old man during his recovery from a right ventral thalamic infarct, where the unusual nature of the movements led to a misdiagnosis of epilepsia partialis continua:

> In the left arm, involuntary semi-rhythmic abduction and flexion movements of the fingers and flexion of the wrist were present regardless of the posture of the limb. In contrast, with the left wrist held in extension and the arms pronated, rhythmic loss of posture resulted in wrist flexion movements typical of those seen in asterixis.[74]

The precise mechanism for the asterixis due to ischemia remains uncertain, but it is thought to be related to lapses of sustained muscular contraction secondary to episodic disturbances in the responsible neuronal circuits.[80] The movements may appear at rest, but gravity is the most effective stimulus to elicit asterixis. Failure to consider ischemia as a diagnostic possibility in the evaluation of episodic unilateral involuntary movements may result in the unwarranted administration of anticonvulsant medication.

Episodic Dyskinesia

Acute hemiballism or choreoathetosis is known to occur from infarcts of the subthalamic nucleus of Luys, striatal and thalamic nuclei.[55] The involuntary movements are usually of sudden onset, without accompanying deficits. The following case report serves to illustrate the clinical presentation:

> An 81-year-old, right-handed woman suddenly developed involuntary movements of the left limbs…. On neurologic examination, she showed choreic and ballistic movements of the left limbs. There was almost constant, small-amplitude, proximal and distal choreic movements, with superimposed brisk, large-amplitude proximal movements, primarily related to action. Magnetic resonance imaging (MRI) revealed a small area of hypointense T1 signal in the right thalamus.[45]

Episodic dyskinesias, while less frequently reported, have been described in association with both vertebrobasilar and carotid occlusive disease. Margolin and Marsden reported on four patients with episodic abnormal involuntary movements affecting the limbs opposite to carotid atheromatous disease.[58a] The clinical spectrum included both choreoathetoid and ballistic involuntary movements, lasting from minutes to 1 hour. The patients used the terms *writhing, wild gyrations*, and *snakelike* to describe the involuntary movements. Cerebral revascularization with carotid endarterectomy resulted in resolution of the movements. Stark described recurrent brief attacks of snakelike movements affecting the left arm in a 53-year-old woman with high-grade stenosis of the right internal carotid artery that responded to endarterectomy:

> She had three attacks within 1 month; each was characterized as sudden inability to "control my left arm." When she was asked to demonstrate the attacks, she raised her left arm and made snakelike movements, proximally and distally, characteristic of choreoathetosis.[72]

Unilateral dyskinetic movements may be mistaken for convulsive phenomena unless a vascular etiology is given careful consideration. Witnessed accounts of such episodic involuntary movements may not be available, and if the nondominant hemisphere is involved, the patient may ignore or trivialize the episode. The presence of vascular risk factors and evidence for infarction on brain imaging should be specifically sought. Both the carotid and vertebrobasilar circulation have been implicated in previous reports, and ultrasound examination using duplex Doppler may reveal abnormalities.

Pure Sensory Spells

Sensory disturbances affecting part or all of the contralateral body are frequent manifestations of hemispheric TIAs. Although TIAs are usually considered to result from large-artery atherothrombotic disease, they may also occur from small penetrating vessel disease. Awareness of these so-called lacunar TIAs is critical to any discussion of pure sensory phenomena. The Stroke Data Bank (SDB) found that lacunar syndromes had a preceding TIA in 13% of the cases versus 40% for large-artery syndromes.[30] Thus, both large- and small-vessel pathology need to be considered in the differential of focal sensory complaints. Isolated fleeting sensory dysfunction can also be the result of a partial seizure syndrome, and it is a diagnostic challenge to separate an ischemic from an ictal mechanism.

Pure sensory symptoms involving the arm occurred in approximately 50% of the cases from a large series of carotid TIAs.[31] The distal arm and hand were the sites most frequently affected in the attacks, with the sensory deficit thought to result from ischemia of the sensory cortex in the distal field of the diseased carotid territory. To confidently attribute pure sensory disturbances in the individual patient to a hemispheric TIA, a search using duplex and transcranial Doppler to find an appropriate carotid lesion should be performed. Failure to document hemodynamically significant stenosis of the extracranial carotid artery or its intracranial branches suggests that large-vessel stenosis is less likely to account for the sensory spells.[55]

Pure sensory stroke (PSS) is a well-recognized vascular syndrome resulting from lacunar infarction of the ventral tier thalamic nuclei. Fisher's case 9 in his original collection of PSS cases was characterized by transient attacks of sensory disturbance affecting the fingers of the right hand; the right side of the lips along with the right side of the tongue were affected, in addition to the fingers, during subsequent spells. At autopsy, a lacune in the ventral posterior thalamic nucleus, measuring 7 mm in diameter, was found. Another case in his collection had intermittent sensory spells affecting the left lower lip, fingers of the left hand, and sole of the left foot. Other patterns of sensory involvement described in PSS cases by Fisher were as follows: Face, arm, and leg; head, cheek, lips, and hand; face, fingers, and foot; shoulder tip and lower jaw; distal forearm alone; fingers alone; and leg alone.[28]

The peculiar nature of sensory complaints in thalamic ischemia may lead the unsuspecting to fail to consider a vascular etiology. The patients may describe the affected body part as feeling stretched, hot, swollen, sunburnt, larger, smaller, or heavier. Eyeglasses, jewelry, and clothing may feel heavier on the affected part, and contact may transiently exacerbate the dysesthetic sensations. Thalamic-origin TIAs can give rise to either a sensory disturbance restricted to a few digits or an extensive abnormality splitting the entire body, including the scalp, neck, trunk, and genitalia.[55] It may not be readily appreciated that such midline splitting can be produced by an ischemic mechanism unless the unique somatosensory organization of the thalamus and the thalamocortical connections is considered in the approach to differential diagnosis.

Speech Arrest

Isolated episodes of language disturbance due to left carotid TIAs must be distinguished from those secondary to seizure activity. Cascino et al. described three patients in whom transient episodes of speech arrest were initially attributed to TIAs, but in which subsequent EEG recordings demonstrated bifrontal seizure activity.[20]

Case 1 was a 66-year-old woman with end-stage renal disease admitted for shunt placement. During her hospitalization, she experienced spells in which she would abruptly stop talking and stare aimlessly. She remained alert throughout the episodes and followed verbal commands.

Case 2 was a 72-year-old hypertensive male admitted with a diagnosis of TIAs. Multiple spells lasting minutes were observed, during which he said he could understand speech but “could not get the words out.”

The final case they described involved an 87-year-old man on long-term warfarin therapy for an artificial heart valve admitted with abdominal complaints. He was noted to experience several spells of “expressive aphasia,” where he could not speak but would follow commands. In all of the cases, the episodes resolved following treatment with anticonvulsants.

Peled et al. provide a further insightful case description of a 65-year-old man with multiple stroke risk factors (smoking, diabetes, hypercholesterolemia) evaluated for transient episodes of sudden inability to talk.[62] These spells lasted from 2 to 5 minutes and occurred up to four times daily. Clinical observation of the spells during the patient's period of hospitalization was remarkable for sudden onset of mutism with preserved comprehension and absence of any forced head, gaze deviation, or focal motor activity. EEG obtained between the episodes proved normal, and a seizure diagnosis was not entertained until the patient was noted to raise his right hand and turn his head to the right during one of his characteristic spells. Closer observation revealed involuntary gaze deviation and clonic motor activity affecting the right face and limbs during some of his spells. Brain imaging demonstrated a probable metastatic lesion in the medial dominant frontal lobe corresponding to supplementary motor area (SMA). Treatment with phenytoin was begun, and the spells resolved.

This case material helps to emphasize that although cerebral ischemia commonly underlies the sudden onset of language disturbances in the elderly, infrequently seizures may be the cause.

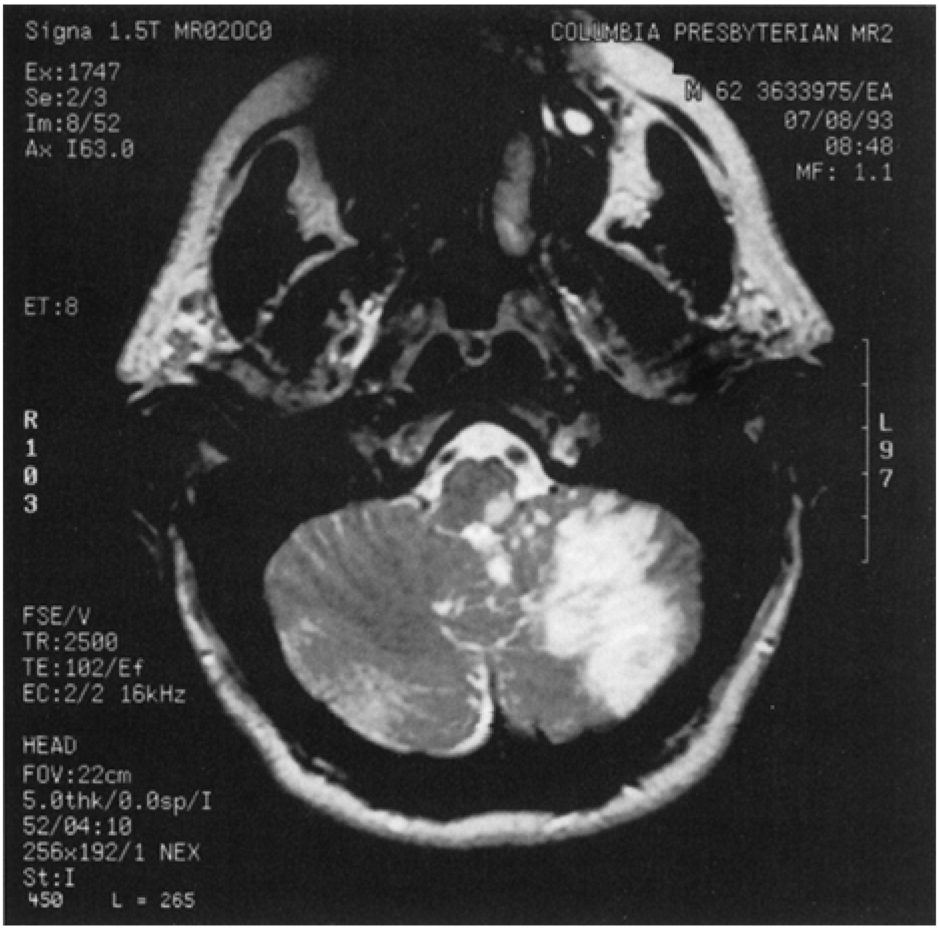
Penfield and Roberts have reported that electrical stimulation of the SMA region anterior to the leg representation can produce speech arrest in humans.[63] Proposed pathogenetic mechanisms include interference with the motor pathway subserving vocalization or a true ictal "aphasic" speech arrest from a primary language disorder. Certainly, when dominant SMA lesions produce this latter type of aphasic speech arrest without accompanying eye-head deviation or tonic posturing, the epileptic nature of the spells may be missed, and an incorrect diagnosis of dominant carotid territory TIA may result. Such a misdiagnosis may lead to inappropriate investigations and a decision to commence long-term anticoagulation, with its attendant risks.

Visual Inversion

Momentary vertical inversion of images has been described in Wallenberg syndrome and vertebrobasilar TIAs and can sometimes be confused with the visual phenomena of seizures.[67,73] Patients present with the unusual complaint of acute "upside-down" vision, their world appearing 180 degrees reversed. The entire visual field is affected, with color and shape perception generally preserved, which helps distinguish it from the visual phenomena (e.g., macro- or micropsia, visual hallucinations) that can be associated with temporal or occipital lobe epilepsy. The following case report of an 83-year-old man serves to illustrate the features of this novel visual illusion:

> He was awakened by severe nausea and vertigo. When he switched on the light next to his bed… the telephone and bedside table appeared 180 degrees reversed, hanging down from the ceiling. This visual experience lasted only a few minutes. Neurologic exam 5 hours later was normal. The inversion of vision recurred several hours later and the patient again graphically described the experience: people surrounding his bed appeared inverted, with their legs up and heads down, the floor became the ceiling.[73]

This unique visual symptomatology may occur in isolation or be accompanied by nausea, vertigo, gait instability, and examination findings (Horner syndrome, limb ataxia, hemihypalgesia) consistent with lateral medullary infarction (Fig. 3).[67] The 180-degree reversal of vision has been attributed to transient ischemia of central vestibulo-ocular integrative control mechanisms, particularly dysfunction of vestibular inflow, which may disturb visual space orientation and result in aberrant egocentric orientation.[73] Such visual field complaints occur infrequently with vertebrobasilar ischemia but, when present, should alert the physician to the possibility of brainstem ischemia.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Se:2/3
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MF: 1.1
ET:8
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FSE/V
TR:2500
TE:102/Ef
EC:2/2 16kHz
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FIGURE 3. Axial (1.5-T) T2-weighted magnetic resonance image in a patient with lateral medullary syndrome showing infarction of the left inferior cerebellar hemisphere and the left lateral medulla.

Brainstem Auditory Hallucinosis

Intermittent auditory hallucinations, which can raise the suspicion of epileptic activity, have been reported in patients with radiologic evidence of vascular lesions affecting the pontine tegmentum.[19,50] The phenomenon is illustrated by the following case description:

> A 55-year-old hypertensive man… complained of hearing low-pitched musical sounds in both ears. The sounds were localized externally but were not associated with any auditory stimuli. He recognized these sounds as abnormal. Examination demonstrated a left Horner's syndrome, nystagmus, and long tract signs. Over the following several days… the auditory hallucinations became like people talking and later like the sound of rain falling on a roof.[50]

There was no alteration in consciousness or other positive motor or sensory phenomena, and an EEG had mild slowing but no epileptiform activity. Audiometry found moderate bilateral sensorineural hearing loss with poor speech discrimination affecting the left ear. Magnetic resonance imaging of the brain demonstrated a left caudal pontine tegmental hemorrhage involving the superior olivary nucleus, the trapezoid body, and the dorsal and intermediate acoustic striae. The authors postulated a “release” mechanism for the hallucinations from hearing loss caused by dysfunction of the central auditory pathways.[50] Although rare, the occurrence of auditory hallucinosis, accompanied by other brainstem findings, should prompt an investigation for a vascular etiology.

Auditory Aprosodia

Episodic loss of pitch perception is another auditory aberration that could be attributed to epileptic phenomena and has been described in right hemisphere cerebral ischemia. The following case illustrates the syndrome:

> A 52-year-old man was well until he experienced the first of two episodes of transient loss of pitch perception. The patient was at a party when he noticed that all of the voices that he heard sounded as if they were spoken in a monotone. He recalled no confusion at that time, nor did he recall experiencing any difficulty comprehending the content of what was said. This episode reportedly lasted less than 20 minutes, and was regarded as a curiosity by the patient. Several days later, a second 20-minute episode occurred while the patient was at home in his kitchen…. The patient noted that the music on the radio lost its melodic quality, sounding flat and monotonous. The patient indicated that the loudness and rhythm sounded normal…. Approximately two weeks after… the patient suffered transient spells of left facial droop, slurred speech, and left-sided weakness. Finally, he experienced the sudden onset of left hemiparesis, and a left hemianopsia. CT scan revealed a right middle cerebral artery territory infarct and angiography revealed a total occlusion at the origin of the right internal carotid artery.[70]

These recurrent spells, during which the patient was unable to perceive normal variations in pitch of conversation and music, were thought to represent transient ischemia affecting the auditory cortex of the nondominant hemisphere.

Transient Anosognosia

Transient anosognosia or failure to appreciate neurologic deficits, which may be confused with postictal behavioral disturbances, have been reported in six patients in association with transitory hemiparesis, paresthesias, and visual field cuts.[34] This unusual behavioral syndrome is illustrated by the following case description:

> A 68-year-old man came out of his room unaware of being improperly dressed with his buttons and belt undone, and his shirt-tail hanging out. He nevertheless declared himself ready to attend a planned choir practice at church. Upon inquiry, he denied being sloppily dressed despite confrontation before a mirror. Intrigued at first, his wife became alarmed after noticing, a few minutes later, an obvious dysarthria and left-sided weakness. Pointing out these deficits to him met with emphatic denial once more. Upon arrival at the hospital he had completely recovered from this initial one-hour episode. An identical 30-minute episode was later witnessed the same evening in our Emergency Room. A head computed tomography (CT) scan was normal. Angiography revealed bilateral internal carotid fibromuscular dysplasia. He remained asymptomatic under anticoagulants, and was discharged 7 days after admission.[34]

The authors concluded that a nondominant hemispheric syndrome from carotid occlusive disease accounted for the change in behavior observed in their patient. Although behavior disturbance can be seen with epileptic phenomena, a vascular etiology should be strongly considered in patients who present with abrupt changes in behavior or personality.

Akinetic Mutism

Akinetic mutism describes patients who appear awake and alert, yet remain mute and motionless, despite intact motor and sensory pathways.[7] This behavioral syndrome may resemble nonconvulsive or absence status, but the differential also includes a vascular etiology.

The disturbance has been described with bilateral frontal lobe lesions and has been attributed to an impaired psychic drive (abulia). Gugliotta et al. described a patient who experienced abrupt onset of akinetic mutism in association with spontaneous bilateral anterior cerebral artery (ACA) occlusion:

> A 65-year-old male had been suffering from sudden mild headache, followed by gait difficulty and limb paresthesia. The day of admission he was found unconscious in bed, with eyes open and rotated upward; he was unable to speak or follow commands. On admission the patient had an alert appearance but was unresponsive to any auditory or visual command. His eyes were open and moved spontaneously as though he was looking around the room, without however following a moving object or person. CT scan of the brain revealed the presence of low density foci, which were localized in the mesial frontal region bilaterally.[35]

Unilateral ACA territory infarction can also present with severe apathy, abulia, and mutism or acute confusional states, and must be considered when the clinical presentation involves transient confusion or stuporous states.[12]

Drop Attacks

Typical drop attacks are characterized by a sudden falling spell that occurs without warning and without loss of consciousness. Drop attacks must be distinguished from akinetic seizures.[7] The patient suddenly falls to the ground while walking or standing and is usually able to get up immediately. The falling spells may recur over a period of years, EEGs obtained are usually normal, and an identifiable mechanism is difficult to find. Such attacks in isolation are not considered typical vertebrobasilar TIAs; however, when associated with other symptomatology, they may suggest brainstem ischemia. The following case illustrates an example:

> A married woman of 52 had a drop attack; she suddenly fell to the ground, hit her face, picking herself up immediately and saying she was all right. There was no loss of consciousness, no warning and no sequels. Since that time there have been repeated attacks of vertigo, some of intense severity, with ataxia. These are associated with occipital headaches, and pains in the neck, which may last up to half an hour. There are intermittent sensory disturbances unrelated to these attacks of vertigo, of a cold sensation and pins and needles over the scalp and upper neck on either side independently. There are also episodes of dysaesthesiae in either arm independently or together.[83]

Carotid occlusive disease may rarely result in spells of transient paraparesis simulating drop attacks. Ho et al. reported a patient with recurrent episodes of transient paraparesis in the setting of a high-grade right internal carotid stenosis and a hypoplastic A1 segment of the left anterior cerebral artery.[51] This vascular anatomy meant that both anterior cerebral artery territories subserving motor control of both legs suffered ischemia from perfusion failure due to the right-sided carotid occlusive disease. In another case reported by the author, a bihemispheric anterior cerebral artery above a left carotid stenosis of 90% led to drop attacks. Shaking of the right arm on reaching for objects provided a clue to the perfusion failure in this case.[32] The spells in both these patients were abolished by revascularization with carotid endarterectomy.

Moyamoya Disease

Moyamoya disease is characterized by chronic progressive multiple stenoses or occlusions of the intracranial arteries of the carotid system.[78] The angiographic hallmark of the condition is the presence of abnormal anastomotic vessels at the base of the brain. It is a form of cerebrovascular disease that predominantly affects children and young adults, where its clinical manifestations may be mistaken for paroxysmal epileptic events. Accurate diagnosis of intermittent spells in this population is hindered by the observation that moyamoya disease may also present with seizures.

The Cooperative Group for the study of moyamoya disease in Japan has described the clinical features of the disease in children and adults. Among 155 children (<15 years), TIAs (39%) and strokes (39%) were the most common presentations, followed by seizures (14%) and hemorrhage (7%).[61] Conversely, the clinical presentation in adults (<15 years) was dominated by hemorrhage (65%), with TIAs (6%) and seizures (6%) occurring less commonly. The recurring ischemic attacks seen in children have certain characteristic features. Hemiplegia and monoplegia are common manifestations at the onset, though sensory, speech, or visual disturbances may also occur. The attacks are typically triggered by crying, coughing, or straining—circumstances that may not immediately suggest an ischemic basis to those unfamiliar with this condition. The hyperventilation associated with these activities results in CBF reductions that are sufficient to induce cerebral ischemia. This observation is consistent with the theory that marginal hemodynamic reserve and perfusion failure affecting the watershed or distal field territory is the underlying mechanism for the ischemic attacks.[76]

Summary and Conclusions

TIAs are a powerful marker of increased stroke risk, myocardial infarction, and death. Accurate clinical identification of TIAs depends on recognizing typical, as well as less typical, symptoms and an awareness of mimicking conditions. A reliable history may prove difficult to obtain because the episodes are usually unwitnessed and tend to be brief and frightening, and nondominant hemisphere ischemic attacks may be ignored by the patient. The neurologic examination is generally not helpful, as it is often normal by the time the physician has the opportunity to assess the patient. The proven value of antiplatelet therapy and carotid endarterectomy and the rapid proliferation of hyperacute stroke protocols emphasize the need for the rapid detection of TIAs. The diagnostic evaluation in the individual patient needs to consider that small-vessel disease may also produce ischemic attacks, in addition to the more accepted large-artery atherothrombotic mechanism. The currently accepted definition of TIA regarding time course and the assumption of no persistent cerebral injury have been proven incorrect and will require revision.

The differential diagnosis of patients presenting with focal neurologic disturbances is broad and includes TIAs, seizures, migraine, syncope, and brain tumors. Each requires specific diagnosis and management. Wider use of event detection questionnaires that have been validated in epidemiologic studies is an attractive option that may improve interobserver reliability in the diagnosis of TIAs. Data from large TIA series have helped to identify particular symptoms that are not typical of ischemic attacks, such as isolated dizziness, unconsciousness or drop attacks without accompanying vertebrobasilar symptoms, scintillating scotomata, and “march” of symptoms over body parts. The occurrence of these symptoms should encourage physicians to consider alternative diagnoses. Atypical TIA symptoms such as limb shaking, other adventitious

movements, visual phenomena, and behavioral change pose a particular dilemma for the physician faced with discriminating TIA from epileptic phenomena. Physician and public awareness that these less frequent clinical features may have an ischemic etiology should enhance diagnostic accuracy and improve selection of the proper therapy.

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Chapter 276

Sleep Disorders

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Introduction

Since sleep and epilepsy are common bedfellows, it stands to reason that sleep disorders may mimic, cause, or even be triggered by epileptic phenomena, and vice versa. It is known that, in some individuals, sleep promotes seizures, as does sleep deprivation.[25,86] Conversely, seizure disorders can affect the wake–sleep cycle.[114] As discussed in Chapter 188, in most cases, epilepsy is highly state-dependent: Non–rapid eye movement (NRM) sleep promotes seizures, while rapid eye movement (REM) sleep is a relatively antiepileptic state.[132,134] This fact reflects the dramatic reorganization of the entire central nervous system (CNS) as it moves across the three states of being: Wakefulness, NREM sleep, and REM sleep.

There are certain predisposing factors in NREM sleep that facilitate epileptic discharges. There may be a relationship between sleep spindles and spike-and-wave bursts in human epilepsy.[57] There may also be a relationship between the cyclic alternating pattern (CAP) of "fluctuating cortical excitability" with both sleep-related epilepsy and a number of other sleep disorders.[136,145]

In simpler times, it was felt that sleep was a unitary phenomenon—the passive absence of wakefulness. In the first half of this century, it was discovered that sleep was an active state. Then, in 1953, it was discovered that sleep was actually composed of two completely different states of being: NREM and REM sleep. We, as humans, as most mammals, spend our lives in three completely different states of being: Wakefulness, REM sleep, and NREM sleep. Each of these states has its unique neuroanatomic, neurophysiologic, neurochemical, and neuropharmacologic correlates and substrates.[55,135] It took centuries to determine that sleep is actually a bimodal process because (a) superficially and from a distance, REM and NREM sleep look similar, and (b) these two states cycle back to back, giving the illusion of homogeneity.

There are five primary determinants of the quality of nighttime sleep and of daytime alertness[117]:

1. Homeostatic (duration of prior wakefulness)
2. Circadian (biologic clock influence)
3. Age
4. Drugs
5. CNS pathology

These factors determine the overall wake–sleep pattern, upon which the parasomnias are superimposed. These same factors also play an integral role in epileptic events.

With the advent of neurophysiologic monitoring techniques, it has become obvious that state determination is a very complex and dynamic phenomenon, involving multiple neural networks, neurotransmitters, neuropeptides, neurohormones, and myriad sleep-promoting substances. Given these complexities, it has become clear that the determination of state may be inexact, with components of two or all three states occurring simultaneously or oscillating rapidly. This concept of state dissociation in animals and humans has been extensively reviewed.[73,74,76]

Parasomnia is the term given to undesirable motor, verbal, or experiential phenomena that occur during the sleep period. It is these sleep disorders that are most commonly confused with epileptic phenomena. Parasomnias may be conveniently categorized as primary (disorders of sleep states per se) and secondary (disorders of other organ systems manifesting themselves during sleep). The primary sleep parasomnias can be classified according to the sleep state of origin: REM sleep, NREM sleep, or miscellaneous (those not respecting sleep state). The secondary sleep parasomnias can be further classified by the organ system involved.[72] Many parasomnias are manifestations of state dissociation. These mixed states result in fascinating and perplexing clinical phenomena that may easily be confused with epileptic events, and conversely, these sleep disorders may be perfectly imitated by epileptic events. Furthermore, other primary sleep disorders may trigger seizures, and, conversely, seizures may trigger abnormal sleep phenomena. In addition to the parasomnias, there is impressive overlap among epileptic, sleep, and psychiatric phenomena (Table 1).

Clinical Description

The following is a listing of various areas of overlap and confusion between sleep disorders and seizures ranging from normal events to hypersomnia, insomnia, and parasomnias.

Normal Sleep Phenomena

Sleep Starts

Sleep starts (hypnic jerks) are experienced by many normal individuals during the transition from wake to sleep. The most common is the motor sleep start, a sudden jerk of all or part of the body, occasionally awakening the victim or bed partner.[106] Variations on this theme include the visual (flashes of light, fragmentary visual hallucinations), auditory (loud bangs, snapping noises), or somesthetic (pain, floating, something flowing through the body) sleep start, occurring without the body jerk.[20,42,70,101,122] Sleep starts represent a normal (although not understood) physiologic event, and should not be confused with seizures or other neurologic conditions. It is likely that the “exploding head syndrome,” characterized by a sensation of a loud sound like an explosion or a sensation of “bursting” of the head, and “explosive tinnitus” are variants of sensory sleep starts.[22,108,121,144,152] Similar phenomena may represent the sole manifestation of a seizure.[37]

Table 1 Overlap among epileptic, sleep, and psychiatric phenomena

Symptom	Sleep disorder	Seizure
Normal sleep phenomena	Sleep starts (hypnic jerks) Nightmares	Seizures manifesting as sleep-onset sensory/motor phenomena or nightmares
Hypersomnia	Sleep deprivation Idiopathic CNS hyperinsomnia	Hypersomnia as a manifestation of having frequent nocturnal seizures resulting in recurrent arousals or hypersomnia as an accompaniment of epilepsy
	Narcolepsy	Akinetic

	Cataplexy	Fugue states
	Sleep paralysis	Partial complex seizures
	Hypnagogic hallucinations	Subclinical status
	Automatic behavior	Poriomania
	Recurrent hypersomnia Kleine-Levin Menstruation-related	Recurrent seizures resulting in prolonged periods of “sleepiness”
	Sleep apnea triggering seizures	Seizures resulting in apnea
Insomnia	Medical Psychiatric Psychological Constitutional	Seizures whose sole manifestation is recurrent arousals
Parasomnias	Disorders of arousal Confusional arousals Sleepwalking Sleep terrors Sleep-eating RBD Dreams/nightmares Enuresis Rhythmic movement disorder Periodic limb movement disorder Posttraumatic stress disorder Cardiopulmonary Cardiac arrhythmias Respiratory dyskinesias Gastrointestinal-paroxysmal choking Panic disorder Psychogenic dissociative disorders	Mesial frontal, temporal lobe seizures presenting with complex, bizarre behaviors, hypnogenic (nocturnal) paroxysmal dystonia, or autonomic (diencephalic) seizures

CNS, central nervous system; RBD, rapid-eye-movement sleep behavior disorder.

Nightmares

Nightmares are frightening dreams that usually awaken the sleeper from REM sleep. Unlike disorders of arousal (see below), they are not usually associated with prominent motor or vocal behavior or autonomic excitation, and the arousal

results in immediate full wakefulness, with memory for the dream sequence of events that caused the awakening.[72] Seizures manifest as recurrent dreams, nightmares, or disorders of arousal such as sleepwalking, and sleep terrors have been well described in both adults and children. The diagnosis of seizure-related dreams and nightmares may be overlooked, as the symptom is misinterpreted as a primary sleep phenomenon.[12,28,29,39,138] Autosomal dominant frontal epilepsy may also present as recurrent "nightmares."[124,125]

Hypersomnia

Epilepsy

Nocturnal seizures may cause severe sleep fragmentation, if the sole manifestation is arousal (which may not be appreciated by the patient). The end result is excessive daytime sleepiness.[130] Some patients with seizures are hypersomnolent during the day—even after antiepileptic medication discontinuation. Seizure-free preadolescent children with epilepsy are sleepier than healthy controls. In one study, there was no difference in objective sleepiness in children with epilepsy on or off medication, suggesting that use of antiepileptic drugs does not necessarily result in daytime sleepiness.[103] The complaint of daytime sleepiness in patients with epilepsy may be due to a number of different conditions (sleep deprivation, sleep-related seizure-induced arousals, coexisting sleep disorders such as sleep apnea or narcolepsy, or medication effect). Thoughtful evaluation of this complaint is encouraged; hypersomnia in patients with epilepsy should not summarily be attributed to the effect of antiepileptic medications.[7,35]

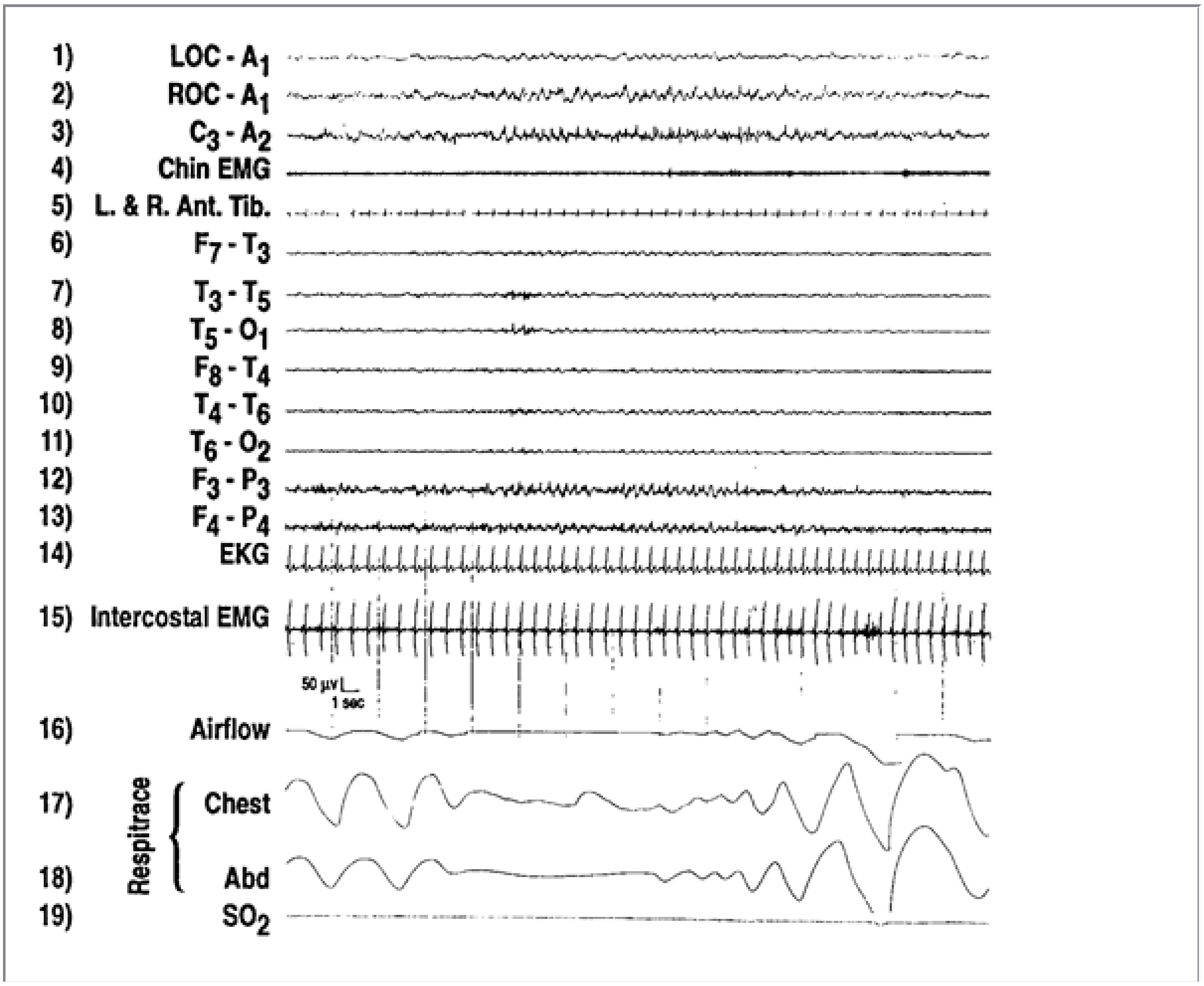

FIGURE 1. Polysomnographic tracing of a 56-year-old male with a long-standing history of well-controlled generalized seizures who developed severe progressive excessive daytime sleepiness. The polysomnogram revealed 22 central apneas per hour as the sole manifestation of seizures. Aggressive medical management was unsuccessful. There was marked improvement in his excessive daytime sleepiness following a right frontal lobectomy.

Narcolepsy

Narcolepsy is a genetically determined disorder characterized by excessive daytime sleepiness, cataplexy (the sudden loss of muscle tone triggered by emotionally laden events), sleep paralysis, hypnagogic hallucinations, and automatic behavior during which prolonged, complex activities may be performed without conscious awareness or recall.[1] The "spell-like" nature of some sleep attacks, cataplexy, and sleep paralysis may be mistaken for seizures. Conversely, atonic or inhibitory seizures may mimic cataplexy,[3,41,45,56,66,139] and the periods of

automatic behavior are often misdiagnosed as partial complex seizures, postictal confusion, or poriomania.[32,60,80] The incomplete and waxing and waning nature of cataplexy can imitate tonic–clonic seizure activity.

Periodic Hypersomnia (Kleine-Levin Syndrome)

The Kleine-Levin syndrome is a poorly understood condition characterized by recurrent periods of hypersomnia. The often-cited association with adolescent males and unusual behaviors such as hypersexuality and megaphagia has been overrated.[6,137] Menstruation-related periodic hypersomnia may represent a variant of the Kleine-Levin syndrome.[11] Similar recurrent episodes of hypersomnia may be caused by "ictal sleep" lasting 1 to 3 days at 10- to 60-day intervals.[94,156]

Sleep-disordered Breathing

There is an interesting and important relationship between sleep-disordered breathing and seizures. Nocturnal seizures, probably triggered by periods of hypoxemia, may be the presenting symptom in some individuals with obstructive sleep apnea or sleep-related hypoventilation.[62] Furthermore, sleep apnea may exacerbate seizures in patients with epilepsy due to sleep disruption, sleep deprivation, hypoxemia, or decreased cerebral blood flow. As would be expected, patients who have both epilepsy and sleep-disordered breathing may have better control of their seizures following effective treatment for the sleep-disordered breathing.[79,148] Not all "spells" associated with sleep apnea are epileptic manifestations. They may be due to episodes of cerebral anoxia.[16]

In yet other cases, seizures may cause apnea, often repetitive, and may closely mimic the conditions of obstructive or central sleep apnea.[17,90,146,151,153] FIGURE 1 shows repetitive apneas as the sole manifestation of seizures.

Insomnia

Paroxysmal, otherwise unexplained awakenings may be the sole manifestation of nocturnal seizures, and will result in the complaint of insomnia.[8,30,31,97,110] Some patients with occasional paroxysmal periodic motor attacks during sleep have very frequent (every 20 to 60 seconds) subclinical arousals resulting in severe sleep fragmentation.[130] These paroxysmal arousals may be due to deep epileptic foci.[92] The arousal preceding nocturnal seizures may be the initial manifestation of the seizure.[78] Animal studies support the concept of frequent arousals as the manifestation of seizures.[133] This may explain the fact that some patients with epilepsy report frequent, otherwise unexplained, nocturnal awakenings and excessive daytime sleepiness.[50]

Parasomnias

Disorders of Arousal

Disorders of arousal are the most common and impressive of the NREM sleep parasomnias, and may readily be confused with epileptic phenomena. These occur on a continuum ranging from confusional arousals to sleepwalking to sleep terrors. The disorders of arousal share common features: A positive family history, suggesting a genetic component; they tend to arise from slow-wave sleep (stages 3 and 4 of NREM sleep), therefore usually occurring in the first third of the sleep cycle (and rarely during naps); and they are common in childhood, usually decreasing in frequency with increasing age.[77] Although they most frequently occur during slow-wave sleep, they may occur during any stage of NREM sleep, and may occur late in the sleep period. Contrary to popular opinion, the appearance or persistence of these events into adulthood is usually not associated with significant psychiatric disease. Specialized forms of arousal disorders may manifest as sleep-related eating or sleep-related sexual activity.[126,131]

The disorders of arousal may be difficult to differentiate from nocturnal seizures, and vice versa.[68,109] Preservation of consciousness during seizures may lead to confusion with disorders of arousal or psychogenic conditions.[26] Crying (dacrystic) or laughing (gelastic) seizures may be misinterpreted as confusional arousals or sleep terrors.[5,69] Both disorders of arousal and seizures may be menstrual related.[52,96,127]

The disorders of arousal may be triggered by arousals induced by other sleep disorders such as sleep apnea or seizures, so the clinical event of a sleepwalking or sleep terror episode may, in fact, represent an epiphenomenon of yet a different underlying sleep disorder.[46] It is common clinical experience to see an improvement in disorders of arousal following effective treatment of obstructive sleep apnea (OSA). Conversely, effective treatment of OSA with nasal continuous positive airway pressure (CPAP) may result in disorders of arousal, presumably associated with deep NREM sleep rebound.[34,89] Sleep terrors and seizures can coexist in the same individual.[143]

Rapid Eye Movement Sleep Behavior Disorder

REM sleep behavior disorder (RBD) is a recently described condition in which the anticipated atonia of REM sleep is absent, hypothetically allowing patients to “act out their dreams,” often with violent or injurious results. It typically is a disorder of older males, and is frequently misdiagnosed as a nocturnal seizure or psychogenic event. RBD is readily diagnosable by formal sleep studies, which reveal the absence of somatic muscle atonia that normally accompanies REM sleep. RBD responds exquisitely to clonazepam.[128] Nocturnal seizures or obstructive sleep apnea may mimic RBD.[19,53]

Dream/Nightmare Disturbances

As mentioned above, recurrent dreams or nightmares as the primary manifestation of nocturnal seizures have been well documented.

Enuresis

Enuresis was formerly classified as a “disorder of arousal,” implying a relationship with NREM or slow-wave sleep.[13] However, enuresis does not respect sleep stage, and may occur during either NREM or REM sleep.[44,88] Enuresis may be the sole manifestation of nocturnal seizures.[4,33,46]

Bruxism

Rarely, bruxism may be the manifestation of a seizure.[84]

Rhythmic Movement Disorder

Rhythmic movement disorder (RMD) refers to a number of behaviors characterized by stereotyped movements (rhythmic oscillation of the head or limbs, head banging or body rocking during sleep) seen most frequently in childhood and, rarely, in adults. RMD may arise from any stage of sleep, may be familial, and is usually not associated with underlying psychiatric or psychological conditions.[118] Rarely, it may be the sole manifestation of a seizure.[46]

Periodic Limb Movements of Sleep

Periodic limb movement of sleep (PLM) is a polysomnographically determined diagnosis. It is characterized by periodic (every 20 to 30 seconds) dorsiflexion of the great toe, foot, or even flexion of the entire leg. These movements are not perceived by the patient, and may be associated with the complaint of excessive daytime sleepiness or insomnia. These movements may also be asymptomatic.[93] When prominent, these movements may be confused with myoclonic seizure activity, or may actually represent epileptic phenomena.[71] These movements may be particularly dramatic in patients with underlying renal failure.[58,111]

Posttraumatic Stress Disorder

Posttraumatic stress disorder (PTSD) is often associated with subjective sleep complaints including "nightmares" and sleep terrorlike experiences.[2] PTSD may be confused with nocturnal panic or seizures manifesting solely as arousals with fearful affect.

Seizures

The behaviors associated with nocturnal seizures are often bizarre, and masquerade as primary sleep parasomnias, secondary sleep parasomnias, or psychiatric conditions.[141] The following are particularly apt to result in diagnostic dilemmas:

1. *Conventional seizures* occur frequently during sleep. In many individuals with epilepsy, seizures occur exclusively during sleep, increasing the likelihood of a misdiagnosis of a primary sleep disorder. Approximately 10% of patients with seizures experience seizures exclusively or predominantly during sleep.[157]
2. *Nocturnal frontal lobe epilepsy* (NFLE), sometimes autosomal dominant, presents a broad spectrum of behaviors, including frequent isolated paroxysmal arousals, episodic nocturnal wanderings, and nocturnal paroxysmal dystonia.[99,112,113,124] NFLE may present as other sleep disorders, particularly disorders of arousal or sleep apnea.[100,125] Nocturnal and diurnal paroxysmal dystonia may exist in the same patient, as can reflex and hypnogenic paroxysmal dystonia. There is considerable overlap among the different clinical categories of paroxysmal dyskinesias.[23,67,91,149] NFLE may be posttraumatic[9] and may coexist with panic disorder.[142] Temporal lobe seizures may also result in hyperkinetic behaviors.[98] Vigilance level-dependent tonic seizures[115] and familial paroxysmal hypnogenic dystonia[65] likely represent variants of this condition. Carbamazepine is often very effective in eliminating these spells.
3. *Pure tonic seizures with arousal* (or paroxysmal polyspike activity with arousal) were mentioned above as seizures presenting as insomnia or hypersomnia due to seizure-induced arousals or sleep fragmentation. An interesting subtype of hypnic tonic postural seizures has been described in ten children, many with a positive family history. This may be a benign epilepsy syndrome similar to benign childhood epilepsy with centrotemporal spikes,[51] and childhood epilepsy with occipital paroxysms.[61,104,105]
4. *Autonomic/diencephalic seizures* are rare, and could present from sleep with such manifestations as intermittent or paroxysmal apnea,[123,151] stridor,[81] coughing,[155] laryngospasm,[116] chest pain and arrhythmias,[24,43,49,59] paroxysmal flushing, localized hyperhidrosis,[63,87] and piloerection,[120] which are easily confused with other primary or secondary sleep parasomnias. Isolated autonomic symptoms are a well-documented manifestation of seizures, and are probably much more common than generally suspected.
5. *Electrical status epilepticus of sleep* (ESES) may be detected during a polysomnogram (PSG) performed for other reasons, and is characterized by continuous spike-and-wave activity during NREM sleep. ESES is seen in children who usually, but not always, have a history of seizures or neurologic dysfunction. The prognosis is variable inasmuch as it may be an asymptomatic finding. This pattern occurs on a broad spectrum including the Landau-Kleffner syndrome and benign childhood epilepsy with centrotemporal spikes.[40]

Cardiopulmonary

1. *Cardiac arrhythmias* may be a manifestation of seizures, masquerading as nocturnal cardiac abnormalities and possibly playing a role in sudden unexplained death in epilepsy.[54,95] Ictal cardiorespiratory arrest in Panayiotopoulos syndrome has recently been reported.[150] Seizures may also result in stunned myo-cardium and pulmonary edema.[15,36] Conversely, primary cardiac (prolonged QT interval) or respiratory events (REM sleep-related hypoventilation) may present as seizures.[62,102]
2. *Respiratory dyskinesias* may occur or persist during the sleep period. These include (a) segmental myoclonus such as palatal myoclonus or diaphragmatic flutter and (b) paroxysmal dystonia. Respiratory dyskinesias may also be the manifestation of neuroleptic-induced dyskinesias, and may or may not persist during sleep.[64] These should be differentiated from unusual nocturnal seizures that present with primarily or exclusively respiratory symptoms.[146,151,154]

Gastrointestinal

The sole manifestation of nocturnal seizures may be paroxysmal choking.[14]

Nocturnal Panic Attacks

Nocturnal panic attacks (NPAs) may occur in patients with diurnal panic, or, rarely, may precede the appearance of diurnal panic, or may be exclusively nocturnal in nature.[18,85,119] The striking similarity of the symptoms of dream anxiety attack, sleep terror, nocturnal seizures, and nighttime panic urges caution in diagnosis. Obstructive sleep apnea can also cause symptoms of NPAs.[27] The common association of the affect of "fear" as an accompaniment of nocturnal seizures intensifies their confusion with nocturnal panic.[21,47,48,82] It must be remembered that seizures and panic may co-exist.[83,140]

Psychogenic Dissociative States

Complex and potentially injurious behaviors, occasionally confined to the sleep period, may be the manifestation of a psychogenic dissociative state. A history of childhood physical and/or sexual abuse is virtually always present (but may be difficult to elicit). In this condition, unlike other parasomnias or nocturnal seizures, the complex behavior, during electroencephalographic (EEG) monitoring, is seen to arise from clear EEG-determined wakefulness.[129] Pseudoseizures may also arise from apparent sleep.[147]

Differential Diagnosis

It should be clear from the above that the clinical differentiation between sleep disorders and epileptic events may often be difficult, if not impossible, as primary or secondary sleep phenomena may perfectly mimic epileptic phenomena, and vice versa. Both epileptic and sleep phenomena should be considered in any case of recurrent unusual sleep-related events.

Diagnostic Investigation

The decision to investigate further unusual nocturnal events will depend upon the clinical situation. The most common condition is the disorder of arousal, which is very common (and normal) in the general population. Simple sleepwalking or sleep terrors can readily be diagnosed clinically. Indications for formal evaluation include behaviors that (a) are potentially injurious or violent, (b) cause disruption for other household members, (c) result in excessive daytime sleepiness, or (d) display unusual clinical features.

Clinical differentiation between sleep and epileptic phenomena may be most difficult, and misdiagnosis in both directions is common. The diagnosis of nocturnal seizures may be enigmatic if there is no history of diurnal spells. Both waking and sleep-deprived EEGs may not reveal the diagnosis,[10,107] necessitating all-night polysomnographic study using a full seizure montage and continuous video recording. Although exclusively nocturnal seizures may be uncommon, they are routinely misdiagnosed, and should never be overlooked as possibly etiologic in any sleep-related behavior that is recurrent, stereotyped, or inappropriate—regardless of the specific nature of that behavior. "Ambulatory" EEG monitoring has led to the misdiagnosis of functional psychiatric disease in a number of our patients subsequently demonstrated to have bona fide nocturnal seizures. Erroneous psychogenic labeling is enhanced by the bizarre nature of the spells and the fact that environmental clues may play a role in the context of psychomotor seizure.[38] Misdiagnosis is common even following formal and appropriate PSG evaluation. Reasons for misdiagnosis include[75]:

1. Obscuration of the scalp EEG by movement artifact
2. Absence of scalp EEG manifestation of the seizure activity
3. EEG seizure manifestation appearing to be an "arousal" pattern
4. Absence of EEG or clinical postictal period

Extensive polysomnographic monitoring employing a full scalp EEG montage is mandatory. Multiple studies may be necessary to capture an event. Continuous audio/visual monitoring and recording are indicated, and detailed technician observation may be invaluable. The difficulties in evaluating unusual sleep-related events emphasize the necessity of extensive, in-person laboratory monitoring with interpretation of all data (clinical, EEG, sleep, video, and technologist-provided information) by personnel experienced in both sleep medicine and epileptology.

Treatment

Effective treatment is available for most sleep disorders and for seizures, and is predicated upon an accurate diagnosis. If seizures are responsible for the sleep–wake complaint, treatment is similar to that for other seizure disorders. If a primary sleep disorder (such as narcolepsy, sleep apnea, or parasomnia) is identified, therapy is dictated by the specific diagnosis.

Summary and Conclusions

The interface between sleep disorders and epileptic phenomena is vast and inexorable, as sleep affects seizures, and seizures affect sleep. The myriad sleep and epileptic phenomena may perfectly counterfeit one another. A high index of suspicion and a full awareness of the broad spectrum of both sleep and epileptic phenomena is instrumental to an accurate diagnosis. A thorough clinical and laboratory evaluation of unusual phenomena that could be either sleep- or seizure-related will usually lead to a specific diagnosis, with important and effective therapeutic implications.

From a broader perspective, the intriguing relationship among these conditions is fertile ground commanding further investigation, the results of which will greatly expand our knowledge of brain function, sleep, and epilepsy, and which will undoubtedly result in deeper understanding and better classification, and identification of yet unknown, unusual clinical events. Close cooperation among the fields of sleep medicine, epileptology, and basic neuroscience in this arena of fascinating interface will be most productive—both from a clinical/therapeutic and scientific standpoint.

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Chapter 277

Myoclonus and Myoclonic Syndromes

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Introduction

The history of myoclonus has been described by Marsden et al.[25] and Hallett.[17] Friedreich first defined myoclonus as a discrete entity in a case report published in 1881 of a patient with essential myoclonus. He wanted to separate the involuntary movement that he saw from epileptic clonus, a single jerk in patients with epilepsy, and chorea. For the next 10 to 20 years, many other types of involuntary movements, such as tic and myokymia, were also called myoclonus, but in 1903 Lundborg[23] proposed a classification of myoclonus that cleared up much of the confusion. Lundborg classified myoclonus into three groups: Symptomatic myoclonus, essential myoclonus, and familial myoclonic epilepsy.

It is important to recognize that certain types of myoclonus are essentially identical to epilepsy. Single jerks in patients with epilepsy have been recognized since ancient times. In the phrase of Muskens,[30] myoclonus can be a “fragment of epilepsy.” One of the tasks for the clinician is to determine what is epilepsy and what is not.

Clinical Description

Myoclonus is characterized by quick muscle jerks, either irregular or rhythmic.[19] Myoclonic movements are always simple in nature, and this is often a critical feature separating myoclonus from other types of involuntary movements. Myoclonus can be focal, involving only a few adjacent muscles; generalized, involving many or most of the muscles in the body; or multifocal, involving many muscles but in different jerks. Myoclonus can be spontaneous, can be activated or accentuated by voluntary movement (action myoclonus), and can be activated or accentuated by sensory stimulation (reflex myoclonus).

In differentiating myoclonus from other movement disorders, in addition to the simplicity, the principal features that favor myoclonus are the quickness of the movement and the absence of ability for voluntary suppression. Some simple tics look identical to myoclonus and cannot be visually distinguished. A point in favor of tic is the ability to suppress the movements voluntarily, with a frequent concomitant rise in psychic tension dispelled when the movements resume. Some movements of chorea are quick, but slower movements and sustained postures are also present. The major differential diagnosis for rhythmic myoclonus is tremor and the distinction here is often just convention.

Some disorders of the peripheral nervous system can be confused with myoclonus. Electrodiagnosis can help make the diagnosis since these disorders all show characteristic physiologic findings. Fasciculation is the spontaneous firing of a single motor unit. Myokymia typically looks like an irregular oscillation of a muscle, but it can have the appearance of small jerks. Hemifacial spasm is characterized by jerks of the facial muscles and occasional tonic spasms.

A brief, paroxysmal pause of tonic muscular activity may also give rise to a jerk in the affected body part that is often visually indistinguishable from a movement produced by a burst of electromyographic (EMG) activity. This is called negative myoclonus, and the most commonly encountered form is asterixis. Negative myoclonus, like positive myoclonus, can also arise as an epileptic event.[36,40]

There are many types of myoclonus, and there are no common etiologic, physiologic, or therapeutic features. For this reason, recognizing that an involuntary movement is myoclonic in nature is only the beginning of the investigation. In those patients with epileptic seizures, it would be reasonable to suspect that the myoclonus would be related.

Classification

There have been many schemes proposed for classifying the large number of myoclonic disorders, and there are at least two useful approaches, etiologic and physiologic, that have usually been discussed separately.[19] From the point of view of differential diagnosis, the physiologic classification is most relevant, and it can help guide symptomatic treatment. The first consideration of therapy, however, should take the etiologic classification into account since the cause should be dealt with first, if possible. Here, the classifications will be combined using the physiologic classification as the primary index and the etiologic classification as a secondary index.

The starting point for a physiologic classification is to decide whether the myoclonus is a fragment of epilepsy. On this basis, the myoclonus is said to be epileptic or nonepileptic.[16,43] There are a number of subtypes in each category.

Epileptic Myoclonus

A significant feature in favor of epileptic myoclonus is if the patient has epileptic seizures. This would be more definitive, of course, if the myoclonus was clearly a fragment of the seizure including a part of the aura. The association of the myoclonus with paroxysmal activity in the electroencephalogram (EEG) is also indicative, and more will be said about the electrophysiologic evaluation in the next section.

Three types of epileptic myoclonus are now recognized: Cortical myoclonus, reticular myoclonus, and primary generalized epileptic myoclonus.[19,37,43] Cortical myoclonus is a fragment of focal or partial epilepsy, and can be subclassified as spontaneous cortical myoclonus, cortical reflex myoclonus, and epilepsia partialis continua. Each myoclonic jerk involves only a few adjacent muscles, but larger jerks with more muscles involved can be seen. The disorder is commonly multifocal and accentuated by action and sensory stimulation.

Reticular reflex myoclonus is a fragment of a type of generalized epilepsy. These jerks are usually generalized with predominance, which is proximal more than distal and flexor more than extensor. Voluntary action and sensory stimulation increase the jerking. Primary generalized epileptic myoclonus is a fragment of primary generalized epilepsy. The most common clinical manifestation is small, focal jerks, often involving only the fingers; thus, the myoclonus is sometimes called minipolymyoclonus. The term minipolymyoclonus was originally coined to refer to small jerks seen in patients with motor neuron disease. Minipolymyoclonus of central origin and minipolymyoclonus of peripheral origin have a similar clinical appearance and are probably most easily separated by the company they keep: Epilepsy and muscle denervation, respectively. A second clinical presentation of primary generalized epileptic myoclonus is generalized, synchronized whole body jerks, not unlike those seen with reticular reflex myoclonus. Electrodiagnosis can help define the type of epileptic myoclonus (see below).

Negative myoclonus can be isolated, but it usually occurs together with positive myoclonus.[15,36,40,43] Clinically, the appearance is called asterixis, and there can be large movements, small multifocal movements, and such frequent movements that the appearance is of an irregular tremor or tremulousness. Negative myoclonus can have a similar physiology to cortical myoclonus with electrophysiologic correlates and production by sensory stimulation. There may be associated seizures.

Myoclonus resulting from a defined pathologic process, the etiologic category of “symptomatic myoclonus,” is usually epileptic in type. The principal conditions follow, along with a brief consideration of their treatment.

Progressive Myoclonus Epilepsies

Progressive myoclonus epilepsy with the principal features of slowly progressive myoclonus and epilepsy is most frequently secondary to a degenerative disorder with some involvement of the cerebellum or cerebellar pathways (see also Chapter 252). The disorder can be sporadic, but is often familial. Typically the symptoms begin between 7 and 15 years of age and include action and reflex myoclonus and grand mal seizures.

Cerebellar ataxia is said to be common, but differentiation of ataxia and intention myoclonus is often very difficult. Occasional features include dementia, spasticity, myopathy, neuropathy, and deafness. The syndrome is clearly heterogeneous. Cases have been described under the names Unverricht-Lundborg syndrome, Ramsay Hunt syndrome, and "Baltic myoclonus epilepsy." The gene for Unverricht-Lundborg disease (EPM1) has now been linked to the long arm of chromosome 21q22.3 in a number of families, and the gene involved codes for cystatin B, a small protein that is a member of a superfamily of cysteine protease inhibitors.[21] Familial cortical myoclonic tremor with epilepsy or familial adult myoclonic epilepsy has been reported from Japan and Europe. This condition is characterized by autosomal dominant inheritance, late onset, benign course, and only infrequent epileptic seizures. Recently van Rootselaar et al.[45] reported an autopsy case of this condition, in which the pathologic changes similar to those seen in spinocerebellar ataxia (SCA) type 6 were found in the cerebellum.

There are no treatments for degenerative conditions, but there are some important therapeutic implications. It is of critical importance in these cases to recognize that phenytoin treatment may be associated with worsening of the condition.[10] Patients can be treated successfully with other anticonvulsants as described below. Storage diseases may also give rise to the syndrome of progressive myoclonus epilepsy, and for this reason the patients may be thought to have a degenerative condition. The most well-known entity is Lafora body disease. Other entities include lipidoses such as GM_2 gangliosidosis (Tay-Sachs disease), ceroid-lipofuscinosis (Batten disease), and sialidosis (cherry red-spot-myoclonus syndrome).

There are at least two clinical differences between Lafora body disease and Baltic myoclonus epilepsy.[10] Age of onset in Lafora body disease is 11 to 18 years, while the age of onset in Baltic myoclonus epilepsy is earlier, 6 to 16 years. For Lafora body disease dementia is present in two thirds of cases by 2 years after onset, and in all by 5 years; in contrast, in Baltic myoclonic epilepsy, only a rare patient shows dementia in the first 5 years (provided the patients do not receive phenytoin). Occipital seizures are frequent in Lafora body disease. The diagnostic feature of Lafora body disease is the periodic acid-Schiff (PAS)-positive inclusion body found in neurons throughout the gray matter of the brain including the dentate nucleus of the cerebellum. These inclusions can sometimes be found in liver, skeletal muscle, and skin. For clinical purposes, the method of first choice for confirming the diagnosis is skin biopsy, particularly of axillary skin. The gene responsible in about 75% of Lafora body cases (EPM2) has been localized to chromosome 6q and has been identified as encoding a protein tyrosine phosphatase (PTP) now called laforin.[27,35] With these storage diseases, there is no treatment, but screening and prenatal detection can be used for prevention.

Noninfantile neuronopathic Gaucher disease can cause myoclonus. There are rapid advances in Gaucher disease, with enzyme replacement therapy already available for the nonneuronopathic forms and gene replacement treatment on the horizon.

Biotin deficiency is especially important to keep in mind since replacement with biotin can lead to cure.[3]

Mitochondrial disorders are increasingly recognized as common causes of myoclonus and the "Ramsay Hunt syndrome" in particular. Indeed, most patients with progressive myoclonus epilepsy may have a mitochondrial abnormality.[2] One well-defined syndrome is MERRF (myoclonus epilepsy and ragged red fiber syndrome). A muscle biopsy looking for ragged red fibers might be helpful. Presently, there is no good treatment for mitochondrial diseases.

Dementias

Creutzfeldt-Jacob disease (subacute spongiform encephalopathy) frequently exhibits myoclonus as a relatively early feature. The myoclonus can be produced by external stimuli, such as noise, or can be spontaneous and rhythmic associated with a periodic EEG. Patients with Alzheimer disease can also exhibit myoclonus, although this feature typically occurs late in the illness. The myoclonus is multifocal and can be stimulus induced. Electrophysiologic investigations of these two disorders show distinctive results, but both are similar to cortical reflex myoclonus. Myoclonus also is seen in patients with the AIDS–dementia complex.[24]

Viral Encephalopathies

A variety of viruses and postviral syndromes cause myoclonus. Herpes simplex encephalitis is probably the most common example. Subacute sclerosing panencephalitis (SSPE) is frequently characterized by a slow periodic movement often called myoclonus, but its duration is on the order of 1 second and it does not fit the definition. At the first International Congress of Movement Disorders in 1990, the attendees voted to no longer use the term *myoclonus* to describe the involuntary movement in SSPE.

Metabolic Encephalopathies Including Endocrine Disorders

Disorders such as hepatic failure, renal failure, hyponatremia, hypoglycemia, and nonketotic hyperglycemia can give rise to myoclonus. Treatment should be directed to the underlying condition. For example, myoclonus in patients with chronic renal failure on hemodialysis can be due to aluminum toxicity and can be successfully treated with chelation therapy with deferoxamine mesylate.[39]

The opsoclonus-myoclonus syndrome is easy to diagnose because of the dramatic clinical feature of opsoclonus.[34,41] It may arise in a variety of settings including infections, toxins, and a paraneoplastic syndrome. In childhood the syndrome is often associated with neuroblastoma. If there is a tumor, it should be treated, and there may be symptomatic relief, but the disorder might be unaffected or even worsened. Symptomatic therapy that should be considered includes steroids or adrenocorticotropic hormone (ACTH). Trazodone may also be helpful.

Toxic Encephalopathies Including Drug Side Effects

Toxic causes include bismuth, heavy metals, methyl bromide, and drugs. Offending drugs include tricyclic antidepressants, opioids, and lithium.

Physical Encephalopathies Including Hypoxia

These conditions include trauma, heat stroke, electric shock, decompression injury, and hypoxia. Posthypoxic myoclonus, the Lance-Adams syndrome,[20] has received a great deal of attention since the demonstration that the myoclonus could be successfully treated with 5-hydroxytryptophan. The clinical syndrome as reported by Lance and Adams noted the precipitating feature of action and the association with cerebellar ataxia, postural lapses, gait disturbance, and grand mal seizures. The site of the responsible lesion in the brain is not certain, but there does appear to be a disorder of serotonin metabolism supported not only by the therapeutic response to 5-hydroxytryptophan, but also by the reduction in cerebrospinal fluid (CSF) levels of 5-HIAA, which improves with successful therapy.

Focal Brain Damage

The etiology of focal cortical myoclonus can be almost any type of focal cortical lesion; tumors, angiomas, and encephalitis should be suspected. Curiously, particularly in patients with epilepsia partialis continua, the cortex can appear normal to pathologic examination. With recent application of diffusion magnetic resonance imaging (MRI), increasing attention has been drawn to focal cortical dysplasia as a cause of neocortical epilepsy including epilepsia partialis continua.[28] In a number of patients, surgical excision of the excitable tissue has cured the myoclonus,[33] and this approach should be considered.

Nonepileptic Myoclonus

The types of nonepileptic myoclonus are particularly heterogeneous. It is important to recognize them, because each has its own treatment, and, in general, use of anticonvulsants is not valuable. Some physiologic phenomena are included in this group including hiccough, sneeze, and the hypnic jerk.

Dystonic Myoclonus and Fragments of Other Involuntary Movement Disorders

Patients with dystonia or chorea, for example, may have quick jerks as well as more prolonged involuntary movements. Other “basal ganglia” disorders such as Wilson disease, neuroaxonal dystrophy, pantothenate kinase-associated neurodegeneration (PKAN; formerly known as Hallervorden-Spatz disease), progressive supranuclear palsy, and Parkinson disease all may manifest myoclonus. The diagnosis is made on the basis of other clinical features. Treatments are available for Parkinson disease, of course. Myoclonus in Huntington disease can be improved with valproic acid, perhaps because of the involvement of the γ-aminobutyric acid (GABA) system in this disorder.[5] Focal myoclonus in the setting of dystonia can often be treated with focal injections with botulinum toxin. Myoclonus dystonia (DYT11) is an autosomal dominant syndrome where symptoms include dystonic myoclonus as well as more prolonged spasms.[13] Tremor, similar to essential tremor, may also be present. There is often a marked response to ethanol. In many families, the genetic abnormality has been identified to be in the protein epsilon-sarcoglycan.[1] In this condition, myoclonus involves mainly proximal or truncal muscles and occurs independently of dystonia in terms of the body sites involved and the time of occurrence.

Essential Myoclonus

This term can be utilized for those patients whose sole neurologic abnormality is myoclonus and specifically do not have seizures, dementia, or ataxia. The EEG and other laboratory investigations should be normal. Familial cases as well as sporadic cases are seen. The most common features of the familial cases are autosomal dominant inheritance with variable severity, equal involvement of males and females, onset in the first or second decade of life, and benign course compatible with normal life span. Essential myoclonus can be generalized or multifocal. The myoclonus is variable in amplitude, and in some cases, the jerks are so small that the disability can be minimal. Jerks can be present at rest and may be improved or worsened by action. Reflex myoclonus has not been described in this group.

In some families with essential myoclonus some involved patients also have essential tremor, and some family members had essential tremor without myoclonus. Some of these patients also may exhibit elements of dystonia, and the diagnosis in these cases may well be myoclonus dystonia (DYT11). The essential tremor, myoclonus, and dystonia may all be sensitive to alcohol in these patients.

Exaggerated Startle

Startle is a normal phenomenon that can be exaggerated if an excessive response occurs to a startling stimulus or if a startle response occurs to a stimulus that ordinarily would not be startling.[26] There are a number of startle syndromes including hereditary hyperekplexia, symptomatic hyperekplexia, startle epilepsy, and Latah syndrome. Startle epilepsy is principally characterized by epileptic seizures triggered by sudden, unexpected stimuli and initiated by a startle.

Periodic Movements in Sleep

There are a variety of types of myoclonus that occur during drowsiness or sleep. There are two physiologic forms, the hypnic jerk and "physiologic fragmentary myoclonus," characterized by small, multifocal jerks maximal in the hands and face but present diffusely. Pathologic types of myoclonus include isolated periodic movements in sleep, restless legs and periodic movements in sleep, and excessive fragmentary myoclonus in non–rapid eye movement (NREM) sleep. Myoclonus associated with epilepsy, intention myoclonus associated with semi-volitional movements, and segmental myoclonus also occur in sleep, but are not primarily nocturnal.

Periodic movements in sleep (PMS) occurs in virtually all groups of patients referred to a sleep disorders laboratory, and the clinical correlation is not always clear. Patients with the restless legs syndrome often have PMS. Certainly, PMS can be asymptomatic for the patient, although, as with all types of nocturnal myoclonus, the disorder may cause distress to the patient's spouse. On some occasions, however, PMS can induce sleep fragmentation and excessive daytime sleepiness (see Chapter 276).

Segmental Myoclonus Including Spinal Myoclonus and Palatal Myoclonus

In this disorder, a segment of the spinal cord or brainstem produces persistent rhythmic repetitive discharges usually unaffected by sleep. A number of contiguous muscles produce synchronous contractions at a rate of 0.5 to 3 Hz. Involved regions can be one limb, one limb and adjacent trunk, or both legs. Lesions of the spinal cord giving rise to focal movements include infection, degenerative disease, tumor, cervical myelopathy, and demyelinating disease, and it may follow spinal anesthesia or the introduction of contrast media into the CSF. Unlike palatal myoclonus, spinal myoclonus would only rarely be idiopathic. Spinal myoclonus usually occurs spontaneously and may persist during sleep.

Another form of spinal myoclonus is propriospinal myoclonus.[4,6] This is clinically characterized by axial jerks that are nonrhythmic and that lead to symmetric flexion of the neck, trunk, hips, and knees. Jerks can be spontaneous or stimulus induced. The myoclonus is identified with electrodiagnostic studies that show the myoclonus starting in the midthoracic region and propagating slowly, about 5 meters/sec, both rostrally and caudally.

Palatal myoclonus, now preferably called palatal tremor, is most common in this group, and has now been shown to consist of two separate disorders, essential palatal tremor, which manifests an ear click, and symptomatic palatal tremor, which is associated with cerebellar disturbances.[8] The ear click in essential palatal tremor is the symptom that requires therapy.

Asterixis

Negative myoclonus may well have a subcortical origin as well as a cortical origin (epileptic), although there are no clinical rules for separating them. The distinction is made on the basis of electrophysiologic studies that may show EEG correlates with the cortical form, but this may not be a definite qualitative difference. Certainly, subcortical lesions may cause asterixis, but that does not necessarily imply where the movement is generated. For example, unilateral asterixis is caused by a vascular lesion in the contralateral thalamus, but this does not necessarily mean that this type of asterixis originates from the thalamus.[42] It is difficult to treat asterixis whether cortical or subcortical, and a search for a metabolic or toxic cause should be the first course of action.

Psychogenic Myoclonus

Myoclonus can also be psychogenic. Monday and Jankovic[29] reported the clinical features of 18 such patients. There were 13 women and five men with an age range of 22 to 75 years. The myoclonus was present for 1 to 110 months; it was segmental in ten, generalized in seven, and focal in one. Stress precipitated or exacerbated the myoclonic movements in 15 patients; 14 had a definite increase in myoclonic activity during periods of anxiety. The following findings helped to establish the psychogenic nature of the myoclonus: Clinical features incongruous with “organic” myoclonus, evidence of underlying psychopathology, an improvement with distraction or placebo, and the presence of incongruous sensory loss or false weakness. Over half of all patients with adequate follow-up improved after gaining insight into the psychogenic mechanisms of their movement disorder.

Diagnostic Investigation

Clearly the first issue is to seek an underlying cause for the condition. This would imply a full neurologic evaluation including blood studies, neuroimaging, and CSF evaluation.

Electrophysiologic assessment can be a significant help in deciding whether the movement is myoclonus, and, if so, which type.[19,37,43] Techniques to be employed include EMG to evaluate the EMG activity associated with the movement, EEG to determine if there is an EEG event related to the movement (averaging of activity may be needed), analysis of whether the involuntary movement can be produced reflexly, and evaluation of the evoked response in the EEG to stimulation that produces reflex involuntary movements. The physiologic characteristics of epileptic myoclonus are EMG burst length of 10 to 50 msec, synchronous antagonist activity, and an EEG correlate. Nonepileptic myoclonus shows EMG burst lengths of 50 to 300 msec, synchronous or asynchronous antagonist activity, and no EEG correlate.

With cortical reflex myoclonus, the EEG reveals a focal positive–negative event over the sensorimotor cortex contralateral to the jerk preceding both spontaneous and reflex-induced myoclonic jerks. With stimulus sensitivity, C-reflexes are seen and are correlated with giant somatosensory-evoked potentials. Some myoclonus is sensitive to flash stimulus, and in this case photic-evoked potential is markedly enhanced. The EEG event associated with reflex jerks is a giant P1–N2 component of the somatosensory-evoked potential. Often the P1–N2 has exactly the same topography as the positive–negative event preceding the spontaneous myoclonus, but at times there are some differences. A final feature is that if the cranial nerve muscles are active, then the timing of onset of activation is from above downward; that is, the masseter (fifth cranial nerve) is active before the orbicularis oculi (seventh cranial nerve), which is itself active before the sternocleidomastoid (11th cranial nerve). With reticular reflex myoclonus, there are brief generalized EMG bursts lasting 10 to 30 msec triggered by sensory stimulation such as touch or muscle stretch or by action; the EEG correlates, if present, are not time locked to the muscle activation, and the pattern of EMG activation in cranial nerve muscles is with the sternocleidomastoid muscle activated first and the other cranial nerve muscles activated in reverse numeric order. In primary generalized epileptic myoclonus, the EEG correlate is a slow, bilateral frontocentrally predominant negativity similar to the wave of a primary generalized paroxysm.

If an EEG event cannot be found with back-averaging, it might be valuable to look at EEG-EMG coherence during the jerking. This technique was used, for example, to identify the cortical involvement in a series of patients with cortical myoclonic tremor.[44]

Treatment

The first approach, as has been emphasized, is to try to find an etiology that can be reversed. Failing that, the myoclonus can be approached symptomatically.

Epileptic Myoclonus

If the myoclonus is part of a defined epileptic syndrome, it should be treated as the syndrome. If the myoclonus needs to be approached by itself, the first approach is anticonvulsants. The most useful agents are clonazepam and valproate, both of which work by promoting GABA action in brain. Primidone may also play a role. Serotonergic agents such as 5-hydroxytryptophan (5-HTP) may also be effective. Piracetam and levetiracetam can be very effective for epileptic myoclonus.[12,14,31] Zonisamide may also be a useful agent.[46] Obeso et al.[32] have pointed out that two or three drugs in combination may well be better than a single drug.

Posthypoxic myoclonus is a special condition to consider because of the specific deficiency of serotonin. 5-HTP, either alone or with carbidopa, is often beneficial in this condition. On the other hand, however, it is not often used as a drug of first choice because of adverse effects. Most patients will respond just as well to clonazepam, valproate, or clonazepam plus valproate. In some cases, posthypoxic myoclonus dramatically responds to levetiracetam.

Essential Myoclonus

Essential myoclonus is a heterogeneous disorder and therapy is largely empiric. Alcohol is most likely to be beneficial, but cannot be recommended for regular use. Sodium oxybate may be successful for alcohol-responsive patients.[11] There are also reports suggesting propranolol, 5-HTP, and clonazepam. Some patients have responded dramatically to benztropine.[9]

Exaggerated Startle

Clonazepam is the therapy of choice.[26] Other benzodiazepines, such as diazepam and chlordiazepoxide, have been used with similar results.

Periodic Movements in Sleep

Treatment of choice is now either dopaminergic therapy or opiate therapy.[22,38] For some patients clonazepam may be helpful.

Segmental Myoclonus

For spinal myoclonus, treatment should be directed to the underlying cause if possible. For example, surgery can ameliorate myoclonus caused by cervical cord compression. Antiviral therapy may improve segmental myoclonus associated with herpes zoster. On the other hand, sometimes drug treatment can be helpful, such as clonazepam, valproate, and L-5-HTP, or trihexyphenidyl. For the ear click of essential palatal myoclonus, a number of drugs may be useful in individual cases, such as clonazepam, tryptophan, carbamazepine, trihexyphenidyl, or ceruletide, but most seem refractory. The ear click can be successfully treated with focal injection of botulinum toxin.[7]

Summary and Conclusions

Myoclonus is a simple, quick involuntary movement that can be seen in a large variety of disorders. There are many types of myoclonus, and it is crucial to make a clear diagnosis before beginning therapy. Hopefully, an underlying cause might be uncovered that could be treated. In many cases myoclonus may be a fragment of epilepsy. If it is a feature of a well-defined epileptic syndrome, then treatment of the myoclonus is the same as the syndrome. If the epileptic myoclonus is not a part of a recognized syndrome, the first approach is still anticonvulsants. If the myoclonus is nonepileptic, then symptomatic treatment needs to be individualized to the particular disorder.

Acknowledgments

This chapter drew heavily on previous reviews including references 18, 19, and 43.

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Chapter 278

Movement Disorders

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Introduction

As early as the late nineteenth century, neurologists noted overlap between certain movement disorders and epilepsy. This is perhaps most apparent in patients with myoclonus, as discussed in the preceding chapter in this book. Many patients afflicted with chronic myoclonus also have epilepsy, and forms of focal epilepsy can precisely mimic myoclonus. Most of the drugs effective at treating myoclonus (clonazepam, valproic acid, levetiracetam, zonisamide, acetazolamide) are antiepileptics. Besides myoclonus, there are other disorders that occur in brief or sustained paroxysms, without alteration in arousal or consciousness; these disorders are the subject of this chapter. Often these patients are referred for evaluation to epileptologists or movement disorder specialists. Video-electroencephalogram (EEG) monitoring may be necessary to rule out an epileptic cause, although most of these disorders can be recognized once the physician is familiar with the syndrome.

Several paroxysmal movement disorders that may be confused with epilepsy are considered elsewhere in this book. Myoclonus, as mentioned previously, is the closest mimic. Patients with hyperekplexia have an inherited disorder of exaggerated startle and sustained tonic contractions due to mutations in the glycine receptor. These patients usually present in the nursery with exaggerated startle, abnormal tone, and lack of habituation to startle. Recognition is critical because appropriate treatment with clonazepam prevents potentially life-threatening apneic episodes. Paroxysmal torticollis is another disorder beginning in early childhood, with episodes of sustained tonic contraction of neck muscles producing sustained head postures for hours or days. Events typically occur periodically, and alertness and arousal are preserved. This migraine variant is also usually easily distinguished from epilepsy. Infants may sometimes evidence paroxysmal, brief episodes of upward gaze, so-called tonic upgaze of infancy, which may raise the notion of epilepsy. These episodes are brief, typically last seconds, are unassociated with other abnormalities, and, although they are disconcerting to parents, usually disappear by early childhood.

Four other movement disorders mimicking epilepsy are considered further in this chapter: (a) stereotypies (complex tics), (b) episodic ataxia, (c) self-stimulatory behavior, and (d) the paroxysmal dyskinesias.

Stereotypies are highly patterned, complex, sustained movements, often lasting seconds, which are typically repeated multiple times. Examples of stereotypic movements include truncal rocking, skin picking, hand clapping, hand twirling, and complex hand-to-mouth routines (feeding, blowing, touching). Phenomenologically, there is little difference between a complex motor tic, that is, a complex sequence of involuntary movements performed in response to an inner urge, and stereotypies. Stereotypies are most commonly seen in patients with autism, pervasive development delay, and Asperger syndrome, but they may also occur in developmentally disabled individuals, in Rett syndrome, and in otherwise normal children.[19,45,87,116] Because these events are brief, involve complex involuntary movements, and may affect patients' ability to interact with the examiner, they may be mistaken for supplementary motor area seizures. It is not uncommon for video-EEG monitoring to be ordered to differentiate long-duration stereotypies from seizures, particularly when they occur in neurologically abnormal individuals.

Episodic ataxia is a rare, genetic paroxysmal movement disorder that should be easy to distinguish from epilepsy. The disorder occurs in two forms, types 1 and 2. Episodic ataxia type 1 is an autosomal-dominant disorder characterized by paroxysms of ataxia lasting several minutes, often with myokymia between attacks. The disorder has been linked to mutations in the voltage-gated K^+ channel gene, *KCNA1*.[14,27,48] Episodic ataxia type 2 is an autosomal-dominant disorder characterized by paroxysms of ataxia lasting hours, often with interictal symptoms of nystagmus or cerebellar dysfunction. The disorder is linked to mutations in the alpha 1A voltage-dependent calcium channel subunit, CACNA1A. Acetazolamide and 4-aminopyridine have been shown to be beneficial in affected patients.[59,60,125,128]

Self-stimulatory behavior is not infrequently encountered at centers that perform video-EEG monitoring. This condition typically begins in early childhood, affects girls more than boys, and is usually first noticed by parents. In a typical event the child crosses his or her legs, lies flat on the floor, or applies pressure to the groin or perineum against furniture. Children can be distracted during an episode, and there may be accompanying autonomic signs such as facial flushing or sweating. Videorecording is extremely useful in documenting the nature of these events. If the clinical appearance is classic, investigative studies are unnecessary. The term "infantile masturbation" should be avoided when discussing this condition with parents because there is significant stigma associated with it. We have encountered parents who refuse to accept this diagnosis, persisting in extensive evaluations to prove a different etiology for the condition. Most children respond to redirection and support.[32,96,103,149]

In the remainder of this chapter, we discuss the paroxysmal dyskinesias, a complex and unusual group of disorders that bear relation to epilepsy. Because the literature of paroxysmal disorders is extensive and often confusing, we first offer a historical review of the development of these disorders and then present current concepts related to their nosology and etiology.

Table 1 Clinical features of paroxysmal kinesigenic, nonkinesigenic, and exertional dyskinesia

Feature	PKD	PNKD	PED
Inheritance	AD	AD	AD
Male-to-female ratio	4:1	1.4:1	4:8 (*n*=12)
Age at onset			
Range	<1–40	<1–30	2–20
Median	12	12	9.5
Mean	12	12	9
Attacks			
Duration	<5 min	2 min–4 h	5–30 min

Frequency	100/d–1/min	3/d–2/y	1/d–2/min
Trigger	Sudden movement, startle, hyperventilation	Nil	Prolonged exercise
Precipitant	Stress	Alcohol, stress, caffeine, excitement, fatigue	Stress, caffeine, fatigue
Treatment	Anticonvulsants (acetazolamide), antimuscarinics	Clonazepam, benzodiazepines	?

AD, autosomal dominant; PED, paroxysmal exertion-induced dyskinesia; PKD, paroxysmal kinesigenic dyskinesia; PNKD, paroxysmal nonkinesigenic dyskinesia.

Paroxsymal Dyskinesias—History

Gowers[44] was probably the first to report “movement-induced seizures,” in this case, in an 11-year-old girl who developed brief attacks that occurred when she suddenly arose after prolonged sitting. Numerous reports of “movement-induced seizures” followed, published under the designations of *ref- lex epilepsy* or *tonic seizures induced by movement*. Some cases demonstrated more than tonic contractions—namely, sustained twisting, athetosis, and chorea. Even the presence of choreoathetosis, however, did not lead the earliest interpreters of these brief attacks to conclude that they represented a movement disorder. Rather, they considered them to be a form of epilepsy, with the cerebral site of the “seizures” in the basal ganglia or subcortical region.

After Gowers, the next report of movement-induced paroxysmal movements appears to be that of Spiller in 1927.[126] He described two patients with brief tonic spasms brought on by voluntary movement of the involved limbs, and in one of them by passive manipulation. Contractions were painful and accompanied by sensations of heat or burning. Wilson[145] later described a 5-year-old boy who had brief attacks of unilateral torsion and tonic spasm that lasted up to 3 minutes and were precipitated by pain. Wilson considered this to be reflex tonic epilepsy, and also thought it to be subcortical in origin.

The concept of attacks of tonic, often twisting, contractions without loss of consciousness as uncommon seizure disorders continued. Lishman et al.[80] described seven patients with tonic and athetoid spasms induced by movement while remaining conscious. Abnormal sensations of numbness, vibration, and tightness were noted in the affected limbs before the attacks. Two years later they reported an additional five cases of movement-induced “seizures,”[143] and Burger et al.[15] described two patients with this label. Some also referred to these cases as forms of epilepsy.[38,52]

In 1940, Mount and Reback[99] introduced a new concept—attacks of tonic spasms plus choreic and athetotic movements with unusual triggers. They described a 23-year-old man who had had “spells” since infancy, both “large” and “small.” Both types were preceded by a sensory aura of tightness in parts of the body or by a feeling of tiredness. Movements involved the arms and legs, usually a combination of sustained twisted posturing and chorea. The “small” attacks lasted from 5 to 10 minutes; longer attacks were considered “large” and also involved the neck (retrocollis), eyes (upward gaze), face (ipsilateral to the limbs, if the limb involvement was unilateral), and speech. These “large” attacks lasted for as long as 2 hours. Drinking alcohol, coffee, tea, or cola would usually precipitate an attack, as would fatigue, smoking, and intense concentration.

The attacks cleared more rapidly if the patient lay down, and they were aborted by sleep. Between attacks, the neurologic examination was normal, and there was never loss of consciousness, clonic convulsive movements, biting of the tongue, or loss of sphincter control. Phenytoin and phenobarbital were without effect, and scopolamine was the only drug found to reduce the frequency, severity, and duration of attacks. The family history revealed 27 other members with similar attacks, with a pedigree showing autosomal-dominant inheritance with complete penetrance. Mount and Reback called this disorder *familial paroxysmal choreoathetosis*.

This paper by Mount and Reback became the seminal report in the field of paroxysmal dyskinesias. After its publication, it was referenced by most reports in the literature over the next five decades, although the next report of a large family with similar attacks of muscle spasms did not reference it. In 1961 Forssman[33] described a family whose members had attacks lasting from 4 minutes to 3 hours; inheritance was autosomal dominant. Attacks were induced by cold, mental tension, irritation, fatigue, lack of sleep, alcohol, and caffeine. Onset of symptoms was in early childhood; an attack might begin with a tonic spasm in one hand and spread up the arm to the other arm, to both legs, and then to the cranial muscles, including the tongue, so that the affected person could not speak during a severe attack. Forssman considered the disorder to be new, possibly related to myotonia and paramyotonia, and did not consider it a form of epilepsy because no alteration of consciousness was involved.

In 1963, Lance[73] reported eight similar patients with attacks of tonic (dystonic) spasms, some with choreoathetosis, usually affecting only one side of the body and often preceded by pain or tingling. Two patients had secondary attacks (static encephalopathy and multiple sclerosis), one case was idiopathic and sporadic, and the remaining five were members of the same family. The attacks lasted <1 minute in two patients, 2 to 5 minutes in the patient with multiple sclerosis, and 5 to 60 minutes in the five familial cases. They were not precipitated by movement, and the familial cases were exacerbated by excitement and fatigue. No EEG abnormality was recorded between attacks.

After the 1963 article by Lance,[73] Weber[142] reported a family of four affected members with nonkinesigenic paroxysmal dystonia and used the term *familial paroxysmal dystonia*. Richards and Barnett[114] reported the next big family with the same type of paroxysmal dyskinesia as Mount and Reback's and thought that Lance's family[73] represented a variant because its members had only tonic spasms and no movements. The family of Richards and Barnett consisted of nine affected members with the trait inherited in an autosomal-dominant pattern. They emphasized the nonkinesigenic nature of the attacks and felt that a wide array of terms could describe the attacks, depending on the severity of each one. Richards and Barnett coined the term *paroxysmal dystonic choreoathetosis* (PDC), which was later adopted by Lance in 1977.[74] The terms *paroxysmal nonkinesigenic choreoathetosis* and *paroxysmal dystonia* were sometimes used instead of PDC.[12] The term *paroxysmal nonkinesigenic dyskinesia* (PNKD), proposed by Demirkiran and Jankovic,[23] is currently the accepted designation for this syndrome (Table 1).

In 1967, Kertesz[65] introduced the label *paroxysmal kinesigenic choreoathetosis* (PKC). This label developed into a most useful and widely accepted designation. Kinesigenicity has an important place in the classification of the paroxysmal dyskinesias, and Demirkiran and Jankovic[23] recommended that the term *paroxysmal kinesigenic dyskinesia* (PKD) be used instead because movements can be dystonic, choreic, or a combination of the two. Rarely, the PKD designation can be applied to certain patients whose dyskinesias are not triggered by sudden movement (or startle).

In his paper, Kertesz reported 10 new cases of paroxysmal dyskinesia and reviewed the literature. It is significant that he differentiated the kinesigenic variety from the cases described by Mount and Reback, Forssman, and Lance, which were not exacerbated by movement but by alcohol, caffeine, or fatigue. Although phenytoin was recognized earlier as a very useful agent for PKD, carbamazepine was later found to be equally useful and was introduced as a treatment by Kato and Araki.[64]

The original cases reported as PNKD were idiopathic and usually familial. It was not long before symptomatic cases began to be reported in patients with perinatal encephalopathy,[119] encephalitis,[100] head injury,[117,144] as a manifestation of multiple sclerosis,[61,90,136] and idiopathic hypoparathyroidism.[2]

The next major advance in classification was by Horner and Jackson,[54] who described two families in which several members had attacks of involuntary movements that occurred during sleep. These appear to be the first reported cases of hypnogenic paroxysmal dyskinesia. In one family, some of the affected members had classic paroxysmal kinesigenic dyskinesia, some hypnogenic, and others a combination of the two. Case 3 in this family began with the hypnogenic variety when the patient was 8 years old. By the time he had reached the age of 11 years, daytime attacks were also occurring, sometimes triggered by sudden movement. The hypnogenic episodes gradually disappeared, leaving him with kinesigenic dyskinesia that responded to antiepileptic drugs.

Lugaresi and colleagues[83,84] independently rediscovered and eventually made known the syndrome of hypnogenic paroxysmal dyskinesia. Lugaresi and Cirignotta[84] described five patients with onset of hypnogenic dystonia at ages 5, 7, 26, 30, and 40 years. Attacks occurred almost every night during sleep, with onset in stages 2 to 4 of sleep. They lasted 15 to 45 seconds and might recur several times in the same night. They could awaken the patient, who might even emit a cry. The movements appeared to be a mixture of dystonia, athetosis, and some more rapid flinging movements. The EEG findings were normal during sleep and wakefulness. Carbamazepine was effective. In their article, Lugaresi and Cirignotta described the movements as choreoathetosis and ballism in addition to dystonia. Maccario and Lustman[85] emphasized that tachycardia is a characteristic occurrence during these episodes.

The disorder was originally described in nonfamilial cases but was later reported in three members of a family.[75] Other sporadic cases have been reported as well,[21,41,113,132] including one with a concurrent reflex dystonic reaction provoked by stimulation of the right foot.[77] Another link with PKD is suggested by the report of Morley,[98] who described a father with hypnogenic dyskinetic attacks and a son with PKD. Both responded to phenytoin.

There has long been considerable speculation as to whether the short-duration hypnogenic attacks might be a manifestation of epilepsy because they respond so well to antiepileptic drugs. The lack of abnormal EEG findings during these attacks has been used to argue against this concept. However, evidence accumulated that many hypnogenic paroxysmal dyskinesias are, indeed, caused by seizures. Tinuper et al.[133] described three patients with this disorder who had EEG evidence of frontal lobe seizures as a cause of their attacks. Sellal et al.[121] and Meierkord et al.[92] studied a series of patients with hypnogenic dystonias and concluded that they represent seizure disorders, particularly of frontal lobe epilepsy, because repeated nocturnal EEG recordings often reveal epileptic patterns of abnormalities. Seizures arising near the mesial posterior frontal supplementary sensorimotor area (SSMA) may be a particular culprit in inducing paroxysmal hypnogenic dyskinesias in children.[5] These types of seizures tend to be brief, frequent, and associated with bilateral tonic posturing, gross proximal limb movements, and preserved consciousness. Dystonic and other dyskinetic features may result from spread of epileptic activity from the mesial frontal region to the basal ganglia because the anatomic connections between these areas are close. The subject of epilepsy masquerading as a movement disorder has been reviewed by Hirsch et al.[51] and Fish and Marsden.[31]

Although most patients with paroxysmal dyskinesias fit into one of these classification schemes, it has become clear that some patients defy easy classification. Several patients have been reported with both nocturnal and daytime paroxysmal events without EEG correlate. Daytime attacks may be triggered by movement or may sometimes occur without trigger.[22,111] Results of imaging and EEG monitoring are usually not helpful, and patients are often difficult to treat.

Paroxysmal Kinesigenic Dyskinesia

Clinical Features

Attacks of PKD consist of any combination of dystonic postures, chorea, athetosis, and ballism. They can be unilateral—always on one side or on either side—or bilateral. Unilateral episodes may be followed by a bilateral episode. The attacks are brief, usually lasting only seconds, but rarely can last up to 5 minutes. A sudden movement or a startle precipitates them, usually after the patient has been sitting quietly for some time. The attacks can be severe enough to cause a patient to fall down and can occur up to 100 times per day. After an attack, there is usually a short refractory period during which an attack cannot be triggered. Speech can sometimes be affected, with an inability to speak resulting from dystonia, but alteration of consciousness never occurs. Attacks can sometimes be aborted if a patient stops moving or warms up slowly. Very often, patients report variable sensations at the beginning of paroxysms. These can consist of paresthesias, a feeling of stiffness, crawling sensations, or a tense feeling.

Equivalent to PKD are equally brief attacks that are not precipitated by sudden movement or startle. Because the duration and therapeutic response are the same as in PKD, these have been included under the PKD rubric rather than in an entirely new category. These attacks lasting a few seconds can often be triggered by hyperventilation.

Plant[109] emphasized the focal and unilateral nature of PKD in many patients. Of the 73 cases of PKD in the literature reviewed by him, he found the following features: unilateral, one side only, 25; unilateral, either side, 12; unilateral and bilateral, 11; bilateral only, 22; not stated, 3.

Idiopathic Paroxysmal Dyskinesias

Most reported cases of PKD are familial, with autosomal-dominant inheritance. The male-to-female ratio is 3.75:1 (75 male patients and 20 female patients reported by Fahn[28]). Symptoms begin in childhood between the ages of 6 and 16 years, but age at onset varies widely, ranging from as early as 6 months to 40 years.[35,78] The mean and median ages at onset are 12 years. Familial cases may be more common among the Japanese[37,64,67] and Chinese.[62] Findings on computed tomography (CT) are also normal[10,43,66,82,129] with a few exceptions: A case reported by Watson and Scott[141] suggested brainstem atrophy and one reported by Gilroy[40] had an ill-defined unilateral hemispheric lesion. EEG findings are generally normal; Hirata et al.,[50] however, demonstrated an abnormal EEG with rhythmic 5-Hz discharges over the entire scalp in a patient during episodes of PKD, raising the possibility of an epileptogenic basis.

Attacks tend to diminish with age. Fortunately, PKD responds dramatically to antiepileptic drugs. The early literature indicates that phenytoin was most popular, followed by phenobarbital and primidone. More recently, carbamazepine appears to be the drug most commonly used. Valproate,[129] oxcarbazepine,[134] and topiramate[55] have also been shown to be effective. Homan et al.[53] reported that children with PKD need doses of phenytoin similar to those used to treat epilepsy, whereas adults may respond to lower doses.

The pathophysiology of PKD is unclear, and its relationship with epilepsy remains speculative. The existence of movement-induced seizures (e.g., the case of Falconer et al.[29]) and the dramatic response of PKD to antiepileptic drugs are not sufficient reasons to consider PKD a form of epilepsy. The retention of consciousness and lack of postictal phenomena, as well as the presence of dystonia and choreoathetosis, should be sufficient to disqualify PKD as epilepsy. Franssen et al.[34] investigated the contingent negative variation (CNV) in one patient. This is a slow cerebral potential that follows a warning stimulus that prepares the subject to expect an imperative stimulus requiring a decision or motor response. The slow negative-wave component of the CNV was more pronounced compared with that of control subjects. It returned to normal after phenytoin treatment. Mir et al.[97] later demonstrated reduced intracortical inhibition, reduced early-phase transcallosal inhibition, and reduced first phase of spinal reciprocal inhibition in PKD patients; treatment with carbamazepine normalized the abnormality of transcallosal inhibition.

Two recent studies suggest that attacks of PKD are associated with contralateral hypermetabolism in subcortical nuclei. Using single photon emission computed tomography (SPECT), Ko et al. studied a 14-year-old patient and demonstrated increased perfusion in the contralateral basal ganglia at onset of attacks.[69] Shirane et al. studied a 6-year-old with PKD, also using SPECT; subtraction of interictal from ictal cerebral blood flow measures showed unilateral increase of thalamic blood flow during an attack.[123]

The differential diagnosis of PKD includes partial epilepsy, tetany, hyperexplexia, and psychogenic disorders, as noted in the misdiagnosis of the case reported by Waller.[140] The clinical features are so distinctive, particularly if triggered by sudden movement, that there is little likelihood of the condition not being diagnosed correctly once the physician is aware of its existence. However, nonkinesigenic brief attacks of hemidystonia, often precipitated by hyperventilation and controlled with antiepileptic drugs, may be a sign of epilepsy.[70] Therefore, each case of suspected nonkinesigenic paroxysmal dyskinesia should be evaluated for a convulsive disorder.

Two autopsies in PKD have been reported. After case 4 of Kertesz[65] died, apparently by suicide, a postmortem examination revealed no clear abnormality in the brain, just the presence of some melanin pigment in macrophages in the locus ceruleus. Stevens[127] had earlier reported the postmortem findings of one of his patients, which were also essentially normal, showing only a slight asymmetry of the substantia nigra.

Recent studies have linked PKD to two separate loci on chromosome 16.[7,50,130,135] In some families, PKD cosegregates with infantile convulsions, whereas in others, it does not.

Symptomatic Paroxysmal Dyskinesias

The overwhelming majority of reported cases of PKD are idiopathic or familial. Occasional cases of symptomatic PKD have been reported, most frequently in association with multiple sclerosis and head injury. Although sudden movement does not trigger most of the paroxysmal dyskinesias associated with multiple sclerosis, sometimes a patient with multiple sclerosis manifests typical PKD.[90] In fact, PKD can be the presenting symptom of multiple sclerosis, as in the case reported by Roos et al.[118]; the patient's attacks were associated with a lesion in the caudate nucleus and responded to phenytoin. In three of the eight patients reported by Berger et al.[8] with paroxysmal dyskinesia associated with multiple sclerosis, attacks were induced by sudden movement and were relieved with antiepileptic drugs.

As mentioned earlier, attacks lasting for seconds are sometimes induced not by sudden movement but by hyperventilation. These also usually respond to antiepileptic drugs, such as carbamazepine, and may be seen in multiple sclerosis.[122,136] Sethi et al.[122] reported successfully treating three patients who had paroxysmal dystonia (not induced by movement, but triggered by hyperventilation and lasting many seconds) using acetazolamide with or without a combination of carbamazepine. The case of PKD with multiple sclerosis reported by Burguera et al.[16] had a lesion in the left thalamus demonstrated by magnetic resonance imaging (MRI). Paroxysmal kinesigenic dyskinesia was the presenting symptom, as in other cases of demyelinating disease. Case 3 of Whitty et al.[143] was a 13-year-old boy with onset 9 months after mild head trauma. Robin[117] reported a 33-year-old man with severe head injury in whom PKD developed 8 months later. In two of the three cases of posttraumatic paroxysmal dyskinesias reported by Drake et al.,[25] movements were induced by sudden movement of the affected body part. Another posttraumatic case was reported by Richardson et al.[115] Like idiopathic PKD, these posttraumatic cases of PKD responded to antiepileptic drugs. Attacks of dystonia lasting several seconds and induced by tactile stimulation were reported secondary to a head injury; they disappeared within 2 months without treatment.[39] Another case of tactilely induced dyskinesias was reported by Nijssen and Tijssen[105] as a result of a thalamic infarct.

In case 2 of the five cases described by Kinast et al.,[66] attacks of left hemidystonia lasted 1 minute and occurred up to 50 times a day. The major precipitating factor was not sudden movement, but rather stress and the anticipation of movement. Technically, this patient does not fulfill the criterion of attacks induced by sudden movement. However, because of their brief duration, frequency, and response to phenytoin, which are features resembling those of PKD, they are placed under the PKD rubric in the classification scheme of this chapter. Examination revealed left-sided hemiatrophy and hyperreflexia, with normal findings on CT. Gilroy[40] reported a 32-year-old man with an abnormal right hemisphere on CT who had had multiple daily brief attacks of left hemidystonia since the age of 5 years that were typical of PKD.

With the advent of MRI, more cases of PKD have been reported as a result of cerebral infarcts—putaminal,[93] thalamic,[99,101,102] and cortical.[36] Paroxysmal kinesigenic dyski-nesia has also been reported in patients with progressive supranuclear palsy,[1] calcifications of the basal ganglia with or without hypoparathyroidism,[41,105,106] and hyperglycemia in the presence of a lenticular vascular malformation.[137]

In one family with X-linked mutations in the thyroid hormone transporter gene *MCT8*, paroxysmal dyskinesias accompanied global mental retardation.[13]

Paroxysmal Nonkinesigenic Dyskinesia

Clinical Features

Like attacks of PKD, attacks of PNKD consist of any combination of dystonic postures, chorea, athetosis, and ballism. They can be unilateral or bilateral, and unilateral episodes can be followed by a bilateral episode. They can affect a single region of the body or be generalized. The neck can be affected by a combination of torticollis and head tremor.[57] Features that distinguish these attacks from those of PKD are the longer duration, lesser frequency, and different aggravating factors. Attacks last minutes to hours, sometimes longer than a day. Usual duration ranges from 5 minutes to 4 hours. Attacks are triggered by consumption of alcohol, coffee, or tea, and also by psychologic stress or excitement and fatigue. There are usually no more than three attacks per day, and often attacks are spaced months apart. The attacks can be severe enough to cause a patient to fall down. Speech is often affected, with inability to speak caused by dystonia, but alteration of consciousness never occurs. The attacks can sometimes be aborted if a patient goes to sleep. As in PKD, patients very often report variable sensations at the beginning of the paroxysms. These can consist of paresthesias, a feeling of stiffness, crawling sensations, or a tense feeling.

Idiopathic Nonkinesigenic Dyskinesias

The initial reports of PNKD were familial with autosomal-dominant transmission. Kinast et al.[66] in 1980 (case 4) and Dunn[26] in 1981 each described a child with PNKD without a positive family history. Since then, Bressman et al.[12] described seven sporadic cases of PNKD, and Nardocci et al.[101] added another one. The familial cases of idiopathic PNKD still greatly outnumber sporadic cases according to the reports in the literature. The sporadic cases are much more difficult to diagnose, however, and they present the added difficulty of having to be differentiated from psychogenic etiology. Based on the experience of Bressman et al.,[12] the sporadic form may actually be more common than the familial form, but is just rarely reported.

There is a slight preponderance of male patients, with a male-to-female ratio of 1.4:1. Onset is usually in childhood between the ages of 6 and 16 years, but age at onset varies widely, ranging from 2 months to 30 years. The mean and median ages at onset are 12 years. Results of CT are normal.[58,91] The EEGs are also generally normal, but the case of Jacome and Risko[58] may be of interest. The patient had unilateral PNKD and normal interictal EEGs. Photic stimulation at low frequencies induced paroxysmal lateralized epileptiform discharges from the contralateral hemisphere. Two patients with PNKD have been studied with functional imaging. del Carmen Garcia et al.[22] performed an ictal SPECT in a 16-year-old patient with PNKD, showing hyperperfusion in the contralateral caudate and thalamus during an attack. Lombroso et al.[81] used fluorodeoxyglucose positron emission tomography (PET) in a patient with PNKD to show no metabolic asymmetry; flurodopa and raclopride PET, however, showed a reduction in presynaptic dopa decarboxylase activity in the striatum and increased postsynaptic D2 dopamine receptors.[81]

The attacks may diminish spontaneously with age. Unfortunately, the attacks of most patients are persistent and are difficult to treat. As a general rule, PNKD does not respond to the antiepileptic drugs that so effectively treat PKD. An occasional patient responds to such agents as carbamazepine and valproate. Clonazepam, as introduced for PNKD by Lance,[74] appears to be the most successful agent, both for idiopathic PNKD and symptomatic PNKD. A number of other drugs have been tried, sometimes with success. These include antimuscarinics,[99] chlordiazepoxide,[106,139] acetazolamide,[12,91] oxazepam and other benzodiazepines,[71,72] and l-tryptophan.[71] Kurlan and Shoulson[72] treated one patient with familial PNKD with clonazepam and oxazepam with relief for 2 to 3 weeks each, and he was placed on a regimen of 40 mg of oxazepam given on alternate days. Trials of the dopamine-receptor antagonist haloperidol were carried out by Przuntek and Monninger[112] and Coulter and Donofrio[20] with benefit; they also found that levodopa worsened the condition of one patient. At least one patient with PNKD has been treated successfully with deep brain stimulation of the globus pallidus interna.[147]

Lance[74] reported autopsies performed on two patients with PNKD with no pathology. Macroscopic findings in his case II.4 were normal. His case IV.2 died of crib death; macroscopic and microscopic findings were normal.

The gene for familial PNKD was cloned in 2004 by a collaborative consortium lead by Ptacek.[76] In 50 individual from eight families, PNKD was shown to be caused by mutations in the myofibrillogenesis regulator gene. The protein product of this gene may be involved in detoxification of methylglyoxal, a compound present in coffee and alcoholic beverages, perhaps explaining the triggering of attacks by these agents.

Symptomatic Paroxysmal Nonkinesigenic Dyskinesia

The overwhelming majority of reported cases of PNKD are idiopathic or familial. A number of cases of symptomatic PNKD have been reported, most frequently in association with multiple sclerosis and perinatal encephalopathy. In multiple sclerosis, the paroxysmal movements may affect only the eyes, lasting several minutes.[86] Other causes of PNKD are encephalitis,[12,100] cystinuria,[18] hypoparathyroidism,[124,148] basal ganglia calcifications without altered serum calcium,[94] thyrotoxicosis,[30] transient ischemic attacks,[6,89] infantile hemiplegia,[56] head trauma,[25,107] hypoglycemia, AIDS,[102] diabetes,[47] moyamoya,[42] anoxia,[12] and brain tumor.[12]

Paroxysmal nonkinesigenic dyskinesia caused by endocrine disorders responds to appropriate treatment. In general, however, treatment of symptomatic PNKD is often ineffective. Positron emission tomography performed in one patient with posttraumatic paroxysmal hemidystonia revealed decreased oxygen metabolism, decreased oxygen extraction, increased blood volume, and increased blood flow in the contralateral basal ganglia.[107]

Paroxysmal Exertional Dyskinesia

Lance[74] was the first to describe what he called an intermediate form of PDC (now better known as exercise-induced or exertional dyskinesia). It affected members of a family with attacks briefer than those of classic PNKD, typically lasting from 5 to 30 minutes. Attacks were precipitated by prolonged exercise but not by cold, heat, stress, ethanol, excitement, or anxiety. The spasms affected mainly the legs. A second family was reported by Plant et al.[110] In both families, the inheritance pattern was autosomal dominant. No one in either family derived any benefit from barbiturate, levodopa, or clonazepam. More recently, three other families have been reported with exercise-induced paroxysmal dyskinesia, each with different accompanying neurologic abnormalities. Guerrini et al.[46] reported a family with autosomal-recessive rolandic epilepsy, paroxysmal exercise-induced dystonia, and writer's cramp. Affected patients developed symptoms in childhood, and the disorder was linked to a locus adjacent to that of autosomal-dominant infantile convulsions and paroxysmal choreoathetosis.[46] Margari et al.[88] described a family with exercise-induced dyskinesias and generalized epilepsy, and Perniola et al.[108] reported a similar family autosomal-dominant inheritance.

A sporadic case (case 3) was later reported by Nardocci et al.[101] This patient, with no family history of a similar condition, also had interictal chorea. Treatment with clonazepam proved helpful. Another sporadic case was reported by Wali[138]; an 18-year-old youth had attacks of right hemidystonia lasting about 10 minutes that were precipitated by prolonged running (about 10 minutes) or by cold. The EEG and CT findings were normal; antiepileptic drugs were not helpful. Demirkiran and Jankovic[23] saw five patients, three of them female. Bhatia et al.[9] reported eight sporadic cases, with age of onset 2 to 30 years. A posttraumatic case has also been reported,[79] which was responsive to oral baclofen.

Paroxysmal exercise-induced dyskinesia is probably a heterogeneous disorder, and the underlying etiologies have not been fully discovered. It is worth noting that rare patients with young-onset Parkinson's disease may present in this manner before any other signs of bradykinesia or rigidity are evident.[11] Of note, a patient with exercise-induced dyskinesias without parkinsonism had increased cerebrospinal fluid levels of homovanillic acid and 5-hydroxyindoleacetic acid after an attack, suggesting that dopaminergic transmission is increased during an attack.[4] Ictal SPECT during attacks in two familial cases showed decreased frontal and striatal perfusion, with increased cerebellar perfusion.[68]

Summary and Conclusions

Overlap between paroxysmal movement disorders and epilepsy has been noted since the end of the nineteenth century. This reflects not only the shared phenomenology of paroxysmal movement disorders and movements that occur in epilepsy, but also a common etiology of subcortical hyperexcitability. Differentiating paroxysmal movement disorders from epilepsy can be challenging, sometimes requires video-EEG monitoring, and, as demonstrated in this chapter, allows for appropriate evaluation and treatment of these patients.

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Chapter 279

Sensory Disorders

Carl W. Bazil

Introduction

Because partial seizures can begin anywhere in the cerebral cortex, their manifestations are diverse, and because large portions of the cortex are devoted to primary and secondary interpretation of sensory stimuli, a wide variety of visual, auditory, vestibular, gustatory, and tactile symptoms can be features of epilepsy. Because seizure-related sensory manifestations are so varied, other sensory abnormalities may sometimes be confused with epilepsy. In distinguishing epileptic from nonepileptic sensory symptoms on clinical grounds, a few general principles are important. First, the context of the symptom must be considered. Purely sensory seizures, without other manifestations at least some of the time, are uncommon, so a careful search for other symptoms or signs supportive of epilepsy should be performed. For example, if a single secondarily generalized seizure begins with focal numbness, it is much more likely that the preceding dozens of similar episodes of isolated numbness were actually simple partial seizures. Second, the time course of the patient's sensory event must be considered. Is it truly paroxysmal? Is the symptom recurrent and unprovoked? How long do the symptoms last? In general, epileptic seizures are unprovoked, paroxysmal, and 1 to 3 minutes in duration. Third, the quality of the sensory experience is relevant. Seizures typically consist of "positive" changes rather than "negative" ones, and this may be helpful in identifying nonepileptic sensory phenomena. For example, visions of swirling colors and shapes are more likely to have an epileptic origin than loss of vision, and localized tingling paresthesias are more likely to be epilepsy than diffuse numbness. Finally, the distribution of the sensory disturbance must be considered and whether it makes anatomic sense. Partial seizures arise from the cerebral cortex, and initial symptoms can therefore often be localized to a fairly discrete brain area. Subsequent evolution of symptoms generally involves adjacent cortex. Thus, visual symptoms typically involve one hemifield. Somatosensory seizures are more likely to involve the face and hand (because these have large areas of representation in the cortex) and should be restricted to one side of the body, at least at onset (insular seizures are an exception[7]).

It is clear that an accurate, detailed description of paroxysmal sensory changes is critical in separating epileptic events from a wide variety of nonepileptic conditions. Important sensory conditions that may be confused with epilepsy are listed in Table 1, and additional testing useful in distinguishing these conditions from epilepsy is listed in Table 2. This chapter describes all of these conditions in further detail and explains how they can best be distinguished from epilepsy.

Disorders of Olfaction

One of the classic (although not the most common) initial symptoms of seizures originating in the medial temporal lobe is a paroxysmal episode involving an unpleasant odor. Typical descriptions include references to burnt rubber, sulfur, and organic solvents,[39] although more commonly the patient is unable to provide a specific analogy. Such "auras" may occur in the absence of other seizure manifestations as an isolated simple partial seizure. However, virtually all such patients experience a complex partial or secondarily generalized seizure at some point, especially if untreated, and this event resolves any diagnostic uncertainty.

Because virtually all abnormalities of the olfactory system result in loss of smell rather than an abnormal sensation of smell, these are not commonly mistaken for epilepsy. The one important exception is psychiatric illness. In such cases, patients will frequently report abnormal smells in association with psychogenic seizures. Although these may superficially resemble the foul odors of temporal lobe epilepsy, more commonly they are described much more precisely and are even reported as pleasant. Thus, a floral scent has been described,[33] as have smells of "perfume," "food," and "pure oxygen." For a more extensive discussion of these seizures, the reader is referred to the section on psychiatric disturbances.

Disorders of Vision

The sudden visual loss that accompanies a *vertebrobasilar transient ischemic attack* (TIA) is not easily confused with an epileptic seizure. Transient ischemic attacks usually last longer than typical seizures. Both, however, may be associated with vertigo, impaired speech, or altered consciousness. The distinction is discussed more fully in Chapter 275. Recurrent, sometimes stereotyped visual hallucinations may also occur in cases of *cerebral amyloid angiopathy*[20] (see also later discussion).

The complex and sometimes confusing relationship between *migraine* and epilepsy is also discussed more fully elsewhere (see Chapter 274). Because of its high prevalence, the visual symptoms of migraine represent a common situation in which the sensory symptoms of another disease may be mistaken for epilepsy. The phenomena of the two disorders can be similar, although the classic hemifield scotoma seen in migraine is rare with epilepsy. On the other hand, patients with migraine may see stars, colored lights, or patterns similar to those seen by patients with epileptic seizures arising from the occipital or posterior temporal lobe.

Table 1 Sensory disturbances that can mimic seizures

Olfactory disorders
Visual disorders
Migraine
Transient ischemic attack
Peduncular hallucination
Other visual hallucinations
Hearing and vestibular disorders
Auditory hallucination
Dizziness
Benign positional vertigo
Paroxysmal vertigo of childhood

Ménière disease

Somatosensory disorders

Transient ischemic attack

Headache

Transient compression neuropathies

Trigeminal neuralgia

Paroxysmal sensory symptoms of multiple sclerosis

Amyloid angiopathy

Gastrointestinal symptoms

Psychogenic sensory symptoms

Table 2 Additional diagnostic testing useful in sensory disorders

Test	Useful condition(s)
MRI	Stroke, TIA, multiple scerosis, brainstem lesion; cerebral amyloid angiopathy
Audiometry	Hearing loss, BPV, Ménière disease
Electronysagmography; rotary chair testing	BPV
BAER	Brainstem lesion
EMG/nerve conduction testing	Peripheral nerve diseases

BAER, brainstem auditory-evoked potentials; BPV, benign positional vertigo; EMG, electromyography; TIA, transient ischemic attack.

Other unusual causes of visual hallucinations that can occasionally be confused with epilepsy include withdrawal from alcohol or sedative drugs and psychiatric disease. In both, the images are typically well formed, but their variability and long duration (hours to days rather than minutes) usually distinguish them from epilepsy, even in the absence of other clinical information. Hallucinations occurring exclusively during the transitions between sleep and wakefulness (hypnic hallucinations) are often visual. These can be associated with narcolepsy, but also occur sporadically in otherwise normal individuals and can be precipitated by sleep deprivation.[2]

Peduncular hallucinations, a more unusual cause of paroxysmal visual symptoms, were first described by Lhermitte.[32] These typically occur in the evening and may last for hours. They are quite vivid and well formed; examples include a brightly colored parrot[9] or other animals.[1,32,41] Affected patients may have alterations in consciousness, adding to the confusion with seizures. Associated symptoms such as cranial nerve palsies, hemiplegia, hemianesthesia, or ataxia are seen in many patients. Hypomania and increased tone occur often,[41] which may also help to distinguish peduncular hallucinations from seizures. The condition results from infarction of the thalamus or the pars reticulata of the substantia nigra.[9]

Disorders of Hearing and the Vestibular System

As with olfactory disturbances, most seizures that affect hearing and balance manifest the “positive” features of auditory hallucinations or distortions and vertigo. Therefore, it is these symptoms that are most often mistaken for epilepsy. Auditory hallucinations are common in schizophrenia (see Chapter 287) and also occur occasionally in acute withdrawal states from alcohol and other sedative drugs. In both cases, the variability of the hallucinations in any single patient and the particular clinical setting usually make the distinction from epilepsy fairly easy. Auditory hallucinations are rare in vascular disease. These may be transient, and the absence of psychiatric disease can lead to confusion with epilepsy. Auditory hallucinations, including musical hallucinations, can occur with hearing loss, drug intoxication, or drug withdrawal.[14]

Episodes of dizziness and, in particular, paroxysmal vertigo are more likely to be confused with epilepsy. Dizziness is a very common complaint, especially in the elderly, and although only a small fraction of cases may be confused with epilepsy, this still represents a substantial number. The causes of vertigo are quite diverse and may involve either central or peripheral vestibular mechanisms. Peripheral vertigo can result from cupulolithiasis, head trauma, acceleration injuries, and middle ear infections and typically lasts seconds to minutes. Central vertigo can be caused by drugs, cerebrovascular disease, tumors, and multiple sclerosis and typically lasts several days,[17] and therefore these would not typically be confused with epilepsy. The most common disorder is *benign positional vertigo,* which is usually idiopathic, the result of head trauma, or related to a viral infection.[5] Unlike vertigo associated with seizures, paroxysmal nonepileptic vertigo is rarely unprovoked. The diagnosis is made when positional changes (including Hallpike and Barany maneuvers) elicit the patient's typical symptoms with accompanying nystagmus. Paroxysmal vertigo is also usually of longer duration than vertiginous symptoms seen with epilepsy.

Benign paroxysmal vertigo of childhood is characterized by sudden, brief episodes of vertigo and nystagmus. It was first described by Basser.[6] The syndrome occurs most often in children, usually beginning after 4 years of age, but occasionally before age 1 year; it typically resolves by age 10 years. Episodes last from 20 seconds to 3 minutes and may be accompanied by nausea, vomiting, or headache. The child may stumble or fall because of disequilibrium and, not surprisingly, becomes frightened or confused, features that may further suggest a complex partial seizure. The typical frequency is one to five spells per month.[13] Results of audiologic, otologic, and neurologic examinations are normal. Findings of caloric/rotatory tests may be normal[13] or abnormal.[12] The electroencephalogram (EEG) is uniformly normal. Nystagmus occurs during the actual episodes and, if observed, helps in the distinction from seizures. Benign paroxysmal vertigo is associated with migraine[13,15,26] and may perhaps be a variant of basilar migraine. The disorder most likely results from a transient disturbance in the vertebrobasilar circulation that produces central vestibular dysfunction.[16]

In adults, *Ménière disease*, especially in its early stages, is sometimes confused with epilepsy. In the famous case of Vincent van Gogh, debate continues about whether he had Ménière disease or epilepsy.[4,35] Like seizures, attacks of Ménière disease are often preceded by a warning, typically a nonspecific feeling of fullness in the ears. Unlike seizures, attacks are usually accompanied by nystagmus, hearing loss, and tinnitus. Episodes of vertigo may last for hours but occasionally last only a few minutes. Patients may feel weak and unsteady after the episode, but there is never any alteration in consciousness during or after the attacks.[44] Spells may be so sudden and so severe that the patient actually falls to the ground (although without loss of consciousness). Diagnostic tests such as electronystagmography, audiometry, or auditory-evoked potentials may be helpful in confirming a peripheral vestibular disorder.

Disorders of the Somatosensory System

Purely sensory transient ischemic attacks (TIAs) are not uncommon and are manifested by a variety of sensory complaints involving the face and limbs. Although patients usually report numbness, they may also describe a variety of "positive" symptoms, such as pain, tingling, heat, or paresthesias. Because many TIAs resolve within 5 minutes, shorter attacks may be confused with epilepsy. The reader is referred to Chapter 275 for a more complete description of TIAs.

Similar symptoms may be seen in *cerebral amyloid angiopathy* (CAA), a common cause of lobar hemorrhage in older, normotensive patients.[24,42] The disease is characterized by deposition of ß-amyloid in the media of small and medium-sized cerebral arteries. Confusion with epilepsy may occur in the prodromal stages, when the patient has recurrent spells of numbness or tingling that spread over the body in minutes. Transient sensory symptoms can occur repeatedly in the same area,[20] mimicking the stereotypy found in partial seizures. Some authors have suggested that "CAA spells" are actually seizures, but most have concluded that they are more likely to be the result of spreading depression,[20] perhaps triggered by small hemorrhages. Although definitive diagnosis requires histologic confirmation, patients with CAA frequently have multiple cortical hemorrhages and are more likely to show the apolipoprotein E e-2 allele than is a population-based sample.[19] Distinction from seizures is clearly important, but CAA must also be differentiated from TIAs because anticoagulation leads to an increased risk for lobar hemorrhage. Finally, patients with CAA can also have true epileptic seizures,[8,20,23] which poses further diagnostic problems for the clinician.

Neuropathies rarely produce symptoms that are confused with seizures. The manifestations of neuropathies are typically indolent rather than paroxysmal, progressive or static rather than recurrent, and involve areas that are uncommonly symptomatic during seizures (e.g., stocking-glove distribution, mononeuritis multiplex). In unusual cases, a particular nerve may be recurrently and reversibly affected, and a patient may offer a description of repeated numbness or tingling in a particular area, which may seem paroxysmal. Examples include meralgia paresthetica, ulnar neuropathy, and carpal tunnel syndrome. These cases can usually be distinguished from epilepsy by careful history; if diagnostic uncertainty persists, electromyographic evaluation will resolve the issue.

Patients occasionally complain of paroxysmal head pain that can resemble a seizure. Headache as a sole manifestation of seizure is, however, exceedingly rare.[25,29] More commonly, headache occurs as a nonspecific prodrome, aura, or postictal phenomenon. Because ictal headache is so uncommon, even unusual types of headache are not usually confused with epilepsy.

Trigeminal neuralgia (*tic douloureux*) is a relatively common condition characterized by paroxysmal attacks of severe pain in the distribution of one or more branches of the trigeminal nerve. As in epilepsy, attacks are sudden and unpredictable, and are usually brief in duration. Sometimes, however, attacks of trigeminal neuralgia last for hours, a duration that is very atypical of seizures. Unlike epileptic seizures, attacks of trigeminal neuralgia occur frequently in clusters. The maxillary branch of the trigeminal nerve is involved most often; the ophthalmic division is rarely involved in isolation.[28] Carbamazepine is the most effective medical treatment; phenytoin can also be used. Attacks of trigeminal neuralgia are frequently provoked by sensory stimuli (e.g., touch, cold) to the affected region, which may suggest a form of "stimulus-sensitive" epilepsy. In fact, Pagni[36] proposed that trigeminal neuralgia represents a form of stimulus-evoked epilepsy. Classic trigeminal neuralgia is easily distinguished from epilepsy by the distribution, time course, and quality of the attacks. Atypical presentations, however, are occasionally mistaken for simple partial seizures, and the incorrect diagnosis seems to be further supported by a good response to antiepileptic drugs.

Paroxysmal sensory symptoms, including trigeminal neuralgia, can occur in patients with *multiple sclerosis* (MS). A common paroxysmal disturbance is burning dysesthesia, often restricted to one limb, that lasts <1 minute and often only a few seconds. There are no associated convulsive movements. Attacks may be induced by voluntary movements and respond well to carbamazepine.[46] Episodes of painful chorea, dystonia, and various tonic postures also occur in MS.[27,34,38] These probably arise from an ectopic generation of action potentials in demyelinated axons, with subsequent spread along sensorimotor pathways.[46]

Gastrointestinal symptoms, such as nausea and vomiting, are treated first by general practitioners or internists, although these can be manifestations of simple partial seizures. Gastrointestinal reflux is unlikely to be confused with epilepsy in adults from whom an accurate history may be obtained. It can pose a diagnostic problem in young children, in whom episodes of reflux may be accompanied by vomiting, cyanosis, and posturing simulating epilepsy.[37] In children, recurrent abdominal pain may develop at about 5 years of age. Episodes usually last several hours and are not associated with any gastrointestinal diagnostic abnormalities.[3] Cyclic vomiting is seen at the age of 2 years and disappears after 3 to 4 years.[22] These episodes are frequently accompanied by severe nausea and abdominal pain. Both recurrent abdominal pain and cyclic vomiting are associated with migraine[37] but not epilepsy. They were formerly often misdiagnosed as “abdominal epilepsy.”

Psychogenic Sensory Symptoms

Psychiatric disorders are discussed in Chapters 281,282,283,284,285,286,287; however, they deserve special mention in a discussion of sensory phenomena. Because sensory symptoms are usually not accompanied by objective changes, the clinician often must rely entirely on the history for an initial diagnosis. Particularly in the case of a patient with psychiatric illness, this description may be vague and unhelpful, adding to the difficulty in distinguishing epileptic from nonepileptic events.

Psychogenic nonepileptic seizures (PNES) are paroxysmal alterations in movement, sensation, or experience that resemble epileptic seizures but arise from purely psychological causes (see also Chapter 282). Although up to 80% of patients with PNES have motor manifestations,[18,21,30] in other cases, PNES are characterized by sensory changes,[43] including numbness, paresthesias, pain, odors, tastes, and visual/auditory hallucinations.[21,31,33] Psychogenic nonepileptic seizures usually have a more gradual onset and longer duration than epileptic seizures, but these features alone cannot reliably be used to make the distinction from epilepsy.[31]

The presenting symptoms of *panic disorder*, with or without hyperventilation, may include dizziness, vertigo, perioral tingling, numbness or tingling of the hands, generalized weakness, or syncope, and panic disorder may be confused with epilepsy.[40] Paroxysms of unexplained fear are typical in panic disorder; these may be confused with a limbic seizure. For a more complete discussion, see Chapter 285.

Distinguishing PNES or panic disorder from epileptic seizures may be difficult. Stereotyped attacks favor epileptic seizures, although subjective descriptions of purely sensory symptoms are often difficult to interpret. When diagnosis remains unclear following a careful history, video-EEG monitoring may be required to make the distinction.

Summary and Conclusions

Many sensory symptoms and disorders have some resemblance to epilepsy and, in certain circumstances, may be confused with it. In most cases, careful history taking supplemented by appropriate diagnostic testing provides a reliable basis for making the distinction. In some patients, recording one or more of the patient's habitual events with concurrent electroencephalography (video-EEG monitoring) may be required to distinguish epileptic from nonepileptic events reliably. A time-linked ictal discharge during an episode is diagnostic of epilepsy. False-negative results may occur with simple partial seizures, which have no scalp EEG correlate in the majority of cases.[11] In such instances, however, video recording and careful clinical testing should reliably establish the clinical semiology and determine whether this is consistent with an epileptic seizure. Prolonged EEG recordings may also show interictal epileptiform discharges; these strongly suggest a diagnosis of epilepsy,[10,47] but their detection is not equivalent to demonstration of a seizure discharge occurring simultaneously with the symptom in question. When spells occur on a daily basis, 6- to 8-hour EEG with video monitoring on an outpatient basis is a reasonable alternative. Infrequent attacks usually require inpatient video-EEG monitoring, and antiepileptic drugs (if used) may need to be withdrawn. Recent advances in extended outpatient EEG monitoring are making this an alternative to inpatient monitoring in selected cases, although these still suffer from the lack of trained personel to ensure proper recording at all times and to test the patient appropriately during spells.

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Chapter 280

Nonepileptic Neurologic Paroxysmal Disorders and Episodic Symptoms in Infants

Natalio Fejerman

Introduction

Misdiagnosis of epileptic seizures in young children is frequent and generally due to considering various paroxysmal or episodic symptoms as epileptic when they are not.[12,59,61,107]

Nonneurologic paroxysmal disorders, such as breath-holding spells, syncope, and psychogenic events, are discussed in Chapter 273. Most of the neurologic conditions listed in Table 1 are uncommon. Nevertheless, they can be an important part of the differential diagnoses of epileptic seizures. Table 1 groups various symptoms and conditions according to their general nature.[116]

Enhanced Normal Phenomena

Sporadic Myoclonic Jerks During Sleep (Hypnic Jerks) or Physiologic Sleep Myoclonus

These are universally present in normal people. They appear during the initial stages of sleep and also during rapid eye movement (REM) sleep. Typically, they manifest as slight contractions of face muscles and brief movements of the fingers or toes. There are no electroencephalographic (EEG) correlates.[69] Massive bilateral jerks, mainly involving the legs, can occur during the initial stages of sleep in association with a change in sleep state or arousal.[114]

Localized Myoclonus During Wakefulness

This represents a rare physiologic phenomenon that usually occurs during and after muscular fatigue and when the linear or a particular group of muscles are placed in unsupported postures. The affected muscle groups may vary, but in any individual, each episode of myoclonus involves the same muscles. The myoclonic jerks last a few seconds to several minutes. There are no EEG changes accompanying the myoclonus, and a spinal origin has been suggested.[69] Even hiccoughs, considered a physiologic phenomenon, may occasionally be intense and simulate a paroxysmal disorder in small infants.

Startle Responses

These have been called *sursaut diurne* in the French literature[69] and are sudden, bilateral myoclonic jerks that may be either tight or massive and appear as a surprise reaction to a sudden sensory stimulus. Although segmental myoclonus is rare in young children, startle responses are very common. The Moro reflex has a startle component, and some kind of startle response can be demonstrated in most normal infants. These normal physiologic responses must be distinguished from the exaggerated Moro reflex and pathologic stimulus-induced myoclonus, often with opisthotonus seen in children with static or progressive encephalopathy.[58]

Bruxism

The majority of adults and children have nocturnal bruxism at some point in their lives.[13] In children with autistic behavior and mental retardation, bruxism also occurs in the waking state and may lead to severe dental attrition.[109]

Parasomnias

More common disorders are considered in Chapter 276 (see also Hanson and Peck[79]).

Transient or Benign Movement Disorders

Benign Neonatal Sleep Myoclonus

In 1982, Coulter and Allen[35] reported three infants who had sleep myoclonus that began in the first month of life. The myoclonic jerks were bilateral, repetitive, and located mainly in the forearm and hands. Neurologic examinations and EEG were normal and continued to be normal during follow-up. Coulter and Allen coined the term *benign neonatal sleep myoclonus* (BNSM) for this phenomenon.

Subsequently, several other small series of cases were published that emphasized the importance of distinguishing BNSM from seizures.[123,143] This condition is probably quite frequent, as suggested in more recent, larger series.[37,42,43]

Table 1 Nonepileptic neurologic paroxysmal disorders and episodic symptoms in infancy

Disorder	Symptoms
Enhanced normal phenomena	Hypnic jerks and waking myoclonic jerks Bruxism
Transient or benign movement disorders	Benign neonatal sleep myoclonus
	Tonic reflex seizures of early infancy
	Benign myoclonus of early infancy (benign nonepileptic infantile spasms)
	Benign paroxysmal tonic upward gaze
	Transient paroxysmal dystonia
	Benign paroxysmal torticollis
	Shuddering attacks
	Adverse reactions to exogenous agents

Habit-type movements and self-gratification phenomena	Head banging Head or body rocking Other stereotypic movements Masturbation-like episodes
Symptomatic abnormal movements	Neonatal posturing and other nonepileptic episodes
	Opsoclonus-myoclonus syndrome
	Bobble-head doll syndrome
	Encephalopathic nonepileptic myoclonus
Other paroxysmal episodes or neurologic conditions	Nonepileptic apnea Hyperexplexia Cogan oculomotor apraxia Benign paroxysmal vertigo Spasmus nutans Alternating hemiplegia of childhood Paroxysmal dystonia and choreoathetosis

Benign neonatal sleep myoclonus appears in term newborns during the first few weeks of life. One infant born prematurely developed BNSM at 42 weeks of conceptional age,[120] and the earliest reported onset is in a 5-hour-old newborn.[35] The intensity and frequency of the muscle jerks increase up to the third week of life; more subtle myoclonus appearing earlier may go unnoticed. Myoclonic jerks are mainly present during non–rapid eye movement (NREM) sleep; they are less frequent during REM sleep. In some children, BNSM occurs exclusively during NREM sleep.[42] In most cases, jerks predominately involve the arms, but the feet, face, axial, and abdominal muscles can also be affected.[29,37,42,118,123] Myoclonic jerks may be bilateral; localized or multifocal; rhythmic or arrhythmic. The jerks occur frequently in clusters repeating at 1 to 5/sec for several seconds. Clusters of jerks usually recur irregularly in series lasting 20 to 30 minutes[42] or up to 90 minutes.[20] Longer-lasting episodes of BNSM have been mistaken for convulsive status epilepticus.[5,148]

Sleep state does not change during the episodes, and arousal always terminates the jerks. Occasionally, BNSM is stimulus sensitive and can be elicited, for instance, by noise.[35] Crib rocking can provoke BNSM, which is helpful diagnostically.[5] Curiously, benzodiazepines may increase the intensity of BNSM.[120]

Benign neonatal sleep myoclonus subsides spontaneously beginning with the second month of life and usually disappears before the sixth month. Ictal EEG is, by definition, normal in BNSM. However, one series reported a higher-than-normal incidence of interictal sharp transients in 4 of 10 newborns.[37] Benign neonatal sleep myoclonus may be genetically determined because affected siblings have been reported in two small series of patients, and a history of night jerks in one of the parents has also been found in several cases.[29,143]

Although Coulter and Allen[35] attributed BNSM to an arousal response, EEG recordings have not demonstrated this. Benign neonatal sleep myoclonus shares some features with nocturnal myoclonus seen in adults,[100] and it may reflect transient immaturity or imbalance of the serotonergic system.[123] In our last series of 21 patients, myoclonus disappeared before the age of 7 months, and 2 cases subsequently developed benign myoclonus of early infancy. Prognosis is uniformly good, and no treatment other than reassurance is necessary.[56]

Tonic Reflex Seizures of Early Infancy

This disorder was described in 1996, and a second series of 13 cases was published in 2001.[153,154] Onset occurs between the first and third month of life, with spontaneous remission 2 to 3 months after onset. These are normal infants presenting diffuse tonic contractions with extension of the four limbs, apnea and cyanosis, without loss of consciousness, lasting 3 to 10 seconds. Seizures occur only during wakefulness and with the child being held in an upright position. Because tactile stimulation often triggers the episodes, reflex myoclonic seizures come to mind. Normal interictal and ictal EEGs help to rule out brief tonic or myoclonic seizures and infantile spasms. The main differential diagnosis is with benign myoclonus of early infancy.

Benign Myoclonus of Early Infancy (Benign Nonepileptic Infantile Spasms)

In 1976, Fejerman[54] reported 10 infants with recurrent spells that resembled infantile spasms but in whom neurologic status, EEG, and outcomes were normal, allowing clear differentiation from West syndrome. Additional cases were added in subsequent reports.[16,30,55,56,67,74,75,98,101,102] Fejerman termed their conditions *benign myoclonus of early infancy* (BMEI).

We have now followed a total of 41 patients (26 male, 15 female) for 2 to 27 years.[60] In general, a diagnosis of West syndrome had been made, even with normal EEGs[137]; the correct diagnosis was established only in retrospect. Infants came to attention because of repeated jerks of the neck or upper limb muscles, causing abrupt flexion or rotation of the head with extension and abduction of the arms. Movements are often described as shuddering of the head and shoulders. In a minority of cases, only the arms are involved; sometimes, shuddering movements alternate with unequivocal myoclonic jerks. Occasionally, the only feature is symmetric or asymmetric extension of one or both arms with abduction, head rotation, or head drops. The jerks may be isolated or repeat in a series. They typically occur multiple times a day.

Consciousness is not affected, even when the myoclonic jerks last as long as 30 minutes. Benign myoclonus of early infancy occurs only rarely during sleep.[45] Although feeding may trigger attacks, this does not justify a separate designation, as has been proposed.[53] Benign myoclonus of early infancy is not related to anger or frustration. Myoclonus appears between 1 and 12 months of age, with onset in 90% of cases between 3 and 9 months. This overlap with the peak occurrence of infantile spasms further confounds diagnosis (Table 2) (see Chapter 229). Furthermore, we reported 4 infants who were normal until onset of typical infantile spasms without hypsarrythmia or other abnormalities in their EEGs. Thus, ictal EEG is very important in differential diagnosis.[27]

Table 2 Differential diagnosis between cryptogenic West syndrome and benign myoclonus of early infancy (BMEI)

Coincidences	Age of onset 3–9 mo
	Normal neuropsychic development (until onset)
	Myoclonic or brief tonic contraction in neck, shoulders, and upper limbs
	Occurring in series
	Several fits per day

Differences	West syndrome	BMEI
Seizures	During waking and during sleep	During waking, exceptionally during sleep
Electroencephalogram	Always abnormal, almost always hypsarrhythmia	Always normal
Psychomotor retardation	In all nontreated cases	Never

Table 3 Differential diagnosis of benign myoclonus of early infancy

1. Other nonepileptic phenomena
    a. Hyperexplexia
    b. Sandifer syndrome
    c. Tonic reflex seizures of early infancy
    d. Adverse reactions or intolerance to exogenous agents (monosodium glutamate, metoclopramide, etc.)
    e. Shuddering attacks (early symptom of familial essential tremor)
    f. Paroxysmal dystonia or choreoathetosis (paroxysmal torticollis, kinesigenic paroxysmal choreoathetosis, benign infantile dystonia)
2. Epileptic seizures
    a. Early myoclonic and tonic epileptic seizures
    b. Benign familial and nonfamilial infantile convulsions
    c. Infantile spasms (West syndrome)

Neurologic examination is always normal, as are interictal and ictal EEG recordings. There are no other laboratory abnormalities, and behavioral and neurologic development is normal.

Symptoms, once present, may increase for several weeks, but they gradually subside over a few months. Most children are free of attacks by the end of their second year and always by the end of their third. Other conditions that used to be considered in the differential diagnosis of BMEI are listed in Table 3.[2,49,56,57,133]

Some authors consider shuddering attacks to be different from benign myoclonus of early infancy, and they were initially described as associated with essential tremor.[82,87,150] In fact, I consider that the syndrome named BMEI includes always normal infants who start with fits frequently repeated in bursts, consisting in myoclonic jerks, brief tonic contractions, or shuddering episodes. We do not know the neurochemical basis of this disorder, but we do know that it is a transient phenomenon that may have different neurophysiologic expressions. This interpretation allows the inclusion of some neurophysiologic findings within the spectrum of BMEI.[108]

Transient immaturity or imbalance of the serotonergic system might underlie various myoclonic phenomena, as has been postulated for BNSM,[123] and which could be genetic, thus accounting for occasional familial cases of both BNSM and BMEI.[29,68] We have seen one child with both BNSM and BMEI. Defining pharmacologic subgroups of the various myoclonic disorders is important, not only for understanding the clinical and neurophysiologic heterogeneity of myoclonus,[112] but also for providing rational pharmacotherapy. The areas of brain involved in BMEI are unknown.

Benign Paroxysmal Tonic Upward Gaze

This syndrome is characterized by bouts of tonic upward eye deviation accompanied by ataxia.[106] Age of onset is between 6 and 24 months, and children are otherwise healthy. The episodes of upward eye deviation occur in clusters every 2 to 8 seconds over a period of several minutes.[37,51] During episodes, consciousness is preserved, and attempts visually to track objects downward produce vertical nystagmus. Affected children usually exhibit a compensatory tilt of the head with the chin down. Symptoms occur only during wakefulness. During attacks, EEG recordings are normal. The frequency of the episodes gradually declines, and attacks disappear after 1 to 2 years. Even when the episodes disappear, patients may show slow motor development.[127] Three cases have shown a familial incidence.[23] The brain of one child who died accidentally was normal.[106]

Some children have benefited from treatment with dopa, and this has suggested a possible relationship to Segawa syndrome.[23,40]

Transient Paroxysmal Dystonia

Episodes of paroxysmal dystonia beginning at 3 to 5 months of age were reported in a group of nine infants. The attacks, which occurred only when the children were awake, were characterized by opisthotonus, symmetric or asymmetric increased tone in the arms with extreme pronation of the wrists, and preserved consciousness. Attacks usually lasted several minutes and occurred from once per month to several per day. Sometimes, however, episodes increased in duration to several hours or even days. In all cases, attacks disappeared in the second year of life.[10]

A similar picture had been described earlier as “benign idiopathic dystonia with onset in the first year of life.” These infants had dystonic postures, mainly of the hands, lasting seconds to minutes and associated with intention tremor of the arms.[38,41,157]

Benign Paroxysmal Torticollis

Of all of these paroxysmal nonepileptic neurologic disorders, benign paroxysmal torticollis probably least resembles epileptic seizures. Benign paroxysmal torticollis is characterized by recurrent episodes of cervical dystonia lasting a few hours or days. Attacks are frequently associated with vomiting, pallor, irritability, and, sometimes, drowsiness or ataxia.[33,39]

Onset occurs in the first year of life, and attacks repeat several times per year. Over time, they decrease in severity and disappear after a few years. Electroencephalography is always normal. Gastroesophageal reflux, brainstem/cerebellar, or vestibular dysfunction should be excluded. The benignity of the condition has been emphasized in new series of 22 and 11 cases each.[46,6] In another report, two of the four cases came from a kindred with familial hemiplegic migraine linked to CACNA1A mutation.[73] Benign paroxysmal torticollis is now regarded as a migraine equivalent.

Adverse Reactions to Exogenous Agents

Adverse reactions or intolerance to various exogenous agents can include dystonic posturing, shuddering, tonic postures, and myoclonic jerks. Drug ingestion should be sought by careful inquiry, and blood or urine drug screens may be necessary. Metoclopramide,[71] carbamazepine,[110] phenothiazines (especially prochlorperazine), droperidol, and trimeprazine[138] have all been implicated. Intolerance to food additives has also been incriminated as a cause of shuddering attacks.[121]

Habit-Type Movement and Self-Gratification Episodes

Head Banging, Head Rolling, Rocking, and Other Stereotypic Movements

These represent a group of repetitive motor behaviors in children that are typically rhythmic and persistent. They are usually not paroxysmal and, therefore, rarely suggest epilepsy.

Head banging and head turning are common in normal infants at the time of going to bed, especially during the first year of life. Occasionally, children seem withdrawn and inattentive, which may suggest a seizure with automatisms. In some children, the rhythmic head movements persist during sleep (jactatio capitis nocturna). Generally, such movements disappear before 3 years of age, and neurologic development is normal.[1] Similar, often exaggerated motor behaviors occur during wakefulness in children with autistic behavior and mental retardation. A unique case of a parasomnia with rhythmic head and body movements and with tongue biting was reported in a 2-year-old girl.[149]

Rocking is less common in normal children and occurs most often in children with mental retardation, developmental disorders, or sensory deficits. The abnormal behavior starts during the first year of life when the child is sitting. Later, lateral or to-and-fro rhythmic movements of the head or body occur while standing as well.[124] A small proportion of normal children has similar behavior.[38,63,129]

Other stereotypic behaviors such as buccal and lingual movements may be mistaken for the oral automatisms of partial seizures, and hand flapping and related mannerisms may be confused with myoclonus.[24] In older children, repetitive hand waving in front of the eyes is used to self-induce photosensitive seizures. In young children, psychogenic seizures can manifest as brief staring episodes that are not easily distinguished from atypical absence seizures. In such cases, video-EEG monitoring will allow definitive diagnosis.[48,103]

Masturbation-like Episodes

Infants, usually girls, are sometimes referred because of brief episodes of staring, adducted thighs, rhythmic contractions of the leg and trunk, flushing, perspiration, and a dazed appearance. Such episodes are frequently mistaken for epileptic seizures, but self-gratification episodes and masturbation should be considered, despite the child's young age.[3,58,135,138] A helpful differential point is that the child is awake and may resist or resent being interrupted.

Symptomatic Abnormal Movements

Neonatal Posturing and Other Nonepileptic Episodes

Motor automatisms and tonic postures are the most common paroxysmal events in newborns who do not have a consistent EEG abnormality. They are usually seen in infants with severe encephalopathies and depression of forebrain function. Kellaway and Hrachovy[88] hypothesized that these behaviors are mediated at a brainstem level due to failure of normal cortical inhibition and proposed that they represent “brain stem release phenomena.”[88,104] Similar motor activities can be epileptic; however, EEG monitoring is usually necessary to define the underlying pathophysiologic mechanisms.[155,156]

Tonic postures in the newborn may be focal or generalized, and some may have myoclonic components. Many of these motor behaviors were formerly classified as “subtle” or “minimal” seizures, but their inconsistent relation to EEG ictal patterns have called their association into question (see Chapter 56). Other nonepileptic motor behaviors in newborns include oral-buccal-lingual movements such as chewing and sucking, random eye movements, rhythmic blinking, and peculiar limb movements like pedaling or swimming. In older infants, such activities may be part of an epileptic ictal event. The argument persists, however, and the question of whether dissociation between scalp EEG findings and stereotypical paroxysmal motor behavior excludes the possibility of an epileptic mechanism can probably never be answered definitively to everyone's satisfaction.[31,99,104] Nonetheless, therapeutic decisions (e.g., whether to use antiepileptic drugs) require an operational decision to be made in individual cases[155,156] (see Chapter 123).

Thus, several observations that can be made at cribside help to distinguish an epileptic seizure from a nonepileptic event with a strong degree of probability for therapeutic purposes. The following criteria reinforce the presumption that a particular event is nonepileptic: (a) It increases with sensory stimulation (spatial or temporal summation, irradiation); (b) it can be suppressed by gentle passive restraint; and (c) it is not accompanied by autonomic features (tachycardia, apnea, changes in blood pressure).[155] In such newborns, antiepileptic drugs are generally neither necessary nor desirable.

Independent of therapeutic decisions or nosologic questions, motor automatisms and tonic postures in newborns have significance in terms of etiology and prognosis. In one study, 53% of infants with tonic postures and 54% of those with automatisms had hypoxic-ischemic encephalopathy, and, of these, only about 25% were normal at hospital discharge.[104]

Segmental or spinal myoclonus in early infancy can be seen with sepsis, birth trauma, and various degenerative diseases. Isolated cases of spinal myoclonus have been reported in a child with hyperglycorrhachia secondary to parenteral nutrition administered through an improperly placed, indwelling femoral catheter[14] and in a 2-month-old infant with a spinal cord tumor.[122]

Opsoclonus-myoclonus Syndrome

Several years after the initial description of opsoclonus-myoclonus syndrome (OMS),[90] its frequent association with neuroblastoma was recognized.[50,136] Mean age of onset is around 14 months, and symptoms usually appear a few days after an apparent viral infection.[64] The following features are typical: (a) ataxia with marked tremor leading to inability to walk; (b) opsoclonus ("eye dancing") with episodes of rapid eyelid flutter; (c) myoclonus of the face of limbs; and (d) marked irritability and excitability. Brain imaging studies, EEG, and cerebrospinal fluid are normal. Brainstem auditory-evoked potentials can be abnormal early in the course.[86]

Some authors have argued that OMS is always associated with neuroblastoma and that such tumors may regress spontaneously,[22] but this is not true. Nonetheless, emphasis must be placed on a systematic search for neuroblastoma. Routine laboratory tests, including catecholamine levels, may be normal. Abdominal computed tomography (CT) may be necessary to detect small (1.5–2.0 cm) neuroblastomas arising from the abdominal sympathetic chain.

Several cases associated with different acute viral infections have been reported.[68,85,94,132] It is clear that there is still much to learn about the neurobiology of OMS.[113] Low concentrations of 5-hydroxyindoleacetic acid and homovanillic acid were found in the cerebrospinal fluid of 27 children with OMS.[115] There are three main etiologic groups for OMS: (a) OMS associated with neuroblastoma, (b) OMS associated with special viral infections, and (c) OMS without a definable etiology. Acute immune pathogenesis is surely involved, and there are new advances in this sense. Autoimmune antibodies binding to the surface of isolated rat cerebellar neurons were found in 10 of 14 children.[19] Children with OMS manifested a four- to sevenfold higher percentage of total B cells in cerebrospinal fluid compared with controls, and its determination is proposed as a biologic marker of the disease.[117]

Some children show a prompt and persistent response to corticosteroids or adrenocorticotropic hormone (ACTH), but most cases follow a chronic course with remissions and relapses often related to new viral infections.[90] Intravenously administered immune globulin seemed to produce remarkable improvement in an 18-month-old infant with OMS associated with a nonresectable abdominal ganglioneuroblastoma.[111]

Long-term follow-up reveals that some children, especially those with neuroblastoma, become symptom free. The majority, however, have chronic neurologic deficits, including cognitive and motor delays, language deficits, and behavioral abnormalities, regardless of etiology.[78,92]

Bobble-head Doll Syndrome

This is a rare disorder associated with obstructive hydrocephalus due to lesions in the region of the third ventricle and aqueduct.[146] In most of the reported cases, head movements have been characteristically to-and-fro nodding, which creates a peculiar 2- to 3-Hz rhythmic head nodding similar to that seen in dolls with weighted heads attached to coil-spring necks. The movement can be stopped voluntarily and is most obvious when the child is in the upright position. It disappears during sleep and when the head is supported. Pendular movements of the arms may also be seen.

Onset can occur in infancy or up to the fourth year of life.[146] Macrocephaly is a constant finding, and remarkable improvement follows treatment of the hydrocephalus. Ventriculocisternostomy through endoscopic treatment was recommended in cases associated with arachnoid cysts.[65,77] The condition is less often confused with epilepsy than with tremors, habit spasms, or even hysterical disorders.[79,146] Eight cases with head stereotypies resembling bobble-head doll syndrome, in association with axial hypotonia, ataxia, oculomotor abnormalities, and motor delay, were reported. In two of them, a congenital cerebellar abnormality without hydrocephalus was found.[83]

Encephalopathic Nonepileptic Myoclonus

Nonepileptic myoclonic jerks often appear in children with static or progressive encephalopathies, including some storage diseases, various toxic encephalopathies, and encephalopathies secondary to physical agents.[53] Different subcortical lesions that affect the basal ganglia may lead to myoclonus with or without dystonic features.

Other Neurologic Conditions with Paroxysmal or Episodic Symptoms

Nonepileptic Apnea

Detailed analysis of nonepileptic apnea in newborns is beyond the scope of this chapter. Apnea during sleep is a common, normal phenomenon in premature and term newborns; it is more common in REM sleep than in NREM sleep.[72] The frequency of these normal respiratory pauses decreases after the neonatal period; apnea is rare in normal infants after a few months of age.[76] Video-EEG and polygraphic studies are fundamental tools for differential diagnosis between epileptic and nonepileptic apnea in newborns. Although apnea is common in the course of neonatal and infantile seizures, it is rare for apnea to be the sole manifestation of an epileptic seizure.[32,104]

Most of the information about infantile apnea has been obtained from polygraphic studies of infants diagnosed as having had near-miss for sudden infant death syndrome (near-miss SIDS). This term defines the infant who is found limp, blue, and not breathing, and who presumably would have died without intervention and resuscitation. Most children with SIDS have had a previous near-miss SIDS event.[76] Sudden infant death syndrome and near-miss SIDS have their peak incidence between 2 and 4 months of age, and different etiologies have been implicated.[12] Gastroesophageal reflux is frequently associated with episodes of apnea and can be confused with epilepsy, especially when apnea, choking, and cyanosis are accompanied by unusual head and neck postures and even opisthotonus (Sandifer syndrome).[140] A near-miss SIDS episode can be complicated by a convulsion due to hypoxia.[12,66]

Hyperekplexia

Hyperekplexia ("startle disease") is a rare condition that is often confused with epilepsy in the first year of life. Both major and minor variants have been reported. Most cases are familial, and both autosomal-dominant[9,139] and recessive[128] transmission have been reported. Other cases are sporadic.[70] Hyperekplexia was linked to the short arm of chromosome 5.[119] Several mutations were later found, and data seem to show a direct relationship between the mechanisms of inheritance and the location of the molecular defect. For instance, mutations in the domain of GLRA1 (alpha subunit of the glycine receptor) are frequent in autosomal dominant hyperekplexia.[96] A report of recessive hyperekplexia with a new mutation in the GLRA1 gene was recently presented.[34] In my experience, however, sporadic hyperekplexia was more frequent than the familial forms.[62] This finding is ratified with a recent series of 39 sporadic cases in neonates and infants.[131]

Most cases involve infants with marked muscular hypertonia and severe jerks induced by sound or tactile stimuli. Touching the dorsum of the nose is especially effective in eliciting symmetric myoclonic jerks of the arms and legs. Tonic and clonic generalized attacks with cyanosis occur during sleep. Such children are usually misdiagnosed as having spastic quadriparesis with stimulus-sensitive myoclonic epilepsy, and artifacts in the EEG are commonly misinterpreted as abnormal discharges. The hypertonia decreases with time, and open pyramidal signs are not present. Affected children walk at 2 to 3 years of age and usually have mild mental retardation.

Clonazepam is the drug of choice, effectively reducing the paroxysmal episodes that occur during sleep and drop attacks due to stimulus-induced myoclonus.[62] "Minor" and atypical cases may lack early hypertonia or a clear response to tactile stimuli.[56,105]

The condition usually improves, although rarely an infant may die from cardiopulmonary arrest during an episode occurring in sleep. This type of attack can be stopped by forced flexion of the head and legs.[151] We reported four sporadic cases with the conviction that they were malignant forms of hyperekplexia.[11] Following this line, two children with hyperekplexia associated with refractory status epilepticus who died were recently reported, suggesting that they might represent a new autosomal-recessive syndrome.[97]

Cogan Oculomotor Apraxia

Oculomotor apraxia may be symptomatic of different congenital and acquired conditions, including brain malformations, mesencephalic-diencephalic lesions, and genetic diseases associated with other neurologic signs and mental retardation.[3]

The form of oculomotor apraxia known as Cogan syndrome is usually recognized after 6 months of age by the peculiar head thrusts and impaired saccadic eye movements. These abnormal movements of the eyes and head are usually horizontal and may be mistaken for tics or even epileptic seizures.[138] There is a tendency for the eyes to improve with time, although persistent clumsiness and learning difficulties are frequent.

In two children with this condition, a newly recognized association with nephronophthisis type 1 was reported. Both patients carried the lesions in the NPHP1 gene.[18] Familial occurrence of congenital oculomotor apraxia was also reported in four patients.[84]

Benign Paroxysmal Vertigo

Benign paroxysmal vertigo (BPV) must be considered in the differential diagnosis of seizures in children from 1 to 4 years of age.[15,58,91] The child usually begins crying, clings to the nearest person, or falls to the floor. Pallor and a frightened expression are constant features, but nystagmus occurs in only 35% to 40% of cases. Vomiting is infrequent.[91]

Children old enough to have developed language express fear of falling and a rotational sensation: "The room is turning around," "the floor is moving," "the walls are falling."[61] Episodes last about 1 minute, and recovery is prompt. Attacks usually recur monthly and tend to disappear in a few years. Electroencephalography and neurologic examination between attacks and development are normal.

According to some investigators, vestibular function tests have been consistently abnormal, with labyrinthine dysfunction on one or both sides.[91] In a more recent series, however, such abnormalities were not found.[47] Relation to migraine, instead, seems to be strong: A family history of migraine in 53% of 19 cases and a family history of kinetosis in 83% of the same series were reported.[47] Cyclic vomiting may be associated and was considered together with BPV as part of the so-called periodic syndrome that may be a precursor to migraine.[47,80] More recently, serum creatine kinase-MB (CK-MB) levels were elevated in 22 children with BPV, and the authors suggested that CK-MP may be a diagnostic marker for this condition.[125]

Benign paroxysmal vertigo must be distinguished from other causes of recurrent vertigo in childhood. When attacks last more than a few minutes and are associated with ataxia and other neurologic symptoms, the diagnosis of BPV is unlikely, and other etiologies should be considered.[61,145]

Spasmus Nutans

Spasmus nutans is characterized by the triad of nystagmus, head nodding, and head tilt. Head nodding is most frequently horizontal and may occur in bursts; nystagmus is more constant and usually monocular. Age of onset is usually from 6 to 18 months.[3,63]

Spasmus nutans tends to disappear within a few months or years. The incidence of new cases seems to have declined in the last few decades.[61] The etiology is unknown. However, a recent comparative study of 23 patients with spasms nutans (SN) and 24 patients with idiopathic infantile nystagmus (IIN) demonstrated significant differences between SN and IIN patients and their families with regard to socioeconomic status and exposure to light early in life, concluding that low socio-economic status is a factor of risk for spasmus nutans.[158] Normal complete neurologic and ophthalomologic examination as well as normal brain magnetic resonance imagining (MRI) are necessary to confirm diagnosis.[44] Differential diagnosis with such pathologies as optic glioma and congenital retinopathies is mandatory.[44,89]

Alternating Hemiplegia

The initial description of alternating hemiplegia (AH) of childhood included eight children described as having complicated migraine beginning in infancy.[151] The condition was later identified as a distinct entity[93] and has been thoroughly reviewed and reconsidered.[7]

A relation of AH with familial hemiplegic migraine (FHM) has been recently suggested, with a novel ATP1A2 mutation reported in a kindred with features in common between AH and FHM.

Differentiation from epilepsy is not easy early because the initial manifestations are usually partial tonic attacks beginning in infancy or even in the neonatal period. Paroxysmal nystagmus, especially monocular nystagmus, is frequently associated with the episodes of unilateral tonic attacks.

Hemiplegia is not usually the first symptom, but it almost always appears during the first year of life. Hemiplegia occurs suddenly and may be preceded by screaming and fussiness. The affected side is hypotonic, with persistent tendon reflexes, and each attack lasts from 30 minutes to several days. A distinct feature of alternating hemiplegia of childhood is the disappearance of all abnormalities when the child falls asleep. Paralysis recurs on awakening in prolonged episodes. Although the hemiplegia, by definition, alternates from side to side in successive attacks, bilateral weakness and variations in tone are not unusual.[4]

Seizures occur in 50% of cases, and partial status epilepticus may occur. The seizures occur independent of, but sometimes in close relationship to, a hemiplegic attack.[4,36]

The episodes of alternating hemiplegia recur at variable intervals but seem to become less severe over time. However, most children develop some degree of ataxia with choreo-athetosis and are left with significant mental retardation. Cases of benign familial alternating hemiplegia of childhood are exceptions to this usual evolution.[8]

Flunarizine has benefited some children with alternating hemiplegia by reducing the duration but not the frequency of hemiplegic attacks. Only rarely has flunarizine abolished attacks completely.[7,134]

The etiology and pathogenesis are still debated. Although a possible relationship to migraine has not been completely rejected, there are abnormalities of energy metabolism and mitochondrial function that merit further investigation.[7]

Paroxysmal Dystonia and Choreoathetosis

Two rare familial conditions are *paroxysmal dystonia and choreoathetosis* and *paroxysmal kinesigenic choreoathe-tosis*.[95,144] In the former, onset is usually between 1 and 2 years of age, and attacks are mainly of dystonia, which lasts from 2 minutes to a few hours. The frequency of attacks ranges from several per day to one every 2 months.[21] Familial cases must be distinguished from the sporadic transient paroxysmal dystonic episodes already discussed.

Paroxysmal kinesigenic choreoathetosis is also an auto-somal-dominant disease, but it starts after 5 years of age.[126] A constant feature is that attacks are precipitated by sudden movement, and episodes last only a few seconds to several minutes; they occur several times a day.[138] Antiepileptic drugs usually suppress attacks, but EEGs have been abnormal in only one case.[81]

A genetic bridge between paroxysmal choreoathetosis and benign familial infantile convulsions was established in 1997 in describing a new neurologic syndrome linked to chromosome 16.[142] Caraballo et al. later reported linkage to chromosome 16 in children with benign familial infantile convulsions. Our group was actively involved in this search, and in our cases, paroxysmal choreoathetosis appeared years after onset of benign familial infantile convulsions.[25,26,28] Paroxysmal kinesigenic choreoathetosis also seems to map to chromosome 16.[17,147]

Acquired nonepileptic paroxysmal dystonia is associated with static encephalopathies, but it begins outside infancy.[52] It probably represents different forms of "delayed-onset dystonia."[63] The differential diagnosis includes hereditary progressive dystonia with marked diurnal fluctuation and other dopa-responsive dystonias.[130]

Summary and Conclusions

All of the conditions reviewed in this chapter are intermittent, often paroxysmal, and have been confused with epileptic seizures. On one extreme are abnormal movements that are symptomatic of severe brain pathologies requiring specific treatments, such as the opsoclonus-myoclonus syndrome and the bobble-head doll syndrome. Alternating hemiplegia includes both abnormal movements early on and, later, negative phenomenon, namely, hemiplegia.

On the other end of the spectrum are exaggerations of movement and conditions that can be collectively considered "transient or benign movement disorders" because they disappear spontaneously in the course of months or a few years without neurologic sequelae.

All of these conditions should be known to pediatricians and neurologists because misdiagnosing them as epilepsy delays appropriate treatment, exposes small children to the risks of antiepileptic drugs, and creates unnecessary physiologic burdens.[59]

EEG is almost always required to rule out epilepsy, and adding video-EEG recordings increases its value in the study of children with frequent paroxysmal events.[157]

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Chapter 281

Overview: Psychiatric Disturbances

Michael R. Trimble

Introduction

This section is dedicated to the many thousands, probably millions, of people who still receive an erroneous diagnosis of epilepsy, even several years after the publication of the first edition of this book. It is a testament to the broad view of the editors that they have again allotted so much space to this topic, but it also reflects the recognition of the serious clinical issues that surround it.

Historical Perspective

The problem of patients with pseudoneurologic symptoms seen by physicians is as old as the history of medicine,[2] and it became of special interest to neurologists around the end of the nineteenth century, notably with the works of Charcot. Patients with seizures have always been of special interest, so much so that the Salpêtrière school reserved a specific category for such attacks, denoted by the term *hysteria major*. For the first three fourths of the twentieth century, however, interest seems to have dwindled. Even those with a great interest in hysteria, such as Freud and succeeding psychoanalysts, wrote little about seizures, and the borderlands between epilepsy and psychiatry for a long time attracted little in the way of clinical or research interest. Things changed in the last quarter of the twentieth century (see Chapter 199), and with this renewed interest, the question of the misdiagnosis of epilepsy for symptomatically related syndromes, especially psychiatry disorders, was reborn.

Current Problems of Differential Diagnosis

The introduction of new techniques of investigating seizure disorder patients, but especially videotelemetry, led to the realization that many patients who at first sight appeared to have epilepsy and who were given that diagnosis along with prescriptions for anticonvulsant drugs with pronounced sedative effects in fact did not have epilepsy at all.

How frequently this problem occurs is hard to say. It has been estimated, however, that the attacks of up to 20% of patients attending clinics for chronic seizure disorders are nonepileptic in nature, but the epidemiologic studies on this vary, as reviewed by Kanner and colleagues in Chapter 282. The important point is that the figures are not going down with time, in spite of the growing clinical awareness of the problem. These patients often attend for many years, consume large amounts of antiepileptic drugs, and have huge social burdens that in part derive from having been given the label of "epileptic." Why should these errors of diagnosis be so frequent? It is difficult to conceive of a medical diagnosis other than epilepsy that has such important consequences for the patient and that is so frequently incorrectly given.

The problems may be said to begin with terminology. If the words used by physicians are unclear, ambiguous, or misleading, then the concepts that relate to those words will likewise be obscured. The term *pseudoseizures* is popular, but it is problematic. The Oxford English Dictionary defines *pseudo* as "that which is false, counterfeit, pretended or spurious." However, the seizures that are being discussed for the most part have none of these characteristics; they are real. They are experienced by patients, observed by bystanders, and thought about by physicians.

Alternative terms, such as *hysterical seizures* or *hysterical pseudoseizures*, *hysteroepilepsy*, and *psychogenic seizures*, all seem to imply pejoratively that the episodes are false and feigned by a patient for motives apparently unknown, although deception of the doctor essentially is one of them. The designation *psychogenic seizures* entails further difficulties. As Fenwick[1] correctly pointed out, this term should logically be reserved for a form of reflex epilepsy induced by mental activity.

For many, the preferred term for the seizures discussed in the following chapters is *nonepileptic seizures*, thereby acknowledging that these episodes are different from epilepsy, but also that the sudden paroxysmal attacks may resemble epilepsy. The preferred term used in this section is *psychogenic nonepileptic seizures* (PNES), but whatever term is used, it is important that the user have a clear idea of why the label is being given and exactly what is meant. Clarification of concepts, and therefore of patients' problems, cannot be achieved in the middle of a semantic muddle.

The semantic problem leads directly to the problem of differential diagnosis and why the seizures of so many patients are misdiagnosed. Thus, the phenomenon of seizures, not epilepsy, should be at the top of the diagnostic tree (Fig. 1). Many people still confuse seizures and epilepsy and can only equate the two. However, patients come to a seizure rather than an epilepsy clinic (however it is labeled), and during the initial differential diagnosis of a seizure, epilepsy can be considered as only one branch of a diagnostic tree; the other options are numerous. The ready acceptance of the notion that paroxysmal episodes of altered consciousness must be epilepsy is a clinical faux pas on a grand scale, and is in part responsible for the diagnostic errors discussed in the following chapters.

As FIGURE 1 illustrates, the diagnostic possibilities in patients with seizures are considerable. Thus, anyone professing to assess and manage patients with seizure disorders needs more than a passing knowledge of this spectrum of disorders. Because many conditions represented fall within a category of psychopathology, psychiatric experience should be seen as central.

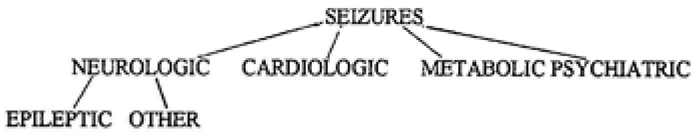

FIGURE 1. Differential diagnosis of seizures.

The chapters in this section cover most of the topics in this diagnostic area, although cross-references are made to some other sections of the book. Although in most cases of epilepsy

a clear diagnosis can be given, it is apparent that this is not so for a significant proportion of patients, who are poorly treated as the consequence of an inadequate diagnostic process. Confusions with psychotic disorders are not frequent, and more often the clinical dilemma falls within the personality disorder/anxiety disorder spectrums. Aggression and its link to epilepsy is an old but important chestnut, and it still remains a problem in psychiatric clinics, where people with spontaneous aggressive outbursts are seen, whose electroencephalogram may be abnormal, and in whom the diagnosis of epilepsy is entertained. The diagnosis rarely turns out to be epilepsy (see Chapter 212), but the referring psychiatrist will need reassurance on diagnosis, and the clinical conclusion may well have important forensic relevance. The space devoted to hyperventilation, panic attacks, dissociation, and PNES reflects both the importance of these overlapping areas for neuropsychiatry and the complexities of the underlying concepts and clinical constructs. Different clinical syndromes within this *olla podrida* of presentations may direct different treatments, and familiarity of referral patterns is therefore important for anyone in a seizure disorder clinic with a broad view on their practice. To simply label someone as having a psychiatric problem and to discharge them from the clinic is simply not helpful because they will appear again sooner or later at another clinic with the same problem, and the expense and morbidity simply increase.

Summary and Conclusions

It is sometimes said that it is better to err on the side of caution and give an uncertain diagnosis of epilepsy if presence of the disorder is suspected but not confirmed. Uncertainties arise, for example, when an electroencephalographic report makes use of the much abused word *epileptiform* or contains unhelpful comments such as "This record does not rule out temporal lobe epilepsy." An uncertainty becomes a probability, and the patient with suspected epilepsy becomes "the epileptic." Ten years later, this has been transformed to "this well-known epileptic." Actually, if the diagnosis is uncertain, it should remain so until further evidence allows clarification. In reality, from a patient's point of view, if an incorrect diagnosis is to be made, it is better to err in favor of a psychiatric diagnosis. The social stigma is rather less, and the drugs given probably have fewer side effects, than if the patient is mistakenly given the diagnosis of epilepsy and treatment based on that diagnosis.

It is hoped that the information in the following chapters will provide helpful information for those wishing to explore the world of seizures beyond epilepsy and for psychiatrists who deal at the interface of epilepsy and psychiatry as well as neurologists. If the seizures of fewer patients are misdiagnosed, the inclusion of this section in a comprehensive textbook of epilepsy will have been justified.

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Chapter 282

Psychogenic Non-Epileptic Seizures

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Tim Betts

Introduction

It has been known since the earliest recorded medical writings[51,100,141,148] that not all seizures in humans are of epileptic origin. From ancient times onward, instruction was given in medical texts about how to determine the clinical difference between epileptic and nonepileptic events. Many modern authorities make an assumption that it is only in recent years, with the advent of the electroencephalogram (EEG), that we have been able to detect this difference, but this is not so. Our forbearers had their own conception of what was epilepsy and what was not. Gowers' meticulous description of the hysterical convulsion bears a close relationship to a type of nonepileptic seizure that we recognize today.

The advent of the EEG and, from the late 1960s, continuous EEG monitoring (with or without video recording) led to an increased interest in distinguishing between seizures of epileptic and nonepileptic origin. It is undoubtedly true that the ability to monitor an EEG over a long period of time and register an EEG during a seizure (and to be able, in tranquility, using video, to retrospectively look at the behavior that the patient displayed during a seizure) has enormously helped our ability to distinguish between events that are epileptic and those that are not.

Nonepileptic seizures (NESs) are paroxysmal events that mimic (or are confused with) epileptic seizures, but which do not result from epileptic activity. NESs can be the expression of organic or psychogenic processes. The type of organic disorders often confused with epileptic seizures include convulsive syncope, various forms of sleep and movement disorders, and migrainous processes and are reviewed in Section XI of this book. The decision as to whether a patient's seizures belong in the domain of epilepsy or nonepileptic events may have to be based on various sets of criteria, in addition to the EEG data. The distinction between epilepsy and nonepilepsy cannot always be made with complete confidence, and the physician working in this field must be able to tolerate some degree of uncertainty. Epileptic and nonepileptic seizures also may coexist. This chapter will focus on nonepileptic seizures of psychogenic origin.

Nomenclature

The most commonly used term for nonepileptic seizures is *pseudoseizure*; this term first came into use in the 1960s and was widely used in the 1970s and 1980s. Yet, psychogenic NESs have been labeled with various eponyms over the last two centuries. For example, Charcot referred to these attacks as "hysteroepilepsy"[77] in the 19th century, and he had recommended the use of ovarian compressors for their treatment, based largely on the theory of the ancient Greeks that such attacks were due to the "wandering of the uterus throughout the body, away from its normal location in the pelvis." Other terms used more recently have included *nonepileptic seizures, psychogenic seizures,* and *hysterical seizures.*

There is an increasing tendency to abandon the term *pseudoseizure* as it is considered to have a pejorative connotation and to imply falseness. Deliberate deceit plays only a small part in the genesis of most nonepileptic seizures (i.e., cases of malingering),[22] although, sadly, many clinicians think otherwise. The term *pseudoseizure* also conveys the implication that anything that is not epilepsy is not interesting and that no further attention need be paid to the attacks.

There is an ongoing debate on the use of the term *seizure* as many patients are unable to discriminate between the concepts of *psychogenic* versus *epileptic* processes and get fixated on the word *seizure*. To avert such potential confusion the term *psychogenic nonepileptic event* has been suggested. Such terms help differentiate the nonepileptic nature of these attacks from epileptic seizures and convey their probable psychogenic cause.

Psychogenic seizures is a term much used in the United States and on the continent of Europe to describe psychologically based nonepileptic seizures. It is correct providing that there is agreement about what it means and the range of disorders it covers. Unfortunately, the term also has been used to refer to those epileptic seizures that are triggered by an emotional experience.[44] Potential confusion could be avoided by using the terms *nonepileptic psychogenic seizure* and *epileptic psychogenic seizure*.

The terms *hysterical seizure*, *hysterical epilepsy*, and *hysterical convulsion* should not be used. The word *hysteria* is no longer used in psychiatric parlance because it is meaningless. It has been so much abused and misused that it should be abandoned,[100] and the term *conversion disorder* should be used instead. Not all nonepileptic attacks are related to conversion disorder.

Functional seizure is also sometimes used, but the term is imprecise and has more than one meaning. An epileptic seizure, for instance, that occurs or is precipitated at a propitious time (e.g., before a stressful event) so that the patient avoids a threatening situation could legitimately be called functional. Blumer[36] has suggested the term *paroxysmal somatoform disorder*. In some ways this is an attractive term. However, it does imply that all nonepileptic events of psychological origin relate to the somatoform disorders when they clearly do not. The term could be used as part of a classification of psychologically based nonepileptic seizures, and this would be more acceptable.

Psychogenic nonepileptic seizure (PNES) is the term that has been chosen for this chapter and is coming into common use. It may not be ideal, but it is less pejorative and more meaningful than *pseudoseizure*; however, clinicians must always ensure that the patients and family understand that the

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inclusion of the term *seizure* does not imply a diagnosis of epilepsy.

Epidemiology of Psychogenic Nonepileptic Seizures

There are relatively little data on the incidence and prevalence rates of PNESs. Various estimates of prevalence have been given by various investigators in different settings. It is important to try to determine the influence that the setting has both on the way that seizures present and on their frequency. Prevalence will be different if patients with new-onset seizures are being assessed in a primary care setting compared with reassessment of patients who have an intractable seizure disorder in a tertiary referral center.

An indirect estimate of the possible incidence of nonepileptic seizures in a primary care setting can be derived from the work of Sander et al.,[121] which was a careful phenomenologic study of patients presenting to their general practitioner with a seizure disorder and who were carefully assessed and followed. It was shown that some 28% of patients suspected of having epilepsy after presentation to their general practitioner either did not have it (7%) or the diagnosis could not be substantiated even a year after the initial presentation (21%). In the only nationwide population-based study done to date, Sigurdardottir and Olafsson found the population-based incidence of PNESs to be 1.4 per 100,000 in Iceland, compared to an incidence of 35 per 100,000 for true epilepsy among persons older than 15 years.[129] In a retrospective study carried out in Hamilton County, OH, investigators established the incidence of PNESs between 1995 and 1998. They found a mean incidence of 3.03 per 100,000, with the highest incidence in 1998 (4.6 per 100,000). Most patients with the diagnosis of PNES were aged 25 to 45 years (4.38 per 100,000).[138]

The prevalence rates of PNESs have been estimated to range from 10% to 40% among patients referred to epilepsy centers for the evaluation of poorly controlled seizures.[26,30,74,77] The prevalence of comorbid PNES and epilepsy varies according to the type of population studied. For example, in a study of 1,590 patients who underwent a video-EEG (V-EEG) monitoring study at the Epilepsy Center of the University of Alabama in Birmingham, 514 (32.3%) were diagnosed with PNES and 29 (5.3%) of these patients were found to have both PNES and epilepsy.[96] Henry and Drury conducted a V-EEG in 145 patients who had temporal interictal EEG spikes and reported ictal semiology characteristic of temporal lobe seizures for presurgical evaluation of medically refractory seizures. PNESs were unexpectedly identified in 12 (8%) of these patients.[57] On the other hand, a study from Germany found that among 329 consecutive patients in whom the diagnosis of PNES was established, 206 (62%) had only PNES, and 123 (37%) had PNES and epilepsy.[118] In a critical review of the literature, Ramsey et al. came to the conclusion that the comorbid occurrence of epilepsy and PNES was rare with prevalence rates ranging between 4% and 10%.[116] Relatively high prevalence rates can be expected when studies are carried out in populations of cognitively impaired or in pediatric patients, however. Neill and Alvarez, for example, reported prevalence rates of up to 40%.[104] Kotagal et al. found that 25% of pediatric patients with PNES also suffered from epilepsy.[75] Higher prevalence rates of comorbid PNES and epilepsy in these two patient populations is not surprising, as they learn that fewer demands are placed on them when they have a seizure. Hence, they are likely to experience a PNES when facing situations that cause distress or that they consciously or unconsciously are trying to avoid.

PNESs are much more common in women than men; in most series 60% to 75% of patients are women.[12,58,77,78,91,93,110,117] The onset of PNESs most often occurs in the third and fourth decades of life,[12,53,77,89] though they have been described in both children and the elderly.[7,42,68,152,153]

Clinical Manifestations

PNESs can mimic convulsive and nonconvulsive epileptic seizures; they may present as isolated events or occur in clusters and, often, may mimic status epilepticus. The advent of V-EEG has facilitated the recognition of PNESs among neurologists and epileptologists, and it appears that nonneurologists are increasingly becoming more aware of this type of paroxysmal event. There have been multiple review articles on the diagnosis of PNES[7,21,54,66,68,71,92,126] and various investigators have tried to emphasize the clinical differences between PNESs and epileptic seizures with lists and tables of distinguishing features.[53,78,89] While certain features of convulsive PNESs may be highly suggestive of this diagnosis, there are no clinical phenomena that are 100% specific to one or the other.[151] Because our ability to recognize PNESs is not infallible and in some patients, with different kinds of events, it is impossible to decide if they have epilepsy or not, a diagnosis cannot be established on the bases of clinical phenomena alone, but has to be corroborated with electrographic recordings, and occasionally, functional neuroimaging studies with ictal single photon emission computed tomography (SPECT) may be necessary to reach a correct diagnosis (see below). In short, the diagnosis of a PNES is based on a considered judgment of all relevant history, seizure phenomena, electrophysiologic data, and results of other investigations and remains a clinical one. Using one or two phenomena in a differential diagnosis table to make a rapid diagnosis would be injudicious and could lead to inadvertent misdiagnosis. Furthermore, several studies published in the last 15 years have demonstrated that clinical phenomena associated with PNESs can occur in certain types of epileptic seizures, a fact that still remains underrecognized by many clinicians, including neurologists, and has often lead to the inverse diagnostic problem (i.e., patients with epilepsy being falsely diagnosed with PNES). For example, in a study of 100 consecutive patients that were undergoing a diagnostic V-EEG, Parra et al.[110] found that referring physicians correctly suspected a diagnosis of epileptic seizures in only 9 (43%) of 21 patients, while 12 (57%) patients were incorrectly thought to have PNESs. This misdiagnosis was especially likely in patients with clinical seizures of mesial frontal or parietal lobe origin. To confuse matters further, there are a number of patients who suffer from both epileptic seizures and PNESs, with coexistence of both types of disorders ranging from 7% to 37%. Most studies have found incidence rates ranging between 10% and 20%.[14,38,58,72,90] This point is examined in greater detail in Chapter 208.

Needless to say, reaching a correct diagnosis is of the essence as a misdiagnosis of PNESs as epileptic seizures, and vice versa, exposes patients to ineffective, costly, and potentially dangerous treatments. Indeed, several investigators have found that 69% to 78% of patients with PNESs have been treated with antiepileptic drugs (AEDs)[14,120] and up to 30% of patients have been misdiagnosed at some point with status epilepticus and admitted to an intensive care unit where they were treated with parenteral medications that are associated with potential serious adverse events, and which in some cases caused respiratory arrest.[59,117,120]

In general, a diagnosis of PNES is easier to suspect in convulsivelike events, while in nonconvulsive events a diagnosis of PNES may be impossible without concurrent electrographic recordings. In the next section we review the value and

limitations of clinical phenomena in suspecting the diagnosis of PNES.

Convulsive Psychogenic Nonepileptic Seizures

Motor Phenomena

In convulsivelike PNES, motor signs include cloniclike, myo-cloniclike, and toniclike movements of the extremities and trunk. However, violent thrashing of the extremities and/or of the entire body, opisthotonic arching of the back, pelvic thrusting motions, and side-to-side head movements are the typical motor phenomena associated with PNESs. Frontal lobe seizures have been shown to present with the same type of motor phenomena; for example, Geyer et al. found pelvic thrusting to be equally common in frontal lobe seizures and PNESs[48] (also see below).

Out-of-phase and asynchronous cloniclike movements in the upper extremities (as opposed to in-phase and synchronous during epileptic seizures) is another "typical" motor sign suggestive of PNESs.[46] However, Leis et al. were not able to make this same distinction in their analysis of the motor phenomena of PNESs.[89]

The absence of any facial cloniclike activity in the presence of generalized cloniclike activity can be another "helpful" sign in suspecting a diagnosis of PNES. Family members need to be instructed ahead of time to look for such sign, however.

Incontinence and Self-injury

Contrary to old beliefs, patients with PNES *do get hurt*. Indeed, in a study by Reuber et al., almost 60% of patients had experienced PNES-related injuries, 32.3% had reported urinary incontinence, and 31.5% tongue biting (patients with both PNESs and epileptic seizures were not included in these percentages).[120] Incontinence has been reported to range between 10% and 44% in PNESs, most of which consist of urinary incontinence, but fecal incontinence has been also described.[95,112,120] Bruising and minor lacerations from falls followed by tongue biting (that may be severe enough to cause bleeding) are among the more common injuries reported in patients with PNESs. Tongue biting, which often does occur in a tonic–clonic seizure, also can occur in complex partial seizures, in faints (if the patient falls and bites the tongue as a result of the fall), and in PNESs (either as a result of falling or as a result of deliberate injurious behavior, not necessarily to simulate a seizure but because the patient is responding to inwardly driven motivation to try to hurt himself or herself). The site of the bite may yield clues but can be misleading. In a tonic–clonic seizure the bite is usually on the side of the tongue and is deep, although it may occur at the tip of it. In tongue injury as a result of falling, the bite is usually at the tip. In complex partial seizures the bite may be at the tip or occasionally at the side of the tongue or may involve the cheek. However, patients having PNESs also can bite the side of the tongue, tip of the tongue, and cheek. Finally, serious injuries, including facial bone fractures, are less common but have also been reported and tend to occur in patients with a psychiatric history of suicide attempts.[112]

Vocalizations

Vocalizations can be often seen in convulsivelike PNESs, but occasionally occur in non–convulsivelike events. Vocalizations associated with shedding of tears tend to suggest a strong possibility of PNESs.[17] In convulsivelike events, vocalizations consist of shouting, screaming, and sobbing often associated with understandable speech.[46,53,89,95] In contrast, in epileptic seizures, vocalizations are typically more primitive, such as grunting or a simple shout.[46] Vocalizations are more likely to occur in the middle of PNESs, unlike epileptic seizures, where vocalizations usually occur at the onset of the event.

Nonconvulsive Psychogenic Nonepileptic Seizures

Nonconvulsive PNESs can mimic either absence and/or partial complex seizures; more often than not, a correct diagnosis is unlikely to be reached until patients are referred for V-EEG with a presumed diagnosis of "intractable epilepsy." Patients may be unresponsive while exhibiting a motionless stare and they may exhibit semipurposeful movements simulating motor automatisms of complex partial seizures.[53] Maintenance of eyes closed and responsiveness to "selective" external stimulation, including verbally, in the course of an event during which they "appear" to be unresponsive are two clinical "clues" that should raise the suspicion of a PNES. More commonly, patients remain nonverbal but display active avoidance to both noxious and nonnoxious stimuli and/or resist attempts at eye opening, but this type of avoidant behavior may also be identified in complex partial seizures.

Other Clinical Characteristics of Psychogenic Nonepileptic Seizures

Sudden collapse to the ground with apparent unconsciousness but no movement can be part of epilepsy and can occur without warning. It is usually a primary generalized seizure (either a tonic seizure in which the patient falls stiffly or an atonic one in which the patient collapses with sudden loss of muscle tone). In both seizures recovery of consciousness (unless the patient has injured the head in falling) is swift and there is little postictal confusion (unless, again, the patient's head has been struck in the fall). Occasionally sudden loss of consciousness with falling can be seen in seizures originating in the temporal or frontal lobe.[28] The fall may be flaccid (but can occur with a tonic spasm), and consciousness usually is regained fairly quickly. The patient who falls in a flaccid way and remains apparently unconscious for some time is unlikely to have epilepsy. Epileptic seizures with falls, if monitored via EEG, may not be detected either because the patient is in bed and the characteristic falling is therefore not seen, or because the fall itself produces such artifact in the recording device that the ictal nature of the event is obscured. It also is possible that the preliminary collapse was due to epilepsy but the subsequent withdrawn behavior is a psychological elaboration of the brief epileptic experience. This may not be an uncommon occurrence.

Psychogenic Nonepileptic Seizures as “Drop Attack”

Physical and emotional causes of collapse are considered in other chapters (e.g., syncope in Chapter 271 and hyperventilation in Chapter 285). A not-uncommon cause of collapse and flaccid unconsciousness of a psychological type of nonepileptic seizure is the so-called swoon.[19] Here the patient, when threatened by external events or unpleasant memories or by a situation reminiscent of an unpleasant experience, will close the eyes, sink to the floor, and lie inert and not moving for various lengths of time, sometimes for over an hour. Passive movement and eye opening may be resisted, but usually the patient just lies inert and unresponsive and comes to quite quickly with little in the way of postictal symptoms. Presumably this is a form of learned behavior; it is a common childhood behavior that may have persisted into adult life. There is some evidence[20,61] that it also may be a common mechanism for avoiding flashbacks and reawakened memories in adults with a chronic posttraumatic stress disorder related to previous childhood sexual abuse, particularly if it was the way that the individual dealt with the abuse at the time it was occurring. Some abused people cope with their abuse by lying inert and retreating into themselves or by splitting their consciousness so that they almost seem to be watching events from a corner of the room and become passive observers of themselves; this may become a persistent unconscious learned pattern of behavior to deal with stressful events and later may be mistaken for epilepsy.

Deliberate Simulation of Unconsciousness

Deliberate simulation of unconsciousness, which may involve falling, is part of the repertoire of people with somatoform disorders or with factitious disorder or malingering (deliberately simulated disease). In the case of factitious disorder, individuals simulate illness to maintain the sick role; malingerers do so for social or financial gain. It is easy to sustain for long periods of time and difficult to detect, particularly if the patient does not resist passive movement or eye opening and does not respond to noxious stimuli. Such behavior (often seen as attention-seeking behavior in nurses and other caring professionals who are particularly prone to factitious disorder) is sometimes mistaken for epilepsy. Some professional simulators may inject themselves with insulin beforehand to add further authenticity to their performance.

Nonstereotypic Events?

PNESs have typically been thought of as nonstereotypic events (within patients), while the reverse has been considered to be a clinical sign supportive of a diagnosis of epileptic seizures. While the absence of a stereotypic semiology within patients should raise suspicions of a diagnosis of PNES, the reverse does not rule out this diagnosis. In fact, in four studies, 60% to 90% of patients with PNESs had spells that varied little from event to event.[38,48,53,99] However, even when clinical features and their sequence is relatively stereotypic, the duration of seizures in patients with PENSs tends to be more variable than in those with epileptic seizures.

Events of Long Duration

PNESs are more often than not significantly longer in duration than epileptic seizures and often lead to a misdiagnosis of status epilepticus (see below). A rapid recovery of cognitive functions following a prolonged convulsivelike or non–convulsivelike event should raise suspicions of possible PNESs (see below).

Psychogenic Nonepileptic Seizures Only Occur in Awake State

PNESs can only occur when the patient is awake, and events occurring out of sleep, documented with electrographic recordings, cannot be considered as PNESs. Having said that, clinicians cannot accept the patients' assertion of events occurring out of sleep without electrographic corroboration, as PNESs have been described in patients that "appear to be asleep" but in reality are awake.[16]

Psychogenic Nonepileptic Seizures Mimicking Status Epilepticus

One of the most serious consequences of PNES is their mimicking "status epilepticus" that is not properly diagnosed, which in turn results in unnecessary admissions to intensive care units, aggressive use of parenteral AEDs, and placement of endotracheal tubes. Iatrogenic damage (respiratory arrests, toxic effects from anticonvulsants) are common, and because PNESs do not respond to AEDs, prolonged hospital stays with expensive and dangerous treatments (including paralysis, anesthesia, and assisted ventilation) often occur.[59,117,120] For example, in a study by Reuber et al., 51% of patients with PNESs presented as "pseudostatus" (lasting more than 30 minutes) and 27.8% were admitted to intensive care units.[120] Howell et al.[59] suggested that perhaps 50% of patients admitted to emergency care in the United Kingdom in status epilepticus do not actually have epilepsy.

Some investigators have suggested that PNES mimicking status epilepticus occurs mainly in women whose seizures relate to a posttraumatic stress disorder from previous sexual abuse,[20,29] in individuals with hyperventilation attacks that are easily prolonged by inadvertent reinforcement, or in patients with conversion or factitious disorder (e.g., Münchhausen syndrome or malingering). Accordingly, emergency room staff should be encouraged to observe seizures critically before starting treatment, to use a pulse oximeter to distinguish patients who need immediate intubation from those who can be safely left to breathe without assistance, and to obtain arterial blood gases, which may also detect those who are hyperventilating.

Epileptic Seizures Mimicking Psychogenic Nonepileptic Seizures

As stated above, a study by Parra et al.[110] suggested that as clinicians have become increasingly aware of PNESs, epileptic seizures with atypical features are being misdiagnosed as PNESs. The error rate in diagnosing nonepileptic seizures in patients who clearly have epilepsy probably lies between 5% and 10%.[116,151] Complex partial seizures of mesial frontal origin can present with complex automatisms, very often with "bizarre" features that mimic the typical phenomena of PNESs. These include kicking or pedaling motions of the lower extremities; thrashing and flailing motions of the extremities or entire body, at times with very violent thrusts; and affect-laden vocalizations, such as screams and loud cries. Other phenomena that may contribute to the diagnostic confusion include a preserved consciousness in seizures originating in supplementary sensory motor area, despite a bilateral tonic posturing, and the absence of postictal lethargy or confusion. Kanner et al.[70] compared the clinical phenomena of supplementary sensory motor seizures with those of PNESs and found clinical phenomena suggestive of PNESs in 82% of all seizures recorded in 91% of the frontal lobe epilepsy patients studied.

The atypical clinical phenomena of these seizures are frequently coupled with undetected interictal and ictal epileptiform activity on scalp recordings. The difficulty in identifying any epileptiform discharges results from the great amount of muscle and movement artifact masking the underlying electrical activity. The inability of the angle subtended by scalp electrodes to identify the source of the epileptic activity in mesial or orbitofrontal regions is another contributing cause to this problem. Thus, it is not surprising that these seizures are frequently confused with PNESs.[70,103,123,147,151] Morris et al.[103] have demonstrated the presence of a subtle rhythmic theta pattern in parasagittal leads, buried within muscle and movement artifact. The use of high-frequency filters may be necessary to recognize such pattern. In addition, the presence of a structural lesion on magnetic resonance imaging (MRI) in mesial or orbitofrontal regions should raise suspicions of epileptic seizures in patients diagnosed with PNESs.

There are certain clinical features that may help the clinician distinguish this type of frontal lobe seizure from PNES: (a) frontal lobe seizures are very short in duration (<30 seconds); (b) they are stereotypic, including the complex automatisms; (c) they often occur out of sleep, whereas PNESa *always* occur in the awake state; and (d) they often display a tonic posturing in abduction of the upper extremities, a sign that was found to be specific to epileptic seizures involving the supplementary sensory-motor area and never seen in PNES.[70,103,147] A cautionary note is in order: PNESs may be reported by patients to arise out of sleep, but V-EEG monitoring demonstrates an awake EEG pattern preceding the onset of the PNESs.[16,139] Benbadis et al.[16] coined the term "pre-ictal pseudosleep" to describe the state of wakefulness while appearing asleep in these patients with PNES.

Comorbidity of Epilepsy and Psychogenic Nonepileptic Seizures

This topic is reviewed in great detail in Chapter 208. Briefly, quoted rates for the coexistence of epilepsy and PNES vary from <10% to >90% of the population studied.[66,68,71,92,116] The literature is confusing because different populations of patients have been studied by different investigators and because of the uncertainty about the diagnosis of PNESs. It is impossible to be dogmatic about how commonly patients with established epilepsy develop PNESs, particularly because the association at times must be purely coincidental, but coexistence of epilepsy with PNESs is not a common problem. Probably no more than 5% of people with established epilepsy develop nonepileptic seizures.

In the literature, completely different methods have been used for diagnosing nonepileptic seizures, based sometimes on EEG criteria (but not necessarily EEGs recorded during the ictus itself), on clinical criteria, or on a mixture of both. It is also sometimes not clear, when the prevalence of the two conditions is compared, whether the investigator is referring to patients with nonepileptic seizures and present epilepsy or merely a history of it in the past. It is likely, as Ramsey et al. have concluded,[116] that if the history is one of past as opposed to present epilepsy, the proportion of patients with both epilepsy and nonepilepsy is likely to be higher, particularly in patients with learning difficulty.[104]

Sometimes the question can only be answered by withdrawing the antiepileptic medication and seeing if epilepsy re-emerges. If it does, one must pose the question, "Was this all epilepsy that I was trying to treat, or am I dealing with somebody who has controllable epilepsy but who has a psychological need for it?"

A review of the literature suggests that 10% to 30% of patients who appear to have established nonepileptic seizures also have a past history of epileptic seizures, which means that even when it is obvious that a patient's seizures are nonepileptic, slow and cautious reduction of anticonvulsant medication is indicated.[66,71] Rapid reduction of anticonvulsant medication, even in patients who do not have epilepsy, may precipitate pharmacologic withdrawal seizures, which will make the picture even more difficult to assess. A final consideration: The literature suggests that if one is assessing a patient with an unknown attack disorder that has two different presentations, 5% to 30% of the time one may be dealing both with epilepsy and a nonepileptic seizure.[116]

Diagnostic Evaluation of Psychogenic Nonepileptic Seizures

Neurologic Workup

The diagnostic workup of PNES consists first and foremost of neurophysiologic studies aimed at capturing the patient's typical events and documenting the absence of a concurrent epileptic ictal pattern. However, the fact that a patient has PNES does not rule out the presence of comorbid neurologic disorders, including a coexisting or past epileptic seizure disorder. In fact, people with a correct diagnosis of NES have been found to have a clearcut history or evidence on examination of cerebral injury,[72,78,118] whereas a significant percentage of people with epilepsy have no such history. Once the diagnosis of NES is established, a psychogenic cause must be investigated with psychiatric and neuropsychological evaluations. Yet, although many people with proven NES have a recognizable psychiatric illness or history or evidence of emotional precipitation of seizures, so do many people with epilepsy. The diagnosis of an NES cannot depend solely on these features but is based on the judicious and considered review of all the evidence available to the clinician. This is particularly important when certain psychological or psychiatric conditions are present in a patient who has an undiagnosed attack disorder. For example, a history of sexual abuse is not uncommon in people with proven epilepsy and may be pathoplastic in the seizure content.[19,52]

The neurologic evaluation of patients with suspected PNES must include V-EEG or ambulatory EEG studies to capture the typical event, and neuroimaging studies including brain MRI to rule out the presence of structural pathology that may be associated with a past or present comorbid neurologic disorder. In addition, the presence of a structural lesion in mesial-frontal regions of the brain may alert the clinician to be cautious on reaching a false-positive diagnosis of PNES and rule out the presence of epileptic seizures mimicking PNESs. In some patients functional neuroimaging studies such as ictal SPECT may be necessary when the distinction between PNES and epileptic seizures with atypical features may be difficult.

Video-electroencephalographic Monitoring

The electrographic diagnosis of PNESs is based on the recording of one of the patient's typical events in the absence of any electrographic change from their baseline "awake" activity. To ensure that a typical event has been captured, the recordings have to be shown to family members who have witnessed the patient's events. Furthermore, it is important to enquire from these family members about the occurrence (in the present or in the past) of events different than those captured during the V-EEG. This will minimize the risk of failing to identify a comorbid epileptic seizure disorder that may be either occurring simultaneously with PNES or a prior seizure disorder that may have remitted with AEDs. Clearly, such information is pivotal on the decision to discontinue AEDs.

When Should Antiepileptic Drug Dosages be Lowered during the Video-electroencephalogram?

PNESs are likely to occur in the early stages of a V-EEG. For example, Parra et al. found that up to 96% of patients with PNESs had a typical event within the first 48 hours of V-EEG.[111] Accordingly, it is reasonable to maintain the patients' usual AED doses during the initial 2 days of the study so as to minimize the risk of facilitating the occurrence of an epileptic seizure early in the monitoring study of patients with both PNES and epilepsy. It has been our experience that once an epileptic seizure has been recorded, clinicians prematurely conclude that all the events are epileptic, leading to a false-negative diagnosis of PNES.

Benzodiazepines should not be discontinued during V-EEG of patients with suspected PNESs, as their abrupt discontinuation may trigger withdrawal seizures or withdrawal psychiatric symptoms, particularly panic attacks and anxiety, resulting in false-negative or false-positive data.

AEDs can be lowered or even discontinued to establish the existence of suspected concurrent epileptic seizures. Such can

be the case in patients with documented PNESs whose V-EEG recordings reveal interictal epileptiform activity and who are reported to exhibit other paroxysmal events that by their semiology may be suspected of being epileptic seizures. In the case of suspected epileptic seizures that preceded the onset of PNESs and remitted with pharmacotherapy, discontinuation of AEDs may not necessarily result in their occurrence during the course of a typical V-EEG.

The Significance of Interictal Epileptiform Activity

Interictal EEGs are reported to be abnormal in 23% to 50% of patients with PNESs; although diffuse or focal slowing is the most common abnormality, interictal epileptiform activity is seen in 35% to 50% of patients with PNESs.[14,38,58,72,78,90,104,116,118] The presence of interictal epileptiform activity in recordings of patients with a documented PNES raises the possibility of comorbid occurrence of PNESs and epileptic seizures, or of a prior history of epileptic seizures. As stated above, this comorbidity has been reported in 5% to 40% of patients with PNESs. Devinsky et al. have shown that the semiology of PNESs and epileptic seizures differ from each other in patients with comorbid disorders.[38]

Ictal Recordings

The absence of any electrographic ictal patterns while the patient is unresponsive documents a diagnosis of

PNES in most patients. However, 10% of patients with epileptic seizures may not show any ictal pattern on scalp recordings, especially when the ictal activity originates from mesial frontal, mesial parietal, and, occasionally, mesial temporal structures.[70,103,123,147,151] In addition, scalp recordings will fail to reveal any electrographic changes in up to 75% of simple partial seizures,[39] given that scalp electrodes are able to detect epileptiform activity only if a cortical area of 6 cm^2 or more has been synchronously activated. Thus, reliance solely on EEG recordings to make a diagnosis of PNES may yield false-positive data. Accordingly, in the presence of paroxysmal events that are not associated with any loss of consciousness and normal concurrent EEG recordings, clinicians must consider the possibility of a diagnosis of simple partial seizures before concluding that they are PNESs. In the presence of events with unresponsiveness, bizarre clinical phenomena, and concurrent undetectable electrographic ictal patterns, a diagnosis of mesial frontal or parietal lobe seizures should be considered in the presence of the clinical characteristics described above. A diagnosis of PNES is more likely in the absence of clinical signs typical of frontal lobe seizures and if these events can be induced and stopped with the use of suggestive techniques.

Special electrodes have been used during the V-EEG to facilitate the detection of electrographic ictal patterns. These include orbitofrontal electrodes and the use of the 10-10 electrodes over parasagittal areas to identify ictal activity of mesial and orbitofrontal origin.[9,67] In these seizures, the electrographic ictal pattern consists of a very subtle rhythmic theta activity over parasagittal regions.[103] Sphenoidal electrodes inserted under fluoroscopic guidance can identify interictal and ictal activity of mesial temporal origin with a very restricted electric field.[69,73]

Induction of Psychogenic Nonepileptic Seizures

The use of induction protocols to trigger a PNES has been the source of much controversy, first with respect to the potential of a false-positive diagnosis (either by provoking atypical events or by facilitating epileptic seizures) and second with respect to the "ethical" use of many of the protocols used that ultimately can lead the patient to feel that he or she was lied to.

There is a general agreement that induction protocols do facilitate the occurrence of PNESs.[11,32,38,87,89,95,111,131,145] Among the different studies, the sensitivity of various protocols has ranged between 37% and 91%, with most studies reporting a successful induction in 77% to 84%.[11,32,38,87,89,131,145] While most studies report the specificity of induction of PNESs to be 100%,[32,38,87,131] there have been reports of epileptic seizures triggered by induction. Walczak et al.[145] reported that 10% of patients with epilepsy experienced seizures after induction; others have also reported similar findings.[92,111] Therefore, a positive induction does not document a diagnosis of PNES, and to avert this type of error, induction protocols should not be carried out in the absence of concurrent electrographic recordings. The study by Parra et al.[111] previously cited is particularly noteworthy as it addresses the question of whether induction protocols are necessary during V-EEG. Indeed, of 100 patients admitted for V-EEG monitoring studies, 87 experienced their typical event and 82 of these did so spontaneously, without induction. Among the patients with PNESs, 96% experienced their typical event without induction in the initial 48 hours. Slater et al.[131] reported similar findings in which 75% of patients with PNESs had spontaneous events without induction.

Several induction protocols have been suggested. Every protocol is based on the use of a "placebo," which raises serious ethical issues and may jeopardize the patient–physician relationship, the patient's trust of all physicians, and the patient's acceptance of the diagnosis of PNESs. The most frequently used protocol consists of intravenous infusion of a saline solution after the patient is told that he or she will be given a medication likely to induce seizures.[32,38,131,145] Other protocols have relied on the placement of an alcohol-soaked patch on the patient's neck after informing the patient that this was likely to provoke a seizure,[87] while other protocols consist of having the patient undergo photic stimulation and hyperventilation, as performed in any routine EEG study. Clearly, with the former two protocols patients may realize that they have been deceived, while the use of hyperventilation and/or photic stimulation does not carry this risk as these are established maneuvers used in all EEG studies to facilitate the occurrence of seizures.

The potential ethical problems associated with induction protocols may put in jeopardy the entire treatment process, as the nature of the protocol precludes informing patients on the true nature of the procedure, and with the exception of protocols using hyperventilation and photic stimulation, clinicians are in essence lying to patients as to the potential effect of the stimulus on seizure activity. Such misrepresentation of the facts can compromise the patient–physician relationship and trust and give the patient reasons to reject outright the diagnosis of PNES and the suggested treatment. Despite these concerns, several authors have defended the use of induction protocols arguing that by aiding in the accurate diagnosis of PNES, induction may help prevent the patient from receiving inappropriate, potentially harmful AEDs and the incorrect diagnosis of epilepsy, with its potential psychological and social hardships, and that therefore the use of induction techniques is ethically justifiable.[37] While no one questions the value of induction protocols, the use of techniques that may lead patients to feel deceived should be a deterrent to the use of induction protocols relying on a "placebo," as the same results can be reached with protocols relying on the use of regular activation methods in EEG such as photic stimulation, hyperventilation, or both combined.[13,111] Finally, the use of hypnosis as a trigger of PNESs has been gaining increasing interest among psychiatrists.[97] Experts in hypnosis, following full disclosure

of the technique, should be the only ones attempting such procedures, however.

Outpatient Electroencephalographic Studies

Attempts to avoid inpatient evaluations and to rely on outpatient diagnostic studies have become necessary with greater frequency in patients suspected of having PNESs, given an increase in medical costs and greater limitations of resources faced by governmental and private third-party payers. Two modalities of outpatient EEG studies have been used: (a) outpatient V-EEG of 2 to 8 hours' duration and (2) ambulatory EEG studies.

Outpatient Video-electroencephalography

There is an increasing body of literature documenting the value of using this type of diagnostic studies. Patients with daily events and those with suspected PNESs are potential candidates. For example, in a prospective study of 37 children with daily paroxysmal episodes, with outpatient V-EEG averaging 3 hours typical events were recorded in 23 patients; in 11 the study allowed clinicians to distinguish epileptic from nonepileptic seizures.[3] In a study of 50 consecutive patients with suspected PNESs, Bahtia et al. used ambulatory V-EEG with the use of an induction protocol consisting of saline infusion.[24] Fifteen patients had a spontaneous event and another 15 had an event induced with induction.

This type of study has an important limitation, as it may fail to record interictal epileptiform activity in patients who may have coexisting rare epileptic seizures or who suffered from epileptic seizures in the past that remitted with AEDs. Clearly, if this type of study is to be used, a detailed history of the patient's present and past events is of the essence, above all when the decision to discontinue AEDs is being considered. Furthermore, some patients may need to undergo a prolonged V-EEG before a definite diagnosis is reached.

Ambulatory Electroencephalography

The advantage of these studies is that the EEG recordings are obtained while the patient is in his or her habitual environment. The disadvantage is that EEG recordings are often masked by movement and muscle artifact during the event, and in the absence of any video, it is impossible for the clinician to establish the nature of the event. Aminoff et al.[6] and Berkovic et al.[18] had concluded that ambulatory EEG studies are useful to identify epileptic seizures. However, events without an electrographic ictal pattern cannot necessarily be considered nonepileptic. Nevertheless, with the availability of ambulatory V-EEG home systems and the ability to use a larger number of channels, and to reformat recordings, ambulatory studies may end up replacing inpatient V-EEG in the future in a significant percentage of cases.

Neuroimaging Studies

Magnetic Resonance Imaging Studies

As stated above, patients with PNES may have abnormal neurologic examinations, EEG studies, and MRI studies. For example, in a study of 45 patients with PNESs, 43% had an abnormal MRI.[72] In these patients, an abnormal MRI finding may identify comorbid neurologic disorders that may explain some of their symptomatology, not related to PNES. More importantly, however, a structural lesion in mesial frontal or parietal regions should lead the physician to seriously reconsider the diagnosis of PNES.

Single Photon Emission Computed Tomography

The use of this type of study can be of great assistance in clarifying whether a paroxysmal event with atypical clinical phenomena is in fact an epileptic seizure mimicking PNES (i.e., partial seizure of mesial frontal origin), provided that the radionuclear marker is injected at the time of the event (ictal SPECT). The epileptogenic zone is represented by an area of hyperperfusion on ictal SPECT. While, the sole use of interictal SPECT yields unreliable data in patients with epilepsy and is of no diagnostic value,[40,105,114,133,135,149] its use in conjunction with an ictal SPECT (SISCOM study) has enhanced the diagnostic yield of data obtained with ictal SPECT. A negative SISCOM or ictal SPECT, however, does not imply a diagnosis of PNES. Conversely, an abnormal SPECT scan does not mean epilepsy is always present. Studies of small series of ictal and interictal SPECT scans in NES revealed a small number of patients with lateralized perfusion abnormalities. The findings did not change, however, when comparing the ictal and the interictal images.[41]

Laboratory Tests

Two blood tests have been used in the differential diagnosis between epileptic and nonepileptic seizures: Prolactin (PRL) and creatine phosphokinase (CPK) serum concentrations.

Serum prolactin levels are commonly elevated following generalized tonic–clonic seizures and complex partial seizures of temporal lobe origin, provided that levels are drawn within 20 to 30 minutes of seizure onset. Prolactin levels are generally not elevated following simple partial seizures, complex partial seizures of frontal lobe origin, or PNESs,[33,35,88,98] though Alving et al. reported a statistically significant increase in prolactin levels in patients following PNESs.[5] Another study reported a significant rise in serum prolactin levels following episodes of hypotensive syncope.[108] The Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology recently published its report on the use of serum PRL in differentiating epileptic seizures from NESs. The authors reviewed the PRL seizure literature and concluded that a twice normal relative or absolute serum PRL rise, drawn 10 to 20 minutes after the onset of the ictus, compared against a baseline nonictal PRL, is a useful adjunct in the differentiation of generalized tonic–clonic seizures or complex partial seizures from NESs.[31] Unfortunately, this test is not useful for differentiating the epileptic seizures that are more likely to be confused with NESs (i.e., frontal lobe seizures) from NES proper, which limits the utility of this test when it is most needed.

Wyllie et al. have reported an increase in serum CPK levels following 15% of generalized tonic–clonic seizures, but not after partial seizures or PNESs.[154] The levels of CPK peak between 18 and 24 hours postictally. Thus, a high serum CPK following a convulsive event is suggestive of an epileptic seizure, but normal CPK *does not confirm* the diagnosis of PNESs. The gap of 18 to 24 hours between event and peak serum concentrations makes this a useful test to consider in outpatients.

Psychiatric Disorders Associated with Psychogenic Nonepileptic Seizures

General Considerations

Two considerations in reviewing the psychiatric diagnoses in PNES are (a) etiologic and (b) epidemiologic. The etiologic

question is, “What is causing the PNES?” The epidemiologic question that arises is, “What are the psychiatric comorbidities in patients with PNES?” We are gaining in our knowledge of the latter, but presently, we have only theoretical approaches for the former issue of etiology. Both etiology and epidemiology of comorbidities are of great importance, as they influence prognosis and may be treatment targets for patients with PNESs.

No single psychopathogenic process is known to cause PNESs. PNESs are clinically classified under different *Diagnostic and Statistical Manual of Mental Disorders,* fourth edition (DSM-IV) diagnoses, including conversion, somatization, and dissociation disorders, and a much smaller percentage as factitious disorder and malingering. A psychosocial stressor (e.g., sexual or physical abuse, loss of a relationship, work stress, parental divorce)[153] is often identified but may take months to uncover.

The presence of a structural lesion in the brain does not preclude a diagnosis of nonepileptic seizures,[90,94] and the presence of a psychological disorder does not preclude a diagnosis of epilepsy. Many psychiatric conditions are overrepresented in the population of people with epilepsy.[85] Thus, mood and anxiety disorders are pervasive both in epilepsy and in PNESs. Neurologists have underrecognized patients who have a severe anxiety or depressive disorder along with their neurologic disorder.[63]

Etiologic Diagnostic Considerations

Somatoform Disorders

These are a group of disorders in which physical symptoms or signs present without any apparent physical cause and which have an assumed psychological cause. They are distinguished from factitious disorder and malingering. There are several subdivisions of the somatoform disorders, of which two are particularly important in patients with PNESs, conversion and somatization disorders.

Conversion Disorder.

The DSM-IV diagnostic criteria for conversion disorder are the presence of one or more symptoms or deficits affecting voluntary motor or sensory function that suggest a neurologic or other general medical condition; psychological factors are judged to be associated with the symptom or deficit because the initiation or exacerbation of the symptom or deficit is preceded by conflicts or other stressors. The symptom or deficit is not intentionally produced or feigned (as in factitious disorder or malingering).

The diagnosis, now, is based not on psychological guesswork as to what is going on in the patient's mind, but on observable phenomena. This laudable attempt to simplify the definition of conversion disorder and therefore make it easier to diagnose has unfortunately resulted in the concept of dissociation (which many European psychiatrists would feel is an essential part of conversion disorder) being relegated to a completely different diagnostic category that will be briefly considered later.

Conversion disorder (unlike the old concept of hysteria and Briquet syndrome) has therefore become almost exclusively neurologic, and seizures feature prominently in its definition. A large proportion of people with PNESs fall into this diagnostic category. It is a diagnosis that is easy to make but one that psychiatrists and neurologists find difficult to substantiate because of each profession's discomfort with the elements of “the other profession.” While it is open to misuse (because it is partly based on subjective criteria), a positive diagnosis of conversion disorder can be made in the context of acknowledging the diagnostic criteria; a thorough history, oftentimes uncovering a series of medically unexplained symptoms; and a nonneuroanatomically based examination.

The emotional problems that are causing the conversion disorder are often discoverable, particularly in the early stages of the condition, but not always. Many people with genuine physical symptoms also have psychological problems that may sometimes exacerbate their symptoms. Examples include patients with multiple sclerosis who might embellish their responses on physical examination, in order to “help” the examiner. It is important for patients to see the connection between the symptom and problem for themselves rather than having someone else's explanation being forced on them.

Somatization Disorder (Previously Known as Briquet Syndrome).

The full DSM-IV diagnostic criteria are basically related to a history of many sustained, relentless, multisystem physical complaints without neuroanatomic basis, but which are not intentionally produced, occurring over a long period of time with many treatment requests and significant social impairment. Some patients whose primary presenting symptoms are PNESs fall into the category of somatization disorder if a careful assessment is made and a complete medical and surgical history is taken. Care must be taken, however, realizing that some somatic and psychiatric disorders (e.g., connective tissue disorders, depression) can cause widespread somatic complaints, often over long periods of time, which can be mistaken for a somatoform disorder.

Dissociative Disorders

Dissociation is defined as disruption in the usually integrated functions of consciousness, memory, identity, and perception. Splitting of apparent consciousness from present experience can present as amnesia, as a fugue state, as an identity disorder, or as depersonalization and thus may enter into the differential diagnosis of paroxysmal behavior. Depersonalization, amnesia, and, occasionally, fuguelike behavior also may occur as symptoms of epileptic activity.[127,134,155] Dissociative amnesia is currently much associated with theories about repression of later recovered memories of previous childhood abuse. There is some evidence[20] that some particular types of PNESs (swoons and abreactive attacks) are more common in people who have disclosed a previous history of sexual abuse as a child. Swoons can be described as a kind of dissociative state related to avoiding unpleasant memories; abreactive attacks can be seen as an acting out of unpleasant memory flashbacks. Some clinicians argue that dissociation is the underlying mechanism in PNESs based on studies showing that patients with PNESs score higher on dissociative experiences scales than patients with epilepsy.[2,115]

Factitious Disorder

Factitious disorder is a deliberately simulated disease, the simulation of which does not appear to convey any advantage except that of assuming the sick role. External incentives, unlike in malingering, are absent. The condition is therefore inwardly driven by psychological forces, although the patient is aware of the deception. Patients may display considerable ingenuity in maintaining the deception and often deny deception. A smaller proportion of people with NESs belong to this group. Their performance may be polished and practiced. They may, in the interests of verisimilitude, even inflict physical damage on themselves and repeatedly present to different emergency rooms, apparently in status epilepticus. This is sometimes referred to as Münchhausen syndrome.[122]

Diagnosis can be difficult and should not be made until the team managing the patient is absolutely certain that it is correct. Premature diagnosis without concrete evidence, based purely on the puzzling nature of the patient's symptoms, can be a costly mistake.

A variant of factitious disorder is Münchhausen disorder by proxy, in which factitious symptoms of a disorder (often a seizure disorder) are produced in a dependent (usually a child) of the complainant.[4] The actual victim is usually a child, but it is the parent or caregiver who has the factitious disorder and the kind of personality that wants not so much to be in the sick role, but to have someone dependent on them in the sick role. In caregivers (such as nurses) who exhibit this behavior, there is also often a compulsive need not just to have people dependent on them, but to be seen as the dramatic rescuer of the victim. Unfortunately, such personality types are often attracted to nursing, and nurses are particularly likely to show factitious disorder or to initiate Münchhausen syndrome by proxy. This can have an unfortunate rebound effect on nurses with genuine illnesses.

Malingering

Malingering is not a psychiatric disorder, but one where there is a voluntary and conscious production of symptoms (and signs) for gain. The motivation might be to avoid a court case or to obtain disability payments or medication. Nonepileptic seizures are infrequently part of the repertoire of someone who is deliberately malingering.[55] Here the false symptoms and signs are being produced to change external circumstances rather than being internally driven and are usually easier to understand. People who use seizures for malingering purposes are often practiced and accomplished and much harder to detect. Unfortunately, some people who have had a chronic disability such as epilepsy and who have gained financial support as a result (as is only right and proper) may be reluctant to abandon their symptoms because they will lose the benefit if they do. Some people in such a situation may unconsciously or consciously simulate their seizures, long after the seizures themselves have stopped, in order to continue to gain benefit.

A clear distinction cannot always be made between somatization disorder, conversion disorder, factitious disorder, and malingering as the conditions blur into each other (it can be difficult to decide sometimes whether someone's motivation is truly unconscious). Apparent motivation is also based to some extent on a clinician's subjective interpretation. Currently, there are no diagnostic tests that definitely rule in or rule out conscious or unconscious motivation.[80]

Epidemiologic Considerations: Comorbid Diagnoses in Psychogenic

Nonepileptic Seizures

Bowman's review revealed that many patients with PNESs also suffer from mood (12% to 100%), anxiety (11% to 80%), personality (33% to 66%), nonseizure conversion/somatoform (20% to 100%), and nonseizure dissociative disorders (up to 90%) co-occurring with their primary PNES diagnosis of conversion, somatoform, or dissociative disorder.[25] The diagnostic frequencies noted in Bowman's PNES population studies using the DSM-III-R were confirmed in a French study using the DSM-IV criteria.[102] Axis II personality disorders also are found in patients with PNES, largely, but not exclusively, of the impulsive, cluster B personality.

Mood Disorder

Mood disorders are common in people with epilepsy. Both depression and hypomania are probably more common than would be expected by chance.[62] The prevalence of mood disorder, particularly depression, is also high in people who have PNESs.[27] It is unlikely that depression itself causes nonepileptic seizures, but the onset of depression is well known for releasing psychopathologic behavior, including conversion disorder.[113] Depression in some patients with PNESs may be related to the environmental stressors and life circumstances that have caused the seizures themselves. Mood disorder is also prominent in somatoform disorder (which may independently be associated with PNESs) and may need to be treated independently.[132]

Anxiety

Nonepileptic seizures are often associated with panic disorder with or without agoraphobia. The DSM-IV defines a panic attack as a discreet period of intense fear or discomfort in which four or more autonomic symptoms develop abruptly and reach a peak within 10 minutes, including palpitations, tachycardia, diaphoresis, tremulousness, dyspnea, feelings of choking, angina, dyspepsia, feeling dizzy, feeling lightheaded, feeling faint, paresthesias, and temperature changes, along with derealization, feelings of unreality, feelings of depersonalization, feelings of being detached from oneself, fear of losing control or going crazy, or fear of dying.

Some panic attacks are, of course, accompanied by hyperventilation (indeed, some of the above panic symptoms are related to hyperventilation) and at times can lead to apparent unconsciousness and be mistaken for epilepsy.[23] Panic attacks also may be mistaken for epilepsy if they occur in the context of agoraphobia or a specific phobia.[124] The agoraphobia or other anxiety symptoms may be mistaken for an emotional reaction to the mistakenly diagnosed epileptic seizure.[47] Patients with generalized anxiety disorder also may be mistakenly diagnosed as having epilepsy if the symptoms of their anxiety are such as to suggest a temporal lobe origin for them.[130] Anxiety also can coexist with a somatoform disorder, which may itself give rise to nonepileptic seizures.

Panic disorder, agoraphobia, specific phobias, anxiety disorder due to epilepsy, or adjustment disorder with anxiety related to epilepsy can all occur in people with genuine epilepsy, making differentiation difficult.[125]

Posttraumatic stress disorder (PTSD), in which sudden intrusive memories (flashbacks) or dissociative experiences occur, can be mistaken for epilepsy, particularly if the flashback leads to an alteration in behavior.[29] Occasionally patients can develop a posttraumatic stress disorder related to their epilepsy if they had a seizure in a particularly frightening or life-threatening situation (e.g., a patient who had a tonic–clonic seizure in the bath and had to be rescued by strangers). Related to their histories of trauma and abuse, patients with PNESs have high frequencies of PTSD.[27] There is a significant literature on the association between childhood or adult trauma and abuse and the development of PNESs with PTSD.[45]

Finally, anxiety commonly co-occurs with a mood disorder, and it can sometimes be difficult to decide which is which. Both can occur in epilepsy, and both may be present in people with PNESs.

Psychotic Illness

A few patients with PNESs also may have a coexistent psychosis, and the seizures may sometimes have a relationship to the patient's disordered psychopathology. Psychoses occur in people with epilepsy, and sometimes the phenomena of schizophrenia (catatonia, made movements) can be mistaken for epilepsy.[142]

The Role of Psychometric Testing in the Diagnosis of Psychogenic Nonepileptic Seizures

Psychological Tests

As an adjunct to the gold standard V-EEG diagnosis of PNES, some clinicians use psychological tests. When used with V-EEG, the Minnesota Multiphasic Personality Inventory (MMPI) is a useful predictor of PNESs[136]; however, its reliability and validity in detecting patients with PNESs also has been criticized.[65] Derry and McLachlan[36] have shown that the revised version of the MMPI (the MMPI-2) discriminated with a 92% rate of accuracy between patients with epilepsy and patients with PNESs. They also felt it useful in detecting those patients who have epileptic seizures but who have marked psychopathology, and who, therefore, also may have PNESs. People with PNESs demonstrate a personality profile suggestive of a conversion or somatoform disorder.

Hypnosis also has been used as a diagnostic tool for PNES for over half a century.[137] Kuyk et al. used the technique for recovering memory in psychogenic amnesia and recalling memory of events taking place during the seizure itself with the premise that if ictal memory can be recovered, then the event is a nonepileptic one, and found 100% specificity and 85% sensitivity for a diagnosis of PNES.[79] Barry found that using the hypnotic induction profile reliably distinguished patients with PNES from those with epilepsy.[10]

Cragar et al. reviewed the literature on adjunctive tests for diagnosing PNES and reported sensitivity and specificity of the different measures.[34] A summary of their findings noted that PNES and ES patients did not differ on intelligence tests or on neuropsychological (NP) measures consistently. Both PNES and ES groups did have cognitive deficits when compared to normal controls, and the PNES group tended to perform better than patients with ES on various NP tests. Similarities and differences in these tests are discussed more fully in Chapter 208.

Prognosis/Predictors of Psychogenic Nonepileptic Seizures Outcome

Depending on the psychiatric makeup of the individual with NES, outcomes vary. Kanner et al. found that the presence of a mood disorder, a history of abuse, and a personality disorder were associated with a higher frequency of a patient having persistent PNESs.[72] Betts and Boden suggested that the short-term prognosis of nonepileptic seizures was relatively good, but that relapse, once the patient was discharged into the community, was frequent.[19] Also, a significant number of patients continue to have PNES, even with the institution of therapy.[1] Walczak et al. investigated the outcome of 72 patients with V-EEG–diagnosed PNESs, followed for a mean period of 15 months (range, 12 to 22 months). Patients were asked about the frequency of PNESs in the last 6 months, AED use, occupational status, and extent of psychotherapeutic treatments. PNESs had ceased in 18 patients (35%), decreased >80% in 21 (41%), and decreased <80% in 12 of 51 (24%). Thirty-three patients (65%) were not taking AEDs. Occupational status improved in 20% and did not change in 75%. Overall, 29 of 51 (57%) rated themselves markedly improved and 15 of 51 (29%) rated themselves unchanged or worse. Persisting PNESs were significantly associated with longer duration of PNES before diagnosis and presence of additional psychiatric disease. Persisting PNESs were not associated with gender, presence of epileptic seizures, or extent of psychotherapeutic treatments after diagnosis.[144]

A handful of studies have demonstrated that a certain population of patients with PNESs experience complete remission of their events after their diagnosis is given, even in the absence of any therapeutic interventions. One group reported that 18 of 22 patients with PNESs had a reduction of PNESs in the 24 hours postdelivery of their V-EEG diagnosis.[43] One-year follow-up, however, revealed that 87% of patients with PNES had the return and persistence of their PNESs.[146] In the study by Kanner et al.,[72] 13 of 45 (29%) patients stopped having PNESs after the diagnosis was established and remained free of events until the last follow-up 6 months later. Unfortunately, most of the studies published to date suggest that only about one third of patients had stopped experiencing PNESs at the time of follow-up, 1 to 5 years after diagnosis.[120]

Long-term outcome studies yield disappointing outcomes. Krumholz and Neidermeyer evaluated the prognosis of PNES in 41 patients discharged from the Johns Hopkins Hospital who had follow-up data of 5 years or longer after discharge.[78] Among these 41 patients, there were coexisting organic neurologic disorders in 18 (44%) and mental retardation was identified in 17%. Concurrent epileptic seizures were found in 37% and EEG abnormalities found in 38%. Persistence of PNESs was found in 56% of patients, which was associated with psychosocial problems.

On the other hand, a significantly better outcome has been found in outcome studies of children and adolescents. For example, Wyllie et al. compared the outcome of PNESs documented by V-EEG in 18 nonepileptic children and adolescents (ages 8 to 18; median, 14.5 years old) and 20 adults (ages 25 to 56; median, 34.0 years old).[152] The outcome was significantly better for the younger patients at 1 year, 2 years, and 3 years after diagnosis, as 73%, 75%, and 81% of children and adolescents were free of events at these follow-up times, respectively; at the same follow-up times, the percentages of adults free of psychogenic attacks were only 25%, 25%, and 40%.

In a recent study of 147 patients with PNESs contacted after a mean of 4.2 years after diagnosis (mean age at follow-up, 38.1 years), Reuber et al. found that 71.4% continued to have PNESs, and 28.6% had achieved seizure remission[119]; 60.0% of patients with continuing PNESs and 42.7% of patients in remission were “unproductive.” More severe psychopathology was associated with persistence of PNES and unemployment.

Understanding the role of certain psychiatric and neuropsychological variables in the PNES outcome of our patients can be of paramount importance in planning treatment strategies. For example, in a prospective study of neurologic and psychiatric predictors of PNES outcome in 45 patients carried out at the Rush Epilepsy Center, the persistence of PNESs was investigated at 1 month and 6 months after diagnosis.[72] Three outcome patterns were identified: (a) uninterrupted PNESs (n = 20), (b) transient cessation of PNESs for a period of at least 3 months with subsequent recurrence (n = 12), and (c) cessation of PNESs since diagnosis (n = 13). The 20 patients that continued with uninterrupted PNESs were significantly more likely to have a history of abuse (physical, emotional, sexual, mixed), a history of recurrent major depression, a personality disorder, and a history of dissociative disorder (not presenting as PNESs). Given the frequent history of abuse, it is reasonable to expect that PNESs are an expression of a dissociative process. This observation is further supported by the higher frequency of a history of dissociative disorder that preceded and presented in forms other than PNESs. Thus, the uninterrupted persistence of PNESs in these patients is not surprising, since the mere fact of being told that they do not have epilepsy is meaningless to them. Indeed, as long as their events are the expression of a “dissociative state” and patients have not found

other means of dealing with stress, PNESs are expected to persist. Furthermore, having made the connection that their events constitute a dissociative process does not necessarily result in their cessation. Of interest is the fact that, despite their severe psychopathology, 17 of these 20 patients readily accepted the psychogenic nature of their events, and were able to recognize their PNESs as a form of dissociation soon after their diagnosis was discussed with them.

Twelve of the 45 patients experienced a transient cessation of PNESs following the diagnostic V-EEG for a period of at least 3 months. They differed from those with the two other outcomes in two areas: They were more likely to deny the presence of any psychiatric or psychological problems. In fact, 8 of the 12 patients with this outcome refused a recommendation to start psychiatric treatment. All patients accepted that their events were not epileptic, however. In addition, patients in this group were more likely to develop new somatic complaints after the diagnosis of PNES was established. In these patients we suspect that somatoform/conversive disorders are mediating their PNESs, in contrast to patients with persistent events who were more likely to have a dissociative disorder.

Thirteen patients stopped experiencing PNES after diagnosis. Paradoxically, this group of patients is the most puzzling from a psychiatric standpoint. Most had psychiatric disorders of mild severity, but in 5 of the 13 patients, *no current psychopathology* was identified during the psychiatric and neuropsychological evaluations. In those cases, no psychiatric treatment was suggested and they were followed in the clinic with visits every 3 months initially and then every 6 months. In the other patients, treatment was tailored to the nature of the identified psychiatric disorder. One of the 13 patients refused referral for psychiatric treatment; yet, there was no PNES recurrence up to the time of the last follow-up visit. The findings of this study provide relevant information to clinicians. Patients who stop having PNESs after disclosure of diagnosis differ significantly in their psychiatric profile from those who experience PNES recurrence. Among the latter patients, a distinct psychiatric profile can be associated with a particular PNES recurrence pattern. These findings suggest that more than one psychopathogenic mechanism is operable in PNES. Second, the psychiatric variables identified commonly in these patients can be predictive of PNES recurrence.

Presentation of the Diagnosis of Psychogenic Nonepileptic Seizures

In any medical disorder, acceptance of the diagnosis is the first step in the therapeutic process. In the case of PNESs, presentation of the diagnosis of PNESs is a pivotal step in helping the patient "come to terms" with a diagnosis that implies a "psychogenic cause." Reluctance to accept the diagnosis of a psychogenic process on the part of the patient may be based on concerns that family members and friends will think that he or she is "crazy" or that he or she is "faking" the spells to get attention or avoid responsibilities. Yet acceptance that the patient's events are not epileptic seizures or events of organic origin is of the essence as the biggest potential source of morbidity and mortality are the physicians in emergency rooms who may not recognize the true nature of the events and treat the patient as one in status epilepticus.

Often the way the diagnosis is presented to the patient and family members accounts for their refusal to accept it and by the same token to refuse recommendation for psychiatric treatment. Interestingly enough, there is no consensus among experts on what is the best way of presenting the diagnosis. At a treatment workshop on PNESs sponsored by the National Institutes of Health and the American Epilepsy Society held in May 2005, it became very clear that there are no systematic data to determine the best protocol to follow in discussing the diagnosis of PNES with patients and family.[140] For example, the following questions were raised: (a) Should a psychogenic cause be implied automatically if no organic cause can be identified, even before a psychogenic cause or evidence of psychopathology has been established? (b) Should the diagnosis be presented by the neurologist or should the psychiatrist (or the psychologist) be present at the meeting?

Shen et al. developed a protocol for the presentation of the diagnosis of PNESs that is now considered classic by many epilepsy centers.[128] This protocol contains six main points:

1. A review of the recorded events with the patient and family to ensure that the captured event is typical for the patient.
2. Explanation in "positive terms" of the nature of the spells (i.e., their nonepileptic cause), and hence the possibility of discontinuing AEDs.
3. An acknowledgement that the nature of the event is yet to be established, and that its cause may not always be found.
4. The observation that in many cases, such events may be of psychogenic origin (with an added explanation that the causes may be related to "upsetting emotions" that remain unconscious (i.e., and therefore the patient is unaware of) and that an evaluation by a psychiatrist, psychologist, or counselor may be indicated. Shen et al. emphasized that having these types of conflicts in no way implies that the patient may be "crazy."
5. Making the observation that a history of sexual abuse is often encountered in patients with these events.
6. A statement to the effect that the spells may spontaneously resolve on their own and that, although one component is subconscious in nature, "one can exert a conscious voluntary effort to abort these attacks."

We have borrowed on most of the points raised in Shen's protocol when discussing the diagnosis of PNES with patients and family members at the Rush Epilepsy Center. We are careful, however, not to impute a psychogenic cause in the absence of evidence obtained in the course of a psychiatric evaluation, informal discussion with the patient and/or family, or neuropsychological data. Furthermore, while we also tell our patients that their spells may stop occurring just by knowing that they are not epileptic in nature, we do not suggest to them that they can exert a conscious voluntary effort to abort these attacks. Our reasons are threefold: First, unless the patient is malingering (which is a minority of the cases), we do not believe that the patients have a conscious control over the occurrence of their events, at least at the beginning. Second, patients (and family members) may often interpret such observation as a suggestion that they are voluntarily faking the events, which in turn raises their resistance to accept the diagnosis further. Third, we are convinced that the exertion of control of the events occur eventually, as a result of the treatment (see later).

It is only after the above-cited explanations that we ask patients if they think that their episodes may be related to a psychogenic process, if they have not volunteered that observation on their own. From this point on, we guide the discussion according to the answer we get from the patient:

1. If patients accept the possibility of a psychogenic process as a cause of their spells, we encourage them to

elaborate on their reasons and to cite examples that may illustrate potential conflicts, and we suggest that they undergo a complete neuropsychological and psychiatric evaluation.

2. If patients acknowledge a history of abuse or having been victims of traumatic experiences, we ask them to recall

how they "dealt" with such situations at the time of their occurrence. It has been our experience, and that of others, that most patients have no recollection of the actual traumatic event(s). We use that "personal" experience to illustrate the phenomenon of dissociation, by again reiterating the fact that "when individuals is facing a traumatic experience, their mind will automatically protect itself by blocking any awareness of their surroundings." We then add, "This is similar to what may happen when you are having a spell" and go on to explain that after repeated traumatic experiences, one's mind may learn to automatically "shut out" the outside world, *even in the presence of less traumatic situations*. We repeat the statement, "There is only so much trauma one person can endure before fending the traumatic experience off one's mind." Usually, patients with a history of abuse can easily relate to these observations. This, in fact, becomes the beginning of the therapeutic process. We emphasize to these patients that their process of dissociation will most likely continue until they learn, with the assistance of a counselor, to identify the precipitants, which by now need not be necessarily of a traumatic nature.

3. In the case where patients *adamantly refute* the possibility of any psychogenic cause to their events, we suggest that they undergo a neuropsychological and neuropsychiatric evaluation to rule out that possibility. We reiterate the unconscious nature of these processes, which may preclude patients from recognizing an underlying psychological process. At the same time, we acknowledge the possibility that their spells may not have a psychogenic cause and that we may not be able to find a cause by the completion of the evaluation. We always add, "If we don't look for it, we'll never find it. It's better to rule out completely a possible psychogenic cause." Patients are told that we would like to continue following them in the clinic and we ask them to keep a diary in which they are to write down the circumstances surrounding the occurrence of future events, were they to continue. Note that we do not push patients to accept a psychogenic cause of their spells when it becomes obvious that they are not ready. In our opinion, the best course to take with such patients is to continue following them in the clinic, strengthening our relationship and their trust in us, while at the same time we continue reminding them that their spells are not epileptic (and that no other organic cause has been identified). In our experience, patients eventually end up accepting our recommendation for psychiatric treatment after a few months. During that time we continue achieving our primary therapeutic goal: Averting that their spells be treated as epileptic seizures by other physicians.

4. Occasionally patients may be adamant about their certainty of some organic or epileptic process triggering their spells, and that we may have erred in our evaluation. While in such patients we are likely to suspect a factitious disorder or malingering, we try to keep an "open mind." We review the diagnostic process with patients, show the captured events and recordings of epileptic seizures, and graphically demonstrate on the actual paper to both patients and family the differences between the two. If the diagnosis was based on an ambulatory EEG study, we repeat the evaluation in an inpatient V-EEG monitoring unit, with the use of sphenoidal electrodes. In fact, we have had three patients in whom an erroneous diagnosis of PPS was reached with ambulatory EEG studies. Two of the three patients had neuropsychological testing that failed to reveal any propensity for conversive disorder. A correct diagnosis of epilepsy was established during V-EEG. In short, we must *always* consider the fact that patients may be correct. After all, they know themselves better, notwithstanding the unconscious nature of a potential psychogenic process.

Treatment of Psychogenic Nonepileptic Seizures

General Considerations

In the treatment section, we address the transition from neurologist to psychiatrist, the use/withdrawal of AEDs, pharmacotherapy, and psychotherapy for PNESs. Before examining the various aspects of the treatment modalities, there are certain important general points that must always be borne in mind in conceptualizing the treatment of patients with PNESs.

The first point is that patients (and their families) may well have been living with the assumed diagnosis of epilepsy for a considerable period. When patients who have been treated for epilepsy are diagnosed with

PNESs, they are immediately transformed from a "neurologic" patient to a "psychiatric" one.[81] Suddenly changing the diagnosis, however justified it may be, can have a profound psychological effect on the person who receives the new diagnosis, particularly because that person may already have a recognizable psychiatric disorder and may be living with a dysfunctional family. We have frequently encountered the patients who react with, "So, you are saying I'm crazy?!?" From the epilepsy monitoring unit, a number of patients are referred, then lost to follow-up. Therefore, the confrontation process must be handled tactfully and appropriately.[22]

Neurologic Treatment (or, "How Long Should the Neurologist Follow the Patient with Psychogenic Nonepileptic Seizures?")

The neurologist's task, once a firm diagnosis of nonepileptic seizures has been made, does not suddenly cease. The neurologist should continue to offer support to the patient while arrangements are being made for ongoing care. The parting of the ways between the patient and the neurologic specialist should certainly not be an abrupt one. The neurologist should certainly remain available for consultation in case new seizure types develop or there remains some doubt about the certainty of the diagnosis (particularly as new investigatory methods emerge). Although reinvestigation can be justified on occasion, this should only be undertaken if there are clear clinical indications that the diagnosis may have been wrong.

In our opinion, discharge of patients with PNESs from their neurologist's practice should not take place before they have had an opportunity to complete the transition of their care to the psychiatrist or psychologist to whom they were referred. Furthermore, the neurologist may well need to remain in contact with the patient while a slow reduction is made in anticonvulsant medication. Reducing medication on which the patient may have become psychologically and pharmacologically dependent should always be slow. Abrupt termination of some anticonvulsants will lead to pharmacologic withdrawal seizures, which complicates the diagnostic picture. As a matter of ethical necessity, the neurologist should make certain that his or her patient has been appropriately placed with another care team or facility that is competent to manage the nonepileptic seizures. Abrupt termination of the relationship between the neurologist and the patient will make the next doctor's job much harder.

Communication and collaboration between neurology, psychiatry, and psychology in the process of diagnosing and treating the patient with PNESs is an essential part of the multidisciplinary approach needed to assess and manage these patients. Harden et al. noted psychiatrists' lack of confidence in the V-EEG diagnosis as compared to neurologists,[56] and interdisciplinary discussion may improve management of PNESs. A model of PNES treatment has been proposed, composed of accurate diagnosis with V-EEG by the epileptologist; presenting the diagnosis to patients and their family; constructing a problem list of precursors, precipitants, and perpetuating factors of PNES; and prescribing psychotropics, with discontinuing AEDs in lone PNESs, or adjusting appropriately in mixed ESs/PNESs.[83] While no single treatment has been shown to treat all NES patients, the National Institutes of Health and the American Epilepsy Society have supported an international PNES treatment workshop where neurologists, psychiatrists, and psychologists convened to discuss and develop various models to be systematically tested.[140]

Psychiatric Treatment

Ideally, a psychiatrist asked to manage a patient with nonepileptic seizures should have had some experience in this area, should be part of the team that has been assessing the patient, should have confidence in the diagnosis of nonepileptic seizures, and, in particular, should not feel (as sometimes happens) that a difficult patient has been dumped in his or her lap by a neurologic service eager to be rid of the patient. Patients being dismissed sometimes results in the rapid return of the patient to the neurologic facility or, worse, the patient being abandoned by everybody and the whole diagnostic process having to be reundertaken.

Psychiatric assessment of the patient should start long before the diagnosis of PNES is finally given so that the patient's upbringing, social background, personality development, present living circumstances, and relationships with other family members (plus the presence or absence of contributing traumas such as abuse) are already established.

Pharmacotherapy

Barbiturates have been used in diagnosing and treating patients with conversion disorder effectively for over a half a century.[86] Open-label trials of antidepressants in patients with conversion disorders have shown some response.[107,143] Controlled studies of the benefit of psychotropics in PNESs, however, have not been completed, and apart from anecdotal reports, their effect in PNES is unknown.[84] Formal medical psychiatric treatment is necessary for the treatment of any underlying psychotic disorder or depression. Whether antidepressants directly treat PNESs has not been studied in a controlled fashion. Another approach being studied in NES treatment is to treat the comorbid psychiatric disorders (depression and anxiety frequently occur with PNESs) to reduce PNESs. A pilot randomized controlled trial of a selective serotonin reuptake inhibitor (SSRI) for depression and anxiety in patients with PNESs is under way.[82] Benzodiazepines have also been shown to reduce PNES in open-label studies.[8] When pharmacotherapy of the patient's mental state is used, it should be accompanied by psychological support, if not formal psychotherapy.

Clarifying the role of AEDs in patients with PNESs is another major pharmacotherapy issue to be addressed by the treating neurologist and psychiatrist. During the process of withdrawing anticonvulsant medication, psychological symptoms may emerge (e.g., a previously undiagnosed mood disorder with carbamazepine withdrawal or significant anxiety symptoms with benzodiazepine withdrawal). Oto et al. showed that AEDs could be safely discontinued in patients with lone PNESs after V-EEG monitoring.[109] Some have argued for the mood-stabilizing benefits of AEDs as a reason to continue the antiseizure medications. AEDs, however, do not treat PNESs, and toxicity may exacerbate PNESs.[106]

Psychotherapies

If the psychiatrist is not delivering the psychotherapy personally, he or she may work in collaboration with psychologists and nurse practitioners who administer the therapy. The various therapies for PNES are described below.

Cognitive and Behavioral Techniques

The general principle of the behavioral techniques used in managing PNESs is to prevent the reinforcement of seizure activity and to reward and reinforce nonseizure activity (operant conditioning).[60] A randomized controlled trial of cognitive behavioral therapy (CBT) for NESs is being conducted based on an open-label CBT trial in the United Kingdom.[50] It is important to recognize that all the behavioral and cognitive techniques described below are equally applicable to epilepsy itself.[49] This is one reason why (in neuropsychiatric practice) people with PNESs continue to be managed within the seizure clinic, particularly if by doing so they can save face. Operant conditioning infrequently causes a sharp increase in seizure frequency of a temporary nature (often with an equally dramatic decrease). This is actually a good prognostic sign but can disrupt the treatment plan if not anticipated.

Specific behavioral techniques exist for the management of nonepileptic seizures.[22] They are based on anxiety control measures to help the patient to recognize the early stages of an impending anxiety attack and then to apply control techniques based on suddenly lowering arousal or on cognitive techniques to interrupt negative thinking so that seizure progression is interrupted. The patient need no longer be afraid of the seizures because he or she is confident they can be stopped. This can be an effective treatment technique for nonepileptic attacks related to panic or hyperventilation and may have a more general use in some of the seizures related to somatoform disorders.

Psychotherapy

Psychotherapy in the sense of dynamic psychoanalytically based therapy probably has little part to play nowadays in the management of PNESs. Kalogjera-Sackellares published her book describing the use of psychodynamic psychotherapy in PNESs, giving a thorough presentation of the psychotherapeutic technique for patients with PNESs.[64] Psychodynamic psychotherapy, however, is relatively unproven in terms of its efficacy, given the limitation that it is a difficult technique to analyze by controlled trials.

Family Therapy

Patients with PNESs and their family members score in the unhealthy range on measures of family functioning.[76,150] Therapeutic work with the patient's family is extremely important in the management of these disorders because, even if family dynamics are not the prime cause of the seizures, often family tension may be conspiring to keep the patient in the sick role. Family anxiety may reinforce seizure behavior. Under those circumstances, managing the patient and the seizures without also managing the family may well be a fruitless exercise. An open trial of family therapy is being conducted in the United States presently. There has been little written about the use of family therapy in PNESs, and it is an area that needs extensive study.

Other

Hypnosis has been recommended for some patients as a treatment strategy.[101] Particularly for those patients in whom the seizure can be seen as a conversion or dissociative disorder, hypnosis might be helpful, although it would usually be used in conjunction with other therapies. It sometimes can be used as an abreactive agent.

Pilot trials of group psychoeducation (Zaroff 2004) and group psychotherapy (Wittenberg 2004) have been reported, and may provide a general support in anxiety reduction or more specifically a support while the patient is transitioning from neurologic care to psychiatric care.

Additional Considerations

Driving and Nonepileptic Seizures

Benbadis et al. found that 49% of neurologists surveyed applied the same restrictions to patients with PNESs as for patients with epilepsy. Driving records of a sample of PNES patients revealed no statistically significant difference compared with the expected number of motor vehicle crashes for the sample. The authors concluded that their small series did not support the use of driving restrictions for patients with PNESs.[15] Kanner has found that restricting driving privileges to patients with PNESs until they become seizure free is a motivational factor for patients to seek psychiatric treatment (Kanner AM, unpublished data). In our opinion, the decision to lift up the usual “seizure precautions” has to be individualized.

Summary and Conclusions

PNESs are commonly mistaken for epilepsy and are often difficult to recognize. Their investigation requires obtaining a thorough history, capturing one of the typical events on V-EEG, and a team prepared to think and act holistically. Like epilepsy, PNESs lie in the disputed territory between the provinces of neurology and psychiatry, and their successful recognition and management require careful and considerate liaison between the two disciplines. This is of particular importance in the small percentage of patients where PNESs and actual epilepsy exist concurrently in the same individual (see Chapter 208). In summarizing the treatment of lone PNESs, along with AED discontinuation, addressing the underlying psychological factors with psychotherapy, with adjunctive antianxiety/antidepressant medication to treat the comorbid axis I disorders, is currently thought to be the preferable treatment regimen for PNESs. Controlled studies are being conducted using pharmacotherapy for the comorbid depression and anxiety found in PNESs, and with cognitive behavioral therapy.

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Chapter 283

Episodic Dyscontrol

Ludger Tebartz van Elst

Michael R. Trimble

Introduction

Episodic dyscontrol (ED) is a rare but severe form of human aggressive behavior. The following case report illustrates the phenomenology of such troubling paroxysmal behaviors.

- A.E. was a 33-year-old white carpenter who was one participant of our study into episodic dyscontrol or intermittent explosive disorder in epilepsy at the Institute of Neurology.[77] A.E. was completely healthy and did not suffer from any major medical, neurologic, or psychiatric condition up to the age of 28 years, when he developed herpes encephalitis and subsequently suffered from temporal lobe epilepsy (TLE). He presented to the Chalfont Centre with complex partial seizures with a frequency of two to three clusters of up to six seizures a day. On these occasions, he would feel agitated somewhat 2 to 3 hours prior to the seizure. He then typically would feel odd; both sides of his face would start twitching, followed by salivation. During these seizures, which lasted 2 to 3 minutes, he would be awake but unresponsive to other people, with eyes wide open. Once to twice a month, a classic secondary–generalized tonic–clonic seizure evolved out of such a complex partial seizure. Neuropsychiatric assessment revealed a normal interictal electroencephalogram (EEG) with no ictal EEG available at time of presentation. Structural magnetic resonance imaging (MRI) displayed bilateral hippocampal and amygdala volume loss and increased hippocampal signal in T2 images. On psychiatric assessment, there was no formal diagnosis, and in particular no evidence for any affective, psychotic, or personality disorder or attention-deficit hyperactivity disorder (ADHD) apart from episodic dyscontrol.
- With a frequency of two to three episodes a year and a duration of 30 to 60 minutes, A.E. could behave in a very aggressive and violent way. Typically, there were no adequate triggers and a sudden onset of severe arousal, anger, and rage. The patient then became physically aggressive, attacking people and objects. The attack did not follow any obvious premeditated plan, and the behavior was poorly organized, with A.E. attacking every person or object at hand.
- On one such occasion at the tertiary referral center, A.E. was queuing for his medication when suddenly he gripped a nearby billiard stick, hitting the nurses and fellow patients at hand. He then left the ward and destroyed three cars before he could be restricted by the police. During this episode, there was no obvious evidence for an epileptic seizure and no evidence for hallucinations or persecutory delusions. The day before the attack, the he had had a pint of lager beer; apart from that, however, there was no evidence for any other drug abuse. The day after the attack, the patient felt extremely ashamed for this behavior. He could not recall and describe his feelings and thoughts during the episode in detail and remained vague in his recollection of the scene. At the same time, he was not absolutely amnesic and felt very guilty and depressed because of this behavior.

This case illustrates the complexity and danger of episodic dyscontrol and illustrates why many authors believe that ED might be related to epilepsy in particular because of its paroxysmal nature. Before we discuss the precise phenomenology and neurobiology of ED, however, we first have to clarify the relationship of this special form of aggressive behavior to aggression and violence as a general phenomenon of human life.

Human aggression is an important social and clinical problem.[32,67,75,82] The phenomenologic and probably neurobiologic heterogeneity of aggressive and violent behaviors is a major scientific problem leading to difficulties in assessment and classification. An important distinction has emerged between the terms *violence* and *aggression*. Treiman defined violence as forceful infliction of abuse or damage on another individual or object.[81] However, according to this concept, violence is not necessarily the result of intentional aggression. Aggression, in contrast, is defined as an offensive action directed toward another individual or object with the premeditated intention to harm, threaten, or control other subjects, groups, or situations.[81]

An advantage of this distinction is that it can be used to describe different destructive behaviors more precisely by referring to a special mental state, that is, the intentionality that does or does not motivate the destructive behavior. It leaves researchers with the problem of assessing intentionality, however, which in clinical practice is often impossible.

Therefore, it seems to be desirable to define phenomenologic criteria of specific behavioral syndromes of interest to obtain a nontheoretical approach to classifying aggressive and violent behaviors.

Classifying Aggression

One approach to doing this is to refer to basic research on animals. Here, aggressive behavior is classified according to the context in which it is observed. Authors like Moyer distinguished different subtypes of aggressive behavior in animals based on a precise characterization of the behavioral context in which such behavior is observed.[55] For example, predatory aggression is defined as violent behavior in which a predator kills its prey. It is characterized by a calm and very concentrated mental state of the aggressive animal and behavior that is well structured and goal directed. Maternal aggression, in contrast, is characterized by high arousal of the aggressive animal and a specific situational trigger when its offspring is menaced by predator. Table 1 summarizes the context-specific classification of aggressive behavior in animals.

Table 1 Subtypes of animal aggression

Aggression type	Example of animal behavior	Behavioral characteristic
Predatory aggression	Cat kills mouse	Calm, concentrated, goal directed, well structured
Intermale (territorial) aggression	Two lions fight for supremacy	Arousal, concentrated, goal directed, well structured
Maternal aggression	Bird attacks cat when it approaches the nest	Arousal, concentrated, goal directed, well structured
Sex-related aggression	Mantis kills male after copulation	Calm, behavioral stereotypes
Fear-induced aggression	Flight–fight Reaction Buffalo fight predator	Arousal, vocalization, less well structured, diverse behavioral pattern, reactive behavior

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Source: Modifed from Moyer KE. *Violence and Aggression—A Physiological Perspective.* New York: Paragon House; 1987.

Contrary to animal behavior, human behavior depends less on external cues and stimuli, and behavioral programs are less preformed. Therefore a simple transfer of the context-based classification of animal aggression to human behavior is not

possible.[42] Nevertheless, there is general agreement that at least two different phenomenologic and neurobiologic subtypes of aggressive behavior can be differentiated in humans: (a) predatory and (b) defensive aggression.[35,42,55,56,85]

Predatory aggression as described earlier is characterized semiologically as a well-structured and goal-directed behavior performed in an emotionally calm and concentrated state of mind. Defensive aggression, in contrast, is generally seen in the context of high emotional arousal and is associated with vocalizations and signs of anger or fear. The behavioral pattern itself is less structured and is defensive.[83]

Most forms of human aggression that are generally seen in a clinical context are considered to be defensive, that is, the behavior is generally poorly structured and a reaction toward a perceived threat, be it adequate or not.[2] Obviously, the perception of whether a stimulus is threatening is decisive in the information processing leading to this kind of aggressive behavior. However, there are also forms of offensive aggression that are often seen in criminals or patients with a diagnosis of dissocial personality disorder (ICD-10 Classification of Mental and Behavioural Disorders [ICD 10] F60.2), conduct disorder in adolescents, or hyperkinetic disorder of social behavior (ICD-10 F90.1).

Aggressive Behavior in Clinical Practice

In clinical practice, aggressive behavior can be observed in the context of different medical, neurologic, and psychiatric disorders and diseases. In patients with mental retardation, it is a common problem, possibly as a consequence of impaired social perception or deficits in expressing personal needs.[9,37,44,67] Furthermore, aggression is often seen in the context of organic brain disease such as frontal or hypothalamic brain tumors, neurodegenerative disease, delirium, or drug abuse. These common forms of aggression in the clinical setting tend to be malstructured, defensive, and generally occur in the context of states of confusion and diffuse emotional arousal.

Well-structured, premeditated, and goal-directed aggressive behaviors can occur on the background of psychiatric disorders such as psychosis with delusional states, ADHD, or bipolar disorder. It is frequently observed in patients with antisocial personality disorder (APD), in which it is part of the characteristic traitlike behavior.[9,53,71]

The only clinical syndrome of aggression that has been identified as a distinct category in the international classificatory system is intermittent explosive disorder (IED) according to the guidelines of the *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. (DSM–IV).[5] The concept of IED has been modeled on the clinical descriptions of episodic dyscontrol.[8]

Phenomenology of Episodic Dyscontrol

As mentioned, IED is basically a synonym for episodic dyscontrol. Because IED is an internationally accepted diagnostic construct, we will use this term in this chapter rather than ED. Both entities are characterized by several discrete episodes of failure to resist aggressive impulses that result in serious assaults or destruction of property. The behavior is out of proportion to any apparent precipitating psychosocial stressors and is not due to substance abuse, another mental disorder such as personality disorder, any other first-axis psychiatric disorder, or a general medical condition such as head trauma or neurodegenerative diseases. Consequently and in spite of the sometimes suggestive paroxysmal semiology, IED cannot be regarded as a special semiology of epilepsy. Whether this distinctive conception will stand the test of time, however, remains to be seen.

Epidemiology of Intermittent Explosive Disorder

There are only a few studies analyzing the prevalence of IED in primary medical settings. One study aimed at determining the lifetime and current prevalence of IED along with other demographic characteristics and patterns of comorbidity in an outpatient psychiatric sample of 1,300 individuals presenting for outpatient psychiatric treatment.[21] Following structured diagnostic assessment for axis I and II disorders, the authors reported a lifetime prevalence of IED of 6.3% (SE, ±0.7%) and a cross-sectional prevalence of 3.1% ± 0.5% of psychiatric patients. IED was the current principal diagnosis in only 0.6% ± 0.2% of patients. Most of these patients (80%) were interested in treatment for their intermittent aggressive behavior. The authors concluded that DSM-IV IED in psychiatric samples is far more common than previously thought and pointed out that IED develops early in life, especially in male patients.

Neurobiology of Intermittent Explosive Disorder

There are few studies looking at neurobiologic mechanisms specifically in IED. The fact that there is some controversy as to the reliability of the clinical diagnosis aggravates the problem of neurobiologic research into this entity.[54] Nevertheless, there is some evidence that disturbances of the functional integrity of frontotemporal brain circuits might play an important role in the genesis of IED and ED.

Clinical Studies

There are numerous studies addressing the relationship between focal lesional brain pathology and aggressive and impulsive behavior. Prefrontal brain damage and in particular orbitofrontal brain pathology have been closely associated with aggressive dyscontrol.[17] The specific entity of ED or IED has scarcely been addressed in any of these studies, however, although there are a few cases in which ED has been related to hypothalamic or basal ganglia lesions.[27,80]

With respect to neurochemical brain pathology, there is some vague evidence that functional disturbances of the serotonergic system might play a critical role in impulsive aggression in general.[43] In fact, one consistent finding in biologic psychiatry is an association between low cerebrospinal fluid 5-hydroxyindole acetic acid levels and impulsive aggressive acts, suggesting a decreased serotonin turnover. Again, however, there no specific studies in IED or ED.

Electroencephalographic and Imaging Studies

EEG studies point to an increased prevalence of unspecific EEG abnormalities in disorders with disturbed impulse control in general and ED in particular.[12,30] Drake et al., for example, reported a significant increase of diffuse or focal slowing in the EEGs of ED patients as compared to healthy volunteers or depressed patients.[30] N100 and P160 auditory-evoked potential amplitudes were lower in episodic-dyscontrol patients than in controls, but the difference was not significant. The authors concluded that such findings suggest that nonspecific cerebral dysfunction and EEG changes may be associated with disordered impulse or behavior control.[30]

A systematic literature review based on PubMed searches did not reveal any positron emission tomography, single photon emission computed tomography, or functional MRI study that specifically looked at neurobiologic mechanisms of ED or IED. There are two studies by our group, however, in which we addressed IED in the context of epilepsy, using structural MRI techniques.[78,88]

In these studies we hypothesized that, in patients with TLE and intermittent affective aggression, amygdala sclerosis in the context of hippocampal sclerosis would be more common as compared to control patients. In addition, we aimed to analyze a possible association between aggression on one hand and hippocampal sclerosis, low IQ, and poor social adjustment on the other in patients with TLE. In a further approach, we analyzed cortical gray matter abnormalities in these patients to gather evidence for frontal lobe pathology in patients with TLE and IED.

Amygdala Pathology in Patients With Temporal Lobe Epilepsy and Episodic

Dyscontrol

For that purpose, we compared 25 patients with TLE and IED with 25 control patients with TLE without any psychopathology and 20 healthy volunteers.[78] Both patient groups were matched for age, gender, demographic background, duration of epilepsy, and seizure severity. There was no significant group difference regarding the history of birth complications, febrile convulsions, or status epilepticus. In the IED group, however, the incidence of encephalitic brain disease (Fisher's exact test: $p = .05$) and left-handedness (chi-square test: $p < .05$) was significantly increased. There was less right-sided focal EEG abnormality and more bilateral EEG abnormality in the aggressive group, and hippocampal sclerosis was significantly less common in patients with TLE and IED. Other left temporal pathology, including 3 patients with amygdala pathology (amygdala sclerosis, amygdala glioma, amygdala dysembryoplastic neuroepithelial tumor), 2 patients with multiple small temporal infarctions, and 2 patients with diffuse left temporal atrophy of unknown origin, was significantly more common in patients with TLE plus IED. In the aggressive patients, a subgroup of 5 patients (20%) showed amygdala atrophy as compared to only 1 in the nonaggressive group (chi-square test: $p = .04$). An increased incidence of encephalitis (chi-square test: $p < .005$; Fisher's exact test: $p = 0.1$) was the only clinical feature that distinguished patients with amygdala atrophy from those with normal amygdala volumes. In 12 of 25 patients, we could prove some evidence of amygdala-related brain pathology as compared to only 1 in the nonaggressive group. Furthermore, there was a highly significant group difference in IQ figures, with the verbal IQ (VIQ), the performance IQ (PIQ), and hence the full IQ (FIQ) all being lower in the aggressive group. In addition, there was a significant group difference in Beck Depression Inventory and Spielberger State Trait Anxiety Index scores, with the aggressive group rating much higher in depression ($p < 0.05$), state ($p < 0.05$), and trait anxiety ($p < 0.01$).[78]

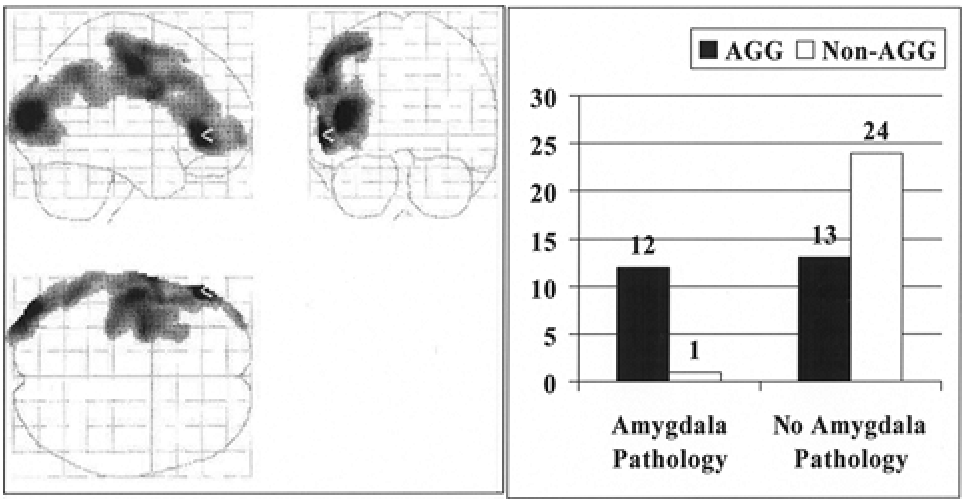

FIGURE 1. Prevalence of amygdala-related brain pathology and cortical gray matter density loss in 25 patients with temporal lobe epilepsy and episodic dyscontrol. AGG, aggression. (Redrawn after Tebartz van Elst L. Aggression and epilepsy. In: Trimble M, Schmitz B, eds. *The Neuropsychiatry of Epilepsy*. Cambridge: Cambridge University Press; 2002:81–106.)

Cortical Abnormalities in Patients With Temporal Lobe Epilepsy and Episodic Dyscontrol

In a second analysis, we employed the method of voxel-based morphometry to detect possible subtle cortical brain pathology that was not present on visual assessment of the MRI scans analyzing the same study sample.[88] Both TLE patient groups were compared with each other and with the control subjects on a voxel-by-voxel basis for increases and decreases of gray matter. Details of the methodology are published elsewhere.[88,89] In this study, we were able to demonstrate reductions of gray matter density over large areas of the left extratemporal neocortex with maxima in the left frontal neocortex; one maximum difference projection had a Z score of 5.67 at Talairach coordinates $x = 58$, $y = 36$, $z = 9$ mm (left anterior frontolateral cortex), the other a Z score of 4.78

in a more-posterior left frontal lobe location (Talairach coordinates $x = 66$, $y = 0$, $z = 28$ mm). Patients with TLE who did not have IED showed no significant decrease of cortical gray matter compared with control individuals. Patients with TLE with IED also had reduction of left frontal gray matter compared with patients with TLE without IED, although this was less marked than when compared with control individuals (Z score of 3.49 at Talairach coordinates $x = 66$, $y = 2$, $z = 26$ mm). The statistical parametric mapping–based voxelwise correlation of social dysfunction and aggression scale scores and automatically segmented gray matter in all patients with TLE showed a left frontal gray matter area

being negatively correlated with these scores, which expressed social consequences of interictal affective aggression (Z score of 3.65 at Talairach coordinates $x = 66$, $y = 2$, $z = 26$ mm). Age, scores of depression and anxiety, IQ measures, or scores of verbal fluency did not significantly correlate with specific decreases in gray matter in all patients with TLE.[88] FIGURE 1 illustrates the main findings from these two studies.

Neurobiology of Aggression in General and Intermittent Explosive Disorder in Particular

Various brain structures are known to play an important role in the generation of aggressive behavior in animals and humans. The most important of these structures are the periaqueductal gray,[10,16] the hypothalamus,[7] the amygdala and associated limbic structures,[1,29,39,45,66] and the frontal lobes.[23,53,61]

Even though the precise function of the aforementioned structures and their role in the complex interplay of the different brain circuits in regulating different aggressive behaviors is unclear, the first elements of a functional anatomy of aggression can be identified (Table 2). Brainstem structures like the periaquaductal gray are crucial for the activation of evolutionarily preformed behavioral programs like attacking or defensive behavior in animals.[10,16] These structures are controlled by higher neuronal centers in the hypothalamus,[13,84] which in addition to controlling these behavioral brainstem programs, adjust the internal endocrinologic and immunologic environment to aggressive behavior in flight-or-fight situations.[50,63,69,90]

The frontal lobes are known to play a critical role in the ability to suppress behavioral impulses. Thus, patients with frontal lobe lesion often lose the ability to suppress aggressive impulses and therefore might present with severe aggressive and violent psychopathology.[23,46,59,71]

Table 2 Functional relevance of different brain structures for aggressive behavior

Brain structure	Assumed function
Frontal lobe	Inhibitory function Suppression of aggressive behavioral drive
Amygdala and limbic circuits	Emotional evaluation of multimodal sensory and cognitive input Emotional drive and arousal
Hypothalamus	Control of brainstem behavioral programs
	Regulation of internal environment
	Coordination of behavioual programs and internal

	environment in flight–fightsituations
Brainstem structures, i.e., periaqueductal gray	Evolutionarily preformed behavioral flight–fight programs

Source: Modified from Tebartz van Elst L. Aggression and epilepsy. In: Trimble M, Schmitz B, eds. *The Neuropsychiatry of Epilepsy*. Cambridge: Cambridge University Press; 2002:81–106.

The amygdala is thought to play a crucial role in the mediation of fear-induced aggression, a subtype of defensive aggression.[1,20,33,48] They receive input from various levels of sensory information processing and project to most of the other critical brain structures, including the brainstem, hypothalamus, thalamus, and frontal lobe.[3,4] From a neurophysiologic perspective, they are in a key position for the affective evaluation of multimodal sensory input. Thus, pathology within the circuits affecting the amygdala might lead to mental states in which the misinterpretation of sensory input as threatening leads to aggressive outbursts. In agreement with this assumption, electrical stimulation of the amygdala can lead to experiences like fear, anxiety, or anger,[19,34] and lesioning of the amygdala severely impairs fear conditioning in animals[25] and humans.[47] Furthermore, in an open retrospective study of 481 cases of bilateral amygdalotomies performed for the control of conservatively untreatable aggressiveness, moderate to excellent improvement of aggressive behavior was reported in 70% to 76% of cases.[62]

Dual Brain Pathology in Patients With Episodic Dyscontrol

Based on our findings in patients with TLE and IED in which significant brain pathology could be observed in amygdala-related circuits on one hand and the prefrontal lobe on the other, we suggested that a dual brain pathology affecting limbic brain structures and prefrontal areas at the same time might be a critical pathogenetic element in the genesis of episodic dyscontrol and intermittent explosive disorder.[77] Within this concept, both clinical entities are understood as hyperarousal-dyscontrol syndromes. The clinical phenomenology of hyperarousal, that is, the sudden onset of extreme arousal, fear, and rage, is probably related to some sort of amygdala-network instability. Following this line of thought, we associate the failure to control the aggressive impulses resulting from emotional arousal in the context of functional amygdala instability with prefrontal lobe dysfunction.

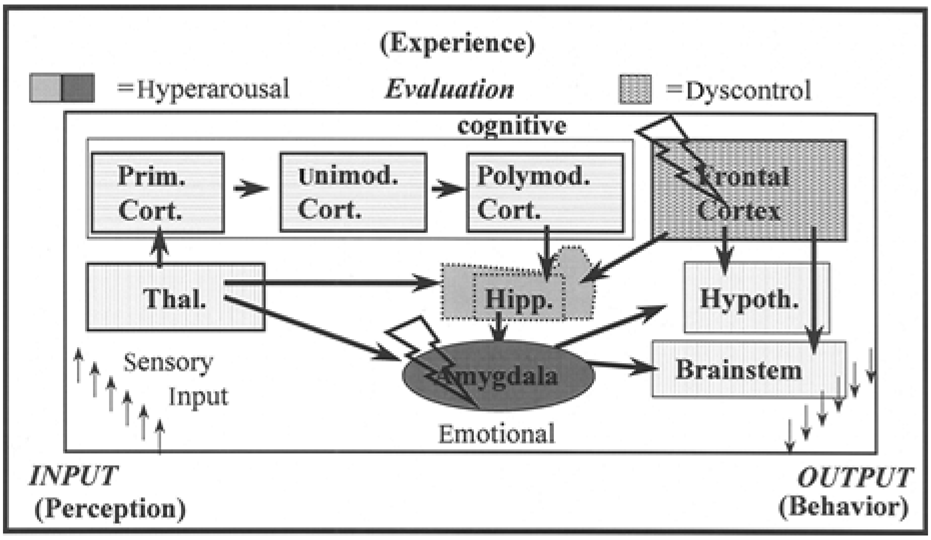

FIGURE 2. Dual brain pathology in hyperarousal-dyscontrol syndromes. Thal, thalamus; Prim Cort, primary cortex; Unimod Cort, unimodal cortex; Polymod Cort, polymodal cortex; Hipp, hippocampus; Hypoth, hypothalamus. (Redrawn after Tebartz van Elst L. Aggression and epilepsy. In: Trimble M, Schmitz B, eds. *The Neuropsychiatry of Epilepsy*. Cambridge: Cambridge University Press; 2002:81–106; and Tebartz van Elst L, Trimble MR, Ebert D, et al. Dual brain pathology in patients with affective aggressive episodes. *Arch Gen Psychiatry.* 2001;58;1187–1188.)

The observations of our study support this notion. Brain pathology in patients with epilepsy and aggression was more diverse in nature and more diffuse in distribution. We found an increased prevalence of a history of encephalitis in patients with epilepsy plus aggression. Encephalitis in the past might have been a pathogenetic element for the more diffuse and widespread pathology in the temporal lobe seen in our aggressive patients. Furthermore, the increased prevalence of left-handedness in our aggressive patients may indicate early brain pathology such as encephalitis affecting the left hemisphere (i.e., lateralization of dominance to the right hemisphere).

Eleven of 12 patients with amygdala-related brain pathology displayed this pathology on the left-hand side, and the only patient with right-sided amygdala atrophy alone was left-handed. Thus, the dominant hemisphere seems to play a more important role in the mediation of affective aggression than the nondominant hemisphere.

The finding of frontal cortical gray matter loss was clearly lateralized too. Patients with TLE plus IED displayed highly significant left frontal gray matter loss that correlated with the aggression psychometry scores. This, together with the left-lateralized finding of amygdala-related brain pathology, could support a theory of left-lateralized dual brain pathology in IED.[77]

This theory is further supported by earlier functional imaging and MR spectroscopy studies showing a reduced prefrontal glucose metabolism in those convicted of murder and significantly lower neuronal markers in the frontal lobes of repetitively violent patients with learning disabilities, although without clear lateralizing effects.[60,61]

Figure 2 illustrates this pathogenetic model of hyperarousal-dyscontrol syndromes. Pathology within the amygdala or amygdaloid circuits might result in hyperarousal states in which patients become angry and aroused without a sufficient external stimulus (hyperarousal syndrome). This dysfunctional arousal resulting in aggressive behavioral impulses normally can be suppressed by learned behavioral rules. In the case of additional frontal lobe pathology, however, the capacity of the affected patients to suppress behavioral impulses arising from the "emotional brain" is limited, and thus an additional dyscontrol syndrome leaves the patients vulnerable to the development of hyperarousal-dyscontrol syndromes, that is, episodic dyscontrol or intermittent explosive disorder.[77]

Intermittent Explosive Disorder—Is It Epilepsy?

When analyzing the phenomenology of episodic aggressive behavior as illustrated in the case report at the beginning of this chapter, the question arises as to whether this episodic aggressive behavior might be understood as some form of frontal or limbic lobe epilepsy. The ictal nature of the aggressive outbursts, the lack of adequate psychosocial triggers, and the discrepancy with the interictal undisturbed personality all support this suspicion. Because frontal or limbic lobe epilepsy can be observed without pathologic findings in the surface EEG and it is difficult anyway to obtain an EEG during the aggressive episodes from the affected patients, this hypothesis is very difficult to investigate.

The observation that antiepileptics often are very effective in controlling impulsive aggression (see later comments) further supports the notion of a link between ED and epilepsy. The fact that they do not help in another substantial subgroup of patients with IED or ED does not contradict the hypothesis because many patients with classical epilepsy do not respond to antiepileptic treatment either.

From deep brain recording in patients with postictal psychosis we know, however, that there are other nonictal but still epilepsy-related pathomechanisms that can result in severe psychiatric symptoms including aggression that are not truly ictal in nature.[68] Therefore, although the hypothesis that IED might be some form of undiagnosed limbic or frontal epileptic attack disorder is far from being falsified, it is not proven either, and other epilepsy-related pathomechamisms could also explain the paroxysmal behavioral dysfunction. Further studies comparing patients with and without various neurologic diseases using even more sophisticated methods of functional brain assessment will be necessary to solve this question.

Social and Psychological Aspects of Aggression in Epilepsy

Another important observation that arose from our studies was that there was a strong link between aggression and high levels

of depression and anxiety, confirming other reports of such an association in the non–psychiatrically ill population.[14] It seems plausible that high levels of anxiety result in states of hyperarousal that might be facilitated by amygdala pathology, as suggested by other authors.[18] Regarding the relationship between depression and aggression, there are only few and inconclusive reports in the general literature.[15] Our findings point to a clear association among depression, anxiety, and hyperarousal-dyscontrol states at least in TLE.

Social disadvantage, prejudice, poor housing, poverty, and poor communication skills are further factors that make hyperarousal states and states of discontentment and anger more likely and thus might increase the probability of aggressive behavior. Disentangling the complex interaction among these different psychobiologic elements, however, is often not possible.

Therapy of Aggression and Episodic Dyscontrol

Intermittent explosive disorder and episodic dyscontrol are not unitary nosologic entities; they are essentially clusters of symptoms or syndromes that may occur in quite different medical, psychological, or social contexts. The most important point for an adequate therapy of ED and IED is a thorough medical and psychosocial diagnosis. Care should be taken to investigate any possible medical, neurologic, or psychiatric problem or comorbidity that might contribute to these most devastating and distressing behavioral syndromes. In case such diagnoses or comorbidities do exist, they have to be treated properly because this might in some cases solve the problem. For those patients in whom IED occurs in the context of established or suspected epilepsy, we refer to Chapter 212, where we outline the treatment principles for aggression in the context of epilepsy. The treatment of IED in the context of other psychiatric disorders such as schizophrenia, bipolar disorder, ADHD, borderline personality disorder, or conduct disorder should basically follow the treatment guideline of these respective disorders (see the standard psychiatric textbooks).

In case there are no medical, neurologic, or psychiatric comorbid or contributing diseases or disorders (which is probably a rare constellation), a symptomatic treatment should be started. To our knowledge, there are no systematic double-blind, placebo-controlled therapy studies in IED or ED. However, there are many case reports of successful therapy of this condition.

The two pharmacologic agents that are most often reported to be successful in IED are selective serotonin reuptake inhibitors (SSRIs)[26,31,38,64] and antiepileptic agents.[6,49,51,58,73,74] Carbamazepine in particular has been reported to be successful in as many as 65% of patients with IED.[28] The latter observation further supports the assumption that IED might be pathogenetically related to epilepsy. An alternative explanation of this observation, however, is the notion that IED might be pathogenetically related to bipolar disorder because most antiepileptics—carbamazepine in particular—are potent mood stabilizers. Following this line of thought, we could see episodic dyscontrol as a brief quasi-manic episode.[52] In line with this assumption, there is some evidence that lithium might be helpful in treating ED or IED.[41,72] Apart from that, there are reports of successful treatment of IED with beta-blockers such as propanolol[36,65] and antipsychotic agents.[40,57,86]

Finally, it must be stressed that anger management, contingency management, and psychotherapy all can be very helpful and successful in treating impulsive aggressive behavior. In particular, in the context of mental handicap and personality disorders, aggression and impulsivity might be part of attention-seeking behavior and role testing. In these cases, the feedback strategies and the reactions of relatives and caregivers are very important, and methods of contingency management may be a critical element of any successful treatment.[11,22] Apart from that, different methods of anger management, cognitive–behavioral therapy, or skills training that have been developed irrespective of whether impulsive behavior is seen in the context of ED or epilepsy or not may be very helpful in the therapy of aggression in whatever context.[24,70,79,87]

It should be stressed again, however, that there are no well-designed treatment studies and that all recommendations basically follow expert opinions.

Summary and Conclusions

Episodic dyscontrol and its DSM-IV correspondent intermittent explosive disorder represent severe forms of a paroxysmal aggressive attack disorder. In contrast to premeditated antisocial aggression, IED is characterized by high levels of arousal, anxiety, anger, and fear. The behavior is generally poorly structured, but it can be very dangerous.

The question of whether IED is pathogenetically related to epilepsy is unresolved. There is evidence that frontolimbic brain pathology does play an important role in the pathogenesis of IED. IED often is accompanied by other neurologic or psychiatric disorders such as epilepsy, other organic brain disorders, or bipolar or schizophreniform disorder even though these are exclusion criteria following DSM-IV. In these cases, basic treatment should follow the principles for the respective disorders. The epilepsy and bipolar or schizophreniform disorders should be treated first. Often, depressive symptoms in the context of IED are undiagnosed, and in these cases, depression again should be treated.

If IED persists in spite of up-to-date treatment of all comorbid conditions or if none of these are recognizable, the clinician should try to implement a symptomatic treatment of the aggressive behavior itself. Although there are no well-designed treatment studies, there is evidence to support attempts for symptomatic relief using antidepressants and SSRIs in particular, antiepileptics, lithium, antipsychotic agents, and even beta-blockers. In these cases, the decision of which of these different drugs should be used first depends on the specific history, family history, response to earlier medication attempts, comorbid and possibly subsyndromal psychopathologic findings, and experience of the specialist. In any case, the target syndrome is of sufficient importance to support systematic trials of all therapeutic options even if they are off-label as is generally the case. If therapists feel unfamiliar with this approach, they should consider referral to specialists or ask for advice from tertiary referral centers. Our experience that some of these interventions in fact help even though all other substances failed to bring any relief motivates this approach.

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Chapter 284

Dissociative Disorders

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Introduction

Within the context of psychiatry and neurology, the term *dissociation* is extremely difficult to define satisfactorily. Since its introduction in the late nineteenth century, the term has been applied to a wide range of neurologic, psychiatric, and psychological phenomena. As a result, there is considerable confusion over what actually constitutes dissociation, and the concept is frequently misapplied. This is particularly true within the field of epilepsy. Many epileptic phenomena have been labeled as dissociative, including the sensory, affective, and cognitive features of partial seizures, behavioral automatisms, postictal amnesia, and fugue.[27] Similarly, certain psychiatric phenomena that mimic epileptic events, so-called "nonepileptic seizures," have been identified as primarily dissociative in nature. Indeed, many authorities have argued that the dissociative nature of nonepileptic seizures could provide the basis for their conceptual and practical differentiation from "genuine" epileptic events.[44] If, however, dissociation is experienced both by individuals with epilepsy and by those with pseudo-epileptic seizures, how can its occurrence aid in the differential diagnosis of these conditions?

Historical Aspects

The term *dissociation* originates in the work of Pierre Janet, who proposed one of the earliest systematic accounts of the psychological mechanisms underlying hysteria. According to Janet,[36,38] a fundamental weakness in the hysterical individual's mental character makes the person susceptible to a breakdown in the normally integrated functions of consciousness when faced by environmental stress or trauma. As a result, organized sets of knowledge pertaining to the trauma may become "dissociated" from the main body of consciousness and may serve to take control of behavior and experience if activated by environmental events. The automatic activation of these dissociated memories results in a hysterical reaction (or "somnambulism") that, in some instances, takes the form of a nonepileptic attack. Following Charcot's demonstrations at the Salpêtrière in which hysterical symptoms were shown to be both induced and removed by hypnosis, Janet's dissociation theory assumed that this process of dissociation was driven by an autohypnotic state. According to this view, two aspects of the hysterical individual's psychophysiologic makeup are responsible for the processes of dissociation and somnambulism. First, the hysterical individual possesses an abnormally high degree of suggestibility that allows ideas from the external environment to develop within him or her in the absence of his or her effort or awareness. Second, the hysterical individual suffers from an attentional dysfunction or "retraction of the field of consciousness" (Janet,[38] p. 314), which prevents them from entertaining alternative states of mind, thereby accentuating their responsivity to external suggestion. The resulting process of dissociation leads to "dedoublément," or double consciousness, whereby two or more discrete but conscious modes of being existed alongside one other, separated by amnesia. In extreme cases, the autonomy of this dissociative consciousness gave rise to one or more alter personalities.[54]

Although it was originally assumed that these processes were triggered by external traumas, subsequent psychoanalytic theory gravitated from external happenings to an inner efficient causation based on traumatic conflict arising from the patient's psychically unacceptable desires and fantasies. Thus, the etiology was expanded to include subjective traumatization or "vehement emotions" whereby "every memory, every thought, competent to arouse strong and lasting emotions, can play the part of a fixed idea, and may originate hysterical symptoms."[39] In these terms, symptomatology became a composite of fact and fantasy, metaphor and symbolism. This was the case even when there was an association with objective traumatic events because, in classical Freudian theory, before the onset of symptoms, there is a reconstruction in memory overlaid with fantasy (Freud,[23] p. 625). Freud also proposed that falsifications are introduced into memory in order "to interrupt disagreeable and causal connections" (Freud,[24] p. 446, footnotes).

These discoveries led Freud to view hysterical etiology as fantastic, so that, as with dreams, the symptoms became the "the royal road" to the unconscious:

> Hysterical symptoms are nothing other than fantasies brought into view through *"conversion."*… So far as the symptoms are somatic ones, they are often enough taken from the circle of the same sexual sensations and motor innervation as those [that] originally accompanied the fantasy when it was still conscious. (Freud,[21] p. 90; italics added)

This move from fact to fantasy is evident in Freud's revision of his early seduction theory,[35] which suggested that some hysterical patients suffered from unconscious memories of childhood seduction. Later he asserted that such memories were infantile wish fulfillments, although not always: "So often they are not fantasies but real memories…. A fantasy of being seduced when no seduction has occurred is usually employed by a child to screen the autoerotic period of his sexual activity" (Freud,[22] p. 417).

Although popular for nearly a century, recent interest in the prevalence of childhood abuse has led to a backlash against Freudian theory, coincidental with a renewed interest in Janet's work on dissociation,[19] adaptations of his theory in cognitive psychology,[30,31] and a mushrooming of publications linking objective traumatic experiences to dissociative psychopathology. This is particularly relevant for the evaluation of nonepileptic seizures. Indeed, both the *Diagnostic and Statistical Manual for Mental Disorders*, 4th edition (DSM-IV),[2] and the *International Classification of Diseases* (ICD-10)[65] make an explicit link between traumatic events and the onset of dissociative symptoms. Moreover, a number of studies have found disproportionately high rates of physical, sexual, and emotional abuse in patients with dissociative disorders.[16,34,53] Bowman,[7]

for example, found that 70% and 77% of her sample of 27 nonepileptic seizure patients had experienced physical or sexual abuse, respectively. Similarly, Betts and Boden[6] obtained positive sexual abuse histories from 54% of 96 patients with nonepileptic seizures.

Table 1 Classification of dissociative disorders in ICD-10 and DSM-IV

ICD-10 dissociative (conversion) disorders	DSM-IV dissociative disorders
Dissociative amnesia	Dissociative amnesia
Dissociative fugue	Dissociative fugue
Dissociative motor disorders	Dissociative identity disorder
Dissociative convulsions	Depersonalization disorder

Dissociative anaesthesia and sensory loss	Dissociative disorder not otherwise specified
Dissociative stupor	
Trance and possession disorders	
Mixed dissociative (conversion) disorders	
Other dissociative (conversion) disorders	
Dissociative (conversion) disorder, unspecified	

ICD-10, *International Classification of Diseases* (ICD-10)[65]; DSM-IV, *Diagnostic and Statistical Manual for Mental Disorders*, 4th edition.[2]

Thus, 100 years of thought about hysteria has brought the traumagenic theory full circle, and yet the difficulties encountered by nineteenth century investigators remain. Trauma is ill conceived and now tends to be exclusively considered only as an objectively measurable event, ranging from natural disasters to childhood abuse. As a result, there is a lack of consideration given to inner efficient causes, such as an individual's perceptions of events, which would seem important in the process of traumatization. Not only could this explain the obvious lack of psychopathology in some victims of abuse,[66] but it might also account for the presence of psychopathology following relatively harmless events. For example, in LaBarbera and Dozier's study of pseudoseizures,[45] three of the four girls reported no history of sexual abuse but had experienced minor sexual events perceived as traumatic. Equally, in cases in which there have been false allegations of serious trauma,[14] there is often an incidence of minor sexual traumatization. Finally, the determinism of trauma in the development of nonepileptic attacks and psychopathologically related disorders is problematic in terms of the unquestioned and overgeneralized evocation of dissociation as a defense mechanism as well as the lack of explanations for its prolonged use, even years after the event.[63]

Classification of Dissociative Disorders

The Dissociative disorders category in the latest edition of the *Diagnostic and Statistical Manual*[2] encompasses dissociative amnesia, dissociative fugue, dissociative identity disorder (formally multiple personality disorder), depersonalization disorder and dissociative disorder not otherwise specified (see Table 1). According to DSM-IV,[2] "the essential feature of the dissociative disorders is a disruption in the usually integrated functions of consciousness, memory, identity, or perception of the environment" (p. 477). A slightly broader definition is offered in the latest edition of the *International Classification of Diseases*,[65] which identifies the loss of control over bodily movements as an additional dissociative phenomenon. As such, the ICD-10 Dissociative (conversion) disorders category encompasses dissociative amnesia, dissociative fugue, dissociative motor disorders, dissociative convulsions, dissociative anesthesia and sensory loss, dissociative stupor, mixed dissociative (conversion) disorders, other dissociative (conversion) disorders, and dissociative (conversion) disorders, unspecified (Table 1). The Somatoform and Dissociative disorders are related in that these phenomena are characterized by symptoms that, on the face of it, resemble those that occur in certain physical conditions but are presumed to be psychological in origin. Dissociative and somatoform phenomena differ in that the symptoms of the former resemble those of neurologic illness, whereas the symptoms of the latter are more akin to those encountered in internal medicine. As Kihlstrom[40] cogently argued, all of the phenomena identified as dissociative disorders within DSM-IV and ICD-10 are linked by the fact that each has a temporary disruption in consciousness or volition as its primary defining feature.

The differences between DSM-IV and ICD-10 in their classification of the Dissociative and Somatoform disorders are readily apparent. First, unlike ICD-10, DSM-IV places nonepileptic attacks in the Somatoform rather than the Dissociative disorders category along with other so-called "conversion" phenomena, such as unexplained motor and sensory symptoms, that are identified as dissociative in ICD-10. This difference is more practical than conceptual, with DSM-IV placing greater emphasis on the importance of excluding physical illness in the differential diagnosis of these phenomena.[2] Second, unlike DSM-IV, ICD-10 does not identify depersonalization as a dissociative phenomenon, due to the lack of any significant loss of control over sensation, memory, or movement in this condition and its limited affect on personal identity. Third, DSM-IV identifies a distinct category for multiple personality disorder, relabeled dissociative identity disorder in the latest edition of this scheme. In contrast, ICD-10 places multiple personality disorder in the other dissociative (conversion) disorders category, reflecting controversy over whether this syndrome is iatrogenic or culturally bound to North America. Inconsistencies aside, both DSM-IV and ICD-10 explicitly state that physical conditions such as epilepsy should be excluded in the differential diagnosis of the Dissociative and Somatoform disorders.

Contemporary Views of Dissociation

To some extent, the differences between DSM-IV and ICD-10 demonstrate ongoing controversy about the definition of the term "dissociation." When the term was originally introduced in the nineteenth century, it was used to refer to a specific mental mechanism thought to be associated with a relatively limited set of psychological symptoms. Over the years, however, the number of phenomena thought to be attributable to dissociation has expanded considerably, and the dissociation label is now applied to an extraordinary range of psychological symptoms, states, and processes. Cardeña[15] described a useful taxonomy that captures the different ways in which the concept of dissociation has been used. According to this scheme, there are three major facets of the dissociation construct: (a) dissociation as nonconscious or nonintegrated mental modules or systems;

(b) dissociation as an alteration in consciousness; and (c) dissociation as a defense mechanism.

Dissociation as Nonintegrated Mental Modules or Systems ("Compartmentalization")

Dissociation in this sense reflects the original meaning of the concept introduced by Janet[36,38] as the basic psychopathologic mechanism underlying hysterical symptoms. This concept encompasses the medically unexplained symptoms characteristic of the DSM-IV conversion disorders, as well as dissociative amnesia, dissociative fugue, and dissociative identity disorder.[33] Holmes et al.[33] used the term *compartmentalization* to refer to the putative process involved in the generation of these conditions.

These phenomena should be distinguished from other pathologic phenomena characterized by a lack of integration between mental modules or systems that are caused by neurologic rather than psychiatric events. Blindsight, a rare condition in which the sufferer displays above-chance visual discrimination despite reporting a lack of visual experience, provides one example of how normally integrated functions can become dissociated through neurologic damage. Many of the unusual behaviors often displayed by patients following commissurotomy also fall within this category, as do those exhibited by individuals suffering from hemi-neglect. In each of these cases, the dissociation is between the individual's ongoing behavior and his or her introspective verbal report.

Neurologic dissociations such as blindsight are superficially analogous to those observed in psychiatric instances of dissociation, such as the preservation of implicit perception[a] in the context of dissociative blindness (see, e.g., Kihlstrom[40]). Neurologic and psychiatric dissociation differ, however, in that the former is often permanent, reflecting irreversible damage to the underlying neurologic subsystems in question.[40] Psychiatric instances of dissociation, in contrast, are thought to be the product of an alteration in the parameters governing otherwise intact psychological functions; they are, therefore, reversible by definition. Similarly, neurologic and psychiatric dissociations differ in that, unlike the former, the latter involves symptoms (e.g., "glove" anesthesia) that need not, and typically do not, relate to the actual organization of the nervous system and its many distributed components. On these grounds, it is apparent the "dissociation" in these cases is an entirely different phenomenon, and the two must not be confused.

The idea that normally integrated psychological processes can become temporarily dissociated and exist in isolation of one another has also been cited as the basis for other, less pathologic, phenomena.[15,32,64] Many apparently "hypnotic" phenomena fall within this category, including profound amnesia, the loss of perceptual experience, and complex behaviors characterized by a sense of involuntariness, all of which can be temporarily produced by appropriate suggestions in certain individuals. The extent to which similar processes are involved in these phenomena and those displayed by individuals with dissociative psychopathology has been a matter of debate since the time of Janet. Conceptually, there are good grounds to assume a common mechanism in hypnotic and dissociative phenomena[11,12] and recent functional imaging evidence provides some support for a link between the two.[29]

According to Cardeña,[15] this particular definition of dissociation has also been inappropriately applied to a number of other normal psychological phenomena. Following Hilgard,[32] the execution of complex behaviors with only minimal conscious awareness, such as the action of driving a car while holding a conversation, has often been identified as a dissociative phenomenon. As Cardeña pointed out, however, the dissociation label should not simply be applied to any behavior or psychological process that, for whatever reason, occurs without full awareness. Such a practice ignores the fact that, in many such cases, the individual can bring the apparently "dissociated" process into awareness by an act of selective attention. Other such cases involve "dissociation" between systems or processes that one would not normally expect to operate in an integrated fashion. According to Cardeña, mental modules or systems should only be regarded as truly dissociated from one another if their dissociation is (a) in contrast to a normal state of integration and (b) cannot be overcome by an act of will.

Dissociation as an Alteration in Consciousness ("Detachment")

A second use of the dissociation concept refers to an altered state of consciousness characterized specifically by a disengagement from the self or the environment.[15,33] Holmes et al.[33] used the term *detachment* to refer to this category of conditions. As Cardeña pointed out, this sense of the dissociation concept should not be applied to everyday phenomena, such as daydreaming and other states of distraction, in which engagement with the environment is less than complete. Instead, it should be reserved specifically for states that are regarded by the experiencing individual as qualitatively different from their normal state of awareness. Although a number of different phenomena fall within the bounds of this definition (e.g., "trance" and "possession" states), probably the most commonly reported are depersonalization and derealization. In depersonalization, the individual experiences a profound feeling of detachment from his or her thoughts, perceptions, actions, and emotions, often characterized by a sense of numbness or disembodiment. In derealization, the individual experiences an intact sense of self coupled with a feeling of detachment from the external environment, which often feels unreal or at a distance. Such feelings are extremely common, and frequently occur in the context of psychiatric illnesses such as depression and anxiety; they also occur as a circumscribed problem in their own right, such as in depersonalization disorder.

Although DSM-IV identifies depersonalization disorder as a dissociative phenomenon, this condition clearly relates to a different sense of dissociation than that which applies to the other members of this category; this difference further justifies the separation of depersonalization disorder from the Dissociative disorders category in ICD-10. Depersonalization and derealization are also found in certain drug states (e.g., those produced by marijuana, LSD, and ketamine) and neurologic conditions such as temporal lobe epilepsy and can occur spontaneously in the context of stress or fatigue.

Table 2 Dissociative disorders and dissociative events[a]

Neurologic	Psychologic
Temporal lobe epilepsy	Dissociative identity disorder

Transient global amnesia	Dissociative amnesia
Epileptic fugues	Dissociative fugues
Body image disorders	Dissociative (conversion) disorders
Somnambulisms	Depersonalization
Drug-dependent learning	Derealization
Sleep amnesia	Déjà-vu
	Hypnosis
	Out-of-body experiences

[a]Showing the main neurologic and psychological states associated with dissociation, with decreasing levels of pathology in descending order.
Source: Adapted from Cardeña. The domain of dissociation. In: Lynn SJ, Rhue JW, eds. *Dissociation. Clinical and Theoretical Perspectives*. New York: Guilford Press; 1994:15–31, with permission.

Dissociation as a Defense Mechanism

Finally, dissociation has been described as a defense mechanism that protects the individual from potentially overwhelming pain or anxiety. In many respects, this account of dissociation is indistinguishable from the Freudian concept of repression.[20]

This sense of the dissociation concept is typically used to describe the psychological *function* served by the creation of a detached state or the compartmentalization of mental modules or systems.[15] In this view, exposure to a traumatic situation may trigger the compartmentalization of memories, which preserves psychological integrity by preventing the distressing material from entering consciousness after the event. Alternatively, such traumatic exposure may spontaneously elicit a depersonalized state that prevents extreme emotion from inhibiting an appropriate behavioral response. As such, this definition of dissociative may relate to either of the definitions described previously. In both cases, dissociation of this sort could be either an acute response to an isolated traumatic event or a trait-like characteristic acquired as a result of repeated exposure to trauma.

Epilepsy and Dissociation

Although the differential diagnosis of ICD-10 and DSM-IV Dissociative disorders explicitly requires the exclusion of symptoms with an identifiable neurologic basis, many of the phenomena associated with epilepsy, particularly temporal lobe epilepsy, have been regarded as dissociative in nature (Table 2).[18,27] Indeed, ICD-10 includes a specific category for Dissociative disorders due to a general medical condition, which encompasses many of the symptoms exhibited by those with epilepsy. The absence of such a category from DSM-IV, however, reflects doubt concerning the value of attaching the dissociative label to these phenomena. In our view, such doubt is well justified in many cases.

The notion that many epileptic phenomena can be regarded as dissociative is based, to a considerable extent, on the frequent occurrence of amnesia in epilepsy (see, e.g., Good[27]). Complex partial and generalized seizures typically provoke profound amnesia for events occurring during the ictus. Moreover, certain individuals experience a postictal fugue state characterized by apparently purposeful behavior for which they are subsequently amnesic, much like dissociative fugue. Despite their prima facie resemblance to dissociative phenomena, however, these events should *not* be regarded as episodes of dissociation.[27] Dissociative amnesia is characterized by an inability to retrieve information that has been learned and is present in memory despite its inaccessibility.[2] Amnesia for ictal events, in contrast, reflects a disruption in normal information processing, resulting from uncontrolled neural activity, that prevents the encoding of new material during the ictus. The ictal amnesia is not a product of a retrieval failure, therefore, but simply the absence of memories to retrieve. It is for this reason that this form of amnesia is irreversible, unlike most cases of dissociative amnesia.[2]

Postictal fugue should not be regarded as a dissociative episode for similar reasons. Unlike dissociative fugue, postictal fugue is characterized by a disruption in consciousness associated with significant confusion and an abnormal electroencephalogram (EEG).[62] The apparently purposeful behavior displayed in postictal fugue is not dissociated from ongoing cognitive activity as it is in dissociative fugue; rather, it occurs in the relative *absence* of such activity. The inability to reverse the amnesia associated with postictal fugue serves as an illustration of this fact. The behavioral automatisms often observed in the context of complex partial seizures and regarded as a dissociative phenomenon by some (e.g., Good[27]) are amenable to a similar interpretation. As with the behaviors exhibited during postictal fugue, ictal automatisms only occur in the context of a disruption in consciousness and disturbed behavioral control; genuinely dissociated behaviors are noteworthy because they occur despite an otherwise intact ability to control action.[b] In both cases, it is likely that these behaviors result from the uncontrolled activation of circumscribed motor programs by epileptic discharges in neural sites associated with behavioral control. The fact that such automatisms are particularly characteristic of seizures originating in the frontal lobes lends support to this view.

Many of the phenomena associated with partial seizures originating in the temporal lobes, such as hallucinations, sensory and cognitive auras, déjà-vu, and déjà-veçu, should also be distinguished from true episodes of dissociation. Although hallucinations and auras have a phenomenology that departs from external reality, these phenomena involve the paradoxical *integration* of information within conscious awareness. As such, they may be more appropriately regarded as phenomena of *association* rather than dissociation.[40] The phenomenology of epileptic hallucinations and auras probably originates in the activation of representational structures in the temporal lobes, either directly, by seizure activity in representational networks, or indirectly, through seizure-related stimulation of limbic structures such as the amygdala and anterior cingulate.[3] Experiences of epileptic déjà-vu and déjà-veçu are also more associative than dissociative and may involve a similar neurophysiologic process. For example, stimulation of the amygdala by seizure-related discharges could imbue current perceptions and cognitions with an unwarranted emotional coloring that may be experienced as a sense of having encountered the situation before (see, e.g., Bancaud et al.[3] and Sierra and Berrios[58]).

Certain phenomena associated with temporal lobe epilepsy, however, can be regarded as examples of dissociation according to the scheme described by Cardeña.[15] Depersonalization and derealization commonly occur in the context of temporal lobe epilepsy and involve an alteration in consciousness characterized by dissociation from the self and/or the environment. According to Sierra and Berrios,[58] depersonalization and derealization are the products of a vestigial defense mechanism evolved to provide the optimum processing conditions for adaptive behavior in the face of threat. By this view, extreme anxiety triggers an inhibitory response from the left prefrontal cortex that dampens output from the sympathetic nervous system via the inhibition of the amygdala and anterior cingulate. In turn, the right prefrontal cortex is activated by ascending arousal systems controlled by uninhibited amygdala circuits, generating further inhibition of the cingulate. As a result, the individual experiences a sense of vigilant alertness devoid of any emotional or cognitive content, a state that is ideally adapted for the control of action in the face of extreme and potentially debilitating danger. If this response is triggered in the absence of threat, however, the resulting sense of depersonalization and derealization can be highly unpleasant and incapacitating. Given the validity of this account, depersonalization and derealization in the context of temporal lobe epilepsy may be the result of seizure activity in the amygdala that prevents the emotional tagging of perceptual and cognitive information prior to its entry into conscious awareness.[c] Alternatively, it may reflect an indirect defensive response in the face of anxiety elicited by seizure-based stimulation of the amygdala. Intuitively, one suspects that the former is the more plausible possibility, although the latter cannot be ruled out a priori. Following this account of depersonalization and derealization, these phenomena can be regarded as dissociative in sense (b) of the term; whether they should, in the context of epilepsy, be regarded as the result of a dissociative defense mechanism remains an empirical issue.[3]

The fact that few epileptic phenomena can be regarded as dissociative in any strict sense reflects widespread confusion over what actually constitutes dissociation. Although widely endorsed, the idea that any breakdown in memory, consciousness, identity, perception, or behavioral control is dissociative overextends the term and diminishes its descriptive validity.[15] Amnesia cannot be considered dissociative unless it involves an inability to retrieve intact information that should, under normal circumstances, be available for recall.[40] Amnesia resulting from a failure to encode information, including that which occurs in the context of epilepsy, does not fall within this category. Loss of behavioral control can only be considered dissociative if it is within the context of an otherwise intact ability to control action. Seizure-related motor phenomena, including complex automatisms, are not dissociative because they occur only in the context of reduced behavioral control in general. Current psychiatric taxonomies do not make these distinctions clearly enough, and rely instead on a purely descriptive approach that precludes precise classification based on the mechanisms underlying different phenomena.

Nonepileptic Seizures and Dissociation

The concept of dissociation is particularly important in relation to nonepileptic attacks because it sheds light on both the mechanisms and, potentially, the differential diagnosis of these phenomena.

In all cases, nonepileptic attacks involve a temporary loss of behavioral, sensory, or cognitive control that occurs in the context of intact neuropsychological functioning, as evidenced by a normal EEG during the nonepileptic ictus. The absence of paroxysmal brain discharges serves as the principal feature that distinguishes nonepileptic from “genuine” epileptic events. By itself, however, the EEG cannot provide a completely reliable basis for the identification of epileptic and nonepileptic seizures,[13] which underlines the potential value of dissociation as a criterion for an inclusive diagnosis of nonepileptic attack disorder.

Several converging lines of evidence indicate that these events involve a dissociative psychological mechanism, namely compartmentalization.[44] In the first instance, nonepileptic seizures are commonly found in the context of other forms of dissociative psychopathology. Bowman[7] and Bowman and Markand[8] found that the vast majority of those with nonepileptic attacks meet criteria for DSM-IV dissociative disorders such as dissociative amnesia and identity disturbance. Posttraumatic stress disorder, commonly assumed to involve a dissociative mechanism, was also particularly common in this group of patients.[7,8] Other studies have found that nonepileptic seizures frequently occur alongside other unexplained physical symptoms (e.g., Krishnamoorthy et al.[41] and Maldonada and Spiegel[47]), suggesting that they may be one aspect of a broader tendency to express psychological distress somatically, so-called “somatization.”[46] A number of authorities have suggested that compartmentalization is an important aspect of this phenomenon also (e.g., Brown[11]). Eating disorder symptoms, which have been linked to a dissociative process (e.g., Pettinati et al.[51]), also appear to be particularly common in patients with nonepileptic seizures.[41]

The frequent cooccurrence of dissociative psychopathology in patients with nonepileptic attacks appears to indicate a general propensity for dissociative experiences in this population. Consistent with this notion is a study by Kuyk et al.[43] showing that individuals with nonepileptic attacks display elevated levels of hypnotic susceptibility. In a related vein, in many cases, nonepileptic attacks can be provoked using suggestion, placebo. or hypnosis (e.g., Dericioglu et al.[17]). High hypnotic susceptibility is commonly found in patients with dissociative psychopathology,[25,57,60] and a dissociative interpretation of hypnosis has been offered by a number of authorities (e.g., Hilgard[32] and Woody and Bowers[64]). Bowman[7] also found that individuals with nonepileptic seizures had elevated scores on the Dissociative Experiences Scale (DES),[5] a self-report measure assessing everyday occurrences of dissociation compared to nonclinical controls. However, in a more recent study, Alper et al.[1] found that DES scores are also elevated in patients with complex partial seizures (see also Devinsky et al.[18]); indeed, there was no significant difference in overall DES scores between these patients and a group with nonepileptic seizures. Nevertheless, both epileptic and nonepileptic groups scored higher on the DES than typically observed in nonclinical populations. This finding demonstrates the danger of conflating the various definitions of dissociation within a single measure such as the DES. Because the DES treats dissociation as a unitary concept, it cannot differentiate between conditions that are characterized by different forms of dissociative phenomena, such as epilepsy and nonepileptic attack disorder.

Evidence implicating high dissociative comorbidity, hypnotic susceptibility, and exposure to trauma in individuals with nonepileptic seizures provides only indirect evidence for a dissociative interpretation of this phenomenon. Although such evidence suggests that a tendency to dissociate may be a common feature of these individuals, it does not constitute conclusive proof that nonepileptic attacks are themselves dissociative. A recent study by Kuyk et al.[43] places such an interpretation on a firmer footing. Like epileptic seizures, nonepileptic attacks are often associated with a dense amnesia for events occurring during the ictus. We have already stated that epileptic amnesia should not be considered a dissociative phenomenon, because it arises from a seizure-related disruption in memory encoding rather than an inability to retrieve intact memory traces. However, Kuyk et al.[43] showed that the amnesia associated with nonepileptic attacks may actually be the product of such a retrieval deficit. They compared a group of individuals with amnesia for events occurring during well-documented non-epileptic attacks with a group displaying amnesia following complex partial and generalized epileptic seizures. All individuals were hypnotized and given suggestions designed to facilitate the recovery of ictal events; the experimenter remained blind to group status at all times. Using a free-recall paradigm, 17 of 20 patients with nonepileptic seizures recovered significant information concerning the designated attack; this information was verified by video recordings or third-party reports. In contrast, not one of the 17 patients with epilepsy retrieved information concerning their attack during hypnosis. Such a finding appears to demonstrate that, unlike that found in epilepsy, nonepileptic amnesia results from a process that prevents the individual from accessing memories successfully encoded during the attack. This apparent separation of intact memorial information from conscious awareness following a nonepileptic attack, coupled with the phenomenologic character of these events, clearly identifies these phenomena as examples of dissociative compartmentalization.

Table 3 Psychogenic amnesias in approximate order of chronicity

Situational amnesia
Posttraumatic stress syndrome[a,b]
Ganser syndrome[c]
Psychogenic fugue[b]
Hysterical dementia
Depressive dementia
Multiple personality disorder[b,c]
Histrionic personality disorder[a]

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[a] Amnesia is not always a feature.

[b] Those disorders are most likely to be confused with epilepsy.

[c] Nosologic validity of these syndromes is in doubt.

Differential Diagnosis of Epilepsy and Dissociative Phenomena

The differential diagnosis of epilepsy and nonepileptic attack disorder is considered elsewhere in this book. In this section, we describe the nature and differential diagnosis of other conditions that are often confused with epilepsy.

Dissociative Amnesia

Dissociative amnesia is one variant of psychogenic amnesia; a list of the differential diagnoses for these conditions is given in Table 3. Dissociative amnesia is often overlooked and mistaken for a diagnosis of complex partial seizures. Thus, it is important to reemphasize that loss of awareness and amnesia should not automatically lead to a diagnosis of epilepsy.

Fugues

Fugues are characterized by the patient "coming to" in a strange place and professing no knowledge of how he or she arrived there. Again, there is a profound amnesia, sometimes extending backward in the patient's life for many years. Patients may adopt a different identity, which may be of brief duration, but in some cases may be retained in a remarkable way for a number of years.[52]

Table 4 Clinical assessment of fugue states

Psychogenic fugues	Postictal fugues
Identifiable emotional precipitant	Unlikely to be first presentation of epilepsy
Wandering is socially appropriate	Associated with obvious confusion
Gradual recovery of orientation	Rapid recovery
Electroencephalogram is usually normal	Abnormal electroencephalogram

Such fugues are often a clinical manifestation of depression, but they often seem to come on after a trauma, and head injury is frequently reported. Some points of differential diagnosis between psychogenic fugue and postictal fugue are given in Table 4. Psychogenic fugues also need to be distinguished from transient global amnesia, poiromania, somnambulism, and postconcussional amnesia.

Somnambulism

Somnambulism implies sleepwalking, and this is much more common in childhood. In adults, it has distinct psychopathologic significance. It is one of the parasomnias, usually arising in non–rapid eye movement (REM) sleep. There may be only brief wandering or lengthier episodes, with the completion of quite complex but purposeless tasks, for which there is profound amnesia. During the attack, the eyes are open; the patient seems confused and expresses surprise if awakened. Its onset in adulthood is usually associated with emotional trauma.

A family history of sleepwalking or night terrors is reported in 80% of somnambulists, and many children have isolated and clinically nonsignificant sleepwalking episodes. It is often considered one of the neurotic traits of childhood, alongside nailbiting, phobias, enuresis, food faddisms, tics, and mannerisms. In themselves they have little import, but they may cluster and suggest a tendency to later neurotic breakdown. Certainly the onset of somnambulism in adult life suggests some underlying psychopathology, often depressive, and, in association with seizures, suggests that the latter will be nonepileptic.

Sometimes the somnambulism can be distinguished from epilepsy only with polysomnography and telemetry, and third-party accounts of the attacks may be misleading.

Dissociative Identity Disorder (Formerly Multiple Personality Disorder)

Dissociative identity disorder is characterized by the presence of two or more identities or personality states. Each state is often, although not always, amnesic for the other. Patients typically complain of an inability to remember the full sequence of their personal history. The sudden switch from one state to another may give rise to a suspicion of epilepsy, and nonspecific EEG changes may add further confusion. Many reported cases give histories of earlier physical and mental deprivation, abuse, and head injuries. The fact that multiple personalities are described in association with epilepsy,[4] especially temporal lobe epilepsy,[56] adds confusion because the nosologic status of this condition is held in doubt by some authors.[49]

Table 5 Criteria for posttraumatic stress disorder[a]

Exposure to a traumatic event
Experienced, witnessed, or confronted with event(s) involving actual or threatened death, serious injury, or threat to integrity of self or others
Response of intense fear, helplessness, or horror
Persistent reexperiencing of the trauma
Recurrent and intrusive distressing recollections
Recurrent and distressing dreams of the event
Acting or feeling as if the traumatic event were recurring
Intense psychological distress at exposure to internal or external cues
Physiologic reactivity on exposure to internal or external cues

- Persistent avoidance of stimuli associated with the trauma and numbing of general responsiveness
  - Efforts to avoid associated thoughts, feelings, or conversations
  - Efforts to avoid associated activities, places, or people
  - Inability to recall an important aspect of the trauma
  - Markedly diminished interest in significant activities
  - Feeling of detachment from others
  - Restricted range of affect
  - Sense of a foreshortened future
- Persistent symptoms of increased arousal
  - Difficulty falling or staying asleep
  - Irritability or outbursts of anger
  - Difficulty concentrating
  - Hypervigilance
  - Exaggerated startle response
- Duration of the disturbance >1 mo
- The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning

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[a] 309.81 in *Diagnostic and Statistical Manual for Mental Disorders*, 4th edition.[2]

Posttraumatic Stress Disorder

Posttraumatic stress disorder (PTSD) has assumed considerable importance in recent years, yet it is an easily missed diagnosis. The current criteria, as laid down by DSM-IV,[2] are given in Table 5. Obviously, the precipitating trauma is the significant criterion for entry, but in many cases the trauma may have occurred in the past and perhaps been reactivated by recent events. The similarity between PTSD and nonepileptic seizure disorder patients has been commented on by some authors (see Chapters 207 and 282), and the hyperexplexia of PTSD may be mistaken for myoclonic seizures. In such cases, the patient's seizures are seen as the central and often only complaint, and the accident that may have preceded them provided a head injury as an etiology for the attacks. However, typically, the posttraumatic amnesia will be brief, and the accident terrifying. Careful history taking will unravel the pervasive underlying symptoms of a PTSD, although in some patients there may be extreme reluctance to discuss the accident. Psychogenic amnesia is a cardinal clinical symptom of this condition.

Déjà-vu

Déjà-vu and its associated states such as jamais-vu and déjà-veçu are experienced by many people and do not necessarily signify psychopathology. The most common medical association with déjà-vu is an anxiety disorder, in which setting the experience fails to have the vivid and clearly repetitive nature that the aura of a temporal lobe focus brings.

Posttraumatic Amnesia

Posttraumatic amnesia is distinguished by the clear relationship to a head injury, although in some cases this is clinically obscure. For example, a patient may deny any such injury, or, more commonly, a seemingly trivial injury may provoke a profound loss of memory that seems enduring. Such cases are unlikely to be taken for a seizure disorder, but if they are associated with some apparent confusion, a partial status needs to be excluded. A prolonged retrograde amnesia, especially with loss of personal identity, in the presence of normal learning abilities or minimal posttraumatic amnesia is usually indicative of a psychogenic amnesia.

Measurement of Dissociation

Several scales to measure symptoms of dissociation have been developed, but few have been evaluated in neurologic populations, such as those with epilepsy. Moreover, the descriptive nature of the scales means that they are unable to separate out the mechanisms responsible for the dissociative symptoms in question. As such, they cannot be used to aid in the differential diagnosis of epilepsy, although they can be useful for determining the extent and nature of dissociative symptoms in research settings.

The Dissociative Experiences Scale (DES) is a brief self-report questionnaire designed to elicit information regarding lifetime experiences of “dissociation” in normal and clinical populations.[5] Although the DES is the most widely used measure of dissociation, the use of total scores on the scale is problematic because they conflate different types of dissociation (e.g., detachment and compartmentalization) within the same measure. It is more appropriate to identify and use separate subscales pertaining to the types of dissociation under scrutiny. Most factor-analytic research suggests that the scale comprises three subscales measuring amnesia, depersonalization–derealization, and absorption.[3] Alternatively, scales specifically developed to assess different types of dissociation, such as the Cambridge Depersonalization Scale,[59] the Multidimensional Dissociation Inventory,[10] or the Somatoform Dissociation Questionnaire,[50] can be used.

The Structured Clinical Interview for DSM-IV Dissociative Disorders (SCID-D) is more specific for diagnosis of DSM-IV dissociative conditions than the DES, having separate subscales for symptoms of dissociative amnesia, depersonalization, derealization, identity confusion, and identity alteration.[61]

Treatment

Pharmacotherapy

When there is an indication for pharmacotherapy, for example, antidepressants with an affective disorder, these should be prescribed. In addition, antidepressants are helpful in countering the symptoms of other disorders such as the intrusive events of posttraumatic stress.[47]

In nonepileptic seizures, anticonvulsants are unnecessary and should be withdrawn. Although some physicians

maintain patients on anticonvulsants such as carbamazepine for their mood-enhancing properties, there is evidence that the prescription of anticonvulsants for pseudoseizures without epilepsy may aggravate such attacks.[28] In many cases, slow withdrawal of anticonvulsants, with reassurance that patients do not have epilepsy, in a supportive clinical environment will lead to a resolution of attacks without further intervention.

For many patients with dissociative disorders, the nonmedical therapeutic interventions described in what follows are the most appropriate.

Hypnotherapy

Both Janet and Freud used hypnosis to access the isolated memories in patients and make "associative corrections." In other words, they attempted to reproduce the supposed hysterical action of autohypnosis under controlled conditions and "disinfect" the dissociated traumatic memories, either by direct countersuggestion or, more indirectly, catharsis. Freud soon abandoned this practice, however, because of its lack of success. He found that patients were either unable to be hypnotized, in spite of the apparent autohypnotizability of such patients, or, more important, they were cured but later produced another set of symptoms (symptom substitution).

Today hypnosis is still used in two ways. It is sometimes used to induce an attack, in other words, to help with the diagnosis. This has variable success and in part relates to the effectiveness of the person doing the hypnosis as a hypnotist. It is not widely used and not recommended to the inexperienced. Furthermore, as with other induction methods, outcome should be viewed with caution because epileptic seizures can also be triggered in this way.[42]

Hypnosis is also used to elicit the traumagenic events of dissociative disorders isolated in memory as part of treatment. It is a controversial option, however, not least because "lost truths" and discovered fantasies are difficult to differentiate, especially in an altered state of consciousness. Evidence gathered by both the British False Memory Syndrome Association and its American equivalent suggests that hypnotherapy and "recovered memory therapy" are major instigators of false allegations.[14]

Psychotherapy

Colloquially known as "the talking cure," psychotherapy encompasses a vast array of theoretical orientations and practices, ranging from individuals to groups. Psychodynamic psychotherapy views dissociative symptoms as signals of individual and/or family distress. As such, they are not the focus of psychotherapeutic treatment but are indirectly alleviated by allowing patients to explore the factors that have contributed to their disorders, including past history and interpersonal difficulties. Cognitive behavior therapy (CBT) aims to identify and alter maladaptive thoughts and behaviors that are contributing to the maintenance of symptoms.[26]

The choice of treatment for the patient depends on a number of factors, including an identifiable cause such as past trauma, age, family dynamics, intellectual impairment, compliance, patient preference, and psychological mindedness. In addition, this is not such an easy option as it at first sounds. Patients with nonepileptic attacks are often difficult to manage, and the combination of apparent neurology with psychopathology is confusing for the inexperienced. It is recommended that patients be referred to therapists with special knowledge, experience, and interest in conversion and dissociative disorders.

There is only very limited evidence demonstrating the efficacy of psychotherapeutic intervention in patients with dissociative disorders, and substantial randomized, controlled trials are urgently needed.

Summary and Conclusions

Dissociation is a complex and multifaceted concept that is frequently misapplied within the field of epilepsy. In this chapter, we have explored the various components of the dissociation concept and how they relate to the phenomena of epilepsy and nonepileptic seizures. We have demonstrated why many epileptic phenomena often thought to be instances of dissociation, such as amnesia, postictal fugue, behavioral automatisms, aura and hallucinations, should not be regarded as dissociative at all. We have also argued, however, that depersonalization and derealization occurring in the context of epilepsy can be regarded as dissociative, in the sense that they involve an altered state of consciousness characterized by disengagement from the self or environment. We have also presented evidence indicating that nonepileptic attacks should be considered dissociative phenomena, in this case involving a temporary disruption in behavioral control and subjective awareness despite intact neuropsychological functioning. Although certain aspects of epilepsy are dissociative, therefore, they do not involve the same type of dissociation as that underlying nonepileptic attacks.

If the dissociation concept is to prove useful in this area, much greater precision, both conceptual and methodologic, is required. Researchers and clinicians should be explicit about which definition of dissociation they are referring to, and efforts should be made to use measures of dissociation that, unlike total scores on the DES, are "phenomenon pure." Assessing the reversibility of nonepileptic amnesia, which may prove to be invaluable as an aid to differential diagnosis in this area, provides one illustration of the potential utility of such an endeavor.

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Chapter 285

Panic Disorder and Hyperventilation Syndrome

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Introduction

Panic disorder and hyperventilation syndrome (HVS) are frequently underrecognized conditions that are easily mistaken for epileptic seizures. This chapter highlights practical diagnostic strategies for distinguishing these disorders. We explore etiologies of HVS and conclude with a discussion of the effects of hyperventilation on seizures and the EEG because these issues may arise in the context of the evaluation of hyperventilation symptoms. Potential areas of commonality in the pathogenesis of panic disorder and epilepsy are discussed in Chapter 206.

Panic Attacks and Panic Disorder

A 28-year-old woman had undergone a subtotal resection of a right temporal ganglioglioma at 11 years of age. This had presented with complex partial seizures associated with déjà-vu sensation followed by altered responsiveness. She was seizure free until 8 years later, when typical seizures recurred, but now with secondary generalization. A further resection of a large part of the right temporal lobe was undertaken. This resulted in significant improvement in the epilepsy, but the patient continued to have occasional complex partial seizures with a rising epigastric aura, déjà-vu sensations, and complex motor automatisms.

She subsequently developed new episodes, different from her typical complex partial seizures. These began with a sense of shortness of breath and a choking feeling. She experienced nausea that was distinct from the earlier rising epigastric aura. The episodes also included dizziness and a perception that things were unreal around her. She also had an overwhelming feeling that she was going to die. With great concern about these episodes, the husband gave up his job to be constantly by her side.

Video-electroencephalographic (EEG) monitoring demonstrated that, although the patient has had ongoing epileptiform discharges and slow waves over the right temporal region, the new episodes were unassociated with electrographic correlate. A diagnosis of panic attacks was rendered. The patient has undergone a process of psychoeducation, reassurance, and discussion with the appropriate neurosurgeons. She began to articulate her fear of dying from her tumor. Panic attacks improved significantly with this treatment but occasionally recurred without clear provocation. Her husband was trained to be observant but not overindulgent in response to the episodes, and he ultimately returned to work.

One of the most common episodic symptoms that can be confused with a seizure is a *panic attack*. Numerous series attest to the common misdiagnosis of seizures in patients with panic attacks[26,38] and the erroneous diagnosis of panic attacks among patients with seizures.[1,14,51,78] Recurrent unexpected panic attacks define the condition termed *panic disorder*.[66] Diagnostic criteria for panic attacks and panic disorder are listed in Table 1. Significant morbidity associated with epilepsy or panic disorder and with the failure to allocate appropriate treatment makes the need to distinguish these two disorders especially crucial.

Epilepsy has a lifetime prevalence of 3% to 4%,[36] and panic disorder has a lifetime prevalence of 1% to 2%.[64] Although there is a fairly equal overall rate of epilepsy in men and women, panic disorder is twice as likely in women.

According to the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV),[3] a panic attack is a “discrete period of intense fear or discomfort” in which four or more of the symptoms listed in Table 1 “develop abruptly and reach a peak within 10 minutes.” Many of the symptoms of panic attacks are reminiscent of symptoms that may appear during some types of epileptic seizures. Differences between panic attacks and seizures are highlighted in Table 2 and elaborated on in the following discussion.

Fear is a commonly encountered component of partial seizures and is the most common ictal psychiatric symp-tom.[13,81] The importance of the temporal lobe as a site of localization for fear auras is validated by electrical stimulation of mesial temporal structures such as the amygdala, which produces many of the symptoms reminiscent of panic attacks (intense fear, dizziness, nausea, tachycardia, chest pain, and depersonalization).[29] Gloor argued that “the aura of fear in a temporal lobe seizure may take exactly the form of a typical panic attack.”[29] He further contended that this “situation is further compounded in those patients with epilepsy who also have panic attacks that may provoke their epileptic seizures, either by hyperventilation or by some direct effect of the CNS arousal.”[29]

Table 1 Symptoms of Panic Attack and Panic Disorder

Panic attack (summary of DSM-IV criteria)
A discrete period of intense fear or discomfort, in which four (or more) of the following symptoms develop abruptly and reach a peak within 10 min
Cardiopulmonary symptoms
Chest pain or discomfort
Sensations of shortness of breath or smothering
Palpitations, pounding heart, or accelerated heart rate
Neurologic symptoms
Trembling or shaking
Paresthesias (numbness or tingling sensation)
Feeling dizzy, unsteady, light-headed, or faint

Psychiatric symptoms

Derealization (feelings of unreality) or depersonalization (being detached from onself)

Fear of losing control or going crazy

Fear of dying

Automic symptoms

Sweating

Chills or hot flushes

Gastrointestinal symptoms

Feeling of choking

Nausea or abdominal distress

Panic disorder (summary of DSM-IV criteria)

With agoraphobia

A. Recurrent, unexpected panic attacks
B. At least one of the attacks has been followed by 1 mo or more of persistent concern about having additional attacks; worry about the implications of the attack or its consequences; a significant change in behavior related to the attack
C. The presence of agoraphobia, i.e., anxiety about being in places or situations in which escape might be difficult (or embarrassing) or in which help might not be available in the event of having a panic attack

Without agoraphobia

A. Both A and B above
B. Absence of agoraphobia

DSM-IV, *Diagnostic and Statistical Manual for Mental Disorders*, 4th edition.

The fear aura tends to be associated more with a typical rising epigastric aura, whereas panic attacks are associated more with a spreading abdominal discomfort. The aura tends to be described as if it has a “harder,” more organic feel. Williams[81] described ictal fear as unnatural rather than seeming more reality based. The intensity of ictal fear sensation is mild to moderate and rarely reaches the intensity of a panic attack.

Anxiety symptoms in panic attacks vary in nature among different individuals. Some experience a nonspecific sensation of “impending doom,” whereas others may experience a fear of having incurred a devastating medical problem such as a heart attack or stroke. Sometimes, the anxiety is less prominent than the other features, such as palpitations or chest discomfort, noted in Table 1. It is thus of little wonder that most patients with a panic attack present initially to an emergency room or a nonpsychiatric medical clinician rather than to a psychiatrist.[34]

In panic attacks, autonomic symptoms and other bodily symptoms appear such as palpitations, sweating paresthesias, dizziness, nausea, feeling faint, and a sense of abdominal or central chest discomfort, and it is not uncommon for patients experiencing a panic attack to be thought of as having an acute coronary attack or a stroke. Autonomic symptomatology is also common in seizures, but these are of lesser “subjective” intensity than in panic attacks. Of note, paroxysmal salivation is a typical autonomic symptom in seizures of mesial temporal or insular origin and not of panic attacks. Salivation may often be copious and associated with nausea and vomiting.

Subjective dyspnea often experienced during a panic attack led to the earlier confusion and often mislabeling of panic attacks as hyperventilation syndrome, although some might argue that they are intimately related (see later discussion).[28] Alteration in breathing pattern is very common to both seizures and panic attacks, so that the documentation of hyperventilation has limited distinguishing value. If hyperventilation is severe, tetany may occur, which could be confused with seizures associated with tonic activity.

In contrast to complex partial seizures, distinct confusion or loss of consciousness is unusual in a panic attack, although patients may become completely absorbed by the panic experience to the point at which they are unable to report what is going on around them. A panic attack associated with profound hyperventilation could also conceivably lead to a “subjective perception” of loss of consciousness. Symptoms of derealization, depersonalization, and déjà-vu may occur in both conditions.[73] The patient with panic attacks associated with these symptoms could end up undergoing an extraordinarily extensive testing if panic is not considered in the differential diagnosis by the medical clinician. Because of dissociation during panic attacks and subsequent claims of amnesia for the episodes, the patient may never make it to a psychiatrist for treatment (M. Trimble, personal communication). Distortion of perception should raise additional suspicion for partial seizures.

“Reported” preservation of awareness of surroundings and responsiveness during the ictus are usually interpreted as supportive evidence of a panic attack. It is important to remember, however, that in seizures of nondominant mesial temporal origin, patients may continue to follow commands and interact with the examiner or other interlocutors during the ictus, giving the appearance of “intact” consciousness.[23] Careful testing of these patients, however, after the event reveals that they do not recall what happened during it. In such cases, recording of these events with video-EEG may be the only way of establishing a correct diagnosis.

Ictal fear usually lasts <30 seconds and is usually more stereotyped than panic attacks. A partial complex seizure during which ictal fear may occur usually lasts only 2 minutes. However, partial complex status epilepticus associated with isolated fear has been reported.[62] In contrast, panic attacks usually last from 5 to 20 minutes and have a longer buildup of anxieties.

Table 2 Differential Diagnosis of Seizure Versus Panic Attack

Characteristics	Seizure	Panic attack
Signs and symptoms		
DSM-IV–based panic symptoms	Less common	Common

Repetitive, highly stereotyped presentations	More common	Rare
Atypical symptoms (aphasia, perceptual distortions)	More common	Less common
Association with rising epigastric sensation	More common	Not present
Disturbed behavior in sleep	More common	Less common
Altered consciousness	May occur	Usually preserved, patient may report it though
Fear duration	Usually 30 s; entire seizure usually <2 min; postictal fear may occur	Usually 5–10 min, up to 20 min
Agoraphobia	Less common, but may occur	More common
Rapid onset of episodes	More common	Less common
Postepisode confusion	Can occur	Not present
Postepisode fatigue	More common	Less common
History		
History of seizure risk factors (e.g., febrile seizures, head trauma)	Common	Less common
Family history of panic	Uncommon	Common
Anticipatory anxiety	Uncommon	Common
Findings		

Interictal neurologic deficits	Common	Uncommon
Abnormal sleep-deprived interictal electroencephalogram	Often present	Usually absent
Electrographic seizure activity during episode	Common, but "surface-negative events" may occur	Not present
Automatisms during episode	Common	Not present
Treatment		
Response to anxiolytics (nonbenzodiazepine)	Not helpful	Helpful
Response to antidepressants	Rarely worsens	Helpful
Response to antiepileptic drugs	Usually	Occasionally and depending on agent

DSM-IV, *Diagnostic and Statistical Manual for Mental Disorders*, 4th edition.
Source: Modified from Lee DO, Helmers SL, Steingard RJ, et al. Case study: seizure disorder presenting as panic disorder with agoraphobia. *J Am Acad Child Adolesc Psychiatry.* 1997;36(9):1295–1298.

Postictal symptoms of panic and symptoms of primary panic disorder can often lead to confusion. For example, in a study of 100 patients with refractory epilepsy, Kanner et al.[44] found that 10% of patients experienced postictal symptoms of panic after >50% of their seizures. The median duration of these symptoms was 24 hours. A careful history of the context in which symptoms occur as well as a review of other clues (Table 2) should help to avoid militate against this potential confusion.

Seizures can begin at any age, although certain forms of seizures, such as absence seizures, are much likelier to begin in childhood. Panic disorder usually begins in late adolescence or early adulthood, although onset in the 30s and even 40s can occur.[64] Symptoms suggestive of panic attacks that begin in older age groups should be vigorously investigated for the possibility of a seizure disorder.

The value of performing a detailed history (including contacting witnesses of an episode) when distinguishing seizures from panic attacks cannot be overemphasized. Anecdotal experience and review of case series of seizures[79] mistaken to be panic attacks often reveals some evidence of associated classic ictal phenomenology during some of the attacks such as automatisms or motor activity suggestive of spread of seizure activity. Patients often fail to recognize or report such associated symptoms such as transient confusion or subtle automatisms, and therefore it behooves the clinician to search for these clues. Sometimes, a frank convulsion following fear symptomatology clinches the epileptic diagnosis. Identifying a past medical history of febrile seizures or other risk factors for spontaneous seizures provides additional diagnostic clues.

Panic attacks tend to be somewhat less stereotyped than seizures, although this is best documented on video-EEG because historical accounts of observers may not necessarily emphasize the obvious replicability of ictal episodes.

Although some panic attacks may be linked to specific situations, panic disorder comprises at least two spontaneous panic attacks, at least one of which is associated with worry about subsequent attacks or avoidance behavior. Controversy

exists whether agoraphobia (a common comorbid condition consisting of fear related to places from which escape may be difficult)[48,64,76] is a component of panic disorder or represents an independent condition that may be provoked by a panic attack. Similar to epilepsy, anticipatory anxiety may become so severe that the individual begins to restrict travel and activity for fear of finding himself or herself in the midst of an attack. Social phobias are common in panic disorder, but agoraphobia may also occur in epilepsy.

Although sleep can be provocative for many types of seizures, it is worth remembering that two thirds of patients with panic attacks have had one or more events at night. Polysomnography has demonstrated panic attacks occurring at sleep onset during stage 2 sleep or slow-wave sleep, but most commonly after awakening.[10,53,61,63]

The EEG may be helpful in suggesting an epileptic disorder both interictally, if epileptiform abnormalities or other focal cerebral abnormalities are found, or ictally, if an episode is caught during an episode while the EEG is running. Not uncommonly, the epileptologist is consulted to help to distinguish a seizure disorder from panic disorder and extended EEG monitoring such as video-EEG is ordered. Video-EEG has the advantage of permitting a detailed review of recorded clinical behavior in addition to detailed EEG analysis. Experienced electroencephalographers are aware, however, of the limitations of the EEG, in that simple partial and sometimes even complex partial seizures may not reveal an obvious correlate on scalp EEG[14] and that, therefore, the absence of an obvious electrographic seizure during an episode does not necessarily exclude seizures.[18] Supplementation of routine EEG recording

with meticulously placed sphenoidal electrodes may enhance the yield on EEG.[43] Elevated serum prolactin levels 15 to 20 minutes after an episode may help to point to a seizure as the etiology, even when there is no obvious change on the surface EEG recording.[9]

It has been suggested that lactate infusion could be used as a diagnostic tool to provoke panic if it is present, but this is rarely necessary or even feasible.[57,70] Hyperventilation may provoke a panic attack in those prone to panic disorder, but evidence suggests that such provoked attacks are subjectively different from natural panic attacks.[31] It is generally considered that both these procedures have their effects by causing alterations in pCO_2 and pH.[66]

As in epilepsy,[19] comorbid depression and possibly bipolar disorder[20,64] are commonly found in panic disorder, as is the development of secondary psychosocial problems.[50] Whereas the risk of suicide among epilepsy patients is five times that in the general population,[5] the combination of panic attacks with major depression raises the risk of suicide beyond that encountered in major depression alone.[64]

Patients with ictal panic may also suffer from interictal panic attacks. However, studies of the comorbidity of panic disorder and epilepsy are limited. One of the few available surveys[68] suggests that up to 21% of epilepsy patients experience panic attacks compared to only 3.8% of the population.[45] Although the timing of the panic attacks in relation to the onset of epilepsy was not revealed by this study, the assumption that panic attacks were reactive to developing epilepsy cannot be made, especially in light of studies of other psychiatric comorbidity (i.e., depression) in epilepsy, which showed that depression may often precede the first seizure.[15,37] Agoraphobia, however, may develop in epilepsy due to the fear of having a seizure while crossing the street or in a public place. Mechanisms of potential commonality between panic disorder and epilepsy are described in Chapter 206.

Long-term outcome studies are lacking in panic disorder, although studies and anecdotal experience suggest that many patients will have a waxing and waning of episode frequency, whereas others may have more prolonged episode-free periods, which is again similar to the variability of outcomes seen among some epilepsy patients.

Similar to the risks among epilepsy patients of seizure exacerbation following abrupt withdrawal of benzodiazepines,[35] misuse of benzodiazepines by patients with panic disorder attempting to relieve their symptoms may be associated with worsened panic attacks during benzodiazepine withdrawal.

Panic disorder should also be distinguished from numerous medical conditions that may give rise to similar symptomatology, such as cardiac dysrhythmias in younger people (e.g., Romano-Ward syndrome; prolonged-QT syndrome) and paroxysmal metabolic disorders (e.g., carcinoid syndrome, hypoglycemia, pheochromocytoma, and Cushing syndrome). All of these disorders, however, are relatively rare. Other conditions to consider include alcohol drug withdrawal, illicit drug effects (amphetamines, cocaine, marijuana-induced tachycardia), vertigo-related disorders, and asthma.[21,46] Such alternative conditions should be strongly considered when panic attacks are unresponsive to the usual treatments or do represent seizures.

As discussed in Chapter 206, treatments for panic disorder (benzodiazepines, selective serotonin reuptake inhibitors, tricyclic antidepressants, and, more rarely, monoamine oxidase inhibitors) may affect the same neurotransmitters (e.g., γ-aminobutyric acid, norepinephrine, and serotonin) that are also crucial in aborting or promoting epileptogenesis. Other treatments for panic disorder include cognitive–behavioral therapy[4] and psychotherapeutic approaches.

Panic symptoms may often be identified in psychogenic nonepileptic events (PNES) that often are misdiagnosed as epileptic seizures. This topic is reviewed in great detail in Chapters 207 and 282.

Hyperventilation Syndrome

A 20-year-old student of environmental studies presented with episodes occurring several times per day in which she would complain of feeling very light-headed and then fall backward. She would appear confused and express uncertainty as to where she was. She would feel cold and numb and experience tingling sensations in her hands. Her hands would subsequently begin to shake with a coarse tremor, which would then evolve into profound hand stiffness. In the most severe episodes, she would experience tetanic contraction of the hands accompanied by considerable distress and crying. After the event, the patient remained distressed and complained of headache.

Video-EEG monitoring demonstrated no epileptiform discharges, but there was notable hyperventilation observed before and during each episode, resulting in diffuse slow wave changes. During an EEG study, hyperventilating volitionally on command reproduced her typical symptoms completely. This case illustrates the clinical expressions of the hyperventilation syndrome (HVS).

Successful treatment involved demonstrating the video-EEG carefully to her and taking her through a course of relaxation training, including exercises in controlled breathing. The episodes of hyperventilation reduced significantly, although it was possible that they could recur during stressful moments. Overall, the patient felt more in control of her symptoms and found them much less disabling. She was able to return to her routine course of studies.

The hyperventilation syndrome is another challenging diagnosis that overlaps with but is distinct from panic disorder. Although some believe that HVS is simply one variety of panic or anxiety disorder, others argue for recognizing it as an independent entity.

The evolution of the recognition of this syndrome is nicely described by Evans.[22] As early as the Civil War, a mysterious condition characterized by palpitations, shortness of breath, dizziness, and headaches afflicting Union soldiers was described by DaCosta.[11,22] Similar symptoms were noted among soldiers in World War I.[56] Gowers described a similar syndrome of difficulty breathing, yawning, reduced concentration, and a sense of unreality influenced by emotion and more commonly seen among women.[32] Goldman identified the relationship of "forced ventilation" with tetany as well as dizziness, paresthesias, and attacks of nervousness and crying associated with hysteria.[30] The term "hyperventilation syndrome" was introduced in the late 1930s to describe diverse symptoms associated with anxiety and often reproduced by having patients willfully hyperventilate. Lewis argued that acute and chronic hyperventilation syndrome presented frequently and ubiquitously.[69a]

Since at least 1929,[80] it has been recognized that some individuals may hyperventilate chronically. White and Hahn[80] called this “sighing dyspnoea”; this is not quite an accurate description, however, because, although “sighing” can describe the form of breathing, patients rarely complain of discomfort of breathing (dyspnea). Some may, however, complain of an inability to breath deeply enough.

Pincus[55] drew neurologic attention to the condition of chronic hyperventilation syndrome in his influential book *Behavioural Neurology*. He commented, “of all psychophysiological reactions, probably the most common one dealt with by physicians is the hyperventilation syndrome.” Lum[58] observed that the typical and known cases of HVS were just the “tip of the iceberg” and that as many as 6% of general medical outpatients may have the syndrome.

HVS occurs in most age groups, with a peak between ages 15 to 55 years[65]; it occurs predominantly in women. It presents as one of two varieties—a less common but much more obvious acute form and a less obvious but more common type termed chronic HVS. Acute HVS presents with obvious overbreathing and tachypnea and may have associated chest pain, dyspnea, dizziness, palpitations, and muscle spasms related to tetany, paresthesias, and syncope.[65] Chronic HVS is more challenging to recognize because it is associated with a diverse array of somatic complaints that are often misdiagnosed based on the organ system suggested by the symptomatology. Furthermore, overbreathing is usually not apparent; instead, intermittent deep sighs and frequent yawning may be seen. Symptoms of chronic HVS are best categorized according to bodily symptoms (Table 3).

Table 3 Symptoms and Signs of the Hyperventilation Syndrome

General
Fatiguability, exhaustion, weakness, sleep disturbance, nausea, sweating
Cardiovascular
Chest pain, palpitations, tachycardia, Raynaud phenomenon
Gastrointestinal
Aerophagia, dry mouth, pressure in throat, dysphagia, globus hystericus, epigastric fullness or pain, belching, flatulence
Neurologic
Headache, pressure in the head, fullness in the head, head warmth
Blurred vision, tunnel vision, momentary flashing lights, diplopia

Dizziness, faintness, vertigo, giddiness, unsteadiness

Tinnitus

Numbness, tingling, coldness of face, extremities, trunk

Muscle spasms, muscle stiffness, carpopedal spasm, generalized tetany, tremor

Ataxia, weakness

Syncope and seizures

Psychological

Impairment of concentration and memory

Feelings of unreality, disorientation, confused or dreamlike feeling, déjá-vu

Hallucinations

Anxiety, apprehension, nervousness, tension, fits of crying, agoraphobia, neuroses, phobia, panic

Respiratory

Shortness of breath, suffocating feeling, smothering spell, unable to get a good breath or breathe deeply enough, frequent sighing, yawning

Source: From Evans RW. Hyperventilation syndrome. In: Kaplan PW, Fisher RS, eds. *Imitators of Epilepsy*. New York: Demos; 2005: 241–252, Table 18.1 .

The neurologist is likely to encounter HVS in the context of one or more diverse symptoms including general dizziness, diffuse weakness, confusion or agitation, paresthesias in the extremities or periorally, and depersonalization sensations. Pincus[69] studied 550 neurologic outpatients and found 30 to suffer from this syndrome. These patients were asked to hyperventilate voluntarily to see if they could evoke the symptoms of which they were complaining. The typical clinical features were light-headedness, headache, paresthesias, giddiness, weakness, and difficulty concentrating. They tended to be aged between 15 and 30 years, to be female, and to have a history of psychosomatic illnesses. The majority (80%) showed some episodes of alteration of consciousness, and 6% had episodes of loss of consciousness, whereas 3% had episodes of tetany. Twenty percent had been given a diagnosis of epilepsy at some stage. Some patients also had gastrointestinal complaints, such as difficulty swallowing and abdominal pain or of chest symptoms such as chest pain, palpitations, and dyspnea.

HVS-related symptoms affecting thinking function and mood are the most likely symptoms to lead to a referral to the epileptologist. Complaints of déjà-vu or hallucinations are rare but have been reported.[2]

Hyperventilation is characterized by ventilation exceeding metabolic demand, leading to hemodynamic and chemical alterations that foster diverse symptomatology. Although a reduction in pCO_2 from willful hyperventilation can often reproduce these symptoms, many individuals with HVS do not in fact have reduced pCO_2 during HVS episodes. The terms “behavioral breathlessness” or “psychogenic dyspnea” have been proposed as alternatives.[65]

Breathing may be atypical in HVS, in which a more thoracic (as opposed to abdominal) breathing occurs. Typically, there is heaving of the upper sternum and a lack of lateral costal expansion—like a normal sigh. This may, therefore, be a learned behavior (a habit). In depression, there may be evident sighing hyperventilation, and chronic hyperventilation may be associated with depression. If chronic, hyperventilation will result in diminished reserve due to chronic mild hypocapnia, and, thus, a slight exacerbation under mild stress may lead to decompensation and marked symptoms. Patients with chronic hyperventilation syndrome are found to have a tendency to a childhood history of emotional problems, a family history of anxiety disorders, and a relative failure of psychosexual adjustment.[71]

Conflict thus may lead to worsening of hyperventilation, which is part of a preparation for “fight or flight.” Hyperventilation may also be a learned way of avoiding conflict in an individual with a strong sense of personal vulnerability. If, however, hyperventilation occurs when the individual is actually at rest (as is often the case, possibly the result of inner conflict), the preparation, as if for fight or flight is physiologically unnecessary.

Although the etiology of HVS is not definitively clear, one theory suggests that some individuals are prone to specific abnormal respiratory responses to stimuli like stress (or chemical or other triggers) that result in excessive and disordered breathing, emphasizing thoracic rather than normal diaphragmatic respiration, thereby producing an expanded chest and increased residual lung volume. This then precludes inspiring the normal volume and produces a sensation of dyspnea. A “suffocation alarm” then leads to an autonomic response with symptoms including palpitations, anxiety, and diaphoresis.[65]

HVS may be medically more benign than some of the alternative diagnoses suggested by its symptoms (e.g., myocardial infarction); therefore some HVS sufferers incur significant morbidity from the numerous testing procedures often performed in search of an explanation for symptoms. Furthermore, HVS patients experience genuine discomfort and psychological distress related to their symptoms.

The most critical aspect of making a diagnosis of HVS is to consider it when considering a differential diagnosis; this helps to temper an otherwise excessive laboratory testing plan. In the face of acute HVS, the clinician may want to exclude internal or external organic causes, including lesions in the pons or midbrain tegmentum, liver disease, and salicylate poisoning. Occasionally, complex partial seizures (arising particularly from the insular cortex) may involve hyperventilation as part of the aura, although this is usually accompanied by automatisms and other obvious signs of a seizure. In the face of presentation with chest pain, diagnoses like pulmonary embolus and myocardial infarction may need to be ruled out.

Diagnosis of chronic hyperventilation syndrome may be made from a careful history taking, possibly combined with an attempt to precipitate or exacerbate the symptoms by voluntary hyperventilation typically by increasing respiration to 60 per minute or encouraging sustained deep breaths for 3 minutes.[59] The validity of this “hyperventilation test” has been challenged more recently.[41] Antecedent anxiety may be more compelling than the hyperventilation itself in bringing about the symptoms A negative test does not necessarily exclude this diagnosis.

Knowledge about the treatment of HVS is based predominantly on small case series and anecdotal experience. The management of acute hyperventilation by the time-honored method of rebreathing from a paper bag should be prescribed with caution because severe complications may arise if the diagnosis is wrong and a more serious condition exists. Some argue that this technique sometimes exacerbates anxiety through retention of CO_2. Simple reassurance alone is often sufficient to attenuate an acute episode. For the longer term, teaching patients how to use abdominal (diaphragmatic) breathing or other breathing retraining techniques (including reducing depth of ventilation) are often effective. Stress reduction methods, sometimes in conjunction with psychotherapy, biofeedback, or hypnosis, have been used. Psychotropic agents for potentially associated anxiety or depression include benzodiazepines, tricyclic antidepressants, and selective serotonin reuptake inhibitors.

Hyperventilation and the Electroencephalogram

Normal and common central manifestations of hyperventilation include light-headedness, a sense of unreality, and, eventually, loss of consciousness. The psychological effects of acute hyperventilation are marked. At first, heightened perception may be reported and may be a partial explanation for certain beatific visions and spiritual experiences in states of religious excitement.[42] However, this is then followed by dulling of consciousness and diminished awareness of the environment. As the dominant rhythm of the EEG drops below 5 Hz, there is increasing impairment of reaction time, memory, and calculation abilities. On recovery, there may be amnesia for the episode. If hyperventilation is prolonged, mental confusion, myoclonic jerking, convulsions, and loss of consciousness may ensue.[27,75]

The quality and nature of respiration have a profound effect on the brain. Two deep breaths significantly reduce arterial carbon dioxide; further hyperventilation results in respiratory alkalosis. There is a direct relationship between pCO_2 and the caliber of the cerebral blood vessels. During hyperventilation, Doppler ultrasound measurements of the mean flow velocity in the middle and posterior cerebral arteries drop by up to 50% after 4 minutes.[7] After cessation of hyperventilation, the mean flow velocity increases briefly to 130% to 140% of normal.

Hyperventilation is a well-established procedure during the performance of the EEG[39] and it is considered helpful for producing focal slow-wave abnormalities suggestive of regions of focal disturbance, as well as generalized epileptiform abnormalities (especially idiopathic generalized epilepsies in the young such as typical absence).[12,40] It is much less useful for bringing out focal interictal epileptiform abnormalities.[49] Hyperventilation results in slowing of EEG rhythms in normal individuals, independent of the inspired oxygen concentration.[47] It is the hypocapnia that causes the decreased cerebral blood flow, as well as increased hemoglobin affinity for oxygen, and results in cerebral tissue hypoxia. Hyperventilation also leads to a marked surface negative direct current shift, possibly due to depolarization of the apical dendritic trees of the cortical pyramidal cells.[72,77] This surface negative shift is likely to represent increased excitability of the cortical neuronal networks and may explain the resultant potential epileptogenicity. It is of interest that certain antiepileptic drugs have the opposing effect of reducing surface negativity in normal controls.[72]

Hyperventilation and hypocapnia significantly increase the length of seizures evoked by electroconvulsive therapy in a progressive fashion[6] directly related to decreasing pCO_2. Thus, hyperventilation has effects in the human cerebral cortex that might be expected to produce epileptic activity.

Hyperventilation-induced Seizures

Voluntary hyperventilation was proposed as a means of eliciting epileptic seizures as early as 1924.[24] There are many case reports in the literature in which a variety of forms of epileptic attack are provoked by this means.[8,25,60,67] Many of these reports involve individuals (adults or children) with mental retardation and often with absence or atypical absence attacks.[8,60] The report by Bruno-Golden and Holmes[8] describes two children with severe mental impairment and a history of infantile spasms followed by tonic seizures. Observation demonstrated that the seizures were often preceded by hyperarousal and hyperventilation. Management involved a behavioral approach, training in uninostril breathing (more successfully completed than training in diaphragmatic breathing in this population), and a program of physical exercise. Very considerable reduction in seizure frequency was recorded. A similar story is described by Magarian and Olney,[60] this time in a 66-year-old man with a 20-year history of absence spells. Educational and behavioral therapy was again successful; however, there remains doubt as to whether these “absence spells” were epileptic. Fried et al.[25] described a group of 18 patients with undoubted intractable epilepsy who were given diaphragmatic breathing training. Ten of them completed the training and had significantly reduced seizure frequency and severity.

As early as 1947 Engel et al.[16] raised doubts that hyperventilation resulted in tonic–clonic or partial seizures. This issue remains controversial. Although Holmes et al.[40] found that hyperventilation elicited a clinical seizure in only 2 of 433 consecutive patients with proven epilepsy, Guaranha et al.[33] found that up to 24 of 97 patients had hyperventilation-induced seizure activation (although in the context of reduction of antiepileptic medications in patients with the most severe seizure disorders undergoing presurgical evaluations.)

There has been debate about whether physical exercise induces seizures or reduces their frequency. In general, exercise is seen as a good thing, and, although it results in fast breathing, this is not regarded as a problem because alkalosis does not ensue. Esquivel et al.[17] compared exercise with voluntary hyperventilation in a group of 12 children with absence epilepsy undergoing EEG monitoring. They found a decrease in the number of absence attacks during the physical exercise and an increase during hyperventilation. Plasma pH was also measured and showed a positive correlation with seizure frequency. In general, therefore, it is felt that moderate exercise is good for epilepsy control. In some individuals, however, seizures are clearly induced by exercise[67,74] but not necessarily by voluntary hyperventilation. The mechanisms of seizure induction in these cases are unclear, nor is it known why some people have seizures during the “let-down” period after physical exercise. Careful history taking, possibly with EEG monitoring during exercise, will be required to give the patient appropriate advice about exercise.

Peripheral physiologic effects of hyperventilation may be as important to the epileptologist as are central effects. Respiratory alkalosis reduces the proportion of ionized calcium in the blood and causes tetany. Peripheral neuromuscular manifestations, short of tetany, include paresthesia, weakness, and muscular cramps. These symptoms and signs may be misdiagnosed as a seizure by the unwary. Nonspecific ST- and T-wave changes will be provoked on the ECG, causing confusion to the cardiologist reviewing an ECG in the absence of careful history taking and observation, especially because an increased pulse rate and palpitations are common autonomic concomitants of hyperventilation, along with epigastric distress and swallowing difficulties.

Finally, hyperventilation is a frequent procedure used to elicit suspected PNES during the course of a diagnostic video-EEG. In fact, the use of hyperventilation and photic stimulation is favored over other induction techniques (e.g., intravenous saline infusions). Given that hyperventilation can induce epileptic seizures and PNES, the diagnosis should not be based solely on clinical observations, but must also be documented with concurrent EEG recordings (see also Chapters 74 and 282).

Summary and Conclusions

Panic disorders and HVS are common conditions that are misdiagnosed as epileptic seizures. A careful history is very often sufficient to reach a correct diagnosis, although in some instances a recording of the paroxysmal episodes with video-EEG may be necessary. Some patients may experience epileptic seizures and panic disorder and/or HVS, and, hence, the presence of one condition should not automatically exclude the other(s). As with any other neurologic or psychiatric disorder, treatment of paroxysmal episodes presenting as panic attacks or recurrent episodes of hyperventilation should be based on robust diagnostic evidence.

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Chapter 286

Obsessive-compulsive Behavior

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Introduction

The neuropsychiatric syndrome of obsessive-compulsive disorder (OCD) was discovered and described >150 years ago. Unfortunately, for many years, OCD was thought to be rare, untreatable, and result from hidden conflicts. All of these notions now appear to be mistaken. Occurring in about 2% of all adults, OCD consists of recurrent intrusive thoughts (obsessions), senseless repetitive actions (compulsions), or both. Although the etiology of OCD is unclear, recent neuroimaging studies and cases of secondary OCD implicate the basal ganglia, cingulate gyrus, and orbital and prefrontal cortex as crucial structures in the pathogenesis of OCD. A true cure for this disorder is elusive. However, OCD symptoms partially respond to treatment with antidepressants, especially selective serotonin reuptake inhibitors (SSRIs),[10,17,25,28,44] and, among tricyclics, clomipramine,[40] and behavioral therapy is effective for some patients in stopping rituals and compulsions.[11] Once thought to be the quintessential psychoanalytic disorder, OCD is now viewed as a largely biologic illness arising from abnormal brain function.

In this chapter, we discuss interesting new findings in OCD, paying particular attention to how OCD patients might be distinguished from patients with epilepsy. The symptoms of senseless repetitive actions (compulsions) or recurrent intrusive thoughts (obsessions) on some occasions might resemble the automatisms that occur with complex partial seizures arising from the temporal or frontal lobes. To make a proper differential diagnosis, the practicing epileptologist must be familiar with both primary OCD and other disorders that might have obsessive-compulsive behaviors (OCB) as part of their presenting symptomatology.

Clinical Presentation

Obsessive-compulsive Disorder

Primary OCD, as defined by the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV),[2] consists of recurrent urges to perform an action (compulsions) or recurrent intrusive thoughts (obsessions), or both. Furthermore, for the symptoms to qualify as true OCD, the compulsions or obsessions must cause significant dysfunction, be recognized by the sufferer as coming from his or her mind (not externally planted), and be egodystonic (i.e., unpleasant and not pleasurable).

An important clinical point is that the obsessions in OCD must be recognized by the individual as senseless, at least at some point in the disorder. A patient with OCD realizes that his or her compulsions do not result from mind control or from some other form of thought insertion, such as might be seen in schizophrenia. Because the obsessions are unpleasant and often of a violent or sexual nature, OCD sufferers attempt to ignore, control, or suppress the obsessions, often with a compulsion. For example, a husband with an obsessional worry about harming his new bride might be forced or compelled to repeatedly check on her welfare to assure himself that he has not harmed her. To summarize, obsessions are recurrent, persistent, resisted by the individual, and unpleasant. Often, obsessions center on certain themes such as contamination, aggressive thoughts concerning harming others or oneself, the need for symmetry or exactness, excessive somatic worries such as about AIDS or terminal cancer, and sexual or religious worries. A common feature of OCD is pathologic doubt and the person's inability to convince himself or herself that he or she has made a correct decision or that the environment is safe.

In contrast, compulsions are repetitive, purposeful, intentional actions sometimes performed in response to an obsession. It is important that the person recognizes or has recognized the senselessness of the actions. Performing the behavior often reduces anxiety. If an OCD sufferer resists performing a compulsion, invariably inner tension mounts until the compulsion is yielded to and the tension disappears. Common compulsions include checking, cleaning, ordering, counting, repeating, and hoarding. The DSM-IV has placed qualifying criteria on compulsions, which must be distressing to the individual, time consuming (>1 hour/d), and cause impairment in function. The phenomenology of obsessions and compulsions varies, depending on whether a person has pure OCD, OCD accompanied by motor tics, or OCD with motor and vocal tics [a disorder known as *Gilles de la Tourette syndrome* (GTS)].[15,21] For example, OCD/GTS subjects have increased touching compulsions and only rarely have washing compulsions—the most common compulsion in pure OCD.

Most cases of OCD begin in middle to late adolescence. The course can vary from chronic and unremitting to a more episodic illness featuring episodes of remission and relapse. Obsessive-compulsive behavior was, until the last few decades, thought to be rare; however, the National Institute of Mental Health (NIMH) Epidemiologic Catchment Area Survey revealed a U.S. prevalence of 2% to 3%.[26,46] Obsessive-compulsive behavior is also often accompanied by other psychiatric disorders. For example, one study found that 30% of OCD patients suffered from a major depressive episode, 27% had simple phobias, 14% had panic disorder, 9% had agoraphobia, and 5% had GTS. The exact gene or genes for OCD and its pattern of transmission are unknown. However, Pauls et al.[41,42,43] established that OCD is linked to GTS and chronic motor tics. OCD in GTS seems to respond in a similar fashion as primary OCD to drug treatment with SSRIs and behavioral therapy.[16,48]

Obsessive-compulsive Disorder Spectrum

In addition to pure OCD as defined earlier, there are many OCD-related disorders that some have labeled an *OCD spectrum*. This spectrum includes a collection of disorders or behaviors that resemble OCD in some way and often respond to treatment with antiobsessional agents. Dysmorphophobia is the fixed idea that a part of one's anatomy is disfigured or wrongly proportioned.[20] Trichotillomania is the compulsive pulling of one's hair, often seen in young to middle-aged women.[1,53] There is interesting research into the relationships between the eating disorders, particularly anorexia nervosa, and OCD. In addition, some obsessions involve sexual themes, and some forms of fetishism respond to treatment with serotonin-reuptake inhibitors.[56] Similarly, some obsessions involve violent, aggressive themes, and new research has shown that periodic impulse dyscontrol disorders respond to treatment (or, paradoxically, can be made worse by) serotonin-reuptake inhibitors.[8,35,37]

The Neuroanatomy of Obsessive-compulsive Behavior—Results of Neuroimaging Studies in Obsessive-compulsive Disorder

Structural studies of OCD subjects have yielded inconsistent but intriguing results. Luxenberg et al. in 1988,[33] using computed tomography (CT) scans, found decreased volume of the caudate heads in OCD subjects compared with controls. Follow-up studies by Garber et al.[12] and Kellner et al.,[27] however, using more sophisticated magnetic resonance imaging (MRI), failed to confirm these initial findings.

With regard to functional neuroimaging studies [positron emission tomography (PET), single photon emission computed tomography (SPECT)], a fairly consistent picture emerges. Numerous studies conducted in different centers with both PET[3,4,5,6,34,39,50,54] and SPECT[19] have consistently found *abnormalities in the orbitofrontal white matter and basal ganglia that change with pharmacologic or behavioral treatment.* This is one of the more consistent and remarkable findings in the recent history of biologic psychiatry and serves as the foundation for the ongoing revolution in understanding OCD.

It is important to realize that the differences noted in OCD are always found only on comparing group means. Unfortunately, we lack the ability to diagnose OCD on an individual basis using PET or SPECT. In addition, for almost all patients studied, as their OCD symptoms improve with either pharmacologic or behavioral treatment, the brain metabolism also changes to a more “normal” pattern.[19] The changes in brain metabolism thus appear to mirror the clinical improvement.

Recently, using oxygen PET and then in a later study with fast MRI, Rauch et al.[47] imaged regional brain activity in OCD patients before and during symptom provocation. Compared with before they are exposed to a provoking stimulus (such as a dirty rag for someone with a cleaning compulsion), OCD patients, when actively obsessing, show greatly increased activity in the right orbitofrontal lobe. At the NIMH, Greenberg et al.[18] attempted to expand on these studies and used noninvasive, repeated transcranial magnetic stimulation (rTMS) over the dorsolateral prefrontal cortex in an attempt to influence OC symptomatology. Results in OCD patients have been mixed with this promising technique of probing brain function.

Putative Neuroanatomic Model

These imaging studies begin to outline a tentative neuroanatomic model of primary OCD. This model may, in turn, help us to understand and organize the secondary causes of OCB. The circuit involved links the orbitofrontal region with the caudate nucleus, which projects to the globus pallidus, which then sends inhibitory fibers to the thalamus. The thalamus then sends excitatory fibers back to the prefrontal cortex, forming a closed loop. The final common pathway for OCD symptoms results from increased thalamofrontal activity. This fronto-caudate-pallidal-thalamo-frontal loop explains most of the cases of secondary OCD. According to this model, irritative lesions (e.g., epilepsy) of the frontal cortex or cingulate gyrus might produce OCD symptoms. Similarly, destructive lesions of the basal ganglia would also be predicted to worsen OCD symptoms by releasing the brake on the thalamus.

Table 1 Differential diagnosis of obsessive-compulsive behavior

Primary or idiopathic obsessive–compulsive disorder
Gilles de la Tourette syndrome[15]
Sydenham chorea[52]
Postencephalitic Parkinsons disease[24]
Stimulant abuse (particularly amphetamines)[9]
Tumors and infarctions of the orbitofrontal lobe [55,57]
Multiple sclerosis[13]
Following closed-head injury with damage to prefrontal, cingulate, or basal ganglia[36]
Manganese toxicity[38]
Epilepsy[32,56]

Differential Diagnosis

Primary or idiopathic OCD is, by definition, not associated with any known gross structural brain pathology. Obsessions or compulsions can, nevertheless, sometimes arise in other conditions or diseases that affect the critical brain regions just outlined (see Table 1) (for review, see George et al.[14]). When evaluating a patient with repetitive senseless actions, it is important to exclude obsessions or compulsions that may arise due to Sydenham chorea,[52] vascular or toxic basal ganglia lesions,[31,32,36,38,45,51,55,57] postencephalitic Parkinson disease (Von Economo encephalitis—encephalitis lethargica),[23,24,49] and central nervous system stimulant use.[9,29] Most of these disorders involve the *prefrontal lobes*, the *cingulate gyrus*, or the *basal ganglia*. These are the same regions that behave abnormally in recent neuroimaging studies of primary OCD subjects.

Properly evaluating the symptom of repetitive behavior can be a diagnostic challenge. Table 2 is an aid in determining whether the behavior is due to OCD or to localization-related epilepsy.

Patients with seizure discharges in the prefrontal or cingulate gyrus can present with OC symptoms. Ward described three patients with no past psychiatric or neurologic history who reported the new onset of the "feeling of compulsion" with no associated movement.[56] A 59-year-old woman suddenly developed an urge to walk to the left that she could not resist. Several weeks later, she developed a mild left hemiparesis. The electroencephalogram (EEG) showed a focal abnormality in the right frontal region, and CT scan revealed a *right frontoparietal glioblastoma*. A 43-year-old man experienced eight episodes over 2 months of a strong urge to shake his right arm, sometimes accompanied by an urge to shout, blurry

vision, or spatial disorientation. He later developed speech arrest and right arm weakness. EEG abnormalities were found in the left frontal and temporal areas, and a CT scan revealed a *left frontal glioblastoma*. Finally, a 62-year-old woman suddenly developed episodes in which she had the urge to shake her right arm, sometimes accompanied by an expressive dysphasia. An EEG showed left temporal slowing but no definite discharges or spikes. A CT scan showed *small lacunar infarcts in the right superior cerebellar peduncle and the left basal ganglia*. Kroll and Drummond[30] reported an interesting case of a 26-year-old man with a 6-year history of bizarre behavior who had been diagnosed as paranoid schizophrenic and was refractory to standard neuroleptic treatment. He had staring episodes, along with left shoulder and arm twitching. During these episodes, he described his thoughts as muddled or blocked, with increases in anxiety and obsessive thoughts, sometimes with an associated smell of sulfur. He had obsessive, intrusive thoughts about harming his mother, women, and babies. His neurologic exam and MRI scan were normal. An unmedicated EEG showed irregular activity at 5 to 7 Hz and focal slowing in the left temporal area. A presumptive diagnosis of *left-sided complex partial seizures* was made, and he was successfully treated with carbamazepine with resolution of the spells and obsessive thoughts.

Table 2 Differential diagnosis of obsessive-compulsive behavior (OCB): primary obsessive-compulsive disorder (OCD) versus OCB related to focal epilepsy

	Primary OCD	**OCB related to focal epilepsy**
History	Chronic, remitting	Acute onset
Family history of OCD	+	–
Other OCD symptoms	+	–

Accompanying mental state	Clear, totally aware	Cloudy, +/- amnestic
Aware of senselessness of action	+	–
Clinical tests		
Neuropsychological tests	++	
Electroancephalogram	–	Slowing, localized discharge[a]
Single photon emission camputed tomography	–	Abnormal[a]
Serum prolactin	–	Increased[a]
Magnetic resonance imaging	–	Possible mesial temporal sclerosis
Clinical neurologic exam	Normal	Possible localization-related signs

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[a] These may often be normal as well in patients with epilepsy.[2]

These cases illustrate that obsessive-compulsive behaviors may arise in the setting of localization-related epilepsy, although this is rare. In all of the reported cases of OCB arising in the setting of epilepsy, key points in the history or physical or clinical investigations point toward the proper diagnosis and away from primary OCD. Thus, in contrast to primary OCD, localization-related seizures with OCB usually have an abrupt onset with no other associated OC behaviors and a negative family history for OCD. Often, focal seizures with OCB are found in someone with a clouded mental state who exhibits other behaviors that are not found in OCD (motor or sensory changes, smells, etc.). In almost all cases, the EEG or brain imaging studies were abnormal. EEG changes are not commonly seen in primary OCD,[22] and, as reviewed earlier, brain imaging studies in individual patients are normal. If the diagnosis remains unclear even after a thorough history, physical examination, and clinical workup, a treatment trial with an anticonvulsant may be in order. In general, anticonvulsants have not been found to be effective in primary OCD.

Investigations

There is no definitive clinical test for primary OCD. Thus, it is quite important to perform a thorough history and physical examination and to use the appropriate diagnostic tests to exclude the other diseases in the clinical differential (Table 1). To distinguish primary OCD from localization-related seizures with OCB, one would likely perform an MRI scan of the head, as well as an EEG (Table 2). Neuropsychological testing does not distinguish between idiopathic OCD and OCB in epilepsy because it is similar in both cases, showing a specific frontal-subcortical dysfunction.[7] If the diagnosis is still unclear, one could possibly obtain a serum prolactin after an OC event (probably elevated in epilepsy, normal in OCD) or even a SPECT scan (focally abnormal in seizures).

Summary and Conclusions

Recurrent obsessions and compulsions arise in a variety of clinical disorders that affect key brain regions (the cingulate, frontal and temporal lobes, and basal ganglia). Localization-related epilepsy is an infrequent cause of obsessions or compulsions. Much more commonly, OCB is due to primary OCD, although other neurologic illnesses must be excluded. In most cases of a patient presenting with obsessions or compulsions, a thorough history, physical exam, and associated diagnostic tests will lead to the proper diagnosis and treatment.

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Chapter 287

Nonaffective Psychoses, Schizophrenia, and Schizophrenia-like Psychoses

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Introduction

In this chapter, in contrast to Chapter 204, we consider the clinical occasions in which some of the symptoms of schizophrenia may be mistaken for those of epilepsy. In reality, there are very few situations in which this arises, and when they do, there are usually obvious causes for the confusion. We do not discuss the clinical phenomenology, investigations, and treatment of schizophrenia per se, and refer the interested reader to Chapter 270 by Jadresic in the first edition of this work.[9a]

In contrast to disorders of affect, psychotic states, although they imply a severe disturbance of neurologic function, are less frequently encountered than disturbances of mood in neurologic practice. There are many reasons for this, not the least being that many people with neurologic disorders and reduced quality of life experience depression as a consequence, and, in general, a number of neurologic disorders influence areas of the brain that are linked to the regulation of mood, emphasizing the frontal-striatal axis.

The brain must allow the individual to interpret the world in which he or she lives in an orderly manner so that he or she can behave in a logical and adaptive way. The symptoms of psychosis, however, such as hallucinations and delusions, suggest deviant neurologic processing, and underlying this will be disturbances of neurologic function, often secondary to structural disease. The close association between some neurologic disorders and psychoses suggests neurochemical and or neuroanatomic bases for the abnormal mental states, for example, the psychoses associated with Parkinson disease and l-dopa therapies. There are biologic underpinnings to the psychotic disorders of epilepsy, and these are discussed in Chapter 204. It is interesting that, as noted, the discussions revolve around similar anatomic deviations as in schizophrenia in the absence of epilepsy and involve medial temporal structures, the amygdala and hippocampus in particular, and their efferent projections.[17]

Terminology

The term *psychosis* generally refers to a condition in which there are hallucinations and delusions associated with abnormalities in behavior such as excitement and overactivity or psychomotor retardation, or catatonia, in which insight is diminished or lost.

A *hallucination* is a perception in the absence of an adequate sensory stimulus, and it must be distinguished from an *illusion*, which is due to a misinterpretation of perceptions. *Pseudo-hallucinations* are hallucinatory experiences that occur in subjective rather than objective space, are less clearly delineated, and thus lack the objectivity of hallucinations proper. The latter have concrete reality and are linked to a lack of insight into their nature.

Delusions are unshakable convictions that are manifestly incorrect. They have to be interpreted within the patients' cultural setting, but it is the tenacity with which patients hold onto their beliefs against all logic that inevitably reveals the delusion. They need to be distinguished from overvalued ideas, which are strongly held beliefs that are not incorrigible.

Delusions are the hallmark of a paranoid illness and occur in a spectrum of psychiatric disorders, including schizophrenia. In the affective disorders, they are characteristically mood congruent, whereas mood-incongruent delusions are typical for schizophrenia. In the *Capgras syndrome*, a significant person in the patient's life is replaced by a supposed identical double, and in the *Fregoli syndrome*, a supposed persecutor can change his or her appearance and appear as other people. These are referred to as *misidentification syndromes*.

Hallucinations that occur in clear consciousness for which there is no insight and that are mood incongruent are very suggestive of schizophrenia. In this condition, they are usually auditory, although patients may experience them in any modality. Specific auditory hallucinations noted in association with schizophrenia are referred to as being among the Schneiderian first-rank symptoms. These are listed in Table 1. When present in clear consciousness, they usually signify schizophrenia, although this is not diagnostic because they are sometimes noted in other psychotic disorders—for example, in mania. Furthermore, the diagnosis of schizophrenia can be made in their absence based on history and other observed abnormal behavior.

Olfactory hallucinations are reported in schizophrenia and in simple partial seizures of the uncinate variety. In epilepsy, these experiences are typically brief, unpleasant, hard to characterize, and consistent in their phenomenology. In schizophrenia, they are much more variable and may last for considerable periods of time, and they are usually accompanied by a delusional interpretation. In coenesthetic hallucinations, the body or part of the body feels altered or distorted, often in quite fantastic ways. Although often reported in schizophrenia, they may occur in migraine or following cerebrovascular accidents.

A characteristic feature of schizophrenia is alteration of thought and language. This may vary from a subtle flattening of the expression and concrete thinking to a florid schizaphasia. In the latter, neologisms (paraphasias) emerge, there are loose connections between thoughts and tangential thinking, and intrusive delusional content can lead to a veritable “word salad.”

Table 1 The First-Rank Symptoms of Schneider[a]

Thought withdrawal
Thought broadcasting
Hearing one's thoughts spoken aloud
Hearing voices arguing about or discussing one
Hearing voices comment on one's actions
Delusional perception[b]
Experiencing bodily sensations as if imposed from outside

Experiencing affects as if imposed and controlled from outside

Experiencing impulses as if imposed and controlled from outside

Experiencing motor actions as if imposed and controlled from outside

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[a] These are not diagnostic of anything, but when present in the setting of clear consciousness, support a diagnosis of schizophrenia.

[b] Abnormal significance is attached to a real perception without any logical explanation.

Paroxysmal Symptoms in Schizophrenia

The diagnosis of schizophrenia is usually not difficult to make in the advanced case, especially with knowledge of the patient's history. However, by the time the patient has revealed his or her aberrant behavior and psychotic thinking, the underlying disorder will be well advanced. There is often evidence of difficult and unusual behavior going back to childhood, with comments about the person being different, a loner, and the like, and perhaps using unusual language or manifesting unusual thought processes for several years. A family history may be revealed (but is often concealed), and typically academic decline becomes apparent in the teenage years, often blamed on either stress or illicit drug taking.

Such cases usually first go to a psychiatrist for diagnostic evaluation, and if the diagnosis is clear, these patients may remain under psychiatric care for many years. In the early, uncertain stages of the disorder, however, patients with a developing schizophrenia may be referred to a neurologist, but usually on the grounds of academic failure and personality change, suggestive of a developing organic brain syndrome—the dementia praecox of Kraepelin. Such referrals, however, are not usually in reference to epilepsy.

The signs and symptoms of schizophrenia that are most likely to be confused with epilepsy are quite limited. They relate especially to the paroxysmal nature of the presentations and to the neurologic-soundingness of them. The signs are those of the motor disturbances of catatonia, and the symptoms are usually hallucinations, especially affecting the body image. Certain first-rank symptoms are also relevant, especially thought withdrawal and thought insertion.

Movement Disorders

The classic motor disorder of schizophrenia is catatonia, and for Kraepelin this deserved a separate nosologic category.[10] It seems that catatonic forms are much less apparent now than 100 years ago; one reason may be the effective intervention of psychotic disorders with neuroleptic drugs. The original descriptions of these movement abnormalities revealed a wide range of motoric instability, from tics and dyskinesias to frank dystonia. Stereotypies, echophenomena, mannerisms, and special signs such as automatic obedience and negativism were reported, and such abnormal movements were thought to be integral to the condition. This was before the introduction of neuroleptic drugs and the later widespread reporting of tardive motor syndromes. It is estimated that around 50% of untreated schizophrenics display such motor abnormalities.[11,12]

Cutting referred to catatonia as follows[6]:

> Catatonia is the generic name for about eight separate disorders of movement and posture, which have in common a tendency to be intermittent, to defy classification as disorders of power, tone, co-ordination, praxis or involuntary movement, and in a general sense to involve the surrender of the affected person's will. (p. 277)

The paradigmatic picture is of immobility, and the classic picture of catatonia with unresponsiveness and postures held sometimes for hours, which may reveal a waxy flexibility, was often illustrated in early pictures and film clips of schizophrenia. However, this represents only a part of the catatonic spectrum. More relevant for the diagnostic issues of epilepsy are the sudden episodes of catatonic excitement. These can vary from brief to longer disruptions of behavior (seconds to hours), in which the patient suddenly becomes overactive with hyperkinesis, even violent, as if being strung from their motoric slumber by the sudden onset of a seizure. These episodes seem free from environmental or emotional precipitants, and after the period of overexcitement, there is a resumption of the status quo.

Other abnormal movements that may occasionally lead to diagnostic confusion are tics. These will only very rarely be myoclonic in form, however, and are much more often brief but repetitive, associated with other behavior changes of the type noted earlier such as in habits and mannerisms.

After noting that patients may have seizures (and in his time epileptic seizures were reported quite often in schizophrenia, presumably because of the number of secondary forms he was witnessing from, e.g., encephalitis and syphilis), Kraepelin continued[10]:

> There are spasms in single muscle groups (face, arm), tetany or even apoplectic seizures with paralysis which last for a considerable time…. In a whole series of patients (6% of the men and 3% of the women) spasms and fainting fits occurred previously in youth…. The spasmodic phenomena in the musculature of the face and of speech… resemble movements of expression, wrinkling of the forehead, distortion of the corners of the mouth, irregular movements of the tongues and lips, twisting of the eyes, opening them wide and shutting them tight. (p. 83) The patient who has been senselessly excited may suddenly become mute and motionless; the patient who has been stuporous, perhaps for weeks, abruptly begins to utter unintelligible screams… or he leaps with long bounds through the room… and then remains again inaccessible, or possibly even passes through a longer period of excitement. (p. 148)

These paroxysmal bursts of abnormal behavior, which were so well described in the past, are much rarer today, and are not recognized by a generation of psychiatrists and neurologists poorly versed in the intricacies of phenomenologic psychiatry. When they do occur, they often lead to a question of an underlying seizure disorder and a request for neurologic evaluation. It is then not uncommon to ask for an electroencephalogram (EEG), which may then be reported as abnormal, raising further the suspicion of epilepsy (see later discussion).

A good history will confirm the diagnosis of schizophrenia, but a clear description of the abnormal behavior from a nurse, physician, or caregiver can be revealing by fairly quickly establishing that the paroxysms are simply not like epileptic seizures in their semiology. There is no clear seizure as such, no alteration or loss of consciousness, and no repetition of the progression of the attack with each recurrence as there is with epileptic seizures. The earlier history is that of schizophrenia, as outlined previously, and not that of epilepsy. In fact, careful questions about attacks resembling complex partial or secondary

generalized seizures note an absence of such a background: There are no febrile convulsions, no clear episodes of loss of consciousness, and no suggestions of a localizing neurologic sign.

Further questioning will reveal the diagnosis; it is the company that such symptoms keep that is relevant. There will be ongoing delusions, a failure of the patient to explain or even describe his or her attacks, and a lack of insight.

Hallucinations

Hallucinations may be in any modality, but the coenesthetic and olfactory ones are the most likely to cause diagnostic confusion. Olfactory hallucinations are reported in patients with simple partial seizures and very rarely as the sole manifestation of the seizure. No more than about 7% to 10% of patients with temporal lobe epilepsy, however, report olfactory hallucinations,[4] and the classification of the seizure is often referred to as an uncinate seizure. In reality, the site of origin of the episode may be in the hippocampal uncinate, but it may arise from elsewhere, such as the insula. The experience, however, is vivid, repeated, unpleasant, and evanescent. It is not usually accompanied by an abnormal taste, but the latter is not perhaps unexpected. In clinical practice, the question is often put to a patient, “Do you have any unusual tastes or smells that accompany your attacks?” The answer is often given in the affirmative, and such replies as “a metallic taste” or a variant of that are given. This is recorded in the patient's notes as an uncinate event, in spite of the fact that it is nothing like the descriptions of patients with epilepsy with established smell auras. Such fleeting metallic tastes and other variant smells are commonly reported in patients who are then misdiagnosed as having epilepsy and are later rediagnosed as nonepileptic.

In a similar way, the smell hallucinations in schizophrenia may be misinterpreted. These are the third-most-common form of hallucination reported in schizophrenia (after auditory and visual ones), but gustatory hallucinations are less frequent. Cutting[5] gave a figure of 6% reporting of olfactory hallucinations in schizophrenia. The latter are rather diffuse; sometimes good and sometimes bad; may be flitting or lasting in an individual patient; and are often characterized, unlike those of the uncinate seizures, which are hard to specify and describe. The schizophrenic smells himself or herself, others, food, or evidence of good or evil, whereas the patient with epilepsy refers to unpleasant smells as unpleasant, perhaps like burning rubber. As with the aberrant motoric behaviors described earlier, further questioning will reveal the psychotic attachments to the smell experience, and the underling schizophrenic disorder.

Coenesthetic hallucinations relate to disturbances of the body and the body image. For probable historical reasons, they are poorly discussed in English-language texts on psychopathology, but they have attracted much more attention on the European continent. Fleeting sensory disturbances, shots of pain, pulling, squeezing, twisting, and the like of the body or parts of the body are described, and their paroxysmal nature gives rise to the suspicion of a simple partial seizure. Many physicians are unaware of the relative frequency of such hallucinations, tending to identify only visual and auditory events with hallucinations proper. Corporeal sensations are common in schizophrenia, however, and like olfactory hallucinations, have a different quality from the equivalent epileptic event. They are usually unpleasant or painful, and may be sexual. They last for varying lengths of time and vary with each description. They come and go over time, without the stereotyped nature of the experiences of a simple partial seizure. Again, a few questions will reveal the attached delusional thinking.

Formal thought disorder refers to patterns of thinking seen in schizophrenia and other psychoses, central to which is disorganization and concretization of thought. Such terms as fusion, derailment, lack of association, and interpenetration of thoughts are self-explanatory, however these are revealed by the patients during history taking, and would not relate to any diagnostic confusion with epilepsy.

The three symptoms that are sometimes confused are thought insertion, in which ideas or words are interpenetrated into the patient's mind; thought blocking; and thought withdrawal. In the latter two, patients claim that their thoughts are being interfered with by some outside agency, with sudden stoppages to the flow of the thoughts. The patient suddenly ceases to speak, his or her line of thought is interrupted, and he or she may momentarily appear blank or confused. The paroxysmal and brief nature of this may make it seem like an epileptic seizure, and the episodes can be frequently repeated, but clinical perception soon reveals the psychotic form underlying these events.

Electroencephalographic Findings in Schizophrenia

Hill[7] reviewed the results of early EEG findings of abnormalities in schizophrenia. Schizophrenic patients typically exhibit low-amplitude irregular EEGs, described as “choppy,”[7] and numerous qualitative studies indicate abnormal conventional EEG findings in 20% to 60% of schizophrenic patients. The abnormalities described in schizophrenia included left-sided slow-wave asymmetries, especially at the left anterior temporal area and occasionally involving the left frontal and parietal areas, slow bursts, and spikes or sharp waves.[13,14] Stevens et al.[15] showed by 24-hour telemetry recordings that temporal EEG abnormalities occur in 30% of schizophrenic patients. Schizophrenic patients with EEG abnormalities that appeared either before or during neuroleptic treatment had more evidence of brain dysfunction than did patients without such EEG abnormalities.

Considerable attention has been devoted to the hypothesis that schizophrenia is primarily associated with dominant hemispheric dysfunction. Abrahams and Taylor[1] showed that schizophrenic patients had twice as many, mostly left-sided, temporal abnormalities compared to patients with affective disorders, who have more right-sided EEG findings.

A recent study by Inui et al.[9] looked into electroencephalographic abnormalities in 143 patients whose discharge diagnoses met the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition,[2] criteria for mood disorder, schizophrenia, and other psychotic disorders. The study revealed that the frequency of epileptiform variants, including the phantom spike and wave, positive spikes, and small sharp spikes, was significantly higher among patients with mood-incongruent psychotic mood disorder (33%), schizoaffective disorder (33%), and schizophreniform disorder (30%) as compared with patients with nonpsychotic mood disorder (3.2%) and schizophrenia (0%). The results implied that patients with "atypical" psychoses, which are located between typical mood disorder and schizophrenia, might have a biologic vulnerability to seizures, as represented by these epileptiform EEG variants. These associations also pose diagnostic challenges, however, because patients with atypical presentations are the ones most likely to lead to diagnostic confusion.

Structural Abnormalities

Another potential source of confusion arises in cases in which a patient with schizophrenia has some paroxysmal behavior

disorder and, in addition to the EEG, a brain scan is performed. It has been known for a long time that schizophrenia is associated with changes on scans, both computed tomography and magnetic resonance imaging, the main findings being ventricular dilation and tissue loss, including loss of hippocampal neurons. Thus, some dilation of the temporal horns of the lateral ventricles may be noted, with decreased temporal lobe volume, increasing the suspicion that the case may be one of epilepsy.[16] This rarely relates to a hippocampal sclerosis, however, and in fact one of the consistent differences in the neuropathology of temporal lobe epilepsy in comparison to schizophrenia is the absence of gliosis in the schizophrenic hippocampus. Nonetheless, cases of hippocampal sclerosis are rarely described in patients with schizophrenia who do not have overt epileptic seizures, and the links between the sclerosis and the subsequent psychosis are unclear.

Comorbidity of Epilepsy and Psychosis Due to a Common Underlying Condition

There are a number of disorders in which epilepsy and psychosis both develop secondary to an underlying usually progressive neurologic disorder. The causes are legion although each individual disorder itself is quite rare. The reader is referred to Cummings and Mega[3] for an extended list of neurologic disorders that can be linked to the development of schizophrenia-like states, but most are not also linked to epilepsy. However, encephalitides, some storage disorders, endocrine disorders such as hypoparathyroidism, and inflammatory conditions such as systemic lupus erythematosis may all occasionally cause diagnostic confusion as to whether the developing psychosis is somehow linked to an underlying epilepsy, although the progressive nature of the disease will likely soon be revealed.

Summary and Conclusions

In clinical practice, schizophrenia is not often confused with epilepsy, but the reasons that this sometimes does occur are clear. Many physicians who manage epilepsy are unfamiliar with the polymorphous presentations of schizophrenia and are unaware of the paroxysmal nature of many of the symptoms, especially the motor disorders. Further confusion may arise with misinterpretations of the EEG and, occasionally, any brain imaging. Careful clinical evaluation should resolve diagnostic confusion, however, although neuropsychiatric evaluation will most likely be essential to this endeavor.

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Chapter 288

Overview: Delivery of Health Care and Socioeconomic Issues

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Introduction

As medical care becomes more sophisticated and thus more expensive, people and governments find that they must make difficult choices about where money earmarked for health will be spent. The expectations for care of people may vary from country to country and from culture to culture, although the desire for good treatment and cure will not. The duties of a conventional health care delivery system in relation to epilepsy, regardless of location, are similar (Table 1). The means to deliver care and the way it is organized, however, differ from country to country.

This section explores the ways in which different countries seek to meet the health needs of people with epilepsy. Before beginning a country-by-country survey, it is worthwhile defining, as far as possible, the general issues that each country must face. This section also reviews the socioeconomic issues that confront epilepsy care. Full socioeconomic appraisals of different epilepsy treatments and health delivery have not been undertaken, and therefore there are many remaining questions in this area.

Levels of Care

Primary Care

Primary care is defined as the care given by the first physician whom the patient ordinarily consults. The primary care physician is expected to possess some knowledge of a broad range of medical problems. Primary care physicians provide excellent care for many medical conditions, especially common problems. It is more difficult, however, for a primary care physician to keep abreast of modern methods of diagnosis and treatment of diseases with a low incidence. For example, in the United States, the average primary care physician sees one new case of epilepsy every 2 years. In the United Kingdom, a general medical practitioner (GP) might expect to diagnose one or two new cases each year, as well as having a caseload of 8 to 12 people with active epilepsy. The responsibility for long-term prescribing for patients varies from country to country. In the United Kingdom, this is an important responsibility of primary care physicians, but in other settings it is usually devolved to secondary care providers.

The ratio of primary care physicians to specialty physicians varies widely from country to country and within countries, especially between urban and rural areas. This ratio affects national policy regarding the management of chronic disease of relatively low incidence. In some countries, primary care is provided by nurses, health visitors, and also by other health care workers. In some resource-poor countries, practitioners of traditional medicine may also play a role.

Secondary Care

Secondary care denotes the most common type of specialty care. A general surgeon, general internist (physician), pediatrician, and, in some parts of the world, a neurologist would be considered to provide secondary care. In some countries, the dividing line is not sharp; in the United States, a general internist may practice some primary care medicine. Nonetheless, the underlying concept is that the practice is limited to certain problems so as to allow for greater in-depth knowledge on the part of the physician. Even so, in secondary care, the range of problems dealt with is relatively broad.

Tertiary Care

Tertiary care is the most specialized level. In epilepsy care, physicians with a prior qualification in neurology usually provide this, although physicians from other specialties are often involved (notably neurosurgery, psychiatry, clinical neurophysiology, and internal medicine). In most countries, tertiary care is available in teaching or university settings.

Specialized Centers or Fourth-level Care

With the increasing complexity of medicine, a fourth level of specialized care is developing in many countries. Patients with complex forms of blood dyscrasias or who require bone marrow transplantation or heart, lung, or liver transplantation are examples of people who receive fourth-level care in highly specialized centers. Epilepsy is one of few chronic diseases for which highly specialized centers have developed, although these are usually restricted to developed countries, with only a few in resource-poor countries.

Table 1 The duties of a health care system in relation to epilepsy

1. Identification of people with the condition
2. Diagnostic evaluation
3. Choice of drug treatment at all stages of the condition
4. Initial management, reevaluation of patients who have not responded to the initial choice of therapy, and long-term management of the disease
5. Management of emergencies
6. Management of complications and secondary consequences of the condition
7. Delivery of preventive care

Organization of Health Care Systems

The organization of systems by which care is delivered varies widely from country to country and often even within countries. In most countries, a mix of systems is found. In some countries, however, practitioners no longer practice alone, and in other, particularly resource-poor countries, multispecialty clinics have not developed, again largely because of socioeconomic factors.

Individual Practitioners

Classically, in the United States, physicians were in private practice, often alone in a solo practice. For reasons of convenience (sharing night calls) or expense (sharing overhead costs), groups of physicians began to practice together in a single office. In the United Kingdom, at the start of the National Health Service in 1948 many GPs were “single handed,” but currently GPs are more likely to work in partnerships of three to six doctors.

Single-specialty Groups

All members of these groups of physicians are ordinarily engaged in a single specialty, for example, family practice or pediatrics. Groups of this sort are found in many parts of the world where there is a private system of medicine, but in the United Kingdom they are generally only found in the case of GP partnerships.

Polyclinics

The term *polyclinic* has different meanings in different countries. It is used here to mean a highly organized group of physicians, usually on a salaried basis, who provide a full range of services, from primary through specialized care. The degree of specialization, of course, varies widely.

Multispecialty Clinics

Much more commonly found in European countries and the United States, multispecialty clinics often do not include primary care physicians. Rather, aggregations or departments based on specialty are housed under an umbrella organization. In most parts of the world, these multispecialty clinics are organized about major hospital centers or universities.

Forms of Hospital-based Practice

There is great variability in the way that hospital-based care is provided throughout the world. In some countries, primary care physicians can admit patients directly to a hospital and decide whether to consult a specialist. In other places, only a specialist can admit a patient to a hospital where specialized care is available, and the primary care physician relinquishes control over the patient. In some countries, these hospital-based practices are essentially run by the government, either through a health authority or under the aegis of a university.

Socioeconomic Considerations

In most countries, health care delivery is often limited by financial considerations and the availability of resources. In each country, therefore, decisions are made about priorities. For instance, in resource-poor countries, the treatment of infection may be more of a priority than the treatment of chronic diseases.

A logical decision on health care provision may involve the most cost-effective treatment for any condition. The cost-effectiveness of delivery of epilepsy care in different systems, however, has not been carried out. For example, surgery is often viewed as a most cost-effective treatment for some forms of epilepsy, but little is known about its use and cost-effectiveness in resource-poor countries.

Government Versus Private Bureaucracy

As soon as medical care involves more than a single doctor, a bureaucratic structure begins to develop. When medical care involves many physicians and large support staffs, bureaucratic considerations become a primary issue. Decisions may be based on health care priorities or other political reasons. In democratic settings, there is at least some degree of accountability, but in many parts of the world, political decisions are made for personal or self-interested reasons. In some parts of the world, government is trusted and the decisions of government authorities respected, but in others, government is mistrusted and the decisions of government authorities are seen at best as a barrier and at worst as malevolent. These same themes exist whether the bureaucracy is part of government or is apparently of a private nature.

In most systems of health services, the allocation of resources becomes a political matter. In some cases, the politics involves the government and health ministers, whereas in other cases, it depend on relationships that exist within a private bureaucracy.

The major difference between public and private bureaucracies is that, in public bureaucracies, decisions are often influenced by broad governmental priorities, for example, the need to win the next election. In private bureaucracies, decisions are influenced usually by primarily financial considerations. Whether high-quality care and serving patients are primary goals varies from provider to provider.

These differences in care are seen in purest form in the private bureaucracies that run large health care systems in a capitalistic market economy, such as that of the United States. The large health service organizations in the United States struggle continuously to instill a customer-oriented attitude in their employees. Although to some extent this orientation toward customer service is altruistically motivated, for the most part it is motivated by the desire to increase market share and expand the business. To do so, the health service organization must offer a low price and, it is hoped, high value to the purchaser of the contract; it must also please the patient. The extent to which the patient can exercise free choice and take business from one group to another is the extent to which the patient can influence the quality of care provided.

Summary and Conclusions

In most areas of the world, care is provided in a tiered system. The ways in which the systems are funded and the funding available vary widely from country to country and particularly between industrialized and resource-poor countries. This section provides a snapshot of service provision for people with epilepsy in a number of countries as well as a brief review of the socioeconomic issues that affect epilepsy.

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Chapter 289

Brazil

Carlos A. M. Guerreiro

Introduction

Brazil is a country of continental dimensions (8,511,965 km^2), divided into 26 states and a federal district. In 2004, its population was estimated to be 178.4 million inhabitants; life expectancy at birth (male/female), 66.0/73.0 years; gross domestic product (GDP) per capita (international $, 2002), U.S. $7,762; health life expectancy at birth (male/female), 57.2/62.4; child mortality (male/female) per 1,000, 39/32; adult mortality (male/female) per 1,000, 240/129; and total health expenditure per capita (international $, 2002), 611; and total health expenditure as percentage of GDP (2002), 7.9.[53] In October 2005 the estimated population was 184.7 million inhabitants.

Brazil has achieved dramatic results in improving living conditions: Infant mortality declined from around 50 per 1,000 live births in 1990 to 33 per 1,000 in 2000, and net enrollment in basic education rose from 84% in 1991 to 97% in 2002. Brazilians with access to an improved water source rose from 73% of the population in 1986 to 87% in 2001.

Despite Brazil's impressive advances, the poorest one fifth of Brazil's 184.7 million people account for only a 2.2% share of the national income. Brazil is second only to South Africa in a world ranking of income inequality. More than one quarter of the population live on <$2 a day and 13% live on <$1 a day. Brazil's northeast contains the single largest concentration of rural poverty in Latin America. Past development programs have failed to make a major dent in a region in which 49% of the population is classified as poor.

Crime is plaguing urban Brazil. Political corruption is also a serious problem in the country.

In global terms, Brazil rates 13th in economic strength and among the first group of countries in agricultural production.[54]

Information related to demographic, socioeconomic, and health indicators of the country is listed in Tables 1 and 2.[16,54]

General Data on the Health System

Some states in the country suffer more than others, particularly from some long-standing endemic diseases such as dengue, cholera, Chagas disease, schistosomiasis, and malaria. New diseases, such as AIDS, are also a growing problem.

The rate of reported AIDS cases increased from 10.6 per 100,000 in 1992 to a high of 18.7 per 100,000 in 1998. Brazil has experienced a stabilizing trend with rates of 16.5, 16.4, and 14.8 per 100,000 in 1999, 2000, and 2001, respectively. In the last decade, heterosexual transmission of reported AIDS cases grew from 25.8% in 1991 to 56.1% in 2002. Since 1998, the death rate from AIDS has stabilized at 6.3 per 100,000. This tendency is attributed to Brazil's guarantee of access to free antiretroviral drugs since 1996.

The country also rose to the challenge posed by the single biggest health threat in the modern world, pioneering an anti-HIV/AIDS strategy that became an international model by guaranteeing universal access to retroviral medication.[15]

Brazil has a constitution that states that health is the right of every citizen and the duty of the state to provide. A law was passed on September 19, 1990, creating the Unified Health System (Sistema Único de Saúde [SUS]). The SUS is composed of the health activities and services provided by municipal, state, and federal organizations and institutions. This same law assumed the coexistence of private medicine in its various forms.

Despite this legislation, a great number of problems remain. These range from the social policies practiced by the federal government to the management of responsibility at the different levels and the effective management of rendering services.

Although SUS theoretically offers total coverage to everyone, in reality, only 77% of the population is covered, according to an estimate that we have applied using data from the federal government from 1994 (from the Bulletin of Ministry of Economy, 1994). Of those not covered, 22% were unassisted, and another 55% received some assistance. The remaining 23% sought assistance from the private sector: Medical insurance, health maintenance organizations (HMOs), traditional fee-for-service providers, and others.

Large portions of citizens receiving private medical care eventually seek, or are directed to, public health services. This happens especially in cases of chronic or terminal diseases and those involving complex and costly procedures. In these cases, there is no reimbursement from the public sector.

Epilepsy Data

An epidemiologic study with a selected sample size of 17,293 individuals revealed that the cumulative prevalence of epilepsy in São José do Rio Preto, a 350,000-inhabitant city in São Paulo state, was 18.6 per 1,000 inhabitants with 8.2 being active, defined as at least one seizure within the last 2 years. The prevalence per 1,000 inhabitants for the age groups (years) was 4.9 (0 to 4), 11.7 (5 to 14), 20.3 (15 to 64), and 32.8 (65 or over).[12]

Table 1 Socioeconomic, Demographic, and Health Indicators Data about Brazil

	Most recent year	Data
Socioeconomic context		
Total population (000s)	2003	176,596
GNI per capita, Atlas method (U.S.$)	2003	2,760
Expected years of schooling	2002	15
Adult literacy rate (% of population ages 15+)	2003	88
Demographic indicators		
Average annual population growth rate (%)	1990–2003	1.4

Age dependency ratio (dependents as a proportion of working-age population)	2003	0.5
Total fertility rate (births per woman)	2003	2.1
Adolescent fertility rate (births per 1,000 women ages 15–19)	2003	68
Contraceptive prevalence rate (% of women ages 15–49), any method	1996	76.7
Health status indicators		
Life expectancy at birth (yr)	2003	69
Infant mortality rate (per 1,000 live births)	2003	33
Under 5 yr of age mortality rate (per 1,000)	2003	35
Maternal mortality ratio (per 100,000 live births), modeled estimates	2000	260
Prevalence of child malnutrition—underweight (% of children under age 5)	1996	6
Health care indicators		
Child immunization rate, measles (% of ages 12–23 months)	2003	99
Child immunization rate, DPT3 (% of ages 12–23 months)	2003	96
Births attended by skilled health staff (% of total)	1996	87.6
Physicians (per 1,000 people)	2001	2.1
Hospital beds (per 1,000 people)	1996	3.1
Tuberculosis treatment success rate (% of registered cases)	2002	75

DOTS detection rate (% of estimated cases)	2003	18
Health finance indicators		
Health expenditure, total (% of GDP)	2002	7.9
Health expenditure, public (% of GDP)	2002	3.6
Health expenditure, public (% of total health expenditure)	2002	45.9
Health expenditure per capita (U.S.$)	2002	206.0
Risk factors and future challenges		
Prevalence of HIV, total (% of population ages 15–49)	2003	0.70
Prevalence of HIV, female (% of population ages 15–24)	2001	0.50
Tuberculosis incidence (per 100,000 people)	2003	62
Tuberculosis death rate (per 100,000 people)	2002	8

DOTS, directly observed treatment strategy; DPT3, three doses of the combined vaccination against diphtheria, pertussis, and tetanus; GDP, gross domestic product. GNI, gross national income.
From World Bank. Health Nutrition Population. Available at: http://web.worldbank.org/WBSITE/EXTERNAL/COUNTRIES/LACEXT/BRAZILEXTN/0, contentMDK:20189430~pagePK:141137~piPK:141127~theSitePK:322341,00.html. Accessed: August, 2005.

Very recent data from the Demonstration Project of Global Campaign Against Epilepsy, in Brazil, supported by the International League Against Epilepsy, the International Bureau for Epilepsy, and the World Health Organization, revealed that the prevalence of cumulative and active epilepsy, respectively, was 9.1 per 1,000 and 5.3 per 1,000 people in Campinas and São José do Rio Preto, both in São Paulo state.[40] The prevalence of active epilepsy was higher in the more deprived social classes (range from A = richest to E = poorest) in Campinas and in São José do Rio Preto (Class D + E = 7.4 vs. Class A = 1.6 per 1,000). Over one third of patients with active epilepsy had inadequate treatment, including 19% who were on no medication. These data illustrate the treatment gap in the area.[40] In another study based on data from the central municipal pharmacy of Campinas and São José do Rio Preto in 2003, it was estimated that in the best-case scenario, 50% of patients with epilepsy were not on medication on a regular basis.[41]

Campinas and São José do Rio Preto are two cities located in one of the wealthier regions of Brazil, where there is a good public and private health care system and where the population has easy access to treatment.

Neurologists

Based on data furnished by a Novartis profile, 4,863 neurologists were identified in Brazil in 2005. This probably included clinical neurologists, pediatric neurologists, and some neurosurgeons who practice clinical neurology. According to the Brazilian Academy of Neurology, there are 1,197 members, and the Brazilian Epilepsy Society had 477 members in 2005. The distribution of the number of neurologists per 100,000 inhabitants in the different states is shown in FIGURE 1. An analysis of FIGURE 1 reveals a distinct relationship between the per capita income of the state and the number of accessible neurologists. The higher-income areas have more neurologists,

as in the case of the Federal District and the states of Rio de Janeiro, São Paulo, and Rio Grande do Sul. The latter state's rates are close to those of the northeastern states in the United States.[38]

Table 2 General Information about Brazil in 2000, 2003, and 2004

	2000	2003	2004
People			
Population, total	170.1 million	176.6 million	178.7 million
Population growth (annual %)	1.2	1.2	1.2
National poverty rate (% of population)	..	..	..
Life expectancy (yr)	..	68.7	..
Fertility rate (births per woman)	..	2.1	..
Infant mortality rate (per 1,000 live births)	35.0	33.0	..
Under 5 yr of age mortality rate (per 1,000 children)	39.0	35.0	..
Births attended by skilled health staff (% of total)	..	..	..
Child malnutrition, weight for age (% of children under age 5)	..	..	..
Child immunization, measles (% of under 12 mo)	99.0	99.0	..
Prevalence of HIV, total (% of population	..	0.7	..

aged 15–49)			
Literacy rate, adult male (% of males ages 15 and above)	..	88.3	..
Literacy rate, adult female (% of females aged 15 and above)	..	88.6	..
Primary completion rate, total (% age group)	111.0	112.0	..
Primary completion rate, female (% age group)	111.0	..	..
Net primary enrollment (% relevant age group)	94.6	..	..
Net secondary enrollment (% relevant age group)	69.2	..	..
Environment			
Surface area (km^2)	8.5 million	8.5 million	..
Forests (1,000 km^2)	5.4 million	..	..
Deforestation (average annual % 1990–2000)	0.4	..	..
Internal freshwater resources per capita (cubic meters)	..	30,680.2	..
CO_2 emissions (metric tons per capita)	1.8	..	..
Access to improved water source (% of total population)	..	..	..
Access to improved sanitation (% of urban population)	..	..	..
Energy use per capita (kg of oil equivalent)	1,091.3	..	..

Electricity use per capita (kWh)	1,877.5	..	..
Economy			
GNI, Atlas method (current U.S.$)	620.8 billion	486.9 billion	552.1 billion
GNI per capita, Atlas method (current U.S.$)	3,650.0	2,760.0	3,090.0
GDP (current U.S.$)	601.7 billion	505.7 billion	604.9 billion
GDP growth (annual %)	4.4	0.5	5.2
GDP implicit price deflator (annual % growth)	9.8	15.0	8.1
Value added in agriculture (% of GDP)	7.3	5.8	5.2
Value added in industry (% of GDP)	28.0	19.1	17.2
Value added in services (% of GDP)	64.7	75.1	77.7
Exports of goods and services (% of GDP)	10.7	16.9	22.5
Imports of goods and services (% of GDP)	12.2	13.1	17.0
Gross capital formation (% of GDP)	21.5	17.3	19.2
Revenue, excluding grants (% of GDP)	..	..	..
Cash surplus/deficit (% of GDP)	..	..	..
Technology and infrastructure			
Fixed lines and mobile telephones (per 1,000 people)	318.7	486.5	..
Telephone average cost of local call (U.S.$	0.0	..	..

per 3 minutes)			
Personal computers (per 1,000 people)	50.1	..	..
Internet users (per 1,000 people)	29.4	..	..
Paved roads (% of total)	5.5	..	..
Aircraft departures	617.8 thousand	486.8 thousand	..
Trade and finance			
Trade in goods as a share of GDP (%)	18.9	25.1	..
High-technology exports (% of manufactured exports)	18.6	12.0	..
Net barter terms of trade (1995 = 100)	100.0	..	..
Foreign direct investment, net inflows in reporting country (current U.S.$)	32.8 billion	10.1 billion	..
Present value of debt (current U.S.$)	223.8 billion	254.1 billion	..
Total debt service (% of exports of goods and services)	93.5	63.8	..
Short-term debt outstanding (current U.S.$)	31.0 billion	19.6 billion	..
Aid per capita (current U.S.$)	1.9	1.7	..

GDP, gross domestic product; GNI, gross national income.
From Development Indicators Database. Available at: http://devdata.worldbank.org/external/CPProfile.asp?SelectedCountry=BRA&CCODE+BRA&CNAME=Brazil&PTYPE=CP. Accessed August 2005.

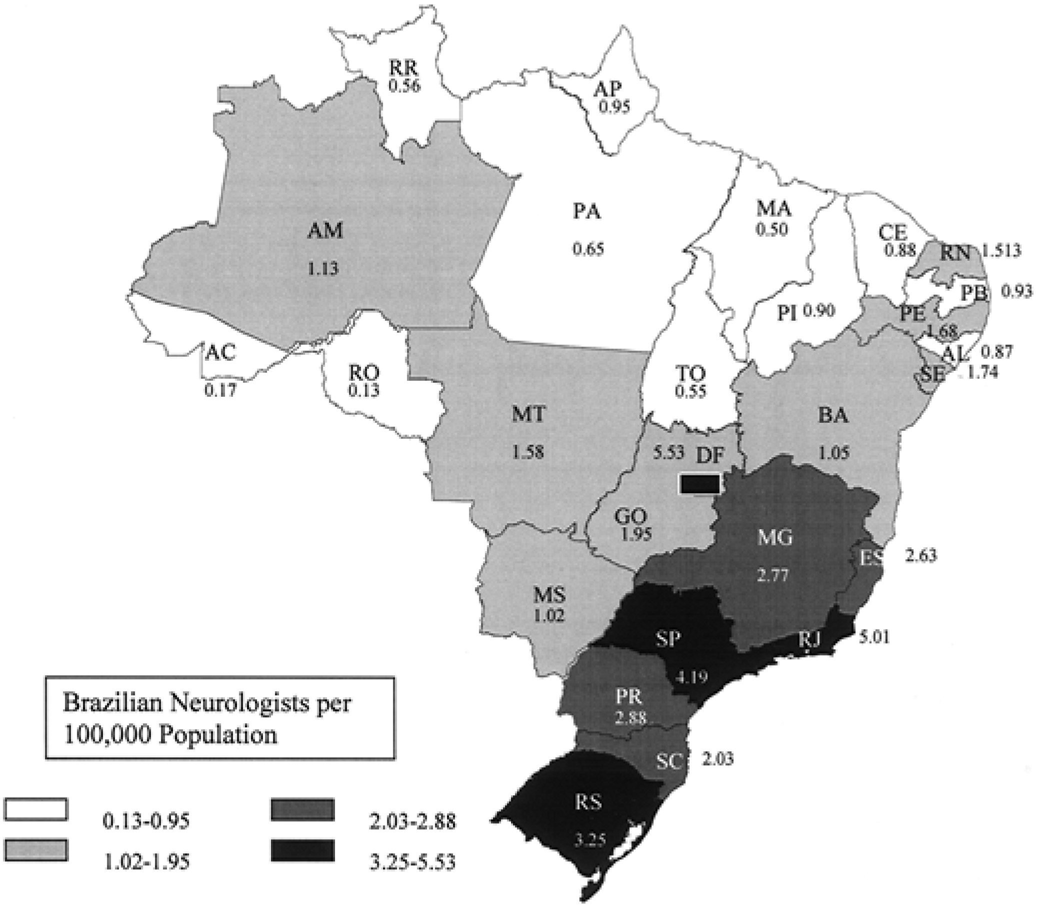

RR 0.56
AP 0.95
AM 1.13
PA 0.65
MA 0.50
CE 0.88
RN 1.513
PB 0.93
PI 0.90
PE 1.68
AL 0.87
SE 1.74
AC 0.17
RO 0.13
TO 0.55
MT 1.58
BA 1.05
5.53 DF
GO 1.95
MG 2.77
ES 2.63
MS 1.02
SP 4.19
RJ 5.01
PR 2.88
SC 2.03
RS 3.25
Brazilian Neurologists per 100,000 Population
0.13-0.95
1.02-1.95
2.03-2.88
3.25-5.53

FIGURE 1. The distribution of neurologists per 100,000 inhabitants in the different states of the federation.

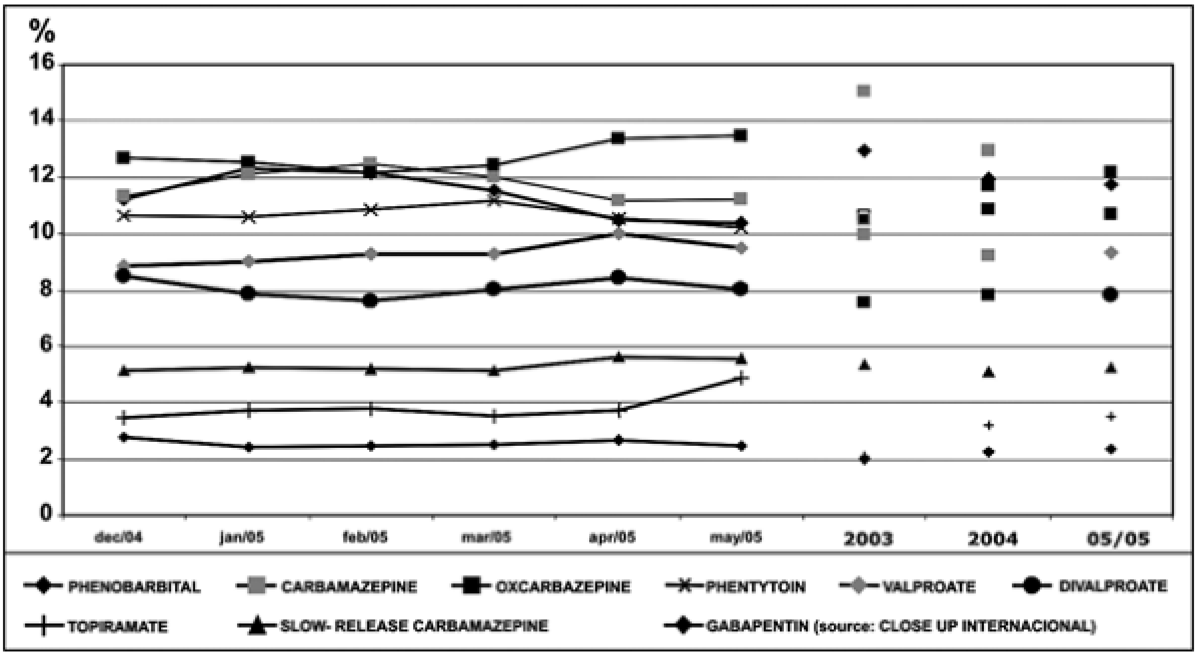


FIGURE 2. Sales of the main antiepileptic drugs available in Brazil by private practices (averages through May

2005).

Neurologists practice principally in the private sector (52%), in specialized outpatient clinics or HMOs (22%), in hospitals (23%), and in the federal health system (3%).

Drugs

Clinicians and Neurologists

In clinical practice, the drugs most prescribed (almost a third of prescriptions) by neurologists are antiepileptic drugs (AEDs). General practitioners and pediatricians are also responsible for a good number of AED prescriptions in Brazil.

Recent research conducted at the end of 2004 and beginning of 2005 in the private sector in Brazil and the relative sales of some basic antiepileptic drugs in private practice are shown in FIGURE 2.[14]

Drug Consumption and Treatment

Recently, there has been a tendency to decrease the use of sedative drugs and to substitute them for carbamazepine or valproate. This indicates a change in the AED prescribing patterns described in 1979 and 1980.[32]

There are few quantitative data about compliance in patients with epilepsy in Brazil.[1] To evaluate adherence, tolerance, and efficacy of the first AED prescribed, the author and colleagues followed 78 diagnosed epilepsy patients, ranging in age from 6 to 61 years (average, 17.96 years) for up to 29 months (average, 12.68 months). It was found that 11 patients (14.10%) did not adhere to the prescribed treatment, and 14 (17.94%) did not tolerate the first drug. Sixty-six percent of the patients were seizure free after 8 weeks of treatment, and 63.8% were seizure free after 56 weeks.[28] These data are consistent with the international literature.[9,13,18]

Brazil is a good example of many intermediate-economy countries where there is unequal wealth distribution and low-income areas where only phenobarbital is available. In other areas, the four basic AEDs (carbamazepine, phenytoin, phenobarbital, and valproate) are available in public health care, and in some more organized parts of the country, the new drugs (gabapentin, lamotrigine, topiramate, and vigabatrin) are available, sponsored by the federal government. The latter scenario is probably found in the black areas of the Brazilian map shown in the FIGURE 1.

The Sistema Único de Saúde Reference System

The data mentioned above demonstrate the political, social, and economic heterogeneity of the country's diverse regions. The public health system in one of the country's most populous and prosperous regions, the state of São Paulo, illustrates this.

The state of São Paulo is divided into five large regions (macroregions). The following will focus on the region of Campinas, which comprises 19 urban communities and a population of approximately 3 million. This region is responsible for approximately 9% of the gross national product (GNP), being three times higher than the Brazilian GNP and twice the state average. Despite this, social inequities such as growing slum areas and urban violence have been revealed.

Health care is divided into three areas: Primary, secondary, and tertiary care. Primary care consists of home care, health centers that support general clinics, and diagnostic and therapeutic support services (SADTs). On a secondary level, besides SADT, there are specialized outpatient clinics and local and macroregional hospitals. Tertiary care includes specialized outpatient clinics (university hospitals), regional hospitals, and SADTs.

Federal government financial resources cover approximately 70% of medical expenditures. The remaining 30% is supplied by the municipalities and the state.

From a neurology practice point of view, electroencephalogram testing and computed tomography scanning are currently available in medium-sized cities, but magnetic resonance imaging is performed by federal services in large cities only.

Aspects Related to Epilepsy in Brazil

Types of Seizures and Epilepsy

In Brazil, there appears to be no significant difference to developed countries in the incidence of the diverse types of epileptic seizures and syndromes.[27,44]

Etiologies

The high incidence of parasitic diseases is one of the factors that contribute to the greater prevalence of epilepsy in Brazil. Neurocysticercosis is the most common of these parasites, and it is the most frequently diagnosed cause of epilepsy in adults.[3,4,10,43,50,51] Seizures often start in childhood,[35,42] and specific clinical and computed tomography findings have been described in children.[24,30]

Malaria, when it presents with cerebral complications, may result in epilepsy. It is also a cause of febrile convulsions in children in tropical regions, in the northern part of the country.[45]

Perinatal brain damage is another factor suggested as a cause for the high incidence of epilepsy. This is possibly true in regions with inadequate prenatal care. However, Sakamoto[46] found that 14% of epilepsy cases were caused by perinatal lesions, which is no different from data collected by the Collaborative Perinatal Project of the National Institute of Neurological Diseases and Stroke in the United States.[37]

Because the incidence of motor vehicle accidents is high in Brazil, craniocerebral trauma is likely to be an important cause of epilepsy.[11] Sakamoto[46] found trauma to be the etiology of epilepsy in 3% of children and adolescents; Gorz et al.[26] found trauma to be the etiology in 13% of adolescents and adults with epilepsy.

In a country like Brazil, basic strategies for the prevention of epilepsy should include prenatal care, safe childbirth, control of infections—especially parasitic diseases—and reduction of brain injury due to trauma and stroke.

Psychosocial Aspects

Lay knowledge of epilepsy in Brazil is clearly unsatisfactory. When evaluating the knowledge of public and private school teachers and those in medical areas, Simonatto et al.[48] found it inadequate. The high rate of illiteracy and low cultural standards help perpetuate old prejudices about epilepsy. A comprehensive educational effort to inform the patients and their families about epilepsy is a basic step in successfully managing this condition.[2]

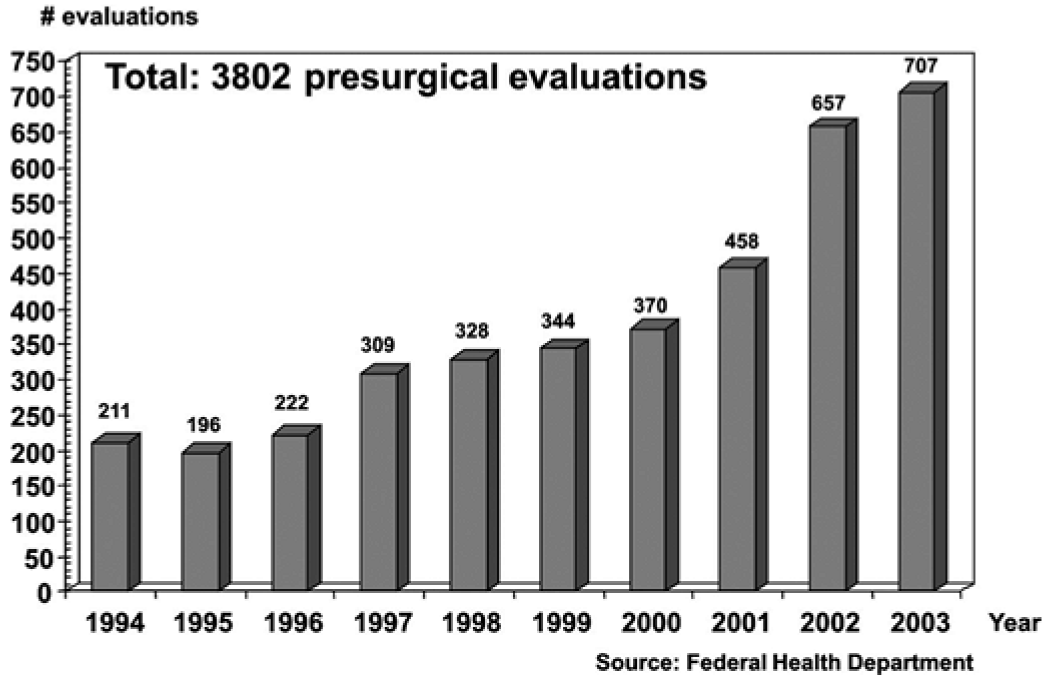


FIGURE 3. The number of presurgical evaluations registered by the Brazilian Epilepsy Program between 1994 and 2003.

Epilepsy is clearly associated with psychosocial difficul-ties.[7,21,47] Prejudice and discrimination are often worse than the seizure itself[7,36] with impact on the daily lives of people with epilepsy. According to studies carried out in Europe[7,25,52] and North America,[5,6,17] epilepsy stigma has been considered one of the most important negative factors on the quality of life of people with epilepsy. The definition of stigma in these studies[8,33] is portrayed slightly differently and, in most cases, is based on qualitative assessment expressed in proportions. Fernandes[23] has developed a scale to measure perception of stigma in epilepsy that consists of ten questions that provide a total score ranging from 0 (no stigma) to 100 (highest level of stigma). In a study carried out in Campinas, 1,850 people were interviewed and the results showed that the magnitude of stigma is different within demographics, such as gender, religion, and level of education, in an urban area. This finding is

relevant as a reference for mass media campaigns to fight prejudice and improve social acceptance of people with epilepsy.

In southeast Brazil, Guerreiro et al.[31] evaluated the impact of epilepsy on the quality of life in 17 recently diagnosed children. The relationship between parents and children was found to be significantly altered. However, culturally and socially, the interaction of these children in school and with their families did not show significant changes after the manifestation of epilepsy.[49]

A famous Brazilian with epilepsy is the writer Machado de Assis. He is considered by some to be the most important 19th-century writer in Latin America; in Brazil, he is considered the greatest of all time. Despite having cryptogenic localization-related epilepsy with complex partial seizures of right temporal lobe origin and despite the strong prejudices existing in the second half of the last century, he made good use of his genius through writing.[29] His life serves as an example to other people with epilepsy and to those who may be prejudiced against the condition.

Specialized Centers

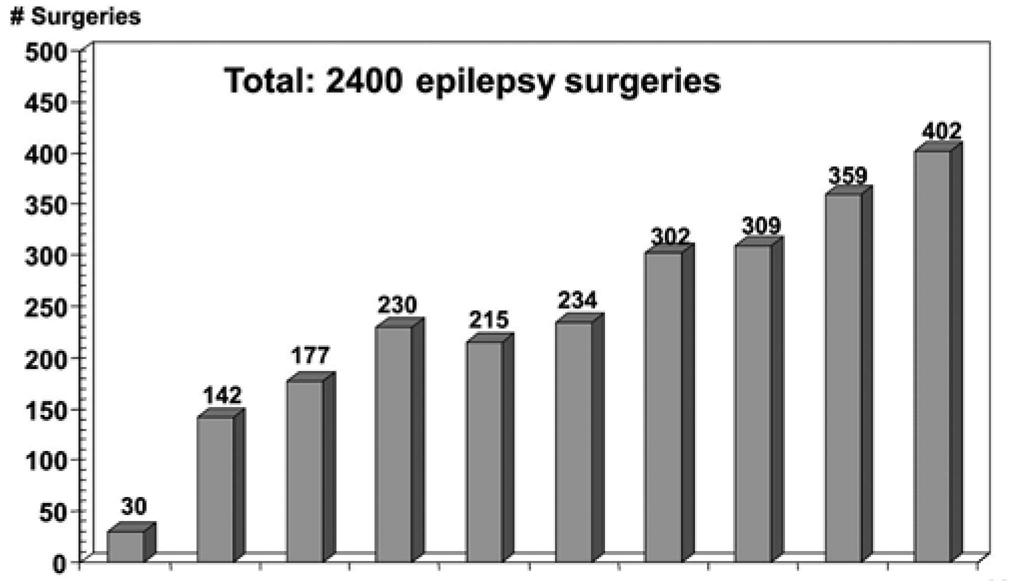
Considering the size of Brazil, there are few centers for the social rehabilitation of people with epilepsy. The ones that do exist have a multidisciplinary structure, are generally affiliated with a university, and are located mainly in the southern and southeastern regions of the country.

Brazilian National Epilepsy Surgery Program

Epilepsy surgery started with Niemeyer in Rio de Janeiro in the late 1950s. Indeed, he was the first to propose amygdalohippocampectomy to treat temporal lobe epilepsy and he described the technique in detail.[39] In the 1970s, São Paulo University Medical School (USP) started a surgical program, followed by the Neurological Institute at Goiânia in the 1980s. In the 1990s, three epilepsy centers joined the group: Catholic University (PUC, Porto Alegre), University of São Paulo (USP-Ribeirão Preto), and State University of Campinas (UNICAMP).

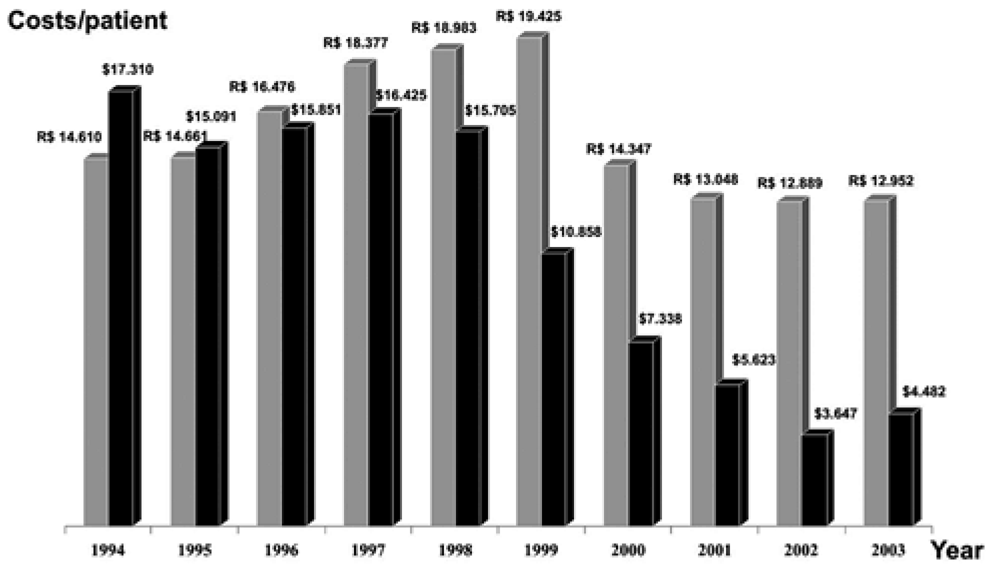
In 1994, the Federal Health Department started the National Epilepsy Program within the Program of High Complexity Medical Procedures. Some of the program's data over 10 years (1994 to 2003) in the eight approved centers are shown in Figures 3, 4, and 5.

Positive aspects of this public health policy were technical criteria for accreditation of epilepsy surgery centers, strong partnership between the Health Department and national medical societies, and a reimbursement policy granting epilepsy surgery the same status as renal transplantation. Of note are that seven of the eight epilepsy surgery centers are university institutions; presurgical investigation and surgeries are at internationally accepted standards; morbidity, mortality, and outcome figures are similar to major epilepsy surgery centers; and there is progressive development of new epilepsy surgery centers and a network of epilepsy centers with potential for collaborative research and training. The limitations observed were that the distribution of centers does not parallel demographic data; a national center for regulation of patient access is still preliminary; and there is a lack of specific policies for more complex cases (invasive procedures) and a lack of long-term planning for the expansion of new epilepsy centers. New challenges of this program include improvement of the current system for referrals of patients from less privileged regions and stimulation of greater cooperation between epilepsy surgery centers, patient care, and scientific cooperation.



Source: Federal Health Department

FIGURE 4. The number of epilepsy surgeries registered by the Brazilian Epilepsy Program between 1994 and 2003.



Source: Federal Health Department

FIGURE 5. Costs per patient of the presurgical evaluation plus surgery in reais (R$) and in U.S.$ ($) between 1994 and 2003.

The Role of Societies

The Brazilian Epilepsy League plays an important role in advising the Ministry of Health on issues regarding epilepsy and in providing education to physicians. The Brazilian Epilepsy

League sends out videos, booklets, and books to its nearly 300 members and to medical schools. It organizes scientific meetings and courses in its various regional chapters and has an annual national scientific meeting.

The National Demonstration Project on Epilepsy in Brazil has galvanized lay epilepsy associations across the country since 2002 in a joint effort to help drive epilepsy out of the shadows in Brazil.[34] The main activities are (a) the National Week of Epilepsy, which takes place in all regions of the country,[22] and (b) the National Meeting of Associations and Support Group of People with Epilepsy, where the achievements and resolutions to drive epilepsy out of the shadows are discussed.[19,20,23] These activities have been coordinated by the ASPE (Assistência à Saúde de Pacientes com Epilepsia) and EPI-Brasil (Federation of Associations of People with Epilepsy of Brazil) and represent an important step toward promoting an awareness of epilepsy, diminishing the associated stigma and improving the quality of life of people with epilepsy and their families.

Summary and Conclusions

The organization of the country's medical system for epilepsy care reflects the low socioeconomic development of the nation.

Some factors that are causing or contributing to the high rate of epilepsy in the country are the high incidence of infectious diseases, mainly parasitic (especially neurocysticercosis); the poor quality of maternal–infant care in the low socioeconomic regions (particularly in the interior of the northeast and in the misery belts around the large cities); and the high rate of traffic accidents with resulting head trauma. Improved health care, basic education, and sanitation can greatly improve these conditions. The role of nongovernmental agencies in educating the public has produced encouraging results, although their efforts are currently limited to a few segments of society.

Basic measures should be taken to bring about a more efficient health care system. With regard to patients with epilepsy, the governmental policies related to epilepsy with referential and counterreferential centers should be reformed. Low-income patients all over the country, and not just in certain areas, should receive AEDs at no cost.

The official recognition of epilepsy surgery by the Ministry of Health is helping organize an algorithm in this increasingly complex medical care field. It is crucial that the Ministry of Health includes epilepsy in the public health priorities as proposed by International League Against Epilepsy.[34] In this setting, the World Health Organization, the International League Against Epilepsy, and the International Bureau for Epilepsy launched the Global Campaign Against Epilepsy in 1997.

Acknowledgments

The author thanks Dr. Américo C. Sakamoto, who provided data on the National Epilepsy Surgery Program, and Drs. Li Li Min, Ana L. Noronha, and Paula T. Fernandes for data related to the Demonstration Project in Brazil.

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Chapter 290

Canada

Samuel Wiebe

Introduction

This monograph describes broadly the health services for epilepsy in Canada. A brief overview of the Canadian health care system provides the basis for a portrayal of services covered, challenges to epilepsy care in Canada, and specific epilepsy health care services by province.

A depiction of the Canadian geography is pertinent as this is directly relevant to health care delivery. Canada spans an area of approximately 10 million km^2, of which a substantial proportion is north of 60th parallel and in the arctic regions. Approximately 31 million people inhabit ten provinces and three territories, with a population density of 3.1 residents per km^2, one of the lowest in the American Continent. The boundaries of the vast Canadian expanse comprise the Atlantic, Pacific, and Arctic oceans. Two thirds of the population (20 million) live in metropolitan areas, most of which are located in proximity to the southern national border. The large northern areas encompassing the Yukon, Northwest Territories, and Nunavik have only 100,000 inhabitants.[7] It is readily apparent that geography poses a gargantuan challenge to equal access to health care services.

The Canadian Health Care System

The Canadian Health Care system rests on the principles enshrined in the Canada Health Act, whose tenets are equity and solidarity. Its objective is to ensure that all eligible Canadian residents have reasonable access to insured health services on a prepaid basis, without direct charges at the point of service. Canada's National Health Insurance Program consists of 13 interlocking provincial and territorial health insurance plans, all of which share certain common features and basic standards of coverage. The roles and responsibilities for Canada's health care system are shared between the federal and provincial-territorial governments. The latter are responsible for the management, organization, and delivery of health services for their residents. Essentially, each province or territory has a list of insured services covered by the national insurance program. These comprise the great majority of medically necessary physician and hospital services. There is interprovincial reciprocity of services with the exception of the province of Quebec. Physicians can refer anywhere in Canada if services are not available locally or if they are justified by complexity. There is variable coverage of medication, eye care, dental care, and allied health care services. In general, medications are not covered except in special populations, such as the elderly, disabled or unemployed, and registered natives and Inuits. Each province has a medication list whose contents vary by province. Restricted use is specified if other drugs fail. A special application is required for unlisted drugs. In jurisdictions that have drug coverage, a copayment by the patient is required. This is widely variable, ranging from the prescription cost up to a maximum yearly of $850 CDN, and then a portion of the excess in some provinces. This coverage may take income into account. A few groups have complete coverage without copayment, including children. All consults to specialists require referral by general practitioners or family doctors, and some allied health care services also require referrals.

Access to Health Care

Statistics Canada carries out national surveys that evaluate access to health care.[6] In 2003, 20% of the general population reported some difficulty accessing specialized care and 15% had some difficulty accessing diagnostic tests. The main barriers to access were long wait times for service, reported by approximately 60% of those patients who identified any type of difficulty. The health access survey also assessed the effect of waiting for specialized care. The main effect of waiting was worry or stress (60% of individuals), whereas only 20% reported worsening of health status as a result of waiting. Interestingly, people with epilepsy in rural areas report fewer barriers to health care than those in urban areas.[9] This somewhat counterintuitive finding may have two possible explanations. Epilepsy care in rural areas occurs mostly through family physicians and emergency rooms, which are more readily accessible than urban specialists with long waiting lists. Alternatively, more complex patients requiring multiple levels of health care, which are often less accessible, may migrate to urban settings. Population surveys in Canada have also shown that patients with epilepsy have a higher use of specialists, nursing, and allied health services than patients with other common chronic conditions.[9]

According to Statistics Canada and the Canadian Institute of Health Information, the ratio of population per hospital in Canada is approximately 31,000, and there is approximately one hospital per 9,260 km^2.[2] The latter varies substantially among regions and provinces, from a low of 3,000 km^2 per hospital in Ontario to a high of 450,000 km^2 per hospital in the northern territories. In general, populated provinces have more and busier hospitals that are often nearly fully occupied, whereas provinces and territories with few inhabitants have fewer hospitals per area, distributed over vast and remote geographic regions, and with more challenging access.

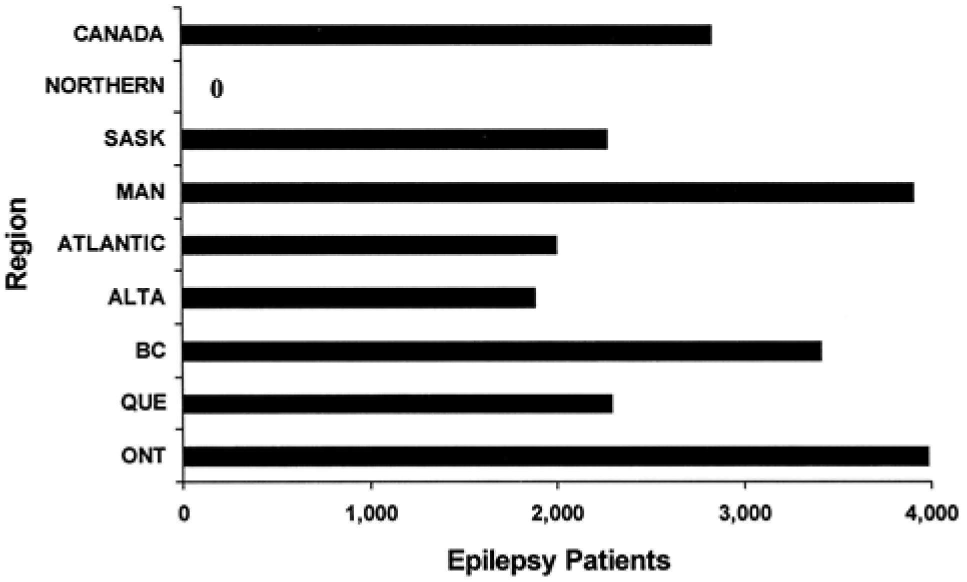

FIGURE 1. Epilepsy patients per epileptologist. In 2004, the ratio of patients with epilepsy to epilepsy neurologists varied across provinces, but with the exception of the Northern territories, it was always <4,000. Northern, Nunavut, Northwest Territories, Yukon; Sask, Saskatchewan; Man, Manitoba; Atlantic, Nova Scotia, Newfoundland & Labrador, New Brunswick, Prince Edward Island; Alta, Alberta; BC, British Columbia; Que, Quebec; Ont, Ontario. (Source: Wiebe, unpublished survey; and Tellez-Zenteno JF, Pondal-Sordo M, Matijevic S, et al. National and regional prevalence of self-reported epilepsy in Canada. *Epilepsia.* 2004;45(12):1623–1629.)

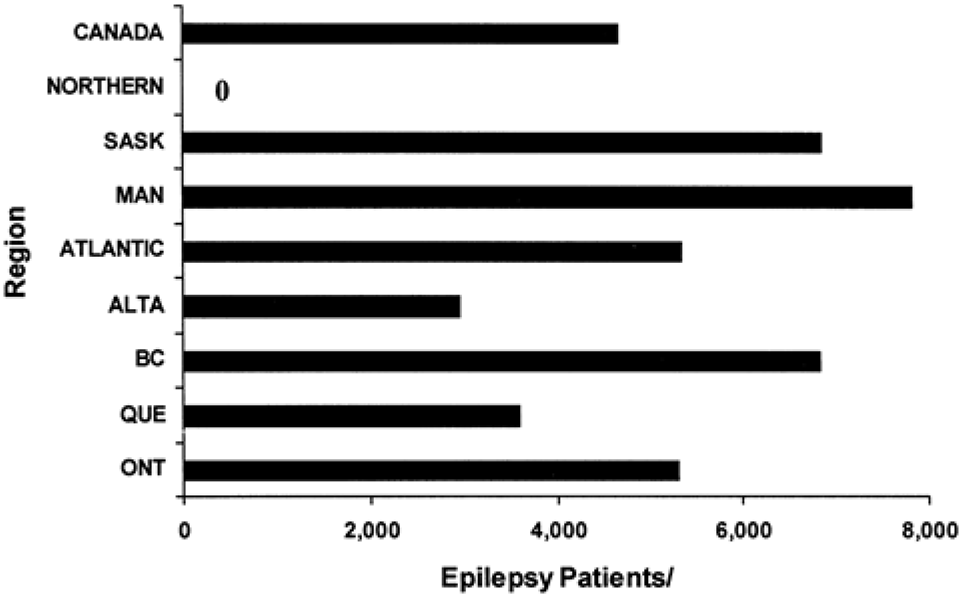

FIGURE 2. Epilepsy patients per electroencephalographic (EEG) monitoring bed. The number of patients with epilepsy per video-EEG monitored bed ranged from 2,500 to 8,000 in different provinces, and there were none in the Northern territories. Northern, Nunavut, Northwest Territories, Yukon; Sask, Saskatchewan; Man, Manitoba; Atlantic, Nova Scotia, Newfoundland & Labrador, New Brunswick, Prince Edward Island; Alta, Alberta; BC, British Columbia; Que, Quebec; Ont, Ontario. (Source: Wiebe, unpublished survey; and Tellez-Zenteno JF, Pondal-Sordo M, Matijevic S, et al. National and regional prevalence of self-reported epilepsy in Canada. *Epilepsia.* 2004;45(12):1623–1629.)

According to a 1996 survey of specialist manpower, the mean distance from a general practitioner to a neurologist was 102 km, and it was 135 km for a neurosurgeon. This is highly variable among regions. In 2002, there were 694 neurologists in Canada, resulting in a ratio of 44,700 people per neurologist. This also is highly variable among regions, ranging from zero neurologists in the three vast northern territories to 218 in Ontario, and resulting in the following population-to-neurologist ratios: British Columbia, 43,000; Alberta, 43,200; Saskatchewan/Manitoba, 74,700; Ontario, 50,100; Quebec, 33,400; and Maritime Provinces, 61,000.[1] In most provinces the ratio has decreased over time (e.g., more neurologists per population), with the exception of Saskatchewan and Manitoba, where the number of neurologists has actually decreased over the last few years.

Epilepsy-specific Health Care Resources

The only existing Canadian study of the epidemiology of epilepsy in the general population reports a prevalence of active epilepsy of 5.6 per 1,000.[8] The prevalence of epilepsy is higher in groups with lower educational level and income, and in the unemployed. Although the prevalence of active epilepsy is fairly constant across provinces, and translates into approximately 210,000 patients with epilepsy nationally, there are minor interprovincial differences (e.g., the prevalence is somewhat lower in the Pacific than in the Atlantic provinces).[8]

The approximate ratio of epilepsy patients per neurologist in Canada is 300, based on a prevalence of epilepsy of 7 per 1,000 and a total of 694 neurologists.[1] Again, this ranges from zero in the northern territories to 245 patients per neurologist in Quebec. Bailey's national survey found that 104 (15%) neurologists in Canada reported an interest in epilepsy.[1] However, a 2004 survey by the author identified only 74 neurologists focusing in adult or pediatric epilepsy, with a provincial median of eight and a range of zero in the vast northern territories to 22 in Quebec. The ratio of adult to pediatric epileptologists in Canada is approximately 3:1, which is remarkable given that a large number of the epilepsies are of childhood onset. This survey also identified 23 neurosurgeons focusing on epilepsy surgery in Canada, with a provincial median of 3.5, ranging from zero in the north to six in Alberta. According to these data, the national ratio of patients with epilepsy per epileptologist is 2,843, the provincial median ratio is 2,300, and the range is zero in the north to 1,800 in Alberta (Fig. 1). The national ratio of patients with epilepsy per epilepsy neurosurgeon is 9,000, with a provincial median ratio of 7,000, and a range of zero neurosurgeons in the northern territories to 3,000 patients per neurosurgeon in the more abundantly served Atlantic provinces and Alberta.

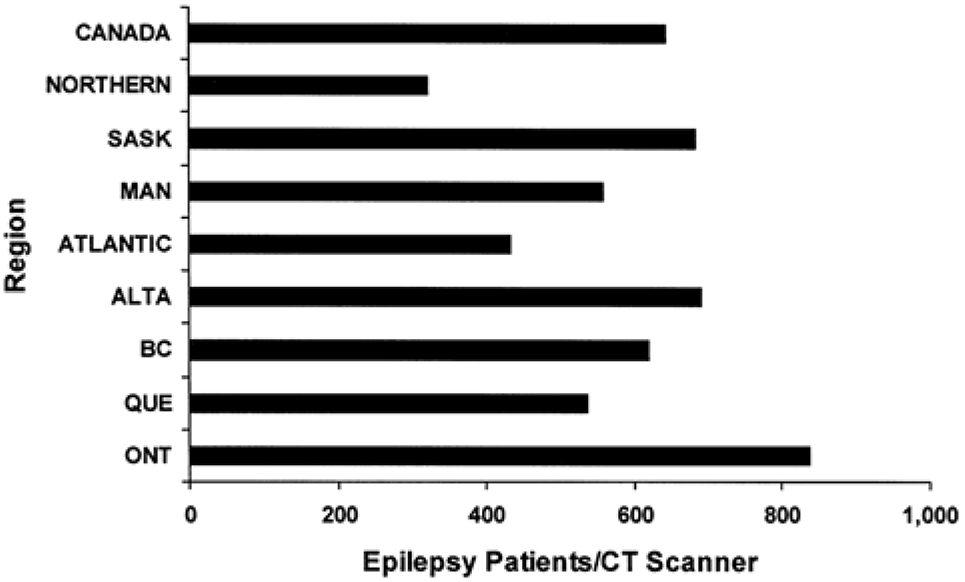

FIGURE 3. Epilepsy patients per computed tomography (CT) scanner. All Canadian provinces have CT scanners. The ratio of patients to scanner is lowest in the North because of its sparse population. Northern, Nunavut, Northwest Territories, Yukon; Sask, Saskatchewan; Man, Manitoba; Atlantic, Nova Scotia, Newfoundland & Labrador, New Brunswick, Prince Edward Island; Alta, Alberta; BC, British Columbia; Que, Quebec; Ont, Ontario. (Source: Canadian Institute for Health Information. *Medical Imaging in Canada: 2004.* Ottawa, Canada: Canadian Institutes for Health Information; 2004; and Tellez-Zenteno JF, Pondal-Sordo M, Matijevic S, et al. National and regional prevalence of self-reported epilepsy in Canada. *Epilepsia.* 2004;45(12):1623–1629.)

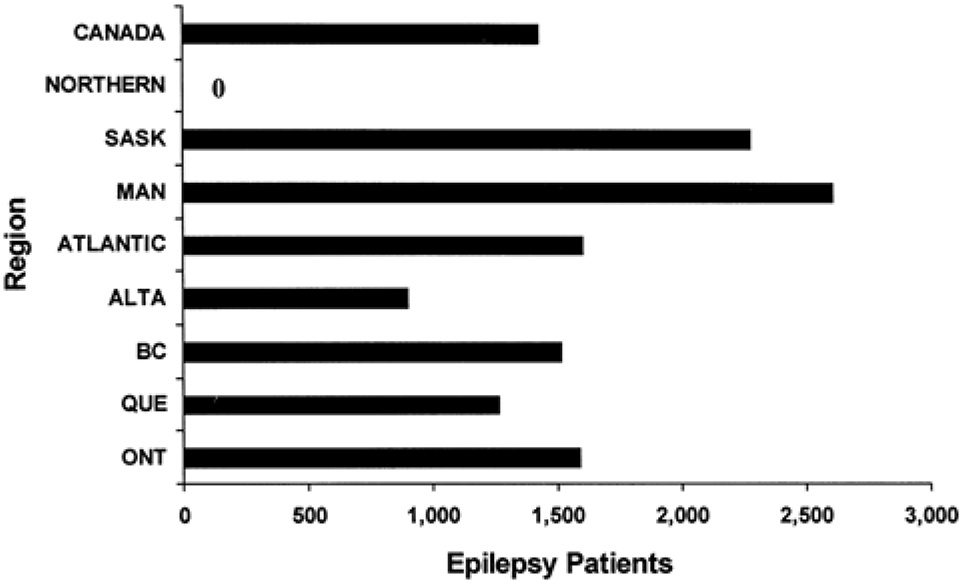

FIGURE 4. Epilepsy patients per magnetic resonance imaging (MRI) scanner. In 2004 there were 167 MRI scanners in Canada. The ratio of patients with epilepsy to MRI scanner was approximately twice that of CT scanners. There was no MRI scanner in the vast North. Northern, Nunavut, Northwest Territories, Yukon; Sask, Saskatchewan; Man, Manitoba; Atlantic, Nova Scotia, Newfoundland & Labrador, New Brunswick, Prince Edward Island; Alta, Alberta; BC, British Columbia; Que, Quebec; Ont, Ontario. (Source: Canadian Institute for Health Information. *Medical Imaging in Canada: 2004.* Ottawa, Canada: Canadian Institutes for Health Information; 2004; and Tellez-Zenteno JF, Pondal-Sordo M, Matijevic S, et al. National and regional prevalence of self-reported epilepsy in Canada. *Epilepsia.* 2004;45(12):1623–1629.)

Our 2004 survey identified approximately 45 video-electroencephalographic (V-EEG) monitoring beds in the country. This results in a national ratio of 4,600 patients with epilepsy per monitored bed, and a provincial median ratio of 5,300, ranging from zero monitored beds in the north to 3,000 patients per monitored bed in Alberta (Fig. 2). The Canadian Institute of Health Information reported a total of 326 computed tomography (CT) scanners nationally, which translates into a ratio of 645 patients with epilepsy per CT scanner, and a provincial median ratio of 600 patients with epilepsy per CT scanner (range: 325 in the northern territories to 840 in Ontario) (Fig. 3).[3] Similar sources revealed a total of 147 magnetic resonance imaging (MRI) scanners nationally, which is equivalent to a national ratio of 1,400 patients with epilepsy per MRI scanner, and a provincial median ratio of 1,500 patients per scanner (range: zero in the North to 900 in Alberta) (Figs. 4 and 5).[3] According to the Canadian Institute of Health Information, in 2004 there were eight positron emission tomography (PET) scanners in the country.[3]

In 2003 there were approximately 17 adult epilepsy clinics and 18 pediatric epilepsy clinics in Canada. These clinics had access to a total of approximately 30 clinical psychologists or social workers and less than two dozen nurses.

Epilepsy Nurses

Best available data revealed that in 2003 in Canada there were less than two dozen nurses working part or full time in epilepsy. Furthermore, three large Canadian provinces have no access to dedicated epilepsy nurses. A recent survey conducted across Canada showed that 68% of epilepsy centers/clinics have dedicated epilepsy nurses, with a median of 1.7 nurses per epilepsy center.[5] Only 58% of centers have dedicated funding for epilepsy nurses. The role of epilepsy nurses is described in Table 1.

Antiepileptic Drugs

Most of the frequently used antiepileptic drugs (AEDs) are included in provincial drug formularies. The latter determine which drugs are available at no cost to special populations, such as the elderly, disabled, unemployed, registered Aboriginals, and Inuits. New AEDs take time to reach provincial formularies and special application can be made for these drugs. In Canada, drugs are licensed by a federal agency following a rigorous process that is similar to that of the Food and Drug Administration in the United States. At the time of this writing, the following commonly used AEDs are licensed and available for use in Canada: Phenytoin, phenobarbital, carbamazepine and carbamazepine controlled release, valproate, ethosuximide, primidone, clobazam, lorazepam, lamotrigine, topiramate, vigabatrin, levetiracetam, and oxcarbazepine. AEDs not available in Canada include zonisamide, tiagabine, and felbamate.

National Epilepsy Organizations

The Canadian League Against Epilepsy is the country's professional organization and is the national chapter of the International League Against Epilepsy. Epilepsy Canada is a national organization whose focus is on research and education, and it is the national chapter of the International Bureau for Epilepsy. The Canadian Epilepsy Alliance is a lay organization, which focuses on patient and public education and support. Regional epilepsy associations often serve the functions of epilepsy support groups and have variable degrees of interaction with epilepsy clinicians. The distribution of regional epilepsy support groups follows closely that of the population density across the country. All of the epilepsy support organizations function as not-for-profit charities.

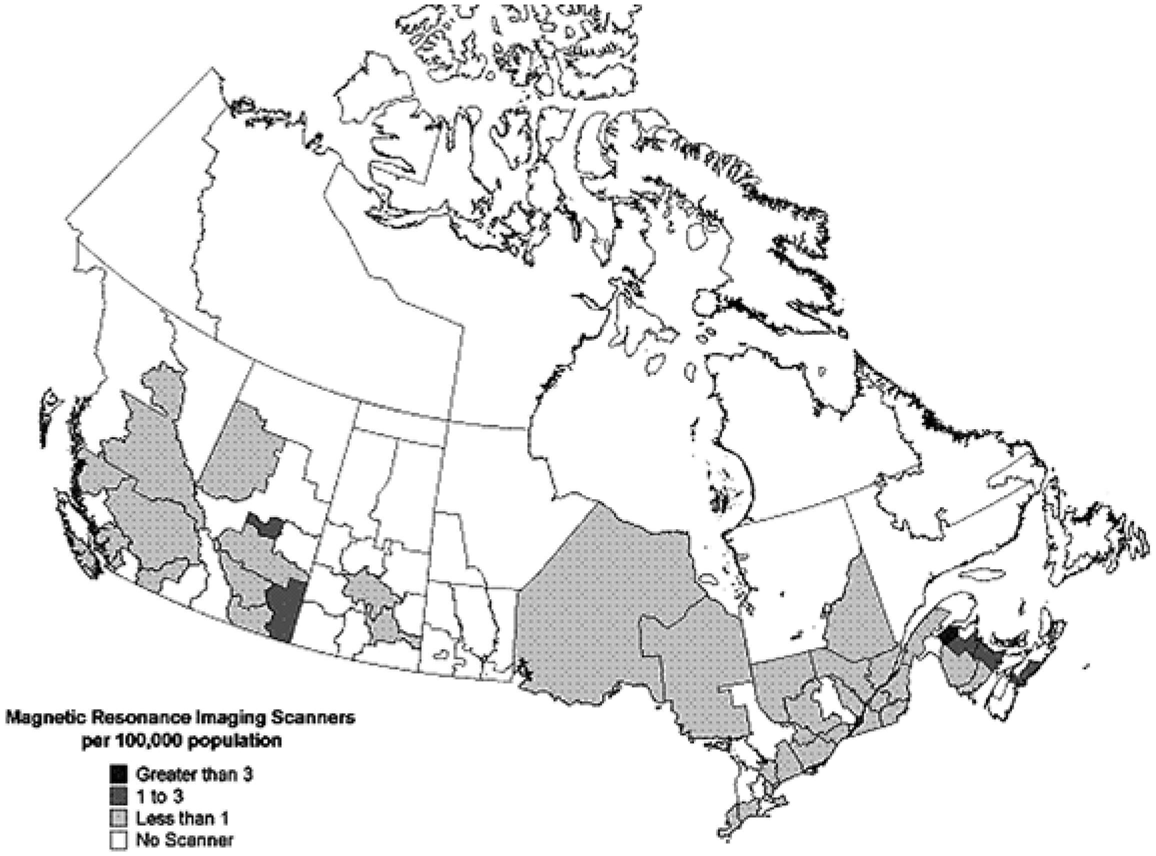

FIGURE 5. Magnetic resonance imaging (MRI) scanners per 100,000 population, 2004. Canadian map illustrating the distribution of MRI scanners in the country in 2004. Notice the distribution of scanners toward the Southern border, and also the clustering around specific large centers located in more heavily populated areas. (Source: Medical Imaging in Canada, 2004. Reprinted with permission from the Canadian Institute for Health Information.)

Table 1 Epilepsy Nurses' Clinical Activities

Activity	Number (%)
Clinical education	14 (76%)
Seizure monitoring unit	12 (65%)
Presurgical evaluation (outpatient)	10 (58%)
Other patient care	15 (82%)

Patient telephone education	15 (82%)

Aboriginal Populations

Canada has the second largest aboriginal population (3.3% of the total population) after New Zealand. For comparison, the percentage of aboriginal population in Australia is 2.2% and in the United States is 1.5%. Little is known about access to health care in general and to epilepsy care in particular in aboriginal populations. However, Canadian national surveys reveal that contact with physicians or with traditional healers varies even within the aboriginal population. Aboriginals residing in urban settings have more frequent contact with physicians than those residing in rural settings. In turn, Aboriginals in the arctic regions have the least contact with physicians or traditional healers (about half as often as those in urban dwellings).[7] This is important because the aboriginal population has higher mortality rate, infant mortality, hospitalization rates, and potential years of life lost from injury than the nonaboriginal Canadian population.[4] Although the incidence and prevalence of epilepsy in aboriginal populations in Canada has not been studied, it is conceivable that lower health indices and a high rate of injuries may have an impact on epilepsy and on access to health care resources for epilepsy.

Summary and Conclusions

The Canadian health care system is based on the principles of equity and solidarity, as embodied in the Canadian Health Act, whose objectives are to ensure that all eligible Canadian residents have reasonable access to insured health services, on a prepaid basis, without direct charges at the point of service delivery. The current main barriers to care, according to Statistics Canada (2), are long waiting lists to access elective specialized care and elective diagnostic tests. Another important challenge is the enormous geographic expanse of the country, which also impacts on access to care.

The availability of epilepsy services across the country differs substantially between more and less densely populated areas, which is often a South-North gradient. Among more populated areas, there is some variability in services, especially in regards to the level of specialization, however access is generally adequate. The ratio of adult to paediatric epileptologists is approximately 3:1, which is remarkable given the large number of epilepsies of childhood onset. Facilities for the investigation and treatment of complex epilepsies are available throughout the country and several provinces have more than one centre. Patients can be referred across centres and across provinces throughout the country, as needed.

Most of the frequently used AEDs are included in provincial drug formularies, which determine availability at no cost to special populations such as the elderly, disabled and unemployed. There is no national insurance plan for AEDs, and each province has a different level of insurance. At the time of this writing, AEDs not marketed in Canada include zonisamide, tiagabine, piracetam, and feldamate.

Funding for research in epilepsy derives mostly from the Canadian Institutes of Health Research, which is a federal health research organization. In addition, provincial agencies have smaller opportunities to fund research in epilepsy in some areas. Canada has representative chapters from the International League Against Epilepsy and from the International Bureau for Epilepsy, with corresponding professional and lay memberships, and it is also a member of the North American Region of the International League Against Epilepsy.

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Chapter 291

China

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Introduction

The People's Republic of China (hereinafter referred to as China) is located in East Asia and on the West Coast of the Pacific Ocean. China has 9.6 million km^2 of area and 1.3 billion of population with 56 ethnic groups. Urban population accounts for 42% of the total. The administrative division of the mainland China is 22 provinces, five autonomous regions, and four municipalities directly under the central government.

The following are some public health indicators in China: National health expenditure (2003) of $63.3 (U.S.) per capita and total of $818.7 hundred million (U.S.), which accounted for 5.6% of the gross domestic product (GDP) and 11% of the central government's expenditure allocated to health; life expectancy at birth (2000), 71, 69, and 73 years for total, male, and female, respectively; birth rate (2003), 12.29 per 1,000; death rate (2003), 6.42 per 1,000; infant mortality rate (2004), 25.5 per 1,000; maternal mortality rate (2004), 50.2 per 100,000; and mortality rate under 5 years of age (2004), 30 per 1,000 live births.

Statistics for public health resources are as follows: doctors per 1,000 inhabitants, 1.7; hospital beds per 1,000 inhabitants, 2.4; total number of health institutes in 2004, 296,492, and among them, 18,396 hospitals; and total number of health personnel in 2004, 5,353,628, and among them, 1,904,771 doctors and assistant doctors.

Since the establishment of the People's Republic of China in 1949, remarkable advances have been made in the public health system and in employment. These include the following: (a) There has been an extraordinary improvement in measures of people's health. The life expectancy at birth in 1949 was 35 years, but in 2004 it was 71.8 years. The infant mortality rate in 1949 was 200 per 1,000 live births, but in 2004 it was 25.5. The maternal mortality rate in 1949 was 1,500 per 100,000, but in 2004 it was 50.2. (b) A medical service system has been established that covers the whole nation. The three-tier healthcare system, in rural (county–township–village) and urban areas (city–district–neighborhood) has made great contributions to the improvement of people's health. (c) A medical insurance system is in development. In urban areas, there are four types of medical insurance systems: (i) "free-of-charge system," which covers about 50 million public servants, university students, etc.; (ii) basic medical insurance and (iii) supplementary medical insurance, both of which cover about 130 million workers; and (iv) commercialized insurance, which covers part of private enterprises employees. In rural areas, a new "cooperative medical service system" has just been implemented in a pilot stage, and this presently covers about 156 million farmers. (d) There has been great improvement in the prevention and control of communicable diseases. For example, deaths caused by communicable/parasitic diseases fell from first (in the 1950s) to the ninth (in 2004) place as a cause of death; smallpox, poliomyelitis, etc., have been eradicated; there has been effective control of severe acute respiratory syndrome (SARS) and avian influenza; and effective measures and networks have been put in place to control HIV/AIDS, tuberculosis, hepatitis B and schistosomiasis. (e) Remarkable improvements have been made in maternal and child healthcare. The prenatal examination rate has now reached 90%; the hospitalized delivery rate has reached 83%; and the mortality rate of children under 5 years of age has reached 29.9 per 1,000, whereas in 1949, it was 250 to 300 per 1,000.

Beginning in the late 1970s, China implemented an "open-door and reform" policy. Since then, public health work has further improved and in a number of diseases controlled. The medical service system is now under reform and the medical/health services are expanding coverage. The Chinese government has made great efforts toward the strategic goal of "health for all."

Epilepsy was recognized and described 2,200 years ago in the oldest Chinese medical monograph *Medical Classic of the Yellow Emperor* (Huang Di Nei Jing). In China, epilepsy has long been treated by traditional Chinese medicine (TCM, meaning herbal medicine, acupuncture/moxibustion, and other folk therapies), and a long experience with epilepsy treatment has accumulated. However, the most effective control of epilepsy has resulted from modern medical practices, including surgical treatment. From the 1950s, clinical diagnosis and treatment of epilepsy in China has improved steadily, but very little research on its public health aspects occured until the 1970s.

What is described in this chapter—that is, the epidemiology, clinical neurologic diagnosis and treatment, epilepsy surgery, basic research, sociopsychological problems, rural community control programs, and TCM recognition of epilepsy in China—covers about the last three decades.

Epidemiology

Epidemiology is the study of the distribution and determinants of disease in human populations. Recently, psychosocial and economic indicators, such as quality of life and standards of care, have been incorporated into epidemiologic research, as their relationship to morbidity became evident.

There are several key difficulties in conducting epidemiologic research on epilepsy and in interpreting the epidemiologic literature.[32,47] These include:

- Variations in the definitions and classification of seizures and of epilepsies
- Poor case ascertainment due to ignorance or concealment by patients or their families, or due to the fact that some patients are not aware of having seizures
- Diagnostic imprecision, even when potential patients are identified
- Differences between studies in the age distribution of study populations, or in the place or mode of recruitment of subjects

Table 1 Prevalence Ratio and Incidence Rate of Epilepsy in China

Year	Study	Reporter	Sample population	Prevalence (per 1,000)	Incidence (per 100,000)
1981	Sichuan		426,789	4.8	35
1983	6 cities	Li	63,195	4.4	35
1985	22	Li	246,812	3.6	26

	provinces				
1992	Jiangsu	Shan	(0–14 yr)	5.9	200
2003	6 rural areas	Wang	55,616	7.0	(active 4.6)

These and other factors all limit the precision and validity of data and comparability among studies. Despite these difficulties, sufficient data are available from a number of studies to give a useful profile of the epidemiologic characteristics of epilepsy in China.

Prevalence Ratio

Researchers use lifetime prevalence to express the magnitude and scope of the burden of a defined disorder in the population. Point prevalence is the proportion of a defined population with a disease at a given point in time (usually the first or last day of a year). The point lifetime prevalence ratio results for epilepsy in China from some studies are shown in Table 1. We may see that the prevalence for epilepsy in China is about 4 to 6 per 1,000, which is similar to the average figure in industrialized countries. In Wang's study, patients with epilepsy who had seizures in the past year were categorized as “active epilepsy”; for those cases, the prevalence ratio was found to be 4.6 per 1,000.[41]

Incidence Rate

Incidence rate is the rate of occurrence of new cases of epilepsy in a defined population in a specified time period (usually 1 year). Table 1 also shows the incidence rates for epilepsy in China as 26 to 35 per 100,000 individuals per year.

Mortality Rate

Unfortunately in most countries epilepsy is not listed in “cause of death” statistics as an independent disease. Deaths of persons with epilepsy (PWE) are always registered as caused by the underlying disease or some other reason, such as “accident.” Reports from China showed 7.9 per 100,000 per year in urban areas and 6.9 per 100,000 per year in rural areas. The figure from China is higher than that from other countries, and this difference is not explained.[47]

In recent years, the *standardized mortality rate* (SMR) has been used in the epidemiologic literature to analyze deaths in epilepsy. These analyses show that the SMR for epilepsy patients is more than twice that for the general population. Causes of mortality include (a) underlying brain diseases, such as tumor or infection; (b) seizure-related deaths (status epilepticus; drowning, burns, or other trauma; severe aspiration or airway obstruction by food, etc.; deaths caused by habitual seizures when coexisting with cardiorespiratory disease); (c) suicide; (d) death as a consequence of medical or surgical treatment of epilepsy; and (e) sudden unexplained death in epilepsy (SUDEP), whose causes remain ill-understood.[29,47]

Research and data on SUDEP are very rare in China. From 1994 to 2004, only three papers on this topic were published, and two of them were literature reviews. Wang et al.[44] analyzed the clinical and pathologic information of seven cases of SUDEP. They found that all seven cases had edema of the brain and lungs. Some of the patients had reduction of neurons and increase of glial cells. There were no tumors or injuries. All seven died when they had a general tonic–clonic seizure. Two occurred in sleep and four had agitation or fright before death.

One hundred and twenty PWE from four provinces in China who had been part of a project, “community control of epilepsy,” in the late 1980s were followed up 5 years later. Thirteen had died. The mortality rate of this group was 2.2% per year and around 3.4 times higher than the rate in the general population. Among the 13 deceased, two (15.4%) might be categorized as SUDEP. This may be the only epidemiologic information for SUDEP in China.[40]

Distribution by Sex and Age

As reported from most of other countries, in China, the prevalence and incidence of epilepsy is more frequent in men than in women. The prevalence in men and women in urban areas is 1.3:1 and the incidence is 1.7:1; in rural areas, it is 1.1:1 and 1.4:1, respectively. These differences are probably related to the more social and physical activities of men than of women and thus more frequently risk factors and causes for epilepsy are encountered by men. For age-specific prevalence, data from China showed that it is rising with age in childhood and adolescence, then plateauing in middle age, and decreasing in old age. As for age-specific incidence, there are two peaks: in childhood and the elderly. A study from Sichuan province indicated that 80% of epilepsy occurred before 15 years of age. Cerebrovascular disease, brain tumors, and other identifiable causes are responsible for the second peak of incidence in the older age group.[23]

Table 2 Relative Frequency of Subtypes of Seizure

Subtype	China 1	China 2	Singapore	Turkey	Tanzania	United States
GS	**89.6**	**77.3**	**65.2**	**78.9**	**58**	**40**
GTCS	81	71.8	56.3	65.4	54.1	23
Absence	4.8	3.9	2.2	4.9	1	6
Other	3.8	1.6	6.7	8.6	2.9	11
PS[a]	**7.6**	**18.6**	**34.8**	**19.7**	**31.9**	**57**
SPS	4.8	4.4	2.2	7.4	0.5	21
CPS	2.8	5.9	4.5	12.3	9.2	36
PS > GS	—	8.3	28.1	—	22.2	—
Other	**2.8**	**4.1**	—	**1.2**	**10.1**	**3**

CPS, complex partial seizure; GS, generalized seizure; GTCS, generalized tonic–clonic seizure; PS, partial seizure; PS > GS, partial seizure with secondary generalization; SPS, simple partial seizure.

Table 3 Risk Factors for Idiopathic Epilepsy (Case-Control Studies in Six Cities and Rural Areas of 22 Provinces of People's Republic of China)

	6 cities		22 rural areas	
Expected risk factor	**RR**[a]	***p*** **<**	**RR**	***p*** **<**
Parents' intermarriage	—	(>0.05)	9	0.001
Epileptics in family	2.5	0.01	15.4	0.001
Previous febrile seizures	7.5	0.01	32.2	0.001
Premature or difficult labor	3.2	0.025	13	0.001
Born when mother >30 yr of age	1.5	0.05	1.4	0.025

[a] RR (relative risk) = B/C; B, case (+), control (-); C, case (-), control (+).

Subtypes of Seizures

Table 2 shows the relative frequency of subtypes of seizures reported from China and some other countries.[23] Much of the variation among countries is probably related to differences in methods of data collection, sample size, classification scheme, and certainty of clinical diagnosis. Therefore, it is difficult to compare them or draw inferences. For example, the apparent high proportions of generalized seizures in the two studies from China reflect the fact that those studies focused on convulsive seizures rather than nonconvulsive seizures.

Risk Factors

In epidemiologic studies, scientists usually use retrospective methods (typically case-control studies) to identify risk factors

for epilepsy. For a number of practical reasons, prospective (cohort) methods, although theoretically preferable, are rarely used.

Table 3 shows the results of two case-control studies that were conducted in six cities of China in 1983 and in rural areas of 22 provinces in 1985.[23] The findings generally match those of a number of studies in other countries.[47] Many epidemiologic studies implicate genetic factors, perinatal factors, and a history of febrile seizures as risk factors for various major kinds of epilepsy, although some controversy persists.

The discovery of epilepsy genes has benefitted from the success of the Human Genome Project, a multinational endeavor that has produced detailed maps of the human chromosomes. The genes responsible for particular genetic epilepsies can now be identified and localized to specific chromosomal regions, ultimately allowing researchers to determine the structure of the encoded molecules. This requires the study of families in which several members are affected with well-characterized epilepsies. The *genetic "lesions"* responsible for idiopathic epilepsies give rise to various familial epilepsy syndromes.[3] A genetic etiology is indicated by, for example, familial incidence and frequent clinical concordance in twin studies.

In most studies, populations with *poor perinatal health care*, high incidence of premature births and head trauma during delivery, and high infant mortality are at high risk for epilepsy. The major perinatal factors include short gestation, low birth weight, prolonged labor, neonatal asphyxia, and assisted de-livery.

Febrile illness of any kind can trigger seizures in young children. About 3% of children who have *febrile convulsions* go on to develop epilepsy in later life.

Some investigations suggest that rural populations with poor health services and disadvantaged urban populations should be included in the epilepsy high-risk group: The relevant factors here are almost certainly poverty and low socio-economic status, which are themselves associated with high rates of epilepsy, as they are with so many other diseases.

Causes of Symptomatic Epilepsy

When epilepsy appears to be caused by an identifiable brain disease, it is categorized as *symptomatic epilepsy*. These causes include head injury; intracranial infection (e.g., neurocysticercosis, malaria); cerebrovascular disease; brain tumor; drugs and alcohol; carbon monoxide poisoning; and effects of ionizing radiation.

Table 4 Putative Causes of Symptomatic Epilepsy Cases in Six Chinese Cities

Putative cause	No. of cases	%
Head injury	29	47.5
Intracranial infection	15	24.6
Cerebrovascular disease	10	16.4
Intracranial tumor	2	3.3
Other	5	8.2
Total	**61**	**100.0**

Table 4 shows the results of a retrospective study in six cities of China in 1983.[3]

Prognosis and Remission

There are very few research reports on the natural history of epilepsy in China. In a survey conducted in the rural areas of 22 provinces in the 1980s, there were 904 cases of epilepsy, 417 of

them were treated, 448 were not, and 39 were unclear. Among the untreated 448 cases, spontaneous remission rate (SRR) at 2 years was 40.4% and at 5 years was 27.4%. Studies showed that SRRs ranged from 20% to 39%. These figures are similar to what Zielinski reported (5-year remission rates of 28.6% to 30.6%).

Factors relative to the prognosis or remission rate (RR) include: (a) *Age of onset*. The highest RR was reported if onset was between 7 and 9 years old. The RR for those whose onset was before 14 years was 71%, and before 20 years, 42%. For those whose onset was before 1 year and after 40 years, the RR is low because of one increase in number of organic disorders that cause epilepsy in those age groups. (b) Seizure types: Generalized tonic–clonic seizures (GTCSs) had a higher RR (38% to 62%). (c) Frequency of seizures: Low frequency of seizures had a higher RR. More than one seizure per day had an RR of 20% to 27%, fewer than ten seizures per year had an RR of 50% to 57%, and fewer than one seizure per year had an RR of 67%. This indicates that seizure frequency before treatment is an important factor that affects prognosis, but it is an exception for absence seizures. (d) Idiopathic or symptomatic epilepsy: The former (RR of 47% to 63%) has a higher RR than the latter (RR of 24% to 27%). (e) Course of the disorder: Shorter course had a higher RR: <1 year, RR 53%; >5 years, RR 17%. (f) Neuropsychological defects: There were higher RRs if the patients were without these defects.[10,23]

The impacts of antiepileptic drug (AED) treatment on prognosis are evident. Regular treatment with AEDs may control 70% to 80% of epileptic seizures, whereas with AEDs taken irregularly the RR is similar to untreated. Good compliance with AED treatment leads to good prognosis. One study showed a 92% control rate in a compliant treatment group of children patients, but 56% in the noncompliant group. Recurrence after stopping AED treatment is a major concern of epileptologists. A report from China showed a 24% recurrence rate for 8 years after stopping AEDs, and 55% of the recurrence occurred in the first 1 years.[10]

Clinical Diagnosis and Treatment

The diagnosis and treatment of epilepsy in China has improved greatly in the past 50 years, which may be attributed to the practical efforts of neurologists/epileptologists, the development of the electroencephalography (EEG) and other diagnostic equipment and technology, and the broad international academic exchanges.[49]

Diagnosis of Epilepsy

Adequately Using the International Seizure and Epilepsy Classification to Diagnose Epilepsy

The accurate categorization and recognition of seizures and epilepsies are the foundation of correct diagnosis and further in-depth research and communication, and are also reflected in the progressive knowledge about epilepsy. The international classifications in the 1980s have been wildly used, including the Seizure Classification in 1981, the Epilepsy and Epilepsy Syndrome Classification in 1985, and its revision in 1989 proposed by the International League Against Epilepsy (ILAE). These have received common acceptance by most epileptologists. The introduction of the 1981 ILAE seizure classification into China occurred at the first National Epilepsy Conference in 1985, and it was revised somewhat to make it suitable to the practical situation in China.[37] The Chinese Classification of Epilepsy and Epilepsy Syndromes, referring to ILAE's proposal, was recommended in the seventh National Pediatric Neurology Conference in 1995.[8] The aforementioned classifications of the 1980s are now wildly used in the clinical and research work in China, as well as in research about mesial temporal lobe epilepsy and absence epilepsy, the study of the relationship between mesial temporal epilepsy and hippocampal sclerosis, and clinical observation on uncommon epilepsy syndromes, such as the acquired epileptic aphasia and West syndrome. Since the 1990s, more attention has been given to the clinical research and EEG analysis of frontal lobe epilepsy, which has complex clinical manifestations, and the recognition and diagnosis level to it has been thus much improved.

For the past few decades, much progress has been made in understanding epilepsy symptomatology, etiology, pathology, diagnosis, and treatment. The same progress can be observed in China. In 2001, the ILAE Task Force, led by Prof. Engel, proposed a new classification of epilepsy that reflected the new knowledge in epileptology and influenced the clinical practice greatly. It introduced some new concepts as “axis” in diagnosis, which was helpful to standardize the clinical diagnosis. The proposal was introduced in China soon after its publication and is now used widely.[1] There have been great changes in the classification of epileptic seizures, which rely mostly on the symptoms reflecting the relationship between the symptom and anatomic location that gives clues about the epilepsy syndrome. In addition, classification now emphasizes the psychosocial impacts on the quality of life of epileptic patients in diagnostic procedures. We found that the new proposal was not easy to use with in clinical practice because of lack of detailed explanation in some parts. Epileptic seizures and their semiology, are the core of epilepsy classification. In some degree the new classification ignores changes in high-level cortical function, for example, by excluding classification criteria based on changes in consciousness and neglecting mental manifestations, which are important features of some epileptic seizures. Furthermore, it is difficult to classify occasional seizures observed in clinical work.

The Development of the Electrophysiological Techniques

There are two key features in epilepsy: Clinical seizure and EEG manifestations. EEG is one of the most important auxiliary examinations in epilepsy diagnosis. With no doubt, the emergence of EEG is a milestone that divided the history of epilepsy diagnosis into two stages.

The first EEG machine in China was imported into the Nanjing Brain Disease Hospital in 1949 in China and used in clinical examinations in 1951. Then a series of training courses about epilepsy and EEG were held by Feng Yingkun from the Peking Union Medical College (PUMC) Hospital. Now EEG testing is used in most hospitals in China. The international system of 10- to 20-electrode placement is used and includes both referential and bipolar recordings. Activating procedures, such as open/close eyes, hyperventilation, intermittent photic stimulation, and sedated sleep are routinely applied in most hospitals. The recording and interpretation of EEG requires expertise, but there are not yet standardized training and qualification systems for EEG technicians in China.

Mesial temporal lobe epilepsy is the most common epilepsy type. Feng Yingkun found that acupuncture pins could be used as substitutes for sphenoidal electrodes with good effect and easy acceptance.[11] There have now been more than 30,000 patients who had acupuncture pins used as sphenoidal electrodes in the PUMC Hospital.

Since the 1990s, video-EEG has been performed in many EEG labs in China. The electrocorticogram and deep electrode EEG have been used in some hospitals, which can give more information in locating the epileptogenic foci.

Other Examination Methods

In addition to electrophysiology, some new diagnostic techniques have been introduced in recent years. Imaging the hippocampus is now performed in China. Hippocampus volumetric quantitative measurement techniques are also very helpful in diagnosing and treating mesial temporal epilepsy.

The Establishment of Epilepsy Centers and Epilepsy Clinics

Since the 1990s, specialized epilepsy clinics and centers have been established in the bigger hospitals. These kinds of centers usually include neurologists, pediatric neurologists, neurosurgeons, psychiatrists and social workers. Sophisticated equipment for diagnosis is available and an operating theater equipped. Multidiscipline cooperation is the most important characteristic of such centers/clinics. They serve not only as clinical work sites, but also as sites for research, training, and public education. These centers are important developments in the prevention and control of epilepsy in China.

Drugs for Epilepsy

Medication is still the most important treatment option for patients with epilepsy. Selection of AEDs depends on the type of seizure and syndrome classification. The common AEDs used in China are valproate, carbamazepine, phenytoin, and phenobarbital. Approximately 60% to 70% of epilepsy patients can achieve remission using monotherapy. Polytherapy is chosen when patients' seizures cannot be controlled by monotherapy. We have found that side effects of rash and neutropenia occur in about 5% to 10% of patients on carbamazepine. Valproate needs careful consideration when it is used in women of child bearing age because of weight-gain and polycystic ovary syndrome effects. Phenytoin and phenobarbital have similar efficacy to carbamazepine but are no longer the first choice because of their adverse effects. However, they are still used as first-line AEDs in rural and poor regions in China. Valproate is drug of first choice in treating generalized seizure, and carbamazepine for focal seizures. Since the 1990s blood levels of AEDs have been available in big hospitals and epilepsy centers.

Since the 1990s, there have become available more than ten new AEDs on the international market, and most of them are useful in cases of intractable epilepsy. With relatively wide spectra, fewer adverse effects, fewer interactions, and better tolerance, the new AEDs offer, more choices for refractory patients. Presently, lamotrigine, topiramate, vigabatrin, gabapentin, and oxcarbazepine are available in China, and zonisamide and levetiracetam are going to be on the market soon. Most new AEDs serve as add-on drugs. The combination of lamotrigine and valproate is better for some refractory epilepsies, but skin rash has occurred.

Epilepsy Surgery: A Review

Although the trephenation opening found on a skull unearthed in Shandong province indicates that the history of surgical treatment of brain disease in China is more than 5,000 years old, modern epilepsy surgery has been available only in recent years. There is no record of epilepsy surgery in the literature or in hospitals' records before the People's Republic of China was established in 1949. The earliest record of epilepsy surgery in China may date to the 1950s to 1960s, for example, "traumatic epilepsy" written by Guosheng Duan, "hemispherectomy for West Syndrome" by Yuquan Shi, and "epilepsy surgery" by Yadu Zhao. In the following two decades, some political and social factors resulted in temporary delay in further development of epilepsy surgery.

In the late 1980s, following implementation of reform and open-door policy, scientific and technologic exchanges between China and Western developed countries resumed quickly. Advanced medical equipment and new techniques were introduced to China. A number of senior neurosurgeons restarted surgical treatment for epilepsy including anterior temporal lobe resection, callosotomy, multiple subpial transection (MST), stereotactic neurosurgery, and cerebellar stimulation. The method of lower-power electrocoagulation of eloquent areas in or adjacent to epileptogenic foci, advocated by Guoming Luan, added a new way to treat eloquent areas in epilepsy.

Localization of Epileptogenic Foci

The effectiveness of epilepsy surgery is mainly based on a precise localization of epileptogenic foci. Currently, many provincial and municipal level hospitals have electrophysiologic examination and sophisticated equipment such as CT, MRI, and even SPECT, PET, and MEG for the diagnosis of epilepsy and synthetic localization of epileptogenic foci. The introduction of MEG has improved the synthetic preoperative evaluation for epilepsy to a new stage. Furthermore, the development of electrophysiologic examination manifested not only in the noninvasion, but also in the invasion technique of using strip or grid or depth electrode. They can give further explanations about which areas have eloquent and noneloquent functions and which areas can be identified as irritating and epileptogenic areas.

The Basic Study Related to Epilepsy Surgery

In recent years, basic scientific research has made great progress, such as the epileptic nets and stereotactic atlas of epileptogenic foci and tissues around them. The various epileptic animal models made by chemical and electrical methods can help neurosurgeons prepare all kinds of operations; the electrophysiologic studies of cerebral cells and tissues can make a ground for treating the intractable epilepsy using electrostimulation methods; the chemical studies of neurosynapse and neuroreceptors in the excitable and suppressive neurotransmitters filed can theoretically support the method of cerebral tissue and neurostem cell transplantation to treat refractory epilepsy; the microstructure studies of epileptogenic foci such as amygdalohippocampus tissues can further expound dual epileptic pathology and its relation to postoperative effects; the neuroimaging studies such as MRI and MRS can clearly define the side and site of epileptogenic foci; and the anatomy studies of epileptic surgical approaches can increase the surgical safety coefficient and reduce the probability of postoperative complications.

The Clinical Studies of Epilepsy Surgery

Most types of epilepsy operations performed elsewhere have been successfully done in China. The number of operations has increased year by year. For example, only 1,840 epilepsy cases were reported in the first epilepsy surgery congress held in 1991, among which there were 933 cases of stereotactic ablation and only half of patients had resections with craniotomy. In the sixth congress of stereotactic and functional neurosurgery in 2004, a total of 2,077 operated cases were reported, among which there were 2,029 epilepsy cases with craniotomy treatment (more than two times the number of 13 years ago) and 48 cases with the stereotactic ablation. There were 680 cases with epileptogenic lesion and neocortical resection reported in the *Chinese Journal of Stereotactic and Functional Neurosurgery* in 2001 and 2002. By 2004, the number of reported cases of epileptogenic lesion and neocortical resection increased to 1,057. The total proportion of Engel I and II levels reached 65% to 85% among them. With regard to temporal lobe epilepsy, about 400 operations were performed each year, and the Engel levels I and II effectiveness reached 75% to 90%. Approximately 400 cases of hemispherectomy, stereotactic radiosurgery, electrostimulation, and other operations have been done each year. What is worth mentioning is that several hospitals recently used lower-power electrocoagulation to treat eloquent epilepsy, amounting to about 200 cases every year, and the proportion of Engel I and II results is around 65%. This fact indicates that the new method has obtained recognition by our domestic colleagues. The number of hospitals with epilepsy surgery capability increased every year. For example, in Beijing, three hospitals had epilepsy departments in the 1990s, whereas nine hospitals had such departments in 2005. Research on "the basic and clinical studies of intractable epilepsy surgery" has been awarded the second prize of the National Science Technology Progress Award.

Application of Neuroimaging and Gamma Knife

A number of hospitals have bought Gamma Knife equipment and begun epilepsy stereotactic radiosurgery programs. In 2004, 15 Leksell Gamma Knifes and 20 OUT-XGD rotation Gamma Knifes were available in China. However, there are still disputes about choice of treatment-site, dose, and effectiveness.

Academic exchanges on epilepsy surgery have been quite active in China in recent years. The Epilepsy Surgery Association was founded in 1990 with around 150 to 200 epilepsy surgeons as members. Several conferences and workshops on epilepsy surgery have been held in the past two decades. The National Epilepsy Surgery Workshop has been held four times since 1991, and the National Stereotactic and Functional Neurosurgery Congress has been held six times since 1987. International academic exchanges about epilepsy surgery have increased remarkably as well.

Three journals of epilepsy surgery are issued in China: *Chinese Journal of Stereotactic and Functional Neurosurgery*, *Asian Journal of Epilepsy*, and *News Letter of Epilepsy Surgery*. In the past 10 years, five monographs were published: Epilepsy Surgery, Temporal Lobe Epilepsy, Temporal Lobe Epilepsy Surgery, Neurosurgery and Epilepsy, and the second edition of Lüders' *Epilepsy Surgery*, in translation.

Basic Research on Genetics and Neurosciences

In recent years studies on the molecular basis of inherited epilepsy have been performed in China. Tang et al. reported a novel frameshift mutation of the *KCNQ2* gene, 1931delG, in a large Chinese family with benign familial neonatal convulsions (BFNC). This mutation is located in the C-terminus of *KCNQ2*, in codon 644, predicting the replacement of the last 201 amino acids with a stretch of 257 amino acids showing a completely different sequence.[36] In a Chinese family with benign familial infantile convulsions (BFICs), Xiao et al. found that it was not linked to the 19q12.1-13.1, 16p12-q12, or 2q24 loci.[50] The results indicated that BFIC showed genetic heterogeneity and the Chinese BFIC families might be mapped on another new locus.

Childhood absence epilepsy (CAE) is one of the most frequently recognized syndromes among the idiopathic generalized epilepsies (IGEs). CAE is considered a genetic disease with a possible polygenic inheritance pattern, but the genes responsible for CAE have not yet been identified. Lu et al. reported that γ-aminobutyric acid $(GABA)_A$ receptor subunit genes, *GABRA5* and *GABRB3*, may be directly involved either in the etiology of CAE in the Chinese population or in linkage disequilibrium with disease-predisposing sites.[28] Their studies suggest that the *GABBR1*, *GABRG2*, T-type calcium channel gene α (1G), and *T-STAR* might not be susceptibility genes for CAE, at least in the Chinese population studied,[7,27] whereas the T-type calcium channel gene *CACNA1H* might be a susceptibility gene to childhood absence epilepsy.[5] The mutation of G773D has been found in one other Chinese family with CAE. Ge et al. concluded that the CAE gene is transmitted with disequilibrium on locus D8S1783, and the CAE gene may be in the ECA1 area on chromosome 8q24. Heterogeneity of the CAE gene in different populations was suspected.[12]

Familial febrile convulsion (FC) is a common pediatric disorder with an obvious inherent predisposition. Qi et al. concluded that FC is linked with chromosome region 19p13.3, but not with chromosomes 6p and 8q.[31] The *CSNK1G2* gene of the region 19p13.3 appears to be a susceptibility gene for FS in the Han population of northern China.[52]

Liu et al. studied the clinical and inherent characteristics of generalized epilepsy with febrile seizures plus (GEFS+) in a large group of Chinese families. This group is screening mutations of *SCN1A, SCN1B, SCN2A*, and *GABRG2* in the Han population, and a new mutation of *SCN1A* has recently been discovered. Huang et al.

reported a GEFS+ gene mapped to 5q34 in two Chinese families and a single nucleotide polymorphism (SNP) from candidate gene *GANRA6* exon 8.[15,26]

Many laboratory facilities are dedicated to exploring the fundamental mechanisms of epilepsy, including drug resistance and the consequences of repeated seizures on brain function, by using different epilepsy models. A model with pharmacoresistent temporal lobe epilepsy features has been developed by repeated intramuscular injection of Coriaria lactone (CL),[45] an abstract from traditional herbs. This model was demonstrated with high kindling efficiency and typical behavioral and electrophysiologic manifestations. CL is reported to increase the release of glutamate and inhibit the synthesis of GABA in cultured neurons; there is also evidence from cerebrospinal fluid (CSF) of an acute CL-induced epilepsy model. In pathologic

studies on the CL model, degeneration of neurons and necrosis of astrocytes appeared widely in different cerebral areas; this was also supported by an increased BCl-2 level in neurons. During the early stage of a CL-induced seizure, an influx of extracellular Ca^{2+} has been found, indicating that Ca^{2+} signals were involved in the CL-induced seizures. One distinct feature of this model was the pharmacoresistance to AEDs, such as carbamazepine, valproate, and phenytoin. An up-regulation of P-GP-multidrug resistance 1 (MDR1) encoded protein P-170 was found in the CL model, especially in the AED-treated CL model, indicating that the mechanism underlying pharmacoresistance to AEDs was associated with overexpression of *MDR1* gene.[8] This model had been widely used in studies of epileptogenesis.

Audiogenic seizure-prone rats were also widely used as epilepsy models. The P77PMC rat has congenital audiogenic seizure (AGS). Zhang et al.[53] found that antisense oligodeoxynucleotides for *N*-methyl-D-aspartate (NMDA) receptor 1 and gap junction protein Cx32 could alleviate AGS and inhibit the frequency and amplitude of neuronal discharges in temporal cortical slices of the P77PMC rat. These results indicate that gap junction protein might play a role in the pathogenesis of epilepsy by controlling functions of electrical synapses. The DBA/2J mouse was another breed of mouse with high-intensity noise-induced audiogenic seizures. Li et al.[24] examined the gene expression profiling of AGS DBA/2J mice by using oligo-microarrays. They specifically tested the effects of Qingyangshenylycosides (QYS), abstracts from TCM, on seizure behavior and gene expression of AGS. Results showed that QYS could effectively prevent AGS and AGS-induced gene expression changes. The antiepileptic effects of some TCM were studied in other research groups. Acorus tatarinowii Schott (ATS), one of the traditional antiepileptic medicines, had been demonstrated to be able to induce sedation, decrease spontaneous activity, and possess anticonvulsive and spasmolytic action in modern pharmacologic studies. Liao et al.[25] reported that both the decoction and volatile oil extracted from ATS exhibited neuroprotection and anticonvulsive effects. Further studies on these Chinese herbs might provide clues for the development of new antiepileptic drugs.

Epileptic seizures might induce neuronal death and secondary epileptic foci. Antiepileptogenesis and neuroprotection may have clinical significance. To evaluate the long-term effects of prolonged neonatal seizures on seizure threshold and neuronal activity in the brain, Ni et al.[30] compared the immunoreactivity changes of c-Fos, NMDA receptor 2C, and $GABA_A$ in single seizure and recurrent seizure models. They found that prolonged seizures had long-term effects on seizure threshold and receptor protein expression, and recurrent seizures could cause obvious neuronal injury. Yin et al.[51] demonstrated that down-regulation of N-ethylmaleimide-sensitive fusion (NSF) protein and the loss of DA neurons were involved in mechanisms underlying the spatial learning memory deficits induced by spontaneous recurrent seizures (SRS). Nitric oxide (NO) is a readily diffusible “intercellular messenger molecule” acting to generate a cascade effect by the second messenger cyclic guanosine monophosphate (cGMP) that mediates excitotoxicity in various brain structures. Sun CK et al.[34] demonstrated that a single injection of kainate (10 mg/kg intraperitoneally) induces progressive seizures with an increased accumulation of nitrite, the stable metabolite of NO, in hippocampal homogenates of rodents, measured by the Griess reaction. L-NG-nitroarginine (NNA), an inhibitor of constitutive NO synthases (cNOS), especially neuronal NOS (nNOS), significantly enhanced the severity of kainate-induced seizures and damage in hippocampal subregions. However, administration of L-arginine (Arg), a substrate for NO synthase, unexpectedly suppressed both seizures and brain damage. The effects of NNA and Arg on kainate-induced seizures and brain damage were accompanied by appositive changes in immunoreactivity of glial fibrillary acidic protein (GFAP) and interleukin-6 in the hippocampus.

The research grants for epilepsy have been increased greatly in China in recent years. As more and more scientists have been interested in epileptology, more detailed discoveries are expected in the future.

Psychosocial Aspects of Epilepsy in China

Fear, misunderstanding, and the resulting social stigma and discrimination surrounding epilepsy often force people with this disorder "into the shadows." The social effect may vary from country to country and culture to culture, but it is clear that throughout the world the social consequences of epilepsy are often more difficult to overcome than the seizures themselves.[48]

Cross-cultural studies on epileptic patients revealed high rates of psychological and social problems.[2,18] Epileptic patients are frequently denied schooling, shunned by their peers, find it difficult to marry, and meet active employment discrimination.

In recent years, psychosocial studies on epilepsy have been performed in China. In 1988 a public awareness of epilepsy study was conducted among 1,278 respondents in Henan province. The study found that 93% of interviewees had heard of epilepsy; more than 75% knew someone with epilepsy; and almost 75% had seen someone have a seizure.[21] Furthermore, expressed negative attitudes were extensive. More than 50% of the sample said that they would object to having their children associate or play with persons with epilepsy; more than 50% also believed epileptics should not be employed in the same jobs as others. Notably, 87%, irrespective of their education level, would object to having their children marry a person with epilepsy.

In 1992, in cooperation with Dr. A. Kleinman from Harvard University, the Beijing Neurosurgical Institute conducted a psychosocial study in adult epileptic patients.[19] Forty patients with epilepsy in urban areas and 40 patients with epilepsy in rural areas were selected from the Ningxia and Shanxi provinces. The patients and their family members were interviewed together and separately during home visits by local research teams composed of neurologists who had been trained to use a semi-structured interview schedule in training workshops. The interview canvassed demographics, experiences of illness and treatment, and both family and patient perspectives on local social responses to and consequences of the illness. The interview format used open-ended questions to encourage extended responses.

Great variation exists in the public's ideas of the cause of epilepsy, ranging from heredity, head injury, possession, geomancy, poverty, and overwork to anger and fright. Patients and their family members showed a tendency to increasingly use overwork, strong effects, and a wide range of new explanations to explain why seizures continued (Table 5). Possession and head injury were less frequently named as likely causes.

Table 5 Perceived Causes of Seizures by Epileptic Patients

"Cause"	%	"Cause"	%
Anger	23%	Wrong food	5%
Possession	19%	Retribution	5%
Fright or anxiety	16%	God's will	3%
Head injury	16%	Heredity	4%
Negative geomancy	8%	Infection	3%
Poverty	8%	Congenital	1%

Overworked	8%	Others[a]	25%

[a] Includes weather change, menstruation, smoking, febrile convulsion, carbon monoxide poisoning, etc.

From Wang WZ, et al. *Chin Ment Health J.* 1995;9:129.

Table 6 Impacts of Epilepsy on Patients and Family

	Ningxia		**Shanxi**		**Total (%)**	
	Patients	**Family**	**Patients**	**Family**	**Patients**	**Family**
Stigma	36	38	35	23	71 (89)	61 (76)
"Loss of face"	28	24	25	10	53 (66)	34 (43)
Self-esteem	33	—	35	—	68 (85)	
Emotional burden	39	40	39	39	78 (98)	79 (99)
School failure	17	—	4	—	21 (26)	
Marital and family conflict	33	30	15	16	48 (60)	46 (58)
Arranging marriage	15	—	6	—	21 (26)	
Work problems	32	15	28	10	60 (75)	25 (31)
Financial problems	33	39	28	26	61 (76)	65 (81)
Relations with others	34	30	24	15	58 (73)	45 (56)
Quality of life	34	38	29	16	63 (79)	54 (68)

From Wang WZ, Li SC, Cheng X, et al. A study on phychological and social aspects in adults with epilepsy. *Chin Ment Health J.* 1995;9:129

Table 6 shows respondents' perception of the chief effects of epilepsy on the patients. Emotional, financial, and family/marital burdens were reported to be extensive. Relations with others and overall quality of life also were strongly affected. These effects appear to be greater in rural areas. Stigma affects both the family members and the patients themselves. Most of them felt “loss of face” (conveying the embodied sense of shameful loss of moral status) and feelings of diminished self-esteem were widespread.

The Western tradition's emphasis on the subjective feeling of the afflicted individual, often viewed as isolated and forlorn, is the dominant analytic paradigm for understanding the suffering that results from serious chronic illness and disability.[20] Furthermore, suffering becomes the pain, hurt, loss, and search for meaning of a unique person who alone must bear the deep burden of his or her troubles. According to this view, suffering is a mode of social experience. The point is not to minimize the seriousness of the problems faced by individual patients with epilepsy in our study, but rather to appreciate the importance that they and their families attribute to the interpersonal, relational locus of hardship among the members of the family. Indeed, this intersubjective sensibility frequently leads family members to emphasize their own adversity as equivalent to or even greater than the patient's experience. The study focused on the concerns by the family and its members. What is most at stake in suffering is the abridgement of the family's aspirations, the threat to the life chances of its members, and the loss and hurt of the others. The result showed that suffering is as much the intersubjective experience of parents, spouses, siblings, and children as that of the patient.

For Chinese parents, the presence of a disabled child means that they are both legally and morally responsible for his or her care until that son or daughter gets married or the child dies. With marriage, the responsibility for care is shifted to the spouse and the couple's future children. Thus, there is great pressure to arrange marriage. To do so, parents try to disguise that their child has epilepsy, but if they are unable to, they will barter for a spouse with promises of an urban residence permit or employment. Illness and disability restrict the pool of potential marital partners to those who also have illness or disability and to those who are poorer, more rural, less educated, and physically less attractive. The consequences of disguise and barter are fraught with interpersonal tensions that the parents, patient, and spouse must negotiate over the long term. But to not marry is far worse: It threatens the centrality of family in Chinese society.

Many respondents believe that the financial consequences of epilepsy are serious and even ruinous. Perhaps no other aspect of social life so clearly shows the power of chronic illness to affect local worlds and reciprocally of local worlds to influence the course of illness and treatment. The current economic transformation of Chinese society marks finances as a major issue, especially in the poor regions where our study was conducted. Some farmers in our sample lived at the brink of financial catastrophe. The social welfare net of communal life is no longer

available to prevent the poorest in China from falling into extreme poverty. The economic constraints on the social course of epilepsy and other chronic illnesses often means that patients cannot afford proper treatment. The illness, in turn, transforms the economic conditions of everyday life, using up very limited reserves, creating or deepening debt, and forcing families into humiliating and often unavailing negotiations with creditors, who are also under financial pressure. The outcome is illness as the precipitant of end-stage misery. This is a powerful social consequence of illness that deserves far more attention in medical anthropology. Those who are most disadvantaged also appear to suffer the most from discrimination on account of epilepsy.

Recent research in the West challenges the idea that the stigma of epilepsy is unrelenting, and its effects always devastating. In those whose seizures are in remission, psychosocial functioning has been reported as high, with low levels of distress.[17] Public information campaigns in Western societies have improved public attitudes toward epilepsy sufferers. But the situation for epilepsy in China and other low-income regions, is extremely different and has not changed. Those with seizures routinely experience discrimination in schools, in the workplace, and in the community.

Most patients in our sample have chronic epilepsy with frequent seizures. For them and their families, the serious consequences of epilepsy are intensified by Chinese society's prioritizing of social control as the chief concern in the societal response to this and to other chronic conditions in which behavior is affected. The emphasis on social control, rather than patient rights, means that students with epilepsy may be refused to enter colleges, universities, and even middle school; people with epilepsy may not be employed, and some work units may discriminate against patients and their families who are requesting more resources for treatment.

On the other hand, overcontrol can also be viewed in a more positive light as an extreme aspect of families' routine supervision of seriously afflicted members at work, play, and home, which supports many members to participate in daily life activities while protecting them from injury. In Chinese society, institutional assistance for the disabled is largely limited to the family. Thus, the family is at once both the source of nurture and assistance but also a potential source of overcontrol.

Stigma is a moral category, yet in the Chinese context, moral blame is applied to the patient and extends to the entire family. Ideas that attribute the cause of epilepsy to bad fate, heredity, negative geomantic forces, and the malign influences of gods, ghosts, or ancestors are all accusations about the moral status of the family. Inasmuch as Chinese society turns on the individual's kinship circle and social network, families and networks that are morally compromised are perceived as ineffective and indeed actually can become so as members drop out and their social-relational power is lost. The moral status of the person is his or her face; social relations "give face" or "save face." To "lose face" is to carry the social experience of shame into the inner experience of the body/self. The indigenous Chinese model of stigma, however, is sociosomatic and frames intersubjective delegitimation, not spoiled personal identity, as the central process. Because the person is constructed in Chinese culture as a relational self, delegitimation of the family and network is the most fundamental assault the person can experience.

Our findings revealed that epilepsy is best regarded as possessing a social course, and it results in many psychosocial problems in China, which including medical workers and governments, society should pay more attention to.

Another study on developing approaches to reducing stigma of epilepsy[16] organized by Ann Jacoby from Liverpool University, United Kingdom, supported by the National Institutes of Health, has been carried out since 2004 in China and Vietnam. Its first phase finished in June 2005, and the results were published in 2006.

Community Control Programs in Rural Areas

In 1985, the Mental Health Division of the World Health Organization (WHO) began designing a project to manage epilepsy care at a community level, because there were so many PWE in developing countries, especially in rural areas, but a lack of neurologists to treat them. With the similar situation and concern, China joined the efforts of the WHO.

In 1989 and 1993, a feasibility study on "community control of epilepsy" was conducted in China. The basic design of this project was to train village public health workers (PHWs) to use flow charts to administer phenobarbital (PB) to patients with GTCSs. Effects of treatment by village PHWs were compared with effects of treatment by neurologists. Compliance and side effects were also compared between the two groups. There were no statistical differences in the outcomes between the two treatment groups. Therefore it was suggested that the "community control of epilepsy" project was feasible in rural areas of China.[22,39]

In 1997, the WHO, in cooperation with the ILAE and the International Bureau for Epilepsy (IBE), launched the Global Campaign Against Epilepsy (GCAE).[9] As part of the GCAE's activities, a demonstration project to test the pragmatic model was set up in five locations worldwide.[33] The project, entitled Epilepsy Management at a Primary Health Level: Protocol for a Demonstration Project in the People's Republic of China, was successfully conducted in China.[42]

The Chinese project included an epidemiologic survey, an intervention trial, and an educational program in target areas. The study found that 63% of the detected people with active epilepsy (PWAE) had not received antiepileptic medication in the week before the survey (i.e., the treatment gap was 63%).[43] More than 85% of PWAE had GTCSs. Commenced from December 2001, the intervention trial was conducted including identifying patents with GTCSs, PB treatment, follow-up, and management. At the same time, education promotion activities were provided to the patients, their family numbers, and the public to broaden their scientific knowledge about epilepsy and reduce their misunderstanding and discrimination against people with epilepsy. This research involved eight counties in six provinces, with a total investigated target of 3,185,067 inhabitants. A total of 2,455 patients (1,381 males) were recruited into the study (demographic details on baseline are shown in Table 7). Duration of follow-up ranged from 1 day to 32 months (mean 20.5 months; median 25 months).

Methods

Patients with GTCSs were identified at a primary care level and provided with PB monotherapy. The starting dose was 60 mg for adults and 15 mg for children, taken once daily at nighttime, and maintenance dosage was 120 to 180 mg/day for adults and 4 to 5 mg/kg/day for children. Patients attended their local clinic every 2 weeks for the first 2 months and monthly thereafter, for dose adjustments, side effect assessment, and adherence checking, and to receive a further supply of medication. Physicians completed a follow-up form at each visit, recording seizure numbers, compliance, and side effects (using a checklist of common side effects of PB) experienced by the patients. Efficacy was evaluated from the percentage reduction in seizure frequency from baseline and as the retention of patients on treatment.

Table 7 Patient Demographics in the China Demonstration Project

Age	Mean 32.6 yr	(SD 20.7 yr)
2–14 years	268	11%
15–44 years	1544	63%
45–59 years	459	19%
≥60 years	184	7%
Age at onset	Mean 17.1 yr	(SD 14.4 yr)
Duration of epilepsy	Mean 15.5 yr	(SD 17.9 yr)
Baseline seizure frequency	Mean 35 seizures per year	

SD, standard deviation.

Table 8 Seizure Frequency after 6, 12, and 24 Months of Treatment

Change in seizure frequency from baseline	6 Months		12 Months		24 Months	
	N	%	N	%	N	%
Seizure free	919	41	644	34	347	26

Reduced by >75%	305	14	415	22	415	31
Reduced by 51%–75%	245	11	230	12	185	14
Reduced by 26%–50%	162	7	146	8	99	7
Reduced by <25%	217	10	156	8	91	7
Increased by ≥25%	369	17	306	16	187	14
Total	2,217		1,897		1,324	

Findings

Efficacy

The efficacy of PB treatment was evaluated over three periods. The first evaluation included 2,217 patients who were treated for 6 months, the second included 1,897 patients who completed 12 months treatment, and the third included 1,324 patients who completed 24 months treatment. The changes of the seizure frequency in the three periods are listed in Table 8. No evident differences in efficacy of PB treatment were observed among the study sites.

Side Effects of Phenobarbital

Over the treatment period the frequency of all side effects was reduced (Table 9). Most patients, including 189 taking at least 180 mg PB per day, experienced few side effects; only 4% and 0.3%, respectively, experienced moderate and severe side effects; and 32 patients (1%) discontinued medication because of side effects.

Adherence and Withdrawal

Tablet counting proved that over 95% of patients had good compliance to the treatment regimen at each follow-up. By the end of 24 months of treatment, adherence in those continuing in the study was estimated at almost 100%.

A total of 562 patients (23%) withdrew from the study before its completion, and 35 patients died during the study period. The causes of withdrawal are shown in Table 10. In the group who did not complete the study, the most common cause for withdrawal (28% of all withdrawals) was the subjective assumption of cure by the patients. Eighty-one individuals had increased seizure frequency of more than 50% from baseline. The reason for this “increase” needs to be further studied. Eighteen percent of those were withdrawn due to noncompliance.

The above-mentioned project was successfully implemented within the existing services in rural areas of China. It confirmed that in this setting the PB treatment protocol is feasible and that PB has high efficacy and tolerability and can help to reduce the large treatment gap. Because of this study's success the same approach has been extended to ten more locations in China and will become a national program. By September 2005, more than 10,500 individuals with GTCS epilepsy had been treated according to this protocol. This project has given hope and confidence to many PWE in China, but the work should be replicated in other countries before it can be fully recommended. Even the best intervention can only succeed when individuals and communities understand enough of the process and are able to fully participate. Furthermore, the integration of such a program into existing services is essential to ensure its sustainability. These issues should be taken into consideration in any future interventions.

Table 9 Side Effects Experienced at Different Time Points

Side effects	1–3 mo (N = 2,455) N (%)	7–12 mo (N = 2,135) N (%)	19–24 mo (N = 1,495) N (%)
Drowsiness	667 (27)	287 (13)	120 (8)
Dizziness	320 (13)	182 (9)	81 (5)
Headache	185 (8)	108 (5)	41 (3)
Ataxia	182 (7)	87 (4)	30 (2)
Anxiety	154 (6)	94 (4)	31 (2)
Hyperactivity	51 (2)	37 (2)	13 (1)
Gastrointestinal complaints	347 (14)	192 (9)	55 (4)
Skin rash	81 (3)	34 (2)	13 (1)
Others	69 (3)	27 (1)	14 (1)

Table 10 Causes of Withdrawal

Withdrawal causes	Patient numbers (%)
Patient perception of “cure”	169 (28)
Noncompliance with regimen	104 (18)
Perception of inefficacy	97 (16)
Lost to follow-up	53 (9)

Migrated from study area	38 (6)
Death	35 (6)
Side effects	32 (5)
Others	69 (12)
Total	597 (100)

Traditional Chinese Medicine and Epilepsy

Knowledge of Epilepsy in Traditional Chinese

In traditional Chinese medicine (TCM), epilepsy belongs to the diagnosis "Xian Bing" and is also called "Yang Dian Feng" (goat stroke). It refers to a seizure caused by organic and mental injury, which results in the loss of spirit control. The etiology of epilepsy is due to congenital and acquired factors, especially mental factors. Congenital factors refer to heredity dysfunction, pregnancy disturbance, and bad gift of embryo. It was said in the TCM classical book *Plain Questions* that "epilepsy of baby after birth come[s] from the outside shock, which frightens the mother and cause[s] Qi stasis." Huo You Xin Shu, another pediatrics book of China noted the following: "An overmuch taking in of sour-salty food or mental disturbance of the mother may interfere [with] the embryo and cause epilepsy." Acquired factors include external pathologic factors such as abnormal diet and mental status, injury, and brain parasites. Stroke may also cause epilepsy.

Pathologic Pivots

Generally, deficiency of the liver, kidney, and spleen, which will cause internal wind, phlegm, and blood stagnation, is the basis of epilepsy.

Seizure Stage

Abnormal circulation of Qi is the pathologic pivot of epilepsy in seizure stage. Every kind of Qi in TCM has its own principle of circulation. If any type of Qi is circulating the wrong way, a reverse flow of Qi will attack and clog the openings of the brain, resulting in dizziness, twitching, or coma.

Truce Stage

Mild epilepsy may have a truce of months or years, while a severe epilepsy may have a truce of only minutes. The truce only means a temporary dissipation of evils, but a recurrence is expectable at any time because of the existence of pathologic factors.

Convalescence Stage

In this stage, epilepsy may stop for more than 3 years. Three outcomes are accessible in this stage: Healing, because of the elimination of pathologic factors and rectification of organic functions; recurrence, only in special conditions such as infections, brain injuries, overeating, fatigue, and menstruation, but with organic function coming back normal; and no recovery of the organs can be expected, especially brain, liver, and kidney.

Treatment in Traditional Chinese Medicine

Treatment Principles

Alerting the consciousness in seizure stage, reinforcing the deficiency, expelling evils in truce and convalescence stages should be the treatment principle. To expel the evils, we should clear the phlegm and repress the internal wind. To reinforce deficiency, we should nourish the spleen, liver, and kidney and calm the heart.

Various TCM therapies are available as medicine, acupuncture and moxibustion, massage, diet, and psychological therapy. For medicinal treatment, we have patent medicine and syndrome-differentiating medicine. For acupuncture, we have body, auricle, and scalp acupuncture. Thread imbedding and fascia cutting are also introduced on the basis of acupuncture.

Recent Development of Treatment on Epilepsy in Traditional Chinese Medicine[4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35]

Pharmacologic Treatment

The controlled clinical trials of the fixed TCM prescriptions for epilepsy treatment developed recently were carried out in China.

Extracts of Chinese Medicine

Extracts of Chinese medicine for epilepsy, which proved to be effective, has been paid more and more attention these days. Distilling of effective ingredients from herbs may help us to better understand their chemical structure and structure activity relationship so that further synthesizing and developing work of new medications can be done. The effective ingredients in some herbs now can already be affirmed, and the mechanism research are now being undertaken.

Nonpharmacological Treatment

Acupuncture and Medicine.

Acupuncture is effective economically and harmless for the treatment of epilepsy. Acupuncture combined with medicine proved to be clinically effective in research comparing traditional acupuncture and scalp acupuncture, electroacupuncture, thread imbedding, and acuinjection.

Summary and Conclusions

There are approximately 9 million people with epilepsy in the People's Republic of China, including 6 million people with active epilepsy. Moreover, there are an additional 0.4 million new cases each year. A survey suggests that nearly 65% of these patients do not receive appropriate medical treatment. In China, epilepsy has been treated by TCM in a long history. Beginning in the 1950s, the clinical diagnosis and treatment of epilepsy made substantial progress. Epidemiology, clinical neurologic diagnosis and treatment, epilepsy surgery, basic research, sociopsychological problems, rural community control programs, and TCM recognition of epilepsy in China have progressed greatly in recent years.

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Chapter 292

Germany

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Introduction

The German social welfare system was introduced between 1883 and 1889 by Chancellor Bismarck in an attempt to maintain his authoritative rule by outmaneuvering the rising social democratic movement. This system, which has survived several political eras—the Kaiserreich, the Weimar Republic, and National Socialism—was created to insure general life risks. State legislation on health insurance was passed in 1883, on state accident insurance in 1884, and on old-age and pension insurance in 1889. In 1927, this system was supplemented by legislation on unemployment insurance (including job-creating measures). Subsequent to the increasing number of senior citizens, a fifth pillar of welfare, the nursing insuring act, was enacted in 1994. Currently, more than 90% of the 82 million inhabitants of Germany are covered by the state-provided social welfare system in regard to sickness, accidents at the workplace, occupational disease, disability, unemployment, nursing needs, and motherhood.[9]

Objectives of German Social Welfare

The principles of state-provided social welfare are listed as follows:

1. Compulsory membership. All adults with incomes below a certain level (3.375 € per month in 2002) must join. Family members (children, spouses) without income are covered as well. Professionals and people with incomes above this level may opt for the social insurance system or obtain private insurance.
2. Solidarity. Payment depends on one's income; services of social welfare depend on one's needs. Everyone receives the same services, independent of premium, health risks, gender, or age. Public pension plans and unemployment insurance are related to former income level and the length of time insured.
3. Principally, health insurance is financed through the members. Nevertheless, insurance fees are divided (e.g., between employers and employees, between pensioners and the state pension insurance). Low-income groups like students pay a fixed fee. With the exception of state accident insurance, which is paid solely by the employers, each person pays around half of the premium. Because the level of the premium is related to income, the basis of the social welfare system is determined by the sum of all wages. The state subsidizes some of the insurance plans.
4. Social welfare insurance plans are self-governing public corporations under federal supervision. Their boards are composed of elected delegates equally representing employers and employees. Numerous organizations back up the insurance plans. However, all are controlled by state health legislation. Unemployment insurance has only one supporting organization, the federal labor office.

The tasks of different insurance plans partially overlap, which can lead to conflicts with respect to responsibility for measures. Who pays is determined by who has the financial risk in case the measure fails. State pension or unemployment insurance is responsible for vocational rehabilitation; state pension or health insurance is responsible for "medical" (functional) rehabilitation. Apart from this, health insurance covers medical treatment. This "division of responsibility" has strings attached. Vocational training, for example, cannot be started during medical treatment or medical rehabilitation, even though this would be advantageous from the patient's point of view. Therefore, comprehensive care relies on the voluntary cooperation of health professionals beyond the limits of administration.

Community welfare completes the system of social welfare. It is founded on the principle of communal welfare, which existed long before Bismarck. Under this plan, persons who are not able to make their own living, who are unemployed (for more than 1 year, currently), and who are not covered by health insurance can ask for income support or welfare. Social welfare is financed primarily by community taxes. The number of people on welfare is determined mainly by employment opportunities. In the past 20 years this number has grown threefold.

Private Insurance Plans

Individuals with incomes above a certain limit can obtain private insurance. Private insurance plans charge according to the covered services. Age, gender, health risks, and chronic illnesses influence the level of premium an individual is charged. Private insurers can reject applicants if the insurance risk is assessed as being too high. About 10% of the population had private health insurance in 2003.[9] Persons with epilepsy who cannot insure themselves in the state health insurance system (e.g., self-employed persons, lawyers, and physicians) may have difficulty finding private health insurance. If they are accepted by a private company, they often have to pay high risk premiums or the insurance plan does not include epilepsy as a covered condition. For persons with epilepsy, private accident insurance plans and disability insurance are especially difficult to obtain. Among 236 privately insured patients with epilepsy, none was able to obtain disability insurance.[10]

State Health Care

State Health Insurance: Budget Organization and Development

Originally, state health insurance was established to guarantee medical care and help avoid loss of income due to sickness. Since 1970, members of the state health insurance system generally receive sickness benefits for 6 weeks. In 2003, more than 72 million inhabitants were insured by state health insurance.[9] Of these, about 30% were covered as noncontributing family members, and 22% were pensioners paying minimal contribution. During the past 20 years, the income from premiums has increased at a far slower rate than the expenditure. Although the average membership rate changed from 8.4% to 14% of salary, expenditure increases continuously, especially expenditure on hospital treatment, which increases every year between 1% and 3%.[2,9] Hospital expenditure accounts for one third of all health care expenditures.

In 1993, a law was passed to keep the increase in expenditures equal to that of the income premium. Expenditure has decreased as a result, but not enough. Therefore, numerous laws have been passed to control expenditures. This process is ongoing. Financial barriers between hospital treatment and primary care are partially torn down through “integrative care” such as disease management plans and managed care programs. Administration has blown up to a great extent, not to the advantage of patent care. Insurance plans independent from employment and wages are in discussion. As a result, the idea of the welfare state is being questioned, with some suggesting that state health insurance should be limited to standard treatment, and optional treatment should be paid for privately. Already, since about 8 years, an increasing amount of health care services has to be paid by the patients themselves in addition to the reimbursements of the insurance.

Health Services

Germany has a high density of medical care services, albeit one that is unevenly distributed between urban and rural areas. In 2003, there was one physician for every 370 inhabitants and one hospital bed for every 150 inhabitants, which is a decrease of about 20% within the last 15 years. Of about 300,000 physicians, 41% worked in hospitals, 3% in rehabilitation units, 42% in solo practice, and 13% in scientific institutions, administration, and federal health services (institutions that control epidemics with measures such as vaccinations and hygiene). When a patient decides to be treated, he or she has free choice among doctors in private practice (general practitioners and specialists, e.g., neurologists) who are contractors of health insurance plans. Often the proximity of a practice or the waiting period rather than the quality of treatment is decisive in determining a patient's choice. Doctors in own practice may refer patients to hospitals or to outpatient treatment units at hospitals. The ratio between doctors in hospitals and nonmedical staff members (e.g., nurses, technical staff members, midwives, social workers, psychologists, pharmacists) was 1:7.5 in 2003.[9]

The basic idea of the German health system is that the doctor provides treatment and advice. Newly, therapeutic psychologists in solo practice are included in the treatment service and refunded by the insurance plans comparable to physicians. Despite this rather physician-centered approach, nonmedical health-related services outside the hospitals have expanded greatly during the past 100 years. Such services include advice centers established by churches and welfare associations and health-related services developed outside the state health systems. These services as a rule are either free of charge for the clients (e.g., advice centers of churches or of the state) or clients can use the service at their own expense (e.g., physiotherapy or psychotherapy in solo practice). Reimbursement by the state health insurance for nonmedical health-related services is possible, as an exception, and often requires bureaucratic procedures.[1] Thus, comprehensive care is affected sometimes by a lack of funding but more often by a lack of communication and competition for patients.

Primary Care

Primary care in Germany does not have as clear a structure as it does in other countries, such as the United Kingdom. There are general practitioners and pediatricians in solo practice,

specialists or consultants (such as neurologists and internists) in solo practice, and specialists in hospital outpatient clinics. The latter depend on permits given by health insurance and physicians organizations. Apart from university clinics, these are only given in exceptional cases. Outpatient clinics may offer comprehensive care because professionals other than doctors, who are employed in the affiliated hospital, may be called on for their services (e.g., neuropsychologists or social workers). However, these additional services are not always refunded by the patient's insurance. There are no clear rules with respect to treatment of specific diseases. Thus, a general practitioner, an internist, or a neurologist might treat a person with epilepsy.

The structure of primary care is negotiated by doctors' organizations and health insurance providers. Arrangements include the guarantee of medical care in a certain region, guarantee of 24-hour availability, and a basic set of covered services. Physicians prescribe medications, confirm a patient's inability to work, and refer patients to specialists or hospitals. Medical treatment in regard to necessity, implementation, and correct calculation is scrutinized. Economic efficiency is evaluated by the doctors' organizations and health insurance providers, as is compensation. Services of physicians are calculated by evaluating every service. Because of the current law that establishes the formula that costs may not increase more than basic wages, physicians working harder get less for their services than before.[1]

Hospital Treatment

Hospitals are one of the oldest services provided. Although their purpose has not changed over the years, their equipment, size, and specialization have. In 2003 hospitals numbered 2,197, of which 373 had a special department for neurology.[9] Hospitals are financed by a dual system. Capital costs for investment are paid through the public budget, and current costs for treatment are paid by the patients, usually through the state health insurance plans. Until 1992, hospitals had cost-based charges. Since then, hospitals have received a budget that is linked to basic wages. Now a complicated account and contract system is instated, which will mean that hospitals are managed more like businesses. Competition between hospitals leads to fusions of hospitals, closing down of smaller houses, and reduction of the number of hospital beds. The financial frames are set through the German version of the DRG system (diagnose related groups). Patients with high nursing needs (e.g., the elderly or chronically ill persons, including persons with epilepsy) may then become unattractive to hospitals. The average hospital stay has shortened from 14.0 days in 1991 to 8.9 days in 2003, and capacity utilization from 84.1% in 1991 to 77.6% in 2003.[9]

Table 1 Patients with Epilepsy per Group of Physicians in Solo Practice and per Year

Physicians	No. of physicians	No. of epilepsy patients		Percentile		
		M +	SD	25%	50%	75%
Neurologists	4,000	48.19	57.45	10	30	65
General practitioners	61,916	4.83	4.68	2	4	6
Pediatricians	6,000	14.45	29.05	3	7	15

M, mean; SD, standard deviation.
From Pfäfflin M, May TW. Wieviele Patienten mit Epilepsien gibt es in Deutschland und wer behandelt sie? *Neurol Rehabil.* 2000;6(2):77–81.

Care for Persons with Epilepsy

Care for Children

Primary Care

As a rule, children with epilepsy in Germany are treated by pediatricians. Newly, a number of pediatric neurologists in solo practice have organized themselves. The list of pediatric neurologists sums up to 107 pediatric neurologists in solo practice. In larger cities only with several pediatricians in solo practice, one usually concentrates on epilepsy, and children with seizures can be referred to him or her by his or her colleagues. Children in Germany have the right to nine medical checkups in the first 6 years of life; more than 90% of families take part in these checkups. After the checkups, a doctor may order nonmedical treatment such as psychological therapy and diagnostics, speech therapy, or psychomotor exercises.

The pediatrician can refer children to a pediatric neurologist who works in an outpatient clinic or a medical center. In Germany there are around 170 pediatric outpatient clinics, of which 103 additionally specialized in epilepsy (in 2004). These specialized outpatient clinics usually have access to psychologists, social workers, physiotherapists, and other specialists, of whom quite a few have expertise in epilepsy. Education of staff members in epilepsy is one of the most important issues now. Nonmedical professionals can attend courses to acquire an additional expertise in epileptology certified through the German chapter of the International League Against Epilepsy (ILAE). Therefore, expertise in pediatric (as well as in adult) epilepsy is growing. The pediatrician in solo practice may also refer a child requiring sophisticated treatment to a hospital specializing in pediatric neurology. There are about 200 such departments in Germany; every outpatient clinic for children with epilepsy is affiliated with one of these.

A pediatrician is more likely to refer a child with epilepsy (especially one with complicated epilepsy) to a colleague with expertise in epilepsy at one of the above-mentioned centers if he or she has already established a good working relationship. Referral to such a center ensures that the pediatrician is expanding the patients' treatment options.

Primary care for children in Germany is, with a few exceptions, sufficient and of good quality. A child's development can be closely tracked through the medical checkup system. Somatic illnesses are usually recognized early. Some problems remain, however. It is often not easy to find the level of specialized care adequate to a patient's needs, and persistence is required. Parents may have to test several options before finding the right one. Pediatricians often misjudge the level of development in children with complicated types of epilepsy, falsely assuring concerned parents that nothing is wrong. When children are finally referred to specialized care, they have often experienced delays in diagnosis and treatment of secondary problems.

Hospital Treatment

Children with febrile or afebrile seizures are usually transferred to the pediatric department of the nearest general hospital or to the nearest pediatric neurology department of a university hospital.[3] Diagnosis and proposal for treatment are offered to the pediatrician in solo practice. Children with more complicated forms of epilepsy, including refractory seizures, are transferred to the hospital again and again. Only if treatment is unsuccessful over a long period of time is a child referred to one of five specialized centers for epilepsy. Regular children's hospitals usually do not have the resources to treat complicated types of epilepsy. They lack the experience in helping parents cope with changes in medication, during which children may have more frequent seizures, and also lack expertise in psychosocial problems accompanying difficult-to-treat epilepsies. Staff members in epilepsy centers, in which medical treatment, psychosocial counseling, and special education are offered, usually believe that early referral prevents delays in achieving optimal treatment.

Children can be treated in all of the five epilepsy centers for children in Germany. The centers provide specialized treatment including epilepsy surgery, neuropsychological assessments, counseling for parents, and educational advice. For adolescents, guidance in vocational training is offered. The Bethel Epilepsy Center is one of the most important referral centers for epilepsy surgery in children in Europe. It is *the* referral center for the very young age group in the German-speaking countries. Epilepsy centers also function as advisory centers, transferring their expertise in treatment and rehabilitation into the home communities of the patients. They also serve as educational centers for medical and nonmedical personnel.

Centers for Medical Rehabilitation

There are five rehabilitative centers for children and adolescents with neurologic diseases. They follow a comprehensive approach with the aims to integrate children into school and into professional education. They teach skills to prepare them for independent living. Apart from medical treatment they offer physiotherapy, speech therapy, (neuro-)psychological treatment, counseling, and special work-preparatory courses. All centers have broad experience with children with epilepsy.

Table 2 Hospital Treatment in 2000

	No. of cases	No. of days hospitalized	Days per case
Total	17,313,222 (100%)	65,821,972 (100%)	9.0
Epilepsy	128,698 (0.74%)	1,312,720 (0.84%)	10.2

Included are all cases with the main diagnosis epilepsy (G40 and G41, International classification of Diseases and Related Health Problems (ICD) version 10, WHO); http://www.who.int/classifications/en/
From Statistisches Bundesamt Deutschland 2005 und Fachserie 12 Gesundheitswesen, Reihe 6.1., Jg. 1994–2003.

Care for Adults

Primary Care for Adults

In Germany little is known about primary care for adults with epilepsy. To remedy this, a widespread survey has been performed.[6] Results show that an average of four to five patients with epilepsy consulted 1 of about 62,000 family doctors per year (Table 1). After the first seizure, in most cases it is the family doctor who is asked for advice and who establishes a diagnosis. Frequently this doctor refers the patient to a neurologist for confirmation of diagnosis, electroencephalography (EEG), and initial treatment. The neurologist usually refers

the patient back to the primary care physician or tries to establish a consulting arrangement. In Germany there are about 4,000 neurologists in solo practice who care for 50% to 60% of patients with epilepsy, the remaining being treated by general practitioners or pediatricians. Within the group of neurologists in solo practice, about 12% concentrate on epilepsy, treating a higher number of patients with epilepsy. They do have a special qualification in the treatment and counseling of persons with epilepsy. Their qualification is certified by the German chapter of the ILAE. The German chapter of the ILAE has established guidelines for the treatment of persons with epilepsy in solo practice specializing in epilepsy treatment. Because of this development, the standard of care for persons with epilepsy has improved in Germany.

The German chapter of the ILAE established guidelines for diagnosis and treatment of epilepsy, which take the position that a division of labor should be established within a multilevel service system. Up to now, the expertise in a multilevel system of care has not been used systematically by physicians or patients. Patients move frequently between family doctors and neurologists. Only a few are treated in outpatient clinics or specialized centers.

In 2005 there were 38 outpatient clinics for adolescents and adults with epilepsy. These clinics have access to EEG and video-EEG, and most of them to computed tomography (CT) and magnetic resonance imaging (MRI). The average waiting period for a first appointment is 1 to 3 months. All outpatient clinics have access to a social worker, who in the some cases has a specialized training in epilepsy. In the last 10 years the social workers have been offered advanced training, and they form a network to support each other in specialized questions. Brochures, leaflets, and Internet information have been developed for patients' service. Problems of prime importance are occupational in nature. About 50% of adult patients with seizures are faced with considerable job problems. They are unemployed, prematurely retired, or employed below their qualifications. Epilepsy was cited as the reason for an inability to work in about half of the cases seen in the outpatient clinic of the Epilepsy Center Bethel in 2003.

Hospital Treatment

The number of hospital treatments and the average length of stay are generally viewed as excessive in Germany (Table 2). Many persons who have seizures with loss of consciousness or body control are admitted to the hospital even when they carry a note stating that no help is necessary. This is because people who witness a seizure may feel that they are providing assistance by taking the person to a hospital. A person who is admitted to a hospital usually has to stay at least 1 night for observation. In theory, patients can leave the hospital on their own volition, but most do not.

In Germany there are eight specialized epilepsy centers, which provide the highest level of care for adults with epilepsy. All these centers provide diagnosis and treatment for in- and outpatients, as well as research and education. Among them four centers have specialized in epilepsy surgery, and three have specialized in social and vocational rehabilitation. The Epilepsy Center Bethel is the only center that combines all functions.[7]

Centers for Medical Rehabilitation

Three centers for medical rehabilitation exist in Germany currently, the first being launched in 1997.[8] Their main aim is to ameliorate the psychological, social, and vocational consequences of epilepsy. All three are run on an inpatient basis. They are funded mainly by the state pension insurances with the aim to reduce early disability in patients with epilepsy. Early retirement in epilepsy patients is prominent and very costly. An evaluation study has shown that such centers are effective in improving quality of life and reducing the frequency of hospital stays and unemployment in those treated.

Summary and Conclusions

The future of epilepsy treatment in Germany is hopeful, although there are several problems to be overcome. The German chapter of the ILAE together with voluntary epilepsy organizations has developed standards of care for persons with epilepsy. The underlying philosophy emphasizes the need for comprehensive care for people with epilepsy apart from high-standard medical treatment counseling and support for the various psychiatric and social difficulties often associated with epilepsy. There are standards for physicians as well as for allied health professionals specializing in epileptology ("Zertifikat Epilepsie plus," "Zusatzausbildung Epilepsie"), and there is an ongoing demonstration project for the development of the qualification of an "epilepsy nurse." A standard for outpatient clinics concentrating on epilepsy ("Anfallsambulanzen") has been established for a while, and in 2000 standards for private practices specializing in the care of persons with epilepsy ("Schwerpunktpraxen") were decided. The German chapter of the ILAE enforces these standards by certifying persons and/or institutions for fulfilling them and publishing their addresses. As of the writing of this paper a standard of "epilepsy centers" proposed by the German chapter of the ILAE is under discussion.

Standards for treatment and care including rehabilitation will become even more important as citizens from the European Union can ask for treatment in various European countries. It is important to include self-help groups in the process of developing these standards because they have the most comprehensive perspective and can act without financial dependency.

Information on epilepsy for the general public, for nonmedical professionals (e.g., teachers, facilitators, personnel from rehabilitation or counseling centers), and for persons with epilepsy and their families is produced by the German chapter of the ILAE, by the German Epilepsy Foundation ("Stiftung Michael"), by national self-help organizations

("Deutsche Epilepsievereinigung," "Epilepsie-Bundes-Elternverband"), and regional self-support groups. One shortcoming in epilepsy information is that it is not developed on a systematic base. In consequence, there are gaps and the quality of information differs highly. There are numerous efforts to use the various possibilities of the Internet for epilepsy information.

Since the end of the 1990s there have been strong efforts to develop patient education programs for adults and children with epilepsy and their families. About 1,500 adult persons with epilepsy are educated with the MOSES program.[4] A version of the program for children and their parents has been ready for administration in the routine medical practice since 2005.[5]

Because counseling and support for psychosocial problems are most often provided by institutions outside the medical systems, various efforts are now under way to bind services closer together to create comprehensive epilepsy networks. Such efforts have been done in Bavaria, North Rhine-Westphalia, and Berlin. Networks serve three functions: First, they facilitate the transfer of new knowledge and experience and reduce competition. Second, they increase the number of referrals (e.g., for early evaluation for surgical treatment or for rehabilitation interventions). A promising development in this field is the installation of specific counseling centers for epilepsy with the function of public education, counseling of schools or other institutions, and individual counseling of persons with epilepsy. Such centers, in which a social worker specialized in epileptology is always present and sometimes also a psychologist, exist in various federal states (e.g., Bavaria, Hessian, Lower Saxony, North Rhine-Westfalia, and Saxony), and hopefully will also be installed in more states.

The most urgent problems in care for people with epilepsy are the following:

- Referring patients much earlier to the most competent institutions and specialized centers
- Developing epilepsy networks for comprehensive care for persons with epilepsy
- Educating and hence empowering more adults and children with epilepsy and their relatives because in the coming structures of our health system, it is even more the patients' responsibility to obtain adequate
- Maintaining specialized epilepsy centers or comparable institutions (even under economic strain) that are experienced in treatment and counseling of patients with difficult-to-treat epilepsy and psychosocial problems.

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Chapter 293

India

Satish Jain

P. Satish Chandra

Introduction

India is the second most populated country in the world with majority of population being rural. Although the economy has been growing at a rapid pace, the per capita expenditure on health, family welfare, water supply and sanitation in recent years has been dismally low. The health services provided by the government are totally free or highly subsidized for the poor and needy. The rapidly emerging private health sector with health insurance facilities is affordable to only a small section of the population.

It is estimated that with a population of more than 1 billion, there are about 6–10 million people living with epilepsy in India, accounting for nearly one fifth of the global burden. The challenge of meeting the needs of the people with epilepsy in a developing country like India is a daunting task for every one involved in the planning and delivery of health care. In a country like India with diverse cultures, castes and low literacy; various myths and misconceptions about epilepsy that exist among the people further add to the societal disease burden and treatment gap. Developing countries such as India need to develop alternative strategies to reach out to the needy people living with epilepsy in different parts of such a vast country. The best approach in a country like India with limited resources for health-care would be to encourage "private-public participation." There is an urgent need to have a separate National Epilepsy Control Programme (NECP) in countries like India. In order to be successful, the proposed NECP must be an initiative of the government and should work in collaboration with the health care providers in the private sector and non-governmental organizations.

Demographic and Socioeconomic Indicators

India is the largest country in the Southeast Asian Region of the World Health Organization (WHO) with an estimated population of more than 1 billion living in an area of 3287.3 thousand km^2 with the population density being 325 per km^2. The majority of the population is rural, with only 27.8% living in urban areas. India has 35 states and union territories accounting for 593 districts, 5,161 towns, and 593,643 inhabited villages as of March 31, 2001.[8] The majority of the population as per the 1991 Census was young, with 37.8% being in the 0- to 14-year and 55.5% in 15- to 59-year age group. The national literacy rate for 2001 was 65.5%, with males (75.96%) having a better literacy rate as compared to females (54.28%).

The combined national crude birth rate for 2002 as per the sample registration system of the Registrar General of India was 25.0, the crude death rate being 8.1 and the natural growth rate of 16.9 per 1,000 population. The average annual exponential growth rate of the population is calculated to be 1.96%. The gross per capita net national product at current price for 2003–2004 was estimated to be about U.S. $463 (INR 20860, 1 U.S.$ = INR 45.00). Only 3.97% of the total expenditure in the budget was allocated to the Health, Family Welfare, and Indian System of Medicine and Homeopathy (ISM & H) for the 10th 5-year plan (2002 to 2007). The per capita expenditure on health, family welfare, water supply, and sanitation during 2002–2007 will be about US $2.53 per year.[8]

Basic Structure of Health Care Delivery System in India

The primary and secondary health care in the government sector is delivered through a vast network of subcenters (SCs; one SC for about 5,000 population and manned by health workers); primary health centers (PHCs; one PHC for 30,000 to 50,000 population); and taluk hospitals/community health centers (CHCs; one CHC for 100,000 population) that are under the administrative control of district hospitals (DHs; one DH for 1.5 to 2 million population). The tertiary health care is provided by hospitals attached to medical colleges, apex institutions, and super-specialized centers. Government health services are totally free/highly subsidized for the poor and needy. A rapidly emerging private health sector, in the absence of government health insurance to the majority, is affordable to only a small section of the population. Though allopathy (modern medicine) takes care of the majority, traditional systems of medicine also are widely used in the country.[6]

There were 189 medical colleges (during 2000–2001) and 185 dental colleges (2003–2004) imparting education and health care facilities in the modern system of medicine. In addition, there were 431 colleges providing training and health care facilities in the ISM&H, with the maximum being in Ayurveda (209) followed by homeopathy (180), Unanai (36), and Siddha (six). There were 15,393 hospitals as of January 1, 2002, with 914,543 hospital beds (of all types) accounting for 89 hospital beds per 100,000 population. In addition to the hospitals, there were 137,311 SCs, 22,842 PHCs, and 3,043 CHCs on March 31, 2001. There were 605,800 medical doctors registered with the Medical Council of India as of December 31, 2002, at the rate of 59 doctors per 100,000 population. In addition, 839,862 nurses and midwives were registered with the Nursing Council of India as of March 31, 2003.[8]

While the primary and secondary health care facilities may at the most provide only the basic health care, some of the private and government hospitals and institutions now are providing “state of the art” facilities often at a fraction of the cost that needs to be paid in the hospitals in the developed nations. Although still not adequate, there has been a phenomenal growth in the health care sector in the last few years, especially in the private sector. The private health insurance agencies also have begun to play a role in the country, though not in a big way. Distribution of these health care facilities leaves much to be desired, and despite the fact that many parts of the country may still be without adequate health care facilities, medical tourism is projected to be a major revenue-earning industry in the next few years.

Mental Health Care in India

India being a land of contrasts, mental health care is provided by a multitude of trained and untrained personnel that include neurologists, neurosurgeons, psychiatrists, physicians, pediatricians, those trained in the ISM&H, and a large number of health and non–health care personnel (registered and unregistered medical practitioners, religious heads, and even faith healers). In urban areas for most people with epilepsy who receive treatment, the expert care is provided mainly by the neurologists and neurosurgeons, though primary care is delivered by family physicians, pediatricians, and internal medicine experts.

Specialist Resources

The challenge of meeting the needs of people with epilepsy in a developing country like India is a daunting task for everyone involved in the planning and delivery of health care. The limited resources and lack of adequate trained manpower complicates the problem further. At present there are about 800 trained neurologists and 1,300 to 1,500 trained neurosurgeons in the country. The paradox of a country like India is that as per the president-elect of the Association for Indo-American Neurologists, there are 600 to 700 neurologists of Indian origin in the United States (personal communication).

A high-powered committee set up by government of India, the Technology, Information, Forecasting, and Assessment Council (TIFAC), examined the technology and manpower requirement for the year 2020. The needs in the discipline of neurology were also assessed by the TIFAC. Assuming even a modest ratio of one neurologist for 200,000 population as against 8,000 in Italy and 18,000 to 50,000 in the United Sates, India would require ≥5,000 neurologists as against the present strength of <1,000 neurologists. Even if a hundred trained neurologists were to be added to the pool annually, giving allowance for outward movement from the country, it would take at least half a century to achieve the goal. A further confounding problem is the distribution of neurologists, because major proportions gravitate to metropolitan cities and big towns, leaving almost 70% of the population in the rural areas deprived of specialists' care. Thus, there is an urgent need to reconsider and conceptualize alternative strategies to organize services at the peripheral, regional, and apex levels, as recommended by the TIFAC.[6]

Magnitude of the Epilepsy Problem in India

Many studies based on well-accepted methods, valid screening and diagnostic tools, and case confirmation methods have been conducted to identify epilepsy in the community in an inexpensive way in different parts of India. Population-based neuroepidemiologic studies conducted in different regions have shown that epilepsy constitutes nearly a third of all neurologic disorders. The prevalence of epilepsy varies from 2.5 to 11.9 per 1,000 population.[2,3,5,6,7,9,10,11,12,13,14] In the Bangalore Urban Rural Neuroepidemiological (BURN) survey, a task force project supported by the Indian Council of Medical Research (ICMR) covering a population of 102,557, a prevalence rate of 8.8 per 1,000 population was observed, with the rate in rural communities (11.9) being twice that of urban areas (5.5). Epilepsy was found to be the second leading neurologic problem in both urban and rural populations, next only to vascular headache.[7] Based on these data and information emanating from various studies, it is estimated that in India (with a population of more than 1 billion), there are about 6 to 10 million people living with epilepsy, accounting for nearly one fifth of the global burden.[2,3,5,6,7,9,10,11,12,13,14] Though most of the epidemiologic studies in India estimated prevalence of epilepsy, one study from Yelandur has provided incidence data.[10] Accordingly, 50 new cases per 100,000 population are added annually, giving an additional burden of 500,000 new-onset epilepsy cases every year in India.

Burden of epilepsy as estimated using disability adjusted life years (DALYs) accounts for 1% of the total burden of disease in the world, excluding that due to social stigma and isolation, which is highly prevalent in India and might account for a much higher disease burden. In a country like India with a diverse culture, caste, and low literacy, various myths and misconceptions exist about epilepsy among the people, which further adds to the treatment gap. The treatment gap in epilepsy ranges between 38% and 80%. The lowest figure is from Kerala, which has a high literacy rate and health-conscious people. The BURN data have demonstrated that even in urban areas, the treatment gap is as high as 50%. This large treatment gap is due to multiple factors, including lack of awareness about epilepsy among the people; social stigma; reluctance to accept the diagnosis; improper distribution of the available medical facilities, especially among rural, tribal, and hilly areas of the country; and availability and/or affordability of the long term antiepilepsy drug treatment.[6]

Delivery of Epilepsy Care in India

In India, with its population of more than 1 billion, a dismally low trained neurologist ratio of 1 in 1,250,000, and a very high epilepsy burden, primary care physicians, general practitioners, pediatricians, and psychiatrists provide 60% to 70% of epilepsy care. Hence, it is imperative that developing countries such as India develop alternative strategies to reach out to the needy people living with epilepsy in different parts of such a vast country. Various models of delivery of epilepsy care have been tried and are in practice. Brief accounts of the same are given below.

Satellite Clinic Model

The National Institute of Mental Health & Neuro Sciences (NIMHANS), Bangalore, has developed a satellite clinic model (SCM), which has been implemented for more than two decades, since 1982. This model is successful in delivering neurologic and psychiatric care to the rural community—an example of joint collaborative work between governmental and nongovernmental agency. The NIMHANS provides expert panels; local governmental agencies along with nongovernmental organizations (NGOs) such as the Lions or Rotary conduct the service camps on a “fixed day at fixed place” every month. This approach results in the delivery of expert care at the patient's doorstep.

Epilepsy accounts for 40% to 50% of all the neuropsychiatric patients seen in these camps. The NIMHANS caters to five places located within a 50- to 100-km radius, on 5 fixed days every month. More than 150 to 300 people attend each camp. First-line standard antiepileptic drugs such as phenobarbital, phenytoin, carbamazepine, and valproate are provided free to needy patients and simple medical records are maintained to follow these individuals. The camps are coupled with awareness campaigns about common neurologic disorders such as stroke, epilepsy, and mental retardation through the NGOs using both electronic and print media. Over the last two decades

thousands of people made use of this satellite clinic model and have benefited from these camps.

Community Health Center Model

The NIMHANS has also developed another model called the “community health center model” to take care of the patients at the community level in the urban areas in Bangalore. CHCs covering a population of 50,000 to 100,000 work in close liaison with medical colleges. There are nearly 200 medical colleges in India that look after the CHCs via their preventive and social medicine departments. The services of medical colleges and CHCs can be used to look after the epilepsy patients in their jurisdiction and also for the distribution of first-line antiepileptic drugs to the needy. The paramedical staff attached to these CHCs maintains health records. The epilepsy patients can be treated and followed up by this trained workforce at the patient's doorstep. The CHCs also have their mobile health care units reaching out to remote villages and far-flung, unreached areas. It has been demonstrated that the community health center model is successful in reaching out to the people at their doorsteps.

District Epilepsy Care Model

The “epilepsy control program” through a district model was developed by the NIMHANS, Bangalore, with the support of the WHO (SEARO) through the Ministry of Health, Government of India. This was implemented between 1999 and 2001. The program has three main objectives:

1. It would sensitize state health administrators regarding epilepsy as a public health problem.
2. It would train district medical officers in the delivery of epilepsy care. The trained doctors could further train other PHC medical officers.
3. “Nodal neurologists” at the state level would coordinate with these district medical officers to sustain this program.

Districts are used for health care delivery in this model since they have the advantage of being an independent administrative unit. The district medical officer (DMO) is the administrative head that implements and monitors various national health programs at district levels. In addition, all health programs at PHCs and Taluks come under jurisdiction of the district. Districts as models for mental health care have already been successfully implemented in India. There are 593 districts with an average population of 1.5 to 2 million people in each district.

The essential step in the district model is training of DMOs. The internal medicine experts/pediatricians /psychiatrists can also be included in the training of the trainer's program. Training is focused on (a) identification of epilepsy, (b) diagnosis, (c) treatment, (d) counseling, (e) psychosocial aspects of epilepsy, and (f) legal aspects of epilepsy. Training is done using training modules, audiovisual aids, and lectures that also include demonstration of practical aspects of managing acute emergencies in epilepsy. Evaluation of the training course is done using pre- and posttraining questionnaires. The training courses need to be followed by periodic workshops. These medical officers would subsequently train other primary health center doctors and also coordinate with the nodal neurologists. Programs of this nature require support from the government and NGOs in getting an uninterrupted free supply of antiepileptic drugs, maintenance of simple medical records, maintenance of epilepsy diaries, and regular follow-up from the patients. This model has also been successfully tested during the 3-year period by the NIMHANS.

Fortis Epilepsy Control Program Model

The Fortis group of hospitals is a part of the Fortis health care that is fast emerging as a leader in the delivery of health care in the private sector in India. As a part of its commitment to provide affordable health care at the community level, the Fortis Epilepsy Control Program (FECP) was launched on November 18, 2005, with an aim to provide some treatment to those with epilepsy who receive no treatment at all at the community level.

As part of the FECP, 18 practicing doctors from different parts of the state of Uttar Pradesh (UP) and the National Capital Region (NCR) with at least an MBBS degree were invited and trained on November 17, 2005 (the

World Epilepsy Day) at Fortis Hospital, NOIDA, to detect grand mal seizures using the protocol prepared under the guidance of the WHO-SEARO.[1] The trained doctors started treating only those patients diagnosed to have grand mal seizures in the area of their practice from January 1, 2006. The doctors trained have been told to exclude and not to treat patients below the age of 10 years and above the age of 60 years; those having any other seizure type or multiple seizure types (probably an epilepsy syndrome); women with a potential to have children or pregnant women; those having serious medical illnesses like hepatic or renal disease; those with known allergies to antiepileptic drugs; and those having any abnormality on neurologic examination like focal deficits and evidence of raised intracranial tension. All patients to be included for treatment under the FECP will be made aware and offered the choice of investigations like electroencephalography, computed tomography scan, or magnetic resonance imaging scan of the brain.

Those epilepsy patients with grand mal seizures selected for treatment will be treated with tablets of Phenytal (100 mg phenytoin and 30 mg phenobarbitone), two tablets once a day at bedtime for an average adult. The participating doctors will provide these tablets to all patients at the nominal cost of about Re 1 per day for two tablets (about U.S. $2 per 3 months of medicinal supply). A complete database of patients with all contact details will be maintained by the treating doctors. The patients included in the treatment plan will be followed up at regular intervals, preferably every month specifically for seizure control and any adverse effects of antiepileptic drugs. Any patient having problems due to poor seizure control or side effects of drugs or any other problem will be referred for an “expert opinion” to Fortis Hospital at NOIDA or any other tertiary care hospital. Neurologists from the Fortis Advanced Centre for Epilepsy, NOIDA, will periodically visit the participating doctor's clinic to review the work being done.

In the first phase, 18 doctors trained are participating in the FECP. During the second phase the plan is to enroll more doctors practicing in 10 to 15 neighboring districts. In the third phase, the program will be extended to all other districts of UP and NCR and also to neighboring states, depending on the resources.

The models outlined above are not exclusive but complementary to one another and will be able to “reach the unreached” with regard to epilepsy.

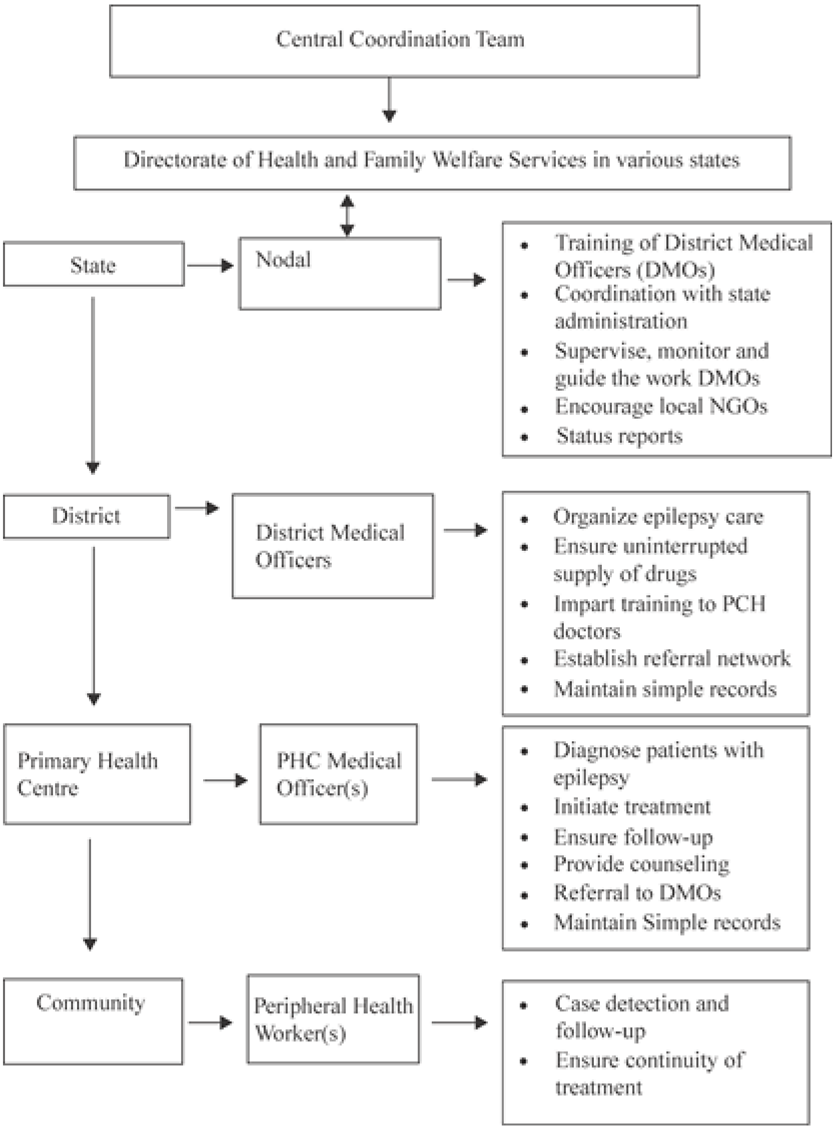
Central Coordination Team
Directorate of Health and Family Welfare Services in various states
State
Nodal
Training of District Medical Officers (DMOs)
Coordination with state administration
Supervise, monitor and guide the work DMOs
Encourage local NGOs
Status reports
District
District Medical Officers
Organize epilepsy care
Ensure uninterrupted supply of drugs
Impart training to PCH doctors
Establish referral network
Maintain simple records
Primary Health Centre
PHC Medical Officer(s)
Diagnose patients with epilepsy
Initiate treatment
Ensure follow-up
Provide counseling
Referral to DMOs
Maintain Simple records
Community
Peripheral Health Worker(s)
Case detection and follow-up
Ensure continuity of treatment

FIGURE 1. National Epilepsy Control Programme: action plan. (Adapted from Gourie-Devi M, Satishchandra P, Gururaj G. Epilepsy control program in India: a district model. *Epilepsia.* 2003;44[Suppl 1]:58–62.)

National Epilepsy Control Program (NECP)

Launch of the WHO/International League Against Epilepsy (ILAE)/International Bureau of Epilepsy (IBE) joint initiative of the “Global Campaign Against Epilepsy” in 1997[4] has given impetus to start a similar National Epilepsy Control Program

in India. This needs to be implemented all around the country with the following objectives:

1. To provide accessible and affordable health care to all people living with epilepsy, particularly to the people living in rural and far-flung areas and vulnerable sections of the society
2. To have joint participation of community and nongovernmental agencies in the delivery of comprehensive epilepsy care to people living with epilepsy
3. To ensure integration of people with epilepsy in various spheres of activity through psychosocial and vocational rehabilitation
4. To reduce the prevalence rate of epilepsy in the community by reducing the birth injuries and controlling

parasitic diseases (neurocysticercosis) and other neuroinfections and road traffic accidents

5. To create and improve awareness among the people about epilepsy

The proposed action plan of the National Epilepsy Control Program is given in FIGURE 1. It is proposed to have one national epilepsy center, which will be linked to four or five regional epilepsy centers in different parts of the country to coordinate with state level centers. To achieve the goal of the National Epilepsy Control Program, the Indian Epilepsy Association (IEA), Indian Epilepsy Society (IES), and other nongovernmental agencies need to actively participate together with the main focus being on improving awareness about epilepsy and providing comprehensive epilepsy care to the people with epilepsy. This can be achieved with the “center to periphery” or “periphery to center” approach. The proposed National Epilepsy Control Program should preferably be a separate program. It could also be integrated into an appropriate ongoing vertical national health program in India for easy implementation.

Summary and Conclusions

India is a land of contrasts. Until recently the ever-increasing population was proving to be a major handicap for the national growth. The availability of a large trained workforce (as a result of the large population) has changed the apparent “disadvantage” into a big national “advantage.” Today, India's economy is rapidly growing and is matched by that of China only. The India growth story has just gotten bigger and better. For the first time, India has emerged stronger on the global investment radar in 2005, overtaking even the most developed economies of the world. India today is one of the most attractive foreign direct investment destinations in the world.

Despite being home to about one fifth of the entire world's population with epilepsy and a rapidly improving economy, there is no national epilepsy control program in India. This is perhaps the right time for the governmental heath planning authorities to take note of the situation and take some remedial steps. There is an urgent need to have a separate NECP in India. Clubbing the epilepsy control program with the National Mental Health Program in India is likely to have serious implications with regard to increased societal stigma. Such a step could be a retrograde action in view of the Global Campaign Against Epilepsy that aims to bring “epilepsy out of the shadows.” The best approach in a country like India with limited resources for health care would be to encourage “private–public participation.” The models adopted by the NIMHANS and the Fortis group have the potential to be applied at the national level with support from the government in collaboration with the health care providers in the private sector and nongovernmental organizations. There are costs for doing all of this, but the costs of not doing this are perhaps much higher.

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Chapter 294

Japan

E. Ann Yeh

Masakazu Seino

Introduction

In 1994, Japanese government officials introduced a new vision of social welfare for the 21st century.[8] Central to this vision was the issue of how to handle problems that stem from the growing population of elderly individuals, many of whom will soon become disabled and utilize health care services to a greater degree than their younger counterparts. These concerns are not limited to the elderly, but extend to all disabled individuals. How these people will be cared for and who will be responsible for their care are questions that need to be addressed.

With these concerns in mind, this chapter examines the current health care policies of the Japanese government, beginning with a review of health insurance in Japan. A discussion of national health care spending follows, along with a description of the organization and distribution of health care personnel. Health care services available to individuals with epilepsy are examined, with special reference to medical specialists treating epilepsy in Japan. The chapter concludes with a brief discussion of the contradictions inherent in current government policy.

Health Insurance

The health insurance system of Japan currently operates on the basic premise that all individuals should have access to affordable health care. However, the original impetus of the government for establishing a health insurance system was not the provision of affordable medical care, but rather the maintenance of a strong workforce. It was but one element of government efforts at nation building in the early 20th century.[4] In 1960, the year that universal health care was instituted, 94.2% of the population of Japan was covered by health insurance. Since then, the proportion of insured individuals has increased annually. In 2002, virtually 100% of the Japanese population was covered by health insurance.[10] Health insurance in Japan is of two main types: Employee insurance (60.3%) and National Health Insurance (NHI) (39.7%). Benefits include compensation for clinical visits and drugs.[5]

Employee Insurance

The number of individuals covered by employee insurance (either as a principal policy holder or as a dependent of a policy holder) grew from 48.5% of the population in 1960 to 60.3% of the population in 2002. There are four distinct categories of employee insurance: Government-managed insurance (46.9% of the total number of employee insurance policy holders), large enterprise insurance (40.0%), mutual aid associations (12.8%), and seamen's insurance (0.3%). Insurance premiums of approximately 8.6% of an employee's salary are deducted monthly. At present, 70% of the medical costs of both policy holders and their dependents are covered, while 80% of medical costs for children younger than 3 years of age and 90% of costs for individuals older than 70 years of age are covered.[5]

National Health Insurance

NHI was established in 1938. In 1960, health insurance coverage through NHI was extended to all residents of Japan not eligible for employee insurance—self-employed individuals, students, farmers, unemployed individuals, and part-time workers, among others. Benefits under NHI are far less comprehensive than those available under employee insurance; 70% of medical costs are covered. Premiums are scaled to income and assets, with an average household yearly payment of 163,842 yen. This amounted to 2.8% of the average national income in 2002. In 1984, a pensioner's plan was introduced that increased benefits for retired persons to 80% of all hospital costs and 70% of outpatient costs of policy holders and to 80% of the hospital costs of dependents. In 2002, approximately 50,297,000 people, or 39.7% of the population of Japan, were insured through NHI.[5]

Payment for Hospital Services: Epilepsy and the General Population

According to a 2002 patient survey, on any given day in Japan, an estimated 7,929,000 people were either hospitalized or used outpatient services. Of these patients, 60.3% were covered by employee insurance (split almost evenly between policy holders [30.1%] and dependents [30.2%], and 39.7% by NHI).[9]

The proportions of types of health insurance used in medical consultations related to epilepsy differ somewhat. According to estimates by the Ministry of Health, Labor and Welfare (MHLW), 38% of visits by patients with epilepsy were paid for with NHI. In addition, although employee insurance was used by almost the same proportion of individuals (11.2%) as in the general population (10.7%), insurance for dependents with epilepsy was used with greater frequency (22.5%). As with the general population (1.8%), there were no clinical visits related to epilepsy that were paid for in full by patients. Health services for 9.2% of patients with epilepsy were paid for through publicly funded Medicaid (Seikatsu Hogo Hou) and through other public funds. These numbers are significantly higher than the proportion estimated for all hospital patients (0.5% under the Mental Health Act, 7.5% under the Social Welfare Act, and 6.1% through other public funds).[10]

These figures indicate that a significantly higher proportion of individuals visiting clinics and hospitals for problems related to epilepsy are self-employed or unemployed and receive some sort of public assistance. The relatively higher numbers of patients using insurance for dependents can be explained partially by the large proportion of people <25 years of age using hospital services for problems related to epilepsy (see Specialists Treating Epilepsy).

Budget Organization and Development

National spending on health care in Japan has increased rapidly since 1954, the year the Ministry of Health and Welfare (MHW) began keeping such records.[5] That year, health care spending equaled 215.2 billion yen (1.871 billion U.S. dollars at the 2005 exchange rate of 115 yen per dollar). Medical costs in Japan have increased in tandem with the standard of living and national income. They have remained at approximately 5% to 6% of national income since 1975, ranging from 5.22% in 1975 to 6.42% in 1987.[3] In 2002, 31.1 trillion yen, or 8.58% of the national income, was spent on health care.[5] Normal births, medical checkups and public health measures, costs of prosthetic devices, and costs related to nursing homes are not included in these figures,[5] nor are costs related to research.[4]

Health care spending as a proportion of national income appears to be low compared with the United States (13.9% in 2001), France (9.4%), Canada (9.4%), and Germany (10.8%).[3] However, according to the Organization for Economic Cooperation and Development (OECD), spending in Japan is underestimated by about 25% because figures do not account for spending in categories included in other national estimates.[12] Even with the added 25%, the figures for Japan are low compared with these countries. With respect to the gross national product (GNP), health care spending in Japan, which was 7.4% of the GNP in 1998, was lower than that of countries such as the United States and France.[5]

Sources of payment for health care range from insurance (employee insurance and NHI) (44.9% of total), the Geriatric Act (34.37%), patient payments (15.3%), and government-sponsored plans (including welfare and the Mental Health Act, and others) (5.5%) (2002 figures).[3]

Regarding the sources of money spent on health care, in 2002, 51.7% came from insurance premiums, a figure that has risen steadily from 45.8% in 1954. Spending from public sources has risen from 16% in 1954; the current rate is 33% (25.1% from federal and 7.9% from regional sources). Patient payments account for 15.3%, and 0.2% comes from other sources.[3]

Whereas in 1955 10.2% of all medical payments came from Medicaid (Iryou Hogo/Seikatsu Hogo), the amount has dropped steadily and was 0.8% in 2002. In addition, medical costs borne by patients not using insurance dropped from 20.7% in 1955 to 1.3% in 2002. Employee insurance covered 60.3% of health care, and NHI covered 39.7% in 2002, proportions roughly equivalent to the relative number of individuals insured under these categories.[5]

Organization of Hospitals, Physicians, and Health Care Workers

Hospitals and Clinics

Medical facilities in Japan (excluding dental facilities) totaled 966,044 in 2002. They are organized into hospitals having more than 20 beds (9,280) and clinics with fewer than 20 beds (86,764).[a]

Most of the facilities fall into one of five major categories, representing ownership: Individual ownership (10.4%); medical juridical persons (nonprofit organizations) (Iryou Houjin) (60.2%); public medical facilities (15.0%); National (3.7%); and employee insurance groups (1%) in 2002. Privately owned clinics and hospitals make up the overwhelming majority of medical facilities, and as the government does not regulate their distribution, the concentration of facilities in different prefectures varies widely. In 2002, the average number of general hospitals was 6.7 per 100,000 people in Japan.[5,b]

In 2002, Japan had one of the highest proportions of medical beds per capita in the world: 1,573 per 100,000 people, which is comparable to Iceland (1,670 per 100,000), Sweden (1,480 per 100,000), and Norway (1,500 per 100,000). The proportion is about twice that of Canada (778 per 100,000) and almost three times that of the United States (586 per 100,000). The percentage of filled hospital beds in Japan was estimated to be 85.3% of general hospital beds and 93.2% of psychiatric beds in 2001.[5]

There were about 1,646,000 hospital beds in 2002 in Japan, with 1,372 general hospital beds per 100,000 people. Of all beds in hospitals with >200 beds, 54% were located in hospitals run by medical juridical persons, 21% in hospitals run by local, and 6% in hospitals run by federal government. As with hospitals, great discrepancies in numbers of beds exist from prefecture to prefecture. The prefecture with the highest concentration of hospital beds, Kagoshima Prefecture, had 2,081 beds per 100,000 people, while the lowest, Saitama Prefecture, had 878 beds per 100,000 people in 2002.[5]

Medical and paramedical services (including physician services and occupational/physical/speech therapies, laboratory testing, and some nursing services) are billed on a fee-for-service basis, with prices for services and drugs regulated by governmental bodies.

Decisions concerning changes in billing rates are highly political. From the mid-20th century to the present, members of the Japanese Medical Association (JMA), the majority of whom operate private clinics, have been extremely powerful in shaping billing decisions, such that current billing decidedly favors clinicians in private practice.[4] In the early 1960s, the JMA was able to bring about an increase in compensation for services by refusing to cooperate with certain public health measures. A second effect of the JMA's lobbying has been that responsibility for chronic, costly health problems has been shifted to the state.

Because physicians working in clinics do not usually have admitting privileges in hospitals, much duplication and fragmentation of medical services takes place in Japan.[4] Referral is only sometimes practiced: According to the MHLW 2002 survey of patients, the majority of patients visiting outpatient services (93.2%) and who were hospitalized (55.2%) did not receive referrals from staff at other hospitals or clinics.[10] The government is attempting to change this practice. Starting in 1988, patients were required to receive referrals to utilize the services of specially designated tertiary care centers. Patients who do not receive referrals to the centers cannot use their health insurance for the first consultation they receive there.

Outpatient services are used with greater frequency in Japan than in the United States. The number of outpatient visits per capita in Japan was more than twice that of the United States in 1996 (16.0 vs. 5.8).[12] On an average day in 2002, 6,478,000

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people, or 5.1% of the general population, visited a hospital or clinic for an outpatient consultation, and 1,451,000 people, or 1.1% of the population, were hospitalized (41.8% in general beds, 17.4% in psychiatric beds, 31.9% in long-term care beds, and the remainder in nursing beds and beds devoted to the care of specific diseases).[10]

Although a relatively small proportion of the population in Japan is admitted to hospitals, Japan has an average length of hospital stay of 37.9 days (24.0 days in general hospital beds, 195 days in rehabilitation hospital beds, and 385.7 days in psychiatric hospital beds).[5] This is just twice the 1998 U.S. average of 20.4 days (7.8 days in acute care hospitals).[11] The staff-to-patient ratio in general hospitals in Japan is low, with an average of 103.3 staff members per 100 beds (including 11.2 physicians, 31.4 nurses, 14.7 assistant nurses, 0.4 occupational therapists, 1.0 physical therapists, and 3.1 technicians). The ratio is even lower at psychiatric hospitals, with an average of 53.2 staff members per 100 beds (including 2.7 physicians, 13.0 nurses, and 14.5 assistant nurses).[5]

Although the staff-to-patient ratio is low in hospitals, technologic apparatus is more readily available in Japan than in other countries.[4] In 1999, 10,693 Japanese medical facilities had either whole-body or head-only computed tomography (CT) scanners. All of the country's 2,938 magnetic resonance imaging (MRI) scanners were located in hospitals.[5]

Physicians

The number of physicians in Japan has nearly doubled since the early 1970s, when the government began its campaign to increase the number of physicians to 150 per 100,000 people. In 2002, there were 255,792 licensed physicians in Japan, or approximately 200 physicians for every 100,000 people.[5] Most physicians in Japan are specialists, the greatest concentration of whom are internists (30.6%), followed by surgeons (10.1%) and pediatricians (5.8%).[5] Because there are almost no general practice physicians in Japan, internists often act as primary care generalists; over one third of all hospital consultations on a given day in 2003 were estimated to be with internists, and 91.3% of all hospitals in Japan had internists on staff.[c] By comparison, 9.7% of all hospital consultations were conducted by surgeons and 66.8% of all general hospitals had surgeons on staff. In general hospitals 4.3% of all consultations were performed by pediatricians and 40.8% of all general hospitals had pediatricians on staff.[5]

Physicians are plentiful in more densely populated areas in Japan. There are, however, regional differences in the distribution of physicians. Saitama prefecture, for example, has the lowest physician-to-population ratio (121.8 per 100,000 people), while Tokushima prefecture has the highest physician-to-population ratio (258 per 10,000 people) in the country.[5]

Services for Epilepsy in Japan

The MHLW estimates that on an average day 26,900 people with epilepsy received treatment at clinics and hospitals around the country in 2002. These visits constituted 0.34% of all clinical encounters.[d] Of the consultations related to epilepsy, approximately 72.5% were outpatient visits. The number of hospitalized patients with epilepsy has decreased over the years, with hospitalized patients with epilepsy totaling 8,997 in 1994, 8,332 in 1996, and 7,400 in 2002.[7,10]

The number of consultations related to epilepsy has risen together with the total estimated number of medical consultations. Estimated figures for all medical consultations between 1984 and 2002 show a decrease in inpatient consultations and a slow rise in outpatient consultations. The number of outpatient consultations for epilepsy increased more significantly than outpatient visits in general, with a rise from 172,000 in the 1980s to 195,000 in the mid-1990s. Ninety-eight to 99% of hospitalizations for patients with epilepsy in any given year began in the previous year.[7,10]

According to MHLW estimates, all hospitalizations and most outpatient consultations related to epilepsy take place in hospitals.[10] The number of patients who received referrals from other hospitals or clinics in 2002 was 55.2% for inpatients and 93.9% for outpatients. The rapid increase in the number of referrals in the 1990s can be attributed to a newly introduced health insurance system that provides physicians with incentives for issuing referrals. Those patients who first visit hospitals or clinics without referrals issued by previous physicians must pay their fees out of pocket. Insurance companies will not cover these visits.

Hospitalizations for individuals with epilepsy represent approximately 0.5% of hospitalizations for all problems. Hospital stays are long, averaging 122.0 days—far longer than the national average of 44.9 days.[10] As with the national average, the average number of days that patients with epilepsy are hospitalized varies greatly from institution to institution. The shortest average length of stay is at company hospitals (14 days). Hospitalizations for epilepsy in other types of hospitals (e.g., nonprofit or public) are similar in length (approximately 16.1 days). The longest average hospitalization for epilepsy is in psychiatric hospitals (688.1 days).[9]

The number of beds in a hospital also determines the length of a hospital stay. In hospitals with between 200 and 699 beds, average stays for problems related to epilepsy range from 131.3 to 254.4 days. In facilities with 20 to 49 beds, epilepsy patients stay an average of 12 days. In 1990, more than half (53%) of the hospitalizations for epilepsy in Japan were estimated to have lasted longer than 5 years. Seventy-three percent of these had lasted longer than 10 years.[9]

Specialists Treating Epilepsy

Although in North America people with epilepsy receive treatment primarily from neurologists or pediatricians, and in some cases general practitioners or family doctors, in Japan neuropsychiatrists and pediatricians are primarily responsible for the treatment of epilepsy. Other specialists who treat epilepsy in significant numbers in Japan are neurologic internists and neurosurgeons. Because internists often act as generalists, they see a significant number of epilepsy patients—10.5% of all cases. Most of these are outpatient visits that are split almost evenly between hospitals and private clinics. Epilepsy cases make up only a small percentage (0.2%) of the total number of cases seen by internists. A small number of consultations for epilepsy are carried out by surgeons (0.9%) and pediatric surgeons (0.3%).[9]

Neuropsychiatrists receive training in areas that in North America would fall under the specialties of psychiatry or neurology. Consequently, they treat conditions that are categorized in North America as psychiatric (i.e., schizophrenia, depression) or neurologic (i.e., stroke, epilepsy, cerebral palsy).[10] Most neuropsychiatrists (92.4%) practice in hospitals. The remaining 7.6% either have their own private clinics or are employees of small clinics.[2]

According to estimates of the MHLW, approximately 50.1% of patients receiving treatment for epilepsy are seen by neuropsychiatrists. Most of these consultations take place in hospitals (93.9%), and the majorities are inpatient consultations (64%). In 1990, 3.6% of all psychiatric consultations were estimated to be related to epilepsy.[9]

In the 1970s, a new specialty was introduced in Japan—neurologic internal medicine. Specialists in this area make up only a small fraction of all practicing physicians (1.3%). Most neurologic internists are hospital based. They conduct an estimated 3.7% of all medical consultations for epilepsy, which make up approximately 3.3% of their total consultations. In 1990, all consultations were hospital based, and most (75%) were outpatient consultations.

In 1990, children under 15 years of age comprised 23.3% of all patients seen for problems related to epilepsy in Japan. An estimated 24.8% of all medical consultations related to epilepsy were treated by pediatricians.[9] Although most pediatricians are hospital based (68.9%), 20% have their own clinics. However, almost all pediatricians treating epilepsy are employed by hospitals (89%). Of all pediatric consultations related to epilepsy, 91% take place through outpatient services.[9]

Finally, although surgery for epilepsy is not performed frequently in Japan (fewer than 500 cases in 2002), neurosurgeons treat a significant number of people with epilepsy—approximately 10% of the total. These consultations make up about 2.8% of the total number of clinical consultations with neurosurgeons and, for the most part, are outpatient, hospital-based appointments (80.0%). Most neurosurgeons (99%) are hospital employees. They made up 2.5% of all physicians in 2002.[10]

Although most people being treated for epilepsy appear to be covered by health insurance, several additional costs may burden individuals with epilepsy. Travel costs to specialized clinics, particularly for individuals with chronic health problems who must visit them frequently, are often prohibitive.

Because epilepsy in and of itself has only recently been recognized by the government as a disability, subsidized transportation was not provided in the past for people with epilepsy unless the individual also had severe mental disabilities, psychiatric problems, or physical disabilities.[e] This changed in 1995, when epilepsy was included in the Comprehensive Welfare Act for Individuals with Disabilities (Sougou Shougaisha Fukuski Hou), which awarded disability certificates (techou) based on an individual's degree of impairment with respect to daily living and degree of seizure frequency and severity. Financial burdens on individuals with severe disabilities have presumably been reduced by this act. However, individuals who must be accompanied by a parent or friend to doctors' appointments incur even greater costs that are not subsidized by the government.

Finally, people who have been given a diagnosis of active epilepsy are prohibited from driving in Japan, unless the length of time they have been seizure free exceeds 2 years. Thus, many people with epilepsy must rely on friends, family, or public transportation to get to their appointments. These barriers constitute perhaps the greatest obstacles to the utilization of hospital services for people with epilepsy.

Summary and Conclusions

Health care in contemporary Japan operates on the fundamental assumption that all residents should have access to medical services of some sort. However, policies are not blind to an individual's “social contribution,” a concept that originated in the early 20th century. This concept linked work with the right to health care. A two-tiered health insurance system continues to exist. It provides full-time company employees with health care benefits that are equivalent to those provided via NHI to the unemployed and people with part-time employment. Premiums for inclusion in NHI are scaled to income and assets. However, payment for medical services is not scaled to income. This therefore constitutes an additional barrier to access to health care for the unemployed and underemployed.

Individuals who are chronically ill, such as those with epilepsy, are most likely to be unemployed or working part time. One result of current policy is that these individuals are therefore more likely to incur larger personal health care bills per hospital visit than the average patient. Individuals with epilepsy who utilize health care services in Japan are far more likely than the average patient to be holders of NHI or to be dependents of policyholders of employee health insurance. When hospitalized, their stays are longer than the national average for all health problems—both chronic and acute. Individuals with epilepsy also incur larger-than-average bills for repeated outpatient visits and long-term drug therapy.

Contemporary political talk in Japan idealizes the concept of welfare, promoting the creation of a society that accommodates individuals who do not necessarily fit into narrow standards of “normalcy.” However, these idealistic visions are not realized in current health policy. Indeed, current policy simply reinforces the notion that productive ability is equivalent to social worth and that the valid contributions to society arise entirely through full-time employment. Unless this message is replaced with a more flexible idea of what constitutes valid social contributions, current policy may actually prevent the realization of the government's much touted social “vision.”

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Chapter 295

Nigeria

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Introduction

Nigeria is a federation of 36 states and a federal capital territory, with a land mass of almost 1 million km^2. With a population estimated at 128 million in 2005, it is Africa's most populous country. The prevalence of epilepsy in Nigeria varies from 0.53% in areas with well-developed primary health care services to 3.7% in the rural areas with poor health care infrastructures.[2] About 70% of the total population live in the rural areas.

Children under 15 years constitute 48% of the total population.[12] Peak age-specific prevalence rates for epilepsy occur in the first and second decades.[13]

The Development of Health Care Services in Nigeria

Traditional Medicine

Traditional medicine may be defined as the sum total of all knowledge and practices used in the prevention, diagnosis, and therapy of physical or mental illnesses and relying exclusively on practical experience and observations handed down from generation to generation, whether orally or written.[2]

Traditional medicine has evolved over centuries as the indigenous health care system in Nigeria. Genuine indigenous health care practices are usually based on the cultural and religious beliefs of the people. In a multiethnic country like Nigeria with over 250 ethnic groups, there are expectedly some variations in the system of traditional medicine, with each variant being strongly bound to the local ethnic culture and beliefs. However, common to all the variants of traditional medicine are dualist explanations of the etiology of illness in natural and supernatural terms and the therapeutic use of herbs and magico-religious rituals.

Nigeria has more traditional healers than Western-trained doctors. Although traditional medicine is well known to be a popular option for Nigerians, official government involvement has been minimal, being generally limited to sponsorship of conferences on traditional medicine and programs for the training of traditional birth attendants.[16]

The only legal reference to traditional medicine was in the Medical and Dental practitioners' decree of 1988, where the government referred to a traditional healer as “any person acknowledged by the members generally of the community to which he belongs as having been trained in a system of therapeutic medicine traditionally in use in that community.” This definition appeared to leave the accreditation of traditional healers to the community. Government boards of traditional medicine were set up first in Lagos in 1981, and subsequently in other states with the purpose of accreditation and attestation of bona fide traditional healers, in response to the endemic problem of infiltration by charlatans. Recently, the Federal Ministry of Health has announced plans to produce a draft traditional medicine policy for Nigeria.

Members or leaders of some of the numerous churches and mosques in Nigeria practice faith healing. They are not officially recognized or funded at any of the three tiers of government because of the constitutional secularity of the Nigerian State, but nevertheless enjoy wide patronage.

Conventional Medicine

Conventional health care services in Nigeria evolved out of the medical services of the British colonial army. The army medical service, initially meant only for its members and dependents, began to provide medical services to government employees and their dependents following the integration of the army with the colonial administration after the Second World War, and later to the public living near such facilities. The colonial government started off the present system of conventional health services with a network of rural dispensaries and maternity homes to which rural health centers and hospitals were subsequently added.

The first national policy on health care services was introduced as part of the 1946–1956 development plan in the colonial era. The second and third development plans included revisions of this national health policy, with the third (1975–1980) containing a provision for primary health care.

The current national health policy[8] was launched in 1989, and provided for a three-tier schedule of responsibilities of the federal, state, and local governments. Under this system, the delivery of primary health care is the responsibility of local governments, while the state governments are responsible for the delivery of secondary health care and the federal government for tertiary health care. This schedule of responsibilities is coordinated by the Federal Ministry of Health. The National Primary Health Care Development Agency (NPHCDA), formed in 1992, is responsible for the delivery of primary health care services and the construction of the new health centers. It establishes and trains local development committees to manage local health care.

Although both traditional and conventional health services form a plural system of health care, they remain functionally unrelated in any way. There are no official avenues for referral between the two systems.

Health Care Financing and Expenditure

Revenue

Government health services are financed from the consolidated revenue fund. There are no special taxes or levies for generating funds for health care. The Western regional government had introduced government lotteries in 1955 and legislated[10] that all monies received from the sale of tickets be paid into a medical development fund. However, this effort was eventually discouraged by poor receipts.

The nonexistence of a special health fund, tax, or levy and the relatively low fees paid by patients for health services have resulted in a widening gap between expenditure and resources. For example, most states devote up to 10% of their total annual budget to health services, whereas their annual health revenue usually constitutes <1% of the health budget. In federal teaching hospitals, internally generated revenue accounts for only 5% to 8% of the total annual expenditure.

In order to reduce the burden of the provision of health finances on the three tiers of government, a National Health Insurance scheme was launched in 2005. Federal government workers constitute the first core group to be covered by the pilot phase of the program. The program will later be extended to the organized private sector, but is unlikely to cover the majority of Nigerians, who are either self-employed or work for small enterprises.

Cost recovery through revolving funds is consistent with the national policy, which states that users shall pay for curative services but preventive services shall be subsidized.[8] A seed fund is provided to purchase a good stock of drugs and other consumables employed in medical care. Subsequently, further replenishment of stocks is provided for by sales. Provision is made for losses, exemptions, inflation, and overheads by adding 5% to 20% of the actual cost to the amount charged to the patient. The revolving fund scheme has been quite successful in many teaching hospitals.

Expenditure

In 2002, the Nigerian public health expenditure as a percentage of the gross domestic product (GDP) was 1.2%, while the private health expenditure as a percentage of the GDP was 3.5%. State governments devote between 5% and 10% of their total annual budget to health care, while local governments spend 10% to 15%.

Government medical care is labor intensive. For example, 70% to 90% of each federal teaching hospital's annual budget is spent on salaries and emoluments, leaving little for health care services and drugs.

The concept of “managed care” is practiced by all public and private companies and corporations who are obliged by law to provide free health care for their workers and their dependents. The companies enter into contracts with selected private hospital groups as health care providers, or provide limited cash reimbursements for medical expenses purchased by employees in the private health sector. The financial expenditure on health by companies is not usually made explicit in company financial statements, but the contribution to health care by this private sector financing of health is quite substantial, given the number of companies that offer this service and the large number of workers and relatives covered.

Public and institutional spending on health probably constitutes <30% of the total health expenditure in Nigeria. The majority of expenditure is by private individuals who purchase care as needed in private for-profit clinics and hospitals. These clinics and hospitals are commonly regarded as providing prompter, more courteous, and more efficient services.

Acutely ill patients receive substantial financial support from the immediate and extended families, which mitigates considerably the overall costs of health care to the patient and makes it possible for such patients to have access to health care that may otherwise be out of reach from pecuniary constraints. However, this family support tends to wane over time in patients with illnesses requiring chronic therapy, such as epilepsy.

Organization of Health Care Services

Numeric Strength and Distribution of Health Care Personnel

Doctors

Nigeria attained the recommended doctor-to-population ratio of 1:8,000 in 1982. In 1993, the ratio was 1:4,379, with wide variations between different states.[12] The 1991 doctor-to-population ratio varied from 1:1,614 in urban and affluent Lagos state to 1:114,069 in Katsina state and to 1:235,827 in Jigawa state with a low level of urbanization and weak economic infrastructures. In general, doctors tend to cluster in urban areas, avoiding rural and economically depressed areas, as is the case elsewhere in the world.

There were about 110 specialists in the clinical neurosciences practicing in Nigeria in 2004. These include 75 psychiatrists, 10 neurosurgeons, and about 25 neurologists.

Nurses

Registered nurses and midwives constitute the largest trained workforce in the health care system, with a nurse-to-population ratio of 1:655. They are also much more evenly spread between and within the states than doctors.

Community Health Workers

Community health officers are drawn from the cadres of public health nurses, community health supervisors, nursing sisters, or rural health superintendents and undergo a special 1-year training program in community health. They are the most senior community health workers.

Community health supervisors are drawn from the cadres of community health assistants, staff nurses, or rural health inspectors and undergo a special 1-year training program in community health.

Community health extension workers are responsible for the direct supervision of volunteer village health workers and spend 80% of their working time in the community. In 1993, the community health worker-to-population ratio was 1:2,166.

Primary Health Care

Traditional Medicine

There are some 200,000 traditional healers in Nigeria.[7] These include specialists such as herbalists, bone setters, traditional birth attendants, and those occupied with simple surgery, mental diseases, and therapeutic occultism.[16] Herbal medicine is the most widely practiced specialty of traditional medicine among Africans. There are also general practitioners who are competent in more than one form of therapy but are not specialized in any.

Herbal Therapy

The traditional mode of treatment of seizures commonly involves consultations with traditional deities in the supernatural world by the rendition of incantations or metaphors, combined with the administration of herbal remedies. The herbal remedies are commonly mixtures of plants with anticonvulsant, antipyretic, or antibacterial activity.

One traditional herbal remedy for generalized convulsions in Western Nigeria is the fruits of *Tetrapleura Tetraptera* Taub and the leaves of *Nicotiana Tabacum* Linn. These plants contain *Scopoletin* and its methyl derivative, *Scoparone,* which have been shown to protect against leptazol-induced convulsions.[1] However, the plants are sometimes extracted into a concoction containing cow's urine or local gin before administration. This concoction has a prolonged hypoglycemic effect, and is known to cause permanent cerebral damage in children.[15]

The health-seeking behavior of patients with epilepsy suggests a strong preference for traditional herbal medicine over conventional medicine, especially in the rural areas. For instance, all of 101 freshly screened patients with epilepsy in a community-based survey in Igbo-Ora, Western Nigeria, had been treated with herbal remedies, while only four (3.9%) were receiving conventional antiepileptic drug therapy.[13] This is particularly remarkable because the village being surveyed had good primary health care facilities, which had been functioning several years prior to the survey.

Spiritual Therapy

Epilepsy is often regarded as a manifestation of visitation of the devil, the effect of witchcraft, or the revenge of an aggrieved ancestral spirit.[14] The management of epilepsy is therefore commonly assumed to be in the domain of spiritual healers who hold out the attractive promise of a complete cure of epilepsy by magico-spiritual therapies. These elaborate therapies include ritual dances, incantations, propitiatory rites, and exorcism. They may take up considerable time, effort, and money, but are of considerable psychotherapeutic value to the patients in view of the deep-rooted beliefs about the supernatural etiology of epilepsy.

An emerging group of spiritual healers are the Islamic and Christian faith healers, who combine the basic concepts of their religions with superstitious customs and practices. They promise an instant and complete cure for epilepsy by exorcism and provide for the psychological needs of their adherents.

Traditional herbal medicine appears to be more popular for epilepsy care than spiritual therapy. Of 265 epileptic patients who have used alternative forms of therapy prior to seeking hospital treatment in one study,[3] 47% had used traditional medicine, 20.4% had used spiritual healing, while the rest had combined both treatments. However, after initiation of drug therapy in hospitals, more than two thirds of patients who had earlier used spiritual therapy tended to continue such therapy, compared with 14.6% of patients who had used traditional herbal medicine. This implies a stronger perception of continuing psychological benefit from spiritual therapy.

Eighty-six percent of patients who chose alternative medicine as their first level of care were influenced to do so by relatives, friends, and neighbors.[3] Most patients with epilepsy reporting for the first time in a conventional hospital facility would have spent between 1 and 5 years in traditional or spiritual therapy before reporting to the hospital. Thus, the intervention of these alternative practitioners often delays the arrival of patients at centers where more adequate therapy may be available.

Government Primary Care Services

The primary health care services of the national health system are provided by the local governments, their combined primary health care clinics, and health center facilities constituting 50% of all health establishments in Nigeria.[12] These facilities are well spread out in rural areas and indeed are often the only access to conventional health care for people domiciled in those areas. Government primary health care is provided at two levels:

1. The Village Health Service is provided by volunteer village health workers under the control and supervision of village health committees.
2. The District Health Center serves as a referral point for the Village Health Service. Services are provided at this level by community health officers, supervisors, and community health extension workers.

The national mental health policy calls for the integration of mental health into the national primary health care program. “Mental health” was used in this context to include the care of major psychosis, epilepsy, mental retardation, and dementia.

Therefore, mental health has been incorporated as the ninth component of primary health care. Standing orders on mental health for community workers have been developed. The orders for the junior community health extension workers at the village level[6] requires that cases of epilepsy be referred to the health center, but kept on the risk register and followed up. Accordingly, there are no antiepileptic drugs on the official drugs list for the village dispensary. The official standing orders for community health officers, supervisors, and assistants working at the district health center,[5] however, only requires the workers to treat acute seizures with paraldehyde or diazepam and to refer suspected cases of epilepsy to the general hospital.

The government primary health care workers are thus not officially required or trained to make a diagnosis of epilepsy or administer drug therapy to patients with epilepsy. Accordingly, most health centers do not have patients with epilepsy on their registers.

General Medical Practitioners

Individuals and private groups own 30.5% of all health establishments in Nigeria. These profit-orientated private health facilities are most often manned by single medical doctors in a solo practice. Some of these doctors are specialists by training, but in practice are general practitioners seeing all cases.

Private hospitals and clinics are most concentrated in the urban areas where they are largely responsible for the availability of health facilities to 75% of the urban Nigerian population within 4 km of their residences.[12] Only 35% of rural dwellers have similar access.

As there are no fee-for-service schemes or other incentives to encourage the participation of private practitioners in government primary care services, they are largely autonomous of the government. Many private hospitals have retainerships with companies and corporations for the primary care of their staff and dependents.

However, most workers will not disclose their history of epilepsy to their employers because of fears about job discrimination[4] and will therefore tend to avoid utilizing health services provided by their employers.

Most cases of epilepsy in urban areas are probably diagnosed and treated by general practitioners in private hospitals and in the general outpatient departments (GOPD) of tertiary hospitals, particularly partial seizures and absences, which are often poorly recognized by nonmedical health care workers.

Secondary Health Care

State governments are responsible for secondary health care. The state general hospitals where secondary care is provided make up 11.6% of all the health establishments in Nigeria. The hospitals serve as a referral center for the district health centers. There is a plan for each local government area to have a general hospital. There are currently 451 general hospitals for the 589 local governments in Nigeria.

The general hospitals have outpatient departments run by general practitioners. The hospitals are also expected to have a full complement of curative care, with specialists in medicine, pediatrics, surgery, and obstetrics. While this complement is often attained in urban general hospitals, it is an exception in general hospitals located in the rural areas. Most rural general hospitals have a single general practitioner to provide services. These may sometimes be young medical doctors on national youth service.

In those where specialist physicians and pediatricians are available, the general hospitals serve as the first level of access to specialist care for patients with epilepsy. The patients are usually referred from private clinics in the catchment area and from the hospitals' own general outpatients department. There are no neurologists at the general hospital level.

There is a full range of routine antiepileptic drugs in the essential drugs list at the secondary care level. Of these, phenobarbitone and phenytoin are readily affordable, but carbamazepine and sodium valproate are more expensive. There are no facilities for therapeutic drug monitoring of serum levels of antiepileptic drugs. There are also no facilities for electroencephalography (EEG) in these hospitals; patients requiring EEG are referred to the teaching hospitals with neurologic services.

There is an increasing number of well-equipped private hospitals in the urban centers that provide a full complement of secondary health care services.

Tertiary Health Care

There are 12 neuropsychiatric hospitals and 25 teaching hospitals in Nigeria. The neuropsychiatric hospitals are run by psychiatrists, while epilepsy care in the teaching hospitals is provided by neurologists, psychiatrists, pediatricians, and internists. Access to epilepsy care in the tertiary centers is by referral from general practitioners in private hospitals and the outpatients departments of the tertiary hospitals.

All the teaching hospitals have neurologic units with facilities for EEG and computed tomography scan. One of these, the University College Hospital, Ibadan, was designated as a center for excellence in neurosciences by the federal government in 1986. Six teaching hospitals have facilities for magnetic resonance imaging. Most routine antiepileptic drugs are available but the newer antiepileptic medications are prohibitively expensive. There are no special centers for epilepsy care in Nigeria.

Summary and Conclusions

Young adults living in rural areas constitute the majority of Nigerians with epilepsy. There is evidence that the majority of them are receiving traditional therapy rather than conventional antiepileptic drug therapy, even in areas where there are well-established and otherwise efficient primary health care facilities. This preference for traditional medicine has been documented to cause delays of up to 5 years before many patients with epilepsy reach centers where they can be better treated.

A review of the standing orders for epilepsy care at the primary health care level in Nigeria showed that the community health workers are not motivated or trained to treat patients with epilepsy. Nigerians have been shown to demonstrate a pragmatic, efficacy-testing health-seeking behavior for any particular complaint[9,11]; decisions on choice of care depend on, among other things, whether the health care facility in question has a reputation for alleviating such complaints. In order to demonstrate the efficacy of conventional antiepileptic drug therapy in the rural areas, there is a need to fully integrate the management of epilepsy into the national primary health care programs along the lines suggested by the World Health Organization in 1990.[17]

The development of efficient tertiary epilepsy care in Nigeria is hampered by the small numbers of specialists in the clinical neurosciences and by poor funding.

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Chapter 296

Saudi Arabia

Sonia Khan

Abdul Aziz Al Semari

Introduction

Although the Kingdom of Saudi Arabia comprises the largest area of the Arabic peninsula southwest of Asia, it continues to provide high standards in health care. Medical technology is continually upgraded. One of the first initiatives of King Abdul Aziz Al Saud, the founder of modern Saudi Arabia, was to improve health care facilities and to provide free medical treatment to all citizens and to pilgrims who travel to Mecca.[10,11]

The report of the World Health Organization (WHO) in 2006[17] shows that the total population of Saudi Arabia is 24,573,000. Life expectancy at birth is 59.8 years for males and 62.9 years for females. Child mortality per 1,000 is 29 for males and 24 for females. Adult mortality per 1,000 is 196 for males and 120 for females.[17] Saudi Arabia's health care achievements now match those of many developed countries. Saudi Arabians are no longer required to travel abroad to get specialized medical treatment. The country has the facilities to train physicians, nurses, and other medical personnel to staff the infrastructures of the Saudi health care system, which extends today to most remote communities in the country (Table 1). The government of Saudi Arabia continues to provide massive support to existing health projects in order to ensure that health services are accessible to all people at all levels.[9,12]

The Saudi health system has developed strategies to achieve the following objectives[9,12]:

1. Identification and treatments of patients
2. Delivery of preventive medicine
3. Improvement of diagnostic facilities
4. Improvement of treatment modalities
5. Optimum clinical and social follow-up of patients with chronic diseases
6. Availability of high-standard tertiary care centers for expert evaluation of complicated patients
7. Improvement of health education

The Saudi health system faces several challenges[9,12]:

1. Limited epidemiologic studies
2. Large mass of inhabited land
3. Diversity of living environments in urban and rural areas
4. Rapidly proliferating numbers of national and expatriate inhabitants

To overcome these challenges, the Saudi health system developed four phases of planning with shifts, changes in priorities, and overtime organizational arrangements. The proliferation of the health system within a short period of time had brought into focus several health-planning issues such as coordination, health information systems, and the need for establishing national bodies for health planning and accreditation. To achieve the objectives of the Saudi health system, the Kingdom organized the delivery of health care into several levels.[9,12]

Primary Care

This service is defined as the health care provided by primary care physicians evaluating patients. In Saudi Arabia, the primary care centers are distributed evenly in the country to include variable urban and rural regions. All major health sectors provide primary care centers in the country, but the Ministry of Health (MOH) remains the largest health sector providing primary health care in Saudi Arabia through a number of hospitals and polyclinics established at a standard design to match the numbers and needs of the population served (Table 2).[6,8,12,13]

Primary care physicians can refer patients to a higher level of health service according to their needs.[6,8,12,13]

Secondary Care

This level comprises most of the general hospitals in Saudi Arabia, and the Ministry of Health represents almost 63% of hospital beds in Saudi Arabia, followed by other hospitals (Table 2). Physicians practicing at this level can refer patients to tertiary care hospitals as needed. The Ministry of Defense and Aviation operates a medical evacuation program consisting of assigned equipped executive jets and helicopter aircrafts with flight physicians and nurses to transport patients to tertiary care centers.

Tertiary Care and Specialized Centers

In Saudi Arabia, a number of tertiary care hospitals are available and receive patients with complex medical conditions from different regions of the country. These centers provide advanced facilities for diagnosis and management of various medical and surgical disorders under the supervision of highly trained medical experts. Some of these centers are world famous for referrals, teaching, and research such as the King Faisal Specialist Hospital and Research Center and the Riyadh Military Hospital.

Major health care–providing sectors include government and private hospitals. Governmental sectors include the Ministry of Health, the Ministry of Defense and Aviation, the Ministry of Interior, the National Guard, University Hospitals, the King Faisal Specialist Hospital and Research Center, and the general organization for social insurance hospitals. The private sector hospitals provide a vital contribution to health service and have expanded dramatically over the past decade; there are a number of these hospitals and clinics in Saudi Arabia.[8]

Table 1 Labor Force in Health Services

Doctors	**1989**	**1993**
Ministry of Health	12,617	14,563
Other government agencies	4,298	5,076
Private sector	5,718	8,135
Total	*22,633*	*27,774*
Nursing staff		

Ministry of Health	28,266	33,373
Other government agencies	9,255	12,485
Private sector	8,319	11,232
Total	*45,840*	*57,090*
Health technicians		
Ministry of Health	15,125	17,868
Other government agencies	6,518	6,899
Private sector	3,549	3,895
Total	*25,192*	*28,662*

From the Ministry of Planning, Kingdom of Saudi Arabia.

Table 2 Hospitals, Hospital Beds, and Primary Health Centers

	(1989) (number)	**(1993) (number)**	**Increase (number)**	**Percent (%)**
Hospitals				
Ministry of Health	162	174	12	7.4
Other government agencies	30	32	2	6.7
Private sector	61	75	14	22.9
Total	*253*	*281*	*28*	*11.1*
Hospital beds				

Ministry of Health	25,918	26,974	1,076	4.1
Other government agencies	6,592	7,338	746	11.3
Private sector	6,445	7,477	1,032	16.0
Total	*38,955*	*41,789*	*2,834*	*7.3*
Primary health centers	1,640	1,707	67	4.1

From the Ministry of Health, Kingdom of Saudi Arabia.

Epilepsy Health Services in Saudi Arabia

Epilepsy is a major neurologic disorder in Saudi Arabia. The incidence and prevalence of epilepsy in Saudi Arabia are underestimated. Head trauma due to road traffic accidents remain a major etiology of epilepsy in Saudi Arabia due to the high rate of road traffic accidents. Other etiologies of epilepsy in Saudi Arabia include cerebrovascular diseases, trauma, central nervous system infections, and developmental and genetic disorders. There is a significant reduction in prenatal injury as an etiology of epilepsy due to advanced obstetric and pediatric care.[2,3,4,5,7,14,15,16] Epileptic patients in Saudi Arabia can be treated by primary care physicians, pediatricians, and internists, but more often they are referred to adult and pediatric neurologists in major cities of the country. Facilities for digital electroencephalography (EEG) and neuroimaging with computed tomography (CT) scans or magnetic resonance imaging (MRI) are available in general hospitals distributed throughout the country.

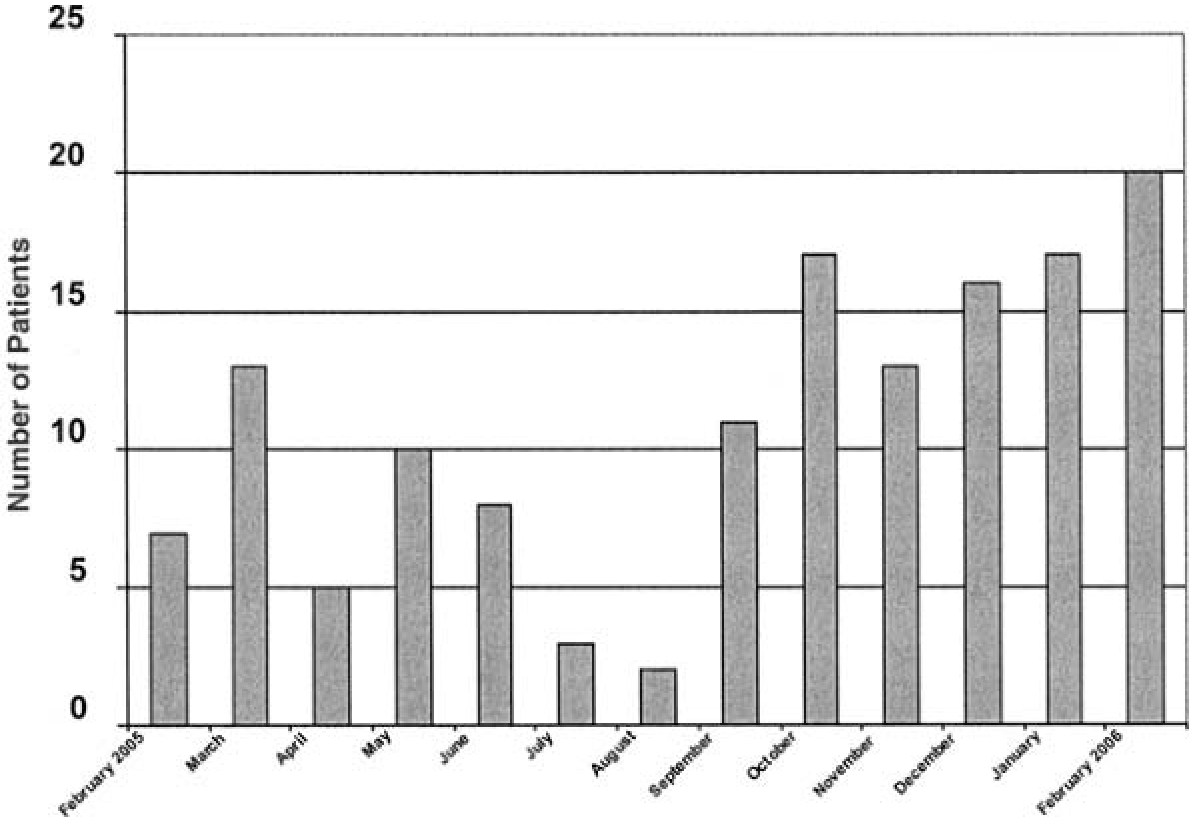


FIGURE 1. Epilepsy monitoring unit admissions (February 2005–present).

Antiepileptic drugs are widely available in Saudi Arabia in different formulations. Traditional antiepileptic drugs include phenytoin, phenobarbitone, primidone, carbamazepine, sodium valproate, ethosuximide, and clonazepam.[1,3] New antiepileptic drugs such as vigabatrin, lamotrigine, topiramate, oxcarbamazepine, gabapentin, and levetiracetam are available in major hospitals and pharmacies. Carbamazepine remains the most common antiepileptic drug prescribed. Patients with unclassified epilepsy or those with intractable epilepsies are referred to tertiary care epilepsy centers for further evaluation and management. Epilepsy centers have advanced structural and functional neuroimaging techniques and facilities for video-EEG monitoring. Trained epileptologists and neurosurgeons supervising investigations of epileptic patients in those centers are available in Riyadh and Jeddah. The largest and oldest epilepsy center in Saudi Arabia is in the King Faisal Specialist Hospital in Riyadh. The second largest epilepsy center is in the Riyadh Military Hospital. More recently, additional units have been introduced at the King Faisal Specialist Hospital in Jeddah, the National Guard Hospital in Riyadh, and the King Faisal University Hospital in Dammam. Facilities for

video-EEG monitoring are also available in the private sector hospitals such as the Saudi German and Erfan Bagedo hospitals in Jeddah. The numbers of advanced epilepsy units are expected to rise in Saudi Arabia, with increasing numbers of trained national epileptologists and epilepsy surgeons returning to Saudi Arabia after finishing their scholarships. The following section provides an overview of the two largest epilepsy comprehensive programs established in Saudi Arabia.

The Comprehensive Epilepsy Program of the King Faisal Specialist Hospital and Research Center

The comprehensive epilepsy program was established in the year 1998 at the King Faisal Specialist Hospital and Research Center. The major aims of this program are to treat the referred patients medically and surgically in specialized adult and pediatric epilepsy clinics, by adult and pediatric epileptologists, neurophysiologists, and neuropsychologists. The majority of approved antiepileptic medications are available. The existing epilepsy monitoring unit has the capacity to monitor five patients at one time for surgical evaluation and classification. The patients who are admitted for surgical management are discussed during a weekly epilepsy conference. Wada tests, subdural EEG recordings, and electrocorticography are performed routinely. Figures 1,2,3,4,5 and Table 3 show data on admissions, surgical procedures, and outcome. Programs for deep brain stimulation and ketogenic diet are being developed to treat refractory cases of epilepsy.

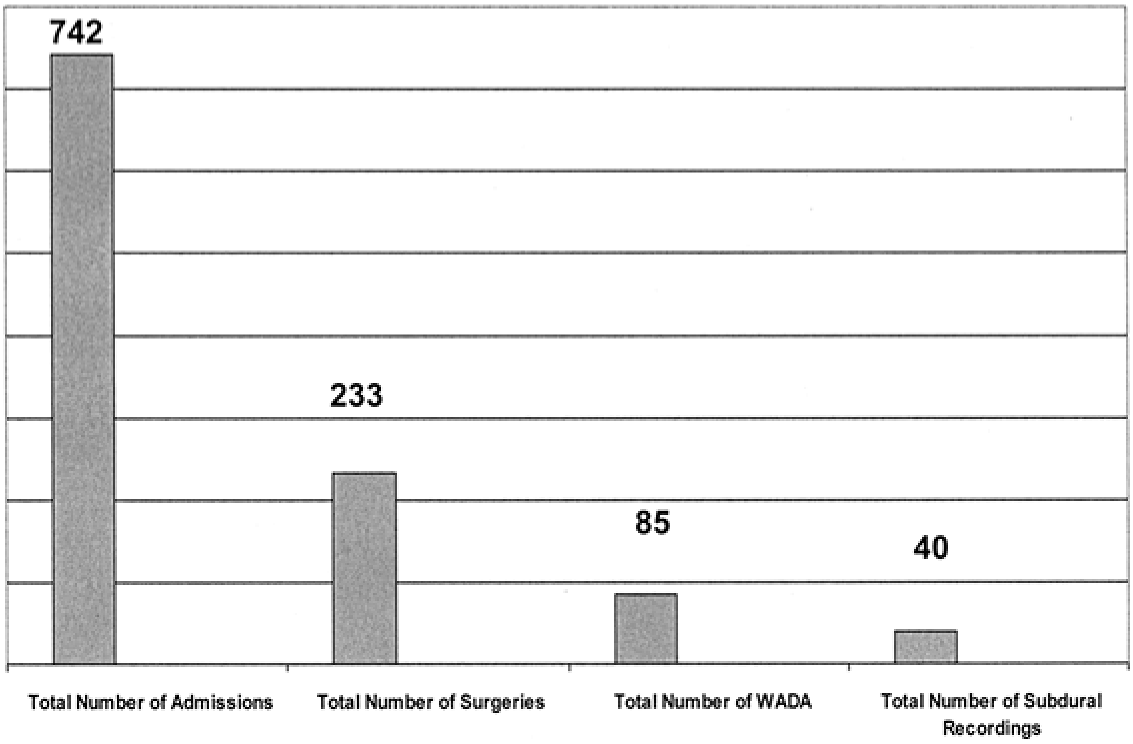


FIGURE 2. Epilepsy monitoring unit statistics.

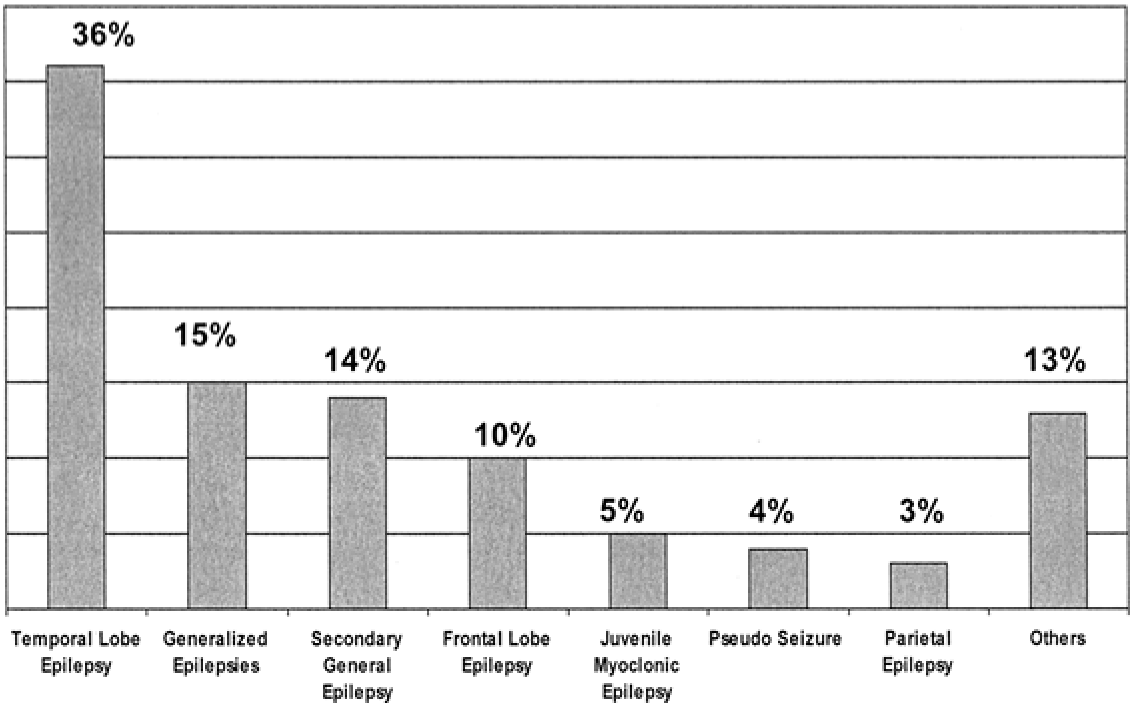


FIGURE 3. Diagnosis based on distribution of epilepsy cases.

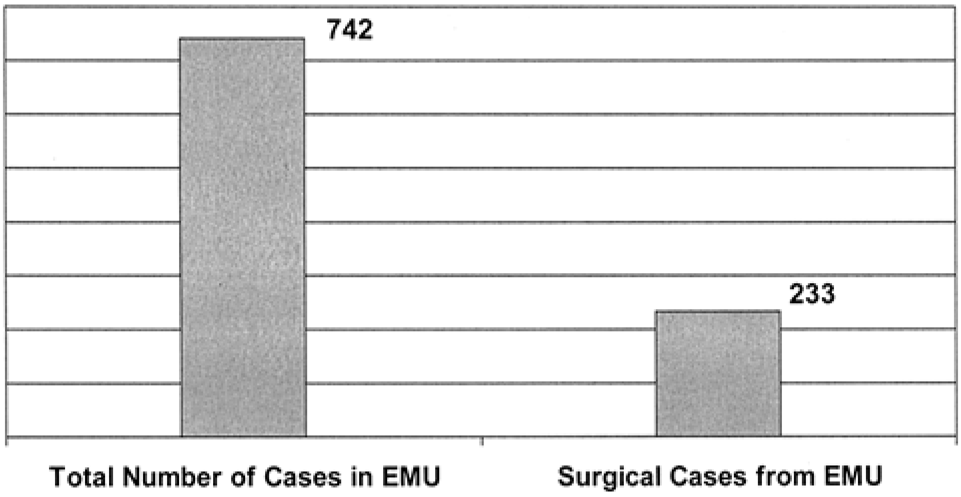


FIGURE 4. Epilepsy monitoring unit (EMU) admissions and surgical cases.

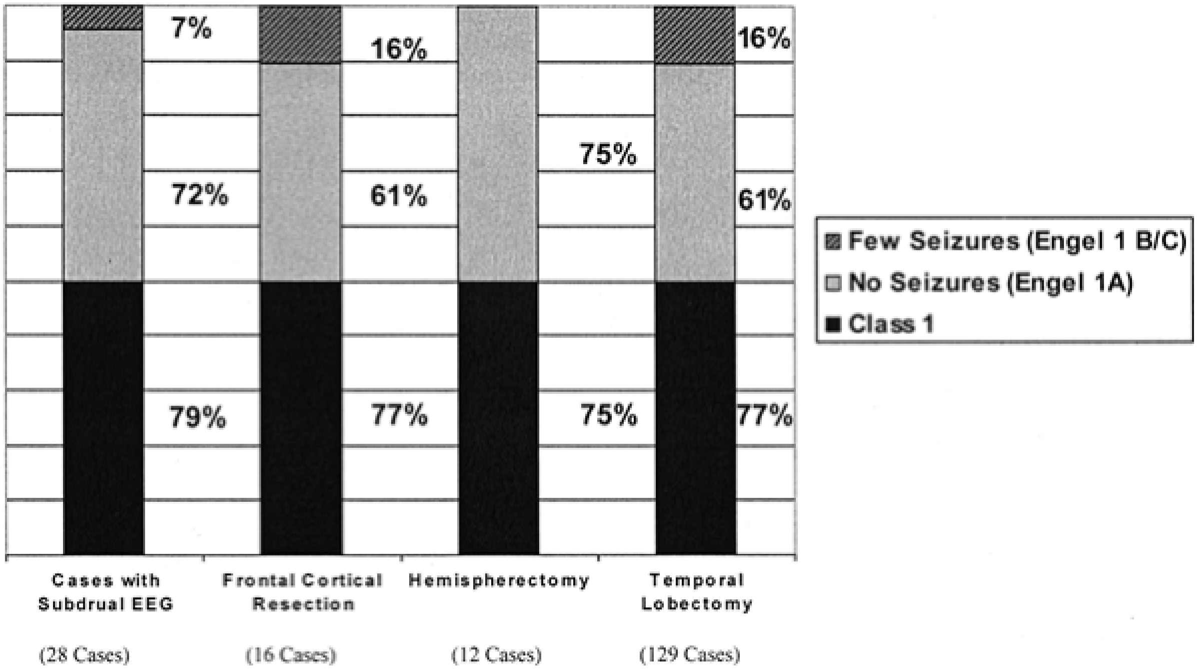


FIGURE 5. First-year outcome by surgical procedure. EEG, electroencephalogram.

An epilepsy registry has been established, and it is the first of its kind in the Kingdom of Saudi Arabia, thus serving as a resource to improve the understanding of epilepsy and to assess the magnitude and impact of this disorder on the society. The major goals of the epilepsy program are to treat the referred patients and collect, analyze, and disseminate accurate and timely data pertaining to their demographics, medical history of risk factors, type of disease, treatment, and outcome to health care providers and researchers. It is hoped that this will also serve as a model for the establishment of a Kingdom-wide registry for this disease.

The neurophysiology technologists training program was developed in 2002. Its objectives are to train and graduate skilled technicians to perform a quality service in the neurophysiology laboratory, and to provide the society with a role model of a well-trained neurophysiology technologist (Fig. 6).

The Epilepsy Comprehensive Program at Riyadh Military Hospital

This epilepsy program was introduced in January 1998 and is the second largest referral program for advanced epilepsy management in the Kingdom of Saudi Arabia. Adult and pediatric epileptic patients are referred to the epilepsy comprehensive program at the Riyadh Military Hospital from all military hospitals as well as from other governmental and private hospitals in all regions of the Kingdom of Saudi Arabia. Through special arrangements, referrals from the Arabic Gulf region and the Middle East can be seen in the Riyadh Military Hospital. The epilepsy comprehensive program receives 15 to 20 new epileptic patients per month in the outpatient clinics, evaluates ten epileptic patients per month in the epilepsy monitoring unit, and provides long-term video-EEG monitoring for ten patients per month. A total of 1,500 active epilepsy patients are followed by the comprehensive epilepsy program (Fig. 7).

The epilepsy program has two adult epileptologists, two pediatric neurologists, two neurophysiologists, two neuropsychologists, one epilepsy surgeon, and two neuroradiologists, in addition to a number of trained neurophysiology technologists and full-time nurses.

Services of the Epilepsy Comprehensive Program at Riyadh Military Hospital

Diagnosis of Epilepsy

Military and nonmilitary personnel are referred for evaluation of episodes of loss of consciousness. A comprehensive workup of high-resolution MRI scans of the brain, 21-electrode digital EEGs, and long-term video-EEG monitoring is performed. Cardiac workup including echocardiography, 24- and 72-hour electrocardiography (ECG) Holter monitoring, advanced electrophysiologic tests of the heart, and other relevant tests are also included in the workup.

A wide variety of epileptic syndromes and nonepileptic conditions such as pseudoseizures, neurocardiac syncope, and other diagnoses are entertained in the epilepsy unit (Table 4).

Medical Management of Epilepsy

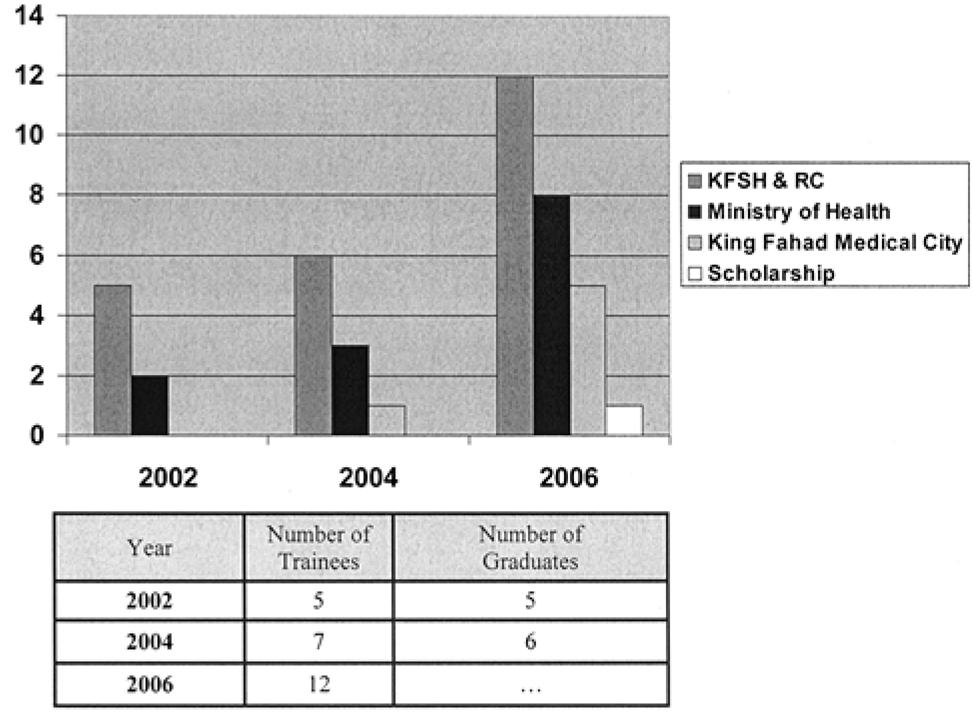
Newly diagnosed epileptic patients and epileptic patients not responding to standard antiepileptic drugs are referred to the epilepsy comprehensive program for medical management or adjustment of antiepileptic drugs. In addition to the standard antiepileptic drugs such as phenytoin, carbamazepine, valproate, ethosuximide, phenobarbitone, and primidone, new antiepileptic drugs are available. These include lamotrigine, topiramate, gabapentin, and levetiracetam.

Surgical Management of Epilepsy

A presurgical workup is performed on patients with intractable epilepsies. This include a detailed history and physical examination of the patients; blood investigations including antiepileptic drug levels; 21-channel digital interictal awake, asleep, and sleep-deprived EEG; full neuropsychological and psychological evaluation; and long-term video-EEG monitoring for 5 to 7 days using scalp EEG electrodes with zygomatic (Zg1, Zg2) or sphenoidal electrodes (Sph1, Sph2). The patient is monitored to capture three to five events and to perform ictal single photon emission tomography (SPECT) scans. Additional presurgical tests are performed as needed such as interictal SPECT scans, interictal positron emission tomography-^{18}F-fluorodeoxyglucose (PET-FDG) scans, and functional MRI for language and memory lateralization and motor function mapping. Nonselective intracarotid amobarbital test function (Wada test) in epilepsy surgery patients remains the standard tool to lateralize memory and language at the epilepsy comprehensive program. Recently, propofol replaced amobarbital in the Wada test due to the unavailability of the amobarbital.

Table 3 Surgical Outcome by Surgical Procedure

Surgical procedure	Total Surgical cases	Followed case	Seizure free Cases	Seizure free Percent
Parietal cortical resection	4	2	1	50%
Parieto-occipital lesionectomy	2	2	2	100%
Multiple subpial transection	1	1	1	100%



Year	Number of Trainees	Number of Graduates
2002	5	5
2004	7	6
2006	12	…

FIGURE 6. Neurophysiology technology training program. KFSH & RC, King Faisal Specialist Hospital and Research Center.

A reasonable number of epilepsy surgeries are performed yearly (Table 5). Decisions and plans for epilepsy surgery for each patient take place after finishing the full presurgical workup and discussing the presurgical data at the weekly epilepsy surgery meeting attended by the epilepsy team. Further plans for epilepsy surgery are made in the meeting. The most common intractable epilepsy encountered is temporal lobe epilepsy with hippocampal sclerosis as the most common surgical substrate. The most common epilepsy surgical procedure is anterior temporal lobectomy. Other epilepsy surgical procedures, such as lesionectomies for foreign tissue lesions such as vascular malformations, tumors, and focal cortical dysplasias, are performed. Functional hemispherectomy for diffuse unilateral hemispheric lesions is performed. Facilities for intraoperative monitoring methods such as electrocorticography, cortical stimulations, and somatosensory-evoked potentials for mapping of the motor cortex and other eloquent regions are available. Surgical outcome of lesional epilepsy surgery is comparable to the international literature (Table 6). No epilepsy surgery for nonlesional epilepsy has been performed yet due to technical limitations. Other palliative surgical procedures for intractable epilepsy can be performed at the epilepsy comprehensive program. The first implantation of vagal nerve stimulation in the Kingdom of Saudi Arabia was performed at the epilepsy comprehensive program in 1998 for three patients with intractable epilepsy. Vagal nerve stimulation as a treatment modality for intractable epilepsy at the epilepsy comprehensive program remains restricted for very selective patients.

Epilepsy Registry Data

Locally registered data of 1,000 active epileptic patients are available, which include demographic, clinical, EEG, and MRI data as well as seizure and epilepsy classification according to the International League Against Epilepsy (ILAE) classification.

Women and the Epilepsy Program

Women with epilepsy at different ages are referred to the specialized epilepsy clinics for counseling and follow-up.

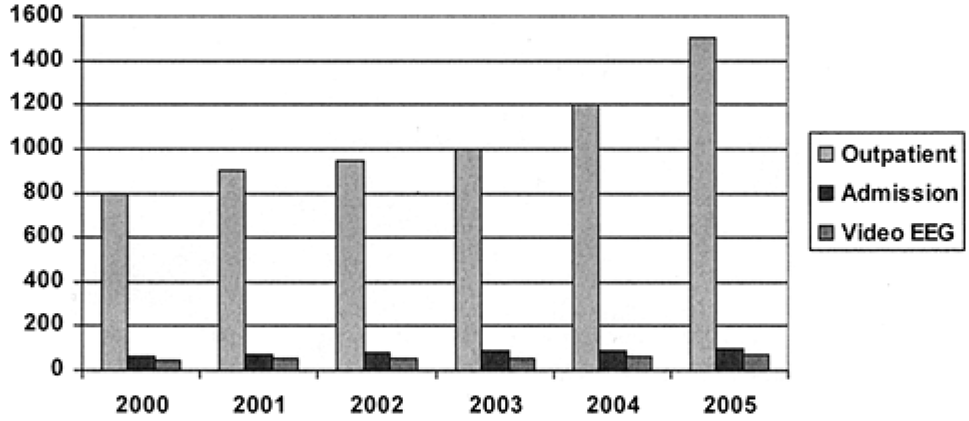


FIGURE 7. Annual statistics of the epilepsy program (2000–2005). EEG, electroencephalogram.

Table 4 Diagnoses at the Comprehensive Epilepsy Program (2002-2005)

Diagnoses	Mean age (yr)	Gender		Total
		Male	Female	
Generalized epilepsy	25	17	30	47 pt (20%)
Partial epilepsy	38	70	60	130 pt (60%)

Pseudo seizure	35	5	30	35 pt (15%)
Others	30	20	3	23 pt (5%)

Newly diagnosed epileptic young and elderly women are referred to the epilepsy program for the choice of appropriate antiepileptic drugs according to their diagnoses, ages, and comorbid conditions such as menstrual irregularities, osteoporosis, etc. Epileptic women of childbearing age are referred to the specialized epilepsy clinic for pre-pregnancy counseling, choice of contraceptive pills, and comprehensive follow-up during the pregnancy delivery and postpartum periods.

Epilepsy Training

The epilepsy comprehensive program provides regular biannual courses on basic and practical epileptology for nurses, technologists, and other health providers interested in epilepsy. These courses are limited to the hospital staff. In addition, neurology and neurosurgery board residents rotate for a 2-month period during their training in the epilepsy unit to learn basic epileptology related to their specialties.

Epilepsy Education and Training

Due to the small number of trained epileptologists and epilepsy surgeons in Saudi Arabia, the government of Saudi Arabia in general and the Saudi neuroscience society in particular encourage young neurologists and neurosurgeons to pursue higher training in epileptology and epilepsy surgery, respectively.

Through fully sponsored governmental scholarships, national neurologists and neurosurgeons are sent to the most prestigious European and North American epilepsy centers to pursue their subspecialty training and to gain the highest level of expertise in epilepsy. Internationally recognized epilepsy centers and programs in Europe and North America receive neurology and neurosurgery graduates on a regular basis. In addition, the government of Saudi Arabia provides local and international scientific scholarships for paramedical personnel to obtain higher training in their fields.

Major epilepsy centers in Saudi Arabia provide limited medical training in epileptology for the neurology and neurosurgery residents. In addition, high-standard training programs are available locally for nurses and neurophysiology technicians. Regular scientific activities include the full-day annual Saudi epilepsy meeting under the annual Saudi neuroscience symposium and regular half-day workshops, lectures, and seminars for neurologists, neurosurgeons, physicians, board residents, and paramedical staff. Every two years a 2-day Saudi epilepsy course takes place in collaboration with the regional commission of the ILAE and the International Bureau of Epilepsy.

Collaborative clinical and research projects take place regularly between the Saudi epilepsy centers and international recognized epilepsy centers with regular visits from international epileptologists and epilepsy surgeons to the epilepsy centers in Saudi Arabia. The Saudi chapter of the ILAE and the Saudi chapter of the International Bureau of Epilepsy represent the scientific body that supervises all academic epilepsy activities in Saudi Arabia. Regular scientific epilepsy papers and abstracts are presented in local, regional, and international neuroscience and epileptology conferences.

Patient Education in Epilepsy

Lay knowledge of epilepsy is unsatisfactory in Saudi Arabia. Despite the improved standards of general education in the Kingdom, significant misunderstanding and social stigma of epilepsy remain in Saudi Arabia.

Table 5 Epilepsy Surgery at the Riyadh Military Hospital (November

1998–June 2006)

Year	Temporal surgery	Extratemporal surgery	Total
1998	1	—	1
1999	10	4	14
2000	12	2	14
2001	8	2	10
2002	8	4	12
2003	13	4	17
2004	10	4	14
2005	8	4	12
2006	3	3	6
Total	73	27	100

Table 6 Surgical Outcome at the Riyadh Military Hospital

	Temporal		Extratemporal	
Surgical outcome	n	%	n	%
Engel I	55	75%	19	70%
Engel II	15	21%	5	19%
Engel III	2	3%	2	7%
Engel IV	1	1%	1	4%

Many patients believe in traditional medicine in the form of herbal or spiritual therapies. Other patients avoid medical management to avoid psychosocial stigma. Despite advanced medical and surgical standards in the management of epilepsy in Saudi Arabia, patient education has remained significantly retarded for a long time. The King Faisal Specialist Hospital and Research Center in Riyadh took the first step toward a comprehensive educational program for patients and the

public by forming the Epilepsy Support and Information Center (ESIC).

Epilepsy Support and Information Center

The ESIC is a community volunteer group affiliated with the comprehensive epilepsy program at the King Faisal Specialist Hospital and Research Center in Riyadh composed of both community volunteers and medical professionals. The center is dedicated to dispersing information about and understanding of epilepsy in Saudi Arabia and the International Arab Community. ESIC's mission is to promote increased awareness, understanding, and acceptance of epilepsy. Other epilepsy centers and ministries of health are organizing a collaborative patient support group with ESIC to improve epilepsy patient education in Saudi Arabia. ESIC endeavors to promote epilepsy health education and support for individuals with epilepsy and their families through the publication and nationwide distribution of printed materials on epilepsy.

List of Publications

The following is a list of ESIC's publications:

- Questions and Answers about Epilepsy
- Febrile Seizures
- Epilepsy and Children
- Advice on Raising a Child with Epilepsy
- Epilepsy Medications and Epilepsy
- Myth and Misunderstanding about Epilepsy
- Epilepsy and Education: The Role of the Teacher (Booklet)
- Epilepsy and Pregnancy (Booklet)
- Questions and Answers about Epilepsy (Booklet)
- Adil and Epilepsy (Children's Story Booklet)
- Epilepsy Information Fact Sheet
- 12 Antiepileptic Drug Wallet Cards

Patient Information Lectures and Conferences

ESIC offers six public information lectures and three public epilepsy conferences.

Website

The ESIC has established the first comprehensive epilepsy Internet Website (www.epilepsyinarabic.com) in the Arabic language. Visitors to the site contact us on a regular basis through e-mail and ESIC receives regular online requests for Arabic language brochures from many countries, including Saudi Arabia and the other Gulf States, Libya, Jordan, Syria, Egypt, Morocco, Spain, Britain, and the United States, to name a few.

Family Festival for Epilepsy Awareness

To date, the ESIC has organized five annual Family Festivals for Epilepsy Awareness. The sixth annual Family Festival is planned for November 2007.

Teacher Awareness Program

To date, the ESIC has organized ten half-day Teacher Awareness Conferences at schools, universities, and government rehabilitation centers in Saudi Arabia.

Epilepsy News/Media Campaign

In May 2006, the ESIC distributed a four-page Epilepsy Public Information Fact Sheet with basic facts and information about epilepsy. The fact sheet was distributed Kingdom-wide as an insert in the Al-Riyadh Daily National Newspaper. Total distribution was 140,000 newspapers nationwide.

Epilepsy Workshops for Health Care Professionals

To promote enhanced medical care and strengthen the medical emergency response to epilepsy, the ESIC organizes regular accredited full-day epilepsy workshops for primary health care professionals. To date, the ESIC has organized three epilepsy workshops. The last workshop was held March 12, 2005 and was organized in cooperation with the Saudi Arabian Ministry of Health.

Research

To highlight the societal impact of epilepsy and the needs of individuals with epilepsy to national health care planners, the ESIC is cooperating with the King Faisal Specialist Hospital and Research Center comprehensive epilepsy program to provide support and assistance in the establishment of a National Epilepsy Registry. The ESIC is also involved in an ongoing research survey aimed at determining the predominant societal attitudes and general level of knowledge about epilepsy in Saudi Arabia.

Awards

In 2001, the ESIC received the internationally recognized Initiative Prize from the Arab Gulf Funding for United Nations Program. The prize, received in the UN offices in Geneva Switzerland, consisted of a trophy and a $40,000 grant.

International Involvement

The ESIC has been a full chapter member of the International Bureau for Epilepsy since 2001, and has participated in the Eastern Mediterranean Epilepsy Task Force and in the drafting of the Eastern Mediterranean Declaration on Epilepsy in Cairo, Egypt.

Summary and Conclusions

Epilepsy is a common neurologic disorder in Saudi Arabia. Delivery of health services in general and of epilepsy in particular in Saudi Arabia is done at the primary care, then secondary care, then tertiary care levels. Despite the rapid proliferation of the population of Saudi Arabia, the advanced epilepsy centers with epilepsy surgery services remain confined to few centers and hospitals with limited capacities. Therefore, the official recognition of the increasing demands on more national epilepsy monitoring units and epilepsy surgical programs should be included in the main health-planning strategies toincrease epilepsy monitoring beds and to advance neurophysiologic and neuroimaging techniques in Saudi Arabia to the highest international standards. Epidemiologic studies are limited on epilepsy in Saudi Arabia. Therefore, national multicenter epidemiologic surveys should be launched to verify the magnitude and demands of epilepsy as a health problem in Saudi Arabia. National multicenter registries for epilepsy patients, pregnancy, and antiepileptic drugs and epilepsy surgery data should be initiated to achieve a better understanding of epilepsy in Saudi Arabia. Patient education of epilepsy is limited; therefore, all efforts should unify to overcome local misconceptions about epilepsy and improve general understanding of epilepsy. General national and local guidelines are needed for various epilepsy-related issues such as driving and pregnancy. Education about epilepsy in the elderly should be generated and approved by higher authorities to reduce morbidity and mortality of epilepsy. Education on epilepsy for health professionals should be optimized to organize a structured algorithm in the management of epilepsy in Saudi Arabia.

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Chapter 297

Senegal

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Introduction

Epilepsy is one the most common neurologic diseases in outpatient and inpatient health management in Senegal, West Africa. It is the same situation in the majority of African and many developing countries, where it constitutes a major public health care problem.[11] From newborns to teenagers, childhood are the most stressed group due to several causes of epilepsy including perinatal problems, febrile convulsions, cerebral malaria, and consanguinity, which is a genetic factor.[1,19,22]

Such as in the majority of African countries, the cultural environment is a limiting factor for early diagnosis and treatment of seizures. Interpreted as a subnatural affliction, epilepsy is mainly managed by traditional healers, reducing the chance for Senegalese people living with seizures to benefit from modern drugs and better opportunities to become seizure free. A heavy burden is generated, leading to school withdrawal, nonemployment, and other social discriminations.

Overview of the Country

Senegal is a Western African country of 196,722 km^2. It is surrounded by Mauritania (at north), Guinea and Guinea-Bissau (at south), Mali (at east), and the Atlantic Ocean (at west). Gambia Republic is situated inside Senegal. Forty-five percent of the population is younger than 15 years old; 53.5% of the population is female, and 52% of the population is rural. The increasing rate for the general population is 2.6% per year. The population of Senegal is estimated to be near 12 million (Table 1). The general life expectancy is estimated at 54 years for males and 58 years for females. The infantile mortality rate is estimated to be 58 of 1,000 births.

The mean population density is estimated at 54 inhabitants per km^2, but it is very disparate: 3,659 inhabitants per km^2 are living in the capital city Dakar region, versus eight inhabitants per km^2 for the region of Tambacounda in the southeastern region, which represents 30% of the surface of the country. This situation can be explained by the large surface of this region, the low-wealth environment, and its aridity. Sixteen ethnic and language clusters are defined, but the main ethnic group and most spoken language is *Wolof*. It is important to be aware of this diversity because it may be considered in any information and education program, because of specific social and cultural values that are correlated to each. The rate of illiteracy is 43% of 15- to 24-year-old males and 62% of 15- to 24-year-old females. Ninety-two percent of the people in Senegal are Muslim.

Senegal is composed of 11 regions. Regions are divided in departments, themselves divided into districts, then into rural communities. These structures are led, respectively, by governors, prefects, and rural community presidents. Cities are led by a mayor. In their intervention domains are included health in coordination with the ministry of health, education, environment, urbanism, agriculture, youth, sport, and art craft.

Senegal is a low-economy country. The gross national product per inhabitant is estimated to be U.S. $480. The economy is mainly based on exploitation of phosphate, fishing, tourism, and agriculture.

General Data on the Health System

Health Organization and General Data

Senegal guarantees in its constitution that health is a right of every citizen and the duty of the state to provide. The medical and health systems are inherited from French colonization. A recent law is trying to organize traditional medicine, but one can guess how difficult it is to do so because of the secrecy surrounding this mystic and intrafamilial legacy. Despite this legislation, total or partial health insurance or coverage is a reality for about one third of the population represented by public and private workers and their families. The remaining two thirds remain in an informal sector, financing their health fees through their own or indirect supports. The health system is structured like a pyramid constituted from the base to the top by health post (for villages and rural communities), health center (inside cities), regional hospital, and two university hospitals. This represents the following (Table 2):

- 11 medical regions (led by the regional head doctor)
- 56 health districts (with one or more doctors and paramedical staff)
- 59 health centers (with nurses and midwives)
- 813 health posts (with nurses)
- 37 private Catholic health posts located in the suburban area of Dakar

The geographic accessibility to a health structure is theoretically 1.2 km for Dakar's patients, versus 16.2, 12.9, 11.0, and 10.3 km for the regions of Tambacounda, Louga, Saint-Louis, and Kolda, respectively.

In the context of the African continent, Senegal has a very low prevalence rate of HIV/AIDS infection: 0.8%. Heterosexual transmission is the major route. Since the early beginning of the AIDS pandemic, a strong policy of information, prevention, and caring has been developed. Reported AIDS cases increased progressively and remain stable now, estimated to be about 45,000 people. This tendency is attributed to Senegal's initiative of access to free antiretroviral drugs since 1996.

Table 1 Socioeconomic, Demographic, and Health Indicator Data about Senegal

Population, total	11.9 million
Population growth (annual %)	2.4
Life expectancy at birth, total (yr)	56.1
Fertility rate, total (births per woman)	4.8
Mortality rate, infant (per 1,000 live births)	77.6
Mortality rate, under 5 yr (per 1,000)	136.6
Births attended by skilled health staff (% of total)	57.8

Malnutrition prevalence, weight for age (% of children under 5)	22.7
Immunization, measles (% of children aged 12–23 months)	57.0
Prevalence of HIV, total (% of population aged 15–49)	0.9
Primary completion rate, total (% of relevant age group)	45.2
School enrollment, primary (% gross)	76.0
School enrollment, secondary (% gross)	19.4
School enrollment, tertiary (% gross)	4.9
Ratio of girls to boys in primary and secondary education (%)	89.8
Literacy rate, adult total (% of people aged 15 and above)	39.3

From www.worldbank.org and www.who.int.

Table 2 Health Infrastructures

Medical regions	Hospitals	Health districts	Health centers	Health posts
Dakar	8	8	11	115
Diourbel	2	4	5	70
Fatick	1	6	6	73
Kaolack	1	4	4	72
Kolda	1	4	3	68
Louga	1	5	5	56
Matam	1	3	3	50

Saint-Louis	2	4	4	81
Tambacounda	1	6	5	58
Thies	2	8	9	91
Ziguinchor	2	4	4	79
Total	22	56	59	813

Health Financing

The health annual budget roses to 9% of the global government budget since 2002. But 65% of the budget of the Ministry of Health is dedicated to pay salaries. There is a decreasing participation of the government financing of health and an increase in the population participation. Thirty percent of credit and expenses are done in the capital region of Dakar. Other sources of finances include development partners and local communities. They contribute in building, training, salary, and daily expenses. But it is difficult to determine their exact contributions. City administrations are also contributing in the health expenses, drugs, and maintenance. Armed forces and police also participate in health expenses of their personnel and families.

Health Personnel

Representing the health personnel are 649 (public and private) doctors and 3,287 paramedical staff (midwives, private nurses, and health agents) (Table 3). The mean general doctor-to-population ratio in Senegal is one doctor for 18,300 inhabitants, one midwife per 6,124 reproductive women and 0- to 4-year-old children, and one nurse for 4,570 inhabitants. The World Health Organization (WHO) recommends one doctor for 5,000 to 10,000 people, one midwife for 300 people, and one nurse for 300 people. There is a wide disparity: 90% of specialized doctors are concentrated in Dakar, the capital. The Dakar region has more than 50% of doctors, pharmacies, surgeons, nurses, and midwives. The national ratio is 11,163 inhabitants per health post. This is not so far from what WHO recommends (10,000 inhabitants).

Excluding two psychiatrists (one at North, one at South), the rest of the neuroscience personnel resides in Dakar: 15 public and two private neurologists, three private and 11 public psychiatrists, and six public neurosurgeons. Postgraduating diplomas in Psychiatry, Neurosurgery, and Neurology have existed in Senegal since 1993, 1998, and 2000, respectively.

Neurologists

Seventeen neurologists were identified in Senegal in 2007, among them eight professors (three with PhDs) and two private. All public-sector neurologists practice in the capital city of Dakar, where the unique service of Neurology of the University Hospital is located. The ratio of one neurologist for 700,000 people, far from the recommended WHO rate of one for 50,000 people, is one the best in the intertropical area of Africa, where the ratio ranges from one neurologist for 1 to 4 million people. This reality demonstrates the strong need to cooperate with psychiatrists, neurosurgeons, general practitioners, pediatricians, and public health staff.

Table 3 Health Personnel Data in Senegal

Physicians (number)	649
Physicians (density per 1,000 population)	0.06
- Including neurologists	17
- Including psychiatrists	14
- Including neurosurgeons	6
Nurses (number)	3,287
Nurses (density per 1,000 population)	0.32
Dentists (number)	97
Dentists (density per 1,000 population)	0.01
Pharmacists (number)	85
Pharmacists (density per 1,000 population)	0.01
Public and environmental health workers (number)	705
Public and environmental health workers (density per 1,000 population)	0.07
Lab technicians (number)	66
Lab technicians (density per 1,000 population)	0.01
Other health workers (number)	704
Other health workers (density per 1,000 population)	0.07
Health management and support workers (number)	564
Health management and support workers (density per 1,000 population)	0.05

Epilepsy in Senegal

Epidemiology

The mean national prevalence rate of epilepsy in Senegal was estimated to be 3.1% in 1970,[4,5] then 8.3% in 1986.[19] Different epidemiologic research has stressed the very different disparities from one region to another. In the suburban area near Dakar, Pikine, characterized by promiscuity and problems of hygiene and water supply, the prevalence was estimated at 12% in 1989.[23] A survey conducted in the same area during the demonstration project of the Global Campaign Against Epilepsy revealed a prevalence rate of 14%.[21] It has been remarked that when there is a good concentration of health

personnel, the rate decreases. This is the case in Saint-Louis (1.9%), the former capital of Senegal, or in Niakhar (3.1%), a village where a hepatitis project is conducted with constant medical visits for the surveillance.[18]

No incidence studies have been conducted, but there is, as described elsewhere, a dramatic presence of epilepsy among children and the elderly.[13] When the results are analyzed regarding age, it is clear that childhood is the most affected group.[2] Epilepsy is the first cause of hospitalization among young patients (16.1% to 32%) in the different hospitals of Dakar.[1,18,22] Among them, 7.46% have been hospitalized for status epilepticus, which is a real problem of public health with a high risk for vital prognosis.[15] Surveys conducted in schools revealed that the mean prevalence rate is 21% in different schools in Dakar and Thies (the second city 75 km from Dakar). The rate is 2.6% in Saint-Louis among 6- to 15-year-old alumni.[2] The question is, Does this reflect a true reality due to the good ratio of health personnel to population? Or is it related to a possible withdrawal of epileptic children from school by their parents and/or teachers because of a frequent cultural allegation of "risk of contamination" to the rest of the classroom?[20]

Concerning the elderly, it has been also demonstrated that the incidence within this group is progressively becoming higher after 50 in Senegal as soon as the life expectancy progressively raises.[14] A prospective follow-up of a group of pregnant epileptic women with a prevalence rate of 1.05% revealed no difference in the occurrence of fetal development versus the nonepileptic group.[16]

The Etiologic Factors

The difficulty to investigate every epilepsy case contributes to enormous bias for the precision of etiologies. Many existing factors can lead to epileptic conditions. It is assumable that leading causes described worldwide and especially in developing countries may be considered in Senegal as well as in other African countries, including pregnancy problems (53% of pregnancies are nonmedically assisted, leading to a possible cause in 10% to 60% of epilepsy due to bad perinatal environment or ischemia from prolonged delivery), febrile convulsions, infections, and febrile diarrhea in children under 5 years old.[11] Bacterial meningitis, cerebral malaria, and other encephalitis were found in 7% to 19% in a hospital study conducted in Senegal. Furthermore, in Senegal, 43% of marriages are celebrated within the (large) family, entertaining the consanguinity and favoring expression of potential genetic epilepsy. A close intrafamilial relation between genitors is reported in 7% to 50% of surveyed people with epilepsy.[3] In the population ever so, vascular factors are reported in 68%, before infections, cerebral tumors, and metabolic factors including diabetes.[6,10]

Diagnosis and investigation of epilepsy in Senegal benefit from a limited number of specialists (the ratio is 1 for 700,000 people, versus 1 for 50,000 people as recommended by the WHO), as described above. In 2007, the available material is composed of six public and five private computed tomography (CT) scans and six public and four private electroencephalograms (EEGs) and two public and two private magnetic resonance imaging (MRI).

Sociocultural Representation

In many developing countries it is estimated that 80% of people with epilepsy are not treated with modern medications. The large majority of Senegalese patients living in rural areas are not consulting modern medical centers. Part of the reason could be geographic and/or economic related to the difficulty of access to health care structures. In a survey conducted in the suburban area of the capital city, Dakar, it has been demonstrated that 35% were taking antiepileptic drugs (AEDs) only, 41% associated them with traditional means, 11% took only traditional means, and 13% were not taking anything. The treatment gap (related to modern AED treatment) was consequently estimated to be 23.3%. But this is just the visible part of the iceberg.[21] The hidden and major part is related to the fact that epilepsy is considered a subnatural affliction and must be managed by traditional healers.[17] In the Senegalese culture, seizures are the manifestation of strong spirits involving the body and shaking it. The various definitions in local language reflect a basic knowledge of epileptic presentations. Some seizures could be considered as a positive but too powerful spirit.[12] In most instances traditional healing is the first treatment sought. In some countries, the traditional belief systems endorse discrimination against people with the condition, leading to their exclusion from mainstream society and restrictions on their accessing basic human and civil rights. However, the role of traditional healing should not be completely discredited as in many instances the person with epilepsy obtains a degree of secondary benefit from this form of intervention in the way of reassurance and emotional support. Efforts should be made to integrate traditional and Western interventions in a way that provides a range of services offering holistic support and care for the person with epilepsy and his or her family.[9] These would include advice, counseling, social support, school-to-work transitioning, job creation and training, rehabilitation, and community integration. The challenge is how to conciliate conflicting convictions that guide the traditional and scientific treatment concepts.[24]

Available Antiepileptic Drugs and Diagnostic Facilities in Senegal

The antiepileptic drugs available in Senegal and the cost of a month's worth of tablets in private pharmacies and in generic public forms are indicated in U.S. dollars (at the rate of December 2006) in Table 4.

Table 4 Antiepileptic Drugs Available in Senegal

Drug	Strength	Public price[a]	Generic price[a]
Phenobarbitone	10 mg	1	0.4
Phenobarbitone	50 mg	1.02	0.4
Phenobarbitone	100 mg	1.24	0.6
Carbamazepine	200 mg	8.7	NA
Carbamazepine	SR 200 mg	14	NA
Carbamazepine	SR 400 mg	16.5	NA
Ethosuximide	NA	NA	NA
Phenytoin	100 mg	3.18	NA
Valproate	200 mg	9.3	NA
Valproate	500 mg	14.5	NA
Valproate	SR 500 mg	17	NA

Clonazepam	2 mg	9.5	NA
Diazepam	10 mg	7.9	NA
Diazepam	5 mg	6.7	1.24

NA, not available.

Primary health care centers can have all forms of phenobarbitone, phenytoin, and intravenous diazepam. In Dakar's pharmacies and in the capital of the nine other regions, one can find all the drugs cited above. A new generation of AEDs and brand new drugs and intravenous valproate and phenytoin are not available in Senegal.

The Role of the Senegalese League Against Epilepsy

The situation described above led to the creation in 1995 of the Senegalese League Against Epilepsy. Its originality is that this International League Against Epilepsy (ILAE)/International Bureau for Epilepsy (IBE) chapter gathers patients, families, and health and social workers and volunteers, with the purpose to improve the knowledge, awareness, and management of epilepsy.

The Senegalese League Against Epilepsy (SLAE) plays an important role in advising the Ministry of Health on issues regarding epilepsy and in providing education to physicians. The SLAE has created videos, leaflets, surveillance books for patients, training and guideline booklets for health personnel, and posters and T-shirts for public advertising. It organizes scientific meetings and courses in its various regional chapters.

Selected as a site of the Global Campaign Against Epilepsy (GCAE) Demonstration Project on Epilepsy, Senegal had conducted an epidemiologic survey about epilepsy quality care and KAP (Knowledge, Attitude, and Practice) evaluation among the general population and health personnel. These public health operational research projects led to concrete interventions deducted from the results. A weekly epilepsy consultation has been set up since then in the suburban area of the capital city of Dakar. Five regional branches have been installed with training and local care activities. The location of the unique neurology service in Dakar and the research results led to the concept of "Caravan for Epilepsy." It consists of a 3-day intervention: Day 1: Arrival of the neurosciences team, meeting with administrative and health leaders, and media talk show on epilepsy. Day 2: Full-day training course with general practitioners and paramedical staff, while some members of the team meet with schools, women associations, and social workers. Day 3: Full-day consultation of patients coming from villages and small cities surrounding the main regional city and informed about this mission by the day 1 radio talk show. If indicated, some patients can be investigated with a portable EEG. Intensive information and education programs are continually conducted via TV, radio, newspapers, and public conferences on epilepsy. A group of traditional healers of the region of Dakar has benefited also from a training program on epilepsy to develop a better collaboration between modern and traditional medicine, which is utilized by the very large majority of people with epilepsy in Senegal and Africa, whatever their instruction level, residence, and concomitant modern health management.

Summary and Conclusions

Describing Senegal realities reflects and summarizes the very common situation of epilepsy in developing countries of the sub-Saharan part of Africa. The management of public health has been dominated since the introduction of modern medicine in Africa via French colonization, many centuries ago. The leading infectious diseases masked the real incidence of nontransmissible disorders, including neurologic ones. Many factors cause a high rate of epilepsy in the country: The high incidence of infectious diseases, the poor quality of maternal–infant care in this low socioeconomic country, consanguineous marriages, and delayed diagnosis and management of tumoral and traumatic causes. Nowadays, more consideration is progressively given to nontransmissible diseases. Many cultural factors maintain epilepsy in the shadows and lead to a dramatic treatment gap. Improved and delocalized epilepsy health care, communication with the different segments of the population, basic education, and intensive training of doctors and paramedical staff, coordinated by a league against epilepsy, raise awareness and begin to give optimism to the improvement of epilepsy management quality and reduction of personal burden and condition of people living with epilepsy. The war will take a long time to win, but step by step, an encouraging and sustainable effort can lead to more success stories for epilepsy in African developing countries such as Senegal.

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Chapter 298

United Kingdom

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Introduction

In 1911 a National Health Insurance Scheme was introduced in the United Kingdom that allowed low-paid workers (but not their families) access to primary health care. This was the first intervention by a British government in the area of general health care delivery. There was interest in taking matters further, and at the end of World War I an election pledge to establish a general health service was made by Lloyd George's coalition. A Consultative Council on Medical and Allied Services was set up, headed by the King's physician, Sir Bertrand Dawson (1864–1945, later Viscount Dawson of Penn), which produced an interim report in 1920. This discussion document suggested a framework for a comprehensive service emphasizing primary care and preventive medicine while defining the roles of secondary and tertiary services, in the event no action was taken and there was no further report. However, the philosophy and ideas of the Dawson Report were to influence the development of the National Health Service as World War II drew to a close more than 20 years later.

Development of the Present System

Shortly after the outbreak of World War II, the national government in Britain, which included representatives of all main political parties, asked Sir William Beveridge (1879–1963), an economist and master of University College Oxford, to chair an interdepartmental committee on the coordination of the Social Services. This was not expected to be completed until after the war, but the report entitled *Social Insurance and Allied Services* was published in 1942, some 18 months after the work started. It proposed a comprehensive social insurance scheme covering the whole population without income limit. The government response, with other pressing priorities, was initially low key, but the report sold 70,000 copies in 4 days and was popular with the public. An understanding then emerged that with the coming of peace a health care service for the nation would be established, free at the point of entry and financed by national taxation, based on a White Paper of 1944. This policy would be carried out by whichever party won the first postwar general election. In 1945, the Labour Party assumed power between the German and Japanese surrenders. Acts of Parliament in 1946 (covering England and Wales) and in 1947 (Scotland) were passed, and the National Health Service (NHS) was inaugurated on July 5, 1948.

The National Health Service Act (1946) defined ministerial responsibility for establishment in England and Wales of "a comprehensive health service designed to secure improvement in the physical and mental health of the people and the prevention, diagnosis and treatment of illness for that purpose.… Service so provided shall be free of charge.…" Responsibility for ushering in the new age fell on the Labour politician Aneurin Bevan (1897–1960), who was the Minister for Health and Housing. There was initial resistance from the medical profession, but Bevan proved an able negotiator, and in his own words overcame doctors' objections by "filling their mouths with gold." Bevan believed that access to free medical care would improve ordinary people's health to the extent that there would be economic benefits, and in particular that the cost of the new NHS would fall with time as the rate of disease was reduced. This thinking was fortunately not enshrined in statute as history proved him completely wrong. Meanwhile private practice was allowed alongside and within the NHS.

Between 1948 and 1974 the NHS consisted of three main branches: Public health services, which were the responsibility of local government; the hospital-based services; and the primary care service in which family practitioners (general practitioners [GPs]) worked. Difficulties in planning and coordinating services led to considerable consultation and debate between 1968 and 1972, and in 1974 a major reorganization created three administrative tiers—at Regional, Area, and District levels—that sought to overcome these problems. This unfortunately proved bureaucratically inefficient, and in 1982, following a Royal Commission report, the middle tier of Area Health Authorities was abolished.

Up to this point stages in the development of the service were a consequence of consultation and forward planning that took place under governments of both main political parties, and the broad policy was bipartisan. From the mid-1980s onward the Conservative government began to introduce changes that deviated from this consensus. In 1985 the NHS was placed under a management board chaired by its own chief executive, accountable to but with some autonomy from the government Department of Health and Social Security. In the late 1980s the NHS was subjected to a private review by the government, after which a major change in its mode of operating was devised. Against concerted opposition from all those relevant professional bodies who expressed an opinion, as well as from other political parties, an amending act was passed in 1991, and a new, reformed NHS appeared on April 1, 1992.

The main changes reflected the adoption of an internal market strategy. This meant that the old District Health Authorities were allocated a grant based on their individual population needs, to purchase health services from provider units such as hospitals. Provider units were given the opportunity to become self-governing trusts, in competition with each other, obtaining their income from purchasing authorities by selling services to them. Doctors working in primary care were allowed (and encouraged) to take responsibility for managing their own budgets for purchasing secondary services (known as GP Fundholders). This controversial purchaser/provider split appeared to lay the foundation for an increase in the establishment of managerial, accounting, and general administrative staff, with a power shift away from health professionals. Some rationalization was attempted by a drastic reduction in the number of Regional Health Authorities in 1994, together with partial devolving of planning to the periphery. At the time of writing, virtually all provider units have self-governing Trust status, while the commissioning of most services is a function

of locality-based Primary Care Trusts. These came about after the Labour Party won the 1997 election with a policy pledge to abolish the internal market of the NHS and to remove the perceived unfair advantage of the fund-holding primary care sector over the non–fund-holding sector. The years since then have seen a series of rapid changes in structure, characterized by the increasing devolution of service commissioning to the primary care level, and a downscaling of the influence of the old Regional Offices, which were eventually abolished. This also happened against a background of devolution of government to Welsh, Scottish, and Northern Irish Assemblies, producing different NHS structures with subtle differences in four jurisdictions. Total spending on health by the government has substantially increased, but not surprisingly some of this has been required to finance the structural reforms and monitoring apparatus that have had to be introduced. In England and Wales recommended treatment guidelines for NHS use are drawn up by a quasi-autonomous government-funded organization, originally called the National Institute for Clinical Excellence, later expanded to the National Institute for Health and Clinical Excellence, but always known by its acronym, NICE. This describes itself as "the independent organization responsible for providing national guidance on the promotion of good health and the prevention and treatment of ill health." NICE also appraises health technologies, including drugs, to make recommendations for use within the NHS based on cost effectiveness, with the economic modeling emphasizing cost to the NHS rather than cost to society as a whole—an approach that has led to considerable criticism; it remains to be seen whether this narrow approach will survive. Nevertheless, NHS organizations in England and Wales are required to audit their practice against NICE guidance, and a degree of performance management is dependent on this. NICE produced comprehensive epilepsy management guidelines in October 2004.[13] In Scotland, some of the equivalent functions of NICE are performed by the Scottish Intercollegiate Guideline Network (SIGN), which produced updated epilepsy guidelines in June 2004.[16] There are some subtle differences in emphasis, which if followed closely could lead to different care pathways being followed by people with epilepsy in the United Kingdom depending on where they live, though whether this is important only time will tell. Both NICE and SIGN guidelines may be accessed through the Internet at www.nice.org.uk and www.sign.ac.uk, respectively. One consequence of current policy is the setting of various clinical and managerial targets (e.g., waiting times) that contribute to performance management of NHS organizations. An early attempt at this in England by a previous government was the publication in 1992 of *The Health of the Nation.*[7] Inclusions and exclusions in this document are somewhat arbitrary. Targets for reduction in HIV and suicide are included, despite the relatively small numbers in England of those affected by HIV and the fact that suicide statistics depend on quality control of coroner's courts. Epilepsy was not mentioned. Later, epilepsy came to move further up the governmental agenda. One of the key influences in this was the National Sentinel Clinical Audit of Epilepsy-related Death, published in 2002.[10] This came about after intensive lobbying of the government by the voluntary sector, and its influence on service development has been significant. The government was moved to produce an Action Plan for epilepsy service improvement, which, although criticized heavily by the voluntary sector and by epilepsy specialists, nevertheless raised the profile of epilepsy considerably.[3] Indeed, much direct representation to government about epilepsy services has been through charitable and voluntary groups, such as the British Epilepsy Association (now called Epilepsy Action), the National Society for Epilepsy, and the Joint Epilepsy Council of Great Britain and Ireland. In the United Kingdom these nonprofit organizations are called charities. In 1994 the government tacitly opposed a Disabled Rights Bill and met with much lobbying and criticism from groups advocating rights for the disabled and from consumer groups. Shortly afterward, the Charity Commission, the government-appointed body that regulates the activities of charities (some of which had been highly critical of the government's failure to support the bill), issued firm guidelines that seemed at first effectively to stop charities from future involvement in political lobbying, unless they were willing to risk losing their charitable status.[6] This advice was subsequently revised.[5] The government then brought forward separate legislation on disability rights, the Disability Discrimination Act, which came into law in 1997.

Budget Organization and Development

National Government

The NHS is financed by taxation. Responsibility for setting and allocating the NHS budget for the United Kingdom lies with the central government. In England this is the responsibility of a politician, the Secretary of State for Health, who heads a ministry, the Department of Health. In Scotland, Wales, and Northern Ireland health issues are the responsibility of different government departments, belonging to the devolved parliamentary assemblies in Scotland, Wales, and, when it is sitting, Northern Ireland.

For the purposes of health administration England was previously divided into a number of Regions, each with a population of approximately 5 million, with strategic overview provided by an NHS Executive Regional outpost, which has replaced the old Regional Health Authority. Each Region contained a number of Health Authorities (HAs), with populations of approximately 250,000 each. NHS Regional outposts were broadly responsible for strategic planning within their areas, but details of service provision were decided and carried out at District level. The process of peripheral devolvement has seen the abolition of Regional outposts and of the old Health Authorities, to be replaced in England by smaller Strategic Health Authorities (SHAs) and Primary Care Trusts (PCTs). At the time of writing there is speculation that many PCTs may be forced to merge for economic and strategic reasons, and SHAs may also combine to larger organizations, which might effectively bring back the old District/Regional boundaries, the process therefore turning full circle within a few years. Not surprisingly many who work in the service find it difficult to embrace these sorts of changes with the same enthusiasm as the politicians.

Board members of NHS organizations are currently appointed by the Secretary of State. There are proposals that may allow some local election to boards in the future, but this has yet to be implemented. Currently PCTs (and to a lesser extent SHAs) in England and their equivalent bodies in other jurisdictions are the authorities with responsibility for purchasing health services on behalf of the community, with funding from central government, the level being fixed by population size and type.

The purchasing authorities, as defined earlier, may contract with health providers such as hospitals, ambulance services, and so on, which are organized as self-governing trusts. There is also the option to purchase from the private sector, so that the public and private sectors become less demarcated.

Table 1 Proportion of Gross Domestic Product (%) Spent on Health

	1980	1987
United States	9.2	11.2
Sweden	9.5	9.0
Canada	7.4	8.6
France	7.6	8.6
Netherlands	8.2	8.5
Austria	7.9	8.4
Germany	7.9	8.2
Iceland	6.4	7.8
Switzerland	7.3	7.7
Luxembourg	6.8	7.5
Norway	6.6	7.5
Finland	6.5	7.4
Belgium	6.6	7.2
Australia	6.5	7.1
Italy	6.8	6.9
New Zealand	7.2	6.9
Japan	6.4	6.8

Portugal	5.9	6.4
United Kingdom	5.8	6.1
Spain	5.9	6.0
Denmark	6.8	6.0
Greece	4.3	5.3
Mean	7.0	7.5

From Heginbotham C. Leading for health: responses: rationing. *BMJ.* 1982;304:496–499.

State Provincial Government

Provincial (local) government below the level of the four jurisdictions (England, Scotland, Wales, Northern Ireland) has no direct role in the United Kingdom as far as health care is concerned. However, local government is responsible for the organization of social services and for the provision of children's education. Therefore long-term care, which can be construed as a social services responsibility, has to be considered in this way, and the special educational needs of children with epilepsy have to be assessed and provided for at this level. Because of this split, opportunities arise for budget holders to attempt to shift financial responsibility away from their own areas, although officially cooperation between different agencies is encouraged.

Insurance Company/Health Schemes by Budget

Since the NHS was founded there has always been a small but flourishing private sector. Only 11% of people have private health insurance.[15] The NHS has traditionally been regarded as superior in emergency care and, until recently, in provision for chronic illness. The private sector offers shorter waiting times for nonurgent surgical procedures, better access to some investigations (especially magnetic resonance imaging), and a more discrete, personalized service.

Finances

In 1987 the United Kingdom spent 6.1% of its gross domestic product (GDP) on health. At first this appears to compare unfavorably with some other industrialized countries (Table 1).

Until 1980 the NHS budget had been increasing by about 4% per year, after inflation. From 1980 to 1986 this rate of increase slowed to 1%, although it increased again after 1986. The slowing of growth in income between 1980 and 1986 was consistent with government policy to increase efficiency in the public sector and to limit public spending. This meant that in 1986 the gap between actual and expected budget was £3.53 billion, a shortfall of nearly 20%. However, increased spending after 1986 had largely closed this gap by 1992. The usual explanation for the discrepancy between GDP spent on health in the United Kingdom and other countries is that the nationalized health system spends less on administration, and so overall costs are kept low. This was especially apparent in the spending squeeze between 1980 and 1986, although evidence from other countries suggests that policy attempts to improve efficiency may have the opposite effect.[18]

Control of Expenditure by Different Segments

At the National Level

The total NHS budget is set after Treasury negotiation each year, and decided by the Cabinet. The Secretary of State for Health has the responsibility of making the case in Cabinet for appropriate funding in the context of total government budget, competing with other departments such as education or defense.

In the past, budgets for the main parts of hospital services were then devolved to Regional Health Authorities. Since the complex and changing reforms of the last 10 years, the trend has been toward establishing local health commissioning organizations such as PCTs, which are allocated funds according to a formula based on local population demographics.

People who have private health insurance are still most likely to use the NHS for primary care by choice. Where contact with hospital-based services is concerned, insurers may be reluctant to provide coverage for expensive or long-term treatment, so these are likely to be met from NHS resources too.

Organization of Physicians

Primary Care

Nurse Practitioners

Epilepsy specialist nurses started appearing as a distinct group in the United Kingdom in the early 1990s. The first appointments came mainly from the charitable sector (the David Lewis Centre, in Manchester, and the National Society for Epilepsy, in London), although NHS funding was involved in an innovative community-based scheme established in Doncaster in Yorkshire.[17] These nurse practitioners bring an added dimension of counseling skills to the clinical team and are able to provide more time to answer patients' questions than physicians. They also assist in liaison between primary and secondary care services, and can supervise previously prescribed changes of medication, thus freeing up the time of doctors. There is now a professional body that sets standards, the Epilepsy Specialist Nurses Association.[8] A major impetus to the development of the specialty has been provided by the British Epilepsy Association (BEA) in collaboration with industrial sponsorship to provide pump-priming finance for the establishment of a number of new posts around the United Kingdom starting in 1995. This project, launched in BEA's 45th anniversary year, is known as the Sapphire Nurses Programme, and represents a potentially major change in the mode of service delivery.

It did not come about by project planning in the NHS, despite published evidence of efficacy of such a service[8] and despite the much-vaunted sensitivity of the NHS reforms to local needs. As in other areas of epilepsy provision in the United Kingdom, the main thrust has come from the voluntary, charitable sector. However, in 1995 the result of raised consumer expectations, pressure from the charitable sector, and interest from within the Department of Health (DOH) combined so that the DOH sponsored a number of pilot projects, mainly in the primary care arena, referred to as the Epilepsy Initiative. Matters altered considerably after the change of government in 1997, and current NICE guidance endorses the value of epilepsy specialist nursing. There are also opportunities for specialist nurses to become prescribers of medication within agreed treatment protocols, although this has yet to have a significant impact in epilepsy.

General Practitioners and Family Practice

In the United Kingdom it is unlikely that antiepileptic drug treatment would be initiated solely by a general practitioner. Where patients present with suspected epilepsy, the primary care physician will virtually always obtain an opinion from a specialist. The United Kingdom has relatively fewer neurologists per capita than other European or North American countries, and so the specialist opinion may be obtained from a general physician (internist) or general pediatrician. Recent data suggest that initiation of treatment for children is carried out by general pediatricians in about 55% of cases, whereas for adults, neurologists initiate treatment in about 66%.[14] The vast majority will be seen in the public (NHS) sector by physicians working in hospital practice. After initial investigation and treatment, most patients are referred back to their GPs for longer-term follow-up.

GPs are mainly organized into partnerships that may be based in health centers providing total primary care services for populations of 12,000 to 20,000 (with six to 10 GPs). A significant number work in smaller partnerships, and there are a few single-handed practitioners. GP partnerships typically employ primary care nurses and other allied professionals. At present in the United Kingdom there is no established model that is equivalent to the polyclinic or multispecialty clinic seen in some other countries, although some areas have commenced a pilot scheme for Primary Care Resource Centres that may fulfill some of these functions, and there is encouragement for the development of specialist GPs (GPSIs—GPs with a Special Interest) in various therapeutic areas and opportunities for this to develop in epilepsy.

GPs have the responsibility to provide all primary care medical services to the whole population registered with them, and so all GPs have a responsibility for epilepsy. Similarly, virtually all people with epilepsy are registered with GPs, although for many the involvement with treatment consists of little more than obtaining repeat prescriptions for antiepileptic drugs. About 20% of patients continue to see hospital physicians.

General Pediatricians and General Physicians (Internists)

General pediatricians and general physicians are hospital-based practitioners. Within the hospital setting there is an increasing trend to specialization, so that a district general hospital will have a group of general physicians that will include some with special interests in cardiology, endocrinology, gastroenterology, and so on. Where there is no staff neurologist, one of the general physicians may take this on as a special interest and will therefore have a broad responsibility for epilepsy. However, it is likely that all general physicians will see some patients with epilepsy, and all will take turns at receiving urgent admissions of patients with epilepsy from accident and emergency departments.

The percentage of the different specialists (other than neurologists) who see epilepsy patients regularly is shown in Table 2.[9]

Table 2 Medical Practitioners Who See Epilepsy Patients Regularly

	Percentage of specialists seeing specialty patients with epilepsy
General medicine (internists)	56
Psychiatrists	20
Pediatricians	80
Gerontologists	73

Neurologists

In the early 1990s the United Kingdom had about 300 trained career neurologists, approximately the same number as Denmark, a country with one-tenth the population. There has been a tendency until recently for neurologic practice to be most concentrated in teaching hospitals. However, the specialty is set for expansion. It is likely that neurologists in the NHS will be concentrated in neuroscience centers, each serving a population of 1.5 to 2.5 million, along with neurosurgeons and neurophysiology services. District hospitals serving much smaller catchments within the neuroscience center areas will obtain neurologic services from the center, on a hub-and-spoke principle. Private practice neurology exists and frequently shares facilities with the NHS service.

Referrals to neurology services will typically be made by GPs or hospital-based physicians. Self-referral is not the usual pattern in the NHS, and is unusual even in the private sector. The main barrier to access is the shortage of neurologists, with the waiting list for nonurgent outpatient appointments varying across the country from 2 to 92 weeks in 1993.[9] Reducing waiting list times such as this has been a high priority of the Labour Government, and it is alleged that the maximum time has been considerably reduced. Data for 2004 suggested that of 84,290 referrals for outpatient neurology consultations in England, only 384 (0.46%) had to wait more than 21 weeks to be seen.[12]

Epilepsy Centers

The term *epilepsy center* has two different meanings in the United Kingdom. It may refer to a residential facility owned and administered by a nonprofit organization specializing in epilepsy, or it may refer to a specialist unit within an NHS neuroscience center. The former typically have close links with the latter, so that there is some integration of service. For example, Chalfont Centre, a residential facility in rural Buckinghamshire run by the nonprofit National Society for Epilepsy, forms part of a service provided also by the National Hospital for Neurology and Neurosurgery in London.

The availability of epilepsy services in different parts of the United Kingdom is a reflection of both the enthusiasm of different local physicians and the local public profile of consumer groups and nonprofit organizations. Epilepsy surgery programs are currently well established at nine major NHS neuroscience centers in the United Kingdom, with several others in development. There are at least four multidisciplinary residential assessment units for adults and two for children, all mainly within the independent nonprofit sector, and there are a larger number of NHS neuroscience centers with specialist hospital-based assessment facilities. The total number of specialist outpatient clinics known to the British Epilepsy Association had increased to 59.[2] The reasons for this increase and the reason why there continues to be a slow but sustained improvement in epilepsy services include:

- New antiepileptic drug licenses and increased activity by the pharmaceutical industry to sponsor continuing medical education, thereby raising awareness among professionals
- Increased consumer expectations and demands
- The BEA Sapphire Nursing scheme (see earlier)
- Continued lobbying from nonprofit organizations, in particular resulting in the National Sentinel Audit of Epilepsy-related Death, the government Action Plan, and the issuing of epilepsy guidance by NICE

As a recognition of and in response to the preceding, the NHS published an Executive Letter (EL 95/120) early in 1996[1] drawing the attention of purchasers and providers to the potential for developing epilepsy services, to the role of voluntary organizations, and to how epilepsy relates to the priorities for service development in the NHS. Needless to say, the voluntary organizations carefully monitored the response and carried out some research into its effectiveness.[4]

Summary and Conclusions

The British National Health Service was established in 1948 as a publicly funded service, free to the consumer at the point of access. Private medical practice continues to exist alongside the state sector, but a large majority of citizens use the NHS exclusively for the services that it provides.

Rising costs and the need to establish more effective management caused the government to introduce a number of structural changes, characterized in the 1980s by the establishment of the NHS Executive and in the 1990s by the introduction of an internal market with a purchaser/provider split. A new government was elected in May 1997, which has reversed some but not all these changes and introduced some new ones.

The priorities for the NHS include (among others) an increasing focus on primary care, the effective use of resources, and working with service users and caregivers.

Neurology as a medical specialty was traditionally more diagnostic than therapeutic, and much of the treatment of common neurologic conditions was carried out by general physicians. Epilepsy services therefore tended not to develop exclusively in neurology departments, and indeed have often been supported by the charitable (nonprofit or voluntary) sector. Consequently, epilepsy services remained fragmentary, variable in quality, and difficult for the consumer to find. A number of factors have contributed to an improved outlook, including a greater commitment to develop neuroscience services, greater consumer empowerment, and development of innovative service models, including enhanced primary care liaison and the use of specialist nursing. Nonprofit organizations representing views of service users and professionals, such as the Epilepsy Action (British Epilepsy Association) and the National Society for Epilepsy, have played an important part in establishing epilepsy on the health planning agenda, and these organizations will continue to fulfill this role.

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Chapter 299

United States

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Introduction

The organization of health care in the United States has undergone major changes in recent years. In this chapter, the historical background is presented, after which the organization of health care as it exists in 2006 is outlined.

Historical Background

Health care in the United States was initially provided by generalist physicians. During the colonial era, they graduated largely from the medical schools of Great Britain. By the time of the Revolutionary War (1776), however, some physicians in the United States developed expertise in certain areas and were considered specialists. Medical schools were established in the United States along with the earliest universities and tended to follow the Scottish model. Under the Constitution, regulation of medical practice in the United States is relegated to the individual states. As a result, each state has its own licensing authority. During the 19th century, the quality of training and care varied widely, and fraudulent claims to medical training were frequently made. This was particularly a problem in rural areas of the western states.

By the time of the Civil War (1861), specialization in neurology had developed, and some of the earliest research in neurologic disease was done at that time. The specialties of neurology and psychiatry were closely intertwined from the earliest days of the medical system.

At the beginning of the 20th century, under the aegis of a charitable foundation, a study of medical education in the United States was carried out (the Flexner report), and a revolution occurred. A national accreditation authority for medical schools was established, and medical schools were reorganized more along the lines of the German system. Training in basic science was required of all students, and organized clinical training began. Still, up to the beginning of World War II (1939), the overwhelming majority of physicians were in primary care, and specialty care was available only in major cities and in association with university schools of medicine.

The end of World War II, the creation of the GI Bill of Rights, and the establishment of federal subsidies for medical insurance, research, and education produced a second revolution. Large numbers of physicians were trained, many more medical schools were established, and specialty training in the form of residencies became the norm. State licensing authorities no longer permitted physicians to practice after only a single year of postgraduate training (internship), and formal residencies and accreditation boards were created in all specialties, including family practice.

Large numbers of dollars flowed into the health care system as health insurance became a fringe benefit provided by nearly all large employers. Health insurance was readily available for purchase by individuals, and the federal government began subsidizing health care for the poor and elderly.

Levels of Care

Nonetheless, today, the United States, despite its enormous wealth, fails to provide for the basic health needs of a large part of its population. It has more levels of care than any other major industrialized country.

Level 1: Provisions for the Very Poor, Whether or Not They Are Homeless

The very poor have no money and no health insurance. Historically, they depended on charitable acts of individual physicians. As practices became more highly organized, and the poor became more concentrated in inner cities, finding access to charity care became increasingly more difficult. The federal government provided large amounts of money to hospitals for capital expansion and modernization under the Hill-Burton Act of 1946. A subsequent law required any hospital that received Hill-Burton funds to provide emergency care to all coming to its emergency department, whether or not they could pay. This was the final safety net, but provided only for the most obvious emergencies. However, the educational needs of physicians in training and the sense of local responsibility on the part of cities and counties has led to a system of county hospitals with outpatient facilities of varying completeness. Some of these are now being closed because of fiscal constraints.

Level 2: Medicaid

From 1966 to 1996, the federal government provided money to the states under Title XIX of the Social Security Act. This provided matching funds to the states to care for sick children, mothers of minor children, and the disabled. Strict federal guidelines were enforced. This broad mandate became eroded during the 1990s. The programs of the individual states now have more variability, and the ability of the poor to choose their own physicians is once again becoming compromised.

Level 3: Medicare

In 1965, the federal government initiated the Medicare program (Title XVIII) to provide health insurance for the elderly. Anyone over the age of 65 is eligible. This is a complicated act that provides for inpatient hospital care (Part A). Hospital care is primarily paid for by the federal government, with deductibles and copayments by patients. Voluntary premium payments by eligible patients, with some support from the federal government, provide funding for outpatient hospital care and physician care (Part B).

The payments from both Title XVIII and Title XIX are far below community standards and stress the physician segment more than the hospital segment of the health care system. In January 2006, Medical Part D was implemented, providing for a benefit to assist in the purchase of pharmaceuticals. This law (and its regulations) is extraordinarily complicated, depends upon a multitude of competing private plans, and is partially needs based. Early implementation was poorly planned, and many patients were denied needed medicines. It is too soon to know how this program will eventually develop.

Level 4: Private Insurance

Individuals were able to buy hospitalization insurance beginning in the early 1930s. A few people were able to purchase physician insurance also. The wage freezes imposed at the time of World War II were circumvented by employers and unions that agreed to purchase health insurance for employees. The cost of insurance was not subject to the wage freeze. These payments started a major industry in the United States—private health insurance. For many years, private health insurance was of the indemnity type. Any service prescribed by a physician and provided by a licensed practitioner or facility was covered. To this extent, it was analogous to the collision insurance that one buys for an automobile. The great majority of the people in the United States are still covered by insurance that is purchased by an employer. However, insurance has become increasingly expensive because of increased demand, increased costs, the complexity of medical treatment, and the failure to obey market forces. A major effort to control costs by setting up large bureaucratic organizations to provide medical service took place in the 1990s. These schemes are called *health maintenance organizations* (*HMOs*), *preferred provider organizations* (*PPOs*), *independent practice organizations* (*IPOs*), or *physician-hospital organizations* (*PHOs*). Over time, the restrictive nature of the HMOs lost favor, and most employers provide some form of PPOs. This type of plan offers more choice of physician to the patient.

Level 5: Indemnity Insurance and Private Payments

Where it still exists, traditional indemnity insurance permits unlimited access to medical and hospital care. Increasingly, certain services are no longer available, because managed care organizations will not purchase them and there are too few indemnity patients to sustain them.

The policy of the Bush administration (2000–2008) is to shift cost and responsibility to the individual patient. Tax-exempt Medical Savings Accounts are now being promoted heavily. Higher deductibles and copayment requirements are becoming burdensome.

Thus, it is extremely difficult in the United States to understand how decisions are made with respect to health care expenditures. They are made by many different groups at many different levels, in many different locations. The United States has failed to initiate a nationwide health care system and relies instead on competition within the marketplace and multiple individual decisions. As the major sources of money become restricted (national, state, and employer), an increasing portion of the money spent on health care comes from individual persons.

Organization of Physicians for Primary Care

In the United States, primary care is largely provided by family practitioners, although increasing numbers of nurse practitioners and physician assistants are being used. The general practitioner who also performs surgery and obstetrics is a dying breed, and the average family practice physician refers most surgical cases to specialists.

Family practitioners are found throughout the United States. Only a few are left in solo practice; most practice together in single-specialty groups that in some areas comprise as many as 30 or 40 people. Others work in large family practice departments of multispecialty clinics. From the standpoint of epilepsy care, most patients with epilepsy receive care from primary care physicians (although in urban areas, many patients are also followed routinely by a neurologist).

In the United States, primary care is also often provided by pediatricians and internists. Internists who subspecialize are known as *cardiologists* or *rheumatologists*, for example. They tend to practice in small, single-specialty groups or in departments of multispecialty clinics. The average internist or pediatrician sees no more patients with epilepsy than the average family practitioner. The average primary care physician cares for between five and ten patients with epilepsy. Pediatricians and internists tend to be located in urban areas, including smaller cities with as few as 10,000 to 20,000 people.

There are roughly 750,000 licensed physicians in the United States and only 12,000 neurologists. Most neurologists practice in large urban areas or in association with medical schools. Very few are in solo practice; most are in single-specialty groups or in departments of multispecialty clinics.

In the United States, many people seek out neurologic care directly, although the majority is still referred by primary care physicians. With the development of managed care organizations of various sorts, new barriers have been created to specialty access for people with epilepsy. In addition to the problems of distribution and distance, barriers exist to accessing a neurologist (or any other specialist) without a referral from a primary care physician.

In the United States, primary care physicians frequently admit a patient to a hospital and call a neurologist in consultation. This is in contrast to what occurs in many other countries, where the patient is referred to a hospital group or a neurologist, who then takes on the primary responsibility for hospital care.

Excellent comprehensive epilepsy centers are available throughout the United States (see Chapter 302).

It is important to note that, in the United States, a license to practice medicine is generic. There is no legal restriction to physicians' describing themselves as specialists in any area. Control over quality is a function of hospital staff privileges. In this way, physicians in major hospitals cannot practice in an area for which they have not had appropriate residency training; specific privileges are granted, and these may often relate to something as narrow as whether or not a lumbar puncture can be performed.

However, what takes place in an individual physician's office is completely unregulated. This allows innovative, less expensive treatments to be provided by highly ethical physicians. It also allows opportunities for misrepresentation and less than ideal treatment by others.

Summary and Conclusions

The United States has at least five different levels of care, largely driven by economics and barriers erected against those with pre-existing physical conditions. The relatively unregulated practice of medicine and the fact that the license to practice medicine is generic leads to wide disparities in quality of care.

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Chapter 300

Zambia

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Introduction

In 2000, epilepsy accounted for 0.5% of the global burden of disease,[22] and appreciation for epilepsy as a public health problem is growing as the full range of medical, psychological, social, and economic morbidities associated with the condition are being recognized and quantified.[20] Use of such measures as the disability-adjusted life year (DALY) to more fully capture the burden of nonfatal, chronic diseases has played an important role in placing epilepsy on the public health agenda in many regions. Of the approximately 50 million people with epilepsy, over 80% reside in developing countries, and less than 10% of these individuals are receiving treatment.[30] A very productive collaboration, The Global Campaign Against Epilepsy, has evolved between the World Health Organization (WHO), International Bureau for Epilepsy (IBE), and the International League Against Epilepsy (ILAE).[14] This consortium's work is aimed at reducing the treatment gap, decreasing the social and physical burden of epilepsy, educating health care personnel, dispelling stigma, and providing support for prevention of epilepsy. These efforts are laudable, but these international efforts rely on individual health care providers working in developing countries to seek and/or accept the role of advocate and push forward the agenda of improving the lives of people epilepsy within their own community, city, country, or region.

No "how to" manual is available to describe the process whereby one would begin to improve epilepsy care for a population. Epilepsy texts typically provide advice on individual case management and sometimes provide guidance on the resources and organization necessary to develop an Epilepsy Surgery Center. Undoubtedly, there are many ways in which a motivated neurologist could approach such a mission, and the most appropriate tactics will vary greatly depending on the physicians' expertise, available time, the burden of disease he faces, the resources and organization of the existing health care system, the local beliefs surrounding epilepsy, and more. Nevertheless, it may prove useful for physicians who have the opportunity and inclination to provide epilepsy care in less developed regions to learn about experiences elsewhere.

The Chikankata Epilepsy Care Team (ECT), located in a rural region of Zambia's Southern Province, has been providing care to a large population of people with epilepsy since 2000. The ECT came into existence after efforts to understand the burden of epilepsy in the region in 1994 eventually resulted in local support (both community- and hospital-based) for the development of such a team. The ECT has since played a significant role in country-wide programs aimed at decreasing epilepsy-associated stigma and narrowing the treatment gap. This chapter provides an overview of our perspective on how care providers "in the trenches" might undertake efforts locally to improve epilepsy care, and goes on to describe the potential to expand such work to a national level under the right circumstances. We will also discuss other "success stories" we've encountered or learned about in the literature.

Barriers to Epilepsy Care in Less Developed Regions

Epilepsy care provision in less developed regions is negatively influenced by several factors (Table 1).

Barriers to care for people in less developed settings are complex, multifactorial, and depend on economic, social, and cultural factors usually considered outside the realm of medicine. Yet, failure to recognize and address these barriers in the organization of health services delivery as well as in the approach to individual patient care will doom any attempts one makes to provide care to such vulnerable populations.

Consider the role that local health beliefs may play in determining whether a person with epilepsy is *ever* brought to your attention for care. Given the often violent and entirely unpredictable nature of seizures, these events are frequently interpreted as the result of supernatural or spiritual forces. As such, even people who would seek care at a health center for a fever or cough may take their seizure-related problems to a traditional or evangelical healer. Health care providers, who may have little formal education and no training in epilepsy, may hold similar beliefs regarding seizures that occur outside of acute infections. Only educational programs aimed at first-line health care providers and case-finding endeavors in the community will overcome these problems.

Table 1 Barriers to Epilepsy Care Delivery in Less Developed Regions[25]

Barrier	Example
Health beliefs[4]	People with epilepsy and their families perceive seizures as a supernatural or spiritual problem and therefore care is sought from traditional or evangelical healers. Health care workers may hold supernatural or spiritual beliefs regarding the etiology of seizures.
Lack of available services[10,31]	Health care providers and facilities may be either geographically or financially unavailable to many people with epilepsy.
Health care worker limitations[6,10]	May have no training in the diagnosis and treatment of epilepsy. May not be allowed to prescribe anticonvulsants. May not have recourse to refer patients for physician-level care. May have only a few minutes to spend with each patient.
Lack of physicians	Too few physicians, with most in the private sector
Lack of diagnostic resources	No recourse to neuroimaging, EEG, or basic laboratory services.
Lack of treatment resources	Few treatment options if first-line medications fail or aren't tolerated. Even first-line agents may not be available in some regions.
Stigma[2]	Fear of drawing further attention to the seizures may result in an unwillingness to seek care. Health care workers may avoid providing care to people with epilepsy, given fears of stigma by association, particularly in regions where contagion beliefs regarding epilepsy care common.
Lack of social support[2,3,7]	Devalued persons with epilepsy may not have sufficient social supports to seek care consistently.

Even if someone wishes to seek medical care for their seizure disorder, medical services may not be accessible. Health care centers offering even first-line anticonvulsants may be either prohibitively expensive or too geographically distant from the person's home to be a feasible source of care. Primary health care centers, usually staffed with nonphysician care providers, are often supplied with only the most basic medications, so that even if the health care provider is able to diagnose the condition and knows what treatment is needed, the treatment may not be available. These barriers are only exacerbated by the continuing brain drain. Physicians from regions such as Africa are leaving developing regions in droves as a consequence of the poor working and social conditions in the home country and the wealthy, aging West's need for a larger pool of health care providers. Finally, epilepsy-associated stigma further may decimate the social capital of the person suffering from epilepsy, making it even more difficult for them to garner the community support needed to seek care. For example, women with epilepsy in Zambia often lack the usual male protector, having been largely abandoned by their families. Therefore, these women are particularly vulnerable to sexual assault if they travel alone. So, although most Zambian women can safely seek medical care alone or accompanied only by their children, this is not true for women with epilepsy, who need an adult to travel with them. The barriers to care listed in Table 1 are certainly not exhaustive, and each setting undoubtedly offers unique barriers. These can only be appreciated if one develops a dialogue with experienced, empathetic health care providers,

community leaders, and most of all people with epilepsy who are actively struggling with the barriers.

Data Gathering

Developing or expanding epilepsy care services requires careful planning and input from stakeholders in the health care system. As neurologists, we may simply assume this is a reasonable health care priority. However, this is not always a safe assumption. Recognize that any program must eventually be self-sustaining. And therefore, the program must have enough value to warrant eventual support within a system that is probably chronically underfunded and that encompasses many other competing health care needs. Eventually, any investment in epilepsy care entails a lost opportunity to invest in some other aspect of care. One must ask the key question: Is epilepsy a significant enough problem in this community, given the other health burdens present, to warrant long-term investment?

This is not a trivial question. But before taking the issue to key stakeholders, some objective data is required to assess the true burden of the disease in the population. The most obvious measure of the epilepsy burden in a population is the prevalence of epilepsy. Standard methods have been described that are ideal for epidemiologic purposes.[19] But the burden of epilepsy cannot be captured in a simple prevalence number. One must consider a far broader range of epilepsy-related morbidity and mortality to appreciate and express the full burden of disease (Table 2).

Formal studies to quantify the burden of disease may offer some academic currency and open doors to extramural funding opportunities. But even simple, hospital-based studies may offer data and insights into the burden of disease in a region sufficient to guide decision-making regarding resource allocation. For example, if your hospital has a busy burn center, consider a study to determine the proportion of burn victims who were burned during a seizure. If the number is substantial, then resources presently allocated to the burn center might be partially directed to epilepsy care, with the goal of burn preventions. Improving epilepsy care has been associated with a decrease in severe burns in some regions.

Table 2 Measures of Epilepsy Morbidity and Mortality

Aspect	Measure
Epidemiologic	Prevalence* Incidence Treatment gap
Health-related quality of life	KENQOL[27] SF-36[9] WHOQOL[23]

Functional status	DALY[11] Karnofsky score
Epilepsy-related physical morbidity	Burns Drowning Fractures
Social morbidity (largely mediated by stigma)	Loss of educational opportunities Loss of marital opportunities
Economic morbidity	Related to lack of education Incapacity to work due to social or physical disability

*Consider age-specific prevalence, given the impact of loss of work-related productivity in young adults.

Small, hospital-based studies can yield important information. In the Chikankata catchment area, anecdotal experiences suggested that a substantial burden of neurologic disease was going unrecognized even in the inpatient setting. By conducting a hospital-based, systematic period prevalence study (which had virtually no cost in addition to the time invested by a senior neurology resident), we were able to determine that 10% of hospital admissions were primarily related to a neurologic disorder, and that neurology patients consumed almost one-third of the intensive care unit bed-days.[5] These data allowed those of us interested in expanding neurologic services to capture the attention of hospital administration, which had previously considered neurologic diseases to be esoteric problems irrelevant

in a large rural bush hospital. Among all the conditions identified, epilepsy appeared to be one that was particularly under-recognized and undertreated. We were then able to leverage matching funds from the administration to conduct a door-to-door survey to determine the prevalence of epilepsy in the region. We found that, although our catchment area of 65,000 people had only 32 individuals with epilepsy registered at the hospital's chronic disease registry, more than 1,000 people with epilepsy eventually came forward for treatment.[8] This deluge of previously under-recognized disease treatable with medications generally available and by existing health care workers allowed us to establish local support for the development of an epilepsy care team.

Involving Key Stakeholders

If, after consideration of the full range of epilepsy-related morbidity and mortality in the region of interest, epilepsy appears to be a significant public health problem, further plans to develop or expand neurologic services should only be undertaken in consultation with relevant stakeholders. Only if individuals who are part of the health care system *and* potential recipients of services are part of the process of service development will those services be appropriate for the circumstances and environment. See Table 3 for considerations of who potential stakeholders might be; this is not a comprehensive list.

Table 3 Stakeholders to Consult when Developing Epilepsy Care Services

Entity	**Example**

Health care providers[16]	Physicians Clinical officers Nurses Community health workers Traditional birth attendants
Other healers[1,13]	Traditional healers Evangelical healers
Administrators	Hospital administrators Nursing directors Local representatives of the ministry of health Pharmacy directors Medical records personnel
Community leaders	Headmen Elected community representatives Elders Church leaders Respected businessmen or -women
People effected by epilepsy[21]	People with epilepsy Parents of children with epilepsy Family members of people with epilepsy
Other important social entities	Clerics Teachers Employers Police

The importance of persuading these stakeholders to guide the priorities of any evolving epilepsy care program cannot be overestimated. For any program to thrive in a sustainable fashion, many different groups must have a vested interest in the well-being of the program, and the program must be developed in a way that recognizes the most urgent problems at hand. A shared partnership with the community may entail delaying or even abandoning one's own academic interests (e.g., an EEG monitoring unit) for something recognized as more important from the community's perspective (e.g., a community-based care program). If an evolving program can offer what is most needed from the stakeholders' perspective, opportunities usually become available to pursue more academic interests, but these interests must be put in perspective. Even if outside funding is available to support the more academic and/or research-oriented questions, research programs that fail to take into consideration the needs of the community will eventually flounder and/or engender suspicion and animosity in the community under study.

Traditional healers are perhaps one of the most critical groups of stakeholders frequently ignored when health system planning is undertaken in developing countries.[1] Historically, the relationship between traditional healers and physicians has been one of animosity and criticism. However, traditional healers play an important social role, even if their treatments offer little therapeutic benefit (and that has not been formally studied in most instances). In developing regions, physicians and traditional healers witness each others' iatrogenic complications and failures on an almost daily basis. Given that most people with epilepsy in developing countries seek care from healers at least initially and often exclusively, we must work to develop more interactive and collaborative relationships with these care providers if we wish to reduce the treatment gap in areas with the greatest need.

As physicians, most of us have received little training and have even less experience in developing working relationships with such a diverse group of individuals. This is doubly compounded if the physician in question is an expatriate or non-native health care provider. Serious consideration should be given to soliciting assistance from more experienced individuals. Consider the value of involving a sociologist, anthropologist, or health services researcher as you engage key stakeholders. Good intentions for meaningful exchange can be entirely lost if the venue or circumstance for a meeting inadvertently offend or imply a lack of respect for those involved. There may be reasons to meet with some stakeholders separately. And the

need to avoid proselytizing is critical. The goal is not to convince stakeholders of your perspective, but to gather theirs.

Care Plans

Once health care delivery priorities have been established in a region, one must consider how to deliver those services. This entails consideration of the actual plan for health care providers' interactions with patients as well as developing algorithms for individual care plans. In resource-limited settings, it is neither feasible nor desirable to anticipate that epilepsy care will be primarily provided by a neurologist. It may not even be possible to expect physician-level input into epilepsy care for the vast majority of patients. The skill and training level of the care provider who will diagnose and then provide chronic treatment to people with epilepsy must be determined by the existing capacity of the health care system. It is essential element to assure that health care providers who are likely to initially encounter people with epilepsy and/or people with epilepsy-related injuries are capable of recognizing the condition when they encounter it. Whether these individuals then go on to treat the condition or refer to someone with more expertise will depend on the geographic and fiscal feasibility of such a referral system. Initial programs for expanding epilepsy care may need to focus on expanding the diagnostic skills of health care providers on the front line and streamlining the referral process when they encounter someone with epilepsy.[12,18,24,26,28,30]

Once stable treatment regimens are established for patients, their care should be transferred back to the health care provider most financially and geographically accessible to them, if they are to be expected to maintain adherence to drug therapy over the long term. Clear, written communications to the health care provider who will assume care of the patient is critical. Epilepsy educational materials for physicians and clinical officers in developing regions are available at low-cost through several routes.[15,17]

Although algorithms for health care provision are not popular in much of the developed world, such clearly delineated and simplified care plans are often critical for health care provision in developing regions, where resources and health care expertise are limited. As much as possible, such epilepsy care algorithms should be evidence-based. When an evidence-base is lacking, expert opinion should be acquired. Ideally, an expert panel should be consulted if an epilepsy care algorithms is being developed that will be applied to a large population. E-mail and Internet access have improved substantially in the past few years, and establishing such an expert panel may now be possible with a minimum of fiscal resources. One must not neglect the importance of including local experts who function within the health care system of interest. Critical aspects of routine nursing and pharmacy practices may be inadvertently ignored if only outside opinions are sought. Key stakeholders (purchasers of medications for the public health care system, hospital administration) must also be included in this process.

Many developing regions may only be able to offer phenobarbitone to the majority of people with epilepsy. If second-line agents are not routinely available, some rational process should be put into place to determine criteria whereby people are placed on second-line agents. Inevitably, a two-tiered system will be in place in most health care systems in which people with resources can purchase drugs within the private sector. But within the public health system, medical criteria should determine the allocation of drugs with limited availability. Predetermined criteria for placing patients on a second- or third-line agent will assist health care providers in decision-making and assure some social equity. Unfortunately, within the private sector, inappropriate utilization of complex drug regimens may be unavoidable.[29]

Table 4 Potential Sources for Additional Revenues and Resources

Source	Approach
Clinical revenues	An allocated day or half-day for private-pay patients, with revenues directed to the upgrade of clinical service.
Churches or philanthropies in wealthier countries	Fundraising when you are abroad or encouraging visitors who become familiar with your operation to do the same on returning

	home
Local businesses	Approach local businesses for support.
Educational grants	Seek funding through educational grants: www.cos.com www.grantsnet.com www.WFNeurology.org
Research grants	Seek funding through research grants: www.cos.com www.grantsnet.com www.wellcome.ac.uk www.nih.gov
International collaborations	Contact researchers conducting studies of interest to you: www.ilae.epilepsy.org www.ibe-epilepsy.org

Acquiring Resources

Developing, enhancing, or expanding neurologic service in a less developed environment goes beyond simply working as a clinician in a one-on-one patient interaction. Services must include clinical care, infrastructural development of the health system, efforts at outreach, education for health care providers and the lay public, and research. Because the limited budgets of developing countries cannot even sustain the essentials for basic care, optimal expansion of neurologic services will require accessing resources beyond those available through public health funds, although partnership with the appropriate health authorities and appropriate allocations for neurologic disorders should be sought. Many options for accessing additional resources exist for those keen clinicians and/or administrator willing to explore these routes (Table 4).

Developing relationships with clinicians and organizations outside your own region or country can serve as a great source of intellectual stimulation and often results in productive collaborations that benefit both parties. Clinicians from developed regions with an interest in working in less developed regions often struggle to make appropriate contacts and identify opportunities to offer their services. The same is true of researchers. Fostering these relationships at every level will help to build bridges that can lead to future opportunities for expanding neurologic care.

In terms of accessing resources for a growing epilepsy care program, consider clinical revenue streams. Where neurologic expertise is limited and concentrated in academic medical centers, private patients are often willing to pay substantial sums to avoid long waits and queues. Although such services shouldn't be offered to the extent that it is detrimental to publicly available services, setting aside some time for such private patients and applying the resulting revenues to care expansion is one option. Where civil servant salaries are quite low, academic specialists may already provide private services to augment their own salaries to a reasonable level. Consider then that visiting volunteer specialists who do not have work permits might be able to provide services in exchange for donations or other services. Or, possibly, such visitors may assist in the established private clinics, with the additional revenues being directed to expansion of epilepsy care services.

Visiting clinicians and interested individuals who become familiar with your program's goals may also serve as fundraisers and advocates. Developing a simple printed brochure that outlines your activities, goals, and fund-raiser campaign and that can be given out freely may help encapsulate your work in a marketable way. Such materials may even be provided to private patients and representatives of local businesses with philanthropic tendencies.

Funding opportunities for educational and research programs can serve as an important source of revenue for building infrastructure, hiring staff, and purchasing equipment. If one has Internet access, several search engines are quite helpful at identifying potential funding sources. Also, make certain to make inquiries to your local, regional and national medical programs. If you do not have experience writing proposals, this may be another opportunity for collaborations with international colleagues. For example, if you read an article describing research that interests you, consider contacting the investigators. Contact information, usually including an e-mail address, is provided in most journal articles. Never doubt that your expertise, experience, interests, and environment offer a great deal to potential collaborators.

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Summary and Conclusions

The global burden of epilepsy is concentrated in resources poor regions with limited healthcare services. Substantial socioeconomic issues impact the quality of care and quality of life for people with epilepsy, particularly in developing regions. To improve epilepsy care delivery, it is imperative to understand the barriers to care delivery and care-seeking in the local environments and develop pragmatic approaches to overcoming these barriers. Accessing resources for optimizing care can be facilitated by acquiring data regarding the magnitude and consequences of epilepsy as well as the potential cost-effectiveness of treatment. Data dissemination and education of policy makers is paramount. Collaborative partnerships to develop local priorities for care and research require meaningful exchange between clinicians, researchers and key stakeholders. For successful and sustainable programs, community representatives must be included in such endeavors. Unique partnerships between clinicians and scientists in developed and less developed regions will be required to tackle the global problem of epilepsy in resource-poor regions where ~80% of people with epilepsy reside.

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Chapter 301

Comparison of Different Systems and the Burden of Epilepsy

Matilde Leonardi
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Introduction

The aim of this chapter is to compare information and data collected on epilepsy around the world and to find a means of comparing them so as to produce indications for further work.

Several authors in the preceding chapters have highlighted the national situation on epilepsy and epilepsy care. However, despite differences, it is important to define ways to overcome these discrepancies and to note the advancement of care and research that could enhance the care of people with epilepsy worldwide.

The past 10 years have been important for progress in epilepsy care, and many initiatives and much research have contributed to raise a lot of attention on the burden of epilepsy.

The Main Pillars for Change in the Field of Epilepsy

Although some traditional epidemiologic data reported in the chapters in this section do not show major changes in epilepsy course, several factors are contributing to change in the care and course of epilepsy worldwide. The main pillars for change could be identified in the following factors: (a) the Global Burden of Disease study and all the research done in the field of summary measures of the population's health; (b) the World Health Organization (WHO), International Bureau for Epilepsy (IBE), and International League Against Epilepsy (ILAE) Campaign on Epilepsy, with the publication of detailed information in the WHO Atlas on Epilepsy in 2005; (c) the publication of the International Classification of Functioning, Disability, and Health (ICF) classification in 2001 and the shift from diagnosis alone to functioning and disability approach to health; and (d) the increasing attention on innovative methodologies to collect information for policy decision making. All these factors will be analyzed here so as to provide a means for future work at the country as well at international level.

The Burden of Epilepsy and the Global Burden of Disease

The Global Burden of Disease (GBD) 2000 study was carried out by the World Bank in collaboration with the WHO and the Harvard School of Public Health. Three main goals were addressed: To provide information about nonfatal health outcomes, to develop unbiased epidemiologic assessment for major disorders, and to quantify the burden of diseases with a measure that could also be used for cost-effectiveness analysis. The GBS study provided the true magnitude of the long underestimated impact of neurologic disorders. With mortality indicators alone, mental and neurologic disorders have never been ranked in the top ten priority list of public health significance. Demographic changes and epidemiologic transition, as well as changes in family structure, are projecting the burden due to neurologic and psychiatric disorders to increase up to 15% of the global disease burden.[15]

There is a growing need to combine information on mortality and nonfatal health outcomes to represent the health of a population that reflects health expectancies and health gaps. Summary health measures can be used for comparing the health status of different populations and health of populations at different points of time, and for balancing priorities between fatal and nonfatal outcomes. These are measures that combine information on mortality and nonfatal health outcomes to represent the health of a particular population as a single number. The GBD study provided the DALY (Disability Adjusted Life Year), a measure that added disability to mortality in the evaluation of the burden of diseases. The allocation of limited resources for health care should be based on the relative importance (or burden) of different conditions to the health of the nation. Mortality as major public health indicator has had the effect of limiting the attention given to highly prevalent, seriously disabling but nonfatal disorders. Use of traditional measurement methods has led, in fact, to a serious underestimation of the relative importance of neurologic disorders worldwide, because they rarely cause death and because several of them produce severe and long-term disability but not death. The number of deaths does not take into consideration the nonfatal outcome of illness, and prevalence rates do not take into consideration the severity and duration of disability produced by a disease. There is also increasing attention being given to the shift from communicable diseases to chronic, noncommunicable diseases: The so-called "epidemiologic transition," which is also related to the increase of life expectancy.

Diagnosis alone does not predict service needs, length of hospitalization, level of care, or functional outcomes. The occurrence of a disorder is not an accurate predictor of receipt of disability benefits, work performance, return to work, or likelihood of social integration. This means that if we use a medical classification of diagnosis alone (e.g., the International Classification of Diseases [ICD]) or the ILAE classification, we will not have the information we need for health planning and management purposes. Neurologic disorders contribute substantially to the overall disease burden of developed and developing societies, but this is generally underestimated by the public health community.[27]

Epilepsy is one of the most common serious disorders of the brain, affecting about 50 million people worldwide. Epilepsy accounts for 1% of the global burden of disease; 80% of the burden of epilepsy is in the developing world, where in some areas 80% to 90% of people with epilepsy receive no treatment at all.[30] It is clear that epilepsy is a major public health problem and that it is important to assess its burden as well its cost to persons and to societies so that health care priorities can be set in a rational way. To highlight differences, we analyzed common epidemiologic data as also reported in previous chapters and through literature assessment.

As stated in *Epilepsy: Out of the Shadows* background booklet, "The suffering and the disability caused by the disease are physical and psychosocial, is bringing a huge burden to people with epilepsy, their families and society at large."[9]

The burden of epilepsy is also strongly associated with significant psychological and social consequences for everyday living. This has been clearly highlighted in the previous chapters of this section. People with hidden disabilities such as epilepsy are among the most vulnerable in any society. While their vulnerability may be partly attributed to the disorder itself, the particular stigma associated with epilepsy brings a susceptibility of its own. Stigmatization leads to discrimination, and people with epilepsy experience prejudicial and discriminatory behavior in many spheres of life and across many cultures.[31]

People with epilepsy experience violations and restrictions of both their civil and human rights. Civil rights violations, such as unequal access to health and life insurance or prejudicial weighting of health insurance provisions; withholding of the right to obtain a driving licence; and limitations to the right to enter particular occupations, certain legal agreements, and in some parts of the world even marriage, are severely aggravated by epilepsy. Discrimination against people with epilepsy in the workplace and in respect of access is not uncommon for many. Violations of human rights are often more subtle and include social ostracism, being overlooked for promotion at work, and denial of the right to participate in many of the social activities taken for granted by others in the community. For example, ineligibility for a driving licence frequently imposes restrictions on social participation and choice of employment.[31]

The World Health Organization–International Bureau for Epilepsy–International League Against Epilepsy Global Campaign Against Epilepsy

The problems related to provision of care and treatment of people with epilepsy are too complex to be solved by individual organizations; therefore, the three leading international organizations working in the field of epilepsy (the WHO, IBE, and ILAE) joined forces to create the Global Campaign Against Epilepsy. The campaign aims to provide better information about epilepsy and its consequences and to assist governments and those concerned with epilepsy to reduce the burden of the disorders. More than 90 countries worldwide have been involved in the campaign.[31]

Regional conferences have been organized in all WHO regions to raise awareness on the public health impact of epilepsy, and a questionnaire was developed in order to make an inventory of country resources for epilepsy worldwide. Regional reports were developed and the main result of this effort was the publication in 2005 of the *Atlas of Epilepsy Care in the World*. The Global Campaign also had some demonstration projects that consisted of assisting countries in the development of their national epilepsy programs. Much of the information about data comparability on epilepsy has been collected in the *Atlas,* and this chapter summarizes some of the main results.[30] This initiative and its results could be considered another pillar to analyze information on epilepsy from different countries in a different way. The results of the WHO/IBE/ILAE Campaign allow a detailed evaluation of differences between developed and developing countries in several epilepsy indicators.

Comparison of Different Systems: Underlying Factors for Regional Differences and Salient Findings

Epidemiologic indicators needed to construct the diagram of each disease are several and can be listed as prevalence, incidence, mean age of onset, course, natural history, duration, severity breakdown, mortality, and impact of treatment. These indicators are the starting point for data comparison as well as for highlighting information gaps. Salient findings on incidence, prevalence, treatment gap, and socioeconomic data are reported in this chapter as they are crucial to highlighting country differences in the field of epilepsy. While data on incidence, prevalence, and treatment gap are available in several publications and are also reported in this section in detail, it is important to also report here some of the data that have been recently published in the WHO *Atlas*[30] that cover a broader spectrum of items and that are a useful indicator of epilepsy burden and care worldwide.

The Prevalence of Epilepsy

The number of people with epilepsy is high in most regions of the world, and 43,704,000 people with epilepsy are reported from 108 countries covering 85.4% of the world population. The mean number of people with epilepsy varies across regions: The prevalence per 1,000 population is 8.93 from 105 responding countries. It is 12.59 and 11.29 in the Americas and Africa, respectively, 9.97 in WHO South East Asia, 9.4 in the Eastern Mediterranean, 8.23 in Europe, and 3.66 in the Western Pacific.[30] The mean number of people with epilepsy per 1,000 population ranges from 7.99 in the high-income countries to 9.5 in the low-income countries.[6,7] The overall prevalence of epilepsy ranges from 2.7 to 41 per 1,000 population, though in the majority of reports the rate of active epilepsy is in the range 4 to 8 per 1,000.[8] The prevalence of active epilepsy is generally lower in industrialized countries than in developing countries, which may reflect a lower prevalence of selected risk factors. In industrialized countries, the prevalence of epilepsy is lower in infancy and tends to increase thereafter, with the highest rate occurring in elderly people.[8] Where available, age-specific prevalence rates of lifetime and active epilepsy from developing countries tend to be higher in the second (254 vs. 148 per 1,000) and third decades of life (94 vs. 145 per 1,000).[1] The differences between industrialized and developing countries may be mostly explained by the differing distribution of the risk factors and by the shorter life expectancy in the latter. Prevalence of epilepsy, as incidence, tends to be higher in men. Socioeconomic background has been found to affect the frequency of epilepsy reports in both industrialized and developing countries, in which prevalence rates have been shown to be greater in the rural compared with the urban context or in the lower compared with the higher socioeconomic classes.[17]

The Incidence of Epilepsy

The annual incidence of unprovoked seizure is 33 to 198 per 100,000, and the incidence of epilepsy is 23 to 190 per

100,000.[10] The overall incidence of epilepsy in Europe and North America ranges from 24 and 53 per 100,000 per year, respectively. In studies from Africa and South America, the peak incidence of epilepsy occurs in young adults, and the dramatic increase in incidence in the elderly has not been identified. It's similar to the patterns of incidence, and therefore risks for epilepsy are different in these populations.

The incidence in children is eventually higher and even more variable, ranging from 25 to 840 per 100,000 per year, most of the differences being explained by the differing populations at risk and by the study design. In developing countries, the incidence of the disease is higher than that in industrialized countries and is up to 190 per 100,000 (the higher incidence of epilepsy may also be explained by the different structure of the populations at risk, which is characterized by a predominant distribution of young individuals and a short life expectancy).

In industrialized countries, epilepsy tends to affect mostly the individuals at the two extremes of the age spectrum. The peak in the elderly is not detected in developing countries, where the disease peaks in the 10- to 20-year-old age group.[1] The incidence of epilepsy and unprovoked seizure has been reported to be higher in men than in women in both industrialized and developing countries.[30]

The incidence of epilepsy is higher in the lower socioeconomic classes. This assumption is supported by the comparison between industrialized and developing countries and by the comparison, within the same population, of people of different ethnic origin.[21]

Several recent studies provide incidence from developing countries. An incidence of epilepsy that is considerably higher than that reported in industrialized countries (114 per 100,000 person-years) has been reported from rural area of Chile.[11] A study in Tanzania reported the incidence of epilepsy to be 77 per 100,000. These data are three times the incidence reported in industrialized countries in which similar definitions have been used.[18] In studies in France and Rochester, Minnesota, at least half of newly occurring afebrile seizures do not fulfil criteria for epilepsy. Nonetheless, the incidence of epilepsy may likely be higher in developing countries then in industrialized countries.[8]

Treatment of Epilepsy: Gaps and Services

Worldwide, the proportion of patients with epilepsy who at any given time remain untreated is large, and is greater than 80% in most low-income countries.[19]

The size of this treatment gap reflects either a failure to identify cases or a failure to deliver treatment. In most situations, however, both factors will apply. Inadequate case finding and treatment have various causes, some of which are specific to low-income countries. They include people's attitudes and beliefs, government health policies and priorities (or the lack of them), treatment costs and drug availability, and the attitude, knowledge, and practice of health workers.[31]

Although most epileptic syndromes cannot be prevented, epilepsy can be treated effectively in the majority of cases. The most common treatment is medication, but brain surgery and, very rarely, vagal nerve stimulation may be used as alternatives in some patients failing to achieve seizure control by medication.[4] Therapeutic drug monitoring is available in 45.1% in Africa, 54.6% in the Western Pacific, 55.6% in WHO South East Asia, 85.7% in the Eastern Mediterranean, 93.3% in Europe, and 95.8% in the Americas. Neuropsychological services are available in 37% of low-income countries. Such facilities are present in 88.6% of high-income countries.[30] In developing countries there is often also limited access to antiepileptic drugs (AEDs), particularly new AEDs; irregular supply of drugs; and poor access to investigations such as electroencephalographic (EEG), computed tomography (CT) brain scan, magnetic resonance imaging (MRI), therapeutic drug monitoring, long-term video-EEG monitoring, and single photon emission computed tomography (SPECT). The patients often have to pay for the medications and investigations out of pocket, which can be astronomical when compare with the family income.

There is also a relative lack of use of epilepsy surgery. In 25% to 30% of people with epilepsy the seizure cannot be controlled with drugs. Epilepsy surgery is a safe and effective alternative treatment in selected cases. Investment in epilepsy surgery centers, even in the poorest regions, could greatly reduce the economic and human burden of epilepsy. There is a marked treatment gap with respect to epilepsy surgery, however, even in industrialized countries. In a survey of epilepsy surgery in Asia, 80% of surgery was done in Japan and South Korea, although the two countries account for less than 10% of the Asian populations surveyed.[12]

Epilepsy surgery is not available in 88.6% in Africa, 68.2% in the Western Pacific, 66.7% in WHO South East Asia, 50% in the Americas and the Eastern Mediterranean, and 33.3% in Europe. Epilepsy surgery is not available in 87% of low-income countries. The facility for epilepsy surgery is also absent in 34.3% of high-income countries.[30]

Epilepsy Care and Health Professionals

It is difficult to quantify the number of medical professionals involved predominantly in epilepsy care. The figures reported in WHO's *Atlas* are based on best estimates by the respondents. Information about the distribution of the medical professionals in countries is not available, but the majority is likely to be concentrated in urban areas. The median number of neurologic nurses per 1,000,000 population in Europe involved in epilepsy care is 0.7 for low-income countries; it is 1.7 for higher middle-income and 1.1% for high-income countries. The median number of neurologic nurses per 1,000,000 population is 1.9 in Europe and 0.3 in WHO South East Asia.

No facility for training in epileptology exists in countries in WHO South East Asia, while such facilities exists in only 2.6% of the countries in Africa, 6.7% in the Eastern Mediterranean, 17.4% in the Western Pacific, 20.8% in the Americas, and 31.8% in Europe. Few studies report the number of health professionals devoted to epilepsy in many of the developing countries. As is the case in Nigeria, the primary care is manned by medical assistants who do not have the medications or skills in managing epilepsy. At the tertiary care level, there is scarcity of neurologists, even more so pediatric neurologists, and epileptologists. This is worse for regions outside the big cities and for public patients. For example, there are only 25 neurologists and 10 neurosurgeons in Nigeria, with 128 million people (see Chapter 295). All 15 neurologists practicing in the public health sector in Senegal, with 12 million people, are in the capital city of Dakar (see Chapter 297). In India, only 10% of the medical workers are employed by the government.[16] The lack of trained specialists and medical facilities needs to be seen in the context of severe deficiencies in health delivery that apply not only to epilepsy, but also to the whole range of medical conditions. Training medical and paramedical personnel and providing the necessary investigatory and treatment facilities will require tremendous effort and financial expenditures and will take time to achieve. A lack of involvement of paramedical professionals such as neuropsychologists, specialist nurses, occupational therapists, and educators in the care of epilepsy has also been noted in the epilepsy care of the East.[20] Nonscientific concepts of causes and treatment of epilepsy are common. For example, in Nigeria, dualist natural and supernatural terms to explain illness are prevalent, with traditional herbal remedy strongly preferred over conventional antiepileptic drugs in the rural areas (see Chapter 296). A significant proportion of countries does not have professional or patient-based epilepsy societies. Even when these are present, they are often limited to large urban centers. For example, a nationwide epilepsy society for both professionals and patients was formed in China only in 2005. With limited resources, research is of low priority, with limited data related to epilepsy.

Socioeconomic Burden and Costs of Epilepsy

The lack of uniformity in the available studies on the cost of illness of epilepsy makes it difficult to compare cost figures from different studies. Some findings, however, can be summarized.

Many socioeconomic factors underlie the differences in care of epilepsy between the developed and developing countries. A low level of general education and high illiteracy is seen in some developing countries. For example, in India, the national literacy rate in 2001 was 65.5%, and 54.3% for females (see Chapter 294). The limited government resources generally are made worse by medical care being considered low priority by some governments. For example, Indian state budgets allocate only 2.3% of their money to health care.[16] The per capita expenditure on health, family welfare, water supply, and sanitation during 2002 to 2007 is about U.S. $2.53 per year (see Chapter 294). As such, in many developing countries, the government-subsidized health care is limited to hospital bed stay and medical consultation. Medications, surgery, and investigations are borne by the patients directly. Various disability benefits enjoyed by the developed countries are also not available. Difficulties of transport and communication in the remote area posing problems to access to modern health care facilities are also common. Nongovernmental organizations that play a crucial role in public health and awareness raising are rare in many parts of the world.

These differences are reflected in many aspects of health care structure and management of epilepsy in developing countries. It is thus not surprising that a large treatment gap for epilepsy has been reported in many developing countries, particularly the rural areas, with a large number of undiagnosed and untreated patients. For example, the treatment gap for China was 63%.[24]

Economic assessments of the national burden of epilepsy have been conducted in a number of high-income countries[2] and in India, all of which have clearly shown the significant economic implications the disorder has in terms of health care service needs, premature mortality, and lost work productivity. The Indian study calculated that the total cost per case of these disease consequences for epilepsy amounted to U.S. $344 per year (equivalent to 88% of average income per capita) and the total cost for the estimated 5 million cases in India was equivalent to 0.5% of the gross national product.[23]

As part of a wider WHO cost-effectiveness work program,[22] information has been generated concerning the amount of burden averted by the current or scaled-up use of treatment with AEDs, together with estimates of cost and cost effectiveness. Effectiveness was expressed in terms of DALYs averted and costs were expressed in international dollars. Compared with a "do-nothing" scenario (i.e., the untreated natural history of epilepsy), results from nine developing epidemiologic subregions suggest that extending AED treatment coverage to 50% of primary epilepsy cases would avert 150 to 650 DALYs per million population (equivalent to 13% to 40% of the current burden), at an annual cost per case of international $55 to $192. Older first-line AEDs (phenobarbitone, phenytoin) were most cost effective on account of their similar efficacy but lower acquisition cost (International $800 to $2,000 for each DALY averted). In all nine developing regions, the cost of securing one extra healthy year of life was less than average per capita income. Extending coverage further to 80% or even 95% of the target population would evidently avert more of burden still, and would remain an efficient strategy despite the large-scale investment in manpower, training, and drug supply/distribution that would be required to implement such a program.[31]

In Europe, a separate budget for epilepsy care and services is present in only 6.4% of the responding countries. Private insurance and private foundations constitute only 1.9% and 1%, respectively, of the primary method of financing. While social insurance is the primary method of financing in 55.6% and 56% of higher middle-income and high-income countries, respectively, none of the low-income countries employs it as the primary method of financing. A study by Ekman and Forsgren on the cost of epilepsy in Europe allowed one to see regional differences and provided an estimate of the economic burden of epilepsy.[4]

Functioning and Disability in Epilepsy and the International Classification of Functioning, Disability, and Health Classification

As shown, the knowledge about prevalence, incidence, socio-economic burden, and prognosis of epilepsy is still limited because of the methodologic weakness of many studies. Data on epilepsy, as well as on several other neuropsychiatric disorders, are still scarce in many parts of the world and inconsistent because of the sampling frames and how samples are defined.

Uncertainty about the prevalence distribution as well as about the variation of severity of epilepsy reflects the limitation of instruments for classifying it in a comparable manner across populations and the limitations in the information available to classify, beyond the diagnostic classification, the severity and, mostly, the disability of the disorder.[15]

Up-to-date international comparable data about functioning and disability are simply not available. The primary reason for this is that different countries, for different purposes, define disability differently. As a recent European Commission study on definition of disability in Europe has shown, data on disability are not consistently gathered because some countries define disability in terms of performance levels in employment or other social activities. In the employment sector specifically, for example, coordinated policy across Europe has been undermined by the inability to collect comparable data about rates of disability and employment.[5] As a rule, disability population surveys focus on a limited number of functional domains (e.g., activities of daily living [ADLs]) and ask questions about a limited number of impairments, making it difficult to identify new and emerging populations of persons with disabilities, such as, for example, those associated with HIV, depression, and substance use disorders. Furthermore, often a priori and arbitrary thresholds for identifying impairments are provided, without any evidence of prevalence levels. Finally, disability surveys ask questions that are not easily or directly linked to data from population health surveys, so there is no obvious way of linking health conditions, such as diseases or injuries, to impairments, nor to identify the role of environmental factors in limiting, or expanding, levels of participation across the range of normal activities. It is clear that at the moment, it is almost impossible

to evaluate the impact of either demographic changes (such as aging) or social change (such as new legislation, policy change, or changes in lifestyles) on disability.[13]

Though there are international disability data gathering efforts by OECD and UNSTAT, these efforts merely reproduce the same wide disparity in the prevalence rates of disability across countries and regions, created by a lack of a common framework and methodology for defining disability.

The WHO has for several years been aware of this widespread problem of data comparability both in health and disability statistics. Following its mandate for producing standards for international data comparability in the health area, the WHO began as early as 1974 to supplement its ICD International Statistical Classification of Diseases and Related Health Problems[26] with a companion classification of functioning and disability, the International Classification of Impairments, Disability, and Handicap (ICIDH).[25] This classification underwent a revision process that lasted several years. After extensive international field testing, the final version of the International Classification of Functioning, Disability, and Health was endorsed by the World Health Assembly in May 2001. The World Health Organization's ICF has been accepted by 191 countries as the international standard to describe and measure health and disability.[29] The ICF is the product of decades of research, refinement, and testing in an international collaborative setting. Both as a model for structuring health and disability information and as a classification and coding tool for collecting this information, ICF fills the gap in our understanding of disability and its dimensions, causes, and prevalence.

The International Statistical Classification of Diseases and Related Health Problems (ICD-10) and the ICF are the two classifications that currently make up the WHO Family of International Classifications (WHO-FIC).

In the evaluation of differences between countries in the field of epilepsy, the presence of the ICF could be considered as a crucial pillar for a change in perspective. The methodology that ICF proposes to overcome data gaps in epilepsy is a shift from diagnosis alone to functioning and disability.

Disability is a multidimensional phenomenon arising out of an interaction between the individual's health status and the physical and social environment. Disability data, and the instruments to measure them, must reflect this biopsychosocial model of disability. Valid and reliable information are essential to design, implement, or evaluate policies and legislation to combat discrimination and promote social integration and participation and to enhance opportunities.

Data currently being collected, nationally and internationally, embody conceptual confusions, inconsistencies, and ambiguities about disability and the relationship between health conditions, impairments, and environmental factors. What we lack is the knowledge about the level of functioning and disability. The ICF provides the framework for documenting the interaction between health status and environmental features, and the differential distribution of disability among different groups in different contexts.

There is no better conceptual model for the measurement of the types and prevalence of impairments that offers a holistic conception of disability suitable for data collection, clinical measurement, and social policy. Using the ICF framework, the WHO estimates that as much as 500 million healthy life years are lost each year due to disability associated with health conditions. This is more than half the years that are lost annually due to premature death. The ICF provides a common measure about this immense problem and makes possible to collect those vital data in a consistent and internationally comparable manner.

ICF defines disability as “difficulty in functioning at the body, person or societal levels, in one or more life domains, as experienced by an individual with a health condition in interaction with contextual factors.” The ICF definition is inclusive of all aspects of disability, captures the interactive dynamic of disability, and acknowledges the equally important contribution of health conditions and environmental factors to disability. In fact, the ICF provides the framework for documenting the interaction between health status and environmental features, and therefore the differential distribution of disability among different groups in different contexts.[13]

This definition includes all aspects of disability, highlights the interactive dynamic nature of disability, and acknowledges the equally important roles of the person's state of health and environmental factors in the production and mediation of the disability experience.

The model described in the ICF will assist in the prediction and understanding of changes in the prevalence and differential distribution of impairments; assess the impact of social, political, demographic, cultural, and environmental factors in the production of disability; and support policy developments for achieving an improved quality of life and equal opportunities for people with disabilities.

Since its endorsement by the World Health Assembly in 2001, the ICF has been applied in a variety of settings at the national and international level and has been translated into 40 languages. ICF-based health and disability surveys have been conducted in many countries worldwide. From these data, population norms can be generated for estimating disability prevalence. At a national level, ICF0-based data sets and questionnaires for census and surveys are being used by numerous countries including Spain, Australia, Canada, Chile, China, Indonesia, Namibia, Nicaragua, and South Africa. Several countries have started the process of streamlining their health and social information standards and legislation within the ICF framework. Development and piloting of ICF-based indicators and reporting systems for use in rehabilitation, home care, age care, and disability evaluation are ongoing in Germany, Italy, Sweden, the Netherlands, the United Kingdom, Australia, Canada, Colombia, India, Mexico, and the United States.

The ICF sets out an internationally comparable language of all dimensions of human functioning at the *body, person, and societal levels*. Difficulties of functioning at the body level, or impairments, can therefore be conceptually and operationally distinguished from difficulties of functioning at the person or societal levels (activity limitations and participation restrictions). The ICF's model of disability is interactive—combining the best of the so-called medical and social models into a fully integrated model. The ICF also contains a classification of environmental factors, that is, the physical, social, and attitudinal factors that, as barriers, contribute to the creation of impairments, activity limitations, and participation restrictions, or as facilitators increase or extend levels of functioning at the body, person, or societal levels. The classification of environmental factors makes it possible, for the first time, to identify, assess, and measure the impact of a person's environment on his or her levels of disability. The underlying theory of the ICF is based on two important principles that directly affect measurement strategies:

1. The principle that disability is a common, indeed universal feature of the human condition, not the mark of a social minority group (universalism)
2. Functioning and disability, both at the population and individual levels, are *continuous* phenomena, matters of “more or less” rather than strict dichotomous categories

Taken together, these principles entail that the measurement of disability must arise from a determination of the range of functioning across all domains, rather than a priori from either self-identification or by allocation into categories merely by the presence of certain bodily impairments such as blindness, deafness, mental retardation, or paralysis.

In the ICF Environmental Factors classification, all discriminatory behaviors and attitudes are included, making it possible for the first time to include questions in surveys and other information-gathering instruments on environmental barriers and facilitators using a common framework that will then make data comparisons more feasible and practical. This might be very relevant for epilepsy because, as previously reported, stigma is still a major issue both in developed and developing countries.

These data can then be compared across countries, populations, and age groups. In addition, the effects of these behaviors and attitudes on individuals' levels of participation can be measured and interventions designed.

Policy Makers and Epilepsy

As stated in the previous edition of this book, although the political, economic, and social changes that are occurring globally take many different forms, and although rapid changes in health care delivery are under way in many countries, there is clearly a convergence of ideas toward the fact that health care is part of the glue that holds each society and the international community together, a social good that should be available to all people on the basis of needs.[14] There is a strong interest among policy makers in monitoring the impact of health care measures, reforms, and other interventions by using common cost-effective measures.

The information that health and disability policy makers require—for developing summary measures and other analytic tools for measuring health, which in turn assist in the tasks of proposing and implementing policies and monitoring the performance of policies for subsequent revision—cover at least the following range of data points: Basic prevalence data about diseases and injuries; data about impairments and capacity levels associated with health conditions; data about actual performance levels; data about the presence of environmental barriers and facilitators (as defined and classified in the ICF), and the extent to which these affect observed performance levels.

All these diverse data could not possibly be collected in a single survey or questionnaire, or at least one that could feasibly be put into the field. More plausibly, one can imagine a range of surveys—both on health issues but also on broader social issues such as health determinants, employment, and other social factors—that are coordinated by a common conception of health and disability, and that altogether could collect a substantial portion of these data. Of course, for most countries of the world, even this approach is far beyond available resources. This is leading, then, to the question that is the object of this chapter: What is the state of the art of collecting basic information about epilepsy, the prevalence of its impairments, and their relationship to health outcomes (however construed) on the one hand, and the burden and quality-of-life assessments on the other hand? The interest here has been not merely in listing only what has been done to date, but, more generally, in highlighting the underlying concepts used and the unresolved issues that researchers have faced, either successfully or not, and are facing.

Differences between developed and developing countries are still large; however, there is an increasing recognition that reducing the incidence and severity of disability due to a disease in the population involves modifying the social and physical environment as well as enhancing the level of functioning of the person.

Designed to meet these growing needs, the ICF has potential uses in many sectors, and it is expected that in the future functioning data might allow a better comparison between countries on the burden of the disease and might serve the needs of policy making to improve the quality of life of people with epilepsy worldwide.[15]

Summary and Conclusions

This chapter summarized some of the salient findings developed in recent years that allow one to move toward new features in data comparison on epilepsy. Disability data, recently published in the Global Burden of Disease study, allow broader comparability in epilepsy, due to the characteristics of the disease. Traditional epidemiologic information has been supported by a full range of data that are useful for policy development.

The WHO/IBE/ILAE Global Campaign focused on the importance of awareness for filling the gap between developed and developing countries and provided the international community with the *Atlas on Epilepsy* that is showing the path for further work and research.

Finally, after the publication in 2001 of the ICF, it became clear that information about the levels of functioning across all areas of life is essential data for policy purposes. Medical diagnostic data alone do not predict health service needs, length of hospitalization, or level of care required, and the presence of a disease is not an accurate predictor of receipt of disability benefits, work performance, return to work potential, or likelihood of social integration or any other important goal for disability policy that is based on human rights. What is missing are data about the full, lived experience of health, which includes functioning and disability.

Intervention costing, in terms of outlines defined by levels of functioning, will in turn open the door to protocols for comparing the cost-effectiveness of interventions aimed at the individuals (medication, rehabilitation, training) as opposed to those aimed at the environment (e.g., normative, architectural, accessibility, fighting stigma).

One of the most difficult, yet most important, decisions in all areas of disability policy is whether resources are better spent in increasing the functioning levels of the person or in making the environment more accessible and accommodating. In a sense, all of disability policy depends on this incredibly difficult decision. Without reliable and relevant data, however, these decisions are not based on evidence. The overall human rights goals of equality and full participation are not served, and never will be served, without this information. In this sense, the ICF is the most important of all human rights instruments for persons with disabilities.

The ICF in the field of epilepsy can therefore be used to capture and structure holistic and multidimensional data about human functioning for a wide variety of uses, including population surveys, administrative data collection, and clinical assessment. Properly used, it can help us to understand the relationship between impairments and environmental factors that together determine levels of participation in education, employment, and all areas of social involvement.

Only when disability data are collected at the population level in terms of the ICF model of disability will this evidence be available. It is only then that data collected will be relevant to the relationship between environmental, political, social, and cultural factors and the occurrence of impairments. This is a clear indication for future new research in the field of epilepsy.

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Chapter 302

Comprehensive Epilepsy Programs—United States

Robert J. Gumnit

Introduction

The difference between a specialty epilepsy clinic and a comprehensive epilepsy program (CEP) is highlighted in this section. CEPs are different from epilepsy centers. Epilepsy centers can be places for the long-term residential treatment of people with seizures, or they can be places where a patient goes for specialized treatment. Specialized centers for the long-term care of people with epilepsy have essentially disappeared from the United States. When patients with epilepsy require long-term care, it is usually because of associated conditions: Severe brain damage, severe psychiatric problems, or mental retardation. Patients with epilepsy who have these conditions are usually cared for in residential centers or small residential programs whose treatment is directed at the primary problem causing the disability.

In the best sense of the term, a CEP is one in which a multispecialty team (physicians, psychologists, nurses, social workers, and specialized technical help) is brought together to provide an organized approach to the management of people with complex problems related to epilepsy.[1]

There is no organization in the United States that accredits a specialized epilepsy center or a CEP (although efforts are underway to establish one). Any physician with any training can print up stationery that says “Comprehensive Epilepsy Program,” mount a sign on the door, and go into business. There are documented cases of physicians without specialized training doing just that. CEPs in the United States vary greatly in quality and organization.

Historical Development

CEPs were originally developed under the aegis of the United States Public Health Service as part of the so-called 314(e) program in the early 1960s. One of the first was established in 1964, at the St. Paul Ramsey Hospital in St. Paul, Minnesota, and evolved into what is now called *MINCEP Epilepsy Care*. In that sense, the MINCEP program is the oldest in the United States. Nonetheless, major university centers devoted to specialized treatment (but without the full, comprehensive approach of medical, surgical, educational, psychologic, social, and community organization) have been in existence for many years.

The National Association of Epilepsy Centers (NAEC) was established in 1986 to help with the development of CEPs. A recent survey indicates that more than 130 places in the United States refer to themselves as *epilepsy centers*. Some of these consist of no more than a single neurologist with a particular interest in epilepsy. Others are CEPs in the fullest sense. The NAEC has published guidelines for classifying epilepsy centers and for the services to be rendered. Member centers (there were 116 in 2007) self-designate and affirm that they meet these guidelines. For more information, consult www.naec-epilepsy.org.

Mechanisms of Referral

In accordance with the free-market economy underlying health care in the United States, patients historically have been able to reach a CEP by a variety of routes. Some are referred by a neurologist, others by primary care physicians. Some learn about a center from social agencies, and others from friends and neighbors.

With the development of managed care organizations, many patients may no longer have free access to a CEP. They may be restricted to one with which the organization has a contract, or the organization may resist any referral at all. Furthermore, the amount paid for care is set by the individual health plan or insurance company. In some cases (certain state medical assistance programs, for example), the amount is so small that the specialized center cannot afford to provide the necessary treatment.

Location of Centers

Some major urban centers in the United States do not have a comprehensive program. Others have two or more. (Los Angeles has nine groups claiming to be CEPs!) In general, it takes a population base of at least 2 to 3 million to support a CEP. In the case of uncommon conditions (e.g., extratemporal lesions requiring subdural arrays, Landau-Kleffner syndrome), a much larger population is necessary if a center is to develop a reasonable experience.

Nearly all comprehensive programs are associated directly or indirectly with major medical centers, and usually medical schools as well. Because of the unique structure of the U.S. health care system, it is possible for a major medical center to exist in a small, rural community and draw patients from many miles around.

Leadership and Staffing

The leadership and staffing of CEPs vary enormously. The major centers are headed by epileptologists with national reputations, have several physicians who specialize in epilepsy on staff, and provide a full range of support services (psychiatry, psychology, neuropsychology, social work, video-electroencephalographic monitoring). Centers in a developmental phase or those that merely aspire to the name may have far fewer resources.

A lack of uniformity exists among centers in regard to programs, size, and funding. Some centers serve only a few

patients, whereas others perform several hundred evaluations a year.

Funding

Centers in general are funded on a fee-for-service basis. Some centers offer medical services as a loss leader so as to generate a high volume of surgical cases. Others try not to get involved in the long-term medical management of patients and seek only to evaluate and operate on patients who need simple types of surgery. This latter approach can be criticized as “skimming the cream.” For a CEP to survive on a long-term basis, it must earn a sufficient profit by caring for a high volume of routine cases in order to subsidize the care of patients with the most complicated problems.

When the center is part of a large organization, bureaucratic imperatives drive the funding (the regular operating budget as well as capital investment). When the center is free-standing in private practice, ensuring the growth of the center and meeting the needs of patients take priority.

Barriers to Access

In the United States, various barriers to access to care exist. Many people who are poor or totally disabled do not have adequate access to health care. Financial barriers are a major issue. Indeed, this is compounded by the tendency of many physicians to treat some patients unsuccessfully until they are so disabled that they lose their jobs and health insurance, then they turn such patients over to public charity.

A second barrier is ignorance. Many patients are unaware of the existence of comprehensive programs despite the best effort of lay organizations and the centers themselves to educate the public. Many primary care physicians are ignorant of their existence as well, and do not know how or when to refer a patient.

Reluctance to refer can also be a major problem. Pride and refusal to admit that someone else may be able to do something that they cannot do exists among physicians everywhere in the world. In a fee-for-service environment that is under stress because of a reduced number of patients with indemnity insurance, the financial implications of making a referral come into play as well. If the patient is covered by a managed care organization, even if the physician wants to refer, the organization may be unwilling to spend the money.

Many patients are reluctant to travel for care. Some people will journey to the ends of the earth to see a physician with marginally better credentials. Other patients are unwilling to travel across town to consult a physician at a highly specialized center. For patients with epilepsy, travel may be difficult and presents a particular problem.

Perhaps the biggest barrier is the sense of hopelessness that develops in many patients who have had uncontrolled seizures for years. After a while, they simply lose their ability to cope and cease to seek better care.

Competing voices in the marketplace also may serve as a barrier to reaching a CEP. Religious healers and practitioners of alternative medical philosophies (homeopathy, naturopathy, food fads) all create a clamor.

Nonetheless, many fine CEPs exist throughout the United States, and most can find some way to help a patient obtain the care needed if only the patient will apply for help.

Summary and Conclusions

The quality of epilepsy care in the United States varies broadly, and CEPs vary widely in quality and distribution. Frequently, socioeconomic factors are a major impediment to patients seeking appropriate help.

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Chapter 303

Comprehensive Epilepsy Programs—Norway*

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Introduction

In Norway, with a population of about 4.5 million people, only one specialized center for epilepsy exists. It is designated as a national center of competence in epileptology and comprehensive epilepsy service. Being an institution with nationwide responsibilities, its role in the National Health Service system and its program for activities are defined by the Department of Health and endorsed by the Norwegian Parliament.*

National CentER for Epilepsy—historical background

At the end of the 19th century, in Kristiania (now Oslo), the deacons established a home for people with epilepsy. In 1910, they bought a farm in Sandvika, 15 kilometers outside Oslo, where they established a nursing home for the residential care of 64 patients with chronic epilepsy. Dr. Monrad Krohn, professor of neurology at the National Hospital (Rikshospitalet) in Oslo was the first medical supervisor. The deacons were inspired by the epilepsy colonies, which at that time had been established in some European countries, including Denmark and Germany.

In 1924, the institution was donated to the State, which for many years ran it as a nursing home/farm for people with severe epilepsy. To the extent possible, the residents took part in the farm work. In 1954, thanks to a donation from the Norwegian Red Cross, a new unit was built for temporary service to 36 children with epilepsy. The new medical director, Dr. Georg F. Henriksen, specializing in neurology, psychiatry, and clinical neurophysiology, had been trained in epileptology in the United States and Canada.

During Dr. Henriksen's tenure (1954–1974), the National Nursing Home for Epileptics developed into the National Hospital for Epileptics with 184 beds: 36 for children, 34 for residential care, and the rest for adolescents and adults with difficult-to-treat epilepsy. The patients were admitted from all over Norway to be diagnosed and treated by a multiprofessional staff of about 150. Most patients had not only epilepsy, but also considerable additional problems, such as mental retardation, psychiatric and behavioral disturbances, and neurologic deficits.

In 1974, Dr. Yngve Løyning, a specialist in neurology and clinical neurophysiology, succeeded Dr. Henriksen. In 1975, the institution was renamed the National Center for Epilepsy (Statens Senter for Epilepsi [SSE]), reflecting its development into a multiprofessional comprehensive service center in epileptology. Residential care was abandoned in 1980.

Epilepsy surgery was introduced in Norway by professor Kristian Kristiansen at the Department of Neurosurgery at Oslo City Hospital (Ullevål) in 1949. He had his training at professor Wilder Penfield's department in Montreal, and Kristiansen was for many years the only Norwegian surgeon who performed epilepsy surgery. In 1976, epilepsy surgery was transferred to the National Hospital (Rikshospitalet) in Oslo. In 1992, the Norwegian Health Authorities decided to centralize this resource-intensive service. Selection of candidates for epilepsy surgery, preoperative investigations, and postoperative follow-up and rehabilitation would take place at the National Center for Epilepsy, whereas neuroradiologic investigations, intracarotid amobarbital (Wada) tests, and diagnostic and therapeutic surgery would be performed at the National Hospital.

In 1971, Norwegian Health Authorities planned to establish additional epilepsy centers in association with the university hospitals in the western, mid, and northern parts of Norway. The center in Sandvika was supposed to serve the southeastern part of the country, increasing its number of beds to 308 (including 92 for residential care) and the number of employees to 340. However, over the next years, it became evident that the additional centers would not be built because (a) the neurologic and pediatric epilepsy service had improved considerably throughout the country, making the need for more centers questionable; (b) the authorities decided that patients in need of permanent care should be treated in their local counties; (c) the economy in all regions had become weaker; and (d) the capacity at the center in Sandvika had improved, owing to the fact that the duration of stays at the center had decreased dramatically. The center would continue its nationwide service with fewer, rather than more beds, provided the staff was increased.

In 2005, the center had 25 buildings, occupying 21,000 m^2 of the 400,000 m^2 land area. There are 87 beds and about 300 employees.

Despite the continuous improvement of medical and psychosocial epilepsy service in Norway, the need for internal and external comprehensive service from the center in Sandvika is still increasing. The average yearly admission of inpatients over the past 30 years (1975–2005) has increased more than fivefold. During the same time, the number of beds was reduced from 183 to 87. This intensification has led to a marked reduction in average length of stay at the center, from 150 days to 17 days.

In the last few years, the center in Sandvika has been designated as a competence center for severely disabled patients with epilepsy, including those with mental retardation, tuberous sclerosis, and autism.

Development of the Norwegian Health-Care System

Regionalized Service

Since 1976, the system for health service in Norway, as in the other Scandinavian countries, has been regionalized. The intention is that each of the five health regions should have the resources to provide its population with most of the medical and psychosocial service needed. Some of the regional hospitals have supraregional or nationwide service functions, which are often resource-intensive and mostly intended for small groups of patients.

In addition, special institutions with supraregional or nationwide service functions exist for special groups of patients: Those with rare diseases or syndromes, those requiring particularly resource-demanding or multiprofessional services (e.g., drug-resistant epilepsies, cerebral palsy, multiple sclerosis), or those with different ailments in need of the same service (e.g., various physical deficits requiring rehabilitation).

Service Levels

Medical and psychosocial service is provided at four levels of increasing competence: In the local district, in the counties, in the regions at university hospitals, and in the special institutions or centers. The goal is to treat patients at the lowest possible service level as close to their own district as possible. A primary care physician, who calls in other professionals as consultants when needed, coordinates all service. Although rehabilitation teams are available in the counties, a complete multiprofessional staff providing the integrated, comprehensive service necessary for patients with difficult-to-treat epilepsy is established at a national epilepsy center at the fourth service level only.

Mechanisms of Referral

According to the outlined service principles, patients with epilepsy should have access to service on all four levels, depending on the severity and complexity of their condition. In Norway, it is recommended that all patients with epilepsy be referred to a specialist in pediatrics or neurology (depending on the age of the patient) to clarify the diagnosis, etiology, and type of seizures and epilepsy, as well as to initiate, change, or terminate antiepileptic drug (AED) treatment. The general practitioner should monitor the patient's AED treatment according to seizure control, side effects, and serum concentrations. The specialist should be available for consultation and renewed investigation when needed. Only those with drug-resistant seizures are referred to the National Center for Epilepsy. The number of referrals is restricted for economic reasons. The expenses are covered by the health regions, which require an approval by a specialist at the local hospital.

Barriers to Care

The service system does not impose any barriers to necessary care except the economic barriers for use of service outside the county (i.e., in the regional hospitals and epilepsy center). However, the numbers of pediatricians and neurologists are not sufficient in all parts of the country to give patients with epilepsy access to a specialist as soon as needed. Rehabilitation teams often do not have the capacity or competence to deal with psychosocial problems associated with seizures.

National Center for Epilepsy

Geographic Location

The National Center for Epilepsy is located just outside Oslo, which is located in the southeast end of the elongated country. The location causes some difficulties for the follow-up of patients and communication with health personnel in distant parts of the country. This is one of the reasons why we at the center in Sandvika (belonging to Health Region South) have advocated establishment of local epilepsy centers in the other four health regions (Health Region East-, West-, Mid-, and North Norway).

For many years, the center has collaborated closely with the National Hospital in Oslo, where neuroradiologic investigations and surgical interventions are performed.

Leadership and Staffing

In 2002, the epilepsy center became a part of the National Hospital. In 2005, great organizational changes took place within the health service in the Oslo area. The Norwegian Radium Hospital (specialized in cancer treatment) was merged with the National Hospital (Rikshospitalet University Hospital) and organized into eight clinics. The National Center for Epilepsy became a part of the Division of Clinical Neuroscience, which also comprises Departments of Neurology, Neurosurgery, as well as Psychosomatic Medicine. The center no longer has a director of its own, but is now under the medical leadership of the Division of Clinical Neuroscience.

Employees at the center for the time being, nearly 300, represent the necessary disciplines for addressing the various problems of the patients. The staff includes 23 physicians who cover neurology, pediatrics, clinical neurophysiology, and psychiatry, and one clinical pharmacologist. Of these, eight are interns training for any of these specialities. There are nine clinical neuropsychologists, three social workers, six vocational therapists, five physiotherapists, and 13 laboratory technicians. In addition, there are about 100 nurses, of whom many have subspecialized in epileptology and/or psychiatry. The nurses are key persons in the epilepsy education offered to all our patients, and the importance of having structured epilepsy nursing for improved quality of life has recently been documented.[4] The center has its own elementary and secondary school, with 18 specially trained educators, including speech therapists.

Services Available

The service offered by the center is established in accordance with the objectives decided upon by the Health Authorities and the Norwegian Parliament. These include service to inpatients and outpatients, consultative assistance to health professionals and others dealing with patients with epilepsy, education of students and health professionals, information to relevant groups in the society, and distribution of results from clinical research.

Internal Service

Patients are admitted to the center for seizures of an unclear nature or difficult-to-treat seizures, for evaluation of surgical treatment, for postoperative controls, and for psychosocial problems related to the epilepsy or epilepsy treatment. Many

patients have multiple medical problems, often with complex causes. Several are in need of family therapy and/or of habilitation and rehabilitation. Most patients profit from a multiprofessional comprehensive service, and some participate in group therapy.

For inpatients, the center has separate wards for children (*n* = 32), 1 to 14 years of age, as well as for adolescents and adults without mental retardation (*n* = 34), with slight retardation (*n* = 14), and with severe retardation (*n* = 7). Other units are designated for intensive monitoring (*n* = 5; *n* = 10 from 2006), vocational observation and training, physiotherapy, and leisure activities. There are as well laboratories for clinical chemistry/clinical pharmacology, clinical neurophysiology, and clinical neuropsychology. The school has a capacity for about 40 children. The center has housing facilities for relatives and guests.

The center also accommodates national centers of competence-related diagnostic groups, such as tuberous sclerosis, autism, and learning disability with epilepsy.

Between 30 and 40 patients undergo epilepsy surgery every year, mostly resective surgery. Analyses of the outcome and its prediction factors have been presented.[1,3] Every year, about 15 drug-resistant patients who were found unsuitable for surgery are offered vagal nerve stimulation.[8]

External Services

External service offered at the center includes preadmission assessment; postdischarge follow-up by long-distance communication and outpatient clinical and laboratory service, visiting service to some residents with learning disabilities, nationwide consultative service to health professionals and authorities, graduate and postgraduate educational service to health personnel and school teachers, and supervision of students in different health professions.

In Norway, two nursing homes are available for patients with severe epilepsy (Kure and Røysumtunet). Physicians from the center serve these two institutions through visits on a regular basis.

Number of Patients Served

In 2004, 1,413 patients were admitted to the National Center for Epilepsy. Their average stay was 16.9 days (1 day–4 months). The number of admissions is increasing slightly year by year. The average waiting time before admission was 110 days. In 2004, about 200 patients were evaluated for epilepsy surgery, but only about 35 of them were actually operated. The need for epilepsy surgery is estimated to be about 50 patients per year.[6]

About 1,400 patients, both children and adults, are admitted to the outpatient clinic for approximately 2,000 consultations per year. Among these, about 50 patients participate in drug trials.

At the Department of Clinical Chemistry/Clinical Pharmacology, about 45,000 blood samples from in- and outpatients were analyzed in 2004, mainly to determine serum concentrations of AEDs.

At the Department of Clinical Neurophysiology, 4,176 recordings were performed in 2004, both standard electroencephalogram and combined video and telemetry, 100 evoked potential studies, 100 electromyograms, and about 20 ictal single-photon emission computed tomograms (SPECT) were recorded.

The Department of Neuropsychology performs about 110 general neuropsychological assessments (including personality inventories) per year, 40 preoperative assessments (including Wada tests), 35 postoperative assessments, 20 online evaluations of cognitive effects of interictal EEG disturbances, and about 15 functional magnetic resonance image (fMRI) scans.

Funding

Funding of Health Service

A part of the salaries of all employees in Norway are taxed to fund the National Health Security System. This tax covers all the expenses for all health service and social service, except for a small amount paid by the patient for service from outpatient clinics and private practitioners. Thus, the health regions offer service to patients in hospitals and institutions from funds allocated by the government.

Barriers to Care

Finances

Because the health regions are underfinanced, the use of service outside the regions is decreasing. This is a concern for special institutions like the epilepsy center. Fortunately, so far, the admissions to the center have not been reduced.

Ignorance

The existence of the epilepsy center is well known to most patients with epilepsy, their relatives, and health care and social service personnel. However, the benefits of comprehensive service, and particularly of surgical treatment, are not sufficiently known. Thus, many patients are referred too late, often when psychosocial problems have become fixed and irreversible.

Research

In recent years, research activities have been pursued in the following fields: Clinical pharmacokinetics of AEDs, evaluation and monitoring of AED treatment, clinical trials of new AEDs in phase III and IV, epilepsy surgery, intensive observation and differential diagnoses of episodic brain dysfunctions, automatic detection and quantification of epileptiform EEG discharges, neuropsychological testing of performance in relation to epileptiform activity, physical fitness and physical exercise in relation to epilepsy,[7] the influence of drug treatment on psychosocial functioning, genetic aspects of epilepsy, analyses of comprehensive service needs,[5] and benefit evaluation of the center service.

Future Epilepsy Service

In 1995, Health Region West established high-level medical services to patients with epilepsy at the Departments of Pediatrics and Neurology at Haukeland University Hospital in Bergen. In Health Region North, a comprehensive epilepsy service has for some years been planned at the Department of Neurology at Tromsø University Hospital, but is not yet realized.

However, in Health Region Mid-Norway no plans exist to establish a unit for patients who need to stay for a longer time than is possible in ordinary hospital wards. Therefore, patients requiring comprehensive service will continue to be referred to the National Center for Epilepsy in Sandvika.

In 1981, the National Center for Epilepsy presented a plan for its future service based on analyses of service needs. We renewed our recommendation to establish similar centers in the other health regions. Whether such centers will be realized is open to the gravest doubt and, until further notice, the present center will need 100 beds for a nationwide inpatient service, with a corresponding level of sufficient staffing.

Summary and Conclusions

The views from the Norwegian Center for Epilepsy can be summarized as follows:

A person with newly diagnosed epilepsy may face long-lasting problems including seizure susceptibility, drug-related side effects, and the psychosocial burden. Fortunately, most patients have minor problems, but all patients will be in need of some comprehensive service.

Ideally, comprehensive service should be provided at all service levels. Those specialists in pediatrics or neurology who establish the diagnosis of epilepsy and initiate drug therapy should cooperate closely with the local general practitioner, nurse, social worker, and, if necessary, school teachers and a psychologist. According to the patients' requirements, information should be given to all those involved. The patient should be informed about the Norwegian Epilepsy Association (and its local branch) and about other sources of epilepsy information. At the regional hospital, a multidisciplinary team at the Departments of Pediatrics and Neurology provides comprehensive service.

About 30% of patients with epilepsy will be in need of comprehensive service from a specialized center or unit, where they can stay for a longer time than in ordinary hospital wards. At such epilepsy centers/units, they will be offered integrated multidisciplinary services, including physical, social, and vocational habilitation and rehabilitation and, if required, patients can attend school. To meet these demands in an optimal way, an epilepsy center should cover a population of about 1 million, thus serving about 2,500 patients with severe epilepsy.[2]

Ideally, in each Health Region, an epilepsy center/unit for long-term comprehensive service should be established, preferably in close collaboration with the regional hospital.

In a small country like Norway, epilepsy surgery should be coordinated from, and centralized to, one epilepsy center and one collaborating regional hospital. Patients with severe epilepsy and considerable comorbidities may not be able to take care of themselves. Earlier, many of these patients lived in big central institutions. In 1991, such institutions were closed in Norway, and today many of these patients are living in small, local, sheltered homes. In addition to the local comprehensive service, these patients should be followed-up on a regular basis by an epileptologist from the nearest epilepsy center/unit, and be admitted for a temporary stay when necessary.

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Chapter 304

Comprehensive Epilepsy Programs—Japan

Masakazu Seino

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Introduction

Epidemiologic studies of epilepsy, which are indispensable to estimate the magnitude of a problem, are limited in Japan. A 1-day population-based survey of children under the age of 13 years, conducted in Okayama Prefecture in 1999, showed the prevalence rate of seizure disorders to be 8.9 per 1,000 population (2,222 per 250,997). When febrile seizures and other single provoked seizures and acute symptomatic seizures were excluded (848 cases), the rate was 5.5 per 1,000.[14] The figures are comparable with those in the United States and Europe.[5] According to a 1-day survey done by the Ministry of Health in 2002, on the estimated number of patients with epilepsy whose medical fees were subsidized by any one of the governmental health insurance systems, 74,000 patients were hospitalized and 195,000 patients visited outpatient clinics.[7]

The issue of medically refractory epilepsy is a topic of special significance in epilepsy treatment. A series of nationwide surveys was carried out to establish the number of people with refractory epilepsy in Japan. People with refractory epilepsy were defined as those with an increase or no change in seizure frequency despite at least 3 years of intensive medical treatment at either a university hospital or a specialized center. The number of patients identified in these surveys as having refractory epilepsy was over 100,000. Most of these patients also had multiple neurologic and psychosocial problems. Of patients 15 years of age or younger, 13.5% were found to have medically refractory epilepsy,[15] and the epilepsy of 25.3% of patients over 16 years of age was medically refractory.[13]

In Japan, epilepsy patients were treated by psychiatrists until 1950s. For this reason, mental hospitals are the final stop for individuals with most refractory and disabling epilepsy. *The Handbook for Mental Health and Hygiene* reported, in 2002, that 4,243 (1.3%) of 330,050 patients institutionalized in mental hospitals in Japan on a long-term basis had intractable seizures in addition to personality and psychiatric disorders or mental disabilities.[8] The number of patients with epilepsy who were admitted to mental hospitals has decreased markedly over the past decade. The numbers have dropped yearly since 1995. Between 1995 and 1997, respectively, 8,997, 8,574, and 8,332 patients with epilepsy were hospitalized in mental hospitals in Japan. This decrease in numbers of hospitalized patients presumably represents improvements in epilepsy care in general in Japan.[1]

Historical Development

In a 1966 article, Wada[20] noted that Japan's progress in the scientific aspects of epileptology was on par with that of North America and Europe, although Japan lagged behind in its support of comprehensive medical services for epilepsy. Unlike the nations of North America and Europe, where custodial facilities for people with epilepsy and other disabilities were established in the middle of the 19th century,[2,3] state-sponsored institutional care for people with disabilities was not introduced in Japan until the mid 20th century. Legislation for the creation of institutions for individuals with severe mental disabilities was introduced in 1959. This legislation was established only after the state was pressured by lay people and professionals to take responsibility for the support for individuals with severe disabilities. Thus, although the influential 1969 Reid

Report[2] was shelved for lack of funding and political will in Great Britain,[18] its recommendations concerning the general care and management of patients with epilepsy, as well as for the creation of special epilepsy centers, were welcomed with great enthusiasm by Japanese professionals.

Although the need for establishing comprehensive multidisciplinary treatment programs for people with epilepsy in Japan was advocated by Nakata as early as 1966,[12] it was only in the 1970s that a special center for the treatment of epilepsy was established.[19] Inspired by the Reid Report,[2] the Japanese Ministry of Health and Welfare decided in 1975 to convert a tuberculosis hospital located in Shizuoka into a special center for epilepsy.[23] The center was defined as an integrated organization from which delivery of the following services would be possible: (a) long-term, longitudinal care of individuals with epilepsy from infancy through adolescence to adulthood; (b) multidisciplinary team treatment by neurologists, pediatricians, neurosurgeons, psychiatrists, nurses, and comedical personnel; (c) occupational therapy and rehabilitation activities; and (d) training and research in epileptology. In addition, during the 1980s and 1990s, several governmental sanatoriums Tokyo, Kyoto, Niigata, and Yamagata converted their neurology/psychiatry clinics into epilepsy assessment centers. The total number of these converted beds was approximately 250 in 2005.

The National Epilepsy Center in Shizuoka, Japan

The remainder of this chapter is devoted to a description of the current therapeutic activities and demographic features of the National Epilepsy Center in Shizuoka, based on statistics from 1975 to 2002. From 1975 to 2001, a total of 22,950 new patients with epilepsy visited our Center. The number of patients younger than 15 years of age has deceased since the mid 1980s, whereas the number of patients older than 15 years of age has gradually increased. The electroencephalogram (EEG) was the most frequently performed clinical investigation. A total of 187,600 EEGs was performed between 1975 and 2001.

Geographic Distribution of Outpatients

A total of 1,451 new patients visited the center's ambulatory services in 2003, including 27% from Shizuoka Prefecture (where the center is located) and 31% from adjacent prefectures situated between Tokyo and Nagoya (about 200 km away, or a 1-hour trip by bullet train from Shizuoka). The remaining lived in areas beyond the Tokyo and Nagoya metropolitan areas.

Geographic Distribution of Inpatients

The center has four wards for patients with epilepsy. There are 100 beds in the two adult wards and another 100 beds in the two wards for children. On average, 178.1 inpatients/day were hospitalized at the center in 2002. Patients come from every prefecture in Japan. Approximately a quarter of the inpatients are residents of Shizuoka Prefecture. The other patients come from other parts of Japan.

Age Distribution

The age of new outpatients ranged from 1 month to 76 years. The mean age was 18.5 years. Forty-five percent were under the age of 15, and 55% were over the age of 15 years. The age of inpatients ranged from 1 month to 62 years, also with a mean age of 18.5 years.

Patient Referrals to the Outpatient Clinic

The center is an officially recognized tertiary center for epilepsy in Japan. Based on statistics from 1991, 79% of outpatients were referred to the center by other physicians. Pediatricians made 37% of the referrals, neurosurgeons 8%, neurologic internists 8%, and general practitioners 7%. Twenty-one percent of the outpatients visited the center without referrals, of whom 8% were without diagnosis or treatment.

The government is attempting to decrease the number of patient self-referrals. Since 1988, under the Standard for Special Medical Treatment Act, patients have been required to receive referrals to utilize the services of specially designated tertiary care centers. Patients who do not receive referrals to the centers cannot use their health insurance for the first consultation they receive there.

The Diagnosis of Epileptic Syndromes and Epilepsies in 100 Consecutive Inpatients in 2002

The diagnosis of epileptic syndromes and epilepsies in 100 consecutive inpatients in 2002 was as follows: Syndrome identified in 39%, syndrome probable in 19%, other epilepsies in 32%, and nonepilepsy in 10%. Of the 39 patients whose syndromic diagnosis was definite, temporal lobe epilepsy was found in 21, frontal lobe epilepsy in eight, occipital lobe epilepsy in four, West syndrome in two, juvenile myoclonic epilepsy in one, and epilepsy with grand mal on awakening in one. Of the 19 patients whose syndromal diagnosis was probable but not definite, frontal lobe epilepsy was diagnosed in eight, occipital lobe epilepsy in four, temporal lobe epilepsy in three, progressive myoclonus epilepsy in two, familial adult myoclonic epilepsy in one, and Doose syndrome in one.

Of another cohort of 659 of the center's outpatients, 349 (53%) were followed for 3 years at the center's ambulatory services; 310 (47%) were sent back to the referring physicians. Treatment outcomes, expressed by rate of reduction in seizure frequency at 3-year follow-up compared with baseline, were as follows: Complete seizure freedom in 121 patients (35%), greater than 75% reduction in seizure frequency in 76 (22%), and greater than 50% reduction in 58 (17%). In other words, seizure frequency was reduced by at least 50% in almost 75% of outpatients treated at the National Epilepsy Center.[15]

Length of Admission of Inpatients

In 1998, the mean duration of admission was 123 days. One obvious reason for the long hospitalizations is that most of the center's inpatients have seizures that are extremely difficult to control, and because hospitalizations are fairly inexpensive, neither staff physicians nor patients and their families have much incentive to keep stays short. However, more complex social reasons exist. Most of the adult patients who are hospitalized at the center say they would like the treatment they receive to help them lead “normal” lives—lives during the course of which they could work, marry, have children, and so on. Because there are major restrictions on the employment (and thus economic independence and marriage) of individuals with epilepsy in Japan, the only way that many patients imagine this ideal can be realized is through full seizure control. These hopes are often nearly impossible to meet. One result has been long hospitalizations.

Epilepsy Surgery

Seven hundred and thirty nine patients have undergone epilepsy surgery at the center since 1982. Decisions regarding surgeries are made by a multidisciplinary team. Twenty-nine percent of the surgery candidates underwent presurgical evaluations with long-term intracranial EEG-video monitoring. Radiographic surveys, computed tomography (CT), magnetic resonance imaging (MRI), single-photon emission computed tomography (SPECT), and magnetoencephalography (MEG) were also used in the presurgical evaluations. Outcomes of 100 patients who underwent temporal lobe surgery and were followed for more than 2 years were as good as or better than results reported for Europe and North America.[10] After a mean follow-up of 8.0 years, 80.5% of 425 patients receiving temporal lobe surgery had seizure outcomes falling into Engel's Class I. Sixty-two percent of 140 extratemporal cases were classified as Engel's Class I after a mean 6.2-year follow-up.[11]

Mihara concluded that resective surgery provides sustained, positive benefits with a high likelihood for seizure freedom (80%) for most medically refractory patients with discrete lesions. In patients without a clear MRI lesion who underwent extra-temporal lobe resection, however, Engel's class I to II was achieved in less than 50% of patients. High-resolution MRI should be performed early in all patients with partial seizures.[11]

Table 1 Comprehensive classification of people with epilepsy

Group 1: People with epilepsy who (a) have had no seizures for 5 years or longer, (b) do not have associated (physical, intellectual, psychiatric) disabilities, and (c) can do all types of work except for that involving heavy lifting.

Group 2: People with epilepsy who have had no seizures for 3 years, and are able to do certain types of work, even if their associated disabilities are taken into account.
Group 3: People with epilepsy who have been seizure-free for less than 3 years, and who are employable even if hazards caused by seizures and interictal disabilities are taken into account.
Group 4: People with epilepsy who are having several seizures a month or even fewer. The seizures may cause hazards. These individuals are employable only in sheltered situations.
Group 5: People with epilepsy who are having several seizures a week or even fewer. Their seizures cause hazards. These individuals are unable to support themselves because of interictal disabilities, and are therefore in need of occasional help from others.
Group 6: People with epilepsy who are having several seizures a day or more (in some cases, fewer), and are entirely unable to care for themselves and always in need of help from others.

From Yagi and Onuma, ref. 21.

Finances in 2002

The National Epilepsy Center operates under the auspices of the Ministry of Health and Welfare of Japan. All income from medical services is considered governmental income, and the hospital's annual budget is issued by the Ministry independently. The approximate income in 2002 was 4.11 billion Yen, while total expenditures amounted to 4.05 billion Yen. (For the sake of conversion, about 115 Japanese Yen were equivalent to 1 U.S. dollar in 2006.) Thus, the hospital operated at a surplus of 1.6% in 2002, whereas the hospital has operated at a yearly deficit of 10% for the past 10 years.

Severity of Epilepsy and Comprehensive Classification

In 1986, Yagi and Onuma[17] introduced a system to classify individuals with epilepsy according to their ictal and interictal levels of disability. The system was designed to evaluate levels of need for health and special services. The six levels of this classification system are summarized in Table 1.

In this classification system, ratings are based not only on patients' inherent seizure types and frequencies, but also on the severity of seizure-related disabilities. For example, higher ratings are given to seizures that (a) cause abrupt falls and injury, (b) are accompanied by prolonged impairment of consciousness including automatisms, and (c) result in immobility, even if consciousness is not impaired. In a survey of 542 outpatients at the center, the breakdown was as follows: Group 1, 8%; group 2, 16%; group 3, 38%; group 4, 22%; group 5, 11%; and group 6, 4%.

Patients classified in groups 1 through 3 (63%) can be managed as outpatients and, in principle, are employable, whereas those in groups 4 and 5 (33%) have been subjected to short- or long-term hospital admissions, depending on the severity of their seizures. Patient classifications are subject to change. For example, a patient in group 4 whose hospital stay is shorter than expected might be shifted up to group 3, and a patient in group 5 whose condition worsens may be moved down to group 6.

Rehabilitation and “Habilitation”

The Reid Report envisaged special centers as being concerned with medical care and rehabilitation, with the ultimate goal of returning people with epilepsy to a normal life in the community. It specified the need for facilities for people with severe epilepsy—individuals whose seizures cannot be adequately controlled and who require long-term accommodation. According to the report, the needs of these patients must be recognized as being different from those of the long-stay resident who is institutionalized for other reasons (mainly custodial care).[2]

With respect to the needs of these patients, Grant argues that specialized services are necessary for individuals “…whose seizures cannot be effectively controlled, and those who require medical supervision under everyday living conditions or in a working setting."[4] These patients would fall into groups 5 and 6 in the comprehensive classification system described above.

Patients who fall into groups 3 and 4 in the system would most nearly approximate the group that Laidlaw and Laidlaw[9] describe as "…people with epilepsy who very nearly but not quite can manage on their own, who are employable, but break down under external environment stresses, who, given just a little bit of support, can be most successful."

In Europe, proposals for the creation of special centers were specifically aimed at the deinstitutionalization of individuals with epilepsy.[2] However, during the years following the North American and European movements for deinstitutionalization, critics have made it clear that deinstitutionalization in itself does not offer a more "humane" solution than institutionalization,[19] and that it must be accompanied by alternatives other than the street and soup kitchens. It is also clear that supportive, residential environments can be of benefit to some individuals. Finally, it is the opinion of the first author (M.S.) of this chapter, based on more than 30 years of experience at the Center, that residential care is necessary for a limited number of individuals who have severe, frequent seizures and intellectual or behavioral problems. The authors suggest that this type of residential care for people with epilepsy be based on a goal of "habilitation"—the provision of schooling (for children) and care (for adults) in livable and supportive environments, rather than on the primary goal of "rehabilitation"—the accommodation of individuals to society. These goals do not conflict with, and indeed may be integrated easily with, the goals of current community care plans.[13]

Summary and Conclusions

Over one million people in Japan have epilepsy. One-tenth of them have medically intractable seizures. Most of these individuals have concomitant physical and/or intellectual disabilities.

Although the need for comprehensive services for epilepsy was established before 1975, it was only in 1975 that the Japanese Ministry of Health decided to convert a tuberculosis hospital into a special center for epilepsy. Our experience over the past 30 years at the National Epilepsy Center in Shizuoka suggests that treatment can improve seizure control in approximately two-thirds of patients. Outcomes for patients who underwent epilepsy surgery were as good as or better than results reported for North America and Europe. The management of epilepsy should be oriented toward seizure control, psychological well-being, and social rehabilitation. To satisfy these goals, it is imperative that different types of health care professionals come together to form multidisciplinary treatment teams. However, in Japan, only a small number of these multidisciplinary teams have been established. Furthermore, the need for residential care for individuals who have severe disabilities related to epilepsy must be addressed. This type of residential care should be oriented toward "habilitation"—the provision of schooling and care in livable and supportive environments—rather than the goal of "rehabilitation"—the accommodation of individuals to normal life in the community.

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Chapter 305

Residential Epilepsy Centers—United Kingdom

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Stephen W. Brown

Introduction

The term *epilepsy center* is used to denote two different situations in the United Kingdom: (a) a collection of professionals specializing in epilepsy and offering different aspects of service at a specified geographical site or area and (b) residential centers for children or adults with epilepsy that offer short- to medium-term assessments, longer-term placements, or both. There are two main types of residential centers, sometimes existing together at one site: The adult centers and the epilepsy special schools.

It might be argued that a comprehensive "epilepsy center" should comprise a group of hospital-based professionals, including physicians who specialize in epilepsy neurosurgery and neuroimaging, in close proximity to a residential center that can offer longer-term assessments or indefinite care in selected cases.

Historical Development

A major change in attitude has occurred, from the earlier concept of an "epileptic colony" to that of a residential center that has strong community links and emphasizes preparation for living within society. This contrasts sharply with the image of an "asylum" that either protects the individual with epilepsy from the community or protects the community from the person with epilepsy; neither of these aims would be considered acceptable in current practice.

It is interesting to note that the early residential centers were actually referred to as "colonies," for example, the Lingfield Colony and the Chalfont Colony. Both these centers have changed their names to reflect the change in attitude.

The history of epilepsy centers in Europe seems to be relatively short. The monks at the priory of St. Valentine at Rufach in Alsace provided a "hospice for epileptics" at the end of the 15th century. The Bishop of Wurzburg started a home for people with epilepsy in 1773. In the United Kingdom, the National Hospital for the Paralyzed and Epileptic opened in Queen Square, London, in 1860. The Lingfield Colony (now The National Centre for Young People with Epilepsy) was founded in 1898 by a group of Christian people who had been inspired by Pastor Friedrich von Bodelschwingh. This man had taken over the center at Bethel near Bielefeld, Germany, in 1872, 5 years after it had been established. Subsequently, The Chalfont Centre was founded in Buckinghamshire in 1894, and the David Lewis Centre in Cheshire was opened in 1904. The Park Hospital in Oxford later provided medium-term residential assessments for children with epilepsy, and Bootham Park Hospital in York has provided specialist services, primarily for adults. St. Elizabeth's School and Home at Much Hadham in Hertfordshire and the Meath Home in Surrey initially provided only for female patients but now accept patients of both sexes. The Quarriers Homes in Scotland also have a long tradition of providing residential care for adults with epilepsy.

What is the role for these epilepsy centers in a country with an advanced system of medical care, in which the emphasis is on moving services out into the community? People with epilepsy certainly should lead lives that are as normal as possible and, for most, this implies that they should be living in the community. However, there are two situations in which the epilepsy center may play a role. The first of these is for short- or medium-term assessment and treatment. If there is real diagnostic doubt that cannot reasonably be resolved by the hospital services, it may be appropriate to use the specialist residential center to clarify the diagnosis. The center may also be used for complex, protracted changes in antiepileptic drugs, particularly if a significant risk for status epilepticus is involved. The second situation arises when longer-term placement is needed for a very small proportion of people with epilepsy whose needs cannot reasonably be fulfilled using resources available in the community. The number of people with epilepsy in this category has, appropriately, diminished steadily over recent years, both because of better treatment and because of changing attitudes.

Reasons for Referral

Some of the possible reasons for referral to a residential center are listed in Tables 1 and 2. It is not simply the presence of these factors but the degree to which they hamper satisfactory management that is likely to determine whether the epilepsy center must play a role or not. The possible reasons for referral have been discussed in detail elsewhere.[2,3]

Location of Centers

It is mandatory that a specialist epilepsy center have a team of doctors, other caregivers, educational specialists, psychologists, physiotherapists, occupational therapists, and speech therapists if it is to provide a full range of services. This necessarily implies that, to be viable, the center has to be of a reasonable size and have a moderately large number of residents at any one time. An alternative would be for the center to share facilities with other establishments. In practice, the centers tend to be moderately large, and consequently they are relatively few in number across the country. The geographical location may not be very convenient. The Winterton Report[7] on services for people with epilepsy recommended that two new special assessment centers be set up, partly to reduce the distances patients have to travel. This document referred to earlier reports

by Morgan and Kurtz[5] and Reid,[6] which stated that “special centres should be provided for those people with epilepsy whose management presents particular problems,”[5] and “the evidence is of a continuing number of young adults, both males and females, requiring a period of inpatient treatment during which they can be observed by trained staff, investigated and started on remedial programmes of treatment—special centres should, therefore, be seen to have a continuing role.”[5] In the current financial climate, however, it seems unlikely that additional centers will be initiated. It might be argued that the centers should be placed closer to large populations. For historical reasons, they have tended to be placed in rather rural situations, because they were founded at a time when close links with the local community were not considered to be essential. There was no particular reason why a “colony” needed to be near a heavily populated region. The current philosophy of facilitating close links with the community, however, implies that the centers should ideally be closer to the communities they serve.

Table 1 Reasons for referral

Difficult epilepsy
Other medical problems
Cognitive problems
Behavioral problems
Peer group problems
Family and social problems
Psychiatric problems
Multiple problems

Table 2 Features of difficult epilepsy

- Frequent seizures
- Injury during seizures
- Risk for status epilepticus
- Variable seizure frequency
- Postictal problems
- Problems with antiepileptic drugs
- Inadequate control
- Difficult-to-recognize epilepsy

Relation to Medical Centers

Notwithstanding the historical reasons for the epilepsy centers being located away from major cities, a clear need exists for them to have very close links with major hospitals. In practice, because the United Kingdom is not very large, it is possible for the centers to be in semirural areas and yet to be relatively close to major hospitals capable of providing specialist services, such as magnetic resonance imaging and neurosurgery.

Leadership and Staffing

Currently, a very healthy trend exists for the residential special centers to be led by professionals who have an international standing in the field of epilepsy. The implication is that they adopt the approach of providing high-quality service, making full use of the multidisciplinary team.

Services Available

Uniformity Among Epilepsy Residential Centers

If it is accepted that the centers should provide a high-quality, specialist, tertiary referral service, it is essential that they have a full range of therapists, as already indicated. It is also essential that they have links with the appropriate hospital-based investigational and neurosurgical treatment facilities. It could certainly be argued that sophisticated encephalographic (EEG) and video-EEG monitoring should be mandatory at such centers. In the United Kingdom, these services are available at most of the centers, but there is the occasional notable exception. In the United States[4] and Australia,[1] attempts have been made to set minimal standards, but no such consensus has yet emerged in Europe.

Number of Patients Served

Only a very small proportion of people with epilepsy require the services of a residential center. However, the individuals who need these services tend to be the more difficult and demanding patients who would, in any case, require much in the way of resources for their needs to be met. Placement in a specialist residential center may be a very efficient way of fulfilling their needs, particularly if the outcome is a beneficial review of drug therapy or a successful referral for neurosurgery.

Funding

In the past, most residents at the special centers have been sponsored by the local authority of their home area. At least for placements in which the department of education plays a role, there appears to be a current trend away from funding by local authorities to a more centralized form of control through the so-called quasi-autonomous nongovernment organizations (QANGOS). In some cases, this may imply that funding is more easily available. However, it is difficult for a central funding agency to have a good appreciation of the needs of individual patients.

There is also an increasing trend to multiagency funding, with, for example, the district health authority and educational and social services all having to contribute toward the payment. This seems to be based on the naïve concept that greater cooperation will be fostered between the actual agencies providing longer-term care. In practice, it often adds to administrative costs and, worse still, delays or jeopardizes placements because of interagency disputes.

Barriers to Access

The families of patients with epilepsy may be faced with a dilemma if they consider that referral to a center represents some failure, on their part, to provide a caring environment. In these circumstances, there is a role for wise professional counsel based on decisions concerning what really is best for the individual with epilepsy.

Professionals may be reluctant to refer because they may view referral as an admission of defeat or because the admission may draw on limited budgets.

The person with epilepsy may also resist referral for a number of reasons, including feelings of hopelessness. What is the point of a further disruption to life if it will not achieve anything? There may also be an understandable fear of changing from the “disabled” role, with its apparent certainties of care, to the less certain role of increasing independence if control of the epilepsy improves. Support of the peer group, both within the center and subsequently through local epilepsy action groups, can be invaluable in this regard.

Comprehensive Epilepsy Programs

Recognition is growing of the need to coordinate all services: Hospital-based services, residential centers, outpatient clinics, and community outreach services. Relatively few groups of professionals anywhere in the world offer this type of comprehensive service. The need has been recognized in the United Kingdom, but much further development is required.

Summary and Conclusions

An unfortunate tendency has emerged to leave referral to specialist services until very late, with the result that the patient's life is disrupted in a major way by epilepsy. Late referral may also be associated with increasing difficulties in treatment. Rather than viewing the epilepsy center as a repository for the long-term care of “hopeless” cases, future emphasis should ideally be on early referral and a much higher volume throughput of cases, with intensive medium-term assessment, investigation, presurgical preparation, and postsurgical rehabilitation as appropriate. Above all, the current trend for preparing patients with epilepsy for life outside the residential establishment should be developed further, either through discharge into the community or through part-time involvement in the community for those who continue to require longer-term residential placement.

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Chapter 306

Comprehensive Epilepsy Centers—The Netherlands

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Albert P. Aldenkamp

Introduction

In the first edition of this handbook, a description of specialized care for epilepsy reflected a rather stable period of health care in The Netherlands. Recent rapid developments in the fields of science, communication, and accessibility with simultaneous changes in demography, and economy however, clash and obstruct the implementation of theoretically feasible improvements in health care. Although most of the objectives of specialized care for people with epilepsy presented in the previous edition are still valid, some must be adapted to present-day requirements. Because this chapter is rewritten during a period in which many of the changes are still in the making, some uncertainties about the future situation are unavoidable.

The objective of special centers for epilepsy are still in essence to (a) offer intramural and extramural care to individuals with epilepsy within the framework of available facilities or facilities to be created in accordance with new developments and knowledge, and (b) promote the control of epilepsy.

Care comprises several elements, including diagnosis, rehabilitation, and temporary or long-term residential care. *Diagnosis*—the examination, observation, and evaluation of the symptoms and signs of disease and the psychic and social functioning of the patient in order to plan assistance—includes one or all of the following:

- Recommendations for the patient and the patient's family, including presentation of all treatment possibilities (drug treatment, diet, surgery, neuro-stimulation, psychological treatment)
- Recommendations for other health care providers to manage or supplement assistance
- A program for continued support by intramural or extramural facilities of the specialized center

Rehabilitation, the second aspect of care, is the integrated treatment of disordered physical, psychic, and social functioning. Finally, as the third element of care, an important precondition for temporary or prolonged residential care is the *verification that the specialized center is the most appropriate provision within the Dutch health care system for the referred patient*.

The second major objective of the specialized epilepsy care center is to promote the control of epilepsy in general by developing conditions that guarantee optimal physical, psychic, and social well-being for people with epilepsy, or that prevent the development of epilepsy. This can be achieved through:

- Research
- Public education
- Assistance of authorities responsible for health care and welfare on a regional, national, and international level

At present, society considers persons with epilepsy and their relatives to be responsible for the management of their own health. In other words, the patient is no longer comparable to a passenger who boards a ship to be transported to his destination. Rather, he has become a private ship's captain, who rents a ship and crew and takes over command, only consulting a trained pilot when the waters get treacherous.

In addition, the cost of illness is usually paid by insurance companies, which feel entitled to make patient care decisions on their behalf. This is exemplified by the way health services presently are paid for based on *diagnosis-treatment combinations.*

Historical Development

In a general article on specialized centers for epilepsy, Meinardi and Pachlatko[4] reviewed the history of some of these centers. The oldest specialized center is reputedly the hospice of St. Valentine in Rufach, France. Although the institution is still there, it no longer functions as a hospice for people with epilepsy. This chapter concentrates on specialized centers in The Netherlands.

Specialized centers for epilepsy in The Netherlands play an important role, both scientifically and with regard to patient care. In 1985, Meinardi[3] described the various theses on epilepsy published in The Netherlands since Prince William the Silent offered a university to Leyden in 1575, in recognition of the city's important contribution to the liberation of The Netherlands from despotic Spanish rule. During the years 1955 to 1985, more than a quarter of these theses were produced by the staff of specialized centers for epilepsy.

The first specialized center for epilepsy in The Netherlands was founded on January 26, 1882, in Haarlem, in the Western part of The Netherlands. The society created to enable the development of a hospital for people with epilepsy originated as part of the so-called *Reveille movement*. This movement was started by well-to-do citizens who wanted to put their Christian principles into practice. Years passed before a specialized center was established. The owner and director of a Deaconesses' Hospice in Haarlem, Lady Teding van Berkhout, was approached several times with a request to admit people with epilepsy. This request was usually rejected, and patients were referred to a psychiatric hospital. Finally, two girls were admitted in 1879, but the experiment was a failure. One of the girls was taken by coach to Bielefeld. In that German city, in 1867, the reverend Von Bodelschwingh had started a specialized center for patients with epilepsy. This experience was decisive; with the help of some friends and allies, the Christian Society for the Care of People with Falling Sickness (the Christian Society) was established, and a small building on the grounds of Lady Teding van Berkhout's home was opened for girls with epilepsy, partly supported by staff from her Deaconesses' Hospice. At first, six girls were admitted, but the pressure for appropriate care for people with epilepsy was such that soon other buildings had to be bought to accommodate an increasing number of patients. In 1885, the mansion “Meer en Bosch” was acquired. For many years, the name “Meer en Bosch” was used as *pars pro toto* for all activities of the specialized center.

In 1966, the national regulations regarding the financing of health care made it desirable to put the facilities of the Christian Society into separate foundations. The new name, Instituut voor Epilepsiebestrijding (Institute for the Fight Against Epilepsy), was for public relations considerations expanded to include the names of the major campuses of the institute, “Meer en Bosch” and “De Cruquiushoeve.” These campuses, in Heemstede and nearby Vijfhuizen, comprise a total area of 155 acres. Early in the 20th century, outpatient centers were created in parts of The Netherlands too remote for patients to make a one-day consultation with doctors at the major epilepsy centers. These outpatient facilities served for the intake of new patients and after-care for those who could go home after successful reduction or complete suppression of their seizures. During the 1980s, experiments started to expand the services of the outpatient units. Two so-called *Polimides* were created that used the technical developments of portable electroencephalogram (EEG)-machines and automatic video-registration linked with a piezo-electric seizure detection device to observe patients in their home situation and thus reduce the need for hospitalization in the epilepsy center. Finally, during the years 1988 to 1992, the political trend of paying more attention to consumer needs resulted in a decision to require the Instituut voor Epilepsiebestrijding to build an annex for 80 patients in the northeastern region of The Netherlands. In particular, parents of children with epilepsy had protested to the Ministry of Health that, when intramural tertiary care was needed, they had no other option but to go to a specialized center either in the south or the west of The Netherlands. Permission to build a new epilepsy center was constrained by an order of the government not to increase the total number of beds in the specialized centers for epilepsy. In consultation with the three centers in Breda, Heeze, and Heemstede, it was decided that the Instituut voor Epilepsiebestrijding would transfer some of its capacity to Zwolle. This new center opened in October 1999. The name of the organization now responsible for the centers in Heemstede and Zwolle and nine outpatient clinics in a circle of strategic towns north of the Rhine was changed into Stichting Epilepsie Instellingen Nederland (SEIN). Presently, the intramural capacity of the centers in Heemstede and Zwolle is 600 beds, of which 440 are designated for residential (long-term) care, while facilities in the nine consultation centers North of the Rhine care for 9,278 outpatients.

Only relatively recently has Dutch society ceased to be subdivided along ecclesiastical lines. It is therefore not surprising that, following the successful establishment of a Protestant Christian institution, a secular society against falling sickness was established in 1902, and in 1920, a home for Catholic men with epilepsy. The former had as one of its leaders Dr. L. J. J. Muskens, cofounder of the International League Against Epilepsy (ILAE). In 1902, this group it opened a hospital for people with epilepsy in Amsterdam. The catholic center was established in the South in Geldrop. It was not until the 1960s (although the initiative dates from 1953), that a residential center for women was established adjacent to the home for Catholic men. This new center also provided advanced intramural medical care to both men and women. These two organizations gradually merged into the Epilepsy Center Kempenhaeghe in Heeze, near Geldrop; it has an intramural capacity of 525 beds and also outpatient departments in five different cities that care for 3,869 outpatients.

Several interesting phenomena relating to the social forces that affect health provision can be observed in the development of epilepsy services in The Netherlands. The Hospital Muskens built in Amsterdam near the Municipal University Hospital was closed in 1986. Factors contributing to its closure were the impossibility of expanding the building, because costs of building in the center of Amsterdam were prohibitive. So, when specialized centers for epilepsy began to engage in rehabilitation and provide sheltered workshops for their patients, Amsterdam had to default. Furthermore, the neighboring University Hospital was very much in need of referrals of other patients with chronic illnesses in addition to epilepsy. Willy-nilly, these referrals were accepted, and thus the advantages of a specialized center for epilepsy were lost.

Another interesting development was that, as late as the 1960s, a new, small Catholic epilepsy center comprising 132 beds, named Hans Berger Kliniek, was started in Breda. This facility presently also cares for 2,000 patients via outpatient departments in four cities. This center in Breda was started mainly because of the rapid emptying of a large sanatorium for tuberculosis patients in that city. The decreased need for care of patients with respiratory disorders was compensated for by establishing departments of epileptology, cardiac surgery, and child psychiatry. However, at the end of the 20th century, it became government policy to merge smaller hospitals with only a few specialties with larger, more general hospitals. Although the special center for epilepsy remained an independent foundation, it had to move its facilities to a general hospital, the AMPHIA in Breda. Its intramural capacity was reduced to 56 beds, with an additional four beds for day care. To achieve a situation similar to the SEIN-managed centers in Heemstede and Zwolle, a merger between Kempenhaeghe and the Hans Berger Kliniek has recently been established.

Although hospitals had to merge in order to increase in size, residential facilities for the long-term care of persons with epilepsy, psychiatric patients, or the mentally handicapped were stimulated to reduce their size. In the Heemstede epilepsy center, but especially in the Southern epilepsy center Kempenhaeghe, developments started to change chronic intramural care. Whereas in the past all facilities were on the campus of the epilepsy centers, this changed to smaller community houses in the surrounding communities, with services provided by the epilepsy center.

In yet another development, the university hospital of Maastricht in the south of The Netherlands has chosen epilepsy as one of its priorities for patient care and research and is cooperating with the epilepsy center Kempenhaeghe. Negotiations aiming at a similar type of cooperation are ongoing between SEIN and the Christian University Hospital in Amsterdam. In both university hospitals, units for epilepsy surgery are in development. Epilepsy surgery is also continuing in the university hospital of Utrecht, where modern epilepsy surgery was initiated during the 1970s.

Although beyond the scope of this chapter to detail, all Special Centers for Epilepsy provide, on request, incidental and regular consultations in homes and institutions for mentally handicapped patients. Among the persons cared for in these establishments, 20% to 30% may have epilepsy, with a rather high prevalence of refractory epilepsies: Among 172 patients with epilepsy on optimal treatment in a home for the mentally retarded, 61 (35%) were seizure-free, whereas at the other extreme, 23 (13%) had a seizure frequency between several per week and daily.[5]

In summary, the three specialized epilepsy centers located in Heemstede/Zwolle, Heeze/Breda, and their outpatient clinics in Heemstede, Amsterdam, Leeuwarden, Groningen, Zwolle, Enschede, Nijmegen, Heeze, Sittard, Arnhem, Utrecht, Breda, Terneuzen, Goes, Rotterdam, and The Hague, make specialized care for people with refractory epilepsy available in

16 areas, each serving approximately 1 million of the 16 million inhabitants of The Netherlands.

Mechanisms of Referral

The specialized centers for epilepsy in The Netherlands must be viewed against the background of health services in that country. In The Netherlands, 16.3 million people inhabit an area of 34,000 square kilometers. One general practitioner is available for every 2,350 inhabitants, and one neurologist for every 22,500 inhabitants. There are 3,015,704 children younger than 14 years old and, for many of them, specialist care is provided by pediatricians. One pediatrician is available for every 2,500 children below the age of 14.

In 2006, a new Health Insurance Act was implemented. Its impact on care for persons with epilepsy can not yet be fully estimated. Under this Act, all Dutch citizens, irrespective of income, must buy a basic package of health insurance. The government has established a list of conditions that must be covered by the basic package. The costs may vary according to the contracts that insurance companies establish with health care providers on the one hand and their clients on the other. The cost will not depend on the age or health of the client. This is made possible through a compensation fund that will reimburse those insurance companies with a higher-than-average proportion of high-risk clients who present extra costs. Once a year, the client can reconsider whether to stay with the same insurance company or switch to one that he expects will better suit his needs. The new Health Insurance Act stipulates that a Netherlands Care Authority be established that will supervise proper execution of the law; it also is mandated with stimulating competition and, where no competition is possible, setting budgets and tariffs for hospitals. (The Netherlands Care Authority absorbs and replaces the present Board for Statutory Control of Health Care Insurances as well as the Board for Health Care Tariffs.)

Many health care items previously covered under the compulsory insurance scheme for low-income people (<31,000 Euro annual income, or those on welfare) are now excluded from basic coverage. Additional insurance to cover these items can be purchased, but is not obligatory.

Consultation with a general practitioner by a person registered as his patient is free of charge. Concomitantly, how insurance companies pay for other services rendered to their clients has drastically changed. A system of diagnosis-treatment combinations has been developed, with input from all parties concerned. Cost elements known to be associated with a particular diagnosis—for example complex partial seizures or appendicitis—are averaged and shown on the bill whether or not all these elements have been utilized for the particular patient named on the bill, such as anesthesia or surgery. How these changes will affect services for people with epilepsy is difficult to predict. An important problem still under debate concerns financing for research needed to optimize diagnosis and treatment. Although special centers for epilepsy in The Netherlands do not have academic hospital status, in the past, the Heemstede center did have permission to include the cost of research personnel in its fees, a practice that has not yet been approved under the new regulations.

An increasing number of neurologists are employed by the hospitals where they practice. Their income is independent of the number of patients seen, or the number of interventions offered. Others are in private practice and have contracts with hospitals for the facilities provided. There are 725 registered neurologists in The Netherlands. There are 90 general hospitals, 85 psychiatric hospitals, ten hospitals for special categories (e.g., three for epilepsy), and ten University hospitals (in all, 22 teaching hospitals). The problem with epilepsy care and the development of a nationwide network of outpatient clinics manned by the staff of specialized centers for epilepsy is rooted in the incompatibility of the needs of teaching hospitals and the quality of care requested by patients with long-term illnesses such as epilepsy. In particular, long-term patients become discouraged by the frequent rotation of the junior physicians directly responsible for their care. In The Netherlands, specialized centers for epilepsy started as hospices at the end of the 19th and beginning of the 20th century. Although located in a semi-rural area, SEIN (Meer en Bosch-de Cruquiushoeve) is surrounded by four universities at distances of 20, 25, 35, and 60 kilometers. It was therefore easy for its staff to keep up with the latest scientific developments and often to take the lead in research. Because epilepsy patients could obtain high-quality care without having to cope with the continuous turnover of physicians inherent in a teaching hospital, they preferred to avoid the university hospitals. As a consequence, interest in epilepsy at the universities slackened, with subsequent deleterious effects on the ability of their graduates to treat patients with chronic epilepsy. In recent years, closer ties have developed between the special centers and university hospitals, Consultative collaboration aimed at the education of neurologic residents has been established between SEIN and the university hospitals of Utrecht, Rotterdam, Amsterdam, and Groningen, and between Kempenhaeghe and the Universities of Nymegen and Maastricht. Both centers offer a short internship to neurologists in training. Furthermore, SEIN has links with the Free University of Amsterdam and is considering moving its short-term care facilities and part of its laboratories to a site adjacent to the Hospital of this University. Kempenhaeghe has established a link with Maastricht University.

The insurance companies cooperated in the development of a nationwide network for tertiary epilepsy care by permitting referrals from neurologists to epileptologists, even though epileptology is not a registered specialty. This was facilitated by the inclusion of epilepsy centers as a special category of hospitals in the law covering hospital provisions. As mentioned, the intramural capacity is presently 1,337 beds, spread over four locations. Furthermore, a network of 17 outpatient clinics is maintained by the specialized centers and cares for 12,300 of the estimated 96,000 people with active epilepsy in The Netherlands.

The epilepsy centers once employed neuropsychiatrists. From the early 1970s on, specialization as a neuropsychiatrist was no longer possible; only the constituent specializations of neurology and psychiatry were thenceforth registered. The medical staff of the epilepsy centers was subsequently selected from neurologists and supplemented with clinical psychologists.

In The Netherlands, epilepsy centers are in fact autonomous organizations, with sometimes divergent interests. However, through the national epilepsy organizations such as the Dutch branch of the ILAE and an umbrella organization (the National Epilepsy Fund), they keep in close contact and work to keep their policies—and, in particular, their relations with the government—consistent.

Funding

The possibility of achieving one's objectives is determined by the means available. A specialized center, like all other health care facilities in The Netherlands, is financed by the fees the insurance companies pay for the services rendered. Because the health insurance premium has a pronounced influence on the national economy, tariffs and the services considered acceptable were negotiated on a national level by the Central

Bureau Tariffs Health Care. The state, insurance companies, and health care providers participated in these negotiations. Only after intensive negotiations were most, but not all, financial consequences of the objectives of Special Centers for Epilepsy accepted. In particular, the provision of psychotherapy on an outpatient basis was rejected on the assumption that other existing institutions could serve that purpose. Unfortunately, a lack of familiarity with specific, epilepsy-related factors has repeatedly caused attempts to assist patients along these lines to go wrong. The full impact of The Netherlands Care Authority cannot yet be estimated.

Not all costs for rehabilitation are paid for by health insurance. To reintegrate people with epilepsy who, because of seizures (and often overprotection) have lost or never acquired job experience, the Instituut voor Epilepsiebestrijding was permitted to open a sheltered workshop with the financial assistance of the Ministry of Social Affairs. This was also motivated by the reluctance of the regular regional sheltered workshops to accept people with epilepsy. Because the cost of maintenance of sheltered workshops was increasingly a problem for the government, negotiations were started during the 1990s to terminate the special arrangement with epilepsy centers and refer patients for rehabilitation to the regional sheltered workshops. Interestingly, a few years after this had been achieved, the regional workshops moved from Haarlem to a location immediately adjacent to the campus of the SEIN in Heemstede, which reflects a further removal of the discrimination between persons with epilepsy and persons with other handicaps.

Similarly, the Ministry of Education finances schools on the campuses of the epilepsy centers. Although, according to their charter, the schools were originally established for “children with epilepsy,” in the 1980s this was changed to “special schools for the multiply handicapped.” This implies that, in addition to epilepsy, another handicap should be present—most often mental retardation. Hospitalized children with normal intelligence and no physical handicap may attend the schools, but the costs are not reimbursed, and therefore the number of children in this category remains small. The Ministry of Education does finance outreach by staff of the schools at the epilepsy centers to other schools, which receive advice on how to manage pupils with epilepsy.

Neurosurgery for Epilepsy

In the budget of the Instituut voor Epilepsiebestrijding, a small amount had been made available for research by the Central Bureau Tariffs Health Care. Fortunately, the Christian Society, which formally is no longer connected with the epilepsy centers, does provide financial support for research and development and for recreational facilities for long-term patients. In the period from 1989 to 1993, a 3-year project was cofunded with the government to establish the optimal protocol for functional neurosurgery for patients with epilepsy. Functional neurosurgery for epilepsy in The Netherlands started in 1971 as a collaborative undertaking of the University Hospital at Utrecht and the Instituut voor Epilepsiebestrijding, the latter being responsible for the presurgical analysis, and in particular the monitoring of patients in whom intracranial electrodes have been placed for detailed analysis. Before any final decision to operate, a counsel, The Dutch Epilepsy Surgery Program, in which all major groups concerned with patients with intractable epilepsy participate, reviews the findings. As of 2005, patients go for presurgical analysis to Heeze or Heemstede. After receiving a verdict from the Dutch Epilepsy Surgery Program, epilepsy surgery still mainly takes place in Utrecht, but now is also being performed at the Free University in Amsterdam and at Maastricht University.

The Christian Society has also funded a project to investigate whether the provision of long-term monitoring facilities on an outpatient basis, including monitoring at home, could effectively make intramural observation redundant. Based on its findings, diagnostic and counseling services at home have been greatly expanded. However, during the late 1990s, the Christian Society has also spent some of its funds assisting SEIN to reorganize, thus reducing its ability to support research.

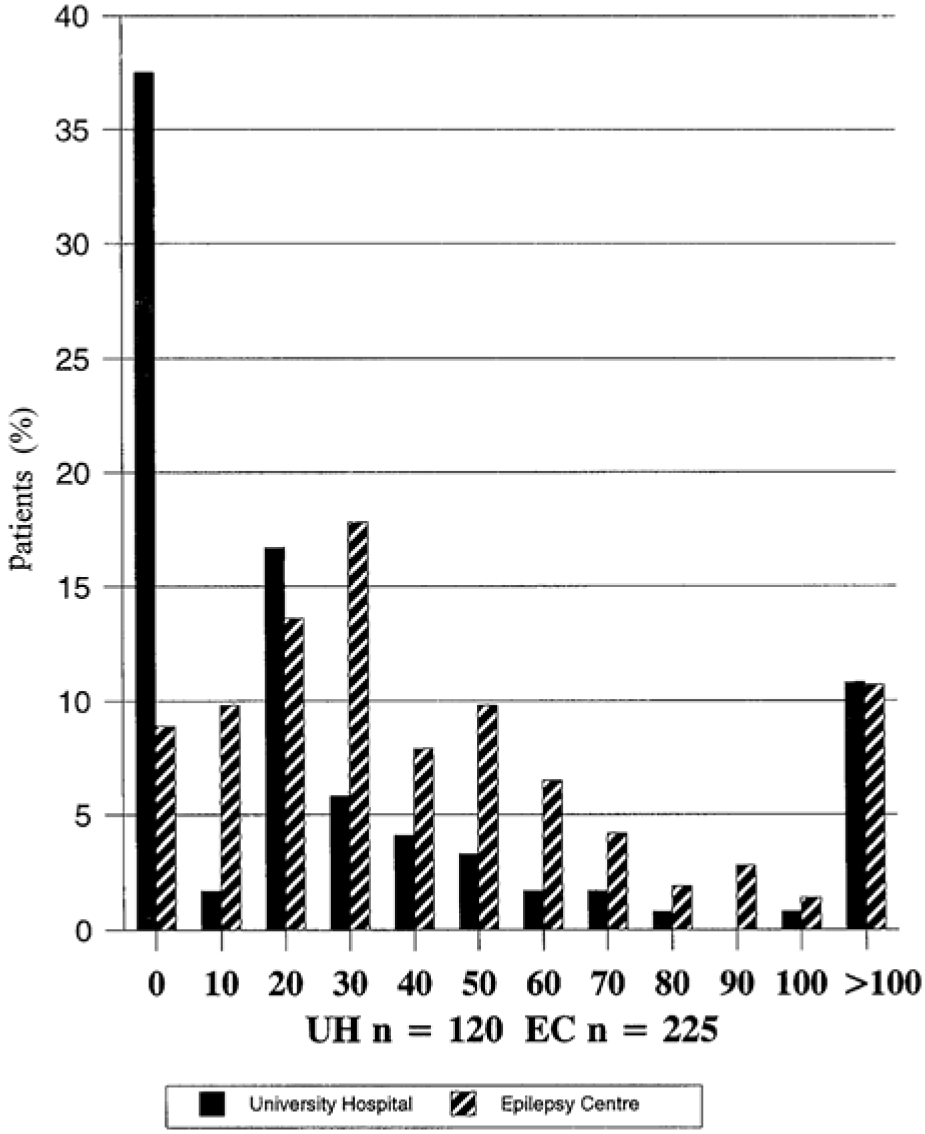
On a national level, research grants for epilepsy are provided annually by the National Epilepsy Fund, which derives its income from charity and legacies. These grants are, however, not restricted for use by the specialized centers. The Christian Society initiated providing monies for an endowed chair in epileptology, which, after prolonged deliberations by the departments of neurology of the Dutch universities, was finally established in 1984, at the University of Nymegen.

After the retirement of the first chair-holder in 2000, this chair was moved to the Free University of Amsterdam. Nij-megen appointed at its own expense a new professor of epileptology; however, this chair will not be continued after his retirement, which is due in 2006. In recent years, the National Epilepsy Fund has established two additional chairs for epileptology at the Universities of Utrecht and Maastricht.

Tertiary Versus Secondary Care

Two articles[2,7] have been published by the Nymegen department of epileptology comparing treatment and outcome in a secondary and tertiary epilepsy care outpatient facility. To compare the two facilities, several characteristics were considered that might influence the course of epilepsy. These were age, gender, type of seizure, duration of epilepsy type, and strength of medication. The strength of medication was determined by the ratio of the prescribed daily dose to the defined daily dose (PDD/DDD ratio). The DDD is the assumed average recommended adult dose for the major indication for prescribing the drug, and it is the unit of comparison recommended by the World Health Organization (WHO) Drug Utilization Research Group.[5] The PDD is the dose actually prescribed for the individual patient. Also, the following indexes have been determined on a clinimetric basis:

- Index of Seizures (IS), indicating seizure type and frequency
- Seizure Activity Index (SA), which modifies the IS to include seizure severity
- Neurotoxicity Index (NTX)
- Systemic Toxicity Index (STX)
- Composite Index of Impairments (CII), reflecting all treatment-related impairments, that is, paroxysmal impairments (seizures) caused by the disorder being treated and drug-induced impairments or adverse effects of treatment (CII = SA + NTX + STX)



Univ	37.5	1.7	16.7	5.8	4.1	3.3	1.7	1.7	0.8	0	0.8	10.8
Epil	8.9	9.8	13.6	17.8	7.9	9.8	6.5	4.2	1.9	2.8	1.4	10.7

FIGURE 1. Distribution of the CII (abscissa) for the UH (*n* = 120) and the EC (*n* = 225). *White bars*, university clinic; *shaded bars*, epilepsy center.

These indexes have been extensively described in previous publications.[1,6] Parameters of other effects, such as psychosocial and occupational impacts caused by disabilities and handicaps, were not included.

In the first part of these studies, patients were examined who regularly visited the outpatient departments of the University Hospital in Nymegen (UH), or the outpatient departments of the Instituut voor Epilepsiebestrijding in Utrecht and

Heemstede (EC), literally cross-secting The Netherlands. Selection criteria were as follows:

- Patient files should be well documented, including an accurate history and adequate neurophysiologic data for a firm diagnosis. The patient should have well-defined types of seizures according to the International Classification of the ILAE.
- No factors should be present that might be considered to complicate the evaluation process. These factors included progressive brain disorders, obvious noncompliance in drug use or seizure registration,

pseudoseizures, and severe mental retardation.

When the data of 120 patients from the UH and 225 from the EC were analyzed, it became clear that there was no significant difference in sex or age between the two groups. However, a significant difference was noted in duration of epilepsy. The median duration of epilepsy was 20 years for the EC group and 10 years for the UH group ($p = 0.0001$). The groups were also different with respect to seizure types. At the UH, a higher percentage of patients had primarily generalized tonic–clonic seizures (45.8% vs. 11.6% for the EC; $p < 0.001$), whereas at the EC, a higher percentage of patients had secondarily generalized tonic–clonic seizures, although the difference was not significantly different (16.4% vs. 9.2% for the UH; $p = .08$). No difference in partial seizures was noted between the EC and the UH. The patients of the EC had a greater diversity of seizure types. Apart from the above-mentioned types, myoclonic, tonic, and atonic seizures were seen in this group, although mostly in combination with other seizure types. Patients with more than one seizure type were more numerous at the EC than at the UH (45.4% vs. 15.1%; $p < 0.001$).

Treatment

The groups were clearly treated differently. More patients were treated with monotherapy at the UH (62.5% vs. 28.0% at the EC; $p < 0.001$). At both centers, if monotherapy was used, carbamazepine was the preferred drug. The average number of antiepileptic drugs (AEDs) used per patient was 2.0 for the EC and 1.4 for the UH. There was a significant difference in the PDD/DDD ratio between the two centers. The median PDD/DDD ratio was 1.7 for the EC and 0.8 for the UH ($p = 0.0001$).

Composite Index of Impairment

The CII was significantly higher at the EC ($p = 0.0001$). At the UH, 37.5% of the patients had complete seizure control and no drug side effects, which resulted in a CII score of 0. This was the case for only 8.9% of patients at the EC ($p < 0.001$). For the group of patients with a CII score of >100, no significant difference was found between the two centers. At the EC, 10.7% had a CII score of >100; at the UH, this was 10.8% ($p = 1.00$) (Fig. 1).

At both centers, no clear correlation was observed between the duration of epilepsy and the outcome of any of the indexes (Spearman correlation coefficient was 0.06 or lower). Also, no significant correlation was seen between the PDD/DDD ratio and the toxicity ratings (Spearman correlation coefficient was 0.49 or lower).

Table 1 Distribution of seizure types (32 matched pairs)

Seizure type	Percentage of patients (*n*)
CPS	28.1 (9)
SGTCS	15.6 (5)
PGTCS	34.4 (11)
SPS + SGTCS	3.1 (1)
CPS + SGTCS	18.8 (6)

CPS, complex partial seizure; SGTCS, secondarily generalized tonic–clonic seizure; PGTCS, primarily generalized tonic–clonic seizure; SPS, simple partial seizure.

Table 2 Duration of epilepsy (32 matched pairs)

Duration of epilepsy	**Percentage of patients (*n*)**
1–5 y	25.0 (8)
6–10 y	43.8 (14)
11–15 y	18.8 (6)
16–20 y	12.5 (4)

Matched Groups of Patients from Secondary and Tertiary Care Facilities

The first study answered in the affirmative that secondary and tertiary referral centers care for different categories of patients. However, there was also clearly an overlap (Fig. 1). It was therefore decided to re-examine the data of two groups from the UH and the EC matched for seizure type and duration of epilepsy. Only 32 pairs could be collected. The seizure types and duration of epilepsy are shown in Tables 1 and 2.

Although the groups were matched for duration of epilepsy, this does not necessarily bring about a match in age groups. However, concerning age distribution, a significant difference was found only in the age group of 15 to 19 years, with six patients (18.8%) at the EC and one patient (3.1%) at the UH. No great differences were observed in the other age groups.

Composite Index of Impairments in Matched Groups

Notwithstanding matching, the two groups were significantly different with respect to the CII ($p = 0.014$). Far more patients at the UH than at the EC had a CII score of 0 (45.9% vs. 9.4%; $p = 0.001$), indicating that more patients were seizure-free and had no drug side effects. On the other hand, 18.8% of the patients at the UH had a CII score of >100; this was the case for only 9.4% of the patients at the EC. This difference, however, was not statistically significant (Fig. 2).

Seizure Activity Index and Toxicity Ratings in Matched Groups

For the SA, no significant difference was observed between the two centers ($p = 0.060$). More patients at the UH than at the EC had an SA score of 0, but twice as many patients at the UH as at the EC had an SA score of >100 (18.8% vs. 9.4%), although this by itself was not statistically significant.

The NTX rating was significantly lower for the patients at the UH than at the EC ($p = 0.003$). At the UH, 71.9% of the patients had an NTX of 0, as opposed to 21.9% at the EC.

The STX rating was likewise significantly lower for the patients at the UH than at the EC ($p = 0.016$). At the EC, 18.1% of the patients had an STX >0, as opposed to only 6.2% at the UH.

Treatment Differences of Matched Groups

Although there were some differences in mode of pharmacotherapy, none reached statistical significance. As for the individual drugs prescribed, it was noticed that the drugs ethosuximide and diazepam were prescribed only at the UH. Clobazam and vigabatrin were prescribed only at the EC (Table 3).

At the UH, more patients were treated with monotherapy (56.2%) than at the EC (40.6%), although this difference was not statistically significant. When the patients were treated with monotherapy, carbamazepine was most frequently prescribed at the EC (53.8% of the patients on monotherapy). At the UH, carbamazepine and valproate were prescribed as monotherapy for an equal number of patients (44.4%). At the EC, 56.2% of the patients were treated with polytherapy and, at the UH, this value was 37.5%. This difference was not statistically significant.

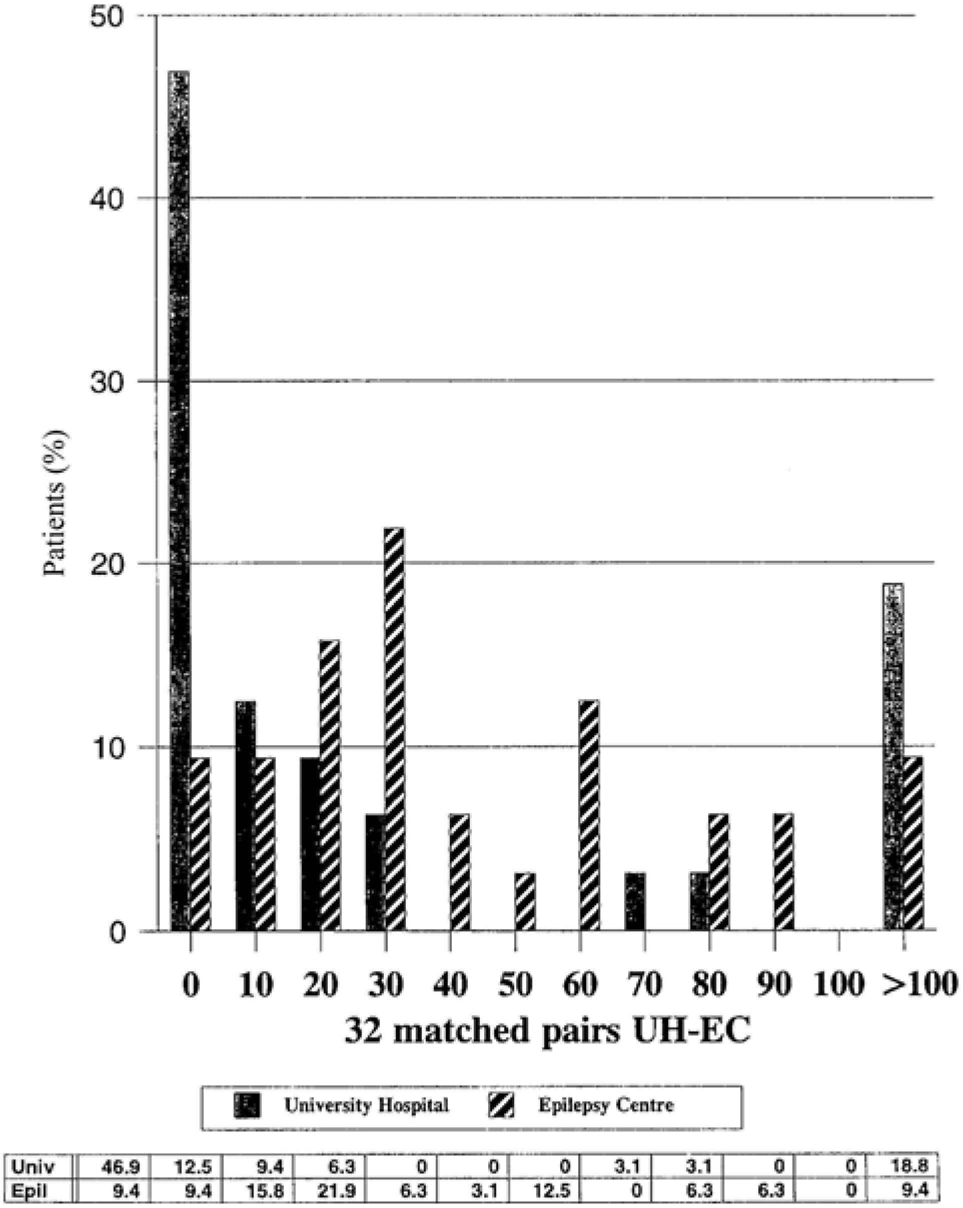
The average number of AEDs used per patient was 1.8 for the EC and 1.4 for the UH.

The difference in the PDD/DDD ratio (EC, 0.80; UH, 0.90) between the two centers was statistically insignificant, but only marginally so.

Psychogenic pseudo-epileptic (non-epileptic) seizures

Paradoxically, the diagnosis and treatment of persons with psychogenic nonepileptic seizures is a service that appears best provided by special centers for epilepsy and not in a psychiatric setting. About 30% of the patients referred to a specialized epilepsy center have nonepileptic seizures in addition to epileptic seizures, and about 10% have nonepileptic seizures

only. Within the centers, specialized expert teams are available for the diagnosis, treatment, and referral of these patients.



Univ	46.9	12.5	9.4	6.3	0	0	0	3.1	3.1	0	0	18.8
Epil	9.4	9.4	15.8	21.9	6.3	3.1	12.5	0	6.3	6.3	0	9.4

FIGURE 2. Distribution of the CII (abscissa) for 32 matched pairs of the UH and the EC. *Black bars*, university hospital; *cross-hatched bars*, epilepsy center.

Table 3 Average dose and ratio of prescribed daily dose to defined daily dose for antiepileptic drug prescribed

	Epilepsy center			University hospital		
Antiepileptic drug	**mg**	**(*n*)**	**PDD/DDD**	**mg**	**(*n*)**	**PDD/DDD**
Carbamazepine	813.64	(22)	0.81	678.33	(16)	0.68

Clobazam	13.33	(3)	0.67	—	—	—
Diazepam	—	—	—	10.00	(1)	1.00
Ethosuximide	—	—	—	1,000.00	(1)	0.80
Phenobarbital	73.33	(3)	0.73	133.00	(7)	1.33
Phenytoin	285.71	(8)	0.95	354.00	(9)	1.18
Primidone	500.00	(2)	0.40	1,250.00	(1)	1.00
Valproate	1250.00	(16)	0.83	1,037.50	(10)	0.69
Vigabatrin	1500.00	(3)	0.75	—	—	—

PDD/DDD, prescribed daily dose/defined daily dose.

Summary and Conclusions

Through a sometimes obscure process of growth, what began as a local appeal to take pity on people in the unenviable position of being afflicted with epilepsy has expanded into a legally constituted tertiary care system covering The Netherlands. This system cares for 14% of the patients with epilepsy in The Netherlands, presumably those with seizures resistant to therapy or those unable to cope unaided with the psychic or social aftermath of their illness. However, as the attitude of society toward people with disorders changes, and as the need to analyze the epilepsies through careful observation by trained personnel is gradually replaced by technical advances, secondary (specialist) care may eventually make tertiary care redundant. As a first step in analyzing the situation during the 1980s, the care provided by a university hospital and an epilepsy center has been studied. Overall, clear differences were observed in the patient groups. The duration of epilepsy of patients from the epilepsy center was longer, and they were more likely to have several seizure types and a higher composite index of impairment.

No distinct differences were found in the treatment policies between the secondary epilepsy care center and the tertiary epilepsy care center after patients were matched according to seizure type and duration of epilepsy. Nonetheless, distinct differences in treatment outcome were noted, as assessed by the CII. The combination of “same treatment but different outcome” agreed with the expected prevalence of more difficult-to-treat patients in a tertiary referral care center. The matching variables of “seizure type” and “duration of epilepsy” were thought to reflect the severity of epilepsy, but selecting patients by matching for seizure type and duration of epilepsy as evidence of similar severity is clearly insufficient to obtain completely comparable groups. Other factors aside from seizure type and duration of epilepsy are apparently important to the outcome of treatment of epilepsy. It will be a challenge to future researchers to find out which factors make the difference. The answer to that question will help determine whether tertiary epilepsy care will continue to be needed in the future, and suggest the appropriate equipment of such service.

During the 1980s, development started toward implementing information technology in patient care. Kempenhaeghe developed a Medical Information System (MIS) that supports patient care and administration, and this MIS system is now implemented in all epilepsy centers. This will eventually lead to a electronic patient file.

Unfortunately, although it was hoped that the electronic recording of patient's data would facilitate future comparisons between type of services and outcome using clinimetric indices, developments along those lines are still unsatisfactory.

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Chapter 307

Economic Aspects of Epilepsy and Antiepileptic Treatment

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Introduction

Significance of Economic Evaluation of Epilepsy and Its Treatment Modalities

Over the last 15 years there has been a dramatic increase in the therapeutic options available for the treatment of epilepsy. Epilepsy can now be treated with 13 different U.S. Food and Drug Administration (FDA)-approved antiepileptic drugs (AEDs);[37] surgery has now been established as an effective treatment for reducing or eliminating seizures in patients with medically intractable epilepsy.[61] Furthermore, vagal nerve stimulation (VNS), which includes the first implantable device with antiseizure properties, is now considered a safe therapeutic procedure, with clinically useful and sustained benefits.[53]

Many of these developments for treating epilepsy have a higher initial cost than the older treatments they replace. On the other hand, they may offer long-term savings if an increasing number of patients undergoing the new treatments become seizure-free. Therefore, it has become necessary to evaluate the economic burden of health care alternatives as well as their therapeutic efficacy. It is no longer sufficient merely to demonstrate a satisfactory degree of efficacy for a particular treatment if the cost of such therapy would cause the health care system to deny an equivalently efficacious yet cheaper remedy to a wider group of the target population.[10]

In addition, with the growing emphasis on cost containment and managed care in health care delivery, evaluations of the cost of epilepsy and its treatment are increasingly required by government agencies, advocacy groups, and health care payers concerned with the allocation of research and treatment resources among disease conditions.

In such a context, it is of interest to review critically the recently published literature on the economic aspects of epilepsy and its treatment in order to:

- Compare the variance and distribution of costs between and within various countries
- Identify and discuss methodologic issues and limitations in calculating the cost of epilepsy
- Evaluate the cost-effectiveness of the different treatments available

In this chapter, we explore these issues by systematically reviewing all the recent epilepsy-related cost-evaluation studies, analyzing their results, comparing their findings and, discussing their implications.

Types of Economics Studies

We identified studies via Medline and hand-searching English-language, epilepsy-related, and health economics journals. To have been included, studies had to have (a) been published between January 1998 and January 2006, (b) followed one of the standard methods of health economics evaluation (cost of illness [COI], cost-minimization analysis [CMA], cost-effectiveness analysis [CEA], cost-benefit analysis [CBA], cost-utility analysis [CUA]) (Table 1), and (c) aimed to provide estimations on the cost of epilepsy alone, not including comorbidities.

We identified 31 studies: 17 COI studies,[1,3,8,9,11,17,19,21,23,24,31,34,35,41,45,63,64] four studies using a CMA,[29,30,48,58] 10 studies performing a CEA,[16,32,40,42,47,49,55,56,59,65] two studies using a CBA,[12,13] and five studies performing a CUA.[18,25,44,50,51] All studies were classified based on how the primary outcome was reported.

The general, transnational comparative, approach presented here takes into account not only the differences in the studies' methods, but the epidemiologic features (incidence and prevalence of epilepsy), stage of economic development, and organization of health care sector in the countries studied.

Table 1 Types of economic evaluation

Type of study	Description
Cost-of-illness studies (COI)	To itemize, value, and sum the costs of a particular problem with the aim of giving an idea of its economic burden
Cost-minimization analysis (CMA)	If the interventions have the same consequences, the economic analysis can concentrate on inputs only. This analysis is concerned with the identification of the intervention with the lowest possible costs
Cost-effectiveness analysis (CEA)	If the outcome of interest is the same in two programs, but they have different success in achieving the outcome
Cost-benefit analysis (CBA)	If neither the consequences nor the outcomes of two programs are the same; cost-benefit analysis aims to compare all social costs and consequences across different interventions or against a do-nothing option
Cost-utility analysis (CUA)	This analysis is preferred by analysts who have reservations about valuing benefits in dollar terms; *utility* refers to the preferences individuals or society may have for any particular set of health outcomes—this approach incorporates quality of life adjustments to treatment outcomes

Transnational Comparison of Cost-of-illness Studies

COI studies enumerate all costs attributable to a disease to arrive at a total cost of that disease. A COI study can follow a variety of perspectives.[2,5,7,14,28,33,36,38] From an epidemiologic point of view, COI studies can be conducted using either a prevalence- or incidence-based approach, depending on whether an annual or longitudinal horizon is adopted. Also, COI evaluations vary in their study design (i.e., prospective or retrospective study design) and method of data collection (e.g., questionnaire, medical database, case report). The sampling strategy is also a significant parameter when evaluating the cost of a disease. This ranges from collecting data from a general practitioner or a hospital, to estimating costs based on administrative databases or national samples. COI studies also vary as to whether the direct or indirect costs of a disease are calculated. *Direct costs* are the monetary value of resources consumed in the prevention, treatment, or rehabilitation of people with the disorder. *Indirect costs* represent the loss of productivity to society due to a disease and its treatment.[7,14]

To achieve a comprehensive transnational comparison of all recent COI studies, these study perspectives were taken into consideration when analyzing, categorizing, and tabulating the studies and their results. The results appear in Tables, 2, 3, and 4.

Comparison of COI Prevalence-based Studies

Table 2 includes only prevalence-based studies, stating the country of the study, data source, method of data collection, direct or indirect costs estimated by the study, and any additional general information in the study that is of significance.

Comparison of COI Incidence-based Studies

Incidence-based studies are shown in Table 3, with an emphasis on the evolution of costs over time. Only the first 4 years after onset were included, because most studies estimated costs up to the fourth year.

Direct Cost Distribution

Table 4 depicts the breakdown of the direct costs of epilepsy treatment. Three categories are included:

- Hospital costs: In- and outpatient visits, admissions, emergency room visits, and emergency transportation (ambulance) costs
- Drug costs: Prescribed antiepileptic drugs (AEDs), as well as costs attributable to adverse drug reactions from the AEDs
- Other costs: Diagnostic procedures, such as laboratory tests, electroencephalography, computed tomography, and magnetic resonance imaging scans as well as medical consultations that are part of the diagnostic procedures.

Six studies that did not categorize direct costs in this way were excluded from the table.[19,23,34,35,41,63]

Cost-minimization Analysis

CMA provides the simplest economic evaluation when the alternate treatments, in this case AEDs, have equivalent clinical efficacy. To be equivalent, the comparators should be of the same efficacy in all patients, under all conditions, with similar risks of adverse events.[10]

Table 5 displays study duration, the configuration of the treatment pathways followed, and the nature of the direct costs included during the cost estimation procedure for four CMA studies, along with the mean cost per patient for each of the four AEDs that were examined.

Cost-effectiveness Analysis

CEA assesses how efficiently a specific health intervention influences health, compared with the next best alternative. Thus, CEAs specifically account for the costs to health of a disease and treatment that are typically excluded from COI studies (i.e., premature mortality, morbidity, disability, as well as pain and suffering).[36]

Tables 6 and 7 include ten CEA studies. Table 6 focuses on CEA studies on AEDs; Table 7 presents CEA studies of alternative treatments which, in this case, only incorporate surgical treatment of epilepsy. The information included relates to the AEDs/treatments compared, patient population, cost and outcome measures, as well as the general findings/results of each specific study.

Cost-benefit Analysis

CBA primarily attempts to reduce outcome measures to monetary terms. Hence, when costs and benefits are expressed in the same unit of measurement, it is possible to judge whether a specific therapeutic modality is desirable from a societal viewpoint.[26] The two published CBA studies were conducted by the same author. Therefore, a tabulation of the CBA studies is not presented.

Table 2 Main characteristics of cost-of-illness studies: prevalence-based studies

Country	Data sources	Data collection		Annual cost per patient (US$)		Comments (costs in US$)	Ref.
				Direct	Indirect		
U.S.	National sample	Retrospective	Database	1,758	—	2,053 for children	24
U.S.	Multiple MCOs	Retrospective	Database	3,007	—	Adults taking CBZ formulation (*n* = 1,767)	22
U.S.	MCO and medical center	Retrospective	Database	935	5,994	Total cost from 1,031–12,612 in different severity groups	8
U.S.	MCO	Retrospective	Database	1,575/3,449	—	1,575 (epilepsy-attributable cost) and 3,449 (case-control estimate)	19
U.K.	GP	Retrospective	Provider and population surveys	3,065	—	866–6,855 depending on seizure frequency	31
Italy	EC	Prospective	Questionnaire	1,098	—	547–3,530 in different prognostic categories (aged 18+)	3

Italy	EC	Prospective	Provider and population surveys	1,055	—	371–3,551 in different severity groups	63
Italy	UH, hospital and outpatient service	Prospective	Case report	1,590	—	760–2,941 in different severity groups (childhood epilepsy)	23
Italy	Referral centers	Retrospective	Case report	1,588	224	Total cost from 1,569 for adults to 2,412 for children	11
Italy	Referral centers	Retrospective	Questionnaire	1,290		411–2,941 in different severity groups	21
The Netherlands	GP, UH and EC	Prospective	Questionnaire and cost diary	2,444	—	808 cost at GP, 2,790 cost at UH, and 4,298 cost at EC	34
India	EC	Retrospective	Case report	55	128	117 cost of annual productivity loss	35
India	Medical centers	Retrospective	Questionnaire	105	283	Cost of travel included in direct cost	64
Hong Kong	EC	Retrospective	Database	433	582	Costs derived from dividing the 4-year total cost by 4	41
Burundi	National sample	Retrospective	Questionnaire	1.8	10.5	12 (epileptics), 7.7 (control group)	45
Oman	UH	Prospective	Case report	1,524	—	Only patients aged 13 and over	1

EC, epilepsy center; GP, general practitioner (physician); MCO, managed care organization; UH: University hospital.

Cost-utility Analysis

In CUA, an attempt is made to directly assess the impact of the treatments on patient well being by using a utility indicator. This approach shifts the focus from clinical indicators to the patients themselves and assesses the treatment effects, via various parameters, to determine the quality of life (QoL).[39] Although an increasing number of published studies focus on the QoL of epileptic patients, only five studies, referring to AED treatment of epilepsy, can be considered to be cost-utility studies.[18,25,44,50,51]

Table 3 Main characteristics of cost-of-illness studies: incidence-based studies

				Annual cost (US$) per patient (direct cost)					
Country	**Data sources**	**Data collection**		**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Comments (costs US$)**	**Ref.**
U.S.	Medical center plus HMO	Retrospective	Database	3,813	848	569	496	3,749 to 7,671 depending on seizure frequency (in 4 years)	9
U.S.	National sample	Retrospective	Database	1,317	892	892	892	Top-down analysis	24
U.S.	Expert panel	Retrospective	Questionnaire	6,506	2,282	2,282	2,282	Bottom-up analysis	24
France	Specialists	Prospective	Cohort	2,379	626	—	—	Second year costs were more sensitive to seizure frequency	17

Conversion of the Results of Cost-of-epilepsy Studies

In transnational comparisons of health economics evaluations, several monetary issues must be considered, such as fluctuating exchange rates and the rate of inflation.

For purposes of comparison, the estimates from different countries were converted into 2003 US$. The rate of inflation was calculated using the Consumer Price Index. The exchange rate used was the mean exchange rate for the US$ for the year 2003.

Table 4 Distribution of direct costs

Country	Hospital costs (%)	Drug costs costs (%)	Others (%)	Ref.
U.S.	51	24	25	24
U.S.	39	31	30	8
U.K.	32	10	58	31

Italy	23	60	17	3
Italy	82	12	6	11
Italy	34	48	18	21
India	17	58	25	64
Burundi	22	71	7	45
Oman	68	23	9	1

Findings Among Economics Studies

Cost-of-illness Studies

The literature identified 17 studies performing a COI analysis. Tables 2, 3, and 4 show the results in US$ at the 2003 exchange rate. A total of 15 of these studies were included in Table 2, as prevalence-based studies. The vast majority of the studies were conducted in the United States or Europe (three in the United States, one in the United Kingdom, five in Italy, and one in The Netherlands). Only four other countries conducted COI studies (India, Hong Kong, Burundi, and Oman). Table 3 shows that only three studies followed an incidence-based approach (one of which calculated the costs in two different ways). Two of these were based in the United States, and the other in France.

Prevalence Based-studies

Direct Costs of Epilepsy.

The estimated annual direct costs of epilepsy vary significantly from study to study and range from US$1.8 to US$3,449 (Table 2). However, a closer look reveals that a smaller disparity of costs tends to exist if they are grouped based on the degree of development of the country in which the studies were conducted. Estimated direct costs vary from US$935 to US$3,449 in the United States, US$3,065 in the United Kingdom, and US$1,055 to US$1,590 in Italy. In the less developed countries, the costs of epilepsy range from US$55 to US$105 in India, to US$1.8 in Burundi (Table 2). Nevertheless, the variation between the costs is large. Heaney et al. found that prices for medical services and AEDs vary widely even between developed countries.[27] In a comparison among eight economically developed European countries, similar medical services were found to vary by as much as 24 times, whereas the prices of similar AEDs varied up to 4.4 times. Previous reviews have speculated on the difficulty of comparing results from COI studies.[2,5,7,14,28,33,36,38] Methodologic issues give rise to such disparities in cost-of-epilepsy estimations. Perhaps future studies could normalize or reduce international disparities; for example, they might be normalized using per capita income, gross domestic product, or some other standard economic indicator.

Indirect Costs of Epilepsy.

Most cost studies in epilepsy have focused on direct medical costs because researchers have easier access to records of medical care. Records of nonmedical care are less centralized, and formal records of time costs, which are necessary for calculating indirect costs, rarely exist.[27] As a consequence, out of the 17 COI studies reviewed in this chapter, only six have estimated the indirect costs incurred by a specific society. Out of these six studies, only one found the indirect costs to be less than the direct costs.[11] This study calculated only productivity losses because of hospital visits and hospitalization to derive direct costs. The other studies reached a consensus in finding indirect costs considerably greater than direct costs. In general, four of the six studies found indirect costs to be from two to six times that of the direct costs (Table 2). Once again, the discrepancy between the findings is largely due to differences in the methodology applied.

Table 5 Cost-minimization studies

Country	Study duration (year)	Treatment pathways	Nature of direct costs	Mean cost (US$) per patient (whole follow-up)				Ref.
				PHT	CBZ	VPA	LTG	

12 European countries	1	First-line switched to second-line mono- or polytherapy	Hospital, drugs, laboratory tests, ADR	30–86	108–328	134–880	683–1,896	29
U.K.	2	First-line switched to second-line mono- or polytherapy	Hospital, ambulatory care, drugs, laboratory tests, ADR	1,337–1,395	1,444–1,506	1,576–1,605	2,770–3,770	30
U.K.	1	If withdrawal, CBZ switched to VPA, and LTG switched to CBZ	Drugs, switching of treatment, ADR	—	337	—	980	58
India	2	First-line switched to second-line mono- or polytherapy	General drug therapy, ADR	—	60	105	—	48

ADR, adverse drug reactions; CBZ, carbamazepine; LTG, lamotrigine; PHT, phenytoin; VPA, valproate.

Distribution of Direct Costs.

Considerable variability exists in the findings among COI studies regarding the distribution of direct costs (Table 4). Four studies found hospital costs to be the highest, four others found drug costs to be the most important, and one study positions other general expenses at the top. This can be explained, once again, by the different methods used, and also by the fact that each country has a unique health care system that functions in a different way. For example, Burundi, which has a health care system that is less well developed than most Western countries, has drug costs as the main cost. The U.K.-based study by Jacoby et al. found other general costs to be most significant.[31] This was also the only study to include the cost of inpatient episodes as a separate cost component. Kotsopoulos et al. discovered that using a more comprehensive list of cost components is associated with a decrease in the contribution of drug and hospital costs to the total direct costs.[33]

Incidence-based Studies

All three studies that estimated the direct costs of epilepsy from an incidence-based approach indicate high initial health care cost at onset for most patients, followed by lower cost in subsequent years (Table 3). This reflects the high cost of initial diagnostic evaluation and the fact that some patients achieve early remission.[7] Costs in subsequent years tend to stabilize around a fixed amount. De Zélicourt et al. found that costs during the first year were highly sensitive to the severity of seizures, whereas second-year costs had a much lower variance and were sensitive to frequency of seizures.[17]

Comparison of COI Studies: Methodological Issues

Any attempt to compare the findings of the reviewed COI studies is hampered by the methodologic variations among the studies. The methodologic differences arise from a variety of sources.

Differences in the Study Population.

Cost estimates will vary according to which population is targeted and how the sample is ascertained. Some studies included the whole spectrum of the epilepsy population, whereas others included only certain specific age groups or severity groups. Certain studies only estimated the cost of childhood epilepsy,[23] whereas others focused entirely on the cost of adult epilepsy.[3] The study by Al-Zakwani et al.

only included patients aged 13 years and above.[1] It is not surprising that no study had the same proportion of young/old people in its population, and this in itself can result in cost variation, because clear evidence suggests that childhood epilepsy is associated with greater costs than is adult epilepsy.[11,23,24] In addition to this, the various COI studies include different population groups regarding seizure frequency or seizure type/severity. Begley et al.,[9] de Zélicourt et al.,[17] and Jacoby et al.[31] found that costs differ significantly relative to seizure frequency, thereby demonstrating how populations with dissimilar seizure frequencies can affect the estimated cost. Similarly, Beghi et al.,[3] Begley et al.,[8] Garattini et al.,[21] Guerrini et al.,[23] and Tetto et al.[63] found a notable difference in costs, depending on which severity group the populations belonged.

Table 6 Cost-effectiveness of antiepileptic drugs as add-on therapy

Drugs compared	Patients	Cost measures	Outcome measures	Results (costs in US$)	Refs.
LTG and TPM	Intractable epilepsy	AED, routine treatment	50% seizure reduction	200 mg/day TPM dominates 500 mg/day LTG (0.875 probability) 400 mg/day TPM dominates 500 mg/day LTG (0.986 probability)	65
CLB, GBP, LTG, and VGB	Intractable epilepsy	AED, ADR, routine treatment	50% seizure reduction, no ADR	GBP: 14,158 per satisfied patient* LTG: 11,474 per satisfied patient* CLB: 2,363 per satisfied patient* VGB: 2,770 per satisfied patient*	56
LTG and TPM	Intractable epilepsy	AED, ADR, routine treatment	50% seizure reduction, no ADR	LTG: 11,472 per satisfied patient* 3,442 per 50% seizure reduction TPM: 6,050 per satisfied patient 2,823 per 50% seizure reduction	55
CBZ, PB, PHT, and VPA	Idiopathic epilepsy	AED, hospital costs	75% treatment response, 70% adherence	PB: $868–1639 per DALY averted $798–2386 ICER PHT: $903–1690 per DALY averted 836–2496 ICER CBZ: $1194–2106 per DALY averted $1138–3399 ICER VPA: $1708–2845 per DALY averted $1675–5003 ICER	16
LTG and standard therapy (first-line AEDs)	Intractable epilepsy	AED, ADR, routine treatment	50% seizure reduction	ICER of LTG: 715 per year	32
LTG and standard therapy (first-line AEDs)	Intractable epilepsy	AED, ADR, routine treatment	Seizure-free days	ICER of LTG: 7.6 per seizure-free day	42

LEV and standard therapy (first-line AEDs)	Intractable epilepsy	AED, ADR, routine treatment, hospitalization	Seizure-free days	ICER of LEV: 60.7 per seizure-free day	59

ADR, adverse drug reactions; CBZ, carbamazepine; CLB, clobazam; DALYs, disability adjusted life years; GBP, gabapentin; ICER, incremental cost-effectiveness ratio; LEV, levetiracetam; LTG, lamotrigine; PB, phenobarbitone; PHT, phenytoin; TPM, topiramate; VGB, vigabatrin; VPA, valproic acid.

*A patient who achieves 50% reduction in the number of seizures and is not affected by any serious adverse drug reaction.

Table 7 Cost-effectiveness of alternative treatments

Treatments compared	Patients	Cost measures	Outcome measures	Results (costs in US$)	Ref.
Surgery, medical therapy	Refractory temporal lobe epilepsy	Direct costs, indirect costs	Seizure-free patients	Surgical therapy more effective —return of high initial surgery costs—in 7.3–35 years (depending on which costs are included in the analysis) Employment income: 29,961 seizure-free (after surgery) 27,968 improved (after surgery) 18,231 unimproved (after surgery) 21,084 (before surgery)	47
Surgery, medical therapy	Refractory temporal lobe epilepsy	AED, hospital costs, transportation	Seizure-free patients	Total direct costs over life-time: 5,646 (no surgery) Cost of surgery: 1,355 70% of patients become seizure-free after surgery 30% of patients off AED within 3 years of surgery	49
Vagal nerve stimulation, medical therapy	Children with Lennox-Gastaut syndrome	Direct costs, indirect costs	Seizure-free patients	VNS therapy more effective —return of high initial therapy costs in 2.3 years. Costs during 6 postoperative months are 3,370 less than costs during 6 months before VNS	40

VNS, vagal nerve stimulation.

Estimating the epilepsy costs of patients treated in the community requires careful case ascertainment to ensure representativeness. Retrospective ascertainment of cases contained in administrative databases has the potential to yield larger and more representative samples than does clinic-based sampling, but the validity of this approach can be highly variable. For example, AED use as a proxy for an epilepsy diagnosis has a high-false positive rate, since AEDs are prescribed for other conditions (e.g., pain, bipolar disorder).[57] Rochat et al. estimated the prevalence of epilepsy, using prescription data from the Danish National Health service.[52] Lacking diagnostic information, the authors excluded from their analysis subjects who also were prescribed high-strength analgesics, under the untested assumption that these subjects were using certain AEDs for pain instead of epilepsy. On the other hand, Frost et al. used a three-step approach that identified cases by procedure codes, followed by physician verification and record review of uncertain cases.[20]

Differences in the Methods of Data Collection.

COI studies used a variety of methods when collecting their data. Some researchers acquired their cost-estimation data from administrative databases, whereas others used a questionnaire or prepared a case report for each patient (Table 2). Langfitt notes that studies relying on questionnaires sent to patients recruited by physicians are likely to obtain unreliable data.[36] A number of studies gathered their data retrospectively, whereas others followed the patient population prospectively (Table 2). Studies that prospectively attribute episodes of care to epilepsy based on a priori criteria are more likely to provide more accurate estimates than are retrospective assessments that rely on coding algorithms or medical record data that were not designed for this purpose. It is encouraging that the number of prospective studies conducted has increased significantly in recent years. The study by Levy et al. revealed that, out of 13 prevalence-based studies reviewed (conducted between 1993 and 2000), not one was prospective.[38] Among studies from 1998 to 2004, and out of 15 prevalence-based studies, five are prospective (Table 2).

Differences in Sampling.

Some COI studies ascertained epilepsy cases from centers/clinics or general hospitals/medical centers, whereas others gathered their data from general practitioners, administrative databases, or national samples; in some studies, the data were collected from a combination of sources (see Tables 2 and 3).[34] Different sampling strategies result in different case mixes. The cost of the same type of epilepsy differed among three health care settings (clinical research hospital, general hospital, and outpatient services).[23] Clinical samples will have a higher proportion of severe cases. Samples drawn from administrative databases may be more representative of the entire spectrum of epilepsy, but also may contain nonepilepsy cases, depending on how rigorously cases are defined, as noted earlier.

Differences in What is Included in the Costs.

Although those studies that estimated the direct costs reached a general level of consensus as to which cost components they should include, this was not the case for studies that estimated indirect costs. Some studies that estimated indirect costs considered lost earnings resulting from excess unemployment and premature mortality,[8] whereas other studies included only work days lost for treatment.[11] One study used a very crude estimation model based on how many patients claimed that epilepsy was the reason they left their jobs or how it generally affected their professional lives.[35] Thomas et al.[64] and Nsengiyumva et al.[45] doubled the estimated indirect costs calculated, arguing that each patient is accompanied by one other person during his transport and admission to the hospital. These different approaches to the measurement of indirect costs illustrate the difficulties in identifying the extent to which epilepsy is to be held responsible for lost productivity. Levy states that the problem is generated by the inherent difficulty of observing the effect of a chronic disease on professional occupation.[38]

Differences in Methods of Calculation.

Two studies demonstrated the variability in costs when different methods of calculation are employed, even if the same population is used.[19,24]

Costs can be estimated using a top-down analysis or a bottom-up analysis. According to the top-down approach, COI is calculated as a percentage of the total health expenditure, whereas the bottom-up approach uses the summation of cost data from individual patients to arrive at total disease costs. The first method is a service-based analysis, whereas the latter is an individual-based analysis.[33] Halpern et al. estimated the costs of epilepsy using both methods and found very different results (US$1,317 using top-down analysis and US$6,506 using bottom-up analysis).[24] Two other approaches to determining the costs of epilepsy are the *epilepsy-attributable cost method* and the *case-control cost method*. Using the epilepsy-attributable cost method, the mean cost per patient is derived by summing all the costs classified a priori as epilepsy related. In the case-control cost method, the overall health care costs of epilepsy patients (cases) are compared with the costs for similar persons without epilepsy (controls), with the difference between cases and controls representing the marginal cost of epilepsy.[38] Frost et al. performed a study comparing the two methods and found very diverse results (US$1,575 for epilepsy-attributable cost and US$3,449 for case-control estimate).[19] Smaller differences between methods (US$1,650 vs. US$1,836) were found in a study of institutionalized mentally retarded persons.[15] This demonstrates that the choice of estimation method can significantly influence the proportion of costs attributed to epilepsy.

Most of these methodologic limitations are not confined to COI studies; they arise in all types of economic analyses.

Cost-minimization Analysis: Methodological Issues

Four studies reported a CMA (see Table 5). Three of those were conducted in Europe (two in the United Kingdom and one a collaborative effort of 12 European countries) and one in India. All four studies restricted their evaluation to include only direct medical costs. Also, all studies used a model relating to the treated patients and treatments prescribed, based on clinical trials specific to each product. Furthermore, all studies took side effects and adverse drug reactions (ADRs) associated with medical treatment into consideration, because it is now established that such ADRs are usually associated with considerable medical costs.[54]

Despite the similarities, the studies differ significantly on many other parameters:

- The studies generally followed differing combinations of treatment pathways, particularly regarding the drugs evaluated. Only the Heaney et al. studies had exactly the same configuration of treatment pathways.[29,30]
- The studies incorporated dissimilar cost components when estimating the total direct costs of the AEDs (Table 5).
- The studies differed in duration. Two of the studies had a drug follow-up period of 1 year,[29,58] whereas the other two lasted for 2

years.[30,48]

Despite the methodologic variations of these studies, there does appear to be a consensus regarding the ranking of the AEDs relevant to their cost. Lamotrigine was by far the most expensive drug, incurring more than twice as many costs as any other drug. Valproate and carbamazepine were the second and third most costly drugs respectively, incurring much more costs than phenytoin, which appears to be the cheapest drug of the four examined.

Equivalent Efficacy in CMA Studies

By definition, CMA studies are only conducted when it can be assumed that the alternate treatments considered are equally effective. All CMA studies of AEDs consider AEDs equally

effective when they result an equal proportion of patients achieving at least a 50% reduction in seizures. However, such an outcome measure leads to inconclusive results, because most clinical trials tend to assess efficacy of AEDs based on seizure reduction alone.[38] However, AEDs differ when judged on other criteria. For example, although carbamazepine and la-motrigine do not reportedly differ in their efficacy in controlling seizures, one study has found lamotrigine to be better tolerated and to have positive effects on subjective well-being.[10] Therefore, lamotrigine may be preferred to carbamazepine treatment. In CMA studies, only the cost-effect of AEDs is included in the evaluation, whereas the effect on patient QoL is ignored because an indicator, based on clinical efficacy rather than effectiveness, was used. Recent literature has been in agreement that it is preferable to use CEA rather than CMA when comparing the various treatments of epilepsy, because CEA avoids conclusions being based on clinical efficacy parameters alone.[10,36,38,39]

Cost-effectiveness Analysis: Methodological Issues

Ten CEA studies described in Tables 6 and 7 are indicative of the two areas in which cost-effectiveness analyses have focused recently:

- AED effectiveness: Whether novel AEDs lead to improved tolerability and seizure control, which accumulate cost savings and better health effects that offset the higher cost of the drugs (Table 6).
- Epilepsy surgery: Whether the high initial resource investment for epilepsy surgery reduces long-term costs due to improved seizure control (Table 7).

As in previous studies, a variety of methodologic limitations exist in CEA. In this type of analysis, comparisons can be made since, by definition, CEA studies include comparisons in their analysis. Therefore, a CEA study can facilitate informed decisions about which treatment pathway to follow.

Cost-effectiveness of Antiepileptic Drugs

Table 6 shows that all seven studies used patients with intractable epilepsy, five included adverse drug reactions in their calculations,[32,42,55,56,59] and five studies defined their outcome measures by calculating the proportion of patients who achieved a 50% seizure reduction[32,55,56,65] or a 75% treatment response,[16] whereas two studies focused on seizure-free days gained due to successful AED therapy.[42,59]

In their study, van Hout et al. adopted a Bayesian statistical analysis to calculate the probability that therapy A dominates or weakly dominates therapy B.[65] They found that 200 mg/day of topiramate is more effective than 500 mg/day of lamotrigine by a probability score of 0.875. If the dose of topiramate was to be increased to 400 mg/day, the probability of it being more effective than lamotrigine would rise to 0.986. It is notable that this study does not incorporate costs related to side effects of the AED. This omission may affect the results, because higher dosages of topiramate than those provided in this study have been associated with higher numbers of patients discontinuing therapy.[60]

Selai et al. attempted to estimate the cost attributable to AED use to achieve patient satisfaction.[55,56] Satisfaction was defined as the achievement of a 50% reduction in the number of seizures, as well as absence of any serious adverse drug reactions in the patient. Results, which are illustrated in Table 6, include topiramate being found to be more cost effective than lamotrigine, a finding that is consistent with those of van Hout et al.[65]

Markowitz et al. adopted a different perspective in calculating the cost-effectiveness of a certain AED therapeutic pathway.[42] The incremental cost per extra day without a seizure was calculated. Results showed that the use of lamotrigine is associated with an overall reduction of use in direct medical care resources (hospitalizations, outpatient visits, diagnostic and laboratory tests, and surgery), and that this would result in a US$ 7.6 saving per seizure-free day gained. Sheehy et al. followed a similar approach and found the incremental cost effectiveness ratio (ICER) of levetiracetam to be US$ 60.7 per seizure-free day.[59] A problem that arises from such an analysis is that there is no published evidence of seizure-free days being correlated with economic cost. Only seizure frequency has been found to be related to medical costs, as explained in the COI analysis.

The studies by Chisholm and Knoester et al. also attempted to calculate the cost-effectiveness of AED therapy based on incremental cost effectiveness ratios (ICERs).[16,32] Where as Chisholm estimated the costs required to achieve a 75% treatment response and 70% adherence, Knoester only estimated the costs required to achieve a 50% reduction in seizures. Knoester et al. measured the cost-effectiveness of lamotrigine and estimated an ICER of US$715 per year.[32] The Chisholm study found that, out of four AEDs (carbamazepine, phenobarbitone, phenytoin, and valproic acid), phenobarbitone was found to be the most cost-effective, with a US$868 to US$1,639 cost per disability-adjusted life years (DALYs) averted and an ICER of US$798 to US$2,386.[16] Costs were found to have great variation depending on which region of the developing world the countries belonged to, with African countries having the lowest costs and Eastern Mediterranean countries the highest.[16]

Cost-effectiveness of Temporal Lobectomy

Table 7 presents the three studies that have focused on the cost-effectiveness of epilepsy surgery. It shows that two of the studies examined similar patient populations using similar outcome measures, the latter being the proportion of patients becoming seizure-free after the surgery.[47,49] The third study referred only to children diagnosed with Lennox-Gastaut syndrome.[40]

Platt and Sperling found surgical therapy to be considerably effective.[47] A return of the high initial surgery costs was attained in a period ranging from 7.3 to 35 years, depending on which costs were included in the analysis. This, by itself, is illustrative of how methodologic variation can affect a study's results. It is interesting to note that the mean employment income was found to increase considerably after the surgery (from US$21,084 to US$29,961) in patients who became seizure-free, but decreased (from US$21,084 to US$18,231) in patients who did not improve after surgery.

Similarly, in their study in India, Rao and Radhakrishnan found temporal lobectomy to be very cost effective, as its initial costs were US$1,355, in comparison with total direct lifetime costs of US$5,646.[49] Because 70% of patients became seizure-free after the surgery and 30% discontinued AED use within 3 years of the surgery, the overall lifetime costs after the surgery were reduced compared to the overall lifetime costs had the surgery not taken place.

Majoie et al. focused on vagal nerve stimulation (VNS) therapy, which they found to be considerably cost-effective, as it returns the high initial therapy costs in just 2.3 years. To illustrate this, epilepsy costs during the 6 post-operative months were found to be US$3,370 less than the costs during the 6 months before the therapy was carried out.[40]

Use of Hypothetical Modeling in CEA Studies

CEA studies showed that hypothetical modeling of certain outcomes is the most common method for such an analysis in epilepsy studies. Such outcomes could result from different treatments, services involved in treatment, treatment of ADRs, and other treatment pathways. This involves combining data from various secondary sources, thus comparing the new AEDs through situations that are not relevant to the specific CEA. Heaney offers a characteristic example of a CEA study of lamotrigine, which used data that included patients who may have failed trials of both vigabatrin and clobazam.[26] Because most of the CEA studies reviewed are retrospective and must rely on existing data, such methodologic flaws are commonly incorporated into the estimations and, consequently, the results.

Selai et al. demonstrated the importance of using an accurate model to estimate the cost effectiveness of an antiepileptic therapy.[55] Significant differences were found when presenting data as cost per patient treated, compared with the cost for reducing seizures by more than 50%, compared with cost per patient satisfied. When only the cost of a patient becoming 50% seizure-free was considered (without indices of satisfaction), the costs dropped considerably. Given that most of the CEA studies reviewed estimated cost effectiveness solely on the grounds of patients achieving a 50% seizure reduction, it is conceivable that many of the costs have been underestimated.

Table 8 Cost-utility studies

Treatment evaluated	Patients	Cost measures	Results (costs in US$)	Ref.
LTG	Refractory epilepsy	Direct costs	49,935 per QALY	44
VNS	Refractory epilepsy	Direct costs, indirect costs	52,349 per QALY (using the time trade-off method) 114,275 per QALY (using the EuroQol EQ-5D)	18
CLB, GBP, LTG, TPM, and VGB	Refractory epilepsy	Direct costs	Only TPM and VGB patients show an increase in EQ-5D scores. TPM has an ICER of 11,767 per QALY compared with VGB.	51
CBZ, LTG, TPM, and VPA	Newly diagnosed and refractory epilepsy	Direct costs	Best treatment scenarios: TPM (first-line treatment) and LTG (second-line treatment) cost 11,372 per additional QALY compared to VPA (first-line treatment) and TPM (second-line treatment).	50

The full range of pharmaceutical therapies feasibly used in the U.K. health system	Newly diagnosed and refractory epilepsy	Direct costs	Best treatment scenarios: Partial seizures: CBZ (monotherapy), VPA (monotherapy), CBZ (second- line treatment) and OXC (adjunctive therapy) if willingness to pay >27,685 per QALY. Generalized seizures: VPA (newly diagnosed epilepsy), and TPM (adjunctive therapy) if willingness to pay >53,831 per QALY.	25

CBZ, carbamazepine; CLB, clobazam; GBP, gabapentin; ICER, incremental cost effectiveness ratio; LTG, lamotrigine; OXC, oxcarbazepine; TPM, topiramate; VGB, vigabatrin; VPA, valproic acid; VNS, vagal nerve stimulation; QALY, quality-adjusted life-year.

Cost-benefit Analysis

Only two studies performed a cost-benefit analysis.[12,13] The earlier study by Boon et al. aimed at estimating the cost-benefits of VNS.[13] A later study by this group went a step further, estimating and comparing costs of daily treatment of patients who were either treated with AED polytherapy only, underwent epilepsy surgery, or had VNS.[12]

VNS was found to be very cost-beneficial on both occasions. The study by Boon et al. estimated that, on average, the annual epilepsy-related direct medical costs dropped from US$10,665 (before the implantation) to US$5,091 (at 12 months after the implantation).[13] This group also found costs reduced from US$5,331 to US$2,757. Both studies reach a consensus, because costs seem to be reduced by half.[12] Direct costs were estimated in dissimilar ways, which might explain the variation in cost figures.

Additionally, the Boon et al. study found that the mean decrease in costs to patients who followed traditional AED polytherapy was minimal.[12] Specifically, costs were reduced from US$2789 to US$2,675 in this patient group. Interestingly, epilepsy surgery was found to be only moderately cost-beneficial, because it reduced average annual costs from US$1,618 to US$1,310. On the other hand, one could argue that a saving of US$308 per patient per year accumulates to a substantial amount over the long term.

In both studies, Boon et al. appear to define CBA idiosyncratically as costs avoided.[12,13] This is a significant shortcoming, since the term benefits should include all types of benefits (e.g., QoL improvements) and not only costs avoided.

It is not surprising that CBA studies are not very favorable to researchers conducting economic evaluations, because they require both costs and consequences to be expressed in monetary terms or ratios. Therefore, CBA studies necessitate the placing of a monetary value even on outcomes that defy economic evaluation in monetary terms. Subsequently, they exclude very important outcome measures that are impossible to equate or express as monetary values.

Cost-utility Analysis

Only five of the studies incorporated a CUA[18,25,44,50,51] (Table 8). All studies utilized the quality adjusted life years (QALY) calculation, which determines the impact of a treatment on both a patient's longevity and on the value of those additional life-years. Messori et al. focused on the use of lamo-trigine in refractory epilepsy and estimated the QoL values by prospectively interviewing a group of patients with refractory epilepsy.[44] Clinical data were obtained from a placebo-controlled clinical trial of lamotrigine,[43] and the various costs were derived from Begley's cost-of-illness study.[4] Only direct costs were taken into account.

This study concluded that the use of adjunctive lamotri-gine in refractory epilepsy costs, on average, US$49,935 per QALY (year of life in which a patient enjoys perfect health). Because this type of evaluation facilitates a comparison of treatments relating to various diseases, the cost of QALYs produced by AEDs may be compared with QALYs produced by different treatments in different areas. This study found lamotrigine to have a worse pharmacoeconomic profile in comparison to other (nonepilepsy) pharmacologic treatments.

Although this study can be considered pioneering, because it was the first CUA on antiepileptic treatment, its validity is questionable, since the data are obtained from three separate studies. As a result, the QoL data were obtained from an ad hoc study on patients not necessarily taking the drugs under evaluation.

Forbes et al. performed a CUA of VNS for adults with medically refractory epilepsy.[18] The study used a meta-analysis of randomized controlled trials of VNS and estimated that six people require the implantation of VNS devices in order for one person to experience a 50% reduction in seizure frequency. Costs saved from improved epilepsy control were taken from previously published literature. The total cost per QALY was found to be US$52,329 when using the time trade-off method and US$114,275 when EuroQol EQ-5D utility values were used.

In this study, most patients were unable to complete the time-trade off valuations, even in the presence of a research nurse; this raises questions regarding the appropriateness of using this method with epilepsy patients.

Remak et al. focused on five different AEDs (clobazam, gabapentin, lamotrigine, topiramate, and vigabatrin) and found that only topiramate and vigabatrin patients showed an increase in their EQ-5D scores. Topiramate was found to have an ICER of US$11,767 per QALY compared with vigabatrin.[51]

Another study by Remak et al. and the study by Hawkins et al. focused on evaluating the costs incurred from a variety of treatment scenarios.[25,50] Remak et al. evaluated a variety of treatment scenarios in which carbamazepine, lamotrigine, topiramate, and valproic acid were used either as first-line or second-line treatment. They concluded that the best treatment scenario would be to administer topiramate as first-line treatment and lamotrigine as second-line treatment. Such a scenario would cost an additional US$11,372 per additional QALY, compared to the second-best treatment scenario, which would involve administering valproic acid as first-line treatment and topiramate as second-line treatment.[50]

Hawkins et al. focused on the full range of pharmaceutical therapies used in the U.K. health system. They found that,

for partial seizures, the best treatment scenarios would use carbamazepine and valproic acid (administered as monotherapy), lamotrigine (administered as second-line treatment), and oxcarbazepine (administered as adjunctive therapy) if the willingness to pay for additional health benefits exceeded US$27,685 per QALY. Similarly, for generalized seizures, valproic acid was found to be the best treatment scenario for newly diagnosed epilepsy and topiramate for adjunctive therapy, if the willingness to pay for additional health benefits exceeded US$53,831 per QALY.[25]

Caution should be used when interpreting cost-utility studies, because it has already been demonstrated that the choice of utility instrument determines the results to a considerable extent.[62] The Stavem study compared four methods of measuring utility weights (time trade-off, standard gamble, 15D, and the EuroQol EQ-5D visual analog scale) and found that these preference instruments measure different aspects of health-related QoL and, therefore yield different results.[62]

Overview of Findings

Over the last 6 years, a plethora of studies have focused on the costs of epilepsy using a number of health cost evaluation methods. In this chapter, the various studies were compared to assess the economic, conceptual, and methodologic issues in this growing literature.

Many of the authors of these studies do not fully explain their methods, which introduces uncertainties into the results and limits their value. This might be partly explained by the researchers' lack of economic expertise, since most studies were performed by medical specialists. Kotsopoulos et al.[33] and Levy[38] observed similar problems in their reviews.

Inevitably, there are many limitations and methodological complexities in epilepsy cost studies, and these limitations should be taken into consideration when interpreting the results. The main issues identified were differences in the study population, differences in the sources used to obtain the data, differences in what is included in the costs, and differences in the methods of cost estimation.

In spite of this methodologic heterogeneity, some interesting interpretations can be made regarding the results of the studies. In particular, COI studies demonstrated a marked difference among costs in various countries and health care systems. Costs tend to be higher in more developed countries in comparison to the lesser developed ones; however, this was an expected outcome (Table 2). Studies found costs in uncontrolled patients to be from 1.5[24] to 3.5[9] times higher in the first year of treatment compared to the second year, when better control is achieved through treatment. Studies examining the longitudinal aspect of epilepsy-related costs found costs to be very high in the year of onset but then decreasing until a steady figure was reached in 2 to 4 years (Table 3). COI studies focusing on the breakdown of costs came to very inconsistent results, but do show that each health care system works in a unique way and has dissimilar cost components (Table 4).

To further our understanding of the total costs of epilepsy, the authors of future COI studies must provide clear methods and analysis of their data. Such studies will continue to be of limited use unless they are conducted with a common set of methods that will allow comparisons across studies. Unfortunately, previous reviews identified the same issues of

concern, and only a limited degree of improvement has occurred.[2,5,7,14,28,33,36,38,46]

CMA evaluations, which mainly focused on four drugs, found lamotrigine to be the most costly and carbamazepine the most economical. Nevertheless, such studies inappropriately assumed equivalent clinical efficacy of these drugs to represent equal seizure reduction rates. This resulted in these drugs being equal in all aspects and therefore being compared as such. Should a broader perspective be placed on equivalent drug efficacy, then CMA will no longer be able to be applied to the majority of AEDs, because they will be found to generate different patient outcomes.

CBA studies, which are the least popular within the literature, generally focused on VNS and epilepsy surgery, and found both these treatments to be significantly cost beneficial.[12,13] The limitations of these studies have been outlined earlier.

CEA studies found topiramate to be more cost-effective than lamotrigine, and phenobarbitone to be more cost-effective than carbamazepine, phenytoin, and valproic acid. Surgical lobectomy and VNS were found to be very cost-effective treatments in the long term. In such studies, the common use of hypothetical modeling based on secondary data is very likely to give rise to inaccurate results. Nevertheless, CEA studies, compared to CMA evaluations, avoid the efficacy of drugs being reduced to clinical efficacy parameters alone and therefore include more dimensions of the consequences of treatment.

CUA studies go a step further by assessing the treatment's effect on the patient, incorporating QoL adjustments to the treatment outcomes. This facilitates the comparison of a variety of therapeutic options across the medical spectrum in terms of patient-perceived preferences, and can ensure that resources are allocated fairly among the various diseases.

Within the span of this review (January 1998 to January 2006), only five CUA studies had been performed so far in the epilepsy field. This small number is disappointing, considering that CUA is becoming the favored tool in the economic evaluation of health care. The scarcity of CUA studies can be partially explained by the fact that there is still difficulty and controversy concerning the way the patients' point of view can be incorporated in an economic analysis and eventually expressed in monetary terms.

Summary and Conclusions

Despite the methodologic heterogeneity and the difficulties of comparing the studies, there are significant findings. If cost-of-epilepsy studies follow more uniform methodology and data collection, they can offer invaluable information about which therapeutic modalities are most effective. Only then can economic evaluations of epilepsy treatment inform decisions about the allocation of scarce health care resources.

Also, future economic studies in epilepsy must aim to evaluate the variability in costs incurred according to the various case definitions of epilepsy, severity of the disease, cost components, and various demographic influences on the disease. This will provide insights regarding the great variations in costs found by the majority of cost-evaluation studies, and will lead to a greater consensus on which specific methodology should be utilized.

The International League Against Epilepsy (ILAE) has recognized the importance of economic considerations in the development of epilepsy care and has focused on improving the methods used to conduct epilepsy cost studies so that comparisons across studies within epilepsy can be made.[51]

The expertise of economists, health service researchers, and epileptologists must be combined if we hope to overcome the methodologic problems that arise during cost evaluation of this disease. Only then will we be able to adequately document the economic burden of epilepsy and evaluate alternative strategies for its prevention and management.

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Chapter 308

The Economic Impact of Epilepsy

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Introduction

Epilepsy imposes a significant clinical, epidemiologic, and economic burden on societies throughout the world. This chapter focuses on the economic dimension of this burden or impact, in particular how it can be measured and, ultimately, how it can be reduced. Three specific questions are addressed: First, what is the relevance of an economic perspective to the management of epilepsy as a public health issue? Second, what is the economic perspective on the burden of epilepsy, and how well do economic studies demonstrate this burden? Third, what is the economic perspective on evaluation, and how does economic evaluation contribute to the evidence on clinical and cost effectiveness? This chapter complements others in this volume that deal with related topics, including the issues surrounding epidemiologic burden and need, treatment effectiveness, and the costs of treatment.

Interest in the economic aspects of epilepsy has been growing in both richer and poorer countries. In the wealthier nations, an ongoing debate continues about how to curb rapidly rising health care costs. State-financed health care systems are facing the problem of an inflation of needs and, therefore, are forced to find ways to limit the expenditures for health care. On the other hand, poorer countries are facing the fact of a tremendous need for health care but inadequate economic resources. The uneven distribution of epilepsy care among countries, and sometimes within countries, does not correspond so much with real needs, but rather with underlying economic conditions. It is a well-known fact that approximately 80% of all health expenditures occur in established market economies, whereas the remaining 20% of financial resources is spent in the rest of the world, where approximately 90% of the people with epilepsy are living.[21] Therefore, it is important to consider the economic aspects of ongoing efforts to improve the situation of people with epilepsy in all regions of the world.

The growing interest in this field has led to an increasing number of publications on economic aspects of epilepsy. Since the early 1990s, attempts have been made to apply general instruments of health care economics to the field of epilepsy care. The first studies mainly concentrated on the calculation of the cost of epilepsy. In a second phase, the economic studies investigated, in particular, selected aspects of the treatment of epilepsy, such as antiepileptic drugs or epilepsy surgery, including its cost-effectiveness.[4,24] In correspondence with the World Health Organization (WHO), the perspective has been broadened once again to the global burden of disease[21] and to the assessment of the performance of different health care systems.[20,32] Furthermore, economic aspects have been included within the Global Campaign on Epilepsy, a joint initiative launched in 1997 by the International League Against Epilepsy, the International Bureau for Epilepsy, and the WHO to improve the situation of people with epilepsy worldwide.

The Rationale and Relevance of an Economic Perspective

Before considering different methods and results from economic analyses of epilepsy and its treatment, it is important to raise the question of why such studies are needed in the first place. In short, the requirement for an economic dimension in planning and evaluating treatments and services for epilepsy stems from a tension between, on the one hand, the epidemiologic or clinical need for intervention, and on the other, the resources available to meet this identified need. In the extreme case of there being no limits on resource availability, there would be little need for an economic dimension, other than to track the steady, unremitting flow of monies being channeled into epilepsy care and prevention. Equally, in the extreme case that care or prevention strategies are entirely ineffective or unavailable, economic considerations might be restricted to considering the economic consequences of the untreated natural history of disease. Of course, the reality for most diseases and most countries is that effective care and/or prevention strategies exist, but the budget is limited, which implies that choices must be made about which interventions to make available within this budget constraint. Assuming that the primary goal of a health system is to optimize potential health improvements in the population, then the choice is made mainly in terms of delivering maximum health gain for least cost. This is in fact a definition of efficiency, and is the concept underlying cost-effectiveness and other forms of economic evaluation (see later sections).

In addition, economic considerations may and certainly should enter into the debate around a number of other components of epilepsy care, including the organization or quality of primary care and neurologic services in a country, plus the financial protection of epilepsy patients and their families from potentially catastrophic payments for drugs and health care services. There is currently very little available epilepsy-specific evidence that can be drawn upon to shed light on these issues, but the experience from comparative international studies undertaken is that reliance on private, out-of-pocket payments by households for health care is a far less equitable financing mechanism than prepayment via taxation or insurance.[34] In countries where there is a high level of out-of-pocket expenditures on health, therefore, an increased likelihood exists of pushing households containing a family member with epilepsy into impoverishment.

The Epidemiologic and Economic Burden of Epilepsy

The “burden” of epilepsy can be considered at a number of levels and from a number of different viewpoints, so it is as

well to distinguish between these different perspectives when thinking about what measured burden is likely to show. Most directly, this “burden” will be felt at the individual or household level in terms of the physical pain and psychological stress associated with epileptic seizures, the (potentially catastrophic) financial implications of treatment or lost work opportunities, and, in all too many societies, the social stigma attached to this condition. By contrast, burden at the community or population level is typically expressed in terms of the epidemiologic profile of the disease (numbers of new or existing cases in the population), the financial resources devoted to prevention and treatment, and societal productivity losses resulting from premature mortality or morbidity. The focus here is on population-level estimates of both the epidemiologic and economic burden attributable to epilepsy at the national and international level, but this should not detract from the importance of establishing and sharing better information concerning the household burden of epilepsy, particularly in low-income countries where the risk of catastrophic out-of-pocket expenditures is highest.

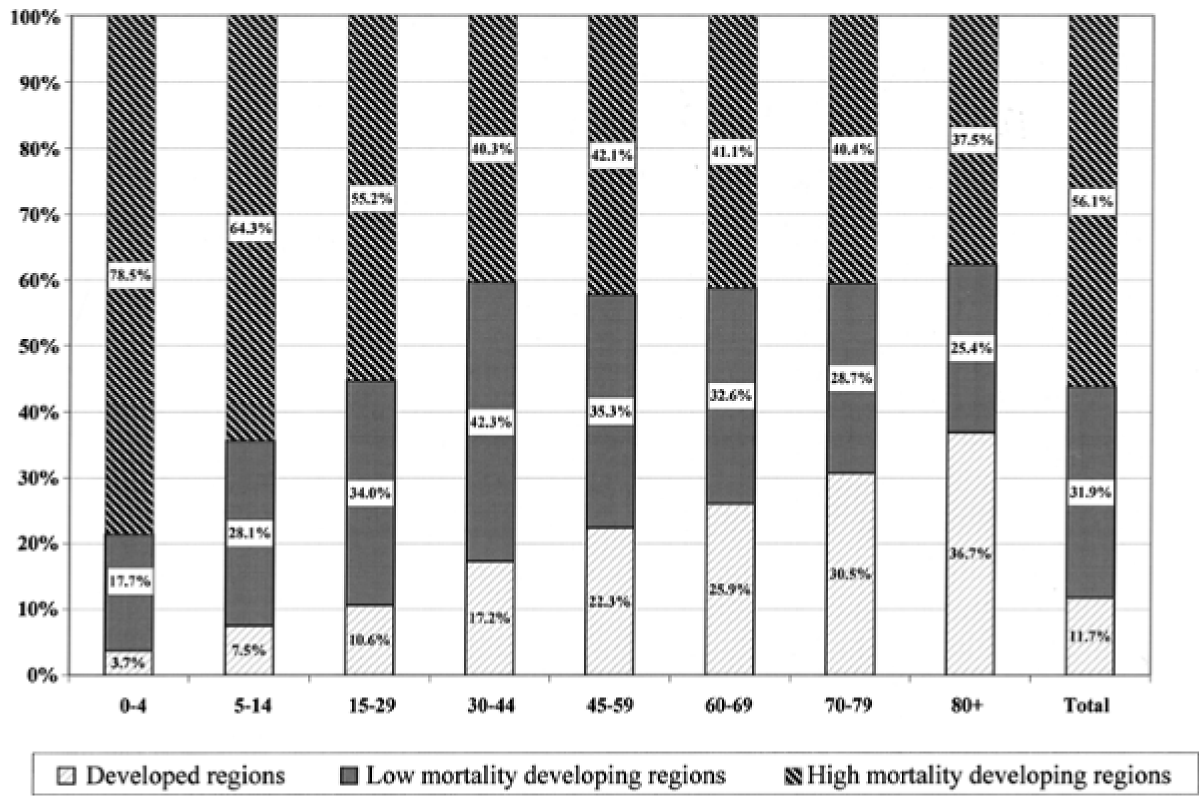

FIGURE 1. Distribution of the global burden of epilepsy by age group and level of economic development. (From World Health Organization. Statistical Annex 3, 2004. In: World Health Report 2004: Changing history (available at http://www.who.int/whr/2004/annex/topic/en/annex_3_en.pdf), with permission.)

Before illustrating the assessment of both the epidemiologic and economic burden of epilepsy, it is important to note that epilepsy is not an uniform disease, but rather a term that summarizes many conditions that have the symptom of an epileptic seizure in common. Policy-makers, such as governments or insurance agents, often do not distinguish between the different forms of epilepsy when evaluating the need for care and the services available, respectively. In economic terms, the consequences of having epilepsy may vary considerably depending on the frequency, severity, and kind of seizures. Furthermore, not all economic consequences may be attributable to epilepsy, because epilepsy is often related to an underlying disease that may continue to exist even after remission of the seizures. Various economic studies in epilepsy have therefore divided up the population with epilepsy into different prognostic groups with similar health care needs.[2]

Epidemiologic Assessment of the Global Burden of Epilepsy

From the epidemiologic perspective, epilepsy is a significant cause of disability and disease burden in the world. Using a metric called the disability-adjusted life years or DALY,[21] which can be thought of as 1 lost year of healthy life, the WHO has calculated the global burden of disease and injury attributable to different causes or risk factors. This measure of burden assesses the gap between current health status and an ideal situation in which everyone lives into old age free of disease and disability. Overall, epilepsy contributed more than 7 million disability-adjusted life years (0.5%) to the global burden of disease in 2000.[15,33] FIGURE 1 shows the distribution of DALYs or lost years of healthy life attributable to epilepsy, both by age group and by level of economic development. It is apparent that close to 90% of the worldwide burden of epilepsy is to be found in developing regions, with more than half occurring in the 39% of global population living in countries with the highest levels of premature mortality (and lowest levels of income). An age gradient is also apparent, with the vast majority of epilepsy-related deaths and disability in childhood and adolescence occurring in developing regions, whereas later on in the lifecycle, the proportion drops because of relatively greater survival rates into older age by people living in more economically developed regions. In terms of the absolute number of healthy life years lost per 1 million population, estimates range from less than 500 in early childhood and older age in developed regions to as much as 2,000 in the younger age groups of high-mortality developing regions. Owing to the consistent and comparative nature of this work, summary estimates of population health such as these provide the most appropriate measure of the relative burden of epilepsy at the international level.

That is not to say, however, that such summary measures of population health are not without limitations. For example, good-quality data on basic epidemiologic parameters (such as rates of incidence or recovery) do not exist for many developing countries, such that estimates for whole subregions of the world may be extrapolated from neighboring regions where such data do exist. Just as importantly, and in common with other disease categories, good-quality descriptive data on disability due to epilepsy were lacking at the time of this study. Recent work on the measurement of health state preferences in epilepsy[14] suggests that the disability weights applied to treated and untreated epilepsy in the Global Burden of Disease study may be underestimated. Finally, DALY estimates of the burden of epilepsy take into account neither the potential health consequences on people other than the diagnosed case (such as the burden on family members or caregivers), nor the nonhealth consequences of disease (such as lost ability to work).

Economic Assessment of the National Burden of Epilepsy

Disease burden has also been gauged from an economic perspective for many years in the form of so-called "cost of illness" studies, which have attempted to attach monetary values—as opposed to DALY estimates—to a variety of societal costs associated with a particular disorder, often expressed as an annual estimate aggregated across all involved agencies. Such studies have direct parallels with epidemiologic estimates of disease burden, in the sense that the principal aim is to influence policy-making and resource allocation by demonstrating the relative magnitude or burden associated with a particular disorder (by multiplying case prevalence by cost per case, put very crudely). The potential advantage of cost of illness studies over DALY-based estimates of burden is that they are able to measure in a single metric (money) not only the direct health-related impact of disease (in terms of health care costs, etc.) but also other economic consequences such as lost work or leisure time, and family or caregiver burden.

Economic assessments of the national burden of epilepsy have been conducted in a number of high-income countries such as Italy and the United States[1,3] and also in two developing countries, India and Burundi.[22,29] A number of comparative reviews have also been produced.[2,12,16,25] Each of these studies or reviews have set out to demonstrate the various economic implications the disorder has in terms of health care service needs and lost work productivity. For example, the Indian study calculated that the total cost per case of these disease consequences for epilepsy amounted to US$344 per year (equivalent to 88% of average income per capita), and that the total cost for the estimated 5 million cases resident in India was equivalent to 0.5% of the gross national product.[29]

An extensive array of costs is associated with epilepsy, including so-called "direct" intervention costs such as inpatient and outpatient care, medication, and diagnostic tests, and also "indirect" costs that cover lost time and productivity. The indirect cost of epilepsy, due to unemployment, underemployment, or premature death, is higher than one may assume. Studies have shown, for example, that in Europe, the unemployment rate among people with epilepsy is two or three times higher than among the general population.[9] To face unemployment or underemployment is a severe problem for these patients. At the same time, it is an (often underestimated) economic burden to society.

The wide range of potentially included cost components has resulted in significant heterogeneity in studies that attempt to capture the cost of illness (COI) of epilepsy. Key methodologic discrepancies include the range of services included in direct cost estimates (e.g., surgery, residential care, special education), the valuation of lost time (loss of productivity, loss of caregiver productivity), the inclusion of mortality costs, sampling frames (patients who are seeing specialists, adults, children), data sources (expert panel estimates, medical records, patient surveys), and the handling of comorbidity.

Table 1 provides a summary of the differing methods used in selected COI studies across a number of developed and developing countries. Most studies include inpatient and outpatient fees, drug costs, diagnostic costs, and laboratory costs. Others include the cost of surgery,[8] ambulatory transportation[5,8] and residential care, day care, and social workers costs.[13] Many of these studies use national tariff costs, which may include profits,[1,5,22] while other studies use insurance fee schedules,[8] payments, or charges. Only one study took into account mortality costs,[5] but many studies did take into account productivity losses due to loss of time from medical treatment. However, the methods with which these costs were calculated varied widely, from including only the patients' lost productivity days due to hospital visits and hospitalization, to productivity losses due to travel, to the loss of productivity time of caregivers.

Because such studies differ with respect to the exact methods used, as well as underlying cost structures within the health system, they are currently of most use at the level of individual countries, where they can serve to draw attention to the wide-ranging resource implications and needs of people suffering from epilepsy. However, like epidemiologic estimates using DALYs or some other measure of population health, COI studies are not in themselves appropriate mechanisms for allocating resources to specific treatment strategies.

The Economic Evaluation of Epilepsy Treatment

Having established the *attributable burden* of epilepsy, two subsequent questions for decision-making and priority-setting relate to *avertable burden* (the proportion of attributable burden that is averted currently or could be avoided via scaled-up use of proven efficacious treatments) and *resource efficiency* (determination of the most cost-effective ways of reducing burden). Analysis of these two issues can reveal the technically most efficient response to the attributable burden of a particular disease. FIGURE 2 provides a schematic overview of these concepts, showing how the total burden of epilepsy can be broken down into the following separate components: (a) disease burden that is already being averted via existing strategies, (b) disease burden that could be avertable via scaled-up implementation of cost-effective interventions such as antiepileptic drug treatment, and (c) disease burden that cannot currently be averted by the set of interventions under consideration.[30]

Economic analysis provides a set of principles and analytical techniques that can be usefully employed to assess the relative costs and consequences of different interventions or treatment strategies.[23] It seeks to address a number of key policy questions about the magnitude of epilepsy, the relative effect and cost of different treatment strategies, and the most appropriate use of scarce resources (Table 2). Economic evidence can be generated in two distinct ways. Preferably, it would be generated on the back of additional empirical studies in a range of socioeconomic settings (particularly in developing countries, where current evidence is most scarce). Well-designed and sufficiently powered economic evaluations of epilepsy treatments are certainly needed and valuable, but they are also difficult, time-consuming, and expensive to carry out (as well as having limited application beyond the immediate confines of the study location). Alternatively, cost-effectiveness information can be generated via appropriate disease modeling of the best available existing data concerning the expected costs and effects of interventions in these different settings. The danger of this latter approach lies in the inevitable assumptions that are required to be made when basing cost-effectiveness estimates on a variety of data sources from different research settings, whereas the obvious attraction is that policy-relevant results can be generated relatively more quickly and cheaply. Over the longer-term, these two approaches can in fact be considered complimentary—empirical studies feed into initial or revised modeling exercises, while modeling studies synthesize and may even stimulate empirical research studies—but this should not detract from the shorter-term need to bring cost-effectiveness arguments into play when arguing for an increased level of resource investment to and prioritization for epilepsy care.

Table 1 Summary of methods used in selected cost-of-illness studies of epilepsy

First author year country (reference)	Inclusion/exclusion criteria	Direct medical costs	Direct nonmedical and indirect	Data sources	Comments

			costs		
Nsengiyumva 2004, Burundi (22)	Reoccurrence of at least two spontaneous seizures within 24 hours	IP, OP, DT, DG,	PC*2	Survey, retrospective	Inclusion standards are very different from other studies; assumed patients came with attendee and so doubled time costs
Thomas 1998, India (29)	Consecutive cases of epilepsy found in outpatient epilepsy service	IP, OP, DT, DG	PC (OP*2+ SE) NT*2	Retrospective questionnaire	Assumed every patient came with attendee and so doubled time and travel costs; all patients were seeing specialists
Krishnan, 2004, India (16a)	All patients at one epilepsy clinic	IP, OP, DG, EC	AT, PC (estimated)	Clinical records	Small sample, weak study
Beghi 2004, Italy (1)	18 years or older with confirmed case of epilepsy, attending epilepsy centers for over 2 years	IP, OP, DT, DG, SP		12-month prospective, questionnaire and patient-held records	Patients kept details of diagnostic tests and visits; no official records used; only adults at referral clinic included
Berto 2000, Italy (5)	Registered since 1996, diagnosed with epilepsy at last visit and had at least one follow-up, and a follow-up period of at least 12 months	IP, OP, DT, DG	PC, PCT	Clinical Records, retro	Excellent study, takes into account employment rate, working days, differentiates between children and adult costs

Jacoby 1998, UK (13)	Patients of GP and must have had active epilepsy in last 2 years or be on AEDs	IP, OP, DT, DG, EC, HV, PS, NU, RS			
Halpern 2000, USA (8)	Bottom-up approach: Expert panel of neurologists, general physicians and pediatricians	IP, OP, DT, DG, **SU,** AD	AT	Expert Panel	Panel estimates are subjective. Excluded opinion of generalists but did include cost of surgery
	Top-down approach: Subset of respondents to 1987 National Medical Expenditure Survey	IP, OP, EC		National Survey	No indirect costs
Begley 2000, USA (3)	Patients seeing specialists and generalists	IP, OP, DT, DG, **SU,** EC, PC, AT, LT	PC, MC, HP	Billing data/medical charts; survey of adult patients in treatment center	Indirect costs may be overestimated because data taken from epilepsy centers, but may be underestimates as based on adults only

Direct Costs: OP, outpatient visits; IP, inpatient visits; SE, seizure events; DT, diagnostic tests; DG, drugs; AD, drug side-effects; SU, surgery; SP, specialists; EC, emergency consultations; AT, ambulatory transportation; LT, lab tests; HV, health visitors; PS, psychiatrists/psychologists; NU, nurses; RS, remedial schooling. **Indirect costs:** PC, productivity costs; PCT, productivity costs due to travel; NT, normal transportation; MC, mortality costs.

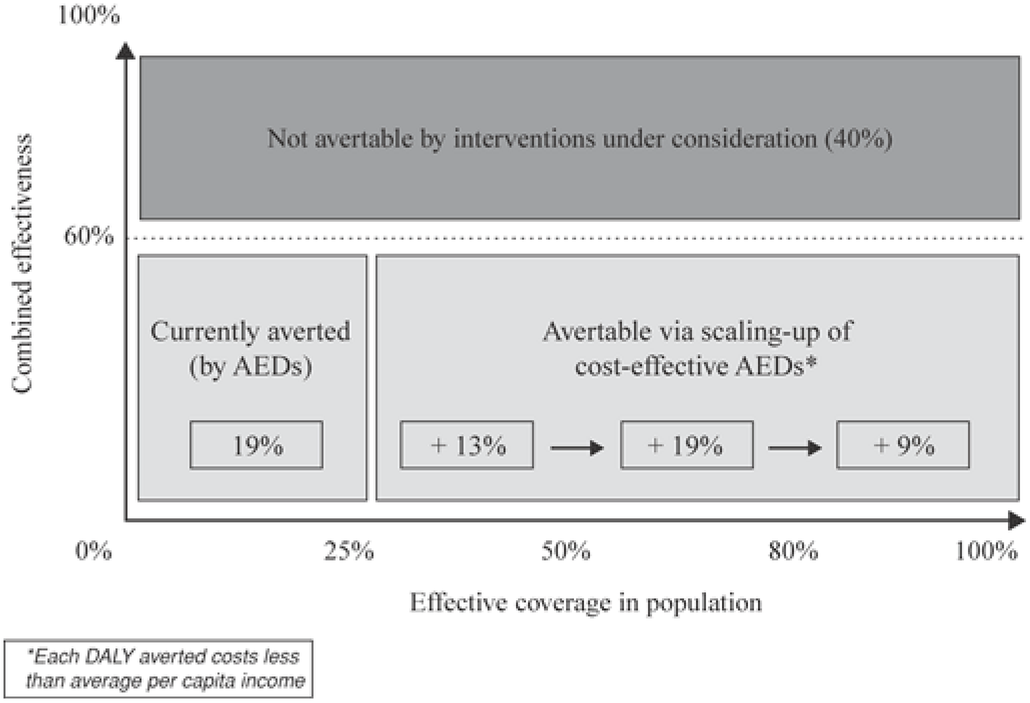

FIGURE 2. Attributable and aver-table burden of epilepsy in a WHO African subregion. (Schema is from World Health Organization. *Investing in Health Research and Development: Report of the ad hoc Committee on Health Research Relating to Future Intervention Options.* Geneva: World Health Organization, 1996; data is from Chisholm D. Cost-effectiveness of first-line anti-epileptic drug treatments in the developing world: a population-level analysis. *Epilepsia.* 2005;46:751–759, with permission.)

Table 2 Policy questions addressed by economic analysis of epilepsy

Policy question	Research task	Evidence generated
1. How significant is the burden of epilepsy?	Estimate burden of disease (DALYs) Identify other social and economic consequences of disorders	% of total disease burden caused by epilepsy Estimates of monetary impact on economy
2. How effective is epilepsy treatment?	Estimate current effective coverage Assess impact of new interventions	Comparative efficacy of interventions % of burden averted with current treatment or avertable with better treatment strategies
3. What will it cost to provide effective care?	Calculate full cost of interventions Estimate cost of scaling-up coverage	Comparative cost of interventions at different levels of treatment coverage

4. What are the most efficient strategies?	Integration of costs and effectiveness Inclusion in essential packages	Evidence-based priorities for the efficient allocation of health care resources

Despite the identified need for cost-effectiveness evidence by, among others, the International League Against Epilepsy[23] and the WHO,[31] there remains a relative paucity of empirically based economic evaluations from developed countries, and a total absence in developing countries. This, despite the likelihood that, due to their low price and established efficacy, use of older AEDs in primary health care settings can be expected to represent a very cost-effective use of health care resources. Most completed economic evaluations have been concerned with specific treatment modalities, in particular the cost-effectiveness of different AEDs—either comparing first-line treatment or considering newer AEDs as add-on pharmacotherapy—and epilepsy surgery.[12,25]

Economic analysis of different first-line AEDs in the context of higher-income countries has been carried out using a form of economic evaluation called *cost-minimization analysis*, which assumes that treatment effectiveness is the same for each comparator, thereby coming down to a simple comparison of which drug produces this effect for the lowest cost. Assuming equal efficacy, and basing estimates of resource use on a consensus panel, an economic appraisal of carbamazepine, lamotrigine, phenytoin, and valproate as initial treatment in adults with newly diagnosed epilepsy was carried out, first in the United Kingdom and subsequently across 12 European countries.[10,11] This study found that lamo-trigine was two or three times more expensive in terms of direct health service costs incurred. Assuming equal efficacy remains a contested area, however, with manufacturers of newer AEDs dedicated—and in some cases mandated by regulatory authorities—to showing reduced sedative effects.

A number of economic evaluations have also been carried out in high-income countries for adjuvant pharmacotherapy using newer AEDs, arguably because that is where new market opportunities (and also regulatory standards) are greatest. For example, one study showed that the use of lamotrigine resulted in an overall reduction in the use of health resources,[17] a phenomenon referred to as a *cost-offset* (i.e., additional drug costs are offset by lower service use). The cost-effectiveness measure in this study was the additional cost associated with the newer drug per extra seizure-free day gained over the study period. An alternative measure that has also been used in this context is the Quality Adjusted Life Year (QALY), which combines both the quantity and quality of life into a composite index of health outcome. Economic evaluations of this kind are called *cost-utility analysis*. One such study using this method calculated that the cost of gaining one QALY as a result of using adjunctive lamotrigine amounted to US$50,000.[19]

For the subset of patients with refractory temporal lobe epilepsy, incremental costs per QALY gained have also been computed for surgery (in comparison to medical therapy), with results in the range US$16,000 to US$27,000.[12] Using a lifetime approach, these studies indicate the potential economic advantages of investing in the shorter-term in order to produce long-term improvements in both seizure control and quality of life.[25]

Economic evaluations of different epilepsy treatments from lower-income countries are few and far between. Two of these come from a tertiary referral center in the Indian state of Kerala, where both a study of the cost and effects of surgery plus a pharmacoeconomic study comparing phenobarbitone, phenytoin, carbamazepine, and valproate (plus combinations) were carried out.[26,27] The annual drug cost of phenobarbitone and phenytoin was estimated at US$15 to US$20, significantly lower than the cost of carbamazepine or valproate (US$50 and US$90, respectively). No estimation was made for the cost of health care visits or program management, however. For patients with refractory temporal lobe epilepsy, the cost of anterior temporal lobectomy was estimated at US$1,200 (compared to US$150 for similar patients not undergoing surgery), and the outcome was that 70% were seizure-free 2 years postoperatively (compared to about 10% for medically treated cases).

Another study stems from Colombia, which, based on an epilepsy surgery program established over the last decades in Cartagena.[7] has shown the feasibility of epilepsy surgery in a developing country. Although the cost of the surgical treatment in Colombia is relatively low (<US$2,000 for an operated patient), the program meets

international standards. Compared with the high cost of lifelong medication, it is evident that epilepsy surgery may be effective also in economic terms.

More recently, information has been generated as part of a wider WHO cost-effectiveness work program[28] on the amount of burden averted by the current or scaled-up use of AED treatments in low- and middle-income regions of the world, together with estimates of cost and cost-effectiveness.[6] Effectiveness was expressed in terms of DALYs averted, and costs were expressed in international dollars (I$, which take into account differences in purchasing power between countries or world regions). Compared to a do-nothing scenario (i.e., the untreated natural history of epilepsy), results from nine developing WHO subregions suggest that extending AED treatment coverage to 50% of primary epilepsy cases would avert between 150 to 650 DALYs per 1 million population (equivalent to 13%–40% of the current burden). This burden can be averted at an annual cost per capita of I$0.20 to I$0.80 for phenobarbitone and phenytoin (I$70–I$120 per treated case), and I$0.25 to I$1.33 for carbamazepine and valproate (I$105–I$207 per treated case). These cost estimates includes the AED drug itself, health care use, and also program implementation costs such as training and administration.

Older first-line AEDs (phenobarbitone, phenytoin) were most cost-effective because of their similar efficacy but lower acquisition cost (I$800–I$2,000 for each DALY averted). In all nine developing regions, the cost of securing 1 extra healthy year of life was less than average per capita income. Extending coverage further to 80% or even 95% of the target population would evidently avert more of the burden still, and would remain an efficient strategy despite the large-scale investment in manpower, training, and drug supply and distribution that would be required to implement such a program.

The results for one WHO developing subregion in Africa—consisting of 20 countries with a high rate of child mortality and a very high level of adult mortality—are depicted in FIGURE 2, which divides the total attributable burden of epilepsy as follows: (a) burden that is averted by AEDs at current levels of effective treatment coverage (19% of total burden), (b) burden that could be averted via the scaling-up of AEDs (up to a further 41% of total burden is averted if complete coverage could be reached), and (c) burden that is not avertable via AEDs (estimated to be 40%, although this assumes that the current level of drug compliance would prevail).

It may be argued that the purchase of the low-cost AEDs (like phenobarbitone) does not resolve the whole problem, because it is known that, in various regions of the developing world, epilepsy is not considered to be a medical problem but rather a trouble with social or spiritual implications. In such regions, medical treatment is not asked for unless there is a basic knowledge among the people offering primary health care. In addition there is a need for securing permanent access to AEDs, since an interruption of the treatment may cause a dangerous deterioration of the disease (indeed, if phenobarbitone is not gradually withdrawn but suddenly stopped, life-threatening status epilepticus may ensue). However, these arguments enhance the high impact of economic factors on the development of epilepsy care, especially in remote rural areas. An improvement of the condition will depend on the sustained access to low-cost treatment and improved knowledge of how to use it. From an economic viewpoint, it still is the most cost-effective approach to use low-cost AEDs for a large number of untreated people.

Summary and Conclusions

The burden of epilepsy manifests itself at a number of different levels. Taking a population-level approach, both epidemiologic

and economic studies have revealed the extent of the negative impact of epilepsy on existing levels of health and health care. It is an unfortunate truth that the current burden, often couched in terms of the "treatment gap in epilepsy,"[18] is most concentrated in regions with the greatest health challenges and the least resources with which to respond to these challenges. More positively, however, one can conclude that, in these very regions, there exists the greatest opportunity to reduce current levels of epilepsy-related deaths and disability, employing efficacious treatments that have been shown to be a highly cost-effective use of scarce resources.

Although the volume of completed studies remains modest, particularly in middle- and low-income countries, increasing economic evidence supports the argument that interventions for epilepsy are not only available and effective but also affordable and cost-effective. This constitutes an important argument both for increased parity with other (noncommunicable) diseases and for increased investment into service development for this condition. This message has been supported and disseminated in all continents by the works and projects of the aforementioned Global Campaign on Epilepsy.

Critical factors in the successful implementation of such a scaled-up level of service delivery, apart from renewed political support and investment, can be expected to relate to appropriate training, continuity of drug supply, and enhanced consumer or community involvement.

Acknowledgment

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Chapter 309

Information Transfer and Education

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Introduction

The purpose of an international textbook on epilepsy is to educate as many people as possible about the field of epilepsy, thus enhancing the care of those with this condition. The ability of those working in the field to provide information to each other, their patients, and their patients' families and to the community at large is an important role. This means not only giving information, but also interpreting, comparing, and objectively evaluating the information and its sources. How this is accomplished is constantly changing. The ability to obtain and evaluate new information is critical to the clinician working with epilepsy. Today's clinicians have limited time to read journals and attend out-of-town meetings, yet they have increasing demands to document ongoing educational credits (CMEs). The sources for new information have changed from the time when the physician depended on scientific journals for the main source to the present, when there are many resources available. Industry is now playing a larger role in the information transfer process, and the ability to evaluate the objectivity of this for the health care provider becomes necessary.

The role of information transfer or dissemination affects all persons in the health field. This service is necessary for the ongoing education of physicians, scientists, physicians- and scientists-in-training, medical students, nurses, other health care providers, patients, their families and the community at large. The means for providing this service vary depending on the group that is involved and the specific goal of the information transfer. Technology advances have improved the way that information may be disseminated. Today, larger portions of the population are computer literate and have access to computers. Information provided via this means may be able to reach larger numbers of people.

The physician as an educator has a role in the information transfer process. In the past, most information was provided through written materials (books, journals) and lectures and seminars. Thus, information was often limited to only those within the medical field and was not readily available to lay people and the community at large. Currently, the means of information transfer include not only books, journals, and seminars, but also peer-developed guidelines for evaluation and treatment of specific diseases, Web-based audio/video seminars, online information with detailed discussions of disease processes, video presentations of surgical procedures, and active support groups for many chronic diseases.[3]

It is important for the treating physician and other health care providers to be knowledgeable about the current social and cultural issues pertinent to the populations that they treat. This means being able to apply these issues to the process of information transfer. Information and means of delivery that are acceptable and appropriate for one population may be totally unacceptable for another.

The dissemination of new research in the epilepsy field is critical to the quality of care for patients with epilepsy. This transfer requires the ability to provide health care providers access to information on new diagnostic tools, technology, and treatment options for patients once they have been evaluated as safe and available. This transfer also requires providing the interpretation of this research to the health care provider and the public.

The role of this chapter is to provide the reader with information about information transfer concerning epilepsy, ways of dissemination, self-education, the role that Health Insurance Portability and Accountability Act (HIPAA) regulations play in this information transfer, and ways of evaluating the effectiveness of this transfer.

Dissemination of Information Pertinent to Epilepsy

Epilepsy is a chronic condition affecting 2.7 million people in the United States and 50 million people worldwide.[55] It affects individuals of all ages, from the newborn to the elderly; 4% of individuals who reach the age of 85 years will have developed epilepsy. Many of these people will be cared for by health care providers who are not epileptologists and whose primary training in epilepsy consists of what they learned during their educational years in medical school and residency. A report by the National Institute for Clinical Excellence (NICE) in the United Kingdom noted epilepsy misdiagnosis rates of 20% to 31%.[37] This report cited the financial impact of these misdiagnoses as £160,125,000 ≠ British pounds, total cost. Krauss et al.[36] reviewed stories published in the media concerning epilepsy. They found that 31% of the stories contained errors; many of these were inaccurate reports on the science of epilepsy. Even physicians and pharmaceutical spokespeople provided incorrect information concerning drug treatments. These facts emphasize the need for education and dissemination of information to treating physicians and the public.

The National Center for Chronic Disease, Prevention and Health Promotion in the United States gathered experts in the field of epilepsy to develop a public agenda. This meeting led in 1997 to the first major public health conference on epilepsy, Living Well with Epilepsy, and the collaboration of multiple organizations in the United States with defined goals that included the following:

- Assessment of evidence linking elements of care to clinical outcomes in special populations of patients with epilepsy.
- Development of health service purchasing specifications for services related to epilepsy.
- Enhancement of awareness and understanding of epilepsy through targeted education and awareness campaigns and increased support of research.

- Development of a bibliography/database of work related to epilepsy self-management.
- Implementation and evaluation of the self-management interventions in epilepsy.
- Support of population-based epidemiologic studies of epilepsy prevalence, incidence, and health care needs in selected communities.
- Assessment of the utility of existing health care data sets for studying trends in access to care, levels of care, and other demographic variables related to epilepsy.
- Continuing development of a tool to assess public perceptions of epilepsy.
- Support of epidemiologic studies of preventable causes of epilepsy, including traumatic brain injury and infections such as cysticercosis.
- Evaluation of the incidence, prevalence, and patterns of care for epilepsy in a managed care setting.[9]

A second conference, Living Well with Epilepsy II, was held in 2003 to revisit the goals set by the first conference and develop new strategies for improved awareness. The organizers noted that there was still a lack of awareness concerning the seriousness of epilepsy and available treatment options. This lack of information involved all segments of society, including health care providers, patients with epilepsy, and the general public.[10] One of the charges from this conference was to address self-management and assure that those with epilepsy have the information and support needed to manage the condition and its treatment.

Learning Methods

Adult learners have different styles and needs for learning. As students, many of us quickly realized which manner of learning works best for us. Most of us experienced the lecture format as we passed through our educational programs. This method involves listening and comprehending and then processing the information for future retrieval. For some this is easy, whereas for others it is not. For some, the process of note taking enhances learning skills with this method. Others find that what they read and visualize leads to better learning and information retrieval. In the field of health care, learning has often been by demonstration and discussion. Technology has added another dimension to learning tools with the development of audio/video formats. Many lectures today are enhanced with digital slides, audio, and/or video. Another new tool that lends itself to the learning process is the ability to access information over the Internet. All of these methods are applicable to all those who need to learn about epilepsy: medical students, physicians-in -training, physician/specialists, nurses, other health care providers, researchers, patients, family members/caregivers, teachers, employers, and the public. For each of these groups, one or more of the methods may be applicable to the learning process.

Information Transfer to Health Care Providers

Traditional and Current Means of Information Transfer

Historically, physicians and other health care providers obtained information from textbooks, formal lectures offered as part of the educational process, peer-reviewed journal articles, annual meetings of their medical specialty, weekly or monthly “grand rounds” in hospital settings, and, more important, discussion with their peers. Other than the lectures in medical school, for which testing procedures existed, there generally were no means for evaluating the effectiveness of the learning process. Textbooks provide good general scientific and treatment information but may not always have the most up-to-date information on current therapeutic options because the publishing of textbook material may be several years behind current accepted therapy practices. Even journals may be somewhat out of date by the time their new information is published.

Technology advances have increased information resources available to health care providers. Information is available electronically. Journals and textbooks also are available via this format. Thus, physicians spend less time in libraries than in the past. There has also been a tremendous increase in the number of scientific journals being published. Educators have had to learn new ways of presenting information for lectures. The use of 35-mm slides has become a technology of the past. Most presentations now use a Power Point format with digitized video images. The problem sometimes is that of information overload. Lowe and Barnett noted that as of 1994 there were 17,000 new biomedical books and 30,000 biomedical journals published annually.[40] They estimated that a physician would have to read 19 original articles per day to maintain knowledge in a field. They also noted that most physicians in this time period obtained their information, not from books or journals, but from other health professionals. However, there is not always a filtering system in place to provide information that is relevant and up to date for a particular physician and clinical setting.

Traditionally, the exposure of medical students to information has been via lecture and bedside teaching methods. The amount of time devoted to teaching about epilepsy has always been small. Many students may complete their training in medicine without having seen a seizure or treated someone with epilepsy. Many training programs in the Western Hemisphere and Europe have implemented problem-based learning that provides exposure to a wide variety of disease states at all levels of medical school training. However, the amount of time spent on epilepsy remains small.

Information on epilepsy in nursing education and other health care education was a small part of the nursing educational process in the past. With the development of specialties in nursing, nurses with interests and talents in working with patients with epilepsy have become valued members of epilepsy teams. These nurses have become active members of the epilepsy community, working in hospital settings and as educators, researchers, and public health advisors. One example of their activities is the guideline for competencies for epilepsy nurse specialists published by the Royal College of Nursing.[12] Nurses have worked to increase knowledge of epilepsy in the school setting and have developed educational tools for of nurses in this field.[46]

Documentation of continuing medical/nursing education (CME/CNE) and maintenance of certification (MOC) are mandated by many states in the United States and many other countries. The numbers and types of CME credits vary from state to state and country to country. This documentation is often imposed by state licensing renewal processes and hospital accreditation. As with other types of learning, CME can be obtained in various formats, including attending accredited seminars, reviewing journal articles answering questions, and engaging in online activity through a hospital-, university-, CME-accredited organization. Continuing education is now required by many health care professions (e.g., physicians, nurses, pharmacists, dentists.)

The Accreditation Council for Continuing Medical Education (ACCME) in the United States reported in 2004 that they sponsored (directly and jointly) 71,564 activities, with 6.5 million participating physicians and 3.2 million participating nonphysicians. The range of activities included courses, regularly scheduled conferences, Internet enduring materials, other enduring materials, and journal-based CME.[2] Enduring materials

are printed, recorded, or computer-assisted instructional materials which may be used over time at various locations. Is continuing education effective in changing the practice of health care providers? Davis et al. reviewed the literature for articles relating to the effectiveness of various educational strategies from 1975 to 1994.[14] They specifically looked for studies that were randomized trials of education strategies that assessed physician performance and/or health care outcomes. Of 99 trials with 160 interventions, they found that 70% demonstrated a change in physician performance and 48% produced a positive change in health care outcomes.

Information Transfer to Students and Physicians-in-Training

Traditionally, information transfer and education have been via didactic lectures and bedside demonstration. The younger generation of students and physicians is very technology savvy and uses computers and other technologies easily. They have grown up using computers for most of their educational years and find that information accessible via this mode is to their liking. They incorporate this into other modes of information storage such as handheld devices (personal digital assistants, PDAs). Their learning modes are often different from those of their senior physicians. They are more comfortable in obtaining information electronically than from textbooks, and read this information off computers. They may be less likely to subscribe to printed journals in the future than this generation of physicians.

Time constraints of resident hours in the United States have changed the ways of educating residents and even medical students. There is often less bedside teaching than in the past. Within medical schools there is a renewed interest in providing quality education. Some schools have established academies of medical educators to advance the mission of education.[33] Although initial evaluations of these academies show that schools recognize teaching efforts by their faculty members and promote them for these efforts, it is unclear what the outcome is relative to student learning.

Epilepsy Information/Education

Epilepsy education constitutes a small portion of the curriculum for the typical medical student and resident. A study performed by Mason et al. evaluated three seminars on epilepsy given to third-year medical students.[41] They found that the seminars improved general knowledge of the subject but did not change attitudes about it.

Education about epilepsy for physicians in training is quite variable. Those in surgical specialties probably never receive any education during their training years. Those in primary care specialties such as medicine, pediatrics, and family practice may receive some, but this varies. Unique programs have been developed to teach neurology and child neurology residents about epilepsy. The J. Kiffin Penry Epilepsy Education Program runs two of these. They consist of a several-day minifellowship, with the curriculum consisting of daily lectures, workshops, and case presentations about epilepsy. Participants take pre- and post-tests to assess the knowledge gained.

Information Transfer to Patients and Caregivers

Patients, families, and other caregivers traditionally depended on their primary physician for information concerning medical status and treatment. A family might have had a general health care book on the bookshelf at home. Much of their information often came from friends or other family members. The patient accepted what was said to him or her and did not question the treating physician. Medicine has changed and now encourages the patient and family to participate in the care as an active member of the team. The availability of information through various media contributes to this participation. The use of the Internet to access information has increased patient knowledge but has also contributed to patient confusion about which treatment option may be the best. Kind et al. studied the availability of computer and Internet access in a low-income urban population in the United States.[35] In a survey of 260 people they found that 58% had access to a computer and 41% had home Internet access. Ninety-two percent of those surveyed indicated that they would like to discuss information on the Internet with a health professional. A Harris Poll from 2003 surveying Internet use reported that 67% of all adults have been online and that 57% use the Internet at home.[30] The estimate for European usage is 35.5%, and for worldwide usage it is about 15.2%.[42] Harrisinteractive surveyed patients in four countries (United States, France, Germany, and Japan) in January 2002.[28] This report noted that those surveyed in United States and Japan were most concerned about using Web sites not based in their own countries. Americans and Japanese were the most likely to purchase drugs online if they were available from pharmaceutical companies.

Patients and their families desire information about their health problems and treatment. This information contributes to improved compliance with medication, better relationships with health care providers, and a more positive outlook about the patients' medical problem.[27,38,48,49,51,52] The Healthy People 2010 Information Access Project is a collaboration of U.S. government agencies, public health organizations, and health science libraries to assist the public health workforce find and use information effectively.[54,55] A study by Deber asked whether patients wanted their physicians to do the problem solving and whether they wanted to be involved in the decision making.[15] Most of the patients wanted the physician to do the problem solving, but a significant percentage wanted to be involved in the decision making part of the process. Deber discussed the problems that occur with patient education, which included the following issues: (a) the importance of the manner in which information is presented; (b) the potential for overwhelming the patient with large amounts of information; (c) the possible confusion for the patient of conflicting treatment options; and (d) the variability in quality of information, its completeness, and its accuracy.

Besides the Internet, other sources of information and education that have been used in the clinical setting are pamphlets, video tapes, drug information sheets, physician/nurse phone calls, and, more recently, e-mail communications. Many patients express interest in the ability to communicate with their health care provider via email because they can do this on their own time, do not have to wait for a phone call from their provider, and feel freer in asking questions. People's learning styles differ, and what may work for one patient may not be as effective for another. Eaden et al. carried out a randomized trial comparing the efficacy of a video plus an informational leaflet to an informational leaflet alone for patients about surveillance and cancer risk in ulcerative colitis.[18] They noted that there was no clear advantage of the video plus the leaflet over the pamphlet. They suggested that staff time and costs should be weighed in the consideration of which medium to use.

Email has become increasingly popular for patients and their health care providers. A Harrisinteractive telephone survey conducted in March 2002 noted that 110 million adults use the Internet for health information.[52] Many of those surveyed indicated a willingness to pay for these services. What they hoped to obtain from this service was the ability to ask questions of the health care provider without having to make a visit, fix appointments, receive results of medical tests, and obtain prescriptions.[29] The results of a University Pediatric Faculty Practice survey of 1,018 adults accompanying a child reported that 47% used the Internet for medical information.[5] Of these, only 47% considered that the information was good.

Epilepsy Information and Education

How does this information translate into the care of patients with epilepsy? Patients and their families have consistently indicated that they wanted information from their physicians about the disorder and its causes and treatments.[8,43] A U.K. study by Buck et al. in 1996 solicited information via questionnaire from patients with epilepsy concerning their satisfaction with their care.[8] Patients were asked whether they thought that their physician had adequate knowledge about epilepsy and whether he or she provided enough information concerning this. Sixty-seven percent of those responding to the survey stated that their physician, usually a general practitioner, gave them enough information about their epilepsy. On the question of whether they felt that the physician had considered their personal views, 71% felt that the general practitioner was more likely to do so compared to the hospital specialist.

Information Transfer to the Community and Public

The public has become more knowledgeable about diseases, treatments, and outcomes. There are many resources for this knowledge; these include television documentaries, news reports, magazine articles, and the Internet. National organizations and parent support groups play significant roles in the dissemination of this information. With some diseases, there is a stigma attached to the disorder, and education of the public is more difficult. Bagley in 1972 studied the attitudes of the public toward epilepsy, cerebral palsy, and mental illness and found that those with epilepsy were rejected more often than those with the other two illnesses.[4] Even 23 years later Baumann found similar results concerning attitudes toward children with epilepsy compared to those with asthma.[6] The Epilepsy Foundation of America and many other chapters of the International League Against Epilepsy (ILAE) have launched public awareness programs aimed at educating employers, teachers, public servants such as police, and the public at large. The ILAE together with the World Health Organization (WHO) and the International Bureau for Epilepsy (IBE) undertook a joint campaign in 1997 called “Out of the Shadows.”[32] The primary goal of this campaign is to increase public and professional awareness of epilepsy and raise epilepsy to a plane of acceptability in the public domain. The Epilepsy Foundation of America has a “Speak Up, Speak Out” campaign encouraging those with epilepsy and their families to advocate for important issues related to epilepsy and health care.[22] They also sponsor a Public Policy Institute each year; children from around the United States travel to Washington, D.C., meet with their representatives, and tell their stories about the impact that epilepsy has had on their lives. The Living Well with Epilepsy II conference in 2003 addressed ways of improving public awareness and acceptance of those with epilepsy.[21] Similar activities are carried out by other affiliates of the ILAE around the world. In third world countries, efforts have been undertaken to improve health access for those with epilepsy and diminish the stigma associated with the disorder.

Self-Education and Self-Management for Those With Epilepsy

Self-management implies that a person has a certain amount of knowledge about his or her medical condition. Data from reports of management of chronic diseases in both the United States and the United Kingdom indicate significant benefits of providing patients with information.[25] This resulted in reductions in outpatient visits by 37% and in accidents by 34%.[25] This type of patient–physician role has been studied in various age groups, including adolescents with chronic illness.[47] Self-management begins with the diagnosis of epilepsy and involves establishing a relationship with the treating physician. Self-management was one of the goals of the Living Well with Epilepsy II Conference that took place in 2003.[10] This is a goal that both the treating physician and the patient/caregiver should work toward from the onset of the diagnosis of epilepsy. Although there has not been much research related to the self-management of epilepsy, the few studies that exist demonstrate positive effects of self-management, control, and social support.[26] Part of self-management is understanding and coping with the diagnosis. This may require an understanding of one's feelings of anger, frustration, depression, or guilt.[49] The physician and epilepsy nurse can play an important role in assisting the patient and family through this initial process. Early referral to community support services is also important in assisting the patient and the family in the role of self-management.

The Centers for Disease Control and Prevention in collaboration with the American Epilepsy Society, the Epilepsy Foundation, and the Agency for Healthcare Research and Quality are developing a bibliographic database for the self-management of epilepsy. The sponsored research project includes the development of a computerized epilepsy self-management project.[17] The goals of these researchers are to use such a program to assist patients with treatment issues, improve knowledge, provide information to help with dealing with stress and sleep issues, and improve compliance with taking of their medication.

Many epilepsy associations in the United States and throughout the world have Web sites with self-help information.[19,20,23] The guidelines from *Epilepsy Action* cite four keys to self-management: (a) working knowledge, (b) personal awareness, (c) confidence, and (d) taking responsibility. The last is especially important and involves knowledge of the roles of the environment, stress, sleep, food and alcohol, illness, and hormones in seizure control.[19] This guideline also gives patients some specific instructions on questions that they can pose to their physician during visits.

As with information transfer to others, learning skills and preferences vary relative to the person. These issues should also be discussed with the health care worker. This opens up the opportunity to provide information in formats that enhance the greatest learning, including pamphlets, lectures, support groups, audiotapes, videos, CDs, books, and Internet resources. The ultimate goal for the patient is to accept the diagnosis, work toward the best control possible without side effects of medication, and be able to continue with his or her activities and employment and enjoy a good quality of life.

The ability to self-manage depends on the ability to establish a good working relationship with the health care worker (physician, nurse practitioner, nurse). Physicians have not always been recognized to be the best listeners. Patients and families of patients with chronic illness frequently complain that physicians in acute care settings do not listen to their explanation of the illness or treatment. This lack of understanding occurs in spite of the fact that these people deal with the chronic

illness on a daily basis. A study by Braddock et al using audiotapes of primary care office visits to evaluate six criteria for informed decision making reported that discussions leading to informed decision making included fewer than two of six described elements.[7] These elements were as follows: (a) discussion of the clinical issue and nature of the decision, (b) discussion of the alternatives, (c) discussion of the pros (or benefits) and cons (or risks) of the alternatives, (d) discussion of uncertainties associated with the decision, (e) assessment of the patient's understanding, and (e) asking the patient to express a preference.[7] There are still patients who prefer to defer to their physicians for final decisions. A study by Levinson et al. noted that this preference was more likely to occur in populations of older and poorer patients.[39] The physician must be able to read patients, understand their desires, and assist them in the process of understanding and working with their illness.

Research Information and Dissemination

Information concerning new treatments and devices needs to be available to the treating physician and to the public in a timely fashion. In the past, the transfer of this information has been through peer-reviewed journals to physicians and then from physicians to patients and their families. The timeline for this transfer can be months after the availability of a new therapy. The explosion of information now available to physicians limits the time that they can spend reviewing new ideas critically. Information comes from peer-reviewed journals, the Internet, and often from pharmaceutical industry representatives. Physicians still feel that the information that they receive from peer-reviewed journals about new therapies represents the best information. Although many physicians use electronic sources of information, they do not consider these as reliable as the peer-reviewed journals.[3] Other forms of information transfer related to research and new technologies occur at national or international society meetings. In these settings, health care providers have the opportunity to experience new ideas and then share them with their peers at home and their patients. Pollock advocated a system in academic institutions that requires health care providers attending a society meeting to return to their home institution and give a presentation of what they heard and learned.[44] Patients today often search for the newest treatments for complex disorders. They come to their physician visits armed with information that they obtained from the Internet or a magazine or newspaper. It is not uncommon that the information that they bring is something that the physician has not read.

Patients and families see the physician as the primary resource for new information about therapies or diagnostic studies. It is important to find ways in which health care providers can find the time to seek out this information from reliable sources.

Role of Epilepsy Organizations and Support Groups

The health care provider, researcher, patient, and patient caregiver have an increasing array of information resources and support groups about epilepsy available to them. Many patients are very resourceful and access these resources without any prompting or difficulties. For others, the health care provider can be very helpful in directing the patient to these services. Among these resources are the following:

1. Epilepsy Foundation of America (EFA)
2. International League Against Epilepsy (ILAE) and it various national chapters
3. World Health Organization
4. International Bureau for Epilepsy (IBE)
5. Centers for Disease Control and Prevention (CDC)

The national chapters of the International League Against Epilepsy provide services to local populations in the form of printed materials, workshops, lectures, support groups, advocacy for employment, information on educational and legal issues, and camps for children with epilepsy. As noted earlier, the ILAE, IBE, and WHO began a joint initiative in 1997 called “Out of the Shadows.” This is a global campaign designed to improve the diagnosis, treatment, prevention, and social acceptance of people with epilepsy. The second phase began in 2001 with the goals of promoting public and professional education, identifying the needs of people with epilepsy, and encouraging governments and departments of health to address the needs of people with epilepsy.[16]

In addition to these global activities, the local chapters of these organizations strive to provide services to people with epilepsy on a daily basis. One difficulty for the person with epilepsy and the family is that often they are unaware of these organizations and the opportunities for services. If the medical care of the person with epilepsy is in the hands of a general physician who does not have much contact with epilepsy services, the patient may not be provided with the information about them. The availability of information on the Internet is changing this somewhat, but there are still many people who do not receive services.

These organizations educate the public about epilepsy and advocate for services for persons with epilepsy. In spite of the increased publicity concerning epilepsy, people with epilepsy still perceive a stigma.[34,50]

Role of the Pharmaceutical Industry in Information Transfer and Education

The role of the pharmaceutical industry in medical education and information dissemination is very significant in the current market. Figueras and Laporte noted that the marketing budgets for pharmaceutical companies exceeds those for research and development.[24] They also noted that these companies play very important roles in medical societies and continuing medical education, and that because health care systems provide limited access to independent information, the pharmaceutical industry therefore becomes the bigger player in the dissemination of health information both to professionals and the public.[24] Many companies now have an “applied therapeutics” team whose primary goal is the development and dissemination of scientific information both internally and externally.

A report by the Accreditation Council for Continuing Medical Education in 2001 noted that more than half of the funding for CME came from commercial resources.[1] This report also noted that about one third of medical schools in the United States receive about half of their CME funding from the industry. Because of the increasing need for physicians to have mandated CME credits, there will be a need for educational resources. Most responders to a survey taken at a CME conference stated that they were there because of the need for CME and to learn about latest treatments.[13]

The other dilemma related to information from pharmaceutical industries is that many health care providers have been investigators in the clinical trials for the drugs or devices in question. One study recommended that patients be informed

of financial and publication agreements between the industry and persons conducting the trials.[11]

There is a need to develop specific relationships with industry that benefit the patient and the health care provider without compromising standards of medical practice.

The Future of Information Transfer

Health Insurance Portability and Accountability Act

The passage of the Health Insurance Portability and Accountability Act (HIPAA) in 1996 and its implementation in 2003 has had a profound impact on information transfer in the medical community. It has affected direct patient care and clinical research. Those with chronic illnesses who seek services from multiple health care providers frequently feel the effect of this regulation. Sharing of medical information from one provider to another is more cumbersome than before. Enrolling patients in clinical studies requires several extra steps to ensure that patient confidentiality is maintained. Sharing of information with school officials, employers, and others involved in the day-to care of the patient may be limited unless permission is obtained from the patient or family member. This limitation of information may affect the care that patients receive if an acute medical problem arises. The epilepsy population is particularly impacted by HIPAA. For children with epilepsy, providing school nurses and teachers with information may be difficult. The same applies to employers of patients with epilepsy.

As we move forward with the development of medical record systems, these regulations will play a role in their design and management.

Electronic Records

Medical information is increasingly collected and stored electronically. Inpatient information is placed in electronic systems. Medical records are available on a number of archival systems throughout the United States and Europe. As technology has permitted the conversion of data to digital forms, the ability to store this information electronically has increased. Many hospitals store all patient orders, laboratory studies and results, and inpatient and outpatient records electronically. The thrust is to eliminate the paper medical record. The hypothesis is that use of electronic medical records will save the health industry billions of dollars, with improved health care efficiency and safety.[31] Another potential advantage of electronic records could be to provide patients with their personal electronic record, giving them more opportunity to participate with the health care provider in their care.[53] There are large-scale projects currently looking at ways to transfer computer-based information over the World Wide Web and maintain patient confidentiality.[45] The hope is that this can prevent repetition of tests, aid in identification of patient allergies and medications, and provide good patient care at a savings.

Many physicians use PDAs when they see patients in the hospital or office. Many of the PDAs now have Internet and phone capabilities, permitting access to many sources of information such as drug databases, Current Procedural Terminology codes, and other resources. Information obtained and stored in this manner is commonplace in the Western medical world.

As we move into the next decades, more and more of the information that we obtain and share will probably occur via electronic sources. Less of this will occur via paper sources such as journals, books, and newspapers. Even today, many medical journals offer an online version of the journal as a subscription option. At this stage, it is difficult to evaluate the efficacy of these various forms as they relate to physician learning, patient learning, and patient care. These are projects for the future.

Summary and Conclusions

The availability of information relative to epilepsy and other medical conditions is available in many formats. The physician as both a learner and an educator needs to be aware of these resources both for his or her education and for the education of his or her patients. With increasing demands on the heath care provider's time, it becomes important for the provider to be able to find information in places that he or she can access off-hours, such as the Internet, online seminars, and journal articles. The public also is increasingly interested in having more medical information available to them. The patient and caregivers are more facile with using the Internet and seeking out information. It is the responsibility of the health care provider to make appropriate resources available to their patients and guide them through the understanding of the information. In addition to standard methods of information resources, nonprofit organizations and support groups are playing greater roles in providing information to patients and their families. As physicians move forward in their training and practices, it is important to remember that learning is a lifelong process. Methods and tools for learning and the information itself will change, and physicians must be aware of these changes.

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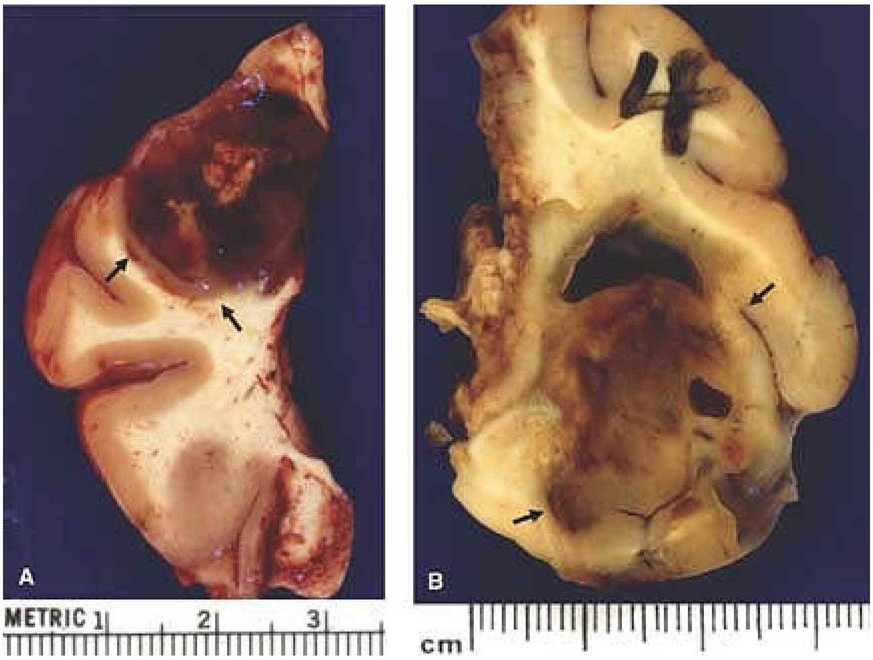

FIGURE 12.1 Tumors associated with intractable epilepsy, resected from two different patients. Note clear demarcation of the tumors from surrounding brain (indicated by *arrows*). Tumor shown in panel **A** is significantly hemorrhagic, whereas neoplasm in panel **B** is relatively homogeneous with focal cavitation. Both tumors clearly involve the cortex. (See black and white image.)

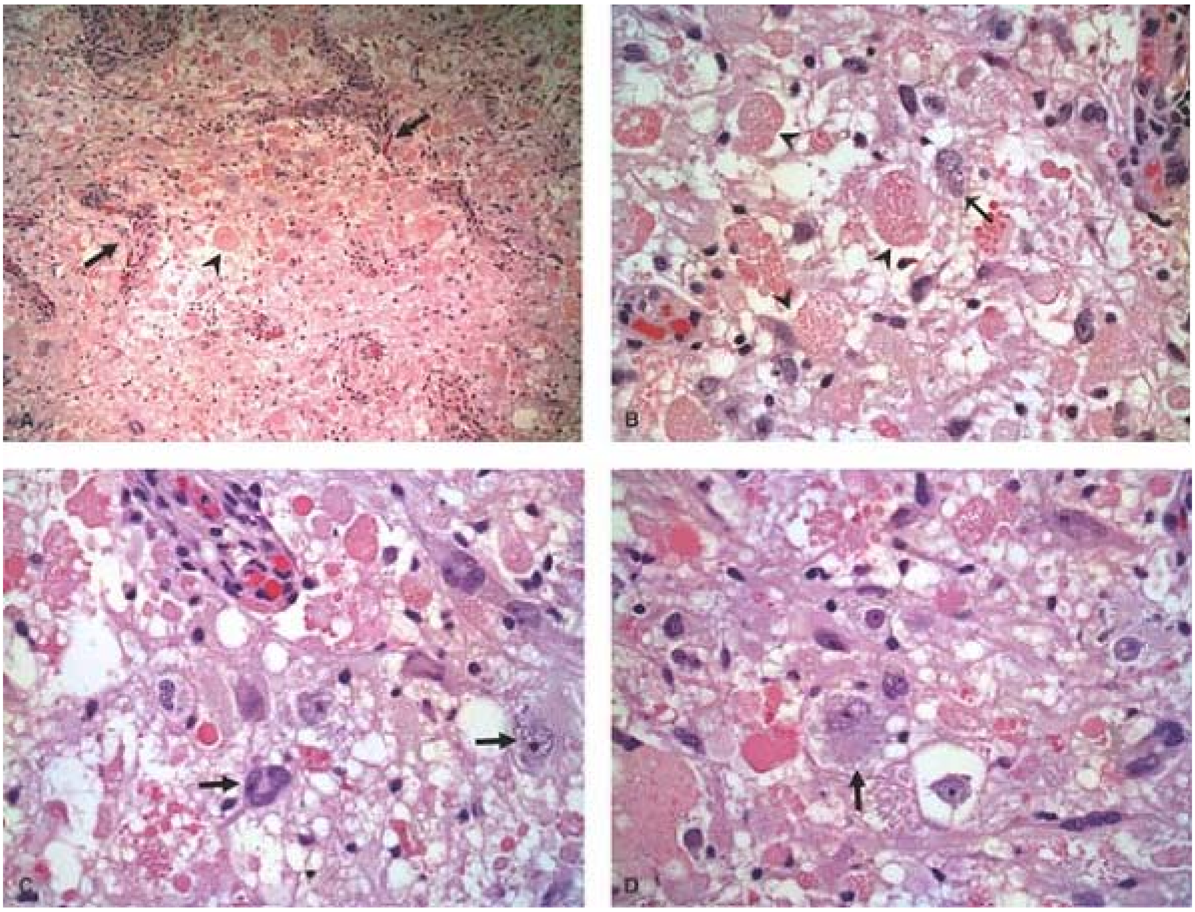

FIGURE 12.2 Ganglioglioma. **A.** Prominent vascularity in the tumor, with scattered perivascular lymphocytes (*arrows*). *Arrowhead* indicates a granular eosinophilic (cytoid) body; several of these are shown at higher magnification in panel **B.** *Arrow* in panel B shows a lobulated, dysmorphic nucleus. **C.** Several lobulated and bizarre nuclei are seen, though at least one cell (at right) retains neuronal features, including nucleolated nucleus and basophilic cytoplasm. **D.** Several dysmorphic neurons (e.g., highlighted by *arrow*). (All sections stained with hematoxylin & eosin.) (See black and white image.)

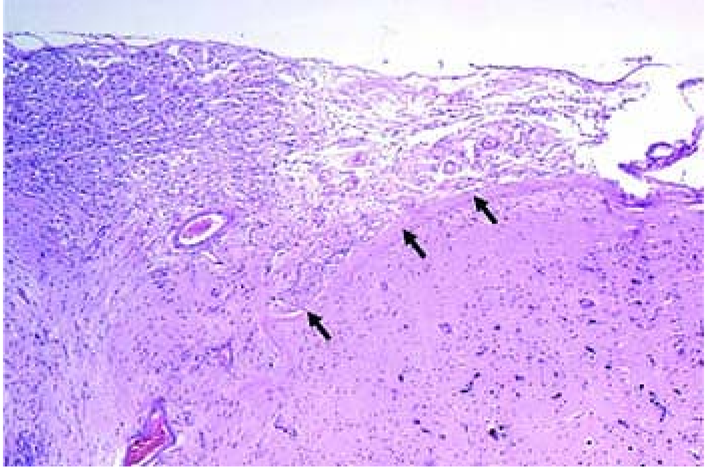

FIGURE 12.3 Gangliogliomas often extend into the subarachnoid space, even when they otherwise lack malignant (high-grade) features. *Arrows* indicate pial margin; large excrescence of tumor is seen at upper left. (Hematoxylin & eosin stain.) (See black and white image.)

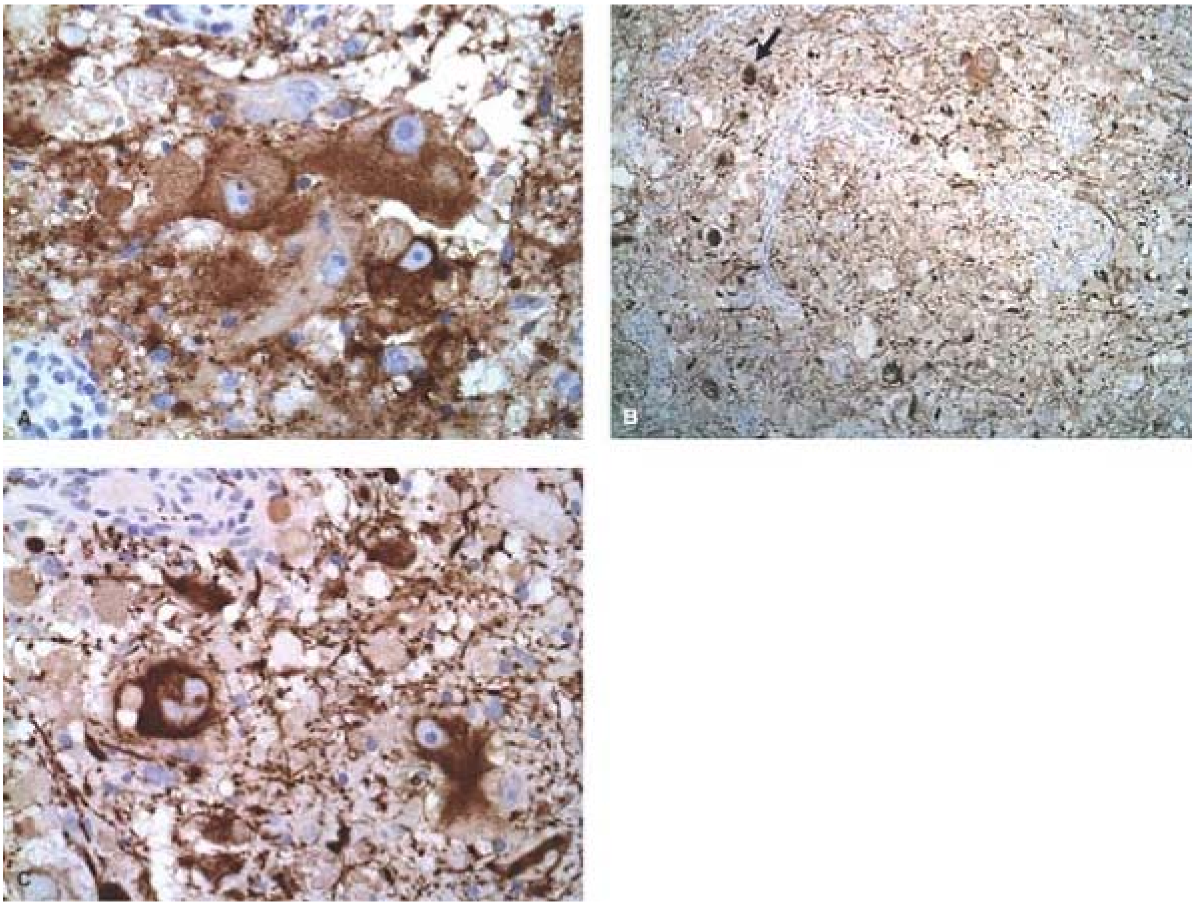

FIGURE 12.4 Immunohistochemical features of ganglioglioma. Panel **A** shows a section immunostained with antisynaptophysin, whereas panels **B** and **C** show sections immunostained with primary antibodies to neurofilament. All antibodies 'decorate' atypical and dysmorphic neurons; antineurofilament also highlights neuronal processes throughout the field. (See black and white image.)

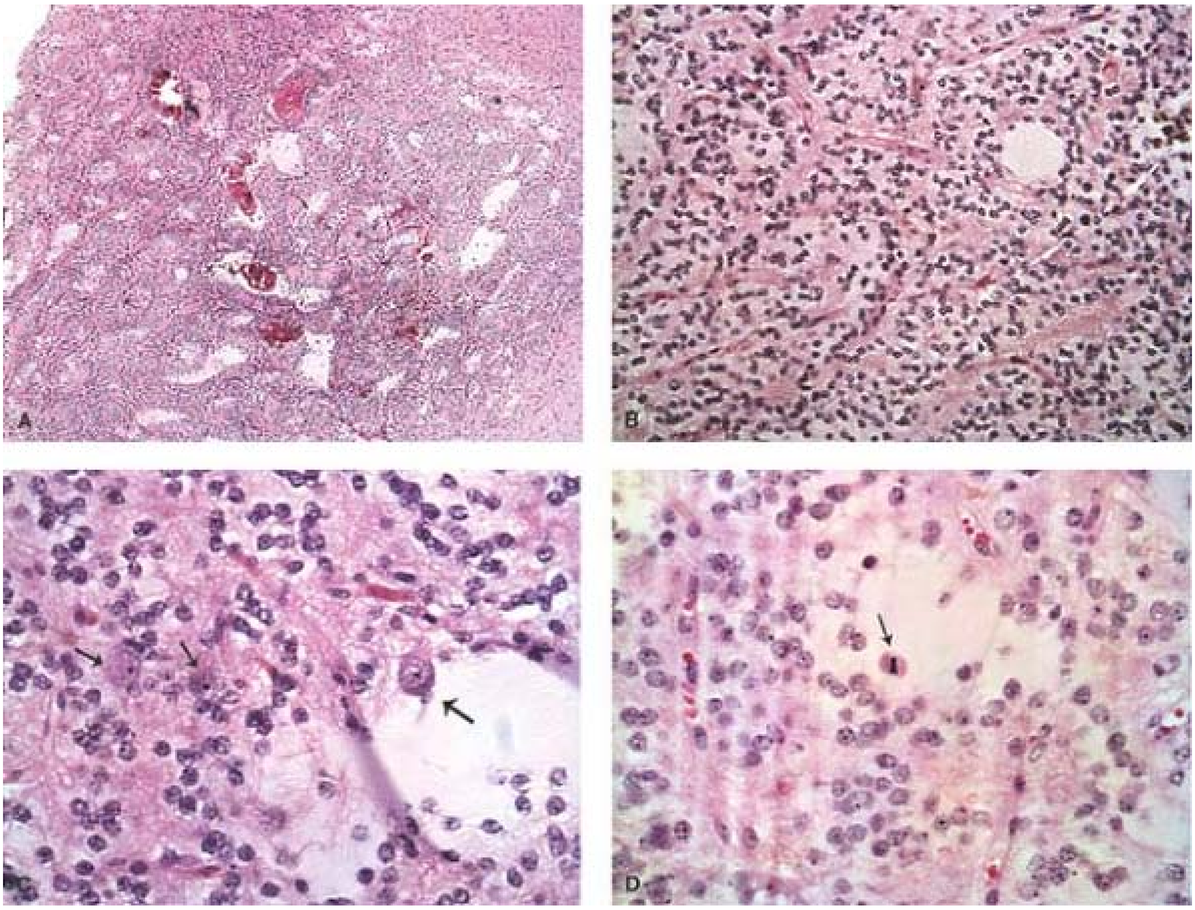

FIGURE 12.5 Dysembryoplastic neuroepithelial tumor. **A, B.** Representative fields in the tumor show sheets of relatively uniform round, oligodendroglia-like cells with compact nuclei and microcystic spaces. Panel **C** shows cells with distinctly neuronal phenotype (*arrows*). Neuron at right of this panel appears to be "suspended" in a vaguely mucoid matrix. Panel **D** shows a mitotic figure (*arrow*), an unusual feature in this neoplasm. (All sections stained with hematoxylin & eosin.) (See black and white image.)

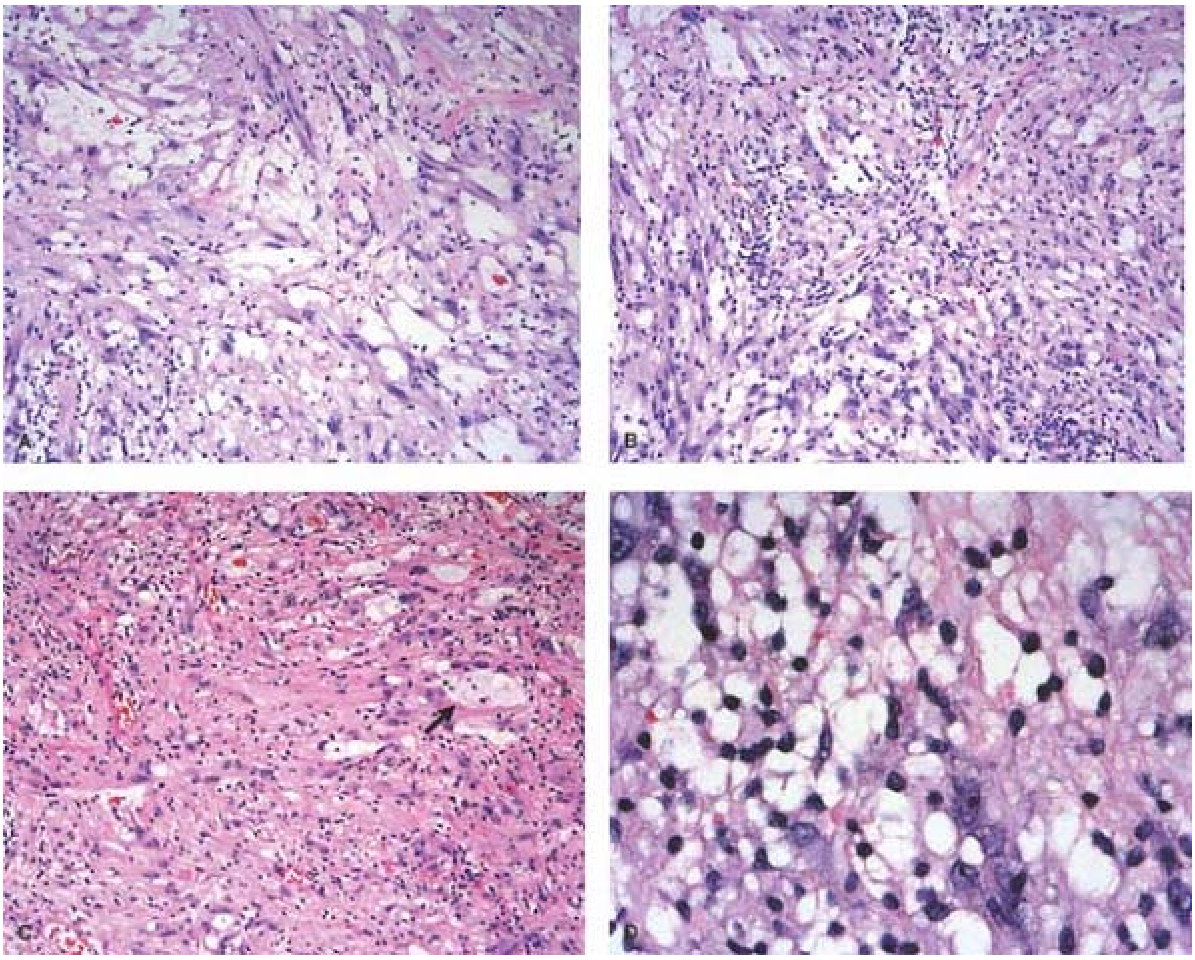

FIGURE 12.6 Pleomorphic xanthoastrocytoma. All panels (from hematoxylin & eosin-stained sections) show a pleomorphic neoplasm composed of spindled or compact cytoplasmic elements. Panel **B** shows a sparse lymphoid infiltrate, a common finding in this tumor. Xanthomatous or foamy cells sometimes aggregate into small groups (*arrow* in panel **C**). Cells with foamy, clear, and multiloculated cytoplasm and pleomorphic nuclei are highlighted in panel **D**. Despite this, mitoses are relatively rare in this tumor. (See black and white image.)

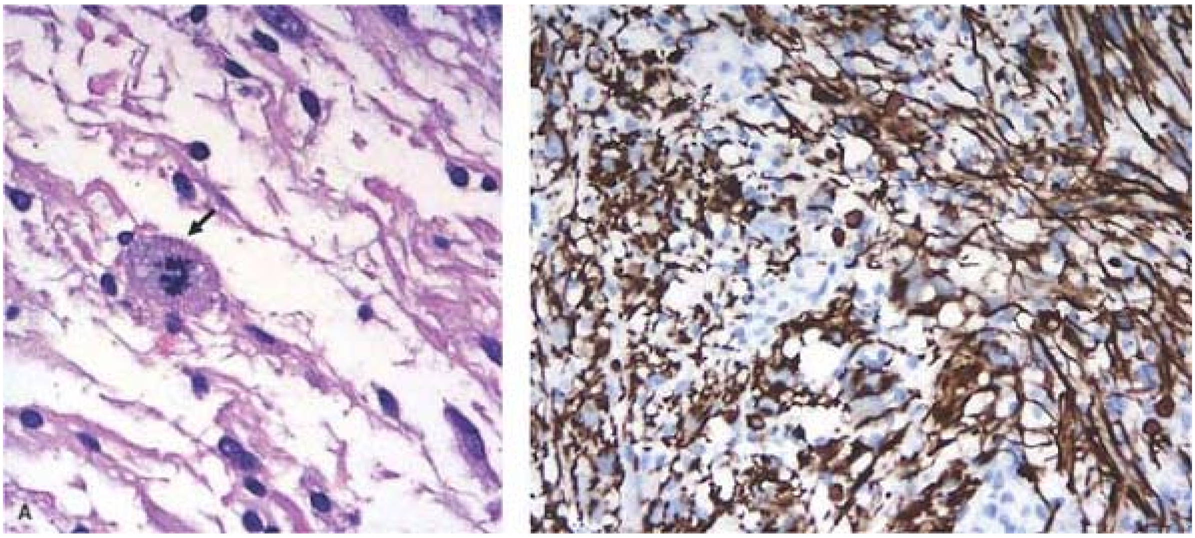

FIGURE 12.7 Pleomorphic xanthoastrocytoma (PXA). **A.** Atypical mitosis, a relatively rare finding in most PXAs (Hematoxylin & eosin-stained section.) **B.** Glial fibrillary acidic protein-immunostained section shows prominent cytoplasmic immunoreactivity. (See black and white image.)

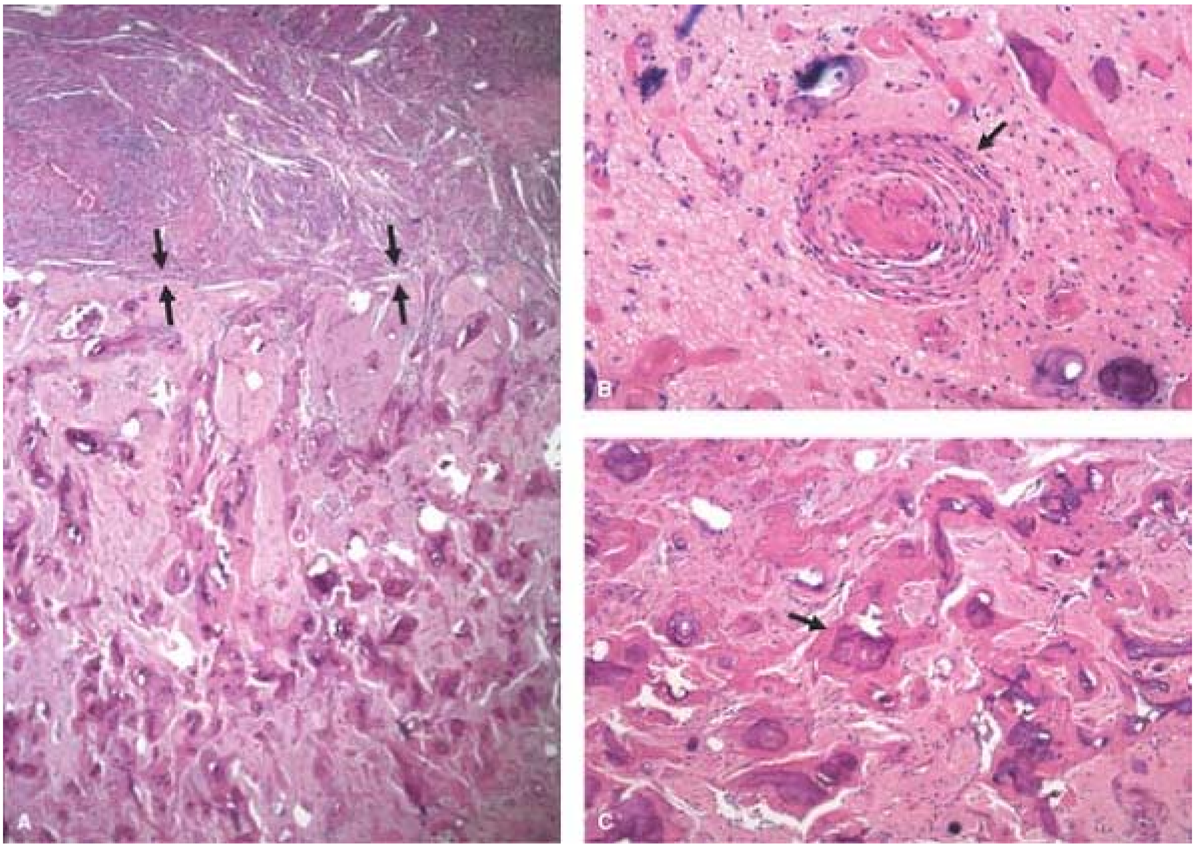

FIGURE 12.8 Meningioangiomatosis, with overlying meningioma. **A.** *Arrows* indicate the interface between brain parenchyma (lower portion of the image) and meningioma (above). The brain parenchyma shows

thickened, focally calcified blood vessels surrounding islands of disorganized neuroglial tissue. Details of the parenchymal abnormality are seen in panel **C**; *arrow* (in C) highlights a region of dystrophic calcification. Panel **B** shows a thrombosed thickened artery (*arrow*) with prominent smooth muscle cell hyperplasia in its wall. (All sections stained with hematoxylin & eosin.) (See black and white image.)

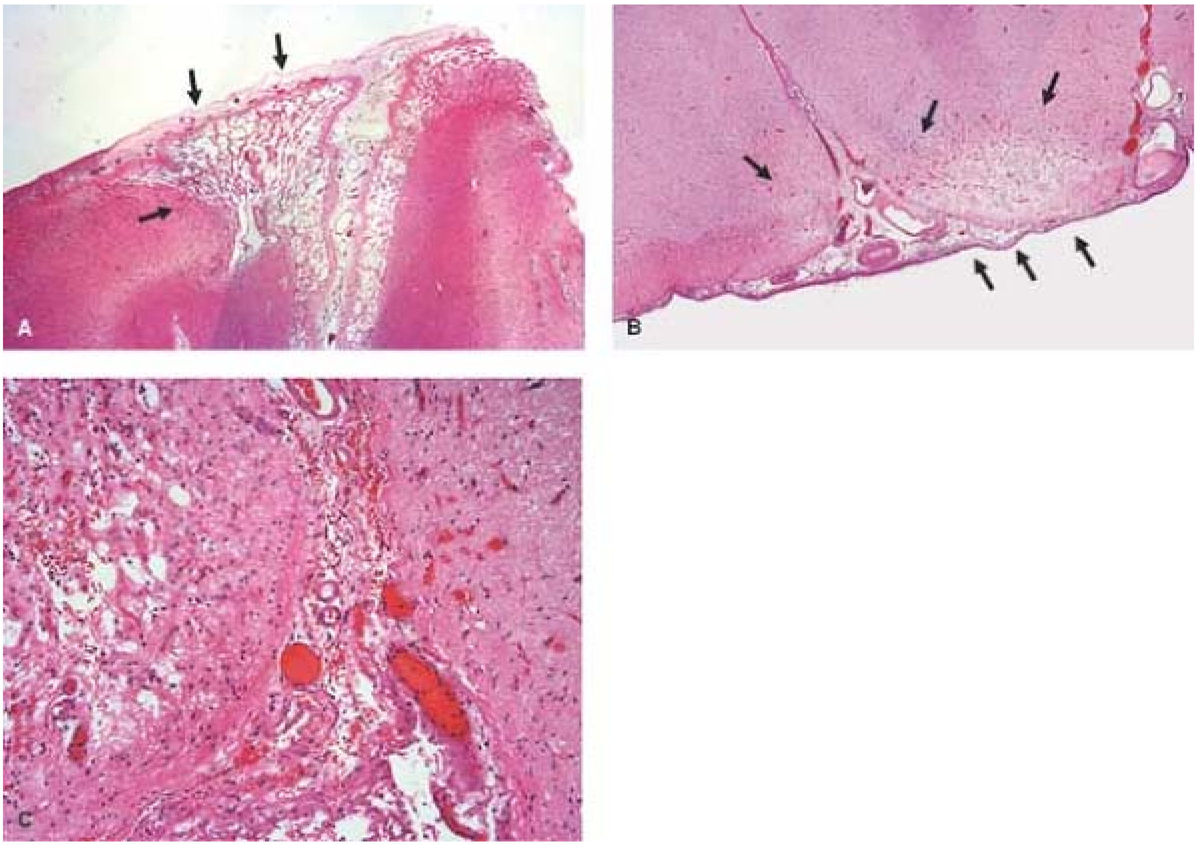

FIGURE 12.9 Rasmussen encephalitis (RE). Panel **A** shows extensive cortical cavitation, in one region affecting an entire gyrus (*arrows*). Panel **B** shows a more circumscribed region of cortical injury showing faint cystic cavitation, delineated by the *arrows*. Panel **C** shows detail of the region of microvacuolization, with intense astrocytic gliosis. (All panels are from sections stained with hematoxylin & eosin.) (See black and white image.)

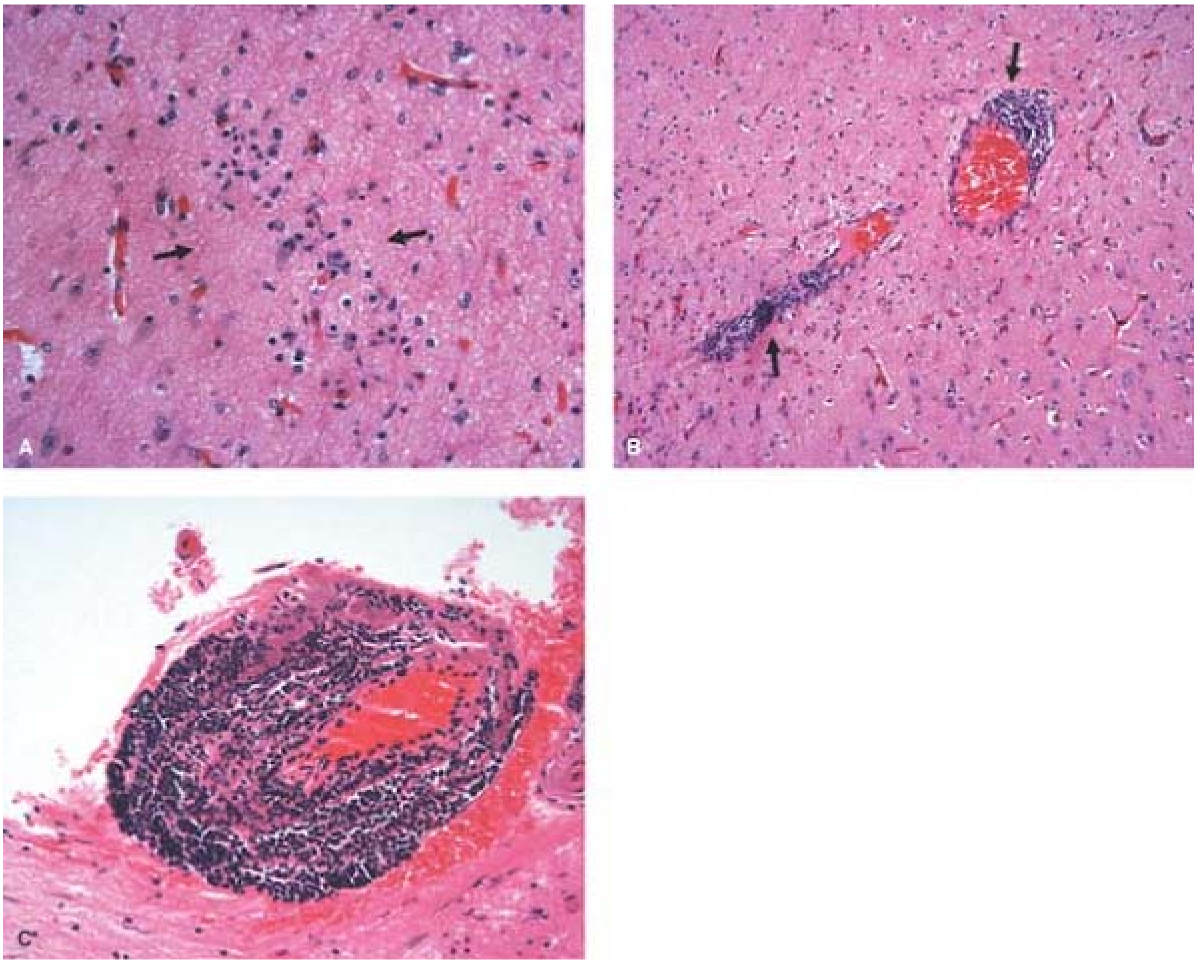

FIGURE 12.10 Rasmussen encephalitis/Rasmussen syndrome. **A.** *Arrows* indicate a poorly defined inflammatory/microglial nodule. **B.** Prominent angiocentric chronic inflammation in a region of brain with slight rarefaction and gliosis. Notice patchy nature of the inflammatory infiltrate. **C.** A meningeal vein showing dense transmural lymphocytic infiltrate *without* evidence of injury of the vessel wall or thrombus. (All panels are from sections stained with hematoxylin & eosin.) (See black and white image.)

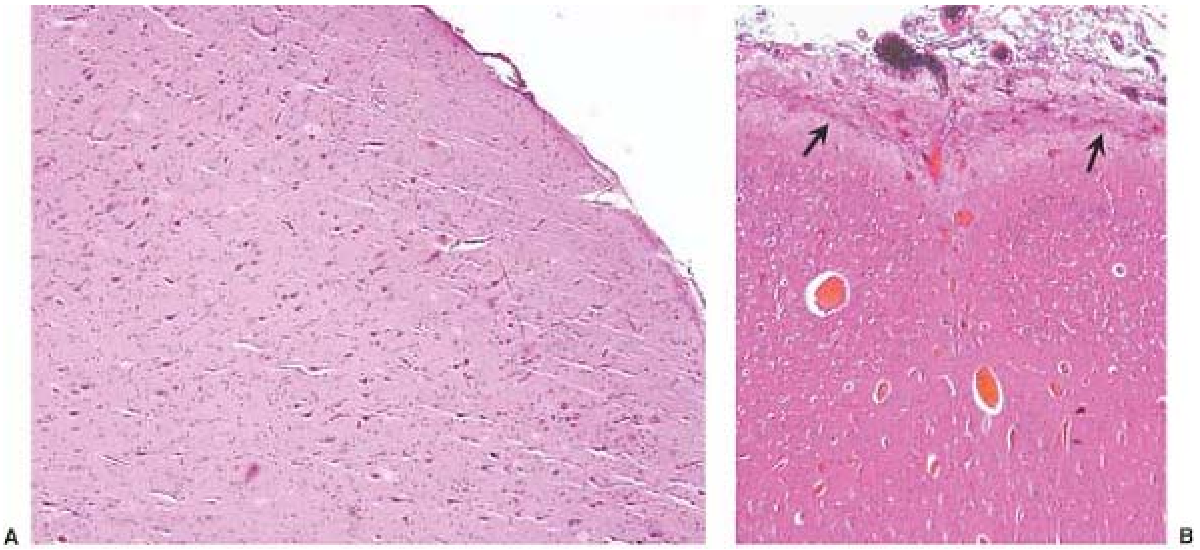

FIGURE 14.2 Representative micrographs of the resection specimen obtained from the child with magnetic resonance imaging (MRI) and intraoperative appearances illustrated in Fig. 1. **A:** Low-magnification view of a representative region of cortex shows a modest degree of neuronal disorganization. **B:** A focus of polymicrogyria, one of many seen in the resection specimen. Also note a "rind" of disorganized glial tissue covering the pia, with apparent extension into the subarachnoid space (*arrows*). (Hematoxylin and eosin stain.) (See black and white image.)

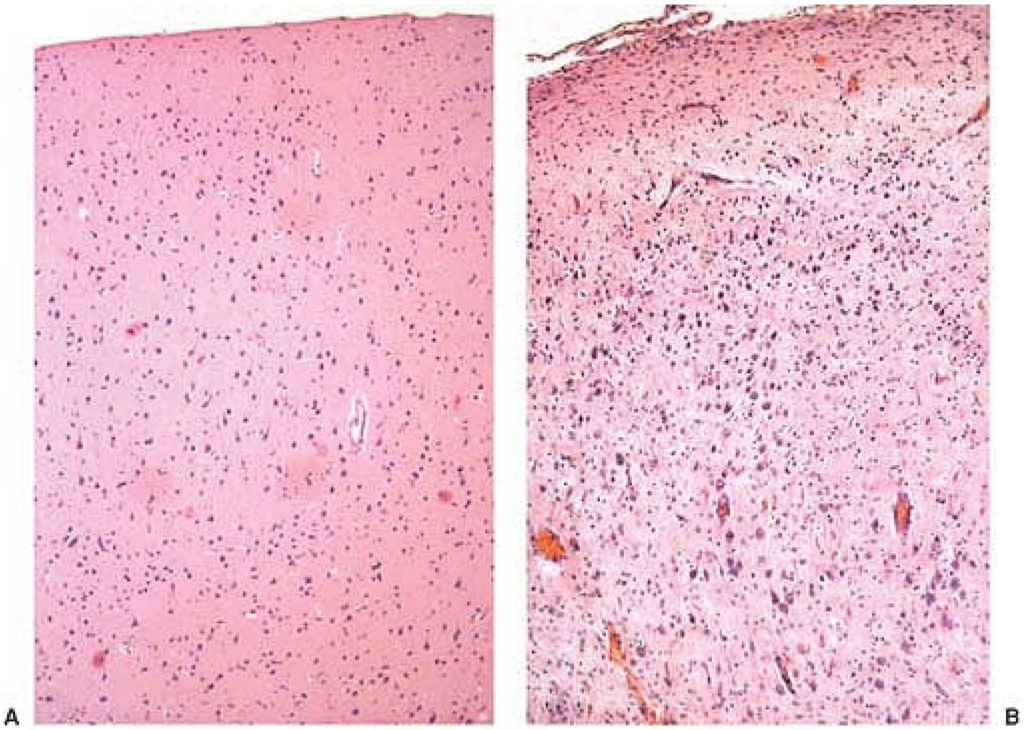

FIGURE 14.5 A: Relatively normally organized cerebral cortex from a surgical resection specimen. **B:** Region with severe cortical dysplasia shows pronounced cortical disorganization, with abnormal

crowding of neurons and abnormal orientation of many cells. Both panels are from micrographs photographed at the same magnification from sections stained with routine hematoxylin and eosin stains. (See black and white image.)

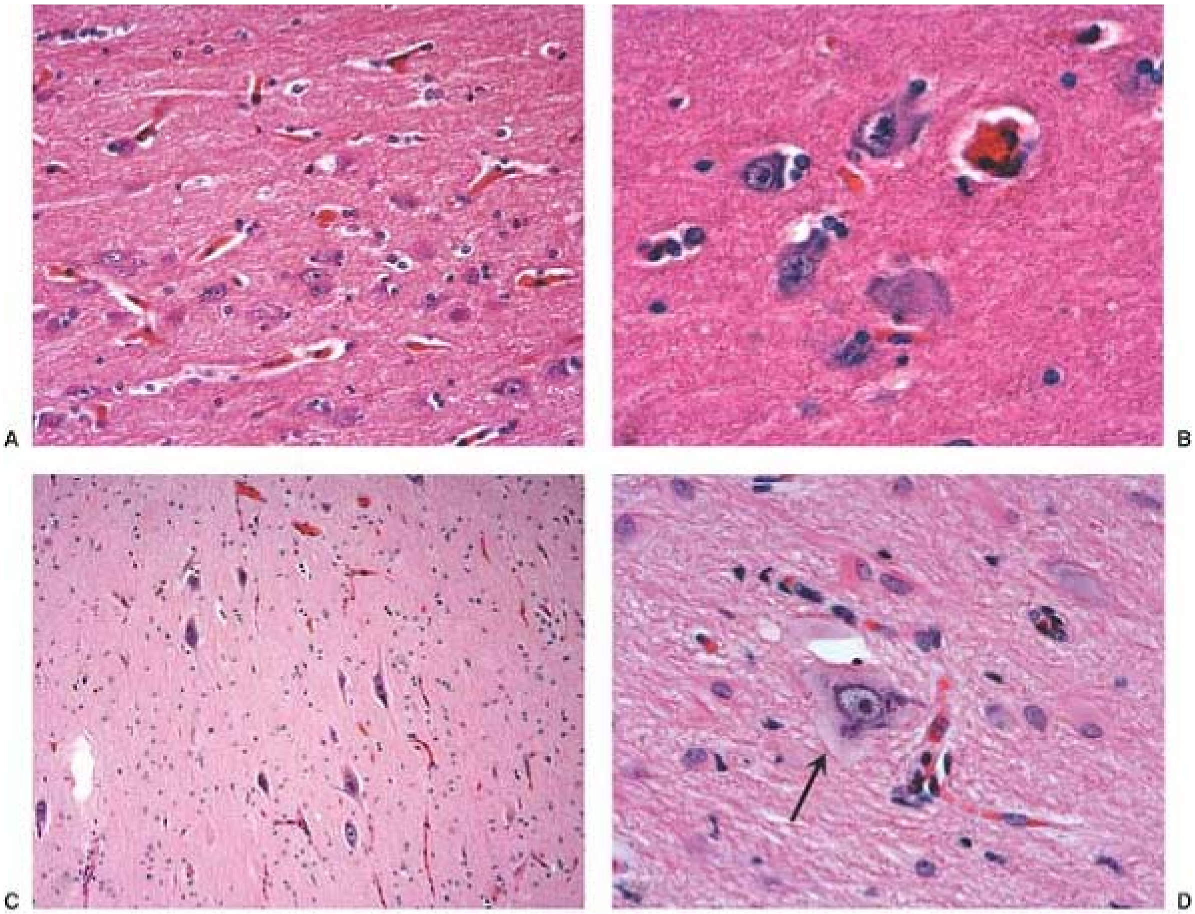

FIGURE 14.6 Neuronal disorganization and dysmorphism in cortical dysplasia/malformations of cortical development. **A:** Intermediate-magnification micrograph shows crowded and abnormally oriented neuronal cell bodies. **B:** Same features shown at a higher magnification. **C:** Variably enlarged and abnormally distributed neurons near the cortex-white matter junction. **D:** Magnified view of a dysmorphic neuron (*arrow*) with clumping of Nissl substance around the nucleus and clearing of the peripheral cytoplasm. Gemistocytic astrocytes are seen distributed around this neuron. (All panels are from hematoxylin and eosin-stained sections.) (See black and white image.)

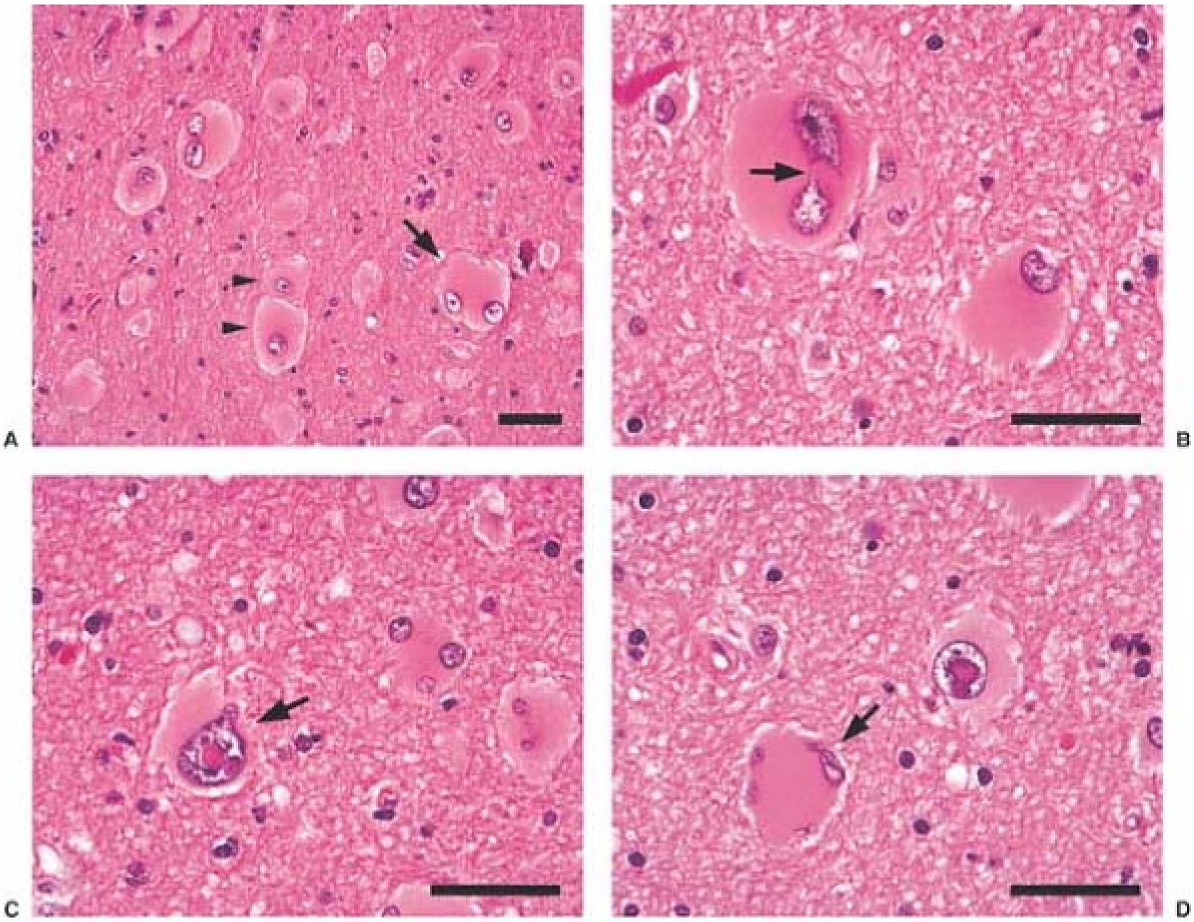

FIGURE 14.7 Typical balloon cells, with variably pronounced nuclear atypia. Hematoxylin and eosin stains. **A:** Balloon cells often show binucleation (*arrow*). Paired balloon cells are also seen (*arrowheads*). **B:** A balloon cell with a nuclear bridge connecting two nuclei (*arrow*). **C:** Balloon cell with marked nuclear atypia and/or nuclear invagination with nuclear budding (*arrow*). Also note the Marinesco body-like intranuclear inclusion. **D:** Balloon cell with multinucleation and/or micronucleation (*arrow*). Bars = 50 µm. (From Crino PB, Miyata H, Vinters HV. Neurodevelopmental disorders as a cause of seizures: neuropathologic, genetic, and mechanistic considerations. *Brain Pathol* 2002;12:212–233; with permission.) (See black and white image.)

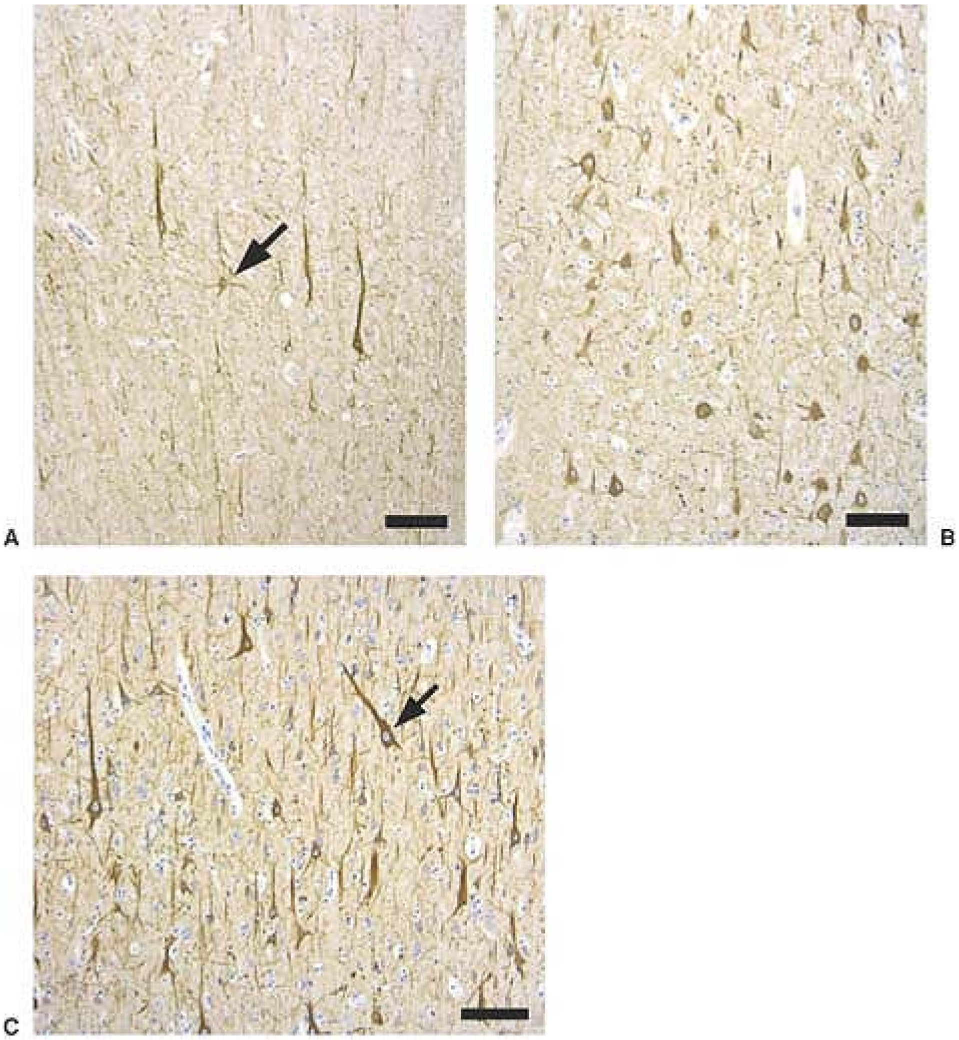

FIGURE 14.8 Neurofilament (N52, high-molecular-weight neurofilament antibody) immunohistochemistry of surgically resected corticectomies. **A:** Relatively normal cortex from a patient with temporal lobe epilepsy. Some, although not all, of the pyramidal neurons in layers III and V as well as multipolar interneurons (*arrow*) are positive for N52. **B:** Focal cortical dysplasia. Neuronal dyslamination and dysmorphic, multipolar, cytomegalic neurons are evident. **C:** Relatively normal cortex adjacent to a region of cortical dysplasia. More pyramidal neurons (in layers III and V) are more strongly immunoreactive for N52 than in control cortex (A), and an abnormally oriented pyramidal neuron (*arrow*) is also easily identified. The pial surface is at the top in each panel. Bars = 100 μm. (From Crino PB, Miyata H, Vinters HV. Neurodevelopmental disorders as a cause of seizures: neuropathologic, genetic, and mechanistic considerations. *Brain Pathol*. 2002;12:212–233; with permission.) (See black and white image.)

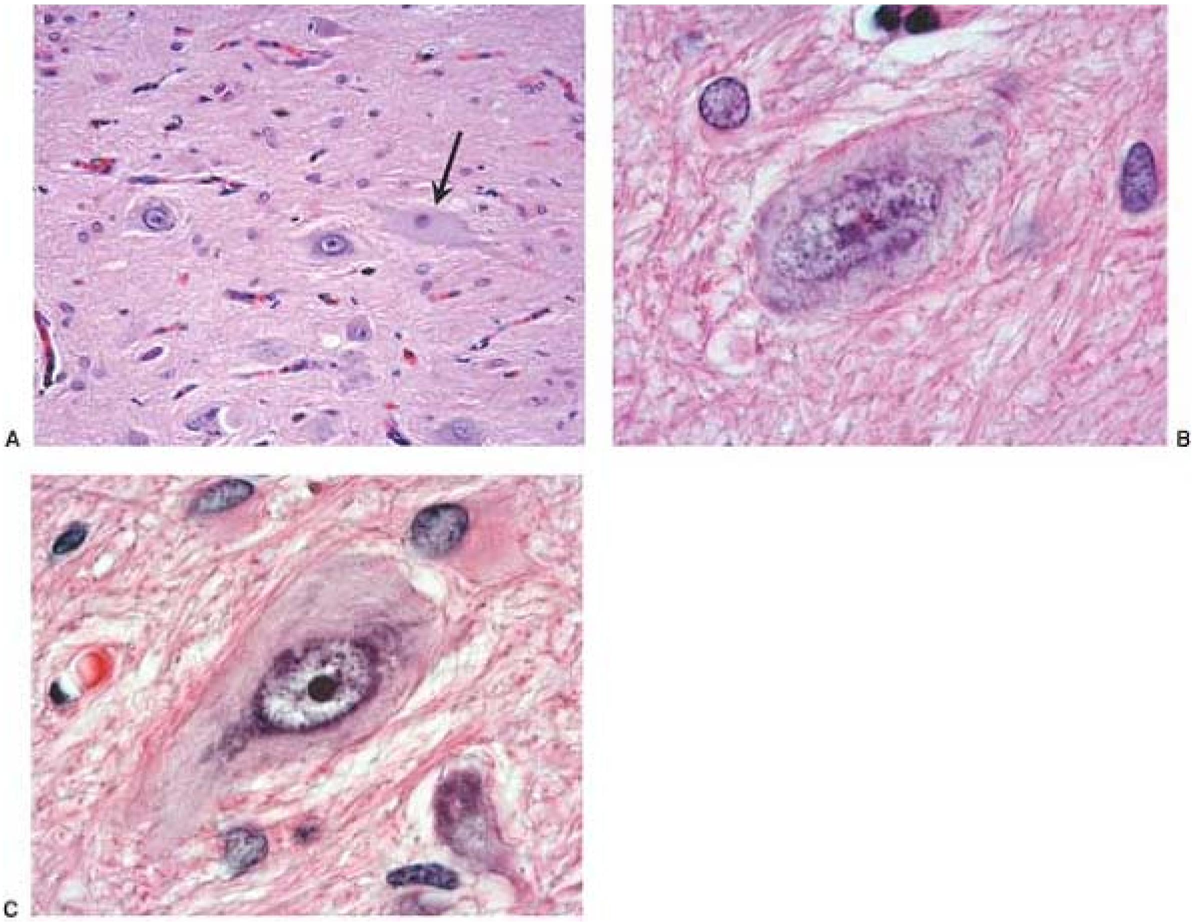

FIGURE 14.9 Histologic features of severe cortical dysplasia. **A:** Dysmorphic and enlarged neuronal cell bodies. Arrow indicates a cell that shows a "neuronal" nucleus but pale, glassy amphophilic cytoplasm (lacking Nissl substance) of the type more commonly seen in gemistocytic astrocytes. **B, C:** Dysmorphic, enlarged neurons with coarseness of the cytoplasm, suggestive of neurofibrillary change. (All panels are micrographs from hematoxylin and eosin-stained sections.). (See black and white image.)

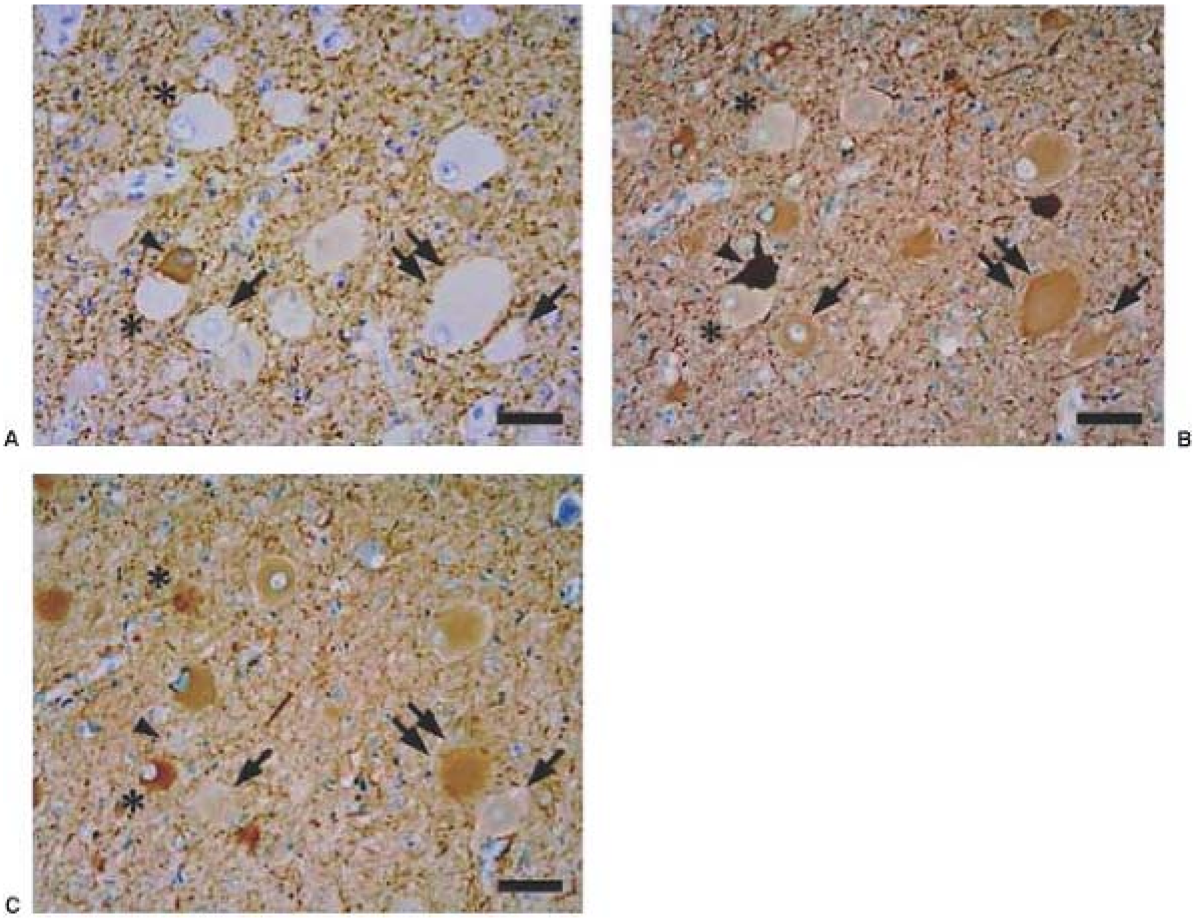

FIGURE 14.10 Balloon cells show various patterns of neuroectodermal differentiation. Some show only glial (glial fibrillary acidic protein [GFAP]) or neuronal (neurofilament) differentiation, whereas others show both GFAP and neurofilament immunoreactivity. Only rare balloon cells are immunoreactive for phosphorylated neurofilament (*arrowhead*, panel A). However, most are immunoreactive with nonphosphorylated neurofilament (panel B) with varying intensities. Some are immunoreactive for both GFAP and nonphosphorylated neurofilament (*double arrows*, panels B and C). Symbols and arrows in all panels indicate the same cell identified in serial sections. Arrowhead indicates a balloon cell that is phosphorylated neurofilament (p-NF)-positive, NF-positive, and GFAP-negative. Arrows indicate balloon cells that are p-NF-negative, NF-positive, and GFAP-negative. Asterisks indicate balloon cells that are p-NF and NF-negative but GFAP-positive. Double arrow indicates a balloon cell that is p-NF-negative, NF-positive, and GFAP-positive. Bars = 50 µm. (Panel A, section stained with primary antibody to phospho-NF, panel B with primary antibody to NF, panel C with primary antibody to GFAP). (From Crino PB, Miyata H, Vinters HV. Neurodevelopmental disorders as a cause of seizures: neuropathologic, genetic, and mechanistic considerations. *Brain Pathol*. 2002;12:212–233; with permission.) (See black and white image.)

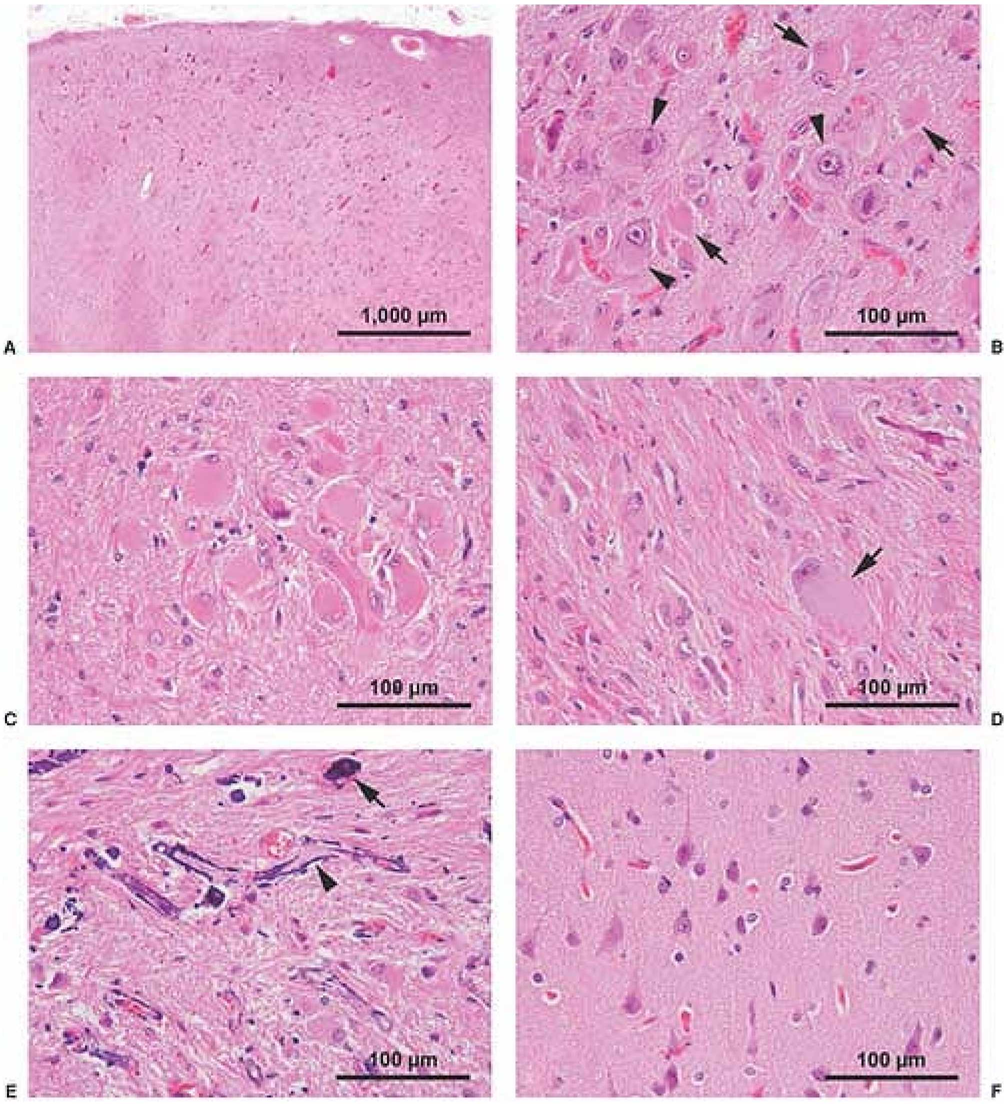

FIGURE 14.13 Cortical tuber in a child with tuberous sclerosis complex (TSC). **A:** Low-magnification view shows a disorganized collection of neuroglial cells, some enlarged. **B:** Magnified view of the lesion showing "balloon cells" with eccentric nuclei and glassy eosinophilic cytoplasm (*arrows*), admixed with dysmorphic, markedly enlarged neurons containing Nissl substance in their cytoplasm (*arrowheads*). **C:** A cluster of balloon cells within the tuber. **D:** An abnormal neuroglial cell showing morphologic features of both dysplastic neuron and balloon cell (*arrow*). Note the eccentric nucleolated nucleus and the enlarged pale but slightly basophilic cytoplasm, raising the possibility that the cell represents a transitional form of neuroglial cell. **E:** Various degrees of punctate calcification (*arrows*) and calcifications along vessel walls (*arrowheads*) are often seen in TSC tubers. **F:** Morphologically normal cerebral cortex (for comparison with features of the tuber). (All panels are micrographs from sections stained with hematoxylin and eosin.) (See black and white image.)

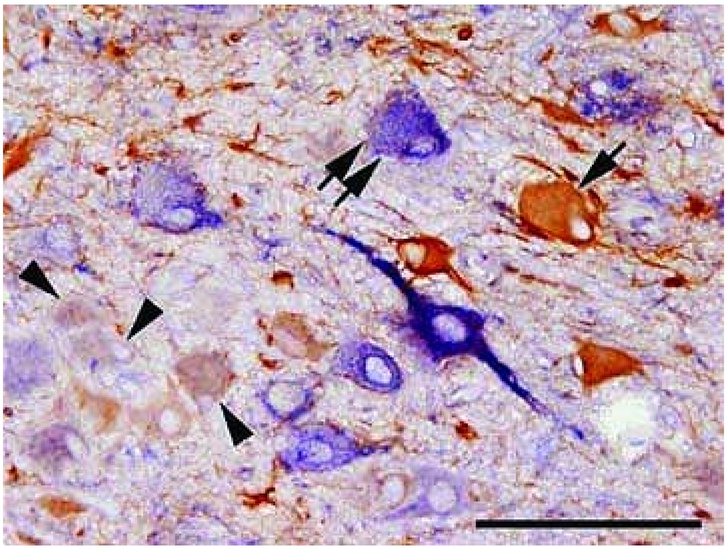

FIGURE 14.14 Immunohistochemical findings in a tuberous sclerosis complex (TSC) tuber. Double-label immunohistochemistry confirms colocalization of glial fibrillary acidic protein (GFAP) (*brown color*) and nonphosphorylated neurofilament (*purplish-blue*) in a subpopulation of balloon cells (*arrowheads*) in a TSC tuber, suggesting a failure of commitment in neuroglial differentiation. Note that some abnormal neuroglial cells are immunoreactive for GFAP (*arrow*) or nonphosphorylated neurofilament (*double arrows*). Scale bar = 100 μm. (See black and white image.)

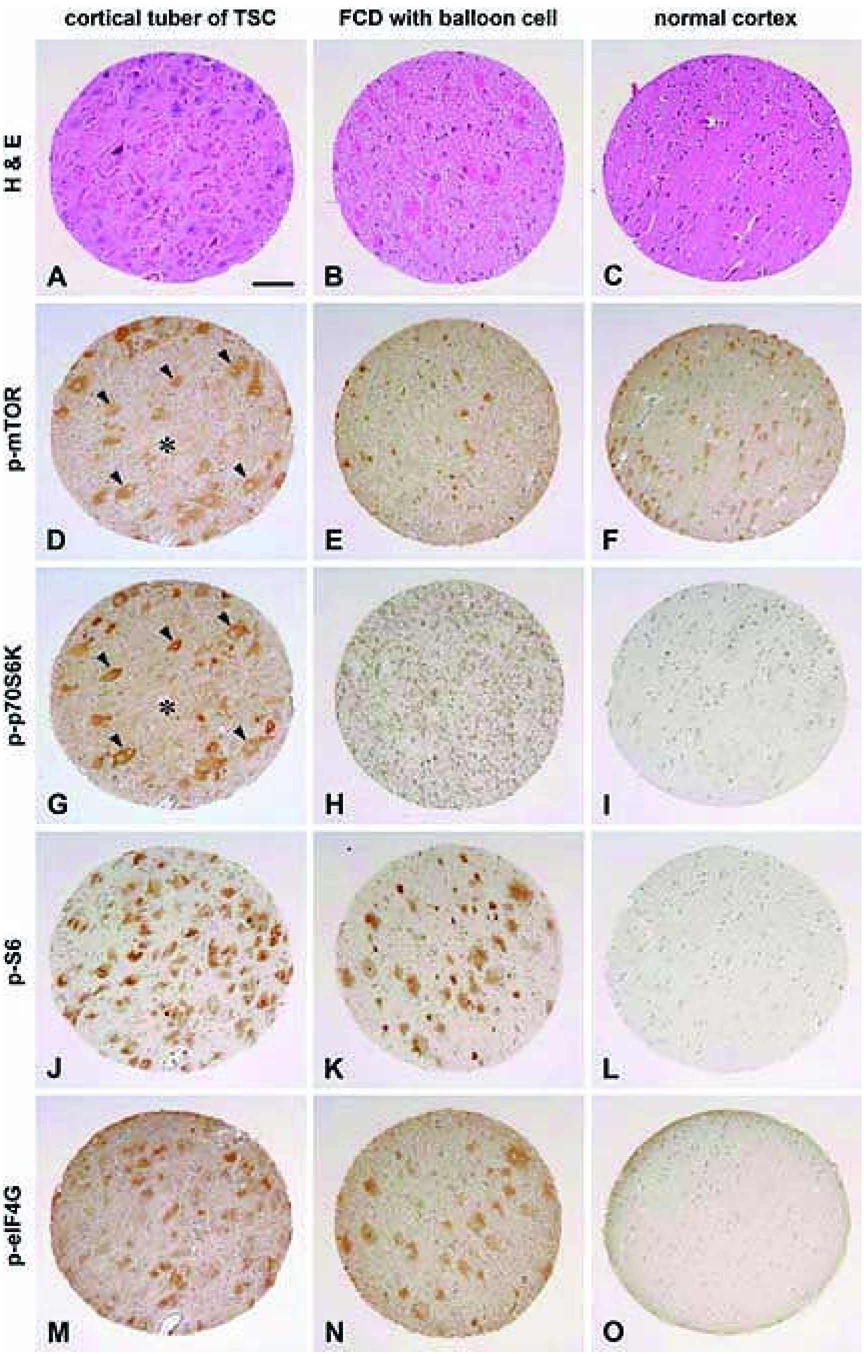

FIGURE 14.16 Tissue microarray (TMA) analysis of insulin signaling pathways in tuberous sclerosis complex (TSC) tubers, focal cortical dysplasia, and control tissues. The left column represents sample cores from a TSC tuber **(A, D, G, J, M)**; the middle column represents focal cortical dysplasia (FCD) with balloon cells (Palmini type IIB) **(B, E, H, K, N)**; and the right column represents histologically normal cerebral cortex **(C, F, I, L, O)**. Stained with hematoxylin and eosin (H&E) (A–C), p-mTOR (D–F), p-p70S6K (G–I), p-S6 (J–L), and p-eIF4G (M–O). Immunostains were performed on consecutive serial sections, and the same cells can be easily identified in different stains (e.g., *arrowheads* in D and G). Expression of p-p70S6K appears to be specific to the TSC tuber (panel G). Note the population of abnormal neuroglial cells in the TSC tuber expressing p-S6 and/or p-eIF4G (e.g., central area of each core shown in panels J and M), despite negative expression of p-mTOR and p-p70S6K (the same areas indicated by asterisks in panels D and G). Each core has a 0.6-mm diameter. Bar = 100 μm. eIF4G, eukaryotic translation initiation factor 4G; mTOR, mammalian target of rapamycin; p-, phospho-; p70S6K, 70-kDa ribosomal

protein S6 kinase; S6, 40S ribosomal protein S6. For details of methodology, see Miyata et al. (2004). (From Miyata H, Chiang ACY, Vinters HV. Insulin signaling pathways in cortical dysplasia and TSC-tubers: tissue microarray analysis. *Ann Neurol*. 2004;56:510–519; with permission.) (See black and white image.)

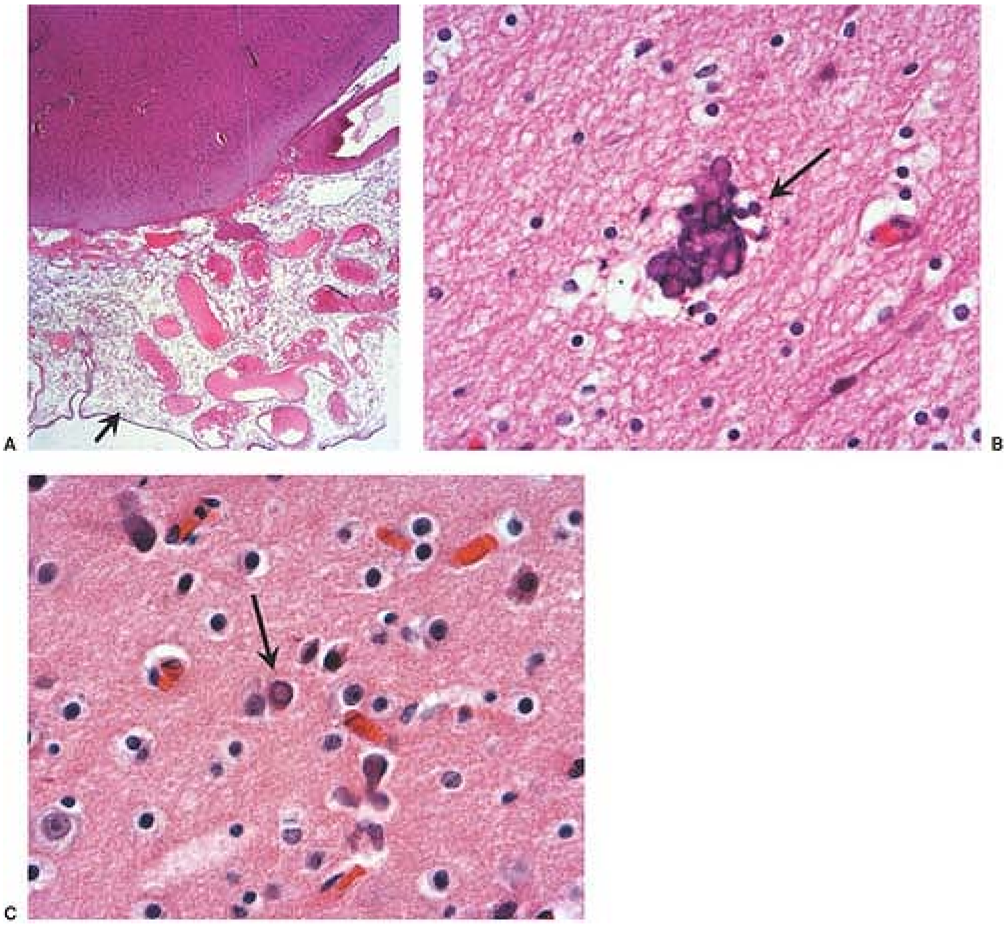

FIGURE 14.18 Sturge-Weber-Dimitri syndrome, microscopic features. **A:** Dense angiomatosis of meningeal vessels in the occipital region (*arrow*). **B, C:** Punctate calcifications (*arrows*) in the underlying brain parenchyma. (See black and white image.)

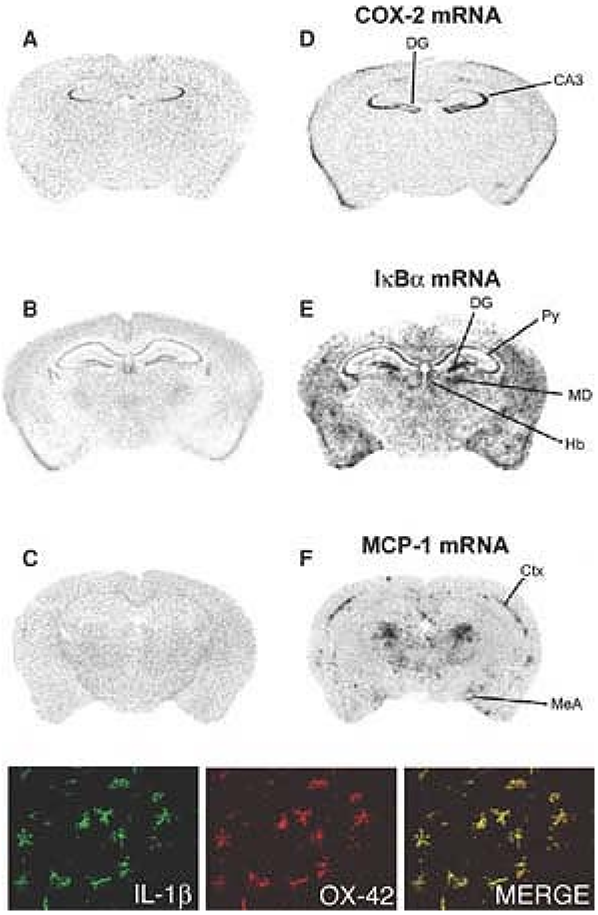

FIGURE 25.2 Seizure-induced expression of genes encoding proinflammatory molecules in rodent forebrain areas after seizures. Panels **D** through **F** show the increased hybridization signal of COX-2, IkBα, (an index of NFκB activation), and the chemokine monocyte-chemoattractant protein (MIP)-1, 24 hours after seizures induced by pilocarpine in mouse forebrain sections (adapted from Turrin NP, Rivest S. Innate immune reaction in response to seizures: Implications for the neuropathology associated with epilepsy. *Neurobiol Dis.* 2004;16:321–334, with permission). Very low or nondetectable expression was found in basal conditions (saline-injected mice), as depicted in corresponding panels **A** through **C**. The phenotype of the expressing cells was identified using selective markers: The majority of cells expressing these inflammatory mediators were infiltrating monocytes and parenchymal microglia; in some instances also endothelial cells were positive. Neurons also overexpressed COX-2 and IkB mRNA. Micrographs in bottom row depict IL-1β and OX-42$^+$ microglia and their merged image, respectively. Ctx, cortex; CA3, pyramidal layer regions; DG, dentate gyrus; Hb, habenular nucleus; MD, mediodorsal thalamic nucleus; MeA, medial amygdala; Py, pyramidal cell layer. (See black and white image.)

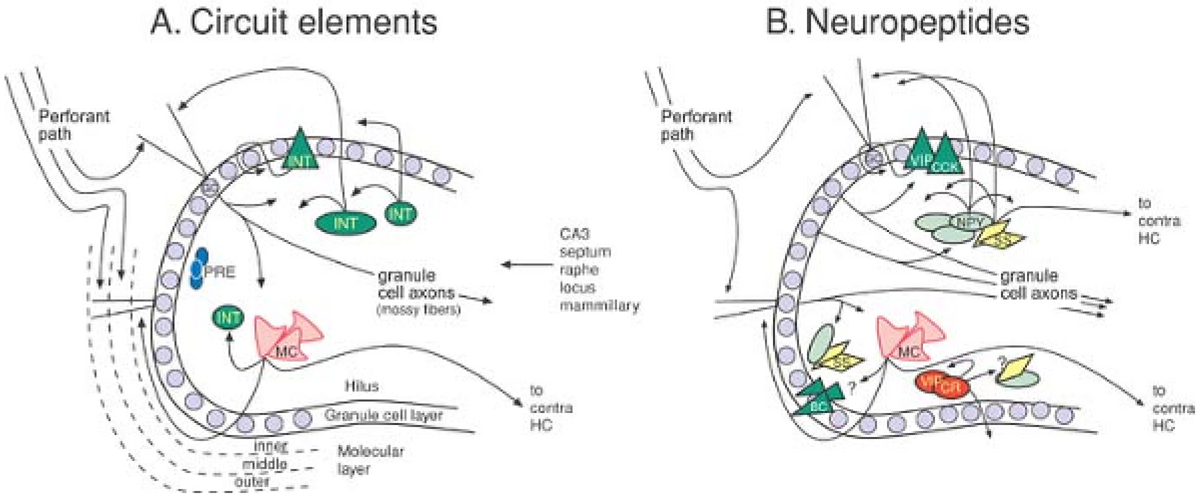
A. Circuit elements
Perforant path
INT
INT
INT
GC
PRE
INT
MC
granule cell axons (mossy fibers)
CA3 septum raphe locus mammillary
Hilus
Granule cell layer
to contra HC
inner
middle
outer
Molecular layer
B. Neuropeptides
Perforant path
GC
VIP
CCK
NPY
SS
to contra HC
granule cell axons
SS
MC
?
BC
VIP
CR
?
to contra HC

FIGURE 27.1 Circuit elements and neuropeptides in the rat dentate gyrus under normal conditions. **A:** Major components of dentate gyrus circuitry. These include the dense layer of granule cells (*GC*); diverse GABAergic "interneurons" (*INT*), hilar mossy cells (*MC*), as well as precursors to granule cells (*PRE*) that are located in the subgranular zone. The major afferent input to the dentate gyrus is the perforant pathway, which contains the axons of neurons in the entorhinal cortex. Lateral entorhinal neurons innervate the outer molecular layer (*outer*) and medial entorhinal neurons innervate the medial molecular layer (*medial*). Mossy cells and other fibers innervate the inner molecular layer (*inner*). In addition, inputs to the dentate gyrus also arise from area CA3 pyramidal cells, the septum, dorsal raphe, locus coeruleus, mammillary bodies, and other areas. The main projections from the dentate gyrus are from the granule cell axons (the mossy fibers), which terminate locally on hilar processes and the layer containing the proximal dendrites of CA3 pyramidal cells (stratum lucidum; not shown). In addition, mossy cells project both ipsilaterally and contralaterally to the dentate gyrus. Some GABAergic neurons also project contralaterally. Reproduced with permission from Freund TF, Buzsaki G. Interneurons of the hippocampus. *Hippocampus*. 1996;6:347–470; and Scharfman HE. The role of nonprincipal cells in dentate gyrus excitability and its relevance to animal models of epilepsy and TLE. In: Delgado-Esqueta AV, Wilson W, Olsen RW, Porter RJ, editors. *Basic mechanisms of the epilepsies: molecular and cellular approaches*, 3rd ed. New York: Lippincott-Raven; 1999:805–820.[77,179] **B:** Many neuropeptides are expressed in the normal dentate gyrus, and some of the most well-studied examples are shown.[77] Opiates are mainly expressed in granule cells. In contrast, other neuropeptides are primarily present in interneurons. Basket cells contain both vasoactive intestinal polypeptide and cholecystokinin; hilar neurons that innervate the outer molecular layer (as well as other targets) express neuropeptide Y and/or somatostatin; vasoactive intestinal polypeptide and calretinin that define a population that innervates the inner molecular layer, as well as other interneurons; in addition, other vasoactive intestinal polypeptide-containing cells exist and may be coupled by gap junctions.[90] Recent studies have indicated that substance P has widespread expression in interneurons.[197] (See black and white image.)

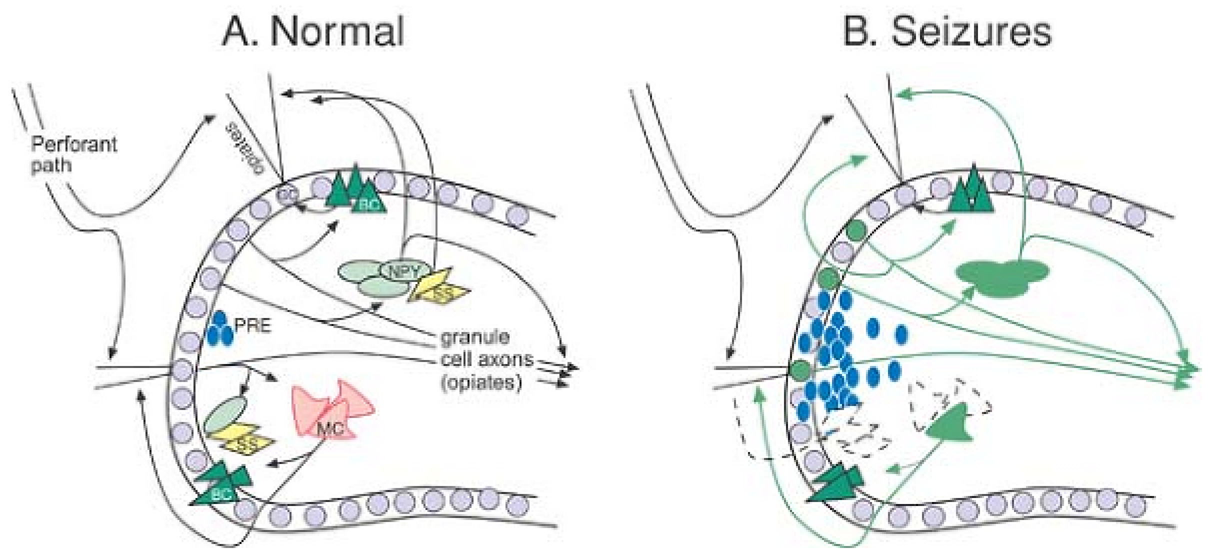
A. Normal
B. Seizures
Perforant path
opiates
BC
BC
NPY
SS
PRE
granule cell axons (opiates)
SS
MC
BC

FIGURE 27.2 Changes in neuropeptide Y and somatostatin in the dentate gyrus after seizures. **A:** Normal circuitry and expression of neuropeptide Y and somatostatin in the rodent dentate gyrus. **B:** Alterations in neuropeptide Y and somatostatin in animal models of epilepsy are illustrated schematically. For the neuropeptide Y system, these changes include: (a) new expression in granule cells and their axons, the mossy fibers; (b) increased expression in interneurons that normally express neuropeptide Y—this effect appears to develop mostly after acute rather than chronic seizures; (c) novel expression of neuropeptide Y in some mossy cells;[88] and (d) expression in newly formed granule cells, although the extent that this occurs is unclear. In addition, changes in receptors occur (not shown). For the somatostatin system, the best documented alteration is seizure-induced cell death of those interneurons that normally express this peptide. (See black and white image.)

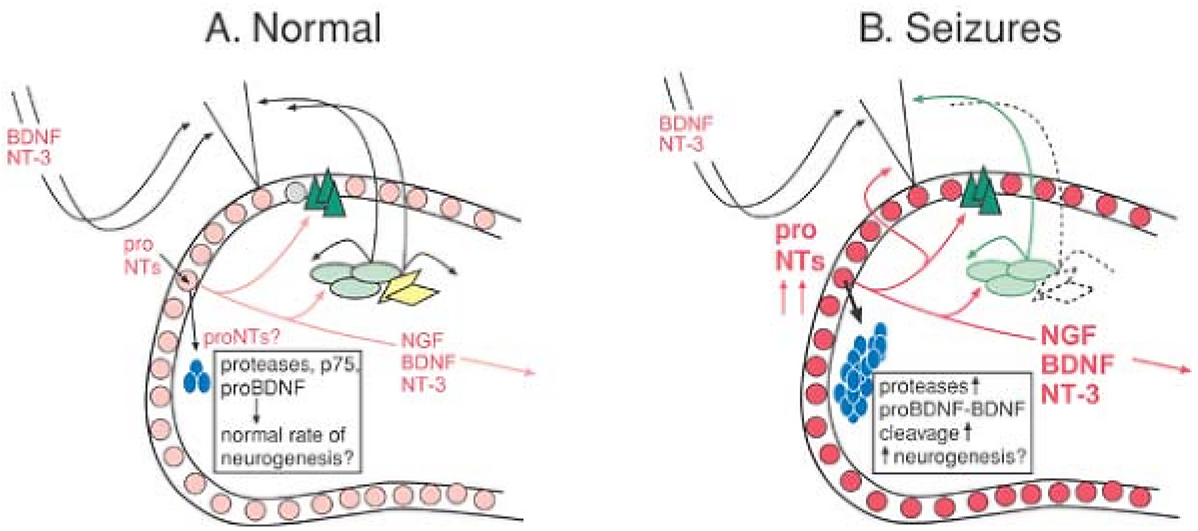
A. Normal
B. Seizures
BDNF
NT-3
pro NTs
proNTs?
proteases, p75, proBDNF
normal rate of neurogenesis?
NGF
BDNF
NT-3
BDNF
NT-3
pro NTs
↑↑
proteases↑
proBDNF-BDNF cleavage↑
↑neurogenesis?
NGF
BDNF
NT-3

FIGURE 27.3 Changes in neurotrophins in the dentate gyrus after seizures. **A:** Normal pattern of expression of the neurotrophins NGF, BDNF, and NT-3. The predominant cell type expressing neurotrophins normally is the

granule cell. In addition, lower levels of BDNF and NT-3 are present in perforant path axons. Proneurotrophins are present in the soma and are thought to be released in the vicinity of the soma. Proneurotrophins are typically cleaved by extracellular proteases, but can also act directly on p75 receptors to modulate survival. **B:** Changes in neurotrophins associated with chronic seizures are schematically illustrated. NGF and BDNF expression is increased in granule cells, and NT-3 levels decline; BDNF and NT-3 decline in the perforant path when seizure-induced entorhinal cell loss occurs. The altered levels of neurotrophins are likely to have diverse effects on granule cell structure and function. In addition, indirect effects may occur, such as induction of neuropeptide Y by BDNF, either in granule cells or adjacent interneurons (cf. Figure 2). Upregulation of proneurotrophins are also likely and, in the case of proBDNF, increased synthesis may influence seizure-induced cell death by increased activation of the p75 neurotrophin receptor, or seizure-induced neurogenesis by the increase in BDNF that would result from proBDNF cleavage. These changes, as well as alterations in receptors for neurotrophins, are likely to have a complex net effect on the excitability of the dentate gyrus. (See black and white image.)

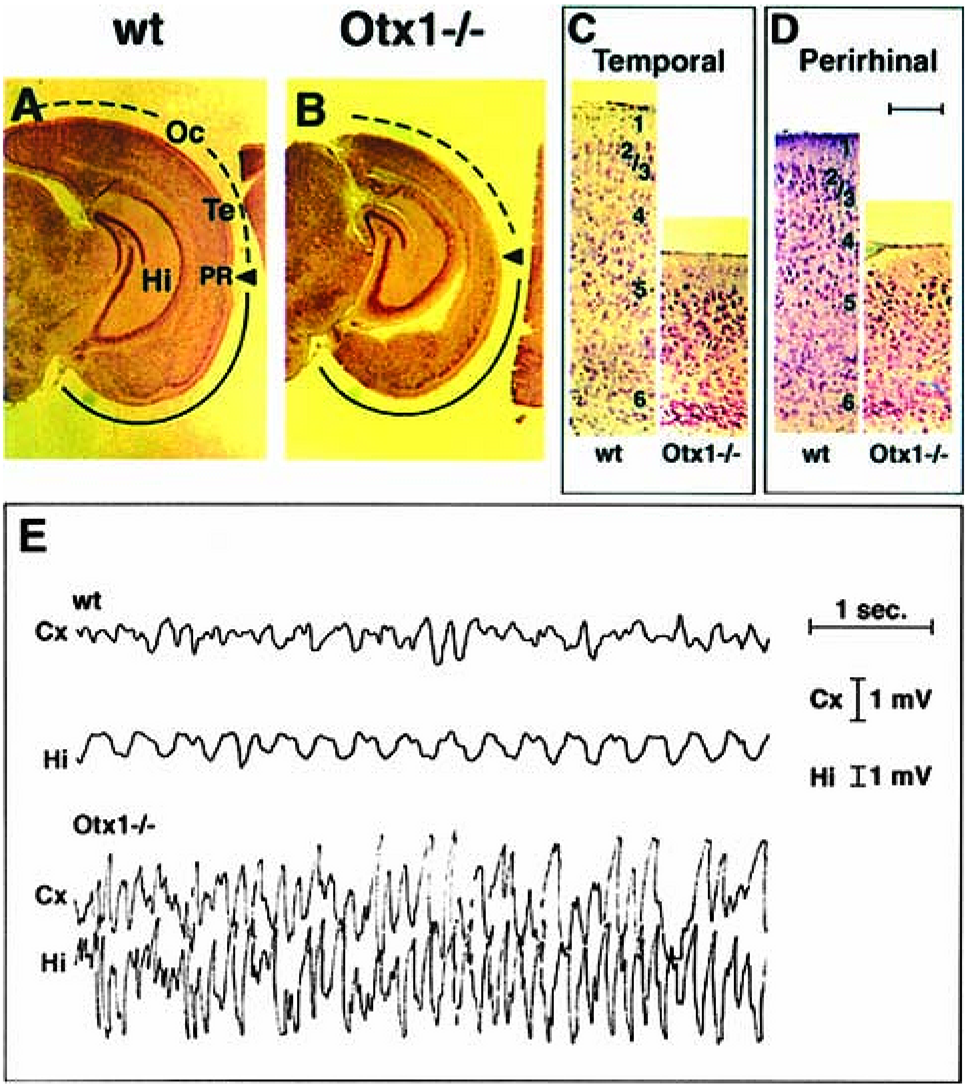

FIGURE 36.13 Morphologic **(A, B)**, histologic **(C, D)**, and electroencephalographic (EEG) **(E)** comparison

of wild-type (wt) and Otx$^{-/-}$ mice. Note the reduction of temporal (Te) perirhinal (PR) cortices and hippocampus (Hi) in Otx$^{-/-}$ mice. Representative EEG recordings from neocortex (Cx) and Hi during a convulsive seizure of Otx$^{-/-}$ mice is shown in panel E, where the EEG recording from a wild-type (wt) animal is shown for comparison. (From Acampora D, Barone P, Simeone A. Otx genes in corticogenesis and brain development. *Cereb Cortex.* 1999;9:533–542; with permission.) (See black and white image.)

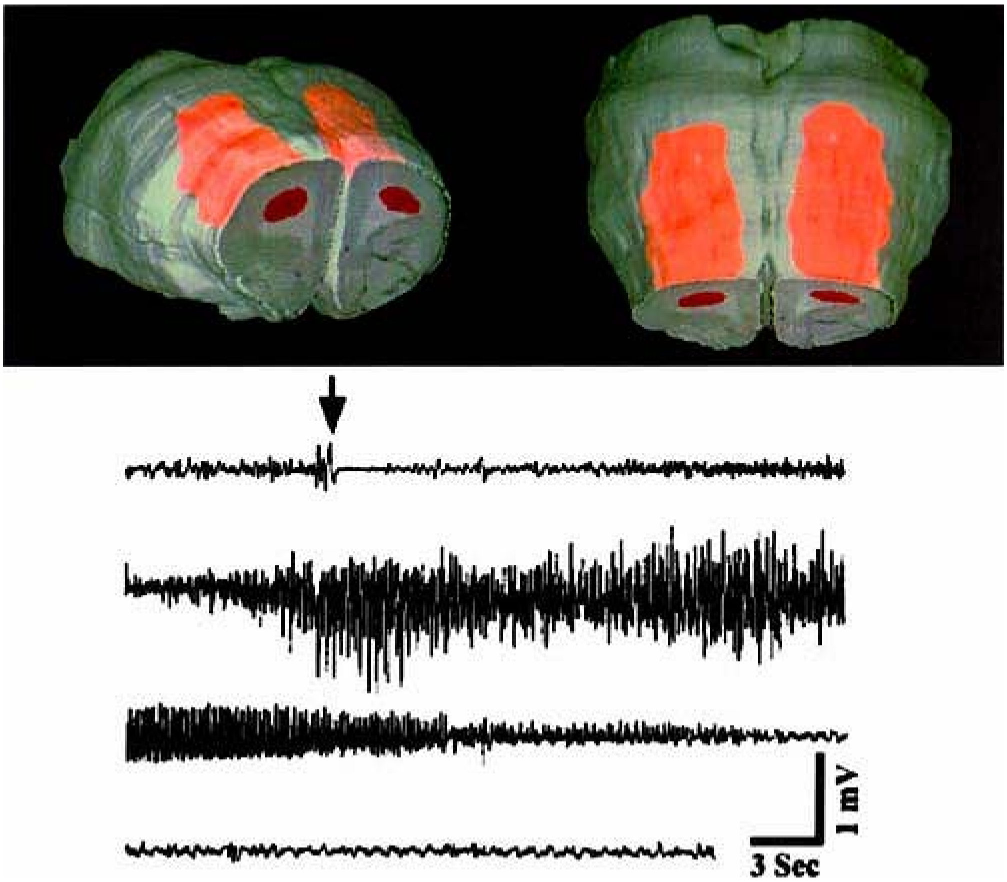

FIGURE 36.15 Top: Three-dimensional reconstruction of the telencephalic internal structural heterotopia (TISH) shown in red at the cut surface of the brain and in pink where it is viewed through the overlying cortex. **Bottom:** Electroencephalographic (EEG) recordings of a convulsive seizure in a TISH rat. The four lines show continuous EEG recording from a single electrode positioned in the normotopic neocortex (*arrow* indicates seizure onset). Seizure activity can be observed as changes in the frequency and amplitude of the EEG. (Modified from Lee KS, Schottler F, Collins JL, et al. A genetic animal model of human neocortical heterotopia associated with seizures. *J Neurosci*. 1997;17:6236–6242). (See black and white image.)

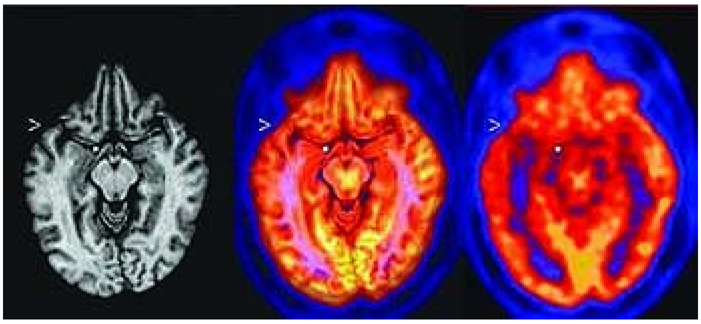

FIGURE 80.1 Coregistered axial image plane of magnetic resonance imaging (MRI) and interictal 2-deoxy-2-[^{18}F]fluoro-D-glucose ([^{18}F]FDG) positron emission tomography (PET) images of a limbic temporal lobe epilepsy (TLE) patient. The gray-scale MR image **(left)** and the color PET image **(right)** are coregistered in the center image. The MRI and PET data were reoriented parallel to a line through the anterior and posterior commissures. A widespread area of reduced [^{18}F]FDG activity is evident on the left side of the PET image; inspection of the PET image alone does not clarify whether the reduction extends from mesial structures (at the dot internal to the brain FDG image) of the temporal lobe into the basal frontal lobe, nor whether the lateral temporal hypometabolism (at the arrowhead) extends above the sylvian fissure. The dot and arrowhead appear at the same coordinates in the MRI and the coregistered MRI-PET images as in the PET image, clarifying that all sites with severe hypometabolism are confined to the temporal lobe. (See black and white image.)

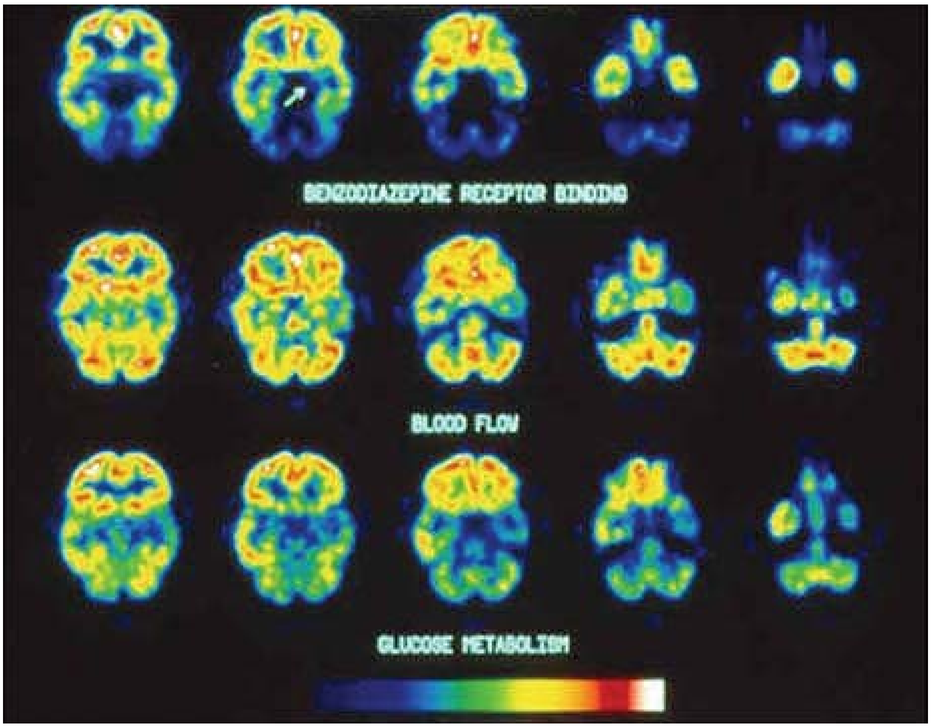

FIGURE 80.7 Coregistered interictal [^{11}C] flumazenil and 2-deoxy-2-[^{18}F]fluoro-D-glucose ([^{18}F]FDG) positron emission tomography (PET) images of a mesial temporal lobe epilepsy (TLE) patient. Flumazenil transport rate is determined predominantly by regional cerebral blood flow. Flumazenil distribution volume is determined by the regional density of central benzodiazepine receptors. Five adjacent image planes are displayed for each modality. The more superior image plane is to the left of each row. The subject's left is on the right of each image. Images of glucose metabolism and flumazenil transport rate show a widespread left mesial and lateral temporal decrease. Images of flumazenil distribution volume show a highly localized left anterior mesial temporal decrease (*arrow*). The specimen at efficacious temporal lobectomy demonstrated sclerosis of the left anterior hippocampus. (From Henry et al. with permission.) (See black and white image.)

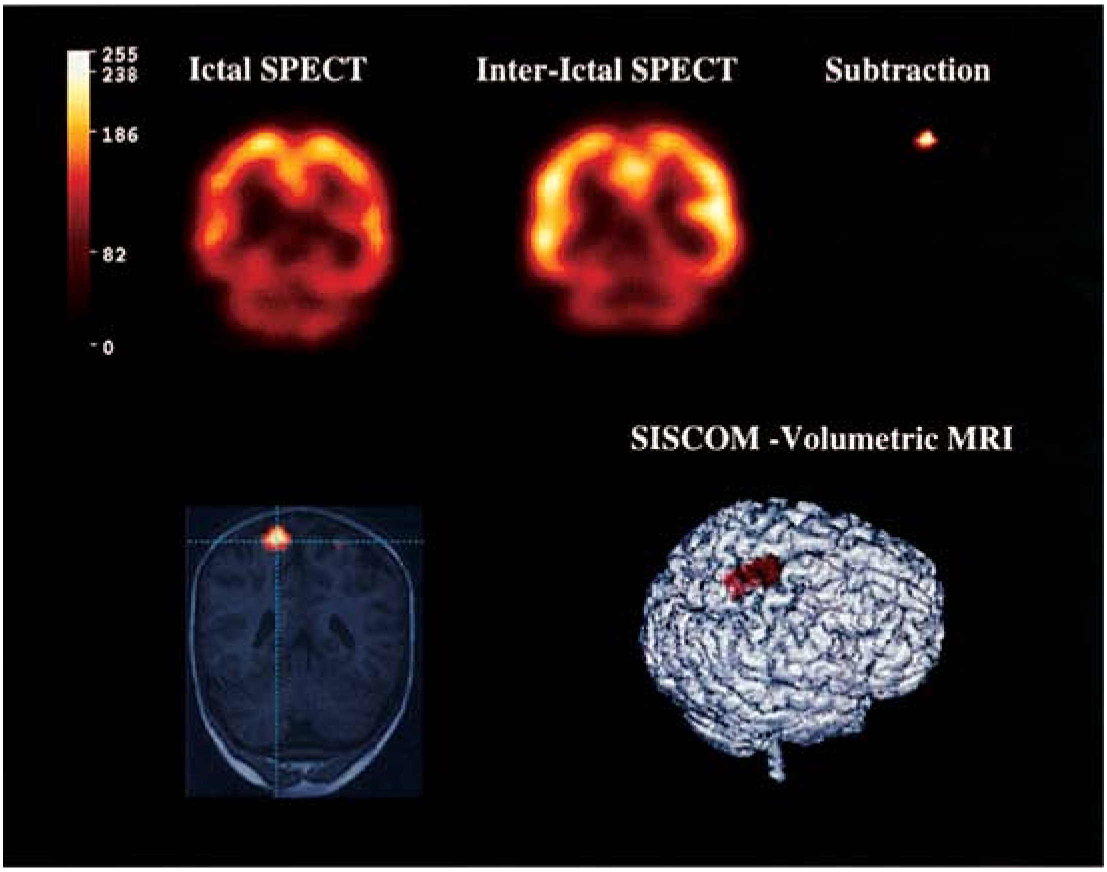

FIGURE 81.2 Steps to obtaining subtraction ictal SPECT (single photon emission computed tomography) coregistered to MRI (magnetic resonance imaging) (SISCOM) image. Ictal (*upper left*) and interictal (*upper middle*) SPECT images are obtained. After normalization of their mean intensities and coregistration with each other, subtraction is performed to obtain a “difference” image (*upper right*). The difference image is then coregistered with MRI at specific planes (*lower left*) or on the surface of a three-dimensional MRI (*lower right*). (From So E. Role of neuroimaging in the management of seizure disorders. *Mayo Clin Proc*. 2002;77:1251–1264, with permission.) (See black and white image.)

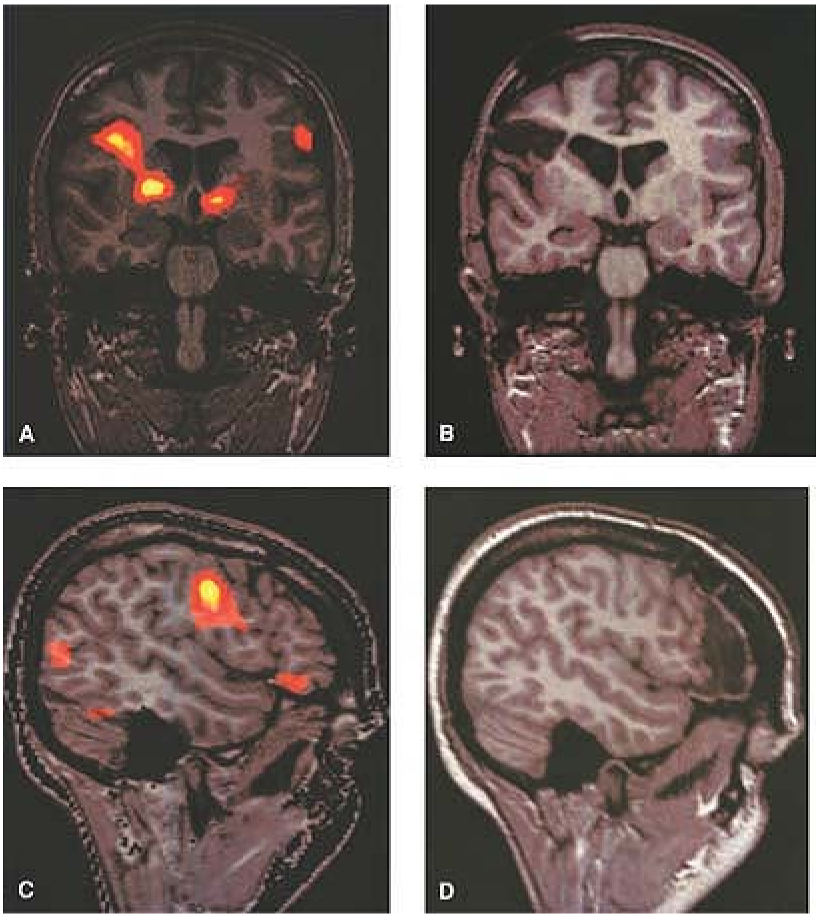

FIGURE 81.3 Preoperative subtraction ictal SPECT (single photon emission computed tomography) coregistered to MRI (magnetic resonance imaging) (SISCOM) images (A and C) and postoperative MRI (B and D). **A, B:** Complete resection of neocortical region underlying SISCOM focus. **C, D:** Nonresection of neocortical region underlying SISCOM focus. (From O'Brien T, So E, Mullan B, et al. Subtraction peri-ictal SPECT is predictive of extratemporal epilepsy surgery outcome. *Neurology*. 2000;55:1668–1677, with permission.) (See black and white image.)

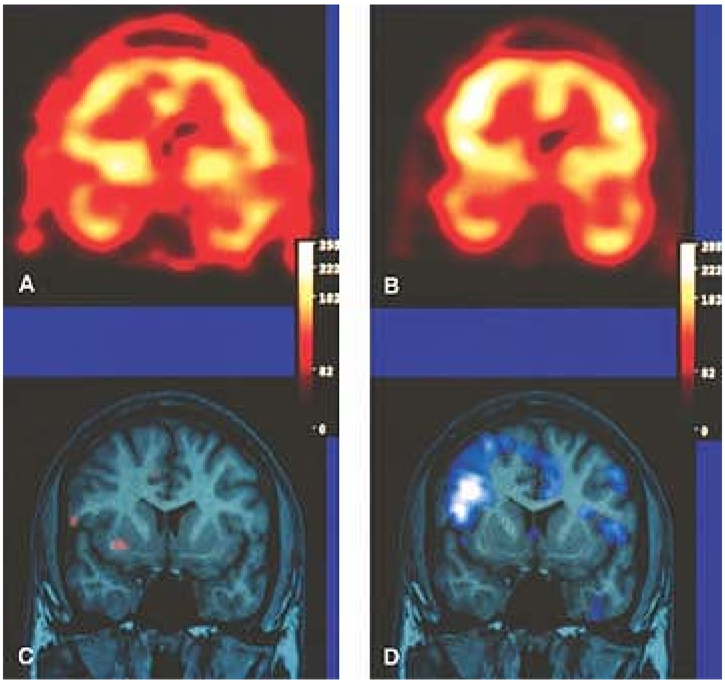

FIGURE 81.4 Subtraction ictal SPECT (single photon emission computed tomography) coregistered to MRI (magnetic resonance imaging) (SISCOM) with "positive" subtraction for detecting hyperperfusion focus and "negative" subtraction for detecting hypoperfusion focus. **A:** Postictal SPECT image obtained from radiotracer injection at 88 seconds after seizure termination. **B:** Interictal SPECT image. **C:** "Positive" subtraction shows no hyperperfusion focus. **D:** "Negative" subtraction shows a hypoperfusion focus at the right frontal region. (See black and white image.)

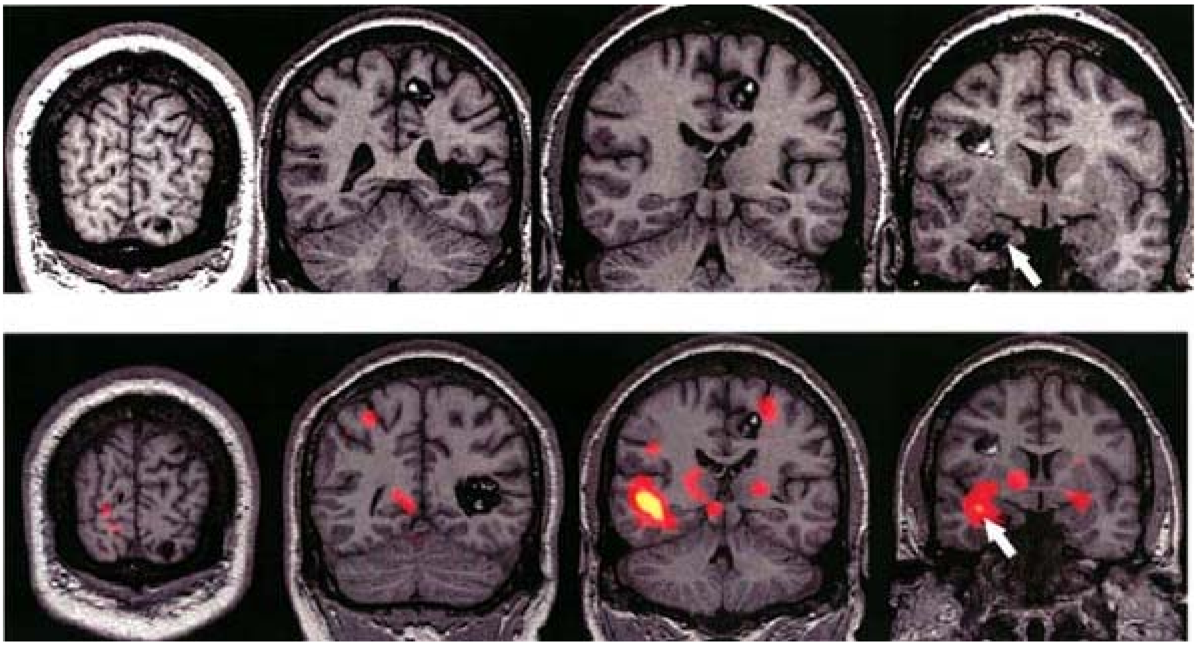

FIGURE 81.5 Coronal MRI (magnetic resonance imaging) (*top row*) and subtraction ictal SPECT (single photon emission computed tomography) coregistered to MRI (SISCOM) (*bottom row*) images of a patient who had medically refractory partial epilepsy associated with multiple cavernous angiomas. Electroencephalography did not localize seizure onset. SISCOM shows ictal hyperperfusion focus at the right mesial temporal angioma, and seizure semiology was compatible with right temporal onset seizures. Resection of the right temporal angioma and its immediate surrounding tissues resulted in seizure freedom. (See black and white image.)

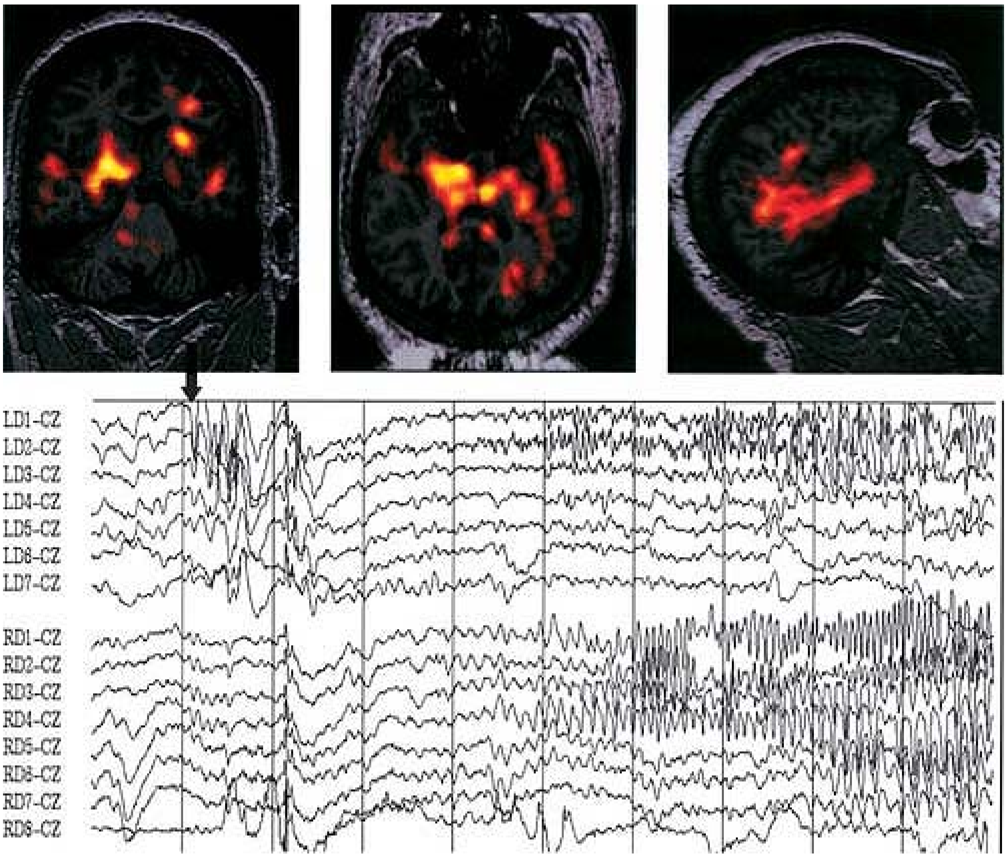

FIGURE 81.6 Subtraction ictal SPECT (single photon emission computed tomography) coregistered on MRI (magnetic resonance imaging) (SISCOM) images (*top*) and bilateral mesial temporal depth electrode recordings (*bottom*) in a patient with left mesial temporal sclerosis and seizure onset. SISCOM shows dominant hyperperfusion focus involving the right mesial temporal and thalamic regions (*upper left* and *middle*). There is also a streak of less intense hyperperfusion at the left temporal region (*upper right*). Left mesial temporal depth electroencephalogram (LD1-7 referred to Cz) shows seizure onset (*arrow*) with subsequent rapid spread to involve the right mesial temporal depth electrodes (RD1-8 referred to Cz). (See black and white image.)

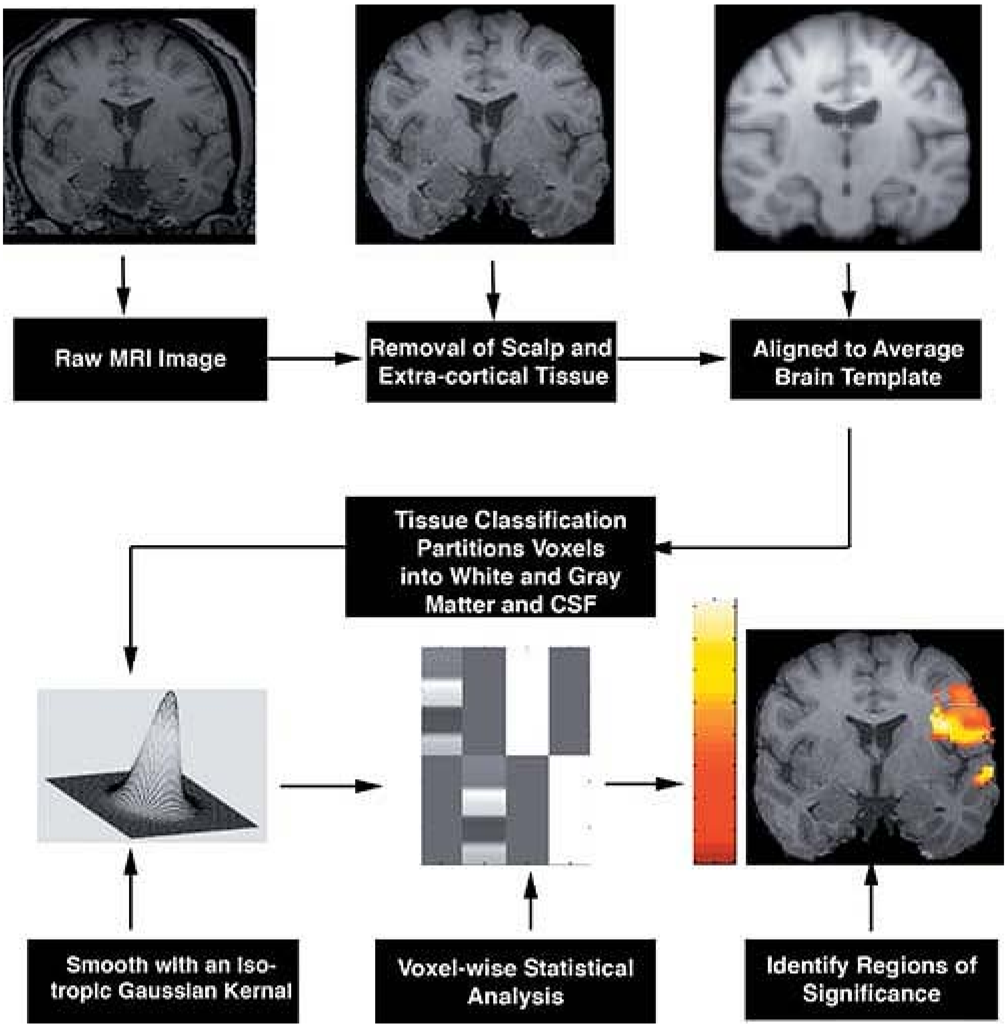
Raw MRI Image
Removal of Scalp and Extra-cortical Tissue
Aligned to Average Brain Template
Tissue Classification Partitions Voxels into White and Gray Matter and CSF
Smooth with an Isotropic Gaussian Kernal
Voxel-wise Statistical Analysis
Identify Regions of Significance

FIGURE 84.1 Steps in voxel-based morphometry. Scalp and extracortical tissues are removed from raw images, and the resulting brain images are normalized to a standard template. Gray and white matter and cerebrospinal fluid (CSF) are automatically classified based on voxel intensity values. Normalized images are smoothed with an isotropic Gaussian kernel. Voxelwise statistical analysis based on generalized linear model is applied to the images to identify regions of significance. MRI, magnetic resonance imaging. (See black and white image.)

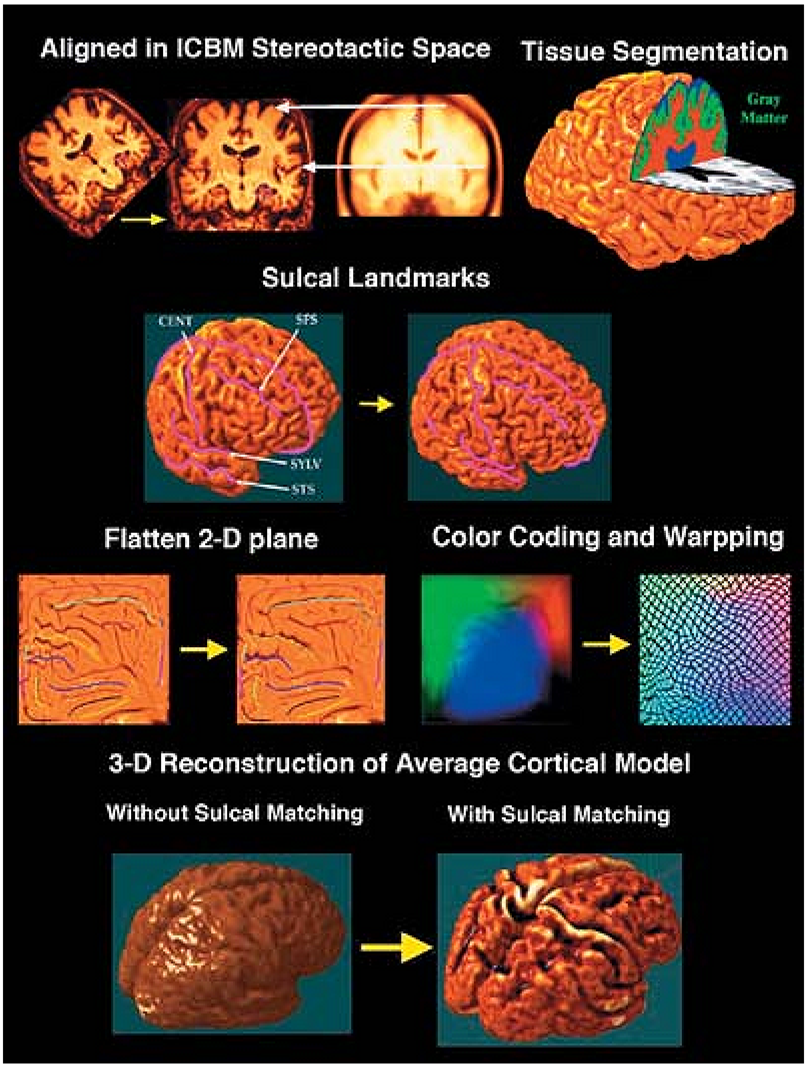
Aligned in ICBM Stereotactic Space
Tissue Segmentation
Gray Matter
Sulcal Landmarks
CENT
SFS
SYLV
STS
Flatten 2-D plane
Color Coding and Warpping
3-D Reconstruction of Average Cortical Model
Without Sulcal Matching
With Sulcal Matching

FIGURE 84.2 Steps in cortical pattern-matching algorithm. Raw images are first globally aligned to a standard template. Tissue classification partitions the image into gray and white matter and cerebrospinal fluid based on voxel intensity. A three-dimensional (3D) cortical model is extracted from each scan, and sulci are traced and labeled directly on the surface model. A geometric flattening process transforms the cortical model into two-dimensional (2D) space with retained sulcal landmarks. A color-coding system with intensities of the red, blue, and green corresponding proportionally to the x, y, z location of the three-dimensional cortical model plot the original coordinates onto the flat map. A warping technique uses the sulcal landmarks to constrain one cortical region onto another. The result produces an averaged cortical model for each group across subjects. ICBM, International Consortium for Brain Mapping; CENT, Central Sulcus; SFS, Superior Frontal Sulcus; STS, Superior Temporal Sulcus; SYLV-Sylvian Fissure. (See black and white image.)

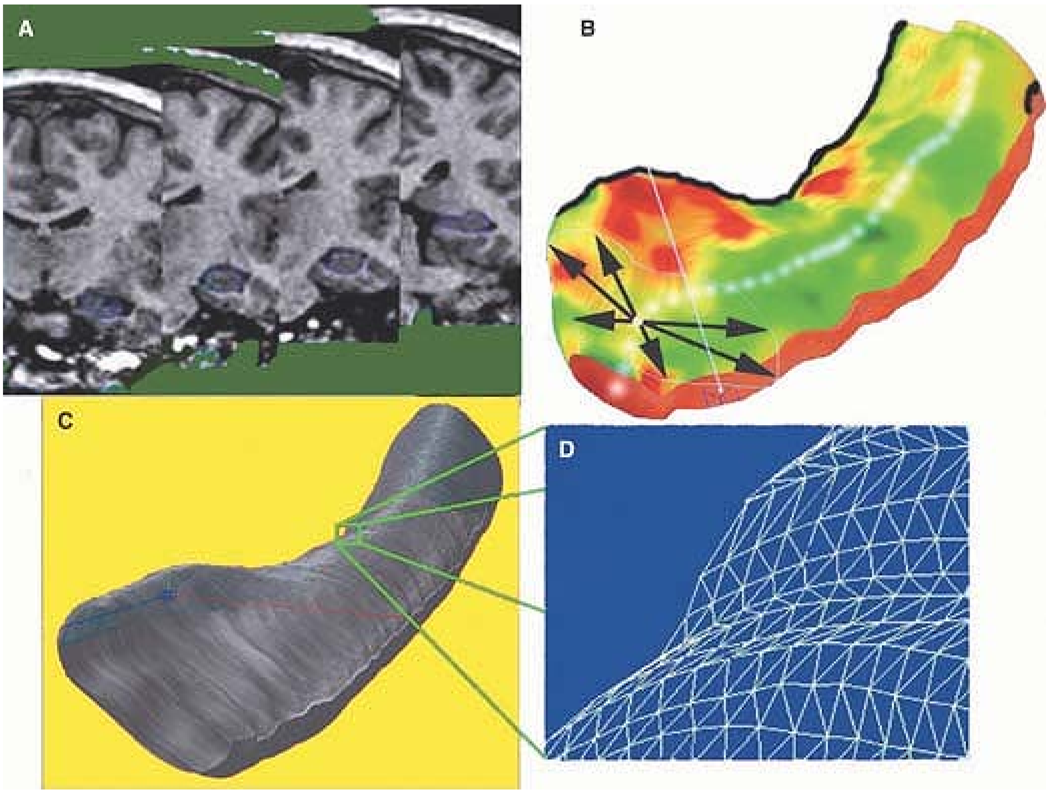

FIGURE 84.3 Steps involved in three-dimensional (3D) hippocampal modeling. Each individual's hippocampus is traced in consecutive coronal magnetic resonance imaging sections **(A)** and converted to a 3D parametric surface **(B)** in which the radial size of the hippocampus is measured from a centerline and plotted in color on the surface to index radial atrophy. These meshes are averaged across subjects **(C)**, and atrophy relative to control means is computed at each surface grid point **(D)**. (See black and white image.)

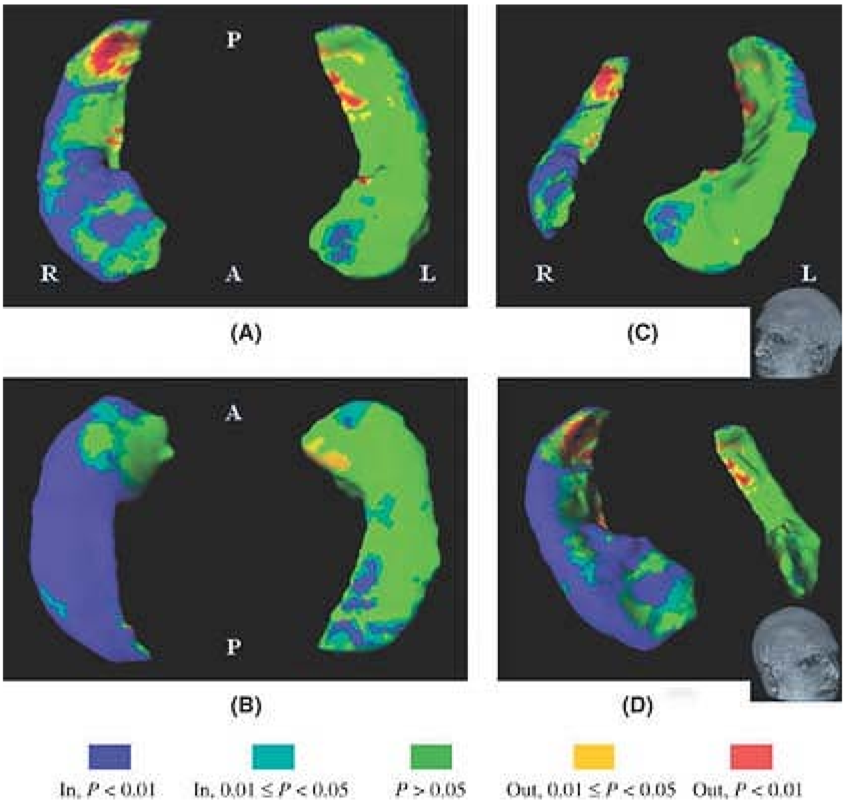
P
R
A
L
R
L
(A)
(C)
A
P
(B)
(D)
In, P < 0.01
In, 0.01 ≤ P < 0.05
P > 0.05
Out, 0.01 ≤ P < 0.05
Out, P < 0.01

FIGURE 84.4 Large-deformation, high-dimensional brain mapping reveals bilateral hippocampal deformity in right mesial temporal lobe epilepsy patients. Similar bilateral changes were found in left temporal lobe epilepsy patients. Inward deviation is shown in purple ($p < .01$) and turquoise ($.01 = p < .05$). Outward deviation is shown in red ($p < .01$) and yellow ($.01 = p < .05$). **A:** View from above. **B:** View from below. **C:** View from a perspective slightly above and to the left of a midline plane, showing the top side. **D:** View from a perspective slightly above and to the right of a midline plane, showing the top side. A, anterior; L, left; P, posterior; R, right. (From Hogan RE, Wang L, Bertrand ME, et al. MRI-based high-dimensional hippocampal mapping in mesial temporal lobe epilepsy. *Brain*. 2004;127:1731–1740, with permission.) (See black and white image.)

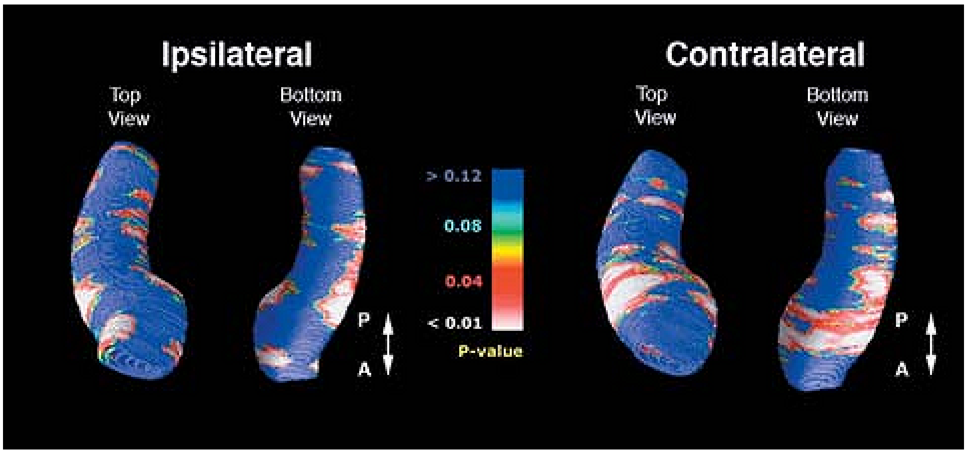
Ipsilateral
Top View
Bottom View
> 0.12
0.08
0.04
< 0.01
P-value
P
A
Contralateral
Top View
Bottom View
P
A

FIGURE 84.5 Maps identifying regions where seizure-free (SF) and not-seizure-free (NSF) surgical outcome groups differ in their degree of atrophy. Group difference maps show mean hippocampal volume differences ipsilateral **(left)** and contralateral **(right)** to the side of seizure onset. Areas of significant atrophy between the two surgical outcome groups are plotted as a map of *p* values. The NSF groups show significantly greater diffuse atrophy in the ipsilateral hippocampus, whereas the contralateral side shows a more region-specific atrophy pattern. The maximal atrophy is seen in the anterior and lateral aspects of the contralateral hippocampus. A, anterior; P, posterior. (Adapted from Lin JJ, Salamon N, Dutton RA, et al. Three-dimensional preoperative maps of hippocampal atrophy predict surgical outcomes in temporal lobe epilepsy. *Neurology*. 2005;65:1094–1097, with permission.) (See black and white image.)

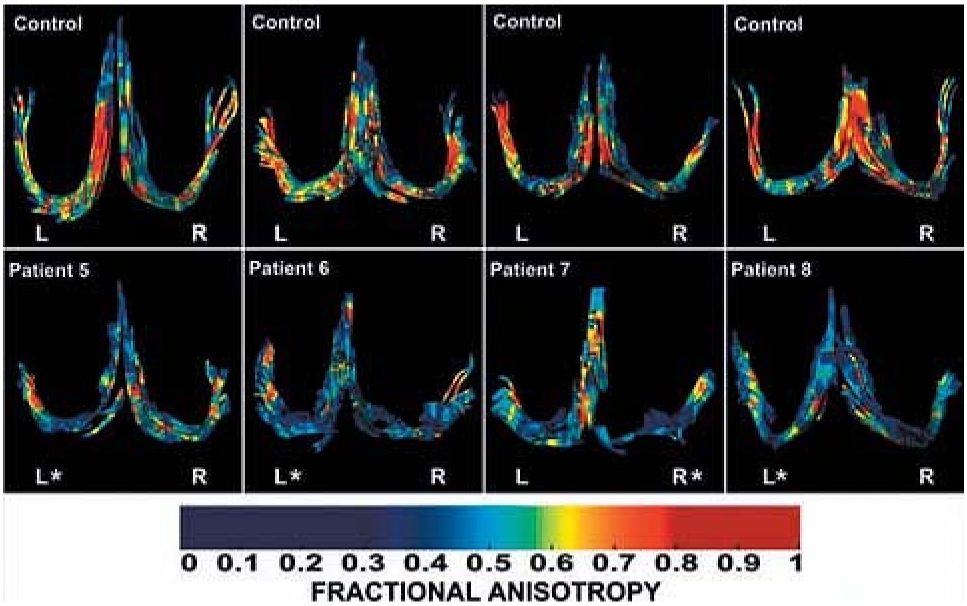

FIGURE 84.6 Diffusion tensor imaging tractography mapped the integrity of the fornix in four healthy controls and four patients with unilateral mesial temporal lobe sclerosis (MTS). Fractional isotropy for each voxel is color coded, with higher values denoting greater structural organization. Fornix of patients with MTS has lower anisotropy and less continuous tracts. Asterisk indicates the side of MTS. L, left; R, right. (From Concha L, Beaulieu C, Gross DW. Bilateral limbic diffusion abnormalities in unilateral temporal lobe epilepsy. *Ann Neurol*. 2005;57:188–196; with permission.) (See black and white image.)

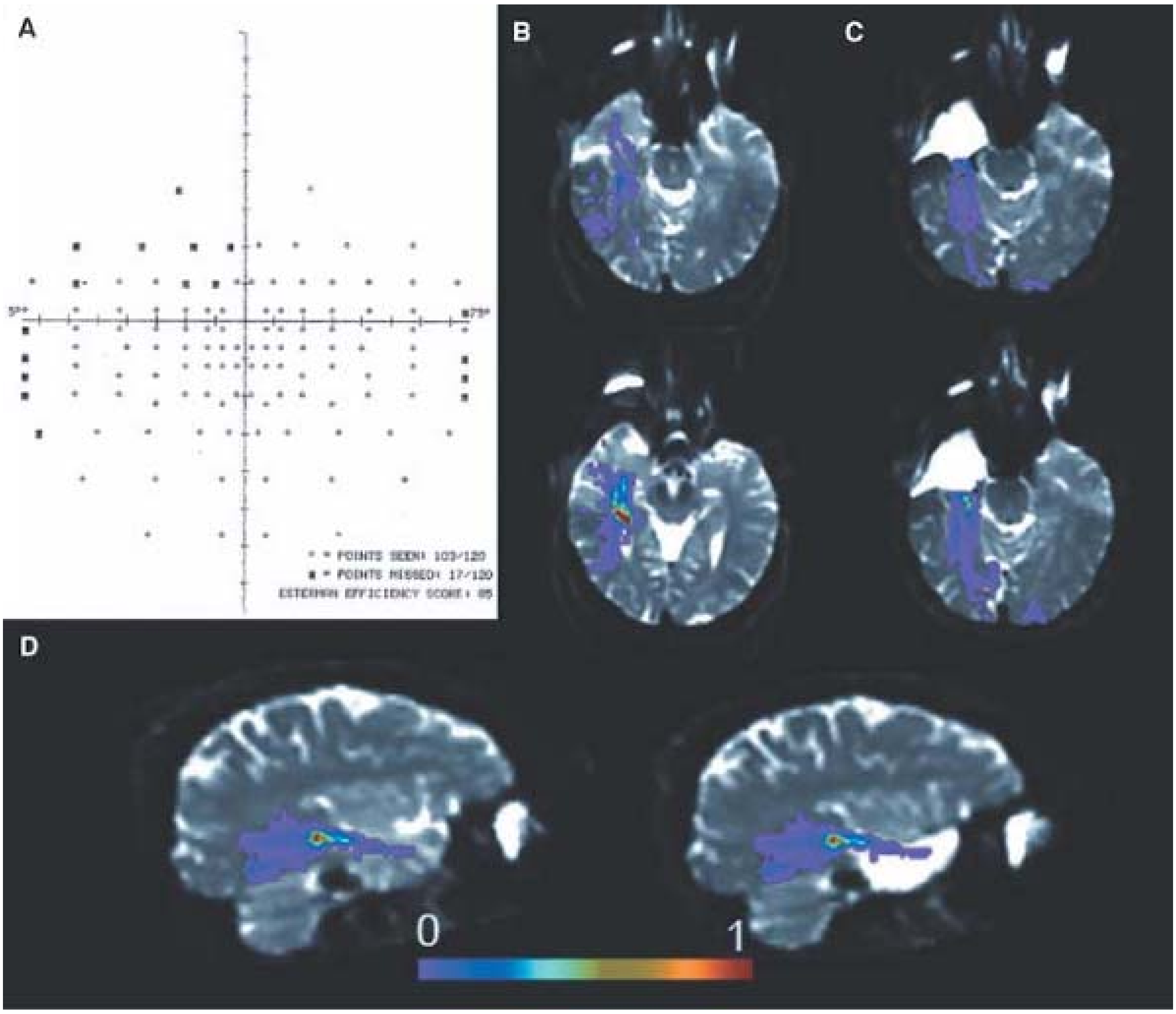

FIGURE 84.7 Postoperative visual field demonstrates a superior homonymous quadrantanopia **(A)**. Preoperative right optic radiation overlaid on preoperative axial **(B)** images; postoperative right optic radiation overlaid on postoperative axial image **(C)**; preoperative optic radiation overlaid on preoperative sagittal **(D, left)** image and postoperative optic radiation overlaid on postoperative sagittal **(D, right)** image. These images show that the preoperative tract overlies the resected anterior temporal lobe, resulting in postoperative visual field deficit. (From Powell HW, Parker GJ, Alexander DC, et al. MR tractography predicts visual field defects following temporal lobe resection. *Neurology*. 2005;65:596–599; with permission.) (See black and white image.)

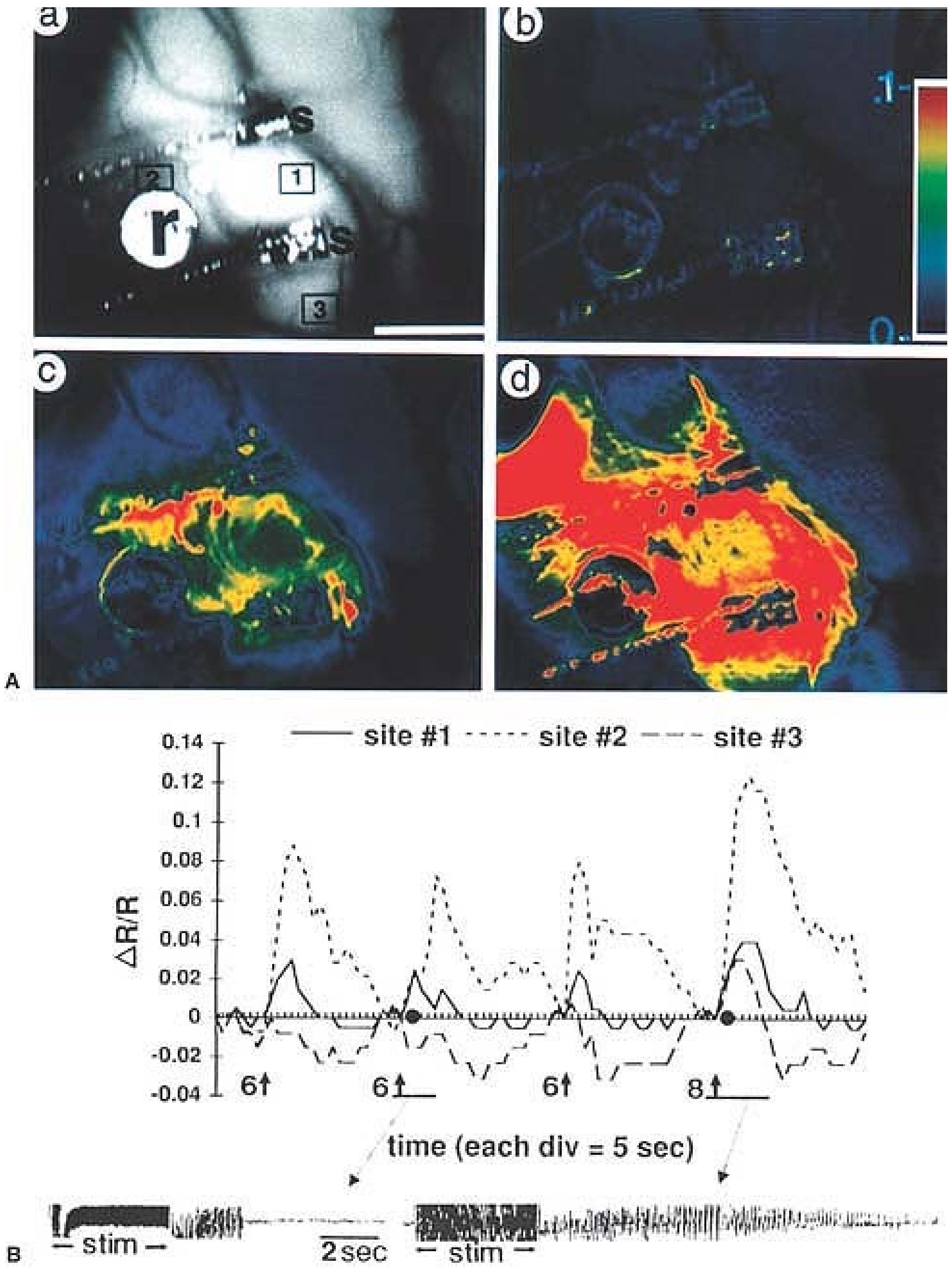

FIGURE 86.3 A: Human frontal cortex exposed at the time of a neurosurgical procedure for treatment of medically intractable epilepsy. Recording surface electroencephalographic (EEG) electrode is represented by *r*, the two stimulating electrodes by *s*. *Boxes 1, 2, and 3* are regions of interest where the optical changes in the intrinsic signal were measured for Figure 3B. Scale bar = 1 cm. **Ab:** Control image subtracted from another control image showing the baseline noise. The pseudocolor scale bar (*right*) shows the intensity of the optical changes, with black being below baseline, blue near baseline, and red maximal. **Ac:** Optical changes at the end of the second stimulation at 6 mÅ, which evoked a short seizure "afterdischarge" episode. The peak changes are near the recording electrode with a surrounding region that is black, suggesting that the optical changes in that region are below baseline. **Ad:** Optical changes after the fourth stimulation are at 8 mÅ, which evoked a more prolonged and intense seizure episode compared with the other intense optical change. **B:** The optical changes from the three boxes shown in Figure 3Aa are shown, as well as the surface EEG recording from the second stimulation (optical changes in Fig. 3Ac; *lower left*) and the surface EEG recording from the second

stimulation (optical changes in Fig. 3Ad; *lower right*). From Haglund MM, Ojemann GA, Hochman DW, Optical imaging of epileptiform and functional activity from human cortex. *Nature*. 1992;358:668–671; with permission. (See black and white image.)

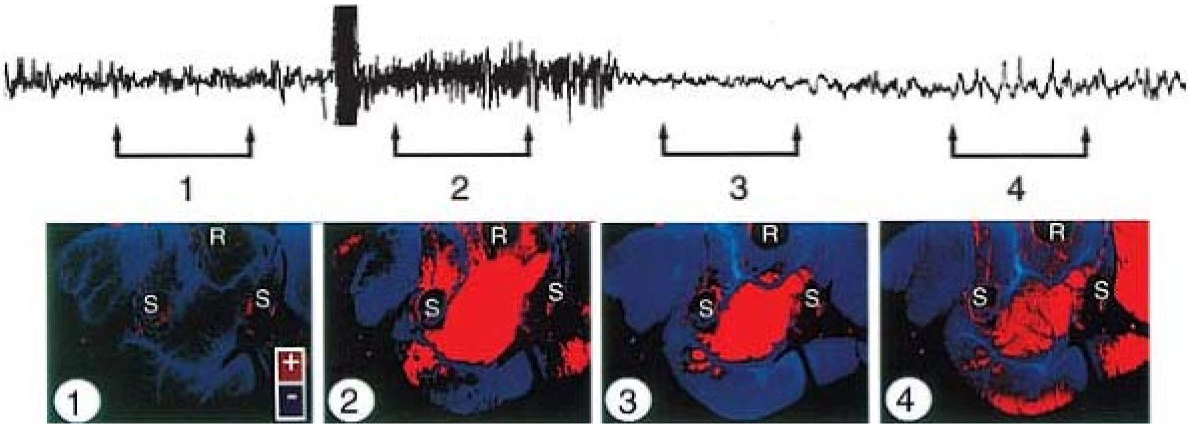

FIGURE 86.4 Upper trace: Surface electroencephalographic (EEG) trace from the recording electrode (*r* in the *lower images*). The brackets represent the period during which the optical images in the *lower panel* were collected and a baseline image was subtracted from each of the images. The four brackets show the baseline, seizure, postictal, and recovery electrical recordings, respectively. **Lower panel:** Optical changes before and after electrical stimulation at the afterdischarge threshold (stimulating electrodes represented by *s*). The optical changes are shown in a two-color scheme, so positive changes correlated with increases in neuronal activation are shown in red, whereas optical changes in the intrinsic signal below baseline are shown in blue. The optical changes in the positive direction correlate with the increases in electrical activity, especially the seizure activity in bracket No. 2. The optical changes also correlate with the quiescent postictal surface EEG recording in bracket No. 3, where the optical changes are below baseline. (See black and white image.)

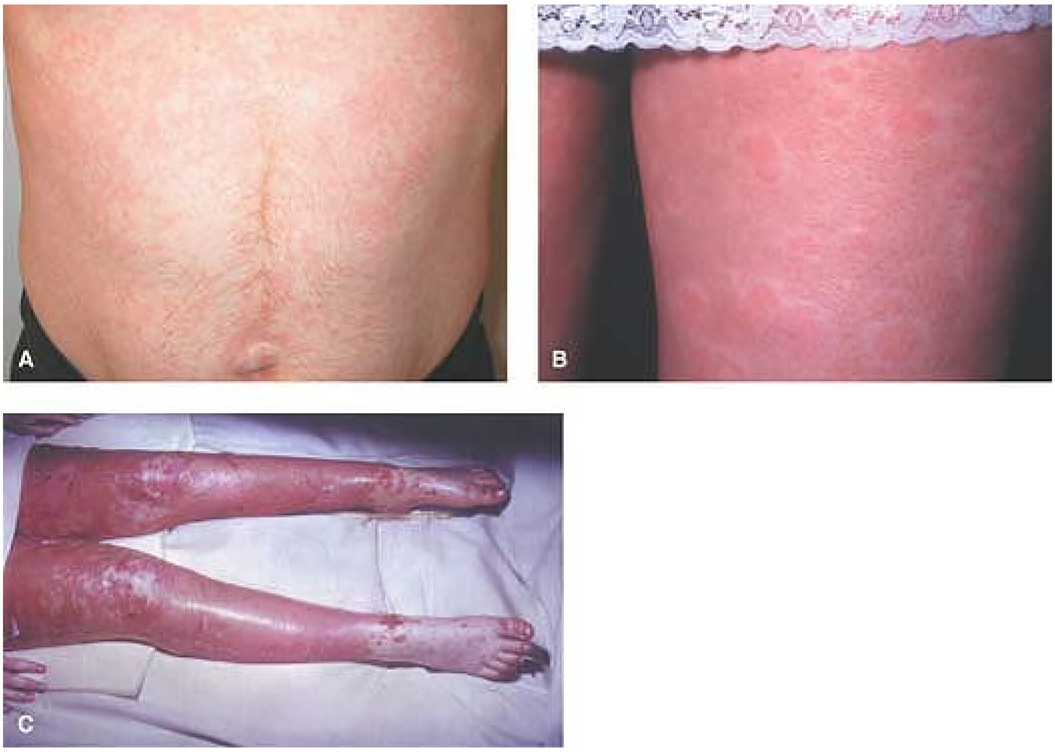

FIGURE 106.1 Cutaneous manifestations of antiep-break ileptic drug hypersensitivity. **A:** Patient with phenytoin-induced maculopapular eruption. (Figure kindly provided by Dr. Gavin Wong, Liverpool, U.K.). **B.** Patient with carbamazepine-induced urticaria. (Figure kindly provided by Dr. Clodagh King, Liverpool, U.K.). **C.** Patient with carbamazepine-induced toxic epidermal necrolysis. (See black and white image.)

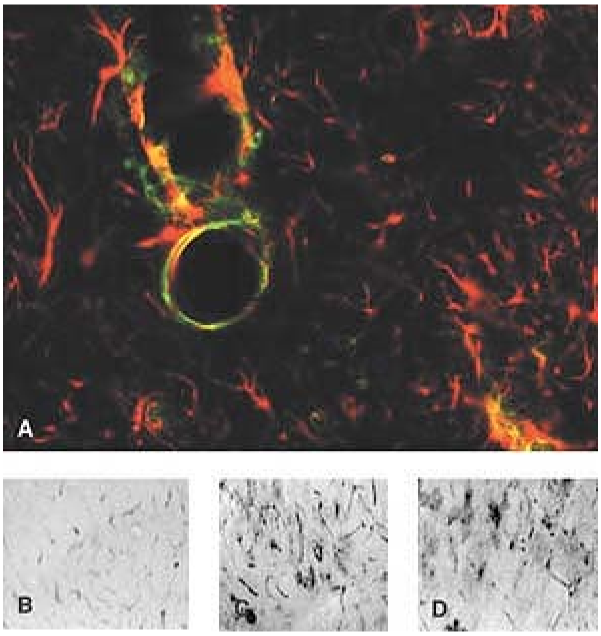

FIGURE 115.3 Overexpression of P-glycoprotein (P-gp) in an animal model. **A:** Merged image (20×) showing P-gp immunolabeling (*green*) and glial fibrillar acidic protein (GFAP)-positive astrocytes (*red*) in the rat cortex 18 hours after pilocarpine-induced status epilepticus. Colocalization signal (*yellow*) depicts P-gp expression in astrocytic endfeet adjacent to brain microvessels. **B, C, D:** Representative immunohistochemical micrographs (10×) depicting P-gp immunolabeling in control rat hippocampus **(B)** and 18 hours after pilocarpine-induced status epilepticus. Note that in the control panel only, vessels are lightly labeled, whereas seizures induced P-gp overexpression both in vessels and in astrocytes **(C, D)**. (See black and white image.)

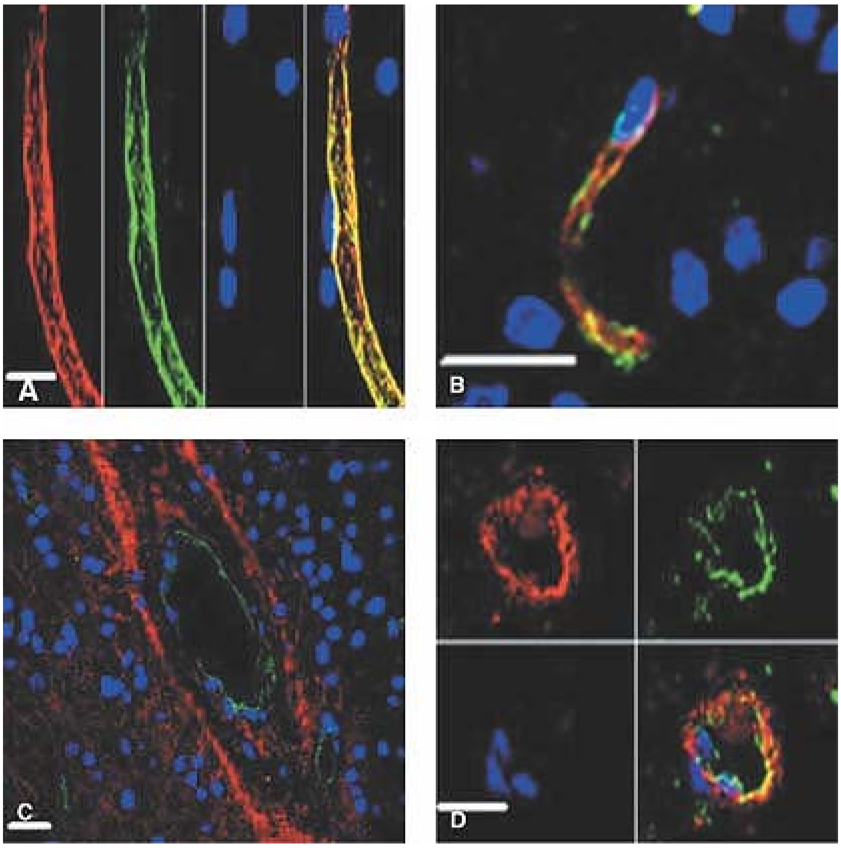

FIGURE 115.4 Overexpression of multidrug transporters in human epileptogenic brain tissue. Immunohistochemistry using fluorescently labeled antibodies shows co-localisation of fluorescence, and thus labeling, for a combination of tranporters and presumptively transporter-related proteins in microvasculature in a section of hippocampus resected from a patient with refractory epilepsy due to hippocampal sclerosis. In **(A)** to **(D)**, blue labels cell nuclei. In **(A)**, red labels P-glycoprotein (-gp), green labels Breast Cancer Resistance Protein (BCRP), and in the extreme right panel, the two are shown to co-localise by the merged yellow colour. In **(B)**, there is co-localisation, though to a lesser extent, of P-gp (red) and major vault protein (labeled green). **(C)** P-gp (green) does not co-localise in these sections with multidrug-resistance associated protein 1 (MRP1, red). In **(D)**, BCRP (green) co-localises with P-gp (red). In all sections, the scale bar represents 30μm. (See black and white image.)

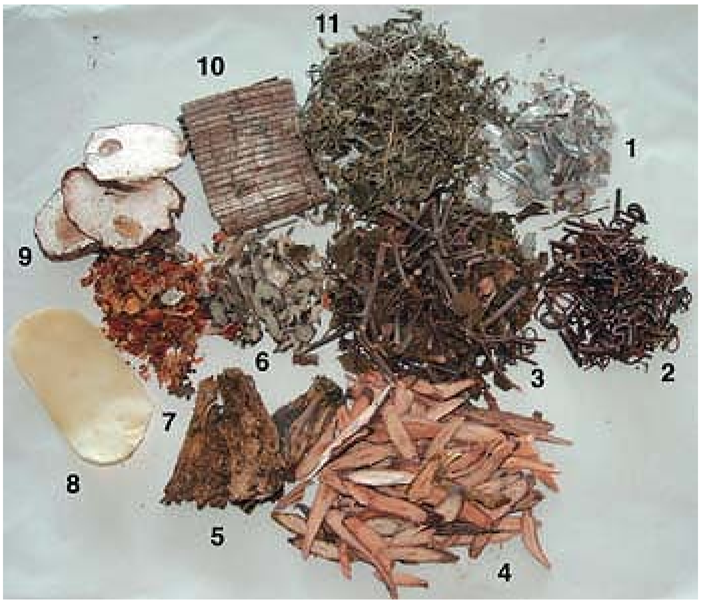

FIGURE 133.1 An example of an herbal formula, called *Tianma Gouteng Yin*. Concha Haliotidis (*1*), Ramulus Uncariae cum uncis (*2*), Herba Taxilli (*3*), Caulis Polygoni multiflori (*4*), Radix Scutellariae (*5*), Radix Achyranthis bidentatae (*6*), Fructus Gardeniae (*7*), Rhizoma Gastrodiae (*8*), Poria cum ligno hospite (*9*), Cortex Eucommiae (*10*, and Herba Leonuri (*11*). (Reprinted from Sucher NJ. Insights from molecular investigations of traditional Chinese herbal stroke medicines: implications for neuroprotective epilepsy therapy. *Epilepsy Behav*. 2006;8:350–362, with permission.) (See black and white image.)

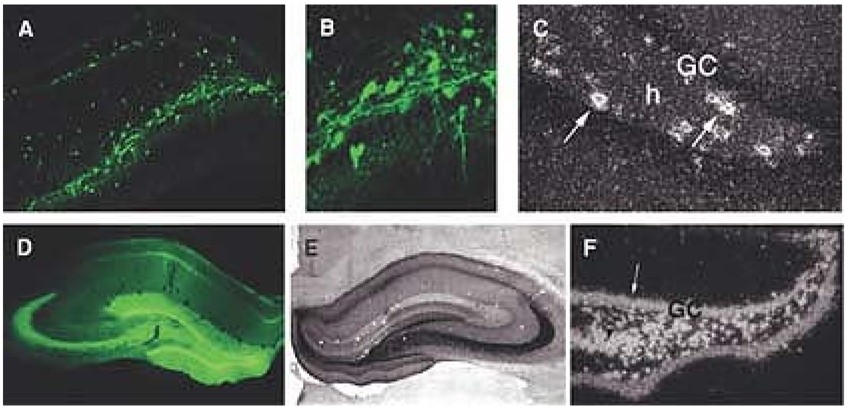

FIGURE 134.6 Influence of viral serotype on green fluorescent protein (GFP) and neuropeptide Y (NPY) expression in the rat hippocampus. Serotype 2 adeno-associated virus (AAV) induces transgene expression specifically in hilar interneurons with a spread of about 1.5 mm around the injection site. Panels **A** and **B** depict GFP in hilar interneurons and their fibers. Panel **C** depicts NPY mRNA in hilar interneurons (*arrows*). Note that granule cells do not express the transgene. Chimeric serotype 1/2 induces a larger transgene expression including hilar interneurons, mossy fibers, and granule cells with an extension of approximately 2.5 mm around the injection site. Panel **D** illustrates GFP distribution throughout the hippocampus. Panels **E** and **F** show NPY immunoreactivity and its mRNA, respectively.

Note that an intense hybridization signal is observed in granule cells (*arrow* in F) and CA3 (*arrowhead* in F). Transgenes were selectively expressed in neurons since they were under control of neuronal enolase promoter. GC, granule cells; h, hilus. (See black and white image.)

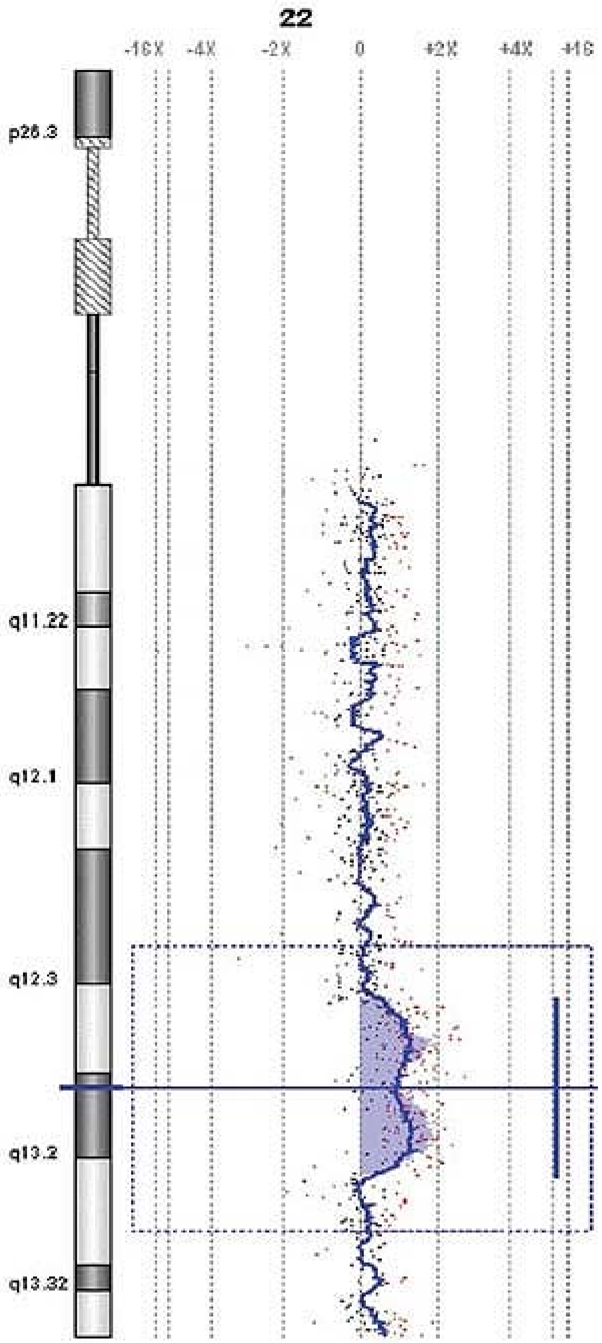

FIGURE 260.1 Eight-year-old girl with early-onset focal epilepsy and dysmorphic features. 6.9 Mb duplication at 22q13.1q13.2 detected through oligo-array-CGH at 75 kb resolution; log2 ratio of signals intensity is increased in the duplication region where red signals are located more proximal to the +2x line than are the remaining ones. This interstitial duplication had not been detected at conventional karyotyping nor, obviously, after FISH with subtelomeric probes. (See black and white image.)